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Part 1
Preliminaries

1.1 Foreword

The text *Heterocyclic Chemistry* by A. R. Katritzky and J. M. Lagowski was the subject's first modern treatment; it appeared 50 years ago, treating structure, reactivity, and synthesis systematically in terms of molecular structure. This text and its sequels, which were translated into Chinese, French, German, Greek, Italian, Japanese, Polish, Russian, and Spanish, revolutionized the practice and teaching of the subject worldwide. The 1st Edition of *Handbook of Heterocyclic Chemistry* (Handbook-I) followed in 1985 as part of *Comprehensive Heterocyclic Chemistry* 1st Edition (CHEC-I). Handbook-II appeared in 2000 alongside CHEC-II. We now present Handbook-III following the publication of CHEC-III in 2008.

The importance and extent of the subject matter of heterocyclic chemistry continues to grow such that it is now clearly the largest subdivision of organic chemistry. It plays a crucial role in biochemistry – increasingly so in medicine – and manifest other areas of chemistry as applied to subjects as diverse as construction and agriculture. Such is the rate of growth that this update is clearly needed.

Handbook-III retains the essentials of the treatments of Handbooks-I and -II in dividing the subject into the three main areas of structure, reactivity, and synthesis. We have striven both to be reasonably comprehensive and to keep the physical size of Handbook-III to a minimum, so it can be conveniently handled and consulted.

Handbook-III has four authors; three have prime responsibility for one section each: C. A. R. for Structure, J. A. J. for Reactivity, and V. V. Z. for Synthesis. Although much of the original content has been retained, each author has brought his own major experience throughout the revision, rewriting, and insertion of new material into the old.

Alan R. Katritzky, Christopher A. Ramsden, John A. Joule, and Viktor V. Zhdankin

1.3
Notes on the Arrangement of the Material in the Handbook

Arrangement of Material in the Structure Chapters

The Structure chapters in Handbook-III follow the same general format as those in the Handbook-II with a few relatively minor variations. Within this format, some sections have been largely rewritten whereas others have new material added with mostly minimum changes. New material has been selected to illustrate principles and trends, or to introduce new developments in the subject. Some material from Handbook-II has been deleted and replaced by examples of more recent work. CHEC-III has been the major source of new material and, in addition to references to the primary literature, relevant sections of CHEC-III are widely cited throughout the chapters.

In Chapter 2.1 a new section on computer-aided techniques has been introduced. This gives an overview of the hierarchy of computational methods available to heterocyclic chemists and a guide to some of the terminology used. This is followed by a glossary of general terms used throughout the structure chapters and an indication of sections where examples can be found.

Chapters 2.2–2.5 cover the structures and related properties of heterocycles according to ring size. Each chapter follows the same general format beginning with a survey of possible structures, their nomenclature, including common names, and an emphasis on rings of special importance. Next, sections on theoretical methods are subdivided into coverage of general trends, illustrated using the results of Hückel and AM1 calculations, followed by descriptions of the results of more sophisticated calculations of molecular properties. Sections on experimentally determined structures (X-ray diffraction and microwave spectroscopy) are then followed by sections on spectroscopic methods (including ^{1}H, ^{13}C, ^{15}N NMR, IR, and UV) and mass spectrometry. Sections on thermodynamic aspects include discussions of aromaticity and antiaromaticity, and conformations of nonconjugated rings. Each chapter concludes with a discussion of tautomerism, which is subdivided into prototropic and valence tautomerism. As appropriate for each ring category, prototropic tautomerism is further subdivided into annular tautomerism, substituent tautomerism, and ring-chain tautomerism.

Chapter 2.2 covers six-membered heterocycles. Chapters 2.3 and 2.4 cover five-membered rings and their benzo derivatives. In this edition the coverage of the structures and spectroscopic properties of bicyclic 5-5 heterocycles has been increased. Recent developments in the measurement of aromaticity using energetic, structural, and magnetic indices are discussed in Chapter 2.2–2.4 and indices tabulated and compared. Chapter 2.5 covers small and large rings and includes heterocycles that are formally antiaromatic if planar. Throughout the structure chapters, numerical data useful to practicing heterocyclic chemists (e.g., bond lengths, chemical shifts, UV spectra) have been presented in Tables for easy reference.

Arrangement of Material in the Reactivity Chapters

The Reactivity chapters in Handbook-III follow the same general format as in the previous edition with only a few relatively minor variations. The philosophy and principles of the categorization and subdivisions of the Reactivity sections have been retained. These include, where relevant, comparisons of heterocyclic reactivity with the chemistry of benzenoid aromatic compounds and with carbonyl/enol/enamine chemistry. The use of 'nucleophilic attack on ring- or side-chain hydrogen,' has been changed to 'base attack on ring- or side-chain hydrogen,' the term 'nucleophile' being reserved for reactions at carbon (or nitrogen or sulfur).

Reactions of organometallic nucleophiles are reviewed mainly under 'Reactivity of Substituents: Metals and Metalloids' – this is a change from the Handbook-II policy of considering these under the reactions of 'Reactivity of Substituents: Halides.' Transition metal-catalyzed reactions of halides are considered partly under 'Reactivity of Substituents: Halides' and partly in the metalloids sections. Transition metal-catalyzed reactions of stannanes, boronic acids, etc., are considered under 'Reactivity of Substituents: Metals and Metalloids.' These areas represent the largest proportion of the additional new material since Handbook-II and are certainly the most important.

Much of the material from Handbook II has been retained, but it was necessary to remove and/or replace substantial portions to accommodate new chemistry and results. The new material is taken from CHEC-III and each item is given its original reference. Most of the older references in Handbook-II, and references to early reviews and to CHEC-II have been removed. Clearly, it was possible to include only a very small fraction of new work from CHEC-III, but it was the aim to summarize representative and important results.

Section 3.1 is a brief overview; Section 3.2 deals with six-membered heterocycles, including those with more than one heteroatom in the ring; Section 3.3 deals with five-membered heterocycles with one heteroatom; Section 3.4 deals with five-membered heterocycles with more than one heteroatom in the ring; Section 3.5 covers small (three- and four-membered) and large (>six) ring heterocycles.

In each of the five sections of Chapter 3, the chemistry is reviewed in the following order: (1) Reactivity of aromatic rings (thermal reactions not involving reagents, substitutions at carbon, additions to nitrogen, metallations); (2) Reactions of nonaromatic compounds (this enormous area, which overlaps extensively with nonheterocyclic chemistry, is reviewed with emphasis on the heterocyclic aspects); (3) Reactions of substituents (with emphasis on situations in which substituents behave somewhat differently when attached to a heterocycle; note that for benzene-fused heterocycles, the benzene ring is treated as a substituent).

Arrangement of Material in the Synthesis Chapters

The Synthesis section (Chapters 4.1–4.6) retains the same general concepts and organization of material as in Handbook-II. Within this format, numerous new synthetic methods have been systematically presented along with the most important previous material from Handbook-II. Preference has been given to the procedures most synthetically useful, essential experimental details, reaction conditions, and original references are provided in our schemes. The relevant sections of CHEC-III, which have been used as the major source of new material, are cited in each subsection of the Synthesis part of Handbook-III.

The main aim of this part of the book is to provide an introduction to the most efficient ways of making a heterocyclic compound, either by using a known method or by analogy with existing methods for related compounds. The organization is in accordance with this aim. The synthesis of a heterocyclic compound can frequently be divided into two parts: ring synthesis, and substituent introduction and modification. The basic principles and experimental methodology for substituent introduction and modification are discussed in the Reactivity sections (Chapters 3.1–3.5); however, brief summaries of these methods with reference to the related sections of the reactivity chapters are also provided in the Synthesis chapters. The major part of the Synthesis section deals with ring synthesis.

The introductory Chapter 4.1 provides an overview of the main types of reactions used in the preparation of heterocyclic rings based upon mechanistic considerations. The material in the following Chapters 4.2–4.6 is organized by types of heterocycle according to increasing number of heteroatoms, size of monocyclic ring, number of fused rings, and type of fused rings. Ring-fused systems with ring junction N- or S-atoms are considered separately from their more numerous analogues with only C-atoms at the ring junctions. Mono-, bi-, and tricyclic systems are classified firstly according to the number and orientation of their heteroatoms and secondly by the degree of unsaturation in the system. Within this main classification, syntheses are further combined in groups as follows: (1) those of related classes of compounds, (2) those from similar precursors, and (3) methods related mechanistically.

1.4
Explanation of the Reference System

As in CHEC-I and CHEC-II references are designated by a number-letter coding of which the first numbers record the year of publication, the next one to three letters denote the journal, and the final numbers give the page. The system is based on that previously used in the following two monographs: (1) A. R. Katritzky and J. M. Lagowski, '*Chemistry of the Heterocyclic N-Oxides*', Academic Press, New York, 1971; (2) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, '*The Tautomerism of Heterocycles*', in '*Advances in Heterocyclic Chemistry*', Supplement 1, Academic Press, New York, 1976, and from Volume 40, 1986 generally in *Advances in Heterocyclic Chemistry*.

A list of journal codes is given in alphabetical order together with the journals to which they refer at the end of this Handbook In addition a full list of references is provided at the end of the volume. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters. Journal volume numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters. Patents are assigned appropriate three-letter codes.

Part 2
Structure of Heterocycles

2.1 Overview

2.1.1 Relationship of Heterocyclic and Carbocyclic Aromatic Compounds

Heterocyclic compounds (like carbocyclic compounds) can be divided into heteroaromatic and heteroalicyclic types. In general, the chemistry of heteroalicyclic compounds is similar to that of their aliphatic analogues, but that of heteroaromatic compounds involves additional principles. Aromatic compounds possess rings in which (1) each of the ring atoms is in the same plane and has a p orbital perpendicular to the ring plane and (2) $(4n + 2)$ π-electrons in cyclic conjugation are associated with each ring.

For a better understanding of the genesis and electronic nature of basic heteroaromatic systems, it is convenient to consider their carbocyclic precursors. The latter can be divided into three main groups: neutral (e.g., benzene **1**), anionic (e.g., the cyclopentadienyl anion **2**), and cationic (e.g., the tropylium ion **3**). Each of these carbocyclic systems is parent to a large number of isoconjugate heteroaromatic compounds. Six-membered aromatic heterocycles are derived from benzene **1** by replacing CH groups with N, O^+, S^+, or BH^-, which are isoelectronic with the CH group. One CH group can be replaced to give pyridine **4**, the pyrylium ion **5**, the thiinium (thiopyrylium) ion **6**, or the 1*H*-boratabenzene anion **7** <1995JA8480>. The heteroatom in all these molecules is in a double-bonded state and formally contributes one π-electron to the aromatic π-system. Such a heteroatom is called 'pyridine-like.' Replacement of two or more CH groups in such a manner is possible with retention of aromaticity, e.g., pyrimidine **14**.

The five-membered aromatic heterocycles pyrrole **8**, furan **9**, and thiophene **10** are formally derived from the cyclopentadienyl anion **2** by replacement of one CH^- group with NH, O, or S, each of which contributes two π-electrons to the aromatic sextet. Heteroatoms of this type have in classical structures only single bonds and are called 'pyrrole-like.' Other five-membered aromatic heterocycles are derived from compounds **8**, **9** and **10** by further replacement of CH groups with N, O^+, or S^+, e.g., imidazole **15**.

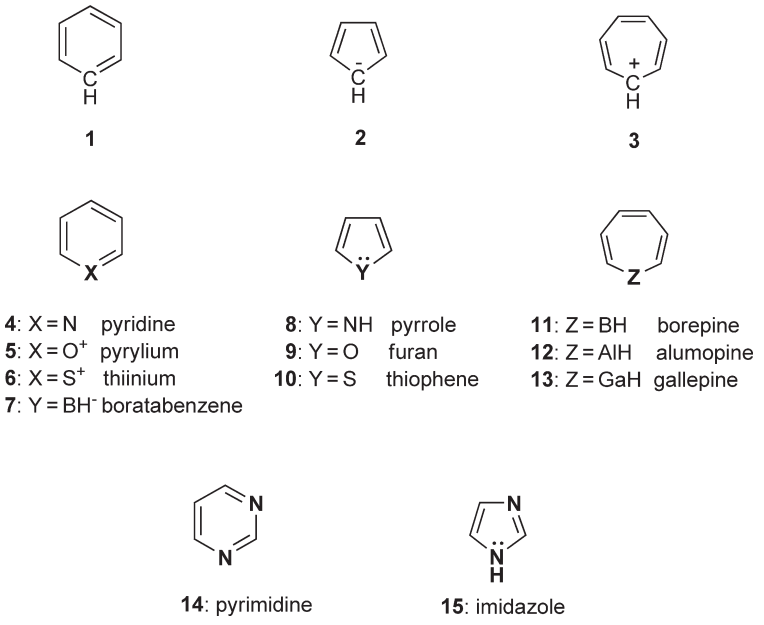
It is important to recognize the difference between 'pyridine-like' and 'pyrrole-like' heteroatoms when considering the properties of heteroaromatic molecules. In pyridine **4** the nitrogen lone pair of electrons is not part of the aromatic sextet, whereas in pyrrole **8** the nitrogen lone pair is part of the aromatic sextet. This results in the two molecules having profoundly different properties. Imidazole **15** contains both types of nitrogen.

Transition from the tropylium ion **3** to its neutral heteroaromatic counterparts is possible by replacement of a CH^+ group by a heteroatom with a vacant p orbital. The latter effectively accepts π-electrons, thus providing ring-electron delocalization. A typical example is the boron atom in 1*H*-borepine **11** <1992AGE1255>. Correspondingly, this type of heteroatom can be referred to as 'borepine-like.' Other little-known representatives of this family are alumopine **12** and gallepine **13**.

The three fundamental types of heteroatom (X, Y, and Z; **Scheme 1**) are also found in small and large heterocycles.

2.1.2 Arrangement of Structure Chapters

Each of the chapters on structure discusses six-membered, five-membered, or small and large rings and begins with a survey of the possible heterocyclic structures covered by the chapter. Structures are generally subdivided into those in



Scheme 1 The relationship between carbocyclic and heterocyclic aromatic systems.

which the ring atoms are in cyclic conjugation (aromatic or antiaromatic) and those in which at least one sp^3-hybridized ring atom interrupts cyclic conjugation. The first class is further subdivided into those possessing exocyclic conjugation and those without.

The results of theoretical methods are surveyed, followed by data on molecular dimensions obtained from X-ray diffraction or microwave spectroscopy. The results of NMR spectroscopy, including ^{1}H, ^{13}C, ^{14}N, and ^{15}N NMR, are then surveyed. This is followed by a discussion of UV, visible, IR, and photoelectron spectroscopy and mass spectrometry. Each of the spectroscopic sections deals with both the parent rings and the effects of substituents.

The next section deals with thermodynamic aspects. This starts with a consideration of the intermolecular forces between heterocyclic molecules and their influence on melting and boiling points, solubilities, and chromatographic properties. This is followed by a section on stability and stabilization, including thermochemistry and the conformations of saturated ring systems, and a discussion of aromaticity.

The last major section deals with tautomerism, including prototropic tautomerism, ring-chain tautomerism, and valence tautomerism.

2.1.3 Nomenclature

A detailed discussion of the nomenclature for heterocyclic compounds can be found in the first edition of Comprehensive Heterocyclic Chemistry (CHEC-I, Section 1.02). Some of the rules of systematic nomenclature used in *Chemical Abstracts* and approved by the International Union of Pure and Applied Chemistry are collected here. Important trivial names are listed at the beginning of individual chapters.

The types of heteroatom present in a ring are indicated by prefixes: 'oxa,' 'thia,' and 'aza' denote oxygen, sulfur, and nitrogen, respectively (the final 'a' is deleted before a vowel). Two or more identical heteroatoms are indicated by 'dioxa,' 'triaza,' etc., and different heteroatoms by combining the above prefixes in the following order of priority: O>S>N.

Ring size and the number of double bonds are indicated by the suffixes shown in **Table 1**. Maximum unsaturation is defined as the largest possible number of non-cumulative double bonds (O, S, and N having valencies of 2, 2, and 3, respectively). Partially-saturated rings are indicated by the prefixes 'dihydro,' 'tetrahydro,' etc.

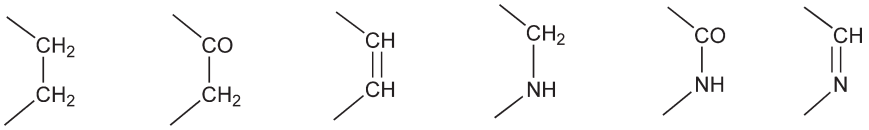
Numbering starts at an oxygen, sulfur, or nitrogen atom (in decreasing order of preference) and continues in such a way that the heteroatoms are assigned the lowest possible numbers. Other things being equal, numbering starts at a substituted rather than at a multiply bonded nitrogen atom. In compounds with maximum unsaturation, if the double

Table 1 Stem suffixes for Hantzsch–Widman names

	Rings with nitrogen			*Rings without nitrogen*		
Ring size	*Maximum unsaturation*	*One double bond*	*Saturated*	*Maximum unsaturation*	*One double bond*	*Saturated*
3	-irine	–	-iridine	-irene	–	-irane
4	-ete	-etine	-etidine	-ete	-etene	-etane
5	-ole	-oline	-olidine	-ole	-olene	-olane
6	-ine	–	–	-in	–	-ane
7	-epine	–	–	-epin	–	-epane
8	-ocine	–	–	-ocin	–	-ocane
9	-onine	–	–	-onin	–	-onane
10	-ecine	–	–	-ecin	–	-ecane

bonds can be arranged in more than one way, their positions are defined by indicating the nitrogen or carbon atoms that are not multiply bonded and consequently carry an 'extra' hydrogen atom, by '1*H*-,' '2*H*-,' etc. In partially-saturated compounds, the positions of the hydrogen atoms can be indicated by '1,2-dihydro,' etc. (together with the 1*H*-type notation, if necessary). Alternatively, the positions of the double bonds can be specified; for example, 'Δ^3-' indicates that a double bond is between atoms 3 and 4. A positively charged ring is denoted by the suffix '-ium.'

The presence of a ring carbonyl group is indicated by the suffix '-one' and its position by a numeral, e.g., '1-one,' '2-one,' etc.; the numeral indicating the position of the carbonyl group is placed immediately before the name of the parent compound unless numerals are used to designate the position of heteroatoms, when it is placed immediately before the suffix. Compounds containing groups **17** or **20** are frequently named as derivatives of either groups **16** and **19** or groups **18** and **21**.



16 **17** **18** **19** **20** **21**

Ring C═S and C═NH groups are denoted by the suffixes '-thione' and '-imine'; cf. '-one' for the C═O group.

2.1.4 Computer-Aided Studies of Heterocycles

Computational methods are now widely used to calculate the properties of heterocyclic molecules and their reaction pathways. An overview of these methods is provided here; the results of specific calculations are given in the appropriate sections of Chapters 2.2–2.5. Although modern computational models are available in packages that are easy to use, a sound knowledge of the underlying theory and the strengths and weaknesses of individual models is necessary for effective and useful applications. The outcome of a theoretical study should be (1) insight into a chemical problem that cannot be obtained using traditional qualitative analysis and/or (2) the direction of attention to new experiments or areas of chemistry worthy of investigation. A study that does not result in either useful predictions or a solution to a well-defined problem is rarely of value. A review of computational studies of heterocycles, including a survey of recommended methods, was published in 2001 <2001AHC(81)1>.

An essential requirement of quantum chemical methods is to solve the Schrödinger equation, i.e., to obtain (1) the eigenfunctions which describe the molecular orbitals (MOs) and (2) the eigenvalues which are the energies of the MOs. In practice the best one can do is to find approximate solutions. Molecular properties are related to the eigenfunctions and eigenvalues, and these properties include molecular geometry, electron density, net atomic charges, bond orders, frontier MO electron densities, free valences, electrostatic potential maps, dipole moments, ionization potentials, electron affinities, and delocalization and localization energies. Several levels of approximation are applied to solving the Schrödinger equation in order to calculate these properties. The accuracy and reliability of the calculated properties depend upon the method used. These methods range from simple Hückel calculations to *ab initio* and density functional theory (DFT) calculations, and these approaches are summarized in the following sections.

2.1.4.1 Hückel Calculations and Related π-Electron Methods

In the simplest MO approximations, the π-electrons are assumed to move independently in MOs which are represented as linear combinations of atomic p orbitals. The distribution of the π-electrons in each MO and their energies depend on the values of certain integrals. The Coulomb integrals (α) are characteristic of individual atomic p orbitals in a molecular environment and can be regarded as the effective electronegativity of that atom. The resonance integrals (β) are characteristic of bonds between pairs of p orbitals and are a measure of the strength of a localized π-bond.

Hückel calculations are based on simplifying assumptions about p orbital overlap and the relative values of the different Coulomb and resonance integrals. For aromatic hydrocarbons, all the carbon atoms are assigned the same Coulomb integral (α_C) and all CC π bonds are assigned the same resonance integral (β_{CC}). For heteroaromatic molecules, the approximate Coulomb integral for heteroatom X (α_X) is defined in terms of α_C and β_{CC} and the electronegativity parameter h_X (Equation 1).

$$\alpha_X = \alpha_C + h_X\beta_{CC} \tag{1}$$

$$\beta_{XY} = k_{XY}\beta_{CC} \tag{2}$$

Resonance integrals (β_{XY}) for bonds between atoms X and Y are defined by Equation (2), where k_{XY} is related to the nature of the atoms and the bond length. There has been considerable variation in the values taken for the Coulomb and resonance integrals for heterocyclic molecules. One of the best available set of parameters is still that originally suggested by A. Streitwieser <B-61MI1>:

$h_N^{\bullet} = 0.5$	$k_{C=N} = 1.0$
$h_N^{\bullet\bullet} = 1.5$	$k_{C-N} = 0.8$
$h_N^{+} = 2.0$	
$h_O^{\bullet} = 1.0$	$k_{C=O} = 1.0$
$h_O^{\bullet\bullet} = 2.0$	$k_{C-O} = 0.8$
$h_O^{+} = 2.5$	

In this notation, heteroatoms which contribute one and two π-electrons to the aromatic system are designated accordingly.

A more sophisticated semiempirical π-electron theory that takes electron repulsion into account is the Pariser–Parr–Pople (PPP) method <B-63MI2>.

Calculations of the Hückel type are too approximate to usefully calculate individual molecular properties and have been superceded by more sophisticated methods. However, because they can give general analytical expressions that show how properties vary as the nature of heteroatoms changes, they can still give useful qualitative insights into trends in molecular properties, e.g., <2004JA11202>.

2.1.4.2 Semiempirical Methods

For reliable quantitative analysis, it is necessary to use methods that take account of all the bonding electrons ($\sigma + \pi$) in a molecule and also to optimize the geometry so that it corresponds to an energy minimum. A major hurdle in such calculations is the computation and storage of a large number of electron-repulsion integrals. Early efforts to reduce this problem led Hoffmann to develop the extended Hückel (EH) approximation <B-91MI3>, and Pople and coworkers to develop the complete neglect of differential overlap (CNDO), intermediate neglect of differential overlap (INDO), and neglect of diatomic differential overlap (NDDO) methods in which sets of integrals are systematically neglected (e.g., CNDO) <1970MI 40100>.

Dewar and coworkers parameterized these approaches to give the modified intermediate neglect of differential overlap/3 (MINDO/3) <1975JA1285> and modified neglect of differential overlap (MNDO) <1977JA4899> methods.

MNDO gives substantially improved results as compared to MINDO/3. In 1985 an improved version of MNDO, called AM1, was published <1985JA3902>. Later MNDO was reparameterized to give MNDO-PM3 <1989JC209, 1990JC543>.

These methods were parameterized primarily to reproduce experimental geometries and heats of formation with the objective of useful applications to organic and heterocyclic molecules. Although the methods are approximate, they are based on the assumption that a judicious choice of the semiempirical parameters, chosen to give the best fit to a training set, will compensate for the approximations made. It is also suggested that the parameters can take account of electron correlation which is neglected in the *ab initio* approach. These semiempirical methods were developed at a time when computational resources were a major constraint, and they have proved to be accurate and reliable enough to study a wide range of heterocyclic systems. They still have a place in a theoretical chemist's repertoire but for accurate studies they have now been largely replaced by more sophisticated methods.

The computer program package Molecular Orbital PACkage (MOPAC) contains MINDO/3, MNDO, AM1, and PM3 [J.J.P.Stewart, MOPAC – 7.0: A semi-empirical Molecular Orbital Program, Program No 455, Quantum Chemistry Program Exchange (QCPE), Indiana University, Bloomington, IN 47405 USA].

2.1.4.3 *Ab Initio* and DFT Calculations

All quantum chemical calculations are based on the self-consistent field (SCF) method of Hatree and Fock (1928–1930) and the MO theory of Hund, Lennard-Jones, and Mulliken (1927–1929). A method of obtaining SCF orbitals for closed shell systems was developed independently by Roothaan and Hall in 1951. In solving the so-called Roothan equations, *ab initio* calculations, in contrast to semiempirical treatments, do not use experimental data other than the values of the fundamental physical constants.

All these calculations require a set of atomic orbitals from which MOs can be calculated (the basis set). The earliest to be used were Slater-type orbitals (STOs) but these are mathematically inconvenient, and the STO-3G minimal basis set, which uses gaussian functions to mimic Slater orbitals, is commonly used. More sophisticated gaussian basis sets, which lead to improved accuracy, carry labels such as 6-31G(d) and 6-31++G(dp). Successive increases in basis set size (STO-3G → 3-21G → 3-31G(d) → 6-311G(3df)) give improved bond-length accuracy.

For reliable results, the geometries of the species being studied must be calculated and optimized at the *ab initio* level. The expense inherent in the use of the more complex basis sets, as well as that of geometry optimization, originally limited the most detailed studies to rather small heterocyclic ring systems <1977JA7806, 1978JA3674, 1983JA309>. However, the developments in computer technology in the period 1990–2010 have very considerably reduced the cost and time required for *ab initio* calculations on medium size molecules and reactions.

One of the inherent problems with *ab initio* calculations is that they do not take full account of electron correlation, which arises from electrons keeping away from the vicinity of other electrons. This can make a significant contribution to the energy and is especially significant for accurate calculations of reaction energies and bond dissociation. One early method used for adding the effects of electron correlation to the Hartree–Fock method incorporated Møller-Plesset perturbation theory and led to methods labeled MP2, MP3, MP4, etc.

A significant development has been density functional theory (DFT) which calculates properties using electron densities rather than by the solution of the Schrödinger equation for individual electrons. The simplification of using only electron density, rather than the many variables required to solve the Schrödinger equation, leads to much faster calculations, but electron correlation is still difficult to calculate. An important advance has been the inclusion of some Hartree–Fock methodology into the exchange correlation terms to give hybrid functionals, and these versions are identified by names such as B3LYP and B3W91. The Becke-style hybrid functional approach B3LYP has been extremely successful and it is estimated that it has been used in more than 80% of DFT applications. Even though now widely used, it is recognized that DFT still has some serious shortcomings and the search for improved hybrid functionals that give improved accuracy without loss of computational efficiency is a rapidly developing area of research <2008CEN(86(26))34>. New versions can be expected to become the methods of choice over the next decade.

A common strategy these days is to use one method to calculate an accurate minimum energy geometry and then use a very high-level single-point calculation to obtain an accurate energy. The following convention is usually used to document the methods used:

energy method/energy basis set//geometry method/geometry basis set

Thus, **HF/6-31G(d)//AM1** indicates that the geometry was optimized using the standard AM1 package and the energy of the optimized geometry was then calculated using Hartree–Fock theory employing the 6-31G(d) basis set. Similarly, **B3LYP/6-31+G(dp)//HF/3-21G(d)** indicates that the geometry was determined using the Hartree–Fock method and then a more accurate energy was calculated using DFT.

2.1.4.4 Molecular Mechanics

The molecular mechanics (MM) or force field method is an empirical method based on classical mechanics and adjustable parameters. It has the disadvantage of being limited in its application to certain kinds of compounds for which the required parameters have been determined (experimentally or by theoretical calculations). Its advantage is a considerably shorter computation time in comparison with other procedures having the same purpose. This method has been shown to be very reliable and efficient in determining molecular geometries, energies, and other properties for a wide variety of compounds.

In the analysis of the structural properties of heterocyclic compounds, the most frequently used force field among several available seems to be Allinger's MM force field. The earlier version was developed for application to conjugated systems by including a π-system molecular orbital treatment in calculations <1987JC581, 1988JA2050> and with parameters extended to include furan and related compounds <1985TL2403, 1988JOC5471, 1989JC635>.

2.1.5 Glossary of General Terms Used in Chapters 2.2–2.5

Annular elementotropy – This is a type of tautomerism involving the reversible migrations of organic and inorganic groups that are analogous to those of a proton in annular tautomerism. For examples see Section 2.4.5.1.2.

Annular tautomers – Annular tautomers are prototropic tautomers (see below) in which the migrating proton is restricted to ring atoms. For examples see Sections 2.3.5.1.1, 2.4.5.1.1, and 2.5.5.1.

Anomeric effect – The stabilization ($n_X \rightarrow \sigma_{CZ}^*$) of a ring conformation by interaction of a lone pair of electrons (n_X) on a ring heteroatom with an antibonding σ orbital (σ_{CZ}^*) of an adjacent electron-withdrawing substituent Z is known as the anomeric effect. This type of stabilization (i.e., $n_O \rightarrow \sigma_{CZ}^*$) was first invoked to explain the preference for the axial orientation of electronegative substituents Z at the 2-position (anomeric position) of tetrahydropyrans. For examples see Sections 2.2.3.1, 2.2.4.3, and 2.4.4.4.

Atropisomers – Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric barrier to rotation is high enough to allow for the isolation of the conformers <2004T4335>. For examples see Section 2.3.4.3.2.

Bird aromaticity index (I) – An index of aromatic character based on a statistical evaluation of the extent of variation of ring bond orders compared to those of the nondelocalized Kekulé structure. Bond orders are determined from experimentally determined bond lengths, or from accurate calculated values. The index was introduced for five-membered ring (I_5) in 1985 by Clive Bird and subsequently extended to six-membered rings (I_6) and bicyclic systems ($I_{5,6}$ and $I_{6,6}$). A universal index I_A unifies the approach ($I_A = I_6 = 1.235$ $I_5 = 1.840$ $I_{6,6} = 2.085$ $I_{5,6}$) <1992T335>. For examples see Sections 2.2.4.2.3, 2.3.4.2.3, and 2.4.4.2.3.

Conjugated mesomeric betaine – Conjugated heterocyclic mesomeric betaines are cyclic mesomeric betaines in which the positive and negative charges are not restricted to separate parts of the π-electron system. The positive and negative charges are in mutual conjugation and both are associated with the common conjugated π-electron system of the molecule <1985T2239>. For examples see Sections 2.2.1.2.2, 2.3.1.2.1, and 2.4.1.1.1.

Cross-conjugated mesomeric betaine – Cross-conjugated heterocyclic mesomeric betaines are cyclic mesomeric betaines in which the positive and negative charges are exclusively restricted to separate parts of the π-electron system of the molecule <1985T2239>. For examples see Sections 2.2.1.2.2 and 2.3.1.2.1.

Degenerate rearrangement – A molecular rearrangement in which the product is indistinguishable (in the absence of isotopic labeling) from the reactant (see also *Topomerization*). For examples see Sections 2.4.3.3.1(v) and 2.5.5.2.

Desmotropes – Desmotropes are prototropic tautomers in which both tautomeric forms have been isolated. They should not be confused with polymorphs in which the same molecule (tautomer) crystallizes in two or more crystal forms <2008SSNMR68>. For examples see Sections 2.4.3.4 and 2.4.5.1.1.

Harmonic oscillator model of aromaticity (HOMA) – This is a geometry-based index of aromaticity that takes into account two effects. These are the increase in bond-length alternation (GEO term) and the increase in mean bond length in the system (EN term) such that HOMA = 1 – EN – GEO <2004PCP249>. For examples see Sections 2.2.4.2.3, 2.3.4.2.3, and 2.4.4.2.3.

Koopmans' theorem – This states that in closed-shell Hartree–Fock theory, the first ionization energy of a molecular system is equal to the negative of the orbital energy of the highest occupied molecular orbital (HOMO). The theorem, published in 1934, is named after Tjalling Koopmans. For examples see Section 2.3.3.9.3.

Mesoionic compounds – These are defined as five-membered heterocycles that cannot be represented satisfactorily by any one covalent or polar structure and possess a sextet of electrons in association with the five atoms comprising the ring <1976AHC(19)1>. Two types of mesoionic compounds have been recognized and these are described as Type A and Type B. Mesoionic heterocycles are a subclass of heterocyclic mesomeric betaines <1985T2239>. For examples see Sections 2.4.1.2, 2.4.1.4, and 2.4.5.4.

Mesomeric betaines – Mesomeric betaines are neutral conjugated molecules that can be represented only by dipolar structures in which both the positive and negative charges are delocalized within the π-electron system <1985T2239>. For examples see Section 2.2.1.2.2.

N-*Heterocyclic carbenes (NHCs)* – These are five-membered heterocyles in which a carbene function is stabilized by adjacent nitrogen (or sulfur) atoms on both sides of the carbene. They are often stable solids with sharp melting points and can be recrystallized from hydrocarbon solvents <2000CRV39>. For examples see Sections 2.4.3.1 and 2.4.4.2.5.

Nucleus-independent chemical shift (NICS) – This is a calculated magnetic index of aromaticity and is the negative of the absolute magnetic shielding of a system <1996JA6317>. It is computed at the center of a ring, NICS(0), or 0.5 and 1.0 Å above the ring, NICS(0.5) and NICS(1). Values above the ring are regarded as better criteria of aromaticity. A negative NICS value indicates aromaticity and a positive value represents antiaromaticity; values around zero signify nonaromatic systems. Values vary depending upon the computational method used. For examples see Sections 2.2.2.2.2, 2.2.4.2.4, 2.3.2.2.1, 2.3.4.2.4, and 2.4.4.2.4.

Prototropic tautomerism – This refers to an equilibrium between two or more constitutional isomers that occurs by migration of a proton from one atom to another <2000AHC(76)1>. For examples see Sections 2.2.5.1.1, 2.3.5.1, and 2.4.5.1.1.

Ring-chain tautomerism – This is a type of prototropic tautomerism in which proton migration is associated with ring cleavage or ring formation. For examples see Sections 2.2.5.2 and 2.4.5.3.

Rotamers – Rotamers are conformational isomers that differ by rotation about only a single σ bond. For examples see Section 2.3.4.3.

Topological charge stabilization rule – Maximum stabilization of fully-conjugated heterocycles occurs when electronegative atoms are placed at ring positions where the topology of the structure and the electron-filling level place high negative charge in the isoelectronic hydrocarbon <1983JA1979>. For examples see Sections 2.3.2.1 and 2.3.2.2.1.

Topomerization – A type of valence tautomerism involving the exchange of identical atoms or ligands to produce a molecule indistinguishable from the starting material (see also *Degenerate rearrangement*). For examples see Sections 2.4.3.3.1(v) and 2.5.5.2.

Valence tautomerism – This refers to the interconversion of isomers simply by reorganization of bonding electrons and without any accompanying rearrangement including proton migration. For examples see Sections 2.2.5.3, 2.4.5.4, and 2.5.5.2.

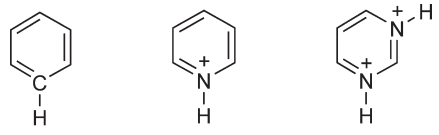
2.2
Structure of Six-membered Rings

2.2.1 Survey of Possible Structures and Nomenclature

2.2.1.1 Nitrogen Rings Without Exocyclic Conjugation

2.2.1.1.1 Fully-conjugated aromatic rings

Since N^+ and C are isoelectronic, the simplest and most direct hetero-analogue of benzene **1** is the pyridinium cation **2**. Further 'azonia substitution' of this kind gives polycations such as the pyrimidine dication **3**.



1 **2** **3**

The simplest neutral fully-conjugated aromatic nitrogen heterocycle is pyridine **4**, which is obtained by deprotonation of the pyridinium ion **2**. In addition to enjoying aromatic stabilization, pyridine is also basic and nucleophilic due to the lone pair of electrons that occupies the position of the CH bond in benzene. Systematic replacement of CH in benzene by N leads to 12 possible monocyclic heteroaromatic nitrogen systems (**Figure 1**), which are known collectively as azines. The diazines and triazines are well known including the parent heterocycles **5–10**. Only one of the three parent tetrazines **11–13** is known, namely 1,2,4,5-tetrazine **13**, but substituted derivatives of all three rings have been reported. Pentazine **14** and its derivatives are unknown. All attempts to prepare hexazine **15** have also failed, although there are reports of its isolation in a matrix. Calculations suggest that the most stable structure of hexazine may not be planar, due to unfavorable interactions between the six nitrogen lone pairs.

When two fused six-membered rings are considered, the number of possible nitrogen heterocycles (which are analogues of naphthalene) becomes quite large (**Figure 2**). The three monoaza analogues of naphthalene are quinoline **16**, isoquinoline **17**, and the quinolizinium cation **18**. There are four diaza analogues **19–22** that have both nitrogens in the same ring (benzodiazines) and six diaza analogues with the nitrogens in different rings (naphthyridines), e.g., **23**. In addition there are diaza analogues of the quinolizinium ion **18**. Higher polyazanaphthalenes with up to six nitrogen atoms are known. The biologically important pteridine system **24**, which occurs, for example, in folic acid, should be noted <CHEC-III(10.18.1)917>.

The most well-known monoaza aromatic systems with three six-membered rings are acridine **25** and phenanthridine **26** (**Figure 3**). Acridine derivatives were among the earliest antibacterial agents. The better known diaza systems include phenazine **27** and 1,10-phenanthroline **28**. Systems with three linearly fused pyridine rings are called anthyridines, e.g., **29**. A derivative of the tetraza ring system **30** is found in vitamin B_2.

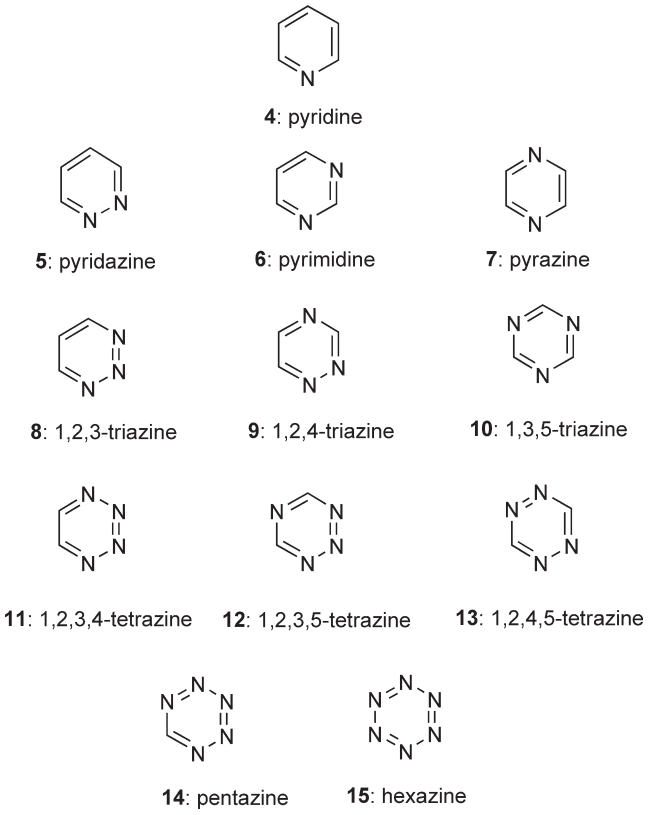


Figure 1 Six-membered monocyclic aromatic nitrogen heterocycles.

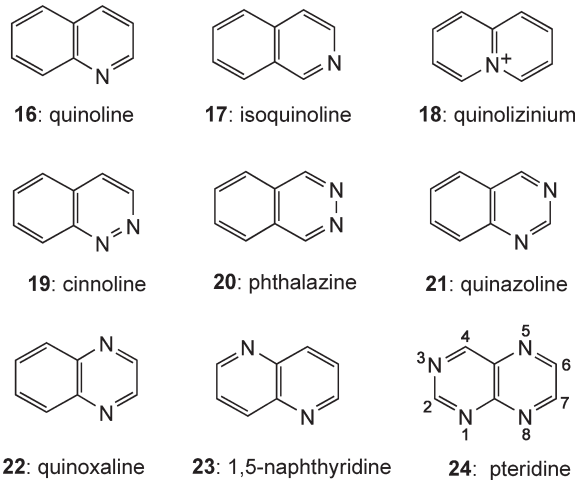


Figure 2 Six-membered bicyclic aromatic nitrogen heterocycles.

The numbering of most ring systems follows a fairly straightforward set of rules <CHEC-I(1.02)7> but there are exceptions that usually arise for historical reasons. The central atoms of acridine **25** are now numbered 9 and 10, but two other numbering systems have been used in the past. This contrasts with phenanthridine **26** and phenazine **27** which are numbered systematically.

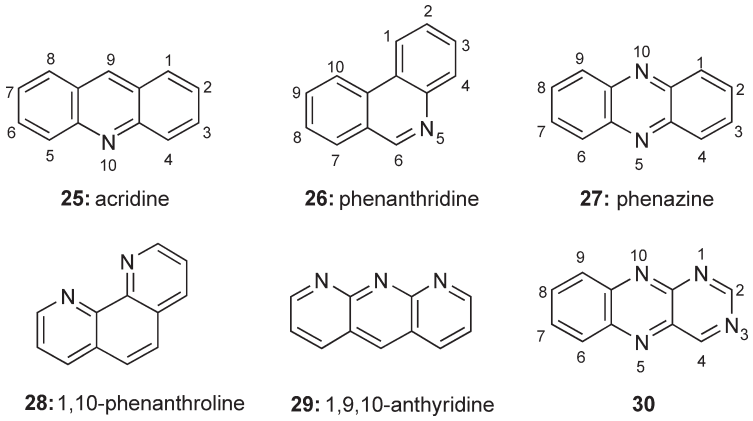
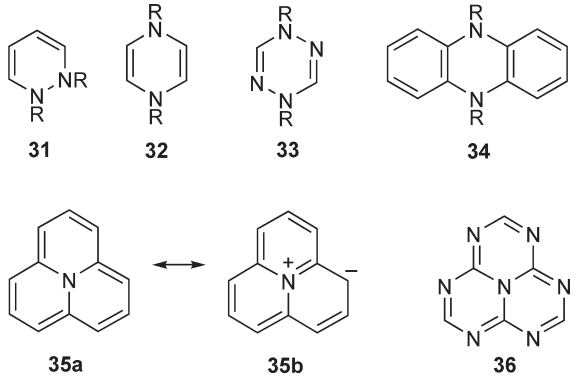


Figure 3 Six-membered tricyclic aromatic nitrogen heterocycles.

2.2.1.1.2 Fully-conjugated nonaromatic rings

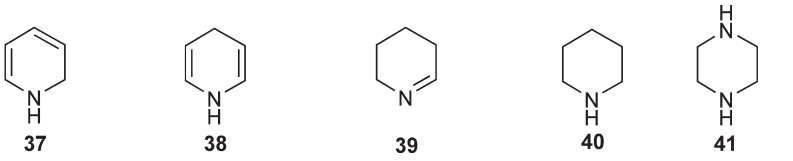
In the dihydrodiazines **31** and **32** each nitrogen atom contributes a lone pair to the cyclic conjugation. If planar these molecules would have eight π-electrons making them antiaromatic. As expected, these molecules are unstable: they minimize cyclic conjugation by distorting to a nonplanar structure and tend to rearrange to more stable isomers. Other systems include the 1,4-dihydrotetrazines **33**. Stability is increased if the substituents R are acyl or aroyl groups, which remove electrons from the ring. The dibenzo derivatives, e.g., 5,10-dihydrophenazine **34**, are also nonplanar.

A more subtle case is that of 9a-azaphenalene ([3,3,3]cyclazine) **35**, which is also unstable. Here the periphery of the molecule has 12 π-electrons ($4n$) in cyclic conjugation, which is antiaromatic. Resonance hybrids of the type **35b**, in which the peripheral electrons are increased to 13 ($4n + 1$), probably make a significant contribution to the structure. Aza substitution, as in the heptaazaphenalene **36**, leads to some stabilization.

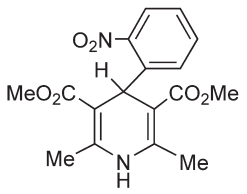


2.2.1.1.3 Rings without cyclic conjugation

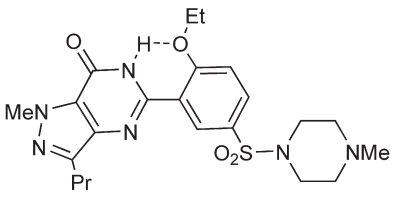
Aromatic sextets are not essential for the stability of heterocyclic rings and saturated and partially-saturated rings occur widely. These are usually named as the corresponding dihydro or tetrahydro derivatives, e.g., **37–39**. The fully-saturated derivatives of pyridine and pyrazine are commonly referred to as piperidine **40** and piperazine **41**. The antihypertensive calcium channel antagonist nifedipine **42** is a 1,4-dihydropyridine derivative <CHEC-III(7.04.5) 210>, and sildenafil **43**, which contains a piperazine ring, is a phosphodiesterase inhibitor used to treat erectile dysfunction <CHEC-III(10.12.9.1)646>.



37 1,2-dihydropyridine; **38** 1,4-dihydropyridine; **39** 2,3,4,5-tetrahydropyridine (piperideine); **40** piperidine; **41** piperazine



42: nifedipine



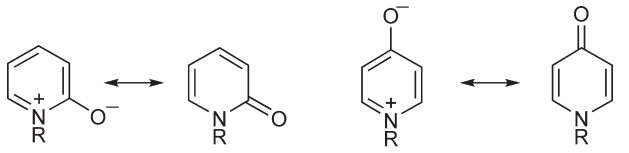
43: sildenafil

2.2.1.2 Nitrogen Rings with Exocyclic Conjugation

To survey six-membered heteroaromatic systems with exocyclic conjugation it is instructive to consider them as being formed by attachment of a positively charged ring (e.g., **2**) to a negatively charged substituent. In this way the following three general classes of heterocycles can be recognized.

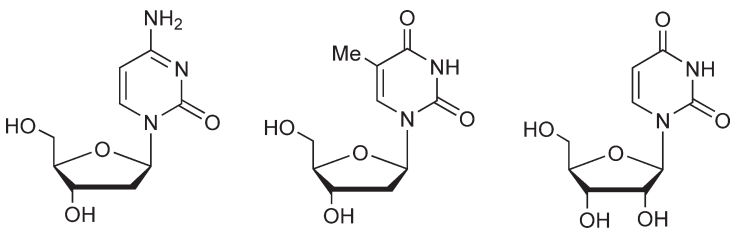
2.2.1.2.1 Pyridones and related systems

If the anionic substituent is placed *ortho* or *para* to the positive heteroatom the charges can formally cancel. This is conveniently illustrated by the structures of 2-pyridones **44** and 4-pyridones **45**. Molecules of this type are usually represented by the uncharged structures **44b** and **45b** but the dipolar resonance hybrids **44a** and **45a** emphasize the aromaticity and polarity of these molecules.



44a **44b** **45a** **45b**

Applying the same analysis to pyrimidines (**3** and **6**) leads to pyrimidones, examples of which are the 'pyrimidine bases' in DNA and RNA. Thus deoxycytidine **46** and deoxythymidine **47** are two of the four 2′-deoxyribonucleosides that are the building blocks of DNA and uridine **48** is one of the four nucleoside building blocks of RNA. As for pyridones, the contribution of dipolar resonance hybrids to pyrimidones and other systems with exocyclic conjugation often helps to understand their properties, including their aromatic character.



46: deoxycytidine **47**: deoxythymidine **48**: uridine

2.2.1.2.2 Mesomeric betaines (1,3-dipoles and 1,4-dipoles)

If the anionic substituent is placed *meta* to the positive heteroatom, uncharged structures cannot be drawn, e.g., **49** and **50** (**Figure 4**). Molecules of this type can only be represented as resonance hybrids of several dipolar structures and are known as conjugated mesomeric betaines <1980AHC(26)1, 1985T2239>. A characteristic reaction of these heterocycles is 1,3-dipolar cycloaddition and they can be regarded as heterocyclic 1,3-dipoles, e.g., **49b**. The exocyclic group is not restricted to oxygen, e.g., **51**. The names of these molecules usually relate to the resonance hybrid with an exocyclic anion. Thus, the derivatives **49** are pyridinium-3-olates and derivatives **50** are 1,7-naphthyridinium-4-olates.

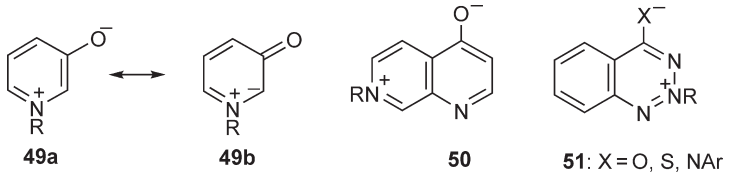


Figure 4 Conjugated mesomeric betaines (1,3-dipoles).

If a heterocyclic cation is associated with two exocyclic groups, a different type of mesomeric betaine can occur, in which the delocalized positive and negative charges are restricted to different regions of the molecule (**Figure 5**). Well-known examples are the 3,6-dihydro-6-oxo-pyridinium-4-olates **52**; polycyclic derivatives are also possible, e.g., **53**. These dipolar heterocycles are described as cross-conjugated mesomeric betaines <1985T2239>, they participate in 1,4-dipolar cycloadditions, and their structures and reactions are quite different to those of conjugated mesomeric betaines (**Figure 4**).

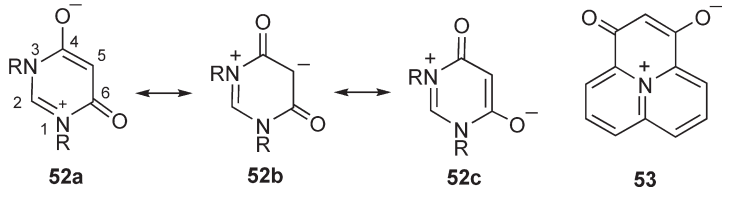
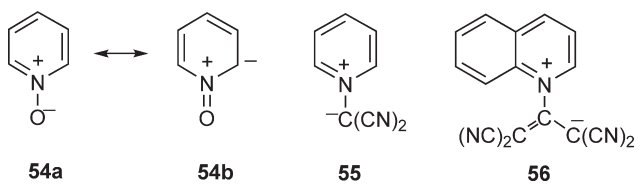


Figure 5 Cross-conjugated mesomeric betaines (1,4-dipoles).

2.2.1.2.3 *N*-Oxides and related systems

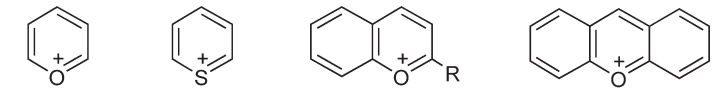
Attachment of an anionic group directly to a positively charged (azonia) nitrogen also leads to dipolar species. The simplest example is pyridine 1-oxide **54**. Compounds of this type are well known and are commonly referred to as *N*-oxides. The exocyclic group can be an imide (RN^-) or carbanion, e.g., **55**, and these derivatives are referred to as *N*-imides and *N*-ylides (e.g., pyridinium *N*-ylides). All members of this class are conjugated mesomeric betaines and, although they are usually treated separately, as here, they have similar properties to the conjugated mesomeric betaines discussed in Section 2.2.1.2.2 and participate in 1,3-dipolar cycloadditions. It should be noted that cross-conjugated (1,4-dipolar) derivatives, such as the quinolinium *N*-ylide **56**, can also arise.



2.2.1.3 Oxygen and Sulfur Rings Without Exocyclic Conjugation

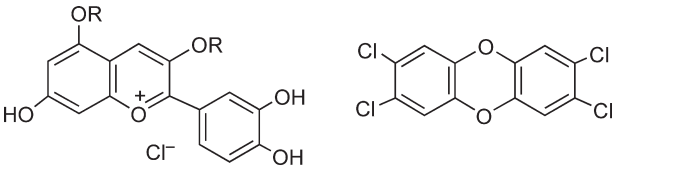
2.2.1.3.1 Fully-conjugated aromatic rings

Replacement of CH in benzene by an oxonia group (O^+) gives the pyrylium cation, but deprotonation cannot occur and no neutral oxygen analogue of pyridine is possible. Representative aromatic oxygen and sulfur rings **57–60** are shown in **Figure 6**. The plant pigment cyanin **61**, which belongs to a family of pigments (anthocyanins) found in flowers and fruit, is a polyhydroxyflavylium derivative isolated as its chloride <CHEC-III(7.09.4.6)714>.



57: pyrylium **58**: thiinium **59**: R=H, 1-benzopyrylium R=Ph, flavylium **60**: xanthylium

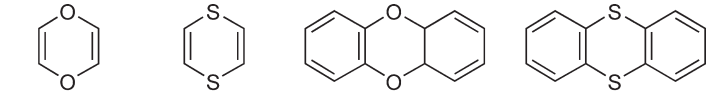
Figure 6 Six-membered aromatic oxygen and sulfur heterocycles.



61: R = β-D-glucose, cyanin **62**: 2,3,7,8-tetrachlorobenzodioxin (TCDD)

2.2.1.3.2 Fully-conjugated nonaromatic rings

Like the dihydrodiazines (Section 2.2.1.1.2), 1,4-dioxin **63** and 1,4-dithiin **64** are 8π systems and are not aromatic (**Figure 7**). 1,4-Dioxin **63** and dibenzo[*b*,*e*][1,4]dioxin (oxanthrene) **65** are planar suggesting little conjugation of the electronegative oxygens. 1,4-Dithiin **64** and thianthrene **66** are nonplanar <CHEC-III(8.12.1)858>. 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) **62** is a class 1 carcinogen, which can be formed during waste incineration, and its presence in the environment is closely monitored <CHEC-II(6.09.11)480>.



63: 1,4-dioxin **64**: 1,4-dithiin **65**: oxanthrene **66**: thianthrene

Figure 7 Six-membered nonaromatic oxygen and sulfur heterocycles.

2.2.1.3.3 Rings without cyclic conjugation

Partially- or fully-saturated six-membered oxygen heterocycles occur widely in nature and trivial names are often used for commonly occurring rings. The more important ring systems **67–76** and their common names are shown in **Figure 8**. The serotonin antagonist (5-HT_{1A}) ebalzotan **77** is a chroman derivative that has been developed as an antidepressant. Rings with two or more oxygen atoms are less common. The antimalarial natural product artimisinin **78** is a rare example of a molecule containing a 1,2,4-trioxane ring <CHEC-III(7.09.4.1.4)709, CHEC-III(10.17.13)905>.

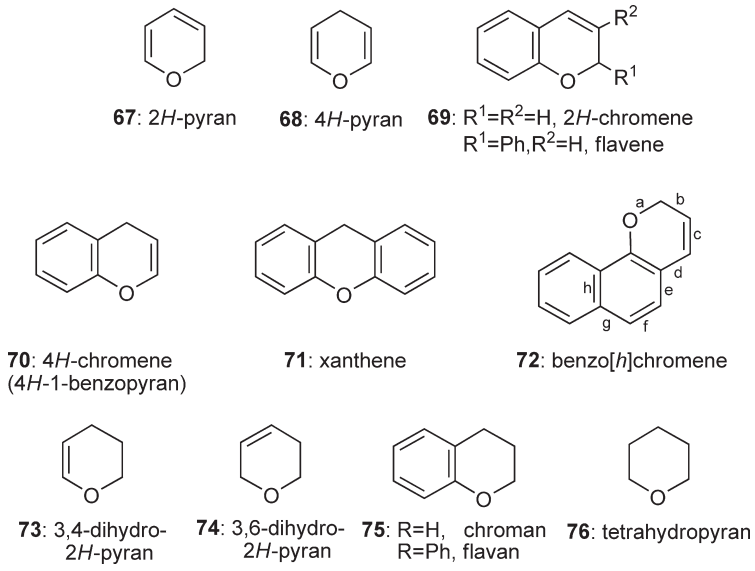
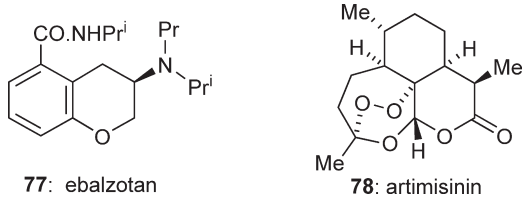


Figure 8 Six-membered nonconjugated oxygen heterocycles.



The corresponding monocyclic sulfur heterocycles **79–83** and their names are shown in **Figure 9**.

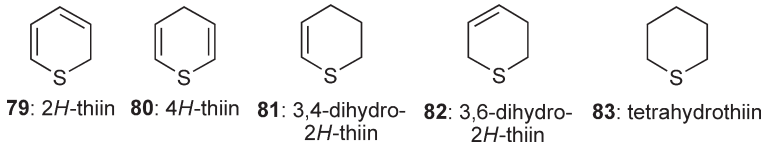


Figure 9 Six-membered nonconjugated sulfur heterocycles.

2.2.1.4 Oxygen and Sulfur Rings with Exocyclic Conjugation

Oxygen and sulfur systems with exocylic conjugation are analogous to those formed by nitrogen (Section 2.2.1.2). The simplest oxygen examples are pyran-2-one **84**, pyran-4-one **85** <2009T7865> and pyrylium-3-olate **86** <2008T3405>. Oxygen is too electronegative to form compounds analogous to pyridine 1-oxide **54**. Oxygen heterocycles of this general class occur widely as natural products and representative ring systems **87–91** and their common names are shown in **Figure 10**. Artimisinin **78** contains a tetrahydropyran-2-one ring, but these are usually described as δ-lactones. The anticoagulant drug warfarin **92** is a coumarin derivative <CHEC-II(5.09.1.2)476>.

2.2.1.5 Rings Containing Nitrogen with Oxygen and/or Sulfur

Compounds with two heteroatoms are illustrated in **Figure 11**. The aromatic cations are named as oxazinium and thiazinium. Oxazines and thiazines contain a saturated carbon atom.

The range of possible ring systems with three, four, or five heteroatoms is considerable: some of the more common systems are shown in **Figure 12**, in which the names correspond to the ring with maximum unsaturation.

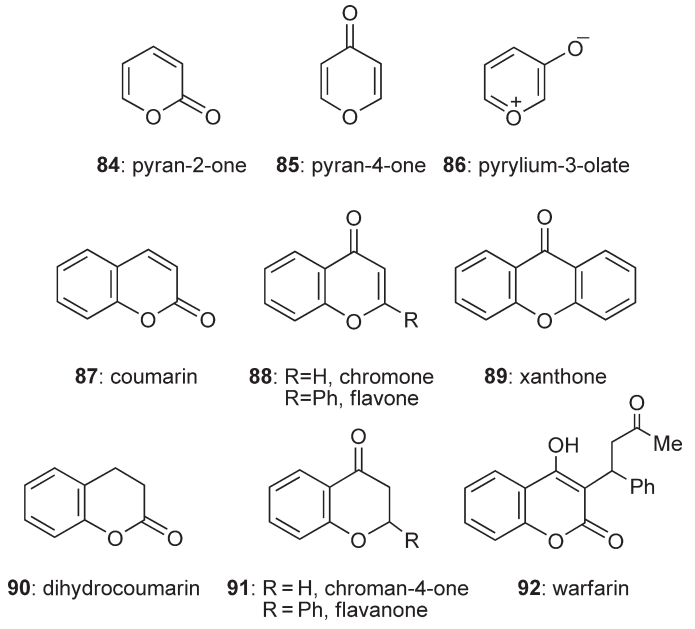


Figure 10 Six-membered oxygen heterocycles with extended conjugation.

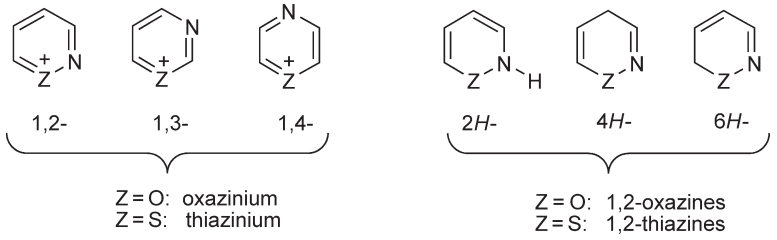
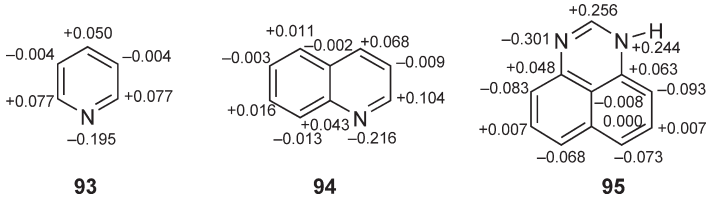


Figure 11 Six-membered N,O- and N,S-heterocycles.

2.2.2 Theoretical Methods

2.2.2.1 General Trends

Introduction of heteroatoms into a benzene ring results in an irregular distribution of electron density, and this strongly influences reactivity and physical properties. In pyridine the electronegative nitrogen atom draws electron density away from the ring carbon atoms resulting in a permanent dipole moment (2.2 D). As a result, some carbon atoms in the ring have a partial positive charge, and pyridine **93** and the other azines are described as electron-poor or π-deficient. Hückel calculations (HMO) (Section 2.1.4.1) give a reasonable indication of the charge distribution in six-membered rings. **Table 1** shows HMO calculated atomic π-charges in selected azine molecules. These estimates of charge distribution are in agreement with the greater deshielding of ^{1}H and ^{13}C nuclei at position 2 of pyridine and pyrimidine and position 3 of pyridazine observed in their NMR spectra (see **Tables 5** and **12**).



93 **94** **95**

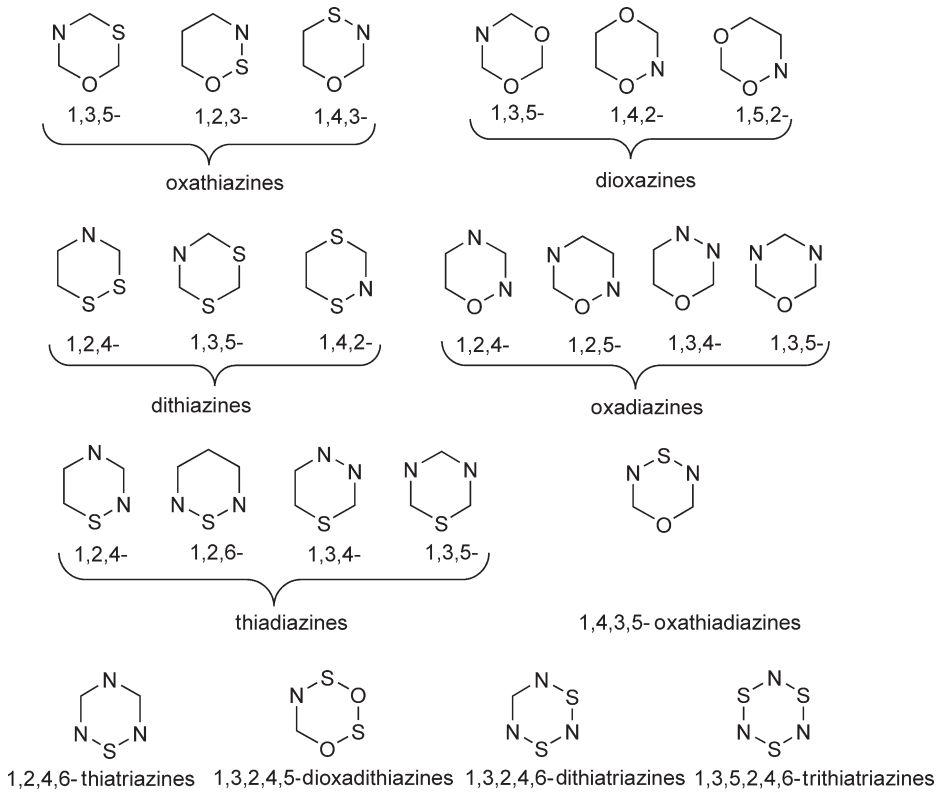


Figure 12 Six-membered monocyclic systems containing multiple nitrogen, oxygen, and/or sulfur atoms (names shown correspond to rings with maximum unsaturation).

Table 1 HMO calculated π-charges and electron deficiencies in azine molecules

Heterocycle	*Position*	*Charge*	$TOT_{\pi D}$	$LOC_{\pi D}$	*Heterocycle*	*Position*	*Charge*	$TOT_{\pi D}$	$LOC_{\pi D}$
Pyridine	1	−0.20	0.21	0.08	1,2,3-Triazine	1,3	−0.12	0.28	0.12
	2,6	+0.08				2	−0.04		
	3,5	-0.00_4				4,6	+0.12		
	4	+0.05				5	+0.04		
Pyridazine	1,2	−0.12	0.26	0.08	1,2,4-Triazine	1	−0.07	0.34	0.15
	3,6	+0.08				2	−0.12		
	4,5	+0.05				3	+0.15		
Pyrimidine	1,3	−0.20	0.42	0.16		4	−0.15		
	2	+0.16				5	+0.12		
	4,6	+0.13				6	+0.07		
	5	−0.01			1,3,5-Triazine	1,3,5	−0.20	0.60	0.20
Pyrazine	1,4	−0.15	0.28	0.07		2,4,6	+0.20		
	2,3,5,6	+0.07			1,2,4,5-Tetrazine	1,2,4,5	−0.07	0.30	0.15
						3,6	+0.15		

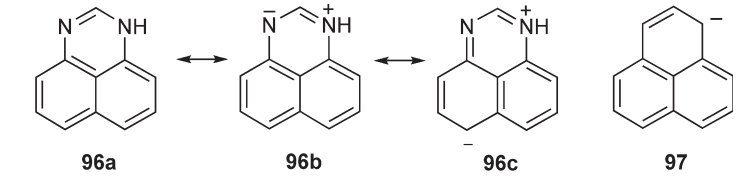
The total π-deficiency ($TOT_{\pi D}$) of a ring can be defined as the sum of the positive charges on all carbon atoms. The π-deficiency of azines is determined by the number of heteroatoms and their mutual disposition. According to HMO calculations (Table 1), the total π-deficiency changes in the sequence: 1,3,5-triazine > pyrimidine > 1,2,4,5-tetrazine ~ pyrazine > pyridazine > pyridine.

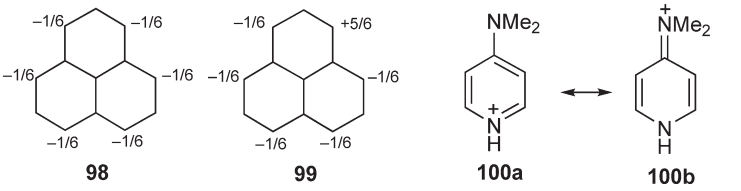
Local π-deficiency ($LOC_{\pi D}$) is the largest positive charge on any one carbon atom in the ring and this property decreases in a different order: 1,3,5-triazine > pyrimidine > 1,2,4,5-tetrazine > pyridazine pyridine > pyrazine. This order is in closer agreement with a π-deficiency scale ($^{\pi}\Delta$) based on ^{13}C NMR chemical shifts <1982OMR192, CHEC-III(9.02.2)97>.

Although 1,2,4,5-tetrazine has the largest number of nitrogen atoms among the stable azines, its π-deficiency is less than that of 1,3,5-triazine and even pyrimidine. The π-acceptor action of nitrogen atoms in azines is most effective when they are *meta* to each other (e.g., 1,3,5-triazine, pyrimidine). *Ortho–para* disposition, as in the case of pyrazine, subjects each carbon atom to two contradictory forces: the strong electron-acceptor influence of an *o*- or *p*-nitrogen and the weak electron-donor influence (due to reorganization of π-cloud) of a *m*-nitrogen. As a result some decrease of π-deficiency can occur which is different for different systems.

The relative π-deficiency sequence of azines does not change significantly on going from neutral molecules to their cations, but total π-deficiency, of course, strongly increases. Most data indicate higher positive charges in positions 2 and 6 of pyridinium and pyrylium cations than in position 4. Although usually represented by structure **57**, only 30–35% of the positive charge is localized on the oxygen atom in the pyrylium cation, and this distribution reflects the electronegativity of oxygen.

On transition from pyridine **93** to quinoline **94** ($TOT_{\pi D}$ 0.24, $LOC_{\pi D}$ 0.10), or isoquinoline, both the total and the local π-deficiencies increase, and the benzene ring is also slightly π-deficient. A different situation arises in perimidine **96** in which the naphthalene fragment is strongly π-excessive. This molecule is related to 9a-azaphenalene ([3,3,3] cyclazine) **35**, which is classified as nonaromatic and different in character to the azines. Like 9a-azaphenalene **35**, perimidine **96** is isoelectronic with the perinaphthenyl anion **97**, which is an alternant anion whose π-electron distributions are well known. To a first approximation, the distribution of the negative charge in the alternant anion **97** is as shown in structure **98**. A first approximation of the electron distribution in perimidine **96** is therefore that shown in structure **99**, which is in qualitative agreement with the HMO calculated values **95** and accounts for the π-excessive naphthalene fragment. Placing electronegative nitrogen atoms at the electron-rich positions results in stabilization and, for example, heptaazaphenalene **36** is thermally very stable. A similar transfer of electron density to a ring occurs in 4-dimethylaminopyridine **100** (DMAP), which is isoelectronic with the benzyl anion. This stabilizes the corresponding pyridinium ring making DMAP a stronger base than pyridine.





Other fundamental characteristics of heteroaromatic systems are their electron-donor and electron-acceptor properties. The energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbitals (the frontier orbitals) can serve as measures of such properties. Pyridine-like heteroatoms lower the energies of all the MOs and compounds containing heteroatoms of this type can be expected to show more π-acceptor and less π-donor character. In accord with this expectation (**Table 2**), π-acceptor properties of azines decrease in the sequence: 1,2,4,5-tetrazine > pyrazine > pyridazine > pyrimidine > pyridine.

This agrees with the relative ease of polarographic reduction of the same heterocycles. However, there is no strict dependence between π-deficiency and π-acceptor strength of the compounds. π-Acceptor properties of azines also increases on transition to benzo derivatives, e.g., acridine > quinoline > pyridine.

Although nitrogen atoms lower the energies of all MOs, the energy gap between HOMO and LUMO (Δ) (**Table 2**) does not change greatly among the monocyclic azines, and this is reflected in the similarity of their $\pi \rightarrow \pi^*$ absorption

Table 2 HMO[a] and AM1[b] energies of the frontier orbitals of six-membered heterocycles

Molecule	*HOMO*	*LUMO*	Δ	*Molecule*	*HOMO*	*LUMO*	Δ
Benzene **1**	1.00	−1.00	2.0	1,2,4,5-Tetrazine **13**	1.19	−0.50	1.7
	−9.65	*0.56*	*10.21*		*−11.02*	*−1.30*	*9.72*
Pyridine **4**	1.00	−0.84	1.8	Quinoline **16**	0.70	−0.53	1.2
	−9.93	*0.14*	*10.07*		*−9.18*	*−0.47*	*8.71*
Pyridazine **5**	1.10	−0.73	1.8	Isoquinoline **17**	0.65	−0.58	1.2
	−10.67	*−0.29*	*10.38*		*−9.03*	*−0.56*	*8.47*
Pyrimidine **6**	1.08	−0.78	1.9	Acridine **25**	−0.51	−0.33	0.8
	−10.58	*−0.24*	*10.34*		*−8.57*	*1.04*	*7.53*
Pyrazine **7**	1.00	−0.69	1.7	Phenanthridine **26**	0.69	−0.53	1.2
	−10.25	*−0.33*	*9.92*		*−8.98*	*−0.60*	*8.38*
1,2,3-Triazine **8**	1.23	−0.78	1.8	Phenazine **27**	0.59	−0.21	0.8
	−11.31	*−0.79*	*10.52*		*−8.98*	*−1.27*	*7.71*
1,2,4-Triazine **9**	1.10	−0.67	1.8	9a-Azaphenalene **35**	0.00	−0.54	0.5
	−10.71	*−0.78*	*9.93*		*−6.94*	*−0.58*	*6.36*
1,3,5-Triazine **10**	1.28	−0.78	2.1	Perimidine **96**	0.33	−0.67	1.0
	−11.32	*−0.55*	*10.77*		*−7.77*	*−0.27*	*7.50*

[a]In β-units (β is a negative value).
[b]Values (eV) in italics.

bands (λ_{max} = 243–264 nm) (Section 2.2.3.6, **Table 19**). An exception is 1,3,5-triazine (λ_{max} = 222 nm) for which the HMO and AM1 frontier orbital gaps are notably larger.

Monocyclic azines are very weak π-donors and behave mainly as n-donors on interaction with electrophiles. However, π-donor character is significantly increased in their benzo derivatives which have higher energy HOMOs (**Table 2**). For example, acridine **25** forms a highly colored 1:1 molecular complex with 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil). Perimidine **96** is one of the strongest heterocyclic π-donors and gives deeply colored molecular complexes with a variety of organic electron acceptors. This is consistent with its electron-rich structure and its separate classification.

For pyridine, monocyclic diazines and benzodiazines a good linear relationship has been demonstrated between experimental pK_a values and *ab initio* calculated HOMO energies, suggesting that the basicities of azines may be directly interpreted in terms of HOMO energies <1995JMT(339)255>.

2.2.2.2 Calculation of Molecular Properties

Computational methods are now widely used to investigate structures, reactions and equilibria of six-membered heterocycles, and this is especially useful for investigating reactive, unstable or currently unknown species. These applications are illustrated in this section by selected examples. Details of computational methods are summarized in Section 2.1.4.

2.2.2.2.1 Geometries

Structural parameters of all 12 azabenzenes **4–15** have been calculated at the MP2(fc)/6-31G* and B3LYP/6-31G* levels <2004CJC50> and results for the higher azines are shown in **Figure 13** <CHEC-III(9.13.2.1)718>. Both B3LYP and MP2 calculations show that hexazine (D_{6h}) is energetically a 'hilltop', whereas hexazine (D_2) is an energy minimum, in agreement with earlier MP2-based results (MP2(fc)/6-31G*//MP2(fc)/6-31G*) <2004CJC50>. However, it should be noted that the latter study demonstrated that the choice of level of theory can have a substantial impact on the results. For hexazine **15** the calculated barrier to fragmentation is so low that this system may not be able to exist.

Calculations have provided the only data available for the structures of fully-conjugated 1,4-oxazines, as these compounds have never been synthesized <CHEC-III(8.06.2)463>. 4*H*-1,4-Oxazine has been calculated to have the bond lengths shown in structure **101** and an aromatic stabilization energy of −2.1 kJ mol^{-1}<1971JST(8)236>. *Ab initio* calculations suggest that its equilibrium conformation has the torsion angles shown in structure **102** <1998JST(446)11>.

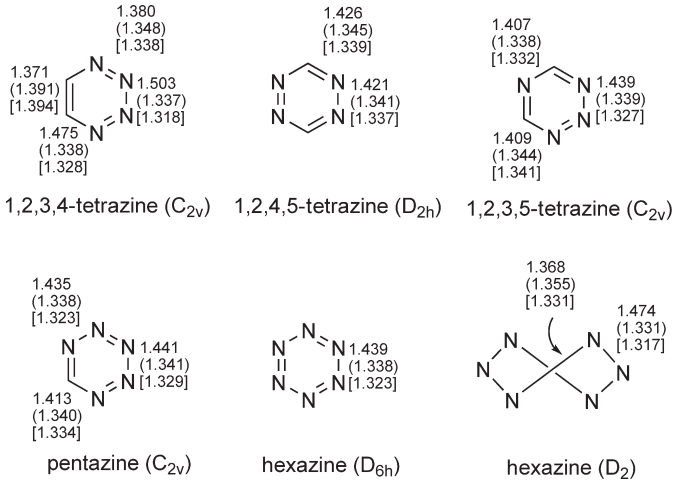
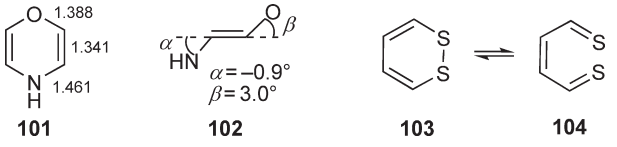


Figure 13 Structural parameters for tetrazines, pentazine, and hexazine <2004CJC50>. Wiberg bond orders from HF/3-21G//MP2(fc)/6-31G* calculations. Bond lengths from MP2(fc)/6-31G* (data in parentheses) and B3LYP/6-31G* (data in square brackets).



Ab initio calculations on 1,2-dithiin **103** (HF/6-31G*) reveal that the compound is essentially nonaromatic with a resonance energy close to zero: antiaromaticity is markedly reduced by assuming a nonplanar structure <1999JST(461/2)553, 2000JMM177>. The nonplanar global minimum structure possesses C_2 symmetry<1998CPL(289)391,1991JST(230)287>, and is thermodynamically less stable by 1.2 kcal mol^{-1} than the open-chain dithialdehyde isomer **104**. The most stable cyclic structure is a half-chair conformer, interconverting via the planar structure to the alternative half-chair conformer. The calculated barrier to interconversion of 8.7 kcal mol^{-1} (MP2/6-31G(2df,g) is relatively low and in good agreement with the only available experimental value of ca. 8 kcal mol^{-1} for 3,6-bis(acetoxymethyl)-1,2-dithiin <2000JMM177, CHEC-III(8.10.2)680>.

2.2.2.2.2 Magnetic properties

Schleyer and coworkers <1996JA6317> introduced the concept of nucleus-independent chemical shift (NICS) values as a theoretical tool to evaluate aromaticity, and NICS values have been widely used for evaluating magnetic criteria for aromaticity. The NICS is an absolute value, and is the negative of the absolute magnetic shielding of a system. It is computed (for example) at the center of a ring, NICS(0), or 0.5 Å above the ring, NICS(0.5). A negative NICS value indicates aromaticity and a positive value represents antiaromaticity. Values around zero signify nonaromatic systems.

Table 3 shows NICS(0) and NICS(0.5) values for selected azabenzenes. The actual values vary with the computational method used. The NICS(0) values decrease as the number of nitrogen atoms increase and this is attributed to an effect of the σ electrons and lone pairs. Calculation of shielding above the ring, NICS(0.5) or NICS(1), is now regarded as a better measure of aromaticity. From **Table 3** it can be seen that all the NICS(0.5) values of azabenzenes are large and negative. It should be noted that D_{6h} hexazine does not correspond to an energy minimum although aromatic by magnetic criteria (NICS(0.5)). A twisted form, D_2 hexazine (**Figure 1**), has a larger NICS(0.5) value and although aromatic by magnetic criteria is probably too unstable to isolate <2004CJC50>.

Table 3 NICS values (ppm) for selected heterocycles

Molecule	*NICS(0)*	*NICS(0.5)*	*Method*	*Reference*
Azabenzenes				
Benzene **1**	−8.9	−10.7	A[a]	1997JA12669
	−11.5	−13.3	B[b]	2004CJC50
Pyridine **4**	−9.6	−12.1	B	2004CJC50
	−8.2	–	C[c]	2004JMT(674)125
Pyridazine **5**	−7.7	−11.2	B	2004CJC50
1,2,3-Triazine **8**	−6.1	−10.5	B	2004CJC50
1,3,5-Triazine **10**	−4.8	−8.6	A	1997JA12669
1,2,3,4-Tetrazine **11**	−4.1	−9.6	B	2004CJC50
	−2.7	–	D[d]	2004JPO303
1,2,4,5-Tetrazine **13**	−1.8	–	D	2004JPO303
Pentazine **14**	−1.7	−8.4	C	2004JMT(674)125
	−0.6	–	D	2004JPO303
Hexazine (D_{6h}) **15**	+0.2	−7.0	A	1997JA12669
	+0.3	−7.6	B	
Hexazine (D_2)	−6.8	−12.6	B	2004CJC50
Pnictogen heterobenzenes				
Pyridine **4**	−8.2	–	C	2004JMT(674)125
Phosphinine **105**	−8.4	–	C	2004JMT(674)125
Arsinine **106**	-7.9_5	–	C	2004JMT(674)125
Stibinine **107**	−7.9	–	C	2004JMT(674)125
Bismuthinine **108**	−8.2	–	C	2004JMT(674)125

[a]PW91/IGLO-III TZ2P//B3LYP/6-311+G**.
[b]GIAO HF/6-31G*//MP2/6-31G*.
[c]HF/6-31+G*//BPW91/6-311G**.
[d]GIAO B3LYP/6-311G**//B3LYP/6-311++G**.

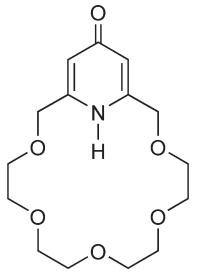
105

106: X = As
107: X = Sb
108: X = Bi

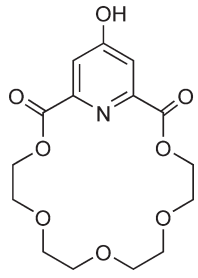
The NICS values for pyridine have been compared with other pnictogen derivatives (P, As, Sb, Bi). Reported NICS values for phosphinine **105** vary from −6.4 to −11.4, but the values are consistently negative and large, and consistent with aromatic character <CHEC-III(7.12.2)1005>. **Table 3** compares NICS values for five pnicogen heterobenzenes and on magnetic criteria they are all aromatic. It should be noted, however, that on thermodynamic criteria the aromaticity decreases with stibinine **107** being very unstable and bismuthine **108** unknown <2004JMT (674)125>. NICS values are not, therefore, an indication of the thermodynamic stability associated with aromatic compounds.

2.2.2.2.3 Tautomerism

Quantum mechanical calculations are increasingly being used to investigate tautomerism. For example, DFT calculations have also been used to calculate the position of tautomeric equilibria of heteroatom substituted pyridines in both the gas phase and under solvation conditions <CHEC-III(7.01.2.1)3>. While gas-phase calculations predominate, computational studies incorporating models of solvation are being evaluated using known equilibria as model systems <1999J(P2)801>. For example, the importance of solvent molecules in the tautomerism of hydroxyl-substituted pyridines has been investigated <1996JPC16141, 2001JST(542)1> and the influence of water molecules and ring cavities on the dominant tautomers of the crown ethers **109** and **110** have been studied <2001JHC1387>.



109



110

2.2.3 Structural Methods

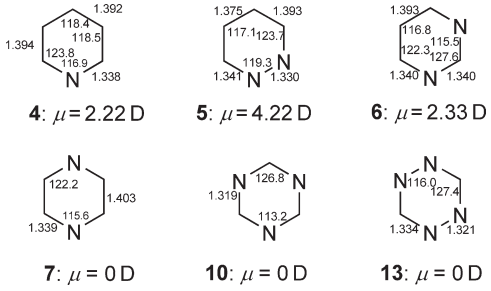
2.2.3.1 X-Ray Diffraction

An early compilation of X-ray data for heterocyclic compounds <1972PMH(5)1> contains many examples of six-membered rings. More recent data are contained in the Cambridge Structural Database (CSD) <www.ccdc.cam.ac.uk>. Determination of structures by X-ray crystallography is now routine and details of structures of specific heterocycles are best found using the CSD or by consulting the appropriate chapters in the three editions of *Comprehensive Heterocyclic Chemistry*.

In **Figure 14** the bond lengths and internal bond angles are given for the fully-conjugated azines **4–7**, **10** and **13**, based on X-ray diffraction, gas-phase electron diffraction, or microwave spectroscopy.

The C–N bond length is usually ~4% shorter than a C–C bond. To accommodate this with minimal disturbance of the other bond angles a small displacement of the N atoms toward the center of the ring, with consequent opening of the CNC bond angle from 120°, is required. This is more or less what is observed in pyridinium salts (where NH^+ replaces one CH in benzene). However, the internal angle at the aza nitrogen in the free bases (where N: replaces CH) is generally found to be slightly less than 120° and the nitrogen nuclei are slightly further from the center of gravity than the carbons. These are comparatively minor deviations from a completely regular hexagon. Available data on pyrylium or thiinium salts is limited to highly substituted ions. In oxygen rings the trend outlined above for pyridines is not observed; in the studied examples the COC angle (about 124°) is slightly larger than that for a regular hexagon, and the interior angles in the ring at the carbons next to the oxygen are smaller (ca. 118°). Thiinium salts are characterized by long C–S bonds (ca. 1.72 Å) and a small CSC angle of ca. 104°.

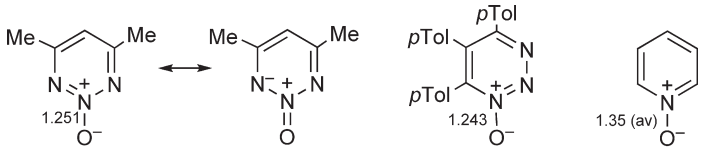
In addition to confirmation of structure, X-ray studies can be particularly useful for gaining insight into bonding and reactivity. A study of 4,6-dimethyl-1,2,3-triazine 2-oxide **111** has shown that the N–O bond (1.251 Å) is significantly shorter than that in pyridine 1-oxide **113** (1.35 Å av.). This shortening is consistent with the donating effect of the oxide function and, compared to pyridine 1-oxide **113**, a greater contribution of the resonance hybrid **111b** due to the electronegative nitrogen atoms in the ring. A similar effect is observed in the 1,2,3-triazine 1-oxide **112** (N-O 1.243 Å) <CHEC-III(9.01.3.1)16>.



4: $\mu = 2.22$ D **5**: $\mu = 4.22$ D **6**: $\mu = 2.33$ D

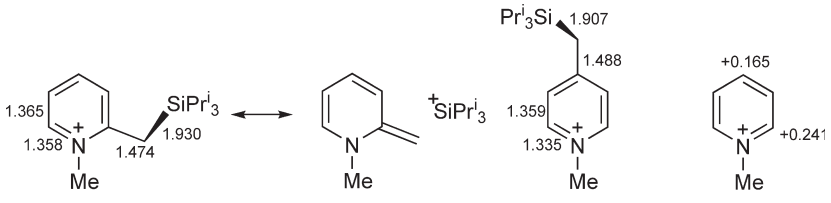
7: $\mu = 0$ D **10**: $\mu = 0$ D **13**: $\mu = 0$ D

Figure 14 Molecular dimensions and dipole moments (μ) of some aromatic azines.



111a **111b** **112** **113**

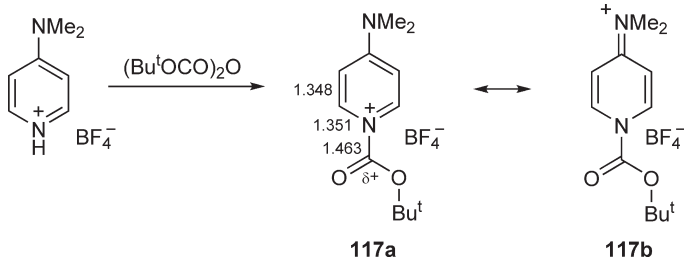
A study of tri-isopropylsilylmethylpyridinium salts shows that σ_{C-Si}–π hyperconjugation (**114a** ↔ **114b**) is greater at the 2-position **114** than at the 4-position **115** based on the relative lengths of the C–C and C–Si bonds. This is consistent with Hückel calculations on the pyridinium cation **116** and pyridine **93**, and with ^{29}Si and ^{13}C NMR chemical shifts, which show that position 2 is more electron deficient than position 4 <CHEC-III(7.01.2.2)4>.



114a **114b** **115** **116**

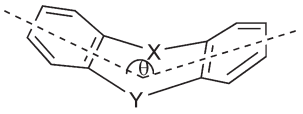
The catalytic effect of pyridines in acylation reactions occurs via *N*-acylpyridinium salt formation (see Section 3.2.1.3.7). Using DMAP, the tetrafluoroborate **117** is involved in the transfer of Boc groups (Boc = *t*-butoxycarbonyl) (**Scheme 1**). X-ray crystallography shows that the carbonyl, pyridinium, and dimethylamino groups are almost coplanar. The N–CO bond is longer by 0.056 Å than those in similar uncharged *O*-*t*-butylurethanes, probably due to adjacent partial positive charges on N and C. The positioning of the BF_4^- anion over the carbonyl carbon atom in the salt **117** indicates the probable reaction trajectory for nucleophilic attack and, together with the weaker N–CO bond, electron deficiency of this position facilitates acyl transfer <1991AGE1656>.

Six-membered rings with two O, S, or NR groups and two C=C double bonds are not aromatic and usually distort from planarity in order to minimize cyclic conjugation. The dibenzo derivatives **118** (X or Y = O, S, NR) are the most stable and well-known examples of this class. Thianthrene **118** (X = Y = S) and its various sulfoxides and sulfones have a relatively small dihedral angle between the planes of the benzene rings (θ = 130–140° in thianthrenes). Phenoxathiin **118** (X = S, Y = O) and phenothiazine **118** (X = S, Y = NH) are also nonplanar (θ = 146° and ca. 158°, respectively) <CHEC-III(8.12.4.3)864>. Since phenothiazines are of pharmaceutical importance, a large number of structures have been determined and these have been tabulated <CHEC-III(8.09.3.1)616>. Dibenzodioxin (oxanthrene) **118** (X = Y = O) is planar (θ = 180°) in the solid state <CHEC-III(8.12.3.1)860>, partly due to the lone pairs of the electronegative oxygen atoms having little participation in cyclic conjugation. Phenoxazine **118** (X = O, Y = NH) probably has coplanar benzene rings with a pyramidal nitrogen atom according to an early study <1940MI20100>.



117a **117b**

Scheme 1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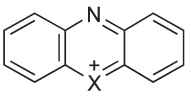
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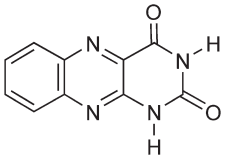
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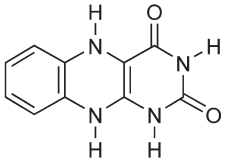
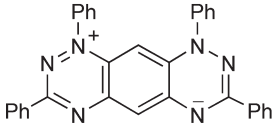
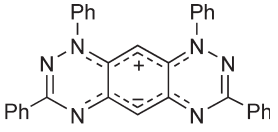

121

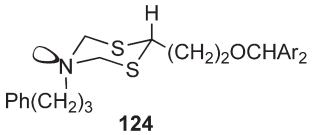
When the central ring is rendered aromatic by oxidation, e.g., the phenoxazinium and phenothiazinium ions **119** (X = O and S), planarity is found as expected. The same effect is seen with alloxazine **120**, which is planar, and dihydroalloxazine **121**, which is not.

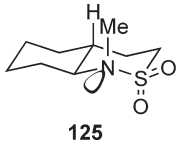
The tetraphenylhexaazaanthracene **122** has an interesting tricyclic structure that can only be represented by dipolar resonance hybrids, e.g., **122**. Although it has a periphery of 16π electrons and, like the derivatives **118**, might be expected to be antiaromatic, it is a stable crystalline solid, which has been shown by X-ray crystallography to have a planar structure. It can be regarded as a cross-conjugated mesomeric betaine (Section 2.2.1.2.2, **Scheme 5**) in which the central C–C bonds have lengthened (1.44 Å (av.)) giving a charge-separated structure **123** <1998JA2989>. Like nonplanarity (e.g., **118**), this polarization appears to reduce unfavorable cyclic conjugation.

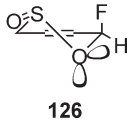

122


123

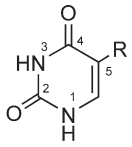
Many X-ray studies have also been carried out on saturated and partially-saturated rings. Studies of ring conformations have identified a number of examples of the anomeric effect, which was originally recognized in tetrahydropyrans **76** in which electron-withdrawing substituents (e.g., OMe, Br) at position 2 (the anomeric position) favor the axial position. The crystal structure of 1,3,5-dithiazine **124** (Ar = *p*-FC_6H_4) reveals a chair conformation for the heterocyclic ring with the *N*-(3-phenylpropyl) group adopting an axial orientation. The preference for axial substituents at nitrogen has been explained in terms of $n_N \rightarrow \sigma^*_{C-S}$ hyperconjugation <2003JHC827, CHEC-III(9.10.3.1) 526>. The crystal structure of the cyclic sulfonamide **125** shows that the N–Me group assumes an axial position in the solid state, and the $n_N \rightarrow \sigma^*_{S-C}$ hyperconjugation effect has been estimated to be >2.0 kcal mol^{-1} <1998CJC164, CHEC-III (8.07.3.1)518>.


124

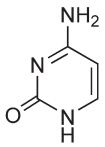

125


126

The *trans*-6-fluoro-3,6-dihydro-1,2-oxathiin 2-oxide **126** prefers a conformation in which the ring oxygen lies almost in the plane of the four carbon centers and the S=O bond resides in a pseudoequatorial orientation. The fluorine substituent adopts a stable pseudoaxial orientation. Quantum–chemical calculations suggest a stabilizing anomeric effect which was interpreted in terms of an $n_O \rightarrow \sigma^*_{C-F}$ hyperconjugative interaction <2002CEJ1336, CHEC-III(8.10.3)688>.



127: (R = H) uracil
128: (R = F) 5-fluorouracil
129: (R = Me) thymine



130: cytosine

X-ray structure analysis has proved to be useful in determining the binding modes of biologically important pyrimidine derivatives to their protein receptors. The crystal structures of uracil **127** and 5-fluorouracil **128** bound to uracil phosphoribosyltransferase (UPRTase) have been determined. UPRTase recognizes uracil through polypeptide backbone hydrogen bonding to O(2), O(4), and N(3). The structural analysis of the requirements of this uracil binding site shows why cytosine **130** and pyrimidines with substituents at position 5 larger than fluorine, e.g., thymine **129**, cannot bind to the enzyme <1998MI3219, CHEC-III(8.02.3.1)121>.

2.2.3.2 Microwave Spectroscopy

Microwave spectroscopy allows the determination of precise bond lengths and angles, conformations, and dipole moments. **Table 4** summarizes some molecular geometries deduced from microwave spectra. A disadvantage is that measurements have to be made in the gas phase and studies are limited to relatively small volatile molecules.

Dipole moments of pyridine derivatives derived from microwave spectra have been tabulated <CHEC-I(2.04.2.1)104>.

A complete analysis of the microwave spectrum of 3,6-dihydro-2*H*-thiin **82** supports a half-chair equilibrium conformation <1994JCF2849>. The angle of twist (32.5°) is slightly larger than that of 3,6-dihydro-2*H*-pyran **76** (31.5°) <1974JCP3987>. The microwave spectrum of 3,6-dihydro-1,2-dioxin shows half-chair conformers which readily interconvert at ambient temperature ($\Delta G^{\#} = 9.82$ kcal mol^{-1}) by ring puckering <1994JST(323)79>.

2.2.3.3 ^{1}H NMR Spectra

2.2.3.3.1 Chemical shifts

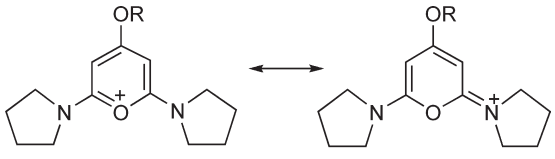
The protons on the benzene ring experience a deshielding effect due to the aromatic ring current, which brings the chemical shift of the benzene protons to $\delta = 7.24$ ppm. The same ring current persists in the polyazabenzenes as in benzene itself. In addition the nitrogen atoms exert a strong deshielding influence on the α-hydrogen atoms, and a similar but smaller effect on the γ-hydrogens. The protons at the β-positions in pyridine are in fact shifted slightly upfield of the benzene resonance. Further aza substitution produces similar effects, but strict additivity is not observed. For instance, two adjacent nitrogen atoms, as in pyridazine, exert a much larger deshielding effect on the α-protons than the sum of the α- and β-effects of a single nitrogen atom. Conversion of pyridine into the pyridinium cation causes a downfield shift of all the hydrogens, especially at the β- and γ-positions.

Table 4 Geometry of six-membered rings from microwave spectra

Shape	*Molecules*
Planar	4-Pyrone,[a] 2-pyrone, 4-pyranthione, 4-thiopyrone
Half-chair	3,6-Dihydro-2*H*-pyran, 3,6-dihydro-2*H*-thiin,[b] 3,6-dihydro-1,2-dioxin[c]
Chair	Piperidine,[d] morpholine, 1-methylmorpholine, 1,3,5-trioxane

Abstracted from <1974PMH(6)53>.
[a]Conjugation shown by bond lengths: short C–O and C–C, long C=C and C=O.
[b]<1994JCF2849>.
[c]<1994JST(323)79>.
[d]Both *ax*-NH and *eq*-NH forms found; the latter predominates.

Strongly electron-releasing groups at the 2-, 4-, and 6-positions of pyrylium salts exert a profound effect on the chemical shift of protons H(3) and H(5). In the cations **131a** these protons are moved upfield by 2–3 ppm and it is proposed that they are better described as oxygen-bridged pentamethine cyanines (**131b**) <1988MRC707>.



131a **131b**

Tables 5 and **6** summarize the chemical shifts of the protons in various aza heterocycles. ^{1}H NMR data for the corresponding heteroaromatic cations are given in **Table 7**.

The spectra of protonated polyaza heterocycles are frequently complicated by the occurrence of covalent hydration. This is more common with polycyclic systems, e.g., pteridine.

Table 5 ^{1}H NMR chemical shifts of the simple monocyclic azines (cf. benzene, $\delta = 7.24$) <B-73NMR>

	δ (^{1}H) (ppm, TMS) (Position of N atoms indicated)							
Position	*Pyridine*	*Pyridazine*	*Pyrimidine*	*Pyrazine*	*1,2,3-Triazine*	*1,2,4-Triazine*	*1,3,5-Triazine*	*1,2,4,5-Tetrazine*
1	N	N	N	N	N	N	N	N
2	8.52	N	9.26[a]	8.6	N	N	9.18	N
3	7.16	9.17	N	8.6	N	9.63	N	(10.48)[b]
4	7.55	7.52	8.78	N	9.06	N	9.18	N
5	7.16	7.52	7.36	8.6	7.45	8.53	N	N
6	8.52	9.17	8.78	8.6	9.06	9.24	9.18	(10.48)

[a]Measured in $CDCl_3$.
[b]Calculated value; shifts for some monosubstituted tetrazine derivatives lie in the range 10.26–10.45 ppm in CD_3OD and 10.11–10.25 ppm in $CDCl_3$ <1981JOC5102>.

Table 6 ^{1}H NMR chemical shifts of protons on the heterocyclic rings of simple benzazines (cf. naphthalene, column 2)

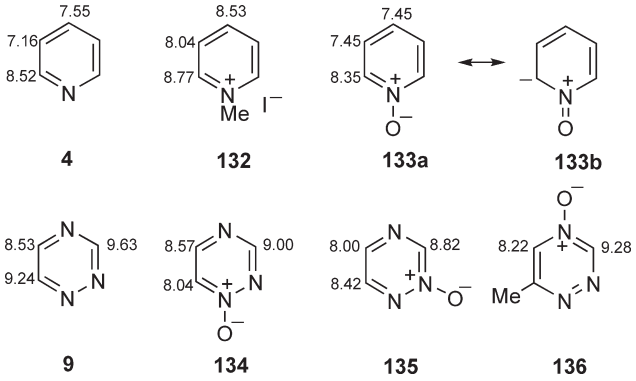
Position	*δ (^{1}H) (ppm, TMS) (Position of N atoms indicated)*							
1	7.72	N	9.15	N	N	N	9.44	N
2	7.33	8.81	N	N	9.23	8.74	N	N
3	7.33	7.27	8.45	9.15	N	8.74	N	N
4	7.72	8.00	7.50	7.75	9.29	N	9.44	9.85

In contrast to pyridinium cations, e.g., **132**, pyridine 1-oxide **133** shows a small upfield shift of the α- and γ-protons due to back donation of the *N*-oxide function (**133a** ↔ **133b**). At the β-position, where the influence of back donation is minimal, there is a downfield shift ($\Delta\delta = 0.29$ ppm) relative to pyridine **4**. Increasing the number of nitrogen atoms in the ring increases the effect of back donation. The ^{1}H NMR spectra of 1,2,4-triazine *N*-oxides exhibit much larger upfield shifts for the α-protons. The H(6) signals in the ^{1}H NMR spectra of 1,2,4-triazine 1-oxides (e.g., **134**) are observed at significantly higher fields ($\Delta\delta = 1.2$–1.4 ppm) relative to those for the corresponding 1,2,4-triazines (e.g., **9**). The same situation arises in the 1,2,4-triazine 2- and 4-oxides **135** and **136**, but because of the positions of the nitrogen atoms the electronic effects of back donation on the chemical shifts of the α-protons are much lower ($\Delta\delta = 0.2$–0.8 ppm) <2002AHC (82)261, CHEC-III(9.02.3.3)100>.

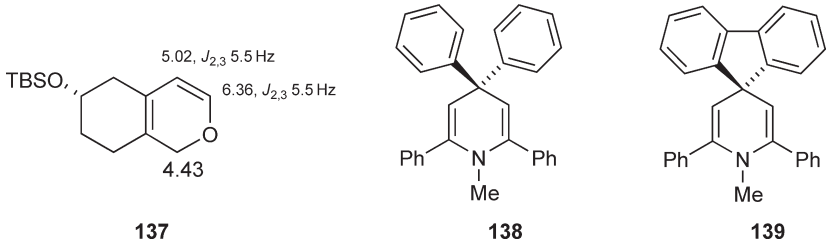
Table 7 ^{1}H NMR spectra data for six-membered heteroaromatic cations

		δ (^{1}H) (ppm)			J (Hz)			
Compound	*Anion/solvent*	*2*	*3*	*4*	*2:3*	*2:4*	*2:6*	*3:4*
Pyridinium	D_2SO_4/D_2O	8.78	8.09	8.62	5.8	1.7	0.7	7.5
1-Methylpyridinium	I^-/D_2O	8.77	8.04	8.53	–	–	–	–
Pyrylium	ClO_4^-/MeCN	9.59	8.40	9.20	3.5	2.4	1.5	8.0
2,6-Dimethylpyrylium	$SbCl_6^-/SO_2$	3.04[a]	7.98	8.86	–	–	–	–
2,4,6-Trimethylpyrylium	ClO_4^-/SO_2	2.90[a]	7.77	2.74[a]	–	–	–	–
Thiinium	ClO_4^-/MeCN	10.13	8.97	9.00	7.7	1.7	1.6	6.1
5-methyl-1,2-thiazinylium[b]	$ClO_4^-/CDCl_3$	–	10.12	8.62[c]	–	–	–	5.0
4,5-Diphenyl-1,2-thiazinylium[d]	$ClO_4^-/CDCl_3$	–	10.25	(10.97)[e]	–	–	–	–

From <B-1973NMR> which contains original references.
[a]Methyl shifts.
[b]<2001TL4183>.
[c]H(6) 11.04 ppm, $J_{3:6}$ = 0.0 Hz.
[d]<1999TL1505>.
[e]H(6), $J_{3:6}$ = 1.5 Hz.



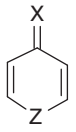
The extensive delocalization and aromatic character of pyridones, pyrones, etc., are shown by their chemical shift and coupling constant values (**Table 8**). By contrast, pyrans and thiins show chemical shifts characteristic of alkenic systems (**Table 9**). *2H*-Pyran **67** is unstable and has not been isolated, but ^{1}H NMR data for the simple bicyclic derivative **137** have been reported <1999S1209>. For these diene derivatives and for rings containing only a single endocyclic bond (**Table 10**), ^{1}H NMR spectroscopy offers a most useful tool for structure determination. However, structural assignment is not always trivial. Numerous NMR studies have been reported on derivatives of 1,4-dihydropyridine **38**, some of which are used for the treatment of hypertension (e.g., nifedipine **42**) <2000MRC680, 2001MRC406, 2005JBS112>. These studies show that many compounds whose structures had previously been assigned by comparison with similar 1,4-dihydropyridines had often been incorrectly characterized. Small structural changes can lead to compounds having widely different physical properties and spectroscopic data. An example is the spectroscopic study of 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridine **138** and 4,4-(biphenyl-2,2'-diyl)-2,6-diphenyl-1-methyl-1,4-dihydropyridine **139** <2002PJC235> which shows that two isomers of compound **139** exist in both solution and the solid state but these features are not exhibited by compound **138.** This is attributed to the extra C–C bond between the two phenyl rings which gives the dihydropyridine derivative **139** enhanced rigidity <CHEC-III(7.04.1.2)173>.



137 **138** **139**

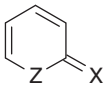
Table 8 ^{1}H NMR spectral data for six-membered heteroaromatic rings with exocyclic carbonyl or thione groups

(A) γ-Compounds



		Neutral species (D_2O, CCl_4 or $CDCl_3$)				*Cation (TFA or D_2SO_4)*			
Compound		*δ(^{1}H) (ppm)*		*J (Hz)*		*δ(^{1}H) (ppm)*		*J (Hz)*	
Z	*X*	*2*	*3*	*2:3*	*2:5*	*2*	*3*	*2.3*	*2:5*
NH	O	7.98	6.63	7.532	0.260	8.5	7.4	7.6	–
NMe	O	7.81	6.49	8.4	–	8.4	7.4	7.6	–
NH	S	8.37	7.87	7.0	–	–	–	–	–
O	O	7.92	6.39	5.9	0.4	8.49	7.06	–	–
O	S	7.51	7.15	5.7	0.5	8.87	8.14	~5.7	~0.5
S	O	7.89	7.09	10.4	0.5	9.40	8.19	~10.1	~0.5
S	S	7.90	7.58	10.1	0.5	–	–	–	–

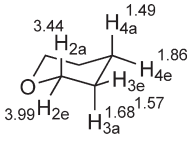
(B) α-Compounds



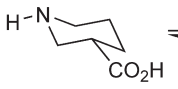
Compound			*δ (^{1}H) (ppm)*			
Z	*X*	*Solvent*	*3*	*4*	*5*	*6*
NH	O	$CDCl_3$	6.60	7.3	6.20	7.23
NH	O	10-20% D_2SO_4	7.3	8.2	7.3	8.2
O	O	$CDCl_3$	6.38	7.56	6.43	7.77
			J (Hz)			
			3:4	*4:5*	*4:6*	*5:6*
NH	O	DMSO	10	7	2	7
O	O	$CDCl_3$	9.4	6.3	2.4	5.0

Data abstracted from <B-73NMR> and <1971PMH(4)121> which contain original references.

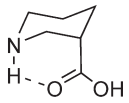
A complete assignment of the ^{1}H NMR data for tetrahydropyran (THP) **140** has been reported <1998J(P2)1751>. At room temperature the 400 MHz spectrum of THP in 1:1 $CDCl_3$:$CFCl_3$ consists of three multiplets at δ 3.63, 1.64, and 1.57 in a ratio of 2:1:2 (H(2), H(4), and H(3)). At −85 °C, all of the resonances are resolved and the assignment of axial and equatorial protons is possible. This data, in conjunction with the previously reported study of the coupling constants of tetrahydropyran and comparison with cyclohexane data (**Table 11**) <1976JOC1380>, provide a complete picture of the NMR of tetrahydropyran.



140



141

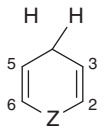


142

Piperidines and related systems have a number of (potentially) readily accessible conformations. In nipecotic acid **141** a hydrogen bond stabilizes the axial conformation **142**. Both conformations have been detected by ^{1}H NMR spectroscopy at low temperature and their spectra fully documented together with the effect of solvent and pH <2000J(P2)2382>.

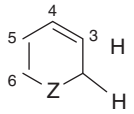
Table 9 ^{1}H NMR data for six-membered heterocyclic rings with two endocyclic double bonds

(A) 4*H*-Systems



		δ (^{1}H) (ppm)			J (Hz)			
Z	*Solvent*	*2*	*3*	*4*	*2:3*	*2:4*	*2:6*	*3:4*
NH	C_6D_6	5.73	4.42	3.15	–	–	–	–
NPh	CCl_4	6.27	4.53	2.92	9.0	1.6	–	3.9
O	–	6.12	4.63	2.66	7.0	1.7	1.5	3.4
S	–	5.97	5.54	2.84	10.0	1.1	2.9	3.9

(B) 2*H*-Systems

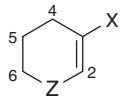


		δ (^{1}H) (ppm)				
Z	*Solvent*	*2*	*3*	*4*	*5*	*6*
NPh	CCl_4	4.26	5.21	5.88	4.94	6.41
S[a]	CCl_4	3.16	4.99	–	6.08	6.08

Data abstracted from <B-73NMR> and <1971PMH(4)121> which contain original references.
[a]Data refer to the 4-methyl derivative.

Table 10 ^{1}H NMR data for six-membered heterocyclic rings with one endocyclic double bond

(A) Δ^2-Systems



Compound			δ (^{1}H) (ppm)				
Z	*X*	*Solvent*	*2*	*3*	*4*	*5*	*6*
NH	COMe	$CDCl_3$	7.12	7.48	2.28	1.77	3.23
O	H	CCl_4	6.22	4.54	1.93	1.93	–

(B) Δ^3-Systems

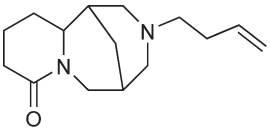
		δ (^{1}H) (ppm)				
Z	*Solvent*	*2*	*3*	*4*	*5*	*6*
NH	$CDCl_3$	3.33	5.75	5.75	2.07	2.95
NMe	CCl_4	2.76	5.58	5.58	–	–
O	–	4.03	5.76	5.76	2.10	–

Data abstracted from <B-73NMR> and <1971PMH(4)121> which contain original references.

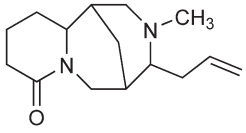
Table 11 ^{1}H NMR data for deuterated analogues of cyclohexane and tetrahydropyran

Compound	$J_{2a,3e}$	$J_{2e,3e}$	$J_{2a,3a}$	$J_{2e,3a}$	$\Delta\nu_{2e,2a}$	$\Delta\nu_{3e,3a}$	*References*
Cyclohexane-d_8	3.65	2.96	13.12	3.65	0.479	0.479	1968JA6543
Tetrahydropyran-d_4 or -d_6	1.9	1.5	12.4	4.5	0.527	0.074	1976JOC1380

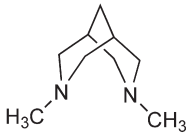
NMR analysis has also been applied to systems containing multiple piperidine units, as exemplified by the quinolizidine–piperidine alkaloids **143** and **144** <1996JST(385)23, 1999JST(474)215, 1999T14501>. Extensive correlation NMR spectroscopy, along with use of coupling constants, allowed the conformations to be assigned through comparison with 3-methyl-3,7-diazabicyclo[3.3.1]nonane, which exists predominantly in the chair–chair conformation **145** <1998JST(446)69>. The alkaloid **143** exists exclusively in the equivalent chair–chair conformation but its isomer **144** has ~30% of the *N*-methyl-2-allylpiperidine ring in the boat conformation <CHECIII(7.01.2.4)10>.



143



144



145

Solvent- and lanthanide-induced shifts are of great value in structure assignments in heterocyclic compounds, because cyclic nitrogen atoms, carbonyl groups, etc., undergo specific hydrogen bonding or coordination resulting in differential shifts of groups in different positions.

2.2.3.3.2 Coupling constants

The normal pattern of coupling constants for aromatic six-membered rings is found in the heterocyclic aza systems, except that the *ortho* coupling to a proton α to a heterocyclic nitrogen is reduced from 7–8 to 4.5–6 Hz. The $J_{2,3}$ of pyrylium salts is still lower (ca. 3.5 Hz), but in pyridinium salts and pyridine *N*-oxide it is of intermediate value (ca. 6.5 Hz) (see **Table 7**).

The 'direct' coupling constants (D_{ij}) of pyridine, obtained from a spectrum of the molecule in a nematic liquid crystal solvent <B-1973NMR>, provide information about the geometry.

2.2.3.4 ^{13}C NMR Spectra

2.2.3.4.1 Aromatic systems: Chemical shifts

Chemical shift data for a number of monocyclic, unsubstituted six-membered heteroaromatic compounds are given in **Table 12**.

Ring carbon atoms α to a heteroatom are most heavily deshielded, those γ to a heteroatom are also deshielded relative to benzene, while those in a β-position are more benzene-like. Introduction of a second nitrogen atom α or γ to a ring carbon atom results in further deshielding by ~10 and 3 ppm, respectively, whereas the effect on a β-carbon atom is a shielding of ~3 ppm. Substituent effects follow the same general trend as in substituted benzenes. The chemical shifts of ring carbon atoms which either carry the substituent or are *para* to it differ in a predictable way relative to the unsubstituted heterocycle, whereas the shifts of ring carbon atoms *meta* to the substituent are little affected. These effects are conveniently exemplified in the pyridine series; typical data for a variety of monosubstituted pyridines are listed in **Table 13**. Fusion of an aromatic or heteroaromatic ring to an azine changes the electronic distribution and hence the chemical shifts of remaining ring

Table 12 ^{13}C NMR chemical shifts of the simple monocyclic azines (cf. benzene, $\delta = 128.5$)

	δ(13C) (ppm, TMS) (position of N atoms indicated)							
Position	*Pyridine*	*Pyridazine*	*Pyrimidine*	*Pyrazine*	*1,2,3-Triazine*	*1,2,4-Triazine*	*1,3,5-Triazine*	*1,2,4,5-Tetrazine*
1	N	N	N	N	N	N	N	N
2	149.5	N	158.4	145.9	N	N	166.1	N
3	125.6	153.0	N	145.9	N	158.1	N	161.9
4	138.7	130.3	156.9	N	149.7	N	166.1	N
5	125.6	130.3	121.9	145.9	117.9	149.6	N	N
6	149.5	153.0	156.9	145.9	149.7	150.8	166.1	161.9

Table 13 ^{13}C NMR chemical shifts of monosubstituted pyridines

Substituent position	*Substituent*	*δ (^{13}C) (ppm)*				
		C(2)	*C(3)*	*C(4)*	*C(5)*	*C(6)*
	H	150.6	124.5	136.4	124.5	150.6
2	Br	*142.9*	129.0	139.5	123.7	151.0
2	CHO	*153.1*	121.6	137.5	128.3	150.3
2	CN	*133.8*	129.2	137.9	127.8	151.5
2	COMe	*153.9*	121.4	136.9	127.5	149.3
2	Me	*158.7*	123.5	136.1	120.8	149.5
2	NH_2[a]	*160.9*	109.5	138.5	113.6	148.7
2	OH[a,b]	*162.3*	119.8	140.8	104.8	135.2
2	OMe[a]	*163.1*	110.5	138.7	116.7	146.6
3	Br	151.7	*121.6*	139.1	125.4	148.7
3	CHO	152.0	*132.1*	136.2	124.8	155.0
3	CN	153.2	*110.5*	140.6	124.8	153.8
3	COMe	150.1	*123.9*	132.5	121.5	153.8
3	Me	150.9	*133.1*	136.4	123.4	147.3
3	NH_2[a]	137.7	*145.7*	122.0	125.1	138.8
3	OH[a]	137.8	*153.5*	121.4	123.8	140.0
3	OMe[a]	137.3	*155.2*	120.0	123.8	141.4
4	Br	152.6	127.6	*133.2*	127.6	152.6
4	CHO	151.3	123.6	*141.7*	123.6	151.3
4	CN	151.7	126.4	*120.5*	126.4	151.7
4	COMe	151.2	121.6	*143.0*	121.6	151.2
4	Me	*150.1*	125.0	*147.0*	125.0	150.1
4	NH_2[a]	148.5	110.4	*155.8*	110.4	148.5
4	OH[a,b]	139.8	115.9	*175.7*	115.9	139.8
4	OMe[a]	150.7	109.8	*164.9*	109.8	150.7

Neat liquids, unless otherwise specified; values for *ipso* position (carrying substituent) italicized; data from <1972CPB429, 1973OMR (5)551>.
[a]In DMSO-d_6.
[b]Compound in NH form.

carbon atoms in the azine portion of the molecule, although the difference from those in the parent azine is usually less than 10 ppm. Shift data for a number of common bicyclic azine systems are given in **Figure 15**.

Protonation of azines results in shielding of the α carbon atoms and deshielding of the β- and γ-carbon atoms (**Table 14**), particularly the latter, and these effects have been accounted for in terms of additivity parameters. The upfield protonation parameter for the α-carbon atom has been assigned to changes in the C–N bond order, while the β- and γ-parameters have been assigned to charge-polarization effects. The parameters are highly reproducible for mono-protonation but deviate significantly from additivity for diprotonated heterocycles. A related effect is observed on quaternization, but in this case the operation of a β-substituent effect results in the overall change at the α-carbon atom normally being small (**Table 14**).

A further important general trend in the azines arises on N-oxidation, which results in shielding of the α- and γ-carbon atoms, especially the former, and clearly indicates the higher electron density at these ring positions (**Figure 16**). The corresponding conjugate acids of the *N*-oxides have chemical shifts very similar to those of the protonated parent heterocycles.

The effect of benzo substitution on thiinium tetrafluoroborate is shown in **Figure 17**. In a study of thiinium salts with different counterions (BF_4^-, BPh_4^-, I^-, TfO^-) and solvents (CD_3CN, DMSO-d_6) it was evident that these changes have the least effect on the C(2) chemical shift <CHEC-III(7.10.2.2.3)775>.

The pyrones and thiinones show general ^{13}C NMR spectral characteristics similar to the pyridones which reflect charge distributions in the heterocyclic rings. Thus, carbon atoms α or γ to the heteroatom are deshielded relative to benzene, while those β are shielded. Substituent effects are in general as expected, although fewer detailed studies have been carried out in this area with the oxygen and sulfur heterocycles than with the azines. Chemical shift data for representative oxygen and sulfur compounds are given in **Figure 18**.

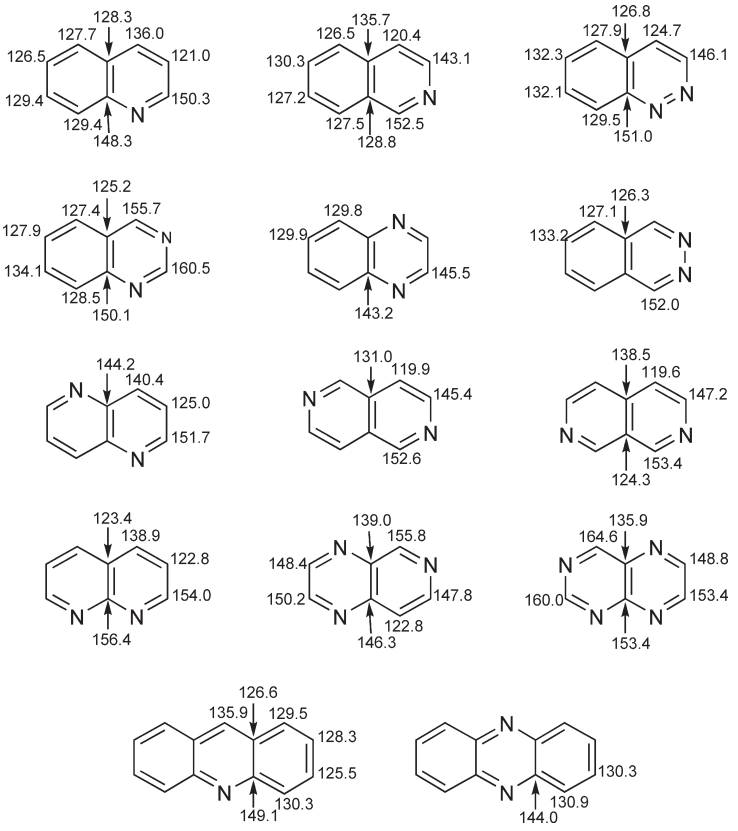


Figure 15 ^{13}C chemical shifts for bicyclic systems.

Table 14 ^{13}C NMR chemical shifts (δ, ppm from TMS) and one-bond ^{13}C–^{1}H coupling constants (Hz) of some simple heterocyclic cations (cf. pyridine, column 2)

Position	*Chemical shift (coupling constant)*					
1	N	O^+	NH^+	NMe^+	NPh^+	S^+
2	150.3 (178)	169.3 (218)	148.3 (192)	145.8	145.3 (191)	158.8
3	124.3 (162)	127.7 (180)	128.6 (173)	128.5	129.5 (178)	138.3
4	136.4 (162)	161.2 (180)	142.2 (173)	145.8	147.8 (174)	150.8
Anion	–	$C1O_4^-$	$CF_3CO_2^-$	I^-	Cl^-	BF_4^-
Solvent	DMSO-d_6	CD_3CN	D_2O	DMSO-d_6	D_2O	CD_3CN
Ref.	1970MP573	1973OMR(5)251	1980CCC2766	1976OMR(8)21	1980CCC2766	2003JFC(120)49
	1976OMR(8)21	1977OMR(9)16	1970MI20100			2001EJO2477

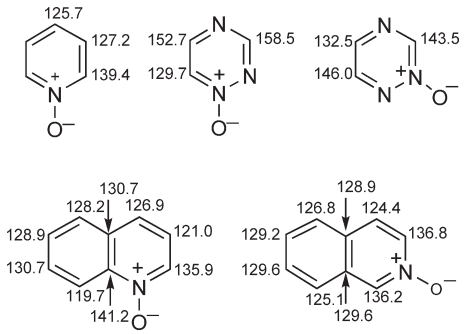


Figure 16 ^{13}C chemical shifts for *N*-oxides.

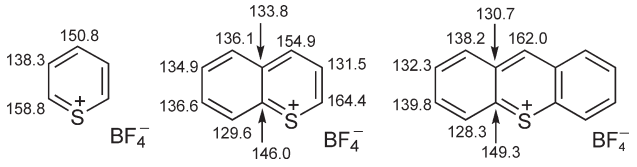


Figure 17 ^{13}C chemical shifts for thiinium salts.

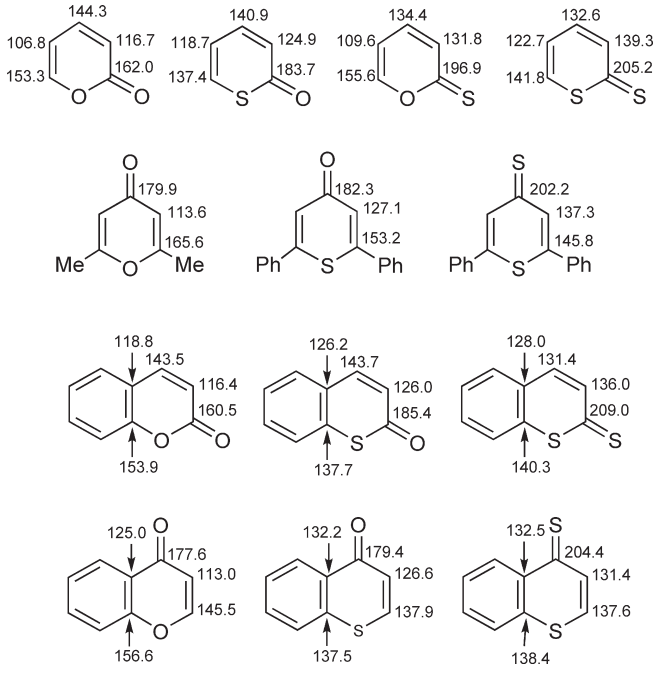


Figure 18 ^{13}C chemical shifts for oxygen and sulfur systems.

2.2.3.4.2 Aromatic systems: Coupling constants

Single-bond ^{13}C–^{1}H coupling constants for six-membered heteroaromatic compounds lie in the approximate range 150–220 Hz, the magnitude varying with substituent electronegativity. Data for simple azines are summarized in **Table 15**. Longer range couplings are much smaller (up to ca. 12 Hz), and the values are difficult to predict.

2.2.3.4.3 Saturated systems

Data are available on the ^{13}C spectra of saturated six-membered ring systems <B-79MI20101>. The chemical shifts of the α-, β-, and γ-methylene carbon atoms of compounds of type **146** are summarized in **Table 16** <1976JA3778>.

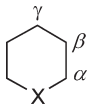
A nitrogen atom at X results in a variable downfield shift of the α-carbons, depending in its extent on what else is attached to the nitrogen. In piperidine **146** (X = NH) the α-carbon signal is shifted by about 20 ppm, to ca. $\delta = 47.7$, while in *N*-methylpiperidine **146** (X = Me) it appears at $\delta = 56.7$. Quaternization at nitrogen produces further effects similar to replacement of NH by *N*-alkyl, but simple protonation has only a small effect. *N*-Acylpiperidines show two distinct α-carbon signals, because of restricted rotation about the amide bond. The chemical shift separation is about 6 ppm, and the mean shift is close to that of the unsubstituted amine **146** (X = NH). The nitroso compound **146** (X = N–NO) is similar, but the shift separation of the two α-carbons is somewhat greater (ca. 12 ppm). The β- and γ-carbon atoms of piperidines, *N*-acylpiperidines, and piperidinium salts are all upfield of the cyclohexane resonance by 0–7 ppm.

The ether oxygen of tetrahydropyran **146** (X = O) induces a large downfield shift of the α-carbons, while the β- and γ-carbons move slightly upfield, the γ more noticeably. In derivatives of pyrano[3,2-*b*]pyrans **147** the C(4a) and C(8a) resonances appear at <76 ppm whereas the C(2) and C(2′) resonances in derivatives containing the 2,2′-bifuranyl skeleton **148** are downfield at >76 ppm. This provides a convenient method of distinguishing between these structures <CHEC-III(7.07.3.1.2)343>.

Table 15 One-bond ^{13}C–^{1}H coupling constants (Hz) in the simple monocyclic aromatic azines (cf. 159 Hz for benzene)

	J (Hz) (position of N atoms indicated)						
Position	*Pyridine*	*Pyridazine*	*Pyrimidine*	*Pyrazine*	*1,2,4-Triazine*	*1,3,5-Triazine*	*1,2,4,5-Tetrazine*
1	N	N	N	N	N	N	N
2	178	N	211	184	N	206	N
3	162	186	N	184	207	N	214
4	162	174	182	N	N	206	N
5	162	174	171	184	188	N	N
6	178	186	182	184	188	206	214

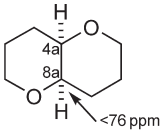
Table 16 ^{13}C NMR chemical shifts (δ, ppm from TMS) in saturated six-membered rings **146**



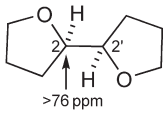
146

	Shift of C at position			
*X in structure **146***	*α*	β	*γ*	*Solvent*
CH_2	27.7	27.7	27.7	None
NH	47.5	27.2	25.5	None
NMe	56.7	26.3	24.3	None
$NH_2^+ I^-$	45.6	23.2	22.5	H_2O
$NHMe^+I^-$	55.6	23.9	21.8	H_2O
$NMe_2^+I^-$	63.5	20.6	21.0	H_2O
NCOPh[a]	42.8, 48.5	25.5, 26.3	24.4	$CDCl_3$
N-NO[b]	39.0, 50.8	25.5, 27.2	24.7	None
O	68.0	26.6	23.6	None
S	29.3	28.2	26.9	None
S–O *(ax)*	45.1	15.5	24.7	CD_2Cl_2
S–O *(eq)*	52.1	23.3	24.7	CD_2Cl_2
SO_2	52.6	25.1	24.3	CD_2Cl_2

From <1976JA3778>, unless otherwise indicated.
[a]<1975JOC3547>.
[b]<1974J(P2)1381>.



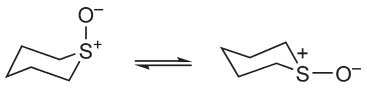
147



148

A sulfur (S^{II}) atom exerts only a very small effect on the chemical shifts of the carbon atoms in the ring: cyclohexane absorbs at $\delta = 27.7$, and the signals of the α-, β-, and γ-carbons of tetrahydrothiin **146** (X = S) are all very close to this value. The corresponding sulfone **146** ($X = SO_2$) shows a rather large shift of the α-carbon (to $\delta = 52.6$), while the β- and γ-protons are moved slightly upfield. The sulfoxide group is variable in its effect, depending on whether the oxygen atom is axial (**149**) (the preferred conformation) or equatorial (**150**) (**Scheme 2**). An equatorial oxygen results in considerably more deshielding of the α- and β-carbons; in the axial conformer the β-carbon absorbs at a field over 11 ppm higher than cyclohexane.

When two heteroatoms are present in a saturated six-membered ring their effects are approximately additive to within 5 ppm. Observed shifts for a few representative examples are shown in **Figure 19**.



149 150

Scheme 2

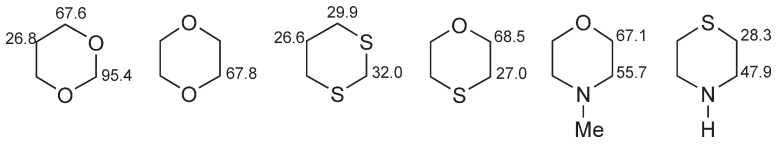


Figure 19 ^{13}C chemical shifts for systems with two heteroatoms.

Many studies have been made of substituent effects in saturated heterocyclic six-membered rings <B-79MI20101>. The so-called 'γ-gauche effect' induces an upfield (screening) shift of the ^{13}C signal from a ring carbon *meta* to an axial substituent **151**. The shielding experienced by a γ-carbon atom caused by an electronegative heteroatom *para* to it, i.e., **152**, is also a manifestation of the γ-gauche effect.

151 152

The one-bond coupling ($^1J_{CH}$) for cyclohexane (an average of couplings to axial and equatorial protons) is 123 Hz, and is increased by substitution adjacent to the carbon by an electronegative element, as with the aromatic systems discussed above.

^{13}C NMR chemical shifts are affected by the stereochemistry of a molecule and this can be useful for demonstrating the existence of isomers. For example, the spectra of the stereoisomers **153** and **154** are significantly different <CHEC-III(8.08.3.2.2)572>.

153 154

2.2.3.5 Nitrogen and Oxygen NMR Spectra <B-1973MI20100, B-1979MI20102>

Because of the large chemical shifts range, which is ~1100 ppm in organic compounds, ^{15}N NMR is a very sensitive tool for investigating structural changes. Increasing attention is focusing on nitrogen in biological structures because of the sensitivity of ^{15}N NMR chemical shifts to hydrogen bonding and to intermolecular and long-range interactions. Nitrogen NMR data has been reviewed <B-1996MI2235>.

Most nitrogen NMR chemical shifts reported in the organic chemistry literature use nitromethane as external reference. However, some data uses ammonia as reference (0.0 ppm) and on this scale $Me^{15}NO_2$ resonates at 380 ppm. In some cases $^{15}NH_4NO_3$ is used as reference and on the $^{15}NH_3$ scale this resonates at 21 ppm. All data given in **Tables 17** and **18** have, where necessary, been converted to the $MeNO_2$ scale using the parameters 380 or 21 ppm as appropriate. As for ^1H and ^{13}C NMR data, a move to more positive values of chemical shift is a result of deshielding and more negative values indicate shielding.

Examples of nitrogen chemical shifts relating to azines are given in **Table 17** and selected azine oxides are shown in **Table 18**.

Table 17 ^{14}N and ^{15}N NMR chemical shifts of representative azines and their salts

		^{15}N chemical shifts (ppm)[a]				
Compound	*Solvent*	*N(1)*	*N(2)*	*N(3)*	*N(4)*	*^{14}N bandwidth (Hz)*[b]
Pyridine	CCl_4	−57	–	–	–	170
Pyridine	MeOH	−83	–	–	–	
1*H*-Pyridinium	HCl/H_2O	−181	–	–	–	20
1-Hydroxypyridinium	HCl/H_2O	−133	–	–	–	570
1-Methylpyridinium	H_2O	−174	–	–	–	(Narrow)
4-Nitropyridine	Acetone	−35	–	–	–	490
4-Bromopyridine	None	−56	–	–	–	1100
4-Methylpyridine	Acetone	−74	–	–	–	480
4-Methoxypyridine	Acetone	−90	–	–	–	1100
4-Aminopyridine	Acetone	−105	–	–	–	680
4(1*H*)-Pyridone **45**	Acetone	−201	–	–	–	390
Pyridazine **5**	$CHCl_3$	20	20	–	–	410
Pyridazine	DMSO	20.3	20.3	–	–	–
Pyrimidine **6**	DMSO	−84.8	–	−84.8	–	–
Pyrazine **7**	DMSO	−46.3	–	–	−46.3	–
2-MeO-Pyrazine[c]	DMSO	−111	–	–	−45	–
1,2,3-Triazine **8**[d]	$CDCl_3$	13.1	81.0	13.1	–	–
4-Me-1,2,3-Triazine[e]	$CDCl_3$	12.5	79.9	3.6	–	–
4,6-DiMe-1,2,3-Triazine[e]	$CDCl_3$	3.8	78.6	3.8	–	–
1,2,4-Triazine **9**[c]	DMSO	40.0	2.0	–	−62.0	–
3-MeO-1,2,4-Triazine[c]	DMSO	36.0	−58.0	–	−126.4	–
1,3,5-Triazine	DMSO	−98.5	–	−98.5	–	–
Quinoline **16**	None	−72	–	–	–	650
Isoquinoline **17**	None	–	−68	–	–	680
Cinnoline **19**	DMSO	44.6	41.3	–	–	–
Phthalazine **20**	Dioxane	–	−11	−11	–	800
4-Me-1,2,3-Benzotriazine[e]	$CDCl_3$	15.9	66.6	−16.1	–	-
4-MeO-1,2,3-Benzotriazine[e]	$CDCl_3$	5.1	61.2	−66.3	–	-
Quinoxaline **22**	Dioxane	−46	–	–	−46	950
Uracil **127**[f]	DMSO	−248	–	−220	–	-

^{14}N data from <B-1973MI20100>; ^{15}N data from <1980HCA504>.
[a]ppm upfield from $MeNO_2$.
[b]At half height; no entry in this column means data are from ^{15}N spectra.
[c]<1984SAA637>.
[d]<1998CPH(228)39>.
[e]<1986J(P2)1249>.
[f]<1998JPC10454, 1977J(P2)1268>.

Table 18 ^{14}N and ^{15}N NMR chemical shifts of representative azine oxides

		N chemical shifts (ppm)[a]			
Compound	*Solvent*	*N(1)*	*N(2)*	*N(3)*	*N(4)*
Pyridine 1-oxide	Acetone	−85	–	–	–
Pyridazine 1-oxide	DMSO	−55.1	−33.6	–	–
Pyrimidine 1-oxide	DMSO	−90.0	–	−80.3	–
Pyrazine 1-oxide	DMSO	−75.7	–	–	−70.4
3-MeO-Pyrazine 1-oxide[b]	DMSO	−75	–	–	−133
3-MeO-1,2,4-Triazine 1-oxide[b]	DMSO	−50.0	−97.1	–	−148.0
4-Me-Benzo-1,2,3-triazine 2-oxide[c]	$CDCl_3$	−49.5	−48.1	−75.6	–
4-MeO-Benzo-1,2,3-triazine 2-oxide[c]	$CDCl_3$	−85.0	−54.4	−95.5	–
4-Me-Benzo-1,2,3-triazine 3-oxide[c]	$CDCl_3$	18.5	39.1	−51.8	–

^{14}N data from <B-1973MI20100>; ^{15}N data from <1980HCA504>.
[a]ppm upfield from $MeNO_2$.
[b]<1984SAA637>.
[c]<1988J(P1)1509>.

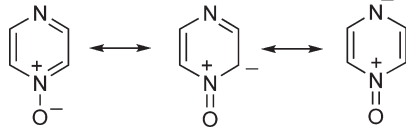
The following general trends are observed:

a. A pyridine-type nitrogen absorbs at comparatively low field (−63 ppm for pure pyridine without solvent).
b. Substituent effects are often considerable, particularly if strongly electron-donating groups are *ortho* or *para* to an aza nitrogen, and upfield shifts of up to 60 ppm (2-NH_2) may be observed. This shielding effect can be seen in 4-aminopyridine, 2-methoxypyrazine [N(1)], 3-methoxy-1,2,4-triazine [N(2) and N(4)] and 4-methoxybenzo-1,2,3-triazine [N(3)] (**Table 17**).
c. Further aza substitution *ortho* or *para* in the same ring deshields the nitrogen; the effect is moderate for a *para*-, and large for an *ortho*-nitrogen. The latter is probably a special 'azo effect,' since the nitrogens of a simple azo group absorb at still lower field (130 ppm, in ether). This deshielding effect can be seen in the chemical shifts of pyridazine, 1,2,3-triazine [particularly N(2)], 1,2,4-triazine [N(1) and N(2)] and cinnoline (**Table 17**).
d. Hydrogen bonding to the nitrogen lone pair leads to an upfield shift, the extent of which depends on the proton-donor ability of the solvent, and the acceptor ability of the base: shifts of some 20 ppm are commonly found.
e. When the lone electron pair is protonated, the nitrogen chemical shift moves by ca. 100 ppm to higher field. Large upfield shifts are also found when a compound exists in a tautomeric form with a proton on the nitrogen. The nitrogen NMR spectrum is often of considerable value in studies of tautomerism of this type <2006AHC(91)1>.

   NMR longitudinal relaxation times can be used for determination of the site of protonation in polyfunctional acids and bases <1993J(P2)283>. Thus, the ^{14}N NMR spectrum of 4-aminopyridine shows clearly, from the sharpening of the signal for the ring nitrogen, that protonation has occurred on the ring. This procedure is an important innovation in the elucidation of heterocyclic tautomeric structures, especially for cases of fast exchange.

   Observation of the one-bond ^{13}C–^{15}N coupling in quaternized heterocycles containing specific labeling with ^{15}N has been used to identify the site of quaternization <1976JOC3051>.
f. N-Oxidation of an azine nitrogen usually shifts the signal upfield by a small amount (10–30 ppm). (In five-membered rings, however, downfield shifts have been claimed <1978JOC2542>.) Back donation also shields nitrogen atoms *ortho* and *para* to the *N*-oxide function and the combined effects of N-oxidation, *N*-oxide position and other substituent effects can be seen in the variation in chemical shifts shown in **Table 18**, and their relationships to the shifts in the parent azines (**Table 17**).

^{17}O NMR spectroscopy has been used to examine the relative back donation of various diazine *N*-oxides. The order of ^{17}O chemical shifts in *N*-oxides is pyridazine (412 ppm) > pyrazine > pyridine (349 ppm) > pyrimidine (338 ppm), with the larger value corresponding to the greater double-bond character for the nitrogen-oxygen bond in the *N*-oxide group. This is in agreement with the ^{15}N chemical shifts of the parent compounds as well as the differences in chemical shifts between the parent and the oxidized nitrogens. This strongly suggests that a ring nitrogen *para* and particularly *ortho* to an *N*-oxide function affects the back donation by attracting electrons from the *N*-oxide oxygen atom. In the case of pyrazine *N*-oxides, the resonance structure **155c** appears to make a greater contribution than others having a nitrogen–oxygen double bond, e.g., **155b** <1985JHC981>.



155a **155b** **155c**

Natural abundance ^{17}O NMR data for lactones have been reported and the relationships between ^{17}O chemical shifts and structure analyzed <1989H(29)301>. It is possible to distinguish between polyfunctionalized coumarins **87** and chromones **88** using ^{17}O NMR<1993CPB211, CHEC-III(7.07.3.1.3)344>.

2.2.3.6 Ultraviolet and Related Spectra <1971PMH(3)67>

The six-membered aza-aromatic compounds possess the basic π-electron systems of benzene and its homologues, and in addition there are nonbonding lone pairs of electrons on the nitrogen atoms. These lone pairs are responsible for weak transitions, denoted $n \rightarrow \pi^*$, at the long-wavelength end of the spectrum. These absorptions are usually weak, in comparison to the transitions ($\pi \rightarrow \pi^*$) of the π-electrons, and are frequently difficult to locate, except when two aza nitrogen atoms are adjacent. In these cases, e.g., pyridazine **5**, the two filled nonbonding orbitals interact (**Figure 20**). The $n \rightarrow \pi^*$

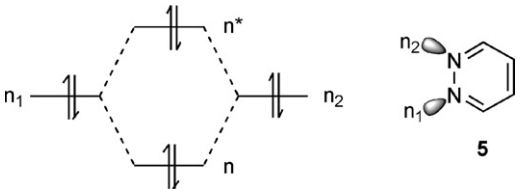


Figure 20 The spilitting of the adjacent nonbonding orbitals in pyridazine **5**.

Table 19 UV absorption bands of the simple monocyclic azines

Compound	$\pi \rightarrow \pi^*$ bands	$n \rightarrow \pi^*$ bands
Benzene **1**	203.5 (3.87), 254 (2.04)	–
Pyridine **4**	251 (3.30)	ca. 270 (sh)
Pyridazine **5**	246 (3.11)	340 (2.50)
Pyrimidine **6**	243 (3.31)	298 (2.51)
Pyrazine **7**	260 (3.75)	328 (3.02)
1,2,4-Triazine **9**[a]	264 (3.71)	384 (2.72)
1,3,5-Triazine **10**	222 (2.18)	272 (2.95)
1,2,4,5-Tetrazine **13**	252 (3.33)	ca. 320 (w), 542 (2.92)

Solvent cyclohexane; the positions of the peak maxima (nm) are given, with $\log_{10} \varepsilon$ values in parentheses; mainly from Mason <1959JCS1240,1247>.
[a]Trimethyl derivative.

bands are more obvious features of the spectra of compounds such as pyridazine **5**, 1,2,4,5-tetrazine **13** and cinnoline **19**. In 1,2,4,5-tetrazine there are two $n \rightarrow \pi^*$ bands, a weak system near 320 nm, and a stronger one, giving a band at ca. 550 nm ($\varepsilon = 830$), which is responsible for the red color. **Table 19** gives the positions of the $n \rightarrow \pi^*$ absorptions of a number of the simpler aza-aromatics.

The transition energies from bonding to antibonding π-orbitals ($\pi \rightarrow \pi^*$) compare fairly well in their levels to those of the corresponding hydrocarbons (see also **Table 2**), although the band intensities are often very different. Thus, the spectra of naphthalene, quinoline, isoquinoline, and the quinolizinium ion bear a remarkable similarity, except in the intensities of the long-wavelength bands. Cinnoline is slightly different, with long-wavelength peaks at 309 nm (log $\varepsilon = 3.29$), 317 (3.25), and 322 (3.32) and the $n \rightarrow \pi^*$ band at 390 nm (log $\varepsilon = 2.43$). The differences are probably a result of the pronounced asymmetry of the molecule, compared with naphthalene. **Table 19** lists the principal bands in the spectra of some representative monocyclic systems, with those of benzene included for comparison. In the aza derivatives of the higher polyarenes, ultraviolet (UV) spectral comparisons have frequently been used as an indication of structural correspondence <1958HC(12)551>. For example, the spectra of the benzo, dibenzo, etc., derivatives of the quinolizinium ion bear similar qualitative relationships to those of the polycyclic hydrocarbons as does quinolizinium ion itself to naphthalene, i.e., a bathochromic shift accompanied by a pronounced intensification (see **Table 20**).

The effects of substituents on UV spectral maxima are illustrated in **Table 21**. The effects are greatest when conjugation is significantly increased, e.g., for strong electron-donor substituents in the pyridinium cation.

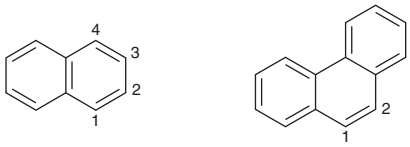
The nonaromatic but fully-conjugated 1,4-dioxin and its sulfur analogues show absorption at quite long wavelengths.

The spectra of saturated nitrogen heterocycles show amine $n \rightarrow \sigma^*$ absorptions and sulfur rings show transitions associated with sulfur. Saturated ethers are usually transparent down to 210 nm.

Some of the useful applications of UV spectroscopy are listed below.

a. UV spectroscopy has been much used in determining ionization constants for both proton addition and proton loss. Conversely, it is important that the pH of a solution is known when a UV spectrum of a potentially basic or acidic compound is obtained.
b. UV spectroscopy has been particularly useful in studies of tautomeric compounds. Thus 2-pyridone has a spectrum very similar to 1-methyl-2-pyridone, and quite different from 2-methoxypyridine <CHEC-I(2.04.3.3)126>.
c. UV absorption spectra are useful in the investigation of covalent hydration, important in polyaza six-membered heteroaromatics, especially when bicyclic (see Section 3.2.1.6.3).
d. UV–visible (UV–Vis) spectra demonstrate charge-transfer complex formation, e.g., between polycyclic quinolizinium ions and polycyclic aromatic hydrocarbons.

Table 20 UV spectral maxima (nm) for benzazines [λ_{max} (log ε)]



N-position	*Neutral*	*Monocation*	*Neutral*	*Monocation*	*Neutral*	*Monocation*
–[a]	275 (4.0) 310 (2.81)	–	292 (4.30) 330 (2.54)	–	375 (4.88)	–
1	312 (3.52)	313 (3.79)	346 (3.24)	365 (3.56)	354 (4.02)	402 (3.48)
2	319 (3.47)	332 (3.63)	–	–	–	–
1,2	321 (3.44)	353 (3.40)	370 (3.2)	–	–	–
1,3	305 (3.38)	260 (3.91)	–	–	–	–
1,4	316 (3.79)	331 (3.93)	–	–	365 (4.2)	430 (3.2)
2,3	305 (3.11)	314 (3.45)	–	–	–	–

Abstracted from <1971PMH(3)67> which contains original references.
[a]Values in this row taken from E. S. Stern and C. J. Timmons, 'Electronic Absorption Spectroscopy in Organic Chemistry', Arnold, London, 1970, apply to the hydrocarbon species.

Table 21 UV spectral maxima (nm) of substituted azines

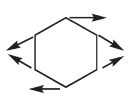
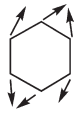
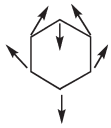
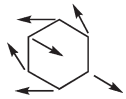
Substituent	*Position*	*Pyridine (neutral)*	*Pyridine (cation)*	*Pyridine 1-oxide*	*Pyridazine*	*Pyrimidine*	*Pyrazine*
–	–	257	256	265	300	243	261
Me	2	262	262	–	–	249	271
	3	263	262	254	310	252[a]	–
	4	255	252	256	292	245	–
Cl	2	264	271	–	–	–	268
	3	267	270	–	308	–	–
	4	258	257	265	–	–	–
OMe	2	269	279	249	–	264	292
	3	276	284	262	265	–	–
	4	245	236	261	254	248	–
NH_2	2	229	229	239	–	292	316
	3	231	250	–	–	298[a]	–
	4	241	263	215	249	268	–
NO_2	2	269	–	–	–	–	–
	3	241	–	–	–	237[a]	–
	4	286	–	328	–	–	–
CO_2H	2	264	265	259	–	246	–
	3	262	260	260	–	247[a]	–
	4	271	275	281	–	253	–
Ph	2	241	294	240	–	250	–
	3	244	–	249	254	256[a]	–
	4	256	286	293	–	275	–

Abstracted from <1971PMH(3)67> which contains original references.
[a]Refers to five-substituted compound.

2.2.3.7 IR and Raman Spectra <1963PMH(2)161, 1971PMH(4)265>

Systematic studies of the IR spectra of substituted pyridines establish: (1) that substituents vibrate largely independently of the rings; (2) that the vibrational modes of the ring skeleton are related, and approximate in position, to those found in benzene derivatives; and (3) that the bending modes of the ring hydrogen atoms are similar to those of the corresponding arrangements of adjacent hydrogen atoms on a benzene ring. Although it is reasonable to assume that these generalizations are applicable to all azines, other systems have not been examined in as much detail as the pyridines.

Table 22 Approximate positions of ring-stretching modes for pyridines, pyrimidines, and benzenes (cm^{-1})

	Mode			
				
Compounds	A	B	C	D
Monosubstituted benzene[a]	1610–1600	1590–1580	1520–1470	1460–1440
Pyridine[b]	1580	1572	1482	1439
4-Substituted pyridines[a]	1610–1595	1570–1550	1520–1480	1420–1410
Pyridine 1-oxides[a]	1645–1590	1585–1560	1540–1470	1440–1410
Pyrimidines[c]	1600–1545	1575–1540	1510–1410	1470–1330

[a]In $CHCl_3$.
[b]Vapor phase.
[c]Various media.

Four ring-stretching modes for pyridines and pyrimidines are listed in **Table 22**, together with the corresponding bands of a monosubstituted benzene. Quinolines and isoquinolines show seven or eight bands in the region 1650–1350 cm^{-1}.

In six-membered aromatic rings the intensity of the ring-stretching mode near 1600 cm^{-1} is related to the square of the normalized Hammett constant $\sigma_R°$ for the substituent R and/or ring atoms. Such intensity measurements on 4-substituted pyridine *N*-oxides confirm the ability of the *N*-oxide group to both donate and withdraw electrons according to the nature of the 4-substituent.

Six-membered heteroaromatic rings show bands characteristic of in-plane CH bending in the region 1300–1000 cm^{-1} (**Table 23**), and of out-of-plane CH bending below 1000 cm^{-1} (**Table 24**).

In the IR spectra of six-membered heterocycles containing one or more carbonyl groups in the ring (pyridin-2- and -4-ones, the pyrones, and pyrimidones) one of the higher frequency bands in the 1700–1500 cm^{-1} region can usually be

Table 23 Azines: characteristic IR bands (cm^{-1}) in the 1300–1000 cm^{-1} region

Compounds	β *CH modes*				*Ring modes*
2-Substituted pyridines	1293–1265	1150–1143	1097–1089	1053–1043	998–990
3-Substituted pyridines	1202–1182	1129–1119	1108–1098	1045–1031	1027–1023
4-Substituted pyridines	1232–1208	–	1070–1064	–	995–991
Pyridine 1-oxides	1158–1142	–	1130–1112	–	–
Pyrimidines	1280–1200	1210–1130	–	–	–
Pyridazines	–	1150–1100	–	–	1065–935

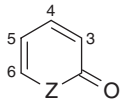
Data taken from <1971PMH(4)265> which contains references to the original literature.

Table 24 Azines: characteristic IR bands (cm^{-1}) below 1000 cm^{-1}

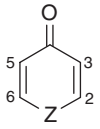
Compounds	*Characteristic IR Bands (cm^{-1})*				
2-Substituted pyridines	794–781[a]	752–746[a]	–	780–740[b]	–
3-Substituted pyridines	810–789[a]	715–712[a]	920–880[b]	820–770[b]	730–690[b]
4-Substituted pyridines	820–794[a]	775–709[a]	–	850–790[b]	ca. 725[b]
Pyridine 1-oxides	–	–	886–858	825–817	–
Pyrimidines	1010–960	–	850–780	–	–
Pyridazines	–	–	860–830	–	–

[a]Based on <1971PMH(4)265> which contains references to the original literature.
[a]Alkyl substituents only.
[b]Other substituents.

Table 25 ν (CO) frequencies (cm^{-1}) for some azinones



α-Series



γ-Series

Other features	*Bond*	*Z = NR*	*Z = O*	*Z = NR*	*Z = O*
–	$\begin{cases} \nu(C=0) \\ ring \end{cases}$	1666–1655 1619–1570	1736–1730 1647–1612	1577–1550 1643–1624	1634 1660
5,6-Benzo	ν(C=O)	1667–1633	1710–1700	1647–1620	1650
6-N	ν(C=O)	1681	–	1662	–
3-N	ν(C=O)	1670	–	1653	–

Abstracted from <1963PMH(2)161> and <1971PMH(4)265> which contain references to the original literature.

assigned to the carbonyl-stretching vibration. However, this is by no means always the highest frequency band; solvent and isotopic substitution effects on the band positions have shown that there is a considerable degree of mixing of the ring and carbonyl modes in the pyridones. The assignments in **Table 25** refer to the principal motion in these nonlocalized vibrations.

The position of the carbonyl group in the IR spectra of various pyranones and pyridones, etc., is indicative of the C–O bond order, and therefore of the relative contribution of dipolar resonance hybrids. However, this criterion must be used with caution because of the nonlocalized nature of the vibrations just mentioned.

Assignments have been suggested for the absorptions of many of the saturated heterocyclic six-membered rings <1963PMH(2)240, 1971PMH(4)339>. As expected, force constants between the atoms of the ring are much lower than in the aromatic rings, and the absorptions which are due to skeletal modes are generally found below ca. 1200 cm^{-1}; bands in the region 1500–1200 cm^{-1} arise from the various deformation modes of the CH bonds. The so-called Bohlmann bands at 2750 cm^{-1} are diagnostic of *trans*-fused quinolizidine structures.

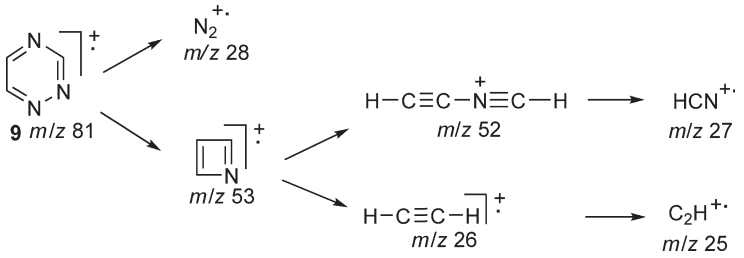
2.2.3.8 Mass Spectrometry <B-1967MI20100, 1966AHC(7)301, 1971PMH(3)223>

The behaviour of the simple azines and their benzo analogues on electron impact under mass spectrometric conditions is complex. Extensive randomization of ring hydrogen atoms, which increases with increasing lifetime of the ions, takes place prior to fragmentation, as does independent scrambling of ring carbon atoms. Skeletal and Dimroth-type rearrangements (see Section 3.2.3.5.4.3) are also common.

The mass spectra of the aromatic six-membered heterocycles and their benzo analogues reflect the stability of the ring systems, with the molecular ion in many cases also being the base peak. Fragmentation of the azines by loss of HCN (*M*-27) is the common pathway and for pyridine the *M*-27 ion is the only fragment of any significance in the spectrum apart from the molecular ion. Fragmentation by successive losses of molecules of HCN is common in polyaza systems. Pyrimidine, for example, loses two molecules of HCN in succession to give the radical cation of acetylene, and pteridine fragments similarly to the dehydropyrazine radical cation. Loss of nitrogen from systems containing an –N=N– unit is also a common feature although the ease with which this occurs can vary substantially. It is, for example, very common with cinnolines and benzo-1,2,3-triazines but is of much less importance with phthalazines.

The general fragmentation pattern of monocyclic 1,2,3-triazines shows ions corresponding to [M^+–N_2], an acetylene, and a nitrile, in accordance with the results of thermolysis and photolysis. The mass spectrum of the parent triazine shows ions as follows: *m/z* 81 (M^+, 47%), 53 (M^+–N_2, 69%), 27 (HCN, 13%), and 26 (C_2H_2, 100%) <1981CC1174>. The mass spectrum of unsubstituted 1,2,4-triazine **9** shows ions at *m/z* 81, 53, 52, 51, 40, 39, 38 28, 27, 26, and 25 (**Scheme 3**) <1967JHC224>. [4-^{15}N]-3-Methyl-1,2,4-triazine shows a similar fragmentation pattern <1972LA(760)102>. From these data it follows that the fragmentation starts with loss of nitrogen.

There has been relatively little detailed study of the mass spectrometry of pyrylium and thiinium salts, due partly no doubt to the involatility of the compounds; elimination of CO or CS is the major fragmentation pathway. *N*-Oxides generally show an abundant *M*-16 ion that is sometimes the base peak and di-*N*-oxides show successive elimination of two atoms of oxygen. The intensity of the *M*-16 ion is often very substantially reduced in compounds containing a

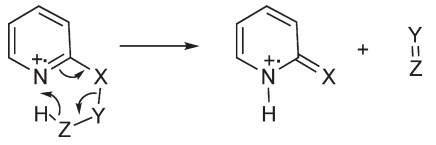


Scheme 3 Mass spectrum fragmentation pattern for 1,2,4-triazine **9**.

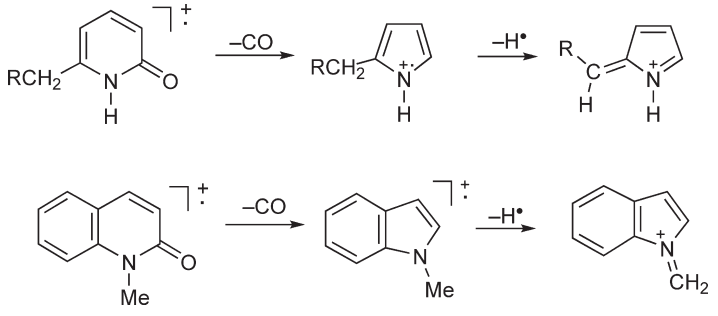
substituent α to the ring *N*-oxide which has at least one C–H bond, due to abstraction of a hydrogen atom by the oxygen of the *N*-oxide followed by elimination of a hydroxyl radical. The *M*-17 ion is then a correspondingly significant fragment. Methyl substitution α to a ring nitrogen atom usually results in fragmentation via elimination of MeCN rather than HCN. In monomethyl polyazines both processes are observed, although which fragmentation occurs first appears to be determined by the position of the methyl substituent. 2-Methylazines also give rise to fragments formed by loss of both a hydrogen atom and a methyl radical. Unlike the general situation pertaining with benzenoid aromatics, where β-cleavage is the preferred fragmentation pathway, the decomposition mode of azines substituted with alkyl groups larger than methyl depends both on the nature of the substituent and on its position relative to the ring nitrogen atom. β-Cleavage occurs with all of the alkylpyridines, but the extent varies in the order $3 > 4 > 2$, reflecting the relative electron densities at these positions. The resulting azabenzylic ions rearrange to the isomeric azatropylium ions, and these in turn fragment with loss of HCN or MeCN. γ-Cleavage of a C–H bond can also be important in 2-alkylazines and may even give rise to the base peak, but this form of fragmentation is generally much less important than β-cleavage with the 3- and 4-isomers. McLafferty-type rearrangements are usually pronounced with 2-substituted azines (**Scheme 4**), and this is a general process.

2-Pyridone undergoes fragmentation by loss of CO and formation of the pyrrole radical cation. 3-Hydroxypyridine, on the other hand, loses HCN to give the furan radical cation while 4-pyridone shows both modes of cleavage. The loss of CO from azinones is highly characteristic (**Scheme 5**) but with compounds such as uracils, their benzo analogues, 1-substituted 4-quinazolinones, quinazolinediones, and related species, retro-Diels–Alder fragmentation is favored, followed by loss of CO, then HCN, or a hydrogen atom, or both. This is illustrated by thiopyran-4-one (**Scheme 6**), which also loses CO from the molecular ion.

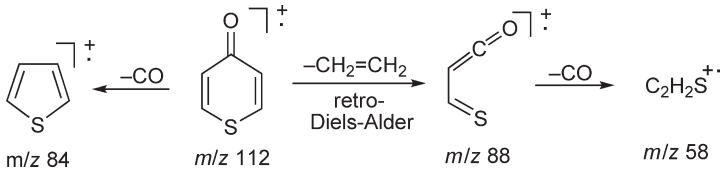
Rather complex fragmentation is often observed with alkoxy-substituted azines, especially with quinolines and isoquinolines, and intramolecular transfer of a hydrogen atom from the ether alkyl group to a ring carbon atom appears



Scheme 4



Scheme 5

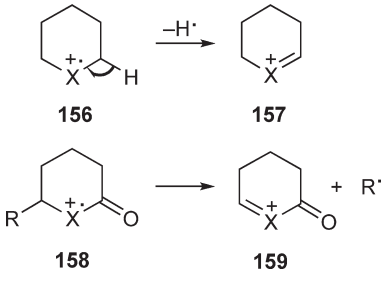


Scheme 6

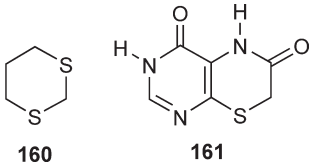
to be common. Loss of the alkyl radical and formation of quinonoid intermediates, followed by loss of CO, also appear to be common. Amino groups are usually eliminated as HCN.

The mass spectrum of 2-pyrone shows an abundant molecular ion and a very prominent ion due to loss of CO and formation of the furan radical cation. Loss of CO from 4-pyrone, on the other hand, is almost negligible, and the retro-Diels–Alder fragmentation pathway dominates. In alkyl-substituted 2-pyrones, loss of CO is followed by loss of a hydrogen atom from the alkyl substituent and ring expansion of the resultant cation to the very stable pyrylium cation. Similar trends are observed with the benzo analogues of the pyrones, although in some cases both modes of fragmentation are observed. Thus, coumarins, chromones, flavones, and xanthones, for example, all show significant (i.e., >20% relative abundance) or dominant fragmentation by loss of CO, while the retro-Diels–Alder pathway is dominant or significant in the fragmentation of 4-hydroxycoumarins, isocoumarins, chromones, and flavones. Dihydrocoumarins fragment with loss of CO while the retro-Diels–Alder mode is important in the fragmentation of dihydrocoumarins, dihydrochromones, chromans, flavanones, isoflavanones, and rotenoids. Not unexpectedly, the retro-Diels–Alder pathway also tends to dominate in the fragmentation of monocyclic dihydroheterocycles.

In the fully-saturated heterocyclic systems, loss of hydrogen atoms from α-carbons, **156** → **157**, and β-cleavage, **158** → **159** are common (**Scheme 7**), but it is often impossible to discern clear trends in the later stages of fragmentation. Fragmentation of sulfur-containing heterocycles almost always proceeds with loss of sulfur atoms or of sulfur-containing fragments. Two of the major fragments from 1,3-dithiane **160** are $(M\text{-}CH_2S)^+$ and $(M\text{-}C_3H_6S)^{+\bullet}$. Transfer of hydrogen atoms to sulfur is common: both tetrahydrothiin **83** and 1,2-dithiane, for example, lose $H_2S^{\bullet}$, in the latter case as a major fragment, while a third major fragment from 1,3-dithiane **160** arises by loss of CH_3S, requiring a hydrogen migration. In other cases, loss of sulfur-containing fragments clearly involves initial rearrangement; the pyrimidothiazinone **161**, for instance, fragments with loss of COS. In cyclic sulfones loss of SO_2 is a major fragmentation process.



Scheme 7



2.2.3.9 Photoelectron Spectroscopy

In the UV photoelectron spectrum, the most readily ionized level of pyridine is the nonbonding orbital (with contributions from the σ-framework). The three diazines show two lone-pair levels, with the greatest splitting in the case of pyridazine but considerable also in pyrimidine and pyrazine. These long-distance splittings are attributed to both through-space and through-bond interactions, particularly the latter.

The energy levels corresponding to the second and subsequent ionization potentials of pyridine have been correlated with those in benzene.

PE spectroscopy offers a method of investigating the tautomeric structure of pyridones and other related compounds in the gas phase by comparison of ionization potentials of the potentially tautomeric compound with those of fixed models. This method is discussed in CHEC-I (2.04.3.6)140.

2.2.4 Thermodynamic Aspects

2.2.4.1 Intermolecular Forces

2.2.4.1.1 Melting and boiling points

The introduction of a pyridine-like nitrogen into a benzene ring tends to make a derivative more crystalline and less volatile; this effect is greater for the diazines, especially pyridazine and pyrazine. When a hydrogen-bond donor substituent is also carried, the difference from the benzenoid compound becomes even more marked (**Table 26**).

Examination of the effects of substituents on the melting and boiling points of the parent compounds is instructive.

a. Methyl and ethyl groups attached to ring carbon atoms usually increase the boiling point by ca. 20–30 and ca. 50–60 °C, respectively.
b. Acids and amides are solids, as are amino and hydroxy compounds. The latter generally exist in the tautomeric oxo structures. Strong hydrogen bonding is possible for all these classes of derivatives.
c. Methoxy, methylthio, and dimethylamino derivatives are often liquids.
d. Chloro compounds usually have boiling points similar to those of the corresponding ethyl compounds. Bromo compounds boil ~25 °C higher than their chloro analogues.

2.2.4.1.2 Solubility

The solubility in water is much enhanced by the presence of a pyridine nitrogen atom due to the possibility of hydrogen bonding. However, if this possibility is increased sufficiently, then the compound may favor intermolecular hydrogen bonding, and this can decrease water solubility. Introduction of amino groups into pteridine **24** lowers the solubility in all solvents despite the fact that the amino group almost invariably increases the solubility in water of aliphatics and aromatics. This reduced solubility of aminopteridines is due to intermolecular hydrogen bonding (**Table 27**).

2.2.4.1.3 Gas–liquid chromatography

Typical operating conditions for the GLC separation of azines are shown in **Table 28**.

Chromatographic techniques in combination with other physical methods have solved difficult chemical problems. Sensitive compounds can be detected and characterized by high-performance liquid chromatography (HPLC) as indicated during the oxidation of the (6*R*)- and (6*S*)-diastereoisomers of 5,6,7,8-tetrahydrobiopterin to the (6*R*)- and (6*S*)-quinonoid 6,7-dihydrobiopterins which rearrange with a half-life of about 5 min. to form the stable 7,8-dihydrobiopterin <1983JCH361, 1984MI718-06>. Separation of regioisomers such as 6,8- and 7,8-dimethylpterin can be achieved under special conditions using strong cation-exchange columns <1992MI718-11>. The identification and determination of the stereoconfiguration of pterins and lumazines with chiral side chains was successfully performed by ligand-exchange chromatography using a reverse-phase column with a chiral mobile phase <1992MI718-05, B-1993MI718-06, 1993MI718-08, 1994MI718-02>. Cation-exchange, reverse-phase, and ion-pair reverse-phase chromatography were evaluated for the separation of various pterins <1984JLC2561>. HPLC methods have also been developed for the determination of pteridines in biological samples <1983MI718-09> and in blood cells and plasma <1983MI718-04>.

Table 26 Melting and boiling points

Ring system	*H*	*Me*	*Et*	*COMe*	*CO_2H*	*CO_2Et*	*$CONH_2$*	*CN*
Benzene	80	111	136	202	**122**	211	**130**	190
Pyridine-2	115	128	148	192	**137**	243	**107**	222
Pyridine-3	115	144	163	220	**235**	223	**129**	**50**
Pyridine-4	115	145	171	211	**306**	219	**156**	**79**
Pyridazine-3	208	215	–	**90**	**200**	**68**	**182**	**44**
Pyridazine-4	208	225	–	–	**240**	255	**191**	**80**
Pyrimidine-2	123	138	–	–	**270**	–	–	–
Pyrimidine-4	123	141	–	–	**240**[d]	–	–	–
Pyrimidine-5	123	153	–	–	**270**	**38**	**212**	–
Pyrazine-2	**57**	135	153	**77**	**229**[d]	**50**	**189**	**205**
	NH_2	*OH*	*OMe*	*SH*	*SMe*	*Cl*	*Br*	*I*
Benzene	184	**43**	**37**	168	187	131	155	188
Pyridine-2	**57**	**107**	252	**128**	197	171	193	52
Pyridine-3	**65**	**125**	179[a]	**79**	–	150	173	**53**
Pyridine-4	**157**	**148**	**93**	**186**	**44**	147	174	–
Pyridazine-3	**169**	**103**	219	**170**	**38**	**35**	**73**	–
Pyridazine-4	**130**	**250**	**44**	**210**[a]	**45**	**76**	–	–
Pyrimidine-2	**127**	**320**	–	**230**[a]	218	**65**	–	–
Pyrimidine-4	**151**	**164**	–	**187**	–	–	–	–
Pyrimidine-5	**170**	**210**[a]	–	–	–	**37**	**75**	–
Pyrazine-2	**120**	**119**	**187**	**215**	**46**	160	180	–

Melting points above 30 °C are given in bold; melting points below 30 °C are not included. Boiling points are given at atmospheric pressure to facilitate comparison; those reported at other than atmospheric pressure were converted using a nomogram *(Ind. Eng. Chem.*, 1957, **49**, 125). A dash indicates that the compound is unstable, unknown, or the data are not readily available.
[a]With decomposition.

Table 27 Solubilities in water (parts soluble in 1 part of water) at 20 °C

Monocyclic compounds		*Polycyclic derivatives*		*OH-substituted derivatives*		*NH_2-substituted derivatives*	
Benzene	0.0015	Naphthalene	0.00002	Phenol	0.07	Aniline	0.03
Pyridine	Miscible	Quinoline	0.007	2-Pyridone	1	2-Aminopyridine	1
Pyridazine	Miscible	Isoquinoline	0.004	3-Hydroxypyridine	0.03	3-Aminopyridine	>1
Pyrimidine	>1	Quinoxaline	0.7	4-Pyridone	1	2,6-Diaminopyridine	0.1
Pyrazine	1.7	Pteridine	0.15	2-Pyrimidinone	0.5	2-Aminopteridine	0.0007

Data abstracted from <1963PMH(1)177>.

Table 28 Operating conditions for the GLC separation of azines

Compounds	*Conditions*
Pyridines	Diphenyl phthalate on 'Tide'
Quinolines	Silicone E-301
Pyrimidines	15% Hallcomid M-18 on firebrick
Pyrazines	Apiezon M and N or Reoplex 400
Piperazines	Flexol 8N8 on firebrick
Phenazines	SE-30 on Chromosorb W
1,3,5-Triazines	Ethylene glycol adibatic on glass beads

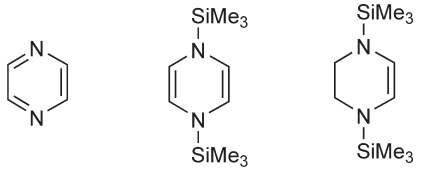
Data abstracted from <1971PMH(3)297> which contains original references and further information.

2.2.4.2 Aromaticity of Fully-Conjugated Rings

2.2.4.2.1 Background

Aromaticity has been long recognized as one of the most useful theoretical concepts in organic chemistry. It is essential in understanding the reactivity, structure, and many physicochemical characteristics of heterocyclic compounds. However, there is no precise quantitative definition of aromaticity that is universally acceptable. Aromaticity is usually

regarded as a feature of cyclic conjugation of π-electrons that leads to enhanced thermodynamic stability, planar geometries, nonlocalized cyclic bonds, induced diamagnetic ring currents, and a tendency to undergo substitution rather than addition reactions. Compounds with $4n + 2$ π-electrons in cyclic conjugation are predicted to be aromatic whereas those with $4n$ π-electrons in cyclic conjugation are not (Hückel's rule). If cyclic conjugation leads to destabilization then compounds are described as antiaromatic. Thus, pyrazine **7** has an aromatic sextet of electrons ($4n + 2 = 6$) and is an aromatic molecule. The 1,4-dihydropyrazine derivative **162** is a representative of antiaromatic compounds ($4n = 8$). In this molecule there is cyclic conjugation but this leads to destabilization since two π-electrons above the Hückel $4n + 2$ limit are forced to occupy antibonding orbitals, and this destabilization is greatest if the molecule is planar. The 1,2,3,4-tetrahydro derivative **163** is nonaromatic since there is no cyclic conjugation of the π-electrons.



7 **162** **163**

Although it is usually not difficult to qualitatively classify a given compound as aromatic, nonaromatic, or antiaromatic, it is much more difficult to describe aromaticity in quantitative terms and to compare the relative aromaticities of a series of similar molecules. The main criteria of aromaticity that are currently accepted can be subdivided into three groups: these are energetic, structural, and magnetic criteria, which are discussed in the following subsections. For further discussion of the inter-relationships of these criteria see Section 2.4.4.2 <1989JA7, 2001CRV1421, 2002JOC1333>.

2.2.4.2.2 Energetic criteria

2.2.4.2.2.1 From heats of reactions and theoretical calculation. The very different thermodynamic stability of aromatic, nonaromatic, and antiaromatic systems provides a good basis for the development of energetic criteria of aromaticity and the resonance energy is accepted as a measure of such stability. The resonance energy is defined as the difference between the electronic energy of a real (conjugated) molecule and a hypothetical Kekulé structure with localized bonds. Since the latter do not exist in reality, the choice of an adequate model of localized structure creates a problem. There are two main approaches to the calculation of resonance energy – purely theoretical and semiempirical. In the first case, both energy values are calculated quantum mechanically. In the second case, the energy of a real molecule is determined experimentally (usually through the measurement of heats of combustion or hydrogenation), whereas for a localized bond structure the energy is calculated by summing tabulated values of the energies of isolated bonds. Energies determined by a semiempirical approach are called empirical resonance energies (EREs). Relatively few ERE values exist for six-membered heterocyclic compounds, some of which are listed in **Table 29**. These ERE values show significant variation but the errors in some early heats of combustion are quite large.

An approach by M. J. S. Dewar is considered to be the most successful. Dewar resonance energies (DRE) are derived from heats of atomization, ΔH_a. For real molecules, ΔH_a values are taken from the experimental heats of combustion. If the experimental data are not available, the ΔH_a value is obtained from a quantum mechanical calculation. A major development by Dewar was the choice of acyclic polyenes or heteropolyenes as reference structures. Unlike classical Kekulé structures, their formal single bonds contain a π-component. To compare the aromaticities of compounds with different numbers of π-electrons, Hess and Shaad introduced REPE indices that denote 'resonance energy per electron.' They are obtained by dividing the full resonance energy by the number of ring π-electrons. **Table 29** shows Dewar resonance energies per electron calculated from experimental quantities (DRE) and from AM1 calculated data (DRE′). Antiaromatic molecules have negative DRE values whereas aromatic values are positive. Hess and Shaad adapted this approach to an HMO method using units of β (HSRE). Another type of resonance energy is the topological resonance energy (TRE).

In **Table 29** resonance energy indices of some simple six-membered heterocycles are given. Although there are some variations in the indices they are relatively small and using resonance energies as the criteria one may reasonably conclude that replacing a benzene-type CH by N does not result in a large change in aromaticity. This is in agreement with the predictions of perturbation molecular orbital (PMO) theory applied to six-membered rings <B-1969MI2242>.

Table 29 Resonance energy indices estimated by various methods

Compounds	*ERE (kJ mol^{-1})*	*DRE (kJ mol^{-1})*[a]	*DRE' (kJ mol^{-1})*[a]	*HSRE (β)*[b]	*TRE (β)*[c]
Benzene	28.5[d]	15.77	16.07	0.065	0.046
Pyridine	17.0[d]	16.12	17.24	0.058	0.038
Pyridazine	8.7[d]	–	–	–	–
Pyrimidine	5.7[d]	14.10	15.06	0.049	0.032
Pyrazine	5.7[d]	11.92	16.74	0.049	0.022
1,3,5-Triazine	–	–	13.93	0.040	–
Naphthalene	–	14.06	14.02	–	–
Quinoline	19.8[e]	13.81	14.14	0.052	0.036
Isoquinoline	–	14.27	15.27	0.051	0.033
Quinoxaline	–	11.76	13.39	–	–
Acridine	–	12.3[f]	–	–	–

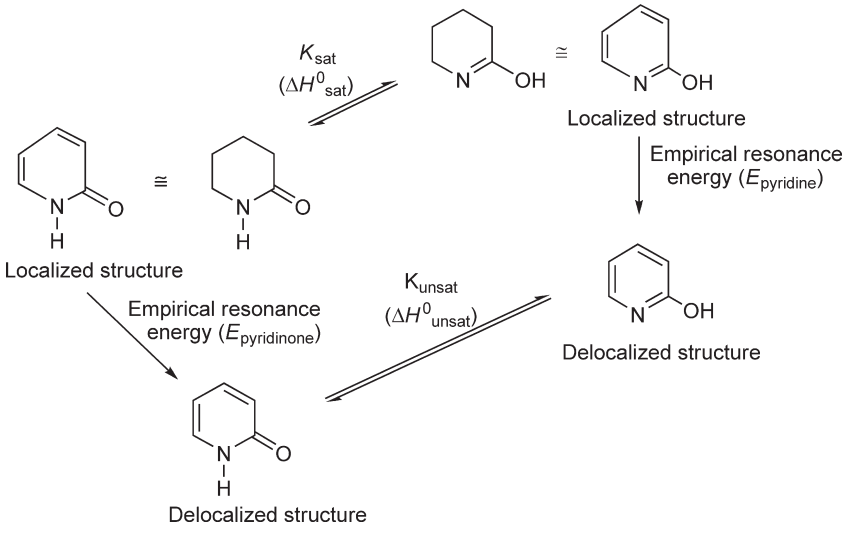
[a]<2001CRV1421>.
[b]<1975T295>.
[c]<1993AHC(56)303>.
[d]From bonding data given in G.W.Wheland, 'Resonance in Organic Chemistry', Wiley, New York, 1955, p. 275.
[e]Derived from heat of combustion <1949CB358, 1951CB916>.
[f]<1970TCA235>.

It is important to note, however, that these predictions and conclusions do not extend to five-membered rings which have a less uniform electron distribution.

2.2.4.2.2.2 From equilibria. A study of equilibria can be used to estimate the relative contributions of aromaticity to equilibrating tautomers by relating their thermodynamic data to that of the corresponding saturated derivatives. This is illustrated by the relationship between the pyridine and pyridone tautomers shown in **Scheme 8**. In this way, 2-pyridone and 4-pyridone are calculated to be ca. 30 kJ mol^{-1} less aromatic than the hydroxypyridines <2001CRV1421>. In the quinolones the difference in aromaticity between the two forms is less. The precise degree of aromatic character possessed by 2- and 4-pyranone is not settled; various methods of estimation give different values.

2.2.4.2.3 Structural criteria

Cyclic π-electron conjugation in aromatic carbocycles equalizes the lengths of the ring bonds. On the substitution of a ring carbon atom by a heteroatom, the even distribution of π-electron density becomes distorted, conjugation is partially



Scheme 8 Estimation of the aromaticity of 2-pyridone using tautomeric equilibrium constants.

disturbed, and bond lengths deviate from the optimum aromatic values. The extent of such deviations can be treated statistically to give a measure of the aromaticity of heterocycles. Several structural indices based on bond lengths and bond orders have been introduced. The two most widely used are the harmonic oscillator model of aromaticity (HOMA) index and the Bird aromaticity indices (I_5 and I_6). In both cases the indices are preferably calculated from experimental geometries but, alternatively, geometries can be calculated using accurate MO calculations.

HOMA is a geometry-based index that is a function of (1) the change in mean bond length relative to the optimal aromatic value and (2) the change in bond length alternation. An increase in both properties is indicative of a decrease in aromaticity <2004PCP249>. HOMA values for selected six-membered heterocycles are shown in **Table 30**. All the azines are indicated to have a high degree of aromatic character. The very high value for 1,3,5-triazine (and also 1,2,4,5-tetrazine) may be partly due to the symmetry of the molecule. Some decrease in the index is associated with adjacent nitrogen atoms and this may partly be due to lone pair interactions. The pyridinium ring shows a small loss of aromaticity relative to pyridine and this can be attributed to the effect of charge on the geometry. The pyrylium ring shows much lower aromaticity.

The Bird index (I_6 for six-membered rings) relates aromaticity to bond order and is a function of the individual bond orders and the arithmetic mean <1986T89>. **Table 30** shows representative values. Like the HOMA index, the I_6 index for the azines classifies them as highly aromatic in character and, again, the aromaticity of the symmetrical molecules is probably overestimated. Allowing for this, aromaticity appears to decrease as the number of pyridine-type nitrogen atoms increases. Surprisingly, the pyridinium ring index is much lower than that of pyridine and quite close to that of pyrylium. However, 2-pyridone (59.0) has a reasonable degree of aromaticity relative to the tautomeric 2-hydroxypyridine (81.0) and is significantly more aromatic than 2-pyrone (32.9). The low aromaticity index of 2-hydroxypyridine compared to pyridine may arise from hydrogen bonding in the crystal. Accurate MO calculated geometries may be a better source of data for these indices.

2.2.4.2.4 Magnetic criteria

All magnetic criteria of aromaticity are based on the ring currents that are induced in conjugated cyclic molecules by external magnetic fields. In particular, ring currents are manifested in the anisotropy and the exaltation of diamagnetic susceptibility of aromatic rings, and in the deshielding of protons outside the conjugated ring and shielding of protons within the conjugated ring.

Magnetic susceptibility anisotropy has been used to estimate relative aromaticities of some azines <1977JOC897>. If the extent of π-electron delocalization for benzene is taken as 1.0, the corresponding values for azines are: pyridine 0.7, pyridazine 0.7, pyrimidine 0.5, and 1,3,5-triazine 0.3. Another quantitative magnetic index is the exaltation of the total magnetic susceptibility (Λ). All aromatic systems reveal large Λ values, whereas for nonaromatic compounds Λ is close to zero and it is assumed that aromaticity increases with Λ. For six-membered monocycles the following values of Λ have been reported (in units of $cm^3\ mol^{-1} \times -10^6$): benzene (17.9), pyridine (18.3), pyridazine (8.7), pyrimidine (18.2), pyrazine (12.7), 1-ethyl-2-pyridone (13.0), and 1,3,5-triazine (19.0).

Proton chemical shifts are also a potential index of aromaticity. Thus, in pyrazine **7** the protons resonate at $\delta = 8.6$ ppm, whereas in its antiaromatic **162** and nonaromatic **163** derivatives the double bond protons show signals at 4.64 and 5.38 ppm, respectively <1983AGE171>. There is qualitative agreement with the ring current influencing

Table 30 HOMA and Bird I_6 structural indices of aromaticity

Compound	*HOMA*[a]	I_6[b]	*Compound*	*HOMA*[a]	I_6[b]
Benzene **1**	1.000	100	Pyridinium **2**	0.973	66.7
Pyridine **4**	0.998	85.7	Pyridine 1-oxide **54**	–	74.4
Pyridazine **5**	0.955	78.9	Pyrylium **57**	0.582	65.8
Pyrimidine **6**	0.999	84.3	Thiinium **58**	0.829	–
Pyrazine **7**	1.000	88.8	2-Pyridone	–	59.0
1,2,3-Triazine **8**	0.982	76.9	2-Hydroxpyridine	–	81.0
1,2,4-Triazine **9**	0.791	86.1	Pyran-2-one **84**	–	32.9
1,3,5-Triazine **10**	1.029	100.0	Phosphinine **104**	0.924	74.1
1,2,4,5-Tetrazine **13**	0.962	97.8	Arsinine **106**	–	66.9

In some cases indices are derived from substituted derivatives.
[a]<1996T10255>.
[b]<1986T89>.

shielding and deshielding but attempts to relate proton chemical shifts to the relative aromaticity of different heteroaromatic systems usually fail. This is understandable because the shielding constant of a nucleus A is determined not only by the contribution from the ring current but also by contributions from the diamagnetic and paramagnetic currents induced in the atom A itself and diamagnetic and paramagnetic currents induced in the adjacent atoms.

A relatively recent introduction for evaluating magnetic criteria for aromaticity is the NICS value. The NICS value is the negative of the absolute magnetic shielding of a system. It is a theoretical concept and NICS values are calculated using high-level MO calculations at or above the center of the ring. NICS values are discussed and tabulated in Section 2.2.2.2.2. Although NICS values may be indicative of a ring current they do not necessarily predict the stability associated with aromatic compounds. Thus the heterobenzenes pyridine **4**, phosphinine **105**, arsinine **106**, stibinine **107**, and bismuthinine **108** have NICS values similar to benzene (**Table 3**) but their stabilities decrease along the series. However, these NICS values are consistent with the ^{1}H chemical shifts of the γ-protons, which are remote from the heteroatom, and which show evidence of a large ring current comparable to that of benzene <CHEC-II(5.13.3.2.3)673>.

2.2.4.3 Conformations of Partially- and Fully-Reduced Rings

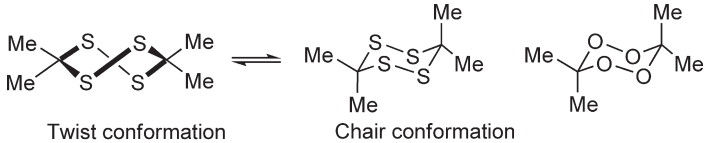
Hetero-substituted cyclohexenes, e.g., 3,6-dihydro-2*H*-pyran, 3,6-dihydro-2*H*-thiin, and 3,6-dihydro-1,2-dioxin, exist in half-chair conformations (see Section 2.2.3.2).

The fully-saturated six-membered heterocycles share with cyclohexane the property of being able to adopt one or more conformations that are virtually free of torsion- or bond-angle strain. Hetero-substituted cyclohexanes in which one or more CH_2 groups is replaced by O or NR almost invariably exist predominantly in chair conformations (see Section 2.2.3.2). Inclusion of a sulfur atom changes the geometry more significantly, because of the different bond lengths and angles, but again the overall shapes of the molecules are generally chair-like. At 180 K 1,3-oxathiane is predominantly in the chair conformation with 8–9% of the 2,5-twist conformation detectable <CHEC-III(8.11.3.2.2) 760>.

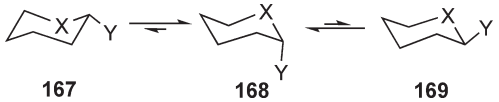
X-ray studies have shown that 3,3,6,6-tetramethyl-1,2,4,5-tetrathiane exists in the twist conformation **164** in the solid state. According to *ab initio* calculations at the HF/6-31G*, MP2/6-31G*, and B3LYP/6-31G* levels the twist conformation **164** is 4 kJ mol^{-1} more stable than the chair conformation **165** and the calculated strain energy for twist-to-chair conversion is 61.1 kJ mol^{-1} (**Scheme 9**). The chair conformation of the parent 1,2,4,5-tetrathiane was calculated to be 10.7 kJ mol^{-1} more stable than the twist form <2004PS2015>. X-ray crystallography has confirmed that in the solid state 3,3,6,6-tetramethyl-1,2,4,5-tetroxane adopts a chair conformation **166** <CHEC-III(9.14.4.5)750>.

In addition to conformations adopted by the heterocyclic rings, considerable attention has also been paid to the conformational preferences (axial or equatorial) of substituents, both on carbon and on the heteroatoms (nitrogen and sulfur). The following points should be noted:

1. An electronegative substituent adjacent to a ring oxygen or sulfur atom shows a preference for the axial orientation. This is known as the 'anomeric effect,' and is summarized in **Scheme 10**, where X = O or S and Y is an electronegative substituent, e.g., halogen, RO, or RCO_2. The preferred axial conformation **168** can be formed either by conformational inversion (**167** ⇄ **168**) or by configurational inversion (**168** ⇄ **169**) <COC(1)856>, which occurs via ring-chain tautomerism (Section 2.2.5.2). The stabilization of the axial conformation **168** is interpreted in terms of an energetically favorable



Scheme 9



Scheme 10 The anomeric effect.

interaction ($n_X \rightarrow \sigma^*_{C-Y}$) between a lone pair on atom X (n_X) and the empty antibonding orbital (σ^*_{C-Y}) of the C–Y bond. For examples of the anomeric effect see Section 2.2.3.1.

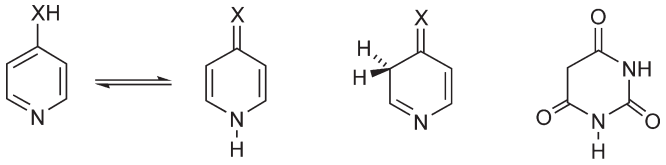
2. Sulfoxide groups tend to occupy an axial rather than an equatorial position in thiane *S*-oxides.
3. Since a nitrogen freely undergoes inversion, an N-substituent can exchange between axial and equatorial positions without interchange of the rest of the ring atoms. The inversion at nitrogen is usually faster than ring inversion, unless an electronegative element is attached to it.
4. The nitrogen lone pair is sterically undemanding and so usually occupies an axial site predominantly.

2.2.5 Tautomerism

2.2.5.1 Prototropic Tautomerism

2.2.5.1.1 Prototropic tautomerism of fully-conjugated rings

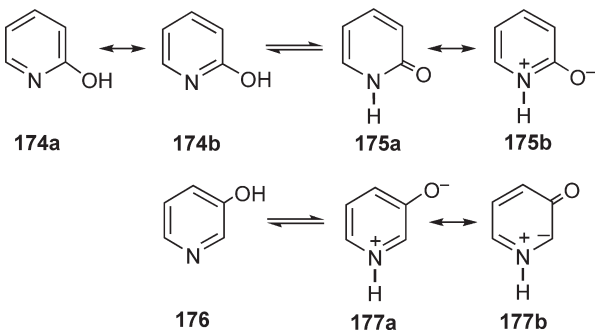
This type of tautomerism occurs by a proton transfer and transforms a substituted azine, e.g., **170**, into an isomer with exocyclic conjugation, e.g., **171**. Transfer of a proton to a ring carbon atom, e.g., **172**, is rarer, due to loss of aromaticity, but can occur in polyhydroxyazines (e.g., barbituric acid **173**). Tautomerism in six-membered heterocycles has been reviewed <2006AHC(91)1>. **Table 31** summarizes the tautomeric equilibria of monosubstituted azines and their benzo derivatives for dilute solutions in water at ca. 20 °C.



170 **171** **172** **173**

2.2.5.1.1.1 Oxo-hydroxy tautomerism of azines. The resonance hybrids **174a,b** and **175a,b** are the only forms that make important contributions to the equilibrating tautomers **174** and **175** (**Scheme 11**). Since positive charge prefers tetravalent nitrogen and negative charge prefers oxygen, the charge-separated structure **175b**, which is also associated with an aromatic sextet, makes a significant contribution to the overall structure of 2-pyridone. A similar resonance hybrid contributes to 4-pyridone. When the exocyclic oxygen atom is replaced by less electronegative atoms, such as =NR in imine tautomers or $=CR_2$ in methylene tautomers, the contribution of forms corresponding to resonance hybrid **175b** is considerably less, and the amino- and methylpyridine tautomers are favored in most instances (see **Table 31**).

In aqueous solution 3-hydroxypyridine **176** equilibrates with the mesomeric betaine **177a** for which no uncharged structure can be written. Since these pyridinium-3-olates **177a** undergo 1,3-dipolar cycloadditions, it is reasonable to assume that there is also a contribution of the 'one' form **177b** to the overall structure.

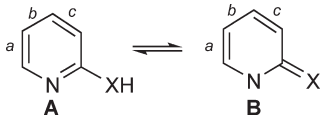
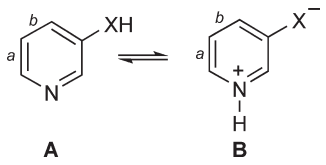
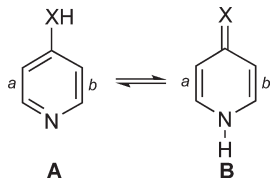
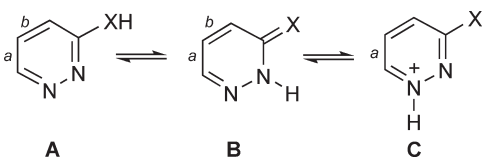
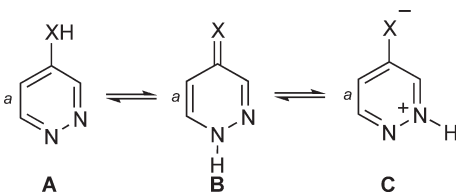
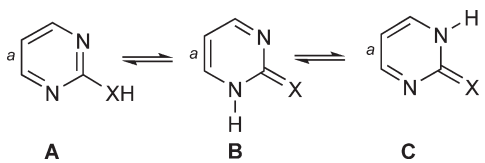
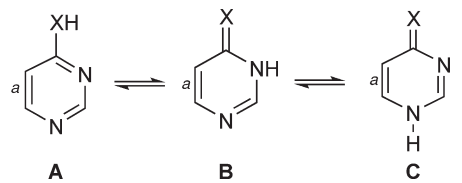
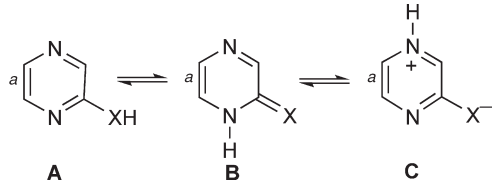


174a **174b** **175a** **175b**

176 **177a** **177b**

Scheme 11 Prototropic tautomerism of hydroxypyridines.

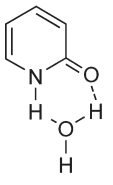
Table 31 Tautomeric equilibria of monofunctional azines and benzazines

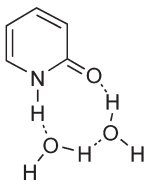
	X =	*O*	*S*	*NH*	*CH_2*
	Parent	B(3.0)	B(4.7)	A(ca. 6)	A(13.3)
	Benzo[*a*]	B(3.9)	B(5.1)	A(4.3)	A(9.4)
	Benzo[*b*]	B(low)	B(3.0)	–	–
	Benzo[*c*]	B(4.8)	B(5.8)	A(3.8)	A(9.5)
	Dibenzo[*a*,*c*]	B(3.9)	–	A(2.8)	A(high)
	Parent	B(0.1)	B(2.2)	A	A
	Benzo[*a*]	A(ca. 1)	B(1.5)	A	A
	Benzo[*b*]	B(ca. 0.5)	–	A	A
	Parent	B(3.3)	B(4.6)	A(8.7)	A(13.4)
	Benzo[*a*]	B(4.2)	B(5.0)	A(3.2)	A
	Dibenzo[*a*,*b*]	B(7.0)	B(high)	A	A
	Parent	B(4.3)	B	A	–
	Benzo[*a*]	B(2.6)	–	A(8.3 vs. B)	–
	Benzo[*b*]	B	B	A	–
	Parent	B(2.6)	B	A	–
	Benzo[*a*]	B(3.6)	B	A(4.1 vs. B)	–
	Parent	B≡C	B≡C	A(6 vs. B)	–
	Benzo[*a*]	B	–	–	–
	Parent	B(0.4 vs. C)	B	A(6 vs. B/C)	–
	Benzo[*a*]	B(0.85 vs. C)	B	A	–
	Parent	B	B	A	–
	Benzo[*a*]	B(>1.6 vs. A)	B	A	–

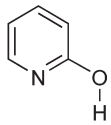
From <1976AHC(S1)206>; results are expressed as log ([major form]/[minor form]); when a form is simply indicated, no quantitative data are available on the equilibrium.

Polar solvents stabilize polar tautomers. In the vapor phase at equilibrium both 2- and 4-hydroxypyridines exist as the pyridine rather than as the pyridone. 3-Hydroxypyridine, which in water is an approximate 1:1 mixture of OH and NH forms, also exists as the OH form in the vapor phase. However, even in the vapor phase, 2- and 4-quinolones remain predominantly in the NH (oxo) forms. Hydrocarbons or other solvents of very low polarity might be expected to give results similar to those in the vapor phase, but intermolecular association by hydrogen bonding often leads to a considerably greater proportion of polar oxo tautomers.

Aqueous solvation is of particular importance and complexity. Hydrogen bonding in 2-pyridone–H_2O and 2-pyridone–$2H_2O$ has been investigated by rotationally resolved fluorescence excitation spectra in both the S_0 and S_1 electronic states <1993JA9708>. The monohydrate shows an increased contribution of the ionic form over the anhydrous species. The monohydrate contains two nonlinear hydrogen bonds with the amine hydrogen and the carbonyl oxygen **178**. The dihydrated species shows stronger hydrogen bonding **179**.


178

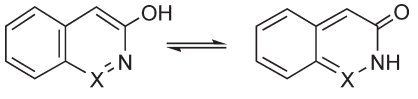

179


180

Experimental assessments of the concentration of the minor hydroxy tautomer of 2-pyridone and substituted derivatives in cyclohexane and acetonitrile solution have been made using fluorescence spectroscopy <1985J(P2) 1423>. For the parent compound, the hydroxypyridine component in cyclohexane is estimated to be 4% and in acetonitrile 1.2%; the higher proportion of the hydroxy form in the former solvent is maintained over a range of substituted pyridones. *Ab initio* calculations on 4-hydroxypyridine, the minor tautomer in aqueous solution, included 92 water molecules in the calculation and give a detailed picture of the solvated molecule <1985JA7569>. Microwave spectroscopy not only gives an accurate estimation of the 2-hydroxypyridine/ 2-pyridone ratio (3:1) in the gas phase but also shows that hydroxypyridine is predominantly in the (*Z*) configuration **180** <1993JPC46>.

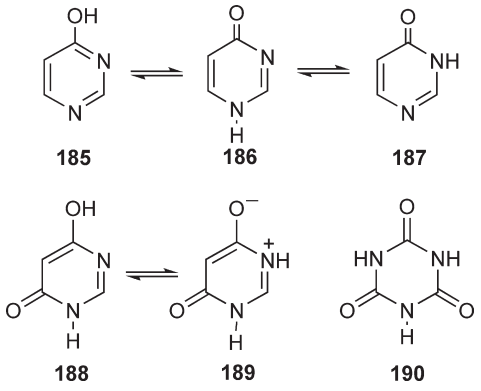
Substituents also influence the position of equilibrium. UV-Vis spectroscopy has been used to determine the tautomeric equilibria of substituted 2-hydroxypyridines. Electron-donating substituents favor the pyridone and electron-withdrawing substituents favor the hydroxypyridine <2002ARK(xi)198>. The effects of substituents on tautomeric equilibria can usually be predicted from general chemical principles. Thus, an electron-withdrawing group adjacent to a ring nitrogen atom tends to decrease its basicity, and so a tautomer with a proton at that nitrogen atom is destabilized, and the equilibrium displaced toward the isomer. Substituents may also favor one tautomer by intramolecular hydrogen bonding.

Benzo fusion to a heterocyclic ring involved in tautomerism has the effect of steering the equilibrium in the direction that tends to retain the full aromaticity of the benzene ring. Thus, while the 3-hydroxyisoquinoline/ 3-isoquinolone equilibrium (**181** ⇄ **182**) and that of the cinnoline derivatives (**183** ⇄ **184**) favor the oxo forms, the proportion of hydroxy tautomers is considerably greater than in the corresponding unfused systems. In contrast, benzo fusion in 2- and 4-quinolone and in 1-isoquinolone retains full aromaticity of the benzo ring, and the proportion of the hydroxy tautomers is less.


181: X = CH
183: X = N

182: X = CH
184: X = N

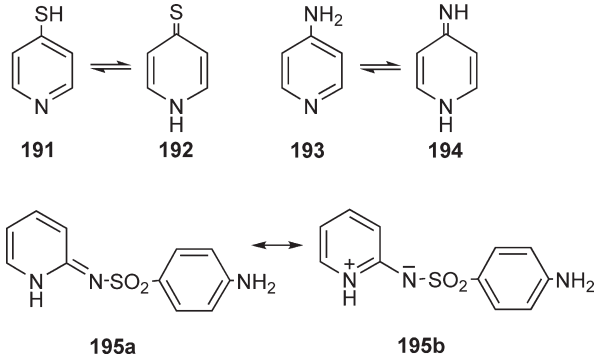
Extra nitrogen heteroatoms in the ring provide alternative sites for the tautomeric proton (**Scheme 12**). 4-Hydroxypyrimidine, for example, can exist as the hydroxy tautomer **185** or as the 1*H*- and 3*H*-pyrimidones **186** and **187**. The general tendency in compounds of this type is for the isomers with amide (or ester) groups, e.g., **187**, to be preferred over the vinylogous amide (or ester), e.g., **186**. In compounds with several potential hydroxy groups, e.g., barbituric acid **173**, nonaromatic structures with interrupted cyclic conjugation are commonly favored. In polar media the cross-conjugated betaine tautomer **189**, with two CONH fragments, predominates over the hydroxy tautomer **188**. Cyanuric acid has been shown to exist as the trioxo structure **190** by UV and X-ray analysis.



Scheme 12

2.2.5.1.1.2 Thiono–mercapto and amino–imino tautomerism of azines. In the same heterocyclic systems, the stability of thiols with respect to the corresponding thione form is considerably higher than hydroxy derivatives with respect to their oxo forms. In the gas phase 2- and 4-mercaptopyridine are the major tautomers, e.g., **191**. ^{15}N NMR spectroscopy is useful for estimating the tautomeric composition of mercaptopyridines in solution. 2-Mercaptopyridine in acetone or methanol and 4-mercaptopyridine **191** in methanol or acetone/DMSO were estimated to be ca. 95% in the thione form, e.g., **192**. This solvent effect can be attributed to the polarity of the thione tautomers <2006AHC(91)1>.

In simple amino–imino systems, e.g., **193** ⇄ **194**, there is little evidence of the imino form in both the gas and solution phases. Imino tautomers can be predominant if the exocyclic nitrogen atom carries a suitable substituent. This is the case for solutions of compound **195** (sulfapyridine, M&B 693) <1975J(P2)522> which was one of the earliest antibacterial drugs. Here the sulfone substituent effectively stabilizes the resonance hybrid **195b**. Alternatively, one can regard the N-substituent as making the nitrogen atom more electronegative and therefore more like oxygen, and thus more like a pyridone. In some systems hydrogen bonding with a substituent can stabilize the imino form <2006AHC(91)1>.

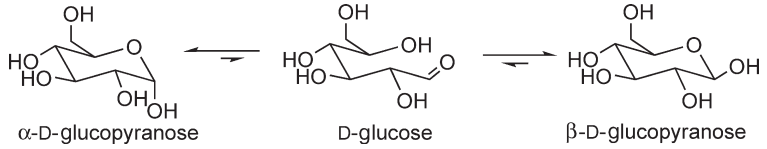


2.2.5.1.2 Prototropic tautomerism of rings without cyclic conjugation

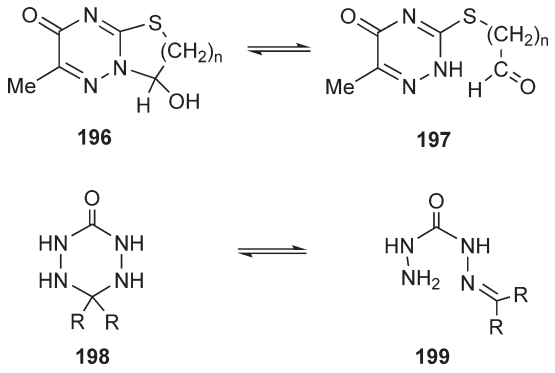
There are many possibilities for tautomerism in partially-saturated derivatives. Dihydropyridines can exist in several tautomeric forms, e.g., **37** and **38**, of which the 1,4-dihydro isomers are usually the most stable. Similarly, dihydro-1,2,4,5-tetrazines have been formulated as the 1,2-, 1,4-, 1,6- and 3,6-dihydro structures but the 1,4-dihydro structure is probably the most stable. In contrast, 2*H*-pyrans, e.g., **67**, are more stable than 4*H*-pyrans, e.g., **68**. Of the five possible dihydropyrimidines most known derivatives have 1,2-, 1,4-, or 1,6-dihydro structures of which the 1,2-structure is calculated to be the most stable <1985AHC(38)1>.

2.2.5.2 Ring-Chain Tautomerism

In the examples discussed in Section 2.2.5.1 proton transfer occurs without cleavage of the heterocyclic ring. When proton transfer is associated with ring cleavage or ring formation the process is referred to as ring-chain tautomerism. This type of equilibration is often associated with long-chain aldehydes with a suitably located OH or NH group. A classic example is the interconversion (mutarotation) of α- and β-D-glucopyranose via acyclic D-glucose (**Scheme 13**). In a similar way the 1,2,4-triazinones **196** and the 1,2,4,5-tetrazin-3-ones **198** equilibrate with the aldehydes **197** and the imines **199**, respectively (**Scheme 14**).



Scheme 13 Mutarotation of D-glucopyranose *via* ring-chain tautomerism.



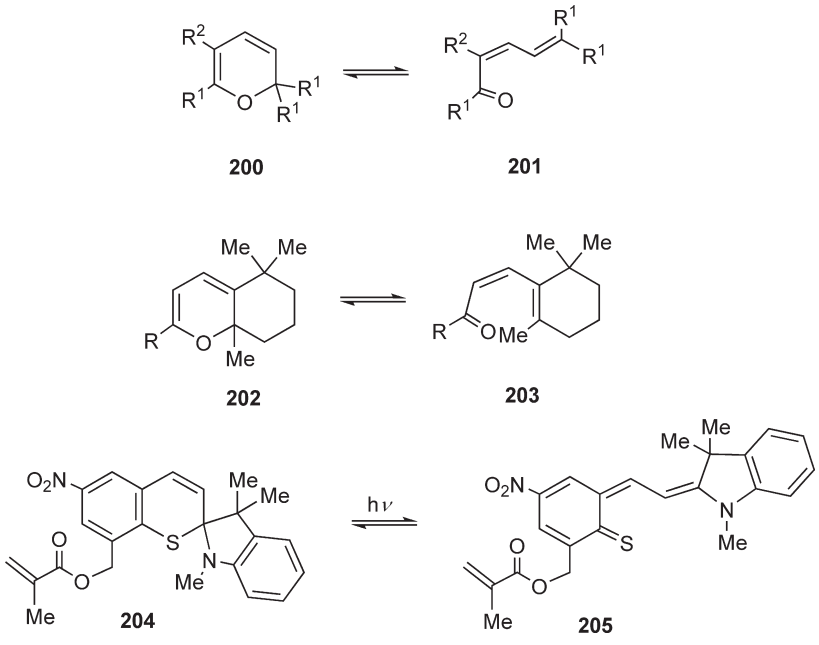
Scheme 14

2.2.5.3 Valence Tautomerism

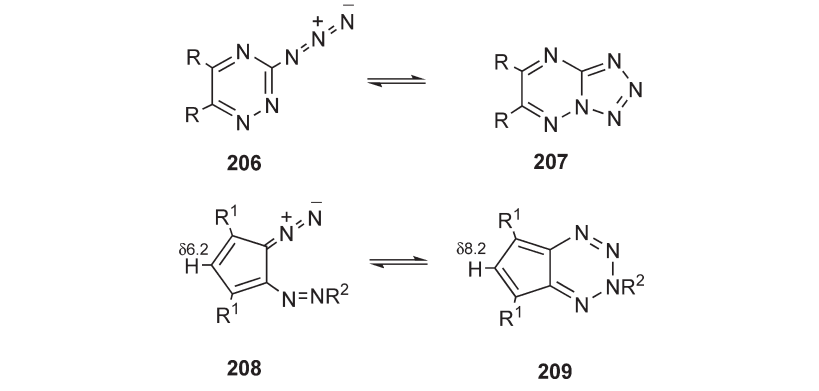
Valence tautomerism refers to the interconversion of isomers without any accompanying rearrangement including proton transfer. Heterocyclic examples are essentially electrocyclic reactions (**Scheme 15**). If one of the isomers is colored and the position of the equilibrium can be changed by heat or light, the heterocycles can have useful thermochromic or photochromic applications.

2*H*-Pyran **200** ($R^1 = R^2 = H$) exists only as its acyclic valence tautomer but 5-acetyl-2,2,6-trimethylpyran **200** ($R^1 = Me$, $R^2 = Ac$) is in equilibrium with only ~35% of the valence tautomer **201** ($R^1 = Me$, $R^2 = Ac$) at 30 °C. The equilibrium of the bicyclic derivatives **202** with the ketone isomers **203** is influenced by solvent and temperature. In tetrachloroethene only 9% of the open-chain form is present at 30 °C but this rises to 40% at 113 °C <1981T1571>. Valence tautomerism of 2*H*-pyran derivatives is the basis of some commercial photochromic materials. Similar properties are shown by 2*H*-thiin derivatives such as the photochromic compound **204**, which forms the thione **205** upon irradiation.

Polyaza heterocycles can sometimes equilibrate with azides and diazo derivatives and this is illustrated by the equilibria shown in **Scheme 16**. Thus, 3-azido-1,2,4-triazines **206** exist predominantly as the tetrazolotriazines **207**. The position of the equilibrium **208** ⇄ **209** can be determined by monitoring the chemical shifts of the H(6) protons (**Scheme 16**) <CHEC-III(9.13.3.2)724>.



Scheme 15 Valence tautomerism of 2*H*-pyrans and 2*H*-thiins.

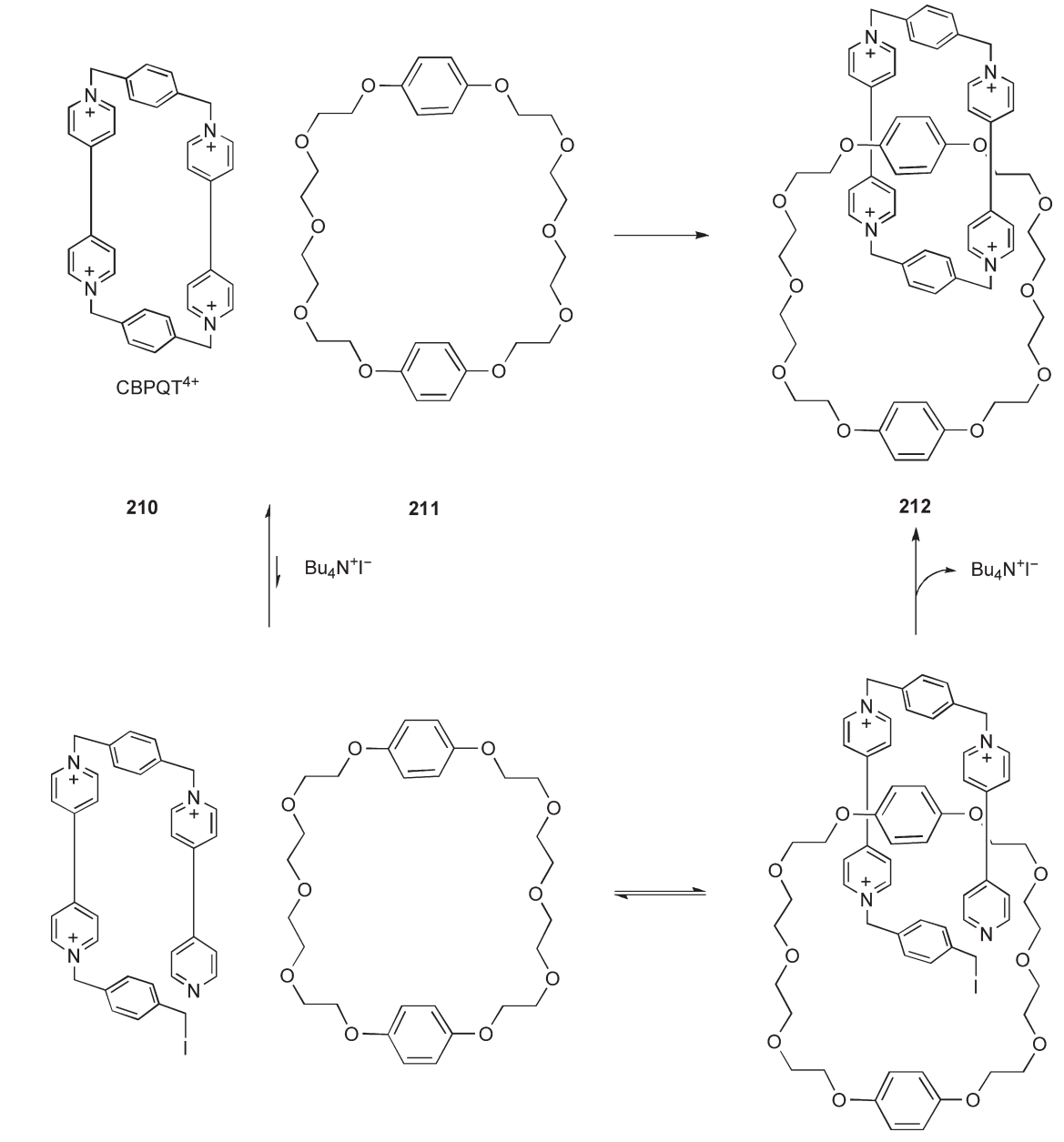


Scheme 16

2.2.6 Supramolecular Structures

The π-electron-deficient pyridinium ring has played an important role in template-directed synthesis in which the interaction of a π-electron acceptor and a π-electron donor facilitate self-assembly. This has led to the construction of a variety of supramolecular assemblies including catenanes (linked rings) and rotaxanes (wheel and axle) <CHEC-III (7.01.3)11, CHEC-III(14.12)667>.

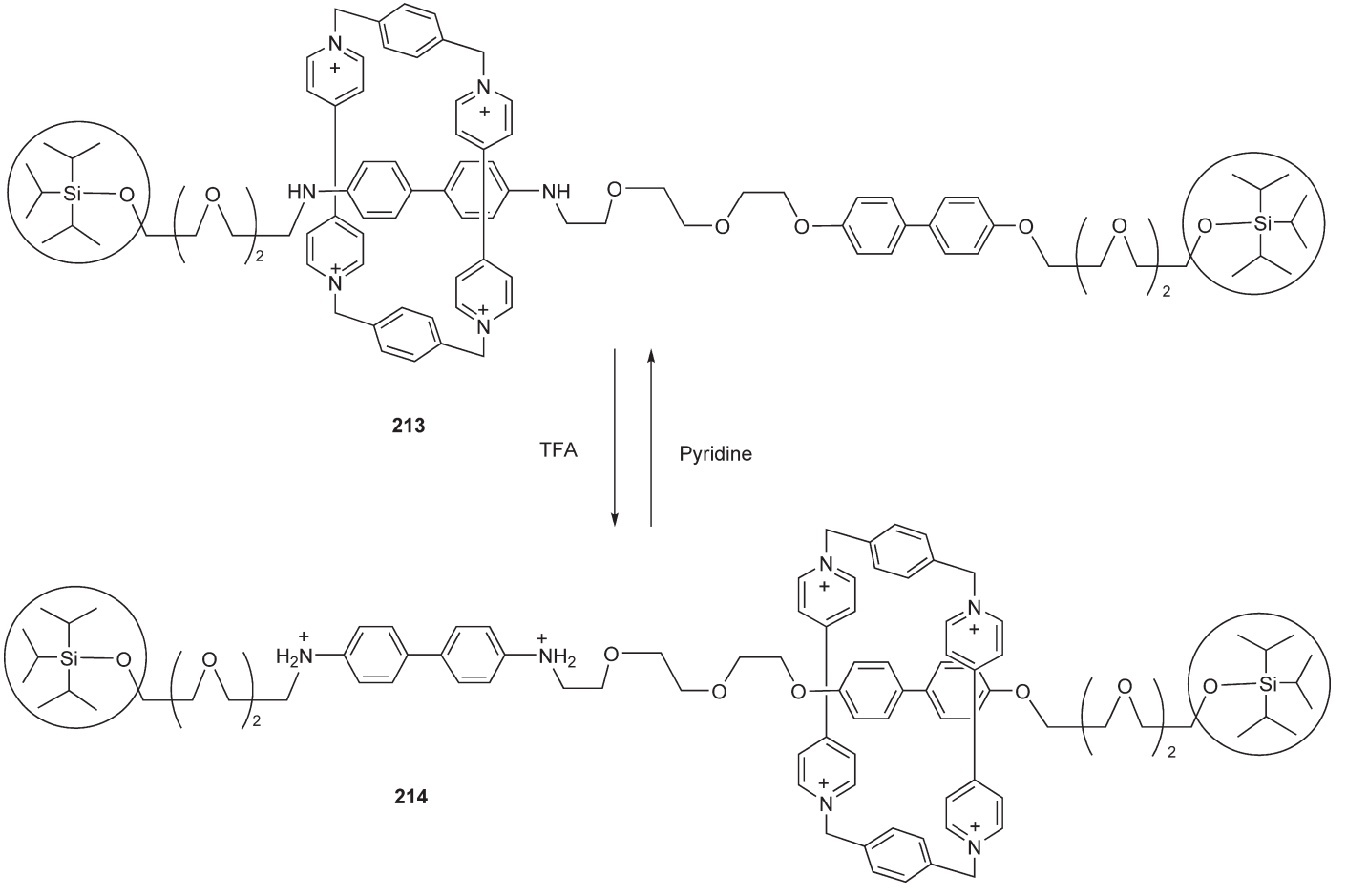
The cyclobis(paraquat-*p*-phenylene) tetracation ($CBPQT^{4+}$) **210**, and its precursors, have proved to be a particularly useful electron-deficient templates for assembling supramolecular structures. For example, the donor–acceptor [2]catenane **212** can be constructed by transient ring opening of $CBPQT^{4+}$ **210**, donor–acceptor-induced threading of the pyridinium π-acceptor through the crown ether π-donor **211** and ring closure (**Scheme 17**) <2008T8231>.



Scheme 17

In a similar manner donor–acceptor [2]rotaxanes such as the derivative **213** can be assembled. This example has been described as a molecular switch. The $CBPQT^{4+}$ ring can occupy two positions as shown in the translational isomers **213** and **214** (**Scheme 18**). At equilibrium in acetonitrile solution the $CBPQT^{4+}$ ring mainly occupies the benzidine site (84%) **213**. Protonation (or electrochemical oxidation) eliminates the favorable $CBPQT^{4+}$/benzidine donor–acceptor interaction and results in preferential occupation of the biphenol site **214** <2008T8231>.

For further examples see Chapter 14.12 of CHEC-III <CHEC-III(14.12)667>.



Scheme 18

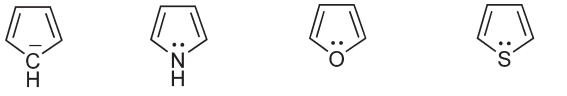
2.3 Structure of Five-Membered Rings with One Heteroatom

2.3.1 Survey of Possible Structures and Nomenclature

2.3.1.1 Rings Without Exocyclic Conjugation

2.3.1.1.1 Fully-conjugated rings

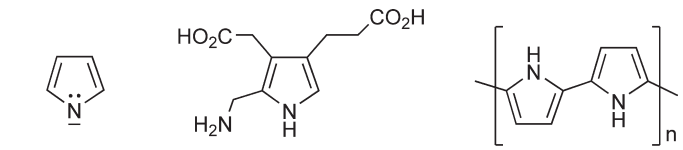
2.3.1.1.1.1 Monocyclic systems. Since N and C^- are isoelectronic, the simplest nitrogen analogue of the aromatic cyclopentadiene anion **1** is pyrrole **2**. The corresponding oxygen and sulfur analogues are furan **3** and thiophene **4**. In each of the aromatic heterocycles **2**–**4**, a lone pair of electrons on the heteroatom is part of the aromatic sextet. It should be noted that furan and thiophene have a second lone pair that is not part of the aromatic sextet. The substituents derived from the rings **2**–**3** are named pyrryl, furyl, and thienyl. Deprotonation of pyrrole **2** gives the pyrryl anion **5**, which retains an aromatic sextet of electrons.



1 **2**: pyrrole **3**: furan **4**: thiophene

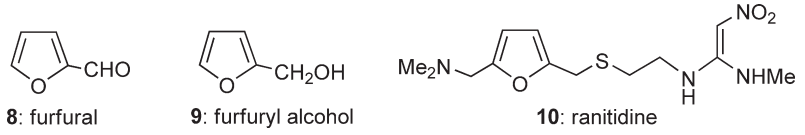
Pyrrole occurs in bone oil and imparts a bright red colour to pine wood moistened with mineral acid; this characteristic behaviour led to its discovery and is used as a qualitative test for pyrrole derivatives. The bile pigments are metabolic products having chains of four pyrrole rings. Their precursors are porphyrins, which include the blood pigments (haem), the chlorophylls, and vitamin B_{12}, and consist of four pyrrole units joined in a macro ring (Section 2.3.1.2). The trisubstituted pyrrole **6** (porphobilinogen) is the biosynthetic precursor of haem and chlorophyll.

There is much current interest in conducting polymers and polypyrrole **7** is by far the most extensively studied conducting polymer, since monomer pyrrole is easily oxidized, water soluble, and commercially available, and possesses environmental stability, good redox properties, and high electrical conductivity. The literature on polypyrrole applications is vast. It is promising for application in batteries, supercapacitors, electrochemical (bio)sensors, conductive textiles and fabrics, mechanical actuators, electromagnetic interference shielding, and antistatic coating <2000SCI1540, CHEC-III(3.04.2.1)354>.



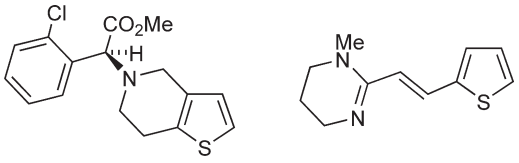
5: pyrryl anion **6**: porphobilinogen **7**: polypyrrole

Furan-2-carbaldehyde **8** is commonly referred to as furfural. It is produced on a large scale by the action of acids on sugars and is a commercially important raw material used in furfural-phenol resins and as a synthetic intermediate <CHEC-I(3.12.5)705>. The 2-furylmethyl radical is called furfuryl and, for example, the alcohol **9** is commonly known as furfuryl alcohol. The furan derivative **10** (ranitidine) was one of the first H_2-antagonists for the treatment of gastric ulcers and a major contribution to modern medicine.



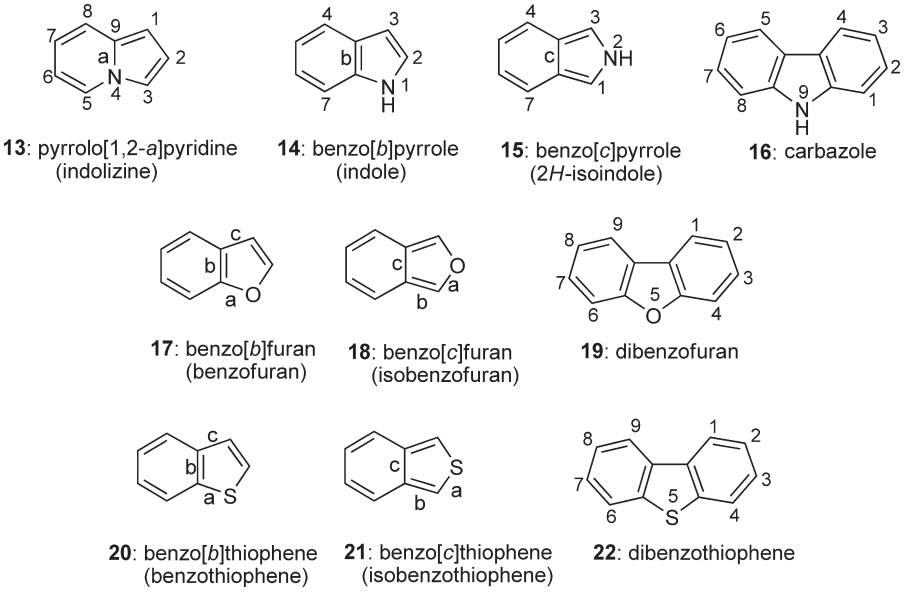
8: furfural **9**: furfuryl alcohol **10**: ranitidine

Thiophene and its homologues occur in coal-tar benzene, shale oil, and crude petroleum. They show the indophenine test (Section 3.3.1.5.7.2), and the discovery of thiophene followed the observation that pure benzene did not give this test. Thiophene has similar properties to benzene and in medicinal chemistry phenyl substituents are often replaced by thienyl groups. The thiophene derivative **11** (clopidogrel), which is a potent oral antiplatelet agent used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease, was the second best-selling drug in the year ending June 2006 <CHEC-III(3.12.2.2)933>. Pyrantel **12** is an effective anthelmintic that is used in veterinary medicine.



11: clopidogrel **12**: pyrantel

2.3.1.1.1.2 Bicyclic systems. The benzo-fused pyrrole heterocycles **13–15** are analogues of naphthalene with carbazole **16** having an electronic relationship to phenanthrene. The systematic names show the position of the benzenoid ring but the common names indolizine **13**, indole **14**, isoindole **15**, and carbazole **16** (**Figure 1**) are still widely used. The benzo derivatives of furan and thiophene are named in a similar manner, but their common names have largely fallen into disuse. For the benzo[*b*] systems **17** and **20**, the [*b*] is commonly omitted.



13: pyrrolo[1,2-*a*]pyridine (indolizine) **14**: benzo[*b*]pyrrole (indole) **15**: benzo[*c*]pyrrole (2*H*-isoindole) **16**: carbazole

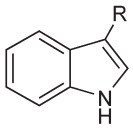
17: benzo[*b*]furan (benzofuran) **18**: benzo[*c*]furan (isobenzofuran) **19**: dibenzofuran

20: benzo[*b*]thiophene (benzothiophene) **21**: benzo[*c*]thiophene (isobenzothiophene) **22**: dibenzothiophene

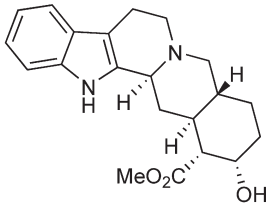
Figure 1 Benzo-fused aromatic heterocycles.

The accepted numbering of the rings is shown in **Figure 1**. Confusion can arise in consulting the literature on indolizine **13** for which differing numbering systems have been used. It should be noted that numbering and lettering in square brackets, e.g., pyrrolo[1,2-*a*]pyridine **13**, refer to the individual rings whereas numbers without square brackets refer to the numbering of the whole system. Note that carbazole **16** is an exception to the IUPAC rules for numbering the other dibenzo heterocycles, e.g., **19**.

The indole ring system **14** is particularly important and occurs widely in nature. Tryptophan **23** is one of the essential amino acids and is found in most proteins. Its metabolites include tryptamine **24**. 3-Indoleacetic acid **25** is an important plant growth hormone. The indole alkaloids, exemplified by yohimbine **26**, are an important family of natural products.

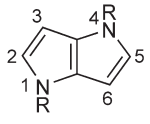


23: tryptophan R = $CH_2CH(NH_2)CO_2H$
24: tryptamine R = $CH_2CH_2NH_2$
25: 3-indoleacetic acid R = CH_2CO_2H

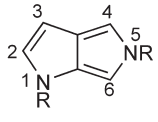


26: yohimbine

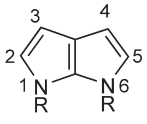
Fusion with other five-membered rings is also well known and these systems are isoconjugate with the heteropentalene dianion. **Figure 2** shows representative examples with names and numbering. Systems with heteroatoms at positions 2 and 5 of the bicyclic system can only be represented by 1,3-dipolar structures, e.g., **30**, and are further examples of conjugated mesomeric betaines (Section 2.2.1.2.2).



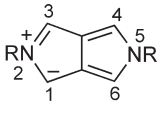
27: pyrrolo[3,2-*b*]pyrroles



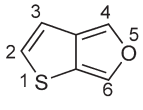
28: pyrrolo[3,4-*b*]pyrroles



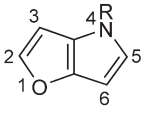
29: pyrrolo[2,3-*b*]pyrroles



30: pyrrolo[3,4-*c*]pyrroles



31: thieno[2,3-*c*]furan

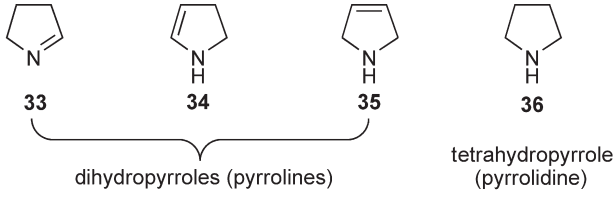


32: furo[3,2-*b*]pyrroles

Figure 2 5,5-Fused aromatic heterocycles.

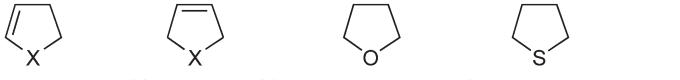
2.3.1.1.2 Rings without cyclic conjugation

Three dihydropyrrole **33–35** and one tetrahydropyrrole **36** ring systems can occur. Trivial names for the dihydropyrroles are Δ^1-, Δ^2-, and Δ^3-pyrroline, where Δ indicates the position of the remaining double bond. Tetrahydropyrroles are known as pyrrolidines. Systematic naming of the reduced rings is illustrated by the following examples: 2,3-dihydrofuran **37** (X = O) and 2,5-dihydrothiophene **38** (X = S). 2,3,4,5-Tetrahydrofuran **39** is the well-known solvent THF. Tetrahydrothiophene **40** has an unpleasant smell and is sometimes used as an odorant in natural gas.



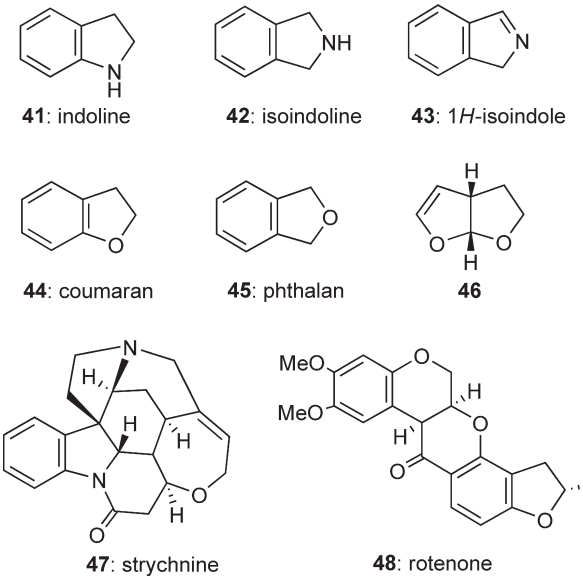
33 **34** **35** dihydropyrroles (pyrrolines)

36 tetrahydropyrrole (pyrrolidine)



37: X = O, S **38**: X = O, S **39**: tetrahydrofuran (THF) **40**: tetrahydrothiophene (thiophane)

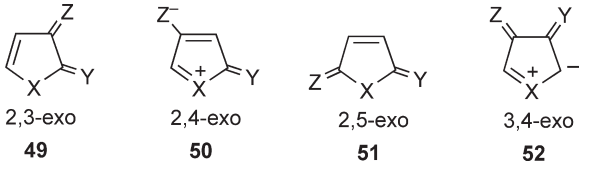
Derivatives of reduced bicyclic systems are also well known. 2,3-Dihydroindole **41** is commonly known as indoline and 1,3-dihydroisoindole **42** is known as isoindoline. It should be noted that 2*H*-isoindole **15** can equilibrate in some solvents with the tautomer 1*H*-isoindole **43**, which lacks cyclic conjugation in the five-membered ring. Derivatives of the reduced benzofurans coumaran **44** and phthalan **45** are also common. The partially-reduced furo[2,3-*b*]furan ring system **46** is found in a large number of natural products including antifeeding agents such as clerodin. The alkaloid strychnine **47** is a 2,3-dihydroindole derivative and the natural insecticide rotenone **48** is a 2,3-dihydrobenzofuran derivative.



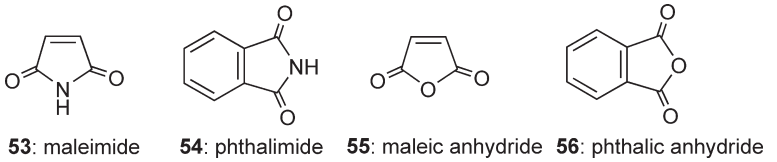
2.3.1.2 Rings with Exocyclic Conjugation

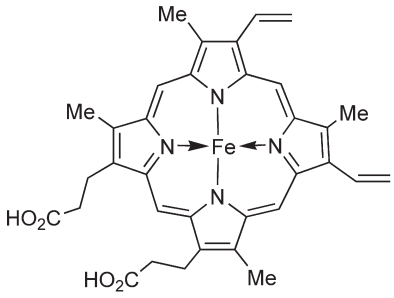
2.3.1.2.1 Fully-conjugated rings

There are four types of fully-conjugated five-membered rings with exocyclic conjugation and these are shown in the general structures **49**–**52**.

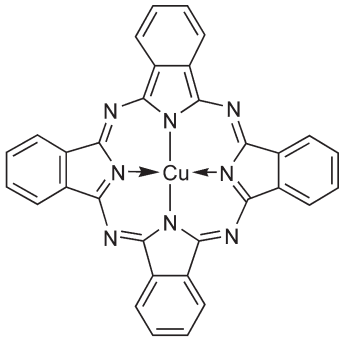


The most common structures of this type are the 2,5-*exo* derivatives **51** of which common examples are maleimide **53**, phthalimide **54**, maleic anhydride **55**, and phthalic anhydride **56**. The structural unit **51** occurs widely and more complex examples are the blood pigment haem **57** and the synthetic phthalocyanine dyes, e.g., **58**.



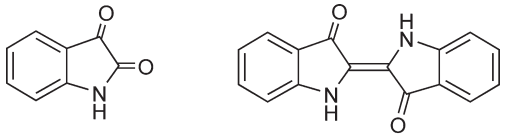


57: haem (blood pigment)



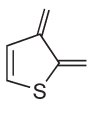
58: monastral blue
(a phthalocyanine pigment)

Systems with 2,3-*exo* conjugation **49** are less common and occur mainly in bicyclic derivatives. Well-known examples are isatin **59** and its derivatives, and the dye indigo **60**, widely used since antiquity and originally obtained from the *O*-glycoside of 3-hydroxyindole, which occurs in some plants. Tyrian purple, a natural dye used since classical times, is 6,6′-dibromoindigo. Monocyclic species, such as 2,3-dihydro-2,3-bis-(methylene) thiophene **61**, can be generated as reactive intermediates and trapped *in situ* <1990TL1491>. Even less common are examples of the 2,4-*exo* and 3,4-*exo* betaines **50** and **52**. The cross-conjugated mesomeric betaines **62** have been prepared by flash vacuum pyrolysis of the appropriate pyridine esters <2000J(P1)401>. The conjugated mesomeric betaines **63** (X = O, S, NR) have been encountered as transient intermediates <1979JOC2667>. They are sometimes formulated as diradicals but are best regarded as 1,3-dipoles with no aromatic stabilization.



59: isatin

60: indigo



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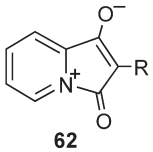


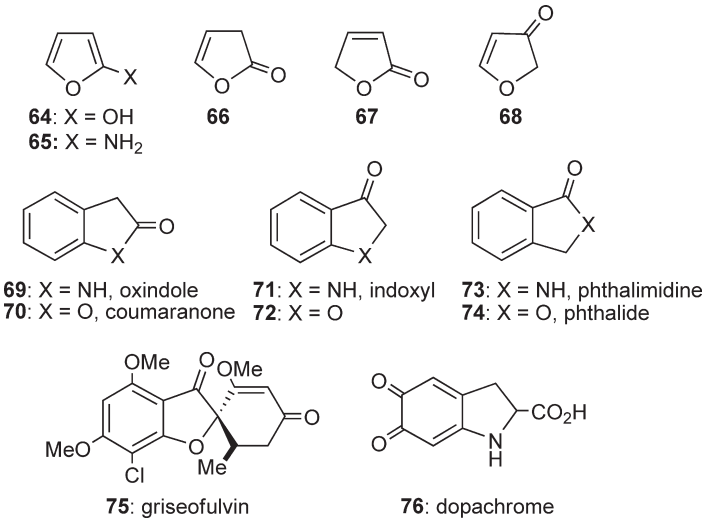
62

63

2.3.1.2.2 Rings without cyclic conjugation

A number of important families of heterocycles belong to this class and many of the important systems are oxo derivatives. 2-Hydroxyfuran **64** exists almost exclusively as the equilibrating 3*H*- and 5*H*-furan-2-one tautomers **66** and **67**. Tautomerism favoring the nonconjugated isomers also occurs in hydroxypyrroles and hydroxythiophenes. Similar behaviour is observed with simple amino derivatives: 2-aminofuran **65** is too unstable to be detected <2006AHC (92)1>. The 3-oxo tautomer **68** is the preferred form of 3-hydroxyfuran.

Bicyclic ring systems that commonly occur are shown in structures **69**–**74**. The antifungal agent griseofulvin **75** contains a 2*H*-benzofuran-3-one fragment **72**. Exocyclic conjugation can also occur on a benzo substituent. Dopachrome **76** is an intermediate in the biosynthesis of the melanin pigments <2005AHC(89)1>.



2.3.2 Theoretical Methods

2.3.2.1 General Trends

The heteroatoms (N, O, and S) in pyrrole **2**, furan **3**, and thiophene **4** contribute two π-electrons to the aromatic sextet and push electron density toward the ring carbons. As a result, the carbon atoms in the ring acquire partial negative charge and pyrrole **2**, furan **3**, and thiophene **4** are described as electron-rich or π-excessive. This contrasts with the azines (e.g., pyridine) (Chapter 2.2) which are electron-poor (π-deficient). Hückel calculations (Hückel molecular orbital (HMO)) (Section 2.1.4.1) give a measure of the distribution of the π-electrons. However, the HMO method is even less reliable for five-membered rings than for six-membered rings and the calculated atomic π-charges shown in Figure 3 must only be regarded as approximations. It should also be remembered that the distribution of the σ-electrons will also contribute to the overall polarity of the molecules.

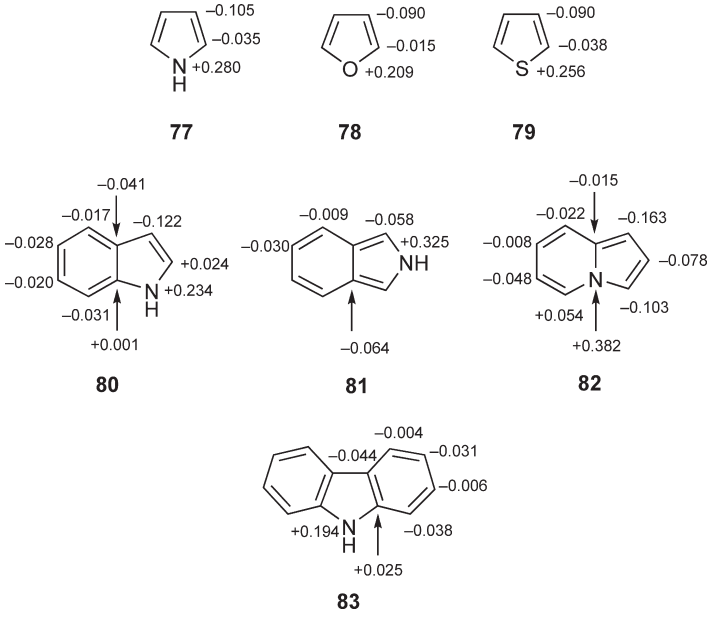


Figure 3 HMO calculated π-electron charges in selected five-membered heterocycles.

The total π-excess ($TOT_{\pi E}$), defined as the sum of the negative charges on all the carbon atoms, decreases in the series pyrrole **77** > thiophene **79** > furan **78** (**Figure 3**). Pyrrole **77** is also the most π-excessive by the criteria of local π-excess ($LOC_{\pi E}$), which is the largest negative charge on any one carbon atom in the ring. The carbon atoms at position 3 carry larger negative π-charges than those at position 2. This distribution of π-electron density is in agreement with larger shielding of the H(3) and C(3) nuclei in the ^{1}H and ^{13}C NMR spectra (**Tables 4** and **9**). In furan **78**, the π-excess at the 3-positions also seems to be higher than that at the 2-positions. ^{13}C NMR chemical shifts even suggest that the C(2) atoms in furan **78** are deshielded in comparison with benzene, and it should be remembered that there will also be polarization of the σ-electrons toward the electronegative oxygen atom. According to the HMO method, the distribution in thiophene **79** is similar to that in furan **77**. However, judged from the ^{13}C NMR chemical shifts, the C(2) atoms of thiophene **79** are more strongly shielded than the C(3) atoms. Also, the ^{13}C NMR data show that the local π-excess of the C(3) atoms of furan is higher than that of any carbon atom of thiophene and, in accord with HMO calculations, the partial negative charges at position 3 of both heterocycles are similar.

The total π-excesses of benzo derivatives of pyrrole **80–83** decrease in the order: indolizine **82** > isoindole **81** > pyrrole **77** > indole **80** > carbazole **83**. Local π-excess shows a different order: indolizine **82** C(1) > indole **80** C(3) > pyrrole **77** C(3) > isoindole **81** C(1) > carbazole **83** C(1). The benzene rings gain considerable negative charge. For example, in the indole and carbazole molecules **80** and **83**, more than 40 and 80%, respectively, of the calculated negative charges are concentrated on the carbon atoms that are not part of the heterocyclic ring. It should also be noted that a shift of π-electron density occurs away from those rings that formally contain more than six π-electrons. For example, the six-membered ring of indolizine **82** formally has seven π-electrons and a transfer of the additional electron to the five-membered ring renders the latter more electron-rich than the six-membered ring.

The 5,5-fused aromatic heterocycles, e.g., **27–32** (**Figure 2**), are isoconjugate with the pentalene dianion **84**. Within the HMO approximation, the highest occupied molecular orbital (HOMO) of this dianion is a nonbonding molecular orbital (NBMO) **85** that is restricted to positions 1, 3, 4, and 6. This results in these positions having particularly high electron density **86**. It follows that in neutral isoconjugate heteroderivatives, there will also be high electron density at these positions. Using pyrrolopyrroles as examples, if both the heteroatoms contributing lone pairs are at positions 2 and 5, as in the parent pyrrolopyrrole **87**, the HMO calculated total and local π-excesses (0.394 and 0.142) are particularly high (**Figure 4**). When the heteroatoms are at positions 1,4 (**88**) or 1,6 (**89**), the total π-excesses (0.290 and 0.296) are much closer to that of pyrrole (0.280) but the local π-excesses at positions 3,6 (**88**: 0.154) and 3,4 (**89**: 0.148) are significantly greater than in pyrrole (0.105). This is in accord with the HOMO having a similar distribution to that of the NBMO **85**. The unsymmetrical system **90** shows a combination of the above properties. From these simple calculations we can conclude that (1) these 5,5-fused heterocycles and their O and S analogues can be expected to be particularly π-excessive compared to their monocyclic analogues and (2) stability will be increased by aza substitution at positions 1, 3, 4, and/or 6 (see Chapter 2.4).

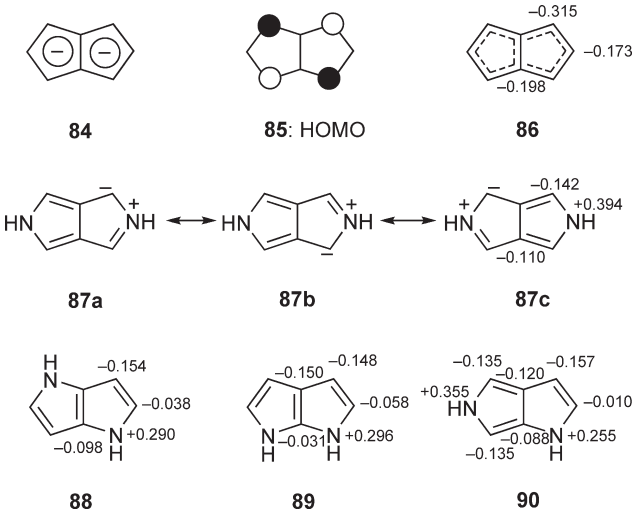
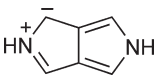
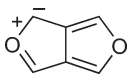
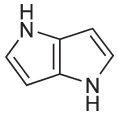
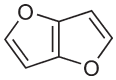
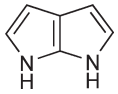
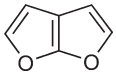
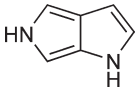
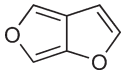
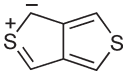


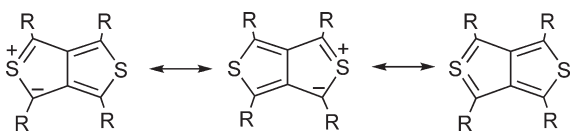
Figure 4 HMO calculated π-electron charges in the pentalene dianion and isoconjugate pyrrolopyrroles.

The π-excess of these five-membered rings is accompanied by high π-donor character. This is reflected in the energies of the HOMOs and their ionization potentials (Section 2.3.3.9). **Table 1** shows the AM1 calculated energies of the frontier orbitals, with benzene and pyridine included for comparison. Furan (−9.32 eV) and thiophene (−9.22 eV) possess almost equal π-donor character, which is considerably lower than that of pyrrole (−8.66 eV). All three heterocycles are calculated to be better π-donors than benzene (−9.65 eV). The more extensive the π-system, the stronger is the electron-donor ability. Thus, benzo substitution increases the HOMO energy with the benzo[*c*] derivatives having particularly high-energy HOMOs. All the 5,5-fused systems have high-energy HOMOs with the mesomeric betaines being exceptionally high. This is consistent with the 5,5-fused HOMOs being perturbed NBMOs (cf. **85**). AM1 studies of furopyrroles have been reported <CHEC-III(10.01.2)5>.

Table 1 AM1 energies (eV) of the frontier orbitals of five-membered heterocycles

Compounds	*HOMO*	*LUMO*	Δ	*Compounds*	*HOMO*	*LUMO*	Δ
Pyridine	−9.93	0.14	10.07	Benzene	−9.65	0.56	10.21
Pyrrole	−8.66	1.38	10.04	Furan	−9.32	0.72	10.04
Benzo[*b*]pyrrole	−8.40	0.30	8.71	Benzo[*b*]furan	−9.01	−0.06	8.95
Benzo[*c*]pyrrole	−7.80	0.14	7.94	Benzo[*c*]furan	−8.26	−0.40	7.86
Dibenzopyrrole	−8.46	−0.16	8.30	Dibenzofuran	−8.94	−0.40	8.54
	−6.76	0.49	7.25		−7.48	−0.76	6.72
	−7.84	0.97	8.81		−8.83	−0.02	8.81
	−8.04	1.17	9.21		−8.94	0.47	9.41
	−7.80	0.76	8.56		−8.78	−0.04	8.74
Thiophene	−9.22	0.24	9.46		−7.71	−0.88	6.83

Inclusion of sulfur 3d-orbitals in *ab initio* calculations on thiophene makes little difference to the total energy <1970CC319, 1972MI301-01>. Their principal role is to act as polarization functions rather than as an extra valence orbital. Thus, the population of the 3d-orbital is very small but its introduction into the basis set causes considerable changes in the population of 3s- and 3p-orbitals so that electron density on sulfur is increased mainly at the expense of the flanking carbon atoms. The general view is that d-orbitals have little influence on the structure and chemistry of thiophene and related neutral molecules. The thieno[3,4-*c*]thiophenes **91** (and other thiocarbonyl ylide derivatives) are sometimes represented by the tetravalent structures **91c** and described as nonclassical. Since the chemistry of these species is very similar to the furan and pyrrole analogues <1977T3193>, it is appropriate to represent these molecules as conjugated mesomeric betaines (**91a** ↔ **91b**).



91a **91b** **91c**

The relative thermodynamic stability of heterocyclic positional isomers can often be rationalized in terms of the topological charge stabilization rule (Figure 5) <1983JA1979>. This states that the best placement of electronegative heteroatoms is at the positions with greatest charge in the isoconjugate isoelectronic hydrocarbon. For example, the indenyl anion **92** has greatest charge density at positions 1 and 3 of the five-membered ring, and these are the positions where introduction of an electronegative heteroatom will produce maximum stabilization of the electron density. It is not surprising, therefore, that the benzo[*b*] heterocycles **93** (X = NH, O, S) are stable compounds. In contrast, the benzo[*c*] heterocycles **94** (X = NH, O, S), in which the heteroatom provides less stabilization, are much less stable and have been prepared and characterized relatively recently.

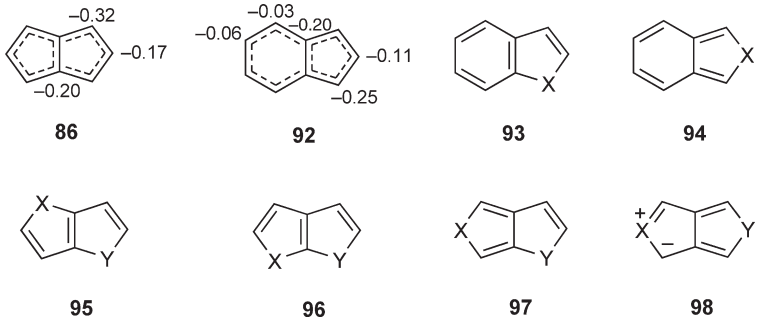


Figure 5 Application of the topological charge stabilization rule to bicyclic heterocycles.

Applying the same rule to the pentalene dianion **86**, the order of stability of the heterocyclic systems **95–98** can be predicted. Maximum stabilization can be expected with heteroatoms at positions 1, 3, 4, and 6, and the systems **95** and **96** have similar stability. The least stable systems are the mesomeric betaines **98** and the systems **97** have intermediate stability. These conclusions are in agreement with more sophisticated MO calculations of relative stability (see Section 2.3.2.2.1) and with experimental observations.

2.3.2.2 Calculation of Molecular Properties

2.3.2.2.1 Structure and energy

Optimized geometries have been calculated for many pyrrole, furan, and thiophene derivatives using a variety of MO methods and the results are tabulated in the appropriate chapters of CHEC-II(2) and CHEC-III(3). These results are useful for validating the accuracy of individual methods but the true value of these techniques is their use in (1) the study of molecules that are too unstable to be studied experimentally and (2) the study of reactions and reaction intermediates. Examples of applications are described in the following paragraphs.

Thiophenes and benzo[*b*]thiophenes form *S*-oxides but the parent molecules **99** and **100** have not been isolated. See Section 2.3.3.1 for examples of substituted derivatives that are stable. Figure 6 shows calculated bond lengths of thiophene and thiophene *S*-oxides <1996JOC1275>. In each *S*-oxide **99–101**, the sulfur atom is slightly below the plane of the four carbon atoms, and the oxygen atom is above the plane. The bond lengths reflect the significant loss of cyclic conjugation and lower aromatic stabilization in the *S*-oxides. The calculated <MP2/6-31G*> barrier to inversion of the pyramidal sulfur in thiophene *S*-oxide **99** is 13.5 kcal mol^{-1} <2000CC439>. This is much lower than for sulfoxides (37–42 kcal mol^{-1}) and reflects the aromaticity of the transition state. The LUMO of thiophene **4** is associated with all five

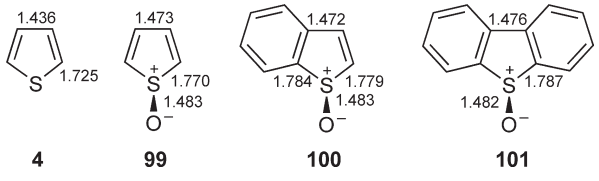
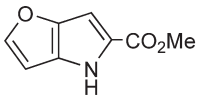


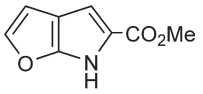
Figure 6 Selected calculated <RHF/6-31G(d,p)> bond lengths (Å) of thiophene and thiophene *S*-oxides <1996JOC1275>.

ring atoms whereas the LUMO of the *S*-oxide **99** (and the corresponding *S*,*S*-dioxide) is restricted to the four carbon atoms. This results in a large increase in electron affinity upon oxidation of thienyl sulfur to *S*-oxide <2000CC439>.

The isomeric furopyrroles **102** and **103** have been studied by X-ray crystallography and B3LYP/6-311+G** calculations. The total energy difference between methyl 4*H*-furo[3,2-*b*]pyrrole-2-carboxylate **102** and methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **103** is small ($-1.7\,kcal\,mol^{-1}$), as expected from the topological charge stabilization rule (Section 2.3.2.1). The slightly higher stability of the isomer **102** is attributed to the closer proximity of the heteroatoms in the isomer **103** leading to unfavorable interactions and bond lengthening <CHEC-III(10.01.4.1)9>.



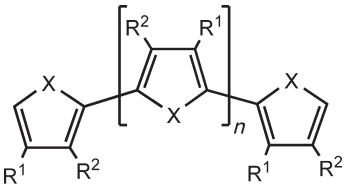
102



103

Furan **3**, benzo[*b*]furan **17**, benzo[*c*]furan **18**, and the four isomeric furofurans **95–98** (X = Y = O) have been the subject of detailed B3LYP/6-311+G** calculations. In accord with the topological charge stabilization rule (Section 2.3.2.1), thermodynamically the oxygen atoms prefer the positions of maximum negative charge in the indenyl anion **92** and pentalene dianion **86**, respectively. The relative thermodynamic energies were found as follows: (1) benzo[*b*]furan ($0.0\,kcal\,mol^{-1}$) and benzo[*c*]furan ($14.2\,kcal\,mol^{-1}$); and (2) furo[3,2-*b*]furan ($0.0\,kcal\,mol^{-1}$), furo[2,3-*b*]furan ($0.7\,kcal\,mol^{-1}$), furo[3,4-*b*]furan ($2.5\,kcal\,mol^{-1}$), and furo[3,4-*c*]furan ($22.6\,kcal\,mol^{-1}$) <1996AGE2638, CHEC-III (3.05.6.1)400>.

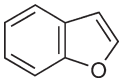
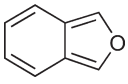
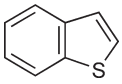
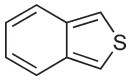
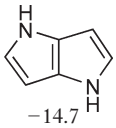
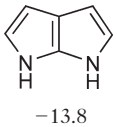
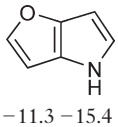
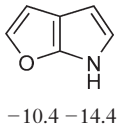
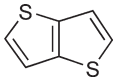
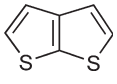
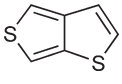
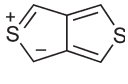
The potential applications of semiconducting and conducting properties of the polyconjugated heterocycles **104** have been the focus of much research. A number of studies have used DFT and time-dependent DFT (TDDFT) calculations to study the electronic properties of the oligomers **104**, and by extrapolation of the polymers. The calculated (B3LYP/6-31G*) reorganization energy of oligofurans appears to determine the intrinsic hole transfer rate responsible for the semiconducting/conducting properties. With the exception of the oligobenzo[*c*]furans, the reorganization energy correlates linearly with the square root of the number of monomer units <2005JA2339, CHEC-III (3.05.3.5)396>. TDDFT calculations suggest a relatively small band gap of 1.52 eV for polythiophene, which is 0.17 eV narrower than the predicted band gap of polyfuran. The chain-length dependence of excitation energies of oligomers of thiophene was studied employing a TDDFT (B3LYP) method. Band gaps of the corresponding polymers were obtained by extrapolating excitation energies of trimers through pentamers to infinite chain length <2002MM1109, CHEC-III(3.09.2.7)641>.



104: X = NH, O, S

Nucleus-independent chemical shift (NICS) values for a number of five-membered heterocycles have been reported and are used as a quantitative magnetic measure of aromaticity. They are a measure of diamagnetic ring current and are not a measure of thermodynamic stability. NICS values are theoretical parameters and the values depend on the computational method used and the position above the ring. **Table 2** shows NICS values for a selection of heterocyclic systems where NICS is the value at the centre of the ring. The aromaticity of five-membered heterocycles is discussed in Sections 2.3.4.2 and 2.4.4.2.

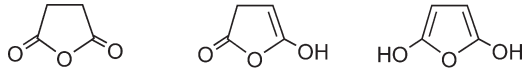
Table 2 NICS values for selected monocyclic and bicyclic heterocycles

Entry	*a*	*b*	*c*	*d*	*Reference*
1					
	−14.86	−12.31	−13.80	−5.43	2002JOC1333
2					
	−11.6 −9.8	−4.2 −15.6	−10.7 −10.1	−4.6 −15.8	1996AGE2638
3					
	−14.7	−13.8	−11.3 −15.4	−10.4 −14.4	2001CRV1385
4					
	−11.3	−11.2	−14.0 −6.1	−14.4	1996AGE2638

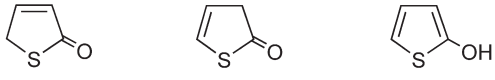
The NICS values of pyrrole, furan, and thiophene (**Table 2**) are entirely consistent with their aromatic character and the accepted view that furan is the least aromatic. Phosphole (Entry 1d) is predicted to have low aromaticity based on magnetic criteria. In benzofurans and benzothiophenes (Entry 2), all the heterocyclic rings have NICS values associated with high magnetic aromaticity but benzo[*c*] fusion leads to low aromaticity for the benzene ring. The 5:5 bicyclic systems (Entries 2 and 3) all have low NICS values (high aromaticity) and it is noteworthy that in, for example, the thienothiophene series, the least stable isomer (the mesomeric betaine, Entry 4d) is the most aromatic based on the NICS parameter <1996AGE2638>.

2.3.2.2.2 Reactions and equilibria

B3LYP/6-31G** calculations on the tautomers of succinic anhydride **105** show that the enols **106** and **107** are disfavored by 24.1 and 41.1 kcal mol^{-1}, respectively. This is in spite of the aromatic stabilization in the furan **107** and in line with the general instability of anhydride enols <CHEC-III(3.05.6.2)401>. For 2-hydroxythiophene **110**, similar calculations show the following relative stability: **108** (0.0 kcal mol^{-1}), **109** (4.23 kcal mol^{-1}), and **110** (15.72 kcal mol^{-1}) <CHEC-III(3.09.4.3)716>.

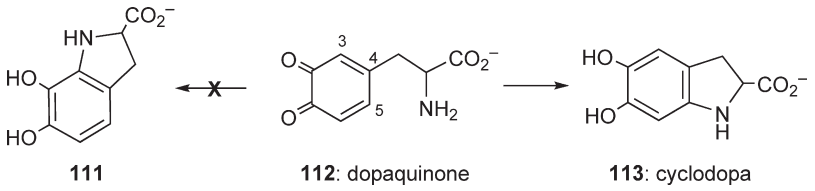


105 **106** **107**



108 **109** **110**

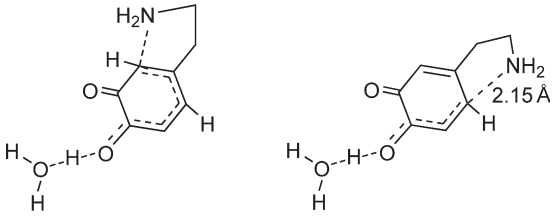
The cyclization of dopaquinone **112** to cyclodopa **113** is an important early step in the biosynthesis of eumelanin, which is the black-brown pigment in hair and skin. Dopaquinone **112**, and longer chain homologues, cyclizes exclusively at position 5 and there is no cyclization at position 3 with formation of the isomeric catechol **111**. The alternative reactions shown in **Scheme 1** have been investigated using the AM1 method <2006T4884>. The transition state **114** for the unobserved product **111** is calculated (RHF/6-31G**//AM1) to be 17.7 kcal mol^{-1} higher in energy



111 **112**: dopaquinone **113**: cyclodopa

Scheme 1 Alternative modes of cyclization of dopaquinone

than the transition state **115** for formation of cyclodopa **113**. For both transition states, the trajectory for nucleophilic attack was found to be close to the optimal angle calculated for intermolecular reaction with methylamine. The calculations suggest that reaction at position 5 is preferred because an energetically favorable α,β-unsaturated ketone function remains unperturbed in the transition state.



114 **115**

Molecular mechanics (MM) has been extensively applied to the conformational analysis of hydrofurans. For 2,3-dihydrofuran and tetrahydrofuran, the MM2 method accurately identifies the preferred equilibrium conformation and predicts reasonably well the barriers to planarity and pseudorotation <1987JSP(124)369, 1990JPC1830>. Application of this methodology to substituted tetrahydrofurans is efficient for the analysis of conformational preferences, both for substituted <1991T1291, 1992JST(265)225> and condensed derivatives <1992CAR(229)245, 1992JOC5271, 1993CAR(244)49>. The MM3 force field is better parametrized for carbohydrates <1989JA8551, 1990JA8293, 1993CAR(244)49>. The state of the art and the incorporation of carbohydrates into macromolecular force fields have been reviewed <B-2000MI1>.

2.3.3 Structural Methods

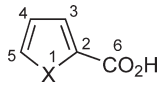
2.3.3.1 X-Ray Diffraction

A summary of bond lengths and angles from X-ray structures of heterocyclic compounds studied up to 1970 has been published <1972PMH(5)1>. This compilation contains many examples, particularly of furans, thiophenes, and pyrroles and their benzo derivatives; further examples are contained in the appropriate chapters of the three editions of *Comprehensive Heterocyclic Chemistry*. The Cambridge Structural Database (CSD) <www.ccdc.cam.ac.uk> maintains a comprehensive collection of heterocyclic structures.

High-accuracy molecular dimensions for the parent monocyclic heterocycles have been determined by microwave spectroscopy and these can be found in Section 2.3.3.2 (**Table 7**). The ring dimensions obtained by X-ray diffraction for the 2-carboxylic acid derivatives of furan, thiophene, selenophene, and tellurophene (**Table 3**) are generally in good agreement with those obtained for the parent heterocycles using microwave spectroscopy (**Table 7**).

Microwave spectroscopy is especially useful in the indole system where the crystal structure is composed of two different molecular orientations with different bond lengths and angles. The values given by microwave spectroscopy

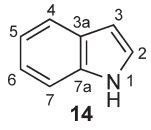
Table 3 Bond lengths and angles of five-membered heterocyclic 2-carboxylic acids



	X = O	*X = S*	*X = Se*	*X = Te*
Bond length (Å)				
X–C(5)	1.312	1.701	1.850	2.047
X–C(2)	1.368	1.693	1.872	2.057
C(5)–C(4)	1.446	1.363	1.355	1.357
C(2)–C(3)	1.288	1.362	1.356	1.384
C(3)–C(4)	1.351	1.414	1.421	1.412
C(2)–C(6)	1.414	1.481	1.438	1.423
Bond angle (degrees)				
C(2)XC(5)	109	92.0	87.1	81.5
XC(5)C(4)	109	111.8	112.25	111.7
XC(2)C(3)	109	111.8	110.7	111.7
C(5)C(4)C(3)	105	111.9	114.2	118.8
C(4)C(3)C(2)	105	112.4	115.7	116.3
XC(2)C(6)	120	122.2	121.0	123.4
C(3)C(2)C(6)	131	125.9	128.3	124.8
Reference	1962AX919	1962AX737	1962AX737	1972CSC273

are generally considered to be more reliable (**Table 4**) <CHEC-II(2.01.3.2)6>. The structures of many derivatives of indole **14**, benzo[*b*]furan **17**, and benzo[*c*]thiophene **20** have been investigated by X-ray diffraction and in general their bond lengths and angles are in accord with their aromatic structures.

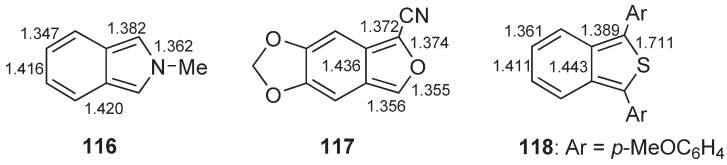
Table 4 X-ray- and microwave-derived bond lengths and bond angles for indole **14**



14

	Bond length (Å)				*Bond angle (degrees)*		
	Microwave	*X-ray 1*	*X-ray 2*		*Microwave*	*X-ray 1*	*X-ray 2*
N-C(2)	1.370	1.406	1.392	NC(2)C(3)	109.1	108.0	108.7
C(2)-C(3)	1.382	1.407	1.399	C(2)C(3)C(3a)		108.4	107.8
C(3)-C(3a)		1.401	1.401	C(3)C(3a)C(7a)		108.4	107.8
C(3a)-C(4)	1.425	1.388	1.410	C(3a)C(7a)N	108.7	107.9	108.1
C(4)-C(5)	1.382	1.390	1.386	C(7a)C(3a)C(4)	121.4	119.7	119.6
C(5)-C(6)		1.399	1.394	C(3a)C(4)C(5)	117.2	120.6	120.3
C(6)-C(7)	1.382	1.382	1.403	C(4)C(5)C(6)		119.8	120.2
C(7)-C(7a)	1.425	1.407	1.398	C(5)C(6)C(7)		120.5	120.1
C(7a)-C(3a)	1.382	1.404	1.408	C(6)C(7)C(7a)	117.2	119.8	120.2
C(7a)-N	1.370	1.402	1.391	C(7)C(7a)C(3a)	121.4	119.8	119.6
				C(7)NC(2)	109.1	108.1	107.9

The benzo[*c*] compounds **15**, **18**, and **21** are all very unstable and only a limited number of structures of derivatives have been determined by X-ray crystallography. Several benzo[*c*]pyrroles have been studied including *N*-methylisoindole **116** (**Figure 7**). The geometry of the pyrrolo ring is not significantly different from that of pyrrole or indole. However, the bond lengths in the carbocyclic ring are alternately shorter and longer than in indoles, suggesting that significant localization of electron density occurs in the six-membered ring. This is consistent with the calculated NICS values for benzo[*c*] systems (**Table 2**).



116 **117** **118**: Ar = *p*-$MeOC_6H_4$

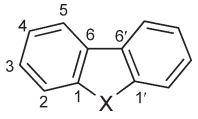
Figure 7 Bond lengths of benzo[*c*] heterocycles from X-ray crystallography.

The crystal structure of the benzo[*c*]furan derivative **117** has been reported <1986JOC3973>. The results indicate that the molecule is essentially planar; only the carbon atom of the methylenedioxy group is slightly out of plane. Remarkably, close agreement is found between the bond lengths of the furan ring in the benzo[*c*]furan **117** (**Figure 7**) and the values for furan (**Table 7**). 4,7-Dimethoxybenzo[*c*]furan has also been examined by X-ray crystallography. The molecule is planar and can be regarded as two independent 1,3-diene systems; the average length of the C—C single bonds is 1.437 Å and that of the C═C double bonds is 1.354 Å <1995AXC780>.

The structure of the benzo[*c*]thiophene **118** has been reported <2005TL4225>. The bond lengths (**Figure 7**) in the thiophene ring are similar to those for thiophene (**Table 7**); as for the isoindole **116**, the bond lengths in the benzo ring show evidence of bond localization.

Table 5 shows the structures of dibenzo heterocycles **119**. Comparison of the data with that for monocyclic systems (**Table 7**) shows that the internal bond angles of the heterocyclic ring do not change appreciably on annulation. However, the bond lengths increase and this is particularly noticeable in the case of the C—X bonds, which are compared in **Table 6**. It may be noted, however, that in no case does the length of the C(6)–C(6') bond reach the length of the interannular bond of biphenyl (1.497 Å) <1961MI30100>, implying that the central heterocyclic ring retains some aromaticity. A feature of these molecules is that they adopt a slightly bow-shaped configuration with small dihedral angles between the planes of the five-membered and benzenoid rings. The observed values are carbazole **16** 1.0°, dibenzofuran **19** 1.12°, dibenzothiophene **22** 0.4–1.2°, and dibenzoselenophene 0.5–1.2°. The X-ray structure of dibenzothiophene *S,S*-dioxide **119** (X = SO_2) is quite similar to that of dibenzothiophene **22** <1968AXB981>.

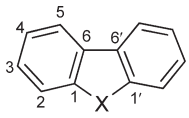
Table 5 Comparison of bond lengths and angles of dibenzo heterocycles **119**



119

	X = NH	*X = O*	*X = S*	*X = Se*	*X = Te*
Bond length (Å)					
C(l)–C(2)	1.403	1.385	1.384	1.395	1.397
C(2)–C(3)	1.372	1.388	1.384	1.371	1.381
C(3)–C(4)	1.393	1.385	1.385	1.377	1.386
C(4)–C(5)	1.392	1.389	1.370	1.380	1.375
C(5)–C(6)	1.391	1.384	1.392	1.395	1.403
C(6)–C(6')	1.477	1.481	1.441	1.453	1.460
C(l)–C(6)	1.408	1.393	1.409	1.398	1.394
C(l)–X	1.393	1.404	1.740	1.899	2.087
X–H	1.02	–	–	–	–
Bond angle (degrees)					
C(1)XC(l')	108.3	104.1	91.5	86.6	81.7
XC(l)C(6)	109.7	112.3	112.3	112.4	112.1
C(1)C(2)C(3)	115.6	116.7	117.8	118.7	119.1
C(2)C(3)C(4)	123.9	120.9	121.6	121.1	120.6
C(3)C(4)C(5)	120.1	121.9	120.5	120.6	120.1
C(4)C(5)C(6)	117.9	117.9	120.0	120.3	120.9
C(5)C(6)C(l)	120.6	119.6	118.7	118.1	118.0
C(6)C(l)C(2)	121.9	123.0	121.6	121.6	121.3
C(l)C(6)C(6')	106.1	105.3	111.9	114.3	117.1
Reference	1969BCJ2174	1972AXB1002	1970JCA1561	1970AXB628	1975IC2639

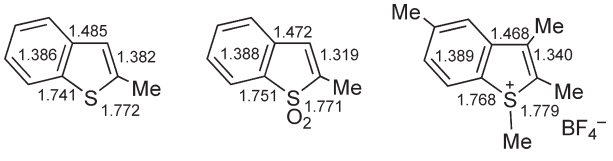
Table 6 Comparison of C—X bond lengths for dibenzo heterocycles **119** and parent ring



119

X	*Dibenzo derivative: C–X (Å)*	*Parent heterocycle: C–X (Å)*
NH	1.393	1.370
O	1.404	1.362
S	1.740	1.714
Se	1.899	1.855
Te	2.087	2.055

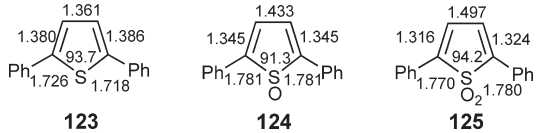
In benzo[*b*]thiophene **20** both rings are coplanar but the introduction of a substituent on the thiophene ring usually causes the two rings to be inclined to each other at about 1°. For benzo[*b*]thiophene *S*,*S*-dioxides, e.g., **121**, the bond lengths and angles are approximately similar to their unoxidized precursors, e.g., **120**. The largest difference is the C(2)–C(3) bond, which is much smaller in the dioxide (**Figure 8**). As for substituted benzo[*b*]thiophenes, the two rings are tilted toward each other at about 1°. The *S*,*S*-dioxide geometries are similar to that of l,2,3,5-tetramethylbenzo[*b*] thiophenium tetrafluoroborate **122**. The bonds of the sulfur atom are pyramidal in nature with the *S*-methyl group being out of the plane of the ring. In comparison to benzo[*b*]thiophene derivatives, e.g., **120** (**Figure 8**), the salt **122** has a shorter C(2)–C(3) bond indicating more bond alternation due to the lack of delocalization but not as low as in the *S*,*S*-dioxide **121** <CHEC-II(2.09.3.1)460>.



120 **121** **122**

Figure 8 A comparison of benzo[*b*]thiophene bond lengths (Å).

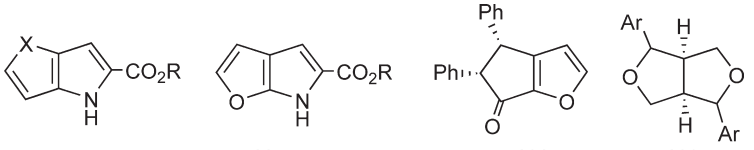
The structures of the 2,5-diphenylthiophenes **123**–**125** have been determined by X-ray diffraction <1997JHC1567>. In agreement with earlier MO calculations on the parent system **99** (Section 2.3.2.2.1), the *S*-oxide **124** is nonplanar. The sulfur atom is below the plane of the four thiophene carbon atoms by 0.278 Å, and the oxygen atom is 0.746 Å above the same plane. The *S*,*S*-dioxide ring is planar. Selected bond lengths and angles are shown in **Figure 9**. There is an increase in bond alternation in the series **123**–**125** indicative of a decrease in cyclic conjugation. The results suggest that the *S*-oxide has some cyclic conjugation of its π-electrons indicative of aromaticity that is lower than that of thiophene but much higher than that of the *S*,*S*-dioxide <1997JHC1567>.



123 **124** **125**

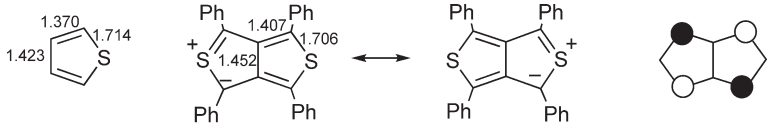
Figure 9 Structures of 2,5-diphenythiophenes.

A limited number of 5:5 heterocyclic systems have been studied by X-ray diffraction and these have been summarized <CHEC-II(7.01.3.1)7, CHEC-III(10.01.3.1)5>. The fully-conjugated systems **126** and **127** are planar or very close to planarity; for the derivative **126** (X = O, R = Et), the dihedral angle between the rings is 1.02° <1988AXC2032>. Bond lengths are in accord with aromatic character; the common CC bonds are ~1.385 Å. For the partially-saturated system **128**, the two fused rings are coplanar and the dimensions of the furan ring are similar to those found for other non-annelated systems <1990AXCl129>. Hexahydrofuro[3,4-*c*]furans of the general type **129** occur naturally as lignans and several structures have been confirmed by X-ray diffraction. The two five-membered rings have *cis*-fused envelope structures with the oxygen atoms at the flap positions <CHEC-II(7.01.3.1)7>.



126: X = O, S **127** **128** **129**

The structure of the tetraphenylthieno[3,4-*c*]thiophene **130** has been reported <1972AXB1336>. The bicyclic ring system is symmetrical and planar with the phenyl groups rotated out of this plane by 39.6 and 58.4°. The average bond lengths are shown in structure **130a** together with thiophene **4** for comparison. Compared with thiophene, the CS bond lengths are slightly shorter and the CC bond lengths are substantially longer. These changes in bond length have been rationalized by invoking a contribution from d-orbitals. However, this is an electron-rich ring system in which the HOMO is an NBMO **85** (see Section 2.3.2.1). As a result, the two electrons in this orbital (**85**) make no contribution to bonding between adjacent atoms in the ring and this probably accounts for the weaker and therefore longer CC bonds.



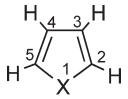
4 **130a** **130a** **85**: HOMO

2.3.3.2 Microwave Spectroscopy

Microwave spectra provide a rich source of minute details of molecular structures. Spectra are primarily analyzed in terms of the accurate values of the moments of inertia. This generally gives the molecular conformation and some precise structural features may emerge. To obtain a complete structure, it is necessary to measure changes in moments of inertia that accompany isotopic replacement of each atom <1974PMH(6)53>. From accurate measurements of the Stark effect, when electrostatic fields are applied, information about the electron distribution is also obtained.

High-accuracy molecular dimensions for the planar parent heterocycles **131** in the gas phase have been obtained by microwave spectroscopy and are recorded in **Table 7**. Increasing size of the heteroatom results in lengthening of the X—C(2) bond and a decrease of the C(2)XC(5) bond angle, so that the shape of the molecule is progressively elongated. Delocalization in the case of pyrrole brings the imino hydrogen into the plane of the other atoms with an N—H bond length of 0.996 Å. Revised structural parameters for *N*-methylpyrrole **131** (X = NMe) have been determined by gas-electron diffraction using rotational constants and liquid crystal NMR measurements <2001JST(567)107>.

Table 7 Comparison of bond lengths and angles of conjugated monoheterocycles **131**



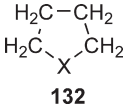
131

	X = NH	*X = O*	*X = S*	*X = Se*	*X = Te*
Bond length (Å)					
X-C(2)	1.370	1.362	1.714	1.855	2.055
C(2)-C(3)	1.382	1.361	1.370	1.369	1.375
C(3)-C(4)	1.417	1.430	1.423	1.433	1.423
C(2)-H	1.076	1.075	1.078	1.070	1.078
C(3)-H	1.077	1.077	1.081	1.079	1.081
Bond angle (degrees)					
C(2)XC(5)	109.8	106.5	92.17	87.76	82.53
XC(2)C(3)	107.7	110.65	111.47	111.56	110.81
C(2)C(3)C(4)	107.4	106.07	112.45	114.55	117.93
XC(2)H	121.5	115.98	119.85	121.73	124.59
C(2)C(3)H	125.5	127.83	123.28	122.59	121.04
Reference	1969JST(3)491	1978JST(48)157	1961JSP(7)58	1969DOK(185)384	1973MI30100

The distortions caused by substitution are usually of small magnitude. Thus, in 2-cyanopyrrole, microwave spectroscopy shows that the N—C(2) and C(2)—C(3) bond lengths are only shortened by 0.009 Å relative to those observed for pyrrole together with consequent increases in the ring bond angles at N and C(3) of 0.1° <1980JPC1767>. Distortions of the same magnitude have also been detected for the 2-cyano derivatives of furan and thiophene <1980JPC1767>, and for 3-cyanothiophene <1980ZNA770>.

The determination of the bond lengths of the fully-saturated heterocycles **132** has been complicated by their conformational mobility, which is discussed in Section 2.3.4.3.2. The data that have been obtained are listed in Table 8 and show the expected trends consonant with increasing size of heteroatom.

Table 8 Bond lengths and angles for saturated monoheterocycles **132**



132

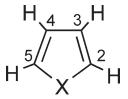
	X = O	*X = S*	*X = Se*
Bond lengths (Å)			
X–C	1.428	1.839	1.975
C–C	1.535	1.536	1.538
Bond angles (degrees)			
CXC	106.4–110.6	93.4	89.1
XCC	103.7–107.5	106.1	105.8
CCC	100.3–104.4	105.0	106.0
Reference	1969ACS2748, 1969T3045	1969ACS3534	1970ACS1903

2.3.3.3 ^{1}H NMR Spectroscopy

2.3.3.3.1 Parent aromatic compounds

The ^{1}H NMR spectra of the parent heterocycles **131** (Table 9), each consists of two multiplets of which the one at lower field is assigned to the α-hydrogens.

Table 9 ^{1}H NMR spectral data for monoheterocycles **131** (in $CDCl_3$)



131

	Pyrrole[a]	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*	*Cyclopentadiene*
H(2)	6.68	7.29	7.18	7.88	8.87	6.28
H(3)	6.22	6.24	6.99	7.22	7.78	6.43
$J_{2,3}$	2.70	1.75	4.90	5.40	6.70	5.05
$J_{2,4}$	1.44	0.85	1.04	1.46	1.30	1.09
$J_{2,5}$	1.87	1.40	2.84	2.34	2.60	1.93
$J_{3,4}$	3.35	3.30	3.50	3.74	4.00	1.93
Reference	[b]	1965SA85	1965SA85	1965SA85	1972J(P1)199	1970JCP(53)2343

Units are ppm and Hz.
[a]For pyrrole the NH proton signal appears at 7–12 ppm.
[b]Varian catalog.

Apart from pyrrole, the chemical shifts of the β-protons increase with decreasing electronegativity of the heteroatom. In contrast, the chemical shifts of the α-protons do not display any obvious regularity, probably due to paramagnetic shielding contributions that become more important with increasing availability of d-orbitals. The chemical shift of the pyrrole N–H is solvent dependent.

In the case of pyrrole **131** (X = NH), the ring protons are also coupled to the N–H proton with $J_{1,2} = J_{1,5} = 2.58$ Hz and $J_{1,3} = J_{1,4} = 2.46$ Hz. Satellites due to spin–spin coupling between the α-protons and the ring heteroatom are observed for selenophene **131** (X = Se), J_{SeH} [^{77}Se] = 47.5 Hz, and tellurophene **131** (X = Te), J_{TeH} [^{125}Te] = 100.4 Hz <1974ACB175>.

The magnitudes of the vicinal vinylic proton coupling constants are much smaller than the 7.6 Hz observed for benzene and reflect in part the greater separation of the protons when attached to five-membered rings. However, factors such as electronegativity and double-bond character also affect coupling sizes: $J_{2,3}$ and $J_{3,4}$ increase systematically, i.e., O < NH < S < Se < Te. Comparison with the corresponding coupling constants of cyclopentadiene indicates the important role of heteroatom electronegativity in determining the magnitude of $J_{2,3}$. The much larger $J_{3,4}$, observed for all of the heterocycles, emphasizes the greatly increased conjugative interaction between carbons 3 and 4 relative to that in cyclopentadiene. The long-range coupling constant $J_{2,4}$ is lower for all of the heterocycles than corresponding benzenoid *meta* coupling constants (ca. 2–3 Hz), whereas the $J_{2,5}$ couplings, which increase in the sequence O < NH < CH_2 < Se < Te < S, are larger than benzenoid *para* coupling constants (ca. 0–1 Hz).

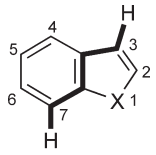
The ring proton chemical shifts of 2*H*-pyrroles and 3*H*-pyrroles are as expected for conjugated imines <B-90MI 201-02>.

2.3.3.3.2 Substituted aromatic compounds

As in benzenoid analogues, electron-withdrawing substituents deshield and electron-releasing groups shield the ring protons. Proton spectra for a variety of 1*H*-pyrroles, 1*H*-indoles, and carbazoles have been tabulated <CHEC-III (3.01.3.3.1)8> and a model (CHARGE7h) for calculation of chemical shifts of pyrroles and indoles has been described <2002J(P2)1081>. Quantitative correlations between the ^{1}H NMR spectral properties of monosubstituted furans <1975CS(7)211>, thiophenes <1975CS(7)76>, selenophenes <1975CS(7)111>, and tellurophenes <1976ACB605> have been extensively explored and rationalizations offered in terms of inductive and mesomeric effects. Linear correlations exist (1) between the relative shifts of H(2) and H(3) in 3-substituted furans, thiophenes, and selenophenes and (b) between heteroatom electronegativity and the shifts of H(5) in 2- and 3-substituted and H(2) in 3-substituted, five-membered heterocycles.

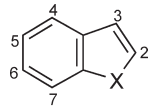
Long-range couplings occur between ring protons and hydrogens attached to substituent atoms. For example, in 2-aldehydes couplings of the order of 1 Hz have been observed.

Annulation of a benzene ring onto the [*b*] bond of a ring does not have any pronounced effect on the chemical shifts of the heterocyclic protons (cf. **Table 10**). The chemical shift of the indole N–H is solvent dependent and as in pyrrole it is also coupled to the ring protons with $J_{1,2} = 2.4$ Hz and $J_{1,3} = 2.1$ Hz. The benzenoid protons H(4) and H(7) appear downfield from H(5) and H(6). Long-range coupling between H(3) and H(7) (cf. **133**) is of considerable diagnostic value in establishing the positions of substituents.



133

Table 10 ^{1}H NMR spectral data for benzo[*b*] heterocycles **134** (in CCl_4)



134

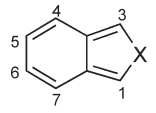
	Indole	*Benzofuran*	*Benzothiophene*	*Benzoselenophene*	*Benzotellurophene*
H(2)	6.52 (7.27)	7.52 (7.78)	7.33	7.90	8.65
H(3)	6.29 (6.45)	6.66 (6.76)	7.22	7.50	7.91
H(4)	(7.55)	7.49 (7.63)	7.72	7.76	7.79
H(5)	(7.00)	7.13 (7.23)	7.26	7.19–7.29	7.08–7.30
H(6)	(7.08)	7.19 (7.30)	7.24	7.19–7.29	7.08–7.30
H(7)	(7.40)	7.42 (7.51)	7.79	7.86	7.90
$J_{2,3}$	3.1	2.19	5.5	6.0	7.1
$J_{2,6}$	–	–	0.5	0.3	–
$J_{3,7}$	0.7	0.87	0.75	0.67	–
$J_{4,5}$	7.8	7.89	8.5	–	–
$J_{4,6}$	1.2	1.28	1.14	–	–
$J_{4,7}$	0.9	0.80	0.7	–	–
$J_{5,6}$	7.0	7.27	7.0–7.5	–	–
$J_{5,7}$	1.2	0.92	0.5–1.0	–	–
$J_{6,7}$	8.0	8.43	8.0–7.5	–	–
Reference	1964JCS981 1965AJC353	1965AJC353	1966BCJ2316	1972BSF3193	1972BSF3193

Units are ppm and Hz.
[a]Chemical shifts in parentheses are for acetone solutions.

^{1}H NMR spectroscopy has provided useful structural information on the unstable benzo[*c*] heterocycles **135** (Table 11). The protons H(1) and H(3), adjacent to the heteroatom, are observed at lower field than are the corresponding protons in the parent heterocycles **131** (Table 9) or their benzo[*b*] isomers **134** (Table 10). However, the same sequence of downfield shifts, namely NR < S < O < Se, is observed and the heterocyclic ring appears to be aromatic.

^{1}H NMR data for dibenzo heterocycles **119** are given in Table 12.

Table 11 ^{1}H NMR spectral data for benzo[*c*] heterocycles **135**

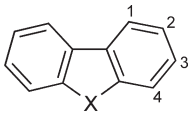


135

	H(1)	*H(4)*	*H(5)*							
	H(3)	*H(7)*	*H(6)*	$J_{1,4}$	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	*Solvent*	*Reference*
Isoindole	6.28	7.5	6.8	–	8.49	–	–	6.29	$(CD_3)_2CO$	1973J(P1)1432
N-Methylisoindole	7.05	7.51	6.92	0.46	8.69	0.90	0.79	6.46	$CDCl_3$	1976J(P2)81
Benzo[*c*]furan	7.99	7.38	6.84	0.64	8.52	1.01	0.57	6.22	$CDCl_3$	1976J(P2)81
Benzo[*c*]thiophene	7.63	7.59	7.04	0.42	8.64	1.03	0.79	6.36	$CDCl_3$	1976J(P2)81
Benzo[*c*]selenophene	8.40	7.33–7.54	6.77 7.02	–	9.16	–	–	6.79	$CDCl_3$	1977JA8248, 1976JA867

Units are ppm and Hz.

Table 12 ^{1}H NMR spectral data for dibenzo heterocycles **119** (in acetone)

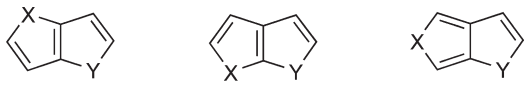


119

	Carbazole[a]	*Dibenzofuran*	*Dibenzothiophene*
H(1)	7.49	7.61	7.95
H(2)	7.36	7.51	7.50
H(3)	7.16	7.37	7.49
H(4)	8.08	8.07	8.29
$J_{1,2}$	8.21	8.42	8.07
$J_{1,3}$	0.89	0.72	1.11
$J_{1,4}$	0.67	0.57	0.70
$J_{2,3}$	7.17	7.56	7.23
$J_{2,4}$	1.18	1.36	1.17
$J_{3,4}$	7.80	7.87	8.06
Reference	1965AJC353	1965AJC353	1971AJC2293

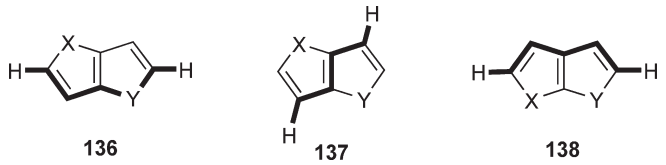
Units are ppm and Hz.
[a]This is not the normal numbering system for carbazole (X = NH).

The proton NMR spectra of the 5:5-fused heterocycles **95–97** have a close similarity to the parent monocycles. The protons at positions α and β to the heteroatoms resonate at frequencies analogous to the parent molecules. The similarity of the ^{1}H NMR spectra of 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole **95** (X = Y = NH) and pyrrole suggests that both ring systems have similar ring currents and aromaticity. An upfield shift (0.17 ppm) of the β-proton in the bicycle **95** (X = Y = NH) reflects the influence of the fused pyrrole ring on electron density <1984TL5669>.

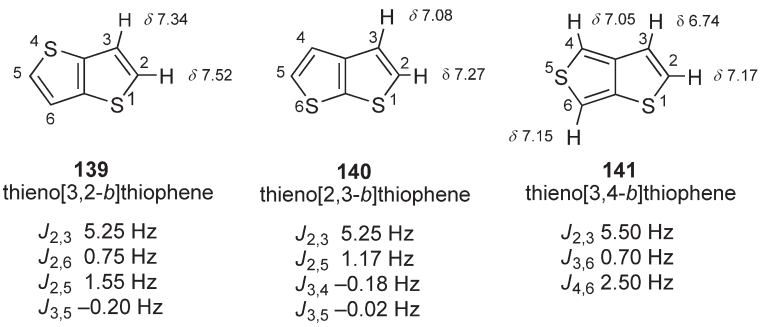


95 **96** **97**

The long-range coupling constants of the ring protons are characteristic of particular ring positions. In general, cross-ring coupling between α-protons ($J_{\alpha,\alpha'}$) separated by six bonds (**136** and **138**) varies from 1.0 to 1.5 Hz. Interactions between αβ′- and ββ′-protons separated by five bonds in a zig-zag manner (e.g. **137**) are not as effective ($J \sim 0.7$ Hz). The chemical shifts and coupling constants for the bicyclic systems **95–97** are illustrated by the values for the parent thienothiophenes **139–141**, which are shown in **Figure 10**.



136 **137** **138**



139
thieno[3,2-*b*]thiophene

$J_{2,3}$ 5.25 Hz
$J_{2,6}$ 0.75 Hz
$J_{2,5}$ 1.55 Hz
$J_{3,5}$ –0.20 Hz

140
thieno[2,3-*b*]thiophene

$J_{2,3}$ 5.25 Hz
$J_{2,5}$ 1.17 Hz
$J_{3,4}$ –0.18 Hz
$J_{3,5}$ –0.02 Hz

141
thieno[3,4-*b*]thiophene

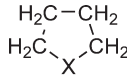
$J_{2,3}$ 5.50 Hz
$J_{3,6}$ 0.70 Hz
$J_{4,6}$ 2.50 Hz

Figure 10 Proton chemical shifts and coupling constants in thienothiophenes.

2.3.3.3.3 Saturated and partially-saturated compounds

The α-hydrogen resonances for the fully-saturated monocycles **132** (Table 13) occur at lower fields than the β-hydrogen resonances. The chemical shifts of the β-hydrogens vary systematically with the electronegativity of the heteroatom, but the chemical shifts of the α-hydrogens do not.

Table 13 ^{1}H NMR spectral data (ppm) for tetrahydro heterocycles **132** (in CCl_4)



132

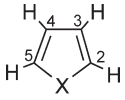
Heterocycle	*X*	*H(2)*	*H(3)*	*Reference*
Pyrrolidine	NH	2.77	1.63	1972JA8854
Tetrahydrofuran	O	3.62	1.79	1972JA8854
Tetrahydrothiophene	S	2.75	1.92	1972JA8854
Tetrahydroselenophene	Se	2.79	1.96	1974JHC827
Tetrahydrotellurophene	Te	3.10	2.03	1974JHC827

The spectra of 2,5-dihydrofuran **38** (X = O) and 2,5-dihydrothiophene **38** (X = S) are simple, showing two singlets at 4.51 and 5.85 ppm for the dihydrofuran, and 3.66 and 5.79 ppm for the sulfur analogue; the lack of coupling is in accord with an almost planar conformation <1973MR(12)244>.

2.3.3.4 ^{13}C NMR Spectroscopy

The ^{13}C NMR spectral properties of the parent heterocycles **131** are summarized in Table 14. The signal for the pyrrole α-carbon is broadened as a result of coupling with the adjacent nitrogen-14 atom (cf. Section 2.3.3.5). While the frequencies observed for the β-carbon atoms show a fairly systematic upfield shift with increasing electronegativity of the heteroatom, the shifts for the α-carbon atoms vary irregularly. All the shifts are in the region of that for benzene (128.7 ppm). Spectra for a variety of 1*H*-pyrrole and 1*H*-indole derivatives have been tabulated <CHEC-III(3.01.3.3.2)12>.

Table 14 ^{13}C NMR spectral data for monoheterocycles **131** (in acetone)



131

	Pyrrole	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
C(2)	118.2	143.6	125.6	131.0	127.3
C(3)	107.2	110.4	127.3	129.8	138.0
$J_{C(2),\ H(2)}$	184	201	185	189	183
$J_{C(3),\ H(3)}$	170	175	168	166	159
$J_{C(2),\ H(3)}$	(7.6)	14	7.35	7.0	–
$J_{C(2),\ H(4)}$	(7.6)	5.8	10.0	10.0	–
$J_{C(2),\ H(5)}$	(7.6)	7.0	5.15	3.5	–
$J_{C(3),\ H(2)}$	7.8	7.0	4.7	4.5	–
$J_{C(3),\ H(4)}$	4.6	4.0	5.9	6.0	–
$J_{C(3),\ H(5)}$	7.8	10.8	9.5	10.4	–
References	1968JA3543	1968JA3543, 1965JA5333	1968JA3543, 1965JA5333	1968JA3543, 1974ACS(B)175	1974ACB175

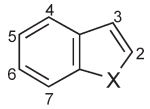
Units are ppm and Hz.

The direct $J_{C(3),H(3)}$ coupling constants decrease regularly along the series O > NH > S > Se > Te. The values for $J_{C(2),H(2)}$, are appreciably larger than the 159 Hz observed for benzene and the 170 Hz for the alkene protons of cyclopentadiene, while the $J_{C(3),H(3)}$ coupling constants span this range.

Similar correlations have been observed <1975CS(7)211> between the ^{13}C NMR spectra of monosubstituted furans, thiophenes, selenophenes, and tellurophenes as with their ^{1}H NMR spectra (cf. Section 2.3.3.3). Thus, for the 2-substituted compounds, the ΔC(3)/ΔC(5) ratios decrease systematically in the series furan (2.58) > thiophene (1.34) = selenophene (1.34) > tellurophene (0.91). Extensive quantitative correlations have been established between the shifts of the corresponding carbon atoms in the different heterocycles <1975CS(7)211>. In most cases $^{1}J_{(C,H\beta)}$ in both 2- and 3-substituted heterocycles can be linearly correlated with the electronegativity of the heteroatom, with the couplings being largest for the furans.

The signals for C(2) in indole, benzo[*b*]furan, and benzo[*b*]thiophene (**Table 15**) are shifted to lower fields than those for C(3). However, the shifts for C(2) (O, 144.8; Se, 128.8; S, 126. 1; NH, 124.7; Te, 120.8) and C(7a) (O, 155.0; Se, 141.3; S, 139.6; NH, 135.7; Te, 133.0) in the benzo[*b*] heterocycles **134** vary irregularly <1980OMR(13)319>, and the sequence is different to that observed for C(2) in the parent heterocycles **131**, namely O > Se > Te > S > NH. Also noteworthy is the upfield position of C(7), especially in indole and benzofuran, relative to the other benzenoid carbons at positions 4–6. Thus for indole, the effect of the heteroatom is strongest at the β-carbons C(3), C(3a), and C(7) with upfield shifts of 29.6, 16.7, and 12.4 ppm, respectively. Only moderate effects (0.1–9.5 ppm) are seen at the other carbons <1987MRC377>.

Table 15 ^{13}C NMR spectral data (ppm) for benzo[*b*] heterocycles **134**



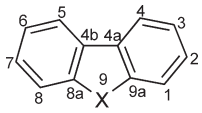
134

	Indole	*Benzofuran*	*Benzothiophene*
C(2)	124.67	145.1	126.21
C(3)	102.14	106.9	123.79
C(4)	120.76	121.6	123.57
C(5)	121.81	123.2	124.10
C(6)	119.76	124.6	124.17
C(7)	111.35	111.8	122.44
C(7a)	135.65	155.5	139.71
C(3a)	128.26	127.9	139.57
Solvent	dioxane	CS_2	$CDCl_3$
References	1970JOC996, 1975JOC3720	1974BCJ1263	1976OMR(8)252

The ^{13}C shifts for indoles have almost no solvent dependence, allowing easy comparison between spectra obtained in different solvents. Substitution on the nitrogen has varying effects on the ring carbons. N-Deprotonation causes large downfield shifts of the C(2) and C(3a) signals, with slight upfield shifts of C(5), C(6), and C(7a). On the other hand, replacement of the N-proton with a phenyl group does not noticeably affect any of the ring carbons. N-Alkyl substitution seems to only affect the chemical shift of the C(2) signal, moving it downfield by about 5 ppm.

In the dibenzo heterocycles **119** (**Table 16**), C(1) and C(8) are shifted upfield in carbazole **119** (X = NH) and dibenzofuran **119** (X = O) relative to the corresponding carbons in dibenzothiophene **119** (X = S) and fluorene **119** ($X = CH_2$), and similar, though smaller, shifts can be discerned for C(3) and C(6) in the former compounds.

Table 16 ^{13}C NMR spectral data (ppm) for dibenzo heterocycles **119** (in DMSO-d_6)

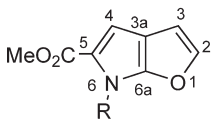


119

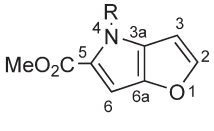
	Carbazole X = NH	*Dibenzofuran*[a] X = O	*Dibenzothiophene*[a] X = S	*Fluorene* X = CH_2
C(1,8)	110.8	111.6	122.9	125.0
C(2,7)	125.4	127.5	127.0	126.7
C(3,6)	118.4	123.0	124.6	126.7
C(4,5)	120.0	121.1	121.9	119.9
C(4a,4b)	122.6	123.5	134.9	141.0
C(8a,9a)	139.6	155.4	138.5	142.8

<1979OMR(12)647>.
[a]This is not the normal numbering system for these molecules.

^{13}C NMR spectral details for 5:5-fused heterocycles have been tabulated <CHEC-II(7.01.3.3)9>. ^{13}C Chemical shifts for the pairs of isomers **142a–c** and **143a–c** are shown in Table 17. Comparison of the ^{13}C chemical shifts of compounds **142a** and **143a** with those of the carbons of furan and methyl pyrrole-2-carboxylate shows that in the 1,4-isomer **143a** the differences are greater than in the 1,6-isomer **142a**. In **143a** C(2) shows a downfield shift ($\Delta\delta = 5.09$ ppm) while C(3) shows an upfield shift ($\Delta\delta = -11.51$ ppm), as does C(6) ($\Delta\delta = -18.17$ ppm). This demonstrates that the electron density of both systems changes due to the fused ring, but the effect is greater in the 1,4 system <CHEC-III(10.01.3.2)6>.



142



143

In structures **142** and **143**: a; R=H; b, R=Me; c, R=Bn

Table 17 ^{13}C chemical shifts (ppm) of isomers **142a–c** and **143a–c** in $CDCl_3$

Carbon	*142a*	*142b*	*142c*	*143a*	*143b*	*143c*
C(2)	143.65	143.48	143.72	148.69	148.29	148.30
C(3)	105.62	105.71	105.67	98.89	97.83	98.64
C(3a)	110.56	107.57	108.05	128.86	133.34	132.99
C(4)	106.36	106.86	107.76	–	–	–
C(5)	120.70	120.76	120.16	123.77	123.40	123.19
C(6)	–	–	–	96.93	97.83	98.80
C(6a)	151.60	153.56	153.52	147.93	145.34	145.80
CO	162.75	162.33	162.12	162.61	162.40	162.28
OCH_3	51.60	50.37	50.90	51.58	50.89	51.04

Units are ppm.

Some information on partially- and fully-saturated heterocycles is summarized in Figure 11. As would be expected, the downfield shift of the α-carbon atom decreases with decreasing electronegativity of the heteroatom in the sequence $O < NH < S < CH_2$.

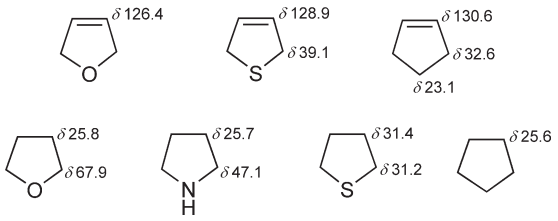


Figure 11 ^{13}C NMR chemical shifts for partially- and fully-saturated rings.

2.3.3.5 Heteroatom NMR Spectroscopy

All of the heteroatoms possess at least one naturally occurring isotope with a magnetic moment (**Table 18**). The electric quadrupole of ^{14}N, ^{17}O, and ^{33}S broadens the NMR signals so that line widths may be 50–1000 Hz or even wider. To some extent this problem is offset by the more extensive chemical shifts that are observed. The low natural abundances and/or sensitivities have necessitated the use of accumulation techniques for all of these heteroatoms. ^{14}N and ^{15}N chemical shifts are interchangeable.

Table 18 Magnetic properties of heteronuclei

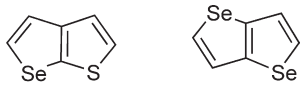
Isotope	*Natural abundance (%)*	*Nuclear spin*	*Electric quadrupole moment*[a]	*NMR frequency for a 23.5 kG field (MHz)*	*Relative sensitivity*
^{1}H	99.98	1/2	–	100	1
^{13}C	1.11	1/2	–	25.19	0.016
^{14}N	99.635	1	2.0	7.224	0.00101
^{15}N	0.365	1/2	–	10.133	0.00104
^{17}O	0.037	5/2	−0.4	13.56	0.029
^{33}S	0.74	3/2	−6.4	7.67	0.0023
^{77}Se	7.58	1/2	–	19.135	0.00693
^{125}Te	7	1/2	–	30.6	0.032

[a] $e \times 10^{-26}\,cm^2$.

Despite its unfavorable NMR properties, the ^{17}O nucleus has attracted considerable interest, since its chemical shift represents a discriminating probe for structural and molecular properties. In a study of some five-membered heterocycles (furan and isoxazole methyl derivatives) <1984OMR(22)55>, it was found that the ^{17}O chemical shifts are primarily determined by the p-electron density on the oxygen atom. A ^{17}O downfield shift of *222* ppm is observed on the formal aromatization of tetrahydrofuran to furan <1961HCA865>.

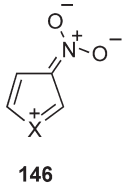
Plotting the ^{17}O chemical shifts of 2,5-disubstituted furans versus those of the 2-substituted analogues has demonstrated the additivity of substituent effects <1985MRC985>. Because they do not correlate with Hammett constants, the electronic character of substituents alone does not determine the ^{17}O chemical shifts.

Downfield shifts are observed for ^{33}S (tetrahydrothiophene → thiophene 309 ppm) <1972JA6579> and ^{14}N (pyrrolidine → pyrrole 106 ppm) <1971TL1653>, and a very much larger shift can be anticipated for tetrahydroselenophene to selenophene <1976OMR(8)354, 1972JCD1397>. Benzoannulation of pyrrole causes a 10–20 ppm upfield shift per benzene ring. Much larger upfield shifts are observed in proceeding from selenophene → benzoselenophene (79 ppm) → dibenzoselenophene (75 ppm) <1976OMR(8)354>. Similar upfield shifts of 65 and 56 ppm, respectively, are observed on annulation with a thiophene ring or selenophene ring to give selenolo[2,3-*b*]thiophene **144** <1976OMR(8)354> and selenolo[3,2-*b*]selenophene **145** <1974CS(5)236>.

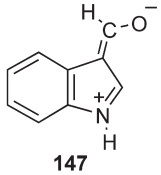


144 **145**

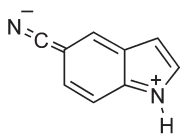
The relatively modest shifts observed for substituted pyrroles are more suitably probed by ^{15}N rather than ^{14}N NMR and seem to parallel the ^{77}Se and ^{125}Te behaviours. Electron-withdrawing groups such as 2-nitro, 2-formyl, and 2-acetyl cause downfield ^{15}N shifts <1976OMR(8)208>. Although electron-withdrawing groups on the nitrogen atom of pyrroles significantly deshield the ring carbons, the effect on ^{15}N chemical shifts shows no straightforward correlation with electron-withdrawing strength <2005MP1113>. A DFT study on a series of substituted pyrroles shows that a correlation exists between the paramagnetic shift and the ^{15}N chemical shift, indicating that the trend for the pyrroles arises entirely from variations of the paramagnetic shift contribution <CHEC-III(3.01.3.3.3)17>. Perhaps unexpected is the much larger downfield shift found for 3-nitropyrrole than its 2-nitro isomer. Similar disparities with electron-accepting groups also arise with selenophenes and may be accounted for in terms of a contribution by the resonance structure **146**. Similar considerations apply to the relatively large ^{15}N downfield shifts observed when such groups are present at positions 3 and 5 of the indole nucleus, the relevant resonance structures being **147** and **148**, respectively <1976OMR(8)117>.



146



147

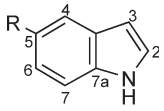


148

In a study of protonation effects <1993MRC791>, ^{15}N NMR spectra were taken for carbazole, *N*-methylcarbazole, and *N*-methylindole in both DMSO-d_6 and acidic media (CF_3CO_2H or H_2SO_4) relative to external CH_3NO_2. The shifts (35–45 ppm) for carbazoles are much larger than those for anilines, probably due to disruption of the carbazole aromaticity. Indole shifts approximately 94 ppm downfield upon protonation: this, combined with the couplings, suggests the formation of a 3*H*-indole cation rather than the N-protonated species, and agrees well with AM1 calculations <1990J(P2)65> (see also Section 3.3.1.3).

^{15}N NMR data for 5-substituted indoles are summarized in **Table 19** <1993MRC238>. As expected, electron-donating substituents induce upfield shifts of up to 3.1 ppm, whereas electron-withdrawing substituents shift the signal downfield by up to 6.8 ppm. In comparison to structurally similar acetanilides, substituent transmission is more efficient through the indole system, possibly due to the greater rigidity of the indole nucleus.

Table 19 ^{15}N NMR data for 5-substituted indoles **149**



149

Substituent (R)	*δ ^{15}N (ppm)*	*Δδ ^{15}N*	*J (N,H)*	*δ C(2)[a]*	*δ C(7a)[a]*
H	−244.5	0.0	97.5	163.6	156.2
CN	−238.9	5.6	98.1	167.2	161.7
CO_2Me	−240.7	4.2	95.7	165.6	161.7
Br	−242.9	1.6	95.3	166.6	157.9
Cl	−243.0	1.5	98.0	167.0	156.4
F	−244.3	0.2	97.5	168.0	153.9
AcO	−244.2	0.3	97.7	164.8	155.6
NO_2	−237.7	6.8	96.5	168.8	165.5
Me	−245.5	−1.0	96.5	164.7	154.2
MeO	−246.0	−1.5	95.1	165.9	151.9
Me_2N	−247.6	−3.1	95.7	166.1	150.9

From external neat $MeNO_2$.
[a]In DMSO-*d*6.

2.3.3.6 UV Spectroscopy

The parent heterocycles **131** (Table 20) display a strong band near 220 nm with one additional band at longer wavelengths for thiophene and selenophene, and two for tellurophene. Analogous weak bands reported in the older literature for furan and pyrrole are now generally accepted as arising from autoxidation products.

Table 20 UV spectra (nm) of monocyclic heterocycles **131**

131

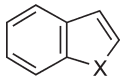
Substituent	λ_{max} (log ε)				
	O	*NH*	*S*	*Se*	*Te*
None	208 (3.90)	210 (4.20)	215 (3.8)	232 (3.56)	209 (3.57)
			231 (3.87)	249 (3.75)	241 (3.36)
					279 (3.93)
2-CO_2H	214sh (3.58)	222sh (3.65)	246 (3.96)	258 (3.94)	–
	243 (4.03)	258 (4.10)	260 (3.84)	282 (3.70)	
2-CO_2Me	252 (4.13)	238sh (3.63)	248 (3.97)	260 (4.0)	–
		263 (4.14)	268 (3.86)	284 (3.80)	
2-COMe	226 (3.38)	250sh (3.70)	260 (4.01)	271 (4.02)	211 (3.93))
	270 (4.15)	287 (4.21)	283 (3.87)	302 (3.70)	282 (3.87)
					346 (3.58)
2-CHO	227 (3.48)	251 (3.49)	260 (4.04)	271 (4.07)	–
	272 (4.12)	287 (4.12)	286 (3.86)	304 (3.71)	
2-NO_2	225 (3.53)	231 (3.61)	270 (3.80)	–	–
	315 (3.91)	335 (4.23)	296 (3.78)		
3-CO_2H	200 (3.85)	223 (3.89)	241 (3.92)	–	–
	235 (3.39)	245 (3.71)			
3-CO_2Me	238 (3.40)	224 (3.90)	241 (3.95)	–	–
		247 (3.73)			
3-COMe	–	243 (3.97)	250 (4.08)	–	–
		270sh (3.66)			
3-CHO	–	243 (3.97)	251 (4.12)	–	–
		270 (3.66)			
Solvent	EtOH	EtOH, MeOH	EtOH	EtOH	*n*-hexane
References	1971PMH(3)79	1971PMH(3)79, 1971T245	1958SA350	1958G453	1972J(P1)199

The marked progressive shift of absorption to longer wavelengths in the sequence furan < pyrrole < thiophene < selenophene < tellurophene is also observed with their 2-substituted derivatives. Increasing conjugating powers of 2-substituents result in displacement of absorption bands to longer wavelengths in the expected sequence CO_2H < COMe < CHO < NO_2. Smaller bathochromic shifts occur when conjugating substituents are introduced into position 3, but now pyrrole displays larger shifts than thiophene.

The cyclopentadiene anion is a carbocyclic analogue of these heterocycles. Simple theoretical treatment shows that, in contrast to iso-π-electronic benzene, there is no breaking of the degeneracy of the low-energy forbidden transitions or the high-energy allowed transitions as a result of the lower symmetry of the anion. The absorption spectrum of the cyclopentadienyl anion and its hetero analogues is thus expected to consist of a moderate intensity band followed by a high intensity band at shorter wavelengths. Bands arising from promotion of an electron from the lone pair orbital of a heteroatom to a π-orbital of the heterocyclic ring ($n \rightarrow \pi^*$) are not expected for pyrrole since the nitrogen lone pair is involved in the π-bonding. For the other heterocycles where additional heteroatom lone pairs are available, they have yet to be identified, even by electron-impact studies <1976JCP(64)1315, 1976CPL(41)535>. These studies did, however, show singlet → triplet transitions at 3.99 eV (311 nm) and 5.22 eV (238 nm) in furan, 3.75 eV (331 nm) and 4.62 eV (268 nm) in thiophene, and 4.21 eV (294 nm) in pyrrole. The positions and energy splitting are analogous to the lowest $n \rightarrow \pi^*$ transitions in benzene and very different to those anticipated for conjugated dienes.

Annulation increases the complexity of the spectra just as it does in the carbocyclic series, and the spectra are not unlike those of the aromatic carbocycles, e.g., naphthalene. Although quantitatively less marked, the same trend for the longest wavelength band to undergo a bathochromic shift in the heteroatom sequence O < NH < S < Se < Te is discernible in the spectra of the benzo[*b*] heterocycles **134** (**Table 21**).

Table 21 UV spectra (nm) of benzo[*b*] heterocycles **134** in heptane



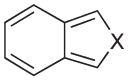
134

Compound	λ_{max} *(log ε)*						
Indole[a]	215 (4.38)	261 (3.69)	266.5 (3.70)	277sh (3.58)	279 (3.62)	287 (3.51)	–
Benzofuran[a]	–	239.5 (4.03)	240.5 (4.03)	244.5 (4.04)	250.5 (3.91)	269 (3.23)	271 (3.25)
						275 (3.40)	281 (3.49)
Benzothiophene[a]	228 (4.45)	263sh (3.71)	258 (3.76)	281 (3.19)	288.5 (3.33)	290.5 (3.33)	297 (3.52)
Benzoselenophene[a]	236 (4.45)	260 (3.70)	270sh (3.52)	296 (3.56)	298 (3.54)	305 (3.79)	–
Benzotellurophene[b]	214 (4.43)	251 (4.43)	–	312sh (4.15)	318 (4.2)	–	–

[a]<1957ACH(11)365>.
[b]<1971BSB521>.

The absorption of the benzo[*c*]heterocycles **135** (**Table 22**) at longer wavelengths than their benzo[*b*] counterparts is a reflection of the lower aromaticity of the former compounds and the consequent differences in the energies of the HOMOs. The smaller energy separation between the frontier orbitals is demonstrated quantitatively by the AM1 calculated HOMO–LUMO gaps shown in **Table 1** (Section 2.3.2.1).

Table 22 UV spectra (nm) of benzo[*c*] heterocycles **135** in hexane



135

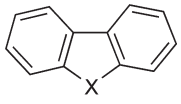
Compound	λ_{max} *(log ε)*
Benzo[*c*]indole[a]	263.5, 268.5, 275, 286.5, 294sh, 300, 306.5, 312.5, 320, 326.5, 335
Benzo[*c*]furan[b]	215 (4.17), 244 (3.4), 249 (3.37), 254 (3.35), 261 (3.12), 292sh (3.35), 299sh (3.47), 305sh (3.56), 313 (3.7), 319 (3.7), 327 (3.87), 334 (3.66), 343 (3.79)
Benzo[*c*]thiophene[c,d]	215 (4.84) 257sh (4.04), 272 (3.94), 278 (3.94), 283sh (3.93), 290 (3.97), 295 (3.96), 298sh (3.94), 305 (4.06), 313 (3.89), 318 (3.90), 322 (3.88), 328 (3.91), 333 (3.90), 343 (3.79)
Benzo[*c*]selenophene[e]	273, 286, 291, 298, 302sh, 305sh, 312, 323, 328, 336sh, 340, 344sh, 353, 357, 362sh

[a]<1973J(P1)1432>.
[b]<1971TL2337>.
[c]<1963JPR(20)244>.
[d]In MeOH.
[e]<1976JA867>.

As might be anticipated, the effect of the fusion of a second benzenoid ring to give the dibenzo heterocycles **119** is to further reduce the differences in their spectroscopic properties (cf. **Table 23**).

Furan, pyrrole, and thiophene do not fluoresce or phosphoresce; however, indole and carbazole both fluoresce and phosphoresce strongly <CHEC-III(3.01.3.4)22, 1974PMH(6)166>. The characteristic fluorescence of indoles has found extensive application in the detection and estimation of naturally occurring derivatives. The fluorescence maximum of indole observed at 297 nm in cyclohexane undergoes dramatic shifts in hydrogen-bonding solvents, possibly due to strong interactions between the solvent and the lowest excited singlet state of the indole. The wavelength of

Table 23 UV spectra (nm) of dibenzo heterocycles **119** in EtOH



119

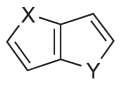
Compound	*Zone A*	*Zone B*	*Zone C*
Dibenzofuran	218 (4.51), 227sh (4.31), 241 (4.04), 244 (4.04), 249 (4.26)	275sh (4.09), 280 (4.22), 286 (4.19)	296 (3.95), 300sh (3.65)
Carbazole (X = NH)	211 (4.43), 227sh (4.53), 233 (4.57), 243 (4.38), 253 (4.25)	282sh (3.99), 291 (4.14)	322 (3.52), 334 (3.44)
Dibenzothiophene	237 (4.57), 258 (4.12), 264 (3.99)	280sh (3.75), 289 (4.05)	317 (3.28), 328 (3.39)
Dibenzoselenophene	238 (4.77), 260sh (4.14)	278 (3.84), 286 (3.98)	316 (3.37), 326 (3.46)
Dibenzotellurophene	212 (4.39), 232sh (4.93), 235 (4.93), 255 (4.32), 263 (4.20)	280sh (3.99), 286 (4.24)	303 (3.45), 312 (3.53), 325 (3.63)

<1958AC(R)738>.

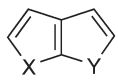
phosphorescence of benzothiophene ($\lambda_p = 416$ nm) is somewhat longer than that of indole (λ_p 404 nm), reflecting the effect of the higher energy $3p_\pi$ orbital of sulfur on the energy of the HOMO as opposed to that of the nitrogen $2p_\pi$ orbital. The effect is less marked in the case of dibenzothiophene ($\lambda_p = 411$ nm), relative to dibenzofuran ($\lambda_p = 408$ nm) and carbazole ($\lambda_p = 407$ nm).

UV spectral data of parent diheteropentalenes **95**–**97** are summarized in **Table 24**. The thienothiophenes and selenolothiophenes show more absorption maxima in their UV spectra than the other systems. The absorption at longer wavelengths, like the benzo derivatives, is consistent with the calculated frontier orbital energies, which are smaller than in the monocyclic analogues (**Table 1**, Section 2.3.2.1). Inspection of **Table 1** reveals that the conjugated mesomeric betaines **98** have a particularly small HOMO–LUMO energy gap. Although examples of the parent systems are not known, it is significant to note that the known examples **150** and **151** (**Figure 12**) are highly coloured with absorption at particularly long wavelengths <1974JA4268>.

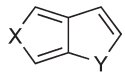
Table 24 UV spectra (nm) of parent diheteropentalenes **95**–**97**



95



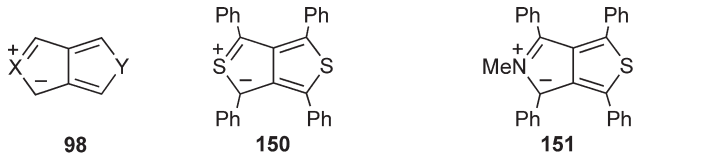
96



97

Structure	*X*	*Y*	λ_{max} *(log ε)*[a]	*Reference*
95	NH	O	248 (4.20)	1978CJC1429
95	NH	S	217 (3.85), 258 (4.10)	1978CJC1429
95	NH	NH	245 (4.15)[b]	1984TL5669
95	NH	Se	219 (3.81), 266 (4.09)	1978CJC1429
95	S	S	259 (4.09), 268 (4.08), 278 (4.04), 305 (1.00)	1976AHC(19)123
95	S	Se	264 (3.58), 276 (3.61), 287 (3.65)	1973JPR850
96	NH	S	212 (4.26), 250 (3.56)	1978CJC1429
96	NH	NH	243 (3.94)	1978CJC1429
96	NH	Se	214 (4.30), 251 (3.61)	1978CJC1429
96	S	S	225 (4.37), 269 (3.28), 278 (2.99), 298 (1.48)	1976AHC(19)123
96	S	Se	229 (4.45), 260 (3.63), 268 (3.61), 278 (3.56) 288 (3.40)	1973JPR850
97	NH	S	230 (4.13), 285 (3.87)	1986CC310
97	S	Se	236 (4.26), 241 (4.25), 266 (3.52), 275 (3.46), 303 (3.64)	1973JPR850
97	S	O	216 (3.65), 221sh (3.62), 259 (3.74)	1986TL3045
97	S	S	235 (4.23), 257 (3.53), 266 (3.56), 275.5 (3.56), 296.5 (3.73)	1967TL761

[a]Solvent EtOH unless otherwise stated.
[b]Solvent cyclohexane.



98 **150** **151**

Purple needles
λ_{max} ($CHCl_3$) 258, 262sh, 292, and 551 nm

Red needles
λ_{max} ($CHCl_3$) 256 and 533 nm

Figure 12 UV spectra of 2,5-diheteropentalene mesomeric betaines.

2.3.3.7 IR Spectroscopy

2.3.3.7.1 Ring vibrations

The literature concerning the IR spectra of these heterocycles has been extensively surveyed <1963PMH(2)165, 1971PMH(4)265, 1991HC(44)1>. Assignment of vibrational modes has been facilitated in recent years by the use of high-level quantum chemical calculations <1996J(P2)2653, 2000JMT(507)75>. Tabulation of recent IR data for pyrroles, furans, and thiophenes can be found in CHEC-III, Volume 3.

Vibrational assignments for the parent heterocycles are summarized in **Table 25**. These have been derived from IR and Raman spectra of both the parent heterocycles and the deuterated derivatives. In the case of the vibrations of A_1 symmetry, these have been further supported by photoelectron spectroscopic studies <1971SAA2525>. The variety of factors responsible for the observed differences precludes a complete rationalization as they may variously operate in concert or in opposition. Pertinent factors include the mass and electronegativity of the heteroatom, π-electron delocalization, ring geometry, and vibrational coupling of normal modes. The ring modes permit the best qualitative

Table 25 Fundamental vibrational frequencies (cm^{-1}) of parent heterocycles

Vibration[a]	*Approximate description*[a]	C_{2v}	*Pyrrole*[b]	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
v_1	C–H stretch	A_1	3133	3159	3110	3110	3084
v_2	C–H stretch		3108	3128	3086	3063	3045
v_5	Ring stretch		1466	1483	1408	1419	1432
v_4	Ring stretch		1384	1380	1360	1341	1316
v_6	C–H def. i.p.		–	1140	1081	1080	1079
v_7	C–H def. i.p.		1076	1061	1033	1010	984
v_3	Ring stretch		–	986	833	758	687
v_8	Ring def. i.p.		–	873	606	456	380
v_9	C–H def. o.o.p.	A_2	869	863	900	905	912
v_{10}	C–H def. o.o.p.		–	728	686	685	690
v_{11}	Ring def. o.o.p.		–	613	565	541	507
v_{12}	C-H stretch	B_1	3133	3148	3110	3100	3084
v_{13}	C-H stretch		3108	3120	3073	3054	3030
v_{14}	Ring stretch		1531	1556	1506	1515	1516
v_{15}	C–H def. i.p.		1047	1270	1250	1243	1246
v_{16}	C–H def. i.p.		1015	1171	1081	1080	1079
v_{17}	Ring (def. + stretch)		–	1040	871	820	797
v_{18}	Ring def. i.p.		652	873	750	623	552
v_{20}	C-H def. o.o.p.	B_2	1047	839	864	870	884
v_{19}	C-H def. o.o.p.		768	745	712	700	674
v_{21}	Ring def. o.o.p.		649	601	453	394	354
	Reference		B-77MI30100	1967JSP(24)133	1965SA689	1970AHC(12)1	1976SAA1089

[a]Numbering and approximate description from <1967JSP(24)133>.
[b]Also 3410 N–H (A_1) stretch, 1146 NH in-plane def. (B_1), 561 NH out-of-plane def. (B_2), 1418 ring stretch (B_1).
def., deformation.

comparison, especially as the interaction of the C—H and N—H in-plane deformation modes of pyrrole precludes direct comparisons of its β-CH vibrations with those of the other heterocycles. The increase in frequency of the υ_5 mode, which is associated with the symmetric stretching of the double bonds, occurs in the sequence thiophene < selenophene < tellurophene < pyrrole < furan and may be related to increasing localization of double bonds attendant upon decreasing aromaticity. The large decreases in frequency of the υ_3 and υ_{17} modes, which depend upon symmetric and antisymmetric C—X—C stretching, respectively, and the ring deformation modes υ_8, υ_{18}, and υ_{21} have been attributed to mass and geometry effects.

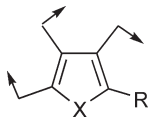
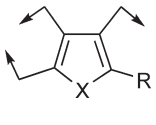
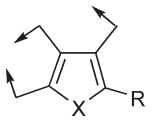
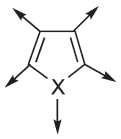
In the case of 2- and 3-substituted heterocycles, bands attributed to three ring-stretching modes are generally observed (cf. **Table 26**) with frequencies decreasing in the order furan > pyrrole > selenophene ≥ thiophene > tellurophene. The intensities of these bands are frequently found to be greater on increasing the electron-withdrawing capabilities of substituents. The effect of this increased electron withdrawal is to cause tighter conjugation, steeper charge gradients, and hence larger dipole moment changes during the vibrations. As a consequence of the occurrence of hydrogen bonding, either between molecules in concentrated solution or between molecules and solvent, the stretching frequency of the pyrrole N—H is subject to considerable variation <1970SAA269>. In the absence of association, the NH stretching vibration is also very susceptible to the electronic character of ring substituents. This is particularly noticeable with electron-withdrawing groups such as ethoxycarbonyl, acetyl, benzoyl, and cyano, and the effect of an α-substituent is always greater than that of a β-analogue <1965SA295, 1966AJC107, 1970MI30100>.

Table 26 Monosubstituted heterocycles: Ring stretching bands in the 1600–1300 cm^{-1} region

			β-CH modes		*Ring breathing*		
Heterocycle	*Substituent*	*Phase*	ε_A (cm^{-1})	ε_A (cm^{-1})	ε_A (cm^{-1})	ε_A (cm^{-1})	*References*
Pyrrole	1-	$CHCl_3$	1549 + 3 (15–25)	1477 ± 7 (25–185)	–	1394 ± 10 (15–35)	1966AJC289
Furan	2-	$CHCl_3$	1585 ± 26 (10–145)	1498 ± 28 (20–290)	1391 ± 14 (5–115)	–	1959JCS657
Thiophene	2-	$CHCl_3$	1523 ± 9 (3–110)	1422 ± 12 (20–280)	1354 ± 7 (15–150)	1231 ± 10	1959JCS3500 1970SAA1651
Selenophene	2-	$CHCl_3$	1532 ± 28 (5–213)	1432 ± 28 (13–290)	1332 ± 28 (6–65)	–	1975JST(27)195
Tellurophene	2-D	liquid	1505	1423	1300	1224	1976SAA1089
Pyrrole	2-	$CHCl_3$	1558 ± 9 (20–80)	1471 ± 3 (20–70)	1415 ± 8 (20–325)	–	1963AJC93
Furan	3-	liquid	ca. 1562	ca. 1512	–	–	1959G913, 1958T(4)68
Thiophene	3-	$CHCl_3$	1512 ± 17 (90–240)	1413 ± 15 (65–135)	1365 ± 11 (5–45)	1210 ± 12	1963JCS3881
Selenophene	3-	$CHCl_3$	1532 ± 28 (6–307)	1432 ± 28 (12–139)	1332 ± 28 (9–360)	–	1975JST(27)195
Pyrrole	3-	$CHCl_3$	1549 ± 7 (20–180)	1491 ± 9 (55–195)	1427 ± 4 (60–160)		1971PMH(4)265

Three β-CH modes corresponding to in-plane C—H deformations are also observed and are probably best depicted as in **152**–**154** (**Table 27**), although those for pyrrole will be modified as a result of interaction with the in-plane N—H deformation. The skeletal ring-breathing mode **155** observed at ca. 1137 cm^{-1} for 2-substituted pyrroles and at 1015 cm^{-1} for 2-substituted furans is displaced to the 800 cm^{-1} region for thiophenes and presumably to even lower wavelengths for selenophene and tellurophene derivatives. The NH-deformation mode of substituted pyrroles is responsible for a band at ca. 1120 cm^{-1} <1963AJC93>.

Table 27 Monosubstituted five-membered heterocycles: Characteristic bands in the 1300–1000 cm^{-1} region

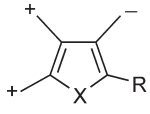
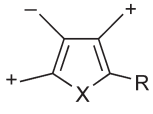
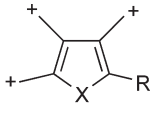





			β-CH **152**	β-CH **153**	β-CH **154**	Ring breathing **155**	
Heterocycle	*Substituent*	*Phase*	ε_A (cm^{-1})	ε_A (cm^{-1})	ε_A (cm^{-1})	ε_A (cm^{-1})	*Reference*
Pyrrole	1-	$CHCl_3$	–	1069 ± 6 (100–240)	1027 ± 9 (35–135)	–	1966AJC289
Furan	2-	$CHCl_3$	1220 ± 20	1158 ± 7 (70–120)	1076 ± 3 (25–65)	1015 ± 4 (60–280)	1959JCS657
Thiophene	2-	$CHCl_3$	–	1081 ± 3 (5–15)	1043 ± 7 (15–95)	–	1959JCS3500, 1970SAA1651
Pyrrole	2-	$CHCl_3$	–	1088 18 (25–450)	1033 ± 13 (40–400)	1137 ± 8 (25–130)	1963AJC93
Selenophene	2-D	liquid	–	1027	1083	–	1970AHC(12)1
Tellurophene	2-D	liquid	–	1079	1021	–	1976SAA1089
Furan	3-	liquid	–	ca. 1156	–	–	1959G913
Selenophene	3-D	liquid	–	1013	1076	–	1970AHC(12)1
Pyrrole	3-	$CHCl_3$	–	1077 ± 3 (60–100)	1041 ± 4 (30–150)	–	B-71MI30100

Modes shown for 2-substituted rings.

The γ-CH modes arising from out-of-plane CH deformations characterize the substitution pattern, and the observed frequencies are summarized in Table 28. For 2-substituted compounds these may be assigned as **156–158** (Table 28). Additional characteristic bands for 2-substituted thiophenes are observed at 870–840 cm^{-1} and 740–690 cm^{-1} <1967RTC37>.

Table 28 Monosubstituted five-membered heterocycles: Characteristic bands in the 1000–600 cm^{-1} region


156

157

158

Heterocycle	*Substituent*	*Phase*	*γ-CH or β-ring modes* (ε_A) (cm^{-1})				*References*
Pyrrole	1-	$CHCl_3$	–	926 ± 4 (20–140)	722 ± 2 (375–475)	– –	1966AJC289
Furan	2-	$CHCl_3$	–	925 ± 9	884 ± 2	808 ± 28 –	1959JCS657
Thiophene	2-	$CHCl_3$	–	925 ± 8 (5–15)	853 ± 7 (50–100)	823 20 (30–70)	752 ± 1 6	1959JCS3500, 1970SAA1651
Selenophene	2-D	Liquid	–	873	785	845	612	1970AHC(12)1
Tellurophene	2-D	Liquid	–	910	856	855	748	1976SAA1089
Pyrrole	2-	–	961 ± 8 (15–45)	929 ± 3 (10–75)	882 ± 4 (10–120)	– –	1963AJC93
Furan	3-	Liquid	–	–	878 ± 8	–	741	1959G913, 1958T(4)68
Thiophene	3-	Liquid	–	–	–	–	755s	1957AK(12)239
Selenophene	3-D	Liquid	–	852	810	794	609	1970AHC(12)1
Pyrrole	3-	–	953 ± 4 (30–110)	–	886 ± 2 (10–20)	– –	1977MI30100

Modes shown for 2-substituted rings.

2.3.3.7.2 Substituent vibrations

In most cases the frequencies of substituent groups attached to these heterocycles differ little from those observed for their benzenoid counterparts. The only notable exception is the spectral behaviour of carbonyl groups attached to position 2. These have attracted much attention as they frequently give rise to doublets, and occasionally multiplets. In the case of **159** and **160** <1976J(P2)1> and **161** <1976J(P2)597>, the doublets arise from the presence of two conformers (cf. Section 2.3.4.3.1), whereas for the aldehydes **162** the doublets are attributed to Fermi resonance <1975J(P2)604>. This phenomenon has also been found to occur with several compounds of types **159–161**, leading to multiple peaks. Fermi resonance is also responsible for the splitting of the –C≡N stretching band of some cyanopyrroles <1970JCB79>. In concentrated solutions 2-acylpyrroles and pyrrole-2-carboxylic esters exist as NH···O=C bonded dimers with a consequent lowering of the carbonyl stretching frequency <2001JST(562)107, 2002NJC165>. In dilute solution the spectra of the monomeric species show a carbonyl frequency for the 2-substituted pyrroles some 20–30 cm^{-1} lower than displayed by the 3-isomers <1966AJC107, 1965SA1011, 1965T2197>. The carbonyl frequencies of 1-acyl- and 1-alkoxycarbonyl-pyrroles are some 70 cm^{-1} higher than those of the corresponding 2- or 3-substituted compounds <1965T2197, 1966AJC289>.

IR and theoretical investigations of indole-2-carboxylic acid in the solid state show two chains of indole molecules forming a planar ribbon held together by intermolecular O–H···O and N–H···O hydrogen bonds <2004JST(688)79>.

159: Z = F, Cl **160**: Z = F, Cl **161** **162**

IR spectroscopy has been particularly helpful in detecting the presence of keto tautomers of the hydroxy heterocycles. Some typical frequencies for such compounds are indicated in **Figure 13**. Here again the doublets observed for some of the carbonyl stretching frequencies have been ascribed to Fermi resonance.

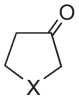
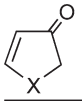
	X = NH	O	S
	1690, 1660 (1638)	1785, 1755 (1630–1620)	1678–1670 (1607)
	–	1800	1715 (1639)
	1695	1770	–
	1757	1770	–
	1675	1712	1680

Figure 13 IR frequencies (cm^{-1}) for keto heterocycles (carbonyl stretching frequencies; bracketed frequencies are for C=C stretches).

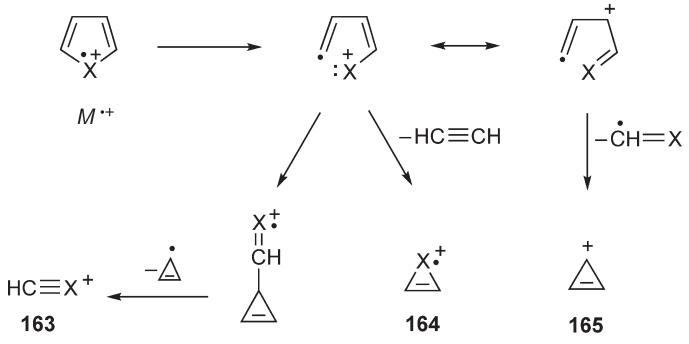
2.3.3.8 Mass Spectrometry

The valency and the even atomic weight of the principal isotope of nitrogen (^{14}N) ensure that pyrroles always display a molecular ion of uneven mass unless bearing a nitrogen-containing substituent. Like nitrogen, oxygen has only one principal naturally occurring isotope but sulfur with a natural isotope distribution $^{32}S/^{34}S$ of 25:1 ensures that thiophenes have two molecular ions which are two mass units apart and of appropriate intensity ratio. A far more complex situation arises with selenium and tellurium, of which each has a number of naturally occurring isotopes, namely ^{76}Se (9.1%), ^{71}Se (7.5%), ^{78}Se (23.6%), ^{80}Se (50%), ^{82}Se (8.8%); and ^{122}Te (2.5%), ^{123}Te (0.9%), ^{124}Te (4.7%), ^{125}Te (7%), ^{126}Te (18.7%), ^{128}Te (31.8%), ^{130}Te (34.8%).

The use of mass spectrometry has become increasingly important in natural product chemistry and biochemistry. In addition to structural elucidation based on analysis of fragmentation patterns, the use of soft-ionization techniques, e.g., matrix-assisted laser desorption ionization (MALDI) and electrospray ionization (ESI), provides information about molecular weights and supramolecular associations without causing extreme breakdown of the molecule <2002JAM1254>.

2.3.3.8.1 Parent monocycles

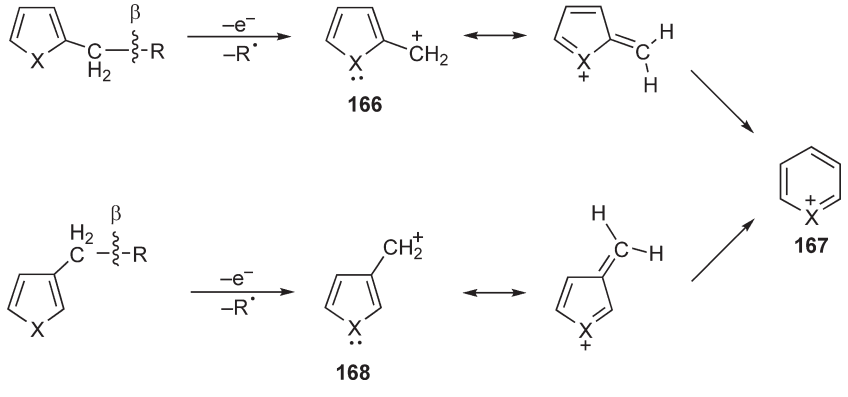
The principal fragmentation pathways encountered for pyrrole <1964JCS1949>, furan <1960BSB449>, thiophene <1959CCC1602>, selenophene <1978JHC137>, and tellurophene <1978JHC137> are shown in **Scheme 2**. The molecular ions (M^+) are usually the base peak of the spectrum, except for furan where the molecular ion is the strongest peak (70%) after the cyclopropenyl cation (100%). The cyclopropenyl ion **165** is also an important feature of the spectrum of pyrrole but much less important in the fragmentation of thiophene and selenophene, and apparently not observed for tellurophene. Another important ion in the spectra of pyrrole, thiophene, and selenophene has a constitution corresponding to **164**, formed by loss of acetylene from the molecular ion, but this ion is of low abundance for tellurophene and absent from the spectrum of furan. The ion **163** is much less abundant in furan and selenophene than for pyrrole or thiophene and only just detectable for tellurophene. In keeping with the much weaker nature of the carbon–tellurium and carbon–selenium bonds, the spectrum of tellurophene contains ions corresponding to *M*-Te and *M*-HTe, and that of selenophene contains less abundant *M*-Se and *M*-HSe ions. The spectrum of tellurophene contains a very intense Te^+ ion and that of selenophene contains a weaker Se^+ ion.



Scheme 2

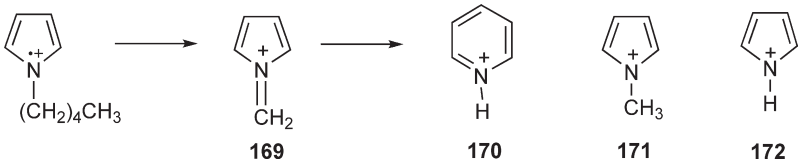
2.3.3.8.2 Substituted monocycles

Similar mass spectra are obtained for 2- and 3-alkyl derivatives of furan <1966T2223>, thiophene <1959CCC1602>, or pyrrole <1964JCS1949>. Apart from modest contributions from ions corresponding to constitutions **163–165** (**Scheme 2**), a major fragmentation pathway is initiated by β-cleavage of the alkyl substituent (**Scheme 3**). The resulting ions **166** and **168** are believed to rearrange to the common ion **167**, which is usually the base peak.



Scheme 3

N-Alkylpyrroles fragment in a somewhat different fashion, typified by *N*-pentylpyrrole (**Scheme 4**) <1964JCS1949>. β-Cleavage of the alkyl groups yields the ion **169**, which is believed to rearrange to the pyridinium ion **170** because it subsequently undergoes the characteristic elimination of HCN. In addition, the molecular ion also generates the *N*-methylpyrrole cation **171**, which is the base peak. Deuterium-labeling experiments <1965JA805> indicate that the hydrogen transferred in the formation of ion **171** comes mainly (78%) from C(3) of the alkyl chain with the remainder supplied by C(4). A lesser amount of the pyrrole cation **172** is also formed with the N–H proton derived mainly from C(2) and C(4).

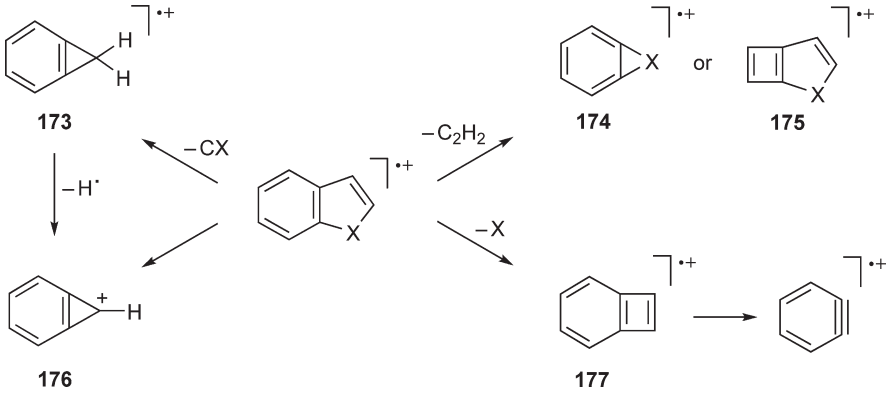


169 **170** **171** **172**

Scheme 4

2.3.3.8.3 Benzo derivatives

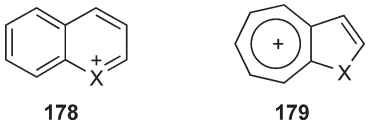
The fragmentation pathways displayed by the benzo[*b*] derivatives of these heterocycles (**Scheme 5**) parallel those of the monocyclic compounds (X = NH <1968AJC997>, O <1964AJC975>, S <1967AJC103>, Se <1969JCB971>, Te <1970JHC219>). As expected for aromatic molecules, the molecular ion is also the base peak except for benzotellurophene. The fragment **174** (or **175**) has only been noted as a minor ion in the spectra of benzo[*b*]thiophene and benzo[*b*]tellurophene. The elimination of the heteroatom resulting in the formation of the benzocyclobutadiene cation radical **177** is most prevalent with benzotellurophene (100%), less important with benzoselenophene, and only just detectable with benzothiophene. The ions **173** and **176** are prominent in the spectra of all of the benzo[*b*] heterocycles apart from benzotellurophene.



173 **174** **175** **176** **177**

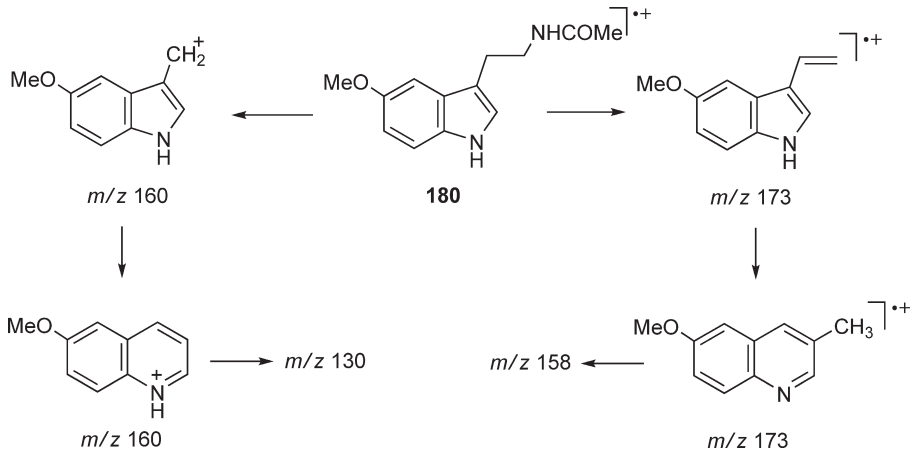
Scheme 5

As with the monocyclic series, 2- and/or 3-alkyl derivatives undergo β-fission of the alkyl group and rearrangement of the resulting ion to the cation **178**. A similar cleavage occurs when the alkyl group is attached to the benzene ring but the resulting ion is probably the isomeric tropylium ion **179**.



178 **179**

Scheme 6 shows the two main fragmentation pathways of the molecular ion of melatonin **180** to give fragment ions at *m/z* 160 and 173. Melatonin and its isomers have been distinguished by their fragmentation patterns and the relative abundance of fragment ions, assigned with the aid of metastable ion studies <1998RCM1538>. The fragmentation of 1-methylindole proceeds via the ion **181**. The gas-phase ion chemistry of a number of simple indoles, studied using several mass spectrometric methods, has been reviewed <2003MI174, 2004MI398>.

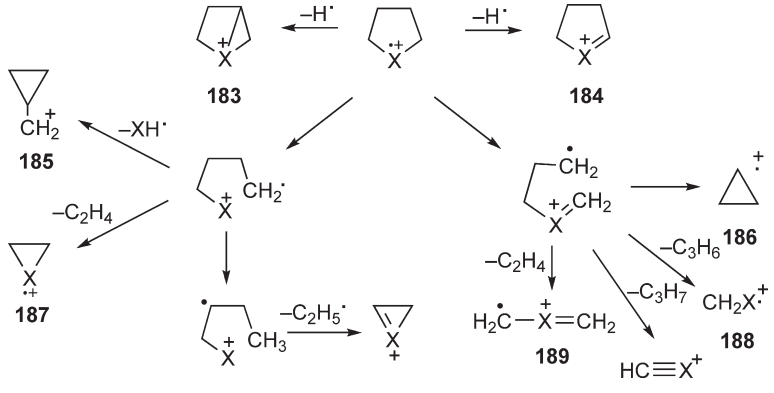


Scheme 6

The only notable fragments derived from the very stable molecular ions of carbazole <1964JA3729>, dibenzofuran <1964AJC975>, and dibenzothiophene <1968T3255> are at *m/e* 140 ($C_{11}H_8$) and 139 ($C_{11}H_7$), corresponding to loss of CX and HCX, respectively: structure **182** has been suggested.

2.3.3.8.4 Saturated compounds

The mass spectral fragmentations of the fully-saturated parent heterocycles <1965JA2920> are summarized in **Scheme 7**. All exhibit appreciably strong molecular ions. The *M*-1 ions **184** from pyrrolidine, tetrahydrofuran, and tetrahydrothiophene are formed predominantly by loss of an α-hydrogen atom (94, 70, and 65%, respectively), while tetrahydroselenophene loses only a β-hydrogen (**183**). The percentage total ionization of the *M*-1 species decreases in the order NH > O > S > Se > Te. The ions **187** and **189**, corresponding to loss of C_2H_4, are generally abundant with a notable exception in the case of tetrahydrofuran.



Scheme 7

The ions **188**, resulting from loss of cyclopropane from the molecular ions, are only observed for the sulfur, selenium, and tellurium analogues. The alternative mode of fragmentation, in which the hydrocarbon fragment **186** carries the charge, provides the base peak for the tetrahydrofuran spectrum, but is only a minor feature of the spectra of the selenium and tellurium analogues. The hydrocarbon ion **185** is a minor feature of the tetrahydrothiophene spectrum but provides the base peak of the spectra of the selenium and tellurium analogues.

2.3.3.9 Photoelectron Spectroscopy

2.3.3.9.1 Parent monocycles

The He(Iα) photoelectron spectra of the parent heterocycles are compared in **Table 29**. The assignments are based upon comparisons with the spectra of the reduced heterocycles, the effect of ring substituents, and comparisons with results of MO calculations. In the case of pyrrole, furan, and thiophene, the assignments have been further supported by measurements of photoelectron angular distribution, which permit evaluation of the asymmetry factors, thereby providing a useful criterion for distinguishing between π- and σ-orbitals <1979MI30100>. Even so, the third π-orbital cannot be unambiguously assigned. The three π-molecular orbitals can be depicted in **Figure 14**. The energy of the π_3-orbital, which extends exclusively over the carbocyclic part of the molecules, is almost constant for the chalcogen heterocycles, whereas the π_2-orbital energy depends markedly on the heteroatom and increases as the electronegativity decreases. As expected, the values for the π_3-orbital are close to the ionization potentials determined by electron impact. There is also excellent agreement with the energies of the π_3- and π_2-orbitals obtained from the charge transfer spectra of these heterocycles with tetracyanoethylene <1975J(F1)2045>.

Table 29 Vertical ionization energies (eV) of parent heterocycles measured by photoelectron spectroscopy

	Heterocycle				
Molecular orbital	*Pyrrole*	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
π_3	8.2[a]	8.89[b]	9.00[c] (9.2)[d]	8.92[b]	8.88[b]
π_2	9.2	10.32	9.50	9.18	8.40
π_1	–	14.4	12.00 (12.9)	12.0	11.8

[a]<1979CPL(61)355>.
[b]<1973CPL132>.
[c]<1992CPH(164)283>.
[d]Measured by electron momentum spectroscopy (EMS).

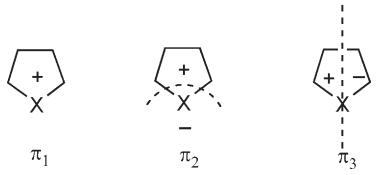


Figure 14 Symmetry of the molecular orbitals π_1-π_3.

2.3.3.9.2 Substituted monocycles

Vertical ionization energies are available for a range of α-substituted heterocycles (**Table 30**) <1976J(P2)276>. Excellent linear correlations of unitary slope are obtained between corresponding π-orbital energies of the different α-substituted heterocycles, such as π_3 for thiophenes versus π_3 for tellurophenes. α-Methyl substitution increases the separation of π_2 and π_3 in furan, thiophene, and selenophene, in agreement with the expectation that electron-releasing substituents in the α-position exert a more pronounced destabilizing effect on the energy of π_3 than on the energy of π_2.

Table 30 Vertical ionization energies (eV) of π_3 and π_2 molecular orbitals of 2-substituted five-membered heterocycles

	Furan		*Thiophene*		*Selenophene*		*Tellurophene*	
Substituent	π_3	π_2	π_3	π_2	π_3	π_2	π_3	π_2
Me	8.37	10.13	8.43	9.23	8.40	8.96	8.20	8.43
H	8.89	10.31	8.87	9.49	8.92	9.18	8.40	8.88
$CONMe_2$	8.86	10.41	8.84	9.40	8.85	9.10	8.39	8.89
Cl	–	–	8.89	9.63	8.83	9.34	8.68	8.89
Br	–	–	8.82	9.58	–	–	8.59	8.84
I	–	–	8.52	9.47	–	–	8.34	8.52
CO_2H	9.16	10.72	9.14	9.73	9.19	9.45	8.62	9.15
CO_2Me	9.00	10.56	8.98	9.61	9.05	9.26	8.51	9.00
NO_2	9.75	11.13	9.73	10.21	9.64	9.88	–	–
CH_2Cl	–	–	8.89	9.49	–	–	–	–
CHO	–	–	9.37	9.87	–	–	–	–
CN	9.47	10.99	–	–	–	–	–	–
SMe	8.58	10.32	8.63	9.37	–	–	–	–

<1976J(P2)276>.

The spectra of the halogen-containing compounds show two bands due to the halogen lone pairs, which are nonequivalent. The peak at lower ionization energy has been assigned to the electrons occupying the p_y-orbital coplanar with the ring. The band at higher energy is thus due to electrons in the p_y-orbital, which is perpendicular to the plane of the ring and overlaps the ring π-orbitals. Linear relationships are observed between the energies of the lone pair orbitals of Cl, Br, and I and their corresponding Pauling electronegativities for 2-halothiophenes and 2-halotellurophenes <1976J(P2)276>. The ionization energies of the halogen lone pairs vary with the ring, decreasing in the series furan > thiophene > selenophene > tellurophene. The energy separation between the lone pairs of a particular halogen is constant (Cl 0.38, Br 0.53, I 0.68 eV) and independent of the heteroatom. This is consistent with the p_y-orbital interacting with the π_3-orbital whose energy is constant for these chalcogen heterocycles. These energy separations are similar to those observed for halobenzenes, namely Cl 0.34, Br 0.55, I 0.84 eV.

2.3.3.9.3 Benzo derivatives

The effect of benzenoid annulation is to lower ionization potentials (**Table 31**). Perhaps the most noteworthy feature is that the ionization potentials of the benzo[*c*] heterocycles are lower than those of the benzo[*b*] isomers. Koopmans'

Table 31 The lowest vertical ionization potentials (eV) of benzo-annulated heterocycles

	Benzo[*b*]	*Benzo*[*c*]	*Dibenzo*
Pyrrole	7.76[a]	6.93[b,c]	7.60[d]
	8.38	8.60	7.99
	9.78	9.61	9.06
Furan	8.37[a]	7.63[b]	8.09[d]
	8.99	9.81	8.48
	10.40	10.30	9.35
Thiophene	8.13[a]	7.50[b]	7.93[d]
	8.73	8.95	8.34
	10.02	10.20	9.26
Selenophene	8.03[e]	–	–
	8.64		
	9.86		
Tellurophene	7.76[e]	–	–
	8.52		
	9.54		

[a]<1976ZNA1051>.
[b]<1976J(P2)81>.
[c]These values are for *N*-methylisoindole.
[d]<1978ZNA1006>.
[e]<1975HCA2646>.

theorem states that the ionization potential required to remove an electron from an orbital is given by the negative value of the energy of the orbital calculated within the Hartree–Fock approximation. The relative magnitudes of the first ionization potentials of pyrrole (8.2 eV) and furan (8.9 eV) and their benzo derivatives (**Table 31**) are in good agreement with the AM1 calculated HOMO energies shown in **Table 1** (Section 2.3.2.1).

The adiabatic ionization energies of indole, *N*-methylindole, 3-methylindole, and 5-methylindole, determined by zero kinetic energy photoelectron spectroscopy and mass-analyzed threshold ionization spectroscopy, are 7.76, 7.53, 7.52, and 7.65 eV, respectively <1997JPCA2384, 2004JCP5057>. These data indicate that N-Me substitution lowers the zero energy level of the cationic ground state to a greater extent than that of the neutral ground state.

2.3.3.9.4 Reduced compounds

Ionization energies for fully-reduced heterocycles are recorded in **Table 32**. Interpretation is based on a local C_{2v} symmetry of the $–CH_2–X–CH_2–$fragment. Mixing of the nonbonding electrons of the heteroatoms (O, S, Se, Te) with the σ-system is greatest for tetrahydrofuran and gradually decreases down to tetrahydrotellurophene. Transannular interaction between the heteroatom and the double bond in 2,5-dihydrofurans and 2,5-dihydrothiophenes is indicated as 'through-bond' rather than 'through-space' <1978H(11)443, 1974CB725, 1973TL1437>.

Table 32 Vertical ionization potentials (eV) of tetrahydro heterocycles

Heterocycle	n_π (b_1)	C_2X (a_1)	C_2X (b_2)	*Reference*
Pyrrolidine	8.82	–	–	1978MI30100
Tetrahydrofuran	9.53	11.4	13.0 ± 0.5	1974MI30100
		9.65	–	–
Tetrahydrothiophene	8.42	10.9	11.9	1974MI30100
Tetrahydroselenophene	8.14	10.5	11.9	1974MI30100
Tetrahydrotellurophene	7.73	10.0	10.7	1974MI30100

2.3.3.9.5 Core-ionization energies

Available core-ionization energies for the parent heterocycles and some of their tetrahydro derivatives are listed in **Table 33**. The main C_{1s} bands of these compounds consist of two overlapping signals about 1 eV apart due to the nonequivalent carbon atoms <1977JCP(67)2596, 1972TCA(26)357>. The core-ionization energy of the heteroatom in the aromatic compounds is higher than that for the corresponding tetrahydro derivatives. Conversely, the averaged C_{1s} ionization energies of the aromatic compounds are lower than those for the corresponding tetrahydro derivatives. These trends are due to the net drift of charge from the heteroatoms toward the carbon atoms that occurs on going from the tetrahydro derivative to the aromatic compound.

Table 33 Core-ionization and shake-up energies (eV) for some heterocycles

	Core-ionization energy		*Shake-up energy*	
	Heteroatom	*Carbon (1s) (average)*	*Heteroatom*	*Carbon (1s)*
Tetrahydrofuran	533.1 (O_{1s})	285.9	–	–
Furan	534.3 (O_{1s})	285.0	8.6 (O_{1s})	7.7
Pyrrolidine	399.7 (N_{1s})	285.7	–	–
Pyrrole	400.4 (N_{1s})	284.8	8.0 (N_{1s})	7.2
Tetrahydrothiophene	163.2 ($S_{2p}^{3/2}$)	285.1	–	–
Thiophene	163.8 ($S_{2p}^{3/2}$)	284.3	7.5 ± 0.5 (S_{2p})	5.7

<1973MI30102>.

2.3.4 Thermodynamic Aspects

2.3.4.1 Intermolecular Forces

2.3.4.1.1 Melting and boiling points

A selection of melting points and boiling points for pyrrole, furan, and thiophene and their derivatives is included in Chapter 2.4 (Table 35, Section 2.4.4.1), together with data for five-membered rings containing two or more heteroatoms. Using this compilation of data, trends for all five-membered rings are discussed in Section 2.4.4.1.1. A computer-assisted QSPR method for predicting the normal boiling point for new furans, tetrahydrofurans, and thiophenes has been described <1991JCI301>.

2.3.4.1.2 Solubility

Pyrrole, furan, and thiophene have limited solubility in water; their aqueous solubilities are 6, 3, and 0.1%, respectively. The hydrogen bond donor property of the pyrrole NH and the hydrogen bond acceptor property of the furan oxygen probably account for their greater solubilities compared to that of thiophene.

2.3.4.1.3 Gas chromatography <1971PMH(3)297>

Hydrogen bonding with polar phases (tristearin, tween, polyethylene glycol 1000) by pyrrole lengthens its retention time. Thus, *N*-methylpyrrole on these stationary phases has a shorter retention time. Ethyl or larger alkyl groups at the 2-position sterically hinder such bonding and also shorten the time. 3-Alkylpyrroles therefore have longer retention times than the 2-isomers.

Furans have been separated on columns using tricresyl phosphate, triethylene glycol, and dinonyl phthalate stationary phases, often with Chromosorb as a support.

Stationary phases used for thiophenes include pentaerythritol benzoate, polyethylene glycol adipate, tricresyl phosphate, and benzyldiphenyl. Celite 545 is a useful support.

2.3.4.2 Aromaticity of Fully-Conjugated Rings

2.3.4.2.1 Background

All of the parent fully-conjugated five-membered heterocycles possess some degree of aromaticity based on their chemical behaviour, such as a tendency to undergo substitution reactions with electrophilic reagents. Quantitative measures of relative aromaticities are more difficult to devise. The range of potential criteria available has been surveyed in the context of six-membered rings (Section 2.2.4.2). To facilitate direct comparison with six-membered rings, the same criteria are tabulated and briefly discussed in this section. A comprehensive discussion of the aromaticity of all five-membered rings can be found in Section 2.4.4.2. In summary, most of the criteria discussed below point to the following order of decreasing aromaticity: benzene > thiophene > selenophene ≈ pyrrole > tellurophene > furan.

2.3.4.2.2 Energetic criteria

Empirical resonance energies (EREs), Dewar resonance energies (DREs), Hess–Shaad resonance energies (HSREs), and topological resonance energies (TREs) for five-membered rings and their benzo derivatives are summarized in Table 34. For a discussion of these terms, see Section 2.2.4.2.2. EREs and DREs indicate a decrease in aromaticity in the sequence benzene > thiophene > pyrrole > furan. However, the Hess–Shaad index and the TRE index place pyrrole before thiophene. A similar order (S > N > O) is found for the benzo[*b*] and dibenzo analogues but a different sequence is found for the benzo[*c*]-fused heterocycles with isoindole > benzo[*c*]thiophene > benzo[*c*]furan. As might be anticipated, the resonance energies for the benzo[*c*] heterocycles are substantially lower than those for their benzo[*b*] isomers. A peculiarity of five-membered rings with one heteroatom, unlike six-membered rings, is that benzoannulation generally stabilizes an aromatic system, e.g., (DRE index): carbazole > indole > isoindole > pyrrole > indolizine. Indolizine, with aromaticity the lowest among benzo derivatives according to all estimates, is the only exception.

Table 34 Resonance energy indices estimated by various methods

Compound	*ERE (kJ mol^{-1})*[a]	*DRE (kJ mol^{-1})*[b]	*DRE′ (kJ mol^{-1})*[b]	*HSRE (β)*[c,d]	*TRE (β)*[d]
Benzene	25.0	15.77	16.07	0.065	0.046
Pyrrole	15.1	5.86	9.00	0.039	0.040
Indole	21.8	9.96	6.15	0.047	–
Isoindole	–	4.85	3.18	0.029	–
Carbazole	28.4	14.3	–	0.051	–
Indolizine	–	2.90	–	0.027	–
Furan	11.3	3.01	2.64	0.007	0.007
Thiophene	20.3	4.52	0.40	0.032	0.033
Benzothiophene	–	10.38	4.94	0.044[b]	–

[a]<1974AHC(17)255>.
[b]<CHEC-II(2.01.4.1)37>.
[c]<1972T3657, 1973JA3907>.
[d]<1993AHC(56)303>.

2.3.4.2.3 Structural criteria

The harmonic oscillator model of aromaticity (HOMA) index and Bird aromaticity indices (I_5, $I_{5,6}$, and I_A) for selected heterocycles are shown in **Table 35** and **Figure 15**. The theoretical background to these indices is discussed in Section 2.2.4.2.3. To facilitate direct comparison between ring systems, Bird introduced a unified aromaticity index I_A that is related to the indices for five- and six-membered rings and fused rings by the expression:

$$I_A = I_6 = 1.235\ I_5 = 2.085\ I_{5,6} = 1.840\ I_{6,6}\ \text{<1992T335>}$$

Table 35 HOMA and Bird structural indices of aromaticity for 5- and 5,6-ring systems

Compound	*HOMA*[a]	I_5[b]	I_A[c]	*Compound*	*HOMA*[a]	$I_{5,6}$[d]	I_A[c]
Benzene	1.000	100	100	Indole	0.909	70	146
Pyrrole	0.857	59	85	Isoindole	–	72	150
Furan	0.200	43	53	Benzo[*b*]furan	–	45	94
Thiophene	0.745	66	82	Benzo[*c*]furan	–	51	106
Selenophene	–	59	73	Benzo[*b*]thiophene	–	57	119
Tellurophene	–	48	59	Benzo[*c*]thiophene	–	–	–
Phosphole	0.346[e]	36	66				

In some cases indices are derived from substituted derivatives.
[a]<2001CRV1385>.
[b]<1985T1409>.
[c]<1992T335>.
[d]<1987T4725>.
[e]<1996T10255>.

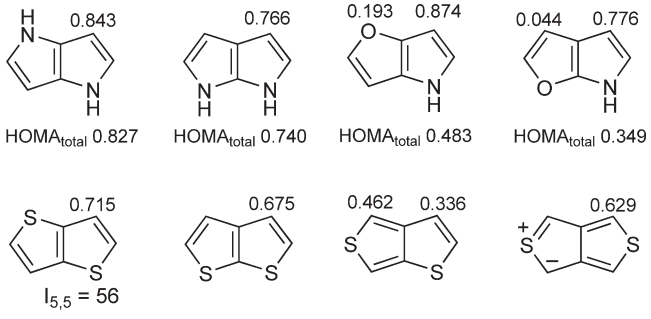


Figure 15 HOMA structural indices of aromaticity for 5:5-bicyclic systems.

Surprisingly, the HOMA index classifies pyrrole as being more aromatic than thiophene but the Bird index gives the order thiophene > pyrrole > furan. Both pyrrole and thiophene are much more aromatic than furan and according to the Bird index indole and isoindole are significantly more aromatic than their oxygen and sulfur analogues.

Figure 15 shows the HOMA indices for selected 5:5 heterocycles; values are given for the individual rings and in some cases for the total ring system. The values indicate that the [3,2-*b*] isomers are always more aromatic than the [2,3-*b*] isomers. The aromaticity of an individual ring depends on the position of the heteroatom in the neighbouring ring but the type of heteroatom is less important <2004PCP249>. The Bird index for thieno[3,2-*b*]thiophene is 56 which is comparable to that for benzo[*b*]thiophene (57) <1987T4725>.

2.3.4.2.4 Magnetic criteria

NMR has been widely invoked in assessing aromaticity. Comparison of the chemical shifts of furan, H(2) 7.46 and H(3) 6.41 ppm, with those observed for 4,5-dihydrofuran, H(2) 6.31 and H(3) 4.95 ppm, indicates a 1–1.5 ppm downfield shift attributable to the presence of an aromatic ring current. The same effect is observed for thiophene, H(2) 7.35 and H(3) 7.13 ppm, and 4,5-dihydrothiophene, H(2) 6.17 and H(3) 5.63 ppm. The similar range of chemical shifts observed for all the parent heterocycles is comparable to that for benzene, 7.27 ppm, and further attests to their possessing appreciable ring currents.

The validity of using chemical shifts as a quantitative measure of ring currents has frequently been questioned. As with other approaches to a quantitative assessment of aromaticity, a major difficulty is the selection of appropriate nonaromatic models. However, the order of decreasing aromaticity arrived at in this way, namely benzene 1.00, thiophene 0.75, pyrrole 0.59, and furan 0.46 <1965CC160, 1965T515>, is in keeping with that derived by other means.

Several methods based on NMR spectroscopy have been devised, which attempt to assess the relative magnetic susceptibilities of aromatic molecules, parallel and perpendicular to the plane of the ring. Values of the dilution shift parameter ($\delta\Delta V_m 2/3$) <1974J(P2)332> give a linear correlation with the Pauling resonance energies for benzene, thiophene, and furan and permit an estimation of resonance energies of 121.3 and 104.6 kJ mol^{-1}, respectively, for selenophene and tellurophene.

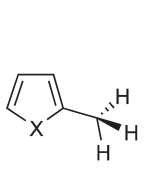
A recent introduction for evaluating magnetic criteria for aromaticity is the nucleus-independent chemical shift (NICS) value, which is the negative of the absolute magnetic shielding of a system. It is a theoretical concept and NICS values are calculated using high-level MO calculations at or above the center of the ring. NICS values are discussed and tabulated in Section 2.3.2.2.1 (**Table 2**). Although NICS values may be indicative of a ring current, they do not necessarily predict the stability associated with aromatic compounds. Like the HOMA structural index, the NICS magnetic index classifies pyrrole as more aromatic than thiophene (**Table 2**). For the simple bicyclic systems, there appears to be a high correlation between HOMA and NICS values for individual rings.

2.3.4.3 Conformations of Heteroaryl Derivatives: Rotamers and Atropisomers

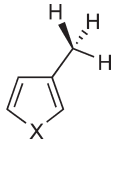
Rotamers are conformational isomers that differ by rotation about a single σ bond. The rotational barrier is the activation energy required to convert one rotamer to another. Atropisomers are rotamers in which the barrier to rotation about a single σ bond is so high, usually due to steric hindrance, that the separate rotamers (stereoisomers) can be isolated <2004T4335>.

2.3.4.3.1 Rotamers

Microwave spectroscopy studies on 2- and 3-methylfuran <1969JCP(51)403, 1970ZNA570, 1971BCJ2344> and -thiophene <1970MI30100, 1974JSP(42)38> show that the preferred conformations are as shown in structures **190–193** with barriers to rotation of 5.0, 2.3, 4.6, and 3.1 kJ mol^{-1}, respectively.



190: X = O
191: X = S

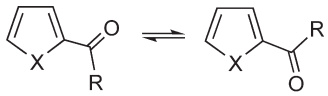


192: X = O
193: X = S

Gas electron diffraction of 2,5-dimethylthiophene shows one of the C—H bonds of the methyl substituents to be *cis* with respect to the S—C bond of thiophene <1993JST(301)107>. The C(2)—Me distance is smaller than a normal C—C single bond and quite close to the C—C bond length in nonconjugated alkenes. The C—S bond length is larger than in thiophene as is also the C—S—C angle.

Early experimental work on the conformational preferences in solution for a variety of 2-substituted heterocycles **194** is summarized in **Table 36**. Most of these conclusions were deduced either from dipole moment measurements in benzene or by the use of lanthanide-induced shifts for chloroform solutions.

Table 36 Conformational preferences of 2-substituted five-membered heterocycles



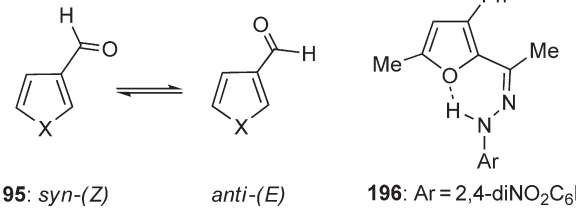
194 *anti* (*E*) *syn* (*Z*)

		Percentage of syn-(Z) *form*				
R	*Phase*	*Pyrrole*	*Furan*	*Thiophene*	*Selenophene*	*Tellurophene*
H	Vapor	Mainly[a]	Minor[b]	Mainly[c]	–	–
	C_6H_6	100[d]	83[e]	100[e]	80[e]	72[e]
	$CDCl_3$	–	70–75[f,g]	99[f,g]	98[f]	96[f]
Me	C_6H_6	100[d]	51[e]	92[e]	70[e]	47[e]
	$CDCl_3$	–	53[f]	79[f]	87[f]	90[f]
NMe_2	C_6H_6	–	11[e]	56[e]	33[e]	11[e]
	$CDCl_3$	–	5[f]	2[f]	5[f]	–
OMe	C_6H_6	Predominates[h]	55[e,i]	33[e]	59[e]	42[e]

[a]<1974JST(23)93>.
[b]<1966ZNA1633>.
[c]<1973JST(17)161>.
[d]<1974J(P2)1318>.
[e]<1977J(P2)775>.
[f]<1974T4129>.
[g]<1982T1485>.
[h]<1980J(P2)1631>.
[i]<1980SAA633>.

In furfural **194** (X = O, R = H) the *anti-(E)*-conformer is the most stable in the gas phase, while the *syn-(Z)*-conformer is the one preferred in the liquid phase and is the only rotamer present in the solid state. This behaviour has been attributed to the difference in polarity [(*E*) is the less polar conformer] and to the small difference in stability between the conformers. The calculated preference of 4.1 kJ mol^{-1} for the *anti* isomer and the barrier to rotation of ca. 24.7 kJ mol^{-1} compare favorably with the values that have been estimated from microwave spectra, 3.1 and 36 kJ mol^{-1} <1966ZNA1633>, and from far-IR spectroscopy, 8.5 and 25 kJ mol^{-1}, respectively <1967SAA891>. The presence of other ring substituents would be expected to modify the *syn–anti* preference *inter alia* by modifying the dipole moment of the ring, and this aspect has been extensively studied for pyrrole-2-carbaldehyde **194** (X = NH, R = H) <1975J(P2) 333, 1975J(P2)337>.

In chloroform solution the furan- and thiophene-3-carbaldehydes **195** adopt the *anti-(E)* conformation to the extent of 100 and 80%, respectively <1982T3245>. However, N-substituted 3-(trifluoroacetyl)pyrroles exist in solution as mixtures of rotational isomers <1980JCM42>.



195: *syn-(Z)* *anti-(E)* **196**: Ar = 2,4-di$NO_2C_6H_3$

The situation in 2-acetylfuran **194** (X = O, R = Me) resembles qualitatively that in the 2-formyl derivative **194** (X = O, R = H). Low-temperature NMR measurements in dimethyl ether enabled direct detection of the two conformers: at 173 K the (*E*)-conformer population for 2-acetylfuran amounts to 53% <1985J(P2)1839>. In 2-acetylfuran-2,4-dinitrophenylhydrazone the (*E*)-conformer **196** is predominant (70%) and its stability has been explained by intramolecular hydrogen bonding <1992MI 205-02>. Such an intramolecular hydrogen bond is supported by the crystal structure of ethyl α-(*p*-tolylhydrazono)-2-furopropionate <1988AXC1252>.

In 2-carboxylic acids **194** (R = OH), the oxygen of the OH group faces the heteroatom in all cases except furoic acid. Progressive shortening of the C(2)–C(CO_2H) bond, presumably indicating an increase in conjugative interaction, occurs in the sequence thiophene > selenophene > tellurophene > furan, which corresponds to the order of decreasing heterocyclic aromaticity.

The rotational isomerism in carbonyl-containing five-membered heterocycles has been extensively reviewed <1977J(P2)1601, 1981RCR336, 1984KGS579, 1987AHC(41)75>. In general, the extent of π-conjugation between the carbonyl group and the ring is the main factor in determining the barrier to rotation. NMR-evaluated free energies of activation for rotation about the C(O)–N bond in 2-*N*,*N*-dimethylcarboxamides of furan, pyrrole, and thiophene **194** (R = NMe_2) and the corresponding 3-isomers are summarized in **Table 37** <1976JOC3591, 1977T1337>. The barrier to rotation arises from resonance interaction between the lone pair on the nitrogen atom and the carbonyl group. An electron donor attached to the carbonyl group will reduce this interaction and hence lower the rotational barrier. As expected, the values show that the order of electron donation is pyrrolyl > thienyl > furyl, and that donation is greater from the 2-position than the 3-position. All the heterocyclic rings are electron donating compared with benzene. Similar barriers to rotation and conclusions have been derived from studies of 3-amino-2-formyl and -thioformyl furans and thiophenes <CHEC-III(3.09.4.2)705>.

Table 37 Free energies of activation (kJ mol^{-1}) for rotation of five-membered heterocyclic *N*,*N*-dimethylcarboxamides

	Substituent position	
Heterocyclic ring	*2*	*3*
Furan	63.1	63.5
Thiophene	60.6	–
Pyrrole	60.2	61.0
Benzene	66.5	

Inspection of **Figure 16** shows that, compared to benzene, *ortho* substituents should experience less steric interference in five-membered heterocycles and for any individual ring system this will be smaller for 2,3-disubstitution rather than 3,4-disubstitution. The tetrasubstituted pyrrole **197** has a planar ring but most substituent atoms deviate significantly from this plane <1972J(P2)902>. The acetyl group is twisted by about 15° out of the ring plane whereas the ester group is only twisted 1°. Distortions of the ring are also obviously present in 3,4-di-*t*-butylthiophene **198** <1980CC922>, where in particular the C(3)—C(4) bond length is 1.667 Å, in contrast to 1.423 Å in the parent heterocycle, and the Bu^t-C—C-Bu^t bond angles are increased to 133° from their preferred value of 124°. No appreciable distortions of the thiophene ring are observed for the dinitrothiophene **199**, the overcrowding being relieved by the nitro groups being twisted out of the plane of the ring by 37 and 44° and the C—N bonds being displaced out of the plane of the ring by 5.3 and 6.7° in opposite directions <1978CSC703>.

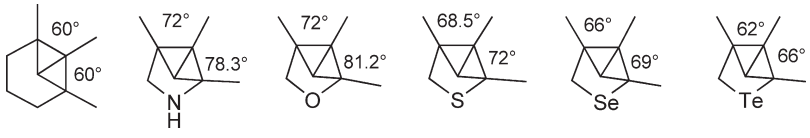
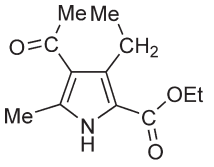
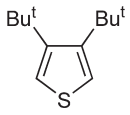


Figure 16 Angular separation of adjacent ring substituents.



197



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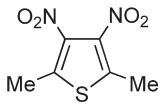
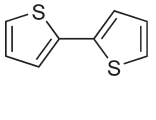


199

2.3.4.3.2 Atropisomers

X-Ray crystallographic studies show that the three isomeric bithienyls are planar in the solid state <1968AXB467>. However, in the vapor phase the principal conformation of 2,2'-bithienyl is shown by electron diffraction to be a nonplanar one with an angle of twist of 34° relative to the planar *transoid* conformation **200** adopted in the solid state <1958ACS1671>. However, 2-(2-furyl)pyrrole and 2-(2-thienyl)pyrrole preferentially adopt a *cis*-planar conformation in solution <1981J(P2)127>. Bulky substituents in the positions adjacent to the inter-ring bond permit the separation of the resulting stereoisomers. Typical examples are provided by the derivatives **201** and **202** <1975CS(7)173>, the X-ray structures of which show that *cis*-skew conformations are adopted in the solid state <1975CS(7)204, 1976CS(9)66>. Circular dichroism spectra of these compounds in solution and in the solid state are very similar and comparable with those of the necessarily *cisoid* dithienothiepins **203** <1976CS(10)120>. Analogous behaviour has been observed for 3,3'-biselenienyls, where both compound **203** and its thiophene analogue have been resolved <1975CS(7)131>.



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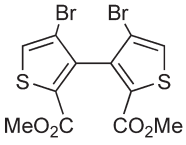

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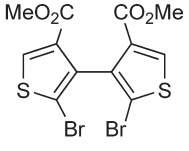

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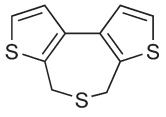

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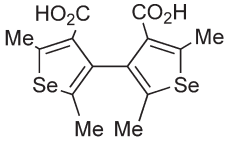
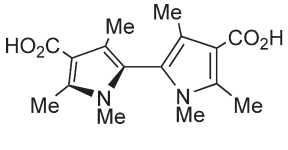


204

Examples of restricted rotation in bis-pyrroles were encountered much earlier and, for example, the resolution of compounds **205** <1953JOC1413>, **206** <1931JA2353>, and **207** <1931JA3519> has been reported. A consequence of the greater separation of adjacent substituents on these five-membered rings relative to six-membered rings (**Figure 16**) is a lower barrier to rotation. Thus, the rotational barrier for pentaarylpyrroles is about 75 kJ mol^{-1} lower than for the corresponding hexaarylbenzenes <1981JOC1499>.



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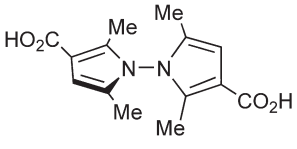

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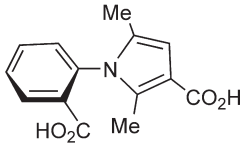
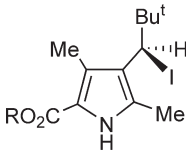


207

For alkyl 3,5-dimethyl-4-[(1′-iodo-2′,2′-dimethyl)propyl]pyrrole-2-carboxylate **208** (R = Me, Et), and other derivatives in which iodine is replaced by methoxy, methylthio, acetic acid esters, propionic acid ester, or malonic esters, restricted rotation about the C(4)–C(1′) bond, due to the bulky *tert*-butyl group and an *ortho*-effect, has been described <2002TA1721>. Dynamic NMR studies gave $\Delta G^{\ddagger}$ values in the range 22–25 kcal mol^{-1} in $C_2D_2Cl_4$. Similarly, malonic ester derivatives of alkyl 3,5-dimethyl-4-(1′-iodoneopentyl)-1*H*-pyrrole-2-carboxylate exhibit restricted rotation about the pyrrole bond C(4)–C(1′) ($\Delta G^{\ddagger}$ ~32 kcal mol^{-1}) <2002M1469>.

Bilirubin and biliverdin congeners with propionic acids replaced by *o*-carboxyphenyl groups exhibit diastereomerism due to axial chirality about the C–C single bond linking the *o*-carboxyphenyl group to a pyrrole ring <2002T7411>.

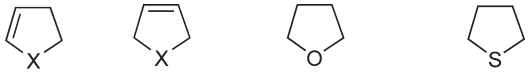


208

2.3.4.4 Conformations of Partially- and Fully-Reduced Rings

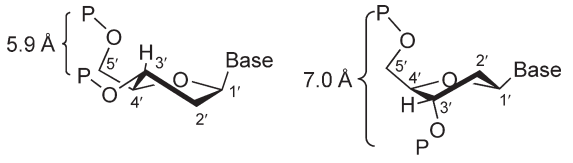
Some reduced heterocyclic rings are nonplanar. In 2,3-dihydrofuran **37** (X = O) and 2,3-dihydrothiophene **38** (X = S), the C(2) methylene group is out of the plane of the other ring atoms with barriers to ring inversion of ~1 and 4 kJ mol^{-1}, respectively <1972JCP(56)5692, 1973JCP(59)2249, 1986JST(147)255>. The higher barrier for the sulfur ring is presumed to be due to a decrease in the ring strain forces relative to those in the dihydrofuran. Torsional forces are comparable for both molecules and tend to overcome the lower ring-strain forces of the dihydrothiophene and pucker the ring to a larger degree. 2,5-Dihydrofuran **38** (X = O) <1967JCP(47)4042, 1984JA20, 1993JSP(160)158> and 2,5-dihydrothiophene **38** (X = S) <1969SAA723> are planar, but 2,5-dihydropyrrole **38** (X = NH) is nonplanar with an asymmetric double minimum potential on account of the axial–equatorial conversion of the N–H bond by ring inversion <1972CPL(12)499>. The equatorial form is favored energetically.

The fully-reduced ring systems are nonplanar. For tetrahydrofuran **39**, analysis of IR <1969JCP(50)124>, dipole moment, microwave <1969JCP(50)2446>, and ^{1}H NMR <1974MR(16)136> data indicates a freely pseudorotating system with 10 twist and 10 envelope conformations. In the envelope conformation, one of the ring atoms is out of the plane of the other four atoms. Intermediate between these envelope conformations are twist conformations (only three adjacent ring atoms coplanar) that are slightly more stable than the envelope conformation and with a barrier to pseudorotation of about 0.7 kJ mol^{-1}. Similarly, pyrrolidine **36** is a free or only slightly restricted pseudorotator <1958JCP(29)966>, but the appreciably increased size of the heteroatom in tetrahydrothiophene **40** <1979MI30102, 1980CJC2340, 1980OMR(13)282> and tetrahydroselenophene <1978JCP(69)3714, 1979MR(36)113> results in higher barriers to pseudorotation and these molecules preferentially adopt twisted conformations.



37 **38** **39** **40**

In solution, rapid interconversion occurs between the nonplanar envelope and twist conformations of saturated five-membered rings, and conformational differences are of little significance. However, in substituted rings in the solid state or macromolecular structures, particular conformations become significant. This is the case for the deoxyribofuranose rings in DNA: only the ring conformations **209** and **210** are compatible with formation of a double helix structure. In conformation **209** the C(3′) carbon atom is above the plane of the other ring atoms and on the same side of the ring as atom C(5′). This is known as the C(3′)-*endo* conformation. In conformation **210** the C(2′) carbon atom is above the plane of the other ring atoms and on the same side of the ring as atom C(5′). This is known as the C(2′)-*endo* conformation. As a result of the conformational differences, the adjacent phosphorus atoms in the sugar-phosphate backbone of a DNA strand are at different separations as indicated in **Figure 17**. A-DNA has the sugar rings in the C(3′)-*endo* conformation **209** and B-DNA has the sugar rings in the C(2′)-*endo* conformation **210**. In Z-DNA the pyrimidine sugars are C(2′)-*endo* and the purine sugars are C(3′)-*endo*. The B conformation of DNA is regarded as the native form and this reversibly converts to the A conformation when the relative humidity is reduced to 75%.



C(3′)-*endo* **209** C(2′)-*endo* **210**

Figure 17 Conformations of the deoxyribofuranose ring in DNA.

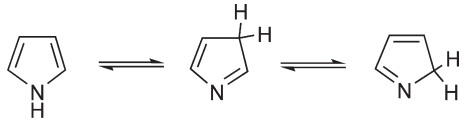
2.3.5 Tautomerism

Prototropic tautomerism is the only significant type of tautomerism of these heterocycles. The tautomerism of five-membered heterocycles has been extensively reviewed <2000AHC(76)85>.

2.3.5.1 Prototropic Tautomerism of Fully-Conjugated Rings

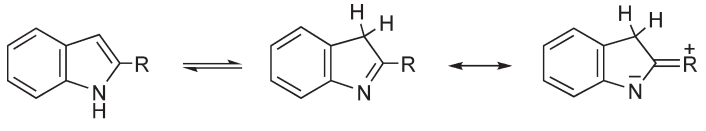
2.3.5.1.1 Annular tautomerism

Annular tautomers are prototropic tautomers in which the migrating proton is restricted to ring atoms. For these five-membered heterocycles, annular tautomerism can only occur with pyrrole **2** and its polycyclic derivatives. There is no authenticated case of the monocyclic pyrrolenine tautomeric forms **211** and **212** predominating, presumably due to the required loss of resonance energy in these nonaromatic tautomers <CHEC-I(3.04.6)196>.



2 **211** **212**

The potential loss of resonance energy is much less for the tautomerism of indoles **213** to the corresponding indolenines **214**; however, most indoles exist in the indole form **213**. The introduction of a strong electron-donating group at C(2) can tip the balance. Thus, the equilibrium is progressively shifted from **213** to **214** as the substituent R is changed from SEt to OEt to NC_5H_{10} (piperidin-1-yl), due to the increasing electron-donating ability implied by the resonance form **214b** <1970T4491, 1971T775>



213 **214a** **214b**

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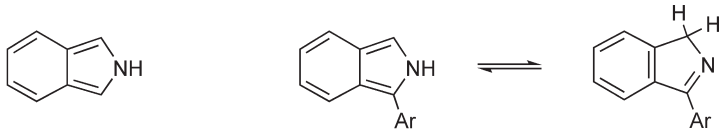
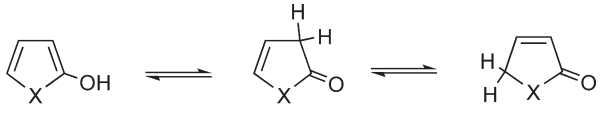
Although isoindole **15** exists in solution as the fully-conjugated 2*H*-tautomer <1973J(P1)1432>, in substituted derivatives the lower resonance energy of the isoindole ring system often results in the isoindole **215** – isoindolenine **216** equilibrium favoring the tautomer **216**. Thus, the presence of an aryl substituent (Ar) at C(1), which is capable of conjugating with C=N, results in increasing proportions of the isoindolenine **216**. In $CDCl_3$ solution the variation of the proportion of tautomer **216** with substituent is as follows: phenyl (9%); 4-methoxyphenyl (31%); 4-dimethylaminophenyl (50%) <1964JA4152>.



15: isoindole **215** **216**

2.3.5.1.2 Oxo-hydroxy tautomerism

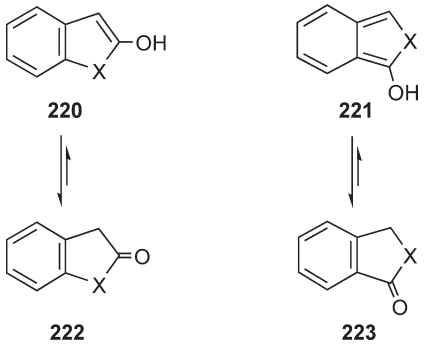
2.3.5.1.2.1 2-Hydroxy derivatives. 2-Hydroxy derivatives usually exist as the oxo tautomers, unless the hydroxy tautomer is appreciably stabilized by electron-withdrawing or chelating substituents. The tendency for enolic hydroxy compounds to revert to the oxo form can be understood by reference to simple aliphatic ketones where the keto-enol equilibrium constants are of the order of 10^8. In the five-membered heterocycles under consideration, this tendency will be in opposition to the loss of aromatic resonance energy that increases in the order furan << thiophene ≤ pyrrole. For the 2-hydroxy compounds **217** some extra stabilization of the oxo tautomers **218** and **219** is derived from the resonance energy of the X–C=O group, which by analogy with open-chain compounds should increase in the sequence thiolester, ester << amide.



217 **218** **219**

Variation in tautomeric behaviour is observed with change of heteroatom. Thus, 2-hydroxyfurans **217** (X = O) exist predominantly as the tautomers **219** (X = O), although the energy of activation for the conversion **218** → **219** is sufficiently high to permit isolation of tautomer **218** <1964CRV353>. 2-Hydroxypyrroles, e.g., **217** (X = NH), behave similarly but equilibration between tautomer **218** and the more stable tautomer **219** occurs in polar solvents at room temperature <1965JOC3824, 1971OMR(3)7, 1980HCA121>. For 2-hydroxythiophenes the ratio of tautomers **218** and **219** depends on the substituent at C(5) <1963T1867, 1964AK(22)211, 1967T3737, 1969AK(29)427>. Whereas only tautomer **219** (X = S) is detected in the parent molecule <2000AHC(76)85, CHEC-III(3.09.4.3)715>, the introduction of a 5-aryl substituent causes the equilibrium to shift largely toward tautomer **218** in the solid state or carbon tetrachloride solution; in methanol the tautomer **218** is accompanied by 25–30% of the hydroxy tautomer **217**. In general, 2(5*H*)-thiophenones **219** (X = S) have higher dipole moments than the 2(3*H*)thiophenones **218** (X = S) and the equilibrium shifts to the former with increasing solvent polarity <CHEC-III(3.09.4.3)715>. Tautomer **219** also predominates in the case of 2-hydroxyselenophene <1971BSF3547>.

In the benzo[*b*] and benzo[*c*] heterocycles **220** and **221**, where the loss of ring resonance energy on tautomerism is much less than in the nonannulated heterocycles **217**, the oxo tautomers **222** and **223** are energetically preferred. 2-Hydroxyindole **220** (X = NH) exists exclusively as the oxo tautomer **222** (X = NH) (oxindole). The hydroxy form of 2-hydroxybenzo[*b*]thiophene **220** (X = S) is detectable by ^{1}H NMR spectroscopy when its trimethylsilyl ether precursor is hydrolyzed (CD_3COCD_3/D_2O/DCl). At 25 °C the signal at 6.45 ppm [C(3)-H] disappears within 15 min and is replaced by a broad singlet at 4.2 ppm, indicating rapid conversion to the oxo form **222** (X = S) <1989JA5346>.



220 **221** **222** **223**

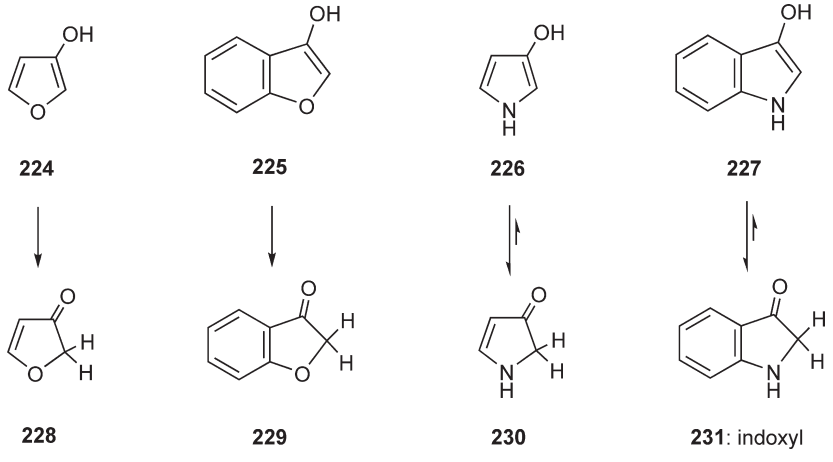
2.3.5.1.2.2 3-Hydroxy derivatives. Most 3-hydroxyfurans, e.g., **224**, and 3-hydroxybenzofurans, e.g., **225**, exist exclusively in the keto forms (**228** and **229**) at equilibrium, but the enolic forms **224** and **225** have been generated transiently in solution by hydrolysis of their trimethylsilyl ether derivatives <1989JA5346>. 3-Hydroxypyrroles, e.g., **226**, (and selenophenes) also exist preferentially as the keto tautomers **230**. Introduction of an acyl function at position 2 of 3-hydroxyfuran or 3-hydroxypyrrole causes the equilibrium to favor the hydroxy tautomers as a result of intramolecular hydrogen bonding <CHEC-I(3.04.6)196>. 3-Hydroxyindole **227** makes a minor contribution to the tautomeric equilibrium and exists mainly as the keto tautomer **231** (indoxyl). In general, 3-hydroxybenzofurans and 3-hydroxyindoles adopt the oxo form, but enolize to the hydroxyl tautomer when an acetyl group is present at position 2.

Equilibrium and rate constants for the keto-enol tautomerization of hydroxy heterocycles are summarized in **Table 38** <1986TL3275>. The pyrroles ketonize (i.e., **226** → **230**) substantially faster (10^3–10^4 times) than their sulfur or oxygen analogues, and still faster than the benzo-fused systems (indole, benzofuran, and benzothiophene).

Table 38 Rate and equilibrium constants for ketonization of hydroxy heterocycles at 25 °C

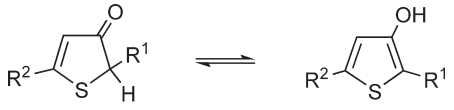
Compound	k_{H^+} $(M^{-1}s^{-1})^a$	k_{H^+} $(M^{-1}s^{-1})^b$	K_{enol} (H_2O)	K_{enol} $(DMSO)$
3-Hydroxypyrrole	2.38×10^4	–	0.13	$>10^2$
1-Methyl-3-hydroxypyrrole	9.65×10^3	–	0.18	$>10^2$
3-Hydroxyindole	3.44	–	0.086	28.3
1-Methyl-3-hydroxyindole	5.82	–	0.303	11.4
2-Hydroxythiophene	–	11.5[c]	$<1 \times 10^{-2}$	$<2 \times 10^{-2}$
3-Hydroxythiophene	5.83	1.78[c]	2.96	$>1 \times 10^2$
3-Hydroxyfuran	50.1	29.7	$<1 \times 10^{-2}$	$<2 \times 10^{-2}$
2-Hydroxybenzo[*b*]thiophene	–	12.4	3.42×10^{-6}	$<2 \times 10^{-2}$
3-Hydroxybenzo[*b*]thiophene	0.53	0.31	0.085	6.7
3-Hydroxybenzo[*b*]furan	0.59	0.87	8.70×10^{-4}	$<2 \times 10^{-2}$
1-Hydroxyindene	9.03×10^2	3.28×10^2	1.85×10^{-8}	$<2 \times 10^{-2}$

<1986TL3275>.
[a] H_2O.
[b] H_2O-MeCN (1:9).
[c] H_2O-MeCN (1:1).



The 3-hydroxy form **233** is more favorable in thiophene systems, which enjoy greater aromaticity <2000J(P2) 1453>. Thus, 2-methyl-3-hydroxythiophene exists at equilibrium as a mixture of the oxo form **232** (R^1 = Me, R^2 = H) (20%) and the enol form **233** (R^1 = Me, R^2 = H) (80%) <1986HC(44/3)1>. For the *tert*-butyl derivative

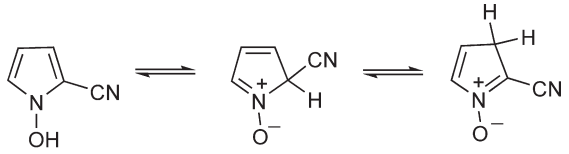
($R^1 = Bu^t$, $R^2 = H$) the equilibrium mixture is **232** (45%) and **233** (55%). 3-Hydroxythiophene **233** ($R^1 = R^2 = H$), prepared from the trimethylsilyl ether, is sufficiently stable for its ^1H NMR spectrum to be obtained in a variety of solvents <1989JA5346>. In CCl_4 both tautomers are observed, contrary to an earlier report where only the oxo form was observed <1986TL5155>. Electron-withdrawing substituents, such as alkoxycarbonyl, generally cause the hydroxy form to predominate <1965T3331>.



232 **233**

The relative rates of ketonization of hydroxythiophenes and hydroxybenzo[*b*]thiophenes in acetonitrile–water (9:1) are as follows: 2-hydroxybenzo[*b*]thiophene > 2,5-dihydroxythiophene > 2-hydroxythiophene > 3-hydroxybenzo[*b*]thiophene > 3-hydroxythiophene (**Table 38**). 3-Hydroxythiophene does not ketonize readily in the above solvent system but in 1:1 acetonitrile–water it ketonizes 6.5 times slower than 2-hydroxythiophene <1987PAC1577>. The solvent has a significant effect on the equilibrium constants <1989JA5346>. In general, for the benzo[*b*] systems, increasing solvent polarity favors the hydroxy tautomer, which becomes the almost exclusive species in 2-acetyl <1965T3331> and 2-aryl <1976CS(9)216> derivatives, even in nonpolar media.

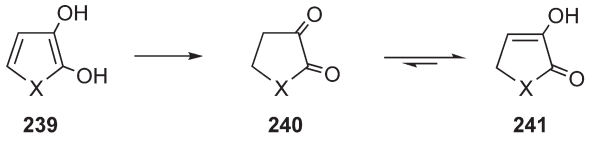
2.3.5.1.2.1.3 *N*-Hydroxy derivatives. Although *N*-hydroxypyrroles can in principle exist in three tautomeric forms, e.g., **234**, **235**, and **236**, only the *N*-hydroxy form **234** is observed for 1-hydroxy-2-cyanopyrrole <1973JOC173>. In the case of *N*-hydroxyindoles, where the potential loss of aromatic resonance energy is much less, both tautomers **237** and **238** coexist in solution with the relative proportions being dependent on the solvent <1967BSF1296>.



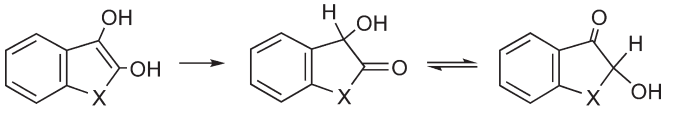
234 **235** **236**

237 **238**

2.3.5.1.2.4 Dihydroxy derivatives. 2,3-Dihydroxyfuran, -pyrrole and -thiophene **239** (X = O, S, NH) all adopt the tautomeric structure **241** rather than the diketo form **240**. 2,3-Dihydroxyindole **242** (X = NH) adopts the structure **243** (X = NH). The behaviour of 2,3-dihydroxybenzofuran **242** (X = O) is strongly temperature dependent; at 20 °C it exists solely as the tautomer **244** (X = O) but as the temperature is raised the equilibrium shifts progressively toward structure **243** (X = O) the proportion of which reaches 95% at 100 °C <1968M2223>.

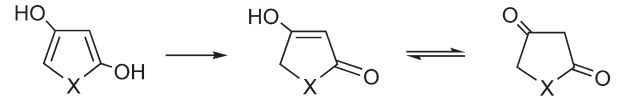


239 240 241

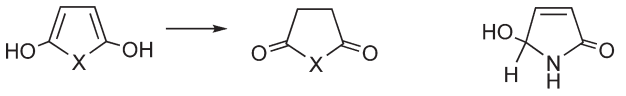


242 243 244

The 2,4-dihydroxy derivatives of furan and thiophene **245** (X = O, S) exist in the solid state and in polar solvents as the monoenols **246** <1971T3839>. However, in nonpolar solvents furan derivatives exist predominantly in the dioxo form **247** (X = O). The 2,5-dioxo structure **249** is well established for X = O, NR, S, and Se <1971BSF3547> and there is no evidence for normal intervention of any enolic species **248**; however, the formal tautomer **250** of succinimide **249** (X = NH) has been reported and is reasonably stable <1962CIL1576>.

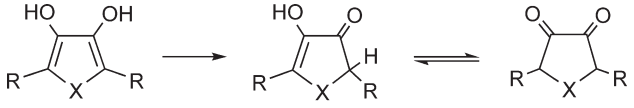


245 246 247



248 249 250

Examples of 3,4-dihydroxy heterocycles **251** are restricted to furans and thiophenes. Although the parent 3,4-dihydroxyfuran apparently exists as the dioxo tautomer **253** (X = O, R = H), derivatives bearing 2-alkyl or 2,5-dialkyl substituents prefer the keto-enol structure **252** (e.g., X = O, R = Me) <1971T3839, 1973HCA1882>. Many thiophene analogues also prefer the tautomeric structures **252** (X = S). However, the 2,5-bis(ethoxycarbonyl) derivative has the fully-aromatic structure **251** (X = S, R = CO_2Et) <2004AXCo338>, as do the 2-ethoxycarbonyl and 2-cyano derivatives <1993TL8229, 2000BML349, CHEC-III(3.09.4.3.2(ii)722>.



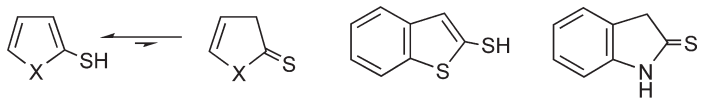
251 252 253

2.3.5.1.3 Thiono-mercapto and amino-imino tautomerism

The mercapto form is much more strongly favored than is the hydroxy form for the corresponding oxygen compounds. In this context it is relevant to note the greatly reduced inclination of enethiols to tautomerize to the corresponding thiocarbonyl compounds, in contrast to the facile ketonization of enols.

2-Mercapto derivatives of furan, thiophene, selenophene, and pyrrole all exist predominantly in the thiol form **254** (X = O, S, Se, NH). 2-Mercaptobenzo[*b*]thiophene **255** is also a thiol <2002JA9189> whereas 2-mercaptoindole is

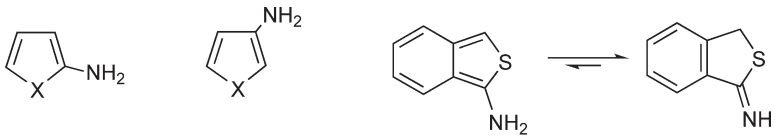
mainly indoline-2-thione **256** <1969CPB550>. This is not due solely to the greater resonance energy associated with thioamides since N-alkylation, which eliminates hydrogen bonding, shifts the tautomeric equilibrium back to the thiol form.



254 **255** **256**

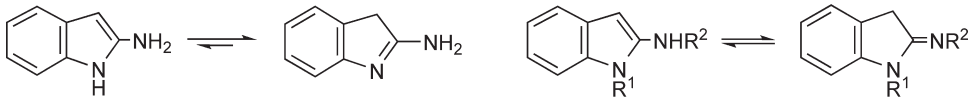
The known 3-mercapto derivatives of furan, thiophene, selenophene, benzothiophene, and indole all exist as the 3-thiol tautomers.

2-Aminofuran **257** (X = O) is too unstable to be detected; this may be due to rapid tautomerism to the imine followed by ring opening <2006AHC(92)1>. 3-Aminofurans appear to be more stable and, although the parent system **258** (X = O) is unknown, 2-methyl derivatives have been reported <2006AHC(92)1>. 2- and 3-Aminothiophene **257** and **258** (X = S) have been isolated and characterized <1973JHC1067> and 2-aminopyrroles **257** (X = NR) have been characterized in solution <1995TL9261>. This preference for the amino tautomers is in agreement with MO calculations <1970JA2929>.



257 **258** **259** **260**

The preference for the amino form is also observed for 2-aminobenzo[*b*]thiophene <1965JOC4074>, 3-aminobenzofurans <1973JPR779>, 3-aminoindoles <1969BSF2004>, and 1-aminoindolizines <1965JCS2948>. Among the few well-established exceptions is 1-aminobenzo[*c*]thiophene **259** which preferentially exists as the imine **260** <1964JOC607>. The existence of 2-aminoindole **261** as the tautomer **262** <1971T775> has been discussed in Section 2.3.5.1.1 (annular tautomerism) and is a consequence of the appreciable resonance energy of the amidine group and the low resonance energy of the indole pyrrole ring. The position of equilibrium is sensitive to N-substituents and solvent polarity. In the *N*-methyl derivative **263** (R^1 = Me, R^2 = H) the equilibrium is displaced toward the imino tautomer **264** (R^1 = Me, R^2 = H) and this displacement increases with solvent polarity. However, replacement of the 2-amino group by a 2-*N*-alkylamino group causes tautomer **263** to predominate over the imine **264**.



261 **262** **263** **264**

2.4 Structure of Five-membered Rings with Two or More Heteroatoms

2.4.1 Survey of Possible Structures and Nomenclature

2.4.1.1 Nitrogen Rings without Exocyclic Conjugation

2.4.1.1.1 Fully-conjugated aromatic rings

Systematic replacement of CH in pyrrole **1** (Chapter 2.3) by N leads to nine additional monocyclic heteroaromatic nitrogen systems **2–10** (**Figure 1**), which are known collectively as azoles. Annular tautomerism is an important feature of all azoles having an NH function. For example, the triazoles **4** and **6**, the triazoles **5** and **7**, and the tetrazoles **8** and **9** can equilibrate by proton transfer (see Section 2.4.5). N-Substituted derivatives cannot equilibrate. Tautomers of the parent ring systems of all the azoles except pentazole **10** are known; *N*-aryl derivatives of pentazole have been characterized <CHEC-III(6.18)739>.

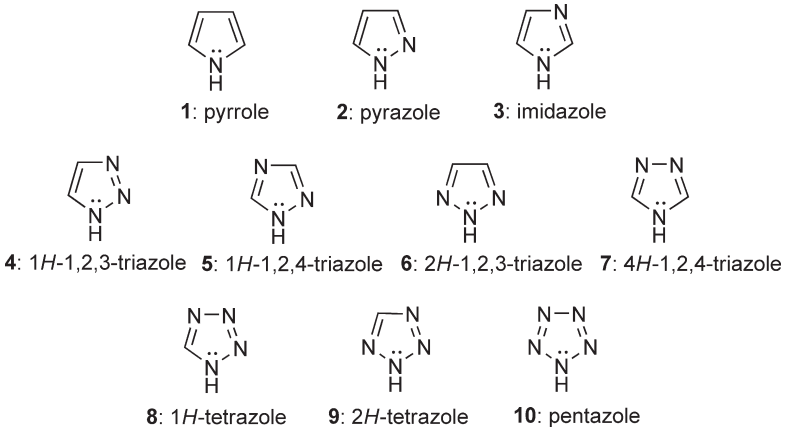
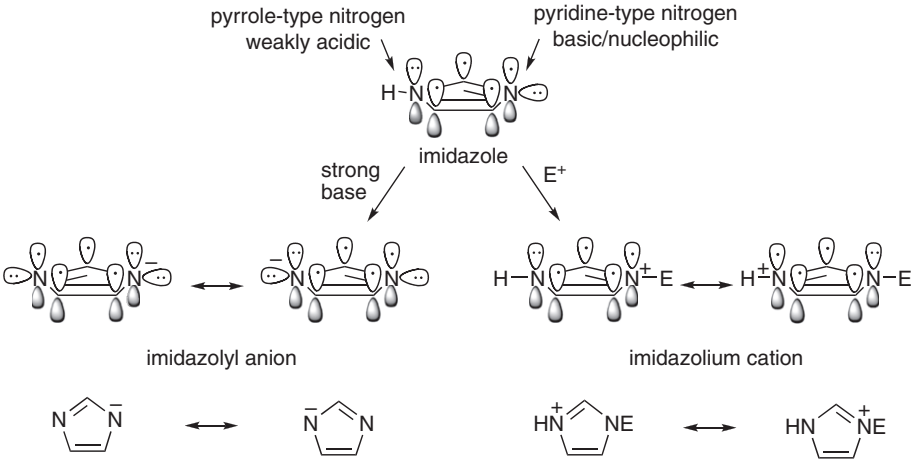


Figure 1 Five-membered monocyclic aromatic nitrogen heterocycles.

A second important structural feature of the azoles is that they contain both a pyrrole-type nitrogen, whose lone pair is part of the aromatic sextet, and up to four pyridine-type nitrogens with lone pairs that are not part of the aromatic sextet. The azole NH bonds are weakly acidic and treatment of imidazole ($pK_a = 14.2$) with a strong base gives the imidazolyl anion, which is stabilized by resonance and retains the aromatic sextet (**Scheme 1**). The acidity increases with the number of pyridine-type nitrogens in the ring: the acidity of tetrazole **9** ($pK_a = 4.8$) is comparable to carboxylic acids. The pyridine-type nitrogens are basic and nucleophilic. Treatment of imidazole, for example, with protons or electrophiles gives imidazolium cations that are also stabilized by resonance and retain an aromatic sextet (**Scheme 1**). The azoles **2–10** and their bicyclic derivatives therefore show both acidic and basic/nucleophilic properties.



Scheme 1 The azoles, illustrated by imidazole, can behave as weak acids or bases giving resonance-stabilized ions that retain the aromatic sextet.

The structures of representative azolyl anions and azolium cations (one resonance form and one isomeric form only) and their names are shown in **Figure 2**.

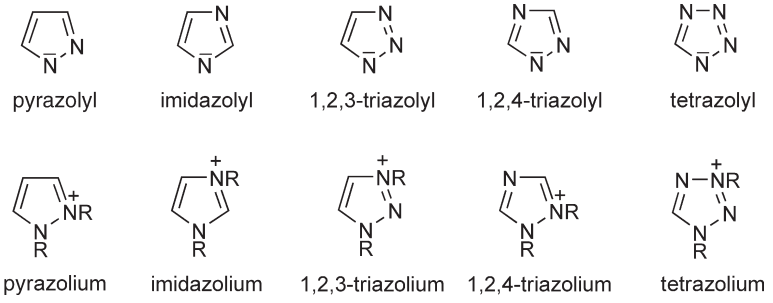


Figure 2 Azolyl anions and azolium cations.

Fusion of a benzene ring to a C–C bond in pyrazole or imidazole gives the bicyclic derivatives **14–16**, which are aza analogues of indole **11** and isoindole **12**. Further substitution of nitrogen leads to a large number of polyaza systems. A biologically important tetraaza ring system is purine **17** which is found in the nucleosides adenosine, guanosine and inosine. The anomalous numbering of the purine ring **17** should be noted. In aqueous solution 9*H*-purine **17** is in equilibrium with the 7*H*-tautomer.

Fusion of a benzene ring to a C–N bond gives the heterocycles **18–20** that are aza analogues of indolizine **13**, and further aza substitution leads to a variety of well-known heterocyclic systems (**Figure 3**).

Fusion of a pair of azoles gives aromatic systems isoconjugate with the heteropentalene dianion. Representative examples **21–24** are given in **Figure 4** and these include further examples of conjugated mesomeric betaines, e.g., **23** and **24**, which can only be represented by 1,3-dipolar structures (cf. Section 2.3.1.1.1.2).

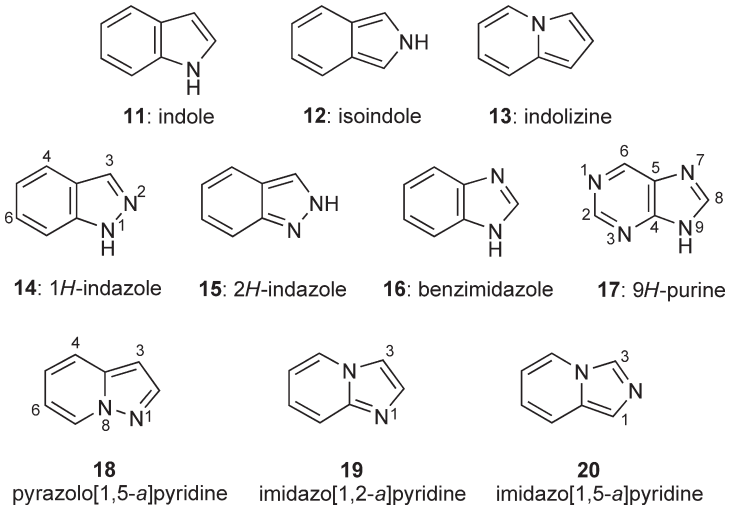


Figure 3 Examples of benzo-fused azoles.

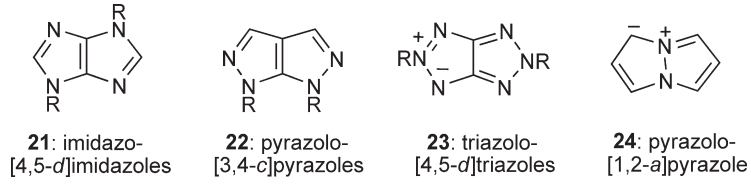
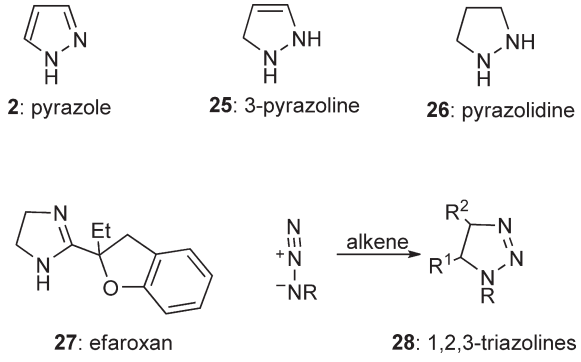


Figure 4 Examples of 5,5-fused aromatic heterocycles.

2.4.1.1.2 Rings without cyclic conjugation

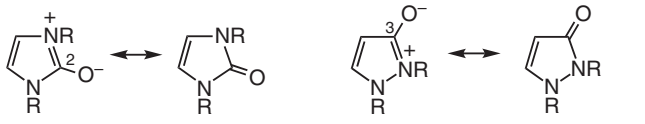
Reduction of one or two double bonds in the azole ring gives nonaromatic systems. Historically, these derivatives have been described as azolines and azolidines, as illustrated by the pyrazole derivatives **25** and **26**. In 3-pyrazoline **25** the 3 indicates the first ring atom associated with the double bond <CHEC-I(1.02.2.1)9>. In the older literature the position of the double bond is indicated by Δ^n, where n is the number of the first ring atom associated with the double bond, e.g., Δ^3-pyrazoline **25**. Alternatively, they are named as dihydro or tetrahydro derivatives of the parent azole (e.g., 2,5-dihydropyrazole **25**) and this nomenclature is IUPAC-preferred nomenclature for rings with more than two heteroatoms <CHEC-I(1.02.2)9>.

Imidazolines are well known and certain derivatives, such as efaroxan **27**, stimulate insulin secretion by binding to imidazoline I_3 receptors <1999ANY(881)217>. Stability decreases as the number of heteroatoms increases: 1,2,3-triazolines **28** are formed from azides as 1,3-dipolar cycloadducts but readily form the aromatic 1,2,3-triazole by oxidation or elimination.



2.4.1.2 Nitrogen Rings with Exocyclic Conjugation

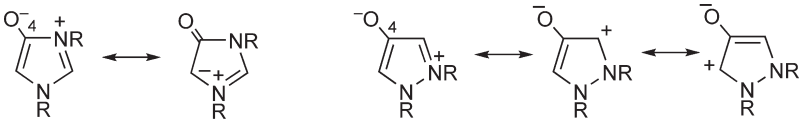
Each of the aromatic azolium cations (**Figure 2**) can be converted into a neutral system by substitution of an anionic O, S, or NR group on to a ring carbon atom. This is illustrated below for the imidazolium and pyrazolium cations. Introduction of an anionic oxygen substituent at position 2 of the imidazolium ring gives an imidazol-2-one structure **29** in which the charges formally cancel. A similar substitution at position 3 of the pyrazolium ring gives pyrazol-3-ones **30**. As for pyridones (Section 2.2.1.2.1), the dipolar resonance hybrids indicate a degree of aromaticity and polarity in these molecules. Aza substitution leads to a wider range of heterocycles.



29: imidazol-2-ones **30**: pyrazol-3-ones

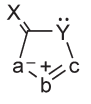
A different situation arises when the anionic group is substituted at other ring carbon atoms. Substitution at position 4 (or 5) of the imidazolium ring leads to the dipolar heterocycles **31** that cannot be represented by uncharged structures. These are conjugated mesomeric betaines, comparable to the pyridinium-3-olates (Section 2.2.1.2.2), and for historical reasons these five-membered mesomeric betaines are described as mesoionic compounds <1976AHC(19)1>. The imidazolium-4-olates **31** are representatives of the general class **33**, which are referred to as type A mesoionic compounds, and which tend to participate in 1,3-dipolar cycloaddition reactions <2010T553>, as might be expected from the resonance structure **33**.

Substitution at position 4 of the pyrazolium ring also gives mesomeric betaines, illustrated by the pyrazolium-4-olates **32**. The structure and chemistry of these mesomeric betaines with general structure **34** are different to those of the type A compounds, and are referred to as type B mesoionic compounds. They often react via an acyclic valence tautomer (see Section 2.4.5).

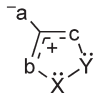


31: imidazolium-4-olates
mesoionic: type A

32: pyrazolium-4-olates
mesoionic: type B



33
general meso-ionic: type A



34
general mesoionic: type B

2.4.1.3 Oxygen and Sulfur Rings without Exocyclic Conjugation

2.4.1.3.1 Fully-conjugated aromatic rings

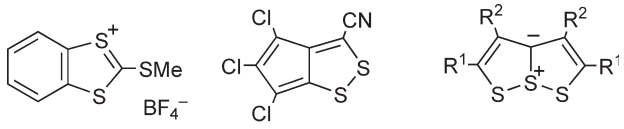
If the heteroatoms are restricted to oxygen and sulfur, then aromatic monocyclic systems with more than one heteroatom are restricted to cations. The six possible aromatic monocations, together with their names, are given in **Figure 5**. In the modern literature the systematic ending -lylium is often simplified to -lium.

Benzo derivatives, such as the benzo[1,3]dithiolium tetrafluoroborate **35** <2004JME5265>, are also known. For polycyclic systems that are isoconjugate with dianions, neutral rings with two oxygen/sulfur atoms, such as the cyclopenta[1,2]dithiole **36** <CHEC-III(4.11.3)896>, can be made. The occurrence of bicyclic systems with a bridgehead sulfur, such as the trithiapentalenes **37**, should also be noted <1971AHC(13)161>.

1,2-dioxolylium (1,2-dioxolium)
1,2-oxathiolylium (1,2-oxathiolium)
1,2-dithiolylium (1,2-dithiolium)

1,3-dioxolylium (1,3-dioxolium)
1,3-oxathiolylium (1,3-oxathiolium)
1,3-dithiolylium (1,3-dithiolium)

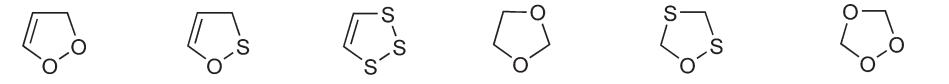
Figure 5 Structure and nomenclature of oxygen/sulfur five-membered cations.



35 **36** **37**

2.4.1.3.2 Rings without cyclic conjugation

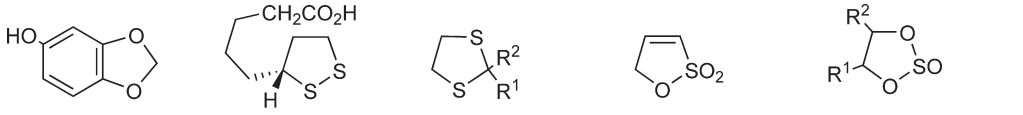
For rings without nitrogen, the endings -ole and -olane are used to name partially- and fully-saturated five-membered rings. Representative examples are given in **Figure 6**.



1,2-dioxole 3*H*(1,2)oxathiole 1,2,3-trithiole 1,3-dioxolane 1,2,4-oxadithiolane 1,2,4-trioxolane

Figure 6 Nomenclature for representative nonconjugated oxygen/sulfur five-membered rings.

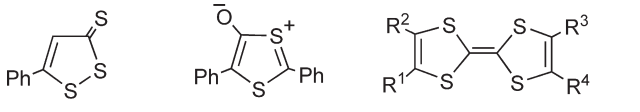
Heterocycles of this type occur widely. The benzo[1,3]dioxole ring system is often found in natural products and their degradation products, e.g., sesamol **38**; lipoic acid **39** is a naturally occurring 1,2-dithiolane derivative. The 1,3-dithiolanes **40** are commonly known as 1,3-dithioacetals and have been extensively used in carbonyl group chemistry. In the absence of cyclic conjugation, ring sulfur atoms can readily exist in higher oxidation states as, for example, in the oxathiole *S*,*S*-dioxide **41**. 1,3,2-Dioxathiolane *S*-oxides **42** (cyclic sulfites) and 1,3,2-dioxathiolane *S*,*S*-dioxides (cyclic sulfates) are useful as synthetic equivalents of epoxides.



38: sesamol **39**: lipoic acid **40**: 1,3-dithioacetals **41**: 5*H*(1,2)-oxathiole *S*,*S*-dioxide **42**: 1,3,2-dioxathiolane *S*-oxides

2.4.1.4 Oxygen and Sulfur Rings with Exocyclic Conjugation

Examples of these systems are the 1,2-dithiole-3-thione **43** and the type A mesoionic 1,3-thiazolium-4-olate **44**. Important members of this class are the tetrathiafulvalenes (TTFs) **45** and related systems, which have been studied extensively because of their potentially useful electrical properties <CHEC-III(4.12.11)1032>.



43 **44** **45**: tetrathiafulvalenes (TTF)

2.4.1.5 Rings Containing Nitrogen with Oxygen and/or Sulfur

When ring atoms can be chosen from oxygen, sulfur, *and* nitrogen a large number of heterocyclic systems with a rich diversity of properties become possible. Representative examples are isoxazole and thiazole and their derivatives (**Figure 7**). The nomenclature closely follows that of the azoles (Section 2.4.1.1).

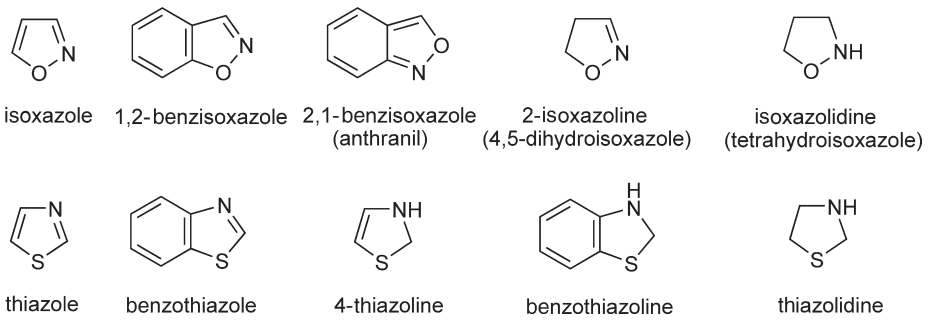


Figure 7 Representative rings with oxygen/sulfur and nitrogen.

Exocyclic conjugation extends the range of ring systems possible and representative examples with their names are shown in **Figure 8**. Ring atoms are numbered with priority O > S > N and the rings are orientated in **Figure 8** to give consistency of numbering around the rings. Sometimes reorientation is necessary for close comparison of common features in pairs of structures.

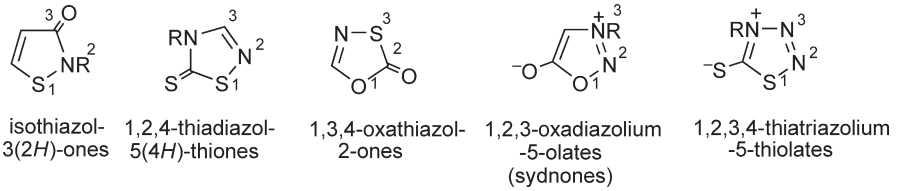


Figure 8 Oxygen/nitrogen/sulfur heterocycles with exocyclic conjugation.

As for azines such as pyridine (Section 2.2.1.2.3), some azoles and their derivatives form *N*-oxides in which the exocyclic oxide is in conjugation with the ring. 1,2,5-Oxadiazoles, e.g., **46**, commonly known as furazans, are oxidized to the *N*-oxides known as furoxans, e.g., **47**. Derivatives of benzofuroxan **48** are well known. Since sulfur can also be oxidized, derivatives such as the 1,2,3-thiadiazole trioxide **49** are not uncommon (**Figure 9**).

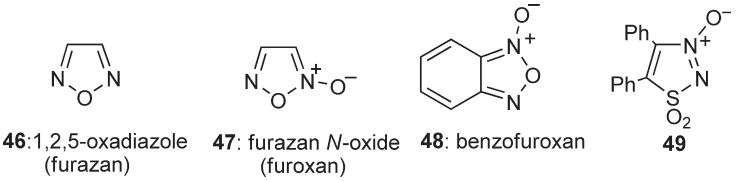


Figure 9 Examples of five-membered *N*-oxides.

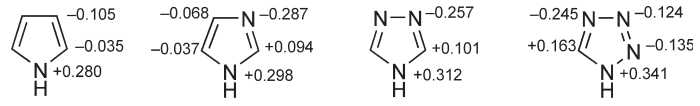
2.4.2 Theoretical Methods

2.4.2.1 General Trends

The influence of the heteroatoms on π-electron distribution in pyrrole, furan, and thiophene is discussed in Section 2.3.2.1 using Hückel π-electron densities to give an indication of electron distribution around the ring. These ring systems are classified as electron-rich or π-excessive; this contrasts with the azines (Chapter 2.2) which are

electron-poor (π-deficient). This chapter is primarily concerned with aza substitution (=CH– replaced by =N–) in pyrrole, furan, thiophene, and related rings, and the influence of this aza substitution on properties. Because nitrogen is an electronegative element, the effect of aza substitution is to make the carbon atoms in the ring increasingly π-deficient.

The application of the Hückel method (HMO) to five-membered rings and to multiple heteroatom systems is not reliable but used cautiously and in a semiquantitative way the results are useful for illustrating general trends associated with aza substitution. **Figure 10** shows HMO π-electron partial charges for pyrrole **50**, imidazole **51**, 4*H*-1,2,4-triazole **52**, and 1*H*-tetrazole **53**. With increasing aza substitution the positive charge on the pyrrole-type nitrogen atoms (NH) increases, reflecting the electron attraction of each additional nitrogen atom. At the same time, the π-electron density on the ring carbon atoms, which is high in π-excessive pyrrole **50**, decreases resulting in π-deficiency on the carbon atoms in triazole **52** and tetrazole **53**. As a result of these trends the azoles often display π-excessive centers together with carbon atoms with a rather high π-deficiency, sometimes even higher than in typical azines. In general, pyrazole **2**, imidazole **3**, and 1*H*-1,2,3-triazole **4**, according to the π-charge on their carbon atoms, can be classified as weakly π-excessive systems, whereas 2*H*-1,2,3-triazole **6**, 1*H*-1,2,4-triazole **5**, 4*H*-1,2,4-triazole **7**, and the tetrazoles **8** and **9** are clearly π-deficient heterocycles.

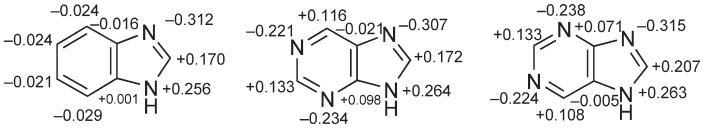


50 **51** **52** **53**

Figure 10 HMO calculated π-electron charges in selected azoles.

The above conclusions are consistent with ^{1}H and ^{13}C chemical shifts. There is a good correlation between the π-electron densities on the corresponding carbon atoms and the chemical shifts of ^{13}C and ^{1}H nuclei of azoles <1966TL2627, 1968JA3543>. As a rule, for positions with negative π-charge the corresponding signals move toward higher field relative to benzene whereas shifts to lower field are observed for nuclei carrying positive charge.

Benzannulation (**Figure 11**) significantly influences both π-electron distribution and reactivity of azoles. Compared to imidazole **51**, benzimidazole **54** has an increased positive charge at position 2 and this is consistent with its tendency to undergo reaction at this position with hard nucleophiles. This behaviour is analogous to the chemistry of azines. Purine is also notable for its high π-deficiency, 7*H*-purine **56** being more π-deficient than the 9*H*-tautomer **55**. Possibly this is responsible for the natural occurrence of the less π-deficient and therefore chemically more stable derivatives of 9*H*-purine.



54 **55** **56**

Figure 11 HMO calculated π-electron charges in benzimidazole and purine.

Due to the electronegativity of nitrogen, aza substitution also weakens the azole NH bond and stabilizes the corresponding azolyl anion (**Figure 2**). **Figure 12** shows how the pK_a values of the azoles decrease in a linear manner with the introduction of each ring nitrogen, regardless of ring position. Each nitrogen atom decreases the pK_a by about 4 units. Extrapolation gives an estimated pK_a of −1 for pentazole, which is comparable to that of iodic acid (HIO_3).

A similar correlation between pK_a and aza substitution is found for the benzoazoles (**Figure 13**). Here the gradient is virtually identical to that for the monocyclic azoles (**Figure 12**) but displaced to more acidic values by about 1 pK_a unit. This suggests that the effect of the nitrogen atoms is identical to that in the azoles and that there is an additional effect attributable to the conjugation provided by the benzo substituent. Nitrogen atoms in the benzo ring will provide additional stabilization of the anion and, as expected, purine (pK_a = 8.9) is more acidic than benzimidazole (pK_a = 13.2) but the effect of aza substitution in the six-membered ring is smaller than in the five-membered ring.

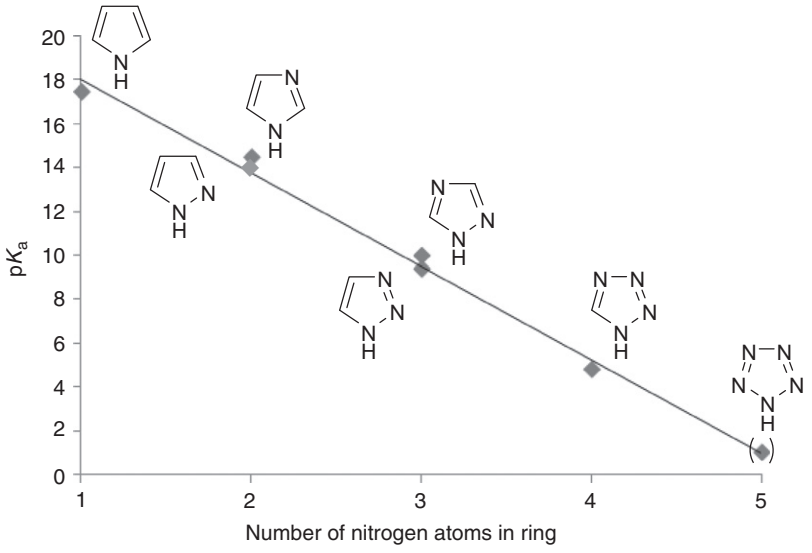


Figure 12 Variation of azole pK_a for proton loss with number of nitrogen atoms.

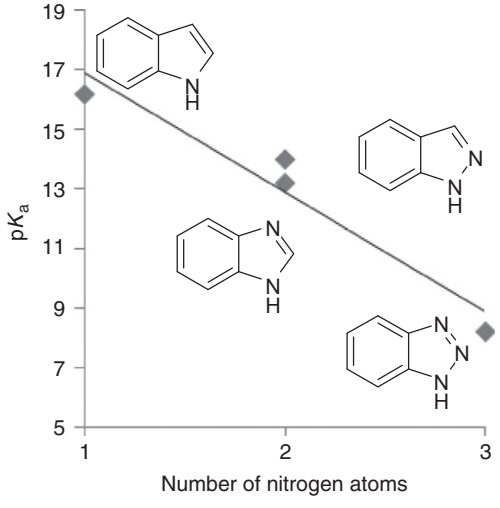


Figure 13 pK_a values for proton loss from benzoazoles.

The stabilization of negative ions by aza substitution is a result of the general lowering of the energies of molecular orbitals. **Table 1** shows the AM1 calculated energies of the frontier orbitals of azoles and related molecules. The results clearly show that orbital energy decreases with increasing aza substitution, as also seen for the azines (Section 2.2.2.1). In accord with Koopmans' theorem, there is a correlation between the AM1 HOMO energies and the first ionization potentials (**Table 2**).

Aza substitution of heteropentalene rings leads to (1) significantly more stable ring systems (cf. **Table 1**) and (2) a change in color and visible spectrum (see Section 2.4.3.6.3). The stabilizing effect of aza substitution also stabilizes decomposition products (e.g., N_2) and, for example, some (but not all) tetrazoles are dangerously explosive.

The energies of the σ orbitals of azoles are also lowered by aza substitution and this influences the basicity of the azole rings. The azole lone pairs are components of the σ orbital framework and increasing aza substitution lowers the energy of the lone pair electrons. Protonation to form an azolium cation, i.e., **57** → **58**, effectively removes one electron from the lone pair to form an NH bond, which can be regarded as a dative bond **58b** (**Scheme 2**). In the formation of a dative bond the energy required to transfer one electron from donor (e.g., azole) to acceptor (e.g., H^+) makes a significant contribution to the bond energy <2004T3293>. If the energy of the donor lone pair electrons is

Table 1 AM1 energies (eV) of the frontier orbitals of five-membered heterocycles

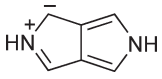
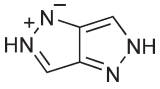
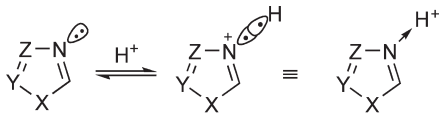
Compound	*HOMO*	*LUMO*	*Δ*	*Compound*	*HOMO*	*LUMO*	*Δ*
Pyrrole	−8.66	1.38	10.04	Indole	−8.40	0.30	8.71
Pyrazole	−9.71	0.96	10.67	1*H*-Indazole	−8.92	−0.07	8.85
Imidazole	−9.16	0.98	10.14	2*H*-Indazole	−8.47	−0.21	8.26
1*H*-1,2,3-Triazole	−10.18	0.42	10.60	Benzimidazole	−9.00	0.06	9.06
2*H*-1,2,3-Triazole	−10.33	0.55	10.88	1*H*-Benzotriazole	−9.43	−0.37	9.06
1*H*-1,2,4-Triazole	−10.27	0.54	10.81	9*H*-Purine	−9.64	−0.57	9.07
4*H*-1,2,4-Triazole	−10.03	0.52	10.55	Isoxazole	−10.47	0.18	10.65
1*H*-Tetrazole	−11.41	−0.09	10.32	Oxazole	−9.89	0.31	10.20
2*H*-Tetrazole	−11.16	−0.02	11.14	Isothiazole	−9.54	−0.10	9.44
Pentazole	−12.72	−0.71	12.01	Thiazole	−9.70	−0.21	9.49
	−6.76	0.49	7.25		−8.03	−0.30	7.73

Table 2 Comparison of AM1 HOMO energies and first ionization potentials

Compound	*AM1 HOMO (eV)*	*Ionization potential (eV)*
Pyrrole	−8.66	8.20
Pyrazole	−9.71	9.15
Imidazole	−9.16	8.78
2*H*-1,2,3-Triazole	−10.33	10.06
1*H*-1,2,4-Triazole	−10.27	10.00
2*H*-Tetrazole	−11.16	11.30

reduced, then the dative NH bond in the conjugate acid **58** becomes weaker. For this reason, the azoles **57** (X = NH) become progressively weaker bases with each additional ring nitrogen (Y and/or Z = N). A significant correlation between calculated σ-ionization potentials of azoles and their protonation energies has been demonstrated <1991JPC7694>.



57 **58a** **58b**

Scheme 2 Formation of azolium cations by N-protonation.

Figure 14 shows the pK_{aH} values of the selected azolium cations **59–66**. The pK_{aH} is the pK_a value for the conjugate acid **58** and should not be confused with the pK_a of the parent azole **57** (X = NH) (**Figures 12** and **13**). Imidazole is a stronger base than pyridine (pK_{aH} = 5.2) and this is attributed to resonance in the conjugate acid **59** which allows sharing of the positive charge. 1,2,4-Triazole (**60**; pK_{aH} = 2.2) is a much weaker base as a result of aza substitution and tetrazole (**61**; pK_{aH} = ca −3) is a very weak base. Replacement of the pyrrole nitrogen by oxygen or sulfur also leads to lower basicity (**62** and **63**) due to a combination of the resonance and electronegativity effects.

Pyrazole is a much weaker base than imidazole. Both have resonance-stabilized conjugate acids (**Figure 14**) but in the case of the pyrazolium cation **64** the direct linking of the quaternary nitrogens has a base-weakening effect. This additional effect also contributes to the low basicities of isothiazoles and isoxazoles (**65** and **66**).

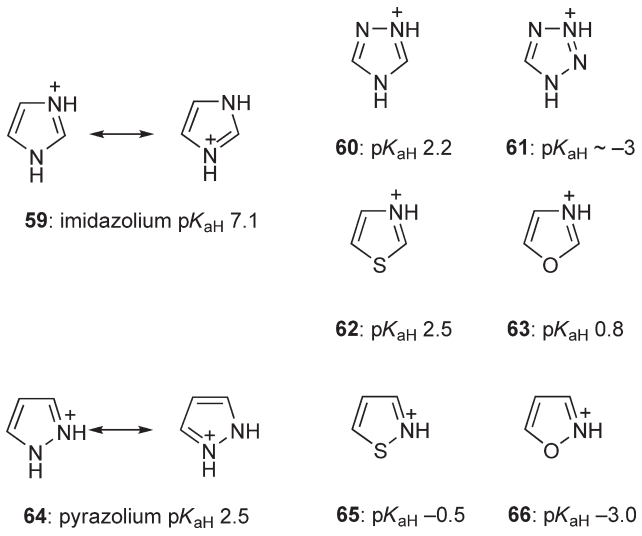


Figure 14 Basicities (pK_{aH}) of selected azoles.

2.4.2.2 Calculation of Molecular Properties

2.4.2.2.1 Structure and energy

There are numerous reports of calculated properties of five-membered heterocycles, using a wide variety of MO methods. Results for individual ring systems can be found in the relevant chapters of CHEC-II and CHEC-III. In this section selected results of general interest are described.

Ab initio calculations at the B3LYP/6-311+G levels on optimized geometries suggest that aromatic stabilization of 2*H*-1,2,3-triazole is the highest of all the azoles <2003T1657>. Calculated values for eight unsubstituted azole rings are compared in **Table 3**. Bond dissociation energies for several azole systems calculated by two *ab initio* methods show similar values <2003JPO883>.

Table 3 Calculated properties of azoles

Ring	*Aromatic stabilization*[a] *(kcal mol^{-1})*	*Dipole moment*[b] *(Debye)*	*K^+ affinities*[c] *(kJ mol^{-1})*
Pyrrole	18.04	1.93	77.1
Pyrazole	20.46	2.33	90.5
Imidazole	16.18	3.84	111.1
1*H*-1,2,3-Triazole	20.21	4.55	118.6
2*H*-1,2,3-Triazole	22.21	0.12	64.5
1*H*-1,2,4-Triazole	18.01	2.93	–
4*H*-1,2,4-Triazole	12.19	5.81	–
1*H*-Tetrazole	14.13	5.34[d]	109.7
2*H*-Tetrazole	21.17	2.27[d]	–

[a]<2003T1657>.
[b]<2003PCA4172>.
[c]<2003CEJ3383>.
[d]<2001PCP3541>

Experimental dipole moments and acidities of azoles show linear correlations with their π-electron excess calculated by the semiempirical AM1 method <2003CHE71>. Experimental dipole moments of azoles agree well with values calculated by the density functional theory (DFT) program ALLCHEM (**Table 3**) <2003PCA4172>. There is an excellent correlation between the experimental microwave dipole moments (μ_{exp}) of a variety of azoles and those calculated (μ_{calc}) using the *ab initio* method (6-31G*//6-31G level) ($\mu_{exp} = 0.942\mu_{calc} + 0.008$) <1986JPC5597>.

Hartree–Fock calculations (3-21G* and 6-31G* basis sets) have been performed to study the structure and energetics of Na^+-, K^+-, and Al^+-azole complexes. Calculated X^+ (X = H, Li, Na, K, Al) binding energies of 1,2,3-triazole show that cation association energies follow the sequence $Li^+ > Al^+ > Na^+ > K^+$, and all of them are much smaller than the corresponding protonation energies <1992JPC3022>. Potassium cation affinities of several azoles in the gas phase have been calculated by hybrid density functional theory [B3LYP/6-311+G(3df,2p) basis set] (**Table 3**) <2003CEJ3383>. There is a striking difference in binding energies of 1*H*- and 2*H*-1,2,3-triazoles, which also have very different calculated dipole moments (**Table 3**).

The electronic nature of the NSN fragment in the series of 1,2,5-thiadiazoles **67–73** has been studied, using both *ab initio* and DFT methods and compared to the structure of naphtha[1,8-*cd*][1,2,6]thiadiazine **72** (**Figure 15**). The S–N bond length and charge distribution analysis support the classical structures of both 1,2,5-thiadiazole **67** and 2,1,3-benzothiadiazole **68**. However, compounds **69–73** display significantly shorter S–N bonds accompanied by large charge separations and are therefore more ylidic in structure. Also, DFT-calculated (B3LYP/6-31G*) S0/T1 splitting energies indicate that the systems are far from diradicaloid <1997JPO33, CHEC-III(5.09.2.3)518>.

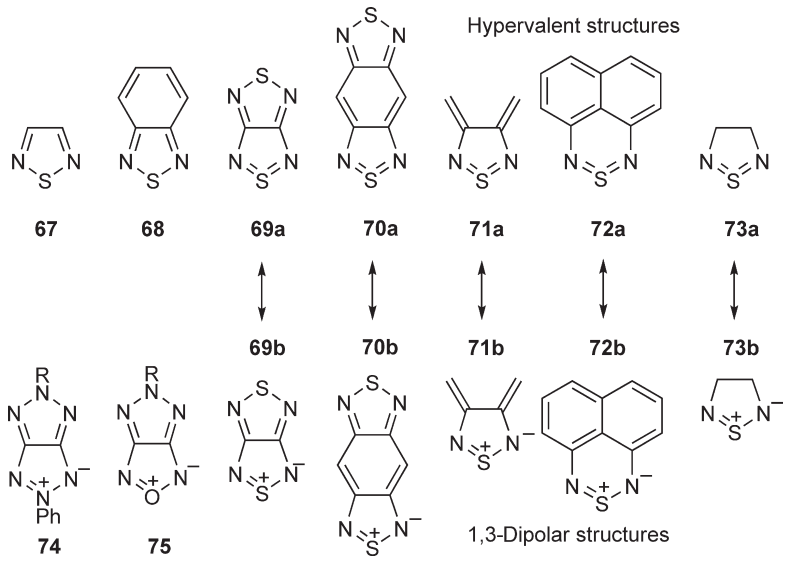
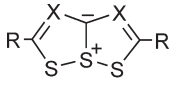


Figure 15 1,2,5-Thiadiazole derivatives and related species.

Structures **69a–73a** are often assumed to imply the participation of sulfur d-orbitals. This is incorrect; d-orbitals play only a small part in their bonding. A common feature of heterocyclic conjugated mesomeric betaines is that their bonding includes a three-center, two-electron bond, which cannot be represented by classical covalent structures <1994CSR111>. Molecules with three-center, two-electron bonds can be represented by hypervalent structures (e.g., –N═S═N–) or 1,3-dipolar structures (e.g., $-N{=}S^{+}{-}N^{-}-$). Since oxygen and nitrogen are also widely associated with this class of heterocycle, e.g., **74** and **75** (**Figure 15**) <1977T3193>, it is inconsistent and misleading to represent nitrogen and oxygen mesomeric betaines by dipolar structures and sulfur heterocycles by hypervalent structures. The consistent use of dipolar structures is preferred, e.g., **69b–73b**.

The molecular geometry and electronic structure of the unknown 3,4-diaza-1,6,6αλ^4-trithiapentalene compound **76** (R = H, X = N) has been examined in detail together with the known nitrogen-free 1,6,6αλ^4-trithiapentalene **76** (R = H, X = CH) <1998PS(140)35, 1997JPCA4475>. Whereas Hartree–Fock calculations predict **76** to be a pair of monocyclic valence tautomers in equilibrium, DFT (B3LYP) as well as *ab initio* MP2 calculations result in single-minimum structures of C_{2v} symmetry.



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2.4.2.2.2 Magnetic properties

The concept of nucleus-independent chemical shifts (NICS) as a quantitative magnetic measure of aromaticity is discussed in Sections 2.2.2.2.2 and 2.3.2.2.1, where NICS values for six-membered rings and five-membered rings with one heteroatom are tabulated. **Table 4** shows NICS values calculated for five-membered rings with more than one heteroatom <2002JOC1333>. Since NICS values are theoretical parameters, they depend on the computational method used. In **Table 4** NICS is the value at the center of the ring and NICS(1) is the value 1 Å above the center.

Table 4 NICS values for aza derivatives of pyrrole, furan, and thiophene

Ring	*NICS*	*NICS(1)*	*Ring*	*NICS*	*NICS(1)*
Pyrrole	−14.86	−10.60	1,2,3,4-Oxatriazole	−12.94	−12.29
Pyrazole	−14.75	−11.93	1,2,3,5-Oxatriazole	−13.84	−13.84
Imidazole	−13.85	−10.83	1,2,3,4,5-Oxatetrazole	−16.16	−15.34
1*H*-1,2,3-Triazole	−14.90	−13.51	Thiophene	−13.80	−10.79
2*H*-1,2,3-Triazole	−14.83	−13.61	Isothiazole	−13.96	−11.66
1*H*-1,2,4-Triazole	−13.66	−11.84	1,3-Thiazole	−13.10	−11.37
4*H*-1,2,4-Triazole	−13.13	−11.52	1,2,3-Thiadiazole	−14.38	−13.72
1*H*-Tetrazole	−14.79	−14.12	1,2,4-Thiadiazole	−13.47	−11.96
2*H*-Tetrazole	−14.96	−14.64	1,2,5-Thiadiazole	−14.57	−12.96
Pentazole	−16.76	−16.59	1,3,4-Thiadiazole	−13.00	−12.34
Furan	−12.31	−9.36	1,2,3,4-Thiatriazole	−15.18	−14.65
Isoxazole	−12.36	−10.58	1,2,3,5-Thiatriazole	−15.49	−14.96
1,3-Oxazole	−11.31	−9.45	1,2,3,4,5-Thiatetrazole	−18.40	−17.48
1,2,3-Oxadiazole	−12.97	−11.99			
1,2,4-Oxadiazole	−11.51	−10.40			
1,2,5-Oxadiazole	−12.72	−12.52			
1,3,4-Oxadiazole	−10.74	−10.00			

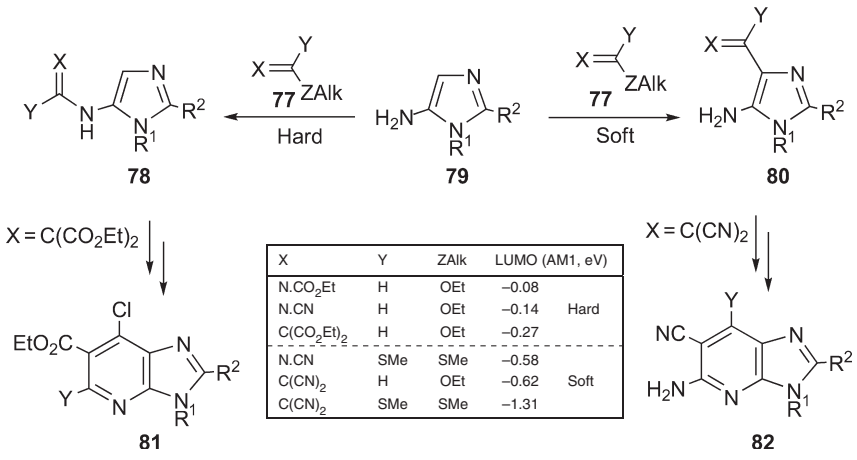
<2002JOC1333>. Calculated using the GIAO/HF/6-311+G** method.

NICS is the negative value of the magnetic shielding and the more negative the NICS value the more aromatic the ring according to magnetic criteria. NICS(1) is regarded as a better indicator of aromaticity than NICS. All the heterocycles in **Table 4** have values that are large and negative indicating a high degree of aromaticity. Based on NICS(1) values, aza substitution leads to increasing aromaticity, but since pentazole has one of the largest NICS(1) values this aromaticity cannot necessarily be equated to ring stability. Similarly, unknown 1,2,3-oxadiazole and 1,2,3,4-oxatriazole (see Section 2.4.2.2.3) are probably unstable rings but have a high degree of aromaticity on the NICS scale. The position of aza substitution is also influential, e.g., pyrazole and imidazole differ by ~1 unit <2010T2695>. For five-membered heterocycles a correlation between aromatic stabilization energy (ASE) and NICS(1) has been demonstrated ($n = 72$, $r = -0.8588$) <2002JOC1333>. In this context, it is noteworthy that based on NICS(1) values 2*H*-1,2,3-triazole is computed to be one of the most aromatic azoles which is in agreement with the calculated aromatic stabilization energies shown in **Table 3**. Similar trends are seen in the azafurans and azathiophenes (**Table 4**).

2.4.2.2.3 Reactions and equilibria

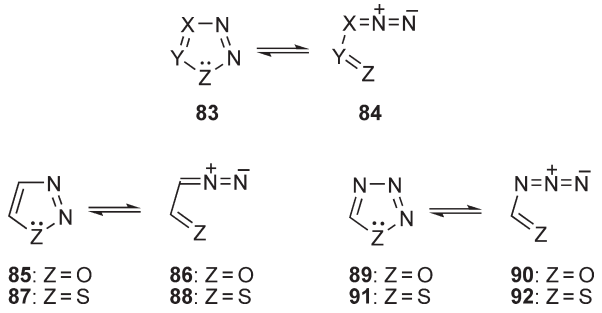
5-Aminoimidazoles **79** can react as either N- or C-nucleophiles with the electrophilic reagents **77** (**Scheme 3**) <1994AHC(61)1>. An MO study has demonstrated that the mode of reaction correlates with the LUMO energy of the reagent **77** calculated by the AM1 method. Hard electrophiles (LUMO > −0.5 eV) give the N-adducts **78** that can be cyclized to the deazapurine derivatives **81**. Soft electrophiles (LUMO < −0.5 eV) give the C-adducts **80** that can be converted to the deazapurines **82** <2009S1271>.

For the azoles **83** (X,Y = CR or N, Z = NR, O, S) with three or more contiguous heteroatoms, the acyclic valence tautomer **84** is sometimes more stable than the ring. Simple 1,2,3-oxadiazoles remain unknown and *ab initio* calculations suggest that the parent ring **85** cannot be isolated as a discrete species, even in an inert matrix at low temperature <1998JOC5801>. A nearly barrierless ring opening to formyldiazomethane **86** was calculated. In contrast, 1,2,3-thiadiazole **87** is remarkably stable and there is no evidence of equilibration with the thioformyl isomer **88**, except possibly as a reaction intermediate. *Ab initio* calculations on the 1,2,3-thiadiazole ring **87** and the ring protonated at N(2) and N(3) reveal that N(2) is the preferred site of protonation by almost 9 kcal mol^{-1}. This observation parallels the preferred site of metal coordination to 1,2,3-thiadiazoles found in several studies <1996CHEC-II(4)289>.



X	Y	ZAlk	LUMO (AM1, eV)	
N.CO_2Et	H	OEt	−0.08	
N.CN	H	OEt	−0.14	Hard
$C(CO_2Et)_2$	H	OEt	−0.27	
N.CN	SMe	SMe	−0.58	
$C(CN)_2$	H	OEt	−0.62	Soft
$C(CN)_2$	SMe	SMe	−1.31	

Scheme 3



Like 1,2,3-oxadiazole **85**, 1,2,3,4-oxatriazole **89** is an unknown compound and the equilibrium between the ring and the also unknown ring-open form **90** has been examined theoretically <2000CPL(318)276, 2005CRV3561>. Calculations predict ΔE values of 20.48 (TZ**), −30 (MP2), and 27 kcal mol^{-1} (MP4-SDQ) for theoretical cyclization of formyl azide **90** to 1,2,3,4-oxatriazole **89**. With the calculated cyclization of azide **90** so highly endothermic, formation of isomer **89** is strongly disfavored. The conversion of the parent 1,2,3,4-thiatriazole **91** to thioformyl azide **92** has been studied by HF/TZ** and MP4-SDQ/6-31G* methods. The calculated activation energy for the 1,2,3,4-thiatriazole–thioformyl azide conversion (**91** → **92**) is 23.09 kcal mol^{-1} and the activation energy for the cyclization of thioformyl azide to 1,2,3,4-thiatriazole (**92** → **91**) is 18.02 kcal mol^{-1} <2000CPL(318)276>.

Ab initio calculations on the equilibrium between the pairs of isomers **93** and **94** (X = O, NH, CH_2) (**Figure 16**), using a 3-21G basis set, demonstrate a linear relationship between the calculated activation energy E_a and the reaction energy ΔE_r for the cyclization **93** → **94** (**Figure 16**) <1990CC882, CHEC-II(4.01.1.5)7>. This provides a striking example of Hammond's postulate, which states that the more exothermic a reaction, the lower in general will be its activation energy.

The Boulton–Katritzky rearrangement (BKR) of 5-methyl-4-nitrobenzofuroxan **96** to 7-methyl-4-nitrobenzofuroxan **95** (**Scheme 4**) has been investigated using *ab initio* and DFT methods with particular emphasis on the influence of 5-substituents. A one-step pathway via a tricyclic transition state was computed. The 5-methyl derivative rearranges on gentle heating, whereas the parent 4-nitrobenzofuroxan does not. In accord with this, the calculated transition state for the 5-methyl derivative is 2 kcal mol^{-1} lower in energy. The reaction barrier for the transformation **96** → **95** (~26 kcal mol^{-1}) is significantly higher than the barrier for the alternative reaction **96** → **97**. However, the BKR (**96** → **95**) is calculated to be exothermic by ~4 kcal mol^{-1} whereas the benzofuroxan isomerization (**96** → **97**) is endothermic by ~2 kcal mol^{-1}. The driving forces for the BKR are complex; a methyl substituent *ortho* to the nitro group leads to out-of-plane torsion, ring strain, and anticonjugative effects <1999JA6700, CHEC-III(5.05.2)316>.

A theoretical study of the ozonolysis of ethylene at the MP(SDQ)/6-31G(d,p) level has suggested a variation of the Criegee mechanism (**Scheme 5**). These results suggest that the primary ozonide **98** (1,2,3-trioxolane) cleaves to give a closely associated dipole pair **99** which does not dissociate but reconfigers to give a dipole–dipole stabilized complex

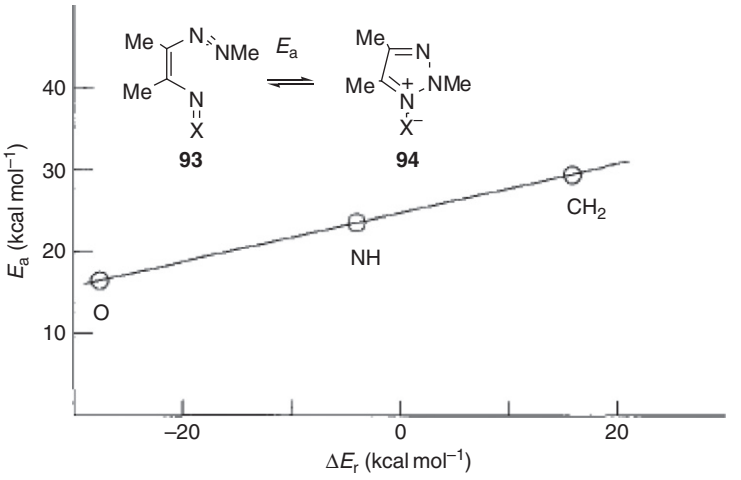
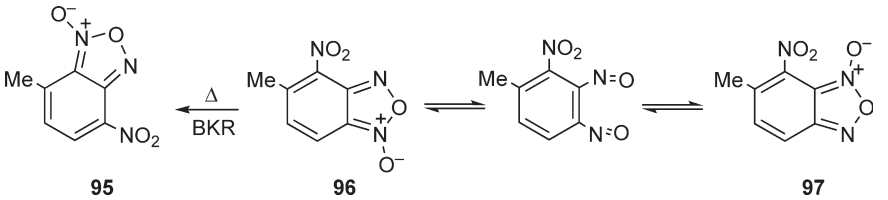
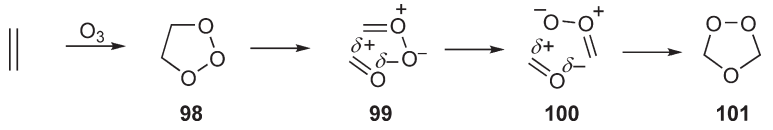


Figure 16 Plot of activation energy (E_a) versus reaction energy (ΔE_r) for the cyclization of **93** to **94** (X = O, NH, CH_2).



Scheme 4

100. The complex **100** is calculated to be more stable than the separated aldehyde and carbonyl oxide by 9 kcal mol^{-1} and the formation of complex **100** from ethylene and ozone is endothermic by only 3.1 kcal mol^{-1} <1991CPL(187) 491>. Cycloaddition then leads to the secondary ozonide **101** (1,2,4-trioxolane). A subsequent study of the stereochemistry of ozonation reactions using the AM1 method provides further support for the modified Criegee mechanism <1997JOC2757, CHEC-III(6.06.2)193>.



Scheme 5

2.4.3 Structural Methods

2.4.3.1 X-Ray Diffraction

Details of bond lengths and bond angles for the X-ray structures of heterocyclic compounds up to 1970 are listed in *Physical Methods in Heterocyclic Chemistry*, Volume 5 <1972PMH(5)1>. This compilation contains many examples for five-membered rings containing two heteroatoms. For compounds with three or four heteroatoms in the ring the number of measurements is less, and some of these, including recent examples, are summarized in **Table 5**. Where CHEC-III is provided as an additional reference in **Table 5**, this usually indicates that CHEC-III contains a tabulation of related crystal structures. Further examples are contained in the appropriate chapters of the three editions of *Comprehensive Heterocyclic Chemistry*. The Cambridge Crystallographic Database (www.ccdc.cam.ac.uk) maintains a comprehensive collection of heterocyclic structures.

Table 5 X-ray structures of five-membered rings with two, three, four, or five heteroatoms

	Atom positions					
Ring	*1*	*2*	*3*	*4*	*5*	*Examples of compounds studied*
N_5	N	N	N	N	N	1-Phenylpentazole[a]
CN_2S_2	S	S	N	C	N	4-(*p*-Chlorobenzylsulfanyl)[1,2,3,5]dithiadiazol-1-ylium chloride[b]
CN_3O	O	N	N	N	C	3-Phenyl-1,2,3,4-oxatriazole-5-phenylimine; 3-phenyl-1,2,3,4-oxatriazolium-5-olate[c]
CN_3S	S	N	N	N	C	5-Phenyl-1,2,3,4-thiatriazole; 5-amino-1,2,3,4-thiatriazole; 5-phenyl-1,2,3,4-thiatriazole 3-oxide; 1,2,3,4-thiatriazol-5-thione[d]
	S	N	N	C	N	2-Acetyl-5-chloro-2*H*-1,2,3,5-thiatriazolo[4,5-*a*]isoquinoline 5-oxide; 2,4-diphenyl-1,2,3,5-thiatriazolium bromide[e]
CN_4	N	N	N	N	C	5-Amino-2-methyltetrazole[f]; 5-aminotetrazole monohydrate; sodium tetrazolate monohydrate[f]; 1-methyltetrazole; 1-phenyltetrazole[g]; 5,5′-bitetrazole[h]
C_2NO_2	O	O	C	N	C	3,3,4,5-Tetraphenyl-1,2,4-dioxazolidine[i]
C_2NOS	O	S	N	C	C	2,4-Dioxo-2-(4-tolyl)-1,2,3-oxathiazoline[j]; 1,2,3-oxathiazolo-[5,4-*d*][1,2,3]-oxathiazole 2,2,5,5-tetraoxide[k]
	O	N	S	C	C	4-Phenyl-1,3,2-oxathiazolin-5-one[l]
	O	S	C	N	C	6,10b-Dihydro-3-(2,2,6,6-tetramethylcyclohexyliden)-1,2,4-oxathiazolo-[5,4-*a*]-isoquinoline[m]
	O	C	S	N	C	2-Trichloromethyl-5-phenyl-Δ^4-1,3,4-oxathiazoline[n]; 5-phenyl-1,3,4-oxathiazol-2-one[o]
C_2NS_2	S	S	N	C	C	2,4,6-Tri-*t*-butyl-7,8,9-dithiazabicyclo[4.3.0]nona-1(9)-2,4-triene;[p] 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt)[q]
	S	S	C	N	C	5-Amino-1,2,4-dithiazolin-3-one (rhodan hydrate);[r] 5-amino-1,2,4-dithiazoline-3-thione (xanthane hydride)[s]; 3,5-diamino-1,2,4-dithiazolium chloride (thiuret hydrochloride)[r]; 3,5-ditolyl-1,2,4-dithiazolium hexafluoroarsenate[u]
C_2N_2O	O	N	N	C	C	*N*-(4-Bromophenyl)sydnone[f]; 4,4′-dichloro-3,3′-ethylene-bis(sydnone); 1,2,3-oxadiazolium-5-olates (sydnones)[v]
	O	N	C	N	C	3-(2-Aminopyridyl)-5-methyl-1,2,4-oxadiazole; 4-acetyl-5-ethyl-3-(4-tolyl)-2,4-dihydro-1,2,4-oxadiazole[w]
	O	N	C	C	N	3-(4-bromophenyl)-4-methyl-1,2,5-oxadiazole 2-oxide;[f] 3-(4-bromophenyl)-4-methyl-1,2,5-oxadiazole 5-oxide[f]; 3,4-diphenyl-1,2,5-oxadiazole; 3,4-dicyano-1,2,5-oxadiazole 2-oxide (dicyanofuroxan)[x]
	O	C	N	N	C	Monoaryl-1,3,4-oxadiazoles[y]; 2,5-di-(4-pyridyl)-1,3,4-oxadiazole[z]
C_2N_2S	S	N	N	C	C	5-Acylamino-3-methyl-1,2,3-thiadiazole; 5-phenyl-1,2,3-thiadiazole 3-oxide; 4-phenyl-1,2,3-thiadiazole[aa]
	S	N	C	N	C	5-Imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline[ab]; 3-phenyl-1,2,4-thiadiazole-5-carboxamide 4-oxide[ac]
	S	N	C	C	N	3,4-Diphenyl-1,2,5-thiadiazole; 1,2,5-thiadiazole-3,4-dicarboxamide; 3,4-diphenyl-1,2,5-thiadiazole[ad]
	S	C	N	N	C	1,3,4-Thiadiazole; 2,5-diphenyl-1,3,4-thiadiazole[f]; 2-amino-5-phenyl-1,3,4-thiadiazole[ae]
C_2N_3	N	N	N	C	C	1,3-Dimethyl-4-(1,2,3-triazolyl)sulfide; 3-methyl-2-phenyl-1,2,3-triazol-1-ine-4-thione; 2-(4-chlorophenyl)-4-amino-5-benzoyl-1,2,3-triazole[af]
	N	N	C	N	C	1,2,4-Triazole[f]
C_2O_2S	O	S	O	C	C	1,3,2-Dioxathiolane 2,2-dioxide[ag]; 1,3,2-dioxathiol 2,2-dioxide[ag]; 4,5-diphenyl-1,3,2-dioxathiolane 2-oxide[ah]
C_2O_3	O	O	C	O	C	*Trans*-5-anisyl-3-methoxycarbonyl-1,2,4-trioxolane[ai]; *cis*-3,5-dinaphthyl-1,2,4-trioxolane[aj]; 6,7,8-trioxa-3-thiabicyclo[3.2.1]octane[ak]
C_2S_3	S	S	C	S	C	1,2,4-Trithiolane-3,5-dione diphenylhydrazone[al]
C_3NO	O	N	C	C	C	5,5′-Bis(isoxazole)[f]; 3-hydroxy-5-phenylisoxazole[f]; 3,3′-bi-2-isoxazoline[f]; 3-hydroxy-5-phenylisoxazole[f]; 3-phenyl-isoxazolin-5-one;[f] 3-hydroxy-5-methylisoxazole[am]
	O	C	N	C	C	2,2′-*p*-Phenylenebis(5-phenyloxazole); 2-(4-pyridyl)oxazole[f]; 2,4-dimethyl-5-(4-nitrophenyl) oxazole[f]; 2-oxazolidinone[f]; methyl 2-(*t*-butyloxycarbonylamino-methyl)-1,3-oxazole-4-carboxylate[an]
C_3NS	S	N	C	C	C	Methyl 3-hydroxy-4-phenylisothiazole-5-sulfonate; saccharin[ao]
	S	C	N	C	C	Thiamine hydrochloride monohydrate[f]; rhodanine[f]; 2-imino-5-phenyl-4-thiazolidinone;[f] 2-amino-4-phenylthiazole[ap]
C_3N_2	N	N	C	C	C	Pyrazole[f]; substituted pyrazoles; Δ^1- and Δ^2-pyrazolines; pyrazolinones; pyrazolidines; pyrazolidinones; 4-methylpyrazole[aq]; 1-(2,4-dinitrophenyl)- Δ^2-pyrazoline[ar]
	N	C	N	C	C	imidazole[f]; 4,5-di-*t*-butylimidazole; histamine dihydrochloride; 2-thiohydantoin; 1-methyl-2,4,5-trinitroimidazole[as]
C_3OS	O	S	C	C	C	5-Methyl-3-phenyl-1,2-oxathiolane 2,2-dioxide[at]; 5*H*-l,2-benzoxathiol 2,2-dioxide
	O	C	S	C	C	Cholestan-4-one-3-spiro(2,5-oxathiolane)[f]

Table 5 (Continued)

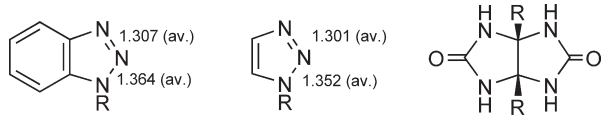
	Atom positions					
Ring	*1*	*2*	*3*	*4*	*5*	*Examples of compounds studied*
C_3O_2	O	O	C	C	C	3,5-Di(trifluoromethyl)-3,5-dihydroxydioxolane[au]
	O	C	O	C	C	Bis(dioxolane); ethylene carbonate; *cis*-2-*t*-butyl-5-carboxymethyl-1,3-dioxolan-4-one; 2-methyl-1,3-dioxolan-2-ylium perchlorate; 5-bromo-4-formyl-1,3-benzodioxole[av]
C_3S_2	S	S	C	C	C	1,2-Dithiolane-4-carboxylic acid[f]; 3-phenyl-1,2-dithiolylium iodide[f]; 4-methyl-1,2-dithiole-3-thione;[f] 5-phenyl-4-thiomethoxy-1,2-dithiol-3-thione[aw]
	S	C	S	C	C	Bis-1,3-dithiol-2-yl;[f] 4,5-dioxo-2-thioxo-1,3-dithiolane;[f] 1,3-dithiolane-2-thione 5-oxide;[f] tetrathiafulvalenes (TTFs)[ax]

Unless otherwise indicated data are taken from the appropriate chapter of *Comprehensive Heterocyclic Chemistry*.
[a]<2002ZFA1933, CHEC-III(6.18.3)749>.
[b]<2002ARK(vi)224>.
[c]<CHEC-II(4)679>.
[d]<2000JA9052, CHEC-III(6.09.3)448>.
[e]<1990J(P2)1619, CHEC-III(6.10.3)487>.
[f]Data taken from <1972PMH(5)1>, which gives references to the original literature.
[g]<1996AXC2818, 1999AXC129>.
[h]<1996JCX399>.
[i]<1995J(P1)41>.
[j]<1971TL4243>.
[k]<1980MI40100>.
[l]<1972G23>.
[m]<1978AGE455>.
[n]<1981J(P1)2991>.
[o]<1995JCX25, CHEC-III(6.04.3)108>.
[p]<1980AXB1466>.
[q]<2002J(P1)1535>.
[r]<1966ACS754>.
[s]<1963ACS2575, 1963AX1157>.
[t]<1966ACS1907>.
[u]<1996AXC2148>.
[v]<CHEC-III(5.03.3)213>.
[w]<2001JST(561)29>.
[x]<1996J(P2)179>.
[y]X-Ray powder data. cf. Chapter 4.23
[z]<2001JST(561)175, CHEC-III(5.06.3.5)404>.
[aa]<1991JOM(405)309>.
[ab]<1978CC652>.
[ac]<1999J(P1)2243, CHEC-III(5.08.3)489>.
[ad]<1976AXB1074, CHEC-III(5.09.3)519>.
[ae]<2001RJO721>.
[af]<2006ARK(xv)53, CHEC-III(5.01.3)6>.
[ag]<1968JA2970>.
[ah]<1996AXC739>.
[ai]<1970ACS2137>.
[aj]<1984JA6087>.
[ak]<2000AXC1510>.
[al]<1971JCS(B)415>.
[am]<1997J(P2)1783>.
[an]<2000J(P2)1081>.
[ao]<1968JCB376>.
[ap]<2004IJY587>.
[aq]<1999NJC237>.
[ar]<2004AJC1103>.
[as]<2001JHC141>.
[at]<2003EJO3939>.
[au]<2001AXEo636>.
[av]<1999JOC8004>.
[aw]<2004TL7671>.
[ax]<CHEC-III(4.12.3.5)971>.

A large number of X-ray structures of derivatives of five-membered heterocycles have been reported and **Table 5** gives only representative examples. In most cases X-ray studies were undertaken to provide proof of structure. Bicyclic derivatives have also been investigated. The structures of a number of benzotriazoles have been reported. In comparison with monocyclic 1,2,3-triazoles **103**, N(1)-substituted benzotriazoles **102** have significantly longer N(1)–N(2) bonds (average 1.364 Å vs. 1.352 Å) and somewhat longer N(2)–N(3) bonds (average 1.307 Å vs. 1.301 Å). In general, the C–N and C–C bonds in the heterocyclic ring of benzotriazole derivatives **102** are also slightly longer than the corresponding bonds in 1,2,3-triazoles **103**. Thus the average heterocyclic ring bond in 1-substituted benzotriazoles is significantly longer than in the 1,2,3-triazoles and this reflects the diminished aromatic character and therefore the higher reactivity of the benzotriazole system <CHEC-III(5.01.3)6>.

X-ray crystallography has shown that the bicyclic mesomeric betaines **69**, **74** (R = Me) and **75** (R = 3-(4-azido)-1,2,5-oxadiazolyl) (**Figure 15**) have planar fully-conjugated aromatic rings <CHEC-III(10.05.3.1)200>.

Intermolecular hydrogen bonding is a common feature in the crystals of polyhetero five-membered heterocycles. Derivatives of glycoluril **104** are concave in shape and are useful building blocks in supramolecular chemistry. X-ray studies of alkylated glycolurils **104** often show the formation of 'capsules' and 'clips,' but in suitably substituted glycolurils the formation of hydrogen-bonded 'tapes' has also been observed <2002T9769, CHEC-III(10.04.3)163>. **Figure 17** shows the structure of the multiple hydrogen-bonded network observed in the crystal state of derivatives **104** (R = H, Me).



102 **103** **104**

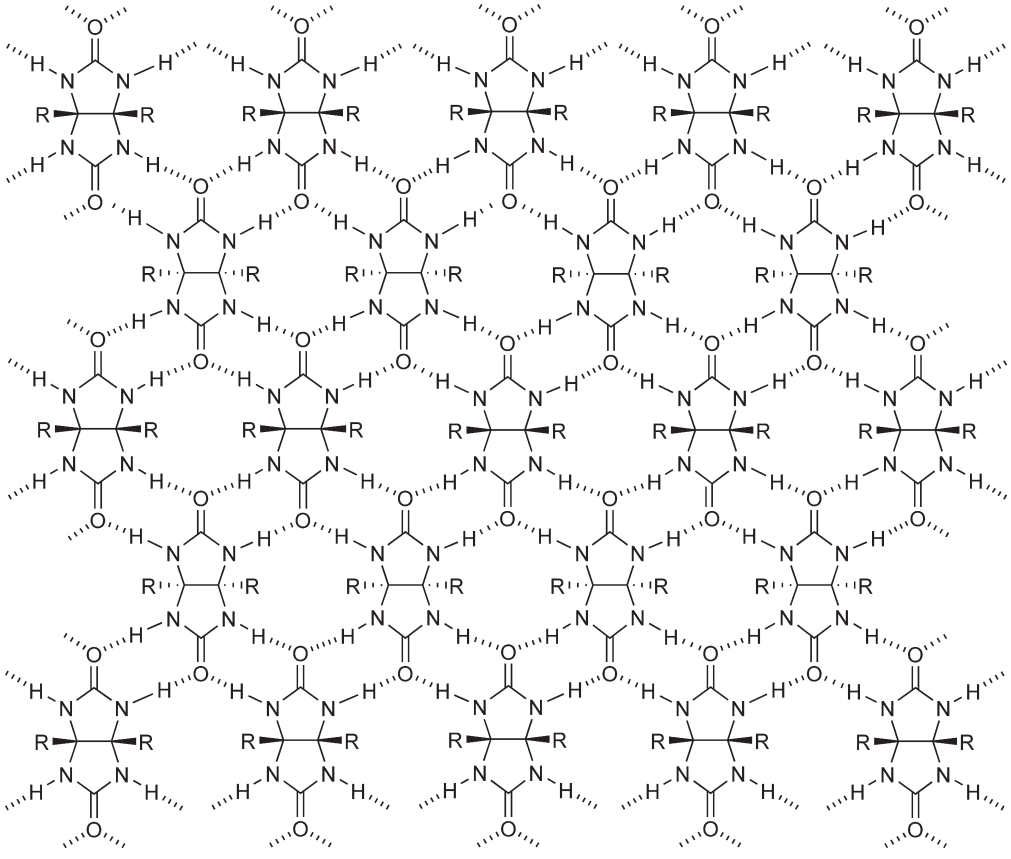
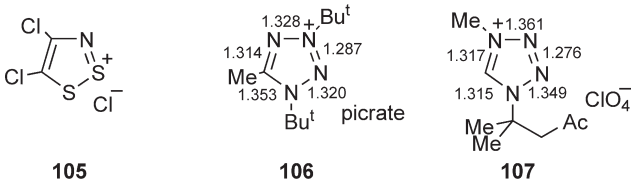


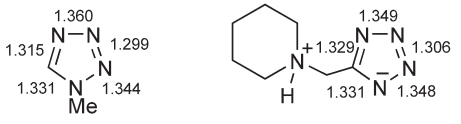
Figure 17 Hydrogen-bonded structure in the crystals of glycoluril derivatives (R = H,Me).

Five-membered rings with more than one heteroatom can also form cations while retaining an aromatic sextet, and structures determined by X-ray crystallography confirm the aromaticity of these species. The X-ray analysis of 4,5-dichloro-1,2,3-dithiazolium chloride **105**, often referred to as the Appel salt, reveals a pattern of bonding within the dithiazole ring that indicates delocalization extending around the ring from one sulfur atom to the other, and there is also evidence for a shortening of the S–S bond length (2.034(2) Å) compared with that normally associated with an S–S single bond <2002J(P1)1535>.

Tetrazoles form both 1,3-tetrazolium salts, e.g., **106**, and 1,4-tetrazolium salts, e.g., **107**, and a number of X-ray structures are available <CHEC-III(6.07.3)265>. The net positive charge leads to stronger bonding and compared to the bond lengths in neutral 1-methyltetrazole **108** there is shortening of ring bond lengths in the tetrazolium rings **106** and **107**. One exception is the N(1)–C(5) bond in the salt **106**, where nucleus–nucleus repulsion between the quaternary nitrogen and the electron-deficient carbon atom probably lengthens the bond. In the tetrazolyl anion **109** the bond lengths do not vary greatly from those in the neutral tetrazole **108**.

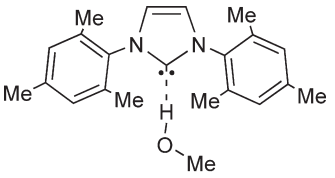


105 **106** **107**



108 **109**

N-Heterocyclic carbenes (NHCs) (see Section 2.4.4.2.5) catalyze the amidation of unactivated esters with amino alcohols. The X-ray structure of the N^1,N^3-bis(mesityl)imidazolylidene–methanol complex **110** reveals a nearly linear (174°) O–H···C hydrogen-bonding interaction within the plane defined by the heterocyclic ring <2005OL2453>. This observation, together with NMR and IR studies, led to the proposal of a new mode of catalysis by stable carbenes. Similar solid-state hydrogen-bonding interactions between the same NHC and diphenylamine to form a previously unobserved N–H···C hydrogen bond were recognized in an earlier study <2002AGE1432>.



110

2.4.3.2 Microwave Spectroscopy

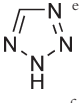
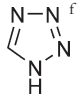
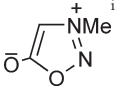
Microwave spectra provide minute details of molecular geometry because the spectra are primarily analyzed in terms of the accurate average values of the reciprocals of the three moments of inertia. This generally gives the molecular conformation and some precise structural features may emerge. To obtain a complete structure it is necessary to measure the changes in moments of inertia that accompany isotopic replacements of each atom in turn <1974PMH(6)53>.

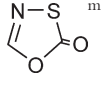
From accurate measurements of the Stark effect, when electrostatic fields are applied, information about the electron distribution is also obtained. Further information is obtained from nuclear quadrupole coupling effects and Zeeman effects <1974PMH(6)53>. Microwave studies also provide important information regarding molecular force fields, particularly with reference to low-frequency vibrational modes in cyclic structures <1974PMH(6)53>.

2.4.3.2.1 Aromatic rings

Structural parameters for aromatic five-membered rings are shown in **Table 6**. All the C–H distances are near 107.5 pm, which is close to the C–H bond in ethylene. With heteroatoms at adjacent ring positions, the C–H groups are displaced from the bisector of the ring angles toward the adjacent heteroatom <1974PMH(6)53>.

Table 6 Structural parameters in five-membered aromatic rings from microwave spectra

	Bond length (pm)[a,b]					*Angle (°)*[b]					*Dipole moment*[a]
Ring/Ref	*a*	*b*	*c*	*d*	*e*	α	*β*	γ	δ	ε	10^{-30} *C m*
 [c]	141.6	133.1	134.9	135.9	137.3	111.9	104.1	113.1	106.4	104.5	7.37
	(137.8)	(132.6)	(134.9)	(136.9)	(135.8)	(105.4)	(111.3)	(107.2)	(106.3)	(109.8)	12.80
 [d]	140.5	134.6	132.3	132.3	134.6	–	–	117.1	–	–	0.73
 [e]	135.9	132.3	135.9	133.1	132.4	114.6	102.1	110.2	110.1	103.0	9.07
 [e]	135.1	128.4	132.4	133.4	131.0	–	–	–	–	–	7.31
 [f]	(134.5)	(128.3)	(134.7)	(135.1)	(129.0)	(112.2)	(106.9)	(105.3)	–	–	17.05
 [g]	–	–	–	–	–	–	–	–	–	–	9.21
 [h]	–	–	–	–	–	–	–	–	–	–	8.67
 [e]	139.5	129.3	135.7	137.0	135.3	103.9	115.0	103.9	108.1	109.1	5.00
 [e]	137.2	130.4	172.4	171.3	136.7	110.1	115.2	89.3	109.6	115.8	5.37
 [i]	(133.4)	(131.3)	(138.9)	–	–	(111.3)	(103.8)	(114.4)	–	–	21.12

 [j]	(138.0)	(130.3)	(141.8)	–	–	(106.1)	(103.2)	(114.2)	–	–	5.44
 [c]	142.1	130.0	138.0	138.0	130.0	109.0	105.8	110.4	105.8	109.0	11.28
 [c]	139.9	129.7	134.8	134.8	129.7	105.6	113.4	102.0	113.4	105.6	10.14
 [k]	136.6	129.0	169.2	168.9	136.9	114.0	111.2	92.9	107.8	114.2	11.98
 [l]	136.6	131.7	164.9	170.7	131.3	120.1	107.1	92.8	112.3	107.7	1.50
 [c]	142.0	132.8	163.1	163.1	132.8	113.8	106.4	99.6	106.4	113.8	5.24
 [c]	137.1	130.2	172.1	172.1	130.2	112.2	114.6	86.4	114.6	112.2	10.94
 [m]	169.0	176.6	140.2	135.6	128.6	93.8	106.3	110.8	121.1	107.9	–

[a]1 Å 100 pm; 1 D 3.336 × 10^{-30} C m.

[b]X-ray diffraction data are enclosed in parentheses.

[c]Data taken from <1974PMH(6)53>, which gives references to the original literature.

[d]<1988ACA500>.

[e]Data taken from appropriate chapter of *Comprehensive Heterocyclic Chemistry*.

[f]No bond lengths or angles given in <1974JSP(49)423>; calculated values taken from <CHEC-I(4.13)791>.

[i]Bond lengths and angles for X-ray data for 4,4′-dichloro-3.3′-ethylenebis(sydnone) <1967JA5977>; calculated dipole moment for 3-methylsydnone <1971JST(9)321>.

[j]Bond lengths and angles from X-ray data for 3-(2-aminopyridyl)-1,2,4-oxadiazole <1979AXB2256>; dipole moment for 3-methyl-5-phenyl-1,2,4-oxadiazole <1935G152>.

[k]Dipole moment from <1976MI40100>.

[l]<1974TH40100>.

[m]Values for 1,3,4-oxathiazolin-2-one determined from electron diffraction measurements and refined using rotational parameters from microwave spectra; cf. CHEC-I (4.34.2.3.2)903.

The N–H bond lengths in pyrazole and imidazole (99.8 pm) are a little shorter than those found in dimethylamine. Delocalization in pyrazole, imidazole, 1,2,3-triazole and 1,2,4-triazole is sufficient to bring the hydrogen attached to nitrogen into the plane of the other atoms. The N–H bond in pyrazole does not lie in the bisector of the ring angle (as is required by symmetry in pyrrole), but is displaced by about 5° toward the second nitrogen <1974PMH(6)53>.

The ring angles at C and N are usually 108 ± 5°, but are nearer to 90° at sulfur and selenium.

Minor variations in the bond lengths reflect variations in the double bond character and, for example, suggest greater delocalization in 1,3,4-thiadiazole than in 1,3,4-oxadiazole <1974PMH(6)53>. In thiazole the geometry of the SCN portion of the ring resembles the corresponding part of 1,3,4-thiadiazole, while the remainder of the ring resembles the corresponding portion in thiophene.

The microwave spectrum of the parent 1,2,3-triazole was interpreted in terms of the 1*H*-tautomer <1970SAA825>. The microwave spectrum of a highly enriched sample of *N*-deuterio-1,2,3-triazole was also apparently assigned unambiguously to the 1-deuterio form <1974CC605>. However, later analysis of the microwave spectra of the parent molecule, the highly enriched $^{15}N_3$ species, and the *N*-deuterated derivative, revealed 1,2,3-triazole to exist as a mixture of two planar tautomers: a 1*H*-form with C_s symmetry and a 2*H*-form with C_{2v} symmetry. This is the first recorded microwave spectrum of the deuteriated 2*H*-tautomer. The population ratio of the two tautomers, estimated from the analysis of the microwave spectrum of the triple ^{15}N sample, is 1*H*:2*H* ≈ 1:1000 at room temperature. The dipole moments of the tautomers are measured as $\mu_{1H} = 4.38$ D and $\mu_{2H} = 0.218$ D for the 1*H*- and 2*H*-forms of the $^{15}N_3$ triazole, respectively <1988ACA500>. These are in good agreement with calculated values (**Table 3**).

1,2,4-Triazole exists in the 1*H*-form. A combination of microwave spectroscopy <1974JSP(49)423> and B3LYP/6-31G* calculations <2001PCP3541> suggest that the 2*H*-isomer of tetrazole is the predominant tautomer in the gas phase. In the crystalline phase tetrazole exists exclusively as the 1*H*-tautomer.

Dipole moments can also be obtained from the microwave spectral data <1974PMH(6)53> and available values are given in **Table 6**. The dipole moment of 2*H*-tetrazole is reported to be 2.19 D <1974JSP(49)423>, which is in good agreement with the calculated value <2001PCP3541> (see **Table 3**).

2.4.3.2.2 Partially- and fully-saturated ring systems

Relatively few such heterocyclic systems have been studied by microwave spectroscopy; some data are included in **Table 7**. In 1,3-dioxolane the twist conformation (see **Table 41**) is more stable than the envelope conformation, and pseudorotation occurs. In 1,2,4-trioxolane the equilibrium conformation is the twist form, in which the peroxide bond straddles the plane of the other three atoms, and there is a barrier of 6.3 kJ mol^{-1} opposing pseudorotation <1974PMH(6)53>. Preference for the twist conformation is also observed in the crystal structures of some 1,2,4-trioxolane derivatives (see **Table 41**, Section 2.4.4.4) <CHEC-III(6.06.3.1)195>.

2.4.3.3 ^{1}H NMR Spectroscopy

2.4.3.3.1 Fully-conjugated aromatic rings

2.4.3.3.1.1 Chemical shifts. ^{1}H NMR spectroscopy is routinely used for the characterization and structure confirmation of this class of heterocycle. Proton chemical shifts for the ring CH of fully-aromatic neutral azoles and their oxygen and sulfur analogues are recorded in **Tables 8** and **9**, respectively. For the NH azoles (**Table 8a**), the tautomeric forms are usually rapidly equilibrating on the NMR timescale (except for 1,2,4-triazole in HMPT). The *N*-methylazoles (**Table 8b**) have fixed structures. Inspection of **Table 8** reveals that, as might be expected, the CH chemical shifts move downfield as the number of nitrogen atoms in the ring increases. Also, deshielding by an adjacent pyridine-type nitrogen atom is usually greater than that by an adjacent pyrrole-type *N*-methyl group. However, solvent effects can sometimes reverse the position of signals. For 1-methyl-1,2,3-triazole in $CDCl_3$ δH(5) < δH(4) but in DMSO-d_6 δH(4) < δH(5) (**Table 8b**) <1991T9783>.

Comparison with the data for azoles containing oxygen or sulfur shows that an adjacent oxygen atom (**Table 9a**) or sulfur atom (**Table 9b**) induces greater shifts to lower field than either type of nitrogen atom. In oxazole the deshielding is δH(2) > δH(3) > δH(4). Significant progress has been made in developing programs that predict ^{1}H (and ^{13}C) chemical shifts of heterocyclic derivatives <2001T4179>.

Table 7 Structural parameters in five-membered saturated rings from microwave spectra

	Bond length (pm)[a]					*Angle* (°)					
Compd	*a*	*b*	*c*	*d*	*e*	*α*	*β*	*γ*	*δ*	*ε*	*Dipole moment* (10^{-30} *C m*)[a]
 [b]	–	–	–	–	–	–	–	–	–	–	3.97
 [c]	156.3	142.8	–	142.8	156.3	105.1	–	–	105.1	101.7	–
 [d]	143.6	139.5	147.0	139.5	143.6	106.2	99.2	99.2	106.2	99.2	3.64

[a] 1 Å 100 pm; 1 D 3.336 × 10^{-30} C m.
[b] Data taken from appropriate chapter of *Comprehensive Heterocyclic Chemistry*.
[c] Values calculated from experimentally derived rotational constants; cf. <CHEC-I(4.30.1.3.2)751.
[d] <1972JA6337>.

Table 8 ^{1}H NMR chemical shifts for ring hydrogens of azoles

		^{1}H chemical shifts (δ, ppm)					
	Compound	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*	*Reference*
(a)	*NH derivatives*						
	Pyrrole	6.68	6.22	6.22	6.68	$CDCl_3$	CHEC-I(3.04.4.1)165
	Pyrazole	–	7.61	7.31	7.61	–	B-1973NMR
	Imidazole	7.86	–	7.25	7.25	$CDCl_3$	B-1973NMR
	1,2,3-Triazole	–	–	7.75	7.75	$CDCl_3$	1967BSF2998
	1,2,4-Triazole	–	7.92	–	8.85	HMPT	CHEC-I(4.12.2.3.3)740
	Tetrazole	–	–	–	9.5	D_2O	CHEC-I(4.13.2.3.3)798
(b)	*NMe derivatives*						
	1-Methylpyrazole	–	7.49	6.22	7.35	$CDCl_3$	1998H(47)301
	1-Methylimidazole	7.47	–	7.08	6.88	$CDCl_3$	B-1973NMR
	1-Methyl-1,2,3-triazole	–	–	7.66	7.52	$CDCl_3$	1991T9783
	1-Methyl-1,2,3-triazole	–	–	7.69	8.04	DMSO-d_6	1991T9783
	2-Methyl-1,2,3-triazole	–	7.75	7.75	–	$CDCl_3$	B-1973NMR
	1-Methyl-1,2,4-triazole	–	7.94	–	8.09	$CDCl_3$	B-1973NMR
	4-Methyl-1,2,4-triazole	8.20	–	–	8.20	$CDCl_3$	1968JOC2956
	1-Methyltetrazole	–	–	–	9.30	DMSO-d_6	CHEC-II(4.17.3)630
	2-Methyltetrazole	–	–	–	8.91	DMSO-d_6	CHEC-II(4.17.3)630

Table 9 ^{1}H NMR spectral data for ring hydrogens of azoles containing oxygen or sulfur

		^{1}H Chemical shifts (δ, ppm)					
	Compound	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*	*Reference*
(a)	*Oxygen derivatives*						
	Isoxazole	–	8.14	6.28	8.39	CS_2	1974CJC833
	Oxazole	7.95	–	7.09	7.69	CCl_4	CHEC-I(4.18.2.3.3)181
	1,2,4-Oxadiazole	–	8.2	–	8.7	C_6D_6	1976AHC(20)65
	1,2,5-Oxadiazole	–	8.19	8.19	–	$CHCl_3$	CHEC-I(4.22.2.3.1)397
	1,3,4-Oxadiazole	8.73	–	–	8.73	$CDCl_3$	CHEC-III(5.06.3.2)401
(b)	*Sulfur derivatives*						
	Isothiazole	–	8.54	7.26	8.72	CCl_4	CHEC-II(3.05.3.2)325
	Thiazole	8.88	–	7.98	7.41	$CDCl_3$	1979HC(34-1)67
	1,2,3-Thiadiazole	–	–	8.80 (m)		CCl_4	1978JOC2487
	1,2,4-Thiadiazole	–	8.66[a]	–	9.90[b]		See footnotes
	1,2,5-Thiadiazole	–	8.70	8.70	–	CCl_4	1964DIS2690
	1,3,4-Thiadiazole	7.55	–	–	7.55	$CDCl_3$	1978BAP291

[a]Value given for the 5-phenyl derivative <1980JOC3750>.
[b]Value given for the 3-phenyl derivative <1974JOC962>.

In fully-conjugated 5:5-fused heterocycles the ring protons are found in the aromatic region but their position is influenced by the adjacent ring. Thus, in the series **111–113** the isothiazole unit has an electron-withdrawing effect and the left-hand ring protons are deshielded relative to the parent monocyclic heterocycles (**Figure 18**) <CHEC-II(7.02.3)502>.

2.4.3.3.1.2 Coupling constants. In monocyclic azoles vicinal CH–CH coupling constants are small and where they have been measured are 1–2 Hz; for *N*-methylpyrazole the coupling constants are $J_{3,4} = 2.0$ Hz, $J_{3,5} = 0.7$ Hz, and $J_{4,5} = 2.3$ Hz and for isoxazole they are $J_{3,4} = 1.8$ Hz, $J_{3,5} = 0.3$ Hz, and $J_{4,5} = 1.7$ Hz. In some derivatives, long-range coupling of ring protons is observed. Compound **114** presents an unusual long-range $^6J_{^1H\text{-}^1H}$ coupling constant between the pyrazole H(3) and azomethine =CH protons <1987AP(320)115>. Long-range 'through–space' spin–spin couplings ($^6J_{^1H\text{-}^{19}F}$ and $^6J_{^{19}F\text{-}^{19}F}$) between the *ortho* fluorine atom and substituent R (R = CH_3, CHF_2, and CF_3) are found in

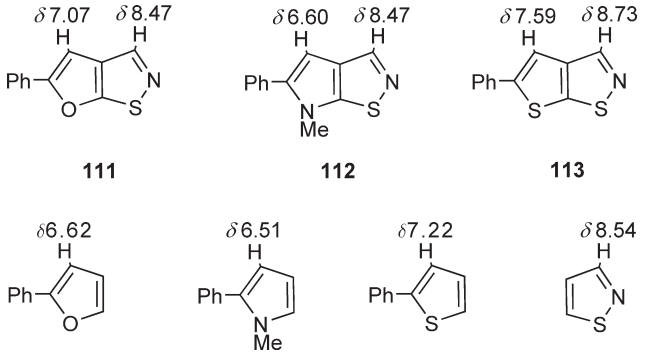
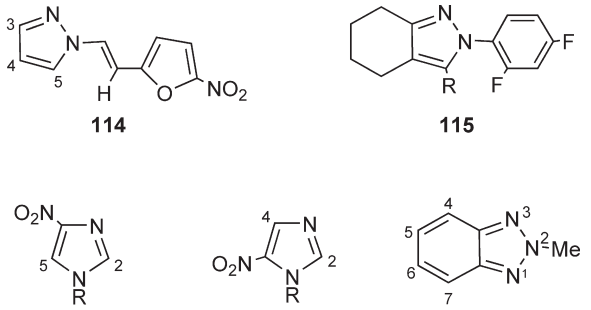


Figure 18 Examples of ^{1}H NMR chemical shifts in heteropentalene derivatives compared to corresponding monocyclic systems.

the pyrazole derivatives **115** <1993MRC323>. A systematic study of *ortho*-benzylic coupling constants $^{4}J_{Me-C=C-H}$ has been published <1992JHC935>: examples are 1,3-dimethylpyrazole (−0.55 Hz), 1,4-dimethylpyrazole (−0.68 Hz with H (3) and −0.92 Hz with H(5)), and 1,5-dimethylpyrazole (−0.83 Hz), with the coupling values being linearly related to bond orders.

Differentiation between 1,4- and 1,5-disubstituted imidazoles is sometimes difficult but examination of cross-ring ^{1}H NMR coupling constants can distinguish between them when appropriate ring protons are present. Usually, $J_{2,5}$ is larger than $J_{2,4}$ (1.1–1.5 and 0.9–1.0 Hz, respectively) <1973JA2297>. Typical examples are the 4- and 5-nitroimidazoles **116** and **117** <1999S985>.



Proton–proton coupling constants of benzo rings of benzazoles can illuminate the bonding in such compounds. Thus, comparison of the coupling constants (J) for naphthalene with those for benzotriazoles (**Table 10**) shows evidence of bond fixation, particularly in the 2-methyl derivative **118** <1971PMH(4)121>.

Table 10 Proton–proton coupling constants (Hz) in benzotriazoles

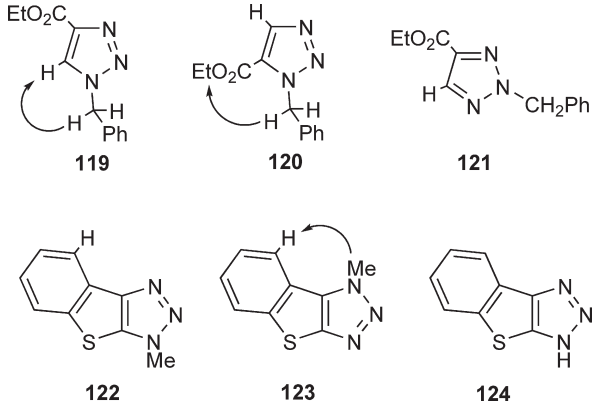
Compound	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$
Benzotriazole[a]	8.3	6.7	1.4
2-Methylbenzotriazole	9.4	3.6	0.5
Naphthalene	8.6	6.0	1.4

Data taken from <1971PMH(4)181> which contains references to the original literature.
[a]Rapid tautomerism between 1- and 3-positions occurs.

2.4.3.3.1.3 Nuclear Overhauser effects. The nuclear Overhauser effect (NOE) is often used to distinguish between alternative structures and has been used for the unambiguous discrimination between H(4) and H(5) signals in 1-substituted 1*H*-1,2,3-triazoles <1991T9783, 1992JHC1203>. The NOE method for discriminating between isomeric disubstituted 1,2,3-triazoles is illustrated by compounds **119–121**. Simple NOE experiments allowed the identification

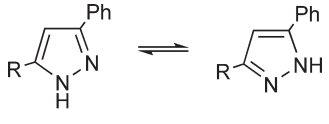
of isomer **119** since only in this compound was an NOE enhancement of the triazole-H singlet observed upon irradiation of the benzyl CH_2 group. Compound **120** can be distinguished from compound **121** by a moderate NOE enhancement between the NCH_2 and the ester group.

Another example of the use of the NOE method to distinguish between isomers is the assignment of the structures **122** and **123** to the products of methylation of 3*H*-[4,5]benzothieno[2,3-*d*]-1,2,3-triazole **124**, since the ^1H and ^{13}C spectra of these products are virtually identical <1993JCM128>.



2.4.3.3.1.4 Anions and cations. The effect of anion and cation formation on ^1H chemical shifts is summarized in **Table 11**. Anion formation always results in shifts to higher field (**Table 11a**); however, the effect is relatively modest except for the 4-position of pyrazole because in all other cases the adjacent nitrogen lone pair partially cancels the effect. Conversely, in the cations (**Table 11b**) the downfield shift is especially large for the CH groups next to nitrogen. Coupling constants appear to be slightly greater in the cations than for neutral species. For pyrazolium the coupling constants are $J_{3,4} = 2.9$ Hz and $J_{4,5} = 2.9$ Hz and for isoxazolium they are $J_{3,4} = 2.8$ Hz and $J_{4,5} = 1.9$ Hz.

2.4.3.3.1.5 Low-temperature studies. A significant development in the ^1H NMR spectroscopy of NH-pyrazoles was the use of a low temperature to block proton transfer (**125** ⇄ **126**) and thus determine tautomeric equilibrium constants by simple integration of the signals. In this way, the K_T values of 3(5)-phenylpyrazole **125** (R = H) <1991G477> and 3(5)-phenyl-5(3)-methylpyrazole **125** (R = Me) <1992J(P2)1737> were obtained. In the latter case, by using the [$^{15}N_2$] derivative, the ^1H–^{15}N coupling constants of each tautomer were measured.



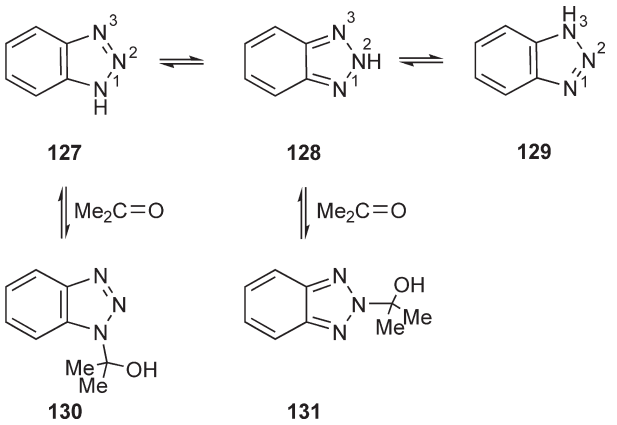
Due to rapid exchange between the benzotriazole tautomers **127–129** (**Scheme 6**) at room temperature, benzotriazole exhibits just two C–H signals (each for two protons) in its ^1H NMR spectrum. However, when the temperature is lowered, the signals broaden and finally split into four separate resonances for the four individual C–H protons: the amount of tautomer **128** is negligible. The results for such a study of an acetone solution of benzotriazole are given in **Table 12** <2002T9089, CHEC-III(5.01.3.2)8>. The situation is complicated by formation of the adducts **130** and **131**, which at −90 °C contribute 25 and 5%, respectively, to the total molecular population.

It is well known that benzofuroxan derivatives exist as a mixture of isomers. At room temperature the ^1H (and ^{13}C) NMR spectra of the benzofuroxans **132** and **133** show benzo-protons as broad peaks, indicating fast benzofuroxan isomerization <2005RMC57>. The broad signals are resolved below 263 K making possible the recording of a complete series of ^1H and ^{13}C spectra <CHEC-III(5.05.3.2)323>. Similar studies on thieno[2,3-*c*][1,2,5]oxadiazole *N*-monoxides have been reported <1974JOC2956, 1989J(P2)127>. For some benzofuroxan derivatives the spectra simplify at higher temperatures and this has been attributed to one of the isomers predominating <1999JME1941, 2000JFA2995, CHEC-III(5.05.3.2)323>.

Table 11 ^{1}H NMR spectral data for ring hydrogens of five-membered anions and cations

		^{1}H Chemical shifts (δ, ppm)					
	Ion	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*	*Reference*
(a)	*Anions*						
	Pyrazolyl	–	7.35	6.05	7.35	KOD/D_2O	1968JA4232
	Imidazolyl	7.80	–	7.21	7.21	–	1971PMH(4)121
	1,2,3-Triazolyl	–	–	7.86	7.86	NaOD/D_2O	1967JCB516
	1,2,4-Triazolyl	–	8.19	–	8.19	NaOD/D_2O	1971PMH(4)121
	Tetrazolyl	–	–	–	8.73	–	1971PMH(4)121
(b)	*Cations*						
	Pyrazolium[a]	–	8.57	6.87	8.57	DMSO-d_6	CHEC-I(4.04.1.3.3)187
	Imidazolium	8.6	–	7.5	7.5	H_2SO_4	1971PMH(4)12
	1,2,3-Triazolium	–	–	8.60	8.60	TFA	1967JCB516
	Isoxazolium	–	9.18	7.26	9.01	D_2SO_4	1983PC40100
	Isothiazolium	–	9.1	7.9	9.6	H_2SO_4	CHEC-I(4.17.3.3)136
	Thiazolium	9.55	–	8.23	7.93	–	1966BSF3524
	1,2-Oxathiolium[b]	–	–	7.64	–	TFA/$HClO_4$	1975J(P1)2097
	1,2-Dithiolium	–	6.71	1.44	–0.26	–	1971PMH(4)12
	1,3-Dioxolium[c]	10.4	–	–	–	–	CHEC-I(4.30.1.4.1)752
	1,3-Oxathiolium[d]	–	–	8.12	–	TFA	1975H(3)217
	1,3-Dithiolium	11.65	–	9.67	9.67	–	1974JOC3608
	1,2,4-Dithiazolium[e]	–	–	–	10.96	TFA	1974AP828
	1,3-Tetrazolium[f]	–	–	–	~10.5	DMSO-d_6	CHEC-III(6.07.3.3)274
	1,4-Tetrazolium[g]	–	–		~11.5	DMSO-d_6	CHEC-III(6.07.3.3)274

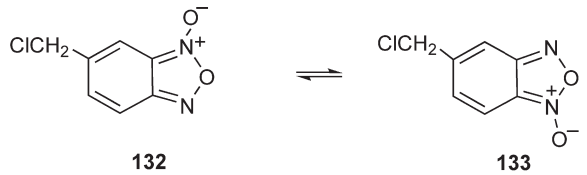
[a]Values given for 1,2-dimethylpyrazolium.
[b]Value given for 5-methyl-3-(2-oxo-l-propyl)-1,2-oxathiolylium perchlorate.
[c]Value given for 1,3-benzodioxolylium fluorosulfonate.
[d]Value given for 2,5-diphenyl-1,3-oxathiolylium perchlorate.
[e]Value for 2-phenyl derivative.
[f]Values for 1,3-dialkyl derivatives.
[g]Values for 1,4-dialkyl derivatives.



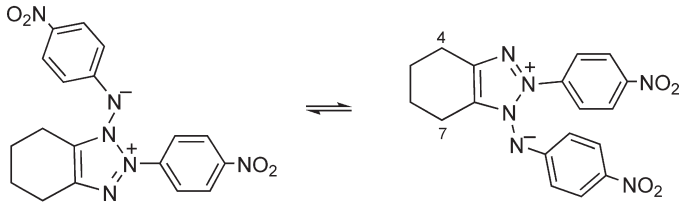
Scheme 6

Table 12 ^{1}H NMR shifts for acetone-d_6 solutions of benzotriazole

		^{1}H chemical shifts (δ, ppm)			
Tautomer(s)	*Temperature*	*H(4)*	*H(5)*	*H(6)*	*H(7)*
127–129	21 °C	8.00	7.44	7.44	8.00
127	−85 °C	8.11	7.48	7.48	8.05
130	21 °C	8.20	7.36	7.47	8.06
130	−85 °C	8.28	7.45	7.56	8.11



132 133



134 135

The degenerate rearrangement (**134** ⇄ **135**) involving rapid exchange of aryl rings in the *N*-aryltriazole *N*-arylimides **134** and **135** has been studied between 120 and −83°C. A single exchange-narrowed AA′BB′ spectrum for the aromatic rings and an averaged signal for $H_4H_{4'}$ and $H_7H_{7'}$ was observed. As the temperature is lowered the signals broaden. The coalescence temperature is 40 °C and the rate of exchange at this point is 20 s^{-1} in DMSO. By −46 °C the exchange is frozen out and the spectrum shows two separate AA′BB′ systems and two separate signals for $H_4H_{4'}$ and $H_7H_{7'}$. Restricted rotation of the *N*-aryl bond was also found at lower temperature (−50 to −83°C) <1987JCM332>.

2.4.3.3.2 Other ring systems

Relatively few data are available on the ^{1}H NMR spectra of azolinones and related thiones and imines (**Table 13**). Some available data on ^{1}H NMR spectra of nonaromatic azoles containing two ring double bonds are given in **Table 14**. Here there is no ring current effect and the chemical shifts are consequently more upfield.

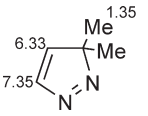
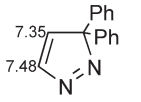
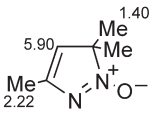
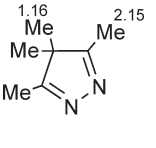
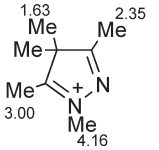
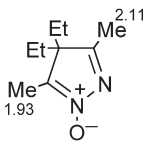
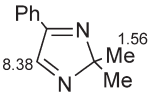
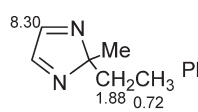
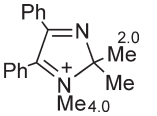
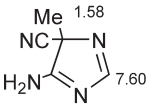
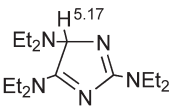
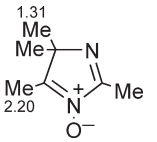
Table 13 ^{1}H NMR spectral data for ring C–H of azolinones, azothiones, and imines

	^{1}H chemical shifts (δ, ppm.)					
Compound	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*	*Reference*
Pyrazolin-3-one[a]	–	–	5.25	7.22	$CDCl_3$	1976AHC(S1)1
Imidazolin-2-one	–	–	6.50	6.50	–	B-73NMR
Pyrazoline-3-thione[b]	–	–	6.23	–	–	1976AHC(S1)1
1,2,4-Triazoline-3-thione	–	–	–	8.20	DMSO-d_6	
Pyrazolin-3-imine[c]	–	–	5.46	–	$CDCl_3$	1972BSF2807
1,2,4-Triazolin-5-imine	–	2.05	–	–	$CDCl_3$	
Δ^2-1,3,4-Oxadiazoline-5-thione	8.88	–	–	–	DMSO-d_6	CHEC-I(4.23.2)428
Isothiazolin-3-one[d]	–	–	6.05	7.98	–	1971JHC571
1,3-Thiazolin-2-one[e]	–	−1.14	3.21	3.7	DMSO-d_6	1979HC(34-2)385
Isothiazoline-3-thione[f]	–	–	6.90	8.25	–	1980CPB487
1,3-Thiazoline-2-thione[g]	–	6.68	2.7	3.05	C_3D_6O	1979HC(34-2)385
1,3-Thiazolin-2-imine[h]	–	–	3.03	3.37	$CDCl_3$	1979HC(34-2)26

[a]Values given for 1,2-dimethylpyrazolin-3-one; $J_{4,5}$ = 3.5 Hz.
[b]Values given for 1,5-dimethyl-2-phenylpyrazoline-3-thione.
[c]Values given for 1,5-dimethyl-2-phenylpyrazolin-3-imine.
[d]Values given for 2-methylisothiazolin-3-one; $J_{4,5}$ = 6.0 Hz.
[e]Coupling constants: $J_{3,4}$ = 2.5 Hz; $J_{3,5}$ = 1.1 Hz; $J_{4,5}$ = 5.3 Hz.
[f]Values given for 2-methylisothiazoline-3-thione; $J_{4,5}$ = 6.0 Hz.
[g]$J_{4,5}$ = 4.6 Hz.
[h]Values given for 2-ethoxycarbonylimino-3-ethyl-Δ^4-1,3-thiazoline.

Tables 15 and **16** give some available chemical shifts for azolines and azolidines, respectively. Unfortunately, data for many of the parent compounds are lacking, sometimes because the compounds themselves are unknown. The ^{1}H NMR spectra of 128 4,5-dihydropyrazoles have been reported <1990JCM200>. Additive contributions of

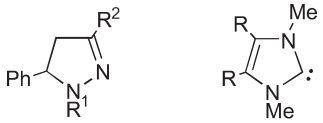
Table 14 ^{1}H NMR spectral data (δ, ppm) for ring hydrogens of nonaromatic azoles with two ring double bonds

3*H*-Pyrazoles[a]			
4*H*-Pyrazoles[b]			
2*H*-Imidazoles[c]			
4*H*-Imidazoles[d]			

[a]<1983AHC(34)2.
[b]<1983AHC(34)54.
[c]<1984AHC(35)376.
[d]<1984AHC(35)414.

substituents were calculated which allowed the prediction of the chemical shifts of unknown pyrazolines. The J_{gem}, J_{cis}, and J_{trans} coupling constants of the protons at positions 4 and 5, are quite sensitive to the nature of the substituent on the nitrogen atom. A series of papers deals with the conformational analysis of fused and spiro pyrazolines using ^{1}H, ^{13}C, and two-dimensional methods <1989J(P2)319, 1993T863>. ^{1}H NMR spectroscopy (chemical shifts and ^{1}H–^{1}H coupling constants) can determine the protonation site of 4,5-dihydropyrazoles **136** (R^1, R^2 = H, Me, Ph) <1987CS283>. ^{1}H NMR chemical shifts for some 1,2-dioxolane, 1,2-oxathiole, and 1,2-oxathiolane derivatives have been compiled <CHEC-III(4.09.3.2)826>.

The stable carbene **137** (R = H) has the ring proton signal at 6.92 ppm. This chemical shift very much resembles those of 1-methylimidazole (**Table 8b**). The 1,3,4,5-tetramethyl carbene **137** (R = Me) has methyl signals at 2.01 (*C*-methyl) and 3.48 ppm (*N*-methyl), cf. methyl shifts for 4-methyl- (2.23 ppm), and 1-methylimidazole (3.70 ppm) <1992JA5530, 1992JA9724> (see also Section 2.4.4.2.3).



136 **137**

2.4.3.4 ^{13}C NMR Spectroscopy

Chemical shifts for aromatic azoles are recorded in **Tables 17** and **18**. Fast tautomerism renders two of the ^{13}C chemical shifts equivalent for the NH derivatives (**Table 17a**), as in the proton spectra (**Table 8a**). However, data for the *N*-methyl derivatives (**Table 17b**) clearly indicate that the carbon adjacent to a pyridine-type nitrogen shows a chemical shift at lower field than that adjacent to a pyrrole-type *N*-methyl group (in contrast to the H chemical shift behaviour). Solid-state studies on imidazole (and pyrazole) show there are three distinct signals for the annular carbon atoms (imidazole: C(2), 136.3; C(4), 126.8; C(5), 115.3 ppm). Proton exchange does not occur in the solid, hence the spectra describe the structure in the crystal. Comparison with the corresponding chemical shifts for 1-methylimidazole (137.6, 129.3, 119.7 ppm) implies that tautomerism has been frozen in the solid state <1981CC1207>. Solid-state examination of 2,2′-bis-1*H*-imidazole also reveals 'frozen' tautomerism.

Table 15 ^{1}H NMR spectral data for ring hydrogens of azolines (one ring double bond)

		^{1}H Chemical shifts (δ, ppm),						*Coupling constants*
Ring	*Substituents*	*H(1)*	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*	*J (Hz)*
(a) Pyrazolines								
2,3-Dihydro[a]	1,2,3-triMe	2.55	2.60	1.71	4.60	3.65	$CDCl_3$	$J_{3,5}$ 1.8; $J_{4,5}$ 1.8
4,5-Dihydro-3*H*[a]	–	–	–	4.27	1.46	4.27	Neat	–
4,5-Dihydro[a]	–	5.33	–	6.88	2.65	3.31	$CDC1_3$	$J_{3,4}$ 1.4; $J_{4,5}$ 9.8
(b) 1,2,3-Triazolines								
4,5-Dihydro[b,d]	–	–	–	–	5.35	4.77	–	$J_{4,5}$ 2.0
4,5-Dihydro[c,d]	–	–	–	–	5.73	4.60	–	$J_{4,5}$ 7.5
(c) 1,2,4-Oxadiazolines								
2,5-Dihydro[e]	2,5-diMe-3Ph	–	–	–	–	6.0	–	–
4,5-Dihydro[f]	5Et-3Ph	–	–	–	5.38	5.64	–	$J_{4,5}$ 4.5
(d) 1,3,4-Oxadiazolines								
2,3-Dihydro[a]	3Bz-5Ph	–	5.9	–	–	–	–	–
(e) Thiazolines								
2,5-Dihydro[i]	–	–	4.79[g]	–	6.12[g]	–	–	–
4,5-Dihydro[j]	–	–	2.26	–	5.83	6.84[h]	–	$J_{2,4}$ = 2.2; $J_{4,5}$ = 8.6
(f) 1,3,4-Thiadiazolines								
2,3-Dihydro[k]	2,3,5-triPh	–	–	–	–	6.38	–	–
(g) 1,2,4-Dioxazolines								
2,3-Dihydro[a]	3CO_2Me-5Ph	–	–	6.39	–	–[1]	$CDCl_3$	–
(h) 1,3,4-Dioxazolines								
2,3-Dihydro	2Bn-5Ph	–	6.20	–	–	–[1]	$CDC1_3$	–
(i) 1,3,4-Oxathiazolines								
2,3-Dihydro[a]	5Me-2CCl_3	–	6.30	–	–	–[1]	$CDC1_3$	–
(j) 1,2,4-Dithiazolines								
2,3-Dihydro	5Ph	–	–	5.70	–	–[1]	CCl_4	–

[a]Data taken from appropriate chapter of *Comprehensive Heterocyclic Chemistry*.
[b]Values given for *trans*-5-propyloxy-4-methyl-l-(4-nitrophenyl) derivative.
[c]Values given for *cis* isomer of compound named in footnote b.
[d]<1965CB1153>.
[e]<1973BSF2996>.
[f]<1977JOC1555>.
[g]Value taken from 5,5-dimethyl-Δ^3-thiazoline.
[h]Value taken from 2,2,4-trimethyl-Δ^3-thiazoline.
[i]<1966BSF3524>.
[j]<1964MI40100>.
[k]<1981J(P1)360>.
[1]Substituent in this position.

In azoles containing oxygen (**Table 18a**) and sulfur (**Table 18b**), the chemical shifts are generally at lower field than those for the wholly nitrogenous analogues, but the precise positions vary.

The reported ^{13}C NMR parameters of 169 N-substituted azoles with no other substitution in the ring show the effect of N-substituents <1988MRC134>, which is usually small but there are a few exceptions, just as for the ^{1}H chemical shifts. Trialkyltin substituents (N–SnR_3) exchange readily between the different nitrogens of azoles. There is a parallel with annular metallotropy (see Section 2.4.5.1.2); thus, the chemical shifts of 1-[tri-(*n*-butyl)stannyl]benzotriazole are quite different from other derivatives <1988MRC134>. 1-Trifluoromethylsulfonyl-1,2,3-triazole does not exist as named but as its open-chain isomer, the diazoimine **84** (X = Y = CH, Z = NSO_2CF_3); thus, the chemical shifts of C(4) and C(5) are 64.6 and 172.6 ppm, respectively <1988MRC134>. This is the normal behaviour of 1-substituted 1,2,3-triazoles with strong electron-withdrawing N-substituents, such as 1-cyano-1,2,3-triazole <1981BSB615> (see also Section 2.4.5.4). The C(4) and C(5) ^{13}C chemical shifts of 1-alkyl-1,2,3-triazolines appear between 41–48 ppm and 63–66 ppm, respectively <1993JOC2097>.

Table 16 ^{1}H NMR spectral data for ring hydrogens of azolidines (no ring double bonds)

		^{1}H Chemical shifts (δ, ppm)				
Ring	*Substituents*	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*Solvent*
Pyrazolidine[a]	1,2-Dimethyl-3-phenyl-	–	6.51	7.85	6.76	$CDCl_3$
Thiazolidine[b,c]	–	5.9	8.2	6.8	7.2	–
1,2,4-Oxadiazolidine[d]	2-*t*-Butyl-3,4-diphenyl-5-thioxo-	–	5.93	–	–	–
1,3,4-Oxadiazolidine[e]	3,4-Dimethyl-	4.27	–	4.27	–	–
1,2,4-Dioxazolidine[e]	3,5-Di-*n*-propyl-	–	4.63	–	4.63	–
1,3,2-Dioxazolidine[e]	*N*-alkyl-	–[f]	–	3.97	3.97	–
1,3,4-Dioxazolidine[e]	2,5-Di-*t*-butyl-4-phenyl-	4.96	–	–[f]	4.58	–
1,2,4-dithiazolidine[e]	3,4-Dialkyl-3-phenyl-	–	–[f]	–[f]	4.72	–
1,3,2-Dithiazolidine[e]	2-Methyl-	–[f]	–	3.58	3.58	–

[a]<1971T133>.
[b]$J_{4,5}$ values are $J_{A,B'} = J_{A',B} = 7.61$ Hz; $J_{A,B} = J_{A',B'} = 4.71$ Hz; $J_{5,5} = -13.7$ Hz; $J_{4,4} = -7.2$ Hz.
[c]<1974JA1465>.
[d]<1974JOC957>.
[e]Data taken from appropriate chapter of *Comprehensive Heterocyclic Chemistry*.
[f]Substituent in this position.

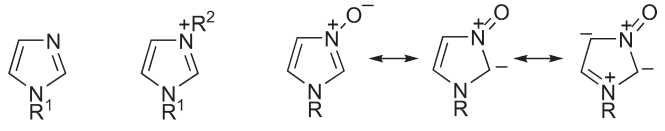
Table 17 ^{13}C NMR chemical shifts for ring carbons of azoles

		^{13}C Chemical shifts (ppm)[a]					
	Compound	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Solvent*	*Reference*
(a)	*NH Derivatives*						
	Pyrazole	–	134.6	105.8	134.6	CD_2Cl_2	CHEC-I[b]
	Imidazole	135.9	–	122.0	122.0	–	1971PMH(4)121
	1,2,3-Triazole	–	–	130.4	130.4	Me_2CO-d_6	CHEC-I
	1,2,4-Triazole	–	147.8	–	147.8	–	1971PMH(4)121
	Tetrazole[c]	–	–	–	144.2	–	1971PMH(4)121
(b)	*NMe Derivatives*						
	Pyrazole	–	139.0	105.3	129.6	$CDC1_3$	1998H(47)301
	Imidazole	138.3	–	129.6	120.3	–	1974JOC357
	1,2,3-Triazole	–	–	134.3	125.5	DMSO-d_6	CHEC-I
	1,2,5-Triazole	–	133.8	133.8	–	–	CHEC-II(4)
	1,2,3,4-Tetrazole	–	–	–	142.1	DMSO-d_6	1974JOC357
	1,2,3,5-Tetrazole	–	–	151.9	–	DMSO-d_6	1974JOC357

[a]All chemical shifts expressed in ppm from TMS (original values converted where necessary).
[b]For pyrazoles ^{13}C NMR data see also <1984OMR(22)603, 1993MRC107>.

A comparison between the ^{13}C NMR chemical shifts of thiadiazole, oxadiazole, and isosydnone derivatives indicates that the effect of substituents is more pronounced for thiadiazoles than for oxadiazoles <1982OMR(18)159>.

Quaternization of imidazoles **138** to give imidazolium salts **139** leads to a shift to lower field of all the imidazole carbon signals except that of C(4). In contrast, the corresponding imidazole 3-oxides **140** show a shift to higher field for all the imidazole carbons. This high-field shift is due to increased negative charge on the ring carbons as a result of resonance contributions from **140b** and **140c** <1998MRC296>.



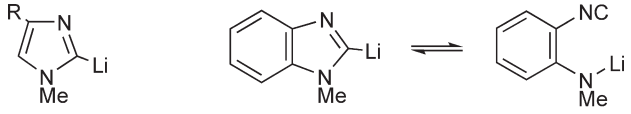
138 **139** **140a** **140b** **140c**

Table 18 ^{13}C NMR chemical shifts for ring carbons of azoles containing oxygen or sulfur

		^{13}C Chemical shifts (ppm)[a]					
	Compound	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Solvent*	*Reference*
(a)	*Oxygen derivatives*						
	Oxazole	150.6	–	125.4	138.1	$CDCl_3$	CHEC-I
	2-Ph-Oxazole	162.0	–	na	138.6	$CDCl_3$	1997J(P1)2665
	1,3,4-Oxadiazole[b]	159.5	–	–	166.3	–	CHEC-I
	1,2,5-Oxadiazoles[c]	–	139–160	–	–	–	CHEC-I
(b)	*Sulfur derivatives*						
	Isothiazole	–	157.0	123.4	147.8	$CDCl_3$	CHEC-I
	Thiazole	153.4	–	143.7	119.7	–	1979HC(34)76
	1,2,3-Thiadiazole	–	–	147.3	135.8	$CDCl_3$	CHEC-I
	1,2,4-Thiadiazole[d]	–	170.0	–	187.1	–	1981JPR279
	1,3,4-Thiadiazole	152.7	–	–	152.7	$CDCl_3$	1978BAP291
	1,2,3,4-Thiatriazole[e]	–	–	–	178.5	$CDC1_3$	CHEC-I

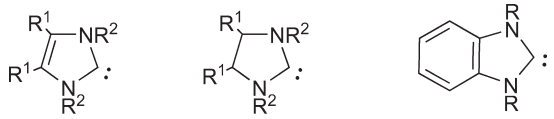
[a]All chemical shifts expressed in ppm from TMS (original values converted where necessary).
[b]Values given for 5-methoxy-2-methyl derivative.
[c]3-Substituted-4-phenyl derivatives.
[d]For 3,5-diphenyl-1,2,4-thiadiazole the following assignments have been reported: C(3) 188.5 ppm, C(5) 173.3 ppm <2000JHC63, CHEC-III(5.08.3.4)490>.
[e]5-Phenyl derivative.

The ^{13}C chemical shifts of 2-lithiated imidazoles **141** and **142** in THF-d_8 are in the range 196–216 ppm. Simple 2-lithioimidazoles such as **141** (R = H, Bu^t, Ph) exist in the ring form even at 20 °C, whereas the benzimidazole exists as a mixture of the ring **142** and ring-opened isonitrile **143** ($\delta_{C(2)} = 158$) <1997CB1213>.



141 **142** **143**

Analysis of the ^{13}C NMR spectra of a series of N-heterocyclic carbenes (NHCs) with general structures **144**, **145** and **146** suggests that the chemical shift of the carbene carbon ($\delta = 211–244$) correlates with the N(1)–C(2)–N(3) bond angle (101–106°) in the solid state <2003AGE5243>. The ^{13}C carbene shifts of the unsaturated systems **144** ($\delta = 205–220$) are ~15–25 ppm upfield from the saturated systems **145** (see also **Table 40**, Section 2.4.4.2.5).



144 **145** **146**

Azolinone derivatives and the corresponding thiones are listed in **Table 19**. The ^{13}C chemical shifts of nonaromatic azole derivatives are given in **Tables 20–22**; relatively few data are available and these are generally for substituted derivatives rather than for the parent compounds.

^{13}C NMR spectroscopy is a powerful technique for distinguishing between closely related isomers and is particularly useful for resolving structural problems. The pyrazole tautomers **125** and **126** (R = H) can be isolated as separate stable solids (i.e., they are desmotropes <2008SSN(34)68>) and they have been characterized using solid-state ^{13}C NMR

Table 19 ^{13}C NMR chemical shifts for azolinones and azothiones

	^{13}C Chemical shifts (ppm)[a]					
Derivative	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Solvent*	*Reference*
3-Me-1-Ph-2-Pyrazolin-5-one	–	156.2	43.0	170.6	–	CHEC-I
2,3-diMe-1-Ph-3-Pyrazolin-5-one	–	156.0	98.1	165.7	–	CHEC-I
Imidazolin-2-one	183.8	–	44.4	44.4	DMSO-d_6	1980CS(15)193
Imidazoline-2-thione	164.8	–	40.3	40.3	DMSO-d_6	1980CS(15)193
1-Ph-Tetrazolin-5-one	–	–	–	148.7	–	CHEC-I
Tetrazoline-5-thione	–	–	–	162.9	–	CHEC-I
Δ^4-Thiazoline-2-thione	–	118.4	128.9	114.0	$CDCl_3$	1979HC(34)388
3-Me-1,2,3-Oxadiazolin-5-imine	–	–	97.3	170.4	–	1980RCR28
Δ^2−1,3,4-Oxadiazolin-5-one	145.7	–	–	155.7	–	1982OMR(18)159
Δ^2−1,3,4-Thiadiazoline-5-thione	157.2	–	–	186.4	–	1977JOC3725
5-Me-1,3,4-Oxathiazolin-2-one	174.2	–	–	158.7	–	CHEC-I
5-PhNH-1,2,4-Dithiazoline-3-thione	–	209.3	–	179.1	–	CHEC-I

[a]All chemical shifts expressed in ppm from TMS (original values converted where necessary).

Table 20 ^{13}C NMR chemical shifts for nonaromatic azoles with two ring double bonds

	^{13}C Chemical shifts (ppm)				
Compound	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Reference*
4*H*-Pyrazoles	–	178–182	63–68	178–182	1983AHC(34)54
3*H*-Pyrazoles	–	93–110	125–150	130–170	1983AHC(34)2
2*H*-Imidazoles	101–119	–	158–165	158–165	1984AHC(35)376
4*H*-Imidazoles	163–181	–	66–115	180–190	1984AHC(35)414

Table 21 ^{13}C NMR chemical shifts for azolines (one ring double bond)

	^{13}C Chemical shifts (ppm)[a]				
Derivative	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Reference*
5*H*-1,2-Oxathiole 2,2-dioxide	–	137.3	123.9	72.5	1997CC611
Δ^2-Pyrazoline	–	142.9	33.2	45.4	1980TH40100
1-Me-2-MeS-Δ^2-Imidazoline	165.3	–	[b]	54.3	1976TL3313
1-Me-Δ^4-Imidazoline-2-thione	161.3	–	[b]	119.8	1976TL3313
Δ^2-Thiazoline	229.4	–	321.7	354.7	1970CR(270)1688
1,3,4-Thiadiazoline[c]	151.5	–	–	149.5	CHEC-I
Δ^2-1,3,4-Oxathiazoline[d]	95.9	–	–	157.6	CHEC-I
1,2,4-Dithiazoline	–	146.36	–	156.19	CHEC-I

[a]All chemical shifts expressed in ppm from TMS (original values converted where necessary).
[b]No C(4) shift reported.
[c]2-Benzylamino-5-phenyl-5-tosyl derivative.
[d]2-Phenyl-5-trichloromethyl derivative.

<2002HCA2763>. The relative values of ^{13}C chemical shifts of ring carbons have also been used to distinguish between 4-nitro and 5-nitroimidazoles, e.g., **116** and **117** <1983T3797>.

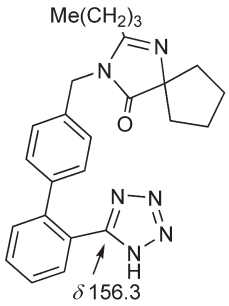
The ^{13}C NMR shift of the tetrazole C(5) atom is particularly sensitive to the substitution pattern of the ring and allows discrimination between isomers. Two crystal forms of the angiotensin II antagonist irbesartan, which is a tetrazole derivative, have been identified as desmotropes using solid-state ^{13}C (and ^{15}N) NMR spectroscopy. Substantial differences between the spectra of these forms were observed and one crystal form was deduced to be the 1*H*-

Table 22 ^{13}C NMR chemical shifts for azolidines (no ring double bonds)

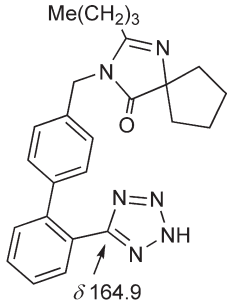
	^{13}C Chemical shifts (ppm)[a]				
Derivative	*C(2)*	*C(3)*	*C(4)*	*C(5)*	*Reference*
1,3-Dioxolane	94.9	–	64.4	64.4	2001MRC657
Imidazolidine-2-thione, 1-methyl-	183.2	–	[b]	50.4	1976TL3313
Oxazolidine, *cis*-4-methyl-5-phenyl-	85.4	–	60.3	80.3	1979MI40100
Thiazole, tetrahydro-	248.4	–	245.9	226.9	1974CRC(279)717
1,3,4-Thiadiazolidine, 2,2-dimethyl-4-phenyl-5-phenylimino-	79.2	–	–	176.3	1980J(P1)574
1,3,2-Dioxazole, tetrahydro-*N*-alkyl-	–	–	67.6	67.6	CHEC-I
1,2,3-Oxathiazole, dihydro-*N*-phenyl, *S*-oxide	–	–	45.9	70.9	CHEC-I

[a]All chemical shifts expressed in ppm from TMS (original values converted where necessary).
[b]C(4) shift not reported.

tautomer **147** ($\delta_{C(5)}$ = 156.3) and the other to be the 2*H*-tautomer **148** ($\delta_{C(5)}$ = 164.9) <1998J(P2)475>. Carbon spectra of irbesartan in solution show that only the 1*H*-tautomer **147** is present under these conditions. In general, the C(5) signal of tetrazoles is deshielded by about 10 ppm in 2,5-disubstituted derivatives, e.g., **148**, relative to the corresponding 1,5-disubstituted derivatives, e.g., **147** <CHEC-II(4.17.3.2.2)628>.

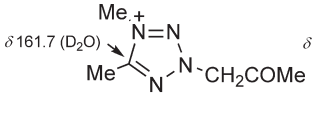


147: irbesartan crystal form A

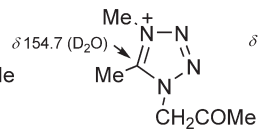


148: irbesartan crystal form B

As for neutral tetrazoles, the ^{13}C NMR spectra of isomeric tetrazolium ions strongly depend on the substitution pattern. The signals for C(5) in 1,3-disubstituted tetrazolium salts, e.g., **149**, are downfield by 7–16 ppm compared to the corresponding signals of 1,4-isomers, e.g., **150**. The ^{13}C NMR spectra of tetrazolate anions are similar to the spectra of 2-substituted tetrazoles, e.g., **151** <CHEC-III(6.07.3.3.2)277>.



149



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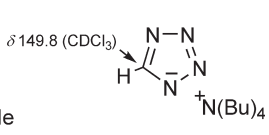
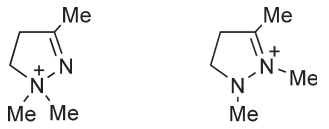


151

The protonation site of 2-pyrazolines has been determined as N(1) using ^{13}C NMR spectroscopy. This behaviour is not followed for 1-phenyl-3-aminopyrazolines which are protonated on N(2) <1995J(P2)1875>. ^{13}C NMR spectroscopy easily differentiates the 1,1- and 1,2-disubstituted pyrazolinium cations **152** and **153**

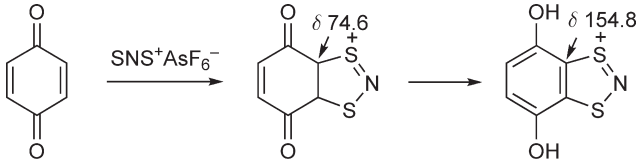
<1986MRC551>. The *N*-methyl groups appear at 54.1 ppm for **152** and at 42.1 ppm (position 1) and 36.0 ppm (position 2) for isomer **153**.



152 **153**

Long-range $^{1}H–^{13}C$ coupling constants in pyrazoles and $^{1}J_{^{13}C-^{13}C}$ coupling constants in 1-methylpyrazole ($J_{3,4} = 51.5$ Hz, $J_{4,5} = 64.6$ Hz) have been used for assignment of isomeric 1,3- and 1,5-disubstituted pyrazoles <1987T4663, 1994MRC62>.

Cycloaddition of $SNS^{+}AsF_6^{-}$ to 1,4-benzoquinone has been monitored by ^{13}C NMR spectroscopy. Immediately after mixing the reagents the spectrum showed resonances centered at $\delta = 140.7$ ($J_{CH} = 176$ Hz) and $\delta = 74.6$ ($J_{CH} = 156$ Hz) that are attributable to the ethylenic and ring junction carbons of cation **154** (**Scheme 7**). After 6 h a new signal at $\delta = 119.5$ ($J_{CH} = 167$ Hz) emerged in the coupled ^{13}C NMR spectrum which is assigned to the aromatic CH in the product **155**. This is accompanied by two new singlets at $\delta = 154.8$ and 146.5 that are attributed to the C–S and C–O of cation **155** <2005CC2366>.



154 **155**

Scheme 7

2.4.3.5 Nitrogen and Oxygen NMR Spectroscopy

A comprehensive ^{15}N study of azoles has been reported <1984OMR(22)215> and representative examples of chemical shifts are shown in **Table 23** and **Figure 19**. ^{15}N Chemical shift values discussed in this section are relative to $MeNO_2$. Values shown in **Table 23** and **Figure 19** are of opposite sign to those in the original paper <1984OMR(22)215>; this change of sign retains the convention, used in ^{1}H and ^{13}C NMR, that a move to more positive values is a result of deshielding.

The following general trends are observed.

a. A pyrrole-type nitrogen resonates at higher field than a pyridine-type nitrogen. This difference can be seen in 1-methylimidazole (**Table 23**) and 1-methylbenzimidazole **158** (**Figure 19**).
b. There is a mutual deshielding interaction between pyrrole-type nitrogens and pyridine-type nitrogens but this effect is much larger when the atoms are adjacent. This effect can be seen by comparing 1-methylpyrazole with 1-methylimidazole (**Table 23**) and the benzo derivatives **156–158** (**Figure 19**).
c. Adjacent pyridine-type nitrogens result in significant mutual deshielding and this can be seen in 1-methylbenzotriazole **159** (**Figure 19**). The same effect is seen in azines (Section 2.2.3.5) and simple azo groups.
d. Fusion of a benzene ring to give benzo derivatives tends to result in shielding of pyrrole-type nitrogens (cf. **156–159**) but quinonoid fusion results in deshielding (cf. **163–165**). Aza substitution in the six-membered ring has little influence on the chemical shifts of nitrogens in the five-membered ring, e.g., **160–162**.

Like pyrrole-type nitrogens, ring oxygen and sulfur atoms also have a deshielding effect on pyridine-type nitrogen atoms with the effect greatest on adjacent atoms. For examples see **Table 23b** and structures **166–173** in **Figure 20**.

Table 23 ^{15}N NMR chemical shifts for ring nitrogens of azoles and their oxygen and sulfur derivatives

		^{15}N Chemical shifts (ppm)[a]					
	Compound	*N(1)*	*N(2)*	*N(3)*	*N(4)*	*N(5)*	*Solvent*
(a)	*Azoles*						
	1-Methylpyrrole	−230.1	–	–	–	–	DMSO-d_6
	1-Methylpyrazole	−180.0	−80.0	–	–	–	MeOH-d_4
	1-Methylimidazole	−218.5	–	−118.1	–	–	DMSO-d_6
	1-Methyl-1,2,3-triazole	−143.3	−16.2	−28.4	–	–	DMSO-d_6
	2-Methyl-1,2,3-triazole	−54.0	135.0	−54.0	–	–	DMSO-d_6
	1-Methyl-1,2,4-Triazole	−171.3	−81.9	–	−127.4	–	DMSO-d_6
	4-Methyl-1,2,4-Triazole	−59.8	−59.8	–	−217.8	–	DMSO-d_6
	1-Methyltetrazole	−151.1	−10.8	+12.7	−49.9	–	DMSO-d_6
	2-Methyltetrazole	−72.8	−101.8	−0.8	−46.8		DMSO-d_6
	1-ArPentazole[b,c]	−80.0	−27.1	+4.9	+4.9	−27.1	$CDCl_3$
(b)	*O and S Derivatives*						
	Isoxazole	–	+2.7	–	–	–	DMSO-d_6
	Oxazole	–	–	−127.0	–	–	MeOH-d_4
	1,2,4-Oxadiazole	–	−20.0	–	−140.0	–	Et_2O-d_6
	1,3,4-Oxadiazole	–	–	−81.0	−81.0	–	Et_2O-d_6
	1,2,5-Oxadiazole	–	+33.8	–	–	+33.8	DMSO-d_6
	Isothiazole	–	−82.0	–	–	–	Neat
	Thiazole	–	–	−57.4	–	–	DMSO-d_6
	1,2,3-Thiadiazole	–	+30.3	+56.2	–	–	DMSO-d_6
	1,2,4-Thiadiazole	–	−106.0	–	−70.0	–	Et_2O-d_6
	1,3,4-Thiadiazole	–	–	−7.9	−7.9	–	DMSO-d_6
	1,2,5-Thiadiazole	–	−34.0	–	–	−34.0	Et_2O-d_6

Values taken from <1984OMR(22)215 with signs reversed so that negative increments correspond to an increase in shielding.
[a]Chemical shifts expressed in ppm relative to external $MeNO_2$.
[b]Values for Ar = 4-$Me_2NC_6H_4$ <1985AGE513, CHEC-II(4.25.3.2)901>.
[c]δ Me_2N = −324.6.

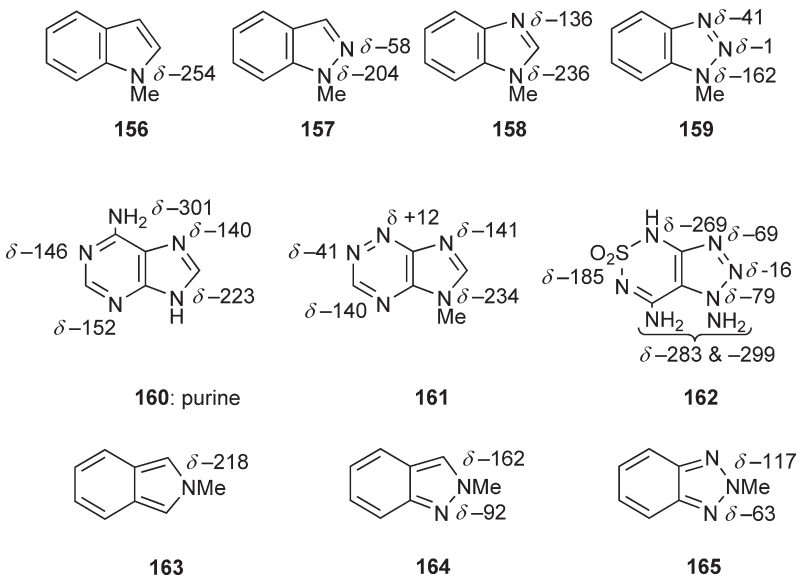
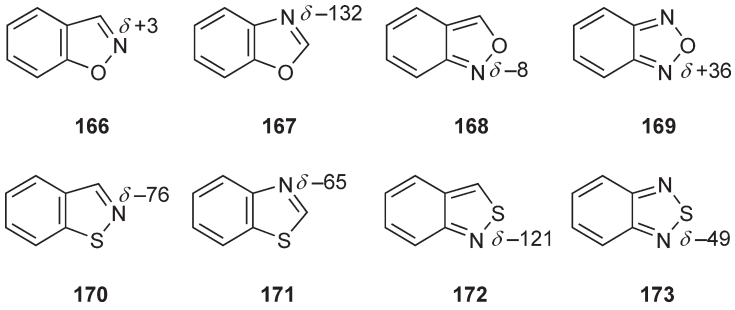


Figure 19 ^{15}N NMR chemical shifts of representative benzoazoles.

However, the deshielding effect of O on adjacent nitrogens is much greater than that of S or NR. This can be seen by comparing 1,2,5-oxadiazole (**Table 23b**) and benzo[1,2-*c*][1,2,5]oxadiazole **169** with related systems. Conversely, the deshielding effect of S on nonadjacent nitrogens appears to be greater than that of O or NR, e.g., **158**, **167**, and **171**.



166 167 168 169

170 171 172 173

Figure 20 ^{15}N NMR chemical shifts of representative oxygen and sulfur heterocycles.

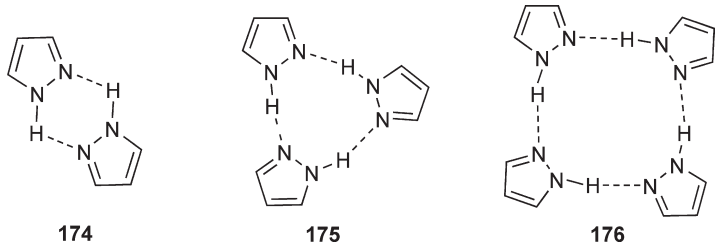
Solvent and hydrogen-bonding effects on chemical shifts can be significant. For high-precision ^{14}N NMR, solvent effects have been investigated for thiazole and thiadiazole systems. **Table 24** shows the chemical shifts in a range of solvents. An increase in solvent polarity favors delocalization of the lone pair of electrons from sulfur to the ring, leading to an increase in electronic charge at nitrogen and consequent shielding <1996J(P2)619>. The same solvent effects have been reported for pyridine-type nitrogens in 1- and 2-methyltetrazoles and 1,3,4-oxadiazole (**Table 24**). As might be expected based on charge distribution, the pyrrole-type nitrogen of 2-methyltetrazole is deshielded as the solvent polarity increases (**Table 24**). The shielding of pyridine-type nitrogen atoms in water can be partially attributed to hydrogen bonding <1996MR(120)148>. Differences in the solution and solid-state ^{15}N NMR chemical shifts of the citrate salt of the phosphodiesterase inhibitor sildenafil (see Section 2.2.1.1.3) have been attributed to hydrogen bonding in the solid state <CHEC-III(10.12.3.4)609>.

There is a growing interest in the use of ^{15}N NMR spectroscopy for elucidation of various structural problems of azole chemistry, especially tautomerism. For example, the mole fractions of prototropic tautomers can be obtained from the ^{15}N chemical shifts of the NH tautomers and the corresponding *N*-methyl derivatives. By this method, the average mol fraction for the 2-NH tautomer of benzotriazole is 0.02 in both $CDCl_3$ and DMSO, and that of 1,2,3-triazole is 0.34 in $CDCl_3$ and 0.55 in DMSO <1982JOC5132>.

Low-temperatures studies, for example, in THF at 175 K, can elucidate annular tautomerism <1992J(P2)1737>; a large collection of ^{15}N chemical shifts of NH-pyrazoles with tautomerism frozen has been published <1994MRC699>. The tautomerism is also frozen in the solid state. Thus two ^{15}N shifts at −230 ppm (NH) and −158 ppm (=N–) are observed for solid imidazole; the average is close to the single signal at −194 ppm found in solution.

The discovery, by the combined use of crystallography and CPMAS NMR, of the dynamic properties of 3,5-dimethylpyrazole (an H-bonded trimer, cf. **175**) in the solid state opened a new field of research <1985JA5290, 1992JA9657, CHEC-III(4.01.2.1)5>. Other cyclic structures, dimers like **174** and tetramers like **176** have been discovered <1994JHC695, 2000AXB1018>. ^{15}N CPMAS (with labeled derivatives) proved to be superior to ^{13}C CPMAS.

Some other examples of application of ^{15}N NMR spectroscopy include establishing the protonation site of 2-pyrazolines <1987MI301-01> and assigning structures to isomeric N(7)- and N(9)-substituted purines <1986T5073>.



174 175 176

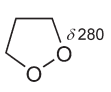
Data on ^{17}O NMR spectra of five-membered oxygen-containing heterocycles are scarce. ^{17}O chemical shifts near 350 ppm (with respect to $H_2{}^{17}O$) have been observed for isoxazoles and chemical shifts for 3,5-diarylisoxazoles and 3,5-diarylisoxazolines in acetonitrile have been reported <2006HCO7>. Values of 280 and 303 ppm are reported for the

Table 24 Solvent effects on ^{14}N NMR chemical shifts

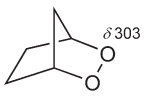
Ring	C_6H_{12}	CCl_4	Et_2O	C_6H_6	*Dioxane*	*DMSO*	Me_2CO	CH_2Cl_2	$CHCl_3$	*MeOH*	H_2O	*TFE*[a]
Isothiazole[b]	−77.9	−79.6	−80.0	−80.6	−81.0	−82.0	−82.1	−84.0	−85.3	−89.9	−95.8	−102.6
1,3-Thiazole[b]	−52.2	−54.1	−54.0	−54.8	−55.0	−56.2	−55.5	−58.5	−60.5	−68.9	−73.2	−78.0
1,2,3-Thiadiazole N(2)[b]	+39.2	+37.2	+36.0	+35.2	+34.3	+31.3	+32.8	+31.5	+31.3	+28.6	+17.8	+17.5
1,2,3-Thiadiazole N(3)[b]	+61.7	+59.8	+60.6	+59.0	+59.1	+57.2	+58.5	+55.7	+54.9	+51.6	+41.1	+37.0
1,2,4-Thiadiazole N(2)[b]	−103.1	−103.7	−104.5	−103.8	−104.4	−103.4	−104.5	−106.1	−106.1	−106.7	−111.1	−113.7
1,2,4-thiadiazole N(4)[b]	−65.7	−67.2	−67.6	−68.3	−68.7	−69.7	−69.5	−70.6	−71.3	−75.2	−81.8	−86.4
1,2,5-Thiadiazole[b]	−30.6	−31.5	−32.3	−32.9	−33.1	−33.6	−33.8	−34.7	−34.8	−35.6	−42.2	−44.2
1,3,4-Thiadiazole[b]	+2.7	−1.4	−1.5	−2.7	−3.9	−7.0	−4.8	−7.1	−7.6	−14.9	−24.1	−26.5
1,3,4-Oxadiazole[c]	–	−66.7	–	–	–	−74.8	–	–	–	–	−85.4	–
2-Methyltetrazole N(1)[d]	−73.1	–	–	–	–	−72.6	−72.9	–	−73.7	−73.4	−77.6	–
2-Methyltetrazole N(2)[d]	−107.0	–	–	–	–	−101.5	−102.9	–	−104.5	−102.8	−102.3	–

[a]2,2,2-Trifluoroethanol.
[b]<1996J(P2)619, CHEC-III(4.05.3.2.3)557>.
[c]<1996MR(120)148, CHEC-III(5.06.3.2)401>.
[d]<1998MR(131)54, CHEC-III(6.07.3.3.3)277>.

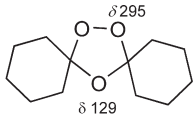
1,2-dioxolane **177** and its bridged analogue **178** <1985JOC4484>. In the 1,2,4-trioxolane **179** the ether oxygen resonates at $\delta = 129$ whereas the peroxide oxygens are at much lower field ($\delta = 295$). A similar difference is observed in the derivative **180** <CHEC-III(6.06.3.3)197>. ^{17}O NMR chemical shifts for a series of dioxolanes have been reported <2001MRC657, CHEC-III(4.10.3.2.3)846>.



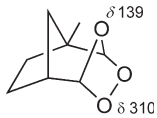
177



178



179



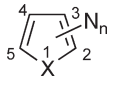
180

2.4.3.6 UV Spectroscopy

2.4.3.6.1 Parent compounds

In general, aza substitution (replacement of cyclic CH by N) has little effect on UV spectra (**Table 25**). Typically, aza analogues of pyrrole show $\lambda_{max} = 217$ nm, or lower, with log ε = ca. 3.5, whereas aza analogues of thiophene show $\lambda_{max} = 230–260$ nm with log ε = ca. 3.7 (**Table 25**); insufficient data are available for aza analogues of furan to generalize but these compounds appear to have maxima below 220 nm.

Table 25 UV absorption maxima for azoles



	X = NH	*X = O*	*X = S*
Derivative	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*
No N	210 (4.20)	208 (3.90	215 (3.80), 231 (3.87)
2-Aza	210 (3.53)	211 (3.60)	244 (3.72)
3-Aza	207–208 (3.07) End absorption	240	207.5 (3.41), 233 (3.57)[a]
2,3-Diaza	210 (3.64)	–	211 (3.64), 249 (3.16), 294 (2.29)[b]
2,4-Diaza	216.5 (3.66)	–	229 (3.73)
2,5-Diaza	–	220	250 (3.86), 253 (3.87), 257 (2.83), 260 (3.68)[c]
3,4-Diaza	–	200[d]	220
2,3,4-Triaza	205	–	280 (4.03)[e]

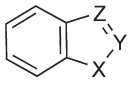
Unless otherwise indicated data taken from <1971PMH(3)67> which contains references to the original literature.
[a]Measured in ethanol.
[b]Measured in cyclohexane.
[c]Measured in isooctane; cf. CHEC-I(4.26.2.4)519.
[d]2-Methyl-1,3,4-oxadiazole exhibits a maximum at 206 nm (log ε = 2.62) in MeOH; cf. CHEC-I(4.23.2.2.2)428.
[e]5-Phenyl-1,2,3,4-thiatriazole.

Relatively few data are available for protonated cationic species; it appears that protonation has little effect on the position and intensity of the absorption.

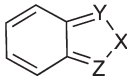
2.4.3.6.2 Benzo derivatives

Benzo derivatives show at least two, and up to seven, maxima in the range 200–320 nm (**Table 26**). The longest wavelength maximum occurs at 275–315 nm and generally at rather longer wavelengths for the sulfur derivatives than for their N or O analogues, and also for the benzo[*c*] compared to the benzo[*b*] derivatives.

Table 26 UV absorption maxima for benzazoles



Derivative		*X = NH*	*X = O*	*X = S*
Y	*Z*	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*
CH	CH	215 (4.38), 261 (3.69), 266 (3.70), 277 (3.58), 279 (3.62), 287 (3.51)	239 (4.03), 240 (4.03), 244 (4.04), 250 (3.91), 269 (3.23), 271 (3.25), 273 (3.40), 281 (3.49)	228 (4.45), 263 (3.71), 258 (3.76), 281 (3.19), 288 (3.33), 290 (3.33), 297 (3.52)
N	CH	250 (3.65), 284 (3.63), 296 (3.52)	235 (4.00), 243 (3.91), 280 (3.46)	205 (4.20), 222 (4.37), 252 (3.56), 261 (3.39), 297 (3.58), 302 (3.57), 3.08 (3.56)[a]
CH	N	242 (3.72), 265 (3.58), 271 (3.70), 277 (3.69)	231 (3.90), 263 (3.38), 270 (3.53), 276 (3.51)	217 (4.27), 251 (3.74), 285 (3.23), 295 (3.13)
N	N	259 (3.75), 275 (3.71)	[b]	213 (4.20), 266 (3.72), 312 (3.40)
S^+	N	–	–	238 (3.91), 350 (4.35), 425 (3.29)[c]



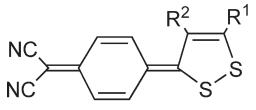
Derivative		*X = NMe*	*X = O*	*X = S*
Z	*Y*	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*	λ_{max} *(nm) (log ε)*
CH	CH	263, 268, 275, 286, 294, 300, 306, 312, 320, 326, 335	215 (4.17), 244 (3.40), 249 (3.37), 254 (3.35), 261 (3.12), 292 (3.35), 299 (3.47), 305 (3.56), 313 (3.70), 319 (3.70), 327 (3.87), 334 (3.66), 343 (3.79)	215 (4.84), 257 (4.04), 272 (3.94), 278 (3.94), 383 (3.93), 290 (3.97), 295 (3.96), 298 (3.94), 305 (4.06), 313 (3.89), 318 (3.90), 322 (3.88), 328 (3.91), 333 (3.90), 343 (3.79)
N	CH	275 (3.80), 292 (3.79), 295 (3.78)	–	203 (4.16), 221 (4.21), 288 (3.88), 298 (3.46), 315 (3.60)[d]
N	N	274 (3.96), 280 (3.98), 285 (3.97)	310 (3.5), 275 (3.6)	221–222 (4.16), 304 (4.14), 310 (4.14), 330 (3.39)

Unless otherwise indicated data taken from <1971PMH(3)67> which contains references to the original literature.
[a]<1973JHC267>.
[b]Unknown <CHEC-I(4.2.1.1)366>.
[c]In concentrated H_2SO_4 <1969ZOR153>.
[d]Data taken from CHEC-I(4.17.3.6)140.

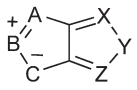
2.4.3.6.3 Effect of substituents

Although UV spectra have been measured for a large number of substituted azoles, there has been little systematic attempt to explain the effects of substituents on spectral maxima. Readily available data are summarized in **Table 27**, and some major trends are apparent. However, detailed interpretation is hindered by the fact that different solvents have been used and that in aqueous media it is not always clear whether a neutral, cationic, or anionic species is being measured. Furthermore, values below 220 nm are of doubtful quantitative significance.

π-Excessive five-membered heterocycles with strong π-acceptor substituents often display intramolecular charge transfer, which can be of practical significance. Thus, intramolecular charge transfer in the 1,2-dithioles **181** allows a photoinduced color response that is of use in optical filters <1988GEP3636157>.



181



182

183: HOMO

The effect of aza substitution is to lower orbital energies (Table 1) and this often lowers HOMO and LUMO energies to a similar extent. In heteropentalene mesomeric betaines of the general type 182, the HOMO 183 is restricted to positions 1,3,4 and 6 (see Section 2.3.2.1). Aza substitution at these positions can therefore be expected to lower the HOMO energy to a greater extent than the LUMO energy with the effect that the gap between the frontier orbitals increases (see Table 1). This effect can be seen in the change of color and visible spectra of mesomeric betaines of this type (Table 28), which can be attributed to a widening of the HOMO–LUMO separation <1977T3193>.

2.4.3.7 IR Spectroscopy

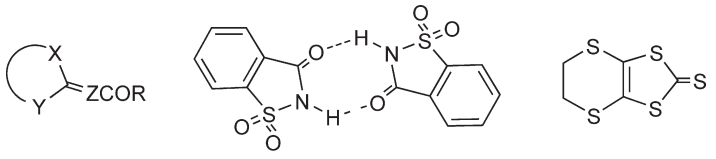
Most fundamental work on the vibrational spectra of azoles appeared in the period 1960–1980 (Table 29). Examples of more recent work include (1) a complete spectrum assignment of the gas-phase IR spectrum of indazole <1993J(F1) 4005>; (2) use of IR spectral data to determine the enthalpies of O–H···N and N–H···O bonds in complexes of formic acid and 3,5-dimethylpyrazole <1987MI301-01>; and (3) the vibrational assignment of the Raman spectrum of polycrystalline pyrazole based on 3-21G calculations <1992MI301-01>.

2.4.3.7.1 Aromatic rings without carbonyl groups

For many of the parent compounds, complete assignments have been made <1971PMH(4)265>. A comprehensive study of the vibrational spectra of 1,2,4-triazole in comparison to those of 1,2,3-triazole and tetrazole has been reported <2000JST (530)183>. For substituted derivatives, group frequencies have been derived. In the ring systems under discussion, IR bands can be placed in the following categories: (1) CH-stretching modes near 3000 cm^{-1} that are of little diagnostic value; (2) ring-stretching modes at 1650–1300 cm^{-1} (Table 29), with four or five bands generally being found in well-defined regions and the intensities varying according to the nature and orientation of substituents; (3) CH and ring-deformation modes at 1300–1000 cm^{-1} (Table 30) and at 1000–800 cm^{-1} (Table 31) (the former are largely in-plane CH and the latter out-of-plane CH and in-plane ring deformation modes); and (4) substituent vibrations, which are discussed in Section 2.4.3.7.3.

2.4.3.7.2 Azole rings containing carbonyl groups

The carbonyl group is found in a wide variety of situations in five-membered rings accommodating diverse heteroatoms. These carbonyl frequencies range from about 1800 to below 1600 cm^{-1}; some such frequencies are so low that they often fail to be recognized as carbonyl absorptions at all, e.g., a carbonyl joined to a heterocyclic ring via an exocyclic double bond, as in structures 184. Low-frequency ν(C=O) bands are widespread because five-membered heterocyclic rings are inherently π-electron donors. The transfer of electrons into the exocyclic double bond [ν(C═Z) of 184] is likely to be extensive when both X and Y are electron-donor atoms.



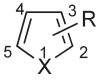
184 **185**: saccharin **186**

In Table 32 the ν(C═O) and other characteristic bands are given for some saturated five-membered heterocycles. Adjacent NH groups and sulfur atoms have the expected bathochromic effect on ν(C═O), whereas an adjacent oxygen atom acts in the reverse direction. The CH_2 vibrations of cyclopentanone are repeated to a considerable extent in the heterocyclic analogues.

Table 33 reports ν(C═O) for a variety of azolinones containing ring double bonds. The hypsochromic effect of an oxygen atom or CR_2 group versus the bathochromic effect of NR, S, or C=C can readily be traced.

IR spectroscopy can be applied to study molecular association with participation of a carbonyl group. Thus, examination of the hydrogen bonding of saccharin, thiosaccharin, and their salts <1986JST(142)275, 1992JST(267) 197> shows that saccharin exists in the solid state as a symmetric dimer 185, which gives three bands in the N–H stretching region (3090, 2970, and 2700 cm^{-1}), one of which is an overtone. The vibrational spectra of solid saccharin and metal saccharinates have been extensively studied and reviewed <2001COR1059, 2001JST(563)335>. The spectrum of free saccharin shows a weak band at 3215 cm^{-1} due to the N–H vibration <CHEC-III(4.05.3.5)561>.

Table 27 Effects of substituents on UV absorption maxima (nm)



		X = NH				*X = O*				*X = S*			
		Substituent position				*Substituent position*				*Substituent position*			
R	*Aza position*	*2*	*3*	*4*	*5*	*2*	*3*	*4*	*5*	*2*	*3*	*4*	*5*
Me	2	–	213	220	(≡3)	–	217	221	213	–	246.5	251[a]	243[a]
	3	210	–	215	(≡4)		–			235	–	241	239
	2,3	–	–	216	(≡4)	–	–			–	–	213	217
	2,4	–	<220	–	(≡3)	–		–		–		–	
	2,5	–	–	–	–	–		(≡3)	–	–	257[b]	(≡3)	–
	3,4	–	–	–	–	206	–	–	(≡2)	<230	–	–	(≡2)
Ph	2	–	248	251	(≡3)	–	239		260	–	270, 291	266[c]	266[c]
	3	271	–	260	(≡4)	263	–	243	267	287	–	252	275
	2,3	–	–	245	(≡4)	–	310[d]			–	–		
	2,4	–	242	–	(≡3)	–	238[d]	–	250[d]	–		–	
	2,5					–		(≡3)	–	–	280[b]	(≡3)	
Ph	3,4					248	–	–	(≡2)	268	–	–	(≡2)
	2,3,4	–	–	–	241	–	–	–		–	–	–	
Br (Cl)	2	–		221	(≡3)	–				–	244[e]	256[a]	241′
	3	220*	–	217	(≡4)		–			245	–	246	247
OMe (OH)	2	–			(≡3)	–	220			–	255[f]		
	3		–		(≡4)		–			239	–		
	2,3	–	–	234*	(≡4)	–	–			–	–		–
	2,5					–		(≡3)	–	–	273	(≡3)	
	2,3,4	–	–	–	213*	–	–	–		–	–	–	258
NH_2 (NMe_2)	2	–	228		(≡3)	–	229		246	–	278[g]	286[a]	
	3		–	230*	(≡4)		–	–		254.4*	–		
	2,3	–	–	228	(≡4)	–	–			–	–		247
	2,4	–	<220	–	(≡3)	–		–		–		–	245[k]
	3,4					–	–	–	(≡2)	251	–	–	(≡2)
	2,3,4	–	–	–	218	–	–	–		–	–	–	263

CO_2Me (CO_2H, CHO)	2	–	217		(≡3)	–		216[h]	244	–		256	250	
	3	285	–	257	(≡4)		–				–		230	–
	2,5	–		–	(≡3)	–		(≡3)	–	–		263	(3)	245[k]
	3,4					243[i]	–	–	(≡2)		–		–	(≡2)
NO_2	2	–	261	275	(≡3)	–		239		–			272	
	3	325	–	298	(≡4)		–				–			–
	2,4	–	215, 245[j]	–	(≡3)	–		–		–			–	
	2,5					–		(≡3)	–	–			(≡3)	

Unless otherwise indicated, data taken from <1971PMH(3)67>, which contains references to the original literature. A dash indicates that a substituent cannot be in that position; a blank means that the value has not been reported. Asterisk (*) indicates, exceptionally, acidified or basified solvent; for details, see references quoted in <1971PMH(3)67>.

[a]<1964JCS446>.

[b]Cf.<CHEC-I(4.26.2.4)519>.

[c]In cyclohexane <1966T2119>.

[d]<1964HCA942>.

[e]Value based on 'average increment' observed for a large number of compounds; cf. CHEC-I 4.17.

[f]<1970T2497>.

[g]Perchlorate salt in MeOH <1971JHC657>.

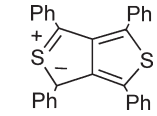
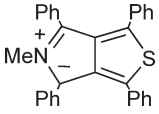
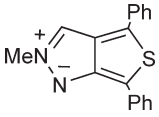
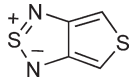
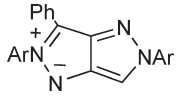
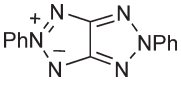
[h]2-Benzyl-5-methyl derivative.

[i]2-Benzyl-5-methyl derivative.

[j]In water.

[k]<1954CB57>.

Table 28 The effect of ring heteroatoms on the visible absorption of heteropentalene mesomeric betaines **182**

Molecule	*Appearance*	λ_{max} *(nm) (log ε)*	*Solvent*	*Reference*
	Purple needles	551 (3.92)	$CHCl_3$	1974JA4268
	Red needles	533 (3.15)	$CHCl_3$	1974JA4268
	Orange prisms	465 (4.44)	MeOH	1974JA4276
	Yellow crystals	413 (3.45)	Et_2O	1994H(37)693
	Pale yellow crystals[a]	398 (4.33)[a]	$CHCl_3$	1974BCJ946
	Colorless leaflets	342 (4.60)	EtOH	1970BCJ3587

[a]Ar = *p*ClC_6H_4.

Table 29 Azoles: IR ring-stretching modes in the 1650–1300 cm^{-1} region

Compound	*Stretching modes (cm^{-1})*				
Isoxazoles	1650–1610	1580–1520	1510–1470	1460–1430	1430–1370
Isothiazoles	–	–	1488	1392	1342
Pyrazoles	–	1600–1570	1540–1510	1490–1470	1380–1370
Oxazoles	1650–1610	1580–1550	1510–1470	1485	1380–1290
Thiazoles	1625–1550	–	1550–1470	1440–1380	1340–1290
Imidazoles	1605	1550–1520	1500–1480	1470–1450	1380–1320
1,2,4-Oxadiazoles	–	1590–1560	–	1470–1430	1390–1360
1,2,5-Oxadiazoles	–	1630–1560	1530–1515	1475–1410	1395–1370
1,3,4-Oxadiazoles	1680–1650	1630–1610	1600–1580	1430–1410	–
1,2,4-Thiadiazoles	–	1590–1560	1540–1490	–	–
1,2,3-Thiadiazoles	1650–1590	–	1560–1420	1350–1325	1260–1180
1,2,5-Thiadiazoles[a]	–	–	–	1461	1350
1,2,3,4-Thiatriazoles	1720–1690	1610–1530	–	–	1300–1260
1,2,3-Triazoles	1650–1615w	–	1530–1485	1440w	1420–1400w
1,2,4-Triazoles	–	–	1545–1535	1470–1460	1365–1335
Tetrazoles	1640–1615	–	1450–1410	1400–1335	1300–1260

Data taken from <1971PMH(4)265>, which contains references to the original literature; w = weak.
[a]Data taken from CHEC-I(4.26.2.5)521.

Raman spectroscopy is an effective method for investigating intermolecular charge transfer, which is accompanied by frequency shifts and a redistribution of band intensities that can give information about the degree of charge transfer and charge redistribution. The reaction of 1,3-dithiole-2-thione **186** as a donor with diiodine as an acceptor has

Table 30 Azoles: characteristic IR bands in the 1300–1000 cm^{-1} region

Compound	*β (CH) modes (cm^{-1})*			*Ring breathing (cm^{-1})*
Isoxazoles	1218m	1155–1130	1088s	1028–1000
Isothiazoles	–	1070m	1060m	980s
Pyrazoles	1310–1130	1160–1090	1090–990	1040–975
Thiazoles	1240–1230	1160–1075	1105–1055	1040
Imidazoles	1285–1260	1140	1100	1060
1,2,4-Oxadiazoles	–	–	1070–1050	–
1,2,5-Oxadiazoles	1360–1175	1190–1150	1160–1150	1035–1000
1,2,4-Thiadiazoles	1270–1215	1185–1170	1160–1080	1050
1,2,3-Thiadiazoles	–	–	1150–950	–
1,2,5-Thiadiazoles[a]	1251–1227	–	1041	–
1,3,4-Thiadiazoles	1230–1165	1190–1120	1075–1045	1040
1,2,3,4-Thiatriazoles	1235–1210	1120–1090	1060–1030	–
1,2,3-Triazoles	1300–1275	1150–1070	1095–1045	1005–970
Tetrazoles	1210–1110	1170–1035	1060	995–900

Data taken from <1971PMH(4)265>, which contains references to the original literature; s = strong, m = medium, w = weak.
[a]Data taken from CHEC-I(4.26.2.5)521.

Table 31 Azoles: characteristic IR bands below 1000 cm^{-1}

Compound	*CH modes (cm^{-1})*		*β-Ring (cm^{-1})*	*CH modes (cm^{-1})*
Isoxazoles	970–920	899	945–845	774
Isothiazoles	915w	–	810s	740vs
Pyrazoles	960–930	860–855	805–790	765–750
Thiazoles	980–880	890–785	800–700	745–715
Imidazoles	970–930	895	840	760
1,2,4-Oxadiazoles	–	–	915–885	750–710
1,2,5-Oxadiazoles	980–900	–	890–825	715–700
1,2,3-Thiadiazoles	–	–	910–890	–
1,2,4-Thiadiazoles	1030–935	890	860–795	750–740
1,2,5-Thiadiazoles	–	–	860–800	780[a]
1,3,4-Thiadiazoles	975–905	905–875	850	775–750
1,2,3,4-Thiatriazoles	960–930	–	910–890	–
1,2,3-Triazoles	–	855–825	970–700	–
1,2,4-Triazoles	–	–	865–855(?)	–
Tetrazoles	960	–	–	810–775

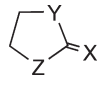
Data taken from <1971PMH(4)265> which contains references to the original literature; vs = very strong, s = strong, w = weak.
[a]Data taken from CHEC-I(4.26.2.5)521.

been investigated at different temperatures providing evidence of formation of a 1:1 adduct <1999IC4626, CHEC-III (4.12.3.1)959>.

2.4.3.7.3 Substituent vibrations

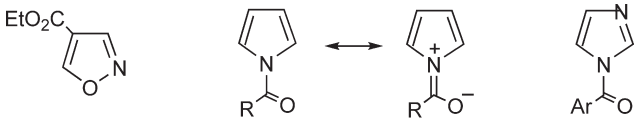
In general, substituent frequencies in azoles are consistent with those typical of the same substituents in other classes of compound. Some characteristic trends are found, and these have been used to measure electronic effects. For example, the ν(C=O) frequencies in 3-, 4-, and 5-alkoxycarbonylisoxazoles (e.g., **187**) are, respectively, 9–12, 2–8, and 17–18 cm^{-1} higher than those of the corresponding alkyl benzoates, indicating the following order of electron-donor power: phenyl > 4- > 3- > 5-position of isoxazole. Similar work has been reported for other ring systems and substituents <1963PMH(2)161>.

Table 32 IR absorption assignments for 2,5-dihetero derivatives of cyclopentanone



C=X	*C=O*	*C=O*	*C=S*	*C=O*	*C=O*	*C=S*	*C=S*	*C=O*	*C=S*	*C=O*	*C=S*
Y	*CH_2*	*CH_2*	*CH_2*	*O*	*S*	*S*	*O*	*O*	*S*	*NH*	*NH*
Z	*O*	*N*	*N*	*O*	*S*	*S*	*NH*	*NH*	*NH*	*NH*	*NH*
Vibration type (cm^{-1})											
ν(C=X)	1770	1695	1109	1795	1638	1058	1171	1724	1047	1661	1208
CH_2 scissor	1490	1494	1478	1483	1434	1416	1464	1485	1458	1488	1459
	1466	1440	1458	1422	1422	1370	1402	1412	1432	1449	1368
	1426	1426	1420	1394					1380		
	1379	1378									
CH_2 wag	1284	1270	1309	1226	1275	1275	1319	1333	1250	1200	–
	1242	1230	1215		1254	1243	1230	1230	1203		
CH_2 twist	1192	1169	1168	1175	1158	1148	1203	–	1160	–	–
CH_2 rock	990	995	970	1005	983	983	969	967	998	988	980
ν ring	1166	1285	1290	1140	888	882	1290	1250	1294	1270	1273
	1037	1068	1059	1071	826	831	1035	1077	1080	1103	1042
	890	915	915	971	677	670	942	1021	650	1037	1003
	929	887	880	894	939	946	914	918	927	933	919
γ ring	800	805	493	773	–	457	–	770	–	768	–

Data taken from <1963PMH(2)161>, which contains references to the original literature.



187 **188a** **188b** **189**

For *N*-acetylazoles (e.g., **188a**) *ν*(C=O) increases with the number of cyclic nitrogen atoms (**Table 34**) <1956CB1940,1957MI40100>. Additional nitrogen atoms in the ring act as powerful electron-withdrawing substituents and decrease the importance of forms such as **188b**. Data for benzo analogues (**Table 34**) show that *ν*(C=O) values for substituted *N*-benzoylimidazoles **189** and *N*-benzoyltriazoles follow the Hammett equation <1957MI40100>; for data on *N*-acylpyrazoles see reference <1959MI40100>.

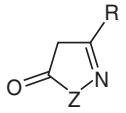
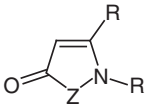
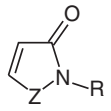
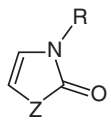
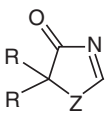
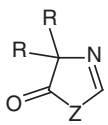
Substituent vibrations in IR spectra have been used extensively to determine tautomeric structure, particularly C=O, NH, OH, and SH stretching modes. For example, 3-hydroxyisoxazoles show broad *ν*(OH) at 2700 cm^{-1} (dimers). Boulton and Katritzky developed a technique for determining the structure of potentially tautomeric amino compounds by partial deuterium exchange. If the compound under investigation contains an amino group, the change from NH_2 to NHD produces a new single *ν*(NH) at a frequency between those of the original doublet for asymmetrical and symmetrical *ν*(NH_2). If the compound does not contain an amino group and the two bands are derived from two separate NH groups, there should be no new band between the original two in the partially deuterated derivative. The method was applied to aminoisoxazoles <1961T(12)51>.

2.4.3.8 Mass Spectrometry

Among the most important fragmentation pathways of the molecular ions of azoles are the following.

a. Loss of RCN or HCN; this occurs particularly readily for systems containing fragment **190**, i.e., imidazoles and thiazoles. It does not occur so readily for oxazoles, but is found again in the 1,2,4-oxadiazoles **191** and also for pyrazoles **192**.

Table 33 ν(C═O) frequencies for some azolinones

Ring substituent(s)			
R = H or Me	*Z = NH (cm^{-1})*	*Z = O (cm^{-1})*	*Z = S (cm^{-1})*
	1705–1695[a]	–	–
	1680–1630	–	–
	–	–	1660[b]
	1684–1677[c]	1780–1750	1640[d]
	–	1770–1740	1780–1700
	–	ca. 1820	1725[e]

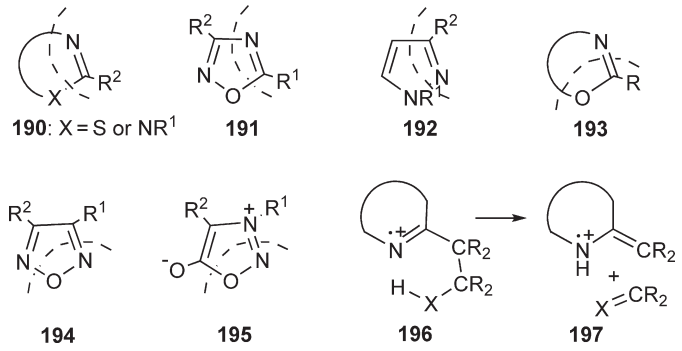
Unless otherwise indicated, data taken from appropriate chapter in *Comprehensive Heterocyclic Chemistry*.
[a]Z = NR, R = alkyl, aryl.
[b]R = Me <1964TL1477>.
[c]Data taken from <1963PMH(2)161> which contains references to the original literature.
[d]<1979HC(34-2)421>.
[e]<1979HC(34-2)430>.

Table 34 Carbonyl frequencies for *N*-acetylazoles

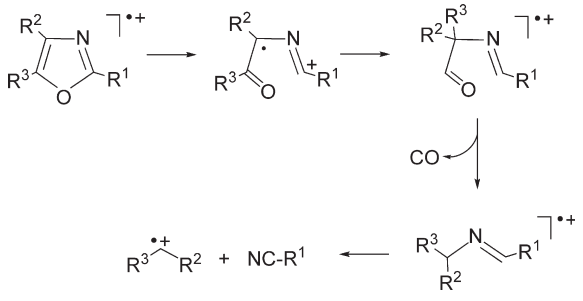
N-Acetylazole	*ν(C═O) (cm^{-1})*	*N-Acetylazole*	*ν(C═O) (cm^{-1})*
Pyrrole	1732	Indole	1711
Imidazole	1747	Benzimidazole	1729
1,2,4-Triazole	1765	Benzotriazole	1735
Tetrazole	1779		

Data taken from <1956CB1940> and <1957MI40100> which contain references to the original literature.

b. Loss of RCO^+; this is important for systems **193** in oxazoles and in 1,3,4-oxadiazoles. It is also found in isoxazoles, where it probably occurs after skeletal rearrangement of the isoxazole to an isomeric oxazole.
c. Loss of NO^+ and/or NO occurs for furazans **194** <CHEC-III(5.05.3.3)324> and sydnones **195** <CHEC-II(4)165>.
d. Loss of N_2 from triazoles and tetrazoles (but *not* pyrazoles).
e. Wherever the structural element **196** occurs, a McLafferty rearrangement can take place (**196** → **197**). For example, this often occurs with 2-alkyloxazoles <CHEC-III(4.04.3.3)492>.
f. Isothiazoles are rather stable and show intense molecular ions with some HCN loss, probably via rearrangements, analogous to those of isoxazoles, to give thiazoles.



The mass spectrometry of oxazole derivatives has been reviewed <1980H(14)847>. The main fragmentation path for most oxazole rings is shown in **Scheme 8** <1992OMS317>.



Scheme 8

The mass spectrometry of 1,2,4-oxadiazoles is dominated by stepwise 1,3-dipolar cycloreversion, i.e., fragmentation **191**. This fragmentation is particularly useful for 1,2,4-oxadiazole characterization and a wide selection of derivatives undergo cleavage to a nitrile oxide fragment <2003H(60)2287, CHEC-III(5.04.3.3)249>. Mass spectrometric analysis of 1,2,4-oxadiazoles and dihydro-1,2,4-oxadiazoles has been reviewed <2005MI328>.

There are correlations between mass spectral fragmentations and thermal and photochemical fragmentations and rearrangements (see Sections 3.4.1.2.1 and 3.4.1.2.2).

2.4.3.9 Photoelectron Spectroscopy

In this method, photons of an energy much above that of the ionization potential are directed onto a molecule. The photoelectron spectrum which results allows assessment of the energies of filled orbitals in the molecule, and thus provides a characterization of a molecule. Comparisons between photoelectron spectra of related compounds give structural information, for example, on the tautomeric structure of a compound by comparison of its spectrum with those of models of each of the fixed forms.

Photoelectron spectroscopy has demonstrated there is no linear correlation between the ionization energies and pK_a values of azoles <1984JHC269>.

Photoelectron spectra have been discussed and assigned in the following series: pyrazole <CHEC-I(4.04.1.3.9)205>, 1,2,3-triazole <CHEC-I(4.11.3.2.9)688>, isothiazole <CHEC-I(4.17.2.2)133>, 1,3,4-oxadiazole <CHEC-I(4.23.2.2.5)429>, 1,2,5-thiadiazole <CHEC-I(4.26.2.2)516>, 1,3,4-thiadiazole <CHEC-I(4.27.2.3.10)553>, 1,3-dioxolane <CHEC-I(4.30.1.4.5)757>, 1,2-dithiole <CHEC-I(4.31.1.4)787>, and 1,2,4-trioxolane and 1,2,4-trithiolane <CHEC-I(4.33.2.2.5)861>.

The photoelectron spectrum of pyrazole has been assigned using *ab initio* CI calculations <1987CPH(111)249>.

2.4.4 Thermodynamic Aspects

2.4.4.1 Intermolecular Forces

2.4.4.1.1 Melting and boiling points

In the parent unsubstituted ring systems (i.e., first column of **Table 35**) replacement of a −CH═CH− group by a sulfur atom has little effect whereas replacement of a −CH═CH− group by an oxygen atom lowers the boiling point by ca. 40 °C.

Introduction of nitrogen atoms into the ring is accompanied by less regular changes. Substitution of (1) a −CH═CH− group by an −NH− group or (2) a ═CH− group by an ═N− atom both increase the boiling point. When both of these changes are made simultaneously the boiling point is increased by an especially large amount due to the possibilities of association by intermolecular hydrogen bonding.

The effect of substituents on melting and boiling points can be summarized as follows.

a. Methyl and ethyl groups attached to ring carbon atoms usually increase the boiling point by ca. 20–30 and ca. 40–60 °C, respectively. However, conversion of an NH group into an NR group results in a large decrease in the boiling point (e.g., pyrazole to 1-methylpyrazole) because of decreased association by hydrogen bonding.
b. Acid and amide derivatives are all solids. Many of the amides melt in the range 130–180 °C; the melting points of the acids vary widely.
c. Compounds containing a hydroxy, mercapto or amino group are usually relatively high-melting solids. For many hydroxy and mercapto compounds this can be attributed to their tautomerism with hydrogen-bonded 'one' and 'thione' forms. However, hydrogen bonding can evidently also occur in amino compounds.
d. Methoxy, methylthio, and dimethylamino derivatives are often liquids.
e. Chloro compounds are usually liquids that have boiling points similar to those of the corresponding ethyl derivatives. Bromo compounds boil 25 °C higher than their chloro analogues.

2.4.4.1.2 Solubility of heterocyclic compounds

In general, the solubility of heterocyclic compounds in water (**Table 36**) is enhanced by the possibility of hydrogen bonding. Pyridine-type nitrogen atoms facilitate this (cf. benzene and pyridine). In the same way, oxazole is miscible with water and isoxazole is very soluble (more so than furan).

The effect of amino, hydroxy, or mercapto substituents is to increase hydrogen-bonding properties. However, if stable hydrogen bonds are formed in the crystal, this can decrease solubility in water <1963PMH(1)177>, e.g., indazole and benzimidazole are less soluble than benzoxazole.

Other solvents can be divided into several classes. In hydrogen bond-breaking solvents (dipolar aprotic solvents), the simple amino, hydroxy, and mercapto heterocycles all dissolve. In hydrophobic solvents, hydrogen-bonding substituents greatly decrease the solubility. Ethanol and other alcohols take up a position intermediate between water and the hydrophobic solvents <1963PMH(1)177>.

2.4.4.1.3 Gas–liquid chromatography

Gas–liquid chromatography has been widely used for the identification of reaction mixtures and for the separation of heterocycles. Some typical conditions are shown in **Table 37**.

2.4.4.2 Aromaticity of Fully-Conjugated Rings

2.4.4.2.1 Background

Some background to the common energetic, structural, and magnetic indices for aromaticity is given in Section 2.2.4.2 of Chapter 2.2. The aromaticities of five-membered rings with one heteroatom are compared in Section 2.3.4.2 of Chapter 2.3. A number of reviews deal with the concept of aromaticity in heterocyclic rings and these should be consulted for further details <1974AHC(17)255, 2000T1783, 2001CRV1385, 2001CRV1421>.

Overall, the aromaticity of azoles is intermediate between that of five-membered heterocycles with one heteroatom and six-membered heterocycles (azines). For example, the HOMA aromaticity index decreases in the sequence pyridine (0.998) > pyrazole (0.922) > pyrrole (0.899). This corresponds with a general rule according to which a pyridine-type nitrogen atom provides more effective cyclic π-conjugation than a pyrrole-type nitrogen atom. However, this is a generalization and although it is generally agreed that pyrazole is more aromatic than pyrrole, it is difficult to make a direct comparison with azines.

Table 35 Melting and boiling points

Ring system	*H*	*Me*	*Et*	*COMe*	*CO_2H*	*CO_2Et*	*$CONH_2$*	*CN*	*NH_2*	*OH*	*OMe*	*SH*	*SMe*	*Cl*	*Br*
Benzene	80	111	136	212	122	211	130	190	184	43	154	168	187	131	155
Pyrrole-1	130	114	129	180	95d	180	166	–	–	–	–	–	–	–	–
Pyrrole-2	130	148	181	90	205d	39	174	–	–	83[a]	–	–	–	–	–
Pyrrole-3	130	158	179	115	148	78d	152	–	–	–	–	–	208	–	–
Furan-2	31	64	92	31	133	34	142	147	68	80	110	–	–	78	103
Furan-3	31	65	–	54	122	179	168	–	–	58	–	–	–	80	103
Thiophene-2	84	113	133	214	129	218	180	196	214	217	156	166	–	128	150
Thiophene-3	84	115	135	57	138	208	178	179	–	–	–	171	–	136	157
Pyrazole-1	70	127	137	234	103	213	141	37	–	–	–	–	–	–	–
Pyrazole-3	70	205	209	101	214d	160	148	150	40	166	–	–	>370[b]	40	70
Pyrazole-4	70	207	244	114	278	79	–	92	81	118	62	–	–	77	97
Isoxazole-3	95	118	139	16	149d	–	134	168	–	–	–	–	–	–	–
Isoxazole-4	95	127	–	–	–	–	–	–	–	–	–	–	–	–	130
Isoxazole-5	95	121	–	52	149	–	174	–	–	–	–	–	–	–	–
Imidazole-1	90	199	226	102	–	218	–	–	–	–	–	–	–	–	–
Imidazole-2	90	141	80	80	164d	–	–	–	–	250d	–	227	139	165	207
Imidazole-4	90	56	–	–	275d	157	215	–	–	–	–	–	–	–	130
Oxazole-2	69	87	–	–	–	–	–	–	97	–	–	–	–	–	–
Oxazole-4	69	–	–	–	142	48	–	–	–	–	–	–	–	–	–
Thiazole-2	118	128	158	226	102d	48	118	31	92	–	164	79	230	145	147
Thiazole-4	118	133	–	56	196	52	150	60	–	–	–	–	–	165	190
Thiazole-5	118	141	142	–	218	217	186	53	83	–	176	–	222	140	192
1,2,3-Triazole-1	206	228	238	–	–	–	–	–	51	–	–	–	–	–	–
1,2,4-Triazole-1	121	20	199	40–2	–	230	138	–	–	–	–	–	–	81d	136d
1,2,4-Triazole-3	121	95	65–6	–	137	178	312	187	159	234	oil	216	105	167	189
1,2,4-Triazole-4	121	90	oil	–	–	–	–	–	76–7	–	–	–	–	–	–
Tetrazole-5	156	148	–	–	–	86	234	99	203	260	154	205	151	73	148
Tetrazole-1	156	39	265	–	–	–	–	–	>370	–	–	–	–	–	–
Tetrazole-2	156	147	163	–	–	–	–	–	>370	–	–	–	–	–	–

Isothiazole-3	113	134	–	**32**	**135**	290	**154**	**60**	**33**	**74**	147	–	–	160	–
Isothiazole-4	113	146	–	–	**161**	**174**	**192**	**94**	**45**	–	–	–	–	143	**34**
Isothiazole-5	113	142	–	250	**201d**	–	**172**	**47**	**112**	–	–	–	–	149	150
1,2,4-Oxadiazole-3	87	*105*	–	–	–	–	–	–	–	–	–	–	–	–	–
1,2,4-Oxadiazole-5	87	104	–	–	–	–	–	–	–	–	–	–	–	–	–
1,3,4-Oxadiazole-2	150	164	174.5	–	–	255	–	–	**156**	**120**	–	**89–91**	–	–	–
1,2,3-Thiadiazole-4	160	**87–9**	–	**140**	**227–8**	**86**	**220–2**	**62–3**	**44–6**	–	–	–	–	170	–
1,2,3-Thiadiazole-5	160	–	–	–	**104–6**	*222*	–	–	145	–	–	–	–	–	–
1,2,4-Thiadiazole-3	121	132	–	–	–	–	–	–	–	–	–	–	**32**	–	–
1,2,4-Thiadiazole-5	121	–	–	–	–	–	–	–	**119**	**120**	–	**93**	220	122	
1,2,3,4-Thiatriazole-5	–	–	–	–	–	–	–	–	**128**	–	**44d**[c]	**50–65d**	**34**	ex.[d]	–
1,3,4-Thiadiazole	**43**	201d	–	–	–	–	**221**	–	**193**	–	–	**143**	–	**33**	**73**
1,3-Dioxole-4	51	76	–	–	–	–	–	–	–	–	–	–	–	–	–
1,2-Dithiol-3-one-4	>370	>370	>370	–	–	–	–	–	**80**	–	–	–	–	**62–3**	–
1,2-Dithiol-3-one-5	>370	–	–	–	**214–6**	>370	**223**	–	–	–	–	–	–	–	–
1,2,4-Trioxolane-3,3-di	116	88	–	–	–	–	–	–	–	–	–	–	–	–	–
1,2,4-Trioxolane-3,5-di	116	90	**140**	–	–	**42**	–	–	–	–	–	–	–	–	–
1,2,4-Trithiolane-3,5-di	78	>200	>230	–	–	–	–	–	–	–	–	–	–	–	–

Melting points are given in bold; melting points below 30 °C are not included. Boiling points are given at atmospheric pressure to facilitate comparison; those reported at other than atmospheric pressure were converted using a nomogram <1957MI40101>. A dash indicates that the compound is unstable, unknown, or the data are not readily available.

[a]Value given for the monohydrate.

[b]Value given for EtS derivative.

[c]Value given for EtO derivative.

[d]Explodes.

Table 36 Solubilities of some five-membered heterocycles in water at 20 °C

Compound	*Parts soluble in 1 part of water*	*Compound*	*Parts soluble in 1 part of water*
Furan	0.03	Pyrrole	0.06
Isoxazole	0.02	Pyrazole	0.40
Oxazole	Misc.[a]	2-amino-4-hydroxy-	0.009
Benzoxazole	0.008	Imidazole	1.8
Sydnone	–	2,5-dihydroxy-	0.02
3-methyl-[b]	Misc.	1-methyl-	Misc.
1,2,4-Oxadiazole[c]	Misc.	1,2,4-Triazole	1
Thiophene	0.001	3-amino-	0.3
Isothiazole	0.03	3-hydroxy-	0.05
Thiazole	–	Tetrazole	1
2-methyl-	Misc.	Benzimidazole	0.002
2-amino-	0.05	Indazole	0.0008
1,2,3-Thiadiazole	0.03	3-hydroxy-	0.002
1,3,4-Thiadiazole	Misc.	Purine	0.5

Unless otherwise indicated, data taken from <1963PMH(1)177> or from appropriate chapter of *Comprehensive Heterocyclic Chemistry*, which contain references to the original literature.
[a]Misc. = miscible.
[b]At 40 °C <1980J(P2)553>.
[c]<1965MI40100>.

Table 37 Operating conditions for GLC separation of five-membered heterocycles with more than one heteroatom

Compound	*Conditions*
Pyrazolines	10% Cyanethylated mannite on Celite 545
Imidazoles	5% OV-t7 on Chromosorb W, AW-DMCS (H.P.)[a]
Thiazoles	Carbowax 4000, dioleate on firebrick, 190 °C
Oxadiazoles	Silicone grease on Chromosorb P
1-Phenylpyrazoles	Apiezon L on firebrick C-22, 220 °C
Purines	15% Hallcomid M-18 on firebrick
Dioxolanes	Carbowax 20M on Gas-Chrom P
Benzotriazole	Ethylene glycol succinate on Diatoport-S

Data taken from <1971PMH(3)297>, which contains references to the original literature.
[a]Simple alkyl- and aryl-imidazoles. N-Unsubstituted compounds are N-acylated prior to injection.

Most of the common aromaticity criteria (energetic, structural, and magnetic) readily discriminate between aromatic, nonaromatic, and antiaromatic systems, and in this sense they are to some extent related. However, within a particular group of aromatic structures the indices do not appear to correlate and in this sense the different criteria are statistically multidimensional. This was demonstrated by a study of 75 five-membered π-electron systems <2002JOC1333>. The accepted aromaticity criteria do not necessarily lead to the same ordering of molecules. Principal component analysis reveals that aromatic heterocycles cannot be characterized by a single scale; there are two principal components that may be linearly related for some subsets. However, in general different physical properties described by appropriate indices of aromaticity will not usually lead to the same classification. Katritzky and coworkers have concluded that the use of a single index to describe aromatic molecules has to be abandoned <2001CRV1421>. Cyrański, Krygowski, and Katritzky have proposed that 'fully-aromatic systems are those cyclic π-electron systems that follow all the main aromatic criteria, including special chemical behaviour toward retaining the type of π-electron structure' <2002JOC1333>. However, Schleyer considers that the induced ring current is most closely related to the cyclic electron delocalization that characterizes aromatic molecules <2002JOC1333>.

Table 38 Energy indices estimated by various methods

Molecule	*ERE (kcal mol^{-1})*[a]	*HSRE (β)*[b]	*ASE (kcal mol^{-1})*[c]
Pyrrole	17.4	0.039	18.04
Pyrazole	32.7	0.055	20.46
Imidazole	17.7	0.042	16.18
1*H*-1,2,4-Triazole	36.2	–	18.01
4*H*-1,2,4-Triazole	–	–	12.19
1*H*-Tetrazole	–	–	14.13
2*H*-Tetrazole	63.1	–	21.17
Indazole	59.5	0.050	–
Benzimidazole	48.8	0.050	–
Benzotriazole	74.7	–	–

[a]From <1974AHC(17)255> using Coates and Sutton's bond energy terms.
[b]<1975T295, 1985KGS867>.
[c]<2003T1657>.

2.4.4.2.2 Energetic criteria

A limited amount of energy data is available for this class of heterocycle. **Table 38** shows empirical resonance energies (ERE) and Hess–Shaad resonance energies (HSRE) for a limited list of azoles. Also included in **Table 38** are aromatic stabilization energies (ASEs). The ASE is a more recent measure of aromaticity based on homodesmotic and isodesmotic reactions. ASE values for a wide range of five-membered heterocycles are available <2003T1657>.

All three energy indices indicate that imidazole is less aromatic than pyrazole. The ASE index even suggests that imidazole is less aromatic than pyrrole. It is interesting to note that structural (HOMA and I_5, **Table 39**) and magnetic (NICS, **Table 4**) indices also classify pyrazole as more aromatic than imidazole. The 1,2-relationship **198** is clearly

Table 39 HOMA and Bird structural indices of aromaticity for five-membered rings

Compound	*HOMA*[a,b]	*I_5*[c]	*I_A*[d]	*Compound*	*HOMA*	*I_5*	*I_A*
Benzene	0.987[a]	–	100	1,2,3-Oxadiazole	0.443[b]	–	–
Pyrrole	0.899[a]	59	85	1,2,4-Oxadiazole	0.553[b]	39	–
Pyrazole	0.922[a]	73	90	1,2,5-Oxadiazole	0.677[b]	43	53
Imidazole	0.918[a]	64	79	1,3,4-Oxadiazole	0.243[b]	50	62
1*H*-1,2,3-Triazole	0.839[a]	73	90	1,2,3,4-Oxatriazole	0.413[b]	–	–
2*H*-1,2,3-Triazole	0.960[b]	88	109	1,2,3,5-Oxatriazole	0.586[b]	–	–
1*H*-1,2,4-Triazole	0.911[a]	81	100	Thiophene	0.654[a]	66	82
4*H*-1,2,4-Triazole	0.823[b]	66	–	Isothiazole	0.774[e]	59	91
1*H*-Tetrazole	0.885[a]	72	89	Thiazole	0.905[b]	64	79
2*H*-Tetrazole	0.973[a]	–	–	1,2,3-Thiadiazole	–	54	67
Pentazole	0.952[a]	–	109	1,2,4-Thiadiazole	–	72	89
Furan	0.029[a]	43	53	1,2,5-Thiadiazole	–	84	104
Isoxazole	0.527[b]	47	52	1,3,4-Thiadiazole	0.849[b]	63	80
Oxazole	0.332[b]	38	47	1,2,3,4-Thiatriazole	–	65	–

[a]<2001CRV1385>.
[b]<2002JOC1333>.
[c]<1985T1409>.
[d]<1992T335>.
[e]<CHEC-III(4.05.4.3)565>.

favorable <2010T2695>. This type of 1,2-interaction also seems to be associated with higher aromaticity in other five-membered heterocycles in agreement with experimental observation. For example, 1*H*-1,2,4-triazole **199** (ASE = 8.01) is more stable than 4*H*-1,2,4-triazole **200** (ASE = 12.19) (**Figure 21**) <CHEC-II(4.02.1)128>. Similarly, in the gas-phase 2*H*-tetrazole **201** (ASE = 21.17) is more stable than 1*H*-tetrazole **202** (ASE 14.13) (**Figure 21**) <CHEC-III(6.07.4.4)

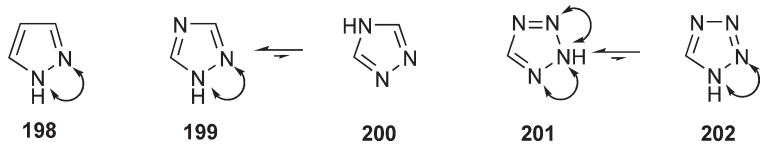


Figure 21 1,2-Interactions associated with increase of aromaticity indices in azoles.

292>. The relative aromaticities of isomers of oxygen and sulfur heterocycles can be predicted in a similar way, e.g., thiatriazoles <CHEC-III(6.09.2.1)443>. Of course, the most stable isomer of a pair, as measured by heat of formation, is not necessarily the most aromatic; in fact, imidazole ($\Delta H_f = 132.9\,kJ\,mol^{-1}$) is thermodynamically more stable than pyrazole ($H_f = 179.4\,kJ\,mol^{-1}$) <1999JPCA9336>. Nevertheless, the empirical rule that 1,2-nitrogen interactions are more favorable for aromaticity than 1,3-nitrogen interactions is a convenient guide to the relative stabilities of closely related azole isomers in the gas phase <2010T2695>.

2.4.4.2.3 Structural criteria

The HOMA index and Bird aromaticity indices (I_5 and I_A) for five-membered heterocyclic rings are shown in **Table 39**. The theoretical background to these indices is discussed in Section 2.2.4.2.3 and the derivation of the Bird unified aromaticity index (I_A) is given in Section 2.3.4.2.3.

The relative aromaticities defined by the HOMA and Bird indices are fairly consistent. Taking into account the positional effect discussed in the previous section, aza substitution tends to result in an increase in aromaticity. On the basis of structural (and magnetic criteria) pentazole is one of the most aromatic heterocycles. It is interesting to note that, on the basis of these structural criteria, 2*H*-1,2,3-triazole and 2*H*-tetrazole have comparable aromaticity and these are the polyaza azoles that have two 1,2-interactions of the type shown in **Figure 21** <2010T2695>. It has been suggested that delocalization of π-electrons increases when the ring atoms have the same electronegativity. Therefore, the all-nitrogen pentazole ring has a higher electron delocalization than the other azoles even though the electronegativity of nitrogen is higher than that of carbon <CHEC-III(6.18.2.8)748>.

Oxygen-containing heterocycles are always less aromatic than their sulfur and nitrogen counterparts, e.g., imidazole ~ thiazole >> oxazole and pyrazole > isothiazole > isoxazole. These trends follow those of pyrrole, thiophene and furan (Section 2.3.4.2). 1,2,3-Oxadiazole is unknown and all attempts to synthesize this compound have been unsuccessful. Although it is not the least aromatic of the oxadiazoles based on the HOMA index (cf. 1,3,4-oxadiazole), its instability can be attributed to easy isomerization to the acyclic valence tautomer (i.e., **85** → **86**).

Aromaticity indices have been derived for 19 mesoionic rings of which eight are shown in **Figure 22** <1985T1409>. The aromaticity of the sydnone ring ($I_5 = 42$) is low but not exceptionally low when compared to other oxadiazoles (**Table 39**). As for other heterocycles, type A mesoionic rings with a ring oxygen atom have appreciably lower aromaticities than their nitrogen and sulfur analogues. A pyrrole-type nitrogen atom adjacent to the carbon atom bearing the exocyclic oxygen or sulfur appears to be particularly favorable. This is consistent with known

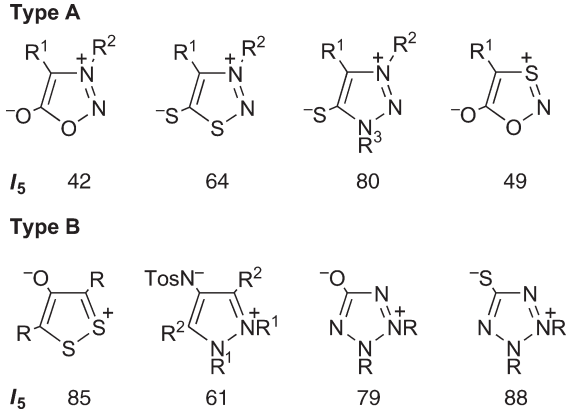
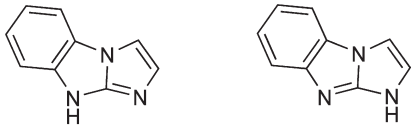


Figure 22 Bird aromaticity indices (I_5) for mesoionic rings.

interconversions of type A mesoionic isomers <1976AHC(19)1>. Overall, the type B mesoionic systems appear to have greater aromatic character than the type A systems.

Bird structural indices have been described for a number of bicyclic heterocycles <1987T4725>. The influence of benzoannulation on the aromaticity of azoles is not unambiguous. Thus, benzimidazole according to energy indices is more stable than imidazole (**Table 38**). On the other hand, transition from pyrazole to indazole is accompanied by a fall in stability. As a result, the extent of π-electron delocalization of benzimidazole and indazole is comparable. The further transition from the benzo derivatives to their naphtho analogues decreases aromaticity, with angular isomers being more stable than linear ones, e.g., benzimidazole (REPE = 0.050) > 1*H*-naphtho[1,2-*d*]imidazole (REPE 0.048) > naphtho[2,3-*d*]imidazole (REPE = 0.046), where REPE is the resonance energy per electron <1975T295, 1985KGS867>. This tendency agrees with a similar well-known sequence among arenes. The aromaticity of polynuclear bridgehead hetero systems, exemplified by the isomeric imidazo[1,2-*a*]benzimidazoles **203** (REPE = 0.046) and **204** (REPE = 0.039), is also lower than in the case of their benzo analogues.



203 **204**

2.4.4.2.4 Magnetic criteria

Magnetic criteria have received wide application mainly as a qualitative test for aromaticity and antiaromaticity. The values of the exaltation of diamagnetic susceptibility (in $10^{-6}\Lambda\,cm^{-3}\,mol^{-1}$), and therefore aromaticity, decrease in the sequence: thiazole (17.0) > pyrazole (15.5) > sydnone (14.1). The relative aromaticity of heterocycles with a similar type of heteroatom can be judged from values of the chemical shifts of ring protons. The latter reveals paramagnetic shifts when π-electron delocalization is weakened. For example, in the series of isomeric naphthoimidazoles aromaticity decreases in the sequence: naphtho[1,2-*d*]imidazole (δ 7.7–8.7) > naphtho[2,3-*d*]imidazole (δ 7.5–8.2)> perimidine (δ 6.1–7.2). This sequence agrees with other estimates, in particular with energetic criteria.

A recent theory-based innovation for evaluating aromaticity is the NICS value, which is the negative of the absolute magnetic shielding of a system. NICS values for five-membered rings with more than one heteroatom are discussed and tabulated in Section 2.4.2.2.2 (**Table 4**). For these heterocycles there appears to be a broad general agreement between the NICS index and other indices of aromaticity but there is poor agreement in the fine detail. **Figure 23** shows a plot of the linear relationship between the NICS(1) and HOMA values for the 23 rings common to **Tables 4** and **39**. Although these

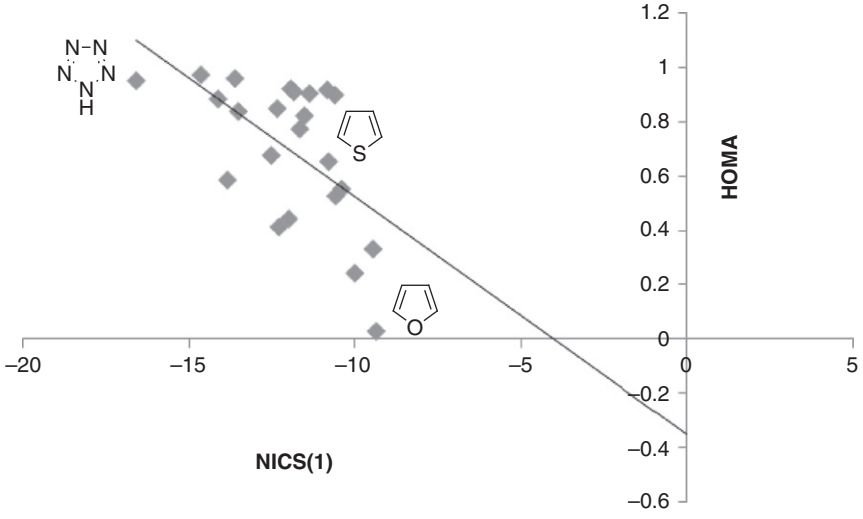
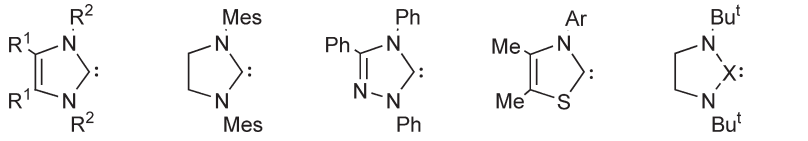


Figure 23 Relationship between NICS(1) and HOMA for 23 rings common to Tables 4 and 39.

two indices agree that furan has low aromaticity, pentazole has high aromaticity, and thiophene is intermediate, the overall correlation between the two indices is poor. For the set shown in **Figure 23**, the correlation coefficient is −0.585, which is comparable to the value of −0.516 for a similar set of 27 compounds <2002JOC1333>. These, and other correlations between aromaticity indices, support the view <2002JOC1333> that they are not necessarily measuring a uniquely defined property and that aromaticity is statistically multidimentional <2010T2695> (see also Section 2.4.4.2.1).

2.4.4.2.5 N-Heterocyclic carbenes (NHCs)

The nitrogen heteroatoms in imidazole and some closely related heterocycles can stabilize a carbene center at the 2-position. Thus, 1,3-disubstituted imidazol-2-ylidenes **205**, 1,3-dimesitylimidazolin-2-ylidene **206**, 1,3,4-triphenyl-1*H*-1,2,4-triazol-5-ylidene **207**, the thiazol-2-ylidene **208** (Ar = 2,6-di$Pr^i$$C_6H_3$) and the silylene and germylene analogues **209** are stable solids (in the absence of oxygen and moisture) with definite melting points, which can be recrystallized from appropriate hydrocarbon solvents. The exception is carbene **205a** which is an unstable liquid; however, it is stable in solution <1999ACR913, 2000CRV39>. Stable 'abnormal' NHCs having a carbene centre adjacent to only one imidazole nitrogen have subsequently been reported <2009SCI(326)556>.



205 **206** **207** **208** **209** X = Si, Ge

In structure **205**,
(a) R^1 = H, R^2 = Me,
(b) R^1 = H, R^2 = Bu^t,
(c) R^1 = H, R^2 = Mes,
(d) R^1 = H, R^2 = 1-adamantyl,
(e) R^1 = H, R^2 = 4-MeC_6H_4,
(f) R^1 = H, R^2 = 4-ClC_6H_4,
(g) R^1 = Me, R^2 = Me,
(h) R^1 = Me, R^2 = Pr^i.

Many crystallographic structures of these carbenes have been solved, indicating: (1) they are true carbenes with electron density expected for a singlet carbene; (2) they have small N–C–N angles at the carbene center (101–102°) in comparison with typical values (108.5–109.7°) for the corresponding angle in imidazolium salts <2003AGE5243>; and (3) the π-delocalization in carbenes is diminished relative to imidazolium cations. The last conclusion is supported by the upfield shift of the imidazole ring protons in carbenes **205a-f** (~7.9 → 6.9 ppm). Other NMR chemical shifts are given in **Table 40**. The position of the ^{13}C shift of C(2) (δ = 210–245) is diagnostic of a carbene carbon since few other ^{13}C signals appear in this range.

Table 40 Heterocyclic carbenes: selected NMR chemical shifts (ppm)

	Nucleus				
Carbene	*$^{13}C(2)$*	*$^{13}C(4/5)$*	*$^{1}H(4/5)$*	*$^{15}N(1/3)$*	*$^{14}N(1/3)$*
205a	215.2	120.5	6.92	−197.3	−197.5
205c	219.7	121.3	7.04 (6.48[a])	−178.9	−180
205d	211.4[a]	113.9[a]	7.02 (6.91[a])	−160.5[a]	−161[a]
205e	215.8	118.8	7.64 (6.96[a])	–	−171
205f	216.3	119.2	7.76 (6.68[a])	–	−174
205g	213.7	123.1	–	−198.5	−198
206	244.5	51.36	3.71	−236.7	−234
207	214.6[a,b]	152.2[a,c]	–	–	–

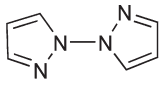
In THF-d_8-solution. References are tetramethylsilane or $NH_4^+NO_3^-$.
[a]In benzene-d_6 solution.
[b]For atom C(5).
[c]For atom C(3).

The aromaticity of the imidazol-2-ylidenes **205** has been investigated. Although cyclic delocalization is not the main stabilizing effect in these carbenes, it is believed to contribute 25 kcal mol^{-1} stabilization relative to the corresponding saturated carbenes, e.g., **206**. In a theoretical investigation, thermodynamic, magnetic, and structural properties all suggest the presence of a ring current although it is significantly smaller than that in the imidazolium cation or benzene <1996JA2023>.

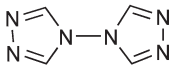
More important for carbene stability is the π-donating σ-attracting character of the pyrrole-type nitrogens at positions 1 and 3. In the π-framework, electron donation into the carbene out-of-plane p-orbital by the electron-rich nitrogen moderates the typical electrophilic reactivity of carbenes. In the σ-framework, additional stability for the carbene electron pair may be gained from the σ-electron-withdrawal effects on the carbene center by the more electronegative nitrogens, which moderates the carbene nucleophilic reactivity. The combination of these σ- and π-effects serves to increase the singlet-triplet gap and stabilize the singlet carbene over the more reactive triplet state. These electronic effects explain why aminocarbenes without cyclic π-conjugation, e.g., **206**, can also be isolated. For carbenes with bulky substituents (*tert*-butyl, 1-adamantyl, etc.) steric effects provide additional stabilization, but steric effects are not essential for stability, e.g., **205g**.

2.4.4.3 Conformations of Heteroaryl Derivatives

The conformations of N,N-linked biazoles have been calculated by the MNDO method. The energy minimum for 1,1′-bipyrazole **210** has a dihedral angle of 108° with the N-atoms being in opposing positions. The triazole rings in 1,1′- and 2,2′-bi-1,2,3-triazole, and 4,4-bi-1,2,4-triazole **211**, are also calculated to be approximately orthogonal <1984CJC687>.



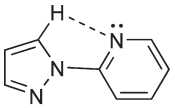
210



211

In some N,C-linked biheteroaryls, e.g., **212–214**, the two rings are virtually coplanar. The conformation in such molecules is controlled by weak hydrogen bonding between an acidic α-hydrogen of one ring and the lone pair of a pyridine-type nitrogen in another ring. Similar stabilization of conformation by hydrogen-bonded five- and six-membered rings is also found in pyrazolylquinolines, e.g., **215** and **216** <1989JHC733>.

Tris(3,5-dimethylpyrazol-1-yl)methane **217** exists as two isolable conformational isomers that can be interconverted by melting, crystallization or sublimation <1995H175>.



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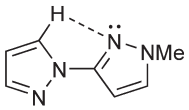

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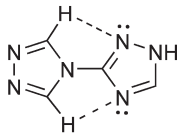

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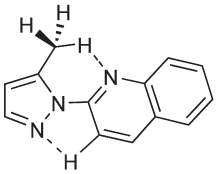

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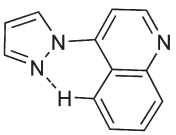

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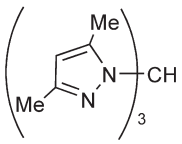
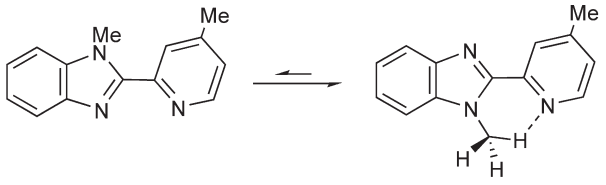


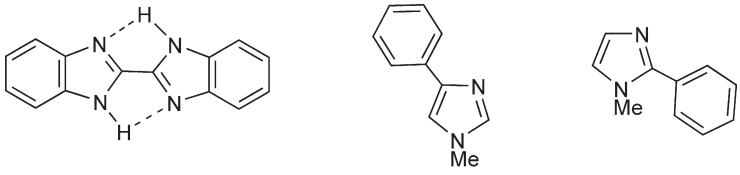
217

In CC-linked biheteroaryls extensive electron delocalization, in addition to hydrogen bonding, can help to favor planar conformations. The planar rotamers **218** and **219** are favored by conjugation, and X-ray crystallography has demonstrated the existence of a hydrogen bond between a benzimidazole methyl proton and the picoline nitrogen <2003JHC129>. Studies of absorption and fluorescence spectra of 2,2′-bis(benzimidazole) **220** demonstrate that its planar conformation in solution is determined by intramolecular hydrogen bonding and considerable conjugation between the rings <1989CJC1200>.

In C-arylazoles the dihedral angle between rings is usually less than in biaryls. According to X-ray measurements the angle between the rings in 1-methyl-4-phenylimidazole **221** is 7.3°. However, steric hindrance can increase this angle considerably, e.g., 32.3° in 1-methyl-2-phenylimidazole **222** <1994JHC899>.



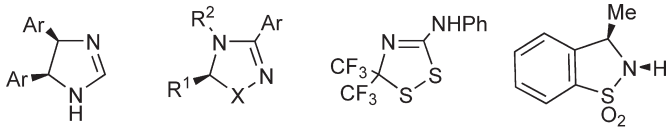
218 219



220 221 222

2.4.4.4 Conformations of Partially- and Fully-Reduced Rings

Depending upon the position of the double bond and the heteroatoms present, partially-reduced five-membered heterocycles are either planar or adopt an envelope conformation with one atom out of the plane of the other four. The imidazoline rings **223** have a symmetrical planar structure <2002JME3356, CHEC-III(4.02.4.2.3)175> whereas the 1,2,4-oxadiazolines **224** (X = O) and the 1,2,4-thiadiazolines **224** (X = S) have envelope conformations with O(1) and C(5) above the plane, respectively <1999AXC650, 1986JCM156>. The 1,2,4-dithiazoline ring **225** deviates only slightly from planarity <CHEC-II(4.13.3.1)456>. In the crystalline state, the 1,2-benzisothiazoline 1,1-dioxide **226** exists as an equimolar mixture of two conformers having the nitrogen atom 3 and 51 pm above the plane of the ring <CHEC-II(3.05.4.4)336>.



223 224 225 226

Fully-saturated five-membered heterocycles usually adopt an envelope conformation **227** but twist conformations **228** are sometimes encountered. **Table 41** gives examples of the conformations of a variety of derivatives. Although envelope conformations **227** are the most common, the energy difference between alternative conformations is often small and the physical environment, substituents and heteroatom sequence all influence the conformation. In solution there is probably rapid equilibration between several conformations.

Anomeric effects can also influence the preferred conformation and this is well documented for 1,2,4-trioxolanes (ozonides). For example, microwave spectroscopy studies show that 3-methoxy- and *cis*-3,5-difluoro-1,2,4-trioxolane adopt envelope conformations whereas the parent ring and the *trans*-3,5-difluoro derivative have twist conformations (**Table 41**) <CHEC-II(4.16.3.2)586>. In the *trans*-difluoro derivative **229** $n_O \rightarrow \sigma^*_{CF}$ hyperconjugation favors the twist conformation with lengthening of the C–F bonds and shortening of the C–O_{peroxy} bonds <1986JPC3092>. In the 3-methoxy derivative **230** the methoxy substituent has a short C–OMe bond and an unusual orientation over the ozonide ring. The preferred conformation of this ring is attributed to anomeric effects, including exo-anomeric $n_O \rightarrow \sigma^*_{CO}$ interactions **231** that determine the location of the methyl group <1988JA2081>.

1,2,3-Trioxolanes (molozonides) **232** are highly unstable species but because of their involvement in ozonolysis they have been the subject of many MO calculations. There is general agreement that the envelope conformation with O(2) out of plane is the most stable. For the 4-halo derivatives **232** (R = F, Cl) the *syn*-conformation is calculated to be the most stable ($\sim$2 kcal mol^{-1}) due to electrostatic repulsion and an anomeric effect <2002JPCA4745, CHEC-III(6.05.4.2)150>.

Table 41 Conformations of some fully-saturated five-membered heterocycles

227: envelope (4 atoms coplanar)

228: twist (3 atoms coplanar)

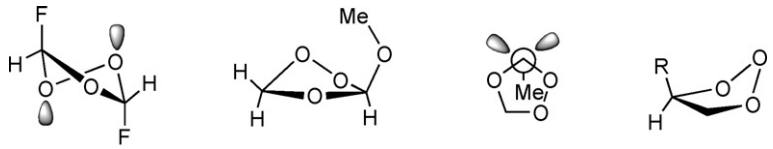
		Conformation		
Ring	*Derivative*	*Atom(s) out of plane*		*Reference*
		Envelope		
	(i) *cis*-2-(2′-cyanoethyl)-3-Ph-5-CN	N(2)		1984J(P1)47
	(ii) *trans*-2-methyl-3-phenyl-5-OEt[a]	O(1)		1982JOC4397
	Dehydromethionine	Envelope C(3)		CHEC-II(3.05.4.4)336
	4-(*N*-Boc)amino-4-carboxylic acid methyl ester	Envelope C(3)		2002BML147
	2-(4-pyridinyl)-1,3-dihydroxy-4,4,5,5-tetramethyl		Twist C(4),C(5)	1997T16911
	2-*tert*-butyl	Envelope C(4) or C(5)		1974JA1465[b]
	(4*R*,5*R*)-4,5-bis(methylcarbamoyl)	Envelope C(2)		1996T8275
	cholestan-4-one-3-spiro(2,5-oxathiolane)	Envelope C(5)		1968JOC3535
	2,2-octahydroisoquinoline	Envelope C(4)		1983JOC227
	3,4-bis(1′-methoxycarbonyl-1′-methylpropyl)[a]		Twist N(3),N(4)	2000AGE2938
	4,4,5,5-tetrafluoro	Envelope S(1)[c]		1993JPC9625
	2-adamantyl-3,3,5,5-tetratrifluoromethyl	Envelope N(2)		1998EJO459
	3,3,4,5-tetraphenyl	Envelope O(1)		1995J(P1)41
	unsubstituted	Envelope O(2)		1988JA7991
	*trans*-4,5-di-cyclohexyl *S*-oxide	Envelope C(4)		1995AXC129
		Envelope		
	(i) 3-methoxy	O(1)		1988JA2081
	(ii) *cis*-3,5-difluoro	O(4)		1984JPC2025
			Twist	
	(iii) unsubstituted		O(1),O(2)	1971JA6337
	(iv) *trans*-3,5-difluoro		O(1),O(2)	1986JPC3092

(Continued)

Table 41 (Continued)

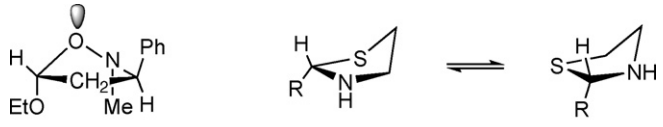
Ring	Derivative	Conformation: Atom(s) out of plane		Reference
	tricyclo[5.2.1.0^{2,6}]decane	Envelope S(2)		1986AXC332
	unsubstituted		Twist S(1),S(2)	1984JA841

[a]In solution.
[b]See also <2001TA711>.
[c]In the gas phase, but S(1) or N(2) alternately in the crystal phase.



229 **230** **231** **232**

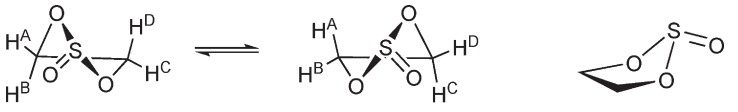
Isoxazolidines are often encountered as 1,3-dipolar cycloadducts of nitrones. In the crystal, the *cis*-2-(2′-cyanoethyl)-3-phenyl-5-cyano derivative has an envelope conformation with N(2) out of the plane <1984J(P1)47>. In solution, the *trans*-2-methyl-3-phenyl-5-ethoxy derivative **233** has been assigned an envelope conformation with O(1) out of the plane. Although conformation **233** has unfavorable 2,5-dipseudoaxial steric interactions, this destabilization is probably offset by the anomeric effect between a lone pair on the ring oxygen and the pseudoaxial ethoxy substituent, which is estimated to be worth about 1.2–1.5 kcal mo1^{-1}. The ethoxy substituent probably also imparts additional stabilization through an exo-anomeric effect <1982JOC4397>. Conformation **233** also minimizes unfavorable O lone pair/N lone pair interactions (the gauche effect) relative to the alternative conformation with the nitrogen lone pair pseudoaxial.



233 **234** **235**

On the basis of a study of coupling constants in the NMR spectra ($CDCl_3$) of 1,3-thiazolidine and 2-*tert*-butyl-1,3-thiazolidine, it was concluded that 2-substituted derivatives exist as the equilibrating envelopes **234** and **235** in which the 2-substituent is *anti* to the 'flap atom' <1974JA1465>.

The ^{1}H NMR spectrum of 1,3,2-dioxathiolane 2-oxide (ethylene sulfite) in CCl_4 shows only two signals at δ 4.45 and 4.81. This is due to the molecule undergoing rapid pseudorotation between the twist conformations **236** and **237** with the result that the *cis* vicinal ring protons (H^B, H^C) and the *trans* vicinal ring protons (H^A, H^D) each become magnetically equivalent <CHEC-II(4.15.3.3.1)552>. In the solid state the IR spectrum of ethylene sulfite suggests that it adopts a symmetrical S(2) envelope conformation **238**. However, electron diffraction studies in the gas phase suggest that it is almost planar although the 4,5-dimethyl derivative is definitely nonplanar. For derivatives the most common conformation found in the crystal state is reported to be the O(1) envelope <2006IZV1095, CHEC-III (6.05.4.2)151>. Overall, the experimental studies suggest that 1,3,2-dioxathiolane 2-oxides are conformationally mobile and the conformation adopted is dependent on the physical state of the sample and the level and nature of substitution <CHEC-II(4.15.4.2)557>.



236 237 238

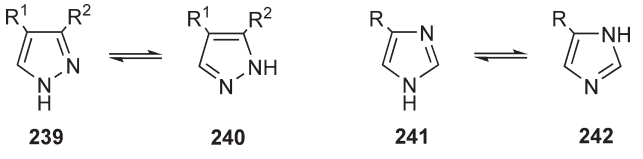
2.4.5 Tautomerism

2.4.5.1 Prototropic Tautomerism of Rings

2.4.5.1.1 Annular tautomerism

2.4.5.1.1.1 Introduction. Annular tautomers are prototropic tautomers in which the migrating proton is restricted to ring atoms, which for azoles are usually nitrogen atoms, e.g., **239** ⇄ **240** and **241** ⇄ **242**. For unsubstituted pyrazole **239** ($R^1 = R^2 = H$) and imidazole **241** (R = H) the two tautomers are identical, but this does not apply to substituted derivatives. For triazoles and tetrazoles the unsubstituted rings can occur as two distinct tautomers. However, interconversion occurs readily and such tautomers cannot usually be separated. In rare examples where prototropic tautomers can be separated as discrete crystal forms they are referred to as desmotropes, e.g., isomers **147** and **148** (Section 2.4.3.4). Further examples of desmotropes are 3-methyl-4-nitropyrazole **239** ($R^1 = NO_2$, $R^2 = Me$) and 5-methyl-4-nitropyrazole **240** ($R^1 = NO_2$, $R^2 = Me$) <1994CC1143>.

Sometimes one tautomeric form predominates; for indazole the aromaticity of the benzenoid ring is greater in tautomer **243** than in **244**, and UV spectral comparisons show that indazole exists predominantly as tautomer **243**.



239 240 241 242

243 244

Table 42 gives an overview of annular tautomerism data for azoles in the gas phase and in solution or crystals. In the gas phase the stability of alternative tautomers largely depends on their relative aromaticities. In Section 2.4.4.2.2 it was noted that 1,2-relationships between pyrrole- and pyridine-type nitrogen atoms favor aromaticity (**Figure 21**) and this is consistent with the relative stabilities of triazole and tetrazole tautomers in the gas phase (**Table 42**) <2010T2695>. In solution (and crystals) other factors such as solvent polarity, hydrogen bonding, and temperature become important and the relative stabilities can be reversed. Polar solvents tend to stabilize the tautomer with the largest dipole moment and this probably accounts for the observation of both 2*H*-1,2,3-triazole (μ = 0.12 D) and 1*H*-1,2,3-triazole (μ = 4.55 D) in

Table 42 Annular tautomerism of azoles

Azole	*Gas phase*	*Solution or crystal*
Pyrazole	Equivalent	Equivalent
Imidazole	Equivalent	Equivalent
1,2,3-Triazole	2*H*-1,2,3 > 1*H*-1,2,3	Both (ratio depends on solvent)
1,2,4-Triazole	1*H*-1,2,4 > 4*H*-1,2,4	1*H*-1,2,4 > 4*H*-1,2,4
Tetrazole	2*H*-1,2,3,4 > 1*H*-1,2,3,4	1*H*-1,2,3,4 > 2*H*-1,2,3,4
Indazole	1*H*- > 2*H*-	1*H*- > 2*H*-
Benzotriazole	1*H*- > 2*H*–	1*H*- only

solution and the predominance of 1*H*-tetrazoles (μ = 5.34 D) in solutions and crystals. For calculated dipole moments of azole tautomers, see **Table 3** (Section 2.4.2.2.1). More detailed information on the tautomerism of key azole systems is given in the following sections and in two reviews <1976AHC(S1)296, 2000AHC(76)159>.

2.4.5.1.1.2 Pyrazoles. The annular tautomerism of pyrazoles has been thoroughly studied both experimentally <2000AHC(76)157> and theoretically <2001AHC(81)1>. A systematic study of annular tautomerism of NH-pyrazoles in the solid state has been published <1988CJC1141>.

^{13}C CPMAS NMR studies of NH-pyrazoles and indazoles <1993CJC678> concluded that: (1) the tautomer present in the solid is also the major tautomer in solution; (2) certain pyrazole C-substituents (CF_3, Br, Ar, Het) prefer position 3 (i.e., they are 3-substituted pyrazoles **239**) whereas others (Bu^t, Pr^i, CH_3) prefer position 5 (i.e., they are 5-substituted pyrazoles **240**); (3) 3(5)-ferrocenylpyrazole should be a 50:50 mixture of both tautomers in the solid state. Low-temperature ^{13}C NMR spectroscopy of 3(5)-phenylpyrazole shows that at −20 °C it exists as a mixture of 80% of the 3-phenyl tautomer **239** (R^1 = H, R^2 = Ph) and 20% of the 5-phenyl tautomer **240** (R^1 = H, R^2 = Ph) <1991G477>.

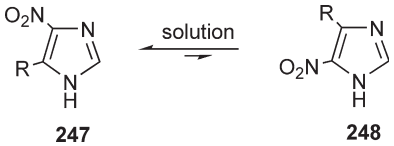
3,5-Dimethylpyrazole shows prototropic tautomerism in the solid state (crystallography and CPMAS NMR) <1985JA5290>, as do other NH-pyrazoles, e.g., 3,5-diphenyl- and 3,5-diphenyl-4-bromopyrazole <1992JA9657>. A theoretical study (INDO, STO-3G) concluded that 1,2-proton shifts are forbidden, and that annular tautomerism of pyrazoles (including the gas phase) always implies other entities (water, alcohols, formic acid, other pyrazole molecules, etc.) <1986BSF429>. ^{15}N CPMAS NMR, ^{14}N quadrupole double resonance, and X-ray studies of solid 3,5-dimethylpyrazole between 270 and 350 K are consistent with a coordinated triple hydrogen jump in a trimer like **175** (activation energy 11 kcal mol^{-1}) <1989JA7304>.

In the case of 3(5),4-polymethylenepyrazoles <1991JHC647>, the 3,4-trimethylene tautomer **246** is more stable than the 4,5 tautomer **245** (ΔG = 1.3 kcal mol^{-1}) <1994NJC269>. The preference for structure **246** has been attributed to the Mills–Nixon effect.

245 **246**

In the gas-phase 1*H*-indazole **243** is 4.7 kcal mol^{-1} more stable than 2*H*-indazole **244**, whereas in water the difference is reduced to 2.2 kcal mol^{-1}. Thus water more effectively stabilizes the 2*H*-tautomer presumably because of its higher dipole moment <1988JA4105, 1994JPC10606>. 1*H*-Indazole **243** is also more stable in the excited state (S_1) <1994JPC10606> although the difference in energy is lower in the excited (1.6 kcal mol^{-1}) than in the ground state.

2.4.5.1.1.3 Imidazoles. 4- and/or 5-Substituted imidazoles are classic examples of prototropic annular tautomerism. Depending upon the nature of the substituents, one tautomer often predominates. Because 1-substituted 5-nitroimidazoles are important antibacterial agents, 4(5)-nitroimidazoles (**247** ⇄ **248**) have been studied in some detail. The 4-nitro tautomers **247** usually predominate in solution. Although 5-nitroimidazole **248** (R = H) is calculated to be slightly more stable than 4-nitroimidazole **247** (R = H), the larger dipole moment of the 4-nitro isomer (μ_{calc} = 7.79 D vs. 4.15 D) probably leads to greater solvation <1992J(P1)2779>. Other electron-withdrawing substituents (e.g., CF_3) also favor the 3-position in solution <CHEC-III(4.02.4.3)176>. In an unusual case, 4(5)-methoxy-5(4)-nitroimidazole was found to be a 1:1 mixture of the tautomers **247** and **248** (R = OMe) in the crystalline state <2004AXB191>.



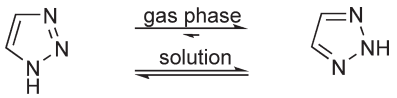
247 **248**

Crystalline 2-methylimidazole exhibits different ^{13}C (CPMAS) chemical shifts for C(4) and C(5) (125.0, 115.7 ppm). The average (120.3 ppm) is close to that reported for imidazole in deuterated DMSO (121.2 ppm). These results imply that solid-state chemical shifts can be used instead of *N*-methyl models in tautomerism studies <1987H(26)333>. For

imidazole the solid-state ^{13}C shifts are 137.6 C(2), 129.3 C(4), and 119.7 C(5) <1981JA6011>. No proton exchange occurs in the solid, and the data support a structure resembling the crystal structure. Cooling imidazole solutions has not yet allowed the detection of individual tautomers, but by symmetry the compound must exist with equal proportions of the two tautomeric forms, as does pyrazole <1981CC1207>.

The two signal ^{15}N NMR spectrum of solid imidazole indicates that tautomerism is slow in the solid state. The average (−186 ppm) is the same as the shift observed in solution. As the solution pH decreases the ^{15}N signal moves progressively upfield until both nitrogens are protonated <1982JA1192>.

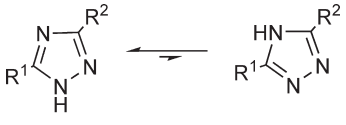
2.4.5.1.1.4 1,2,3-Triazoles. Tautomerism in 1,2,3-triazole has been extensively investigated using various spectroscopic methods. Microwave and photoelectron spectroscopic studies conclude that in the gas phase the 2*H*-tautomer **250** strongly dominates <1981ZNA34, 1981ZNA1246>. In solution, both the 2*H*- and the 1*H*-tautomers **249** and **250** are present with their relative proportion depending upon temperature, solvent, and concentration <1984J(P2)1025>. 1*H*-1,2,3-Triazole is more stable (66%) in $CDCl_3$, but in DMSO-d_6 the 2*H*-1,2,3-triazole is favored (55%) <1982JOC5132>. In aqueous solution, however, the 2*H*-tautomer is favored over the 1*H*-tautomer by a factor of about 2 based on arguments from basicity and partitioning <1989J(P2)1903>.



249 **250**

The tautomeric equilibrium of unsubstituted benzotriazole has been studied extensively and the results summarized in reviews <1963AHC(2)27, 1976AHCS295>. In the crystalline state the sole existence of 1*H*-benzotriazole is demonstrated by X-ray <1974AXB1490>, ^{13}C NMR <1983H(20)1713>, and microwave spectroscopy <1993JSP(161)136>. The 1*H*-form also predominates strongly under most other conditions. However, measurements of gas-phase UV spectra of benzotriazole and its 1-methyl- and 2-methyl derivatives have shown that the percentage of 2*H*-tautomer is 45% at 30 °C, 35% at 50 °C, and 25% at 80 °C <1993JOC5276>.

2.4.5.1.1.5 1,2,4-Triazoles. Theoretical studies on a number of derivatives agree that the 1*H*-structure **251** for 1,2,4-triazoles is more stable than the 4*H*-structure **252**. The tautomer **251** ($R^1 = R^2 = CH_2OMe$) was calculated to be more stable than tautomer **252** ($R^1 = R^2 = CH_2OMe$) by 4.32 kcal mol^{-1} <2001JHC1387>. In spite of tautomers **252** ($R^1 = R^2 = H$) having a much larger dipole moment (**Table 3**), the 1*H*-tautomers **251** also dominate solution chemistry <CHEC-III(5.02.1)160>.

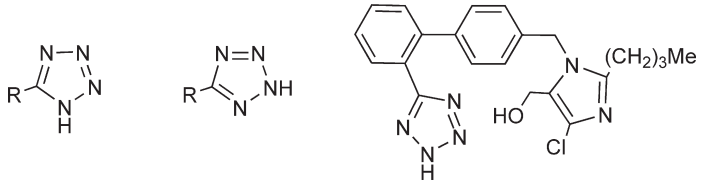


251 **252**

2.4.5.1.1.6 Tetrazoles. According to photoelectron and microwave spectroscopy, and some other experimental methods, the 2-tautomer **254** prevails in the gas phase <1994RCR797, CHEC-II(4)621, 2000AHC(76)157, 2006RJO1585>. However, some studies indicate the presence of both the 1*H*- and 2*H*-forms of 5-substituted tetrazoles **253** (R = H, CH_3, CD_3, CF_3, NH_2) in the gas phase <1994RCR797, 2000AHC(76)157>. A more recent UV-photoelectron spectroscopy investigation <2003SAA1725> confirmed that tetrazole in the gas phase exists predominantly as the 2*H*-tautomer **254** (R = H). Similar results have been obtained with unsubstituted and 5-chlorotetrazoles isolated in an argon matrix at low temperature (8–12 K), where the experimental and calculated (BLYP/6-31G*) IR spectra were compared and excellent correlation between computed and experimentally determined intensities were only obtained for the 2*H*-tautomers **254** <1996LA1041, CHEC-III(6.07.4.4)291>. An enthalpy difference of $\Delta H = 1.9$ kcal mol^{-1} between the tautomers **253** and **254** for 5-chlorotetrazole (R = Cl) was estimated from the matrix experiment <2002PCP1725>. However, in the case of the parent tetrazole, although the 2*H*-tautomer **254** (R = H) is the major form, a minor contribution (10%) of the 1*H*-form **253** (R = H) is also present in low-temperature inert matrices <2001PCP3541>.

Experimental investigations of the annular tautomerism of tetrazoles in solution have been carried out using various procedures, but the most significant and reproducible results have been obtained using ^{13}C and ^{15}N NMR spectroscopy (see Section 2.4.3.4), and by the use of dipole moments <CHEC-II(4)621, 2006RJO1585>. Accordingly, the 1*H*-tautomer **253** prevails in various solvents. It has been noted, however, that for some 5-substituted tetrazoles the amount of 2*H*-tautomer **254** in solution can be significant and reach 15–20% <CHEC-II(4)621, 2006RJO1585>. An enhanced content of the 2*H*-form is possible in the following cases: (1) decrease in the dielectric permittivity of the medium; (2) increased electron-withdrawing properties of the substituent in position 5; and (3) steric effects of the substituent on carbon.

In the crystalline state 1*H*-tetrazole and many of its 5-substituted derivatives have been shown by X-ray diffraction analysis, vibration spectroscopy, and ^{13}C NMR spectroscopy to be individual 1*H*-tautomers **253** <CHEC-II(4)621, 2000AHC(76)157, 2005CRV3561, 2006RJO1585>. Some 5-substituted tetrazoles are capable of forming hybrid crystals containing both 1*H*- and 2*H*-tautomers. However, the acidic form of the angiotensin II antagonist losartan was found to crystallize as the 2*H*-tautomer **255** stabilized by intermolecular O–H---N and N–H---N hydrogen bonds <2004AXEo1830>. (For administration losartan is formulated as its potassium salt.) It is relevant to note that the closely related angiotensin II anatagonist irbesartan forms desmotropes **147** and **148** (Section 2.4.3.4).



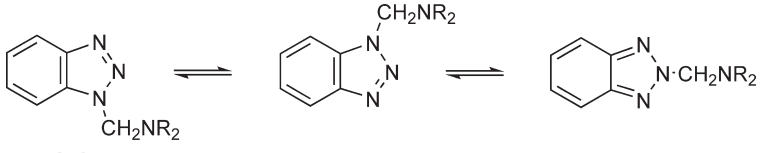
253 **254** **255**: losartan

2.4.5.1.2 Annular elementotropy

There are a number of examples of isomerisms involving reversible migrations of organic and inorganic groups that are analogous to those of protons. This is called elementotropy <2000AHC(76)159>. Annular elementotropy includes alkylotropy, acylotropy, silylotropy, and metallotropy.

At room temperature, solutions of 1-trimethylsilylbenzimidazole show an averaged ^{13}C NMR spectrum, but once the tautomerism is frozen the molecule loses its symmetry <1983H(20)1713>. Migrations of acyl, trimethylsilyl, trialkylstannyl, and 4-methoxybenzyl groups between the nitrogen atoms of 1,2,3-triazoles are also well known <1966CB2512, 1970TL5225, 1972JOM(44)117, 1982JCM292>.

N-Dialkylaminomethylbenzotriazoles usually exist in the crystalline state solely as the N(1) isomers, but in solution they form equilibrium mixtures of the N(1) (e.g., **256** and **257**) and N(2) (e.g., **258**) isomers <1975J(P1) 1181, 1987J(P1)2673>. The N(1) and N(2) isomers are of nearly equal stability in nonpolar solvents and in the gas phase (2:1 ratio on statistical grounds). Polar solvents favor the 1- and 3-substituted forms over the 2-substituted, and conversely substituents at positions four and seven favor the 2-substituted form. The interconversion of these N(1) and N(2) isomers proceeds intermolecularly, as demonstrated by crossover experiments, by a dissociation–recombination mechanism involving the formation of intermediate iminium cations and the benzotriazole anion.



256 **257** **258**

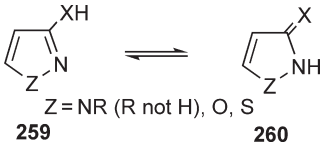
Under flash vacuum pyrolysis conditions 1- and 2-(1-adamantyl)indazoles, and also 1-, 2-, and 3-tritylindazoles, are mutually interconverted <1991BSF592, 1989BSB349>. Gas-phase thermal isomerizations of 1-methyl- to 2-methyltetrazoles have been reported <1990MI 417-04>.

2.4.5.2 Prototropic Tautomerism of OH, NH_2, and SH Substituents

2.4.5.2.1 Pyrazoles, isoxazoles, and isothiazoles

2.4.5.2.1.1 3-Substituted derivatives. 3-Substituted isoxazoles, pyrazoles, and isothiazoles of general type **259** can exist in the two tautomeric forms **259** or **260** (Z = NR, O, or S) (**Table 43**). With a few exceptions, amino and hydroxy derivatives exist as the tautomers **259** (X = NH, O) under most conditions. The stability of the OH forms of the 3-hydroxy-1,2-azoles is explained by the weakened basicity of the ring nitrogen atom at position 2, due to the adjacent heteroatom at position 1 and the oxygen substituent at position 3. This concentration of electron-withdrawing groups near the basic nitrogen atom disfavors the NH form **260** (X = O). The general situation is summarized in **Table 43**.

Table 43 Tautomerism of 3-substituted azoles with heteroatoms-1,2

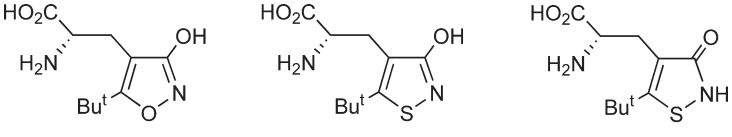


259 **260**

Substituent (XH)	*Ring*	*Phase(s)*	*Conclusions*
OH	Pyrazole	C_6H_{12}, $CHC1_3$, crystal	OH
		H_2O	OH/NH coexist in H_2O
	Isoxazole	C_6H_{12}, $CHC1_3$, H_2O, crystal	Mainly OH in all media
	Isothiazole	MeOH	OH (possibly NH in H_2O)[a]
		crystal	Sometimes NH[a]
NH_2	Pyrazole	MeOH, KBr	NH_2
	Isoxazole	$CHC1_3$, H_2O	NH_2
	Isothiazole	CCl_4	NH_2
SH	Isothiazole	CCl_4	SH

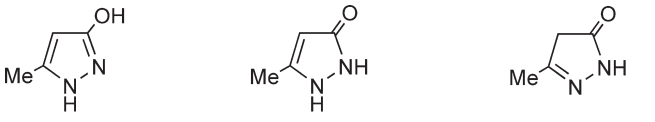
For further details and original references see <1970C134> and <1976AHC(S1)1>.
[a]<2002STC479>.

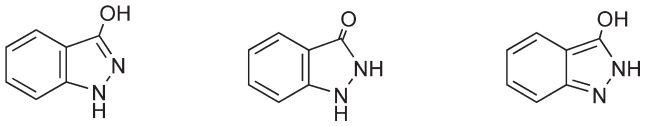
A crystal structure determination of (*S*)-ATPA **261**, which is a 3-hydroxyisoxazole and an agonist of the GluR5 (*S*)-glutamic acid receptor, showed it to have the hydroxy structure **261**. The more potent isothiazole analogue [(*S*)-thio-ATPA] was found to occur in the crystal as both the hydroxy tautomer **262** and the oxo tautomer **263** in the ratio 1:3 <2002STC479>. Associated high-level *ab initio* calculations (gas-phase and aqueous solvation) on the 4,5-dimethyl analogues predict that the hydroxy form of the isoxazole should predominate under all conditions but that the oxo form of the isothiazole may be favored in aqueous solution <2002STC479>.



261 **262** **263**

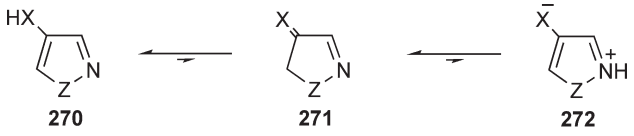
Tautomerism of 3-hydroxypyrazoles unsubstituted on nitrogen is more complex. A detailed investigation of 3-hydroxy-5-methylpyrazole disclosed that the major tautomers in aqueous solution (polar medium) are **264** and **265**, whereas in cyclohexane solution (nonpolar medium) the major tautomers are **264** and **266** <1976AHC(S1)346>.

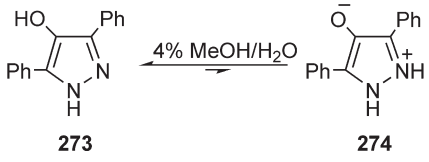




Indazolinone occurs in the oxo form **268** in the solid state but only as a minor tautomer (15%) in DMSO solution in which the 3-hydroxy-1*H*-indazole tautomer **267** predominates (85%) <1986J(P2)1677>. No evidence for the existence of 3-hydroxy-2*H*-indazole **269** has been found.

2.4.5.2.1.2 4-Substituted derivatives. The 4-substituted analogues can in principle exist as two uncharged tautomeric forms **270** and **271** and as the type B mesoionic tautomer **272**. All the evidence shows that these compounds exist predominantly as the NH_2, OH, or SH tautomers **270**. The equilibrium between the pyrazole **273** and the mesoionic tautomer **274** has been shown to favor the hydroxypyrazole **273** strongly (ΔG 6.15 kcal mol^{-1}) <1972T463>.





2.4.5.2.1.3 5-Substituted derivatives. For 5-substituted isoxazoles, pyrazoles, and isothiazoles, three tautomeric forms are possible: **275–277**. Some generalizations are recorded in **Table 44**. The amino derivatives always exist in the amino form **275** (X = NH). In the case of the hydroxy compounds, the hydroxy form is of little importance, except in special cases where a suitable substituent in the 4-position can form a hydrogen bond with the 5-hydroxy group. However, an IR study of 3-substituted(Ph,Me)-1-phenylpyrazol-5-ones suggests that aprotic solvents stabilize the oxo tautomers but protic solvents favor the hydroxy form <2006SPL1, CHEC-III(4.01.3.7)15, CHEC-III(4.01.4.2.2)19>. The relative occurrence of the 4*H*-oxo form **276** and 2*H*-oxo tautomer **277** depends on the substitution pattern and on the solvent. Tautomer **277** is considerably more polar than **276**, with a large contribution from the charge-separated resonance structure **277b**. Hence, it is not unexpected that the 2*H*-oxo tautomer **277** is favored by polar media. A substituent at the 4-position also tends to favor form **277** over **276** because of conjugation or hyperconjugation of the 4-substituent with the 3,4-double bond.

2.4.5.2.2 Imidazoles, oxazoles, and thiazoles

2.4.5.2.2.1 2-Substituted derivatives. The tautomerism of 2-substituted 1,3-azoles (**278** ⇄ **279**) is summarized in **Table 45**. Whereas amino compounds occur invariably as the primary amine **278** (X = NH), all the potential hydroxy

Table 44 Tautomerism of 5-substituted azoles with heteroatoms-1,2

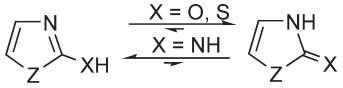
Z = NR (R not H), O, S

275 **276** **277a** **277b**

Substituent (XH)	*Ring*	*Phase(s)*	*Conclusions*
OH	Pyrazole	C_6H_{12}, $CHCl_3$, EtOH, H_2O, crystal	CH in nonpolar; NH in polar media
	Isoxazole	C_6H_{12}, $CHCl_3$, EtOH, H_2O, crystal	Increasing NH in polar media; NH favored by 4-substituent
NH_2	Pyrazole	CCl_4	NH_2
	Isoxazole	$CHCl_3$, H_2O	NH_2
	Isothiazole	$CC1_4$	NH_2
SH	Isoxazole	C_6H_{12}, CCl_4, MeOH, crystal	SH

For further details and original references see <1970C134> and <1976AHC(Sl)l>.

Table 45 Tautomerism of 2-substituted azoles with heteroatoms-1,3



Z = NR (R not H), O, S

278 **279**

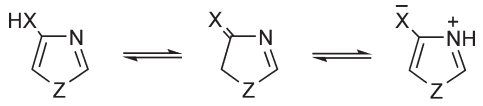
Substituent	*Ring*	*Phase(s)*	*Conclusions*
OH	Imidazole	KBr disc	NH, C=O
	Oxazole	MeOH, CCl_4	NH, C=O
	Thiazole	Alcohol, CS_2	NH, C=O
NH_2	Imidazole	0.1N aq.KCl, EtOH/aq. KCl	NH_2
	Oxazole	MeOH	NH_2
	Thiazole	EtOH, $CDCl_3$	NH_2
SH	Imidazole	Liquid film, MeOH, EtOH	NH, C=S
	Oxazole	CCl_4, MeOH	NH, C=S
	Thiazole	CCl_4, EtOH	NH, C=S

For further details and original references see <1970C134> and <1976AHC(S1)1>.

derivatives exist in the oxo form **279** (X = O), and in this series the sulfur compounds resemble their oxygen analogues. There is a close analogy between the tautomerism for all these derivatives with the corresponding 2-substituted pyridines.

For 2-aminoazoles the tautomeric equilibrium can be expected to shift towards the imino form when electron-withdrawing substituents (e.g., acyl groups) are attached to the exocyclic nitrogen <1966ZOR917, 1987KGS113>. The tautomeric constants for the amine–imine equilibrium have been determined by measuring pK_a values <1966ZOR917, 1997KGS807, 1982J(P2)535>. The effect of the solvent and/or additives can be important. In fact, the tautomeric equilibrium in 2-aminothiazoles in toluene or carbon tetrachloride is shifted toward the imino form by adding small amounts of tetrabutylammonium bromide <1992JHC1461> or dimethyl sulfoxide <1994J(P2)615>.

2.4.5.2.2.2 4- and 5-Substituted derivatives. 4-Substituted 1,3-azoles can exist in two noncharged tautomeric forms **280** and **281** together with a type A mesoionic form **282**.



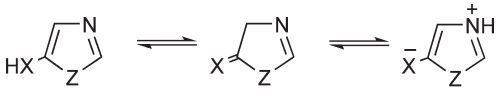
280 **281** **282**

Similarly, 5-substituted 1,3-azoles can also exist in two noncharged forms **283** and **284** together with a type A mesoionic form **285**. Some results are summarized in **Table 46**. For the potential hydroxy forms, the nonaromatic tautomers of types **281** and **284** clearly can be of importance. Evidence that the oxazolones **281** (Z = X = O) are in equilibrium with the mesoionic tautomers **282** has been presented <1979JOC626>.

Table 46 Tautomerism of 4- and 5-substituted azoles with heteroatoms-1,3

Substituent	*Ring*	*Phase(s)*	*Conclusions*
4-OH	Oxazole	EtOH, crystal, Me_2SO	C=O
4-OH	Thiazole	Me_2SO, Me_2CO	OH and C=O
5-OH	Oxazole	Crystal	C=O
		Me_2SO, DMF	C=O + NH
5-NH_2	Oxazole	$CHCl_3$, crystal	NH_2

For further details and original references, see <1970C134> and <1976AHC(S1)1>.



283 **284** **285**

286 **287**

Huisgen and coworkers examined the solvent dependence of the equilibrium between the azlactone **286** and the mesoionic tautomer **287**. The following estimates of the equilibrium concentration of the mesoionic tautomer **287** were obtained: DMF (49%), DMSO (32%), acetone (0.26%), and chloroform (0.007%) <1970JA4340>. Both tautomers (**286** and **287**) have been isolated and characterized <1976CB2648>. The equilibrium (**284** ⇄ **285**) accounts for the participation of azlactones (e.g., **286**) in 1,3-dipolar cycloadditions with alkenes and alkynes.

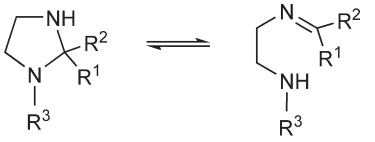
2.4.5.3 Ring-Chain Tautomerism

In the examples of prototropic tautomerism discussed in Sections 2.4.5.1 and 2.4.5.2, proton transfer occurs without cleavage of the heterocyclic ring. When proton transfer is associated with ring cleavage or ring formation the process is referred to as ring-chain tautomerism. This type of equilibration is often associated with long-chain aldehydes or imines with suitably located OH or NH groups.

Oxazolidines **288** are subject to ring-chain tautomerism. The process can be considered as a reversible intramolecular nucleophilic addition to the C=N bond. A variety of substituted oxazolidines exist in the open-chain form **289** in the solid state <1985T5919, 1992T4979>. In solution, the two forms are in equilibrium, the position of which depends on the solvent and the substituents.

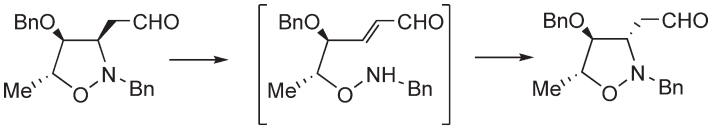
288 **289**

In the case of imidazolidines **290** (and 1,3-thiazolidines) the system usually prefers the ring form **290**, probably because of the higher nucleophilicity of an NHR^3 (or SH) group in **291** in comparison with OH groups. However, the position of the equilibrium can be significantly influenced by the solvent and the substituents R^1–R^3. 1-Phenylimidazolidines **290** (R^3 = Ph) are preferred in $CDCl_3$ solution whereas the corresponding ring-open forms **291** (R^3 = Ph) are preferred in DMSO-d_6 <1998T13639>. The electronic character of substituents on the aryl groups also influences the equilibrium <1999H(51)2431, CHEC-III(4.02.4.3.3)180>. For primary amines **291** (R^3 = H) in solution, the cyclic form is preferred when R^1 = H and R^2 = alkyl, whereas the linear form is preferred when R^1 = H and R^2 = phenyl <1998OPP109, CHEC-III(4.02.4.3.3)180>.



290 **291**

For some ring systems, open-chain isomers are not detectable but their formation is implicated by inversion of configuration. Upon chromatographic purification on silica gel, the aldehyde **292** slowly epimerizes to the all-*trans* isoxazolidine **294** via ring opening to the α,β-unsaturated aldehyde **293** <1997T739>.



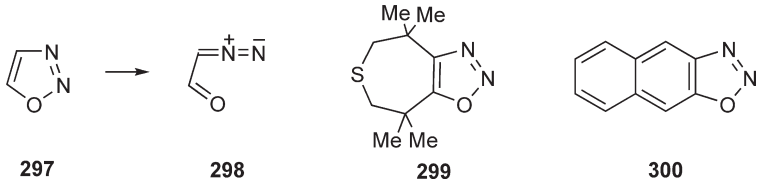
292 **293** **294**

2.4.5.4 Valence Tautomerism

Valence tautomerism refers to the interconversion of isomers without any accompanying rearrangement including proton transfer. Heterocyclic examples of valence tautomerism are essentially electrocyclic reactions.

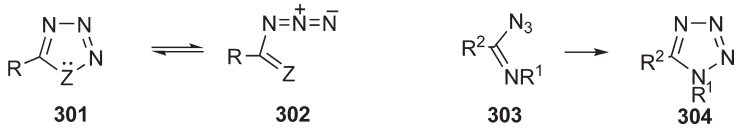
Heterocycles with the general structure **295** can equilibrate with the valence tautomers **296** and the position of the equilibrium depends on the nature of the atoms or groups X, Y, and Z. 1,2,3-Oxadiazole **297** and its simple derivatives, for example, are unknown. Calculations (Section 2.4.2.2.3) agree that there is a low-energy barrier to ring opening to diazoacetaldehyde **298**, and it is unlikely that 1,2,3-oxadiazole can be isolated, even in a matrix at low temperature <1998JOC5801>. The sterically protected 1,2,3-oxadiazole **299** is the only known oxadiazole-bearing alkyl substituents; it exists in the cyclic form in the crystalline state but as the diazoketone in chloroform solution <1980TH403-01>. 1,2,3-Benzoxadiazole has been detected in a matrix at 15 K <1984AGE509>; this and some substituted 1,2,3-benzoxadiazoles have been shown to exist in equilibrium with their open-chain tautomers <1991JST(247)135, CHEC-III (5.03.3.4)219>. Naphtho[2,3-*d*]-1,2,3-oxadiazole **300** is stable in the solid state at −15 °C in the absence of light <1991AGE1476>. In contrast to 1,2,3-oxadiazoles, 1,2,3-thiadiazoles are stable in the cyclic form **295** (Z = S, X = Y = CR) in both the solid state and solution.

295 **296**

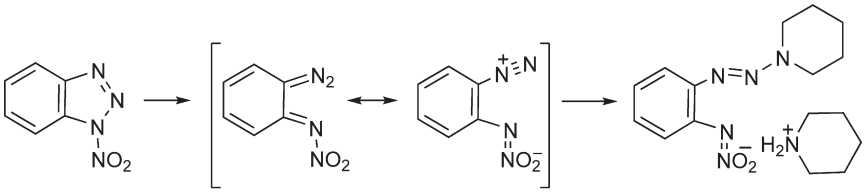


297 **298** **299** **300**

The azole–azide equilibrium **301** ⇄ **302** is an important subgroup of this type of valence tautomerism of azoles. 1,2,3,4-Oxatriazoles **301** (Z = O), like 1,2,3-oxadiazoles, are unstable. In contrast, 1,2,3,4-thiatriazoles **301** (Z = S) and tetrazoles **301** (Z = NR) are usually stable in the cyclic form. In fact, generation and rapid cyclization of imidoyl azides **303** is one of the main synthetic routes to tetrazoles **304**. However, when strongly electron-withdrawing groups are present on the imidoyl azide, cyclization to the tetrazole is not observed; presumably the more electronegative nitrogen atom (like oxygen) does not favor cyclization.



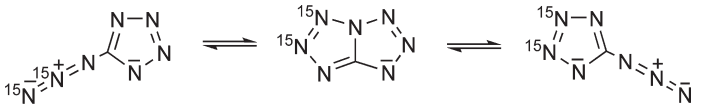
Benzotriazoles can also be induced to undergo ring opening if the nitrogen atom at position 1 is made more electronegative. 1-Nitrobenzotriazole **305** is in equilibrium with the isomeric α-diazo-1-nitroimine **306**. In the presence of nucleophiles, such as piperidine, this open-chain tautomer can be trapped by attack at the diazo group. A second molecule of the amine acts as a base to afford the piperidinium salt **307** <1984JOC2197>. Similar equilibria of 1-substituted-1,2,3-triazoles with strongly electron-withdrawing groups on nitrogen, such as CN or OSO_2CF_3, are also known (see ^{13}C NMR evidence in Section 2.4.3.4).



Higher temperatures also favor azido tautomers. Thermal ring opening to intermediate azidoamidines **309** is responsible for the Dimroth rearrangement of 5-alkylamino-1-aryltetrazoles **308** to 5-arylamino-1-alkyltetrazoles **310** on heating at 180–200 °C <1982JHC943, 1984JHC627>.

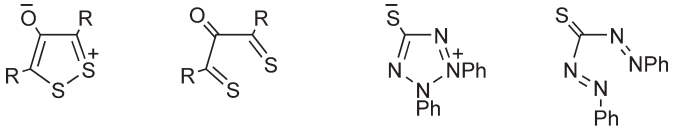
Azide derivatives of azines also equilibrate to give polyaza bicyclic heterocycles <2010T2863>. In the tetrazolo[1,5-*a*]pyridine–2-azidopyridine equilibrium **311** ⇄ **312**, substituents on the pyridine ring influence the position of the equilibrium <1997MRC237>. For another example, see **Scheme 16** in Section 2.2.5.3.

Quantum–mechanical calculations on the heptaazapentalene anion **314** show it to be a true minimum on the potential hypersurface of CN_7^- and suggested that it is only 6.6 kcal mol^{-1} higher in energy than 5-azidotetrazolate anion **313**. The existence of the anion **314** is supported experimentally by the observation of ^{15}N scrambling between the 5-azido group and the 2- and 3-positions of the tetrazole ring in the anions **313** and **315** <1986CC959>.



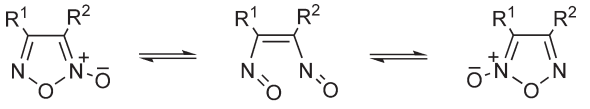
313 314 315

Type B mesoionic heterocycles have the capacity to tautomerize to an acyclic isomer <1976AHC(19)1>. For the 1,2-dithiolium-4-olates, IR studies indicate that the cyclic structure **316** is favored over the acyclic structure **317**, except where R is an amino substituent <1987PS(31)109>. A crystal structure of dehydrodithizone **318** has confirmed the cyclic mesoionic structure <1970JA1965> but most of the reactions of this compound can be interpreted in terms of initial valence tautomerism to the bisphenylazo isomer **319** <1979COC(4)1221>.



316 317 318 319

A final example of valence tautomerism is the interconversion of furoxan-2- and furoxan-5-oxides (**320** ⇌ **322**). The equilibration is presumed to proceed via an intermediate *cis*-1,2-dinitrosoalkene **321**. In the benzofuroxan series the involvement of the corresponding 1,2-dinitrosoarenes as intermediates has been firmly established by matrix isolation experiments <1991CC1178, 1991JOC5216, 1992CL57>.



320 321 322

2.5
Structure of Small and Large Rings

The division of compounds of small and large rings into aromatic, nonaromatic, and antiaromatic types is much less clear-cut than that of the five- and six-membered rings. Heterocyclic aromaticity requires a planar or nearly planar conjugated system containing $4n + 2$ -electrons. Sometimes planarity cannot be achieved because of increased strain in going from puckered to planar geometries. The Hückel condition can often be met by utilizing the systems -bonds and n electron pairs, and sometimes by forming cations or anions to adjust the number of participating electrons. The subject has been reviewed <1974AHC(17)339, 1985KGS867, 1993AHC(56)303>. Larger heteroaromatic systems are known with 721 ring members. However, a great many heterocycles having an appropriate number of electrons are

polyenic rather than aromatic due to the excessive energy required to achieve near planarity. In the survey in Section 2.5.1 the emphasis is on known ring systems rather than all the possible systems.

2.5.1 Survey of Possible Structures and Nomenclature

The systematic endings for naming heterocyclic rings with up to 10 atoms are summarized in Section 2.1.3. A more detailed account of heterocyclic nomenclature can be found in CHEC-I <CHEC-I(1.02)7>.

2.5.1.1 Three- and Four-Membered Rings

2.5.1.1.1 Without exocyclic conjugation

Figure 1 shows the structures and systematic names of representative three-membered rings and **Figure 2** shows the structures and systematic names of representative four-membered rings.

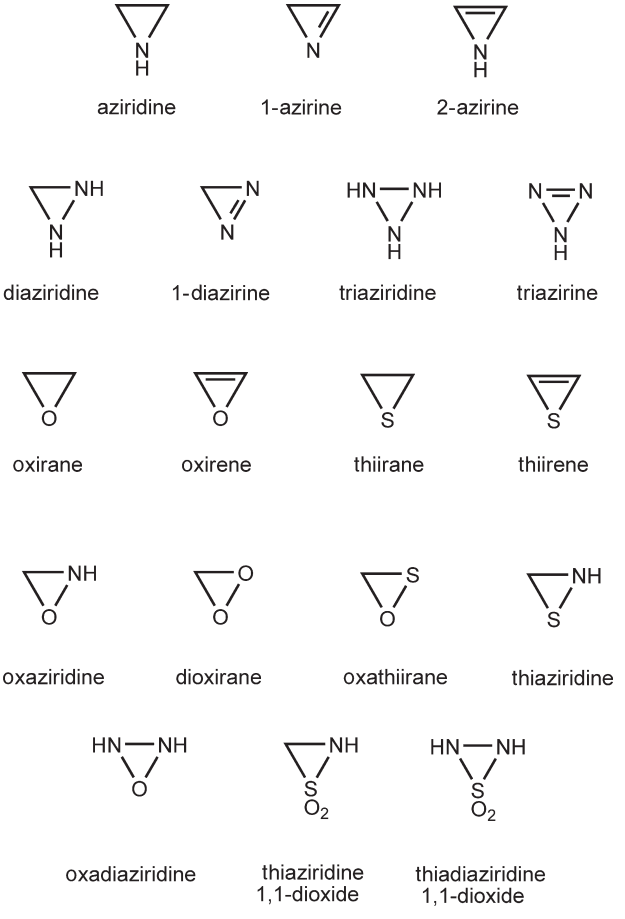


Figure 1 Structures and names of three-membered heterocyclic rings.

2.5.1.1.2 With exocyclic conjugation

The introduction of one or more exocyclic double bonds into a three- or four-membered heterocyclic ring extends the number of possible systems. Representative examples with their systematic names are shown in **Figure 3**.

Three- and four-membered heterocyclic rings commonly occur either as intermediates or as products with important applications. Derivatives of oxirane (epoxides) are widely used as synthetic intermediates due to their ease of preparation and their useful ring-opening reactions that usually occur with predictable regioselectivity and stereospecificity. There are many examples of natural products containing an oxirane ring fused to another ring system <CHEC-III(1.04.2.9)285>. The aziridine ring plays a crucial role in the DNA cross-linking mechanism of the antitumor agent mitomycin C **1** and a

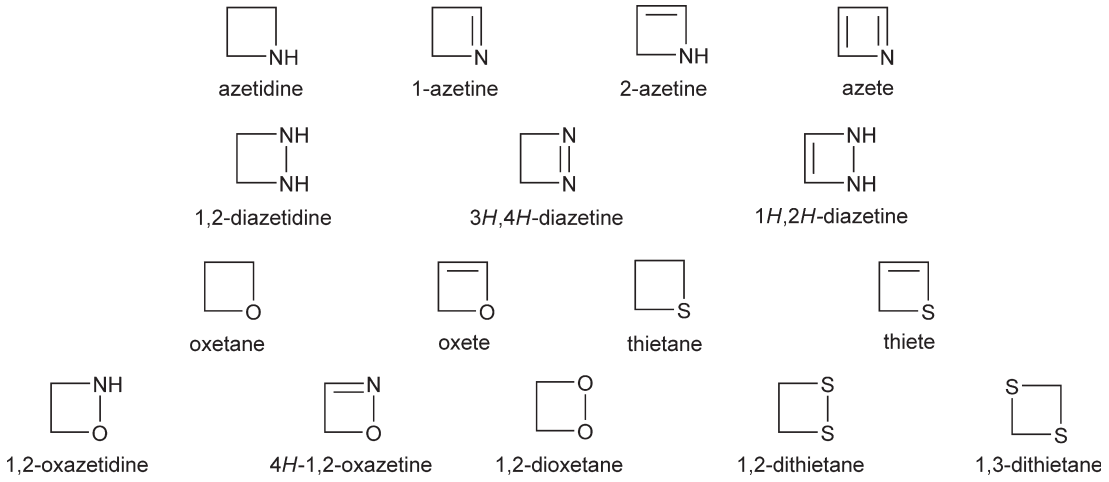


Figure 2 Structures and names of four-membered heterocyclic rings.

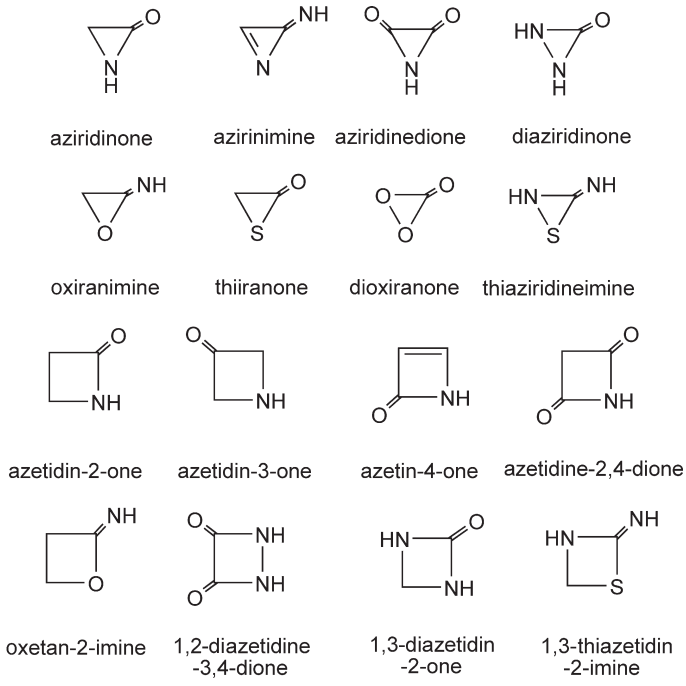
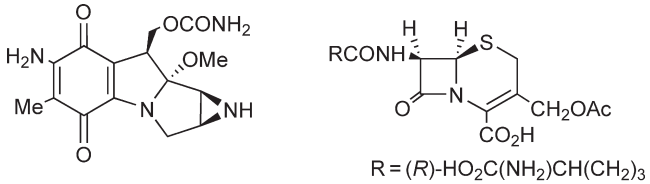


Figure 3 Structures and names of small heterocyclic rings with exocyclic double bonds.

number of other biologically active aziridine-containing natural products <CHEC-III(1.02.7)153>. The azetidin-2-one ring, commonly referred to as a -lactam ring, is an important feature of the cephalosporin and penicillin antibiotics <CHEC-III(2.02)111, CHEC-III(2.03)173>, exemplified by cephalosporin C **2**. In both these therapeutic agents ring opening of the small ring by a nucleophile is a key feature of their mechanism of action.



2.5.1.2 Seven-Membered Rings

The number of possible heterocyclic rings of seven or more members is enormous, and many are known. Representative examples of seven-membered heterocyclic rings are shown in **Figure 4**. Fully-conjugated rings, such as thiepin derivatives, usually adopt a nonplanar geometry, which minimizes unfavorable cyclic conjugation and angle strain.

Benzo derivatives are well known (**Figure 4**) and some are the basis of important therapeutic agents such as the tricyclic antidepressant clomipramine **3** and the anxiolytic agent diazepam **4**. In these molecules the seven-membered rings act as extremely good scaffolds that allow a wide variety of substituent variation and exploration of conformational space during the discovery phase of drug development.

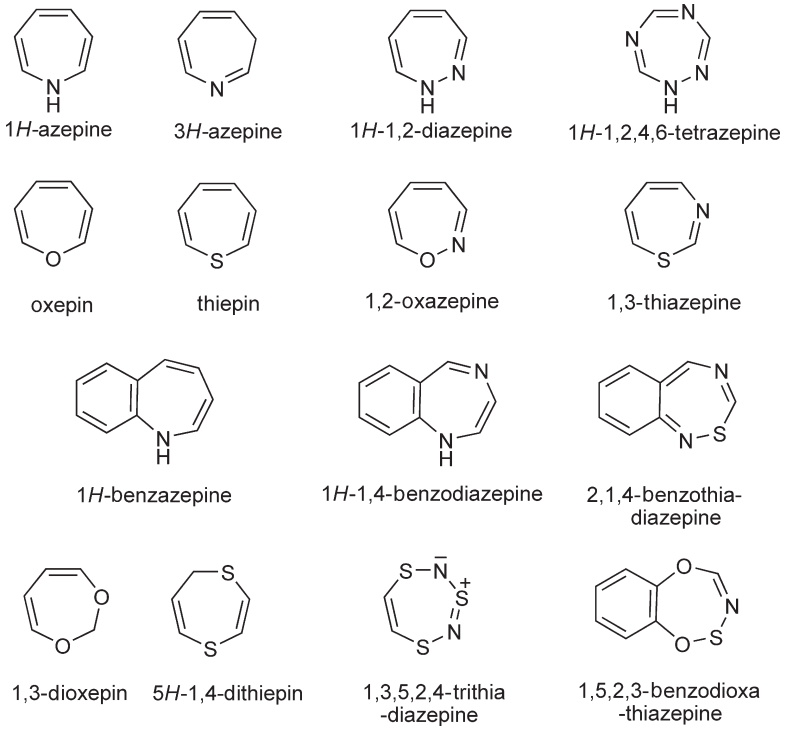
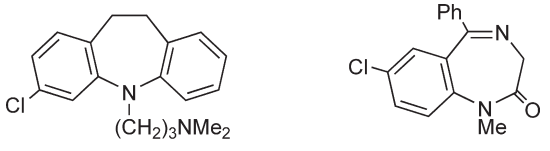


Figure 4 Structures and names of representative seven-membered heterocyclic rings.



2.5.1.3 Larger Rings

Figure 5 shows the structures and names of representative eight- and nine-membered rings.

Figure 6 shows representatives of classes of larger heterocyclic rings of special significance. The crown ethers and cryptands have cavities that form tightly bound complexes with metal ions <CHEC-III(14.12.2)668>. For example, 18-crown-6, which is an 18-membered ring with six oxygen atoms, forms a complex with potassium ions and will solubilize potassium permanganate in organic solvents. The crown ethers are also important building blocks for supramolecular assemblies and this has been an area of intense activity <CHEC-III(14.12.4)702>; for example see Section 2.2.6. Cryptands are multiple heterocycles that act as hosts to electron-deficient guests <CHEC-III(14.22) 1071>. A wide variety of macrocyclic heterocycles are reviewed in Volume 14 of CHEC-III.

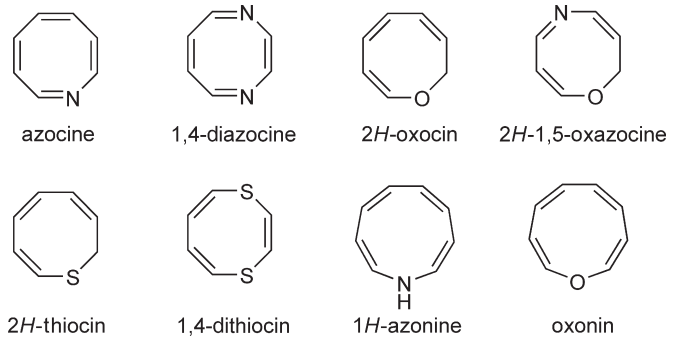


Figure 5 Structures and names of representative eight- and nine-membered heterocyclic rings.

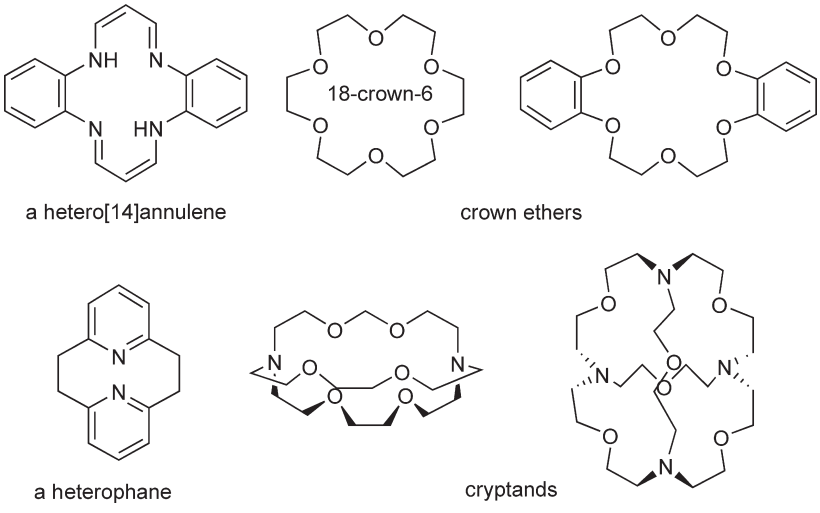


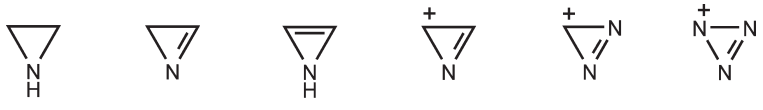
Figure 6 Examples of large heterocyclic rings.

2.5.2 Theoretical Methods

2.5.2.1 Three- and Four-Membered Rings

A large number of quantum mechanical calculations have been conducted on three- and four-membered heterocyclic rings. The appropriate chapters of CHEC-III, and previous editions, contain comprehensive summaries of published calculations.

Calculated proton affinities of aziridine **5** (ca. 218.2223.3 kcal mol^{1}) <1993JA11074> agree with experimental values (215.7 kcal mol^{1}) <1981JA486>. *Ab initio* modeling of the pyramidal inversion of the nitrogen of aziridine and simple substituted aziridines provided inversion barriers (1222.3 kcal mol^{1}, depending on the method), transition state structures, and calculated rate constants for inversion <1987JA3224, 1987JA6290, 1989JC468, 1993CPL(204)175>.

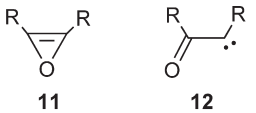


The structures of 1-azirine **6** and its complexes with H^+ and Li^+ have been calculated using *ab initio* methods <1993JA11074>. An unsuccessful study aimed at matrix isolation of 2-azirine **7** used *ab initio* methods to calculate its infrared spectrum and predicted that 2-azirine **7** is 32.733.2 kcal mol^{1} higher in energy than 1-azirine **6** <1993CB2337>.

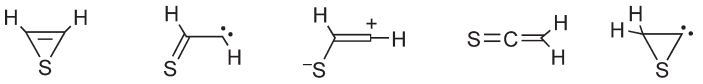
The relative basicities of the nitrogen heterocycles **5**, **6**, and **7** have been calculated: 2-azirine **7** is more basic than aziridine **5**, which is more basic than 1-azirine **6**. The antiaromaticity of 2-azirine **7** (4*n* -electrons in cyclic conjugation) is relieved upon protonation, thus accounting for its higher calculated basicity. Whereas 2-azirine **7** is considerably higher in energy than 1-azirine **6** (see above), protonated 2-azirine is only 4.7 kcal mol^{1} higher in energy than protonated 1-azirine.

The structures of the potentially aromatic azirinyl, diazirinyl, and triazirinyl cations **8**–**10**, and related radical cations, have been investigated using a 6-31G** basis set <1991JA3689>. In accord with Hückels rule, the calculated properties of the species **8**–**10** are consistent with aromatic structures. The triazirinyl cation **10** is the minimum energy structure of the N_3^+ singlet potential surface and 11 kcal mol^{1} below the energy of the open-chain form.

The antiaromatic oxirenes **11** are extremely elusive but their potential involvement in photochemical Wolff rearrangements by equilibration with the -oxocarbenes **12** has generated both theoretical and experimental interest and the subject has been reviewed <2004MRO291>. Experimental evidence for participation of oxirenes <2004MRO291> is supported by DFT calculations that suggest that oxirene corresponds to an energy minimum <2003JMT(629)263, CHEC-III(1.03.7)215>.



11 **12**



13 **14** **15** **16** **17**

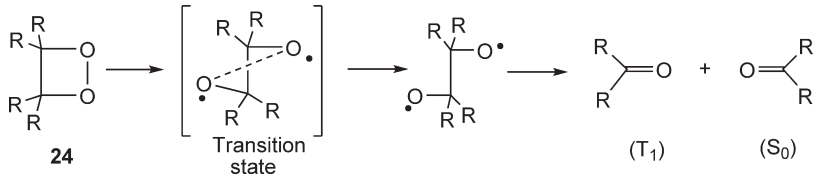
Semiempirical calculations have been applied to antiaromatic three-membered rings and indicate that they correspond to energy minima <1973CC688>. For example, thiirene **13** corresponds to a local energy minimum relative to the isomeric carbene **14**, zwitterion **15**, heterocumulene **16**, and heterocyclic carbene **17**.

Structures and energies of the cyclic $C_3H_6N^+$ cations have been examined by *ab initio* molecular orbital calculations with the 3-21G basis set. The iminium ion **18** is the most stable of the four-membered ring isomers <1989JA5560>. Significant theoretical effort has been directed to antiaromatic four-membered rings. Early calculations predicted that azete **19** has a negative resonance energy of 15.5 kcal mol^{1}, which means that it is slightly more stable than cyclobutadiene <1970TCA235, 1975T295>; this is consistent with the isolation of sterically hindered 2,3,4-tri-*tert*-butylazete (see Section 2.5.5.2) <1986AGE842>.

Calculations at the multiconfigurational SCF (MCSCF) level on 1,2-diazetes **20** and **21** and 1,3-diazete **22** have been reported <1993AGE617, CHEC-III(2.13.2)625>. The 1,2-diazetes are higher in energy than their 1,3-isomers. The 1,2-diazete **21** with two C═N bonds is higher in energy by 50.7 kJ mol^{1}, and that with N═N and C═C bonds **20** by 94.2 kJ mol^{1}, than the 1,3-isomer **22**. The 1,3-diazete **22** can be considered as a push-pull cyclobutadiene; its singlet ground state is stabilized relative to that of cyclobutadiene. A number of calculations on 1,2-dihydro-1,2-diazete **23**, including nucleus-independent chemical shift (NICS) calculations, conclude that this ring has no significant aromatic character <CHEC-III(2.13.2)625>.

18 **19** **20** **21** **22** **23**

1,2-Dioxetanes **24** contain high strain energy and are inherently unstable. They liberate much energy during their decomposition into two carbonyl fragments and are associated with chemiluminescence properties. This aspect has received considerable attention from both theoreticians and experimentalists. A detailed account of current theoretical and experimental understanding of the mechanism has been published <2005BCJ1899>. Calculations indicate that simple 1,2-dioxetanes **24** decompose thermally through a twisted diradical-like transition state to afford predominantly a triplet-excited carbonyl with no direct emission of light (**Scheme 1**), whereas dioxetanes bearing an aromatic electron donor moiety display intramolecular charge-transfer-induced decomposition with accompanying emission of light <CHEC-III(2.16.2)776>.

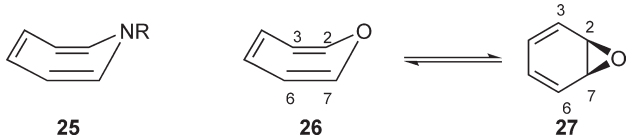


Scheme 1 Thermal fragmentation of 1,2-dioxetanes.

A theoretical study of substituent effects on the strain energies of small-ring compounds has provided insight into differences between 1,2-dioxetanes and 1,3-dioxetanes. The CH bonds in 1,2-dioxetane have been calculated to be stronger than those in 1,3-dioxetane by 8 kcal mol^{1}. Calculations at the same level of theory indicate that 1,2-dioxetane is more strained than 1,3-dioxetane by 6 kcal mol^{1}. Surprisingly, this study also suggests that 1,2-dioxetanes **24** are more strained than dioxiranes (**Figure 1**) by some 712 kcal mol^{1}, which is in contrast with the parent hydrocarbons <2002JOC2588, CHEC-III(2.16.2)776>.

2.5.2.2 Seven- and Eight-Membered Rings

The structures, stability, and degree of cyclic conjugation of fully-conjugated seven- and eight-membered heterocycles are of fundamental interest and have been the topic of numerous MO studies. Restricted HartreeFock (HF) calculations have been carried out on 1*H*-azepine **25** (R = H) and the results compared with those obtained using the semiempirical MNDO method <1984JST(109)277>. The results indicate that 1*H*-azepine has a boat configuration **25** that permits -delocalization of the cyclic double bond system to a level comparable to that of a linear polyene. The data further suggest that the ring puckering is a consequence of ring strain rather than a destabilizing antiaromatic 8-interaction. Overall ring shape is better predicted by the HF calculation; however, alternating bond distances are more accurately represented by MNDO calculations. MOMM calculations show that the -electrons of 3*H*-azepine are highly localized and that the molecule prefers a boat conformation, which is predicted to be 4.7 kcal mol^{1} more stable than the planar form and 17 kcal mol^{1} more stable than 1*H*-azepine <1988MI901-01>.

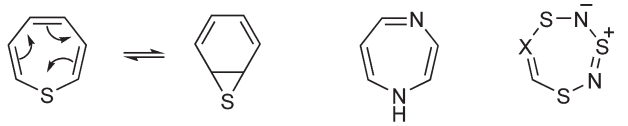


25 **26** **27**

Oxepin **26**, benzene oxide **27**, and the equilibrium between them have been studied using both semiempirical and *ab initio* calculations. The fully-optimized nonplanar oxepin geometry <1990MI 902-01> is in agreement with that found experimentally for several substituted oxepins. The carbon skeleton of benzene oxide is practically planar; the angle between the epoxide ring and the adjacent plane is ca. 10$\bar{6}$. The oxepin molecule is boat shaped with calculated fold angles between C(2)C(7) and C(3)C(6) of ca. 137 and 15$\bar{9}$, respectively. In a QCISD(r)/6-31G*//MP2/6-31G* *ab initio* study the enthalpy calculated for the benzene oxideoxepin system was 0.59 kJ mol^{1} <1997JPCA3371> and the calculated MO energies are in a linear relationship to those obtained from PE spectra <1996JCF1447>. Protonation stabilizes the oxide form relative to the oxepin <1997JPCA3371>. In a study at the MP4(SDQ)/6-31 +G**//HF/6-31 G** level the transition state for the tautomerization was fully characterized and the activation energies for the forward and reverse reactions estimated to be ca. 9.5 and 11.0 kcal mol^{1}. The solvent polarity exerts a reasonable effect decreasing the activation energies by up to 4 kcal mol^{1} <2001MI203-01>.

Ab initio calculations on thiepin **28** and its valence tautomer benzene sulfide **29** estimate the enthalpy change (*H*) for isomerization from benzene sulfide **29** to thiepin **28** at 298 K to be 7.02 kcal mol^{1}. The enthalpy difference *H* is larger than that for the oxepin **26**benzene oxide **27** system and this is attributed to a combination of greater stability of the sulfide relative to oxide and the relative instability of thiepin compared to oxepin. The entropy change at 298 K was calculated to be 6.68 J mol^{1} K^{1} <1997JPCA3371>. For the benzene sulfidethiepin system, the rate of valence tautomerism is predicted to be much slower than that for the benzene oxideoxepin system since the enthalpy of activation for **29** **28** is 20.5 kcal mol^{1} compared to 7.03 kcal mol^{1} for benzene oxideoxepin using the same method <1997JPCA3371, CHEC-III(13.03.2)98>. The calculated nucleus-independent chemical shifts (NICSs) for thiepin **28** suggest that the

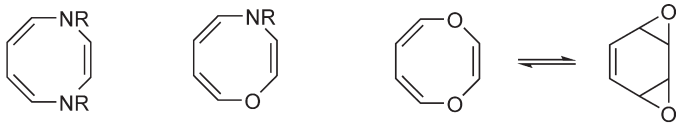
most stable boat-like structure is nonaromatic (NICS −1.3) and the planar structure is antiaromatic (NICS 12.6) <CHEC-III(13.03.2)98>.



28: thiepin **29** **30** **31**

Because 1,4-diazepine **30** and its tautomers are extensively used in the design of molecules that bind to enzymes or receptors, a large body of computational structural analysis has been published. A refined set of force-field parameters useful for evaluating the preferred conformations of 1,4-benzodiazepines using AMBER or other molecular mechanics (MM) programs, particularly those that also include protein and DNA parameters, has been developed <1997JCI951>. The Cambridge Crystallographic Database served as the source of equilibrium parameters while semiempirical methods (AM1 and PM3) were used for estimating bond-stretching and torsion-potential force constants. Modeling of representative 1,4-benzodiazepinones accurately predicted their X-ray crystallographic structure to within 0.01 é for bond lengths, 0.8̄ for bond angles, and 5̄ for torsional angles. *Ab initio* and DFT calculations have been used to predict ^{13}C NMR chemical shifts of azepines and diazepines <1997J(P2)1851>. Based on the comparison of these results with experimental data, it was concluded that Becke3LYP/ and HF/6-31G* and /6-31+G** single point calculations based on MP2 geometries give the lowest average errors and the Becke3LYP calculations are better at predicting the correct order of chemical shifts.

Seven-membered rings can accommodate 10-electrons ($4n + 2$) in cyclic conjugation. In this context, a possible role in commercially useful conducting polymers has stimulated significant interest in the calculated properties of such rings incorporating sulfur and nitrogen <1980JA6687, 1982JA2691, 1984JA312>. The delocalized 10 aromatic nature of the trithiadiazepine **31** (X = CH) and trithiatriazepine **31** (X = N) rings is supported by MNDO and *ab initio* MO calculations. The results are consistent with the photoelectron spectra (PES) of the heterocycles **31** and confirm the fundamental aromatic nature of these systems, in accord with their stability, chemical reactivity, and other spectroscopic properties <1985CC398, 1987J(P1)203>.



32: 1,4-diazocines **33**: 1,4-oxazocines **34**: 1,4-dioxocin **35**

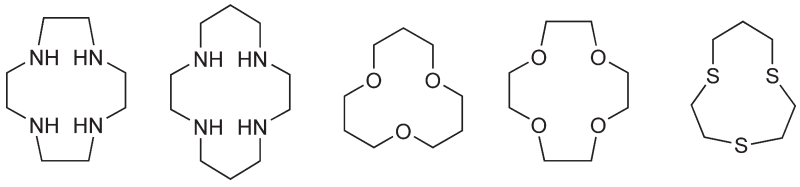
On the basis of topological criteria, Balaban predicted in 1965 the aromaticity of compounds with 10-electron systems in eight-membered rings with two heteroatoms <1965RRC1059, 2004CRV2777>, although since then surprisingly few calculations have been reported on 1,4-diheterocines <CHEC-II(9.23.2)529, CHEC-III(14.06.2)256>. 1,4-Diazocines **32** are aromatic when R is a donor group; a ring current is evidenced by NMR. If R is an acceptor group, such as arylsulfonyl, **32** is nonplanar and shows no ring current <2004CRV2777>. 1,4-Oxazocines **33** are planar and diatropic if R = H or alkyl but the *N*-tosyl derivative is nonplanar <1975AGE348>. 1,4-Dioxocins, e.g., **34**, are paratropic and exist in equilibrium with *syn*-benzene dioxides, e.g., **35** <CHEC-III(14.06.2)256, 2000CC2151, 2004CRV2777>.

2.5.2.3 Larger Rings

Most of the theoretical work dealing with macrocycles is devoted to the calculation of the structure and properties of their complexes. Molecular mechanics (MM) has become increasingly important in the study of the correlation between cavity size and ionic radius of coordinated metal ions <1984CCR(53)1, 1993CCR(126)177>. Aspects of metal ion reactivity and ligand design for specific and selective binding can be modeled and understood in detail. The concept of matching between macrocyclic cavity size and size of the complexed metal ion is supported by several lines of evidence <1978ACR49>.

Solvation of cyclen **36** was studied using Monte Carlo (MC) simulations <1996JPC17655, 1997JCF3045>. Potentials for cyclen were calculated by an *ab initio* method. It was found that the water hydration sphere is composed of three layers: two water molecules are strongly bound in close vicinity, six molecules form the inner hydration sphere, and

fifty-four molecules are in the outer hydration sphere. *Ab initio* calculations of conformations of cyclen **36**, 1,4,7-triazacyclodecane, 1,4,8-triazacycloundecane, and 1,5,9-triazacyclododecane in different protonation states showed that the conformations are stabilized by intramolecular hydrogen bonds and, therefore, some nitrogen atoms are oriented inwards to the cycle cavity <1996J(P2)1161>. Ethylene bridges are in a gauche conformation and propylene bridges exhibit some conformational freedom. MM simulations were used for the determination of stable conformations of all protonated forms of cyclam **37** <1996J(P2)1925>. It was found that less protonated forms are stabilized by intramolecular hydrogen bonds that lead to a very stable arrangement with inward orientation of all nitrogen atoms, especially in the diprotonated form H_2cyclam^{2+}. MM modeling was used to find the lowest energy conformations in a benzotetraaza ligand <2003JCD1852>. Anion recognition by a large 30-membered hexaazamacrocycle has been investigated by MM and/or molecular dynamics (MD) <2003JCD4261, 2006NJC247>.



36: cyclen **37**: cyclam **38**: 12-crown-3 **39**: 12-crown-4 **40**: 10-S-3

Bis(crown ethers) connected by a flexible spacer are a source of intramolecular sandwich-type complexes with alkali metal ions <1992MI1>. A conformational analysis (based on a combination of semiempirical and *ab initio* methods) performed on 12-crown-3 **38** and 12-crown-4 **39** predicted that, in the case of sandwich-type complexation, the nucleophilic cavity of 12-crown-3 rather than that of 12-crown-4 is more prone to complexation with the Na^+ ion. Accordingly, ion-selective electrodes based on bis(12-crown-3) derivatives with dialkylmalonate spacers displayed the highest selectivity for Na^+ ions among the alkali and alkaline earths investigated, and superior to the Na^+ selectivity reached with the bis(12-crown-4) analogue <2003ANA(480)291>.

MM has been used to calculate the lowest energy conformers (the global minimum) of diverse sulfur macrocycles <1995IC5410, 1997JCD1889, 1998JOC181, 1999JOM(587)207, 2000JPCA652, 2001ICA(317)91, 2001JPCA11266, 2004JMM55>. The lowest energy structures of 10-S-3 **40**, for example, do not completely exhibit endodentate orientation of the sulfur atoms meaning that endodentate complexation of transition metals with 10-S-3 requires higher energies than for complex formation with 9-S-3 where all three sulfur atoms are endodentate in the lowest energy conformers <1999JOM(587)207>. A detailed discussion of programs for calculation in molecular modeling has been presented <1999JPR202> and the results for relative conformational energies of 9-S-3 **40** by various programs have been compared <2004JMM55>. Further data obtained for the conformers of 12-S-4 and 15-S-5 <2000JPCA652> and for those of 12-S-4 and 14-S-4 <2001JPCA11266> have been listed. In the latter work, the 36 lowest energy structures of 14-S-4 were theoretically examined. In some other cases, the calculated values were compared with the experimental data provided by X-ray crystallography and relatively good correlations found <1998JOC181, 1999JPR202>.

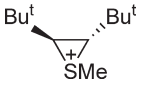
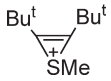
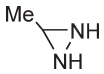
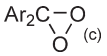
2.5.3 Structural Methods

2.5.3.1 X-Ray Diffraction

The geometry of many three- and four-membered rings has been determined by X-ray diffraction on crystalline materials <1972PMH(5)12>. Three-membered heterocycles generally have shorter CC bonds than cyclopropane (1.510 é), an exception being thiirane 1,1-dioxide (1.590 é). The CX bonds are longer than in CH_3XCH_3. The CXC angles in oxirane and aziridine are close to 6$\bar{0}$, and the peripheral HCH bond angles are near 11$\bar{8}$. **Table 1** gives representative data.

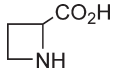
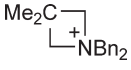
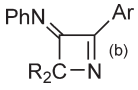
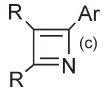
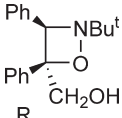
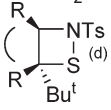
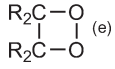
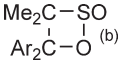
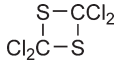
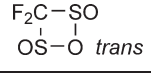
The geometry of four-membered rings is more complex; the rings are often nonplanar. An X-ray crystal structure of the parent oxetane revealed exact C_S ring symmetry puckered with an angle of 10.$\bar{7}$ at 90 K and 8.$\bar{7}$ at 140 K. Interestingly, the carbonoxygen bond lengths (1.45 é) are large compared with tetrahydrofuran (1.429 é) and dioxane

Table 1 Bond lengths and bond angles of three-membered heterocyclic compounds

Structure	Bond lengths (é)			Bond angles (degrees)			CRSE[a]	Reference
	a	*b*	*c*	*ca*	*ab*	*bc*	(kJ mol^{1})	
	1.482	1.491	1.482				113	CHEC-I(5.04.2)48
	1.49	1.49	1.50	59.9	60.4	59.8		1974PMH(6)1
	1.44	1.47	1.44	61.24	59.18	59.18	114	CHEC-I(5.04.2)48
	1.815	1.484	1.815	48.3				1974CPL(24)111 CHEC-II(1.05.3)184
	1.731	1.590	1.731	54.7				1976AXB2171 CHEC-II(1.05.3)184
	1.876	1.452	1.860	45.7	66.6	67.2		2000JOC3367
	1.256	1.463	1.598	60.3		48.2		CHEC-I(5.04.2)48
	1.831	1.278	1.831	40.85	69.5	69.6		2000JOC3367
	1.468	1.479	1.479	59.5	59.5	61		CHEC-I(5.08.2)198
	1.50	1.405	1.434	57.2	59.0	63.8		CHEC-I(5.08.2)198
	1.503	1.413	1.414	57.9	57.9	64.2		1997JA7265
	2.047	1.843	1.826	56.5	55.7	67.8		2003JOC1555
	1.228	1.428	1.428	64.5	64.5	50.9		CHEC-I(5.08.2)198
	1.33	1.45	1.51	60.9		53.4		CHEC-I(5.04.2)48
	1.726	1.460	1.916	49.6	73.4	59.7		CHEC-I(5.06.2)132

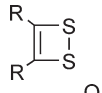
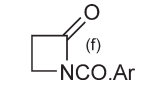
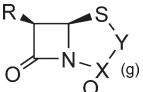
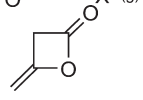
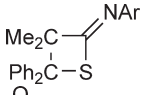
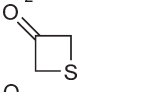
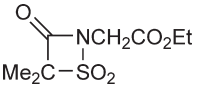
[a]Conventional ring strain energy.
[b]R = CH(OH)CCl_3.
[c]Ar = mesityl.
[d]R = 1-adamantyl.

Table 2 Bond lengths and bond angles of four-membered heterocyclic compounds

	Bond lengths (é)				*Bond angles (degrees)*					
Structure	*a*	*b*	*c*	*d*	*da*	*ab*	*bc*	*cd*	*Pucker (degrees)*	*Reference*
	1.477	1.560	1.560	1.477	88				33 (5.3)[a]	CHEC-I(5.09.2)238 1980CRV231
	1.51	1.54	1.53	1.52	88	90	88	90		CHEC-I(5.09.2)238
	1.51	1.53	1.51	1.51	84	96	84	97		1979MI50100
	1.443 1.449	1.517 1.549	1.517 1.549	1.443 1.449	90.5 91.9	91.9 91.7	85.0 84.6	92.6 91.7	 10	1984JA7118 1980CRV231
	1.847	1.549	1.549	1.847	76.8	90.6	95.6	90.6	26 (3.3)[a]	1980CRV231 1974MI50100
	1.307	1.467	1.575	1.504	92.4	97.9	83.6	86.1	planar	CHEC-I(5.09.4)267
	1.581	1.351	1.591	1.281	87.5	92.7	85.0	95.2	planar	1988AGE1559
	1.79	1.43	1.39	1.77	80.5			104.5	planar	CHEC-I(5.14.2)404
	1.427	1.481	1.537	1.471					24.3	CHEC-I(5.15.1)451
	1.506	1.490	1.548	1.450	89.3	89.1	86.3	88.9		2006ZK398
	1.791	1.490	1.533	1.874	76.8	90.7	97.7	86.3	30.8	2003JA8255
	1.48	1.549	1.475	1.549					21.3	CHEC-I(5.15.1)451
	1.667	1.856	1.588	1.487	97.1	109.6	79.0	93.8		1981J(P1)1826
	2.146	1.835	1.564	1.835	99.1		80.9			CHEC-I(5.15.1)451
	1.801		1.77		83.9		96.1		planar	CHEC-I(5.15.1)451
	1.671	1.892	1.894	1.679	107.9	80.7	91.2	80.4	planar	1998JFC(89)55

(*Continued*)

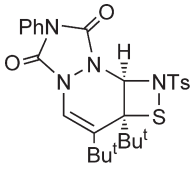
Table 2 (Continued)

Structure	Bond lengths (é)				Bond angles (degrees)				Pucker (degrees)	Reference
	a	*b*	*c*	*d*	*da*	*ab*	*bc*	*cd*		
	2.052.12		1.361.40						planar	2000JOM(611)106 CHEC-III(2.18.2) 812
	1.38	1.51	1.57	1.50	94.0	93.4	86.3	86.3		CHEC-I(5.09.3)267
	1.451.52	1.53 1.58	1.511.55	1.361.46	8894	8792	8386	9296		CHEC-II(1.20.3)625
	1.39	1.51	1.54	1.47	95.8	83	91.3	90	planar	1980CRV231 1972PMH(5)12
	1.777	1.524	1.591	1.868	77	95.8		90.1	20	CHEC-I(5.14.2)404
	1.826	1.528	1.528	1.826			100.5		planar	CHEC-I(5.14.2)404
	1.677	1.360	1.539	1.823	78.7	96.6	99.9	84.8		1997HCA671

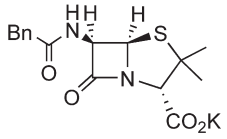
[a]Ring inversion barrier (kJ mol[1]).
[b]Ar = 4-FC_6H_4, R = CF_3.
[c]Ar = mesityl, R = Bu^t.
[d]Values for structure **41**.
[e]R_2 = adamantylidene.
[f]Ar = 2-BrC_6H_4.
[g]Limiting values for the penicillin skeleton (e.g., **42**).

(1.433 é). **Table 2** shows dimensions that have been determined using X-ray crystallography for a range of four-membered heterocycles. The dimensions for the 1,2-thiazetine ring were obtained for the derivative **41**.

Since the first X-ray structure determination of benzylpenicillin potassium **42** (a penam) in 1949, the structures of a large number of -lactam antibiotics have been reported <CHEC-III(2.03.3.1)182>. **Table 2** shows the limiting values of the -lactam ring dimensions in a range of penicillin derivatives <CHEC-II(1.20.3.1)625>. More recent X-ray studies on the penicillin <CHEC-III(2.03.3.1)182> and cephalosporin <CHEC-II(1.19.3.1)593> families of antibiotics have been summarized.



41



42

In heterocycles with seven and more ring members, the flexibility of the ring rapidly increases. Fully-unsaturated seven-membered heterocycles adopt boat conformations that minimize angle strain and antiaromatic cyclic conjugation (see structures **25** and **26**). **Figure 7** summarizes geometries of representative derivatives that have been determined by X-ray crystallography. Bond alternation is clearly present between the ring carbon atoms, although the oxepin shows a greater tendency to bond equalization. 3*H*-Azepines (see **Figure 4**) also adopt a boat conformation with the saturated ring carbon at the bow <1972CB982, CHEC-I(5.16.2.2)494>.

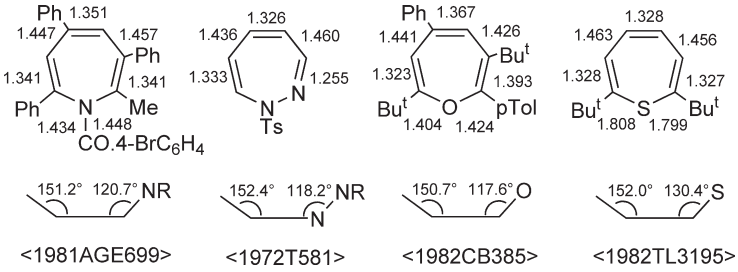
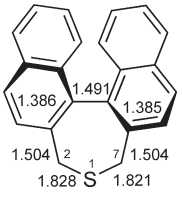


Figure 7 Selected geometrical parameters for fully-unsaturated seven-membered heterocycles determined by X-ray crystallography.

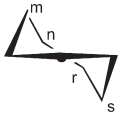
The dissymmetic (C_2 symmetry) dihydrodinaphthothiepin **43** and related bridged diaryl derivatives are of interest because the stereoisomers can be separated (atropisomers) and have potential applications as chiral reagents. An X-ray crystal study of compound **43** shows that it has a *cisoid* arrangement around the biaryl bond with an interplane angle of 66.1̄ <1995T787, CHEC-III(13.03.3.1)102>.



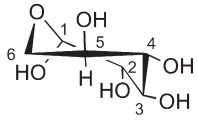
43

C(2)-S(1)-C(7) 99.5°
S(1)-C(2)-C(3) 112.3°
C(2)-C(3)-C(4) 120.0°
C(3)-C(4)-C(5) 118.6°
C(7)-S(1)-C(2)-C(3) 45.9°
C(3)-C(4)-C(5)-C(6) 66.1°

The bond lengths of fully-saturated seven-membered rings are the same as those in the corresponding open-chain compounds, while the bond angles tend to be larger. In principle, oxepane rings can adopt boat (B), chair (C), twist-boat (TB), and twist-chair (TC) conformations. Crystallographic evidence suggests that twist-chair conformations are the lowest in energy but for each derivative several TC conformations are possible. In TC conformations three atoms are in a plane, two atoms (n and m) are above the plane, and two atoms (r and s) are below the plane, and this conformation is designated $^{n,m}TC_{r,s}$ (e.g., **44**). A crystal structure of the 5-*O*-acetyl-2-*O*-benzoyl-3,4-*O*-isopropylidene-1-*O*-methyl derivative of -L-idoseptanose has shown that it has the $^{O,1}TC_{2,3}$ conformation **45** <1996CAR(284)265>. However, the preferred TC conformation of an oxepane ring depends upon the substituents. In solution methyl -D-*glycero*-D-idoseptanoside and methyl -D-glycero-D-guloseptanoside have been reported to have the $^{3,4}TC_{5,6}$ and $^{6,O}TC_{4,5}$ conformations, respectively <2005JOC24>.



44 $^{m,n}TC_{r,s}$



45 $^{O,1}TC_{2,3}$

2.5.3.2 Microwave Spectroscopy

Microwave spectra have been used to determine molecular dimensions for, *inter alia*, aziridines and 1-azirines <CHEC-I (5.04.2.2)48>, diazirine and substituted derivatives <CHEC-I(5.08.2.2)198>, diazetidines <CHEC-III(2.13.3.2)633>, oxetanes <CHEC-I(5.13.2.2)365, CHEC-III(2.05.3.5)326>, and thietanes and thietes <CHEC-I(5.14.2.1)404, CHEC-III (2.07.3.1)392>.

2.5.3.3 ^{1}H NMR Spectroscopy

2.5.3.3.1 Three- and four-membered rings

The NMR spectra of three- and four-membered heterocycles display regularities of great value to structure determination. For protons on adjacent carbons the coupling constants J_{cis} seem to be always greater than J_{trans}. In three-membered rings J_{gem} is almost always smaller than J_{cis} and J_{trans}. Extensive tables of data have been published <B-73NMR138>. The average values for 64 aziridines are $J_{gem} = 1.4$ Hz, $J_{trans} = 3.3$ Hz, and $J_{cis} = 6.4$ Hz <1971PMH(4)121>. The size of J_{gem} and the vicinal CH coupling constants seems to depend more on the number of nonbonding electron pairs at the heteroatom than on its electronegativity. Each electron pair contributes +5.5 Hz to J_{gem}, 2.5 Hz to J_{cis}, and 2.7 Hz to J_{trans} <1980OMR(13)45>. **Table 3** gives some examples, the data being taken from the relevant chapters of CHEC-I and from <B-73NMR, 1971PMH(4)121, 1980OMR(13)45>. Regression formulae for calculating chemical shifts have been reported <2005JMM175>; for thiirane the predicted values were ^{1}H 2.28 ppm (found 2.27 ppm) and ^{13}C 20.63 ppm (found 18.0 ppm). Data on some three-membered heterocycles with an *exo*-methylene group are shown in **Table 4** <1978RTC214>.

Table 3 Ranges of NMR data for three-membered heterocyclic rings

Ring	*(^{1}H) (ppm)*	*J_{gem} (Hz)*	*J_{cis} (Hz)*	*J_{trans} (Hz)*	*$J(^{13}CH)$ (Hz)*	*(^{13}C) ppm*
Cyclopropane	0.22	3 to 1	612	4 to 8	164	2.2
Aziridine[a]	1.48	0.94	59	27	168	1822
Oxirane	2.54	57	25	13	176	39.7
Thiirane	2.27	14 to 1	67	56	170	18
1-Azirine C(2)	10					160170
1-Azirine C(3)	0.22.5					1945
Diaziridine	1.2					56
1-Diazirine	0.4					
Oxaziridine	4.55					56

[a](^{15}N) = 8.5 (vs. NH_3).

Table 4 Ranges of NMR data for three-membered heterocycles with exocyclic unsaturation

Skeleton	*(C_2) (ppm)*	*(C_3) (ppm)*	*(C_{exo}) (ppm)*	*$J(C_3H)$ (ppm)*	*$J(C_{exo}H)$ (ppm)*
Cyclopropane	2.6	2.6		160.5	
Methylenecyclopropane	131.0	3.0	103.5	161.5	160.8
N-t-Butyl-2-methyleneaziridine	134.0	23.8	80.6	170.7	165
2-Methylene-3-*t*-butyloxirane	144.3	68	70.5		
2-Methylenethiirane	130.1	18.5	99.5	174	166

In azetidine derivatives the protonproton coupling constants J_{gem} on the carbons adjacent to N are 57.5 Hz, and J_{cis} is larger than J_{trans}. Long-range coupling between ring protons is common. **Figure 8** gives some representative examples <B-1973NMR142, 1971PMH(4)144, 2005S3508, 2001TL2373, 2000JOC2253, CHEC-III(2.01.2.3)4>. A significant variation in the geminal coupling constants of methylene groups adjacent to nitrogen has been noted and appears to be influenced by the substituent on nitrogen and the conformation of the ring <CHEC-III(2.01.2.3)4>. Nuclear Overhauser effect (NOE) experiments have been used to determine the stereochemical relationship between groups on adjacent ring carbon atoms <2005SL1559>.

The -protons in oxetanes have much higher chemical shifts than any other class of ether. Representative values are given in **Figure 8**. Introduction of substituents often causes special shielding effects due to proximity effects in the small ring and changes in the puckering of the ring <CHEC-I(5.13.2.3.1)366>. Spinspin coupling in ^{1}H NMR spectra of oxetanes can be complex because of cross-ring interactions and the different signs of the coupling constants. A study of the coupling constants provides a measure of the predominant direction and degree of ring puckering <CHEC-I(5.13.2.3.1)366>.

^{1}H NMR spectral data for representative thietane and thiete derivatives have been tabulated <CHEC-I(5.14.2.2.1)409>. In general the -protons of thietanes are deshielded relative to analogous protons in larger rings, e.g., thietane (= 3.21) and tetrahydrothiophene (= 2.82).

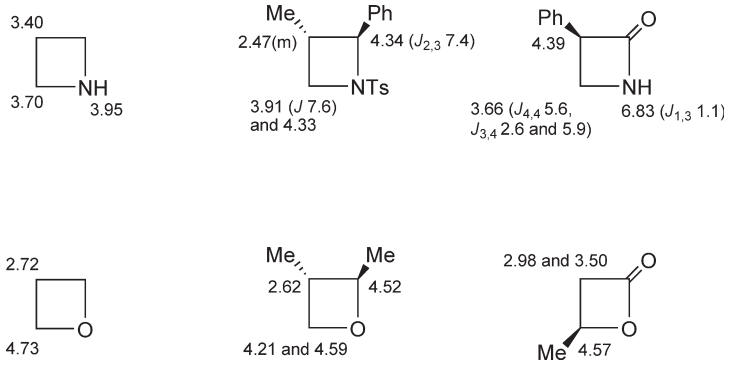
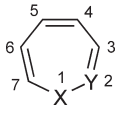


Figure 8 ^{1}H NMR shifts (ppm) and coupling constants (Hz) of azetidine, oxetane, and derivatives.

2.5.3.3.2 Seven or more ring atoms

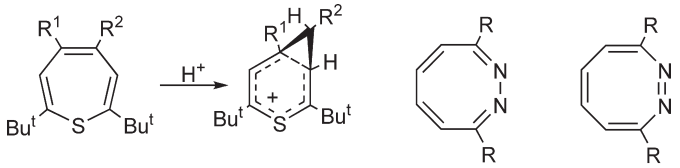
The NMR spectra of heterocyclic compounds with seven or more ring members are as diverse as the shape, size, and degree of unsaturation of the compounds. Protonproton coupling constants provide a wealth of data on the shape of the molecules, while chemical shift data, heteroatomproton coupling constants, and heteronuclear spectra give information of the electronic structure. Some data on seven-membered rings are included in **Table 5**.

Table 5 ^{1}H NMR data for seven-membered unsaturated heterocycles



		^{1}H NMR chemical shifts (ppm)						
X	*Y*	*H(2)*	*H(3)*	*H(4)*	*H(5)*	*H(6)*	*H(7)*	*References*
CH_2	CH	5.28	6.12	6.55	6.55	6.12	5.28	1980AGE1016
O	CH	5.5	5.6	6.3	6.3	5.6	5.5	1965TL4085
NH	CH	5.22	4.69	5.57	5.57	4.69	5.22	1980AGE1016
NCO_2H	CH	5.90	5.78	6.25	6.25	5.78	5.90	1980AGE1016
NCO_2Et	CH	5.95	5.51	6.15	6.16	5.51	5.95	1966TL787
NCO_2Et	N	N	7.44	6.30	6.60	5.80	6.29	1970JOC433
S	CH	Bu^t	6.27	6.27	6.27	6.27	Bu^t	CHEC-II(9.03.2.2)71
S	CH	Bu^t	6.76	CO_2Et	7.43	6.40	Bu^t	CHEC-II(9.03.2.2)71
S	CH	5.89	6.72	[4,5]benzo		6.72	5.89	2003CPB1283

4*H*-Thiepinium ions **47**, generated from thiepins **46** in $FSO_3H/SO_2/CD_2Cl_2$ (-70°C), have been shown to possess a homothiopyrylium ion structure <1984CC604>. The ^{1}H NMR spectrum of **47** ($R^1 = R^2 = H$) indicates charge delocalization, with a chemical shift difference (= 2.5 ppm) between the methylene protons and a geminal coupling constant of 11.6 Hz.



46 **47** **48** **49**

Accidental degeneracy can lead to extraordinarily simple ^{1}H NMR spectra. Compound **48** (R = Ph) displays a singlet (6.49 ppm in $CDCl_3$) for the four ring protons <1982CL1579>, while the parent 1,2-diazocine **48** (R = H) shows a broad singlet at 6.93 ppm (2H) and a sharp singlet at 6.03 ppm (4H). A europium-shift reagent splits the last resonance into an AB pair of doublets, ruling out an isomeric bicyclic structure. This indicates that compound **48** (R = H) exists as the

bond-localized 2,4,6,8-tetraene **48** rather than the 1,3,5,7-tetraene **49** <1979JOC1264> which, by virtue of the non-planarity of the ring, is a distinct isomer rather than a resonance hybrid.

2.5.3.4 ^{13}C and Heteronuclear NMR Spectroscopy

The ^{13}CH coupling constants (often obtained from ^{13}C satellites in ^{1}H NMR spectra) of small heterocycles have been listed <1979MI50101>. A ^{13}C NMR study of 1,2-dimethyl-3-*tert*-butyldiaziridine showed that the population of the 1,2-*cis* isomer increases with solvent polarity (see Section 2.5.3.8) <1998MC113>. ^{13}C Chemical shifts for the ring carbons of representative derivatives of dithiiranes <CHEC-III(1.14.3.1.2)647>, azetidines <CHEC-III(2.01.2.3)5>, diazetidines <CHEC-III(2.13.3.6)642>, thiazetidines <CHEC-III(2.15.3.3)723>, dioxetanes <CHEC-III(2.16.3.1.4)778>, and 1,2-oxathietane *S,S*-dioxides (-sultones) <CHEC-III(2.17.3.1.4)798> have been tabulated.

^{15}N NMR spectra of aziridines and azetidines have been measured <1980JOC1277>. Relative to anhydrous ammonia, the aziridine nitrogen absorbs at -8.5 ppm and N-alkylation moves this shift downfield. For N-Me the signal is at 0.7 ppm, for N-CHMe$_2$ at 30.2 ppm, and for N-CMe$_3$ at 33.5 ppm. Substitution on the -carbon moves the ^{15}N resonance downfield relative to unsubstituted aziridine. This effect decreases with increasing bulk of the substituent, e.g., 2-methylaziridine (10.5 ppm) and 2-*tert*-butylaziridine (3.4 ppm). Further substitution on one or both -carbons causes a downfield shift, the effect being only poorly reproduced by assuming group contributions to be additive.

Aziridine ^{15}N shifts parallel the ^{13}C shifts; in a plot of ^{13}C versus ^{15}N shifts of 13 aziridines, the correlation coefficient was 0.953 and the slope 2.1 ppm N/ppm C <1980JOC1277>. Azetidine ^{15}N shifts are similar to those of the aziridines. Unsubstituted azetidine has its ^{15}N resonance (relative to anhydrous ammonia) at 25.3 ppm, and *N-tert*-butylazetidine shows the signal at 52 ppm <1980JOC1277>.

^{17}O NMR shift data can distinguish different molecular configurations for isomeric compounds. The ^{17}O NMR data of some substituted oxiranes are shown in **Table 6** <1983OMR(21)403, B-91MI 103-01>. The ^{17}O chemical shifts of mono- and disubstituted oxiranes can be calculated using additivity parameters <1986MRC15> and discrepancies between experimental and calculated values fall in the range 14 to +14 ppm. An ^{17}O NMR study of thiirene 1-oxides concluded that the ring is not antiaromatic <1998MRC137>. The ^{17}O NMR shifts have been reported for 2-oxetanone (carbonyl O, 347 ppm; ether O, 241 ppm) and oxetane (13 ppm), and the ^{17}O chemical shift data for 30 lactones, including some oxetanones, have been compiled <1989H(29)301>.

Table 6 ^{17}O NMR chemical shifts for oxiranes

R	*H*	*Me*	*Et*	*CH=CH$_2$*	*Ph*
Chemical shift (ppm)	49	16	18	9.5	8

Chemical shifts of ^{33}S (relative to CS$_2$) in thiirane, thiirane 1-oxide, and thiirane 1,1-dioxide were observed at -240, 120, and 245 ppm, respectively <1987JOC3857>.

2.5.3.5 UV Spectroscopy

2.5.3.5.1 Electronic spectra of small-ring heterocyclic compounds

Saturated three- and four-membered heterocycles absorb little in the readily accessible UV regions. Sulfur-containing rings are an exception, as can be seen by inspection of **Table 7**. The UVVis spectra of dithiiranes reveal an absorption maximum in the range 435455 nm due to the SS bond <1995TL1867, 2003JOC1555, CHEC-III(1.14.3.1.2)649>, and this has been used to monitor the decomposition of dithiiranes <1995TL1867>.

Despite the lack of absorption of most parent compounds, there is a wealth of photochemistry of small heterocycles. Light absorption by substituents and energy transfer from photoexcited molecules present in the photoreactive system make photoconversion of the heterocycles practical. On the other hand, the lack of substantial absorption of their own can be exploited in the preparation of small heterocycles, by designing the system to be unsuitable for destructive energy transfer.

The introduction of a second heteroatom (other than sulfur) does not drastically change the absorption characteristics of small heterocycles. Oxaziridine and diaziridine are still transparent to light of wavelengths above 220 nm <CHEC-I

Table 7 Electronic absorption spectra of small heterocyclic systems

Ring	$_{max}$ *(nm)*	*Absorption coefficient*	*References*
	179 145 118	4200 6100 6300	1969JCP(51)52 1972BCJ3026
	171 158 143	5600	CHEC-I(5.05.2.5)99 1976JCP(64)2062
	260 205	40 4000	CHEC-I(5.06.2.4)136
	454[a]	93	2003JOC1555
	191		1976JCP(64)2062
	187 174 161 153	2000 2750	1976JCP(64)2062
	275 218	30 600	CHEC-I(5.14.2.4)417
	340 238	80 7440	CHEC-I(5.15.1.2.9)455

[a]3,3-Di(1-adamantyl) derivative.

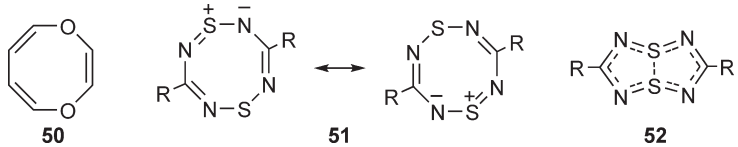
(5.08.2.3.2)201>. The absorption maximum of dioxetanes occurs in the region 280300 nm (< 30) with weak tailing up to 450 nm, which is responsible for the yellow color <1975CJC1103, CHEC-III(2.16.3.1.2)777>.

2.5.3.5.2 Electronic spectra of large-ring heterocyclic compounds

Electronic spectra, so very important in the characterization of five- and six-membered heterocycles, have played a lesser role in the study of large heterocyclic rings, and fewer data are available for comparison. **Table 8** shows UVVis spectral data for representative seven-membered unsaturated heterocycles.

Many 1,2-diazocines, including the parent **48** (R = H) <1979JOC1264> and its 3,8-diaryl-4,7-dichloro derivatives, are yellow <1986CJC1087>. However, the color is quite sensitive to substituents and replacing one or both chlorines in the 4 and 7 positions by nitrogen or sulfur substituents leads to colorless compounds <1987BCJ731>.

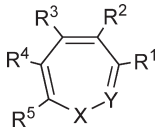
The parent 1,4-dioxocin **50** is colorless, with its major absorption band well into the ultraviolet [238 nm (3.86)] with a weak shoulder at 285 nm (2.50), a spectrum similar to that of 1,3,6-cyclooctatriene <1972AGE935>.



50 **51** **52**

The ultraviolet spectra of 1,5-dithia-2,4,6,8-tetrazocines **51** (R = Ph) ($_{max}$ 306.5 nm) and **51** (R = NMe_2) ($_{max}$ 229 nm) reflect the unusual structural dependence on substitution that exists for these compounds <1981JA1540>. Whereas the

Table 8 UV-Vis data for seven-membered unsaturated heterocycles



X	Y	R^1	R^2	R^3	R^4	R^5	$_{max}$ ($log\ _{max}$)	Reference
O	CH	H	H	H	H	H	305sh (2.95)	1967AGE385
O	CMe	H	H	H	H	H	297 (3.26)	1967AGE385
O	CMe	H	H	H	H	Me	297 (3.26)	1967AGE385
O	CCN	H	H	H	H	H	204 (4.04), 307 (3.23)	1981JOC813
O	CCN	H	H	H	H	CN	323 (3.41)	1976TL1167
NCO_2Me	CH	H	H	H	H	H	208 (4.34), 242sh (3.44), 318 (2.83)	1969JOC2866
NCO_2Me	CH	Me	H	H	Me	H	215 (4.36), 244sh (3.35), 301 (2.83)	1969JOC2866
NSO_2Me	CH	H	H	H	H	H	205 (4.24), 307 (2.88)	1969JOC2866
NSO_2Me	CH	H	$(CH_2)_4$		H	H	205 (4.34), 274 (3.51), 350 (2.54)	1969JOC2866
NCO_2Et	N	H	H	H	H	H	217 (4.05), 362 (2.45), 221 (4.06), 255sh (3.55)	1968TL4541 1970JOC433
NCO_2Et	N	H	Me	H	Me	H	222 (3.94), 250sh (3.77)	1970JOC433
S	CBu^t	H	H	H	H	Bu^t	226 (4.02), 252 (3.35), 362 (2.51)	1982TL3195
S	CBu^t	H	Me	Me	H	Bu^t	206 (4.26), 226 (4.00), 253 (3.58), 336 (2.68)	1982CL1843

former compound **51** (R = Ph) has a perfectly planar eight-membered ring, the 3,7-bis(dimethylamino) derivative is in fact folded about an axis drawn through the two sulfur atoms as shown in structure **52** (see also Section 2.5.4.2.2).

2.5.3.6 IR Spectroscopy

IR spectroscopy can give a great deal of information on small-ring heterocycles, because of the effects of ring strain on the frequencies of vibration of substituents attached to the ring and because the ring vibrations fall into a readily accessible region of the IR spectrum. A wealth of data has been gathered and can be found in the monograph chapters of CHEC-I and in the following reviews <1963PMH(2)161, 1971PMH(4)265, 1975MI50100, 1975MI50101>. This section concentrates on vibrations of general diagnostic value. A treatment emphasizing the theoretical foundations is available <1963PMH(2)161, 1971PMH(4)265>.

Small rings show high CH absorption frequencies for the ring CH bonds (between 3080 and 3000 cm^1). The asymmetric CH stretching frequency decreases with increasing ring size, from 3047 cm^1 for aziridine to 2966 cm^1 for azetidine and 2950 cm^1 for pyrrolidine. Analogous changes are found in saturated oxygen heterocycles (3052, 2978, 2958 cm^1) and their sulfur analogues (3047, 2968, 2959 cm^1) <1971PMH(4)278>. The stretching frequencies for exocyclic C═X bonds follow a similar sequence, with the smallest rings having the highest frequencies, as seen in **Table 9**. Four-membered rings have somewhat lower C═X frequencies; the carbonyl frequency of azetidin-2-one is 1786 cm^1 and that of oxetan-2-one is 1832 cm^1.

Ring-breathing frequencies are shown in **Table 10**, together with some CH IR absorptions. As expected, the ring-breathing frequencies are lower for four-membered rings than for three-membered rings <1963PMH(2)161, 1971PMH(4)265>.

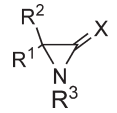
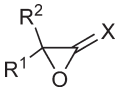
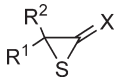
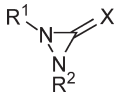
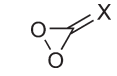
IR spectra are less useful for the structure determination of large heterocyclic rings than for small ones. The ring-breathing vibrations fall into a range well below that commonly used in the laboratory, and the absorptions are often broad and ill defined. Owing to the almost infinite variety of special effects, the bond angle deformation and the consequent effect on the absorption frequencies of ring CH, C═O, and C═X bands are not easily used in the diagnosis of an unknown structure.

The IR spectra of, for example, oxepanes (COC, CH stretching, and CH_2 deformation) are similar to analogous noncyclic compounds.

2.5.3.7 Mass Spectrometry

The mass spectrometric fragmentation patterns of three- and four-membered heterocycles consist of: (1) cleavages typical for substituents; (2) cleavages due to the formation of particularly stable and accessible fragments (such as N_2); and (3) more characteristic patterns attributable to fragmentations promoted by ring strain and by stereochemical

Table 9 Infrared stretching frequencies for exocyclic double bonds on small rings

	Stretching frequencies					
Ring	*X = CR₂*		*X = NR*		*X = O*	
	$R^1 = R^2 = H$, $R^3 = Et$, X = CH_2	1770 cm^1	$R^1 = H$, $R^2 = Bu^t$, $R^3 = Me$, X = NMe	1805 cm^1	$R^1 = R^2 = Me$, $R^3 = Bu^t$,	1837 cm^1
	$R^1 = R^2 = Bu^t$, X = $CHBu^t$	1780 cm^1			$R^1 = R^2 = Bu^t$ $R^1 = R^2 = CF_3$	1890 cm^1 1990, 1945[a] cm^1
	$R^1 = R^2 = Me$, X = CMe_2	1738 cm^1	$R^1 = R^2 = Ph$, X = NTs	1700, 1630[b] cm^1	($R^1R^2 = CH_2$=)	1785 cm^1
	R^1 = Ar, $R^2 = SO_2Me$, X = CMe_2	16901650[c] cm^1	$R^1 = R^2$ = *trans*-Bu^t, X = NBu^t	1790 cm^1	$R^1 = R^2 = Me$	1882[d] cm^1
						2045 cm^1

Taken from <1980AGE276> unless otherwise stated.
[a]<1982CC362>.
[b]<1978AGE195>.
[c]<1977AGE475>.
[d]<1975AGE428>.

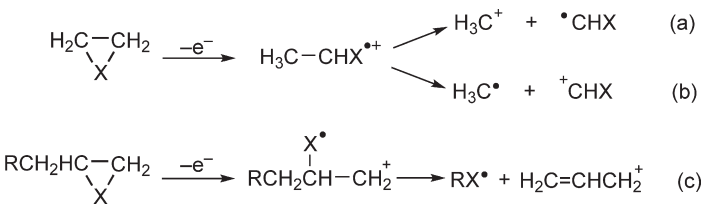
Table 10 Ring-breathing and CH IR absorptions of small heterocycles[a]

Ring	*Symmetry*	*Ring breathing*	*CH stretching*	*CH_2 scissoring*	*CH_2 wagging*	*References*
	C_s	1268, 1210	3078, 3012	1475, 1455	1128, 1131, 1088, 998	1963PMH(2)161 1971PMH(4)277
	C_{2v}	1266	3079, 3063, 3016, 3005	1490, 1470	1153, 1120	1963PMH(2)161 1971PMH(4)277
	C_{2v}	1112	3080, 3000	1446, 1427	1051,1025	1963PMH(2)161 1971PMH(4)277
		980970, 900				1963PMH(2)161 1971PMH(4)277
		738	2980, 2942	1438	1187	1979MI50102

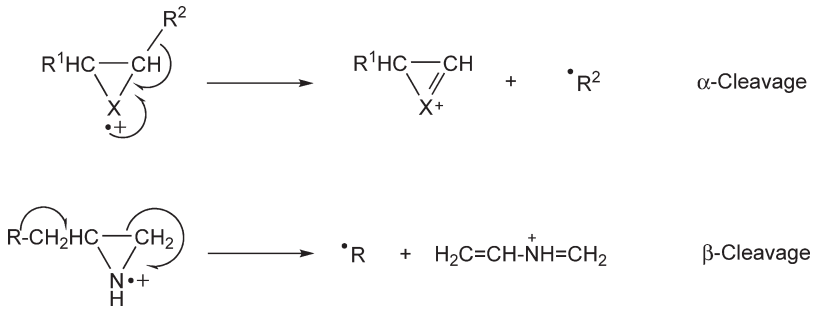
[a]cm^1.

factors. Thus, small rings usually open after ionization. In aziridines this can be accomplished by loss of the substituent on the nitrogen, i.e., H, R, etc., to give ions of the type $R_2C{=}N^+{=}CR_2$ <B-71MS296>. More generally, three-membered heterocycles cleave into a radical and a cation, either of which can contain one or two of the original ring atoms (**Scheme 2**) <CHEC-I(5.04.2.8)52, CHEC-I(5.05.2.4)99, CHEC-I(5.06.2.3)135>. Especially in thiiranes, this may involve rearrangements, such as path (c) in **Scheme 2**. -Cleavage, particularly important in oxiranes and thiiranes, may give a substituent radical and a cyclic ion (**Scheme 3**). -Cleavage, more important in aziridines, gives a radical and an ion (**Scheme 3**). Longer side-chains permit rearrangements, such as those shown in **Scheme 4** <B-71MS11>.

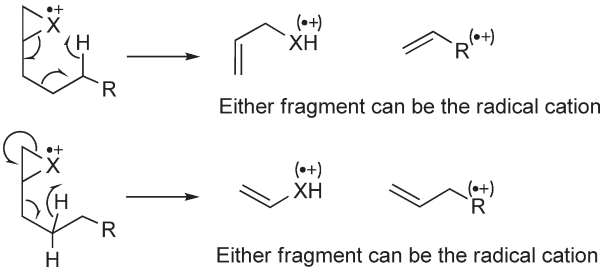
Four-membered heterocycles upon ionization prefer to cleave into two fragments, each containing two of the ring atoms. Further cleavages commence from these initial fragments (**Scheme 5**). Specific details can be found as follows: azetidines <B-71MS296>, oxetanes <B-71MS34>, and thietanes <CHEC-I(5.14.2.3)417, B-71MS229>. The cleavage to two sets of two ring-atom fragments is illustrated by the formation of fragments with the masses of ethylene,



Scheme 2



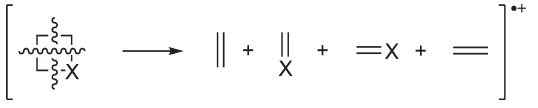
Scheme 3



Scheme 4

methyleneimine, and HC≡CNH from azetidine, and fragments with the masses of RNCO, ketenes, and imines from azetidin-2-ones <B-71MS300>. The common fragmentation of -lactams corresponds to a [2 + 2] cycloreversion cleavage of the CC and NCO bonds (cf. **Scheme 5**) <CHEC-II(1.20.3.3)627, CHEC-III(2.03.3.3)185>.

As an example of general trends of fragmentation of large heterocycles, one can mention 1,2-diazocine **48** (R = H).



Scheme 5

This displays the anticipated parent ion as well as significant fragments of *m/z* 79 (base peak) and *m/z* 80 (15%) that have been assigned to pyridine and pyridazine, respectively <1979JOC1264>. The mass spectrometric fragmentation more or less parallels the thermal decomposition of compound **48** (R = H); both afford pyridine as the major product. However, the thermal reaction affords benzene rather than pyridazine whereas mass spectrometric analysis does not suggest formation of benzene as a major fragmentation path.

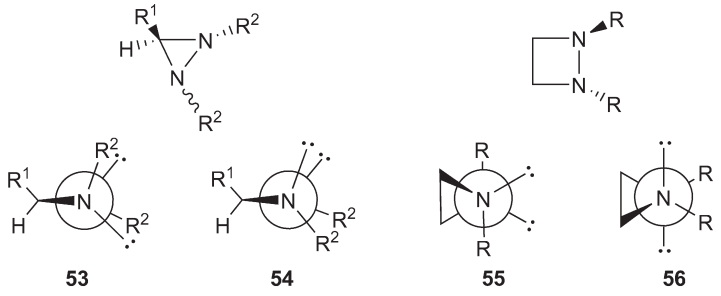
Soft-ionization mass spectrometry techniques such as matrix-assisted laser desorption ionization (MALDI) and fast atom bombardment (FAB) allow the molecular ions of cryptands and their complexes (cryptates) to be observed. The

choice of matrix is important because many cryptands easily bind alkali metals, which can even displace a cryptates guest species <CHEC-III(14.22.3.3)1080>.

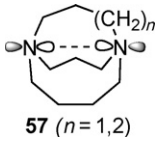
2.5.3.8 Photoelectron spectroscopy (PES)

The photoelectron spectra of the following ring systems are mentioned in the sections of CHEC-I quoted: thiiranes <CHEC-I(5.06.2.3)135>, diaziridines <CHEC-I(5.08.2.3.2)201>, diazirines <CHEC-I(5.08.2.3.3)202>, azetidines <CHEC-I(5.09.2.1)238>, oxetanes <CHEC-I(5.13.2.3.4)368>, thietanes <CHEC-I(5.14.2.4)417>, 1,2-diazetidines <CHEC-I(5.15.1.2.1)451>, dibenzazepines <CHEC-I(5.16.2.6)501>.

Based on PES, an empirical correlation between the interaction energy of adjacent nitrogen lone pairs and the dihedral angle between them has been established. PES has shown that in the case of tri- and tetraalkylated diaziridines, compounds exist in the *trans* conformation **53** with a lone pairlone pair dihedral angle of $10\bar{0}11\bar{0}$ <1994J(P2)2059>. An exception is 1,2-dimethyl-3-*tert*-butyldiaziridine; ^{13}C NMR experiments have shown that the population of the 1,2-*cis* conformation **54** ($R^1 = Bu^t$, $R^2 = Me$) increases with solvent polarity and is the major conformation in D_2O (**53**:**54** 1:2) <1998MC113>. A PES study of 1,2-dialkyl-1,2-diazetidines established that the dimethyl derivative adopts the diequatorial *trans* conformation **55** (R = Me) whereas a significant proportion of the diaxial *trans* conformation **56** ($R = Pr^i$) is present for the diisopropyl derivative <1978JA2806>.



The photoelectron spectra of the bridged diazonines **57** show two bands due to lone pair ionization and the first ionization energies are exceptionally low (<7 eV). They are probably among the most easily ionized saturated organic molecules. This is attributed to a flattening of the nitrogen atoms and a direct through-space overlap of the nitrogen lone pairs <1981JA6137>.



57 (*n* = 1,2)

2.5.4 Thermodynamic Aspects

2.5.4.1 Stability and Stabilization

2.5.4.1.1 Ring strain

The strain in three- and four-membered rings is mostly due to bond angle deformation. Some conventional ring strain energies (CRSEs) <1974PMH(6)228> are given in **Table 11**. The ring strains in three- and four-membered rings are of roughly the same magnitude and depend more on the nature of the heteroatom(s) than on the ring size. As long as nonbonding interactions are avoided, alkyl substituents stabilize small rings by a few kJ mol^1. For example, 2-methyloxirane is more stable than oxirane by 4 kJ mol^1 <1974PMH(6)229>.

Exocyclic unsaturation can stabilize small-ring heterocycles. In three-membered rings it is difficult to separate the contributions from increased angle strain from electronic interactions between the unsaturation and the heteroatom. In four-membered rings such separation has been achieved <1974PMH(6)235>. The CRSE changes by -11 kJ mol^1

Table 11 Conventional ring strain energies (CRSEs) of small rings

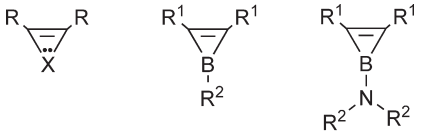
Ring					
CRSE (kJ mol^{1})	115	113	114	111	106

between oxetane (106 kJ mol^{1}) and oxetan-2-one (95 kJ mol^{1}) (corrected for electronic effects) and 4-methyleneoxetan-2-one (95 kJ mol^{1}). In contrast, an increase of 10 kJ mol^{1} over the value for cyclobutane (111 kJ mol^{1}) is observed on going to both methylenecyclobutane and 1,3-bismethylenecyclobutane.

Strain enormously influences the tendency for cyclization to give azetidines. Within the homologous series of azaheterocycles, the tendency for cyclization is smallest for the nitrogen-containing four-membered ring (5 > 3 > 6 > 7 4) <1985J(P2)1345>.

2.5.4.1.2 Aromaticity and antiaromaticity

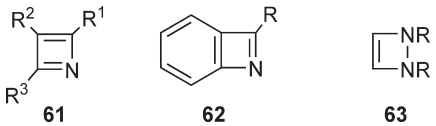
2.5.4.1.2.1 Small rings. 1*H*-Azirine, oxirene, and thiirene **58** (X = NH, O, S) are antiaromatic (4*n* -electrons in cyclic conjugation) and have not been observed, although calculations suggest that these structures correspond to local energy minima. Theoretical studies of these species are discussed in Section 2.5.2.1. Oxirenes **58** (X = O) may be transiently formed during photochemical Wolff rearrangements <2004RMC291>.



58 **59** **60**

The -systems of borirenes **59** are isoconjugate with the cyclopropenium ion and are aromatic (4*n* + 2 -electrons). In the borirene **59** ($R^1 = R^2$ = 2,3,4,5-tetramethylphenyl) the three-atom ring forms an equilateral triangle with all bond distances at 1.42 é and bond angles at 60 <1987JA2526>, strongly supporting the complete delocalization of the two -electrons in the ring. This agrees with the result of molecular orbital calculations on the parent molecule **59** ($R^1 = R^2$ = H) <1981JA2589, 1984JOC4475>. The *B*-amino derivatives **60** have also been prepared and fully characterized <2005AGE7461, 2006AGE5254>. These derivatives are isoconjugate with cyclopropenone; in the tetratrimethylsilyl derivative **60** ($R^1 = R^2 = SiMe_3$), the CC bond is 1.376 é and the CB bonds are both 1.485 é <CHEC-III (1.10.2.1.6)517>.

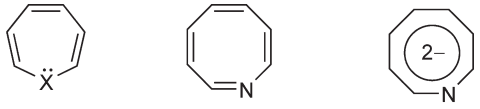
From the point of view of cyclic conjugation, an intriguing four-membered heterocycle is azete **61** ($R^1 = R^2 = R^3$ = H). Theory predicts that azete possesses a negative resonance energy of -15.5 kcal mol^{1} and is therefore slightly more stable than cyclobutadiene <CHEC-II(1.18.5.2)584>. Molecular orbital calculations on azete and diazetes are discussed in Section 2.5.2.1. There are two general approaches to stabilizing the azete system. The first involves obtaining thermodynamically stabilized compounds such as tris(dimethylamino)azete **61** ($R^1 = R^2 = R^3 = NMe_2$) <1973AGE847> and benzo-fused azete **62** (R = Ph) <1975J(P1)45>. The second approach is the synthesis of kinetically stabilized compounds having bulky ring substituents. A remarkable example is 2,3,4-tri-*tert*-butylazete **61** ($R^1 = R^2 = R^3 = Bu^t$) which has been isolated as reddish-brown needles that are stable for several days at 100 C <1986AGE842>. An X-ray structure (**Table 2**) of the 2-mesityl-3,4-di-*tert*-butyl derivative **61** (R^1 = mesityl, $R^2 = R^3 = Bu^t$) has shown that it has a rectangular structure that minimizes cyclic conjugation <1988AGE1559>.



61 **62** **63**

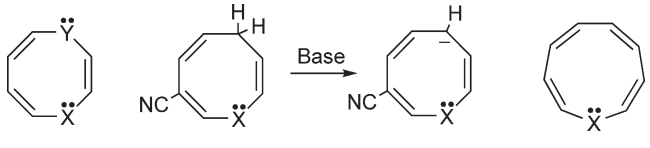
Calculations on 1,2- and 1,3-diazetes (**20–22**) are discussed in Section 2.5.2.1. Although associated with six -electrons, there is no evidence that the 1,2-dihydro-1,2-diazetes **63** have any aromatic character, presumably due in part to ring strain and nitrogen lone pair interactions <CHEC-III(2.13.2)625>.

2.5.4.1.2.2 Large rings. The heteropines **64** (X = NH, O, S) are isoconjugate with the antiaromatic 8-electron cycloheptatrienide ion. It is well established that they adopt a nonplanar boat conformation (**Figure 7**) that minimizes the unfavorable cyclic conjugation and relieves angle strain. Planar thiepin **64** (X = S) has been calculated to have a negative resonance energy (29.7 kJ mol[1]). In the boat conformations the -delocalization of the cyclic double bond is comparable to that of linear polyenes. The nonaromatic nature of the heteropines **64**, and the diazepines, is also evident in their NMR spectra (**Table 5**), where the ring protons are found in the range typical for alkenic protons, i.e., 5.07.0 ppm.



boat **64** *tub* **65** *planar* **66**

Unlike the antiaromatic and tub-shaped parent azocine **65**, the 10-electron dianions, e.g., **66**, formed by two-electron reduction of azocines are planar and aromatic in nature <1971JA161>. In a study of 3,8-dimethyl-2-methoxyazocine, an intermediate radical anion was obtained and this showed a strong tendency to disproportionate into the dianion and the neutral azocine <1983JA6078>.



67 **68** **69** **70**

The ring systems **67** are formally 10-electron systems and aromatic if planar. In practice, the geometry is dependent on the nature of the heteroatom. As might be expected from a comparison with furan, 1,4-dioxocin **67** (X = O) behaves chemically as an alkene rather than as an aromatic compound. It is readily hydrogenated to 1,4-dioxocane, tautomerizes to benzene dioxide **35**, and polymerizes readily upon standing <1972AGE935>.

Proton and ^{13}C NMR analyses have allowed assessment of both the conformation and the potential aromaticity of 1,4-dihydro-1,4-diazocines **67** (X = NR) as a function of the N-substituents (R) <1979AGE964>. Derivatives **67** (X = NH, NMe, NTMS, $NCONMe_2$) display downfield chemical shifts for the ring protons relative to those predicted for nonplanar, localized bond structures. More dramatically, the ^{13}C shifts of these derivatives appear substantially upfield from those in derivatives **67** (X = NSO_2Me, NCO_2Me). In addition, $^3J_{HH}$ coupling constants for the diene portion of the latter compounds are unequal ($^3J_{56}$ ca. 9 Hz, $^3J_{67}$ ca. 57 Hz) whereas they are nearly equal in the former derivatives (ca. 10.5 Hz), suggesting that the former are planar, with substantially delocalized bonding, while the latter are nonplanar, bond-localized structures.

The ^{1}H NMR spectra of 1*H*-aza and oxaheterocinyl anions **69** (X = NBu^t, NTs, O), formed by deprotonation of the precursors **68**, show that **69** are planar-diatropic 10-systems. Evidently, the availability of heteroatom lone pair electrons strongly influences the aromaticity of fully-unsaturated large heterocycles <1987TL2517>.

Studies of heteronines **70** have centered on the question of their aromaticity, which was surveyed as a part of a general study of heterocyclic aromaticity <2004CRV2777>. Full geometry optimization for 1*H*-azonine **70** (X = NH), oxonin **70** (X = O), and thionin **70** (X = S) was carried out at the B3LYP/6-311G(2d,p) level without symmetry constraints using the Gaussian-94 code (2001T8759). 1*H*-Azonine has a planar aromatic structure <1970TL823>, whereas the electronegativity of the oxygen atom in oxonin leads to localized electron pairs and a distorted nonplanar polyenic structure <1969CC905>. Thionin, in spite of having the same number of valence electrons as oxonin, is partially aromatic, as the sulfur atom is less electronegative than oxygen. The aromaticity of heteronines has been further quantified using NICSs criteria <2005JPCA11870>. Calculated NICS(0) values are 1*H*-azonine (13.6), thionin (0.5), and oxonin (4.2), and these suggest a fully aromatic structure for 1*H*-azonine and antiaromatic character for oxonin. The topological resonance energy model also predicts 1*H*-azonine and thionin to be aromatic and oxonin nonaromatic <1984JHC273>. A set of N-substituted azonines with Me, Et, CHO, COMe, CO_2Me, CO_2Et, CN, $CONMe_2$, and SO_2Ph substituents has been studied. With the exception of *N*-Et and *N*-Me, the nitrogen lone pairs in

these derivatives are not completely available for the cyclic delocalization. As a result, the optimized molecular structures show that planarity is lost in all the molecules and the NICS(0) values indicate that they are all nonaromatic <CHEC-III(14.10.2.1)549>.

2.5.4.2 Conformation

2.5.4.2.1 Small rings

2.5.4.2.1.1 Ring trends. Three-membered rings are necessarily planar. Four-membered heterocycles are often puckered rather than planar (**Table 2**). As expected, *exo*- and *endo*-unsaturation tend to make these systems planar. Substituted rings have ring inversion conformers of different energies (e.g., process b in **Figure 9**). Moreover, inversion of the configuration of nitrogen (process a in **Figure 9**) may multiply the number of stereoisomers of different energies. The ring inversion barriers of saturated four-membered systems are often very low. From IR and microwave data the barriers are 5.27 kJ mol^{1} for azetidine, nearly zero for oxetane, and 3.14 kJ mol^{1} for thietane <1974MI50100>. **Table 2** gives bond lengths and angles for some four-membered heterocycles. Nitrogen inversion barriers are discussed below.

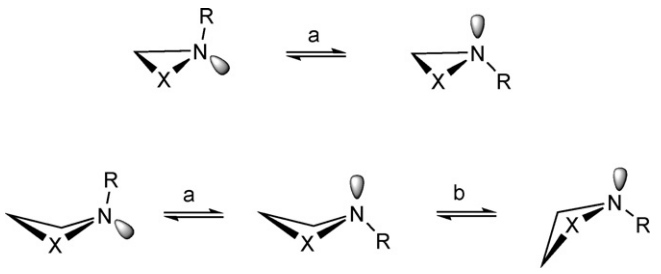


Figure 9 Nitrogen inversion (a) and ring inversion (b) in three- and four-membered heterocycles.

2.5.4.2.1.2 Pyramidal inversion at ring nitrogen.

Aziridines: The barrier to pyramidal inversion of the nitrogen atom of aziridines is considerably higher than in acyclic amines. The nitrogen-inversion barrier in aziridine itself is 19.5 kcal mol^{1} <CHEC-II(1.01.4.2)7>. Typical barriers (G) for the nitrogen inversion of N-unsubstituted aziridines are in the range 15.517.9 kcal mol^{1}, although values as low as 12.8 kcal mol^{1} have been reported. Nitrogen inversion barriers in aziridines bearing an *N*-alkyl group of low steric bulk are about 11.5 kcal mol^{1} higher than in N-unsubstituted aziridines. Compared to *N*-methylaziridine, the presence of a bulky alkyl group on nitrogen and *gem* dialkyl groups at C(2) lower G by 23 kcal mol^{1} and 1.7 kcal mol^{1}, respectively. Electron-delocalizing substituents on small-ring nitrogen atoms lower the inversion barrier by lowering the energy of the transitional flat geometry in which three substituents on the nitrogen are all in the same plane <1967JA352>.

N-Substituents bearing unshared electron pairs raise the barrier to nitrogen inversion when compared to *N*-alkylaziridines: NR_2 (+4 kcal mol^{1}), Br (+5 kcal mol^{1}), Cl (+9 kcal mol^{1}), and OR (+15 kcal mol^{1}). This trend correlates with increasing electronegativity, which increases the p-character in the NX bond. Since reaching the transition state formally involves a change from sp^3 to sp^2 hybridization, the higher p-character in the NX bond makes this change more difficult. Four-electron repulsion between the heteroatom lone pair and the nitrogen lone pair is also greatest in the trigonal transition state. The substantial barrier to inversion encountered in *N*-chloro- and *N*-alkoxyaziridines results in configurational stability of the nitrogen at room temperature. The separation of the diastereomers or enantiomers, which is made possible by this increased configurational stability, has been an active area of research <B-83MI101-01, 1990TA5, 1990TA865, 1992MI101-01, 1993JA10267>. The inversion barriers for these aziridines have been determined by racemization or epimerization studies. For example, the inversion barrier (G) of l-chloro-2,2-diphenylaziridine was determined to be 24.7 kcal mol^{1} in cyclohexane at 60C, by following the rate of racemization of optically active material <1984J(P2)791>.

Dynamic NMR and theoretical methods used to study nitrogen inversion barriers have been reviewed and data on the inversion barriers of many types of aziridines tabulated <B-92MI101-01>.

Oxaziridines: For oxaziridines the N-inversion barrier is considerably higher than that for similar aziridines. *N*-Alkyloxaziridines show a high degree of configurational stability of the pyramidal nitrogen with inversion barriers

of 3133 kcal mol^{1}. *N*-Alkyl-3,3-dialkyloxaziridines are resolvable and absolute configurations have been determined <CHEC-I(5.08.2.3.1)199>. The barrier to pyramidal inversion of *N*-sulfonyloxaziridines is also assumed to be high since chiral nonracemic derivatives have been isolated <CHEC-II(1.12.2.3)368>.

Diaziridines: Diaziridines also show slow nitrogen inversion, and carbon-substituted compounds can be resolved into enantiomers that racemize slowly at room temperature. For example, 1-methyl-3-benzyl-3-methyldiaziridine in tetrachloroethylene has a half-life of 431 min at 70 C <1969AGE212>. Preparative resolution has been achieved by classical methods, using chiral partners <1977DOK(232)1081> or chromatography on triacetyl cellulose <1979CB2028, CHEC-I(5.08.2.3.1)200>. Inversion barriers were believed to be in the range 108113 kcal mol^{1} but a more recent study of 3,3-unsubstituted diaziridines has found inversion barriers that are much higher <2004CEJ951>. The enantiomers of 1,2-di-*t*-butyldiaziridine have been separated and the inversion barrier found to be 135.8 0.2 kcal mol^{1} at 150.7 C. This is the highest recorded value for nitrogen inversion in a three-membered heterocycle <CHEC-III(1.11.5)545>.

Azetidines: N-Inversion in azetidine and azetidin-2-one is rapid, even at 77 and 40 C, respectively <B-73NMR144>. Again, halogen substituents on nitrogen drastically slow the inversion rate, so that *N*-chloro-2-methylazetidine can be separated into two diastereomers <B-77SH(1)54>. Substituent effects on nitrogen inversion are much the same as in the aziridines: *N*-aryl and *N*-acyl compounds undergo N-inversion faster, whereas *N*-halo, *N*-amino, and *N*-nitroso compounds are slower <B-77SH(1)56>. By and large, the N-inversion barriers of azetidines are ~9 kcal mol^{1} lower than those of similarly substituted aziridines <B-77SH(1)55, 1985JA4335>. In 1,2-diazetidines one finds the N-inversion rate lowered (see also Section 2.5.3.8), and coalescence temperatures and free energies of activation have been reported for a number of 1,2-diaryldiazetidin-3-ones <B-77SH(1)61>.

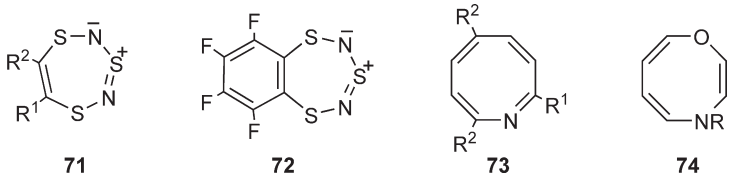
The rotational barriers of *N*-nitroso-, *N*-formyl, and *N*-(*N*,*N*-dimethylcarbamoyl)-azetidines, compared with those of analogous acyclic amides, suggest that amide conjugation is weaker when the nitrogen is part of an azetidine ring <1987KGS912>.

2.5.4.2.2 Large rings

2.5.4.2.2.1 Ring conformation.

Fully-unsaturated seven-membered heterocycles have alternating bond lengths and adopt boat conformations (**Figure 7**). Ring inversion barriers are 42.7 kJ mol^{1} for 3-methyl-3*H*-azepine and 35.6 kJ mol^{1} for 3*H*-azepin-2-one <CHEC-I(5.16.2.3)495>. The barriers for oxepin and thiepin are somewhat lower. Annulation can introduce large conformational barriers to the extent of making possible the resolution of a tribenzoxepin derivative into enantiomers <1971CB2923>.

A systematic conformational analysis of saturated seven-membered compounds including oxepane, -caprolactone as well as azepane and -caprolactam fragments (based on crystallographic results derived from the Cambridge Crystallographic Database) shows that the ring conformations in these fragments fall almost exclusively on the chair/twist-chair pseudorotational pathway, e.g., **45** (Section 2.5.3.1). There is a good qualitative agreement between the conformations observed in the crystal state and the calculated features of the potential energy hypersurface, despite the wide variety of substitution patterns covered by the X-ray data <1994AXB382, CHEC-III(13.02.3)48>.



71 **72** **73** **74**

The trithiadiazepine rings **71** and **72**, which are 14-electron Hückel systems, are planar <1984CC55, 1997CBR247>. In the derivative **71** ($R^1 = R^2 = CO_2Me$), the SN bond lengths (1.541.60 é) are all similar and are nearer to double (1.55 é) than to single (1.67 é) bonds. The ring CC and CS bonds are very similar in length to the corresponding bonds in thiophene <1984CC55>. Minimal interaction between the lone pairs of amine substituents and the delocalized -system of the rings **71** has been confirmed by X-ray crystal structures of the derivatives **71** ($R^1 = H$, $R^2 = NH_2$, NMe_2, morpholino) <1990CC1315>. In each case, the amino group is tetrahedral and rotated out of the plane of the ring such that the nitrogen lone pair is approximately orthogonal to the -system.

X-ray diffraction studies on 8 azocines **73** revealed normal dimensions and a tub conformation with N(1), C(2), C(5), C(6) in one plane and C(3), C(4), C(7), C(8) in another. In the derivative **73** ($R^1 = OMe$, $R^2 = CN$, $R^3 = CH{=}CH_2$) the two planes are 0.81 é apart and approximately parallel (angle of intersection 2.2(1)) <1985CC85>.

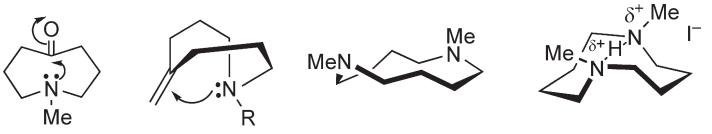
Unsubstituted 10 1,4-dihydro-1,4-diazocine **67** (X = Y = NH) and its *N,N*-bis(trimethylsilyl) derivative both display planar diazocine rings; some -electron delocalization is suggested by partial bond-length equalization. In contrast, monocyclic derivatives bearing electron-withdrawing substituents ($MeSO_2$, MeO_2C) on both nitrogens display markedly nonplanar diazocine rings and completely localized bonding <1979AGE964> (see also Section 2.5.4.1.2). The oxazocine **74** (R = 4-$MeC_6H_4SO_2$) is markedly nonplanar with pyramidal nitrogen. In contrast, the derivative **74** (R = 3,4,5-$(MeO)_3C_6H_2CH_2$) is planar, with an average deviation from the ring plane of only 0.021 é.

The 1,5-dithia-2,4,6,8-tetrazocine system **51**, e.g., R = Ph, (Section 2.5.3.5.2) prefers to adopt a planar 10-electron monocyclic structure. However, substituents at the carbon atoms with -donor properties (e.g., NMe_2) can induce pseudo-JahnTeller distortion leading to the bent, bicyclic 8-system of type **52** (R = NMe_2) with an SS transannular partial bond. X-Ray crystallographic analysis showed that the diamino derivative **52** (R = NMe_2) is folded about an axis drawn through the two sulfur atoms. The SS transannular distance in derivative **51** (R = Ph) is 3.79 é which is reduced to 2.428 é in **52** (R = NMe_2); this is longer than a disulfide bond (ca. 2.06 é) but shorter than the sum of two sulfur van der Waals radii (3.6 é) suggesting a partial bond <1981JA1540>. One dimethylamino substituent is sufficient to destroy the planarity and aromaticity of dithiatetrazocines <1989CC1137>. *Ab initio* calculations on the diamino derivative **52** (R = NH_2) estimate activation energies of amine rotation and ring inversion to be 17.1 and 17.3 kcal mol^{1}, respectively, which is in good agreement with values derived from NMR experiments <1994JA5167>.

The structures of nine-membered heterocycles as determined by X-ray crystallography seldom show strikingly unusual bond lengths or angles compared with acyclic analogues, other than a general increase in the magnitude of the endocyclic bond angles. Rings containing *trans*-C═C bonds, ester bonds, or amide bonds, however, often exhibit significant deviations from planarity of these bonds.

2.5.4.2.2.2 Transannular interactions. Transannular interactions are a feature of medium-sized heterocycles. The chemistry of eight-membered rings with two functional groups in appropriate positions may be dominated by transannular interactions. The aminoketone **75** and aminoalkene **76** represent typical examples. Photoelectron spectroscopy has been used to study the transannular interactions and conformations in these molecules. The results indicate that considerable lone pair/ interactions occur in eight-membered rings. This is consistent with IR studies in which the C═O frequency is observed to be 2030 cm^{1} lower than that in a cyclic ketone, indicating that partial single-bond character of the ketone C═O is due to the transannular amide resonance **75**. In aminoalkene **76** the C═C stretching vibration is located at 1625 cm^{1}, indicating a weaker C═C bond due to the transannular interaction with the amino group. The preferred conformation **76** may be due to the transannular interaction <1986JOC592>.

The transannular interaction of the nitrogen lone pairs in bridged diazonines **57** is discussed in Section 2.5.3.8.



75 **76** **77** **78**

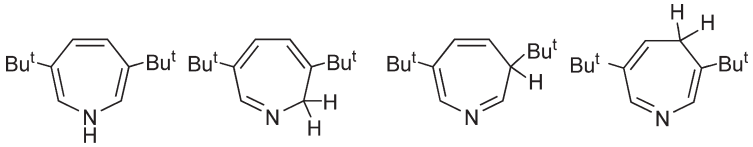
Transannular hydrogen bonding can also considerably influence the conformations of large rings. Monoprotonation of 1,6-dimethyl-1,6-diazacyclodecane **77** results in the formation of a symmetrical transannular hydrogen bond. An X-ray study of the monoprotonated iodide salt showed that it has a *cis*-decalin type structure **78** with an NN distance of 2.600 é and an NHN angle of 169 <1988CC1528>.

2.5.5 Tautomerism

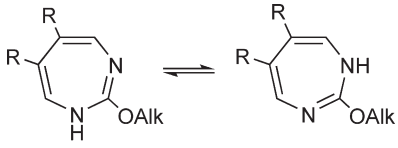
2.5.5.1 Annular Tautomerism

1*H*-azepines, e.g., **79**, are unstable and have not been isolated. In solution 8 1*H*-azepine **64** (X = NH) is stable for a few hours at -78 C but readily tautomerizes (catalyzed by acid or base) to 3*H*-azepine <1980AGE1016>. This contrasts with aromatic analogues (i.e., 6 pyrrole and 10 1*H*-azonin **70** (X = NH) <1970TL823>) for which the NH tautomers are the most stable. Heating either the 2*H*-tautomer **80** or the 3*H*-tautomer **81** at 125 C in toluene gave

similar mixtures of the isomers **8082** (12:55:1). This ratio is presumed to be determined by the relative thermodynamic stabilities of the annular tautomers **8082** as they interconvert via symmetry-allowed 1,5-hydrogen shifts <1994J(P1)1753>.

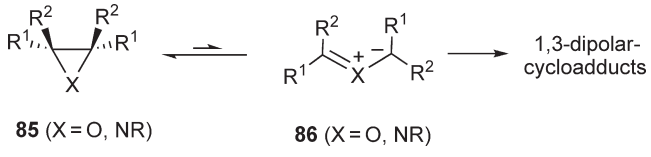


The 1,3-diazepine **83** (R = CF_3, Alk = CH_3) has been shown to have the NH structure in the solid state <2004OBC1227>. The average free energy of activation for interconversion of the tautomers **83** and **84** (R = H, Alk = Me, Et, Pr^i) has been determined to be 16.2 kcal mol^1 by the ForsénHoffman double resonance saturation transfer method <2004OBC1227>. The most stable tautomeric forms of a variety of diazepine derivatives have been documented in CHEC-III(13) and earlier editions.



2.5.5.2 Valence Tautomerism

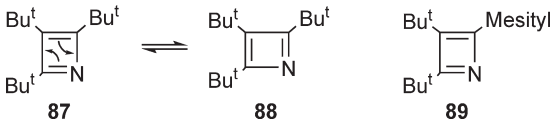
Probably one of the most useful examples of valence tautomerism in small heterocycles is the ring opening of aziridines and oxiranes **85** to give 1,3-dipoles **86** that can be trapped as cycloadducts. Thermal opening occurs via a conrotatory mode (**Scheme 6**). Photochemical opening gives the disrotatory products. Thermal opening of oxiranes **85** (X = O) to carbonyl ylides **86** (X = O) can be facilitated using microwave radiation <2003SC1861>. Opening of aziridines **85** (X = NR) to azomethine ylides **86** (X = NR) is conveniently catalyzed by Lewis acids <CHEC-III(1.01.5.5)33>. Intramolecular cycloaddition reactions of azomethine ylides generated from substituted aziridines have been reviewed <2005CRV2765>.



Scheme 6 Ring opening of oxiranes and aziridines to 1,3-dipolar valence tautomers.

In a similar way, oxaziridines open to nitrones <CHEC-III(1.12.3)560> and oxadiaziridines give diazine oxides <1970JOC2482> (see also Section 3.5.2.2).

An NMR study of the kinetically stable azete **87** has shown that at 100°C rapid equilibration between the valence tautomers **87** and **88** occurs. However, at -100°C three discrete *tert*-butyl signals are observed and equilibration is no longer taking place <1986AGE842>. This type of reaction involving the exchange of identical atoms or ligands to produce a molecule indistinguishable from the starting material is known as topomerization. In the case of the 2,3-di-*tert*-butyl-4-mesityl derivative, for which a crystal structure has been reported (**Table 2**), only the isomer **89** is detected and the population of the valence tautomer is deduced to be less than 5% <1988AGE1559>.

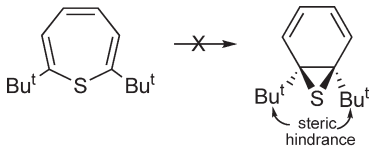


87 88 89

The position of the heteropineheteronorcaradiene equilibrium (**90** ⇄ **91**) depends on the nature of the heteroatom X and ring substituents. 1*H*-Azepine **90** (X = NH) shows no tendency to cyclize to the valence-tautomeric benzene imine **91** (X = NH) <1980AGE1016>. In contrast, oxepin **90** (X = O) is in spontaneous equilibrium with benzene oxide **91** (X = O) and ring substituents can significantly alter the position of the equilibrium <1986JOC2784, CHEC-I(5.17.1.2)550>.

90 **91**

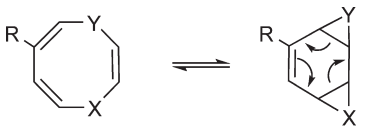
Thiepin **90** (X = S) is thermally unstable due to ready sulfur extrusion that is attributed to loss from the benzene episulfide valence tautomer **91** (X = S). The thiepin ring can be stabilized by the introduction of bulky substituents at positions 2 and 7. Thus, 2,7-di-*t*-butylthiepin **92** is thermally stable ($t_{1/2}$ = 195 h at 130°C) and this is attributed to steric hindrance between the *t*-butyl substituents inhibiting formation of the valence tautomer **93** <1982TL3195>.



92 **93**

Thermal cyclization of 6-bromo-1,4-dioxocin **94** (X = Y = O, R = Br) to the *syn*-benzene dioxide valence tautomer **95** (X = Y = O, R = Br) has an activation energy of 28.5 kcal mol^{-1}, with an *A* factor of 3.8×10^{13} in CCl_4. Tautomerization back to the dioxocin has a barrier of 25.6 kcal mol^{-1}, with an *A* factor of 3.2×10^{12}, giving a 65:35 mixture of dioxocin and benzene dioxide at 77°C <1972AGE935>. The parent 1,4-dioxocin **94** (X = Y = O, R = H) shows no evidence of tautomerizing in CCl_4 at 100°C, but gives a 95:5 ratio of dioxocin and *syn*-benzene dioxide at 60°C in benzene <1972AGE937, CHEC-II(9.23.6.2)570, CHEC-III(14.06.6.2)286>.

In contrast to dioxocins, the thermal opening of diaza and oxoaza benzene tautomers **95** (X = NR, Y = NR or O, R = H) to the corresponding 1,4-dihydro-1,4-diazocines or 1,4-dihydro-1-oxa-4-azaazocines **94** appears to be irreversible (see also Section 2.5.2.2) <1979AGE964, 1983CB2492>.



94 **95**

Part 3

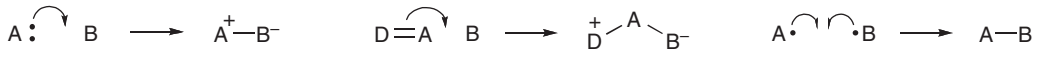
Reactivity of Heterocycles

3.1 Overview

3.1.1 Reaction Types

All organic transformations can be broken down into a succession of individual steps in each of which bonds are broken and/or formed. A chemical bond can be formed (or broken) in three ways:

1. In a generalized ionic reaction step, one of the atoms contributes both electrons to the bond either from a lone pair **1** or from another bond, often a multiple bond **2**. The atom, molecule, or ion which contributes the electron pair is a nucleophile and that which accepts it is an electrophile.
2. In a free radical step, each atom contributes one electron to the bond (**3**; the single-headed arrows represent the movement of a single electron). At least one of the reactants or products must contain an unpaired electron.
3. In a cyclic transition state, the bond is formed or broken by the electrons moving in a ring.



1 **2** **3**

3.1.2 Heteroaromatic Reactivity

The basic principles governing the degree and type of reactivity shown by heteroaromatic compounds are familiar from aliphatic and benzenoid chemistry. The following three are very important:

1. Oxygen, nitrogen, or sulfur multiply bonded to carbon can accept the whole of a pair of electrons **4** and thus allow a nucleophilic reagent to attack the carbon atom, as in many common reactions of carbonyl compounds. The attack by a nucleophilic reagent is easier when the heteroatom carries a positive charge **5**.

4 **5** **6** **7**

2. A pair of electrons on oxygen, nitrogen, or sulfur adjacent to an unsaturated system can be made available for reaction through that system **6**. This can also happen when the heteroatom carries a negative charge **7**; the alkylation of the acetoacetate anion on carbon is an analogous reaction in aliphatic chemistry.
3. Aromatic compounds tend to 'revert to type,' i.e., to return to their initial system of unsaturation, if disturbed.

These basic principles give much insight into the reactions of aromatic heterocyclic compounds.

3.1.3 Arrangement of the Reactivity Sections

Within each of the main groups of ring systems, the reactivity chapters are arranged in the same way, as is described in Part 5 (Appendix *'A,'* Section 4).

Space restrictions mean that the reactivity of multiheteroatom systems or fused systems where both rings are heterocyclic cannot be covered in this section – the reader is referred to the relevant CHEC volumes. Space again dictates that the chemistries of oxygen- and sulfur-containing six-membered heterocycles, and the chemistry of monocyclic six-membered heterocycles with more than one heteroatom, are only briefly indicated alongside the description of pyridine/quinoline/isoquinoline chemistry, but especially where these are not shown by the pyridine prototypes, but again the reader should study the CHEC volumes for a full discussion. The inclusion of an extra heteroatom in a six-membered system exaggerates the effect of the first and so often it is possible to predict properties by extrapolation; however, the same is not true for the five-membered systems, so these heterocycles with more than one heteroatom are considered in detail and separately.

3.2
Reactivity of Six-membered Rings

3.2.1 Reactivity of Aromatic Rings

3.2.1.1 General Survey of Reactivity

3.2.1.1.1 Pyridines

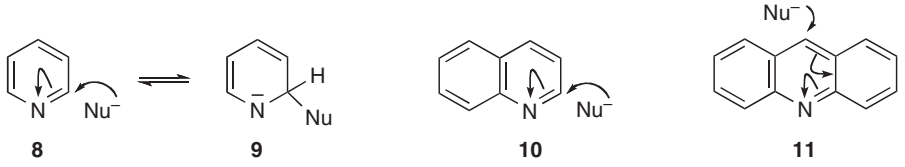
1. Most pyridines are thermally and photochemically stable but, just as in benzenes, polysubstitution can lead to susceptibility to such reaction modes.
2. As a first approximation, the reactions of pyridines with electrophiles can be compared with those of trimethylamine and benzene. Thus, pyridine reacts easily at the nitrogen atom with reagents such as proton acids, Lewis acids, metal ions, and reactive halides to form salts, coordination compounds, complexes, and quaternary salts, respectively. Under much more vigorous conditions it reacts at ring carbons to form C-substitution products in nitration, sulfonation, and halogenation reactions.

   Pyridine is a weaker base ($pK_a = 5.2$) than trimethylamine ($pK_a = 9.8$): the sp^2-hybridized lone pair of the pyridine nitrogen atom is less available than the sp^3 lone pair. The conditions required for nitration or sulfonation of pyridine under classical conditions are far harsher than those needed for benzene. The substitution of a CH group in benzene with a nitrogen atom is equivalent to introducing an electron-withdrawing group (nitrogen is more electronegative than carbon); thus, pyridine itself is substituted at the 3-position (like *meta*-substitution of nitrobenzene and about as readily). However, electrophilic reagents react at the pyridine nitrogen atom very readily, and when strongly acid media are used for nitration and sulfonation, conversion to pyridinium cation is essentially complete. Thus, the CH in benzene is replaced by NH^+ and the positively charged nitrogen reduces the reactivity toward electrophilic substitution even more markedly. It is for this reason that unactivated pyridines are nitrated and sulfonated only with difficulty, and at high

temperatures. Halogenation of pyridines is easier: N-halogenation is incomplete and C-halogenation can occur on the free base. Dihalogenation occurs since a halogen atom causes relatively little additional deactivation of the ring.

3. The drift of electron density toward the nitrogen atom allows nucleophilic reagents to attack pyridines. Such attack occurs preferentially at - or -ring-carbon atoms.

   Nucleophilic attack at ring carbon occurs in benzenes only when strongly electron-withdrawing substituents are present. Even with pyridine, only the strongest nucleophiles react. This is because the formation of the initial adduct **9** from pyridine **8** involves dearomatization and consequently, once formed, many such adducts tend to rearomatize by dissociation (**8** **9**). Benzo fusion decreases the loss in aromaticity for the formation of an adduct and thus quinoline **10** and especially acridine **11** react more readily with nucleophiles.



8 **9** **10** **11**

Reaction with strong bases by deprotonation at a C-hydrogen occurs in pyridine much more readily than in benzene. The intrinsic reactivity order is > > rather than , > because of lone pairlone pair repulsion in the -deprotonated species; however, the use of special bases or the presence of *ortho*-directing substituents can alter this order (cf. discussion in Section 3.2.1.8).

4. Pyridines undergo a variety of reactions with radical reagents, and at surfaces: many of these parallel the corresponding reactions of benzenes; however, the reaction of nucleophilic radicals with protonated pyridines is important (the Minisci reaction). Electron uptake from a metal to form a radical anion occurs readily.
5. Propensity toward cyclic transition state reactions again shows a parallel with benzenes: generally it is small for pyridines, but increases with suitable polysubstitution.

3.2.1.1.2 Azines

Extrapolation from benzene through pyridine to the diazines and then to the triazines and tetrazines delineates the main trends of azine chemistry.

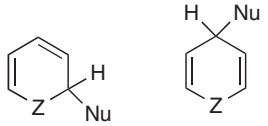
1. Reactions with electrophilic reagents become successively more difficult than with pyridine, both at nitrogen (weakened basicity) and at ring carbon atoms (no reaction at all without activation, even in diazines).
2. Conversely, nucleophilic attack is increasingly easier than in pyridine. Nucleophiles which react only with quaternized pyridines will sometimes react with the parent diazines. Triazines and tetrazines are even attacked by weak nucleophiles.
3. Successive introduction of nitrogen atoms into benzene causes a gradual reduction in aromatic stabilization. The diazines still show typical aromatic behavior in that in most of their reactions they revert to type. However, with the triazines and tetrazines, decreasing aromaticity increases the ease of both thermal and photochemical fragmentations and rearrangements, and of cyclic transition state reactions with other reagents.
4. Successive substitution of carbon by nitrogen lowers the energy of the LUMO. As a consequence, the ease of reduction and the stability of radical anions are increased from benzene to pyridine, diazines, triazines, and tetrazines.

3.2.1.1.3 Cationic rings

1. In the pyridinium, pyrylium, and thiopyrylium cations, there is no available heteroatom lone pair, and electrophilic attack at ring carbon is severely discouraged by the positive charge, although it can occur if sufficiently activating substituents are present.

   Diazinium, oxazinium, and thiazinium cations possess a pyridine-like nitrogen atom, but it is of very weak basicity and nucleophilicity. However, pyridazines do form diquaternary salts with very strong alkylating agents such as oxonium compounds. Electrophilic attack at ring carbon in these compounds is practically unknown. These trends are emphasized in cationic rings with an increased number of nitrogen atoms.
2. A positive charge facilitates attack by nucleophilic reagents at positions or to the heteroatom. Amines, hydroxide, alkoxide, sulfide, cyanide and borohydride ions, certain carbanions, and in some cases chloride ions react with pyridinium, pyrylium, and thiopyrylium cations under mild conditions to give initial adducts of types **12** and **13**.

These adducts undergo a wide variety of further transformations. Such reactions are further encouraged by the additional nitrogen atoms in diazinium, triazinium, etc., cations.



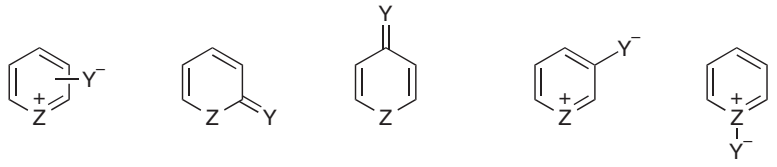
12 **13**

3. A positive charge perturbs the electron distribution and thus reduces the aromaticity of a six-membered cationic ring. As expected, reaction with free radicals and reactions via cyclic transition states (both intra- and intermolecular) are facilitated. The uptake of an electron to form a neutral radical is especially easy.

3.2.1.1.4 Pyridones, *N*-oxides, and mesomeric betaines

Three types of compound can be considered (see Section 2.2.1.2) to be derived from a cationic ring carrying a negatively charged substituent **14**.

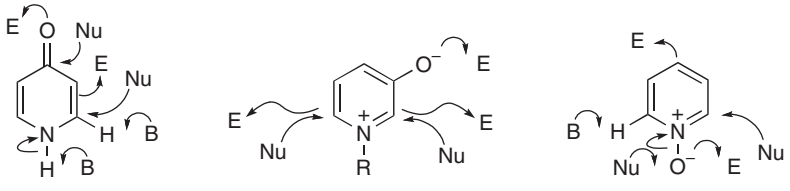
1. If Y is or to Z, then alternative uncharged canonical structures **15** and **16** exist as in pyridones, pyridinethiones, etc. (see Section 3.2.3.7.2 for an overall survey of the reactivity of this type of compounds).



14 **15** **16** **17** **18**

2. If Y is in the -position, the compounds are true zwitterions **17** as in pyridinium-3-olates, etc.
3. If Z is nitrogen, then the substituent Y can be directly attached to it, to give pyridine *N*-oxides, *N*-imides, etc., **18** (see Section 3.2.3.12.5 for an overall survey of their reactivity).

These compounds all contain both an electron source (Y) and an electron sink (Z^+). Furthermore, their aromaticity is significantly reduced by the nonuniform electron distribution. Hence they are highly reactive. The orientations of the reactions of these compounds with electrophilic and nucleophilic reagents are deducible from their canonical forms (see structures **19**–**21**).



19 **20** **21**

1. Electrophiles (E) readily attack at the Y (not at the Z) atom and at C atoms *ortho* and *para* to Y. As a generalization, electrophilic attack at Y is relatively easy and relatively easily reversible while that at C is more difficult, but less easily reversible.
2. Nucleophiles (Nu) readily attack at C atoms and to Z and bases (B) at hydrogens attached to C atoms to Z. If Z is NH, then bases can remove the N-hydrogen to give a pyridone (etc.) anion.
3. Compounds of this type undergo a wide variety of thermal and photochemical rearrangements, and cycloaddition reactions via cyclic transition states.
4. Additional ring nitrogen atoms, as in, e.g., diazinones and thiazinones, alter but little the reactivity patterns of these compounds.

3.2.1.1.5 Anionic rings

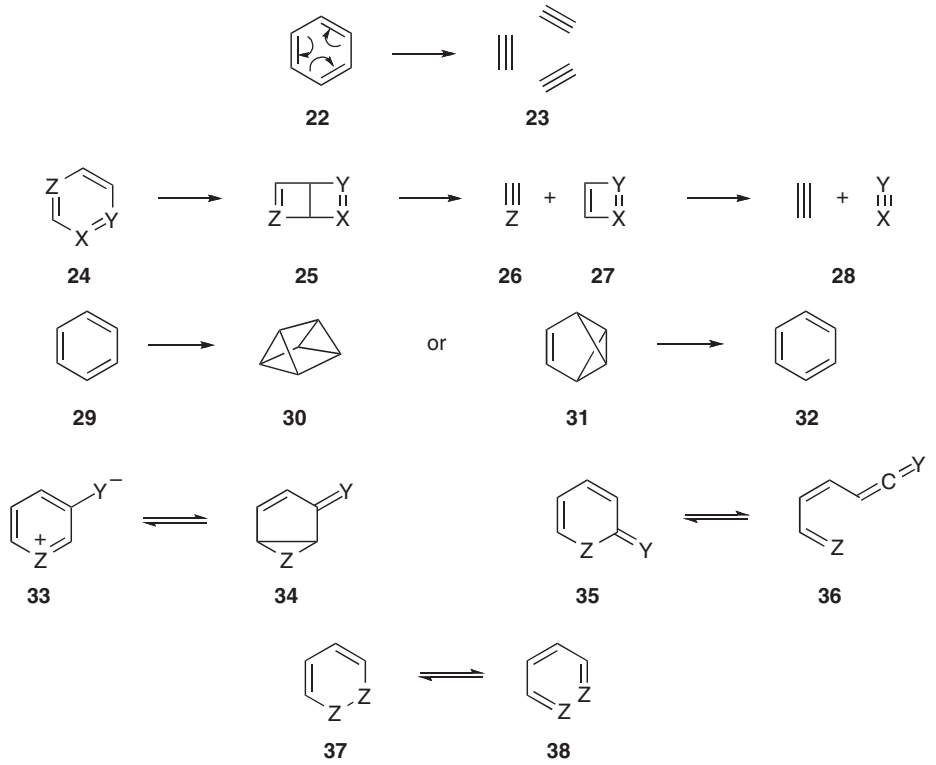
Stable anions can be formed by the loss of a proton from N-unsubstituted pyridones or hydroxypyridines. They are the pyridine analogues of phenolate anions and react very readily with electrophilic agents at N, O, or ring carbon (see Section 3.2.1.8.4).

3.2.1.1.6 Aromaticity and reversion to type

The aromaticity of six-membered rings is discussed in Section 2.2.4.2. In general most of these compounds tend to react typically by substitution rather than addition, i.e. they tend to revert to type. However, ring oxygen atoms, an increasing number of ring heteroatoms, benzannulation, and ring carbonyl groups all reduce the aromaticity. Thus, phenoxazinium and phenothiazinium salts, oxazones, and thiazones show an increasing tendency to addition reactions.

3.2.1.2 Intramolecular Thermal and Photochemical Reactions

The fundamental types of thermally and photochemically induced intramolecular transformations are summarized in **Scheme 1**. All reactions of this class involve intermediates in which aromaticity is lost; hence, they are most common in the heterocycles of lower aromaticity, i.e., polyhetero rings, cationic rings, and rings containing carbonyl groups. However, polysubstitution, especially by bulky groups, can also induce reactions via strain relief in transition states. Most of the reactions known are photochemical.

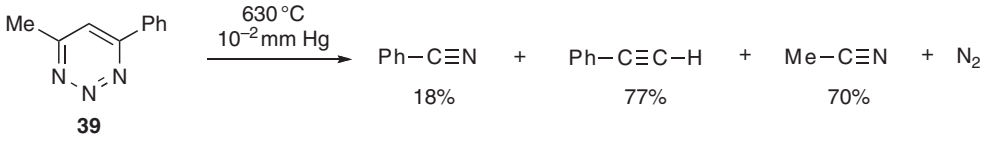


Scheme 1

3.2.1.2.1 Fragmentation (**22** **23**)

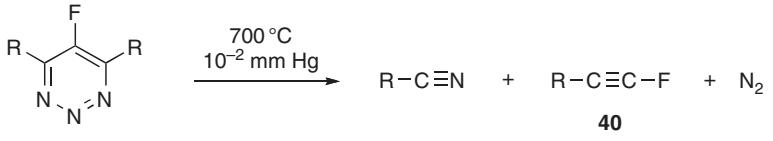
Direct fragmentation (as opposed to those via rearrangement; see next section) most often occurs in polyhetero rings. It is implicit in **Scheme 1** that the presence of contiguous nitrogen atoms tends to labilize the rings, as well as provide extra stability to the fragmentation products (by increasing the possibilities for generating N_2 molecules). Thus, 1,2,4,5-tetrazines are thermolyzed to nitrogen and nitriles (photolysis affords the same products, but this may involve intermediates of type **25**).

Under flash vacuum thermolysis (FVT) the 1,2,3-triazine **39** is readily thermolyzed to an alkyne, a nitrile, and nitrogen in high yields. For unsymmetrically substituted 1,2,3-triazines as FVT substrates, fragmentation proceeds selectively: a bulky substituent at C(4)(C(6)) makes the adjacent CN bond break more easily than the opposite CN bond (**Scheme 2**).



Scheme 2

The FVT method can be applied for the synthesis of the fluorinated alkynes, perfluoro-3-methyl-1-butyne and difluoroethyne **40** (R = $(CF_3)_2CF$, F) (**Scheme 3**) <1989CC1657, 1991CC456>. It has been claimed, however, that tris (dimethylamino)-1,2,3-triazine forms the monocyclic azete.

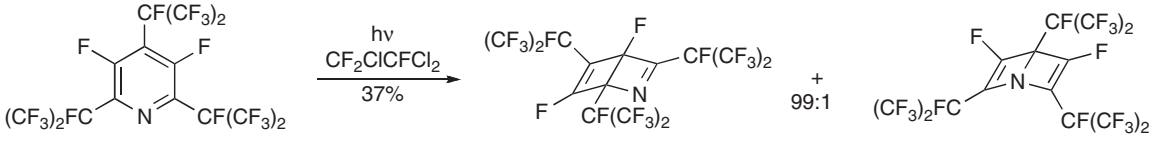


Scheme 3

Above 600°C, and also photochemically, 1,3,5-triazine decomposes to three molecules of hydrogen cyanide. Most 1,2,4-triazines are thermally very stable.

3.2.1.2.2 Rearrangement to or elimination via Dewar heterobenzenes (**24 25 26, 27 28**)

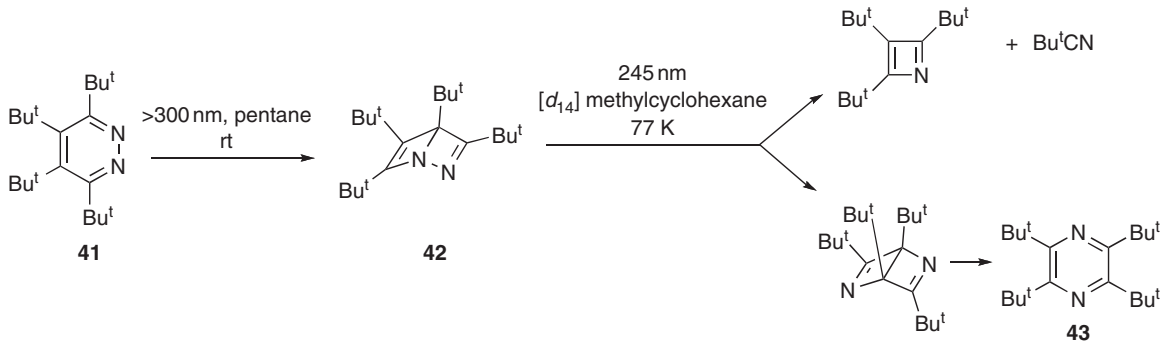
Certain polysubstituted pyridines yield isolable Dewar pyridines, as illustrated in **Scheme 4**.



Scheme 4

Irradiation of pyridine itself gives Dewar pyridine, observable spectroscopically, which in water is hydrolytically ring opened to form $H_2N(CH{=}CH)_2CHO$, but in a matrix fragments to cyclobutadiene and HCN.

3,4,5,6-Tetra-*t*-butylpyridazine **41** is converted into its Dewar isomer **42** when irradiated in pentane with light of wavelength >300 nm. Irradiation of this product at shorter wavelengths, or thermolysis, gives rise to further reaction including formation of pyrazine **43** (**Scheme 5**) <1995LA169>. Irradiation of 4-amino-2,6-dimethylpyrimidine gives an acyclic amino imine via the Dewar pyrimidine as shown in **Scheme 6**. The photoisomerization of perfluoropyridazines to pyrazines is also considered to involve Dewar diazine intermediates.

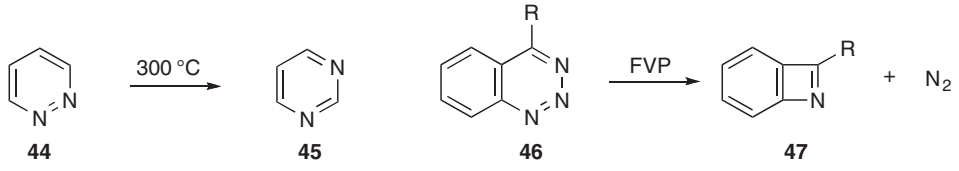


41 **42** **43**

Scheme 5

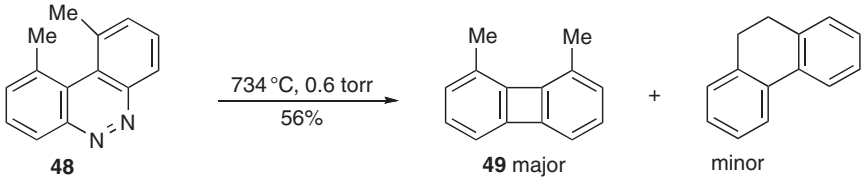
Scheme 6

Thermal reactions of this type are also known, thus, pyridazine **44** is isomerized to pyrimidine **45** at 300°C. Flash vacuum pyrolysis of 1,2,3-benzotriazines **46** gives benzazetes **47**.



44 **45** **46** **47**

Pyrolysis of 1,10-dimethylbenzo[*c*]cinnoline **48** produces 1,8-dimethylbiphenylene **49** as the major product (**Scheme 7**).

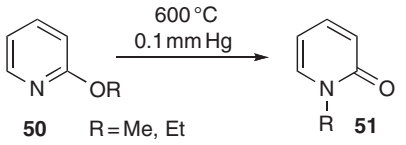


48 **49** major minor

Scheme 7

This type of isomerization is much more common in carbonyl-containing rings. A well-known example is the generation of cyclobutadiene by photolysis of pyran-2-one with the loss of CO_2. 1-Methyl-2-pyridone **24** (XY = MeNC═O, Z = CH) gives **25** (XY = MeNC═O, Z = CH); 1,3-oxazin-6-ones **24** (XY = OC═O, Z = N) form the corresponding bicycles, which can eliminate CO_2, and the 1,2,3-benzotriazin-4-ones similarly give the corresponding benzazetones.

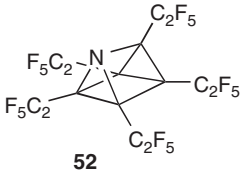
2-Alkoxypyridines such as **50** undergo thermally induced rearrangement to *N*-alkylpyridones under flash vacuum pyrolysis <2003AJC913>. 2-Methoxy-4-methylquinoline and 1-methoxyisoquinoline undergo comparable rearrangements. (The same transformation can be achieved somewhat more conveniently by heating with lithium iodide at 100°C <2008JOC6425>.)



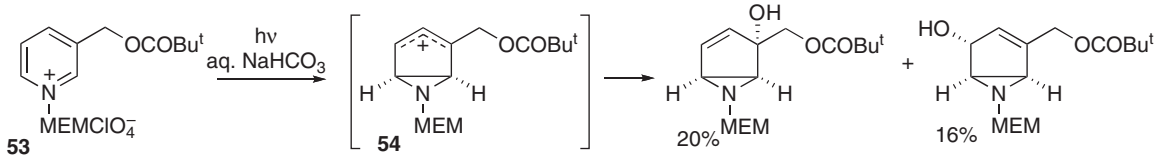
3.2.1.2.3 Rearrangement to or via heteroprismanes and heterobenzvalenes (**30, 31**)

Pentakis(pentafluoroethyl)-1-azaprismane 52 can be isolated in 91% yield by irradiation of the corresponding pyridine. The photolytic isomerization of alkylpyridines (e.g., 2-picoline to 3- and 4-picolines) is also believed to involve azaprismane intermediates.

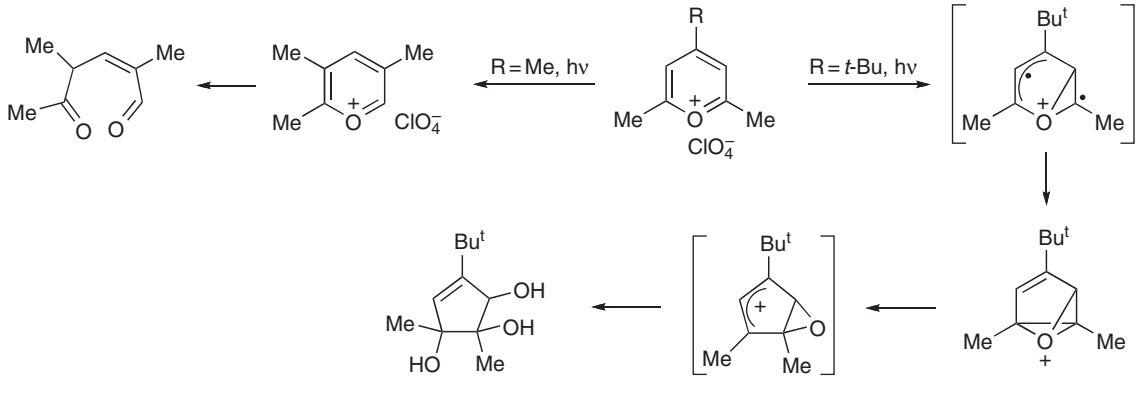
Photolysis of 1-alkylpyridinium salts, e.g., **53**, is considered to involve bicyclic aziridine allylic cations **54** as intermediates (**Scheme 8**) <2005JOC5618>, and similar behavior has been found in certain pyrylium cations (**Schemes 9** and **10**). Diazabenzvalenes are implicated in the rearrangement at 300°C of certain perfluoropyridazines to pyrimidines and pyrazines (**Scheme 11**).



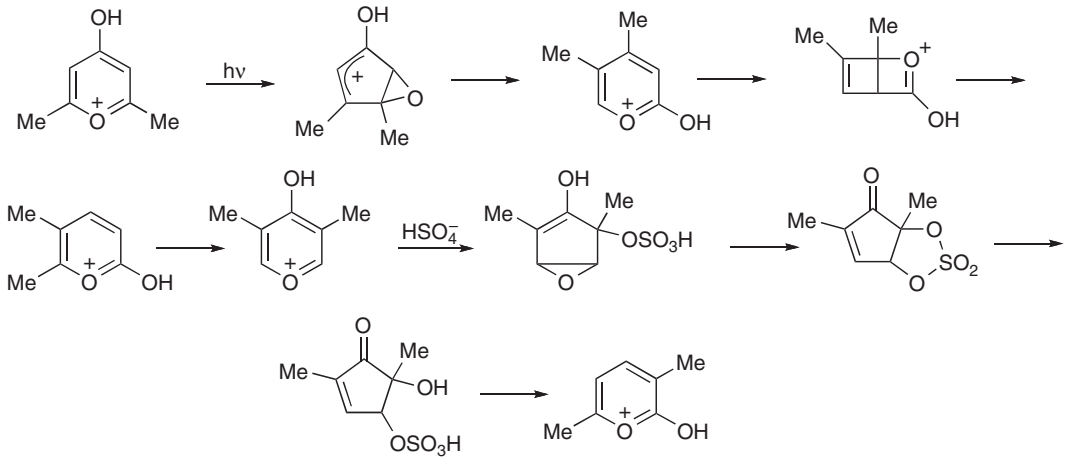
52



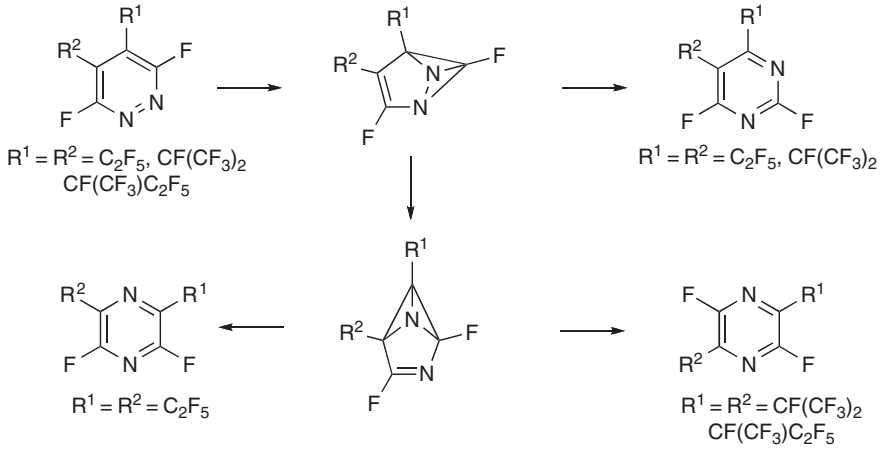
Scheme 8



Scheme 9



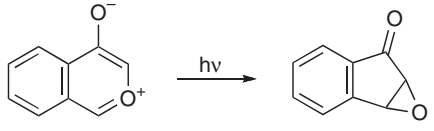
Scheme 10



Scheme 11

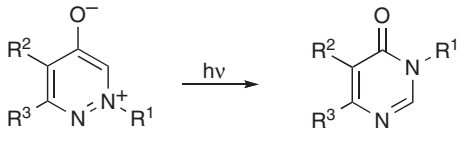
3.2.1.2.4 Rearrangement to or via 1,3-bridged heterocycles (**33 34**)

Pyridinium-3-olates **33** (Z = NR, Y = O) are converted photochemically into the bicycle **34** (Z = NR, Y = O); corresponding pyrylium-3-olates and especially isochromylium-4-olates isomerize more easily (cf. **55 56**).



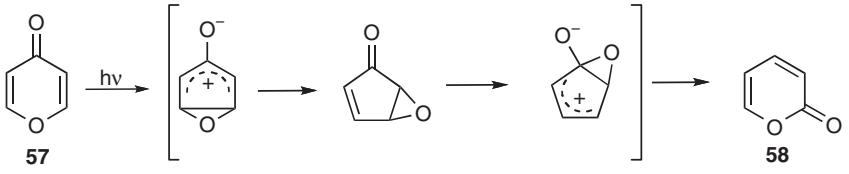
55 **56**

Pyridazinium-5-olate betaines are isomerized photochemically to corresponding pyrimidin-4-ones by a similar path (**Scheme 12**).



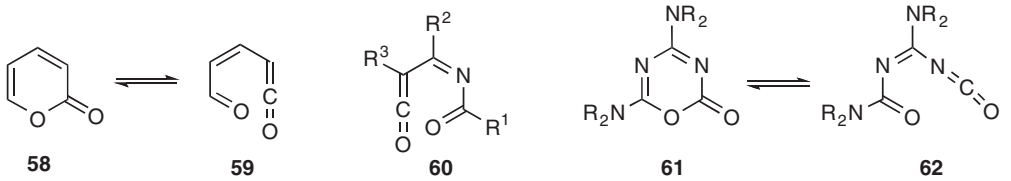
Scheme 12

Photoisomerization of pyran-4-one **57**, and substituted derivatives, to pyran-2-one **58** and analogues, involves a zwitterionic intermediate of similar type.

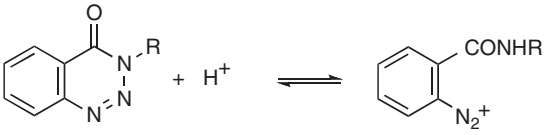


3.2.1.2.5 Ring opening (**35 36, 37 38**)

Irradiation of pyran-2-one **58** gives the ketene **59** reversibly. Similar reactions are known for aza and diaza analogues. Thus, 1,3-oxazin-6-ones isomerize photochemically to ketene imines 60, and flash vacuum pyrolysis converts the oxadiazinone **61** reversibly into isocyanate **62**.



2H-1,2-Oxazines and thiazines are unstable with respect to ring-opened isomers (cf. **30 31**). 1,2,3-Benzotriazin-4-ones on protonation undergo ring-chain tautomerism to yield diazonium ions (**Scheme 13**).



Scheme 13

3.2.1.3 Electrophilic Attack at Nitrogen

3.2.1.3.1 Introduction

Pyridines and azines behave as tertiary amines in their reactions with a wide range of electrophiles:

1. proton acids give salts;
2. Lewis acids form coordination compounds;
3. transition metal ions form complex ions;
4. reactive halogen compounds give quaternary salts;
5. electron-deficient (conjugated) alkenes (and alkynes) give quaternary salts (by Michael addition);
6. halogens form adducts;
7. certain oxidizing agents yield amine oxides;
8. electrophilic amination reagents form *N*-aminoazinium salts.

The ease of such reactions depends on two major factors: the nucleophilicity of the nitrogen atom, dominated by its charge density, and the degree of steric hindrance. A minor factor is the juxtaposition of nitrogen lone pairs (the -effect), which increases the reactivity at nitrogen in pyridazines, but not sufficiently to overcome the unfavorable electronic effect (see below).

The pK_a of an amine is a convenient measure of its nucleophilicity: in proton addition steric effects are unimportant. All other types of electrophilic attack at nitrogen are sensitive in varying degrees to steric effects from -substituents. (Exception: certain ring-formation reactions as in metal chelation.)

Additional aza substitution decreases nitrogen charge density considerably, and the azines are all less nucleophilic than pyridine. Pyridine-like nitrogen atoms in cationic rings, e.g., diazinonium, oxazinium and thiazinium, are still less nucleophilic and few reactions with electrophiles are known, although diazines can be converted by reactive alkylating agents into diquaternary salts.

3.2.1.3.2 Effect of substituents

The electronic effects are summarized in (1)(3): these are quantified by the pK_a values of pyridines in Section 3.2.1.3.3. Steric effects (4) are illustrated in Sections 3.2.1.3.43.2.1.3.11.

1. Strongly electron-withdrawing substituents, e.g., NO_2, COR, and Cl, make these reactions more difficult by decreasing the electron density on the nitrogen atom; the effect is largely inductive and therefore is particularly strong from the -position.
2. Strongly electron-donating substituents, e.g., NH_2 and OR, facilitate electrophilic attack by increasing the electron density on the nitrogen. This operates by the mesomeric effect and is strongest from the -position. From the -position opposing inductive effects possessed by these same substituents can partially or wholly cancel the increase in reactivity caused by -NH_2 or -OR. The especially powerful donor O is formed in azinone anions, which can react with electrophiles at O (see Section 3.2.3.7), at C (see Section 3.2.1.4) or N (considered in this section).
3. Fused benzene rings, aryl and alkyl groups, and other groups with relatively weak electronic effects have little influence.
4. Reactions other than proton addition are hindered by all types of -group. The shape of the substituent is important: thus, Me, Et, and *i*-Pr generally show rather similar effects whereas *t*-Bu shows a much larger steric effect. However, buttressing and the gear effect <1976JA2847> can alter this situation. A fused five-membered ring generally has a lesser hindering effect than a fused six-membered ring.

3.2.1.3.3 Orientation of reaction of azines

The position of attack in azines containing more than one ring nitrogen atom is determined by the substituents according to the guidelines given above. Thus, in 3-substituted pyridazines protonation will occur at position 2 only for strong electron-donor substituents (effectively NR_2, O). All other protonations, and all other reactions with electrophiles occur predominantly at N(1). In 4-substituted pyridazines, where steric effects are unimportant and inductive effects of the substituent less important, reaction will occur at N(1) for electron donor and N(2) for electron acceptor substituents. In 3,6-disubstituted pyridazines, the less bulky and most activating substituent will direct the addition to its nitrogen. In monocyclic 1,2,3-triazines, N(2) is the site of electrophilic attack, except in N-oxidation.

3.2.1.3.4 Proton acids

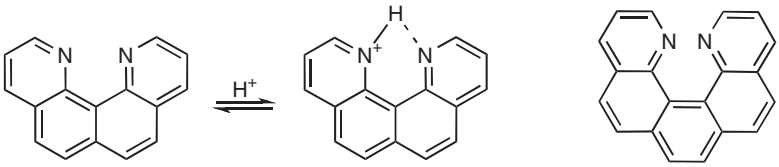
3.2.1.3.4.1 Pyridine. Pyridines form stable salts with strong acids. Pyridine itself is often used to neutralize acid formed in a reaction and as a basic solvent. The basicity of pyridine (as measured by the dissociation constant of its conjugate acid, pK_a = 5.2) is less than that of aliphatic amines (cf. NH_3, pK_a = 9.5; NMe_3, pK_a = 9.8). This reduced basicity is probably due to the different bond hybridization of the nitrogen atom: in ammonia the lone electron pair is in an sp^3-orbital, but in pyridine it is in an sp^2-orbital. The higher the s character of an orbital, the more it is concentrated near the nucleus, and the less available for bond formation. Nitriles, where the lone electron pair is in an sp-orbital, are of low basicity.

3.2.1.3.4.2 Azines. The basicity of the diazines is sharply reduced from that of pyridine: the pK_a of pyrazine is 0.4, pyrimidine is 1.1, and pyridazine is 2.1. The significantly higher basicity of pyridazine as compared to pyrazine, unexpected from a consideration of mesomeric and inductive effects, is attributed to the lone pairlone pair repulsion which is removed in the cation.

The basicities of triazines and tetrazines are undoubtedly considerably lower than those of the diazines, but few quantitative data are available.

A fused benzene ring has little effect on the pK_a values in the cases of quinoxaline (ca. 0.6) and cinnoline (2.6). Quinazoline has an apparent pK_a of 3.3 which makes it a much stronger base than pyrimidine, but this is due to covalent hydration of the quinazolinium cation (see Section 3.2.1.6.3); the true anhydrous pK_a for equilibrium between the anhydrous cation and anhydrous neutral species of quinazoline is 1.95 <1976AHC(20)117>.

Quino[7,8-*h*]quinoline **63** and benzo[1,2-*h*:4,3-*h*]diquinoline **65** belong to the so-called proton sponges and possess abnormally high basicities, pK_a = 12.8 and 10.3, respectively <1989AGE84, 1989AGE86>. This is mostly due to strongly unfavourable electrostatic repulsion between the nitrogen electron pairs in each compound. Such repulsion is canceled on transition to the protonated forms (e.g., **64**), which generates a strong intramolecular hydrogen bond. Both compounds give only monocations.



63 **64** **65**

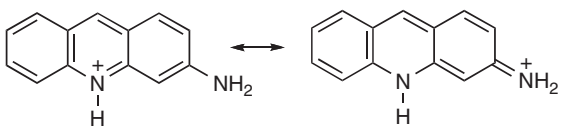
3.2.1.3.4.3 Effects of substituents on the basicity of pyridine. The pK_a values of representative substituted pyridines as compared with pyridine itself are shown in **Table 1**. Substituent effects are in line with the discussion in Section 3.2.1.3.2.

Table 1 pK_a values for monosubstituted pyridines (in H_2O)

	Me	*Ph*	*NH_2*	*OMe*	*Cl*	*NO_2*
2-Position	0.8	0.1	1.7	1.9	4.5	7.8
3-Position	0.5	0.4	0.9	0.3	2.4	4.4
4-Position	0.8	0.3	4.0	1.4	1.4	3.6

Cf. pyridine, pK_a = 5.2.

1. Methyl groups are weakly base strengthening due to hyperconjugative and inductive effects. The increase in pK_a is somewhat greater for - and - than for -methyl groups.
2. Phenyl groups are weakly electron withdrawing by the inductive effect but can release electrons by the mesomeric effect. The mesomeric effect does not operate for the *meta*-position, and 3-phenylpyridine has a reduced basicity. The inductive effect for the 4-position is weak leading to an increased basicity, whereas the two effects cancel in 2-phenylpyridine.
3. Amino groups are strong mesomeric electron donors and hence base strengthening. The order of base strength is 4-amino > 2-amino (increased importance of opposing inductive effect) > 3-amino (minimal mesomeric effect).
4. Methoxy groups are mesomeric donors but inductive acceptors. The inductive effect is dominant for the 2-position; the mesomeric effect dominates for the 4-position.
5. Halogen atoms are strong inductive acceptors and weak mesomeric donors: they cause a marked decrease in basicity, especially from -positions.
6. The nitro group, strongly electron withdrawing by both inductive and mesomeric effects, causes an especially large drop in basicity.
7. Fused benzene rings usually have little effect; cf. pK_a values: quinoline, 4.85; isoquinoline, 5.14; acridine, 5.6. Substituents on the fused rings usually have little effect on the basicity. However, those which can lead to significant charge delocalization in the conjugate acid by a *p*-quinoid canonical form are base strengthening (cf. pK_a values: 7-aminoquinoline, 6.5; 3-aminoacridine **66**, 8.04).



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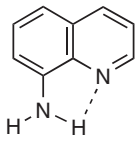


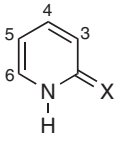
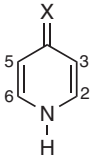
67

8. Intramolecular hydrogen bond formation with the pyridine nitrogen atom is base weakening; cf. pK_a values: 8-aminoquinoline **67**, 3.93; 4-aminoacridine, 4.40.
9. Steric effects are usually unimportant; however, in extreme cases as in 2,6-di-*t*-butylpyridine (pK_a = 3.6) the pK_a, does fall significantly below that of pyridine. This is attributed to entropy rather than enthalpy effects as it is the entropy change for the transfer of the protonated 2,6-di-*t*-butylpyridine from the gas phase to the aqueous phase that is abnormal. Aqueous protonated 2,6-di-*t*-butylpyridine is hydrogen bonded to a water molecule via the NH bond and the observed loss of entropy is due to the substantial restrictions in the internal rotations in the solution complex of protonated 2,6-di-*t*-butylpyridine <1984JA4341>.

Much work has been done on the quantitative correlation of the basicity of pyridines with Hammett substituent constants. The best single parameter correlation for 4-substituents is with $_p$ <1978AHC(22)71>.

3.2.1.3.4.4 Proton acids and azinone anions: Acidity of azinones. Some pK_a values are collected in **Table 2**. Thiones are ca. 2 pK units more acidic than the corresponding azinones. Fused benzene rings have little effect except in the 3-substituted isoquinoline series where partial bond fixation lowers the acidity. Additional aza substitution increases the acidity significantly.

Table 2 Acidity of azinones and azinethiones

Additional structural features	*-Series* 		*-Series* 	
	X = *O*	*X* = *S*	*X* = *O*	*X* = *S*
	11.7	9.97	11.09	8.83
3,4-Benzo	>11	10.82		
4,5-Benzo	9.62	8.58		
5,6-Benzo	>11	10.21	11.25	8.83
2N			8.68	6.54
3N	9.17	7.14	8.59	6.90
4N	8.23	6.32		
5N	8.59	6.90		
6N	10.46	8.30		

pK_a values in aqueous solution.

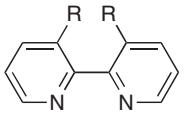
3.2.1.3.5 Metal ions

3.2.1.3.5.1 Simple complexes. Many transition and B-subgroup metals form complex ions with pyridines in aqueous solution, e.g., Ni^{2+} $Ni(C_5H_5N)_4^{2+}$; Ag^+ $Ag(C_5H_5N)_2^+$; if certain anions are also present, uncharged complexes can result, e.g., $Cu^{2+} + 2OCN + 2C_5H_5N$ $Cu(OCN)_2$ñ$(C_5H_5N)_2$, soluble in both H_2O and $CHCl_3$; Ni^{2+}, Cd^{2+}, and Zn^{2+} react similarly.

The diazines also form metal complexes. Thus, pyrazine forms tetrahedral and octahedral complexes with Co^{2+} and other transition metals: it functions as a monodentate, and also as a bidentate bridging ligand, to give polymeric complexes. The stability of these complexes is increased by back-bonding.

Pyridine and pyrazine can also replace up to three of the carbonyl groups in Group VI metal carbonyls to form compounds of type $Cr(CO)_3py_3$. The reaction of 4,5,6-triphenyl-1,2,3-triazine with nonacarbonyldiiron affords 3,4,5-triphenylpyrazole in 80% yield, probably through the initial n-donor complexation of the triazine to iron carbonyl <1987BCJ3062>.

3.2.1.3.5.2 Chelate complexes. Chelate rings can be formed by pyridines containing -substituents such as carboxyl or CH═NR. Important bicyclic chelating agents are 2,2-bipyridyl **68** (R = H), *o*-phenanthroline **69** and 8-hydroxyquinoline **70**, which all form bis and tris complexes with many metals <1994CSR327>. This type of complex formation has many analytical applications. Overlap between the d-orbitals of the metal atom and the pyridine -orbitals is believed to increase the stability of many of these complexes. Steric effects can hinder complex formation as in **68** (R = Me).



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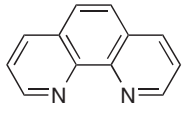

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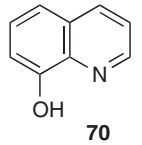

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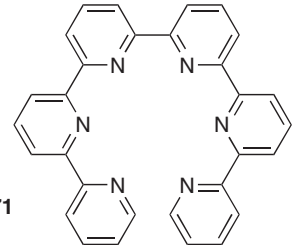
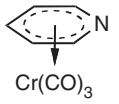


71

Suitably substituted diazines also form chelate complexes, e.g., 2,3,5,6-tetrakis(-pyridyl)pyrazine yields red tridentate complexes with Fe^{2+}. In the fast development of metallosupramolecular chemistry, many other polydentate ligands, based on 2,2-bipyridyl units, have been obtained and studied. For example, two molecules of oligopyridine **71** interact with various metal ions (Fe^{2+}, Co^{2+}, Cu^{2+}, etc.) to form a double helical $[M_2L_2]^{4+}$ complex in which each metal is bonded to a tridentate region from each ligand.

3.2.1.3.5.3 -Complexes. Azine -complexes, e.g., **7274** can also be formed from their components and their X-ray structures and reactivity have been studied <1988CB1983, 1991J(P1)757>.



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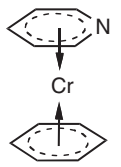

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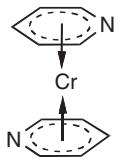


74

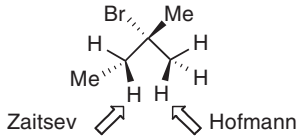
3.2.1.3.6 Alkyl and aryl halides and related compounds

3.2.1.3.6.1 N-Alkylation of pyridines. Pyridines displace halide, sulfate, toluene-*p*-sulfonate, and other ions from the corresponding alkyl compounds to form *N*-alkyl pyridinium salts. These reactions are of the S_N2 type and are sensitive to steric changes in the pyridine or electrophilic components. Pyridine reacts exothermically with iodomethane or dimethyl sulfate. Reactions involving pyridines with -substituents of any type, electron-withdrawing - or -substituents, or alkyl halides other than methyl, are slower and are often carried out by heating in a solvent of suitable high dielectric constant, such as acetonitrile, to promote ion formation. Alternatively, a highly active alkylating agent can be used, such as an alkyl triflate.

The quantitative effects of -substituents in decreasing the rates of these reactions are not additive and also depend considerably on solvent and alkylating agent. They are low in liquid sulfur dioxide as a solvent where solvation effects are small and the high dielectric constant increases the bond breaking in the transition state. For 3- and 4-substituted pyridines a Br½nsted correlation exists between the rates of quaternization and the pK_a values <1978AHC(22)71>.

With tertiary halides, bimolecular elimination usually occurs; if isomeric alkenes can result, the proportions formed depend on the steric requirements of the pyridine because formation of the more substituted alkene (Zaitsev Rule) is

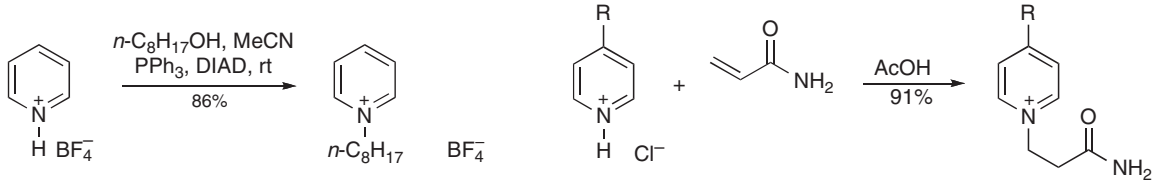
more sensitive to steric hindrance than formation of the less substituted alkene (Hofmann Rule). Pyridine and *t*-amyl bromide give 25% of 2-methylbut-1-ene (less substituted alkene), but 2,6-lutidine gives it in 45% yield (cf. **75**). However, pyridine and *t*-butyl bromide in the presence of $AgBF_4$ yield the 1-*t*-butylpyridinium ion.



75

Chiral pyridinium-based ionic liquids can be prepared by N-alkylation of pyridines with chloromethyl ()-menthyl ether <2006TA1728>. A room temperature ionic liquid brominating agent is obtained when *N*-*n*-pentylpyridinium bromide is reacted with bromine <2004SL1318>.

When an alcohol, but not the halide, is available one can use the protonic borofluoride of the pyridine and react this with the alcohol in a Mitsunobu reaction <2008TL3663>, and similarly the use of protopyridinium halides allows N-alkylation with acrylamide (**Scheme 14**) <2005DP21>.



Scheme 14

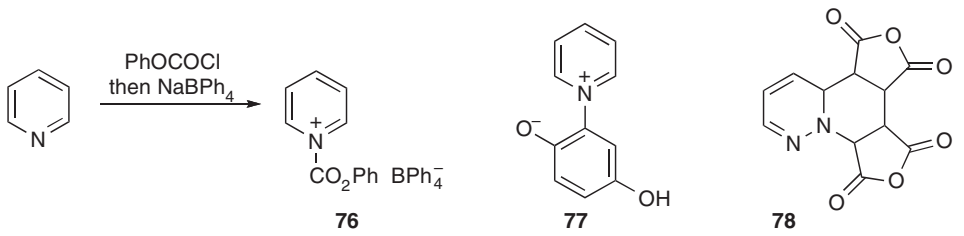
3.2.1.3.6.2 Diazines and triazines. Alkyl halides react with diazines less readily than with pyridines. All the diazines are, nevertheless, more reactive toward methyl iodide than predicted by their pK_a values and the Br½nsted relationship. The significant although modest rate enhancements found are considered to arise from interactions between the two lone pairs on the nitrogen atoms; this interaction is largest in pyridazine. 1,2,3-Triazines, for example, alkylate at C(2), e.g., <2003H(59)477>. Use of oxonium ions can convert the diazines into diquaternary salts. Quinoxalines and phenazines similarly yield diquaternary salts under forcing conditions.

The alkylation of pyridones and azinones is considered in Section 3.2.1.8.4.

3.2.1.3.6.3 N-Arylation. Only highly activated aryl halides react with pyridines. Thus, 2,4-dinitrochlorobenzene with pyridine forms 1-(2,4-dinitrophenyl)pyridinium chloride (Zinckes salt); active heteroaryl halides such as 2-chloropyrimidine react similarly. To N-phenylate pyridine, diphenyliodonium ions are needed: $Ph_2I^+BF_4^-$ + pyridine l-phenylpyridinium BF_4 + PhI. This reaction may involve initial electron transfer.

3.2.1.3.7 Acyl halides and related compounds and Michael-type reactions

Acyl and sulfonyl halides and anhydrides react instantaneously with pyridine to form quaternary salts which are excellent acylating and sulfonylating agents. The familiar use of pyridine as a solvent in such reactions reflects this. While usually generated and used *in situ*, stable *N*-acylpyridinium and *N*-acylisoquinolinium salts, e.g., **76**, have been isolated and their structures confirmed by X-ray analysis <1992JOC5136, 1994AXB25> (see also Section 2.2.3.1).



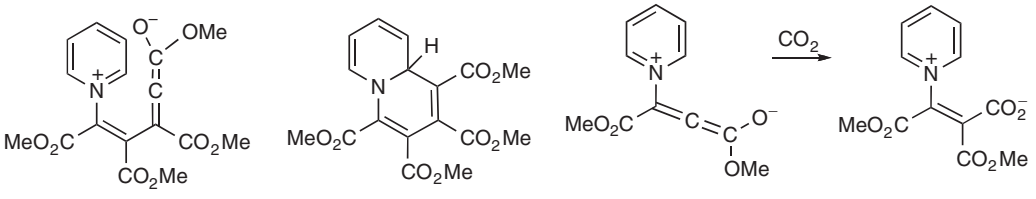
76 77 78

4-Dimethylaminopyridine (DMAP) is very much more effective than pyridine in catalyzing acylation and related reactions, and in this case many of the highly reactive intermediates can be isolated.

Bromocyanogen and pyridine give 1-cyanopyridinium bromide, important for ring-opening reactions (see, e.g., Section 3.2.1.6.3.4).

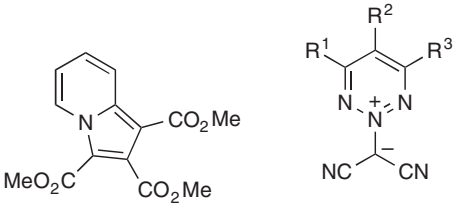
Pyridines add to quinones in Michael-type reactions to give phenolbetaines **77**. Many other Michael acceptors behave similarly. Pyridazine at room temperature with maleic anhydride gives the 2:1 adduct **78**.

Such reactions occur readily with alkynic esters, but the products isolated are often complex. Thus, the initial Michael adduct of type **79** from pyridine with dimethyl acetylenedicarboxylate reacts with a second equivalent of alkynic diester to yield **80**, and thence **81** and other products. Quinoline and isoquinoline react similarly.



80 81 79 82

Betaine **79** can also be trapped by carbon dioxide to give **82**. In the presence of water the reaction can take a different course and gives the indolizine **83** <1978AHC(23)263>.

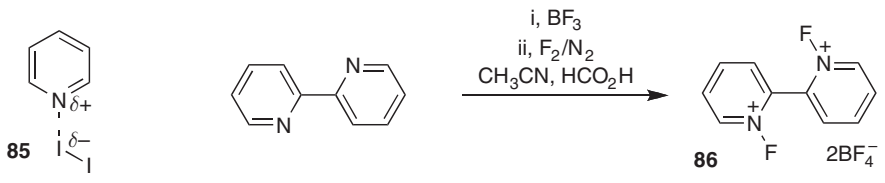


83 84

1,2,3-Triazines react with tetracyanoethylene oxide (TCNEO) to afford the stable triazinium 2-dicyanomethylides **84**.

3.2.1.3.8 Halogens

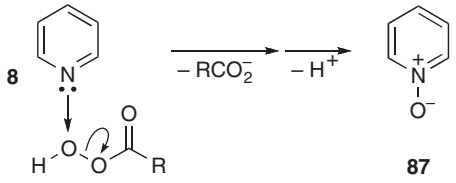
At room temperature, pyridines react reversibly with halogens and interhalogens, e.g., ICl, to give unstable adducts, which can be used as mild halogenating agents. X-ray diffraction studies of the pyridineiodine complex showed its structure to be **85**.



85 86

The molar enthalpies of complexation of pyridine with iodine are 36 kJ mol^{1} (CCl_4) and 34 kJ mol^{1} (C_6H_{12}) by calorimetry, with corresponding values of 33.1 and 34.6, respectively, using the UV absorbance of the pyridine/iodine complex <1984J(P2)731, 1987J(P2)1713>. For 2,6-dimethylpyridine the complex formation constant is reduced considerably from that for pyridine itself (from 106 to 46 in cyclohexane), but the enthalpy of formation remains sensibly constant, and thus independent of steric considerations.

Study of the complexes of pyridine, methyl nicotinate, and methyl isonicotinate with chlorine <1987JA7204> suggests that the pyridine/chlorine complex has a long three-electron bond between nitrogen and chlorine. *N*-Iodopyridinium salts can be prepared by treating $TiI_3[AsF_6]$ with pyridines, from which $[C_5H_5NI]^+[AsF_6]$ was isolated and characterized <1990ZFA(586)93>. *N*-Fluoropyridinium salts, of interest as fluorinating agents <1991MI 502-01>, are synthesized using either $FONO_2$ or CF_3SO_3Na/F_2. A highly reactive electrophilic fluorinating agent, *N*,*N*-difluoro-2,2-bipyridinium bis(tetrafluoroborate) **86**, can be prepared in one pot by introducing BF_3 gas into 2,2-bipyridine at 0 °C followed by fluorine gas diluted with nitrogen <2003JFC(120)173>.

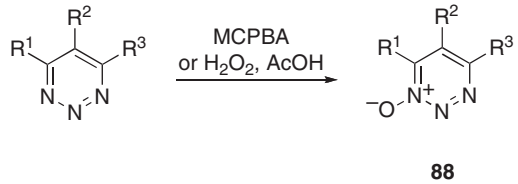


3.2.1.3.9 Peracids

Pyridine *N*-oxides are formed by the treatment of pyridines with peracids **8** **87**. Typical conditions are $MeCO_2HH_2O_2$ at 100 °C or *m*-$ClC_6H_4CO_3H$ (MCPBA)$CHCl_3$ at 0 °C, but many other variants have been described <CHEC-III (6.02.2.7)> The pyridine nitrogen atom reacts less readily with peracids than do aliphatic tertiary amines. Large -substituents and any electron-withdrawing substituents slow the reaction; thus the N-oxidation of 2,6-diphenylpyridine proceeds in poor yield, and efficient conversion of pentachloropyridine into the *N*-oxide requires a more powerful oxidant such as peroxytrifluoroacetic acid.

The formation of *N*-oxides by peracid oxidation of azines proceeds less readily than in the pyridine series. The orientation of *N*-oxide formation in diazines follows the rules outlined in Section 3.2.1.3.2. Thus, 3-aminopyridazines give mainly 2-oxides; other 3-substituted pyridazines form 1-oxides. However, the orientation of *N*-oxide formation in pyrazines can depend on the conditions: 2-chloropyrazine normally forms the 4-oxide as expected, but in strongly acidic conditions the 4-nitrogen atom is protonated, and *N*-oxide formation takes place at the 1-position. Pyrimidines and methylpyrimidines are susceptible to decomposition, ring-carbon oxidation, and ring-opening reactions on direct N-oxidation, resulting in low yields of *N*-oxides. Activating substituents are required <1984CJC1176>. In strong acid, low yields of pyrimidinones may result <1985JOC3073>. With *m*-chloroperbenzoic acid in chloroform, pyrimidine *N*-oxides result: 48% from pyrimidine and 55% from 2-methylpyrimidine <1981H(16)573>. Unsymmetrical pyrimidines are oxidized preferentially at sites *para* to strong electron donors. Bulky groups and electron-withdrawing substituents decrease oxidation, and direct the attack to the more remote nitrogen <1984CJC1176>.

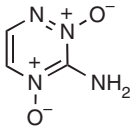
Monocyclic 1,2,3-triazines on treatment with MCPBA or $AcOHH_2O_2$, give 1- and/or 2-oxides **88** and/or **89**. 1,2,3-Triazines with bulky aryl groups on C(4) and C(6) give 2-oxides predominantly, whereas 4- and/or 6-alkyl groups allow 1-oxides to form; **Scheme 15** summarizes. The synthesis of benzo-1,2,3-triazine 2-oxides has also been reported using MCPBA <1988J(P1)1509>.



	88	**89**
$R^1=R^3=Ph$, $R^2=H$	0	81%
$R^1=Me$, $R^2=H$, $R^3=Ph$	29%	60%
$R^1=R^3=Me$, $R^2=H$	20%	48%
$R^1=Me$, $R^2=R^3=H$	15%	32%

Scheme 15

Only pyrazine and its benzo derivatives are easily converted into di-*N*-oxides, although di-*N*-oxides have been reported, for example, in the pyridazine, pyrimidine, and cinnoline series. Oxidation of 3-amino-1,2,4-triazine 2-oxide with H_2O_2 in polyphosphoric acid at 24 °C affords 3-amino-1,2,4-triazine 2,4-dioxide **90**. However, 3-amino-1,2,4-triazine with peracetic or peroxytrifluoroacetic acid at 60 °C formed only 3-amino-1,2,4-triazin-5(2*H*)-one **91** <1986H(24)951>.



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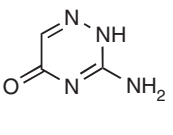

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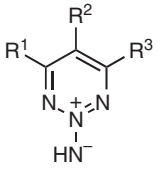

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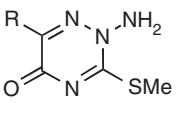


93

With hydrogen peroxide in acetic acid 1,2,4-benzotriazine gave 1,2,4-benzotriazine 1-oxide and benzotriazole, but oxidation with MCPBA afforded a mixture of the 1-oxide and the 2-oxide <1982T1793>.

3.2.1.3.10 Aminating agents

Hydroxylamine *O*-sulfonic acid converts pyridine into the 1-aminopyridinium cation. Pyridazines undergo *N*-amination readily. 1,2,3-Triazine *N*-imines **92** are obtained from the reaction with *O*-mesitylenesulfonylhydroxylamine (MSH), followed by neutralization with potassium carbonate.

3-Methylthio-1,2,4-triazin-5(2*H*)-ones are aminated regioselectively with *O*-(2,4-dinitrophenyl)hydroxylamine to give 2-amino-3-methylthio-1,2,4-triazin-5(2*H*)-ones **93** <1982JHC1583, 1983JHC1671>.

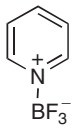
Reactions with nitrenes, which also give rise to N-amination, are considered in Section 3.2.1.9.1.

3.2.1.3.11 Other Lewis acids

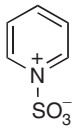
Pyridine readily forms stable coordination compounds. Thus, boron, aluminum, and gallium trihalides react at 0 °C in an inert solvent to give 1:1 adducts, e.g., **94**. Steric factors are important, and -substituents decrease the ease of reaction. This is illustrated by the heats of reaction of pyridine, 2-methylpyridine, and 2,6-dimethylpyridine with boron trifluoride which are 101.3, 94.1, and 73.2 kJ mol^{1}, respectively. The marked decrease in exothermicity here should be contrasted with the small steric requirement of the proton as shown by the pK_a values of substituted pyridines (see Section 3.2.1.3.4).

Alkyl-substituted pyridines have been complexed with a wide variety of other boron Lewis acids, BH_3, $B(OH)_3$, and BX_3, where X is a selection of alkyl, aryl, hydroxy, alkoxy, and aryloxy groups <1987J(P2)771>.

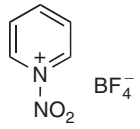
Sulfur trioxide gives an *N*-adduct **95**, which can be used as a sulfonating agent; similarly *N*-nitropyridinium tetrafluoroborate **96** is formed with NO_2^+ BF_4^-



94



95



96

3.2.1.4 Electrophilic Attack at Carbon

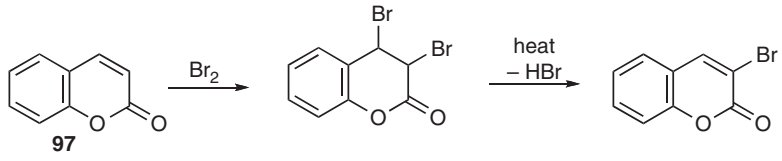
3.2.1.4.1 Species undergoing reaction and the reaction mechanism

The intrinsic difficulty of electrophilic substitution of pyridines and azines is exacerbated because many of these reactions are carried out in acidic conditions where the pyridine nitrogen atom has become protonated <2005OBC538>. However, although electrophilic reagents react at the nitrogen atoms very readily, these reactions are often reversible, and even in strongly acidic solution there is a small proportion of the free base present. Thus, *a priori* reaction is possible either on the conjugate acid majority species or on the minority free base species. In fact, considerable work has shown that some reactions do occur on the pyridine or diazine free base, while other reactions involve the conjugate acid.

The weaker the basicity of the pyridine nitrogen, the more likely it is that the reaction involves the free base. -Halogen atoms are particularly effective, in that they sharply reduce basicity but do not markedly impair susceptibility toward electrophilic substitution.

Halogenation of pyridines is easier than nitration or sulfonation because it can be carried out in nonacidic media and the pyridinehalogen adducts are appreciably dissociated. Dihalogenation can occur since one halogen atom causes little additional deactivation of the ring. The mercuration of pyridines (Section 3.2.1.4.9) probably involves initial coordination of the pyridine nitrogen to the mercury atom, and such coordination causes less ring deactivation than N-protonation.

In some instances, especially with the oxygen and sulfur heterocycles, the overall reaction leading to a substituted product does not involve an S_EAr mechanism but proceeds by an addition followed by elimination sequence, as outlined for the bromination of coumarin **97** in **Scheme 16**. The choice of experimental conditions can affect the outcome of such reactions, as illustrated by the bromination of 2-pyrone (Section 3.2.1.4.7).

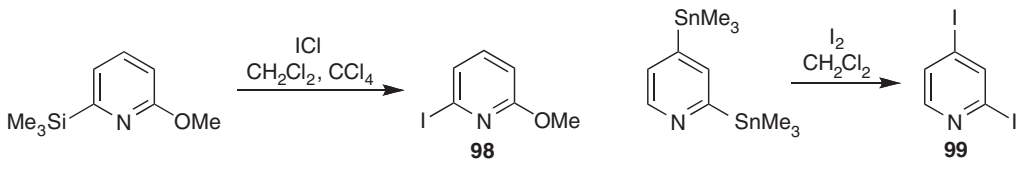


Scheme 16

3.2.1.4.2 Reactivity and effect of substituents

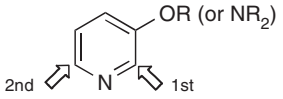
The reactivity of six-membered rings toward electrophilic substitution reactions can be summarized as follows:

1. Triazines, diazines *without* strongly activating substituents (NH_2, OR) and pyridines *with* strongly deactivating substituents (NO_2, SO_3H, COR, etc.), do not react.
2. Pyridines without strong activation, diazines with a single strongly activating substituent and diazinones, undergo nitration and sulfonation under classical conditions with difficulty (reactivity approximately that of *m*-dinitrobenzene) and halogenation somewhat more readily.
3. Pyridones, aminopyridines, and diazines with two strongly activating substituents, readily undergo nitration, sulfonation, and halogenation (reactivity approximately that of benzene).
4. Pyridines with two, and diazines with three strongly activating substituents, are very reactive toward electrophilic substitution.
5. Pyridines, pyridones, and pyrones containing an amino or hydroxy group also undergo diazo coupling, nitrosation, and Mannich reactions, as do their benzenoid analogues, phenol or aniline. Such reactions take place under conditions of relatively low acidity where less of the compound is in the form of an unreactive cation.
6. Alkyl groups and halogen atoms behave normally as weakly activating and deactivating substituents, respectively.
7. Fused benzene rings do not much affect the intrinsic reactivity, but electrophilic substitution frequently occurs in the benzene ring (see next section).
8. It follows from the above that the influence of substituent groups on the ease of electrophilic attack on ring carbon atoms can be largely predicted from a knowledge of benzene chemistry.
9. *ipso*-Displacement of silicon or tin can allow substitutions under much milder conditions: for example, introduction of an iodine on a pyridine derivative can be easily accomplished via iododesilylation or iododestannylation, exemplified by the synthesis of iodides **98** and **99** <2005JOC2494, 2005SL1188>



3.2.1.4.3 Orientation

Substituents exert their normal directive effects, and aza substitution directs *meta*. If there is conflict, then a strongly *para*-directing substituent dominates. Thus, 3-hydroxypyridine (or 3-alkoxy- or 3-dialkylaminopyridines) reacts first at the 2- and then at the 6-position **100**. *meta*-Disubstituted benzenes containing one strongly *ortho*/*para*-directing and one strongly *meta*-directing group are often further substituted between the two groups, and this may be compared with the orientation observed in **100**. Pyridine *N*-oxide is nitrated at position 4 as the free base but sulfonated at position 3 via the conjugate acid.



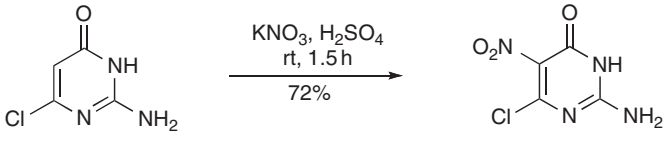
100

In benzo- and phenylpyridines and in phenylpyridine 1-oxides, electrophilic substitution usually takes place in the benzene ring. In benzopyridones, benzopyrones, and benzopyridine *N*-oxides, electrophilic substitution can occur in either the benzene or the heterocyclic ring depending on the conditions; sometimes mixtures are formed (see Section 3.2.3.2.1).

3.2.1.4.4 Nitration

3.2.1.4.4.1 Pyridines. Pyridine itself requires vigorous conditions for classical nitration ($H_2SO_4SO_3KNO_3$ at 300°C); 3-nitropyridine is obtained but only in negligible yield. A single methyl group is insufficient activation; on attempted nitration, the picolines are extensively oxidized. However, 2,6-lutidine and 2,4,6-collidine afford the corresponding 3-nitro derivatives in fair yield under milder conditions ($H_2SO_4SO_3HNO_3$ at 100°C).

An amino group facilitates nitration strongly. 2-, 3-, and 4-Aminopyridines are nitrated smoothly ($H_2SO_4HNO_3$ at 40 70°C to form mono- (5-, 2-, and 3-, respectively) and dinitro- (3,5-, 2,6-, and 3,5-, respectively) derivatives (Section 3.2.1.3.2). Alkylamino-, alkoxy- and 3-hydroxypyridines react analogously to give the corresponding nitro compounds. Activating groups also allow nitration of some diazines: for example, 2-chloro-4,6-dimethoxypyrimidine is nitrated at C(5) with a mixture of tetramethylammonium nitrate and trifluoromethanesulfonic anhydride in dichloromethane at 78°C rt, in yields up to 98% even on a molar scale <2006JME3362>. Or again, 2-amino-6-chloro-4(3*H*)-pyrimidinone is readily nitrated with potassium nitrate in concentrated sulfuric acid at room temperature (**Scheme 17**) <2001TL1793>.



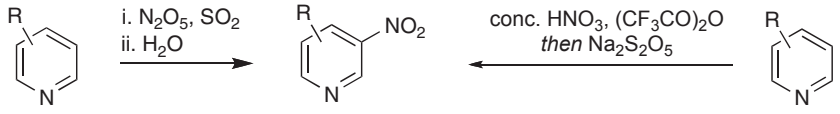
Scheme 17

Most strong acid nitrations of pyridines take place on the N-protonated species, and this includes the conversion of 2,6-dimethoxypyridine into the 3-nitro derivative. However, the further nitration of 2,6-dimethoxy-3-nitropyridine to the 3,5-dinitro derivative occurs on the free base. The introduction of the first nitro group reduces the basicity such that sufficient free base is now present for the reaction to take place through this minority species. 2,6-Dihalopyridines also undergo nitration as free bases.

In general, pyridines with $pK_a > 1$ nitrate as conjugate acids at the - or -position depending on the orientating effect of the attached substituents, while derivatives with $pK_a < 2.5$ nitrate as free bases. Those pyridines with intermediate pK_a values often show a mechanistic changeover, with change in pH (H_o).

A breakthrough in the nitration of pyridines came with the report by Bakke of the use of dinitrogen pentoxide in sulfur dioxide solution to give 3-nitropyridines in good yields <2005JHC463>. The reaction proceeds by a [1,5]-sigmatropic shift of the nitro group from the 1- to the 3-position of the ring via a dihydropyridine intermediate, rather than an electrophilic aromatic substitution.

Katritzky and coworkers described more convenient conditions wherein the dinitrogen pentoxide is prepared *in situ* from a nitric acidTFAA system, sodium metabisulfite being added later (**Scheme 18**) <2005OBC538>. Isoquinoline can thus be nitrated at C(4) and quinoline at C(3).



Scheme 18

3.2.1.4.4.2 Azines. Two or more electron-releasing substituents make 5-nitration in pyrimidines relatively easy: 2,4-diamino-6-chloropyrimidine yields the 5-nitro compound via a nitroamino intermediate. Similarly, 4-amino-3,6-dimethoxypyridazine undergoes easy nitration to the corresponding 5-nitro compound. The less activated 3-methoxy-5-methylpyridazine requires more vigorous conditions, yielding 4-, 6-, and 4,6-di-nitro derivatives.

3.2.1.4.4.3 Cationic rings. Few examples are known, but 1,2,4,6-tetramethylpyridinium can be nitrated to yield the 3-nitro derivative.

3.2.1.4.4.4 Pyridones, pyrones, and azinones. 2- and 4-Pyridone and their 1-alkyl derivatives are readily nitrated to form first the 3- or 5-mono- (H_2SO_4/HNO_3, 30 °C) and then the 3,5-di-nitro derivatives. These nitrations involve reactions of the neutral pyridone species. The proportions of 3- and 5-nitration in 2-pyridone vary with the conditions. 3-Nitration is favored at low acidity and high temperature and 5-nitration by the reverse.

Quinolin-2- and -4-ones can be nitrated in the 3-position (HNO_3, 100 °C); under conditions of higher acidity, reaction occurs on the protonated species, and hence in the benzene ring (see Section 3.2.3.2.1).

Nitration of 6-phenyl-2-pyrone depends on the conditions: the free base reacts at the 3-position, the conjugate acid which is present at higher acidities, at the *para*-position of the phenyl group.

Nitration of 4,5-dichloro-2-methylpyridazin-3-one occurs at position 6. Pyrimidin-2-one is nitrated under vigorous conditions to give the 5-nitro derivative, whereas 1-methylpyrimidine-2,4-dione yields the 5-nitro derivative at 25 °C.

3.2.1.4.4.5 Azine N-oxides. Pyridine *N*-oxide is nitrated (H_2SO_4/HNO_3, 100 °C) to give the 4-nitro derivative in good yield. Substituted pyridine oxides such as the 2- and 3-methyl, -halo, and -methoxy derivatives also give 4-nitro compounds in high yield. Quinoline *N*-oxides are selectively nitrated at the 4-position at temperatures above ca. 80 °C whereas at lower temperatures nitration occurs in the benzene ring (Section 3.2.3.2.1).

Nitrations of pyridine *N*-oxides at the 4-position take place on the neutral free base species. 2,6-Dimethoxypyridine *N*-oxide is nitrated as the conjugate acid to yield the 3-nitro derivative; a second nitration to give the 3,5-dinitro analogue takes place on the free base.

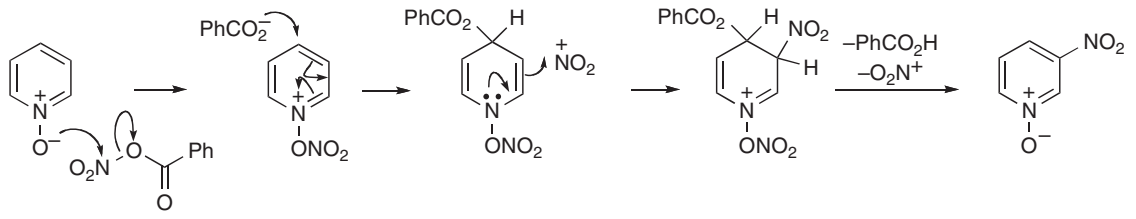
Pyridazine 1-oxide and many of its substituted derivatives undergo nitration with nitric and sulfuric acids at position 4 to form the corresponding 4-nitropyridazine 1-oxides. If the 4-position is occupied, nitration can occur at the 6-position.

Pyrimidine *N*-oxides cannot be nitrated unless they possess electron-donating substituents, e.g., 5-nitration of 2,6-diamino-4-ethylaminopyrimidine *N*-oxide <1979AJC2049>.

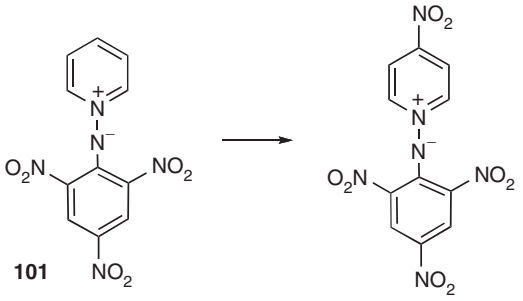
Reaction of pyridine 1-oxide with benzoyl nitrate leads to the 3-nitro derivative: the postulated mechanism is shown in **Scheme 19**.

Nitration of pyridazine *N*-oxides with acyl nitrates prepared from acyl chlorides and silver nitrate also occurs at the -position relative to the *N*-oxide group. Thus, pyridazine 1-oxide yields 3-nitropyridazine 1-oxide.

Pyridine-*N*-(2,4,6-trinitrophenyl)imine **101** can be nitrated at the pyridine 4-position.



Scheme 19



101

3.2.1.4.5 Sulfonation

Sulfonation of pyridine affords the 3-sulfonic acid in 70% yield, but vigorous conditions ($H_2SO_4SO_3$, 230°C) and $HgSO_4$ catalyst are required. The picolines form -sulfonic acids similarly. Sulfonation of pyridine at 360°C gives a considerable amount of the 4-sulfonic acid. Heating the 3-sulfonic acid at this temperature produces a similar result; presumably, thermodynamic control takes over.

2-Aminopyridine and 1-methyl-2-pyridone are sulfonated under milder conditions ($H_2SO_4SO_3$, 140°C) at the 5-position. 2,6-Di-*t*-butylpyridine is converted into the 3-sulfonic acid under mild conditions (SO_2SO_3, 0°C) because reaction of SO_3 at the nitrogen atom is prevented sterically: thus, reaction occurs on the free base, under conditions where this is the majority species.

Sulfonation of pyridine 1-oxide requires vigorous conditions ($H_2SO_4SO_3Hg^{2+}$, 230°C) and gives the 3-sulfonic acid (cf. Section 3.2.1.4.1).

3.2.1.4.6 Acid-catalyzed hydrogen exchange

Acid-catalyzed hydrogen exchange can be detected by isotopic labeling. Deuteration (followed by NMR) and tritiation (followed by radioactivity measurements) rates of exchange at various ring positions at different acidities and temperatures have been investigated. By extrapolating all measurements to 100°C and pH = 0, standardized rates of hydrogen exchange have been established for a large number of heterocycles, some of which are given in **Figure 1**.

Compared to the rate for one position in benzene (log $k_0 = 11$), the large effect of the N^+ is apparent: from the *meta*-position it more than cancels the activating effect of three *ortho*/*para* methyl groups. A neutral nitrogen has a much smaller effect as is seen by the comparisons **104**/**105** and **106**/**107**. In a protonated *N*-oxide, the rate-decreasing effect of N^+OH is little different from that of N^+H (cf. **103**/**111**); however, the neutral N^+O group is much less deactivating at the 2- and 4-positions (cf. **102**/**110**). Pyridones exchange rapidly as their neutral species.

Considerable work has also been done with activated derivatives of the diazines. 4-Aminopyridazine and pyridazin-2-one undergo exchange in the form of their free bases at position 5. Comparisons of **107** with **114** and **115** show the considerable effect of a *para*-N, while that of the *meta*-N is much less.

In the quinolinium cation, there is little difference in reactivity between position 3 and all the positions of the benzene ring **117**.

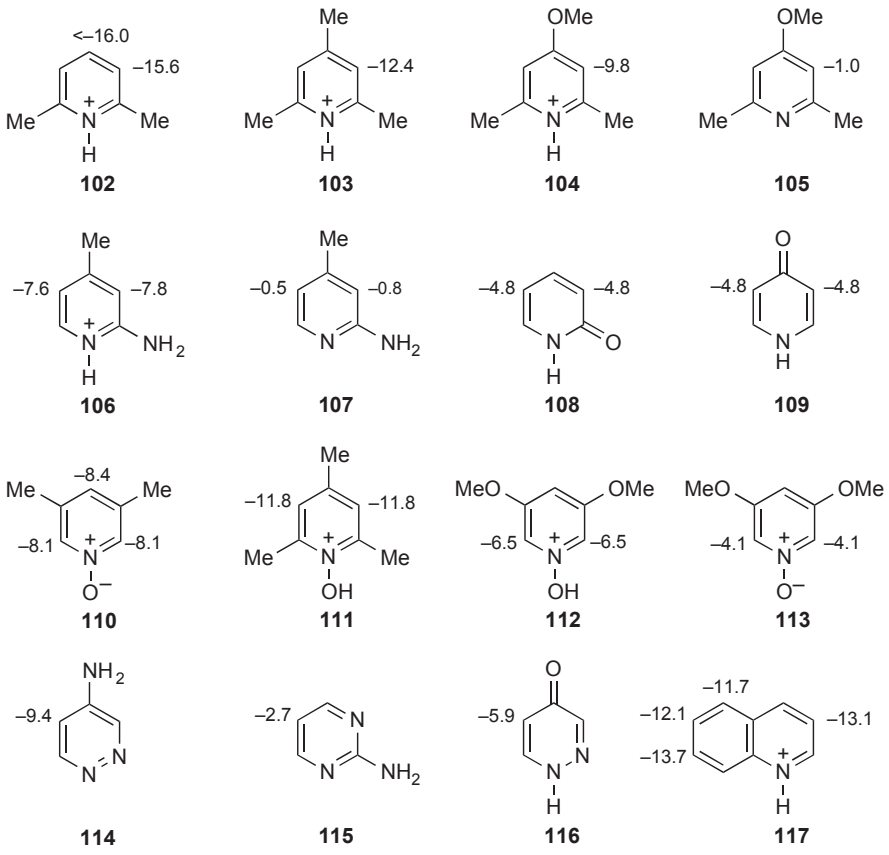
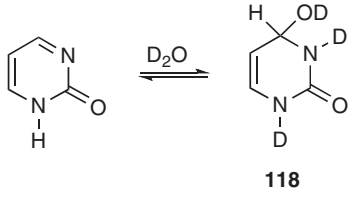


Figure 1 Rates of hydrogen exchange standardized to 100°C and pH 0 ($\log k_o$).

Pyrimidin-2-one exchanges its 5-hydrogen much faster than pyridin-2-one. However, this is due to the existence of a small proportion of the covalent hydrate **118** that undergoes rapid exchange via -protonation of the enamide unit (**Scheme 20**).



Scheme 20

3.2.1.4.7 Halogenation

3.2.1.4.7.1 Pyridines. There are several reviews on the halogenation of pyridines <1984AHC(35)281, 1988AHC(44)199, 1990AHC(47)303, 1993AHC(58)272, 1994AHC(59)286>. Electrophilic halogenation of pyridine at carbon follows the orientation order $3 > 4 \geq 2$, whereas radical halogenations occur at the 2-position (see Section 3.2.1.9.2.).

Pyridine gives perfluoropiperidine with CoF_3F_2; conversion of pyridine into mainly 2-fluoropyridine occurs with xenon difluoride.

Vapor phase chlorination at 150200°C and bromination at 300°C of pyridine give fair yields of the 3-mono- and 3,5-dihalo derivatives. As the temperature is raised, increasing amounts of -substitution occur (Section 3.2.1.9.2). Vapor-phase chlorination of quinoline yields first the 3-chloro derivatives which undergo further substitution, but alkylpyridines generally undergo side-chain halogenation (Section 3.2.3.3.3).

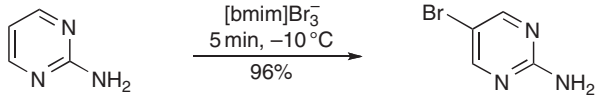
Chlorination and bromination of pyridine and some alkylpyridines at the -position can be effected in the liquid phase at ~100°C using excess $AlCl_3$ promoter. -Bromination of pyridine and 2- and 4-picoline is conveniently effected in oleum at 80120°C. Bromination kinetics using HOBr in aqueous $HClO_4$ indicate that the partial rate factor for bromination of the pyridinium cation is $\sim 10^{13}$ comparable to that for nitration.

Electrophilic iodinations of pyridines are less common: iodine in oleum produces only a low yield of 3-iodopyridine <1957JCS387>.

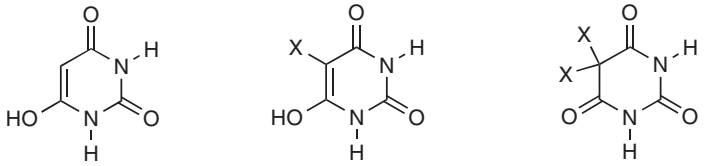
Halogenation of 3-hydroxy- and 2-, 3-, and 4-aminopyridines proceeds under milder conditions (e.g., Cl_2, Br_2, or I_2 in EtOH or H_2O, 20100°C) to form the mono- and dihalo derivatives, *ortho* and *para* to the activating group.

Electrophilic chlorination of quinoline under neutral conditions occurs in the orientation order $3 > 6 > 8$. Hammett $^+$ values predict an order for electrophilic substitution of $5 > 8$ $6 > 3$. The reactivity order can be affected by substitution of an electron-withdrawing group in the benzene ring, which directs the chlorination to the pyridine ring. Thus NCS in acetic acid or sulfuryl chloride in *o*-dichlorobenzene convert 8-nitroquinoline into 3-chloro-8-nitroquinoline in high yield <1991M935>.

3.2.1.4.7.2 Azines. Unsubstituted pyrimidine undergoes 5-halogenation under vigorous conditions. 5-Bromopyrimidine is formed in 7188% yield using bromine in solvents like benzene or nitrobenzene. Substitution on carbon is preceded by a vigorous reaction at lower temperatures involving N-bromination and perbromide formation <1990AHC(47)325>. Bromination in the vapor phase at 230°C gives 5-bromopyrimidine in 62% yield <1973JHC153>. Halogenation of diazines containing one or more activating groups proceeds easily (Br_2 or Cl_2 in H_2O, AcOH, or $CHCl_3$, 20100°C) for example, of 2-aminopyrimidine which proceeds at 10°C (**Scheme 21**) <2004S2809>. Similarly, bromination of uracil with NBS in tetrabutylammonium bromide gives 5-bromouracil in 96% yield in 4 min with microwave assistance <2005S1103>. Sometimes, 5,5-dihalo products are formed resulting in ring dearomatization, e.g., barbituric acid **119** gives successively **120** and **121**.



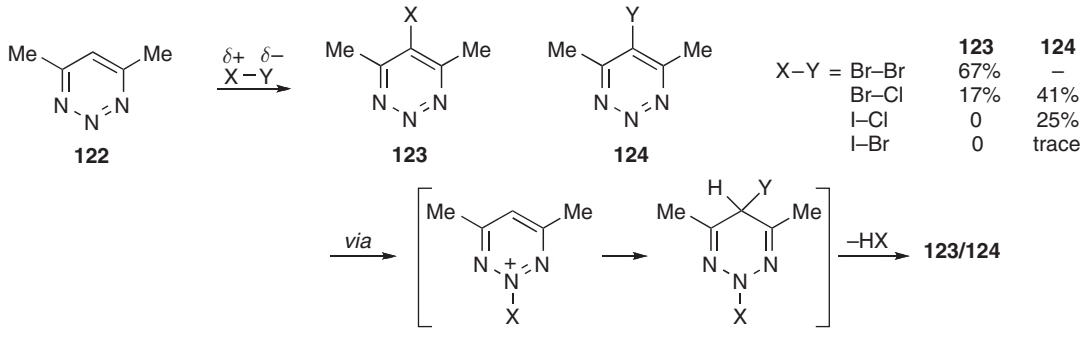
Scheme 21



119 **120** **121**

Pyrazine is chlorinated at 400°C to give a mixture of mono-, di-, tri- and tetra-chloropyrazines, presumably via a radical mechanism.

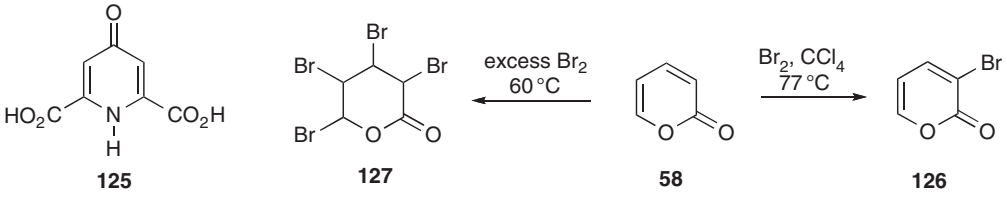
Electrophiles do not attack ring carbons of 1,2,3-triazine because of the extreme -electron deficiency of the ring system. The reaction of halogenating reagents with 4,6-dimethyl-1,2,3-triazine **122** to afford 5-halotriazines **123** and **124** is probably not a classical electrophilic substitution: the use of interhalogen reagents affords 5-halotriazines derived completely or mainly from the more electronegative halogen, which suggests that the reaction is initiated by the quaternization of N(2) with cationic halogen, followed by *nucleophilic addition* of halide ion and finally elimination of hydrogen halide (**Scheme 22**) <1986CPB4432>.



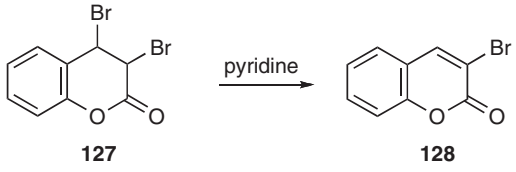
X–Y =	123	124
Br–Br	67%	–
Br–Cl	17%	41%
I–Cl	0	25%
I–Br	0	trace

Scheme 22

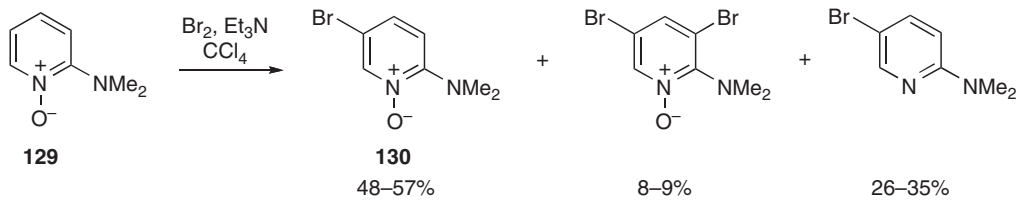
3.2.1.4.7.3 Pyridones, pyrones, azinones, and *N*-oxides. 2- and 4-Pyridones and 2- and 4-pyrones readily give their 3-mono- and 3,5-dihalo derivatives; even chelidamic acid **125** reacts in this way. Bromination of pyran-2-one **58** gives the substitution product **126** or the addition product **127** depending on the conditions.



Quinolin-4-one forms a 3-bromo derivative, but coumarin gives the addition compound **127** which is easily rearomatized to give **128**. 4-Thiopyrones are halogenated in position 3. Pyridazinones and cinnolinones are also readily halogenated in the expected positions.



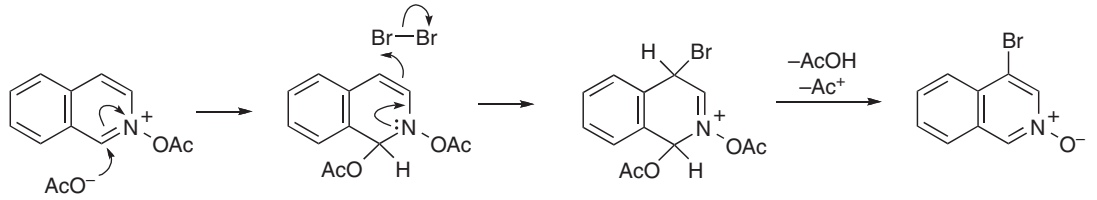
Halogenation of pyridine *N*-oxide is not easy. Bromination in oleum gives the 3-bromo derivative, presumably via the conjugate acid, but only small yields of 4-bromopyridine *N*-oxide have been obtained under less acidic conditions. The electrophilic bromination of substituted pyridine *N*-oxides has been more widely studied than the corresponding chlorination. Strong electron-releasing groups on the pyridine *N*-oxide favor nuclear bromination. In the case of 4-methoxypyridine 1-oxide, bromination occurs at C(3) along with ether dealkylation. Bromination of 2-dimethylaminopyridine *N*-oxide **129** gives the 5-bromo-derivative **130** as the major product (**Scheme 23**) <1983JOC1064>.



Scheme 23

Electrophilic chlorination of pyridine *N*-oxides is more difficult than for the analogous pyridines. An example is chlorination of 2-acetamidopyridine *N*-oxide with hydrogen chloride and hydrogen peroxide, which gives a mixture of 5-chloro- and 3,5-dichloro derivatives.

Quinoline *N*-oxide gives a 4-bromo derivative (Br_2H_2O, 100°C). Isoquinoline *N*-oxide is brominated at the 4-position via the mechanism of **Scheme 24**.

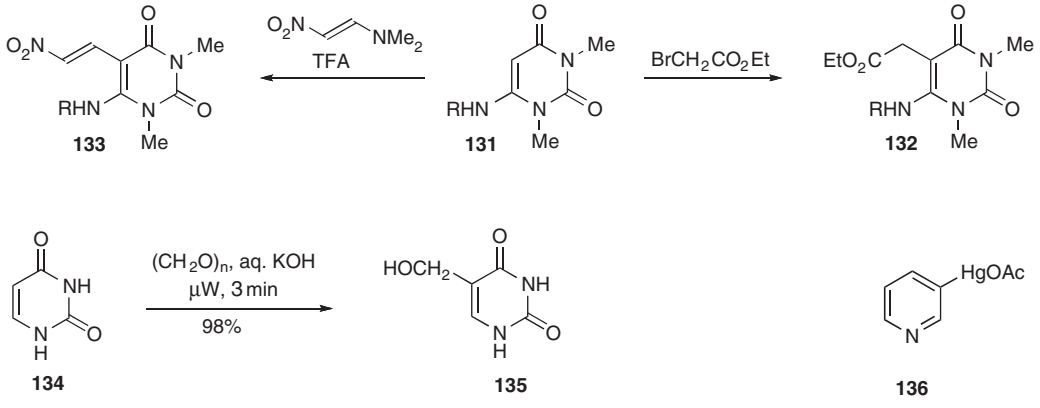


Scheme 24

Direct 5-fluorination can be effected on activated pyrimidines; for example, F_2 in HOAc or anhydrous HF can be used for the preparation of 5-fluoro-2(1*H*)-pyrimidinones <1977CCC2694>, and for 5,5-difluorination of 6-*O*-cyclouridines <1983TL1055>. Uracil and cytosine are 5-fluorinated by the same procedure <1980TL4605, 1982CPB887>.

3.2.1.4.8 Acylation and alkylation

FriedelCrafts reactions are almost unknown in pyridine and azine chemistry. Direct electrophilic alkylation at the pyrimidine 5-position can be carried out on pyrimidines which have at least two strongly donating groups, and more readily with three such groups. Thus, -haloketones and -bromocarboxylic esters can be used for direct alkylation of 6-aminouracils **131**, for example, in the formation of **132**. The 5-position can also act as the nucleophile for Michael additions (e.g., **131** **133**) <1992AHC(55)129>. A microwave-assisted procedure allows formation of 5-hydroxymethyluracil **135** from **134** in 98% yield, in just 3 min <2002SL2043>. Barbituric acids also add to Michael acceptors <1985AHC(38)229>.



3.2.1.4.9 Mercuration

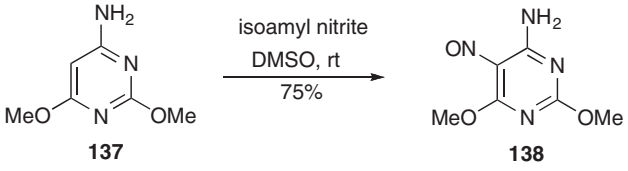
Pyridine forms 3-acetoxymercuripyridine **136** ($Hg(OAc)_2$, H_2O, 155°C); 2-amino- and 4-methylpyridine give the 5- and 3-acetoxymercuri compounds, respectively, at somewhat lower temperatures. Mercuric acetate mercurates 4-pyridone at the 3-position and 3-hydroxypyridine at the 2-position.

Isoquinoline forms a 4-acetoxymercuri derivative. Pyridine *N*-oxide is mercurated predominantly at the 2-position, but increasing acidity increases the proportion of 3-mercuri product formed.

3.2.1.4.10 Nitrosation, diazo coupling, Mannich reaction, Kolbe reaction, and reaction with aldehydes

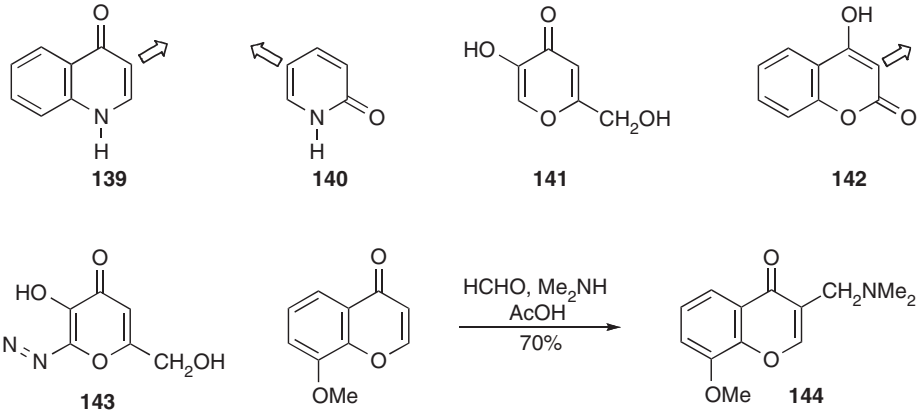
In general, only those pyridines containing hydroxy or amino groups, diazines with multiple amino or hydroxy substitution, and pyridones will undergo these reactions. Some examples are given below.

3.2.1.4.10.1 Nitrosation. 2,6-Diaminopyridine with nitrous acid forms the 3-nitroso derivatives. Nitrosation has been much used in pyrimidine chemisty: nitrosation of pyrimidines occurs readily in the presence of three electron-releasing substituents; pyrimidine-4,6-diamine is also nitrosated to the blue 5-nitroso derivative; treatment of 4-amino-2,6-dimethoxypyrimidine **137** with isoamyl nitrite in DMSO at room temperature gives the 5-nitroso derivative **138** in 75% yield <2002SL255>.



137 **138**

3.2.1.4.10.2 Diazo coupling and Mannich reaction. 4-Quinolone **139**, 2-pyridone **140**, kojic acid **141** and 4-hydroxycoumarin **142** couple with diazonium salts to form azo compounds, (e.g., **143**) and undergo Mannich reactions, at the positions indicated. Chromones undergo the Mannich reaction to give, e.g., **144**.



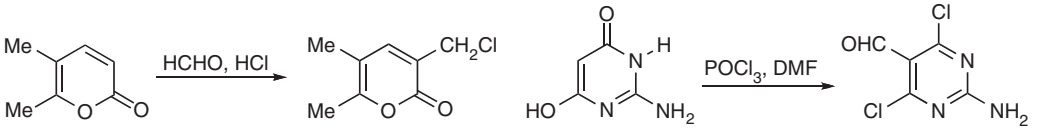
139 **140** **141** **142**

143 **144**

Mannich reactions and diazo coupling proceed readily in pyrimidines provided activating groups are present in each of the 2-, 4-, and 6-positions.

3.2.1.4.10.3 Kolbe and ReimerTiemann reactions. 3-Hydroxypyridine undergoes the Kolbe reaction (with carbon dioxide to give the carboxylic acid); the Na salt reacts mainly at the 2-, and the K salt at the 6-position. Uracil undergoes the ReimerTiemann reaction with sodium hydroxide/chloroform to give 5-formyluracil.

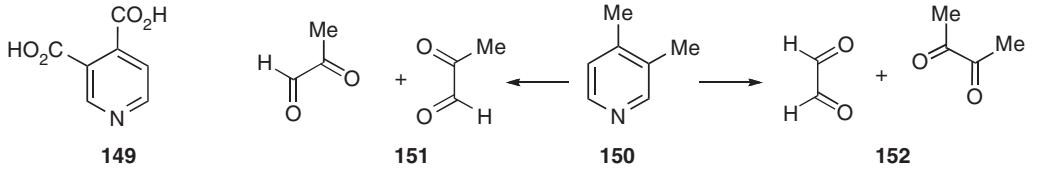
3.2.1.4.10.4 Reactions with aldehydes. 3-Hydroxypyridine and formaldehyde give 2-hydroxymethyl-3-hydroxypyridine. Pyrones can be chloromethylated, e.g., **145** **146**. Under VilsmeierHaack conditions, pyrimidinones are converted into 5-formylchloropyrimidines; for example, **147** gives the aldehyde **148**.



145 **146** **147** **148**

3.2.1.4.11 Oxidation

It is convenient to discuss oxidative attack at ring carbon here although this can involve radical as well as electrophilic oxidizing agents. Pyridine rings are generally very resistant to oxidation. CrO_3, dissolved in pyridine, is used as a reagent to oxidize alcohols. Many pyridine substituent groups can be selectively oxidized by $KMnO_4$, O_2, or $K_2Cr_2O_7$, especially under acidic conditions. In alkaline media, some oxidative degradation of pyridine rings occurs; thus, isoquinoline gives both cinchomeronic **149** and phthalic acids ($KMnO_4$, NaOH, H_2O) (Section 3.2.3.2.1). Ozone reacts with pyridines, although less readily than with benzenes; products corresponding to both KekulÕ forms can be isolated, e.g., **150** **151** and **152**.

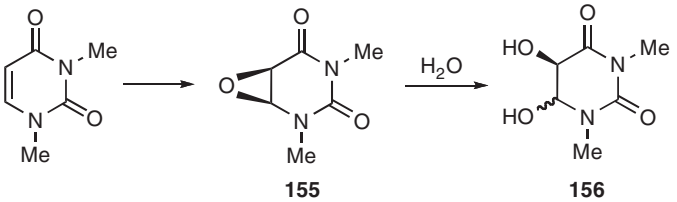


149 **151** **150** **152**

Acridine is less stable toward oxidizing agents and yields acridone (with $Na_2Cr_2O_7$, HOAc). Some diazine derivatives are apparently oxidized directly to diazinones: quinoxaline gives **153** (with $K_2S_2O_8$, H_2O) and quinazol-4-one yields **154** (with $KMnO_4$, CrO_3). These reactions probably involve nucleophilic attack of water followed by oxidation of the adduct (see Section 3.2.1.6.3).

153 **154**

Highly activated rings are hydroxylated by $K_2S_2O_8$, $FeSO_4$: 2-pyridone and 3-hydroxypyridine are both hydroxylated *para* to the substituent; thus, each gives the same compound (5-hydroxy-2-pyridone). 2-Pyrimidinone affords the 5-hydroxy derivative. Addition of hydrogen peroxide to the 5,6-double bond of pyrimidines gives 5,6-dihydroxy adducts. When 1,3-dimethyluracil was oxidized by dimethyldioxirane, which allows mild reaction conditions, a mixture of 1,3-dimethyl-5,6-epoxy-5,6-dihydrouracil (10%) **155** and 5,6-dihydroxy-5,6-dihydrouracils **156** as the *cis* (50%) and the *trans* (25%) isomers was formed. Under conditions where most of the water was removed from the reagent, the oxirane was obtained in 50% yield, and in water only the diols were obtained. 5- and 6-Methyl-*N*-alkyluracils give higher yields of the epoxides <1993TL6313>.



155 **156**

3.2.1.5 Attack at Ring Sulfur Atoms

Reactions of this type are rare. Heterocyclic sulfur is usually electron-deficient, which hinders the normal attack of electrophiles, and the normal position for nucleophilic attack is at a ring carbon or hydrogen. However, examples of both types of reactions are known.

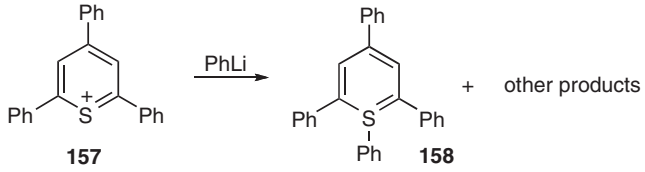
3.2.1.5.1 Reactions with electrophiles

Reactions take place under two circumstances:

1. in formally 8-electron compounds (see Section 3.2.2.1.2);
2. if the S atom is already in a higher oxidation state (see Section 3.2.2.2).

3.2.1.5.2 Reactions with nucleophiles

Thiopyrylium cations, e.g., **157**, react with aryllithiums to give complex mixtures containing some 1,2,4,6-tetrasubstituted thiabenzenes **158**.



157 **158**

3.2.1.6 Nucleophilic Attack at Carbon

Before discussing nucleophilic attack specifically at ring carbon we enumerate five general pathways which can be recognized for the attack of nucleophiles (and bases) on heteroaromatic six-membered rings:

Path A: Base attack at a hydrogen atom of a substituent with a subsequent elimination (discussed under the relevant substituent in Section 3.2.3.1).

Path B: Nucleophilic attack at - or -ring carbon, with subsequent reaction not involving ring opening (discussed in this section).

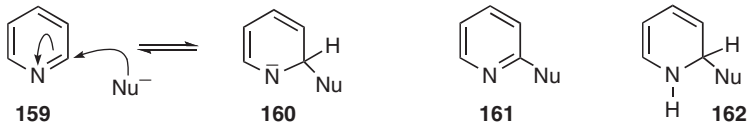
Path C: Nucleophilic attack at a substituent atom other than hydrogen (discussed under the relevant substituent in Section 3.2.3.1).

Path D: Metallation by removal of a ring hydrogen atom followed by (1) addition of an electrophile (discussed in Section 3.2.1.8), (2) dimerization, and (3) use in palladium(0) chemistry.

Path E: Ylide formation by removal of a ring hydrogen atom followed by (1) addition of an electrophile (discussed in Section 3.2.1.8) or (2) dimerization.

3.2.1.6.1 Ease of reaction

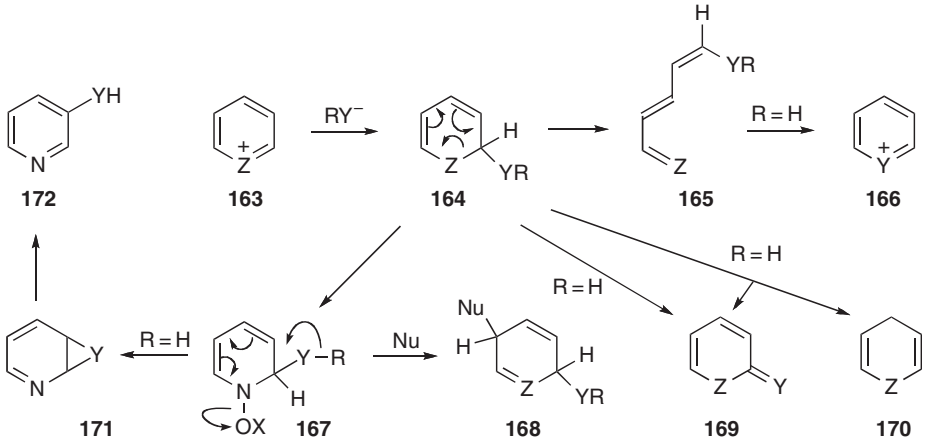
3.2.1.6.1.1 Pyridines. The electron displacement toward the nitrogen atom allows nucleophilic reagents to attack pyridines at the -position **159**, a type of reactivity shown in benzenoid chemistry only by derivatives with electron-withdrawing substituents. However, formation of the initial adduct **160** in an appreciable amount is difficult because this involves dearomatization of the pyridine ring and, once formed, the adduct tends to rearomatize by dissociation (**160** **159**). Only very strong nucleophilic reagents (e.g., NH_2, LiR, $LiAlH_4$, Na/NH_3, and, at high temperatures, OH) react. The tiny proportion of adducts of type **160** formed by the addition of amide or hydroxide ions can also rearomatize by hydride ion loss, thus gradually completing a nucleophilic substitution (**159** **161**). The adducts formed by the addition of hydride ions (from $LiAlH_4$) or carbanions (from LiR) are more stable; at low temperatures they are converted to dihydropyridines **162** by proton addition, but at higher temperatures rearomatization occurs by hydride ion loss.



159 **160** **161** **162**

3.2.1.6.1.2 Azines. Diazines are considerably more reactive toward nucleophiles than pyridines and as the number of ring nitrogens increases the propensity for nucleophilic addition reactions increases still more. The limit is reached with 1,3,5-triazine. This reacts very easily even with weak nucleophiles, and ring cleavage nearly always follows. Thus, it behaves as a formylating agent toward amines and other active hydrogen compounds.

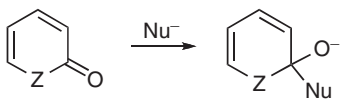
3.2.1.6.1.3 Cationic rings. In a pyridinium ring, the positive charge facilitates attack by nucleophilic reagents at positions or to the heteroatom. Hydroxide, alkoxide, sulfide, cyanide, and hydride (from borohydride) ions, certain carbanions and amines react, usually at the -position, under mild conditions, to give initial adducts of type **164**. These nonaromatic adducts can be isolated in certain cases but undergo further reactions with alacrity. The most important of these include variations (a)(d) listed below. If the group Z^+ of **163** is a nitrogen with a leaving group, usually N^+OX, then the further possibilities (e) and (f) exist.



a. Oxidation: e.g., **164** (YR = OH) pyridones **169; 164** (YR = CH_2heterocycle) cyanine dyes.
b. Disproportionation: e.g., **164** (YR = OH) pyridone **169** and dihydropyridine **170**.
c. Ring opening with subsequent closure (**163 166**): e.g., reaction of pyrylium salts with RNH_2 or S^2.
d. Ring opening without subsequent closure (**163 165**): e.g., reactions of OH with salts carrying electron-withdrawing groups on nitrogen, or pyrylium salts.
e. Rearrangement of attacking group to the 3-position (**167 171 172**).
f. Addition of a second equivalent of nucleophile (**167 168**).

3.2.1.6.1.4 Pyridones and azinones.

a. In both - and -pyridones the carbon atom of the carbonyl group can be attacked by a powerful nucleophile (as in **173**). The reaction then proceeds by complete loss of the carbonyl oxygen atom and aromatization. These reactions, which also occur in - and -pyrones, are all considered as substituent reactions in Section 3.2.3.7.2.
b. Adducts **173** formed by reaction of -pyrones at the carbonyl carbon atom can react further by ring opening as in the reactions with hydroxide ion, ammonia, and amines (see Sections 3.2.1.6.3 and 3.2.1.6.4).



173

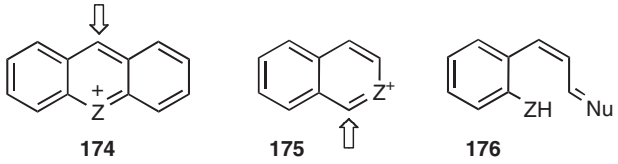
3.2.1.6.1.5 *N*-Oxides. The intrinsic reactivity of pyridine *N*-oxides toward nucleophiles is little greater than that of pyridine: the strongest nucleophiles react. However, after initial reaction with an electrophile at the *N*-oxide oxygen, subsequent attack by nucleophiles is easy: see the above discussion in Section 3.2.1.6.1.3.

3.2.1.6.2 Effect of substituents

Nucleophilic attack on the ring carbon atoms of pyridines is facilitated by electron-withdrawing substituents and hindered by electron-donating substituents. In pyridinium salts the effect of strongly electron-withdrawing substituents attached to the nitrogen atom, e.g., $C_6H_3(NO_2)_2$ or CN, is particularly marked and facilitates ring opening (Section 3.2.1.6) which is otherwise unusual.

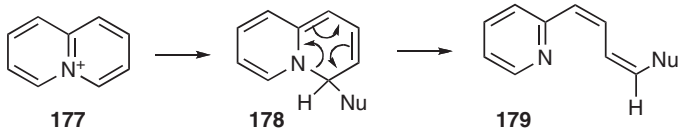
Fused benzene rings aid nucleophilic attack on pyridines, pyridinium, and pyrylium ions, and pyrones; the loss of aromaticity involved in the formation of the initial adduct is less in monobenzo derivatives and still less in linear dibenzo derivatives than in monocyclic compounds. For the same reason, the tendency for this initial adduct to rearomatize is less for benzopyridines. Fused benzene rings also influence the point of attack by nucleophilic reagents; attack rarely occurs on a carbon atom shared with a benzene ring. Thus, in linear dibenzo derivatives, nucleophilic attack is at the -position **174**.

Similarly, reclosure to a new heterocyclic system after ring opening is possible in benzo[*c*] derivatives **175** and initial attack is always at that -position which is adjacent to the benzene ring, because of partial double bond fixation. By contrast, ring opening of a benzo[*b*] derivative gives a phenol or aniline **176** because the ZC bond is not easily broken.



174 **175** **176**

However, in the quinolizinium ion **177** the fused ring increases the stability and makes it more difficult for nucleophiles to attack, because now the aromaticity of both rings is lost in the intermediate addition product **178**. Conversely, once the addition product is formed, ring opening is particularly easy to give the aromatic **179**.

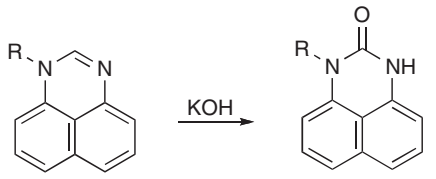


177 **178** **179**

3.2.1.6.3 Hydroxide ion

3.2.1.6.3.1 Pyridine and its benzoderivatives. Uncharged pyridines are resistant to hydroxide ion at normal temperatures. Pyridine itself reacts with hydroxide ions under extreme conditions (KOHair, 300 °C) to give 2-pyridone, the stable tautomer of 2-hydroxypyridine which is formed by oxidation of the initial adduct. As is expected, this reaction is facilitated by electron-withdrawing groups and fused benzene rings; quinoline and isoquinoline form 2-quinolone and 1-isoquinolone, respectively, much more readily. However, -hydroxylation is more difficult. Thus, acridine is hydroxylated with KOH at 300 °C to give 9-acridone in 28% yield.

3.2.1.6.3.2 Other azines. 1-Substituted perimidines **180** are hydroxylated (KOH, 180 °C) to form 1-substituted perimidin-2-ones **181** in excellent yields via oxidation of the presumed initial adduct.

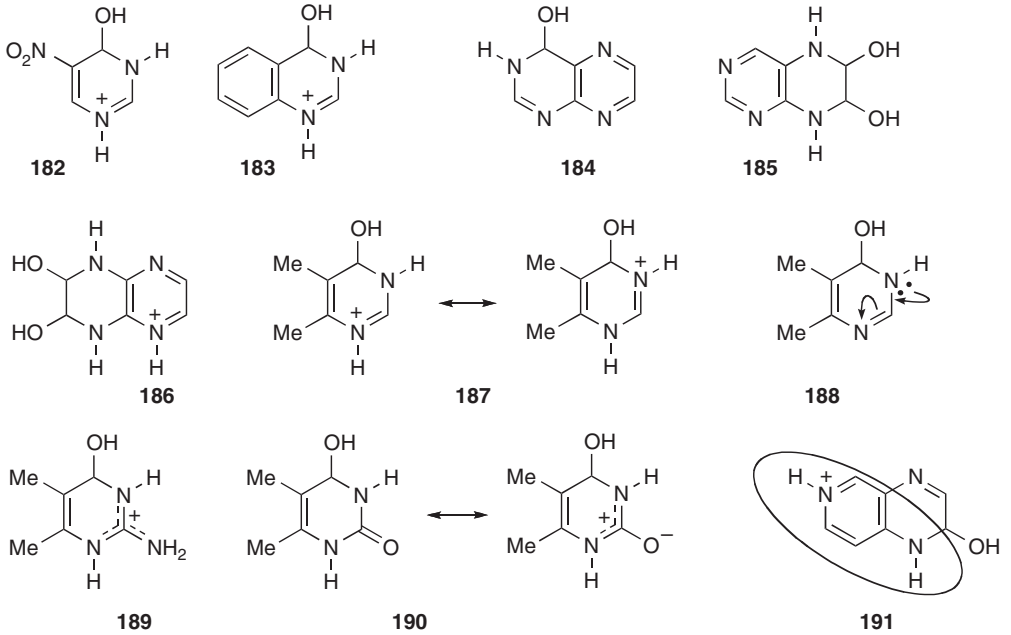


180 **181**

The presence of additional nitrogen atoms increases not only the kinetic susceptibility toward attack but also the thermodynamic stability of the adducts. The reversible covalent hydration of C=N bonds has been observed in a number of heterocyclic systems <1976AHC(20)117>. Pyrimidines with electron-withdrawing groups and most quinazolines show this phenomenon. Thus, in aqueous solution, the cation of 5-nitropyrimidine exists as **182** and quinazoline cation largely as **183**. These cations possess amidinium cation resonance. The neutral pteridine molecule is covalently hydrated in aqueous solution. Solvent isotope effects on the equilibria of monohydration **184** and dihydration **185** of pteridine as followed by NMR are near unity <1983JOC2280>. The cation of 1,4,5,8-tetraazanaphthalene exists as a bis-covalent hydrate **186**.

The following factors help stabilize covalent hydrates <1965AHC(4)1>:

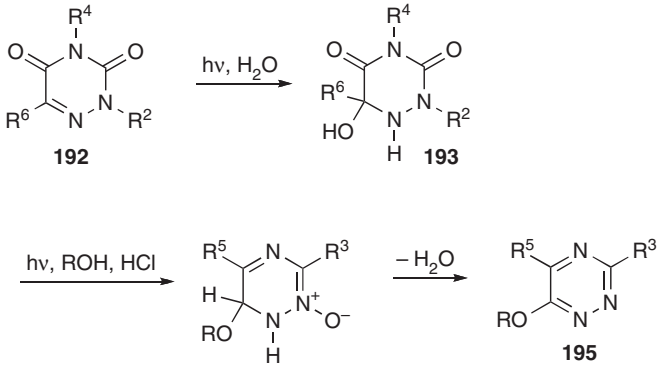
1. amidine-type resonance, particularly in cationic (e.g., **187**) but also in neutral species (e.g., **188**);
2. guanidinium-type resonance **189**;
3. urea-type resonance (e.g., **190**);
4. 4-aminopyridinium-type resonance **191**.



On irradiation, uracil and related pyrimidines undergo photohydration across the 5,6-bond.

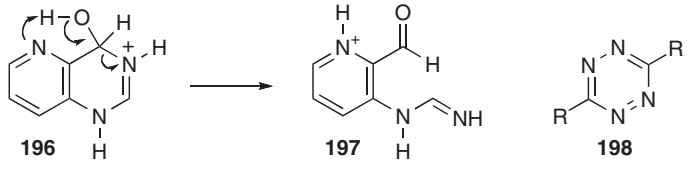
Many 1,2,4-triazine derivatives undergo photochemical hydration reactions, e.g., **192** **193**. Such reactions with 1,2,4-triazine 2-oxides are followed by loss of hydroxide ion to give overall substitution **194** **195**.

Insertion of a methyl group at the site where nucleophilic attack occurs during hydration considerably hinders the reaction and lowers the percentage of covalently hydrated species at equilibrium. Covalent hydrates are converted by mild oxidation into oxo compounds.



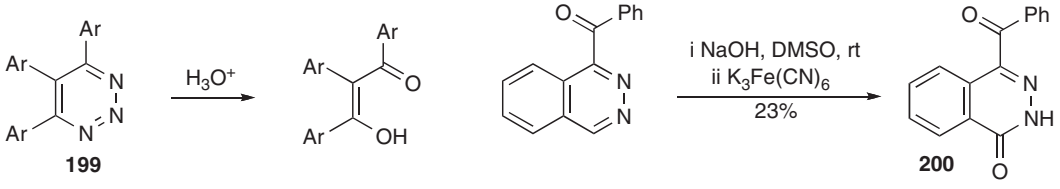
192 193 194 195

Covalent hydrates can undergo ring opening especially in acidic media, for example, the triazanaphthalene (**196** **197**). 1,2,4,5-Tetrazines **198** are hydrolyzed with a base to give aldehyde hydrazones, RCH=NNHCOR. Polyaza rings suffer complete hydrolytic ring cleavage. 1,2,3-Benzotriazines are easily converted into derivatives of 2-aminobenzaldehyde.



196 197 198

Monocyclic 1,2,3-triazines, e.g., **199** are hydrolyzed by acid to yield 1,3-dicarbonyl compounds, and 1-benzoylphthalazine is hydroxylated with sodium hydroxide in dimethyl sulfoxide to give, after oxidation, 4-benzoyl-1(2*H*)phthalazinone **200** <1985CPB4193>.



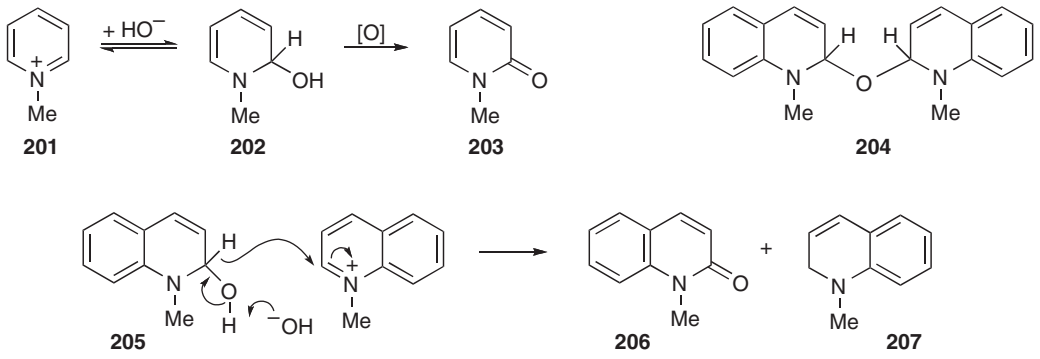
199 200

3.2.1.6.3.3 Alkylpyridinium cations. 1-Methylpyridinium ions **201** react reversibly with hydroxide to form a small proportion of the pseudo-base **202**. The term pseudo is used to designate bases that react with acids measurably slowly, not instantaneously as for normal acidbase reactions. Fused benzene rings reduce the loss of resonance energy when the hetero ring loses its aromaticity and hence pseudo-bases are formed somewhat more readily by 1-methylquinolinium, 2-methylisoquinolinium, and 10-methylphenanthridinium, and much more readily by 10-methylacridinium ions. Pseudo-bases carrying the hydroxy group in the -position are usually formed preferentially, but acridinium ions react at the -position.

Pseudo-bases can undergo a number of further reactions:

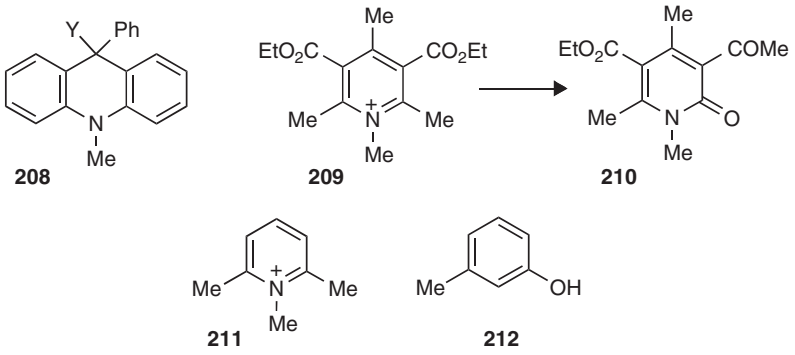
a. Oxidation. 1-Alkylpyridinium ions in alkaline solution are oxidized by $K_3Fe(CN)_6$, to give 2-pyridones (e.g., **203**). 2-Quinolones, 1-isoquinolones, 9-phenanthridones, and 9-acridones can be prepared similarly. Oxidation of 3-substituted pyridinium salts produce mainly the 2-one <1998TA2027>; however, an increasing percentage of oxidation at C(6) is observed with a bulkier C(3) substituent <2000MOL1175>. $KMnO_4$ and a catalytic amount of 18-crown-6 at room temperature have also been used for such oxidations in the isoquinoline and quinoline series; even N^+-acyl salts can be oxidized, when the N-hydrogen-one is the final product <1996T1451>.

b. Many pseudo-bases disproportionate to dihydropyridines and pyridones, e.g., **205** **206** + **207**. The mechanism shown, which resembles that for the Cannizzaro reaction, is supported by kinetic studies.

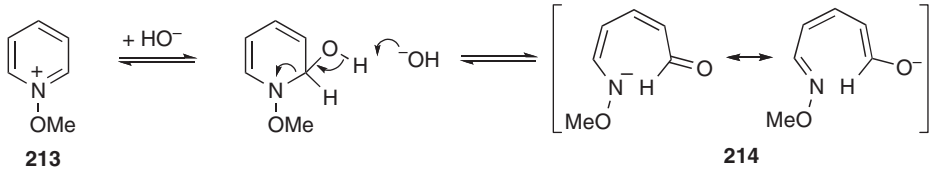


c. Ether formation can occur: recrystallization of (**208**; Y = OH) from ethanol forms (**208**; Y = OEt) via the acridinium ion. Pseudo-bases on keeping often lose water to give bimolecular products (e.g., **204**).

d. Ring fission followed by closure to form a new heterocyclic or homocyclic ring can occur in pyridinium ions carrying suitable substituents. Examples are **209** + KOH + H_2O **210** + EtOH, and also, at 200°C, **211** + NaOH 10% of **212**.



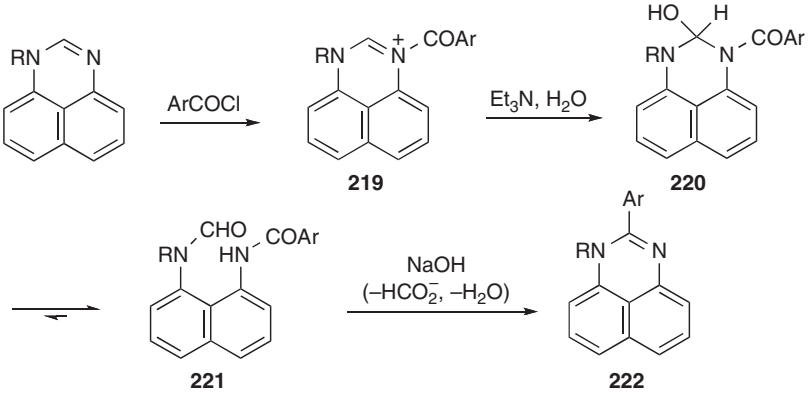
e. Ring fission can be reversible as in, for example, 1-methoxypyridinium **213** giving the glutaconic aldehyde derivative **214**; this is followed by irreversible scission of the NO bond (see Section 3.2.3.12.5).



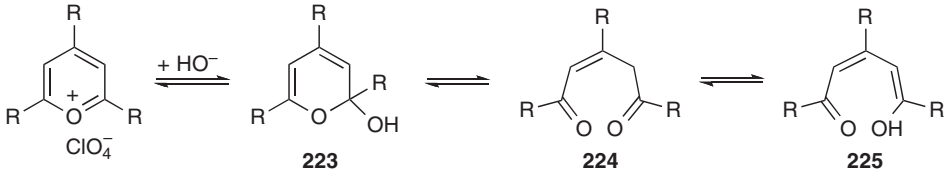
3.2.1.6.3.4 Other pyridinium ions. Pseudo-bases derived from pyridinium ions carrying a strongly electron-withdrawing substituent on the nitrogen atom are unstable and undergo ring fission with hydroxide ions under mild conditions ($NaOHH_2O$, 20°C). Pyridinesulfur trioxide **215** (Y = SO_3) and 1-cyano- and 1-(4-pyridyl)-pyridinium ions all give glutaconic aldehyde (**215** **216**); the other products are sulfamic acid, cyanamide ($NH_3 + CO_2$), and 4-aminopyridine, respectively. Similarly, isoquinolinesulfur trioxide complex gives homophthalaldehyde.

3.2.1.6.3.5 Other cationic rings. Diazinium salts resemble pyridinium salts in their behavior. They form pseudo-bases with hydroxide ions which can disproportionate (e.g., 2-methylphthalazinium ion **217** 2-methylphthalazin-1-one + 2-methyl-1,2-dihydrophthalazine) or undergo ring fission (e.g., 3-methylquinazolinium ion **218**). 2-Alkyl-1,2,3-triazinium salts add nucleophiles at C(5) <2003S413>.

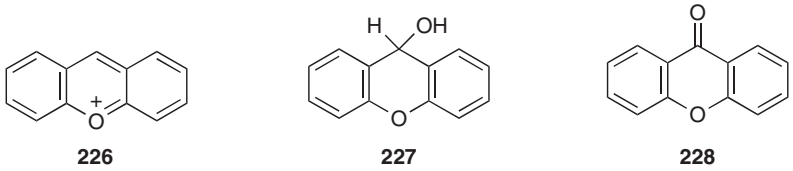
Pseudo-bases derived from 2-unsubstituted 1,3-dialkylperimidinium salts disproportionate to 1,3-dialkylperimidones and 1,3-dialkyl-2,3-dihydroperimidines, the former always predominate. By contrast, 1-aroyl-3-alkylperimidinium salts **219**, formed *in situ* from 1-substituted perimidines and aroyl chlorides, produce pseudobases **220** which exist exclusively in the acyclic form **221**. Heating with alkali cleanly converts **221** into the corresponding 1,2-disubstituted perimidines **222**. This reaction is of preparative significance for the introduction of aryl and heteroaryl groups into position 2 of perimidines <1981RCR1559>.



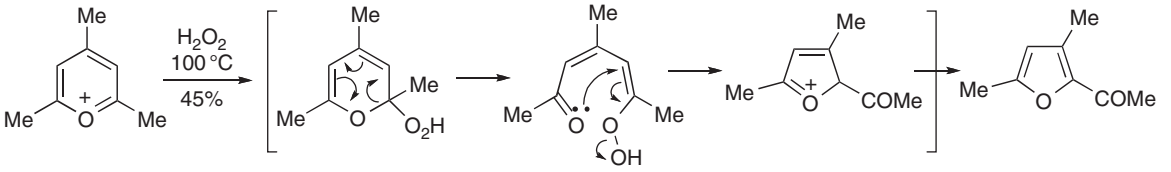
Pyrylium salts react with hydroxide ions in a series of equilibria involving the pseudo-base **223** and ring-opened forms **224** and **225**.



Some pseudo-bases do not ring open; the xanthylium ion **226** gives xanthydrol **227** which can be isolated or oxidized with dilute nitric acid to xanthone **228**.

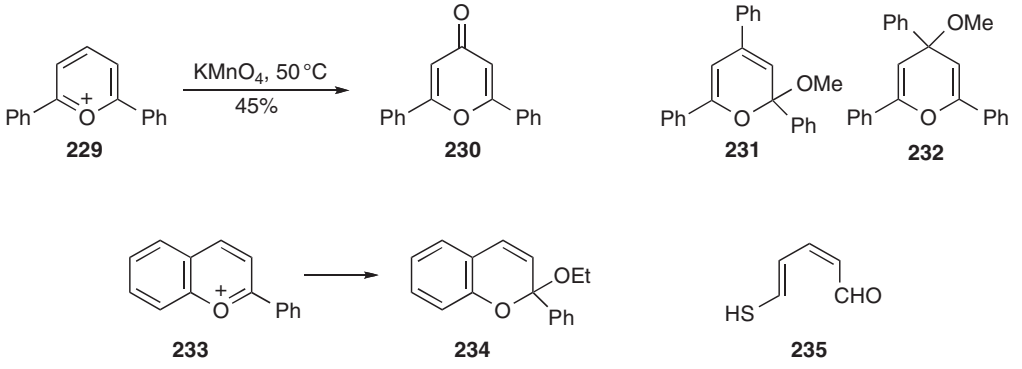


Hydrogen peroxide reacts with 2,4,6-trisubstituted pyrylium salts to cause ring contraction (**Scheme 25**). If there is a free - or -position, pyrylium salts can be oxidized to pyrones, e.g., **229** **230**.



Scheme 25

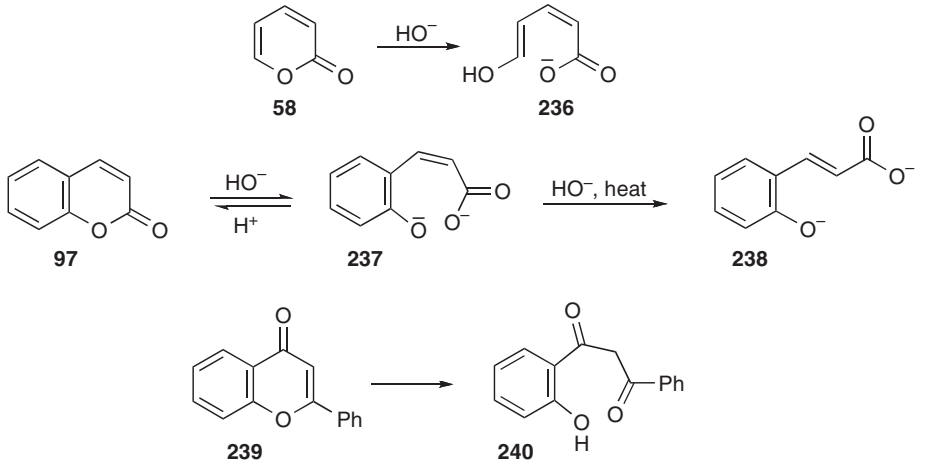
Methoxide adds to pyrylium salts to give methoxypyrans, e.g., **231, 232**. Flavylium ion **233** gives **234** with NaOAc and EtOH.



229 **230** **231** **232** **233** **234** **235**

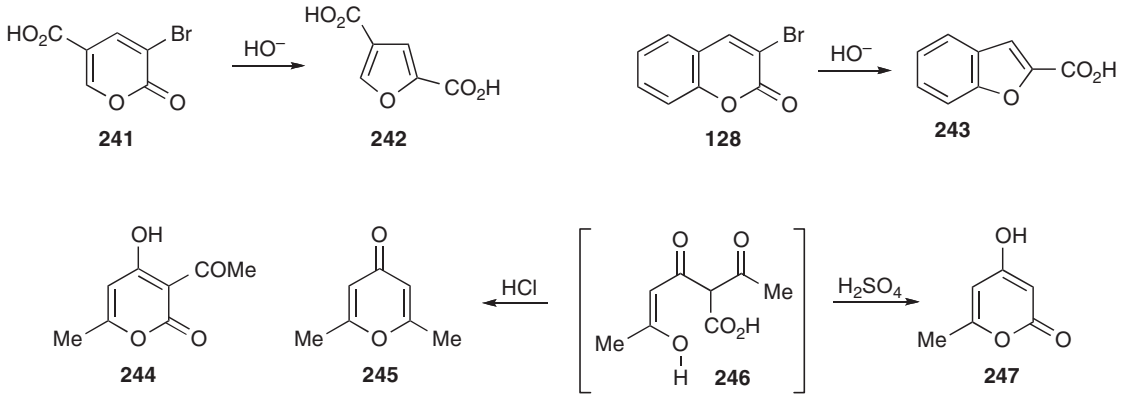
The unsubstituted thiopyrylium cation is stable up to pH 6 in aqueous solution; at higher pH it ring opens to the aldehyde **235**. Methoxide adds to 4-alkyl-2,6-diphenylthiopyrylium cations to give a mixture of the 4-methoxy-4*H*- and 2-methoxy-2*H*-thiins under kinetic control, the mixture then equilibrates toward the thermodynamically favored 2*H*-system.

3.2.1.6.3.6 Pyridones, pyrones, azinones, etc. Although pyridones are usually resistant to alkali, pyrone rings are often easily opened. Pyran-2-one **58** is reversibly ring-opened by aqueous alkali to carboxylate anions **236**. Hydroxide ions convert coumarin **97** reversibly into salts of coumarinic acids **237** which can be converted into the *trans* isomers **238**, and chromones **239** into -dicarbonyl compounds **240**.

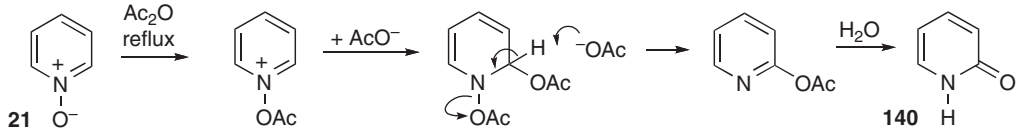


58 **236** **97** **237** **238** **239** **240**

3-Bromo-2-pyrones and 3-bromocoumarins give furan- and benzofuran-2-carboxylic acids by ring fission and subsequent closure, e.g., **241** **242**; **128** **243**. Pyrone rings are opened by aqueous acid in some cases, probably by successive protonation and attack of a water molecule, e.g., dehydroacetic acid **244** gives **246** which immediately forms **245** or **247** with HCl or H_2SO_4, respectively.



3.2.1.6.3.7 *N*-Oxides. *N*-Oxides are normally resistant to hydroxide attack. However, acetic anhydride converts *N*-oxides into *N*-acetoxy cations, and such compounds can be attacked by acetate. Thus, the reaction of acetic anhydride with pyridine *N*-oxide **21** gives 2-pyridone **140** (**Scheme 26**). This is a very general reaction; thus, for example, pyridazine 1-oxides unsubstituted at position 6 rearrange in the presence of acetic anhydride to the pyridazin-6-ones.

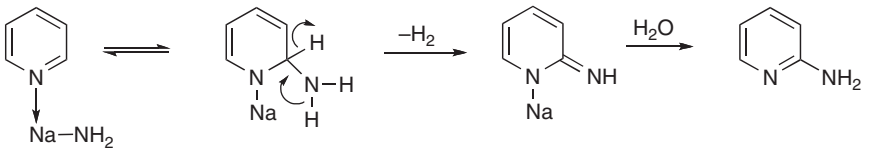


Scheme 26

3.2.1.6.4 Amines and amide ions

3.2.1.6.4.1 Pyridines and azines. Amines are insufficiently nucleophilic to react with pyridines, so the stronger nucleophile NH_2 is required. Pyridine reacts with sodium amide (toluene, 110°C) giving 2-aminopyridine (75%) and a small amount of 4-aminopyridine. At 180°C 2,6-diaminopyridine is produced in good yield along with a small amount of 2,4,6-triaminopyridine. This, the Chichibabin reaction, is widely used for direct introduction of an amino group into electron-deficient positions of many azines and some azoles (Section 3.4.1.7.2) <1983AHC(33)95, 1988AHC(44)2> Quinoline is aminated at atoms C(2) and C(4), isoquinoline at C(1), acridine at C(9), phenanthridine at C(6), quinazoline at C(4), and 1-substituted perimidines at C(2).

There are two general procedures for conducting the Chichibabin reaction. According to the classical procedure, the reaction is conducted at relatively high temperatures, in a solvent inert toward sodium amide (arenes, *N*,*N*-dialkylanilines, mineral oil, etc.) or without any solvent. In this case, the reaction proceeds under heterogeneous conditions. Under such conditions, heterocycles with pK_a values of 56 are aminated smoothly, but for heterocycles of lower basicity, the ease of amination is markedly decreased. Dependence of the reaction on basicity suggests that formation of a complex of type **248** with a weak coordination bond between the cyclic nitrogen and a sodium ion may be important. Obviously, such coordination increases positive charge on the ring -carbon atom and thus favors the amination.



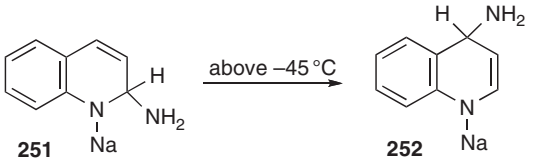
248 **249** **250**

Under the alternative low-temperature procedure, amination is conducted in liquid ammonia. The use of KNH_2, which is more soluble than $NaNH_2$ in this solvent, is preferable. The reaction occurs under homogeneous conditions and does not show the previous dependence on substrate basicity. Diazines, triazines, and tetrazines, which usually undergo destruction in the high-temperature process, are aminated successfully in liquid ammonia.

Formally the Chichibabin reaction consists of the nucleophilic substitution of hydride ion by the group NH_2. In the first stage, anionic complex **249** is formed (and can be observed in liquid ammonia solution by NMR spectroscopy) which is then aromatized with the formation of the sodium derivative **250** of product amine. From the latter, the free amine is obtained by the addition of water or NH_4Cl. In the high-temperature method, hydride ion is eliminated as hydrogen gas (the second hydrogen atom in H_2 comes as a proton from an amino group). It is convenient to follow the reaction by the volume of emitted hydrogen gas. There is indirect evidence that under heterogeneous conditions, one-electron transfer from the NH_2 nucleophile to substrate may play a significant role. Thus, the formation of dimers or reduced dimers of the starting heterocycle is often observed. For example, the yield of 4,4-dipyridyl in the sodamide amination of pyridine in mixtures of xylenehexamethylphosphorotriamide reaches *20%*. Note: in structures such as **249, 250** and **251**, the NaN bond is probably essentially ionic.

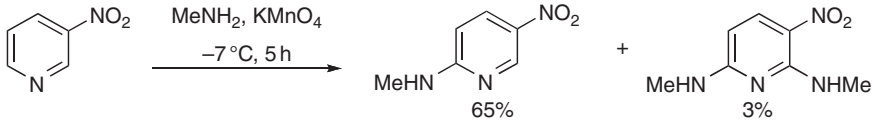
In liquid ammonia, hydride ion, which is a very poor leaving group, cannot eliminate spontaneously. An oxidant (KNO_3 or better $KMnO_4$) is usually added to aromatize the -complex.

In the amination of quinoline in liquid ammonia, the initially formed -complex **251** is fully isomerized on heating to the more stable -complex **252**. Adding potassium permanganate to either -complex, allows 2-amino- or 4-aminoquinolines to be obtained in good yields.

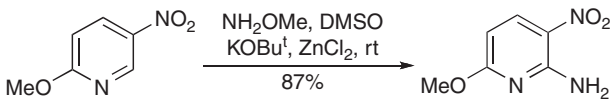


251 **252**

Of all the aza-heterocycles, pyridine possesses the least electron deficiency. Because of this, pyridine itself does not form a -complex in liquid ammonia and cannot be aminated under these conditions. By contrast, highly -deficient polyaza-heterocycles (diazines, triazines, tetrazines, pteridines, etc.) undergo oxidative amination, sometimes even by liquid ammonia itself. Sodamide converts 4-methylpyrimidine successively into the 2-mono- and 2,6-di-amino derivatives, and pyrazine gives 2-aminopyrazine. Nitro groups, the activating ability of which is even stronger than that of an aza-group, facilitate the amination. For instance, 4-nitroquinoline on treatment with liquid ammonia and $KMnO_4$ at 33^{-} C gives 3-amino-4-nitroquinoline in 86% yield. Similarly, amination of 3-nitropyridine with potassium permanganate in liquid ammonia, or an aliphatic amine, affords mainly the 2-amino-5-nitropyridine (**Scheme 27**) <1999JPR75>. 2-Methoxy-5-nitropyridine is aminated at C(6) with *O*-methylhydroxylamine in the presence of $ZnCl_2$ to give 2-amino-6-methoxy-3-nitropyridine in high yield (**Scheme 28**) <1998CC1519>.

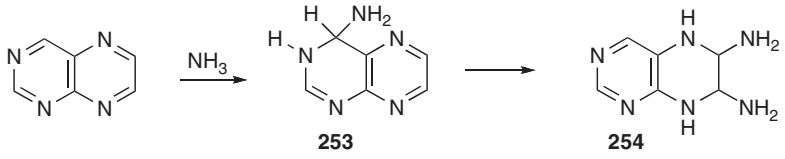


Scheme 27

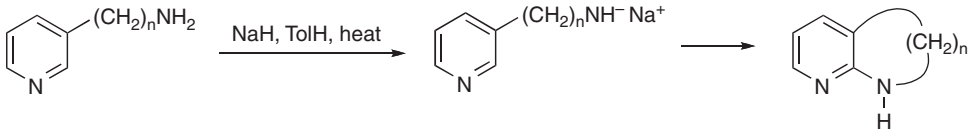


Scheme 28

Pteridine adds ammonia at low temperature to form 4-amino-3,4-dihydropteridine **253** which is transformed in a slower reaction into 6,7-diamino-5,6,7,8-tetrahydropteridine **254** (cf. similar adducts with water, **184** and **185**).

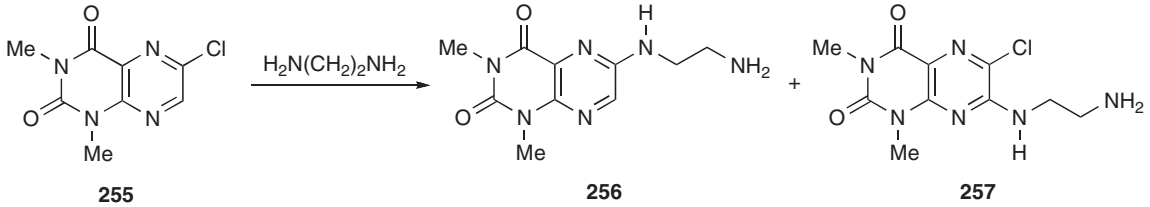


Sodium alkylamides (AlkNH Na^+) (but not sodium dialkylamides) under heterogeneous conditions convert pyridine into 2-alkylamino derivatives; an intramolecular example of the reaction is shown in **Scheme 29**.

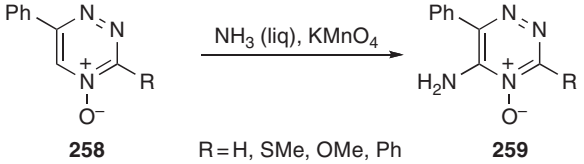


Scheme 29

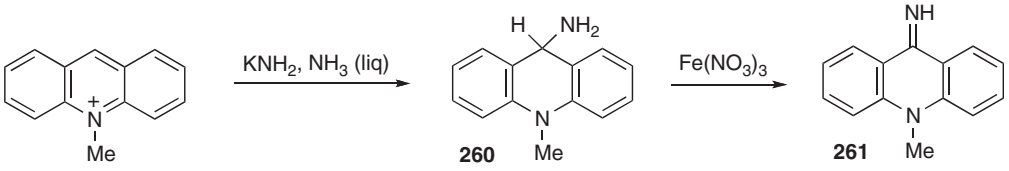
During the amination or alkylamination of halogeno azines, amino dehalogenation and amino dehydrogenation reactions can compete. Thus, 6-chloro-1,3-dimethyllumazine **255** reacts with 1,2-diaminoethane in the presence of $[Ag(C_5H_5N)_2]MnO_4$ (this oxidant is more soluble in alkylamines than $KMnO_4$) producing compounds **256** (30%) and **257** (38%) <1992KGS1202>.



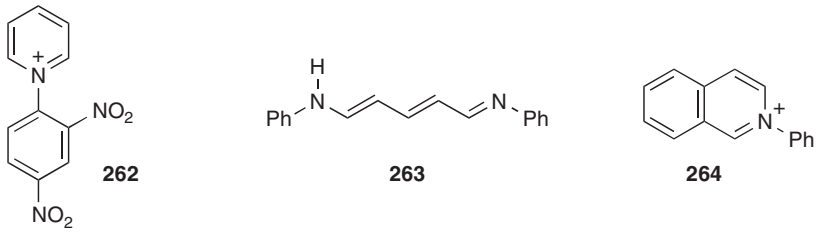
Some azine *N*-oxides can also be aminated, e.g., **258** **259**. Usually the reaction proceeds better in the presence of an oxidant such as $KMnO_4$ or *i*-PrONO.



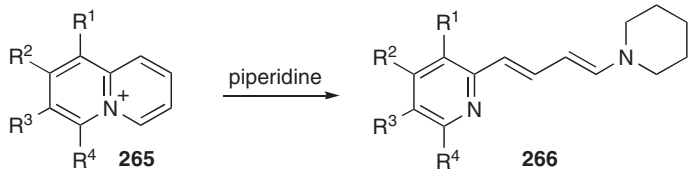
3.2.1.6.4.2 Pyridinium ions. Azinium cations are very reactive toward N-nucleophiles and readily undergo oxidative imination. Thus, *N*-methylacridinium reacts with $NaNH_2$ in liquid ammonia in the presence of $Fe(NO_3)_3$ to give 9-acridonimine **261**. *N*-Alkylpyridinium, *N*-alkylquinolinium and *N*-alkylisoquinolinium salts also enter into this reaction with $KMnO_4$ instead of $Fe(NO_3)_3$ as oxidant <1985JHC765, 1987JHC1377>. Intermediate adducts of type **260** can be observed by NMR spectroscopy <1973JOC1949>.



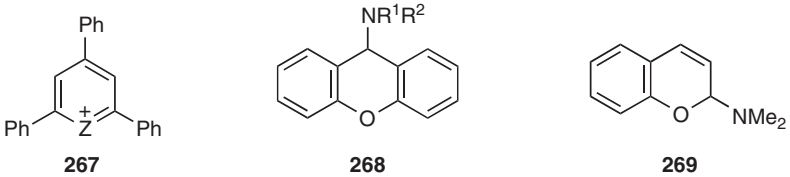
The charged rings are sufficiently reactive to be attacked by amines. Pyridinium ions carrying strongly electron-withdrawing substituents on the nitrogen react to give open-chain products. Thus, 1-(2,4-dinitrophenyl)pyridinium ion **262** gives glutaconic dialdehyde dianil **263** and 2,4-dinitroaniline ($PhNH_2$, 100°C) in the so-called Zinke reaction. Pyridinesulfur trioxide, 1-(4-pyridyl)pyridinium ion, and 1-cyanopyridinium ion react similarly. Subsequent closure of the ring can also occur, e.g., 2-(2,4-dinitrophenyl)isoquinolinium ion with $PhNH_2$ at 190°C forms **264**.



Quinolizinium ions **265** react with piperidine to give the ring-opened products **266**.



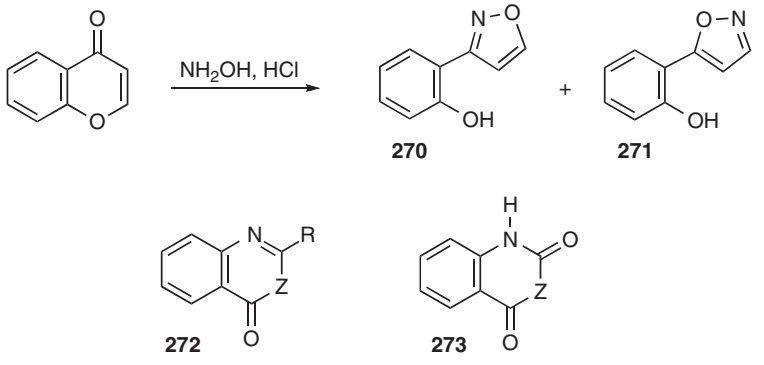
3.2.1.6.4.3 Other cationic rings. Pyrylium cations form pyridines with ammonia and pyridinium salts with primary amines. For example, 2,4,6-triphenylpyrylium cation (**267**; Z = O) yields 2,4,6-triphenylpyridine with ammonia, the corresponding 1-methylpyridinium salt with methylamine, and 1-phenylamino pyridinium with phenylhydrazine. Xanthylium ions, where ring opening cannot readily occur, form adducts **268** with ammonia, amines, amides, ureas, sulfonamides, and imides. Similar adducts (e.g., **269**) are formed by benzo[*b*]pyrylium ions.



Amines also react with thiopyrylium salts to give pyridinium salts, but the reaction goes less easily than with the pyrylium analogues. 1,3-Oxazinium and 1,3-thiazinium cations react with ammonia and primary amines to give pyrimidines and pyridinium cations, respectively.

3.2.1.6.4.4 Pyridones, pyrones, and azinones. Both 2- and 4-pyridones undergo the Chichibabin reaction to give the 6- and 2-amino derivatives, respectively. Pyran-4-ones react with ammonia and amines to give ring-opened products, which reclose to yield 4-pyridones; pyran-2-ones are similarly converted by ammonia or amines into 2-pyridones. Isocoumarins form isoquinolones on treatment with ammonia or primary amines. Chromones, however, react differently, because the phenolic hydroxy group in the ring-opened intermediate is unreactive. Thus, isoxazoles **270** and **271** result from the reaction with hydroxylamine, and a pyrazole is formed with hydrazine. -Pyrones also give pyrazoles with hydrazine.

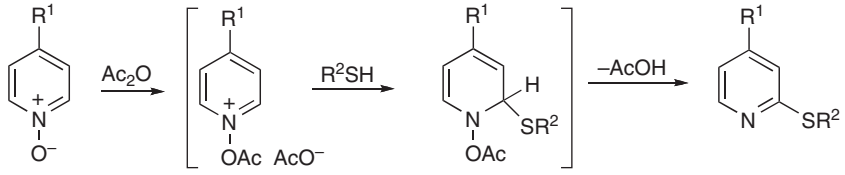
Oxazinones in which the heteroatoms are not adjacent react with ammonia and amines to give diazinones, e.g., **272, 273** (Z = O) yield **272, 273** (Z = NR).



3.2.1.6.5 Sulfur nucleophiles

Neutral pyridines do not normally react with sulfur nucleophiles. Such reactions are known, however, for *N*-oxides and cationic rings.

Pyridine *N*-oxide and methyl analogues undergo thioalkylation at the - and -positions with alkanethiols in acetic anhydride (**Scheme 30**).



Scheme 30

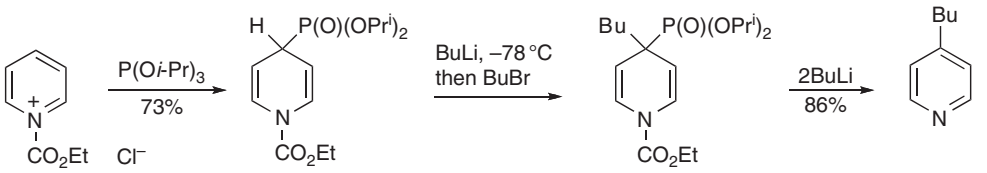
Pyrylium salts are converted by sodium sulfide into thiopyrylium salts, e.g., **267** (Z = O) **267** (Z = S).

The 5,6-double bond in uracil, 5-fluorouracil, *N*-alkyluracils, thiouracils, and uridines adds sodium sulfite or bisulfite to give the corresponding 5,6-dihydro-6-sulfonic acid salts. Bisulfite addition to cytosines and cytidine may be succeeded by a second reaction involving nucleophilic replacement of the amino group, for example, by water.

Perimidine and its N-substituted derivatives on heating with sulfur undergo thiation to form perimidine-2-thiones in good yields <1981RCR1559>.

3.2.1.6.6 Phosphorus nucleophiles

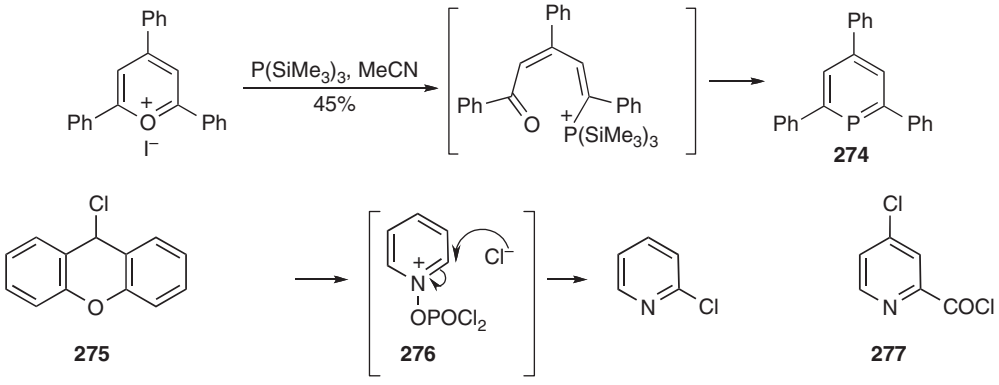
1-Ethoxycarbonylpyridinium cations are attacked by phosphites (**Scheme 31**). The intermediates can be further reacted to give 4-alkylpyridines as shown. Pyrylium salts with nucleophilic phosphines yield phosphinines **274**.



Scheme 31

3.2.1.6.7 Halide ions

Chloride ions are comparatively weak nucleophiles, and do not react with pyridines. In general, there is also no interaction with pyridinium and pyrylium compounds, but xanthylium chloride is in equilibrium with an appreciable amount of adduct **275**, this being a particularly favorable case with relatively little loss of resonance energy on adduct formation.



Pyridine and quinoline *N*-oxides react with phosphorus oxychloride or sulfuryl chloride to form mixtures of the corresponding - and -chloropyridines. The reaction sequence involves first formation of a salt (e.g., **276**), then attack of a chloride ion on this, followed by rearomatization (see also Section 3.2.3.12.5) involving the loss of the *N*-oxide oxygen and thence formation of 2-chloropyridine. Treatment of pyridazine 1-oxides with phosphorus oxychloride also results in an -chlorination with respect to the *N*-oxide group and simultaneous deoxygenation. If the -position is blocked substitution occurs at the -position. Thionyl chloride chlorinates the nucleus of certain pyridine carboxylic acids, e.g., picolinic acid **277**, probably by a similar mechanism.

Regioselectivity in the chlorination of pyrazine *N*-oxides with phosphoryl chloride depends upon the substituent on C(3). Thus, 3-aminopyrazine 1-oxide is chlorinated with loss of the *N*-oxide oxygen to give 2-amino-3-chloropyrazine as the sole product whereas 3-methoxy and 3-chloropyrazine 1-oxides form approximately equal amounts of 3-chloro- and 6-chloro-2-substituted pyrazines along with a trace of the 5-chloro derivative.

Ring fluorination of pyridine and its benzo derivatives is suggested to occur through nucleophilic attack of fluoride ion on an initial pyridine fluorine complex <1987TL255, 1991BCJ1081, 1993AHC(58)291>. In electron-deficient pyridines and their benzo derivatives, fluorination on the pyridine ring is kinetically competitive with annular and side-chain fluorination. An initial pyridine fluorine complex is formed <1987TL255, 1991BCJ1081, 1993AHC (58)291>.

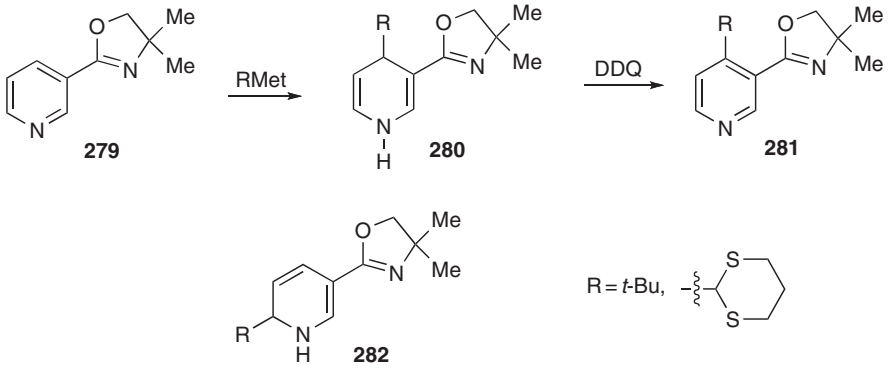
Xenon difluoride and xenon hexafluoride fluorinate pyridine to give a mixture of 2- and 3-fluoropyridines along with 2,6-difluoropyridine <1976JFC(7)179>. Cesium fluoroxysulfate at room temperature in ether or chloroform converts pyridine into 2-fluoropyridine in 61 and 47% yields, respectively, along with 2-fluorosulfoxypyridine <1990TL775>.

3.2.1.6.8 Carbon nucleophiles

3.2.1.6.8.1 Organometallic compounds. Pyridine reacts with alkyllithiums and aryllithiums under rather vigorous conditions (e.g., xylene at 100°C) to afford 2-alkyl- and 2-aryl-pyridines. The reaction proceeds by way of the corresponding adduct **278**; 1,2-dihydropyridines can be isolated at lower temperatures. The less reactive Grignard reagents give poorer yields of the same products.

278

In the presence of free magnesium, considerable 4-substitution is also observed, and when pyridine is reacted with, for example, *n*-butyl chloride and magnesium directly, 4-*n*-butylpyridine is formed without appreciable contamination by the 2-isomer. Possible reasons for this change in orientation are discussed in <CHEC-I(2.05)>. In 3-substituted pyridines, attack at C(2) is favored over C(6) unless the C(3) substituent or the attacking alkyl group is very large. Thus, a 4,4-dimethyloxazolin-2-yl group at the 3-position of a pyridine ring can be used to direct addition of Grignard reactions and alkyllithiums to the 4-position, the intermediate 1,4-dihydropyridines being further oxidized (e.g., **279 280 281**); however, the same reaction with *t*-butyllithium or lithiodithiane results in the formation of the 2-substituted 1,2-dihydropyridines **282** <1982JOC2633>. The regioselectivity of the organolithium reaction with 3-pyridyloxazolines also depends on the temperature and solvent.

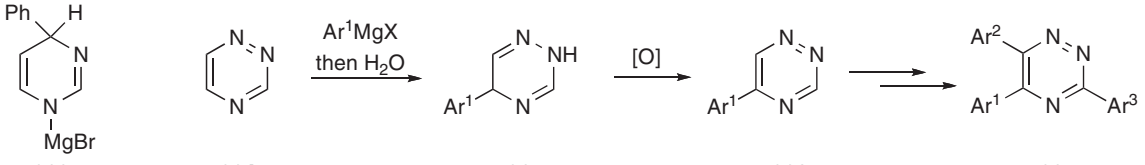


279 **280** **281** **282**

Benzopyridines are attacked by organometallic compounds at a position to the nitrogen unless -positions are blocked. The dihydro adducts from quinoline and isoquinoline are more stable and less easily aromatized than those from pyridine, and are hence more frequently isolated.

Diazines also react more readily than pyridine. Thus, pyrimidine and phenylmagnesium bromide give adduct **283** which can be oxidized to 4-phenylpyrimidine. Aryl- and heteroaryl-lithium reagents at low temperature <1979AG1, 1980RTC234> add across the 3,4-double bond of pyrimidines to give dihydropyrimidines. 2,5-Dimethylpyrazine and aryllithiums afford the 3-aryl derivatives.

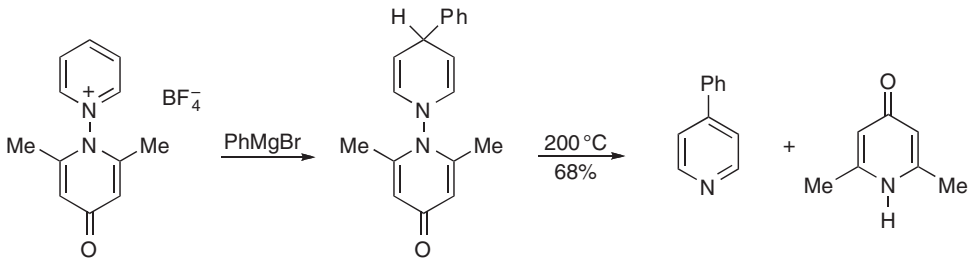
Grignard reagents add to 1,2,4-triazines. Initial attack at the 5-position is favored (**284 285 286**); if this position is already substituted, the nucleophile adds to the 6-position, and finally to the 3-position. Starting from the parent 1,2,4-triazine **284**, 3,5,6-triaryl-1,2,4-triazines **287** can be prepared by successive addition of Grignard reagents to the ring and oxidation of the dihydro-1,2,4-triazine, e.g., **285** so formed.



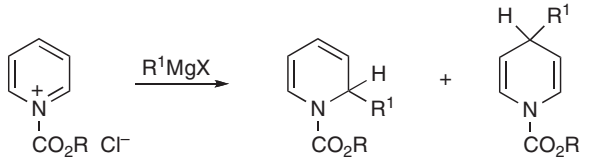
283 **284** **285** **286** **287**

Cationic rings react readily with organometallic compounds: Grignard reagents with *N*-alkylpyridinium salts generally give 1,2-dihydropyridines. If the size of the *N*-substituent is increased, then the orientation can be directed to the 4-position. If the *N*-substituent is also a leaving group, then rearomatization can occur, for example, as shown in **Scheme 32**.

N-Alkoxycarbonylpyridinium salts (usually generated *in situ*) react with organometallic reagents and other carbon nuclophiles efficiently and in many cases regioselectively. Numerous examples have been described including Grignard reagents, organolithiums, organocuprates, metallo enolates, silyl enol ethers, organotins, and organosilanes <CHEC-III (6.02.4.2.2)>. With alkyl Grignard reagents, *N*-alkoxycarbonylpyridinium salts **288** give mixtures of 1,2- **289** and 1,4-dihydropyridines **290**, whereas aryl, vinyl, and alkynyl Grignard reagents yield mainly the 1,2-dihydropyridine products <1988AHC(44)199>. Reaction between *N*-acylated quinoline and allyltrimethylsilane requires a catalytic amount of silver triflate which increases the electrophilicity of the *N*-acylquinolinium salt <2001T109>.



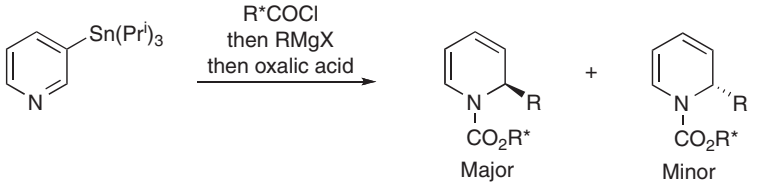
Scheme 32



288 **289** **290**

The regioselectivity of Grignard addition to *N*-alkoxycarbonylpyridinium salts can often be controlled by changing the conditions. For example, C(4) addition can be enhanced by the presence of catalytic amounts of copper salts: reaction of salt **288** (R = Me) with lithium dimethylcuprate gives also almost exclusively the 1,4-dihydro product **290** (R = Me, R^1 = Me).

Asymmetric synthesis of 1,2-dihydropyridines has been achieved by the addition of Grignard reagents to the pyridinium salt generated from 3-(triisopropylstannyl)pyridine and the chloroformate of 8-arylmenthyl based chiral auxiliaries (**Scheme 33**) <1991JOC7167>.

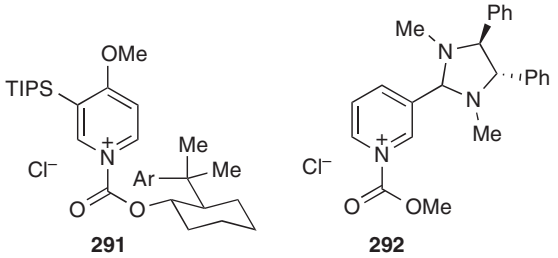


R* = (–)-8-phenylmenthyl R* = (–)-8-(4-phenoxyphenyl)menthyl

R	de	de
n-Pr	78	82
c-C_6H_{11}		91
Bn		76
vinyl		90
Ph	84	89
4-MeC_6H_4		92

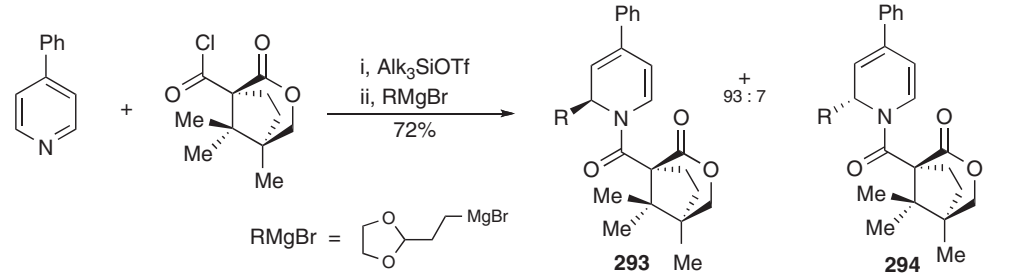
Scheme 33

Asymmetric versions of this chemistry continue to be developed using N^+-acyl salts containing a chiral auxiliary, as examples, **291** and **292**. There are now many examples <CHEC-III(6.04.4.2.2)> of the use of chiral *N*-acylpyridinium salts in this way, e.g., <2005OL5227>.

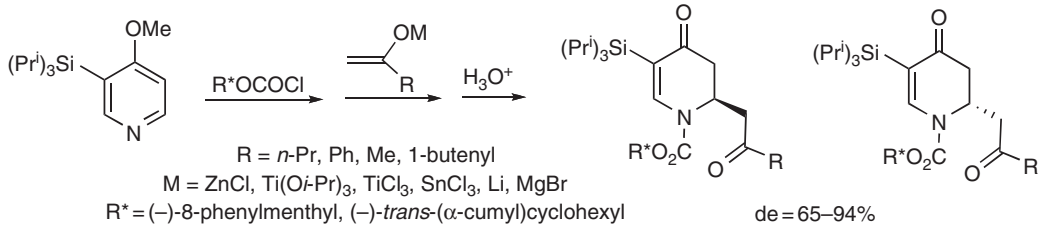


291 **292**

It is advantageous to employ trialkylsilyl triflates as additives: these conditions improve the yields of the subsequent addition reactions, for example, in forming **293** and **294** <2000JOC9272>.

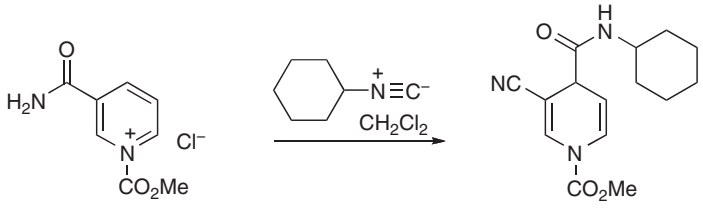


Zinc enolates have also been shown to react with chiral *N*-alkoxycarbonylpyridinium salts with high diastereoselectivity (**Scheme 34**) <1993JOC5035>. Other metallo enolates give products with lower diastereoselectivity. Titanium enolates react with *N*-alkoxycarbonylpyridinium salts to yield 1,4-dihydropyridines, which on subsequent oxidation (aromatization) give 4-(2-oxoalkyl)pyridines <1984TL3297>.



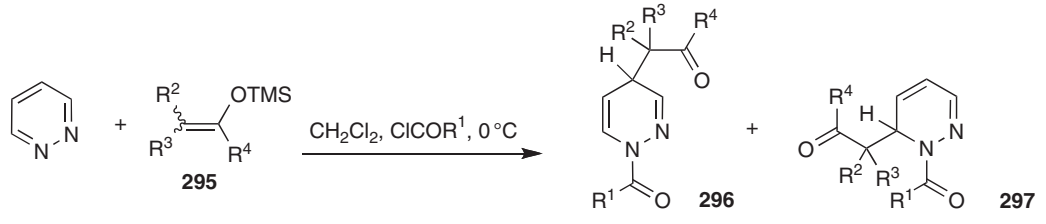
Scheme 34

With either *N*-alkyl- or *N*-acylpyridinium salts, isonitriles add efficiently when a carboxamido group is present at C(3). The outcome of the reaction involves the stabilization of the nitrilium intermediates by the amide, which suffers a mild dehydration providing 3-cyano-4-carbamoyl-1,4-dihydropyridines (**Scheme 35**). This method also works with the corresponding *N*-acylquinolinium and *N*-acylisoquinolinium salts <2004JOC3550, 2006OL5789>.

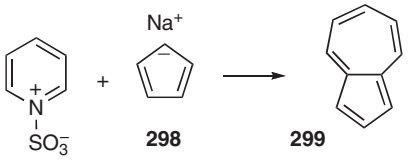


Scheme 35

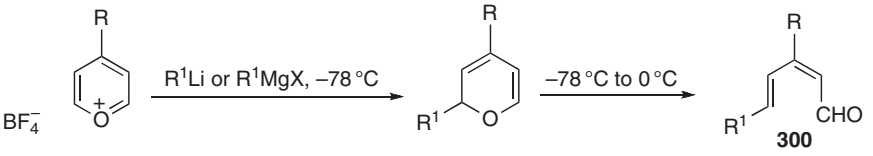
Pyridazines can be activated to addition in a similar fashion: in a reaction with silyl enol ethers **295**, attack in the (**296**) and (**297**) positions occurred <1997H(46)83>.



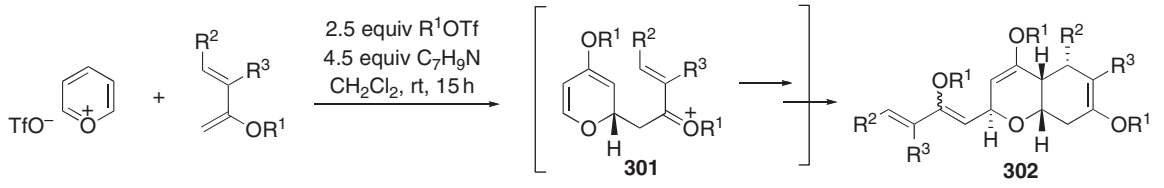
A notable reaction is that between the pyridinesulfur trioxide complex and sodium cyclopentadienide **298** which forms azulene **299** by a sequence involving opening of the pyridinium ring and subsequent closure to the seven-membered carbocyclic ring.



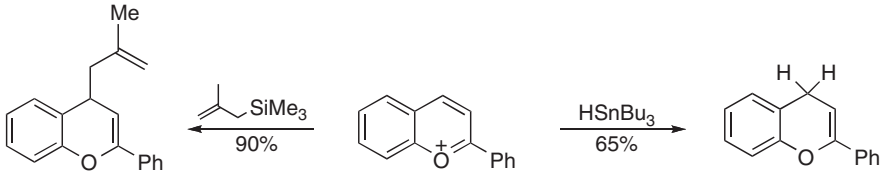
Pyrylium ions also add nucleophiles at an -position. The adducts open to give stereochemically defined dienes, e.g., **300** <CHEC-III(6.07.5.1)>.



Multiple sequential functionalizations of pyryliums with silyl enol ethers give rise to a variety of products, for example, **302** via **301** <2001AGE568>.

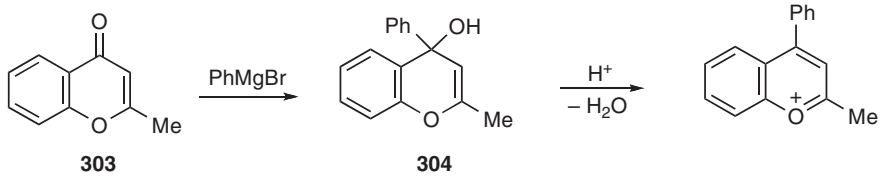


Benzopyrylium cations add nucleophiles at C(4) (**Scheme 36**) <2001EJO4451>.

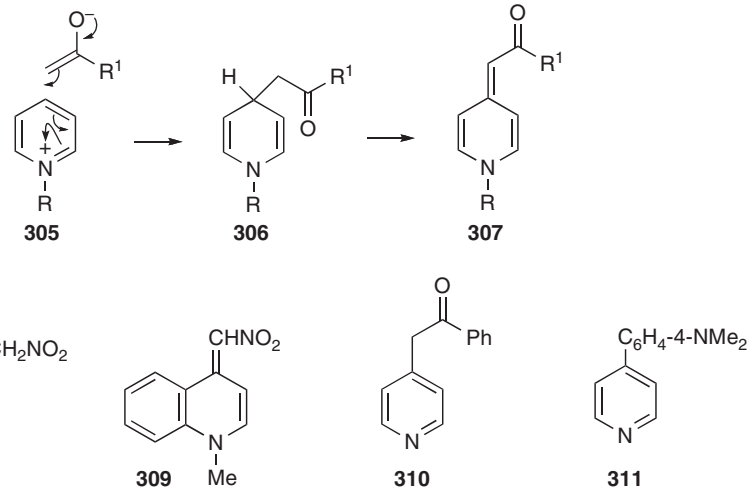


Scheme 36

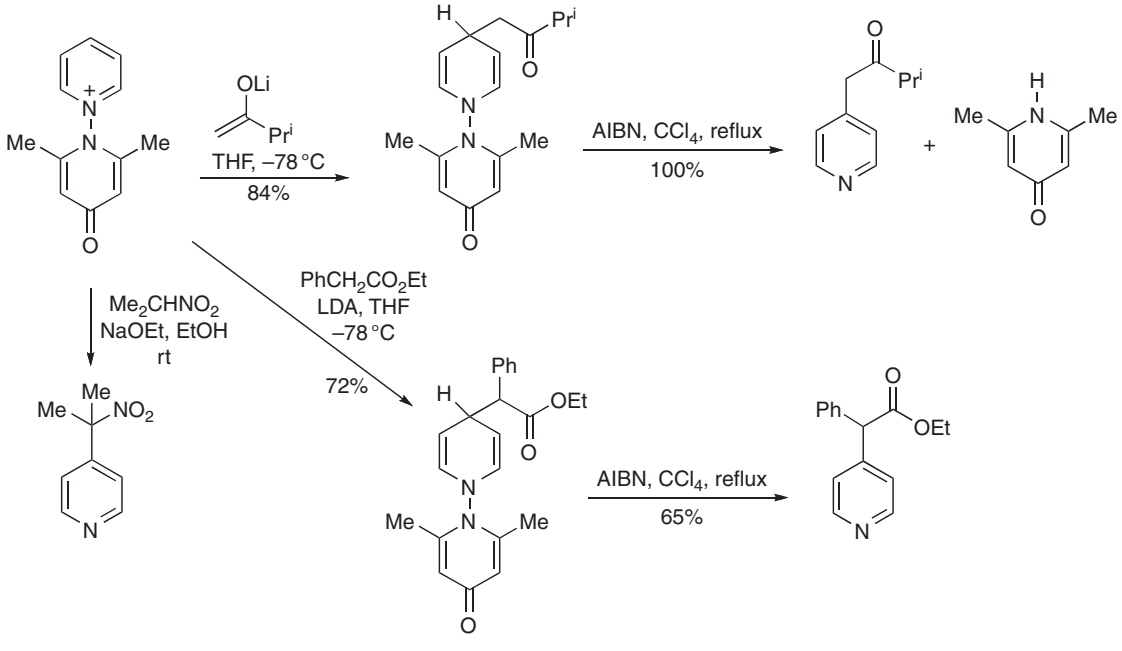
Benzopyran-4-ones with Grignard reagents give pseudo-bases, e.g., **303** **304**, which form the benzopyrylium salts with acid.



3.2.1.6.8.2 Activated methyl and methylene carbanions. The mesomeric anions of activated methyl and methylene compounds react with pyridinium and pyrylium cations, generally at the -position. Pyridinium ions combine with ketone enolates as in **305** to give products of type **306**, which can be isolated or oxidized *in situ* to mesomeric anhydro-bases **307**. Quinolinium, isoquinolinium, and acridinium ions give similar adducts of stability increasing in the order given. Aliphatic nitro compounds react analogously, e.g., 1-methylquinolinium ion gives successively **308** and **309** (with $MeNO_2$, piperidine). 1-Benzoylpyridinium ions react similarly with acetophenone and dimethylaniline to give, after oxidation, aromatized products **310** and **311**.



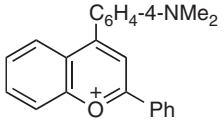
The application of *NN*-linked pyridinium salts to induce reaction with active hydrogen compounds at the 4-position is illustrated in **Scheme 37**.



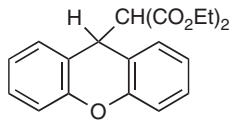
Scheme 37

1-Trimethylsilylpyrimidinium triflate, derived from pyrimidine and trimethylsilyl triflate, adds silylated enol ethers to form 1,4-dihydropyrimidines. *N*-Acylpyrimidinium tetrafluoroborates undergo analogous reactions <1985H(23)207>.

Pyrylium salts with a free - or -position react in a similar way without ring fission, flavylium adds dimethylaniline and the product aromatizes to give cation **312**; xanthylium ions form adducts at the 9-position with -diketones, -keto esters, and malonic esters (e.g., **313**).

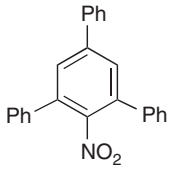


312

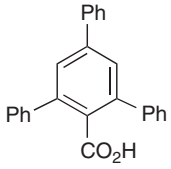


313

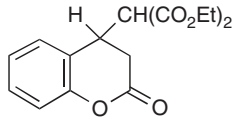
However, 2,4,6-trisubstituted pyrylium salts with certain active methyl and methylene compounds undergo ring fission and subsequent cyclization to benzenoid products. 2,4,6-Triphenylpyrylium ion in this way forms 2,4,6-triphenylnitrobenzene **314** with nitromethane and the substituted benzoic acid **315** with malonic acid, the latter reaction also involving a decarboxylation.



314

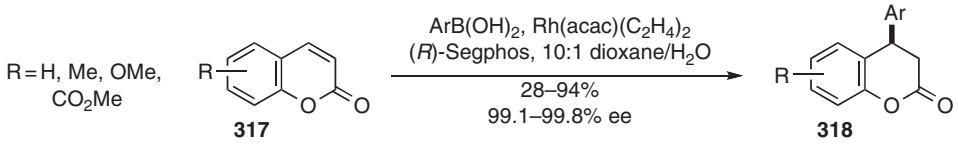


315



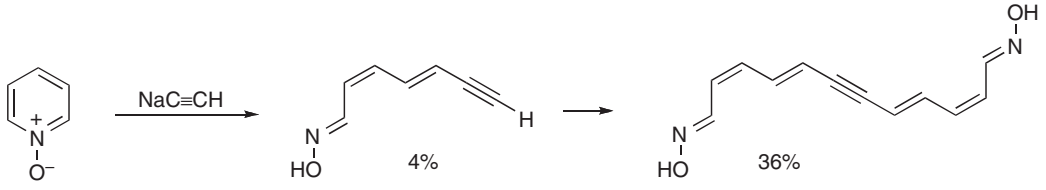
316

Certain pyrones react with active hydrogen compounds in a quite different way: they display their alkenic character by participating in Michael reactions, thus coumarin itself gives **316** with malonate anion, and coumarins **317** react with arylboronic acids catalyzed by rhodium giving **318** in greater than 99% ee <2005OL2285>.

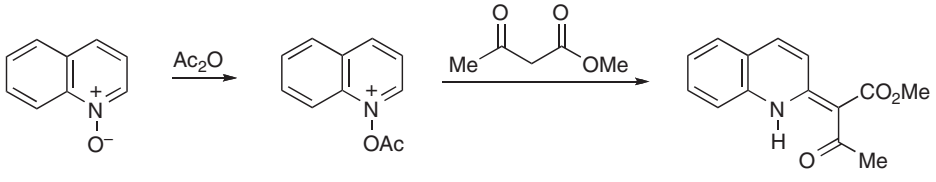


317 **318**

Sodium acetylide reacts with pyridine *N*-oxide to give ring-opened products (**Scheme 38**). However, in general, *N*-oxides react only after addition of an electrophile to the oxygen (**Scheme 39**).

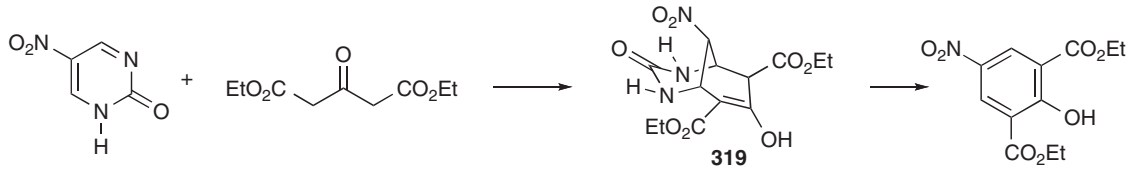


Scheme 38

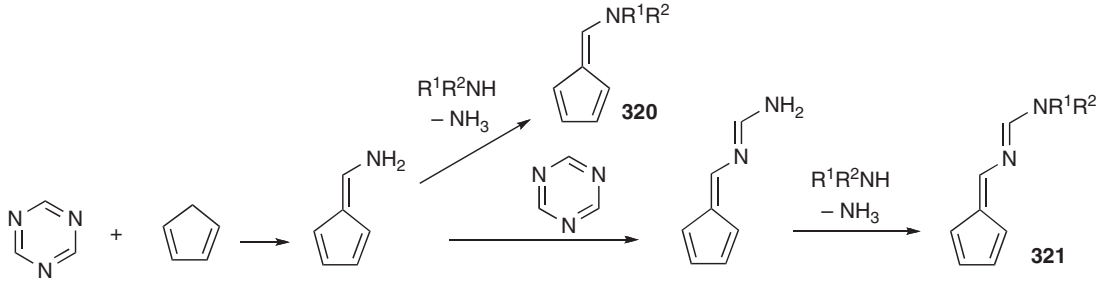


Scheme 39

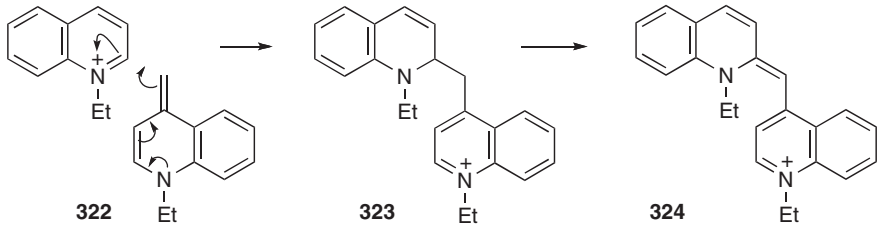
Bifunctional C-nucleophiles react with azines to cause *meta*-bridging cyclization in two steps <1988AHC(43)301>. Transformation of 5-nitropyrimidin-2-one into nitrophenols by -dicarbonyl compounds proceeds via the bicyclic *meta*-bridged intermediate **319** <1982JOC1018>. During the course of the reaction, the N(1)CN(3) part of the uracil is replaced by the CCC part of the 1,3-dinucleophilic reagent.



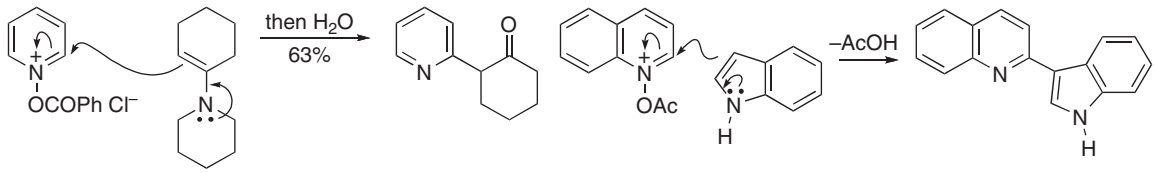
Nucleophilic attack on a fully-conjugated 1,3,5-triazine usually results in ring cleavage. Thus, active methylene compounds react with 1,3,5-triazine in aminomethylenation reactions. A three-component reaction of cyclopentadiene with 1,3,5-triazine and a secondary amine leads to *N*,*N*-disubstituted pentafulven-6-amines **320** and N^2-(6-pentafulvenyl)formamidines **321** <1986LA374>.



3.2.1.6.8.3 Anhydro-bases and enamines. Anhydro-bases with cationic rings give adducts (e.g., **322** **323**) which are spontaneously oxidized to cyanine dyes, e.g., **324**.

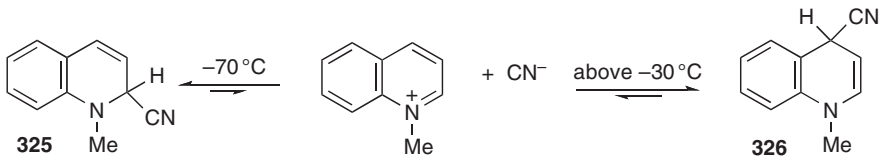


Pyridine *N*-oxides in the presence of acyl halides react with enamines, or indole, as shown in **Scheme 40**.

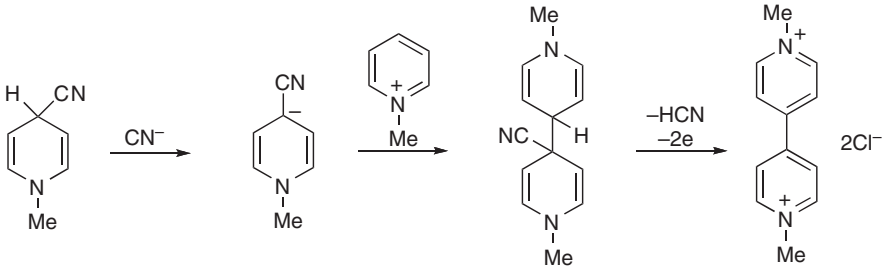


Scheme 40

3.2.1.6.8.4 Cyanide ions. So-called pseudocyanides, analogous to pseudo-bases, are formed by reaction of cyanide with benzopyridinium cations. Quite often, different isomeric pseudocyanides are formed depending on the temperature. Thus, at 70 to 30 °C (kinetic control), 1-methylquinolinium ion gives only the 2-cyanoadduct **325**, whereas at 20 °C (thermodynamic control) exclusively the 4-isomer **326** is observed by NMR spectroscopy.

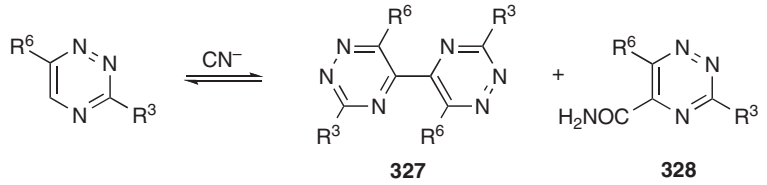


Pseudocyanides are important intermediates in the conversion of 1-alkylpyridines into 4,4-bipyridyl diquaternary salts (**Scheme 41**).



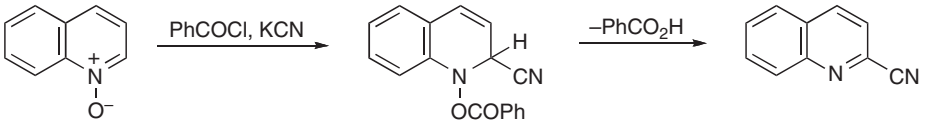
Scheme 41

Analogously, 5-unsubstituted 1,2,4-triazines with cyanide ions afford bi-1,2,4-triazin-5,5-yls **327** and 1,2,4-triazine-5-carboxamides **328** <1987CPB1378>.

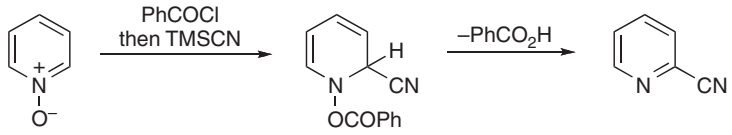


In the Reissert reaction, 1-benzoylquinolinium ions (formed *in situ* from quinolines and PhCOCl) and cyanide ions give Reissert compounds; thus, quinoline itself forms **329**. Reissert compounds are hydrolyzed by dilute alkali to, for example, quinoline-2-carboxylic acids and benzaldehyde. Isoquinolines also form Reissert compounds (e.g., **330**). Reissert adducts can also be formed enantioselectively in the presence of a suitable catalyst <2001JA6801>.

In the ReissertHenze reaction, quinoline *N*-oxide reacts with benzoyl chloride and potassium cyanide to give 2-cyanoquinoline in good yield (**Scheme 42**). Pyridine 1-oxides undergo the ReissertHenze reaction readily when the reaction is carried out in nonaqueous medium using $PhCOClMe_3SiCN$ (**Scheme 43**). Pyrimidine *N*-oxides and pyrazine *N*-oxides also undergo ReissertHenze reactions.



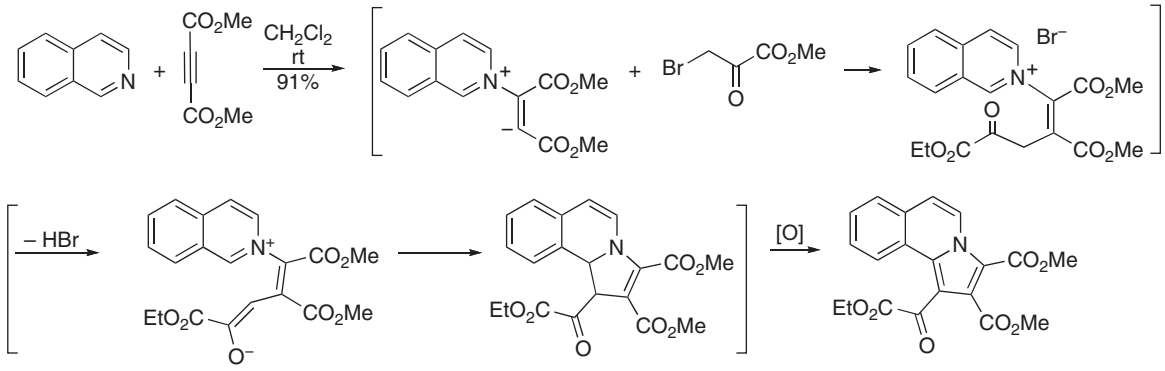
Scheme 42



Scheme 43

1-Alkoxypyridinium and 1-methoxypyridazinium salts yield cyanopyridines and cyanopyridazines, respectively, on treatment with potassium cyanide; the cyano group enters the -position with respect to the *N*-oxide of the starting material.

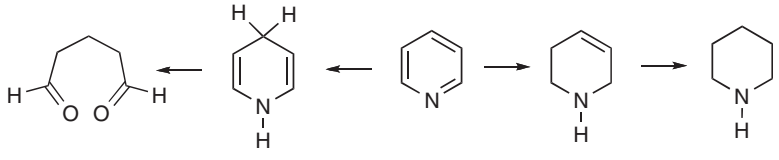
Pyridines (and quinolines, isoquinolines) react with electron-deficient alkynes via N-alkylation and then intramolecular nucleophilic addition to an -position. Thus, for example, DMAD reacts with isoquinoline in the presence of ethyl bromopyruvate to yield pyrrole[2,1-*a*]isoquinolines in excellent yields (**Scheme 44**) <2006TL6037>. A zwitterionic mechanism is proposed, and implies an enolate intermediate with a final spontaneous oxidation.



Scheme 44

3.2.1.6.9 Chemical reduction

3.2.1.6.9.1 Pyridines. Pyridines are more susceptible to reduction than benzenes. Sodium in ethanol or liquid ammonia evidently reduces pyridine to 1,4-dihydropyridine (or a tautomer) because hydrolysis of the reaction mixture affords glutaric dialdehyde (**8 331 332**). Reduction of pyridines with sodium and ethanol can proceed past the dihydro stages to 1,2,5,6-tetrahydropyridines (sometimes termed ^{3}-tetrahydropyridines) and piperidines (**8 333** and **334**).



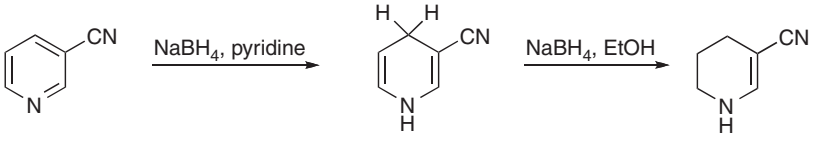
332 **331** **8** **333** **334**

Comparison of the experimental results with theoretical calculations (MNDO/3MO) of the isomeric anions formed by addition of hydride to pyridines and azines suggests that the thermodynamically most stable products are obtained with mild reducing agents. By monitoring reduction of pyridine with strong reducing agents (i.e., MgH_2 and AlH_3), it was shown by ^{1}H NMR that initially there is a mixture of 1,2- and 1,4-dihydro-1-pyridyl anions, but the final product is the 1,4-dihydro-1-pyridyl anion. The proposed mechanism for this selective reduction is a hydride exchange between reduced and unreduced substrate molecules coordinated to the same metal ion <1983J(P2)989>. Reduction of

pyridines with diisobutylaluminum hydride <1985JOC2443>, lithium 9-boratabicyclo[3.3.1]nonane <1984JOC3091>, 9-*sec*-amyl-9-borabicyclo[3.3.1]nonane <1989MI 502-01>, aluminum hydridetriethylamine complex <1993JOC3974>, bis(diethylamino)aluminum hydride <1994MI 502-01>, and sodium diethyldihydroaluminate <1992MI 502-03> has been reported to occur slowly, whereas lithium triethylborohydride (super hydride) reduces isoquinolines, quinoline, and pyridines effectively to give 1,2,3,4-tetrahydroisoquinolines, 1,2,3,4-tetrahydroquinolines, and piperidines. The mechanism of this reduction has been explored using lithium triethylborodeuteride <1993TL7239>. $H_2/Pd(OH)_2$/AcOH reduction of pyridines carrying a chiral auxiliary affords piperidines in good yields and with high enantiopurity <2004AGE2850>.

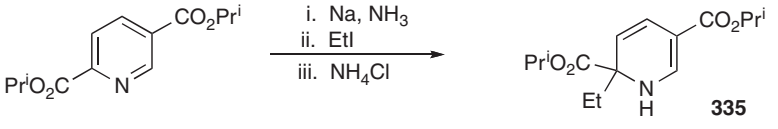
Samarium diiodide rapidly reduces pyridine to piperidine in the presence of water at room temperature in excellent yield <1993H(36)2383>, and various substituted pyridines have been reduced similarly.

Reduction of quinoline with lithium aluminum hydride gives 1,2-dihydroquinoline. Neutral pyridines bearing electron-withdrawing substituents are also reduced by sodium borohydride (**Scheme 45**).

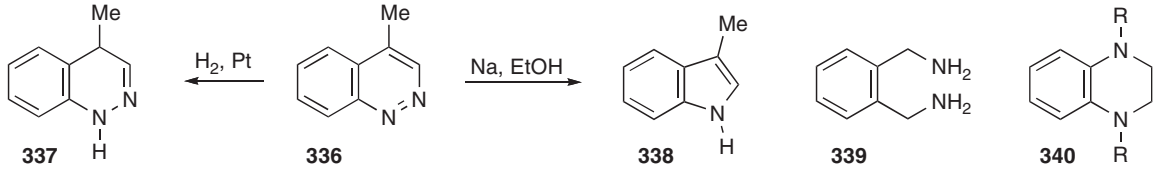


Scheme 45

Pyridines containing electron-withdrawing groups can be reduced with sodium/ammonia, with alkylative trapping giving 1,2-dihydropyridines, e.g., **335** <2001J(P1)1435>.



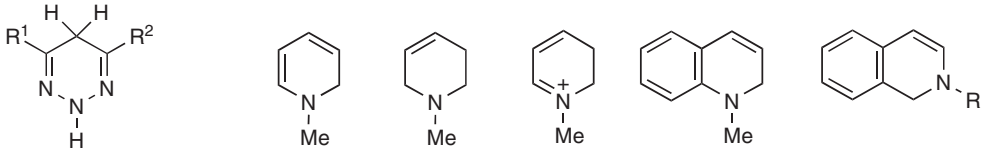
3.2.1.6.9.2 Azines. Diazines are readily reduced. The ring can be cleaved when the two nitrogens are adjacent; thus, pyridazine gives tetramethylenediamine as well as partially hydrogenated products on reduction with sodium and ethanol. Cinnolines form either dihydro derivatives, e.g., **336** **337**, or indoles by ring opening and reclosure, e.g., **336** **338**. Phthalazine gives 1,2,3,4-tetrahydrophthalazine (with Na/Hg) or the ring-opened product **339** (with ZnHCl). Pyrazines are normally reduced to hexahydro derivatives (e.g., with nickelaluminium alloy in potassium hydroxide <1987JOC1043>), whereas quinoxalines usually give 1,2,3,4-tetrahydro derivatives. Thus, treatment of quinoxalines with sodium borohydride and benzyl chloroformate in methanol at 78̄C forms tetrahydro derivatives **340** (R = CO_2Bn) <1992J(P1)1245>.



Pyrimidine and simple alkyl derivatives are not reduced by $NaBH_4$. Lithium aluminum hydride converts pyrimidines into di- or tetrahydro derivatives. In general, electron-withdrawing substituents promote reduction of the ring, while electron-releasing substituents have the opposite effect. The metal hydride may act as a base and abstract a proton from the -position in a substituent, in which case the anionic substrate may resist reduction in the ring.

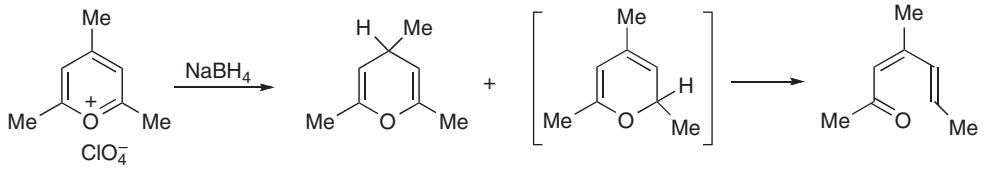
Sodium borohydride reduction of 4,6-disubstituted 1,2,3-triazines in methanol affords 2,5-dihydro-1,2,3-triazines **341** in good yields. 1,2,4,5-Tetrazines with mild reducing agents give dihydro derivatives.

3.2.1.6.9.3 Cationic rings. Cationic rings are readily reduced under relatively mild conditions. 1-Methylpyridinium ion with sodium borohydride (in H_2O, 15°C) gives the 1,2-dihydro derivative **342** at pH >7 and the 1,2,3,6-tetrahydro derivative **343** at pH 25. The tetrahydro compound is probably formed via **344** which results from proton addition to dienamine **342**. Pyridine cations are also reduced to 1,2-dihydropyridines by dissolving metals, e.g., Na/Hg.



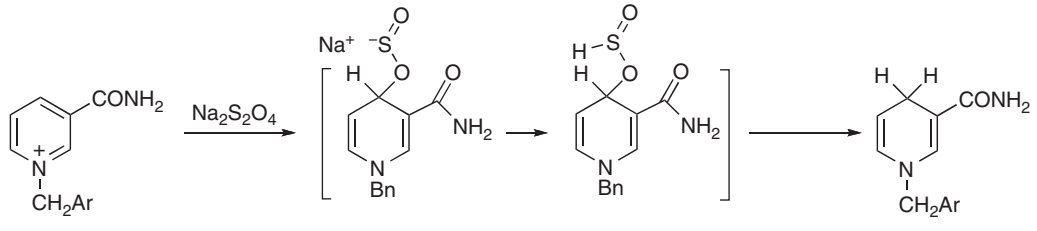
341 **342** **343** **344** **345** **346**

Complex hydride reduction ($NaBH_4$ or $LiAlH_4$) of 1-methylquinolinium ions proceeds analogously to 1,2-dihydro compounds (e.g., **345**). 2-Methyl- and 2-acylisoquinolinium ions (the latter with Bu_3SnH <1988CL913>) give the corresponding 1,2-dihydro compounds **346**. Borohydride reduces pyrylium salts to mixtures of 2*H*- and 4*H*-pyrans; the former immediately ring open to form the dienone (**Scheme 46**).

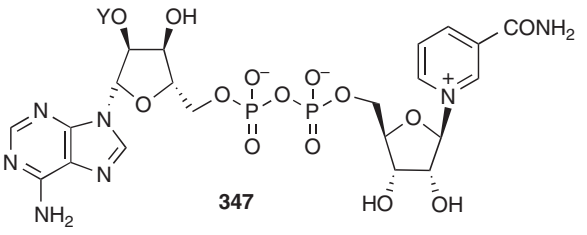


Scheme 46

Reduction of pyridinium ions with sodium dithionite ($Na_2S_2O_4$, H_2O, Na_2CO_3), usually when substituted with electron-withdrawing groups in the 3- or 3,5-positions, affords mainly the corresponding 1,4-dihydropyridines. The regioselectivity of formation of the dithionite adducts and mechanisms of decomposition has been studied; it is the oxygen which adds initially at the 4-position (**Scheme 47**) <2005T10331>. However, reductions without the 3-acyl group are possible: Lavilla and coworkers developed a dithionite reduction of -substituted *N*-alkylpyridinium salts to afford the corresponding 1,4-dihydropyridines or piperidines. In the absence of $NaHCO_3$, full reduction occurs to give piperidines in high yields <2005TL3513>. Reversible reduction of the pyridinium ring of coenzymes I and II (**347**; Y = H and PO_3H_2, respectively) is an important biochemical process.



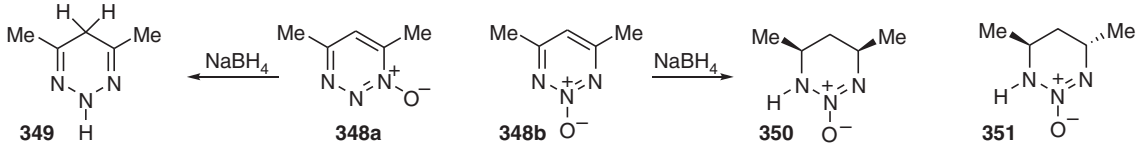
Scheme 47



347

Vigorous chemical reduction (e.g., Sn, HCl or Zn, HCl) affects complete reduction of the heterocyclic ring, e.g., 1-methylquinolinium ion yields 1-methyl-1,2,3,4-tetrahydroquinoline; however, a common and often efficient method for the preparation of saturated piperidines is the catalytic reduction of pyridines, pyridine *N*-oxides, or pyridinium salts <2001CHE797, 2003T2953, 2004AGE2850>. Ammonium formate and palladium on carbon also convert pyridine *N*-oxides into piperidines <2001JOC5264>.

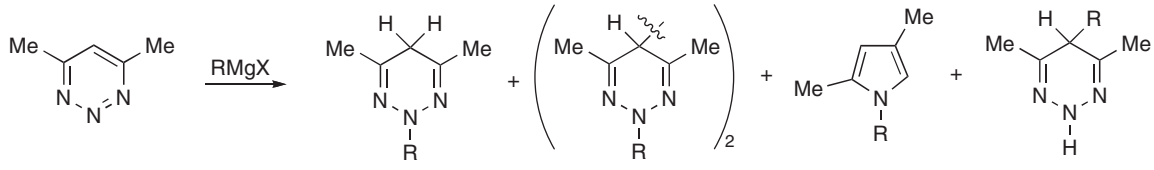
Chemical reduction of azine *N*-oxides, depending on substrate structure, reductant, and reaction conditions, can proceed both with or without deoxygenation of the N-atom. Thus, 1,2,3-triazine 1-oxide (cf. **348a**) with $NaBH_4$ gives 2,5-dihydro-1,2,3-triazine **349**, suggesting that the *N*-oxide moiety back-donates electrons to the triazine ring. On the other hand, on reduction of the isomeric 2-oxide (cf. **348b**) leading to tetrahydro derivatives **350** and **351**, the *N*-oxide function is not touched <1982H(17)317>.



349 **348a** **348b** **350** **351**

3.2.1.7 Nucleophilic Attack at Ring Nitrogen

Some azines can add organometallic compounds at a ring nitrogen, though this is very much the exception. Thus, 4,6-dimethyl-1,2,3-triazine reacts with alkyl and aryl Grignard reagents to form N-2 addition compounds **352** and products of deeper transformation **353** and **354** along with normal C(4) addition product **355**. Such azaphilic addition has also been demonstrated in 1,2,3-benzotriazines and 1,2,4,5-tetrazines. The driving force for azaphilic addition is believed to be strongly decreased electron density on the nitrogen atom in poly-aza heterocyclic compounds.



17–37% **352** 6–8% **353** 10% **354** 6–15% **355**

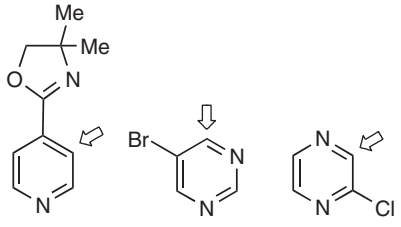
3.2.1.8 Attack by Bases at Hydrogen Attached to Ring Carbon or Ring Nitrogen

Hydrogen attached to ring carbon atoms of neutral azines, and especially azinium cations, is acidic and can be replaced by a metal formally being removed as a proton. Alkyllithiums can be used as bases for this purpose; however, the reaction can be accompanied by addition of the alkyl anion to the ring C═N bond. To avoid this, sterically hindered bases with strong basicity but low nucleophilicity can be utilized. Among these are lithium tetramethylpiperidide (LiTMP) and lithium diisopropylamide (LDA). If the anion contains an *ortho* halogen atom, then this can be eliminated to form a pyridyne (see Section 3.2.3.10.1).

The reactivity of pyridine organometallic nucleophiles is of course the same whether they are prepared by direct lithiation or by halogenmetal exchange from pyridine halides. Accordingly, the reactions of these organometallic intermediates are discussed partly here but mainly in Section 3.2.3.11, Reactions of substituents: Metals and Metalloid Derivatives.

3.2.1.8.1 Metallation at a ring carbon atom (see also Sections 3.2.3.10.2.23.2.3.10.2.5 and 3.2.3.11.1)

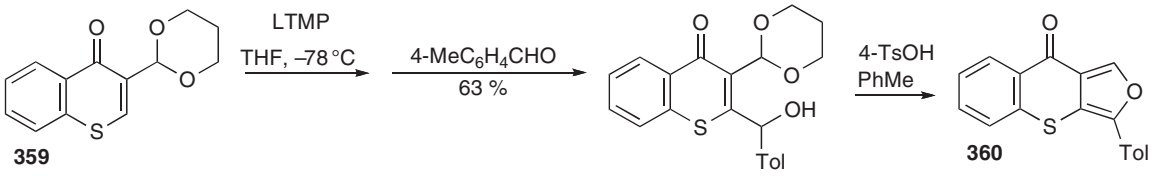
Direct ring metallation of azines generally requires some additional activating substituent. The following groups direct *ortho* metallation <2001T4059>: halo, NHCOR, $NHCO_2R$, OR, $OCONR_2$, 2-oxazolinyl, CONHR, $CONR_2$, and masked RCHO, RCOR, and SO_2NR_2 groups. The directing groups have lone pairs of electrons on heteroatoms that enable formation of coordination complexes with metals such as lithium, resulting in metallation at sites adjacent to the substituent. For example, 2-(4-pyridyl)oxazoline **356** is metallated at C(3) with methyllithium while the 3-isomer reacts at C(4) with lithium LiTMP <1982JOC2633>. Treatment of 3-ethoxy- or 3-*n*-butoxypyridine with *n*-butyllithium in the presence of TMEDA results in apparently exclusive metallation at the 2-position <1982S235>. Examples of halogen-directed metallations include the lithiation of 5-bromopyrimidine **357** or chloropyrazine **358** by LDA. 3-Halopyridines are also lithiated regiospecifically at C(4), but pyridyne formation is then rapid.



356 **357** **358**

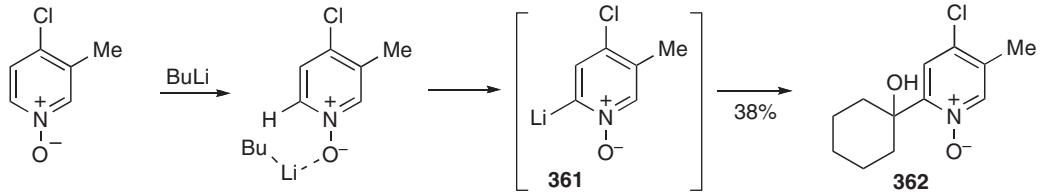
The carbanion can usually be masked or trapped as a more metalloid derivative and be released in the presence of an electrophile. Trialkylsilane and trialkylstannane derivatives are most often used <1981T4069, 1988G211>, for example, in *ipso* substitution with acyl halides.

ortho-Assistance for metallation applies in other systems too, for example, the use of lithium LiTMP metallated a benzothiopyranone **359** and thence allowed the formation of furo[3,4-*b*]benzothiopyran-9-one **360** <2002TL4507>. Pyridazines with an *ortho*-directing group at C(4) are lithiated regioselectively at C(5) <1995JHC841>. 3-Bromo-6-phenylpyridazine gives C(4) metallation. LDA is a better base for this purpose than LiTMP <2005JHC509>.



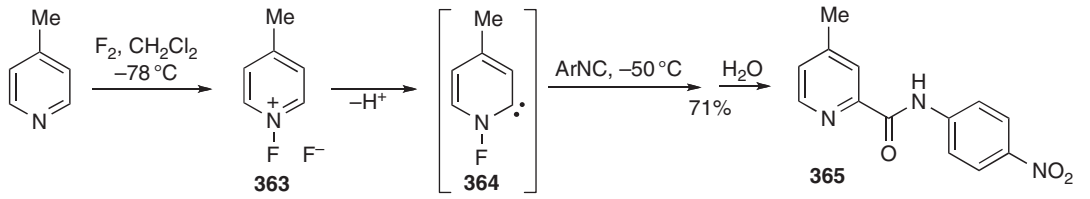
359 **360**

Pyridine *N*-oxides are readily deprotonated at C(2) using LDA or *n*-butyllithium as base in THF and the reagents thus produced react in the usual way in high yields with a variety of electrophiles including iodine, alkyl halides, aldehydes, and ketones <1995J(P1)2503>. For example, -lithio derivative **361** can be generated and intercepted by various electrophiles, e.g., carbon dioxide, elementary sulfur, or cyclohexanone giving **362**; note that the lithiation prefers the carbon to the oxide rather than that *ortho* to the chlorine.

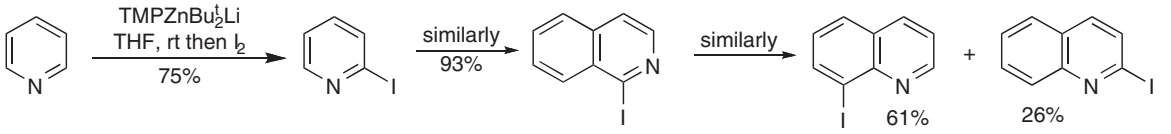


361 **362**

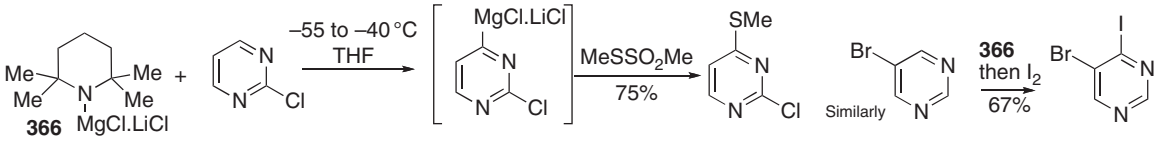
-Deprotonation of *N*-fluoropyridinium fluorides, e.g., **363**, generated *in situ* by reaction of pyridines with fluorine gas, undergoes reaction with isonitriles to give 2-picolinamides **365** in moderate to good yields, the carbene **364** being the reactive intermediate <2005TL2279>.



The iodination of pyridine, quinoline, and isoquinoline can be achieved via metallation to the nitrogen using lithium di-*tert*-butyltetramethylpiperidinozincate (TMP-zincate) at room temperature. Quinoline metallated preferentially at C (8) to give a 61% yield of the 8-iodoquinoline and isoquinoline gave a good yield of 1-iodoisoquinoline (**Scheme 48**) <1999JA3539>.



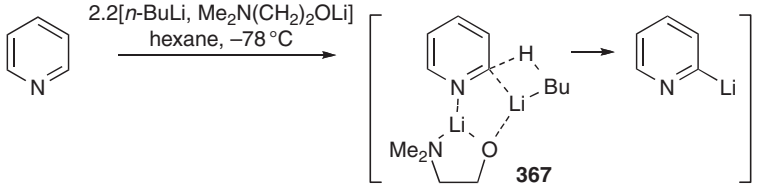
Scheme 48



Scheme 49

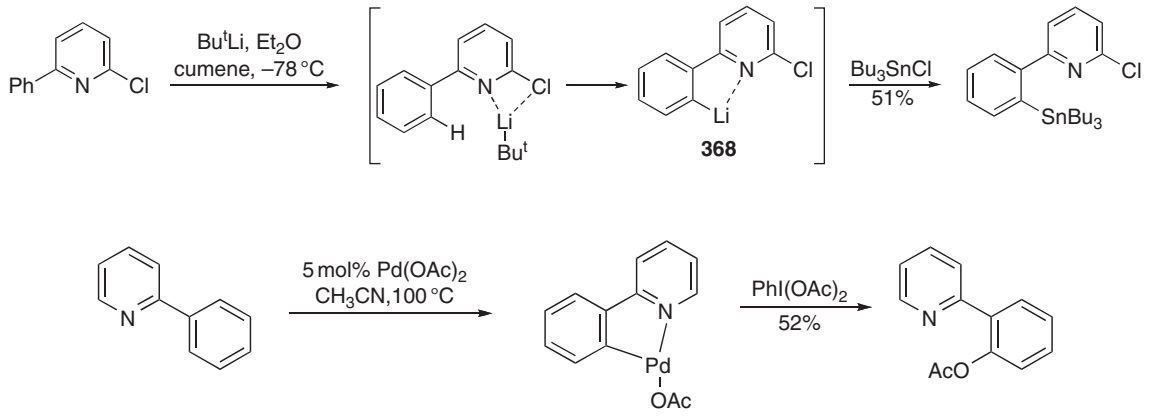
Direct magnesiation can be achieved with TMPMgCl.LiCl **366** at 55°C, for example, 4-chloro- and 5-bromopyrimidines were metallated completely regioselectively (**Scheme 49**) <2006AGE2958>.

A major advance in pyridine lithiation is the use of the mixed base produced from two mole equivalents of *n*-butyllithium with one of dimethylaminoethanol, i.e., it is a 1:1 mixture of *n*-BuLi and $Me_2N(CH_2)_2OLi$ (BuLi-LiDMAE); structure **367** shows how this regioselective -lithiation is believed to occur. <2002EJO3375, 2003JOC2028>.



Lithiation of pyrazines <(CHEC-III(7.03.5.5)> can be achieved without *ortho*-assistance: for example, pyrazine itself can be lithiated with four equivalents of LiTMP at 75°C <1995JOC3781>. 4-Methoxy-1,2,3-triazine metallates with LiTMP at 100°C to produce a mixture of the 5- and 6-lithiotriazines <1998SP119>.

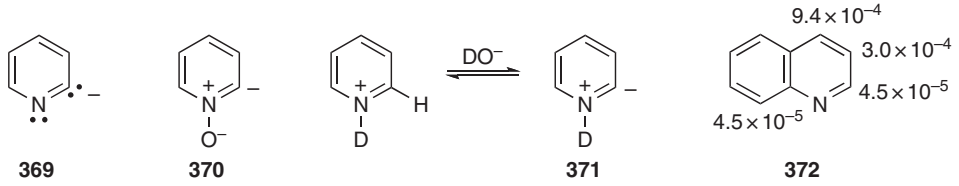
On occasions, a pyridine carrying a 2-aryl group is lithiated, with *ortho*-assistance from the pyridine nitrogen, in the benzene ring; for example, lithiation of 2-chloro-6-phenylpyridine does not take place *ortho* to the chlorine but generates **368** <2003JOC4918>. Similarly, chelate-directed electrophilic palladation of 2-phenylpyridine with 5 mol% $Pd(OAc)_2$ leads to the formation of a palladacycle that undergoes oxidation with $PhI(OAc)_2$ followed by carbonheteroatom bond formation and reductive elimination to give 2-(2-acetoxyphenyl)pyridine (**Scheme 50**) <2004JA2300>.



Scheme 50

3.2.1.8.2 Hydrogen exchange at ring carbon in neutral azines, *N*-oxides, and azinones

Pyridine undergoes base-catalyzed hydrogendeuterium exchange much more readily than benzene, resulting in eventual replacement of all hydrogen atoms by deprotonation followed by rapid deuteration of the intermediate negatively charged species in a sequential manner. The reactivity order $> >$ is found for exchange in NaOMe, MeOD at 160 °C, NaOD, D_2O at 200 °C, and $NaND_2$, ND_3 at 25 °C. The low reactivity of the 2-position reflects the unfavorable lone pairlone pair interaction in the intermediate carbanion **369**. Pyridine *N*-oxides exchange all protons, but the C(2) protons react most readily via the anion **370**. In aqueous solution at low pH, base-catalyzed hydrogen deuterium exchange of pyridine can involve the pyridinium ylide **371** <1974AHC(16)1>. The exchange is facilitated by electron-withdrawing groups; in particular an electron-withdrawing group at the 3-position of pyridine accelerates exchange at the 4-position and vice versa. Quinoline undergoes hydrogendeuterium exchange in NaOMe, MeOD at 191 °C at the 2-, 3-, 4-, and 8-positions **372** <1973JA3928>.



369 **370** **371** **372**

In pyridazines, base-catalyzed hydrogendeuterium exchange takes place at positions 4 and 5 more easily than at positions 3 and 6. Pyridazine 1-oxide reacts first at positions 5 and 6 and then at C(3) and C(4). Pyrimidine exchanges most readily at the 5-position, next at the 4-position, and least readily at the 2-position. In pyrimidine 1-oxide, the reactivity order is $2 > 6 > 4 >> 5$. 1,2,4-Triazines easily undergo base-catalyzed hydrogen exchange at the 2-position.

1-Methylpyridin-4-one (and 1-methylpyridin-2-one) undergoes hydrogendeuterium (HD) exchange at the 2- and 6-positions in basic D_2O at 100 °C.

3.2.1.8.3 Hydrogen exchange at ring carbon in azinium cations

Hydrogen isotope exchange is facile at the -position in pyridinium salts. 3-Methyl- and 3-cyano-pyridinium methiodides undergo exchange in the order $2 > 6 >> 4, 5$ in 0.01 M NaOD, D_2O. The relative rates of HD exchange for the -, -, and -positions in 1-methylpyridinium chloride are 3400:3:1.

The rates of HD exchange at the -positions for a series of N-substituted pyridinium cations and pyridine 1-oxide derivatives in D_2O at 75 °C (**Figure 2**) <1970JA7547> correlate well with the Tafts inductive parameter $_I$ ($_I = 15$). A positively charged nitrogen in a ring is estimated to activate the -position toward deprotonation and ylide formation by a factor of 10^{15}.

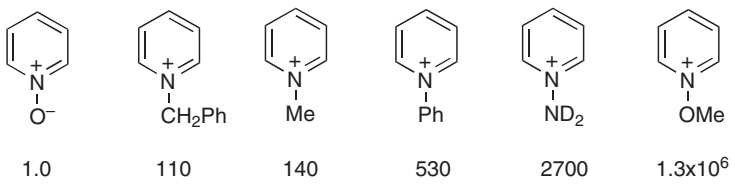
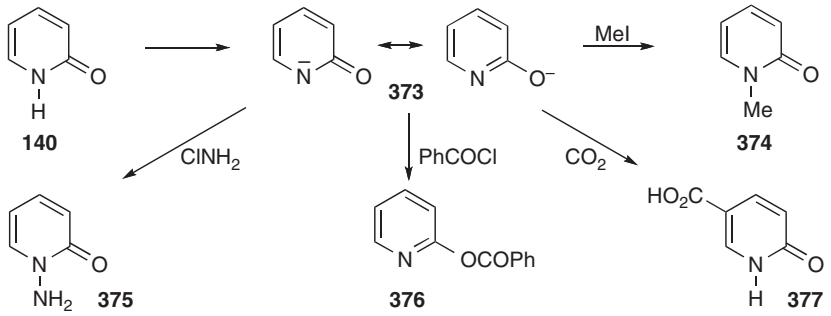


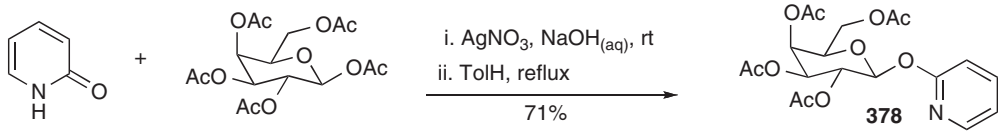
Figure 2 Rates of HD exchange at the -positions of pyridinium and related cations.

3.2.1.8.4 Proton loss from a ring nitrogen atom

Pyridones and azinones are weak acids of pK_a ca. 11 (see Section 3.2.1.3.4.4). They form mesomeric anions (cf. **140** **373**) that react very readily with electrophilic reagents at the nitrogen, oxygen, or carbon atom, depending on the circumstances (see Section 3.2.3.7.2). The anion **373** from 2-pyridone is alkylated and aminated mainly on nitrogen (**373** **374, 375**), is acylated on oxygen (**373** **376**), and reacts at a ring carbon atom in the KolbÕ reaction (**373** **377**). Attack on a pyridone anion (cf. **373**) is probably involved in certain other electrophilic substitutions, e.g., the diazo coupling of 4-quinolone (see Section 3.2.1.4.10).



The position of alkylation can depend on counter ion, solvent, and reagent. Thus, Ag salts tend to give O-alkylation, whereas Na or K salts predominantly undergo N-alkylation <CHEC-I(2.05.2.5)>. For example -D-galactopyranose pentaacetate reacts with silver 2-pyridoxide in toluene under reflux to give the pyridylgalactopyranoside **378** in good yield <2001T3267>.

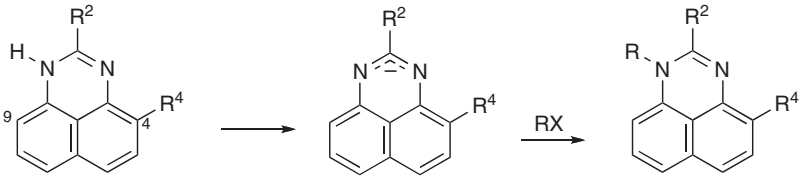


O-Alkylation is also favored using more sterically hindered electrophiles such as secondary alkyl halides; thus, alkylation of 2-pyridone with isopropyl iodide under mild conditions in the presence of cesium fluoride at room temperature leads to the formation of a mixture of N- and O-alkylated products in a 11:89 ratio <1995SL845>.

Reaction of pyridones with diazoalkanes involves deprotonation as the first step, forming an alkyldiazonium cation that then rapidly alkylates the pyridone anion; 2-pyridone gives mainly 2-methoxypyridine, but 4-pyridone gives a mixture of *O*- and *N*-methyl derivatives. Selective O-alkylation of 2-pyridones can be effected by reaction with diazoacetic esters in the presence of 2 mol% $Rh_2(OCOCF_3)_4$ <2000OL1641>.

The reactivity pattern of azinones containing an NH group is similar to that of the pyridones just discussed. Thus, for example, the alkylation of pyridazinones under basic conditions also gives mixtures of N- and O-substitution products. At the same time, uracil, unlike 2-pyridone, is benzoylated at a nitrogen, not an oxygen, atom; depending on the quantity of benzoyl chloride, 1-benzoyl or 1,3-dibenzoyl derivatives can be obtained. Selective removal of the 1-benzoyl group can be effected under mild basic conditions to furnish the 3-benzoyl derivative <1984T681>.

Perimidines with a free NH group **379** form readily oxidizable anions **380**, but which can be N-alkylated in an inert atmosphere, the reaction being sensitive to steric interference from 2- and 4(9)-substituents <1981RCR1559>.



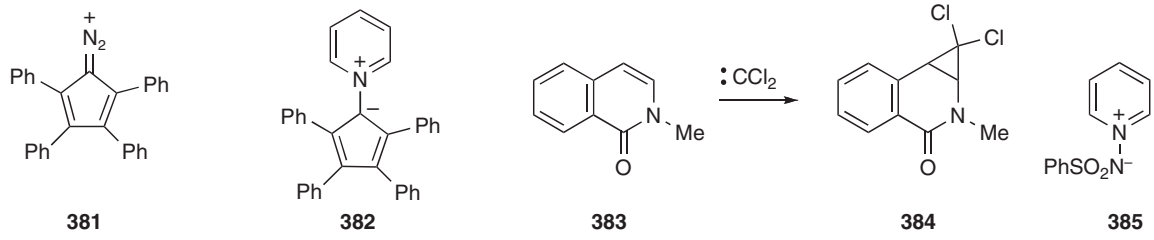
3.2.1.9 Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces

3.2.1.9.1 Carbenes and nitrenes

With both carbenes and nitrenes, attack generally occurs at a pyridine nitrogen atom.

The reaction of triplet diphenylcarbene with pyridine has been well studied, and a mechanism proposed from kinetic data <1990TL953>. The carbenes generated from laser flash photolysis of alkylbromo- and alkylfluoro-diazirines were trapped by pyridine to form the pyridinium ylides <1994JPO24>.

Ylide **382** has been obtained by heating **381** in pyridine. Isoquinoline yields a stable ylide upon reaction with ethoxycarbonylcarbene <1970TL941> and the relative rates of reaction of ethoxycarbonylcarbene with pyridine, quinoline, and acridine have been studied <1988JOC4374>. However, the isoquinolone **383** undergoes attack at the 3,4-double bond to give **384**.



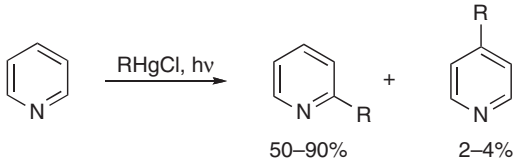
Sulfonyl azides react with pyridine to give pyridine 1-sulfonylimides (e.g., **385**); however, the analogous reaction with 2,4,6-trimethylpyridine gives some 3-(phenylsulfonylamino) derivative together with the 1-sulfonylimide. Nitrenes derived from photolysis of acyl azides also add to the nitrogen atom to form the corresponding pyridine *N*-imines <1974AHC(17)213>.

3.2.1.9.2 Radical attack at ring carbon atoms

3.2.1.9.2.1 Halogen atoms. Regiospecific chlorination of pyridine at the -position occurs rapidly during irradiation in the presence of chlorine dissolved in carbon tetrachloride <1967JHC375, 1993AHC(58)274>. Both ring and side-chain chlorination of 4-picoline occurs under -irradiation conditions <1980JGU354>.

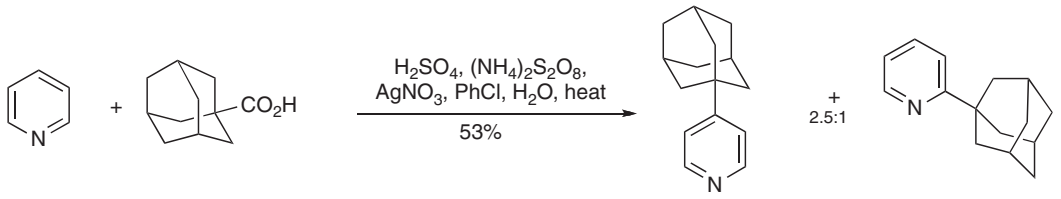
Vapor-phase halogenation of pyridine at high temperatures gives mixtures of 2- and 2,6-dibromopyridine (Br_2, 500°C or CuBr, Br_2, 350°C) and 2- and 2,6-di-chloropyridine (Cl_2, 270°C). 2-Fluoropyridines have been prepared by direct reaction of fluorine diluted in an inert gas and dissolved in a polyhalogenated solvent <1991BCJ1081>. Presumably, these reactions involve attack by free halogen atoms as distinct from the ionic halogenations at lower temperatures which give -orientation (cf. Section 3.2.1.4.7). Under similar conditions (Br_2, 450°C), quinoline gives 2-bromoquinoline.

3.2.1.9.2.2 Alkyl and -hydroxyalkyl radicals. Alkyl radicals, prepared *in situ*, react with pyridine to form mainly 2-alkyl derivatives and this regioselectivity is shown in the radical reactions of alkylmercurial compounds with pyridines (**Scheme 51**).



Scheme 51

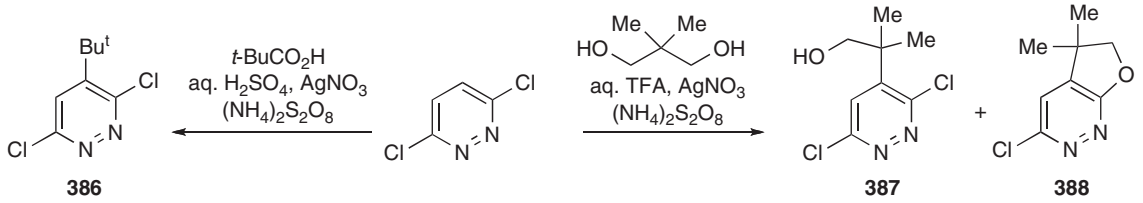
These and other homolytic alkylations of neutral heteroaromatics usually proceed in poor yields, but if protonated heteroaromatic bases are used, many of the side reactions are minimized and selectivity is high and yields are good. These reactions are generally referred to as Minisci reactions. Selectivity is increased because the alkyl radicals are nucleophilic in character and thus selectively attack the - and -positions; reaction with adamantyl radical illustrates this (**Scheme 52**) <1995ZOR670>.



Scheme 52

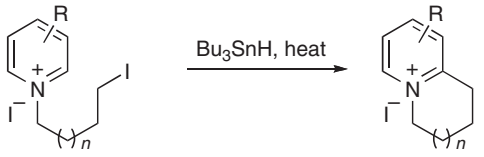
Alkyl radicals for such reactions are available from many sources such as acyl peroxides and alkyl hydroperoxides, particularly by the oxidative decarboxylation of carboxylic acids using peroxydisulfate catalyzed by silver. Pyridine and various substituted pyridines have been alkylated at the 2-position in high yields by these methods. Quinoline similarly reacts at the 2-position, isoquinoline at the 1-position, and acridine at the 9-position. Pyrazine and quinoxaline also give high yields of 2-substituted alkyl derivatives <1974AHC(16)123>.

3,6-Dichloropyridazine can be *tert*-butylated to give 4-*tert*-butyl-3,6-dichloropyridazine **386** in high yield <1988OPP117>, and 2-(hydroxymethyl)-*i*-propyl radicals, generated *in situ* from 2,2-dimethyl-1,3-propanediol, give **387** (55%) along with some of the fused dihydrofuropyridazine by-product **388**.



386 **387** **388**

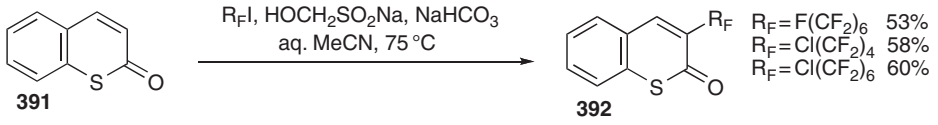
N--Iodoalkylpyridinium salts **389** (R = H, Me, *n* = 13) undergo intramolecular radical cyclization upon treatment with tributyltin hydride and AIBN to give the [6,5], [6,6], and [6,7] fused pyridinium salts **390** in good yields <1990TL1625>.



389 **390**

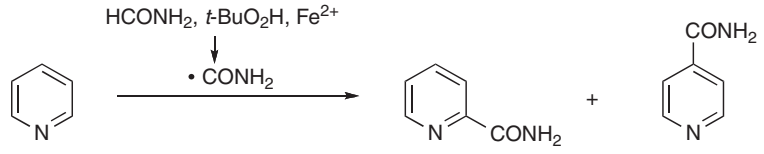
Hydrogen abstraction from a position to the oxygen of alcohols and ethers gives -oxyalkyl radicals which add readily to electron-deficient heterocycles; for example, pyridine is hydroxymethylated at C(2) and C(4) using methanol and ammonium persulfate; 4-methylquinoline yields the 2-CH_2OH derivative with $NH_2OSO_3H + MeOH + FeCl_3$ <1983CC916>.

In what is probably a radical-based substitution, thiocoumarins **391** react with perfluoroalkyl iodides in the presence of rongalite, $HOCH_2SO_2Na$, to give 3-perfluoroalkyl derivatives **392** <1994J(P1)101>.



391 **392**

3.2.1.9.2.3 Acyl radicals. Acyl radicals obtained by the oxidation of aldehydes or the oxidative decarboxylation of -keto acids react selectively at the - or -position to the nitrogen of protonated pyridines, quinolines, pyrazines, and quinoxalines, in yields typically in the range 4070%; for example, 4-cyanopyridine gives 2-benzoyl-4-cyanopyridine in 96% yield <2003JHC325>. Similarly, pyridines can be carbamoylated in acid media at C(2)/C(4) (**Scheme 53**).



Scheme 53

Such reactions also succeed with diazines. Homolytic acylations of methoxy- and chloro-substituted pyrazines are directed *ortho*, giving the corresponding 2,3-disubstituted pyrazines. Acetyl, alkoxycarbonyl, carboxy, cyano, and carbamoyl groups direct radical substitution *para*, leading to the corresponding 2,5-disubstituted pyrazines. These selectivities result from a combination of the inductive and resonance effects of the substituents <1988S119, 1989JOC640, 1991S581, 1992JHC1685>. The Minisci-type alkoxycarbonylation reaction produces an 89% yield of ethyl 2-pyrazinecarboxylate by redox treatment of pyrazine with ethyl pyruvate <1986T5973>.

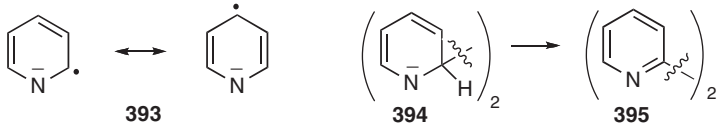
3.2.1.9.2.4 Aryl radicals. In sharp contrast, homolytic arylation is unselective and gives low yields. Phenyl radicals attack pyridine unselectively to form a mixture of 2-, 3-, and 4-phenylpyridines in proportions of *ca.* 53: 33: 14. The phenyl radicals can be prepared from precursors such as PhN(NO)COMe, $Pb(OCOPh)_4$, $(PhCO_2)_2$, or $PhI(OCOPh)_2$. Substituted phenyl radicals react similarly.

Photolysis of aryl or pyridyl oxime esters in pyridine provides -phenylpyridines as the major products together with bipyridyls <1984TL3887>. Rate constants for the addition of phenyl radical to protonated and nonprotonated 4-substituted pyridines have been determined by studying the competition between phenyl radical addition and chlorine abstraction from carbon. The 4-arylpyridines are the major products, and no 3-substituted pyridines were observed. Among the solvents studied (MeCN, DMF, DMSO, and HMPA), MeCN gave the highest yields and selectivity <1991OPP438>.

3.2.1.9.2.5 Hydrogen atoms. As for any other organic molecules containing CH bonds, heteroaromatics can be labeled with tritium by reaction with energetic tritium atoms from neutron irradiation.

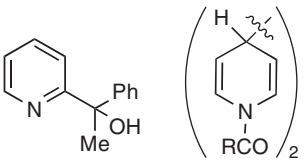
3.2.1.9.3 Electrochemical reactions and reactions with free electrons *(see also Section 3.2.1.6.9)*

3.2.1.9.3.1 Neutral species: Reactions with metals. Certain metals (e.g., Na, Zn) add one electron to pyridine to form a radical anion **393** which can dimerize by reaction at the - or -position; these dimers form bipyridyls by hydride ion loss. On treatment with sodium at 20°C, pyridine forms mixtures of 2,2-, 2,3-, 2,4-, and 4,4-bipyridyls, probably by aromatization of intermediate dihydro compounds (**394** **395**). The reaction can be directed to give largely 4,4-bipyridyl, a product of commercial importance.

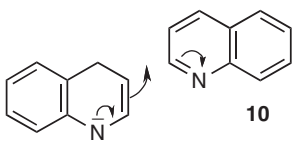


Pyridine is converted by a modified Raney nickel catalyst into 2,2-bipyridyl, and the reaction has been extended to many substituted pyridines and quinolines. 2-Substituted pyridines give the 6,6-bipyridyls. 3-Methylpyridine gives 5,5-dimethyl-2,2-bipyridyl, but none of the other isomers are formed.

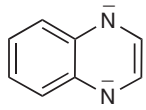
These dimerizations are analogous to those of the radical anions $R_2C{\cdot}O$ which are intermediates in the reduction of ketones to pinacols. Indeed, in the presence of magnesium amalgam, pyridine condenses with acetophenone to give alcohol **396** by oxidation of the intermediate dihydropyridine. In a similar reaction type, pyridine with zinc and acetic anhydride or ethyl chloroformate yields (**397**; R = Me or OEt, respectively).



396 397



398 10



399

Treatment of quinoline with sodium gives mainly 2,3-biquinolyl, the formation of which can possibly be explained as initial reduction followed by reaction of the dihydroquinoline anion **398** with another molecule of quinoline **10**. Quinoxaline derivatives in an ether solvent are reduced by sodium to the corresponding antiaromatic doubly charged anions, e.g., **399** <1985JA1501>.

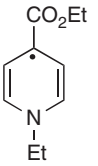
3.2.1.9.3.2 Neutral species: Electrochemical reduction. Electrochemical reduction of pyridines to piperidines can be achieved using various methods. Piperidines can be obtained in high yield by the electrochemical reduction of pyridine on a lead cathode in the presence of carbon dioxide and Pd-Ni or Cu-Ni catalysts <1989KFZ1120>. In the absence of catalyst, 4,4-bipyridine is produced as the major product.

Electron-attracting substituents facilitate electrochemical reduction. The reduction potentials for the polarographic reduction of quinoline and isoquinoline derivatives are much less negative than those for the pyridine analogues. Diazines are reduced electrochemically stepwise, usually as far as tetrahydro derivatives <1970AHC(12)213>.

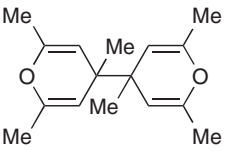
The behavior of pyrimidine during polarographic reduction depends on the pH of the aqueous solution. In acidic solution two one-electron waves are observed, while in neutral solution two two-electron waves result. In alkaline solution four-electron reduction is effected via 1,6-dihydropyrimidine to give tetrahydropyrimidine <1984AHC(36)235>.

3.2.1.9.3.3 Cationic rings. Pyridinium cations are reduced electrochemically or by metals to neutral radicals of considerable stability, especially when merostabilization by an - or -substituent occurs; thus, **400** has been isolated. Bispyridinium compounds are particularly readily reduced to radical cations, such as **401**. Radical (**401**; R = Me) is the active species of the herbicide paraquat. Pyridyl radicals without such stabilization dimerize and form bispyridinium compounds by oxidation.

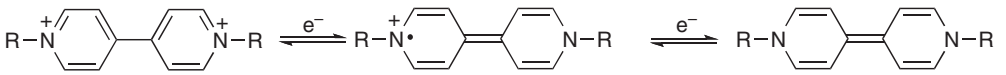
One-electron reduction of pyrylium salts, with dissolving metals or electrochemically, gives dimers (e.g., **402**) via pyranyl radicals <1980AHC(27)31>.



400



402



401

3.2.1.9.4 Other reactions at surfaces

3.2.1.9.4.1 Catalytic hydrogenation (see also Section 3.2.1.6.9). Hydrogenation of pyridines and their benzo derivatives can be carried out with various catalysts. Pyridines are readily hydrogenated to piperidines over Raney nickel at 120°C. The optimal pressure for hydrogenation of pyridine to piperidine over platinum is reported to be 2.02.5 mpa, and at 2.08.1 mpa the activation energy is 35.542.2 kJ mol^{1} <1985ZPK322>.

Reductions with noble metal catalysts proceed smoothly (at 20°C) when the bases are in the form of hydrochlorides; the free bases tend to poison the catalyst. A pyridine ring is reduced more easily than a benzene ring; thus, 2-phenylpyridine gives 2-phenylpiperidine, quinoline gives 1,2,3,4-tetrahydroquinoline, and acridine gives 9,10-dihydroacridine.

Pyridinium and pyrylium cations, pyridones, and pyrones are all readily hydrogenated; for example, flavylium (2-phenylbenzopyrylium) and coumarin **97** yield 1,2,3,4-tetrahydro- and 3,4-dihydro-derivatives, respectively.

Palladium on charcoal (Pd/C) is commonly used in the catalytic hydrogenation of pyrimidines in acidic media which halts the reduction at the 1,2,4,5-tetrahydro level because these, as amidinium salts, are stabilized <1962JOC2170, 1965JCS1406>. Platinum effects hydrogenation of the 5,6-double bond of uracils, for example, in the addition of deuterium to produce [5,6-$^2H_2$]5,6-dihydrouracil. The addition of hydrogen to the 5,6-double bond of thymidine and other 5-substituted uridines is stereospecific with rhodium-on-alumina as catalyst.

3.2.1.9.4.2 Isotopic hydrogen exchange. Transition metals also catalyze isotopic exchange reactions. Platinum is the most active catalyst for most heterocycles. The mechanism may involve metallation, addition, -addition, and -complex formation. -Hydrogen exchange in pyridine is favored over - and -positions, particularly by a cobalt catalyst, whereas platinum is much less selective. In isoquinoline, both the l- and 3-position protons are exchanged at almost the same rates with very little exchange at any other position. In 3-substituted pyridines exchange is preferred at the 6-position, the more so as the size of the 3-substituent increases <1973AHC(15)137>.

3.2.1.10 Reactions with Cyclic Transition States

3.2.1.10.1 Introduction

Reactions of this type are characteristic of compounds with low aromaticity. While rare in pyridine, they are favored by the following structural modifications which lower the aromatic stabilization energy:

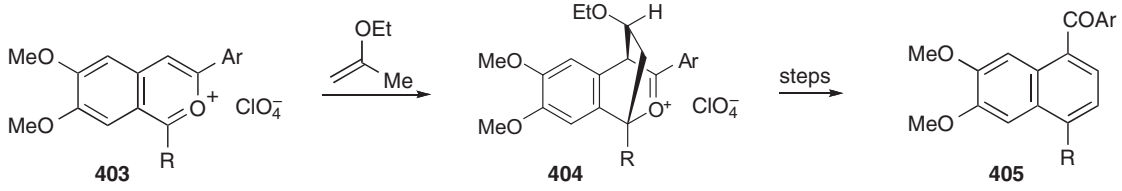
1. Benzo ring fusion, especially three or more rings linearly fused
2. Polyhetero rings, especially two adjacent ring nitrogens or a ring oxygen
3. Enhanced -deficiency, especially caused by the presence of positively charged heteroatom
4. Exocyclic carbonyl groups, especially betaine structures

We classify these reactions according to the type of cycloaddition reaction and the type of heterocyclic systems that participate in it.

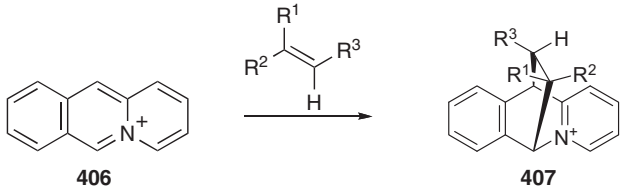
3.2.1.10.2 Heterocycles as inner dienes in [2 + 4] cycloadditions

Because of the strong -deficiency of most six-membered heteroaromatic compounds, cycloadditions of this type belong to DielsAlder reactions with inverse electron demands; in other words, they are $LUMO_{diene}HOMO_{phile}$ controlled reactions. Acceptor substituents in the heterocyclic diene and donor substituents in the dienophile accelerate such reactions <1983TL1481, 1984TL2541, 1990TL6851>.

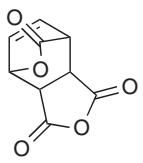
3.2.1.10.2.1 Heterocyclic systems with one heteroatom. Condensed heteroaromatic cations are reactive in [2 + 4] cycloaddition reactions with inverse electron demand. For instance, 2-benzopyrylium salts **403** react with vinyl ethyl ether to afford naphthalene derivatives **405** in good yields via initial adducts **404** <1990KGS315>. Similar transformations (Bradsher reaction) are also known for isoquinolinium salts <1984CC761>.



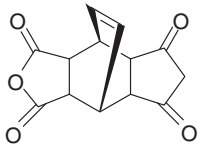
The acridizinium ion **403** adds to various dienophiles to give products of the type **407**.



2-Pyranones undergo DielsAlder reactions: with maleic anhydride; adducts of type **408** are formed which can lose carbon dioxide and react with more anhydride to give **409**. 2-Pyranones also react with singlet oxygen to give endoperoxides **410**. Benzyne reacts with 1-methyl-2-pyridone to give **411**.



408



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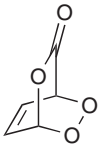
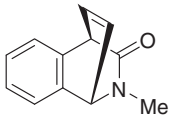
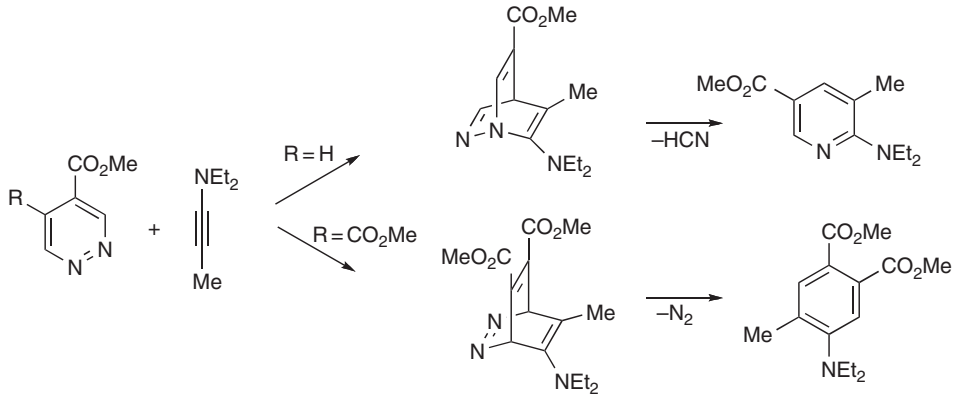


410



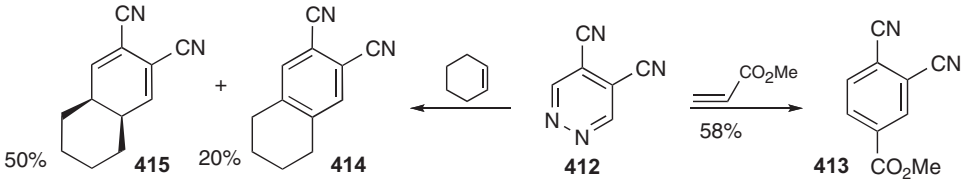
411

3.2.1.10.2.2 Diazines. Pyridazine carboxylic esters undergo cycloaddition reactions as exemplified in **Scheme 54**.

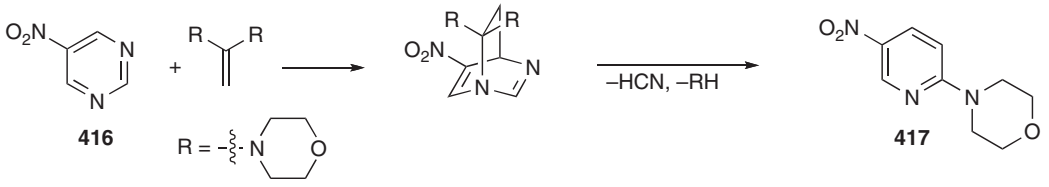


Scheme 54

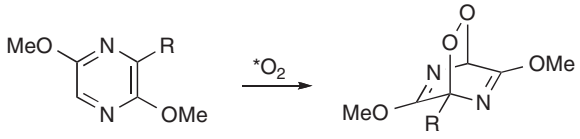
Pyridazine-4,5-dicarbonitrile **412** is a strongly electron-deficient diazadiene reagent <1994T9189> and has been put to extensive use, for example, in forming **413** or **414/415** <1995CC2201>.



Phthalazines undergo [2 + 4] cycloaddition with enamines to give naphthalene derivatives. Pyrimidines also react as azadienes in reactions with enamines, e.g., **416** **417** (R = morpholino).

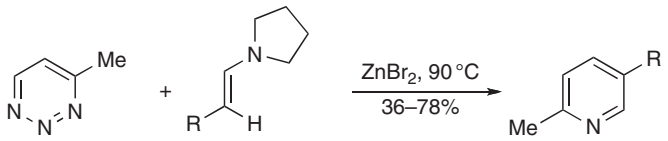


2,5-Dimethoxy-3-alkenyl-substituted pyrazines **418** undergo facile addition of singlet oxygen to form relatively stable endoperoxides **419**, which decompose when heated; the peroxides having a benzyl or isobutyl substituent at C(3) decompose mainly by loss of oxygen, regenerating the pyrazines in high yields <1989J(P1)453>.



418 **419**

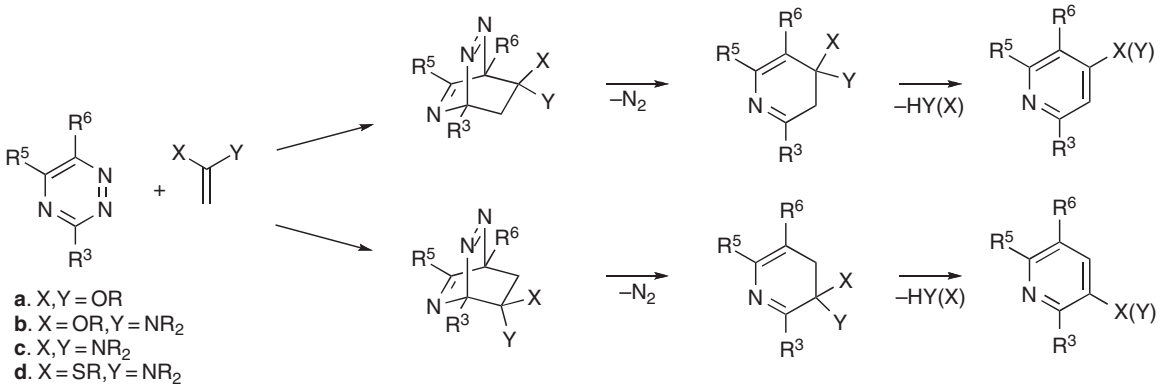
3.2.1.10.2.3 Triazines. 1,2,3-Triazines react with various enamines to afford pyridines (see **Scheme 55**).



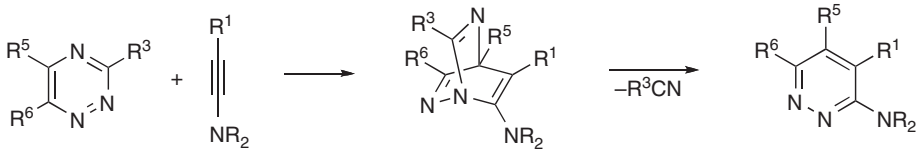
Scheme 55

1,2,4-Triazines are generally more reactive in [2 + 4] cycloaddition in comparison with 1,2,3-triazines. A wide variety of dienophiles can be employed: enamines, enaminones, vinyl silyl ethers, vinyl thioethers, cyclic ketene *N,O*-acetals, *N*-phenylmaleimide, 6-dimethylaminopentafulvene, 2-alkylidene-imidazolidines (cyclic ketene aminals), cyclic vinyl ethers, arynes, benzocyclopropene, acetylenes, and alkenes such as ethylene, (*Z*)-but-2-ene, cyclopentene, cyclooctene, bicyclo[2.2.1]hept-2-ene, hexa-1,5-diene, cycloocta-1,5-diene, diallyl ether, cyclododeca-1,5,9-triene, di-(3-methylcyclopropen-3-yl), and norbornadiene.

In most cases, dienophile addition occurs across the 3- and 6-positions of the 1,2,4-triazine ring as shown in **Scheme 56**, but acetylenes can also add across the 2- and 5-positions (**Scheme 57**). The orientations can be explained using the frontier orbital method, or through secondary orbital interactions.

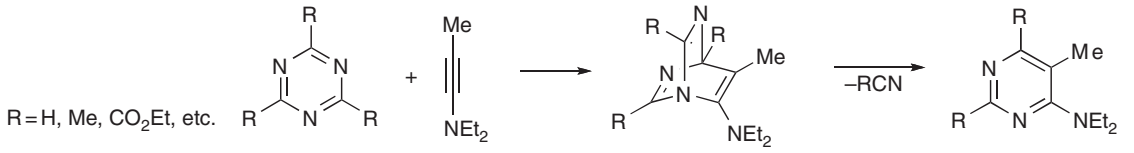


Scheme 56



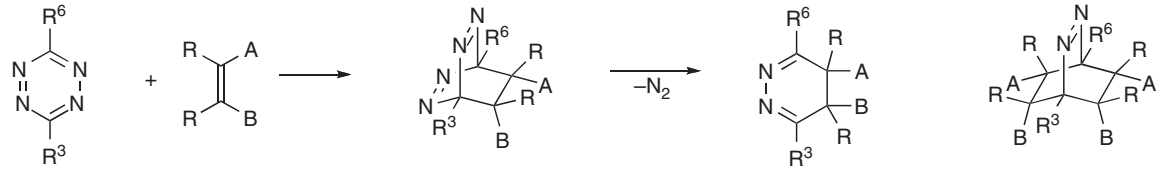
Scheme 57

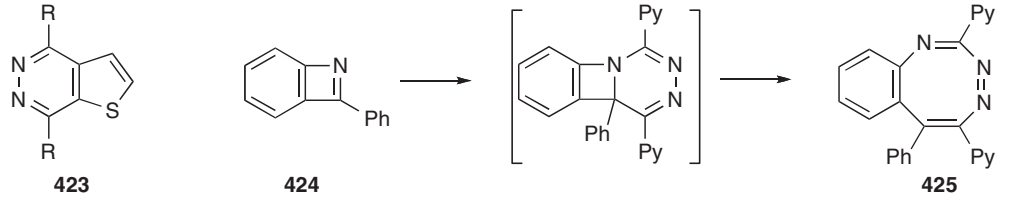
1,3,5-Triazines usually react with dienophiles to afford pyrimidines (**Scheme 58**), or similarly with cyclohex-2-en-1-ones producing 5,6,7,8-tetrahydroquinazoline-ketones <2002TL3551>.



Scheme 58

3.2.1.10.2.4 Tetrazines. 1,2,4,5-Tetrazines react with alkenes to give bicycles **420** that lose nitrogen to give a 4,5-dihydropyridazine **421** which can either tautomerize to a 1,4-dihydropyridazine, be oxidized to the aromatic pyridazine, or undergo a second DielsAlder reaction to give **422**. Some heterocycles can act as the dienophiles in such reactions; for example, thiophene gives **423**. The reaction is also used to trap unstable compounds, for example, 2-phenylbenzazete **424** as compound **425**.



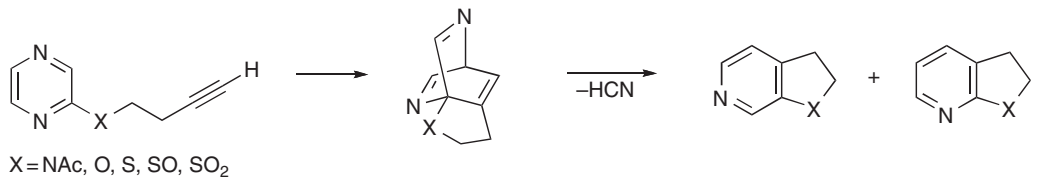


The reactivity of tetrazines carrying electron-attracting substituents (e.g., $R^3 = R^6 = CO_2Me$) is so high that they can be used as titrating agents to determine the purity of liquid alkenes <1962CB2248>.

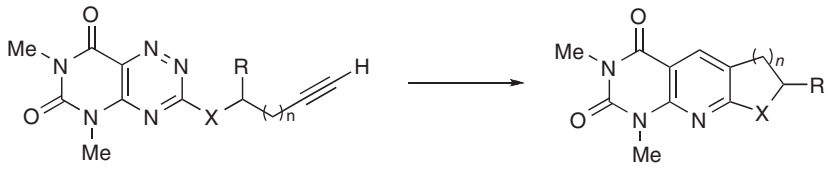
3.2.1.10.2.5 Intramolecular cycloadditions. Intramolecular DielsAlder reactions with inverse electron demand are widely used for the synthesis of condensed pyridines, pyrimidines, and pyrazines. Typical examples are shown in **Schemes 59–62**. The heterocyclic substrate should possess a long dienophilic side chain with a terminal alkyne or nitrile group. The yields as a rule are high though the reactions usually demand prolonged heating in high boiling solvents. Reactivity in intramolecular [2 + 4] cycloadditions is strongly related to the conformational properties of the side chain. Rate reduction has been found for molecules that are able to form stable conformations in which the azadiene and dienophile side chain are positioned in such a way that their interactive approach becomes more difficult <1992JOC3000>. Alkynylsulfinyl compounds are particularly reactive <1985TL2419>.

3.2.1.10.3 Heterocycles as inner dienes in [1 + 4] cycloadditions

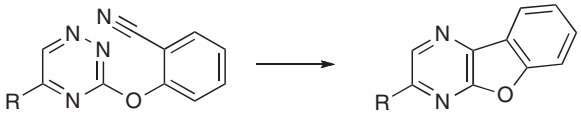
Donor-substituted carbenes can be trapped in good yields by 1,2,4,5-tetrazines in [1 + 4] cycloaddition reactions (**Scheme 63**); in a subsequent cycloreversion step nitrogen is lost from the intermediate **427** with the formation of stable 4,4-disubstituted 4*H*-pyrazoles **428**. As carbene precursors, orthoformic acid derivatives, diazines <1991TL2743>, and Wanzlicks alkene can be used, leading to the electron-rich carbenes shown in **Scheme 63**. Substituents R^1 in the tetrazine **426** can be CF_3, CO_2Me, Ph, SMe, SO_2Me/NMe_2, and SMe/NMe_2.



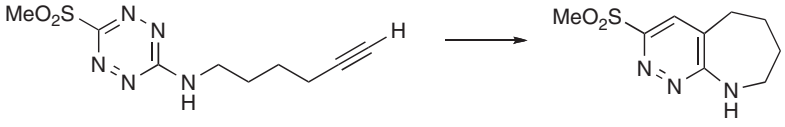
Scheme 59



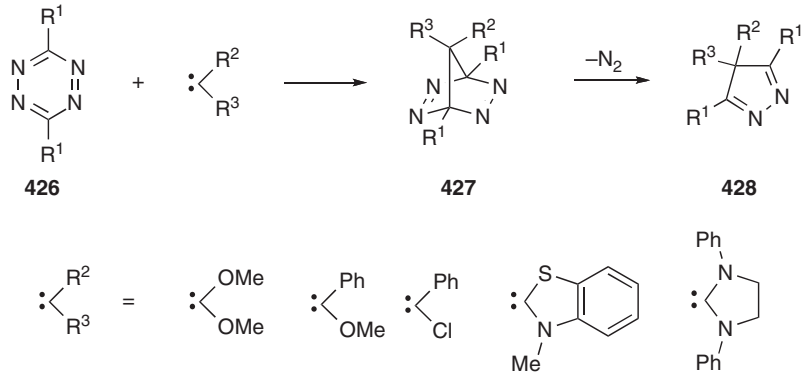
Scheme 60



Scheme 61



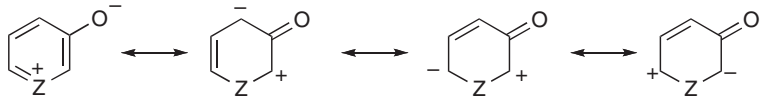
Scheme 62



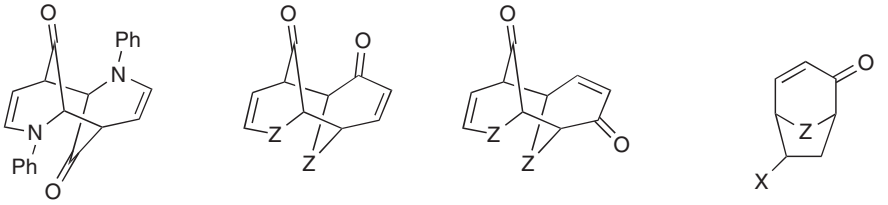
Scheme 63

3.2.1.10.4 Heterocycles as 1,3-dipoles

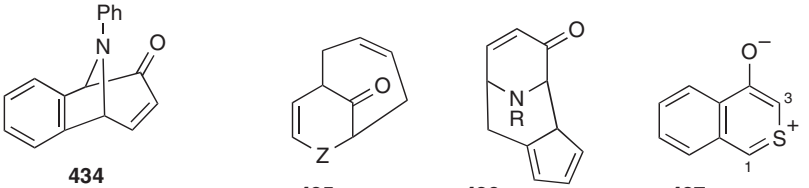
3.2.1.10.4.1 Inner 1,3-dipoles. In many cycloaddition reactions pyridinium-3-olates (**429**; Z = NR) and related cations behave as inner 1,3-dipoles with formal structures (**429a–d**). Thus, irradiation of 1-phenylpyridinium-3-olate (**429**; Z = NPh) yields the symmetrical dimer **430**. Its formation can be represented as connection of oppositely charged carbon atoms in two molecules (cf. **429b**). 3-Pyridinium-3-olates with a strong electron-withdrawing substituent at the 1-position (such as 2-pyrimidinyl) spontaneously dimerize giving **431** and **432**. Formally this is the dimerization of types **429b** + **429c** and **429b** + **429d**. Pyrylium-3-olates and thiopyrylium-3-olates behave similarly. These cyclodimerizations are reversible.



429a **429b** **429c** **429d**



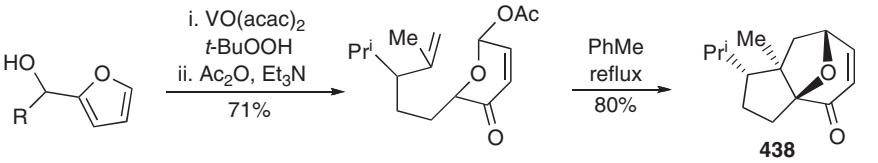
430 **431** **432** **433**



434 **435** **436** **437**

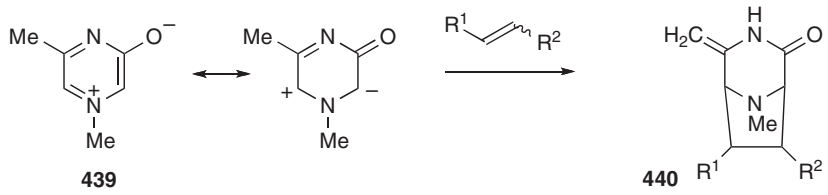
Pyridinium-3-olates and pyrylium-3-olates react with a variety of monoenes, dienes, and trienes. Each of these systems react readily with dienophiles to yield cycloadducts of type **433**. For Z = NMe, an electron-withdrawing X group is required in the dienophile, but with Z = O or *N*-(2-pyridyl) even unactivated alkenes react. 1-Phenylpyridinium-3-olate and benzyne give **434**; dienes give adducts of type **435**. Fulvenes behave as trienes to give adducts across the 2,6-positions **436**. 2-Benzothiopyrylium-4-olate **437** gives a thermal dimer across the 1,3-positions.

A heavily used sequence has the formation of a pyrylium-3-olate produced *in situ* from oxidation of a furan and thence to a 2-acetoxypyran-4-one, which loses acetate, as illustrated by the example forming **438** <2001TL4947>.



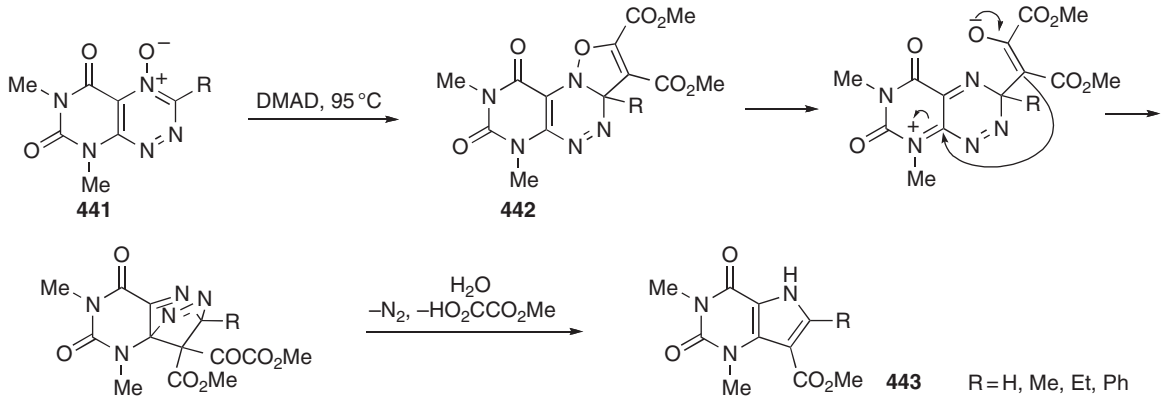
438

1,5-Dimethylpyrazinium-3-olate **439** undergoes 1,3-dipolar cycloaddition with a variety of dipolarophiles to give the bicyclic compounds **440** existing in the enamide tautomeric form <1995H(40)983>.



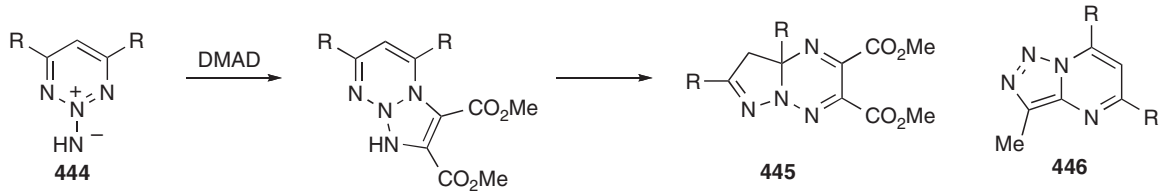
439 **440**

3.2.1.10.4.2 Innerouter 1,3-dipoles. Azine *N*-oxides and azine *N*-imides undergo deep ring transformations on interaction with various dipolarophiles. Thus, fervenulin 4-oxides **441** react with DMAD to afford derivatives of pyrrolo[3,2-*d*]pyrimidines **443**. The first step of the reaction is assumed to involve the formation of cycloaddition products **442** which transform via a subsequent multistage process <1979JOC3830>.



441 **442** **443** R = H, Me, Et, Ph

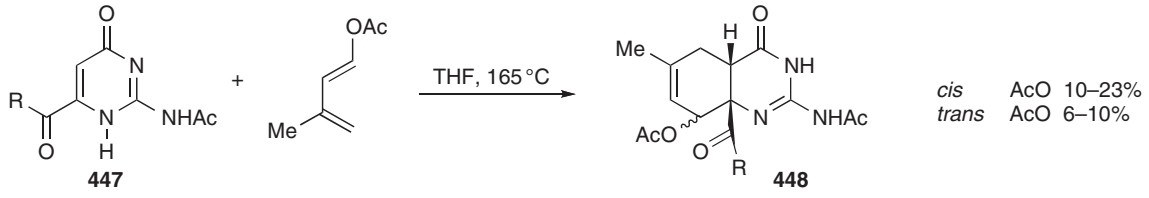
Similarly, 1,2,3-triazine *N*-imines react with DMAD and 1-(*N*,*N*-diethylamino)propyne to give the products **445** and **446**, respectively <1990CPB2108>. See also Sections 3.2.3.12.4 and 3.2.3.12.5.



444 **445** **446**

3.2.1.10.5 Heterocycles as dienophiles

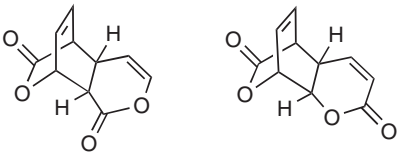
The 5,6-double bonds in activated pyrimidines such as 2-acylamino-6-acetyl-4(1*H*)-pyrimidinones **447** participate in DielsAlder reactions to yield, for example, hydroquinazolines **448** <1983JOC3627>.



447 **448**

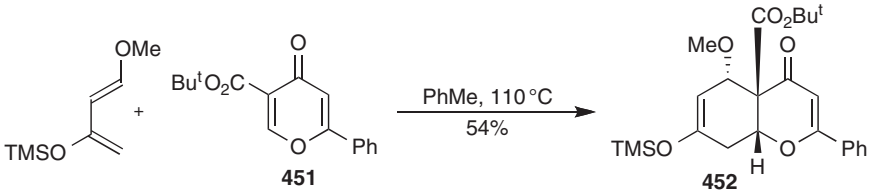
cis	AcO 10–23%
trans	AcO 6–10%

2-Pyranones can give unsymmetrical dimers **449** and **450** where one molecule behaves as diene and another as dienophile.



449 450

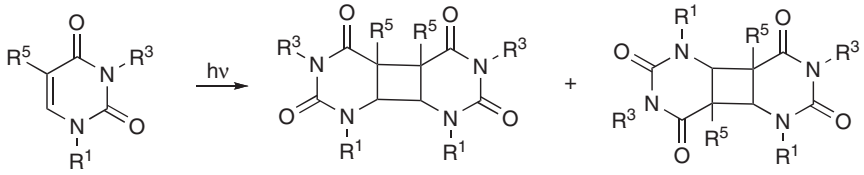
The DielsAlder reaction of 4*H*-pyran-4-one **451** with Danishefskys diene gives cycloadduct **452** <1996H(43)745>.



451 452

3.2.1.10.6 [2 + 2] Cycloadditions

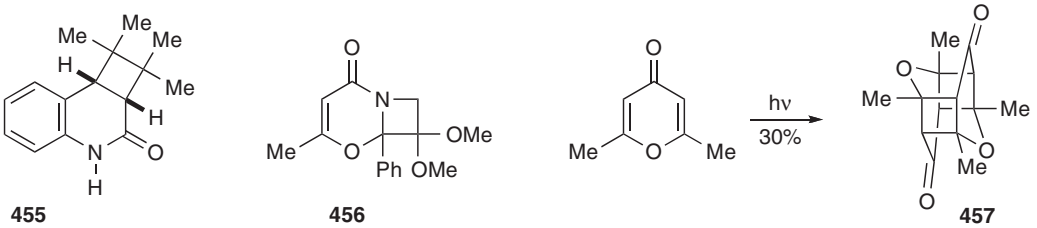
Uracil and thymine, their 5- and/or 6-substituted derivatives, *N*-alkyl derivatives, and their nucleosides and nucleotides dimerize in solution when irradiated by UV light in the range 200300 nm to yield cyclobutane dimers (**Scheme 64**). This reaction also occurs in living tissue between adjacent thymine residues in a polynucleotide to form cyclobutane-type dimers, which are lethal in a variety of organisms. Photolyses repair damaged DNA by utilizing the energy of near-UV or visible light (300500 nm) to cleave the cyclobutane ring of the dimer <1994JA3115>. In the dimerization of uracils, two regioisomers are formed in which the pyrimidine rings can be regarded as parallel or antiparallel, and which are referred to as *syn* **453** or *anti* **454**, respectively. Each regioisomer can have a *cis* or *trans* form in which the pyrimidine rings are on the same or opposite sides of the cyclobutane.



453 *syn*: *cis, trans* **454** *anti*: *cis, trans*

Scheme 64

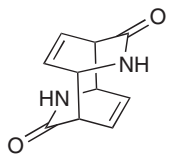
2-Quinolone undergoes photochemical addition of tetramethylethylene to give **455** <1970AHC(11)1>, 1,3-oxazin-4-ones photocycloadd ketene acetals to give **456**, and irradiation of 2,6-dimethylpyran-4-one yields the cage dimer **457**. 2-Pyranones form [2 + 2] photodimers, the structures of which are similar to those of uracil dimers.



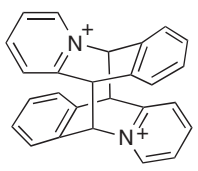
455 **456** **457**

3.2.1.10.7 Heterocycles as 4-components in [4 + 4] cycloaddition

2-Pyridone on irradiation in concentrated solution gives the dimer **458**; 2-aminopyridine behaves similarly. The acridizinium ion, like anthracene, undergoes [4 + 4] photocycloaddition to yield **459**.



458



459

3.2.2 Reactions of Nonaromatic Compounds

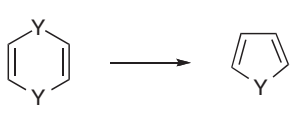
We classify these compounds according to their degree of unsaturation. There is a class of eight -electron systems containing two O, S, or NR atoms in the ring, which possess significant stability. We then consider the thiabenzenes, which behave as cyclic sulfonium betaines, and related compounds.

Among the hydrogenated derivatives, we distinguish dihydro from the tetrahydro/hexahydro class, as the former bears an intimate relationship to their aromatic analogues.

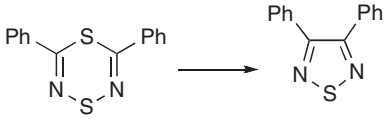
3.2.2.1 8-Electron Systems: 1,2- and 1,4-Dioxins, -Oxathiins, and -Dithiins

3.2.2.1.1 Intramolecular thermolysis and photolysis reactions

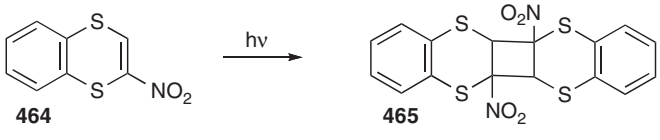
Substituted 1,4-dioxins thermolyze and photolyze to complex mixtures. By contrast, 1,4-dithiins and the corresponding sulfoxides generally extrude sulfur or sulfur monoxide to give the corresponding thiophene [**460** **461**; Y = S]. 1,4,2,6-Dithiadiazines (e.g., **462**) similarly extrude sulfur to give 1,2,5-thiadiazoles **463**. 2-Nitro-1,4-benzodithiin **464** undergoes photochemical dimerization to **465** <1970AHC(11)1>. The dibenzo-fused systems are rather stable.



460 **461**



462 **463**



464 **465**

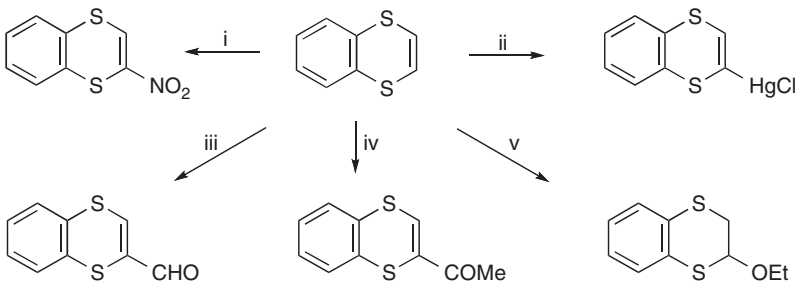
3.2.2.1.2 Reactions with electrophiles

3.2.2.1.2.1 By addition to C═C double bonds. 1,4-Dioxin and 1,4-dithiin both undergo easy electrophilic addition reactions, e.g., of halogens to the double bonds. Alcohols under acid catalysis form ketal addition products.

3.2.2.1.2.2 By electrophilic substitution. Substitution products can be obtained from some 1,4-dithiins. Thus, 2,5-diphenyldithiin is formylated under Vilsmeier conditions, and mono- or di-nitrated and -brominated in the heterocyclic ring. 1,4-Benzodithiin shows similar properties (**Scheme 65**).

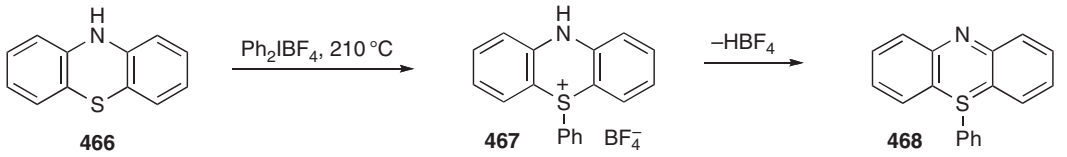
3.2.2.1.2.3 By reaction at sulfur. 1,4-Dithiins react readily at sulfur with peracids, alkyl halides, and hydroxylamine *O*-sulfonic acid to give sulfoxides, thiinium salts, and sulfilimines, respectively. Similar reactions are known for 1,4-benzodithiins.

N-Alkylphenothiazines are oxidized to *S*-monoxides and *S*,*S*-dioxides with hydrogen peroxide in acetic acid. Phenothiazine **466** can also be S-phenylated to form a phenothiazinium cation **467**, which loses HBF_4 to give **468**.

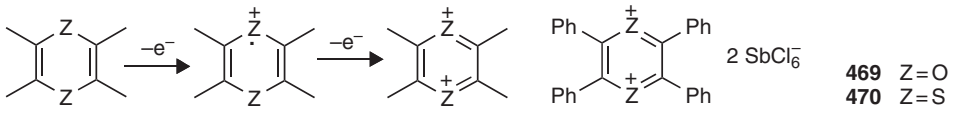


i, HNO_3, AcOH; ii, $HgCl_2$; iii, PhN(Me)CHO, $POCl_3$; iv, Ac_2O, H_3PO_4; v, EtOH, H^+

Scheme 65

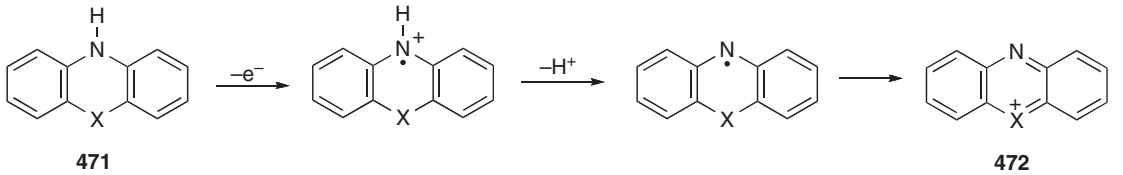


3.2.2.1.2.4 By electron loss. These compounds undergo one-electron oxidations electrochemically or chemically to give radical cations and further loss of a second electron to give a 6-electron dication (**Scheme 66**). Dications such as **469** and **470** can be isolated as hexachloroantimonates.



Scheme 66

Phenoxazines and phenothiazines (**471**; X = O, S) can be oxidized to phenoxazonium and phenothiazinium salts (**472**; X = O, S). Radical cations are intermediates; these lose H^+ to form a neutral radical followed by another electron to form the 6-electron system (**Scheme 67**).

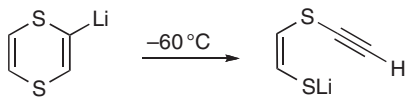


Scheme 67

3.2.2.1.3 Reactions with nucleophiles

These electron-rich systems usually show little tendency to react with nucleophiles, but 1,2-dithiins suffer nucleophilic attack at sulfur followed by ring cleavage.

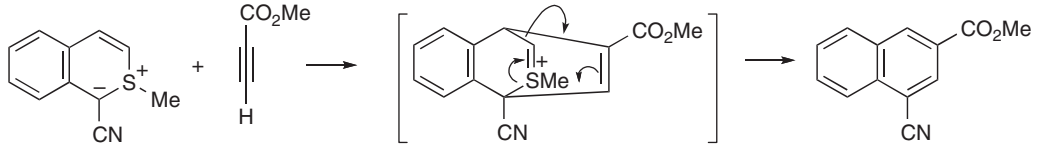
1,4-Dithiin is readily metallated at the 2-position by *n*-butyllithium at 110 °C, and **473** can be trapped at this temperature. At 60 °C ring opening occurs to give **474**.



473 **474**

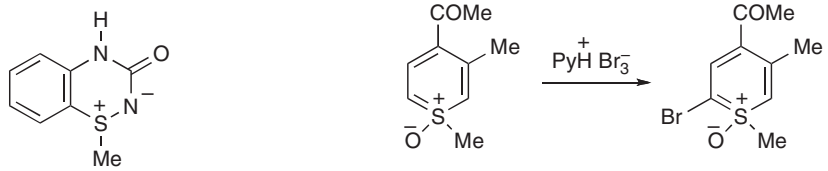
3.2.2.2 Thiabenzenes and Related Compounds

Thiabenzenes should be viewed as sulfonium betaines. They react readily with acids to give mixtures of 2*H*- and 4*H*-thiinium salts, behave as dienes with dienophiles (**Scheme 68**), and can be oxidized to sulfoxides. The sulfimide **475** is an aza analogue of a thiabenzene and it is oxidized by $KMnO_4$ to the corresponding sulfoximide.



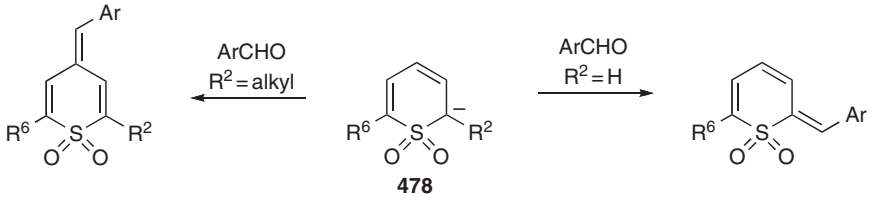
Scheme 68

Thiabenzene sulfoxides can be nitrated and brominated, for example, **476** gives **477**.



475 **476** **477**

2*H*-Thiin dioxides form anions **478** that appear to have some aromatic stability. The anions react with aldehydes (**Scheme 69**).

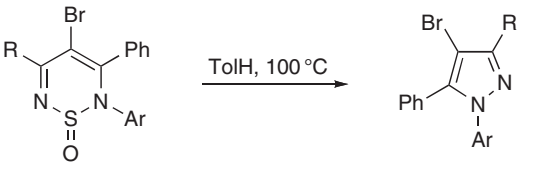


478

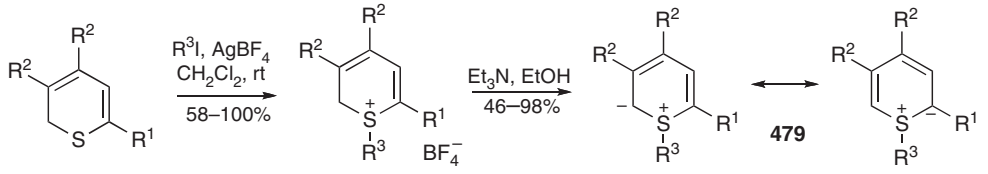
Scheme 69

2*H*-1,2,6-Thiadiazine 1-oxides extrude sulfur monoxide on heating in toluene to give pyrazoles in high yields (**Scheme 70**) <1983J(P1)2273>.

6-Aroyl-2*H*-thiopyrans are alkylated at sulfur to give 1-alkylthiopyranium salts, deprotonation of which affords the stable, dark-red thiabenzenes **479**, a reaction which can be reversed by treatment with HBF_4 (**Scheme 71**) <2001J(P1)2269>.



Scheme 70



Scheme 71

3.2.2.3 Dihydro Compounds

3.2.2.3.1 Introduction

We consider as dihydro derivatives those rings that contain either one or two sp^3-hybridized carbon atoms. According to this definition, all reactions of the aromatic compounds with electrophiles, nucleophiles, or free radicals involve dihydro intermediates. Such reactions with electrophiles afford Wheland intermediates that usually easily lose H^+ to rearomatize. However, nucleophilic substitution (in the absence of a leaving group such as halogen) gives an intermediate that must lose H and such intermediates often possess considerable stability. Radical attack at ring carbon affords another radical that usually reacts further rapidly. In this section we consider the reactions of isolable dihydro compounds; it is obvious that much of the discussion on the aromatic heterocycles is concerned with dihydro derivatives as intermediates.

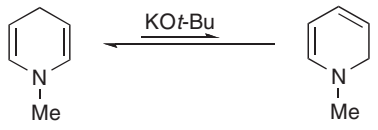
4-Aryl-1,4-dihydropyridine-3,5-dicarboxylates are widely studied due to their use in the treatment of cardiovascular diseases. Most of these compounds are synthesized using the Hantzsch method (Section 4.2.3.4.2) but this is less suitable for the synthesis of unsymmetrical or chiral derivatives. Enzymatic desymmetrization of bis(ethoxycarbonylmethyl)-1,4-dihydropyridine-3,5-dicarboxylates, using *Candida antarctica* lipase B, can generate enantiopure 1,4-dihydropyridines in reasonable to high yields with good enantiomeric selectivity <2000TA4559>.

The reactions of dihydro compounds are of two main classes. The first class comprises reactions to gain aromaticity which depend intrinsically on the dihydro six-membered heterocyclic structure and these can in turn be subdivided into the following four groups, of which the first is by far the most important:

1. Loss of a group attached to an sp^3-hybridized ring carbon, with its bonding electrons, to gain aromaticity
2. Electrocyclic ring opening
3. Loss of a group attached to an sp^3-hybridized ring carbon, without its bonding electrons, to form an 8-electron-conjugated ring
4. Loss of an electron or H from a radical cation or neutral radical
5. Reactions that are common to alicyclic analogues: reactions with electrophiles and nucleophiles, and through cyclic transition states

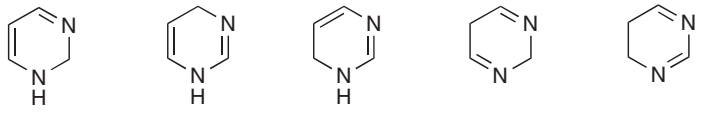
3.2.2.3.2 Annular tautomerism

N-Unsubstituted dihydropyridines can exist in at least five tautomeric forms (Section 2.2.5.2). At least for N-substituted compounds, 1,4-dihydropyridines (e.g., **480**) are generally more stable, by ca. 9 kJ mol^1, than the 3,4-dihydro and the 1,2-dihydro isomers (e.g., **481**). 2,3-Dihydropyridines are highly unstable compounds susceptible to 1,2- or 1,4-addition; 2,5-dihydropyridines are also highly unstable, quickly isomerizing to the more stable 1,2-dihydropyridines; 3,4-dihydropyridines are inherently unstable and rapidly isomerize to other dihydropyridine isomers; many also rapidly eliminate H_2 to form pyridines; 1,2-dihydropyridines are far more stable. 2*H*-Pyrans appear to be thermodynamically more stable than 4*H*-pyrans. All three types of 1,3-oxazine are known.



480 **481**

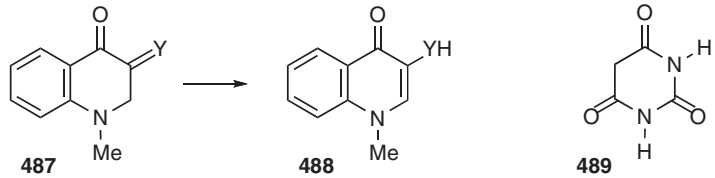
There are in principle five dihydropyrimidines but most of those known have either the 1,2- or the tautomeric 1,4- or 1,6-dihydro structures, **482484**. Gaussian 70 *ab initio* calculations of the energy of unsubstituted dihydropyrimidines yielded the following order of stability: **484** > **483** > **482** > **485** > **486**; and these agree with the experimentally observed behavior of these compounds <1985AHC(38)1>.



482 **483** **484** **485** **486**

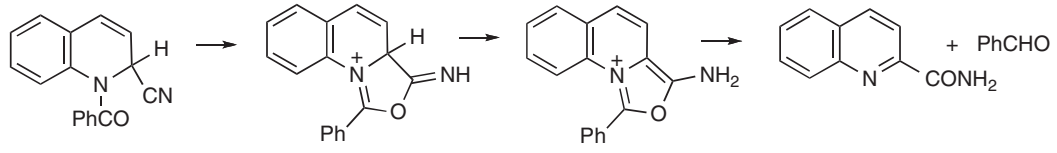
3.2.2.3.3 Aromatization

3.2.2.3.3.1 By prototropic tautomerism. Compounds of type **487** can aromatize by isomerization (**487** **488**; Y = CHR, NR). In a few cases such tautomerism is reversible: barbituric acid **489** exists mainly in the trioxo form.



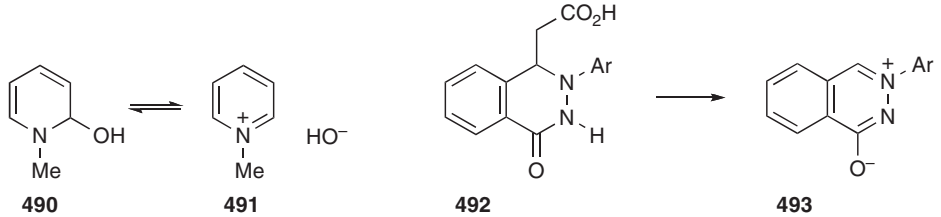
487 **488** **489**

1-Benzoyl-2-cyano-1,2-dihydroquinolines and the corresponding isoquinolines (Reissert compounds) (cf. Section 3.2.1.6.8.4) are cleaved by acid into aldehydes plus quinoline-2- or isoquinoline-1-carboxamides. The mechanism of this reaction involves the sequence shown in **Scheme 72** for the quinoline Reissert compound.



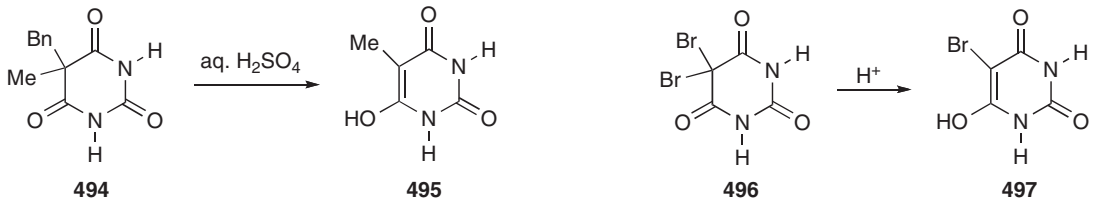
Scheme 72

3.2.2.3.3.2 By loss of attached leaving groups with bonding electrons. Those dihydro compounds that carry a leaving group attached to their single sp^3-hybridized carbon atom exist in equilibrium with the corresponding aromatic compounds (e.g., the pseudobases **490491**; see Section 3.2.1.6.3.4). A similar example is that of the covalently hydrated cations of neutral azines (see Section 3.2.1.6.3). A somewhat less obvious example is the acid-catalyzed cleavage **492** **493** with the loss of acetic acid.



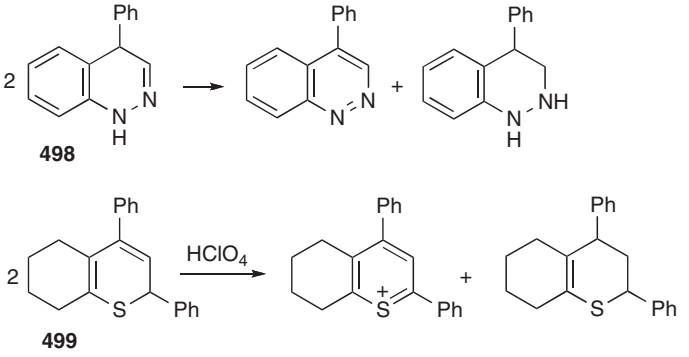
490 **491** **492** **493**

3.2.2.3.3.3 By loss of attached group without bonding electrons. This includes expulsion of a carbonium ion (e.g., **494** **495** + $PhCH_2OH$) or nucleophilic removal of a positive halogen atom (**496** **497** + Br^+).



494 **495** **496** **497**

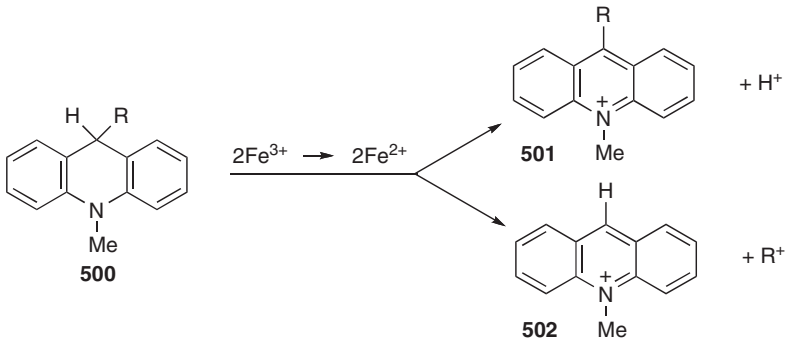
3.2.2.3.3.4 By disproportionation. Dihydro compounds often disproportionate (**Scheme 73**), i.e., form a mole equivalent of aromatic and a mole equivalent of tetrahydro derivative; for example, the dihydrocinnoline **498** on treatment with hydrochloric acid gives 4-phenylcinnoline and 4-phenyl-1,2,3,4-tetrahydrocinnoline; 2*H*- (e.g., **499**) and 4*H*-thiins on treatment with acid form thiinium salts and the corresponding tetrahydrothiin.



498 **499**

Scheme 73

3.2.2.3.3.5 By oxidation or dehydrogenation. Dihydropyridines, 1,2-dihydro-quinolines and -isoquinolines, pyrans, and chromenes are very easily oxidized. The oxidation mechanism, which can involve either hydride transfer or single electron steps, has been extensively studied. Thus, oxidative aromatization of 10-methyl-9-*R*-9,10-dihydroacridines **500** with $Fe(ClO_4)_3$ in MeCN occurs with cleavage of either the C(9)H or C(9)R bond to yield acridinium ions **501** or **502** or both. Fission of the CC bond is facilitated by a substituent R which is capable of forming a stable carbenium ion. This gives strong support to a single electron transfer mechanism for the reaction and participation of radical cations as key intermediates. Indeed, the latter have been observed by ESR studies <1993JA8960>.



500 **501** **502**

R	**501**	**502**
Me	100	0
Ph	100	0
Bn	45	55
i-Pr	40	60
t-Bu	0	100

In the 1,4-dihydropyridine series, there has been much discussion on detailed mechanism. In a study of reduction of -cyanocinnamates with a 4,4-dideutero Hantzsch dihydropyridine, a product that was singly deuterated at only the benzylic position together with the oxidized pyridine product **503** was obtained. This seems to show that the mechanism involves hydride transfer from the 4-position of the 1,4-dihydropyridine followed by proton extraction from the nitrogen of the dihydropyridine <2000J(P2)1857>.

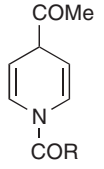
503

1-Substituted dihydropyridines can be aromatized in various ways, e.g., with nitrous fumes ($NO\text{-}N_2O_4$). Compound **504** is converted into 4-acetylpyridine by sulfur, or into 4-ethylpyridine by Zn, HOAc.

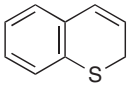
Pyrans and thiins are also easily aromatized, e.g., **505** + S_2Cl_2 1-benzothiinium ion. *2H*-Thiins are aromatized by hydride acceptors such as triphenylmethyl cations to give thiinium salts, and similar conversions produce pyrylium salts from pyrans.

3,4-Dihydroisoquinolines (e.g., **506**), 3,4-dihydrocoumarins (e.g., **507**), and 2,3-dihydrochromones (e.g., **508**) are aromatized either by oxidation or by dehydrogenation with S or Se at 300°C or Pd at 200°C. 9,10-Dihydroacridines (e.g., **509**) and 5,6-dihydrophenanthridines (e.g., **510**) with NH groups are oxidized to the fully aromatic compounds on exposure to air or by other oxidizing agents such as chromic oxide.

Oxidizing agents for dihydrodiazines include $KMnO_4$, $K_3Fe(CN)_6$, MnO_2, and the widely used DDQ. 2,3-Dihydro-perimidines **511** with NH groups can be effectively aromatized with $Na_2S_2O_5$. Some dihydrodiazines are oxidized directly to diazinones (e.g., **512** **513** with $KMnO_4$, OH). Dihydro-triazines and -tetrazines also readily yield the corresponding aromatic azine (e.g., **514** + Br_2 or O_2 **515**).



504



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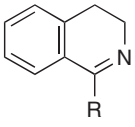

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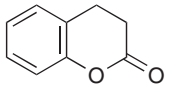

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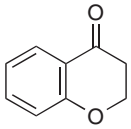

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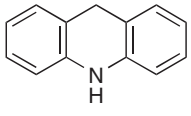

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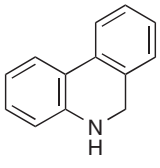

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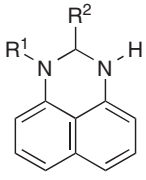

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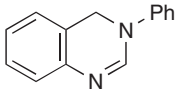
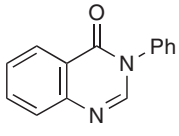
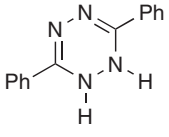
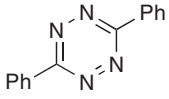




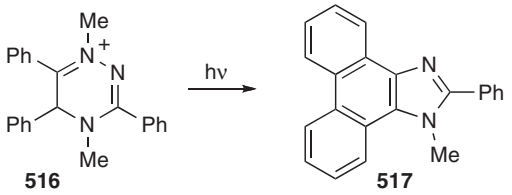
512 **513**





514 **515**

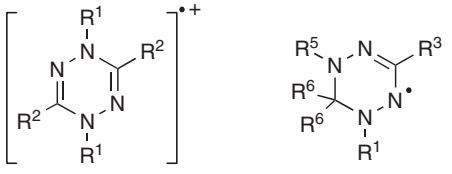
3.2.2.3.3.6 By ring contraction. Photolysis of 1,4-dimethyl-3,5,6-triphenyl-4,5-dihydro-1,2,4-triazinium iodide **516** gave 1-methyl-2-phenylphenanthro[9,10-*d*]imidazole **517** in 90% yield.



516 **517**

3.2.2.3.4 Electron loss to form radicals

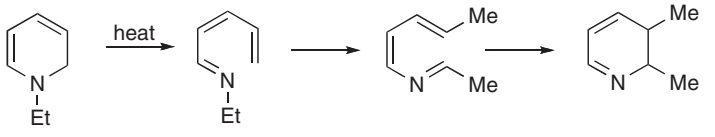
The formation of a radical cation by electron loss or a neutral radical by successive loss of e and H^+ is probably an important pathway in many of the oxidative and other reactions of these dihydro compounds. In most cases, the radical is merely a transient intermediate, but 1,4-dihydro-1,2,4,5-tetrazines are electrochemically oxidized to stable radical cations **518** or to neutral verdazyls **519**.



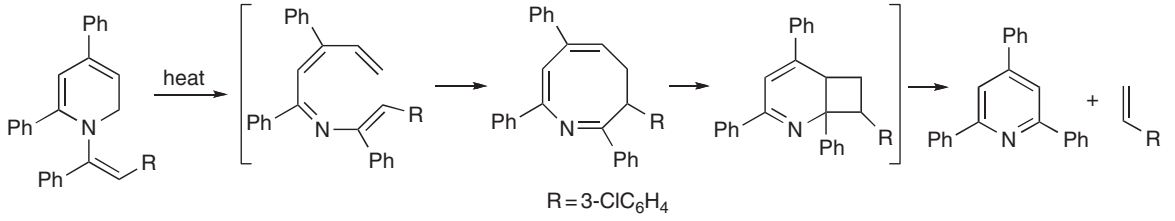
518 **519**

3.2.2.3.5 Electrocyclic ring opening (valence tautomerism)

The concept of electrocyclic ring opening of 1,2-dihydro six-membered heterocycles is familiar from the numerous examples found after nucleophilic attack, especially on cationic rings. Similar reactions occur with isolated 1,2-dihydro derivatives. Dihydropyridines can undergo isomerization by electrocyclic ring opening (**Scheme 74**). 1-Vinyl-1,2-dihydropyridines in a somewhat similar sequence yield pyridines via azacyclooctatrienes (**Scheme 75**).

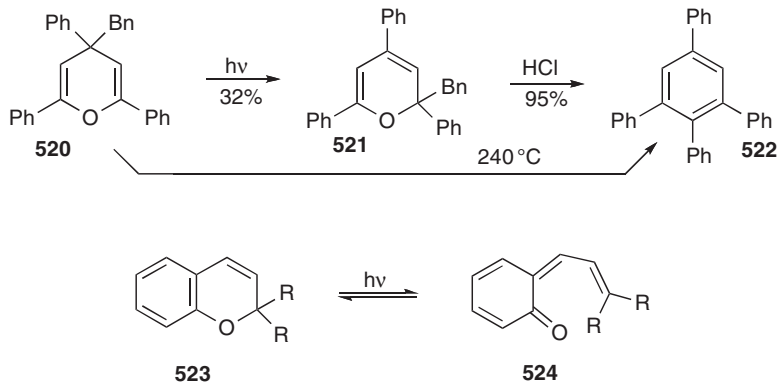


Scheme 74

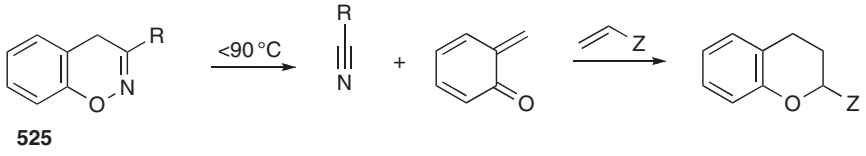


Scheme 75

The 4-benzyl 1,4-dihydropyran **520** rearranges on irriadiation, or thermally to the 2-benzyl isomer **521** which yields **522** via electrocyclic ring opening. Irradiation of 2*H*-chromenes **523** gives an intensely red photoproduct **524**.



Several types of 1,2-oxazines undergo thermal pericyclic reactions in which the NO bond is cleaved. Thus **525** (R = Me, Ph) undergo a thermal retro-DielsAlder reaction on heating to give the corresponding nitrile and *ortho*-benzoquinone methide, which can be intercepted by alkenes (**Scheme 76**) <1990JA5341, 1994TL7273>.

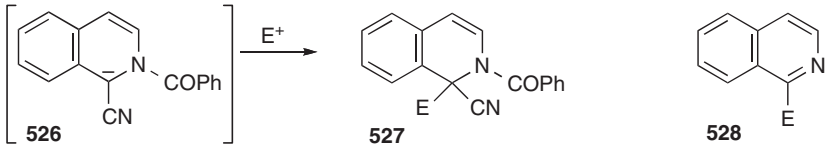


Scheme 76

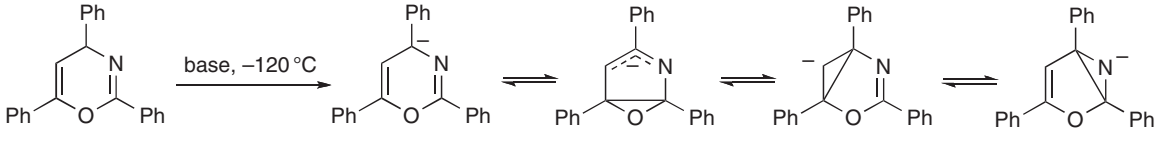
3.2.2.3.6 Proton loss to an 8-electron-conjugated system

Very strong bases can extract a proton from the 1,2- or 1,4-dihydropyridine ring giving a fully-conjugated 8-electron antiaromatic system, which can be trapped by electrophiles.

Reissert compounds (cf. Section 3.2.1.6.8.4) can be deprotonated (NaH, $HCONMe_2$) to give anions (e.g., **526**) that react with electrophiles to give products **527** that can be hydrolyzed to substituted heterocycles **528**. Electrophiles which have been utilized include alkyl and reactive aryl halides and carbonyl compounds.



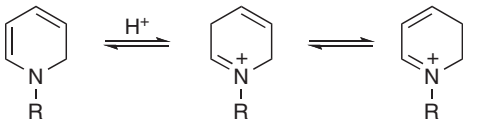
Oxizinyl anions obtained from 4*H*-1,3-oxazines are considered to exist in equilibrium with valence-bond tautomers (**Scheme 77**).



Scheme 77

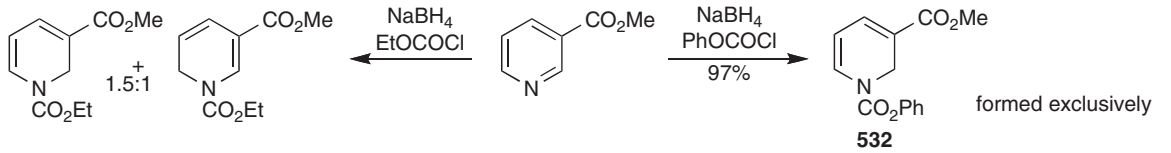
3.2.2.3.7 Electrophilic substitution

1,2-Dihydropyridines **529** are susceptible to electrophilic attack at the -carbon, e.g., protonation giving a 2,5-dihydropyridinium cation **530** that slowly rearranges to the thermodynamically more stable 2,3-dihydropyridinium ion **531**.



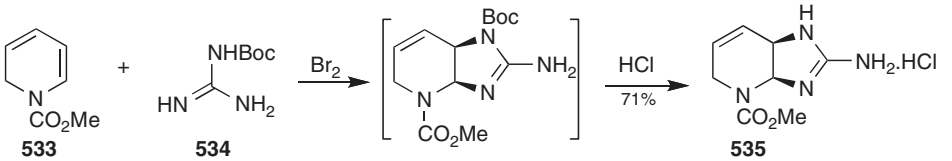
529 530 531

Most work has involved N-protected dihydropyridines, and to make these compounds the use of phenyl chloroformate rather than ethyl or benzyl chloroformate in reduction of 3-substituted pyridines, where the substituent is an electron-withdrawing group, usefully increases the yield and selectivity for the 3-substituted-1,2-dihydropyridine **532** <2001OL201>.

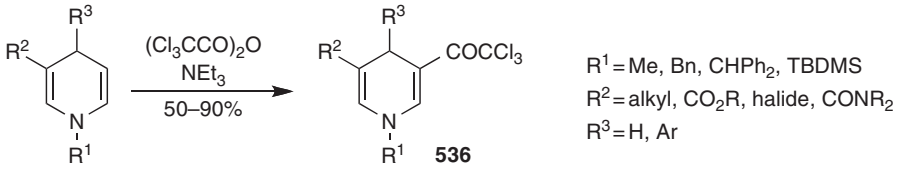


532

Examples of electrophilic attack on N-protected 1,2-dihydropyridines include bromine-mediated addition of Boc-protected-guanidine **534** to dihydropyridine **533** giving, after acid deprotection, *cis*-2-amino-1,3a,5,7a-dihydroimidazo [4,5-*b*]pyridine **535** <2004OL3933>; formation of 5-trichloroacetyl-1,4-dihydropyridines **536** <2003TL4711>; and -formylation with the Vilsmeier reagent <2006OL179>. -Aminonitriles which are formed by trapping 2,3-dihydropyridinium salts with cyanide ion are stable, but easily converted back into 2,3-dihydropyridinium salts with Lewis acids.

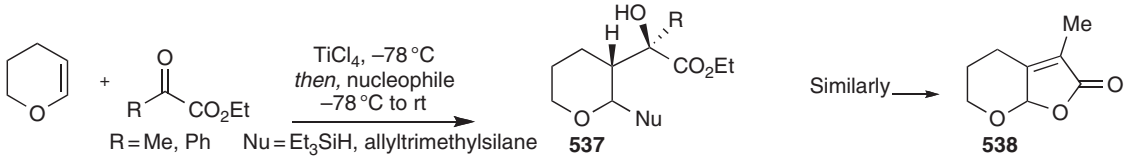


533 **534** **535**



536

Similarly, $TiCl_4$-promoted coupling of pyruvates with 3,4-dihydro-2*H*-pyran provides products **537** <2000TL8425>. The use of (2-trimethylsilyl)ethyl pyruvate in this transformation results in a one-pot addition sequence to deliver functionalized furo[2,3-*b*]pyran derivatives, e.g., **538**, in good yields <2003SL1491>.

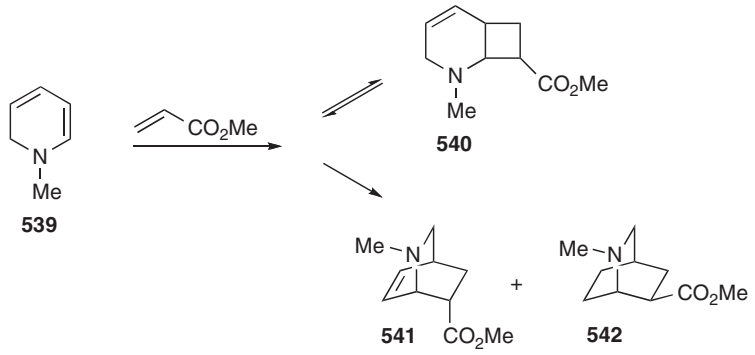


537 **538**

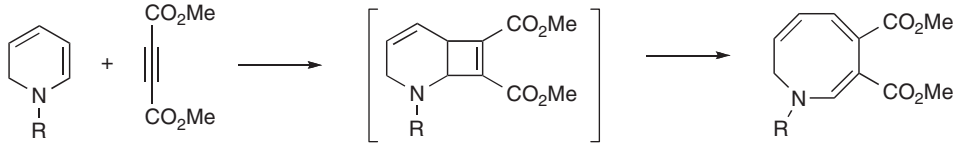
3.2.2.3.8 Cycloaddition reactions

1,2-Dihydropyridines are reactive 1,3-dienes, but their reactions with dienophiles are strongly dependent on the nature of the latter and the reaction conditions. Thus, 1-methyl-1,2-dihydropyridine **539** reacts with methyl acrylate at 10 °C to give a product of overall [2 + 2] cycloaddition **540** by reaction as an enamine. On the other hand, at +80 °C compound **539**

behaves as a 1,3-diene forming adducts **541** and **542** in a 3.2:1 ratio. Adduct **540** is isomerized on heating to the thermodynamically more stable **541**/**542**.

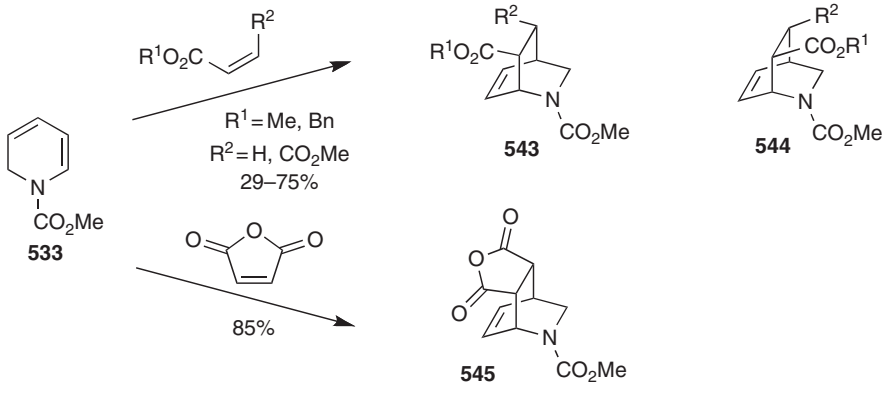


The 1,2-dihydropyridine ring can also undergo [2 + 2] cycloaddition with alkynes (**Scheme 78**).



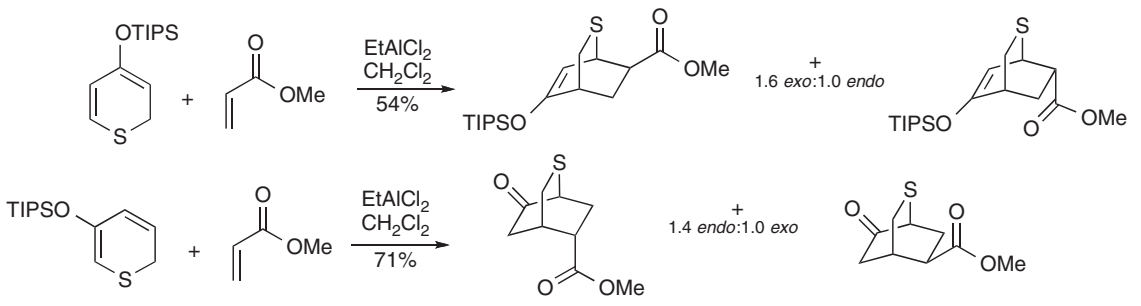
Scheme 78

Much more work has involved N-protected 1,2-dihydropyridines; thus, DielsAlder reactions between dihydropyridine **533** and many acrylic acid esters or dimethyl maleate have been described, though variable yields of *endo* **543** and *exo* **544** 2-azabicyclo[2.2.2]octene products are obtained. The reaction with maleic anhydride yielded only the *endo* product **545** <2003T7555>. Chiral catalysts have been developed to allow the enantioselective DielsAlder reactions of 1,2-dihydropyridines <2002T8299>.

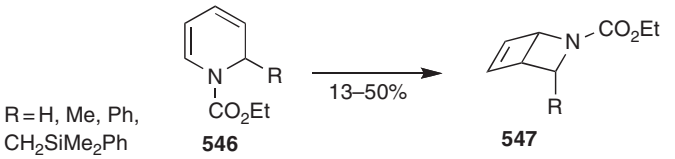


2*H*-Thiopyrans also behave as dienes in DielsAlder reactions, though less reactive dienophiles such as acrylates require catalysis by a Lewis acid to prevent the need for the elevated temperatures which might cause decomposition of the thiopyran (**Scheme 79**). Thus, thiopyrans can serve as equivalents for (unreactive) *cis*-dienes, since desulfurization of adducts is easy, e.g., <1991CJC1487>

Irradiation of 2-substituted-1,2-dihydropyridines **546** proceeds via a torquoselective process to give only the *endo* product **547** <2001JOC1805, 2000T9227>.

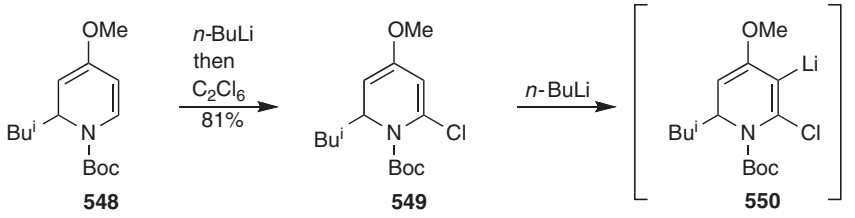


Scheme 79

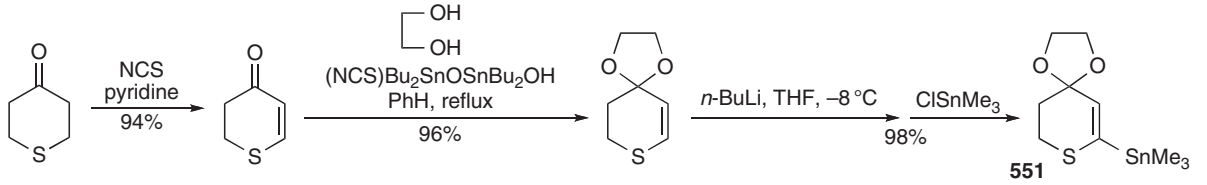


3.2.2.3.9 Other reactions

Lithiation of **548** and trapping using hexachloroethane gives the 6-chloro-1,2-dihydropyridine **549**, lithiation of which now proceeds at C(5) to give **550** <2005OL5661>.

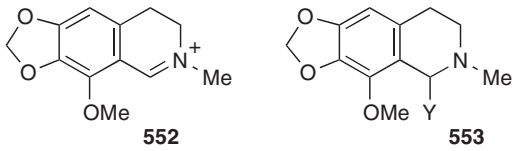


A protected 5,6-dihydro-4*H*-thiopyran-4-one will lithiate at the 2-position allowing, for example, the introduction of a 2-$SnMe_3$ group to give compound **551** <1998EJO1989>.



3,4-Dihydroisoquinolines form quaternary salts, e.g., **552**, which with alkali give carbinolamine pseudo-bases, e.g., cotarnine (**553**; Y = OH), which can be oxidized to lactams, or which disproportionate on standing, but which are in equilibrium with open-chain compounds as evidenced by the ability to prepare aldehyde derivatives. The quaternary ions can also react with other nucleophilic reagents, e.g., **552** + RMgBr **553** (Y = R); **552** + MeCOMe **553** (Y = CH_2COMe); **552** + CN **553** (Y = CN); and **552** + RNH_2 **553** (Y = NHR).

Reduction of dihydro compounds to the tetra- or hexahydro derivatives is usually possible, for example, with H_2, Pd or with Na/Hg, EtOH.

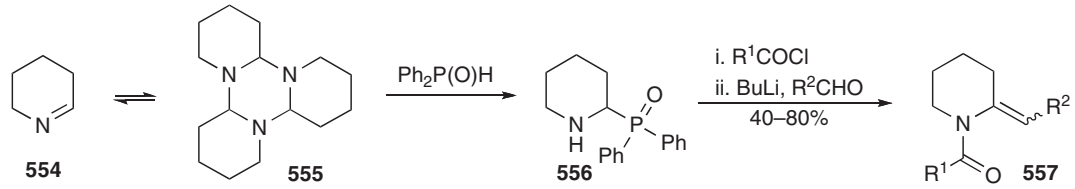


3.2.2.4 Tetra- and Hexahydro Compounds

3.2.2.4.1 Tautomeric equilibria

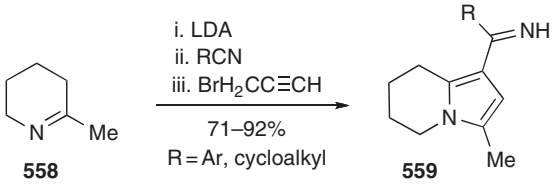
Tetrahydro compounds still contain one ring double bond and thus can exist in several tautomeric forms (cf. Section 2.2.5.2). Little systematic work is available regarding the position of such equilibria, but 1-methyl-1,4,5,6-tetrahydropyridine is more stable than the 3,4-unsaturated isomer by 16 kJ mol[1].

3,4,5,6-Tetrahydropyridine itself, **554**, exists as a monomer in solution where it is highly reactive but conveniently exists in air as a stable crystalline trimeric solid **555** <1977OS118>. Reaction of the trimer with diphenylphosphine oxide forms phosphinoyl piperidine **556** which, after N-acylation, can be condensed with aldehydes to form 2-methylene piperidines **557** <1996TL7749>. *N*-Tosyl-2-allyl piperidines result from additions to **554** in high enantiomeric excess using an allylzinc reagents, tosyl chloride, and a chiral-lithiated bisoxazoline catalyst <1996JA8489>.

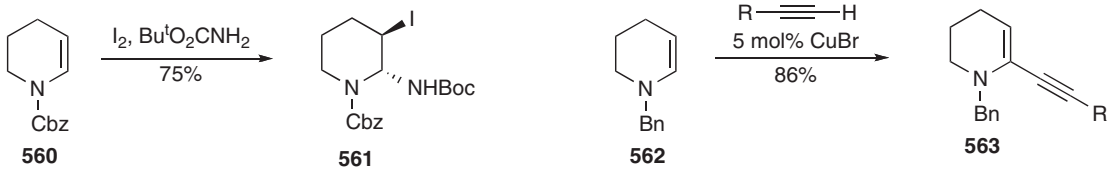


The *N*-oxide of **554**, i.e., a nitrone, readily undergoes dipolar cycloadditions with a variety of substrates, often with very high stereoselectivity, generating bicyclic isoxazolidines <1998CHE387, 2000JIC637>.

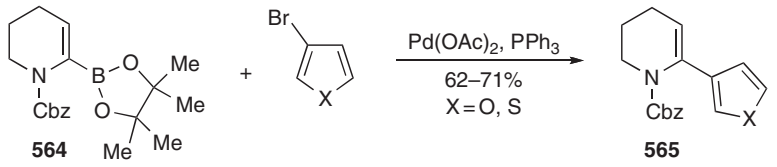
6-Methyl-2,3,4,5-tetrahydropyridine **558** can be deprotonated at the methyl group and thus utilized in heterocyclic ring synthesis, for example, to make **559** <1996JOC2185>.



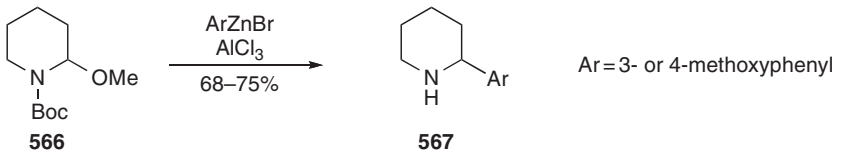
The N-protected 1,4,5,6-tetrahydropyridine **560** reacts as an enamine, the immediate iminium product being trapped by a nucleophile, for example, with primary carbamates in the presence of iodine 2-amino-3-iodopiperidines **561**, with a *trans* relationship between the substituents being formed <2005T1221>. *N*-Benzyl-1,4,5,6-tetrahydropyridine **562** can be coupled with alkynes giving products **563** <2002AGE2535>.



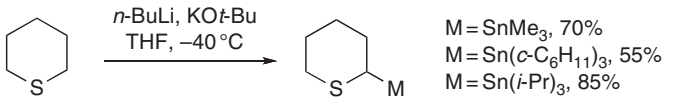
N-Protected-1,2,3,4-tetrahydropyridines can be lithiated at C(6) to give nucleophiles that react with various electrophiles <2000OL155>; for example, the boronate **564** prepared in this way can be used in SuzukiMiyaura couplings giving **565** <2005JOC7324>.



N-tert-Butoxycarbonyl-2-methoxypiperidine **566**, generated by electrochemical oxidation of *N*-Boc-piperidine, reacts with aromatic organozinc reagents, with concomitant hydrolysis of the carbamate, to give 2-arylpiperidines **567** <2006TL455>.



n-Butyllithium together with KO*t*-Bu metallates tetrahydrothiopyran at the 2-position allowing the introduction of trialkyltin moieties at this site (**Scheme 80**) <1997TL8615>.



Scheme 80

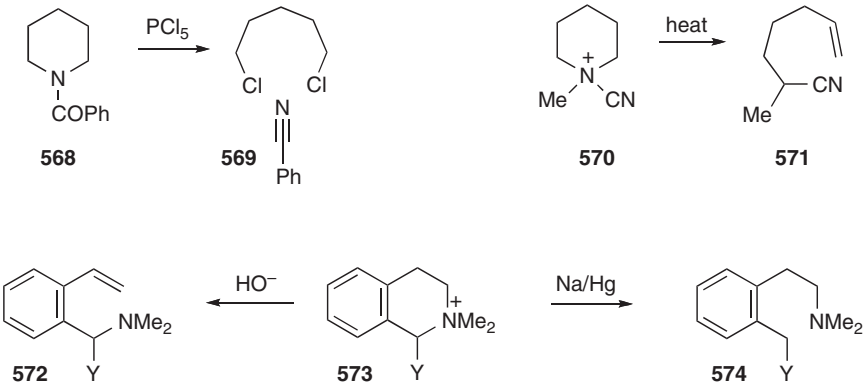
3.2.2.4.2 Aromatization

Tetra- and hexahydro compounds can often be aromatized, but this is more difficult than in the dihydro series. Thus, the conversion of piperidines to pyridines typically requires dehydrogenation with Pd at 250°C.

3.2.2.4.3 Ring fission

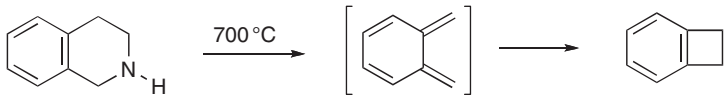
Cleavage of a saturated heterocyclic ring can be accomplished using the same degradative procedures that are also applicable to corresponding aliphatic compounds. Thus, a nitrogen-containing ring is opened by

1. the von Braun amide and PCl_5 method for NH compounds, e.g., **568** **569**;
2. the von Braun cyano-ammonium route for tertiary amines, e.g., **570** **571**;
3. the Hofmann exhaustive methylation for tertiary amines, e.g., **573** **572**; and
4. the Emde reaction, specifically for tetrahydroisoquinolines, e.g., **573** (Y = Me) and **574** (Y = Me).



Cyclic ethers are cleaved, with consequent ring opening, more readily than in the acyclic series; for example, tetrahydropyran with aqueous hydrochloric acid at 100°C gives $Cl(CH_2)_5Cl$.

1,2,3,4-Tetrahydroisoquinoline undergoes a thermal retro-DielsAlder reaction to give *o*-quinodimethane (**Scheme 81**).



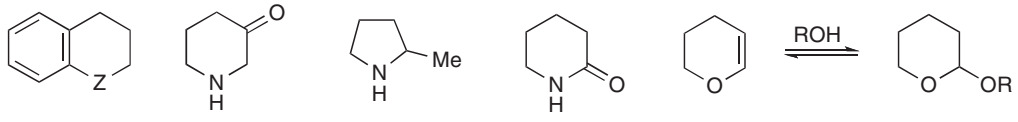
Scheme 81

3.2.2.4.4 Other reactions

These compounds usually show other reactions typical of their aliphatic analogues. 1,2,3,4-Tetrahydroquinoline **575** (Z = NH) is an *N*-alkyl aniline; chroman **575** (Z = O) is an alkyl aryl ether.

3-Piperidone **576** behaves as an amino ketone, although on Clemmensen reduction it gives 2-methylpyrrolidine **577**. 2-Piperidone **578** is a typical lactam.

Compound **579** behaves as an enol ether and as such adds alcohols to give adducts **580** which dissociate on heating.

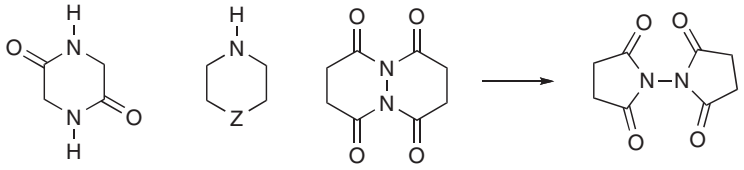


575 **576** **577** **578** **579** **580**

N-Methylpiperidine is a tertiary amine, and as such it is oxidized by mercuric acetate to 1-methyl-1,4,5,6-tetrahydropyridine.

1,3-Dioxane behaves as an acetal, 1,4-dioxane as a bis-ether, and 2,5-dioxopiperazine **581** as a bis-lactam.

Piperazine **582** (Z = NH) and morpholine **582** (Z = O) show typical aliphatic secondary amine properties, but their pK_a values, 9.8 and 8.4, respectively, (cf. piperidine pK_a 11.2) reflect the inductive effect of the second heteroatom.



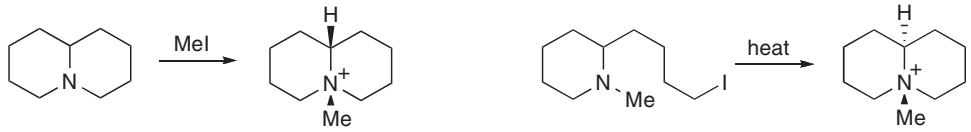
581 **582** **583** **584**

Tetrone **583** rearranges to *N*,*N*-bissuccinimide **584** either on heating or on reaction with succinyl chloride or hydrogen chloride in dioxane.

3.2.2.4.5 Stereochemistry

Steric effects can alter the reactivity of a heterocyclic compound as compared to its aliphatic analogue. For example, piperidine is less sterically hindered and thus more strongly nucleophilic than diethylamine. Conformations of these compounds are discussed elsewhere (Section 2.2.4.3).

The quaternization of quinolizidine **585** and related alkaloids has attracted much attention, directed primarily at the stereochemistry of the reaction. Thus, methylation of quinolizidine affords the *cis*-fused 5-methylquinolizidinium salt **586**; its isomer **588** is available only by the cyclization of piperidine derivative **587**.



585 **586** **587** **588**

3.2.3 Reactions of Substituents

3.2.3.1 General Survey of Reactivity of Substituents on Ring Carbon Atoms

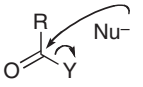
We consider here substituents attached to carbon (see Section 3.2.3.12.1 for a general discussion of substituents attached to nitrogen).

The differences in the reactivities of the same substituents on heteroaromatic nuclei and on benzene rings are a measure of the influence of the heteroatom(s). For six-membered heteroaromatic rings, the typical effect of the heteroatom(s) is to attract electrons away from the carbon atoms of the ring. This influence is relatively small when the heteroatom is to the substituent, but large for the - and -orientations.

3.2.3.1.1 The carbonyl analogy

The reactions of many of the typical functional groups of organic chemistry are influenced to a large extent by an adjacent carbonyl group because of the electron-withdrawing effect. As would be expected from the discussion in the preceding section, the reactions of substituents in six-membered heterocyclic rings can be similarly influenced. It is therefore helpful to consider systematically the familiar effects on substituents attached to carbonyl groups in aliphatic chemistry. These can be classified into six groups:

1. Groups which can form anions are readily displaced by nucleophilic reagents **589**;
2. -Hydrogen atoms are easily lost as protons **590**;
3. As a consequence of (2) tautomerism is possible (**591** **592**);
4. Carbon dioxide is lost very easily from carboxymethyl groups **593** and readily from carboxyl groups **594**;
5. These effects are transferred through a vinyl group, and nucleophilic reagents will add to vinyl and ethynyl groups **595** (Michael reaction);
6. Electrons are withdrawn from aryl groups, mainly from *ortho* and *para* positions; thus, electrophiles attack the *meta* position **596**.



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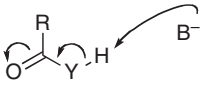
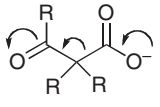


590

591 **592**



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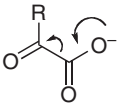

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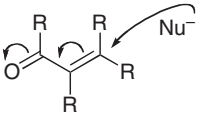

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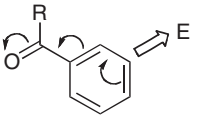


596

In **Table 3** the consequences of effects (1)(6) are listed systematically for heterocycles and compared with the similar effect found in the corresponding aliphatic carbonyl compound.

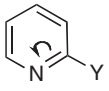
3.2.3.1.2 Effect of number, type, and orientation of heteroatoms

3.2.3.1.2.1 Pyridines and azines. An -substituent in pyridine **597** is in an electronic environment approaching that of a substituent in the imino compound **598**. Since the reactions of the carbonyl compounds **599** are better known than those of the imino compounds **598**, the reactions of -substituted pyridines are compared with those of the analogous carbonyl compounds (see preceding section 3.2.3.1.1). However, the electron pull is much greater in carbonyl compounds than in pyridine; -substituents on pyridine accordingly show reactivities intermediate between those of substituents on benzene and those attached to carbonyl groups.

The electron withdrawal to the cyclic nitrogen atom can be transmitted to the -position of pyridine **600** (illustrating the principle of vinylogy). Hence, -substituents have properties similar to those of -substituents. -Substituents in pyridine are not directly conjugated with the heteroatom; usually the reactivity is intermediate between that of the same substituent attached to a benzene ring, and that of an - or -substituted pyridine.

Table 3 The carbonyl analogy for reactions of azine substituents

Reaction type	*Group*	*Tendency for substituent in azine*	*Section*	*Compare with*
Nucleophilic displacement	Nitro	Readily displaced	3.2.3.6.1	
	Halogen	Displaced	3.2.3.10	Acid chloride
	Alkoxy	Displaced when additionally activated	3.2.3.8.1	Ester
	Amino	Displaced when additionally activated	3.2.3.5.4	Amide
	Cyano	Displaced when additionally activated	3.2.3.4.2.4	Acyl cyanide
Proton loss	Hydroxy	Acidity raised	3.2.3.7.1	Carboxylic acid
	Amino	Basicity lowered	3.2.3.5.4	Amide
	Alkyl	Active	3.2.3.3.2	Ketone
Tautomerism	Hydroxy	Exist in oxo form	3.2.3.7.1	Carboxylic acid (two equivalent structures)
	Amino	Exist as amine	3.2.3.5.6	Amide
	Mercapto	Exist in thione form	3.2.3.9.1	Thiocarboxylic acid
Decarboxylation	Carboxyl	Decarboxylate	3.2.3.4.2	-Keto acids
	Carboxymethyl	Decarboxylate easily	3.2.3.4.2	-Keto acids
Michael reactions	Vinyl	Undergo Michael addition	3.2.3.4.5	,-Unsaturated ketones
	-Hydroxyethyl	Undergo reverse Michael reaction (loss of H_2O)	3.2.3.4.4	-Hydroxy ketone
Electrophilic attack on phenyl group	Phenyl	Undergo electrophilic substitution in the *meta*- and *para*-positions	3.2.3.4.1	Phenyl ketones



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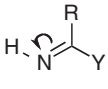

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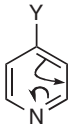


600

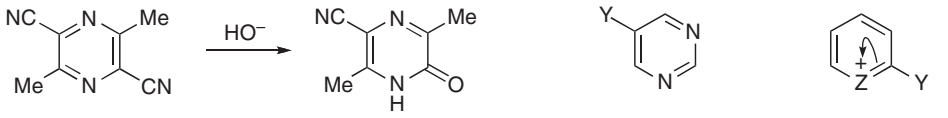
In the diazines, triazines, and tetrazines, the effects of the additional nitrogen atom(s) are roughly additive. In Table 4 the positions of substituents in the common azine ring systems are listed in the order of increasing reactivity. The limit is reached in 2-, 4-, or 6-substituted 1,3,5-triazines for which the reactivity approximates to that in a carbonyl compound **599**.

Table 4 Substituent environments in azines listed in order of increasing reactivity

Position of substituent	*Ring system*	*Number of - or -N*	*Number of -N*
Any	Benzene		
3 or 5	Pyridine		1
5	Pyrimidine		*2*
2, 4, or 6	Pyridine	1	
3, 4, 5, or 6	Pyridazine	1	1
2, 3, 5, or 6	Pyrazine		
6	1,2,4-Triazine	1	*2*
2, 4, or 6	Pyrimidine	*2*	
3 or 5	1,2,4-Triazine	*2*	
3 or 6	1 2,4,5-Tetrazine	*2*	*2*
2, 4, or 6	1,3,5-Triazine	3	

The influence of additional nitrogen atoms in the azines sometimes allows reactions not found in benzene chemistry. An example of this is the nucleophilic displacement of a cyano group, as in **601** **602**; this does not normally occur in the pyridine series, but is analogous to a reaction of an acyl cyanide (RCOCN).

Substituents in the 5-position of pyrimidines **603** are the only substituents on diazines which are not or to a ring nitrogen atom, and these behave like the substituents at the 3-position of pyridines.



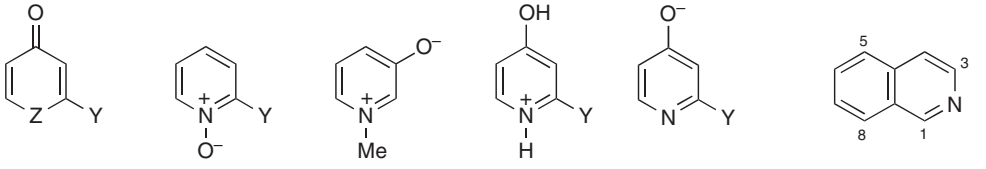
601 **602** **603** **604**

The above considerations apply to the reactivity of *neutral species*. If a proton or other electrophile adds to a pyridine nitrogen atom, this is now transformed into a positive pole, with a far greater influence, as outlined in the next section.

3.2.3.1.2.2 Cationic rings. In cationic rings the electron pull of the positively charged heteroatom is much greater than that of an uncharged nitrogen atom. The effect of a single positively charged N, O, or S atom at the - or -position is somewhat stronger than that of *three* -, -nitrogen atoms and significantly stronger than that of a carbonyl group. Hence substituents attached to the - or -positions of pyridinium, pyrylium, and thiopyrylium ions **604** show reactivity greater than that of the analogous carbonyl derivative **599**. Additional nitrogen atoms, and especially a second positively charged atom, enhance the reactivity still further.

3.2.3.1.2.3 Rings with exocyclic conjugation. For pyridones, pyrones, and azinones e.g., **605** (Z=O), and also for *N*-oxides (e.g., **606**) and -oxidocationic rings (e.g., **607**), the situation is more complex. The combined effect of the heteroatoms in such compounds is to act either as an electron source or as an electron sink depending on the requirements of the reaction (see Section 3.2.1.1.4). In practice, in reactions involving neutral species, substituents Y, , or to the heteroatom in 2- and 4-pyridones, 2- and 4-pyrones, 2- and 4-thiinones, and pyridine *N*-oxides **606** are usually activated by electron withdrawal almost as much as they are in pyridine itself. Additional nitrogen atoms increase the reactivity.

However, an important consideration again here is the species undergoing reaction. The reactivity of Y in the cation **608** will be much more, and in the anion **609** much less, affected by electron withdrawal than that of Y in **605**.



605 **606** **607** **608** **609** **610**

3.2.3.1.3 The effect of one substituent on the reactivity of another

This effect is generally similar to that observed in polysubstituted benzenes. Thus, groups such as NO_2 and CN reinforce the electron withdrawal that is caused by the heteroatom(s).

As in naphthalene, a fused benzene ring induces bond fixation. Hence, whereas substituents in the 1-position of isoquinoline (**610**; note numbering) behave like substituents in the 2-position of the pyridine nucleus, substituents in the 3-position of isoquinoline show reactivity less than that of true -substituents and about midway between those of 2- and 3-substituents on pyridine.

3.2.3.1.4 Reactions of substituents not directly attached to the heterocyclic ring

In general, substituents removed from the ring by two or more saturated carbon atoms undergo normal aliphatic reactions. A notable exception is the reverse Michael reaction which -substituted ethyl compounds such as 2-(-hydroxyethyl)pyridine undergo (see Section 3.2.3.4.4).

Substituents directly attached to fused benzene rings or aryl groups mostly show the reactions of those on benzenoid rings. Thus, a substituent on the benzenoid ring in quinoline or isoquinoline should be compared with that on a naphthalene rather than with a benzene nucleus; for example, such hydroxy derivatives undergo the Bucherer reaction, $ArOH + (NH_4)_2SO_3$ $ArNH_2$, typical for naphthols (see also Section 3.2.3.2.2).

3.2.3.2 Benzenoid Rings

3.2.3.2.1 Fused benzene rings: Unsubstituted

3.2.3.2.1.1 Electrophilic substitution of benzazines. In azines with fused benzene rings, electrophilic substitution on carbon usually occurs in the benzenoid ring in preference to the heterocyclic ring. For quinoline and isoquinoline the only common exception is mercuration which, in both, occurs in the pyridine ring. However, a strong electron-donor substituent such as NH_2 in the pyridine ring, or one or two strong electron-acceptor substituents such as NO_2 in the benzenoid ring, can also direct attack toward the pyridine ring. Frequently, the orientation of substitution in benzazines parallels that of naphthalene.

Nitration ($H_2SO_4HNO_3$, $\bar{0}$C) of quinoline and isoquinoline proceeds in positions corresponding to -substitution in naphthalene as shown in **611** and **612**; similarly, solid-supported sulfuric acid catalyzes the nitration of quinoline in nitric acid to give a mixture of 5-nitroquinoline and 8-nitroquinoline along with small quantities of the 6-isomer <1996TL513>. Sulfonation of isoquinoline gives the 5- and 8-sulfonic acids, the former predominating below 180$\bar{}$C. Sulfonation of quinoline ($H_2SO_4SO_3$) is also temperature dependent (100300$\bar{}$C) yielding 5-, 7-, and 8-quinolinesulfonic acids. Heating at 170$\bar{}$C gives a mixture of the 8- and 5-isomers with the former predominating. At higher temperatures (300$\bar{}$C) the main product is the thermodynamically favored 6-isomer and both the 5- and the 8-isomers undergo rearrangement to the 6-isomer under the appropriate conditions. Chlorosulfonation of electron-rich quinolines and isoquinolines, using neat chlorosulfonic acid at 20$\bar{}$C, occurs *ortho* or *para* to an electron-donating substituent <2003SC3427>. Halogenation follows a somewhat similar pattern; for example, isoquinoline is selectively brominated at the 5-position using NBS in sulfuric acid acid at 18 to 25$\bar{}$C; nitration of 5-bromoisoquinoline gives 5-bromo-8-nitroisoquinoline <2005OS98>. Fluorine gas and quinoline in sulfuric acid at 5$\bar{}$C produces a mixture of 5-,6-, and 8-fluoroquinolines in good yield <2002JFC(117)99, 2004JFC(125)661>.

Acridine **613**, phenanthridine **614**, cinnoline **615**, and quinazoline **616** are nitrated as shown in **Figure 3**.

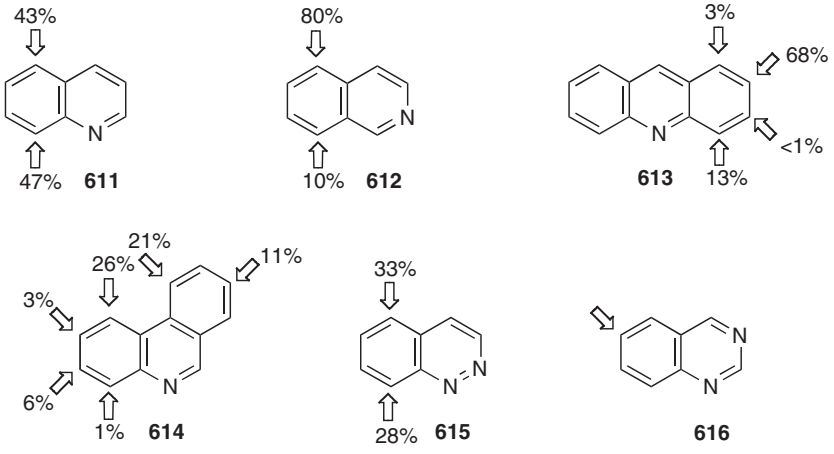


Figure 3 Positions of nitration of benzazines.

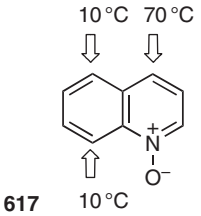
These substitution reactions probably all occur on the conjugate acid species as supported by the fact that cations, such as *N*-methylquinolinium, undergo nitration at approximately the same rate as the quinoline.

The relative reactivity of different positions towards electrophilic substitution is conveniently studied by acid-catalyzed deuterium exchange; reaction rates can be followed by NMR and introduction of deuterium hardly affects the reactivity of the remaining positions. In D_2SO_4 both quinoline and quinoline 1-oxide react as the conjugate acids at positions $8 > 5$, $6 > 7 > 3$.

3.2.3.2.1.2 Electrophilic substitution of benzopyridones and related compounds. If the hetero ring is in the form of a pyridone, pyrone, or *N*-oxide, or contains a strongly electron-donating substituent (OR or NR_2), electrophilic substitution in the hetero ring can compete with substitution in a fused benzene ring. In some such compounds, substitution occurs entirely in the heterocyclic ring; for example, nitration of 2-quinolone (carbostyril in the older literature) with fuming HNO_3 gives a 3-substituted product (see Section 3.2.1.4.4).

In other compounds, reaction can occur in both rings. Under such circumstances the orientation can depend on the conditions; frequently reaction in the benzene ring involves the cationic species, whereas that in the pyridine ring involves the free base. Thus, the temperature-dependent nitration of quinoline *N*-oxide **617** reflects the decrease in intrinsic acidity as the temperature rises, which in turn increases the available amount of free base.

Coumarins undergo nitration readily in the 6-position, while bromination results in substitution at the 3-position as a consequence of an additionelimination sequence. Quinazolines nitrate in the benzene ring; for example, 5-chloro-4(3*H*)-quinazolinone nitrates at C(8) <2005BMC5613> and 5-fluoro-4(3*H*)-quinazolinone gives a 4:1 mixture of the 6- and 8-nitro derivatives <1991JHC1459>.



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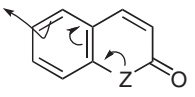
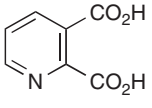


618

As outlined above, the orientation of substitution in bicyclic benzazines frequently occurs preferentially at the 5- and/or 8-positions. However, when the heterocyclic ring contains a carbonyl group, the orientation of substitution in a fused benzene ring frequently occurs in the 6-position, for example for 2-quinolone **618** (Z = NH) (nitration, $H_2SO_4HNO_3$, 20 °C) and for coumarin **618** (Z = O) [nitration ($H_2SO_4HNO_3$) and sulfonation (H_2SO_4)], and this can be compared with the *para*-substitution of acetanilide and phenyl acetate, respectively.

3.2.3.2.1.3 Oxidation. Vigorous oxidation (e.g., $KMnO_4$) usually degrades fused benzene rings in preference to pyridine rings, especially under acidic conditions. Quinoline and isoquinoline yield the dicarboxylic acids **619** and **620**, respectively; phthalazine gives **621** and phenazine yields **622** and **623**. Oxidation of such a fused benzene ring is facilitated when it carries electron-donating groups and is hindered by electron-withdrawing groups.



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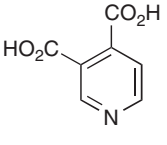

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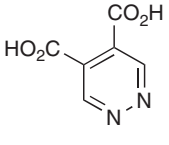

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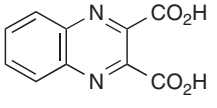

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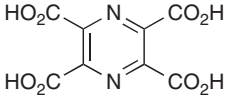
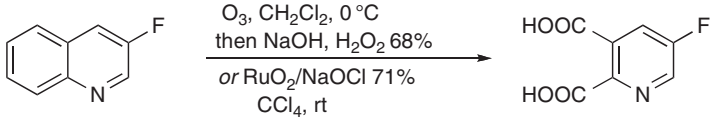


623

Ozonolysis of quinoline gives glyoxal and pyridine-2,3-dicarboxaldehyde; similarly, 3-fluoroquinoline is converted into 5-fluoropyridine-2,3-dicarboxylic acid, for example, using ozoneH_2O_2 (**Scheme 82**) <2001S2495>.

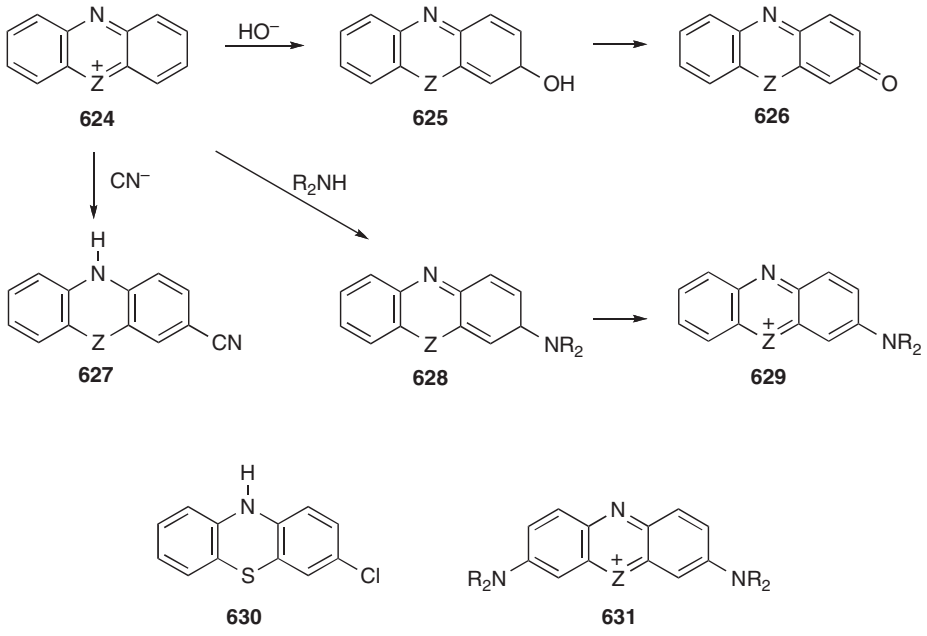


Scheme 82

3.2.3.2.1.4 Radical reactions. Reactions with radicals are often unselective and form complex mixtures; thus, phenylation of quinoline with benzoyl peroxide gives all seven phenylquinolines.

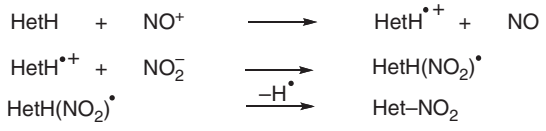
3.2.3.2.1.5 Nucleophilic attack. Nucleophiles normally attack the heterocyclic ring (Section 3.2.1.6). However, if all positions on the heterocyclic ring are blocked, and if it is highly electron deficient, reactivity toward nucleophilic attack is found in a fused benzene ring. Such conditions apply in phenazinium, phenoxazinylium, and phenothiazinylium ions (**624**; Z = NR, O, S). Hydroxide ions give pseudo-base intermediates **625** that are easily oxidized (with air, Br_2, etc.) to the quinone imines **626**.

Similarly, ammonia and amines give initial adducts of type **628**, which are then oxidized (with air, Br_2, etc.) to new onium salts **629**. The adduct with cyanide ion tautomerizes to **627**; phenothiazonium chloride forms **630** via a similar addition and tautomerism ($HClH_2O$, 100°C). Reaction with excess amine under forcing conditions gives products of type **631**.



624 **625** **626** **627** **628** **629** **630** **631**

An important analogue of these conversions is radical-cation electrophilic substitution in such -excessive six-membered heterocycles as phenothiazines, perimidines, and 1,6-diazaphenalenes. These compounds can be quite effectively nitrated with nitrous acid ($NaNO_2AcOH$). The process probably occurs in accordance with **Scheme 83**. In the first step, a radical cation is generated *in situ*; it is then attacked by nitrite anion at the positions of the benzene ring carrying the largest positive charge (spin density). These radical-cation salts can be isolated and subsequently treated with various nucleophiles, e.g., Hal, SCN, to produce the corresponding substitution products. Only heterocycles with extended -systems, which can form relatively stable radical cations, display this type of reactivity.

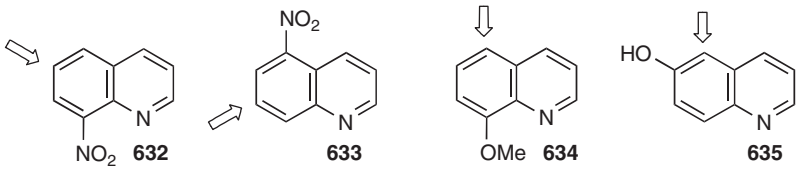


Scheme 83

3.2.3.2.1.6 Reduction of the benzene ring. Both the heterocyclic and carbocyclic rings of quinoline undergo hydrogenation with selectivity depending on the pH of the reaction medium: in neutral or weakly acidic media the pyridine ring is reduced, while reduction in strong acid gives the 5,6,7,8-tetrahydroquinoline. Acidic media can be avoided by the use of Rh/Al_2O_3 as catalyst; selective reduction can then be effected in hexafluoroisopropanol or methanol <2004SL2827>; in methanol the 1,2,3,4-tetrahydroquinoline is formed while in hexafluoroisopropanol total reduction to the decahydro product results.

3.2.3.2.2 Fused benzene rings: Substituted

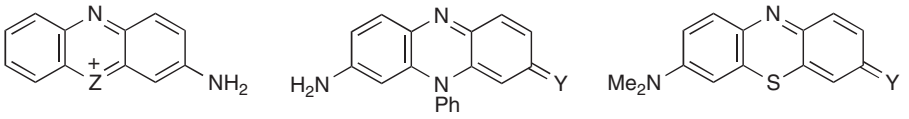
3.2.3.2.2.1 Electrophilic substitution. Substituents on the benzene rings exert their usual influence on the orientation and ease of electrophilic substitution reactions. For example, further nitration ($HNO_3H_2SO_4SO_3$) of nitroquinolines occurs *meta* to the nitro group as shown in **632** and **633**. FriedelCrafts acylation of 8-methoxyquinoline succeeds (cf. **634**) although this reaction fails with quinoline itself.



A heterocyclic ring induces partial double-bond fixation in a fused benzene ring. Hence, diazo coupling occurs at the 5-position of 6-hydroxyquinoline **635**, and not at the 7-position.

3.2.3.2.2.2 Amino groups. Amino groups on fused benzene rings in benzopyridines show basicity lower than aniline (initial proton addition occurs mainly on the hetero nitrogen atom) but are diazotized normally. Displacements of a diazonium group often occur under Gattermann but not under Sandmeyer conditions, probably because complexes are formed with Cu^{2+}.

However, a strongly electron-deficient heterocyclic ring can induce unusual reactivity as occurs for the 3-amino groups in phenazonium, phenoxazonium, and phenothiazonium salts **636** (Z = NR, O, or S) that are important in dye chemistry. Thus, phenosafranine **631** (Z = NPh, R = H) is converted by alkali into the imine **637** (Y = NH) or, on more vigorous treatment, into the phenazone **637** (Y = O). Methylene blue **631** (Z = S, R = Me) on oxidation ($K_2Cr_2O_7HCl$) gives the imine **638** (Y = NMe) and on treatment with alkali gives the oxo derivative **638** (Y = O).

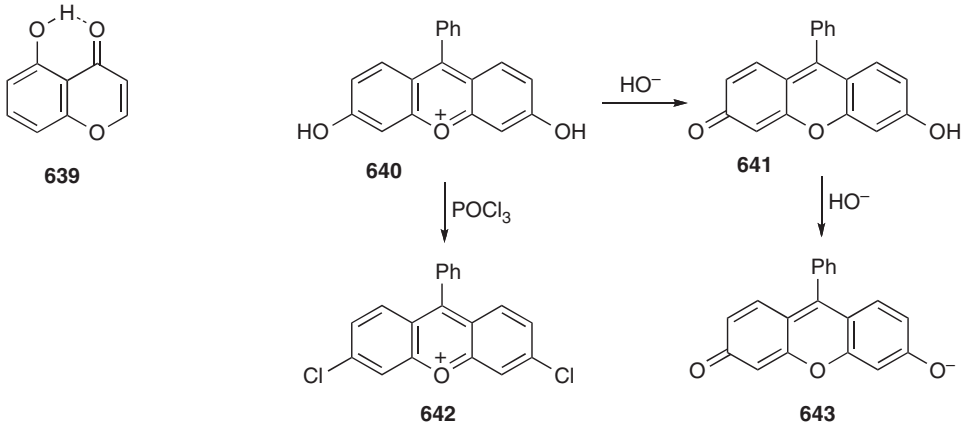


3.2.3.2.2.3 Hydroxy groups. In general, hydroxy groups on fused benzene rings undergo the expected reactions. O-Methylation is effected by diazomethane, methyl iodide, or dimethyl sulfate. O-Alkylation is reversed by aluminum trichloride or tribromide in benzene or nitrobenzene.

However, the reactivity of phenolic hydroxy groups can be modified by a fused heterocyclic ring. Thus, hydroxy groups *peri* to a carbonyl group (e.g., **639**) are hydrogen bonded; they do not react with diazomethane and are difficult to acylate. This allows selective reactions in polyhydroxychromones.

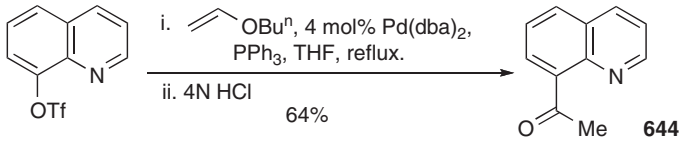
Hydroxy group acidity is increased quite dramatically sometimes. Thus, hydroxy groups on benzene rings fused to pyrylium or pyridinium rings can lose a proton if the resulting anhydrobases are stabilized by mesomerism with a noncharged *p*-quinonoid canonical form, e.g., **640 641**; the corresponding *o*-quinonoid anhydro-bases are less stable. If two suitably oriented hydroxy groups are present, a further proton can be lost to give a mesomeric anion (e.g., **643**).

In favorable cases, a phenolic hydroxy group can show a reactivity usually associated only with hydroxy on a heterocyclic ring and be converted into a chloro group (**640 642**).



Quinolyl triflates and tosylates take part in cross-coupling reactions with alkyl Grignard reagents <2002JA13856>. Stille coupling of 8-trifluoromethanesulfonyloxyquinoline with (1-ethoxyvinyl)tri(*n*-butyl)stannane in the presence of

$Pd(dba)_2$ followed by acid hydrolysis gives 8-acetylquinoline <2001T2507>, but utilizing *n*-butyl vinyl ether as coupling partner in a Heck reaction gives 8-acetylquinoline **644** in a better yield.



644

Suzuki reactions of the more easily handled but relatively unreactive tosyloxyquinolines are also possible using bulky biaryl monophosphines as supporting ligands in the presence of palladium(II) acetate <2003JA11818>.

3.2.3.2.2.4 Halogens. Heck reaction of 5- and 7-bromoquinolines with ethyl acrylate <2005TL2201> or *(E)*-ethyl crotonate <2003BML2291> proceeds in the presence of $Pd(OAc)_2$. Sonogashira coupling of 5- and 7-bromoquinolines with alkynes in the presence of palladium(0) and copper(I) iodide gives alkynyl-substituted quinolines in good yields; for example, 7-bromoquinoline couples with ethynylpyridines and ethynylbenzene using $Pd(PPh_3)_4$ as catalyst in the presence of CuI <2004BML2155>.

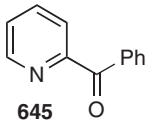
3.2.3.2.2.4 Organometallic derivatives. 5-Lithioquinolines <1995TL8415> and 7-lithioquinolines <1995S1159> can be C-formylated with *N*-formylpiperidine at 78°C. A wide variety of 6-quinolylalkanones can be accessed by quenching 6-lithioquinoline with a Weinreb amide <2005JME2134>.

3.2.3.3 Alkyl Groups

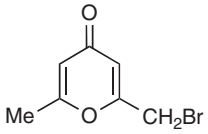
3.2.3.3.1 Reactions similar to those of toluene

The typical reactions of alkyl groups attached to benzenoid rings involve benzyl-type radical intermediates. An azine ring can stabilize a side-chain radical just as can a phenyl ring, and thus most alkylpyridines and azines show these reactions.

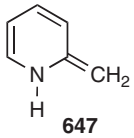
1. Oxidation in solution ($KMnO_4$, CrO_3, etc.*)* gives carboxylic acid, e.g., 3-picoline nicotinic acid, or ketone, e.g., 2-benzylpyridine 2-benzoylpyridine **645**.
2. Controlled catalytic vapor-phase oxidation converts, for example, 2-, 3-, and 4-picolines into 2-, 3-, and 4-pyridine carboxaldehydes.
3. Radical bromination with *N*-bromosuccinimide succeeds, e.g., 2,6-dimethyl-4-pyrone **646**.
4. So-called am-ox vapor-phase conversion by O_2–NH_3 of CH_3 into CN.



645



646



647

3.2.3.3.2 Alkyl groups: Reactions via proton loss

Alkyl groups or to a pyridine nitrogen show additional reactions because of the possibility of losing a proton from the carbon atom of the alkyl group which is adjacent to the ring. The ease of proton loss depends on the number, orientation, and nature of the heteroatoms in the ring carrying the alkyl groups as discussed in Section 3.2.3.1. Reactions of this type consist of two essential steps: loss of the proton and then subsequent reaction with an electrophile. For the neutral alkylazines, we distinguish between

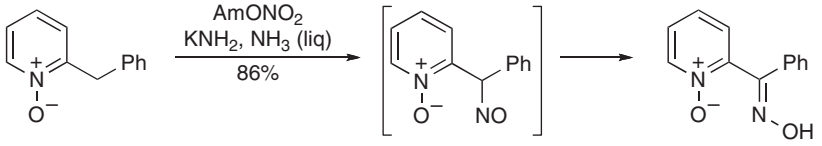
1. use of a strong base which removes the proton completely before addition of electrophile;
2. use of a weaker base which sets up a pre-equilibrium giving traces of reactive anion which reacts with the electrophile and is then replenished by the equilibrium; and
3. use of an *acid* catalyst which may produce small amounts of the tautomeric methylene form (e.g., **647**) which then reacts as an enamine at the side-chain carbon.

3.2.3.3.3 Alkylazines: Reactions involving essentially complete anion formation

The strongest bases such as sodamide ($NaNH_2NH_3$, 40°C), lithium diisopropylamide, or organometallic compounds ($PhLiEt_2O$, 40°C) convert 2- and 4-alkylpyridines, 2- and 4-methylpyrimidines, and 3- and 4-methylpyridazines, essentially completely into the corresponding anions (e.g., **648**). The regioselectivity of deprotonation of 2,4-lutidine is influenced by the reaction conditions: the 4-methyl position is the more reactive and the corresponding anion of greater thermodynamic stability; however, deprotonation using *n*-butyllithium, under kinetic control, results in the formation of the 2-lithiomethylpyridine. The selectivity of this process arises from prior coordination of the base to the neighboring nitrogen <1974JOC3834>. Similarly, with 2,4-dimethylquinoline, *n*-butyllithium promotes ionization at the 2-methyl group, whereas lithium diisopropylamide reacts at the 4-methyl group.

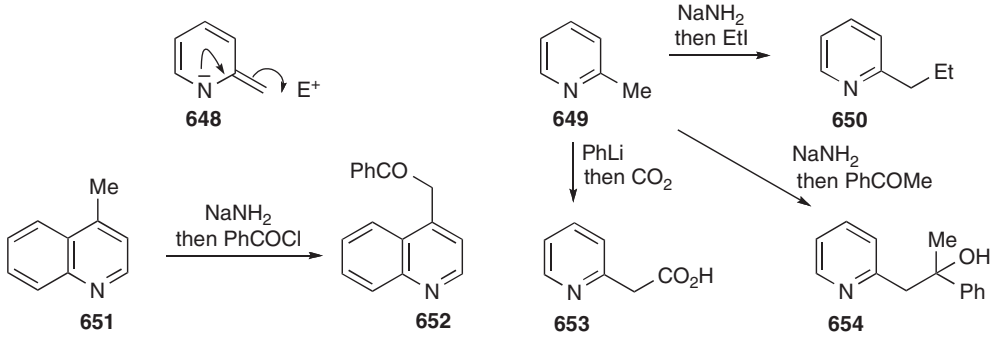
The side-chain anions react readily (as **648**) with even mild electrophilic reagents; thus, the original alkyl groups can be substituted in the following ways:

1. Alkylation with alkyl or allyl halides (e.g., <2005OL315, 2004EJO835>), thus 2-picoline **649** 2-*n*-propylpyridine **650**.
2. Acylation with acid chlorides, e.g., lepidine **651** 4-phenacylquinoline **652**, or with chloroformates <2004BML1795>.
3. Carboxylation, e.g., 2-picoline **649** 2-pyridylacetic acid **653** (best esterified before isolation cf. Section 3.2.3.4.2).
4. Reaction with carbonyl compounds (e.g., <2004JHC443>) or epoxides (e.g. <2002JOC9354>) to form alcohols, thus 2-picoline **649** the tertiary alcohol **654**.
5. An alkyl nitrite and sodamide in liquid ammonia give an oxime (**Scheme 84**).



Scheme 84

6. Benzylic sulfonylation of 2-picoline results from quenching of 2-lithiomethylpyridine with 1-(phenylsulfonyl)benzotriazole at 78°C <2005JOC9191>.



Side-chain deprotonation of 3-methylpyridines does occur but strong bases must be used. These anions react in a manner similar to the 2- and 4-methyl analogues, with aldehydes, esters and alkyl halides, etc. <2005T1127>.

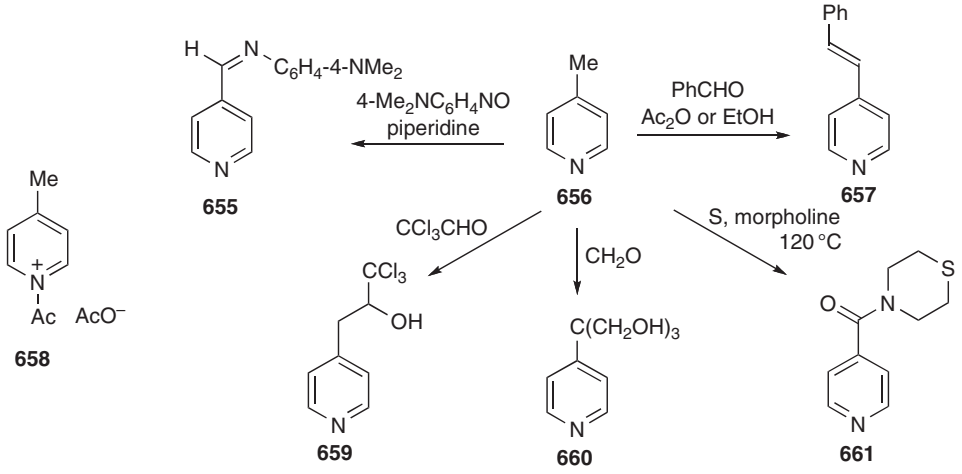
3.2.3.3.4 Alkylazines: Reactions involving traces of reactive anions or traces of methylene enamines

In aqueous or alcoholic solution, activated alkyl groups in heterocyclic rings react with bases to give traces of anions of type **648**. In such reactions, alkoxide or hydroxide ions, aliphatic amines (e.g., NEt_3, piperidine), or the alkylpyridine itself can act as the base. With suitable electrophilic reagents the anions can undergo reasonably rapid and essentially nonreversible reaction, gradually converting the whole of the heterocyclic compound. An obvious prerequisite for reaction under these conditions is that the base used does not react irreversibly with the electrophile.

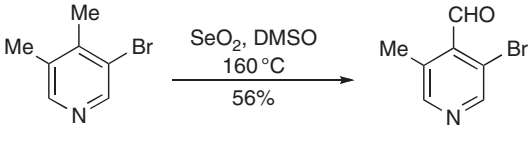
In acidic media, loss of a proton may give traces of methylene forms of type **647**. Alternatively, acetic anhydride can be used which involves formation of *N*-acylpyridinium species of type **658** from which proton loss is easy giving an *N*-acetylenamine which can also react with electrophiles.

Reactions of these types are illustrated below using 4-picoline **656** and quinaldine **662**:

1. Formaldehyde gives polyalcohols (**656** → **660**).
2. Other aliphatic aldehydes form monoalcohols (**656** → **659**).
3. Aromatic aldehydes give styryl derivatives (**656** → **657**) by spontaneous dehydration of the intermediate alcohol (cf. Section 3.2.3.4.4).
4. Nitroso compounds form Schiff bases (**656** → **655**).



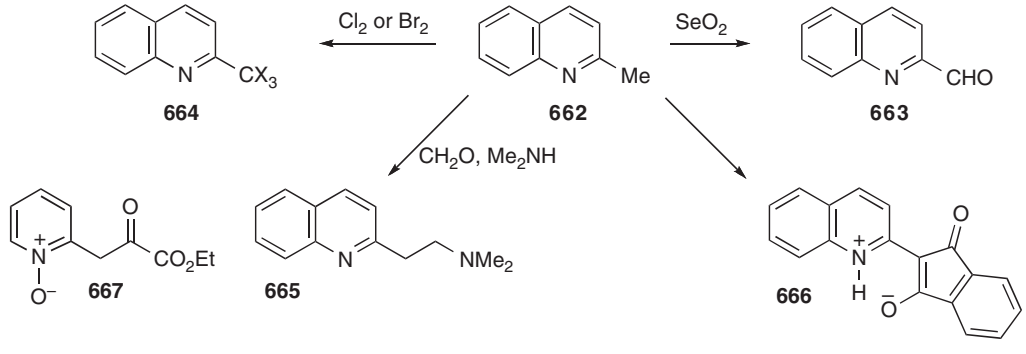
5. Halogens substitute all adjacent hydrogen atoms (**662** → **664**) but phosphoryl chloride can be used to prepare monochloromethylpyridines <2004OL4527>.
6. Formaldehyde plus amines yield Mannich bases (**662** → **665**).
7. Phthalic anhydride gives indane-1,3-dione derivatives (**662** → **666**).
8. Selenium dioxide oxidizes CH_3 to CHO (**662** → **663**) and this differentiates 2- and 4-methyls from 3-methyl, e.g., **Scheme 85** <2003SC475>. Conversion of 2- and 3-alkylpyridines into chiral hydroxyalkyl derivatives can be achieved with the enzyme toluene dioxygenase from the mutant soil bacterium *Pseudomonas putida* in high ee <2002TA2201>.



Scheme 85

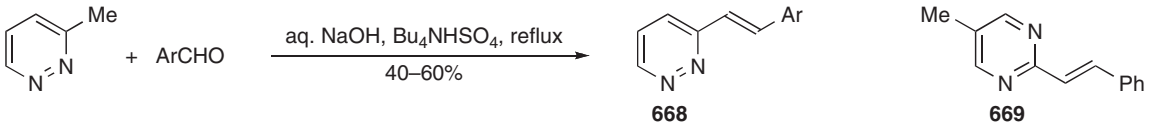
9. Willgerodt conversion of CH_3 $CSNR_2$ with S/R_2NH (**656** → **661**).

Although the last two examples have radical intermediates, they probably involve electron transfer from the type **648** anion to the reagent in the rate-limiting step.

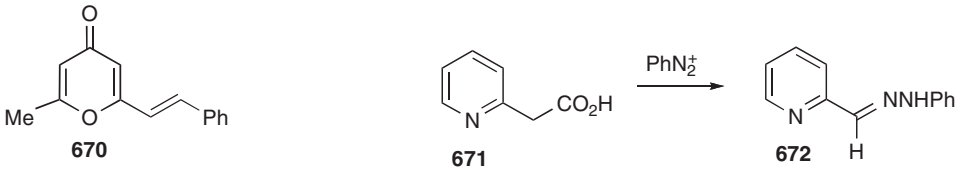


The above reactions have been illustrated for 2- and 4-alkylpyridines. They generally fail if no heteroatom is or , as in 3-alkylpyridines and 5-alkylpyrimidines. - and -Alkyl groups in pyridine *N*-oxides are somewhat more reactive than those in the corresponding pyridines. In addition to the reactions already mentioned, 2-picoline *N*-oxide undergoes Claisen condensation with ethyl oxalate to yield the pyruvic ester **667** (for the conversion of alkyl substituents in *N*-oxides into CH_2OAc groups, see Section 3.2.3.12.5.4).

In the diazines, methyl acidity can also be utilized: condensation of 3-methylpyridazine with substituted araldehydes in basic medium gives alkenes **668** <2005T10227>.



Methyl groups at the 2-, 4-, or 6-positions of pyrimidine are also reactive. In addition to typical reactions such as condensation with benzaldehyde, selenium dioxide oxidation, and halogenation, they can be converted into oximino groups by nitrous acid and undergo Claisen condensation with $(CO_2Et)_2$. In the reaction of 2,5-dimethylpyrimidine with benzaldehyde, only the 2-methyl group reacts to yield the 2-styryl derivative **669**. In quinazolines partial double-bond fixation makes a methyl group at the 4-position more reactive than one at the 2-position.

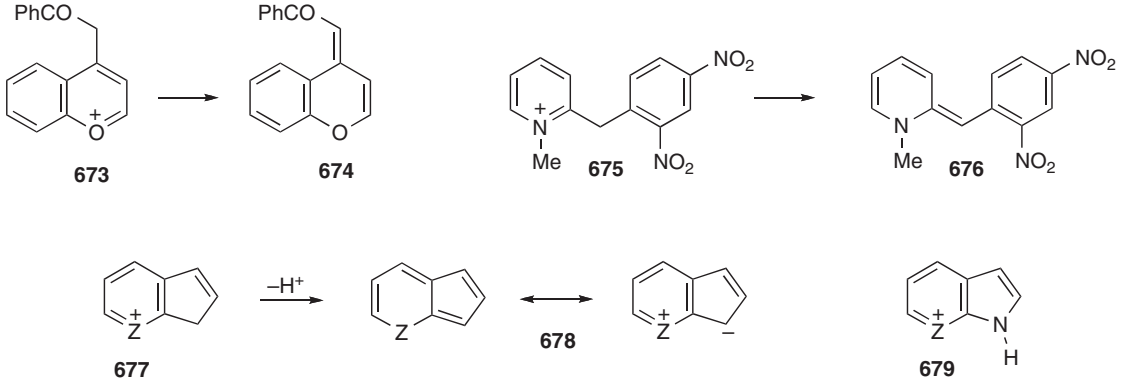


- and -Alkyl groups in pyrones and pyridones also undergo many reactions of these types. For example, with benzaldehyde, 2,6-dimethylpyrone gives the styryl derivative **670** and 1,4- and 1,6-dimethylpyridin-2-ones condense with ethyl oxalate. 2-Methyl groups in pyran-4-ones and chromones condense with benzaldehyde and can be halogenated.

If an - or -alkyl group itself carries an electron-withdrawing substituent, proton loss is facilitated, and additional reactions can occur (e.g., **671** **672** + CO_2) (cf. the JappKlingemann reaction: $MeCOCH_2CO_2H + PhN_2^+$ MeCOCH=NNHPh).

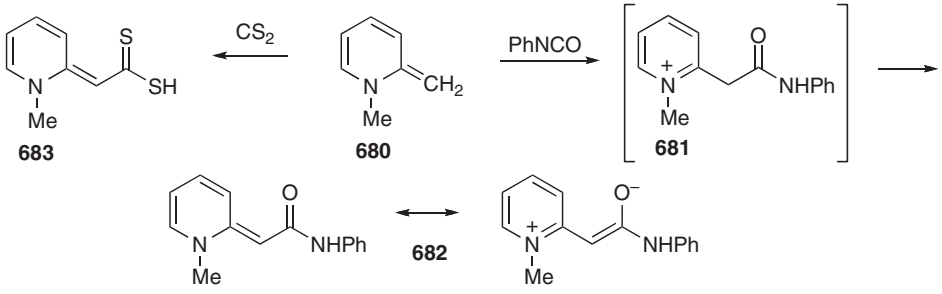
3.2.3.3.5 Alkyl-azonium and -pyrylium compounds

3.2.3.3.5.1 Formation of stable anhydro-bases. Compounds containing methylene groups activated by both a cationic ring and another electron-withdrawing group easily form stable anhydro-bases, e.g., **673** **674**, **675** **676**. Stabilization can also be achieved by utilization of the aromatic character of the cyclopentadiene anion or the pyrrole anion; compounds of types **677** (Z = NR, O, S) and **679** readily lose protons to give the anhydro-bases, e.g., **678**.

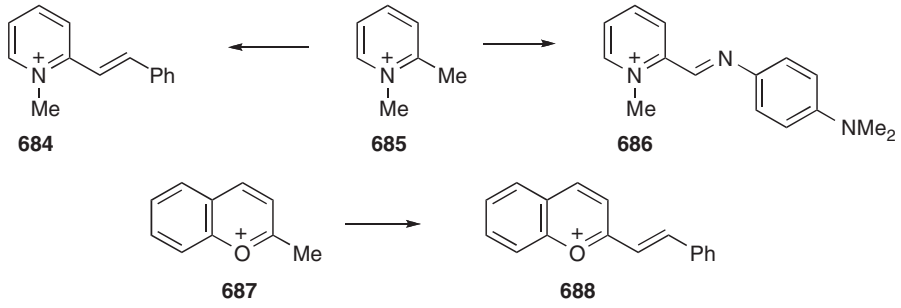


3.2.3.3.5.2 Anhydro-bases as intermediates. Proton loss from - and -alkyl groups on a cationic (pyridinium, pyrylium, or thiopyrylium) ring is comparatively easy. The resulting unstable and highly reactive neutral anhydro-bases (e.g., **680**) can be isolated by using 10 M sodium hydroxide, but are generally used *in situ*.

These anhydro-bases are heterocyclic enamines and enol ethers and react readily with electrophilic reagents to give products that can often lose a proton to give a new resonance-stabilized anhydro-base. Thus, **680** reacts with phenyl isocyanate to give an adduct **681** which is converted by proton loss into the conjugated final product **682**. A similar sequence with carbon disulfide yields the dithio acid **683**.

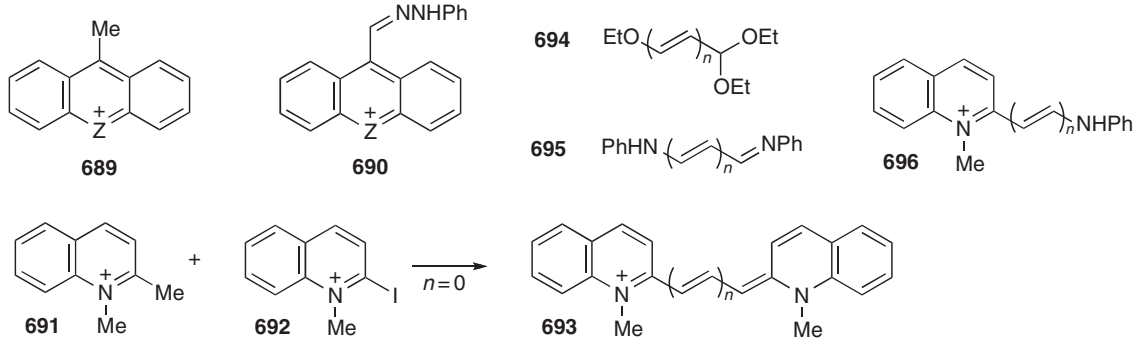


- and -Alkyl cationic heterocycles, like the 2- and 4-alkylpyridines, can also react with electrophilic reagents without initial complete deprotonation. They undergo the same types of reaction as the alkylpyridines under milder conditions, for example, with piperidine as base. Thus, 1,2-dimethylpyridinium cation **685** with PhCHO and with *p*-$Me_2NC_6H_4NO$ yields **684** and **686**, respectively, and 2-methylchromylium **687** gives **688**.



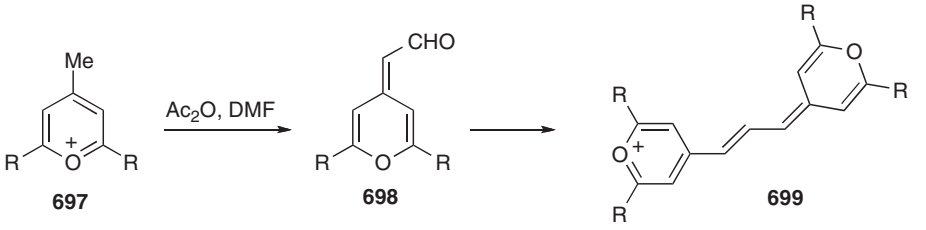
Some weakly electrophilic reagents, which are usually inert toward neutral pyridines and azines, also react:

a. Diazonium salts yield phenylhydrazones, e.g., **689** **690** (Z = NMe, O).
b. Monomethine cyanines are formed by reaction with an iodoquaternary salt, e.g., **691**+**692** **693** (*n* = 0).



c. Tri-, penta-, and heptacarbocyanines, e.g., **693** (*n* = 1, 2 and 3, respectively), are obtained by the reaction of two molecules of a quaternary salt with one molecule of ethyl orthoformate **694** (*n* = 0), -ethoxyacrolein acetal **694** (*n* = 1), or glutacondialdehyde dianil **695** (*n* = 2), respectively.

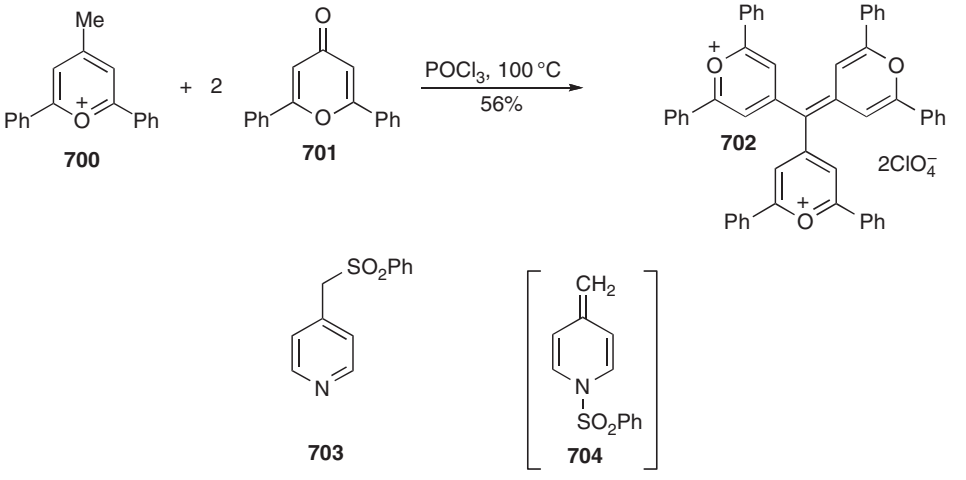
d. With the anils **695** ($n = 0$, 1, or 2), it is possible to isolate intermediates of type **696** ($n = 1$, 2, or 3) which react with another molecule of the same or a different quaternary base to give symmetrical or unsymmetrical tri-, penta-, and heptacarbocyanines. A similar reaction sequence in the pyrylium series is shown by **697** **698** **699**.



697 **698** **699**

e. - and -Alkyl groups of pyrylium salts condense with pyrones to yield trinuclear cyanine dyes, e.g., **700** + 2 × **701** **702**.

f. -Alkylpyridines with benzenesulfonyl chloride yield products of type **703**, probably via intermediates such as **704** (cf. Section 3.2.3.3.3.6).



700 **701** **702** **703** **704**

3.2.3.3.6 Tautomerism of alkyl derivatives

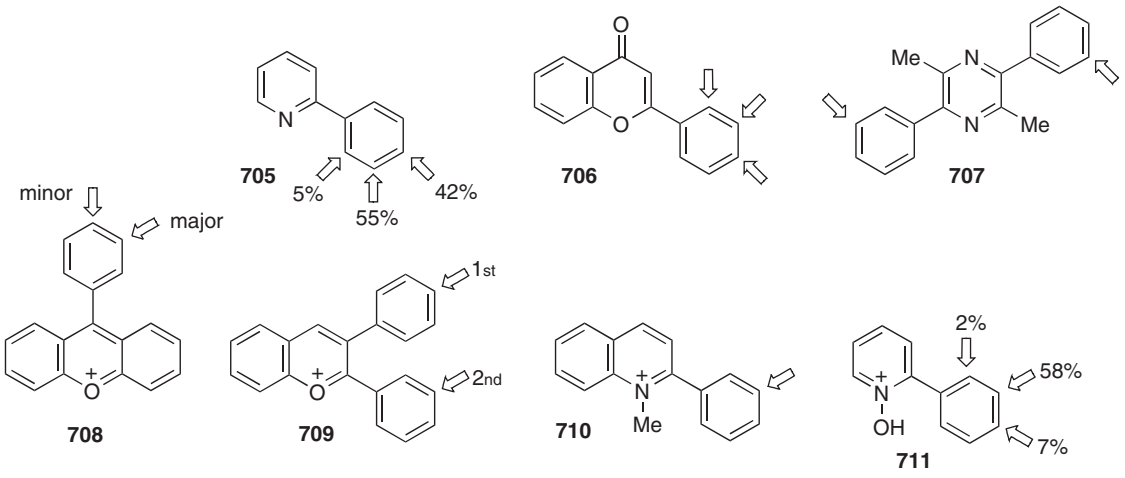
Like the tautomerism of the hydroxy- and aminopyridines (Sections 3.2.3.7.1 and 3.2.3.5.5), there are alternative tautomeric alkylidene forms of the 2- and 4-alkylpyridines (e.g., **647** for 2-picoline). Although the proportion of alkylidene form at equilibrium is very small (discussed in Section 2.2.5.1.2), it can be important as a reactive intermediate (see above).

3.2.3.4 Further Carbon Functional Groups

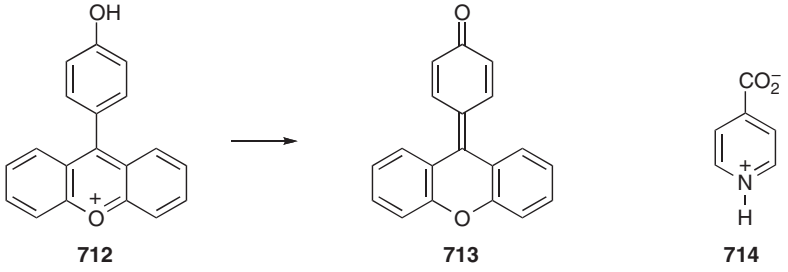
3.2.3.4.1 Aryl groups

3.2.3.4.1.1 Electrophilic substitution. Electrophilic substitution usually occurs preferentially in the aryl group (**Figure 3**). In compounds containing both an aryl group and a fused benzene ring, electrophiles usually attack the aryl group exclusively. - and -Phenylpyridines are nitrated to form mixtures of the - and -(*o*-, *m*-, and *p*-nitrophenyl)pyridines (cf. **705**). Likewise, nitration (H_2SO_4, MeOH, HNO_3, $0\,\bar{}\,C$) of flavone also gives a mixture of the 2-, 3-, and 4-nitro derivatives (cf. **706**). This represents reactivity midway between the corresponding carbonyl and benzenoid derivatives: acetophenone is nitrated exclusively *meta*; biphenyl, exclusively *ortho* and *para*.

The tendency for *meta* nitration increases with the electron deficiency of the parent ring and also depends on the species that reacts. 4-Phenylpyrimidine is nitrated in the phenyl group at all positions in proportions depending on the conditions, whereas the pyrazine derivative **707** reacts at the *meta*-positions as shown. Positively charged heterocyclic rings direct the substitution to the *meta*-position of - or -phenyl groups but to the *ortho*, *para*-positions of -phenyl groups as exemplified by the orientation for nitration in **708–710**. The activating and *para*-directing influence of an *N*-oxide group toward electrophilic substitution (cf. Section 3.2.1.4.4.5) does not extend to phenyl substituents, e.g., 2-phenylpyridine 1-oxide is nitrated as shown in **711**.



3.2.3.4.1.2 Reactions of substituents. An example of a significant effect on the reactivity of a substituent on a phenyl ring is found in the easy proton loss in **712** **713**.



3.2.3.4.2 Carboxylic acids and derivatives

3.2.3.4.2.1 General. Pyridine- and azine-carboxylic acids, as amino acids, exist partly as betaines (e.g., **714**) in aqueous solution, but very dominantly as neutral molecules in ethanol which has a lower dielectric constant.

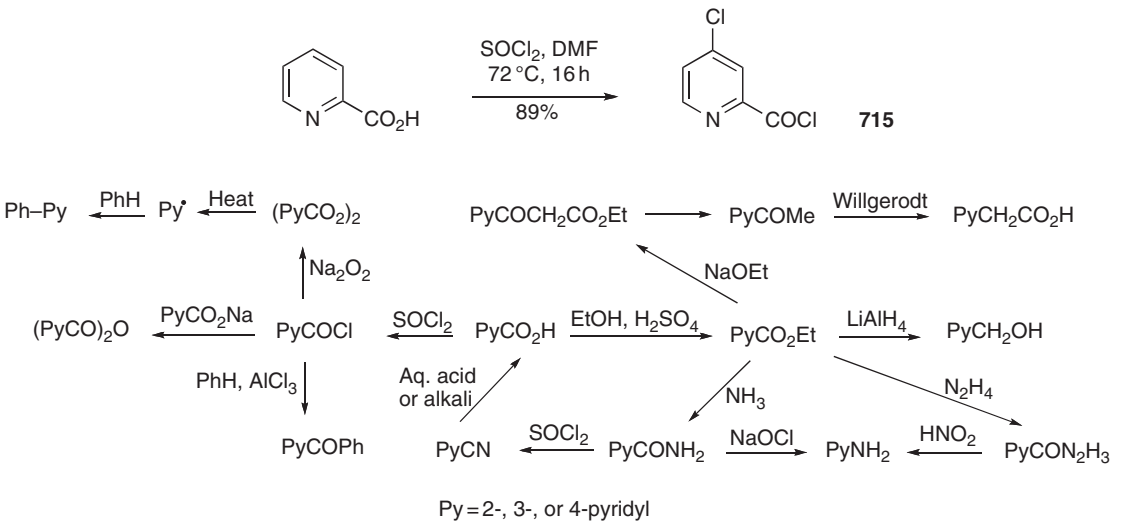
In most of their reactions, the pyridine- and azinecarboxylic acids and their derivatives behave as any other acid (cf. **Scheme 86**). However, some acid chlorides can be obtained only as hydrochlorides, and we must also consider decarboxylation. Esterification of pyridine carboxylic acids can be usefully achieved via *in situ* generation of the acid fluoride. For example, treatment of picolinic acid with a stoichiometric amount of *N*,*N*,*N*,*N*-tetramethylfluoroformamidinium hexafluorophosphate (TFFH) in dichloromethane and triethylamine leads to generation of the acid fluoride, which reacts with (3-methyloxetan-3-yl)methanol to give the corresponding ester in 95% yield <2004S2485>.

A useful method for conversion of esters into amides involves treatment with primary or secondary amines in the presence $MgCl_2$ or $MgBr_2$ <2001TL1843>. Dimethylpyridine-2,3-dicarboxylate and the 2,5-isomer react selectively at the 2-ester.

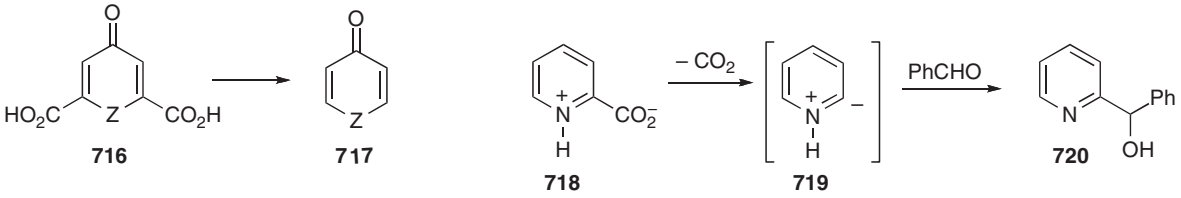
The usefully functionalized 4-chloropicolinyl chloride **715** can be prepared from picolinic acid in high yield by reaction with thionyl chloride <2002OPD777>.

3.2.3.4.2.2 Decarboxylation of carboxy groups directly attached to ring. Azine carboxylic acids lose CO_2 significantly more easily than benzoic acids. Pyridinecarboxylic acids decarboxylate on heating with increasing ease in the order $\ll <$. 2-Pyridazinecarboxylic acid gives pyrazine at 200°C, and 4,5-pyrimidinedicarboxylic acid forms the 5-mono-acid on vacuum distillation. Pyrone- and pyridonecarboxylic acids also decarboxylate relatively easily; thus, chelidonic acid **716** (Z = O) at 160°C over copper powder and chelidamic acid **716** (Z = NH) at 260°C give **717** (Z = O, NH).

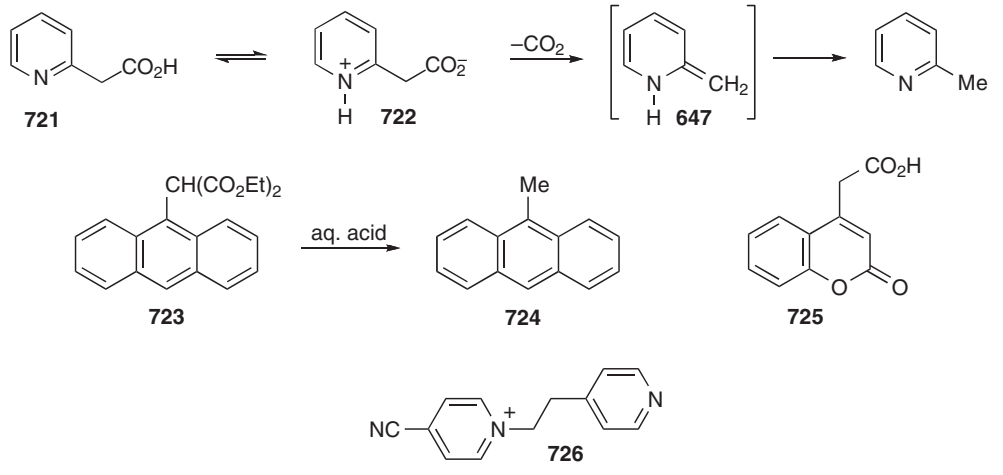
The relatively easy decarboxylation of - (**718**) and -carboxylic acids is a result of inductive stabilization of intermediate ylides of type **719** (cf. Section 3.2.1.8.2). By carrying out the decarboxylation in the presence of aldehydes or ketones, products of type **720** are formed (Hammick Reaction).



Scheme 86



3.2.3.4.2.3 Decarboxylation of carboxymethyl groups. Pyridines with an - or -carboxymethyl group (e.g., **721**) undergo easy decarboxylation by a zwitterion mechanism (**722** **647**) somewhat similar to that for the decarboxylation of -keto acids (cf. Section 3.2.3.1.1). Carboxymethylpyridines often decarboxylate spontaneously on formation; thus, hydrolysis of **723** gives **724**. The corresponding 2- and 4-pyridone and 2- and 4-pyrone acids are somewhat more stable, e.g., **725** decarboxylates at 170°C. 3-Pyridineacetic acid shows no pronounced tendency to decarboxylate.



3.2.3.4.2.4 Nucleophilic displacement of cyano groups. Pyridine nitriles show normal reactions. However, with rather more electron-deficient rings, such as those in pyrimidine nitriles or pyridinium nitriles, nucleophilic displacement of the CN becomes possible (cf. **601** **602**, Section 3.2.3.1.2.1). The nucleophilic displacement of CN in cationic ring **726** is important in the manufacture of 4-dimethylaminopyridine.

Cyanopyridines are good coupling partners in transition metal-mediated CC bond-forming reactions. The CCN bond is readily activated by oxidative insertion of nickel catalysts and the resulting nickel(II) complexes undergo transmetallation with other organometallic species and carbometallation across alkynes. Treatment of 2- and 3-cyanopyridines with aryl Grignard reagents, 5 mol% dichlorobis(trimethylphosphine)nickel, and sterically bulky alkoxides, which prevent the

formation of imines and homo-coupled products, leads to the synthesis of biaryls in good yields <2003S1643>. This cross-coupling can also be performed with alkenyl Grignard reagents to give alkenyl-substituted pyridines.

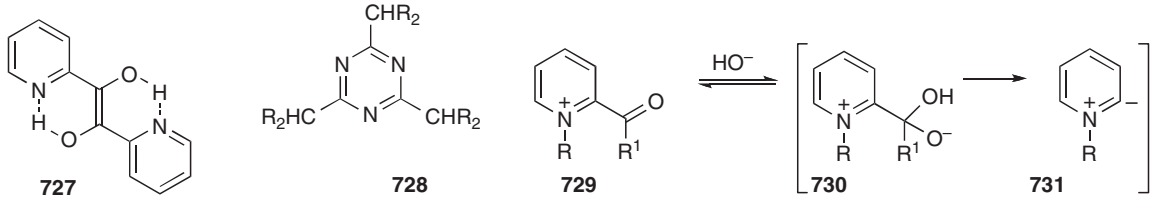
3.2.3.4.2.5 Reactions of anhydrides. Treatment of 2,3-pyridinedicarboxylic anhydride with methanol leads to the formation of 2-(methoxycarbonyl)nicotinic acid <2003TL2745>.

3.2.3.4.3 Aldehydes and ketones

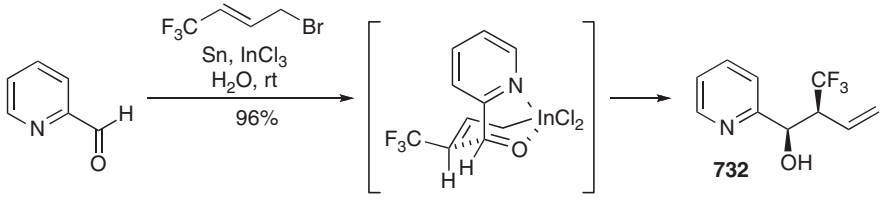
In general, the properties of these compounds and those of their benzenoid analogues are similar; thus, pyrimidine carbaldehydes show the usual reactions, as do aldehyde groups attached to chromone and pyrone rings. Aldehyde groups to a cyclic nitrogen atom undergo the benzoin condensation very readily because the end products are stabilized as hydrogen-bonded ene-diols (e.g., **727**).

2,4,6-Tris(dimorpholinomethyl)-1,3,5-triazine **728** (R = morpholino) can serve as a synthetic equivalent of 1,3,5-triazine-tricarbaldehyde. Trisphenylhydrazones, trioximes, or trisemicarbazones of this tricarbaldehyde can be obtained from **728**.

Acyl groups adjacent to a quaternized pyridinium nitrogen atom (e.g., **729**) are susceptible to removal by nucleophilic attack via **730** and the ylide **731**.



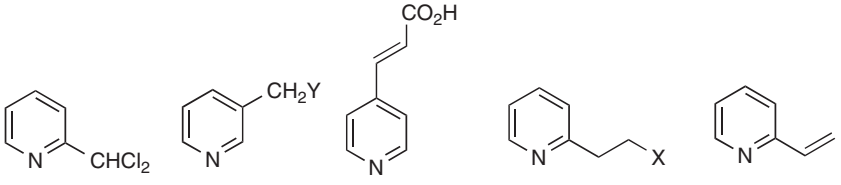
Pyridine-2-carboxaldehyde reacts with the allylindium reagent derived from 1,1,1-trifluoro-4-bromobut-2-ene to give the *syn*-allyl alcohol as the major product in high yield <1997AGE980>. The reaction proceeds by initial formation of an allyltin reagent that undergoes transmetallation with $InCl_3$ and proceeds to give the *anti*-product **732** owing to an equatorial orientation of the aldehyde substituent in the six-membered transition state and coordination of the pyridine nitrogen to the metal centre.



3-Pyridinecarboxaldehyde reacts with trimethylsilyl cyanide in the presence of asymmetric catalysts to give the cyanohydrin in high yield and enantiomeric ratio <2004T10487>. Reactions of 2-pyridinecarboxaldehydes can also be effected using asymmetric catalysis, for example, Mukaiyama aldol reaction of 6-chloro-5-hydroxypyridinecarbaldehyde with methyl trimethylsilyl ketene acetal occurs in 90% yield and 94% ee in the presence of Carrieras binaphthyl ligand, $Ti(OPr^i)_4$ and 3,5-di-*tert*-butylsalicylic acid <2002AGE1062>. Asymmetric hydrogenation of 2- and 3-acetylpyridines occurs in high yield and ≥94% ee to give the (*S*)-alcohols using 2.5 mol% of a chiral ruthenium complex <2000OL1749>, and chiral alcohols can also be obtained by biocatalytic reductions; for example, 2,6-diacetylpyridine is reduced to the (*S*)-monoalcohol in 91% yield and 95% ee using bakers yeast in the presence of sucrose and phosphate buffer <1997TA3467> and 3- and 4-acetylpyridine are reduced to the corresponding (*S*)-alcohols in 99% yield and 99% ee using whole cells obtained from the spores of *Geotrichum candidum* <2000J(P1)3205>.

3.2.3.4.4 Other substituted alkyl groups

3.2.3.4.4.1 Examples of normal reactivity. These include halogen atoms in side chains: **733** + H_2SO_4 + H_2O pyridine-2-carboxaldehyde; **734** (Y = Cl) + KCN **734** (Y = CN); **659** + KOH **735**.

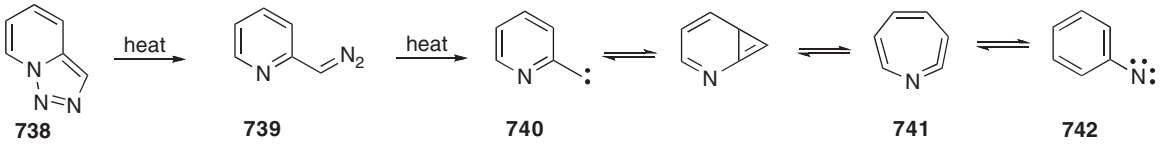


733 734 735 736 737

Hydroxymethyl pyridines can be converted into aldehydes using MnO_2 in chlorinated solvents <2003T4873> or into a mixture of the nitrile and amide using 15 equivalents of MnO_2 in the presence of ammonia in isopropanol and anhydrous magnesium sulfate <2002SL1291> or into the corresponding methyl ester with excess MnO_2 and NaCN in methanol <2002SL1293>.

3.2.3.4.4.2 Reverse Michael reactions. Compounds of type Py-CH_2CH_2X where X is a leaving group (e.g., halogen, OR, NR_2, SR, etc.) undergo reverse Michael reaction, e.g., by ready dehydration of - or -(2-hydroxyethyl) groups, **736** (X = OH) **737**.

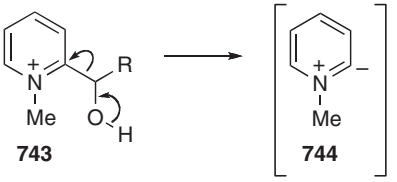
3.2.3.4.4.3 Diazoalkyl groups and related carbenes. 2-(Diazomethyl)pyridine **739** which normally exists in the ring-closed form **738** thermolyzes to 2-pyridylcarbene **740** which interconverts in the gas phase with phenylnitrene **742**. Photolysis of 2-(diazomethyl)pyridine in an argon matrix allows identification of 1-aza-1,2,4,6-cycloheptatetraene **741**. 3- and 4-Pyridylcarbenes also interconvert with phenylnitrene.



738 739 740 741 742

3.2.3.4.4.4 Nucleophilic displacements. Trihalomethyl groups can be replaced in nucleophilic substitution reactions in sufficiently activated systems, as, for example, in *s*-triazines. 2,4,6-Tris(trichloromethyl)-*s*-triazine is converted into 2,4,6-triamino-*s*-triazine by ammonia.

3.2.3.4.4.5 Formation of zwitterionic intermediate. 2-(-Hydroxyalkyl) groups on pyridinium ions **743** can be removed by nucleophiles via ylide, **744**.



743 744

3.2.3.4.5 Vinyl groups

Vinyl groups or to the pyridine nitrogen atom readily undergo Michael additions. Water, alcohols, ammonia, amines, and hydrogen cyanide are among the nucleophiles that can be added. For example, 2-vinylpyridine and dimethylamine give **736** (X = NMe_2).

The usual alkenic reactions are also shown by *C*-vinyl heterocycles, including ready radical or nucleophilic polymerization.

3.2.3.5 Amino and Imino Groups

3.2.3.5.1 Orientation of reactions of aminopyridines and -azines with electrophiles

These compounds contain three types of site for electrophilic attack: ring nitrogen, amino nitrogen, and ring carbon. In 2- and 4-aminopyridines, the nucleophilicity of the hetero nitrogen atom and of the - and -carbon atoms is increased, but

that of the amino group is decreased. Consequently, all electrophiles would be expected to attack the ring nitrogen preferentially. Indeed, as is discussed in Section 3.2.1.3, protons, alkylating agents, metal ions, and percarboxylic acids do react at the ring nitrogen atom.

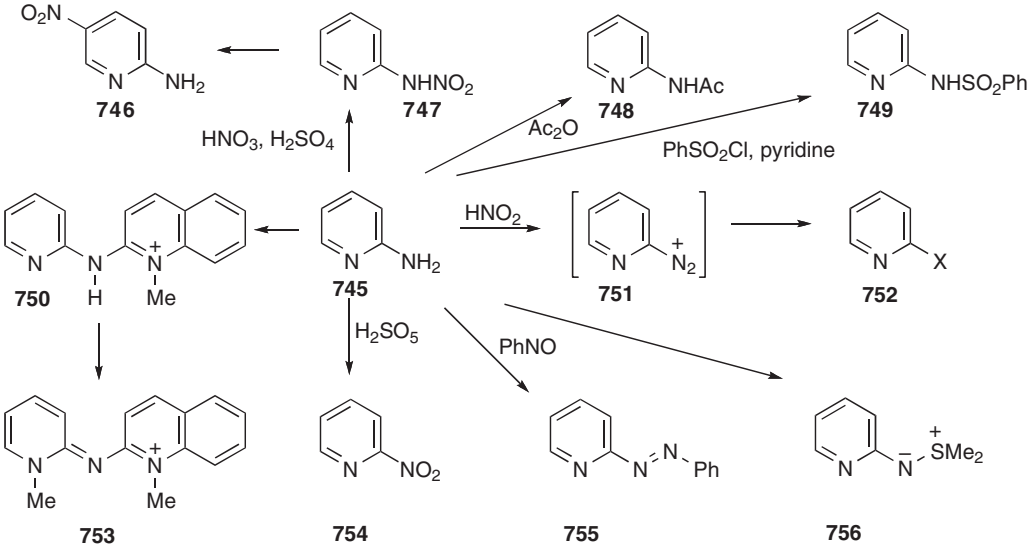
However, certain other electrophilic reagents form products derived by reaction at the amino group or at a ring carbon atom. There are four different sets of circumstances under which this behavior is found:

1. The initial reversible reaction at the pyridine nitrogen forms an unstable product which dissociates to regenerate the reactants or undergoes inter- or intramolecular rearrangement [see examples (1), (4)(6), and (8) in Section 3.2.3.5.2].
2. In acid media the pyridine nitrogen is protonated, and reaction on this species now occurs on the amino nitrogen [see examples (2), (3), and (7) in Section 3.2.3.5.2].
3. Reaction at the ring nitrogen can be sterically hindered. 4-Dimethylaminopyridine undergoes methylation and *N*-oxide formation at the ring nitrogen as expected, but in 2-dimethylaminopyridine it is the dimethylamino nitrogen that is both quaternized and N-oxidized, because the ring nitrogen is shielded.
4. If the reaction of the electrophile at the amino nitrogen is also reversible, then subsequent slower but irreversible reaction at the ring carbon can proceed to completion. In this way, the electrophiles responsible for nitration, sulfonation, and halogenation react at the ring carbon atoms, as discussed in Section 3.2.1.4.

3.2.3.5.2 Reaction of aminoazines with electrophiles at the amino group

These reactions are illustrated by **746–756** for 2-aminopyridine.

1. Carboxylic and sulfonic acid chlorides and anhydrides give acylamino- and sulfonamidopyridines **748** and **749**. Evidence exists that initial products of the reaction, the corresponding N_1-acyl-2-aminopyridinium salts, are unstable and rapidly rearrange to the thermodynamically more stable 2-acylaminoderivatives.
2. Nitric acidsulfuric acid gives nitramino compounds **747** which are easily rearranged to *C*-nitro derivatives **746** (cf. Section 3.2.1.4.4).
3. Oxidation by permonosulfuric acid (H_2SO_5) yields nitropyridines **754**.
4. Nitrosobenzene yields phenylazopyridines **755**.
5. Sodium hypochlorite gives symmetrical azopyridines.
6. With dimethyl sulfide and *N*-chlorosuccinimide the sulfilimine **756** is formed, which can be oxidized to the corresponding nitroso heterocycle.
7. Nitrous acid gives highly unstable diazonium salts **751** (cf. next section).
8. Quaternary heterocyclic iodides give products (e.g., **750** from 1-methylquinolinium iodide) which can be converted into azacyanine dyes (e.g., **753**).
9. Amino group N-ethylation can be achieved using acetonitrile as alkylating agent in the presence of Pd/C in MeOH under an atmosphere of hydrogen <2004OL4977>.
10. Amino group N-arylation requires catalysis usually with palladium <2002OL3481>.



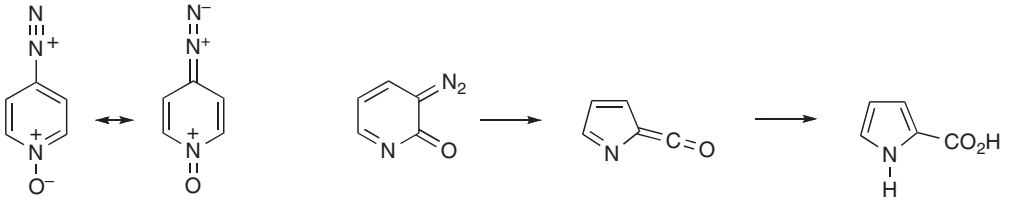
3.2.3.5.3 Diazotization of amino compounds

The stabilities of pyridine-2- and -4-diazonium ions resemble those of aliphatic rather than benzenoid diazonium cations. Benzenediazonium ions are stabilized by mesomerism which involves electron donation from the ring, but such electron donation is unfavorable in 2- and 4-substituted pyridines. On formation, pyridine diazonium cations normally immediately react with the aqueous solvent to form pyridones. However, by carrying out the diazotization in concentrated HCl or HBr, useful yields of chloro- and bromopyridines **752** can be obtained. Iodinated pyridines can be obtained in good yield using the Sandmeyer reaction. Aminopyridazines and -pyrazines, 2- and 4-aminopyrimidines, and amino-1,2,4-triazines behave similarly. Nucleophilic fluorination via the BalzSchiemann reaction of diazonium fluoroborates yields fluoropyridines, including 2-fluoropyridines. Fluoroborates can also be converted into fluoro compounds by ultraviolet irradiation.

The reactions of 3-amino groups in pyridines and 5-amino groups in pyrimidines, by contrast, are close to those of the amino group in aniline. The diazonium salts are reasonably stable and undergo coupling and replacement reactions and can be reduced to hydrazines. Amino groups at the 3-position of isoquinolines are subject to bond fixation and react in a manner intermediate between those of pyridine - and -amino groups; they can be diazotized under normal conditions.

Aminopyridine *N*-oxides can be diazotized and the diazonium salts **757** undergo coupling. These diazonium salts *are* resonance stabilized. Amino groups in pyridazine *N*-oxides can also be diazotized and the diazonium group further replaced by other functionality. Nitrosation of 3-amino-1,2,4-triazine 2-oxides and subsequent thermolysis of the diazonium tetrafluoroborate salts affords 3-fluoro-1,2,4-triazine 2-oxides.

-Aminopyridones form diazo anhydrides (e.g., **758**) (cf. aminophenols) which on irradiation give pyrrole carboxylic acids, e.g., **760** via **759**.

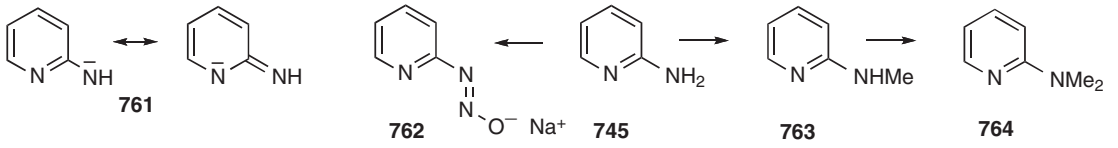


757 **758** **759** **760**

3.2.3.5.4 Reactions of amino compounds with nucleophiles and bases

Three modes of reaction are possible: proton loss, nucleophilic displacement, and Dimroth rearrangement.

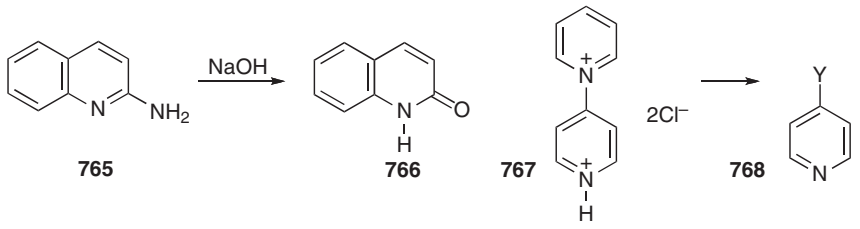
3.2.3.5.4.1 Proton loss. The side-chain anions from 2- and 4-aminopyridines are stabilized by resonance **761**. Aminoazines are thus weak acids; their anions react with electrophilic reagents preferentially at the amino nitrogen. 2-Aminopyridine **745** is thus converted by $NaNH_2$/MeI to the 2-methylamino- **763** or 2-dimethylamino-derivatives **764**. With EtONO/NaOEt, a sodium diazotate **762** is formed which will couple with phenols.



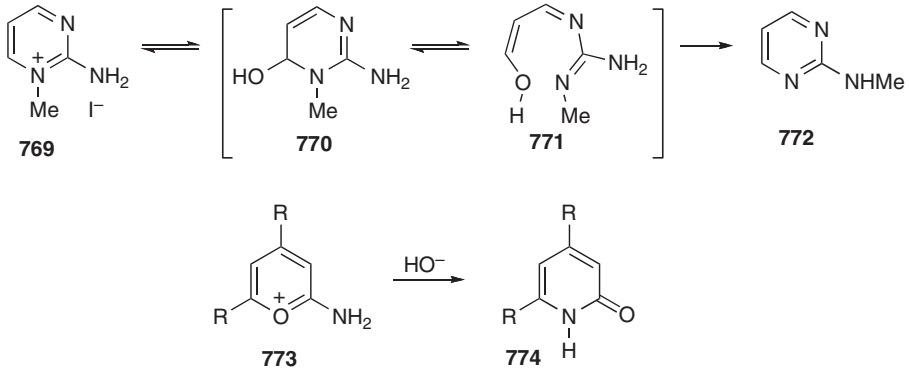
761 **762** **745** **763** **764**

3.2.3.5.4.2 Nucleophilic displacement. Nucleophilic reagents can also react with 2- and 4-aminopyridines at the carbon atom which carries the amino group in a replacement reaction (e.g., **765** **766**) similar to, but far less easy than, that undergone by chloro and alkoxy compounds. In this way aminopyrimidines can be converted into pyrimidinones by direct acidic or alkaline hydrolysis under rather vigorous conditions.

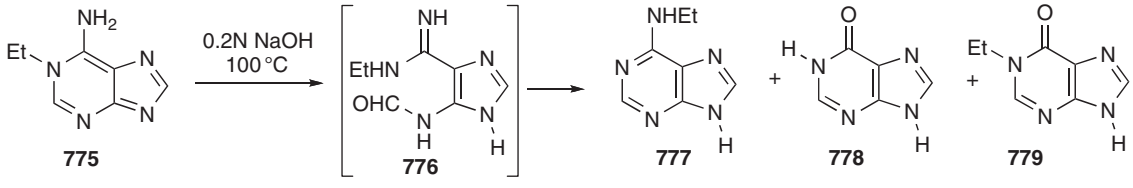
Reactions of this type are easy if the amino group is quaternized as in, for example, 1-(4-pyridyl)pyridinium chloride **767**, which gives pyridine and 4-substituted pyridines **768** [Y = Cl, Br (with PX_5); Y = SH, SR (with SH, SR); Y = NH_2, NHR (with NH_3, NH_2R)]. Similarly, NMe_3^+ groups in pyrimidines undergo nucleophilic displacement.



3.2.3.5.4.3 Dimroth rearrangement. Cationic -amino derivatives with base undergo a rearrangement in which the two nitrogen atoms change places. Thus, 1-methyl-2-aminopyrimidinium iodide **769** yields 2-methylaminopyrimidine **772**. This, the Dimroth rearrangement, involves nucleophilic (usually OH) addition at the 6-position **770**, followed by electrocyclic ring opening to **771** and reclosure to **772**. 2-Aminopyrylium salts similarly rearrange readily to substituted pyridones (**773** **774**).



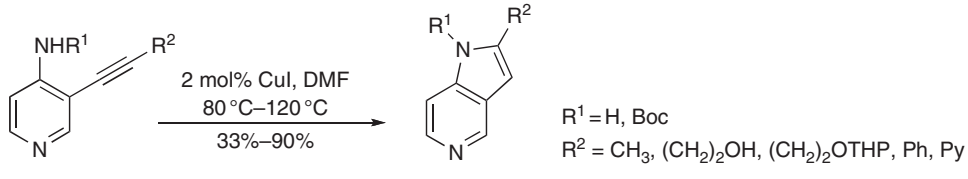
Dimroth rearrangement of neutral heterocyclic bases is also possible. For example, the adenine derivative **775** heated in NaOH produces 6-ethylaminoadenine **777** (91%), hypoxanthine **778** (2%), and 1-ethylhypoxanthine **779** (2%). The minor products are formed by hydrolysis of the first formed imidazole carboxamidine **776** and recyclization (**Scheme 87**).



Scheme 87

3.2.3.5.5 Intramolecular reactions of amino group producing rings

Azaindoles can be prepared by cyclizations of *o*-alkynyl aminopyridines (**Scheme 88**) <1998TL5159>.



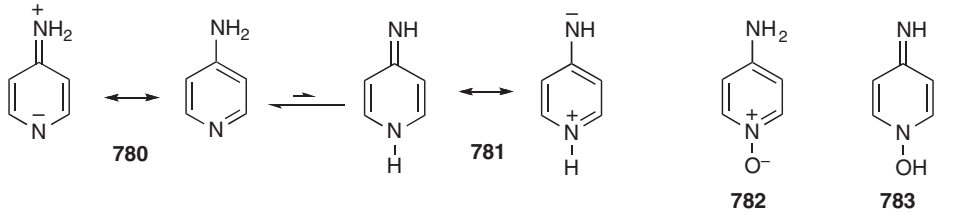
Scheme 88

Imines and enamines, formed from *o*-haloaminopyridines and ketones, can be converted into substituted 4-, 5-, 6-, and 7-azaindoles by microwave-assisted intramolecular Heck reactions <2005S2571>.

3.2.3.5.6 Amino-imino tautomerism

2- and 4-Aminopyridines (e.g., **780**) can in principle exist in tautomeric pyridonimine forms (e.g., **781**), but these are unimportant (Section 2.2.5.1), in direct contrast to the 2- and 4-hydroxypyridines which exist largely as pyridones. This difference can be rationalized by consideration of the mesomerism of the alternative forms. Resonance stabilization of aminopyridines **780** is greater than that of hydroxypyridines, while resonance stabilization of pyridonimines **781** is less than that of pyridones.

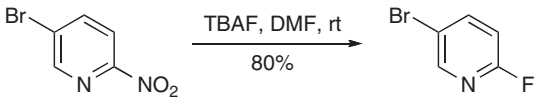
- and -Amino *N*-oxides also exist predominantly in the amino form, e.g., as **782** rather than **783**.



3.2.3.6 Other N-Linked Substituents

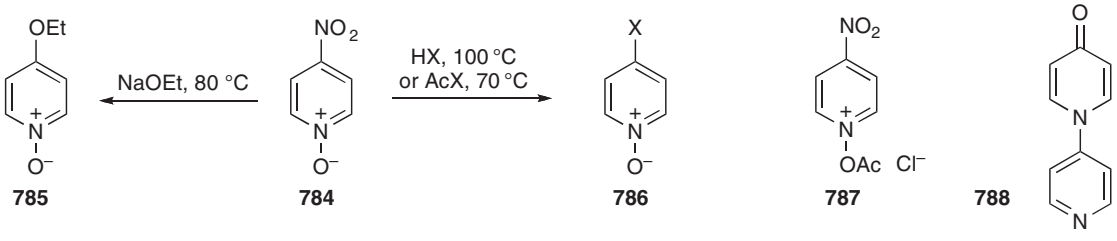
3.2.3.6.1 Nitro groups

2- and 4-Nitro groups on pyridines and pyridine *N*-oxides are smoothly displaced by nucleophilic reagents, indeed, more readily than the corresponding halides, e.g., to give 4-alkoxy or 4-alkylthiopyridines <2004EJO3477>. In other examples, 2- and 4-nitropyridines undergo fluorodenitration in the presence of TBAF in DMF to give the corresponding fluoropyridines (**Scheme 89**) <2005OL577>.

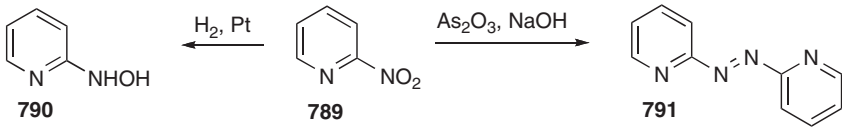


Scheme 89

Displacements of nitro are of particular importance in *N*-oxides where the nitro derivatives are readily available by direct nitration and are exemplified by the transformations **784** → **785** and **784** → **786** (X = Cl, Br). A good method for preparing bromopyridines is the nucleophilic displacement of nitro groups using HBr, either on the substituted pyridine or on the corresponding *N*-oxide. The reactions involving hydrogen bromide and chloride are acid catalyzed, while those with acetyl chloride probably proceed via intermediates of type **787**. 4-Nitropyridine gives **788** and other products on keeping; cf. polymerization of 4-halopyridines (Section 3.2.3.10.6). Nitro groups at all positions of pyridazine 1-oxide are easily substituted by halogen or other nucleophiles. Alkoxides, alkylthiolates, and amines all substitute a nitro group on a pyridazin-3(2*H*)-one nucleus, e.g., <2001JME2403>.



Nitro compounds are easily reduced, catalytically or chemically, to amino compounds. Incomplete reduction can lead to a hydroxylamino derivative or to binuclear azo, azoxy, and hydrazo compouds, e.g., **789** **790**, **791**. Examples include reduction of 3-nitropyridines using aqueous sodium hydrosulfite at room temperature <2005JME5104> and of 2-nitropyridine by transfer hydrogenation in the presence of 10% Pd/C and recyclable polymer-supported formate, prepared from aminomethylpolystyrene resin and ammonium formate <2005SC223>. A nitro group can be reduced in the presence of an *N*-oxide group, e.g., **784** **782**.



790 **789** **791**

3.2.3.6.2 Nitramino compounds

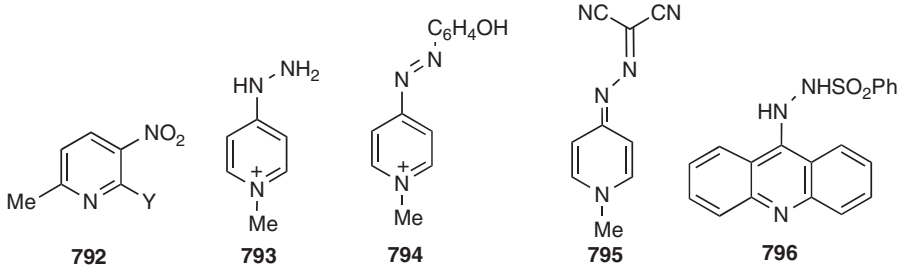
These compounds can be rearranged (cf. Section 3.2.3.5.1.4), reduced to hydrazino derivatives, or hydrolyzed to pyridones.

3.2.3.6.3 Hydrazino groups

These form derivatives with carbonyl compounds and can be acylated, sulfonylated, eliminated by mild oxidation [e.g., **792** (Y = $NHNH_2$) + $CuSO_4$ + AcOH **792** (Y = H)]. They are converted by nitrous acid into azides as in benzenoid chemistry.

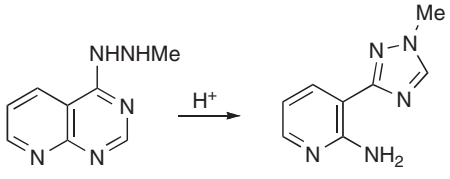
Hydrazino groups attached to cationic rings, as in **793**, undergo oxidative coupling reactions with amines, phenols (to give e.g., **794**), and reactive methylene compounds, e.g., **793** + $CH_2(CN)_2$ **795**.

- or -Phenylsulfonylhydrazino groups are eliminated by alkali (e.g., **796** acridine + N_2 + $PhSO_2H$); cf. the McFadyenStevens reaction ($RCONHNHSO_2Ph$ RCHO + N_2 + $PhSO_2H$).



792 **793** **794** **795** **796**

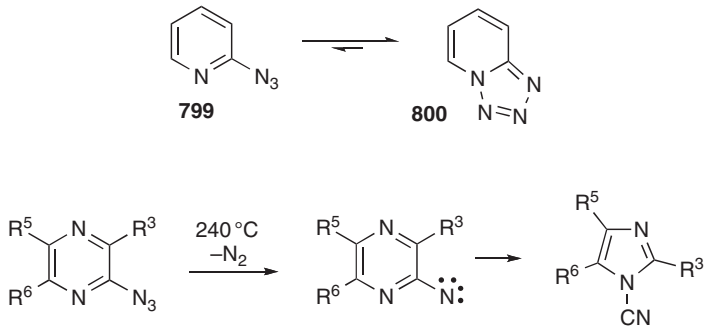
Thermolysis of hydrazine **797** in toluenemethanol catalyzed by TFA results in a rearrangement to give the 2-aminopyridine derivative **798**.



797 **798**

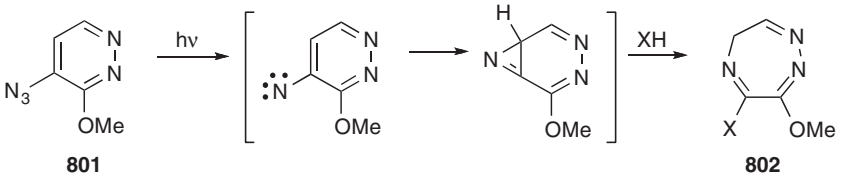
3.2.3.6.4 Azides

2-Azidopyridines exist largely, and 3-azidopyridazines completely, in the bicyclic form (e.g. **799** **800**) (see also Section 2.2.5.4). A synthetically useful reaction of azidoazines is their thermal fragmentation with loss of a nitrogen molecule. This leads to formation of a nitrene which undergoes subsequent deep-seated rearrangements leading to ring-contraction or ring-enlargement products. Thus, pyrolysis of 2-azidopyrazines or their irradiation in ethanol gives 1-cyanoimidazoles in excellent yields (**Scheme 90**).

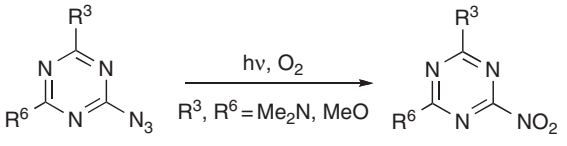


Scheme 90

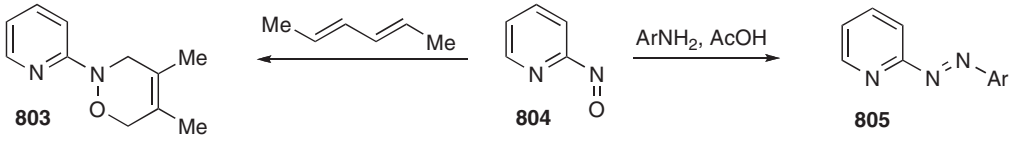
The photolysis of 4-azidopyridazines gives significant yields of the ring-expansion products, unsaturated 1,2,5-triazepines. Thus, 3-methoxy derivative **801** reacts, via formation of a nitrene and ring opening of an intermediate fused azirine, with methoxide or diethylamine to give 4-methoxy (or 4-diethylamino)-1,2,5-triazepines **802** (X = OMe, NEt_2).



Nitrotriazines are formed by photolysis of azido-1,3,5-triazines in $CHCl_3$ or MeCN in the presence of air (**Scheme 91**).



Scheme 91



3.2.3.6.5 Nitroso groups

Ready addition of 2-nitrosopyridine **804** to 1,3-dienes gives 3,6-dihydro-1,2-oxazines, e.g., **804** → **803**, and condensation with aromatic amines gives azo compounds, e.g., **804** → **805**. Nitroso compounds are oxidized by ozone or sodium hypochlorite to the corresponding nitro compounds. 5-Nitrosopyrimidines can be reduced to the 5-amino derivatives or condensed with activated methylene groups.

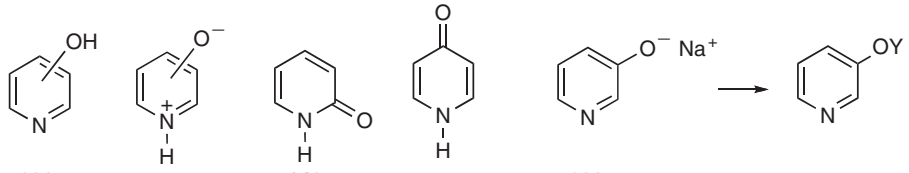
3.2.3.7 Hydroxy and Oxo Groups

3.2.3.7.1 Hydroxy groups and hydroxyoxo tautomeric equilibria

Hydroxypyridines **806** are both weak acids and bases and can therefore exist as zwitterions **807** (see Section 2.2.5.1). The zwitterions of 2- and 4-hydroxypyridines are known as 2- and 4-pyridones because of their uncharged canonical

forms, e.g., **140** and **808**. - and -Hydroxypyridines exist in aqueous solution very predominantly as the oxo or pyridone form. For - and -hydroxybenzopyridines and -benzazines, the equilibrium favors the benzopyridone form still more, with the exception of 3-hydroxyisoquinoline. The reactivity of the pyridones and azinones is considered in Sections 3.2.3.7.2–3.2.3.7.4.

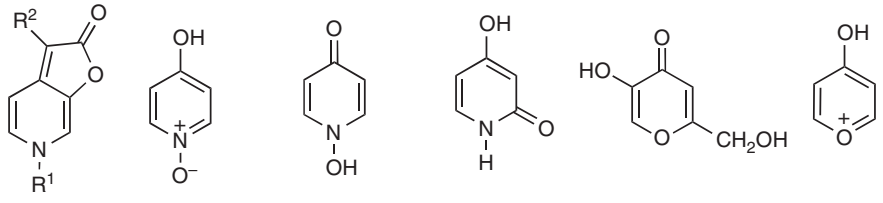
In aqueous solutions the hydroxy and zwitterionic forms of -hydroxypyridines coexist in comparable amounts. 3-Hydroxypyridine behaves in many ways as a typical phenol. It gives an intense violet color with ferric chloride and forms a salt **809** with sodium hydroxide which can be alkylated by alkyl halides [to give **810** (Y = alkyl)] and acylated by acid chlorides [to give **810** (Y = acyl)]. 5-Hydroxypyrimidines also exist as such; they behave as phenols and are easily O-acylated.



806 **807** **140** **808** **809** **810**

Cycloaddition reactions of pyridinium-3-olates involving addition at two of the ring atoms have been discussed in Section 3.2.1.10. However, with chloroketenes reaction occurs across the exocyclic oxygen atom and either the 4-position or the 2-position giving compounds of type **811**.

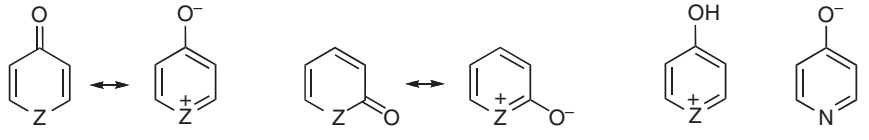
Hydroxypyridine *N*-oxides are also tautomeric; the 4-isomer exists in about equal amounts of forms **812** and **813**. In 4-hydroxypyrones and -pyridones, the -one (e.g., **814**) structure is favored relative to the -one. -Hydroxy-4-pyrones such as kojic acid **815** show phenolic properties. - and -Hydroxy cations (e.g., **816**) are the conjugate acids of pyridones and pyrones and are considered in the next section.



811 **812** **813** **814** **815** **816**

3.2.3.7.2 Pyridones, pyrones, thiinones, azinones, etc.: General pattern of reactivity

These compounds are usually written in the uncharged form **817, 819** (Z = NH, NR, O, S), but canonical forms of types **818** and **820** are of comparable importance, i.e., the compounds can also be considered as betaines derived from pyridinium, pyrylium, and thiopyrylium cations. They possess considerable stability and aromaticity in that in many of their reactions they revert to type.

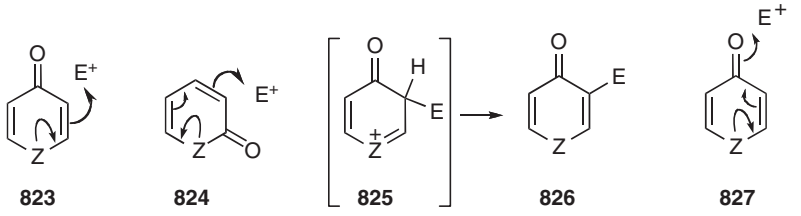


817 **818** **819** **820** **821** **822**

The reactivity pattern of these compounds considered briefly in Section 3.2.1.1.4 will now be summarized. The system of heteroatoms in these molecules can act either as an electron source or as an electron sink. This, together with the possibility of readily forming cationic **821** and anionic **822** species, increases considerably the possibilities for reaction in these compounds.

3.2.3.7.2.1 Reactions with electrophiles. These can attack ring carbon atoms to the ring heteroatom as shown in **823** and **824**; the intermediates (e.g., **825**) usually revert to type by proton loss (**825** → **826**). These electrophilic substitution reactions are considered in Section 3.2.1.4.

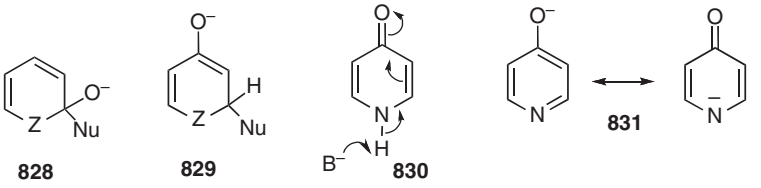
Electrophilic reagents can also attack the carbonyl oxygen atom (e.g., **827**); reactions of this type are considered in Section 3.2.3.7.3.



823 **824** **825** **826** **827**

3.2.3.7.2.2 Reactions with nucleophiles and bases. Four modes of reaction are possible:

1. Attack at a ring carbon atom, other than that of the carbonyl group, can be followed by proton addition, i.e., overall Michael-type reaction. Examples of this rather rare reaction type, which involves loss of aromaticity, are given in Section 3.2.1.6.8.
2. Nucleophilic reagents can attack the carbon atom of the carbonyl group (as in **828**). The reaction sequence proceeds by complete loss of the carbonyl oxygen and subsequent rearomatization. These reactions are considered in Section 3.2.3.7.4.
3. Nucleophiles can attack - and -pyrones and oxazinones at a carbon or to the ring oxygen to give initial adducts (**828, 829**) that undergo ring opening (e.g., with OH) which can be followed by reclosure in suitable cases (e.g., with NH_3, RNH_2). These reactions are considered in Section 3.2.1.6.
4. A hydrogen atom on the heterocyclic nitrogen atom of pyridones can be removed as a proton by basic reagents, e.g., **830**, the resulting mesomeric anion, e.g., **831**, reacting readily with electrophilic reagents at the nitrogen, and -carbon or oxygen atoms as discussed in Section 3.2.1.8.4.



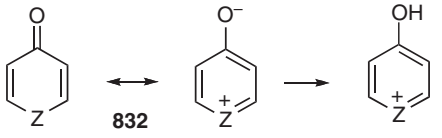
828 **829** **830** **831**

3.2.3.7.2.3 Reactions with radicals and electron-deficient species. These reactions are discussed in Section 3.2.1.9. Pyridones and pyrones are easily reduced catalytically.

3.2.3.7.2.4 Intra- and intermolecular reactions with cyclic transition states. Reactions of these types are discussed in Sections 3.2.1.2 and 3.2.1.10, respectively; due to the reduced aromaticity and polarizability, reactions of these types are of considerable importance.

3.2.3.7.3 Pyridones, pyrones, and azinones: Electrophilic attack at carbonyl oxygen

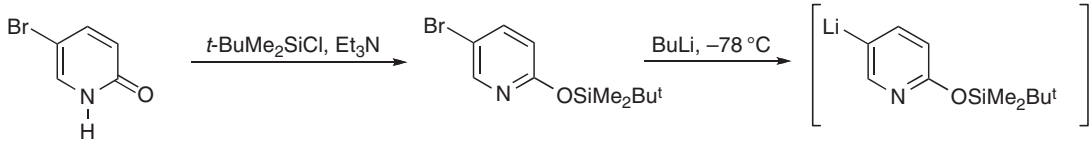
Pyridones and pyrones are weak bases: 4- and 2-pyridone have pK_a values of 3.3 and 0.8, respectively, for proton addition to the carbonyl oxygen atom, e.g., **832** **833** (Z = NH).



832 **833**

O-Alkylation of pyridones can be effected with diazomethane: 2-pyridone forms 2-methoxypyridine. Frequently, both O- and N-alkylation occur together: 4-pyridone with CH_2N_2 yields 4-methoxypyridine and 1-methyl-4-pyridone. Et_3O^+ and similar active alkylating agents also alkylate the carbonyl oxygen of pyridones and pyrones. 3-Hydroxypyridines are readily alkylated under a variety of conditions: for example, Mitsunobu reaction with alcohols occurs selectively at oxygen at room temperature <2003TL725>. 2-Ethynyl-3-pyridinols undergo Pd(0)-catalyzed coupling with iodoarenes, aryl triflates, or enol triflates, with concurrent nucleophilic attack of oxygen onto the arylated alkyne *in situ* to give 2-aryl furo[3,2-*b*]pyridines <2002SL453>.

Silylation is important for hydroxyl group protection during synthetic transformations (e.g., **834 835 836**). Treatment of a pyrimidinone with chlorotrimethylsilane in the presence of a tertiary base, or often more conveniently by heating the pyrimidinone with hexamethyldisilazane, gives the corresponding *O*-trimethylsilane. The silyl ethers of hydroxypyrimidines are very sensitive to hydrolysis, more so than alkyl silyl ethers. The stability increases with the size of the silyl substituents. The dimethylthexylsilyl group is very useful when a relatively resistant silyl group is desirable. 2-Pyridones can be selectively acylated at oxygen by treatment with acetyl chloride in acetone in the presence of potassium carbonate <2001JOC3646>.



834 **835** **836**

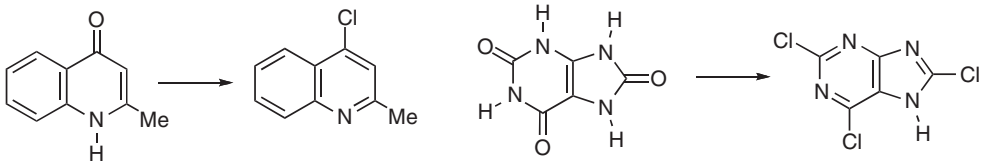
Alkylation of pyridones via the anion is discussed in Section 3.2.1.8.4.

3.2.3.7.4 Pyridones, pyrones, and azinones: Nucleophilic displacement of carbonyl oxygen

Nucleophilic attack on the carbon atom of the carbonyl group, in reactions that lead to substitution rather than to ring opening, is discussed in this section.

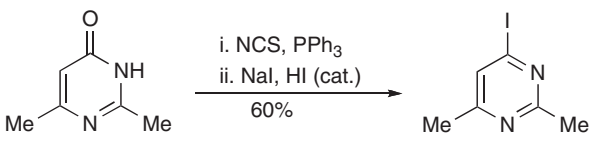
Pyridones and pyrones behave as cyclic amides and esters and, predictably, do not normally react with nucleophilic reagents such as HCN, RNH_2, $NaHSO_3$, NH_2OH, N_2H_4, PhN_2H_3, and $NH_2CON_2H_3$. Strong nucleophiles of the type that attack amides generally do react with pyridones and pyrones, as described in (1)(5) below. However, in all these reactions, the nucleophilic attack is preceded by electrophilic attack at the carbonyl oxygen and it is this that allows the subsequent nucleophilic attack.

1. Pyridones are converted into chloropyridines with $POCl_3$ (e.g., <2005JOC6204>), PCl_5, $SOCl_2$, or $COCl_2$ in DMF, e.g., 2-methyl-4-quinolinone **837** gives chloride **838**. Bromopyridines can be prepared using $POBr_3$ or PBr_5. Azinones react similarly; thus, pyrimidinones yield chloropyrimidines, and uric acid **839** yields 2,6,8-trichloropurine **840**. Alternatively, 2-chloropyridines and 2-bromopyridines and halopyrimidines can be obtained using triphenylphosphine and NCS or NBS <2001HCA1112>.



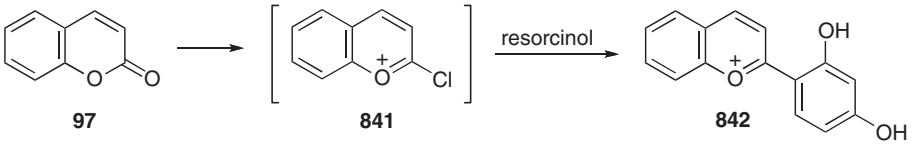
837 **838** **839** **840**

Iodopyrimidines can be obtained in one pot, via the chloro compound (**Scheme 92**) <2001HCA1112>.



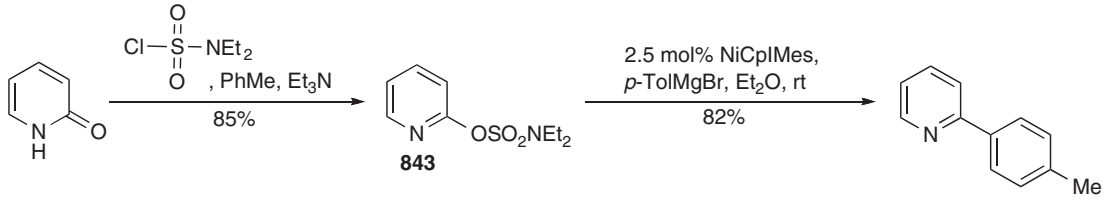
Scheme 92

Alkyl substituents on the pyridone nitrogen atom are usually lost in reactions of this type, but the quaternary salts from N-substituted acridones can be isolated. Pyrones (with PCl_5 or $POCl_3$) form highly reactive chloropyrylium ions which are used *in situ* as reaction intermediates, e.g., **97** **841** **842**.



97 **841** **842**

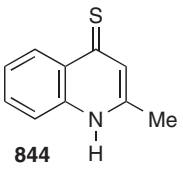
Similarly, *O*-sulfamates **843** can be obtained by treatment of 2- and 3-hydroxypyridines with *N,N*-diethylsulfamoyl chloride in the presence of triethylamine and these compounds undergo KumadaCorriu cross-coupling with aryl Grignard reagents to give biaryls (**Scheme 93**) <2005OL2519> and using Tf_2O in the presence of lutidine, 2- and 3-hydroxypyridines are converted to the corresponding triflates, which undergo, for example, Stille couplings <1996JOC4623> or SuzukiMiyaura couplings <2001JOC2654>.



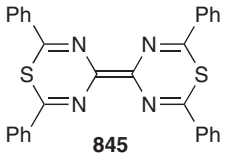
843

Scheme 93

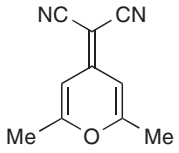
2. Phosphorus pentasulfide by heating in an inert solvent, in pyridine or another tertiary amine, converts carbonyl groups into thiocarbonyl groups, e.g., **844**. Pyridazinethiones, pyrimidinethiones, and triazinethiones are similarly prepared. Direct thiation of pyrimidinones can also be effected with Lawessons reagent (2,4-bis-*p*-methoxyphenyl-1,3,2,4-dithiadiphosphetane-2,4-disulfide) and has been found useful in the conversion of oxo to thioxo groups in nucleosides. 4(6)-Oxo substituents undergo thiation more readily than 2-oxo substituents, which allows for 4-monothiation in 2,4-pyrimidinediones. Treatment of 2,5-diphenyl-1,3,5-thiadiazin-4-one with Lawessons reagent yields (instead of the 4-thione) the 4,4-bis(1,3,5-thiadiazinylidene) **845** which, with iodine, forms an electrical conducting charge-transfer couple.



844

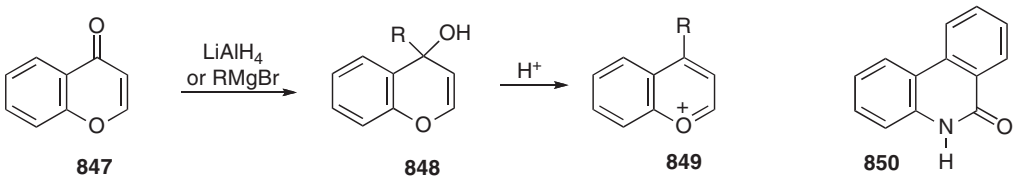


845



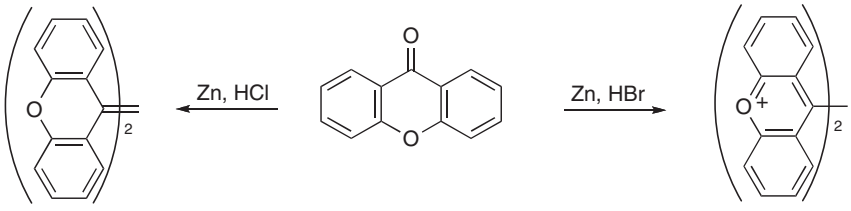
846

3. Pyrones react with active methylene compounds with Ac_2O as a catalyst, e.g., 2,6-dimethyl-4-pyrone and malononitrile give **846**.
4. Lithium aluminum hydride and Grignard reagents react with chromones, coumarins, and xanthones to give adducts, e.g., **847** **848** (R = alkyl, H) convertible into pyrylium salts (e.g., **849**). Some pyridones react analogously (e.g., **850** + $LiAlH_4$ phenanthridine **614**). $LiAlH_4$ will reduce a C(4)[C(6)] carbonyl group in pyrimidinones to CH_2 before reducing a C(2) carbonyl group.



847 **848** **849** **850**

5. Reduction of xanthones **851** in acid solution gives bimolecular reduction products (**852, 853**).



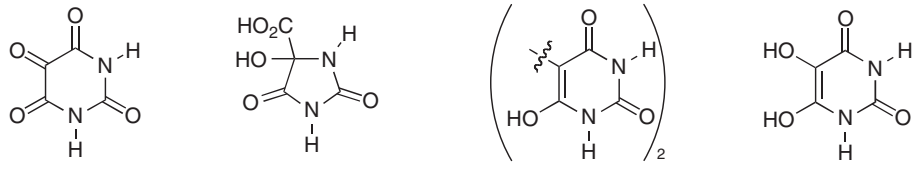
852 **851** **853**

6. Amines can be formed directly from tautomeric pyrimidinones by heating with an amide of phosphoric or phosphorous acid, but the vigorous reaction conditions limit the application of this method.

   Pyrimidinones are efficiently aminated in a one-pot procedure via silylation. The silylating agent converts the hydroxy groups into silyl ethers which are activated for nucleophilic substitution and react *in situ* with ammonia, primary, or secondary amines to form the corresponding amines. With Lewis acid catalysis, the reactions usually proceed in high yield if the trimethylsilanol leaving group is converted *in situ* into hexamethyldisiloxane by an excess of the silylating agent; for example, 2(1*H*)-pyrimidinone is aminated and uracil diaminated in amination reactions with HMDS. This is a sufficiently mild amination method that it can be applied nucleosides.

3.2.3.7.5 Heterocyclic quinones

Pyridine quinones are little known, but the diazine analogues of benzoquinones include alloxan **854** in which the carbonyl group in the 5-position shows ketonic properties. Alloxan undergoes the benzylic acid rearrangement (Na_2CO_3 alloxanic acid **855**) and can be reduced to a dimeric product (H_2S alloxantoin **856**) or to the hydroquinone analogue ($SnCl_2$ dialuric acid **857**).

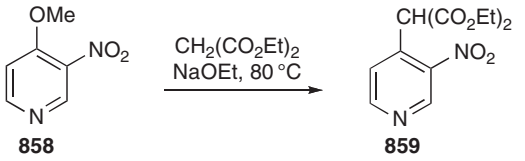


854 **855** **856** **857**

3.2.3.8 Other O-Linked Substituents

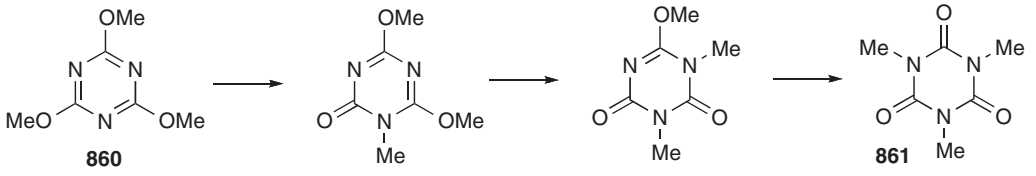
3.2.3.8.1 Alkoxy and aryloxy groups

2- and 4-Alkoxy groups in pyridines undergo nucleophilic replacement when some additional activation is present as is the case for 3-nitro-4-methoxypyridine (**858 859**). Such reactions are facilitated in the pyrimidine series for 2-, 4-, and 6-alkoxy groups that are and to *two* nitrogen atoms; they are often used to prepare aminopyrimidines. Alkyl cyanurates **860** behave as esters being hydrolyzed to cyanuric acid and the alcohol and readily undergoing transesterification. Nucleophilic displacement of alkoxy groups on cationic rings occurs exceedingly readily as illustrated for 4-methoxy-2,6-dimethylpyrylium cation **862 863** (Nu = OEt, NMe_2).



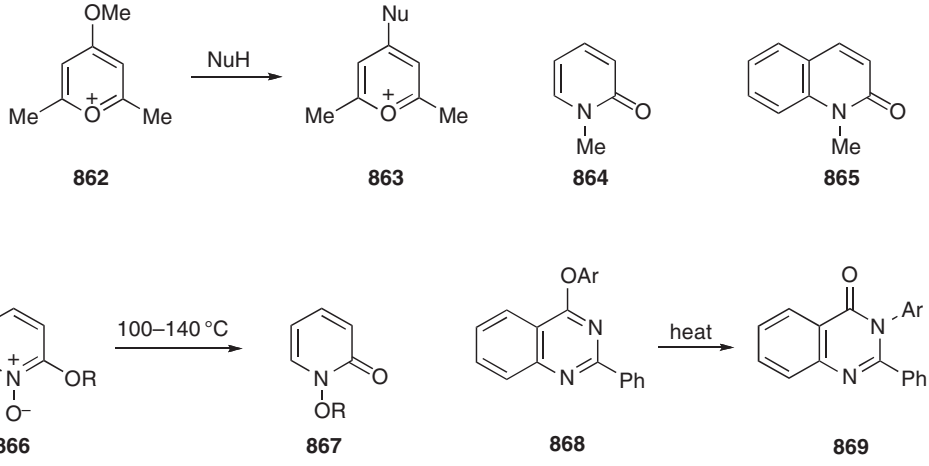
858 859

Pyridines and benzopyridines with alkoxy groups in the - or -position rearrange to *N*-alkyl-2-pyridones and *N*-alkyl-4-pyridones on heating. 2-Methoxypyridine gives **864** at 300°C, whereas 2-methoxyquinoline forms **865** at 100°C. One molecule of alkoxy compound acts as an alkylating agent for another in these intermolecular reactions (see also Section 3.2.1.2.2). Similarly, 2-alkoxypyridine *N*-oxides rearrange thermally to *N*-alkoxy-2-pyridones (**866** **867**). The thermal rearrangement of alkoxypyrimidines to *N*-alkylpyrimidinones is known as the HilbertJohnson reaction. Alkyl cyanurates **860** on heating isomerize to isocyanurates **861** in a stepwise manner (**Scheme 94**).



860 861

Scheme 94

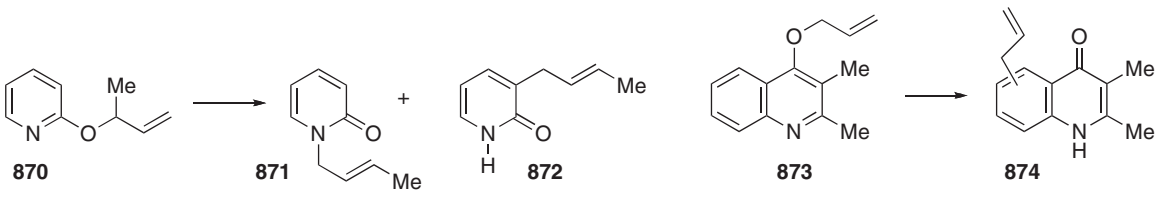


862 863 864 865

866 867 868 869

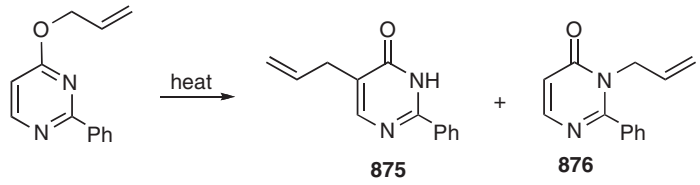
Aryloxy groups are more resistant to rearrangement (unless nitro-activation of the aryl group is present); however, under forcing conditions this can sometimes be achieved (**868** **869**).

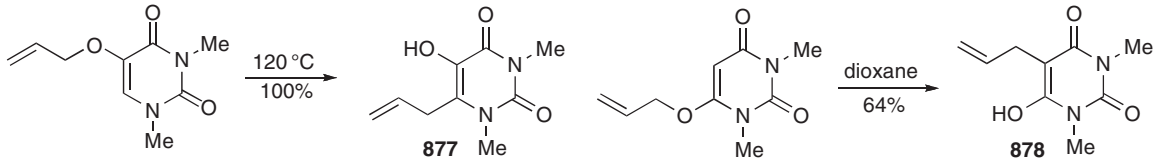
Allyl ethers undergo intramolecular rearrangement from oxygen to nitrogen or ring carbon. Thus, 2-(1-methylallyloxy)pyridine **870** gives approximately equal amounts of 1- and 3-crotyl-2-pyridone (**871** and **872**, respectively). 4-Allyloxyquinolines rearrange to 3-allyl-4-quinolones. If the 3-position is occupied by a methyl group (cf. **873**), the allyl group rearranges to the benzene ring to give a product **874** of uncertain orientation.



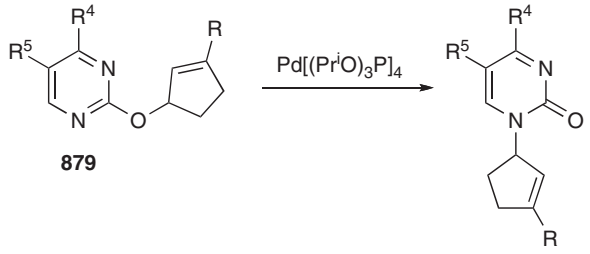
870 871 872 873 874

Thermally promoted Claisen rearrangement of simple allyloxypyrimidines is difficult to achieve. 4-Allyloxypyrimidines can be rearranged at elevated temperatures; a mixture of the C(5)- and the N(3)-allyl derivatives (**875** and **876**, respectively) is formed from 4-allyloxy-2-phenylpyrimidine on heating in aniline. 4-Allyloxyquinazoline is rearranged at 190–200 °C to form 3-allylquinazolin-4(3*H*)-one. Rearrangement of 5-allyloxy-1,3-dimethyluracil proceeds with quantitative conversion to the 6-allyl derivative and 6-allyloxy-1,3-dimethyluracil converts to the 5-allyl derivatives **878**.



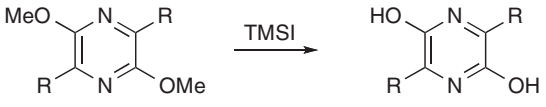


2-Allyloxypyrimidine largely resists rearrangement even at 200 °C. However, allylic cyclopentenyl 2-pyrimidinyl ethers **879** can be rearranged on catalysis by tetrakis(tri-isopropyl phosphite)palladium (**Scheme 95**).



Scheme 95

2- and 4-Alkoxypyridines are readily dealkylated under a variety of acidic conditions, for example, 2-methoxypyridines give the 2-pyridones on heating with 12 N HCl <2005JME1948>. Alternatively, the O-demethylation of methoxypyridines can also be achieved in high yield using TMSI in chloroform <2003EJO4445> and comparable ether cleavage can be achieved in methoxypyrazines, whereby 3,6-disubstituted 2,5-dimethoxypyrazines are converted into the corresponding 2,5-dihydroxypyrazines (or tautomers thereof) (**Scheme 96**). 3-Alkoxypyridines require relatively forcing conditions for O-dealkylation, typically a strong Brønsted or Lewis acids at elevated temperatures <2004T11751>.



Scheme 96

3.2.3.8.2 Acyloxy groups

2- and 4-Acyloxypyridines are so easily hydrolyzed that they are difficult to isolate; the reactions of 3-acyloxypyridines parallel those of phenyl acetate.

3.2.3.9 S-Linked Substituents

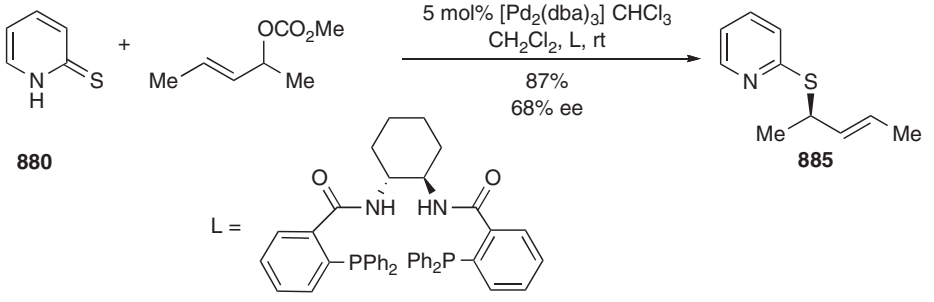
3.2.3.9.1 Mercaptothione tautomerism

Pyridines and azines with - or -mercapto groups exist predominantly in the pyridinethione forms, e.g., as **880** rather than in the mercapto form **881**. This behavior is analogous to that of the corresponding hydroxypyridines (Section 3.2.3.7); see also Section 2.2.5.1.

3.2.3.9.2 Thiones

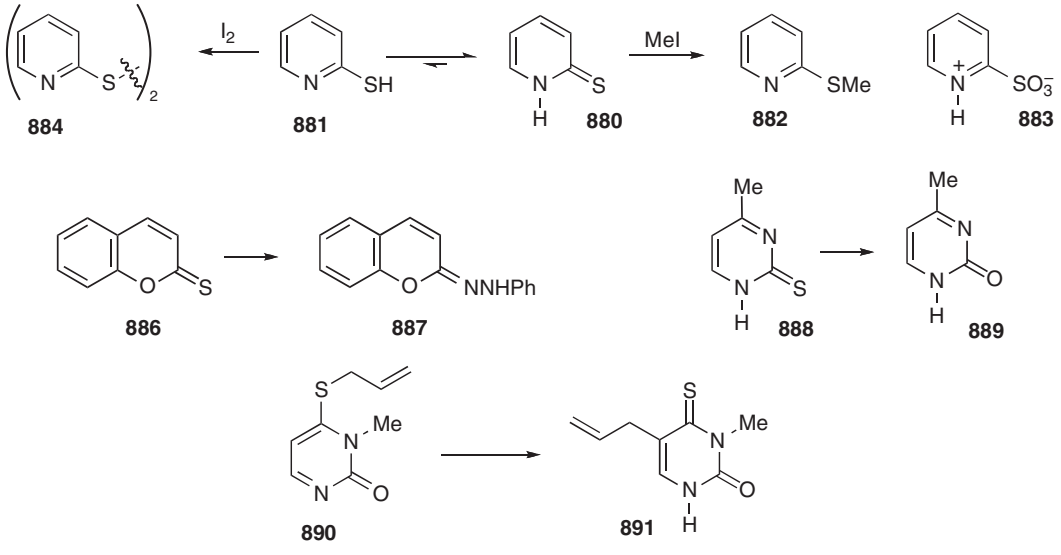
Pyridine-, pyran-, and azinethiones behave as cyclic thioamides or thioesters and show their typical reactions. Thus, they react with electrophiles at the sulfur atom [as exemplified in (1)(4)] and with nucleophiles including the typical ketonic reagents at the thione carbon atom [as exemplified in (6)(8)].

1. Alkyl halides give alkylthiopyridines or -azines, e.g., **880** **882**, or in the absence of an NH group, alkylthio pyridinium rings. 2-Pyridinethiones undergo palladium(0)-catalyzed enantioselective S-allylation with cyclic and acyclic allylcarbonates to give allylic sulfides, for example, **885**, with moderate enantiomeric selectivity (**Scheme 97**) <2003CEJ4202>.



Scheme 97

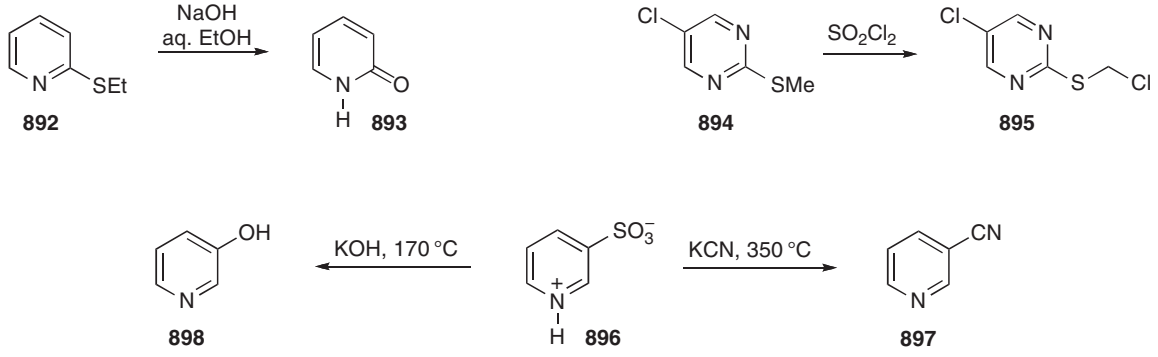
2. Iodine oxidation, or cleanly by reaction with sulfuryl chloride in dichloromethane generating only SO_2 and HCl as by-products, forms disulfides (**880** **884**).
3. Oxidation with H_2O_2 forms the sulfinic acid that usually spontaneously loses SO_2. Mercapto groups in any position of the pyrimidine ring can be replaced by hydrogen in this way. Oxidation at low temperature using $NaOCl/CH_2Cl_2$/aq. HCl produces the sulfonyl chloride; the sulfonyl fluoride can be obtained in the presence of KHF_2 and tetrabutylammonium sulfate <2006JOC1080>.
4. Strong oxidation forms a sulfonic acid (**880** **883**).
5. S-Amination is possible in some situations using an oxaziridine or hydroxylamine-*O*-sulfonic acid.
6. Phenylhydrazine forms **887** with thiocoumarin **886**.
7. PCl_5 gives chloro compounds, e.g., chloropyrimidines from pyrimidinethiones (e.g., **888**).
8. Acidic hydrolysis converts compounds such as pyrimidinethiones into pyrimidinones (**888** **889**).



9. 4-Allylthio-3-methyl-2(3*H*)-pyrimidinone **890** yields the 5-allyl-4-thiouracil **891** quantitatively on heating, although the 1-methyl isomer resists rearrangement.

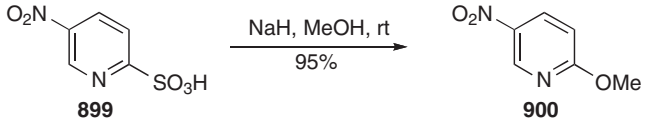
3.2.3.9.3 Alkylthio, alkylsulfinyl, and alkylsulfonyl groups

The SR substituent can be displaced by amines and hydroxide (**892 893**) and replaced with hydrogen by dissolving metals, e.g., Zn/H^+. Oxidation gives the corresponding sulfoxide and sulfone, which undergo nucleophilic displacement more easily. Thus, 2- and 4-(phenylsulfonyl)pyrimidines give the corresponding replacement products with various nitrogen and oxygen nucleophiles. Direct C-halogenation of the SMe group in methylthioazines is possible, e.g., **894 895**.



3.2.3.9.4 Sulfonic acid groups

Pyridinesulfonic acids exist as zwitterions (e.g., **896**). As for benzenesulfonic acid, the sulfonic acid group can be replaced by hydroxy or cyano groups under vigorous conditions, e.g., **896 897, 898**, or under milder conditions when activated by conjugation, as in the conversion of **899** into **900** <2003OBC2710, 2004OBC2671>.



Sulfonamides can be directly synthesized from sulfonic acid salts by treatment with triphenylphosphine ditriflate followed by an amine <2004JA1024>.

3.2.3.10 Halogen Atoms

3.2.3.10.1 Pattern of reactivity

Halogen atoms attached to ring carbon of heteroaromatic six-membered rings show reactions typical of both aryl halides and their own characteristic reactions.

Just as in aryl halides, the halogen can be replaced by hydrogen and by a metal, or be involved in transition metal-catalyzed processes (covered in Section 3.2.3.11.2). Three of the mechanisms of such nucleophilic substitutions are familiar from benzene chemistry: via arynes, $S_{RN}1$ processes, and Pd(0)-catalyzed sequences. However, of the two further mechanisms of nucleophilic replacement, the ANRORC (*A*ddition of *N*ucleophile, *R*ing *O*pening, *R*ing *C*losure) is unique to heterocycles, and S_{AE} reactions occur only with strongly activated benzenoid systems.

3.2.3.10.2 Replacement of halogen by hydrogen or a metal (including transmetallation) or by coupling

Heterocyclic nuclear halogen atoms undergo the following reactions which are typical of aryl halides:

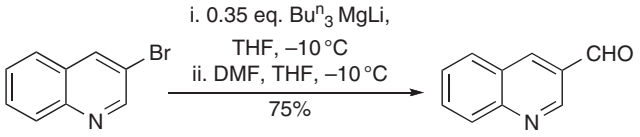
1. They can be replaced with hydrogen atoms by catalytic (Pd, Ni, etc.) or chemical reduction (HI or Zn/H_2SO_4). Reductive removal of halogen atoms may be accompanied by reduction of the ring in compounds of relatively low aromaticity (e.g., quinazolines). Hydrogenolysis of all isomeric halo pyridines is relatively easy, catalytically, a 4-halide being slightly the most easily removed and a 3-halide the least. Palladium catalysis can facilitate these conversions; thus,

high yields are obtained using 5 mol% $Pd(OAc)_2$ in the presence of polymethylhydrosiloxane (PMHS) and potassium fluoride in THF <2002TL8823>.

2. They can be converted into Grignard reagents, which show the normal reactions. The most common method for the generation of pyridylmagnesium halides is by metalhalogen exchange of bromo- or iodopyridines with isopropylmagnesium chloride in THF at room temperature <1999TL4339>. Dibromopyridines undergo a single exchange, with bromine substituents at a -position being the most readily replaced <2005AGE3133>. However, 5-bromo-2-iodopyridine is converted into 5-bromopyridin-2-ylmagnesium chloride on treatment with Pr^iMgCl in THF at 0 °C, demonstrating that the higher reactivity of iodides than bromides can overcome the normal positional selectivity <2004OL4905>.

   The brominemagnesium exchange of 2-, 3-, and 4-bromoquinolines can be achieved using the ate complex Bu_3MgLi in THF at 10 °C to give lithium tri(quinolyl)magnesates (**Scheme 98**) <2003T8629>, thus avoiding the increased risk of Grignard addition to the hetero ring in bicyclic systems.

   In pyridazine chemistry, *n*-Bu_3MgLi is also a valuable metal exchange reagent since, in comparison to *n*-BuLi, a low



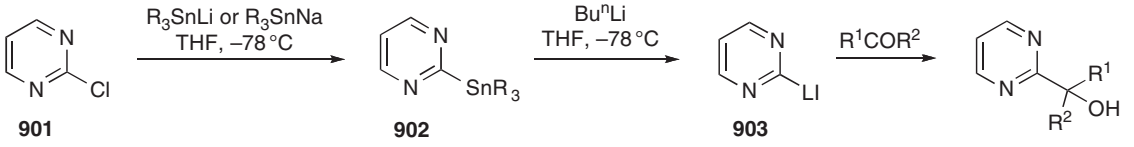
Scheme 98

temperature is not required <2006SL1586>.

   Halo 2-picolines are often poor substrates for metalhalogen exchange procedure using isopropylmagnesium chloride owing to competing deprotonation of the methyl group. This limitation can be overcome using lithium dibutylisopropylmagnesate; thus, 5-bromo-2-picoline undergoes smooth exchange with this reagent at 10 °C <2006TL1877>.

   Pyrimidinyl Grignard reagents are also obtained via exchange with Pr^iMgCl or Pr^iMgBr <2003AGE4302>. The addition of one equivalent of LiCl considerably accelerates brominemagnesium exchange reactions <2004AGE3333>; thus, *i*-PrMgCl.LiCl is able to produce pyrimidinyl magnesium species within 15 min at room temperature <2006OL3737>.

3. Pyridyllithium reagents can be formed by halogenmetal exchange using *n*-butyllithium at low temperature (to avoid nucleophilic addition to the ring). Attempts to lithiate 2-chloro-, 2-bromo-, or 2-iodo-pyrimidine meet with little success: addition of lithiated species to electrophilic pyrimidine positions is a major competing process. 2-Lithiopyrimidine **903**, however, is formed selectively by metal exchange, i.e., 2-stannylpyrimidines **902** react with *n*-butyllithium by metal metal exchange to form the organolithium **903**.

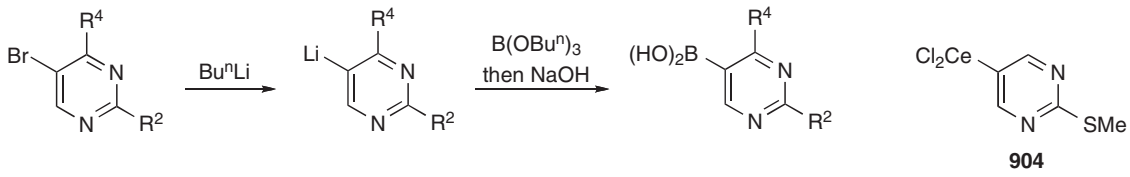


   Metalhalogen exchange of 2-, 3-, and 4-chloropyridines, and 2-chloroquinoline can be effected by naphthalene-catalyzed reductive lithiation using lithium powder in the presence of catalytic quantities of naphthalene in THF at 78 °C <2000T4043>.

4. Organotin reagents can be prepared: 2-chloropyrimidine **901**, for example, is stannylated by reaction with tributyl-, trimethyl-, or triphenylstannyllithium giving, e.g., **902**. Stannanes can be obtained in the opposite sense too: 4-iodo-2-methylthiopyrimidine can be stannylated by way of lithiation followed by quenching with a stannyl chloride.

5. Organometallics by transmetallation: pyridylzinc chlorides can be accessed either by transmetallation of a pyridyllithium with anhydrous zinc chloride <2001EJO4207> or by direct insertion of zinc into carbonhalogen bonds using Rieke zinc in THF under reflux <2003SL852>.

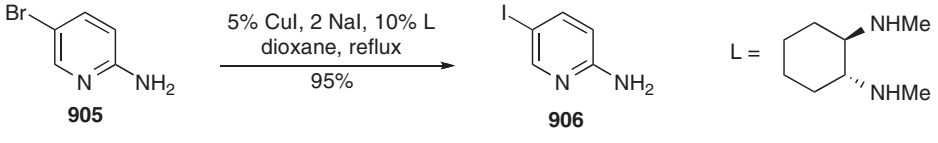
   Boronic acids and boronate esters are usually prepared from lithium compounds, for example, from pyrimidines lithiated at the 5-position (**Scheme 99**). Boronates can also be obtained conveniently by Pd(0)-catalyzed couplings with, for example, pinacol diboron.



Scheme 99

Organocerium derivatives possess low basicity. 5-Pyrimidylcerium dichlorides (e.g., **904**) are available via low-temperature metalmetal exchange using cerium trichloride and 5-lithiated pyrimidines. The 5-pyrimidinylcerium dichloride is superior to its 5-lithio analogue in addition reactions to aldehydes and ketones, especially in reactions when the carbonyl compound is enolizable.

6. Ullmann reactions succeed; e.g., 2-bromopyridine yields 2,2-bipyridyl (with Cu).
7. Interconversion of halides. Bromides can be converted into iodides using a catalyst system comprising CuI and a 1,2- or 1,3-diamine ligand. In this manner, 5-bromo-2-aminopyridine **905** is converted into the iodopyridine **906** <2002JA14844>. Chloropyridines are converted into their fluoro analogues at room temperature using anhydrous TBAF in DMSO <2006AGE2720> or KF in sulfolane <2000BML411>. 2-Chloropyridines are readily converted into the related 2-iodo- or 2-bromopyridine using iodotrimethylsilane or bromotrimethylsilane via the intermediacy of an *N*-silylpyridinium salt that activates the ring to halide attack <2002EJO4181, 2003EJO1559>.

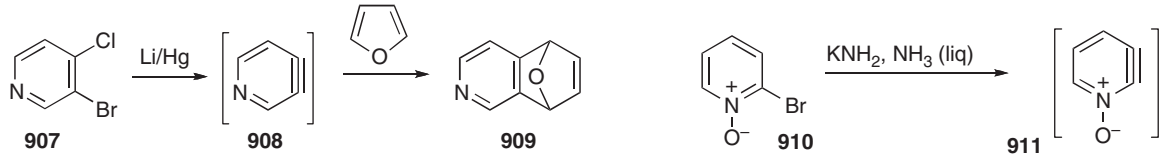


3.2.3.10.3 Reactions via hetarynes

Strong bases such as $NaNH_2$ convert unactivated aryl halides into benzyne intermediates which react rapidly with nucleophiles to form the products of an apparent nucleophilic substitution.

Thus, reaction of 3-chloro-, 3-bromo-, and 3-iodopyridine with potassium amide in liquid ammonia gives in each case the same mixture of 3- and 4-aminopyridines, showing the intermediacy of 3,4-pyridyne. Under these conditions the corresponding 4-halopyridines react entirely through 3,4-pyridyne **908**.

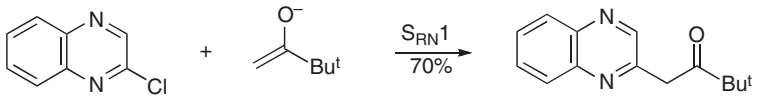
Pyridynes are also formed from *ortho*-dihalides and alkali metals. Thus, reaction of 3-bromo-4-chloropyridine **907** with lithium amalgam and furan gives product **909** by trapping of the 3,4-pyridyne **908**. Although 2,3-pyridyne is not formed from 3-halopyridines, because of the weaker acidity of the 2-hydrogen atom as compared to the 4-hydrogen atom (see Section 3.2.1.8.2), it can be trapped by furan in low yield from the reaction of 3-bromo-2-chloropyridine with lithium amalgam.



2,3-Pyridyne *N*-oxide **911** is obtained by the action of potassium amide on 2-bromopyridine *N*-oxide **910**, as shown by the formation of a mixture of the 2- and 3-aminopyridine oxides. Reaction of 5-bromopyrimidine with sodium amide in liquid ammonia involves 4,5-pyrimidyne as an intermediate.

3.2.3.10.4 The S_{RN} mechanistic pathway

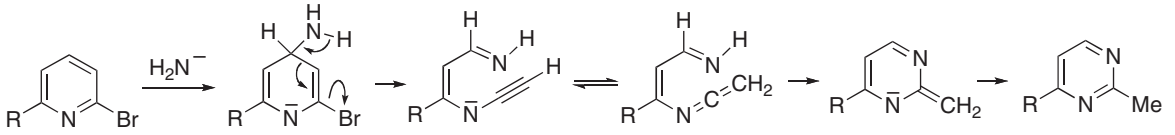
Unactivated aryl halides will undergo nucleophilic displacement via electron transfer in the initial step: the so-called $S_{RN}1$ mechanism. It is now clear that in the case of heteroaromatic compounds, nucleophilic substitution by the S_{RN} process often competes with the additionelimination pathway. S_{RN} reactions are radical chain processes and are usually photochemically promoted. For example, ketone **913** is formed by the $S_{RN}1$ pathway from 2-chloroquinoxaline **912**.



912 **913**

3.2.3.10.5 ANRORC reactions

ANRORC processes involve the initial addition of a nucleophile to a ring carbon atom *not* carrying the halogen followed by electrocyclic ring opening. The sequence, exemplified in **Scheme 100**, is similar to that of the Dimroth rearrangement (Section 3.2.3.5.4.3), but in the ANRORC reaction the initial ring opening involves elimination of the halogen atom. The ring formed can be the same or different to the original.



Scheme 100

Further examples of ANRORC reactions are the conversions of 2-bromoquinoline into quinazoline **914** and of pyrimidine **915** into triazine **916**.

914 **915** **916**

3.2.3.10.6 Nucleophilic displacement by classical S_{AE} mechanism

3.2.3.10.6.1 Dichotomy of mechanisms. Nucleophilic displacement of an - or -halogen atom by the classical S_{AE} mechanism of nucleophilic displacement via a Meisenheimer intermediate (e.g., **917**) is facilitated by mesomeric stabilization of the transition state. However, the mechanistic balance is fine: whereas 4-bromopyridine *N*-oxide reacts with potassium amide by the AE mechanism, the 2-bromo analogue prefers the EA route. Again, nucleophilic displacement in chloropyrazines can involve the ANRORC mechanism.

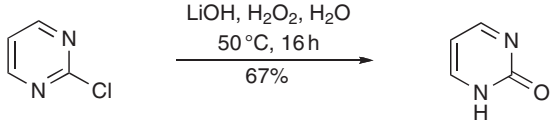
Some reactions of - and -halopyridines can be acid catalyzed, i.e., ions of type **918** are formed and react better with nucleophilic reagents (e.g., 2-chloro-5-nitropyridine + $PhNH_2$ 2-anilino-5-nitropyridine, catalyzed by H_2O-HCl).

917 **918**

3.2.3.10.6.2 Reactivity dependence on halogen and nucleophile. The relative reactivities with respect to nucleophilic S_{AE} displacement increase in the order Cl ≤ Br ≤ I ≤ F. For example, 2-fluoropyridines undergo amination in good yield on treatment with lithium aminoborohydride reagents in THF at 65°C <2003OL3867> and 2-fluoropyridine also reacts with a range of primary and secondary lithium amides in THF at room temperature to give the 2-aminopyridines in moderate to high yields <2004TL6417>.

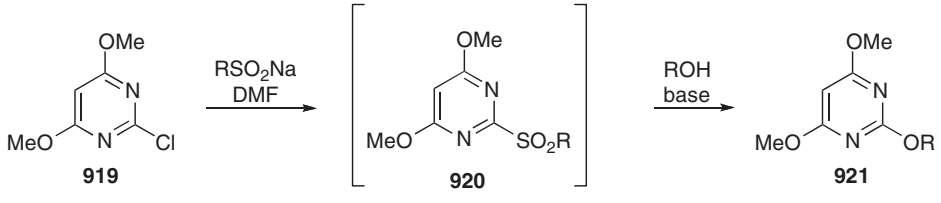
The relative reactivities of nucleophiles are illustrated by the reactions of 2-bromopyridine: replacement by the following groups occurs under the conditions given (* indicates that the product spontaneously tautomerizes):

a. Hydroxy*, by NaOHH_2O, 150°C. Reactivity can be greatly increased by including hydrogen peroxide (a much better nucleophile), as shown for 2-chloropyrimidine (**Scheme 101**) <2006TL4249>.



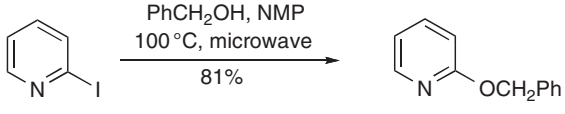
Scheme 101

b. Alkoxy, e.g., methoxy by NaOMeMeOH, 65°C.
c. Phenoxy, PhONaEtOH.
d. Mercapto*, KSHpropylene glycol.
e. Methylmercapto, NaSMeMeOH, 65°C.
f. Amino (NH_3H_2O, 200°C), dimethylamino ($NHMe_2$, 150°C), or hydrazino (N_2H_4, 100°C).
g. Cyano, by distillation with CuCN.
h. Di(ethoxycarbonyl)methyl by the sodio derivative of malonic ester.
i. Isothiouronium, $(NH_2)_2$CSEtOH, reflux; the product is converted by alkali into urea and pyridine-2-thione.
j. Sulfonic acid, $NaHSO_3$. A sulfonyl substituent can be introduced by nucleophilic displacement with sulfinates, and this has been used catalytically to greatly enhance the rate of substitution of halides, for example, of 2-chloro-4,6-dimethoxypyrimidine **919** with alkoxy and aryloxy nucleophiles giving **921** via **920** <2000T4739>.



k. *Halogen interchange*. Treatment of 2,6-dichloropyridine with iodide ion in a high concentration gives 2,6-diiodopyridine. Nucleophilic fluorination via chlorinefluorine exchange also yields fluoropyridines (see also Section 3.2.3.10.2.7).

A wide range of heteroatom-based nucleophiles, and cyanide, react with 2-, 3-, and 4-halopyridines in minutes at elevated temperature in polar solvents such as HMPA, DMSO, or *N*-methylpyrrolidine (NMP) under microwave irradiation (e.g., **Scheme 102**) <2002T4931>. Aminations of halopyridines are likewise greatly accelerated in this way, e.g., <2004TL757>.

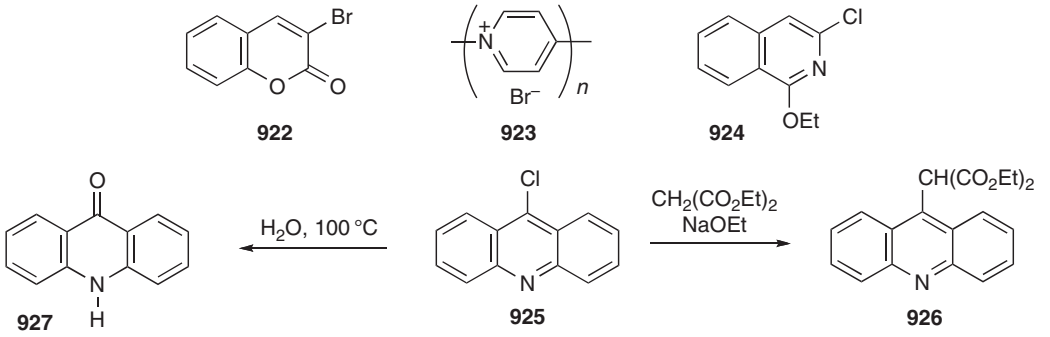


Scheme 102

Nucleophilic displacement with thiolate anions occurs under relatively mild conditions when the halogen is activated by the presence of an *ortho* or *para* electron-withdrawing group. For instance, 2-chloro-3-nitropyridine reacts with 1-propanethiol in the presence of NaOH in EtOH at room temperature to give the alkylthiopyridine in 94% yield <2004JOC2551>. 2-Chloropyridine is efficiently converted to the 2-pyridinethiol using thiourea in aq. HCl <1997BML2223>.

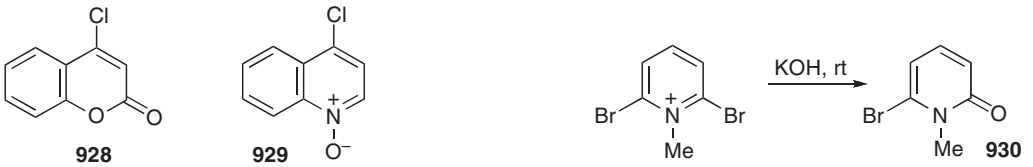
3.2.3.10.6.3 Reactivity dependence on nature of heterocyclic rings. The reactivity of halogen atoms in azines toward S_{AE} displacement is in line with the sequence discussed in Section 3.2.3.1.1.

-Halogen atoms in pyrones (e.g., **922**) and pyridones are unreactive toward S_{AE} nucleophilic displacement. -Halopyridines are less reactive than the - and -isomers but distinctly more reactive than unactivated benzenoid halides. Thus, a bromine atom in the 3-position of pyridine or quinoline can be replaced only under very vigorous, classical conditions by methoxy (NaOMeMeOH, 150°C), amino ($NH_3H_2OCuSO_4$, 160°C), or cyano (CuCN, 165°C). 5-Halogens in pyrimidines are also relatively unreactive.



The reactions of the 4-halopyridines parallel those of the corresponding 2-isomers, with the exception that 4-halopyridines polymerize much more readily (e.g., to **923**) because the pyridine nitrogen atom is not sterically hindered and is more nucleophilic (cf. Section 3.2.1.3.4). A halogen at the isoquinoline 1-position is more reactive than one at the 3-position; thus, mild treatment of 1,3-dichloroisoquinoline with sodium ethoxide gives **924**. Halogens at the 9-position of acridine are more reactive, e.g., **925 926, 927**.

-and -Halogen atoms on benzopyridines, -pyridones, -pyrones (e.g., **928**), and -pyridine *N*-oxides (e.g., **929**) are about as reactive as those in the corresponding monocyclic compounds. A 2-chlorine atom in chromone is readily displaced by nucleophiles; a 3-halogen atom is less reactive, but can still undergo nucleophilic displacement.



Reactivity increases in the diazines as compared with pyridines. 3-Chloropyridazine and 2-chloropyrazine, for example, undergo the usual nucleophilic replacements (cf. Section 3.2.3.10.6.2) rather more readily than does 2-chloropyridine. 2-, 4-, and 6-Halogen atoms in pyrimidines are easily displaced. The reactivity of halogens in pyridazine 1-oxides toward nucleophilic substitution is in the sequence $5 > 3 > 6 > 4$.

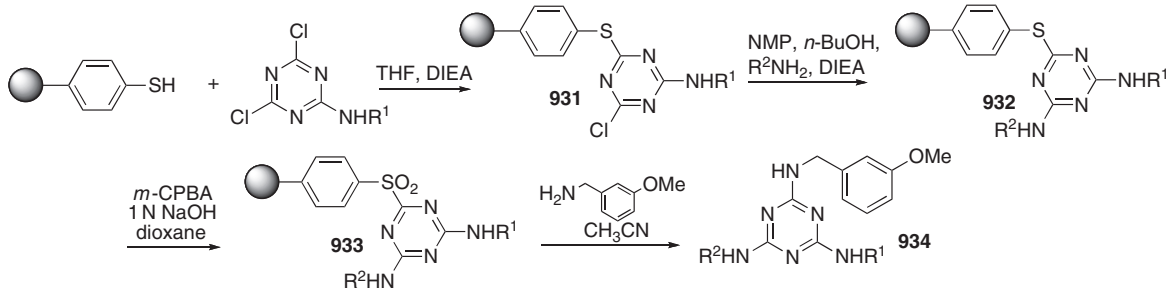
Amides aminate 2-fluoropyrazine smoothly at 40–50°C in excellent yield. The amination of 2-chloropyrazine 1-oxide needs a higher temperature (100–110°C).

Halogen atoms at the - and -positions of cationic nuclei are very reactive, as illustrated by the hydrolysis to 2,6-dibromo-l-methylpyridinium ion at 20°C **930**. Halogen groups in the - or -positions of thiopyrylium cations are also highly reactive.

3.2.3.10.6.4 Reactivity in polyhalo compounds. Regioselective substitutions in di- and trihalogenopyrimidines can be achieved in many cases. Chloro, bromo, and iodo substituents undergo aminolysis at approximately the same rates, whereas a fluoro substituent reacts 60200 times faster. 4(6)-Halo substituents react up to 10 times faster than 2-halo substituents. Electron-donating substituents (e.g., Me, Ph, OMe, NMe_2) decrease the rate of aminolysis, whereas electron-withdrawing substituents (Cl, CF_3, NO_2) have the opposite effect.

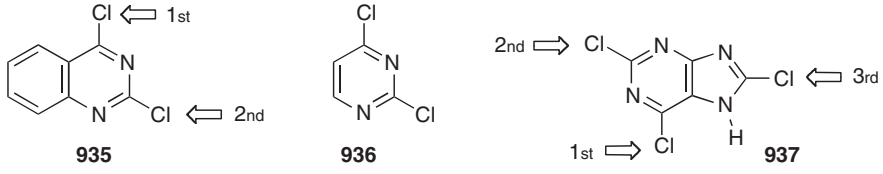
Hence, in polyhalo compounds such as 2,4,6-trichloropyrimidine, each successive chlorine atom is replaced more slowly than the last because the groups introduced (e.g., NH_2) partially cancel the activating effect of the annular

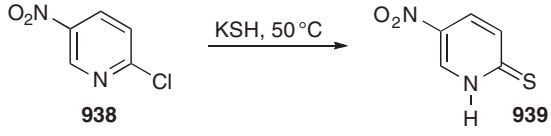
nitrogen atoms. Each of the halogens of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) can be replaced successively, the first displacement being the easiest. An example (**Scheme 103**) uses a PS-thiophenol resin to anchor a triazine in which the first displacement has taken place giving **931**. The second chlorine site can be aminated at 120°C in the presence of *N*,*N*-diisopropylethylamine to yield **932**. Finally, oxidation by *m*-CPBA converts the sulfide into sulfone **933**, then an amine can be used to displace the activated sulfone from solid support and release the trisubstituted triazines **934** <2004JCO474>.



Scheme 103

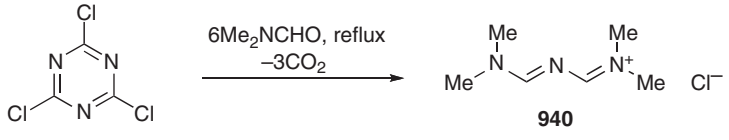
A halogen atom at the 4-position of quinazoline is more reactive than one at the 2-position because of partial double-bond fixation. Thus, in 2,4-dichloroquinazoline **935**, replacement occurs almost exclusively in the 4-position, whereas 2,4-dichloropyrimidine **936** yields approximately equal amounts of the 2- and 4-mono-replacement products. Similarly, in 2,6,8-trichloropurine **937** the order of replacement of the halogen atoms is 6, 2, and 8, successively. Only the 4-chlorine atom in 3,4-dichlorocinnoline is readily replaced. In tetrachloropteridine, the 6- and 7-chlorine atoms are the most reactive followed by the 2-chlorine.





Just as in benzene chemistry, all types of halogen atom are activated toward nucleophilic displacement by the presence of other electron-withdrawing substituents. This is illustrated by the conversion of 2-chloro-5-nitropyridine **938** to the 2-hydrazine derivative (N_2H_4, 20°C) or the 2-thione **939** under relatively mild conditions.

Nitrogen nucleophiles can ring open azine rings under some conditions. Thus, cyanuryl chloride is ring cleaved with DMF to form [3-(dimethylamino)-2-azaprop-2-en-1-ylidene]dimethyl ammonium chloride (Golds reagent) **940**, a general -dimethylaminomethylenating agent, in 95% yield <1986OS(64)85>.



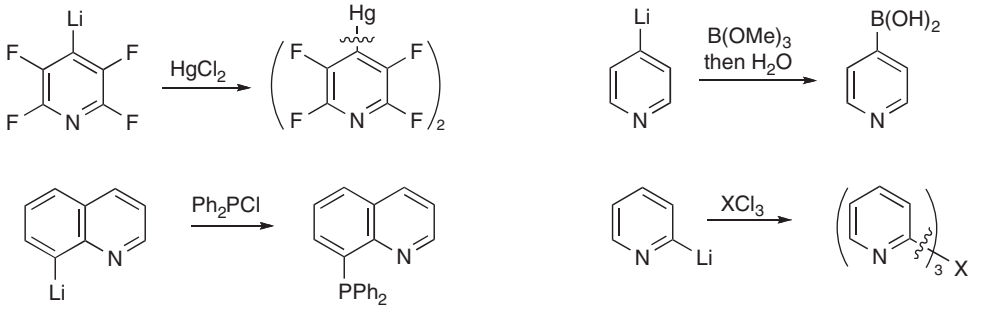
3.2.3.10.6.5 Catalyzed displacements. The very important use of transition metals to catalyze displacements of halides is covered in Section 3.2.3.11.2 displacements with nucleophiles which were previously difficult or impossible can now be achieved with ease using such catalysis.

3.2.3.11 Metals and Metalloids

Azine Grignard reagents and lithium compounds in which the metal atom is attached directly to the ring are considered partly under the corresponding halogen compounds (Section 3.2.3.10) because they are sometimes prepared from the halides by metalhalogen exchange. However, direct lithiation (or even magnesiation) (Section 3.2.1.8) can also be used and the reactivity of the organometallic is the same, by whatever method it is generated, and thus some reactions are considered in this section. Lithium derivatives of azine *N*-oxides are likewise considered in Section 3.2.1.8.1 because they are generally prepared by direct lithiation of the *N*-oxide. Organometallic derivatives of azines in which the metal is separated from the ring by one carbon atom are considered under the corresponding alkyl compound (Section 3.2.3.3).

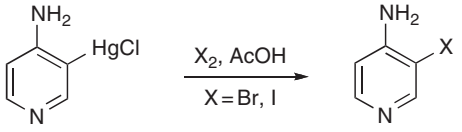
3.2.3.11.1 Organometallic nucleophiles

These organometallic nucleophiles show most of the typical reactions with carbon electrophiles associated with benzenoid Grignard reagents and aryllithiums They also allow the introduction of other metals, and nonmetals, on to the ring, such as mercury, boron, phosphorus, tin, and arsenic (**Scheme 104**) (see also Section 3.2.3.10.2.5), some of which are of great use as partners in transition metal-catalyzed processes.



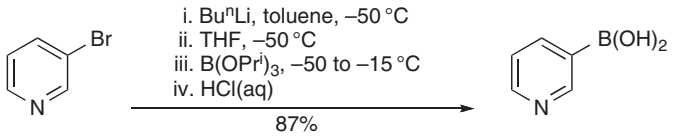
Scheme 104

Organomercury derivatives can be converted into bromides and iodides by electrophilic *ipso* displacement (**Scheme 105**).



Scheme 105

Lithiumhalogen exchange in THF by inverse addition and at very low temperature minimizes competing deprotonation. This process can be performed at higher temperature using toluene as solvent making large-scale preparations more convenient For instance, addition of 3-bromopyridine to *n*-BuLi in toluene at 50°C gives the lithiopyridine as a yellow solid that dissolves on addition of THF. Quenching of this mixture with triisopropyl borate gives the boronic acid in 87% yield (**Scheme 106**) <2002TL4285>. Grignard reagents can also be used to prepare pyridylboronic acids <2005AGE3133>. Dibromohydroxypyridines can be monolithiated in a regioselective manner using the normal mode of addition but with two equivalents of *n*-BuLi in THF at 90°C <2003SL1678>.



Scheme 106

4-Pyridylithium reacts with gaseous dinitrogen tetroxide in frozen THF to give 4-nitropyridine in 57% yield <1997JA1476>.

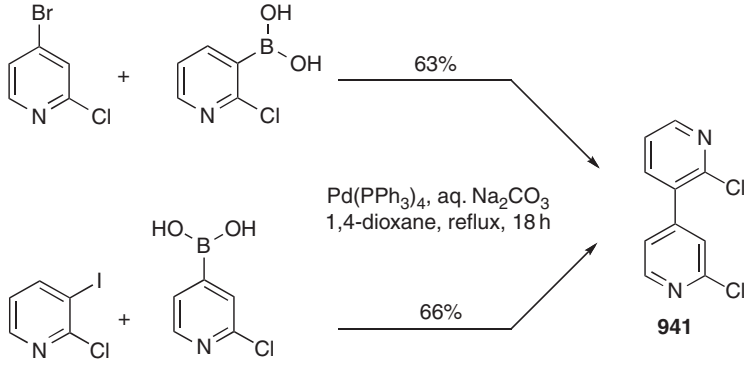
3.2.3.11.2 Transition metal-catalyzed processes

Palladium-catalyzed processes are perhaps the most important developments in heterocyclic chemistry since CHEC-II and certainly since the original CHEC. The intermediates are never isolated, but, nonetheless, are essential to the transformations. Oxidative insertions of palladium (or less often, nickel, or iron), especially into bromo- or iodoazines, or triflates (prepared from -ols or - or -ones), or alternatively, the use of pyridine boronic acids, boronates, stannanes, silanes, and organmetallic species such as Grignard and zinc derivatives, form the basis of these methodologies.

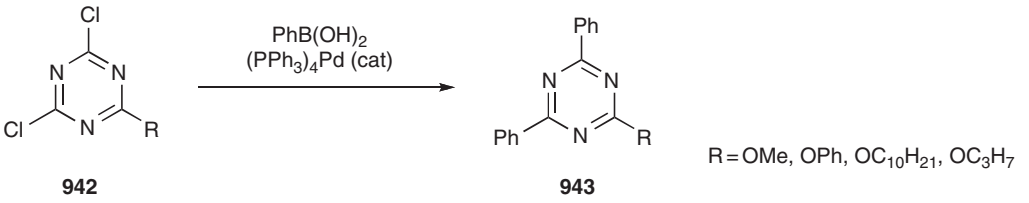
Palladium(0) oxidative insertions occur regioselectively when performed on dihalopyridines, quinolines, and isoquinolines. Generally, insertion of palladium occurs preferentially at the most electrophilic position. Thus, halogens at the 2- or 6-positions of pyridines are substituted in preference to those at the 3- or 5-positions while halogens at the 2- and 1-positions are preferentially replaced in quinolines and isoquinolines, respectively. Due to the electronegativity of the two nitrogen atoms, palladium chemistry takes place more readily with halodiazines than with halopyridines, with the order of oxidative addition correlating to that of nucleophilic substitution. Not only are 2-, 4-, and 6-chloropyrimidines viable substrates for palladium-catalyzed reactions, but good selectivity can also be achieved, with 4- and 6-chloropyrimidines reacting more readily than their 2-chloro isomers.

Palladium chemistry has featured large in the manipulation of diazines; for example, for pyridazines <CHEC-III (7.01.7.15.2)> Suzuki, Stille, and Sonogashira reactions have been well explored <2006COR377, 2006SL3185>.

3.2.3.11.2.1 SuzukiMiyaura reactions. In the SuzukiMiyaura reactions of pyridine systems, the heterocycle can be used either as the electrophile (2-, 3-, and 4-iodo- and bromopyridines) using tetrakis(triphenylphosphine)-palladium(0) as catalyst in the presence of oxygen bases such as potassium carbonate in DME <2002TL4935> or as the organoborate nucleophile, e.g., <2003T10043, 2005TL3573>. Selectivity is such that either coupling partner can carry a chlorine atom on the pyridine ring, which does not react, as is nicely demonstrated in the formation of bipyridyl **941** by two different routes <2003JOC10178>. Suzuki cross-coupling reactions of 2,4-dibromopyridine are regioselective for the 2-position with several alkenyl(aryl)boronic acids affording 2-substituted 4-bromopyridines <2006T11063>.

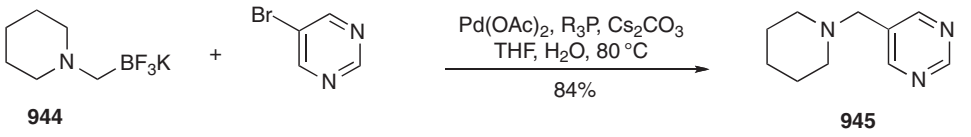


2-Substituted 4,6-diphenyl-1,3,5-triazines **943** can be obtained in high yields by palladium(0)-catalyzed reaction of the corresponding chloro-1,3,5-triazines **942** with phenylboronic acid <1993S33>.



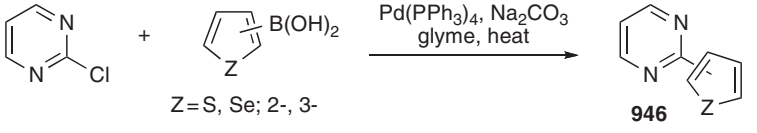
942 **943**

Direct aminomethylation at the 5-position of 5-bromopyrimidine giving **945** uses potassium *N*-(trifluoroboratomethyl)piperidine **944** as the boron species <2007OL1597>.



944 **945**

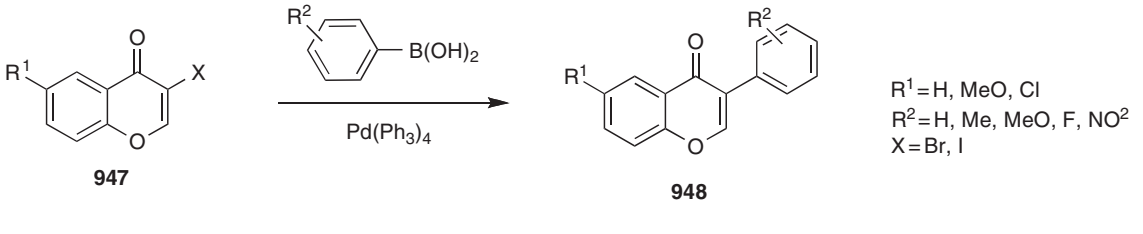
Cross-coupling reactions between organoboranes and boronic acids and heteroaryl halides are effectively catalyzed by Pd(0) in the presence of a base. Couplings in simple pyrimidines are illustrated by the reaction between 2-chloropyrimidine and 2- or 3-thiophene- and selenophene-boronic acids which give the corresponding 2-substituted pyrimidines **946** (**Scheme 107**). In 2,4-dichloro- or 2,4-dibromo-pyrimidine it is the 4-halo substituent which is the more reactive.



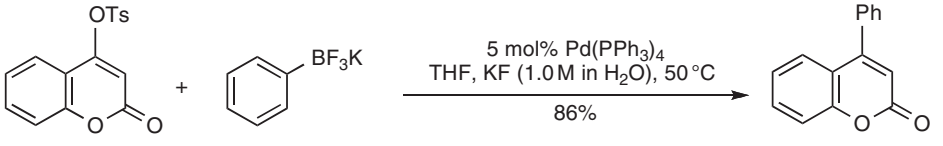
946

Scheme 107

Isoflavone and derivatives, e.g., **948**, can be prepared efficiently by the Suzuki cross-coupling of 3-bromo- or 3-iodochromones **947** (X = I) with arylboronic acids <1989CPB529> and 4-tosyloxycoumarins can be 4-arylated (**Scheme 108**) <2003S2564>.

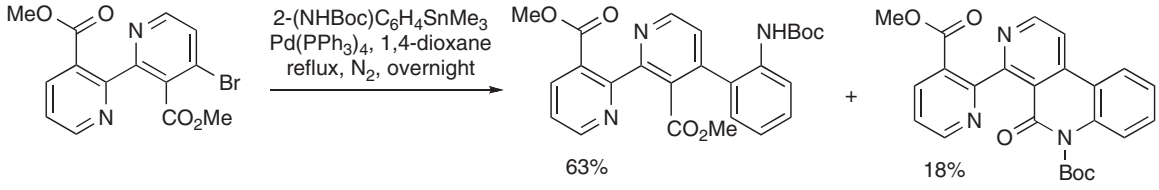


947 **948**



Scheme 108

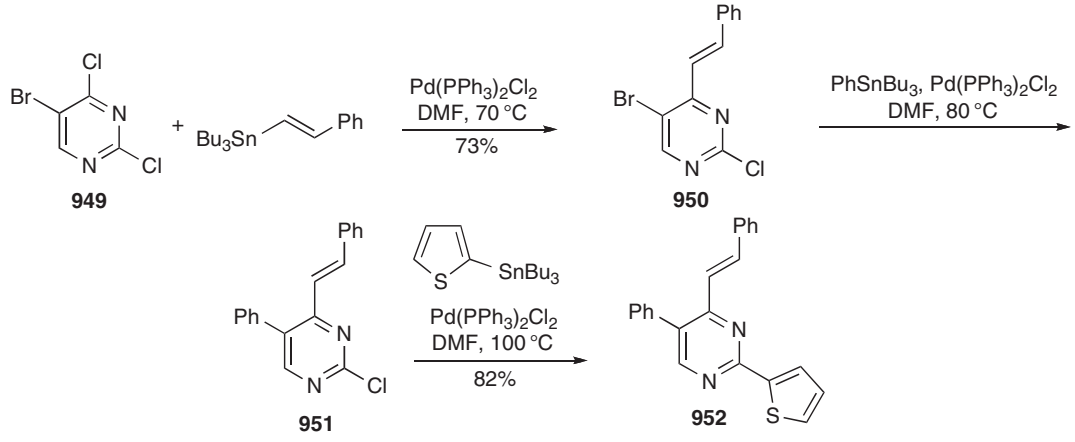
3.2.3.11.2.2 Stille reactions. The Stille reaction is very tolerant of most functional groups, making it effective for the preparation of complex pyridine derivatives <2004EJO1891>. It is possible to generate the organostannane *in situ* through the palladium-mediated reaction of a pyridyl halide or triflate with hexamethylditin <2001JOC1500>. The Stille cross-coupling reaction has been used profusely in the pyridine series, for example, for the preparation of substituted pyridines, bipyridines (e.g., **Scheme 109**), poly(bipyridines), and terpyridines <2004CRV2667>, or vinylation with tributylvinyltin <2000TL8053, 2005JOC1698>.



Scheme 109

Palladium-mediated Stille coupling of bromopyrazines with aryltributylstannanes produces good yields of arylpyrazines <2005T9637> and halogenoquinoxalines undergo Stille (and Suzuki) cross-coupling reactions <1999TL4507>.

The regio- and chemoselectivity in these reactions is demonstrated by the stepwise introduction of three different carbosubstituents into 5-bromo-2,4-dichloropyrimidine **949** (**Scheme 110**). Initial styrylation occurs at the 4-position giving **950**, subsequent phenylation is at the 5-position **951**, and finally thienylation is at the 2-position **952**.

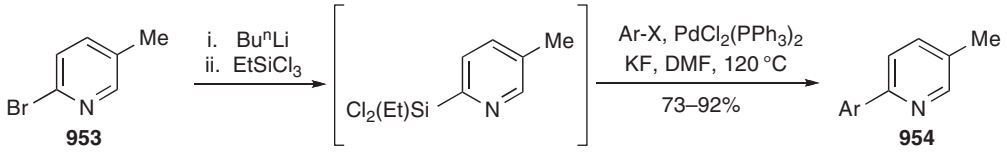


Scheme 110

sp^3-Hybridized carbon attached directly to a metal is less reactive than sp^2- or sp-hybridized carbon in Pd-catalyzed reactions. Tetramethyl- or tetrabutylstannane can be used for the preparation of methyl and butyl derivatives, but these reactions require extended heating in DMF. ***N.B.*** *All stannanes are highly toxic, tetramethylstannane especially so: great care must be taken in the handling of all such tin compounds*. Reactivity is enhanced when the sp^3-hybridized carbon carries an electronegative group. Therefore, in the reaction between benzyltributylstannane and 4-iodopyrimidine, it is the benzyl group which is transferred to the pyrimidine. With allyltributylstannane the product is the 4-*trans*-propenylpyrimidine.

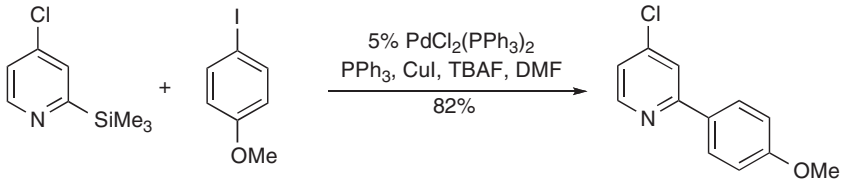
Stille couplings on 3,5-dibromo-2-pyrones are normally selective for C(3), but the presence of Cu(I) reverses this selectivity <2003JA14288>.

3.2.3.11.2.3 Hiyama reactions. The Hiyama cross-coupling of organosilanes is attractive, as the intermediates are often easy to prepare and the silicon by-products are environmentally benign. A one-pot synthesis of 2-aryl-3-methylpyridines **954** from 2-bromo-3-methylpyridine **953** is illustrative (**Scheme 111**) <2003JOM(686)58>.



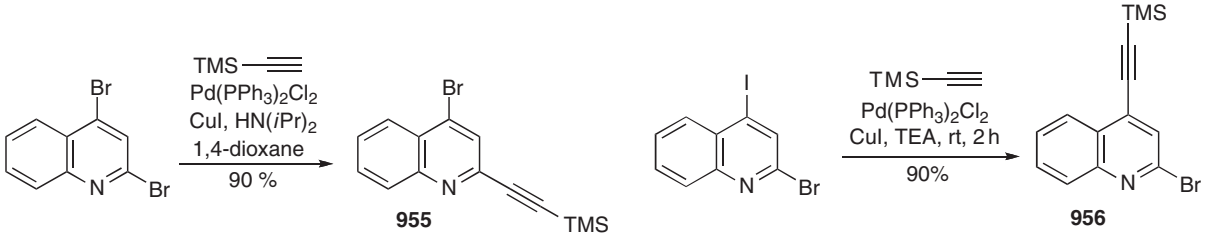
Scheme 111

The presence of electron-withdrawing substituents on the pyridine ring of 2-trimethylsilylpyridines allows them to be useful partners in the Hiyama cross-coupling at room temperature with various heteroaryl halides (**Scheme 112**) <2005OL697>.

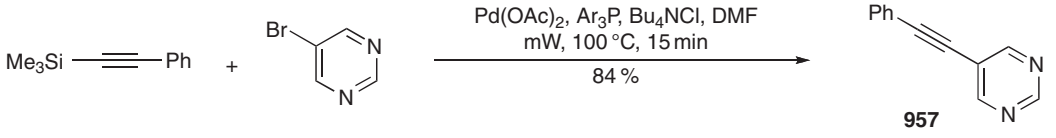


Scheme 112

3.2.3.11.2.4 Sonogashira reactions. The Sonogashira reaction has been routinely used to prepare alkynylpyridines from pyridine halides e.g., <2005OL1793>. With dihalopyridines, bisalkynylation is easily achieved using excess alkyne. Regioselective monoacetylenation of polyhalopyridines favors the -position in most cases <2005T2245, 2004JA10389>. The reaction is most commonly performed using $PdCl_2(PPh_3)_2$ as catalyst <2006JOC167>. The Sonogashira coupling of 2,4-dibromoquinoline with trimethylsilylacetylene affords **955** in high yield; 2-bromo-4-iodoquinoline reacts selectively at C(4) giving **956** <2003JOC3736>.

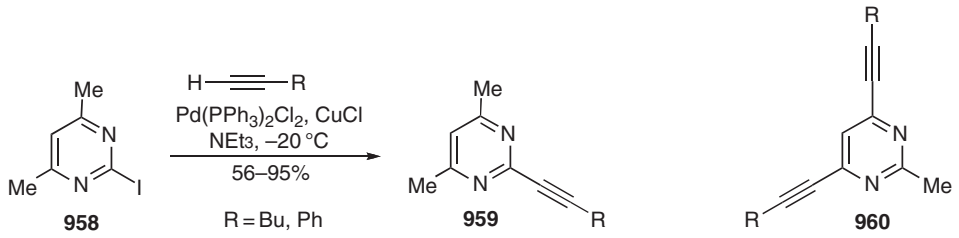


Another example is 1-phenyl-2-trimethylsilylacetylene which reacts efficiently with 5-bromopyrimidine giving **957** but in poorer yield with 2-bromopyrimidine <2005T2697>.

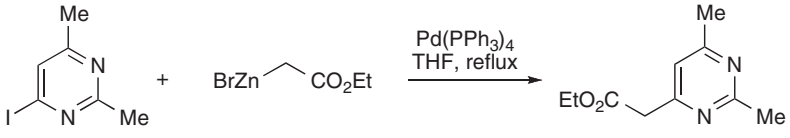


Sonogashira coupling involves the 5-iodine in 4-chloro-5-iodo-2,4-dimethoxypyrimidine <2000OL3761>, but the 4-chlorine in 4-chloro-5-bromopyrimidine <2006TL3923>.

2-Iodo- and 4-iodopyrimidines are readily alkynylated, e.g., **958** **959**, and 4,6-diiodo-2-methylpyrimidine can be dialkynylated to **960**.



3.2.3.11.2.5 Negishi reactions. 2,2-Bipyridines can be accessed in high yields by Negishi coupling of 2-pyridylzinc bromides with 2-chloro- and 2-bromopyridines <2003SL852>. Cross-coupling with organozinc reagents using transition metal catalysis proceeds with high chemo-, regio-, and stereoselectivity. Organozinc reagents are more useful for the transfer of alkyl groups than organotin analogues. This is exemplified by the introduction of an acetic acid unit through substitution of a 4-iodopyrimidine (**Scheme 113**).

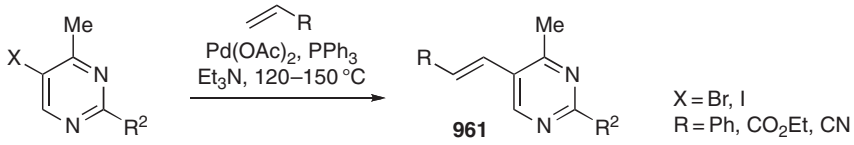


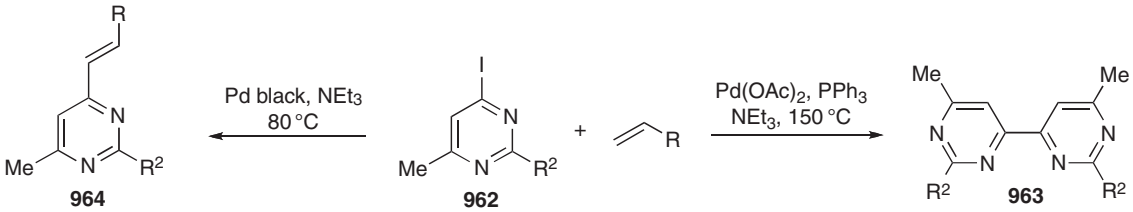
Scheme 113

Negishi couplings (and Sonagashira reactions) also work for substitution in a 4-bromopyran-2-one <2003S2564>.

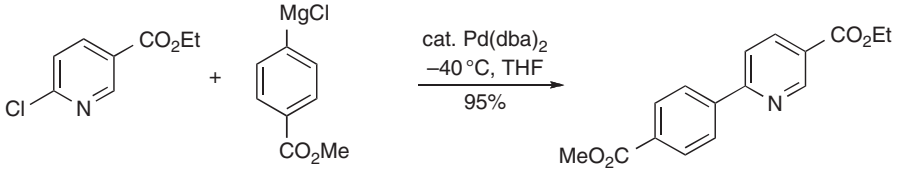
3.2.3.11.2.6 Heck reactions. Heck alkenylation of 2-, 3-, or 4-bromo- or -iodopyridines with monosubstituted alkenes is most commonly achieved by heating in the presence of catalytic quantities of palladium(II) acetate, triarylphosphines, and a base such as triethylamine <2005OL363> or potassium carbonate <2005S2193>.

The alkenylation protocol between styrene, ethyl acrylate or acrylonitrile, and 5-bromo- and 5-iodopyrimidine gives the coupling products **961**. Formation of 4,4-bipyrimidines **963** is a major pathway from 4-iodopyrimidines **962** under the relatively vigorous conditions required to form the cross-coupled product **964**. In the absence of alkenes, the homocoupling (160°C) is almost quantitative.



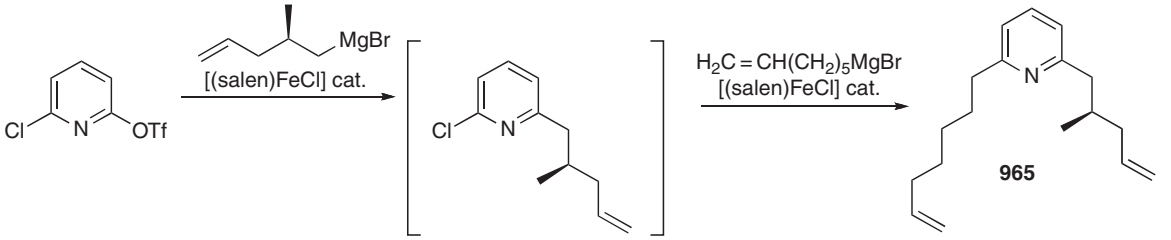


3.2.3.11.2.7 Kumada reactions. Polyfunctional pyridines can be prepared by Pd(0)-catalyzed cross-coupling of functionalized arylmagnesium halides with chloro- or bromopyridines at temperatures as low as 40°C, e.g., **Scheme 114** <2001TL5717>.

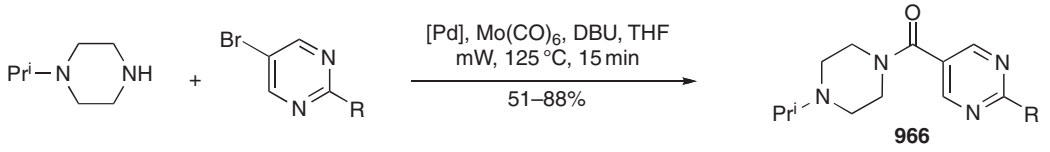


Scheme 114

3.2.3.11.2.8 Iron-catalyzed reactions. Iron-catalyzed cross-coupling reactions <2005CL624> work very well for the coupling of alkyl Grignard reagents as exemplified by formation of double coupling product **965** <2003AGE308>.

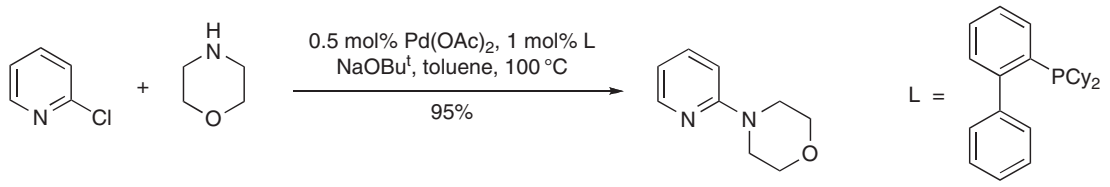


3.2.3.11.2.9 Carbonylation reactions. The formation of derivatives **966** is an example of palladium-catalyzed aminocarbonylation This reaction, which uses solid $Mo(CO)_6$ as the carbon monoxide source, proceeds well with 5-bromopyrimidines <2007TL2339>.

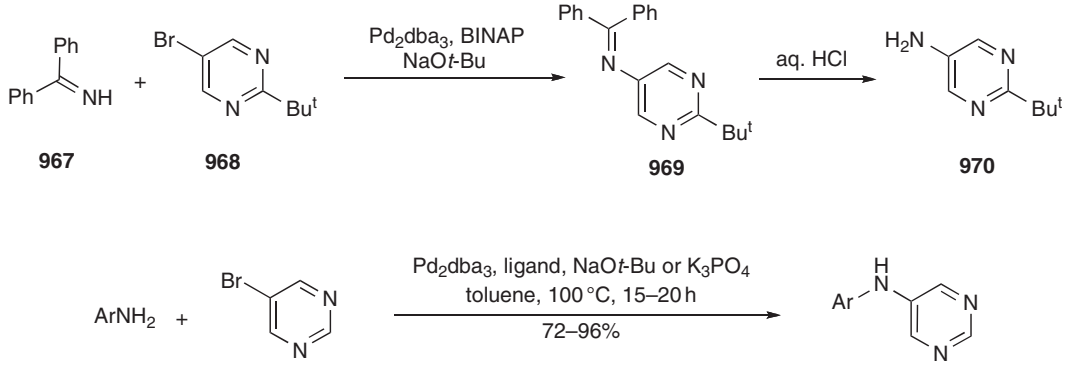


3.2.3.1.2.10 Amination, alkoxylation, and alkthiolation reactions. The metal-catalyzed displacement of halogens with heteroatom nucleophiles, at *any* of the positions of a pyridine, has emerged as a powerful method <CHEC-III(6.02.4.3.3)> which makes these displacements very much easier than formerly, using classical conditions. For example, 3-iodopyridine undergoes cross-coupling with *n*-butanol or isopropanol to give the corresponding 2-alkoxypyridine in 87 and 92% yields, respectively, in the presence of 10 mol% CuI, 20 mol% 1,10-phenanthrolene, and cesium carbonate at 110°C <2002OL973>. This Buchwald protocol also proceeds in a regioselective manner when applied to dihalopyridines: 2,5-dibromopyridine reacts with (*S*)-2-methyl-1-butanol selectively at the 2-position in 70% yield in toluene at 110°C.

Utilizing 2 mol% $Pd(dba)_3$, 4 mol% (±)-BINAP, and sodium *tert*-butoxide in toluene at 70°C, a variety of primary and secondary amines cross-couple with 2-, 3-, or 4-bromopyridines in high yields. Higher catalyst loadings are required to effect amination of chloropyridines (e.g., **Scheme 115**) but this loading can be much reduced by using catalytic quantities of the efficient bis(phosphines) (*o*-biphenyl)P(*t*-Bu)$_2$ or (*o*-biphenyl)PCy_2 <2001JOC7729, 2005SL87>. The cross-coupling of bromopyridines with secondary acyclic amines must employ ferrocinylphosphine ligands <1997JOC1568>. Chloropyridines undergo palladium-catalyzed substitution with both aryl and aliphatic ureas in good yields in the presence of catalytic quantities of $Pd(OAc)_2$ and Xantphos as ligand with $NaOBu^t$ or NaOH as base <2005S915>.



Benzophenone imine or allylamine can be used as ammonia equivalents in the CN coupling reactions of halopyridines <1996JOC7240, 1998TL1313>. Primary 5-aminopyrimidines can also be prepared using benzophenone imine as the amine source, as demonstrated by the synthesis of **970** from **968** via **969** <2006OPD70>. Aromatic amines also efficiently aminate 5-bromopyrimidine (**Scheme 115**) <2005OL3965>.

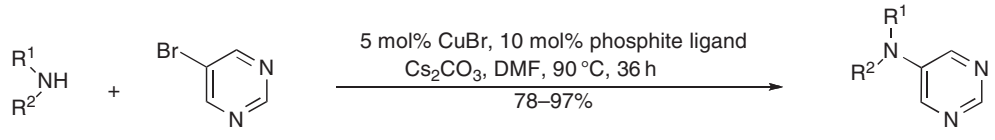


Scheme 115

2-Iodopyridine is converted into 2-butylaminopyridine in 80% yield on treatment with *n*-butylamine and 0.5 equivalents of relatively inexpensive copper(I) iodide with cesium acetate in DMF <2003OL4987>. Using copper(I) iodide as catalyst, in ethylene glycol with potassium phosphate as base, in air, 3-bromopyridine couples with *n*-hexylamine in 85% yield at 80 °C <2002OL581>.

2-Fluoropyridines undergo amination in good yields on treatment with lithium aminoborohydride reagents in THF at 65 °C <2003OL3867>; however, 2-fluoropyridine also reacts with a range of primary and secondary lithium amides in THF at room temperature in the absence of boron reagents to give the 2-aminopyridines in moderate to high yields <2004TL6417>.

For amination with aliphatic amines, copper catalysis is normally superior to palladium catalysis, e.g., <2006T4435>. Thus, reactions of primary or secondary amines, including pyrrolidine and morpholine, with 5-bromopyrimidine using copper bromide and a phosphite ligand give 5-aminopyrimidines in excellent yields (**Scheme 116**) <2006T4435, 2005OL3965>.



Scheme 116

The introduction of a primary amino group can also be achieved via treatment of 2-bromopyridine with 2 mol% Pd(dba)$_2$, P(*t*-Bu)$_3$, and lithium bis(trimethylsilyl)amide in toluene in 87% yield <2001OL2729>.

Palladium-catalyzed methods can also be applied to the synthesis of thiopyridines from halopyridines: 3-chloropyridine cross-couples with 1-hexanethiol to give the hexylthiopyridine in 97% yield using 2.5 mol% of an air-stable palladium(II) complex in the presence of sodium *tert*-butoxide in toluene under reflux <2001JOC8677>.

3.2.3.11.2.11 N-Arylation of pyridones. The Cu-mediated ChanLam reaction <1999T12757> can be used for N-arylation of pyridones or pyridazinones. Alternative methods use $Pb(OAc)_4ZnCl_2$ <2004TL8781> or catalytic amounts of a copper(II) hydroxyquinolinate complex under standard UllmannGoldberg reaction conditions <2006TL149>.

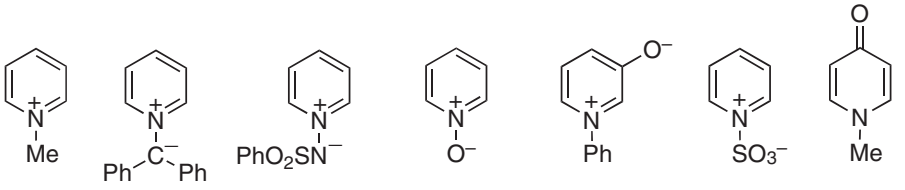
3.2.3.12 Substituents Attached to Ring Nitrogen Atoms

3.2.3.12.1 Introduction

3.2.3.12.1.1 Types. Substituents attached to a nitrogen atom in a six-membered heteroaromatic ring are to be found in compounds of the following types:

a. cations, e.g., **971**;
b. ylides, including *C*-ylides **972**, *N*-ylides **973**, and *N*-oxides **974**;
c. conjugated betaines and zwitterions, e.g., **975, 976**; and
d. compounds with exocyclic conjugation, e.g., **977**.

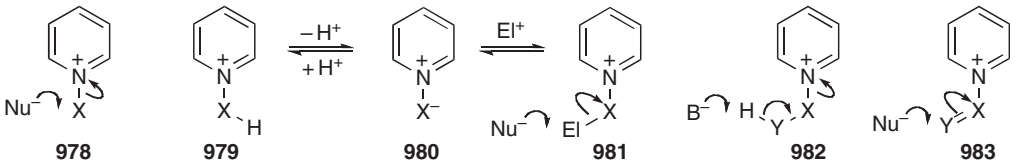
Significantly, types (b), (c), and (d) can all be derived from a compound of type (a) by deprotonation.



971 **972** **973** **974** **975** **976** **977**

3.2.3.12.1.2 Overall survey of reactivity. We survey the reactions of N-linked substituents classified by the atom attached to the cyclic nitrogen. Unlike heterocyclic C-substituents, where the benzene prototype and the carbonyl analogy link much of the typical chemical behavior to familiar compounds, no simple model exists for N-substituents. However, certain trends are clear. The existence of the positive pole in cations of type **971** ensures that nucleophilic attack (a)(d) is the most important of the following reaction types, many of which occur for several of the different classes of N-substituents.

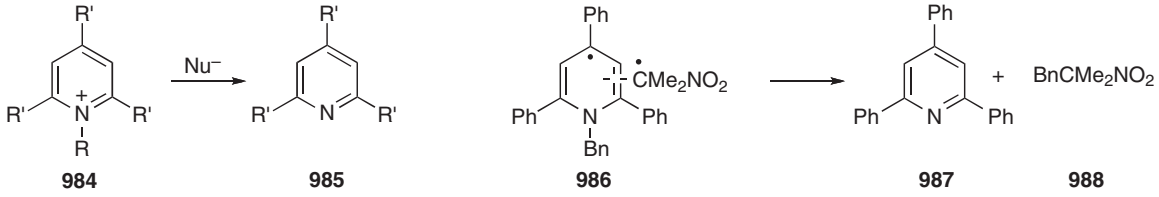
a. The N-substituent can be completely removed (**978**). This is the reverse of the reaction of an electrophile at the pyridine nitrogen atom (Section 3.2.1.3).
b. An -proton in the substituent can be removed (**979 980**); this gives an ylide (cf. **972, 973** above). Such ylides can revert to their precursors by protonation or react with other electrophiles (**980 981**).
c. An , bond can cleave in a substituent by nucleophilic attack or spontaneously, in the reverse (**981 980**) of the reaction just mentioned.
d. An elimination reaction **982** can occur.
e. A nucleophile can add to an ,-multiple bond **983** to give an ylide.
f. Rearrangement of an N-substituent into the ring can occur. A variety of thermal and photochemical rearrangements are known for C-, N-, and O-linked substituents.
g. Electrocyclic addition can involve an N-linked substituent and an -position of the ring.



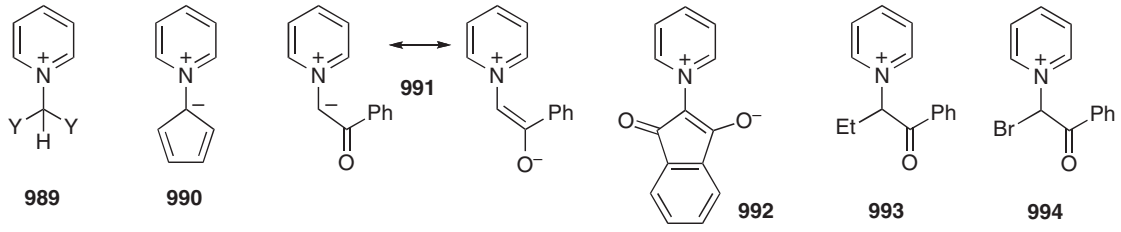
3.2.3.12.2 Alkyl groups

3.2.3.12.2.1 Loss of alkyl groups. 1-Alkylpyridinium halides dissociate reversibly into the alkyl halide and pyridine on vacuum distillation. Reactions of type (984 985) + RNu are accelerated by bulky -substituents R and also by electron-withdrawing groups in the ring. Reactions occur with a wide range of halogen, oxygen, sulfur, nitrogen, phosphorus, and carbon nucleophiles. If R can form a stabilized carbocation (*p*-methoxybenzyl, *sec*-alkyl, etc.), the N C cleavage can occur by the S_N1 as well as the S_N2 mechanism.

Transfer of an *N*-alkyl group to certain nucleophiles can also occur by a radicaloid nonchain mechanism, e.g., 985 (R=CH_2Ph, R=Ph) + CMe_2NO_2 986 987 + 988.



3.2.3.12.2.2 Proton loss from a carbon atom. The ease with which this occurs is determined by the other groups attached to the carbon (cf. 989). The resulting *N*-ylide can be isolated only in special cases where ylide stability is increased by charge delocalization.

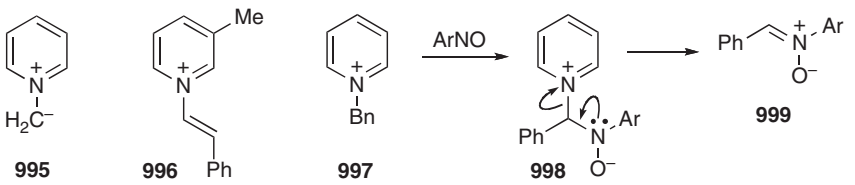


Stabilized ylides show the following properties:

a. They form salts 989 with proton acids.
b. They can be alkylated, e.g., 991 + EtBr + OH 993.
c. They can be halogenated, e.g., 991 + Br_2 + H_2O PhCOCHO + C_5H_5N at 20°C probably via 994.

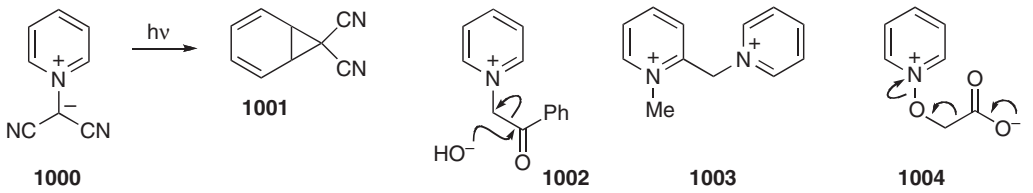
Ylides of type 995 are important as intermediates in the following reactions:

a. the formation of -hydroxyalkyl derivatives with aldehydes and subsequent dehydration, e.g., 1,3-dimethylpyridinium + PhCHO + NaOH 996;
b. the Kr—hnke reaction of *N*-benzylpyridinium ions 997 with nitroso compounds to give nitrones 999 via 998; and
c. Ylide thermolysis and photolysis can cause NC cleavage to give carbene intermediates, e.g., 1000 1001 + pyridine.



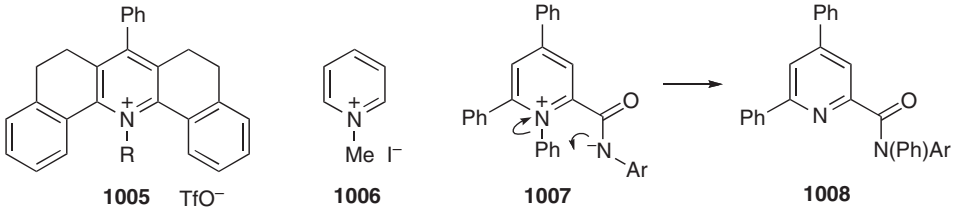
3.2.3.12.2.3 Cleavage of an ,-substituted bond. Nucleophilic reagents can remove a part of the N-substituent because of the relative stability of the resulting zwitterions. Examples include:

a. **1002** 1-methylpyridinium ion + $PhCO_2$;
b. **1003** + OH 1-methylpyridinium ion + 1-methyl-2-pyridone; and
c. decarboxylation of 1-carboxymethoxypyridiniums **1004**.



3.2.3.12.2.4 Elimination reactions (cf. **982**, Section 3.2.3.12.1.2). If salts like **1005** are heated in the absence of nucleophile, E_1 elimination occurs; thus, the pentacyclic triflates (**1005**; R = primary alkyl) decompose at 150°C. The *sec*-alkyl analogues form alkenes even at 20°C.

3.2.3.12.2.5 Rearrangements. 1-Alkylpyridinium halides give mixtures of alkylpyridines on heating, e.g., **1006** gives 2- and 4-picolines, with other minor products. This reaction is known as the Ladenburg rearrangement and involves *N*-alkyl bond homolysis.



3.2.3.12.3 Other C-linked substituents

3.2.3.12.3.1 *N*-Aryl groups. Typical reactions include the following:

a. Electrophilic substitution. Nitration and sulfonation of the 1-phenylpyridinium cation occurs at the position *meta* to the pyridinium substituent.
b. CN bond cleavage. Normally this is very difficult, but it can be observed intramolecularly in special situations, e.g., **1007** **1008**.

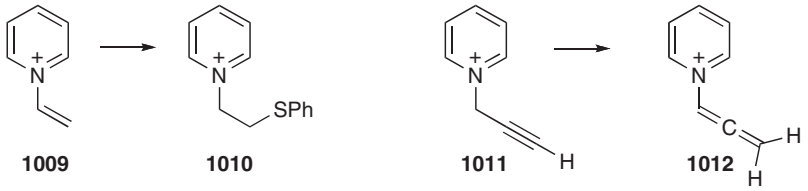
3.2.3.12.3.2 *N*-Acyl and related groups. 1-Acylpyridinium ions are very susceptible to attack by nucleophilic reagents at the carbonyl carbon and thus are good acylating agents. They are generally encountered only as

intermediates (Section 3.2.1.3.7). *N*-Cyano and *N*-imidoyl groups are also easily transferred to nucleophiles; the former render the -ring position particularly susceptible to nucleophilic attack (see Section 3.2.1.6).

Derivatives of this type formed from 4-dimethylaminopyridine possess considerably more stability and can be isolated readily.

3.2.3.12.3.3 *N*-Vinyl groups. The typical reaction is Michael addition of nucleophiles; thus, 1-vinylpyridinium ion **1009** adds N-, S-, and C-nucleophiles to give products of type **1010**. *N*-Vinyl pyridiniums can also undergo polymerization.

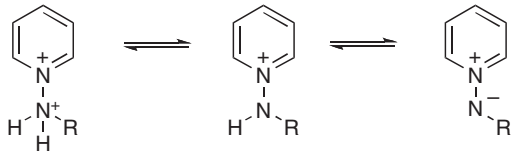
3.2.3.12.3.4 Other substituted alkyl groups. N-Allyl compounds can be rearranged to N-propenyl derivatives. Similarly, N-propargyl salts **1011** give N-allenyl derivatives **1012**.



1009 **1010** **1011** **1012**

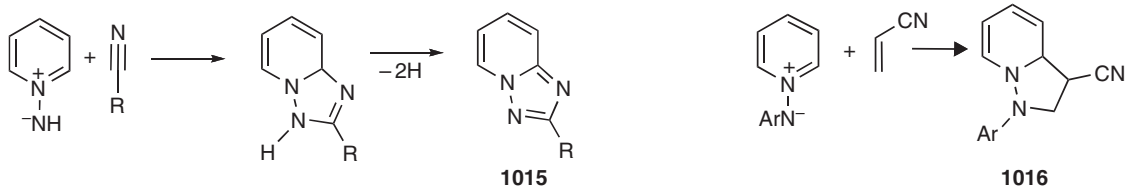
3.2.3.12.4 N-Linked substituents

3.2.3.12.4.1 Prototropic equilibria. *N*-(Monosubstituted amino)pyridiniums are in prototropic equilibrium with *N*-imides **1013** and dications **1014**. For R=H or allyl, the *N*-imides **1013** are very strong bases and cannot usually be isolated; if R is an electron-withdrawing group (e.g., acyl, sulfonyl, nitro), then the imides **1013** can be isolated. Cations such as **1014** can only be obtained in very strongly acid media.



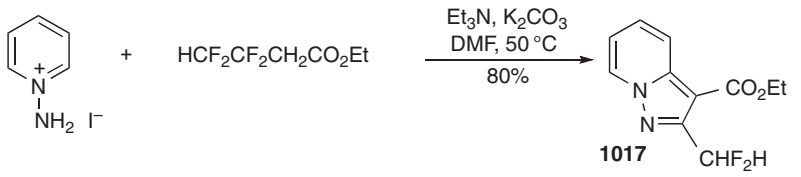
1014 **1013**

N-Aminopyridinium chemistry is largely dominated by the reactions of the corresponding pyridinium ylides generated by deprotonation of the amino group. Heteroaromatic *N*-imines take part in 1,3-dipolar cycloaddition reactions involving the *N*-imine nitrogen atom and the -position of the ring; for example, with nitriles, triazolopyridines **1015** are formed by dehydrogenation of intermediate adducts. The more stable the *N*-imine, the more reactive the dipolarophile has to be. Anions from *N*-arylaminopyridiniums react with acrylonitrile to give similar adducts **1016**.



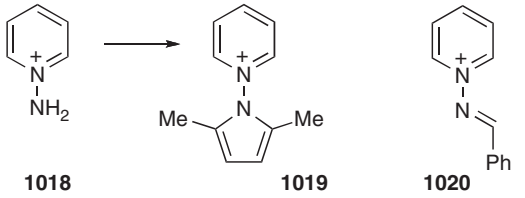
1015 **1016**

The 1,3-dipole can be generated *in situ* by treatment with a weak base, for example, with ethyl 2,2-dihydropolyperfluoroalkanoates in the presence of K_2CO_3, polyfluorosubstituted pyrazolo[1,5-*a*]pyridines **1017** are formed <1998JFC (87)57>.

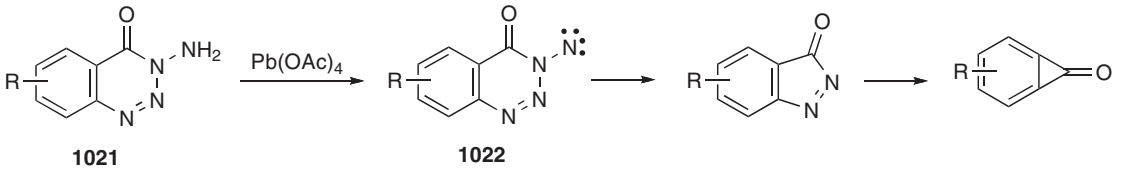


3.2.3.12.4.2 Reactions of *N*-amino compounds with electrophiles. *N*-Aminopyridinium cations can be acylated or sulfonylated (with acid halides) and nitrated (H_2SO_4-HNO_3) to give the corresponding N-(substituted amino)pyridines, often isolated as the imides (**1014**; R = COR, SO_2R, or NO_2).

The amino group in **1018** can be condensed with 1,4-dicarbonyl compounds; for example, with hexane-2,5-dione, the *N*-(pyrrol-1-yl)pyridinium **1019** is formed, or with aldehydes, imines **1020** are formed. Reaction with aryldiazonium salts forms aryl azides and pyridine, presumably via $ArN{=}NNPy^+$. Nitrous acid and *N*-aminopyridinium cations yield pyridine and N_2O.

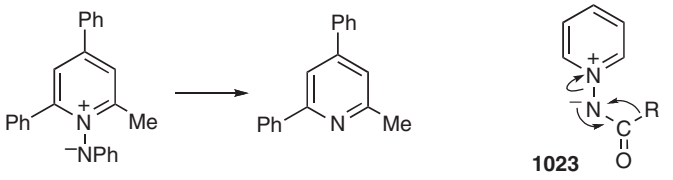


3.2.3.12.4.3 Other reactions of *N*-amino compounds. *N*-Aminopyridones can be oxidized to nitrenes. Thus, 3-amino-1,2,3-benzotriazin-4-ones **1021** with lead tetraacetate leads to a nitrene **1022**, which can lose one or two molecules of nitrogen (**Scheme 117**).



Scheme 117

The NN bond in *N*-aminopyridiniums and *N*-imines can be easily reductively cleaved to yield pyridines and amines, e.g., H_2Pt or ZnNaOH. Thermolysis of pyridine *N*-acylimides **1023** gives isocyanates RNCO and pyridine.



3.2.3.12.4.4 Other N-linked substituents. *N*-Nitropyridiniums are mild nitrating agents.

3.2.3.12.5 O-Linked substituents

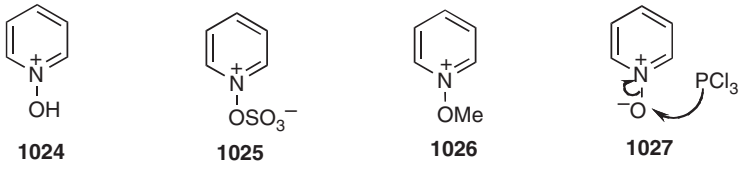
3.2.3.12.5.1 Reactivity pattern of *N*-oxides. 1-Hydroxypyridinium ions **1024** readily lose a proton to give *N*-oxides; *N*-oxides are weak bases which form 1-hydroxypyridinium ions by proton addition.

Pyridine *N*-oxides possess a unique pattern of reactivity:

a. Electrophiles can attack *either* at ring carbon (usually to the *N*-oxide on the free base, -position on the conjugate acid) in electrophilic substitution reactions (see Section 3.2.1.4) *or* at the oxygen atom as discussed below.
b. Nucleophiles can attack at *either or* ring carbon atoms (strong nucleophiles on free bases and weaker nucleophiles on intermediates first formed by electrophilic addition to the *N*-oxide oxygen - see Section 3.2.1.6). Certain nucleophiles also lead to *N*-oxygen removal as discussed below.
c. *N*-Oxides undergo a variety of electrocyclic additions and rearrangements as discussed below.
d. *N*-Oxides being reactive 1,3-dipoles can enter various cycloaddition reactions (cf. Section 3.2.1.10.4).

3.2.3.12.5.2 Reactions of *N*-oxides with electrophiles at the *N*-oxide oxygen. These include the following:

a. Proton acids give 1-hydroxypyridinium salts **1024**.
b. Lewis acids give complexes, e.g., SO_3 **1025**.
c. Alkyl halides form 1-alkoxypyridinium salts **1026**.
d. Pyridine *N*-oxides with arenediazonium salts yield *N*-aryloxypyridinium salts.
e. Metal ions give coordination compounds.



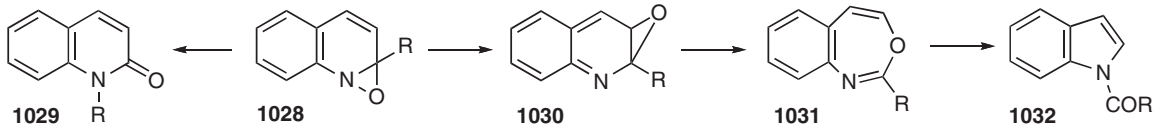
1024 **1025** **1026** **1027**

3.2.3.12.5.3 Loss of the *N*-oxide group. Reduction of *N*-oxides affords the parent heterocycle and can be achieved by a large variety of reductive methods <CHEC-III(6.03.5.5)>, principal among which are the following:

a. Catalytic hydrogenation, e.g., over Pd
b. Chemical reduction, e.g., with Fe-HOAc
c. Electrochemical means
d. Deoxygenation with a trivalent phosphorus compound, e.g., PCl_3, PPh_3, $P(OEt)_3$. This can be formulated as nucleophilic attack on oxygen **1027**, but probably initial electron donation of the *N*-oxide lone pair into the vacant phosphorus d-orbital is involved.

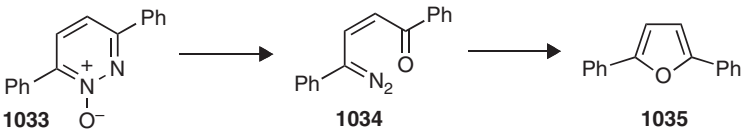
3.2.3.12.5.4 Rearrangement reactions. The most important rearrangements include the following:

a. *Photochemical*. Irradiation of pyridine *N*-oxide in benzene solution yields, via the excited triplet state, phenol and pyridine. Iradiation of quinoline *N*-oxide in a polar solvent like water proceeds via the oxaziridine **1028** to 2-quinolinone **1029**, (R=H). Rearrangements can occur in such reactions: **1028** **1030** (R=Me). The primary oxaziridine can isomerize and undergo valence-bond tautomerism to an oxepin, e.g., **1031**. Hydrolytic ring opening of the oxepin followed by ring closure can give an indole **1032**.

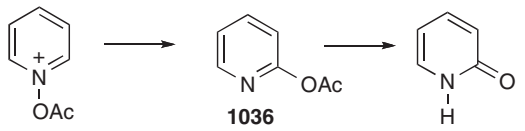


1029 **1028** **1030** **1031** **1032**

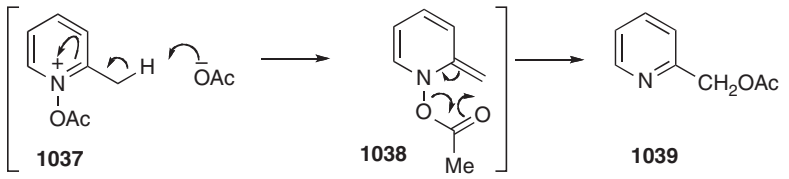
Certain pyridazine *N*-oxides are isomerized to the corresponding diazoketones, e.g., **1033** **1034**; conversion to the furan **1035** can then occur.



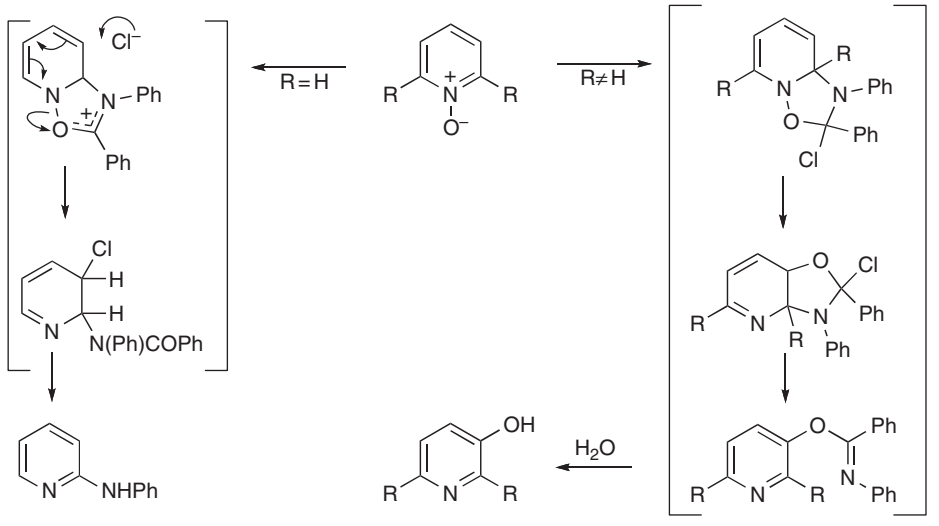
b. *Acid anhydrides*. Pyridine *N*-oxides heated with acid anhydrides are converted in good yield via **1036** into pyridones after hydrolysis (**Scheme 118**) (see Section 3.2.1.6.3.7) unless the *N*-oxide contains an - or -alkyl group. In the latter case, an alternative reaction occurs with acetic anhydride to form an - or -(acetoxyalkyl)pyridine (e.g., **1039**). For attack on - (**1037 1038 1039**) and -alkyl groups, these reactions appear to be similar to the *ortho*- and *para*-Claisen rearrangements, respectively, of allyl phenol ethers. In these reactions, -acetoxy compounds are formed as by-products, e.g., 3-acetoxy-2-methylpyridine from **1037**.



Scheme 118

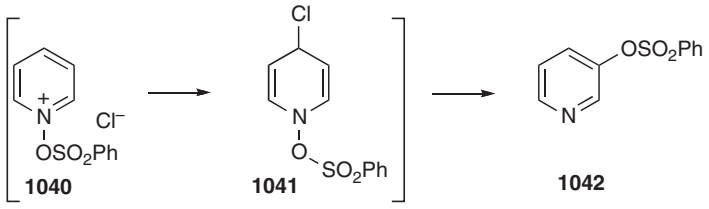


c. *Imidoyl chlorides*. The treatment of *N*-oxides with imidoyl chlorides leads to intramolecular amination via the intermediates as shown. When the 2- and 6-positions are both substituted, reaction goes further to give a 3-hydroxypyridine (**Scheme 119**).



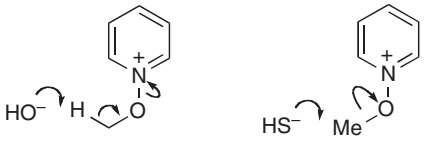
Scheme 119

d. *Benzenesulfonyl chlorides*. The reaction with *N*-oxides gives -benzenesulfonyloxy pyridines, e.g., **1042** via **1040** and **1041**.



3.2.3.12.5.5 Reactions of *N*-alkoxypyridines and -azines. Two distinct types of reaction are common:

a. 1-Alkoxypyridinium compounds react with hydroxide ions to give aldehydes and pyridines in an elimination reaction (cf. **1043**).
b. Soft nucleophiles can remove the alkyl group, e.g., **1044** pyridine *N*-oxide + MeSH.



3.2.3.12.6 Other substituents attached to nitrogen

3.2.3.12.6.1 S-Linked. Pyridine *N*-sulfides are known only in the form of their derivatives. Thus, 1-arylthiopyridinium cations (from pyridine and sulfenyl chloride) react with KCN to form ArSCN and pyridine.

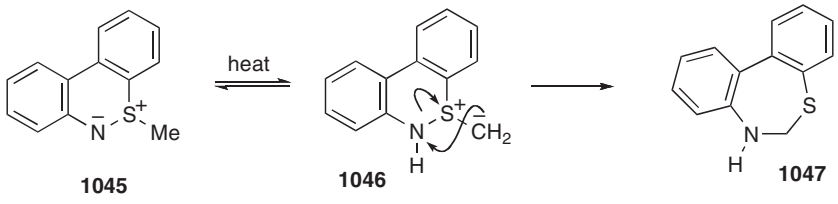
Pyridine-sulfur trioxide is a mild sulfonating reagent, which has been used for sulfonation of furan and pyrrole.

3.2.3.12.6.2 Halogens. Pyridinehalogen complexes dissociate on heating; halogen is lost so readily that these compounds act as mild halogenating agents towards phenol or aniline, for example (see Section 3.2.1.3.8).

3.2.3.12.6.3 Metalloids. The complexes formed with boron trihalides are decomposed into pyridine by boiling water. Complexes with other Lewis acids behave similarly.

3.2.3.13 Substituents Attached to Ring Sulfur Atoms

The azathiaphenanthrene **1045** undergoes a thermal rearrangement in refluxing xylene involving ring expansion to yield the dibenzothiazepine **1047** via a Stevens-type rearrangement of the methylide intermediate **1046**.



3.3 Reactivity of Five-Membered Rings with One Heteroatom

3.3.1 Reactions at Heteroaromatic Rings

3.3.1.1 General Survey of Reactivity

We first consider the different types of reactivity of which five-membered heteroaromatic rings with one heteroatom are capable. We compare and contrast the effects of the different heteroatoms and compare these compounds with analogous aliphatic and benzenoid derivatives. All these reactions are considered later in this chapter in more detail.

Electrophilic attack at ring heteroatoms is rare for the neutral compounds, although examples are known for thiophenes and selenophenes. However, pyrrole N-anions undergo easy reaction with electrophiles at either the N or a C atom.

The most important reactions involve electrophilic attack on ring carbon atoms, a wide variety of which are known for pyrroles, furans, and thiophenes. Most frequently, such electrophilic attack is followed by proton loss, resulting in overall substitution.

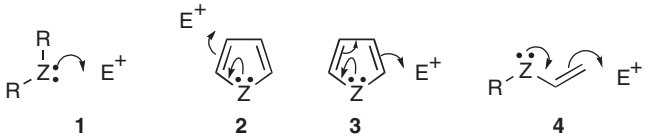
Nucleophilic attack on neutral pyrroles, furans, and thiophenes which do not have strongly electron-withdrawing substituents does not occur. There are a limited number of examples, particularly in thiophene chemistry, of nucleophilic displacements of activated (e.g., by *ortho* or *para* nitro groups) leaving groups and some examples of vicarious nucleophilic substitution (VNS) of hydrogen. The cations formed by electrophilic addition to carbon in pyrrole, furan, and thiophene rings react readily with weak nucleophiles, sometimes resulting in overall addition or ring-opening processes. Strong base N-deprotonation of a pyrrole and C-deprotonation (metallation) of N-substituted pyrroles, furans, and thiophenes are very important, leading to reactive nucleophiles for substitution at N and C.

The neutral rings react readily with radicals and other electron-deficient species, and a variety of reactions at surfaces are known.

Several types of reaction involving cyclic transition states are known.

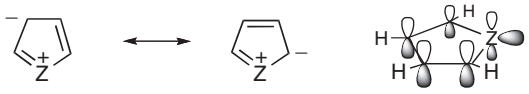
Extensive use can be made of palladium (and other transition metals) catalysis, especially for the formation of carbon carbon bonds and for N-arylation.

The five-membered ring heterocycles possess DielsAlder reactivity of varying degree. This is most pronounced in the case of furan and benzo[*c*]-fused heterocycles such as isoindole. In this capacity they are functioning as heterocyclic analogues of cyclopentadiene, and high DielsAlder reactivity can be correlated with low aromaticity.



3.3.1.1.1 Comparison with aliphatic series

Many common reactions of aliphatic amines, ethers, and sulfides **1** involve initial addition of an electrophilic reagent utilizing the lone pair of electrons on the heteroatom; salts, quaternary salts, coordination compounds, amine oxides, sulfoxides, and sulfones are formed in this way. Corresponding reactions are very rare (cf. Section 3.3.1.3) with pyrroles, furans, and thiophenes. These heterocycles react with electrophilic reagents at the carbon atoms **2, 3** rather than at the heteroatom. Vinyl ethers and enamines **4** show intermediate behavior, reacting frequently at the -carbon but sometimes at the heteroatom.

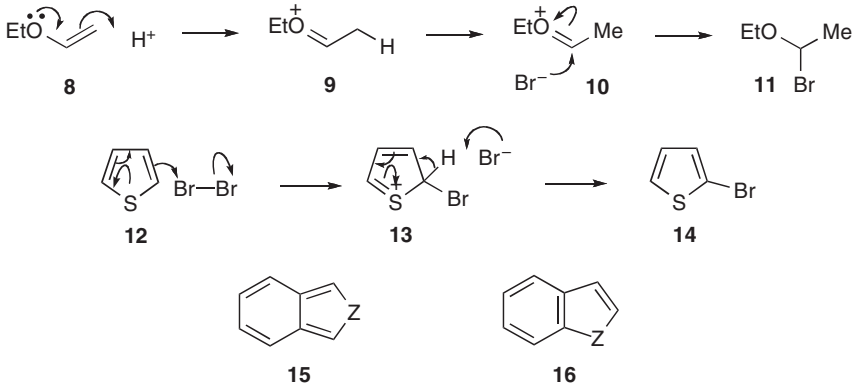


5 **6** **7**

The heteroatoms of pyrrole, furan, and thiophene carry partial positive charges in the ground state which hinder reaction with electrophilic reagents. Conversely, the carbon atoms of these compounds are partially negatively charged, which aids reaction with electrophilic reagents at the ring carbons. This charge distribution follows from the valence-bond theory as a consequence of contributions to the resonance hybrids of mesomeric forms **5 6**. Molecular orbital theory leads to similar predictions, the heteroatom contributing two electrons to the -molecular orbitals and the carbon atoms one each **7**.

3.3.1.1.2 Effect of aromaticity

Vinyl ethers and amines disclose little tendency to revert to type; thus, the intermediate formed by reaction with an electrophilic reagent reacts further by adding a nucleophilic species to yield an addition compound; cf. the sequence **8 11**. Thiophene and pyrrole have a high degree of aromatic character; consequently, the initial product formed by reaction of thiophene or pyrrole with an electrophilic species subsequently loses a proton to give a substituted compound; cf. the reaction sequence **12 14**. Furan has less aromatic character and therefore sometimes reacts by overall addition and sometimes by substitution. In electrophilic addition, the first step is the same as in substitution, i.e., the formation of a -complex (like **13**), but instead of losing a proton this now adds a nucleophile.



8 **9** **10** **11** **12** **13** **14** **15** **16**

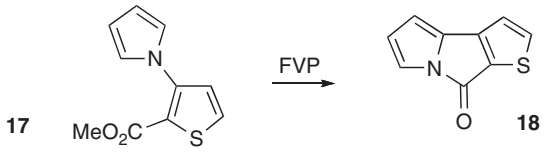
The KekulÕ resonance of the benzene ring is impaired in the benzo[*c*]-derivatives **15**, and these compounds are unstable and usually react by overall addition. Benzo[*b*]-derivatives **16** have appreciable resonance energies and usually revert to type.

3.3.1.2 Thermal and Photochemical Reactions Involving No Other Species

Pyrrole, furan, and thiophene rings are thermally very stable, requiring extreme conditions for changes to occur. Thus, at 10501450 K the main products from pyrrole are (*Z*)- and (*E*)-1-cyanoprop-1-ene and 1-cyanoprop-2-ene, from 2*H*-pyrrole formed in a first step via a [1,2]-H shift from the nitrogen to C(2) <1989JPC5802>. Infrared laser-powered homogeneous pyrolysis (IR LPHP) <2004NJC606> confirmed the dominant [1,2]-H shift. Similarly, in the

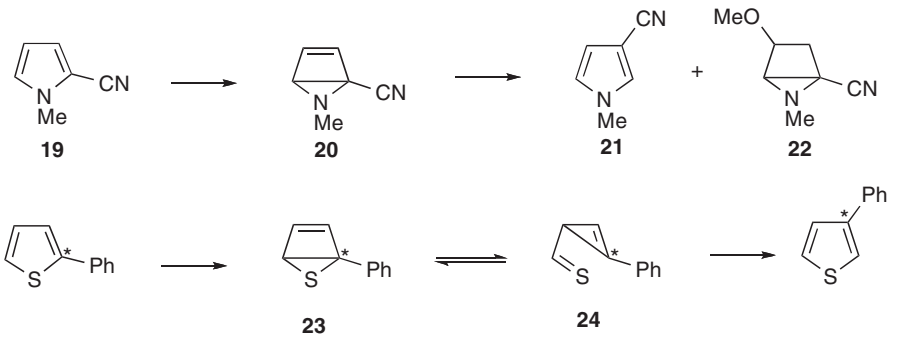
temperature range of 10501700 K, the main thermal reactions of indole are isomerization to produce 2-phenylacetonitrile and 2-methyl- and 3-methylbenzenecarbonitriles as a result of pyrrole ring opening <1997JPCA7787>.

The 1-thienylpyrrole **17** produced **18** (79%) at 925°C (0.01 Torr) <1999J(P1)2047>.

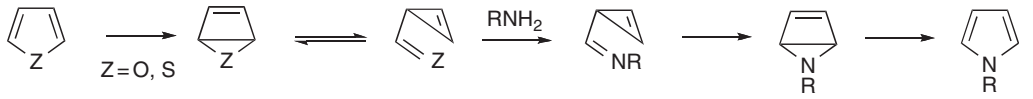


Photochemical scrambling of ring atoms can involve a ring-walk or a cyclopropene mechanism. For example, 2-cyanopyrrole undergoes photochemical rearrangement to 3-cyanopyrrole. Analogous rearrangement of *N*-methyl-2-cyanopyrrole **19** in methanol gives, in addition to the 3-cyanopyrrole **21**, the bicyclic intermediate **20** trapped as the methanol adduct **22**.

The light-induced rearrangement of 2-phenyl- to 3-phenylthiophene may involve an equilibrium between the bicyclic intermediate **23** and the cyclopropenylthioaldehyde **24** (**Scheme 1**). The formation of N-substituted pyrroles on irradiation of either furans or thiophenes in the presence of a primary amine supports this suggestion (**Scheme 2**).

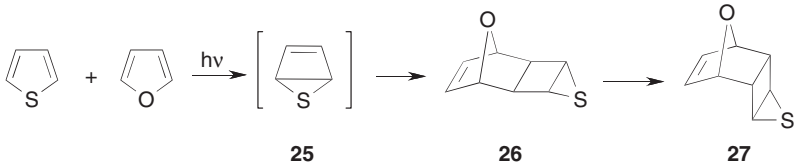


Scheme 1



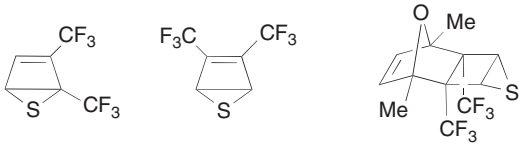
Scheme 2

The photofragmentation of thiophene on irradiation at 193 nm <1995JPC1760> produces vinylacetylene, acetylene, thioketene, and sulfur. The parent Dewar thiophene **25** has been generated and trapped; thus, when a solution of thiophene in furan (molar ratio, 1:10) is irradiated at 229 nm at 25°C, two 1:1 adducts **26** and **27** are formed.



2,3-Bis(trifluoromethyl)thiophene, on irradiation, gives an equilibrium mixture of the two Dewar thiophenes **28** and **29** (8:1), along with the rearranged 2,5-, 2,4-, and 3,4-bis(trifluoromethyl)thiophenes. The Dewar isomer **29** seems to be

more reactive than **28** toward dienes; thus, on reaction with 2,5-dimethylfuran, the mixture of **28** and **29** gives exclusively the adduct **30** derived from **29**. Irradiation of 2,5-bis(trifluoromethyl)thiophene gives no Dewar isomers; only the rearranged 2,4-disubstituted isomer is formed, probably via a cyclopropenylthioketone or a tricyclic isomer. Irradiation of 3,4-bis(trifluoromethyl)thiophene also does not lead to any Dewar thiophene.



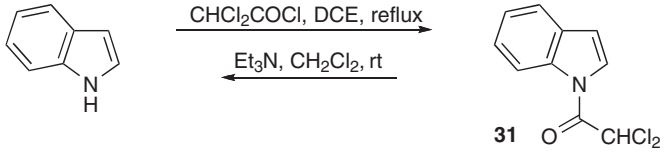
28 **29** **30**

3.3.1.3 Electrophilic Attack on Ring Heteroatoms

Reactions of this type are rare for reasons discussed in Section 3.3.1.4. No examples are known of electrophilic attack at the furan oxygen atom.

Neutral pyrroles and indoles are also not generally susceptible to attack at the cyclic nitrogen. However, the pK_a of carbazole and 9-methylcarbazole being 6.0 and 8.2, respectively, (in H_2SO_4, EtOH, 4:1) refers to N-protonation. Pyrrole anions undergo easy reaction with various electrophiles. An increasing tendency to electrophilic attack at the ring heteroatom is shown in thiophenes, selenophenes, and tellurophenes.

There are certain situations in which, despite the general view, it seems likely that electrophilic attack on neutral pyrrole ring nitrogen does take place. One example is reaction of indole with 2,2-dichloroacetyl chloride in refluxing DCE yielding 2,2-dichloro-1-(indol-1-yl)-1-ethanone **31** in 88% yield <1997TL7813>; N-deprotection of **31** is easy with Et_3N at room temperature.



31

3.3.1.3.1 Pyrrole anions

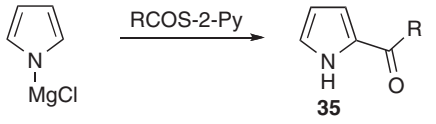
As discussed in Section 3.3.1.6.1, pyrroles are weak acids. The resulting ions react exceedingly readily, even with weak electrophilic reagents at either carbon **32** or nitrogen **33**; this behavior is similar to that of an enolate which can react at oxygen or carbon.

32 **33** **34**

3.3.1.3.1.1 Pyrrole Grignard reagents.

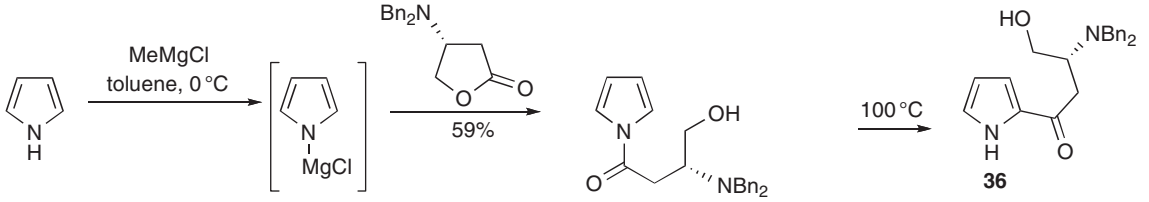
Pyrroles and indoles with Grignard reagents give the corresponding hydrocarbon and partially ionic Grignard reagents derived from the pyrrole or indole (e.g., **34**). Pyrrolyl- and indolylmagnesium halides undergo many of the normal Grignard reactions to give 1- or 2-substituted pyrroles (cf. **32, 33**) or 1- or 3-substituted indoles (cf. the discussion in Section 3.3.1.4.2). Mixtures of the N- and C-substituted products are often formed, the proportions of which are frequently altered by changing the solvent, temperature, or reagent.

A classical method for preparing C-acylated pyrroles involves the acylation of pyrrylmagnesium bromide. In general, tightly coordinated N-pyrryl and N-indolyl salts, exemplified by their Grignard derivatives, undergo preferential C-acylation (**Scheme 3**) and C-alkylation. Ketones and esters usually react further with Grignard reagents; however, both ketones and esters of type **35** are stabilized by mesomerism and are therefore less reactive.



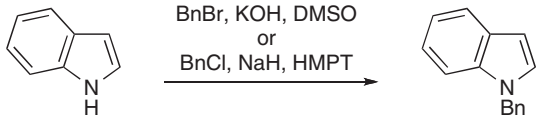
Scheme 3

However, Grignard derivatives of pyrroles and indoles can be used for N-substitution, e.g., **Scheme 4** <2004T1197>; using the two equivalents of the pyrrolyl Grignard reagent, and at 100°C, gives the C(2)-acylated product **36** via N-acylation then C(2)-metallation and C-acylation.



Scheme 4

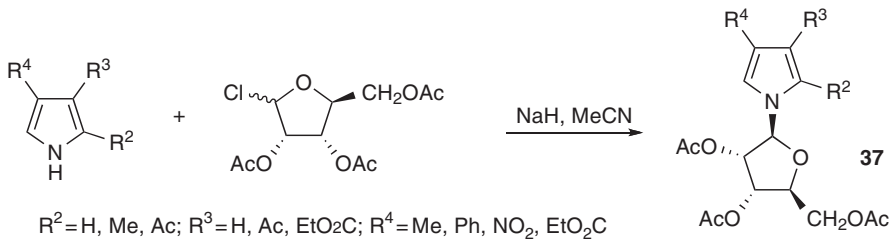
3.3.1.3.1.2 Other pyrrole anion nucleophiles. The main method for N-alkylation or N-acylation of the pyrrole ring involves conversion into an alkali metal salt (e.g., with $NaNH_2/NH_3$ in early work, but more recently NaH or KH (e.g., <1998JOC4510, 1998OM1134, 2000ARK(iv)486, 2003JME417> or *n*-BuLi (e.g., <1997JOC7447, 2002JME2160>). The use of pyrrolyl or indolyl sodium or potassium salts under ionizing conditions strongly favors the formation of *N*-acyl or *N*-alkyl derivatives (e.g., **Scheme 5**). N-Alkylation is favored by polar solvents and the use of tosylates rather than iodides.



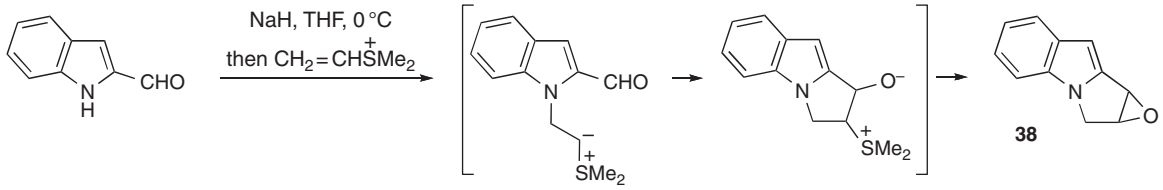
Scheme 5

In other examples of the use of preformed sodium and lithium salts, stereoselective glycosylation of pyrroles leads only to the -anomer **37** (**Scheme 6**) <2000ARK(iv)486>; sodio-indoles react with epoxides giving 2-(indol-1-yl) ethanols <1997JME2762> [in reaction with epichlorhydrin the epoxide is not attacked but chloride is displaced <2002BMC2511>]; the sodium salt of skatole with butyrolactone gives 4-(3-methylindoly-1-yl)butanoic acid <1996TL5207>; and a neat annelation to give **38** can be achieved with dimethyl allyl sulfonium as the electrophile (**Scheme 7**) <1999T10659>.

Hexapyrrol-1-ylbenzene and octapyrrol-1-ylnaphthalene can be obtained in high yields by the reaction of sodium pyrrolide with hexafluorobenzene or octafluoronaphthalene, respectively, at room temperature in DMF <1996JOC9012>.

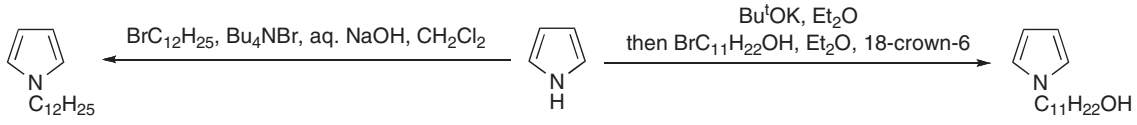


Scheme 6



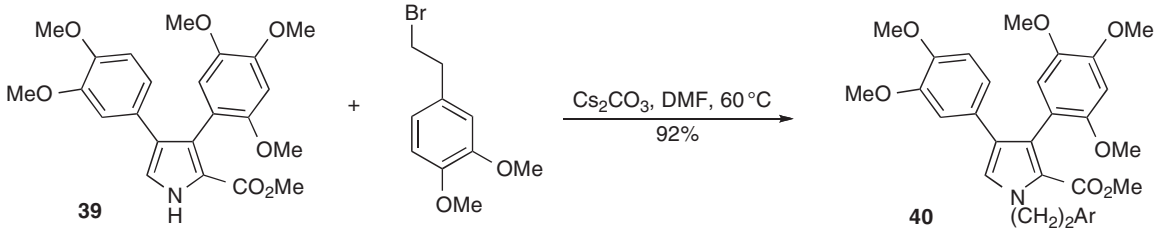
Scheme 7

Many conditions for N-substitutions utilize partial conversion into anions, i.e., utilize equilibrium concentrations of the N-anion especially under phase-transfer conditions (e.g., <2004JOC8668> and **Scheme 8** <1997CM644>), or in ionic liquids, [Bmim][PF_6] or [Bmim][PF_4] <2004S1951>, or using DMAP <1999TL2733>. Under phase-transfer conditions, the preference for N-alkylation in indoles ranges from 1.5:1 for benzyl bromide to 10:1 for benzyl chloride and *n*-alkyl bromides, over 3-alkylation. Another variant is to use cesium fluoride/Celite as a solid base <2001T9951> which is convenient and efficient. N-Chlorination of pyrrole occurs when a solution of pyrrole in carbon tetrachloride is stirred at 0 °C with an aqueous solution of sodium hypochlorite.



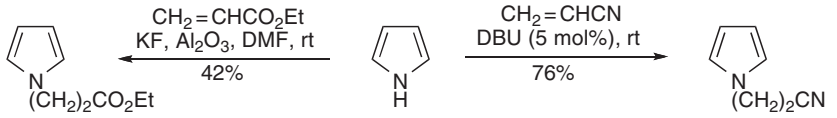
Scheme 8

Using potassium carbonate in DMF did not permit the N-alkylation of complex pyrrole **39** to go to completion even after heating at 70 °C for 24 h; however, substituting cesium carbonate for K_2CO_3 allowed the reaction to proceed easily to compound **40** (**Scheme 9**) <2002JOC9439>. Others have also recommended the Cs_2CO_3, DMF, 50 °C combination for N-alkylation on a multikilogram scale <1998JOC1961> and for N-allylation <2002S1810>.



Scheme 9

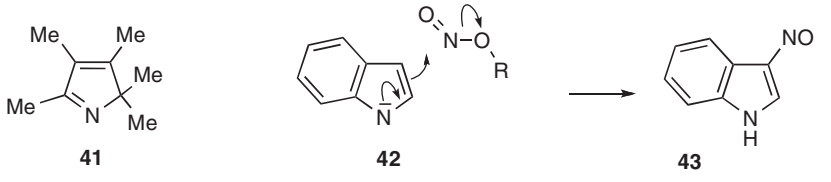
Substoichiometric loadings of DBU, or the use of KF as base, allow the efficient 1,4-addition of pyrrole to activated alkenes (**Scheme 10**) <2005CC227, 2005TL3279>.



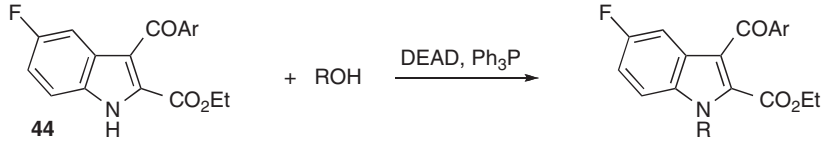
Scheme 10

Despite the strong tendency for N-substitution of pyrrolyl and indolyl anions, 2-substituted pyrroles and 3-substituted indoles can also result; the following exemplify reactions of this type:

a. Boiling aqueous potassium carbonate converts pyrrole into its 2-carboxylic acid; the anion reacts with carbon dioxide.
b. 1,2,3,4-Tetramethylpyrrole with MgOMeI gives 2,2,3,4,5-pentamethyl-2*H*-pyrrole **41**.
c. Alkyl nitrites or nitrates with sodium ethoxide convert indole into 3-nitroso- (e.g., **42** **43**) or 3-nitro-indoles, respectively.

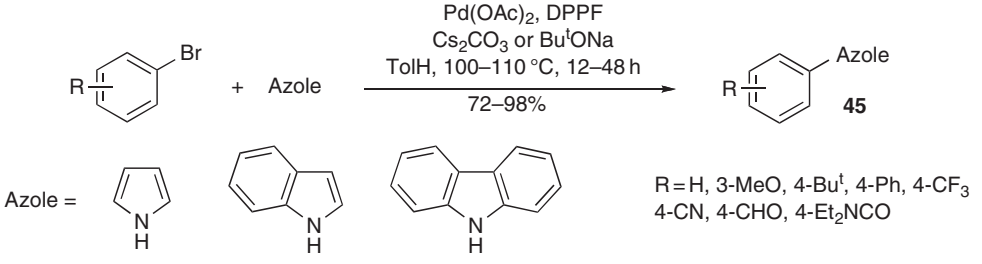


Relatively acidic indoles such as **44** can be alkylated on nitrogen using an alcohol and diethyl azodicarboxylate (DEAD), i.e. Mitsunobu reaction conditions (**Scheme 11**).



Scheme 11

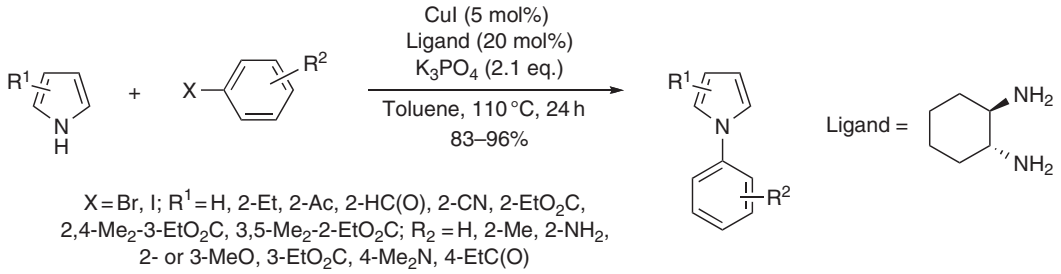
3.3.1.3.1.3 N-Arylation. The development of palladium chemistry now allows relatively easy N-arylations of pyrroles and indoles, using aryl iodides and bromides <1998JA827, 2000OL1403>. The combination of $Pd(OAc)_2$ and DPPF catalyzes the formation of N-aryl azoles **45** in the presence of Cs_2CO_3 or *t*-BuONa with electron-rich, electron-neutral, or electron-poor aryl halides (**Scheme 12**) <1998JA827>. The system $Pd(OAc)_2$, SIPrñHCl, NaOH [where SIPr = 1,3-bis



Scheme 12

(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene] is efficient for the N-arylation of diverse indoles with aryl bromides but, again, is not effective for the reaction with aryl chlorides <2001JOC7729>.

A catalytic system involving *t*-Bu_3P as ligand allows for arylation of indoles and pyrroles with aryl chlorides at 100°C in 12 h; the use of Cs_2CO_3 as base, rather than *t*-BuONa, is crucial <1999JOC5575, 2000OL1403>. CuI and *trans*-1,2-cyclohexanediamine in the presence of K_3PO_4 is an extremely efficient, inexpensive, and general catalyst system for the N-arylation of a number of azoles, including azaindoles (e.g., **Scheme 13**) <2001JA7727, 2004JOC5578>.

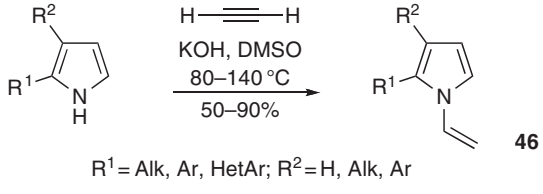


Scheme 13

The conditions developed by Chan and Lam <1998TL2933, 1998TL2941> can also be applied to pyrroles and indoles for N-arylation with arylboronic acids in the presence of cupric acetate and either triethylamine or pyridine at room temperature <1999T12757>. The use of microwave heating makes Ullman N-arylations of pyrroles and indoles a practical proposition <2003TL4217>.

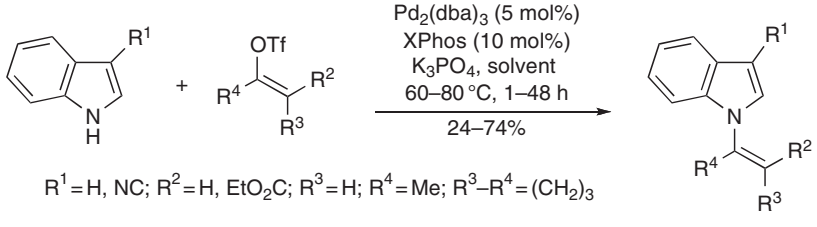
3.3.1.3.1.4 N-Vinylation. *N*-Vinylpyrroles **46** can be made by addition to alkynes (**Scheme 14**), including *in situ* vinylation following Trofimov pyrrole ring synthesis from ketoximes and acetylene, e.g., <1998JOC10022, 2000S1585, 2003S1272, 2005JME5140>, Pd-catalyzed reaction with vinyl bromides or triflates, e.g., <2002OL623, 2005JOC8638>, or vinylation via substitutionelimination with dihaloalkanes, e.g., <1998JOC10022, 2005JME5140>.

Addition to alkynes can also be carried out with catalytic $CsOH.H_2O$ at 90110°C <1999TL6193>. The palladium-



Scheme 14

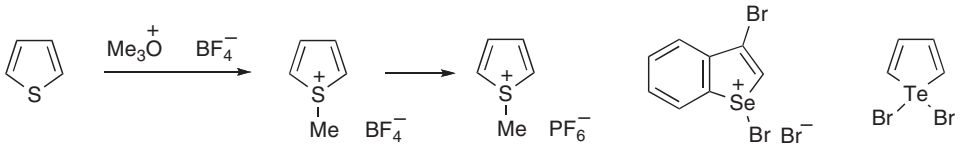
catalyzed processes are well illustrated by reactions of indoles (**Scheme 15**) and pyrroles using XPhos (2-dicyclohexylphosphino-2,4,6-triisopropyl-1,1-biphenyl) <2005JOC8638>.



Scheme 15

3.3.1.3.2 Thiophenes, selenophenes, and tellurophenes

3.3.1.3.2.1 Alkylation and halogenation. Alkylating agents capable of forming thiophenium salts include trimethyloxonium tetrafluoroborate (Me_3O^+ BF_4) and alkyl fluorosulfonates ($ROSO_2F$). The salts (e.g., **47**) are conveniently isolated as hexafluorophosphates **48**.



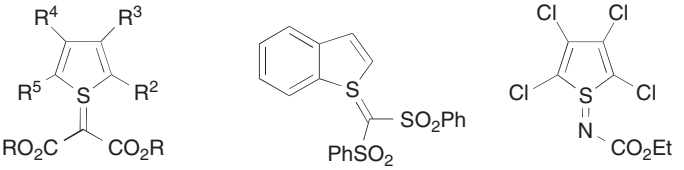
47 **48** **49** **50**

Halogens attack the ring heteroatom in selenophene and tellurophene. Thus, the selenienyl bromide **49** is among the bromination products of benzo[*b*]selenophene. Tellurophene reacts with halogens to give 1,1-dihalo derivatives (e.g., **50**).

3.3.1.3.2.2 Ylide formation. Thiophenium bis(alkoxycarbonyl)methylides **51** are obtained in high yield by rhodium(II) carboxylate-catalyzed reaction of diazomalonate esters with thiophenes. Likewise, ylides (e.g., **52**) from benzo[*b*]thiophene and dibenzothiophene are obtained by *trans*-ylidation using phenyliodonium bis(phenylsulfonyl) methylide.

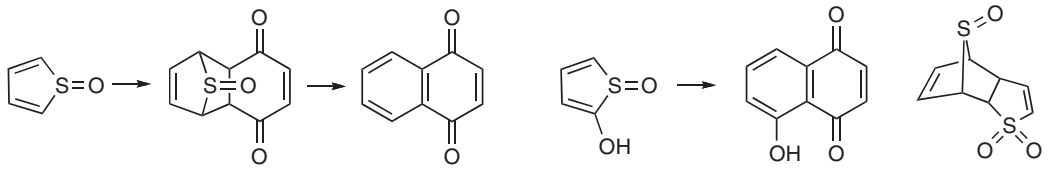
It was formerly considered that nitrenes attack only the carbon atoms of thiophene; however, several *S,N*-ylides formed by the attack of a nitrene on the ring sulfur atom of thiophene have been prepared. Thus, ethoxycarbonyl nitrene with polyhalogenothiophenes forms *S,N*-ylides, e.g., **53**, in 44% yield; X-ray analysis reveals that the sulfur in such ylides is pyramidal.

Thiophene *S,N*-ylides are comparable to the 1-mono- and 1,1-dioxides in that they exhibit diene rather than aromatic properties. The *S,S*-ylides appear to be more sluggish in cycloaddition reactions and are therefore considered more aromatic.



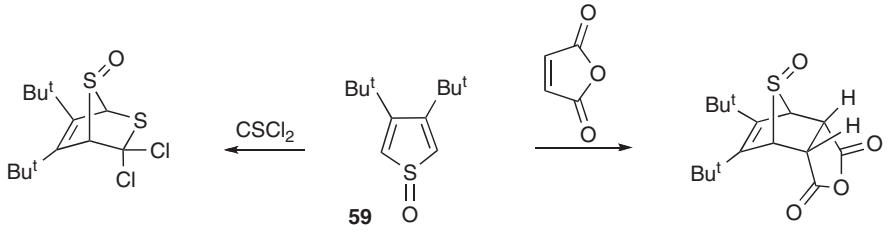
51 **52** **53**

3.3.1.3.2.3 Oxidation. Very vigorous oxidation of the thiophene ring results in breakdown to maleic and oxalic acids and ring sulfur is oxidized to sulfuric acid. Oxidation of thiophene with peracid under carefully controlled conditions gives a mixture of thiophene sulfoxide **54** and 2-hydroxythiophene sulfoxide **56**. These compounds can be trapped by addition to benzoquinone to give ultimately naphthoquinones **55** and **57**. Dimerization via a DielsAlder reaction gives **58**.



54 **55** **56** **57** **58**

3,4-Di-*tert*-butylthiophene 1-oxide **59**, which is thermally stable, can be prepared by S-oxidation with *m*CPBA. It undergoes DielsAlder reaction with electron-deficient <2003JA8255> as well as electron-rich dienophiles with very high -facial and *endo*-selectivities <2005TL4165>. The approach of dienophile in each case is from *syn*--face with respect to the S═O bond (**Scheme 16**).

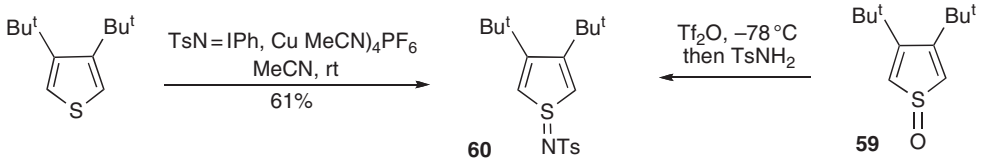


Scheme 16

Unsubstituted thiophene 1,1-dioxide is highly unstable and difficult to isolate. It was prepared for the first time by oxidation of thiophene with dimethyldioxirane at 20°C under neutral conditions <1997JA9077, 1999BCJ1919>. The compound has a very short half-life and undergoes [2 + 4] dimerization followed by SO_2 extrusion to give dihydrobenzothiophene 1,1-dioxide, which reacts further by cycloaddition with thiophene 1,1-dioxide.

Stable sulfones have been obtained from oxidation of 2,5-dimethylthiophene and benzo[*b*]thiophene with dimethyldioxirane. Trifluoroperacetic acid in MeCN in the absence of water is an effective reagent for the oxidation of thiophenes bearing electron-withdrawing groups to the corresponding thiophene 1,1-dioxides <2001TL4397>.

3,4-Di-*t*-butyl-1-tosyliminothiophene **60** is obtained by reaction of the thiophene with tosylnitrene generated from [*N*-(*p*-tolylsulfonyl)imino]phenyl-^{3}-iodinane (TsN═IPh) at room temperature, best in the presence of $Cu(MeCN)_4PF_6$ <1999TL5549>; traces of the corresponding 1,1-ditosyliminothiophene are also formed. Alternatively, compound **60** can be obtained from the oxide by reaction with Tf_2O at 78°C then $TsNH_2$ (**Scheme 17**) <2000TL8461>.



Scheme 17

3.3.1.4 Electrophilic Attack on Carbon: General Considerations

3.3.1.4.1 Relative reactivities of heterocycles

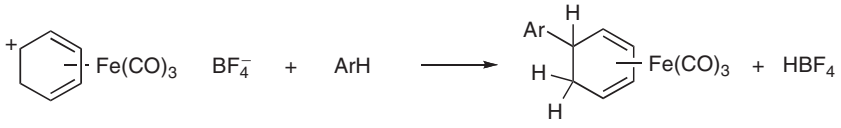
Electrophilic substitution is much easier than in benzene. Thiophene reacts about as readily as mesitylene; pyrrole and furan react as readily as phenol or even resorcinol. The following generalizations can be made:

1. *Aromaticity and relative reactivity*: The ground-state stability and aromaticity decrease in the order benzene > thiophene pyrrole > selenophene > tellurophene > furan. Hence, all these heterocycles are more reactive than benzene. However, among them, the reactivity is governed by the polarizability of the heteroatom. Thus, sulfur is more polarizable than oxygen, but thiophene has greater ground-state stability than furan. A single $^+$-parameter will therefore not accurately describe the quantitative reactivities of these heterocycles under all conditions.
2. *Relative rates*: The order of reactivities at position 2 is pyrrole > furan > tellurophene > selenophene > thiophene. Where data are available for both 2- and 3-positions, the following order is seen: 2-furan > 2-thiophene > 3-furan > 3-thiophene. Reactivity parameters ($^+$) for the 2- and 3-positions of thiophene for reactions of varying -values (ranging from 0.66 to 12.0) have been established.

The reactivity of five-membered rings with one heteroatom to electrophilic reagents has been quantitatively compared. **Table 1** shows that the rates of substitution for (1) formylation by phosgene and *N*,*N*-dimethylformamide, (2) acetylation by acetic anhydride and tin(IV) chloride, and (3) trifluoroacetylation with trifluoroacetic anhydride are all in the sequence furan > tellurophene > selenophene > thiophene. Pyrrole is still more reactive as shown by the rate of trifluoroacetylation, the relative rates of bromination of the 2-methoxycarbonyl derivatives (pyrrole > furan > selenophene > thiophene), and the rate data for the reaction of the iron tricarbonyl-complexed carbocation $[C_6H_7Fe(CO)_3]^+$ (**Scheme 18**) (2-methylindole *N*-methylindole > indole > pyrrole > furan > thiophene).

Table 1 Relative rates of reaction of thiophene, selenophene, tellurophene, and furan in selected electrophilic substitution reactions

Heterocycle	*Acetylation (25°C)*	*Trifluoroacetylation (75°C)*	*Formylation (30°C)*
Thiophene	1	1	1
Selenophene	2.28	7.33	3.64
Tellurophene	7.75	46.4	36.8
Furan	11.9	140.0	107.0



Scheme 18

The electrophilic substitution of thiophene is much easier than that of benzene; thus, thiophene is protonated in aqueous sulfuric acid about 10^3 times more rapidly than benzene, and it is brominated by molecular bromine in acetic acid about 10^9 times more rapidly than benzene.

3. *Sensitivity to substituent effect*: conjugative effects are strongly transmitted in the five-membered heterocycles. The greater the degree of bond fixation in the heterocycle, the more difficult it will be to place a double bond across C(3) and C(4). The ease of transmission will therefore parallel the aromaticity, namely benzene > thiophene > pyrrole > selenophene tellurophene > furan. Thiophene is less effective at transmitting substituent effects than benzene (except in protodesilylation). Hammett factors for benzene and thiophene have been compared. The greater ability of substituents on thiophene to attain coplanarity with the heteroaromatic ring, when compared with the situation with benzene, may result in a magnification of the resonance effect (+M or M). For the same reason, for reactions involving side-chain carbocations, the heterocycle may appear to be a better transmitter than benzene.

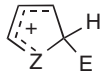
   The effect of substituents on the reactivity of heterocyclic nuclei is broadly similar to that on benzene. Thus, *meta*-directing groups such as methoxycarbonyl and nitro are deactivating. The effects of strongly activating groups such as amino and hydroxy are difficult to assess since simple amino compounds are unstable, and hydroxy compounds exist in an alternative tautomeric form. Comparison of the rates of formylation and trifluoroacetylation of the parent heterocycle and its 2-methyl derivative indicates the following order of sensitivity to substituent effects: furan > tellurophene > selenophene thiophene.

4. The effect on electrophilic substitution reactions of the fusion of a benzene ring to the *b* face of a furan or thiophene ring is to decrease reactivity; this decrease is much more pronounced in the case of fusion to a furan than to a thiophene ring. As a consequence the overall reactivities of benzo[*b*]furan and benzo[*b*]thiophene are approximately equal.

Partial rate factors and $^+$ values for detritiation have been calculated from the rates of deuteriation for indole, 1-methylindole, 2-methylindole, 1,2-dimethylindole, and *N*-methylisoindole and confirm the known reactivity patterns. Isoindole is the most reactive, being approximately 10^4 times more reactive than indole.

3.3.1.4.2 Directing effects of the ring heteroatom

Monocyclic five-membered heteroaromatics with one heteroatom all undergo preferential - rather than -electrophilic substitution. This is rationalized in terms of the more effective delocalization of charge in the intermediate **61** leading to -substitution than in the intermediate **62** leading to -substitution.



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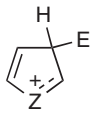


62

Z = NH, O, S, Se, or Te

However, these considerations apply to reactions in solution. In the dilute gas phase, where the intrinsic orientating properties of pyrrole can be examined without the complication of variable phenomena such as solvation, ion pairing, and catalyst which are attendant on electrophilic substitution reactions in solution, preferential -attack occurs on pyrrole. In gas-phase *tert*-butylation, the relative order of reactivity at -carbon, -carbon, and nitrogen is 10.3:3.0:1.0.

The -directing effect of the heteroatom is in the order furan >> thiophene selenophene >> pyrrole. The -directing effect in tellurophene is also pronounced.

Possible reasons for the high regioselectivity of furan in electrophilic substitution reactions include complex formation between substrates and reagents and the ability of heteroatoms to assist in the stabilization of cationic intermediates.

The observed ratio of - to -substitution products can also be influenced by reaction temperature. For example, in the acylation of thiophene a higher proportion of -substituted product is obtained by reaction at higher temperatures. The isolated product ratios may reflect thermodynamic rather than kinetic control because of acid-catalyzed rearrangements. 2- or 3-Substituted pyrroles undergo acid-mediated rearrangement, in some cases under extremely mild conditions. Migration of bromo, chloro, acyl, sulfinyl, sulfonyl, and sulfenyl groups has all been observed. Acid-mediated rearrangements also occur in the thiophene series.

Positional selectivity in electrophilic substitution reactions, including methods of orientation control, has been reviewed <1994H(37)2029>.

3.3.1.4.3 Directing effects of substituents in monocyclic compounds

Large 1-alkyl substituents increase -substitution in the Vilsmeier formylation of pyrroles. A similar trend occurs in trifluoroacetylation of N-alkyl pyrroles. The trifluoroacetylation, formylation, and bromination of 1-tritylpyrrole occur regioselectively at the 3-position in high yield. The same effect is seen in 1-triisopropylsilylpyrrole and the ease of removal of the *N*-silyl substituent makes the use of such substitutions for the synthesis of 3-substituted N-unsubstituted pyrroles very important.

Electron-donor 2-substituents orient substitution in furan, thiophene, and selenophene to the 5-position. In pyrrole, although the ratio of to reactivity is much smaller than in the other five-membered rings, 5-substituted 2-alkylpyrroles still appear to be the major products.

Electron-donor 3-substituents supplement the -directing effect of the heteroatom and direct the incoming electrophile to the 2-position. However, steric effects can offset this trend, leading to an increased proportion of 5-substitution.

For pyrroles with electron-acceptor substituents at the 1-position, electrophilic substitution with soft electrophiles can be frontier orbital controlled and occur at the 2-position, whereas electrophilic substitution with hard electrophiles can be charge controlled and occur at the 3-position.

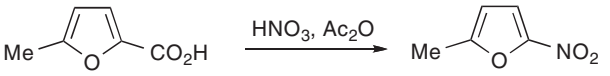
Nitration and FriedelCrafts acylation of 1-phenylsulfonylpyrrole occur at the 3-position, whereas the softer electrophiles generated in the Mannich reaction ($R_2N^+{=}CH_2$), in formylation under Vilsmeier conditions ($R_2N^+{=}CHCl$) or in formylation with dichloromethyl methyl ether and aluminum chloride ($MeO^+{=}CHCl$), effect substitution mainly in the 2-position.

For electron-acceptor substituents such as NO_2, CN, and COR in the 2-position, position 4 is least deactivated by the substituent, but position 5 is most activated by the ring heteroatoms. In practice, such 2-substituted furans give exclusively 5-substitution, whereas for analogous thiophenes and especially pyrroles, increasing amounts of 4-substitution occur. For example, nitration of 1-methylpyrrole-2-carboxylic acid with Ac_2OHNO_3 gives the 4-nitro compound in 40% yield <1999TL3621, 2002EJO3604>, and comparable treatment of 2-trifluoroacetylpyrroles similarly proceeds at C(4) <2005ARK(iii)179>. The harder the electrophile, the greater the tendency for 4-substitution.

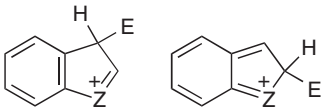
Formylation of methyl l-methylpyrrole-2-carboxylate with dichloromethyl methyl ether and aluminum chloride occurs in the 4-position, while under Vilsmeier conditions the main product is the 5-formyl derivative.

With electron-withdrawing substituents at the 3-position, mutually reinforcing directing effects combine to direct substitution into the 5-position.

Electrophilic substitution of 2,5-disubstituted compounds normally occurs at a remaining -position, but in some cases displacement of an -substituent such as carboxyl, acyl, or halogen takes place (e.g. **Scheme 19**).



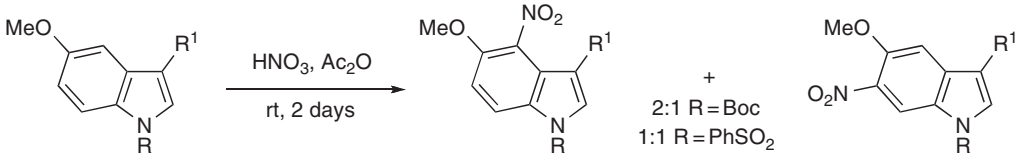
Scheme 19



63 **64**

3.3.1.4.4 Directing effects of fused benzene rings

A [*b*]-fused benzene ring would be expected to favor -substitution in the heterocyclic ring **63** over -substitution **64** based on the expected -complex stability as a measure of relative transition state energies. The presence of activating groups on the benzene ring of indoles can influence regioselectivity, e.g., **Scheme 20** <2002JME1853>.



Scheme 20

Benzo[*b*]furan undergoes mainly -substitution, benzo[*b*]thiophene undergoes mainly -substitution, and indole undergoes almost exclusive -substitution. This again illustrates the very strong directing effect of the oxygen atom in the - position.

Electrophilic reactions of benzo[*b*]thiophenes have been analyzed but there are no quantitative reactivity data for benzo[*c*]thiophenes because of stability problems. In benzo[*b*]thiophene, position 3 is usually more reactive than position 2; this can be easily rationalized in terms of the number of mesomeric structures having an aromatic benzene ring for the transition state for substitution. Thus, when conjugative effects are relatively unimportant, the reactivity order is $3 > 2$. But for reactions with transition states nearer to the Wheland intermediate, position 2 might become as reactive as position 3. Turning to the quantitative aspect, the $^{+}$ values are not constant; they generally increase with increasing demand for resonance stabilization of the transition state, such as in acetylation and molecular halogenation.

3.3.1.4.5 Range of substitution reactions

The range of preparatively useful electrophilic substitution reactions is often limited by the acid sensitivity of the substrates. Whereas thiophene can be successfully sulfonated in 95% sulfuric acid at room temperature, such strongly acidic conditions cannot be used for the sulfonation of furan or pyrrole. Attempts to nitrate thiophene, furan, or pyrrole under conditions used to nitrate benzene and its derivatives invariably result in failure. In the case of sulfonation and nitration, milder reagents can be employed, i.e., the pyridinesulfur trioxide complex and acetyl nitrate, respectively. Attempts to carry out the FriedelCrafts alkylation of furan are often unsuccessful because the required catalysts cause polymerization.

The higher relative rate of reaction of pyrrole with electrophilic reagents, compared with the other five-membered rings with one heteroatom, is paralleled by the greater range of reactions it undergoes. Thus pyrrole, unlike furan and thiophene, can be C-nitrosated and can undergo diazo coupling reactions, probably involving the pyrryl anion. In a similar fashion, *N,N*-dimethylaniline and enamines show enhanced reactivity over anisole and enol ethers, respectively.

The benzo[*b*]-heterocycles are generally less reactive than their monocyclic counterparts.

3.3.1.5 Electrophilic Attack on Carbon: Specific Reactions

3.3.1.5.1 Proton acids

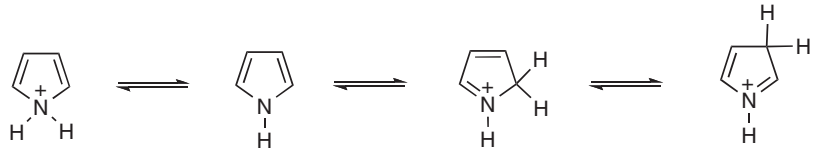
The -complexes formed by proton addition to a carbon atom can sometimes be isolated to give, for example, pyrrole salts. Reversal by proton loss results in acid-catalyzed hydrogen exchange of the ring hydrogen atoms. The -complex can undergo rearrangement before proton loss. The -complex can itself react as an electrophile, with other molecules of heterocycle, leading to oligomerization or polymerization, or with other nucleophiles; such reactions are discussed in Section 3.3.1.6.3.

3.3.1.5.1.1 Base strengths. The pK_a values of pyrroles and benzopyrroles are given in **Table 2**. These basicities are lower than those of enamines in consequence of the loss of aromaticity which accompanies protonation on the ring nitrogen or on C(2) or C(3).

Table 2 pK_a values of some pyrroles and benzopyrroles

Parent heterocycle	*Substituent*	*p*K$_a$	*Position of protonation*	*Reference*
Pyrrole		3.8	2	1963JA2763
	1-methyl	2.9	2	1963JA2763
	2-methyl	0.2	2	1963JA2763
	3-methyl	1.0	2	1963JA2763
Indole		3.6	3	1964JA3796
	1-methyl	2.3	3	1964JA3796
	2-methyl	0.3	3	1964JA3796
	3-methyl	4.6	3	1964JA3796
Isoindole			1 or 3	
	2,5-dimethyl-1,3-diphenyl	+2.05	1 or 3	1976T1767
Indolizine		+3.9	3	1976T1767
Carbazole		6.0	9	1976T1767

The pK_a for protonation of pyrrole at C(2) to the thermodynamically stable 2*H*-pyrrolium ion is 3.8; the corresponding pK_a values for protonation at C(3) and at nitrogen are 5.9 and ca. 10 (**Scheme 21**).

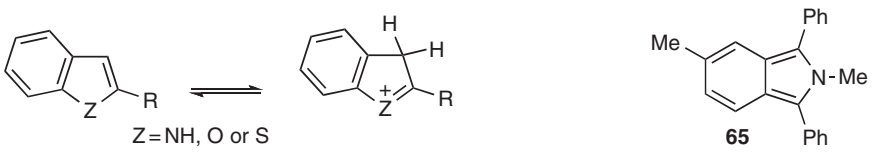


Scheme 21

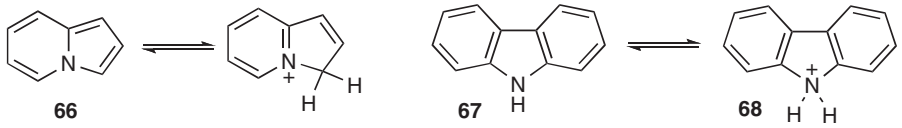
For pyrrole, furan, and thiophene, the pK_a values of their 2,5-di-*tert*-butyl derivatives are 1.01, 10.01, and 10.16, respectively. In each case, protonation occurs at position 2. Thiophene itself similarly protonates at C(2) <2000AHC (76)85>. The base-strengthening effect of alkyl substitution is clearly apparent by comparison of pyrrole and its alkyl derivatives; for example, *N*-methylpyrrole has a pK_a of 2.9 for -protonation and 2,3,4,5-tetramethylpyrrole has a pK_a of +3.7. In general, protonation of -alkylpyrroles occurs at the -position, whereas -alkylpyrroles are protonated at the adjacent -position. As expected, electron-withdrawing groups are base weakening; thus, *N*-phenylpyrrole is reported to have a pK_a of 5.8.

The pK_a for the protonation of indole at position 3 is 3.6 and the pK_a values of 2-methylindole, 2-methylbenzo[*b*]furan, and 2-methylbenzo[*b*]thiophene for -protonation are 0.3, 13.3, and 10.4, respectively (**Scheme 22**).

Isoindoles are more basic than indoles or pyrroles. For example, 2,5-dimethyl-1,3-diphenyl-isoindole **65** has a pK_a of +2.05; protonation of isoindoles occurs at position 1 or 3. The pK_a for protonation of indolizine **66** at position 3 is +3.94 and that of carbazole for protonation on nitrogen (**67** **68**) is estimated as 6.0.



Scheme 22



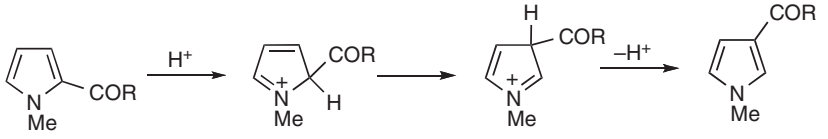
Stable -protonated pyrrolium salts have been obtained by treating di- and tri-*tert*-butylpyrroles with tetrafluoroboric acid, and stable -protonated thiophenium salts result from the reaction of thiophenes with hydrogen chloride and aluminum trichloride in an inert solvent.

The gas-phase basicities at both the - and -positions in five-membered heterocycles have been studied by ion cyclotron resonance equilibrium and bracketing experiments on deuteriated substrates. -Protonation is preferred by 2.8 4.6 kcal mol^{1} for both furan and thiophene as compared to 02.9 kcal mol^{1} for pyrrole, and heteroatom protonation is much less favored than -protonation. Semiempirical (MNDO) molecular orbital calculations are in agreement with the above conclusions.

3.3.1.5.1.2 Acid-catalyzed hydrogen exchange. The ring hydrogen atoms of pyrrole, furan, and thiophene exchange in acid. Relative rates are in the order 2-pyrrole > 3-pyrrole > 2-thiophene > 3-thiophene 2-furan. No exchange of the 3-position in furan could be found; ring opening intervenes. For pyrrole, the exchange rate is ca. 10^{15} times that for benzene. The N-hydrogen of pyrroles exchanges in neutral solution, presumably via the N-anion (see Section 3.3.1.3.1).

Acid-catalyzed hydrogen exchange in thiophenes has been reviewed <1990AHC(47)87>. The recognition that thiophene (as well as furan and pyrrole) can participate in hydrogen-bond formation in certain acidic solvents explains a reduction in reactivity. Evidence for this small effect comes from the determination of rate coefficients for detritiation of 2-tritio- and 3-tritiothiophene in 100% TFA and TFAHOAc (35:65). The relative rate of thiophene in these two systems is 2420, compared with 5230 for mesitylene. The lower value for thiophene is ascribed to hydrogen bonding of the solvent to sulfur, thereby reducing the availability of the lone pair for resonance with the -system of the ring.

3.3.1.5.1.3 Rearrangement. The acid-catalyzed rearrangements of substituted pyrroles and thiophenes consequent on *ipso* protonation have been referred to previously (Section 3.3.1.4.2). There is some evidence that these rearrangements are intramolecular in nature, since in the case of acid-induced rearrangement of 2-acylpyrroles to 3-acylpyrroles, no intermolecular acylation of suitable substrates could be demonstrated (**Scheme 23**).



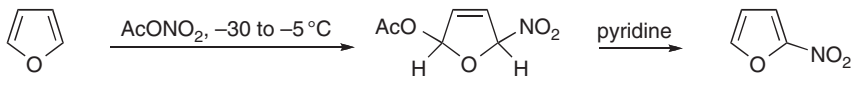
Scheme 23

3.3.1.5.2 Nitration

The acid sensitivity of pyrrole dictates the use of acetyl nitrate as nitrating agent; the main product is the 2-nitro derivative together with some of the 3-nitro compound. The nitration of N-substituted pyrroles yields relatively more -substituted product, and with electron-withdrawing groups such as acetyl or ethoxycarbonyl at the 2-position,

comparable amounts of 4- and 5-nitro derivatives are obtained. 3-Nitropyrrole is efficiently prepared by nitration of 1-phenylsulfonylpyrrole followed by hydrolysis of the N-substituent.

Furan and acetyl nitrate give an addition product which is converted by pyridine into 2-nitrofuran (**Scheme 24**). The positions in which substituted furans undergo nitration with acetyl nitrate are shown in **Figure 1** and illustrate the rules of orientation.



Scheme 24

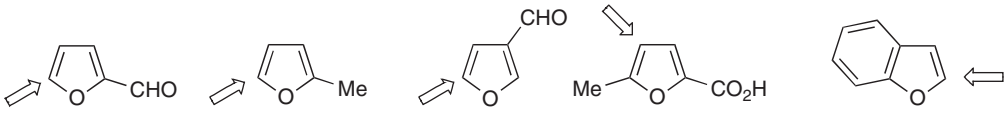


Figure 1 Positions of nitration of substituted furans.

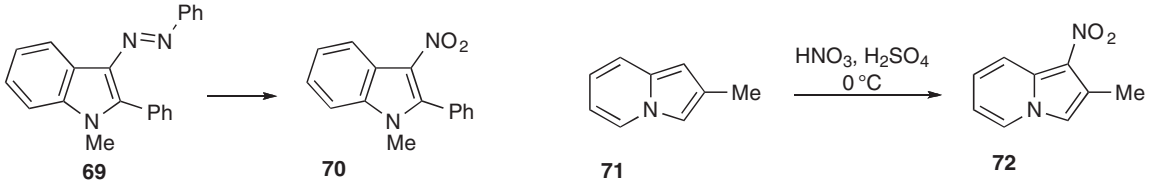
The nitration of furfural in the presence of acetic anhydride gives 5-nitrofurfural diacetate (74%).

Thiophene is nitrated by mild nitrating agents such as acetyl or benzoyl nitrate, mainly in the 2-position. The selectivity decreases with increasing vigor of the reagent and up to 15% of the 3-isomer can be obtained. 2-Cyanothiophene is nitrated predominantly at position 4.

Indole with benzoyl nitrate at low temperatures gives 3-nitroindole; this can also be obtained by reaction of the indolyl anion with ethyl nitrate. More vigorous conditions can be used for the nitration of 2-methylindole because of its resistance to acid-catalyzed polymerization. In nitric acid alone it is converted into the 3-nitro derivative, but in a mixture of concentrated nitric and sulfuric acids 2-methyl-5-nitroindole is formed, by conjugate acid nitration (see Section 3.3.3.2.1).

There are examples of *ipso* attack during the nitration of pyrroles, furans, and thiophenes and in the corresponding benzo-fused systems. Reactions resulting in nitro-dealkylation, nitro-deacylation, nitro-decarboxylation, and nitro-dehalogenation are known. Treatment of the 3-phenylazoindole **69** with nitric acid in acetic acid at room temperature gives 80% of the 3-nitroindole **70**.

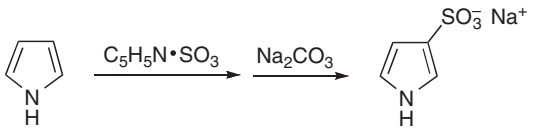
Nitration of benzo[*b*]thiophene (HNO_3/AcOH) yields mainly the 3-nitro derivative with about 17% product whereas indole itself undergoes almost exclusive substitution. Benzo[*b*]furan undergoes nitration to give 2-nitrobenzo[*b*]furan in 62% yield using sodium nitrate and ceric ammonium nitrate under ultrasonic conditions <1996OM499>; the same nitro compound can be obtained by *ipso* displacement of tin from 2-trimethylstannylbenzo[*b*]furan <2003EJO1711>. Indolizines are readily nitrated, e.g., brief treatment of 2-methylindolizine **71** with a mixture of concentrated nitric and sulfuric acids gives 2-methyl-l-nitroindolizine **72**.



69 **70** **71** **72**

3.3.1.5.3 Sulfonation

Both pyrrole and furan can be sulfonated with the pyridinesulfur trioxide complex. The pyrrole product is now known to be the 3-sulfonic acid (**Scheme 25**) <2000TL6605>. The reaction of 1-methyl-2-tri-*n*-butylstannylpyrrole with trimethylsilyl chlorosulfonate, followed by quenching with aqueous $NaHCO_3$ generates sodium 1-methylpyrrole-3-sulfonate. Furan-2-sulfonic acid can be further sulfonated with pyridineSO_3 to give the 2,5-disulfonate.



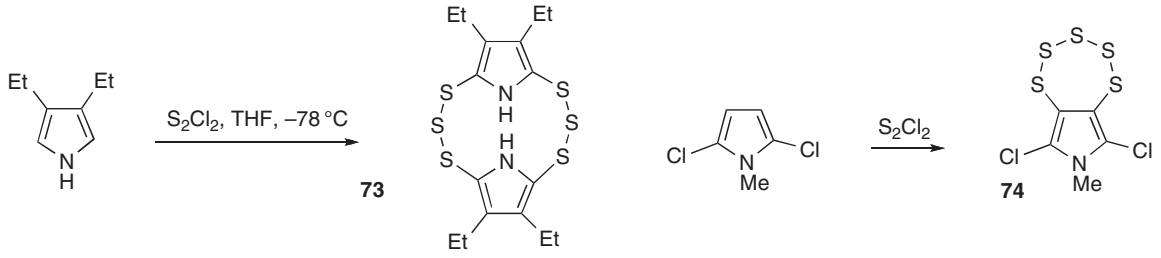
Scheme 25

Thiophene, which is more stable to acid, is readily sulfonated by shaking with concentrated sulfuric acid at room temperature. Benzene is not reactive under these conditions and this is the basis for the classical purification of benzene from thiophene contamination. Historically, use of this reaction enabled the first identification of thiophene. With all three heterocycles, if the -positions are blocked, then sulfonation occurs at the -position.

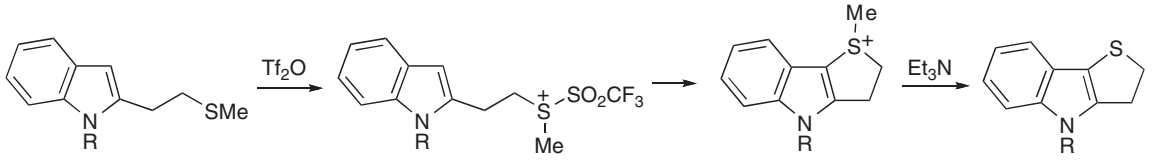
Indole and benzo[*b*]thiophene are sulfonated under similar conditions to pyrrole; the 3-sulfonic acid is formed in each case.

The direct introduction of a thiocyanato group to C(3) of indoles results from reaction with $NH_4SCNFeCl_3$ at room temperature <2005S961>.

Sulfur groups at lower oxidation level can also be substituted into indoles and pyrroles. Disulfur dichloride, for example, reacts with 3,4-diethylpyrrole to produce 12-membered ring compound **73** <2005CC2122>. Reaction with 2,5-dichloropyrrole (no free -positions) formed a ring across carbons C(3) and C(4) giving **74** <2003ARB161>. Reaction of *N*-methylindole also produced a pentathiepin, across the 2- and 3-positions.



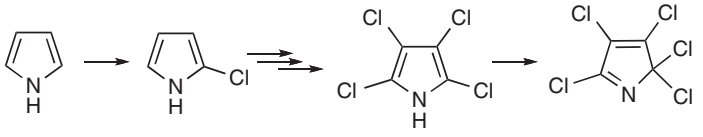
S-Alkylations in an intramolecular sense are achieved by treatment of thioethers with Tf_2O, as exemplified in **Scheme 26** <2003S1191>. 3-Phenylsulfanylindole <1988S480> can be converted into the 2-isomer by exposure to PPA <1992JOC2694>.



Scheme 26

3.3.1.5.4 Halogenation

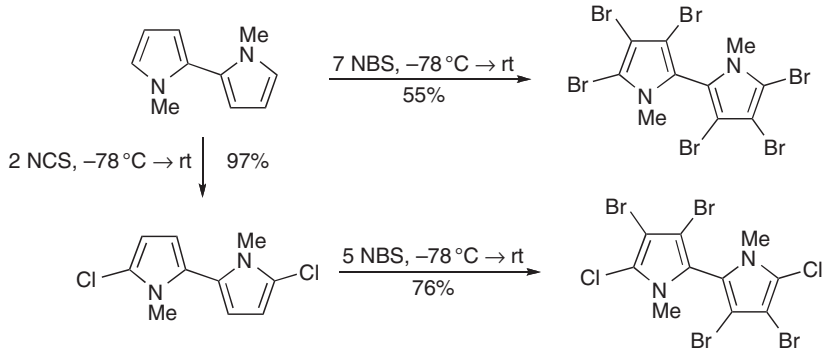
Pyrrole is readily halogenated. Chlorination with one equivalent of sulfuryl chloride in ether at 0 °C gives 2-chloropyrrole; further chlorination with this reagent yields di-, tri-, and tetra-chloro derivatives and ultimately pentachloro-2*H*-pyrrole **75**.



75

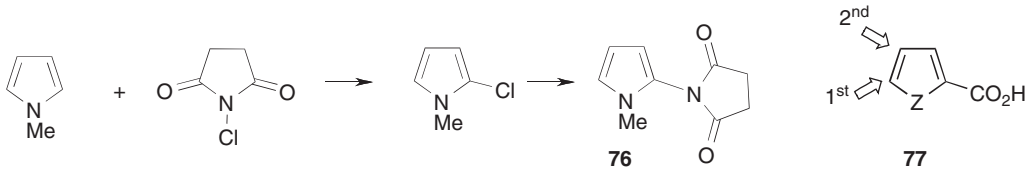
Treatment of pyrrole, 1-methyl-, 1-benzyl-, and 1-phenylpyrrole with one mole of *N*-bromosuccinimide in THF results in the regiospecific formation of the corresponding 2-bromopyrroles. Pyrroles with electron-withdrawing groups such as acyl or ethoxycarbonyl at C(3), undergo bromination using copper(II) bromide. Pyrrole with bromine in acetic acid gives 2,3,4,5-tetrabromopyrrole; iodine in aqueous potassium iodide yields the corresponding tetraiodo compound. 2-Trichloroacetylpyrrole mono-brominates with Br_2 at room temperature at C(4) <1997J(P1)1443>. *N*-Boc-pyrrole gives the 2,5-dibromo derivative cleanly on reaction with NBS at low temperature <2002T6373>; -iodination can also be achieved with *N*-Boc-pyrroles <2004T11283>.

A nice example showing both the -regioselectivity of halogenation and also just how reactive pyrroles are (halogenation at all available positions) is shown in **Scheme 27** <1999CC2195>.



Scheme 27

Chlorination with *N*-chlorosuccinimide is less selective. 1-Methylpyrrole reacts with *N*-chloroimides to give **76** in which the imidyl group is attached to C(2); the 2-chloro compound is proposed as an intermediate (**Scheme 28**). Chlorination of 2-methylpyrrole with *N*-chlorobenzamides, catalyzed with dichloroacetic acid at 40°C, proceeds cleanly at C(2) and then further to give the 2,5-dichloropyrrole <2003T2125>.



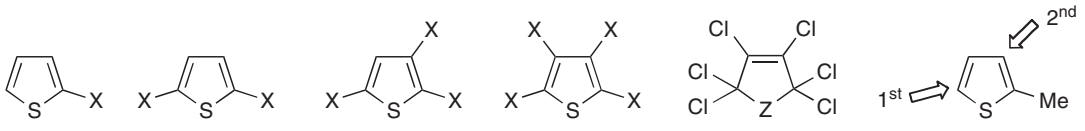
Scheme 28

Pyrroles containing an electron-withdrawing group at C(2) undergo fluorination only at C(5) in 2554% yield using xenon difluoride in acetonitrile. The reaction fails if the pyrroles contain no electron-withdrawing groups or two electron-withdrawing groups. Replacement of the solvent acetonitrile with dichloromethane results in chlorination instead of fluorination.

Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products. Low-temperature (40°C) reaction of furan with chlorine in dichloromethane yields mainly 2-chlorofuran and reaction of furan with dioxane dibromide at 0°C affords 2-bromofuran in good yield. Furans stabilized by electron-withdrawing groups are halogenated more smoothly; thus, 2-furoic acid is brominated to form successively the 5-monobromo and 4,5-dibromo derivatives [cf. **77** (Z = O)]. The bromination of furan when carried out in DMF using one or two equivalents of bromine gives 2-bromo- or 2,5-dibromo-furan. Bromination occurs at the 4-position of 5-methylfuran-2-carboxaldehyde. 2-Iodofuran is obtained by treatment of 2-furoic acid with iodine and potassium iodide in aqueous sodium hydroxide.

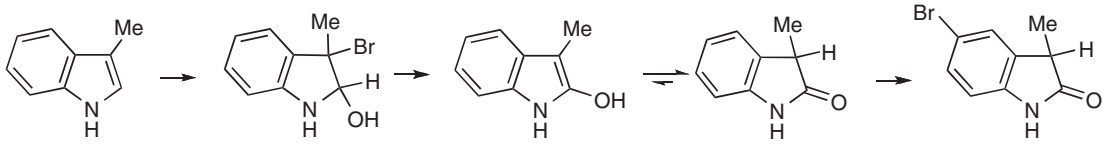
Chlorine and bromine react with thiophene to give successively the halogenation products shown (**7881**). The bromination can be interrupted at the intermediate stages; monochloro and dichloro derivatives have been obtained

preparatively by chlorination with MeCONHCl. Addition products are also formed during chlorination; prolonged action (with Cl_2I_2) gives the dihydrothiophene derivative **82** (Z = S). Iodination (I_2HgO) results in mono- and diiodothiophenes **78** and **79** (X = I) only. Substituted compounds are halogenated as expected, e.g., **83**.



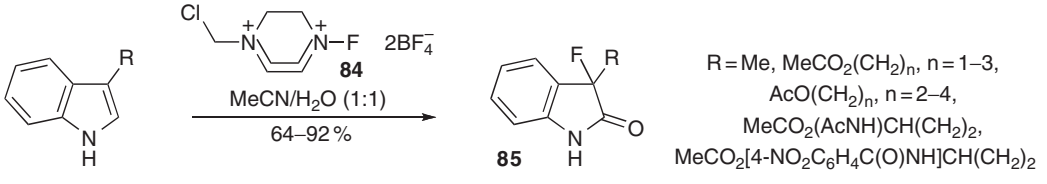
78 **79** **80** **81** **82** **83**

3-Chloroindole has been prepared from indole and sulfuryl chloride and 3-bromo- and 3-iodo-indole have been obtained by direct halogenation in DMF (e.g., <2003TL3927>) or dioxane (e.g., <2004H(62)191>). 3-Iodoindoles can also be obtained easily by reaction with I_2KOH, though this process probably involves reaction with the indolyl anion <2004S0610>. 3-Bromoindole is obtained in high yield by reaction of 1-trimethylstannylindole with bromine <2002OL2321>; 9-trimethylstannylcarbazole gives 3-bromocarbazole. 2-Methylindole reacts with sodium hypochlorite in carbon tetrachloride to give a 2:1 mixture of 1,3- and 3,3-dichloro derivatives. 3-Substituted indoles are halogenated to yield 3-halo-3*H*-indolium ions which react in a variety of ways, as illustrated by the reaction of 3-methylindole with NBS in aqueous acetic acid (**Scheme 29**). However, *N*-Boc- or *N*-phenylsulfonyl-3-methylindoles can be cleanly 2-brominated with NBS in refluxing CCl_4; in the presence of AIBN as radical initiator, 3-bromomethylindoles result <1995TL3103>.



Scheme 29

3-Substituted indoles react with Selectfluor [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **84**] as an electrophilic fluorinating reagent <2004ACR31>, either in $MeCN/H_2O$ <2000OL639> or in an ionic liquid/alkanol mixture <2002TL6573>, producing 3-fluoro-1,3-dihydro-2*H*-indol-2-ones **85** in good to excellent yields (**Scheme 30**).



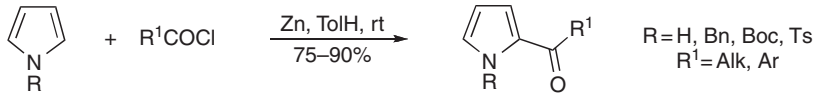
Scheme 30

Halogens react with benzo[*b*]furan by an additionelimination mechanism to give 2- and 3-substituted products. Treatment of benzo[*b*]thiophene with chlorine or bromine in acetic acid gives predominantly 3-substituted products and bromination of a 3-bromobenzo[*b*]furan gives the 2,3-dibromo derivative <2003S925>. 2,2,3,3,4,5,6,7-Octachloro-2,3-dihydrobenzothiophene is obtained when benzo[*b*]thiophene is treated with chlorine in the presence of one equivalent of iodine.

3.3.1.5.5 Acylation

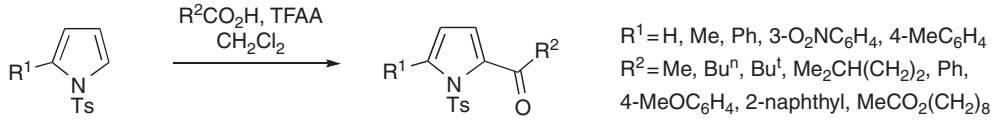
3.3.1.5.5.1 Pyrroles. Pyrrole and alkylpyrroles are acylated by acid anhydrides above 100°C thus pyrrole itself gives a mixture of 2-acetyl- and 2,5-diacetylpyrrole on heating with acetic anhydride at 150–200°C. *N*-Acylpyrroles are obtained by reaction of the alkali metal salts of pyrrole with an acyl halide. *N*-Acetylimidazole efficiently acetylates pyrrole on

nitrogen. Pyrrole-2-carbaldehyde is acetylated on nitrogen in 80% yield by reaction with acetic anhydride in methylene chloride and in the presence of triethylamine and 4-dimethylaminopyridine. An acylation protocol that utilizes metallic zinc powder as promoter in toluene under very mild and neutral conditions gives 2-acylpyrroles in high yields with high regioselectivity (**Scheme 31**) <2002TL8133>.



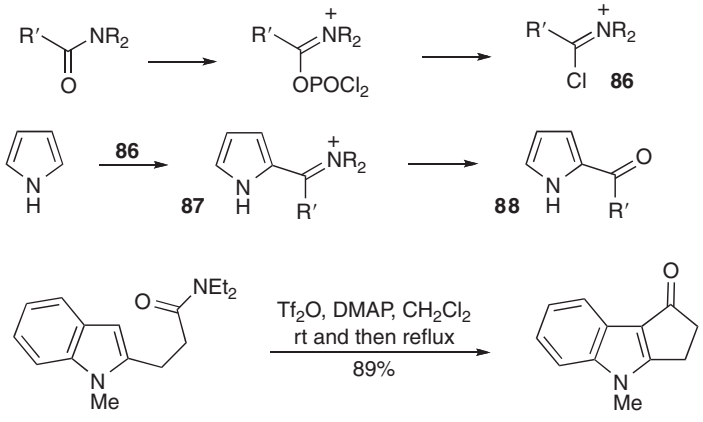
Scheme 31

Carboxylic acids can be used to 2-acylate *N*-tosyl pyrroles via activation with TFAA (**Scheme 32**) <2004TL9573, 2006OL163>.



Scheme 32

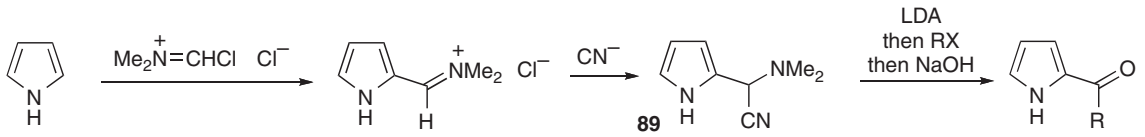
Perhaps the most useful general method for the C-acylation of pyrroles is the VilsmeierHaack procedure with the chloro-iminium salt **86** derived from an *N*,*N*-dialkylamide with phosphoryl chloride. Activation of an amide with Tf_2O can also be used (an intramolecular example is shown in **Scheme 33** <2006JOC704>). The intermediate iminium salt **87** is hydrolyzed under alkaline work-up conditions to give the acylated pyrrole **88**. On treatment of the iminium salt **87** (R = H) with hydroxylamine hydrochloride and one equivalent of pyridine and heating in DMF, 2-cyanopyrrole is formed. A significant test case is the formylation of 3-phenyl-5,7-dimethoxybenzo[*b*]furan; Vilsmeier formylation proceeds at C(2), despite the two activating groups on the benzene ring <2002T5125>.



Scheme 33

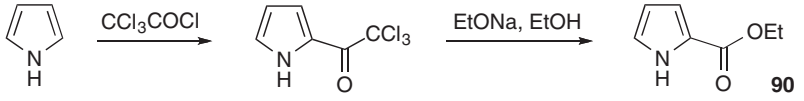
N-Methylnitrilium fluoroborates react readily at low temperatures with indoles and pyrroles to give iminium salts, which can be isolated in high yields and hydrolyzed to the corresponding acyl products. The iminium salts prepared from pyrroles and *N*,*N*-dimethylchloroformiminium chloride can be converted into acyl pyrroles by a sequence of

reactions involving addition of cyanide ion, alkylation of the resulting intermediate **89**, and hydrolysis (**Scheme 34**). These transformations apply both to the normal 2-iminium salts and also to 3-iminium salts, the latter arising from reaction of the hindered *N*-(triisopropylsilyl)pyrrole.

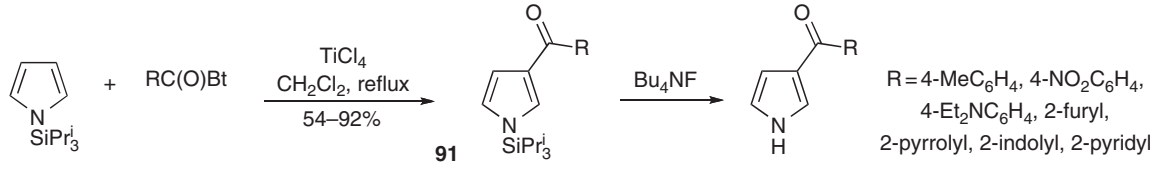


Scheme 34

Though pyrroles are very sensitive to acids and Lewis acids, FriedelCrafts type acylation, using e.g., $SnCl_4$ or $AlCl_3$ can be carried out providing an N-protected pyrrole is used e.g., *N*-tosylpyrrole gives a mixture of 2-(2-nitrobenzoyl)- and 3-(2-nitrobenzoyl)-derivatives <2000T9675>. 3-Aroyl- and 3-acetyl-pyrroles can be obtained by FriedelCrafts acylation of 1-phenylsulfonylpyrrole (e.g., 3-propionyl-1-phenylsulfonylpyrrole <1995TL6185>) followed by removal of the *N*-blocking group by mild alkaline hydrolysis. However, using dichloromethyl methyl ether as the acylating agent, substitution occurs at the 2-position to give 2-formyl-l-phenylsulfonylpyrrole, exclusively. 2-Trichloroacetylpyrrole, formed on treating pyrrole with trichloroacetyl chloride (no catalyst required), is readily transformed into ethyl pyrrole-2-carboxylate **90**.

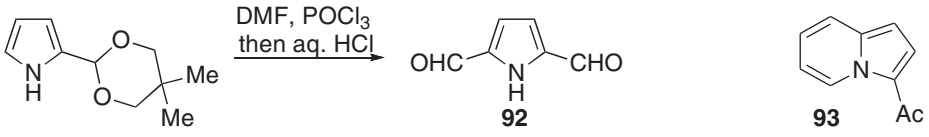


The sensitivity to strong Lewis acids can be avoided, and useful acylations achieved, by using *N*-acylbenzotriazoles in the presence of $TiCl_4$ to give 2-acylpyrroles in good to excellent yields, without the need for N-protection <2003JOC5720>. These conditions also give 3-acylindoles and 1-trisopropylpyrrole gives rise to 3-acylpyrroles **91** (**Scheme 35**) <2003JOC5720>.



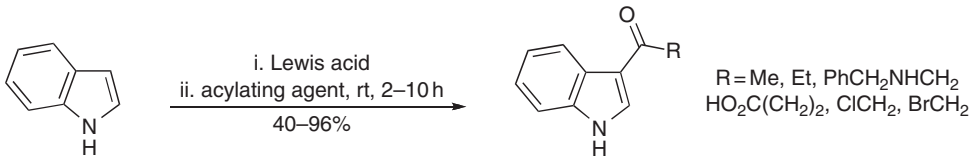
Scheme 35

Although a 2-acylpyrrole will undergo a second acylation at C(4), yields are variable. A more consistent route to 2,4-diacylpyrroles is by the acylation of a 3-acylpyrrole, which can in turn be obtained through the acylation of a 1-benzenesulfonylpyrrole. An indirect method for preparing pyrrole-2,5-dicarbaldehydes **92** utilizes a protected 2-formylpyrrole as a starting point.



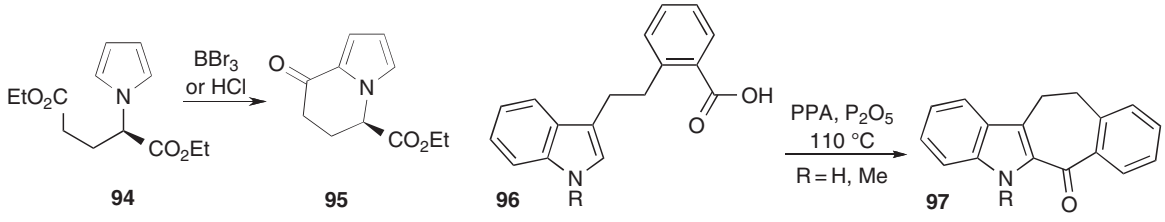
Indole with acetic anhydride at 140°C gives 1,3-diacetylindole via the 3-acetyl compound. In the presence of sodium acetate, acetic anhydride gives exclusively 1-acetylindole. The VilsmeierHaack reaction is an efficient route to 3-acylindoles, including working on solid phase <2001JCO542>. The usual difference in orientation of substitution is observed in the acetylation (Ac_2O, $SnCl_4$) of benzo[*b*]furan and benzo[*b*]thiophene. Thus, the oxygen heterocycle yields mainly the 2-acetyl derivative and the sulfur heterocycle yields mainly the 3-acetyl derivative. 1-Phenylisoindole readily undergoes acetylation to give a 3-acetyl derivative (Ac_2O, pyridine, room temperature) and indolizine gives a 3-acetyl derivative **93** on heating with acetic anhydride and acetic acid; it also undergoes VilsmeierHaack formylation.

FriedelCrafts-type reaction of indole itself with various acid chlorides, anhydrides, nitriles, and amino acid derivatives in the presence of a Lewis acid ($AlCl_3$, $TiCl_4$, $SnCl_4$) gives 3-acylindoles regioselectively and in high yields without laborious work-up (**Scheme 36**) <2001OL1005>. The Lewis acid must be added to a solution of indole in dichloromethane at 0°C with the acylating agent added to the resulting suspension, followed by nitromethane as cosolvent. The use of Et_2AlCl or Me_2AlCl brings comparable results and was also shown to work with variously benzene-ring-substituted indoles <2000OL1485>.



Scheme 36

Intramolecular acylations of pyrroles and indoles are useful synthetically, for example, *N*-glutamyl-substituted pyrrole **94** gives **95**, regioselectively, with retention of configuration, on brief treatment with methanolic hydrogen chloride or boron tribromide. A seven-membered ketone **97** was produced from **96**; no cyclization onto the indole 4-position was observed <1999T4341>.



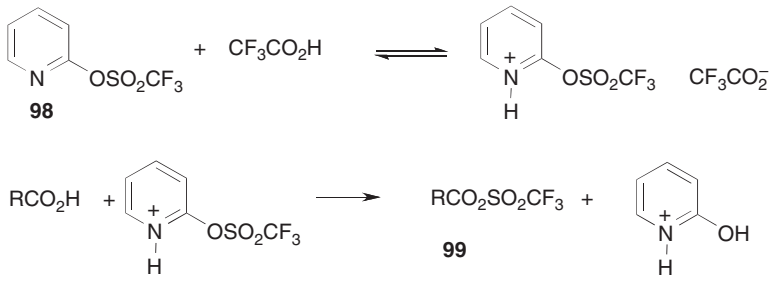
94 **95** **96** **97**

3.3.1.5.5.2 Furans. Furan can also be acylated by the VilsmeierHaack method or with acid anhydrides and acyl halides in the presence of FriedelCrafts catalysts (BF_3 Et_2O, $SnCl_4$ or H_3PO_4). Reactive anhydrides such as trifluoroacetic anhydride, however, require no catalyst. Acetylation with acetyl *p*-toluenesulfonate gives high yields.

Pyrroles and furans also undergo the Gattermann aldehyde synthesis: with HCl and HCN, furan gives furfuraldehyde. The HoubenHoesch ketone synthesis is also applicable to the preparation of acyl derivatives of furans and pyrroles, e.g., ethyl 2,4-dimethylpyrrole-3-carboxylate with MeCN and HCl yields ethyl 5-acetyl-2,4-dimethyl-3-carboxylate.

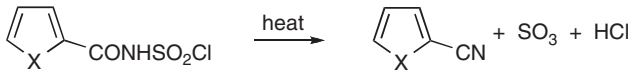
3.3.1.5.5.3 Thiophenes. The best catalyst for the FriedelCrafts acylation of thiophene, using free carboxylic acids, appears to be 2-(trifluoromethylsulfonyloxy)pyridine **98** in conjunction with TFA. A 2-acylthiophene is formed in quantitative yield, without any evidence of the thiophene dimerizing. The transformation is probably mediated by the mixed anhydride **99** (**Scheme 37**).

Thiophene is also readily 2-acylated under both FriedelCrafts and VilsmeierHaack conditions. An almost quantitative conversion of thiophene into its 2-benzoyl derivative is obtained by reaction with 2-benzoyloxypyridine and trifluoroacetic acid.



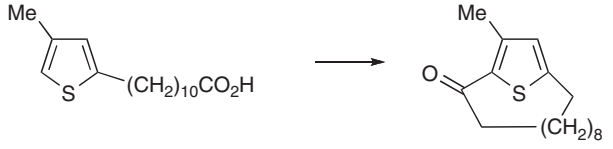
Scheme 37

Acylation of either pyrrole or thiophene with chlorosulfonyl isocyanate gives a 2-substituted amide which fragments on heating to give the corresponding 2-cyano derivative (**Scheme 38**). An alternative procedure for obtaining 2-cyanopyrrole and 3-cyanoindole involves treatment of the parent heterocycle with thiocyanogen and triphenylphosphine.

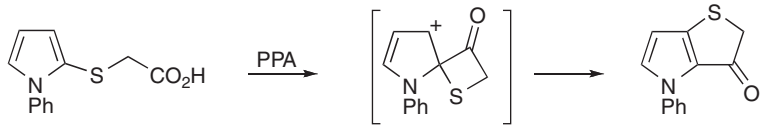


Scheme 38

A muscone synthesis involves selective intramolecular acylation at a vacant thiophene -position (**Scheme 39**). When intramolecular acylation reactions onto a -position of a thiophene or a pyrrole are attempted, a spirocyclic intermediate is formed in some cases with the result that rearranged products are formed (**Scheme 40**).

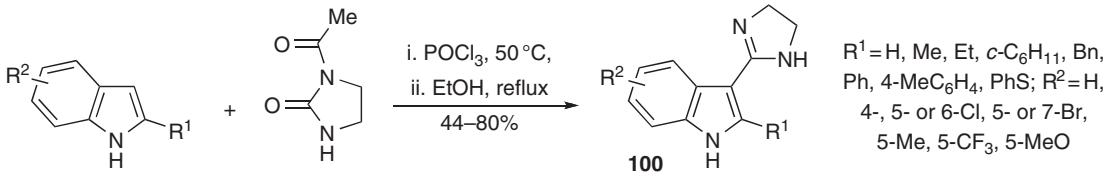


Scheme 39



Scheme 40

In what can be viewed as a type of Vilsmeier process, a dihydroimidazole unit can be directly introduced into an indole 3-position, e.g. **100** (**Scheme 41**) <2001TL5187>.



Scheme 41

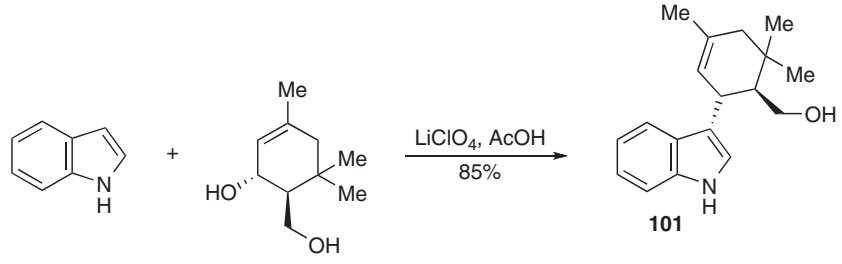
Pyrrole-2-carboxylate decarboxylase from *Bacillus megaterium* PYR2910 will catalyze the introduction of CO_2 to indole in the presence of bicarbonate <1998TL4309, 2001JMOB179>. Bioconversion is carried out at 20°C in a mixture of ammonium acetate (as enzyme cofactor), potassium phosphate buffer (KPB), sodium L-ascorbate (as antioxidizing, enzyme protecting agent), pyrrole, $KHCO_3$, and concentrated cells as biocatalyst. The yield is 80%, limited by the equilibrium.

Ethoxycarbonyl isothiocyanate ($EtO_2CN=C=S$) will introduce an ethoxycarbonylaminothiocarbonyl substituent ($EtO_2CNHC=S$) to a pyrrole C(2) <2001JME1217>.

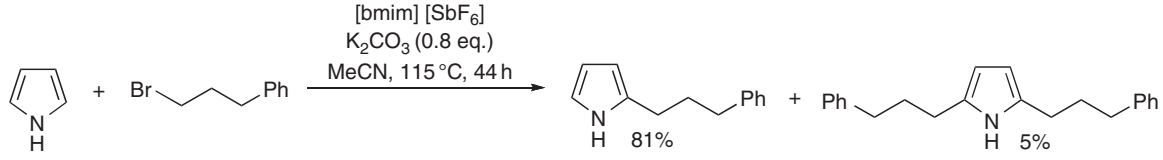
3.3.1.5.6 Alkylation (see also Section 3.3.3.8.8)

Pyrroles give polyalkylated products on reaction with methyl iodide at elevated temperatures. The more reactive allyl and benzyl halides react very efficiently with indoles in aqueous acetone in the presence of NH_4HCO_3 at room temperature, but mixtures of 3- and 2-substituted products are formed in an approximate ratio of 4:1 <2006OL4791>. 2-Trifluoromethylation of pyrrole can be achieved with a diaryl-trifluoromethylsulfonium triflate in refluxing THF <1998JOC2656>. Alkylation of pyrrole Grignard reagents gives mainly 2-alkylated pyrroles whereas *N*-alkylated pyrroles are obtained by alkylation of pyrrole alkali metal salts in ionizing solvents (see Section 3.3.1.3.1). 2,2-Disubstituted 2*H*-pyrroles can be formed by the C-alkylation of the Grignard derivatives of polyalkylated pyrroles.

Indoles can be 3-alkylated by allyl alcohols in the presence of lithium perchlorate and acetic acid: **101** is an example (**Scheme 42**). Pyrrole -alkylation can be achieved with simple alkyl halides [1-bromopentadecane, 1-(bromomethyl)-, 1-(3-chloropropyl)- and 1-(3-iodopropyl)benzenes, 2-(2-bromoethyl)- and 2-(3-bromopropyl)naphthalenes] and mesylates [3-phenylpropyl-, 1-methyl-3-phenylpropyl-, 2-(2-naphthyl)ethyl- and 3-(2-naphthyl)propyl methanesulfonates] selectively at C(2) and C(5) positions via reaction in various ionic liquids (e.g., **Scheme 43**) <2005OL1231>.



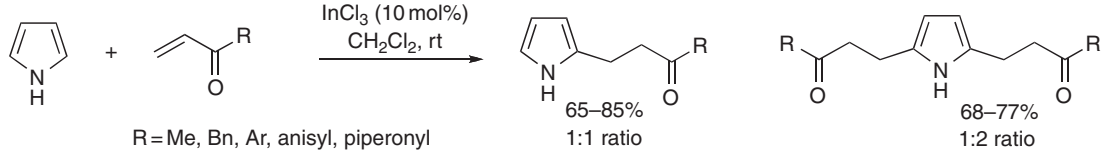
Scheme 42



Scheme 43

Much effort has been devoted to the alkylation of pyrroles and indoles with electrophilic alkenes. Such reactions can be catalyzed by acidic clays or Lewis acids. Indoles are alkylated as usual at C(3), and the alkylation of 3-substituted indoles has also been shown to take place at C(3) with subsequent migration occurring to C(2).

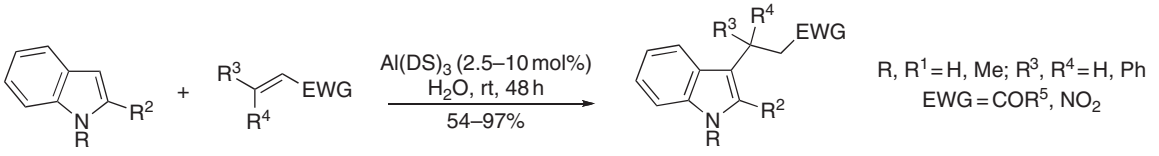
Both $InBr_3$ and $InCl_3$ mediate the conjugate addition of pyrroles and indoles to enones <2001S2165, 2002JOC3700>, without problems of acid-catalyzed oligomerization, e.g., **Scheme 44**. Cerium(III) chloride heptahydrate and sodium



Scheme 44

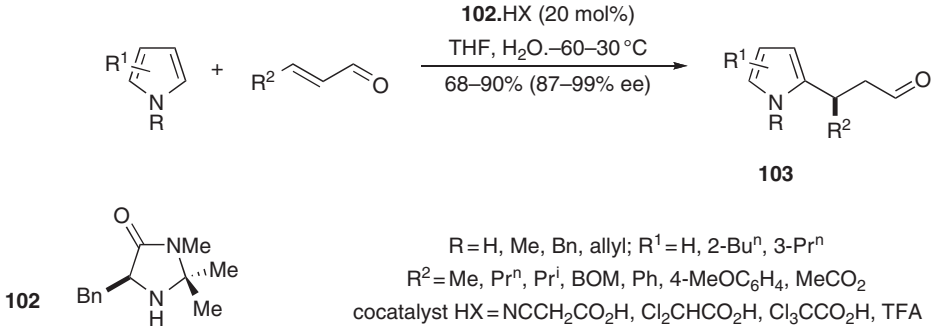
iodide supported on silica gel also give 3-(3-oxoalkyl)indoles in good yields <2003JOC4594>. Cyclic and acyclic unsaturated ketones react in the presence of 1 mol% of iodine as catalyst at room temperature under solvent-free conditions providing a very simple method for these enone alkylations <2005TL2479>. Pyrroles carrying a chiral N-substituent react with ,-unsaturated esters (e.g., PhCH═CHCOCO$_2$Et) using Y(OTf)$_3$ to give 2-alkylated products in good yields without racemization <2004S2574>.

An alternative protocol has structurally diverse electron-deficient olefins reacting in aqueous media at room temperature using aluminum dodecyl sulfate trihydrate, [Al(DS)$_3$]ñ3H$_2$O, as a Lewis acid surfactant catalyst affording 2-substituted pyrroles and 3-substituted indoles in high isolated yields (**Scheme 45**) <2005CC789>.



Scheme 45

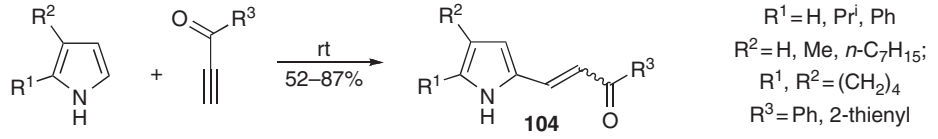
Enantioselective organocatalytic (with tetrahydro-4*H*-imidazol-4-one-based catalysts of type **102**ñHX) 2-alkylation of pyrroles by ,-unsaturated aldehydes generates 3-(pyrrol-2-yl) aldehydes **103** (**Scheme 46**) <2001JA4370, 2002JA1172, 2005JA15051 and references therein>.



Scheme 46

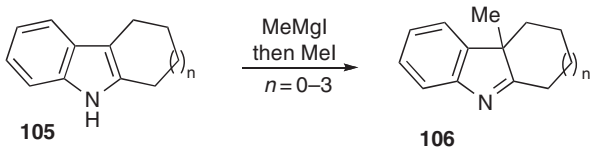
Chiral 2-(3-oxoalkyl)pyrroles and 3-(3-oxoalkyl)indoles can also be accessed by reaction in the presence of 10 mol% of chiral bis(oxazoline)/metal complexes in CH_2Cl_2 in very high yields and with ee values over 90% <2005JA4154>. Alkylation of pyrrole and of substituted indoles with ,-unsaturated acyl phosphonates <2003JA10780> or 2-acyl *N*-methylimidazoles catalyzed by a chiral bis(oxazolinyl)pyridine (pybox)/scandium(III) triflate complex also exhibits good enantioselectivity over a broad range of substrates <2005JA8942>.

Reactions of pyrroles with terminal aroylethynes proceed under mild conditions, either without a solvent or in methanol or ethanol, or in diethyl ether, benzene, hexane, or acetonitrile to give 2-(2-acylvinyl)pyrroles **104** [predominantly, the (*Z*)-isomers] (**Scheme 47**). In the course of isolation and purification and even upon storage, the (*Z*)-isomers are readily transformed into the (*E*)-isomers <1998MC119, 1999RCB1542>. For reaction of pyrroles with non-terminal alkynyl ketones, heating in the presence of silica is required <2002RCB111, 2003RJO1636>.



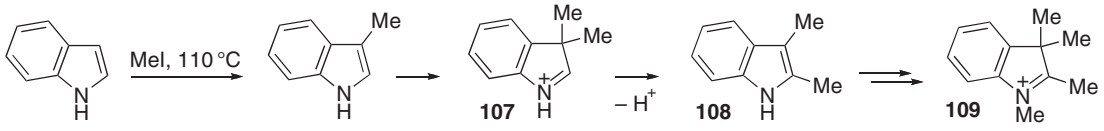
Scheme 47

C-Alkylation of pyrroles and indoles can be mediated by alumina in association with the appropriate halide. 3-Indolyl sugar derivatives have been obtained by alkylation reactions of indolylmagnesium bromide. This type of alkylation has been extended to ring-fused indoles **105** and yields 3*H*-indole derivatives **106** in good yields.



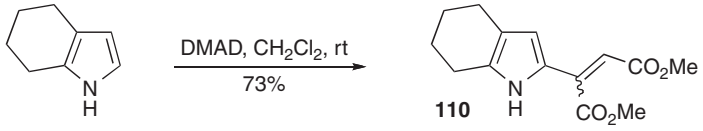
105 **106**

Indole with excess methyl iodide at 110°C gives a tetramethyl derivative **109**. The intermediate 2,3-dimethylindole **108** is thought to arise by rearrangement of the 3,3-dimethyl-3*H*-indolium cation **107**.



107 **108** **109**

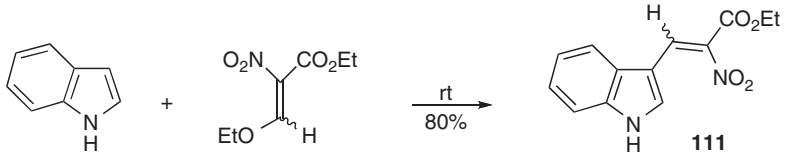
Pyrroles can be -alkenylated by reaction with acetylenedicarboxylic ester, for example, to give an *E*/*Z* mixture (1:3.3) of alkenes **110** (**Scheme 48**) <2006JOC7793>.



110

Scheme 48

Alkenylindoles can also be produced using a conjugated alkene which also carries a leaving group at the conjugated position; thus, ethyl 2-nitro-3-ethoxyacrylate reacts with indole to give compound **111** (**Scheme 49**) <1996TL3309>. Similarly, EtOCH=CHCOCF$_3$ alkenylates pyrroles at C(2) with $ZnCl_2$ catalysis, at room temperature <1999RCR437>.



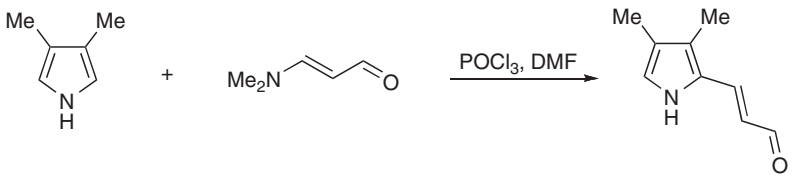
111

Scheme 49

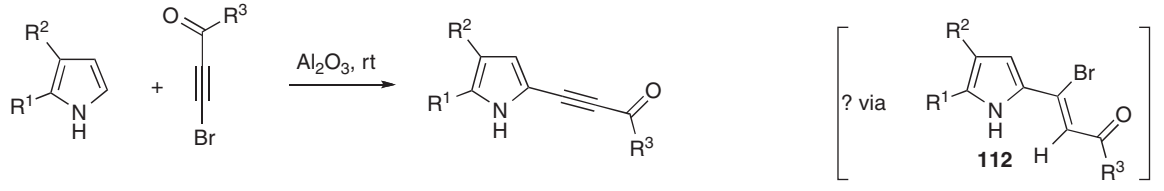
A process that can be regarded as a vinylogous Vilsmeier reaction, is a further means to access alkenylated pyrroles, e.g., **Scheme 50** <1996M77>.

The reaction between 2-(thien-2-yl)pyrroles and tetracyanoethene nicely illustrates the relative reactivities of the two heterocycles 1,2,2-tricyanoethenylation takes place only in the pyrrole ring <2005T11991>.

Direct ethynylation of pyrroles results from the use of bromoethynyl ketones at room temperature on alumina (**Scheme 51**); the process may involve initial addition to the alkyne followed by elimination of HBr from **112** <2004TL6513, 2005MC229, 2006RJO1348>.



Scheme 50



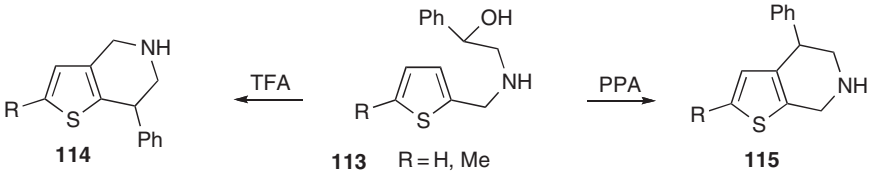
R^1 = H, Ph, 4-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4; R^2 = H; R^1, R^2 = $(CH_2)_4$; R^3 = Ph, 2-thienyl

Scheme 51

Alkylation of furan and thiophene has been effected with alkenes and catalysts such as phosphoric acid and boron trifluoride. In general, FriedelCrafts alkylation of furans or thiophenes is not preparatively useful, partly because of polymerization caused by the catalyst and partly because of polyalkylation.

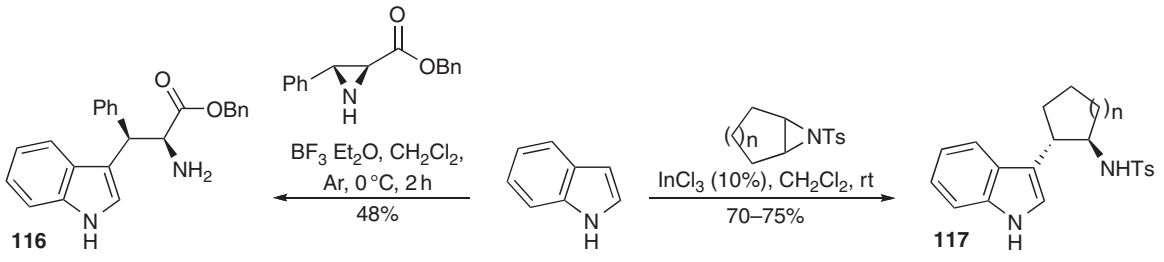
A successful procedure for the formation of 2,5-di-*t*-butylfuran involves reaction of the parent heterocycle with *t*-butyl chloride in the presence of iron(III) chloride and iron(III) oxide.

Exposure of the amino alcohols **113** to trifluoroacetic acid gives a rearranged intramolecular alkylation product **114**; polyphosphoric acid gives the nonrearranged thieno-pyridine **115**.



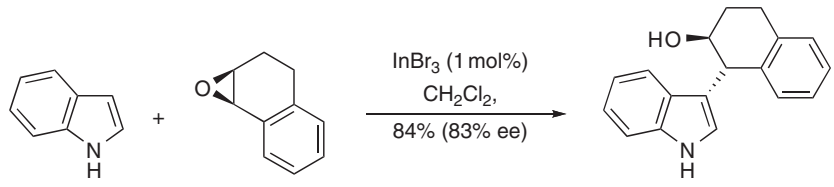
Silica gel is an effective catalyst for the *t*-butylation of thiophene and benzo[*b*]thiophene using *t*-butyl bromide. 2,5-Di-*t*-butylthiophene and 3-*t*-butylbenzo[*b*]thiophene can be prepared easily by this procedure. Alkylation of thiophene with *t*-butyl chloride, isopropyl chloride, or ethyl chloride at 70°C in the presence of $AlCl_3$ produced -complexes under kinetic control. On thermal equilibration, migration of alkyl from C(3) to C(2), as well as disproportionation to dialkyl and trialkyl thiophenes can occur.

Reaction of indoles with (usually *N*-tosyl)-aziridines using a mild Lewis acid is a route to substituted tryptamines, e.g., **117** and tryptophans, e.g., **116**. Thus, regiospecific ring opening of optically pure benzyl 3-phenylaziridine-2-carboxylate with indole in dichloromethane in the presence of BF_3ñEt_2O produces the phenyl-substituted tryptophan ester **116** (**Scheme 52**) <2002JOC1399>. Pyrrole, likewise, reacts with *N*-tosylaziridines using $InCl_3$ as catalyst giving mixtures of 2- and 3-(2-aminoalkyl)pyrroles <2002TL1565>.



Scheme 52

Epoxides too will react with indoles using Lewis acid catalysis: with (1*R*,2*S*)-1,2-dihydronaphthalene oxide, high enantioselectivity (83% ee) shows the effectiveness of $InBr_3$ (**Scheme 53**) <2002JOC5386>.

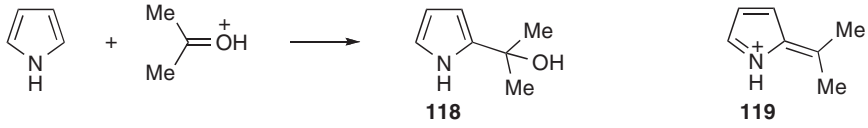


Scheme 53

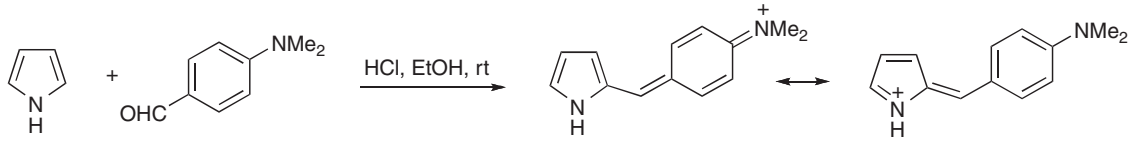
The condensation of indoles with epoxides or aziridines can also be conducted on the surface of silica <2005JOC3490>.

3.3.1.5.7 Reactions with aldehydes and ketones

3.3.1.5.7.1 Formation of carbinols or carbonium ions. Thiophenes, pyrroles, and furans react with the conjugate acids of aldehydes and ketones to give carbinols (e.g., **118**) that cannot normally be isolated and which undergo proton-catalyzed loss of water to give reactive electrophiles (e.g. **119**).

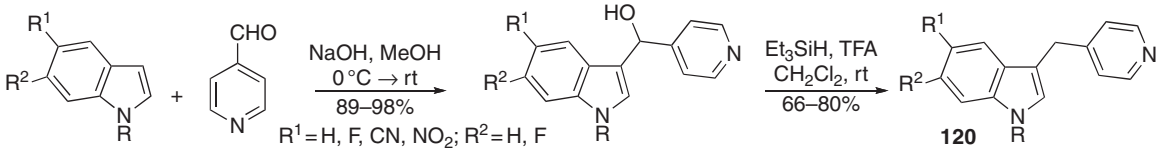


By using an aromatic aldehyde carrying an electron-releasing group, the intermediate cation can be stabilized. This is the basis of the classical Ehrlich color reaction for pyrroles, indoles, and furans which have a free reactive nuclear position (**Scheme 54**). As expected, pyrroles react preferentially in the -position and indoles in the -position, but if these positions are filled, reaction can occur at other sites.



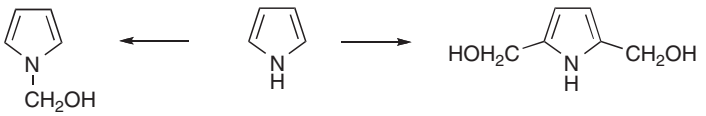
Scheme 54

Conversely, isonicotinaldehyde, in which the aromatic ring is electron-withdrawing, reacts with pyrrole to give isolable carbinols (which can in turn be reduced **120**) (**Scheme 55**) <2001TL7333>.



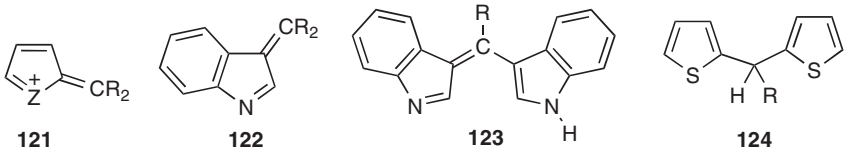
Scheme 55

Pyrrole can be condensed under alkaline conditions with formaldehyde to give products of either N- or C-hydroxymethylation (**Scheme 56**). Benzo[*b*]furan gives an isolable alcohol on reaction with glyoxylate using Y $(OTf)_3$ as catalyst where attack has taken place at C(3) <2000JOC4732>.

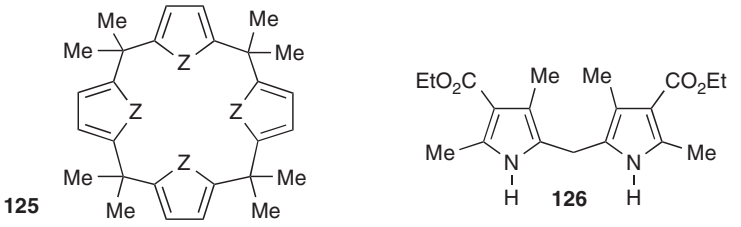


Scheme 56

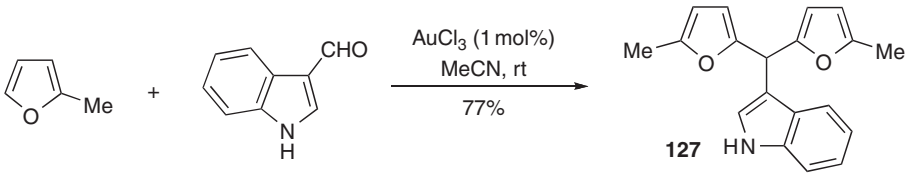
3.3.1.5.7.2 Further reactions of carbonium ions. With N-unsubstituted pyrroles, ions of types **121** (Z = NH) can lose a proton from the ring nitrogen, e.g., indole with Ph_2CO or PhCHO in HCl/EtOH gives products of type **122**. Indole with HCO_2H or PhCOCl gives rosindoles **123** (R = H, Ph), involving the formation of ketones (cf. discussion in Section 3.3.1.5.5.1) and a subsequent reaction of this type with a second molecule of indole.



The ion **121**, acting as an electrophilic reagent, can also attack another molecule of the heterocyclic compound. Thiophene with benzaldehyde or chloral gives the dinuclear product **124** (R = Ph or CCl_3). Pyrrole and furan react with acetone to form tetranuclear derivatives of type **125** (Z═NH, O). Pyrroles with a single free position react like thiophene; e.g., two molecules of 3-ethoxycarbonyl-2,4-dimethylpyrrole with formaldehyde afford the dipyrromethane **126**.

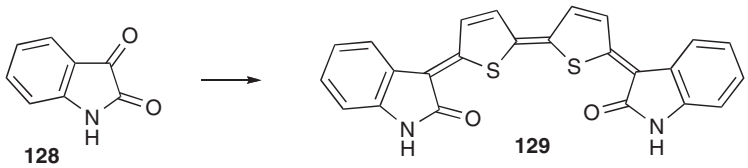


In another example, indole and 2-methylfuran generate compound **127** with $AuCl_3$ catalysis (**Scheme 57**) <2005OL5857>.

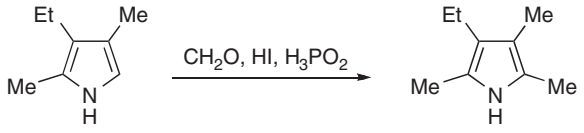


Scheme 57

More rarely, ions of type **121** form dimeric products (possibly by initial loss of nuclear protons); thus, thiophenes with two free -positions, or free adjacent - and -positions, give indophenines, e.g., **129** from isatin **128**. This reaction was used historically as a test for thiophene the so-called indophenine test.

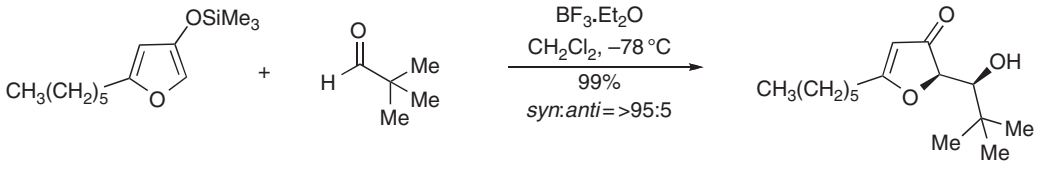


Although acid-catalyzed hydroxymethylation is not a practical possibility, by the addition of a reducing agent to the reaction mixture overall reductive alkylation can be achieved (**Scheme 58**).

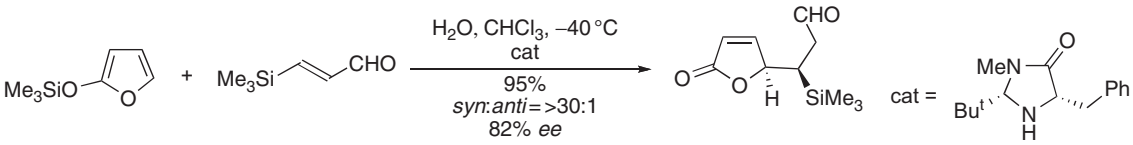


Scheme 58

Extensive studies have been made of the reactions between aldehydes and oxygenated furans most often *t*-butoxyfurans or trimethylsilyloxyfurans. The products of these condensations lose the oxygen substituent and finish as butenolide (from 2-oxygenated furans) or 3(2*H*)-furanone (from 3-oxygenated furans) products: **Schemes 59** <2005OL387> and **60** <2003JA1192> show typical examples.



Scheme 59

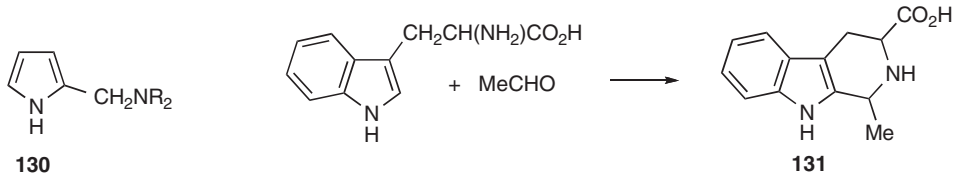


Scheme 60

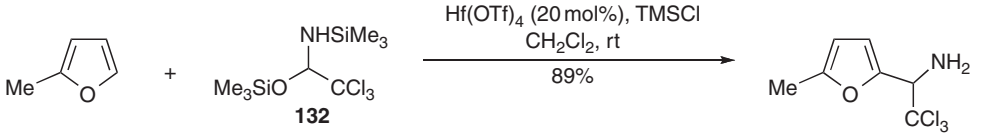
3.3.1.5.7.3 Chloromethylation. Thiophene and selenophene can be chloromethylated by treatment with formaldehyde and hydrochloric acid. Depending on the conditions, 2-chloromethyl or 2,5-bis(chloromethyl) derivatives are obtained. The chloromethylation of benzo[*b*]thiophene gives the 3-chloromethyl derivative and that of benzo[*b*]furan the 2-chloromethyl compound. Furan is destroyed by this treatment, but 2,5-diphenylfuran, for example, gives a 3,4-bischloromethyl derivative.

3.3.1.5.7.4 Mannich reaction. Pyrrole is aminoalkylated to give products of type **130**. The intermediate immonium ion generated from formaldehyde, dimethylamine, and acetic acid is not sufficiently reactive to aminomethylate furan, but it will form substitution products with alkyl furans. The Mannich reaction appears to be still more limited in its application to thiophene chemistry, although 2-aminomethylthiophene has been prepared by reaction of thiophene with formaldehyde and ammonium chloride and 3-methoxythiophene reacts satisfactorily at C(2) <2001J(P1)2595>. The use of the preformed *N*,*N*-dimethyl(methylene)ammonium chloride ($Me_2N^+{=}CH_2C1$) has been recommended for the N,N-dimethylaminomethylation of thiophenes.

An important application of the Mannich reaction is the synthesis of 3-dialkylaminoindoles. Intramolecular versions of this reaction are also possible, as illustrated by the formation of the tetrahydro--carboline **131**.

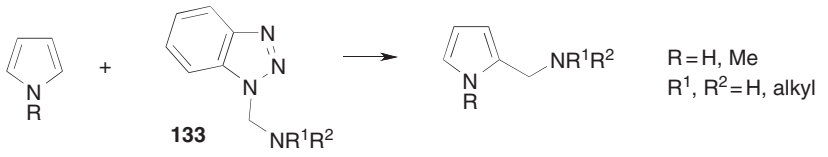


A reagent that will bring about aminomethylation of furans as well as pyrroles is the *N*-silyl-*N,O*-acetal **132**, used with a Lewis acid, and this also gives primary amines, not available from the classical procedures, e.g., **Scheme 61** <2003JOC483>.



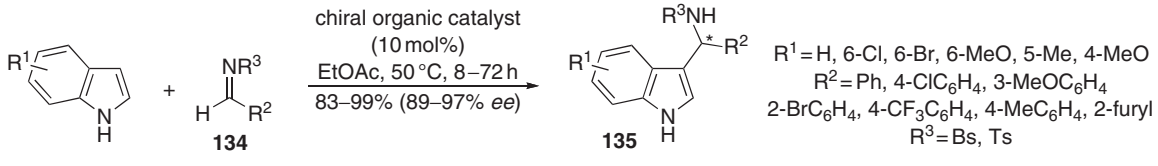
Scheme 61

Secondary and tertiary aminoalkylbenzotriazoles **133** react with pyrrole, indole, and their *N*-methyl analogues under mild conditions in the presence of a Lewis acid to afford selectively the corresponding secondary or tertiary aminoalkyl derivatives (**Scheme 62**). *N,N*-Bis(alkoxymethyl)amines can also be used to give secondary alkylamines, which operate via reactive iminium salts formed by treatment with trimethylsilyl chloride.



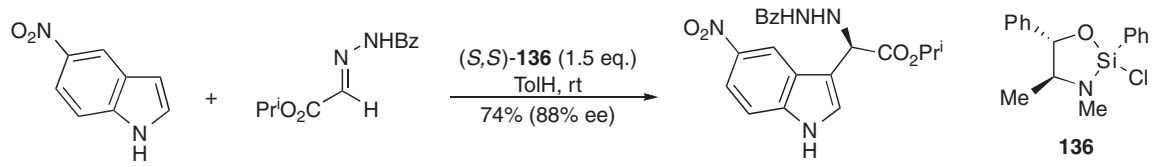
Scheme 62

Indoles react with imines **134** to provide a direct, convergent, and versatile method for the highly enantioselective construction of 3-indolyl methanamines **135** (**Scheme 63**) <2006JA8156>; quinidine- or quinine-derived 9-thiourea cinchona alkaloids (10 mol%) as bifunctional chiral organic catalysts promote the asymmetric CC bond-forming reaction. Another approach to optically active 3-indolylmethanamines utilizes the enantioselective copper(II)-catalyzed addition of indoles to *N*-sulfonyl aldimines, RN=CHAr (R=Ts or Ns), with chiral bisoxazoline ligands [10 mol% Cu $(OTf)_2$, 15 mol% l, CH_2Cl_2, rt, 35 days] <2006OL1621>. 2-Methoxyfuran can also be added enantioselectively to *N*-Boc-imines, reaction occurring at C(5) <2004JA11804>.



Scheme 63

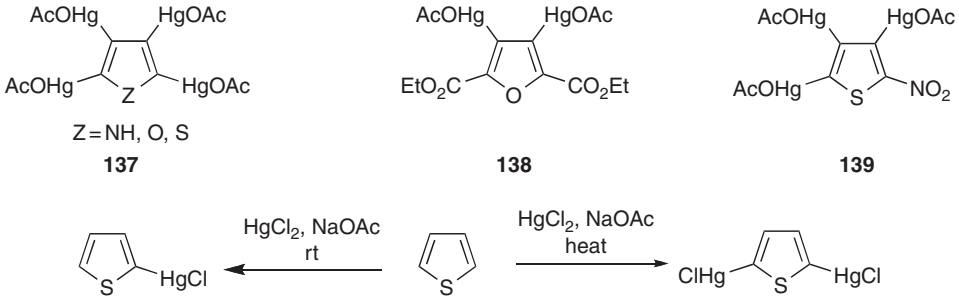
A quite different chiral catalyst **136** can be used to promote the reaction of some pyrroles and indoles with benzoylhydrazones (**Scheme 64**) <2005JA2858>. Condensations of indoles with a variety of imines can be conducted in water with decanoic acid (n-$C_9H_{19}CO_2H$) as the catalyst <2006OL4939>.



Scheme 64

3.3.1.5.8 Mercuration

Mercury(II) acetate tends to mercurate all the free nuclear positions in pyrrole, furan, and thiophene to give derivatives of type **137**. The acetoxymercuration of thiophene proceeds ca. 10^5 times faster than that of benzene. Mercuration of rings with deactivating substituents such as ethoxycarbonyl and nitro is still possible with this reagent, as shown by the formation of compounds **138** and **139**. Mercury(II) chloride is a milder mercurating agent, as illustrated by the chloromercuration of thiophene to give either the 2- or 2,5-disubstituted product (**Scheme 65**).

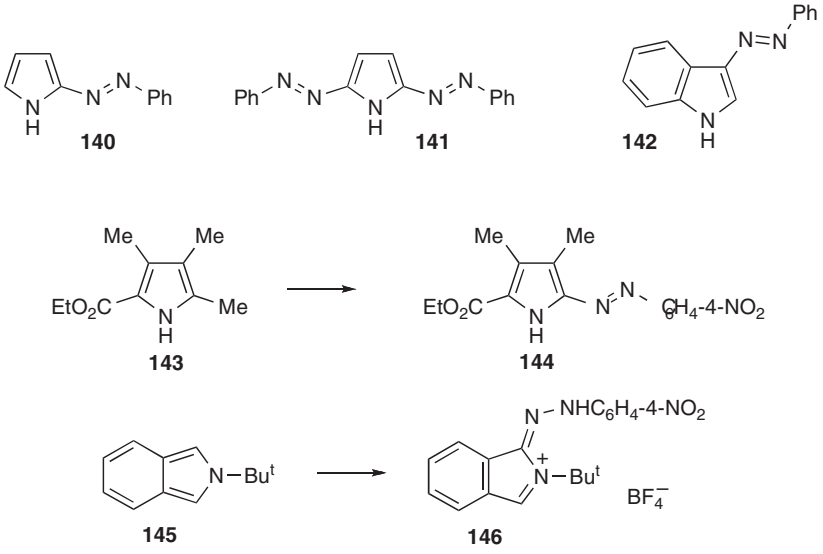


Scheme 65

3.3.1.5.9 Diazo coupling

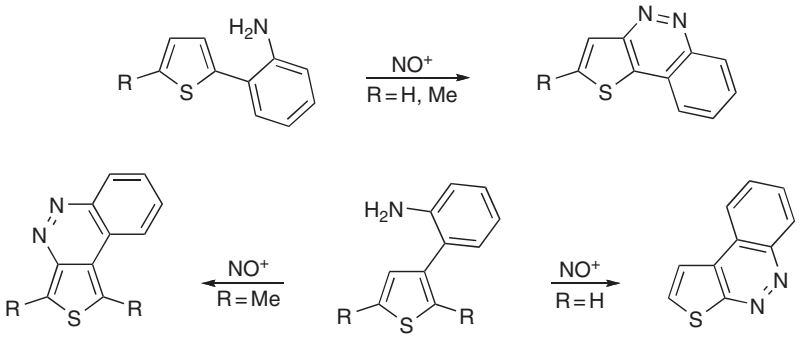
Diazo coupling occurs readily between pyrroles and indoles and benzenediazonium salts. Reaction is much more rapid in alkaline solution when the species undergoing reaction is the N-deprotonated heterocycle. Depending on the conditions, pyrrole yields either 2-azo or 2,5-bis(azo) derivatives, e.g., **140** or **141**, and indole gives a 3-substituted product **142**.

An -demethylated product **144** is formed when the tetrasubstituted pyrrole **143** is reacted with *p*-nitrobenzenediazonium chloride. *N*-*t*-Butylisoindole **145** couples with *p*-nitrobenzenediazonium fluoroborate to give the hydrazone salt **146**.



Furan undergoes phenylation rather than diazo coupling on reaction with benzenediazonium salts, and thiophene similarly yields 2- or 2,5-diaryl derivatives rather than coupled products (see Section 3.3.1.7.2). However, 2,5-dimethylfuran and 2-*t*-butylfuran give normal coupled products with the 2,4-dinitrobenzenediazonium ion.

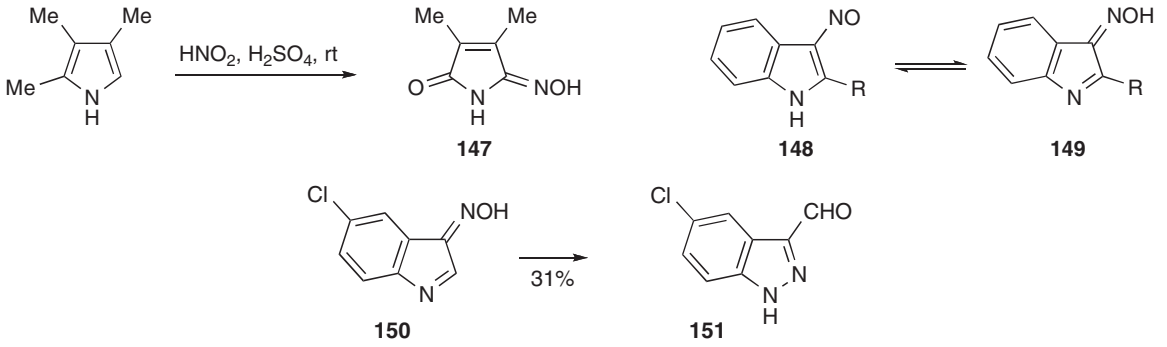
Starting from suitable (*o*-aminophenyl)thiophenes, intramolecular diazo coupling can be also achieved: various isomeric thieno[*c*]cinnolines can be obtained in this way (**Scheme 66**). The reaction can proceed either at an - or at a -position of the thiophene ring.



Scheme 66

3.3.1.5.10 Nitrosation

Nitrosation of pyrrole or alkylpyrroles can result in ring opening or oxidation of the ring and removal of the alkyl groups. This is illustrated by the formation of the maleimide derivative **147** from 2,3,4-trimethylpyrrole.

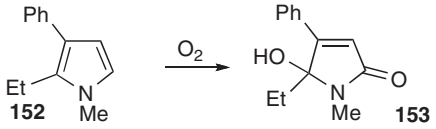


3-Nitroso derivatives **148** are obtained from indoles; they exist largely in oximino forms **149**. The N-nitrosation of 5-chloroindole is followed by a migration of the nitroso group from N to C(3), to give a 3-oxime **150**: hydrolysis and recyclization leads to an indazole carbaldehyde **151**.

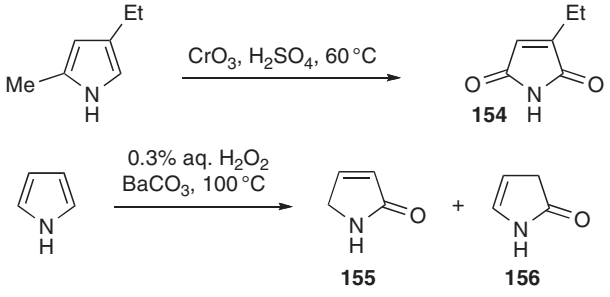
3.3.1.5.11 Electrophilic oxidation

Pyrroles and furans are particularly easily oxidized. The mechanism of primary attack can be electrophilic, radical, or via a cyclic transition state, and the assignment of individual transformations to these classes is sometimes arbitrary.

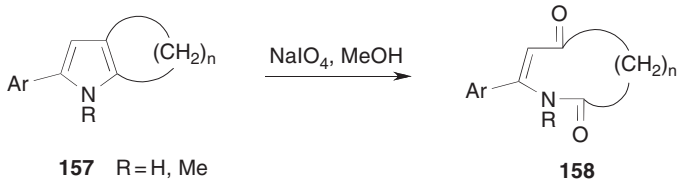
Simple pyrroles frequently give complex breakdown products. Oxidation with oxygen (UV-irradiation, a photosensitizer, or an radical initiator) produces hydroxypyrrolones <1991JOC6942, 1999TL4519, 2002TA601>. For example, pyrrole **152** (30°C) leads to 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one **153** <2003T8499>.



With strong oxidizing agents such as chromium trioxide in aqueous sulfuric acid, alkylpyrroles are converted into maleimides, e.g., **154**. This oxidative technique played an important part in the classical determination of porphyrin structures. Milder oxidizing agents, such as hydrogen peroxide, convert pyrroles into pyrrolinones, e.g., oxidation of the parent heterocycle gives a tautomeric mixture of pyrrolin-2-ones **155** and **156**.

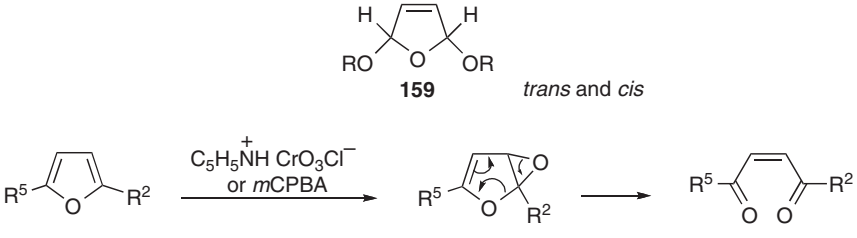


An example of the synthetic utility of the oxidative cleavage of the pyrrole C(2) to C(3) bond is the ring expansion of bicyclic pyrroles **157** to lactams **158**.



Bromine or electrolytic oxidation of furan in alcoholic solution gives the corresponding 2,5-dialkoxy-2,5-dihydrofuran **159** (R = Alk). Lead tetraacetate in acetic acid oxidation yields 2,5-diacetoxy-2,5-dihydrofuran **159** (R = Ac).

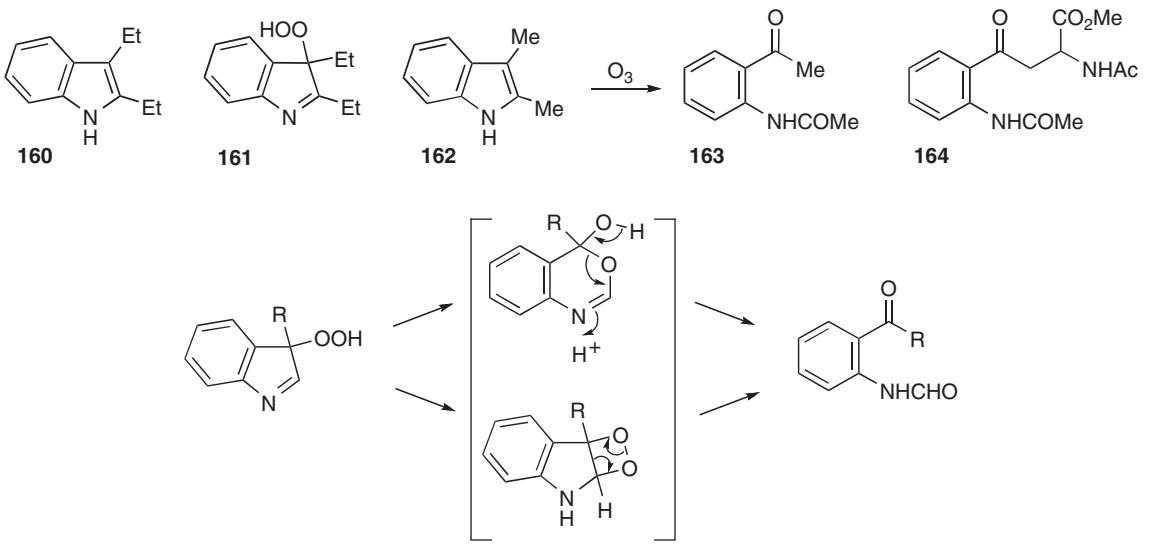
Oxidation of 2,5-dialkylfurans with pyridinium chlorochromate results in high yields of ,-unsaturated -dicarbonyl compounds. Similar results are obtained by peracid oxidation of furans, most frequently *m*CPBA. It is assumed that the first step involves epoxidation as shown in **Scheme 67**. Mono-, di-, and trisubstituted furans are oxidized to (*Z*)-enediones by methyltrioxorheniumureaH_2O_2 <1998TL5651>. $Mo(CO)_6$-catalyzed oxidation of 2,5-dialkyl furans by cumyl hydroperoxide provides (*E*)-enediones selectively. In the presence of Na_2CO_3, the corresponding (*Z*)-isomers are obtained <2003TL835>.



Scheme 67

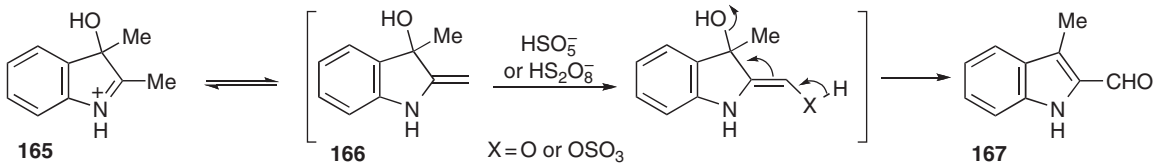
Oxidants and electrophilic reagents attack pyrroles and furans at positions 2 and 5; in the case of indoles the common point of attack is position 3. Thus, autoxidation of indoles (e.g., **160**) gives 3-hydroperoxy-3*H*-indoles (e.g., **161**). Lead tetraacetate similarly reacts at the 3-position to give a 3-acetoxy-3*H*-indole. Ozone and other oxidants have been used to cleave the 2,3-bond in indoles **162** **163**. The dioxygenolysis (THF or CH_2Cl_2, air, 25°C) of methyl *N*-acetyltryptophanate with achiral metalloporphyrins [M^{II}TPP (M = Mn, Fe, or Co)] likewise gives a ring-opened product **164** in yields of 932% amongst a complex mixture of minor products <1996JMOA269>; the 3*H*-indol-3-yl hydroperoxide was

observed (NMR) as a stable precursor of **164**. These 2,3-bond cleavages may proceed by one of the routes shown in **Scheme 68**.



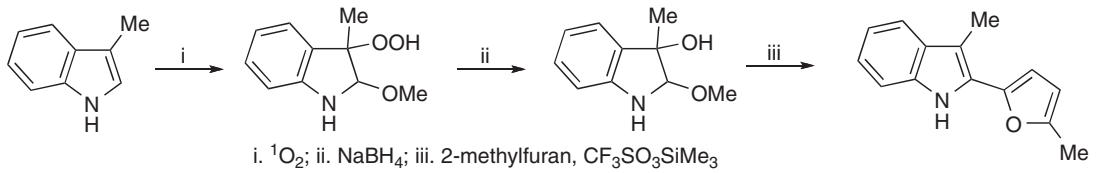
Scheme 68

The oxidation of 2,3-dimethylindole with peroxodisulfate or peroxomonosulfate yields 3-methylindole-2-carbaldehyde **167**. The reaction proceeds in three steps, namely, electrophilic attack of the peroxide at C(3) to give an indolenine intermediate **165**, then peroxide attack on the enamine tautomer **166**, and hydrolysis (**Scheme 69**).

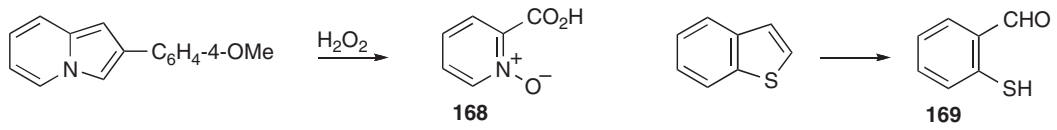


Scheme 69

Singlet oxygen oxidation of 3-substituted indoles in the presence of alcohols followed by treatment with sodium borohydride gives 2-alkoxy-3-hydroxyindolines in high yields. Further reaction with a nucleophile and a Lewis acid forms the basis of a synthesis of 2-substituted indoles (**Scheme 70**). This represents an alternative approach to CC bond formation at the 2-position of indoles to that involving the reaction of 2-lithioindoles with electrophiles. Isoindoles and indolizines are also preferentially oxidized in the five-membered ring to give phthalic acid and picolinic acid derivatives, e.g., **168**, respectively.



Scheme 70



The oxidation of indoles with H_2O_2 in the presence of the fungal chloroperoxidase from *Caldariomyces fumago* affords the 1,3-dihydro-2*H*-indol-2-ones <2001T8581>.

Thiophenes are reasonably stable to atmospheric oxidation. Ozone attacks the C=C bonds, e.g., benzothiophene yields *o*-mercaptobenzaldehyde **169**. For S-oxidation see Section 3.3.1.3.2.3.

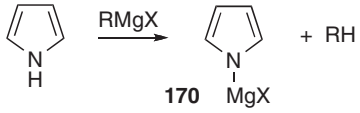
3.3.1.6 Reactions with Nucleophiles and Bases

Pyrrole, furan, and thiophene quite generally react with basic reagents by proton transfer, and not by substitution or addition. However, after discussion of proton loss from nitrogen and from carbon atoms we consider two major exceptions: (1) the cationic species formed by reaction with electrophiles are highly susceptible to nucleophilic attack and (2) vicarious nucleophilic substitution (VNS) and related reactions in rings containing strongly electron-withdrawing substituents.

Five-membered heterocycles are also susceptible to ring-opening and recyclization processes by nucleophile action. Well-known examples include the interconversions of pyrrole, furan, thiophene, and selenophene rings: e.g., furan and ammonia over a suitable catalyst can give pyrrole.

3.3.1.6.1 Deprotonation at nitrogen

Pyrrole is very much less basic than secondary amines but much more acidic. Pyrrole is, however, still a very weak acid ($pK_a = 17.5$). The nitrogen-bound proton can be abstracted from pyrrole by the use of strong bases such as sodium amide in liquid ammonia and *n*-butyllithium in hexane. Reaction of pyrrole with Grignard reagents results in the formation of halomagnesyl derivatives **170**. These nucleophiles have ambident properties and can react with electrophiles at nitrogen, C(2) or C(3). N-Unsubstituted indoles similarly form metal derivatives when treated with a variety of reagents such as *n*-butyllithium, sodamide, Grignard reagents and thallium(I) ethoxide.



170

The reactions of the pyrrole and indole anions with electrophiles are discussed in Section 3.3.1.3.1.

3.3.1.6.2 Deprotonation at carbon

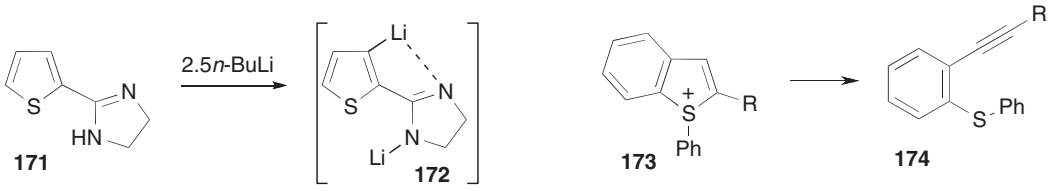
The first proton to be removed from *N*-methylpyrrole by *n*-butyllithium is from an -position; a second deprotonation occurs to give a mixture of 2,4- and 2,5-dilithiated derivatives. In both furan and thiophene, initial abstraction of a proton at C(2) is followed by proton abstraction from C(5). *N*-Methylindole, benzo[*b*]furan, benzo[*b*]thiophene, selenophene, benzo[*b*]selenophene, tellurophene, and benzo[*b*]tellurophene similarly yield 2-lithio derivatives.

Competitive metallation experiments with *N*-methylpyrrole and thiophene and with *N*-methylindole and benzo[*b*]thiophene indicate that the sulfur-containing heterocycles react more rapidly with *n*-butyllithium in ether. The comparative reactivity of thiophene and furan with *n*-butyllithium depends on the metallation conditions. In hexane, furan reacts more rapidly than thiophene but in ether, in the presence of tetramethylethylenediamine (TMEDA), the order of reactivity is reversed.

Directive effects on lithiation have also been studied. Regiospecific -metallation of *N*-methylpyrrole derivatives and 2-substituted furans can be effected by employing the *ortho*-directing effect of, for example, an oxazolino group; 2-lithio-3-bromofuran is the result of treatment of 3-bromofuran with lithium diisopropylamide (LDA) at 80 C in THF.

3-Methylthiophene is metallated at the 5-position whereas 3-methoxy-, 3-methylthio-, 3-carboxy-, and 3-bromothiophenes are metallated at the 2-position. 2-Substituents which have been used to direct metallation to C(3) of thiophene include oxazoline, imidazoline, secondary carboxamide, carboxylate, sulfonamide, and -aminoalkoxide. For

example, treatment of the imidazoline **171** with 2.5 equivalents of *n*-BuLi in THF at 78°C gave regiospecific lithiation at position 3 **172**. In contrast to this, treatment of **171** with LDA (2.2 eq.) in THF at 78°C led only to the 5-lithio derivative.

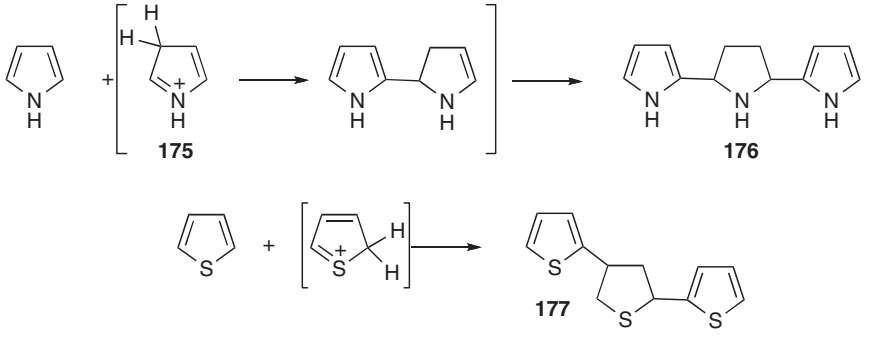


The reactions of the lithiated derivatives with electrophiles are discussed in Section 3.3.3.8.

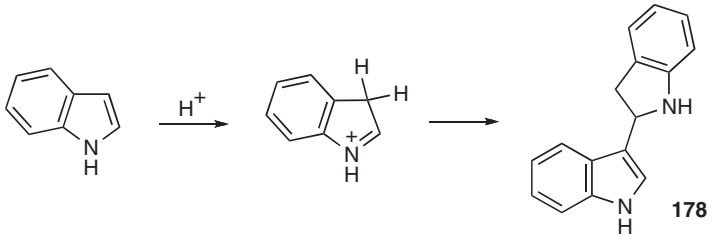
C(3)-Unsubstituted *S*-arylbenzo[*b*]thiophenium ions **173** undergo ring opening by cleavage of the SC(2) bond when treated with NaOMe in MeOH, the primary process is abstraction of the proton attached to C(3); subsequent cleavage of the SC(2) bond results in the formation of acetylenes **174** in quantitative yield.

3.3.1.6.3 Reactions of cationic species with nucleophiles

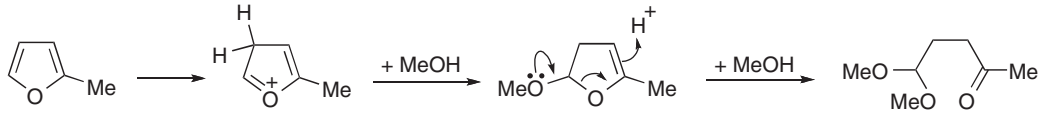
Protonation of pyrrole, furan, and thiophene derivatives generates reactive electrophilic intermediates which participate in polymerization, rearrangement, and ring-opening reactions. Pyrrole itself gives a mixture of polymers (pyrrole red) on treatment with mineral acid and a trimer **176** under carefully controlled conditions. Trimer formation involves attack on a neutral pyrrole molecule by the less thermodynamically favored, but more reactive, -protonated pyrrole **175** <1997JCR(M)0401>. The trimer **177** formed on treatment of thiophene with phosphoric acid involves thiophene attack on an -protonated species.



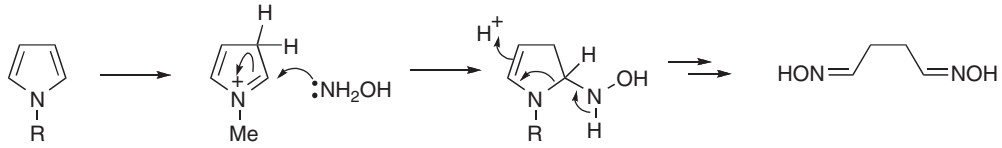
Indolizine gives a stable pyridinium ion and does not polymerize in the presence of acid. Indole undergoes acid-catalyzed dimerization; the 3*H*-indolium ion acts as an electrophile and attacks an unprotonated molecule to give the dimer **178**. Protonation of the dimer in turn gives an electrophilic species from which a trimeric product can be derived. *N*-Methylisoindole undergoes acid-catalyzed polymerization, indicating that protonation at C(1) gives a reactive electrophilic intermediate.



The chemical consequences of -protonation are illustrated further by the ring-opening reactions of furans with methanolic hydrogen chloride (**Scheme 71**) and of *N*-substituted pyrroles with hydroxylamine hydrochloride (**Scheme 72**). Proton catalyzed ring opening followed by recyclization is involved in the interconversion of furan and selenophene derivatives using either aqueous hydrolysis followed by reaction with hydrogen selenide or directly using hydrogen selenide. These conversions require initial protonation at the -position.

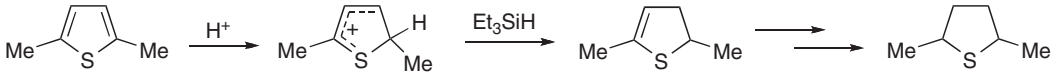


Scheme 71



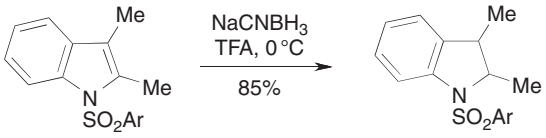
Scheme 72

The so-called ionic method for hydrogenating thiophenes is a further illustration of what can be the chemical consequences of protonation. Protonation of the thiophene ring renders the ring susceptible to hydride attack, conveniently derived from triethylsilane (**Scheme 73**).



Scheme 73

2,3-Dihydroindoles are produced in good yield from 1-phenylsulfonylindoles by reduction with sodium cyanoborohydride in TFA at 0°C (e.g. **Scheme 74**). If acyl groups are present at C(2) or C(3) in the substrate, they are reduced to alkyl groups. Indole itself is also reduced to 2,3-dihydroindole by sodium cyanoborohydride and acetic acid or triethylamineborane and hydrochloric acid. An alternative method for preparing indolines involves treatment of indoles with formic acid (or a mixture of formic acid and ammonium formate) and a palladium catalyst. Reduction of the heterocyclic ring under acidic conditions must involve initial -protonation followed by reaction with hydride.

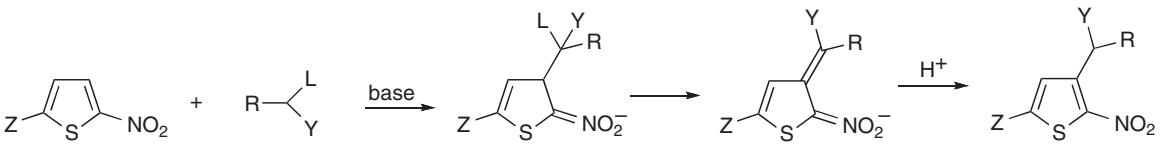


Scheme 74

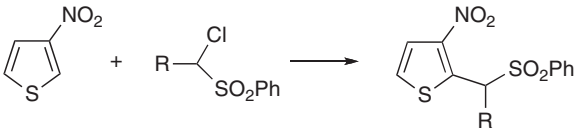
3.3.1.6.4 Vicarious nucleophilic substitution and related reactions

The vicarious nucleophilic substitution (VNS) of hydrogen in nitrothiophenes is of great synthetic potential. Carbanions bearing leaving groups (L) at the carbanion center can initially add to nitrothiophenes forming ^{H} adducts; subsequent elimination of HL, followed by protonation, leads to products which have formally been obtained by

substitution of Nu for H. The carbanions are usually generated *in situ* by the action of base on the corresponding CH acids (**Scheme 75**). With 2-nitrothiophenes, usually H(3) of the thiophene is replaced, if the carbanion is CHLY, but with tertiary carbanions, some 5-substitution can also occur. 3-Nitrothiophene gives only the 2-substituted product (**Scheme 76**). The base employed is usually KO*t*-Bu, KOH, NaOH, or NaH; the preferred solvents are DMSO, liquid ammonia, or DMF.

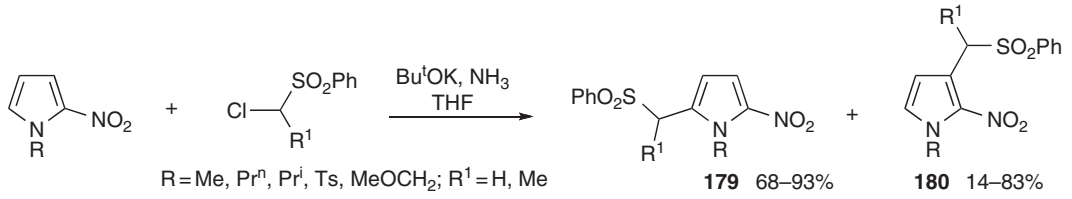


Scheme 75



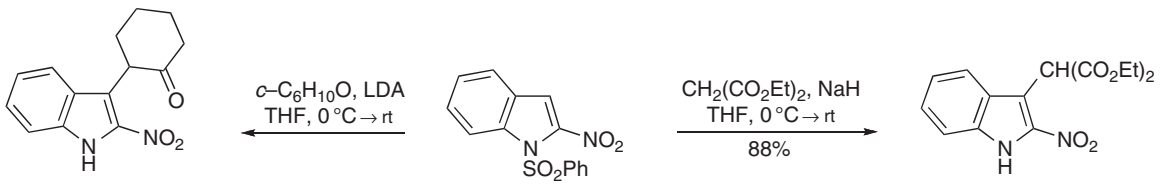
Scheme 76

The products **179** and **180** result from VNS on 2-nitropyrrole with chloromethyl sulfones <1995T8339>. 3-Nitropyrrole is attacked only at C(2).

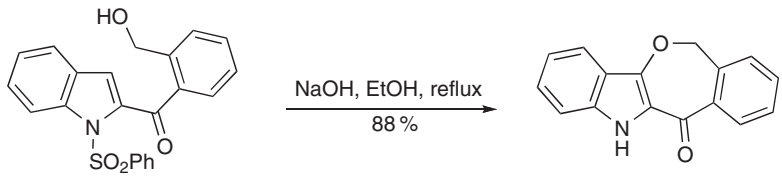


Grignard reagents add to 2-nitrofuran providing *trans*-2,3-disubstituted 2,3-dihydrofurans as the predominant isomers <2003TL3167>.

2-Nitro-1-(phenylsulfonyl)indole undergoes nucleophilic substitution reactions with enolates, for example, of diethyl malonate and cyclohexanone (**Scheme 77**), to afford the corresponding 3-substituted 2-nitroindoles <1997TL5603, 1999TL7615>. Similar S_N2'-type displacements of phenylsulfinate work very efficiently in an intramolecular sense (e.g., **Scheme 78**) <1999PHC45>.

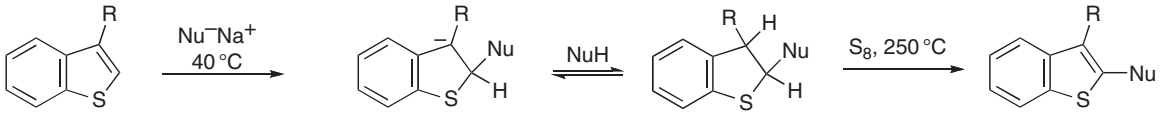


Scheme 77



Scheme 78

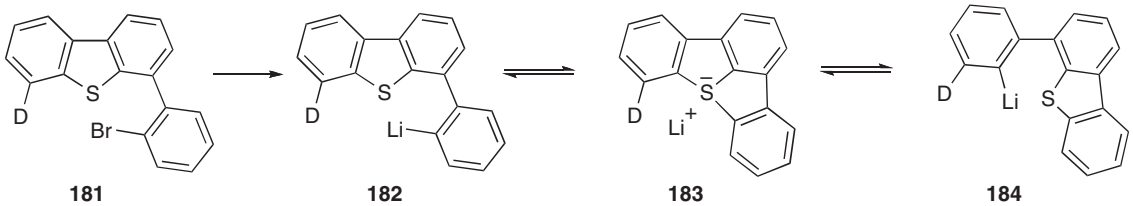
In the thiophene and benzothiophene series, nucleophilic substitution of hydrogen (**Scheme 79**) becomes possible due to the ability of 3d-orbitals of the sulfur atom to stabilize negative charge arising in an anionic -complex. Thiophene 1,1-dioxides are very good Michael acceptors. The addition of MeSNa to 3,4-di-*tert*-butylthiophene 1,1-dioxide <2000CL744> takes place in a 2,5- and 2,3-fashion to give a 56:44 mixture of adducts in 94% yield.



Scheme 79

3.3.1.6.5 Nucleophilic attack on sulfur

Convincing evidence has been presented for the possible intermediacy of an organosulfur ate complex in which the sulfur is linked to three carbon atoms. The strategy adopted was to synthesize a rigid molecule with ideal geometry favoring formation of the ate complex. The deuterium-labeled bromo compound **181** was converted into the lithio derivative **182**. This resulted in equilibration of the isotope label in less than 1 min at 78°C in THF. This means that **182** must have been converted into **184** via the ate complex **183**. This Li/S exchange at 0°C was 10^9 times faster than the comparable intermolecular Li/S exchange of Ph_2S with PhLi.

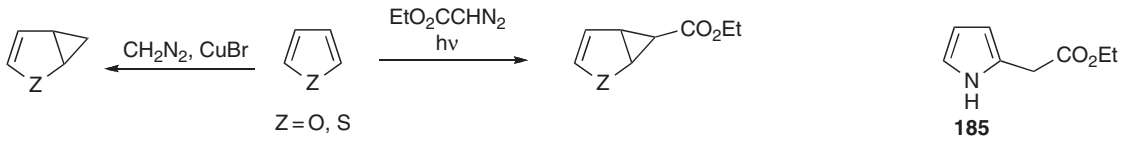


Treatment of 3-chloro-2-phenylbenzo[*b*]thiophene with *n*-butyllithium, followed by quenching with NH_4Cl, gave a 71% yield of the 1-phenyl-2-(2-*n*-butylthiophenyl)acetylene, which is obviously the result of nucleophilic attack at the sulfur with cleavage of the ring and elimination of chloride.

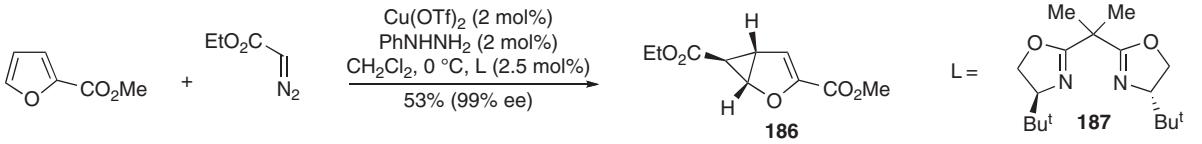
3.3.1.7 Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces

3.3.1.7.1 Carbenes and nitrenes

Furan and thiophene undergo addition reactions with carbenes. Thus, cyclopropane derivatives are obtained from these heterocycles on copper(I) bromide-catalyzed reaction with diazomethane or light-promoted reaction with diazoacetic acid ester (**Scheme 80**). The copper-catalyzed reaction of pyrrole with diazoacetic acid ester, however, gives a 2-substituted product **185**. The copper(I)-catalyzed asymmetric cyclopropanation of methyl furan-2-carboxylate with ethyl diazoacetate using the bisoxazoline ligand **187** yields the *exo*-isomer 2-oxa[3.0.1]bicyclohexene **186** (**Scheme 81**) <2003CEJ260>. Rh_2(*S*-DOSP)$_4$-catalyzed intermolecular cyclopropanation of benzo[*b*]furan with diazobutenoates gives a cyclopropane across C(2)C(3) in a diastereo- and enantioselective manner <1998JOC6586>.

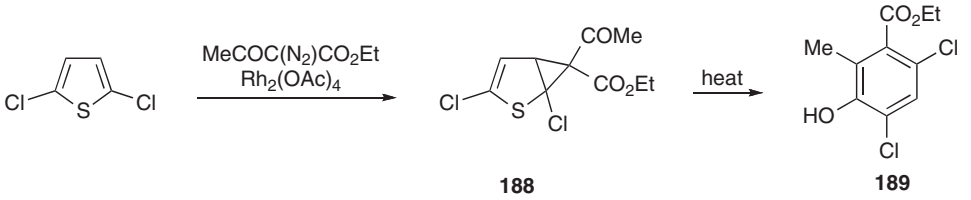


Scheme 80

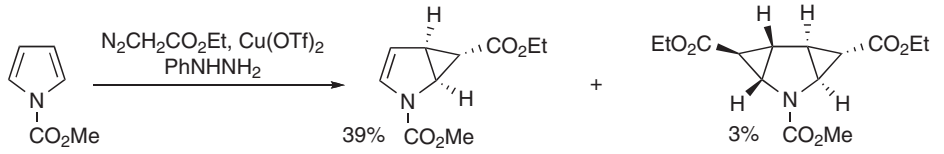


Scheme 81

Copper-promoted reaction of ethyl 2-diazoacetoacetate [$N_2C(COMe)CO_2Et$] and dimethyl diazomalonate [$N_2C(CO_2Me)_2$] with *N*-methylpyrrole also furnishes 2-substituted derivatives. Indole similarly yields a 3-substituted product on reaction with diazoacetic acid ester. In the rhodium acetate-catalyzed reaction of 2,5-dichlorothiophene with ethyl 2-diazoacetoacetate, the initial 2,3-cycloadduct **188** fragments with sulfur extrusion and subsequent rearrangement yields the dichlorophenol **189** (**Scheme 82**). A mixture of cyclopropanes is obtained, best with a copper(I) triflate-catalyzed reaction <2000JOC8960, 2006JOC2173> of 1-methoxycarbonylpyrrole with diazoacetic acid ester. This is thought to be indicative of the reduced aromaticity of a pyrrole substituted on nitrogen with an electron-withdrawing substituent (**Scheme 83**).

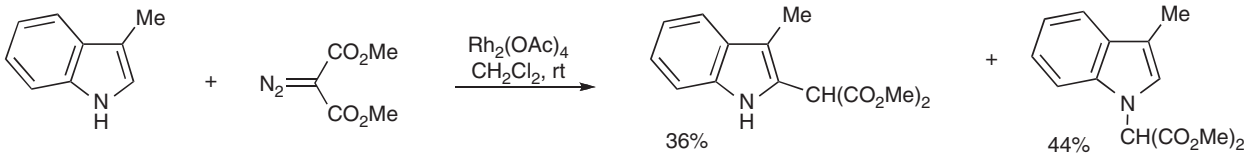


Scheme 82



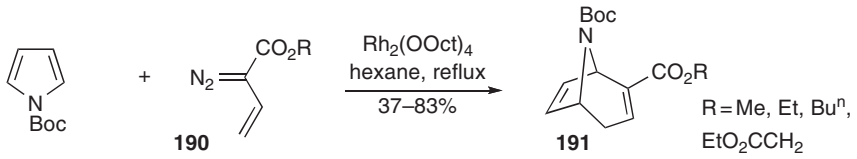
Scheme 83

Indoles treated with dimethyl diazomalonate under catalysis by rhodium(II) acetate undergo CH and NH insertion reactions depending on the substitution pattern on the indole moiety (e.g., **Scheme 84**) <2002JOC6247>.



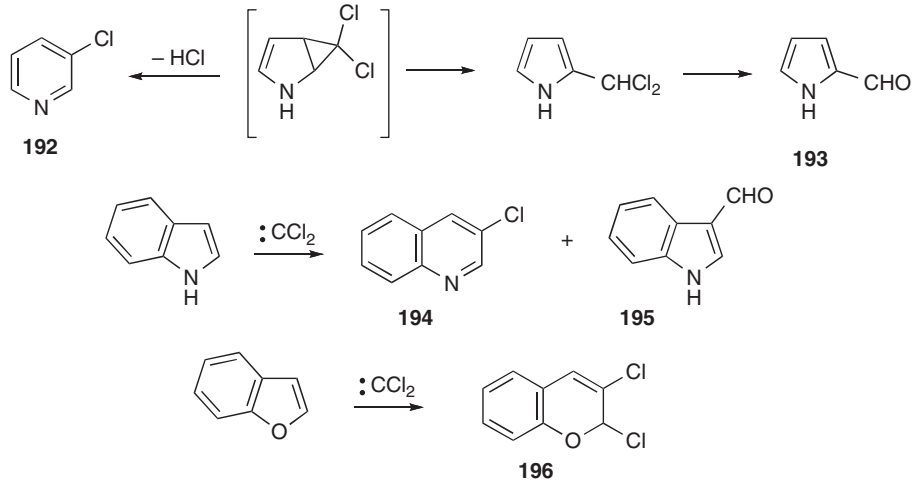
Scheme 84

Rhodium(II) octanoate-catalyzed decomposition of the vinyldiazomethane **190** in refluxing hexane in the presence of *N*-Boc-pyrrole results in the formation of tropanes **191**, the products of a tandem 2,3-cyclopropanation/Cope rearrangement <1991JOC5696, 1995TL7205>.



190 **191**

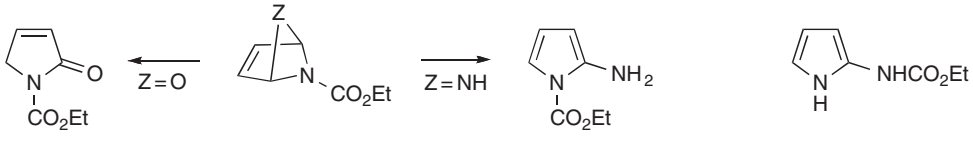
The reaction of pyrrole with dichlorocarbene, generated from chloroform and strong base, gives a bicyclic intermediate which can be transformed into either 3-chloropyridine **192** or pyrrole-2-carbaldehyde **193**. Indole gives a mixture of 3-chloroquinoline **194** and indole-3-carbaldehyde **195**; the optimum conditions utilize phase transfer. Benzofuran reacts with dichlorocarbene in hexane solution to give the benzopyran **196**, whereas benzothiophene fails to react.



192 **193** **194** **195** **196**

Furan undergoes 1,4-addition with ethoxycarbonylnitrene to give **197** (Z = O) which rearranges to the pyrrolinone **198**. The corresponding reaction with pyrrole gives a mixture of **199** and **200**. Ethoxycarbonylnitrene attacks thiophene and its simple alkyl derivatives at the -position; subsequent ring opening and reclosure with loss of sulfur leads to pyrroles.

The formation of *S,C*- and *S,N*-ylides of thiophenes is discussed in Section 3.3.1.3.2.2.

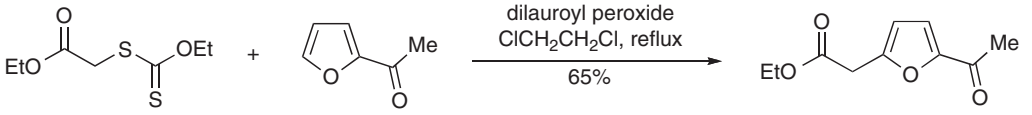


198 **197** **199** **200**

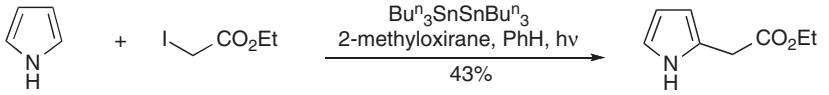
3.3.1.7.2 Radical attack

Pyrroles, furans, and thiophenes react preferentially with radicals at the 2-position. Thus, reaction of pyrrole with benzyl radicals gives 2-benzylpyrrole. In rather better yields, pyrrole and indole treated with per(poly)fluoroalkyl chlorides (R_FCl) in the presence of sodium dithionite in DMSO produce 2-perfluoroalkyl products <2001JFC(111) 107>. Furans trap aryl radicals, generated from the $Mn(OAc)_3$ oxidation of arylboronic acids <2003JOC578> or

arylhydrazines <2002T8055>, to give 2-arylfurans. Xanthate-derived radicals bring about 5-substitution of 2-acylpyrroles and 2-acylfurans (Scheme 85) <2003CC2316> and 2-substitution of indoles <2003CC2316>. Pyrrole can be substituted using the combination $ICH_2CO_2EtBu_3SnSnBu_3$ in the presence of 2-methyloxirane (Scheme 86) <1999TL2677>; iodoacetonitrile, iodoacetamide, and diethyl bromomalonate can also be used and indole is substituted at C(2). The electrophilic radical, CH_2CO_2Et, can also be generated from ICH_2CO_2Et, H_2O_2 and catalytic Fe^{2+} in DMSO.



Scheme 85



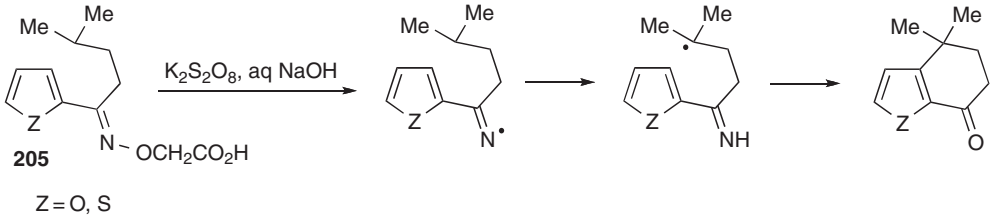
Scheme 86

With triphenylmethyl radicals, pyrrole behaves like a 1,3-diene giving the adduct **201**. *N*-Methylpyrrole undergoes radical benzoyloxylation with dibenzoyl peroxide to give the 2-benzoyloxypyrrole **202** and 2,5-dibenzoyloxypyrrole **203**. Furan, however, is converted in good yield into a mixture of *cis* and *trans* addition products analogous in structure to **201**.

201 **202** **203** **204**

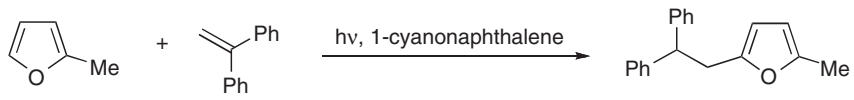
Arylation of N-substituted pyrroles, thiophenes, and furans occurs preferentially in the 2-position, e.g., the o-nitrophenylation of thiophene by phase-transfer catalysis yields **204**.

Thiophene reacts with phenyl radicals approximately three times as fast as benzene. Intramolecular radical attack on furan and thiophene rings occurs when oxime derivatives of type **205** are treated with peroxysulfate (Scheme 87). Intramolecular homolytic alkylation occurs with equal facility at the 2- and 3-positions of the thiophene nucleus, whereas intermolecular homolytic substitution occurs mainly at position 2.



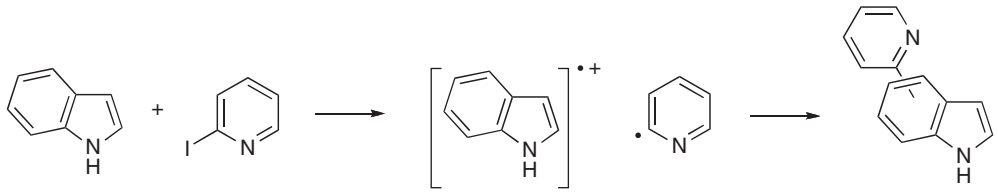
Scheme 87

Pyrroles, furans, and thiophenes undergo photoinduced alkylation with diarylalkenes, provided that the alkene and heteroaromatic compounds have similar oxidation potentials, indicating that alkylation can occur by a nonionic mechanism (Scheme 88).



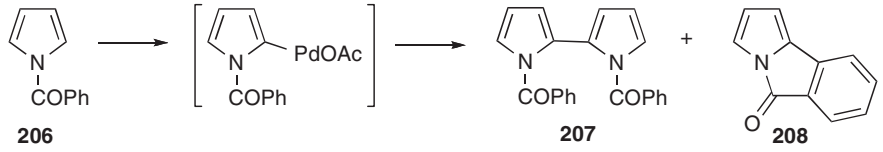
Scheme 88

Radical reactions are facilitated by the fact that pyrroles and indoles can form reasonably stable radical cations in some cases. For instance, photoarylation of indole by 2-iodopyridine is controlled by a photochemical electron-transfer reaction leading to the combination of the indole radical cation and the 2-pyridyl radical. The position of attack is controlled by the relative spin densities of the possible radical cations. In polar solvents, substitution is favored at positions 3, 6, and 4, while in nonpolar solvents, there is a preference for substitution at positions 2 and 7 (**Scheme 89**).

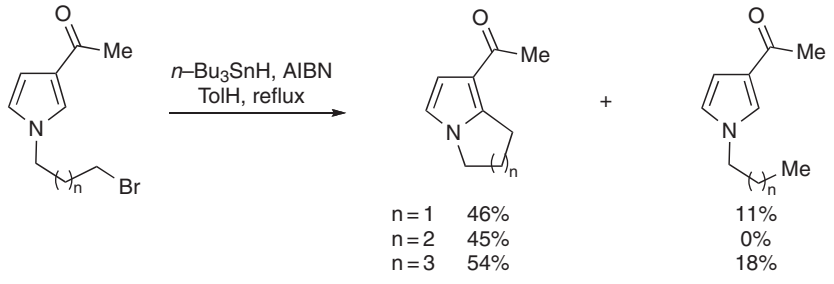


Scheme 89

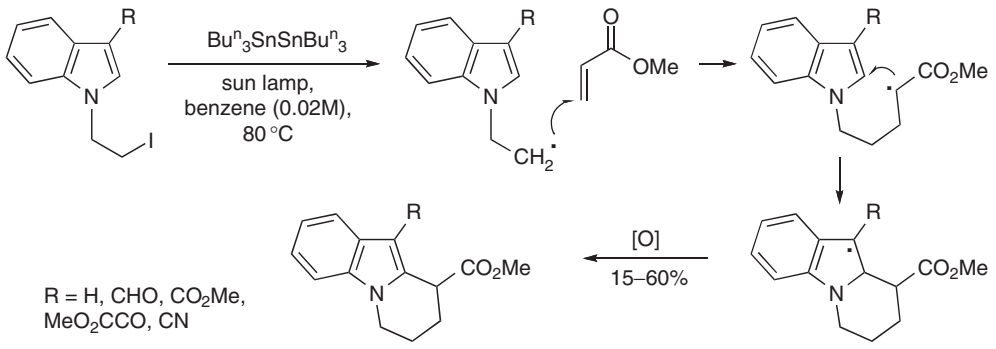
1-Aroylpyrroles dimerize on treatment with palladium(II) salts; thus, oxidation of 1-benzoylpyrrole **206** with palladium acetate in acetic acid gives the 2,2-bipyrrole **207**. The ring-closed compound **208** is formed as a by-product.



Intramolecular radical substitution of pyrroles and indoles has been well studied; this is exemplified in **Schemes 90** <1997TL7937> and **91** <2000TL10181>. Intramolecular radical acylation of 1-(-halogenoalkyl)-2-methylsulfonyl-5-substituted pyrroles leads to bicyclic ketones with displacement of the sulfonyl moiety <2000TL3035>. Similar cyclizations can be achieved using acyl selenide precursors to generate an acyl radical <2001TL7887>.



Scheme 90



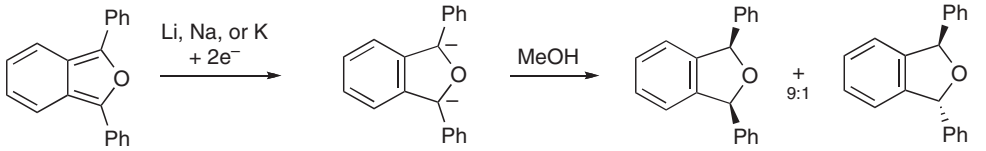
Scheme 91

3.3.1.7.3 Electrochemical reactions

Electrolytic oxidation of furan in alcoholic solution gives the corresponding 2,5-dialkoxy-2,5-dihydrofuran.

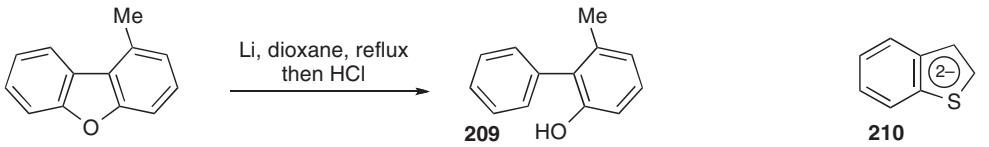
3.3.1.7.4 Reactions with free electrons

Pyrroles are not reduced by sodium in liquid ammonia, but the Birch reduction of 2-furoic acid with lithium in liquid ammonia gives the 2,5-dihydro derivative in 90% yield. Sodium-liquid ammonia-methanol reduction of thiophene gives a mixture of 3,4- and 2,5-dihydrothiophenes together with butenethiols. Reductive metallation of 1,3-diphenylisobenzofuran results in stereoselective formation of the *cis*-1,3-dihydro derivative (**Scheme 92**).



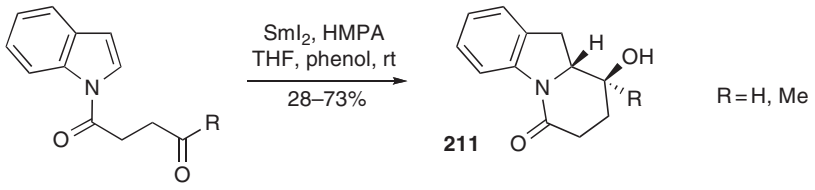
Scheme 92

Regioselective cleavage of dibenzofuran derivatives has been achieved with lithium metal, as exemplified by the preparation of 3-methyl-2-phenylphenol **209**.



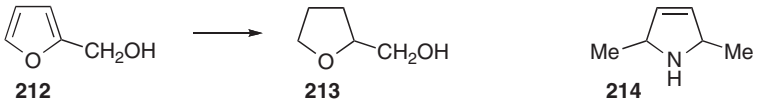
Benzo[*b*]thiophene dianion **210** can be prepared by reduction of benzo[*b*]thiophene with sodium metal at 78 K in [$^2H_8$]THF. The ^1H and ^{13}C NMR spectra of the purple solution obtained prove that it is the dianion and not a radical anion. This is the first example of a sulfur-containing (4*n*)-polycyclic dianion. The dianion is converted back to benzo[*b*]thiophene with oxygen.

N-Acylated indoles are converted into tricyclic compounds **211** in the presence of samarium diiodide (2.5 eq.) along with hexamethylphosphoramide (10 eq.) and phenol (2.0 eq.) as proton source <2003OL4305>.

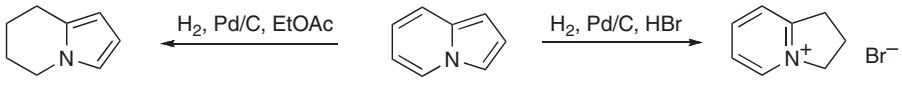


3.3.1.7.5 Catalytic hydrogenation

Catalytic reduction of pyrroles gives successively 2,5-dihydropyrroles then pyrrolidines. Tetrahydrofurans are formed by the catalytic reduction of furans with Raney nickel and hydrogen; ring-cleavage products may also be formed, e.g., **212** **213** $Me(CH_2)_2CH(OH)CH_2OH + Me(CH_2)_4OH$.



Vigorous catalytic reduction of indole (H_2, Pd, AcOH, HCl, 80°C) results in the formation of *cis*-octahydroindole. Catalytic reduction of isoindoles occurs preferentially in the pyrrole ring. Reduction of indolizine with hydrogen and a platinum catalyst gives an octahydro derivative. With a palladium catalyst in neutral solution, reduction occurs in the pyridine ring but in the presence of acid, reduction occurs in the five-membered ring (**Scheme 93**).



Scheme 93

3.3.1.7.6 Reduction by dissolving metals

2,5-Dihydropyrroles, e.g., **214**, are formed on the reduction of pyrroles and simple alkylpyrroles with zinc and acid. These are derived from the corresponding -protonated species.

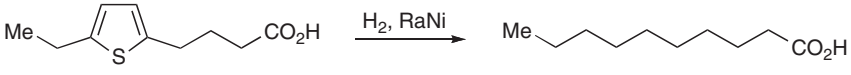
Indole-2-carboxylic esters undergo reduction with magnesium in methanol to give the 2,3-dihydroindole (indoline).

Dissolving metals reduce the heterocyclic ring of isoindoles.

Reduction of thiophene and 2-ethylthiophene to the corresponding 2,5-dihydrothiophenes can be carried out with zinc and trifluoroacetic acid. The mechanism is again thought to involve protonation of the thiophene ring followed by transfer of two electrons from zinc and a second proton from the acid. The reduction of thiophenes with alkali metals in liquid ammonia can lead to 2,5-dihydrothiophenes, ring-opened products, or desulfurized products.

3.3.1.7.7 Desulfurization

Raney nickel desulfurization of thiophenes is an important technique for chain extension. Ring fission is accompanied by saturation of the ring carbon atoms and chain extension by four carbon atoms is effected. This method has been widely used to prepare alkanes, ketones, and carboxylic acids and their derivatives. An illustrative example is given in **Scheme 94**.



Scheme 94

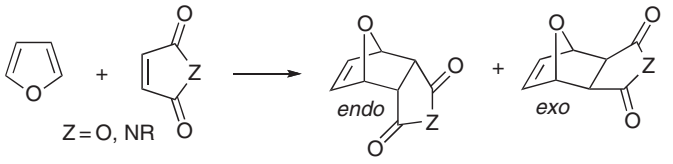
Nickel boride (prepared by adding $NaBH_4$ to nickel chloride in methanolTHF) is an efficient, nonpyrophoric reagent for the desulfurization of benzo[*b*]thiophene and dibenzothiophene. The reaction proceeds under very mild conditions and is probably mediated by nickel hydride.

3.3.1.8 Reactions with Cyclic Transition States

3.3.1.8.1 Heterocycles as inner ring dienes

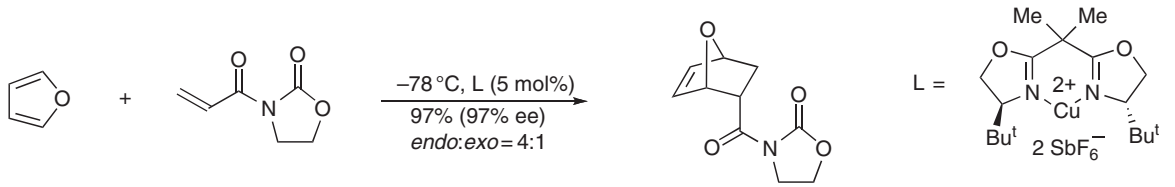
Furan has much greater reactivity in cycloaddition reactions compared to pyrrole and thiophene; the latter is the least reactive as a diene. N-Substituted pyrroles often show enhanced diene character compared with the parent heterocycle, especially when the N-substituent is electron withdrawing.

Furan reacts as a diene with powerful dienophiles such as maleic anhydride, maleimide, and benzyne to give Diels Alder adducts. The kinetically favored products are the *endo* adducts but the *exo* adducts are thermodynamically preferred (**Scheme 95**). Thus, on prolonged reaction at room temperature, or on heating, the proportion of *exo* to *endo* adduct is increased.



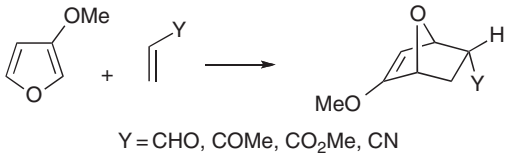
Scheme 95

Thermal DielsAlder reactions of furans are problematic with some dienophiles because of the ease with which they take part in competitive aromatic substitution reactions. Lewis acid catalysis often helps to avoid that problem and may also influence the stereoselectivity for example, $HfCl_4$ promotes *endo*-selective intermolecular DielsAlder cycloadditions of furans with ,-unsaturated esters <2002AGE4079>. The reaction of furan with less reactive dienophiles such as acrylonitrile and methyl acrylate is greatly accelerated by zinc(II) iodide. The reaction of methyl acrylate with furan proceeds in good yield when catalyzed by boron trifluoride etherate. Enantioselective DielsAlder reaction between a furan and an acryloyl oxazolidinone provides the *endo*-adduct in 97% ee using a cationic bis(4-*tert*-butyloxazoline)copper (II) complex (**Scheme 96**) <1997TL57>.



Scheme 96

Copper(I) and copper(II) salts have been shown to catalyze the reaction of furan with -acetoxyacrylonitrile (CH_2═C(OAc)CN). Alkoxy and silyloxy groups activate the furan nucleus to cycloaddition reactions, e.g., 3-methoxyfuran readily undergoes [4 + 2] cycloaddition with electron-deficient dienophiles with regio- and stereo-control to give *endo*-adducts (**Scheme 97**).

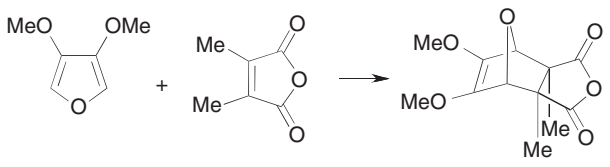


Scheme 97

Conversely, furans with electron-withdrawing groups (e.g., CHO, CN, CO_2Me) in the 2-position show reduced Diels Alder reactivity. Although furan-2-carboxaldehyde is a poor diene, the related *N*,*N*-dimethylhydrazones do take part in reactions with a range of dienophiles including maleic anhydride, maleimides, and fumaronitrile.

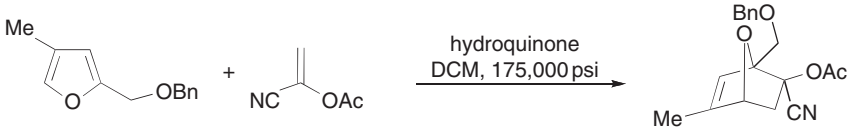
Electron-releasing groups in the 3- or 4-position appear to have little effect on the diene character of the furan ring. Although 3,4-dimethoxyfuran readily undergoes [4 + 2] cycloaddition with maleic anhydride or methylmaleic anhydride, high pressure is required to carry out cycloaddition with dimethylmaleic anhydride (**Scheme 98**).

A disadvantage of traditional DielsAlder methodology is the ease with which the retro-reaction occurs in some cases, particularly when the reactions have to be conducted at high temperatures. The transition state in the DielsAlder



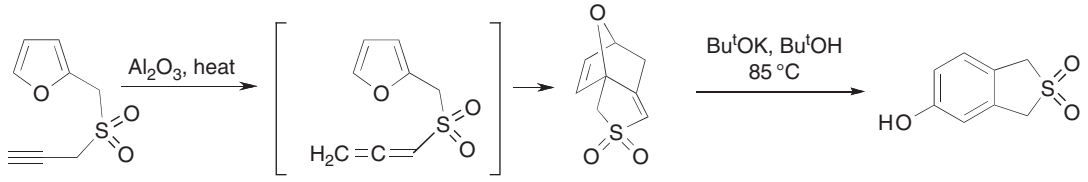
Scheme 98

reaction occupies a smaller volume than the coreactants and so rates of reactions are significantly increased by methods that produce compression. This can be achieved either by using high pressures, including examples when 1,4-benzoquinone functions as the dienophile, or by carrying out the reactions in water. This is exemplified in Scheme 99. DielsAlder reactions of 2-acetoxy- and 2-methylthio-furan proceed smoothly at room temperature and 15 kbar.



Scheme 99

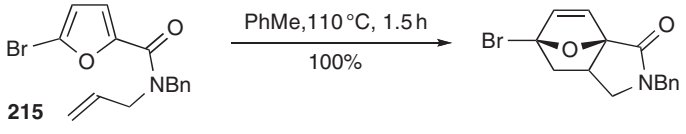
The development of intramolecular DielsAlder (IMDA) reactions has proved important for the synthesis of natural products. Formation of the IMDA product from the propargyl sulfone shown in Scheme 100 proceeds via the allene; it was converted subsequently into the benzenoid sulfone by base.



Scheme 100

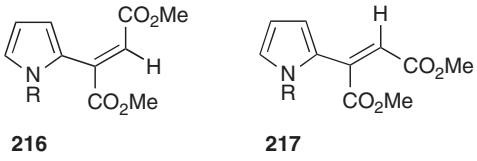
Although IMDA reactions are entropically less disfavored than the intermolecular versions, they are nonetheless not as simple as might at first appear. The well-known Alder *endo* rule and its frontier molecular orbital theoretical interpretation involving secondary orbital interactions, together with steric considerations, serve to explain the kinetic preference for the *endo*-product and the thermodynamic preference for the *exo*-product in IMDAs. For the IMDA reaction, an additional parameter, the effect of the tether that connects the diene to the dienophile to control the conformation available to a transition state has to be considered.

The presence of a halogen substituent at the 5-position of 2-furanyl amides markedly enhances the rate of IMDAs; for example, 5-bromofuran **215** provided the oxatricyclic adduct after heating for 90 min but the corresponding 5-unsubstituted furan required 1 week for the cycloaddition to be completed <2003OL3337>.



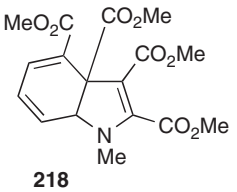
Pyrroles and indoles can take part in a wide variety of cycloaddition reactions. The reactions of pyrroles with dienophiles generally follow two different pathways involving either a [4 + 2] cycloaddition or a Michael-type addition to a free -position of the pyrrole ring. Pyrrole itself gives a complex mixture of products with maleic anhydride or maleic acid.

The reactions of pyrroles with dimethyl acetylenedicarboxylate (DMAD) have been extensively investigated: in the presence of a proton donor, the Michael adducts **216** and **217** are formed. However, under aprotic conditions, and especially with an electron-withdrawing N-substituent, the reversible formation of the 1:1 DielsAlder adduct is an important reaction, e.g., **Scheme 101** <2005OL1003>. In the case of the adduct from 1-methylpyrrole, reaction with a further molecule of DMAD occurs to give a dihydroindole **218**.

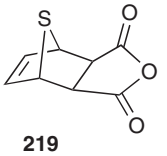


216

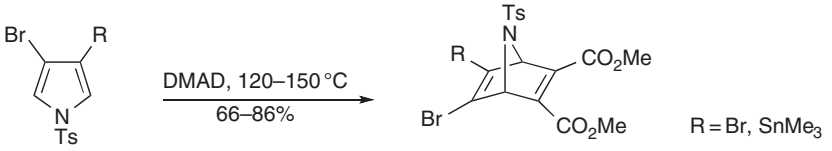
217



218

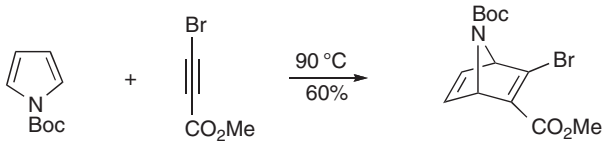


219



Scheme 101

In other examples, reaction of 3,4-dibromo-*N*-tosylpyrrole occurs with benzyne <2005OL1003> and *N*-Boc-pyrrole adds to methyl bromopropynoate (**Scheme 102**) <1996JOC7189>.

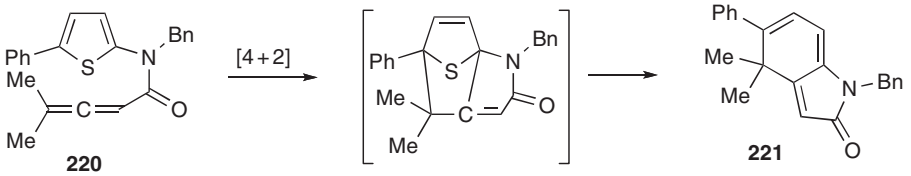


Scheme 102

N-Amino- and N-substituted aminopyrroles readily undergo DielsAlder additions and add to activated alkynes at room temperature.

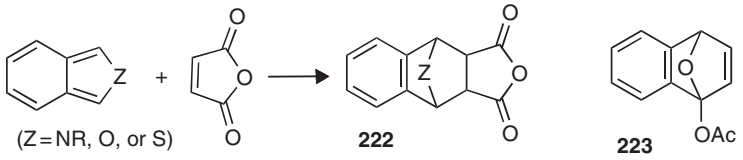
Thiophene fails to undergo cycloaddition reactions with common dienophiles under normal conditions. However, when thiophene is heated under pressure with maleic anhydride, the *exo*-adduct **219** is formed in moderate yield.

Thiophenes can function either as a diene or as a dienophile in an IMDA; for example, *N*-(2-thienyl)allene carboxamide **220** on heating at 130°C leads to **221** by a [4 + 2] cycloaddition in which the thiophene functions as a 4-component, followed by extrusion of sulfur.



220 **221**

Benzo[*b*]furans and indoles do not take part in DielsAlder reactions as dienes. By contrast, the benzo[*c*]-fused heterocycles function as highly reactive dienes in [4 + 2] cycloaddition reactions. Thus, benzo[*c*]furan, isoindole (benzo[*c*]pyrrole), and benzo[*c*]thiophene all yield DielsAlder adducts **222** with maleic anhydride. Adducts of this type are used to characterize these unstable molecules and in a similar way benzo[*c*]selenophene, which polymerizes on attempted isolation, was characterized by formation of an adduct with tetracyanoethylene.

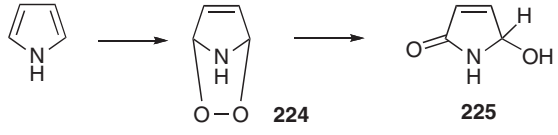


Benzo[*c*]furan, generated *in situ* in boiling xylene in the presence of dimethylmaleic anhydride, gives mainly the *exo*-adduct; furan itself fails to react with this dienophile. 1,3-Diphenylbenzo[*c*]furan is also a reactive diene but the corresponding 1,3-dimesityl derivative is inert to several dienophiles, even under forcing conditions.

Furans react readily with benzynes, e.g., 2-acetoxyfuran yields **223**. *N*-Methylpyrrole also reacts across the 2,5-positions, but pyrrole itself yields 2-phenylpyrrole.

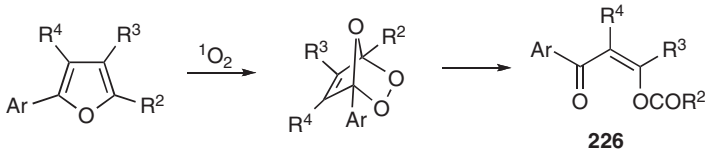
Benzyne, generated from diphenyliodonium 2-carboxylate, reacts with various thiophenes by addition to the sulfur and -carbon to give, after loss of an acetylene moiety, benzo[*b*]thiophenes in low (<4%) yields.

The photosensitized reaction of pyrrole and oxygen yields 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one **225**, probably by way of an intermediate cyclic peroxide **224** (**Scheme 103**).



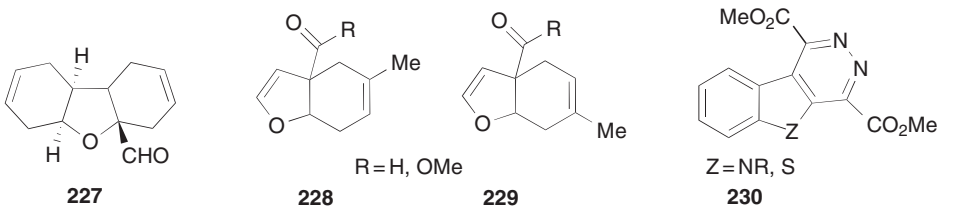
Scheme 103

Furans also form cyclic peroxides on reaction with singlet oxygen; these undergo some interesting rearrangements as shown by the formation of the 2-aroyl enol esters **226** from the peroxides derived from 2-arylfurans.

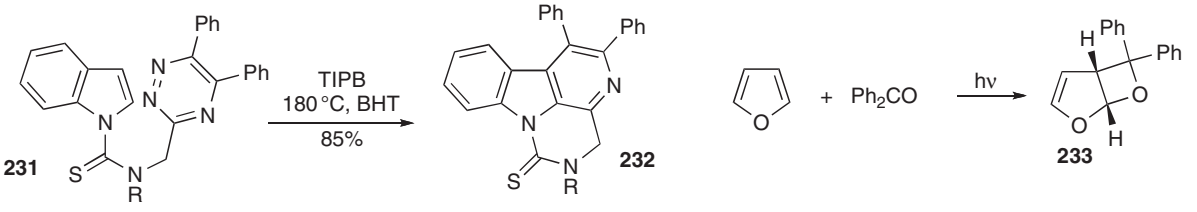


3.3.1.8.2 Five-membered heterocycles as dienophiles

Many five-membered, aromatic heterocycles act as dienophiles in DielsAlder reactions, both with normal and inverse electron demands. Reactions with normal electron demand occur only for compounds with electron-withdrawing groups in the heterocyclic ring. A classical example is the formation (though only 10%) of a 2:1 adduct **227** on thermal reaction of 1,3-butadiene with furfural. Much better results can be obtained if the electron-withdrawing group is in the -position. Thus, such derivatives of furan interact with isoprene producing with a good yield a mixture of isomers **228** and **229** though regioselectivity is low. In pyrroles and indoles, more than one electron-withdrawing group is required. Thiophenes, in analogy with their behavior as dienes, are poor dienophiles. 2-Thiophenecarboxaldehyde remains unchanged on being heated with 12 equivalents of isoprene at 195°C for 72 h, while 3-thiophenecarboxaldehyde undergoes cycloaddition in less than 6% yield.

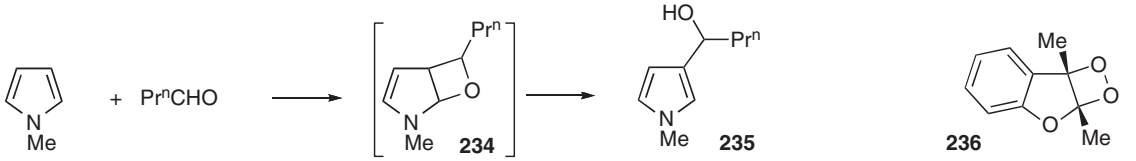


Pyrroles, indoles, and benzo[*b*]thiophene act as good dienophiles in inverse electron demand DielsAlder reactions with 1,2-diazines, 1,2,4-triazines, and *sym*-tetrazines. This is exemplified by the formation of compounds **230** in excellent yields on interaction of indoles or benzo[*c*]thiophene with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate. There are also many examples in which the azadiene is tethered, i.e., the processes are intramolecular; for example, **231** heated in triisopropylbenzene gives **232** <1995TL6591>.

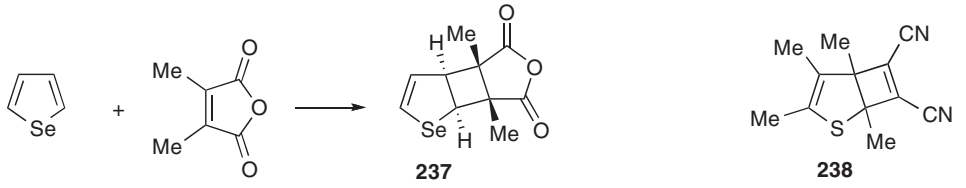


3.3.1.8.3 [2 + 2] Cycloaddition reactions

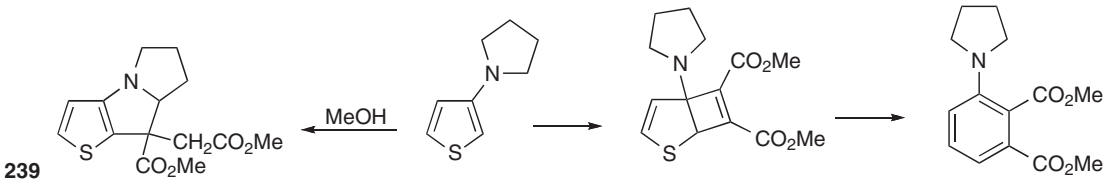
N-Substituted pyrroles, furans, and dialkylthiophenes undergo photopromoted [2 + 2] cycloadditions with carbonyl compounds to give oxetanes, for example, furan and benzophenone give **233**. The photochemical reaction of pyrroles with aliphatic aldehydes and ketones results in the regiospecific formation of 3-(1-hydroxyalkyl)pyrroles (e.g., **235**), via intermediate oxetanes (e.g., **234**) that undergo rearrangement under the reaction conditions. Photooxygenation of 2,3-dimethylbenzo[*b*]furan at 78°C produces dioxetane **236**, which isomerizes at room temperature to give 2-acetoxyacetophenone <1995ACR289>.



The photochemically induced [2 + 2] cycloaddition of selenophene with dimethylmaleic anhydride gives a 1:1 adduct **237**, but attempts to form an oxetane by photoreaction with benzophenone fail.



3-Aminothiophenes and 3-aminobenzo[*b*]thiophene undergo thermal [2 + 2] cycloaddition reactions with activated alkynes. The reactions are solvent dependent; thus, in nonpolar solvents at 30°C, 3-pyrrolidinothiophene adds to DMAD to give a [2 + 2] cycloadduct which is ultimately converted into a phthalic ester. In methanol, however, the tricyclic product **239** is formed (**Scheme 104**).

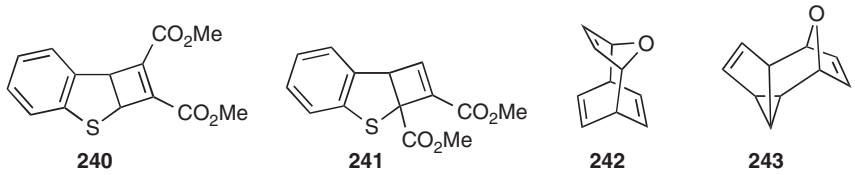


239

Scheme 104

Thiophenes have been observed to undergo aluminum chloride-catalyzed [2 + 2] cycloaddition with dicyanoacetylene; thus, 2,3,4,5-tetramethyl thiophene gives **238**.

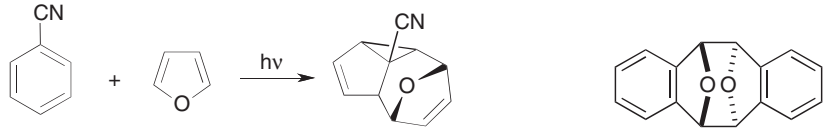
The benzo[*b*]-fused systems participate in a number of [2 + 2] cycloaddition reactions. The photocycloaddition products of benzo[*b*]thiophenes and DMAD are dependent on the irradiation wavelength; at 330 nm **240** is formed, while at 360 nm the rearranged product **241** is produced.



240 **241** **242** **243**

3.3.1.8.4 Other cycloaddition reactions

Irradiation of a mixture of furan and benzene gives mainly the [4 + 4] cycloadduct **242**; a substantial amount of the adduct **243** derived by addition of carbons 2 and 5 of furan and 1 and 3 of benzene is also obtained. Both phenylacetylene and benzonitrile undergo regio- and stereospecific 2,6,2,5-photocycloaddition to furan, illustrated in **Scheme 105** for the benzonitrile reaction, to give the [4 + 3] cycloadducts.

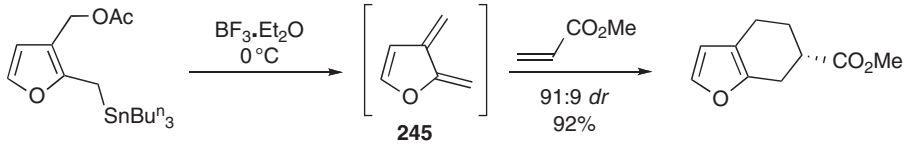


244

Scheme 105

N-Methylisoindole and isobenzofuran give [8 + 8] photodimers; the dimer **244** obtained from isobenzofuran at 60°C has *anti*-stereochemistry.

2,3-Dimethylene-2,3-dihydrofuran **245** can be generated from 3-(acetoxymethyl)-2-(tributylstannylmethyl)furan using BF_3Et_2O and captured by dienophiles to form adducts in a regioselective manner (**Scheme 106**) <1996CC2251>.



245

Scheme 106

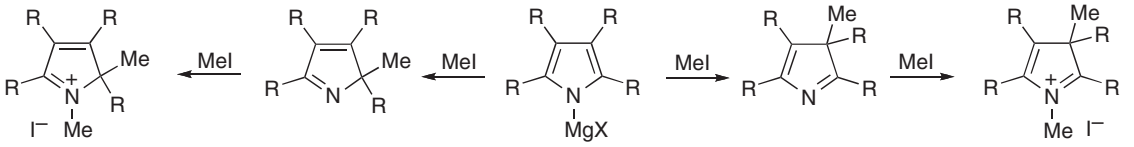
Cycloaddition reactions of *C*-vinyl derivatives of five-membered heterocycles are discussed in Section 3.3.3.3.2.

3.3.2 Reactivity of Nonaromatic Compounds

Before turning to the dihydro and tetrahydro derivatives of the fundamental ring systems, we deal with two special classes. The 2,2-disubstituted 2*H*-pyrroles and the thiophene sulfones both contain two double bonds in the heterocyclic ring, but in each case the conjugation does not include all the ring atoms. Finally, we consider hydroxy derivatives, most of which exist predominantly as the nonaromatic carbonyl tautomers.

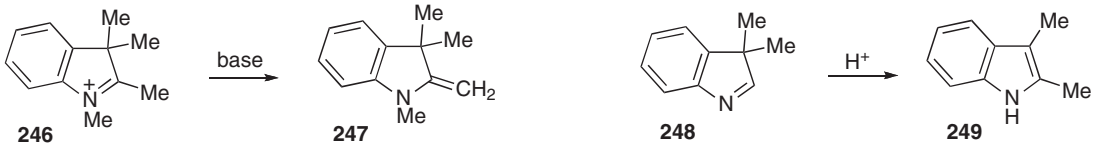
3.3.2.1 2*H*-Pyrroles (Pyrrolenines) and 3*H*-Indoles (Indolenines)

2*H*-Pyrroles and 3*H*-indoles only exist as 2,2-disubstituted and 3,3-disubstituted examples. Both types are stronger bases than their aromatic analogues; thus, each type readily undergoes N-alkylation to give quaternary salts (**Scheme 107**) and each forms stable protic salts.

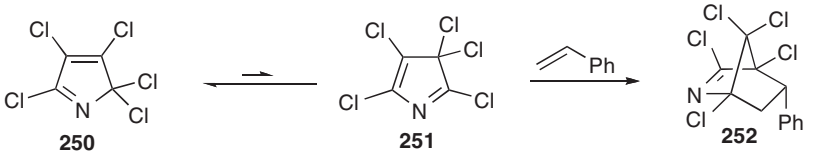


Scheme 107

The derived quaternary salts (e.g., **246**) give anhydro compounds (e.g., **247**) on treatment with alkali. -Pentamethylpyrrolenine (2,3,3,4,5-pentamethyl-3*H*-pyrrole) undergoes quantitative conversion to the -isomer (2,2,3,4,5-pentamethyl-2*H*-pyrrole) either on heating (>200°C) or in 1 M HCl at room temperature. 3*H*-Indoles also undergo an acid-catalyzed rearrangement (e.g., **248** **249**), known as the Plancher rearrangement.



Reduction of 3*H*-indoles with sodium and ethanol gives 2,3-dihydroindoles. 2,2,3,4,5-Pentachloro-2*H*-pyrrole **250** is in equilibrium with small but finite amounts of an isomeric 3*H*-pyrrole **251**, since the latter can be trapped as **252** with styrene.

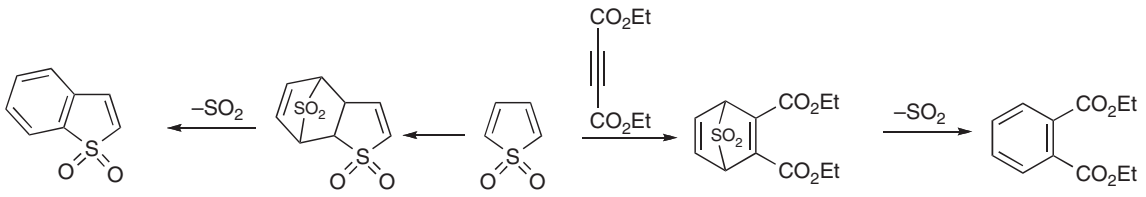


2*H*-Pyrrole 1-oxides undergo 1,3-dipolar cycloaddition with DMAD and *N*-phenylmaleimide.

3.3.2.2 Thiophene Sulfones and Sulfoxides (see also Section 3.3.1.3.2.3)

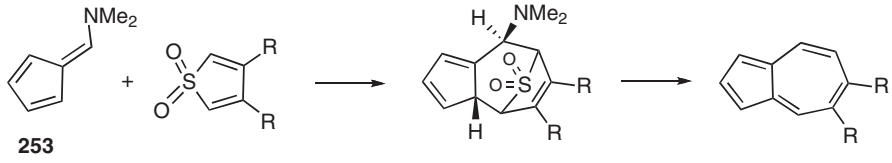
Thiophene sulfones show no aromatic character; they behave as dienes and also show reactions of compounds containing a C=C bond conjugated with an electron-withdrawing group. Thiophene sulfone itself is highly unstable, but alkyl and aryl groups and fused benzene rings increase the stability.

Thiophene sulfones undergo DielsAlder reactions which are followed by spontaneous loss of sulfur dioxide from the products, e.g., **Scheme 108**.



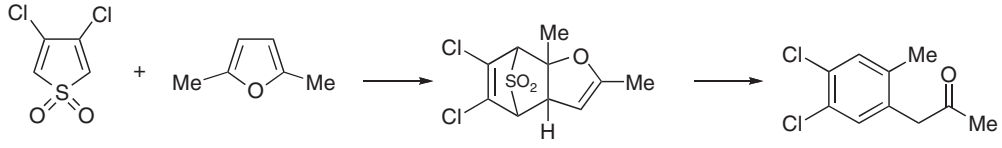
Scheme 108

An azulene synthesis involves the addition of 6-(*N*,*N*-dimethylamino)fulvene **253** to a thiophene sulfone (**Scheme 109**).



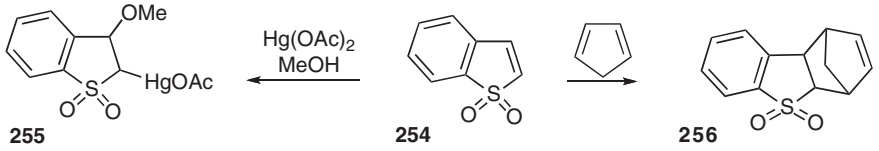
Scheme 109

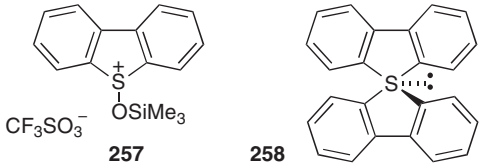
Halogenated thiophene sulfones (1,1-dioxides) are more stable than the parent sulfone. They have been employed as dienes in DielsAlder reactions and found to add to a large variety of alkenic bonds, including the formal double bonds of *N*-methylpyrrole, furan, and thiophene. The adducts subsequently lose sulfur dioxide and in some cases undergo further rearrangement and aromatization (**Scheme 110**) <1980JOC856, 1980JOC867>. Reducing agents (e.g., Zn/HCl) convert thiophene sulfones into thiophenes in contrast to the resistance to reduction of normal sulfones.



Scheme 110

Benzo[*b*]thiophene sulfone **254** reacts as a vinyl sulfone and forms adducts **255** and **256** when treated with mercury (II) acetate in methanol and with cyclopentadiene, respectively.



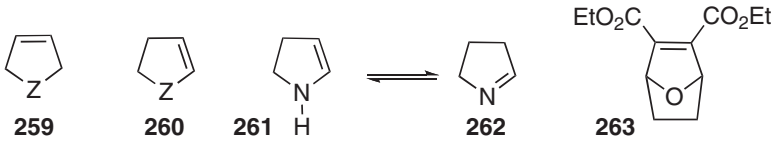


The *O*-trimethylsilyl derivative **257** of dibenzothiophene *S*-oxide on treatment at 78°C with 2,2-dilithiobiphenyl gave the first stable tetracoordinated sulfur compound **258** with four CS bonds in 96% yield.

3.3.2.3 Dihydro Derivatives

There are two possible types of dihydrofurans and -thiophenes (cf. **259**, **260**) and examples of both are known. There are three possible classes of dihydropyrroles: N-unsubstituted 4,5-dihydropyrroles **261** are in tautomeric equilibrium with the corresponding imines **262**.

The reactions of these dihydro compounds can be divided into three categories: a pronounced tendency to aromatize, behavior analogous to aliphatic compounds of similar functionality, and other reactions. These are considered in turn.

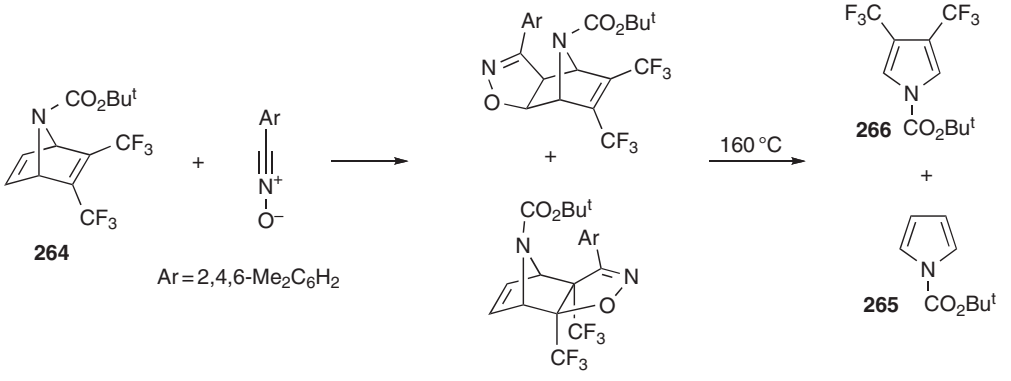


259 **260** **261** **262** **263**

3.3.2.3.1 Aromatization of dihydro compounds

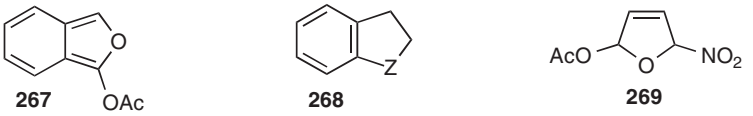
The following reactions illustrate some of the possible routes:

a. Retro-DielsAlder reaction (e.g., **Scheme 111**): **263** on pyrolysis gives ethyl 3,4-furandicarboxylate and ethylene. Similarly, azanorbornadienes with bulky or electron-withdrawing substituents undergo retro-DielsAlder extrusion of acetylene to give 3,4-disubstituted pyrroles. The adduct **264** from *N-tert*-butoxycarbonylpyrrole and hexafluorobutyne with 2,4,6-trimethylbenzonitrile oxide gives a product mixture which undergoes smooth fragmentation to give mainly the 3,4-bis(trifluoromethyl)pyrrole **265** together with some *N-tert*-butoxycarbonylpyrrole **266**. Alternatively, selective hydrogenation of adducts of type **264** at the less hindered double bond, followed by thermal extrusion of ethylene, provides a convenient route to 3,4-bis(trifluoromethyl)pyrroles. The cycloadduct from 2-acetoxyfuran and benzyne has been used in an analogous manner in the preparation of 1-acetoxybenzo[*c*]furan **267**.



Scheme 111

b. Dehydrogenation: 2,3-dihydroindole **268** (Z = NH) + chloranil indole.
c. Loss of acetic acid: **269** 2-nitrofuran.
d. Disproportionation: 2,5-dihydropyrrole heated over Pt pyrrole + pyrrolidine.

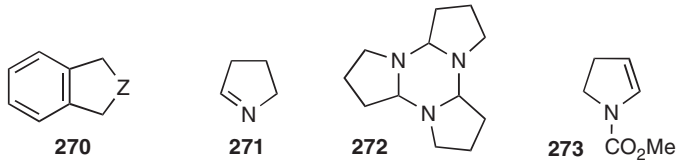


267 **268** **269**

3.3.2.3.2 Behavior analogous to aliphatic analogues

In many reactions, the dihydro compounds resemble their aliphatic analogues. Thus, when Z is nitrogen, **270** behaves as a benzylamine, **268** (Z = NH) as an aromatic amine, and **271** as a Schiff base. Similar comparisons apply when Z is oxygen or sulfur; **268** (Z = O) is an aromatic ether, **270** (Z = O) is a dibenzyl-type ether, and **268** (Z = S) is an aromatic sulfide. Some of this behavior is illustrated by the following examples.

3,4-Dihydro-2*H*-pyrroles readily form trimers of type **272**. The trimer dissociates in boiling THF to the imine; trimerization is relatively slow at 78°C and the monomer can be trapped by reaction with acylating reagents to give *N*-acyl-4,5-dihydropyrroles, e.g., **273** with $ClCO_2Me$.

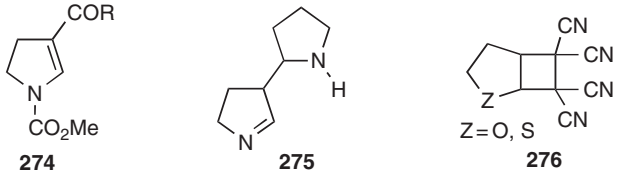


270 **271** **272** **273**

N-Methoxycarbonyl-3,4-dihydropyrrole undergoes Vilsmeier formylation and FriedelCrafts acylation at the 3-position to give products of type **274**. At pH 7, two molecules of 2,3-dihydropyrrole add together to give **275**, thus exemplifying the dual characteristics of 2,3-dihydropyrroles and their tautomers, as enamines and imines respectively. Similarly, 4,5-dihydrofurans react as enol ethers: examples include conversion into 2-substituted tetrahydrofurans via reaction with 1,3-diketones and catalytic $AuCl_3AgOTf$ <2005OL673>; palladium-catalyzed regioselective hydroamination with secondary amines, under ligand-free and neutral conditions, giving 2-dialkylamino tetrahydrofurans <2001T5445>; Heck coupling with enol triflates leading to 2-alkenyl 2,5-dihydrofurans <1996AGE200>, enantioselectively with appropriate chiral ligands e.g., <2004SL106, 2005OL5597>; 1,3-dipolar cycloaddition with dipoles derived from aziridines under $Sc(OTf)_3$-catalyzed conditions, forming *cis*-fused furopyrrolidines <2001TL9089>; and use of 2-methyl-4,5-dihydrofuran as a ketone synthon in a Fischer-type indole synthesis <2004OL79>.

1-Benzyl-2,5-dihydropyrrol-3-yl trifluoromethanesulfonate, prepared from 1-benzyl-3-pyrrolidinone by trapping the enolate with a triflating reagent, undergoes coupling with boronic acid derivatives to lead to 3-arylpyrroles in good yields <2000TL3423>.

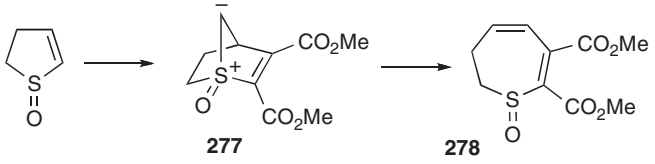
Both 2,3-dihydrofuran and 2,3-dihydrothiophene are converted into a [2 + 2] cycloadduct **276** on treatment with tetracyanoethylene under mild conditions.



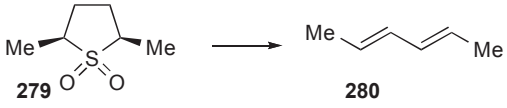
274 **275** **276**

3.3.2.3.3 Other reactions

2,3-Dihydrothiophene and its 1-oxide undergo [2 + 3] cycloaddition with DMAD to give unstable sulfonium ylides (e.g., **277**). The latter undergoes ring expansion to give the thiepin 1-oxide **278**.



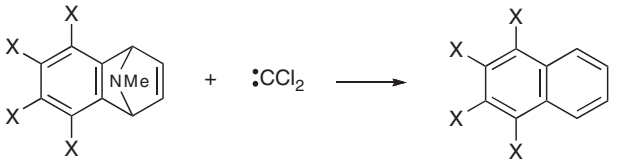
277 **278**



279 **280**

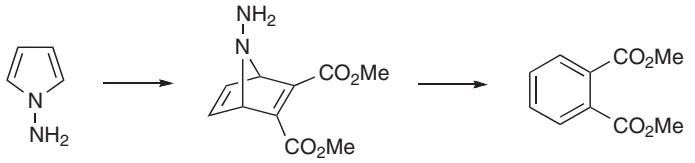
The thermal cheletropic extrusion of sulfur dioxide from both *cis* and *trans* isomers of 2,5-dihydrothiophene 1,1-dioxides is highly stereospecific. For example, *cis*-2,5-dimethyl-2,5-dihydrothiophene 1,1-dioxide **279** yields (*E*,*E*)-hexa-2,4-diene **280** and sulfur dioxide.

The benzyne adducts prepared from *N*-methylpyrrole (and *N*-methylisoindole) are deaminated conveniently by dichlorocarbene generated under phase-transfer conditions to give a route to substituted naphthalenes and anthracenes (**Scheme 112**).



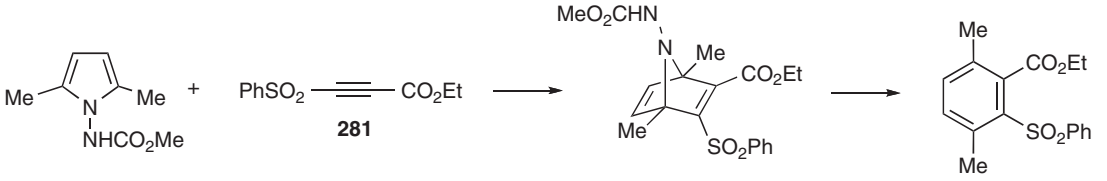
Scheme 112

N-Amino- and N-substituted aminopyrroles readily undergo DielsAlder reactions and add to activated alkynes at room temperature. Loss of *N*-aminonitrene from the resulting adducts yields benzene derivatives (**Scheme 113**).



Scheme 113

Ethyl -phenylsulfonylpropiolate **281** is superior to DMAD as a dienophile (**Scheme 114**).



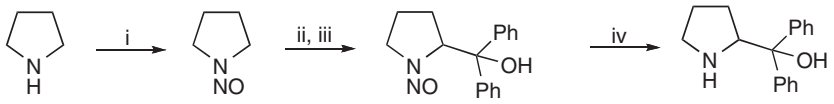
Scheme 114

2,3-Dihydrobenzo[*b*]furan is reductively cleaved by treatment with hydrosilanes in the presence of catalytic amounts of $B(C_6F_5)_3$ in high yield giving 2-phenylethanol <2000JOC6179>. 1,3-Dihydrobenzo[*c*]furan is cleaved to the lithium alkoxide of 2-hydroxymethylphenylmethyllithium, which can be usefully trapped with electrophiles <2004S1115>.

3.3.2.4 Tetrahydro Derivatives

These show marked similarities to their acyclic counterparts, e.g., tetrahydrofuran closely resembles diethyl ether. Minor differences arise due to the less sterically hindered nature of the heteroatoms in the cyclic compounds. The basicities are: tetrahydropyrrole (pyrrolidine) (pK_a 10.4), tetrahydrofuran (2.1), and tetrahydrothiophene (thiolane) (4.5).

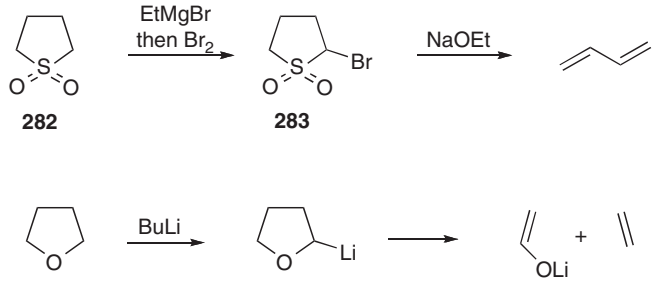
Pyrrolidine readily forms an *N*-nitroso derivative. This can be lithiated in the 2-position, and subsequent reaction with electrophiles and deprotection yields 2-substituted pyrrolidines, as illustrated in **Scheme 115**. The transformation of tetrahydrothiophene 1,1-dioxide **282** into its 2-bromo derivative **283** is similar in principle. This involves deprotonation with ethylmagnesium bromide followed by electrophilic attack by bromine. Sodium ethoxide treatment of **283** gives buta-1,3-diene in 74% yield.



i. EtONO; ii. LDA, THF, –78 °C; iii. Ph_2CO; iv. Raney Ni, H_2

Scheme 115

Although tetrahydrofuran is commonly used as a solvent in organometallic chemistry, it does react with *n*-butyllithium. Protonlithium exchange at an -position is followed by cleavage to ethylene and the enolate anion of acetaldehyde. The half-life of -lithio-THF is 10 min at 35 °C (**Scheme 116**).



282 **283**

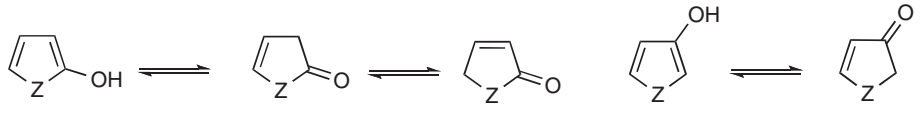
Scheme 116

Ring opening of tetrahydrofuran derivatives has been studied using chlorotrimethylsilane and sodium iodide: 2-methyltetrahydrofuran is opened predominantly to give 5-iodopentan-2-ol but the reaction involving 3-methyltetrahydrofuran is less selective. Lithium 4,4-di-*t*-butylbiphenylide has also been used to cause the ring opening of tetrahydrofuran at 80 °C in the presence of boron trifluoride etherate.

3.3.2.5 Ring Carbonyl Compounds and their Hydroxy Tautomers

3.3.2.5.1 Survey of structures

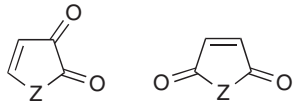
Hydroxy derivatives of thiophene, pyrrole, and furan (**284** and **287**) are tautomeric with alternative nonaromatic carbonyl forms (**285**, **286**, and **288**), as discussed in Section 2.3.5.1.2.



284 **285** **286** **287** **288**

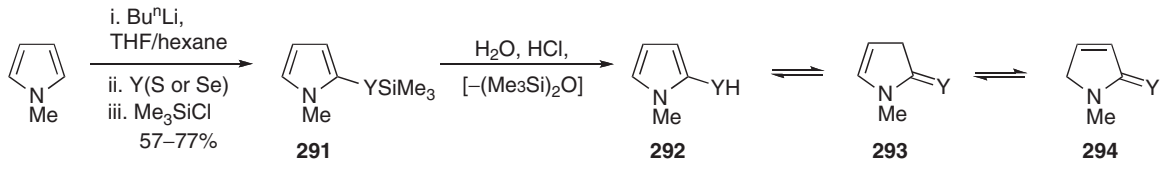
In the majority of cases, the equilibrium lies predominantly in favor of the carbonyl tautomer, and for this reason these compounds are considered in the present section. (Most amino and mercapto analogues, while also tautomeric, exist predominantly as such, and they are therefore considered as substituted aromatic compounds.)

Compounds of types **289** and **290** bear a formal structural resemblance to quinones but have little similarity in properties; this can be ascribed to the lower aromaticity of the parent heterocyclic systems.



289 **290**

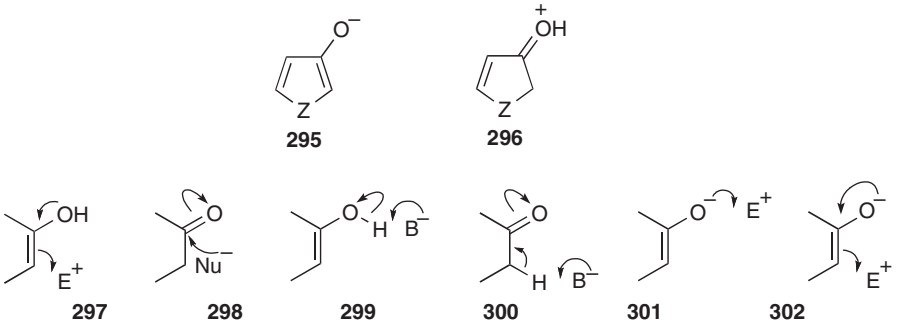
2-Mercapto-1-methylpyrrole **292** (Y = S) and the analogous selenol **292** (Y = Se) have been generated by desilylation of 1-methyl-2-[(trimethylsilyl)sulfanyl]-1*H*-pyrrole **291** (Y = S) and the corresponding seleno derivative **291** (Y = Se) obtained as depicted in **Scheme 117** <1997T13079>. The predominant tautomers in both series were **294**.



Scheme 117

3.3.2.5.2 Interconversion and reactivity of tautomeric forms

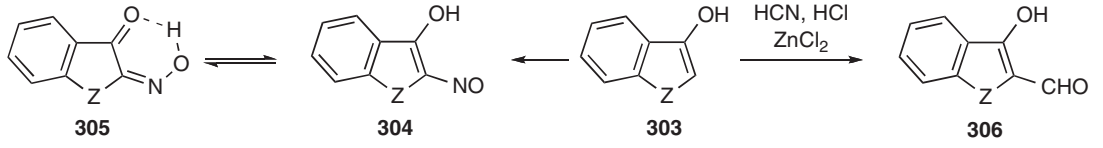
Interconversion of the hydroxy and carbonyl forms of these heterocycles proceeds through an anion (as **295**) or a cation (as **296**) just as the enol and keto forms of a ketone are interconverted. Reactions of the various species derived from the heterocyclic compounds are analogous to those of the corresponding species from a ketone: hydroxy forms react with electrophilic reagents **297** and carbonyl forms with nucleophilic reagents **298**. In addition, either form can lose a proton (**299, 300**) to give an anion which reacts very readily (more so than the parent heterocycles) with electrophilic reagents on either oxygen **301** or carbon **302**.



3.3.2.5.3 Reactions of hydroxy compounds with electrophiles

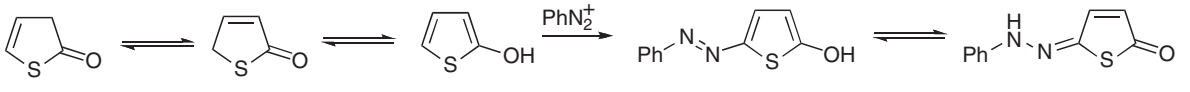
Electrophilic substitution reactions at low pH values probably involve the hydroxy form:

a. Nitrosation ($NaNO_2$, H_2O, HCl) to give tautomeric products, e.g., **303 304** ⇄ **305**, (Z = NH, O, S).



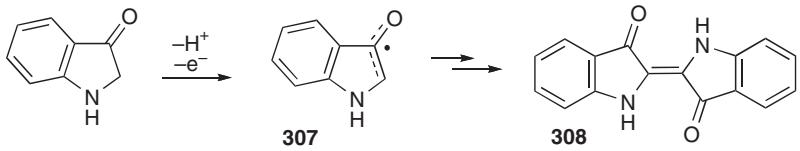
b. Gattermann reaction (HCN, HCl, $ZnCl_2$) (**303 306**).

c. Coupling with diazonium salts (**Scheme 118**).



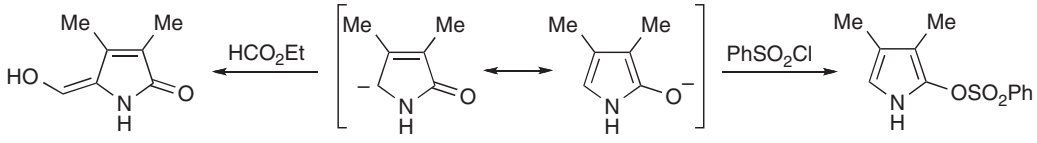
Scheme 118

Indoxyl and thioindoxyl are easily oxidized, e.g., by $K_3Fe(CN)_6$, to indigo **308** and thioindigo, respectively, via dimerization of radical intermediates **307**.



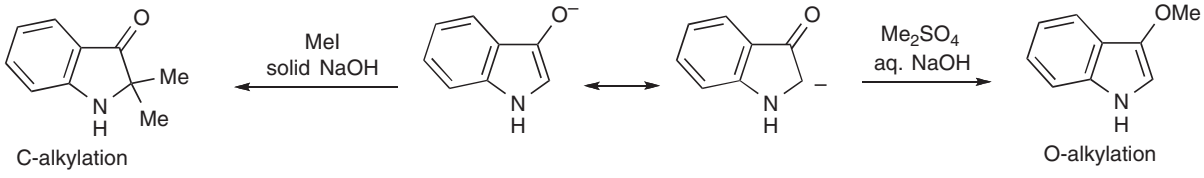
3.3.2.5.4 Reactions of anions with electrophiles

These heterocyclic compounds undergo many reactions which are similar to those of enolates. Thus, Claisen condensation and O-sulfonylation are exemplified by **Scheme 119**.



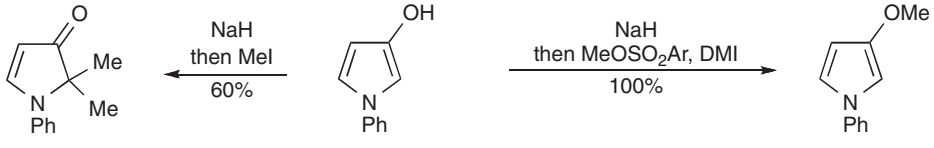
Scheme 119

The indoxyl (3-hydroxyindole) anion undergoes carbon or oxygen alkylation (**Scheme 120**).



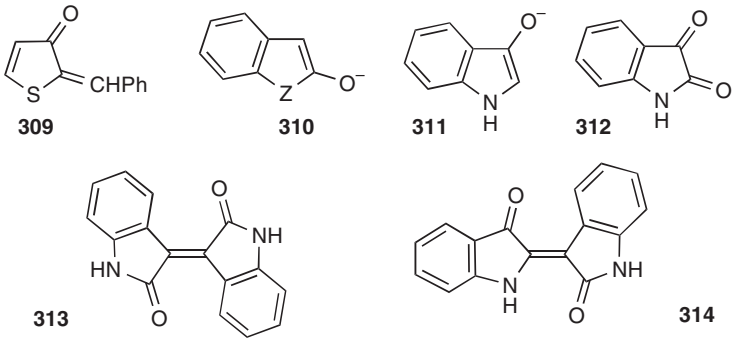
Scheme 120

1*H*-Pyrrol-3(2*H*)-ones are preferentially C-alkylated with alkyl halides, but O-alkylated with methyl tosylate in the dipolar aprotic solvent *N*,*N*-dimethylimidazolidinone (DMI) (**Scheme 121**). Similarly, soft electrophiles like iodomethane lead to C-methylation of the ambident anion derived from hydroxythiophenes, while the hard electrophile, dimethyl sulfate, gives predominantly the O-methylated product. Acyl chlorides and acid anhydrides give only the O-acylated products.



Scheme 121

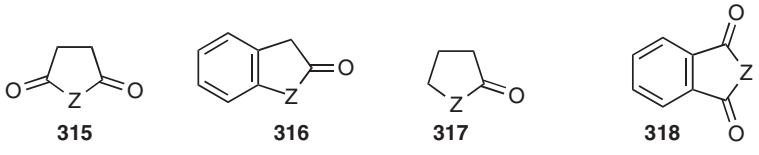
The following exemplify reactions of the aldol type. 3-Hydroxythiophene with benzaldehyde forms **309**. Anions **310** (Z = NH) and **311** derived from oxindole and indoxyl, respectively, react with isatin **312** to give isoindigo **313** and indirubin **314**.



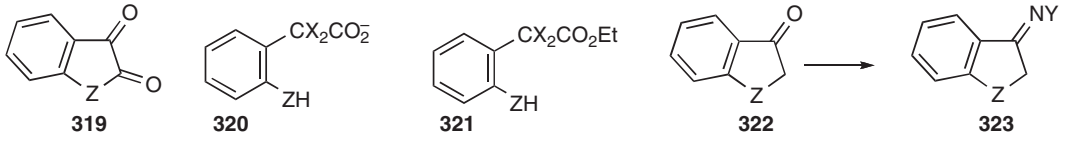
3.3.2.5.5 Reactions of carbonyl compounds with nucleophiles

Nucleophilic reagents attack the carbonyl carbon atom; the subsequent course of this reaction parallels that in aliphatic chemistry. If the carbonyl group and the heteroatom are adjacent, the ring is usually opened. If they are not adjacent, a carbonyl addition compound results, which often eliminates water spontaneously. The reactions of carbonyl groups in both environments are discussed.

3.3.2.5.5.1 Carbonyl adjacent to heteroatom. Ring opening by nucleophilic reagents necessitates group Z gaining a negative charge, the ease of which depends on the heteroatom (S > O >> NH) and on the ring type (e.g., **315** > **316** > **317**). Succinic **315** (Z = O), maleic, and phthalic anhydrides and imides behave like acyclic acid anhydrides and imides.



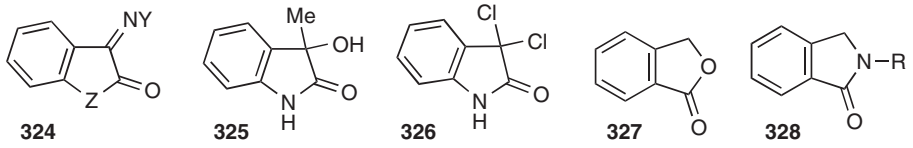
The ring opening of phthalimides **318** (Z = NR) by hydrazine to give a primary amino compound and 1,4-phthalazinedione **319** (Z = NHNH) (IngManske reaction) is important in the modified Gabriel synthesis. 2-Coumaranone, its S-analogue **316** (Z = O, S) and the diones **319** (Z = O, S) react reversibly with hydroxide and alkoxide ions to give salts such as **320** ($X_2 = H_2$ or $X_2 = O$) and esters such as **321** ($X_2 = H_2$ or $X_2 = O$) of the ring-opened acid. The corresponding reactions with indoxyl **322** (Z = NH) are much more difficult, but in the case of isatin **319** (Z = NH), the second carbonyl group facilitates ring fission, e.g., treatment with sodium hydroxide gives sodium isatinate **320** (Z = NH, $X_2 = O$).



3.3.2.5.5.2 Carbonyl not adjacent to heteroatom. Carbonyl groups not adjacent to a heteroatom are less stabilized by resonance and react with the relatively weakly nucleophilic ketonic reagents. If carbonyl groups of both types are present, as in **319** (Z = O, NH), then the carbonyl group not adjacent to the heteroatom is preferentially attacked. Thus, isatin and indoxyl and their O- and S-analogues (**319, 322**) react with hydroxylamine, hydrazine, phenylhydrazine, semicarbazide, etc., to give oximes, hydrazones, phenylhydrazones, semicarbazones, etc. (**322 323; 319 324**).

The reactive 3-carbonyl group in compounds of type **319** undergoes aldol condensation with active methylene compounds; such reactions of isatin with indoxyl, oxindole (Section 3.3.2.5.4), and with thiophenes (Section 3.3.1.5.7.2)

have already been mentioned. These compounds also react with Grignard reagents and phosphorus halides, e.g., isatin **319** (Z = NH) with MeMgBr and PCl_3 yields **325** and **326**, respectively.



324 **325** **326** **327** **328**

3.3.2.5.6 Reductions of carbonyl and hydroxy compounds

In cyclic anhydrides and imides, one carbonyl group is usually easily reduced; thus, phthalic anhydride with H_2Ni gives phthalide **327**, and phthalimides with ZnHCl yield phthalamides **328**. Indoxyl and its O- and S-analogues can be reduced (Zn-HOAc) to indole, etc.

3.3.3 Reactivity of Substituents

3.3.3.1 General Survey of Reactivity

3.3.3.1.1 Reaction types

In general, substituents attached to furan, thiophene, and pyrrole ring carbon atoms (we consider separately substituents attached to pyrrole nitrogen or thiophene sulfur) react like those on benzenoid nuclei, but there are some important differences:

a. Some reactions requiring vigorous conditions which succeed in the benzene series fail because the heterocyclic rings are susceptible to attack by electrophilic reagents; see Section 3.3.1.4.
b. Hydroxy groups attached directly to the heterocyclic nuclei usually exist largely, or entirely, in an alternative, nonaromatic tautomeric form (Section 2.3.5.1.2); their reactions show little resemblance to those of phenols, and they have been considered with the nonaromatic compounds in Section 3.3.2.5. Amino derivatives, although highly reactive, generally exist in the amino form (see Section 3.3.3.4.2).
c. Benzyl halides are more reactive than other alkyl halides and this effect is enhanced in thienyl- and especially in pyrryl- and furyl-methyl halides.
d. Hydroxymethyl and aminomethyl groups on these heterocyclic compounds are activated in a manner similar to, although less marked than, the chloromethyl derivatives.

The validity of the Hammett relationship log $K/K_0 =$, has been extensively investigated for five-membered heteroaromatic compounds and their benzo analogues. The ratio (heterocycle): (benzene) is closest to unity for thiophene. Judged from work on the polarographic reduction of nitro compounds, the ability to transmit electronic effects is HC = CH S < O < NH.

3.3.3.1.2 Nucleophilic substitution of substituents

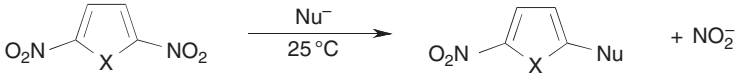
The tremendous difference in reactivity toward electrophiles, which distinguishes -deficient and -excessive heterocycles, is considerably diminished for nucleophilic substitution reactions in which ring substituents are replaced. The reasons for this are the lesser aromaticity of five-membered heterocycles and a rather high polarizability of the pyrrole-type heteroatoms which, depending on the nature of reagent, may function as an electron donor or electron acceptor. It is not therefore surprising that five-membered heterocycles show higher than benzene activity not only in reactions with electrophiles but also in reactions of their substituents in nucleophilic substitutions, though of course they remain much less reactive than azines. **Table 3** gives a picture of the relative activity of benzene and heterocyclic derivatives in substitution reactions of a nitro group with *p*-tolylthio and piperidino groups (**Scheme 122**) (see also Section 3.3.3.7.1).

For both nucleophiles, 2,5-dinitrofuran is the most active substrate, the thiophene derivative follows. On the other hand, the relative reactivity of 1-methyl-2,5-dinitropyrrole and 1,4-dinitrobenzene depends on the nature of the nucleophile. For the 4-MeC_6H_4S anion, the former is more active by about two powers of 10, but in the piperidinolysis reaction 1,4-dinitrobenzene is superior. These phenomena appear to be caused by differences in the polarizability of both substrate and nucleophiles. *p*-Tolylthiolate anion is a softer nucleophile in comparison with piperidine and the pyrrole system is certainly more polarizable than that of a benzene. Therefore, softsoft interaction of

1-methyl-2,5-dinitropyrrole with 4-MeC_6H_4S and hardhard interaction of 1,4-dinitrobenzene with piperidine should occur more easily than interactions between reagents with opposite types of softness and hardness.

Table 3 Relative reactivity of 2,5-dinitro derivatives of five-membered heterocycles and 1,4-dinitrobenzene toward some nucleophiles

	Nucleophile	
X	*4-MeC6H4S (in MeOH)*	*Piperidine (in MeCN)*
NMe	1	1
O	1.7×10^3	2.4×10^6
S	1.6×10^2	4.4×10^3
1,4-Dinitrobenzene	8.8×10^3	9.6

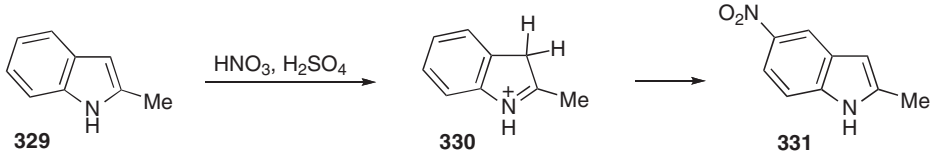


Scheme 122

3.3.3.2 Fused Benzene Rings

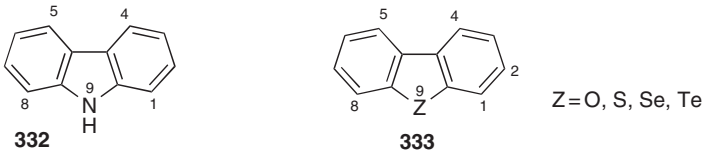
3.3.3.2.1 Electrophilic attack

Most common reactions of benzene rings involve attack by electrophilic reagents; but since thiophene, pyrrole, and furan are more readily attacked than benzene, reaction in fused-ring compounds should occur at a free position in the heterocyclic ring in preference to the benzene ring. This generalization may become invalid if (1) there is a strongly deactivating substituent (e.g., CHO, CO_2Et, NO_2) in the heterocyclic ring or (2) a strongly activating substituent (e.g., NH_2, OH) is present in the benzene ring (e.g., bromination of several 4,6-dimethoxyindoles occurs at C(7)). When both positions of the heterocyclic ring are substituted, substitution in the benzene ring is generally observed, though many examples of hetero-ring substituent displacement (*ipso* substitution) are known. Indole conjugate acids are nitrated in the benzene ring (e.g., **329** **330** **331**). 3,3-Dialkyl-3*H*-indolium salts similarly nitrate at the 5-position.



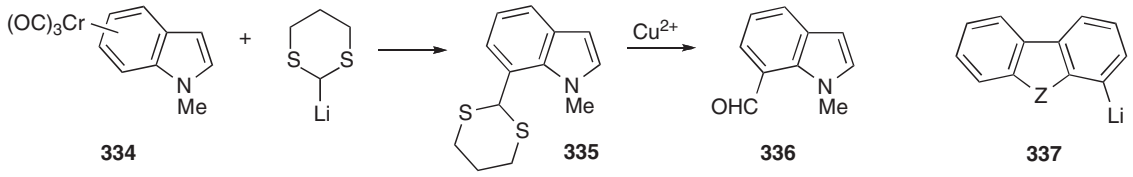
Carbazole **332**, dibenzofuran **333** (Z═O), and dibenzothiophene **333** (Z═S) behave as diphenylamine, diphenyl ether, and diphenyl sulfide, respectively, in their substitution reactions and thus electrophilic substitution occurs at the positions *para* to the heterocyclic atom, as exemplified for:

a. Dibenzofuran: bromination (Br_2, CS_2), sulfonation ($ClSO_3H$), and formylation (HCN, HCl, $AlCl_3$).
   The positional reactivity of dibenzofuran in electrophilic substitution reactions depends on the electrophile. Reaction occurs mostly at the 2- and 3-positions but the ratio of the two products varies. The reaction of cyanogen bromide catalyzed by aluminum chloride gives an 80% yield of the 2-substituted product together with 15% of the 3-cyano-derivative. Oxidative acetoxylation of dibenzofuran occurs predominantly at the 3-position (60%) together with some attack at the 1-position (30%). In this latter reaction, the attack by acetate is on the dibenzofuranium radical cation.
b. Dibenzothiophene: nitration (HNO_3, AcOH) and bromination (Br_2, CS_2). The positional reactivity is $3 > 4 > 1$.
c. Carbazole: acylation (RCOCl, $AlCl_3$), amidation (Me_2NCOCl, $AlCl_3$ <1999SM(99)181>), halogenation ($SOCl_2$ or Br_2, CS_2), and sulfonation (H_2SO_4).
d. Dibenzoselenophene and dibenzotellurophene **333** (Z = Se, Te) undergo nitration in the 2 position.

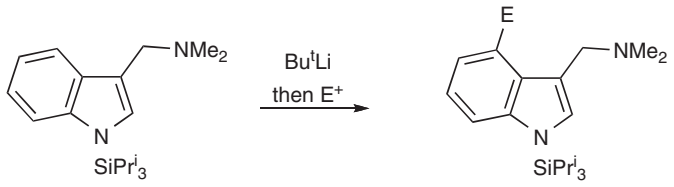


3.3.3.2.2 Nucleophilic attack

The possibility of activating the benzene ring of the indole nucleus to nucleophilic substitution has been realized by formation of chromium tricarbonyl complexes. For example, the complex **334** from *N*-methylindole undergoes nucleophilic substitution with 2-lithio-1,3-dithiane to give a product **335** which can be transformed into 1-methylindole-7-carbaldehyde **336**.



Lithiation can be diverted away from C(2) of indole by the use of a bulky N-substituent. Although 1-methylgramine is cleanly lithiated at C(2), 1-(triisopropylsilyl)gramine is lithiated selectively at C(4) and can usefully lead to 4-substituted indoles: electrophiles used include 1,2-dibromoethane, DMF, and diphenyl sulfide (**Scheme 123**).



Scheme 123

Lithio compounds can also be obtained by exchange reactions with halo compounds, for example, the sodium salt of 5-bromoindole can be converted to the 5-lithio derivative by treatment with *t*-butyllithium, and this in turn allows synthesis of various 5-substituted indoles.

Thallation of 3-acylindoles gives the 4-thallated products, which can be converted to both the 4-nitro and 4-azido derivatives in copper(II)-promoted processes. The nitro compound is formed by heating the organothallium intermediate with sodium nitrite and copper sulfate in DMF at 100°C.

Thallation also provides a route to 4-iodoindoles from the related 3-acyl compounds. Here the intermediate thallium compound can be treated with iodine and copper(I) iodide in DMF to effect the transformation.

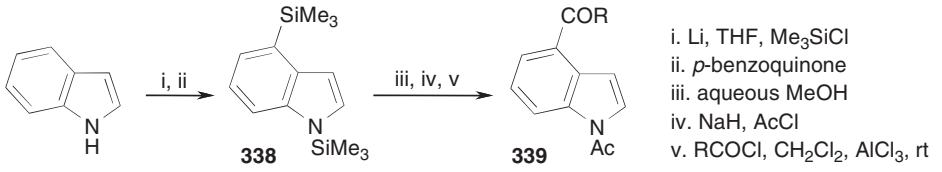
Alkyllithium compounds metallate dibenzofuran, dibenzothiophene, and *N*-alkylcarbazoles (in increasing order of difficulty) to form compounds of type **337**; substitution occurs *ortho* to the heteroatom as expected from benzene chemistry.

3.3.3.2.3 Reactions with electrons reduction reactions

Selective reduction of indole in the benzene ring can be achieved by treatment with lithium in liquid ammonia, which gives a mixture of the 4,7-dihydro and 4,5,6,7-tetrahydro derivatives.

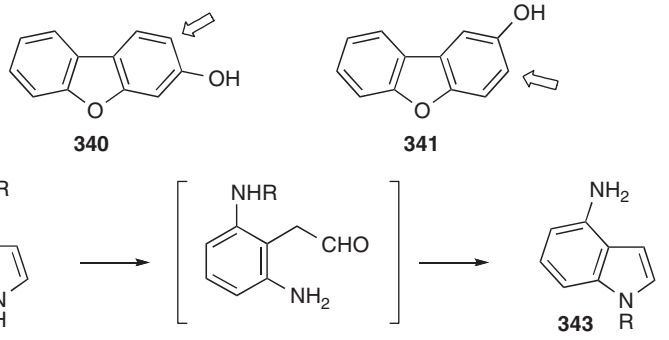
Birch reduction of indole with lithium metal in THF in the presence of trimethylsilyl chloride followed by oxidation with *p*-benzoquinone gave 1,4-bis(trimethylsilyl)indole **338**. This is readily converted in two steps into 1-acetyl-4-trimethylsilylindole. FriedelCrafts acylation of the latter compound in the presence of aluminum chloride yields the corresponding 4-acylindole **339**.

For the reduction of indolizine see Section 3.3.1.7.5.



3.3.3.2.4 Reactions of substituents on benzene rings

Substituents on fused benzene rings undergo the usual reactions expected in the benzene series. The orientation in the diazo coupling reactions with hydroxy compounds **340** and **341** indicates that there is little bond fixation in dibenzofuran, a distinct contrast to naphthalene.

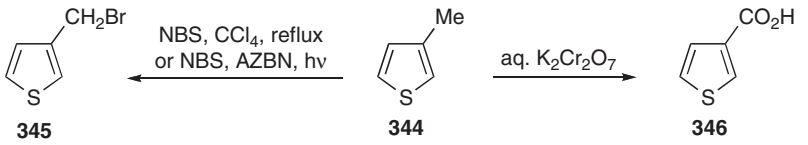


4-Alkylaminoindoles **342** rearrange to 4-amino-l-alkylindoles **343** when heated with *p*-toluenesulfonic acid hydrate.

3.3.3.3 Other C-Linked Substituents

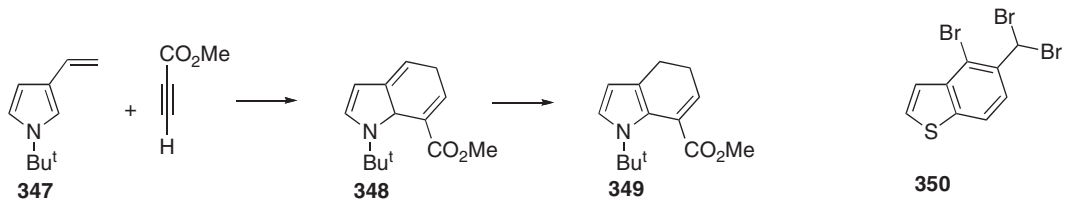
3.3.3.3.1 Alkyl groups

The reactivity of alkyl groups on five-membered rings with one heteroatom is similar to that of alkyl groups on benzenoid rings. Because of the high reactivity of the heterocyclic nuclei, specific reactions of the alkyl groups may be difficult to carry out. However, oxidation of alkyl to carboxyl (e.g., **344** **346**) and selective bromination of alkyl groups (e.g., **344** **345**) can be achieved. Further bromination of **345** yields the dibromomethyl derivative. The practical application of these reactions may require either nuclear deactivation by substitution of electron-withdrawing groups or, in the case of halogenation, that all the nuclear carbon atoms carry substituents.



3.3.3.3.2 Vinyl groups

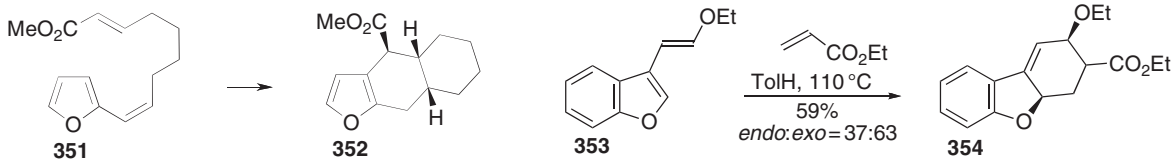
2-Vinyl and 3-vinyl derivatives of pyrrole, furan, thiophene, and their benzologues behave as outerinner dienes and react with -electron-deficient alkenes and alkynes to produce the corresponding DielsAlder adducts. Thus, 3-vinylpyrrole **347** in combination with methyl propiolate gives dihydroindole **348** leading to **349**.



347 348 349 350

By analogy, 2-vinylthiophene reacts with tetrabromocyclopropene by [4 + 2] cycloaddition; subsequent loss of HBr with concomitant opening of the cyclopropane ring leads to the benzo[*b*]thiophene derivative **350**.

Intramolecular DielsAlder methodology is exemplified in the heating of **351** that gives **352** in almost quantitative yield by cyclization followed by isomerization of the exocyclic double bond to rearomatize the furan residue. The transformation is highly stereoselective. Comparable intermolecular processes occur with vinyl benzo[*b*]furans (**353 354**) <2002OL2791>.



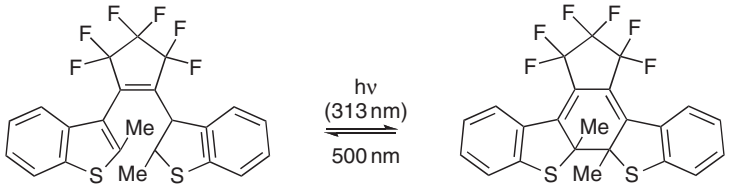
351 352 353 354

The fulgides are derivatives of bismethylenesuccinic anhydride; irradiation of the (*E*)-fulgide **355** at 366 nm results in the formation of **356** which has a deep red color. The reverse ring opening can be brought about by irradiation with visible light.

The 2-thienylfulgide **357** is similarly photochromic, leading to **358** on irradiation at 366 nm.

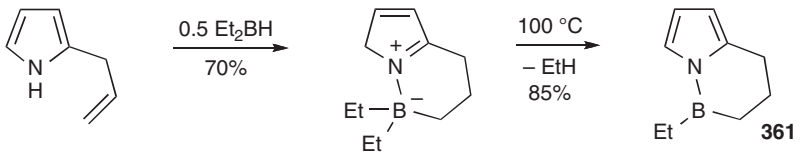
355 356 357 358

1,2-Diarylethenes containing heterocyclic rings have the advantage that they can undergo reversible photocyclization, but at the same time are thermally stable. The closed-ring molecules absorb light at significantly longer wavelengths. In a significant advance, the central double bond of a diarylethene has been incorporated into a perfluorocyclopentene ring. The diarylethene is thus locked in the *cis*-configuration, thereby preventing fatigue due to *cistrans* isomerization. The fluorine atoms give added thermal stability to the products. In hexane solution **359** has $_{max}$ at 258 nm. On irradiation with light at 313 nm, cyclization takes place to produce **360** with $_{max}$ at 517 nm. At photostationary conditions, the ratio **359**:**360** is 55:45. The reverse reaction can be brought about by irradiating with light of wavelength $\geq$ 500 nm. The coloration (cyclization)decoloration (ring-opening) cycle can be repeated 14,000 times without significant loss of performance (90%).



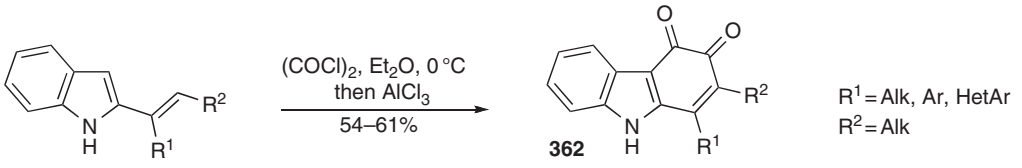
359 360

The hydroboration of 2-allylpyrrole with various hydroborating agents leads to B-substituted bicyclic *N*-pyrrolylboranes, e.g., **361** (**Scheme 124**) <1997JOM(534)181>.



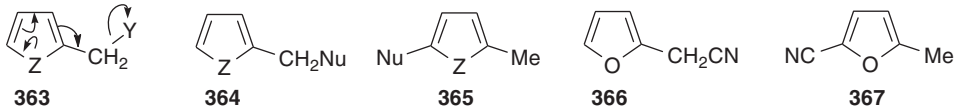
Scheme 124

A cyclization reaction of 2-vinylindoles with oxalyl chloride leads to *o*-quinones **362** <2000SL1757, 2004OL329>.

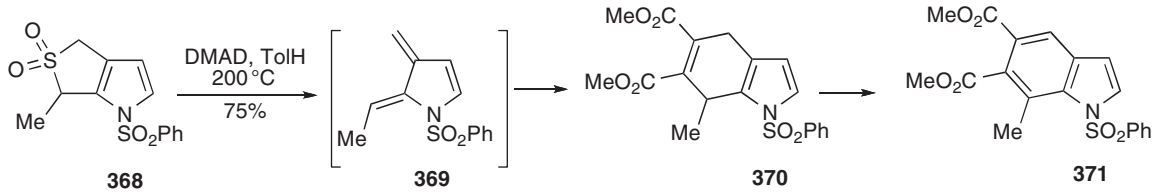


3.3.3.3.3 Substituted alkyl groups: General

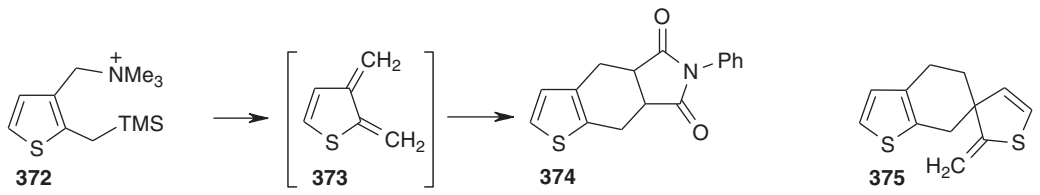
As discussed previously (Section 3.3.3.1), halomethyl, hydroxymethyl, and aminomethyl groups show enhanced reactivity toward nucleophilic attack because of the ease with which the halogen, hydroxy, or amino group is lost in **363**. Both side-chain **364** and nuclear substitution products **365** have been obtained. These two possibilities are exemplified by the reaction of furfuryl chloride with sodium cyanide to give **366** and **367**.



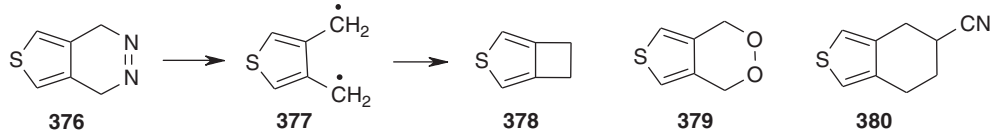
Many examples of DielsAlder reactions have been carried out on heterocyclic ,-quinodimethanes derived in a variety of ways from the corresponding precursors containing substituted alkyl groups. For example in the case of pyrrole derivatives, this methodology leads to the synthesis of indoles and particularly those substituted in the benzene ring. The thieno[3,4-*b*]pyrrole 1,1-dioxide **368** reacts with DMAD to give the cycloadduct **370**, presumably by trapping a pyrrole-2,3-quinodimethane **369**. The cycloadduct can then be dehydrogenated to the indole **371**.



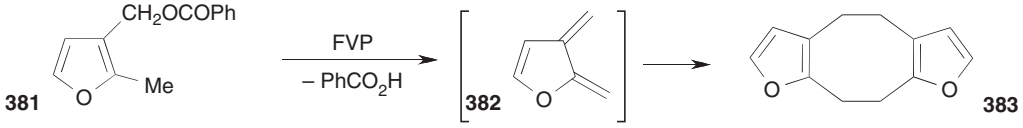
The fluoride ion-induced fragmentation of **372** is a mild and efficient way of generating 2,3-dimethylene-2,3-dihydrothiophene **373**. In the presence of *N*-phenylmaleimide it gives the adduct **374**. In the absence of dienophile, **373** dimerizes to unstable spiro-compound **375** acting at the same time as diene and dienophile.

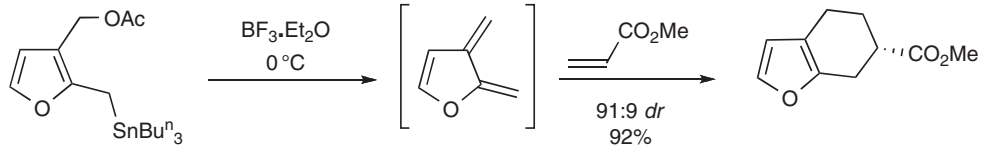


The diradical **377** is generated from diazene **376** by either thermolysis or photolysis (310380 nm). The purple-colored biradical **377** closes to **378** at 78°C (the formation of intermolecular dimers is possible at higher temperatures). However, **377** is quite stable up to 160 K as a frozen glassy solution in 2-methyltetrahydrofuran. It reacts with oxygen to form the peroxide **379** and can be trapped by electron-poor alkenes: the yields of cycloadducts are almost quantitative, thus, acrylonitrile gives **380**.



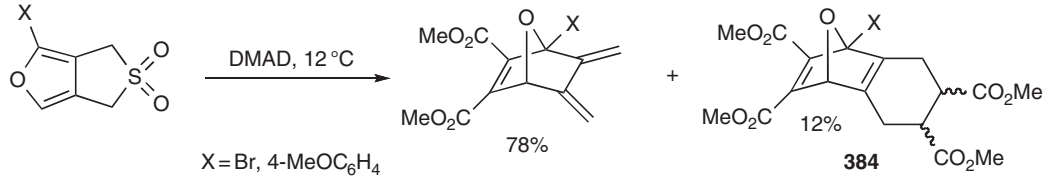
2,3-Dimethylene-2,3-dihydrofuran **382** formed, e.g., from **381** at a very high temperature, has been studied in detail and shown to dimerize to **383** in high yield at temperatures above 30°C. 2,3-Dimethylene-2,3-dihydrofuran **382** can however be generated from 3-(acetoxymethyl)-2-(tributylstannylmethyl)furan at 0°C using BF_3·Et_2O, and captured by dienophiles to form adducts in a regioselective manner (**Scheme 125**) <1996CC2251>.





Scheme 125

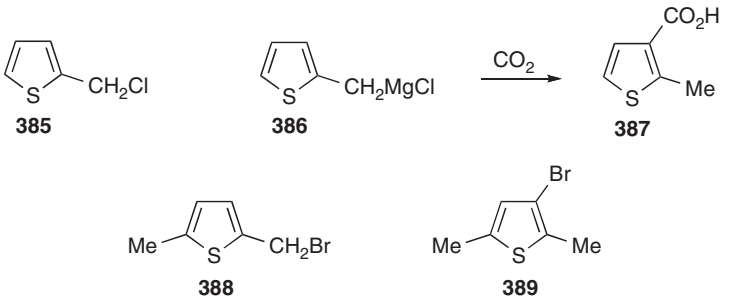
In the majority of the reactions of 3,4-dimethylene-3,4-dihydrofuran with dienophiles, the first reaction involves a conventional DielsAlder reaction of the furan ring so that the final product, e.g., **384**, may incorporate two molecules of the dienophile (**Scheme 126**).



Scheme 126

3.3.3.3.4 Halomethyl

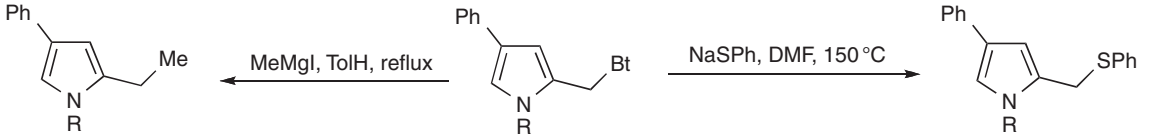
The furfuryl halides [cf. **385** (Z = O)] are exceedingly reactive; they are usually not isolated but are used in solution as intermediates because of their instability. The halogen can be replaced directly by amino or alkoxy groups, but with potassium cyanide the S_N product **367** (see Section 3.3.3.3.3) is also formed. 2,5-bis(chloromethyl)furan is a precursor for highly conductive high-molecular-weight poly(2,5-furylene vinylene).



2-Chloromethylthiophene shows reactivity like that of benzyl chloride in that it is readily converted into 2-cyanomethylthiophene, thiophene-2-carbaldehyde (by treatment with hexamethylenetetramine), and a Grignard reagent **386** that reacts with electrophiles to give 2-methyl-3-substituted thiophenes (e.g. **387**).

2-Bromomethyl-5-methylthiophene gives normal displacement products with amines but it is isomerized on attempted reaction with copper(I) cyanide (**388** **389**).

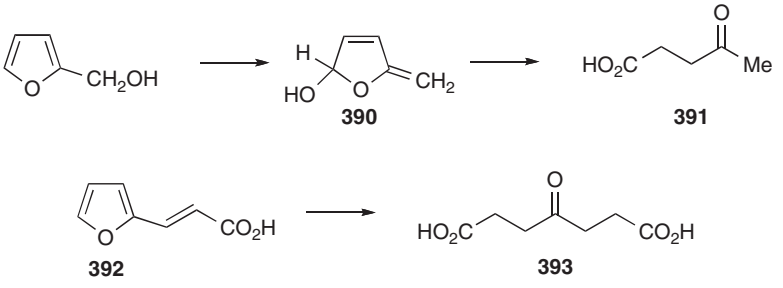
An excellent alternative to the use of side-chain halides is the use of benzotriazolyl-methyl ($BtCH_2$) groups: **Scheme 127** exemplifies <1989CL1107, 1996JOC1624>.



Scheme 127

3.3.3.3.5 Hydroxymethyl

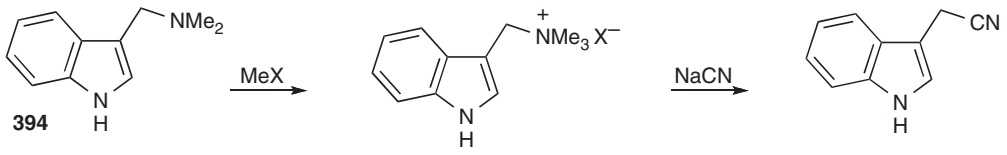
Whereas 2-hydroxymethylthiophene reacts normally with hydrogen halides to give 2-halomethylthiophenes, reaction of 2-hydroxymethylfuran (furfuryl alcohol) with hydrochloric acid results in formation of levulinic acid **391** via the S_N intermediate **390**. The conversion of 3-(furan-2-yl)acrylic acid **392** into an ester of -oxopimelic acid **393** by ethanolic hydrochloric acid is a related reaction involving an analogous intermediate.



Reduction of 2-hydroxymethylpyrroles with lithium aluminum hydride or diborane yields the corresponding 2-methylpyrroles.

3.3.3.3.6 Aminomethyl

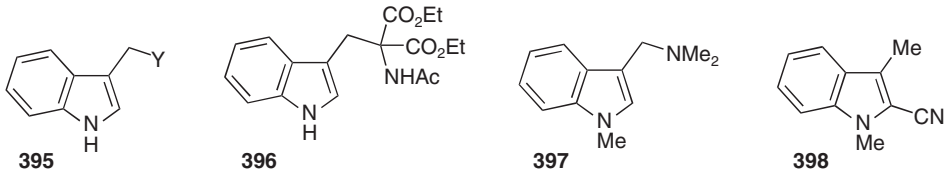
Aminomethylindoles are particularly important synthetic intermediates. 3-Dimethylaminomethylindole (gramine) **394**, and especially its quaternary salts, readily undergo displacement reactions with nucleophiles (**Scheme 128**).



Scheme 128

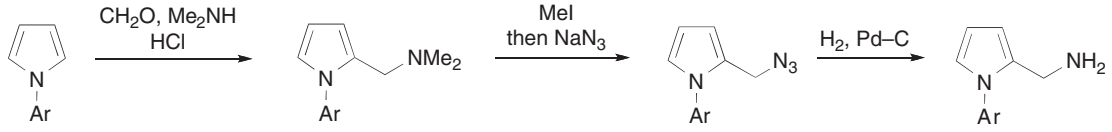
a. Potassium cyanide gives 3-indoleacetonitrile which can in turn be reduced to tryptamine **395** ($Y = CH_2NH_2$), or hydrolyzed to 3-indoleacetic acid **395** ($Y = CO_2H$).
b. Diethyl acetamidomalonate gives **396** that can be hydrolyzed and decarboxylated to (±)-tryptophan.
c. Nitroethane forms **395** ($Y = CHMeNO_2$).

1-Methylgramine **397** generally reacts analogously to gramine, but with potassium cyanide it yields a mixture of the 2-cyano-3-methyl **398** (by S_N reaction) and the 3-cyanomethyl derivatives.



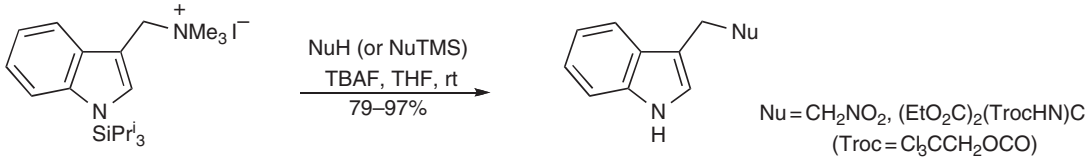
Indole-2,3-quinodimethanes, generated from 2-methylgramine, undergo intermolecular cycloaddition reactions with dienophiles similar to those of **369**.

The dialkylamino group of a 2-dialkylaminomethyl pyrrole can also be displaced by various nucleophiles. In a typical example, displacement of trimethylamine from the quaternary salt derived from the Mannich base of a 1-arylpyrrole gives an azide which can be reduced to give the aminomethylpyrrole (**Scheme 129**).



Scheme 129

Fluoride-induced reactions of 1-trimethylsilyl-3-dimethylaminomethylindoles are an elegant and mild way of displacing the amine (e.g., **Scheme 130** <1995TL5929>).



Scheme 130

3.3.3.3.7 Carboxylic acids, esters, and anhydrides

Five-membered heterocyclic carboxylic acids show most of the standard reactions of benzoic acid. Amides, esters (for a very efficient method see <2002S1810>), hydrazides, azides, and nitriles can be prepared by standard methods. Thiophenes form stable acid chlorides, furans unstable ones, and N-unsubstituted pyrroles do not form them.

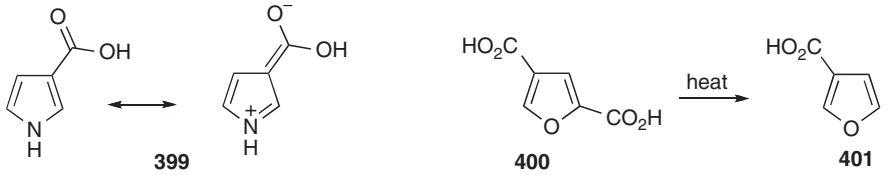
The acid dissociation constants of some representative carboxylic acids are given in **Table 4**.

Table 4 pK_a values of pyrrole-, furan-, thiophene-, selenophene-, and tellurophene-carboxylic acids

Acid	pK_a (H_2O, 25°C)
Pyrrole-2-carboxylic acid	4.4
Pyrrole-3-carboxylic acid	5.0
Furan-2-carboxylic acid	3.15
Furan-3-carboxylic acid	4.0
Thiophene-2-carboxylic acid	3.5
Thiophene-3-carboxylic acid	4.1
Selenophene-2-carboxylic acid	3.6
Tellurophene-2-carboxylic acid	4.0
Benzoic acid	4.2

Pyrrole-3-carboxylic acid **399** is appreciably weaker than benzoic acid and this is attributed to the stabilization of the undissociated acid by electron release from nitrogen. The 2-carboxylic acids of furan, thiophene, selenophene, and tellurophene are all stronger acids than benzoic acid.

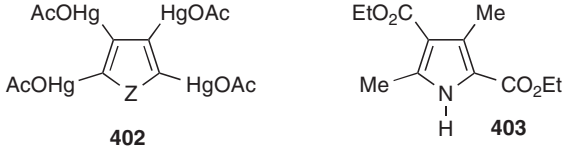
pK_a Measurements of 4-substituted thiophene-2-carboxylic acids and 2-substituted thiophene-4-carboxylic acids show that the transmission of substituent effects in the *meta*-like position is quite similar to that observed in *meta*-substituted benzoic acids. The thiophene values are very similar to the benzene values. In both *meta*- and *para*-like disubstituted thiophenes, the hetero ring is able to transmit the electronic effects of the substituents as in the benzene ring, i.e., through the heterocycle as a whole and not via the heteroatom.



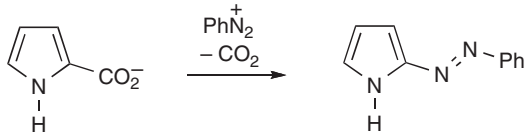
Pyrrole-2-carboxylic acid easily loses the carboxylic group thermally. Pyrrole-3-carboxylic acid and furan-2- and -3-carboxylic acids also readily decarboxylate on heating to about 200°C. Thiophenecarboxylic acids require higher temperatures or a copperquinoline catalyst. In furans, 2-carboxylic acid groups are lost more readily than 3-carboxylic acid groups (e.g., **400** **401**).

Decarboxylation often takes place during electrophilic substitution of the nucleus, for example:

a. Thiophene-2-carboxylic acid and mercuric acetate give tetraacetoxymercurithiophene **402** (Z = S).
b. 2-Furoic acid and acetyl nitrate give 2-nitrofuran.



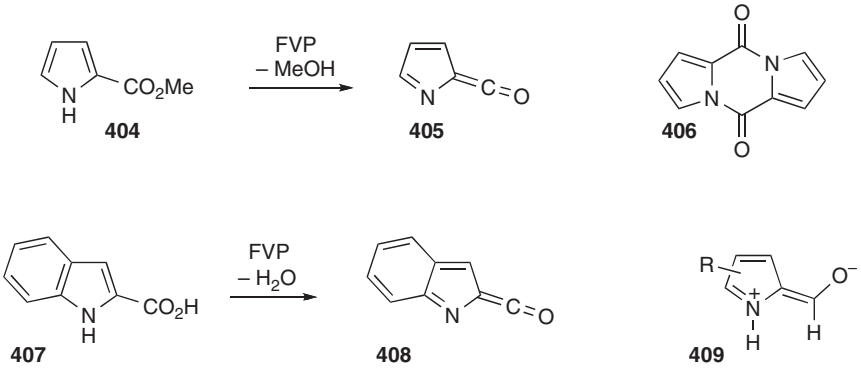
c. Reaction of the anion of pyrrole-2-carboxylic acid with benzenediazonium ion results in the displacement of carbon dioxide rather than hydrogen (**Scheme 131**).



Scheme 131

In the pyrrole series, ester groups to nitrogen are more readily hydrolyzed by alkali, but those in a position more readily by acid. Thus, in compounds such as diethyl 2,4-dimethylpyrrole-3,5-dicarboxylate **403** either ethoxycarbonyl group can be selectively hydrolyzed and, if desired, subsequently eliminated by decarboxylation of the resulting acid.

Flash vacuum pyrolysis of 2-methoxycarbonylpyrrole **404** gives the ketene **405**, trapped on a cold finger, characterized by IR absorption at 2110 cm^{1}. On warming to 100 to 90 C the dimer **406** is formed. Flash vacuum pyrolysis of indole-2-carboxylic acid **407** results in loss of water and the formation of a ketene **408** showing absorption at 2106 cm^{1}.



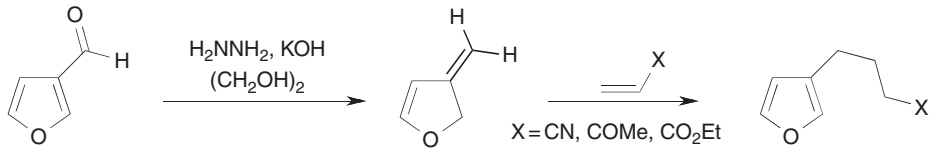
The anhydride of thiophene-2,3-dicarboxylic acid is a precursor of 2,3-didehydrothiophene which can be trapped as [4 + 2] and [2 + 2] cycloaddition products with dienes.

3.3.3.3.8 Acyl groups

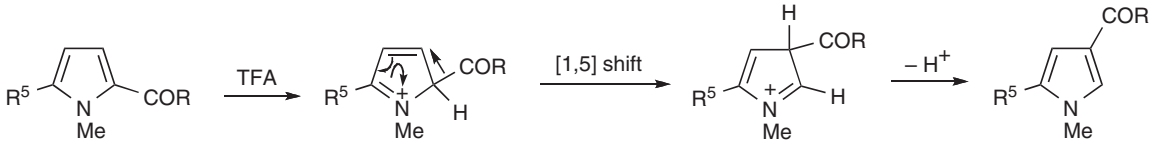
The carbonyl reactivity of pyrrole-, furan-, thiophene- and selenophene-2- and -3-carbaldehydes is very similar to that of benzaldehyde. A quantitative study of the reaction of *N*-methylpyrrole-2-carbaldehyde, furan-2-carbaldehyde, and thiophene-2-carbaldehyde with hydroxide ions showed that the difference in reactivity between furan- and thiophene-2-carbaldehydes is small but that both of these aldehydes are considerably more reactive to hydroxide addition at the carbonyl carbon than *N*-methylpyrrole-2-carbaldehyde. Pyrrole-2-aldehydes cannot be prepared by partial reduction of esters, it being necessary to form the alcohol and then reoxidise with MnO_2 <2002S1810>. Pyrrole-2-aldehydes fail to undergo Cannizzaro and benzoin reactions, which is attributed to mesomerism involving the ring nitrogen (cf. **409**), but will form hydrazones <1999T13703>. Wittig reactions can be used to access 2-vinylindoles from indole-2-carbaldehydes <2002S1810>. They yield 2-methylpyrroles by borohydride <2005T4631> or WolffKishner reduction; 2-ketones are reduced to methylene with borane or $Bu^{t}NH_2.BH_3AlCl_3$ <2004T1197>. The IR spectrum of the hydrochloride of 2-formylpyrrole indicates that protonation occurs mainly at the carbonyl oxygen atom and only to a limited extent at C(5).

The HuangMinlon reduction of 3-formylfuran gives 3-methylene-2,3-dihydrofuran. The product undergoes ene reactions with a number of electron-deficient alkenes and provides a route to functionalize the 3-position in furan as shown in **Scheme 132**.

Acyl-pyrroles, -furans, and -thiophenes in general have a similar pattern of reactivity to benzenoid ketones. Acyl groups in 2,5-disubstituted derivatives are sometimes displaced during the course of electrophilic substitution reactions. *N*-Alkyl-2-acylpyrroles are converted by strong anhydrous acid to *N*-alkyl-3-acylpyrroles. Similar treatment of N-unsubstituted 2- or 3-acylpyrroles yields an equilibrium mixture of 2- and 3-acylpyrroles; pyrrolecarbaldehydes also afford isomeric mixtures. The probable mechanism of these rearrangements is shown in **Scheme 133**. A similar mechanism has been proposed for the isomerization of acetyl indoles.

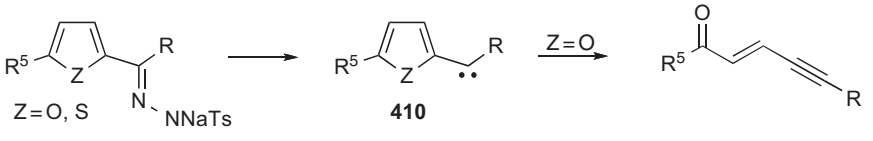


Scheme 132



Scheme 133

Carbenes of type **410**, generated by thermal decomposition of the appropriate tosylhydrazone salts, undergo ring opening more readily when the ring heteroatom is oxygen than when it is sulfur.



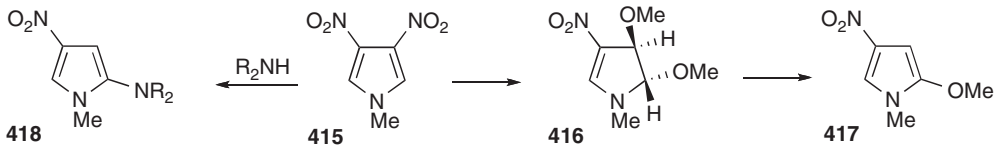
3.3.3.4 N-Linked Substituents

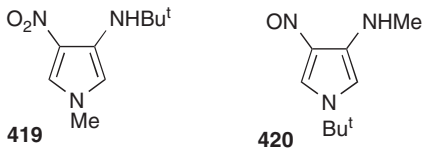
3.3.3.4.1 Nitro

Both 2- and 3-nitrothiophenes are reduced by tin and hydrochloric acid to the corresponding aminothiophenes. Reduction of 2,5-dibromo-3,4-dinitrothiophene gives 3,4-diaminothiophene as a stable crystalline solid. 2-Acetamidofurans are prepared by the reduction of 2-nitrofurans in the presence of acetic anhydride. 2-Substituted 5-nitrofurans can be reduced to the 5-aminofurans by an electrochemical method. Although catalytic reduction gives 2-aminofurans only in low yields, they can be trapped using ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile. Benzofuranone **412** and not 2-aminobenzofuran is obtained from tin and hydrochloric acid treatment of 2-nitrobenzo[*b*]furan **411**.

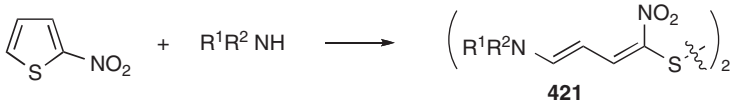
Although, in general, the -excessive nature of the heterocyclic rings under discussion reduces their reactivity to nucleophilic substitution, there are a number of reactions in which the leaving group is a nitro group. An example of intramolecular nucleophilic displacement of a pyrrole nitro group is provided by the base-induced cyclization of 2-acetyl-l-(2-hydroxyethyl)-5-nitropyrrole (**413** **414**).

1-Methyl-3,4-dinitropyrrole **415** with methanolic sodium methoxide yields **416** which on treatment with trifluoroacetic acid gives the 2-methoxypyrrole **417**.





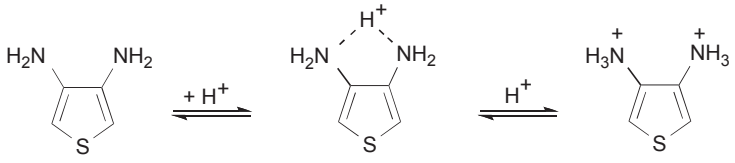
With secondary amines such as piperidine or dimethylamine, the formal products **418** of *cine*-substitution are obtained; with primary amines (e.g., *tert*-butylamine), in addition to the displacement product **419**, a rearranged product **420** is obtained in which the nitrogen-bearing methyl becomes exocyclic. 2-Nitrothiophene with secondary amines gives ring-opened products **421**.



3.3.3.4.2 Amino

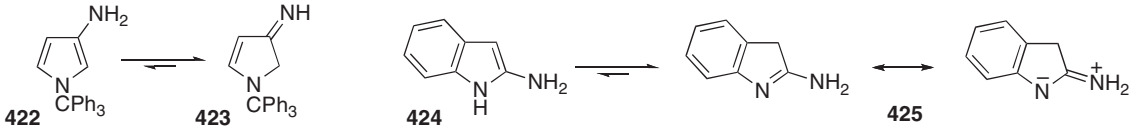
The free bases are much less stable than aniline, particularly 2-aminopyrroles and -furans which are very easily oxidized or hydrolyzed. 2-Aminofurans substituted with electron-withdrawing groups (e.g., NO_2) are known and 3-amino-2-methylfuran is a relatively stable amine which can be acylated and diazotized. 2-Aminothiophene can be diazotized and the resulting diazonium salt coupled with -naphthol. 2,3-Diaminothiophene has been prepared and isolated as the hydrobromide; the free base is not stable.

Both 3-amino- and 3,4-diaminothiophene exhibit enamine character. On acid-catalyzed deuteration, deuterium enters the thiophene -positions. However, a detailed potentiometric as well as ^{1}H NMR study of the protonation of 3,4-diaminothiophene revealed that both monoprotonation as well as diprotonation occurs on the nitrogen atoms (**Scheme 134**). The pK_a values in 50% DMSOwater mixture are 3.96 and 0.98.



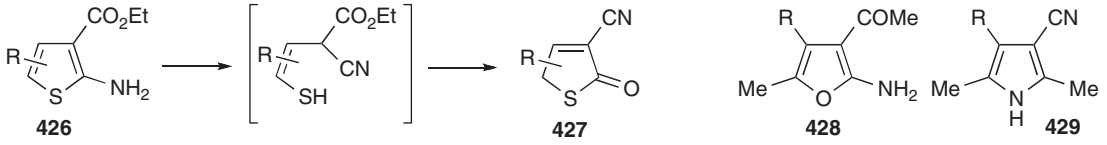
Scheme 134

Most of these compounds exist predominantly in the amino form. However, there are exceptions. 3-Amino-l-tritylpyrrole **422** appears to exist in solution exclusively in the form **423**. 2-Aminoindole **424** exists mainly as the 3*H*-tautomer **425**, which is stabilized by amidine resonance.



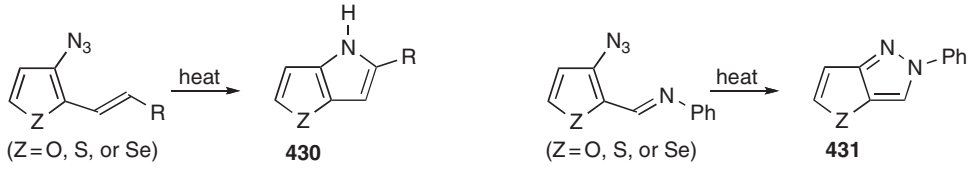
The amino compounds form salts and acylamino derivatives which are considerably more stable.

Ring-opening reactions can be initiated by proton loss from the amino group. Thus, 2-amino-3-ethoxycarbonylthiophenes **426** with ethanolic sodium ethoxide give cyanothiolenones **427**. In a similar sequence 2-amino-3-acetylfurans **428** are converted into 3-cyano-2-methylpyrroles **429** by aqueous ammonia.

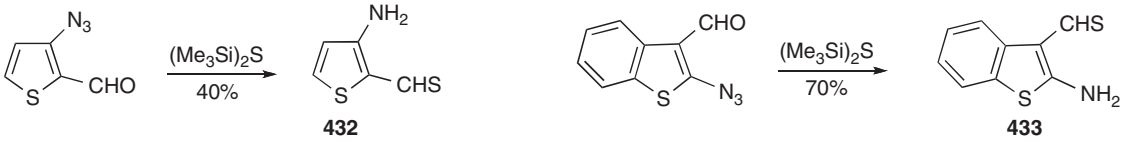


3.3.3.4.3 Azides

Five-membered ring heterocyclic azides are readily reduced (H_2S, $LiAlH_4$) to the corresponding amines. On thermolysis they lose nitrogen, thereby generating nitrenes. For example, 3-azido-2-vinyl derivatives in xylene at 120130°C yield [3,2-*b*]-fused pyrroles **430**; nitrene insertion into an *ortho*-disposed imino function similarly yields [3,2-*b*]-fused pyrazoles **431**.



Hexamethyldisilathiane applied to azido-aldehydes both thionates and reduces the azido groups of heterocyclic 2,3-azidoaldehydes, for example, **432** and **433** <1996S1185>.



3.3.3.5 O-Linked Substituents

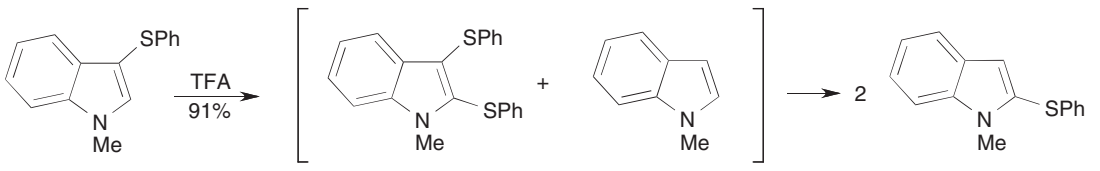
Hydroxy compounds are considered in Section 3.3.2.5, with their nonaromatic carbonyl tautomers.

3.3.3.6 S-Linked Substituents

Thiophene-2-sulfonic acid is a strong acid, similar to benzenesulfonic acid. It forms a sulfonyl chloride with phosphoryl chloride which on reduction with zinc yields thiophene-2-sulfinic acid.

Pyrrolethiols, readily obtained from the corresponding thiocyanates by reduction or treatment with alkali, rapidly oxidize to the corresponding disulfides. They are converted into thioethers by reaction with alkyl halides in the presence of base. Pyrrole-, furan-, and thiophenethiols exist predominantly as such rather than in tautomeric thione forms.

The acid-catalyzed rearrangement of 1-methyl-3-phenylthioindole to 1-methyl-2-phenylthioindole proceeds by disproportionation to the 2,3-disulfide and 1-methylindole (**Scheme 135**).



Scheme 135

3.3.3.7 Halo Groups

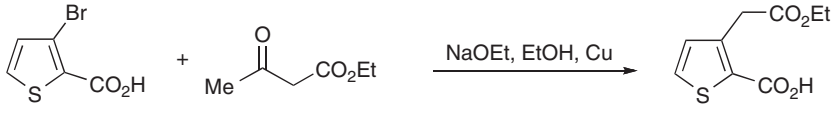
3.3.3.7.1 Nucleophilic displacement (see Section 3.3.3.8.8 for palladium and nickel-catalyzed displacements)

Halopyrroles do not readily undergo nucleophilic displacement. Halogen-substituted furans and thiophenes are also relatively inert, although their reactivity is greater than that of the corresponding aryl halides. Kinetic data are available for the nucleophilic displacement of halogen from 2-halofurans with piperidine. 2-Chlorofuran has about the same reactivity as bromobenzene and 2-chloro- and 2-bromothiophene have about a 10-fold greater rate of reaction than the corresponding benzene compounds. As in the benzene series, the introduction of powerfully electron-withdrawing groups, such as nitro, carboxy, or ester groups, greatly facilitates nucleophilic substitution. Halothiophenes which contain a nitro group react very much faster with nucleophilic reagents than the corresponding benzene derivatives, as shown by the rate data in **Table 5**.

Table 5 Relative pseudo-first-order rates of displacement of bromonitrothiophenes and bromonitrobenzenes with piperidine at 25°C

Compound	*Rate*
m-Bromonitrobenzene	1
p-Bromonitrobenzene	1.85×10^2
o-Bromonitrobenzene	1.62×10^3
5-Bromo-2-nitrothiophene	2.84×10^4
2-Bromo-3-nitrothiophene	6.32×10^5
5-Bromo-3-nitrothiophene	Very fast
4-Bromo-2-nitrothiophene	1.36×10^3
4-Bromo-3-nitrothiophene	Very fast

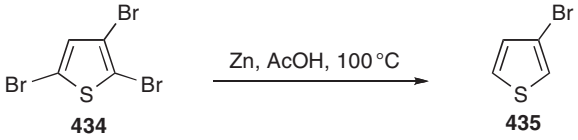
As in benzenoid chemistry, some nucleophilic displacement reactions can be copper catalyzed. Illustrative of these reactions is the displacement of bromide from 3-bromothiophene-2-carboxylic acid and 3-bromothiophene-4-carboxylic acid by active methylene compounds (e.g., $AcCH_2CO_2Et$) in the presence of copper and sodium ethoxide (**Scheme 136**). Analogously, 2-methoxythiophene can be prepared in 83% yield by refluxing 2-bromothiophene in methanol containing excess sodium methoxide, along with copper(I) bromide as catalyst. For the analogous preparation of 3-methoxythiophene, addition of a polar cosolvent (e.g., 1-methyl-2-pyrrolidone) is beneficial. In the case of halothiophenes, an $S_{RN}1$ mechanism is involved.



Scheme 136

3.3.3.7.2 Reductive dehalogenation

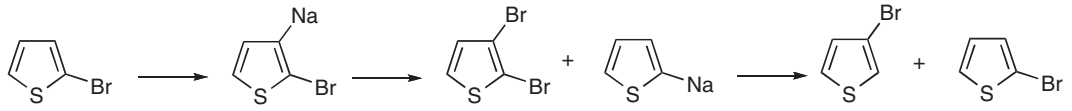
Halogen can be removed by catalytic hydrogenation and so it is possible to use halogen as a blocking group in pyrrole chemistry. In the thiophene and selenophene series, -halogens are preferentially removed by reduction with zinc and acetic acid, as illustrated by the preparation of 3-bromothiophene **435** from 2,3,5-tribromothiophene **434**.



434 **435**

3.3.3.7.3 Rearrangement

-Halothiophenes undergo rearrangement reactions in strongly basic media, resulting in the formation of thermodynamically more stable products. Based on this halogen dance of thienyl halides, methods have been developed for the large-scale synthesis of 3-bromo- and 3,4-dibromothiophene. Treatment of 2-bromothiophene with excess sodamide in liquid ammonia, and subsequent quenching with solid NH_4Cl, gives 3-bromothiophene in 73% yield; with potassium amide 3-aminothiophene is formed. The sequence of steps is given in **Scheme 137**. The second step is a disproportionation between the metallated molecule and a second molecule of 2-bromothiophene to give 2,3-dibromothiophene which can then form the 3-bromo compound.



Scheme 137

3.3.3.7.4 Formation of Grignard reagents

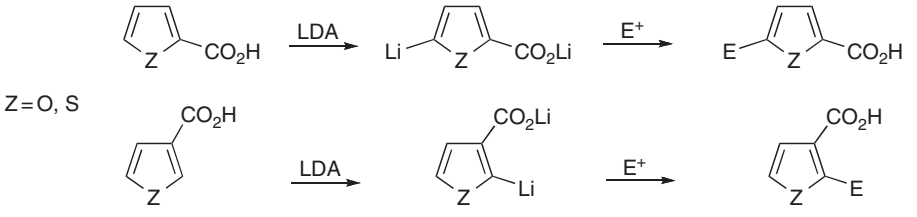
Grignard reagents can be prepared from 2-bromothiophene and 2-iodofuran; these Grignard reagents show normal nucleophilic reactivity. 3-Iodothiophenes also react with magnesium and 3-bromothiophene by the entrainment method. However, 3-thienylzinc- and 3-thienylmagnesium iodides can be prepared easily at room temperature by the oxidative addition of activated zinc or magnesium (reduction of $ZnCl_2$ or $MgCl_2$ by lithium using naphthalene as the electron carrier) to 3-iodothiophene <1995JOC6658, 1997JOC6921> and these organometallic compounds are regiostable giving rise to 3-substituted products. For example, thien-3-ylmagnesium iodide reacts with diphenyl disulfide producing 3-phenylthiothiophene. The 3-bromo compound reacts smoothly with butyllithium at 70°C to give 3-thienyllithium. If the reaction is carried out at room temperature, 3-thienyllithium acts as a lithiating agent and an equilibrium mixture of thiophene, 2-lithiothiophene, and 3-bromo-2-lithiothiophene is formed. 3-Lithiofurans can similarly be obtained from 3-halofurans and butyllithium.

3.3.3.8 Metals and Metalloids

3.3.3.8.1 General

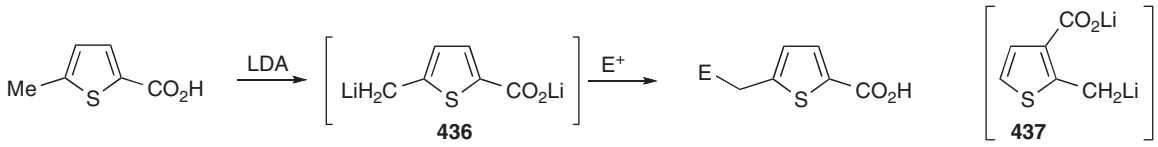
Although a limited range of Grignard reagents is available, the most widely used group is undoubtedly the lithio group introduced by direct lithiation (see Section 3.3.1.6.2) or by metalhalogen exchange. The ready formation of the lithio derivatives of pyrroles, furans, and thiophenes and their benzo-fused derivatives has had a most important impact on the chemistry of these heterocyclic systems. Reaction of the lithiated heterocycles with a wide range of electrophiles leads to derivatives with carbon, nitrogen, oxygen, sulfur, and halogen-linked substituents.

Lithiation with the assistance of an *ortho* substituent is also valuable; for example, the dianions derived from furan- and thiophenecarboxylic acids by deprotonation with LDA can be reacted with various electrophiles (**Scheme 138**).



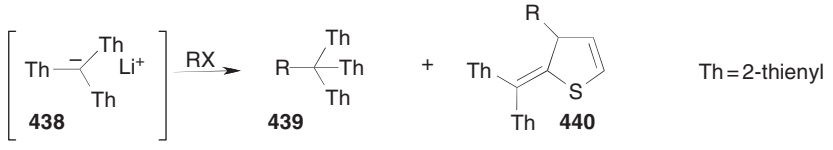
Scheme 138

The dianions of methylthiophenecarboxylic acids (e.g., **436, 437**) are also readily generated by reaction with LDA; they undergo preparatively useful reactions with a range of carbon electrophiles.

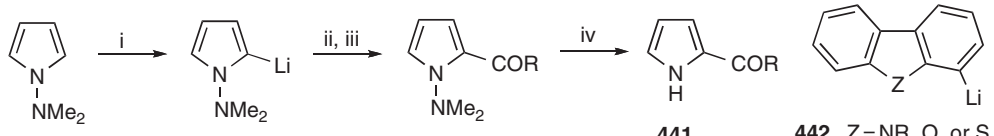


Regioselective side-chain lithiation can also be carried out on 2-methylthiophene-3-carboxylic acid. By contrast, the isomeric 3-methylthiophene-2-carboxylic acid gives a 35:65 mixture of side-chain and nuclear (at position 5) lithiation. Dilithiation of 2-methylthiophene-3-carboxylic acid with two equivalents of LDA in THF at 30̄C gives the dilithium derivative **437**, which can be reacted with electrophiles at the side-chain carbon.

Treatment of tri-(2-thienyl)methane with *n*-BuLi in the presence of TMEDA in THF at 78̄C gives exclusively the tri-(2-thienyl)methyllithium **438** without any nuclear lithiation. This lithiation is faster than that of triphenylmethane. Treatment of **438** with primary alkyl halides leads to alkylation at the carbanion center, forming **439**. However, secondary alkyl halides give a mixture of **439** and **440**.



To exploit the reactions of the *C*-lithio derivatives of N-unsubstituted pyrroles and indoles, N-protecting/masking groups such as *tert*-butoxycarbonyl, *tert*-butylcarbamoyl, benzenesulfonyl, dimethylamino, and dimethylaminomethyl must be used. This is illustrated by a route to C-acylated pyrroles **441**. Another very useful process involves N-lithiation, N-carbonation, and lithiation of the resulting indol-1-ylcarboxylate at C(2); reaction with an electrophile and loss of carbon dioxide during work-up give N-unsubstituted 2-substituted indoles, for example, 2-haloindoles in excellent yields.



i. BuLi; ii. RCHO; iii. MnO_2; iv. $Cr_2(OAc)_4 2H_2O$

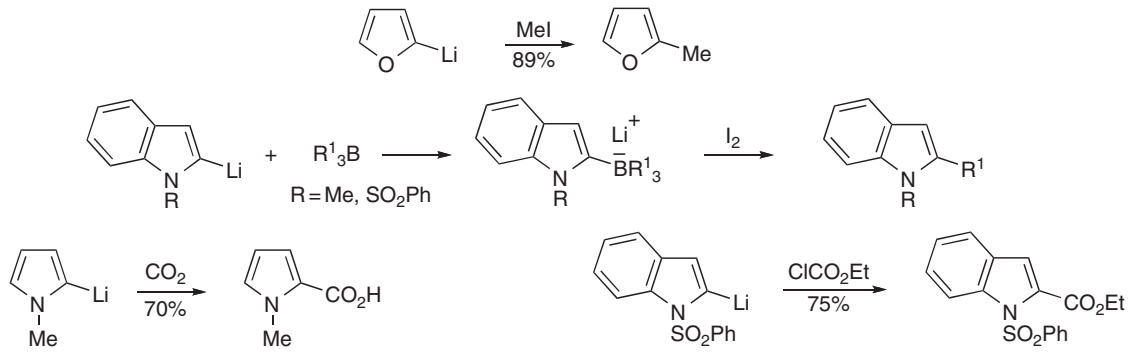
The reactions of the lithio derivatives of benzo[*b*]-fused systems indole, benzo[*b*]furan, and benzo[*b*]thiophene are similarly diverse. Since indole and benzo[*b*]thiophene undergo electrophilic substitution mainly in the 3-position, the ready availability of 2-lithio derivatives by deprotonation with *n*-butyllithium is particularly significant. The ready availability of 3-iodoselenophene and hence of 3-lithioselenophene provides a convenient route to 3-substituted selenophenes. 2-Lithiotellurophenes are especially important precursors of tellurophene derivatives because of the restricted range of electrophilic substitution reactions which are possible on tellurophenes.

Two cautions regarding the use of lithio derivatives need to be given: these relate to the possible incursion of rearrangement and of ring-opening reactions. For example, the 3-lithio derivative of 1-benzenesulfonylindole, generated from the 3-iodo compound at very low temperature (100̄C) by treatment with *tert*-butyllithium, rearranges on warming to room temperature to the thermodynamically more stable 2-lithio species. For synthetic applications of ring-opening reactions, see Section 3.3.3.8.7.

The lithio derivatives of the dibenzo heterocycles **442** are also preparatively useful since electrophiles attack these systems *para* to the heteroatom.

3.3.3.8.2 Formation of CC bonds

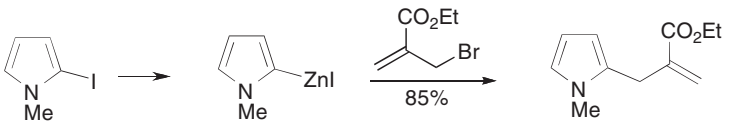
The reaction of lithio derivatives with appropriate electrophiles has been utilized in the preparation of alkyl, aryl, acyl, and carboxylic acid derivatives. Some representative examples of these conversions are given in **Scheme 139**. Noteworthy is the two-step method of alkylation involving reaction with trialkylborane followed by treatment with iodine.



Scheme 139

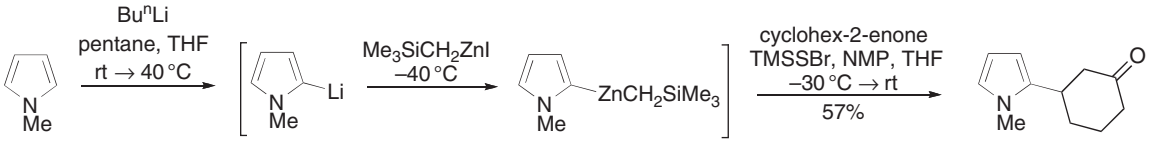
Carbon electrophiles which are frequently employed include aldehydes, ketones (e.g., 2-lithio-1-phenylsulfonylindole with 3-decanone <2000SL1757>), esters, epoxides (e.g., 2-lithio-1-methylindole with ethylene oxide <2003S1191>), carbon disulfide (e.g., 2-phenylpyrrole with KOHDMSO <2001S0293>), nitroethenes (e.g., 3-lithio-2-trityloxymethylfuran with 1-nitrocyclohexene <2004JA1954>), imines (e.g., 3-furanylmagnesium bromide with chiral *N*-[*para*-tolylsulfinyl]-bornane-10,2-sultam <1997TL2825>), chloroformates (e.g., 2-lithio-3-(*N*-*tert*-butoxycarbonylamino)furan with ethyl chloroformate <2006SL789> [In contrast, the lithiation of 2-(*N*-*tert*-butoxycarbonylamino)furan takes place exclusively at the 5-position <2003T5831>]), benzyl halides (e.g., 2-lithio-3,5-bis(trimethylsilyl)furan with benzyl bromide <1997T3497>), quinones (e.g., 2-lithiobenzo[*b*]furan with *para*-benzoquinone <2005TL7511>), benzotriazolyl-alkynes (e.g., 2-lithiobenzo[*b*]furan with *N*-phenylethynylbenzotriazole giving 2-phenylethynylbenzo[*b*]furan <2002JOC7526>), nitriles, and amides of the type $RCONMe_2$. An indirect method of acylation involves the initial reaction of a lithio compound with an aldehyde followed by oxidation of the resulting secondary alcohol to the corresponding acyl derivative.

Heterocyclic derivatives of a range of metals other than lithium have received considerable attention, especially as precursors for coupling reactions. These derivatives can be prepared either directly from halo compounds or from the lithio compounds. Thus, direct formation of the pyrrolylzinc compounds can be effected under very mild conditions by treatment of an iodide with a zincsilver couple deposited on graphite. The zinc reagents are formed in excellent yields and can be converted into acylated or allylated products (**Scheme 140**). For further discussion on this theme, see Section 3.3.3.8.8.



Scheme 140

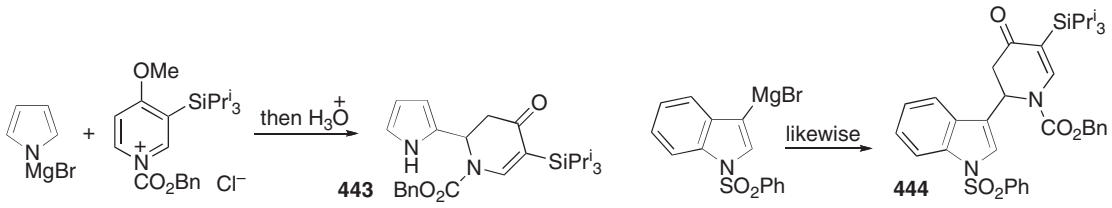
A class of mixed zinc reagents, e.g., (trimethylsilylmethyl)(2-pyrrolyl or 2-indolyl)zincs, bearing one transferable functional group (2-pyrrolyl or 2-indolyl) and one nontransferable group (the trimethylsilylmethyl group), add efficiently to Michael acceptors, for example, as in **Scheme 141** <1998T1471>.



Scheme 141

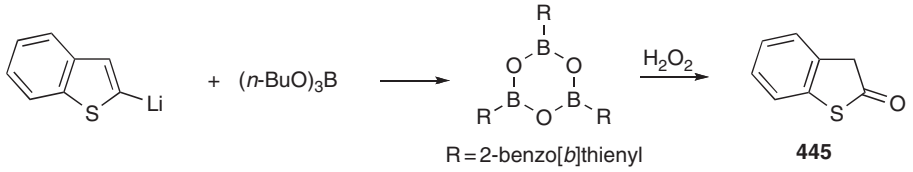
Thienylzincates are available using lithium di-*tert*-butyltetramethylpiperidinozincate (TMP-zincate) <1999JA3539>; thus, ethyl thiophene-3-carboxylate is easily metallated at C(2) at room temperature, subsequent reaction with iodine giving ethyl 2-iodothiophene-3-carboxylate in 89% yield. Similarly ethyl thiophene-2-carboxylate gives the 5-iodo derivative in 62% yield.

Addition of pyrrolyl and indolyl Grignard reagents to 1-acyl salts of 4-methoxy-3-(triisopropylsilyl)pyridine affords the corresponding 1-acyl-2-heteroaryl-2,3-dihydro-4(1*H*)-pyridones, e.g., **443** (main product) and **444** <2004JOC2863>, respectively.



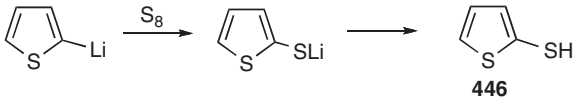
3.3.3.8.3 Formation of CO bonds

This can be achieved by an indirect method. The lithio derivative is first reacted with a borate ester. Sequential acid hydrolysis and oxidation yields the corresponding hydroxy derivative. This procedure is illustrated by the conversion of 2-lithiobenzo[*b*]thiophene to 2-hydroxybenzo[*b*]thiophene, which exists predominantly in the 2(3*H*)-one tautomeric form **445**.

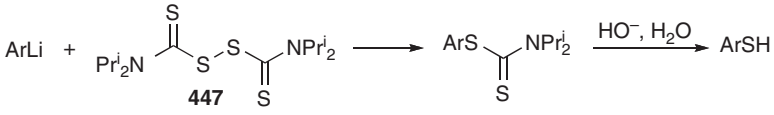


3.3.3.8.4 Formation of CS bonds

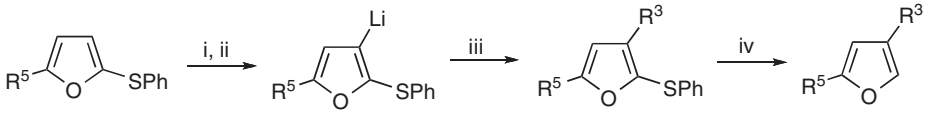
Carbonsulfur bonds can be formed by the reaction of elemental sulfur with a lithio derivative, as illustrated by the preparation of thiophene-2-thiol **446**. If dialkyl or diaryl disulfides are used as reagents to introduce sulfur, then alkyl or aryl sulfides are formed; sulfinic acids are available by reaction of lithium derivatives with sulfur dioxide. In the pyrrole series, a 2-thiol and the corresponding selenol can be prepared via reaction of 2-lithio-1-methylpyrrole with sulfur or selenium, then trapping with Me_3SiCl leading to the 2-Me_3SiX-substituted derivatives <1997T13079>.



Tetraisopropylthiuram disulfide **447** is a reagent of choice for preparing thiols from the corresponding lithio derivatives (**Scheme 142**). 2,4-Disubstituted furans, difficult to prepare by classical methods, have been prepared from 2-phenylthio-5-alkylfurans as shown in **Scheme 143**. The starting material is obtained by treatment of 2-alkylfurans with *n*-butyllithium followed by diphenyl disulfide. The practicality of this approach thus illustrates the potential of the phenylthio group as a protecting group.



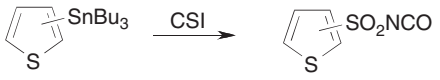
Scheme 142



i. Br_2; ii. Bu^tLi; iii. alkyl iodide, aldehyde, carbon dioxide or trimethylsilyl chloride; iv. Raney Ni

Scheme 143

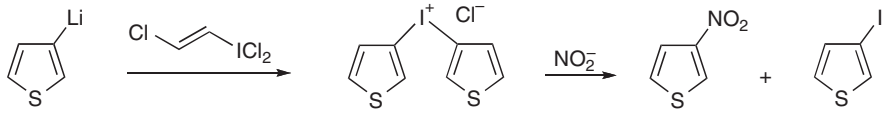
2-Thienyl- and 3-thienyl-(tributyl)stannanes react with chlorosulfonyl isocyanate (CSI) at 20°C to give the corresponding sulfonyl isocyanates by *ipso*-substitution (**Scheme 144**). The yields are above 90%.



Scheme 144

3.3.3.8.5 Formation of CN bonds

Azides are formed by the reaction of lithio derivatives with *p*-toluenesulfonyl azide, and these in turn can be converted into the corresponding amino compounds by a variety of reductive procedures. Nitro compounds are available by a novel reversal of the general pattern of reaction with electrophiles. This approach requires the initial conversion of the lithio compound into an iodonium salt followed by reaction with nitrite ion. This is illustrated by the preparation of 3-nitrothiophene (**Scheme 145**). Other nucleophiles, such as thiocyanate ion which yields the 3-thiocyanate, can be employed. The preparative significance of these reactions is again that products not accessible by electrophilic substitution can be obtained.



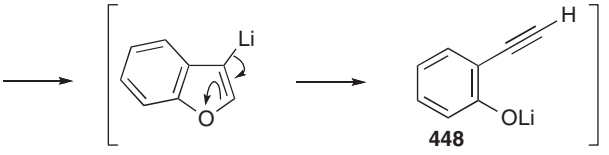
Scheme 145

3.3.3.8.6 Formation of Chalogen bonds

Synthetic procedures are available for the preparation of fluoro (e.g., 2-lithio-1-methyl-5-octylpyrrole with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide <2003JFC(124)159>), chloro, bromo, and iodo compounds from the corresponding lithio derivatives, for example, 2-iodobenzo[*b*]furan via lithiation of the heterocycle then reaction with iodine <2002JOC7048>. Perchloryl fluoride ($FClO_3$), *N*-chlorosuccinimide, bromine, and iodine are examples of reagents which can be used to introduce fluorine, chlorine, bromine, and iodine, respectively.

3.3.3.8.7 Ring-opening reactions

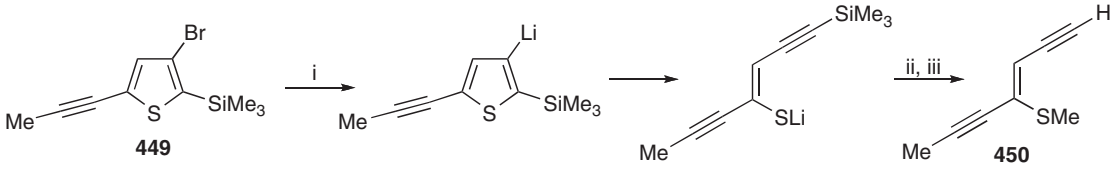
There are many ring-opening reactions of lithiated derivatives. A well-known example of this is the ring opening of 3-lithiobenzo[*b*]furan to the lithium salt of 2-ethynylphenol **448**.



448

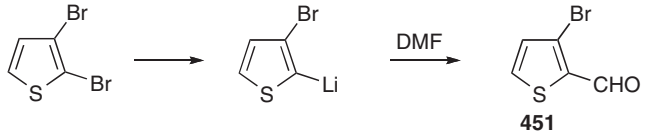
The tendency for the 3-lithio derivatives of furans and thiophenes to undergo ring opening has been exploited for the synthesis of polyunsaturated acyclic compounds. A trimethylsilyl group in the 2-position increases the ring-opening

tendency of 3-thienyllithium derivatives. For example, the trimethylsilyl derivative **449**, prepared by lithiating the 3-bromothiophene with LDA followed by reaction with trimethylsilyl chloride, smoothly ring opened on treatment with butyllithium. Subsequent reaction with methyl iodide and desilylation with potassium fluoride gave the terminal alkyne **450** (**Scheme 146**). This sequence also shows that *o*-halolithiothiophenes are significantly more stable than the corresponding benzenoid derivatives, which are used as benzyne precursors. The preparation of 3-bromothiophene-2-carbaldehyde **451** also illustrates this point (**Scheme 147**).



i. Bu^{n}Li, hexane, ether, –20 °C; ii. MeI; iii. KF.2H$_2$O

Scheme 146



Scheme 147

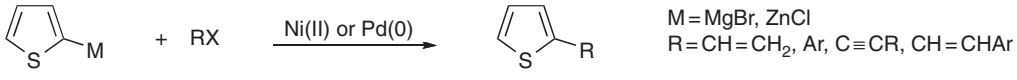
3-Lithio-2,5-dimethylselenophene shows a much greater tendency to undergo ring opening than 3-lithio-2,5-dimethylthiophene.

3.3.3.8.8 Transition metal-catalyzed cross-coupling reactions

A dominant theme since the mid-1980s in the chemistry of five-membered rings with one heretoatom has been the application of transition metal catalysis, especially the use of Pd or Ni as catalyst for bond formation.

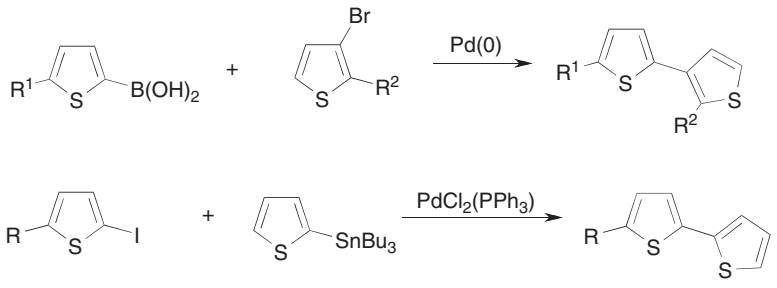
The reaction of heterocyclic lithium derivatives with organic halides to form a CC bond has been discussed in Section 3.3.3.8.2. This cannot, however, be extended to aryl, alkenyl, or heteroaryl halides in which the halogen is attached to an sp^2 carbon. Such cross-couplings can be successfully achieved by nickel- or palladium-catalyzed reactions of the unsaturated organo halide with a suitable heterocyclic metal derivative. The metal is usually zinc, magnesium, boron, or tin; occasionally lithium, mercury, copper, and silicon derivatives of thiophene have also found application in such reactions. In addition to this type, the Pd-catalyzed reactions of halogenated heterocycles with suitable alkenes (Heck reaction) and alkynes (Sonogashira reaction) are also discussed in this section. The Suzuki couplings of boronic acids have also been much utilized, for example, with *N*-Boc-protected ethyl 4-bromopyrrol-2-carboxylate <2003TL427> and benzo[*b*]furan-2-boronic acid with the 3-bromine of 3,5-dibromopyrone <2004SL2197>. Couplings of a 3-iodoindoles have been accomplished in solution <2006JOC62> or on solid phase <2005JCO809>. Couplings of thienylboronic acids with aryl bromides utilized [Pd(C$_3$H$_5$)Cl]$_2$ in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) <2005SL2057>.

2-Thienylmagnesium or zinc derivatives can be coupled with vinyl halides, bromo- or iodobenzene, or ethynyl bromide under Ni or Pd catalysis (**Scheme 148**); a thien-2-yl Grignard reagent was coupled twice to 3,6-dibromocarbazole using nickel catalysis <1997CM1578>. The reaction can be extended to the synthesis of -styrylthiophene; in this case the double-bond configuration is retained in the product.



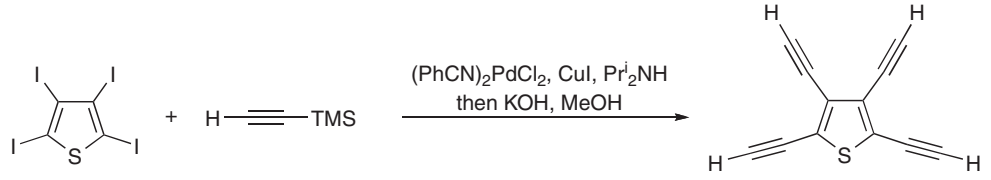
Scheme 148

Di- and polythienyls can be prepared by cross-coupling of 2- and 3-thienylboronic acids in the presence of Pd(0) catalyst. Iodothiophenes with stannylthiophenes similarly generate dithiophenes (**Scheme 149**).



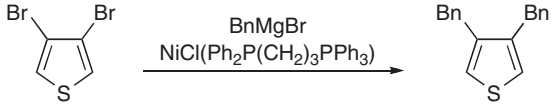
Scheme 149

An intriguing application of acetylene coupling is the preparation of 2,3,4,5-tetra(ethynyl)thiophene (**Scheme 150**). It is significant that both 2,3-dibromothiophene <1998TL1729, 1999EJO2045> and 2,3-dibromobenzo[*b*]furan <2003S925> couple with an acetylene selectively involving the 2-bromide; similar discrimination is found in 2,4-dibromothiophene <2001T7871>. Successive couplings with different boronic acids produce 2,3-di(different)aryl-substituted benzo[*b*]thiophenes <2005T2245>. 2-Iodothiophene reacts with terminal alkynes at room temperature in the presence of a bulky phenanthrylimidazolium hexafluorophosphate-derived ligand <2003OL3317> and also in an ionic liquid without copper salts or a phosphine; the catalyst was [(bisimidazole)PdClMe] <2004CC1306>. It is perfectly possible to couple a thienyl-3-halide: reaction of 3-bromothiophene itself with phenacetylene was achieved using (allylPdCl)$_2$P(*t*-Bu)$_3$DABCO <2003OL4191>. In other examples, 3-iodo-4-trimethylsilylthiophene was reacted in Sonogashira and Suzuki processes <1997LA459>.



Scheme 150

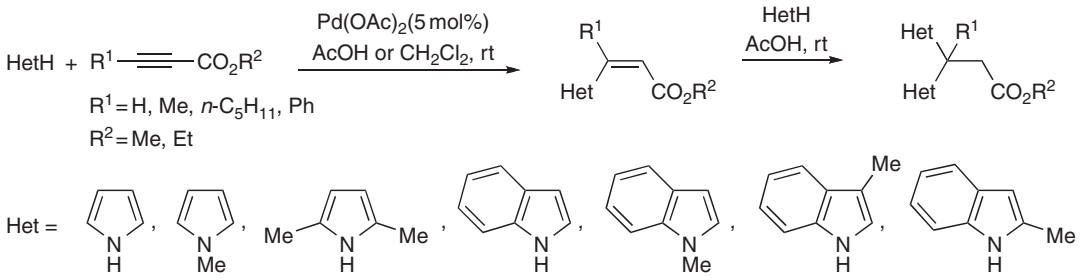
3-Bromothiophenes give cross-coupled products by reaction with Grignard reagents in the presence of a nickel catalyst (**Scheme 151**).



Scheme 151

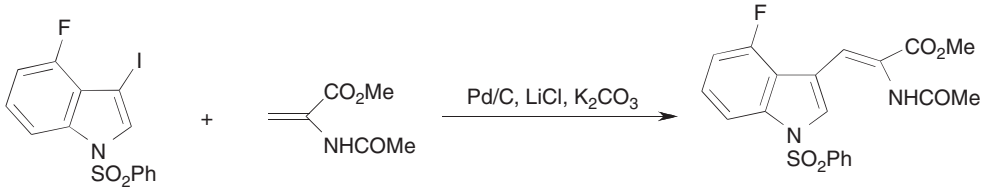
A quite different interaction with activated alkynes leads to alkenylations: **Scheme 152** summarizes what can be achieved <2000OL2927, 2002CL20>.

Much work has been directed toward the synthesis of thiophene oligomers and polymers. This is due to interest in conducting polymers and molecular electronics. Two main approaches have been used for making such polymers: (1) chemical (e.g., $FeCl_3$) or electrochemical oxidation of monomeric thiophenes and (2) transition metal-catalyzed cross-coupling reactions.

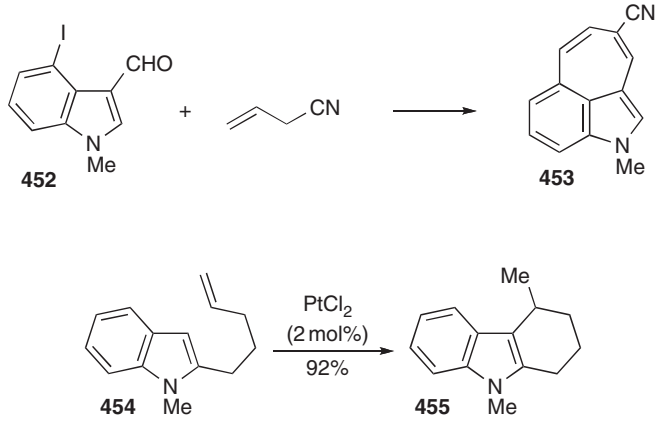


Scheme 152

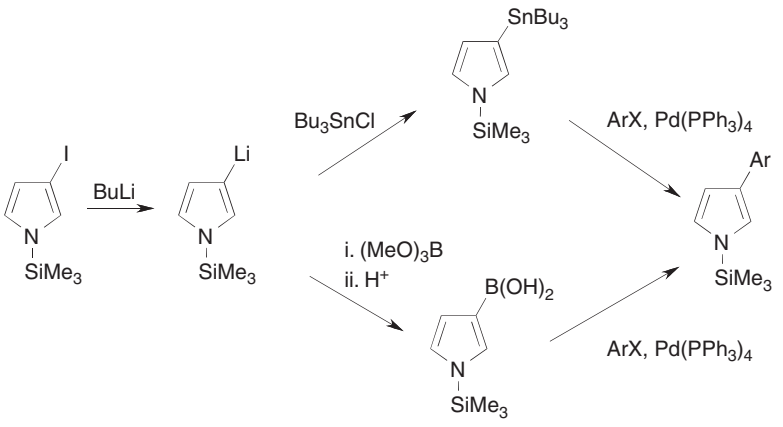
Palladium-catalyzed coupling reactions of the Heck type have often been used for indole and pyrrole derivatives. Vinylation of N-substituted-3-iodoindoles with amidoacrylate groups provides dehydro-tryptophan derivatives (**Scheme 153**). A catalyst system utilizing 10 mol% of $Pd(OAc)_2$, *t*-BuOOBz, dioxane, AcOH, and DMSO can be used for direct pyrrole CH bond alkenylation by acrylates. *N*-Benzyl and *N*-SEM pyrroles form C(2)- and C(3)-vinylpyrroles in a 2:1 ratio; however, with an electron-withdrawing N-protecting group (N-Ac, N-Ts, N-Boc) only C (2) products are obtained and with *N*-TIPS-pyrrole only C(3) products result <2006JA2528>. Yields are good in intramolecular reactions, e.g., **452** **453** and **454** **455** <2004JA3700>.



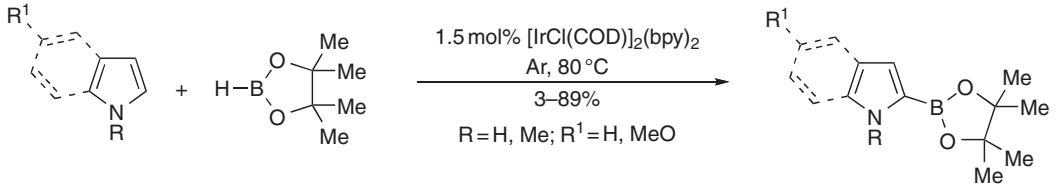
Scheme 153



Pyrrolyl- and indolyl-stannanes and -boronic acids, which can be prepared from the corresponding organolithium derivatives (e.g., 2-lithio-1-Boc-indole with triisopropyl borate then aqueous acid to the 2-boronic acid <2002JOC7551>), have received increasing use in palladium-catalyzed coupling reactions with aryl halides (**Scheme 154**). Iridium complexes generated from $[IrCl(COD)]_2$ and 2,2-bipyridine (bpy) catalyze the direct borylation of pyrrole and indole derivatives at their -positions (**Scheme 155**) <2004JMOA21>. Direct borylation of benzo[*b*]furan with bis(pinacolato)diboron funcitionalizes C(2) <2002TL5649>.

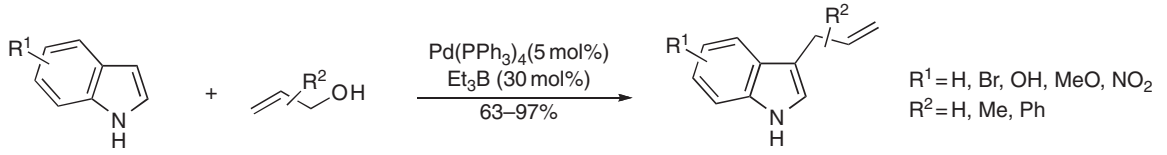


Scheme 154

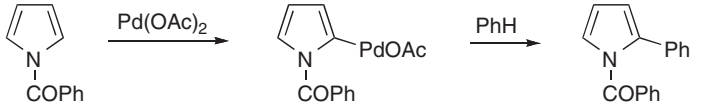


Scheme 155

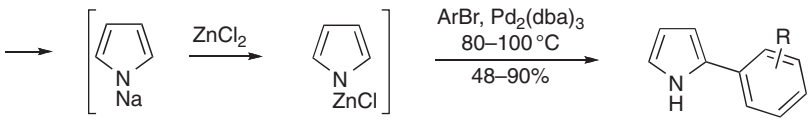
Under palladium catalysis, triethylborane promotes C(3)-selective allylation of indoles and tryptophans using a wide structural variety of allyl alcohols (**Scheme 156**) <2005JA4592>. Allyl carbonates can be used to effect comparable substitutions using $[PdCl(\text{-allyl})]_2$ with a base <2004OL3199>. The arylation of pyrroles can be effected by treatment with palladium acetate and an arene (**Scheme 157**). An alternative method utilizes pyrrol-1-ylzinc chloride to achieve 2-arylations (**Scheme 158**) <2004OL3981>. Indol-1-ylmagnesium halides likewise can be converted into 2-arylindoles <2003JA5274, 2003OL3607, 2004OL3981>. Direct 2-arylation of furfural takes place at C(5) using $PdCl_2Cy_3P$ <2001OL1677>. Direct arylation of ethyl furan-3-carboxylate can be achieved at C(2) or C(5) depending on conditions <2003OL301>. Direct arylations of thiophenes show that 3-substituted thiophenes react at C(2); 2-substituted thiophenes react at C(5); electron-withdrawing groups on the heterocycle facilitate such couplings <2002TL1829, 2004T3221>.



Scheme 156

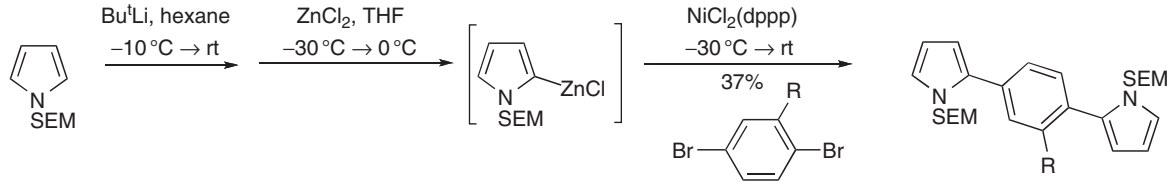


Scheme 157



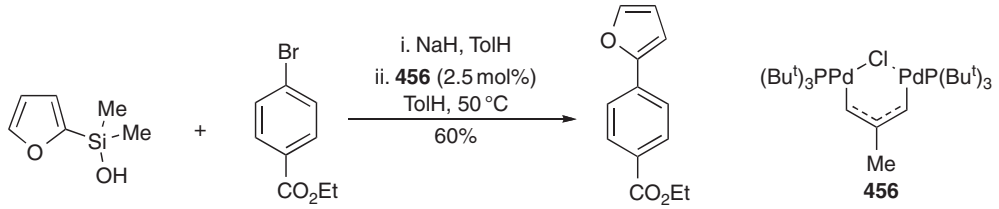
Scheme 158

Dimethylamino on the nitrogen of pyrroles is best for achieving couplings of 2-zincates with aryl bromides; the N-protection can be removed hydrogenolytically using Raney nickel <1999SM(99)181>. N-SEM protection can also be used in this context (**Scheme 159**) <1997CM2876>.



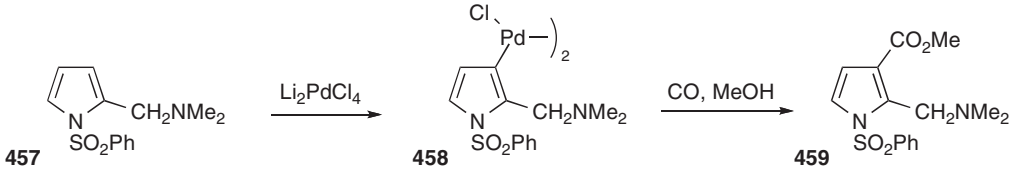
Scheme 159

A mild and general cross-coupling reaction of 2-indolylsilanols with aryl iodides or bromides uses Bu^tONa as the activator, copper(I) iodide in stoichiometric quantities, and $Pd_2(dba)_3$ñ$CHCl_3$ as the catalyst to give 2-arylindoles <2004OL3649>. Similarly, sodium 2-furanylsilanolate reacts with aryl iodides and aryl bromides catalyzed by palladium species **456** (**Scheme 160**) <2006OL793>.



Scheme 160

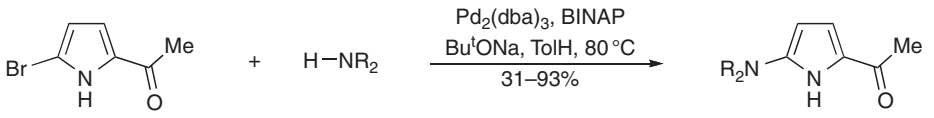
The N-protected pyrrole **457** can be palladated, but not lithiated, in the 3-position to give the stable complex **458**; this is readily converted into the 3-methoxycarbonylpyrrole **459**.



Palladium catalysis can also be used for the introduction of nitrogen substituents, e.g., **Scheme 161** <2004TL769>. 3-Bromothiophene can be coupled with 2-pyridone to form the *N*-(3-thienyl) derivative using a catalyst consisting of CuI in the presence of *N*,*N*-dimethylcyclohexane-1,2-diamine and KOAc or K_2CO_3 <2005T2931>.

3.3.3.8.9 Mercury derivatives

The classical uses of organomercurials include the replacement of the mercuri group (HgCl or RHgOAc) by hydrogen or halogen. Chloromercurated derivatives of furan, thiophene, and selenophene can be acylated with acyl halides; the range of application of organomercurials seems likely to grow since they have been shown to undergo transmetallation by a variety of transition metal reagents, particularly palladium salts, thus increasing their synthetic potential.



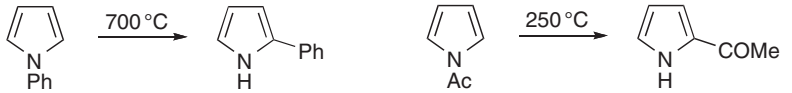
Scheme 161

The mercuric derivatives can be used instead of the magnesium derivatives in cross-coupling reactions (**Scheme 162**).

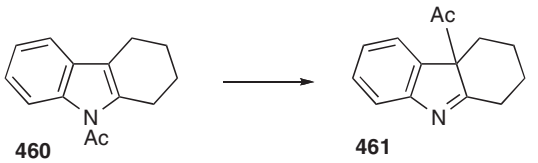
Scheme 162

3.3.3.9 Substituents Attached to the Pyrrole Nitrogen Atom

The thermal reactions of pyrroles include the rearrangement of N-substituted pyrroles to C-substituted derivatives (**Scheme 163**). The rearrangement of *N*-acylpyrroles has also been reported to occur in the vapor phase, on irradiation.



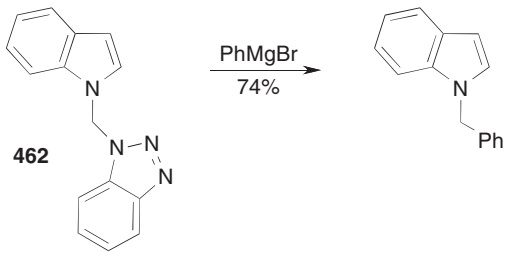
Scheme 163



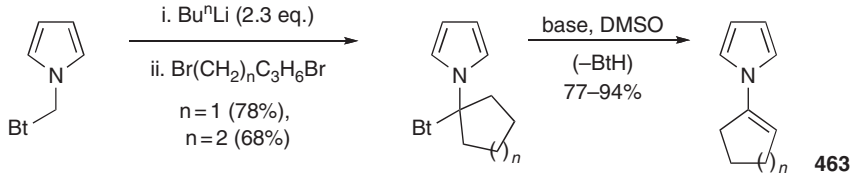
Photoisomerization of 1-acylindoles can yield 3-acyl-3*H*-indoles, as exemplified by the conversion of compound **460** into compound **461**.

Thermal rearrangement of *N*-chloropyrrole in methanol yields 2-chloropyrrole, whereas acid-catalyzed rearrangement gives a mixture of 2- and 3-chloropyrrole and some 2,5-dichloropyrrole.

Reactions can be induced on pyrrole or indole *N*-alkyl groups by the device of having a benzotriazole group to acidify the hydrogens or to act as a leaving group. Thus, reaction of such compounds with Grignard reagents gives substitution products, for example, phenylmagnesium bromide reacts with indole **462** to give 1-benzylindole.

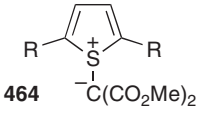


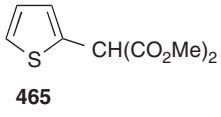
In another example, *N*-(1-cycloalkenyl)pyrroles **463** were prepared in three steps starting from *N*-(benzotriazol-1-ylmethyl)pyrrole <2002JOC8230>.

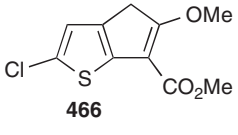


3.3.3.10 Substituents Attached to the Thiophene Sulfur Atom

On heating the sulfonium ylide **464** (R = H) the isomeric bis(methoxycarbonyl)methyl-thiophene **465** is formed. Thermolysis of the ylide **464** (R = Cl) yields the thienofuran **466**. When heated in the presence of copper or rhodium catalysts, **464** (R = Cl) undergoes cleavage of the carbonsulfur bond resulting in the formation of carbenoid intermediates which can trapped with activated aromatic substrates or alkenes to yield the corresponding arylmalonates or cyclopropanes, respectively.







3.4 Reactivity of Five-membered Rings with Two or More Heteroatoms

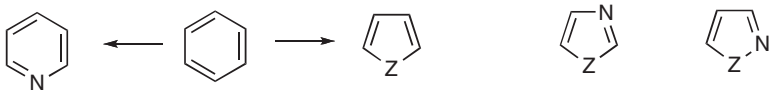
3.4.1 Reactions at Heteroaromatic Rings

3.4.1.1 General Survey of Reactivity

In Section 3.4.1.1 the reactivities of the major types of azole aromatic rings are briefly considered in comparison with those which would be expected on the basis of electronic theory, and the reactions of these heteroaromatic systems are compared among themselves and with similar reactions of aliphatic and benzenoid compounds. Later, in Sections 3.4.1.23.4.1.10 these reactions are reconsidered in more detail. Reactions of nonaromatic five-membered compounds with more than one heteroatom are considered in Section 3.4.2 and reactions of substituents attached to aromatic azoles are covered in Section 3.4.3. The reactions of azoles can only be rationalized and understood with reference to the complex tautomeric and acidbase equilibria shown by these systems. Tautomeric equilibria are discussed in Chapter 2.4. Acidbase equilibria are considered in Section 3.4.1.3 of the present chapter.

3.4.1.1.1 Reactivity of neutral azoles

Replacing a CH group of benzene **2** with a nitrogen atom gives pyridine **1**; replacing a CH=CH group of benzene with NH, O, or S gives pyrrole, furan, or thiophene **3**, respectively.



1 **2** **3** **4** **5**

The azoles **4** and **5** can be considered to be derived from benzene by two successive steps, one of each of these types. Five-membered heterocycles with more than two heteroatoms require further replacement(s) of the first type. Hence, the chemistry of five-membered aromatic rings with two or more heteroatoms shows similarities to both that of the five- and that of the six-membered aromatic rings containing one heteroatom. Thus, electrophilic reagents attack lone electron pairs on multiply bonded nitrogen atoms of azoles (cf. pyridine) (see Section 3.4.1.3), but they do not commonly attack electron pairs on heterocyclic nitrogen atoms in NR groups or on heterocyclic oxygen or sulfur atoms (cf. pyrrole, furan, thiophene) (e.g., see Section 3.4.1.5.1).

The carbon atoms of azole rings can be attacked by nucleophilic (Section 3.4.1.6), electrophilic (Section 3.4.1.4), and radical reagents (Section 3.4.1.9.2). Some systems, for example the thiazole, imidazole, and pyrazole nuclei, show a high degree of aromatic character and usually revert to type if the aromatic sextet is involved in a reaction. Others such as the isoxazole and oxazole nuclei are less aromatic, and hence more prone to addition reactions.

Electron donation from pyrrole-like nitrogen, or to a lesser extent from analogous sulfur or oxygen atoms, assists electrophilic attack at azole carbon atoms, but as the number of heteroatoms in the ring increases, the tendency for electrophilic attack, at either C or N, decreases rapidly.

Just as electron displacement toward the nitrogen atoms allows nucleophilic reagents to attack pyridines at an - position, similar displacements toward imine nitrogens in azoles also facilitates nucleophilic attack at carbon. As in similar reactions with pyridine, formation of the initial adduct involves dearomatization of the ring. The subsequent fate of the adduct depends in part on the degree of aromaticity. Those derived from highly aromatic azoles tend to rearomatize, whereas those of lower aromaticity can take alternative reaction paths. For most neutral azoles, nucleophilic attack at a ring carbon atom is only possible with very strong nucleophiles.

Where azoles contain ring N-hydrogen, this group is acidic and bases can remove the N-hydrogen. In the absence of an N-hydrogen, strong bases can also remove ring-hydrogen atoms, particularly those that are to a ring sulfur, oxygen, or N-R, as in base-catalyzed hydrogen exchange and importantly in metallation reactions (Section 3.4.1.8).

3.4.1.1.2 Azolium salts

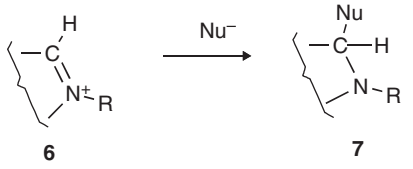
All neutral azoles possess a positively charged azolium counterpart. In addition, as discussed in Chapter 2.4, certain olylium species exist which have no neutral counterparts, for example, dithiolylium salts.

Azolium systems show essentially no reactivity towards electrophilic attack at ring carbon. Even if an azolium ion contains an additional unquaternized pyridine-like nitrogen, this nitrogen is hardly basic/nucleophilic in character. By contrast, azolium cations show a high reactivity toward nucleophiles and bases: at ring carbon atoms, at the hydrogen of ring CH and NH groups, and even at ring sulfur atoms.

In all these azoliums, oxolyliums, and thiolyliums, the positive charge facilitates attack by nucleophilic reagents at ring carbon atoms or to the charged heteroatom (Section 3.4.1.6). Hydroxide, alkoxide, sulfide, cyanide and borohydride ions, certain carbanions, amines, and organometallic compounds react under mild conditions, usually at a position to the quaternary center as in **6**, to give initial nonaromatic adducts **7** which can be isolated in certain cases but undergo further reaction with alacrity. The most important of these subsequent reactions include the following:

1. oxidation, e.g., the formation of cyanine dyes, e.g., in the thiazole series (Section 3.4.1.6.5.2);
2. ring opening with subsequent alternative closure, e.g., the reactions of oxazoliums with amines (Section 3.4.1.6.2);
3. ring opening without subsequent closure, e.g., the reactions of oxazoliums with hydroxide ion (Section 3.4.1.6.5.2).

Ring hydrogen atoms can be abstracted from the -carbon atoms of azolium ions by strong bases, as demonstrated in base-catalyzed hydrogen exchange (Section 3.4.1.8.3).



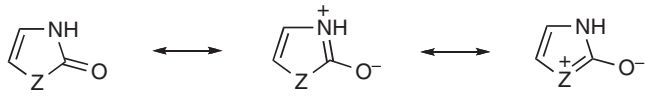
6 **7**

3.4.1.1.3 Azole anions

Azole anions are derived from imidazoles, pyrazoles, triazoles, or tetrazoles by proton loss from a ring N-hydrogen. Azole anions show markedly enhanced reactivity toward electrophiles, both at the nitrogen (Section 3.4.1.3.6) and carbon atoms (Section 3.4.1.4.1.1). They are correspondingly totally unreactive toward nucleophiles.

3.4.1.1.4 Azolinones, azolinethiones, azolinimines

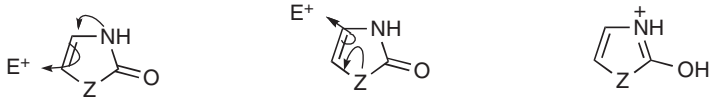
These compounds are usually written in the unionized form as in **8** (Z = NH, NR, O, S). Canonical forms of types **9** or **10** are important, i.e., these compounds can also be considered as betaines formally derived from azolium ions. Many compounds of this type are tautomeric and such tautomerism is discussed in Section 2.4.5.2.



8 **9** **10**

Reactions of these compounds follow logically from the expected electron displacements in the molecules. Their very varied chemical reactivity includes four main possibilities for heterolytic reactions: electrophilic attack at a ring carbon atom to a ring heteroatom (e.g., Section 3.4.1.4.2), or at a carbonyl oxygen atom (Section 3.4.3.7), a thiocarbonyl sulfur atom (Section 3.4.3.8.2), or an imine nitrogen atom (Section 3.4.3.5.5). Base attack to remove hydrogen from an NH group (Section 3.4.1.3.6), or a ring carbon atom (Section 3.4.3.12.3), also needs to be considered.

The mode of attack of electrophilic reagents (E^+) at ring carbon atoms is to the heteroatoms as shown, for example, in **11** and **12**; the resulting intermediates usually revert to type by proton loss. Halogenation takes place more readily than it does in benzene (Section 3.4.1.4.5). Nitration and sulfonation also occur; however, in the strongly acidic environment, the compounds required are present mainly as less reactive hydroxyazolium ions, e.g., **13**.

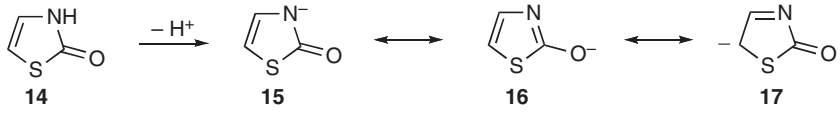


11 **12** **13**

The reactions of electrophilic reagents at a carbonyl oxygen atom, a thiocarbonyl sulfur, and an imino nitrogen atom are considered as reactions of substituents (see Sections 3.4.3.7, 3.4.3.8.2, 3.4.3.5.4, and 3.4.3.5.5).

The removal of a hydrogen atom from the heterocyclic nitrogen atom of azolones by bases, e.g., **14** **15**, gives mesomeric anions, e.g., **15** **16** **17**, which react exceedingly readily with electrophilic reagents, typically:

1. at nitrogen, e.g., with alkyl halides (Section 3.4.1.3.10);
2. at oxygen, e.g., with acylating reagents (Section 3.4.3.7);
3. at the -carbon atoms, e.g., with halogens (Section 3.4.1.4.5), and in the ReimerTiemann reaction (Section 3.4.1.4.6).

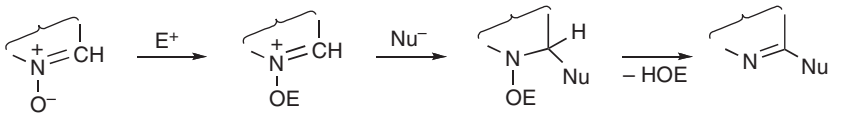


14 **15** **16** **17**

3.4.1.1.5 *N*-Oxides, *N*-imides, *N*-ylides of azoles

Azole *N*-oxides, *N*-imides, and *N*-ylides are formally betaines derived from *N*-hydroxy-, *N*-amino-, and *N*-alkyl-azolium compounds. Whereas *N*-oxides (Section 3.4.3.12.7) are usually stable as such, in most cases the *N*-imides (Section 3.4.3.12.5) and *N*-ylides (Section 3.4.3.12.3) are found as salts, which deprotonate readily only if the exocyclic nitrogen or carbon atom carries strongly electron-withdrawing groups.

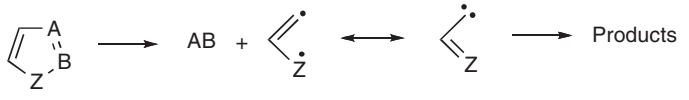
The reactivity of these compounds is somewhat similar to that of the azolonium ions, particularly when cationic species (**18** **19**) are involved. However, although typical reactions are with nucleophiles, an intermediate **20** can eliminate HOE, where E is an electrophile added to the *N*-oxide, to give the simple -substituted azole **21**, for example, benzimidazole 3-oxides are readily converted into 2-chlorobenzimidazoles in this way.



18 19 20 21

3.4.1.2 Thermal and Photochemical Reactions Formally Involving No Other Species

We consider here fragmentations and rearrangements that involve only the azole molecule itself, without the involvement of any substituent or other molecule. Many fragmentations of azoles can be summarized by the transformation **22** → **23** + **24**, where **23** represents a stable fragment, particularly N_2, but also CO_2, N_2O, COS, or HCN.

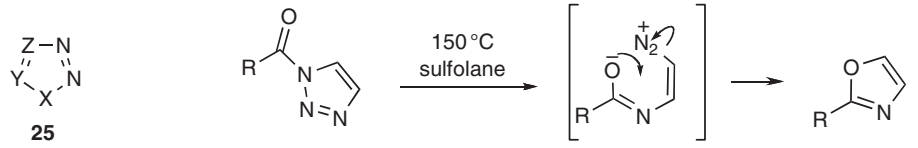


22 **23** **24**

3.4.1.2.1 Thermal fragmentation

Thermal and photochemical fragmentations of azoles often follow a similar pathway to their breakdown in a mass spectrometer (see Section 2.4.3.8). Such fragmentations are facilitated in the polynitrogenous azoles, thus azoles containing several nitrogen atoms undergo ring fission with loss of nitrogen. This is particularly noticeable when two adjacent pyridine-like nitrogen atoms are present. Thermolysis of **25** to give N_2 and $PhC{\equiv}N^+O$, a 1,3-dipole is a useful and general reaction. Azoles containing only two heteroatoms, such as the pyrazole and thiazole systems, are thermally very stable.

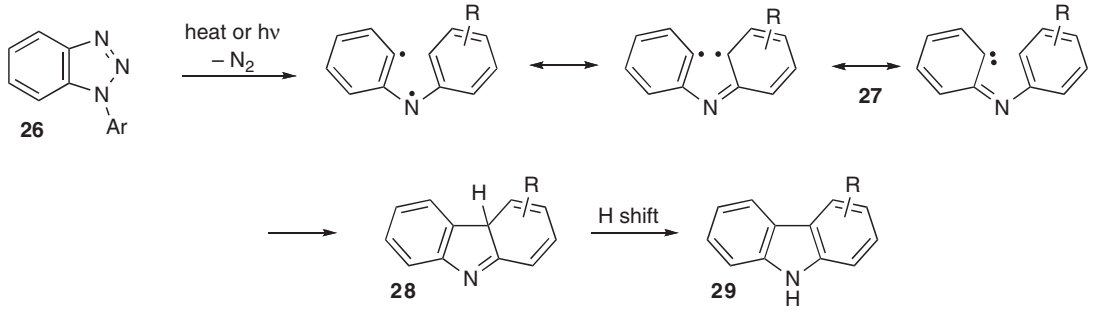
Simple triazoles are thermally stable to ca. 300 °C. However, triazole *N*-carboxamides, when heated to 150 °C in sulfolane, rearrange with the elimination of nitrogen to give 2-substituted oxazoles. The reaction is general and it is useful for the synthesis of oxazoles with diverse 2-substituents in excellent yields even for bulky substituents (**Scheme 1**). 4-Ethyl-3,5-diphenyl-4*H*-1,2,4-triazole is converted into 1-ethyl-3,5-diphenyl-1,2,4-triazole in the presence of 15-crown-5 in octadecane at 330 °C <2001JHC955>.



25

Scheme 1

Thermal or photochemical extrusion of nitrogen from 1-arylbenzotriazoles **26** leads to the formation of carbazoles **29** (**Scheme 2**). The mechanism is believed to involve cyclization of a species **27** to the 4a*H*-carbazole **28** followed by an

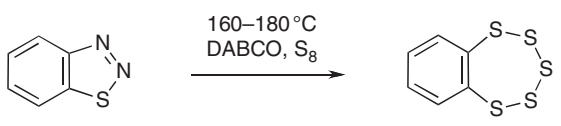


26 **27** **28** **29**

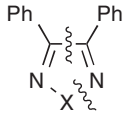
Scheme 2

aromatizing hydrogen shift. In practice, such thermolyses are conveniently carried out in hot diphenyl ether <1997J(P1) 2739, 2002JME590>.

1,2,3-Benzothiadiazole, when heated in the presence of sulfur, first loses nitrogen and then the species produced reacts with sulfur to form benzopentathiepin **30** <1984JOC1221>.



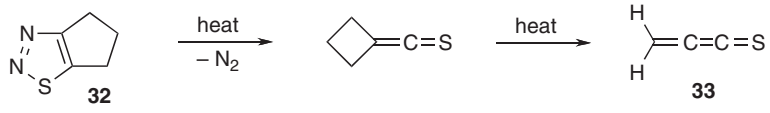
30



31

1-Vinylbenzotriazoles give indoles on flash pyrolysis at 600 °C/10^2 Torr. However, depending on the vinyl substituents, side reactions leading to *N*-phenylketenimines or benzonitrile are also observed.

1,2,5-Oxadiazoles undergo thermal and photochemical ring cleavage at the O(1)N(2) and C(3)C(4) bonds to yield nitrile and nitrile oxide fragments, and products derived therefrom. Thus, diphenylfurazan **31** (X = O) decomposes under flash vacuum pyrolysis conditions (600 °C, 10^3 mm Hg) affording benzonitrile and benzonitrile oxide in nearly quantitative yields. Benzofurazans are thermally more stable but can be cleaved photolytically. 1,2,3-Thiadiazoles extrude nitrogen and thiirenes can be formed, but their lifetime is fleeting as they rearrange to thioketenes; **Scheme 3** shows the eventual formation of propadienethione **33** from **32** <1988JA789, 1990CPL (168)1>.

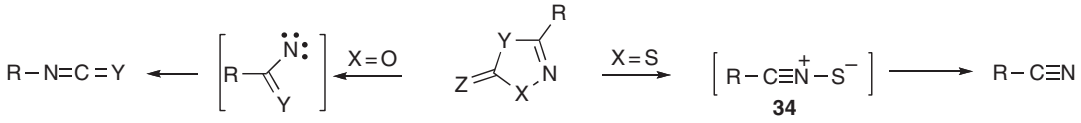


32 **33**

Scheme 3

Although unsubstituted 1,2,5-thiadiazole is stable on heating at 220 °C, 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **31** (X = SO_2) produces benzonitrile and sulfur dioxide at 250 °C.

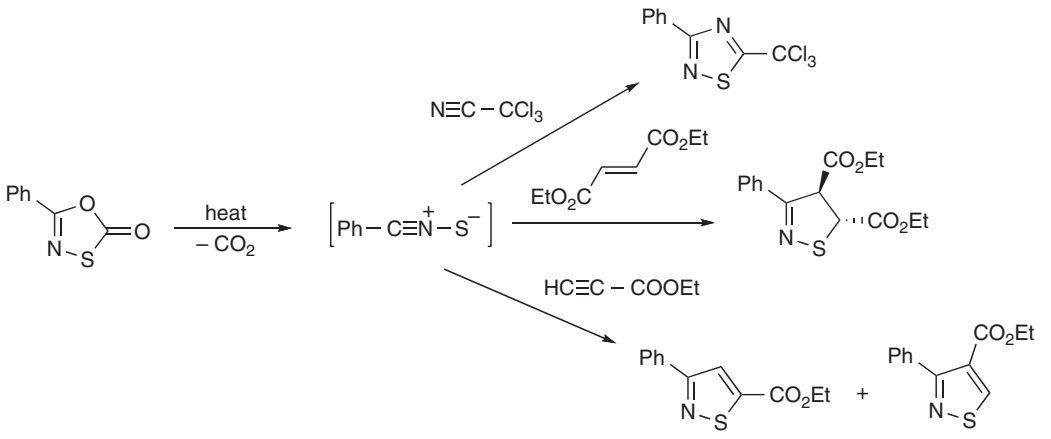
Thermal reactions of 1,4,2-dioxazoles, 1,4,2-oxathiazoles, and 1,4,2-dithiazoles are summarized in **Scheme 4**. The reactive intermediates generated in these thermolyses can often be trapped, e.g., the nitrile sulfide **34** participates in a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate.



34

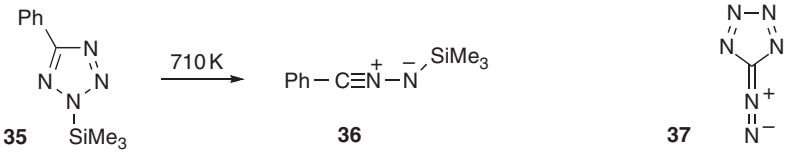
Scheme 4

The decarboxylation of 1,3,4-oxathiazolones, especially microwave-assisted <2005SC807, 2006CR41>, is the method of choice for nitrile sulfide generation. The rate of thermolysis is decreased by electron-withdrawing groups and increased by electron-donating groups <2000ARK(v)720>. Examples of the subsequent 1,3-dipolar trapping of nitrile sulfides thus generated are shown in **Scheme 5**.



Scheme 5

A much-studied, but complex topic, is the thermolysis of tetrazole itself and substituted tetrazoles. One of the reasons for this interest is that thermal decomposition of tetrazoles is accompanied by the release of a large amount of utilizable energy <1999THS467>. Prototropic tautomerism of tetrazole and 5-substituted NH-tetrazoles plays a significant role in the decomposition process <1996RCB2101>. The nature of tetrazole decomposition depends not only on its state of aggregation but also on the reaction temperature. Reaction temperatures and gas-phase reaction products (in parentheses) are as follows: 225°C (HCN, HN_3), 280°C (N_2, HCN, H_2), and 800°C, flash-photolysis (N_2, NH_2CN, CH_2N_2) <1997JHC113, 1999THS467, 2005JPC7967>. The parent nitrile imine, HCNNH, has also been generated by the photolysis of tetrazole <1996LA1041>. Thermolyses of 2,5-disubstituted tetrazoles give nitrile imines by loss of N_2; an example is shown in **Scheme 6**. The reaction is used not only for its synthetic potential but also as a source of nitrile imines for direct observation and exploration of their behavior. The first direct detection of a thermally generated nitrile imine was the species **36** produced by flash-vacuum pyrolysis of 5-phenyl-2-trimethylsilyltetrazole **35**.

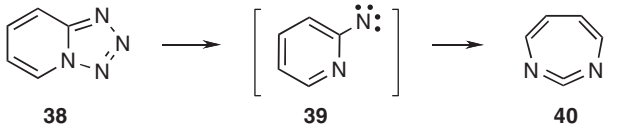


35 **36** **37**

Scheme 6

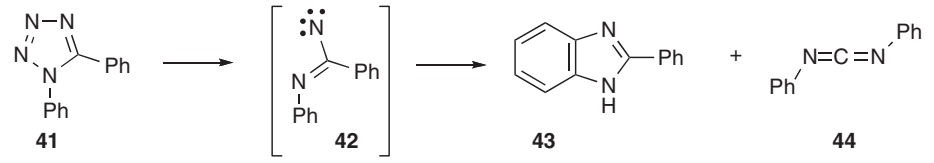
Thermal degradation of 5-diazotetrazole **37** produces atomic carbon.

The flash-vacuum pyrolysis of tetrazolo[1,5-*a*]pyridine **38**, and its benzologues, gives nitrenes that rapidly undergo subsequent ring insertion, affording cyclic carbodiimides, e.g., **39** **40**.



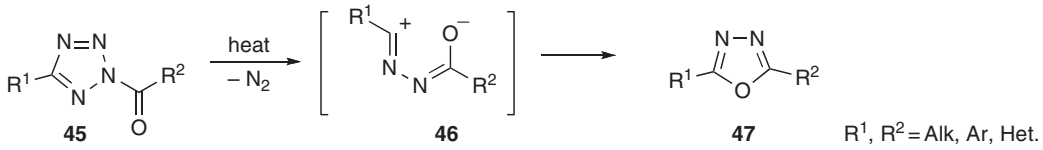
38 **39** **40**

Other classes of heterocycles undergo thermolytic fragmentation to give imido-nitrenes, as typified by the thermolysis of 1,5-diphenyltetrazole **41**, the intermediates **42** can either cyclize on to an aromatic ring to form benzimidazoles **43** or undergo a Wolff-type rearrangement to carbodiimides **44** (**Scheme 7**). Thermal decomposition of 2-acyltetrazoles



Scheme 7

45 is an efficient procedure for the preparation of 2,5-disubstituted-1,3,4-oxadiazoles **47**, which arise from electrocyclization of the intermediate dipolar ions **46** (**Scheme 8**) <1999IJC(B)188, 1999S999, 2003S899>.



Scheme 8

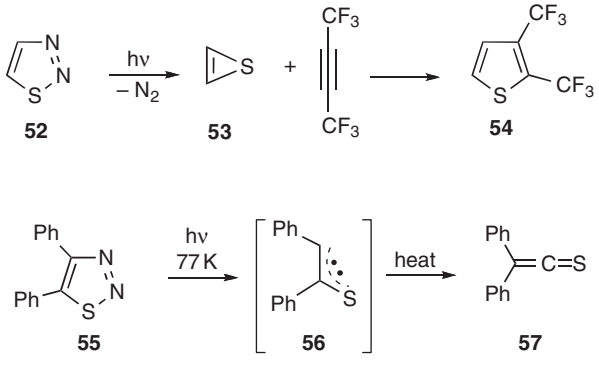
Compounds **48** and **49** thermolyse to give mainly the carbodiimide **44**. Pentazoles **50** spontaneously form azides, usually below 20°C.

1,2,3,4-Thiatriazoles readily decompose thermally into nitrogen, sulfur, and an organic fragment, usually a cyanide, e.g., **51** *iso*-BuOCN + $^{15}N^{14}N$ + S.

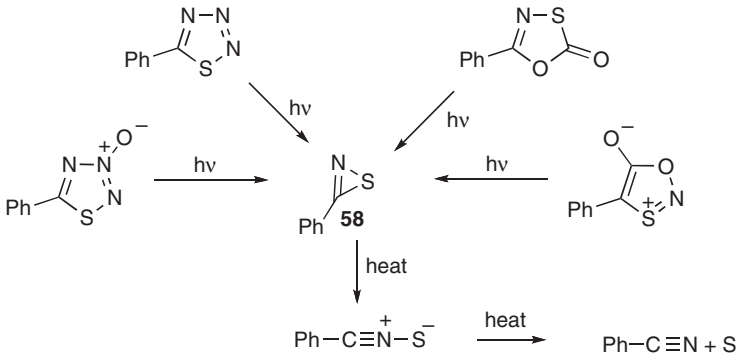
3.4.1.2.2 Photochemical fragmentation

Irradiation is very effective in promoting extrusion of nitrogen from triazoles and benzotriazoles. For example, the photolysis of 1-arylbenzotriazoles affords a high yield of the corresponding carbazoles (see **Scheme 2**).

Photolysis of 1,2,3-thiadiazole **52** gives thiirene **53** which can be trapped by an alkyne (e.g., **54**). 4,5-Diphenyl-1,2,3-thiadiazole **55** is photolyzed at low temperatures to the triplet thiobenzoylphenylcarbene **56** and diphenylthioketene **57** is formed on warming.

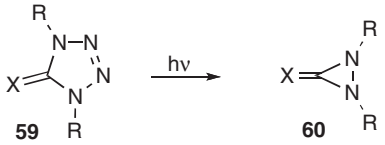


3-Phenylthiazirine **58** can be isolated as an intermediate in the photolysis of 5-phenyl-1,2,3,4-thiatriazole and also from other five-membered ring heterocycles capable of losing stable fragments; see **Scheme 9**. Photolysis of 5-phenylthiatriazole in the presence of cyclohexene yields cyclohexene episulfide by trapping the sulfur atom.

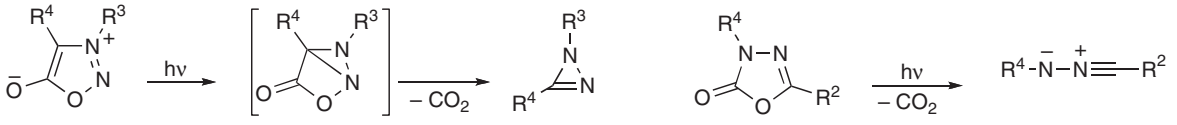


Scheme 9

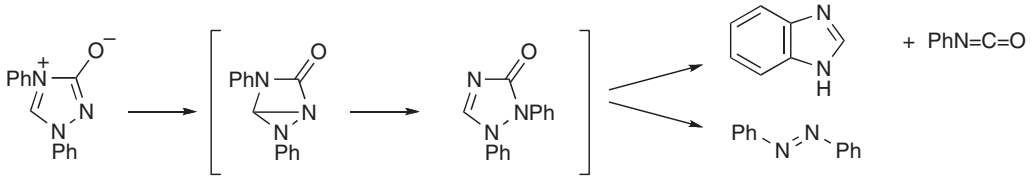
Diaziridine derivatives **60** (X = O) can be obtained from tetrazoles of type **59** (X = O).



Mesoionic compounds undergo a variety of photochemical fragmentations. Examples are shown in **Schemes 10** and **11** in which CO_2 or PhNCO is extruded, respectively. Diarylfuroxans give diarylacetylenes upon irradiation at 254 nm <1997T17407>.



Scheme 10

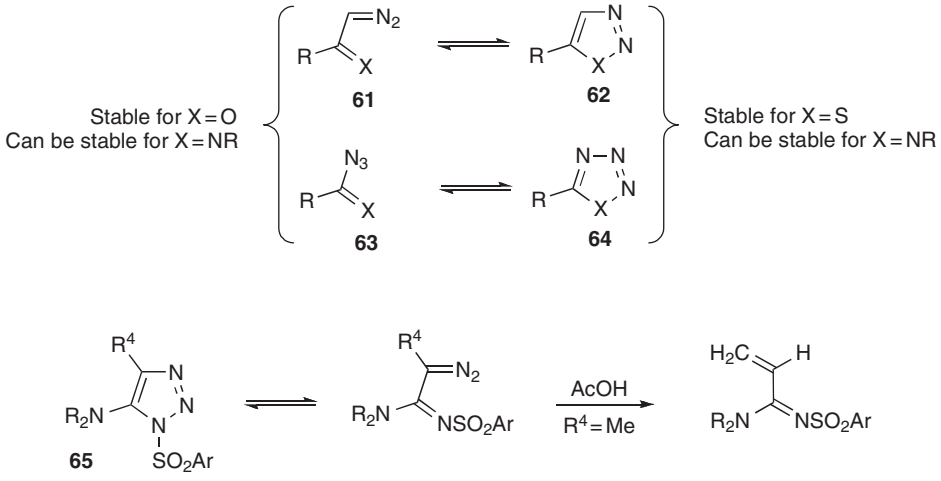


Scheme 11

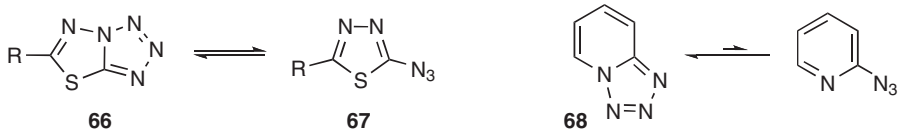
3.4.1.2.3 Equilibria with open-chain compounds

Azoles of types **62** and **64** are isomeric with the open-chain compounds **61** and **63**, respectively. Rearrangement between the two is rapid, and the thermodynamically stable isomer is encountered. Thus diazoketones **61** (X = O) exist as such, but diazothioketones **61** (X = S) spontaneously ring close to thiadiazoles **62** (X = S). 1,2,3-Triazoles generally

exist as such unless the nitrogen carries a strong electron-withdrawing substituent. Thus 1-cyano- and 1-arylsulfonyl-1,2,3-triazoles **65** undergo easy reversible ring opening to diazoimine tautomers.



A similar situation exists for molecules containing an azido group bonded to a doubly bound carbon atom as in **63**. When X is oxygen, the acyl azide exists in the acyclic form **63**, but when X is sulfur the cyclic thiatriazole **64** (X = S) predominates. When X is nitrogen, as in tetrazoles, the imidoyl azide **63** (X = NR) or the tetrazole **64** (X = NR) may predominate, or both may exist in equilibrium. The position of the tetrazoleimidoyl azide equilibrium depends on the following factors: (1) electron-withdrawing substituents favor the azide form; (2) higher temperatures favor the azide form; and (3) polar solvents tend to favor the tetrazole form, and nonpolar solvents favor the azide form. Ring strain is also important and two fused five-membered rings are in general avoided. For example, in the thiadiazolotetrazole equilibrium **66** **67**, the system exists in the bicyclic form in the solid state and in the azide form in carbon tetrachloride solution. Fusion with six-membered rings generally is more favorable to a bicyclic tetrazole form. For example, pyridine fusion gives essentially all tetrazole **68**.

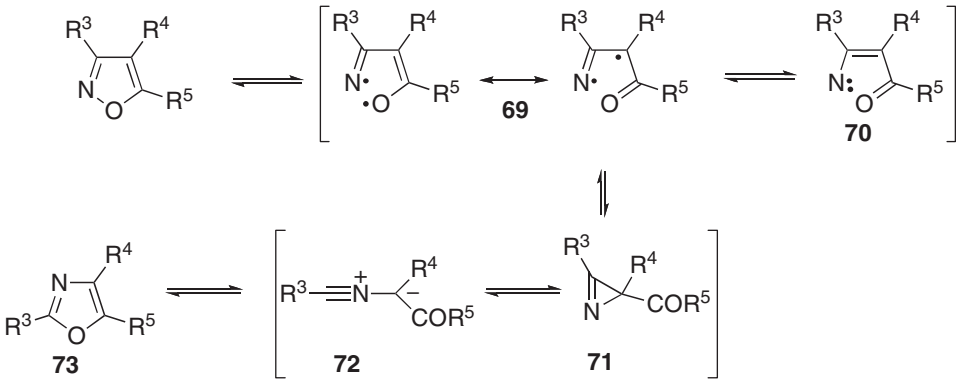


3.4.1.2.4 Rearrangement to other heterocyclic species

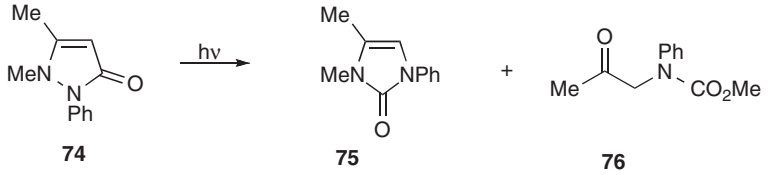
Many examples are known of rearrangement of azoles involving scrambling of the ring atoms to give a new isomeric azole molecule and some of these have been mentioned above. Various mechanisms are involved.

For isoxazoles the first step is the fission of the weak NO bond to give the diradical **69** which is in equilibrium with the vinylnitrene **70**. Recyclization now gives the substituted 2*H*-azirine **71** which, via the carbonyl-stabilized nitrile ylide **72**, can give the oxazole **73**. In some cases the 2*H*-azirine, which is formed both photochemically and thermally, has been isolated, in other cases it is transformed rapidly into the oxazole. Thermal isomerization of 4-nitro-3-phenylisoxazole derivatives to 4-nitro-2-phenyloxazoles works well by heating in xylene at 155°C in the presence of $FeCl_3SiO_2$ <1998JOC6050>.

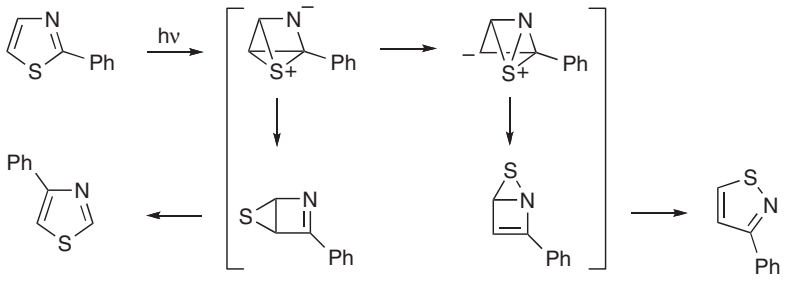
MNDO results suggest that the activation energies are similar for the gas-phase thermal isomerization of isoxazole to oxazole via either a nitrile ylide or a keteneimine, through an azirine intermediate. The first step is rate limiting, which is in good agreement with experimental results. The photorearrangement of pyrazoles to imidazoles is probably analogous, proceeding via iminoylazirines (isomerization enthalpy 42 kJ mol^{-1}); indazoles similarly rearrange to benzimidazoles.



3-Pyrazolin-5-ones e.g., **74** are photochemically converted into imidazolones e.g., **75** and open-chain products e.g., **76**. 1,2- and 1,4-Disubstituted imidazoles are interconverted photochemically.

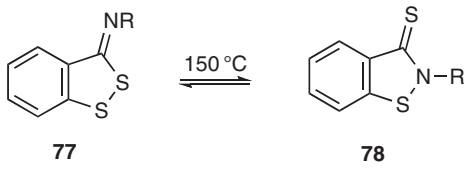


Irradiation of isothiazole gives thiazole in low yield. Irradiation of 3-, 4-, or 5-phenyl-substituted isothiazoles generates an equilibrium mixture of phenylthiazoles with the starting phenylisothiazole <2000JOC3626>. A mechanism for 2-phenylthiazole/3-phenylisothiazole/4-phenylthiazole photoisomerization is shown in **Scheme 12** <2002T8037>.

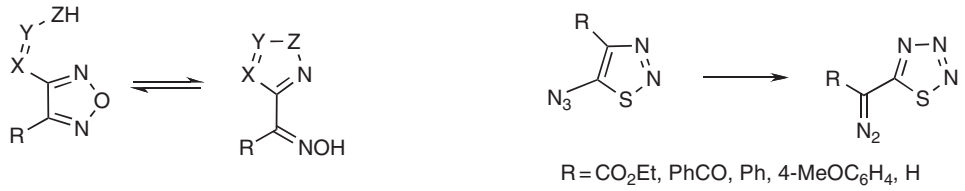


Scheme 12

Iminobenzodithioles **77** and benzoisothiazolethiones **78** thermally equilibrate.



Various 3-heteroallyl-substituted furazans undergo rearrangements in which the oxadiazole is converted into a new five-membered heterocycle bearing a hydroxyiminoalkyl group (**Scheme 13**). The role of X=YZ can be fulfilled by,

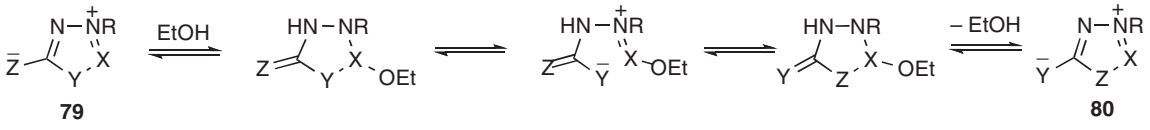


Scheme 13

for example, C═NO, C═NN, N═CN, and N═CS, yielding 3-hydroxyiminoalkyl-1,2,5-oxadiazoles, -1,2,3-triazoles, -1,2,4-triazoles, and -1,2,4-thiadiazoles, respectively.

1,2,3-Thiadiazoles rearrange to variously substituted 1,2,3-thiadiazoles. Many 5-azido-1,2,3-thiadiazoles rearrange to 1,2,3,4-thiatriazoles (**Scheme 13**).

Mesoionic compounds of the type designated as A <1976AHC(19)1> are capable of isomerism. In one case in the 1,2,4-triazole series, isomerism of the pair **79** **80** has been demonstrated.



79 **80**

3.4.1.2.5 Polymerization

lmidazoles and pyrazoles with free NH groups form hydrogen-bonded dimers and oligomers.

3.4.1.3 Electrophilic Attack at Nitrogen

3.4.1.3.1 Introduction

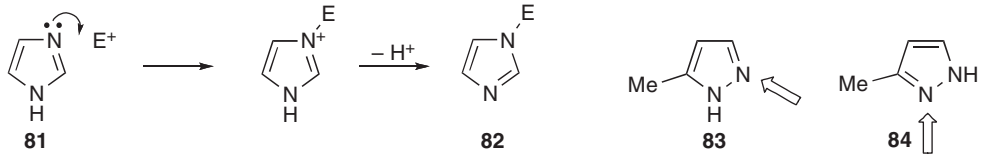
Reactions of this type can be related to the chemistry of simple tertiary aliphatic amines. Thus the lone pair of electrons on the nitrogen atom in trimethylamine reacts under mild conditions with the following types of electrophilic reagents:

1. proton acids give salts;
2. Lewis acids give coordination compounds;
3. transition metal ions give complex formation;
4. reactive halides give quaternary salts;
5. halogens give adducts;
6. certain oxidizing agents give amine oxides.

All neutral azoles contain a pyridine-like nitrogen atom and therefore reactions similar to those of electrophiles with the nitrogen of pyridines occur. However, the tendency for such reactions varies considerably; in particular, successive heteroatom substitutions markedly decrease the ease of reaction. One convenient quantitative measure of the tendency for such reactions to occur is found in the basicity of these compounds; this is treated in Sections 3.4.1.3.5 and 3.4.1.3.7.

3.4.1.3.2 Reaction sequence

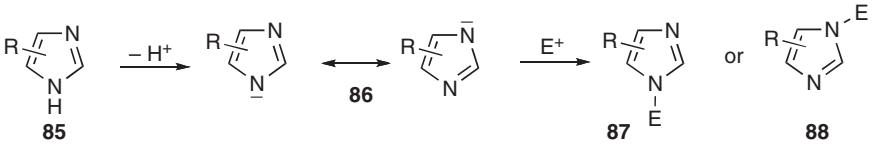
In azoles containing at least two annular nitrogen atoms, one of which is an NH group and the other a multiply bonded nitrogen atom, electrophilic attack occurs at the latter nitrogen. Such an attack is frequently followed by proton loss from the NH group, e.g., **81** **82**. If the electrophilic reagent is a proton, this reaction sequence simply means tautomer interconversion (see Section 2.4.5.1.1), but in other cases it leads to a new product.



81 **82** **83** **84**

Since the electrophilic reagent attacks the multiply bonded nitrogen atom, as shown for **83** and **84**, the orientation of the reaction product is related to the tautomeric structure of the starting material. However, any conclusion regarding tautomeric equilibria from chemical reactivity can be misleading since a minor component can react preferentially and then be continually replenished by isomerization of the major component.

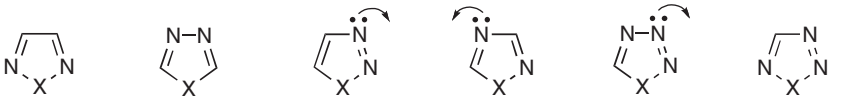
In addition to reaction sequences of type **81** **82** electrophilic reagents can attack at either one of the ring nitrogen atoms in the mesomeric anions **86** formed by proton loss (e.g., **85** **87** or **88**; see Section 3.4.1.3.6). In unsymmetrical ambident anions, the composition of the reaction product **87** + **88** is dictated by steric and electronic factors.



85 **86** **87** **88**

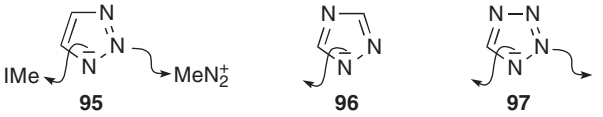
3.4.1.3.3 Orientation in azole rings containing three or four heteroatoms

These compounds contain two or three pyridine-like heteroatoms. For the symmetrical systems **89** and **90** no ambiguity occurs, but for systems **91**–**94** there are at least two alternative reaction sites. It appears that reaction takes place at the nitrogen atom furthest away from the pyrrole-like heteroatom, as shown in **91**–**93**, where evidence is available from reactions with alkylating reagents (Section 3.4.1.3.9).



89 **90** **91** **92** **93** **94**

Similar ambiguities arise in the reactions of azole anions. At least as regards alkylation reactions in the 1,2,3-triazole series **95**, the product appears to depend on the reagent used. In the 1,2,4-triazole series **96** a single product is formed, whereas tetrazole anion **97** gives mixtures.



95 **96** **97**

3.4.1.3.4 Effect of azole ring structure and of substituents

The ease of attack by an electrophilic reagent at the nitrogen atom of any azole is proportional to E between the ground state and transition state energies. However, ground-state structure largely controls the variation in these differences, which hence depend on the electron density on the nucleophilic nitrogen atom and the degree of steric hindrance. The number, orientation and type of heteroatoms are very important in determining electron density. Additional pyridine-like nitrogen atoms always reduce the electron density at another pyridine-like nitrogen (cf. the reduced basicities of diazines relative to pyridine). Unshared electron pairs on two pyridine-like nitrogen atoms can interact, but the effect on reactivity appears to be small. In the case of pyrrole-like nitrogen, oxygen, and sulfur there are two mutually opposed effects: base-strengthening mesomeric electron donation and base-weakening inductive electron withdrawal. The latter is particularly strong for oxygen and sulfur and always dominates over the base-strengthening effect.

The effects of substituents can be summarized as follows:

1. Strongly electron-withdrawing substituents (e.g., NO_2, COR, CHO) make these reactions more difficult by decreasing the electron density on the nitrogen atom(s). The effect is largely inductive and therefore is particularly strong from an - position.
2. Strongly electron-donating substituents (e.g., NH_2, OR) facilitate electrophilic attack by increasing the electron density on the nitrogen. This is caused by the mesomeric effect and is therefore strongest from - and -positions.

3. Fused benzene rings, aryl and alkyl groups, and other groups with relatively weak electronic effects have a relatively small electronic influence.

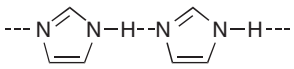
The foregoing electronic effects are illustrated by the pK_a values given in Section 3.4.1.3.5. Reactions other than proton addition are hindered by all types of -substituents. However, steric hindrance is less in the five-membered ring heterocycles than in pyridines because the angle subtended between the nitrogen lone pair and the -substituent is significantly greater in the five-membered ring compounds and thus the substituent is held further away from the lone pair.

3.4.1.3.5 Proton acids on neutral azoles: Basicity of azoles

For a general account of the basicity and acidity of azoles see <1987AHC(41)187>. Gas-phase pK_a values are discussed in Section 3.4.1.3.7.

Mesomeric shifts of the types shown in structures **98** and **99** increase the electron density on the nitrogen atom and facilitate reaction with electrophilic reagents. However, the heteroatom Z also has an adverse inductive effect; the pK_a of NH_2OH is 6.0 and that of N_2H_4 is 8.0, both considerably lower than that of NH_3, which is 9.5.

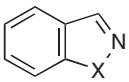
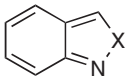
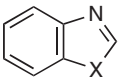
98 **99**



100

The basicities of the parent azole systems in water are shown in **Table 1**. When both heteroatoms are nitrogen, the mesomeric effect predominates when the heteroatoms are in the 1,3-positions, whereas the inductive effect predominates when they are in the 1,2-positions. The predominance of the mesomeric effect is illustrated by the pK_a value of imidazole **98** (Z = NH), which is 7.0, whereas that of pyrazole **99** (Z = NH) is 2.5 (cf. pyridine, 5.2). An *N*-methyl group

Table 1 pK_a values for proton addition

Ring systems	*X = NH*	*X = NMe*	*X = O*	*X = S*
	2.52	2.06	2.97	0.51
	6.95	7.33	0.8	2.53
	1.17	1.25		
	2.45	3.20		
	(1.17)	<1	4.9[a]	4.9
	1.31	0.42	4.7	
		2.02	2.20	0.05
	5.53	5.57	0.13	1.2

[a]For methylphenylfurazan.

is base-strengthening in imidazole, but base-weakening in pyrazole, probably because of steric hindrance to solvation. When the second heteroatom is oxygen or sulfur, the inductive, base-weakening effect increases; the pK_a of thiazole **98** (Z = S) is 3.5 and that of isoxazole **99** (Z = O) is 1.3.

The most basic sites of 2-methyl- and 1-methyltetrazole were calculated at the 6-31G level to be N(4) in both cases, with protonation energies of 220.5 and 224.1 kcal mol^{-1}, respectively. The experimental pK_a values of the conjugate acids are 2-methyltetrazole, 3.25, and 1-methyltetrazole, 3.00.

Substituents are expected to alter the electron density at the multiply bonded nitrogen atom, and therefore the basicity, in a manner similar to that found in the pyridine series. The rather limited data available appear to bear out this assumption. The additional ring nitrogen atoms in triazoles, oxadiazoles, etc. are quite strongly base-weakening; cf. diazines are weaker bases than pyridine. As regards C-substituents, their effects on the pK_a of the parent compounds are as follows:

1. Methyl groups are weakly base-strengthening due to their inductive electron donor effect: thus in the methyl thiazoles the base strengths decrease in the order $2 > 4 > 5$.
2. Phenyl groups are weak resonance donors, but inductive acceptors. Phenyl groups are therefore expected to reduce the basicity of azoles.
3. Amino groups are strong resonance electron donors and hence base-strengthening, particularly if directly conjugated with the basic center.
4. Methoxy groups are resonance donors but inductive acceptors. The inductive effect would be expected to be dominant for azoles.
5. Halogen atoms are inductive acceptors (and weak resonance donors); they are expected to cause a marked decrease in basicity, especially from -positions.
6. Fused benzene rings usually have a considerably base-weakening effect; cf. the pK_a values of imidazole and benzimidazole. Substituents on the benzene ring in benzazoles have little effect on the basicity.

Annular nitrogen atoms can form hydrogen bonds, and if the azole contains an NH group, association occurs. Imidazole **100** shows a cryoscopic molecular weight in benzene 20 times that expected. Its boiling point is 256°C, which is higher than that of 1-methylimidazole (198°C).

Hydrogen bond basicity is of much relevance to drug design. Hydrogen bond basicity has been shown to correlate with the location of the electrostatic potential local minimum along the axis of the nitrogen lone pair in a series of heterocycles. The experimental and calculated basicities for oxazole, 2,4,5-trimethyloxazole, and pyridine are shown in **Table 2**.

Table 2 Hydrogen bond basicities (log K_b)

Compound	*Experimental*	*Calculated*
Oxazole	1.67	1.91
2,4,5-Trimethyloxazole	2.65	2.59
Pyridine	2.52	2.51

3.4.1.3.6 N-Hydrogen acidity of azoles

The acidities of the five parent compounds are compared with that of pyrrole in **Table 3**. The acidity of the ring system increases as the number of nitrogens increases, the acidity of pyrrole increasing by approximately 2, 4.5, and 5 pK_a units for each successive inclusion of a nitrogen atom. 1,2,3-Triazole is slightly more acidic than 1,2,4-triazole, but the effect on NH acidity of nitrogen orientation is much less than the effect of the total number of nitrogens.

Table 3 pK_a values of azoles for proton loss

Nitrogen positions	*p*K$_a$	*Nitrogen positions*	*p*K$_a$
1	16.5	1,2,3	9.26
1,2	14.21	1,2,4	10.04
1,3	14.44	1,2,3,4	4.89

The following data show the NH acidity (water, 20 C) of some benzazoles. The benzene ring significantly increases the acidity:

Indazole pK_a 13.8
Benzimidazole pK_a 12.9
Purine pK_a 8.93
Benzotriazole pK_a 8.57

Ring substituents can have a considerable effect on the acidity of a system. In the 1,2,4-triazole series, a 3-amino group decreases the acidity to 11.1, a 3-methyl group to 10.7, whereas a 3-phenyl group increases the acidity to 9.6, and 3,5-dichloro substitution, to 5.2.

3.4.1.3.7 Basicity and acidity in gas phase

Understanding the behaviour of organic bases in solution requires some knowledge of their gas-phase (intrinsic) basicities [proton affinities (PAs)]. These can be determined by ICR methods or by variable-temperature pulsed high-pressure mass spectrometry. Both methods afford basicities termed thermodynamic versus kinetic basicity.

Some PA values (kJ mol^{1}) are imidazole, 935; 2-methylimidazole, 954; 1-methylimidazole, 950; 4-methylimidazole, 946, 2,4,5-trimethylimidazole, 975; pyrazole, 890, oxazole, and 892 (cf. pyridine, 952). Azolium ions are more sensitive to methyl substituent effects than their conjugate bases. Indeed, the effect of a methyl group on PA comes primarily (>70%) from interactions in the charged form. C-Methyl groups vicinal to the basic center N(3) confer extra stabilization because of methyl hydrogenlone pair interactions, but a methyl group at N(1) has a different influence due to partial loss of hyperconjugation. Plots of gas-phase basicity against aqueous phase basicity gives different straight lines for NH- and 1-methyl-imidazoles.

Theoretical studies of the basicity of pyrazoles, using the semiempirical approximations as well as the STO-3G and 4-31G methods have enhanced the understanding of the differences in basicity between the gas phase and the aqueous solution. To rationalize the relative gas-phase and solution basicity and acidity of pyrazole, it is necessary to take into account the lone pair/lone pair repulsion in the pyrazolate anion (6.5 kcal mol^{1}), the adjacent NH/lone pair attraction in pyrazole (1.0 kcal mol^{1}) and the NH^+/NH^+ repulsion in the pyrazolium cation (6.5 kcal mol^{1}). Solvation by water, and to a lesser extent by DMSO, modifies these values to the point that the position of the equilibria can be reversed.

The acidity and basicity in the gas phase and in aqueous solution of pyrazole, 1-methylpyrazole, indazole, 1-methyl-, and 2-methylindazole have been measured. From these data it is possible to determine the annulation effect on going from an azole to the corresponding benzazole on the gas-phase acidity (68 kcal mol^{1} increase) and on the gas-phase basicity (2 kcal mol^{1} increase). Similarly, it was shown that benzimidazole (PA = 954962 kJ mol^{1}) is protonated about 40 times faster than imidazole (PA = 934 kJ mol^{1}). The reason for the difference between gas-phase and solution basicities is mainly a function of the polarizability of the annulated ring system; this effect disappears in aqueous solution by dispersion of the positive charge through hydrogen bonds.

Although imidazole is a stronger acid than pyrazole in the gas phase (by 2.6 pK_a units) and in DMSO (by 1.3 pK_a units), pyrazole is a slightly stronger acid (by 0.2 pK units) in aqueous solution. This can be explained in terms of the equilibrium shown in **Scheme 14**. In the gas phase, electrostatic repulsion between adjacent lone pairs of electrons shifts the equilibrium to the left.

Scheme 14

Calculated protonation energies of azoles can be used as measures of basicity where the protonation energy is calculated as the difference between the energy of the azole molecule and the most stable protonated species. *Ab initio* calculations at 6-31G*//6-31G level give the following protonation energies for the azole series: imidazole, 210.1 (318) kcal mol^{1}; pyrazole, 227.0 (312); 4*H*-1,2,4-triazole, 231.8 (307); 1*H*-1,2,4-triazole, 225.1 (300); 2*H*-tetrazole, 209.6 (294); and 1*H*-tetrazole, 213.4 (293). The data follow the reverse order of the ionization potentials and suggest that the protonation energy of an azole is related to the energy of ionizing an electron from the -framework of the molecule.

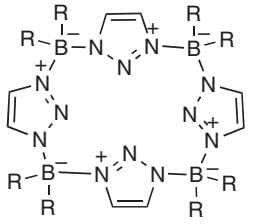
Tetrazoles are the weakest bases among the azoles. Protonation of both 1*H*- and 2*H*-tetrazole is predicted to occur at N (4).

3.4.1.3.8 Metal ions

3.4.1.3.8.1 Simple complexes. Many examples are known of complexes between metal cations and both neutral azoles and azole anions. Azoles can form stable compounds in which metallic and metalloid atoms are linked to nitrogen. For example, pyrazoles and imidazoles N-substituted by B, Si, P, Ga, Ge, Sn, and Hg groups are made in this way. Overlap between the d-orbitals of the metal atom and the azole -orbitals is believed to increase the stability of many of these complexes.

Despite the weak basicity of isoxazoles, complexes of the parent methyl and phenyl derivatives with numerous metal ions such as copper, zinc, and cobalt. have been described. Many transition metal cations form complexes with imidazoles; the coordination number is four to six. The chemistry of pyrazole complexes has been especially well studied for example dioxomolybdenum and dioxotungsten compounds containing sterically demanding pyrazolate ligands are synthesized by treatment of dioxometal halides with the potassium salts of 3,5-di-*tert*-butylpyrazole (*t*-Bu_2pzH) and 3,5-di-*tert*-butyl-4-bromopyrazole (*t*-Bu_2-4-BrpzH) giving products such as [$MoO_2Cl(^2$-*t*-Bu_2pz)] and [$MoO_2(^2$-*t*-Bu_2pz$)_2$] <2005ASC463>. Coordination compounds are also known with thiazoles and 1,2,4-triazoles. Tetrazole anions are good ligands for heavy metals. Isothiazoles react with hexacarbonyls $M(CO)_6$ to give N-coordinated $M(CO)_5$ derivatives.

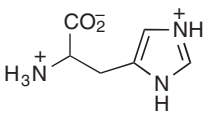
In transition-metal derivatives of triazoles and benzotriazoles, the generally preferred coordination positions appear to be N(3) for 1,2,3-triazoles and N(1) for triazolate anions. When 1-(trimethylsilyl)-1,2,3-triazole is treated with halodiorganylboranes R_2BX (X = Br, Cl), a cyclic tetramer **101** is obtained exclusively.



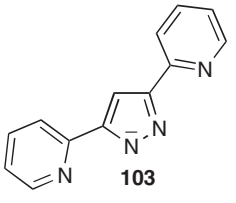
101

3.4.1.3.8.2 Chelate complexes. Chelate rings can be formed by azoles containing -substituents such as *o*-hydroxyphenyl, carbonyl, or CH═NH groups. An important bidentate chelating agent is histidine **102**, and many pyrazoles with substituent groups are known which form bis and tris complexes with many metals, e.g., **103**. Similarly, 2- and 4--pyridylthiazoles are bidentate chelating agents. Complex formation of this type has analytical applications; thus, 1,3,4-thiadiazole-2,5-dithione has been used as a spot test for bismuth and other metals. Especially important are a series of poly(1-pyrazolyl)borates ligands (scorpionates) which are well established, versatile, and easily accessible ligands in coordination chemistry, with widespread applications ranging from analytical chemistry to homogeneous catalysis and materials science, e.g., <2000JCD3136, 2003EJI2475, 2003JA3768>.

The ability of tetrazoles to form stable complexes with metal ions has been known for a long time and still attracts much attention <1994RCR797, 2005CCR1201>. High-energy coordination compounds of nitrogen-rich tetrazolate anions (5-nitrotetrazolate, *N*,*N*′-bistetrazolatohydrazine, etc.) with Co(III), Ni(III), Ba(II), and Zn(II) ions have been suggested as effective lead-free safe primary explosives and gas generators <2001RJC664, 2003ZFA2117>.



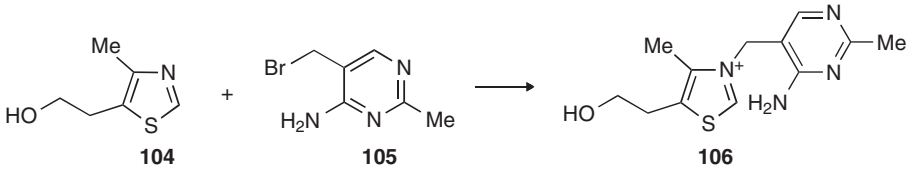
102



103

3.4.1.3.9 Alkyl halides and related compounds: Azoles without a free NH group

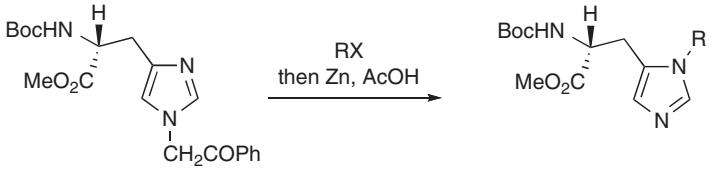
Pyrazoles and imidazoles carrying a substituent on nitrogen, as well as oxazoles, thiazoles, etc., are converted by alkyl halides into quaternary salts. This is illustrated by the preparation of thiamine **106** from the thiazole **104** and bromide **105**.



Azoles having heteroatoms in the 1,3-orientation are more reactive than those in which the arrangement is 1,2. However, the magnitude of the factor varies, thus oxazole is 68 times more reactive than isoxazole, whereas benzoxazole quaternizes 26 times faster than does 1,2-benzisoxazole.

These reactions are of the S_N2 type and are sensitive to steric effects of substituents in the azole ring. However, these steric effects are significantly less than, for example, in the analogous pyridine derivatives because the angle subtended by the nitrogen lone pair and an -substituent is about 70 in an azole as opposed to 60 in pyridine. Thus the rate constant for methylation of 2-*t*-butylthiazole by methyl iodide is only 40 times less than that for the corresponding 2-methyl compound. By comparison, in the pyridine series the retardation factor is over 2000.

The quaternization of 1-substituted imidazoles is usually easy unless steric factors intervene, or strongly electron-attracting groups are present, for example, 1-acylimidazoles can only be alkylated at N(3) with powerful alkylating agents such as methyl fluorosulfonate or trialkyloxonium fluoroborates. Trimethyloxonium fluoroborate does not methylate 1-dimethylaminosulfonylimidazole. Regiospecific synthesis of 3-substituted L-histidines can be achieved by alkylation of *N*-*t*-butoxycarbonyl-1-phenacyl-L-histidine methyl ester at N(3), followed by reductive removal of the phenacyl group (**Scheme 15**).



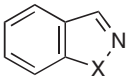
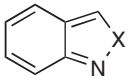
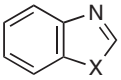
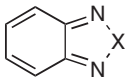
Scheme 15

Certain quaternary salts of imidazoles have become important as ionic liquids, in particular salts of 1-butyl-3-methylimidazolium (bmim). Preparation of imidazolium-containing ionic liquids, in the desired product ionic liquid as a solvent, is a virtually solvent-free, one-pot process proceeding in good to excellent yields <2003S2626>. There are also microwave-assisted, solvent-free processes for the preparation of imidazolium-based ionic liquids <2001CC643, 2003GC181>.

Annulation of a five-membered aza ring to a benzo ring generally leads to a rate retardation in N-quaternization reactions similar in magnitude to that for six-membered rings. Exceptions are known: 2,1-benzisoxazole undergoes N-methylation faster than isoxazole, and in 2,1,3-benzoxadiazole and 2,1-benzisothiazole the rates are little changed from the corresponding monocyclic rings; however, here we are dealing with *o*-quinonoid structures. The more usual situation is rate retardation by a moderate amount. This is probably caused not by steric effects, but by electronic effects, as is shown by a corresponding influence on the pK_a values. Satisfactory Br—nsted correlations for -substituted azoles offer further evidence of the lesser importance of steric effects in the azole series.

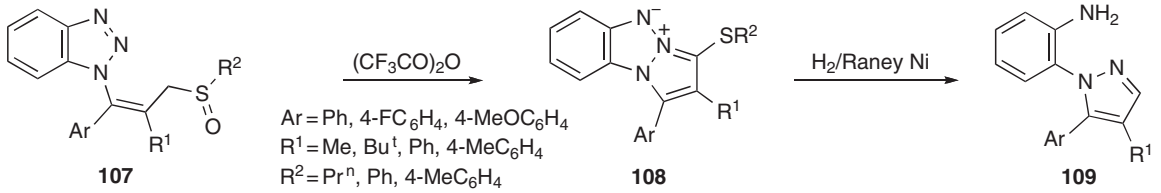
For both azole and benzazole rings the introduction of further heteroatoms into the ring affects the ease of quaternization. In series with the same number and orientation of heteroatoms, rate constants increase in the order X = O < S < NMe (cf. **Table 4**). 5-Chloroisoxazoles, can be methylated with methyl triflate <2003TL9247>. The quaternization of triazoles, thiadiazoles, and tetrazoles requires stronger reagents and conditions, for example, 1- or

Table 4 Heteroatom and benzo-fusion effects on relative rate constants for N-methylation

	k_{rel}		
Heterocycle	*O*	*S*	*NMe*
	1	6.9	120
	1	15	912
	1	20	56
	1	3.6	33
	1	9.3	708
		2.8	1

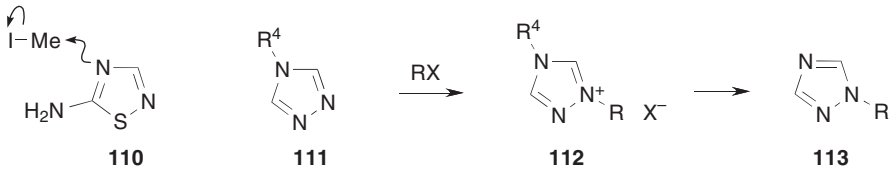
2-substituted 1,2,3-triazoles are difficult to alkylate, but methyl fluorosulfonate succeeds. The alkylation of N(1)-substituted tetrazoles generally produces mixtures of 1,4-disubstituted and 1,3-disubstituted tetrazolium salts. N(2)-Substituted tetrazoles can be alkylated only at N(4) to give 1,3-disubstituted tetrazolium salts.

Intramolecular alkylation at N(2) of benzotriazole derivative **107** results from Pummerer reaction giving salt **108** which, on hydrogenolysis, leads to *N*-arylpyrazole **109** <2002EJO493>.



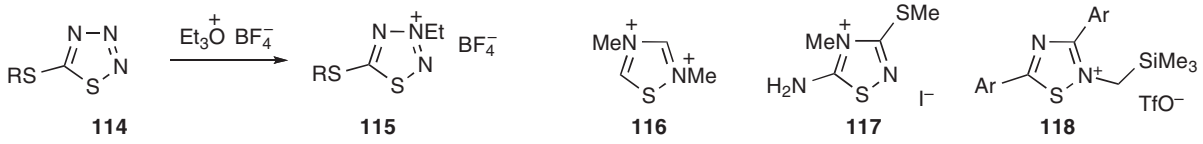
Oxadiazoles are difficult to alkylate. However, *N*-methylfurazinium salts are formed on heating furazans with dimethyl sulfate; the reaction is approximately 7 and 62 times slower, respectively, than the corresponding methylations of 1,2,5-thiadiazole and isoxazole. The *N*-ethyl salts of furazan itself and 3-phenylfurazan have been prepared using triethyloxonium tetrafluoroborate.

1,2,3-Thiadiazoles are quaternized to give 3- or mixtures of 2- and 3-alkyl quaternary salts <1993JHC301>. In 5-amino-1,2,4-thiadiazole, quaternization takes place at the 4-position **110**. 1-Substituted 1,2,4-triazoles are quaternized in the 4-position, and 4-substituted 1,2,4-triazoles are quaternized at the 1- or the 2-position. Treatment of 4-alkylated 1,2,4-triazoles **111** with a catalytic amount of the alkylating halide at 150180°C gives the corresponding 1-alkylated triazole **113**. The reaction seems to proceed via an intermediate quaternary salt **112** that is then dealkylated to the thermodynamically more stable isomer. Similarly, 1-alkyl-5-phenyltetrazoles are converted into 2-alkyl isomers on heating with alkyl iodide.



110 111 112 113

5-Alkylthio 1,2,3,4-thiatriazoles **114** are alkylated only under very forcing conditions with triethyloxonium fluoroborate, but then give products **115**.

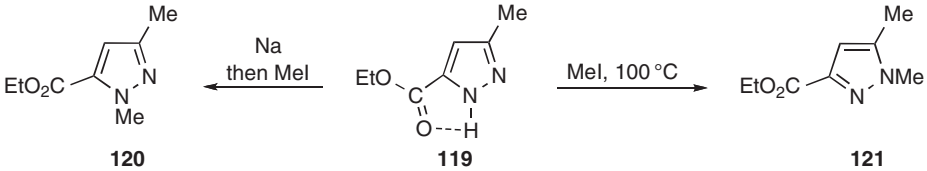


114 115 116 117 118

1,2,4-Thiadiazole with $Me_3O^+BF_4$ gives the diquaternary salt **116**; diquaternary salts are also known in the 1,2,4-triazole series. 5-Amino-3-methylthio-1,2,4-thiadiazole methylates at N(4) giving salt **117** <2001CHE1005>; 3,5-diaryl-1,2,4-thiadiazoles react with trimethylsilylmethyl triflate at N(2) to afford salts **118**; 3,4-diphenyl-1,2,5-thiadiazole reacts with the same reagent at N(2) <1999J(P1)1709> and 2,5-diphenyl- and 2,5-dimethyl-1,3,4-thiadiazoles also gives salts with TMS triflate, by reaction at N(3) <1999J(P1)1709>.

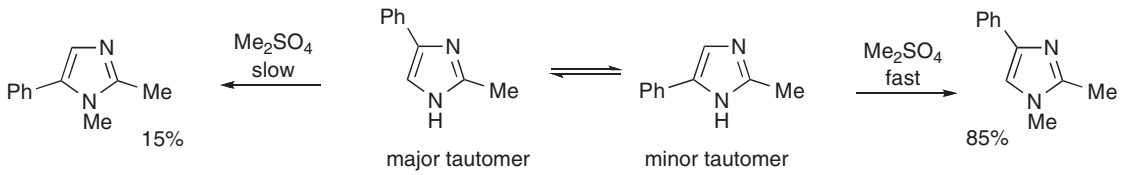
3.4.1.3.10 Alkyl halides and related compounds: Compounds with a free NH group

Pyrazoles and imidazoles with free NH groups are readily alkylated, e.g., by MeI or Me_2SO_4. Dipolar aprotic solvents, especially acetone and dimethylsulfoxide, have found wide application since they strongly enhance the nucleophilicity of N-anions. Direct microwave heating is also advantageous <1998JHC1263> as is the use of sintered silicon carbide (SiC) as a chemically inert and strongly microwave absorbing material (passive heating element) <2006JOC4651>. A useful procedure is to use the sodium salt of the azole. Benzyl halides react well with pyrazole and indazole using cesium fluorideCelite in acetonitrile <2001T9951> and deprotonation of indazole with NaH allows alkylation with dibromodifluoromethane, a 1:0.75 mixture of 1- and 2-difluorobromomethyl derivatives resulting <2000JFC181>. Alkylation of NH-azoles under neutral conditions is preferable for alkylating agents that are unstable toward strong bases ($MeOCH_2Cl$, $PhCOCH_2Br$, Ph_3CCl, etc.). In some instances, e.g., in preparation of 1-tritylimidazole, the use of the silver salt of the azole in an inert solvent is also recommended. There are very few examples of alkylation of azoles with *tert*-butyl halides in aprotic media. The yield of 1-*tert*-butylimidazole is low because of a strong tendency for an E_2-elimination process. Efficient and regioselective syntheses of 2-methyl- and 2-ethyl-2*H*-indazoles are accomplished with trimethyloxonium tetrafluoroborate or with triethyloxonium hexafluorophosphate, respectively, at room temperature <2003JOC4093>. *N*-(2-Hydroxyethyl)pyrazoles can be prepared efficiently from the regioselective ring opening of epoxides <2004TL5697>. Unsymmetrical imidazoles and pyrazoles usually give a mixture of products, the composition of which may depend on the reaction conditions. Thus, the pyrazole ester **119** gives the isomeric *N*-methyl derivatives **120** and **121** under the conditions indicated. The difference in orientation can be related to the stabilization of the tautomeric structure **119** by hydrogen bonding (possibly intramolecular as shown), which means that alkylation of the free base gives **121**. The isomer **120** is formed via the anion.



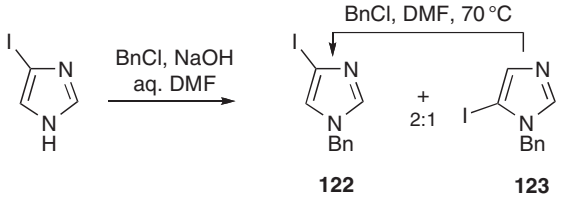
120 119 121

The differential effects of steric hindrance and tautomeric content in the imidazole series are illustrated in **Scheme 16**.



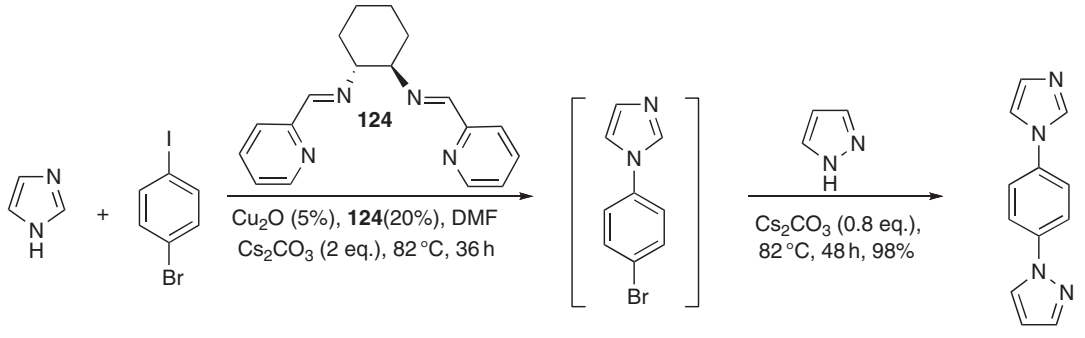
Scheme 16

Benzylation of 4(5)-iodoimidazole gives a mixture; however, heating with the benzyl halide converts the 1,5-isomer **123** into the less hindered 1,4-isomer **122** (**Scheme 17**). This is interpreted as further N-benzylation of **123** followed by debenzylation of the bisalkylated product to form **122** <2004TL5529>. This isomerization approach also works with MOMCl, SEMCl, BnCl, and MeI, to form exclusively 1,4-disubstituted imidazoles <2004TL5529>.



Scheme 17

N-Arylation of pyrazoles and imidazoles employs various metal-assisted processes: for pyrazoles, an arylboronic acid with copper(II) acetate (indazole gave 1- and 2-aryl derivatives in a ratio of 9:2) <1998TL2941>; aryl iodide with proline and copper <2004SL128> (also for imidazoles <2005JOC5164>) or copper with an oxime phosphine oxide ligand <2005T6553>; for imidazoles and benzimidazoles, $(CuOTf)_2$-benzene with 1,10-phenanthroline, Cs_2CO_3, and dibenzylideneacetone (dba) <1999TL2657>, catalytic CuI and aryl iodides <2001JA7727, 2004JOC5578>, polyethyleneglycol (PEG) with 4,7-dimethoxy-1,10-phenanthroline and Cs_2CO_3 for copper-catalyzed N-arylation <2006OL2779>, and salicylaldehyde Schiff bases with Cu_2O <2004CEJ5607>. Heterogeneous catalytic systems comprising zeolite- and FAP-supported copper complexes are also rather effective for the N-arylation of imidazole and benzimidazole <2006SL2195, 2006TL3897>, with no additional organic ligands required. Other ligandless catalysts for Ullmann-type reactions use CuO or Cu_2OCu nanoparticles <2003OL4847, 2004CC778>. Benzotriazole reacts selectively at N(1) with iodoarenes using CuI complexed with *trans*-1,2-bis(methylamino)cyclohexane as ligand <2004JOC5578>. N-Arylation of 5-phenyltetrazole with bis-(4-methoxyphenyl)iodonium bromide in the presence of Et_3N yields only the N(2)-isomer <2001CHE372>. It is even possible to differentiate halides, as shown in **Scheme 18** <2004CEJ5607>.



Scheme 18

Benzynes react with imidazoles to give *N*-arylimidazoles. 1-(4-Nitrophenyl)azoles are obtained in good yields by direct arylation of the corresponding azole with *p*-fluoronitrobenzene using PTC without a solvent. 1,2,4-Triazole gives a 10:1 mixture of 2-[1,2,4]-triazol-1-ylbenzonitrile and the corresponding 4-isomer on reaction with 2-fluorobenzonitrile with Cs_2CO_3, DMF at 50°C <2004JME2995>; with 2,5-dichlorobenzonitrile only 5-chloro-2-[1,2,4]triazol-1-ylbenzonitrile is formed, in quantitative yield <2004JME2995>. Hexa(pyrazol-1-yl)benzene is easily prepared from hexafluorobenzene and the pyrazolyl anion.

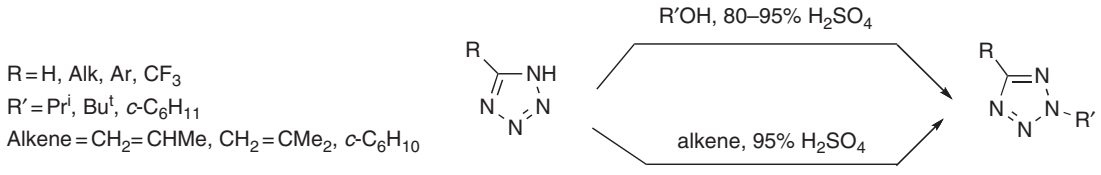
N-Alkylation of 1,2,3-triazoles and benzotriazoles is readily achieved using (1) alkyl halides, dialkyl sulfates, diazoalkanes, and *p*-tosylates or (2) the Mannich reaction. When alkyl halides are used, sodium alkoxide, sodium hydride, or sodium hydroxide is usually employed as the base. The N-alkylation of benzotriazole with alkyl halides proceeds efficiently using powdered NaOH as the base in DMF. The highest yields (80100%) of the alkylated benzotriazoles are obtained when a fourfold excess of NaOH is employed. *N*-Alkylbenzotriazoles have been prepared from benzotriazole and alkyl halides using phase-transfer catalysts, e.g., KOH, benzene, tetrabutyl-ammonium salts or KOH, benzene, polyethylene glycol.

N-Unsubstituted 1,2,3-triazoles are methylated to give mainly 1-methyl products with methyl iodide and silver or thallium salts, but mainly at the 2-position by diazomethane. There is also some steric control, for example, 4-phenyl-1,2,3-triazole with dimethyl sulfate gives the 2-methyl-4-phenyl (38%) and 1-methyl-4-phenyl isomers (62%), but none of the more hindered 1-methyl-5-phenyl-1,2,3-triazole. Diazomethane methylates tetrazoles giving a mixture of 1- and 2-methyl products <2000H1421>. 4-Nitro-1,2,3-triazole reacts with propargyl bromide in the presence of KOH giving a mixture of isomeric 1-propargyl-4-nitro- and -5-nitro-1,2,3-triazoles in equimolar ratio <2003RJO1792>. However, in acidic media, when N(1) and N(3) are protonated, 2-substituted derivatives of 1,2,3-triazole are formed. Thus, isopropyl alcohol reacts with 1,2,3-triazole in 95% sulfuric acid to provide 2-isopropyl-1,2,3-triazole in 80% yield <2002JHC1111>.

N-Unsubstituted 1,2,4-triazoles under a variety of conditions give 1-alkyl- and 4-alkyl-1,2,4-triazoles always in the approximate ratio of 9:1 <2000TL1297>. Benzotriazole gives mixtures of 1- and 2-products in general, but greater selectivity is achieved using ionic liquids as media <2004H(63)1077>. Benzotriazole can also be N-alkylated conveniently with microwave heating using no solvent <2003T865>.

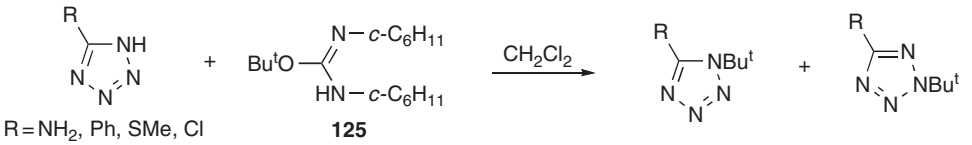
Alkylation of tetrazoles as the tetrazolate anions gives mixtures of 1- and 2-alkyl isomers <1998SL528, 2000H1421>. In general, electron-donating substituents at the 5-position slightly favor alkylation of the 1-position and electron-withdrawing 5-substituents slightly favor the 2-position. Nonpolar solvents generally favor N(2) alkylation of 5-aryltetrazoles while polar solvents favor attack at N(1).

N-Unsubstituted tetrazoles react with a wide range of secondary and tertiary alcohols, or the corresponding alkenes, in sulfuric acid giving 2-alkyltetrazoles (**Scheme 19**) <2000H1421>, examples include diacetone alcohol, <1999CHE1078>, dimethyl-2,5-hexandiol <2000CHE326>, 1-adamantanol <1997RJO571, 1999RJO1069, 2004RJC752>, and triphenylmethanol <2001RJO1670>. Direct alkylation of 5-substituted tetrazoles with *t*-butyl alcohol in the presence of conc. H_2SO_4 gives high yields of 2-*t*-butyltetrazoles with a small amount of 1-*t*-butylation in the case of 5-methyltetrazole. With -methylstyrene in the presence of trichloroacetic acid, 2-(,-dimethylbenzyl) tetrazoles are formed in high yields <1999JOC9301, 2004RJO551> but benzotriazole adds to styrene in the presence of TsOH, giving a mixture of 1- and 2-(1-phenethyl) products <1995J(P2)1645>. Tetrazoles can also be N-alkylated, again giving 1- and 2-alkyl mixtures, using the Mitsunobu protocol <1996SC2687> and benzotriazole is regioselectively N(1)-alkylated with alcohols in the presence of Ph_3P and NBS <1997SC1613>.



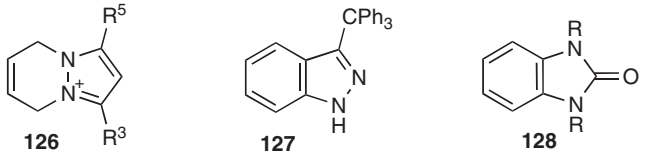
Scheme 19

Alkylation of N-unsubstituted tetrazoles with *O-tert*-butyl-*N*,*N*-dicyclohexylisourea **125** provides mixtures of isomeric 1- and 2-*tert*-butyltetrazoles and seems to be the only practical method for the synthesis of 1-*tert*-butyltetrazoles (**Scheme 20**) <1976JHC391>.



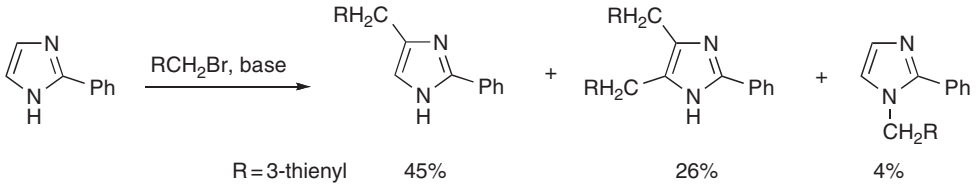
Scheme 20

Polyhalogenoalkanes and dihalogenoethanes have been extensively used to prepare, under PTC conditions, poly(pyrazol-1-yl)alkanes (number of pyrazoles = 2,3,4) and 1,2-di(pyrazol-1-yl)ethanes. The reaction of both nitrogen atoms with a double alkylating agent has been extended to the reaction with *cis*-1,4-dichlorobut-2-ene to afford salt **126**.



The reaction of indazole with trityl chloride yields, together with expected 1- and 2-substituted derivatives, 3-tritylindazole **127**, i.e., the C-substitution product.

A number of 2-substituted imidazoles are also C-alkylated by soft electrophiles at C(4)/C(5). Thus, 2-phenylimidazole reacts with 3-thienylmethyl bromide to give mainly 4- and 4,5-di-substituted products; N-alkylation occurs only to a minor extent (**Scheme 21**). Similarly, 2-methoxybenzyl chloride gives rise mainly to C-substituted products; benzyl bromide, a harder electrophile, gives largely *N*-benzyl derivatives.

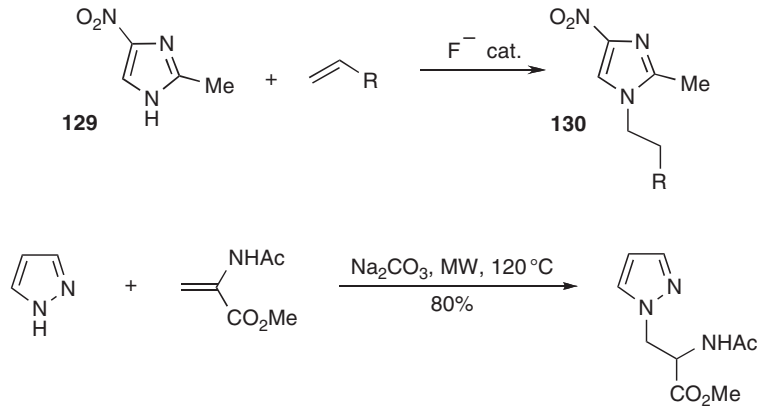


Scheme 21

Azolone anions are readily alkylated at nitrogen, e.g., benzimidazol-2-one **128** (R = H) with alkyl halides gives the 1,3-alkyl derivatives **128** (R = Alk).

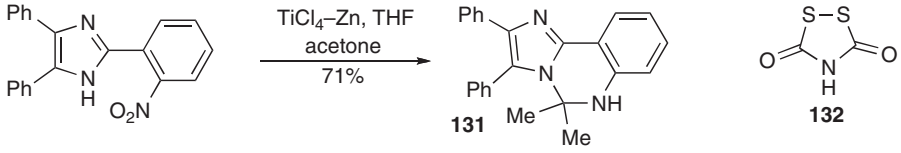
N-Unsubstituted pyrazoles and imidazoles add to unsaturated compounds in Michael reactions; for example, acetylenecarboxylic esters and acrylonitrile readily form the expected addition products. Benzotriazole will similarly add to activated allenes <2006T3710>.

Some Michael additions of imidazoles to unsaturated reagents involve the neutral heterocycles, but others may be reactions of the anion. Fluoride ion-catalyzed addition of 2-methyl-4-nitroimidazole **129** to a suitable Michael acceptor gives almost quantitative yields of the 1-substituted 4-nitroisomers **130**. **Scheme 22** illustrates the use of microwave heating in such processes <2001T5421>.



Scheme 22

Benzimidazole reacts with formaldehyde and secondary amines in a Mannich reaction to give 1-aminomethyl products. Intramolecular Mannich reactions at ring nitrogen can produce bicyclic products, for example, **131** in **Scheme 23** <2005JHC173>.



Scheme 23

N-Alkylation of saccharin can be achieved with KF in ionic liquid (bmim)PF_6 <2004JCR276>. For N-arylation of saccharin one can use cupric acetate with a triarylbismuth <1996TL9013>, *p*-tolyllead triacetate <1996JOC5865>, or an arylboronic acid in the presence of an oxidant <1998TL2933, 2001TL3415>.

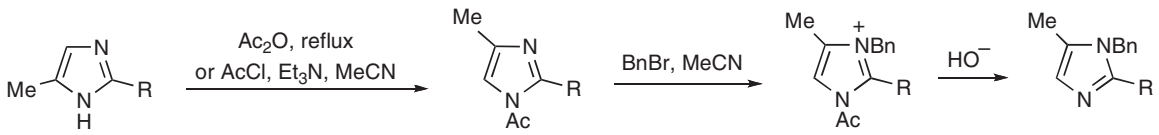
The remarkably high acidity of 1,2,4-dithiazolidine-3,5-dione **132** ($pK_a = 2.8$) <2000SL1622> means that it can be used in modified Mitsunobu N-alkylations <2002J(P1)2046, 2005T2141>; similarly, though stronger bases can be used, $NaHCO_3$ is all that is required for N-alkylations of **132** with halides <2000SL1622, 2003OBC3015>.

3.4.1.3.11 Acyl halides and related compounds

Azoles containing a free NH group react comparatively readily with acyl halides. *N*-Acyl-pyrazoles, *N*-acyl-imidazoles, etc. can be prepared by reaction sequences of either type **81** **82** or type **85** **87** or **88**. Such reactions have been carried out with benzoyl halides, sulfonyl halides, isocyanates, isothiocyanates, and chloroformates. Reactions occur under SchottenBaumann conditions or in inert solvents. Alkyl pyrazole-1-carboxylates, readily prepared using an alkyl chloroformate, pyrazole with Et_3N, are useful alkoxycarbonylating agents toward Grignard reagents or amines <1998T14679>.

When two isomeric products could result, only the thermodynamically stable one is usually obtained because the acylation reactions are reversible and the products interconvert readily. Thus, benzotriazole forms 1-acyl derivatives that preserve the KÕkulÕ resonance of the benzene ring and are therefore more stable than the isomeric 2-acyl derivatives. Similar reaction with 2-chloropyridine also takes place at N(1) <2006OL415>. Acylation of pyrazoles also usually gives the more stable isomer as the sole product. The imidazole-catalyzed hydrolysis of esters can be classified as an electrophilic attack on the multiply bonded imidazole nitrogen.

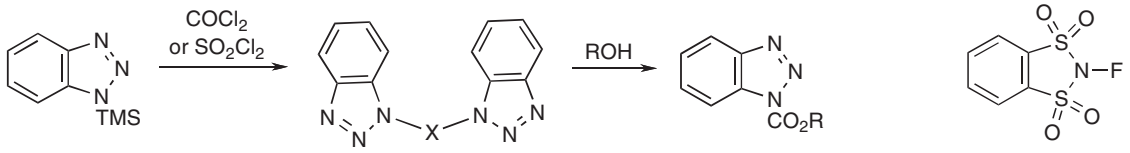
Since N-acylation is a reversible process, it has allowed the regiospecific alkylation of, for example, imidazoles to give the sterically less favored derivative. This principle is illustrated in **Scheme 24** (see also **Scheme 15**).



Scheme 24

1,2,3-Triazoles are acylated with acyl halides, usually initially at the 1-position, but the acyl group may migrate to the 2-position on heating or on treatment with base. Thus acetylation with acetyl chloride often gives 1-acetyl derivatives, which rearrange to the 2-isomers above 120°C.

The more general preparations of *N*-acyltriazoles and *N*-acylbenzotriazoles have utilized acid chlorides in reactions with 2-trimethylsilyl-1,2,3-triazole, 1-(trimethylsilyl)benzotriazole **133** or 1-(tributylstannyl)benzotriazole. Thus **133** reacts with phosgene or sulfuryl chloride to give 1,1-carbonyl- **134** and 1,1-sulfonyl-di(benzotriazole) **135**. Treatment of **134** with an alkanol affords 1-alkoxycarbonylbenzotriazoles **136**.



133 **134** X = CO; **135** X = SO_2 **136** **137**

Whether tetrazoles are acylated at the 1- or 2-position depends on the 5-substituent <2003EJO885>. 2-Acyltetrazoles are unstable (see Section 3.4.3.12.4); 1-alkylsulfonyltriazoles are also unstable (see Section 3.4.1.2.3).

3.4.1.3.12 Halogens

At room temperature, N-unsubstituted azoles react with halogens and interhalogens (e.g., ICl) to give *N*-haloazoles, probably via unstable adducts. Thus imidazoles with halogens form *N*-halo compounds, which easily rearrange to form *C*-haloimidazoles. *N*-Halopyrazoles are unstable and act as halogenating agents. *N*-Halo-1,2,4-triazoles are more easily isolated, especially when the 3,5-positions are substituted. *o*-Benzenedisulfonimide (1,3,2-benzodithiazole 1,1,3,3-tetraoxide) is efficiently N-fluorinated by reaction with F_2 in N_2 <1995JOC4730> and this stable product **137** is a reagent of choice for the electrophilic fluorination of carbanions, enolates, enols, and silyl enol esters.

Benzotriazole can be chlorinated at N(1) by NaOCl. 1-Chlorobenzotriazole is a rather stable crystalline compound that has found application in organic synthesis as a selective chlorinating reagent and mild oxidant. N-Fluorination of benzotriazole with cesium fluoroxysulfate gives 1-fluorobenzotriazole.

Correlations between pK_a values and the equilibrium constants for the formation of iodine complexes with imidazoles suggest that the charge transfer complexes are of the *n*-type involving donation of the unshared electron pair at N(3). Examples of K_{CT}^{298} and corresponding pK_a values are: imidazole, 202, 6.95; 1-methylimidazole, 333, 7.33; 4-phenylimidazole, 152, 6.10; and 4,5-diphenylimidazole, 141, 5.90.

3.4.1.3.13 Peracids

Azaaromatic systems are usually oxidized to their *N*-oxides. Peracetic acid is the oxidant most used though for unstable substrates perbenzoic or perphthalic acids are preferable; these permit the use of nonpolar solvents and milder conditions. Heterocycles relatively inert to oxidation can be converted into *N*-oxides by the more active performic or trifluoroperacetic acids. *m*-Chloroperbenzoic acid (MCPBA) also gives good results, especially when other easily oxidizable groups are present in a heterocyclic molecule and therefore the question of selectivity is important.

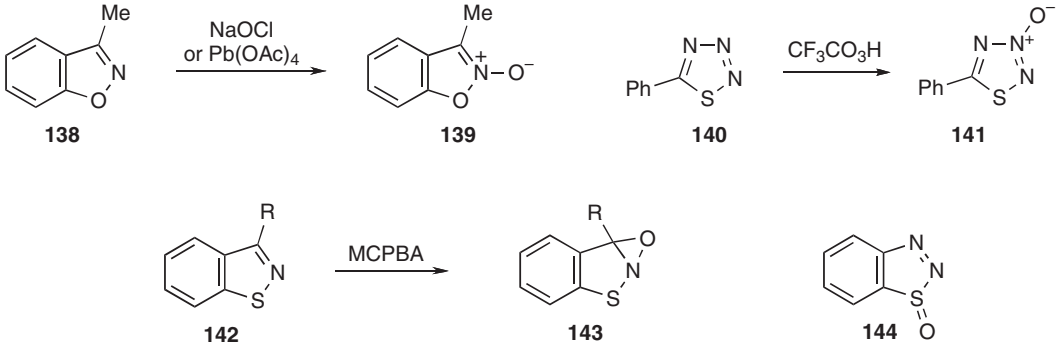
N-Oxidation proceeds on the free base form of heterocycles; in strongly acidic media the substrate exists mainly in the protonated form and this reaction does not occur. Under strongly alkaline conditions the oxidation is hampered because of conversion of the peracid into an unreactive anion.

N-Oxidation can be formally considered a quaternization of a pyridine-type nitrogen atom by the HO^+ cation, formed by heterolysis of OO bond in the peracid molecule. Indeed, common features exist between N-alkylation and

N-oxidation: both reactions are second order (first order in each reagent). The reaction constant, , for oxidation of 3- and 4-substituted pyridines by $PhCO_3H$ in aqueous dioxane is 2.35, close to the value for N-alkylation.

Despite the rather high basicity of imidazole and benzimidazole, attempts to prepare their *N*-oxides by direct oxidation are unsuccessful. Peracids destroy imidazole, depending on the reaction conditions, to give oxamide or urea and ammonia. Oxidation of benzimidazole leads to formation of imidazole-4,5-dicarboxylic acid in low yield. The attempted conversion of oxazoles into *N*-oxides fails and leads to ring opening. Oxidation of other azoles also rarely gives the corresponding *N*-oxides (see below). One can assume that the different ease of N-oxidation of azines and azoles follows the different nature of their highest occupied molecular orbital (HOMO). In the case of the azines, the HOMO is of the *n*-type, therefore the nonbonded electron pair of the nitrogen atom is most available for coordination with an electrophile. By contrast the HOMO of azoles is believed to be a -orbital. In this case an oxidant most likely first removes from the substrate a single -electron, thus forming a radical cation that undergoes subsequent reactions, e.g., nucleophilic attack of peroxide anion with further formation of azolones or ring-cleaved derivatives.

Nevertheless, in some azoles the energies of n- and upper -orbitals are probably comparable and in such cases *N*-oxide formation is observed. Thus, 1-methylpyrazole is oxidized by peracetic acid to the 2-oxide in 10% yield. 1-Substituted 1,2,3-triazoles are oxidized by MCPBA at N(3) to give the corresponding triazole *N*-oxides. The yield is lower if an electron-withdrawing substituent is present at C(4) or C(5). 1-Alkylbenzotriazoles give N(3)-oxides using dimethyldioxirane <2001JOC5585>. Ethyl tetrazole-5-carboxylate is oxidized by Oxone (potassium peroxymonosulfate, $2KHSO_5$, $KHSO_4$, K_2SO_4) in aqueous acetone at pH 7.5 producing ethyl 2-hydroxytetrazole-5-carboxylate in 80% yield <1999TL6093>. Reaction of 3-methylbenzisoxazole **138** with sodium hypochlorite or lead tetraacetate gives the 2-oxide **139**.



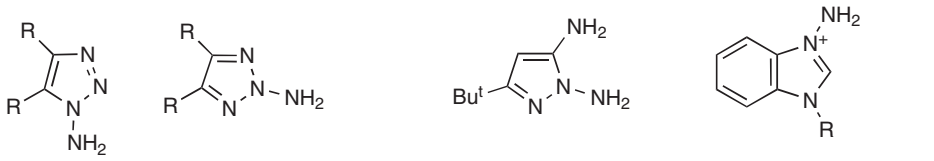
138 **139** **140** **141** **142** **143** **144**

The oxidation of thiazoles by peroxy acids leads to the corresponding *N*-oxides. Peracetic, MCPBA, permaleic, and trifluoroperacetic acid have been employed for this reaction. The more basic thiazoles produce higher yields. Thus, thiazole, 2,4-dimethyl- and 4,5-dimethylthiazoles, and 2-phenylthiazole can be oxidized in moderate to good yields. However, neither 4-chloro-2-phenylthiazole nor 5-chloro-2-phenylthiazole can be thus oxidized. 3-Oxides are also obtained by oxidation of 1,2,3-thiadiazoles and 5-phenylthiatriazole (**140** **141**).

Oxidation of sulfur-containing azoles quite often leads to the formation of sulfones and sulfoxides. Thus, 3-alkyl-1,2-benzisothiazoles **142** with MCPBA give the oxaziridines **143**, and the use of a chiral 3-alkyl substituent leads to pure diastereomers. Reaction of 1,2,3-benzothiadiazole with 30% hydrogen peroxide in a mixture of acetic acid and methanol for 45 days affords **144** in 60% yield.

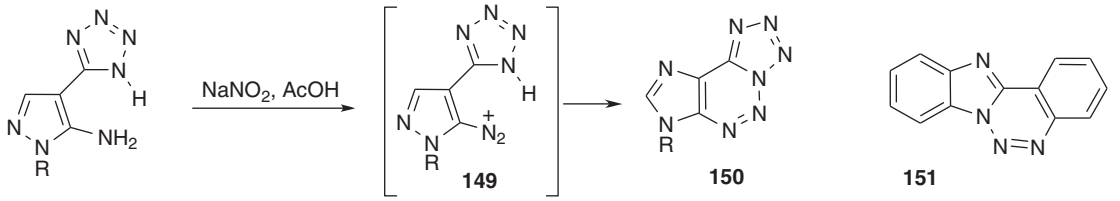
3.4.1.3.14 Aminating agents

Amination at an azole ring nitrogen is known for N-unsubstituted azoles. Thus, 1,2,3-triazole and 4,5-diphenyl-1,2,3-triazole with hydroxylamine-*O*-sulfonic acid give 1-amino **145** and 2-amino **146** derivatives in a ratio of ~4:1 and 1:3, respectively. 3-Amino-5-*tert*-butylpyrazole affords **147** and indazole and tetrazole give comparable amounts of the 1- and 2-amino derivatives, and ethyl benzothiazol-2-ylcarboxylate reacts at room temperature <2001JOC8528>. Pyrazole is easily N-nitrated with nitrogen dioxide in the presence of ozone <1996JCR(S)388>.



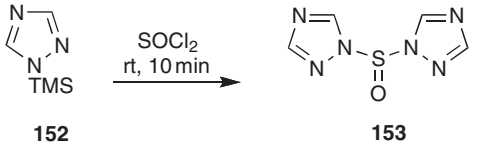
Azoles without a free NH group are also aminated (usually with *O*-mesitylsulfonylhydroxylamine or *O*-picrylhydroxylamine), giving *N*-aminoazolium salts, e.g., **148** <1994J(P1)841>.

Diazonium ions of type **149** located at a -position to a nitrogen-unsubstituted tetrazole cyclize onto the N(1) position giving the fused tetrazolotriazines **150**. Similarly, compound **151** is formed from 2-(*o*-aminophenyl)benzimidazole.



3.4.1.3.15 Other electrophiles

Bis(1,2,4-triazolyl)sulfoxide **153** results from the reaction of 1-trimethylsilyl-1,2,4-triazole **152** with thionyl chloride. This compound is a triazole-donor reagent <2000JHC743>.



3.4.1.4 Electrophilic Attack at Carbon

3.4.1.4.1 Reactivity and orientation

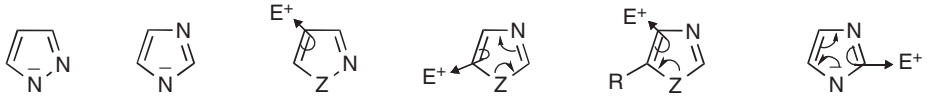
3.4.1.4.1.1 Ease of reaction. Replacing a CH═CH group in benzene with a heteroatom (Z) *increases* the susceptibility of the ring carbon atoms to electrophilic attack noticeably when Z is S, more when Z is O, and very markedly when Z is NH (cf. Chapter 3.3.1.4). Replacing one CH group in benzene with a nitrogen atom *decreases* the ease of electrophilic attack at the remaining carbon atoms (cf. Chapter 3.2.1.4); replacement of two CH groups with nitrogen atoms decreases it further (cf. Chapter 3.2.1.4). Such deactivation is very strong in nitration, sulfonation and FriedelCrafts reactions, which proceed in strongly acidic media, i.e., under conditions in which the nitrogen atom is largely protonated (or complexed). The effect of a protonated nitrogen atom is considerably greater than, for example, the two nitro groups in *m*-dinitrobenzene. The deactivating effect is less pronounced in reactions conducted under neutral or weakly acidic conditions, where a large proportion of unprotonated free base exists, i.e., as in halogenation and mercuration reactions.

In azole chemistry the total effect of the several heteroatoms in one ring approximates the superposition of their separate effects. It is found that pyrazole, imidazole, and isoxazole undergo nitration and sulfonation about as readily as nitrobenzene; thiazole and isothiazole react less readily (approximately equal to *m*-dinitrobenzene), and oxadiazoles, thiadiazoles, triazoles, etc. with great difficulty. In each case, halogenation is easier than nitration or sulfonation. Strong electron-donor substituents assist the substitution.

Another important way in which to achieve reaction with electrophiles is to utilize silyl derivatives (prepared in turn via metallation chemistry). Thus, for example, 2-silyl-thiazoles and -benzothiazoles react readily with esters <2001JME1286>, ketones <2005JOC8556>, and aldehydes <2001T4729>, all facilitated by fluoride from TBAF. Acid chlorides <2004JOC8903> do not require fluoride assistance.

Pyrazoles and imidazoles exist partly as anions (e.g., **154** and **155**) in neutral and basic solution. Under these conditions they react with electrophilic reagents almost as readily as phenol, undergoing diazo coupling, nitrosation and Mannich reactions (cf. the increased reactivity of pyrrole anions over the neutral pyrrole species).

3.4.1.4.1.2 Orientation. A multiply bonded nitrogen atom deactivates carbon atoms or to it toward electrophilic attack; thus initial substitution in 1,2- and 1,3-dihetero compounds is generally as shown in structures **156** and **157**. Pyrazoles **156** (Z = NH), isoxazoles **156** (Z = O), isothiazoles **156** (Z = S), imidazoles **157** (Z = NH, tautomerism can make the 4- and 5-positions equivalent), and thiazoles **157** (Z = S) do indeed undergo electrophilic substitution as shown. Little is known of the electrophilic substitution reactions of oxazoles **157** (Z = O) or compounds containing three or more heteroatoms in one ring. Deactivation of the 4-position in 1,3-dihetero compounds **157** is less effective because of considerable double bond fixation (cf. Sections 2.4.3.2.1 and 3.4.3.1.7), and if the 5-position of imidazoles or thiazoles is blocked, substitution can occur at the 4-position **158**.



154 **155** **156** **157** **158** **159**

The above considerations do not necessarily apply to reactions of electrophilic reagents with pyrazole and imidazole anions, **154** and **155**. The imidazole anion is sometimes (diazo coupling, halogenation, deuterium exchange) substituted at the 2-position cf. **159** and the indazole anion at its 3-position (cf. Section 3.4.1.4.5).

The Hammett $^{+}$ constant for the 4(5)-position of imidazole is around 1; for C(2) it is of the order of 0.8. The electrophilic substitutions that do occur at the 2-position invariably involve preformation of an anion. The 2-proton, which should be the least active in a conventional S_EAr sense, turns out to be the most labile over a wide pH range, and there is a marked rate acceleration on going from imidazole to the imidazolium cation. Any negative charge generated at C(2) is stabilized by the adjacent pyrrole-type nitrogen (see Section 3.4.1.8.2).

In condensed heteroaromatic systems with a ring-junction pyrrolic nitrogen atom, -electron density is always shifted from the electron-rich six-membered ring (formally contains seven -electrons) toward the five-membered ring (formally has six -electrons). As a result, electrophiles are directed to carbon atoms of the latter. Thus, imidazo[1,2-*a*]pyridines **160** unsubstituted at C(3) almost always react with electrophiles at that position.

As predicted by theoretical calculations, the site of electrophilic attack on pyrazolo[3,4-*c*]pyridines **161** is C(3).

160 **161**

3.4.1.4.1.2.3 Effect of substituents. Just as in benzene, substituents can strongly activate (e.g., NH_2, NMe_2, OMe), strongly deactivate (e.g., NO_2, SO_3H, CO_2Et), or have relatively little effect (e.g., Me, Cl) on the ring toward further substitution. Further electrophilic substitution generally will not take place on an azole that carries a strong electron-donor group or is strongly activated, as it is in the azolone form. However, these considerations can be affected by basicity considerations: thus a strongly deactivating group can also increase the proportion of more reactive neutral molecule.

When the preferred substitution position (cf. **156–158**) is occupied, activating substituents can facilitate substitution in other positions (cf. examples in Sections 3.4.1.4.2 and 3.4.1.4.5); *ipso* attack can also occur if the substituent is itself easily displaced.

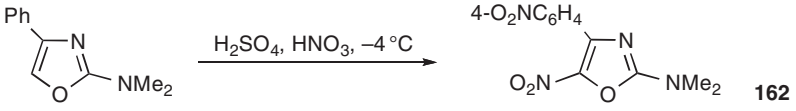
In benz- and phenyl-azolones, electrophilic substitution often occurs in the benzene ring; such reactions are considered as reactions of substituents (see Section 3.4.3.2.1 and 3.4.3.4.1).

3.4.1.4.2 Nitration

Nitration of monocyclic compounds is summarized in **Table 5**. Substitution occurs at the positions discussed above. The reaction conditions required are more vigorous than those needed for benzene, but less than those for pyridine. Ring nitration of oxazoles is rare, but **162** has been obtained in this way.

Table 5 Nitration and sulfonation of azoles

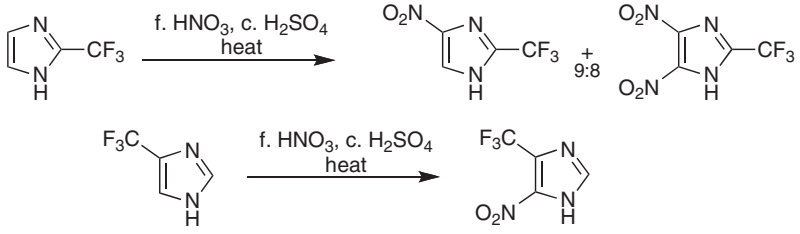
	Position	*Reaction conditions*	
Heterocycle	*Substituted*	*Sulfonation*	*Nitration*
Pyrazole	4	H_2SO_4, SO_3, 100 °C	HNO_3, H_2SO_4, SO_3, 100 °C
Imidazole	4(5)	H_2SO_4, SO_3, 160 °C	HNO_3, H_2SO_4, 160 °C
3-Methylisoxazole	4	HSO_3Cl, 100 °C	HNO_3, H_2SO_4, SO_3, 70 °C
Isothiazole	4	H_2SO_4, SO_3, 150 °C	HNO_3, H_2SO_4, 230 °C
Thiazole	5	H_2SO_4, SO_3, Hg, 250 °C	-
4-Methylthiazole	5	H_2SO_4, SO_3, 200 °C	HNO_3, H_2SO_4, SO_3, 160 °C
2,5-Dimethylthiazole	4	H_2SO_4, SO_3, 200 °C	HNO_3, H_2SO_4, SO_3, 160 °C



162

Substituents are sometimes displaced: thus chloroimidazoles are nitrated normally, but iodo analogues suffer nitrodeiodination.

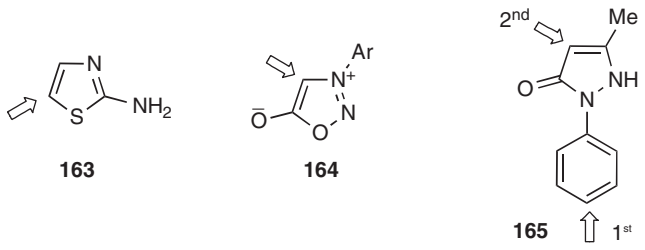
Most widely used protocols for nitration of imidazoles still use HNO_3 in conc. H_2SO_4 <2003SC1977>. For trifluoromethyl-substituted imidazoles, stronger conditions are required (**Scheme 25**) <1998JOC9448>. Conversion of 1-substituted imidazoles into 2-nitro derivatives can be achieved by successive 2-lithiation then reaction with N_2O_4, propyl nitrate, or tetranitromethane as quenching agents.



Scheme 25

Pyrazoles can undergo nitration at several positions: 4-bromo-l-methylpyrazole yields the 3,5-dinitro product. Pyrazole itself gives 3,4-dinitropyrazole with fuming HNO_3, $(CF_3CO)_2O$ <2005ARK(iii)179>. 1-Methylpyrazole 2-oxide yields the 5-nitro derivative. Nitration using Me_4NNO_3 in CH_2Cl_2 at room temperature converts 3,5-dimethylisoxazole to its 4-nitro derivative in high yield and purity <2003JOC267>. Direct nitration of isoxazoles can also be performed with HNO_3, $(CF_3CO)_2O$ affording mononitro derivatives and this reagent combination also mononitrates 2,5-dimethylthiazole <2005ARK(iii)179>.

Nitration is facilitated by activating groups such as amino groups; for example, nitration of **163** occurs at about 20 °C (HNO_3, H_2SO_4). Sydnones **164** are nitrated readily. The pyrazolinone **165** is nitrated as indicated, and 1,2,4-triazolinones have also been ring nitrated.



3.4.1.4.3 Sulfonation

Sulfonation conditions are given in **Table 5**. The orientation is as expected. Azolinones react as readily as the corresponding azoles; sulfonation of **165** occurs at the positions indicated (H_2SO_4, SO_3 at 100 °C). Imidazoles are readily chlorosulfonated at C(4). 4-Substituted 2-aminothiazoles with chlorosulfonic acid give 2-aminothiazole-5-sulfonic acids, which upon heating in sulfuric acid, rearrange to give stable thiazole-2-sulfamoylic acids <2004ZOR1695>.

3.4.1.4.4 Acid-catalyzed hydrogen exchange

Acid-catalyzed hydrogen exchange is used as a measure of the comparative reactivity of different aromatic rings (see **Table 6**). These reactions take place on the neutral molecules or, at high acidities, on the cations. At the preferred positions, the neutral isoxazole, isothiazole, and pyrazole rings are all considerably more reactive than benzene. Although the 4-position of isothiazole is somewhat less reactive than the 4-position in thiophene, a similar situation does not exist with the isoxazole/furan comparison.

Imidazoles, because of their high basicity, are very unreactive unless electron-withdrawing substituents are present.

Table 6 Reactivities toward acid-catalyzed deuterodeprotonation

	Log (partial rate factor)[a] *at the ring positions*			
Heterocycle	*2*	*3*	*4*	*5*
Isoxazole			4.3	
Isothiazole			3.6	
Furan	8.2	ca. 4.5	ca. 4.5	8.2
Thiophene	8.6	5.0	5.0	8.6
1-Methylpyrazole		5.6	9.8	5.6

[a]Relative to a position of benzene = 1.

Deuteration of oxazole using CF_3CO_2D/D_2O occurs exclusively at the 2-position.

3.4.1.4.5 Halogenation

Imidazoles and pyrazoles containing an unsubstituted NH group are easily chlorinated (Cl_2, H_2O, or *N*-chlorosuccinimide, $CHCl_3$), brominated (Br_2, $CHCl_3$; KOBr, H_2O), and iodinated (I_2, HIO_3; aq. $KICl_2$ <2001TL2089>; iodine, cerium(IV) ammonium nitrate (even of deactivated pyrazoles) <2001TL863>). Bromine, DMF, and K_2CO_3, which does not affect other acid- or base-sensitive substituents, has been recommended as a general brominating agent for imidazoles. *N*-Halosuccinimides with ultrasound are useful for pyrazoles <2005TL6833> and NBS brominates benzimidazole at the 2-position <1996H1375>. Oxidative iodination with I_2 and H_5IO_6 produces 2-iodoimidazole in 72% yield <2005MOL401>. *N*-Chlorosuccinimide converts 4,5-disubstituted imidazoles into the corresponding 2-chloroimidazoles; if other positions are available, chlorination goes first at C(5), then C(4), and lastly, C(2). Selective chlorination (or halogenation in general) at the 2-position can be achieved via deprotonation, followed by quenching with NCS or NBS <2003JME3463>. Access via lithiated imidazoles is also an attractive route to 2-iodo-, 5-iodo-, and 2,4-diiodoimidazoles.

Substitution generally occurs first at the 4-position, but further reaction at other available nuclear positions takes place readily, especially in the imidazole series. In 1-substituted imidazoles, C(5) is slightly more reactive than C(4). When halogenation of the nucleus involves electrophilic attack on anions of type **155**, the 4-position of imidazole is

initially substituted. The benzimidazole anion is iodinated at the 2-position and a copper-2-iodobenzimidazole complex results from treatment of benzimidazole with CuI and KI in aqueous ammonium hydroxide <2005CEC514>; other halogenations generally occur in the benzene ring.

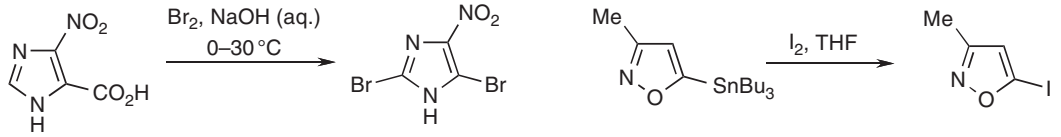
Imidazoles and halogens form charge-transfer complexes, and also rather unstable N-halogeno derivatives which rearrange into C-halogeno products. *N*-Halogenoimidazoles may be intermediates in C-halogenation processes.

Even apparently deactivated compounds can be quite easily brominated at vacant ring positions, for example, 4,5-dicyanoimidazole, 2-methyl-4-nitroimidazole, 2-nitro-, and 1-methyl-2-nitroimidazole.

Methods are available for the preparation of 2,4,5-triiodoimidazole, 4,5-diiodoimidazole, and, by reduction of this, 4-iodoimidazole.

Bromodecarboxylation is known (**Scheme 26**).

Isoxazoles can be halogenated at the 4-position. Ring bromination of oxazoles with bromine or NBS occurs



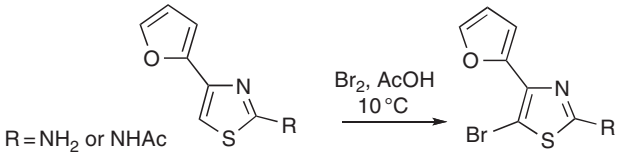
Scheme 26

preferentially at the 5-position and, if this is occupied, at the 4-position. Amino-oxazoles are readily halogenated. Iodinations of isoxazoles can be accomplished by using iodine in nitric acid, but only if the 4-position is free. Unlike NCS and NBS, NIS is not a successful iodinating agent for isoxazole. Halogenation of 3,5-diarylisoxazoles with *N*-halosuccinimides is conducted in acetic acid, while the corresponding fluorination uses Selectfluor$^{\hat{U}}$ <2003S1586, 2004JFC(125)1939>. 3-Methyl-5-tributylstannylisoxazole undergoes *ipso* substitution with iodine to give the 5-iodo derivative (**Scheme 26**).

Bromination 2,4-disubstituted thiazoles at C(5) in good yields utilizes Br_2, AcOH <1999T1977>. Isothiazoles with electron-releasing substituents such as amino, hydroxy, or alkoxy in the 3- or 5-positions are brominated in high yield at the 4-position. Alkyl-isothiazoles give lower yields, but 3-methylisothiazole-5-carboxylic acid can be brominated efficiently. Thiazoles with an electron-releasing substituent at the 2- or 4-position are brominated at C(5).

The selectivity illustrated in **Scheme 27** illustrates the activating effect of the substituent overcoming the intrinsically greater reactivity of a furan ring <2002CHE1014>.

The hydrogen at C(4) in sydnones can be substituted in good yield by chlorine <1996SC1441>, bromine <2002ARK



Scheme 27

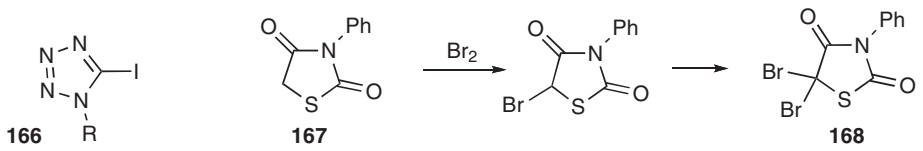
(ii)80>, and iodine <1997LA2613, 2002RRC315>.

1,2,3-Triazoles are brominated at the 4- or 5-positions, but only if there is no N-substituent. This also applies to 1,2,4-triazoles. *N*-Halo derivatives are frequently isolated as intermediates.

3-Amino-1,2,5-thiadiazole is chlorinated or brominated at the 4-position at 20°C in acetic acid. 3-Methyl-1,2,5-thiadiazole can also be chlorinated at the 4-position. Bromination of 2-amino-1,3,4-thiadiazole succeeds at the 5-position.

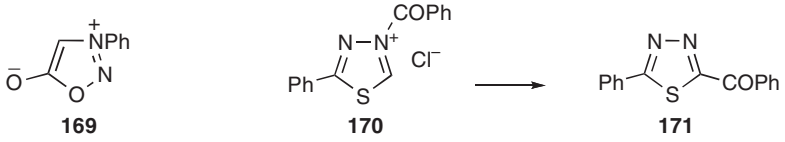
1-Substituted tetrazoles undergo electrophilic iodination to give the 5-iodo-derivatives **166** (R = Alk, Ar, CH_2=CH) in yields of 5575% on treatment with I_2, $KMnO_4$, and H_2SO_4 <2005RJO1565>.

Azolidinones are very easily halogenated, e.g., **167** gives **168**; similar reactions occur in the isothiazolidinone series.



3.4.1.4.6 Acylation, formylation, and alkylation

Although in general azoles do not undergo FriedelCrafts-type alkylation or acylation, several isolated reactions of this general type are known. 3-Phenylsydnone **169** undergoes FriedelCrafts acetylation and Vilsmeier formylation at the 4-position, and the 5-alkylation of thiazoles by carbonium ions is known. Heating N-substituted pyrazoles with benzoyl chloride at 200°C gives quite high yields of 4-benzoylpyrazoles, even in the absence of catalysts. Benzoylation of N-substituted pyrazoles proceeds similarly at the 4-position. Vilsmeier formylation of pyrazoles at the 4-position is also well known, e.g., <2006RJO550>.

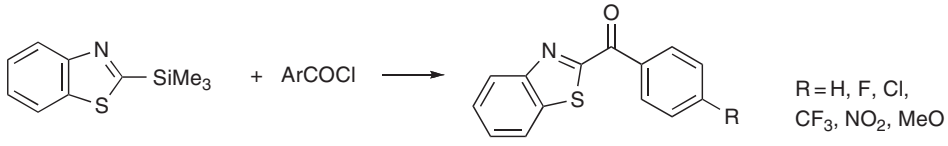


Heating 2-phenyl-4-benzoyl-1,3,4-thiadiazolium chloride **170** at 200°C causes the benzoyl group to move to the 2-position as in **171**, probably via 2-deprotonation forming an ylide.

For the C-acylation of imidazoles via deprotonation, see Section 3.4.1.8.4.

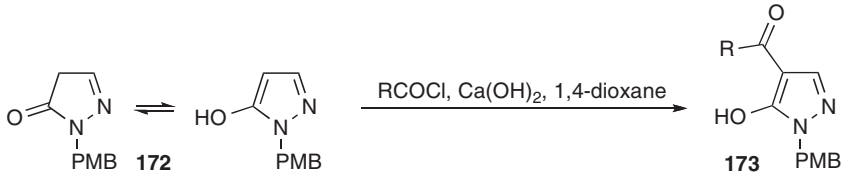
4-Aminotriazole is carboxylated at the 5-position by heating with aqueous sodium bicarbonate in a Kolbe-type reaction. 2-Thiazolinones undergo the Gattermann and ReimerTiemann reactions at the 4-position, and 3- and 4-pyrazolinone anions upon alkylation give 4-alkyl as well as O- and N-alkyl derivatives.

Treatment of 2-trimethylsilylbenzothiazole with various aroyl chlorides forms the 2-acylated products in good yields (**Scheme 28**) <2004JOC8903>.



Scheme 28

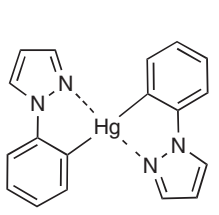
Reaction of pyrazol-3-one **172** with carboxylic acid chlorides and $Ca(OH)_2$ affords 4-acyl-derivatives **173** <2004H(63)2537>.



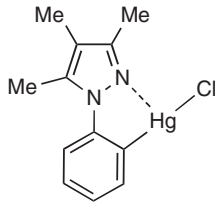
Treatment of pyrazole with 1-bromoadamantane affords either 4-(1-adamantyl)pyrazole or 3(5)-(1-adamantyl)pyrazole depending on the conditions (heating in a sealed tube or heating in a microwave oven). Other cases of C-alkylation of azoles are discussed in Section 3.4.1.3.10.

3.4.1.4.7 Mercuration

While there appears to have been no general study of the mercuration of azoles, the reaction seems to proceed readily in several systems. Thus pyrazoles are 4-chloromercurated by $HgCl_2$. Mercuration of 1-phenylpyrazole and 1-phenyl-3,4,5-trimethylpyrazole affords organomercury derivatives **174** and **175**, the structures being established using ^{199}Hg NMR spectroscopy.



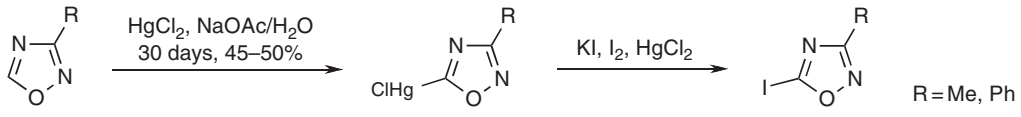
174



175

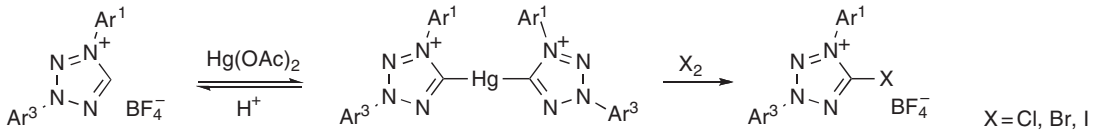
Oxazoles are mercurated in acetic acid in the order 5 > 4 > 2. Thiazoles react under the same conditions and show the same relative positional order. Isoxazoles can be easily mercurated at the 4-position with mercury(II) acetate. 3-Arylsydnones are mercurated at C(4).

1,2,4-Oxadiazoles are rather inert to electrophilic attack; however, mercuration of 5-unsubstituted oxadiazoles is possible. 5-Halooxadiazoles can be prepared from the 5-mercurio compounds (**Scheme 29**); only the 5-iodo derivatives are obtained in good yields.



Scheme 29

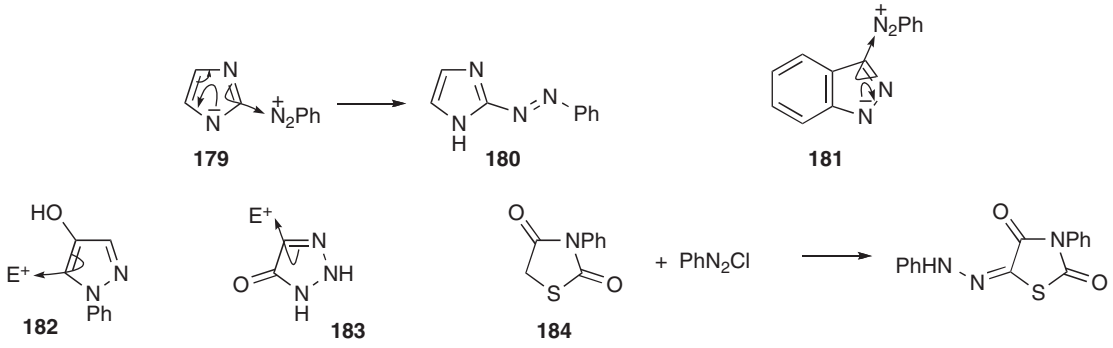
Treatment of tetrazolium salts **176** with mercuric acetate gives the bistetrazolium mercury salts **177**, which represent essentially a metalcarbene trapping of the tetrazolium ylide species. Replacement of the mercury atom of **177** is readily achieved with halogens to give the 5-halotetrazolium compounds **178**. These electrophilic reactions at tetrazole C(5) arise from the lability of the 5-CH proton and they show the necessity of generating carbanionic character at C(5) before electrophilic attack can occur on this strongly -deficient system.



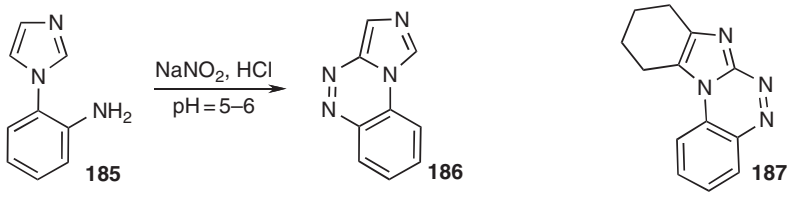
176 **177** **178**

3.4.1.4.8 Diazo coupling

Diazo coupling occurs only with highly reactive systems. Diazonium ions couple with the anions of N-unsubstituted imidazoles at the 2-position (e.g., **179** yields **180**) and with indazoles **181** at the 3-position. In general, other azoles react only when they contain an amino, hydroxy, or potential hydroxy group, e.g., the 4-hydroxypyrazole **182**, the triazolinone **183**, and the thiazolidinedione **184**, all of these involving the anions.

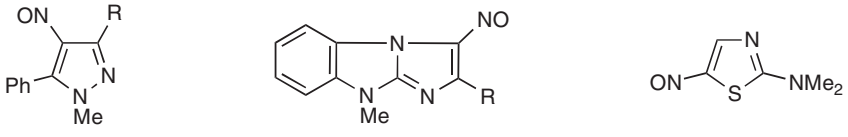


N-Substituted imidazoles do not undergo azocoupling with diazonium salts. However, the diazonium salt formed by diazotization of 1-*o*-aminophenylimidazole **185** easily undergoes an intramolecular azocoupling reaction at imidazole C(5) to give compound **186**. When position 5 is occupied, as in 1-*o*-aminophenyltetrahydrobenzimidazole, azocoupling can occur at position 2 of the imidazole ring though with greater difficulty; in this case compound **187** is obtained.



3.4.1.4.9 Nitrosation

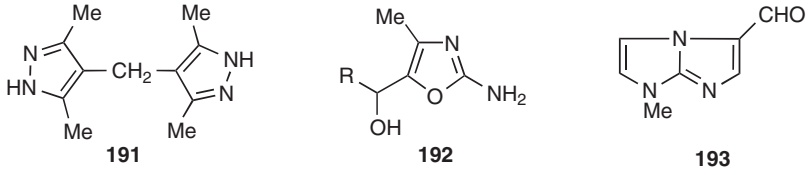
Under alkaline conditions, alkyl nitrites nitrosate imidazoles that possess a free NH group, at the 4-position. Nitrosation of 3,5-dimethylpyrazoles gives the 4-diazonium salt by further reaction of the nitroso compound with more NO^+. 4-Nitrosopyrazoles **188** can be used as spin traps. 5-Pyrazolinones are nitrosated readily at the 4-position. Imidazo[1,2-*a*] benzimidazoles are nitrosated with $NaNO_2$ in acetic acid giving 3-nitrosoderivatives **189**. Nitrosation of 2-(dimethylamino)thiazoles under acid conditions gives 5-nitroso-derivatives **190**. 3-Alkyl-5-acetamidoisothiazoles undergo 4-nitrosation.



3.4.1.4.10 Reactions with aldehydes and ketones

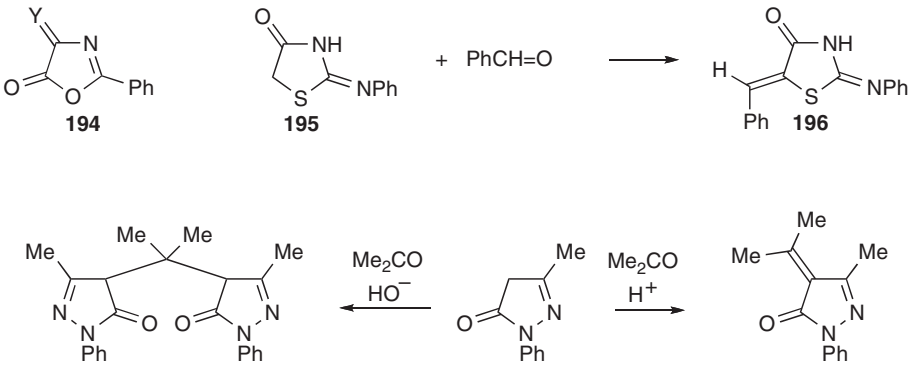
Bis(pyrazole) **191** was prepared by the reaction of 3,5-dimethylpyrazole with formaldehyde (a 4-CH_2OH derivative is the probable intermediate).

Imidazoles are hydroxymethylated by CH_2O at the 4-position; 1-substituted imidazoles react at C(2). Isoxazoles can be chloromethylated at C(4); 1,2,4-triazoles with paraformaldehyde in refluxing xylene give 2-hydroxymethyl derivatives <2006S156>.



2-Amino-4-methyloxazole reacts with aldehydes to give oxazole-5-hydroxymethyl derivatives **192**. Oxazoles without strong electron-donating groups are inert to aldehydes. Some -excessive heterocycles with an angular nitrogen atom can be effectively formylated by chloral; thus, 1-methylimidazo[1,2-*a*]imidazole gives aldehyde **193**.

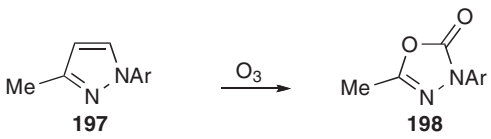
Aldehydes and ketones react with azolinones. The reaction between aldehydes and 2-phenyl-5-oxazolinone **194** (Y = H_2), formed *in situ* from $PhCONHCH_2CO_2H$ and Ac_2O, gives azlactones **194** (Y = RCH). Similar reactions are given by 4-thiazolidinones, e.g., **195** gives **196**, and 4-imidazolinones. In pyrazolin-5-ones the 4-position is sufficiently activated for condensation to occur with ketones in acidic media (**Scheme 30**).



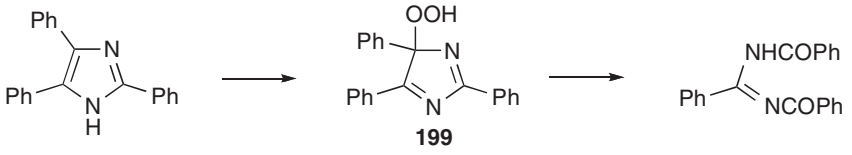
Scheme 30

3.4.1.4.11 Oxidation

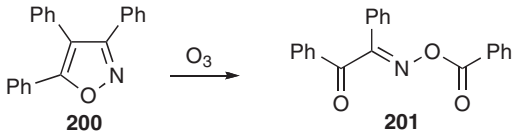
The pyrazole ring is generally stable to oxidation and side-chains are oxidized to carbonyl groups. 1-Aryl-3-methylpyrazoles **197** react with ozone to yield 1,3,4-oxadiazolinones **198**.



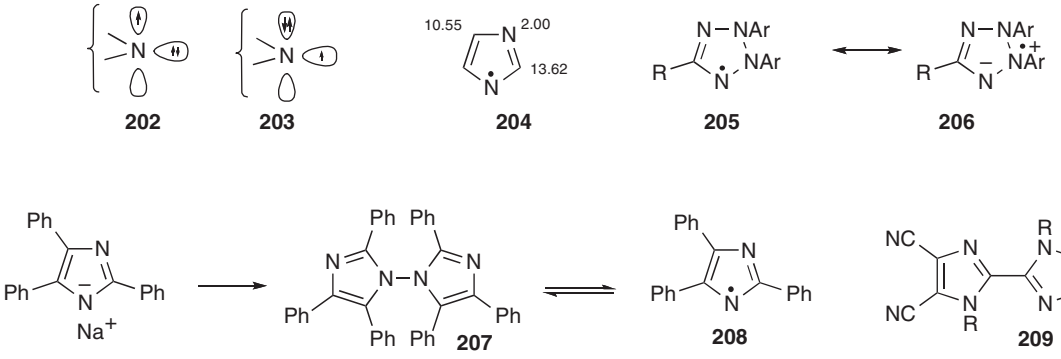
Imidazole rings also survive most oxidation conditions, but photosensitized oxidation of imidazoles can give diarylbenzamidines through a hydroperoxide, e.g. **199**.



Thiazole, triazole, and tetrazole rings are resistant to oxidation (e.g.,. by $KMnO_4$, CrO_3). Isoxazoles are more susceptible (e.g., **200** **201**, benzil monoxime benzoate). The oxazole ring is relatively readily cleaved by oxidizing agents such as potassium permanganate, chromic acid, or hydrogen peroxide to give acids or amides. Oxidation of 4,5-diaryloxazoles with chlorine or bromine gives the corresponding benzils in high yield.



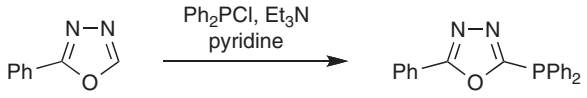
Oxidation of azole anions can give neutral azole radicals which could, in principle, be **202** or **203** in nature. ESR spectra indicate the -structure (**204**; hyperfine splitting in G) for imidazolyl radicals, but both - and -character have been observed for pyrazolyl radicals. Tetrazolyl radicals (**205 206**) are also well known. Oxidation of 2,4,5-triarylimidazole anions with bromine gives 1,1-diimidazolyls **207** that are in equilibrium with the radical **208** formed by dissociation.



Oxidative dimerization of the lithium derivatives of 1-substituted 4,5-dicyanoimidazoles gives **209**.

3.4.1.4.12 Other electrophiles

1-Methyl-1,2,4-triazole undergoes electrophilic substitution with Me_3SiCl, Et_3N to give 1-methyl-5-trimethylsilyl-1*H*-1,2,4-triazole <2006S1279>. 2-Phenyl-l,3,4-oxadiazole interacts over 24 hours with chlorodiphenylphosphine and dichlorophenylphosphine at room temperature to give phosphines (e.g. **Scheme 31**) <1999CHE1117>.

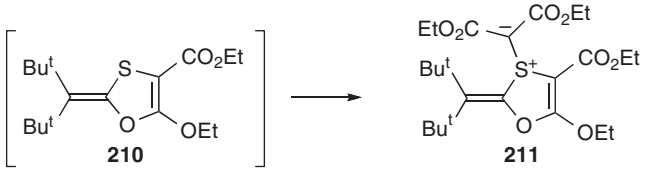


Scheme 31

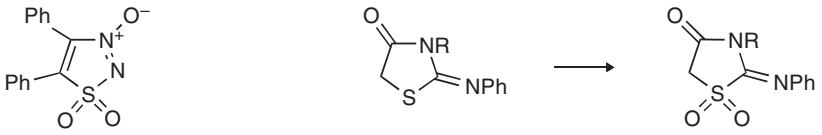
3.4.1.5 Attack at Sulfur

3.4.1.5.1 Electrophilic attack

A rare example of this type of reaction is the formation of **211** in the rhodium-catalyzed reaction of di-*t*-butylthioketene with diethyl diazomalonate. This involves the oxathiole **210** as an intermediate, which undergoes electrophilic attack by the carbenoid to give **211**.



Certain thiazoles, isothiazoles, and benzoisothiazoles have been directly oxidized to sulfoxides and sulfones. 1,2,3-Benzothiadiazole gives a sulfoxide with 30% H_2O_2, AcOH, MeOH and methanol for 45 days <1990CJC1950>. Optically active benzisoselenazol-3(2*H*)-one 1-oxides (seleninamides) having various bulky substituents can be prepared from the corresponding benzisoselenazol-3(2*H*)-ones by oxidation with hydrogen peroxide or ozone followed by chromatographic resolution on a chiral column <2005JOC868>. 4,5-Diphenyl-1,2,3-thiadiazole is converted by peracid into the trioxide **212**. Although 1,2,5-thiadiazole 1,1-dioxides are known, they cannot be prepared in good yield by direct oxidation, which usually gives sulfate, like the results obtained with 1,2,4- and 1,3,4-thiadiazoles (see also Section 3.4.1.3.13).



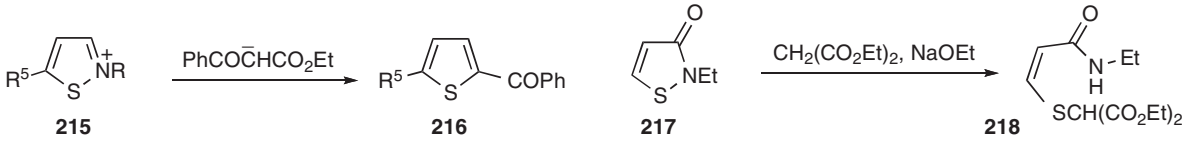
212 **213** **214**

When a hydroxyazole can tautomerize to a nonaromatic structure, oxidation at an annular sulfur atom becomes easy, e.g., **213** **giving** **214**.

Thiazoles are desulfurized by Raney nickel, a reaction probably initiated by coordination of the sulfur at Ni. The products are generally anions and carbonyl compounds (see Section 3.4.1.9.5).

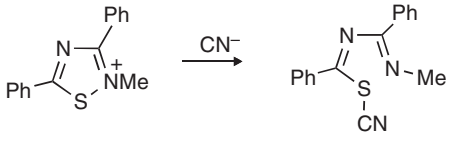
3.4.1.5.2 Nucleophilic attack

Isothiazoles and isothiazolium cations are attacked by carbanions at sulfur and on recyclization can give thiophenes, as illustrated by **215** **216**. 2-Alkyl-3-isothiazolinones (e.g., **217**) are also vulnerable to nucleophilic attack at sulfur, e.g., giving **218**.



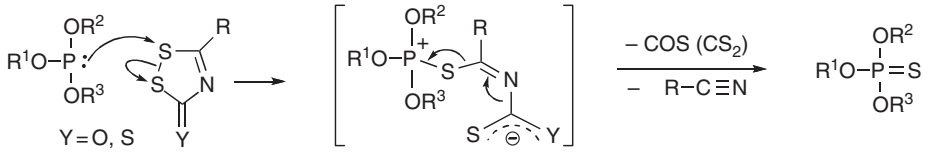
215 **216** **217** **218**

Nucleophilic attack at sulfur is implicated in many reactions of 1,2,4-thiadiazoles; generally, soft nucleophiles attack at sulfur, e.g., **219** **220**. *n*-Butyllithium with 4,5-diphenyl-1,2,3-thiadiazole yields PhCCPh, probably by initial nucleophilic attack at sulfur.



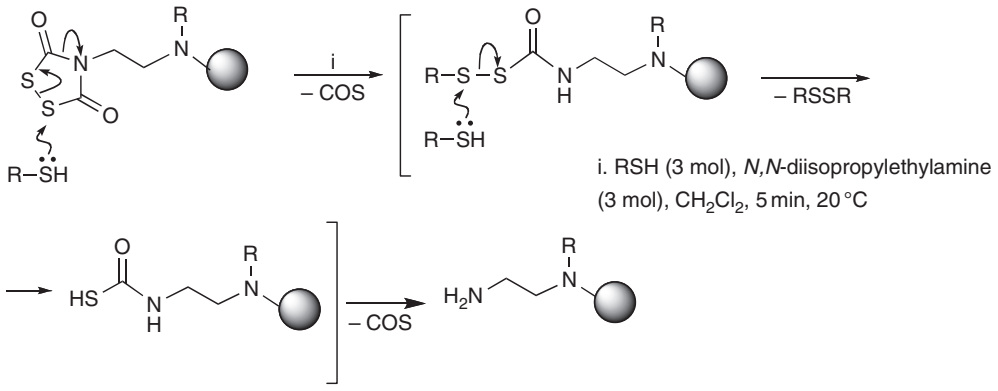
219 **220**

The chemistry of dithiazole derivatives has received a new impetus due to their sulfur-transfer applications in the solid-phase synthesis of oligodeoxyribonucleotide phosphorothioates via the phosphoramidite method: they are advantageous alternatives to the previously used Beaucage reagent. The general mechanism of the sulfur-transfer reaction is presented in **Scheme 32** <e.g. 2000OPD194, 2002TL4347>.



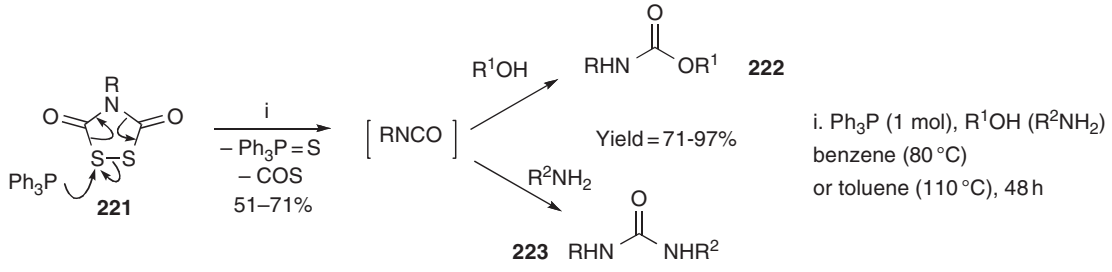
Scheme 32

The known susceptibility of the 1,2,4-dithiazolidine ring to SS bond reduction is intrinsic to the removal of the dithiosuccinoyl (Dts) protecting group (**Scheme 33**) in the synthesis of peptides, *O*-glucopeptides, etc., e.g., <1995J(P1)405, 1996JA3148, 1996J(P1)985, 1996MI501, 1997J(P1)871, 1999JOC7281>.



Scheme 33

Various isocyanates (and thence primary aliphatic amines) can be prepared from corresponding alcohols, utilizing 1,2,4-dithiazolidine-3,5-dione **221** as a nucleophilic isocyanate building block. The isocyanates are synthesized by heating compounds **221** with one equivalent of Ph_3P in benzene or toluene under reflux and trapped as urethanes **222** or ureas **223** by addition of alcohols or amines (**Scheme 34**), e.g., <1996JA3148, 2000SL1622, 2002J(P1)2046, 2003OBC3015, 2005T2141>.



Scheme 34

Grignard reagents commonly react at S of 1,2-dithiole-3-ones with ring opening (**Scheme 35**).

Scheme 35

3.4.1.6 Nucleophilic Attack at Carbon

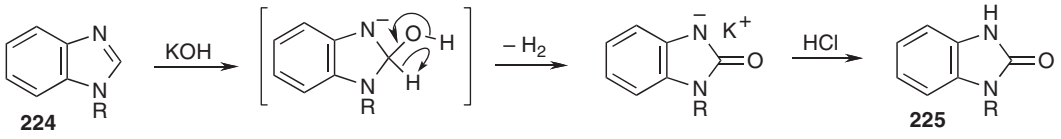
Because of the increased importance of inductive electron withdrawal, nucleophilic attack on uncharged azole rings generally occurs under milder conditions than those required for analogous reactions with pyridines or pyridones. Azolium rings are very easily attacked by nucleophilic reagents; reactions similar to those of pyridinium and pyrylium compounds are known; azolium rings open particularly readily.

Nucleophilic attack on the ring carbon atoms of azoles occurs readily with oxazole and aza analogues. Such reactions are generally facilitated by additional ring heteroatoms and by electron-attracting substituents, and hindered by electron-donating substituents. A fused benzene ring aids nucleophilic attack on azoles, azolium ions, and azolones;

this can be rationalized because the loss of aromaticity involved in the formation of the initial adduct is less than that in monocyclic compounds. The orientation of attack is generally between two heteroatoms.

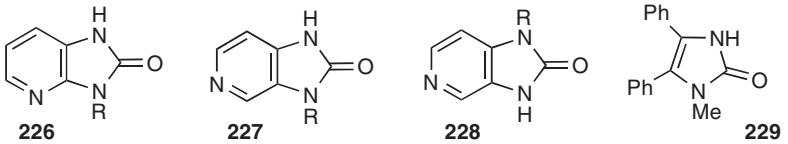
3.4.1.6.1 Hydroxide ion and other O-nucleophiles

3.4.1.6.1.1 Neutral azoles. Uncharged azoles not containing oxygen or sulfur are often resistant to attack by hydroxide ions at temperatures up to 100°C and above. However, neutral azoles do react with hydroxide ions under extreme conditions. A remarkable reaction of this type is the direct hydroxylation of 1-substituted benzimidazoles, naphtho[1,2-*d*]- and naphtho[2,3-*d*]imidazoles and other condensed imidazole systems with powdered anhydrous (molten) potassium or sodium hydroxides. The reaction proceeds at temperature of 230 250°C and leads to formation of the corresponding N-monosubstituted imidazolone in high yield (e.g., **224** **225**, **Scheme 36**). Imidazo[4,5-*b*]- and imidazo[4,5-*c*]pyridines are hydroxylated exclusively in the imidazole ring, giving compounds **226**–**228**. Noncondensed imidazoles cannot usually be hydroxylated; however, 1-methyl-4,5-diphenylimidazole under drastic conditions (300°C) gives imidazolone **229** (30%). The ease of hydroxylation and the orientation of the nucleophilic attack are well predicted by the value of the largest atomic positive charge. The reaction can be considered to be the oxygen analogue of the Chichibabin amination reaction (see Section 3.4.1.6.2). Indeed, in both cases the process is accompanied by evolution of hydrogen gas and can be rationalized in accordance with **Scheme 36**.



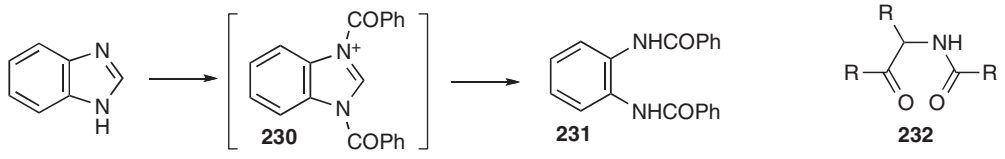
224 **225**

Scheme 36



226 **227** **228** **229**

Imidazoles and benzimidazoles react with acid chlorides and alkali to give compounds of type **231**, but these are reactions of the cation **230**. 1,2,4-Triazoles and tetrazoles similarly undergo ring opening.

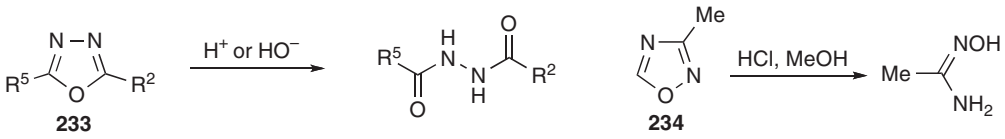


230 **231** **232**

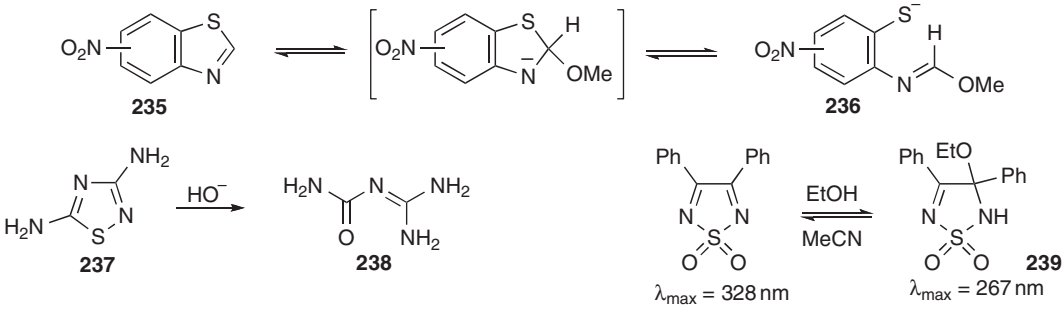
Isoxazoles are also rather stable to nucleophilic attack by OH at carbon. For reactions with base at a ring hydrogen atom, leading, for example, to ring opening of isoxazoles, see Section 3.4.1.8.1.

Oxazoles give acylamino ketones **232** by acid-catalyzed ring scission, although they are somewhat more stable than furans. The oxazole ring is also moderately stable to alkali; reaction with hydroxide ions is facilitated by electron-withdrawing substituents and fused benzene rings.

Oxadiazoles are easily cleaved. 2,5-Dialkyl-1,3,4-oxadiazoles **233** in aqueous solution with acid or base give hydrazides (if suitable substituents are present, further reaction can occur; see Section 3.4.3.5.1). 3-Methyl-1,2,4-oxadiazole **234** is easily hydrolyzed to acetamidoxime.

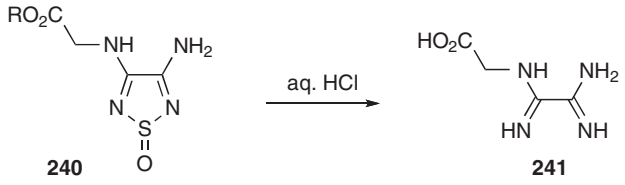


Isothiazoles and thiazoles are rather stable toward nucleophilic attack. Both 5- and 6-nitrobenzothiazole **235** add methoxide at C(2); the initial adduct undergoes ring opening to give **236**. Unsubstituted 1,2,4-thiadiazole is sensitive to alkali. Substituents stabilize the ring somewhat, but ring-opening reactions are still common, e.g., **237** **238**. 5-Alkylamino-1,2,3,4-thiatriazoles are cleaved by alkali to azide ion and an isothiocyanate; in addition, a Dimroth rearrangement occurs to give a mercaptotetrazole.

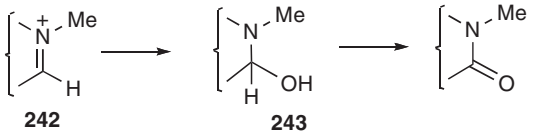


UV spectroscopy can be used to clarify the strong interactions of 1,2,5-thiadiazole dioxides with protic solvents. Based on shifts in the maximum from 328 to 267 nm, as well as a doubling in the extinction coefficient, it is likely that the adduct **239** is formed in alcoholic media.

Hydrolysis of amino-alkylamino-1,2,5-thiadiazole 1-oxides **240** with concentrated aqueous HCl gives the amidines **241** <2001JME1231>.



3.4.1.6.1.2 Azolium ions. Azolium ions **242** react reversibly with hydroxide ions to form a small proportion of the pseudobases **243**. The term pseudo is used to designate bases that react with acids at a measurable rate, not instantaneously as is normal for acidbase reactions. Fused benzene rings reduce the loss of resonance energy when the hetero ring loses its aromaticity, and hence pseudo bases are formed even more readily by benzothiazolium cations than by thiazolium ions. Pseudo bases carrying the hydroxy group in the -position are usually formed preferentially. As expected, pseudo base formation for S-containing azoliums is easiest with the dithiolylium and least easy with thiazolium.



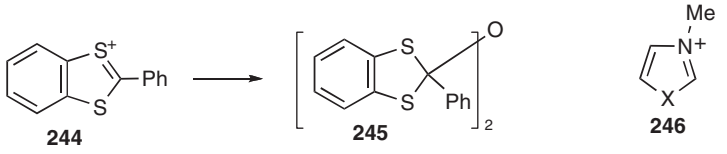
pK_R^+ values for pseudo base formation are defined by the equation:

$$K_{R^+} = [H^+] \times \frac{[QOH]}{[Q^+]}$$

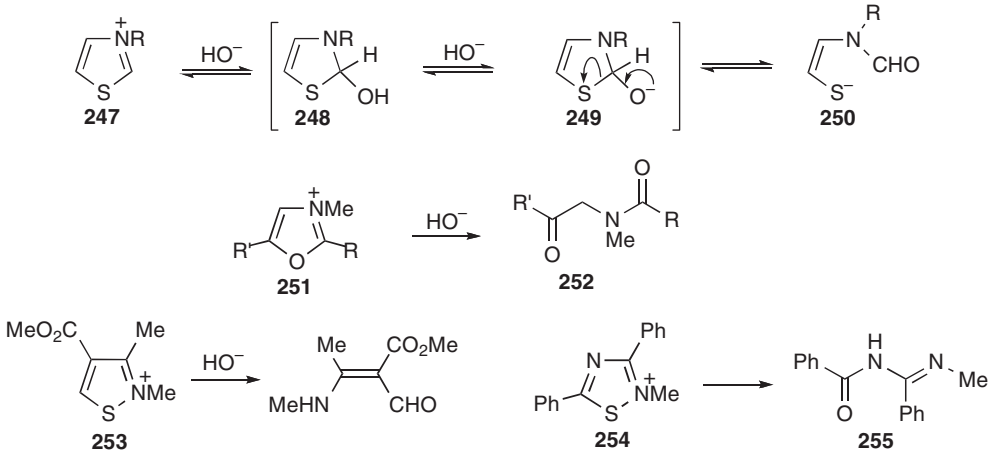
where Q^+ and QOH denote the azolium cation and pseudo base, respectively. Some pK_R^+ values are given in Figure 1.

Figure 1 pK_R^+ values for azolium and related cations.

Some pseudo bases are stable. 1,3-Dithiolylium adds alkoxide ions at the 2-position to give stable adducts which regenerate the starting salts with acids. Pseudo bases can also dimerize with loss of water to give an ether (e.g., pseudobase of **244** **245**).

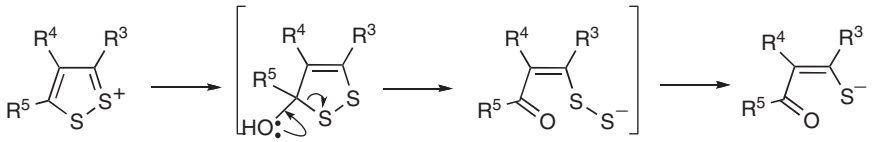


Oxidation to an azolone is an expected reaction for a pseudo base, but little appears to be known of such reactions. Most commonly, pseudo bases suffer ring fission. Estimated rates of ring opening of **246** are in the ratio 10^9:$10^{4.5}$:1 for X = O, S, and NMe, respectively. Thiazolium salts **247** consume two equivalents of OH on titration because the pseudo bases **248** lose a proton to give **249**, which then form anions **250**. Quaternized oxazoles **251** are readily attacked by hydroxide to give open-chain products such as **252**, and quaternized 1,3,4-oxadiazoles behave similarly. Quaternary isothiazoles (e.g., **253**) are cleaved by hydroxide, as are 1,2,4-thiadiazolium salts (**254** **255**).

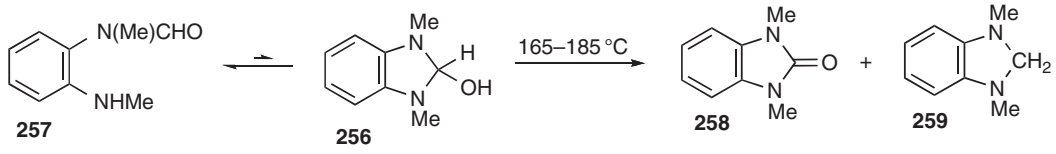


1,2-Dithiolylium ions undergo ring opening and degradation with hydroxide (**Scheme 37**). 1,2-Dimethylpyrazolium is degraded to MeNHNHMe.

Oxidativereductive disproportionation is a rather typical property of some pseudo bases. Thus, 1,3-dimethyl-2-hydroxybenzimidazoline **256**, which exists in the solid state in the open-chain form **257**, on heating at 165185$\bar{}$C, is converted into a mixture of 1,3-dimethylbenzimidazolone **258** (49%) and 1,3-dimethylbenzimidazoline **259** (46%). Evidently, the process proceeds via **256** expelling hydride.

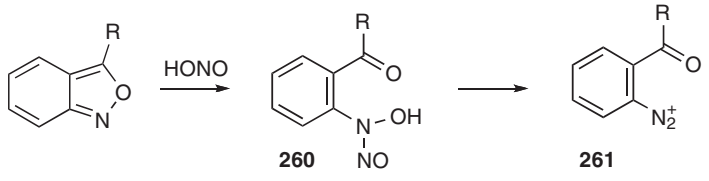


Scheme 37

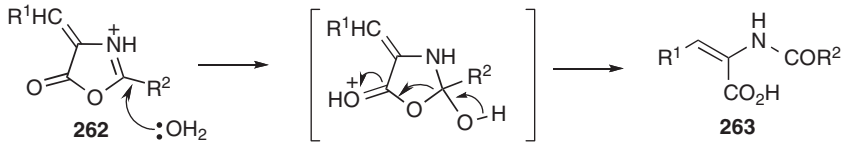


Reclosure to form a new heterocyclic or homocyclic ring occurs in azolium ions carrying suitable substituents; these reactions are considered under the appropriate substituents.

Anthranils are readily cleaved by nitrous acid, presumably by attack of water on N-nitroso cations. The first product that can be observed is the nitrosohydroxylamino compound **260**, which is reduced to the diazonium salt **261**.

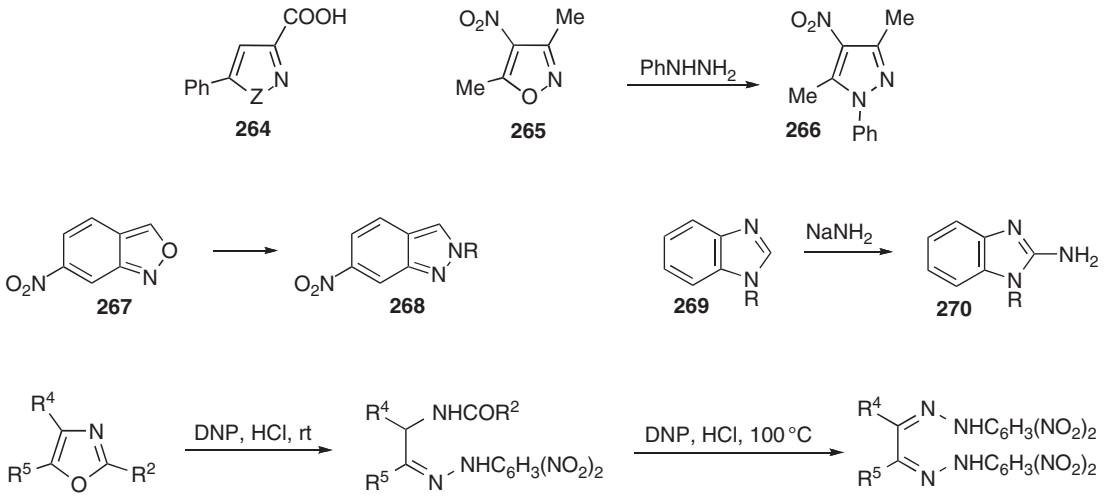


3.4.1.6.1.3 Azolinones. Although imidazolinones are usually resistant to hydrolysis, oxazolinone rings are often easily opened. In acid-catalyzed reactions of this type, water converts azlactones **262** into -acylamino-,-unsaturated acids **263**. 1,3,4-Oxadiazolinones are readily opened by hot water to give hydrazine carboxylic acids, which undergo decarboxylation.

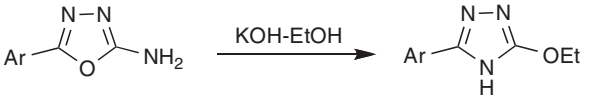


3.4.1.6.2 Amines and amide ions

3.4.1.6.2.1 Azoles. Oxygen-containing rings can be opened by amines; frequently, this is followed by reclosure of the intermediate to form a new heterocycle. Thus, isoxazoles containing electron-withdrawing substituents give pyrazoles with hydrazine, e.g., **264** (Z = O) **264** (Z = NH), and **265 266**. In the benzo series a rather different reaction can occur: 6-nitroanthranil **267** is converted by amines into 2-R indazoles **268**. Oxazoles heated at 180°C with formamide are transformed into imidazoles. With 2,4-dinitrophenylhydrazine (DNP), oxazoles form hydrazones by ring fission (**Scheme 38**). Benzoxazole with hydroxylamine gives 2-aminobenzoxazole by elimination of water from an initial adduct. 1,3,4-Oxadiazoles react readily with ammonia, primary amines, or hydrazine to give 1,2,4-triazoles, e.g., <2000EJM267>; in the special case shown in **Scheme 39**, the extra ring nitrogen is provided by an amino substituent in the starting material <2003BMC769>. 1,2,3-Thiadiazole-4-carboxaldehydes upon treatment with amines are comparably transformed into 1,2,3-triazoles <1993J(P1)1719>.



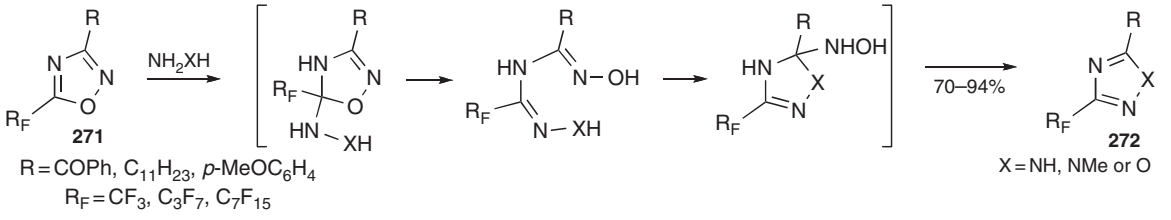
Scheme 38



Scheme 39

Amines are insufficiently nucleophilic to react with most azoles which do not contain a ring oxygen and the stronger nucleophile NH_2 is required. Thus, many N-substituted benzimidazoles, naphtho[1,2-*d*]-, and naphtho[2,3-*d*]-imidazoles are readily aminated by sodamide at 110130°C, forming in good yields the corresponding 2-amino derivatives, e.g., **269** **270**. Thiazoles can be aminated at the 2-position by $NaNH_2$ at 150°C. Noncondensed imidazoles, as well as condensed imidazoles with a free NH-group, do not undergo Chichibabin amination. 9-Substituted purines by the action of KNH_2 in liquid ammonia at 80°C undergo two types of reaction: (1) ionization of the C(8)H bond and (2) addition of amide ion to C(8) with subsequent opening of the imidazole ring. *C*-Nitroimidazoles are aminated by alkaline NH_2OH.

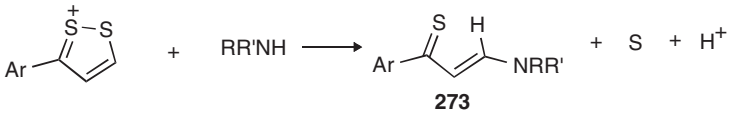
5-Perfluoroalkyl-1,2,4-oxadiazoles **271** react with hydrazine or hydroxylamine to furnish 3-perfluoroalkyl-1,2,4-triazoles **272** (X = NH) or 3-perfluoroalkyl-1,2,4-oxadiazoles **272** (X = O), reactions that proceed via addition of the nitrogen nucleophile to the 5-position (**Scheme 40**), e.g., <2003JOC605, 2004EJO974, 2005JOC3288>. 5-Trichloromethyl-1,2,4-oxadiazoles react with amines with displacement of the trichloromethyl group, e.g., <2001MI504-01, 2002H1891, 2002RCB1857>.



Scheme 40

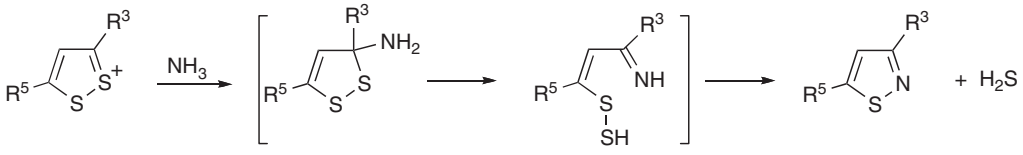
3.4.1.6.2.2 Azolium ions. Most azolium ions are sufficiently reactive to be attacked by amines. Sometimes the initial adducts are stable: ammonia and primary and secondary amines add to 1,3-dithiolylium salts at the 2-position to give compounds of the types NT_3, RNT_2, and R_2NT, respectively, where T = the 1,3-thiol-2-yl group.

Some azoliums give open-chain products: primary and secondary amines with 1,2-dithiolyliums generally give **273**.



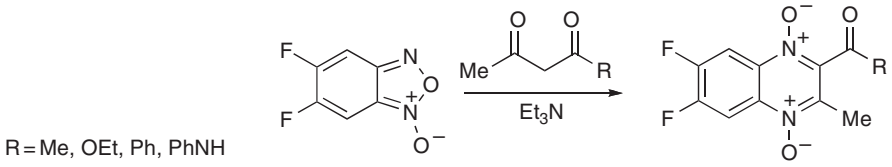
273

In other cases, reclosure to a new ring occurs: 1,2-dithiolylium ions with ammonia give isothiazoles according to the mechanism shown in **Scheme 41**. Treatment of isothiazoliums with hydrazine or phenylhydrazine gives pyrazoles (**Scheme 42**), 1,2,4-thiadiazoliums similarly yield 1,2,4-thiazoles, and oxazolium ions react with ammonium acetate in acetic acid to give the corresponding imidazoles (**Scheme 42**). 3-Amino-4-nitrofuroxan is transformed into 4-amino-2-*tert*-butyl-5-nitro-1,2,3-triazole 1-oxide by reaction with butylamine <2003CHE608>. Benzofuroxans react with -dicarbonyl compounds <2001RJO891, 2003BMC2149, 2003EJM791, 2005JME2019> generating quinoxaline di-*N*-oxides (e.g., **Scheme 43**) <2005JME2019>.



Scheme 41

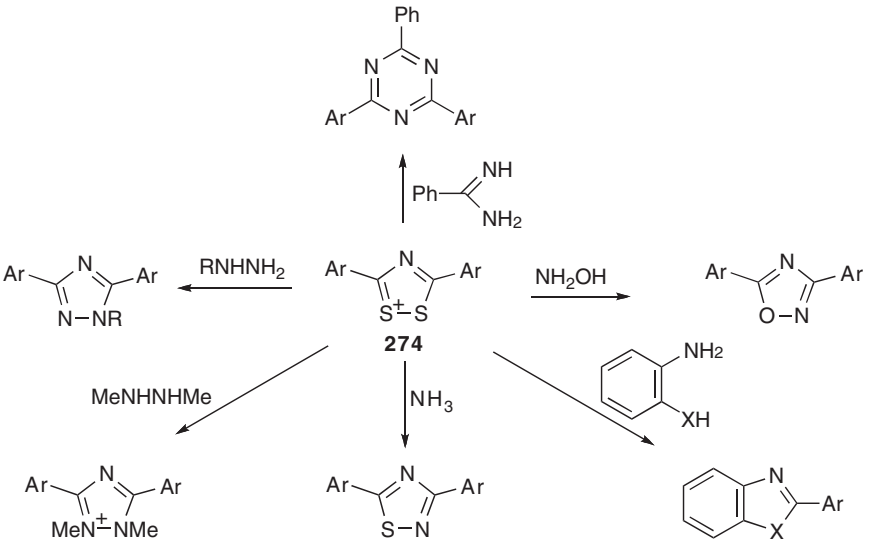
Scheme 42



Scheme 43

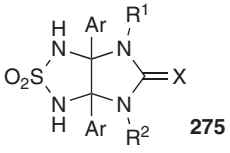
3,5-Diaryl-1,2,4-dithiazolium salts **274** are highly reactive 3,5-dielectrophiles and readily interact with nucleophiles to give a broad variety of heterocyclic compounds (**Scheme 44**).

Alcohols, thiols, amines, and amides add reversibly in aprotic solvent to one of the two C=N bonds of 3,4-disubstituted-1,2,5-thiadiazole 1,1-dioxides to give the corresponding thiadiazoline 1,1-dioxides <1996CJC1564,



Scheme 44

2000JPO272, 2003JPO220>. Grignard reagents behave similarly <1998SL623>. Bis-addition occurs with urea <2003JPO220> and thioureas <2004JPO1091> to give the bicyclic thiadiazolidines **275** (X = O) and **275** (X = S), respectively.



275

3.4.1.6.3 S-Nucleophiles

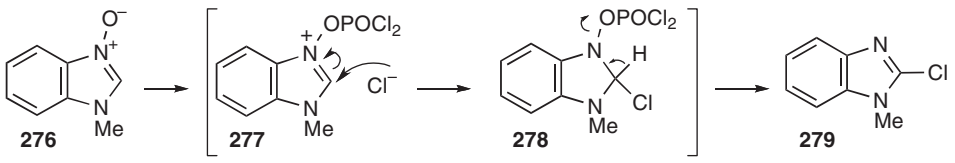
Data on reactions of sulfur nucleophiles with azoles are sparse. Oxazoles are transformed in low yield into the corresponding thiazoles over alumina with H_2S at 350°C. Sulfur nucleophiles such as HS and RS add to 1,3-dithiolylium salts at the 2-position.

There are a number of examples in which 1-alkoxybenzimidazoles, 1-alkoxy-3-methylbenzimidazolium salts, and 1-alkylbenzimidazole 3-oxides react with anionic sulfur species to give 2-substitution with simultaneous deoxygenation.

3.4.1.6.4 Halide ions

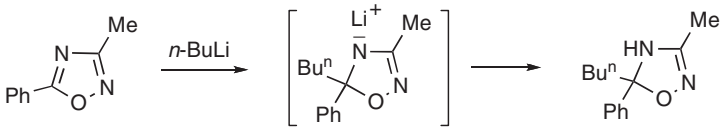
In general, there is also no interaction between halide ions with azolium compounds.

Benzimidazole 3-oxides, e.g., **276**, react with phosphorus oxychloride or sulfuryl chloride to form the corresponding 2-chlorobenzimidazoles. The reaction sequence involves first formation of a complex **277**, then attack by chloride on the complex, followed by rearomatization involving loss of the *N*-oxide oxygen (**278** **279**).



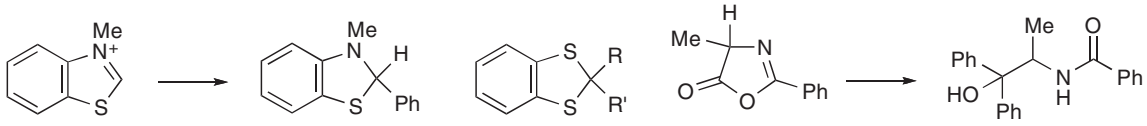
3.4.1.6.5 Carbanions

3.4.1.6.5.1 Organometallic compounds. In contrast to pyridine chemistry, the range of nucleophilic alkylations that can be effected on neutral azoles is quite limited. Lithium reagents can add at the 5-position of 1,2,4-oxadiazoles (**Scheme 45**). Benzazoles are attacked by organometallic compounds at the C=N carbon unless it is blocked.



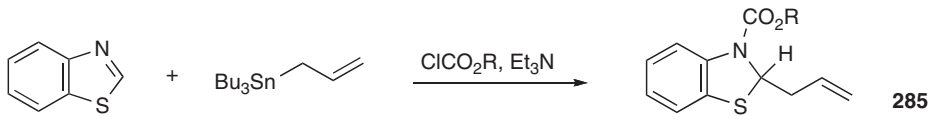
Scheme 45

Azolium rings react readily with organometallic compounds. With a Grignard reagent, conversion **280** **281** is known in the benzothiazolium series, and 1,3-benzodithiolyliums give products of type **282**. 4-Methyl-2-phenyl-5-oxazolinone **283** with phenylmagnesium bromide gives **284**.



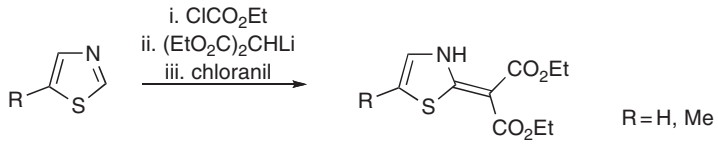
280 **281** **282** **283** **284**

Dihydro adducts like **285** are obtained by reaction of thiazoles with allyltributyl tin in the presence of chloroformates acting as activators of the thiazole ring (**Scheme 46**). Under these conditions organolithium compounds also add to thiazoles, e.g., **Scheme 47** <2002JME1887>. Similarly, direct ethynylation of thiazole and benzothiazole can be achieved by reaction with bis(tributylstannyl)acetylene (**Scheme 48**).



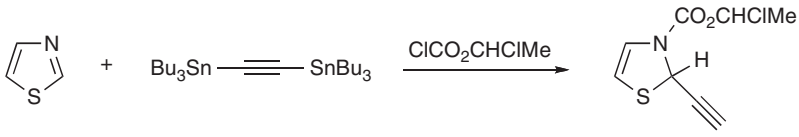
285

Scheme 46



R = H, Me

Scheme 47

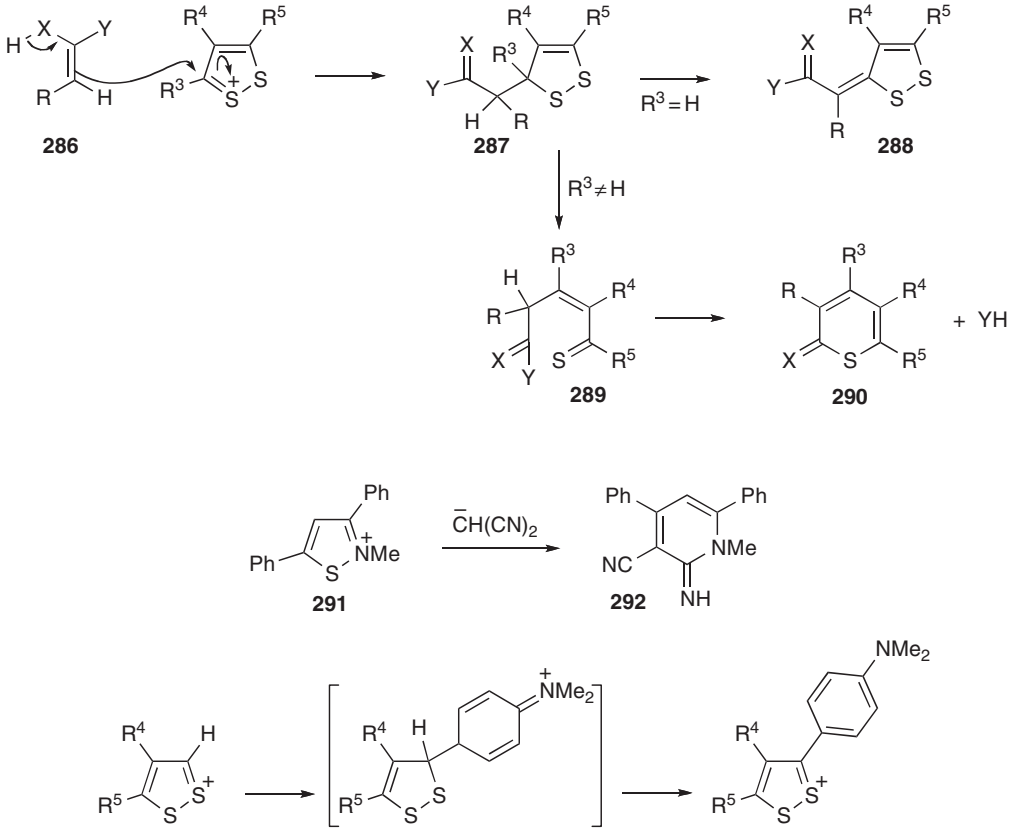


Scheme 48

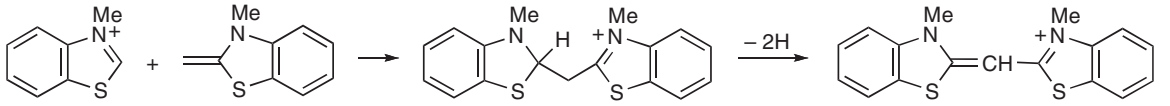
3.4.1.6.5.2 Activated methyl and methylene carbanions. The mesomeric anions of activated methyl and methylene compounds react with azolium ions. Thus, 1,2-dithiolylium ions with a free 3- or 5-position react with various carbon nucleophiles to give products which are oxidized *in situ* to mesomeric anhydro bases (286 287 288). However, in 3,5-disubstituted 1,2-dithiolylium cations an alternative ring scission can occur (287 289 290). In this sequence, 286 can be $ArCOCH_2CS_2Me$, $NCCH_2CSNH_2$, or $NCCH_2CO_2Et$. The conversion in the 1,2,4-thiadiazole series of 291 into 292 is analogous. Dimethylaniline gives an intermediate that is oxidized to a new dithiolylium salt (Scheme 49).

Anhydro bases can attack the -position, e.g., of thiazolium cations, with the formation of adducts capable of oxidation to cyanine dyes, e.g., Scheme 50 (see Section 3.4.3.3.4).

Active methylene compounds, for example, $CH_2(CN)_2$, $CH_2(COMe)_2$, or even MeCOMe, can add to 1,3-dithio-

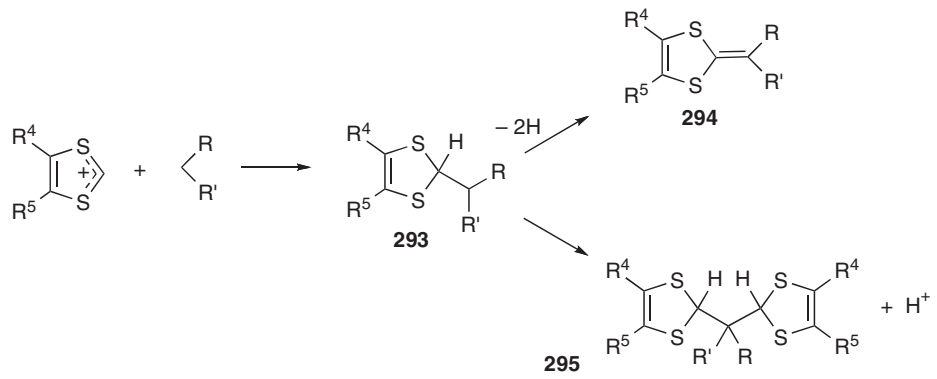


Scheme 49



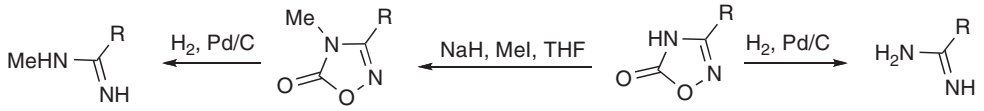
Scheme 50

lylium ions to give 2-substituted 1,2-dihydro-1,3-dithioles 293. Again, addition is often followed by oxidation (to 294). Alternatively, further addition can occur (to 295). Somewhat similar reactions are shown by 1,3-diarylimidazolium ions.

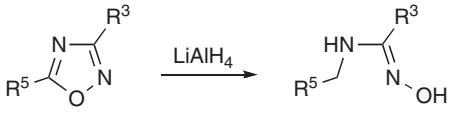


3.4.1.6.6 Reduction by complex hydrides

Oxygen-containing azoles are readily reduced, usually with ring scission. Only acyclic products have been reported from the reductions with complex metal hydrides of oxazoles (e.g., **296 297**), isoxazoles (e.g., **298 299**), benzoxazoles (e.g., **300 301**), and benzoxazolinones (e.g., **302, 303 301**). Reductions of 1,2,4-oxadiazoles always involve ring scission, for example, Fe, aq. AcOH converts 5-methyl derivatives into acetylamidines which undergo hydrolysis *in situ* to give the amidines and thus allows 1,2,4-oxadiazoles to be used as masked amidines (**Scheme 51**) <2003TL8697>. Similarly, catalytic hydrogenation of 4,5-dihydro-1,2,4-oxadiazol-5-ones also reveals amidines <1995TL4471>. Lithium aluminum hydride with 1,2,3-oxadiazoles breaks the CO bond (**Scheme 52**).

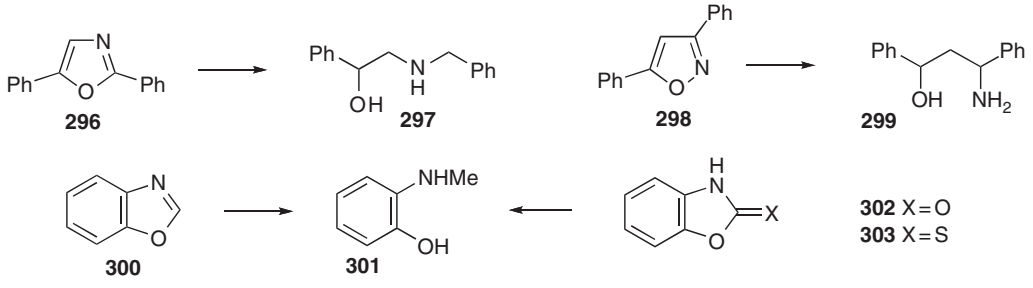


Scheme 51

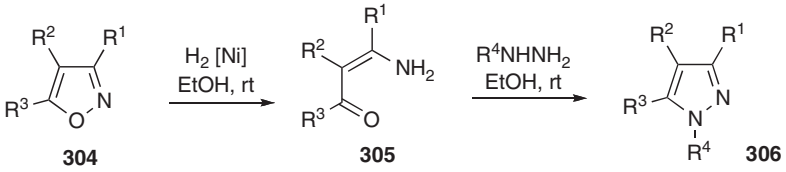


Scheme 52

Nitrogen azoles are less easily reductively ring opened: benzimidazole with lithium aluminum hydride simply gives 2,3-dihydrobenzimidazole.



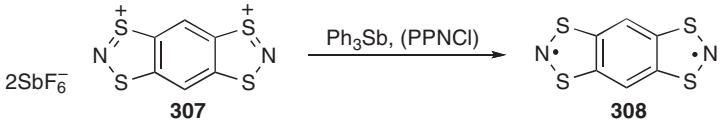
Reductive cleavage of 5-silyl-, and 3- and 5-silylmethylisoxazoles **304** gives -enaminones **305**, which are useful synthons in the regioselective synthesis of silyl- and silylmethylpyrazoles **306** (**Scheme 53**), as well as for pyrroles, pyrimidines, and pyridines <2006T611>.



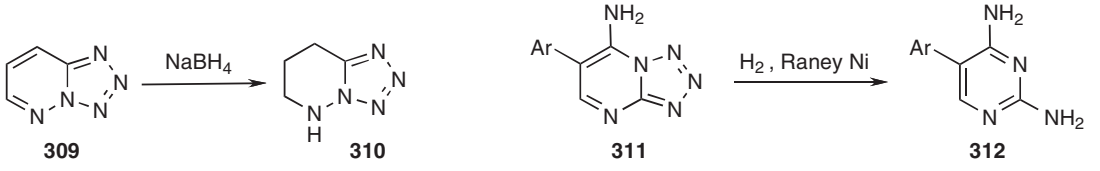
Scheme 53

Reductive cleavage of 2,1,3-benzothiadiazoles to afford the corresponding 1,2-diamines requires vigorous conditions. Both Zn, AcOH <2005JOC2754> and $SnCl_2$, aq. HCl <1997JCM250> afford benzenediamines.

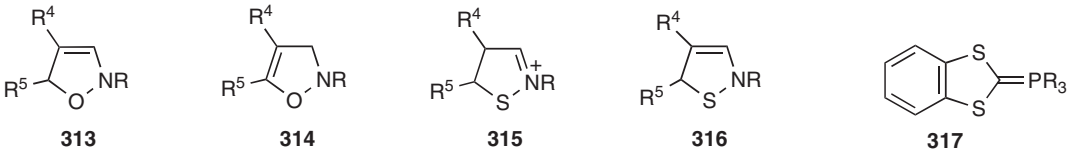
1,3,2-Dithiazolium cations can be readily reduced to stable radicals. Thus reduction of the disalt **307** by electrolysis or by chemical reduction using triphenylantimony bis(triphenylphosphine)iminium chloride [(PPNCl)] <1997JA2633> gave product **308** which is remarkably stable in the solid state, in air, and in organic solutions.

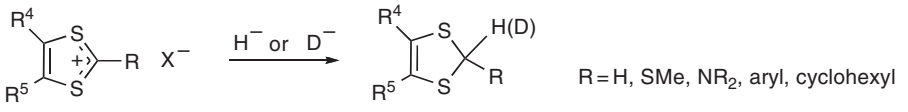


Reduction of tetrazolo[1,5-*b*]pyridazine **309** by sodium borohydride results in the partial reduction of the pyridazine moiety (tetrahydro compound **310** is formed). The catalytic reduction of the substituted tetrazolo[1,5-*b*]pyrimidine **311** affords the diaminopyrimidine **312**.



Cationic rings are readily reduced by complex hydrides under relatively mild conditions. Thus, isoxazolium salts with sodium borohydride give the 2,5-dihydro derivatives **313** in ethanol, but yield the 2,3-dihydro compound **314** in MeCN, H_2O. Thiazolyl ions are reduced to 1,2-dihydrothiazoles by lithium aluminum hydride and to tetrahydrothiazoles by sodium borohydride. The tetrahydro compound is probably formed via **315**, which results from proton addition to the dihydro derivatives **316** containing an enamine function. 1,3-Dithiolylium salts easily add hydride ion from sodium borohydride (**Scheme 54**).





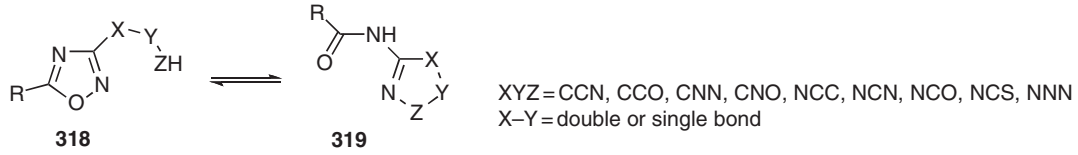
Scheme 54

3.4.1.6.7 Phosphorus nucleophiles

Trialkyl- and triarylphosphines react with 1,3-benzodithiolylium ions to give phosphonium salts which are deprotonated by *n*-butyllithium to give **317**.

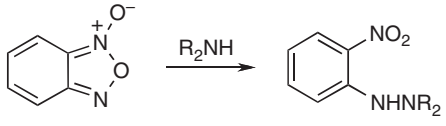
3.4.1.7 Nucleophilic Attack at Nitrogen Heteroatom

1,2,4-Oxadiazoles (and also other 1-oxa-2-azoles) undergo intramolecular nucleophilic displacements of O(1) of the general type (**318** **319**) via the intramolecular attack on N(2) of oxygen, sulfur, nitrogen, and carbon nucleophiles Z forming the third atom of a side-chain at the 3-position of the heterocycle.



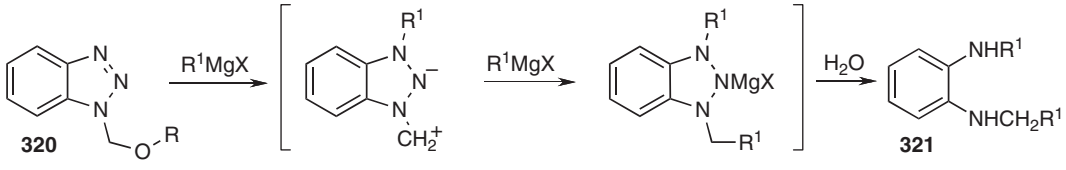
318 **319**

Examples include the synthesis of 3-amino-1,2,4-oxadiazoles starting from 3-acylamino-5-methyl-1,2,4-oxadiazole <2002H811> and 2-aryl-1,2,3-triazoles from 1,2,4-oxadiazole-3-ketone arylhydrazones <1999T12885, 2006JOC5616>. Oximes, hydrazones, formamidines, and thioureas of the furazan series also undergo base-catalyzed mononuclear rearrangements <2004RCB1121>. Nucleophilic attack at N(3) takes place in the benzofuroxan series. For example, reaction with secondary amines leads to *o*-nitroarylhydrazines (**Scheme 55**).



Scheme 55

There are a few examples in which pyridine-like nitrogen atoms of the benzotriazole ring appear to undergo nucleophilic attack by organometallic reagents. Thus, the N(3) atom is attacked by Grignard reagents in (benzotriazol-1-yl)methyl ethers **320** (**Scheme 56**), and in (benzotriazol-1-yl)methyl ammonium salts, to give *o*-phenylenediamines **321** in 1040% yield.

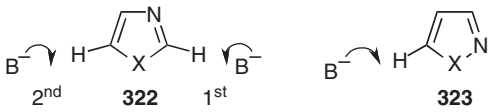


320 **321**

Scheme 56

3.4.1.8 Base Attack at Hydrogen Attached to Ring Carbon or Ring Nitrogen

Hydrogens attached to ring carbon atoms of neutral azoles, and especially azolium ions, are acidic and can be removed as protons by bases. Reaction follows the orientations shown in **322** and **323**. The anions from neutral azoles can be obtained as lithium derivatives, except in isoxazoles where ring cleavage occurs. The zwitterions from azolium rings can react as carbenes.



3.4.1.8.1 Metallation at a ring carbon atom

Neutral azoles are readily C-lithiated by *n*-butyllithium, provided they do not contain a free NH group (**Table 7**). Derivatives with two heteroatoms in the 1,3-orientation undergo lithiation preferentially at the 2-position; other compounds are lithiated at the 5-position.

Table 7 Some typical conditions for lithiation of azoles by *n*-butyllithium

Heterocycle	*Position lithiated*	*Temperature (°C)*
3-Methyl-l-phenylpyrazole	5	
3,5-Disubstituted isoxazoles	4	70 to 65
3,5-Disubstituted isothiazoles	5	70
1-Substituted imidazoles	2	
1-Substituted oxazoles	2	low
1-Substituted thiazoles	2	60
2-Substituted thiazoles	5	100
1-Phenyl-1,2,3-triazoles	5	60 to 20
1-Phenyl-1,2,4-triazole	5	low
1-Substituted tetrazoles	5	60

N-Unsubstituted pyrazole is readily converted into 3(5)-substituted derivatives in a one-pot sequence, using formaldehyde both for N-protection and to mediate the lithiation at the 5-position; the transient *N*-(hydroxymethyl) unit is readily removed during work-up. Direct lithiation of 1-substituted pyrazoles provides an efficient entry to 1,5-disubstituted pyrazoles.

Provided that the annular nitrogen is substituted, imidazoles can be lithiated at ring carbon atoms with the reactivity order C(2) > C(5) > C(4). Suitable N-protecting groups have been developed considering the ease of attachment and removal, steric, and electronic properties. Whereas *n*-butyllithium is frequently the reagent of choice for making lithioimidazoles, LDA has advantages when there are substituents susceptible to nucleophilic attack. Lithium in the presence of isoprene as catalyst at room temperature with near quantitative yield <2005T11148> avoids the need for the typical 78 °C required for lithation with *n*-BuLi.

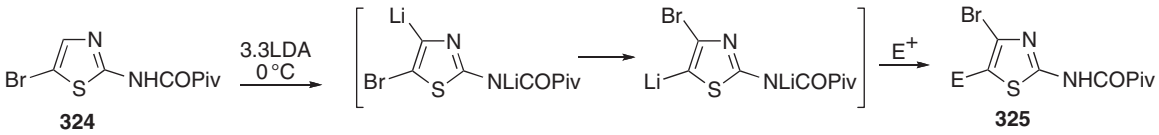
Careful choice of reaction conditions also allows 2-lithiation of imidazoles even in the presence of groups susceptible to attack by the reagent. At 100 °C in THF, 4,5-dicyano-1-methylimidazole forms the 2-lithio compound; at 80 °C, *n*-butyllithium attacks one of the nitrile functions.

Polylithiation at both the 2- and 5-positions gives access to 1,2,5-trisubstituted imidazoles in yields depending on the ability of the 2-anion to further deprotonate at C(5). As the 5-anion is the more reactive, sequential quenching by different electrophiles is possible.

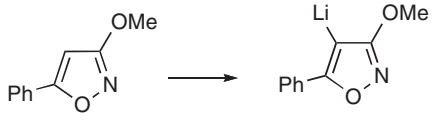
1-Substituted benzimidazoles are readily lithiated in the 2-position, for example, the 2-iodo <2003OL3209, 2003TL8967> and 2-chloro derivatives <2004JOC8115, 2004SL1306, 2005H(65)2721> can be prepared in this way .

Thiazole can be iodinated at C(2) via metallation with *i*-Pr_2MgCl <2001J(P1)442> or chlorinated/brominated after activation with lithium and then reaction with CCl_4/CBr_4 <2000JOM(601)233>; reactions of the organometallic intermediate with typical electrophiles aldehydes <2004AGE3333, 2005BML5241>, tributyltin chloride <2004BML1119>, triisopropylchlorosilane <2004JOC2381>, isocyanates <2004JME6658>, esters <2006JOC4599> are all straightforward. Benzothiazole lithiates at C-2 <2004TL6295>.

The use of halogen dance methodology has been developed in the thiazole series; thus, for example, exposure of bromothiazole **324** to LDA, then an electrophile, gave rise to 4-bromo-5-substituted thiazoles **325** <2005JOC567>.

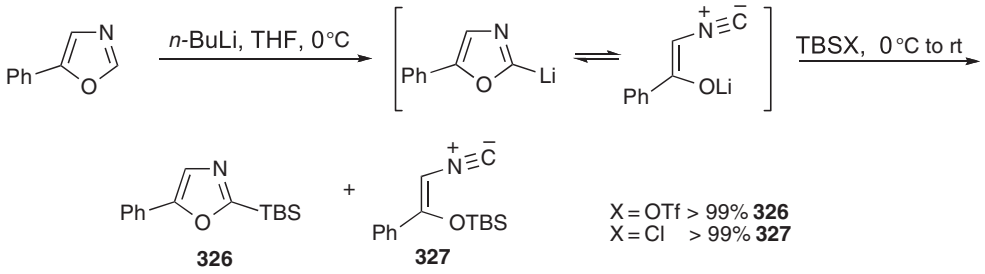


Attempted metallation of isoxazoles usually causes ring opening via proton loss at the 3- or 5-position (Section 3.4.1.8.6); thus, treatment of 5-methylisoxazole with two equivalents of LDA affords the dianion of -cyanoacetone <2001JOC6057, 2004EJO1897>. However, if both 3- and 5-positions are substituted, normal lithiation occurs at C(4) (**Scheme 57**).



Scheme 57

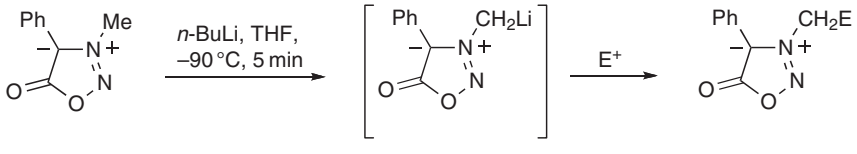
2-Lithiooxazoles exist in equilibrium with their open chain forms: one solution for the synthesis of 2-substituted oxazoles involves 2-silylation (and then reaction with an electrophile). By correct choice of silylating agent, it is possible to trap the ring-closed or ring-opened forms (**Scheme 58**) <2002TL935>.



Scheme 58

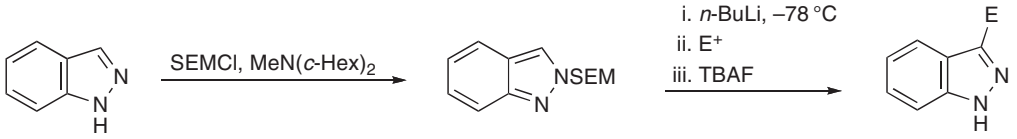
Direct lithiation of 3-(Boc-amino)-5-methylisoxazole and 5-(Boc-amino)-3-methylisoxazole gives N/C-dianions which react with a variety of electrophiles to afford 4-substituted aminoisoxazoles in good yields <1996TL3339>. Metallation of 3-substituted isothiazoles <2002JOC2375, 2004JOC1401> and isoselenazoles proceeds satisfactorily at the 5-positions.

The treatment of thiazole with *n*-butyl- or phenyllithium leads to exclusive deprotonation at C(2). When the 2-position is blocked, deprotonation occurs at C(5). However, if the substituent at C(2) is an alkyl group, the kinetic acidities of the side-chain protons at the 2-position and the ring 5-proton are similar. Similarly, metallation of 1-methylpyrazole with *n*-BuLi takes place mainly at C(5) but also at the methyl (2:1), whereas using $LiNEt_2$ allows exclusive ring lithiation <2002H(57)1211>. Analogous differentiations were achieved with 2-methyloxazoles <1999OL87>. *N*-Methyl metallation of sydnones, for example, to produce 3-lithiomethyl-4-phenylsydnone, is facilitated by the formal positive charge on the nitrogen (**Scheme 59**) <1998RCB1725>.



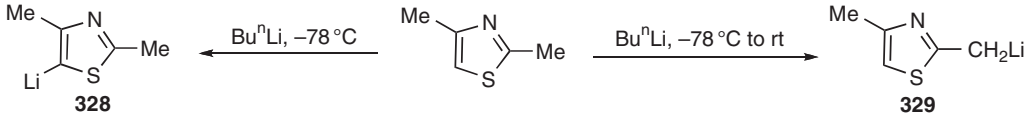
Scheme 59

Straightforward 5-lithiation results using *n*-BuLi with ethyl 3-methoxy-1-methyl-1*H*-pyrazol-4-carboxylate and halides, zincates, or boronic acids can thus be produced <2002SL769>. A neat device allows 3-lithiation of indazole: silylation at N(2) allows the desired 3-metallation (**Scheme 60**) <2006EJO2417>.



Scheme 60

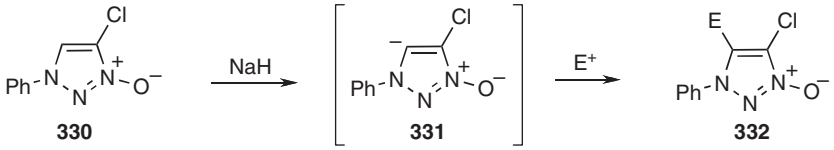
The reaction of 2,4-dimethylthiazole with *n*-butyllithium at 78°C yields the 5-lithio derivative **328** as the major product but if the reaction is carried out at higher temperature, the thermodynamically more stable 2-lithiomethyl derivative **329** is obtained (**Scheme 61**). The metallation at these two positions is also dependent on the strength and bulk of the base employed: lithium diisopropylamide is preferred for selective deprotonations at the 5-position.



Scheme 61

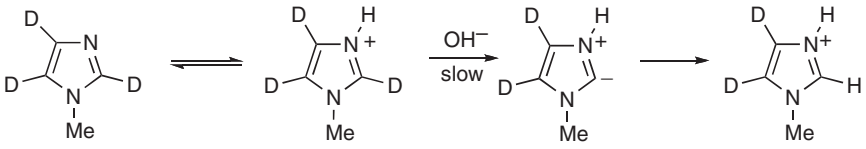
1-Substituted 1,2,3-triazoles (e.g., <1997JOC9177>), 1,2,4-triazoles, and tetrazoles are metallated by *n*-butyllithium at low temperature at the 5-position. At room temperature 5-lithium derivatives tend to undergo ring opening. No direct lithiation of a 2-substituted 1,2,3-triazole has been reported. 2-*tert*-Butyl-1,3,4-oxadiazoles can be lithiated in the usual manner allowing substitution at C(5) <2001JME1268> (see <1995H(41)1525> for a review). Side-chain lithiation of 2,5-dimethyl-1,3,4-thiadiazole can be conducted to give a mono- or a dianion simply by varying the amount of LDA <1999SC145>.

3-Phenyl-5-chlorotriazole 1-oxides **330** are deprotonated with NaH in DMF. The resulting species **331** react with carbon, silicon, and sulfur electrophiles to give substituted products **332** in good yields. Similarly, deprotonation of 1-substituted pyrazole 2-oxides followed by addition of dimethyl disulfide affords 3- and 5-methylthio as well as 3,5-bis (methylthio)pyrazoles.



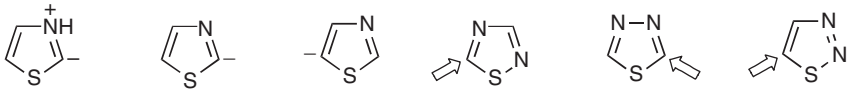
3.4.1.8.2 Hydrogen exchange at ring carbon in neutral azoles

In many examples of base-catalyzed exchange, the protonated azole is attacked by hydroxide ion to form an ylide in the rate-determining step, e.g., for imidazole (**Scheme 62**). Deuteration of imidazole is fast at the 2-position and much slower at the 4- and 5-positions. Rates fall off for N-unsubstituted imidazoles at high pH values because of the formation of unreactive anions. In the case of 1-methylbenzimidazole, the rate of hydrogen exchange in the 2-position is independent of the acidity over a wide range, in agreement with the mechanism shown in **Scheme 62**.



Scheme 62

Under strongly basic conditions, oxazoles undergo fast 2-deuteration and slower 5-deuteration. The hydrogen at the 5-position of isothiazoles exchanges rapidly under basic conditions. Neutral thiazoles exchange by two competitive mechanisms: at pD 011 the conjugated acid exchanges the 2-H via the ylide **333**, whereas at higher pD, exchange is at the 2- and 5-positions via the carbanions **334** and **335**. The acidities of thiazole (pK_a ~28.3) and benzothiazole (pK_a ~28.9) have been measured in THF at 60°C. The 1,2,4- **336**, 1,3,4- **337**, and 1,2,3-thiadiazoles **338** all undergo rapid exchange at 5-, 2-, and 5-positions, respectively.

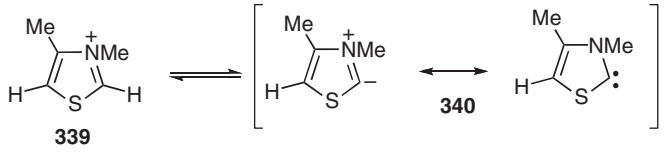


333 **334** **335** **336** **337** **338**

1-Substituted tetrazoles readily exchange the 5-hydrogen for deuterium in aqueous solution. A major rate-enhancing effect is observed with copper(II) or zinc ions due to -complexation with the heterocycle. The rate of base-induced protondeuterium exchange of 1-methyltetrazole is 10^5 times faster than that of 2-methyltetrazole.

3.4.1.8.3 Hydrogen exchange at ring carbon in azolium ions and dimerization

Hydrogen atoms in azolium ions can be removed easily as protons (e.g., **339** **340**); exchange with deuterium occurs in heavy water. The intermediate zwitterion (e.g., **340**) can also be viewed as a carbene as indicated by the resonance contribtor. The pK_a values of thiazolium ions range from 16 to 20.



339 **340**

The relative rates of H-isotope exchange in D_2O, DO for oxazolium, thiazolium, and imidazolium are shown in **Figure 2**. The intermediate ylide/carbene, e.g., **340**, can form a dimer **341** (simply by exposure of the precursor salt to Et_3N <2006OL2377>) or be trapped with azides **342**. It is believed that dimerization of **340** in nonhydroxylic solvents occurs by an additionelimination mechanism involving the ylide acting as a nucleophile and adding to salt, rather than two carbene moieties combining (**Scheme 63**). Thiadiazolium salts are deprotonated 10,000 times faster than thiazolium salts. Hydrogen atoms in positions 3 and 5 of 1,2-dithiolylium ions undergo deprotonation and can be replaced by deuterium. Thiadiazolium salts **343** and **344**, and especially tetrazolium salts (e.g., **345**), exchange particularly rapidly.

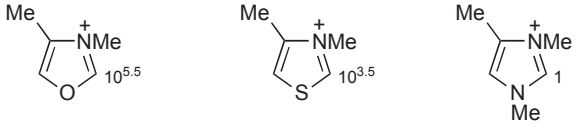
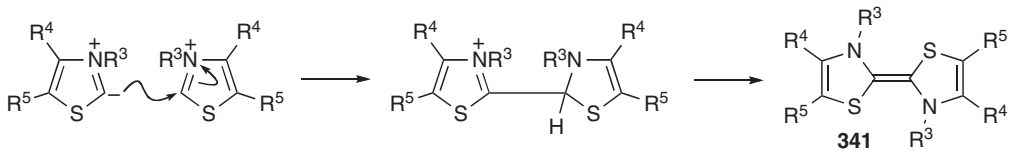
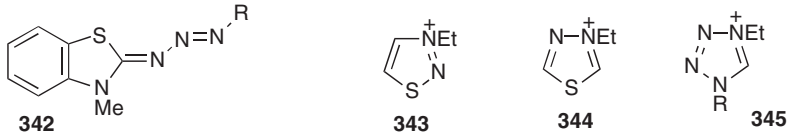


Figure 2 Relative rates of H-isotope exchange in D_2O, DO.

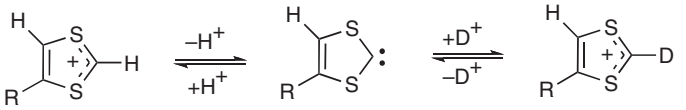


Scheme 63



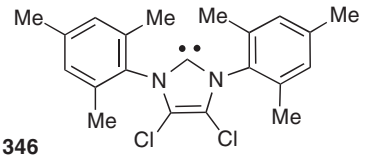
342 **343** **344** **345**

Base-catalyzed hydrogen exchange occurs at the 3- and 5-positions of 1,2-dimethylpyrazolium salts. 2-Unsubstituted 1,3-dithiolylium salts are easily deprotonated by base; the carbene produced easily dimerizes. Hydrogen exchange can also occur (**Scheme 64**).



Scheme 64

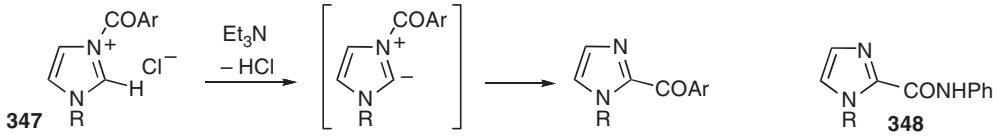
Some carbenes of these types are stable enough for isolation, for example, **346** is air stable <1997JA12742>.



346

3.4.1.8.4 C-Substitution via electrophilic attack at N, deprotonation, and rearrangement

1-Substituted imidazoles can be acylated at the 2-position by acid chlorides in the presence of triethylamine, e.g., <2005JME2154>. This reaction proceeds by proton loss from the N-acylated intermediate **347**. An analogous reaction with phenyl isocyanate gives **348**, probably via a similar mechanism. Benzimidazoles react similarly, but most pyrazoles do not *(*cf. Section 3.4.1.4.6).

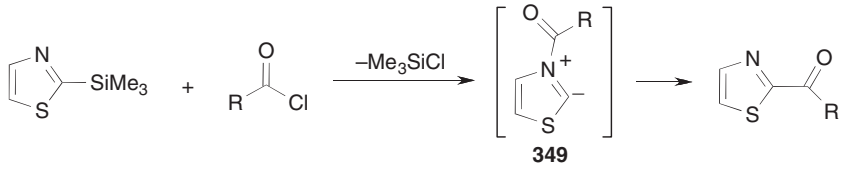


347 **348**

Similar imidazolium ylides are implicated in the aroylation of *N*-phenylbenzimidoyl chlorides and in reactions of 1-substituted imidazoles with cyanogen bromide to form 2-cyano- or 2-bromoimidazoles.

Acid chlorides convert 1-methylbenzimidazol-2-yl-silanes and -stannanes into 2-acylbenzimidazoles. The reaction also works with imidazoles, with the stannanes being more reactive than the silanes. The mechanism is believed to involve initial N-acylation, then loss of the silicon or tin substituent to give a zwitterion, and finally N C migration of the acyl group.

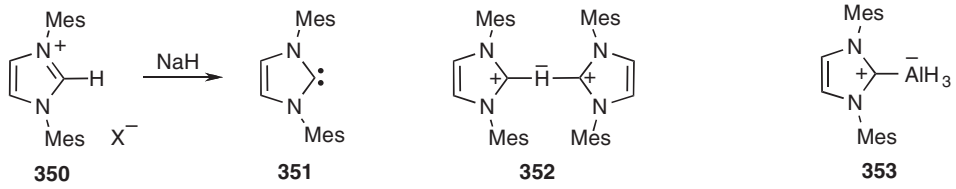
In the case of 2-(trimethylsilyl)thiazole, the acylation of nitrogen and the desilylation at C(2) are likely to be concerted giving rise directly to an *N*-acylthiazolium 2-ylide **349** which then evolves to the 2-acylthiazole by a multistep process (**Scheme 65**).



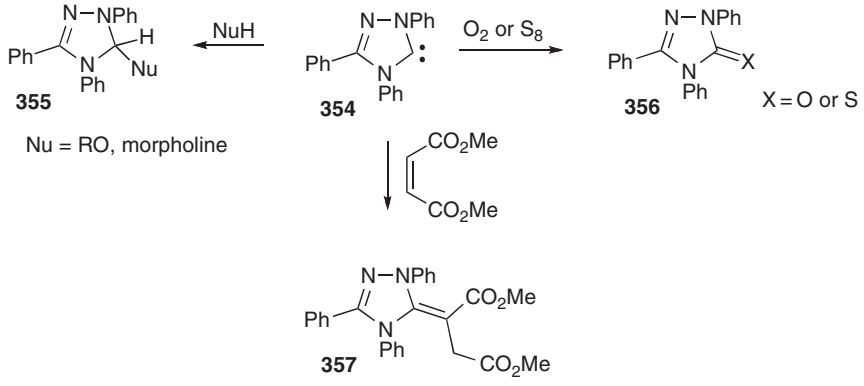
Scheme 65

3.4.1.8.5 Formation and reactions of stable carbenes

Careful treatment of 1,3-disubstituted imidazolium salts (e.g., **350**) with sodium hydride (in some cases addition of a small amount of potassium *tert*-butoxide is also recommended) in tetrahydrofuran gives stable carbenes of type **351** (see also Section 2.4.4.2.3). They behave as rather strong bases (pK_a ~24 in DMSO) and nucleophiles. Thus, carbene **351** and salt **350** form a crystalline bis(carbene)proton complex **352** which is a rare example of an asymmetrical hydrogen bridge between two carbon centers. By the action of BF_3, B_2H_6 or AlH_3NMe_3 stable mesoionic adducts of type **353** are obtained.



By contrast, 1,2,4-triazole carbene **354** displays electrophilic character. Thus, it reacts with alcohols and amines producing triazoline derivatives **355** in quantitative yields. Oxygen or sulfur gives triazolinone and triazolinethione derivatives **356** (similar reaction with tellurium is known for imidazol-2-ylidenes). Reactions of **354** with dimethyl maleate or dimethyl fumarate lead to compounds **357**, probably via ring opening of a cyclopropane intermediate with subsequent 1,2-hydrogen shift.



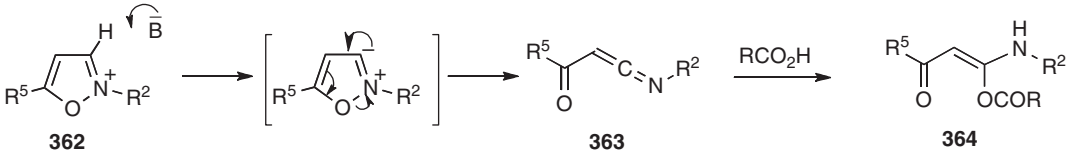
3.4.1.8.6 Ring cleavage via C-deprotonation

Isoxazoles unsubstituted in the 3-position react with hydroxide or ethoxide ions to give -keto nitriles **358** **359**. This reaction involves base attack at the 3-CH group. 1,2-Benzisoxazoles unsubstituted in the 3-position similarly readily

give salicylyl nitriles, and 5-phenyl-1,3,4-oxadiazole **360** is rapidly converted in alkaline solution into benzoylcyanamide **361**. A similar cleavage is known for 3-unsubstituted pyrazoles and indazoles; the latter yield *o*-cyanoanilines.

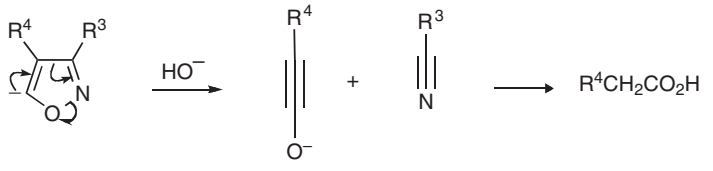
358 **359** **360** **361**

3-Unsubstituted isoxazolium salts **362** lose the 3-proton under very mild conditions, e.g., at pH 7 in aqueous solution, to give intermediate acylketenimines **363** which react with carboxylic acids to form species **364** which can act as efficient acylating agents.

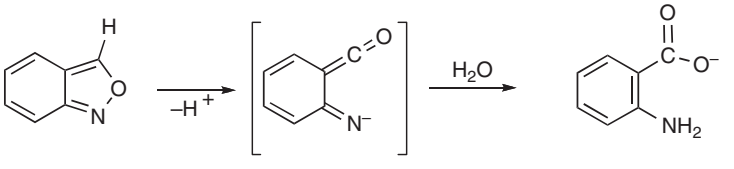


362 **363** **364**

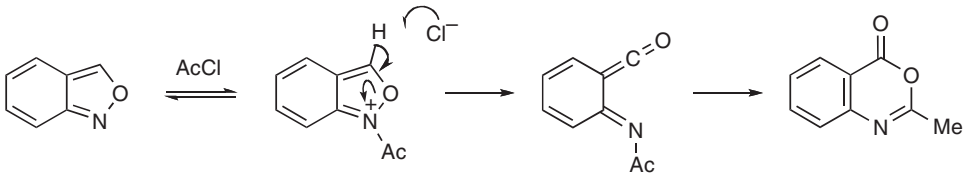
Isoxazoles substituted at the 3-position, but unsubstituted at the 5-position, react under more vigorous conditions to give acids and nitriles (**Scheme 66**). Anthranils unsubstituted at the 3-position are similarly converted into anthranilic acids by bases (**Scheme 67**). Attempted acylation of anthranils gives benzoxazine derivatives via a similar ring opening (**Scheme 68**).



Scheme 66



Scheme 67



Scheme 68

For ring-opening reactions of C-metallated azoles, see Section 3.4.3.8.

3.4.1.8.7 Proton loss from a ring nitrogen atom

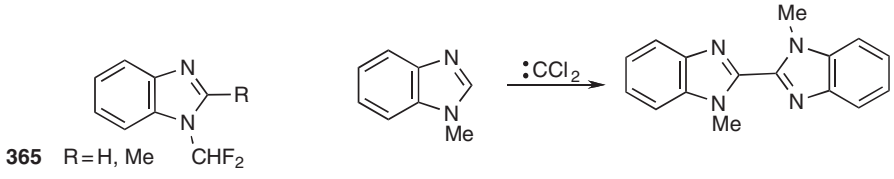
Pyrazoles, imidazoles, triazoles, and tetrazoles are weak NH acids. They form metallic salts (e.g., with $NaNH_2$, RMgBr) that are hydrolyzed by water. The anions react very readily with electrophilic reagents on either ring nitrogen or carbon atoms, as discussed in Sections 3.4.1.3 and 3.4.1.4. For example, proton loss from a ring nitrogen gives the highly nucleophilic imidazole anions. This anion can be formed even with sodium hydroxide or sodium alkoxide; normal practice would be to use a base such as NaH.

Azolinones are weak to medium strong acids of pK_a 411. They form mesomeric anions that react very readily with electrophilic reagents at the nitrogen, oxygen, or carbon atoms, depending on the conditions; see Section 3.4.1.1.4.

3.4.1.9 Reactions with Radicals and Electron-Deficient Species; Reactions at Surfaces

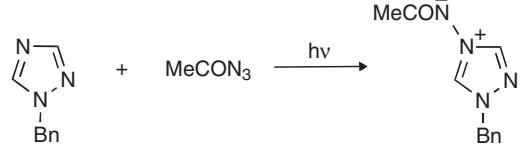
3.4.1.9.1 Carbenes and nitrenes

Imidazoles react with chloroform at high temperature to form azines by carbene insertion and trichloromethyl radicals behave similarly, but carbenes do not always induce ring expansion. In alkaline medium, chlorodifluoromethane converts benzimidazole and its 2-methyl analogue into the 1-difluoromethyl derivatives **365**. Dichlorocarbene under basic conditions N-alkylates benzimidazole, and 1-methylbenzimidazole couples under the influence of the same reagent (**Scheme 69**), perhaps involving initial attack of the carbene at N(3).



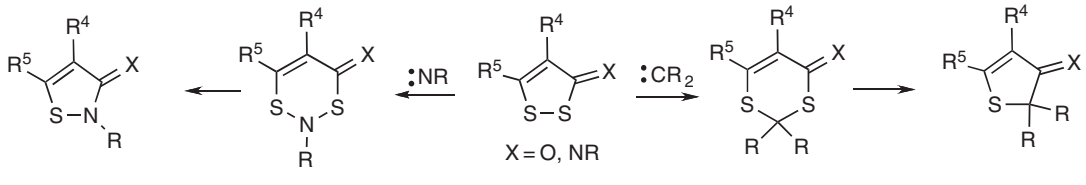
Scheme 69

Pyrazole reacts with chloroform at 550°C (with $:CCl_2$ formation) to give 2-chloropyrimidine in good yield. 1-Alkyl-1,2,4-triazoles react with nitrenes formed by the irradiation of azides to give *N*-imines (**Scheme 70**).



Scheme 70

Most 1,2-dithioles react with carbenes and nitrenes at the SS bond, leading to insertion and possible further loss of sulfur, to form thiophenes and isothiazoles, respectively (**Scheme 71**).



Scheme 71

3.4.1.9.2 Radical attack at the ring carbon atoms

Radical substitution reactions are less developed in azole chemistry than those involving electrophilic or nucleophilic reagents. In some reactions involving radicals, substituents have little orienting effect; however, some rather selective radical reactions are now known.

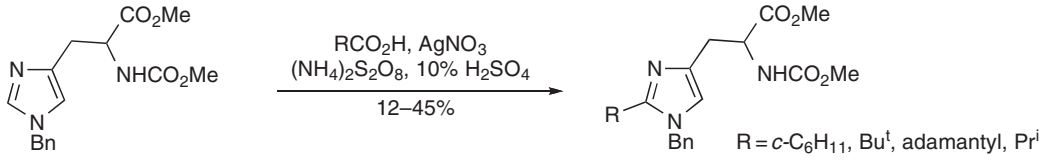
3.4.1.9.2.1 Aryl radicals. Phenyl radicals attack azoles unselectively to form a mixture of phenylated products. Relative rates and partial rate factors are given in **Table 8**. The phenyl radicals can be prepared from PhN(NO)COMe, $Pb(OCOPh)_2$, $(PhCO_2)_2$, or $PhI(OCOPh)_2$.

Table 8 Relative rates and partial rate factors for the homolytic phenylation of azoles

		Partial rate factors			
Heterocycle	*Relative rates*	*2*	*3*	*4*	*5*
Thiazole	1.6	6.2		1.0	2.8
2-Methylthiazole	0.6			1.0	2.4
4-Methylthiazole	1.2	2.9			4.3
5-Methylthiazole	0.8	3.8		1.0	
Isothiazole	0.95		2.7	0.5	2.5
1-Methylpyrazole	0.6		0.18	0.03	3.4
1-Methylimidazole	1.2		2.7	0.5	2.5

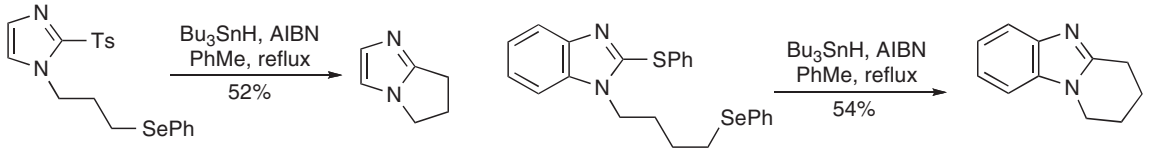
Benzoyl peroxide is the source of the phenyl radicals, except for the first entry, where it is nitrosoacetanilide.

3.4.1.9.2.2 Alkyl radicals. Alkyl radicals produced by oxidative decarboxylation of carboxylic acids are nucleophilic and attack protonated azoles at the most electron-deficient sites. Thus, imidazole and 1-alkylimidazoles are alkylated exclusively at the 2-position. **Scheme 72** shows the substitution of a protected histidine <2001BML1133>. Similarly, thiazoles are attacked in acidic media by methyl and propyl radicals to give 2-substituted derivatives in moderate yields, with smaller amounts of 5-substitution. *N*-Alkyl-1,2,4-triazoles can be radical substituted at C(5) <2001TL7353>.



Scheme 72

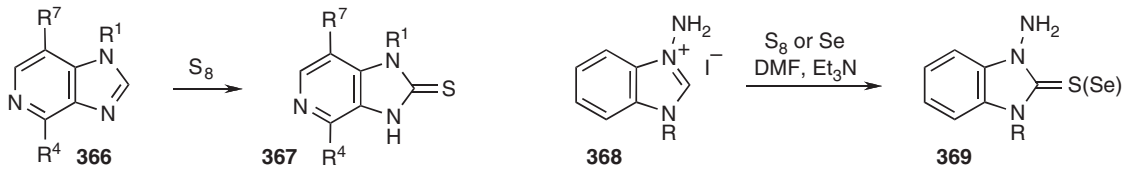
Intramolecular displacements of sulfur substitutents lead to ring formation, e.g., **Scheme 73** <1999T4109>. Similar reactions occur with acyl radicals, for example, with the $CONH_2$ radical from formamide.



Scheme 73

3.4.1.9.3 Thiation

Numerous derivatives of benzimidazoles, naphthoimidazoles, and other condensed imidazole systems can be very effectively thiated with elemental sulfur on heating without solvent at 230260 C. The product of this reaction is the corresponding imidazolin-2-thione formed in excellent yield. For example, imidazo[4,5-*c*]pyridines **366** (R^1 = H, Alk, Ar, $C_6H_5CH_2$) gave 1,3-dihydro-2*H*-imidazo[4,5-*c*]pyridine-2-thiones **367**.



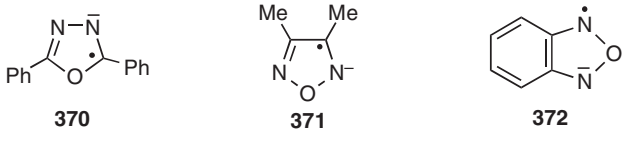
By analogy, imidazolium salts, e.g., **368**, can be converted with a high yield into the corresponding 2-thione or 2-selenone derivatives **369** by heating with sulfur or selenium in DMF in the presence of triethylamine <1990CHE1689>.

Thiation of N-substituted 1,2,4-triazole can also be achieved.

The mechanism of the thiation reaction is unknown, though in the case of quaternary salts one can speculate that it includes formation of the corresponding carbene as a possible intermediate.

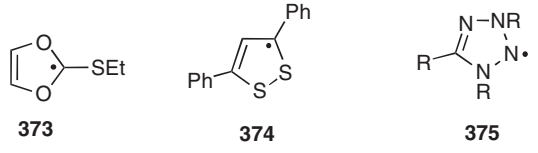
3.4.1.9.4 Electrochemical reactions and reactions with free electrons

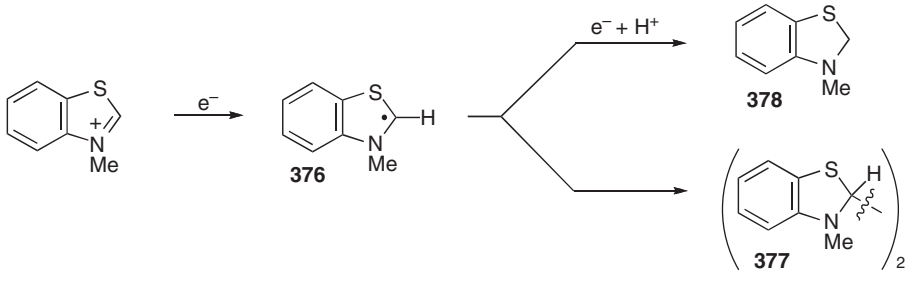
Neutral rings are reduced by the uptake of an electron to form anion radicals. In isoxazole and oxazole, this can be achieved in an argon matrix, but normally ring fission occurs; reduction of 1,2,4-thiadiazoles also usually results in ring cleavage. Thiazoles containing electron-withdrawing groups, 1,3,4-oxadiazoles, 1,2,5-oxadiazoles, and 1,2,5-thiadiazoles, on electrochemical reduction yield transient anion radicals which can be characterized by ESR, e.g., **370** and **371**. Anion radicals from benzazoles can be more stable, e.g., **372**.



Electrochemical reduction of 1-vinylazoles in acetonitrile or DMF is also a one-electron process in which the generated radical anions dimerize.

Cationic rings are reduced with the uptake of one electron (e.g., electrochemically) to give neutral radicals. Examples of radicals which have been detected by ESR are **373** and **374**. Such radicals, e.g., those **376** from benzothiazolium ions, can dimerize (to **377**) or undergo further reduction (to **378**); in practice, a mixture of the dihydro derivative **378** and the dimer **377** is obtained. Benzofurazan is reduced polarographically in a six-electron reaction to *o*-phenylenediamine.

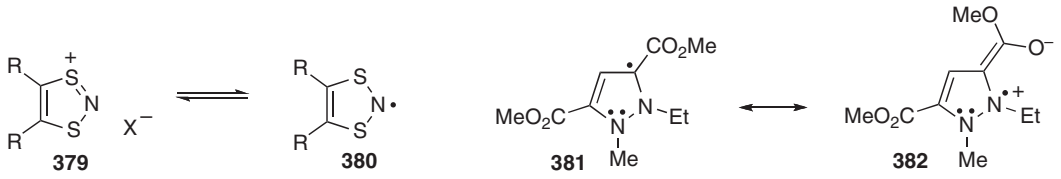




Calculations indicate that 1,2-dithiolyl radicals have large spin densities at the 3,5-positions and that 1,3-dithiolyl radicals have large spin densities at the 2-position. In agreement, radicals of these types unsubstituted at such positions

dimerize very readily; when the position is substituted, the radical is more stable (**373** and **374**). Reduction of tetrazolium salts gives tetrazolyl radicals **325** that show appreciable spin density on all four ring nitrogen atoms.

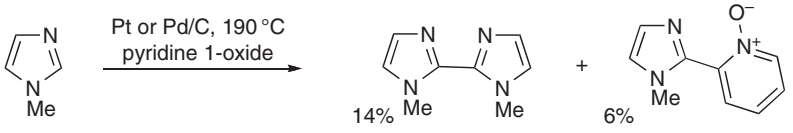
1,3,2-Dithiazolium cations **379** are easily reduced to the corresponding stable radicals **380** which in turn can be smoothly oxidized back to the cation. The cations can also be reduced electrochemically; cyclic voltammetry shows this to be a reversible process.



Electron-withdrawing substitutents stablilize such neutral radicals considerably; thus, merostabilization is found, for example, in the pyrazolyl derivative **381** **382**.

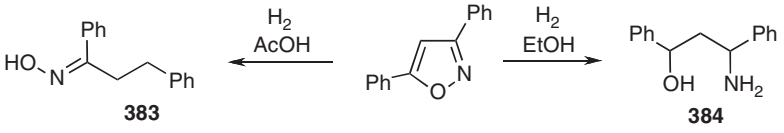
3.4.1.9.5 Other reactions at surfaces (catalytic hydrogenation and reduction by dissolving metals)

In general, azoles containing a cyclic oxygen atom are readily reduced, those with cyclic sulfur with more difficulty, and wholly nitrogenous azoles not at all. Pyrazoles are very resistant to catalytic reduction, resisting hydrogenation over nickel at 150°C and 100 atm. So resistant are imidazoles to catalytic hydrogenation that 1-methylimidazole, benzimidazole, and its 1-methyl derivative condense dehydrogenatively in the presence of platinum- or palladium-carbon catalyst and pyridine 1-oxide (**Scheme 74**). Imidazole itself does not appear to dimerize to any extent under the same conditions.

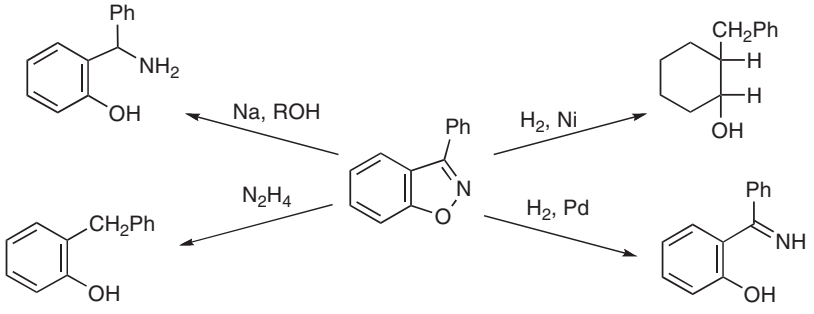


Scheme 74

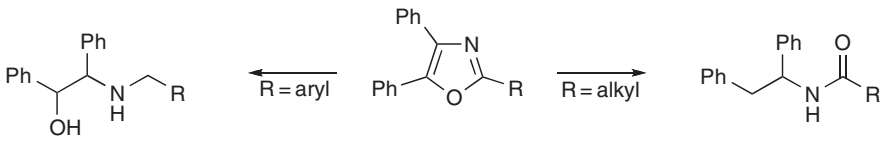
Isoxazoles are readily reduced, usually with concomitant ring fission. Thus, solvent-dependent hydrogenolysis of 3,5-diphenylisoxazole in the presence of palladium on charcoal resulted in open-chain products **383** and **384**.



1,2-Benzisoxazoles are easily reduced to various products (**Scheme 75**). Chemical or catalytic reduction of oxazoles invariably cleaves the heterocyclic ring (**Scheme 76**). For similar reactions of thiazoles, see Section 3.4.1.5.1.

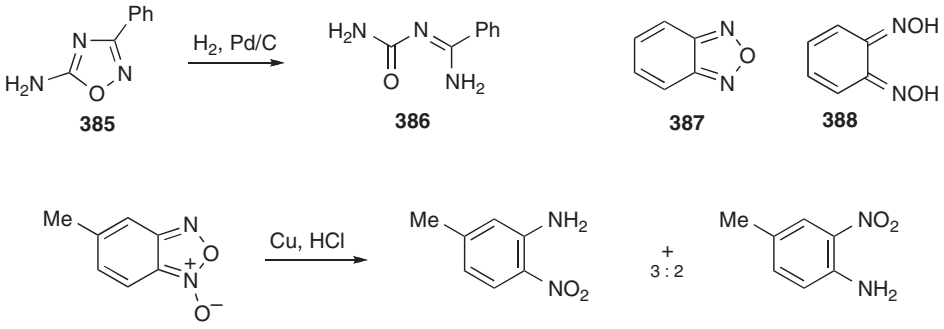


Scheme 75



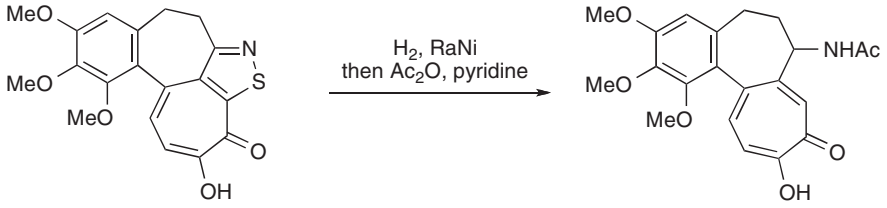
Scheme 76

Catalytic reduction of 1,2,4-oxadiazoles also breaks the NO bond; e.g., **385** gives **386**. Benzofuroxan can be reduced under various conditions to benzofurazan **387**, the bis-oxime **388**, or *o*-phenylenediamine. Reduction using copper and hydrochloric acid produces *o*-nitroanilines (**Scheme 77**).

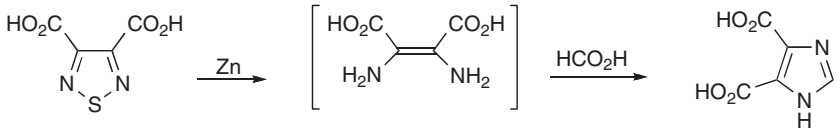


Scheme 77

Isothiazoles are reductively desulfurized by Raney nickel, e.g., as in **Scheme 78**. 1,2,5-Thiadiazoles are subject to reductive cleavage by zinc in acid, sodium in alcohol, or Raney nickel, e.g., **Scheme 79**.

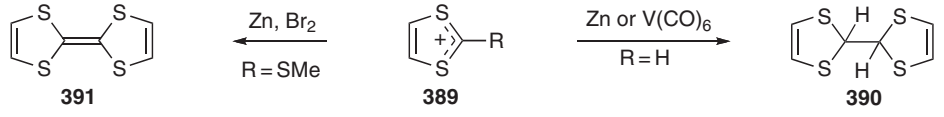


Scheme 78



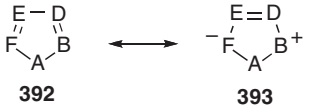
Scheme 79

Reduction of 2-unsubstituted 1,3-dithiolylium salts, e.g., **389** (R = H), with zinc or hexacarbonyl-vanadate leads to dimerization affording **390**; the reduction of 2-methylthio-dithiolylium iodide **389** (R = SMe) with zinc in the presence of bromine, however, gives TTF **391**.



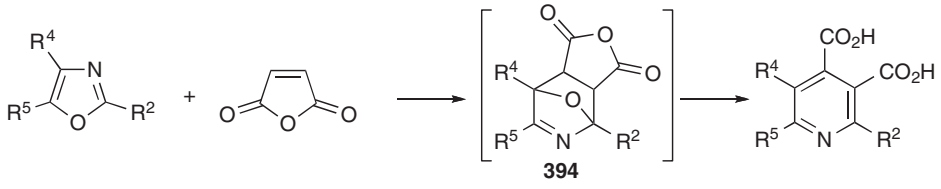
3.4.1.10 Reactions with Cyclic Transition States

The distinction between DielsAlder reactions and 1,3-dipolar cycloadditions is semantic for the five-membered rings: DielsAlder reaction at the F/B positions in **392** (four-atom fragment) is equivalent to 1,3-dipolar cycloaddition in **393** across the three-atom fragment, both providing the 4-electron component of the cycloaddition. Oxazoles and isoxazoles and their polyaza analogues show reduced aromatic character and will undergo many cycloadditions, whereas fully nitrogenous azoles such as pyrazoles and imidazoles do not, except in certain isolated cases.

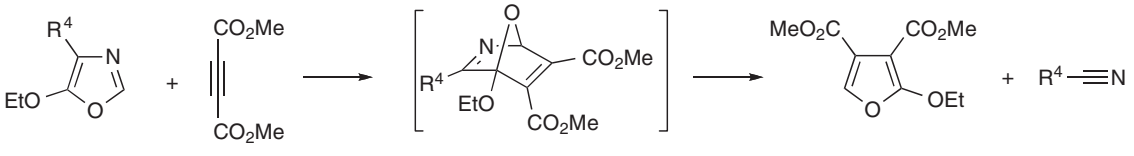


3.4.1.10.1 Heterocycles as inner ring dienes

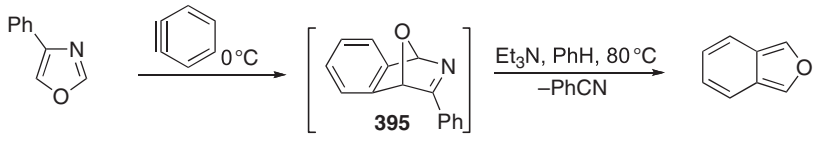
DielsAlder reactions of oxazoles afford useful syntheses of pyridines (**Scheme 80**). A study of the effect of substituents on the DielsAlder reactivity of oxazoles has indicated that rates decrease with the following substituents: alkoxy > alkyl > acyl >> phenyl. The failure of 2- and 5-phenyl-substituted oxazoles to react with dienophiles is probably due to steric crowding. In certain cases, bicyclic adducts of type **394** have been isolated; they can also decompose to yield furans (**Scheme 81**). With benzyne, generated at 0 °C from 1-aminobenzotriazole and lead tetraacetate under dilute conditions, oxazoles form cycloadducts (e.g., **395**) in essentially quantitative yields. The adducts can be handled at room temperature and are decomposed at elevated temperatures to isobenzofuran (**Scheme 82**).



Scheme 80

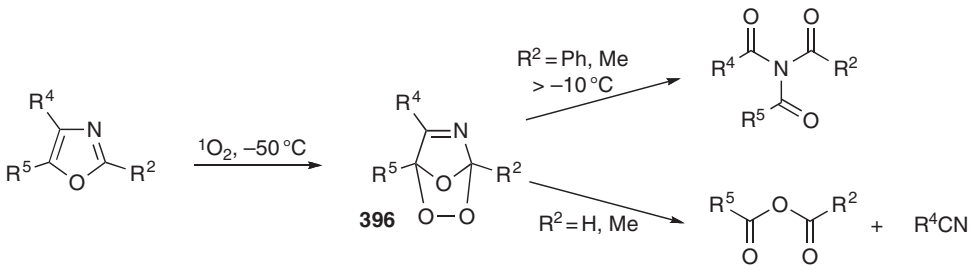


Scheme 81



Scheme 82

Reactions of oxazoles with heterodienophiles, including N=N, C=N, C=O, and C=S types, give new heterocycles. Oxazoles react with singlet oxygen to give bicyclic adducts of type **396**. Direct evidence (^{1}H and ^{13}C NMR) for these adducts was obtained by running the reactions at temperatures below 50 °C. Between 10 °C and RT, the peroxide products rearrange or fragment (**Scheme 83**). The reaction pathway depends on the nature of the substituent at the 2



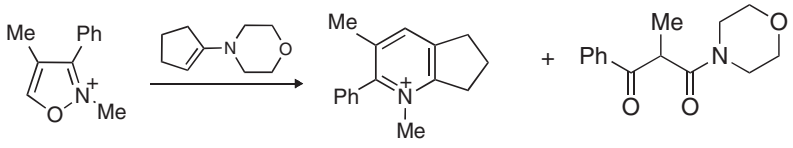
Scheme 83

position of the oxazole: for R^2 = phenyl, triacylamides are formed quantitatively; for R^2 = H, a 1:1 mixture of R^4CN and anhydrides is obtained and for R^2=methyl, both pathways occur with the ratio of the former to the latter changing with the number and nature of R^4 and R^5 substituents.

Singlet oxygen will also cycloadd to 4,5-diphenylimidazole to form a 2,5-endoperoxide, the subsequent decomposition of which is complex <2002JA9629>.

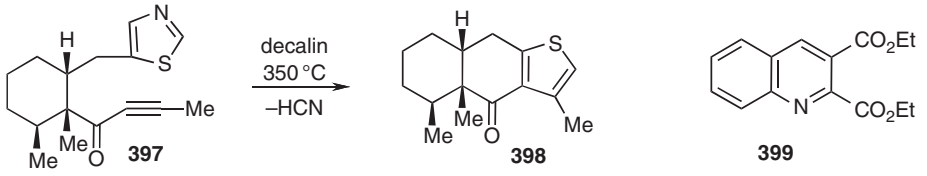
5-Aminopyrazoles react as dienophiles in inverse electron demand DielsAlder reactions of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine in a synthesis of pyrazolo[3,4-*d*]pyrimidines <1996JOC5204>.

Isoxazolium salts react with enamines to give pyridinium salts (**Scheme 84**).



Scheme 84

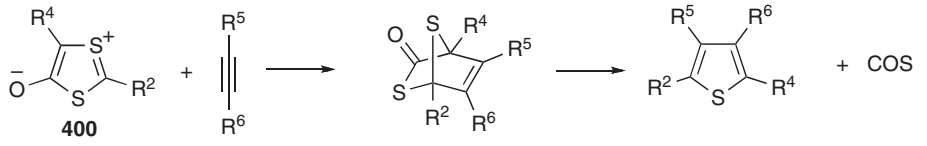
Thiazoles have a low reactivity in cycloaddition reactions. However, it has been possible to achieve intramolecular DielsAlder reactions in some cases (e.g., **397** **398**).



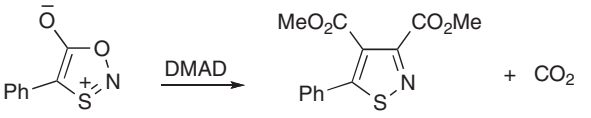
Singlet oxygen adds in a [4 + 2] fashion to the thiazole nucleus forming adducts similar to those of oxazoles (cf. **395**).

Ethyne-dicarboxylate esters add to 2,1-benzoisothiazole to generate quinoline esters **399**, and benzyne reacts to yield acridine.

1,3-Dithiolylium-4-olates **400** undergo cycloaddition reactions, e.g., as in **Scheme 85**. The mesoionic 1,3-dioxolium-4-olates show a similar pattern of reactivity to produce furans. **Scheme 86** gives an example of cycloaddition in the oxathiazole series.

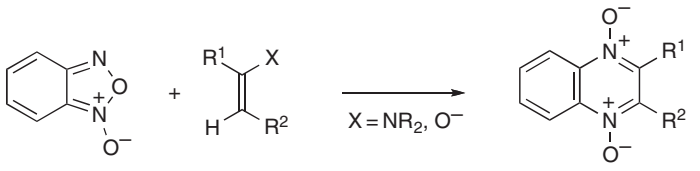


Scheme 85

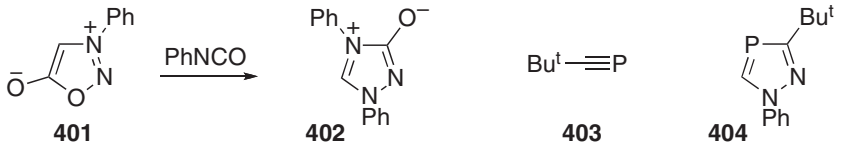


Scheme 86

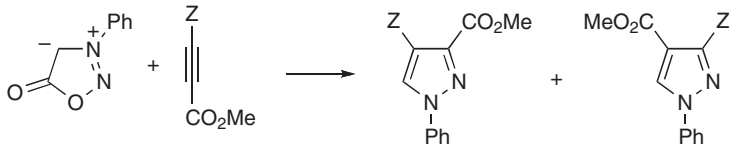
Enamines and enolate anions react with benzofuroxan to give quinoxaline di-*N*-oxides (**Scheme 87**).



Scheme 87



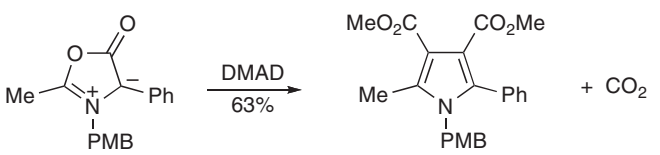
Sydnones can be regarded as cyclic azomethine imines and as such they undergo thermal cycloaddition reactions with a range of dipolarophiles. Thus, reaction with phenyl isocyanate converts **401** into 1,2,4-triazole **402**. On photolysis, 3,4-diarylsydnones lose carbon dioxide and give nitrile imines, which can also be intercepted by dipolarophiles. Thermal reactions with acetylenic dipolarophiles lead to the formation of pyrazoles (**Scheme 88**); however, these reactions are rarely completely regioselective with unsymmetrical alkynes, e.g., <2000BKC761, 2000TL1687>.



Z = CH(OMe)$_2$, 84%	79	21
Z = CHO, 93%	34	66
Z = CH$_2$OH, 79%	40	60

Scheme 88

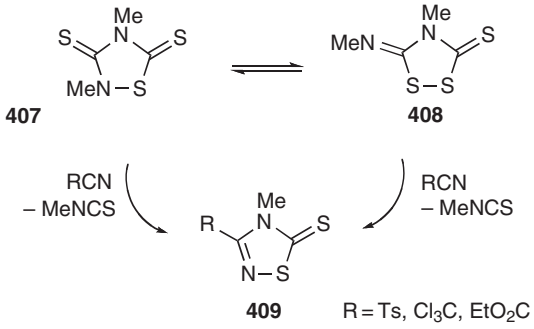
The phosphaalkyne **403** adds to 3-phenylsydnone regioselectively to give the heterocycle **404** in high yield. Mnchnones (1,3-oxazolium-5-olates), traditionally generated by the cyclodehydration of *N*-acylamino acids using acetic anhydride or a carbodiimide, also take part in cycloadditions, as exemplified in **Scheme 89** <1996JA2574>. The



Scheme 89

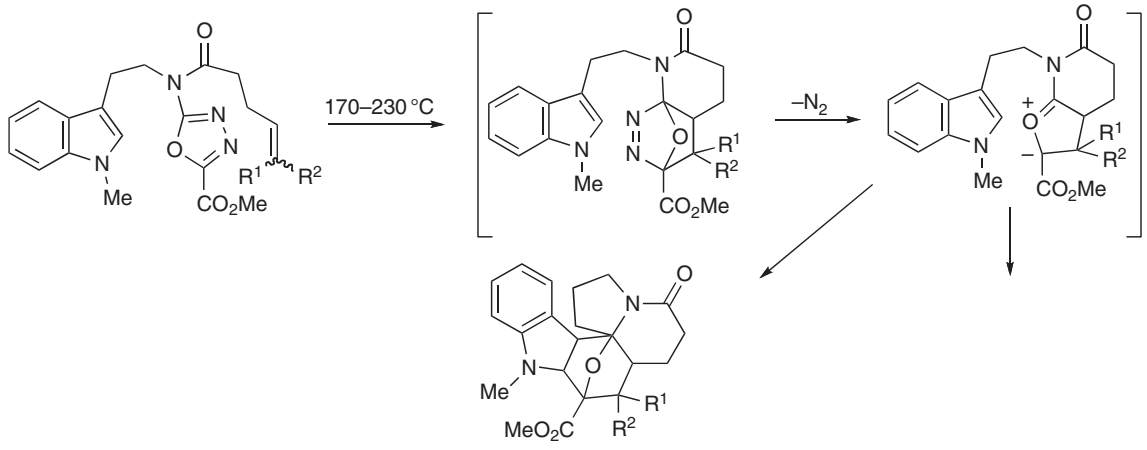
tautomerization of azlactones [5(4*H*)-oxazolones] also gives mnchnones; thus, a crystalline mnchnone has been isolated and fully characterized; the tautomerization favors **406** over **405** in the presence of triethylamine <1997PJC1045>.

The 1,2,4-thiadiazolidine **407** and the 1,2,4-dithiazolidine **408** are interconvertible in the presence of electrophilic nitriles and give the 1,2,4-thiadiazolin-5-ones **409** as products (**Scheme 90**). It is suggested that the reaction goes through a consecutive cycloadditionelimination mechanism via hypervalent sulfur intermediates in which the nitrile approaches in the plane of the heterocycle.



Scheme 90

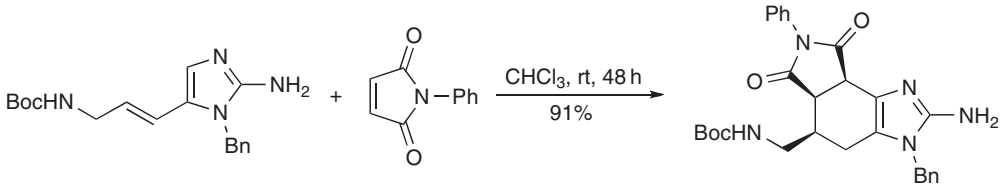
Most of the reports of cycloadditions involving electron-deficient 1,3,4-oxadiazoles in intermolecular reactions have employed symmetrical oxadiazoles bearing strongly electron-withdrawing substituents (CF_3, SO_2Et, CO_2Me): alkynyl dienophiles, for example, produce good yields of furans following subsequent loss of nitrogen <2002JOC7361>. Extensive and elegant use has been made of intramolecular cycloadditions to 1,3,4-oxadiazoles in complex skeleton synthesis as illustrated in **Scheme 91** <2002JA11292>.



Scheme 91

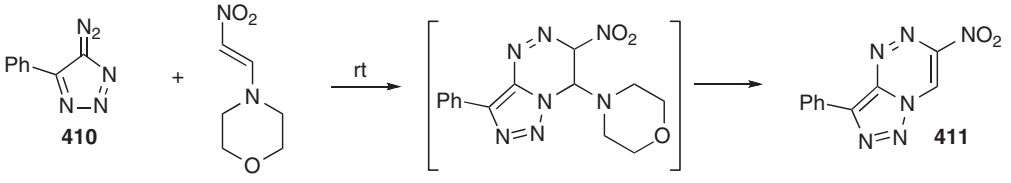
3.4.1.10.2 Heterocyclic derivatives as innerouter ring dienes

N-Acetyl-5-styrylpyrazoles undergo DielsAlder cycloadditions with *N*-methylmaleimide to give tetrahydroindazoles in good yields <2006SL1369>. Similarly, 5-vinyl-1-substituted-2-aminoimidazoles react to produce tetrahydrobenzimidazoles, e.g., **Scheme 92** <2006SL965>.

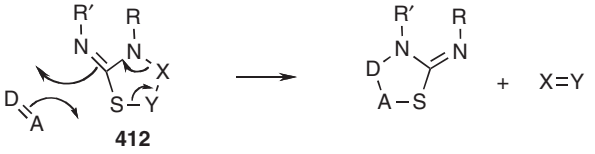


Scheme 92

Diazo-substituted 1,2,3-triazoles undergo regiospecific dipolar cycloaddition reactions with electron-rich unsaturated compounds. Thus, 4-diazo-5-phenyl-4*H*-1,2,3-triazole **410** reacts with 1-morpholinyl-2-nitroethene by a net 1,7-cycloaddition and elimination of morpholine to give the product **411**.



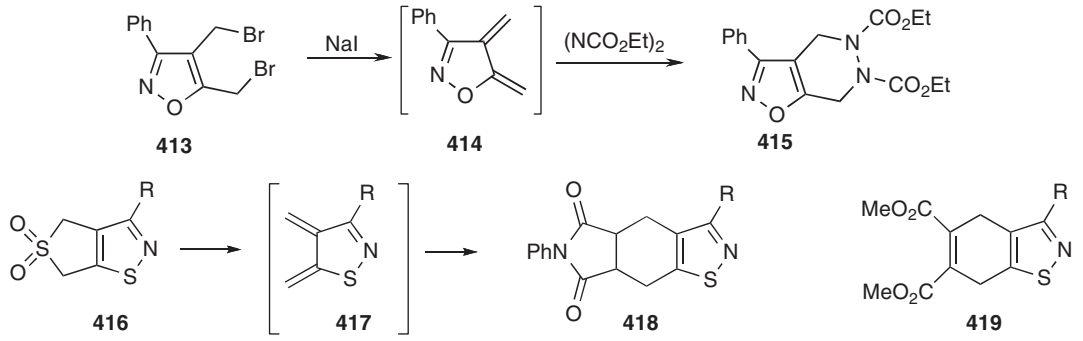
LabbÕ formulated a general rule on the basis of extensive investigations of the reaction of sulfur-containing five-membered heterocycles with isocyanates and isothiocyanates: a heterocycle having an imino group conjugated with the ring sulfur atom **412** should interact with heteracumulenes by the pattern of cycloadditionelimination with extrusion of the XY fragment (**Scheme 93**).



Scheme 93

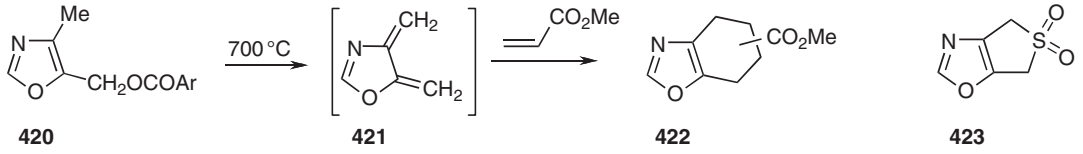
3.4.1.10.3 Heterocyclic derivatives as outer ring dienes

Treatment of 4,5-bis(bromomethyl)-3-phenylisoxazole **413** with sodium iodide and subsequently with diethyl azodicarboxylate gives DielsAlder cycloadduct **415**. Intermediate 1,2-quinodimethide **414** participates in the reaction as a 1,3-diene. Similarly, microwave heating provides a general methodology for the generation of *o*-quinodimethanes derived from 4,5-bis(bromomethyl)-1-phenylpyrazole in the presence of excess NaI in DMF <2006SL579>. The thermolysis of isothiazolo-3-sulfolenes **416** allows the generation of diene **417** which can be trapped with dienophiles, for example, giving **418** or **419** (**Scheme 94**) <1996TL4189>.



Scheme 94

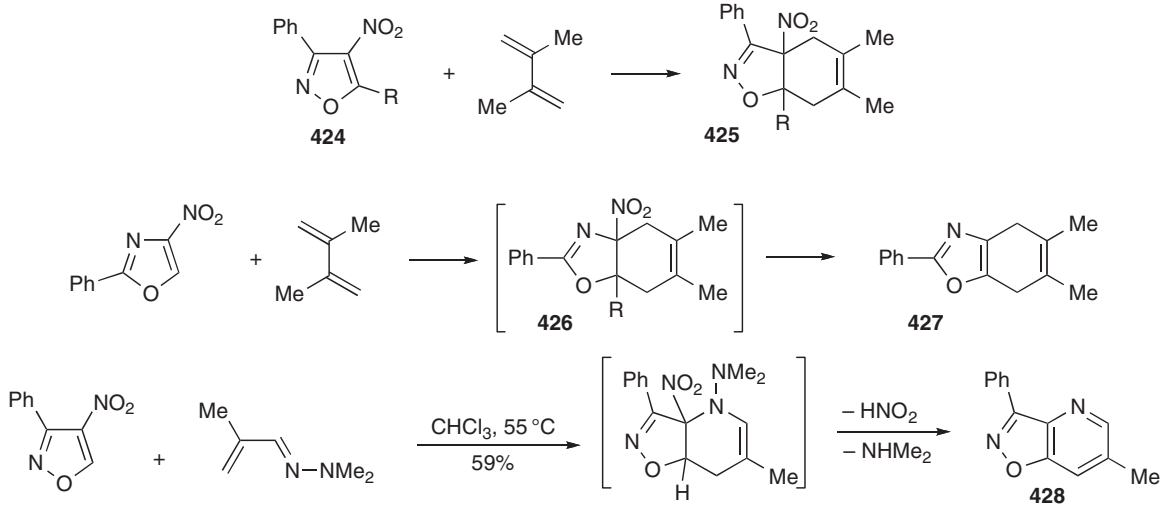
By analogy, flash vacuum pyrolysis of a *p*-chlorobenzoate ester **420** (Ar = 4-ClC_6H_4) produces oxazole-4,5-xylylene **421**, which can be trapped with SO_2 to give adduct **423**. The unstable intermediate also gives a DielsAlder adduct with methyl acrylate **422**.



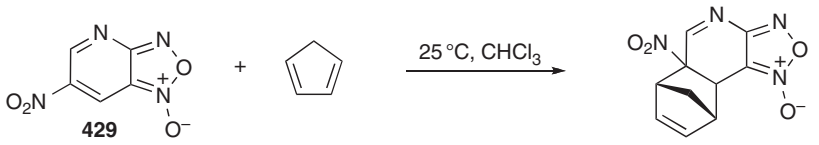
3.4.1.10.4 Heterocycles as dienophiles

Isoxazoles with electron-withdrawing substituents readily undergo cycloadditions as dienophiles, e.g., <1995T7085>. For example, the nitroisoxazoles **424** with 2,3-dimethylbutadiene form the adducts **425**. Similar reaction with 4-nitro-2-phenyloxazole leads to **427** possibly via initial adducts **426**. A nice example, leading to a pyrido-isoxazole **428**, is shown in **Scheme 95** where the diene is the dimethylhydrazone of methacrolein <1995T7085>.

In nitrobenzofuroxans, e.g., **429**, there is low aromaticity in the carbocyclic ring, and the nitroalkene fragment participates as a dienophile in a variety of DielsAlder processes under extraordinarily mild conditions, e.g., **Scheme 96** <1997JOC7178, 1997JOC8687, 2000J(P2)51, 2000JOC7391, 2002T3249, 2004ARK(iii)85, 2006OBC1910>.

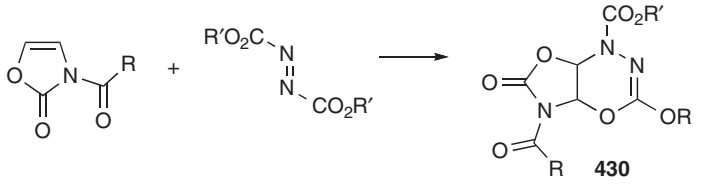


Scheme 95



Scheme 96

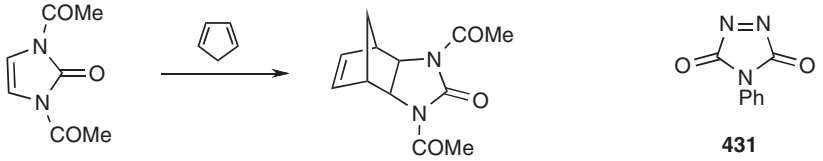
The 4,5-double bond of 2(3*H*)-oxazolones participates in thermal [4 + 2] cycloaddition reactions. With dialkyl azodicarboxylates the addition occurs at 80°C to give the cycloadducts **430** (**Scheme 97**). With a chiral substituent attached to N(3), diastereoselectivities as high as 72% can be obtained. Cycloadditions with cyclopentadiene or benzofuran require higher temperatures and longer reaction times, but can yield highly efficient chiral oxazolidin-2-one auxiliaries.



Scheme 97

1,3-Diacetyl-2-imidazolone reacts with cyclopentadiene in what appears to be a DielsAlder reaction (**Scheme 98**).

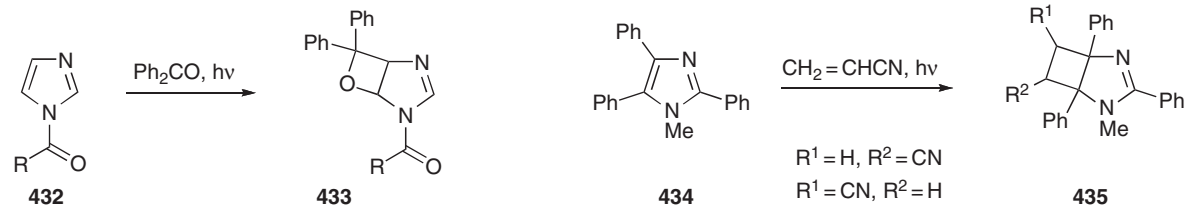
4-Phenyltriazolinedione (PTAD) **431** finds extensive use as a dienophile. PTAD has been used as a protecting group for dienes, for example, in steroids, since it can be readily removed under mild conditions by treatment with a base (e.g., K_2CO_3, DMSO).



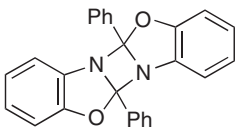
Scheme 98

3.4.1.10.5 [2+2] Cycloaddition reactions

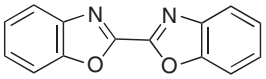
Photochemical additions to give four-membered rings are known. Thus, the reactions of imidazoles across the 4,5-bond with benzophenone and acrylonitrile are illustrated by **432** **433** and **434** **435**, respectively. Oxazolin-2-one undergoes acetone-photosensitized photochemical addition to ethylene.



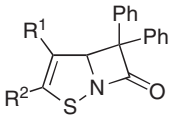
Irradiation of 2-phenylbenzoxazole forms a head-to-tail dimer, 1,3-diazetidine **436**, whereas benzoxazole itself, in the presence of oxygen, gives the dimeric product, **437**. Isothiazoles yield lactams **438** on reaction with diphenylketene. Benzotriazole and its 2-alkyl derivatives undergo photochemical (> 290 nm) [2 + 2] cycloaddition to maleinimides to give adducts **439** <2002OL1487>.



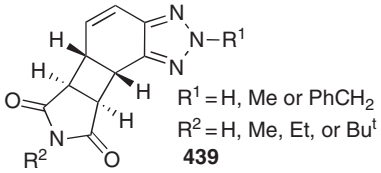
436



437



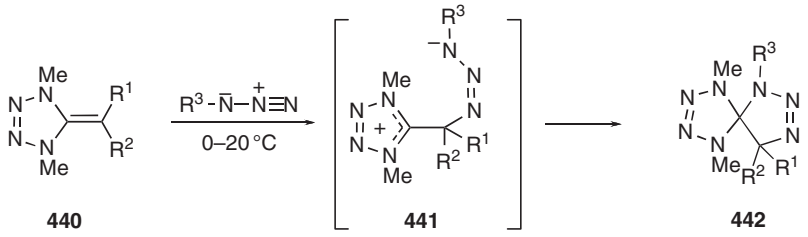
438



439

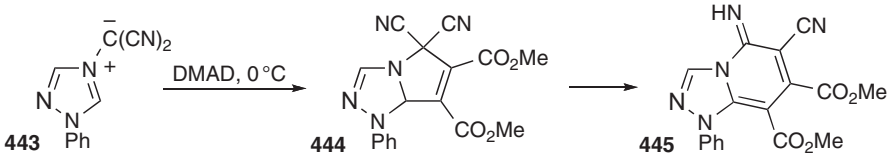
3.4.1.10.6 Other cycloaddition reactions

5-Alkylidene-1,4-dimethyltetrazolines **440** behave as electron-rich enamines for inverse-electron demand cycloadditions with electrophilic 4-systems such as covalent azides. Cycloaddition reactions with alkyl and aryl azides at 020 C give high yields of the spirotriazolines **442**. These are formed from a nonconcerted two-step cycloaddition which is at the extreme of the 1,3-dipolar cycloaddition mechanistic range. Remarkably, when R^3 is strongly electron withdrawing, some of the zwitterionic intermediates **441** are sufficiently stable for isolation. Heating intermediates **441** in $CDCl_3$ converts them into the 1,2,3,4-tetrazine derivatives with loss of N_2.



440 441 442

1-Phenyl-1,2,4-triazolium dicyanomethylide **443** undergoes 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate. The primary product of the reaction **444** can be isolated under carefully controlled conditions. On gentle heating, it is transformed into a 1,2,4-triazolo[3,4-*a*]pyridine derivative **445**. Many other azolium ylides undergo similar reactions.



443 444 445

3.4.2 Reactions of Nonaromatic Compounds

Discussion of these compounds is divided into (1) isomers of aromatic compounds and (2) dihydro and tetrahydro derivatives. The isomers of aromatic azoles are a relatively little-studied class of compounds. Dihydro and tetrahydro derivatives with two heteroatoms are quite well studied, but such compounds become more obscure and elusive as the number of heteroatoms increases. Thus, dihydrotriazoles are rare; dihydrotetrazoles and tetrahydrotriazoles and tetrahydrotetrazoles are unknown unless they contain doubly bonded exocyclic substituents.

S-Oxides of sulfur-containing azoles comprise another class of nonaromatic azoles.

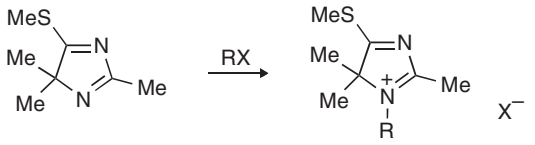
3.4.2.1 Isomers of Aromatic Derivatives

3.4.2.1.1 Compounds not in tautomeric equilibrium with aromatic derivatives

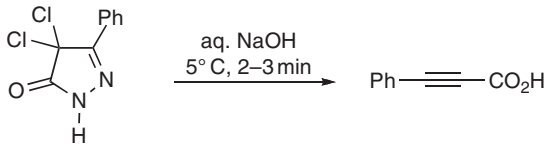
The 3*H*- and 4*H*-pyrazoles and 2*H*- and 4*H*-imidazoles contain two double bonds in the heterocyclic ring, but in each case the conjugation does not include all the ring atoms; hence, the compounds are not aromatic.

The quaternization of 5*H*-imidazoles occurs at the 1-position (**Scheme 99**). 4*H*-Pyrazoles are also readily monoquaternized.

Dichloropyrazolinones with alkali give alkynoic acids (**Scheme 100**).

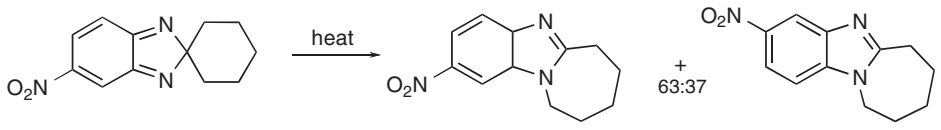


Scheme 99



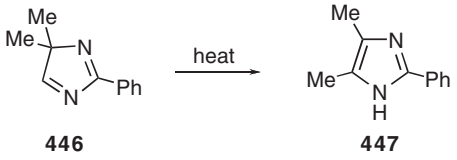
Scheme 100

Migrations of C-linked substituents around the ring, on to carbon or nitrogen atoms, are common among these compounds. This is known as the van AlphenHuttel rearrangement and by it 3*H*-pyrazoles are converted thermally into 1*H*-pyrazoles. Similarly, 2*H*-imidazoles rearrange thermally to their 1*H*-counterparts. Migratory aptitudes in a series of 4,5-diphenyl-2*H*-imidazoles are in the order $PhCH_2 > Ph > Et > Me$, while spiro-2*H*-imidazoles and -benzimidazoles form bi- and tricyclic species when the C N rearrangement takes place (**Scheme 101**).



Scheme 101

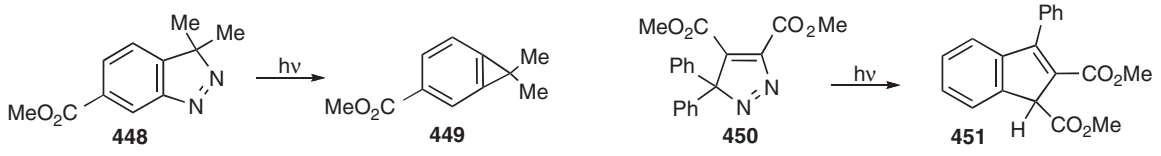
Like 2*H*-imidazoles, 4*H*-imidazoles also rearrange thermally to the more stable 1*H*-compounds, but migration is to carbon in this instance; thus 4,4-dimethyl-4*H*-imidazole **446** rearranges quantitatively to the 4,5-dimethyl-1*H*-isomer **447** by successive [1,5]-methyl and -hydrogen shifts.



446 **447**

3*H*-Pyrazoles are photochemically converted into cyclopropenes, and 3*H*-indazoles react similarly, e.g., (**448** **449**). If a 3-aryl group is present, an indene can be formed, e.g., **450** **451**.

Peracids can oxidize 2*H*-imidazoles to *N*-oxides and *N*,*N*-dioxides, and sometimes to imidazolinones. Lead dioxide in methanol converts 2*H*-imidazole 1,3-dioxides into stable nitroxide radicals.

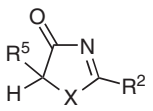


448 **449** **450** **451**

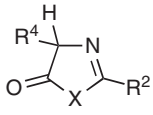
Addition of nucleophiles to C=N bonds is common in these compounds.

3.4.2.1.2 Compounds in tautomeric equilibria with aromatic derivatives

Compounds of types **452** and **453** are in tautomeric equilibria with 4- or 5-hydroxyazoles. However, the nonaromatic form is sometimes by far the more stable. Thus, oxazolinone derivatives of type **452** have been obtained in optically active forms. Reactions of these derivatives are considered under the aromatic tautomer.



452



453

3.4.2.2 Dihydro Compounds

3.4.2.2.1 Tautomerism

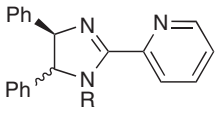
Dihydroazoles can exist in at least three forms (cf. Section 2.4.1.3), which in the absence of blocking substituents are in tautomeric equilibrium with each other. The forms in which there is no hydrogen on at least one ring nitrogen normally predominate, because imines are generally more stable than vinylamines. Thus, for dihydropyrazoles the stability order is **454** (hydrazone) > **455** (azo) > **456** (enehydrazine).

454

455

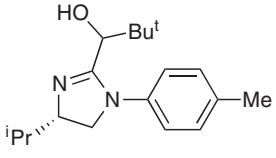
456

One of the emerging applications of 4,5-dihydroimidazole-based compounds is as chiral auxiliaries in metal complexes used for asymmetric synthesis: for example, **457** in ruthenium-catalyzed DielsAlder reactions <2001J(P1)1500, 2006JOM(691)3445>; **458** in diethylzinc addition to aldehydes <2003SL102>; **459** in asymmetric intramolecular Heck reactions <2003OL595>; and **460** in ruthenium-catalyzed epoxidation <2005OL3393> and iridium-catalyzed hydrogenation of imines <2004TA3365>.

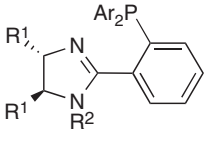


R = H, Bn, Ts, Tf

457



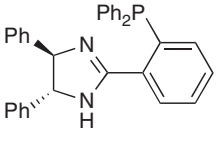
458



R^1 = 3,5-$F_2C_6H_3$

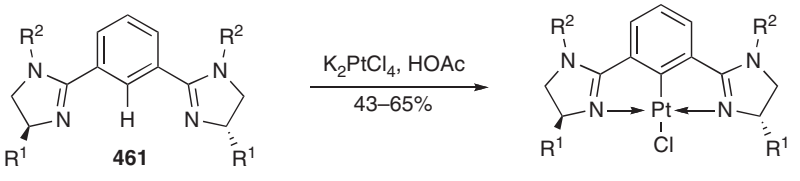
R^2 = 2-naphthoyl

459



460

Appropriate placing of dihydroimidazole nitrogens can assist aromatic C-metallation, as in the conversion of **461** into **462** <2006TL5033>.

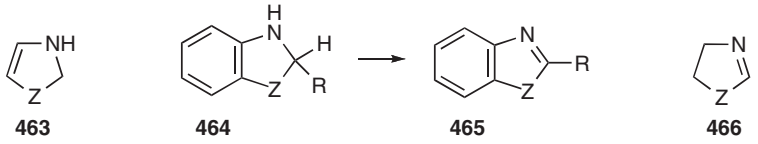


461 **462**

3.4.2.2.2 Aromatization

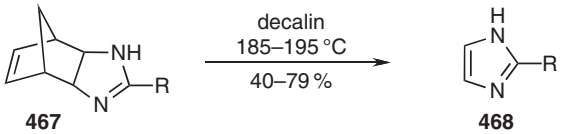
2,3-Dihydroimidazoles, -oxazoles, and -thiazoles **463**, and their benzo derivatives **464**, are all very easily aromatized (e.g., **464** **465**), and syntheses which might be expected to yield such dihydro compounds often afford the corresponding aromatic products. Among reagents which can be used for aromatization of 4,5-dihydropyrazoles are chloranil in

toluene <2000EJO2593>, O_2 with activated carbon <2004S1015>, $Cu(NO_3)_2$ on clay with ultrasound <2004TL4143>, and $Ca(OCl)_2$ in CH_2Cl_2 <2006H(68)1209>; and for 4,5-dihydrothiazoles, MnO_2 <2005TL2567, 2005JOC1389> or $CBrCl_3$ and DBU <2004T12139>.



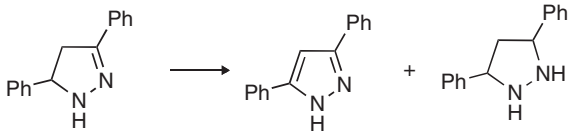
463 **464** **465** **466**

Dehydrogenation of 4,5-dihydroimidazoles **466** (Z=NR) gives imidazoles, but requires quite high temperatures and a catalyst such as nickel or platinum. Alternatively, hydrogen acceptors such as sulfur or selenium can also be used. Dehydrogenation of 4,5-dihydroimidazoles can be achieved with trichloroisocyanuric acid <2004SL2803> or $KMnO_4$ absorbed on supports such as silica gel <2004TL8687>, alumina <2004BML6079>, or Montmorillonite K-10 <2005CJC110>. Bicyclic derivatives **467** are thermally converted into imidazoles **468** via a retro-DielsAlder sequence.



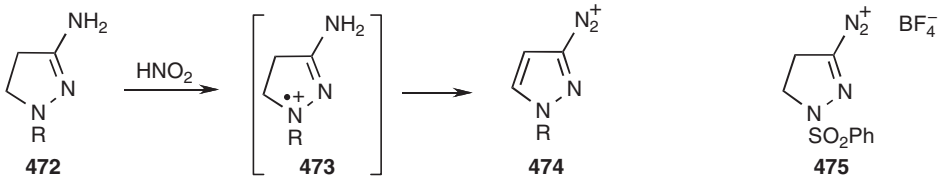
467 **468**

4,5-Dihydropyrazoles are converted into pyrazoles by oxidation with bromine or $Pb(OAc)_4$ and they can also be dehydrogenated with sulfur. 3,5-Diphenylpyrazoline **469** on heating with platinum disproportionates to the pyrazole **470** and the pyrazolidine **471**.



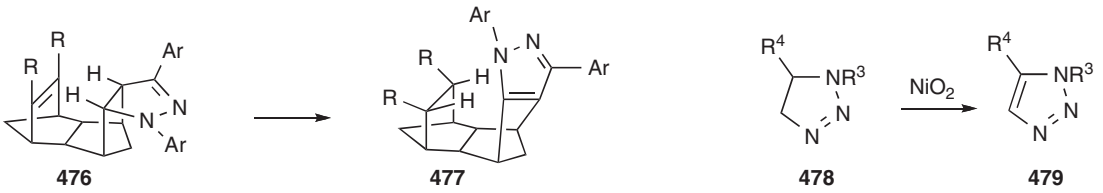
469 **470** **471**

3-Amino-4,5-dihydropyrazole **472** (R = H) and its 1-phenyl derivative **472** (R = Ph) react with two equivalents of nitrous acid giving, in a combined dehydrogenationdiazotization sequence, pyrazole-3-diazonium ions **474**. Some evidence suggests that the reaction proceeds via intermediate red-colored radical cations **473**. Indeed, when R in **472** is a strongly electron-withdrawing group, the formation of the corresponding radical cation becomes difficult and rather stable 4,5-dihydropyrazole-3-diazonium salts can be isolated, for example, 1-phenylsulfonyl-4,5-dihydropyrazole-3-diazonium tetrafluoroborate **475**.

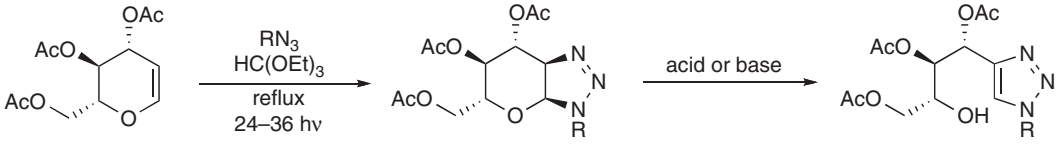


472 **473** **474** **475**

4,5-Dihydropyrazoles have been used as models of intramolecular dyotropy. By combining primary deuterium kinetic isotope effects and X-ray crystallography, polycyclic systems, like **476**, were shown to undergo a double proton transfer to produce **477**.



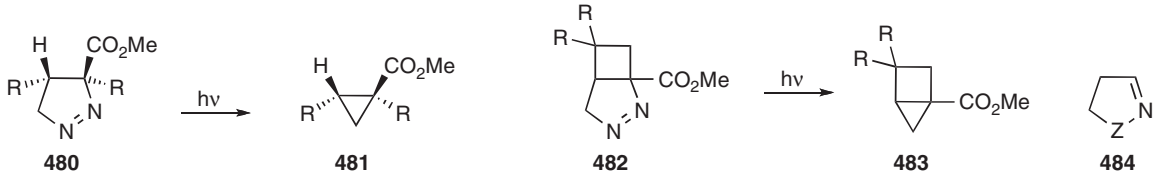
Phase-transfer-catalyzed oxidative dehydrogenation of 4,5-dihydro-1,2,3-triazoles by potassium permanganate affords a convenient route to various 1,2,3-triazoles. However, the reaction has limited scope when electron-withdrawing and/or sterically crowded groups are present. Nickel peroxide (NiO_2) is a selective oxidant for dihydrotriazoles. Yields are usually better than those obtained using potassium permanganate (478 479) perhaps because steric crowding prevents the bulky permanganate ion from closely approaching the reaction site, whereas the effectiveness of the NiO_2 oxidation, possibly via a hydroxyl radical, is unaltered. For conversion of 4,5-dihydro-1,2,4-oxadiazoles into the corresponding aromatic systems, oxidants include *N*-chlorosuccinimide <1996JHC1583>, MnO_2 <2000HCO41, 2003BMC1821>, and concentrated HNO_3 in $CHCl_3$ <2000HCO41>. When 1,2,3-triazoles are generated by dipolar cycloaddition of azides to enols, aromatization follows very easily with elimination of the oxygen, as illustrated in **Scheme 102** <2004JA8356>.



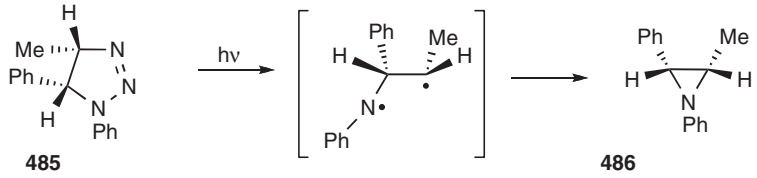
Scheme 102

3.4.2.2.3 Ring contraction

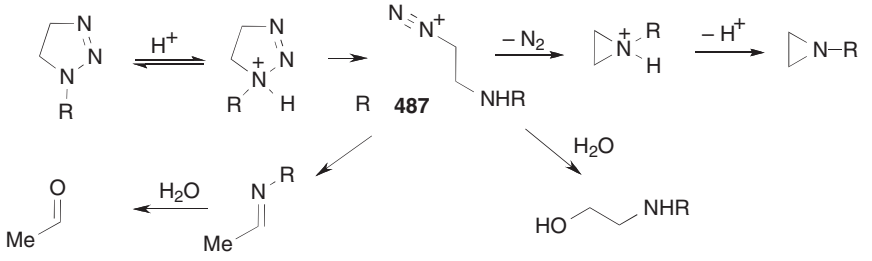
The majority of thermolysis, photolysis, and pyrolysis reactions with dihydropyrazoles give cyclopropane products; thus, 480, for example, undergoes photochemically induced nitrogen elimination and ring contraction giving 481. This is particularly useful for the preparation of strained rings, e.g., 482 483. 4,5-Dihydropyrazoles unsubstituted at the 1-position lose nitrogen on pyrolysis to give cyclopropanes, e.g., 484 (Z=NH) cyclopropane.



Photodecomposition of 4,5-dihydro-1,2,3-triazoles gives aziridines. In cyclohexane solution, the *cis* derivative 485 gives the *cis* product 486, whereas photolysis in benzene in the presence of benzophenone as sensitizer gives the same ratio of *cis*- and *trans*-aziridines from both triazolines which is accounted for in terms of a triplet excited state. 4,5-Dihydrotetrazoles are photolyzed to diaziridines.

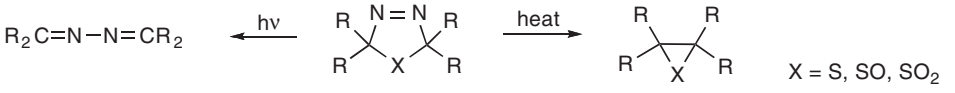


The hydrolytic decomposition of 1-alkyl-4,5-dihydrotriazoles in aqueous buffers leads predominantly to 1-alkylaziridines with lesser amounts of 2-(alkylamino)ethanol, alkylamines, and acetaldehyde. The rate of hydrolysis of 1-alkyltriazolines is about twice as fast as that of the analogous acyclic 1,3,3-trialkyltriazenes and varies in the order *tert*-butyl > isopropyl > ethyl > butyl > methyl > propyl > benzyl. The proposed mechanism, involving rate-limiting formation of a 2-(alkylamino)ethyldiazonium ion **487**, is shown in **Scheme 103**.

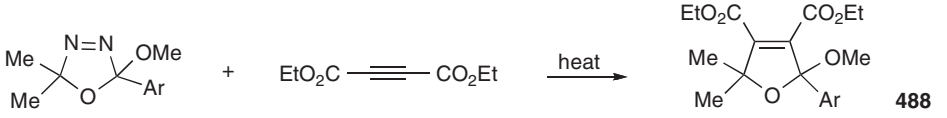


Scheme 103

Fragmentation of 2,5-dihydro-1,3,4-thiadiazole derivatives is summarized in **Scheme 104**. When comparable 2,5-dihydro-1,3,4-oxadiazoles are thermolyzed, the ylides formed by loss of nitrogen can be trapped, for example, with diethyl acetylenedicarboxylate or diethyl azodicarboxylate, giving 2,5-dihydrofurans, for example, **488** (**Scheme 105**) <2003TL5029>.

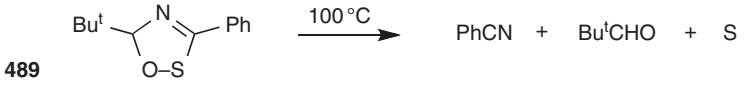


Scheme 104



Scheme 105

Heating a $CDCl_3$ solution of 1,2,4-oxathiazoline **489** at 100°C produces a 1:1 mixture of benzonitrile and pivaldehyde along with elemental sulfur <2003TL2517, 2004HAC175>.

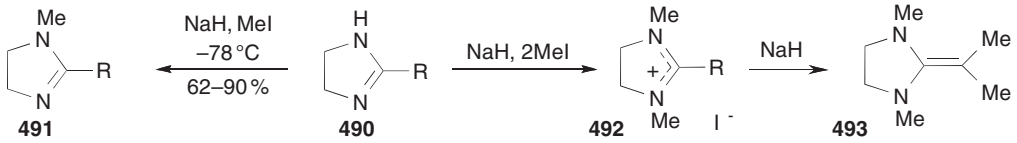


3.4.2.2.4 Other reactions

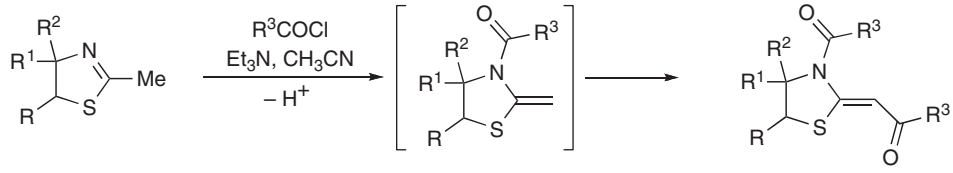
Dihydro compounds show reactions which parallel those of acyclic analogues, provided that the aromatization or ring contraction reactions discussed above do not interfere.

4,5-Dihydroimidazoles **466** (Z═NH) are cyclic amidines and exhibit the characteristic resonance stabilization and high basicity. 4,5-Dihydrooxazoles **466** (Z═O) are cyclic imino ethers, and 4,5-dihydrothiazoles **466** (Z=S) are imino thioethers; both are consequently easily hydrolyzed by dilute acid with ring opening.

4,5-Dihydroimidazoles **490** are readily N-alkylated or N-acylated to form 1-alkyl **491** or 1-acyl derivatives; more efficient alkylations involve pregeneration of an N-anion. With excess alkyl halide, a quaternary salt **492** is formed, and suitable 2-substituents allow side-chain deprotonation to give enamines, 2-alkylideneimidazolidines, e.g., **493**.

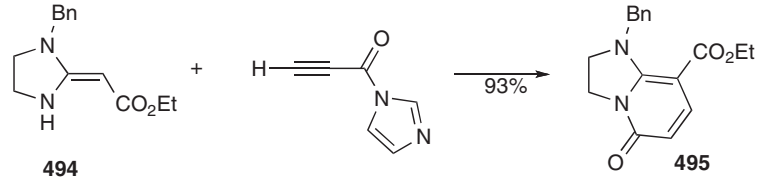


Comparably, C-acylation of such enamines can also result (**Scheme 106**) <2004TL8899>.



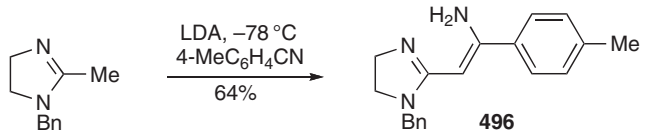
Scheme 106

Extensive use has been made of the enamino ester **494**; it reacts with various doubly electrophilic species at the enamine -carbon, and nitrogen, to produce bicyclic products, such as **495** using propiolic acid imidazolide, **Scheme 107** <1998T6191>.



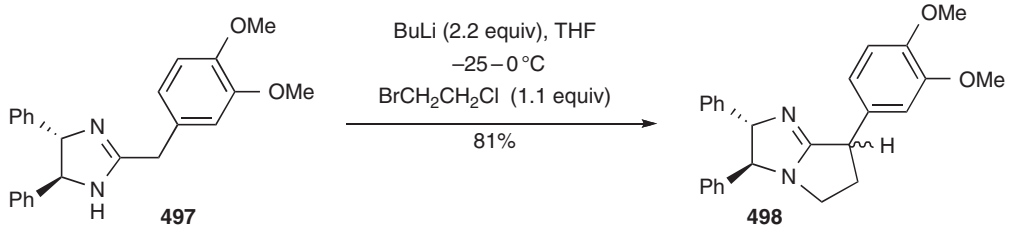
Scheme 107

Strong bases can deprotonate the 2-alkyl group of neutral 1-alkyl-4,5-dihydroimidazoles, for example, leading to **496** by trapping with a nitrile, then tautomerism (**Scheme 108**) <1999T2695>.

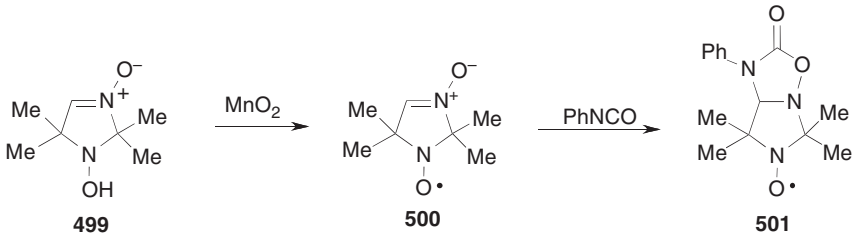


Scheme 108

Even *N*-hydrogen-4,5-dihydroimidazoles can be side-chain deprotonated when the side-chain carbon is also benzylic; thus, the N,C-dianion formed from **497** can be N,C-dialkylated producing **498**, for example, <1998JOC8107>.

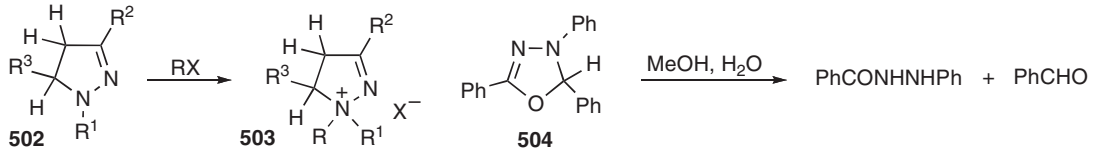


2,5-Dihydroimidazole *N*-oxides have been extensively studied. 1-Hydroxy-2,5-dihydroimidazole 3-oxides **499** are in tautomeric equilibrium with open-chain nitrones. Electron-withdrawing 2-substituents and a donor group in the 4-position favor the cyclic form. Oxidation gives stable radicals **500** that form cycloadducts with dipolarophiles (e.g., **501**). Radicals formed from 2,5-dihydroimidazole 1-oxides or 1-hydroxy-2,5-dihydroimidazoles can be formylated on nitrogen under Vilsmeier conditions and halogenated (NBS or NCS) on a 4-methyl group.



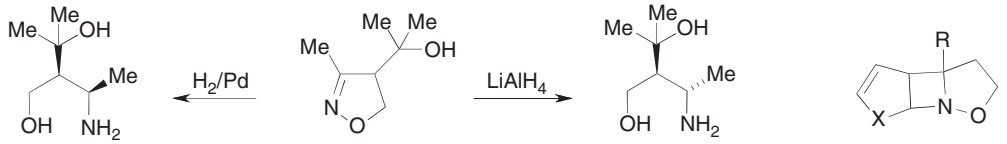
499 **500** **501**

4,5-Dihydropyrazoles and -isoxazoles **502** (Z = NH, O) are cyclic hydrazones and oximes, respectively. 4,5-Dihydropyrazoles are quaternized at the 1-position (**502** **503**). 2,3-Dihydro-1,3,4-oxadiazoles (e.g., **504**) are very easily ring opened hydrolytically.



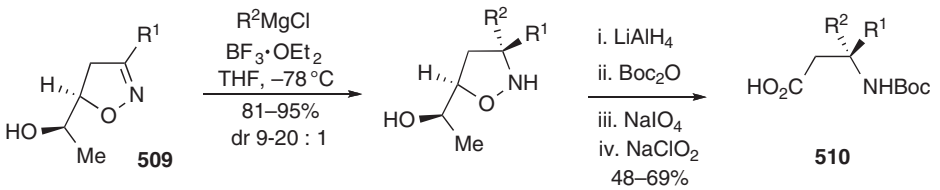
502 **503** **504**

Several reducing agents have been used to cleave the NO bond of dihydroisoxazoles. The reductive cleavage method is a well-exploited route to amino alcohols, aziridines, or both, depending upon the reaction conditions. Ring opening of 3-methyl-4--hydroxypropyl-4,5-dihydroisoxazole **506** with $LiAlH_4$ affords -amino alcohols **507** and **505** in a 95:5 ratio, but with hydrogen and palladium, the stereoselection is reversed to 3:97 of *trans*:*cis*, **507**:**505**.



505 **506** **507** **508**

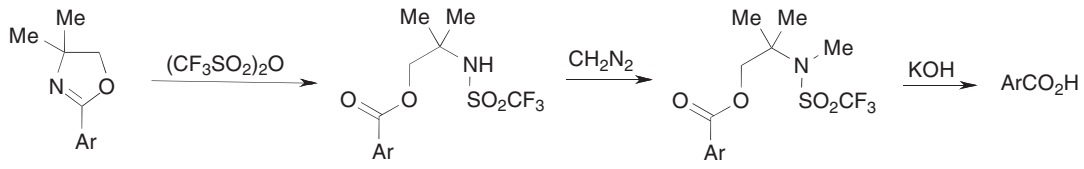
4,5-Dihydroisoxazoles undergo [2 + 2] cycloaddition with furan or thiophene to yield the photocycloadducts **508**. 4,5-Dihydroisoxazoles can be formed by stereoselective 1,3-dipolar cycloaddition of nitrile oxides, for example, to enantiopure allylic alcohols, and these products can be converted into -amino acids **510** by a characteristic nucleophilic addition to the C═N bond in **509** followed by reductive cleavage of the N—O bond and oxidative cleavage of the diol moiety. The facial selectivity in the nucleophilic addition is dictated by the C(5) substituent (**Scheme 109**), e.g., <2003JA6846, 2004SL1409, 2005JA5376>.



509 **510**

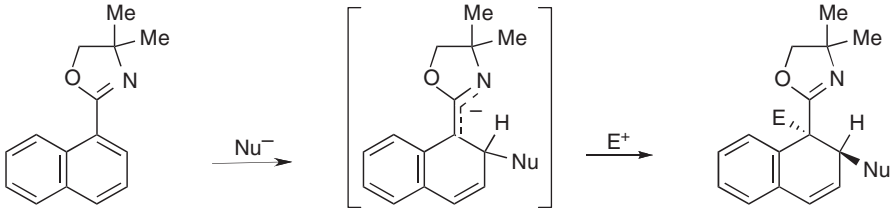
Scheme 109

4,5-Dihydrooxazoles are very useful in organic synthesis. They are inert to a variety of reagents, including Grignard reagents, $NaBH_4$, and $LiAlH_4$, and are useful protecting groups for carboxylic acids. There are many methods for the cleavage of 4,5-dihydrooxazoles once they have served their purpose. An effective method for hydrolyzing them back to carboxylic acids employs trifluoromethanesulfonic anhydride (**Scheme 110**).



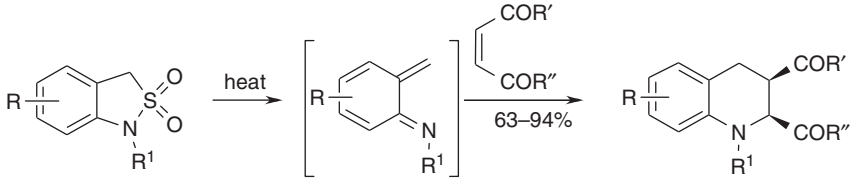
Scheme 110

4,5-Dihydrooxazoles are also effective *ortho* directors for nucleophilic dearomatizing addition to naphthalene and some heteroaromatic derivatives. Tandem additions result if the reaction mixtures are quenched with electrophiles (**Scheme 111**).



Scheme 111

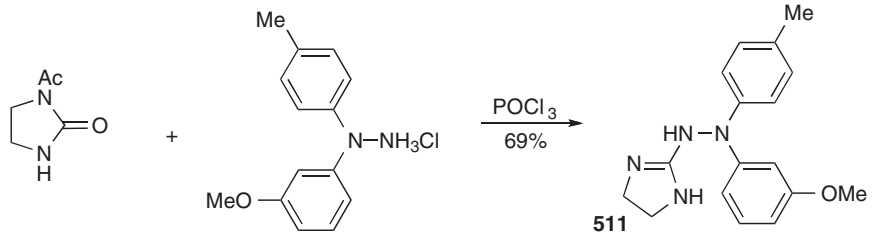
The thermolysis of 2,1-benzothiazoline 2,2-dioxides generates aza-*o*-xylenes which can be trapped with maleic acid derivatives to give *cis*-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylic acid derivatives (**Scheme 112**).



Scheme 112

Reduction of dihydro compounds to the tetrahydro derivatives is sometimes possible. For example, dihydrothiazoles are reduced to thiazolidines by aluminum amalgam; N-acylated dihydropyrazoles are reduced with boranepyridine to *N*-acyltetrahydropyrazoles <2006JOC5035>.

2-Halo-4,5-dihydroimidazoles are commonly generated *in situ* for the preparation of heteroatom substitutions at the 2-position, for example, (**Scheme 113**) by interaction with $POCl_3$, as in the formation of **511** <2005BML4691>.



Scheme 113

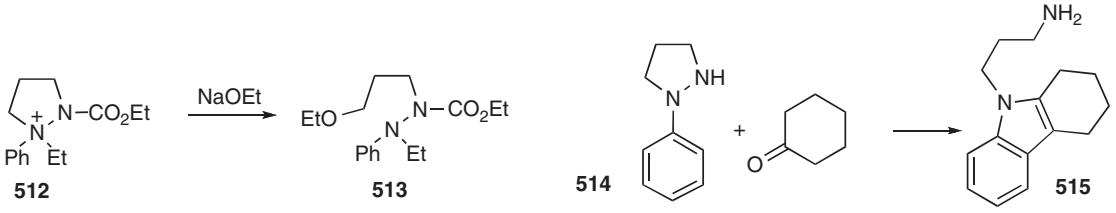
3.4.2.3 Tetrahydro Compounds

3.4.2.3.1 Aromatization

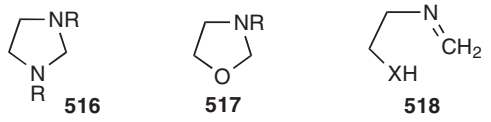
Some tetrahydro azoles can be aromatized, but this is more difficult than in the corresponding dihydro series. Thus, the conversion of pyrazolidines into pyrazoles is accomplished with chloranil. Imidazolidines are aromatized with great difficulty. Thiazolidines have been aromatized with activated MnO_2 in benzenepyridine <1999TL7951> or *N*-bromosuccinimide in CCl_4 <2005JME2584>.

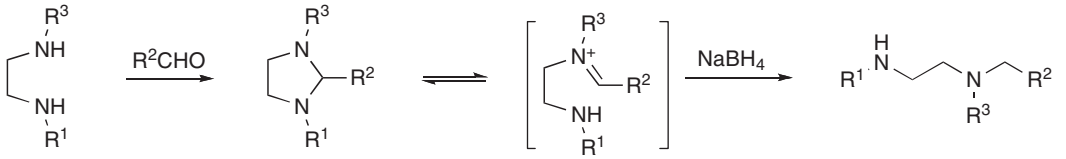
3.4.2.3.2 Ring fission

Cleavage of the heterocyclic ring can be accomplished using degradative procedures that are also applicable to acyclic analogues, e.g., Hofmann degradation; nucleophilic displacement of a quaternary nitrogen can also occur (e.g., **512** **513**). Pyrazolidines, as arylhydrazines, take part in Fischer indole syntheses (**514** **515**). The sulfur-containing ring of thiazolidines can be opened via Raney nickel desulfurization.



Compounds of types **516** (R=H) and **517** (R=H) are in equilibrium with open-chain forms **518**, the ratios of which can be measured in $CDCl_3$ using ^1H NMR spectra. Electron-withdrawing groups on an *N*-aryl ring favor the ring tautomers, whereas bulky *N*-substituents favor the chain tautomers <1997J(P2)169>. These tetrahydro compounds are readily hydrolyzed by dilute acid. Reductive opening of imidazolidines are probably involved in the one-pot synthesis of N,N,N-trisubstituted ethylenediamines from N,N-disubstituted ethylene diamines and an aldehyde R^2CHO (**Scheme 114**) <2003SC3193>.

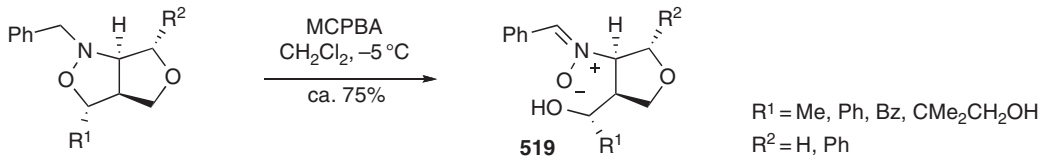




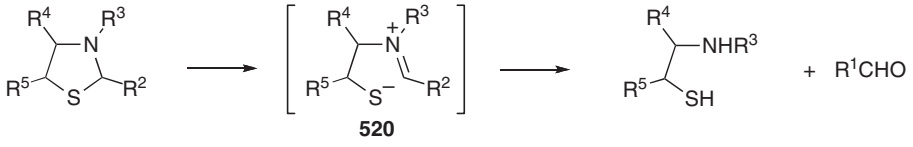
Scheme 114

The presence of the labile NO bond, which can be easily cleaved under mild reducing conditions, accounts for the common use of isoxazolidines as masked 1,3-amino alcohols. The reductive ring opening of an isoxazolidine is usually performed by hydrogenation in the presence of catalysts such as Pd/C, PtO_2, $Pd(OH)_2$, and RaNi or by Zn/acetic acid, but other reducing agents can also be used, for example, $NiCl_2NaBH_4$ or SmI_2 are selective and mild if sensitive functionalities are present, e.g., <1998J(P1)3471, 2001OL1375, 2004TL8375, 2005TL3037>.

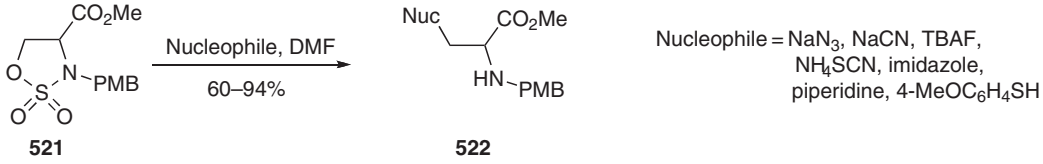
A completely different ring cleavage of isoxazolidines can be achieved oxidatively: here, a nitrone, e.g., **519** is generated that can then, if desired, be further utilized as a 1,3-dipole, e.g., <1998T12249, 1998T12959>.



Thiazolidines undergo hydrolysis to aldehyde and aminothiol under acidic or basic aqueous conditions. The reaction involves C—S bond breaking and proceeds by the formation of an iminium thiolate zwitterion intermediate **520**. The hydrolysis of thiazolidines to aldehydes is conveniently carried out under neutral conditions with the assistance of metal ions such as Hg(II) or Cu(II), e.g., <1997TL2459>.



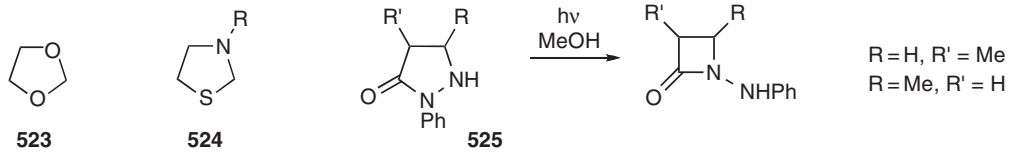
Various nucleophiles substitute cyclic sulfamidates such as **521** at C(5) at room temperature and provide good yields of **522**, e.g., <1996S259, 1999J(P1)1421, 1999TL3831, 2002TL1915>. The introduction of the N-substitutent to make compounds like **521** is best achieved via a base-catalyzed phase-transfer method or using the Mitsunobu protocol <2002JOC5164>.



3.4.2.3.3 Other reactions

The XCX units in 1,3-dioxolanes **523**, tetrahydroimidazoles **516**, tetrahydrooxazoles **517**, and tetrahydrothiazoles **524** are somewhat less easily cleaved (with ring opening) than their acyclic analogues (cf. previous section), but their properties are otherwise similar.

1-Aryl-5-pyrazolidinones **525** can be photochemically ring contracted to -lactams.

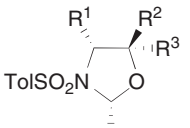


Alkylation of imidazolidines (and their oxo and thio derivatives) is usually carried out in the presence of a strong base such as sodium hydride, potassium carbonate in DMF, or potassium hydroxide in DMSO.

Isoxazolidines display properties consistent with their cyclic hydroxylamine structures. Thus, isoxazolidines behave as nucleophiles and thus can be N-alkylated or N-acylated. Isoxazolidines are also strong bases (pK_a 5.05) and undergo other reactions such as hydrogenolysis, oxidation, thermolysis, photolysis, and decomposition by bases.

The chemistry of the oxazolidines, like the dihydrooxazoles, is characterized by reactions that take advantage of the opportunity for stereoselectivity. A chiral environment is often provided by the same amino alcohols, such as phenylglycinol or norephedrine, used to prepare dihydrooxazoles.

2-Methoxyoxazolidines **526** are useful for the asymmetric formylation of various nucleophiles including silyl enol ethers, trimethylsilyl cyanide, enamines, and allyl silanes. The reaction of nucleophiles with 2-alkyl-2-methoxyoxazolidines offers a general method for asymmetric acylation.



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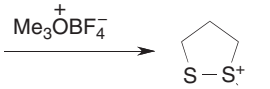
527



528

The sulfur in 1,2-dithiolanes is nucleophilic and can be alkylated to form 1,2-dithiolanium salts (**527** **528**). S-Oxidation and/or formation of sulfones of thiazolidines results in certain situations, for example, with penams <2001BMC2113>. Pyrolysis of thiazolidin-2-one 1,1-dioxides results in loss of SO_2 and the formation of -lactams <1997J(P1)2139>.

3.4.3 Reactions of Substituents

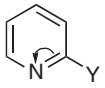
Substituents attached to carbon are considered by classes; substituents linked to ring nitrogen are considered separately because of their differing character.

3.4.3.1 General Survey of Substituents on Carbon

If the reactions of the same substituents on heteroaromatic azoles and on benzene rings are compared, the differences in the reactivities are a measure of the influence of the hetero atom. Such influence by the mesomeric effect is smaller when the substituent is to a heteroatom than when it is or . The influence by the inductive effect is largest when the substituent is to a heteroatom.

3.4.3.1.1 Substituent environment

The electronic environment of an -substituent on pyridine **529** approaches that of a substituent on the corresponding imino compound **530** and is intermediate between those of substituents on benzene and substituents attached to carbonyl groups (**531, 532**) (cf. discussion in Chapter 3.2). Substituents attached to certain positions in azole rings show similar properties to those of - and -substituents on pyridine. However, the azoles also possess one heteroatom which behaves as an electron source and which tends to oppose the effect of other heteroatom(s).



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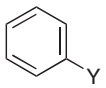

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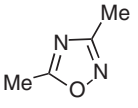


533

Substituents cannot directly conjugate with nitrogen atoms located as in a pyridine -position. Azole substituents which are not or to a pyridine-like nitrogen react as they would on a benzene ring. Conjugation with an -pyridine-like nitrogen is much more effective through formal double bonds; thus, the 5-methyl group in 3,5-dimethyl-1,2,4-oxadiazole **533** is by far the more reactive as it is activated by both nitrogen atoms.

In azolium cations, the electron pull of the positively charged heteroatom is strong, and substituents attached or to positive poles in azolium rings show correspondingly enhanced reactivity.

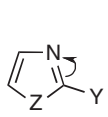
Azolinones and azole *N*-oxides possess systems that can act either as an electron source or as an electron sink, depending on the requirements of the reaction.

3.4.3.1.2 The carbonyl analogy

Reactions of functional groups are often modified very significantly by an adjacent carbonyl group. The reactions of certain substituents and to pyridine-like nitrogen atoms in azole rings are similarly influenced. Such effects are discussed fully and classified in Section 3.2.3.1.1.

3.4.3.1.3 Two heteroatoms in the 1,3-positions

The 2-position in imidazoles, thiazoles, and oxazoles is electron deficient, and substituents in the 2-position **534** generally show the same reactivity as - or -substituents on pyridines. 2-Substituents in azoliums of this type, including 1,3-dithiolyliums, are highly activated.



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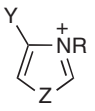

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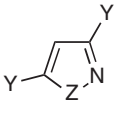

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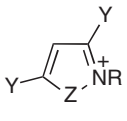

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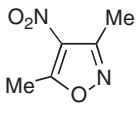


538

Substituents at the 4-position of these compounds are also to a multiply bonded nitrogen atom, but because of bond fixation they are relatively little influenced by this nitrogen atom even when it is quaternized **535**. This is similar to the situation for 3-substituents in isoquinolines (cf. Chapter 3.2). In general, substituents at the 4- and 5-positions of imidazoles, thiazoles, and oxazoles show much the same reactivity as do the same substituents on benzenoid compounds (but see Section 3.4.3.9. 1).

3.4.3.1.4 Two heteroatoms in the 1,2-positions

Substituents on pyrazoles and isoxazoles, regardless of their positions, generally show reactivity closer to that of the same substituent on a benzene ring rather than to that of - or -substituents on pyridine. The (electron-releasing) mesomeric effect of the pyrrole-type NH group and furan-type oxygen atom appears to be more important than their (electron-withdrawing) inductive effect in pyrazole and isoxazole **536**. However, some reactions of these types are known (see, e.g., Section 3.4.3.3.3) and halogen atoms and methyl groups in the 3- and 5-positions of pyrazoles and isoxazoles become active if the ring is quaternized **537**.

Substituents on the isothiazole ring are a little more reactive, especially at the 5-position. In cationic rings reactivity is much higher, e.g., for substituents in 1,2-dithiolylium salts.

3.4.3.1.5 Three heteroatoms

In the 1,2,4-thiadiazole ring, the electron density at the 5-position is markedly lower than at the 3-position, and this affects substituent reactions. 5-Halo derivatives, for example, approach the reactivity of 4-halopyrimidines. The 1,2,4-oxadiazole ring shows a similar difference between the 3- and 5-positions.

Substituents in 1,3,4-thiadiazoles are quite strongly activated, like at the 2-position of pyridine.

In contrast, substituents in 1,2,4-triazoles are usually rather similar in reactivity to those in benzene; although nucleophilic substitution of halogen is somewhat easier, forcing conditions are required.

3.4.3.1.6 Four heteroatoms

Alkyl groups and halogen atoms in tetrazoles are not highly activated unless the ring is quaternized.

3.4.3.1.7 The effect of one substituent on the reactivity of another

The effect of one substituent on the reactivity of another is generally similar to that observed in the corresponding polysubstituted benzenes. However, the partial bond fixation in an azole can lead to differential effects in the mutual interactions of substituents, similar to those found in naphthalene where the benzene ring fusion induces bond fixation.

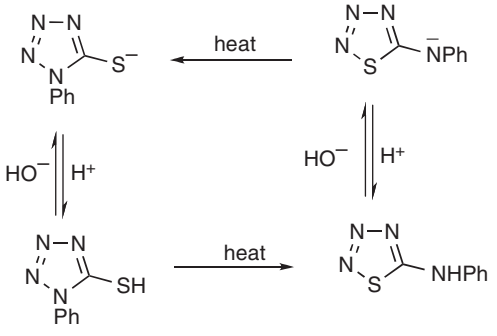
A good example is in the comparison of methyl group reactivity in **538**; the 5-methyl group condenses with aldehydes easily, whereas the 3-methyl group does not. However, quaternization at nitrogen renders the 3-methyl group reactive.

3.4.3.1.8 Reactions of substituents not directly attached to the heterocyclic ring

In general, substituents removed from the ring by two or more saturated carbon atoms undergo normal aliphatic reactions, and substituents attached directly to fused benzene rings or aryl groups undergo the same reactions as those on normal benzenoid rings.

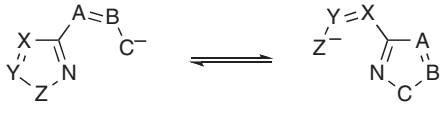
3.4.3.1.9 Reactions of substituents involving ring transformations

Several classes are known. Dimroth-type rearrangements occur by ring opening and reclosure so that one ring atom changes places with an exocyclic atom. The rearrangement of 5-phenylaminothiatriazole to 1-phenyl-5-mercaptotetrazole in basic solution is reversible (**Scheme 115**). As the anion, the tetrazole system is the more stable; whereas as the neutral species, the thiatriazole, is more stable.



Scheme 115

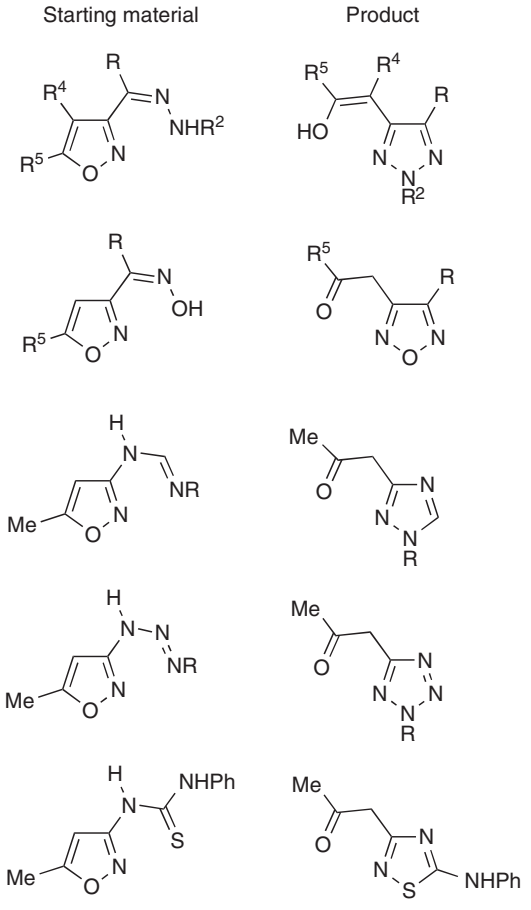
A different type of rearrangement occurs when suitable side-chains are to a pyridine-like nitrogen atom. In the monocyclic series, this can be generalized by **Scheme 116**. For a given side-chain, the rate of rearrangement is 1,2,4-oxadiazoles > isoxazoles > 1,2,5-oxadiazoles. Typical side-chains include hydrazone, oxime, and amidine. Some examples are shown in **Table 9**. Similar rearrangements for benzazoles are discussed in Section 3.4.3.2.4.

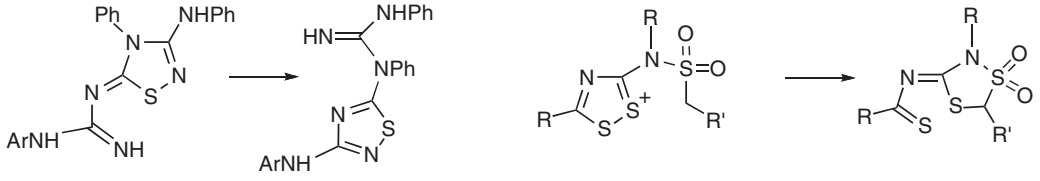


Scheme 116

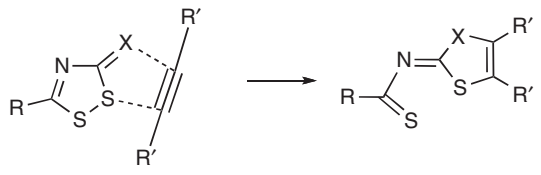
A somewhat similar type of ring interconversion involving attack on sulfur has been postulated in the 1,2,4-thiadiazole series, e.g., **539** **540**. Such reactions are common in the 1,2,4-dithiazolium series, e.g., **541** **542**.

Table 9 Examples of rearrangements involving three-atom side-chains of azoles





Cycloadditions including a cyclic S atom and an exocyclic C=X bond are known in the dithiazole series, e.g., as shown in **Scheme 117**.

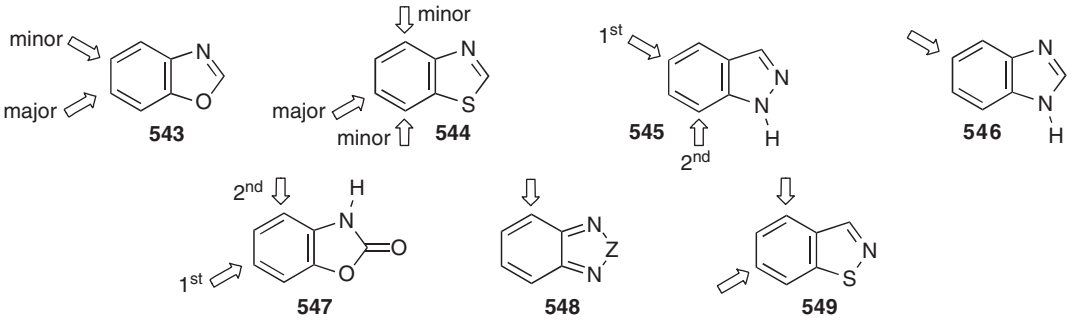


Scheme 117

3.4.3.2 Fused Benzene Rings

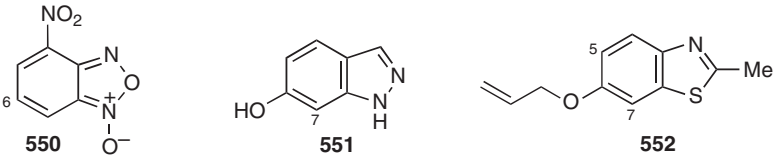
3.4.3.2.1 Electrophilic substitution

In compounds with a fused benzene ring, electrophilic substitution on carbon usually occurs in the benzenoid ring in preference to the heterocyclic ring. Frequently, the orientation of substitution in these compounds parallels that in naphthalene. Conditions are often similar to those used for benzene itself. The actual position attacked varies; compare formulae **543549** where the orientation is shown for nitration; sulfonation is usually similar.



Indazoles show most of the typical benzene electrophilic substitution reactions. However, unsubstituted indazole can be nitrated by acetyl nitrate to 3,5-dinitroindazole (20%) as well as 3-nitroindazole (55%). Anthranil is halogenated and nitrated in the benzene ring at position 5. Nitration of 1,2-benzisothiazole gives a mixture of the 5- and 7-nitro derivatives **549**. 6-Methylbenzothiazole is nitrated at the 7-position with HNO_3 at 45°C <2001ZOR570>, benzothazolin-2-ones are acylated at the 6-position with a range of acid chlorides and catalytic $ZnCl_2$ <2002KGS380>, and 2,1-benzisothiazole undergoes electrophilic bromination and nitration at the 5- and 7-positions. Nitration of benzofuroxan gives the 4-nitro and then the 4,6-dinitro compound. 5,6-Dibromobenzotriazole is prepared by treatment of benzotriazole with Br_2, Ag_2SO_4, and conc. H_2SO_4 <2004BMC2617>; in refluxing HNO_3, 4,5,6,7-tetrabromobenzotriazole is formed <1957JA4395>. Benzofurazan reacts with $ClSO_3H$ at 120°C to give the 4-chlorosulfonyl product <2004S2999>. Bromination of 7-methylbenzo-2,1,3-thiadiazole in aqueous HBr using Br_2 gave 4-bromo-7-methylbenzothiadiazole <2005JOC6004> but the bromomethyl derivative using NBS, AIBN <2004JME3163>.

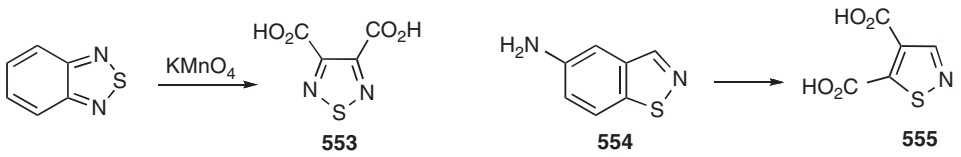
Substituents on the benzene rings exert their usual influence on the orientation and ease of electrophilic substitution reactions. For example, further nitration (H_2SO_4, SO_3, HNO_3) of 4-nitrobenzofuroxan **550** gives the 4,6-dinitro derivative, the first nitro group directing *meta*. Strong electron-donating groups enhance electrophilic substitution and direct *ortho*/*para*. Thus, dimethylaminobenzofuroxans can be nitrosated and diazo coupled; bromination of 4-, 5-, 6-, and 7-aminobenzothiazoles occurs *ortho* and *para* to the amino group.



A heterocyclic ring induces partial double-bond fixation in a fused benzene ring. Hence, for example, diazo coupling occurs only at the 7-position of 6-hydroxyindazole **551**, and Claisen rearrangement of 6-allyloxy-2-methylbenzothiazole **552** gives the 7- and 5-allyl products in a ratio of 20:1.

3.4.3.2.2 Oxidative degradation

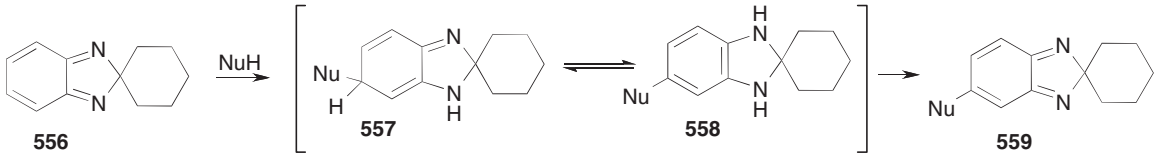
Vigorous oxidation (e.g., with $KMnO_4$) usually degrades fused benzene rings in preference to many azole rings, especially under acidic conditions. Thus, benzimidazoles are oxidized by chromic acid or 30% hydrogen peroxide to imidazole-4,5-dicarboxylic acid, and 2,1,3-benzothiadiazole is oxidized by ozone or potassium permanganate to the dicarboxylic acid **553**.



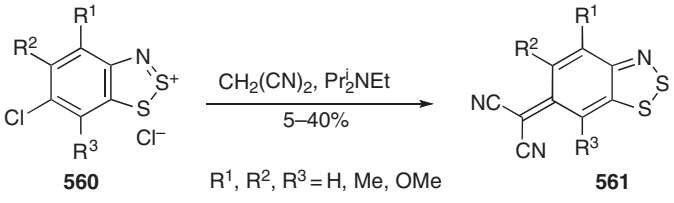
As expected, oxidative degradation of a fused benzene ring is facilitated when it carries electron-donating groups and is hindered by electron-withdrawing substituents. 5-Aminobenzisothiazole **554** with potassium permanganate gives the carboxylic acid **555**.

3.4.3.2.3 Nucleophilic attack

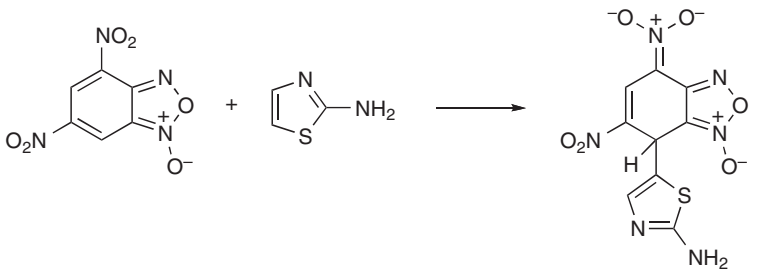
Most fused benzene rings are stable toward nucleophilic attack but exceptions are known for highly electron-deficient benzazoles having *o*-quinonoid structures. Thus, sulfur nucleophiles attack 2*H*-benzimidazole-2-spirocyclohexane **556** via an initial Michael-type 1,4-conjugate addition, followed by a prototropic shift in the adduct **557**. When the nucleophile is electron withdrawing (e.g., phenylsulfonyl), 1,3-dihydro products **558** are isolated. If the nucleophile is electron donating, the adducts are oxidized *in situ* to **559**.



Halogen atoms on benzazole rings can be activated toward nucleophilic displacement by electron-withdrawing groups; for example, Herz salts bearing chlorine at the 6-position **560** react with malononitrile to afford highly colored ylidenes **561** <2002J(P1)315>.



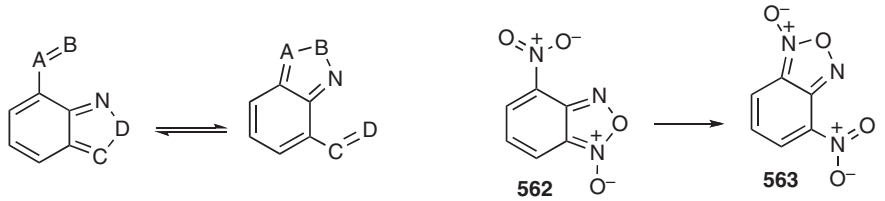
Nitro-substituted 2,1,3-benzoxadiazoles and related 1-oxides (nitrobenzofurazans and nitrobenzofuroxans) are neutral 10-electron-deficient heteroaromatic substrates, which in many processes exhibit extremely high electrophilic character. For example, 4,6-dinitrobenzofuroxan (DNBF), the reference compound in this family behaves as a stronger electrophile than the 4-nitrobenzenediazonium cation. This electrophilicity has led to many analytical applications with the use of DNBF as a suitable probe to assess the reactivity of extremely weak carbon nucleophiles such as benzenoid aromatic or -excessive heteroaromatics with large negative pK_a values, e.g., 1,3-dimethoxybenzene (pK_a = 9), 3-methoxythiophene (pK_a = 6.5), or aniline (pK_a = 6). Covalent addition of the carbon nucleophile takes place at C(7) of the carbocyclic ring of DNBF to give stable anionic -complexes, as it also does in all interactions of DNBF with oxygen, sulfur, or nitrogen nucleophiles, e.g., <2001J(P2)1408, 2003OBC1757, 2003OBC2192, 2004RCB2075, 2004RJO1384>. The reactivity is exemplified in **Scheme 118** <2006JOC5527>.



Scheme 118

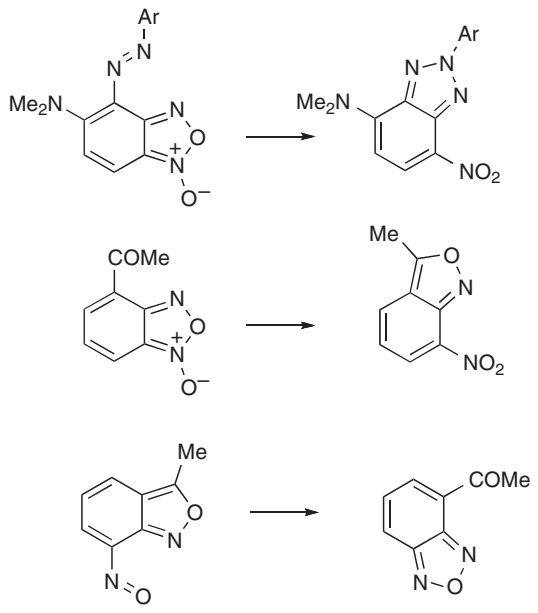
3.4.3.2.4 Rearrangements

In the benzazole series, reactions of the type discussed for monocyclic derivatives in Section 3.4.3.1.9 are generalized by **Scheme 119** and examples are given in **Table 10**.



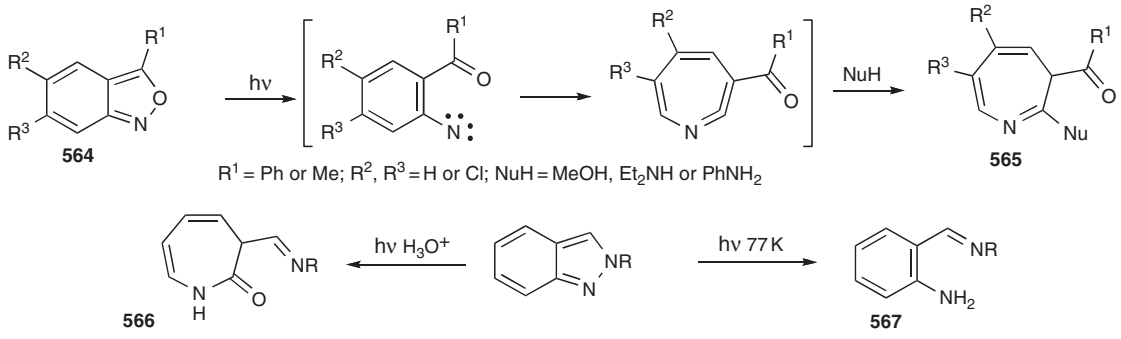
Scheme 119

Table 10 Benzazole rearrangements. Examples of involvement of two-atom side-chains



4-Nitrobenzofuroxan **562** undergoes a rearrangement (**563**) (recognizable as an isomerization in unsymmetrically substituted derivatives), which is an example of this general rearrangement (**Scheme 119**). This can be utilized to prepare differently ring-fluorinated heterocycles <2004RJO1167>.

Photolysis of anthranils **564** in methanol or amines gives 2-methoxy- or 2-amino-3*H*-azepines **565** via ring expansion of intermediate nitrenes. Photolysis of 2-alkylindazoles probably also goes through a nitrene intermediate, which either abstracts hydrogen from the solvent to give **567** or ring expands to yield **566**.

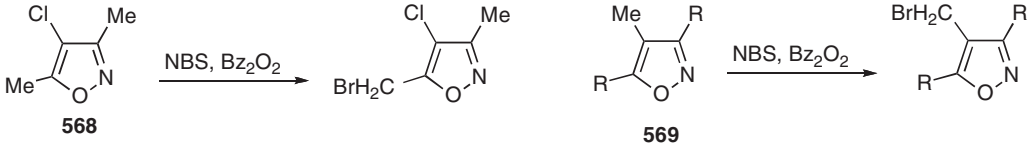


3.4.3.3 Alkyl Groups

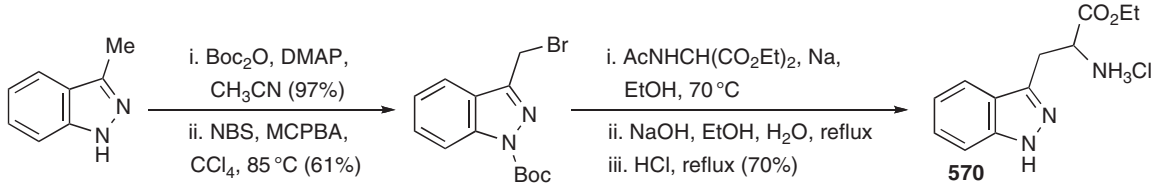
3.4.3.3.1 Reactions similar to those of toluene

Alkyl groups attached to heterocyclic systems undergo many of the same reactions as those on benzenoid rings.

1. Oxidation in solution ($KMnO_4$, CrO_3, etc.) gives the corresponding carboxylic acid or ketone; for example, alkyl groups on pyrazoles are oxidized with permanganate to carboxylic acids, 3-methylisothiazoles are converted by chromium trioxide into the 3-carboxylic acids, and methylthiazoles with SeO_2 give thiazole-carbaldehydes.
2. Radical bromination with *N*-bromosuccinimide often succeeds. Thus, 2,5-disubstituted 4-methyloxazoles on bromination give the 4-bromomethyl compounds, and methyl groups at the 4- or 5-positions of isoxazoles **568** and **569** can be brominated with NBS. Controlled mono- or dibromination of 3-aryl-5-methylisoxazole-4-carboxylates allows access to aldehydes <2004T2301>.

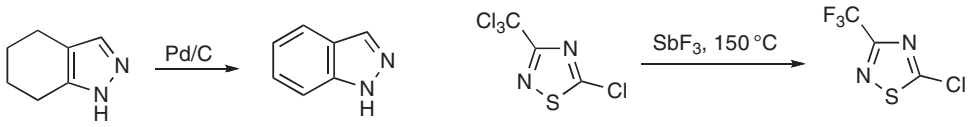


1-Boc-3-methylindazole can also be converted into its bromomethyl derivative, and this was used in a synthesis of the indazole analogue **570** of tryptophan involving nucleophilic displacement of the halide (**Scheme 120**) <2006T7772>. Chloromethylpyrazoles similarly undergo easy side-chain chloride displacements <2005RJO238>; however, one must be aware that *tele*-substitution products can sometimes arise, i.e., in which the side-chain halide displacement is accompanied by attack of the nucleophile on a ring carbon, e.g., <2001OL157, 2002OL4017>. Bromination of the methyl group of 2-methyl-5-cyanobenzothiazole and 2-methyl-6-cyanobenzothiazole utilized NBS, AIBN in CCl_4 at reflux <2004BMC2099>.



Scheme 120

3. A fused cyclohexeno ring can be converted into a fused benzene ring (**Scheme 121**).



Scheme 121

4. A trichloromethyl group can be converted by antimony trifluoride into a trifluoromethyl group in the 1,2,4-thiadiazole series (**Scheme 121**).

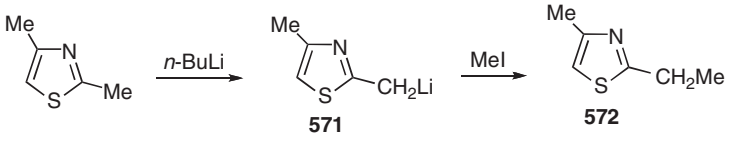
3.4.3.3.2 Alkylazoles: Reactions involving essentially complete anion formation

In addition to the reactions described in the preceding section, alkyl groups in the 2-positions of imidazole, oxazole, and thiazole rings show reactions which result from the relatively easy loss of a proton from the carbon atoms of the alkyl group which is adjacent to the ring (see Section 3.4.3.1.2).

Additional nitrogen atoms facilitate such reactions, particularly if they are or to the alkyl group and if act across a formal double bond. Thus, the 5-methyl group in 3,5-dimethyl-1,2,4-oxadiazole is much more reactive than the 3-methyl group in this compound or the methyl groups in 2,5-dimethyl-1,3,4-oxadiazole.

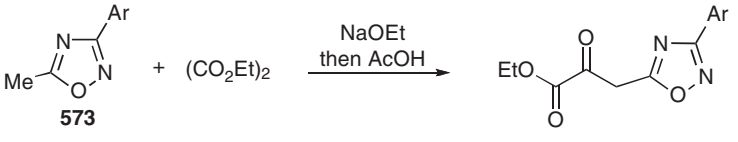
The strongest bases, such as sodamide ($NaNH_2$, NH_3, 40̄C) or *n*-BuLi, Et_2O, 40̄C, convert, for example, 2-methyloxazole and -thiazole and 1,2-dimethylimidazole, essentially completely into the corresponding side-chain anions (e.g., **571**), although some ring metallation also occurs (cf. Section 3.4.1.8.1). Alkylfurazans are deprotonated by *n*-BuLi at 50̄ C <2003RCB679>; 3,4-dimethyl-1,2,5-oxadiazole can be lithiated at one of the methyl groups; 2-methyl-5-phenyl-1,3,4-oxadiazole requires HMPS for its *n*-BuLi side-chain metallation <1995H(41)1525>. These anions all react readily even with mild electrophilic reagents; thus, the original alkyl groups can be substituted in the following ways.

1. Alkylation, e.g., MeI CH_2Me for the formation of **572**.



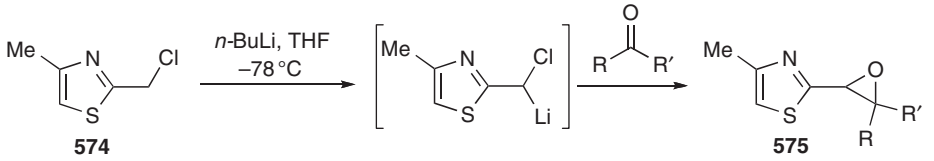
571 **572**

2. Acylation, e.g., the oxadiazole **573** undergoes Claisen-like condensation with diethyl oxalate.



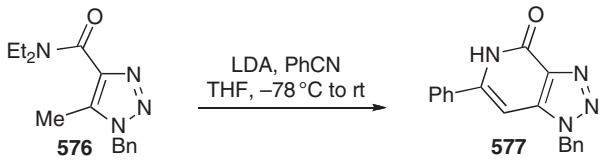
573

3. Carboxylation, e.g., CO_2 CH_2CO_2H in the tetrazole series.
4. Reactions with aldehydes and ketones in the 1,2-dimethylimidazole series. Side-chain lithiation of a 2-chloromethylthiazole **574** leads to epoxides **575** (**Scheme 122**) <2003T1381>. Exposure of triazole **576** to LDA and then benzonitrile generates the bicyclic **577** <2003EJM959>.



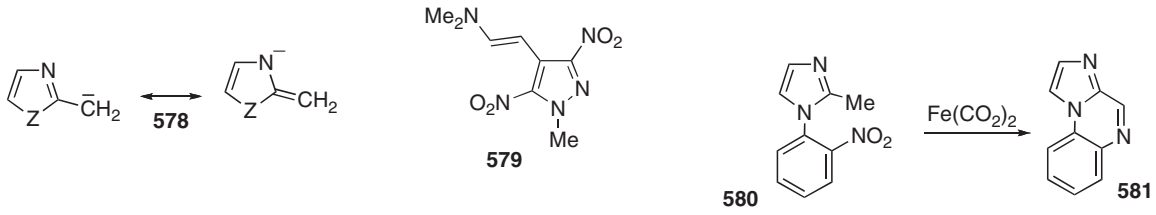
574 **575**

Scheme 122

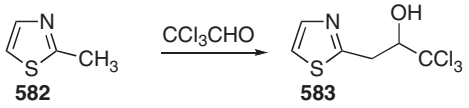


3.4.3.3.3 Reactions of alkylazoles involving traces of reactive anions

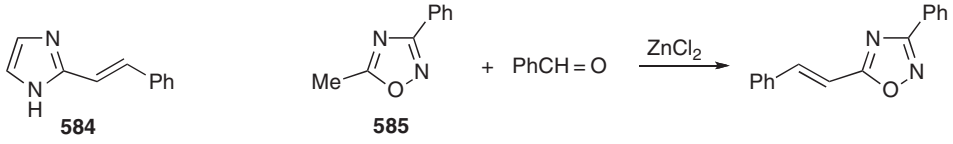
In appropriate situations, certain alkylazoles react with bases to give traces of anions of type **578** that can be trapped with suitable electrophilic reagents. An example is the reaction of 1,4-dimethyl-3,5-dinitropyrazole with DMFDMA giving **579** <2005RJO238>.



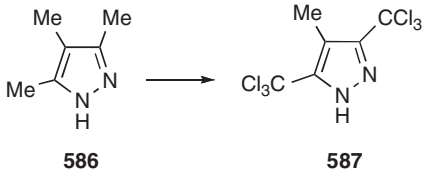
1. A nitroso group gives an imine, as in the probable mechanism of the conversion of **580** into **581**.
2. Aliphatic aldehydes can form monoalcohols, e.g., **582** gives **583**.



3. Aromatic aldehydes give styryl derivatives (e.g., **584**) by spontaneous dehydration of the intermediate alcohol (cf. Section 3.4.3.1.2). 5-Methyl-3-phenyl-1,2,4-oxadiazole **585** thus reacts with benzaldehyde in the presence of zinc chloride. 3-Nitrobenzaldehyde reacts with 5-methylisothiazole. The 4- and 5-methylthiazoles are unreactive.

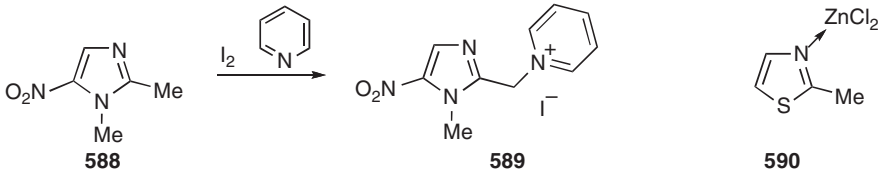


4. Halogens displace hydrogen atoms, e.g., 3,4,5-trimethylpyrazole **586** is converted into **587**.



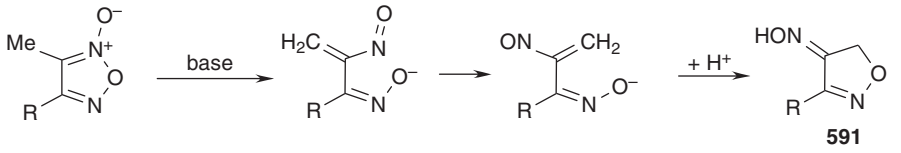
5. Pyridine and iodine give pyridylmethyl compounds, e.g., **588** yields **589**.

Reactions of types 14 can be catalyzed by alkoxide or hydroxide ions, or amines. Alternatively, an acid catalyst forms a complex of type **590** from which proton loss is facilitated.



588 **589** **590**

The so-called isoxazoline transposition or Angelis rearrangement (**Scheme 123**) involves the conversion of methylfuroxans by treatment with alkoxides or alcoholic alkali hydroxides into the oximes of isoxazolidin-4-ones **591**.



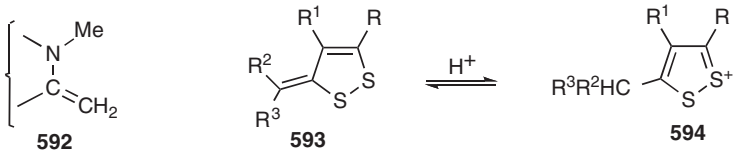
591

Scheme 123

It seems likely that a small concentration of anion is involved in the interaction of 1-aryl-5-methyltetrazoles with benzyne that produces 1-aryl-5-benzyltetrazoles efficiently <2005TL2679>.

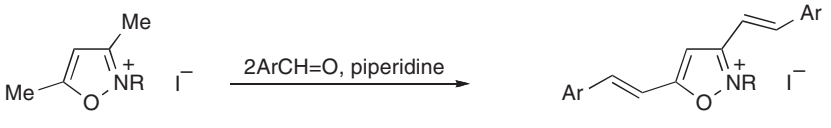
3.4.3.3.4 *C*-Alkyl-azoliums, -dithiolyliums, *etc.*

Proton loss from alkyl groups or to a cationic center in an azolium ring is often easy. The resulting neutral anhydro bases or methides (cf. **592**) can sometimes be isolated; they react readily with electrophilic reagents to give products which can often lose another proton to give new resonance-stabilized anhydro bases. Thus, the trithione methides are anhydro bases derived from 3-alkyl-1,2-dithiolylium salts (**593 594**). These methides are stabilized by electron-acceptor substituents such as CN or CO_2R.

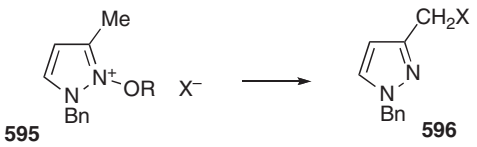


592 **593** **594**

Both - and -alkylazolium ions, like the 2- and 4-alkylazoles themselves, can also react with electrophilic reagents without initial complete deprotonation. They undergo the same types of reactions as the alkylazoles but under milder conditions, and these reactions can often be catalyzed by piperidine. Thus, in quaternized pyrazoles, 5-methyl groups react with benzaldehyde to give styryl derivatives. The methyl groups in quaternized isoxazoles are also reactive, and here piperidine is sufficient as catalyst (**Scheme 124**).

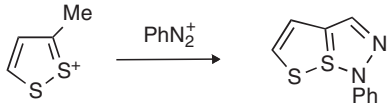


Scheme 124

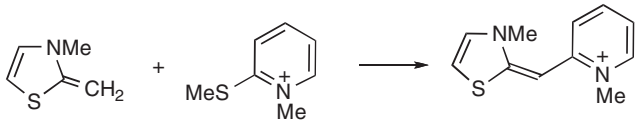


In 2-alkoxypyrazoliums **595**, methyl groups at positions 3 and 5 are active; in this way, for example, pyrazoles **596** were prepared (X = D, I, OMe).

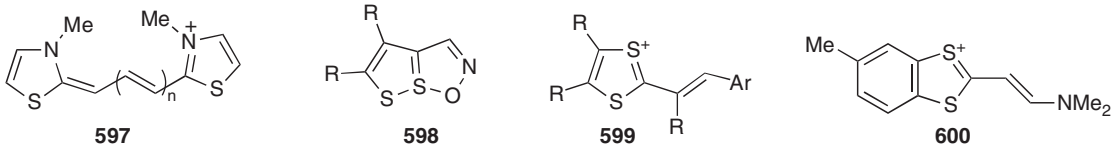
Some weak electrophilic reagents, which are usually inert toward neutral azoles, also react with quaternized azoles. Diazonium salts yield phenylhydrazones (**Scheme 125**) in a reaction analogous to the JappKlingemann transformation of -keto esters into phenylhydrazones; in the dithiolylium series illustrated, the product has bicyclic character. Cyanine dye preparations fall under this heading (see also Section 3.4.1.6.5). Monomethine cyanines are formed by reaction with a quaternary salt, e.g., **Scheme 126**. Tri- and pentamethinecarbocyanines **597** ($n = 1$ and 2, respectively) are obtained by the reaction of two molecules of a quaternary salt with one molecule of ethyl orthoformate **597** ($n = 1$) or -ethoxyacrolein acetal **597** ($n = 2$), respectively.



Scheme 125

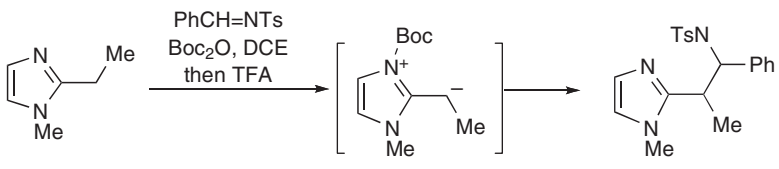


Scheme 126



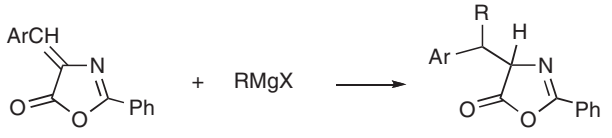
3-Methyl-1,2-dithiolyliums react with aldehydes to give styryl derivatives and with DMF to give Vilsmeier salts, and on nitrosation form the bicyclic products **598**. 2-Alkyl groups in 1,3-dithiolylium ions also react with aromatic aldehydes to give **599** and with DMF to give **600**.

In general, methyl groups at the 4- and 5-positions of imidazole, oxazole, and thiazole do not undergo such deprotonation-mediated reactions, even when the ring is cationic. A quaternary form can be generated *in situ* by N-acylation (**Scheme 127**) <2005TL4789>.



Scheme 127

Compounds which can formally be considered as anhydro bases can sometimes react with nucleophiles. Thus, unsaturated azlactones with Grignard reagents give saturated azlactones (**Scheme 128**).



Scheme 128

3.4.3.4 Other C-Linked Substituents

3.4.3.4.1 Aryl groups: Electrophilic substitution

Electrophilic substitution occurs readily in C-aryl groups, often predominantly at the *para* position. Thus, nitrations of phenylthiazoles, -oxazoles, and -imidazoles (HNO_3, H_2SO_4, 100°C) all yield the corresponding *p*-nitrophenyl derivatives. Phenyl groups attached to oxazole rings are nitrated or sulfonated at the *para* position, with relative positional reactivities of the phenyl groups in the order 5 > 4 > 2. This should be contrasted with the situation for 2-phenylpyridine, where a mixture of mainly *m*- and *p*-nitrophenyl derivatives is formed. Although in strongly acidic media a C-linked aryl group is generally more readily substituted than the ring, the orientation often changes when *C*-phenylazole derivatives are nitrated under less acidic conditions. Thus, 3- and 5-phenylpyrazoles under such conditions can give the 4-nitro derivatives. Such orientation changes have been demonstrated to result from changes in the species undergoing reaction, from the azolium ion to the neutral azole. For example, 5-methyl-3-phenylisoxazole is nitrated as a conjugate acid at the *meta* position but as the free base at the *para* position of the phenyl group.

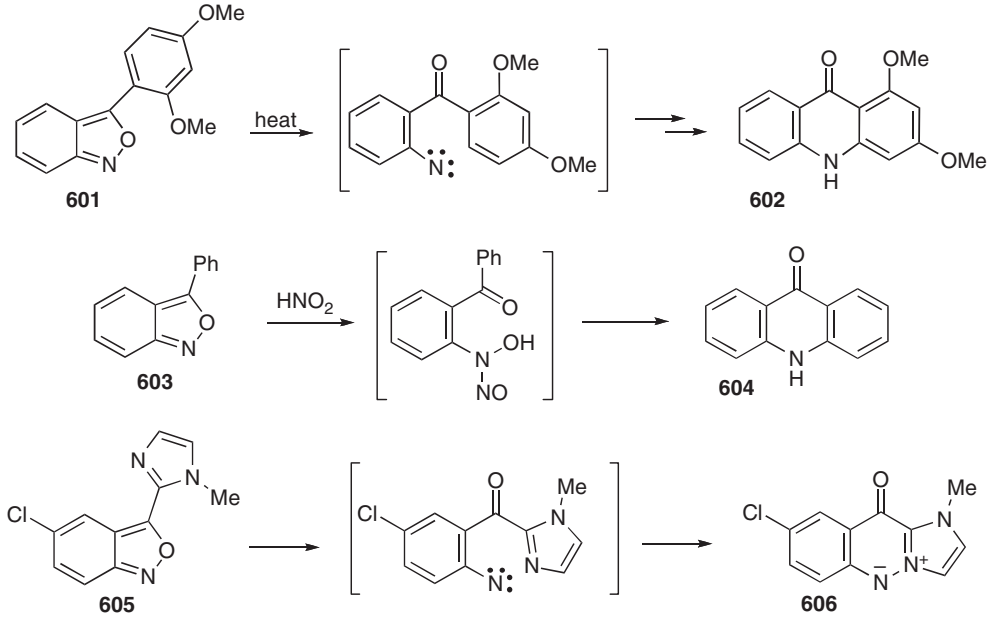
3-Phenylisothiazole is nitrated predominantly at the *meta* position of the phenyl group, whereas 4-phenylisothiazole is nitrated *ortho* and *para* in the phenyl group. Nitration of 3-phenyl-1,2,4-oxadiazole gives a mixture of *m*- and *p*-nitrophenyl derivatives.

In the 1,2-dithiolylium ion system, 3- and 5-phenyl groups on nitration give mixtures of *para* and *meta* orientation, whereas nitration of a 4-phenyl group gives *para* substitution only.

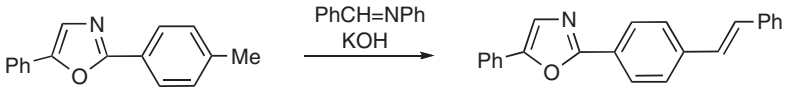
3.4.3.4.2 Aryl groups: Other reactions

In an elegant series of experiments, the benzene ring lithiation of 5-(*para*-substituted-aryl)tetrazoles, both *N*-hydrogen and *N*-trityl, was used to develop an order for the relative directing strengths of the tetrazoles and the benzene ring substituents <2002TL3137>: MeO < 1*H*-tetrazol-5-yl < $CONEt_2$ < 2-(triphenylmethyl)-2*H*-tetrazol-5-yl < $NHCOCMe_3$, $OCONEt_2$.

3-Arylanthranils **601** on thermolysis give acridones **602**. 3-Phenylanthranils e.g., **603**, also form acridones e.g., **604**, on treatment with nitrous acid. Related rearrangements are found with 3-heteroarylanthranils (e.g., **605** **606**).



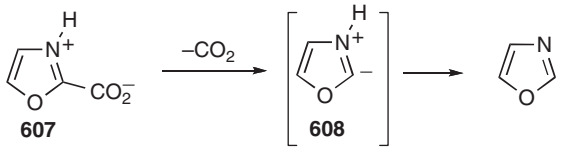
Methyl groups on C-linked phenyl attached to oxazoles, isoxazoles, and oxadiazoles react with benzylideneaniline to give stilbene derivatives (Scheme 129).



Scheme 129

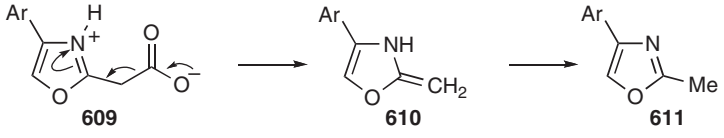
3.4.3.4.3 Carboxylic acids

Azolecarboxylic acids can be quite strongly acidic. Thus, 1,2,5-thiadiazole-3,4-dicarboxylic acid has first and second pK_a values of 1.6 and 4.1, respectively. The acidic strengths of the oxazolecarboxylic acids are in the order $2 > 5 > 4$, in agreement with the electron distribution within the oxazole ring. Azolecarboxylic acids are amino acids and can exist partly in the zwitterionic, or betaine, form (e.g., 607).

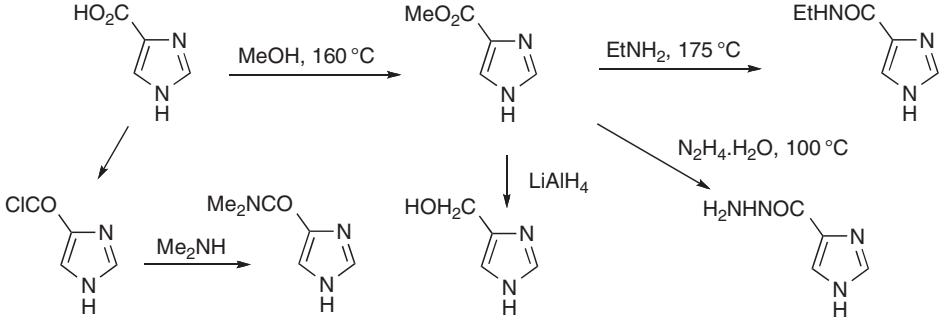


The relatively easy decarboxylation of many azolecarboxylic acids is a result of inductive stabilization of intermediate zwitterions of type 608 (cf. Section 3.4.1.8.1). Kinetic studies show that oxazole-2- and -5-carboxylic acids are both decarboxylated via the zwitterionic tautomers. Thiazole-2-carboxylic acids, and to a lesser extent -5-carboxylic acids, are decarboxylated readily; thiazole-4-carboxylic acids are relatively stable. Isothiazole-5-carboxylic acids are decarboxylated readily, the 3-isomers less so while the 4-isomers require high temperatures. The 1,2,4-, 1,2,5-, and 1,3,4-thiadiazolecarboxylic acids are also easily decarboxylated; their stability is increased by electron-donating substituents. Most 1,2,3-triazolecarboxylic acids lose carbon dioxide when heated above their melting points. Decarboxylation of 2-hydroxytetrazole-5-carboxylic acid requires severe conditions (HCl, reflux, 90 h) to produce 2-hydroxytetrazole (40%) <1999TL6093>.

Azoleacetic acids with a carboxymethyl group are also decarboxylated readily, e.g., all three thiazole isomers, by a mechanism similar to that for the decarboxylation of -keto acids (cf. Section 3.4.3.1.2). The mechanism has been investigated in the oxazole case, 609 610 611.

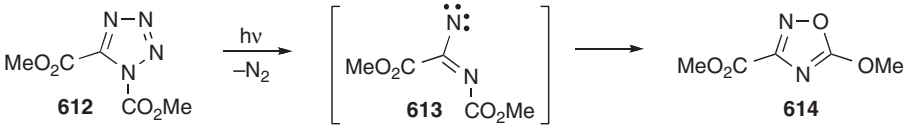


In most other reactions, the azolecarboxylic acids and their derivatives behave as expected (cf. the imidazole-3-carboxylic acid derivatives in Scheme 130), although some acid chlorides can be obtained only as hydrochlorides.



Scheme 130

Thus, imidazolecarboxylic acids show the normal reactions: they can be converted into hydrazides, acid halides, amides, and esters, and reduced by lithium aluminum hydride to alcohols. Thiazole- and isothiazolecarboxylic acid derivatives also show the normal range of reactions.

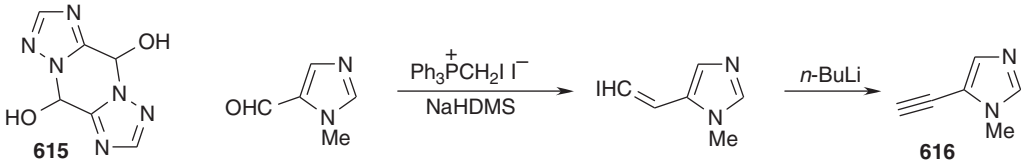


In some cases, however, carboxylic acid-derived groups can participate in ring fissionreclosure reactions. Thus, photolysis of 1,5-disubstituted tetrazole **612** gives nitrogen and appears to involve the nitrene intermediate **613**, which reacts further to give **614**.

3.4.3.4.4 Aldehydes and ketones

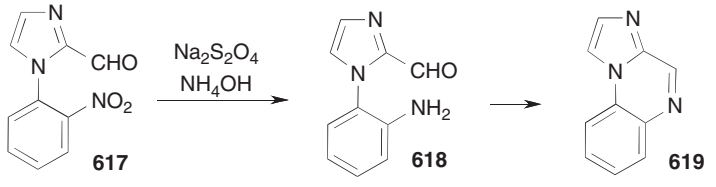
In general, the properties of these compounds and those of their benzenoid analogues are similar. Thus, isothiazole aldehydes and ketones behave normally and form the usual derivatives. Imidazole-2-carbaldehyde exists as a hydrate in aqueous solution. 4-Acetyloxazoles are oxidized to the corresponding acids with sodium hypobromite. Thiazole aldehydes undergo the benzoin and Cannizzaro reactions. Compounds with aldehyde groups to an NH group sometimes form dimers, e.g., as in the 1,2,4-triazole series **615**.

Wittig reactions are commonly used for the elaboration of side-chains. When 1-methylimidazole-5-carbaldehyde is heated with iodomethyltriphenylphosphonium iodide, and the iodoethenyl product is treated with *n*-butyllithium in THF, the ultimate product is the highly toxic 5-ethynyl-1-methylimidazole **616** (**Scheme 131**).

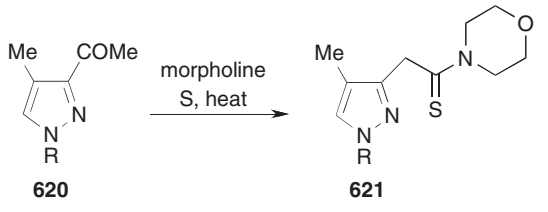


Scheme 131

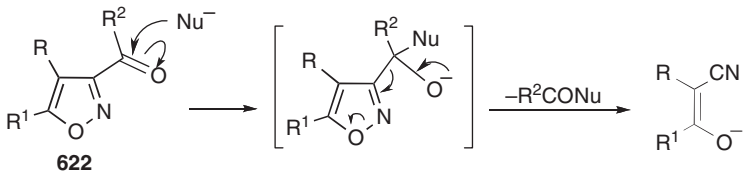
Aldehyde groups in *C*-formylazoles can participate in intramolecular cyclizations. Thus, reduction of 1-(2-nitrophenyl)imidazole-2-carbaldehyde **617** with sodium dithionite leads via amine **618** to imidazo[1,2-*a*]quinoxaline **619** in good yield.



The Willgerodt reaction can proceed normally; thus, 3-acetylpyrazoles **620** are converted into the morpholides **621**.

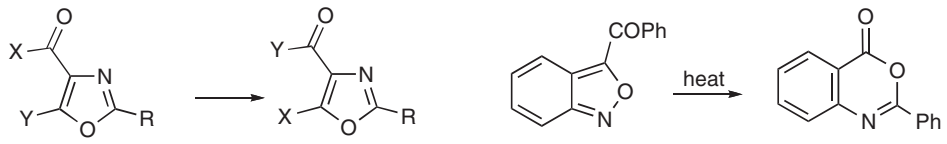


Deacylations are known: C-acyl groups in 1,3,4-thiadiazoles are cleaved by sodium ethoxide in ethanol. Imidazole-2-carbaldehyde behaves similarly, yielding imidazole and ethyl formate; this reaction involves an ylide intermediate. 3-Acylisoxazoles **622** are attacked by nucleophiles in a reaction that involves ring opening.



622

Sometimes ring opening and reclosure can occur with participation of a C-acyl group. Thus, oxazole derivatives of type **623** (X=H, Cl or NH_2; Y=OH or OEt) rearrange on heating to 255°C by ring opening and recyclization. 3-Acylanthranils **624** rearrange to benzoxazinones **625** on heating.

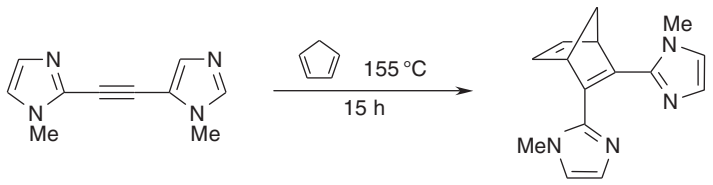


623 R = alkyl or aryl **624** **625**

3.4.3.4.5 Vinyl and ethynyl groups

Such groups to a pyridine-like nitrogen atom might be expected to undergo Michael additions and indeed examples are known in the imidazole series.

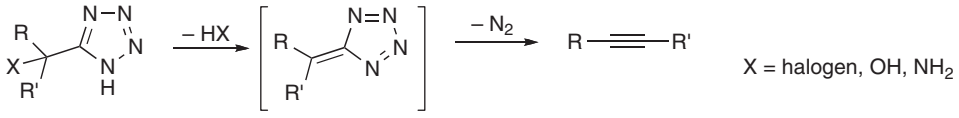
Vinyl and ethynyl groups attached to an imidazole ring can be catalytically reduced to the saturated (or less unsaturated) species and cleaved by oxidation. The corresponding 4-carbaldehyde is formed in 71% yield when 1-methyl-2,5-diphenyl-4-styrylimidazole is oxidized with osmium tetroxide. However, they may not react like aliphatic alkenes and alkynes; not all addition reactions occur normally, Michael additions are known, and the compounds can act as dienophiles in DielsAlder reactions (e.g., **Scheme 132**).



Scheme 132

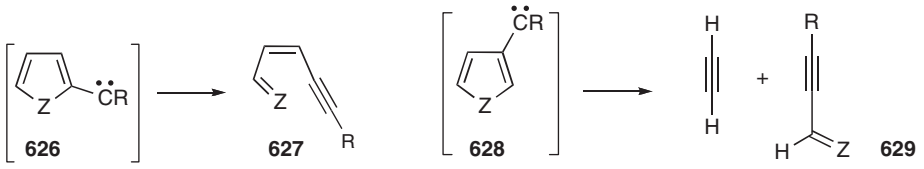
3.4.3.4.6 Ring fission

Certain 5-substituted alkyltetrazoles on pyrolysis yield nitrogen and an alkyne by the mechanism shown in **Scheme 133**.



Scheme 133

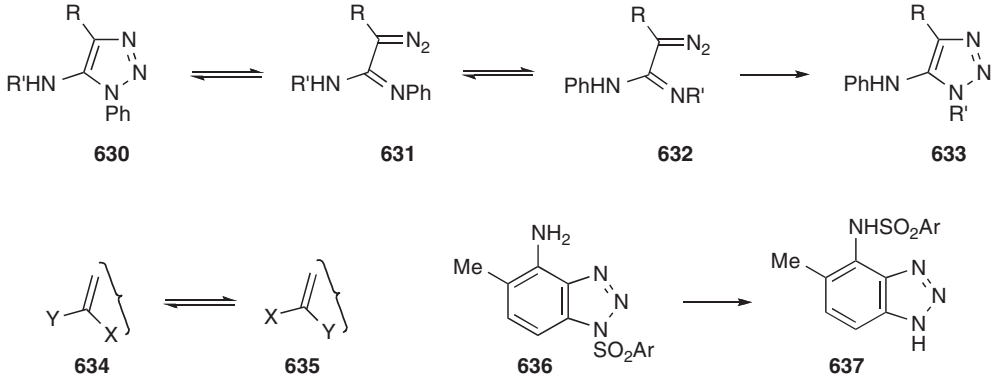
When an azole carbene is formed, spontaneous ring fission can occur. The prototypes for these reactions are shown: **626 627, 628 629**; cf. corresponding nitrene reactions (Section 3.4.3.6.2).



3.4.3.5 Aminoazoles

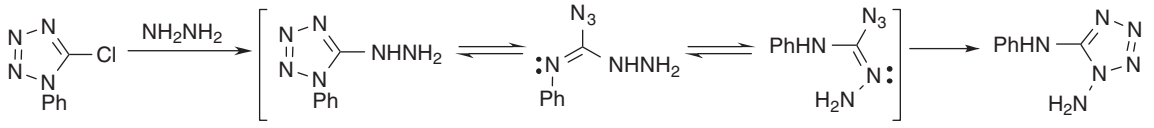
3.4.3.5.1 Dimroth rearrangements

The thermal acid- or base-catalyzed interconversion of 5-amino-l-phenyltriazoles **630** to 5-anilinotriazoles **633** was discovered by Dimroth. It is an example of a general class of heterocyclic rearrangements (**634** **635**) now known by the name Dimroth rearrangements. The original Dimroth rearrangement probably involves the tautomeric intermediates **631** and **632**. Electron-attracting and large groups tend to favor the tautomer in which they are located on the exocyclic nitrogen. Alkyl groups tend to prefer to reside on the cyclic nitrogen. Many other Dimroth rearrangements of 4- and/or 5-substituted 1,2,3-triazoles are also known.



The benzotriazole ring is more stable and less susceptible to ring opening. Nevertheless, thermal rearrangements of 4-aminobenzotriazoles occur when the N(1) substituent is strongly electron withdrawing (**636** **637**) (the reverse rearrangement is not observed). Similar rearrangements are known for 1,2,3-triazolo-fused pyrimidines and triazines.

The thermal behavior of substituted 5-aminotetrazoles involves wide-ranging examples of the Dimroth rearrangement together with imidoyl azide-tetrazole ring-chain isomerism. An example with 5-hydrazinotetrazoles is shown in **Scheme 134**.

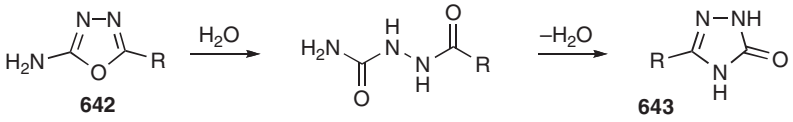


Scheme 134

Many related examples are now known as Dimroth rearrangements. For example, 3-ethylamino-1,2-benzisothiazole **638** is in equilibrium in aqueous solution with the 2-ethyl-3-imino isomer **639**. Dimroth rearrangements are known in the 1,2,4-thiadiazoles **640** **641**; see Section 3.4.3.9.1. For a similar example in the 1,2,3,4-thiatriazole series, see Section 3.4.3.1.9.

638 639 640 641

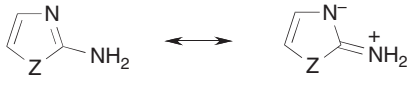
2-Amino-1,3,4-oxadiazoles **642** ring open and the products immediately recyclize to triazolinones **643**.



642 643

3.4.3.5.2 Reactions with electrophiles (except nitrous acid)

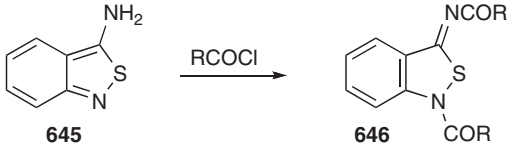
In aminoazoles with the amino group or to C═N, canonical forms of type **644** illustrate an increased nucleophilic reactivity of the pyridine-like nitrogen atom toward electrophilic reagents, but a decrease of that of the amino group. Even when the amino group is to C═N, there is still a small electron flow in the same sense. Consequently, protons, alkylating agents, and metal ions usually react with aminoazoles at the annular nitrogen atom (cf. Section 3.4.1.3). There are exceptions to this generalization; for example, 4-aminoisothiazole is methylated to the 4-trimethylammonioisothiazole and both 3- and 4-dimethylaminopyrazoles are alkylated on the NMe_2 group.



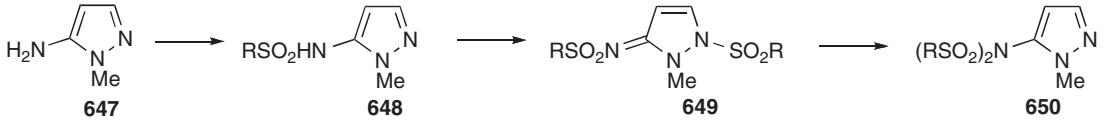
644

Other electrophilic reagents form products of reaction at the amino group. This occurs when initial attack at the pyridine-like nitrogen atom forms an unstable product which either dissociates to regenerate the reactants or undergoes rearrangement inter- or intramolecularly. In reactions of this type, carboxylic and sulfonic acid chlorides and anhydrides give acylamino- and sulfonamidoazoles, respectively. Thus, 3-, 4-, and 5-aminothiazoles form acetyl derivatives, sulfonamides, and ureas. The 3- and 5-amino-1,2,4-thiadiazoles can be acylated and sulfonylated; 3-amino-1,2,5- and 2-amino-1,3,4-thiadiazoles also behave normally on acylation.

3-Amino-2,1-benzisothiazole **645** is acylated at both the cyclic and exocyclic nitrogen atoms to give **646**. 5-Aminotetrazoles with nitric acid give nitramines. Sulfonation of the 5-aminopyrazole **647** first gives the expected product, **648**, then a disulfonyl derivative **649**, which rearranges on heating to the more stable **650**. Aminothiazoles react with aldehydes to give Schiff bases.



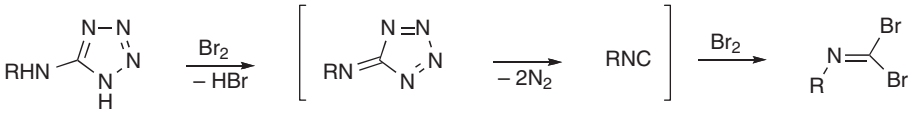
645 646



647 648 649 650

In still other cases, the product of reaction of an electrophile with an aminoazole is from electrophilic attack at a ring carbon. This is electrophilic substitution and is the general result of nitration and halogenation (see Section 3.4.1.4). In such cases, reactions at both cyclic nitrogen and an amino group are reversible.

In a rather different reaction, aminotetrazoles treated with bromine lose nitrogen and give isocyanide dibromides; the probable mechanism is shown in **Scheme 135**.

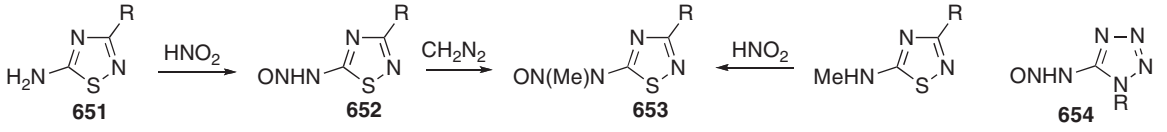


Scheme 135

3.4.3.5.3 Reaction with nitrous acid; diazotization

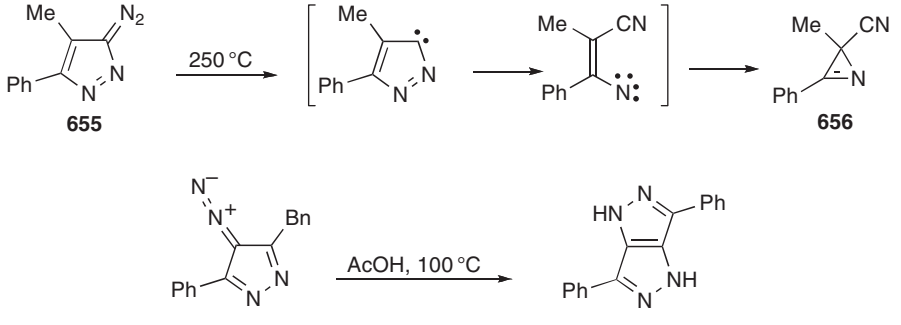
Primary amino groups attached to azole rings react normally with nitrous acid to give diazonium compounds via primary nitroso compounds. However, the azole series shows two special characteristics: the primary nitroso compounds can be stable enough to be isolated, and diazo anhydrides are formed easily from azoles containing ring NH groups.

3.4.3.5.3.1 Primary nitroso compounds. Attempted diazotization in dilute acid sometimes yields primary nitroso compounds. Reactions of 3- and 5-amino-1,2,4-thiadiazoles with sodium nitrite and acid give primary nitrosamines (e.g., **651 652**) which can be converted into the secondary nitrosamines **653** prepared in the normal way. 1-Substituted 5-aminotetrazoles with nitrous acid give stable primary nitrosamines **654**. Primary nitrosamines have been isolated in the imidazole series.

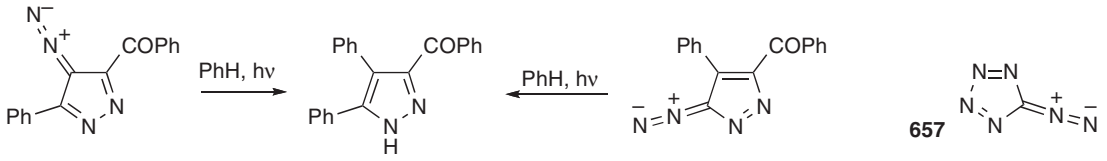


3.4.3.5.3.2 Diazo anhydrides. Diazotization of aminoazoles with a free cyclic NH can give diazo anhydrides which show many of the normal reactions of diazonium ions. In the pyrazole series, these diazo anhydrides (e.g., **655**) are particularly stable.

3-Diazopyrazole **655** undergoes gas-phase thermal extrusion to form an azirine **656**, probably by the mechanism shown; 4-diazopyrazoles show normal diazonium-type reactions (**Schemes 136** and **137**). Analogous diazoimidazoles and diazopurines are known.

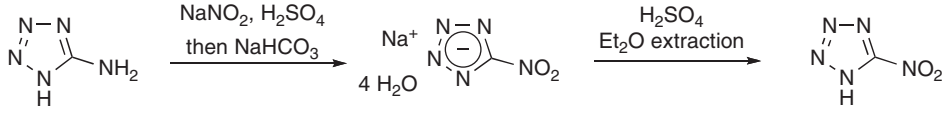


Scheme 136



Scheme 137

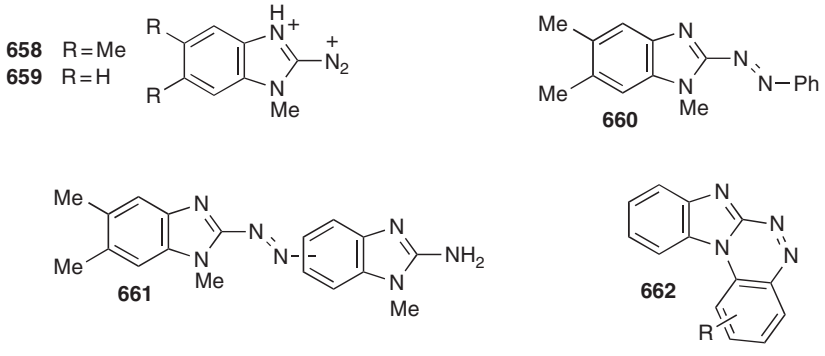
5-Aminotetrazole can be diazotized and the diazonium salt used for synthesis of a wide range of 5-substituted tetrazoles <2005CM3784, 2006AGE3584>. Notably 5-nitrotetrazole was prepared in this way via 5-nitrotetrazole sodium salt tetrahydrate <1997RJO1771>. [*Caution! 5-Nitrotetrazole sodium salt (tetrahydrate) when heated to temperatures higher than 50°C loses water molecules. The anhydrous salt has high sensitivity to impact and friction.*] Diazotetrazole **657** can be prepared; on pyrolysis it yields carbon atoms and nitrogen.



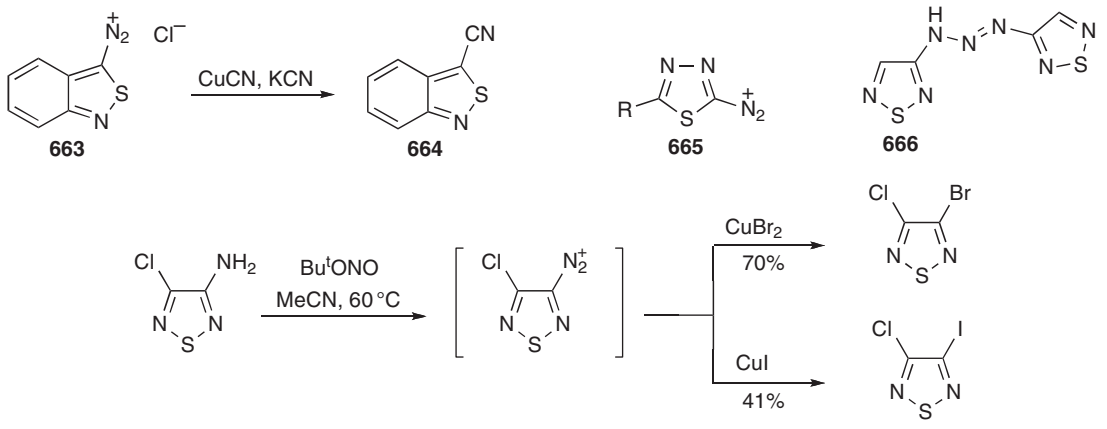
3.4.3.5.3.3 Diazonium salts. Pyridine-2- and -4-diazonium ions are far less stable than benzenediazonium cations. Azolediazonium salts generally show intermediate stability; provided diazotization is carried out in concentrated acid, many of the usual diazonium reactions succeed. Indeed, azolediazonium salts are often very reactive in coupling reactions.

2-Nitroimidazoles and 2-azidoimidazoles are available via the diazonium fluoroborates, and photolytic decomposition of the fluoroborates gives 2-fluoroimidazoles. Conversions of diazonium salts into other halogenoimidazoles are quite common.

1-Alkyl-2-aminobenzimidazoles can be diazotized only in nitrosylsulfuric acid. Under these extremely acidic conditions, the diazonium salts thus formed exist as highly electrophilic dications. When positions 5 and 6 in such salts (e.g., **658**) are occupied, azocoupling occurs even with benzene, toluene, and xylene, producing azo compounds of type **660**. If positions 5 or 6 are free, as in salt **659**, it undergoes self-azocoupling with a molecule of the starting amine to afford a mixture of 5- and 6-azo compounds **661**. In *N*-arylbenzimidazole-2-diazonium salts, intramolecular azocoupling leading to 1,2,4-benzotriazine derivatives **662** is also possible.



2-Aminothiazole and 2-aminobenzothiazole readily undergo diazotization upon treatment with nitrous acid/phosphoric acid <2001DP(50)93>. 3-Amino-2,1-benzisothiazole is readily diazotized to **663**, which gives coupling products or the cyanide **664**. Diazonium salts from 3-, 4-, and 5-aminothiazoles undergo Sandmeyer reactions (to give haloisothiazoles), reductive deaminations, and GombergHey reactions. 5-Aminooxazoles can be satisfactorily diazotized, but the 2-amino compounds cannot. Sandmeyer reactions can also be used to form 5-iodoimidazoles <1999JOC7158> and H_3PO_2 reductions allow replacements of imidazole-5-diazonium groups with hydrogen <2003JHC159>. Diazotization of 3-amino-4-chloro-1,2,5-thiadiazole leads to 3-chloro-4-bromo- and 3-chloro-4-iodo-1,2,5-thiadiazoles (**Scheme 138**)



Scheme 138

<2003H(60)29>. 1,3,4-Thiadiazol-2-amines undergo Sandmeyer reactions to afford 2-halo-1,3,4-thiadiazoles <2003JME427, 2005BML1983, 2005BML4488, 2006BML1164, 2006BML1735, 2006OL1447>. 2-Bromo-5-phenyl-1,3,4-oxadiazole can be prepared in over 90% yield from 2-amino-5-phenyloxadiazole via the corresponding diazonium compound <2004TL7157>.

The 4- and 5-amino-1,2,3-triazoles are diazotizable, e.g., the diazonium salt from 4-aminotriazole-5-carboxamide with potassium iodide gives the 4-iodo derivative and that from 4-amino-1,5-diphenyltriazole gives 1,5-diphenyltriazole.

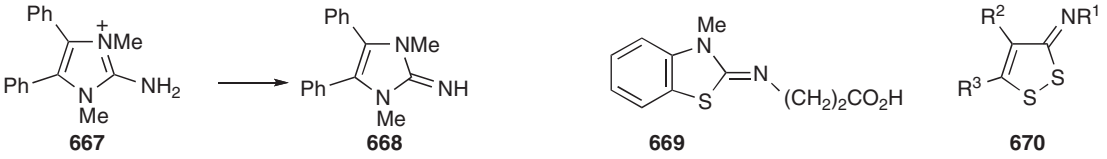
The 1,2,4-thiadiazole-3- and -5-diazonium salts have been prepared in strong acid; the 5-derivatives are very reactive in coupling reactions and undergo Sandmeyer reactions. Diazonium salts from 3-amino-1,2,4-thiadiazoles are less reactive with coupling reagents. Amino-1,3,4-thiadiazoles undergo diazotization smoothly, provided the solution is sufficiently acidic. The diazonium salts **665** show strong coupling activity and will even couple with mesitylene. 3-Amino-1,2,5-thiadiazole on attempted diazotization forms only the diazoamino compound **666**.

3.4.3.5.4 Deprotonation of aminoazoles

Proton loss from the amino groups is relatively easy; the anions formed react with electrophilic reagents, usually preferentially at the exocyclic nitrogen atom. Thus, mono-N-anions of aminoazoles are easily formed when the latter are treated with metallic sodium or $NaNH_2$ (KNH_2) in liquid ammonia. They can be further alkylated to afford dialkylamino derivatives in good yields. Di-N-anions are also obtained when *n*-butyllithium is used as a base. However, the best method to generate dianions appears to be reductive cleavage of hetaryl azides with sodium in liquid ammonia.

3.4.3.5.5 Aminoazolium ions/neutral imines

Amino groups on azolium rings can lose a proton to form strongly basic azolinimines, e.g., **667** yields **668**. 2-Iminobenzothiazoline with acrylic acid yields **669**.

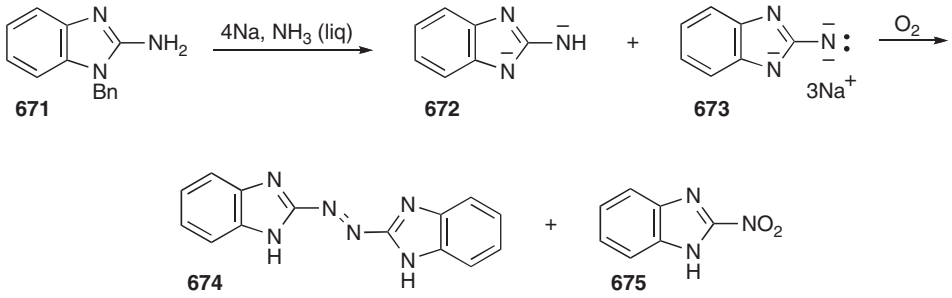


In the 1,2-dithiole series imines such as **670**, are readily isolated; they can be alkylated or protonated.

3.4.3.5.6 Oxidation of aminoazoles

2-Aminobenzimidazoles and 2-aminobenzothiazoles can be oxidized with sodium hypochlorite to afford the corresponding 2,2-azo compounds. A rather unusual autooxidation of a heteroaromatic *C*-amino group occurs on treatment of 1-benzyl-2-aminobenzimidazole **671** with excess sodium or potassium in liquid ammonia. The products are 2,2-azobenzimidazole **674** and 2-nitrobenzimidazole **675**, formed in 60 and 40% yields, respectively. It is supposed that

di-**672** and tri-**673** *N*-anions are generated which are extremely reactive toward oxygen of the air. This is the only known example of such easy autooxidation of an amino group to a nitro group.

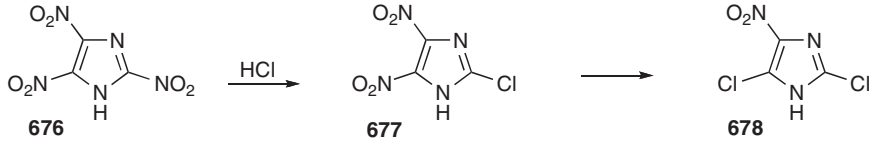


671 672 673 674 675

3.4.3.6 Other N-Linked Substituents

3.4.3.6.1 Nitro groups

Nitro groups on azole rings are often smoothly displaced by nucleophiles, even more readily than are halogen atoms in the corresponding position. Thus, 2,4,5-trinitroimidazole **676** is converted by HCl successively into **677** and **678**. Comparable easy nitro mono-displacements with amines are achieved with dinitrofurazan <2004RCB596>.

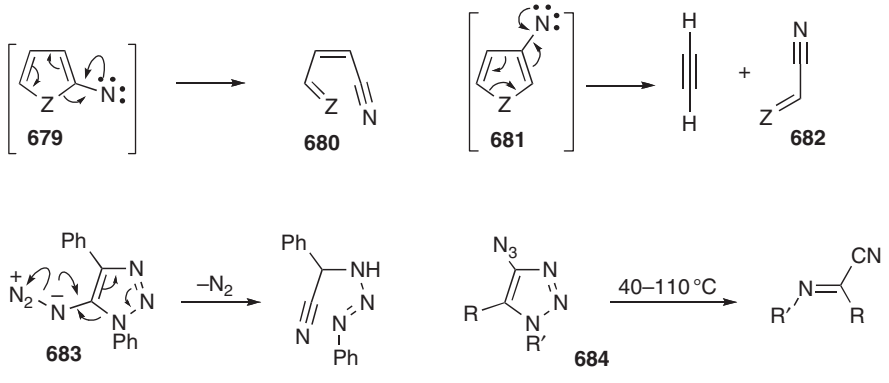


676 677 678

Nitro groups are easily reduced, catalytically or chemically, to give amino compounds; for example, 4-nitroisothiazoles give the corresponding 4-amino derivatives and nitrobenzo-2,1,3-thiadiazoles can be readily reduced to the aminobenzothiadiazoles without degradation of the heterocyclic moiety using iron powder, AcOH at 30°C <1997T10169, 2005JA5186>; the use of Zn in AcOH leads to complete reduction of both the nitro group and the thiadiazole ring <2005JOC2754>. In the pyrazole series, intermediate nitroso compounds can be isolated. Nitrosoimidazoles are also relatively stable.

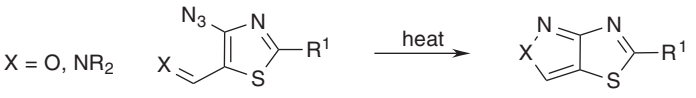
3.4.3.6.2 Azidoazoles

The most important chemistry of azidoazoles is the fragmentation of derived nitrenes of which the prototypes are **679 680** and **681 682**. Thus, 5-azido- 1,4-diphenyltriazole **683** evolves nitrogen at 50°C. 4-Azido-pyrazoles and -1,2,3-triazoles **684** undergo fragmentation with formation of unsaturated nitriles; cf. corresponding carbene reactions (Section 3.4.3.4.6).



679 680 681 682 683 684

Heating 4-azidothiazoles having an imino or aldehyde group at the 5-position affords fused pyrazolo- and isoxazolo [3,4-*d*]thiazoles (**Scheme 139**). When an alkenyl group is at the 5-position of the triazole ring, 4*H*-pyrrolo[2,3-*d*] thiazoles are obtained.

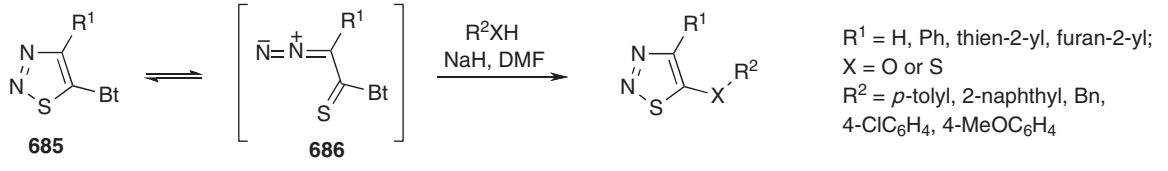


Scheme 139

For azidotetrazole tautomerism in the azole series, see Section 2.4.5.3.2.

3.4.3.6.3 Benzotriazole

1,2,3-Thiadiazoles that have a 5-benzotriazolyl substituent, **685**, can be reacted with oxygen and sulfur nucleophiles with overall displacement of the benzotriazolyl group. The mechanism probably involves ring-chain isomerization involving cleavage of the 1,2-bond to afford 2-diazothione tautomers **686** that then undergo nucleophilic substitution and subsequent ring closure (**Scheme 140**) <2001JOC4045>.

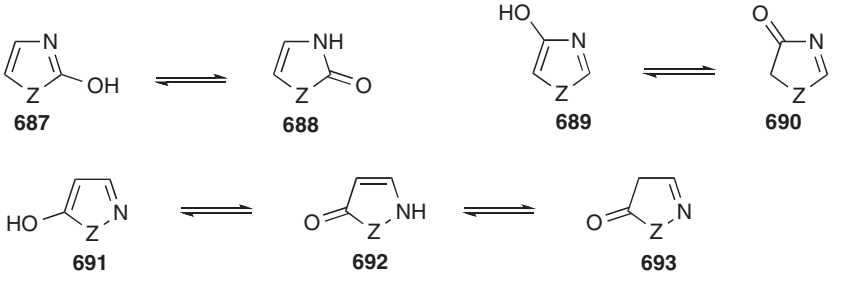


Scheme 140

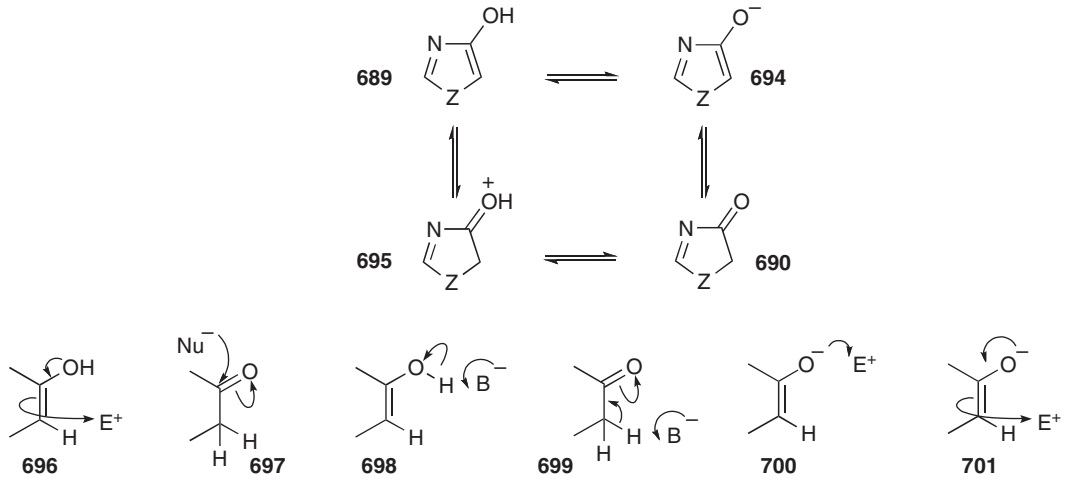
3.4.3.7 O-Linked Substituents

3.4.3.7.1 Tautomeric forms: Interconversion and modes of reaction

As discussed in Section 2.4.5.2, hydroxy derivatives of azoles (e.g., **687, 689, 691**) are tautomeric with either (1) aromatic carbonyl forms (e.g., **688, 692**) (as in pyridones) or (2) nonaromatic carbonyl forms (e.g., **690, 693**) or both. In the hydroxy enolic form, the reactivity of these compounds toward electrophilic reagents is greater than that of the parent heterocycles; these are analogues of phenol.

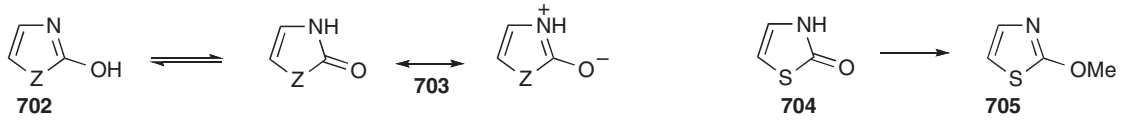


Interconversion of the hydroxy and carbonyl forms of these heterocycles proceeds through an anion (as **694**) or a cation (as **695**), just as the enol and keto forms of acetone are interconverted through the ions. Reactions of the various species derived from the heterocyclic compounds are analogous to those of the corresponding species from acetone: hydroxy forms react with electrophilic reagents **696** and carbonyl forms with nucleophilic reagents **697**. In addition, either form can lose a proton (**698, 699**) to give an anion that reacts very readily with electrophilic reagents on either oxygen **700** or carbon **701**.



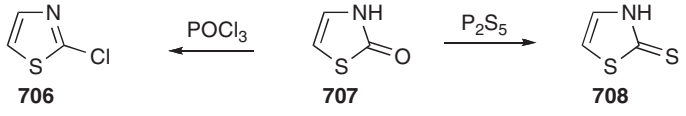
The completely conjugated carbonyl forms are usually quite stable and highly aromatic in that after reaction they revert to type. An overall treatment of their reactivity is given in Section 3.4.1.1.4. Electrophilic attack on the oxygen atom of the carbonyl groups and nucleophilic attack at the carbonyl carbon atom, in reactions which lead to substitution rather than ring opening, are discussed in this section. Electrophilic attack at ring carbon (Section 3.4.1.4) and ring nitrogen (Section 3.4.1.3) and nucleophilic attack at ring carbon (Section 3.4.1.6) (other than C=O replacement) are discussed in the sections indicated.

3.4.3.7.2 Hydroxyazoles, heteroatoms-1,3. 2-Hydroxyimidazoles, -oxazoles, and -thiazoles **702** (Z = NR, O, S) can isomerize to 2-azolinones **703**. These compounds all exist predominantly in the azolinone form and show many reactions similar to those of the pyridones.



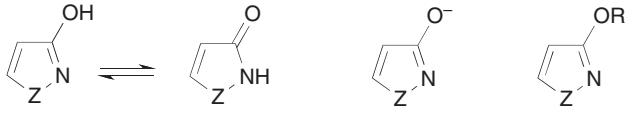
3.4.3.7.2.1 Electrophilic attack on oxygen. 2-Azolinones are protonated on oxygen in strongly acidic media. O-Alkylation of 2-azolinones can be effected with diazomethane; thiazolinone **704** forms **705**. Frequently O- and N-alkylation occur together, especially in basic media where proton loss gives an ambident anion (see also Section 3.4.1.3.10).

3.4.3.7.2.2 Nucleophilic displacement. 2-Imidazolinones, 2-oxazolinones, and 2-thiazolinones behave as cyclic ureas, thiocarbamates, and carbamates, and predictably do not normally react with nucleophilic ketonic reagents such as HCN, RNH_2, $NaHSO_3$, NH_2OH, N_2H_4, PhN_2H_3, or $NH_2CON_2H_3$. Stronger nucleophilic reagents, i.e., those of the type that attack amides, generally also react with azolinones. Thus, they can be converted into chloroazoles with $POCl_3$ or PCl_5, e.g., **707** **706** or benzimidazol-2-one into 2-chlorobenzimidazole <2006JME3719>. Alkyl substituents on the azole nitrogen atom are usually lost in reactions of this type. Phosphorus pentasulfide converts carbonyl groups into thiocarbonyl groups (e.g., **707** **708**).



3.4.3.7.3 3-Hydroxyazoles, heteroatoms-1,2

Pyrazoles, isoxazoles, and isothiazoles with a hydroxy group in the 3-position **709** (Z = NR, O, S) could in principle isomerize to 3-azolinones **710**. However, these compounds behave as true hydroxy derivatives and show phenolic properties. They give an intense violet color with iron(III) chloride and form a salt **711** with sodium hydroxide which can be O-alkylated by alkyl halides to give **712** (R = alkyl) and acylated by acid chlorides to give **712** (R = acyl).

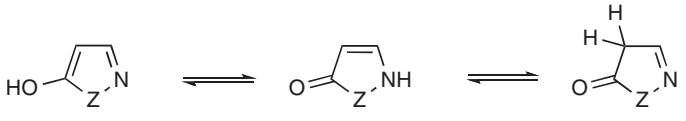


709 **710** **711** **712**

Sometimes compounds that exist predominantly in the hydroxy form give products of N-methylation with diazomethane, for example, 3-hydroxy-5-phenylisothiazole. 3-Hydroxypyrazoles, under rather severe conditions, can be converted into 3-chloropyrazoles with $POCl_3$.

3.4.3.7.4 5-Hydroxyazoles with heteroatoms-1,2

5-Hydroxyisoxazoles and -pyrazoles can tautomerize in both of the ways discussed in Sections 3.4.3.7.3 and 3.4.3.7.5 (**713 714 715**). The hydroxy form is generally the least stable; the alternative azolinone forms coexist in proportions depending on the substituents and the solvent, with nonpolar media favoring the CH form **715** and polar media the NH form **714**. The derived ambident anion can react with electrophiles at N, C, or O depending on the reagent and conditions.

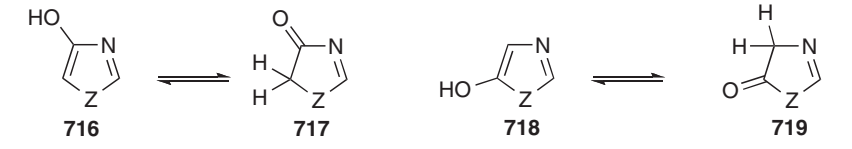


713 **714** **715**

The hydroxy groups of 5-hydroxypyrazoles are readily replaced by halogens by the action of phosphorus halides.

3.4.3.7.5 4- and 5-Hydroxyazoles with heteroatoms-1,3 and 4-hydroxyazoles with heteroatoms-1,2

The 4- and 5-hydroxy-imidazoles, -oxazoles, and -thiazoles (**716, 718**) and 4-hydroxypyrazoles, -isoxazoles, and -isothiazoles **720** cannot tautomerize to an aromatic carbonyl form. However, tautomerism similar to that which occurs in hydroxyfurans, -thiophenes, and -pyrroles is possible (**716 717; 720 721; 718 719**), as well as a zwitterionic NH form (e.g., **722**). Most 4- and 5-oxy compounds exist largely as nonaromatic azolinone forms **717** and **719**, although the hydroxy form can be stabilized by chelation (e.g., **723**). The derived ambident anions react with electrophiles at O or C. Replacement of the hydroxy group is sometimes possible provided electron-withdrawing groups are present as, for example, in 5-substituted 4-hydroxypyrazoles.



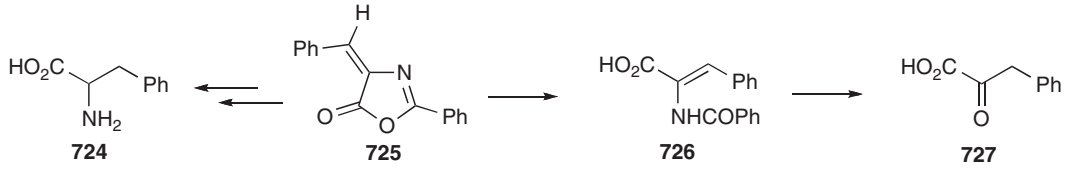
716 **717** **718** **719**

720 **721** **722** **723**

4-Hydroxy derivatives of type **720** show more phenolic character; thus 4-hydroxyisothiazoles are normally O-methylated and O-acylated.

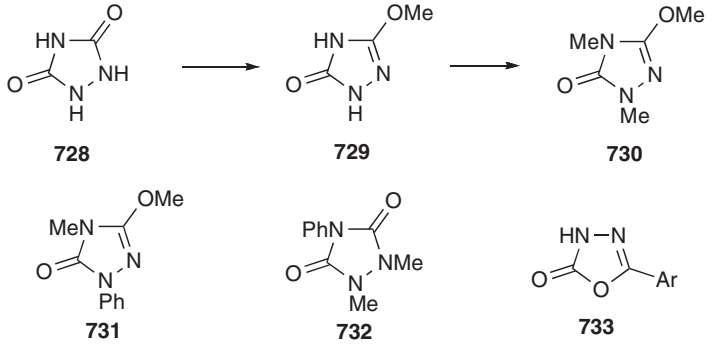
4-Chloro-substituted thiazoles can be prepared by the reaction of phosphorus oxychloride with the corresponding 4-hydroxythiazoles. This method is also applicable for the preparation of 4-bromo-2-phenylthiazole. Conversion of 3-hydroxy-1,2,5-thiadiazoles into the bromo compounds can be achieved using phosphorus oxybromide, but vigorous conditions are required <1996H(43)2435>.

Ring fission occurs readily in many of these compounds. For example, azlactones, i.e., 4*H*-oxazolin-5-ones containing an exocyclic C═C bond at the 4-position **725**, are hydrolyzed to -benzamido-,-unsaturated acids **726**, further hydrolysis of which gives -keto acids **727**. Reduction and subsequent hydrolysis *in situ* of azlactones is used in the synthesis of -amino acids (e.g., **725** **724**).



3.4.3.7.6 Hydroxy derivatives with three heteroatoms

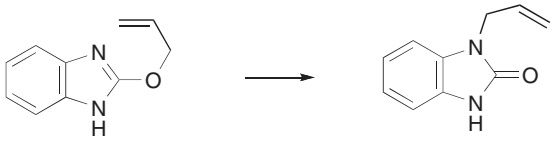
These compounds generally exist in carbonyl forms. The oxygen function can be converted into halogen by phosphorus halides. Reactions with electrophiles are quite complex. Thus, urazole **728** reacts with diazomethane rapidly to yield **729**, which is more slowly converted into **730**. 1-Phenylurazole gives **731**; 4-phenylurazole yields **732**. Oxadiazolinones of type **733** can be alkylated at both O- and N-atoms.



3.4.3.7.7 Alkoxy and aryloxy groups

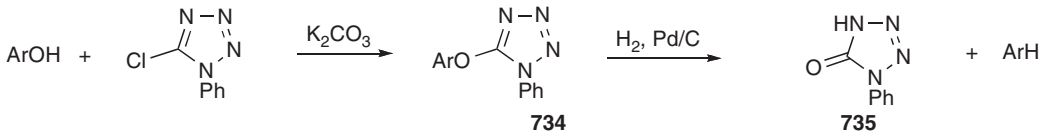
The alkoxy groups in alkoxyazoles undergo easy dealkylation to the corresponding hydroxyazoles (azolinones) when several nitrogen atoms are present or when they are additionally activated by another substituent. Nucleophilic displacement of alkoxy groups on cationic rings occurs readily.

Azoles with alkoxy groups to nitrogen can rearrange to *N*-alkylazolinones on heating; thus 2-alkoxy-l-methylimidazoles give 3-alkylimidazolin-2-ones and 2-methoxythiazoles behave similarly. O-Allyl groups rearrange considerably more readily, e.g., 2-allyloxybenzimidazole gives 1-allyl-2-benzimidazolinone at 180°C (**Scheme 141**). 5-Allyloxypyrazoles undergo Claisen rearrangement of the allyl group to the 4-position.



Scheme 141

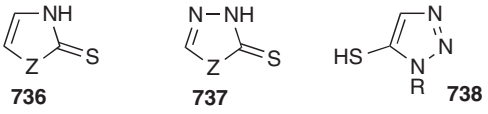
Aryl tetrazolyl ethers **734** are reduced by hydrogen over Pd/C to give the arene and the tetrazolinone **735**; this reaction is used for the removal of a phenolic functionality.



3.4.3.8 *S*-Linked Substituents

3.4.3.8.1 Mercapto compounds: Tautomerism

Many mercaptoazoles exist predominantly as thiones. This behavior is analogous to that of the corresponding hydroxyazoles (cf. Section 3.4.3.7). Thus oxazoline-, thiazoline-, and imidazoline-2-thiones **736** all exist as such, as do compounds of type **737**. However again, as for the corresponding hydroxy derivatives, some mercaptoazoles exist as such. 5-Mercaptothiazoles and 5-mercapto-1,2,3-thiazoles, e.g., **738**, for example, are true SH compounds.

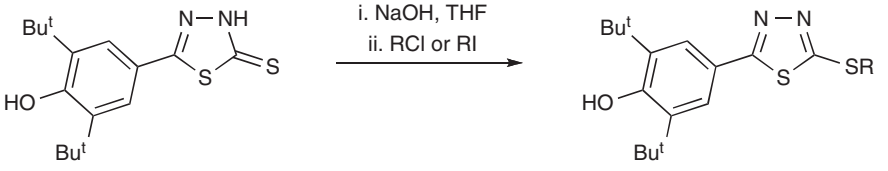


The pattern of reactivity is similar to that discussed for the azolinones in Sections 3.4.1.1.4 and 3.4.3.7.1. A difference is the greater nucleophilicity of sulfur, and thus most reactions of the ambident anion with electrophiles occur at sulfur.

3.4.3.8.2 Thiones

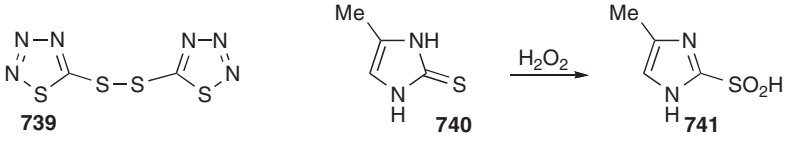
Many azolinethiones show reactions typical of thioamides; in particular, they react with electrophiles at the sulfur atom.

1. Alkyl halides give alkylthio derivatives, e.g., in the imidazoline-2-thione, thiazoline-2-thione, and 1-arylpyrazoline-5-thione series. Often base is used to increase reactivity (**Scheme 142**) <1999JME1161, 2004RJO447>, sometimes even Et_3N is sufficient (e.g., 1,3,4-oxadiazole-2-thiones <2003CHE1364>). Dimethyl sulfate *S*-methylates 5-aryl-1,3,4-oxadiazole-2-thiones without base <1997CHE1109>.

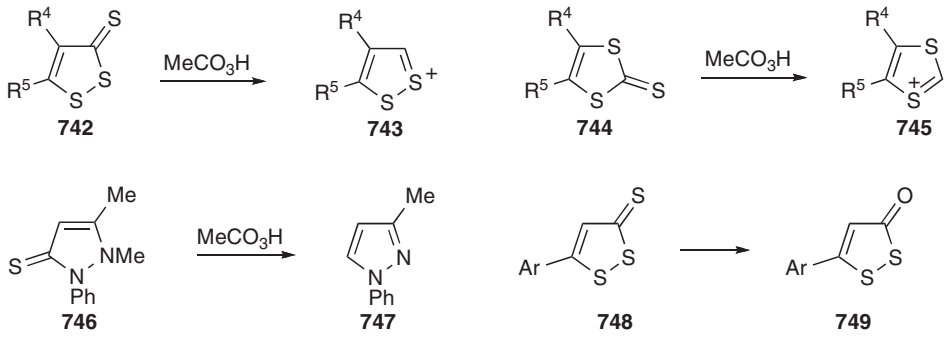


Scheme 142

2. Thiones are oxidized, e.g., by iodine, to disulfides. Thus 5-mercapto-1,2,3,4-thiatriazole is converted into the disulfide **739**; similar behavior is known in the tetrazole series.



3. Thione groups can often be eliminated by oxidation; probably the sulfinic acid is the intermediate. Sometimes the sulfinic acid can be isolated (e.g., **740** **741**), but more often it spontaneously loses SO_2. In this way, thiazoline-2-thiones give thiazoles, 1,2-dithiole-3-thiones **742** are converted into 1,2-dithiolylium salts **743**, 1,3-dithiole-2-thiones **744** into 1,3-dithiolylium salts **745**, 1,5-disubstituted imidazole-2-thiones into imidazoles <2003JHC229>, and 3-mercapto-1,2,4-triazoles into the parent triazole <2006S156>. In the pyrazole series, **746** also loses an *N*-methyl group to yield **747**.

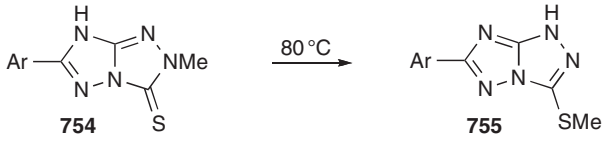


742 743 744 745 746 747 748 749

4. However, 5-aryl-1,2,4-dithiazoline-3-thiones are oxidized to the 3-ones (748 749).
5. Strong oxidation (e.g., by $KMnO_4$) forms a sulfonic acid or betaine as, for example, in the pyrazole (750 751), imidazole, thiazole, and tetrazole series.

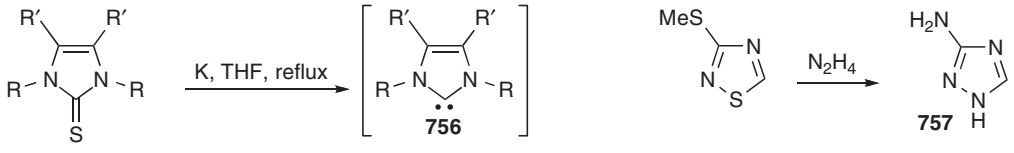
750 751 752 753

6. Cycloaddition across the C=S bond can lead to spiro derivatives, e.g., 752 753.
7. Like carbonyl oxygen in azolinones, sulfur in azolinethiones can be displaced by a halogen atom. For example, benzimidazoline-2-thiones react with thionyl chloride producing 2-chlorobenzimidazoles.
8. On heating, compounds 754 undergo N to S migration of the methyl group, yielding products 755.



754 755

9. Imidazoline-2-thiones are reduced by potassium metal in THF forming stable carbenes (imidazol-2-ylidenes) 756 that react very readily with electrophiles (see also Section 3.4.1.8.5).



756 757

3.4.3.8.3 Alkylthio groups

2-Alkylthiothiazoles rearrange thermally into the 3-alkylthiazoline-2-thiones; in the imidazole series, a thermal equilibrium is reached.

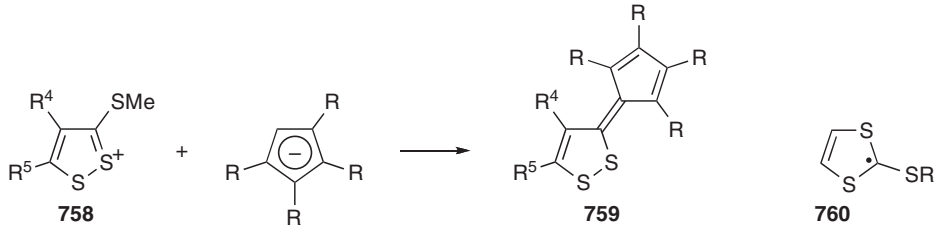
Alkylthio groups are oxidized to sulfoxides by H_2O_2 and readily by various oxidizing reagents to sulfones, e.g., in the imidazole series. The control of such S-oxidations is illustrated by 1,3,4-thiadiazoles: sulfoxides can be achieved using stoichiometric amounts of MCPBA <1998BML2473, 1999JME1161, 2006BML1164>, whereas the use of excess MCPBA or hydrogen peroxide leads to the corresponding sulfones <2005BML4488, 2006BML1164>.

The combination $Mo_7O_{24}(NH_4)_6$, H_2O_2 has been used for conversion of 1-*t*-butyl-5-methylthiotetrazole into its sulfone <2006JOC360>. Peroxyacetic acid in acetone at 15°C allows selective conversion of 1-aryl-5-alkylthiotetrazoles into their sulfoxides in high yields <2004TL7955>.

An SR group can be replaced by hydrogen using Raney nickel, and dealkylation is possible, e.g., of 3-alkylthio-1,2-dithiolyliums to give 1,2-dithiole-3-thiones with various nucleophiles.

Alkylthio groups are sometimes replaced in nucleophilic substitutions, but such reactions are difficult in most neutral azoles. Thus, 3-alkylthio-1,2,4-thiadiazoles resist the action of aniline at 100°C, ammonia at 120°C, molten urea, and ammonium acetate. However, hydrazine attacks 3-methylthio-1,2,4-thiadiazole forming 3-amino-1,2,4-triazole **757**.

Such reactions are especially easy in cationic derivatives; for example, in the 1,2-dithiolylium series **758**, with a substituted cyclopentadienyl ion gives fulvene derivatives **759**. 2-Methylthio groups in 1,3-dithiolylium ions are substituted by primary amines or secondary amines, and similar reactions are known for 2-alkylthiothiazoles.

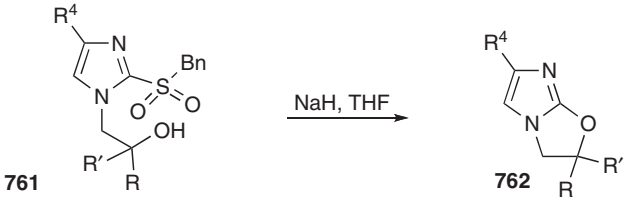


1,3-Dithiole-2-thione traps radicals to give neutral stabilized radicals **760**.

3.4.3.8.4 Sulfonic acid and sulfonyl groups

Azolesulfonic acids frequently exist as zwitterions. The usual derivatives are formed, e.g., pyrazole-3-, -4-, and -5-sulfonic acids all give sulfonyl chlorides with PCl_5. The sulfonic acid groups can be replaced by nucleophiles under more or less vigorous conditions, e.g., by hydroxy in imidazole-4-sulfonic acids at 170°C, and by hydroxy or amino in thiazole-2-sulfonic acids. Benzimidazole-2-sulfonic acids react similarly.

Alkyl- and arylsulfonyl substituents are excellent leaving groups on azoles, often better than halide, especially for carbon nucleophiles. Examples include 2-aryl-5-methanesulfonyl-1,3,4-oxadiazoles with malonate <2001JA6179, 2004MI 506-02>, alkanesulfonyl 1,2,5-thiazoles under mild conditions and in good yields with primary and secondary alkoxides <1998JME379, 1999JME1999>, primary alkanethiolates <1998JME379> and sulfides <1997JME538, 1998BML2897> and similarly on 1,3,4-thiadiazoles to give ethers <1999JME1161, 2004T8627> or amines <1997CHE1219, 2004CHE1185, 2006PS609>, 1-aryl-5-methanesulfonyltetrazole with malonates <1996CHE1300> and alcohols <2002RJO1356, 2004RJO1318> (more reactive than the isomeric 2-aryl-5-methansulfonyltetrazoles <2001CHE1493, 2002RJO1356>), and 3,4-bis(phenylsulfonyl)-1,2,5-oxadiazole oxide with alcohols and thiols (mono-displacement) <2001JME3463, 2005EJM1335>. In an intramolecular sense, alcohol **761** is converted into **762** by nucleophilic displacement of the benzylsulfonyl group <1999S1613, 2002S2691>.



3.4.3.9 Halogen Atoms

3.4.3.9.1 Nucleophilic displacements: Neutral azoles

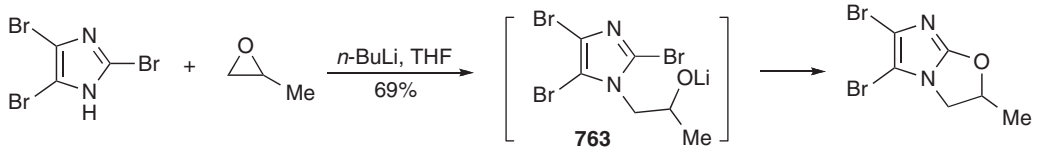
As discussed in Section 3.4.3.1, nucleophilic replacements of halogen atoms are facilitated by mesomeric stabilization in the transition state for some haloazoles, depending on the number and orientation of the ring heteroatoms and halogen. In addition to this, and just as in benzene chemistry, all types of halogen atoms are activated toward nucleophilic

displacement by the presence of other electron-withdrawing substituents. Halogen atoms in the 4- and 5-positions of imidazoles, thiazoles, and oxazoles and those in all positions of pyrazoles and isoxazoles are normally rather unreactive, but are labilized by an or electron-withdrawing substituent. Reactions of N-unsubstituted azoles containing a ring NH group are often difficult because of NH deprotonation and the formation of unreactive anions under basic conditions.

Halogen atoms at the 2-position of imidazoles, thiazoles, and oxazoles can be replaced by the groups NHR, OR, SR, etc. The conditions required are more vigorous than those used, for example, for - and -halopyridines, but much less severe than those required for chlorobenzene.

The 4- and 5-haloimidazoles and 4- and 5-halooxazoles are less reactive toward nucleophilic substitution than the 2-halo analogues, but still distinctly more reactive than unactivated phenyl halides. Thus, a bromine atom in the 4- and 5-position of 1-methylimidazole requires lithium piperidide to react, whereas the 2-bromo analogue is converted into 2-piperidinoimidazole by piperidine at 200°C. Sodium isopropoxide replaces the 2-bromine of 1-substituted 2,4,5-tribromoimidazole by an isopropoxy group. Halogenoimidazoles with a nitro group in the ring are readily subject to halide displacement by thiolate anions with 5-halogeno-4-nitro compounds being 310 times more reactive than the 4-halogeno-5-nitroimidazoles. Bromide is substituted slightly more readily than iodide, perhaps because of the greater capacity of bromine to help to stabilize a Meisenheimer complex, or there could be steric factors. As an example, 2-bromo-4,5-dicyano-1-methylimidazole is converted into the 2-fluoro (spray-dried KF, 18-crown-6, diglyme, reflux) or 2-chloro derivatives (CuCl, diglyme, reflux) <1996JOC6666>. 2-Chlorobenzimidazole is converted into the corresponding fluoride with TBAF in DMSO at room temperature <2006ACIE2720>. Whereas 2,4,5-tribromoimidazole does not react with NaOMe <2003S659>, it does undergo intramolecular nucleophilic displacement at C(2) in intermediate **763** (**Scheme 143**) <2002S2691>. 2,4,5-Tribromo- and 2,4,5-triiodoimidazoles undergo reductive dehalogenation by phenylthiolate ion to produce the 4,5-dihalogenated products.

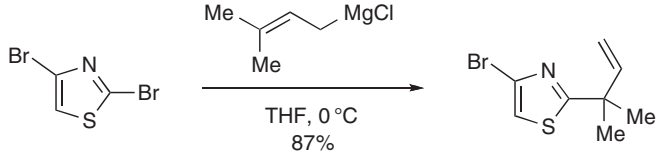
5-Halothiazoles react unexpectedly rapidly with methoxide, the 4-halothiazoles less readily. 2,4-Dibromothiazole



Scheme 143

reacts selectively at C(2) with Grignard reagents (**Scheme 144**) <2005OL339>. Thiazole-2-halides are also displaced by azide <1999T1977> and by alcohols and thiols <2006JME3770>.

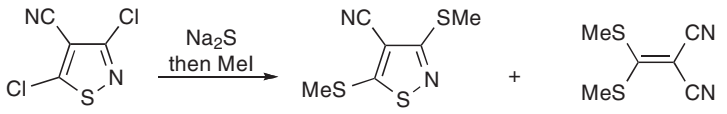
3-Chloro-5-arylisoxazoles undergo nucleophilic displacement with alkoxide ions. 3-Bromoisoxazoles can be induced



Scheme 144

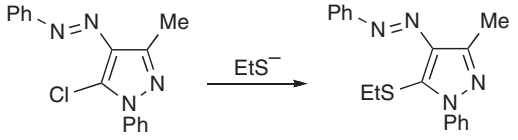
to react with amines by using a phosphazene base <2004TL3189>. Halogen atoms at the 5-position of the isoxazole nucleus are readily displaced if an activating group is present at the 4-position.

5-Halogens attached to the isothiazole nucleus are more reactive, particularly if there is an electron-withdrawing substituent at the 4-position. However, a 3-halogen atom, even when activated, is less reactive than a halogen at the 5-position, and replacement is often accompanied by ring cleavage, e.g. **Scheme 145**. 4-Haloisothiazoles are still less reactive, but can react with copper(I) cyanide to give the corresponding nitrile.



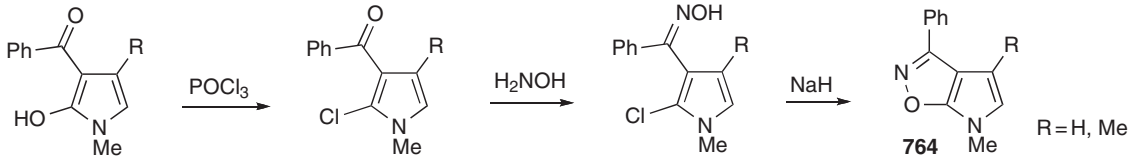
Scheme 145

Halogens attached to the pyrazole nucleus are normally very inert; however, if there is an electron-withdrawing group at the 4-position, then the halogen atom in the 5-position of a pyrazole ring becomes activated, as, for example, in **Scheme 146**, or by a 4-aldehyde with heteroatom nucleophiles <2004SC1541, 2003TL7629>. However, such an electron-withdrawing group at the 4-position only activates the chlorine atom in the 5-position and not one at the 3-position because of the influence of partial bond fixation (see discussion in Section 3.4.3.1).



Scheme 146

An intramolecular example (**Scheme 147**) has chloride being displaced by oxime oxygen generating the bicyclic products **764** <2003JHC303>.

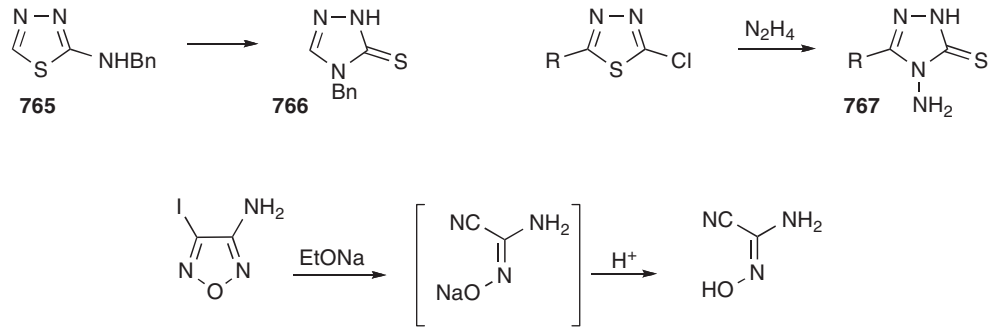


Scheme 147

5-Halo-l-methyl-1,2,3-triazoles undergo substitution reactions with amines, but the 4-halo analogues do not. 5-Chloro-1,4-diphenyl-1,2,3-triazole with sodium cyanide in DMSO gives the cyano derivative. 1-Substituted 3-chloro- and 5-chloro-1,2,4-triazoles both react with amines, and alcohols <2006T2677> but selectivity is illustrated by the reaction of 1-benzyl-3,5-dibromo-1,2,4-triazole with CsF only at C(5) <1998S1357>.

5-Chlorine atoms in 1,2,4-oxadiazoles can be replaced by amino, hydroxy, or alkoxy groups, e.g., <1995TL4471>. 5-Halo-1,2,4-thiadiazoles are also quite reactive: silver fluoride gives the fluorides, in concentrated hydrochloric acid a 5-hydroxy group is introduced, and thiourea reacts, as do various amines. Sodium sulfite gives sulfonic acids, and reactive methylene compounds give the expected substitution products. By contrast, halogens at the 3-position of 1,2,4-thiadiazoles are inert toward most nucleophilic reagents: thus 3-chloro-5-phenyl-1,2,4-thiadiazole resists aminolysis and thiourea; however, a 3-alkoxy group is introduced by sodium alkoxide.

Halogens on the 1,2,5-thiadiazole ring are highly reactive, for example, with aq. NaOH, DMSO at 100°C <1995JME2273, 1998JME379> or with alkali metal sulfides in DMF or ethanol giving the corresponding thiadiazole thiolate salts, e.g., <1996JPC17452, 1998JME379, 1998BML2897, 1999JME1999, 2001JME4563>. Halo-1,3,4-thiadiazoles are highly activated and react with a wide range of nucleophiles: examples include malonates <2006OL1447> as well as oxygen, sulfur <1999AF1035, 2006BML1164>, and nitrogen, e.g., <2003EJM851, 2005EJM1346, 2006BML1735> nucleophiles. 2-Chloro-1,3,4-thiadiazole and benzylamine give a mixture of **765** and **766**, the latter resulting from a Dimroth rearrangement (see Section 3.4.3.5.1). With hydrazine, **767** is similarly formed. Degradation of the ring can occur on attempted displacements of 1,2,5-oxadiazoles (**Scheme 148**) <2004RCB1124>.



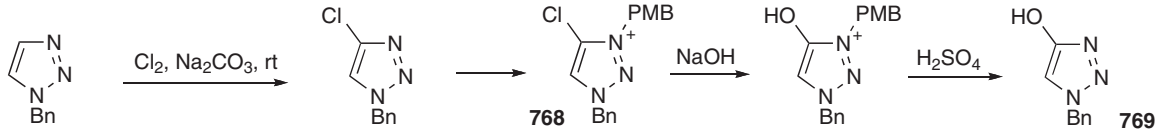
Scheme 148

Halogen atoms at the 5-position of tetrazoles are reactive and easily replaced by nucleophiles, for example, with NaN_3, DMF, 60°C <2005MI17>. 5-Bromo-1-methyltetrazole is significantly more reactive than the 2-methyl isomer.

3.4.3.9.2 Nucleophilic displacements: Haloazoliums

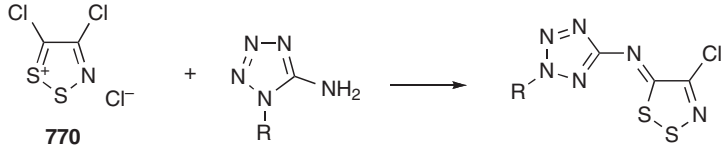
Halogen atoms in cationic olium rings are very reactive. The halogen atom in the quaternary salts of 3- and 5-halo-1-phenylpyrazoles is replaced at 80100°C by hydroxy, alkoxy, thiol, amino, or cyano groups. 3-Halo-1,2-dithiolyliums are converted into 1,2-dithiol-3-ones by water and react readily with other nucleophiles.

Quaternization of triazole nitrogen atoms activates the heterocycle toward nucleophilic attack. Thus, the synthetic strategy shown in **Scheme 149** can be applied for the preparation of 1-benzyl-4-hydroxy-1,2,3-triazole **769** using *p*-methoxybenzyl (PMB) as a removable activating group. Generally, this synthetic sequence can be used for the preparation of 1-alkyl-4-substituted triazoles by reaction of the intermediate **768** with various nucleophiles, followed by removal of the activating group.

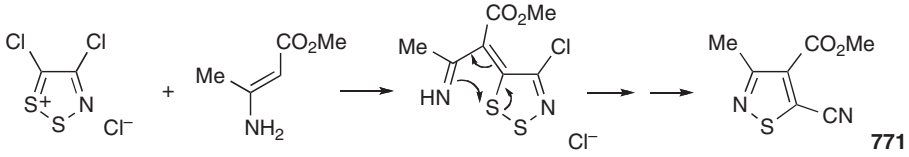


Scheme 149

Since its discovery in 1985, Appel salt **770** has been exploited for nucleophilic displacement reactions. For example, it reacts readily with amines, e.g., **Scheme 150** <2002J(P1)1535> (or hydrazine <1996TL3709>), a more exotic example being its reaction with methyl 3-aminocrotonate resulting in formation of an isothiazole **771** (**Scheme 151**) <1998J(P1)77>.



Scheme 150

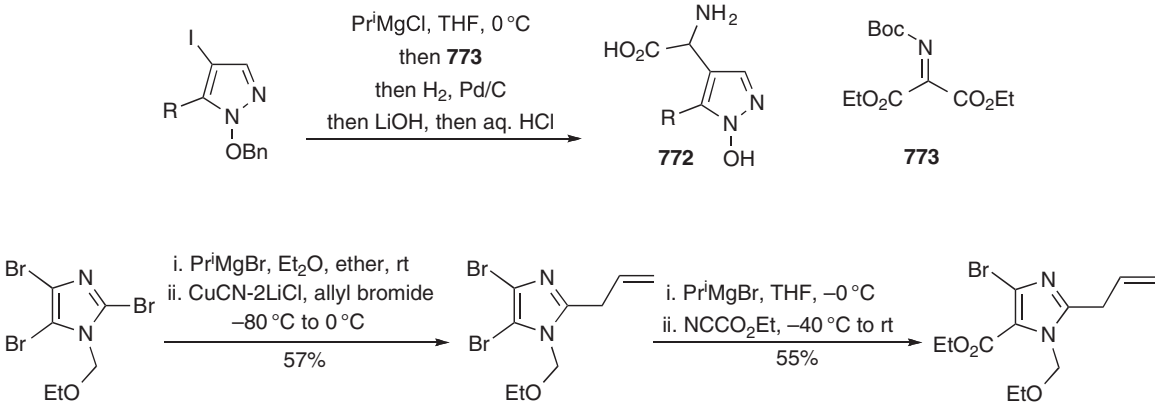


Scheme 151

3.4.3.9.3 Other reactions

Nuclear halogen atoms also show many of the reactions typical of aryl halogens.

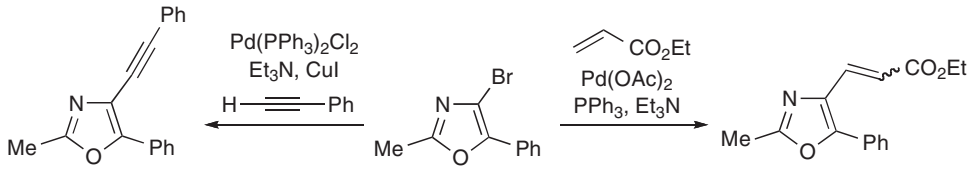
1. They can be replaced with hydrogen atoms by catalytic (Pd, Ni, etc.) or chemical reduction (HI or Zn/H_2SO_4). For example, halopyrazoles with HI and red phosphorus at 150°C give pyrazoles, and 5-bromo-1,2,4-thiadiazole is reduced by Raney nickel to the parent heterocycle. 2-Bromothiazole can be reduced electrochemically.
2. They give Grignard reagents; however, in the preparation of these it is sometimes necessary to add ethyl bromide to activate the magnesium (entrainment method) or more often, now, to use *i*-PrMgCl. Pyrazolyl Grignard reagents can be obtained, for example, via iodinemagnesium exchange of 1-benzyloxy-4-iodopyrazole with *i*-PrMgCl <1999JOC4196>; the glycine derivatives **772** were thus obtained <2002T1595>. 4-Iodoisoxazoles give Grignard reagents. Sequential halogenmagnesium exchange reactions <2003AGE4302> of 2,4,5-tribromoimidazole occurs in the order 2 > 5 (**Scheme 152**).



Scheme 152

Bromine and iodine groups at any position in N-substituted imidazoles undergo lithium exchange with *n*-BuLi at 78°C. 1-Substituted 2,4,5-tribromoimidazoles (or 2,4,5-triiodoimidazoles <2005S136>) exchange in excellent yields at low temperatures in the order 2 > 5 > 4, making selective replacement possible. Double brominelithium exchange in 1-methyl-2,5-dibromoimidazole gives the 2,5-dilithium compound which selectively forms the aldehyde at C(5) when treated with DMF. The 4- and 5-halooxazoles undergo halogenmetal exchange with *n*-butyllithium to give 4- and 5-lithiooxazoles. Treatment of 2,4-dibromothiazole with *i*-PrLi leads to exchange exclusively at C(2) <2006JOC4599>. Halothiazoles give Grignard reagents and lithio derivatives. 2- and 5-Bromothiazoles undergo halogenlithium exchange on treatment with *n*-butyllithium to afford 2- and 5-lithiothiazoles, respectively. The reaction with 4-bromothiazole under the same conditions leads exclusively to deprotonation at C(2), although a number of substituted 4-bromothiazoles react with *n*-butyllithium to give the corresponding 4-lithio derivatives. The low reactivity of a bromine atom at C(4) is attributed to the effect of the adjacent nitrogen lone pair that destabilizes a developing negative charge at C(4).

3. Haloheterocycles undergo palladium-catalyzed coupling with terminal alkynes and alkenes, for example, 4-bromo- (**Scheme 153**) and 5-bromooxazoles give coupled products in fair to good yields. (See also Section 3.4.3.10.2 for other palladium-catalyzed cross coupling examples.)

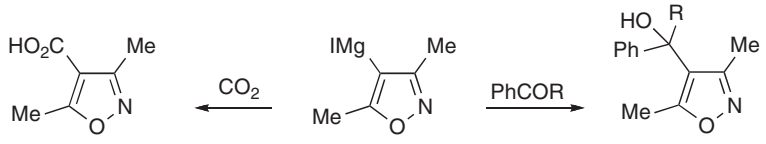


Scheme 153

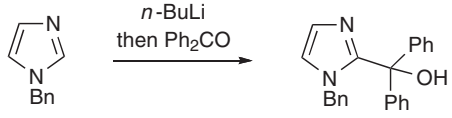
3.4.3.10 Metals and Metalloids

3.4.3.10.1 Reactions of organometallic nucleophiles

Metallated azoles frequently show expected properties, especially if not too many heteroatoms are present. Thus, Grignard reagents prepared from halogeno-azoles (see Section 3.4.3.9.3) show normal reactions, as in **Scheme 154**. 2-Lithioimidazoles react normally, e.g., with benzophenone (**Scheme 155**). Lithiated imidazoles are not always particularly reactive toward electrophiles and yields may be low. The nature of the quenching electrophile is the critical factor. Hard reagents like benzophenone tend to give better yields than the softer methyl iodide; heteroaryl lithiums have hard carbanion centers.



Scheme 154

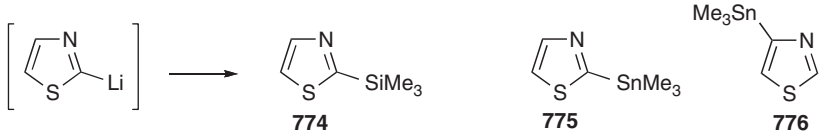


Scheme 155

2-Lithioimidazoles are thermodynamically (and possible kinetically) more stable than the 5- or 4-isomers. The adjacent lone pair effect makes 4-lithioimidazoles difficult to prepare, though they are accessible through metalhalogen exchange under certain conditions. Before 5-lithioimidazoles can be prepared, the 2-position needs to be blocked, but if a 2,5-dilithioimidazole is made, it is possible to quench the more reactive 5-anion before the 2-anion. If the 2-position is unsubstituted, a 4- or 5-lithioimidazole (made by metalhalogen exchange) rapidly isomerizes to the 2-isomer. Only very reactive electrophiles are able to functionalize a 5-lithioimidazole when the 2-position is unsubstituted because the reaction must take place at a sufficiently low temperature to prevent transmetallation.

5-Lithioisothiazoles and 2-lithiothiazoles undergo many of the expected reactions, including reaction with CO_2, formylation (with DMF), alkylation (with alkyl halides), acylation (with acid anhydrides), and halogenation (with Br_2 or I_2).

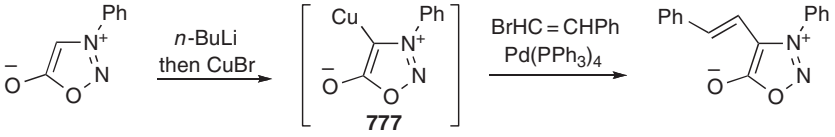
Lithiothiazoles are the starting material for the preparation of other metallated thiazoles. Thus, transmetallation of 2-lithiothiazole with trimethylsilyl chloride can be carried out in one-pot and multigram scale to give the stable and synthetically important 2-trimethylsilylthiazole **774**. In the same way, 2- and 4-trimethylstannylthiazoles **775** and **776** can be obtained from the corresponding lithio derivatives and trimethyltin chloride. 4-Methyl-2-trimethylstannyloxazole reacts with a variety of aryl and heteroaryl halides and tetrakis(triphenylphosphine)palladium to give the 2-substituted products in high yield.



The crystal structure of a dimer of 4-*t*-butyl-2-lithiothiazole shows it to contain two molecules of diglyme with the lithium atom positioned halfway between nitrogen and C(2), thus providing a carbenoid nature to this metallated thiazole.

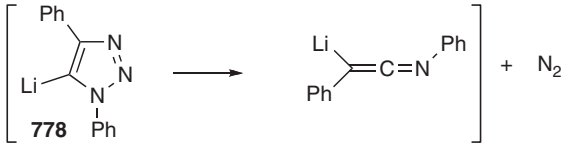
A variety of electrophiles can be introduced into the 4-position of 3-arylsydnones by way of 4-lithio intermediates. The method has been used to introduce sulfur, selenium, and tellurium electrophiles and to introduce formyl and acetyl

substituents. Other organometallic species have been used to introduce vinyl and aryl substituents at C(4), 4-lithio-3-phenylsydnone reacts with copper(I) bromide to give a thermally stable copper species **777** which undergoes palladium (0) catalyzed coupling to iodobenzenes and to vinyl bromides (**Scheme 156**).



Scheme 156

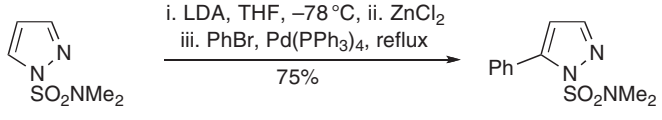
As the number of nitrogen heteroatoms increases, the stability of lithium azoles decreases: the 5-lithio derivatives of 1,2,3-triazoles **778** ring-open spontaneously. 1-Methyltetrazol-5-yllithium decomposes to nitrogen and lithium methylcyanamide above 50 °C, although it gives the expected Grignard-like reactions with bromocyanogen, esters, ketones, and sulfur at lower temperatures.



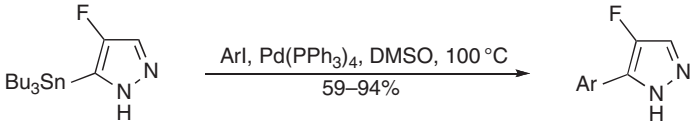
Acetoxymercurioxazoles and acetoxymercurithiazoles react with halogens to give the corresponding halooxazoles in good yields. 4-Acetoxymercuripyrazoles show many of the reactions of phenylmercury(II) acetate: removal by HCl, conversion to Br by bromine, and to SCH_2Ph by $(SCN)_2$, $PhCH_2Cl$.

3.4.3.10.2 Transition metal-catalyzed cross-coupling reactions

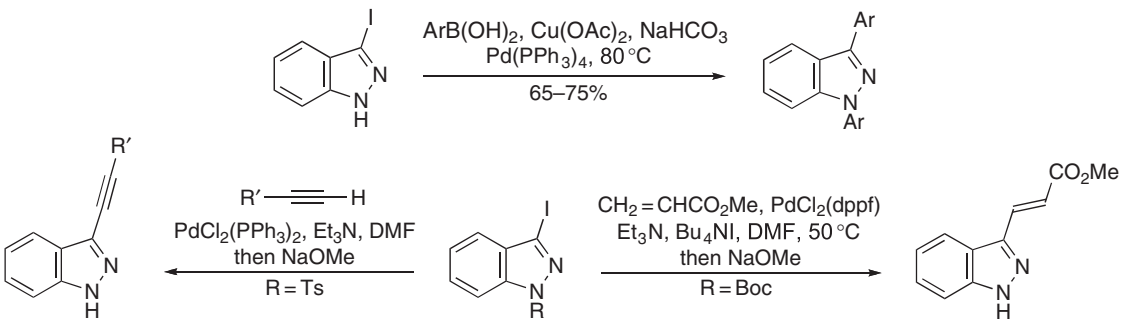
This area has seen great expansion and all of the standard coupling processes have been exemplified in one system or another, though there are not examples of all types for all heterocycles considered in this chapter. Where heterocycles with an N-hydrogen are considered, it is generally necessary to mask the N-hydrogen, thus for pyrazoles and indazoles, a dimethylsulfamoyl group, as an electron-withdrawing group, gives the highest yields, as exemplified in **Scheme 157** <1997H(45)1463>. That protection is not always employed is shown in **Scheme 158** <2004TL7573, 2005CC2041> though in the Suzuki coupling in **Scheme 159** reaction at nitrogen can then interfere (or may be desired) <2002TL2695>. Suzuki coupling in the benzene ring of 5-(2-bromophenyl)tetrazole can be achieved without N-protection using [1,10-bis(diphenylphosphino)ferrocene dichloropalladium(II) [$PdCl_2$(dppf)] as catalyst and Na_2CO_3 as base <2005TL6529>. 5-Hydroxypyrazoles can be converted into their corresponding sulfonates, which can then be used in Suzuki cross-coupling reactions <2005JOC4188>.



Scheme 157

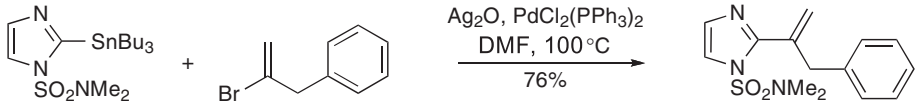


Scheme 158



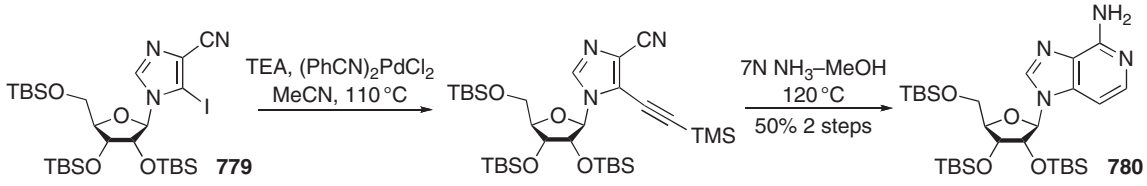
Scheme 159

4-Iodoimidazoles <2003TL7115, 2004TL1869> and 4-bromoimidazole <2004SP15> cross-couple with methyl acrylate in high yields catalyzed by $Pd(OAc)_2$, PPh_3 in the presence of Et_3N in DMF, and **Scheme 160** shows a typical coupling with an N-protected imidazole stannane <2005HCA707>. All three isomeric thiazole stannanes couple with vinyl halides <1998AGE84>. 5-Tributylstannylisoxazole can be coupled with 4-bromofuran-2(5*H*)-ones leading to isoxazolefuranones under very mild conditions <1996S164> and the use of organostannyl oxazoles in Stille reactions is unexceptional <2001JOC9033>. N-Substituted 4-bromoisothiazolin-3-ones couple with alkynyl, alkenyl, and aryl stannanes in Pd(0)-catalyzed Stille reactions <1999T12313>.

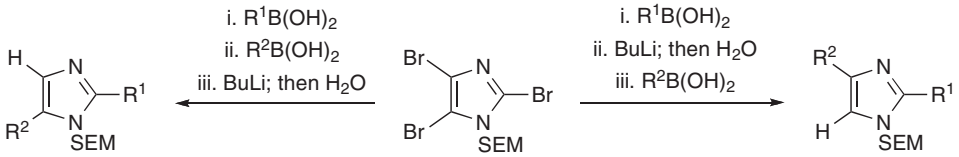


Scheme 160

2-Lithiation of an N-SEM-protected imidazole, followed by transmetallation with $ZnCl_2$ allows coupling with a pyridone 3-triflate <1999TL4069> and 2-iodo-1-methylimidazole reacts directly with zinc and this reagent takes part in coupling with aryl and alkenyl halides <1997T7237>. 2-Thiazolylzinc bromide couples with alkyl and aryl halides <1997T7237> and alkyl triflates <2005BMC4667>. The use of a 5-iodoimidazole **779** allowed a synthesis of a 3-deazaadenosine **780** <2006JA4453>.



Suzuki coupling of 2-iodoimidazoles <2005H(65)2721> and Stille, Heck <1999JOC7158, 2006SL965>, Sonogashira <2004TL3621>, and Suzuki reactions of polyhaloimidazoles proceed with high regioselectivities, e.g., **Scheme 161** <1998H1887, 2005H(65)1975>. 2-Iodoimidazole couples efficiently with TMS-acetylene to produce the 2-alkynylimidazole in the presence of CuI and $PdCl_2(PPh_3)_2$, and at only 35°C <2006JA4119>.

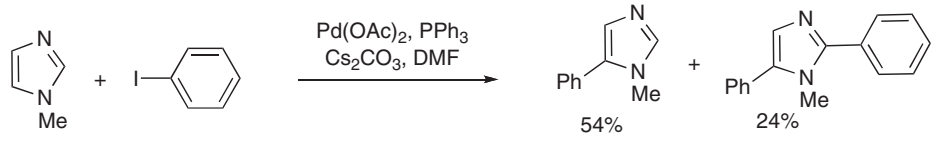


Scheme 161

Thiazole 2-halides react normally in cross-couplings <2002JOC5789>, including with boronic acids <2002JOC7541>. 2,4-Dibromothiazole reacts selectively at C(2) in Pd(0)-catalyzed cross-coupling reaction with various organozinc halides <2002JOC5789>. Trihalogenated isothiazoles couple with alkynes at C(5) in Sonogashira reactions using CuI, $PdCl_2(PPh_3)_2$; a second alkynylation occurs at C(4) if there is a 4-iodine <1998RCB519, 2004JOC1401>.

3,5-Dimethylisoxazol-4-ylboronic acid <2005JOC3741> takes part in Suzuki couplings and 2-(5-iodoisoxazol-3-yl) pyridine in Sonogashira, Suzuki, Negishi, and Stille reactions <2001OL4185>. Sequential Stille or Suzuki reactions on 4-bromomethyl-2-chlorooxazole generate 2,4-disubstituted oxazoles <2002TL3797>.

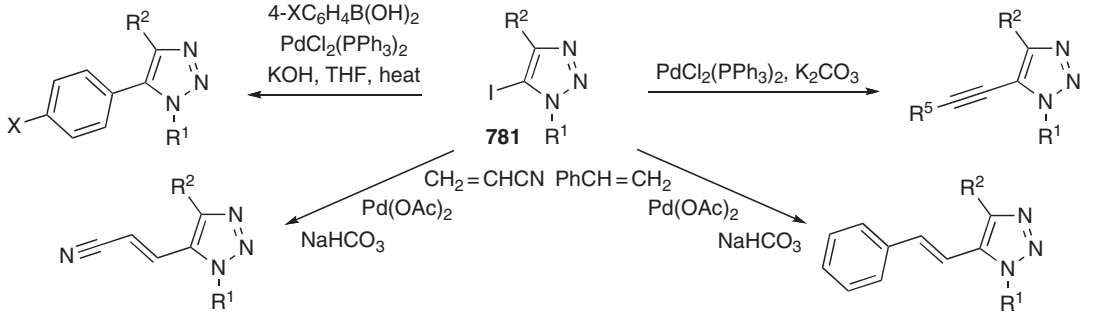
Direct palladium-catalyzed CC bond formation can be achieved between *N*-methylimidazole and an aryl halide with selectivity for the more electron-rich C(5) position (**Scheme 162**); if C(5) is already substituted, then C(2) is preferred. *N*-Methylbenzimidazole can be similarly arylated by various aryl iodides at the 2-position when catalyzed by copper(I) iodide to give excellent yields <1998BCJ467>. Rhodium can also catalyze direct C(2) arylation of N-alkyl benzimidazoles <2004OL35>.



Scheme 162

2-Chlorobenzothiazole undergoes an iron-catalyzed cross-coupling reaction to give the 2-alkylated product using *n*-$C_{14}H_{29}MgBr$ <2002AGE609>; it seems likely that more use will be made of iron-catalyzed coupling chemistry in the future.

5-Iodo-1,2,3-triazoles **781** are versatile starting materials for substitution of the triazole ring with sp^2 and sp carbon substituents (**Scheme 163**) <2005S2730>. Selective Suzuki coupling at C(5) of 3,5-dihalo-1,2,4-triazoles is observed <2006T3301>. Halogenated 1,2,5-thiadiazoles undergo both Stille <1996H(43)2435, 2003H(60)29> and Suzuki <2003H (60)29> reactions. 3-Trifluoromethylsulfonyloxy-4-phenyl-1,2,5-thiadiazole takes part in palladium-catalyzed cross-coupling with tributyl(4-chlorophenyl)stannane <1996H(43)2435>. 2-Bromo-5-phenyl-1,3,4-oxadiazole undergoes palladium-catalyzed Suzuki cross-coupling with arylboronic acids to afford 5-aryl-2-phenyloxadiazoles <2004TL7157>.

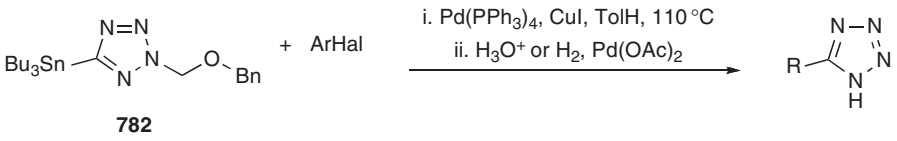


Scheme 163

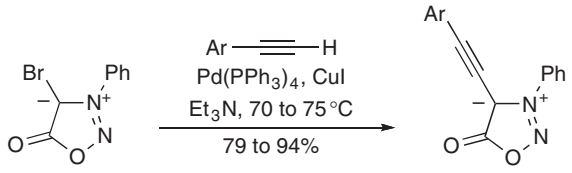
2-Benzyloxymethyl-5-(tributylstannyl)tetrazole **782** can be used for coupling with aryl- and heteroaryl bromides and iodides (**Scheme 164**) <2000TL2805>.

Modified Sonogashira coupling conditions give excellent yields of alkynylsydnones when 4-bromo-3-phenylsydnone is reacted with terminal alkynes (**Scheme 165**) <2003SC2209>.

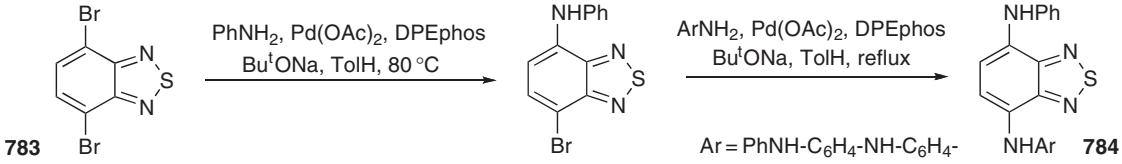
Relatively few Buchwald aminations have been reported for the five-membered heterocycles with more than one heteroatom: an example is the stepwise conversion of 4,7-dibromobenzothiadiazole **783** into diamine **784** (**Scheme 166**) <2002TL9009, 2005JOC2754>. This same dibromide has proved to be versatile and popular and takes part in Negishi <1996H(42)597>, Stille, <e.g. 1995JA6791, 2005CC3183, 2005JOC6004, 2005MM244>, Suzuki <e.g. 2000CC939, 2005CC1468, 2005MM7636, 2005JA3172>, Heck <2004CC2342> and Sonogashira reactions, e.g., <2001MM7592, 2002HCA2195, 2004SL169, 2005JA5186>.



Scheme 164



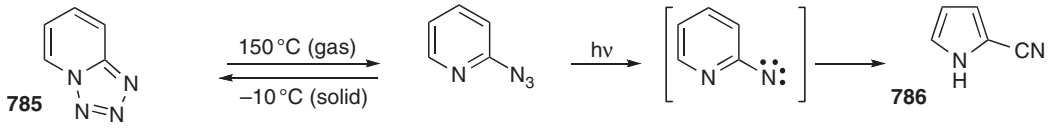
Scheme 165



Scheme 166

3.4.3.11 Fused Heterocyclic Rings

A wide variety of such derivatives is known and cannot be dealt with comprehensively here; however, the mutual influence of heterocyclic rings in them is as expected from their electronic nature and number of heteroatoms. Some unique reactions arise from the juxtaposition of the two rings, e.g., tetrazolopyridine **785** on photolysis yields 2-cyanopyrrole **786**. See also Section 3.2.3.6.4.



3.4.3.12 Substituents Attached to Ring Nitrogen Atoms

3.4.3.12.1 N-Linked azole as a substituent

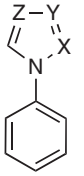
It is instructive to consider N-substituted azoles in reverse, i.e., the azole ring as the substituent linked to some other group. Hammett and Taft -constant values for azoles as substituents are given in **Table 11**. The values show that all *N*-azolyl groups are rather weak net resonance donors, imidazol-1-yl being the strongest. They are all rather strong inductive acceptors, with pyrazole considerably weaker in this respect than imidazole or the triazoles.

N-Linked azole rings behave as good leaving groups, the more so the more nitrogen atoms contained in the ring (cf. Section 3.4.3.12.4).

3.4.3.12.2 Aryl groups

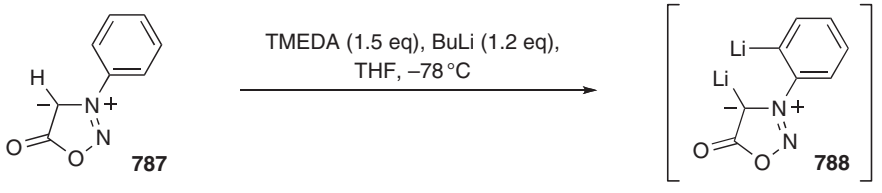
Electrophilic substitution occurs readily in *N*-phenyl groups, e.g., 1-phenyl-pyrazoles, -imidazoles and -pyrazolinones are all nitrated and halogenated at the *para* position. The aryl group is attacked preferentially when the reactions are carried out in strongly acidic media where the azole ring is protonated.

Table 11 Hammett and Taft -constant values for azoles as substituents in a benzene ring <1981JCR(S)364>



Azole *X*	*Y*	*Z*	σ_I	σ_R^-
N			0.30	0.06
	N		0.51	0.15
N	N		0.53	0.10
N		N	0.53	0.12
	N	N	0.66	0.10

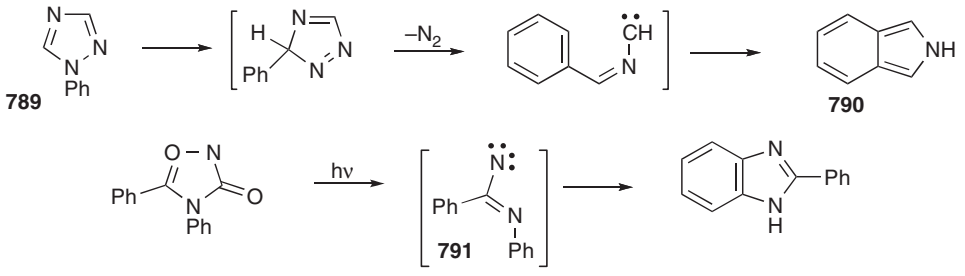
The azole ring can activate metallation at the *ortho* position of an *N*-phenyl group, as in 1-phenylpyrazoles; similarly, direct *ortho*-palladation of 1-phenylpyrazoles with *in situ* coupling to an aryl iodide or tosylate produces 1-biarylpyrazoles <2002OL2657, 2006AGE2619>. The sydnone ring acts as an *ortho* director of lithiation when 3-phenylsydnone **787** is dilithiated to give intermediate **788**. By judicious choice of reaction conditions and electrophiles, C(4) monosubstituted <1998HAC549>, *ortho* monosubstituted <1998TL1509>, or C(4)/*ortho* disubstituted <1997TL1165> products can be obtained via **788**.



787 **788**

If the *N*-aryl group is strongly activated, then it can be removed in nucleophilic substitution reactions in which the azole anion acts as leaving group. Thus 1-(2,4-dinitrophenyl)-pyrazole and -imidazole react with N_2H_4 or NaOMe. Their *N*-picryl derivatives react similarly with $BuNH_2$ or water at a range of pH values.

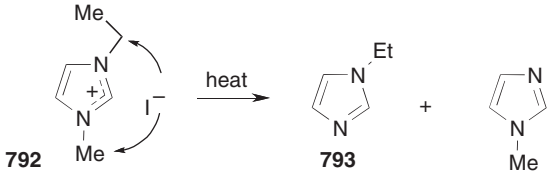
On pyrolysis, 1-arylimidazoles rearrange to 2-arylimidazoles. In other systems, pyrolysis causes more deep-seated changes. 1-Arylbenzotriazoles on pyrolysis or photolysis give carbazoles via intermediate nitrenes (see Section 3.4.1.2.1). 1-Phenyl-1,2,4-triazole **789** is converted by pyrolysis into isoindole **790** via a carbene intermediate and another example of the participation of *N*-phenyl groups is found in the formation of benzimidazoles from tetrazoles (see Section 3.4.1.2.1). In the oxadiazolinone series, a nitrene intermediate **791** is also probably formed, which then ring closes.



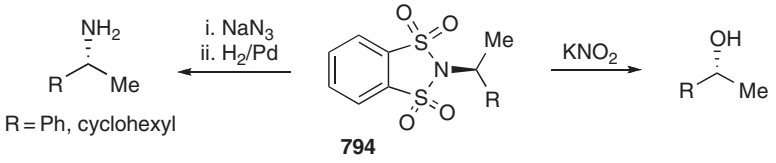
789 **790** **791**

3.4.3.12.3 Alkyl and alkenyl groups

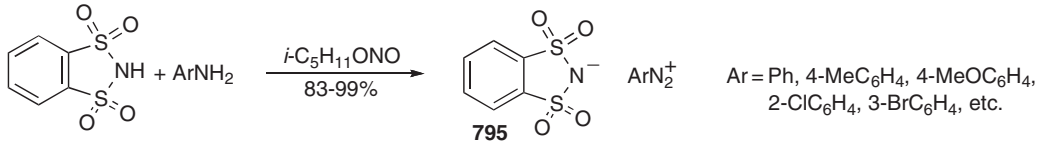
N-Alkyl groups in azolium salts can be removed by nucleophilic S_N2 reactions; soft nucleophiles such as PPh_3 and I are effective. Sometimes there is competition; for example, in **792** the methyl group is the more readily removed to give mainly *N*-ethylimidazole **793**. This reaction has been studied quite extensively in the imidazolium series. The 1,2- and 1,3-dialkyltriazolium salts undergo nucleophilic displacement on heating, and 2-alkylisothiazolium salts are converted into isothiazoles on distillation. Pyrazolium salts similarly give pyrazoles. The benzyl group in *N*-benzylazoles is removed by reduction with sodium in liquid ammonia or catalytic reduction.



N,*N*-1,2-Benzene- (**794**) and naphthalene-disulfonamides act as leaving groups for stereoselective nucleophilic substitution of amines <1998TA681, 1999TA2627>. Nucleophilic attack by KNO_2 affords the respective alcohols with 83 90% inversion of configuration. Reaction with sodium azide gives the corresponding azides that can be reduced to the inverted amines (7099% inversion) (**Scheme 167**). This same property stability of the *N*,*N*-1,2-benzene-disulfonamide anion is responsible for the possibility of preparing stable dry diazonium salts **795** (**Scheme 168**) <1998S1171>.



Scheme 167

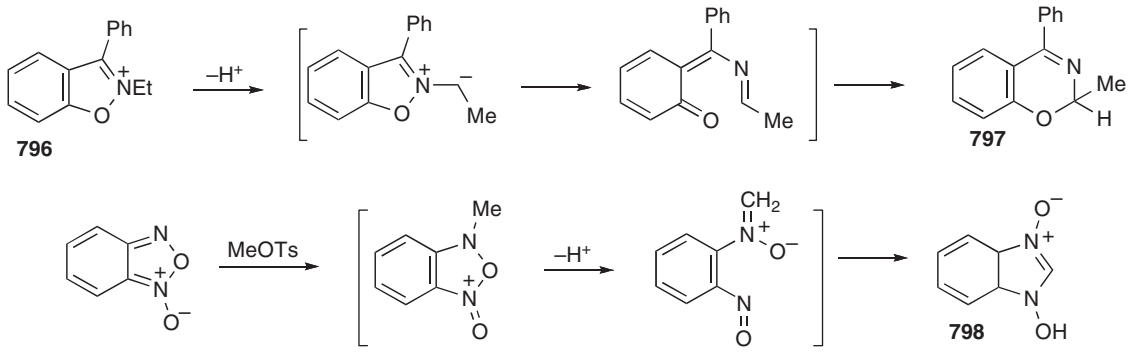


Scheme 168

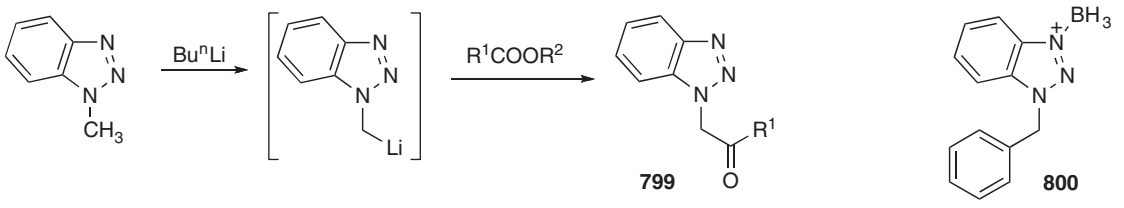
N-Alkyl groups in neutral azoles can rearrange thermally to carbon. For example, 2-alkylimidazoles can be prepared in this way in a reaction that is irreversible, uncatalyzed, intramolecular and does not involve radicals. *N*-Vinyl and *N*-alkyl groups in imidazoles also rearrange thermally to the 2- and 4-ring positions.

Methyl and methylene groups attached to an imidazole nitrogen can be metallated. In 1-benzylimidazole the extent of benzylic metallation increases with temperature and with the amount of butyllithium used. Although 1-phenylthiomethylbenzimidazole is initially lithiated at C(2) at low temperatures, when the temperature is raised, rearrangement to the rather unstable methylene-lithiated species occurs, but this anion can be trapped by electrophiles.

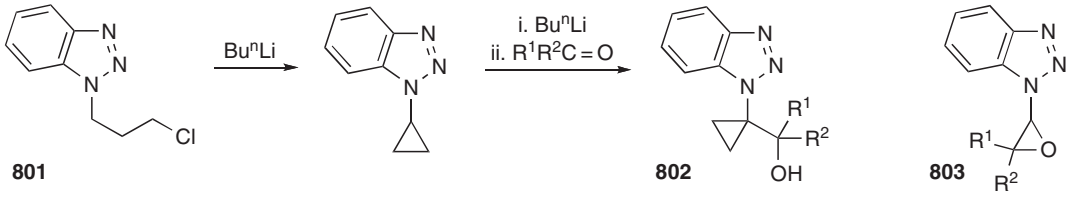
Deprotonation can occur at the -CH of pyrazole *N*-alkyl groups for example 1-methylpyrazole with *n*-BuLi. Such proton loss is facilitated in cationic azido rings, and the ylides so formed sometimes undergo rearrangement. Thus, quaternized 1,2-benzisoxazoles **796** lose a proton and then rearrange to 1,3-benzoxazines, e.g., **797**. Quaternized derivatives of benzofuroxan formed *in situ* undergo rearrangement to 1-hydroxybenzimidazole *N*-oxides **798**. Reactions of this type are also known for *N*-alkylazolinones.



Extensive studies have revolved around the ability of alkyl substituents on benzotriazole nitrogen to be deprotonated: for example, 1-methylbenzotriazole is lithiated readily with *n*-BuLi or LDA at the methyl group and the subsequent reactions with various electrophiles provide 1-substituted benzotriazoles, e.g., **799** <1997JOC4142>. 1-Alkyl- and 1-benzylbenzotriazoles react with borane to give air- and water-stable complexes **800**; these can also be deprotonated at the alkyl group; removal of the borane unit is achieved by refluxing in ethanol <1998OPP325>.

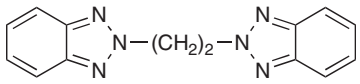


In another nice example, cyclopropyl carbinols **802** can be produced in two deprotonative steps from 1-(3-chlopropyl) benzotriazole **801**, itself obtained from reaction of benzotriazole with 1-bromo-3-chloropropane and NaOH (**Scheme 169**) <1998JOC6710>. 1-Chloromethylbenzotriazole is metallated with LDA at 40̄C, the anion thus generated can be trapped by ketones ($R^1R^2C{=}O$) to provide a synthesis of (benzotriazol-1-yl)oxiranes **803** <2003JOC407>. Nucleophilic displacement of the chlorine in 1-chloromethylbenzotriazole is also synthetically useful. 1-Alkoxymethylbenzotriazoles are lithiated with *n*-BuLi, subsequent reaction with alkyl halides, then hydrolytic removal of the benzotriazole unit, reveals ketones <1996OM486>. Exactly analogous processes with 1-(methylthiomethyl)benzotriazoles also provides a route to ketones <1998JOC2110>. 1-Arylmethylbenzotriazoles <1998JOC3438> and 1- and 2-allylbenzotriazoles <1998TL363> can be similarly deprotonated. 1-Vinylbenzotriazole can be lithiated with one molar equivalent of *n*-BuLi at the carbon adjacent to nitrogen <2003JOC5713>.



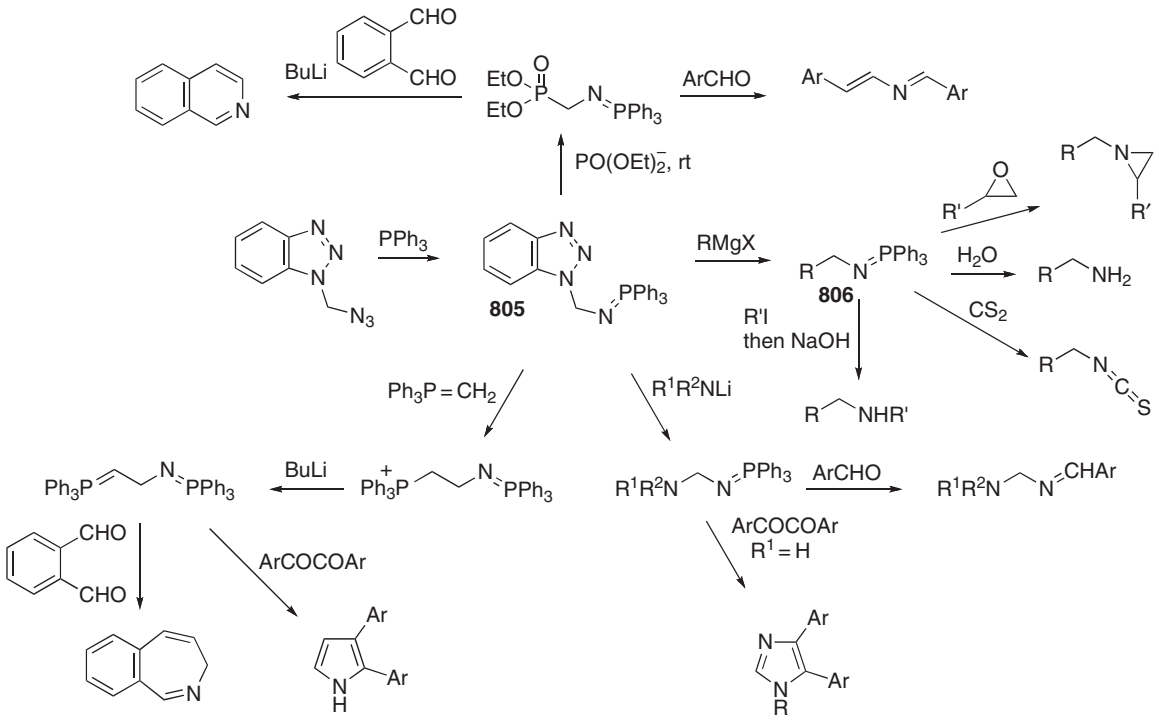
Scheme 169

2-Alkylbenzotriazoles behave differently on lithiation, thus treatment of 2-methylbenzotriazole with LDA at 78̄C produces a dimeric product **804**.

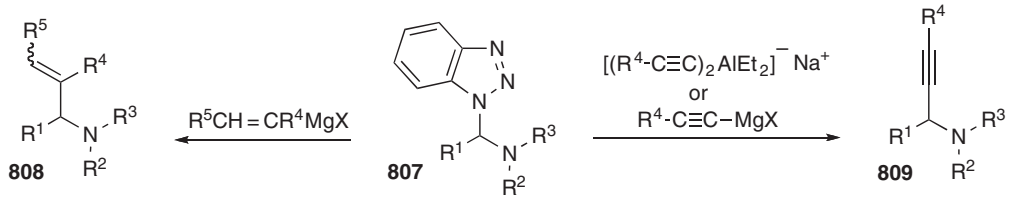


804

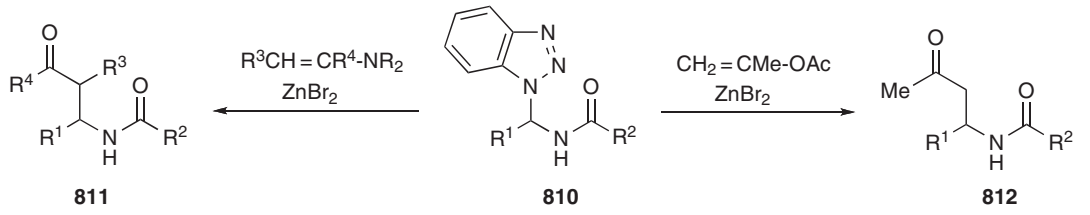
The synthetic potential of metallation and subsequent substitution of the lithiated 1-alkylbenzotriazoles discussed above, is complemented by the ability of the benzotriazolate anion to act as a good leaving group, and indeed it can be used with advantage in place of a halogen in many reactions. Benzotriazole derivatives are frequently more stable than their chloro or bromo analogues and are easy to prepare. The benzotriazole ring is extremely stable and is opened only under severe conditions, offering advantages over 1,2,3-triazole. Thus, benzotriazole has become one of the most useful synthetic auxiliary groups. These properties are illustrated in several ways in what follows (**Schemes 170174**).



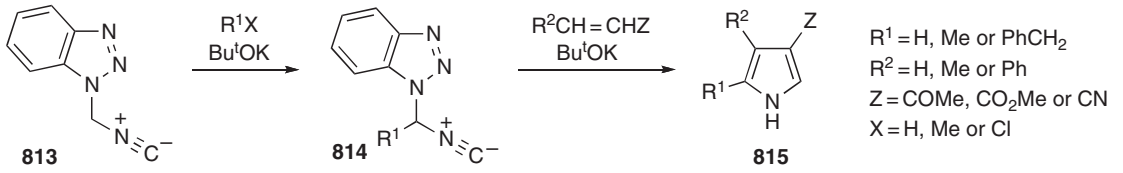
Scheme 170



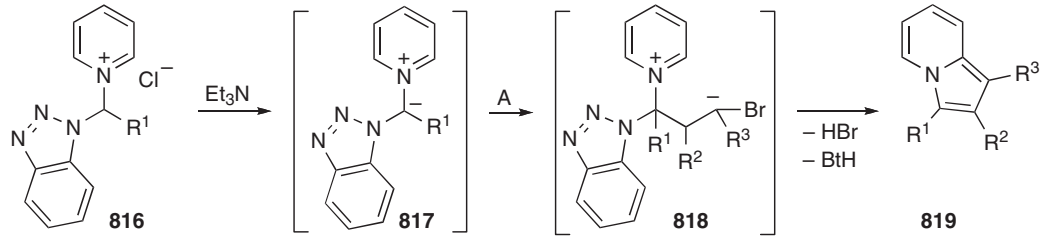
Scheme 171



Scheme 172



Scheme 173



R^1 = H, Et or *p*-tolyl; A = R^2-CH = CBr-R^3; R^2 = H, Ph, CO_2Me or CO_2Et; R^3 = CO_2Me, CO_2Et or CN

Scheme 174

The benzotriazole moiety of *N*-(-aminoalkyl)benzotriazoles is readily replaced by hydride upon reduction with sodium borohydride, or with a carbanion by reaction with Grignard or lithium reagents providing versatile routes for the synthesis of primary, secondary, and tertiary amines. 1-(Benzotriazol-1-yl)-*N*-triphenylphosphoranylidenemethylamine **805**, readily available from *N*-(azidomethyl)benzotriazole and PPh_3, reacts with Grignard reagents followed by hydrolysis of the intermediates **806** to give primary amines. The initial products **806** also react with isocyanates, carbon disulfide, aldehydes, epoxides, and alkyl halides to afford a wide variety of carbodiimides, imines, isothiocyanates, aziridines, and secondary amines (**Scheme 170**).

1-Aminoalkylbenzotriazoles **807** undergo displacement of the benzotriazole unit with alkenylmagnesium and alkynylmagnesium reagents in toluene leading to allylamines **808** and propargylamines **809** in excellent yields (**Scheme 171**) <2002S199>. Less stable perfluoroalkylmagnesium reagents give the corresponding amines at low temperature and using $BF_3.Et_2O$ <1997TL7015>.

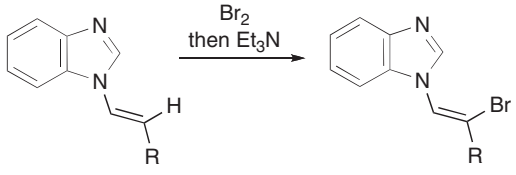
Benzotriazolylalkyl amides **810** are easy to prepare by condensation of amides with aldehydes and benzotriazole. Nucleophilic displacement of the benzotriazole, in this case with organozinc reagents, leads to amides <1998T7167, 2000TL9691>; **810** will also react with sodium alkoxides producing *N*-(-alkoxyalkyl)amides <1995JOC4002, 2003JOC4338>, reaction with enamines gives ketoamides **811** <1999JOC7622>, and with enol esters, ketones, e.g. **812** result (**Scheme 172**) <1995JOC4002>. Anions derived from *t*-butyl esters can also be used for substitution of benzotriazole to give -amido-esters <2002JOC4957>.

(Benzotriazole-1-yl)methyl isocyanide (BetMIC) **813** can be used instead of TosMIC in pyrrole syntheses; thus, C-alkylation on the methylene group using *t*-BuOK and then reaction of the resulting give isocyanide **814** with ,-unsaturated ketones, esters, or nitriles produces pyrroles **815** (**Scheme 173**) <1997H67>.

In another example of heterocyclic ring synthesis, pyridinium salts **816** require only Et_3N for deprotonation, the resulting ylides **817** add to esters of 2-bromo-2-alkenecarboxylic acids or analogous benzonitriles to give intermediate betaines **818** which, via intramolecular nucleophilic attack, give indolizines **819** (**Scheme 174**) <1999JOC7618>.

Alkenyl groups in *N*-alkenylazoles act as weak or moderate -electron acceptors. Thus, the basic pK_a of 1-vinylimidazole (5.14) is nearly 2 pK units lower than that of imidazole. Examination of ^{15}N NMR spectra of 1-vinylimidazoles and -benzimidazoles shows that the nitrogen attached to the vinyl group resonates in at a higher field than N(3). In accord with these results 1-vinylimidazoles form less stable complexes with transition metals than 1-alkylimidazoles.

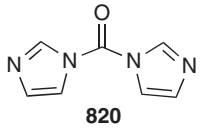
Additions to *N*-alkenylimidazoles are influenced by conjugation with the hetero ring (**Scheme 175**); a vinyl group is not cleaved when 1-vinyl-3-alkyl quaternary salts are thermolyzed and 1-vinylimidazole is not subject to thermal rearrangement.



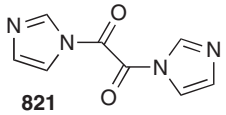
Scheme 175

3.4.3.12.4 Acyl and carboxy groups

An azole ring is quite a good leaving group, far better than NR_2. Hence *N*-acylazoles are readily hydrolyzed. Their susceptibility to nucleophilic attack gives rise to the synthetic utility of compounds such as carbonyldiimidazole **820** that have been used, for example, in peptide syntheses. *N*-Acylazoles offer mild and neutral equivalents of acid chlorides. The leaving group ability of the azole ring increases with the number of nitrogen atoms it contains. 1-Alkyl-3-acylazolium salts are even more powerful acylating agents.



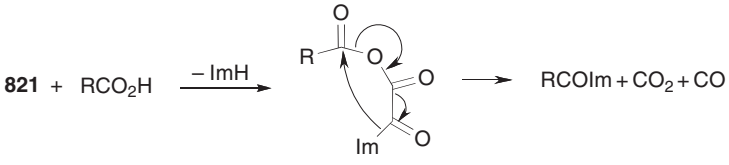
820



821

The synthetic utility of azolides is exemplified by many examples of their use in the synthesis of carboxylic acids, esters, and thioesters, amides and thioamides, aldehydes and ketones, and phosphorylated imidazoles and benzimidazoles.

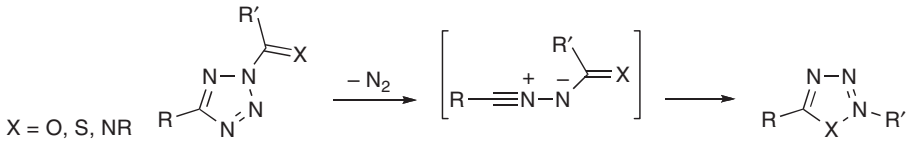
Carbonyldiimidazole **820** can be used to convert alcohols into alkyl halides by a one-step reaction using an excess of such reactive halides as allyl bromide or methyl iodide, and **820** can be made even more reactive by quaternization. The disadvantages of **820** are its cost and the fact that phosgene must be used in its preparation. An alternative is 1,1-oxalyldiimidazole **821** (made from 1-trimethylsilylimidazole and oxalyl chloride). Transacylation reactions occur very readily with this reagent (**Scheme 176**).



Scheme 176

Acyl derivatives of azoles containing nitrogen atoms in two different environments can rearrange. For example, 1-acyl-1,2,3-triazoles are readily isomerized to the 2*H*-isomers in the presence of triethylamine or other bases; the reaction is intermolecular and probably involves nucleophilic attack by N(2) of one triazole on the carbonyl group attached to another.

2-Acyltetrazoles can lose nitrogen spontaneously to give oxadiazoles, and thiadiazoles can be prepared similarly from 2-thioacyltetrazoles (**Scheme 177**).

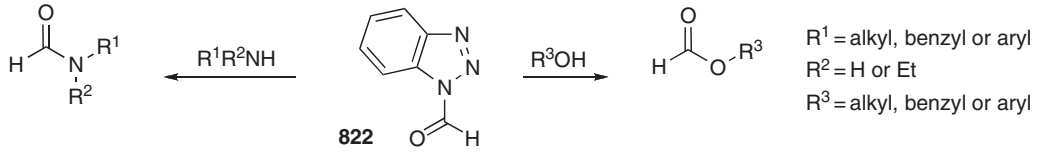


Scheme 177

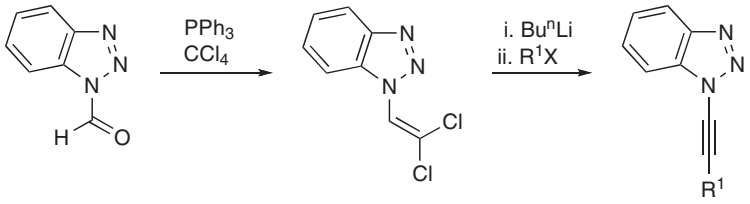
N-Carboxyazoles, e.g., 1-carboxyimidazole, are unstable compounds which readily decarboxylate. However, the ethyl ester of 1-carboxyimidazole is stable enough to be distilled and to form stable salts with acids.

N-Acylbenzotriazoles are convenient acylating agents for all kinds of amines, sometimes using microwave heating <2006JOC3375>, or on a solid phase support <2002BML1809> for hydroxamic acids and Weinreb amides <2002ARK (xi)39, 2003S2777> and for dipeptides <2004S2645, 2005S397, 2005TL6537>. They can be prepared under mild conditions via reactions of carboxylic acids with thionyl chloride in the presence of fourfold excess of benzotriazole <2003S2795, 2004RSQM275>. Synthetic applications of such compounds have been reviewed <2005SL1656>. C-Acylation of reactive aromatic compounds can also be achieved: thiophenes and furans <2004CCA175> and pyrroles and indoles (without N-protection) <2003JOC5720>. Ketones are acylated in the presence of LDA to give -diketones <2000JOC3679>. Acylation of aliphatic nitriles leads to the corresponding -ketonitriles <2003JOC4932> and of sulfones to -ketosulfones <2003JOC1443>. 2-Picoline is readily acylated to produce (pyridin-2-yl)methyl ketones; 4-picoline, 4-methylquinoline and the corresponding benzyl derivatives react similarly <2005ARK(iii)329>.

The simplest 1-acylbenzotriazole, 1-formylbenzotriazole **822**, can be conveniently prepared from benzotriazole and formic acid in the presence of dicyclohexylcarbodiimide <1995S503>. Its reactions with amines provide formamides under mild conditions and with alcohols, formates (**Scheme 178**) <1995S503, 2002JA12950>. Even 2-nitroaniline and 2-aminopyridine can be efficiently N-formylated in this way <1995S503>. 1-Formylbenzotriazole reacts with Ph_3P and CCl_4 to give 1-(2,2-dichloroethenyl)benzotriazole as a crystalline solid, treatment of which with two molar equivalents of *n*-BuLi followed by alkylating agents leads to 1-alkynylbenzotriazoles (**Scheme 179**) <2000OL3789, 2002JOC7526, 2006T3794>.

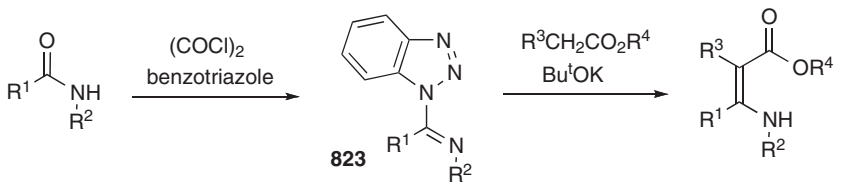


Scheme 178



Scheme 179

1-Imidoylbenzotriazoles **823** are prepared in good yields from amides with benzotriazole and oxalyl chloride in the presence of pyridine <2006JOC3375>. These compounds bring about imidoylation of methylene groups activated by electron-withdrawing substituents, for example, with ester enolates, to give -enaminoesters (**Scheme 180**).



Scheme 180

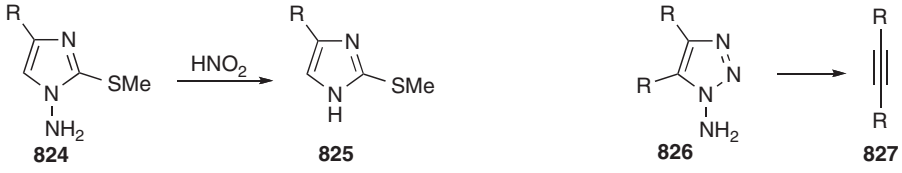
1-Cyanobenzotriazole is readily prepared in 92% yield by treatment of benzotriazole with sodium hydride followed by cyanogen bromide. This solid and stable compound is a convenient reagent for introduction of the nitrile functional group into activated methylene compounds RCH_2X, via lithiation <2007ARK5>.

3.4.3.12.5 N-Amino groups

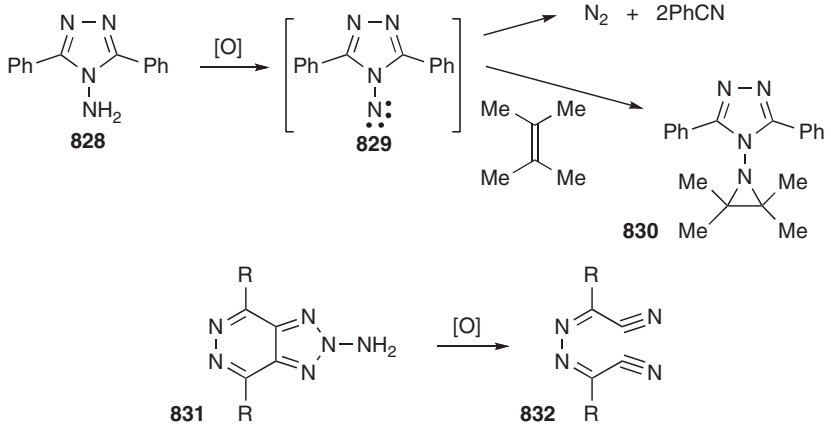
N-Amino groups have little -interaction with the imidazole ring, and only small inductive effects are apparent when the pK_a values are examined. By contrast, the hetero ring has a strong base-weakening effect on an exocyclic amino group. Protonation of 1-aminobenzimidazole, for example, occurs at N(3), the basicity of which is reduced by the amino substituent (pK_a = 4.95). As an NH-acid, 1-aminobenzimidazole has a pK_a of 28.4 (DMSO, 20°C) (cf. pK_a = 30.7 for aniline).

N-Amino groups can be alkylated and acylated by way of their anions, and they take part in the usual reactions with carbonyl compounds, with carbodiimides, and in aza-Wittig reactions. 1-Aminobenzimidazoles and their quaternary salts react similarly, and the Schiff bases formed can lead to cyclized products.

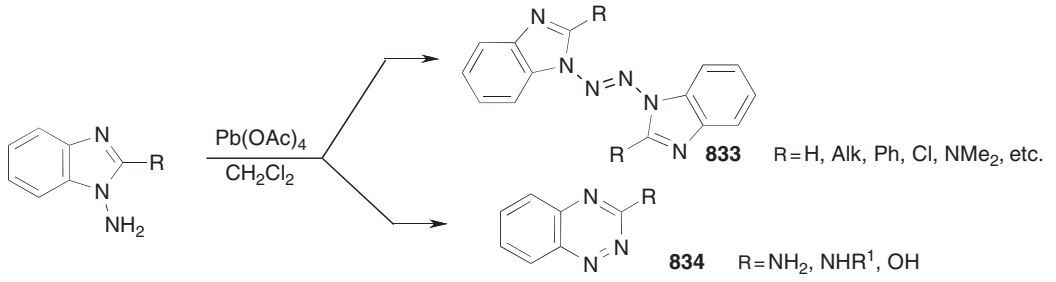
N-Amino groups are replaced by hydrogen on treatment with phosphorus trichloride (1,2,4-triazole-4-acylimines are converted into triazoles) or with nitrous acid (e.g., **824** **825**). 4-Amino-3,5-diaryl-1,2,4-triazoles are deaminated efficiently by reduction of the diazonium salt with aqueous hypophosphorous acid <2002JHC93>. *N*-Alkylaminoazoles form stable N-nitroso compounds, normally existing as a mixture of *E*- and *Z*-rotamers.



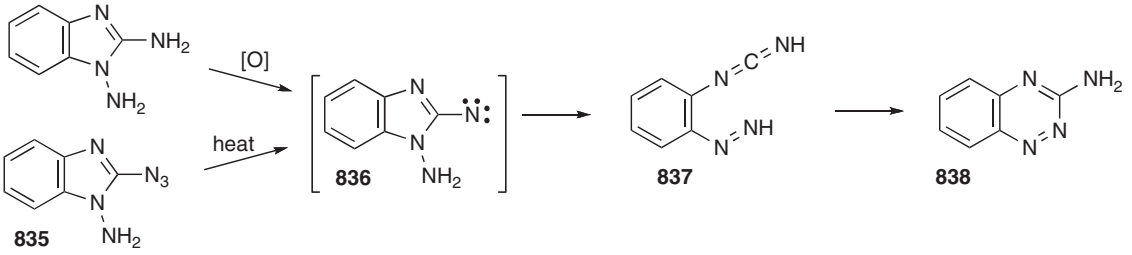
N-Aminoazoles can be oxidized to nitrenes which then fragment or ring expand in various ways. 1-Amino-1,2,3-triazoles lose two moles of nitrogen to give alkynes (**826** **827**). Oxidation of 1-aminobenzotriazole is one of the most effective methods of generation of benzyne. *N*-Amino-triazoles **828** and -tetrazoles on oxidation with lead tetraacetate fragment to nitriles; however, the intermediate nitrene, e.g., **829**, can be trapped as an aziridine **830**. Similarly, the *N*-aminopyridazinotriazoles **831** undergo oxidative fragmentation to give open-chain compounds **832**. *N*-Aminopyrazoles can ring expand to 1,2,3-triazines.



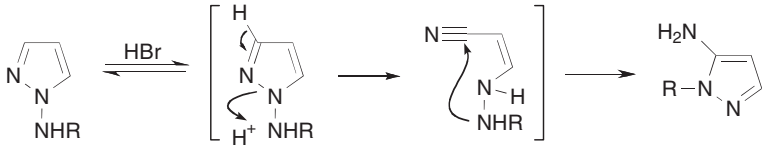
Oxidation of 1-aminobenzimidazoles with manganese dioxide or lead tetraacetate can give either 1,1-azobenzimidazoles **833** or 3-substituted benzo-1,2,4-triazines **834**. Electrochemical measurements have shown that the first step in this reaction is removal of an electron from a -orbital of benzimidazole rather than from the N-amino group. Because the cation radical that is formed must be stabilized by loss of a proton, for **834** to form the 2-substituent must contain an NH or OH group. This is unnecessary for the formation of the azo product **833** that may form via a nitrene intermediate.



Oxidation of 1,2-diaminobenzimidazole, leading to the formation in high yield of 3-aminobenzo-1,2,4-triazine **838**, is thought to proceed through recyclization of an intermediate nitrene **836** (possibly via diazene intermediate **837**) as evidenced by the formation of amine **838**, with a high efficiency on the thermolysis of 1-amino-2-azidobenzimidazole **835**. The reaction works well also for other *N*-amino--azidoimidazoles and 4-amino-3-azido-1,2,4-triazoles.



Rearrangement of 1-aminopyrazole and 1-alkylaminopyrazoles to the corresponding 5-aminopyrazoles can be achieved in 48% aqueous hydrobromic acid; the reaction proceeds by protonation followed by ring opening/ring cyclization in accordance with **Scheme 181**. 1-Alkylaminoindazoles rearrange into 2-alkyl-3-aminoindazoles.

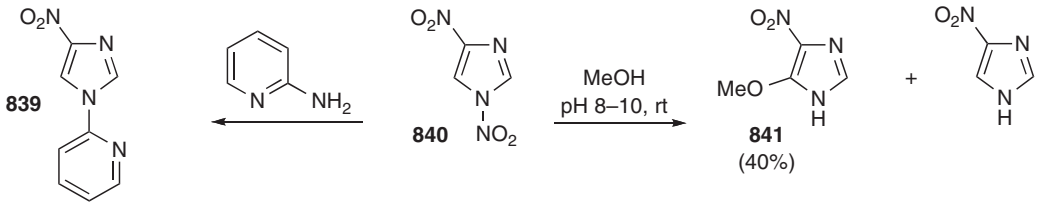


Scheme 181

3.4.3.12.6 N-Nitro groups

1-Nitropyrazoles rearrange to 4-nitropyrazoles in H_2SO_4 and to 3-nitropyrazoles thermally. Similar rearrangements are known for *N*-nitro-1,2,4-triazoles.

The *N*-nitroimidazoles are stable for a time even in the presence of water, but treatment with concentrated sulfuric acid cleaves the N-nitro group, and strong base opens the ring. Much of the interest in such compounds is related to their multistep complex substitution reactions in which sequential nucleophilic addition of arylamines, ring opening, ring closure, nitroamide elimination, and rearomatization gives 1-aryl-4-nitroimidazoles, e.g., **840** **839**. This method can also be used to prepare isotopically labeled imidazoles when labeled amino acids are used as the amine.

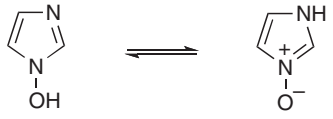


Reaction of 1,4-dinitroimidazole with methanol leads to **841** also via *cine*-substitution, the reaction being first order with respect to both reactants and also to hydroxide ions.

When heated at 130140°C in anisole or benzonitrile, 1,4-dinitroimidazole **840** forms 4-nitroimidazole (major) and 2,4-dinitroimidazole. The 2-methyl analogue of **840** gives 2-methyl-4-nitroimidazole and 2-methyl-4,5-dinitroimidazole (major).

3.4.3.12.7 N-Hydroxy groups and N-oxides

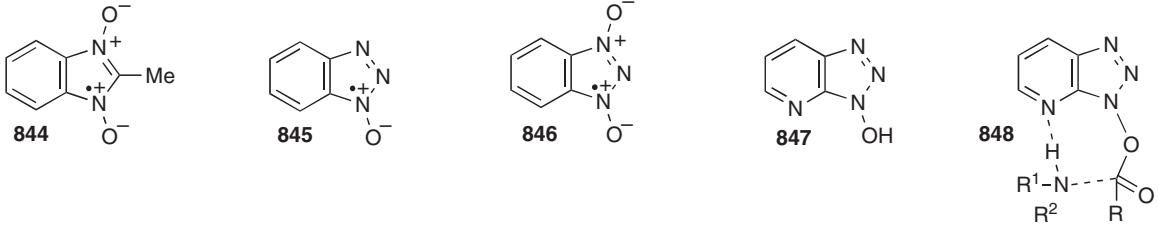
Compounds of this type are often tautomeric: in general, the *N*-oxide form (e.g., **843**) is favored by polar media and the N-hydroxy form (e.g., **842**) by nonpolar media.



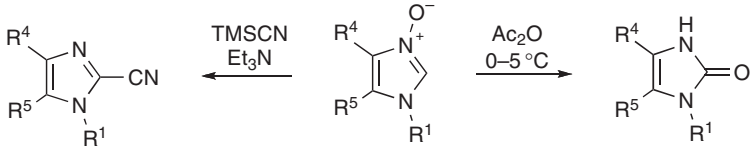
1-Hydroxypyrazole 2-oxides are quite strong acids.

Alkylation of *N*-oxides, e.g., in basic media by methyl iodide, usually takes place at the oxygen as does acylation (by, e.g., Ac_2O).

Deoxygenation of azole *N*-oxides can be accomplished by catalytic hydrogenation, with Raney nickel, with titanium(III) chloride in methanol, by metalacid reduction, or with phosphorus halides. When imidazole *N*-oxides do not have a 2-substituent, they readily rearrange to the corresponding 2-imidazolones or 2-benzimidazolones, but 1-hydroxyimidazole 3-oxides do not undergo this rearrangement. 1,2,3-Thiadiazole 3-oxides isomerize on irradiation to the corresponding 2-oxides. The *N*-oxide function in imidazole *N*-oxides, in conjunction with the adjacent carbon atom, gives the molecule properties of a 1,3-dipole, dipolar cycloadditions are known. Oxidation of *N*-hydroxyazoles can give cyclic nitroxyl radicals (e.g., **844-846**).

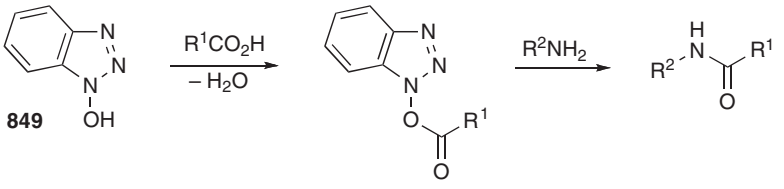


Imidazole and benzimidazole *N*-oxides are thermally unstable and may be explosive. However, more substituted imidazole *N*-oxides behave much like azine *N*-oxides, as illustrated by a couple of examples in **Scheme 182** <1998HCA1585, 2000HCA728, 2002AGE2290>.



Scheme 182

Due to its wide application in peptide synthesis, 1-hydroxybenzotriazole **849** is the most commonly used benzotriazole derivative with hundreds of references in *Chemical Abstracts* each year. The utility of **849** (**Scheme 183**) rests essentially on its readiness to form esters with carboxylic acids in the presence of dehydrating agents. 1-Hydroxy-7-azabenzotriazole **847** is also used in peptide coupling reactions, especially with sterically encumbered amines. The faster reaction rates and reduced racemization is attributed to base catalysis by the adjacent pyridine nitrogen **848** during the coupling reactions.



Scheme 183

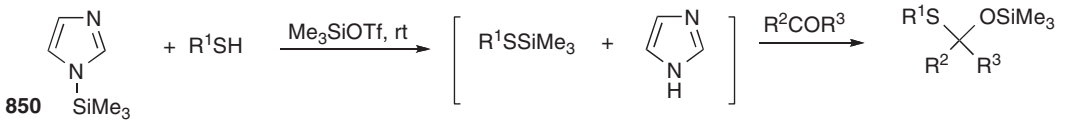
3.4.3.12.8 N-Halo groups

Generally these derivatives are rather unstable and behave as oxidizing and halogenating agents. 1-Iodoimidazoles are more stable than other analogues. *N*-Chlorobenzotriazole is a useful oxidizing and chlorinating agent.

3.4.3.12.9 N-Silicon, phosphorus, sulfur, and related groups

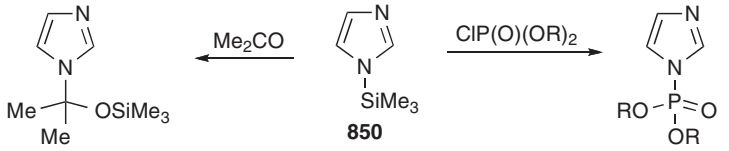
N-Trialkylsilyl- and *N*-trialkylstannylazoles are useful N-protected derivatives for a number of transformations, and suitably volatile for GC analysis. The groups are thermally stable, but susceptible to hydrolytic and analogous displacements, with the stannyl compounds less readily hydrolyzed than the silyl species.

1-Trimethylsilylimidazole **850** is used, with trimethylsilyltriflate as catalyst, to make 1-alkylthio- and 1-phenylthio-1-trimethylsilyloxy-alkanes and -cycloalkanes. The use of two equivalents of the thiol prevents the formation of imidazole adducts (**Scheme 184**).



Scheme 184

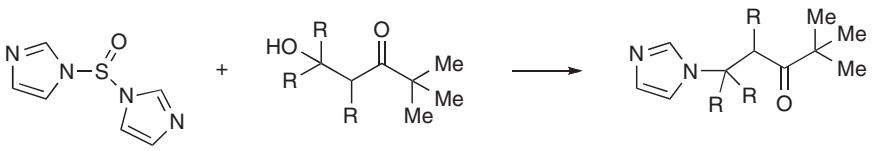
Analogues of **850** react with derivatives of phosphorus-containing acids to form 1-phosphorylimidazoles. The same compound also silylates ketones to give enol silyl ethers and/or siloxyalkylimidazoles (**Scheme 185**).



Scheme 185

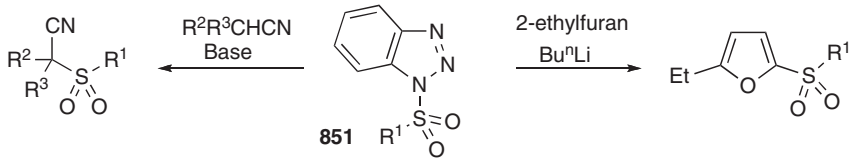
N-Phosphorylimidazoles are useful phosphorylating agents.

1,1-Sulfonyldiimidazoles and 1-chlorosulfinylimidazole have similar applications to the carbonyl analogues in transfer reactions (**Scheme 186**). Treatment of arylsulfonylimidazoles with hydrogen peroxide in alkaline medium gives arylsulfonyl peracids, which are useful epoxidizing agents. The dimethylaminosulfonyl group is useful for N-protection in lithiation procedures; it can be removed by refluxing with dilute hydrochloric acid.



Scheme 186

1-Sulfonylbenzotriazoles **851** are readily available from reactions of benzotriazole with sulfonyl chlorides <2000JOC8210> or of 1-chlorobenzotriazole with sulfinic acids <2004JOC1849> and can be used for sulfonation of carbanions (**Scheme 187**) <2005JOC9191>.



Scheme 187

3.5
Reactivity of Small and Large Rings

3.5.1 General Survey

Chapter 3.5 attempts to give an overview of the reactivity of small and large ring systems. The great diversity of these systems presents a serious problem of organization. In structuring this chapter on reactivity, the nature of the reaction and the distance of the site of attack from the heteroatoms are used. For the nonconjugated systems, whether fully saturated or partially unsaturated, much of the reactivity is simply that to be expected of noncyclic analogues, with exceptions relating to (1) strain in small rings leading to ring openings and (2) a tendency for ring contraction in medium-sized systems. Space dictates that this unexceptional reactivity is simply exemplified in just a few instances.

3.5.1.1 Neutral Molecules

The reactivity of small (three- and four-membered) heterocyclic rings is dominated by the effects of ring strain, which facilitates various modes of ring opening. Aromaticity is seldom observed; antiaromaticity is present in only a few isolated examples and thus does not play a general role. Many reactions are initiated by unimolecular ring opening, to give diradicals or ylides, from which the reaction products are derived. Extrusion of stable as well as unstable moieties is assisted by the ring strain. Four-membered systems often cleave into two two-membered fragments (each consisting of two former ring atoms and their ligands). Attack on ring carbons concomitant with ring opening is very common and is usually subject to electrophilic catalysis.

Large heterocycles, i.e., those with more than six ring members, often show little effect of ring strain on the reactivities of the neutral molecules. Factors important for large ring reactivity are unsaturation, especially of polyenic and aromatic character, and the steric accessibility of heteroatoms and functional groups, as well as the possibility of transannular reactions. However, the majority of unsaturated large rings are not aromatic, even where the Hckel rule is obeyed formally.

3.5.1.2 Cations

Onium ions of small and large heterocyclic compounds are usually produced by electrophilic attack on a heteroatom. In most three- and four-membered rings, nucleophilic attack on an adjacent carbon and ring opening follow immediately, stabilizing the system. In large rings the onium ion behaves as would an acyclic analogue, except where aromaticity or transannular reactions come into play (each with its electronic and steric preconditions).

Cations of a different kind may be derived by removing a leaving group with its bonding electrons, e.g., a halide ion from an N-halo moiety; such cations (nitrenium ions) are reactive intermediates.

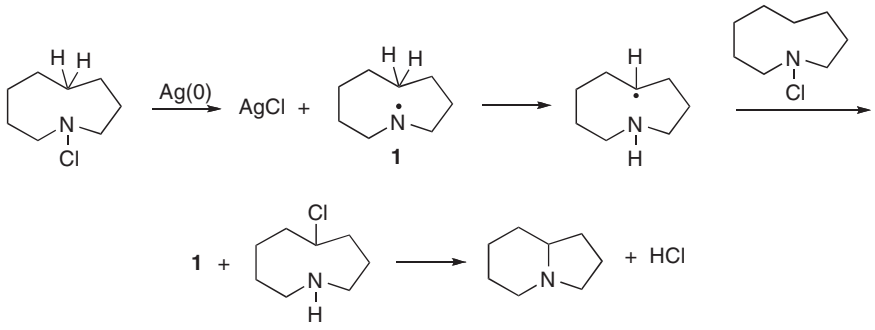
3.5.1.3 Anions

Anions of small-ring heterocycles can be generated in certain circumstances, but anions from large heterocycles often resemble their acyclic counterparts. However, in some cases, anion formation can adjust the number of electrons so as to make a system conform to the Hckel rule, and render it aromatic if planar geometry can be attained. Anion formation in certain large heterocycles can also initiate transannular reactions (see also Section 3.5.6).

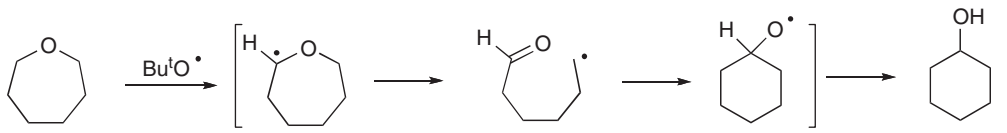
3.5.1.4 Radicals

Small-ring radicals with the unpaired electron at the heteroatom or at a carbon adjacent to a heteroatom undergo ring cleavage as the predominant mode of stabilization, as known for oxaziranes, aziridines, diaziridines, diazirines, oxaziridines, and thietanes. The heteroatom is usually retained in the product, except in thiirane cleavages, where desulfurization occurs. Thietanes, in contrast, are less readily desulfurized. Oxaziridinyls display a variety of reactions, including NO and NC cleavage; diaziridinyls behave analogously, with CN and NN cleavage.

Large-ring heterocyclic radicals are not particularly well known as a class. Their behavior often resembles that of their acyclic counterparts, except for transannular reactions, such as the intramolecular hydrogen transfer in 1-azacyclononan-1-yl **1** (**Scheme 1**). As is the case with acyclic ethers, oxepane in the reaction with *tert*-butoxy radical suffers abstraction of a hydrogen atom from the 2-position in the first reaction step (**Scheme 2**).



Scheme 1

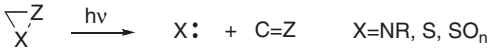


Scheme 2

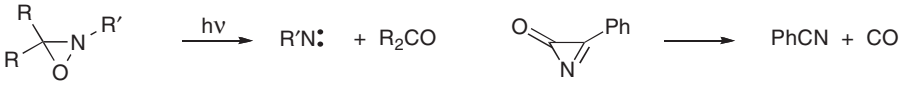
3.5.2 Thermal and Photochemical Reactions, Not Formally Involving Other Species

3.5.2.1 Fragmentation Reactions

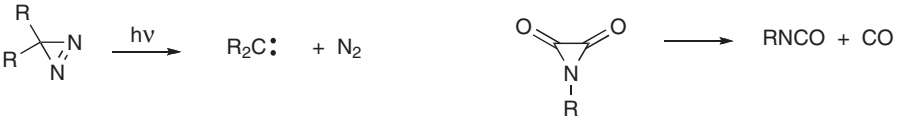
Fragmentation reactions are particularly common in small rings. The relief of strain and the gain in stability in forming certain stable fragments (such as N_2, CO_2), as felt in the transition state of the rate-determining step, are important driving forces. Three-membered rings fragment to give moieties ab (usually unsaturated) and c. The latter might be a stable molecule, such as CO, but also a carbene or nitrene, atomic sulfur, or singlet SO, to name common examples, as generalized in **Scheme 3** and exemplified in **Schemes 4 and 5**.



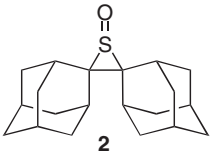
Scheme 3



Scheme 4



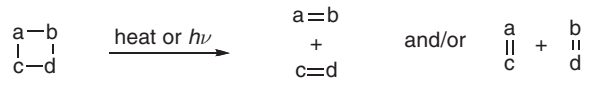
Scheme 5



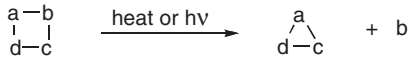
2

Extrusion (or elimination) of sulfur from thiiranes and thiirenes is a facile process. Virtually all thiiranes and thiirenes, as well as their *S*-oxides and *S*,*S*-dioxides, undergo thermal extrusion of the sulfur moiety with increasing facility according to the trend S << SO < SO_2. Sulfur monoxide produced in this way can be utilized in cycloaddition processes, for example, from **2** in refluxing toluene with 2,3-dimethyl-1,3-butadiene in a chelotropic addition <1997JOC8366>.

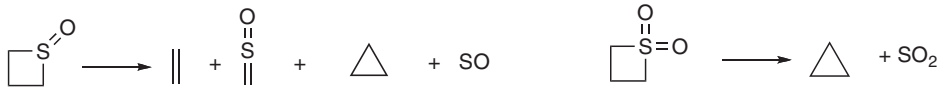
Four-membered heterocycles most often give fragments containing two ring atoms with their respective ligands (**Scheme 6**). Nitrogen, CO_2, SO_2, RCN, RNCO, and RNCS are particularly common fragments containing two of the original four ring atoms. However, [3 + 1] fragmentation is also known, giving an atom (such as S) or a stable species (such as SO_2) frequently together with a three-membered ring product (**Scheme 7**). Examples are found in **Schemes 8–11**. The [2 + 2] fragmentations are often stereospecific and can be reversible. The reversibility can lead to interconversions as seen in **Scheme 11**; the RN: moieties of isocyanate and carbodiimide are exchanged via a 3-imino-1,3-diazetidin-2-one.



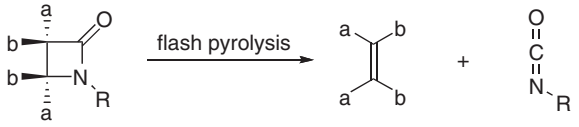
Scheme 6



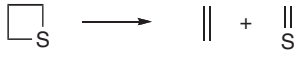
Scheme 7



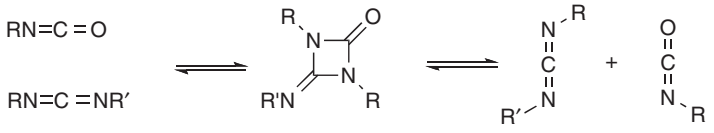
Scheme 8



Scheme 9

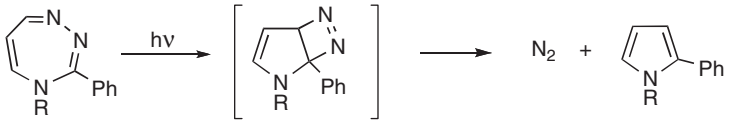


Scheme 10



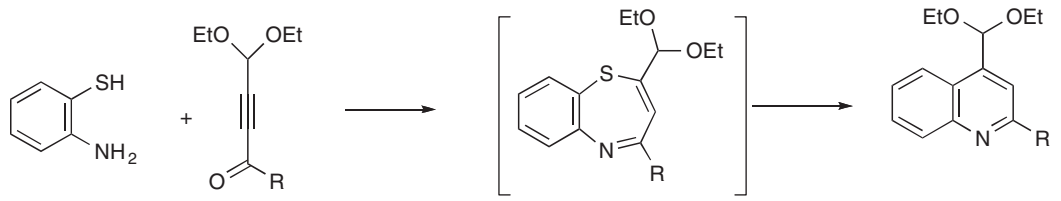
Scheme 11

The fragmentation of a large-ring heterocyclic compound occurs less readily, since the ring strain is usually less. The most favorable leaving moieties, such as N_2, can of course be extruded easily (often giving l,n diradical species). Thus, 1,2,4-triazepines can lose nitrogen to give pyrroles (**Scheme 12**).



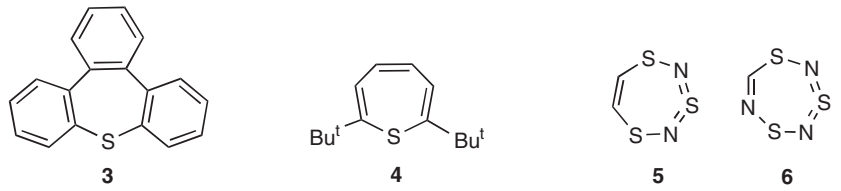
Scheme 12

Most often, fragmentations of large heterocyclic compounds can be classified as retrocycloadditions and may be orbital symmetry controlled. For example, 2,7-dihydrothiepin 1,1-dioxide loses SO_2 to give *cis*-hexatriene. In general, simple thiepines thermally extrude sulfur readily, by a valence tautomerism to the corresponding benzene episulfide, followed by irreversible loss of sulfur. An example involving a transient benzo[*b*]-1,4-thiazepine is shown in **Scheme 13** <1997T641>.



Scheme 13

The thermal stability of the thiepine ring increases with an increasing number of annulated benzene rings, e.g., the thiepine **3** is thermally quite stable. Thiepines can be also stabilized by steric effects. Monocyclic thiepines such as **4** with a *tert*-butyl group at both C(2) and C(7) positions show no sulfur extrusion at room temperature.



3 **4** **5** **6**

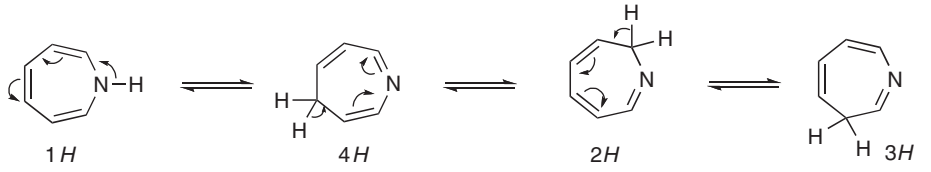
1,3,5,2,4-Trithiadiazepine **5** and 1,3,5,2,4,6-trithiazepine **6** have remarkable thermal stability for molecules with such a high proportion of heteroatoms; they do not decompose even on prolonged heating at 180°C. Such unusual stability indicates that these heterocycles are delocalized 10-aromatic systems.

3.5.2.2 Rearrangements

a. *Cistrans* isomerizations of substituents are commonly observed upon heating or irradiating saturated three-membered heterocycles. The formation of 1,3-diradicals allows rotation about the single bonds, and the isomerization has been used to probe the bond strengths of the 2,3-bond of such molecules (**Scheme 14**). *Cistrans* isomerizations in large rings can be due to retrocycloadditions or temporary conversions of parts of the heterocycle, such as dehydrogenationhydrogenation reactions. Diradical formation to give longer chain l,-diradicals does not usually lead to recyclization due to unfavorable entropy factors.

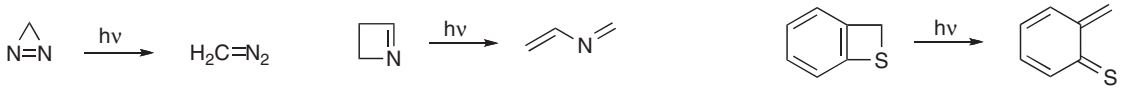
Scheme 14

b. Hydrogen shifts are common in large, unsaturated rings (see Section 2.5.5.2). Thus, a series of 1,5-hydrogen shifts, thermally allowed, connect the 1*H*-, 2*H*-, 3*H*-, and 4*H*-isomers of N-unsubstituted azepines (**Scheme 15**). A sigmatropic mechanism does allow the interconversion of the isomers, but an ionic mechanism(s) must also be considered since base catalysis has been observed in some cases.

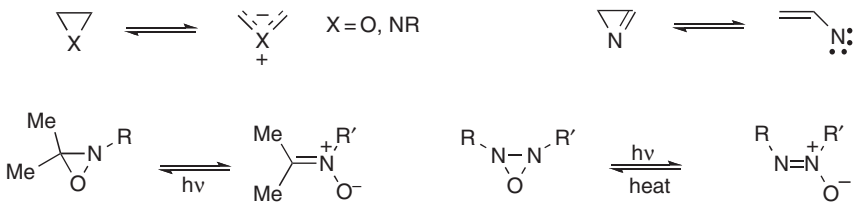


Scheme 15

c. Ring-chain isomerizations are common with small heterocycles, with the ring strain assisting the opening. The reverse reaction is often found where reactive open products are obtained (see isomerizations). **Scheme 16** gives examples of irreversible ring openings, and **Scheme 17** shows some which are readily or spontaneously reversed.

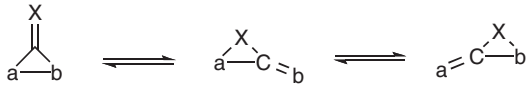


Scheme 16



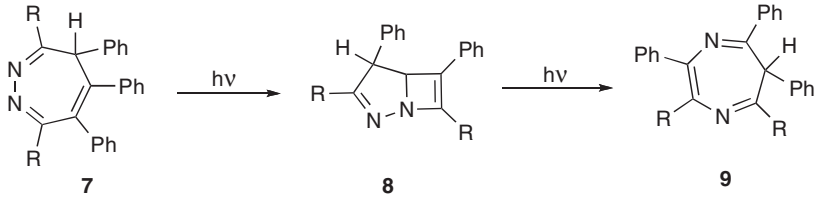
Scheme 17

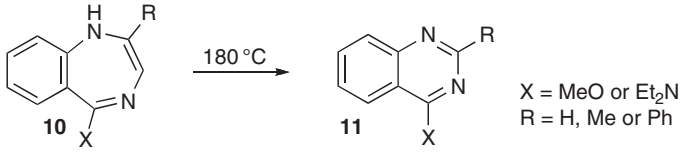
d. Ringring valence tautomerism occurs in small and large rings, with or without changes in ring size. An example of the latter course is the intriguing interconversion of three-membered rings with exocyclic double bonds (**Scheme 18**) observed with methylene-aziridines, -aziridinimines, and -diaziridinimines.



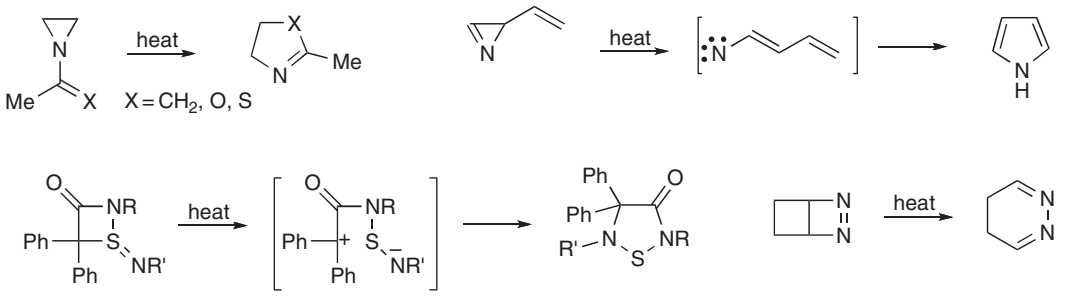
Scheme 18

Another example is the rearrangement of 4*H*-1,2-diazepine **7** to 6*H*-1,4-diazepine **9**, which occurs via an aza-di--methane reaction with 1,2-diazabicyclo[3.2.0]hepta-2,6-diene **8**, as the intermediate <1996CRV3065>. The thermal ring contraction of **10** generates quinazolines **11** <1999H(51)2407>.



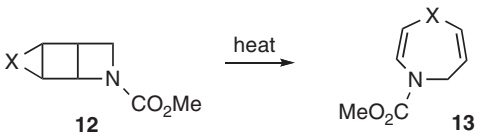


Ring expansion of small rings is favored by ring strain, and many 3 5 conversions are known. Four-membered rings can expand to five- or six-membered systems. Examples are given in **Scheme 19**.

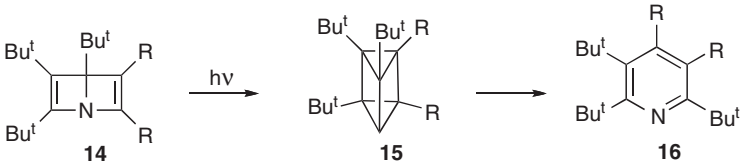


Scheme 19

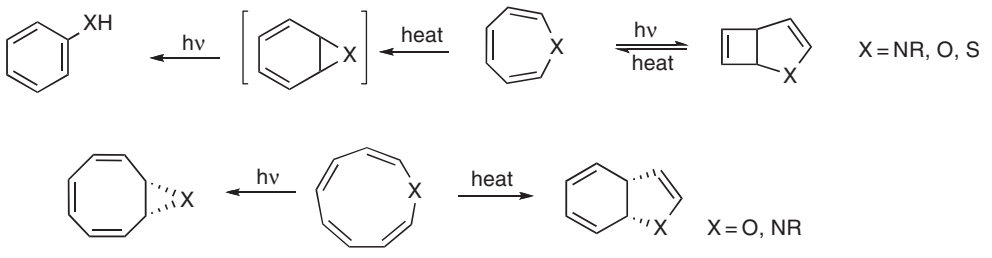
Thermolysis of the tricyclic azetidines **12** (X = O, NCO_2Et, S, or CH_2) in solution gives the seven-membered ring heterocycles **13** in high yields.



Photolysis of fully substituted tricyclic Dewar pyridines **14** carrying *tert*-butyl substituents at C(2), C(3), C(4), and C(7) produces azaprismanes **15**, which, on standing or further irradiation, give the pyridine derivatives **16**.

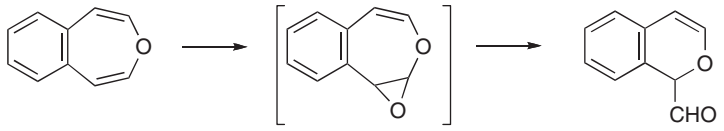


Large rings isomerize to two condensed smaller ones, by transannular reactions of many bond-making mechanisms and by electrocyclic reactions. Seven-membered, fully unsaturated systems can convert into [3.2.0] or into [4.1.0] isomers. The former conversion is allowed photochemically, the latter thermally. Consequently, the chemistry of azepins, oxepins, and thiepins is often governed by the rate and activation barrier (or the photochemical conditions and parameters) prevailing. Thiepins, for example, extrude sulfur via the thianorcaradiene isomer, and sulfur loss is likely to occur when a given system isomerizes to the [4.1.0] isomer more rapidly than competing reactions that occur through the monocyclic isomer. Depending on the nature of the heteroatom (and the presence of other heteroatoms in the ring) and the substituents, the heterepine/heteronorcaradiene rearrangement can be fast or slow, and one or the other component can be dominant in the equilibrium. Photoinduced rearrangement leads to [3.2.0] systems, which can revert to the seven-membered monocycle thermally perhaps by homolytic cleavage of the common bond. Both types of bicyclizations are observed in systems containing N, O, or S (including SO and SO_2) as heteroatoms. **Scheme 20** gives examples.



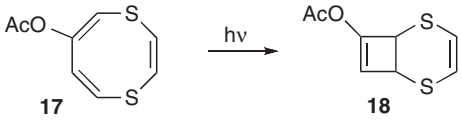
Scheme 20

In another example, 3-benzoxepine reacts with dimethyldioxirane at 50̄C to give the 2,3-oxide, which, between 5 and 10̄C, undergoes rapid ring-opening rearrangement to its isomer, 1*H*-2-benzopyran-1-carbaldehyde (**Scheme 21**) <2004TL4789>.



Scheme 21

2*H*-Azocinones are in thermal equilibrium with 8-azabicyclo[4.2.0]octa-3,5-dienones, as measured by NMR. Acetoxydithiocin **17** is converted photochemically into its dithiabicyclooctadiene valence tautomer **18**.



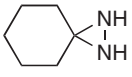
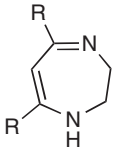
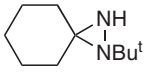
For other examples of valence isomerizations of small and large rings, see Section 2.5.5.1.

3.5.3 Electrophilic Attack on Ring Heteroatoms (see also Section 3.5.7.2)

3.5.3.1 Protonation

The basicities of saturated heterocycles are similar to those of analogous open-chain systems, with the exception of three-membered heterocycles, in which the basicity is markedly reduced. **Table 1** gives pK_a values for the equilibria

Table 1 Basicities for some heterocycles: pK_a values for the equilibria between parent and monoprotonated species in water

Parent species	*p*K_a	*Parent species*	*p*K_a
	8.04		11.27
	4.6		1314
	6.4		2.02
	0.13 to 1.81		2.08
	11.29		

between free and monoprotonated heterocycles. As the ring size increases, the protonated species become more stable and the pK_a values approach those of the open-chain analogues. Increasing basicity in the order thiirane < oxirane < aziridine, prevails in gas phase proton affinities (**Table 2**). Azetidine presents a gas-phase basicity practically equal to that of *N*-methylethanamine.

Table 2 Gas-phase proton affinities of small heterocycles

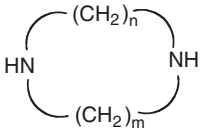
Heterocycle	*Proton affinity (kJ mol^{1})*	*Open-chain analogue*	*Proton (kJ mol^{1})*
	902.5	MeNHMe	922.6
	793.3	MeOMe	807.9
	812.9	MeSMe	839.7

In the gas phase, -lactams are weaker bases than acyclic amides. *Ab initio* calculations show that -lactams are oxygen bases, but the gap between the oxygen and nitrogen intrinsic basicities is much smaller than in normal amides, a result of redistribution due to hybridization changes.

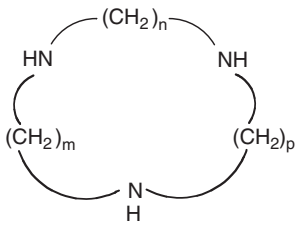
While lactones are frequently more basic than the corresponding acyclic esters, 2-oxetanone is less basic (6 kcal mol^{1}) than methyl acetate as a consequence of substantial hybridization changes incurred upon cyclization to the four-membered ring. The effect of cyclization of ethers on basicity is the opposite; thus, oxetane is a stronger base than methyl ethyl ether. Lactones and esters normally undergo protonation on the carbonyl oxygen, favored over the ether oxygen by nearly 18 kcal mol^{1}. Since the 2-oxetanone carbonyl is less basic, the energy difference on protonation at the carbonyl oxygen versus protonation at the ether oxygen is substantially reduced to a value of 3 kcal mol^{1}.

Medium-ring-saturated monocyclic diamines **19** have pK_a values $\geq$12 in aqueous solution; **19** ($n = m = 4$) has the highest pK_a^{1} resulting from internal hydrogen bonding.

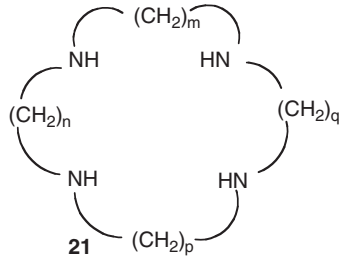
The pK_as for 10- to 12-membered ring triazacycloalkanes **20** are much higher (pK_a^{1} 12.713.4) than those of open-chain secondary amines, whereas the 13-membered ligand **20**, ($n = m = 2$, $p = 6$) has a normal value (pK_a^{1} = 10.36).



19 *n*, *m* = 3-5



20



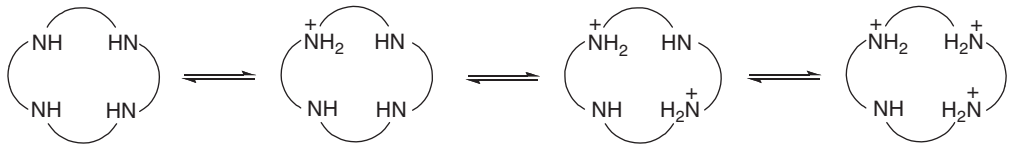
21

Tetraazamacrocycles **21** generally show two high pK_a values (pK_a^{1} 10.511.5; pK_a^{2} 9.510.5), whereas the other values are distinctly lower (pK_a^{3} 1.66.9; pK_a^{4} 0.85.7) (**Table 3**). The second proton can bind to a nitrogen atom across the ring

Table 3 pK_a Values of tetraazacycloalkanes **21** (in 0.2 M $NaClO_4$).

Compound 21	*pK_a^{1}*	*pK_a^{2}*	*pK_a^{3}*	*pK_a^{4}*	*Temperature (˜C)*
(n = m = p = q = 2)	10.51	9.49	1.6	0.8	35
(n = m = p = 2, q = 3)	10.91	9.91	1.6	0.9	35
(n = p = 2, m = q = 2)	11.50	10.30			25
	11.23	10.30	1.5	0.8	35
(n = m = 2, p = q = 3)	11.05	9.98	3.5	1.0	25
(n = m = p = 2, q = 4)	10.57	9.56	4.13	2	25
(n = m = p = 3, q = 2)	10.76	9.94	3.6	1.5	25

from the first one, whereas the third and fourth must bind close to an ammonium group and thus feel the effect of the neighboring positive charge more strongly (Scheme 22). As the size of the macrocycle ring increases from 12 to 16, such interactions decrease and the values of the third and fourth pK_a become larger.



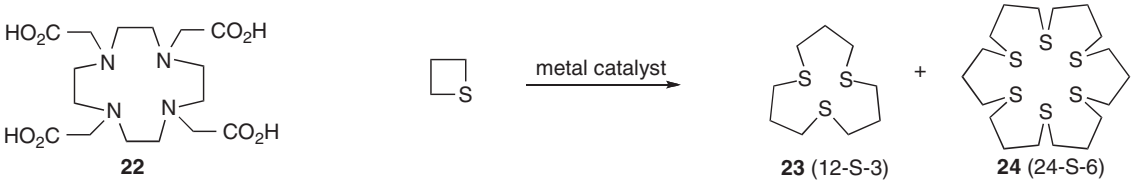
Scheme 22

Similar observations have been made for larger macrocycles containing five or more nitrogen atoms. These compounds behave as strong bases in their first protonation steps and as weaker bases in the later protonation steps.

3.5.3.2 Complex Formation

Numerous stability constants for metal complexes with triaza-, tetraaza-, and polyaza-macrocycles have been measured. Smaller rings, with three and four nitrogen atoms, generally form 1:1 species ML (but sometimes also ML_2). Larger rings with more nitrogen donors can give protonated species MLH_n and/or binuclear complexes M_2L.

Many of these complexes are more stable than those formed with the corresponding open-chain ligands. This macrocyclic effect is determined by enthalpic as well as by entropic contributions. Still higher stability constants are obtained when side chains with additional donor groups are attached to the macrocycle; thus, tetraacetic acid **22** forms complexes with most metal ions, including alkaline earth ions and transition metal ions; these complexes show stabilities among the highest known.



22 **23** (12-S-3) **24** (24-S-6)

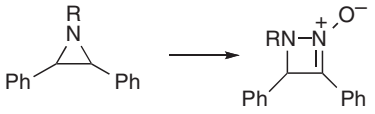
Cationic polymerization of oxetanes is a commonly used method of synthesizing polyethers. A Lewis acid catalyst is generally used to initiate the cationic polymerization chain reaction by activation of the oxetane ring oxygen, allowing nucleophilic attack from the ring oxygen atom of a second oxetane molecule and ring opening. Branched polyethers can be formed by intramolecular chain transfer and the prevalence of branched units can be increased by using monomers with pendant hydroxyl groups, e.g., 2001MM5112, 2002MI155.

Thietane-containing complexes $M(CO)_5L$ (M = Cr and W, L = thietane), obtained by the displacement of acetonitrile with thietane in the complex $M(CO)_5(NCMe)$ catalyze ring-opening cyclooligomerization of thietane, for example, giving a mixture of products **23** (12S3) and **24** (24S6). The activity of the chromium complex was relatively low, whereas the vanadium compound exhibited significantly higher catalytic activity <1996CB313>. Thiacrown ethers obtained in this way have been reviewed <2000ACR171>.

3.5.3.3 Alkylation, Arylation, and Acylation

Alkylation, arylation, and acylation, at the heteroatom, lead to substitution of an NH or to onium salts. Three-membered ring onium salts are difficult to isolate, and very weakly nucleophilic counterions must be used, such as BF_4.

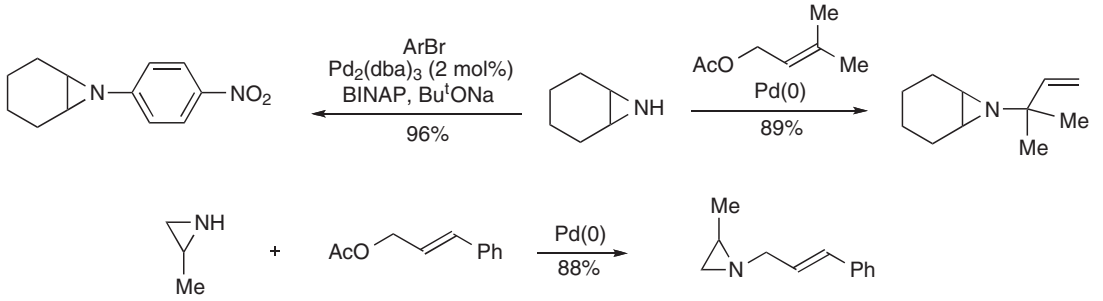
Primary electrophilic attack at N in aziridines is followed by ring transformation of some type or the other. Thus, nitrosation of aziridines **25** (R = Bu, CH_2Ph) in AcOH at 25°C gives the 1-alkyl-1,4-dihydro-3,4-diphenyl-1,2-diazete 2-oxide **26**.



25 **26**

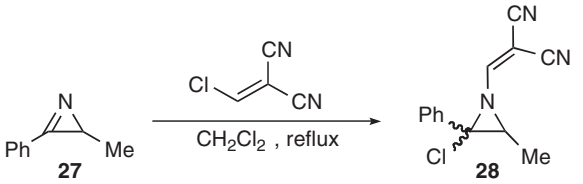
Despite this tendency, examples of alkylation, acylation, sulfonylation, halogenation, silylation, and phosphorylation of aziridines at nitrogen abound. Aziridinium salts can be prepared by further alkylation of the aziridine nitrogen. Aziridines can also be alkylated on nitrogen with epoxides producing -hydroxyamines.

NH-Aziridines will undergo a palladium-catalyzed allylic N-allylation with various allyl acetates in high isolated yields (**Scheme 23**) <2004JA5086, 2005JA17516>. Arylation using a $Pd_2(dba)_3$/BINAP system proceeds best using electron-deficient aryl bromides, and not at all with aryl chlorides <2003JOC2045>.



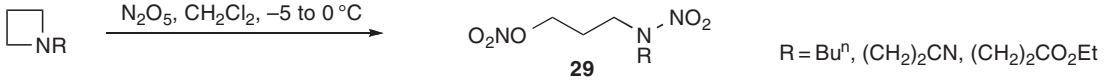
Scheme 23

Azirines react with activated -chloroalkenes, e.g., **27** **28**, leading to N-alkenylated chloroaziridines.



27 **28**

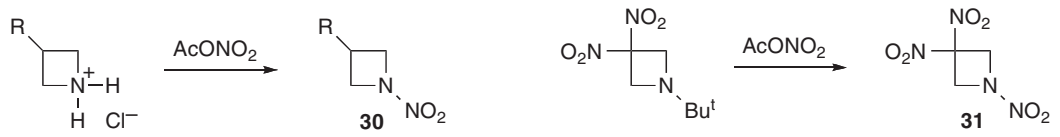
Azetidines are readily alkylated at nitrogen by alkyl halides. The N-chlorination of azetidines occurs smoothly with *N*-chlorosuccinimide or *tert*-butyl hypochlorite. Azetidine forms salts and can be acylated, e.g., with RCOCl, or nitrosated with HNO_2; however, treatment of N-alkylazetidines with dinitrogen pentoxide leads to azetidine ring opening forming 1,3-nitramine nitrates **29** (**Scheme 24**) <1995T5073>.



29

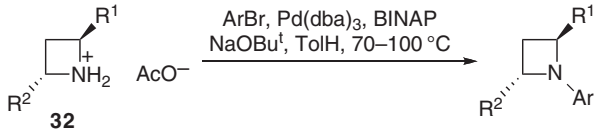
Scheme 24

Nitration of azetidines with acetyl nitrate or, indirectly, via dealkylative nitration using HNO_3 and acetic anhydride furnishes N-nitroazetidines **30** and **31**.



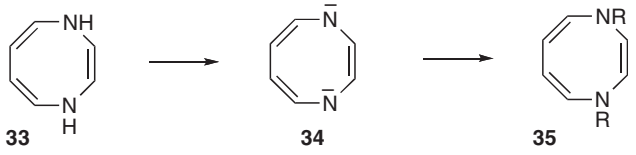
N-Protection of azetidines can be conveniently achieved using benzyl chloroformate and sodium hydroxide in water <2004TL3607> and removal of Cbz protection results from the use of TMSI <2004TL3607> or catalytic hydrogenolysis <2004TL3607>, which last method can also be used for the removal of an *N*--phenylethyl group <2005JOC9028>. An N-Boc group can be removed by HCl in diethyl ether <2004TL3607> or ethyl acetate <2003CPB96>.

Azetidinium acetates **32** are suitable substrates for the synthesis of 1-arylazetidines <2000EJO1815>.



In large rings, the fate of the onium ions depends mostly on the structure and degree of unsaturation of the particular compound, thus onium salts range from completely stable to highly unstable.

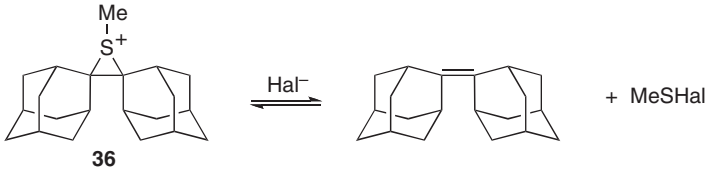
1,4-Dihydro-1,4-diazocine is deprotonated by potassium in liquid ammonia to the dianion which reacts with electrophiles such as methyl iodide, trimethylsilyl chloride, and methyl chloroformate to form the corresponding 1,4-disubstituted derivatives (**33 34 35**).



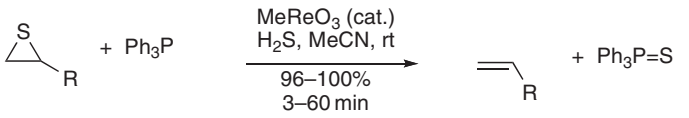
3.5.4 Nucleophilic Attack on Ring Heteroatoms

Nucleophilic attack on ring heteroatoms is found most often in two situations: (1) where the heteroatom in question is sulfur and (2) in small rings with two heteroatoms. Oxaziridines are attacked on oxygen when bulky ring substituents are present, otherwise the nitrogen is attacked, resulting in nitrogen transfer and the formation of a carbonyl compound, while the ring carbon is altogether inert toward nucleophilic attack.

S-Alkylthiiranium salts, e.g., **36**, can be disulfurized by fluoride, chloride, bromide, or most conveniently by iodide ions (**Scheme 25**). Thiiranes themselves are rapidly desulfurized by reaction with Ph_3P and catalytic methyltrioxorhenium in the presence of H_2S at room temperature (**Scheme 26**) <1999CC1003>.

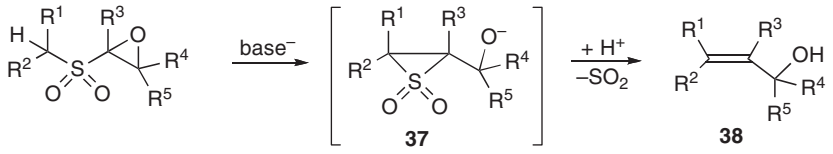


Scheme 25



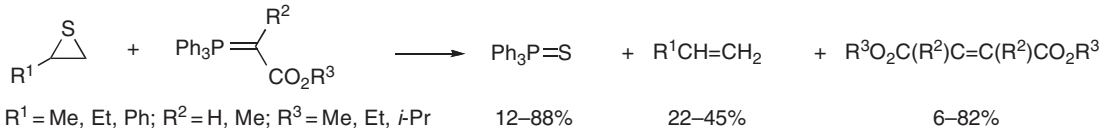
Scheme 26

In a neat combination of thirane *S,S*-dioxide and epoxide chemistry, a RambergBðcklund reaction gives allyl alcohols **38** via thiirane *S,S*-dioxides **37**, the latter losing sulfur dioxide under the reaction conditions (**Scheme 27**) <1997TL3055>.



Scheme 27

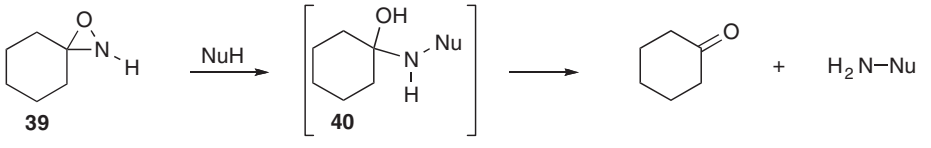
Stable Wittig reagents react with episulfides to afford the corresponding alkenes (**Scheme 28**), probably via a thiocarbonyl intermediate.



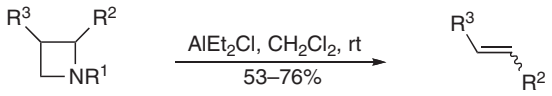
Scheme 28

Epoxides can be deoxygenated to the corresponding alkenes using a number of reagents, including molybdenum hexacarbonyl <2003TL2355>, the low-valent titanium catalyst Cp_2TiCl (readily available by the *in situ* reduction of Cp_2TiCl_2 with activated zinc) <2003TL435>, [tris(3,5-dimethylpyrazolyl)hydridoborato]rhenium oxides <2000OM944>, indium metal <2005JOC4118>, phosphonium anhydrides <1996SL661>, thiourea dioxide <1997TL745>, phosphines <2002T7037, 2004JOC689>, zirconium chloride and sodium iodide <2005TL4107>, and metalsalen complexes <1999TL8747>.

Nucleophiles react with NH or N-acyl oxaziridines at the nitrogen. Much of this chemistry has been carried out with cyclohexanespiro-3-oxaziridine **39**; an intermediate **40** proceeds to cyclohexanone, the result being amination of the nucleophile. Transfers of NH to N-, O-, S-, and C-nucleophiles enable the syntheses of hydrazines, N-amino-peptides, hydroxyamines, sulfenamides, thiooximes, sulfonamides, aziridines, and -amino acids.

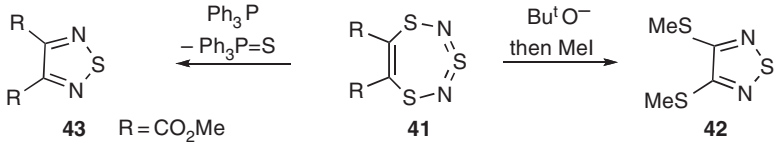


Azetidines having a 4-methoxyphenyl, styryl, or 2-furyl group at C(2) and a benzyl or allyl substituent on nitrogen, when exposed to diethylaluminium chloride, give alkenes, stereoselectively through a fragmentation process (**Scheme 29**) <1999JOC9596>.



Scheme 29

Nucleophiles attack the imide sulfur atom of trithiadiazepines. Trithiadiazepine **41** (R = H) is converted by potassium *tert*-butoxide and iodomethane into 3,4-bis(methylthio)-1,2,5-thiadiazole **42** by a rearrangement in which two of the ring sulfur atoms have become exocyclic; with triphenylphosphine **41** ($R = CO_2Me$) gives dimethyl 1,2,5-thiadiazole-3,4-dicarboxylate **43**.



3.5.5 Nucleophilic Attack on Ring Carbon Atoms

The ring opening of small heterocycles by nucleophilic attack on a carbon adjacent to a heteroatom is exceedingly common. Only in oxaziridines is the ring carbon inert relative to the two ring heteroatoms. In the other three-membered rings, nucleophilic ring opening leads to the corresponding heteroanion or to the XH compound, according to whether the heteroatom is being protonated before or concurrently with the ring opening, respectively. The reaction can be stereospecific in any of these cases. Alternatively, ring opening can occur before the nucleophilic attack, either after protonation of the heteroatom (to give a carbocation) or due to ylide formation. In the latter case the reactions become nonstereospecific or partially stereospecific, depending on the timing of the processes involved.

Protonation or Lewis acid complexation of a heteroatom invites nucleophilic attack, including nucleophilic attack by a nonprotonated molecule. Oligomerization and polymerization are thus often the results of bringing such heterocycles into an acid environment.

3.5.5.1 Reactions of Three-Membered Rings

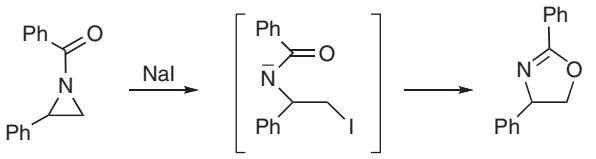
The three-membered rings containing one heteroatom, because of ring strain, are much more reactive than normal ethers, sulfides, and amines. Under basic or neutral conditions ring fission takes place preferentially at the least substituted carbon and is accompanied by inversion, i.e., S_N2 type; under acid conditions these rules do not always apply because of the increasing S_N1 character of the transition state.

The reactions of these heterocyclic systems include those initiated by the following reagents:

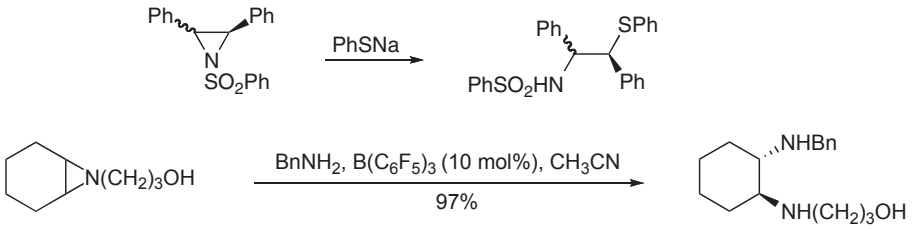
1. Hydroxide ions: oxiranes glycols; aziridines amino alcohols.
2. Amines: oxiranes amino alcohols; aziridines diamines.
3. Hydrogen halides: oxiranes halohydrins; thiiranes mercaptohalides; aziridines halo amines.
4. Grignard reagents: oxiranes alcohols, e.g., $C_2H_4O + RMgBr\ RCH_2CH_2OH$.
5. Catalytic amounts of either a nucleophilic or an electrophilic reagent can induce polymerization; ring fission occurs first, and the ring fission product reacts with additional molecules of the cyclic starting material giving dimers or high polymers, e.g., ($CH_2CH_2ZCH_2CH_2ZCH_2CH_2$). The importance of epoxides in the generation of polyesters is undisputed. The copolymerization between oxiranes and carbon dioxide under the influence of a variety of catalysts has been studied <2004ACR836, 2004AGE6618>. Initiators to induce polymerization include titanium reagents <2004JA15932>; zinc complexes, e.g., <2000AGE4096, 2005JA3031>; fluorenylphosphonium salts <2001MM1518>; chromium complexes; e.g., <2004IC7278, 2005CEJ6298>; and cobalt complexes, e.g., <2003AGE5484, 2006JA1664> among many others.

Thiiranes are easily converted into -chlorothioacetates in reaction with acid chlorides at room temperature in the presence of catalytic amounts of a Lewis acid, the best being $CoCl_2$ <2003SC2321>.

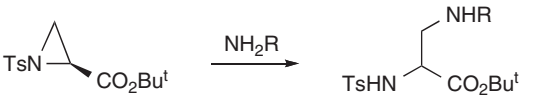
Direct nucleophilic attack at a ring carbon atom of an aziridine is best accomplished when an electron-withdrawing group is present on the nitrogen atom, e.g., <2004T2701> and/or using a Lewis acid catalyst <1996H2473, 2001J(P1)1314>. Examples are shown in **Schemes 30–32** (note attack at the least hindered carbon) <1995TL4955>.



Scheme 30

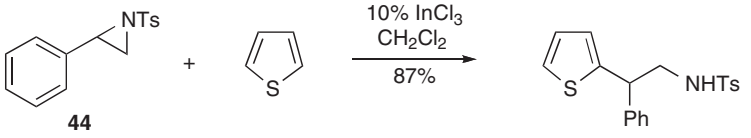


Scheme 31



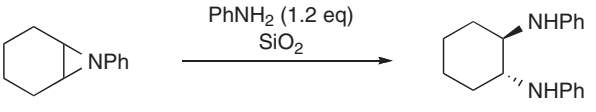
Scheme 32

The reaction of thiophene with the styrene-derived aziridine **44** with $InCl_3$ catalysis involves attack mainly at the more hindered and benzylic carbon, although ca. 10% of product formation derives from terminal attack (**Scheme 33**) <2002TL1565>. Similarly, $In(OTf)_3$ can be used to promote the reaction of **44** with reactive benzenes, with the same regioselectivity <2001TL8067>.



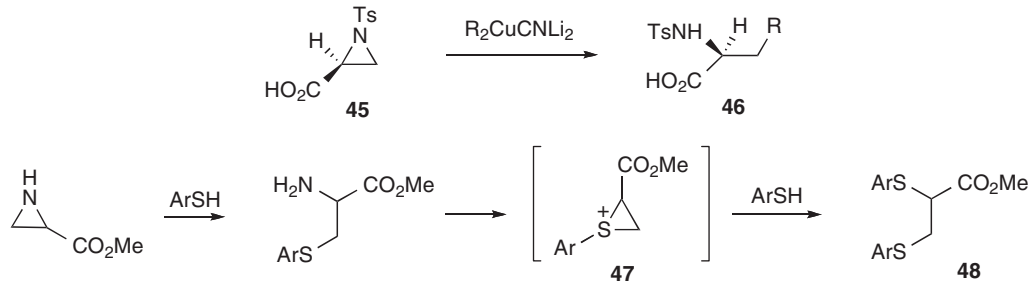
Scheme 33

Silica gel can also be used to encourage nucleophilic ring opening (**Scheme 34**) <2002TL3975>.



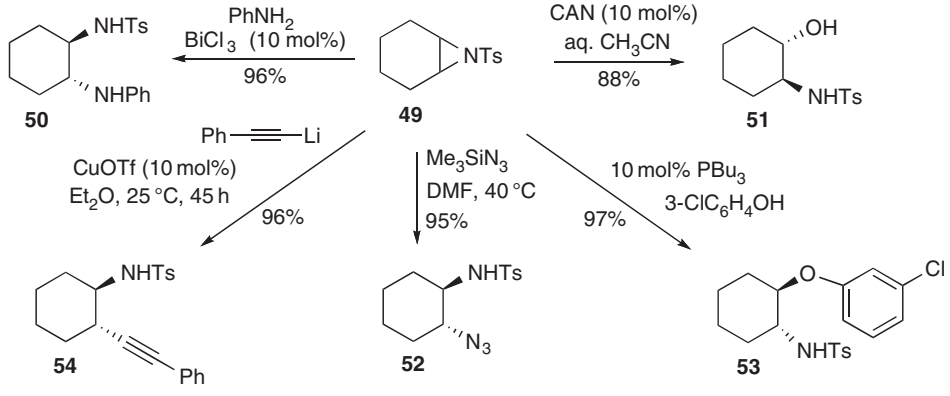
Scheme 34

Aziridine-2-carboxylic acid **45** can be ring opened with higher order cuprates to give the protected amino acid derivatives **46**, corresponding to attack at the less-substituted aziridine carbon <1995TL151>. In an intriguing reaction of the corresponding ester with a thiol, a doubly sulfur-substituted product **48** was obtained via the intermediacy of an episulfonium ion **47** (**Scheme 35**) <2006TL3949>.

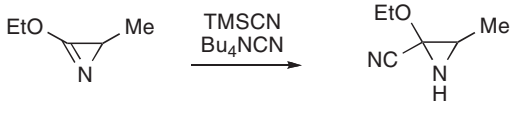


Scheme 35

N-Tosylaziridine **49** reacts smoothly with aniline in the presence of $BiCl_3$ to give the diamine **50** <2003SC547>. Ceric ammonium nitrate (CAN) catalyzes the ring opening of **49** with water to afford the amino alcohol **51** in 88% yield <2003CL82>. Cerium(III) chloride promotes the regioselective ring opening of unsymmetrical *N*-nosyl aziridines at the less-substituted carbon, for example, with azide anion <2002OL343>. However, using trimethylsilyl azide, for example, with **49** to give **52**, no catalyst is required and the reactions proceed in neutral solution <2000JOC1344, 2005EJO4769>. Phosphines can also be used to promote aziridine ring-opening processes, for example, the transformation of **49** into **53** <2002JOC5295>. Reaction of **49** with a lithium acetylide giving **54** is promoted with copper(I) triflate <2004SL1691>.

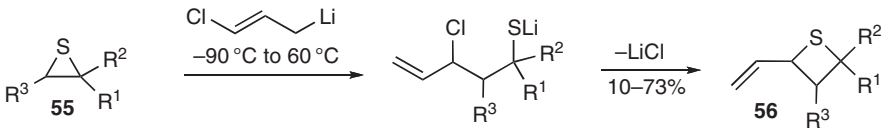


Nucleophilic attack on azirines at the C═N double bond is useful for the preparation of substituted aziridines. The C═N bond is more electrophilic than a normal imine due to the strain of the three-membered ring. Nucleophilic additions to 3-alkoxy- and 3-amino-2*H*-azirines are especially well studied, e.g., **Scheme 36**. Many of these reactions involve assistance by protonation of the nitrogen.

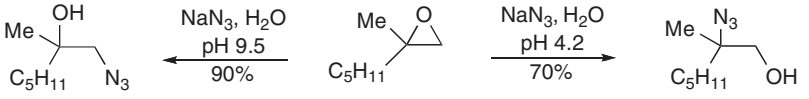


Scheme 36

Alkyl-substituted thiiranes **55** react with 3-chloroallyllithium to give pure 2-vinylthietanes **56** in good yields.



Nucleophilic ring openings are among the most important reactions of oxiranes, driven by (1) the ring strain, (2) the polarization of the CO bonds in the small ring system, and (3) the basicity of the oxirane oxygen. The stereoselectivity of the ring opening of oxiranes is usually completely *anti*. Regioselectivity depends on oxirane structure and reaction conditions: the S_N2 reaction between strong nucleophiles and oxiranes takes place typically at the least substituted carbon atom for steric reasons. In the presence of Br½nsted or Lewis acids (aside from the obvious catalysts and among these one can cite a phosphazircocene catalyst with trimethylsilyl chloride <2003OL2543>; *bis*(chlorodibutyl)tin oxide <2001SL65>; bismuth salts <2005TL8229>; magnesium bromide <2004TL5969>; crown ethers <1998JOC1455>; $TiCl_3(OTf)$ or $TiO(TFA)_2$; anhydrides, e.g., <2002TL1759, 2005TL1601, 2005T3659>; or ionic liquids, e.g., <2004TL2435, 2005JOC4517>), the activation of the epoxide can lead to so-called borderline S_N2 (i.e., bimolecular substitution having considerable S_N1 character in the transition state) or S_N1 processes; in these instances, reactions can occur at the more substituted carbon atom. The difference is nicely illustrated by the change in regiochemistry with pH shown in Scheme 37 <1999JOC6094>.

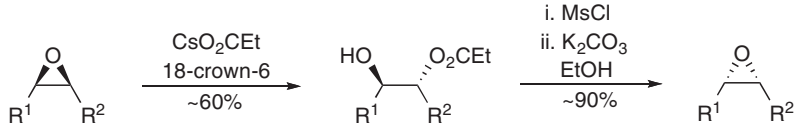


Scheme 37

The ring-opening reaction between epoxides and nucleophiles in its many forms has been of enormous importance in complex molecule synthesis. There are so many instances that only a very small representative sample of relatively simple examples can be shown here.

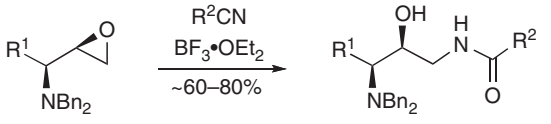
The hydrolytic kinetic resolution of racemic terminal epoxides using metal salen catalysts is one of the premier methods for the formation of enantioenriched oxiranes and/or 1,2-diols, e.g., <1997SCI936, 1998JOC6776, 2000AGE3604, 2002JA1307>.

Scheme 38 shows how the stereochemistry of an epoxide can be inverted <2002TL4111, 2002TL4111>.



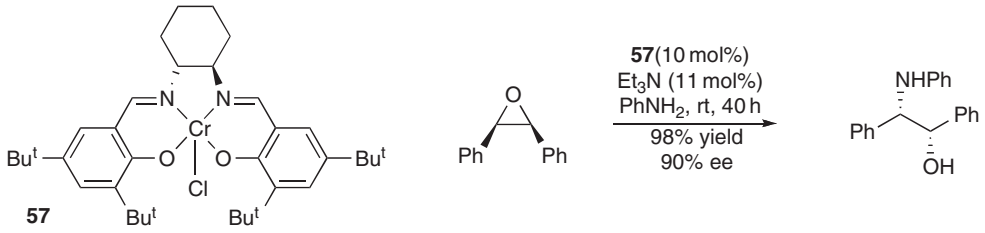
Scheme 38

Nitriles can react with functionalized oxiranes in a regioselective manner in a tandem epoxide-opening Ritter reaction (Scheme 39) <2005JOC7447>.



Scheme 39

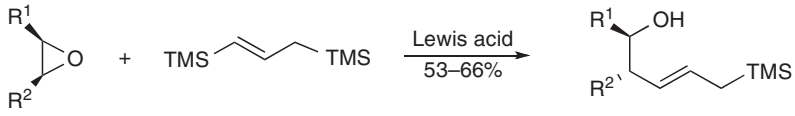
The examples of epoxide ring opening with amines are legend; many salts promote such reactions including lithium *bis*-trifluoromethanesulfonimide <1997TL2027, 2002TL7083>, lithium trifluoromethanesulfonate <1996TL7715>, lithium bromide <2004EJO3597>, stannic trifluoromethanesulfonate <1999JOC287>, cupric trifluoromethanesulfonate <1999JOC287>, zirconium (IV) chloride <2003TL8315>, bismuth trifluoromethanesulfonate <2004CL304, 2004TL49>, calcium trifluoromethanesulfonate <2003T2435> to name but a few. Chiral catalysts can lead to desymmetrization of *meso* epoxides, for example, as shown in Scheme 40 <2004OL2173>. When an optically pure



Scheme 40

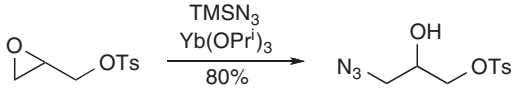
nonsymmetrical 1,2-disubstituted epoxide is treated with a chiral (salen)chromium(III) azide complex, only one approach results in a chiral match; thus, azide is delivered selectively to one position; using this protocol, (1*S*,2*S*)-norpseudoephedrine was synthesized in three steps with 42% overall yield and >99% ee <2001SL1013>.

Epoxides can react smoothly with allylsilane reagents, for example, 1,3-bis-trimethylsilyl-1-propene under Lewis acid catalysis, to generate a highly functionalized alkenols (**Scheme 41**) <1998TL529>.



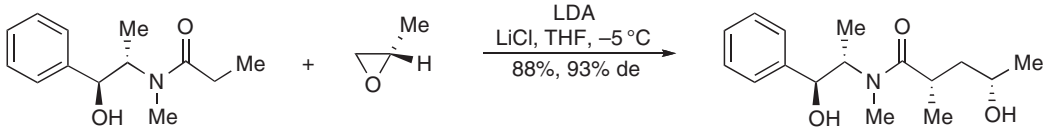
Scheme 41

Azides are excellent nucleophiles for the ring-opening reactions of oxiranes (**Scheme 42**) <1995CC1021>.



Scheme 42

An enormous number of examples of the opening of epoxides with carbon nucleophiles has been described. Indoles and oxiranes react readily under catalysis using indium(III) bromide giving indol-3-yl-CH_2CH_2OH in a simple example <2002JOC5386>. Isocyanides react with epoxides in the presence of gallium(III) chloride to form ,-unsaturated -amino iminolactones <2003OL4991>. Oxazolidinones can be generated from the reactions of terminal epoxides with carbenes <2005OL1983>. The reactions between enolate anions and epoxides have been reviewed <2000T1149>; terminal epoxides react selectively at the terminus: typical examples are the lithium enolates of ketones with epoxides in the presence of $BF_3.Et_2O$ <2003JOC3049>. One lithium enolate example from many is shown in **Scheme 43** <1996JOC2428>.



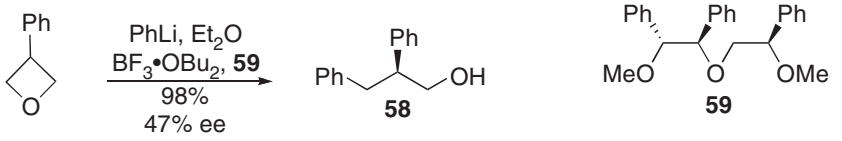
Scheme 43

Reductive ring opening of epoxides is a standard method for the formation of chiral secondary alcohols, as in a recent synthesis of chiral - and -hydroxy amides <2004AGE317>. A number of reagents can be used to accomplish this transformation: nucleophilic hydride reagents <1998JHC865>, hydride reagents in the presence of borane <1997JOC9223>, transfer hydrogenolysis using ammonium formate and palladium catalysis <1995SC2267, 1995JOC4922>, microencapsulated Pd(0) nanoparticles <2003OL4665>, and many others.

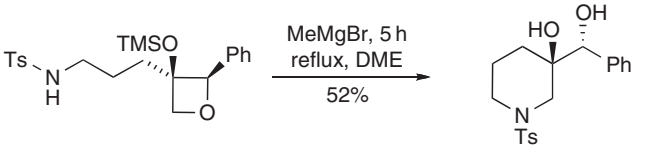
3.5.5.2 Reactions of Four-Membered Rings

The properties of azetidine, oxetane, and thietane are intermediate between those of aliphatic amines, ethers, and sulfides on the one hand and those of the corresponding three-membered ring systems on the other. Ring fission occurs quite readily. Oxetanes are generally much more stable to nucleophilic attack than the more strained three-membered ring oxiranes; however, activation of the oxygen atom by a Lewis acid does allow nucleophilic ring-opening reactions, for example, oxetane reacts with Grignard reagents to give alcohols of type $R(CH_2)_3OH$ and with hydrogen bromide to give 1,3-dibromopropane. Hydrogen halides convert azetidine into -halo amines.

Lewis acid-catalyzed oxetane ring opening by carbon nucleophiles using chiral ligands, e.g., **59**, enables ring opening of 3-phenyloxetane with phenyllithium to form the chiral alcohol **58** in 47% ee <1996TA2483, 1997T10699>.

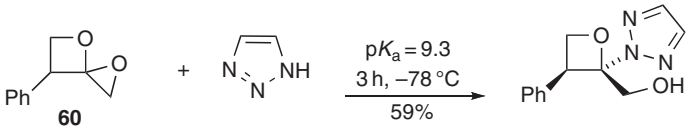


The intermolecular ring opening of oxetanes by nitrogen nucleophiles has been widely reported. These are usually Lewis acid catalyzed and are highly regiospecific, with the nucleophile attacking the least substituted -carbon of the oxetane. In an intramolecular sense, nitrogen-containing rings of various sizes can be formed, e.g., **Scheme 44** <1996JOC7642>.

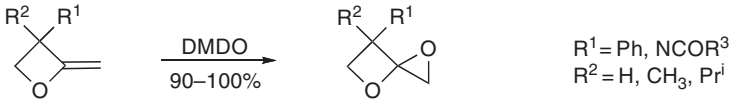


Scheme 44

A nice example illustrating the different reactivity of the three- and four-membered oxygen-containing heterocycles is the reaction of 1,5-dioxaspiro[3.2]hexane **60** with 1,2,3-triazole (**Scheme 45**) <1999OL825, 2003JOC1480>. Such intriguing bicycles can be obtained from methylene-oxetanes using dimethyldioxirane, e.g., **Scheme 46** <1998JOC6098>.



Scheme 45

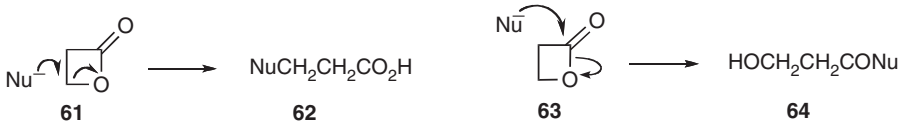


Scheme 46

3.5.5.3 Reactions of Carbonyl Derivatives of Four-Membered Rings

2-Oxetanones (-lactones) are readily attacked by nucleophilic reagents. Reactions occur by:

1. Alkyloxygen fission (**61** **62**), e.g., propiolactone with NaOAc-H_2O yields **62** (Nu = OAc), with MeOH-NaOMe it forms **62** (Nu = OMe).

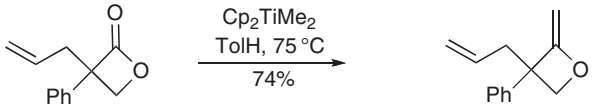


61 **62** **63** **64**

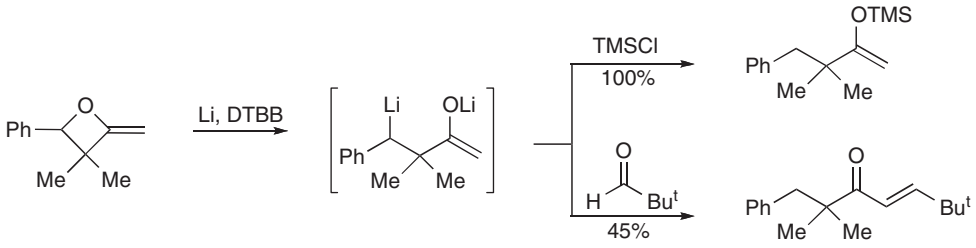
2. Acyloxygen fission (**63** **64**), e.g., propiolactone reacts with MeOH, H^+ to give **64** (Nu = OMe). A *Pseudomonas* sp. lipase-promoted asymmetric transesterification reaction allows kinetic resolution of racemic 2-oxetanones <2000J(PI)71>.

Oxetanones can be converted into methylene-oxetanes using dimethyltitanocene (**Scheme 47**) <1996JOC7248, 1999JOC7074>. Methylene-oxetanes undergo a range of useful transformations; for example, ring opening by reaction with a nucleophile, followed by a reaction of the enolate, thus formed with an electrophile, e.g., 1998JOC6782, 1999TL7051, 2000TL1855. Reductive ring opening with lithium and 4,4-di-*tert*-butylbiphenyl (DTBB) generates dianions which can be trapped (**Scheme 48**) <2000TL1855>.

Methylene-substituted 2-oxetanones, and in particular diketene, have attracted a vast amount of work: **Schemes 49**

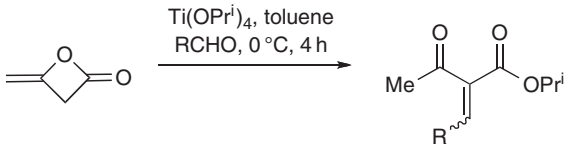


Scheme 47

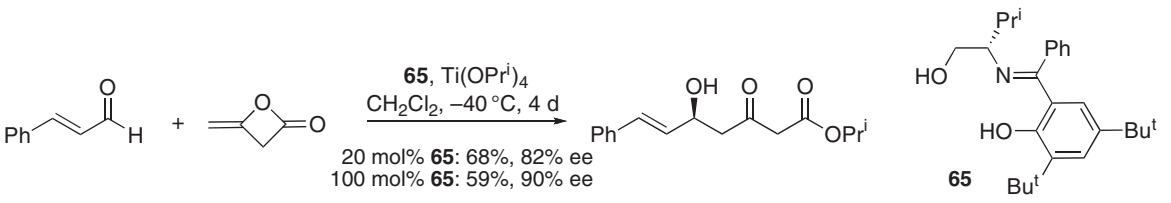


Scheme 48

(in a Knoevenagel reaction) <2004T6777> and **50** (in an enantioselective carboncarbon bond formation) <1998SL601> are a couple of examples from many.



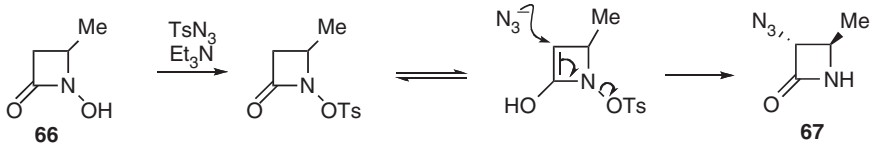
Scheme 49



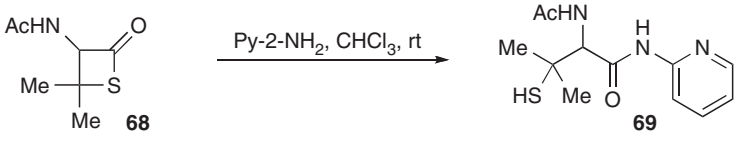
Scheme 50

On account of its relevance to penicillin chemistry, a great deal of work has been carried out on -lactams, but only a flavor of that chemistry can be included here. The reaction of 2-azetidinones (-lactams) with nucleophilic reagents is accompanied by acylnitrogen fission, as is normal for amides (cf. **63** **64**), e.g., propiolactam yields -alanine ($H_2NCH_2CH_2CO_2H$) on hydrolysis.

Various nucleophilic attacks at C(3) and C(4) of -lactams have been employed to introduce desired functionalities. Nucleophilic displacement of a halogen at C(3) by nucleophiles, for example, potassium phthalimide, can be performed. The -azidation of 1-hydroxy-2-azetidinones, for example, **66**, with arenesulfonyl azides in the presence of triethylamine affords 3-azido-2-azetidinones **67** via O-tosylation and S_N2-type of displacement of the tosyloxy group on an enol tautomer



Simple <2000MRC468> and more complex <2000BML1347, 2001T825, 2001T7173, 2002BMC2303> thietan-2-ones undergo acylsulfur cleavage with amines; for example, **68** gives **69**.



3.5.5.4 Large Rings

Nucleophilic attack on ring atoms of large heterocycles is largely confined to saturated systems, saturated parts of partially unsaturated systems, and carbonyl functions and the like. These reactions are not fundamentally different from those of the corresponding acyclic systems, except for transannular reactions.

Transannular nucleophilic attack on ring atoms is best known in systems with seven or more ring members. For example, nucleophilic attack by the ring nitrogen on suitably substituted ring carbons in the 3- or 4-position in azepine derivatives. However, transannular nucleophilic attack can be found even in four-membered heterocycles. The nitrogen of *N-tert*-butyl-3-chloroazetidine is, because of the puckered conformation, close enough to the 3-carbon to displace chloride giving an azabicyclobutanonium ion which, in turn, is opened by chloride generating *N-tert*-butyl-2-chloromethylaziridine.

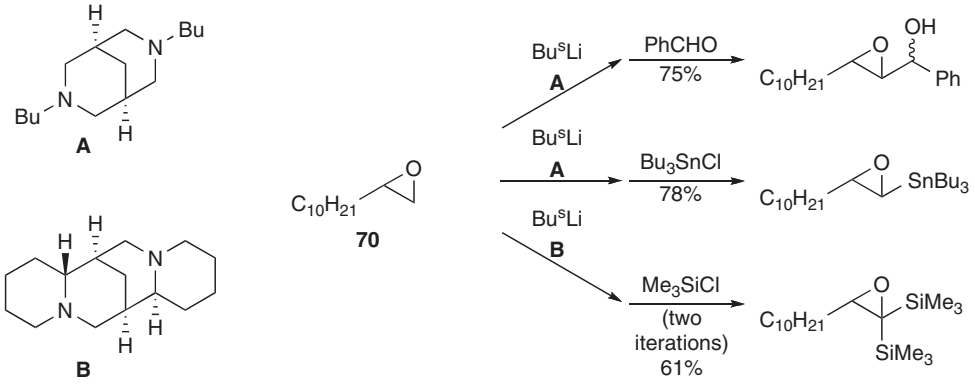
In systems of appropriate geometry, nucleophiles within a side chain may be well oriented for attack on ring atoms. For example, an aminomethyl group at the 5-position of a dibenzazepin-2-one attacks the carbonyl group. Such reactions should be possible in rings of any size.

Apparent nucleophilic attack on large, fully unsaturated rings may occur by way of attack on a valence tautomer, such as the reaction of oxepin with azide ion. Attack on the oxanorcaradiene valence tautomer leads to ring opening of the three-membered ring and formation of 5-azido-6-hydroxy-1,3-cyclohexadiene.

3.5.6 Base Attack on Protons Attached to Ring Atoms

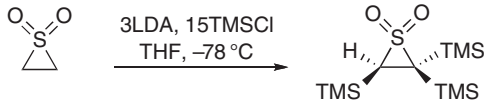
The formation of anions by proton abstraction leads to highly diversified types of reactions in small and large heterocycles. However, a few rules do generally apply. In the absence of complicating substituents, nitrogen anions can often be formed from small and large heterocycles, and subsequent N-alkylation, N-acylation, etc., can be achieved. The N-anions of large rings are usually unexceptional (barring transannular reaction). N-Anions of unsaturated large heterocycles are obtained with difficulty, but they are synthetically useful in the azepine field.

Proton abstraction from ring carbons of small and large heterocycles often leads to ring opening. Oxiranes, for example, are sometimes converted into carbenes under conditions under which a carbanion is formed but there are significant exceptions, such as the synthetically useful 2-triphenylsilyl-2-lithiooxirane. If the oxiranyl anion is sufficiently stabilized (by an electron-withdrawing group, for example), a carbanion can be alkylated by electrophiles without ring opening <1998SL337, 2002S1625, 2005SL1359>, and it is even possible to trap lithiated nonstabilized epoxides with electrophiles <2001OL461, 2002TL7895, 2004OL4187>. An example is the lithiation of terminal epoxides **70** with *sec*-butyllithium assisted by diamine ligands, such as dibutylbispidine **A** or ()-sparteine **B**. The oxiranyl anions thus formed add smoothly to aldehydes or can be used for stannylation or silylation (**Scheme 51**) <2004SL1610>.

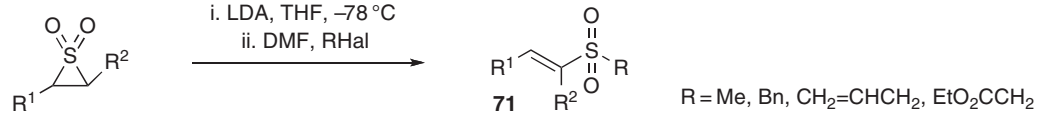


Scheme 51

Thiirane *S*,*S*-dioxides with LDA followed by TMSCl at 78°C give, depending on the structure of the starting material, mono-, bis-, or tris-trimethylsilylthiirane *S*,*S*-dioxides, e.g., **Scheme 52** <1997J(P1)323>. However, ring opening occurs with alkyl halides and vinyl sulfones **71** are formed (**Scheme 53**).

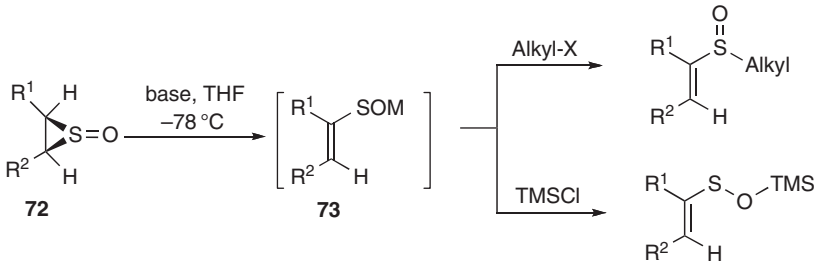


Scheme 52



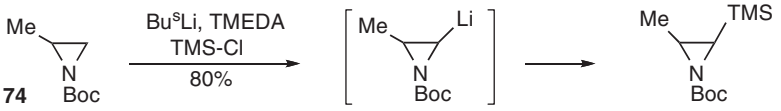
Scheme 53

Ring opening is also observed when thiirane *S*-oxides **72** react with strong bases (e.g., LDA, $MN(TMS)_2$ (M = Li, Na, K), RLi (R = *n*-Bu, Me, Ph, *t*-Bu) to give (*E*)-1-alkenesulfeneate anions **73** in good yields, which can be trapped with electrophiles (**Scheme 54**), e.g., <1995JA184, 1996JOC4232, 1998CJC213, 1998SL96>.



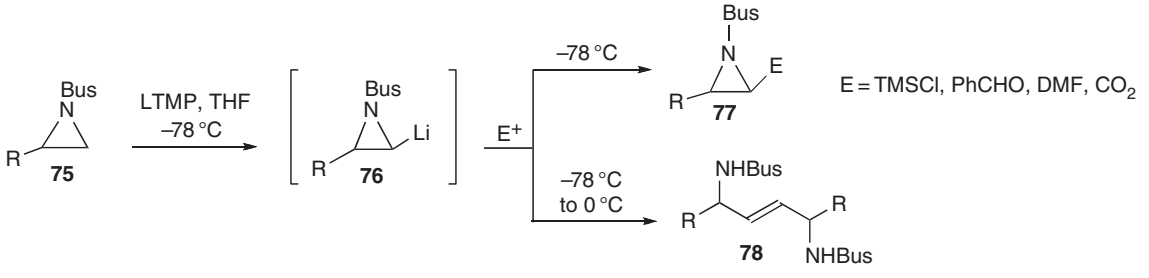
Scheme 54

Carbanions at C(2) of aziridines can be generated by deprotonation or by exchange, e.g., tinlithium. A major problem with the deprotonation approach is the necessity for a strong base that may also react by a nucleophilic ring-opening process; however, *N*-(*tert*-butoxycarbonyl)aziridines **74** can be deprotonated with *s*-BuLi, TMEDA, as shown in **Scheme 55**.

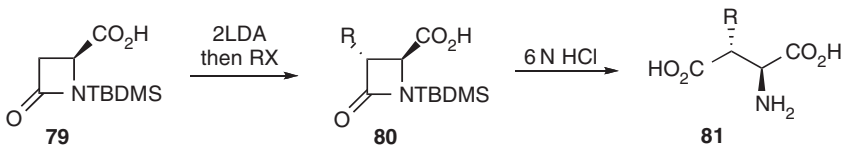


Scheme 55

Similarly, regio- and stereoselective deprotonation of N-Bus (Bus = *t*-butylsulfonyl)-protected terminal aziridines **75** with lithium 2,2,6,6-tetramethylpiperidide proceeds smoothly to generate a nonstabilized aziridinyl anion **76** that undergoes *in situ* or external electrophile trapping to give *trans*-disubstituted aziridines **77** <2005OL1153>. Note that allowing the temperature to rise results in dimers of the type **78**, which is taken as evidence of the carbenoid character of the lithiated species **76**. Several other complex outcomes can follow for lithiated aziridines generated by aziridine deprotonation using strong bases, including transannular CH insertion, insertion into an adjacent -CH bond to produce an allylic amine, insertion into an organolithium reagent (reductive alkylation), and electrophilic trapping, as illustrated by the formation of **77**.

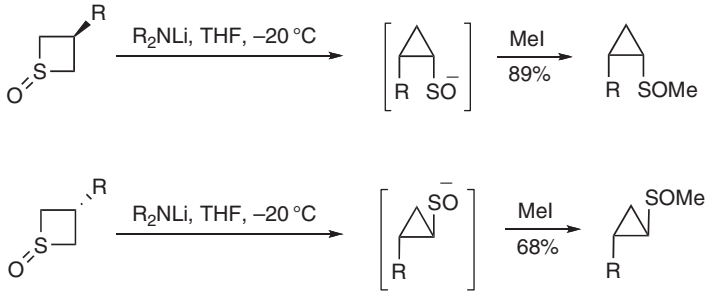


Various substitutions of hydrogen at positions 3 and 4 in -lactams can be performed with electrophilic reagents. The 3-position is activated by the carbonyl group. Alkylation at the 3-position is readily executed via the enolate with alkyl halides, aldehydes, ketones, carbon dioxide, etc. A carboxyl group at C(4) as in **79** does not interfere, the dilithium salt being alkylated at C(3) with excellent stereocontrol, giving the *trans*-disubstituted lactams **80**. Hydrolysis leads to -alkyl aspartic acids **81**.



79 80 81

3-Alkyl- and 2,3-dialkyl-thietane 1-oxides, upon deprotonation to the sulfinyl group, undergo stereospecific ring contraction giving cyclopropylsulfenate anions, which react with methyl iodide to give the corresponding cyclopropyl methyl sulfoxides (**Scheme 56**). Deprotonation, achieved with lithium cyclohexylisopropylamide, occurs at the -proton *syn* to the sulfinyl oxygen. Rearrangement occurs stereospecifically with respect to configuration at sulfur, at the migrating residue (retention), and at the migration terminus (inversion).



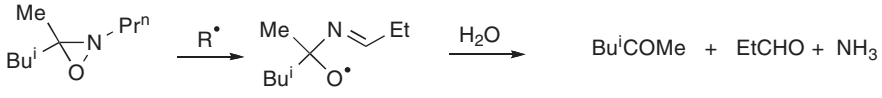
Scheme 56

Large heterocyclic systems offer a greater variety for ring opening, such as the abstraction of protons from not only the 2-position but also the 3-position, leading to ring opening by -elimination and the formation of -unsaturated compounds, such as 6-hydroxy-1-hexene from oxepane.

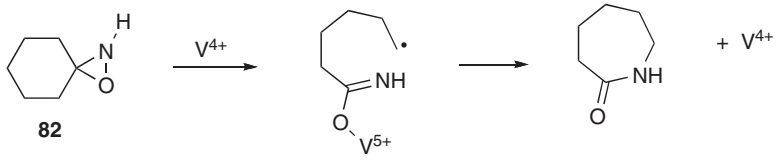
3.5.7 Attack by Radicals or Electron-Deficient Species. Oxidation and Reduction (see also Section 3.5.4)

3.5.7.1 Reactions with Radicals and Carbenes

Little is known about the attack of radicals on small and large heterocycles. Hydrogen abstraction from the heteroatom of small rings leads to ring opening and, in the case of thiiranes, to removal of the sulfur (cf. Section 3.5.1.4 above). Abstraction of H exocyclic and to nitrogen in oxaziranes leads to NO cleavage (**Scheme 57**), and the reaction of vanadium(IV) with the oxygen of 1-oxa-2-azaspiro[2.5]octane **82** gives NO cleavage and ring expansion to caprolactam (**Scheme 58**).



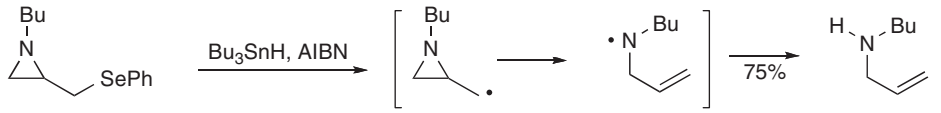
Scheme 57



82

Scheme 58

The formation of a radical on a carbon adjacent to an aziridine ring by cleavage of a carbonbromine or carbonselenium bond using Bu_3SnH, AIBN causes ring opening in much the same fashion as a cyclopropylcarbinyl radical, as shown in Scheme 59.



Scheme 59

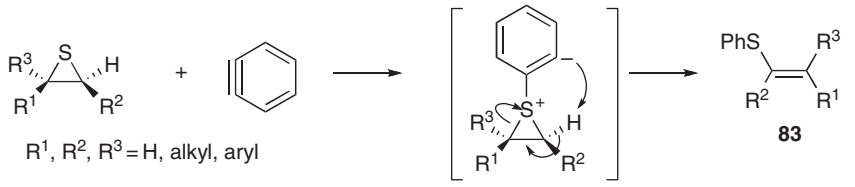
Thiiranes are desulfurized by radicals, singlet carbenes, and electrolysis.

Azetidine derivatives, which are less strained, are less sensitive and removal of a hydrogen in the -position of a substituent on nitrogen does not necessarily lead to ring opening. Thietane rings are opened by radicals attacking at S, while the less strained thiolanes are attacked by hydrogen abstraction at C(2). In thietane 1,1-dioxides, radicals abstract a hydrogen from the 3-position to give a cyclic radical. Producing radicals exocyclic in the -position of *N*-substituents of azetidin-2-ones does not result in ring opening.

Saturated large rings can form nitrogen radicals by H abstraction from N, or abstraction may occur in the - or -positions in non-nitrogen systems. Oxepane gives the radical in the 2-position, with subsequent cleavage and reclosure of the intermediate carbenoid to cyclohexanol. In unsaturated large systems, a variety of reactions, unexceptional in their nature, are found. Some azepines can be brominated by *N*-bromosuccinimide; others decompose under similar conditions.

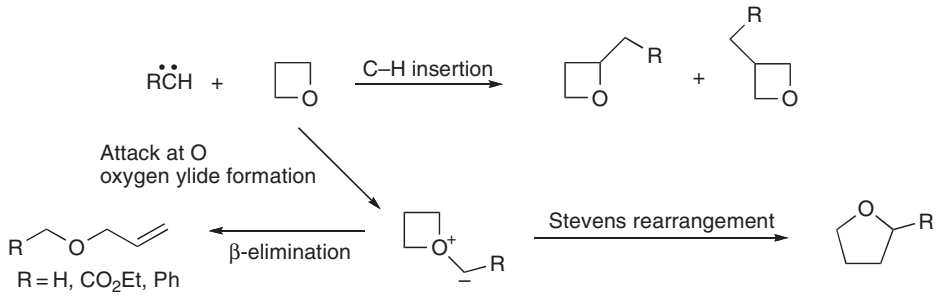
Electron-deficient species can attack heteroatoms to form ylides, which then undergo further conversions. Thus, treatment of thiiranes with a substituted carbene often gives the corresponding alkenes in good yields via electrophilic attack by carbene on the sulfur atom.

Thiiranes react with benzyne in an efficient synthesis of phenyl vinyl sulfides **83**. The reaction is stereospecific, thus producing *cis*-(phenylthio)stilbene from *cis*-2,3-diphenylthiirane and *trans*-(phenylthio)stilbene from *trans*-2,3-diphenylthiirane (Scheme 60).



Scheme 60

The reaction of oxetane with carbenes follows two major pathways: carbonhydrogen insertion or the formation of an oxygen ylide by reaction of the carbene and the oxetane oxygen. The oxygen ylide can produce a tetrahydrofuran by a Wittig rearrangement or generate an allyl ether by an intermolecular -elimination process (Scheme 61).

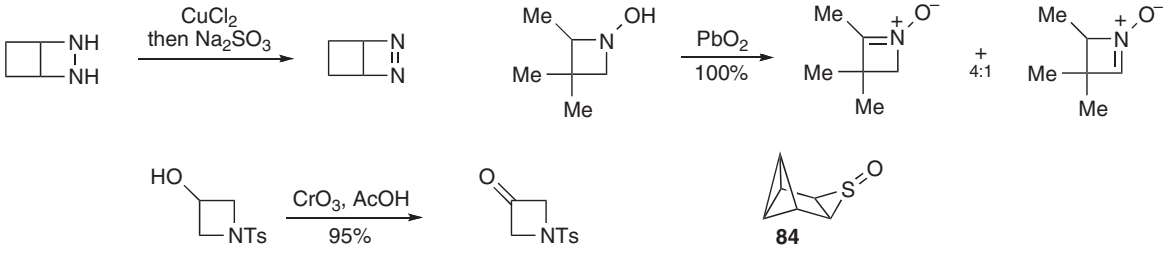


Scheme 61

Thietane reacts with bis(methoxycarbonyl)carbene to give a S^+C ylide which rearranges to 2,2-bis(methoxycarbonyl) thiolane. *N*-Ethoxycarbonylazepine however, is attacked by dichlorocarbene at the C═C double bonds, with formation of the *trans* tris-homo compound.

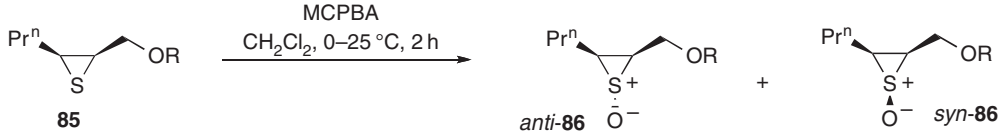
3.5.7.2 Oxidation

Oxidation reactions of small and large heterocycles sometimes have little in common with their open-chain analogues. Oxidations of small heterocycles include (1) dehydrogenation leading to the formation of ring C═C, C═N, or N═N double bonds; (2) oxidation of functional groups; and (3) oxidation at the heteroatom, which is typical for sulfur-containing systems. Examples, illustrating items (1) and (2), are shown in **Scheme 62**.

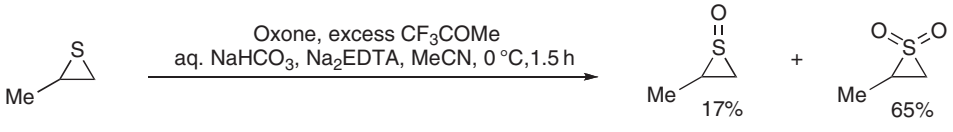


Scheme 62

The isolation of thiirane *S*-oxides prepared by oxidation of the corresponding thiiranes can be problematic. Strained fused-ring thiiranes can be successfully oxidized to thiirane oxides (e.g., **84**) with MCPBA or $NaIO_4$ under carefully controlled conditions. Oxidation of thiiranes **85** with MCPBA, in dichloromethane at 025°C, gives a mixture of *anti*- and *syn*-**86**. The stable *anti*-**86** are isolated in satisfactory yields <1997PS223>.

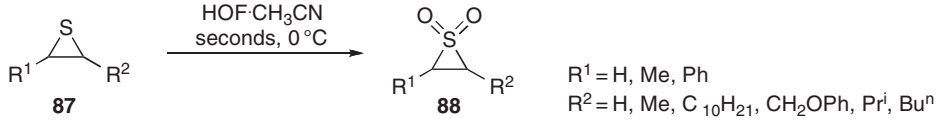


Thiirane *S*,*S*-dioxides are quite unstable and are difficult compounds to make. The first stable thiirane *S*,*S*-dioxide was synthesized by oxidation of a thiirane using a mixture of Oxone®/trifluoroacetone (Oxone® = $2KHSO_5KHSO_4K_2SO_4$) (**Scheme 63**) <1997TL5873>.



Scheme 63

Oxidation of thiiranes **87** to *S*,*S*-dioxides **88** can be carried out using $HOF{\cdot}CH_3CN$ under very mild conditions, in a few seconds (**Scheme 64**) <2006OL1213>.

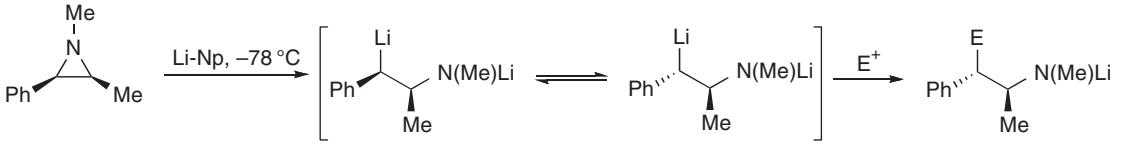


Scheme 64

An efficient and easy method for oxidation of thietane to thietane *S*-oxide uses nitric acid in the presence of P_2O_5 supported on silica gel, under solvent-free conditions <2005TL5503>; the use of 1-butyl-4-aza-1-azoniabicyclo[2.2.2] octane dichromate (BAAOD) in refluxing MeCN is also very efficient for this transformation <2003PS2441>.

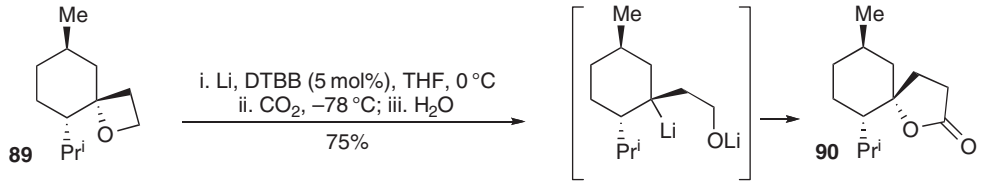
3.5.7.3 Reduction (see also Section 3.5.5)

Oxiranes and aziridines are reduced to alcohols and amines, respectively, for example, by Ni, H_2; Zn, NH_4Cl; P_4, I_2; Al-Hg; Na, NH_3; Li, $EtNH_2$. Cleavage of aziridines with lithium naphthalenide provides synthetically useful dianions as shown in **Scheme 65**.



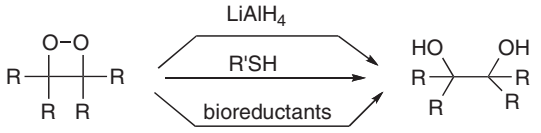
Scheme 65

Using lithium and 4-4-di-*tert*-butyldiphenyl (DTBB) as the electron carrier allows reductive ring opening of oxetanes <1997TA2633>. The intermediate lithium dianion can be reacted with a range of electrophiles (e.g., D_2O, *t*-BuCHO, PhCHO, Me_2CO, CO_2). An interesting example is shown in **Scheme 66**, where the chiral oxetane **89** leads to the spirolactone **90**. Thietanes are also cleaved by these reducing conditions, the ring-opened dianion reacting in the same way with electrophiles <1997T5563, 2003PAC1453>.



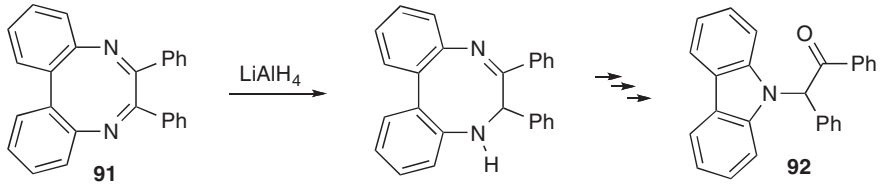
Scheme 66

1,2-Dioxetanes are readily reduced to 1,2-diols (**Scheme 67**) by lithium aluminum hydride, thiols, and biologically important reductants such as ascorbic acid, tocopherol, dihydronicotinamide adenine dinucleotide (NADH), and riboflavin adenosine diphosphate ($FADH_2$).



Scheme 67

Lithium aluminum hydride reduction of 6,7-diphenyldibenzo[*e*,*g*][1,4]diazocine **91** affords a ring-contracted product **92**.



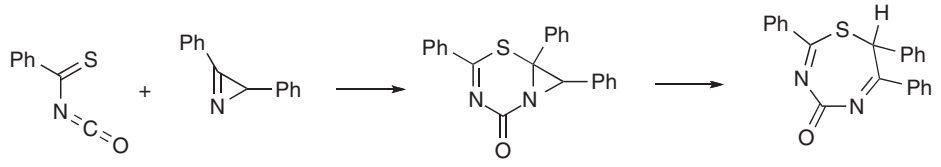
3.5.8 Reactions with Cyclic Transition States

Concerted cycloadditions are observed with heterocycles of all ring sizes. The heterocycles can react directly, or via a valence tautomer, and they can utilize all or just a part of the unsaturated moieties in their rings. With three-membered rings, ylides are common reactive valence tautomers. Open-chain 4-systems are observed as intermediates with four-membered rings, and bicyclic valence tautomers are commonly reactive species in additions by large rings. Very often these reactive valence tautomers are formed under orbital symmetry control, by both thermal and photochemical routes.

3.5.8.1 [2 + 4] Cycloadditions

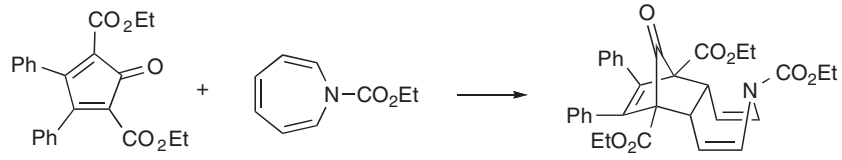
3.5.8.1.1 Heterocycles as dienophiles

Cycloaddition reactions of the C=N bond of azirines are common, e.g., Scheme 68. Azirines can also participate in [4 + 2] cycloadditions with cyclopentadienones, isobenzofurans, triazines, and tetrazines.



Scheme 68

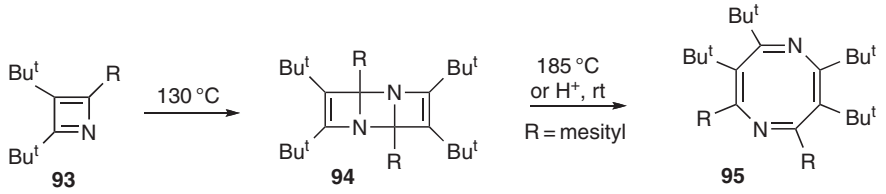
The participation of a single double bond of a heterocycle is found in additions of thietes. Azepines and nonaromatic heteronins react in this mode, especially with electron-deficient dienes (Scheme 69).



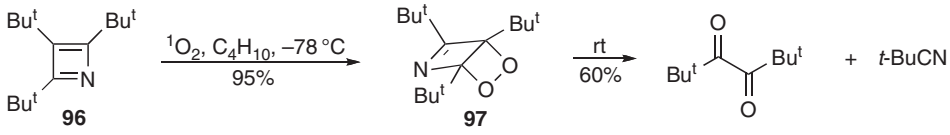
Scheme 69

3.5.8.1.2 Heterocycles as dienes

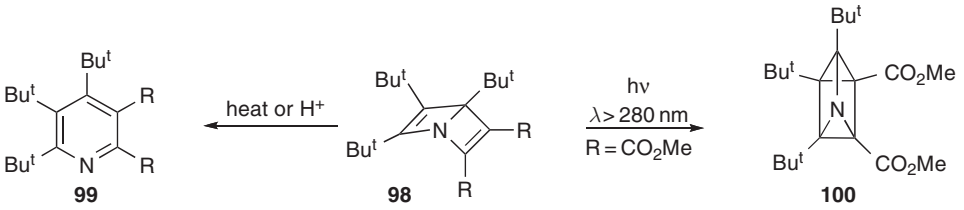
2,3-Di-*tert*-butyl-4-mesitylazete **93** dimerizes at 130 °C to **94**, while further heating at 185 °C affords 1,5-diazocin **95**.



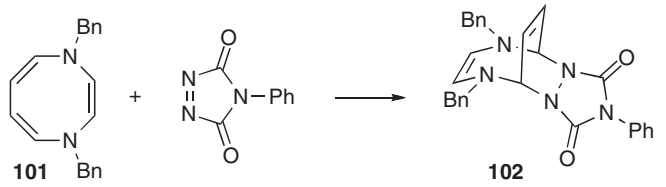
Kinetically stabilized azetes also show a high tendency for cycloaddition with a variety of other reagents. Cycloaddition of **96** with singlet oxygen produced an isolable dioxetan adduct **97**, which decomposes at 25 °C into *tert*-butyl cyanide and a 1,2-dione.



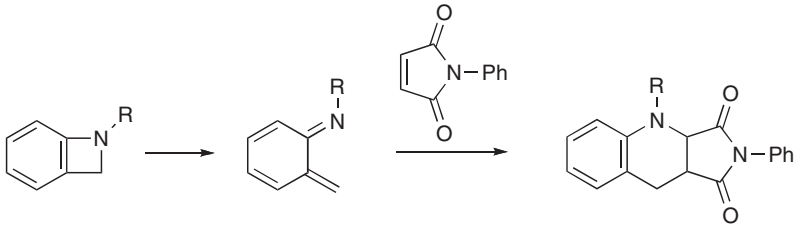
The cycloaddition potential of compound **96** is also demonstrated by its reaction with alkynes leading to isolable Dewar pyridines **98**. The latter were rearranged thermally or by acid catalysis into pyridines **99**. Irradiation of **98** leads to the azaprismane derivative **100**.



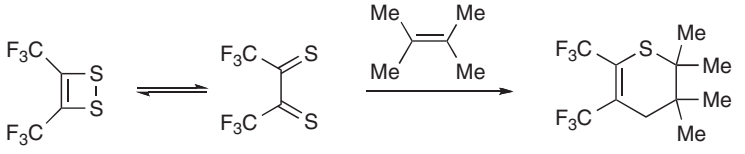
Nonaromatic 1,4-dihydro-1,4-diazocine derivatives e.g. **101** react readily as 1,3-dienes with *N*-phenyltriazolinedione, affording DielsAlder adducts e.g. **102**. 1,4-Oxazocine derivatives behave similarly.



Diene moieties, reactive in [2 + 4] additions, can be formed from benzazetines by ring opening to azaxylylenes (**Scheme 70**). 3,4-Bis(trifluoromethyl)-1,2-dithietene is in equilibrium with hexafluorobutane-2,3-dithione, which adds alkenes to form 2,3-bis(trifluoromethyl)-1,4-dithiins (**Scheme 71**).



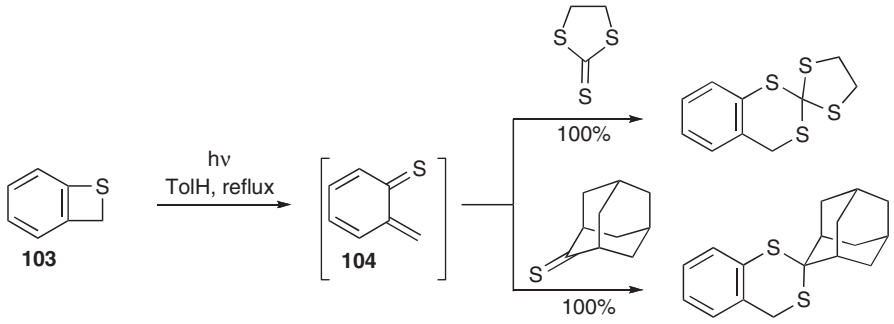
Scheme 70



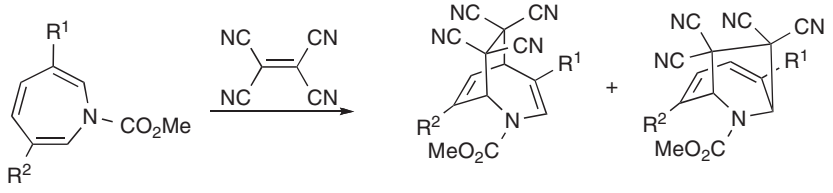
Scheme 71

The four-membered ring of 2*H*-benzo[*b*]thiete **103** can readily undergo retro-[2 + 2] ring opening under thermal or photochemical conditions forming an *ortho*-thiobenzoquinone methide **104**. This highly reactive 8-electron species can participate in cycloaddition reactions with a variety of dienophiles; two examples are shown in **Scheme 72** <1997LA1603>.

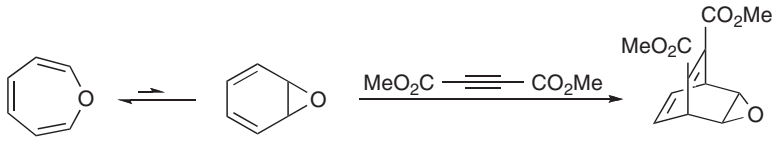
Systems with more than two conjugated double bonds can react by [6 + 2] processes, which in azepines can compete with the [4 + 2] reaction (**Scheme 73**). Oxepins prefer to react as 4-components, through their oxanorcaradiene isomer, in which the 4-system is nearly planar (**Scheme 74**). Thiepins behave similarly. Nonaromatic heteronins also react in orbital symmetry-controlled [4 + 2] and [8 + 2] cycloadditions.



Scheme 72



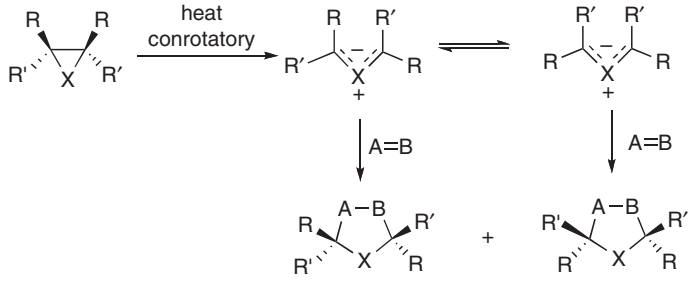
Scheme 73



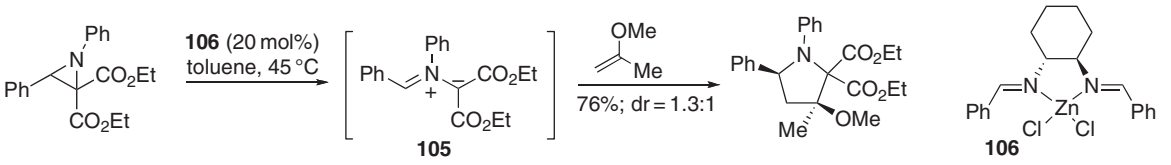
Scheme 74

3.5.8.2 1,3-Dipolar Cycloadditions

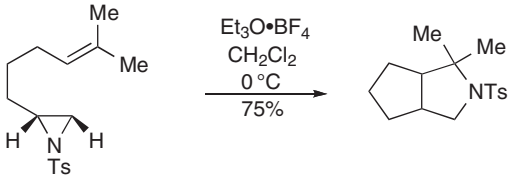
1,3-Dipolar cycloadditions in which the heterocycle provides the 1,3-dipole are common with three-membered rings, which can provide ylide intermediates. Ylide formation is usually orbital symmetry controlled and can be achieved by thermolysis or photolysis with the expected stereochemical consequences. Rotation about one of the ylide CX bonds results in loss of the original stereochemistry. These interconversions are often slow compared to the cycloaddition reactions of the ylides, so that partial stereospecificity is observed. **Scheme 75** shows a generalized scheme and **Scheme 76** gives a typical process showing the role of electron-withdrawing substituents to stabilize the azomethine ylide **105** and thus facilitate the ring opening <2004JA2294>. Lewis acid catalysis is often used and the intramolecular example in **Scheme 77** shows the use of Et_3OBF_4 <2004TL5011>.



Scheme 75

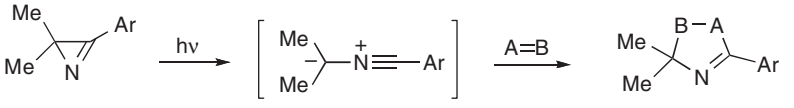


Scheme 76

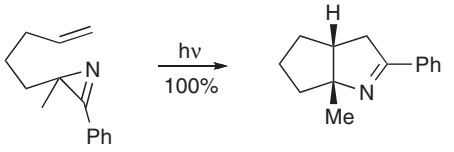


Scheme 77

Diaziridines behave similarly. Azirines produce nitrile ylides upon photolysis (**Scheme 78**). The intramolecular version of this reaction is also possible (**Scheme 79**).

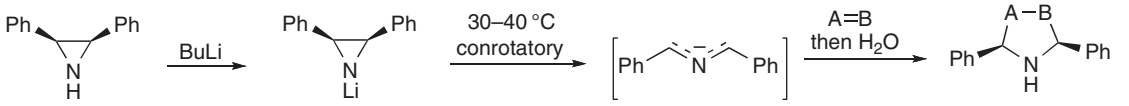


Scheme 78



Scheme 79

Heating N-lithioaziridines provides 2-azaallyl anions, which undergo concerted cycloaddition reactions with certain alkenes and other anionophiles (**Scheme 80**).

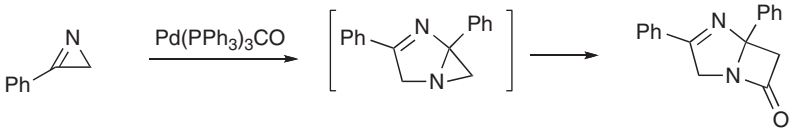


Scheme 80

Heterocyclic systems of all sizes, as long as they are unsaturated, can serve as dipolarophiles and add to external 1,3-dipoles. Examples involving small rings are not numerous. Thiirene oxides add 1,3-dipoles, such as diazomethane, with subsequent loss of the sulfur moiety. As one would expect, unsaturated large heterocyclic molecules readily provide the two-atom component for 1,3-dipolar cycloadditions, e.g., azepines and thiepins.

3.5.9 Reactivity of Transition Metal Complexes

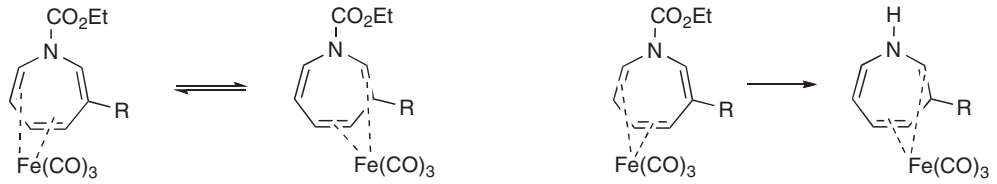
Metal complexes of heterocyclic compounds display reactivities changed greatly from those of the uncomplexed parent systems. All of the -electron system(s) of the parent heterocycle can be tied up in the complex formation, or part can be left to take part in alkenic reactions. The system may be greatly stabilized in the complex, so that reactions, on a heteroatom, for example, can be performed which the parent compound itself would not survive. Orbital energy levels may be split and symmetries changed, allowing hitherto forbidden reactions to occur. In short, a multitude of new reaction modes can be made possible by using complexes: dimerization of azirines with a palladium catalyst serves as a typical example (Scheme 81). A variety of other insertion reactions, dimerizations, intramolecular cyclizations, and intermolecular addition reactions of azirines are promoted by transition metals.



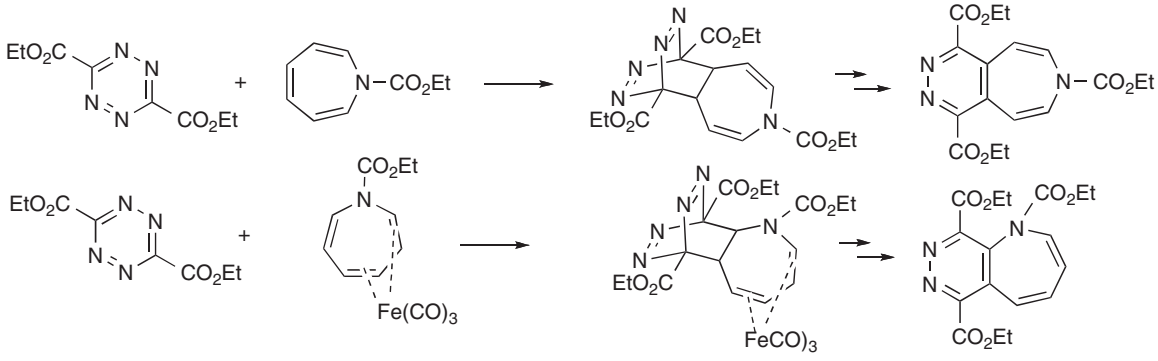
Scheme 81

Since decomplexing is usually possible, many applications await realization. The chemistry of azepines and diazepines already provides examples.

1*H*-Azepine derivatives form a diene complex with (tricarbonyl)iron, leaving the third of the double bonds uncomplexed. If the 3-position is substituted, two different such complexes are possible and are in equilibrium, as seen in the ^{1}H NMR spectrum. An ester group in the 1-position of the complex can be removed by hydrolysis to give an NH compound that, in contrast to the free 1*H*-azepine, is stable (Scheme 82). The 1-position can then be derivatized in the manner usual for amines. The same (tricarbonyl)iron complex can, by virtue of the uncomplexed 2,3-double bond, serve as a dienophile with 1,2,4,5-tetrazines. The uncomplexed N-ethoxycarbonylazepine also adds the tetrazine, but to the 5,6-double bond. Thus, two isomeric adducts can be synthesized by using or not using the complex (Scheme 83).



Scheme 82



Scheme 83

(Tricarbonyl)iron complexes of 1,2-diazepines do not show the rapid isomerization found in their azepine counterparts: the iron forms a diene complex with the C═C double bonds in the 4- and 6-positions. The chemistry of the 1,2-diazepine complexes is similar to that of the azepine complexes.

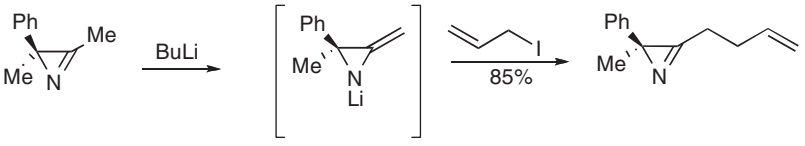
Oxepin also forms a diene complex with (tricarbonyl)iron.

3.5.10 Reactivity of Substituents Attached to Heteroatom or Ring Carbon Atoms

Since small rings are easily opened by various reagents, the development of synthetic procedures involving side-chain functionalization which leaves the heterocyclic ring unchanged is important. Some typical examples are given below.

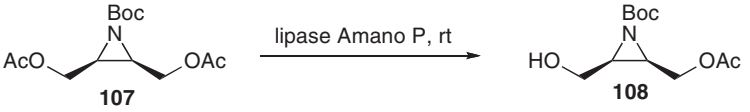
3.5.10.1 C-Linked Substituents

Deprotonation of alkyl groups attached to C(3) of 2*H*-azirines leads to formation of metalloenamines, which can react with a variety of electrophiles to yield C-alkylated products (**Scheme 84**).

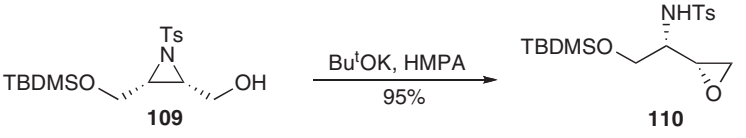


Scheme 84

Optically active aziridines can be prepared in high enantiomeric excess by the enzymatic resolution of *meso* diesters. For example, when the *meso*-bis(acetoxymethyl)aziridine **107** was subjected to enzymatic hydrolysis with lipase Amano P, the aziridine **108** was obtained in 98% ee.

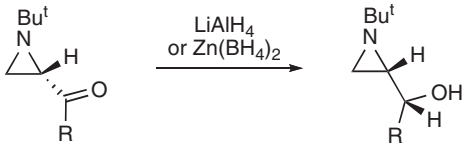


Treatment of certain 2-(hydroxymethyl)aziridines with base can lead to an intramolecular ring-opening reaction to yield an ∝-amino epoxide, a reaction analogous to the Payne rearrangement of (hydroxymethyl)epoxides. For example, treatment of the aziridine **109** with potassium *tert*-butoxide provides the epoxide **110** in good yield.

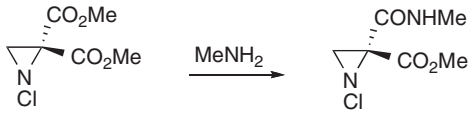


Conventional reactions of oxygen-containing functional groups attached to aziridines, include the addition of hydride and organometallic reagents to ketones and aldehydes, Wittig reactions, carbonyl group reductions, imine and enamine formation from aldehydes and ketones, halide formation from alcohols, and substitution reactions of sulfonates and halides. The example shown in **Scheme 85** illustrates chelation-controlled hydride reductions proceeding with high diastereoselectivity.

An example of the aminolysis of an ester is shown in **Scheme 86**. The reaction proceeds with complete stereoselectivity, and neither the ring nor the N-chloro group is affected.

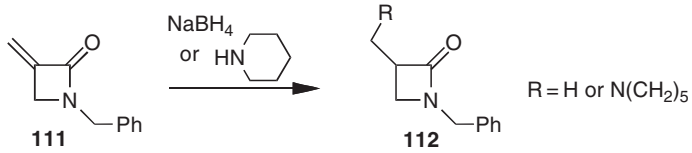


Scheme 85

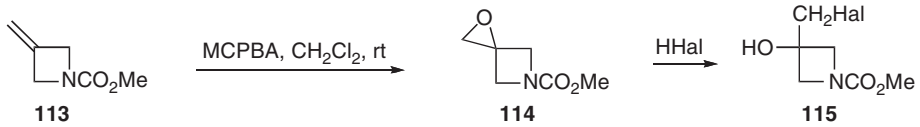


Scheme 86

Conjugate addition of hydride or piperidine to 3-methyleneazetidin-2-one **111** affords the products **112**. 4-(Iodomethyl)azetidin-2-one undergoes nucleophilic substitution by sodium azide in DMF to give the azido compound.

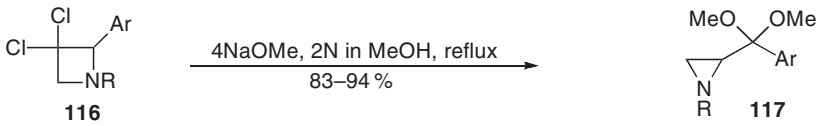


Epoxidation of the carboncarbon double bond in methyl 3-methyleneazetidine-1-carboxylate **113** produces epoxide **114** which with HBr (or HCl) produces the halohydrins **115** <1997JOC4434>.

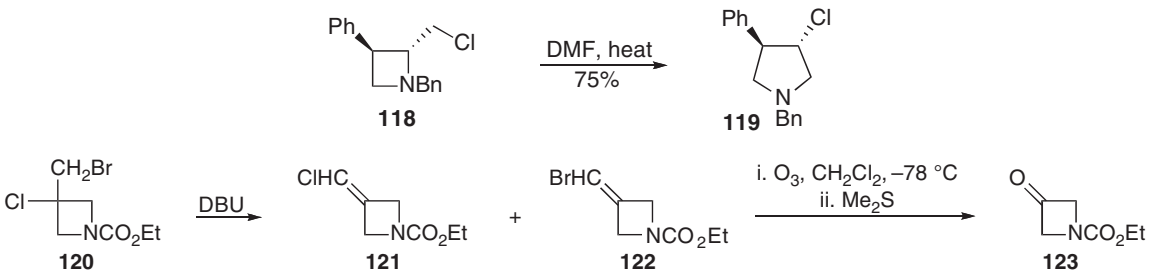


2-Cyanoazetidines can be hydrolyzed unexceptionally to the acids <2005JOC9028> and the aromatic ring of N-tosyl-protected phenylazetidines can be oxidatively destroyed, without disrupting the ring, to produce the acid, using $RuCl_3$-H_5IO_6 <2005S3508>.

3,3-Dichloroazetidines **116** are converted into aziridines **117** by sodium methoxide in methanol via the intermediacy of a 2-azetine ring system <2002JOC2075>.



Mild heating of the 2-(chloromethyl)azetidine **118** induces a stereospecific ring enlargement to give 3-chloropyrrolidine **119** <2003TL5209>; however, it *is* possible to operate on side-chain halides, without disturbing the ring system, provided the ring nitrogen is neutral, as, for example, in the carbamate **120** being converted into a mixture of **121** and **122** ozonolysis of the latter producing the protected azetidin-3-one **123** <1997JOC4434>. Aqueous acid hydrolysis of N-alkyl azetidin-3-one dimethyl acetals reveals the ketone without complications <2001TL2373>.

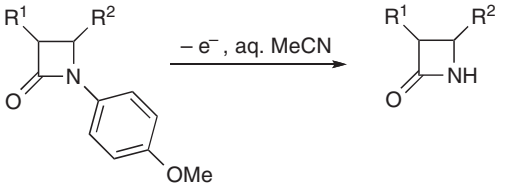


3.5.10.2 N- and S-Linked Substituents

Deprotection of a nitrogen heteroatom is often needed for N-linked substituents in small and large heterocycles. The classical removal of suitable substituents at nitrogen has been applied routinely with azetidine derivatives. It has been shown that N-debenzylation or N-debenzhydrylation works well by hydrogenolysis over a palladium catalyst, with or without added hydrogen chloride. The N-benzyloxycarbonyl and Boc groups are easily removed on azetidine derivatives by means of hydrogenolysis and trifluoroacetic acid, respectively. Removal of N-tosyl groups can be accomplished by alkali metals in an alcoholic solvent.

The protectiondeprotection procedure of the nitrogen atom of 2-azetidinones holds a prime position in synthetic methodologies leading to functionalized -lactam derivatives.

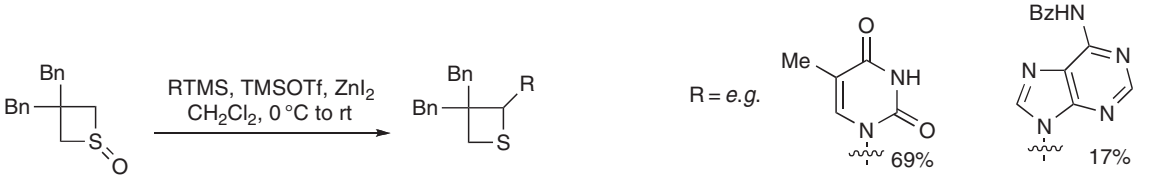
The N-desilylation of 1-trimethylsilyl- or 1-(*tert*-butyldimethylsilyl)-2-azetidinones is a commonly used process in 2-azetidinone chemistry. The *tert*-butoxycarbonyl group is readily removed with trifluoroacetic acid, while the 4-methoxyphenyl protecting group is conveniently removed by ceric ammonium nitrate, or anodic oxidation (**Scheme 87**).



Scheme 87

Removal of an N-phthalimido group can be accomplished with hydrazine without destruction of an aziridine ring. Reduction of the N-phthalimido group with $LiAlH_4$ produces *N*-(isoindolino)aziridines. N-Aminoaziridines form hydrazones readily. Iminophosphoranes bearing an N-aziridinyl group have been used to carry out aza-Wittig reactions with carbonyl compounds, resulting in the formation of cumulenes.

Thietane *S*-oxides undergo Pummerer reactions which allow the introduction of groups at C(2), as illustrated in **Scheme 88** <1996TL7569, 1997SL1247>.



Scheme 88

Part 4
Synthesis of Heterocycles

4.1 Overview

4.1.1 Aims and Organization

The main aim of this part of the book is to provide an introduction to the most efficient ways of making a heterocyclic compound, either by using a known method or by analogy with existing methods for related compounds. The organization is in accordance with this aim.

The synthesis of a heterocyclic compound can be divided into two parts: ring synthesis and substituent introduction and modification. The relative importance of the two parts can vary for different classes of heterocycles.

The following features generally render the ring synthesis steps of increasing importance relative to substituent modification:

1. increasing number of heteroatoms,
2. increasing number of fused rings, and
3. decreasing number of endocyclic double bonds.

Substituent modification is based on substituent reactivity as outlined in the reactivity chapters; brief summaries of the scope and limitations of substituent introduction and modification are given for the following important ring systems as they are dealt with:

1. pyrroles, furans, and thiophenes (Section 4.2.3.2);
2. pyridines (Section 4.2.4.1);
3. azoles (Section 4.3.1.2);
4. azines (Section 4.3.1.3); and
5. benzo-fused heterocycles (Section 4.4.1).

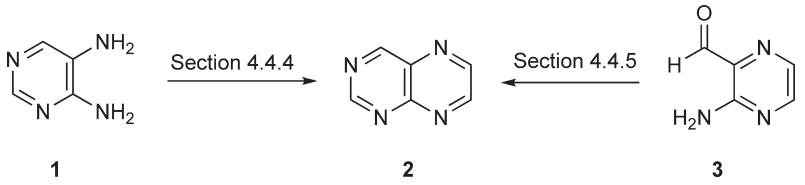
In classifying ring syntheses, we believe that it is important to group syntheses as follows: (1) those of related classes of compounds, (2) those from similar precursors, and (3) methods related mechanistically. The system adopted herein attempts to achieve these (not always completely compatible) aims as far as possible.

The synthesis of ring-fused systems is almost always effected sequentially, i.e., a bicyclic ring system is formed by the annulation of a second ring on a monocyclic compound (typified by a substituted benzene). (Intramolecular cycloadditions form an important exception to this generalization). Thus we subdivide ring syntheses first into those leading to monocyclic and those forming polycyclic compounds. This division is not a rigid one. It applies principally to cases where the preformed ring of a bicyclic system is *aromatic*: thus, syntheses of benzimidazoles, for example, are treated separately from those of imidazoles. However, the methods of synthesis of 4,5,6,7-tetrahydrobenzimidazole would show closer analogies to those of 4,5-dimethylimidazole than to those of benzimidazole. Similarly, spiro ring systems are considered with their monocyclic analogues.

Ring-fused systems with ring junction N- or S-atoms are considered separately from their more numerous analogues with only C-atoms at the ring junctions because of considerable differences in the synthetic methods employed.

Mono-, bi-, and tri-cyclic systems are further classified, first according to the number and orientation of their heteroatoms and second by the degree of unsaturation in the system. Hence, the classification is *not* primarily by ring size, and this enables many related synthetic methods to be discussed together.

In the case of ring-fused systems containing two or more heterocyclic rings, synthetic methods are classified according to the ring being formed. This means that pteridine syntheses are placed in different sections according to routes **1** → **2** or **3** → **2**.



1 **2** **3**

The system just outlined is that adopted in Chapters 4.2–4.5. The remainder of this chapter (Sections 4.1.2–4.1.4) now reviews from a mechanistic standpoint the main types of reactions used in the preparation of heterocyclic rings.

4.1.2 Ring Formation from Two Components

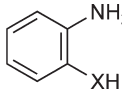
4.1.2.1 By Reaction between Electrophilic and Nucleophilic Centers

Reactions of this type can occur either between a binucleophile and a bielectrophile or between two molecules each containing both a nucleophilic and an electrophilic center, e.g., $HSCH_2CO_2H$.

Rings of many sizes can be made by this approach. Thus, reaction of a 1,2-binucleophile with a 1,3-bielectrophile leads to a five-membered heterocycle, as would the reaction of a 1,4-binucleophile with a 1,1-bielectrophile.

Table 1 lists some of the common binucleophiles utilized in heterocyclic synthesis, the numerical prefixes referring to the positions of the nucleophilic centers relative to each other. Higher order binucleophiles, e.g., 1,5-systems, are analogous.

Table 1 Some examples of commonly encountered binucleophiles

1,2-Systems	*1,2-Systems*	*1,3-Systems*	*1,3-Systems*	*1,4-Systems*	*1,4-Systems*
H_2NNH_2	H_2NOH	R–C(S)NH_2	R–C(=NH)NH_2	$H_2N(CH_2)_2NH_2$	R–C(S)$NHNH_2$
RNHNHR	RNHOH	R–C(S)NHR	R–C(=NH)NHR	$H_2N(CH_2)_2OH$	R–C(Se)$NHNH_2$
H_2NNR_2	R_2NOH	R–C(Se)NH_2	H_2N–C(=NH)NH_2	$H_2N(CH_2)_2SH$	R–C(=NH)$NHNH_2$
$RNHNR_2$	RCH=NNH_2	R–C(Se)NHR	H_2N–C(S)NH_2		R–C(=NH)NHOH
	RCH=NOH		H_2N–C(Se)NH_2		H_2N–C(S)$NHNH_2$

4.1.2.2 Ring Formation via Cycloaddition

Three reactions are of great importance: [2 + 2] cycloaddition, 1,3-dipolar cycloaddition([3+2] cycloaddition), and Diels–Alder reaction ([4 + 2] cycloaddition), which lead to four-, five-, and six-membered rings, respectively. [3 + 3] Cycloadditions are known but are of less importance.

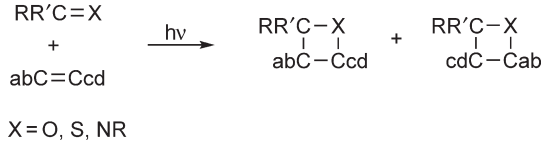
4.1.2.2.1 [2 + 2] Cycloadditions

Concerted thermal [2 + 2] cycloadditions forming heterocycles have been reviewed <1977AHC(21)253> and cross-references to some examples discussed in this book are given in **Table 2**.

Table 2 Four-membered heterocyclic rings from [2 + 2] cycloaddition reactions

Heteroatom position(s)	*Section*	*Precursors with Heteroatom(s)*
1	4.2.1.1.2	C═O, C═S
1,2	4.3.2.2.1	N═N
1,2	4.3.2.2.2	N═O
1,2	4.3.2.2.4	O═O
1,2	4.3.2.2.5	S═O
1,3	4.3.3.1.3	C═S, C═N

The Woodward–Hoffmann rules predict high activation energies for the suprafacial–suprafacial addition of two carbon–carbon double bonds, which can be lowered, however, by polar effects. [2 + 2] Photocycloadditions are common and usually involve diradical intermediates; e.g., photoexcited ketones react with a variety of unsaturated systems (**Scheme 1**). Both the singlet and triplet (n, π^*) excited states of the ketones will form oxetanes with electron-rich alkenes. With electron-deficient alkenes only the singlet states give oxetanes. Diradicals are the immediate precursors to the oxetanes in all cases, but the diradicals are formed by different mechanisms, depending on the availability of electrons in the two components.



Scheme 1 [2 + 2] Photocycloadditions.

4.1.2.2.2 1,3-Dipolar cycloadditions

The synthesis of a variety of five-membered heterocycles involves the reaction of a neutral 4π-electron three-atom system, the dipole, with a 2π-electron system, the dipolarophile (**Scheme 2**). **Table 3** illustrates 1,3-dipoles with a double bond and with internal octet stabilization, the propargyl–allenyl anion type. The application of 1,3-dipolar cycloadditions to the synthesis of heterocyles is discussed in several comprehensive reviews <2007T12247, 2007T3235, 2006H(68)2177>.

Scheme 2 1,3-Dipolar cycloadditions.

1,3-Dipoles without a double bond but with internal octet stabilization, the allyl anion type, are shown in **Table 4**. 1,3-Dipoles without octet stabilization, such as vinylcarbenes and iminonitrenes, are all highly reactive intermediates with only transient existence.

Table 3 1,3-Dipoles with a double bond and internal octet stabilization: propargyl–allenyl anion type

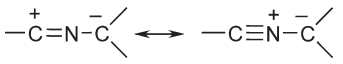
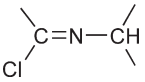
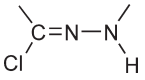
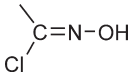
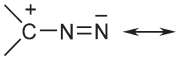
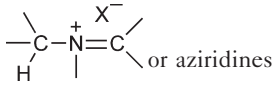
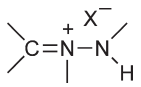
Nitrile ylide		*in situ* from 
Nitrile imine		*in situ* from 
Nitrile oxide		*in situ* from 
Nitrile sulfide		Thermal fragmentation of an oxathiazolone
Diazoalkane		Usually stable
Azide		Usually stable
Nitrous oxide		Stable

Table 4 1,3-Dipoles without a double bond but with internal octet stabilization: allyl anion type

Azomethine ylide		*in situ* from  or aziridines
Azomethine imine		*in situ* from 
Nitrone		Stable
Azimine		From heterocycles
Azoxy compound		Stable
Nitro compound		Stable
Nitroso imine		
Nitroso oxide		
Carbonyl ylide		From oxiranes or heterocycles
Carbonyl oxide		From carbene + O_2
Carbonyl imine		

(*Continued*)

Table 4 (Continued)

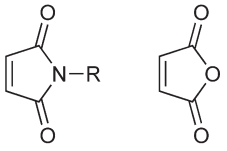
Ozone		Stable
Thiocarbonyl ylide		From heterocycles
Selenocarbonyl ylide		From heterocycles

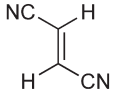
Dipolarophiles utilized in these cycloadditions lead to five-membered heterocycles containing either double or triple bonds between two carbon atoms, a carbon atom and a heteroatom, or two heteroatoms. These are shown in **Scheme 3** listed in approximate order of decreasing reactivity from left to right.

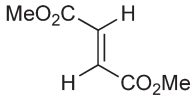
Alkynic dipolarophiles

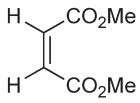
NCC≡CCN, $CF_3C{\equiv}CCF_3$, $RO_2CC{\equiv}CCO_2R$, benzyne, $R^1COC{\equiv}CCOR$, $HC{\equiv}CCO_2R$, $R^2C{\equiv}CCO_2R$, $R^2C{\equiv}CR^2$, $R^2C{\equiv}CH$ (R = Me, Et; R^1 = alkyl, aryl; R^2 = aryl, heteroaryl)

Alkenic dipolarophiles









R = Me, Et, Ph

CH_2=CHCN, CH_2=CHCOMe, CH_2=$CHCO_2Et$, CH_2=$CMeCO_2Me$, EtO_2CN=NCO_2Et, PhCH=$CHNO_2$, PhCCl=$CHNO_2$, PhCH=CH_2, PhCH=CHPh

Heterocumulenes

R^1CONCO, R^1CONCS, RNCO, RNCS

R^1 = aryl, CCl_3; R = alkyl, aryl

Scheme 3 Frequently used dipolarophiles.

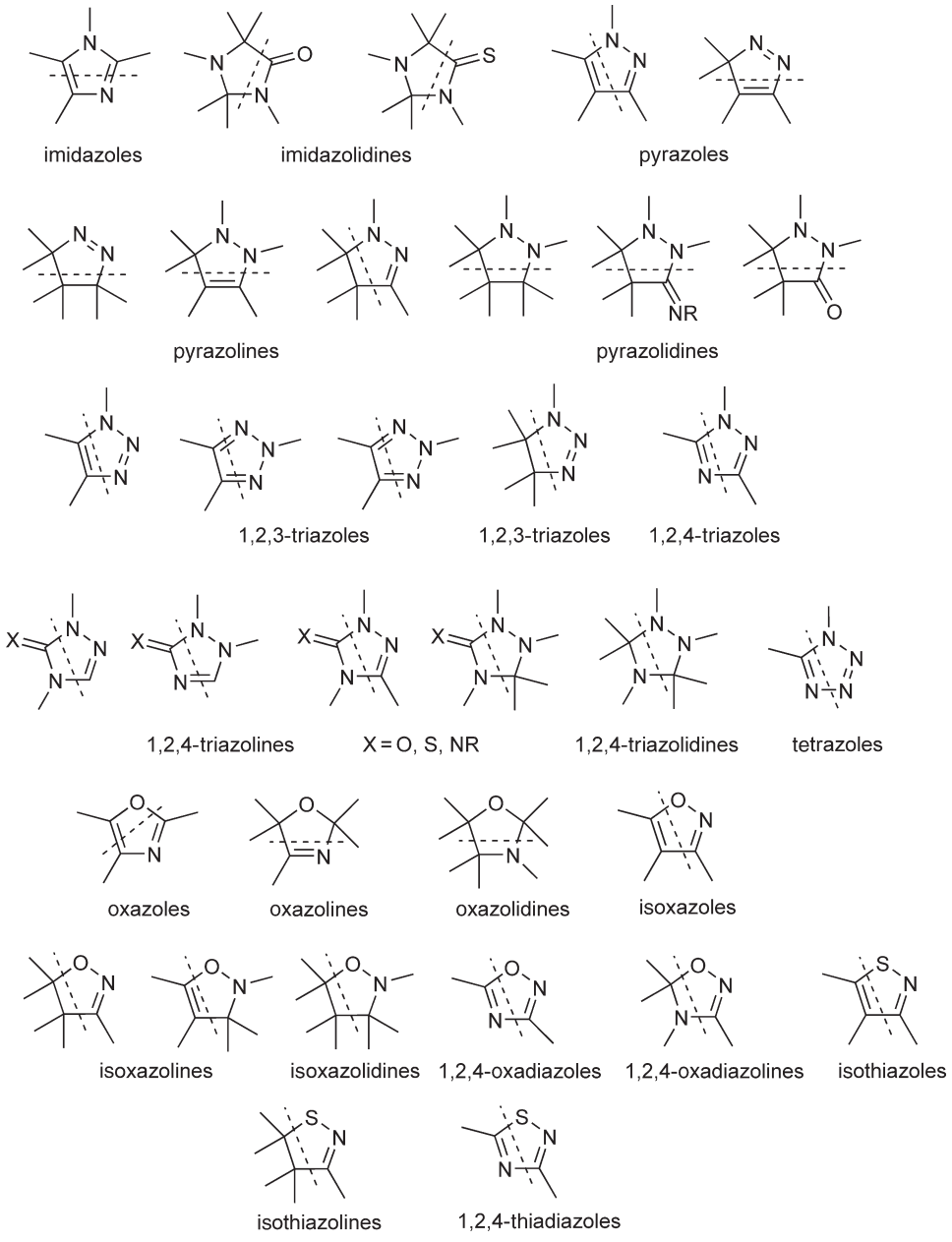
Several five-membered ring systems readily available via 1,3-dipolar cycloadditions are shown in **Scheme 4**. The dashed line indicates how the system was constructed, the line bisecting the two new bonds being formed in the cycloaddition.

4.1.2.2.3 Diels–Alder reactions

One or several heteroatoms can be introduced into a six-membered ring from either the diene or the dienophile component of a Diels–Alder reaction. **Table 5** gives examples of both these possibilities together with the section where the reaction is covered.

4.1.3 Ring Closure of a Single Component

In general, syntheses in which a C–Z bond is formed in the last stage are more important for the preparation of monocyclic compounds, whereas those syntheses in which a C–C bond is formed in the last stage are important for the benzo derivatives. The ring closure may be of a chain containing a nucleophile and an electrophile at the ends, or homolytic, or electrocyclic in nature.



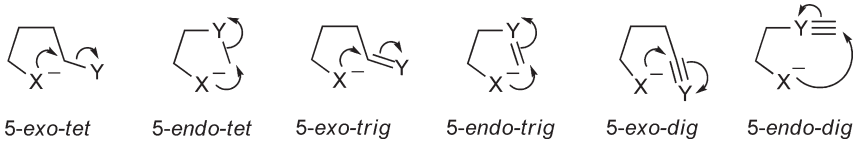
Scheme 4 Some five-membered ring systems available via 1,3-dipolar cycloadditions.

Table 5 Six-membered heterocyclic rings prepared by Diels–Alder reactions

Type	*Heteroatom position(s)*	*Section*	*Heterodienes*	*Heterodienophiles*
Monocyclic	1	4.2.2.1	C=C–C=O, C=C–C=N	C=N, C=O, C=S
Monocyclic	1	4.2.4.3.2	1,2,4-Triazines	–
Monocyclic	1,2	4.3.2.4.2	–	N=N, N=O, O=O, N=S
Bicyclic	1	4.4.2.3.4	Ph–N=C	–
Bicyclic	1,4	4.4.6.2	*o*-Nitrosophenol	–
Bicyclic	1,3,5	4.6.1	–	Azirine

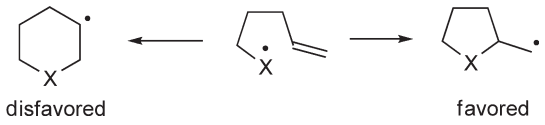
4.1.3.1 By Reaction between Electrophilic and Nucleophilic Centers

A set of guidelines (Baldwin's rules) predicts the facility of different ring closures <1976CC734>. For a process involving formation of a five-membered ring by nucleophilic attack of one terminal atom upon the other, the possibilities are shown in **Scheme 5**. The prefixes *exo* and *endo* indicate whether the breaking bond is exocyclic or endocyclic to the ring being formed. The suffixes *tet*, *trig*, and *dig* refer to tetrahedral, trigonal, and digonal carbon atoms, respectively. Of the cases indicated, those termed 5-*endo-tet* and 5-*endo-trig* are disfavored when X is a first-row element, in this case nitrogen or oxygen. These restrictions arise from the stereochemical requirements of the respective transition states, but these may not apply when atoms such as sulfur, selenium, and tellurium are involved because of the larger atomic radii and bond distances. Thus, a 5-*endo-trig* ring closure involving sulfur has been observed <1976CC736>.

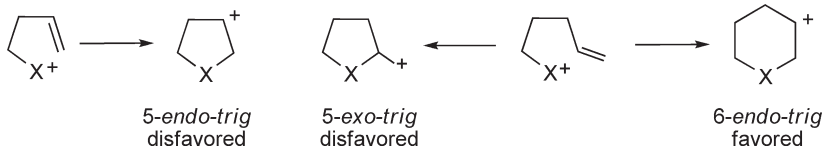


Scheme 5

Application of similar considerations to homolytic ring closures indicates that a 5-*exo-trig* closure will be preferred to a 6-*endo-trig* mode (**Scheme 6**) <1980CC482>. For cationic closures the 5-*endo-trig* mode is unknown in contrast to the well-established 6-*endo-trig* closure (**Scheme 7**). The rules have been extended to rings of other sizes.



Scheme 6



Scheme 7

4.1.3.2 Electrocyclic Reactions

Electrocyclic ring closures are particularly important in the formation of six-membered rings; many are hetero analogues of the hexatriene–cyclohexadiene transformation **4** → **5**. As discussed in Section 3.2.1.6.1, they are frequently involved in ring interconversions initiated by nucleophilic attack on a six-membered ring. Further examples are discussed in Sections 4.2.3.6 (preparation of seven-membered rings) and 4.4.8.2.2.2 (formation of bicyclic 6,6 ring systems).

Photochemically initiated electrocyclizations can be used to form five-membered rings (e.g., Section 4.5.1.1.2.1).

The formation or rupture of ring bridges often involves electrocyclic reactions (e.g., Sections 4.4.4.1, 4.4.8.3.4, and 4.6.1).

4.1.3.3 By Radical, Carbene, or Nitrene Intermediates

The formation of five- and six-membered heterocycles by radical cyclization is discussed in a comprehensive review <2004H(63)1903>. Representative examples of ring syntheses involving carbenoid (Table 6) or nitrenoid (Table 7) intermediates are given. In many cases, the free carbene or nitrene is probably not involved, and the distinction between insertion and addition reactions given in the tables is not always clear cut. Such reactions are particularly useful for the preparation of tricyclic compounds. The application of carbenes and carbenoids in the synthesis of heterocyles is summarized in a review <1996AHC(65)93>.

Table 6 Heterocyclic rings prepared from carbenoid intermediates

Ring size	*Heteroatom position (s)*	*No. of rings*	*Section*	*Carbene precursor*	*Other reaction site*	*Reaction type*
3	1	1	4.2.1.1.1.3	CH_2N_2	C=O, C=S, C=N^+	Addition
6	1,2	3	4.4.4.4	$R-C\equiv\overset{+}{N}-\overset{-}{N}-R^1$	C=C	Addition
5	1	3	4.5.1.1.4	RNC	Benzene ring	Insertion
6	1	3	4.5.5	Triazole	Benzene ring	Insertion

Table 7 Heterocyclic rings prepared from nitrenoid intermediates

Ring size	*Heteroatom position(s)*	*No. of rings*	*Section*	*Nitrenoid precursor(s)*	*Other reaction site*	*Reaction type*
3	1	1	4.2.1.1.1.2	RN_3, $R_2S^+NH^-$	C=C	Addition
3	1,2	1	4.3.2.1	NH_2OSO_3H	C=N	Addition
5	1,3	2	4.4.5.1.2	Tetrazole, oxadiazole	Benzene ring	Insertion
5	1	3	4.5.1.1.2.3	Benzotriazole, pyridotriazole	Benzene ring	Insertion
5	1	3	4.5.1.1.3	RNO_2, RN_3	Benzene ring	Insertion
5 (or 6)	1,2,3	3	4.5.5	RN_3	N=N	Addition
6	1,2	3	4.5.2	RN_3	N=O	Addition
6	1,4	3	4.5.4.2	RNO_2	Benzene ring	Insertion
5	1,2,3	4	4.6.5.1	RN_3	N	Addition

4.1.3.4 By Intramolecular Cycloadditions

An intramolecular cycloaddition reaction results in the simultaneous formation of two new rings. Examples include the formation of a tetrahydroquinoline derivative (Section 4.4.2.3.4), the asymmetric synthesis of 1,2-oxazine derivatives (Section 4.3.2.4.2), and the preparation of a hexahydrothiazino[2,3-*a*]quinoline (Section 4.6.3.4) by intramolecular Diels–Alder reactions.

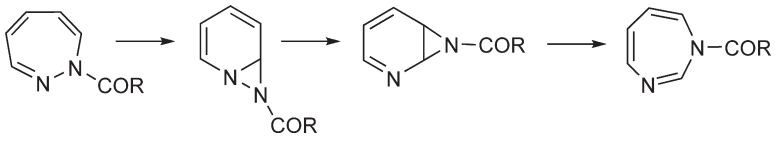
4.1.4 Modification of an Existing Ring

The conversion of one heterocyclic ring into another is treated as a reaction of the initial compound in the appropriate reactivity section in Chapters 3.2–3.5. Here we present a brief overview.

4.1.4.1 Ring Atom Interchange

Such reactions are particularly important in the photochemical isomerization of five- (Sections 3.3.1.2 and 3.4.1.2) and six-membered rings (Section 3.2.1.2); however, they possess relatively little synthetic importance.

Reactions of this type are also implicated in the isomerization of large ring systems through bicyclic ones, e.g., the 1,2- to 1,3-diazepine conversion (Scheme 8).



Scheme 8

4.1.4.2 Incorporation of New Ring Atoms: No Change in Ring Size

Important reactions of this type include the replacement of a ring oxygen by a ring sulfur or nitrogen. Table 8 gives some examples and references to the section where they are discussed.

Table 8 Heterocyclic ring interconversions: no change in ring size

Product: Ring size	*Product: Heteroatom position(s)*	*No. of rings*	*Section*	*Interconversion(s)*
3	1	1	4.2.1.5.2	Oxirane → thiirane; oxirane → aziridine
5	1	1	4.2.3.5.2	Furan → thiophene or pyrrole; oxazole or various mesoionics → furan, thiophene, or pyrrole
6	1	1	4.2.3.5.2	α- or γ-Pyrone → α- or γ-pyridone
6	1	1	4.2.4.3.2	Pyrylium → pyridine, pyridinium, thiinium
5	1,2	1	4.3.2.3.4	1,2-Dithiolylium → pyrazole, isothiazole; isoxazole → pyrazole
6	1,3	1	4.3.3.3.4	1,3-Oxazine, 1,3-thiazine → pyrimidine
5	1,2,4	1	4.3.6.1.3	Tetrazole → oxadiazole, thiadiazole, triazole
6	1,3,5	1	4.3.7.3	Pyrimidine, 1,3,5-oxadiazine → *s*-triazine
6	1,3	2	4.4.5.2.3	3,1-Benzoxazine → quinazolone

4.1.4.3 Ring Expansions

Examples treated in this book are summarized in Table 9. One frequently found type consists of ring expansions of cyclic conjugated systems with an exocyclic ylide function, such as pyridine *N*-oxides or *N*-imides; incorporation of the exocyclic component of the ylide function expands the ring by one member.

Table 9 Formation of a new heterocycle by ring expansion of an existing heterocycle

Product: Ring size	*Product: Heteroatom position(s)*	*No. of rings*	*Section*	*Interconversion(s)*
4, 5, 6	1	1	4.2.1.5.1	Oxiranes → oxetanes, tetrahydrofurans; azirines → pyrrolidines; tetrahydrofurans → pyrans
5, 6	1	1	4.2.3.5.1	Oxiranes → furans; azirine → pyrrole; diketene → pyrones; isoxazoles → pyridones
6	1	1	4.2.4.3.1	Furans → pyridines, pyrones
7	1	1	4.2.4.4	Bicyclic azirines and oxiranes → azepines, oxepins
6	1,2	1	4.3.2.4.4	Pyrrolidines → 1,2-oxazines
7	1,3	1	4.3.3.4.2	Pyridine oxides, 1,3-oxaziniums, pyryliums → 1,3-oxazepines
6	1,4	1	4.3.4.1.4	Aziridines → piperazine, pyrazines; oxiranes → 1,4-dioxanes, 1,4-oxazines; thiiranes → 1,4-dithianes
6	1,2,3	1	4.3.5.3	*N*-aminopyrazoles → 1,2,3-triazines
6	1	2	4.4.2.3.5	Indoles, isatins, anthranils → quinolines
7	1	2	4.4.4.4	Quinolines → benzodiazepine
6	1,3	2	4.4.5.2.3	Benzisoxazoles → 1,3-benzoxazines
6	1,4	2	4.4.6.4	Benzofuroxans → quinoxalines
7	1,3,5	2	4.4.8.3.4	Benzazetes → 1,3,5-benzoxadiazepines

4.1.4.4 Ring Contractions

The isomerization of large rings into bicyclic systems via electrocyclic reactions is mentioned in Section 4.1.3.2.

Other examples of ring contractions are given in **Table 10**. They fall into three main classes. The total loss of one or two (or sometimes more) ring members from the heterocycle, concerted with or followed by formation of a new ring, is a versatile synthetic method. Loss of N_2, CO, CO_2, S, SO, SO_2, $H_2C{=}CH_2$, etc., is common.

Table 10 Formation of a new heterocycle by ring contraction of an existing heterocycle

Product: Ring size	*Product: Heteroatom position(s)*	*No. of rings in product*	*Section*	*Reaction types*
3–6	1	1	4.2.1.5.3	Loss of SO_2, C_2H_4; extrusion of C
5,6	1	1	4.2.3.5.3	Extrusion of C
4	1,2	1	4.3.2.2.6	Loss of CO
5	1,2	1	4.3.2.3.4	Extrusion of C_2
4	1	2	4.4.2.1.2.2	Loss of N_2
5	1	2	4.4.2.2.6	Extrusion of C (Wolff, Meerwein, *N*-oxide rearrangements)

The second major reaction type is the extrusion of one or more atoms from the ring to form a new substituent or side chain.

Finally the ring can react with another reagent to exchange two or three ring atoms for one or two provided by the reagent.

4.1.4.5 Ring Closure with Simultaneous Ring Opening

A generalized monocyclic rearrangement is discussed in Section 3.4.3.1.9; it results in the conversion of one five-membered ring into another.

4.2
Synthesis of Monocyclic Rings with One Heteroatom

4.2.1 Rings Containing No Endocyclic Double Bonds

For all the saturated monocycles with one heteroatom, intramolecular nucleophilic displacement with the formation of C–Z bond(s) is an important preparative method (Section 4.2.1.2.).

Further significant synthetic routes for the various ring sizes are as follows:

1. for three-membered rings, electrocyclic addition to double bonds (Section 4.2.1.1);
2. for four-membered rings, [2+2] photocyclizations;
3. for five- and six-membered rings, formation of one C–C bond; and
4. for six-membered and larger rings, ring expansion of carbocycles (Section 4.2.1.4).

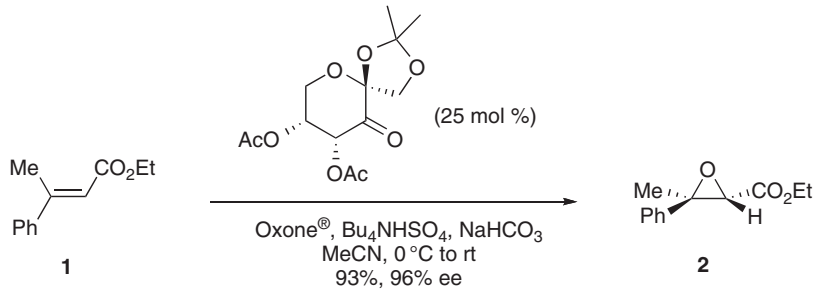
4.2.1.1 From Acyclic Compounds by Concerted Formation of Two Bonds

4.2.1.1.1 Three-membered rings

4.2.1.1.1.1 Oxiranes. The epoxidation of an alkene using a peracid is arguably the most common technique for oxirane formation <CHEC-III(1.03.4.2.3)199>. This reaction is facilitated by alkyl substituents at the C=C bond of the alkene and hindered by electron-withdrawing groups. Peracids commonly react stereospecifically the formation of both bonds takes place at the same time and is followed by loss of carboxylate ion or carboxylic acid. The rate constants for peroxy acid reaction with a variety of alkenes correlate well with ionization potential, suggesting that frontier molecular orbital interactions are important, with minimal electron transfer from the alkene to the peracid <1998JA9513>. The primary and secondary kinetic isotope effects for epoxidation using *m*-chloroperoxybenzoic acid have been examined, giving results consistent with a spiro transition state <1999JOC196>. The influence of allylic strain and hydrogen bonding on the stereoselectivity of hydroxyl-directed epoxidations of chiral allylic alcohols has been summarized <1999ACR703>.

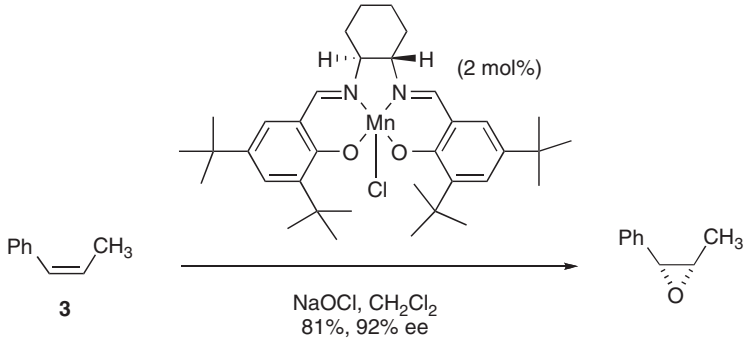
Several convenient epoxidation reagents other than peracids are known, such as hydrogen peroxide in the presence of a transition metal catalyst or other promoter (e.g., fluorinated alcohols or a carbodiimide); molecular oxygen in the presence of a metal-centered catalyst; oxaziridines generated *in situ* from iminium salts and Oxone® or other oxidant; and dioxiranes <CHEC-III(1.03.4.2.3)199>. Particularly useful are dioxirane-mediated enantioselective epoxidations using chiral ketone catalysts and a terminal oxidant such as Oxone® <2000S1979, 2002OR219, 2004ACR488, 2004ACR497>. As an example, the epoxidation reaction of cinnamate derivative **1** using a fructose-derived catalyst provides the epoxide product **2** in 96% ee in an excellent yield (**Scheme 1**) <2002JA8792>. This process has been used in a number of approaches to chiral, nonracemic epoxides <CHEC-III(1.03.4.2.3)199>.

The Sharpless asymmetric epoxidation is a powerful synthetic method for enantioselective epoxidation of allylic alcohols <B-2000MI2>. The original procedure employed a mixture of $Ti(OPr^i)_4$, Bu^tO_2H, and (*R*,*R*)-(+)-diethyl tartrate <1980JA5974>. Numerous modifications of this technique utilizing various transition metals, ligands, and oxidants are known and widely used in organic synthesis <CHEC-III(1.03.4.3.4)210>. Particularly useful is the enantioselective epoxidation of unfunctionalized alkenes using Mn complexes coordinated to salen ligands <B-2000MI4, 2003SL281,>. These metal complexes in the presence of an external oxidant such as NaOCl or PhIO are



Scheme 1

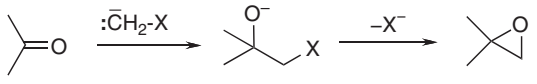
capable of converting conjugated alkenes (e.g., alkene **3**) to their corresponding epoxides in high yields and with high ee values (**Scheme 2**).



Scheme 2

Electron-deficient C═C double bonds are resistant to electrophilic attack, but are converted into oxiranes by nucleophilic oxidants such as HO_2, lithium *tert*-butylperoxide <CHEC-III(1.03.4.2.5)206>, or *m*-chloroperoxybenzoic acid and KOH <2005JOC9610>.

Reactions of carbonyl compounds with methylene equivalents represent another general route to oxiranes (**Scheme 3**) <CHEC-III(1.03.4.2.2)199>. Thus, benzaldehyde is converted to styrene oxide in high yield by treatment with diiodomethane and methyllithium at 0 °C via the initial formation of $LiCH_2I$ followed by carbonyl addition and ring closure <2001T8983>. Likewise, diazomethane is an efficient reagent for transfer of methylene to a carbonyl group with high chemo- and stereoselectivity.

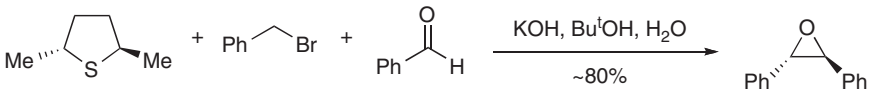


X = N_2^+, Br, I, $^+SR_2$, OS^+Me_2, $^+AsR_2$, $^+SeR_2$

Scheme 3

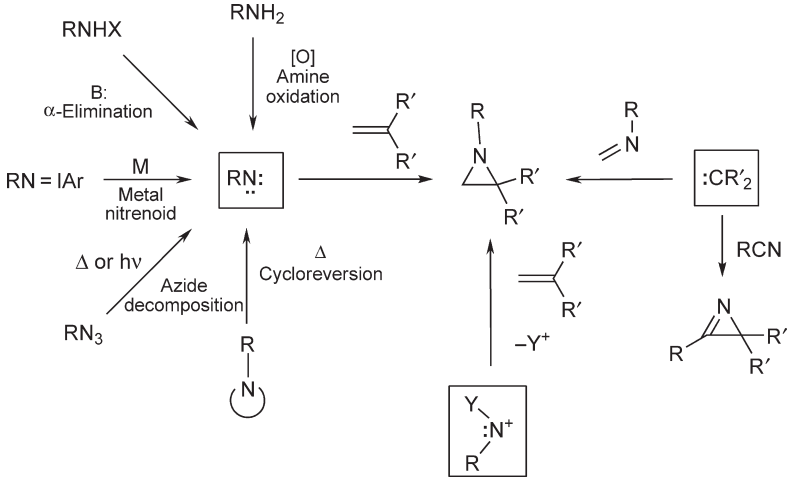
Dimethylsulfonium methylide, $Me_2S{=}CH_2$, dimethyloxosulfonium methylide, $Me_2S(O){=}CH_2$ (Coreys reagent), and other sulfur ylides are efficient methylene transfer agents, except for hindered or highly enolizable ketones. A catalytic, enantioselective preparation of oxiranes using sulfur ylides as intermediates has been developed <2004ACR611>. This procedure has the advantage of directly converting aldehydes to the desired products

(Scheme 4). Various chiral sulfides have been designed to enable high enantioselectivities and diastereoselectivities in this reaction <CHEC-III(1.03.4.3.2)207>.



Scheme 4

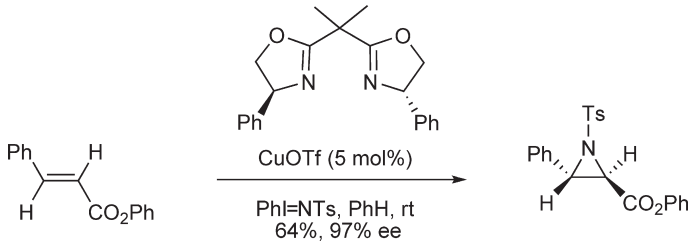
4.2.1.1.1.2 Aziridines. The synthesis of aziridines has been covered in several major reviews <2003CRV2905, 2004T2701, B-2006MI1>. The intermolecular cycloaddition of an electron-deficient species such as a nitrene, a nitrenium cation, or a carbene (or their formal equivalents) to the -bond of an alkene, alkyne, imine, or nitrile is a significant approach to aziridines and azirines (Scheme 5). These reactions are often named aziridinations.



Scheme 5

The nitrogen source for the aziridination of alkenes, a nitrene or nitrenoid, can be generated in various ways: (1) oxidation of a primary amine; (2) base-induced -elimination of HX from an amine or amide with an electronegative atom X (X = halogen, O) attached to the NH group or by -elimination of metal halides from metal *N*-arenesulfonyl-*N*-haloamides; (3) metal-catalyzed reaction of [*N*-(alkane/arenesulfonyl)imino]aryliodanes; (4) thermolytic or photolytic decomposition of organyl azides; and (5) thermally induced cycloreversion reactions <CHEC-III(1.01.6)43>.

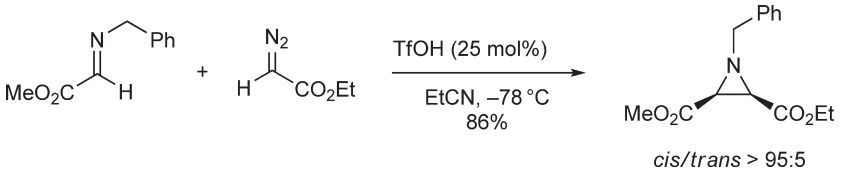
Since the 1990s, transition metal-mediated nitrene transfer reactions have been commonly utilized in organic synthesis employing various nitrogen sources and metal complexes. The use of iminoiodanes, PhI=NSO_2Ar, as nitrenoid precursors in copper- or rhodium-catalyzed reactions with alkenes allows the synthesis of aziridines in high yields and excellent enantioselectivities (Scheme 6) <1993JA5328>. The degree of asymmetric induction in these reactions varies widely with the metal ligand <CHEC-I(1.01.6)43>.



Scheme 6

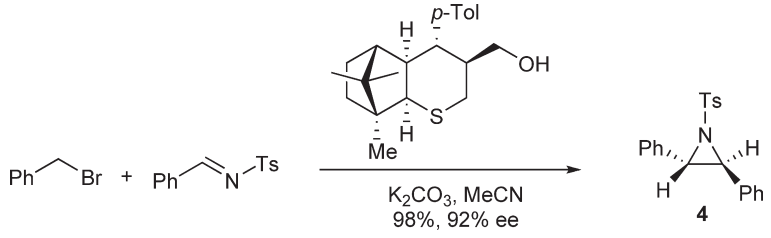
Among other convenient nitrene precursors are chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide), bromamine-T, sulfonamides in the presence of (diacetoxyiodo)benzene and various transition metal catalysts, and sulfonyl azides in the presence of ruthenium complexes <CHEC-III(1.01.6.2)50>.

Another major route used for the preparation of aziridines is the formal addition of carbenoids across an imine -bond [C + C═N]. The carbon fragment is typically provided by diazo compounds under the influence of various catalysts, such as metal catalysts [e.g., $SnCl_4$, $Yb(OTf)_3$, $Ln(OTf)_3$, complexes of Fe, Rh, and Ir] or strong acids <CHEC-III (1.01.6.3)64>. For example, ethyl diazoacetate under acidic conditions reacts with *N*-alkyl aldimines to afford the corresponding aziridines with very high *cis*-selectivity (**Scheme 7**) <2004JA1612>. The conditions are mild enough that acid-catalyzed ring opening of the products is not observed (**Scheme 7**).



Scheme 7

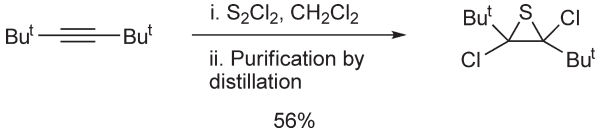
A variation of the [C + C═N] pathway involves the addition of sulfur ylides to imines and this method has been effectively used to access a wide range of substituted aziridines under mild reaction conditions. Although high enantiomeric excesses can be achieved by using a chiral sulfur ylide (up to 98%), the *cis*/*trans*-diastereoselectivity in this process is, in most cases, poor due to a stepwise mechanism via a betaine intermediate <CHEC-III(1.01.6.3.2)68>. Sulfur ylides can be conveniently generated *in situ* from alkyl halides and chiral sulfides; thus, benzyl bromide and tosyl imine in the presence of a camphor-derived chiral sulfide mediator provide aziridine **4** in practically quantitative yield as a 3:1 mixture of *E*/*Z*-isomers and in 92% ee (*E*-isomer) (**Scheme 8**) <2001TL5451>.



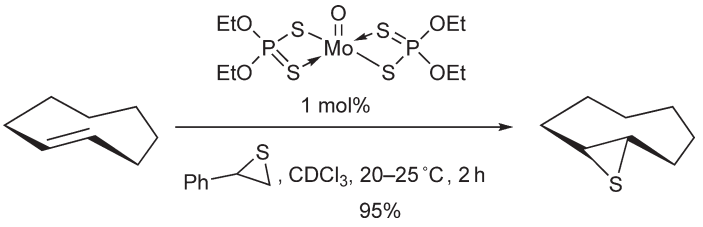
Scheme 8

4.2.1.1.1.3 Thiiranes. Thiiranes can be made by the addition of an appropriate sulfur atom donor (e.g., nascent sulfur, S_8, 2-phenylthiirane, S_2Cl_2, SCl_2, etc.) to an alkene or alkyne (the [S + C═C] route), or by the addition of a carbenoid to a thiocarbonyl compound (the [C + C═S] pathway) <CHEC-III(1.05.9.1)360>.

The [S + C═C] route is illustrated by reaction of disulfur dichloride or sulfur dichloride with alkynes (**Scheme 9**), or by episulfidation of alkenes by sulfur atom donors in the presence of molybdenum oxocomplexes (**Scheme 10**) <CHEC-III(1.05.9.1)360>. 2-Phenylthiirane is the most efficient sulfur donor in the molybdenum-catalyzed episulfidation and the reaction proceeds stereoselectively as *syn*-addition; e.g., the episulfidation reaction of *trans*-cyclooctene affords *trans*-epithiocyclooctane (**Scheme 10**) <2003JA3871>.

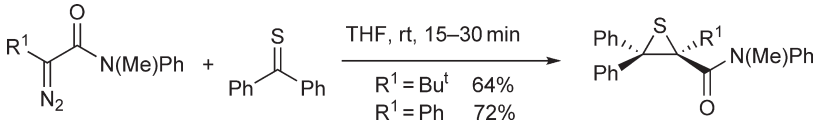


Scheme 9



Scheme 10

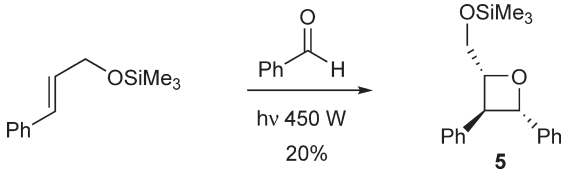
The formal addition of carbenoids to the thiocarbonyl -bond [C + C═S] represents another major route used for the preparation of thiiranes. The reaction of thiocarbonyl compounds with diazoalkenes generally gives good yields of thiiranes (**Scheme 11**). The mechanism may involve an addition of a carbene across the thiocarbonyl group, especially in the presence of Rh(II) acetate, CuCl, $CuSO_4$, or other metal catalysts, but involvement of a zwitterion is also possible <CHEC-III(1.05.9.2)372>.



Scheme 11

4.2.1.1.2 Four-membered rings

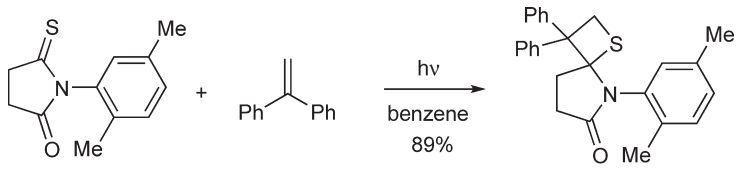
1. The photochemical [2 + 2] cyclization between alkenes and carbonyl compounds, known as the PaternŒBchi reaction, is one of the most commonly used methods to synthesize oxetanes. The scope of the reaction is however limited and only occurs readily between electron-rich alkenes and electron-poor carbonyls. The importance of the reaction is that, with careful selection of alkenes and carbonyl compounds, high regio- and stereoselectivities can be achieved <CHEC-III(2.05.9.3)348>. For example, the photocycloaddition between benzaldehyde and trimethylsilyl cinnamyl ether proceeded to give the corresponding all *trans*-oxetane **5** as the only cyclic adduct in a 20% isolated yield (**Scheme 12**). By comparison, the reaction between benzaldehyde and styrene under the same conditions leads to the formation of 2,3-*trans* and 2,3-*cis* oxetane isomers in a 3:1 ratio. The much higher stereoselectivity in the former reaction is likely to be due to a favourable interaction between the silyl group of the ether and the carbonyl oxygen, with the phenyl groups held *trans* to each other for steric reasons <1997TL5407>.



Scheme 12

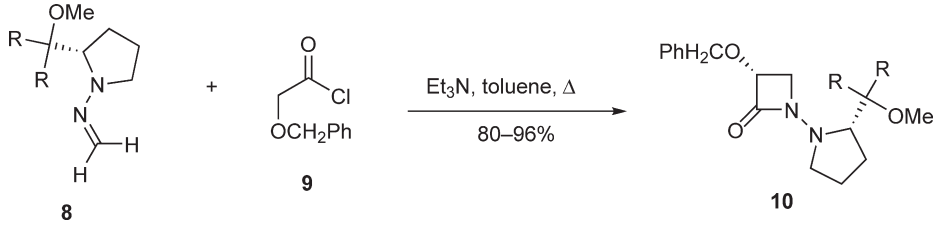
2-Oxetanones (-lactones) are commonly prepared by the [2 + 2] cycloaddition of aldehydes and ketenes <CHEC-III (2.05.9.2)345>.

2. Thietanes are produced efficiently from [2 + 2] photoaddition of thiones to alkenes <CHEC-III(2.08.9.2)448>. The photochemical reaction of thiosuccinimides (e.g., **6**) with 1,1-diphenylethene in benzene affords spirothietanes **7** in high yield (**Scheme 13**) <2003CC2218>. Sulfenes ($RCH{=}SO_2$) add to electron-rich alkenes to give thietane 1,1-dioxides <CHEC-III(2.07.9.2.2)415>.
3. Another common method for the synthesis of 2-azetidinones is the cycloaddition of imines with ketenes, which is known as the Staudinger reaction <CHEC-III(2.01.3.10.11)73>. Although commonly described as a [2 + 2]



Scheme 13

cycloaddition, it is generally accepted that this reaction is in fact stepwise. The first step of the reaction involves a nucleophilic attack of an imino nitrogen on the *sp*-hybridized carbon of a ketene to form a zwitterionic intermediate, which cyclizes to form the azetidin-2-one ring. The ketene is mostly generated either from acid chlorides and related derivatives in the presence of tertiary amines thermally, or from 2-diazoketones either thermally or photochemically <2005CSY377>. The imine component in these reactions can be represented by hydrazones, tosylimines, *N*-silylimines, amidines, etc. For example, hydrazones **8**, derived from formaldehyde, react with benzyloxyketene formed *in situ* from benzyloxyacetyl chloride **9** to afford 4-unsubstituted azetidin-2-ones **10** in 8096% yields and dr up to 99:1 (**Scheme 14**) <2004CEJ6111>.

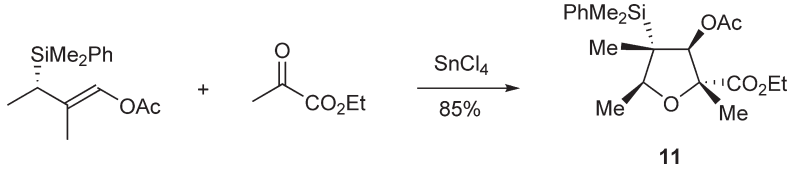


Scheme 14

A number of cycloadditions of imines or imino compounds with a variety of alkenes, including allenes, vinyl ethers, enolates, ketene acetals, and electrophilic alkenes, afford functionalized azetidines <CHEC-III(2.01.3.10.10)69>.

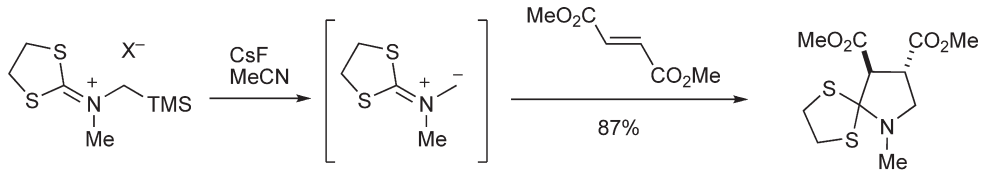
4.2.1.1.3 Five-membered rings

1. 1,3-Dipolar cycloaddition of alkenes with carbonyl ylides generated *in situ* is a versatile method for tetrahydrofuran synthesis. The synthetic potential of such transformations has been reviewed <2005JOM(690)5533, 2003BMI6-253>. In addition, the stereoselective [3 + 2] annulation of allyl silanes has become a reliable protocol for the synthesis of tetrahydrofurans as demonstrated in several total syntheses <CHEC-III(3.07.4.2)540>. Such a [3 + 2] annulation, for example, affords the tetrahydrofuran product **11** as a single stereoisomer (**Scheme 15**) <2002OL2945>. Lanthanide salts serve as efficient Lewis acid catalysts in similar [3 + 2] cycloaddition reactions <CHEC-III(3.07.4.2)540>.



Scheme 15

2. Application of azomethine ylides in dipolar cycloaddition reactions with alkenes provides a route to pyrrolidine derivatives, as illustrated by the generation of the intermediate **12**, and its subsequent conversion to the target system **13** (**Scheme 16**) <1995TL9409, CHEC-III(3.03.9)327>.



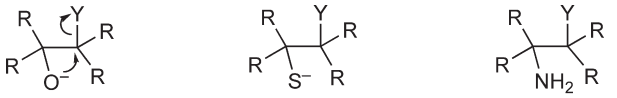
12 13

Scheme 16

4.2.1.2 From Acyclic Compounds by Formation of One or Two C–Z Bonds

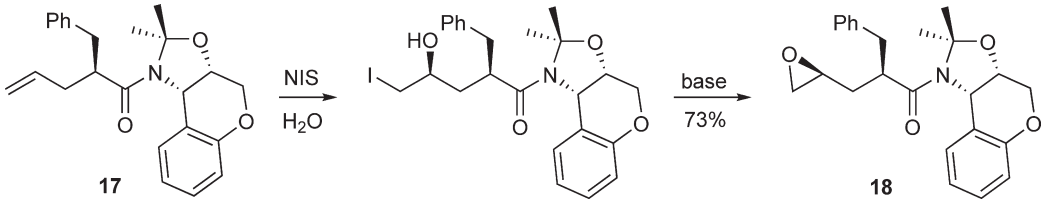
4.2.1.2.1 Three-membered rings

Oxiranes are formed by intramolecular substitution in alkoxides **14** bearing an appropriate leaving group Y at the -position (Y = Br, Cl, TsO, OH, NMe_3^+, etc.) <CHEC-III(1.03.4.2.1) and CHEC-III(1.03.4.3.1)>. Thiiranes are prepared by a similar method, alkali treatment of -mercaptohalides **15** <CHEC-III(1.05.9.1)360>. -Aminohalides and -aminosulfates **16** (Y = Br, Cl, SO_4, etc.) give aziridines on heating or on treatment with alkali <CHEC-III(1.01.6.5)79>. Several modifications of this general approach for oxiranes and aziridines are discussed below. The most important methods are those which provide high enantio- and stereoselectivities in the product formed.



14 **15** **16**

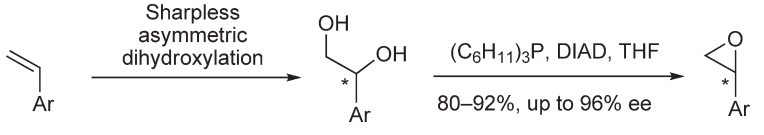
4.2.1.2.1.1 Oxiranes. Intramolecular substitution is a straightforward approach to stereoselective formation of oxiranes <CHEC-III(1.03.4.2.1)198, CHEC-III(1.03.4.3.1)207>. A two-step protocol involving diastereoselective iodohydration of the terminal double bond in compound **17** followed by ring closure affords chiral terminal oxirane **18** in good overall yield (**Scheme 17**) <2003TA3557>.



17 **18**

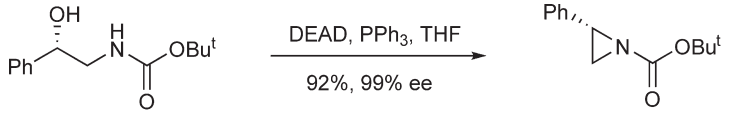
Scheme 17

1,2-Diols are directly converted into oxiranes with Ph_3P or other phosphines in the presence of diisopropyl azodicarboxylate (Mitsunobu reaction). Simple alkenes can be converted into nonracemic epoxides in high yields and with excellent ee values via a two-step sequence of asymmetric dihydroxylation and Mitsunobu cyclodehydration of the intermediate diol (**Scheme 18**) <2001OL2513>. These reactions give best results using electron-poor alkenes <CHEC-III(1.03.4.3.1)207>.



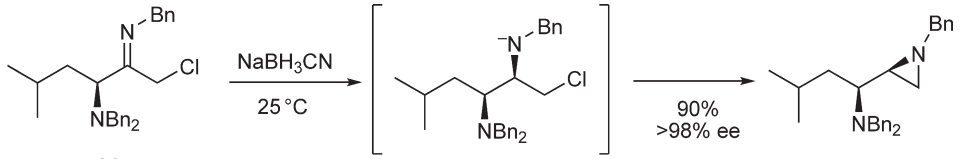
Scheme 18

4.2.1.2.1.2 Aziridines. Aziridines can be synthesized by the ring-closing reactions of appropriately substituted amines <CHEC-III(1.01.6.5)79>. For example, treatment of *N*-aryl--amino alcohols with *p*-toluenesulfonyl chloride under phase transfer conditions provides *N*-aryl aziridines in 8090% yields <2001SC1105>. Enantiomerically pure aziridines can be prepared starting with optically pure amino alcohols derived from the enantioselective reduction of -amino ketones. Thus, treatment of the amino alcohol **19** with DEAD and Ph_3P in THF under Mitsunobu conditions affords aziridine **20** in high yield and 99% ee (**Scheme 19**) <2001J(P1)1916>. The chiral chloroimine **21** is converted into the optically pure aziridine **23** via diastereoselective reduction with sodium cyanoborohydride to produce the intermediate amide anion **22**, which cyclizes to form final product in high yield and with excellent enantioselectivity (**Scheme 20**) <2001JOC2764>.



19 **20**

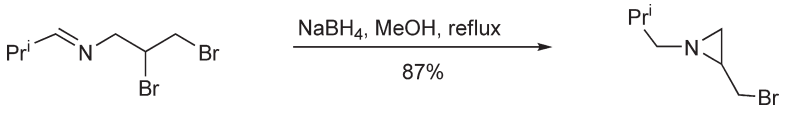
Scheme 19



21 **22** **23**

Scheme 20

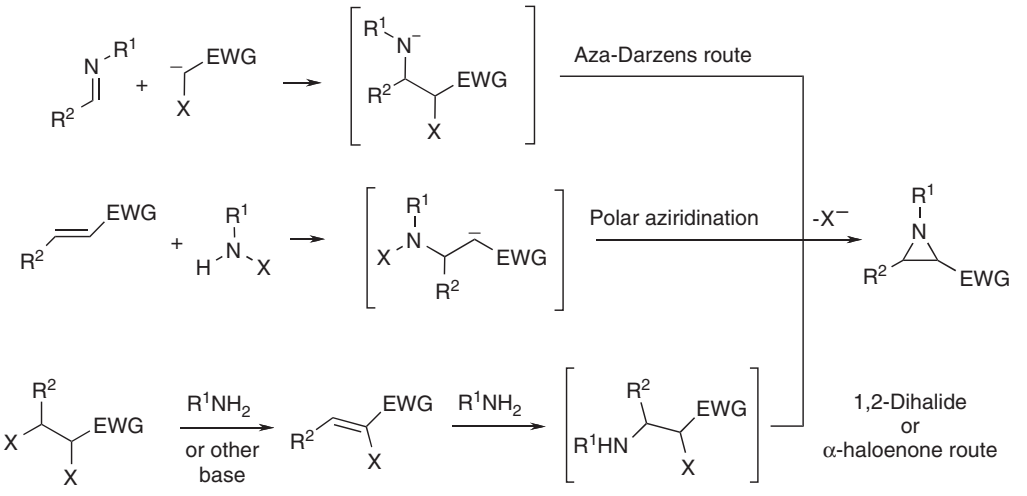
The cyclization of -haloamines is known as the Gabriel synthesis of aziridines <B-1983MI 101-01>. Imines with halogen-containing side chains on the nitrogen atom can be reductively cyclized via the -haloamines, as shown in **Scheme 21** <1994SL287>.



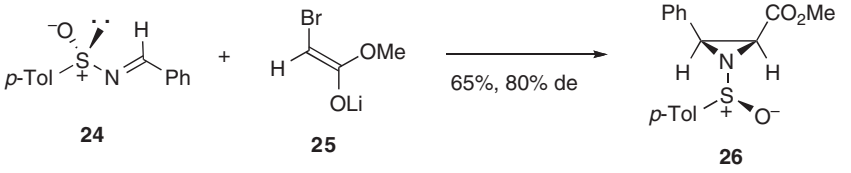
Scheme 21

-Haloamines and other precursors to aziridines can be generated by various polar additions <CHEC-III(1.01.6.4)72>. Three important groups of polar processes leading to aziridines are shown in **Scheme 22**. In the aza-Darzens route <B-1983MI 101-01>, the imine acts as an electrophile at carbon and later as a nucleophile at nitrogen, while the -haloenolate acts initially as a nucleophile at carbon and later as an electrophile at the same carbon. The roles of the two components are reversed for the polar aziridination route, which is related to the epoxidation reaction. In the -haloenone route, the 1,2-dihalide or -haloenone acts formally as a bis-electrophile while the amine acts as a bis-nucleophile.

A one-step aza-Darzens reaction of sulfinimines **24** with lithium -bromoenolates **25** gives the corresponding aziridines **26** in good yield and good to excellent diastereomeric excess (**Scheme 23**). The *cis*/*trans*-isomer ratio is dependent upon the nature of the bromoenolate, with the anion of -bromoacetate itself giving rise to predominantly the *cis*-isomer **26** and substituted analogues producing mainly the *trans*-isomer. This selectivity was rationalized on the basis of a chair-like transition state <1999JOC7559>.



Scheme 22



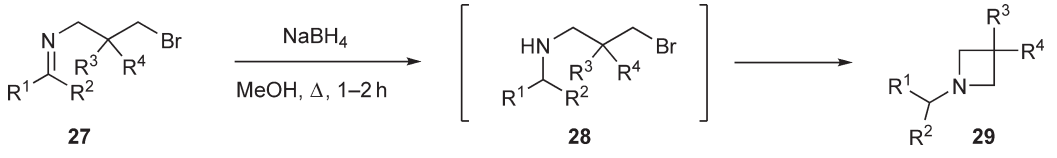
24 **25** **26**

Scheme 23

4.2.1.2.2 Four-membered rings

Bond formation to the heteroatom is a common path to azetidines, oxetanes, thietanes, and many oxo derivatives. Attack by the heteroatom on the -position is disfavored by the entropy factor; the reaction rates for cyclization are about 100 times less than for attack on -positions. However, *exo*-unsaturation can change this relation drastically: in dimethyl sulfoxide at 50 C, -bromopropionate ion cyclizes about 250 times more rapidly than bromoacetate.

A powerful method for the synthesis of azetidines is the cyclization of amines carrying a leaving group at the -position. Leaving groups such as bromo, chloro, iodo, tosyloxy, mesyloxy, and trifluoromethanesulfonyloxy have been used, while the amino group can have substituents such as alkyl, aryl, or tosyl <CHEC-III(2.01.2.8.1)21>. *N*-(Alkylidene)--bromoamines **27** have proved to be excellent starting materials for such a transformation. The reduction of these imines with sodium borohydride in methanol to the corresponding -bromoamines **28** followed by cyclization affords azetidines **29** (**Scheme 24**) <1995T5465, 2001TL2373>.

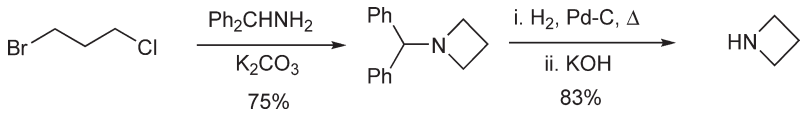


27 **28** **29**

Scheme 24

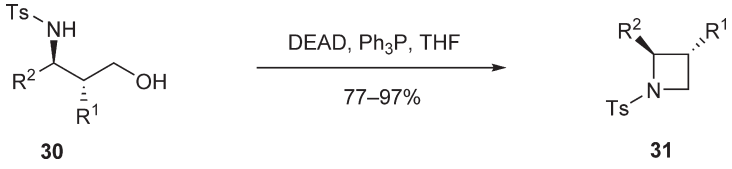
Azetidine itself can be synthesized on the kilogram scale by the condensation of 1-bromo-3-chloropropane with benzhydrylamine to give 1-benzhydrylazetidine followed by hydrogenolysis and basic work-up (**Scheme 25**) <1988SC205>.

Intramolecular nucleophilic displacement of an activated alcohol by amines using -aminoalcohols constitutes a very powerful method for the synthesis of azetidines <CHEC-III(2.01.2.8.2)24>. Particularly useful is the cyclization of



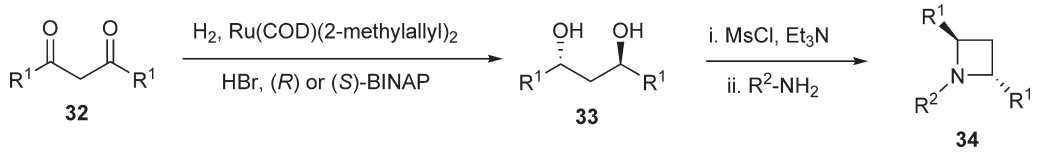
Scheme 25

-aminoalcohols via activation with phosphines (Mitsunobu reactions). For example, the reaction of *N*-tosyl-substituted -aminoalcohols **30** affords the corresponding 1-tosylazetidines **31** with excellent diastereomeric (de = 99%) and enantiomeric excess (ee up to 99%) (**Scheme 26**) <2004EJO4471, 2005S3508>.



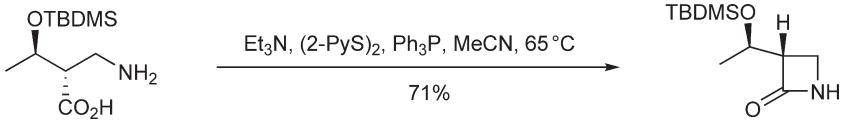
Scheme 26

The C_2-symmetric azetidines **34** can be synthesized from *anti*-1,3-diols <2000EJO1815>. An enantioselective reduction of diketones **32** using [Ru/(*R*)or(*S*)-BINAP] catalytic systems leads to the synthesis of *anti*-1,3-diols **33**, which, after mesylation followed by cyclization with amines, afford azetidines **34** with ee higher than 95% (**Scheme 27**).



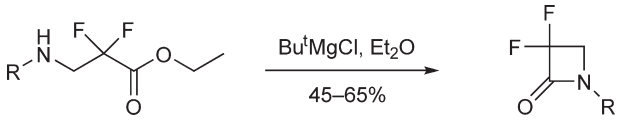
Scheme 27

The cyclization of an appropriate amino acid is the most obvious approach to the synthesis of azetidin-2-ones (-lactams) <CHEC-III(2.01.3.10.1)59>. The intramolecular condensation of -amino acids is accomplished by a large variety of activating agents including phenyl phosphorodichloridate and triethylamine in benzene <2001T1883>, 1-methylpyridinium iodide and triethylamine in acetonitrile <2001TL4519>, camphor-derived oxazoline *N*-oxide <2000OL1053, 2000EJO1595>, phenylphosphonic dichloride <2001T1883>, and a mixture of 2,2-dipyridyl sulfide, triethylamine, and triphenylphosphine (Mukaiyamas reagent) (**Scheme 28**) <2000JOC8372>.



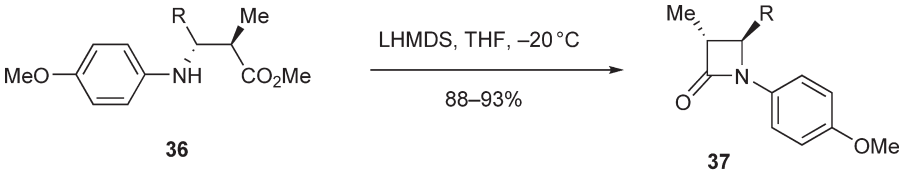
Scheme 28

The cyclocondensation of -amino esters to give -lactams can be performed with Grignard reagents (Breckpot reaction) <CHEC-III(2.01.3.10.2)60>; for example, 3,3-difluoroazetidin-2-ones **35** have been synthesized in moderate to good yields using this methodology (**Scheme 29**) <2003S2483>. As an alternative procedure, -amino esters **36** have been cyclized in the presence of lithium hexamethyldisilazide (LHMDS) to furnish the *trans*-3,4-disubstituted azetidin-2-ones **37** (**Scheme 30**) <2001JOC9030>. Carboxylic amides, hydroxamates, or related substrates, substituted with leaving groups at the -position, are also suitable substrates for the synthesis of azetidin-2-ones <CHEC-III (2.01.3.10.3)61, CHEC-III(2.01.3.10.4)63>.



R = 4-MeOC$_6$H$_4$CH$_2$, 4-MeOC$_6$H$_4$, Ph$_2$CH

Scheme 29



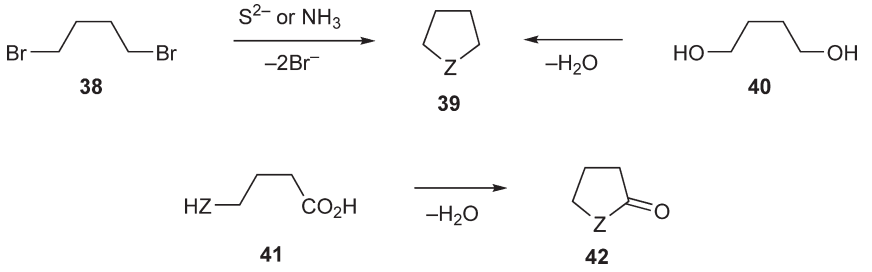
R = Me, Et, Pr^i, Ph

Scheme 30

Oxetanes are commonly obtained by intramolecular ether synthesis from a suitably functionalized alcohol. Leaving groups employed include halides, tosylates, and others. The base can range from an alkoxide to a non-nucleophilic amine <CHEC-III(2.05.9.1)343>. The classical, straightforward approach to 2-oxetanones (-lactones) is by the lactonization of the salts of -halocarboxylic acids and similar precursors <CHEC-III(2.05.9.2)345>. Thietanes and -thiolactones are obtained analogously <CHEC-III(2.07.9)409>.

4.2.1.2.3 Five-membered rings

Pyrrolidine (**39**; Z = NH) and thiolane (**39**; Z = S) can be prepared from tetramethylene dibromide **38**, and tetrahydrofuran (**39**; Z = O) is obtained from the diol **40**. -Hydroxy and -thiol acids (**41**; Z = O, S) usually cyclize spontaneously to give lactones and thiolactones **42**. -Amino acids (**41**; Z = NH) require heating to effect lactam formation (**42**; Z = NH) (**Scheme 31**).

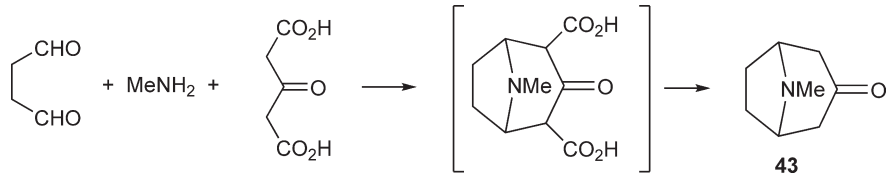


Scheme 31

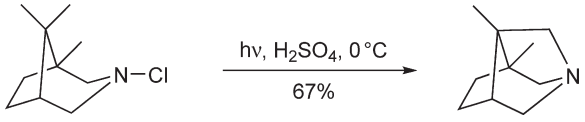
Pyrrolidines can also be prepared by Mannich reactions; a classical example is the synthesis of tropinone **43** from succindialdehyde, methylamine, and acetone dicarboxylic acid (**Scheme 32**) <1917JCS762>; reactions of this type are involved in alkaloid biogenesis.

The synthesis of pyrrolidines by the free radical transformation of *N*-chloroamines, the HofmannLoefflerFreytag reaction, is of preparative significance. A typical example is shown in **Scheme 33** <1959JOC572>.

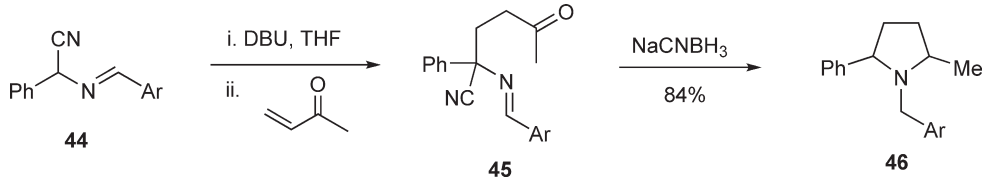
Substituted pyrrolidines **46** can be prepared by a one-pot approach via the reductive cyclization of the precursor **45**, which is prepared by conjugate addition of the -(alkylideneamino)nitrile **44** to methyl vinyl ketone (**Scheme 34**) <2005S945, CHEC-III(3.03.7)321>.



Scheme 32

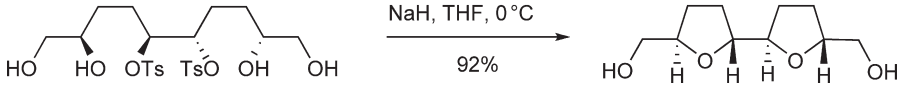


Scheme 33



Scheme 34

Newer methods for the synthesis of tetrahydrofurans with a focus on stereoselective processes have been reviewed <2007T261>. Particularly useful are synthetic methods based on the monotopic cyclization resulting in the formation of a C–O bond <CHEC-III(3.07.4.1)527>. A variety of oxygen-based leaving groups can be utilized in intramolecular etherification reactions leading to tetrahydrofurans. For example, in the total syntheses of squamocin A and squamocin D, acetogenins from Annonaceae, a double cyclization has been demonstrated to be feasible for the assembly of bitetrahydrofuran motifs (**Scheme 35**) <2000EJO1889>. Intramolecular dehydration to afford tetrahydrofurans can be carried out efficiently by the Mitsunobu reaction <2003JOC4422> and by a cationic platinum-catalyzed dehydration <2005SL152>.

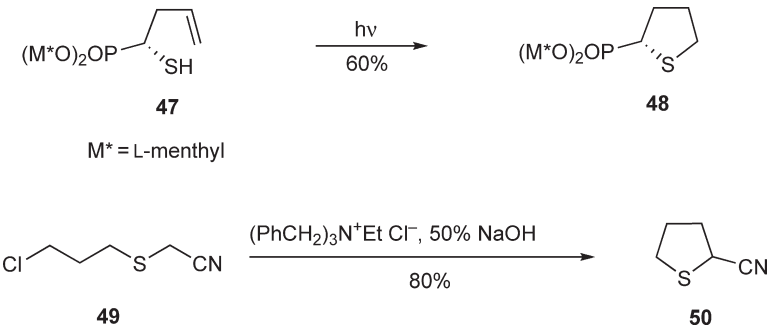


Scheme 35

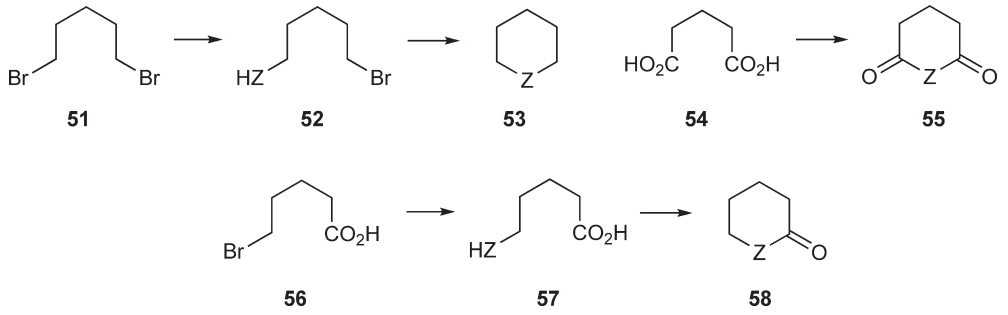
Tetrahydrothiophenes are usually prepared by cyclizations resulting in the formation of a C–S bond <CHEC-III (3.11.2.1)845> or a new C–C bond in the -position to the sulfur atom <CHEC-III(3.11.2.2)860>. Two examples of such cyclizations are shown in **Scheme 36**. UV irradiation of chiral thiol **47** in the presence of AIBN affords tetrahydrothiophene **48** without epimerization <2000OL3757>. Intramolecular cyclization of compound **49** gives 2-cyanotetrahydrothiophene **50** <1987S452>.

4.2.1.2.4 Six-membered rings

These methods parallel the syntheses just described for the five-membered rings. As indicated in structures **51**–**58**, standard reactions of aliphatic chemistry can be extended to the preparation of piperidines, tetrahydropyrans, and tetrahydrothiopyrans (**53**; Z = N, O, S); glutarimides, glutaric anhydrides, and glutaric thioanhydrides (**55**; Z = N, O, S); and -lactams, -lactones, and -thiolactones (**58**; Z = N, O, S) (**Scheme 37**).

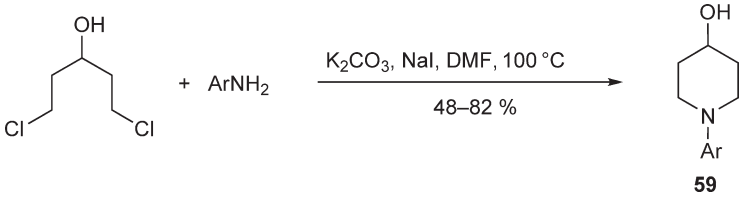


Scheme 36



Scheme 37

The traditional route to piperidines by reaction between a 1,5-dihalopentane and ammonia or an amine is illustrated by the synthesis of 4-hydroxypiperidines **59** (**Scheme 38**) <1988J(P1)2881>.



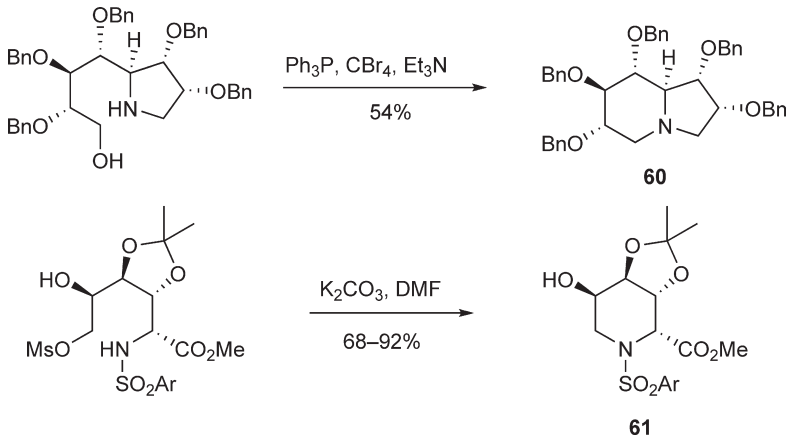
Scheme 38

Numerous examples of cyclizations by attack of a nitrogen nucleophile on an electrophilic carbon leading to piperidines have been reported in recent literature <CHEC-III(7.05.2.1)218>; these examples are illustrated by the synthesis of polyhydroxylated indolizidine scaffold **60** <2004JOC3139> and the synthesis of azasugar type compounds **61** (**Scheme 39**) <2004JME1930>.

Many examples of the synthesis of tetrahydropyrans are based on the cyclization of 1,5-diols and related compounds which can provide an electrophilic site for ring closure <CHEC-III(7.08.10.1)218>. Thus, pentane-1,5-diols can be quantitatively cyclized to the pyran in the presence of $BuSnCl_3$ <1988G483> or via an intramolecular Mitsunobu condensation with cyanomethylenetributylphosphorane <1996TL2463>. Tetrahydrothiopyrans are prepared similarly by cyclizations of suitably substituted thiols <CHEC-III(7.10.4.2.2)881>.

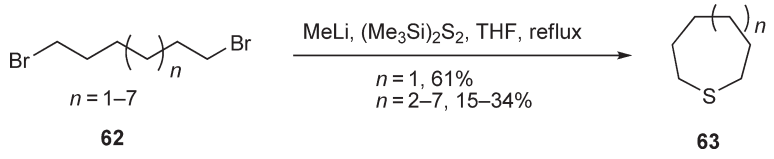
4.2.1.2.5 Larger rings

Similar methods can also be used for seven-membered and larger rings; however, high dilution techniques are often required. Oxepanes are obtained by the dehydration of 1,6-diols at high temperature or in the presence of a Pt(II) catalyst <CHEC-III(13.02.7.1.2)54>.



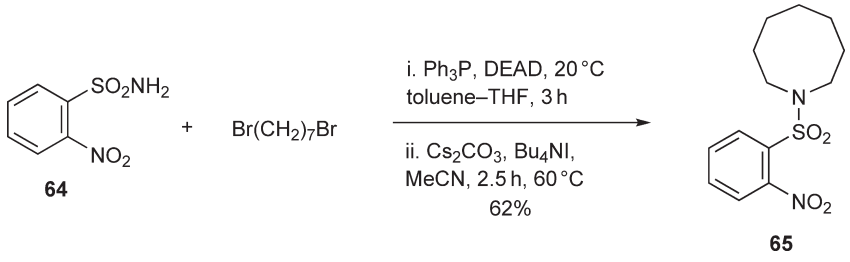
Scheme 39

Thiepanes **63** (n = 1) and larger S-heterocycles can be prepared by double nucleophilic substitution reactions of appropriate dibromoalkanes **62** with Li_2S generated *in situ* from hexamethyldisilathiane and methyllithium (**Scheme 40**) <1985JOC4969>.



Scheme 40

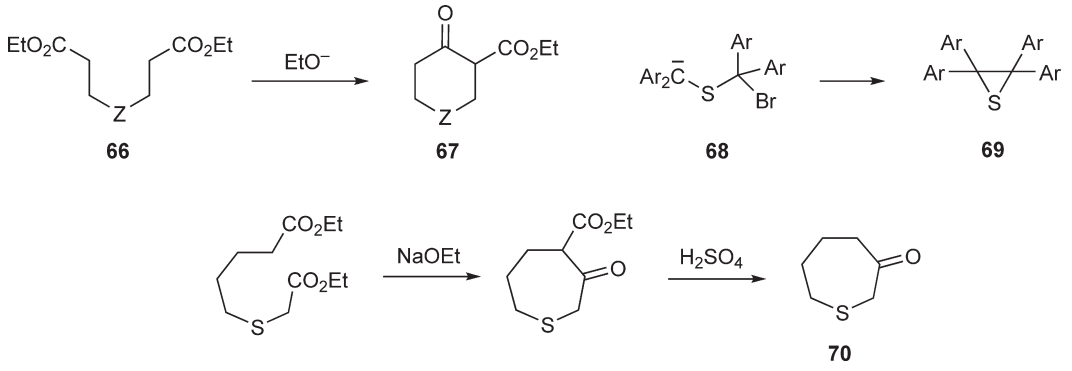
An efficient synthesis of the azocane cycle **65** is accomplished by N-alkylation of 2-nitrobenzenesulfonamide **64** with 1,7-bromoheptane and subsequent cyclization of the sulfonamide thus obtained (**Scheme 41**) <2002T6267, CHEC-III (14.01.5.3)20>.



Scheme 41

4.2.1.3 From Acyclic Compounds by Formation of One C–C Bond

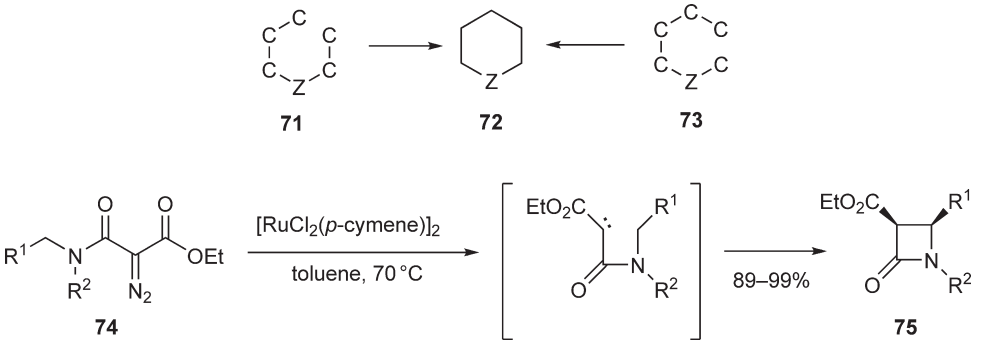
Many of the standard methods of C–C bond formation in aliphatic systems can be extended to heterocyclic systems, e.g., the Dieckmann reaction (cf. **66** **67**) and alkylation of active methylene compounds (e.g., **68** **69**). An example of the application of the Dieckmann reaction to the preparation of 3-thiepanone **70** is shown in **Scheme 42** <1952JA917>. Several more recent examples of applications of the Dieckmann condensation in the synthesis of substituted 4- and 3-piperidones are discussed in CHEC-III <CHEC-III(7.05.2.1.3)234>.



66 67 68 69 70

Scheme 42

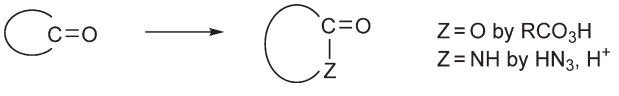
Of the syntheses involving C–C bond formation, those in which the C(3)–C(4) bond is formed (**71** → **72**) are in general more important than those involving C(2)–C(3) bond formation (**73** → **72**). However, carbenoid insertions leading to C(2)–C(3) bond formation are commonly used to make -lactams <CHEC-III(2.01.3.10.6)64>. For example, a ruthenium-catalyzed carbenoid cyclization of -diazoacetamides **74** via intramolecular CH insertion affords azetidin-2-ones **75** in excellent yields and excellent (>99%) *cis*-stereoselectivity (**Scheme 43**) <2005OL1081>.



Scheme 43

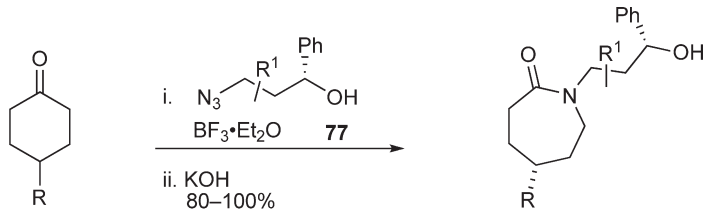
4.2.1.4 From Carbocyclic Compounds

Reactions which insert an O or NH group next to a carbonyl can be used to form heterocycles (**Scheme 44**). The Schmidt reaction or the Beckmann rearrangement can accomplish this for nitrogen, whereas the BaeyerVilliger oxidation does it for oxygen. For example, cyclohexanone is converted in this way into 2-azepinone and into 2-oxepinone; cycloheptanone yields the corresponding eight-membered heterocycles <CHEC-III(14.01.5.3)20>.



Scheme 44

An asymmetric Schmidt ring expansion of the 4-substituted cyclohexanones **76** using chiral azido alcohols **77** gives the azepan-2-ones **78** in high yields and good diastereomeric ratios depending on the nature and position of R^1 (**Scheme 45**) <2003JA7914, CHEC-III(13.01.7)30>.



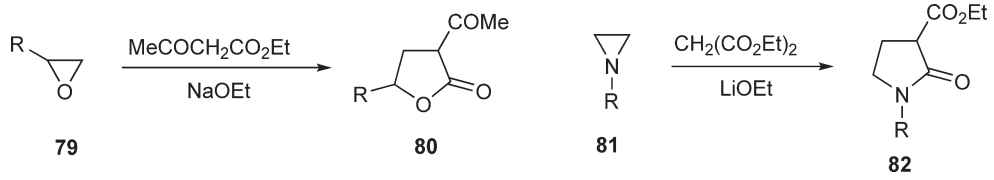
Scheme 45

4.2.1.5 From Other Heterocyclic Compounds

Such syntheses are also considered as reactions of the corresponding starting heterocycles in the relevant reactivity chapter.

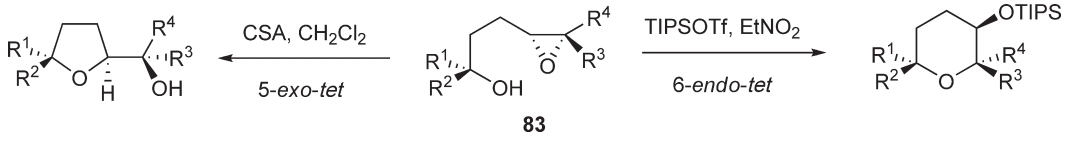
4.2.1.5.1 Reactions involving ring expansion

The facility with which oxiranes and aziridines may be prepared and the ease with which they undergo ring opening with nucleophiles or electrophiles make them useful precursors to larger heterocycles. Examples of ring-opening reactions with carbanions leading to five-membered heterocyclic ring formation are shown in **Scheme 46** (**79** **80**, <1950JA4368> and **81** **82**, <1966CB2556>).



Scheme 46

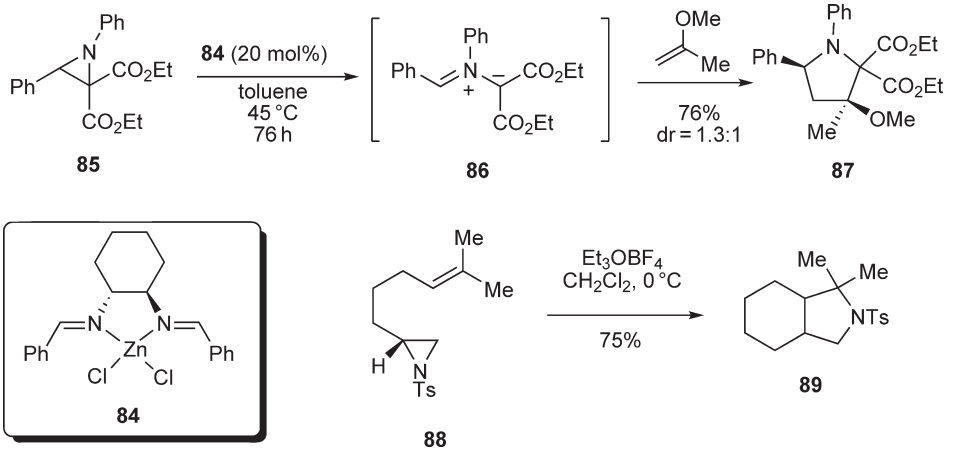
3,4-Epoxyalcohols give hydroxymethyloxetanes by ring expansion <1980BCJ2895>. 4,5-Epoxyalcohols **83** are valuable intermediates for the regioselective synthesis of tetrahydrofurans and tetrahydropyrans <CHEC-III(3.07.4.1.1) 527>. In general, 5-*exo-tet* cyclizations are preferred to the 6-*endo*-tet mode because of a dominant stereoelectronic effect. However, with judicious choice of reagents and solvent polarity, a switching of the epoxide opening mode can been achieved. A bulky silyl reagent (TIPSOTf) in nitroethane as the solvent leads to preferential tetrahydropyran formation, whereas camphorsulfonic acid (CSA) in dichloromethane leads to tetrahydrofuran formation (**Scheme 47**) <2006AGE810>. Aziridines can also be employed as electrophiles in such intramolecular nucleophilic substitutions <2003T1483>.



Scheme 47

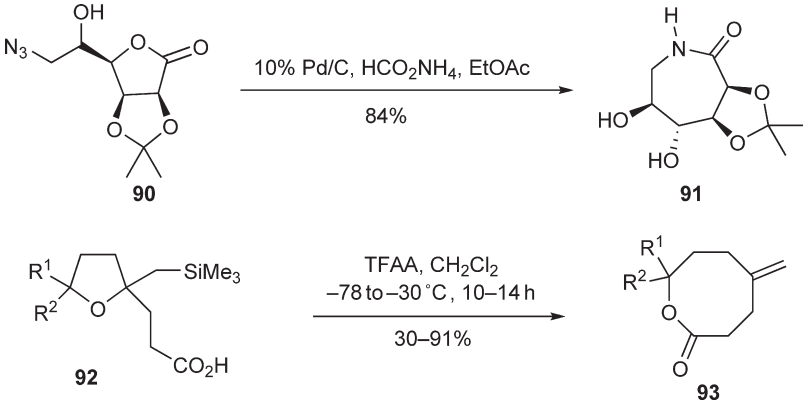
Certain aziridines undergo ring opening to azomethine ylides (e.g., **85** **86**), a process which can also be facilitated by Lewis acid catalysts <CHEC-III(1.01.5.5.1)33>. These reactive intermediates can be trapped by a variety of dipolarophiles to give new heterocyclic species. For example, methyl vinyl ethers convert aziridines such as **85** into pyrrolidines (i.e., **87**) in the presence of a zinc(salen) Lewis acid catalyst **84** <2004JA2294>. Likewise, under the

catalysis of boron triethyloxonium tetrafluoroborate, the aziridine moiety can be trapped with -nucleophiles, such as a tethered alkene **88**, to provide fused bicyclic pyrrolidines (e.g., **89**) (**Scheme 48**) <2004TL5011>. The intramolecular dipolar cycloaddition reactions of azomethine ylides derived from substituted aziridines have been summarized in a review <2005CRV2765>.



Scheme 48

The ring expansion approach is particularly useful in the synthesis of seven- and eight-membered heterocycles; specific examples are shown in **Scheme 49** <CHEC-III(13.01.7)30, CHEC-III(14.02.10)76>. The synthesis of the D-gulonolactam **91** involves reduction of the azido group in compound **90**, followed by intramolecular nucleophilic attack on the lactone moiety <2006T7455>. Treatment of tetrahydrofuran derivatives **92** with trifluoroacetic anhydride (TFAA) results in intramolecular acylative ring opening to give the corresponding eight-membered lactones **93** in moderate to good yields (**Scheme 49**) <1999SL1757>.

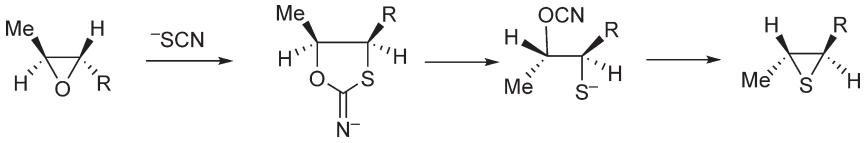


Scheme 49

4.2.1.5.2 Reactions without change in ring size

A classic prototype of these reactions is the conversion of oxiranes into thiiranes by thiocyanate ion <CHEC-III (1.05.10.1)374>. Inversion at both ring carbons makes the reaction stereospecific with respect to the *cis*/*trans* relationship of the substituents on the oxirane carbons (**Scheme 50**).

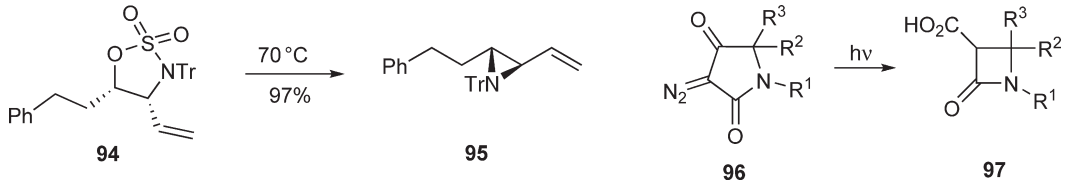
Aziridines are obtained similarly in one step from oxiranes with iminophosphoranes <1976CB814> or phosphoramidate esters <1976TL4003>.



Scheme 50

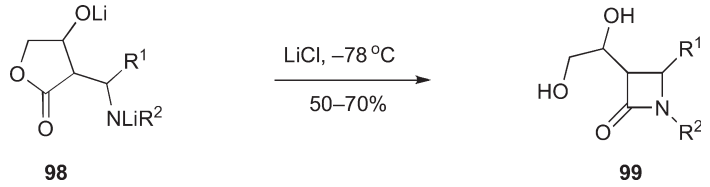
4.2.1.5.3 Ring contraction

The loss of CO, S, SO, SO_2, SO_3, and N_2 by thermolysis or photolysis has been used to make three- and four-membered rings; for example, the cyclic sulfamidate **94** undergoes clean thermolysis at 70°C to form the vinyl aziridine **95** in excellent yield <2002T5979, CHEC-III(1.01.6.5)79> and Wolff rearrangement of diazo compounds **96** gives -lactams **97** (**Scheme 51**) <1973J(P1)2024>.



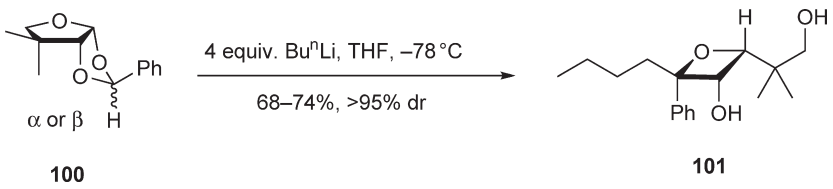
Scheme 51

The lithium amides **98**, prepared from 4-hydroxy--lactone and imines, rearranges in the presence of lithium chloride at low temperature to form -lactams **99** (**Scheme 52**) with cholesterol absorption inhibition properties <1999JOC3714, CHEC-III(2.01.3.10.10)69>.



Scheme 52

A generally applicable oxetane synthesis (e.g., **100** **101**) can be achieved by the anionic ring contraction of cyclic acetals fused to butanolide using organolithium reagents (**Scheme 53**) <2004SL651, CHEC-III(2.05.10.2)352>.



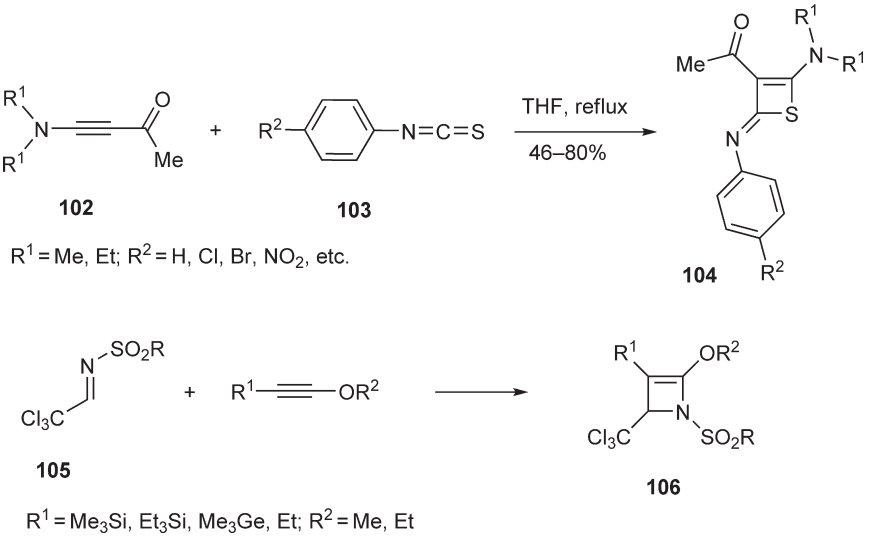
Scheme 53

4.2.2 Rings Containing One Endocyclic Double Bond

Most monoheterocycles with one cyclic double bond are prepared by C–Z bond formation in which the Z atom acts as the nucleophile. However, for six-membered rings of this type, DielsAlder reactions are especially important. Three-membered rings are also atypical: azirines are often made by C–N bond formation from precursors in which N is electrophilic or has nitrene character (cf. **Scheme 5**), while oxirenes are generally unstable and can only be generated as transient intermediates <CHEC-III(1.03.7)215>. Ring-closing metathesis (RCM) has emerged since the mid-1990s as one of the most significant methodologies applicable to the synthesis of a broad range of partially unsaturated heterocycles with five-membered and larger rings <2004CRV2199>.

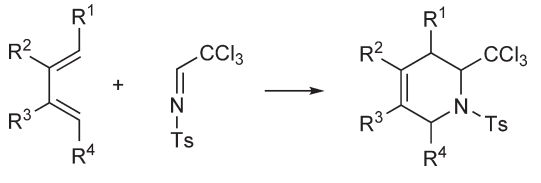
4.2.2.1 From Acyclic Compounds by Concerted Formation of Two Bonds

1. The [2 + 2] cycloaddition reactions of various 4-dialkylamino-3-butyn-2-ones **102** with substituted phenyl isothiocyanates **103** provide access to a series of thietimines **104** in moderate yields <2001SL361, CHEC-III(2.07.9.2)415>. Likewise, cycloaddition of *N*-sulfonylimines **105** with alkynyl ethers affords functionalized 2-azetines **106** in a quantitative yield (**Scheme 54**) <1991ZOB1389>.

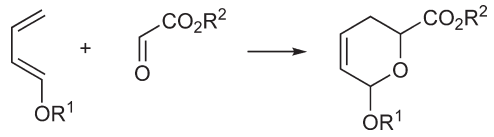


Scheme 54

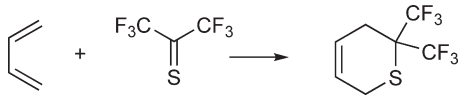
2. By far the most important reactions of this type are [4 + 2] heterocyclization analogues of the DielsAlder reaction which present a versatile route to six-membered rings <B-1987MI 505-01>. The heteroatom can originate from the dienophile (e.g., **Schemes 55–57**) or from the diene (e.g., **Schemes 58** and **59**). Whereas ,-unsaturated carbonyl compounds react best with electron-rich alkenes (**Scheme 58**), enaminothiones prefer electron-deficient dienophiles (**Scheme 59**).



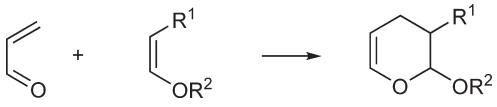
Scheme 55



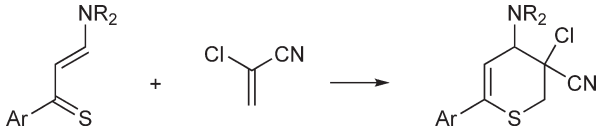
Scheme 56



Scheme 57

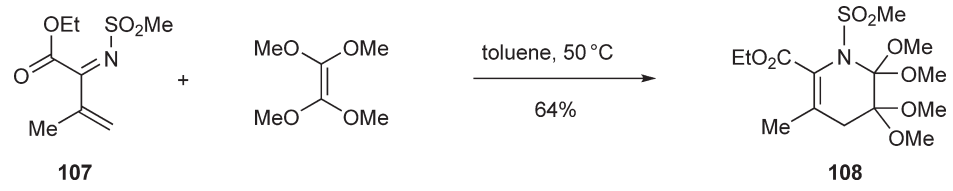


Scheme 58



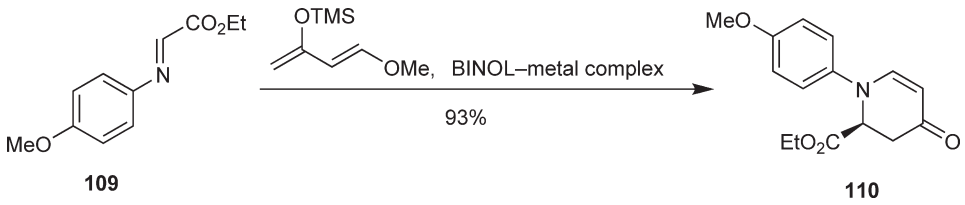
Scheme 59

The hetero-DielsAlder reaction (hDA) using iminium species has been commonly used for the synthesis of reduced pyridines and pyridones <CHEC-III(7.05.2.2.2)254>. The aza-1,3-butadiene **107** was employed in hDA reaction to synthesize the key intermediate **108** in the total synthesis of the pyridine-based natural product piericidin (**Scheme 60**) <2005JA15704>. The reaction of Danishefskys diene with N-functionalized imine **109** in the presence of (*S*)-BINOL zinc complex has been utilized to produce 4-piperidones **110** in moderate to high enantioselectivity (**Scheme 61**) <2004SL711>.



107 **108**

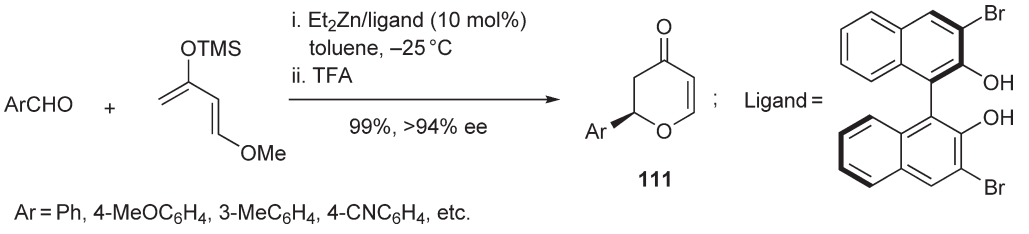
Scheme 60



109 **110**

Scheme 61

The hDA reactions exemplified in **Schemes 56** and **58** provide a powerful tool for the synthesis of 3,6-dihydropyrans <CHEC-III(7.08.9.2.2)485> and 3,4-dihydropyrans <CHEC-III(7.08.9.1.2)485>, respectively. Several reviews concerning the enantioselective hDA reaction as a means of accessing the dihydropyran ring system are available <2000AGE3558, 2004EJO2093, 2000ACR325>. As an example, the hDA reaction between Danishefskys diene and aldehydes in the presence of BINOLzinc complex proceeds in excellent yield and enantioselectivity to afford dihydropyran-4-ones **111** (**Scheme 62**) <2002OL4349>.



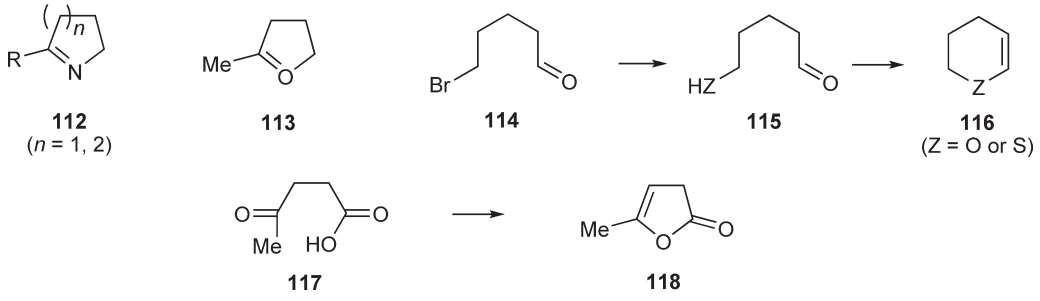
Scheme 62

4.2.2.2 From Acyclic Compounds by Formation of One or Consecutive Formation of Two C–Z Bond(s)

4.2.2.2.1 Z Atom component acting as nucleophile

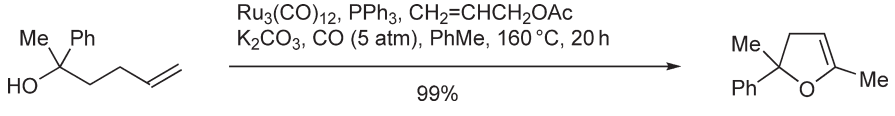
The appropriate reactions of aliphatic chemistry are applicable and take place particularly readily for the formation of five- and six-membered rings. For example:

1. 4- and 5-Oxo primary amines yield 3,4-dihydropyrroles and 2,3,4,5-tetrahydropyridines, respectively (**112**; n = 1, 2).
2. Cyclic enol ethers and their thio analogues are formed from keto alcohols and thiols: $Ac(CH_2)_3OH$ gives the dihydrofuran **113** on distillation; cf. **114 115 116** for the preparation of 3,4-dihydropyrans and -thiopyrans **116** (Z═O or S).
3. Unsaturated lactones are prepared from keto acids, e.g., **117 118** (**Scheme 63**).



Scheme 63

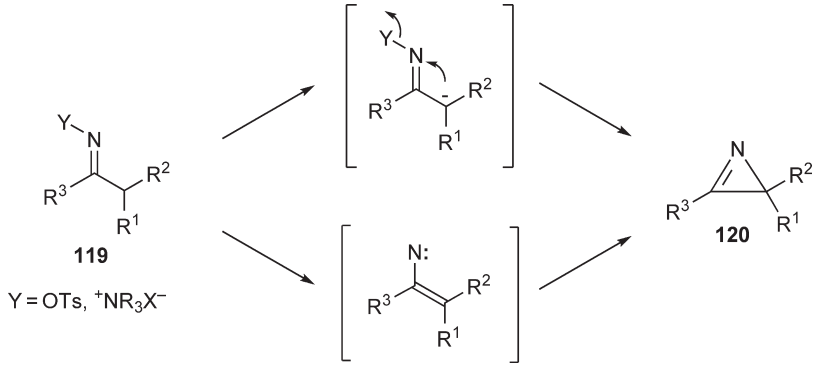
Transition metal-catalyzed cyclizations leading to formation of a new CO bond provide a particularly useful approach to dihydrofurans <CHEC-III(3.07.3.1)515>. For example, a high-yielding method for the synthesis of 2,3-dihydrofurans is provided by a ruthenium-catalyzed oxidative cyclization of 4-penten-1-ols (**Scheme 64**) <2003CL24>.



Scheme 64

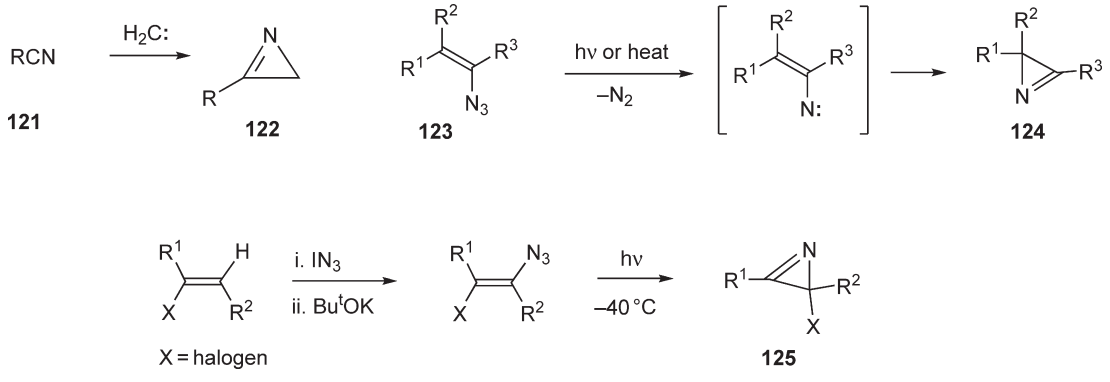
4.2.2.2.2 Z Atom component acting as electrophile

A significant preparative pathway to the 2*H*-azirine system **120** is the Neber rearrangement of oxime sulfonates **119** (**Scheme 65**) <CHEC-III(1.01.10.3)94>. The presence of strong electron-withdrawing groups in the -position to the oxime increases the acidity of those protons and thus favors the cycloelimination reaction under mild conditions. The Neber reaction occurs either through an internal concerted nucleophilic displacement or through a vinyl nitrene (**Scheme 65**) <2001EJO2401>.



Scheme 65

1-Azirines are also made by carbene addition to nitriles (**121** **122**) and by thermal or photochemical elimination of N_2 from vinyl azides (**123** **124**) <CHEC-III(1.01.10.1)91>. Vinyl azides are prepared by the Hassner reaction, where iodine azide is first added to an alkene and the resultant -iodoazide is dehydrohalogenated with a base; this approach is illustrated by the preparation of haloazirines **125** (**Scheme 66**) <2001T6203>.

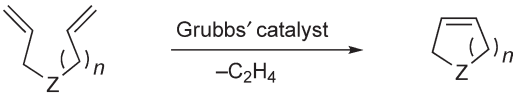


Scheme 66

4.2.2.3 From Acyclic Compounds by Ring-Closing Metathesis

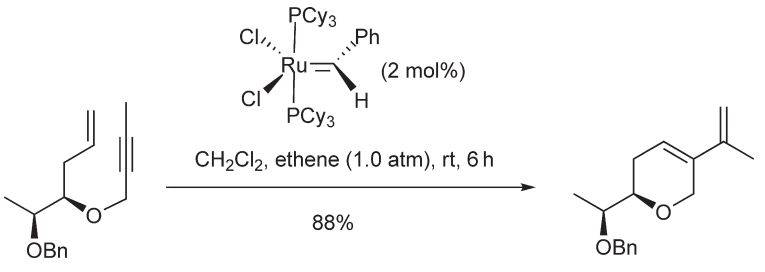
RCM has become a major approach to the synthesis of partially unsaturated heterocycles with five-membered and larger rings (**Scheme 67**) <2004CRV2199>.

RCM reactions are most frequently employed in the synthesis of 2,5-dihydrofurans <CHEC-III(3.07.3.1.3)520> as well as dihydropyrrole derivatives <CHEC-III(3.03.4)290>. Likewise, RCM provides the most general approach to 3,6-dihydropyrans <CHEC-III(7.08.9.2.1)481>. In a specific example, dihydropyran **127** bearing a chiral oxacyclic diene can be constructed via enyne metathesis of the chiral ether **126** (**Scheme 68**) <2002T5627>. The analogous tetrahydropyridine derivatives are prepared by a similar RCM procedure <CHEC-III(7.0.5.2.1.3)240>.



Z = O, NR; n ≥ 1

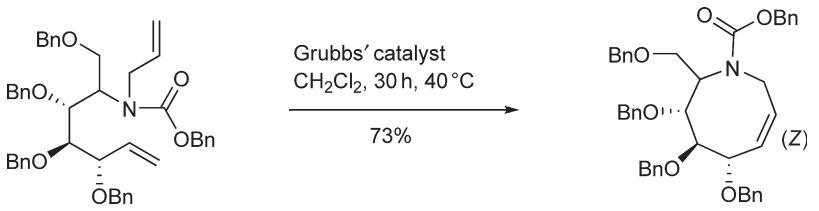
Scheme 67



126 **127**

Scheme 68

The RCM approach is particularly useful in the synthesis of seven- <CHEC-III(13.01.6.3)16> and eight-membered <CHEC-III(14.01.5.2)12> heterocycles (e.g., **Scheme 69**, <2004T10385>).

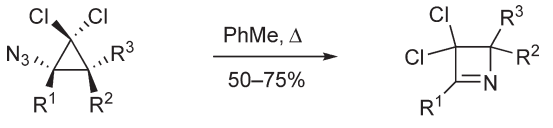


Scheme 69

4.2.2.4 From Carbocycles

The methods discussed in Section 4.2.1.4 can also be used in the synthesis of partially unsaturated heterocycles.

Thermal ring expansion of cyclopropyl azides (e.g., **128**) provides a general route to alkyl- and aryl-azetines (**Scheme 70**) <1979CB3914>.

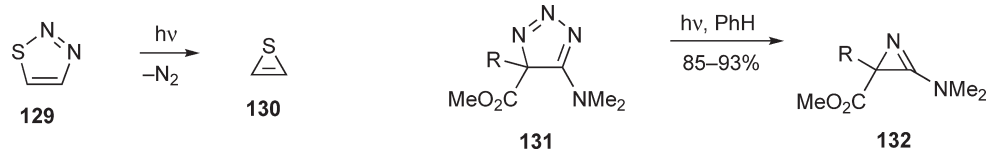


128

Scheme 70

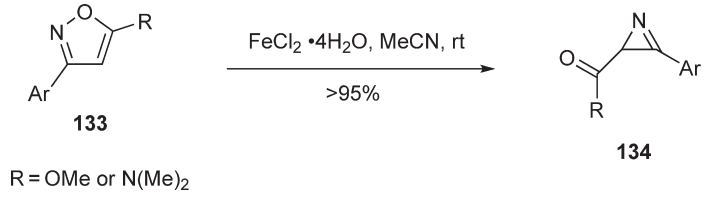
4.2.2.5 From Heterocycles

Nitrogen extrusion has been used to make fragile molecules: 2-thiirene **130** has been obtained by matrix photolysis of 1,2,3-thiadiazole **129** <1981JA486> and azirines **132** from 4*H*-triazoles **131** (**Scheme 71**) <1980CC940>.



Scheme 71

The ring contraction reaction of of isoxazoles **133** promoted by iron(II) catalysts affords acyl 2*H*-azirines **134** in nearly quantitative yield (**Scheme 72**) <1997T10911>.



Scheme 72

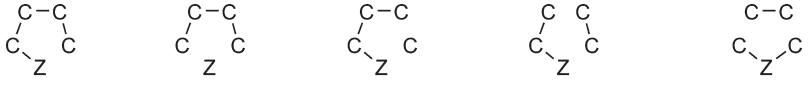
The photoisomerization of certain pyridines to Dewar pyridines is described in Section 3.2.1.2.2 and the formation of bridged ring 6*H*-1,2-dihydro-3-pyridones in Section 3.2.1.10.4.

4.2.3 Rings Containing Two Endocyclic Double Bonds

4.2.3.1 Overview

The only four-membered heterocycles with two endocyclic double bonds are the highly reactive azetes; an approach to their synthesis via photolysis of pyridazines is discussed in CHEC-III <CHEC-III(2.01.5.6)99>.

Very importantly, this section also includes the pyrroles, furans, and thiophenes. We deal with their preparation by cyclization methods of types **135** and **136** (Section 4.2.3.3.1), **137** (Section 4.2.3.3.2), **138** (Section 4.2.3.3.3), and **139** (Section 4.2.3.3.4), successively, but precede this by a discussion of their preparation by substituent introduction or modification.



The most important methods of synthesis for these ring systems and the sections in which they are considered are as follows:

1. Pyrroles: PaalKnorr (4.2.3.3.1.1), Knorr (4.2.3.3.3.1), Hantzsch (4.2.3.3.3.2).
2. Furans: PaalKnorr (4.2.3.3.1.1), FeistBenary (4.2.3.3.3.2).
3. Thiophenes: PaalKnorr (4.2.3.3.1.1), Hinsberg (4.2.3.3.4).

We then consider methods for the synthesis of pyrans, dihydropyridines, and their oxo derivatives, and finally methods for compounds with larger ring sizes.

4.2.3.2 Synthesis of Pyrroles, Furans, and Thiophenes by Substituent Introduction or Modification

For detailed discussion of this topic for pyrroles <CHEC-III(3.02)45>, furans <CHEC-III(3.06)407>, and thiophenes <CHEC-III(3.10)741>, see the quoted CHEC-III chapters and the related sections in Part 3.

All these rings undergo easy electrophilic substitution at the 2-position. Particularly for pyrrole and furan the high reactivity often leads to low yields and sometimes it is useful to incorporate deactivating substituents such as CO_2H which can later be removed.

N-Substituted pyrroles, furans, and thiophenes can be 2-lithiated, and these lithio derivatives are important synthetic intermediates (Section 3.3.3.8). 2-Mercurio and 2-palladio derivatives are also important (Sections 3.3.3.8.8 and 3.3.3.8.9).

The preparation of -substituted derivatives is more difficult and different methods have been used in the various series. 1-Tritylpyrrole undergoes electrophilic substitution selectively at the 3-position (Section 3.3.1.4.3) and the trityl group can then be removed. Again, in the pyrrole series the selective hydrolysis of -CO_2Et in alkali and -CO_2Et in acid, followed by decarboxylation, allows the introduction of -substituents into compounds such as 2,4-dialkylpyrrole-3,5-dicarboxylic esters to afford 3-substituted 2,4-dialkylpyrroles (Section 3.3.3.3.7).

2,4-Disubstituted furans can be prepared by the 3-lithiation of 2-phenylthio-5-alkylfurans, followed by reaction with an electrophile and then desulfurization with Raney nickel (Section 3.3.3.8.4). 3-Furylmercury acetate can be obtained from furan-2-carboxylic acid and transformed to other 3-substituted furans via the lithio compound.

3-Lithiothiophene is a key to the synthesis of many 3-substituted thiophenes. It is prepared from 3-bromothiophene, itself obtained from 2,3,4-tribromothiophene by selective Zn reduction or by rearrangement of 2-bromothiophene with $NaNH_2/NH_3$.

4.2.3.3 Synthesis of Pyrroles, Furans, and Thiophenes from Acyclic Precursors

4.2.3.3.1 From C_4Z or C_4 units

Three prominent types of reactions fall in this classification: cyclizations by condensation, metal-mediated cyclizations, and nitrenoid insertion reactions.

1. The versatile PaalKnorr synthesis (**Scheme 73**) is an important preparative method for furans and thiophenes; it is also extensively used for pyrroles. The common starting materials are 1,4-dicarbonyl compounds **140** or synthetic equivalents.

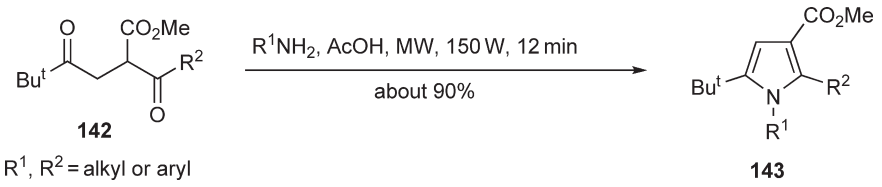
140 **141**

Scheme 73

   a. Pyrroles (**141**; Z = NH or NR) are synthesized by reaction of 1,4-diketones **140** with NH_3 or RNH_2 (**Scheme 73**) <CHEC-III(3.03.8)322>.

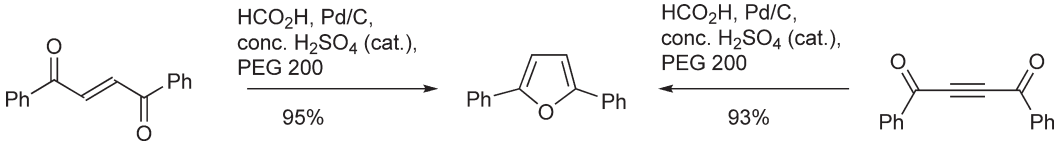
      Classical PaalKnorr conditions have been applied in syntheses of 1-aryl-2,5-di(2-thienyl)pyrroles by condensation of suitable 1,4-di(2-thienyl)-1,4-butanedione precursors with appropriate aniline derivatives <2002T3467>, or 1-(pyrrol-3-yl)pyrroles from 3-aminopyrroles and 1,4-dicarbonyl compounds <2001T10147>. This well-established reaction has also been used in the preparation of a series of 1,2-diarylpyrroles which displayed potency as selective inhibitors of cyclooxygenase-2 <1997JME1619>. It has also been demonstrated that the PaalKnorr reaction is a reversible process under certain conditions, which allows exchange of *N*-substituents in pyrroles via ring opening to a 1,4-dicarbonyl compound and subsequent ring closure involving a new amine component <2006SL1428>. A microwave-assisted PaalKnorr reaction has been used for efficient preparation of a library of pyrroles **143** (40 members) from the substrates **142** (**Scheme 74**) <2005EJO5277>.

   b. Furans (**141**; Z = O) are prepared by treatment of 1,4-diketones **140** with an acidic catalyst (**Scheme 73**) <CHEC-III(3.07.2.1)498>. A mechanistic study indicates that the cyclization follows a pathway of rapid protonation of one of the carbonyl groups followed by attack of the enol hydroxyl formed at the other carbonyl group <1995JOC301>.



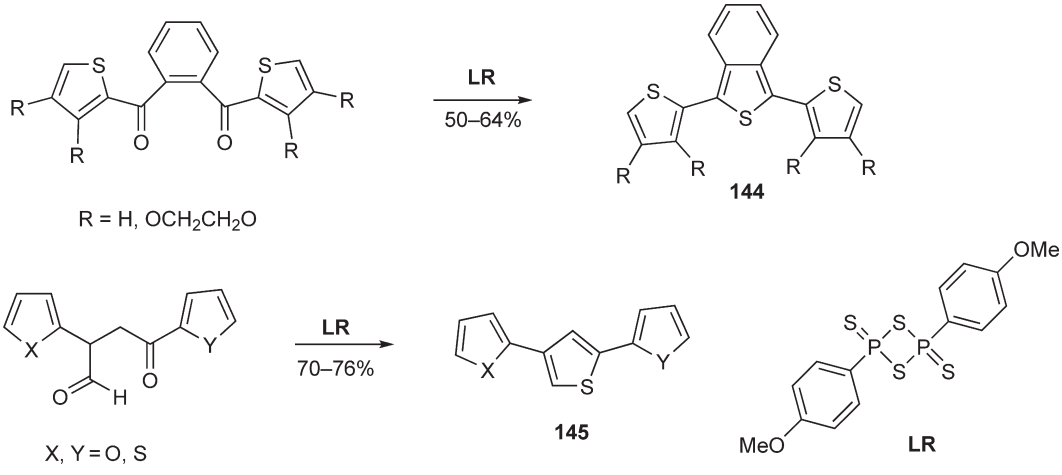
Scheme 74

The reaction can be carried out under milder conditions and with improved yields using catalysts other than Br½nsted acids. The acid-catalyzed synthesis of 2,3,4-trisubstituted furans from 1,4-diketones can be assisted by microwave irradiation <2004OL389>. 2-Butene-1,4-diones and 2-butyne-1,4-diones can also serve as starting materials in furan syntheses by the PaalKnorr method. For example, 2,5-diaryl- and 2,3,5-triarylfurans are obtained in high yield in the presence of Pd/C and H_2SO_4 with formic acid as reductant and poly(ethylene glycol)-200 as a solvent under microwave irradiation (**Scheme 75**) <2003JOC5392>.



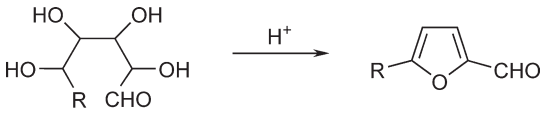
Scheme 75

c. Thiophenes **141** (Z = S) are prepared by thionation of 1,4-diketones **140** with P_4S_{10}, Lawessons reagent (LR), bis (tributyltin) sulfide, hexamethyldisilathiane, or a combination of hydrogen sulfide and an acid catalyst (**Scheme 73**) <CHEC-III(3.11.3.1.3)894>. LR is particularly useful as the sulfurating agent. For example, it has been used for the preparation of 1,3-dithienylisothianaphthenes **144** <2000CC939> and 2,4-disubstituted thiophenes **145** <1997H (45)2425> from the appropriate precursors (**Scheme 76**). The preparation of thiophenes via LR-mediated cyclization of 1,4-carbonyl compounds can be performed efficiently under microwave irradiation without solvent <2001JOC7925, 2005EJO5277>.



Scheme 76

2. 1,2,3,4-Tetrahydroxy compounds are used in further reactions of the same general type. Thus, hexoses (**146**; R = CH_2OH) and pentoses (**146**; R = H) give 5-hydroxymethylfurfural (**147**; R = CH_2OH) and furfural (**147**; R = H), respectively. In the presence of hydrochloric acid (or other chlorinating agents), 5-chloromethylfuran-2-carbaldehyde is obtained (**Scheme 77**) <1982CL617, 1992S541>.

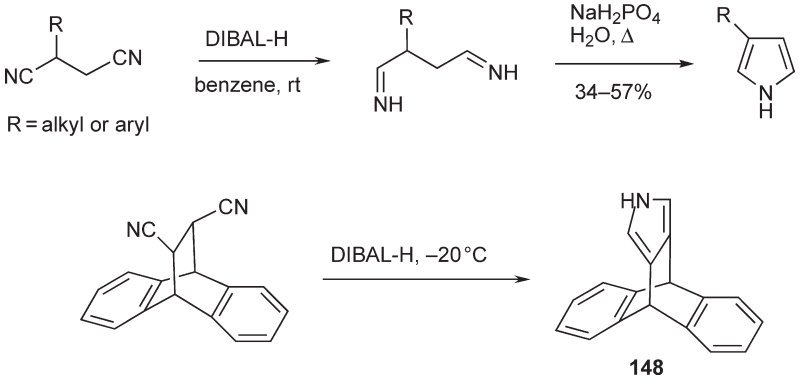


146 **147**

Scheme 77

3. A variety of other cyclizations of C_4 systems to pyrroles include the following <CHEC-III(3.03.2)270>.

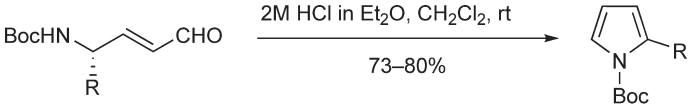
Substituted succinonitriles give 3-substituted pyrroles on reduction with DIBAL-H <1984TL1659> via diimine intermediates which undergo cyclization and aromatization (**Scheme 78**). This reaction was used in the synthesis of unusual pyrroles (e.g., **148**), which are important precursors to sterically shielded porphyrins <1994AGE889>.



148

Scheme 78

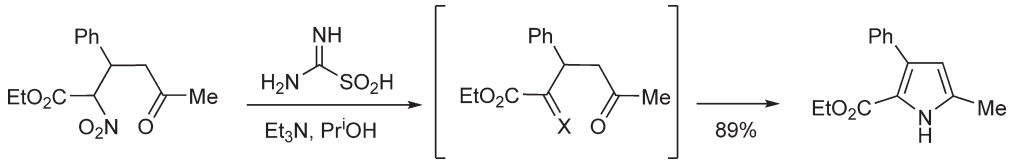
Protected -amino-,-enals **149** can be annulated to the products **150** upon exposure to acidic reaction conditions without touching the Boc protecting group (**Scheme 79**) <2002EJO2565>. Likewise, Boc-protected -amino-,-enones have been converted to pyrroles with concomitant removal of the Boc functionality by cyclization employing the phenol/TMSCl reagent combination <2000OL2283>. An organoaluminum-mediated approach starting from structurally related ,-disubstituted -amino-,-enones lacking the Boc group has also been realized <2004TL9315>.



149 R = Me, Et, Bn, Pr^i **150**

Scheme 79

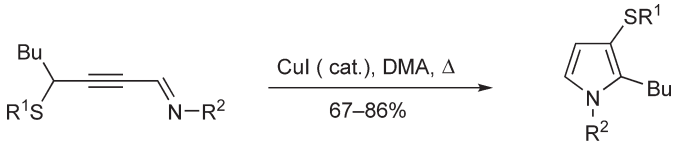
The -nitroketone **151**, prepared by Michael addition of ethyl nitroacetate to the appropriate enone, reacts with formamidinesulfinic acid and triethylamine to afford pyrrole-2-carboxylate **153**, presumably via the oxime or imine **152** (**Scheme 80**) <1995TL9469>.



151 **152** X = NH or NOH **153**

Scheme 80

Pyrrole and indole rings can also be constructed by intramolecular addition of nitrogen to a multiple bond activated by metal ion complexation. Copper-catalyzed cyclization of the thiopropargyl imines **154**, featuring a 1,2-migration of the alkylthio or arylthio substituents, has been demonstrated to provide good yields of pyrroles **155** (**Scheme 81**) <2003AGE98>. Similar cyclization reactions of related precursors bearing a hydrogen atom instead of the sulfur-containing moiety leading to pyrroles have also been reported <2001JA2074>.

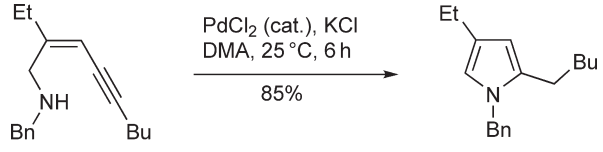


154 **155**

R^1 = Ph, *n*-$C_{12}H_{25}$; R^2 = Bu^t, Tr, $CH(Me)CH_2CO_2Et$

Scheme 81

The Pd(II)-catalyzed annulation of 2-en-4-ynylamine **156** gives pyrrole **157** in a good yield (**Scheme 82**) <2001TL1339>. Related copper-catalyzed reactions leading to pyrroles require higher temperatures <2003JOC7853>.



156 **157**

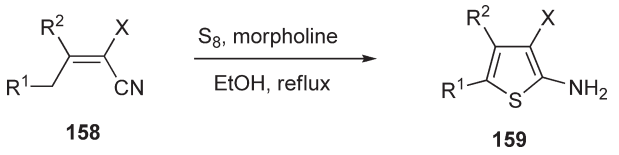
Scheme 82

4. Other cyclizations of a C_4 system to give thiophene include pyrolysis of butane with sulfur; this reaction is probably the source of thiophene in coal-tar benzene.

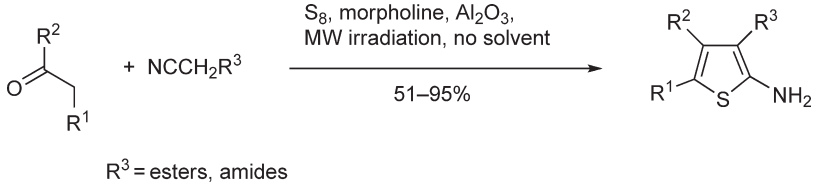
Cyclization reactions effected by intramolecular attack of a heteroatom on a nitrile group provide a useful source of 2-amino heterocycles, and numerous syntheses employ this strategy. Thus, the reaction of ,-unsaturated nitriles **158** with elemental sulfur in basic media, the Gewald synthesis (for a review see <1999JHC333>), provides a very convenient route to 2-aminothiophenes **159**, many of which are useful intermediates in the preparation of dyestuffs and pharmaceuticals (**Scheme 83**) <CHEC-III(3.11.3.1.2)891>.

The Gewald reaction can be conveniently performed via a multicomponent condensation between sulfur, an -methylene carbonyl compound, and an -cyanoester. The use of ionic liquids as solvents <2004SC3801>, or performing this condensation under microwave irradiation without solvent (**Scheme 84**) <2005SC1351>, leads to generally better yields of 2-aminothiophenes <CHEC-III(3.11.3.1.2)893>.

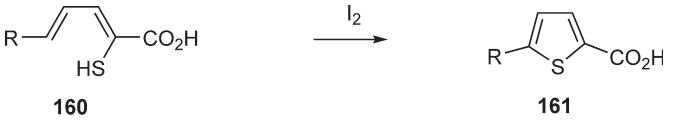
In the previous examples, the sulfur atom acted as a nucleophile. Electron-deficient sulfur species such as sulfenyl ion and its equivalents (e.g., disulfide/Lewis acid complexes, sulfenic acids, sulfenyl halides, sulfonium ions, sulfines, etc.), can alternatively serve as an electrophile <CHEC-III(3.11.2.1.2)851>. Oxidative ring closure of enethiols (-thioketocarboxylic acid) **160**, which proceeds via disulfides, produces thiophenes **161** in good yields (**Scheme 85**) <1988JHC367>.



Scheme 83



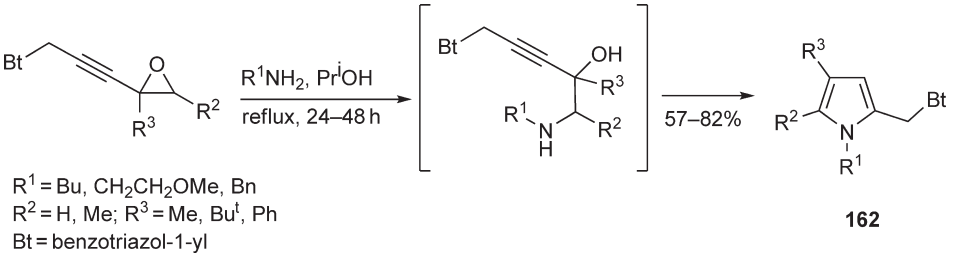
Scheme 84



R = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl, 2-chloro-3-thienyl, 2,5-dichloro-3-thienyl, 2-furyl

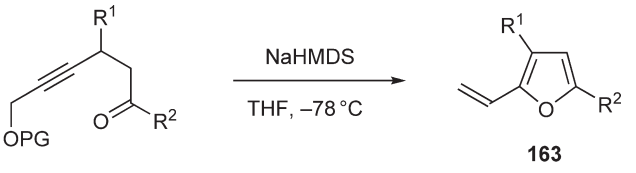
Scheme 85

5. Triple bonds are susceptible to nucleophilic addition, which can be utilized in intramolecular cyclizations leading to pyrroles **162** (**Scheme 86**) <1996JOC1624, 1997JOC4148> and furans **163** <1998JOC7132> (**Scheme 87**).



R^1 = Bu, CH$_2$CH$_2$OMe, Bn
R^2 = H, Me; R^3 = Me, Bu^t, Ph
Bt = benzotriazol-1-yl

Scheme 86

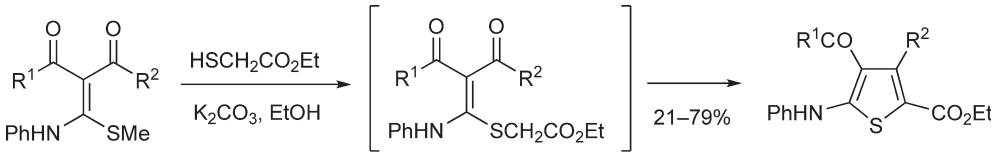


PG = MOM, MEM, Bn; R^1, R^2 = Ph, alkyl, H

Scheme 87

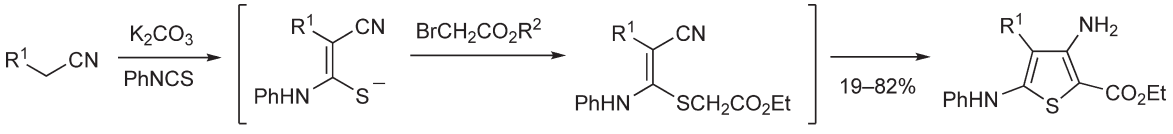
4.2.3.3.2 From C_3ZC or C_3 and CZ units

Many variations of this route involve the formation of the 2,3-bond of a thiophene by the 2-carbon atom acting as a nucleophilic center in an intramolecular addition to a carbonyl or a cyano group <CHEC-III(3.11.2.2)860>. Examples are shown in **Schemes 88** <2002TL257> and **89** <2003T1557>.



R^1 = Me, Ph, OEt; R^2 = Me, Ph

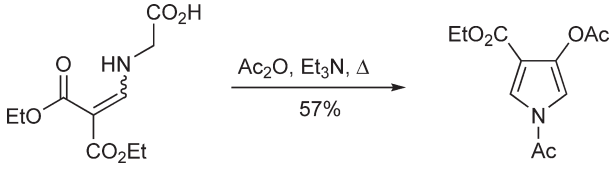
Scheme 88



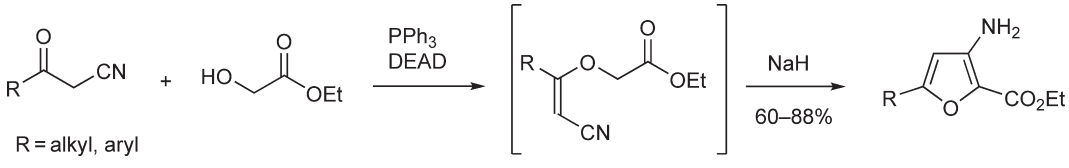
R^1 = CN, CO_2Et, COPh

Scheme 89

Pyrroles <CHEC-III(3.03.3)286> and furans <CHEC-III(3.07.2.1.2)506> can be prepared by a similar intramolecular condensation to that exemplified in **Schemes 90** <2002J(P1)2799> and **91** <2000OL2061>.



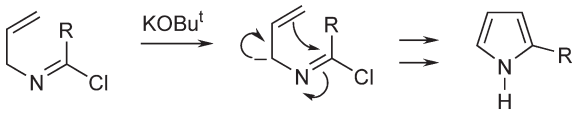
Scheme 90



R = alkyl, aryl

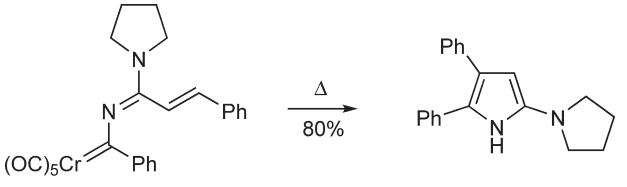
Scheme 91

Electrocyclization of a suitable carbanion (e.g., **164**) can also occur as illustrated in **Scheme 92** <1978AGE676>. Likewise, the electrocyclization of the precursor **165**, which can be prepared by condensation of a chromiumaminocarbene complex with a suitable amide, provides the pyrrole **166** (**Scheme 93**) <2002OM1819>.



164

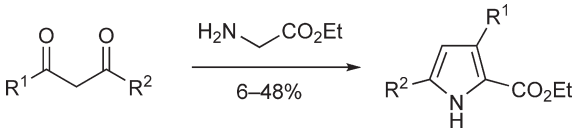
Scheme 92



165 166

Scheme 93

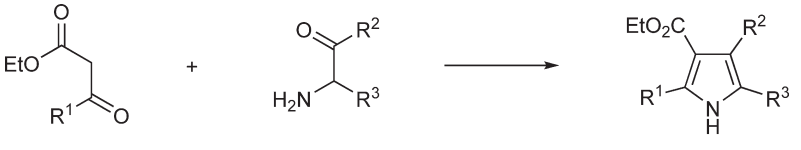
1,3-Dicarbonyl compounds and their synthetic equivalents can give pyrroles by condensation with amines having an electron-withdrawing substituent such as an ester or a ketone (**Scheme 94**) <1982S157>. Such condensations can produce two isomers when the dicarbonyl component is unsymmetrical.



Scheme 94

4.2.3.3.3 From C_2 and ZCC units

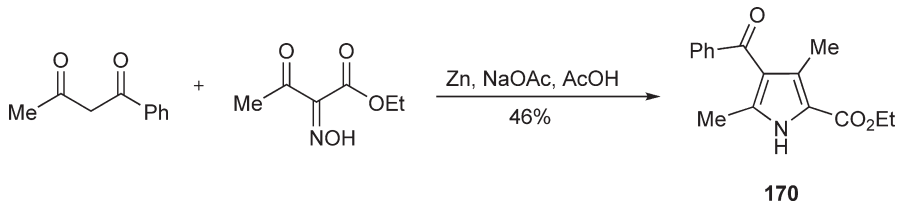
1. The versatile Knorr pyrrole synthesis is an important route to pyrroles **169**: it involves the condensation of a -keto ester **167** with an -amino ketone **168** (**Scheme 95**). The -keto ester can be replaced by a -diketone; simple ketones give poor yields. The amino ketone is frequently prepared *in situ* by nitrosation and reduction (e.g., with Zn—AcOH) of a second molecule of the -keto ester.



167 168 169

Scheme 95

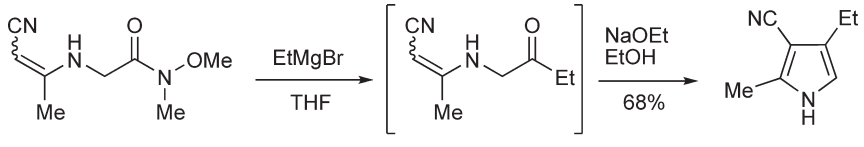
The Knorr synthesis offers a valuable and practical route to a number of pyrrolecarboxylates <CHEC-III(3.03.6) 302>, as illustrated by preparation of ethyl 4-acetyl-5-methyl-3-propyl-1*H*-pyrrole-2-carboxylate by reaction of an oxime derived from a 3-oxohexanoate with acetylacetone <1998JOC8769> or scale synthesis of the -opioid antagonist SB-342219 featuring generation of an aminoketone intermediate <2004OPD279>. A regioselective variant has been described, involving use of 1,3-dicarbonyl compounds bearing sterically demanding substituents, providing, for example, access to the product **170** (**Scheme 96**).



170

Scheme 96

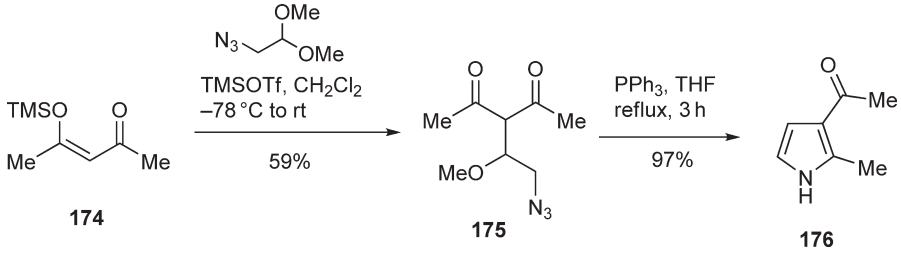
In an example illustrating a modification of the Knorr synthesis, the Weinreb amide derivative **171** is converted to the -enaminoketone **172** and annulated to the target pyrrole **173** (**Scheme 97**). Numerous pyrrole derivatives can be prepared using variations of this approach <1999T6555>.



171 172 173

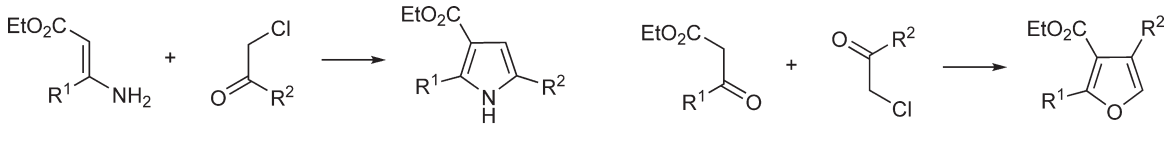
Scheme 97

Exposure of the substrate **174** to dimethyl acetal of azidoacetaldehyde in the presence of TMSOTf gives the intermediate **175**, which affords the pyrrole **176** under conditions of intramolecular aza-Wittig reaction (**Scheme 98**) <2005JOC4751>.



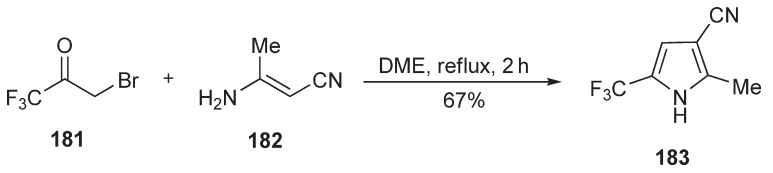
Scheme 98

2. -Halo ketones react with enamines **177** to form pyrroles (the Hantzsch pyrrole synthesis, <CHEC-III(3.03.6)302>) and with -keto esters **179** under basic conditions to give furans **180** (the FeistBenary furan synthesis, <CHEC-III(3.07.2.2.1) 508>). The orientation in the Hantzsch pyrrole synthesis **177** **178** differs from that in the FeistBenary furan synthesis **179** **180** (**Scheme 99**). In an example of a modified Hantzsch synthesis, the -aminoacrylonitrile **182** reacts with ketone **181** to give pyrrole **183** in a moderate yield (**Scheme 100**); a series of similar compounds can be synthesized using this approach <1997S530>. A solid-phase extension of the Hantzsch synthesis has also been reported <1998BML2381>.



177 178 179 180

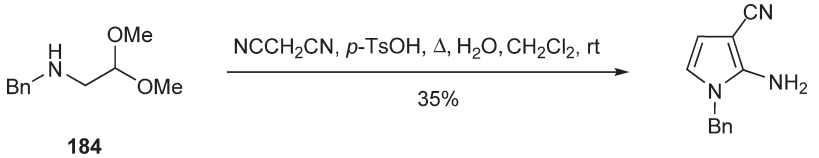
Scheme 99



181 **182** **183**

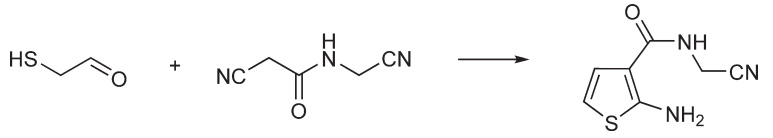
Scheme 100

The employment of activated cyanomethylene compounds (e.g., malononitrile) for condensation with -amino carbonyl derivatives (e.g., the protected aminoacetaldehyde **184**) provides 2-aminopyrroles **185** (**Scheme 101**) <2004OL2857>. In a comparable fashion, the condensation of -mercapto carbonyl compounds with malononitrile derivatives provides 2-aminothiophenes (**Scheme 102**) <1979LA328>. Similarly, 2-aminofuran-3-nitriles can be obtained by base-catalyzed condensation of -hydroxy ketones with malononitrile <1966CB1002>.



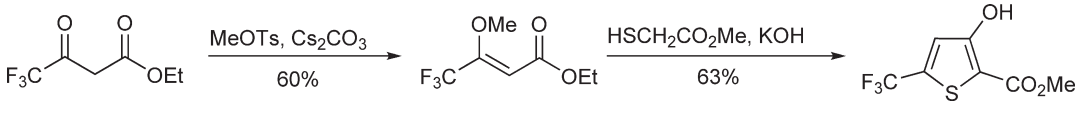
184 **185**

Scheme 101



Scheme 102

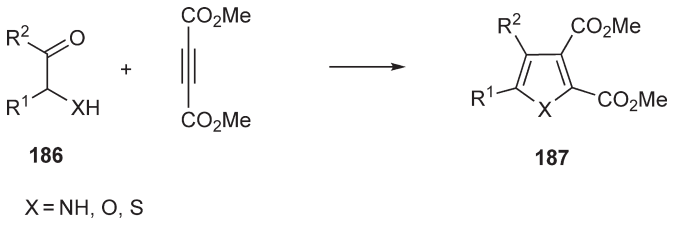
One of the most common strategies for the preparation of thiophenes involves the intramolecular condensation of -thioglycolates with adjacent carbonyls (Knoevenagel synthesis) <CHEC-III(3.11.2.2)860>; a representative example is shown in **Scheme 103**.



Scheme 103

3. Additions to conjugated triple bonds occur with facility. Thus, base-catalyzed addition of benzoin to dimethyl acetylenedicarboxylate provides a route to furans (**186** **187**; X = O), while pyrroles and thiophenes result from an analogous addition of -amino ketones (**186** **187**; X = NH) and -mercapto ketones (**186** **187**; X = S), respectively (**Scheme 104**) <1964JA107>.

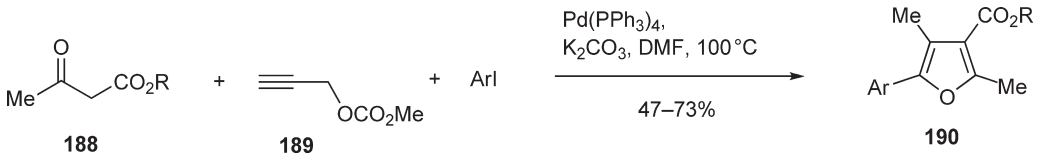
Regioselective [3 + 2] annulation has been reported for the preparation of various furans <CHEC-III(3.07.2.2.1) 508>. These annulations can be catalyzed effectively by transition metals. For example, simple propargyl compounds (e.g., methyl propargyl carbonate **189**) react with -ketoesters **188** using $Pd(PPh_3)_4$ as catalyst, and the furylpalladium intermediate can be further utilized for cross-coupling with an aryl iodide in order to introduce a substituent in the 2-position producing polysubstituted furans **190** in good yields (**Scheme 105**) <2005JOC6980>.



186 187

X = NH, O, S

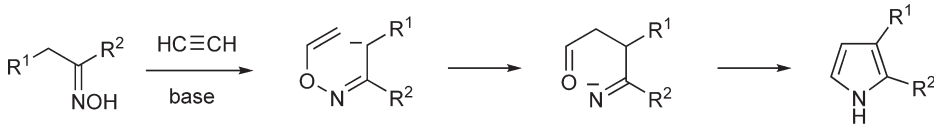
Scheme 104



188 189 190

Scheme 105

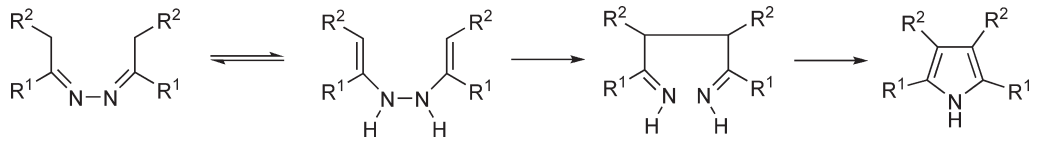
In Trofimovs pyrrole synthesis ketoximes **191** react with alkynes under strongly basic conditions (**Scheme 106**) <1994H(37)1193>. A key sigmatropic rearrangement of an *O*-vinyloxime (**192 193**) followed by a typical imine-carbonyl condensation affords the final product **194**.



191 192 193 194

Scheme 106

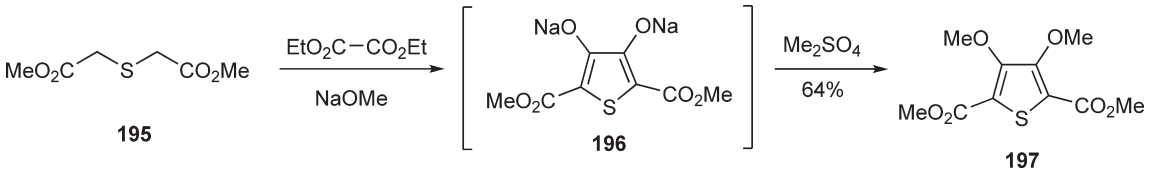
4. The PilotyRobinson pyrrole synthesis (**Scheme 107**) is the monocyclic equivalent of the Fischer indole synthesis. The conversion of ketazines into pyrroles under strongly acidic conditions proceeds through a [3,3] sigmatropic rearrangement of the tautomeric divinylhydrazine <1974JOC2575>. The reaction can be conducted under relatively mild conditions by converting the azine into the *N*,*N*-dibenzoyl derivative prior to thermal (140°C) rearrangement <1982CC624>.



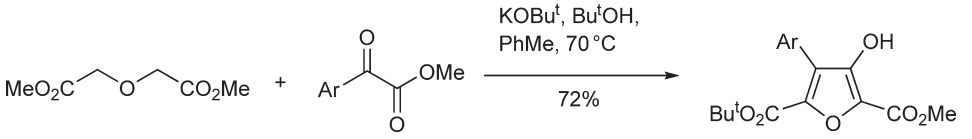
Scheme 107

4.2.3.3.4 From C_2 and CZC units

-Dicarbonyl compounds condense with thioglycolic acid esters in the presence of sodium alkoxide to give thiophene-2,5-dicarboxylic acid derivatives (Hinsberg thiophene synthesis) <CHEC-III(3.11.3.4.1)901>. For example, treatment of diester **195** with diethyl oxalate gives the disodium salt **196**, which is methylated by dimethyl sulfate to afford tetrasubstituted thiophene **197** (**Scheme 108**) <2004T10671>. The same basic method has been used for the synthesis of furans <CHEC-III(3.07.2.2)511>, selenophenes <CHEC-III(3.13.9.2.5)993>, and pyrroles <CHEC-III (3.03.9)327>. In a representative example, a simple access to 4-aryl-3-furanols is provided by the condensation of bis (alkoxycarbonylmethyl)ethers with various arylglyoxylates (**Scheme 109**) <2001TL6429>. Other carbanion-stabilizing groups such as cyano can be used in place of the ethoxycarbonyl group.

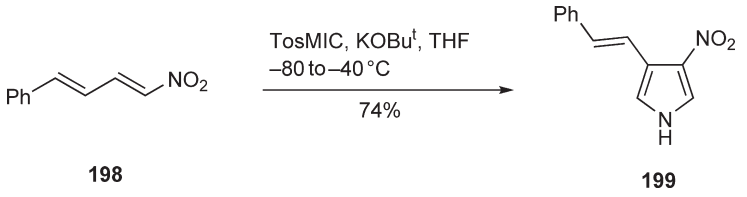


Scheme 108



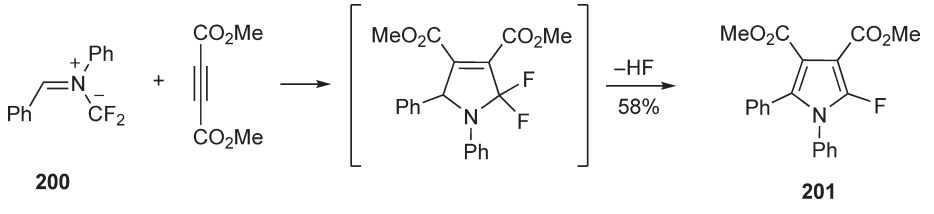
Scheme 109

A useful pyrrole synthesis depends upon the addition of the anion of *p*-toluenesulfonylmethyl isocyanide (TosMIC) to ,-unsaturated ketones or other Michael acceptors (van Leusen synthesis) <CHEC-III(3.03.9)327>. In an illustrative example, the diene **198** is converted into the pyrrole **199** in a good yield (**Scheme 110**). Related reactions starting from nitroalkenes or nitrodienes gave rise to a series of -nitropyrroles <1996S871>. The van Leusen method has also been used for construction of an intermediate in a total synthesis of dictyodendrin B <2005JA11620>, as well as a 3-aroyl-4-naphthylpyrrole *en route* to new antifungal agents <2005JME5140>.

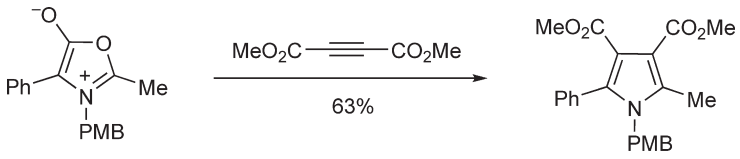


Scheme 110

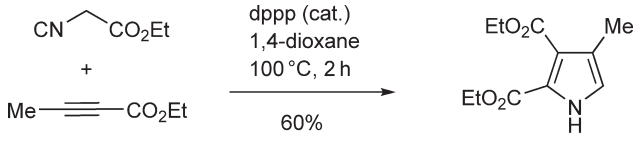
Other important pyrrole syntheses of this type are cycloadditions involving azomethine ylides (e.g., **200**), mesoionic oxazolium-5-olates (e.g., **202**), or isonitriles <CHEC-III(3.03.9)329>, as illustrated by the conversion of the reactant **200** into the fluoropyrrole **201** (**Scheme 111**) <1998JFC(90)117, 2005TL8337> and by the cycloaddition of mnchnone **202** leading to pyrrole **203** (**Scheme 112**) <1996JA2574>. An elegant pyrrole synthesis involving isocyanides and electron-deficient acetylenes affords the pyrrole **205** by exposure of ethyl isocyanoacetate to the alkyne **204** in the presence of 1,3-bis(diphenylphosphino)propane (dppp) (**Scheme 113**) <2005TL2563>.



Scheme 111



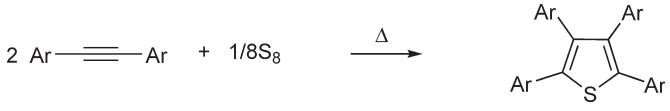
Scheme 112



Scheme 113

4.2.3.3.5 From two C_2 and Z units

Diarylethynes react with elemental sulfur to give tetraarylthiophenes in good yields (**Scheme 114**) <1993SUL273>. Although the reaction requires rather forcing conditions, it is a practical method, e.g., diphenylethyne and elemental sulfur at 220240°C affords tetraphenylthiophene. The method is also applicable to tetraarylselenophenes <CHEC-III (3.13.9.3)993>.

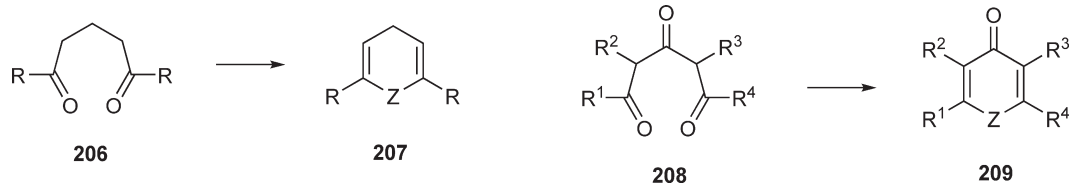


Scheme 114

4.2.3.4 Synthesis of Pyrans, Dihydropyridines, and their Thio and Oxo Derivatives from Acyclic Precursors

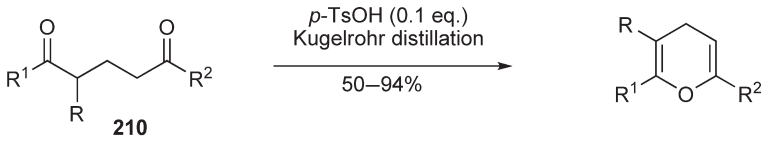
4.2.3.4.1 From C_5 units

These heterocycles are commonly prepared by the cyclization of appropriate 1,5-dicarbonyl precursors: 1,5-diones yield 4*H*-pyrans or dihydropyridines (**206 207**, Z = O, S, or NH) (which are sometimes oxidized *in situ*); 1,3,5-triones **208** give -pyrones (**209**; Z = O) by dehydration; and -pyridones (**209**; Z = NH) by the action of ammonia (**Scheme 115**).



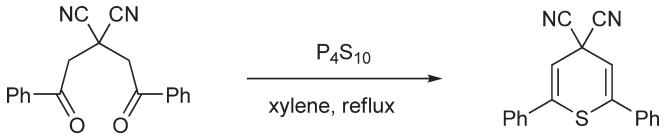
Scheme 115

The synthesis of 4*H*-pyrans by the ring closure of 1,5-dicarbonyl compounds or their equivalents was the subject of a review <2000CHE1007>. In a specific example, 2,6-bis(silyl)-4*H*-pyrans **211** are synthesized by the cyclodehydration of the corresponding 1,5-bis(silyl)pentane-1,5-diones **210** in good yields (**Scheme 116**) <CHEC-III(7.08.4.1)446, 2000S843>.



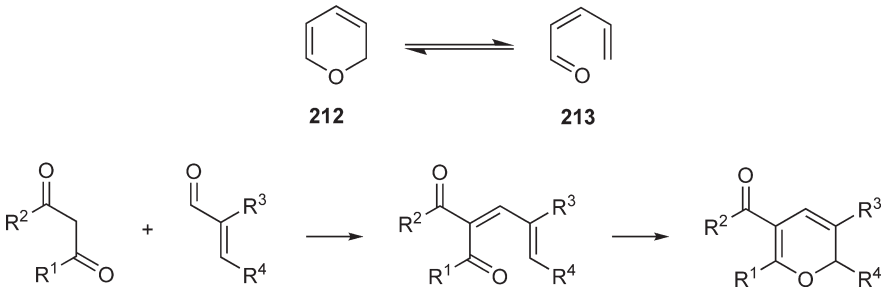
Scheme 116

4*H*-Thiopyrans are prepared similarly by the intramolecular cyclization of 1,5-dicarbonyl compounds in the presence of a thionating reagent (e.g., **Scheme 117**) <CHEC-III(7.10.4.1.4)865, 2002PS2791>.



Scheme 117

The 2*H*-pyran system can undergo relatively facile electrocyclic ring opening to form *cis*-2,4-dienones <CHEC-III (7.08.2)425> and several syntheses of 2*H*-pyrans are based on the preparation of the acyclic precursors **213** in the hope that the dienone 2*H*-pyran equilibrium will favor the heterocycle **212**. Such dienone precursors can be obtained by Knoevenagel condensation of 1,3-dicarbonyl compounds with ,-unsaturated aldehydes (**Scheme 118**). Simple 1,3-diketones yield the 2*H*-pyran directly <1988IZV1815> and cyclohexan-1,3-diones afford fused pyrans <1987JOC1972>.

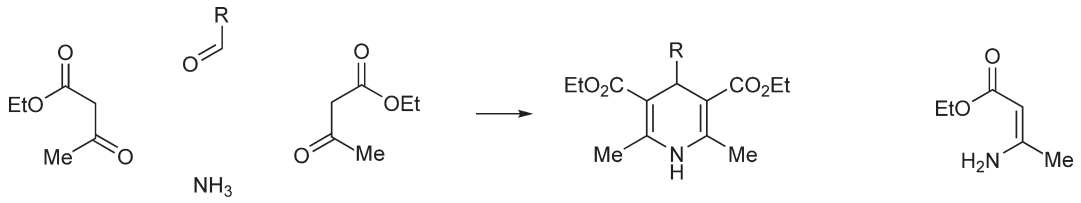


Scheme 118

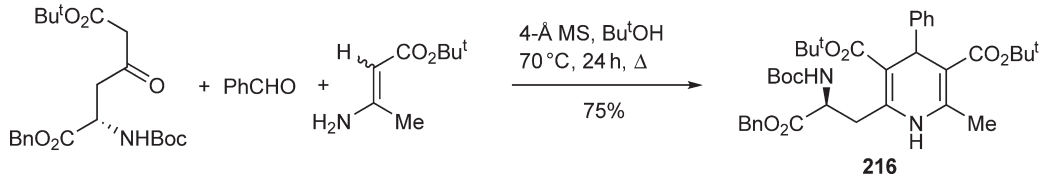
4.2.3.4.2 With C–C bond formation

1. The Hantzsch pyridine synthesis affords 1,4-dihydropyridines **214**, although spontaneous oxidation to pyridines often occurs. In its simplest form it involves the condensation of two molecules of a -keto ester with an aldehyde and ammonia (**Scheme 119**) <CHEC-III(7.05.2.3)285>. Compounds resulting from the condensation of ammonia with one of the carbonyl components can be used in the Hantzsch synthesis. Thus, -aminocrotonic ester **215** can replace the ammonia and one mole of acetoacetic ester in **Scheme 119**. The mechanism of the Hantzsch synthesis has been clarified by ^{13}C and ^{15}N NMR spectroscopy <1987T5171>.

   Further modifications of the Hantzsch pyridine synthesis include a solvent-free approach <2004SL827> and the use of phase-transfer catalysis and diethylene glycol as solvent <2004TL9011>. Highly functionalized 1,4-dihydropyridines **216** are produced in one pot with a simplified purification involving polymer-supported scavengers to remove excess reagents (**Scheme 120**) <2004T2311>.

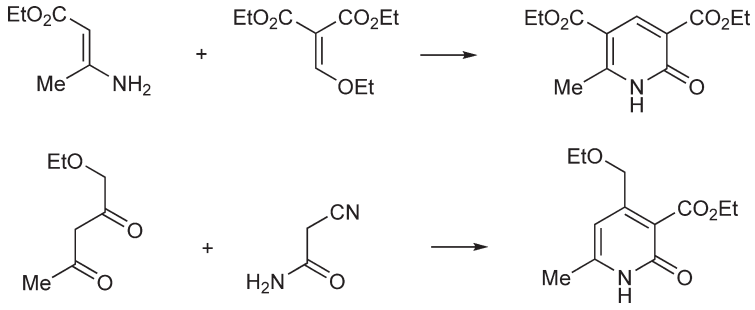


Scheme 119



Scheme 120

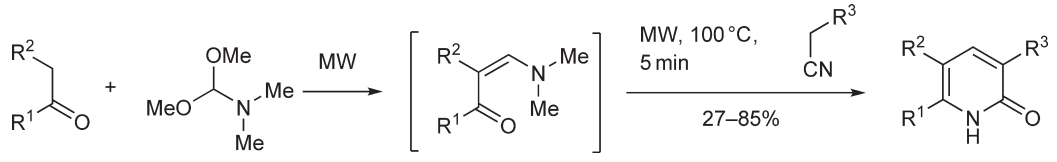
2. Related preparations of 2-pyridones involve condensation of enamines and enamides with 1,3-bielectrophiles, e.g., Scheme 121.



Scheme 121

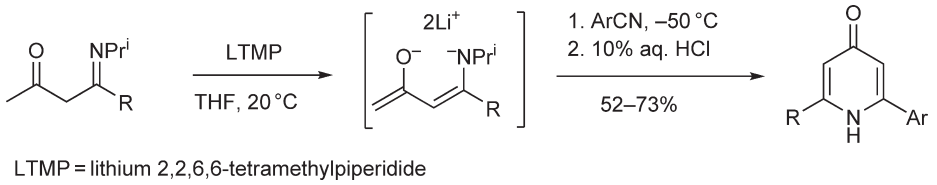
Numerous pyridines have been synthesized using cyanoacetamide (or cyanothioacetamide), malononitrile, malonamide, and closely related compounds, which provide the NC(2)C(3) fragment; for reviews see <1986H(24)2023, 1987H(26)205, 1993CRV1991>. Principal coreagents are ,-unsaturated ketones, arylidene malononitriles (for a review see <1983H(20)519>), and -diketones or -ketoaldehydes. Microwave reaction conditions can be used for the synthesis of 2-pyridones in a modern version of the traditional 3-component condensation reaction <2004T8633> (Scheme 122).

3. 4-Pyridones can be made by the condensation of nitriles with dianions of -diketones or 3-iminoketones (e.g.,



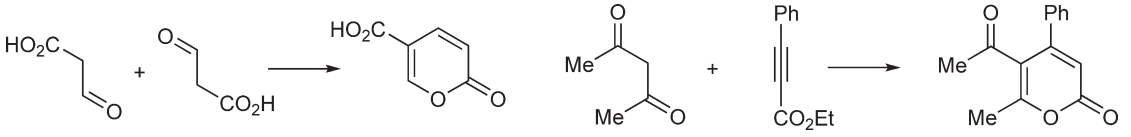
Scheme 122

Scheme 123) <1992JOC6020>.

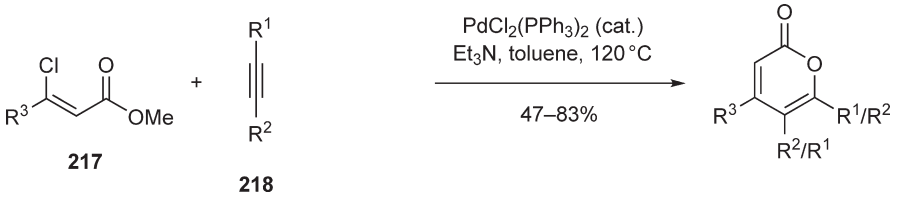


Scheme 123

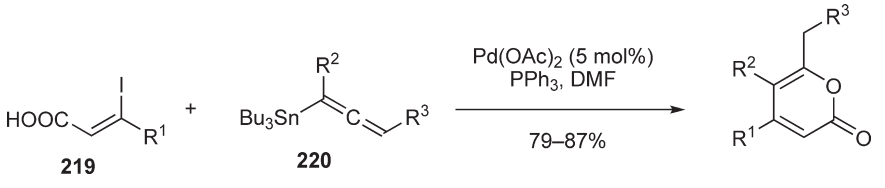
4. The classical routes to 2*H*-pyran-2-ones (-pyrones) are illustrated in **Scheme 124** <CHEC-III(7.08.13)544>. Additional examples include various transition metal-catalyzed cyclizations <CHEC-III(7.08.13.2)551>, e.g., the palladium-catalyzed reaction of -chloroacrylates with internal alkynes (**Scheme 125**) <2001NJC179> and the coupling of tributylstannyl allenes with (*Z*)--iodoacrylic acid (**Scheme 126**) <2005JOC6669>.



Scheme 124



Scheme 125



Scheme 126

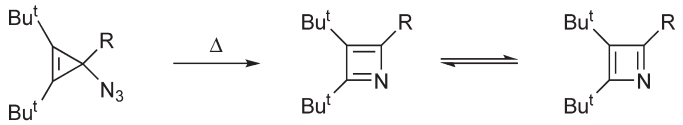
4.2.3.5 Synthesis of Four-, Five-, and Six-Membered Rings from Carbocyclic or Heterocyclic Precursors

4.2.3.5.1 With ring expansion

Heating 3-azidocyclopropenes **221** neat at 125°C results in a concerted N_2 expulsion and 1,2-C shift to afford the corresponding 2,3,4-trisubstituted azetes **222** (**Scheme 127**) <1986AGE842>.

The isomerization of ethynyl-oxiranes **223** leads to furans **224**, as illustrated in **Scheme 128** <1969JCC12>. A similar reaction of ethynyl-oxiranes with amines gives pyrroles (see **Scheme 86** in Section 4.2.3.3.1). Aziridine **225** reacts with bis(trimethylsilyl)acetylene upon heating to provide pyrrole **226** (**Scheme 129**) <1999JOC1630>.

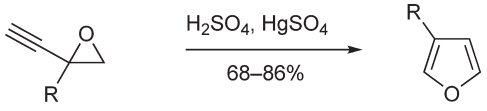
Base-catalyzed dimerization of diketene **227** efficiently yields dehydroacetic acid **228** (**Scheme 130**); treatment of diketene with aqueous triethylamine gives 2,6-dimethyl-4-pyrone **229**.



221 **222a** **222b**

R = But, mesityl, 1-adamantyl

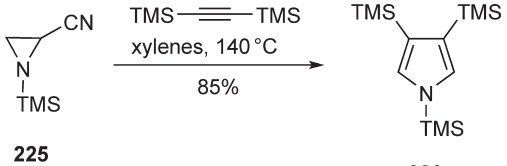
Scheme 127



223 **224**

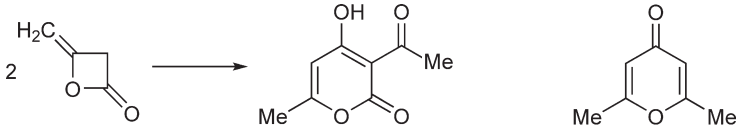
R = Me, But, Ph

Scheme 128



225 **226**

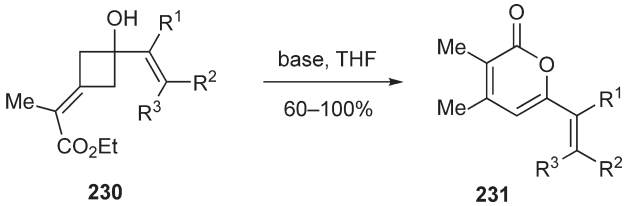
Scheme 129



227 **228** **229**

Scheme 130

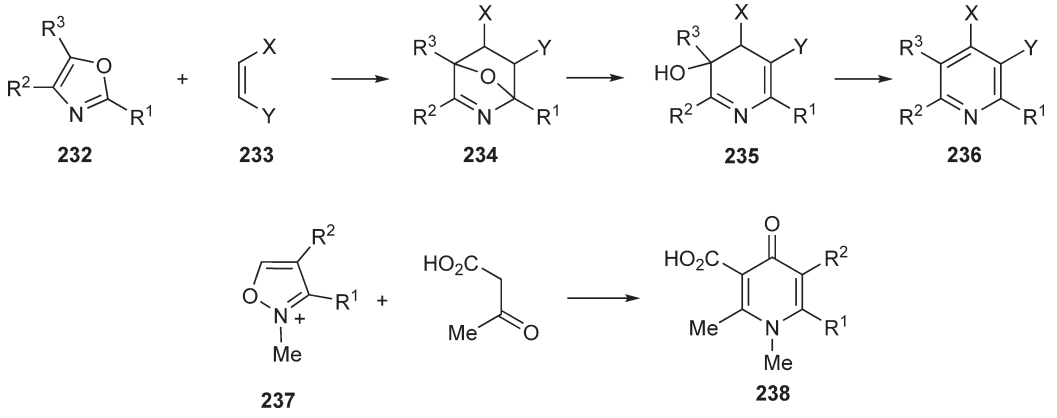
Various substituted cyclobutanes and cyclobutenes can be utilized in the synthesis of 2-pyrones <CHEC-III(7.08.13) 549>. For example, 2-hydroxyl cyclobutylidenes **230** undergo base-promoted rearrangements to afford 2*H*-pyran-2-ones **231** via formation and ring closure of an intermediate 1,5-keto ester (**Scheme 131**) <2005TL8237>.



230 **231**

Scheme 131

Ring opening of the cycloadducts **234** from oxazoles **232** and dienophiles **233** gives dihydropyridines **235** and frequently pyridines **236**; entities such as XR^3, HR^3, or XOH can also be lost in the aromatization of intermediate **235**. Isoxazolium salts with active methylene compounds can undergo ring expansion; thus, isoxazolium salt **237** with acetoacetic ester gives the 4-pyridone **238** (**Scheme 132**) <CHEC-III(7.05.3.3.3)293>.

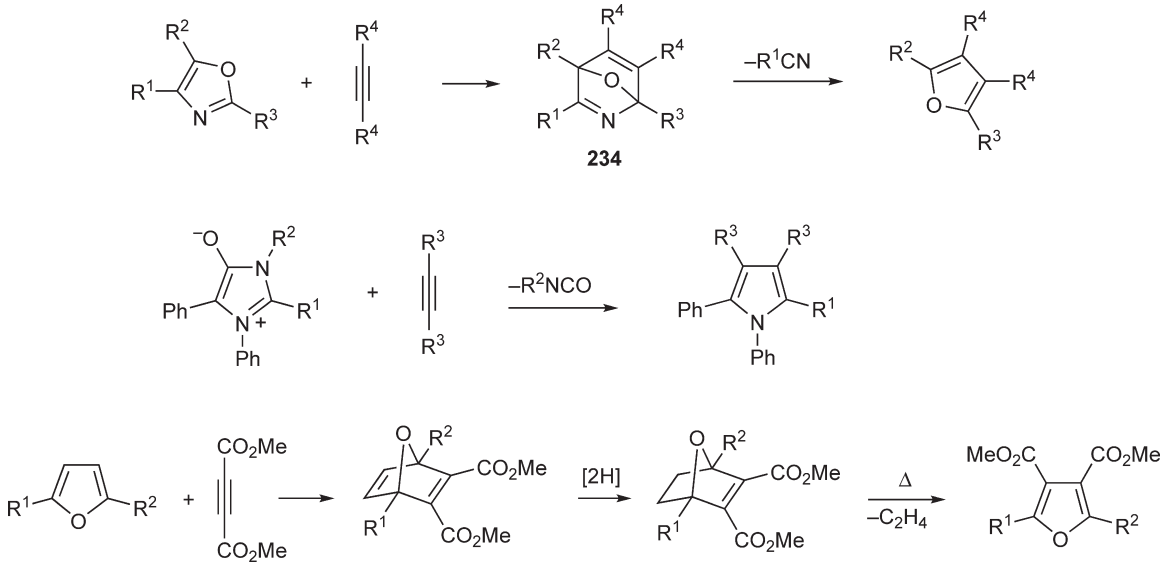


Scheme 132

See the sections (3.3.2.3.3 and 3.4.1.6.5.2) for ring expansion of 2,3-dihydrothiophenes to thiophene derivatives and 1,2-dithiolium cations to thiinthiones.

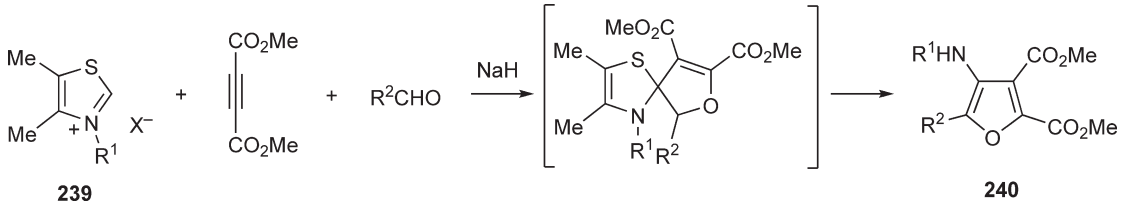
4.2.3.5.2 No change in ring size

Furans <CHEC-III(3.07.2.4)515>, thiophenes <CHEC-III(3.11.5.2)905>, and pyrroles <CHEC-III(3.03.10)331, 2005COR261> have all been obtained by addition of alkyne dienophiles to a variety of other five-membered heterocycles, as illustrated in **Scheme 133** (see also Section 4.2.3.3.4). As the alkyne moiety provides carbons 3 and 4 of the resulting heterocycle, this synthetic approach represents an attractive way of introducing carbonyl-containing substituents at these positions, especially as many of the heterocyclic substrates are readily available. Even furans can be converted into other furan derivatives by this method (**Scheme 133**) <1985JHC1233>.



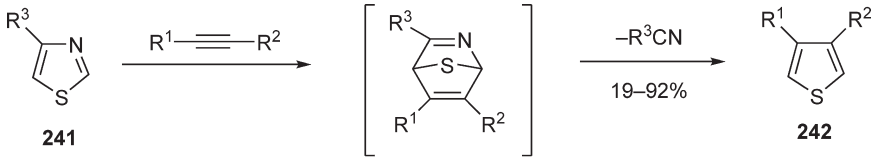
Scheme 133

The highly substituted 3-aminofurans **240** can be conveniently prepared via a three-component reaction of thiazolium salts **239**, aldehydes, and dimethyl acetylenedicarboxylate (**Scheme 134**) <2005JOC8919>, and 3,4-disubstituted thiophenes **242** are synthesized by an intermolecular cycloadditioncycloreversion procedure between substituted acetylenes and 4-substituted thiazoles **241** (**Scheme 135**) <1996CC339>.



239 **240**

Scheme 134



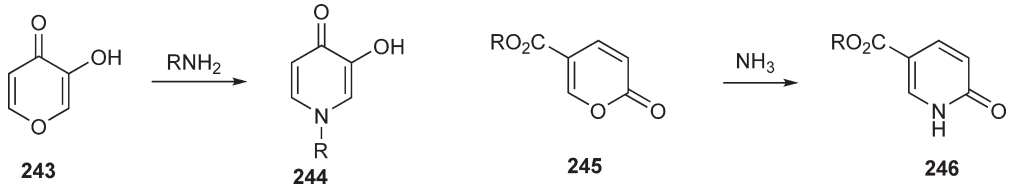
241 **242**

R^1, R^2 = H, Me, Bu, Ph, TMS; R^3 = Me, Ph

Scheme 135

Furans can be converted into the corresponding thiophenes or pyrroles by passing the furan with hydrogen sulfide or ammonia over an alumina-based catalyst at elevated temperatures. Conversions of furans into thiophenes are also achieved with hydrogen sulfide and hydrogen chloride at 80100°C <1980DOK(255)1144>. Selenophenes can be obtained similarly.

Aminolysis of - and -pyrones is important for the preparation of 2- and 4-pyridones, e.g., **243** **244** and **245** **246** (**Scheme 136**) (see also Section 3.2.1.6.4).



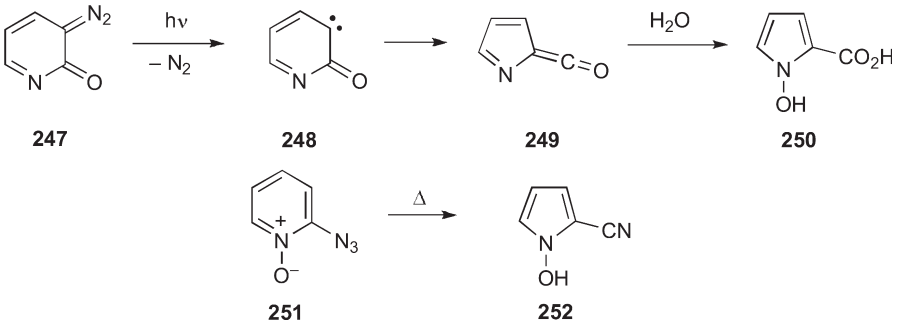
243 **244** **245** **246**

Scheme 136

4.2.3.5.3 With ring contraction

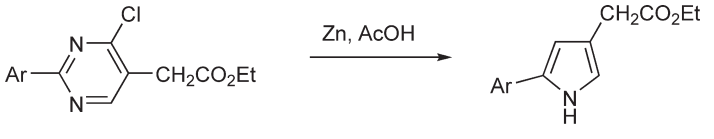
The photolytic Wolff ring contraction of diazopyridones **247** leads to pyrrole-2-carboxylic acids **250** via carbene **248** and ketene **249** intermediates <1976S754>. The thermolysis of 2-azidopyridine *N*-oxides **251** affords *N*-hydroxy-2-cyanopyrroles **252** (**Scheme 137**) <1973JOC173> (see also Section 3.4.3.11).

Reduction of appropriate 2-arylpyrimidines **253** with zinc in acetic acid provides pyrrolylacetic acids **254** (**Scheme 138**) <1970JCC1658>. Likewise, 1,2-diazines can be converted into pyrroles via a ring-contraction protocol. For example, DielsAlder cycloaddition involving the alkyne **255** and the 1,2,4,5-tetrazine **256** results in formation of the intermediate diazine **257**, which can be converted to the densely substituted pyrrole **258** by treatment with zinc in acetic acid (**Scheme 139**) *en route* to the natural product ningalin A <1999JA54>. This methodology also proved efficient in total syntheses of ningalin B <2000JOC2479> and isochrysohermidindistamycin hybrids <2003JOC5249>.



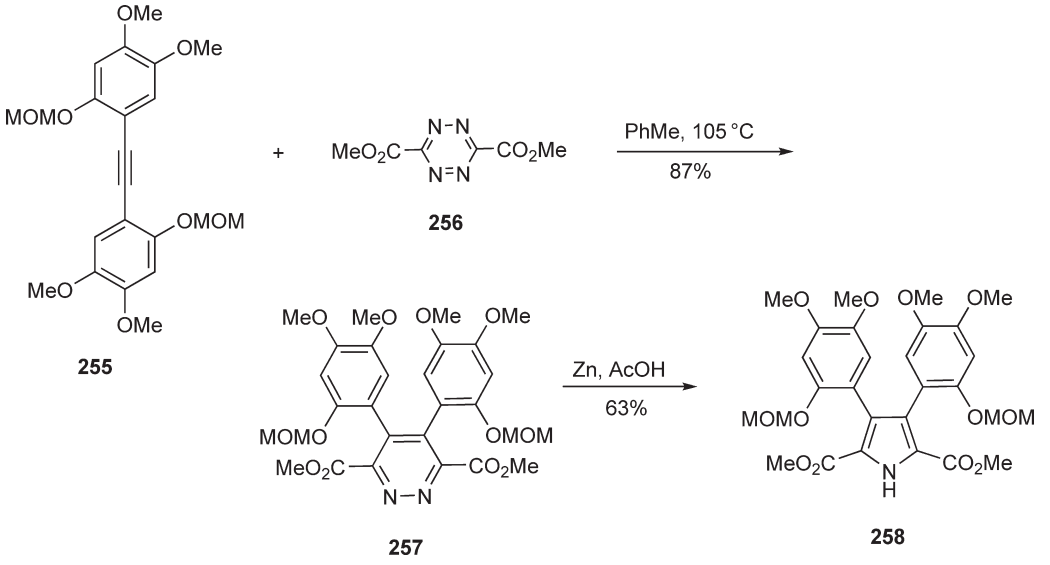
247 248 249 250 251 252

Scheme 137



253 254

Scheme 138



255 256 257 258

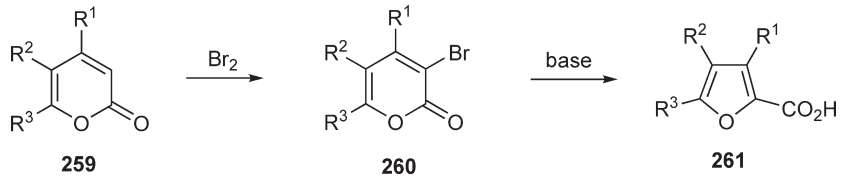
Scheme 139

3-Bromopyrones **260**, which are available from the bromination of pyrones **259**, on treatment with base yield furancarboxylic acids **261** (**Scheme 140**) <1980JOC1524>. Related reactions include preparations of furans from pyrylium cations (Section 3.2.1.6.3.5).

3,6-Dihydro-1,2-dioxines **262** (available from dienes and singlet oxygen) can be transformed into furans **264** by reduction and rearrangement into intermediate products **263** and subsequent elimination of water, usually by treatment with base (**Scheme 141**) . In some cases Co(II) and Fe(II) catalysts have been used <CHEC-III(3.07.2.3)513, 2005JOC6995>.

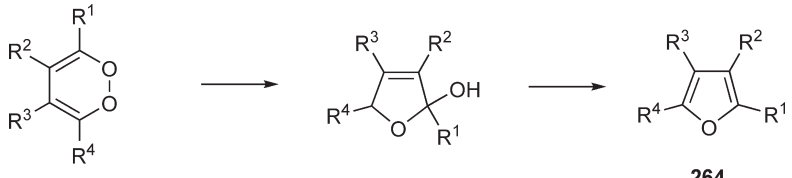
1,4-Dithiins **265** and 1,2-dithiins **266** readily lose sulfur on heating or photolysis yielding the corresponding thiophenes **266** and **268** (**Scheme 142**) <CHEC-III(3.11.5.3)909>.

For a triazepine to pyrrole ring contraction, see Section 3.5.2.1.



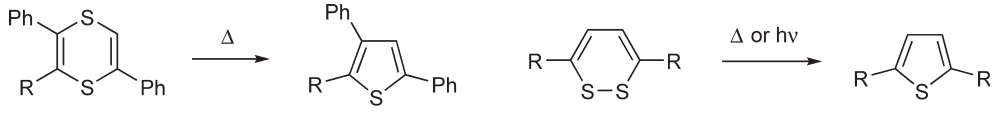
259 260 261

Scheme 140



262 263 264

Scheme 141

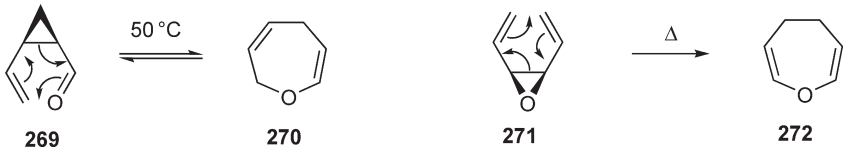


265 266 267 268

Scheme 142

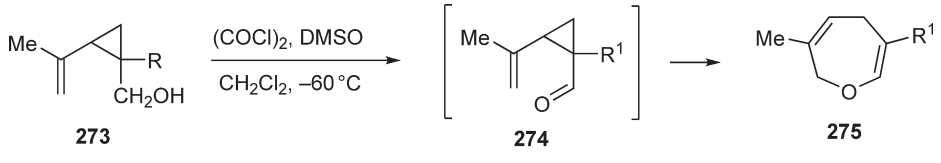
4.2.3.6 Synthesis of Seven- and Eight-Membered Rings

A common synthetic route of dihydrooxepins is based on the interconversions between *cis*-2-vinylcyclopropanecarboxaldehyde **269** and 2,5-dihydrooxepin **270** <1969JA2813> and *cis*-1,2-divinyloxirane **271** and 4,5-dihydrooxepin **272** (**Scheme 143**) <1963JOC1383, 1999J(P1)605>. For example, the Swern oxidation of isopropenyl-substituted cyclopropylcarbinols **273** (**Scheme 144**) results in ring expansion to respective methyldihydrooxepins via the intermediate vinylcyclopropanecarboxaldehyde **274** <CHEC-III(13.02.8)66, 1997BCJ2215>.



269 270 271 272

Scheme 143



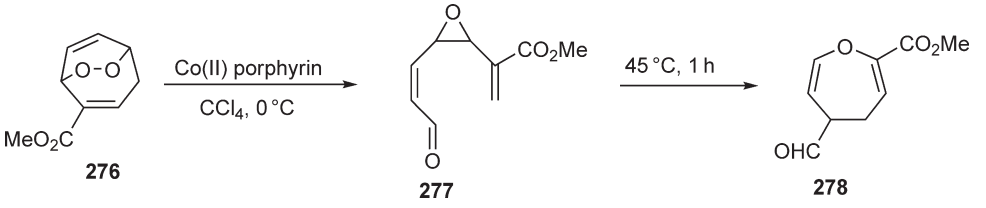
273 274 275

R = CH_2OH, CO_2Me, CO_2Bu

R^1 = CHO, CO_2Me, CO_2Bu

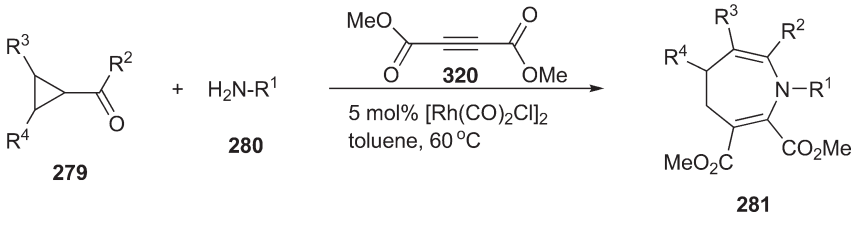
Scheme 144

Substituted cycloheptatriene endoperoxide **276** when treated with Co(II) porphyrin undergoes ring opening (**Scheme 145**) to give in moderate yield the oxirane **277**, which is quantitatively converted into the 4,5-dihydrooxepin derivative **278** <1997J(P1)2071>.



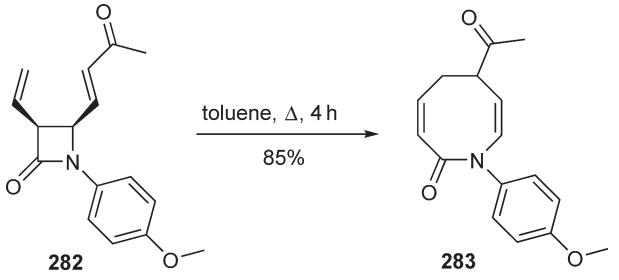
Scheme 145

Substituted 4,5-dihydroazepines **281** can be prepared in high yield by a rhodium-mediated hetero-[5 + 2]-cycloaddition of the cyclopropyl imines derived from ketones **279** on reaction with the primary amines **280**, with dimethyl acetylenedicarboxylate (**Scheme 146**) <2002JA15154>.



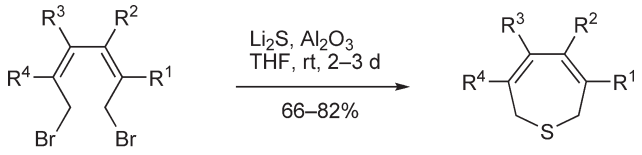
Scheme 146

cis-Divinyl--lactam **282** with alkenyl groups at both C(3) and C(4) positions undergoes thermally induced [3,3] sigmatropic (Cope) rearrangement to produce tetrahydroazocinone **283** (**Scheme 147**) <2001TL3081> by a concerted C(3)–C(4) bond breakage of the azetidine ring. The process is thermodynamically favored by relief of the four-membered ring strain.



Scheme 147

The reaction of dibromides **284** and Li_2S affords dihydrothiepines **285** in good yields (**Scheme 148**) <2000H897>.



284 **285**

Scheme 148

4.2.4 Rings Containing Three Endocyclic Double Bonds

4.2.4.1 Synthetic Methods for Substituted Pyridines

There are several significant ring syntheses for pyridines, of which the most important is the Hantzsch synthesis of dihydropyridines (Section 4.2.3.4.2). However, the majority of substituted pyridines are prepared from pyridine itself or from a simple alkyl derivative.

Frequently used methods for introducing substituents into the various positions of the pyridine nucleus include the following:

1. *Substituents in the 2-position*. They are often introduced via the Chichibabin reaction, which gives 2-aminopyridines (Section 3.2.1.6.4). These can be converted into 2-halopyridines and 2-pyridones (Section 3.2.3.5.3); all are versatile intermediates.
2. *Substituents in the 4-position*. They are most frequently introduced by further transformations of the readily available 4-nitropyridine 1-oxides (Section 3.2.1.4.4).
3. *Substituents in the 3-position*. Pyridines can be halogenated (Section 3.2.1.4.7) and sulfonated (Section 3.2.1.4.5) in the 3-position. Yields are better if an activating substituent (which can subsequently be removed) is present in the 2-position and in this case nitration is also feasible. The resulting 3-nitro- and 3-halo-pyridines and pyridine-3-sulfonic acids can be converted into other compounds by the usual methods of benzenoid chemistry.

4.2.4.2 Synthesis of Six-Membered Rings from Acyclic Compounds

4.2.4.2.1 From or via pentane-1,5-diones

As discussed in Section 4.2.3.4.1, pentane-1,5-diones **288** can undergo ring closure to give a pyran **287** or, in the presence of ammonia, a dihydropyridine **289**. Oxidative aromatization of these products occurs so easily that it frequently takes place prior to isolation, giving a pyrylium salt **286** or a pyridine **290**. The Hantzsch dihydropyridine synthesis is described in Section 4.2.3.4.2 (see also <CHEC-III(3.03.6)302>).

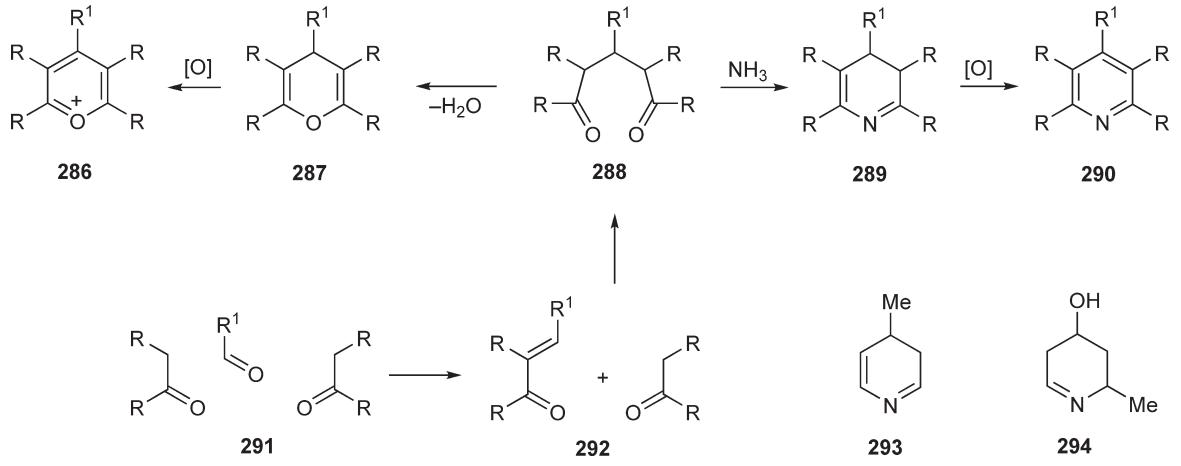
The pentane-1,5-dione is usually formed *in situ* by aldol- or Michael-type reactions (**291** **292** **288**). Thus, acetaldehyde (**291**; R = H, R^1 = Me) and ammonia give 4-picoline and 3-ethyl-4-methylpyridine by formation of the possible intermediate **293**, condensation with another molecule of MeCHO, and subsequent dehydrogenation. The same reaction also yields 2-picoline and 5-ethyl-2-methylpyridine possibly via the intermediate **294** (**Scheme 149**). Such reactions are used industrially.

4.2.4.2.2 From pent-2-ene-1,5-diones

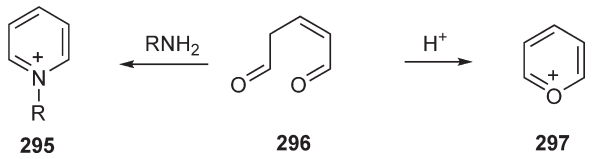
Ring closure of glutaconic dialdehyde **296** with ammonia gives pyridine and with hydroxylamine forms pyridine *N*-oxide, while primary amines yield pyridinium salts **295** and acids afford pyrylium cations **297** (**Scheme 150**). Substituted glutaconic dialdehydes and related diketones react similarly. If one of the carbonyl groups is incorporated in a carboxyl group or a modified carboxyl group, -pyridones and -pyrones are formed. Pent-2-ene-1,5-diones or nitrogen analogues can be built up from components and subsequently cyclized, e.g., NH_3 + **298** **299** and Me_2CO + 2$(CO_2Et_2)_2$ **300** (**Scheme 151**). The conjugate addition of the potassium enolate of methyl ketones to -oxoketene dithioacetals gives pent-2-ene-1,5-diones; ring closure with ammonium acetate in hot acetic acid then affords excellent yields of 2,6-disubstituted 4-(methylthio)pyridines.

4.2.4.2.3 Other methods

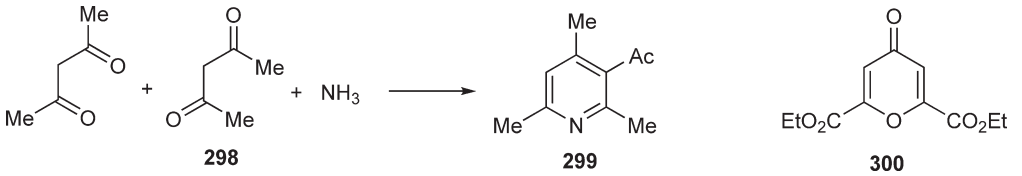
[4 + 2] Cycloaddition reactions with participation of azadienes are important in pyridine synthesis <CHEC-III(7.05.2.2.2)254>. Although a dihydropyridine is an intermediate, spontaneous conversion into a pyridine occurs when a suitable leaving group is present, e.g., **301** **302** (**Scheme 152**) (the process can be accelerated by sonication) <1994T10047>.



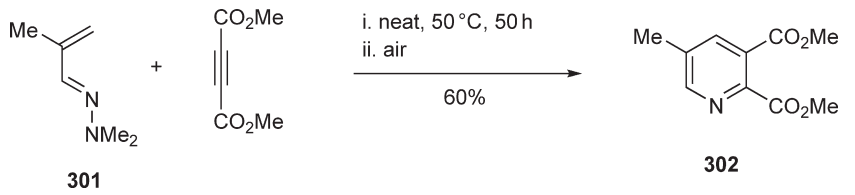
Scheme 149



Scheme 150

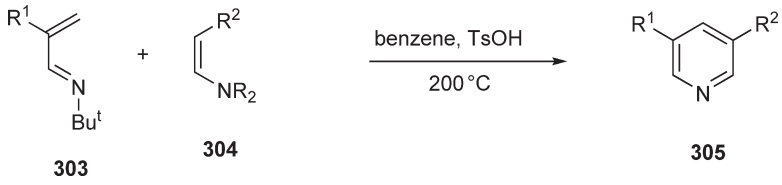


Scheme 151

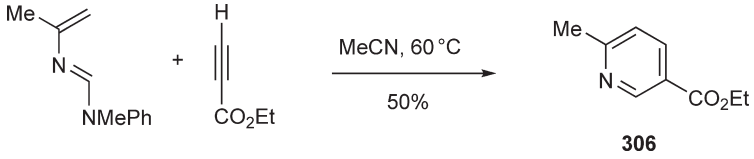


Scheme 152

Similarly, 1-azabutadienes **303** with an *N*-alkyl substituent react with enamines **304** to give a range of 3,5-disubstituted pyridines **305** in moderate to good yields (**Scheme 153**) <1984JOC2691>. 2-Azabutadienes are popular choices for [4 + 2] cycloaddition reactions; *ab initio* calculations are available <1992JOC6736>. Electron-rich 2-azabutadienes react with alkynes to give pyridines, e.g., **306** (**Scheme 154**) <1982JA1428>.



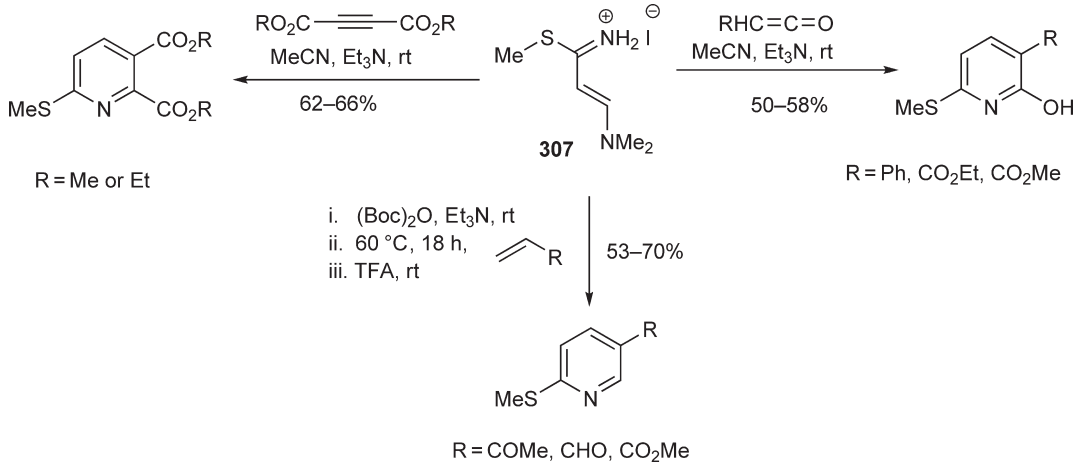
Scheme 153



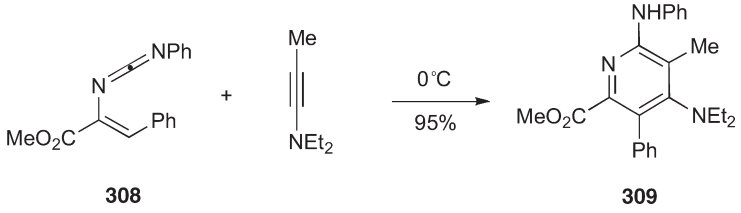
Scheme 154

An extension to the azadiene method is the use of a diazadienium iodide, e.g., **307**; its reaction with acetylenes, ketenes, and acrylic dienophiles yields pyridines of varying substitution patterns (**Scheme 155**) <2004TL9557>.

Conjugated heterocumulenes (e.g., **308**) can also act as heterodienes in [4 + 2] cycloadditions reacting with aminoalkynes to give pentasubstituted pyridines **309** (**Scheme 156**) <1997T4521>.

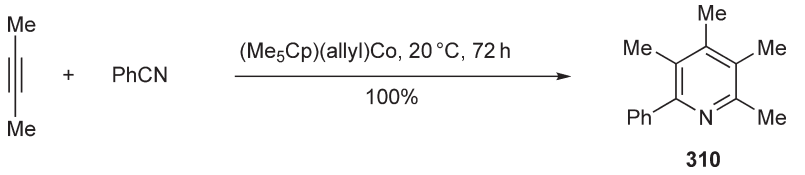


Scheme 155

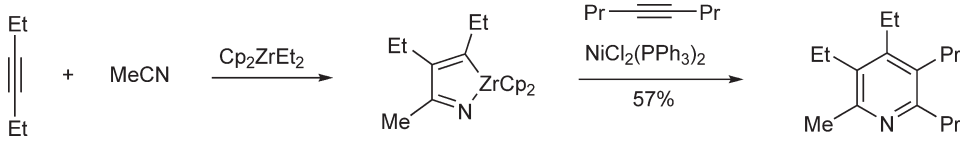


Scheme 156

Numerous transition metal-mediated [2 + 2+ 2] cycloadditions have been utilized in the synthesis of pyridines <CHEC-III(7.05.2.3.3)287>. Selective cyclotrimerization of alkynes with nitriles leads to pentasubstituted pyridines **310** with minimal formation of benzenoid byproducts (**Scheme 157**) <2000OL3131>. Different alkynes can be utilized in the same strategy if a sequential approach is used (**Scheme 158**) <2000JA4994>.



Scheme 157



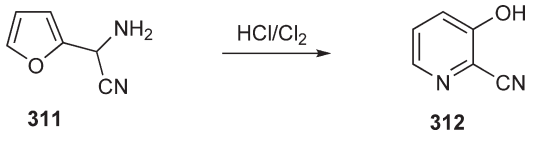
Scheme 158

4.2.4.3 Synthesis of Six-Membered Rings from Other Heterocycles

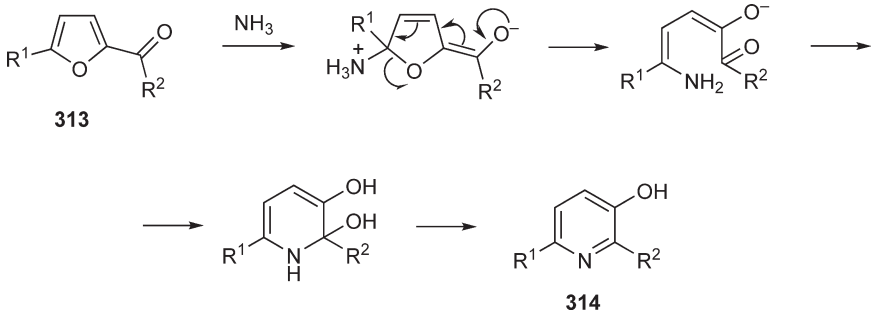
4.2.4.3.1 From five-membered rings

Aminomethylfurans (e.g., **311**) are converted into 3-hydroxypyridines **312** by acid and an oxidizing agent (**Scheme 159**). 2-Hydroxymethylfurans react with chlorine in aqueous methanol to give 3-hydroxy-4-pyrones. 3-Hydroxypyridines **314** can conveniently be prepared by reaction of 2-acylfurans **313** with ammonia (**Scheme 160**). Pyrrole and dichlorocarbene give some 3-chloropyridine (Section 3.3.1.7.1).

Oxazoles and dienophiles give pyridines in good yield as discussed in Section 3.4.1.10.1.



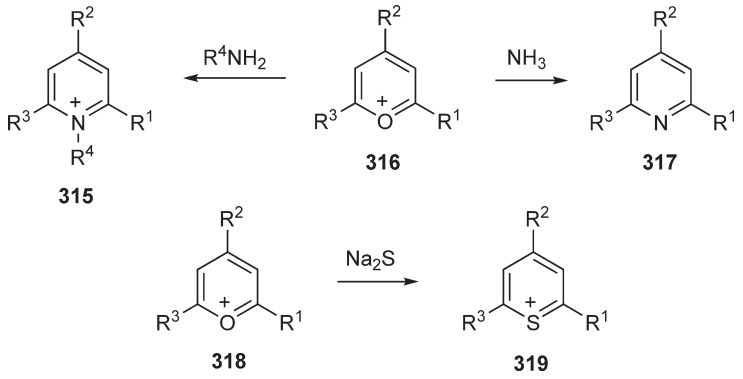
Scheme 159



Scheme 160

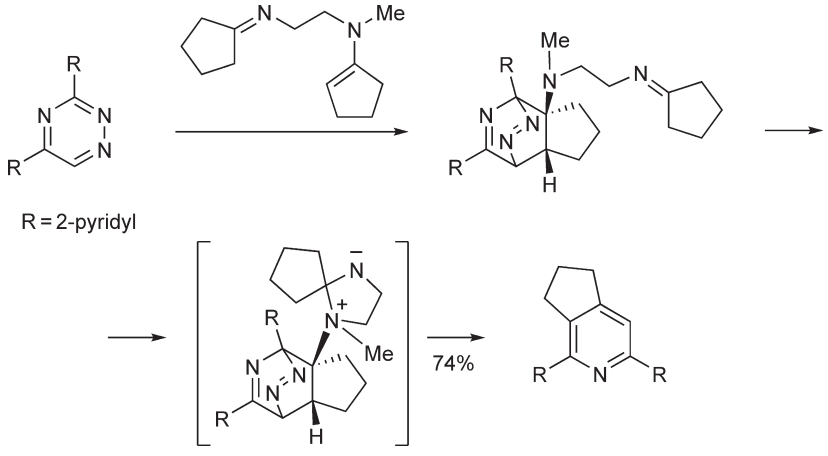
4.2.4.3.2 From other six-membered rings

Nucleophilic addition at the 2-position of pyrylium salts **316** occurs readily under mild conditions, and when ammonia or primary amines are used the subsequent ring-opening/ring-closure sequences give pyridines **317** and pyridinium salts **315**, respectively (Section 3.2.1.6.4.3). The process is most useful for the synthesis of 2,4,6-trisubstituted pyridine derivatives. Thiinium salts **319** are conveniently prepared from pyrylium salts **318** by treatment with sodium sulfide (**Scheme 161**) (Section 3.2.1.6.5). Thiinium salts **319** react with ammonia and amines like their pyrylium analogues.



Scheme 161

Diazines, polyazines, and azapyrylium salts participate in inverse electron demand DielsAlder/retro-DielsAlder-type reactions with electron-rich dienophiles leading to pyridines <CHEC-III(7.05.3.4.2)297>. 1,2,4-Triazines react with enamines and enol ethers to give pyridines as illustrated in **Scheme 162** <2004T6021, 2004CC508>.

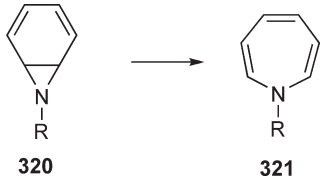


Scheme 162

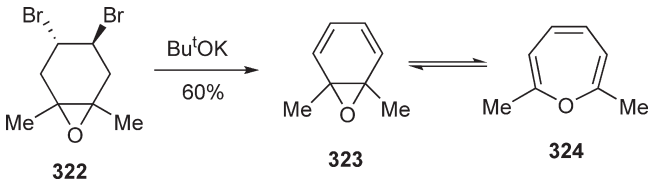
4.2.4.4 Synthesis of Seven-Membered and Larger Rings

The synthesis of medium-ring nitrogen heterocycles, such as azepines, azocines, and azonines, has been reviewed <1991T9131>. 1*H*-Azepines **321** result from spontaneous valence-bond isomerization of azanorcaradienes **320** (**Scheme 163**), which are themselves made by reaction of arenes with nitrenes. Oxepins are prepared by an analogous method (**323** **324**); the starting material is made from the dibromide **322** (**Scheme 164**) <1964AGE510>.

Photolysis of PhN_3 in aniline gives 3*H*-azepine <1981AHC(28)231>. For related preparation of azepines from indazole derivatives, see Section 3.4.3.2.4.

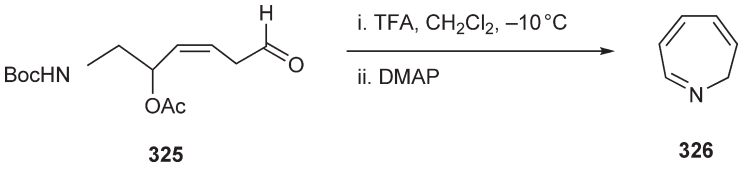


Scheme 163



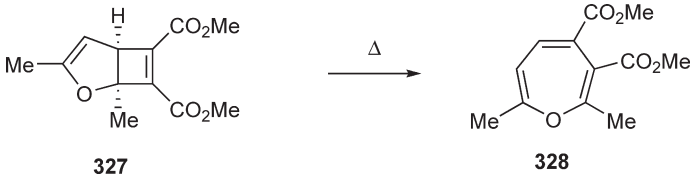
Scheme 164

The parent 2*H*-azepine **326** can be prepared in low yield via *N*-Boc deprotection of precursor **325** followed by treatment with strong base to afford **326** after intramolecular imine formation and base-induced elimination of acetate (**Scheme 165**) <CHEC-III(13.01.6.1)287, 1995AGE1469>.



Scheme 165

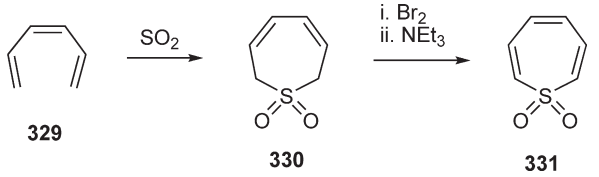
A substituted oxepin **328** can be prepared by the thermolysis of a cyclobuta[*b*]furan derivative **327** (**Scheme 166**) <CHEC-III(13.02.8.2.3)75, 2002JA7395>.



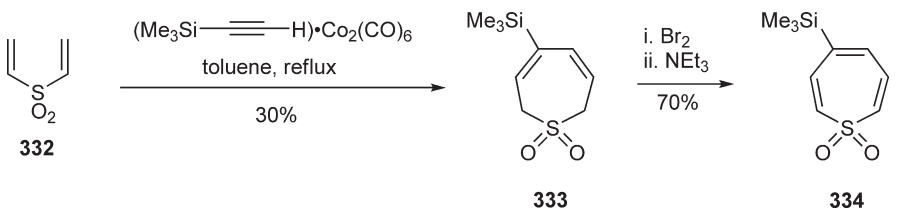
Scheme 166

cis-Hexatriene **329** reacts with sulfur dioxide to yield 2,7-dihydrothiepine 1,1-dioxide **330**, which with excess bromine gives 3,4-dibromo-2,3,4,7-tetrahydrothiepine 1,1-dioxide. Treatment of the dibromide with triethylamine gives thiepine 1,1-dioxide **331** (**Scheme 167**). In an alternative procedure, the reaction of divinyl sulfone **332** with trimethylsilylacetylenedicobalt hexacarbonyl complex in refluxing toluene affords a dihydrothiepine 1,1-dioxide **333**, which is converted into 4-trimethylsilylthiepine 1,1-dioxide **334** via a subsequent brominationdehydrobromination sequence (**Scheme 168**) <CHEC-III(13.02.8.2.3)75, 1999JA8237>.

[2 + 2] Cycloaddition of DMAD to 1,2-dihydropyridines <1977JOC2903> is a fairly general route to 1,2-dihydroazocines which proceeds via a bicyclic intermediate as described in Section 3.2.2.3.8.



Scheme 167



Scheme 168

4.3 Synthesis of Monocyclic Rings with Two or More Heteroatoms

4.3.1 Substituent Introduction and Modification

4.3.1.1 Overview

In this chapter, synthetic methods are classified by the ring that is being formed. We deal successively with rings containing two, three, and four or more heteroatoms. Within each category, classification is first by the relative orientation of the heteroatoms, and then by the ring size.

However, we commence with two brief sections dealing with preparative methods involving substituent introduction and modification for the two large and important classes of monocyclic compounds: those with five and six members and with various heteroatoms.

4.3.1.2 Substituent Introduction and Modification in Azoles

The azoles encompass a very wide range of reactivity (see Chapter 3.4) and possibilities of substituent introduction and modification are very varied. Figure 1 gives a classification in terms of reactivity type for each position in the various rings.

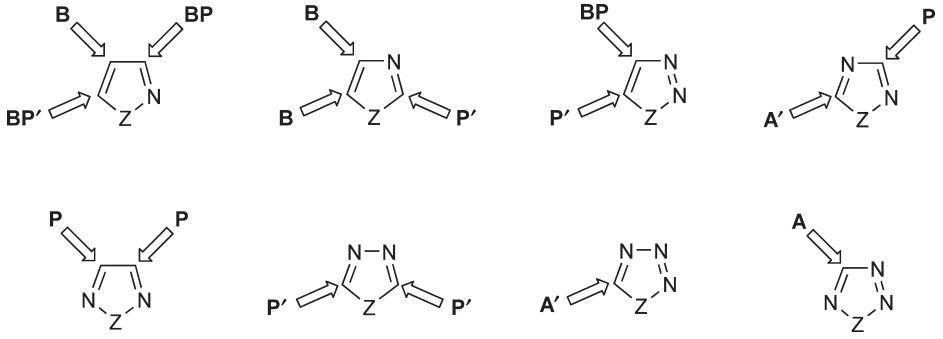


Figure 1 Types of reactivity of azole ring positions (Z = NR, O or S).

1. Positions marked **B** show reactivity comparable to that of ring carbons in benzene. Substituents can be introduced by electrophilic substitution reactions (Section 3.4.1.4) and show reactivity similar to those of the analogous benzene. Thus, amino groups can be diazotized (Section 3.4.3.5.3) and halogens are unreactive.
2. Positions marked **P** show reactivity similar to those of the 2- and 4-positions in pyridine. The substituents can be introduced by very strong nucleophiles (Section 3.4.1.6); hydroxy compounds exist in the oxo form and can be converted (Section 3.4.3.7) into chloro compounds which are reactive (Section 3.4.3.9.1). Alkyl groups can be deprotonated giving anions which undergo various substitution reactions (Section 3.4.3.3).
3. Positions marked **BP** have reactivity intermediate between benzene and pyridine and can be compared to the 3-position of pyridine.
4. Positions marked **A** resemble azines and have the reactivity of the 2-position of pyrimidine, i.e., comparable to **P** but more marked.
5. Positions marked with a prime (**B**, **P**, **A**) additionally can be lithiated and the lithium replaced in a wide variety of synthetically interesting ways.

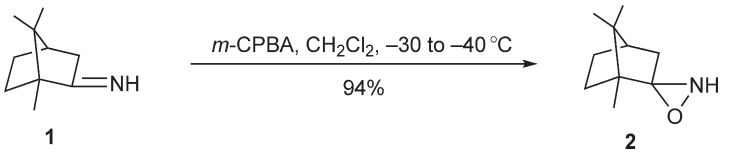
4.3.1.3 Substituent Introduction and Modification in Azines

As explained in Chapter 3.2, the reactivity of six-membered rings containing two heteroatoms bears the same relationship to six-membered rings containing one heteroatom as do the latter to benzene. Hence many of the methods listed for the preparation of pyridines by substituent introduction and modification in Section 4.2.4.1 are also applicable to the preparation of analogous azines.

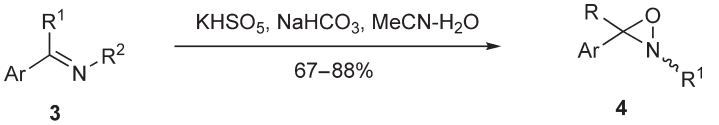
4.3.2 Two Heteroatoms in the 1,2-Positions

4.3.2.1 Three-membered Rings

1. Oxaziridines are prepared by oxidation of imines using peracids, Oxone® (potassium peroxymonosulfate), hydrogen peroxide and other common oxidants <CHEC-III(1.12.4.1)606>. For example, treatment of camphor imine **1** with one equivalent of *m*-CPBA at low temperature in dichloromethane affords NH oxaziridine **2** in high yield (**Scheme 1**) <2000JOC4204>. Treatment of imines **3** with Oxone® in the presence of $NaHCO_3$ gives *N*-alkyl oxaziridines **4** in good yields (**Scheme 2**); optically active oxaziridines of this type can be obtained using 1-phenylethanamine as the chiral directing group <2005JOC301>.



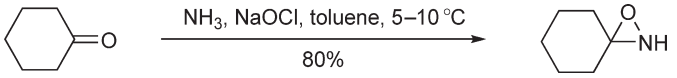
Scheme 1



R^1 = H or 2-pyridyl; R^2 = alkyl

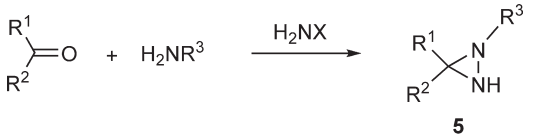
Scheme 2

Oxaziridines unsubstituted at nitrogen (in general used as aminating reagents, see Sections 3.5.4 and 3.5.6), can be prepared by treatment of carbonyl compounds with chloramine or hydroxylamine-*O*-sulfonic acid as exemplified in **Scheme 3** <1991S327>. This method is, however, limited to certain carbonyl compounds with cyclohexanone, butanone, benzaldehyde, and trichloroacetaldehyde giving the best results.



Scheme 3

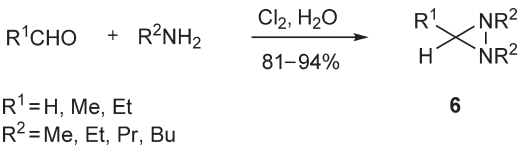
2. Diaziridines **5** are commonly synthesized from carbonyl compounds by the well-established method of Schmitz (**Scheme 4**) <1961CB2166, CHEC-III(1.11.8)549>.



R^1–R^3 = H, alkyl; X = Cl, OSO_3H

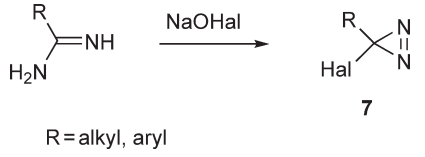
Scheme 4

Modifications of the Schmitz procedure include the use of electrochemical methods <2002RJE1220> and the application of chlorine instead of chloramine for the synthesis of symmetrical diaziridines **6** (**Scheme 5**) <2006RCB2056>.

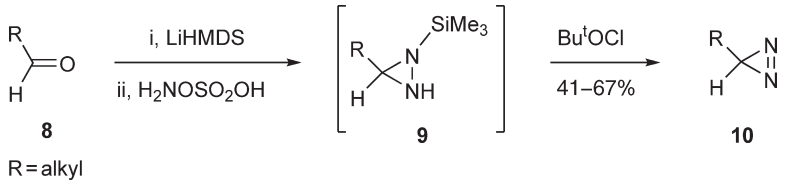


Scheme 5

3. Diazirines **7** are usually produced by the Graham procedure (**Scheme 6**) <1965JA4396> or by the oxidation of N-unsubstituted diaziridines using silver oxide or *tert*-butyl hypochlorite as oxidants <CHEC-III(1.11.8)550>. For example, the unstable diaziridines **10**, which can be generated from aldehydes **8** by a modified Schmitz reaction, are converted *in situ* to diazirines **9** by oxidation with *tert*-butyl hypochlorite (**Scheme 7**) <2000TL795>.

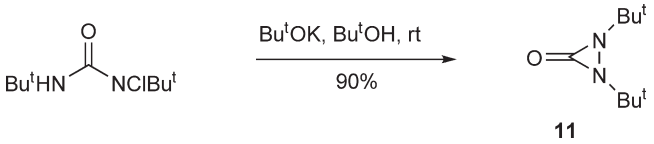


Scheme 6



Scheme 7

4. Diaziridinones (e.g., **11**) can be prepared by the reaction of 1-chloro-1,3-di-*tert*-alkylurea with potassium *tert*-butoxide (**Scheme 8**); bulky substituents are required to obtain stable products <1969JOC2254>.

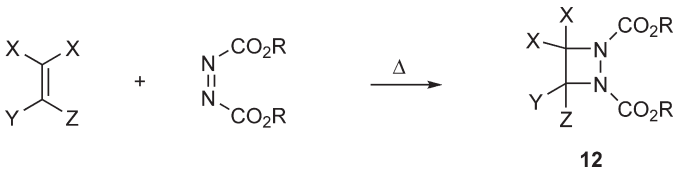


Scheme 8

4.3.2.2 Four-membered Rings

4.3.2.2.1 1,2-Diazetidines

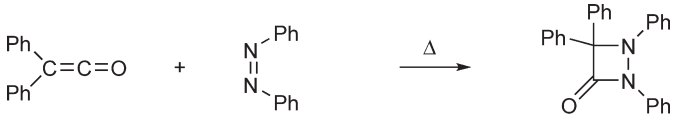
1,2-Diazetidine derivatives **12** are best prepared by [2+2] cycloaddition of an alkene with diazo compounds <CHEC-III(2.13.9.4.2)674>. The reaction proceeds smoothly when a C=C bond is activated by electron-donating groups such as OR or NR_2 and an azo group by electron-withdrawing functionality (COR, COOR, $CONH_2$, etc.) (**Scheme 9**) <1983HC(42)443>. The alternative route to 1,2-diazetidine derivatives is by direct double alkylation of substituted hydrazines with 1,2-dihaloalkanes <1978JA2806, 1978JOC2785>.



12

Scheme 9

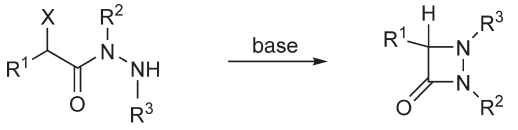
1,2-Diazetidinones (e.g., **13**) are prepared by the thermal [2+2] cycloaddition of ketenes with diazo compounds (**Scheme 10**) <1983HC(42)443>. The use of ketenimines instead of ketene furnished imino derivatives <1967JHC155>.



13

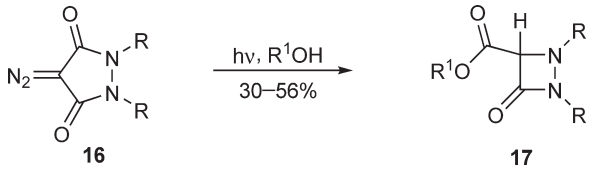
Scheme 10

A large number of diazetidinones **15** have been synthesized by an intramolecular cyclization of haloacetylhydrazones **14** with suitable bases (**Scheme 11**) <CHEC-II(1.30.6.1)952>. A photochemical Wolff rearrangement of 4-diazopyrazolidine-3,5-diones **16** in the presence of some nucleophiles (H_2O or alcohols) leads to diazetidinones **17** in moderate yields (**Scheme 12**) <1987J(P1)899>.



14 15

Scheme 11

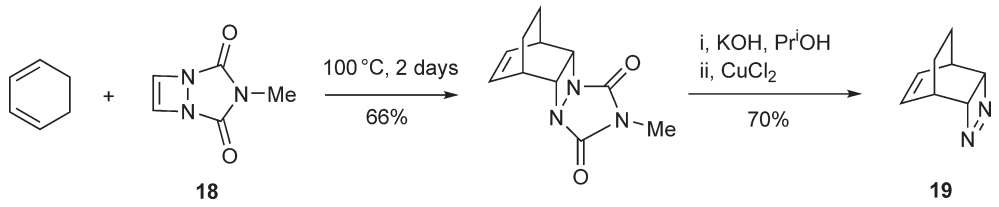


16 17

R = $PhCH_2$, Pr; R^1 = H, Me, Et, Bu^t

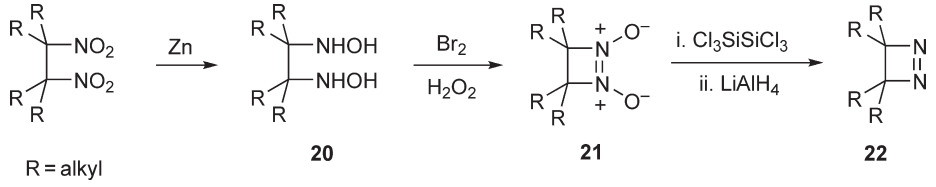
Scheme 12

Several fused diazetines (e.g., **19**) have been prepared in high yields via DielsAlder cycloaddition of dienophile **18** with dienes followed by a hydrolysis/oxidation sequence (**Scheme 13**) <2001OL3185>.



Scheme 13

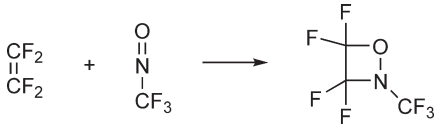
Oxidative closure of 1,2-bis(hydroxylamines) **20** leads to diazetine dioxides **21** which can be reduced in two steps to 1,2-diazetines **22** (**Scheme 14**) <1975JOC1409>.



Scheme 14

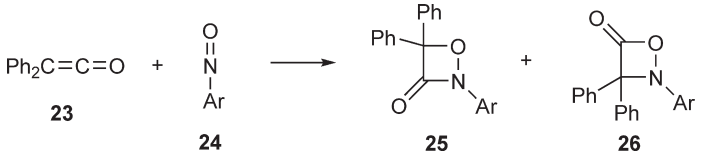
4.3.2.2.2 1,2-Oxazetidines

1,2-Oxazetidines are commonly obtained by [2 + 2] addition of nitroso compounds to appropriate alkenes <CHEC-III (2.14.9.2)704>. Trifluoronitrosomethane reacts with polyhalogenated ethylenes <1969JCC2119> or with allenes <1973J(P1)1561> to give oxazetidines (e.g., **Scheme 15**).



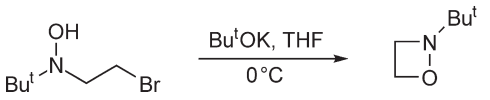
Scheme 15

The addition of nitrosoarenes **24** to diphenylketene **23** gives two isomeric products. Product **26** predominates with *p*-dimethylamino- and the product **25** with *p*-methoxycarbonyl-nitrosobenzene (**Scheme 16**) <1974JOC2552>.

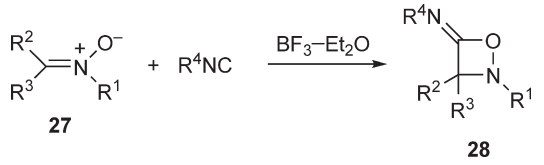


Scheme 16

-Haloalkylhydroxylamines can be converted into oxazetidines (**Scheme 17**) <1971JA4082> and similar cyclizations give N-substituted 4,4-diaryl-1,2-oxazetidin-3-ones <1968JOC3619>. Nitrones **27** add to isocyanides to afford 4-imino-1,2-oxazetidines **28** (**Scheme 18**) <1985S1083>; for a review see <1993JHC579>.

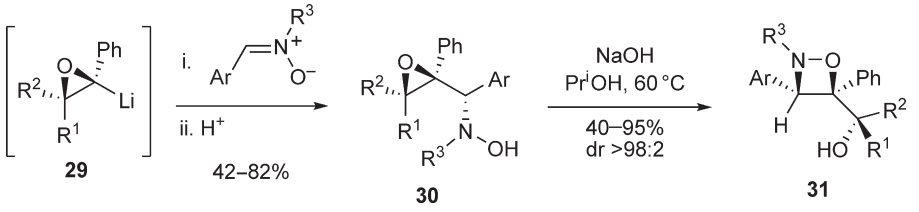


Scheme 17



Scheme 18

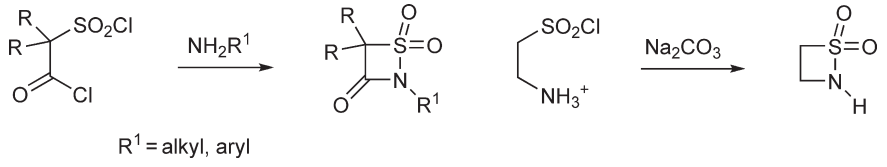
A simple and efficient stereoselective synthesis of 4-hydroxyalkyl-1,2-oxazetidines **31** is based on the addition of -lithiated aryloxiranes **29** to aryl nitrones and subsequent 4-*exo-tet* cyclization of the corresponding intermediates **30** (**Scheme 19**) <2006OL3923>.



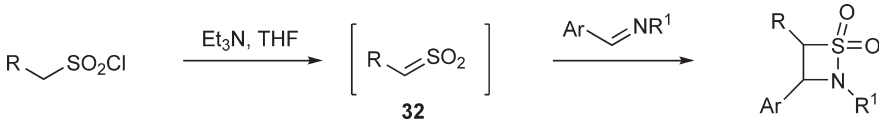
Scheme 19

4.3.2.2.3 1,2-Thiazetidines

1,2-Thiazetidine 1,1-dioxides (-sultams) are prepared by cyclization of appropriate precursors (e.g., **Scheme 20**) <1975BSF(2)807> or via [2 + 2] cycloaddition of imines with sulfenes **32**, generated *in situ* from the corresponding sulfonyl chloride and an organic base (**Scheme 21**) <CHEC-III(2.15.8.2)751>.

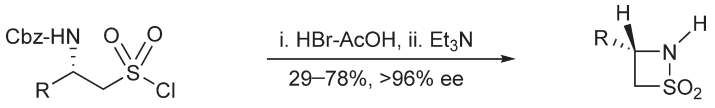


Scheme 20



Scheme 21

An efficient asymmetric synthesis of the 3-substituted -sultams **34** in high enantioselectivity includes an acidic N-deprotection of sulfonyl chlorides **33** followed by *in situ* cyclization promoted by triethylamine (**Scheme 22**) <2002TL5109, 2003S1856>.



33

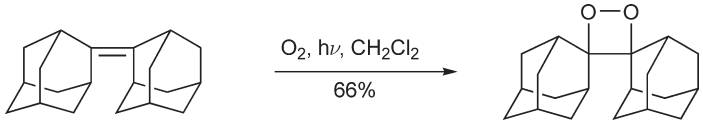
34

R = Et, Pr^n, Pr^i, Bu^n, $Ph(CH_2)_2$

Scheme 22

4.3.2.2.4 1,2-Dioxetanes

The [2 + 2] cycloaddition of singlet oxygen ($^1O_2$) to electron-rich alkenes is the most convenient and versatile method for the preparation of 1,2-dioxetanes. Reactions can conveniently be carried out from low temperature to ambient temperature, in a large range of organic solvents and employ a range of singlet oxygen sensitizers <CHEC-III (2.16.7.1.1)788>. This approach can be illustrated by the preparation of an unusually stable dioxetane **36** from bisadamantylidene **35** (**Scheme 23**) <1975JA7110>. In a modified procedure, calcium peroxide diperoxohydrate (CaO_2ñ$2H_2O_2$) is used as a convenient source of singlet oxygen allowing the preparation of 1,2-dioxetane **36** from alkene **35** in 75% isolated yield <2002JOC2418>.

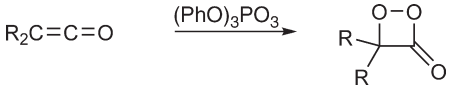


35

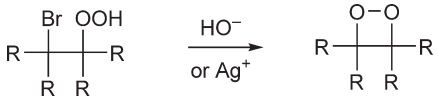
36

Scheme 23

Ketenes can be converted into 1,2-dioxetan-3-ones using triphenyl phosphite ozonide (**Scheme 24**) <1977JA5836, 1980CC898>. The Kopecky method for the formation of 1,2-dioxetanes involves the dehydrohalogenation of -halo hydroperoxides and is promoted by the action of a base or a silver salt (**Scheme 25**) <1975CJC1103>.

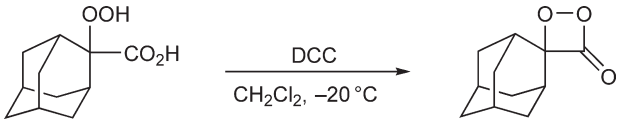


Scheme 24



Scheme 25

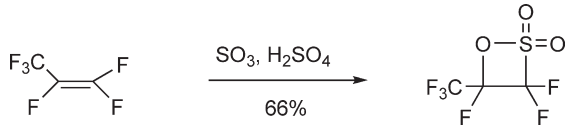
-Peroxylactones or 1,2-dioxetan-3-ones are prepared from -hydroperoxy acids which are cyclized with dicyclohexylcarbodiimide (e.g. **Scheme 26**) <CHEC-III(2.16.7.2)791, 1997JOC1623>.



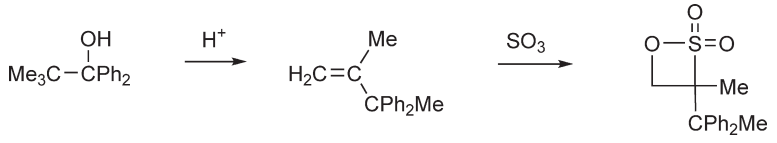
Scheme 26

4.3.2.2.5 1,2-Oxathietanes

1,2-Oxathietane 2,2-dioxides (-sultones) are prepared by [2 + 2] cycloaddition of sulfur trioxide to alkenes (e.g., **Scheme 27**) <CHEC-III(2.17.8.1)804, 2003JFC(121)147>. Likewise, acid-catalyzed rearrangement of 1,1-diphenyl-2,2-dimethylpropanol in the presence of sulfur trioxide forms a stable 1,2-oxathietane 2,2-dioxide (**Scheme 28**) <1977J(P1)247>.



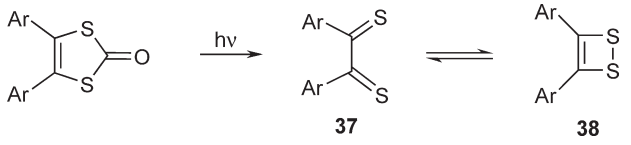
Scheme 27



Scheme 28

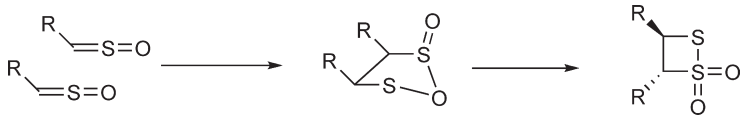
4.3.2.2.6 1,2-Dithietanes

Photochemically induced extrusions of carbon monoxide generate 1,2-dithietes **38** which are in equilibrium with the valence bond tautomers **37** (**Scheme 29**) <1974JA3502, 2003JA12114>.



Scheme 29

The intermediacy of 1,2-dithietanes has been proposed in several transformations <CHEC-III(2.18.4)8835, 1985JOC1550, 1987JA926>. The isolable and well-characterized 1,2-dithietane 1,1-dioxides **40** are synthesized via a cycloaddition reaction of methanethial *S*-oxides **39** (**Scheme 30**) <1996JA7492>.



39 R = Et or Me_3Si **40**

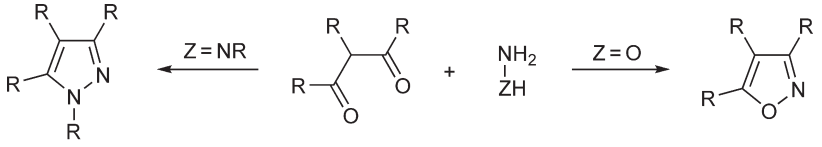
Scheme 30

4.3.2.3 Five-membered Rings: Pyrazoles, Isoxazoles, Isothiazoles, etc.

Five-membered rings with two adjacent heteroatoms are most frequently made using a hydroxylamine or hydrazine derivative. However, dipolar cycloadditions are also significant. Methods forming a Z–Z bond are important particularly for sulfur-containing derivatives.

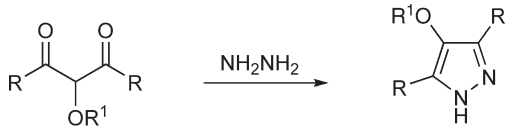
4.3.2.3.1 Synthesis from hydrazine, hydroxylamine, and hydrogen disulfide derivatives

4.3.2.3.1.1 Pyrazoles and isoxazoles from 1,3-diketones. The standard syntheses for pyrazoles **41** <CHEC-III (4.01.9.1.2)74> and isoxazoles **43** <CHEC-III(4.03.9.1)422> involve the reactions of -dicarbonyl compounds **42** with hydrazines and hydroxylamine, respectively (**Scheme 31**). These reactions take place under mild conditions and are of very wide applicability; the substituents R can be H, alkyl, aryl, CN, CO_2Et, etc. For example, 4-alkoxypyrazoles **45** can be prepared from diketones **44** and hydrazine (**Scheme 32**) <2002SL1170>, while diketooximes **46** react with excess hydrazine in ethanol to give 4-amino-3,5-disubstituted pyrazoles **47** in generally good yields (**Scheme 33**) <2004TL2137>.



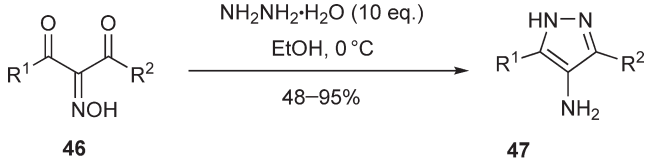
41 **42** **43**

Scheme 31



44 **45**

Scheme 32



46 **47**

R^1 = Ph, Ar, 2-furyl, 2-thienyl

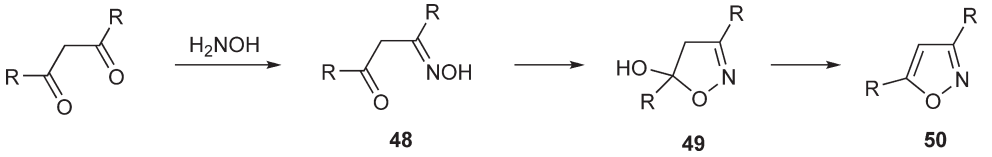
R^2 = Me, Et, $CHMe_2$, CO_2Et

Scheme 33

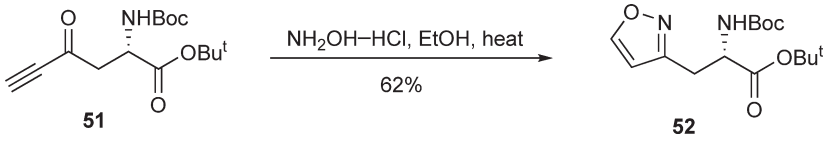
Mechanistic details of the reaction of arylhydrazines and 1,3-dicarbonyl compounds in the preparation of pyrazoles, including the isolable hydroxypyrazoline intermediates, subtle regioselectivity, the relative reaction rate variations observed during acid-catalyzed and neutral pyrazole cyclizations have been discussed <2005OBC1844>. The factors affecting regioselectivity during the formation of 1,5-diarylpyrazoles from arylhydrazines and 1,3-diketones were identified and the regioisomers were characterized by 1D NOESY, LCNMR, and X-ray analyses <2004TL7679>.

A modified procedure for the preparation of pyrazoles includes the solventless condensation of diketones and hydrazines in the presence of a catalytic amount of sulfuric acid at ambient temperature <2004GC90>. 1,3-Diketones can be synthesized directly from ketones and acid chlorides and then converted *in situ* into pyrazoles by the addition of hydrazine <2006OL2675>. The possible modifications to the 1,3-dioxo component in the reaction with hydrazines include the use of -ketoesters, -ketonitriles, -halocarbonyl compounds, -hydroxyketones, -sulfonylketones, and 1,3-dihaloalkanes <CHEC-III(4.01.9.1.2)74>.

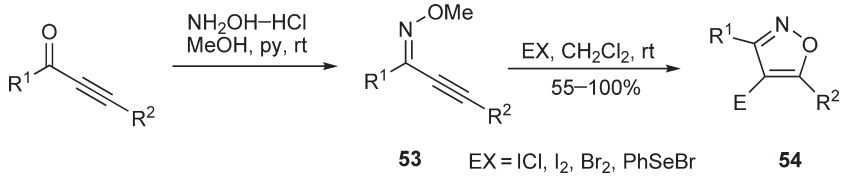
Reaction of a 1,3-diketone with hydroxylamine gives an isoxazole **50** via the isolable monoxime **48** and 5-hydroxydihydroisoxazole **49** (**Scheme 34**). Various modifications of this procedure involving other 1,3-dielectrophiles are known <CHEC-III(4.03.9.1)422>; the examples can be represented by the reaction of alkynyl ketone **51** with hydroxylamine hydrochloride leading to the 3-substituted isoxazole **52** (**Scheme 35**) <2000J(P1)2311>, and the electrophilic cyclization of *O*-methyl oximes **53** allowing access to a variety of 3,5-disubstituted-4-halo- or -4-selenoisoxazoles **54** under mild reaction conditions (**Scheme 36**) <2005OL5203>.



Scheme 34

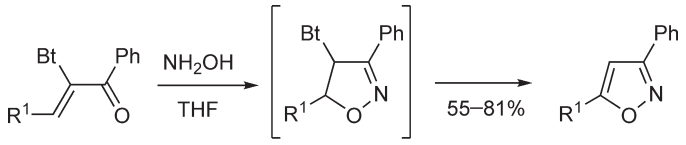


Scheme 35



Scheme 36

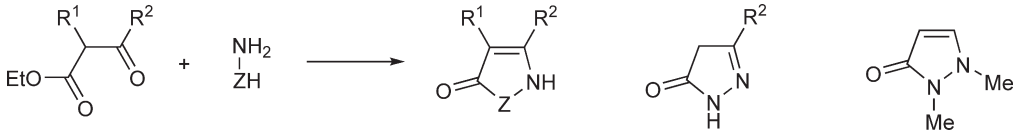
A regioselective method affording directly 3-phenyl-5-substituted isoxazoles **57**, without isolation of isoxazoline intermediates **56**, is based on the reaction of hydroxylamine and -benzotriazolyl-,-unsaturated ketones **55** (**Scheme 37**) <2001JOC6787>.



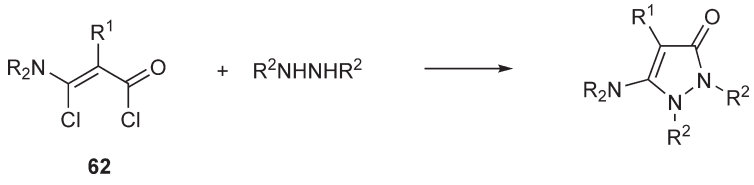
R^1 = Ph, *p*-Tol, 3-py, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 37

4.3.2.3.1.2 Pyrazolinones and isoxazolinones. Pyrazolinones and isoxazolinones are prepared from -keto esters **58** and hydrazine or hydroxylamine by reactions such as **58** **59** (**Scheme 38**) similar to those in Section 4.3.2.3.1.1 above. Diketene behaves as a masked -keto ester. Acetylenecarboxylic esters can be used in place of -keto esters to give pyrazolinones such as **60** and **61** and the corresponding isoxazolinones. -Chloro-,-unsaturated acid chlorides **62** react similarly (**Scheme 39**).

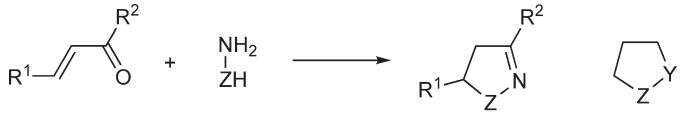


Scheme 38



Scheme 39

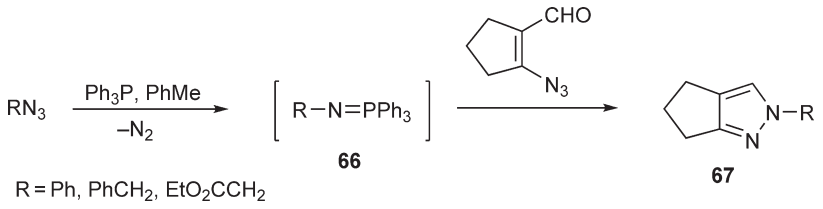
4.3.2.3.1.3 Pyrazolines, isoxazolines, pyrazolidines, isoxazolidines, and 1,2-dithiolanes. ,-Unsaturated ketones **63** form pyrazolines and isoxazolines **64** (**Scheme 40**) and the intermediate hydrazones and oximes are often isolated (cf. **Scheme 37**). Tetrahydro compounds **65** can be obtained from 1,3-dibromides with N_2H_4, NH_2OH, S_2^2, etc.



Scheme 40

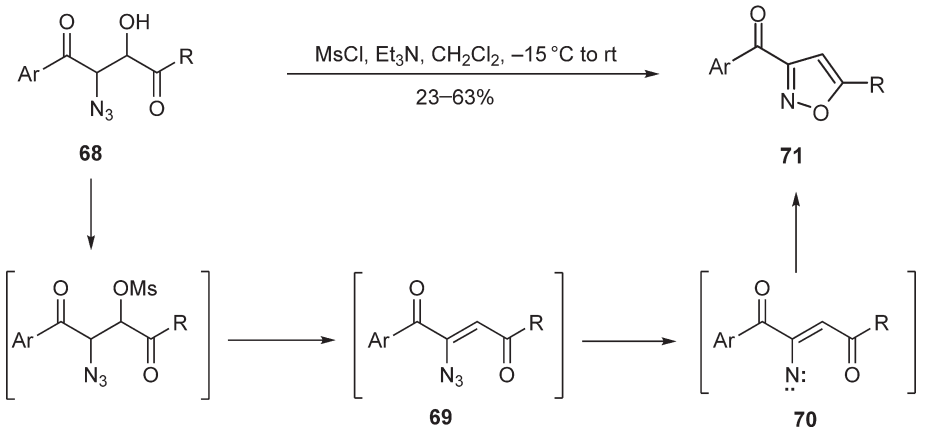
4.3.2.3.2 Synthesis by ZZ bond formation

The synthesis of N-substituted-3,4-trimethylenepyrazoles **67** from iminophosphoranes **66** and 2-azidocyclopentene-1-carbaldehyde has been described (**Scheme 41**) <1988S742>.



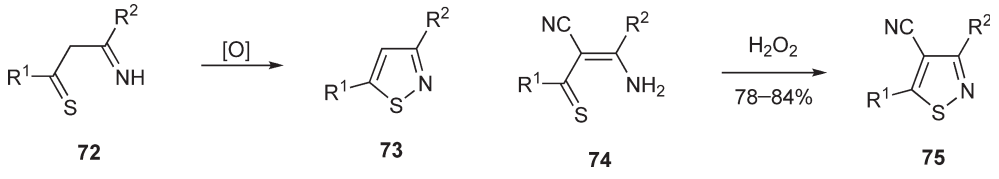
Scheme 41

Treatment of 2-azido-3-hydroxy-1,4-diones **68** with mesyl chloride in the presence of base affords 5-substituted 3-acylisoxazoles **71**, probably through vinyl azide **69** and nitrene **70** intermediates (**Scheme 42**) <2002EJO3055>. In a similar way, thermolysis of 3-azido-2-halopropenones gave 4-haloisoxazoles in high yields <2002S605, CHEC-III (4.03.9.1.3)426>.



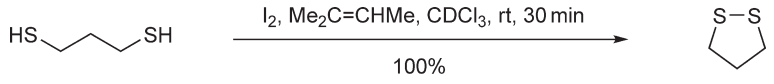
Scheme 42

The main synthetic approach to isothiazoles **73** is based on cyclization of compounds containing an NCCCS fragment <CHEC-III(4.05.9.1)592>, e.g., the cyclization of -thioxoimines **72** <1989AJC1291, 1989JHC1575>. Likewise, the oxidative cyclization of -cyano--thioenaminones **74** affords a series of 3,5-disubstituted-4-isothiazolecarbonitriles **75** in high yields (**Scheme 43**) <2004SC2681>.



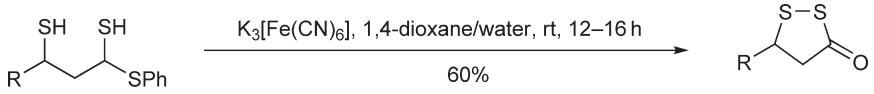
Scheme 43

1,2-Dithiolanes are efficiently synthesized by the oxidative cyclization of 1,3-dithiols <CHEC-III(4.11.10.1)930>, as illustrated by the preparation of 1,2-dithiolane **77** in quantitative yield from 1,3-propanethiol **76** by oxidation with iodine in the presence of 2-methyl-2-butene (**Scheme 44**) <2000OL369> and a similar synthesis of the 1,2-dithiol-3-one **78** (**Scheme 45**) <2004TL4307, 2006JME5626>.



76 77

Scheme 44

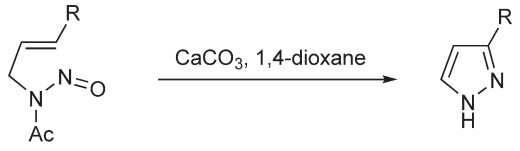


R = $PhCH_2CH_2$ 78

Scheme 45

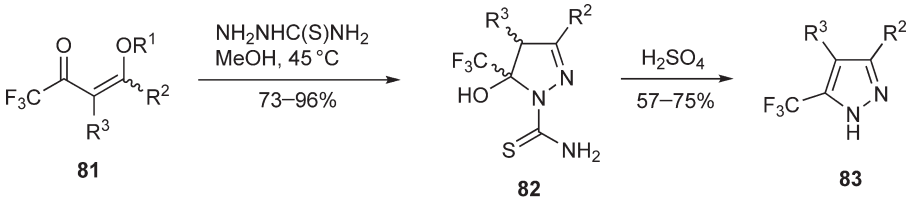
4.3.2.3.3 Other methods from acyclic precursors

Many N-unsubstituted pyrazoles **80** can be obtained from *N*-allyl-*N*-nitrosamides **79** (**Scheme 46**) <1990H(30)789>. Cyclocondensation of -alkoxyvinyl trifluoromethyl ketones **81** with thiosemicarbazide under mild conditions affords 4,5-dihydro-1*H*-pyrazole-1-thiocarboxamides **82**, which can be easily dehydrated with concomitant thiocarboxamide group hydrolysis in concentrated sulfuric acid to give N-unsubstituted pyrazoles **83** (**Scheme 47**) <1998JFC(92)23>.



79 **80**

Scheme 46

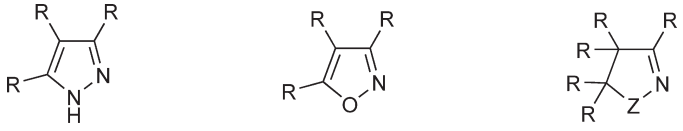


81 **82** **83**

R^1 = Me, Et; R^2 = H, Me, Ar; R = H, Me

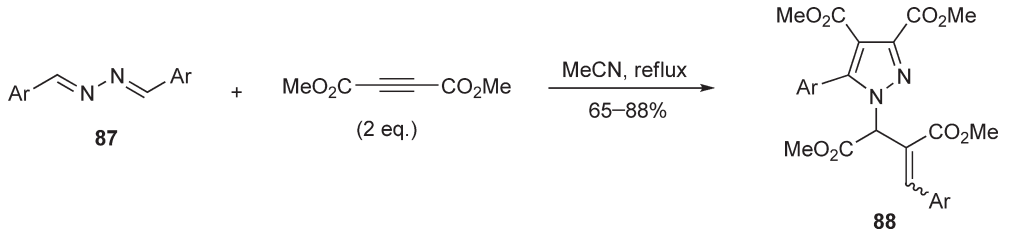
Scheme 47

1,3-Dipolar cycloadditions provide an important approach to pyrazoles <CHEC-III(4.01.9.1.2)101> and isoxazoles <CHEC-III(4.03.9.1.6)427>. Alkynes add diazoalkanes and nitrile oxides to give pyrazoles **84** and isoxazoles **85**, respectively. If an alkene is used instead of an alkyne the nonaromatic analogues (**86**; Z = NH, O) result <1994AHC(60)261>; yields are best when the alkene contains an electron-withdrawing substituent.

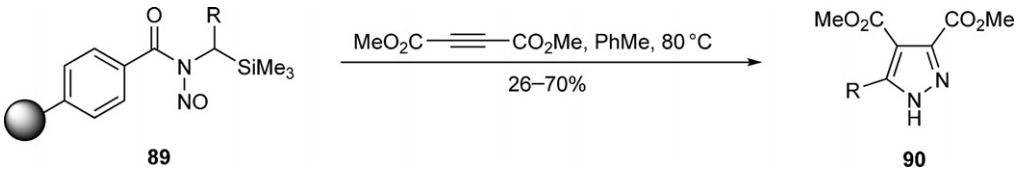


84 **85** **86**

Aldehyde azines **87** react with two equivalents of dimethyl acetylenedicarboxylate in a 1,3-dipolar reaction to give *N*-allyl pyrazoles **88** in good yields (**Scheme 48**) <2002CJC1293>. 1,3-Dipolar cycloaddition of polymer-supported -silylnitrosoamides **89** with dimethyl acetylenedicarboxylate gives pyrazole derivatives **90** without the necessity for a separate cleavage operation (**Scheme 49**) <2000TL691>.

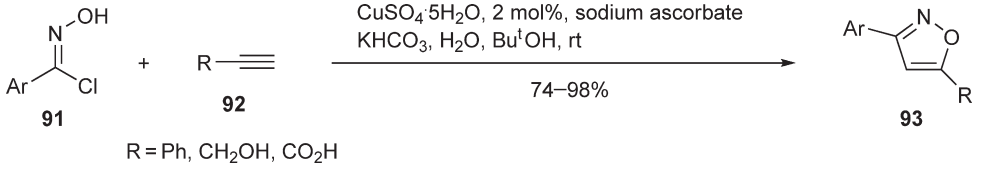


Scheme 48



Scheme 49

The use of catalysts in 1,3-dipolar cycloaddition of nitrile oxides and alkynes permits significant improvements of yields and regioselectivity, which in general are quite low in the uncatalyzed processes. In particular, a copper catalyst allows easy access to 3,5-disubstituted isoxazoles **93** as single regioisomers through nonconcerted additions of nitrile oxides, produced from imidoyl chlorides **91**, with terminal alkynes **92** (**Scheme 50**) <2005JA210, 2005JOC7761>.



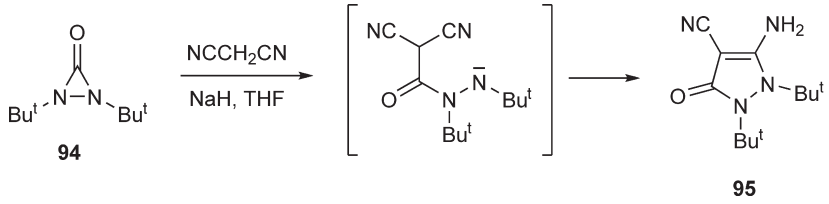
Scheme 50

Isoxazolidines result from 1,3-dipolar cycloadditions of nitrone or nitrone esters and alkenes (e.g., **Scheme 51**) <1995PHC179>.

Scheme 51

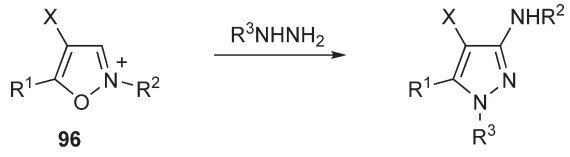
4.3.2.3.4 From other heterocycles

Diaziridinones react with bifunctional carbanions by ring enlargement to give pyrazolinones <1992JOC7359>; thus diaziridinone **94** with malononitrile affords 1,2-bis-*tert*-butyl-3-aminopyrazolin-5-one **95** (**Scheme 52**).

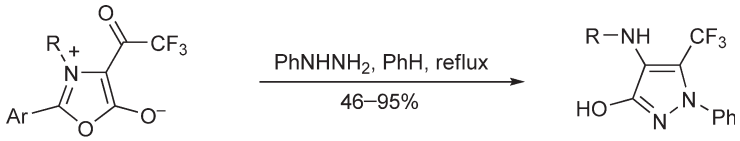


Scheme 52

3-Unsubstituted isoxazolium salts **96** react with hydrazines to yield 3-aminopyrazoles **97** (**Scheme 53**) <1988S203>. Likewise, 5-trifluoromethyl-3-hydroxypyrazoles **99** were obtained selectively through the regioselective attack of phenylhydrazine on mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **98** in refluxing benzene (**Scheme 54**) <1998TL663, CHEC-III(4.01.9.1.2)103>.

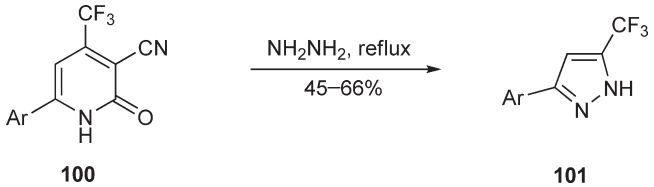


Scheme 53



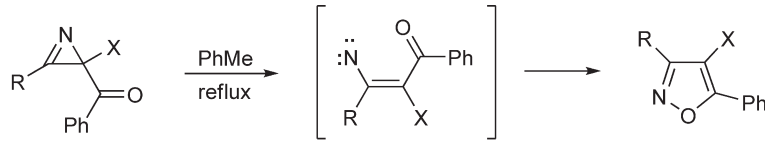
Scheme 54

3-Cyano-4-trifluoromethyl-6-aryl-2(1*H*)-pyridones **100** react with hydrazine hydrate to give exclusively 5-trifluoromethyl-3-arylpyrazoles **101** (**Scheme 55**) <2002JFC(115)9>.



Scheme 55

Thermolysis of 2-benzoyl-2-halo-2*H*-azirines **102** in toluene under reflux affords 4-haloisoxazoles **104** in high yields via an intermediate nitrene **103** (**Scheme 56**) <2002S605>.

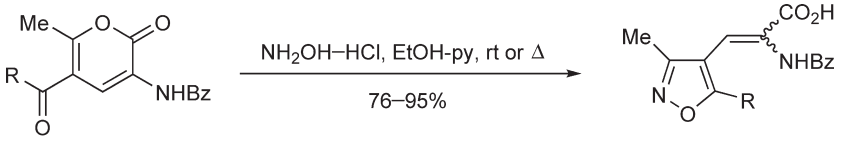


102 **103** **104**

R = Ph, CO_2Me; X = Cl, Br

Scheme 56

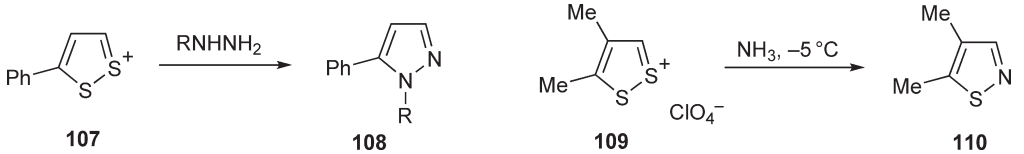
Nucleophilic attack of hydroxylamine at position 6 of 2*H*-pyran-2-ones **105** affords stereoselectively, through pyran ring opening and subsequent cyclization, (-isoxazol-4-yl)-,-dehydroamino acids **106** mainly as (*Z*)-isomers (**Scheme 57**) <2002J(P1)675>.



105 R = Me, Ph **106**

Scheme 57

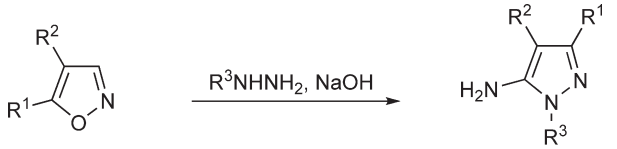
1,2-Dithiolylium salts can be converted into pyrazoles, pyrazolium salts, and isothiazoles (see Section 3.4.1.6.2.2). For example, 4-phenyl-1,2-thiolylium salt **107** with hydrazine, methylhydrazine, or phenylhydrazine yields the corresponding pyrazoles **108**. 3,4-Dimethyl-1,2-dithiolylium perchlorate **109** with ammonia gives 4,5-dimethylisothiazole **110** (**Scheme 58**).



107 **108** **109** **110**

Scheme 58

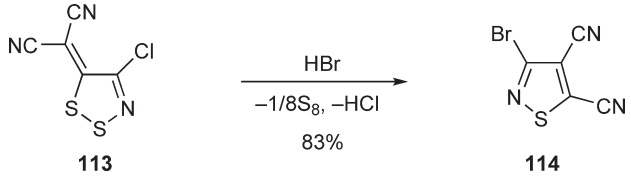
Isoxazoles **111** in the presence of base undergo ring opening to -ketonitriles. In the presence of hydrazines, 5-aminopyrazoles **112** are obtained (**Scheme 59**).



111 **112**

Scheme 59

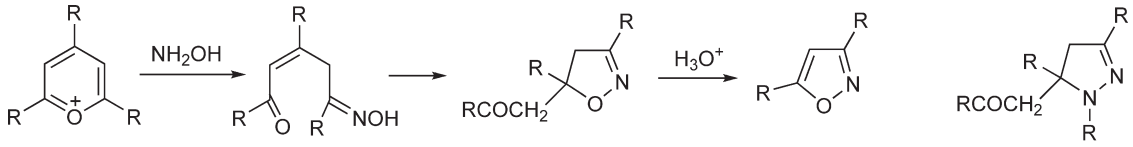
Numerous examples of heteroring transformations leading to isothiazoles are known <CHEC-III(4.05.10.2)609>. In particular, (dicyanomethylene)dithiazole **113** is readily converted into bromoisothiazole **114** in high yield by treatment with anhydrous gaseous HBr at room temperature (**Scheme 60**) <2002J(P1)1236>.



113 **114**

Scheme 60

With hydroxylamine, the pyrylium salt **115** undergoes ring opening to an intermediate 1,5-enedione oxime **116**; intramolecular conjugate addition of the ,-unsaturated ketone gives **117**, which in the presence of acid forms the isoxazole **118** (**Scheme 61**). Likewise, the reaction of pyrylium salt **115** with a hydrazine results in the pyrazoline **119**. A similar transformation of chromone is described in Section 3.2.1.6.4.4.



115 **116** **117** **118** **119**

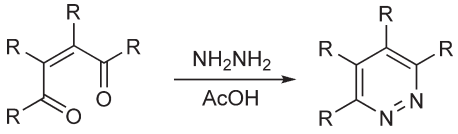
Scheme 61

4.3.2.4 Six-membered Rings: Pyridazines, 1,2-Oxazines, etc.

The most important synthetic methods involve condensation of hydrazine, hydroxylamine, or hydrogen peroxide with a 1,4-dioxygenated carbon chain, and these procedures are particularly useful for the preparation of pyridazines and 1,2-oxazines. Other methods include DielsAlder reactions of a diene with an azo or nitroso compound.

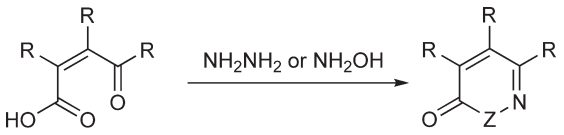
4.3.2.4.1 Synthesis from hydrazine or hydroxylamine derivatives

The most straightforward method used to prepare pyridazine derivatives is the reaction of a 1,4-dicarbonyl compound with hydrazines <CHEC-III(8.01.9.2.2)79>. 1,4-Dicarbonyl compounds with a double bond in the 2,3-position **120** condense with hydrazine to give pyridazines **121** (**Scheme 62**). If one of the carbonyl groups in the starting material is part of a carboxyl group or a potential carboxyl group (e.g., **122**), then reactions with hydrazines or hydroxylamine lead to pyridazinones **123** (Z = NH) or 1,2-oxazinones **123** (Z = O) (**Scheme 63**). Similarly a cyano group leads to an amino or imino product.



120 **121**

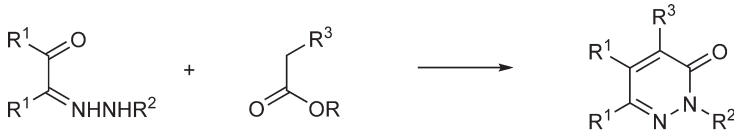
Scheme 62



122 123

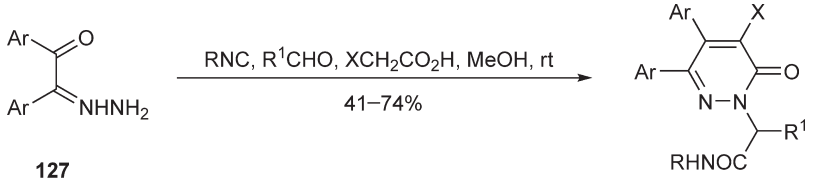
Scheme 63

Saturated 1,4-dicarbonyl compounds give 1,4-dihydro-pyridazines or -pyridazinones, etc., which are easily oxidized. 1,2-Diketone monohydrazones **124** and esters **125** containing a reactive CH_2 group give 3-pyridazinones **126** (**Scheme 64**) <CHEC-III(8.01.9.2.2)80>. A popular modification of this approach is the Ugi four-component condensation of diarylethane-1,2-dione monohydrazones **127** with isocyanides, aldehydes, and methylene active acids leading to the corresponding substituted pyridazin-3(2*H*)-ones **128** (**Scheme 65**) The intermediate Ugi condensation products have never been observed because of their tendency to cyclize <2003S691>.



124 125 126

Scheme 64



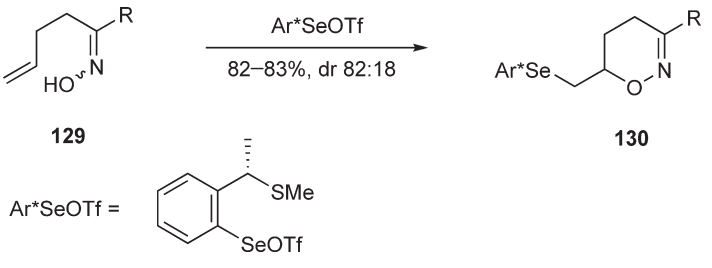
127

R = c-C_6H_{11}, 4-MeC_6H_4; R^1 = Me, Et, Bn
X = CN, 4-$MeC_6H_4SO_2$, CO_2Et

128

Scheme 65

A standard synthetic approach to 1,2-oxazines of various types is the cyclization of an oxime bearing a side-chain with an appropriate electrophilic center <CHEC-III(8.04.9.2)354>. For example, the intramolecular electrophilic cyclization of -alkenyl oxime **129** gives 1,2-oxazines **130** in excellent yield, complete regioselectivity, and good diastereoselectivity (**Scheme 66**) <2001TA3297>.

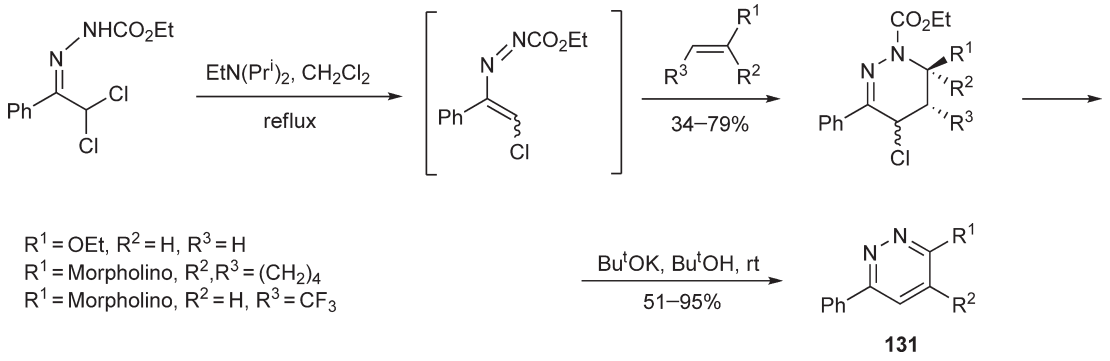


129 130

Scheme 66

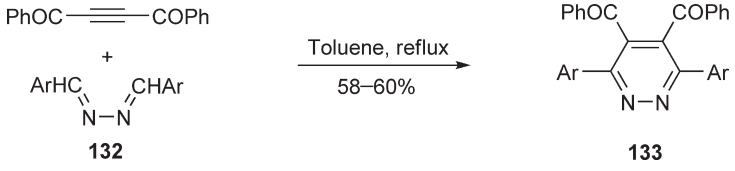
4.3.2.4.2 By cycloaddition reactions

[4+2] Cycloaddition reaction of diazadienes (generated *in situ* from an -halogenated hydrazone) with alkenes yielding 2,3,4,5-tetrahydropyridazines followed by aromatization is a general synthetic approach to substituted pyridazines (e.g., **131**) <CHEC-III(8.01.9.2.2)84, 2005EJO1142>; a representative example is shown in **Scheme 67** <1995TL5703>.



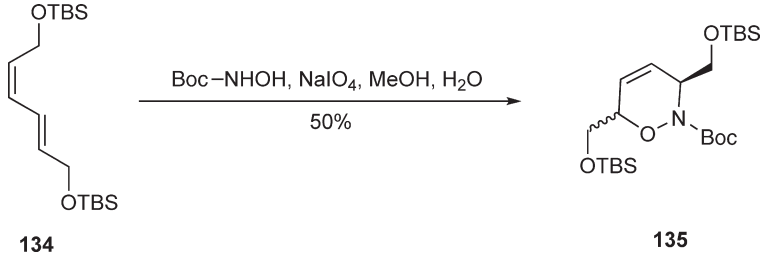
Scheme 67

Procedures based on benzylidene azines (e.g., **132**) are also known. Reactions of dibenzoylacetylene with compound **132** afford tetrasubstituted pyridazines **133** via cycloaddition and subsequent spontaneous oxidation of the intermediate dihydropyridazines (**Scheme 68**) <2005CJC57>.



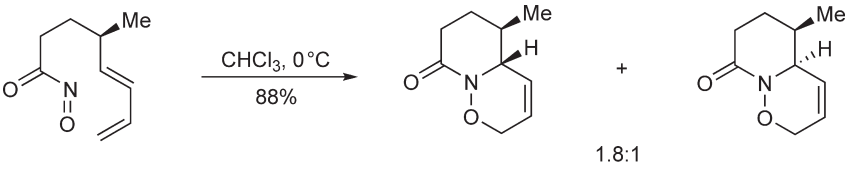
Scheme 68

Various reduced 1,2-oxazines can be also prepared by DielsAlder-type reactions <CHEC-III(8.04.9.5)357>. For example, nitroso DielsAlder cycloaddition of *E*,*Z*-diene **134** with BocN=O generated *in situ* provides oxazine **135** as a mixture of *cis* and *trans* isomers (**Scheme 69**) <2004OL1805>.



Scheme 69

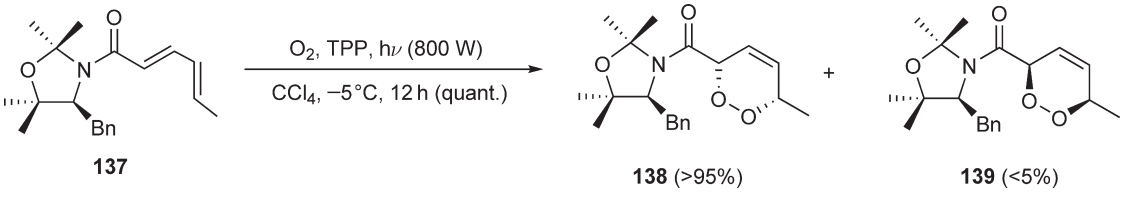
Chiral nitroso dienophiles (e.g., **136**) useful for asymmetric synthesis of 1,2-oxazine derivatives via the intramolecular DielsAlder reaction have been developed (**Scheme 70**) <1994S1107>.



136

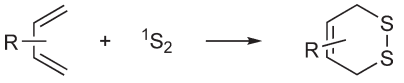
Scheme 70

1,2-Dioxine derivatives are prepared by [4 + 2] cycloaddition reactions of 1,3-dienes with singlet oxygen. The stereoselectivity of this reaction has been studied in detail <CHEC-III(8.10.9.1)707>. For example, the addition of singlet oxygen to sorbate derivatives was tested using the optically active amides **137** containing the 2,2-dimethyloxazolidine chiral auxiliary (**Scheme 71**); the 1,2-dioxine derivatives **138** and **139** were the only detectable products in this reaction <2002EJO3944, 1998JA4091>. Dihydro-1,2-dithiines **140** are prepared similarly by [4+2] cycloaddition reaction of 1,3-dienes with singlet sulfur (**Scheme 72**) <CHEC-III(8.10.9.4) 720>. A number of synthetically useful procedures to generate and transfer singlet sulfur for this reaction have been reported; for example, $^1S_2$ can be liberated from aliphatic and aromatic dialkoxy disulfides <2002TL8781, 1995JA9067>.



137 **138** (>95%) **139** (<5%)

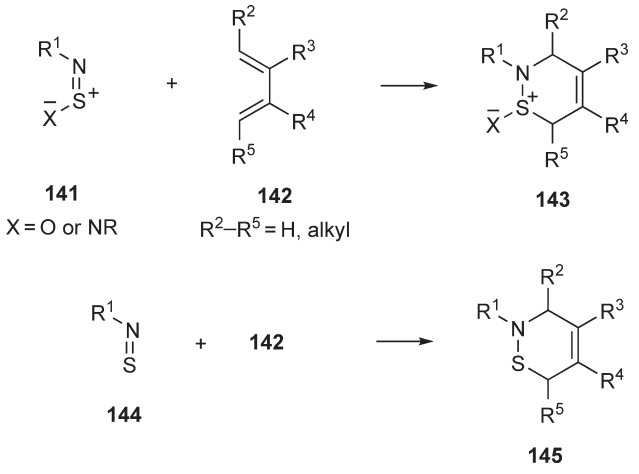
Scheme 71



140

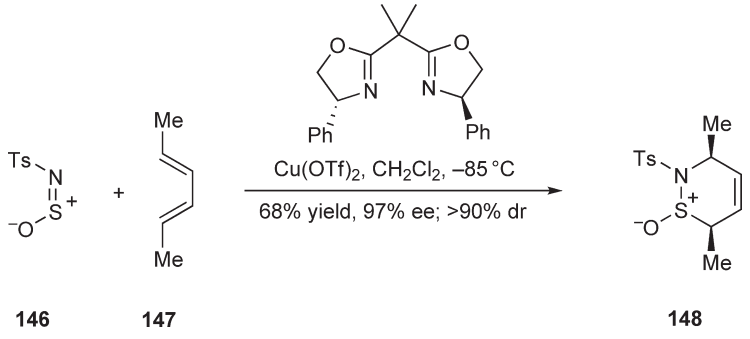
Scheme 72

The hetero-DielsAlder reaction of *N*-sulfinyl **141** (X = O or NR) or thionitrosoarene **144** dienophiles with dienes **142** is the main method for the formation of 3,6-dihydro-2*H*-1,2-thiazine 1-oxides **143** or 3,6-dihydro-2*H*-1,2-thiazines **145** (**Scheme 73**) <CHEC-III(8.07.9.3.1)552>. The mechanistic and stereochemical aspects of this reaction are covered in detail in CHEC-II <CHEC-II(6.5.3.2).376>. In general, thionitrosoarenes **144** are transient in nature, rather difficult to prepare, and thus have a limited role in the synthesis of 1,2-thiazines. On the other hand, *N*-sulfinyl compounds **141** and related sulfur diimines are more stable and are isolable species. The common method of preparation of the *N*-sulfinyl compounds involves treatment of an amine or amide with $SOCl_2$ and base.



Scheme 73

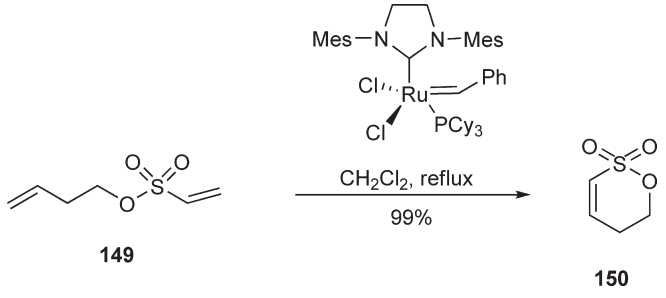
Asymmetric [4 + 2] cycloaddition reactions of *N*-sulfinyl compounds and dienes have been developed <2002TA2407, 2000TL3743>. Excellent enantioselectivity is observed for the preparation of product **148** by the reaction of *N*-sulfinyl dienophiles **146** and acyclic diene **147** catalyzed with Cu(II) and Zn(II) complexes of Evans bis(oxazolidinone) ligands (**Scheme 74**) <2004JOC7198>.



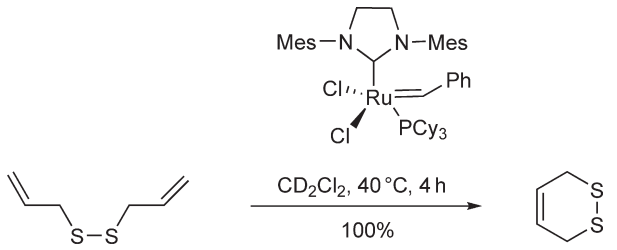
Scheme 74

4.3.2.4.3 Other methods from acyclic precursors

1,2-Oxathiin 2,2-dioxides (sultones) (e.g., **150**) are obtained by the addition of sulfur trioxide to dienes or by ring-closing metathesis (RCM) of sulfonates using the second-generation Grubbs ruthenium catalyst (**Scheme 75**) <CHEC-III(8.10.9.3)718>. The same catalyst was also successfully employed in the RCM of diallyl disulfide **151** which led quantitatively to 3,6-dihydro-1,2-dithiin **152** (**Scheme 76**) <2002OL1767>.



Scheme 75



151 152

Scheme 76

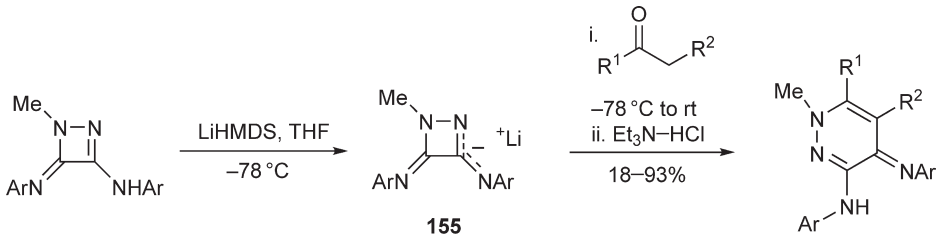
1,2-Dithiins are also synthesized from conjugated diynes using benzyl thiol: reductive debenzylation of intermediate **153** by sodium in liquid ammonia at 70°C gives, after aerial oxidation, the 1,2-dithiin **154** (**Scheme 77**) <1967AGE698>. Additional examples of 1,2-dithiins synthesis utilizing this approach are provided in CHEC-III <CHEC-III(8.10.9.4.4)722>.

153 154

Scheme 77

4.3.2.4.4 From other heterocycles

Reaction of deprotonated 1,2-diazetines **155** with ketones containing an acidic methylene group affords dihydropyridazine derivatives **156** via a sequence of ring opening and recyclization (**Scheme 78**) <2006S2885, CHEC-III (8.01.10.1)85>.



155 156

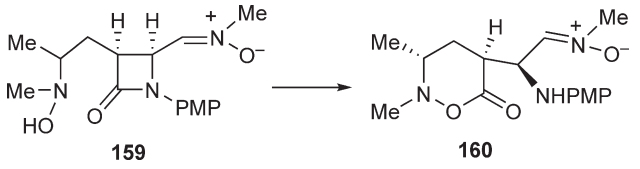
R^1 = alkyl, aryl; R^2 = H, alkyl

Scheme 78

The Meisenheimer-type rearrangement of 1-substituted pyrrolidine 1-oxides **157** gives tetrahydro-2*H*-1,2-oxazines **158** (**Scheme 79**). The -lactam **159** undergoes ring expansion to give 1,2-oxazinone **160** (**Scheme 80**) <2005EJO1680, CHEC-III(8.04.10)364>.

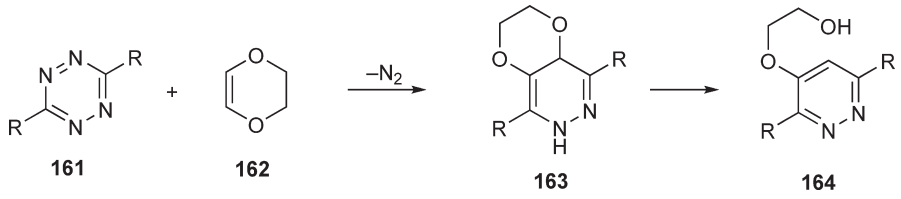
157 158

Scheme 79



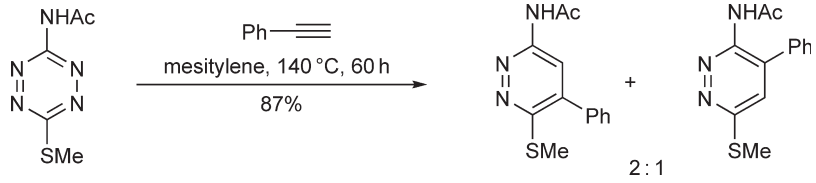
Scheme 80

1,4-Dihydropyridazines **163** result from DielsAlder addition of 1,2,4,5-tetrazines **161** with electron-rich alkenes (e.g., **162**). Frequently the products **163** aromatize to give pyridazine **164** (**Scheme 81**) (see also Section 3.2.1.10.2.4).



Scheme 81

Inverse electron demand DielsAlder reactions of 1,2,4,5-tetrazines with alkynes produce pyridazines directly with the elimination of nitrogen and retention of the substituents on the acetylene; a representative example is shown in **Scheme 82** <1998JOC6329> (see also Section 3.2.1.10.2.4).

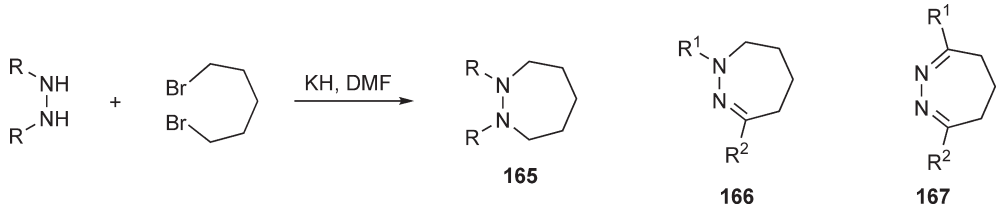


Scheme 82

4.3.2.5 Seven-membered Rings

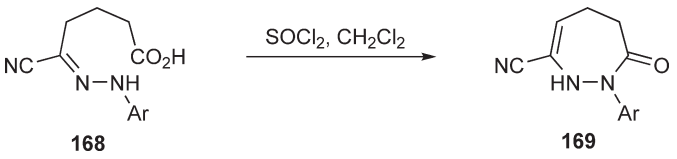
4.3.2.5.1 1,2-Diazepines

1,5-Dihalides and 1,5-ditosylates have been used for the preparation of fully-saturated monocyclic 1,2-diazepines **165** (**Scheme 83**). 5-Halo-aldehydes and 5-halo-ketones react with a wide range of substituted hydrazines to give 4,5,6,7-tetrahydro-1,2-diazepines **166** <1976H(4)1509>. The reaction of 1,5-diketones with hydrazine has been much used as a source of 5,6-dihydro-4*H*-1,2-diazepines **167** <CHEC-III(13.04.9.5)151>.



Scheme 83

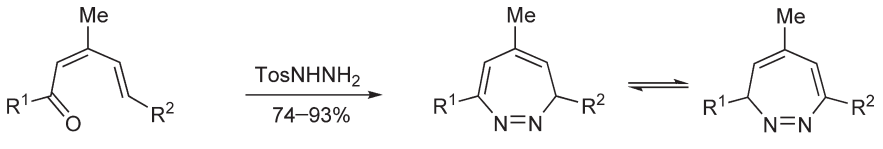
Arylhydrazones **168** are cyclized with $SOCl_2$ or PCl_3 to 2-aryl-2,3,4,5-tetrahydro-1,2-diazepin-3-ones **169** (**Scheme 84**) <1984CRB929>.



168 **169**

Scheme 84

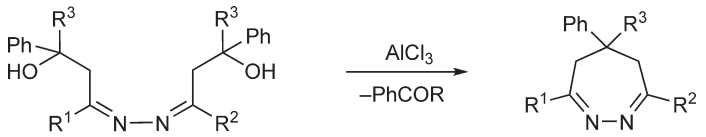
Reaction of tosylhydrazide with ,-,-unsaturated ketones, followed by dehydrotoluenesulfonylation affords 3*H*-1,2-diazepines (**Scheme 85**) <1984J(P1)1581>. The tautomeric products **170** and **171** are in dynamic equilibrium at room temperature but can be separated by high-pressure liquid chromatography at 0°C.



R^1 = alkyl; R^2 = H, Me **170** **171**

Scheme 85

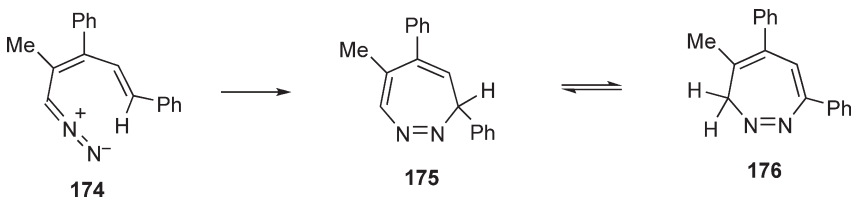
The dihydroxy dihydrazones **172** with $AlCl_3$ cyclize to dihydrodiazepines **173** in 8090% yield (**Scheme 86**) <1987CC582>.



172 **173**

Scheme 86

1,7-Electrocyclization of dienyldiazoalkanes, e.g., **174**, provides a general route to 3*H*-1,2-diazepines, e.g., **176** (**Scheme 87**). In the example shown the eight--electron cyclization is followed by a 1,5-sigmatropic hydrogen shift



174 **175** **176**

Scheme 87

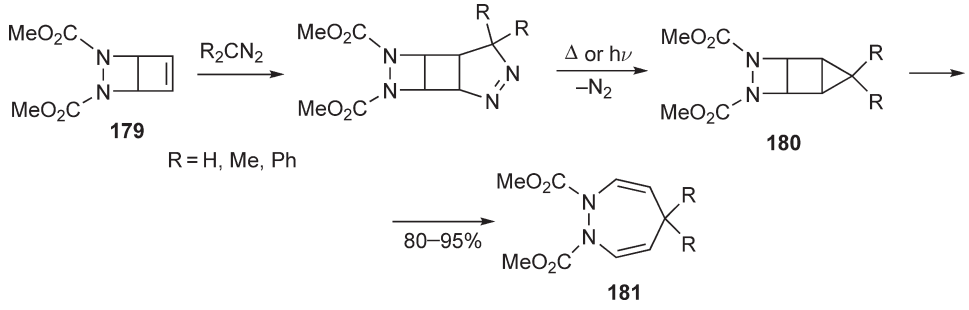
in the initial product **175** <1983CC1003>. Such hydrogen shifts are rapid at room temperature and the isomer ratio reflects thermodynamic stability.

Photochemical conversion of pyridine *N*-imides, e.g., **177**, gives 1*H*-1,2-diazepines **178** (**Scheme 88**) <1981ACR348>.

177 **178**

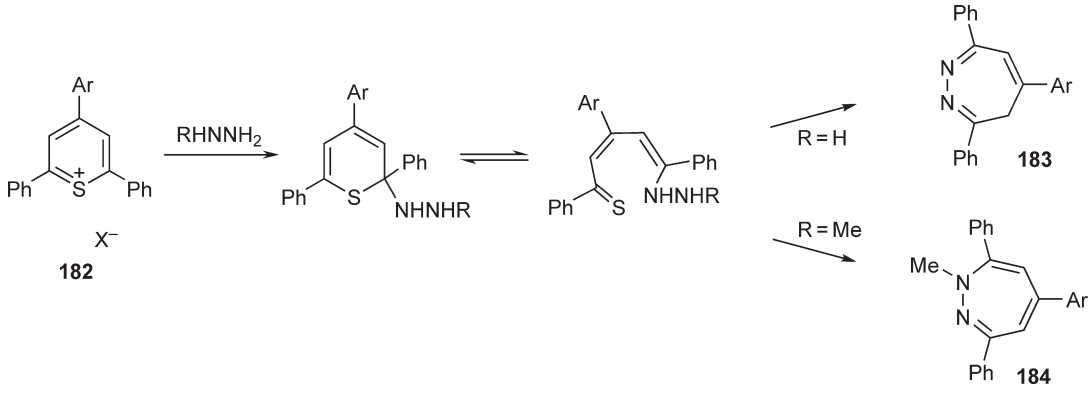
Scheme 88

Cycloaddition of diazoalkanes to diazabicyclo[2.2.0]hexanes **179** and subsequent extrusion of nitrogen affords diazatricyclo[3.2.0.0^{2,4}]heptanes **180** that are easily valence-isomerized to dihydrodiazepines **181** (**Scheme 89**) <1984TL297>.



Scheme 89

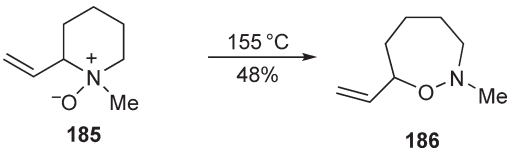
Reactions of hydrazine and methylhydrazine with pyrylium or thiinium salts, e.g., **182**, provide major routes to 4*H*-1,2-diazepines **183** and 1*H*-1,2-diazepines **184** <1980CJC494>. Selenopyrylium salts react with anhydrous hydrazine in dry acetonitrile in a similar fashion (**Scheme 90**) <2005CPB60, CHEC-III(13.04.10)154>.



Scheme 90

4.3.2.5.2 1,2-Oxazepines and 1,2-thiazepines

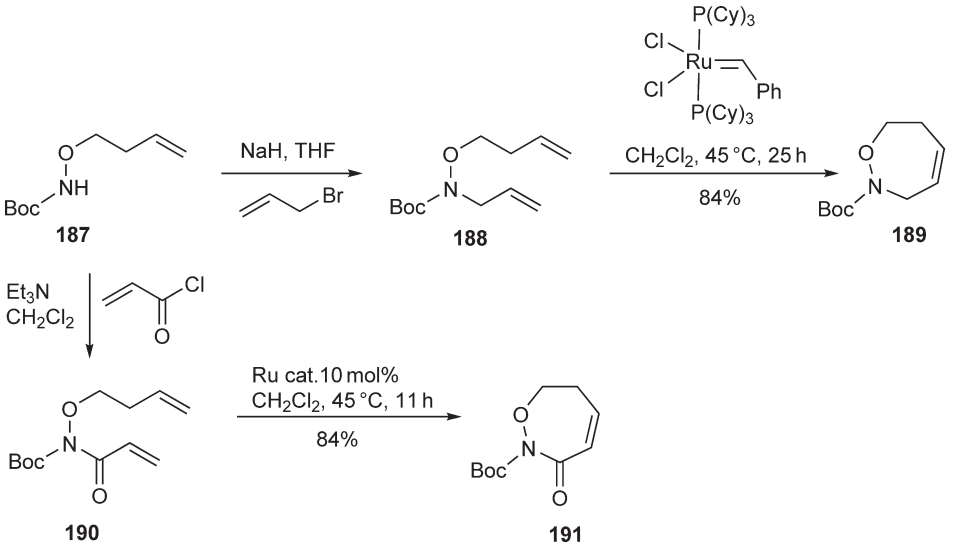
The Meisenheimer rearrangement of *tert*-amine *N*-oxides (e.g., **185**) has been applied to the synthesis of monocyclic 1,2-oxazepines, e.g., **186** (**Scheme 91**) <1984CPB4117>.



185 **186**

Scheme 91

RCM methodology can be used for the synthesis of 1,2-oxazepine derivatives. Thus, compounds **189** and **191** were prepared in good yields from the respective diene precursors **188** and **190** both accessed in turn from **187** (**Scheme 92**) <2003SL1043, CHEC-III(13.07.3)239>.



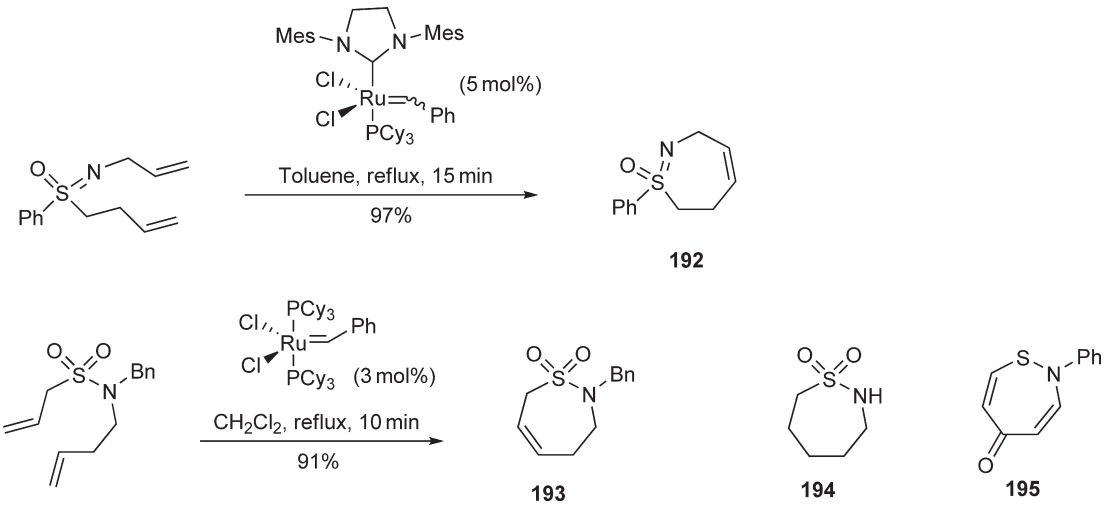
187 **188** **189** **190** **191**

Scheme 92

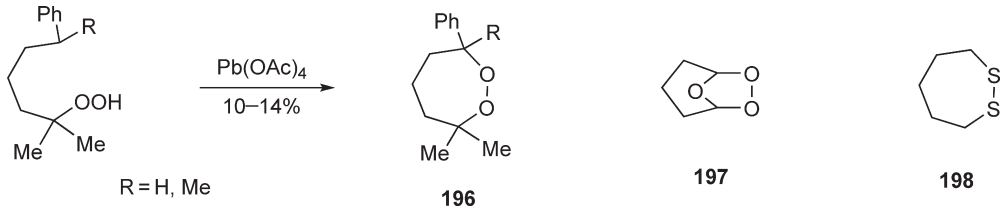
Likewise, RCM was utilized to access 1,2-thiazepine derivatives **192** and **193** (**Scheme 93**) <2005S1421, 1999TL4761>. The cyclic sulfonamide **194** can be prepared by heating 5-aminopentanesulfonyl chloride. The ketone HCCC(O)CH=CHSCN reacts with amines to give the 1,2-thiazepin-5-one system **195** <1961CB1606>.

4.3.2.5.3 1,2-Dioxepans and 1,2-dithiepans

The monocyclic saturated peroxides **196** have been prepared by the treatment of the respective hydroperoxides with lead tetraacetate (**Scheme 94**) <1981S633>. Another general approach to the 1,2-dioxepan ring system involves the ozonolysis of appropriate precursors with a double bond; e.g., the ozonolysis of cyclopentene gives 1,2-dioxepan (trioxane) **197** <CHEC-III(13.10.8.1)310>.



Scheme 93



Scheme 94

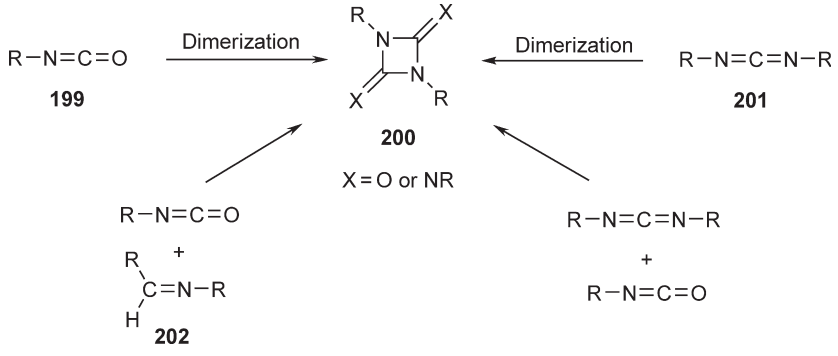
Simple 1,2-dithiepanes are prepared by the oxidation of ,-alkanedithiols using hydrogen peroxide, iodine, oxygen, or other oxidants <CHEC-III(13.10.8.3)315>. For example, potassium permanganate adsorbed on copper sulfate pentahydrate oxidizes 1,5-pentanedithiol into 1,2-dithiepane **198** <1998S1587>.

4.3.3 Two Heteroatoms in the 1,3-Positions

4.3.3.1 Four-membered Rings

4.3.3.1.1 1,3-Diazetidines

General syntheses of 1,3-diazetidines **200** are [2 + 2] cycloadditions of C=N-containing substrates (**Scheme 95**) <CHEC-III(2.13.9.4.3)677>. The dimerization of aryl isocyanates **199** to 1,3-diarylazetidin-2,4-diones is one of the classical methods for the synthesis of 1,3-diazetidinones. Carbodiimides **201** undergo [2 + 2] cycloaddition reactions to

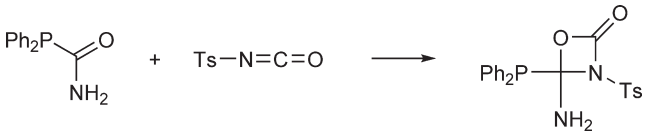


Scheme 95

furnish 1,3-disubstituted-2,4-bisalkyl or arylimino-1,3-diazetidine. Cycloaddition of imines **202** and isocyanates furnishes substituted 1,3-diazetidines. Cycloadditions of carbodiimides with isocyanates and iminophosphoranes with isocyanates <2001H(55)1641, 1986J(P1)2037> are alternative syntheses of 1,3-diazetidines.

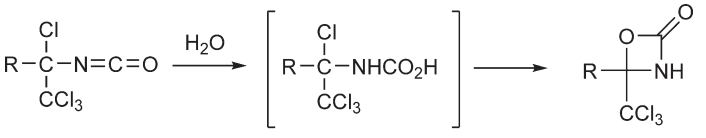
4.3.3.1.2 1,3-Oxazetidines

[2+2] Cycloaddition is a useful method to synthesize 1,3-oxazetidin-2-ones <CHEC-III(2.14.9.2)704>; an example is shown in **Scheme 96** <1968JOC3088>.



Scheme 96

1,3-Oxazetidin-2-ones **205** have been prepared by the cyclization of N-substituted carbamic acid derivatives **204**, formed *in situ* from isocyanates **203** (**Scheme 97**) <1980S571>.

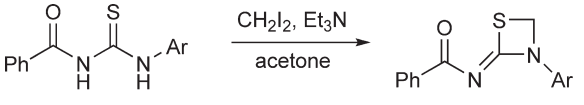


203 **204** **205**

Scheme 97

4.3.3.1.3 1,3-Thiazetidines

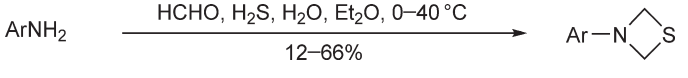
1,3-Thiazetidine rings are obtained by reaction of thioamides with carbon compounds bearing two displaceable geminal halogens. Thus *N*-benzoyl-*N*-arylthioureas **206** with diiodomethane give the corresponding 2-benzoylimino-1,3-thiazetidine **207** in high yield **Scheme 98** <1991JHC177>.



206 **207**

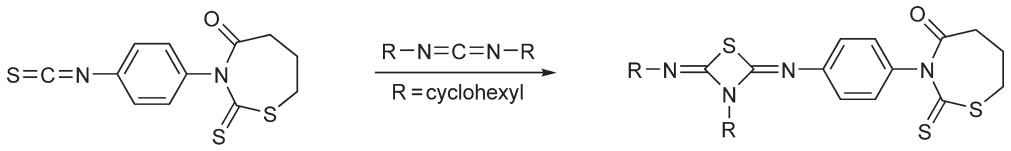
Scheme 98

Primary aromatic amines can be converted to 1,3-thiazetidines using formaldehyde and hydrogen sulfide (**Scheme 99**) <2003RCB1817>.



Scheme 99

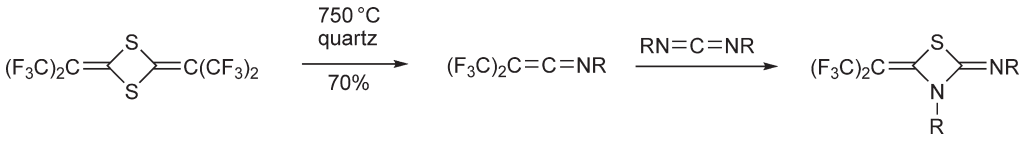
[2 + 2] Cycloaddition reactions are important in the construction of 1,3-thiazetidine rings <CHEC-III(2.15.8.3)759>. Isothiocyanates add carbodiimides across the carbonsulfur bond <1975J(P2)1475>. For example, the reaction of the 2-thioxo-1,3-thiazepan-4-one derivative **208** with *N,N*-dicyclohexylcarbodiimide affords the 1,3-thiazetidine system **209** (**Scheme 100**) <1999JHC1167>.



208 **209**

Scheme 100

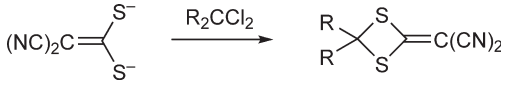
Thioketene dimers crack at high temperatures into monomers, which then undergo [2 + 2] cycloadditions (**Scheme 101**) <1970JOC3470>.



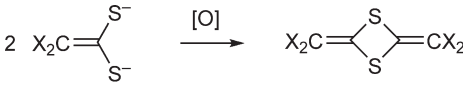
Scheme 101

4.3.3.1.4 1,3-Dithietanes

Active methylene compounds with carbon disulfide and base form reactive salts which undergo [3 + 1] additions to a variety of alkylating agents, even *gem*-dihaloethylenes (**Scheme 102**) <1977CC207>. The salts can be oxidized to symmetrical desaurin derivatives **210** (**Scheme 103**) <1962CB2861>. Similarly, the reaction of nitroketene dithioacetate with dibromomethane in methanol gives 2-nitromethylene-1,3-dithietane **211** (**Scheme 104**) <2002SUL207, CHEC-III(2.18.4.2)841>.

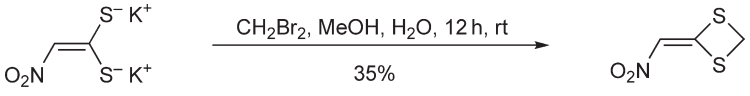


Scheme 102



210

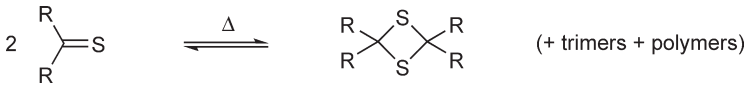
Scheme 103



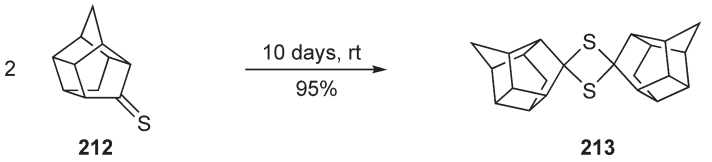
211

Scheme 104

Head-to-tail dimerization of thiocarbonyl compounds to 1,3-dithietanes (**Scheme 105**) occurs thermally <1977JOC2345> and photochemically <1981JOC3911>, or catalyzed either by a base <1973T2759> or a sulfonic acid <1997BCJ509>. For example, synthesis of dithietane **213** in excellent yield was performed by the room temperature dimerization of the thione **212** (**Scheme 106**) <2004TL7655, CHEC-III(2.18.4.2)838>. Diaryl thioketones are resistant to dimerization. Some thiones dimerize to 1,3-dithietanes <1975BSF(2)1670>.

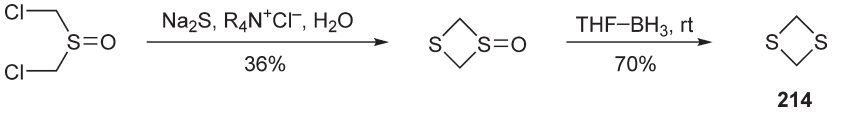


Scheme 105



Scheme 106

The parent compound 1,3-dithietane **214** was successfully prepared according to **Scheme 107** <1976JA5715, 1982JA3119>.

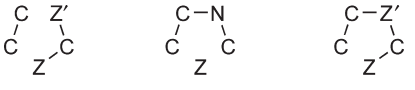


Scheme 107

4.3.3.2 Five-membered Rings: Imidazoles, Oxazoles, Thiazoles, Dithiolium Salts, and Derivatives

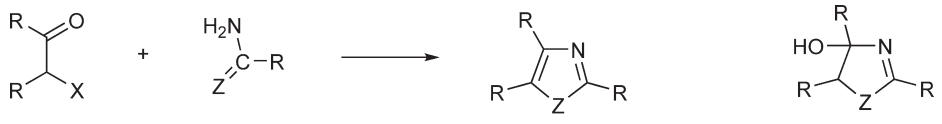
4.3.3.2.1 Overview

We consider successively the synthesis of fully-conjugated derivatives by ring closures of type **215** (Section 4.3.3.2.2), **216** (Section 4.3.3.2.3), and **217** (Section 4.3.3.2.4). This is followed by a consideration of methods involving C-C bond formation and/or 1,3-dipolar cycloadditions (Section 4.3.3.2.5), and syntheses of oxo-containing and reduced rings from acyclic precursors (Section 4.3.3.2.6). Finally, transformations from other heterocycles are described (Section 4.3.3.2.7).



4.3.3.2.2 Synthesis from $C_2 + ZCZ$ components

-Halo ketones **218** react with amides (100°C, no solvent), thioamides (reflux in EtOH), and amidines to give oxazoles, thiazoles, and imidazoles (**219 220**; Z = O, S, NH), respectively (**Scheme 108**). Intermediates of type **221** can sometimes be isolated. This is the most important thiazole synthesis, and both the thioamide and the halo ketone components can be varied widely <CHEC-III(4.06.9.1.1)679>.

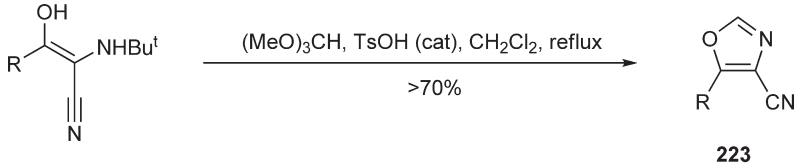


218 219 220 221

Scheme 108

Guanidines with -halo ketones form 2-aminoimidazoles. -Hydroxy ketones also react with amidines to form imidazoles, and a variety of substituents can be introduced into the imidazole nucleus <CHEC-III(4.02.9.2.2)318>.

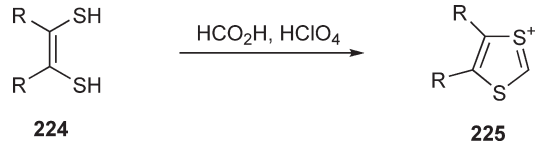
The reaction of -halo carbonyl compounds with primary amides is appropriate for oxazoles containing one or more aryl groups <CHEC-III(4.04.9.2)519>. Ureas form 2-aminooxazoles. Formamide can be used resulting in a free 2-position in the oxazole. A convenient synthesis of 5-substituted-4-cyanooxazoles **223** is based on the condensation of -hydroxy--cyanoenamines **222** with trimethyl orthoformate (**Scheme 109**). The cyanoenamine intermediates **222** are derived from Lewis acid-catalyzed Passerini reactions between *t*-butyl isonitrile and aldehydes <2002S1969>.



222 223

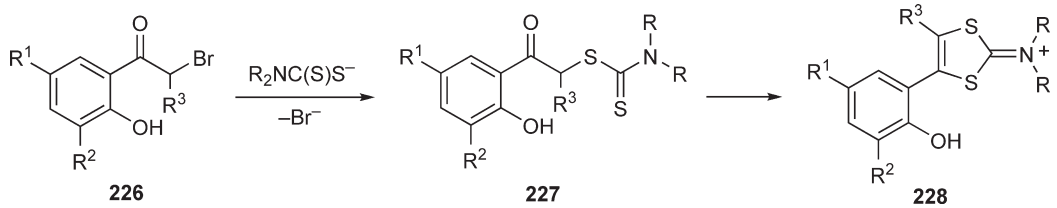
Scheme 109

-Halo ketones react with thioacids to form 1,3-dithiolylium salts **225** which are also obtained from -dimercaptoethylenes **224** (**Scheme 110**) <CHEC-II(3.12.7.1.1)631>. A new approach to the synthesis of 1,3-dithiolylium salts **228** involves an acid-catalyzed cyclization of the corresponding dithiocarbamates **227**, obtained from -bromo ketones **226** in a high yield (**Scheme 111**) <2001SC1271, 2003SUL155, CHEC-III(4.12.9.1)1015>.



224 225

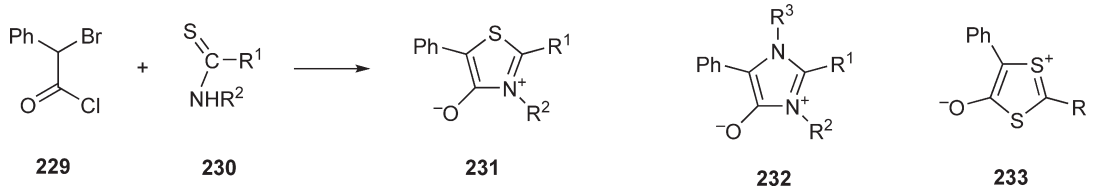
Scheme 110



226 227 228

Scheme 111

-Haloacyl halides are used for the synthesis of mesoionic rings. Secondary thioamides **230** with -bromophenylacetyl chloride **229** give the 4-oxidothiazolium hydroxides **231** (**Scheme 112**) <1996M1251>. Similarly substituted amidines and dithioic acids with the same reagents formed the corresponding imidazolium **232** and dithiolylium **233** mesoionic systems <1977JOC1633, 1977JOC1639>.

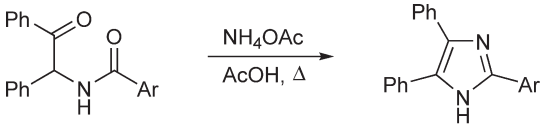


229 **230** **231** **232** **233**

Scheme 112

4.3.3.2.3 Synthesis of imidazoles, oxazoles, and thiazoles from acylamino ketones

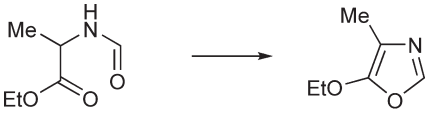
-Acylamino ketones on heating with ammonium acetate are converted into imidazoles. 2,4,5-Triarylimidazoles **235** were prepared in this way from the amides **234** (**Scheme 113**) <1973CB2415>, and numerous variations are possible for this reaction.



234 **235**

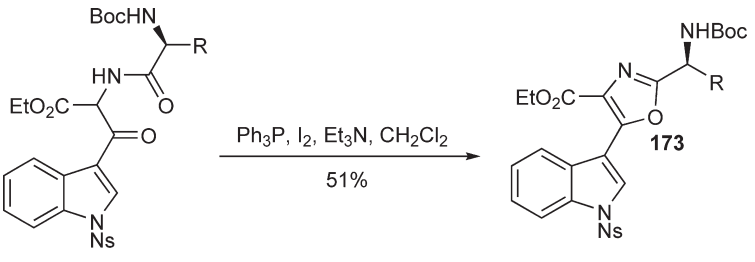
Scheme 113

Oxazoles can be similarly prepared in good yields. Thus, 5-ethoxy-4-methyloxazole **237** was obtained by treating ethyl 2-formamidopropionate **236** with phosphorus pentoxide in chloroform at 55°C (**Scheme 114**) <1972JCS(Pl)909>. Known collectively as the RobinsonGabriel synthesis, these cyclodehydrations can be effected using dehydrating reagents such as $POCl_3$, H_2SO_4, $SOCl_2$, P_2O_5, polyphosphoric acid, *p*-toluenesulfonic acid, and trifluoroacetic acid <CHEC-III(4.04.9.1) 517>. Newer reagent combinations such as $Ph_3PI_2Et_3N$, $Ph_3PBCl_2CCCl_2BrDBU$, and $Ph_3P(O)Tf_2O$ have gained broader use in the context of natural product syntheses. In a synthetic study of martefragin A, a -keto-ester **238** was cyclodehydrated by $Ph_3PI_2Et_3N$ to give an oxazole product **239** (**Scheme 115**) <2005JOC5840>.



236 **237**

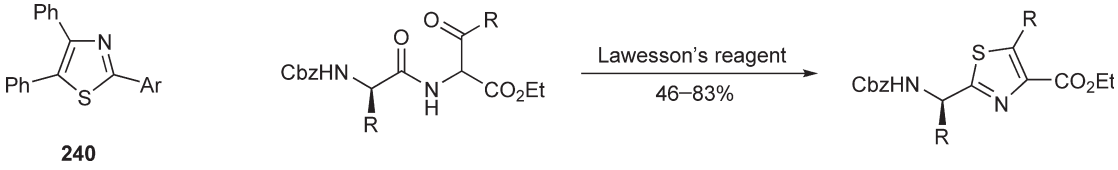
Scheme 114



238 **239**

Scheme 115

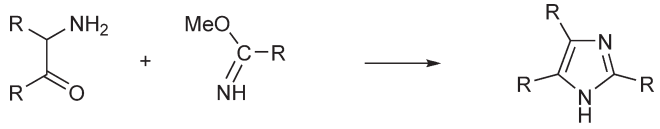
-Acylamino ketones also provide a convenient synthesis of thiazoles on treatment with phosphorus pentasulfide (Gabriels method). Substituents are usually restricted to alkyl, aryl, and alkoxy derivatives. Thus, the -acylamino ketone **234** with P_4S_{10} gave the thiazole **240**. Lawessons reagent (LR) can be effectively used as the source of sulfur in these cyclizations (e.g., **Scheme 116**) <1996JME957, 2006TL2361, CHEC-III(4.06.9.1.3)682>.



240

Scheme 116

In a related reaction, -amino ketones **241** with iminoesters **242** give imidazoles **243** (**Scheme 117**) (see also <CHEC-III(4.02.9.2.2)307>.

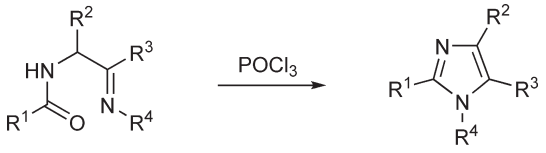


241 **242** **243**

Scheme 117

4.3.3.2.4 Other syntheses of imidazoles, oxazoles, thiazoles, dithiolyliums, and oxathiolyliums by cyclization of C_2ZCZ components

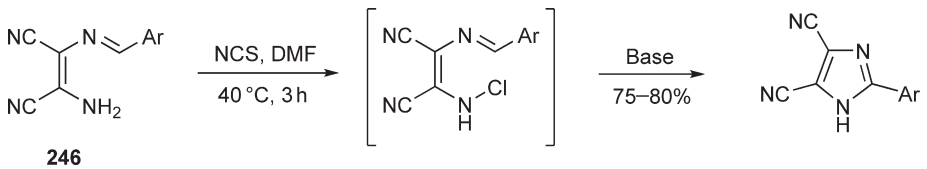
1. Formation of the CN bond via the activation of an amide or urea group is a versatile method to synthesize imidazoles. Many reagents, such as PCl_5, $POCl_3$, PPh_3-CCl_4, and acids, have been used for this cyclization process <CHEC-III (4.02.9.1)281>. -Acylamino Schiff bases **244** with phosphoryl chloride or PCl_5 give the 1-substituted imidazoles **245** (**Scheme 118**) <1978LA1916, 2002TL7687>.



244 **245**

Scheme 118

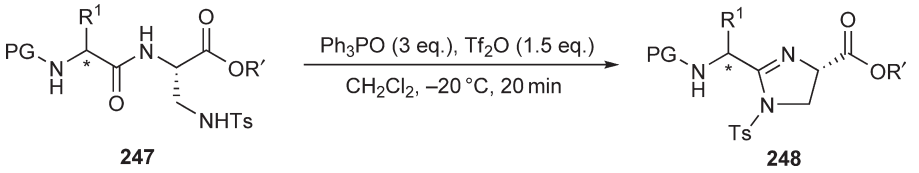
Oxidative cyclizations of Schiff bases of 1,2-diaminomaleonitrile **246** are conveniently accomplished using *N*-chlorosuccinimide under basic conditions (**Scheme 119**) <1984S1057>.



246

Scheme 119

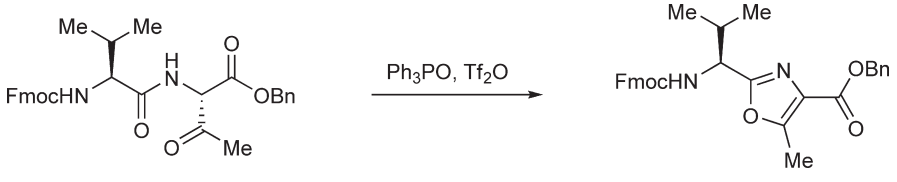
Dipeptides **247** undergo cyclization in the presence of Ph_3PO/Tf_2O to give imidazolines **248** in moderate to very good yields and with excellent enantioselectivity (**Scheme 120**) <2004OL1681>. The method was also utilized for the synthesis of imidazole-containing peptides on solid support <2006OL2417>.



247 **248**

Scheme 120

2. A Ph_3PO/Tf_2O-mediated cyclodehydration was utilized in the conversion of -keto-ester **249** to give a key oxazole building block **250** (**Scheme 121**), which was used in a total synthesis of the marine natural product bistratamide F-I <2005T241, CHEC-III(4.04.9.1)517>.



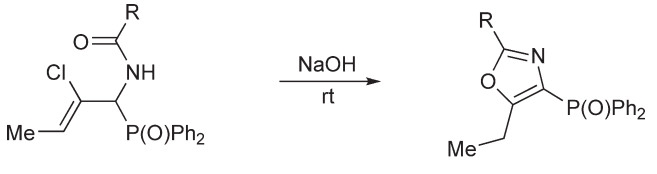
249 **250**

Scheme 121

Propargylamine amides can readily undergo cycloisomerization to oxazole products using a number of conditions. Conjugated alkynyl amide **251** was converted to oxazole **252** with the aid of silica gel (**Scheme 122**) <2004OL3593>. Likewise, allylamine amides such as **253** undergo 5-*exo* cyclization in NaOH to give phosphine oxide-substituted oxazoles **254** (**Scheme 123**) <2004T8937>.

251 **252**

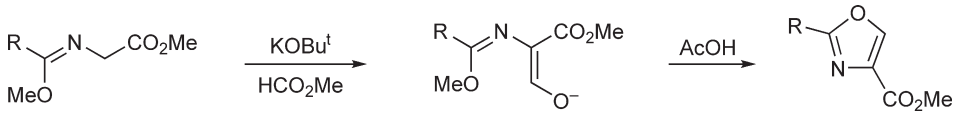
Scheme 122



253 R = alkyl or vinyl **254**

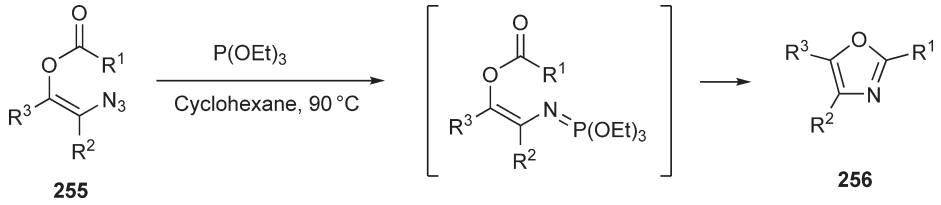
Scheme 123

The Cornforth synthesis of oxazoles is useful for the preparation of 4-methoxycarbonyl derivatives, which are found in many natural products <1992CC1240>. In this method, a glycine imidate is reacted with a strong base and methyl formate to give an enolate that cyclizes upon treatment with acetic acid (**Scheme 124**).



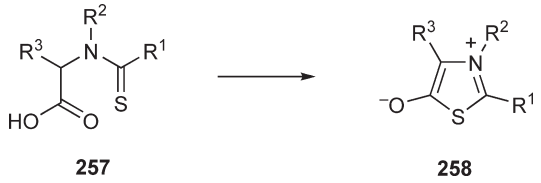
Scheme 124

A synthesis of 2,5-di- and 2,4,5-trisubstituted oxazoles **256** begins with -(acyloxy)vinyl azides **255** <1989JOC431>. An intramolecular aza-Wittig reaction ensues upon treatment of the azides with phosphorus(III) reagents (**Scheme 125**). Yields of oxazoles, including furyl- and pyridyl-substituted oxazoles that are difficult to obtain by routes that use strong dehydrating conditions, range from 48 to 93% when $P(OEt)_3$ is used.



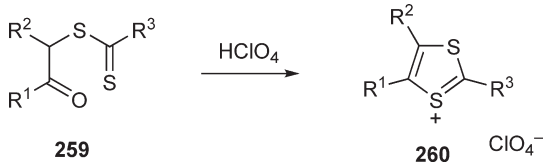
Scheme 125

3. Ring closure of the precursor **257** under acid cyclodehydration conditions gives the mesoionic thiazolium-5-olate system **258** (**Scheme 126**) <CHEC-I(6)253>.

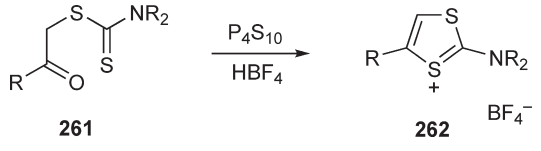


Scheme 126

4. -Oxoalkyl dithioesters **259** are cyclized by perchloric acid to dithiolylium salts **260** (**Scheme 127**) <1980AHC(27)151>. Similarly, dithiocarbamate **261** with phosphorus pentasulfide and tetrafluoroboric acid gives the 2-amino-1,3-dithiolylium tetrafluoroborate **262** (**Scheme 128**) <1969CPB1924>.

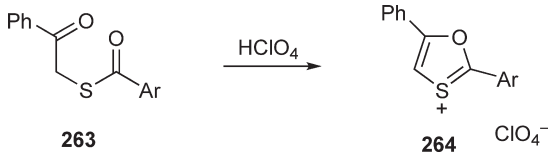


Scheme 127



Scheme 128

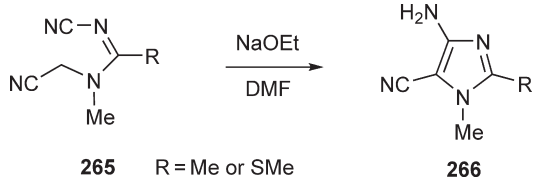
5. 2,5-Diaryl derivatives of the 1,3-oxathiolylium system **264** are prepared by acid-catalyzed cyclization of the -keto thioesters **263** (**Scheme 129**) <CHEC-I(6)749, CHEC-III(3.10.8.1)546>.



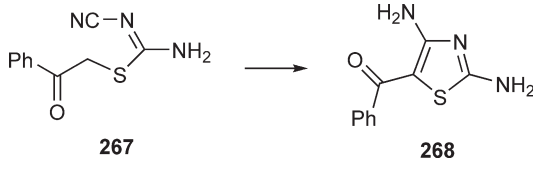
Scheme 129

4.3.3.2.5 Synthesis of imidazoles, oxazoles, and thiazoles by CC bond formation or 1,3-dipolar addition

4-Aminoimidazoles **266** are formed on base treatment of the appropriate precursors **265** (**Scheme 130**) <1975HCA2192>. Similarly the 4-aminothiazole **268** is obtained from the cyanoamidine **267** (**Scheme 131**) <1973JPR497>.

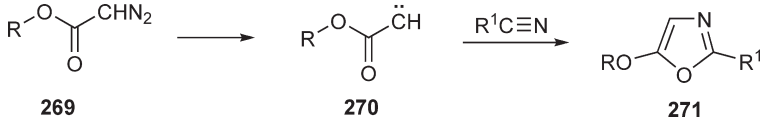


Scheme 130



Scheme 131

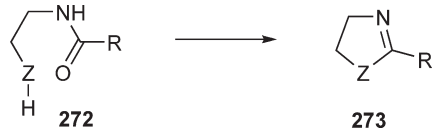
Decomposition of the diazoacetic ester **269** to the carbene **270** is promoted by copper(II) trifluoromethanesulfonate. In the presence of nitriles, **270** is captured by 1,3-dipolar addition giving the oxazole **271** (**Scheme 132**) <1975JOM(88)115> (see also <CHEC-III(4.04.9.2.2)522>).



Scheme 132

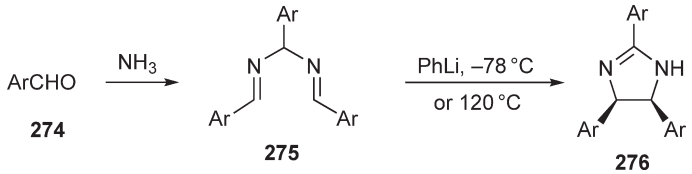
4.3.3.2.6 Synthesis of azolinones and reduced rings from acyclic precursors

1. -Hydroxy-, -amino-, and -mercapto-acylamines (**272**; Z = O, NH, S) cyclize to give the respective oxazolines, imidazolines, and thiazolines **273** (**Scheme 133**).



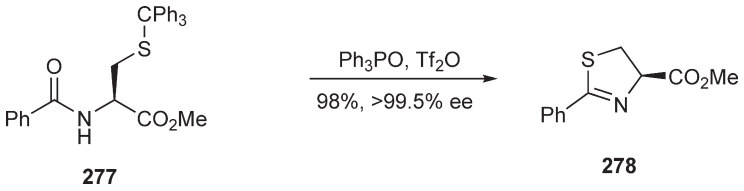
Scheme 133

A simple, stereocontrolled, and economical synthesis of *cis*-2,4,5-triarylimidazolines **276** starts from the reaction of aromatic aldehydes **274** with ammonia to form 2,4-diazapentadienes **275**. Deprotonation of 2,4-diazapentadienes **275** with a strong base or under thermal conditions results in formation of the transient 2,4-diazapentadienyl anion that cyclizes in a disrotatory fashion to furnish *cis*-imidazolines **276** (**Scheme 134**); microwave irradiation facilitates the ring closure <1997TL8631, 2003S1236, 2005H(65)353, CHEC-III(4.02.9.1.3)295>.



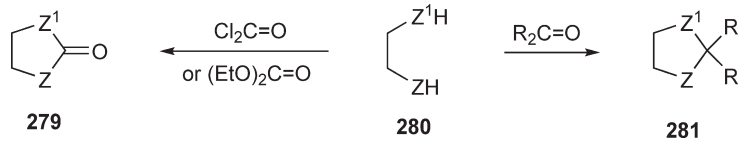
Scheme 134

Synthesis of thiazoline **278** in excellent yield and with high enantioselectivity was accomplished from fully protected cysteine **277** using the Ph_3PO/Tf_2O reagent (**Scheme 135**) <2003AGE83, CHEC-III(4.06.9.2.8)690>.



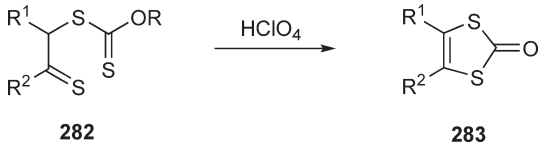
Scheme 135

2. 1,2-Difunctional ethanes **280** (Z, Z^1 = O, S, NH) react with phosgene and carbonate esters to give 2-oxazolidinones and analogous derivatives **279** (**Scheme 136**). Likewise, compounds **280** react with aldehydes and ketones to form oxazolidines **281**. Such reactions are used extensively to protect *cis*-hydroxy groups (e.g., sugars + acetone isopropylidene sugars) and carbonyl groups (e.g., steroidal ketones + ethylene glycol ethylene ketals).



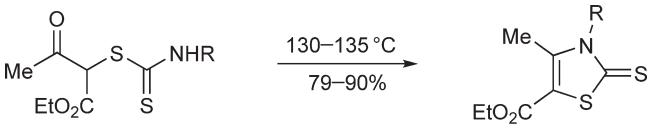
Scheme 136

3. The 1,3-dithiol-2-one **283** is obtained by ring closure of the dithiocarbonate **282** (**Scheme 137**) <1976S489>.



Scheme 137

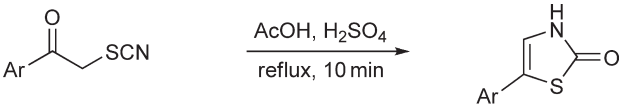
Dithiocarbamoyl derivatives of acetoacetic ester **284** cyclize on standing (and more rapidly upon heating) to give 2-thiooxy-l,3-thiazolinyl derivatives **285** in good yields (**Scheme 138**) <CHEC-III(4.06.9.4.3)691>.



284 **285**

Scheme 138

4-Arylthiazol-2(3*H*)-ones **287** have been prepared by treatment of the corresponding -thiocyanatoacetophenones **286** with glacial acetic acid and sulfuric acid (**Scheme 139**) <2002J(P2)329>.



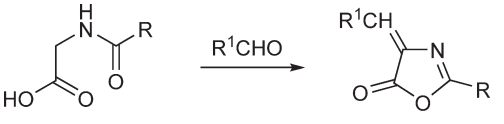
286 **287**

Scheme 139

4. -Acylaminocarboxylic acids **288** are converted into 5(4*H*)-oxazolinones **289** by acid anhydrides (**Scheme 140**). In an extension of this reaction, *N*-acyl derivatives of glycine **290** react with aldehydes with concomitant cyclization to give azlactones **291** (**Scheme 141**); this is the basis of the Erlenmeyer synthesis of amino acids. Treatment of amino acid derivatives **292** with PBr_3 affords the thiazolidine-2,5-dione **293** (**Scheme 142**) <1971CB3146>.

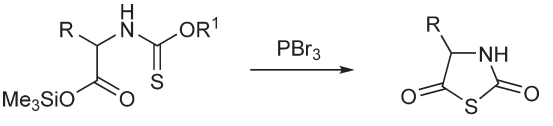
288 **289**

Scheme 140



290 **291**

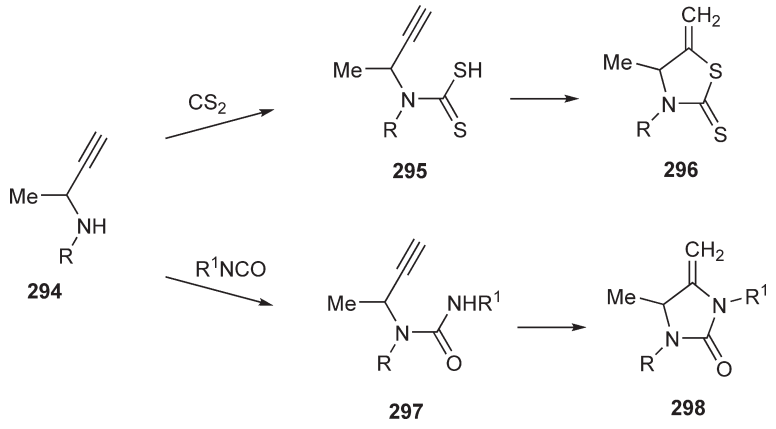
Scheme 141



292 **293**

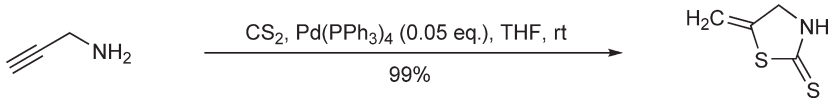
Scheme 142

5. Nitrogen, oxygen, and sulfur nucleophiles can add intramolecularly to unsaturated carboncarbon systems forming a heterocyclic ring. This synthetic approach is illustrated by the reaction of the propargylamine **294** with carbon disulfide. The intermediate dithiocarbamic acid **295** cyclizes to the thiazole **296** (**Scheme 143**) <1949JCS786>. The NH group of the propargylamine **294** adds isocyanates to give ureas **297** which are converted by sodium methoxide into 4-methylene-2-imidazolinones **298** (**Scheme 143**) <1963JOC991>.



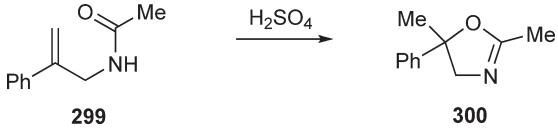
Scheme 143

The palladium-catalyzed cyclization of various propargylic amines with carbon disulfide leading to thiazole derivatives has been reported (e.g., **Scheme 144**) <2002JOC16, 2001HAC610, CHEC-III(4.06.9.2.2)686>.



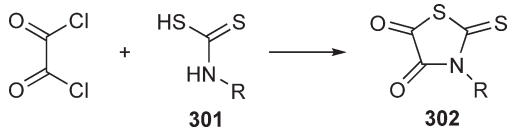
Scheme 144

N-Allyl-amides, -urethanes, -ureas, and -thioureas undergo intramolecular cyclization in 6096% sulfuric acid to give 2-oxazolines and 2-thiazolines as illustrated by the conversion of *N*-2-phenylallylacetamide **299** into 2,5-dimethyl-5-phenyl-2-oxazoline **300** (**Scheme 145**) <1970JOC3768>.

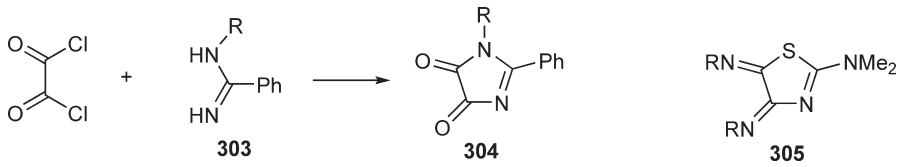


Scheme 145

6. Reaction of oxalyl chloride with compound **301** gives the thiazolidine-4,5-dione **302** (**Scheme 146**), and the same reagent with *N*-alkylbenzamidine **303** at 100-140°C affords the 1-alkyl-2-phenylimidazole-4,5-dione **304** (**Scheme 147**). Iminochlorides of oxalic acid react with N,N-disubstituted thioureas to give the 2-dialkylaminothiazolidine-4,5-dione bisimides **305**. Phenyliminooxalic acid dichloride likewise yielded thiazolidine derivatives on reaction with thioureas <1971KGS471>.



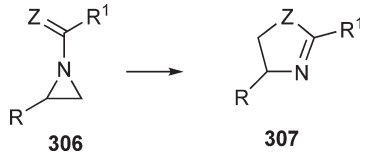
Scheme 146



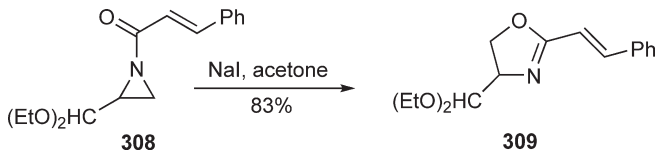
Scheme 147

4.3.3.2.7 Synthesis from other heterocycles

Appropriately substituted aziridines **306** (Z = O, S, NR) undergo a facile ring opening and subsequent closure forming five-membered heterocycles **307** (**Scheme 148**). For example, the reaction of *N*-acylaziridine **308** in the presence of sodium iodide in acetone affords oxazoline **309** in good yield (**Scheme 149**) <1994TL2039, CHEC-III(4.04.10)525>. A similar aziridine ring-opening reaction is a particularly attractive route to imidazolines and ring-fused imidazolines **307** (Z = NR) <1962JOC2943> (see Section 3.5.2.2).

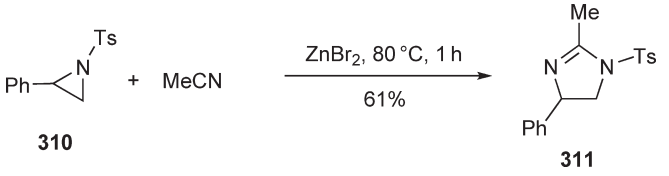


Scheme 148



Scheme 149

A wide range of aziridine derivatives can react with nitriles in the presence of Lewis acids to yield imidazolines in a regio- and stereoselective manner (Ritter reactions) <CHEC-III(4.04.10)525>. For example, a BF_3OEt_2 or $ZnBr_2$-catalyzed ring opening of phenyl *N*-tosylaziridine **310** with acetonitrile affords imidazoline **311** in good yield (**Scheme 150**) <2004TL1137, 2005TL4103>; the same reaction can be promoted by $Sc(OTf)_3$ in the absence of organic solvents to give the corresponding imidazolines in excellent yields <2006TL1509>.



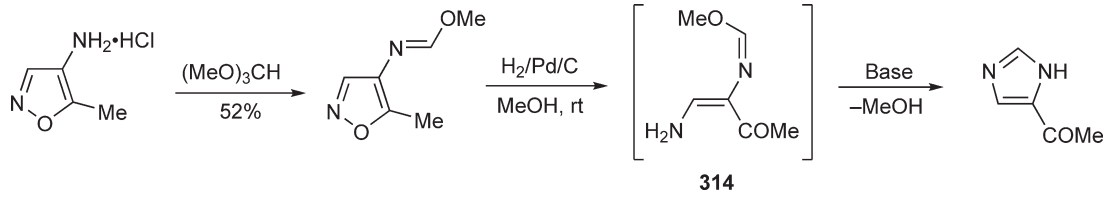
Scheme 150

Aziridines also undergo ring enlargement on treatment with thiocyanic acid: *cis*- and *trans*-2,3-dimethylaziridines **312** thus give *trans*- and *cis*-2-amino-4,5-dimethyl-2-thiazolines **313** stereospecifically (**Scheme 151**) <1972JOC4401>.

Scheme 151

Photoisomerizations of pyrazoles, isoxazoles, and isothiazoles into imidazoles, oxazoles, and thiazoles, respectively, are described in Section 3.4.1.2.4.

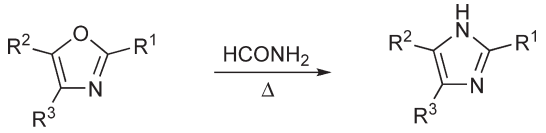
Catalytic reduction of iminoethers derived from 4-aminoisoxazoles <1987JOC2714> or 4-amino-5(4*H*)-isoxazolones <1991S127> leads to -(acylamino)enaminones **314** which cyclize in the presence of bases to form 4-acylimidazoles (**Scheme 152**). Treatment of the enaminone **314** with a primary amine incorporates a substituted amino function in the -position with concomitant expulsion of ammonia and allows access to 1-substituted and 1,2-disubstituted 4-acylimidazoles in high yields <1987JOC2714>.



314

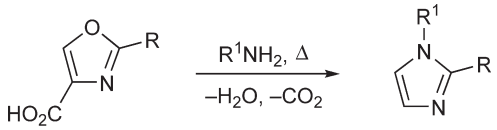
Scheme 152

The oxazole **315** heated with formamide gave the imidazole **316** (**Scheme 153**); oxazolium cations undergo similar conversions. Primary amines convert oxazole-4-carboxylic acids **317** at 150°C into imidazoles **318** with accompanying decarboxylation (**Scheme 154**) <1953CB88>.



315 **316**

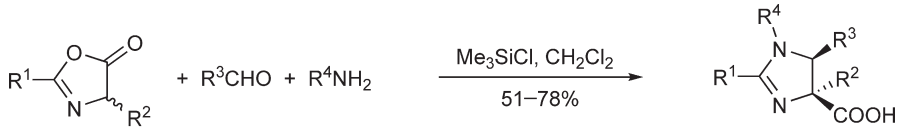
Scheme 153



317 **318**

Scheme 154

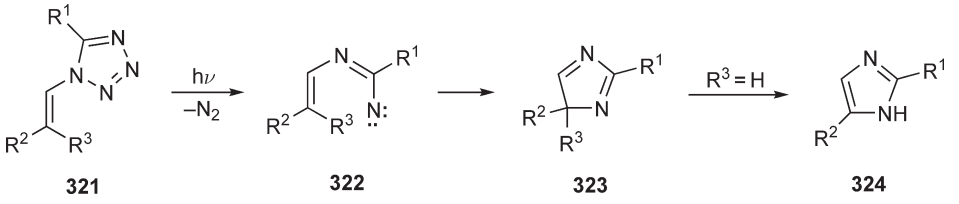
1,3-Dipolar cycloaddition reactions of N-substituted mesoionic oxazolones (mnchnones) with imines provide a general route for the syntheses of imidazoles and imidazolines <1998JOC2800, 2002OL3533>. For example, the TMSCl-promoted reaction of 2-phenyl-4-methyl-4*H*-oxazolin-5-ones **319** with imines generated *in situ* afforded imidazolines **320** in good yields with excellent diastereoselectivity (**Scheme 155**) <2002OL3533, 2005OL5091, 2003S1433, 2004JA12776>.



319 **320**

Scheme 155

A widely applicable route to substituted imidazoles is photochemical degradation of 1-alkenyltetrazoles **321** (**Scheme 156**). Evolution of N_2 gives *N*-vinylimidoyl nitrenes **322** which cyclize to the 4*H*-imidazoles **323** in good to moderate yields <1987J(P1)1389, 1991J(P1)335>. When $R^3 = H$, a 1,5-shift in 4*H*-imidazoles **323** results in aromatic imidazoles **324** <1984J(P1)1933, 1985J(P1)741>. When the vinyl double bond in the starting tetrazole is part of a benzene ring the products are benzimidazoles and carbodiimides <1985J(P1)1471>.



Scheme 156

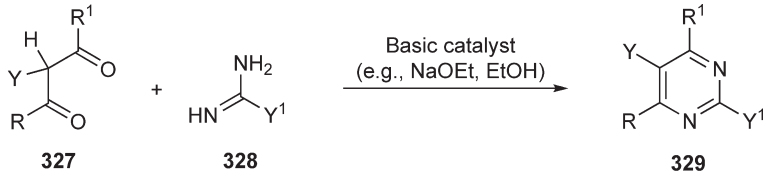
Photochemical transformations of 2-azidopyrazines into imidazoles are well known. The reaction appears to be more versatile and gives higher yields under thermolysis conditions <1983JHC1277, 1990JHC711> (see Section 3.2.3.6.4).

4.3.3.3 Six-membered Rings

There are two major routes to six-membered rings, and these are summarized by the disconnections **325** and **326**. For the preparation of pyrimidines, methods corresponding to disconnection **325** are the most important. Saturated compounds, i.e., 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes, result from syntheses of type **326**.

4.3.3.3.1 $C_3 + ZCZ$-type cyclizations

Numerous pyrimidines **329** have been synthesized by reaction of a 1,3-dicarbonyl compound **327**, or a potential 1,3-dicarbonyl compound, with an amidine **328**; representative substituents are shown in **Scheme 157**.

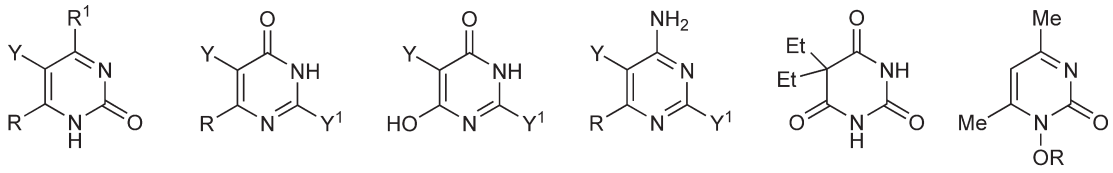


R, R^1 = H, Me, Ph, CO_2Et
Y = H, Me, Ph, Br, NO, NO_2; Y^1 = H, Me, Ph, OMe, SMe, NH_2

Scheme 157

The following modifications are noteworthy (see <CHEC-III(8.02.9.1.4)195> for a full discussion).

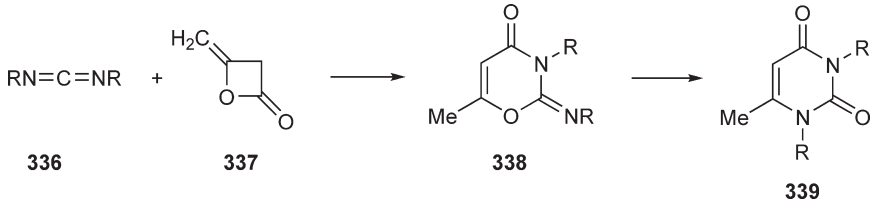
1. The amidine component **328** can be replaced by urea, thiourea, or guanidine resulting in the formation of 2-pyrimidinones **330**, 2-thiones, or 2-aminopyrimidines respectively.
2. If one or both of the carbonyl groups in the 1,3-dicarbonyl compound is in the form of an ester, 4-pyrimidinones **331** and their 6-hydroxy derivatives **332** are formed.



330 **331** **332** **333** **334** **335**

3. Replacement of one or both of the carbonyl groups by a cyano group leads to 4-amino- **333** or 4,6-diamino-pyrimidines.
4. If the central carbon atom of the carbonyl compound is tetrasubstituted, nonaromatic derivatives are produced, e.g., $Et_2C(CO_2Et)_2$ reacts with urea to yield veronal **334**.
5. Use of *N*-methoxyurea gives *N*-oxide derivatives such as **335**.
6. Use of an ,-unsaturated compound gives a dihydropyrimidine.

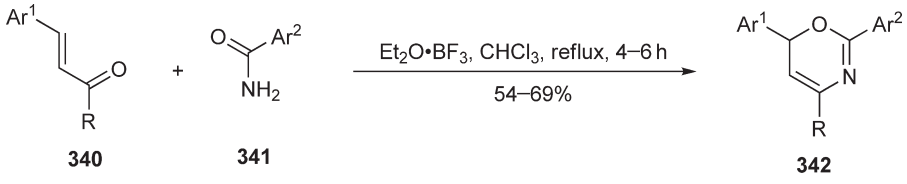
Amidines, ureas, thioureas, *S*-alkylisothioureas, and carbodiimides **336** also react with diketene **337** to give pyrimidines (e.g., **339**). Amidines, *S*-alkylisothioureas, and carbodiimides, however, initially form 1,3-oxazines (e.g., **338**) that are converted into pyrimidines on subsequent treatment with acid or base (**Scheme 158**).



336 **337** **338** **339**

Scheme 158

The Lewis acid-catalyzed condensation of ,-unsaturated ketones **340** with amides **341** furnishes 2,4,6-trisubstituted 6*H*-1,3-oxazines **342** (**Scheme 159**). An environmentally benign solvent-free version of this process, based on the application of Montmorillonite K-10 clay and a brief microwave irradiation, provides oxazines **342** in higher yields (9197%) than in the conventional solution-phase method <2004BCJ2265, CHEC-III(8.05.9.1)411>.

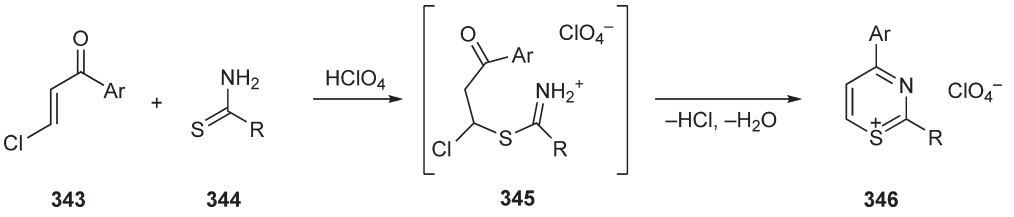


340 **341** **342**

Ar^1 = Ph, 2-furanyl, 3-indolyl, 4-$MeOC_6H_4$
Ar^2 = Ph, 2-furyl; R = Me, Ph, 4-BrC_6H_4Br

Scheme 159

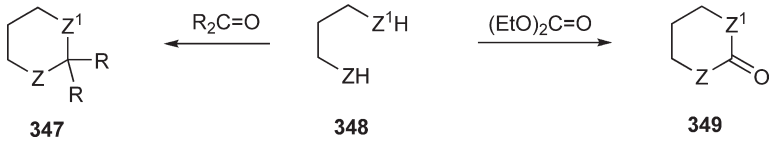
Condensation of thioamides or thiourea with ,-unsaturated ketones is a general method for the construction of the 1,3-thiazine skeleton <CHEC-III(8.08.9.1)585>. -Chlorovinyl ketones **343** and the thioamide **344** in the presence of perchloric acid give intermediate thioimidium salts **345**, which cyclize to yield 1,3-thiazinium salts **346** (**Scheme 160**) <1982T937>.



Scheme 160

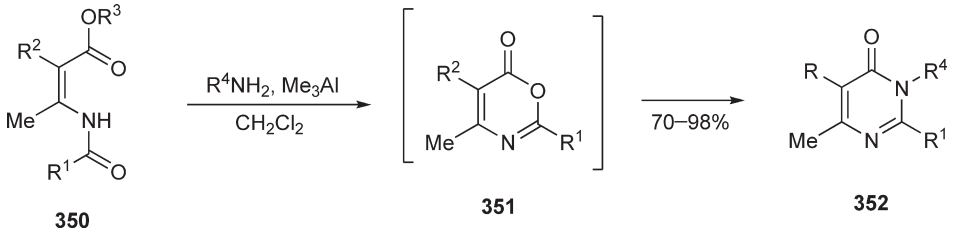
4.3.3.3.2 $ZC_3Z + C$ (5 + 1) and (6 + 0) cyclizations

The method $ZC_3Z + C$ is used for the preparation of reduced pyrimidines, oxazines, and thiazines as well as for dioxanes, dithianes, and oxathianes, e.g., **348** **347**, **349**; Z, Z = NH, O, S (**Scheme 161**). The Prins reaction yields 1,3-dioxanes <1977S661>; it involves the acid-catalyzed condensation of alkenes with aldehydes, with 1,3-diols as intermediates (for related reactions, see <CHEC-III(8.11.9.1)821>).



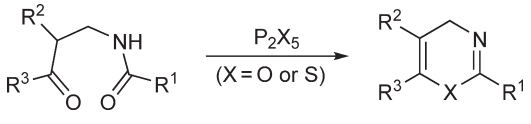
Scheme 161

A general route to 3-substituted 3*H*-pyrimidin-4-ones **352** involves the cyclization of enamide esters **350**, derived from -keto esters, with trimethylaluminium and primary amines (**Scheme 162**) <2004OL1013, CHEC-III(8.02.9.1.2)192>. The reaction proceeds through an oxazinone intermediate **351** which undergoes ring opening and subsequent ring closure by reaction with the primary amine; both aliphatic and aromatic primary amines can be used <2004OL1013>.

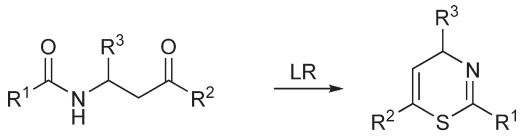


Scheme 162

Routes to 4*H*-1,3-oxazines and 4*H*-1,3-thiazines involve the cyclization of amides or thioamides with acidic reagents or the appropriate sulfur atom donor (e.g., **Scheme 163**) <1978AHC(23)1, CHEC-III(8.08.9.6)594>. For example, thionation of 3-*N*-acylamino ketones **353** with Lawesson reagent (LR) gives the intermediate 3-*N*-thioacylamino thiones which cyclize to the 1,3-thiazines **354** with loss of H_2S (**Scheme 164**) <2001HCA2347>.



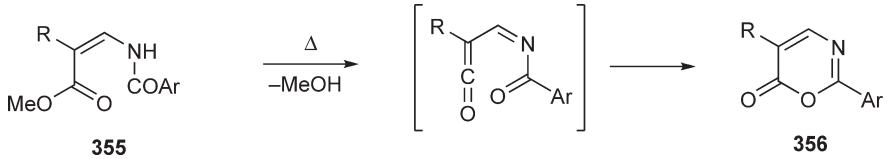
Scheme 163



353 354

Scheme 164

1,3-Oxazin-6-ones **356** are made by heating -acylamino esters **355** (**Scheme 165**) <1974AGE533>. For additional examples of similar preparations of 1,3-oxazine derivatives see <CHEC-III(8.05.9.4)430>.

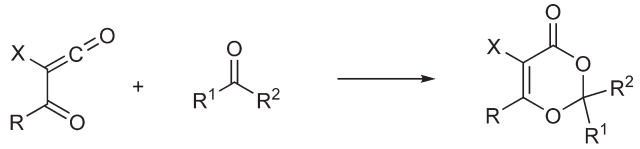


355 356

Scheme 165

4.3.3.3.3 [4 + 2] Cyclizations

1,3-Dioxin-4-ones **358** are obtained in good yields by [4 + 2] cycloadditions of -oxoketenes **357** with aldehydes or ketones (**Scheme 166**) <2003JHC697, 2004CHE245, CHEC-III(8.11.9.2)824>.

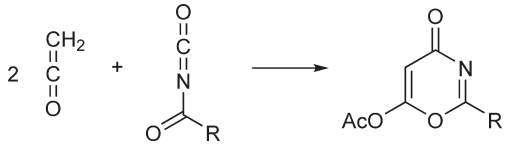


357 358

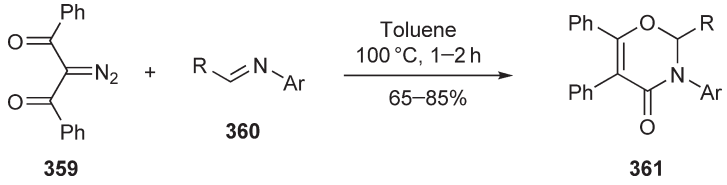
X = R, COR, CO_2R

Scheme 166

Oxazin-4-ones are obtained by cycloadditions between ketenes and isocyanates (**Scheme 167**). The benzoylphenylketene generated from diazo compound **359** forms [4 + 2] DielsAlder adducts **361** with the C=N group of aldehyde imines **360** (**Scheme 168**) <2001J(P1)2266, CHEC-III(8.05.9.2)417>.



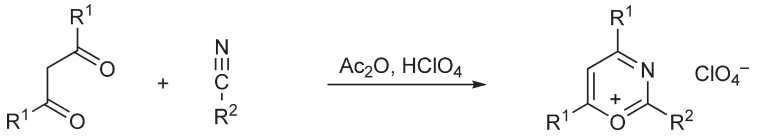
Scheme 167



359 360 361

Scheme 168

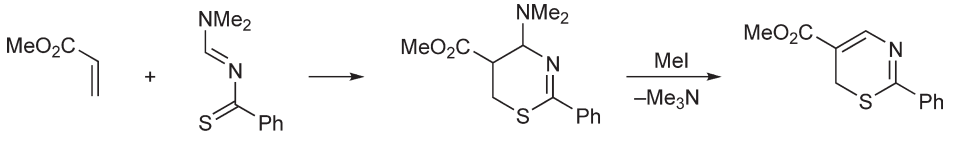
1,3-Oxazinium perchlorates **362** are obtained by reactions of 1,3-diketones and benzonitrile in the presence of perchloric acid and acetic anhydride (**Scheme 169**) <1988ZOR1561, 1991ZOR1986>. 1,3-Thiazinium perchlorates are synthesized by treating oxazinium salts with hydrogen sulfide in absolute acetonitrile and then with perchloric acid <1972S333>.



362

Scheme 169

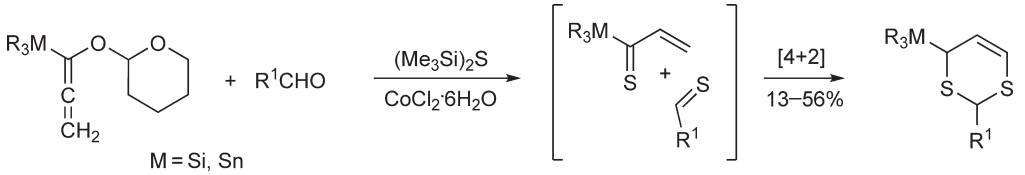
The cycloaddition of methyl acrylate with *N*-thiobenzoyl-*N*,*N*-dimethylformamidine **363** under pressure affords the 4-dimethylamino-5,6-dihydro-4*H*-1,3-thiazine **364**. On treatment with methyl iodide and triethylamine, **364** eliminates trimethylamine to give 6*H*-1,3-thiazine **365** which can also be obtained directly through the cycloaddition of methyl acrylate and the methiodide salt of the formamidine <1987SC1971>. The same methodology has been extended to other 1,3-thiazines by varying the formamidine or electron-deficient cyclic dienophile (**Scheme 170**) <1988SUL205>.



363 **364** **365**

Scheme 170

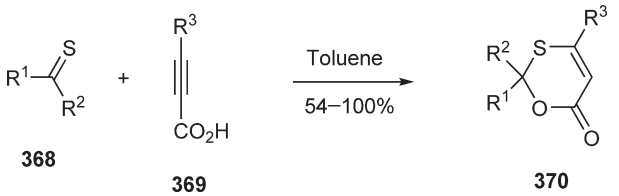
1,3-Dithiins **367** have been prepared in moderate yields by [4 + 2] cycloaddition of *in situ* formed thioenones with thiocarbonyl groups (**Scheme 171**) <2004SL2159, CHEC-III(8.11.9.2)824>. The thio compounds were generated from trialkylsilyl- or trialkylstannyl-tetrahydropyranyloxy allenes **366** using bis(trimethylsilyl)sulfide (HMDST) and $CoCl_2$ñ6H_2O.



366 **367**

Scheme 171

1,3-Oxathiin-6-ones **370** have been conveniently prepared by cycloaddition-type reactions of alkynoic acids **369** and thiocarbonyl compounds **368** in refluxing toluene (**Scheme 172**) <2003EJO3727, 2004BCJ1933, CHEC-III(8.11.9.2)824>.

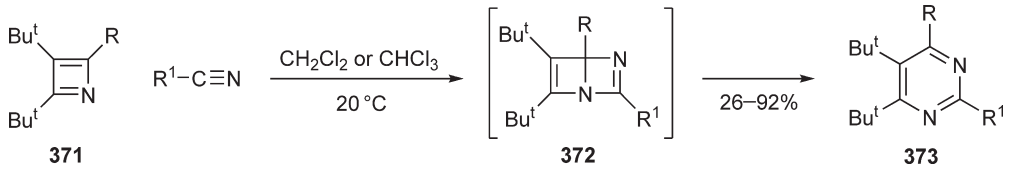


368 **369** **370**

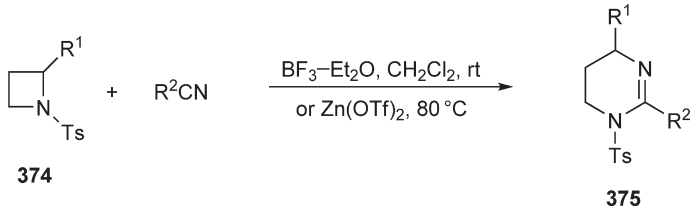
Scheme 172

4.3.3.3.4 Syntheses from other heterocycles

Kinetically stabilized azetes **371** cycloadd acceptor-substituted nitriles. The initially formed Dewar pyrimidine **372** is subsequently isomerized to the pyrimidine **373** (**Scheme 173**) <1990SL401>. Likewise, tetrahydropyrimidines **375** are produced by the reaction of *N*-tosylazetidines **374** with nitriles under the influence of boron trifluoride or zinc triflate catalysis (**Scheme 174**) <2005JA16366, 2006TL5393, CHEC-III(8.02.10.1.1)226>.

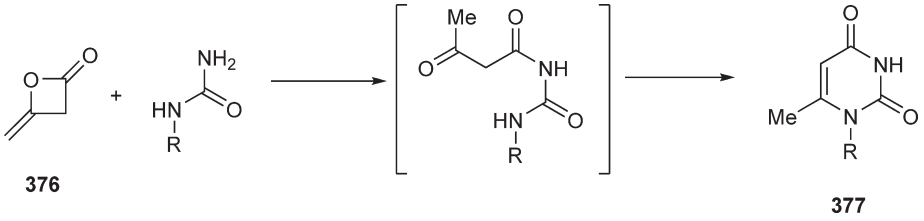


Scheme 173



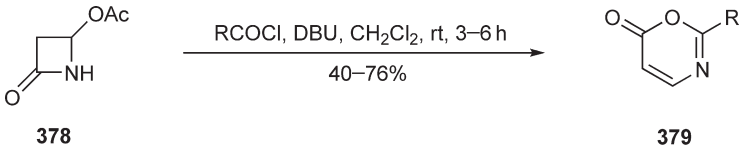
Scheme 174

6-Methyluracils **377** are readily prepared by reaction of ureas with diketene **376** in acetic acid (**Scheme 175**), and although mixtures of products are obtained with substituted ureas, this procedure has been used synthetically to prepare a variety of 1-substituted and 1,3-disubstituted 6-methyluracils, using both solution- and solid-phase procedures <2000TL1487, 2004JME1259>.



Scheme 175

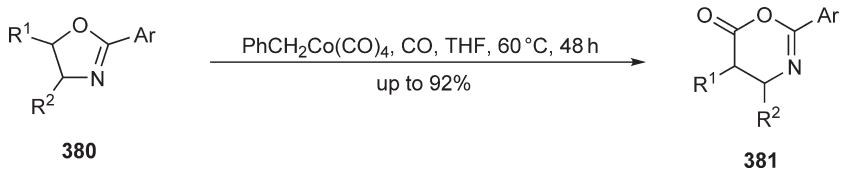
4-Acyloxy--lactams **378** are converted into 1,3-oxazin-6-ones **379** under basic conditions in a one-pot procedure (**Scheme 176**) <2000OL965, CHEC-III(8.05.10)441>. The mechanism of the conversion has been investigated using *ab initio* and density functional methods <2001JOC8470>.



R = Et, But, (*E*)-cinnamyl, Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-furyl

Scheme 176

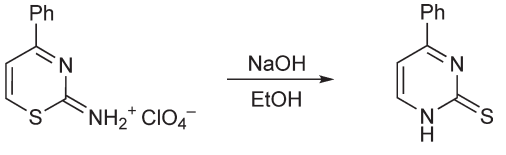
2-Aryl-4,5-dihydrooxazoles **380** undergo cobalt-catalyzed carbonylation to give 4,5-dihydro-1,3-oxazin-6-ones **381**, generally in good yields (**Scheme 177**) <2003OL1575>.



380 **381**

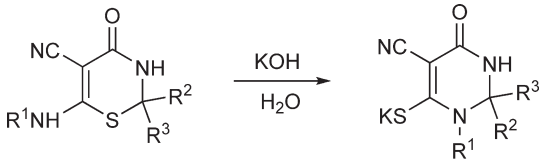
Scheme 177

1,3-Oxazines and 1,3-thiazines are commonly used as substrates in pyrimidine syntheses <1994HC(52)1, CHEC-III(8.02.10.1.3)227>. Rearrangement reactions involving 1,3-thiazines are often very easy. For example, reaction of 2-imino-4-phenyl-2*H*-1,3-thiazinium perchlorate **382** with NaOH at room temperature affords 4-phenylpyrimidine-2(1*H*)-thione **383** (**Scheme 178**) <2004CHE1595>, while treatment of 6-amino-2,3-dihydro-1,3-thiazin-4(1*H*)-ones **384** with KOH readily gives the potassium salt of the dihydropyrimidinone **385** (**Scheme 179**) <2005HAC426>.



382 **383**

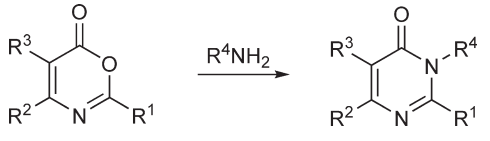
Scheme 178



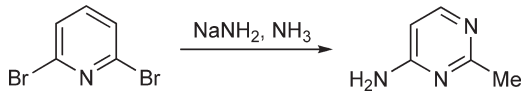
384 **385**

Scheme 179

1,3-Oxazin-6-ones are converted by amines into 4-pyrimidinones (**Scheme 180**) and the ANRORC reaction (e.g., **Scheme 181**) can be used to prepare pyrimidines from 2-bromopyridines (cf. Section 3.2.3.10.5).



Scheme 180

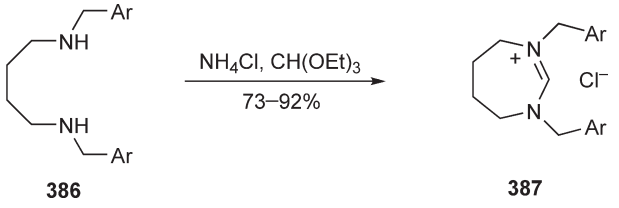


Scheme 181

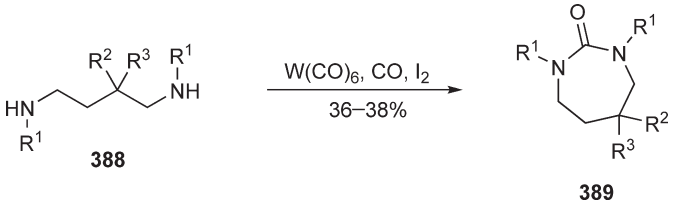
4.3.3.4 Seven-membered Rings

4.3.3.4.1 1,3-Diazepines

The condensation of 1,4-diamines with a variety of carboxylic acid derivatives, e.g., imidate esters, orthoformic esters, *N*-ethoxycarbonylthioamides <1977JOC2530>, nitriles, and ethoxyacetylene, produces the 1,3-diazepine ring <1967AHC(8)219>; for example, tetrahydrodiazepinium salts **387** were prepared from the diamines **386** and triethyl orthoformate in the presence of ammonium chloride (**Scheme 182**) <2005SL2394>. Cyclic ureas have been similarly produced using carbonyl chloride, *N*,*N*-carbonyldiimidazole, carbon monoxide, thiocarbonyl chloride, or carbon disulfide <1967AHC(8)21>. This approach can be illustrated by the catalytic carbonylation of primary and secondary diamines **388** leading to the ureas **389** in modest yields (**Scheme 183**) <2002JOC4086, CHEC-III(13.05.9.1.4)173>.

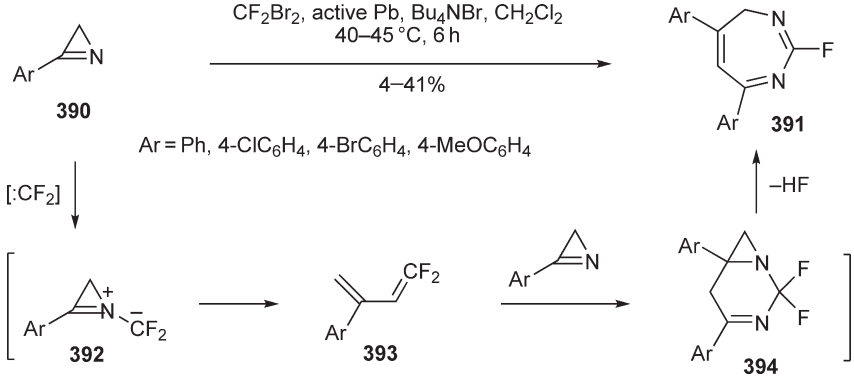


Scheme 182



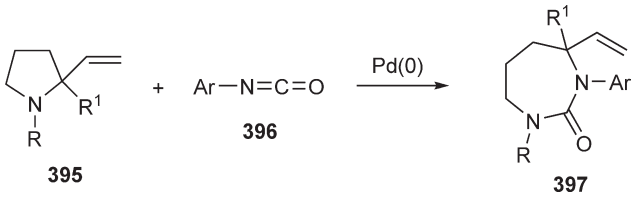
Scheme 183

The 5,7-diaryl-2-fluoro-4*H*-1,3-diazepines **391** have been synthesized from 3-aryl substituted 2*H*-azirines **390** and difluorocarbene generated from CF_2Br_2 (**Scheme 184**). This reaction involves isomerization of the initial azirinium ylide **392** into a 2-aza-1,3-diene **393**, which undergoes [4 + 2] cycloaddition with the starting azirine, followed by ring expansion of cycloadduct **394** and dehydrofluorination <2006TL639>.



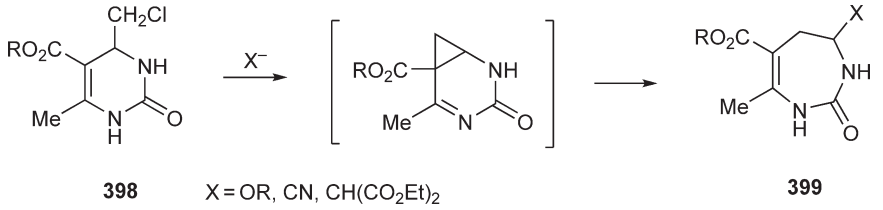
Scheme 184

The 2-vinylpyrrolidines **395** undergo a Pd(0)-catalyzed ring expansion upon treating with aryl isocyanates **396** to afford diazepinones **397** (**Scheme 185**) <2003JOC3439, CHEC-III(13.05.10.2)177>.



Scheme 185

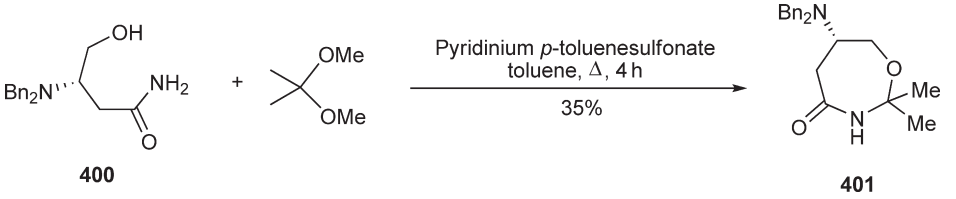
4-Chloromethylpyrimidines, e.g., **398**, with bases (X) undergo ring expansion to 1,3-diazepin-2-ones **399** (**Scheme 186**) <1977CJC895>.



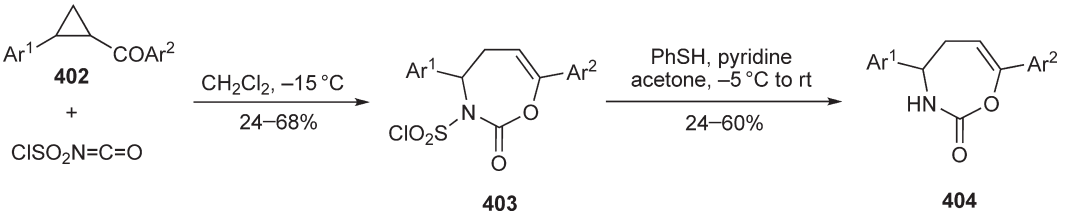
Scheme 186

4.3.3.4.2 1,3-Oxazepines and 1,3-thiazepines

The enantiopure (*S*)-(+)-6-amino-1,3-oxazepan-4-one **401** is obtained in moderate yield by acid-catalyzed condensation of **400** with 2,2-dimethoxypropane (**Scheme 187**) <1999H365>. The 4,7-diaryl-4,5-dihydro-1,3-oxazepinones **404** can be accessed from a two-step sequence involving the reaction of 1-aryl-2-phenacylcyclopropanes **402** with chlorosulfonyl isocyanate, followed by removal of the chlorosulfonyl group from **403** with benzenethiol in pyridine (**Scheme 188**) <1995SC1939>.

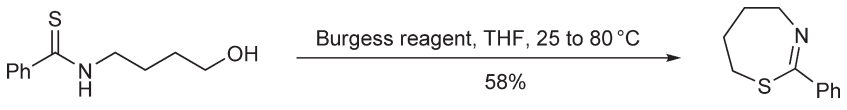


Scheme 187



Scheme 188

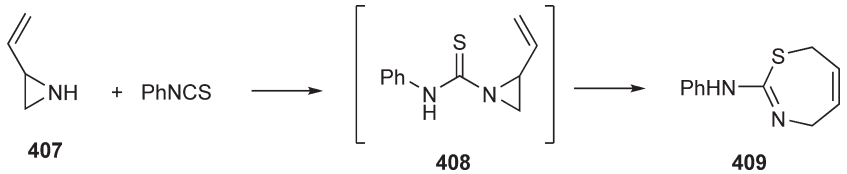
Cyclodehydration of hydroxythioamide **405** with Burgess reagent [methyl *N*-(triethylammoniumsulfonyl)carbamate] affords the 1,3-thiazepine **406** in a good yield (**Scheme 189**) <1998T6987>.



405 **406**

Scheme 189

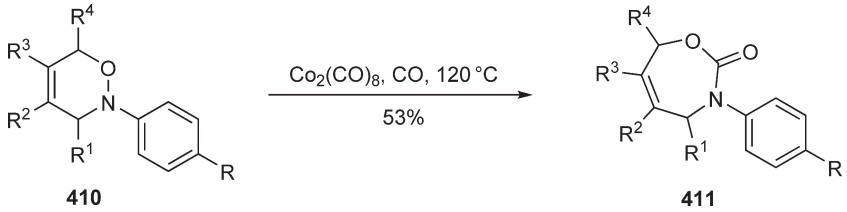
2-Vinylaziridine **407** with phenyl isothiocyanate or 4-chlorothiobenzoyl thioglycolate gives 1,3-thiazepine **409**, presumably via the intermediate thiourea **408** (**Scheme 190**) <1971JOC3076>.



407 **408** **409**

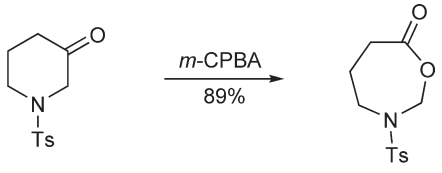
Scheme 190

A one-atom cobalt carbonyl-mediated ring-expansion of the 3,6-dihydro-2*H*-1,2-oxazines **410** provides access to the 4,7-dihydro-1,3-oxazepin-2(3*H*)-ones **411** in modest yields (**Scheme 191**) <1996TL2713>. The BaeyerVilliger ring expansion is a useful methodology for accessing 1,3-oxazepinones, as illustrated by the reaction of **412** with *m*-CPBA giving product **413** in high yield (**Scheme 192**); this 7-membered lactone **413** was a key intermediate in the synthesis of the anticonvulsant SKF 89976A <2006TL6389>.



410 **411**

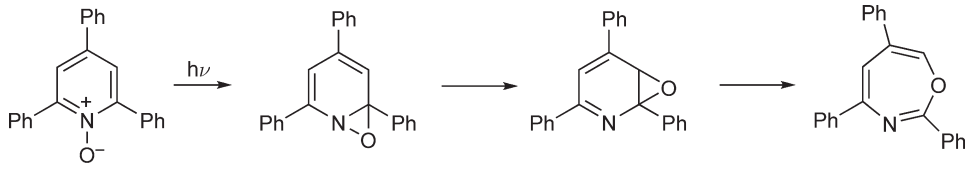
Scheme 191



412 **413**

Scheme 192

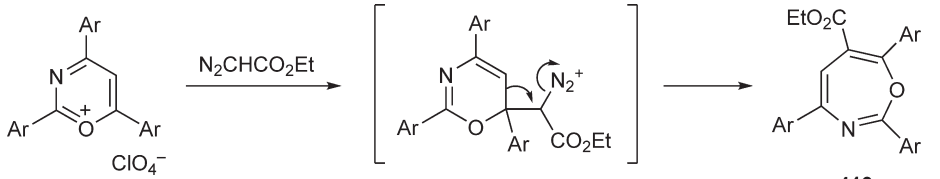
The photochemical rearrangement of aromatic *N*-oxides, e.g., **414**, gives the fully-unsaturated 1,3-oxazepine system, e.g., **417**, via an oxaziridine intermediate **415** which rearranges by a 1,5-sigmatropic shift to **416** and is converted to the product by disrotatory ring opening <1976H(4)1391>. Similar oxaziridine intermediates appear to participate in thermolytic rearrangement of 1,4-oxazepine derivatives into 1,3-oxazepines (**Scheme 193**) <1987CPB3166>.



414 415 416 417

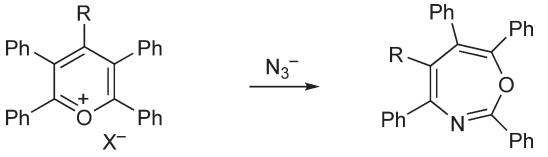
Scheme 193

Monocyclic 1,3-oxazepines **419** can be prepared by reaction of aliphatic diazo compounds with 1,3-oxazinium perchlorates **418** (**Scheme 194**) <1974S187>. Tetra- and penta-phenyl-1,3-oxazepines **421** (R = H or Ph) have been obtained by the reaction of azide ion with pyrylium salts **420** (**Scheme 195**) <1978H(11)331>.



418 419

Scheme 194

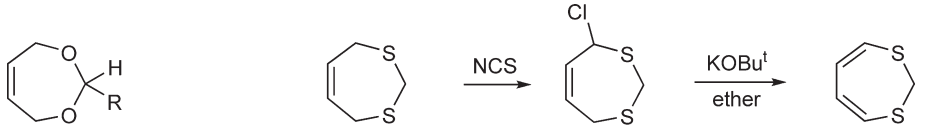


420 421

Scheme 195

4.3.3.4.3 1,3-Dioxepins and 1,3-dithiepins

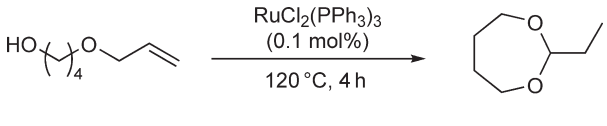
4,7-Dihydro-1,3-dioxepins **422** are prepared by the reaction of *cis*-butene-1,4-diols with aldehydes, and a similar route gives the dithia derivative **423** which is converted into the more unsaturated compound **425** *via* **424** (**Scheme 196**) <1976TL1251>.



422 423 424 425

Scheme 196

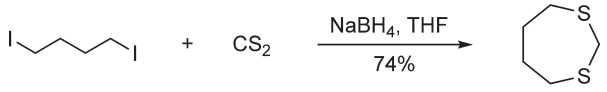
The transition-metal-catalyzed formation of 1,3-dioxepanes from vinyl ethers has also been described <CHEC-III (13.11.9.1)348>. For example, reaction of allyl ether **426** with a nonhydridic ruthenium complex at higher temperatures and without any solvent produce 1,3-dioxepane **427** (**Scheme 197**). It was suggested that cyclic acetal formation proceeds via a -allyl-hydrido transient complex, which undergoes nucleophilic attack by the OH group at the coordinated -allyl <2004SL1203>.



426 427

Scheme 197

Dithiepanes and benzodithiepanes, e.g., **428**, are conveniently prepared by treatment of a corresponding 1,4-dibromo or diiodo compound with carbon disulfide activated by sodium borohydride (**Scheme 198**) <2000OL1133, CHEC-III (13.11.9.4)356>.



428

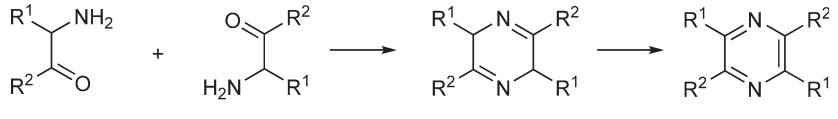
Scheme 198

4.3.4 Two Heteroatoms in the 1,4-Positions

4.3.4.1 Six-membered Rings

4.3.4.1.1 Pyrazines from acyclic compounds

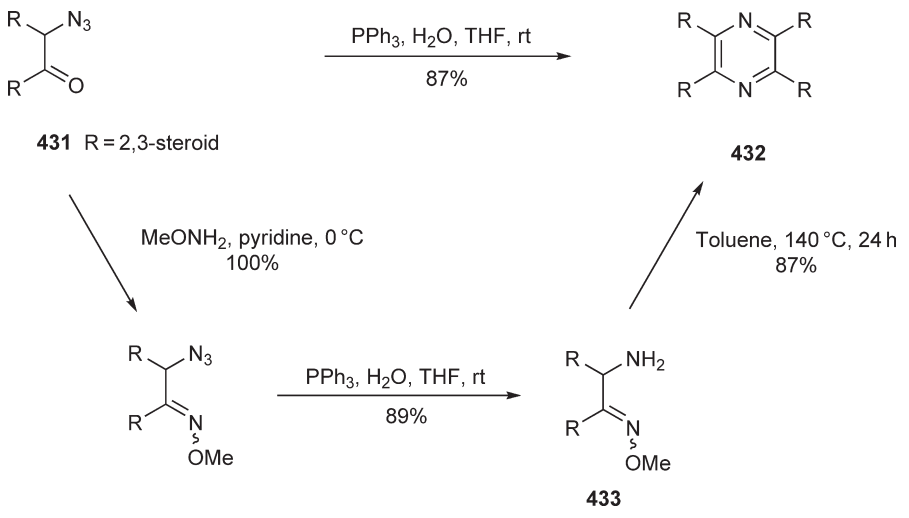
An important preparation of pyrazines **430** is from -amino ketones or their monooximes which spontaneously condense to give 2,5-dihydropyrazines **429** (**Scheme 199**) <CHEC-III(8.03.9.2)307>. The -amino ketones are often prepared *in situ* by reduction of appropriate precursors, and the dihydropyrazines are usually oxidized to pyrazines before isolation (cf. Section 3.2.2.3.3). Catalytic reduction of -azido ketones <1980OPP265> or -nitro ketones leads to -amino ketones, which dimerize spontaneously.



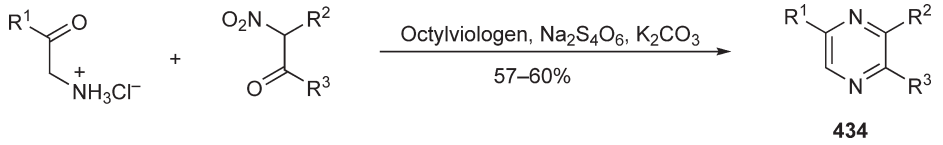
429 **430**

Scheme 199

Cyclic dimerization of the -amino ketone that is formed by reduction of -azido ketone **431** with triphenylphosphine, leads to the formation of a pyrazine derivative **432** (**Scheme 200**) <1994JOC6828>. Elemental tellurium also catalyzes dimerization of -keto azide **431** to give pyrazine **432** <2006JOC2797>. O-Methylated -amino oxime **433** also undergoes self-condensation by heating in toluene to give the pyrazine **432**. The trialkyl-substituted pyrazines **434** can also be prepared via reaction of -amino ketones with -nitro ketones using octylviologen as reducing agent to convert the nitro into an amino group (**Scheme 201**) <2005OL5529>.

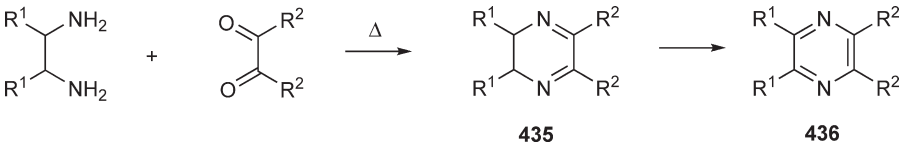


Scheme 200

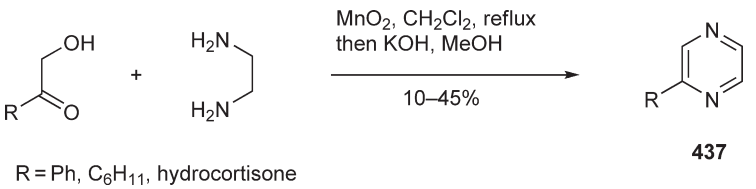


Scheme 201

The condensation of an -diketone or its synthetic equivalent (e.g., aroyl cyanide <1987S914>) with a 1,2-diaminoalkane gives 2,3-dihydropyrazines **435** (**Scheme 202**), which like their 2,5-analogues **429** can be oxidized by air, or better by a mild oxidizing reagent, to pyrazines **436** <CHEC-III(8.03.9.1)303>. For example, in a manganese dioxide-based tandem oxidation process, -hydroxyketones are converted into 1,2-carbonyl compounds followed by trapping with 1,2-diamines and finally oxidation of the resulting dihydropyrazines to produce pyrazines **437** (**Scheme 203**) <2003CC2286>.

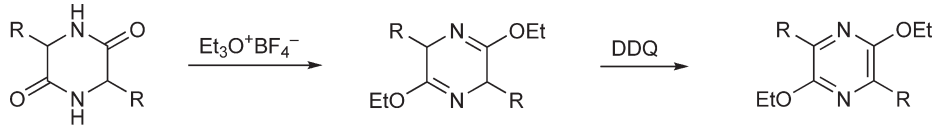


Scheme 202



Scheme 203

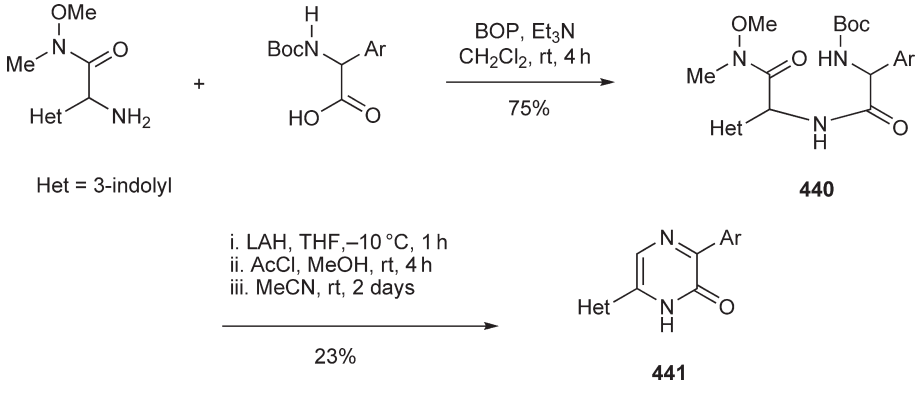
Cyclodimerization of -amino acids gives 2,5-dioxopiperazines **438**. Treatment of 2,5-dioxopiperazines **438** with triethyl- or trimethyloxonium fluoroborate followed by oxidation with DDQ, chloranil, or iodine results in the formation of pyrazines **439** (**Scheme 204**) <1972J(P1)2494>.



438 **439**

Scheme 204

Useful building blocks for the synthesis of 2-(1*H*)-pyrazinones are *N*-Boc amino acids, whose carboxylic acid moiety reacts with the amino group of another component having cyano or carbonyl functionality at the position, such as -amino nitriles <2004T835>, -amino amide (e.g., **Scheme 205**) <2000H1559>, or -amino ketones <2004SL2031>. The initial dipeptidyl products (e.g., **440**) are, after removal of the Boc protecting group, cyclized to yield 2(1*H*)-pyrazinones **441** (**Scheme 205**) <CHEC-III(8.03.9.4)310>.

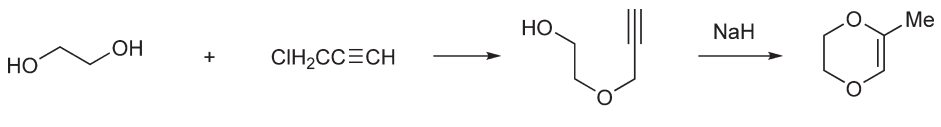


440 **441**

Scheme 205

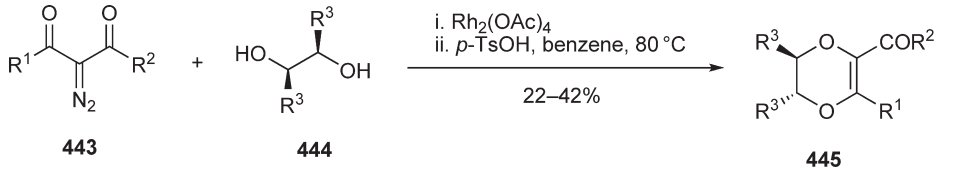
4.3.4.1.2 1,4-Dioxins, 1,4-dithiins, 1,4-oxazines, and 1,4-thiazines

1,4-Dioxins, 1,4-oxathiins, and 1,4-dithiins are commonly prepared by elimination reactions from saturated analogues (see Section 4.3.4.1.4). A convenient synthesis of 2,3-dihydro-1,4-dioxins (e.g., **442**) starts from propargyl chloride and 1,2-ethanediol (**Scheme 206**) <CHEC-III(8.12.9.2)891, 1998JFA2827>. Another approach to substituted 2,3-dihydro-1,4-dioxins **445** involves the reaction between 1,2-diols **444** and rhodium carbenoids generated from -diazo--ketoester **443** (**Scheme 207**) <1999H(51)1073>.



442

Scheme 206

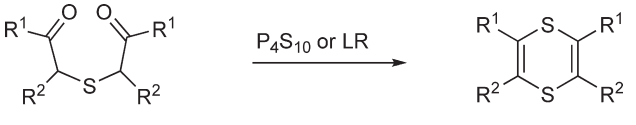


443 444 445

R^1 = Ph, PhCH = CH, *n*-C_4H_9
R^2 = Me, Et; R^3 = H, –$(CH_2)_4$–

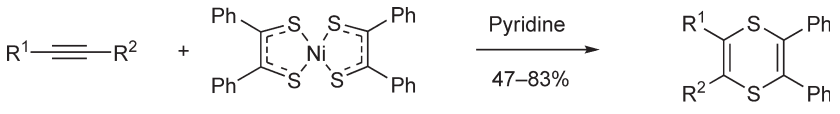
Scheme 207

Dithiin derivatives can be prepared from ,-dioxodialkyl sulfides and either phosphorus pentasulfide or LR. Such treatment of the sulfides **446** (readily obtainable from -haloketones and sodium sulfide) in refluxing toluene or benzene affords a variety of 1,4-dithiins **447** in good yields (**Scheme 208**) <1984H(22)1527, 1989H(29)391, 1991PS(57)227>. Another approach is based on cyclization between a two-atom and a four-atom fragment. This involves treating alkynes **448** with nickel bisdiphenyldithiolene **449** in refluxing chlorobenzene in the presence of pyridine. Pyridine appears to be essential in order to avoid further transformation of 1,4-dithiins **450** to thiophenes <1987SC1683> (**Scheme 209**). Addition of sodium sulfide to alkynyl sulfides, $S(CCR)_2$, also yields 2,6-disubstituted 1,4-dithiins <1975RTC163>.



446 447

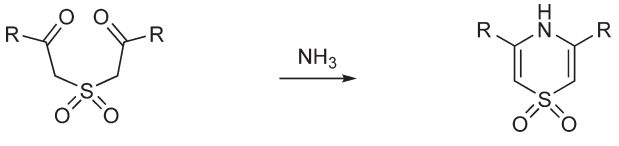
Scheme 208



448 449 450

Scheme 209

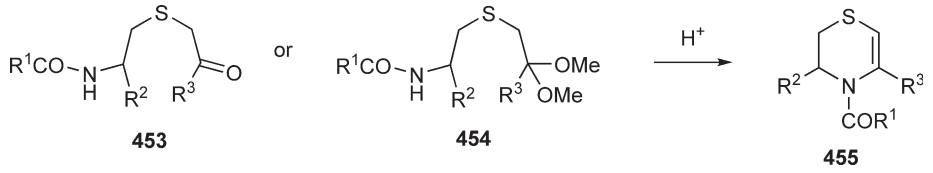
The reaction of 3-thia-1,5-diketones with amines forms fully-conjugated 1,4-thiazines, as well as 1,4-thiazine *S*, *S*-dioxides <CHEC-III(8.09.9.2)654>; for example, 1,4-thiazine 1,1-dioxides **452** are formed by the cyclodehydration of diacyl sulfones **451** and ammonia (**Scheme 210**) <1972OS(52)135>.



451 452

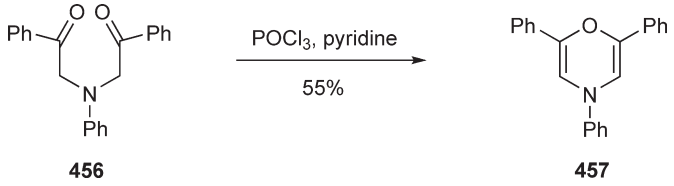
Scheme 210

Dihydro-1,4-thiazines **455** are available through the cyclization of compounds with a general structure **453** <1992CB1507, 2006SL3259> or **454** <2002SC1579> using an acid catalyst (**Scheme 211**) <CHEC-III(8.09.9.1.2)651>.



Scheme 211

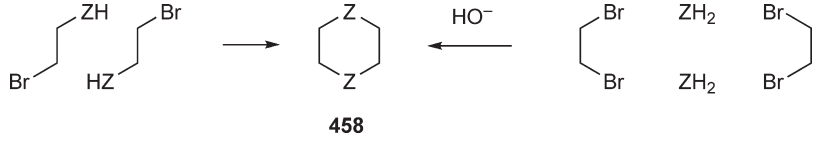
Dehydrations provide the most general approach to 1,4-oxazines <CHEC-III(8.06.9.1)489>, as illustrated by the synthesis of the fully-unsaturated oxazine **457** by dehydration of diketone **456** using phosphorus oxychloride in pyridine (**Scheme 212**) <1973JOC3433>.



Scheme 212

4.3.4.1.3 Nonaromatic rings from acyclic compounds

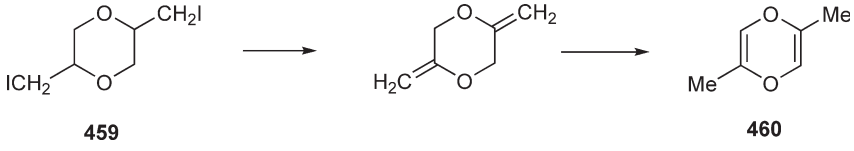
Piperazines, dioxanes, and dithianes **458** (Z = NH, O, S) can be prepared as shown in **Scheme 213** from fragments CCZ + CCZ or $C_2 + C_2 + Z + Z$.



Scheme 213

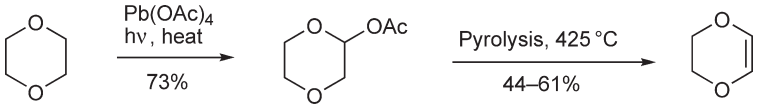
4.3.4.1.4 From heterocyclic precursors

1,4-Dioxins, 1,4-oxathiins, and 1,4-dithiins have often been prepared by elimination reactions from saturated analogues <CHEC-III(8.12.10)892>. A two-step synthesis of 1,4-dioxin from dioxane is via 2,3,5,6-tetrachloro-1,4-dioxane which is dechlorinated using magnesium and iodine <1939JA3020>. The route to 2,5-dimethyl-1,4-dioxin **460** uses 2,5-diiodomethyl-1,4-dioxane **459** (diepiiodohydrin) as precursor (**Scheme 214**) <1957JA6219>.



Scheme 214

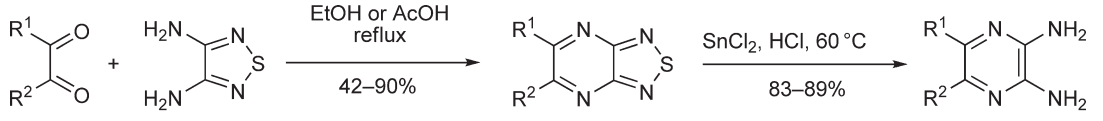
A clean formation of 2,3-dihydro-1,4-dioxane **461** has been described in a two-step process starting from 1,4-dioxane. This approach take advantage of the capability of lead tetraacetate to engage in the acetoxylation of CH bonds adjacent to ethereal oxygen centers (**Scheme 215**) <2005OS99>.



461

Scheme 215

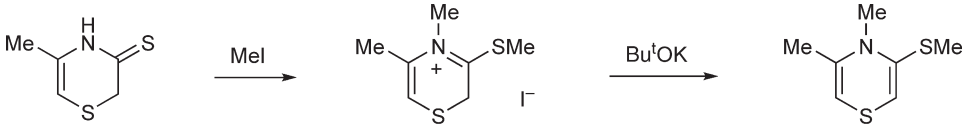
Condensation of 3,4-diamino-1,2,5-thiadiazole **462** with -diketones produces [1,2,5]thiadiazole[3,4-*b*]pyrazines **463**, which are reduced to provide 2,3-diaminopyrazines **464** (**Scheme 216**) <1997JCM250, CHEC-III(8.03.10)313>.



462 463 464

Scheme 216

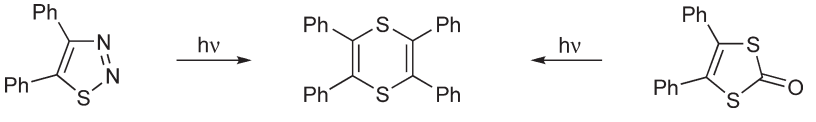
The 3,4-dihydrothiazine-3-thione **465** is converted by methyl iodide into the thiazinium salt **466**, deprotonation of which yields a 4*H*-thiazine **467** (**Scheme 217**) <1969JHC247>.



465 466 467

Scheme 217

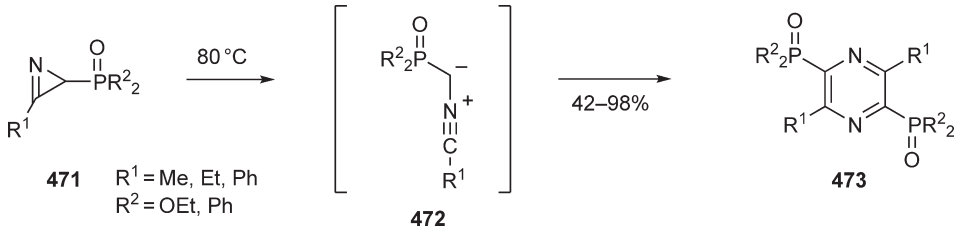
1,4-Dithiins are obtained upon photolysis of thiadiazoles, e.g., **468** **469** <1981JA486>. Photolysis of the dithiocarbonate **470** also gives thiadiazole **469** (**Scheme 218**) <1973ZC424>.



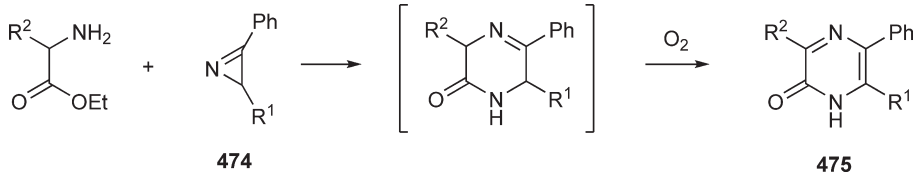
468 469 470

Scheme 218

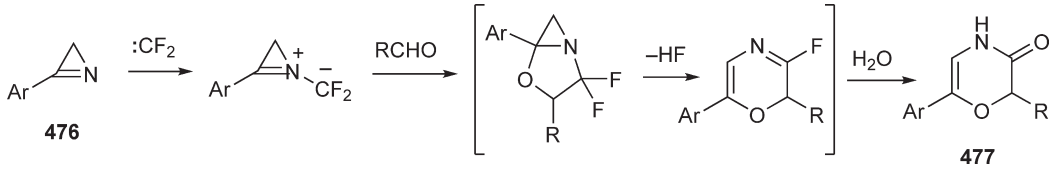
Aziridine is converted into piperazine on NH_3 treatment; 1-substituted aziridines give 1,4-disubstituted piperazines when reacted with Grignard reagents. Azirines are dimerized under various conditions to dihydropyrazines or pyrazines <CHEC-III(8.03.10)313>. Azirines **471** undergo ring opening by heating at 80°C without solvent to form nitrile ylide **472**, which dimerizes to symmetrically phosphorus-substituted pyrazine **473** (**Scheme 219**) <2002OL2405>. Azirines **474** can be used for the preparation of pyrazinones **475** from -amino esters (**Scheme 220**) and of 1,4-oxazinones from -hydroxy esters <1983TL1153>. Azirines are also used in the synthesis of 1,4-oxazines <CHEC-III(8.06.10)500>; for example, 4*H*-dihydrooxazin-3-ones **477** are prepared by treatment of azirines **476** with difluorocarbene and aldehydes (**Scheme 221**) <2004RCB1092>.



Scheme 219

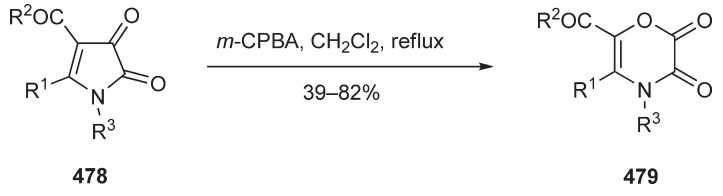


Scheme 220



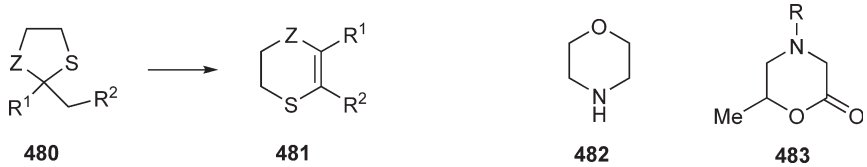
Scheme 221

Dihydrooxazin-2,3-diones **479** can be prepared by BayerVilliger oxidation of dihydropyrrole-2,3-diones **478** (**Scheme 222**) <1994H(37)523, CHEC-III(8.06.10)500>.



Scheme 222

5,6-Dihydro-1,4-oxathiins **481** (Z = O) and 5,6-dihydro-1,4-dithiins **481** (Z = S) are easily obtained from 1,3-oxathiolanes **480** (Z = O) and 1,3-dithiolanes **480** (Z = S), respectively (**Scheme 223**), by treatment with bromine <1991S223>, *N*-bromosuccinimide <1994T7265>, or chlorine <1987JOC5374, 1991S223>.



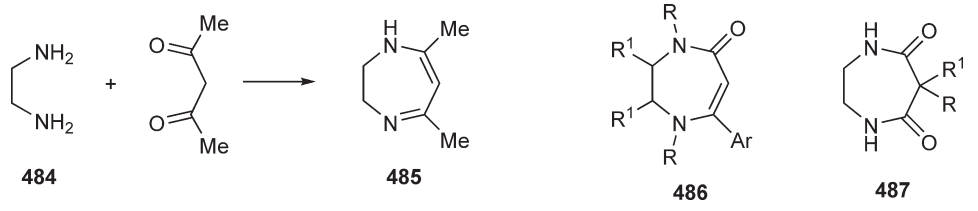
Scheme 223

1,4-Dioxanes are produced in excellent yields from oxiranes and dilute sulfuric acid. 1,4-Dioxanes are also conveniently obtained by acid-catalyzed condensation of oxiranes with glycols, while the reaction of oxirane with ethanolamine gives morpholine **482**. Base-catalyzed reaction of oxiranes with -amino acids and esters gives tetrahydro-1,4-oxazin-2-ones, e.g., propene oxide + $RNHCH_2CO_2H$ **483**. 1,4-Dithianes have been prepared by the dimerization of thiiranes either in the vapor phase or in the presence of acid catalysts.

4.3.4.2 Seven-membered Rings

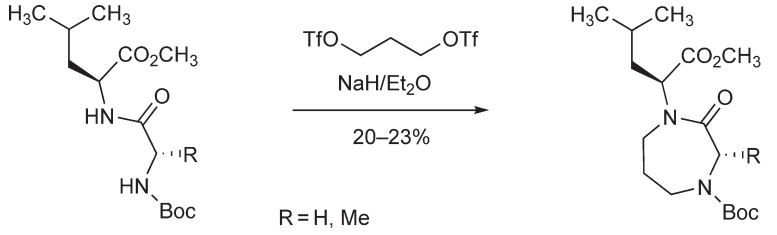
4.3.4.2.1 1,4-Diazepines

The most straightforward approach to the construction of 1,4-diazepine rings is via the ring-forming reaction of a nucleophilic NCCN substrate with a CCC substrate incorporating electrophilic elements at the terminal atoms <CHEC-III(13.06.9.1.9)212>. Ethylenediamine **484** and its N-substituted analogues with 1,3-dialdehydes or 1,3-diketones give 2,3-dihydro-1,4-diazepines, e.g., **485** (**Scheme 224**). 1,4-Diazepin-5-ones, e.g., **486**, and 1,4-diazepine-5,7-diones **487** can be readily prepared by the reactions of 1,2-diamines with -keto esters or with malonic esters, respectively <1968CRV747>. The double alkylation of the amino acid amides **488** with propane-1,3-diyl-bis(trifluoromethanesulfonate) using NaH as the base affords the 1,4-diazepines **489** in a modest yield with complete preservation of chirality (**Scheme 225**) <1997TL5809>.



484 **485** **486** **487**

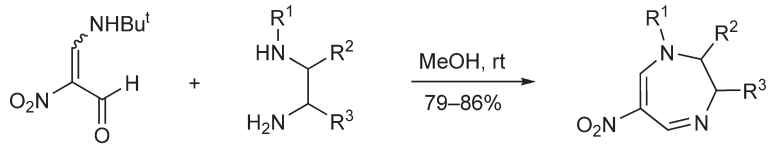
Scheme 224



488 **489**

Scheme 225

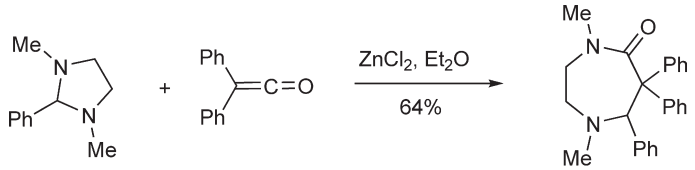
The 3-(*tert*-butylamino)-2-nitroacrylaldehyde **490** is a synthetic equivalent to nitromalonaldehyde and reacts with substituted ethylenediamines **491** in methanol to provide 6-nitro-2,3-dihydro-1*H*-1,4-diazepines **492** in excellent yields (**Scheme 226**) <2004JOC8382, 2002H425>.



490 **491** **492**

Scheme 226

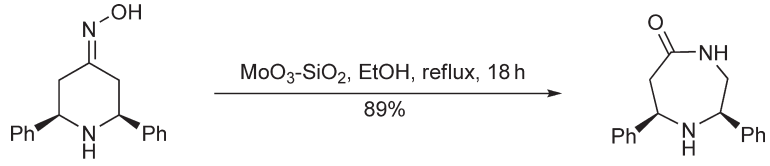
The reaction of diphenylketene with the imidazolidine **493**, catalyzed by $ZnCl_2$ in Et_2O, affords the 1,4-diazepin-5-one **494** in a high yield (**Scheme 227**) <1998S653>. This reaction is thought to be initiated by nucleophilic attack of an aminal nitrogen atom on the ketene, followed by ring opening of the imidazolidinium and intramolecular capture of the resultant iminium by the enolate <CHEC-III(13.06.10)221>.



493 **494**

Scheme 227

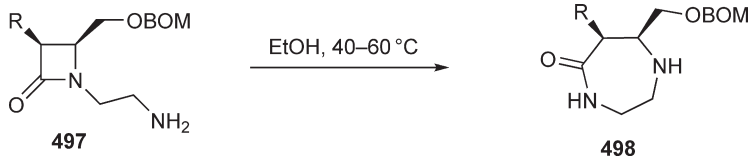
Improved preparative procedures for the Beckmann rearrangement of a piperidinone oxime to afford ring-expanded diazepine derivatives are based on the use of silica-supported MoO_3 <CHEC-III(13.06.10)222>. An illustrative example is the rearrangement of the oxime of 2,6-diphenylpiperidin-4-one **495** which afforded the diazepin-5-one **496** in excellent yield after exposure to silica-supported MoO_3 in ethanol at reflux (**Scheme 228**) <2004TL4759>.



495 **496**

Scheme 228

The thermally induced intramolecular transamidation of aminoethyl-substituted -lactams **497**, readily obtained by the Staudinger reaction of ketenes with imines, offers a useful approach to monocyclic and fused bicyclic 1,4-diazepin-5-ones **498** (**Scheme 229**) <2004OL3361, 2003EJO1319, 2005T1531>.



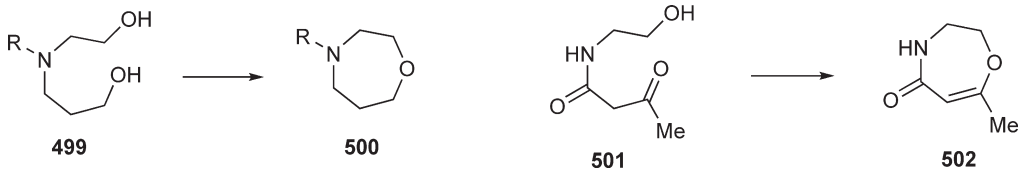
497 **498**

Scheme 229

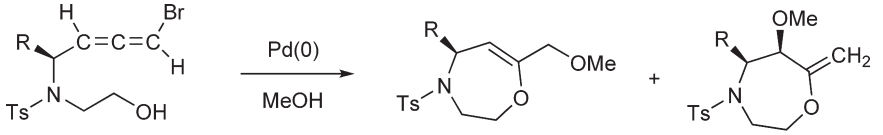
4-Azidopyridines under photolysis or thermolysis can be converted into derivatives of 6*H*-1,4-diazepine <1984CPB4694> (cf. Section 3.2.3.6.4).

4.3.4.2.2 1,4-Oxazepines and 1,4-thiazepines

The monocyclic systems, e.g., **500** and **502**, can be obtained by the dehydrative cyclization of the appropriate precursors, e.g., **499** and **501** (**Scheme 230**) <CHEC-II(9.09.1.1)218>. A modification of this approach is represented by the palladium-catalyzed cyclization of bromoallene **503** leading to a mixture of regioisomers **504** (major) and **505** (minor) (**Scheme 231**) <2004JA8744, CHEC-III(13.09.1)275>.

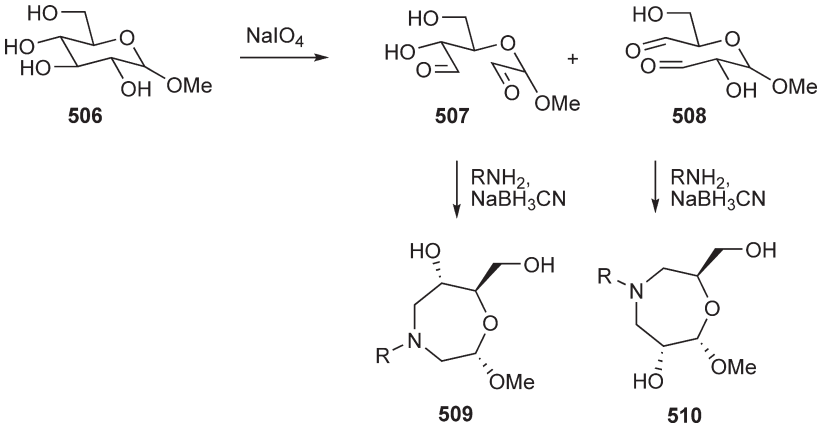


Scheme 230



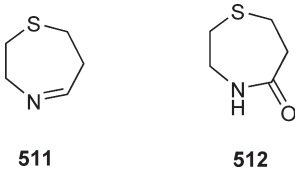
Scheme 231

1,4-Oxazepanes **509** and **510** are conveniently synthesized via ring-cleavage reaction of methyl -D-glucopyranoside **506** to dialdehydes **507** and **508** followed by their reductive amination (**Scheme 232**) <2004TA3643, 2004T4959>. Oxazepines have been prepared from other biscarbonyl electrophiles in an Ugi three-component reaction involving a ketoester, an amine, and an isonitrile <2006JOC2811, CHEC-III(13.09.1)274>.

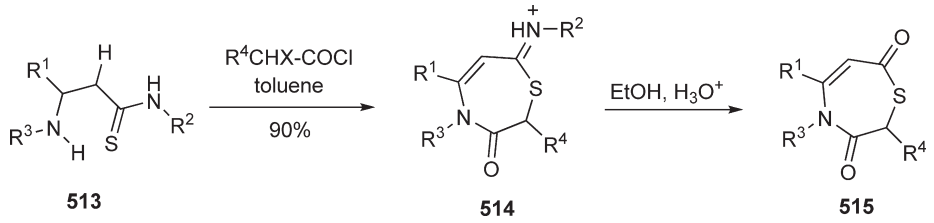


Scheme 232

2-Aminoethanethiol reacts with ,-unsaturated or -halo ketones to give 1,4-thiazepine **511**. Similarly, reaction with ,-unsaturated acids, esters or acid chlorides, and with 3-halopropionyl halides yields 5-oxo derivatives such as **512**.

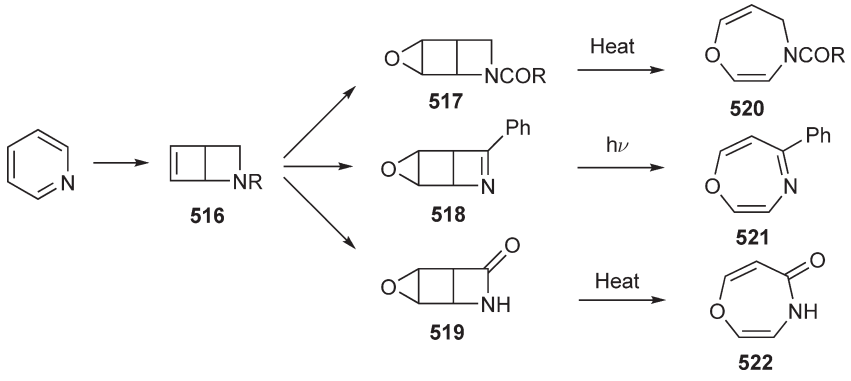


Regioselective cyclocondensation of thioamides **513** with -haloacid chlorides leads to 1,4-thiazepines **514** in excellent yields. After hydrolysis in ethanol with 1% hydrochloric acid, 1,4-thiazepin-3,7-diones **515** are formed (**Scheme 233**) <1996LA211, CHEC-III(13.09.2.2)281>.



Scheme 233

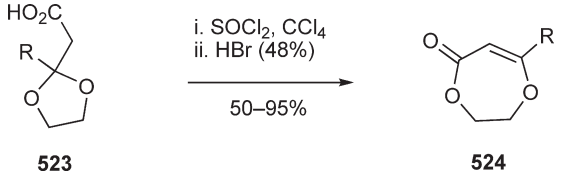
Pyridine is easily converted into 2-azabicyclo[2.2.0]hex-5-enes **516** by treatment with phenylmagnesium bromide in the presence of benzyl chloroformate followed by irradiation, and product **516** can be further transformed into useful 3-aza-7-oxatricyclo[4.1.0.0^{2,5}]hept-3-enes **517519**. Irradiation of **517519** in acetonitrile gives the corresponding 1,4-oxazepines **520522** in 9095% yield (**Scheme 234**). This type of valence isomerization has been applied to the synthesis of fully-aromatized 1,4-epines with two heteroatoms, such as 1,4-oxazepines, 1,4-thiazepines, 1,4-diazepines, and azepines <1985CPB4572, 1986CC1188, 1987JOC5247, 1990CPB2911>.



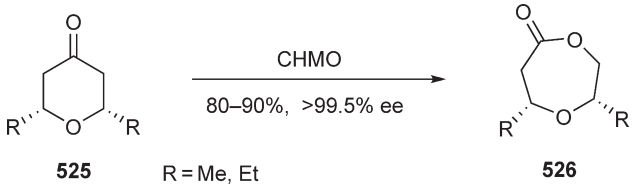
Scheme 234

4.3.4.2.3 1,4-Dioxepins and 1,4-dithiepins

A general approach to the preparation of 1,4-dioxepins involves ring expansion; thus, treatment of 1,3-dioxalanes **523** with thionyl chloride and then 48% hydrobromic acid affords 1,4-dioxepin-5-ones **524** in generally high yields (**Scheme 235**) <2001TL2305, CHEC-III(13.12.8.2)374>. A powerful method is the BaeyerVilliger oxidation of six-membered ring ketones leading to dioxepinones <CHEC-III(13.12.10)377>; the BaeyerVilliger enzyme, cyclohexanone monooxygenase (CHMO), has been applied to the oxidative ring expansion of *cis*-2,6-dialkylperhydropyrans **525** to afford products **526** in very high yields and with excellent enantioselectivity (**Scheme 236**) <2001JMC349, 2003SL1973>.

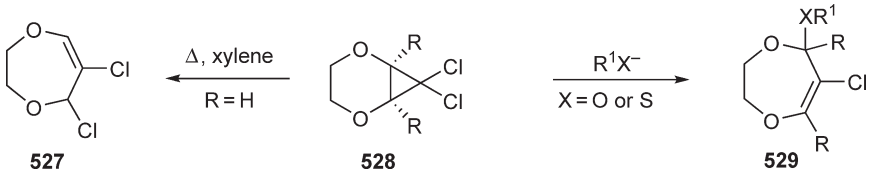


Scheme 235



Scheme 236

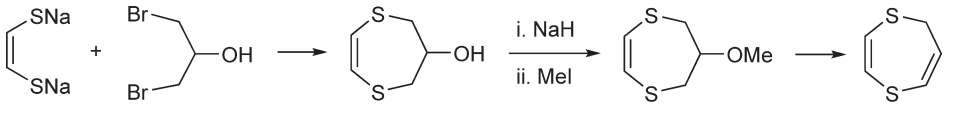
The 2,3-dihydro-5*H*-1,4-dioxepins **527** and **529** can be obtained from 1,4-dioxin-dichlorocarbene adducts **528** (**Scheme 237**) <1977ZC331>.



527 **528** **529**

Scheme 237

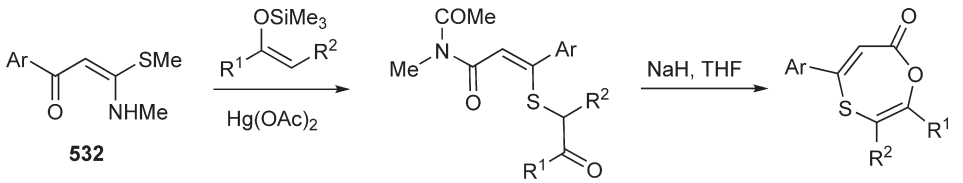
The unsaturated 5*H*-1,4-dithiepin **531** is synthesized by an elimination reaction of the methyl ether **530** (**Scheme 238**) <1975TL1895>.



530 **531**

Scheme 238

3-Alkyl-2,5-diaryl-1,4-oxathiepin-7-ones **533** have been prepared from propenamides **532** in high yield (**Scheme 239**) <2001TL4637>.



532 **533**

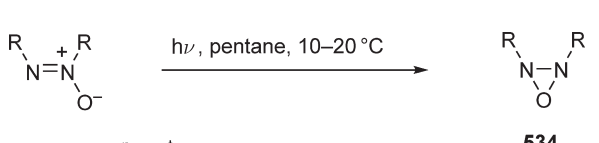
Scheme 239

The fully saturated 1,4-dithiepane system can be prepared by reactions of propane-1,3-dithiol with 1,2-dibromoethane, and of ethane-1,2-dithiol with 1,3-dihalopropanes.

4.3.5 Three Heteroatoms in the 1,2,3-Positions

4.3.5.1 Three- and Four-membered Rings

Valence isomerization is used in the formation of oxadiaziridines **534** (**Scheme 240**) <1970JOC2482> and triaziridines <1980CC1197>.



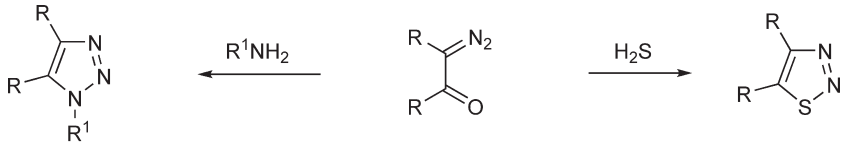
534

Scheme 240

4.3.5.2 Five-membered Rings

4.3.5.2.1 Formation of a bond between two of the heteroatoms

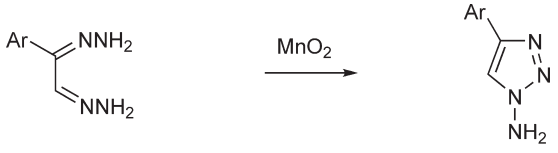
4.3.5.2.1.1 1,2,3-Triazoles and 1,2,3-thiadiazoles. Diazo ketones **536** are converted by amines into 1,2,3-triazoles **535** and by hydrogen sulfide into 1,2,3-thiadiazoles **537** (**Scheme 241**). The intramolecular cyclization of suitable precursors is a useful method for the preparation of the 1,2,3-triazole ring, including *N*-amino- and *N*-imino-triazoles and triazole *N*-oxides.



535 **536** **537**

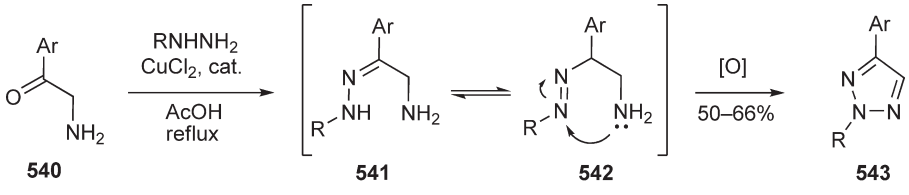
Scheme 241

Oxidative processes using mild oxidants (e.g., HgO or MnO_2) leading to NN bond formation convert *bis*-hydrazones **538** into the 1-amino-1,2,3-triazole derivatives **539** (**Scheme 242**) <1967TL3295, 1971JPR882>. A regioselective synthesis of 2,4-disubstituted 1,2,3-triazoles is based on a reaction of aminoacetophenones **540** with hydrazines (**Scheme 243**) <CHEC-III(5.01.11.1.5)138>. The reaction with methylhydrazine proceeds well without any catalysis, but that with phenylhydrazine requires cupric chloride as a catalyst. It is assumed that hydrazone **541** that forms in the first step is in a tautomeric equilibrium with its azo form **542** <2003SC3513>.



538 **539**

Scheme 242

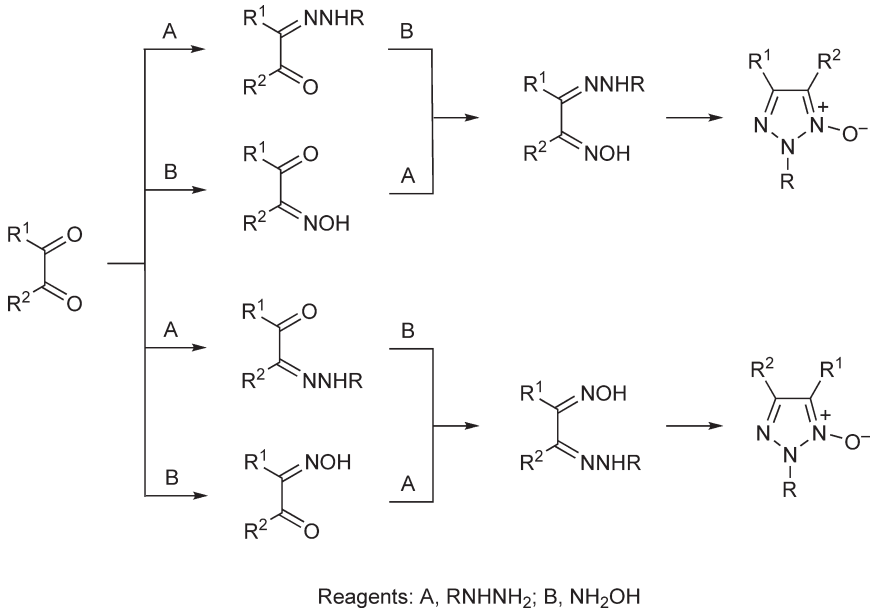


540 **541** **542** **543**

Ar = 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$; R = Me or Ph

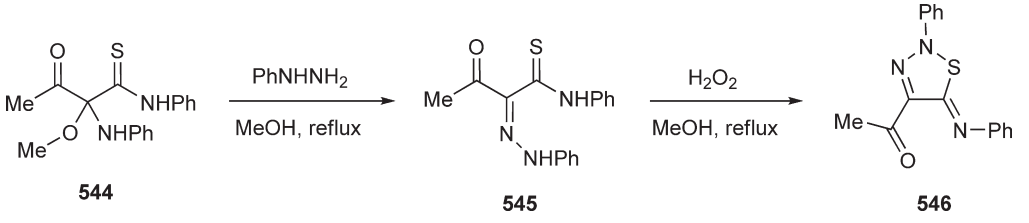
Scheme 243

Two alternative routes lead to 2-alkyltriazole 1-oxides from -dicarbonyl compounds (**Scheme 244**, routes A and B). Unsymmetrical dicarbonyl compounds frequently, but not invariably, give rise to two isomeric hydrazones and two isomeric oximes and hence two isomeric 1,2,3-triazole 1-oxides <1981J(P1)503>. 2-Phenyltriazole 1-oxide is obtained from glyoxal via route A. However, 2-methyltriazole 1-oxide is prepared from glyoxal by route B in a one-pot process under neutral conditions. 2-Benzyltriazole 1-oxide is obtained similarly. 2,5-Dimethyltriazole 1-oxides are accessible through both routes <1986ACB262>. For reviews on N-substituted 1,2,3-triazoles see <1992AHC(53)85, 1994H(37)1951>.

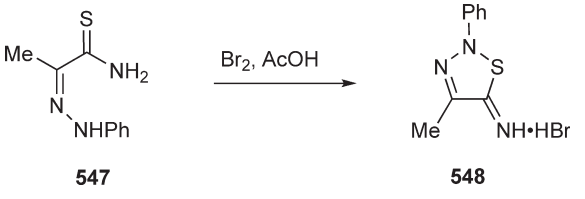


Scheme 244

A convenient synthesis of 1,2,3-thiadiazoles starts with the thioanilide derivative **544**, which is converted into the hydrazone **545**. Oxidative heterocyclization by treatment with hydrogen peroxide gives exclusively the 1,2,3-thiadiazoline **546** (**Scheme 245**) <2003S2559>. This method has been extended to include arylhydrazono thioacetamides, such as **547**, which undergo oxidative cyclization using bromine to afford 2-aryl-1,2,3-thiadiazol-5(2*H*)imines **548** (**Scheme 246**) <2004RJO818, CHEC-III(5.07.9.5)482>.

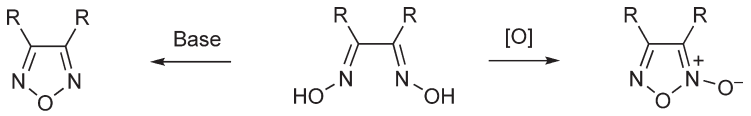


Scheme 245



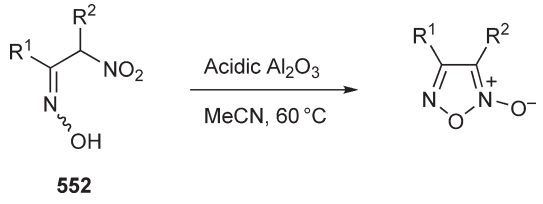
Scheme 246

4.3.5.2.1.2 1,2,5-Oxadiazoles. -Dioximes **550** can be cyclized to furazans **549** and furoxans **551** (**Scheme 247**) <CHEC-III(5.05.7)368>. A modified procedure for the preparation of furazans **549** exploits the dehydration of vicinal dioximes **550** using the Mitsunobu reaction conditions (Ph_3P/diisopropyl azodicarboxylate); advantages of this procedure are the mild conditions allowing for the presence of highly functionalized substrates and deactivated aromatic rings <2005JME3260>.



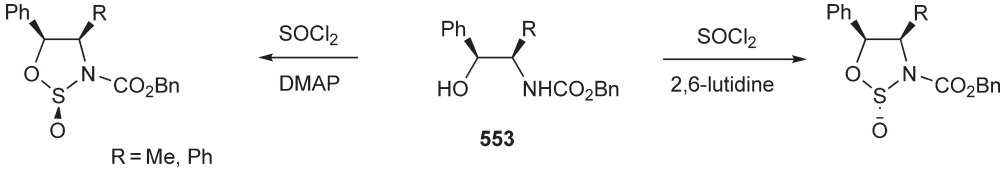
Scheme 247

Furoxans **551** are usually prepared by the oxidative cyclization of dioximes **550** using such oxidants as $K_3[Fe(CN)_6]$ <1997CHE471>, HNO_3 <2005RJC457, 2004CHE361>, MnO_2 <2001RCB874>, and NaOBr <1997CHE343>. Other important approaches to furoxans are based on the dehydration of -nitroketoximes **552** (**Scheme 248**) <2000TL8817> and the dimerization of nitrile oxides <2003JA15420>.



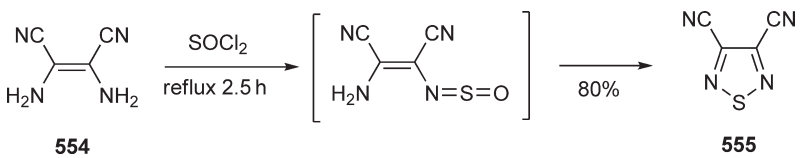
Scheme 248

4.3.5.2.1.3 1,2,3-Oxathiazoles. 1,2,3-Oxathiazole *S*-oxides are commonly prepared by the reaction of thionyl chloride with -aminoalcohols in the presence of an amine as a base <CHEC-III(6.01.9.2)26>. Various bases have been employed: Et_3N <1999J(P1)1421>, *N*-ethyldiisopropylamine <1999TL3831>, and pyridine <2002JOC5164>. The most effective reagent is a mixture of Et_3N and imidazole (yield 99%) <2000OL2595>. Depending on the base, a stereoselective cyclization of -aminoalcohol derivatives **553** can be achieved in the preparation of monocyclic (**Scheme 249**) <2003OL75, 2004JOC8533> and fused <2002JA7880, 2003AGE2032> 1,2,3-oxathiazole *S*-oxides.



Scheme 249

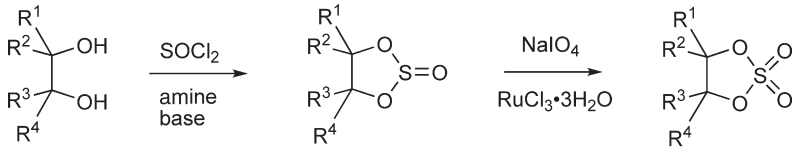
4.3.5.2.1.4 1,2,5-Thiadiazoles. An acyclic NCCN system in which the NC links may be sp, sp^2, or sp^3 hybridized reacts with sulfur monochloride or sulfur dichloride to form the appropriate 1,2,5-thiadiazole <1968AHC(9)107, CHEC-III(5.09.9.1.5)545>. Aliphatic 1,2-diamines can be converted into 1,2,5-thiadiazoles using various sulfur sources such as tetrasulfur tetranitride, disulfur dichloride, sulfur dichloride, thionyl chloride, and *N*,*N*-ditosylsulfur diimide. Thus, 1,2,5-thiadiazole-3,4-dicarbonitrile **555** is prepared from diaminomaleonitrile **554** using neat excess thionyl chloride (**Scheme 250**) <1995SR299>.



Scheme 250

Other acyclic NCCN precursors in the synthesis of 1,2,5-thiadiazoles are represented by 1,2-diimines, 2-oximinoacetonitriles, cyanoformamide and its esters, cyanoaminium salts, and related compounds <CHEC-III(5.09.9.1.5)545>.

4.3.5.2.1.5 1,2,3-Trithioles and 1,3,2-dioxathiolanes. 1,2,3-Trithiolanes are prepared by reaction of alkenes with elemental sulfur <CHEC-III(6.05.10.3)183>. The synthesis of 1,3,2-dioxathiolane *S*-oxides (cyclic sulfites) and 1,3,2-dioxathiolane *S*,*S*-dioxides (cyclic sulfates) is discussed in comprehensive reviews <1997AHC(68)89, 2000T7051>. The most widely used method for the preparation of 1,3,2-dioxathiolane *S*-oxides **557** is the reaction of the corresponding 1,2-diols **556** with thionyl chloride in the presence of pyridine or triethylamine (**Scheme 251**). More reactive 1,3,2-dioxathiolane *S*,*S*-dioxides **558** are usually obtained by oxidation of sulfites **557** with sodium periodate, which is mediated by ruthenium tetroxide generated *in situ* from a catalytic amount of ruthenium trichloride <1997AHC89, 2000T7051, CHEC-III(6.05.10.3)183>.

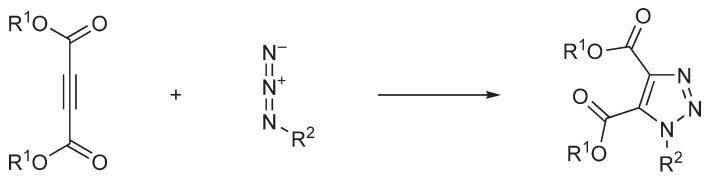


556 **557** **558**

Scheme 251

4.3.5.2.2 Other methods

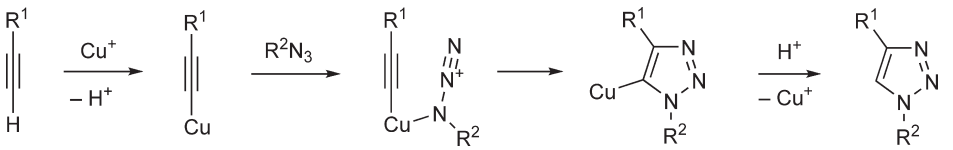
4.3.5.2.2.1 1,2,3-Triazoles by dipolar cycloadditions. Cycloadditions of azides to alkynes and their derivatives is the main synthetic route to 1,2,3-triazoles <CHEC-III(5.01.9.1)114>. Some aspects of these reactions with focus on cycloadditions at low temperature are discussed in a review <2003H(60)1225>. Esters of acetylenedicarboxylic acid **559** are very reactive as dipolarophiles and are often used as substrates for 1,3-dipolar cycloaddition to azides **560** (Huisgen reaction). The reactions are carried out at room or elevated temperature, and the yields of 1,2,3-triazoles **561** are usually high to quantitative (**Scheme 252**) <2004BML3655, 2006EJO2081, 2005T4701, 2005H(65)1035, CHEC-III (5.01.9.1)114>.



559 **560** **561**

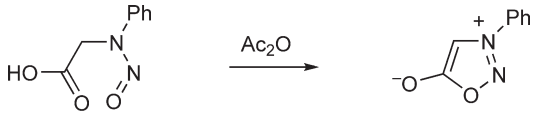
Scheme 252

The discovery of copper(I) catalysis in 1,3-dipolar cycloadditions of terminal alkynes to azides (click chemistry) in 2002 <2002AGE2596, 2002JOC3057> has revolutionized the field <CHEC-III(5.01.9.4)123>. It is not only that the catalyzed reactions proceed faster under mild conditions, but full regioselectivity of the products is also achieved. Terminal alkynes generate only 1,4-disubstituted triazoles. A brief outline of the reaction mechanism is given in **Scheme 253** <CHEC-III (5.01.9.4)124>. Some aspects of this new methodology are discussed in a review <2007ALD7>.



Scheme 253

4.3.5.2.2.2 1,2,3-Oxadiazoles by cyclodehydration. Reaction of the *N*-nitrosoglycine derivatives (e.g., **562**) with acetic anhydride gives 1,2,3-oxadiazolium-5-olates (sydnones) (e.g., **563**) (**Scheme 254**). Additional synthetic approaches to 1,2,3-oxadiazoles are discussed in CHEC-III <CHEC-III(5.03.9)230>.



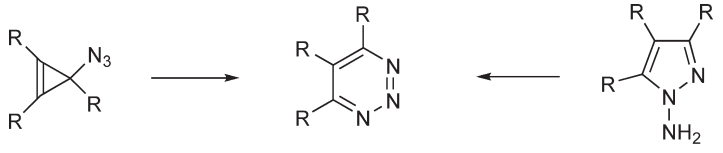
562 **563**

Scheme 254

4.3.5.2.2.3 From other heterocycles. See Sections 3.5.2.2 (ring expansion and ring contraction) and 3.4.3.1.9 (monocyclic rearrangement) for further preparations by the types of reaction indicated.

4.3.5.3 Six-membered Rings

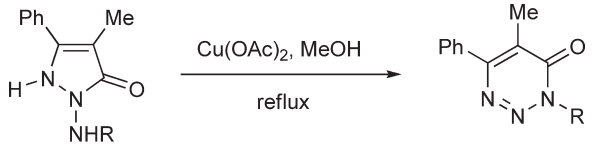
A detailed analysis of synthetic approaches to the 1,2,3-triazine system is provided in CHEC-III <CHEC-III(9.01.9)72>. The methods based on transformation of another ring are particularly useful <CHEC-III(9.01.10)77>. The rearrangement of cyclopropenyl azides **564** is used for the synthesis of monocyclic 1,2,3-triazines **565** (**Scheme 255**) <1979CB1514, 2003H(59)477, 2005AXE93>. However, the most general method is the oxidation of *N*-aminopyrazoles **566** with LTA or a variety of other oxidants <1992AHC(53)85>.



564 **565** **566**

Scheme 255

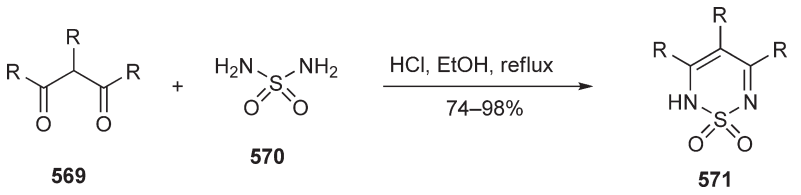
Copper(II) acetate in refluxing methanol has been used to prepare 3-alkyl-5-methyl-6-phenyl-3,4-dihydro-1,2,3-triazin-4-ones **568** from 2-(alkylamino)-4-methyl-5-phenyl-1,2-dihydropyrazol-3-ones **567** (**Scheme 256**). Alternatively, this conversion may be achieved, albeit in a slow reaction, using airoxygen in the presence of sodium hydrogencarbonate <2006EJO3021>.



567 **568**

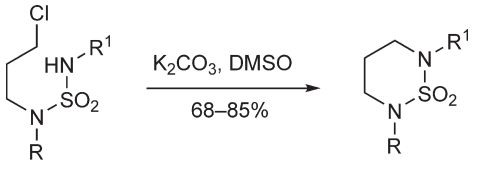
Scheme 256

The 1,2,6-thiadiazines **571** are prepared from the -diketones **569** and sulfamide **570** in high yields (**Scheme 257**) <1965M216>. An efficient synthesis of *N*-aryl-1,2,6-thiadiazine 1,1-dioxides **573** is based on the cyclization of 3-chloropropyl phenylsulfamide **572** using potassium carbonate in dimethyl sulfoxide (**Scheme 258**) <2003TL5483, 2003T6051, CHEC-III(9.07.9)385>.



569 570 571

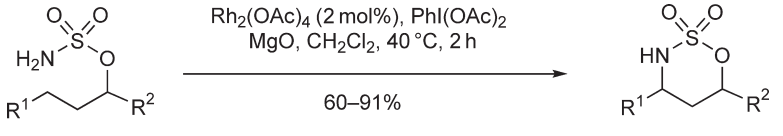
Scheme 257



572 573

Scheme 258

Oxathiazines **575** have been prepared by the reaction of sulfamates **574** with (diacetoxyiodo)benzene in the presence of rhodium catalysts (**Scheme 259**) <2001JA6935>. This type of reaction can also be catalyzed by silver(I) complexes <2004AGE4210, CHEC-III(9.10.9.1)548>.



574 575

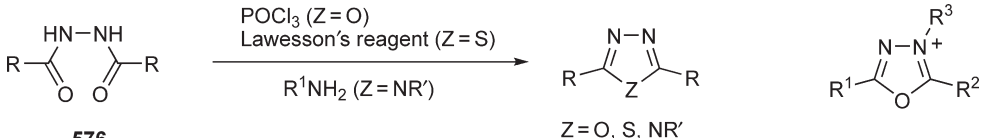
Scheme 259

4.3.6 Three Heteroatoms in the 1,2,4-Positions

4.3.6.1 Five-membered Rings

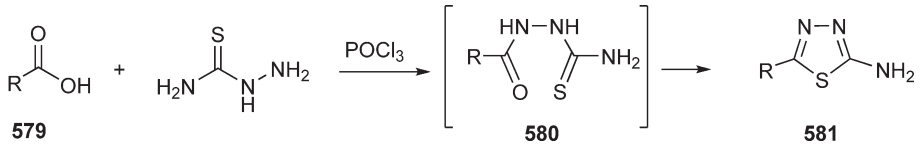
4.3.6.1.1 From acyclic intermediates containing the preformed ZZ bond

1. Diacylhydrazines **576** yield 1,3,4-oxadiazoles **577** (Z = O) on heating or on treatment with a dehydrating reagent (e.g., $SOCl_2$ or $POCl_3$) <CHEC-III(5.06.9.1.1)429>, 1,3,4-thiadiazoles **577** (Z = S) by reaction with a sulfur source (e.g., P_4S_{10} or LR) <CHEC-III(5.10.9.2.1)592>, and 1,2,4-triazoles **577** (Z = NR) with primary amines (**Scheme 260**) <CHEC-III (5.02.9.3)187>. 1-Substituted 1,2-diacylhydrazines are cyclized by strong acid to 2,3,5-trisubstituted 1,3,4-oxadiazolium salts **578** <1970JCC1397>. Cyclization of acyl thiosemicarbazides **580** (generated *in situ* from carboxylic acids **579**) with sulfuric acid or phosphorus halides affords 5-substituted 2-amino-1,3,4-thiadiazoles **581** in excellent yields (**Scheme 261**) <2005OBC222, 2003ARK(vii)297, 2001CHE1102>.



576 577 578

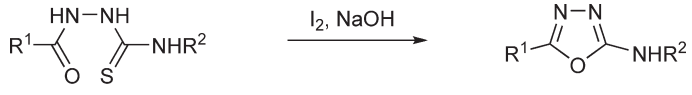
Scheme 260



579 580 581

Scheme 261

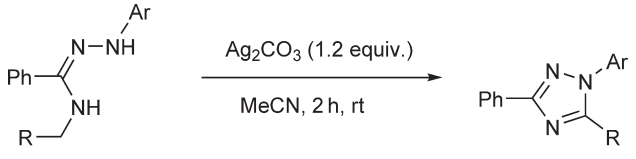
2. Similar ring closures can be carried out oxidatively. Aminooxadiazoles **583** are commonly prepared by oxidative cyclization of thiosemicarbazides **582** using iodine in alkaline solution (**Scheme 262**) <1999JFC(93)39, 2001CHE1102> or other reagents <CHEC-III(5.06.9.1.3)434>.



582 583

Scheme 262

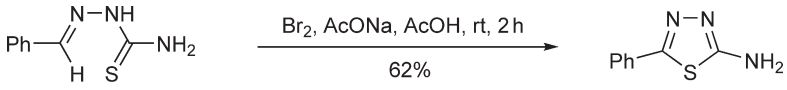
1,3,5-Trisubstituted 1,2,4-triazoles **585** are prepared in good yields from amidrazones **584** using various oxidizing agents, including Ag_2CO_3 and the DessMartin periodinane (**Scheme 263**) <2000T8071, 2001T9677, 2002TL8925, CHEC-III(5.02.9.4)191>.



584 585

Scheme 263

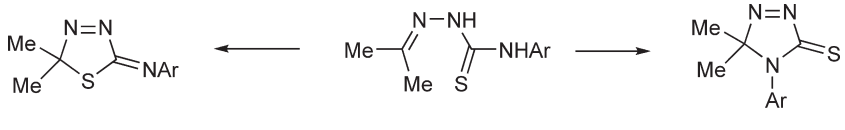
Oxidative cyclization of thioacylhydrazone **586** provides 1,3,4-thiadiazole **587** (**Scheme 264**) <CHEC-III (5.10.9.1.1)591>. Common oxidants include bromine <1997PHA350>, ferric chloride <2004BMC613, 2005T10917, 2003PHA367>, ferric ammonium sulfate <2003JME427, 2003EJM851, 2005BML1983>, and potassium permanganate <2004H(63)2243>.



586 587

Scheme 264

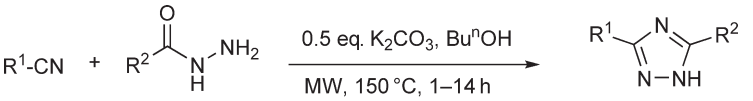
The direction of ring closure can often be influenced by the conditions. The substituted thiosemicarbazone **589** with $Al_2O_3/CHCl_3$ formed the 1,2,4-triazoline-3-thione **590** but treatment with MnO_2/C_6H_6 afforded the thiadiazoline **588** (**Scheme 265**) <1970JCC63>.



588 589 590

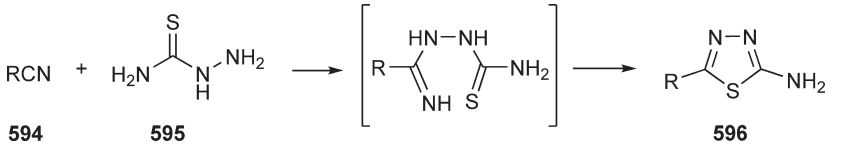
Scheme 265

3. Various 3,5-disubstituted 1,2,4-triazoles **593** have been prepared in good yields by the reaction of nitriles **591** with acylhydrazides **592** in the presence of catalytic potassium carbonate under microwave heating (**Scheme 266**) <2005TL3429, CHEC-III(5.02.9.2)182>. Likewise, alkyl and aryl nitriles **594** react with thiosemicarbazide **595** under acidic conditions to give 1,3,4-thiadiazoles **596** (**Scheme 267**) <1995BML1995, CHEC-III(5.10.9.2.2)595>.



591 **592** **593**

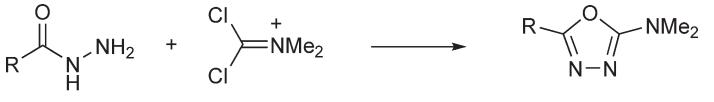
Scheme 266



594 **595** **596**

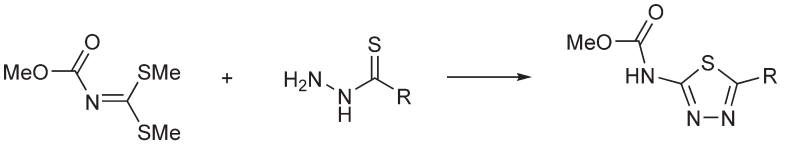
Scheme 267

4. Reaction of a hydrazide with dichloromethylene-dimethyliminium chloride (also known as phosgeneimonium chloride) **597** led to the 2-dimethylamino-1,3,4-oxadiazole **598** (**Scheme 268**) <1973AGE806>. The 1,3,4-thiadiazole **601** was made by an analogous reaction from **599** and **600** (**Scheme 269**).



597 **598**

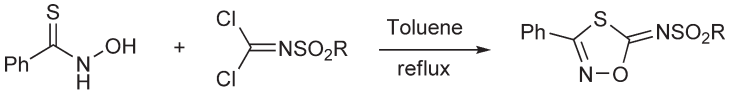
Scheme 268



599 **600** **601**

Scheme 269

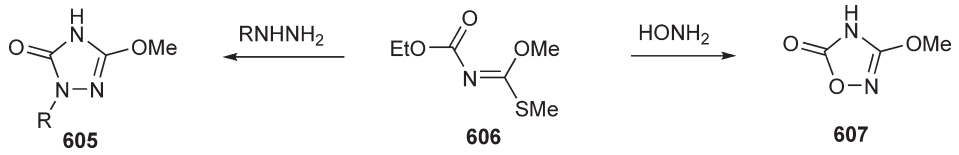
Dichloromethyleneimine sulfonamide **603** with the *N*-hydroxythioamide **602** gives the 1,3,5-oxathiazole **604** (**Scheme 270**) <1971AP763>.



602 **603** **604**

Scheme 270

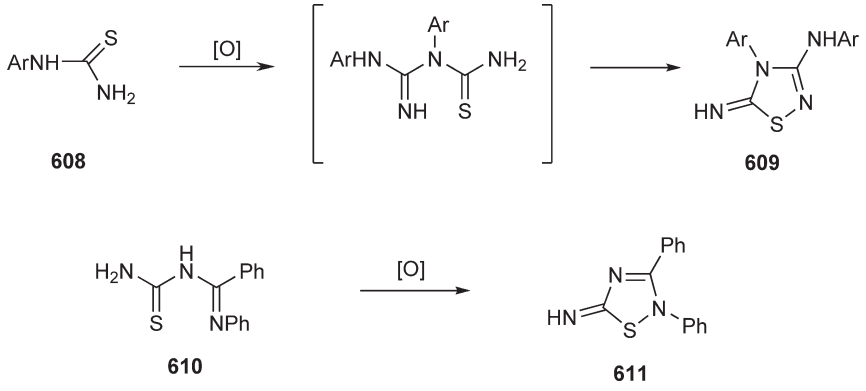
5. Dimethyl *N*-ethoxycarbonylthiocarbonimidate **606** with a monosubstituted hydrazine gives the 1,2,4-triazolinone **605**, and with hydroxylamine the 1,2,4-oxadiazolinone **607** (**Scheme 271**) <1973J(P1)2644>.



Scheme 271

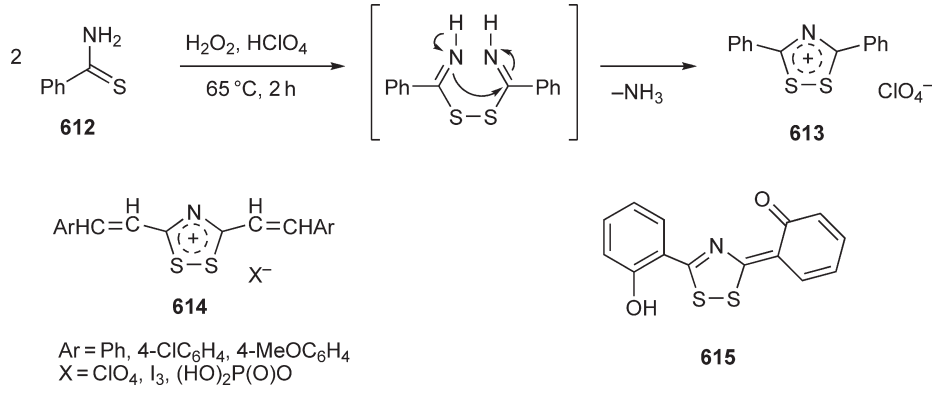
4.3.6.1.2 From acyclic intermediates by formation of the ZZ bond

1,2,4-Thiadiazoles are conveniently prepared from thioamides or analogous substrates by oxidative dimerization which can be effected by halogens, hydrogen peroxide, sulfur halides, etc., <CHEC-III(5.08.9.2)501>; cf. the conversion of thioamides **608** into thiadiazole derivatives **609** (Hectors bases) by hydrogen peroxide. Commencing with the thiourea **610** gives the alternatively substituted product **611** (**Scheme 272**) <1972ZC130, 1982AHC(32)285>.



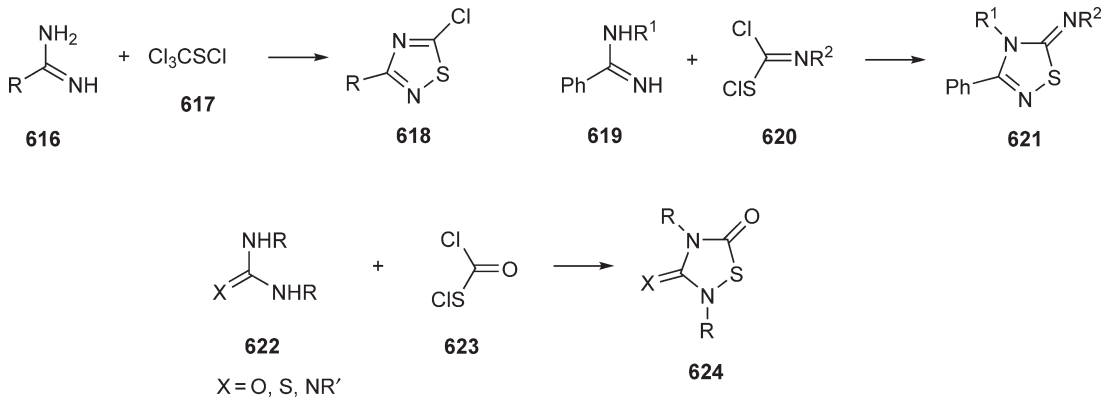
Scheme 272

In a similar reaction, *N*-acylthioureas, thioamides, and thioanilides of 3-oxoacids can be converted into 1,2,4-dithiazole derivatives by treatment with different oxidants <CHEC-III(6.03.8.2)88>. This reaction begins with SS bond formation followed by cyclization to the target compounds with primary amine or ammonia extrusion. Thus, thiobenzamide **612** gives 3,5-diphenyl-1,2,4-dithiazolium perchlorate **613** in 80% yield upon treatment with H_2O_2 and $HClO_4$ (**Scheme 273**) <2001MI5131>. 3,5-Bis(,-unsaturated)-1,2,4-dithiazolium salts **614** and 1,2,4-dithiazole **615** were prepared by a similar procedure <2005H(65)1295>.



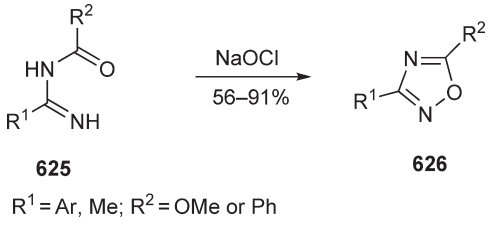
Scheme 273

The reaction of trichloromethanesulfenyl chloride **617** with amidines **616** and a mild base is a general preparation for 5-chloro-1,2,4-thiadiazoles **618** <1965AHC(5)119>. Iminochloromethanesulfenyl chlorides **620** (from RNCS + Cl_2) react with amidines **619** to give 1,2,4-thiadiazolines **621** <1971T4117>. Chlorocarbonylsulfenyl chloride **623** (prepared from trichloromethanesulfenyl chloride and sulfuric acid) reacts with ureas, thioureas, and guanidines to give 1,2,4-thiadiazolidine derivatives **624** (**Scheme 274**) <1973CB3391> (see also <CHEC-III(5.08.9.2)502>).



Scheme 274

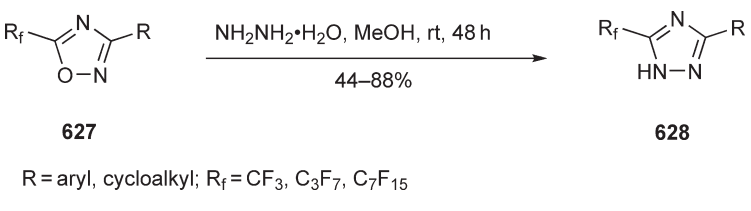
N-O Bond formation by oxidative procedures has found less application <CHEC-III(5.04.9.1.1)270>. However, the 1,2,4-oxadiazole system **626** can be prepared by the action of sodium hypochlorite on *N*-acylamidines **625** in generally high yields (**Scheme 275**) <1976S268>.



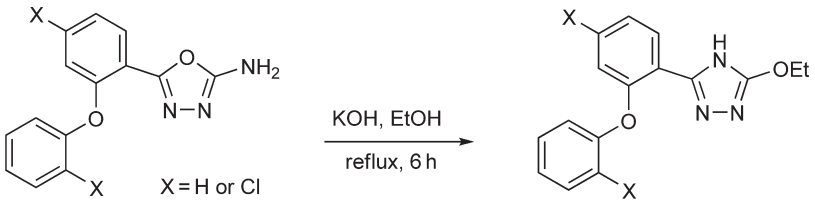
Scheme 275

4.3.6.1.3 From heterocyclic precursors

4.3.6.1.3.1 From other five-membered heterocycles. Reaction of the fluoroalkyl substituted 1,2,4-oxadiazoles **627** with hydrazine gives the corresponding 1,2,4-triazoles **628** in good yield via a ring-opening rearrangement of the oxadiazole (**Scheme 276**) <2003JOC605>. The rearrangement of 1,3,4-oxadiazoles **629** in the presence of a base has been employed in the synthesis of the phenoxyphenyl 1,2,4-triazoles **630** (**Scheme 277**) <2003BMC769, CHEC-III (5.02.10)199>.



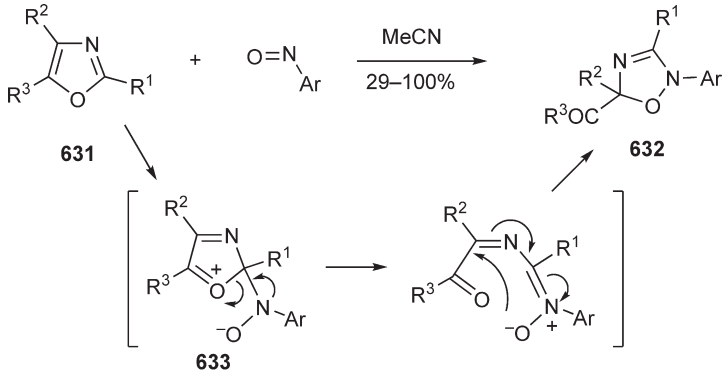
Scheme 276



629 630

Scheme 277

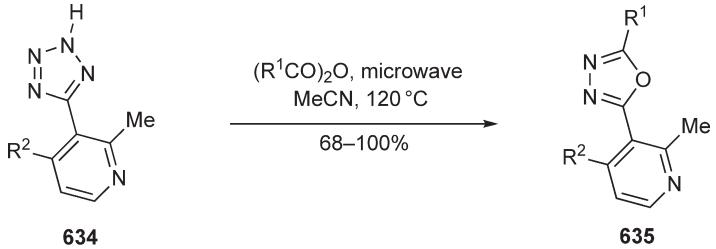
The reaction of substituted oxazoles **631** with nitrosoarenes in acetonitrile at room temperature gives 2,5-dihydro-1,2,4-oxadiazoles **632**, a reaction that is believed to proceed via a nucleophilic attack of the nitrosoarene by the 2-position of the oxazole to give the intermediate **633**, which undergoes ring opening followed by cyclization to afford the isolated 2,5-dihydro-1,2,4-oxadiazoles **632** (**Scheme 278**) <1998BCJ1231, CHEC-III(5.04.10.2)297>.



Ar = Ph, 4-Tol, 4-ClC_6H_4; R^1 = Me, 4-Tol, nonyl, 4-$MeOC_6H_4$
R^2 = 4-$NO_2C_6H_4$, Me, CO_2Et, H, Ph; R^3 = OMe, OEt, Me

Scheme 278

Several 3-(5-tetrazolyl)pyridines **634** containing bulky groups on the pyridine ring were acylated in acetonitrile at elevated temperature and under microwave irradiation to afford various 3-(1,3,4-oxadiazol-2-yl)pyridines **635** in good yields (**Scheme 279**) <2006T1849, CHEC-III(5.06.10)444>. See also Section 3.4.3.12.4 for the preparation of oxadiazoles and thiadiazoles by the elimination of N_2 from 2-acyltetrazoles and 2-thioacyltetrazoles, respectively.

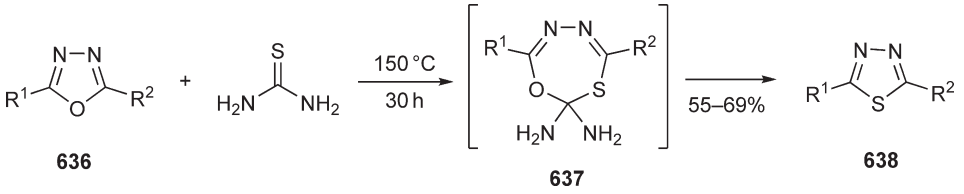


634 635

R^1 = Me, CF_3, Bu^t, Pr^i, 4-ClC_6H_4
R^2 = alkyl or aryl

Scheme 279

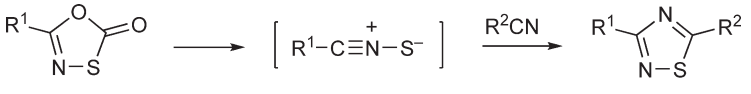
2,5-Diaryl-1,3,4-oxadiazoles **636** react with thiourea to give 2,5-diaryl-1,3,4-thiadiazoles **638** <1998SC4611>. The proposed mechanism proceeds via ring contraction of an intermediate oxathiadiazepine **637** to give the thiadiazole **638** (**Scheme 280**) <CHEC-III(5.10.10)598>.



636 **637** **638**

Scheme 280

The 1,3-dipolar cycloaddition reaction between nitrile sulfides **640**, produced by the thermal decomposition of oxathiazolones **639**, and nitriles is a general method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles **641** of unambiguous structure (**Scheme 281**) <1984CHEC-I(6)463>. More recently trichloroacetonitrile <1986PS(26)151> and tosyl cyanide <1993JHC357> have been used as acceptor molecules to give the 5-trichloromethyl and 5-tosyl derivatives in high and moderate yields, respectively. Displacement of the tosyl group by a range of nucleophiles leads to a wide variety of 5-substituted analogues.



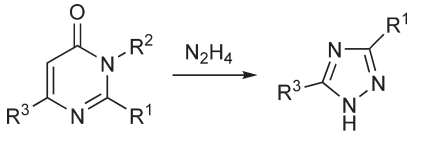
639 **640** **641**

Scheme 281

4.3.6.1.4 By the monocyclic rearrangement

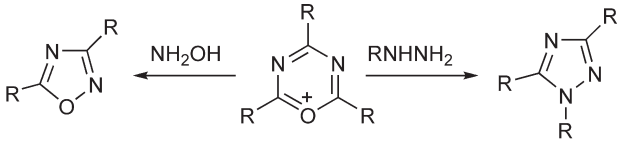
Section 3.4.3.1.9 gives details of ring interconversions involving three-atom side chain displacements at both N and S ring atoms.

4.3.6.1.4.1 By ring contraction. 4-Pyrimidones **642** react with hydrazine hydrate at 130140 C to give the 1,2,4-triazoles **643** (**Scheme 282**) <1983H(20)1243>. 1,3,5-Oxadiazinium salts **645** with hydroxylamine give the 1,2,4-oxadiazoles **644** and with hydrazines form the 1,2,4-triazole derivatives **646** (**Scheme 283**). The substituents in these cationic species are usually aryl, restricting the appeal of these ring interconversions <1967CB3736>.



642 **643**

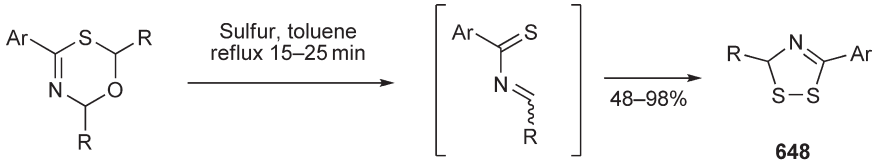
Scheme 282



644 **645** **646**

Scheme 283

1,2,4-Dithiazolines **648** are formed in high yields via the thermally induced retro-[4 + 2]-cycloaddition of 6*H*-1,3,5-oxathiazines **647** in the presence of sulfur <2001BCJ511, 2004TL6187, 2004HAC208>. The same transformation takes place with 6*H*-1,3,5-oxaselenaazines in the presence of selenium leading to the formation of the selenium analogs of **648** in 4498% yield (**Scheme 284**) <CHEC-III(6.03.8.3)89>.



647 Ar = Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$; R = Bu^t, Me

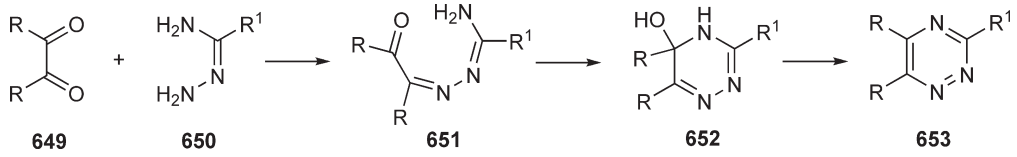
648

Scheme 284

4.3.6.2 Six-membered Rings

4.3.6.2.1 1,2,4- Triazines

The reaction of 1,2-dicarbonyl compounds **649** with amidrazones **650** is the best method for the synthesis of alkyl-, aryl-, or hetaryl-substituted 1,2,4-triazines **653** (**Scheme 285**) <CHEC-III(9.02.7.2.1)160>. Mixtures result unless the dione **649** is symmetrical.

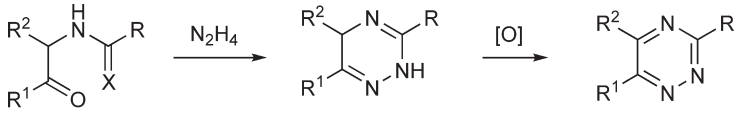


649 **650** **651** **652** **653**

Scheme 285

Various extensions are possible (see <CHEC-III(9.02.7.2.1)160> for full details), Use of aminoguanidines, semicarbazide, and thiosemicarbazide gives, respectively, the 3-amino-1,2,4-triazine, and the 3-one and 3-thione derivatives. Use of -keto esters and -keto cyanides gives 5-ones and 5-amino derivatives, respectively. -Hydroxy ketones afford dihydro-1,2,4-triazines. Intermediates **651** and **652** can sometimes be isolated.

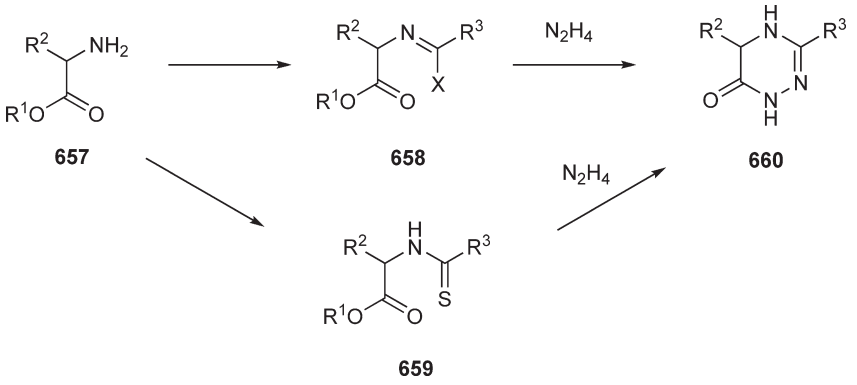
For the synthesis of 1,2,4-triazines, another frequently used method is the reaction of -acylamino and -thioacyl-amino ketones **654** (X = O, S) with hydrazine to give dihydro derivatives **655** which can be oxidized to the 1,2,4-triazines **656** (**Scheme 286**) <CHEC-III(9.02.7.2.3)170>.



654 X = O or S **655** **656**

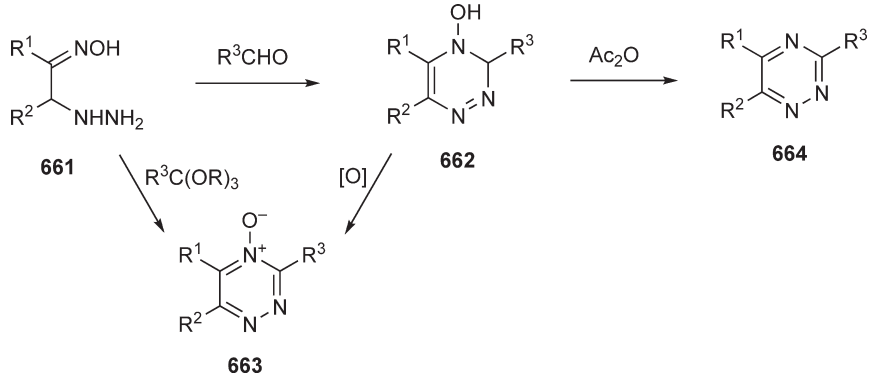
Scheme 286

In order to obtain 4,5-dihydro-1,2,4-triazin-6-ones **660**, -amino-substituted alkyl carboxylates **657** are transformed into the corresponding imidates **658** (X = OR), amidines **658** (X = NR$_2$), chloroformamidines **658** (X = Cl), or thioacyl aminoacids **659** followed by condensation with hydrazine or substituted hydrazines (**Scheme 287**) <1999AJC379, 2000JFC(106)83, 2001TL6455, 2002RJO602, 2002TL8165, 2003TL4593, 2004BML2323>.



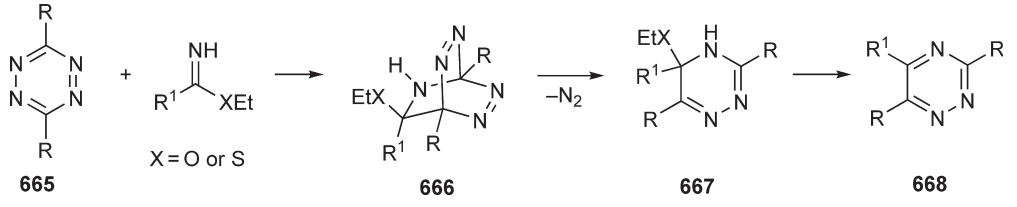
Scheme 287

The cyclization of -hydrazinoximes **661** with *ortho*-carboxylates or aldehydes is a useful synthetic approach to 1,2,4-triazine 4-oxides **663** (**Scheme 288**) <CHEC-III(9.02.7.3.1)172>. For example, interaction of oximes **661** with aldehydes affords 4-hydroxy-3,4-dihydro-1,2,4-triazines **662**. Oxidative aromatization of the dihydro derivatives **662** results in the formation of 1,2,4-triazine 4-oxides **663**, while tretment of **662** with acetic anhydride leads to 1,2,4-triazines **664** (**Scheme 288**) <2002AHC(82)261, 2002MC30, 2003JOC2882>.



Scheme 288

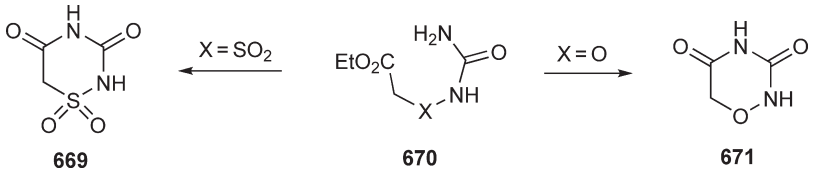
1,2,4,5-Tetrazines **665** undergo DielsAlder reactions with CN multiple bonds. Imidates <1969JHC497> or better, thioimidates <1983JOC621, 1983TL4511, 1985JA5745> thus afford 1,2,4-triazines **668** which are formed via intermediate bicycles **666** and dihydro-1,2,4-triazines **667** (**Scheme 289**).



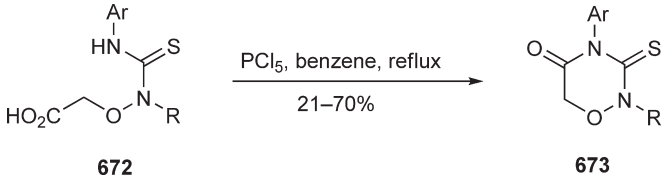
Scheme 289

4.3.6.2.2 Rings containing O or S atoms

-(Ethoxycarbonyl)methylsulfonylurea **670** (X = SO_2) cyclizes to the 1,2,4-thiadiazine **669** on treatment with base <1959JA5655>, and a similar cyclization occurs with the oxygen analogue **670** (X = O) to give **671** (**Scheme 290**) <1979JHC161>. Likewise, thioureas **672** (R = Me, Et) react with PCl_5 in boiling benzene to furnish 1-oxa-2,4-diazines **673** (**Scheme 291**), which were found to have serum high-density lipoprotein cholesterol-elevating activity <2004JME681, CHEC-III(9.05.9.1.3)324>.

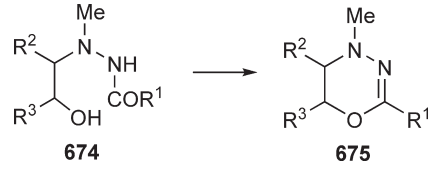


Scheme 290

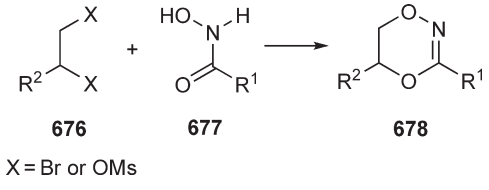


Scheme 291

Acid-catalyzed dehydration of *N*-(2-hydroxyethyl)-*N*-acylhydrazines **674** is a general route to 4,5-dihydro-1,3,-4-oxadiazines **675** (**Scheme 292**) <1964JOC668>. 4,2-Dioxazines **678** are prepared by di-O-alkylation of hydroxamic acids using 1,2-dihalides or 1,2-dimesylates **676** (**Scheme 293**) <1971JOC284>.

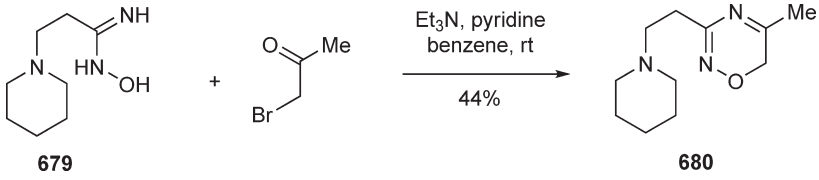


Scheme 292



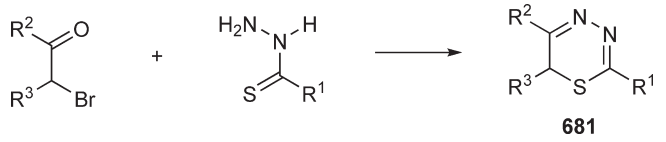
Scheme 293

Reaction of amidoximes with -haloketones or 1,2-dibromoalkanes in the presence of base leads to the 1-oxa-2,4-diazine system; for example, the -aminopropionamidoxime **679** and bromoacetone yield **680** (**Scheme 294**) <CHEC-III (9.05.9.2.2)328>.

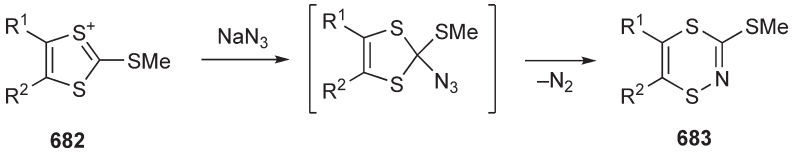


Scheme 294

Condensation of -halo ketones with thiohydrazides is a general route to 1,3,4-thiadiazines **681** (**Scheme 295**) <1976JPR(318)971>. Preparation of 1,4,2-dithiazines **683** involves the ring expansion of 1,3-dithiolium salts **682** with sodium azide (**Scheme 296**) <1976JPR(318)127>.

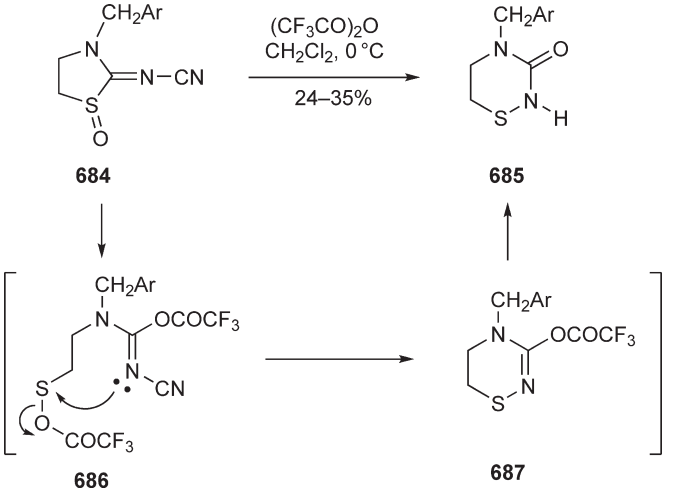


Scheme 295



Scheme 296

3-Alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxides **684** undergo a ring-enlargement process in the presence of trifluoroacetic anhydride to afford 5,6-dihydro-2*H*-1-thia-2,4-diazin-3(4*H*)-ones **685** (**Scheme 297**). Initial reaction of **684** with the anhydride leads to open-chain imidate **686**, intramolecular displacement of trifluoroacetate gives 4*H*-1-thia-2,4-diazine **687**, which finally hydrolyzes to the isolated product **685** (**Scheme 297**) <1997SL316, CHEC-III(9.05.10)334>.



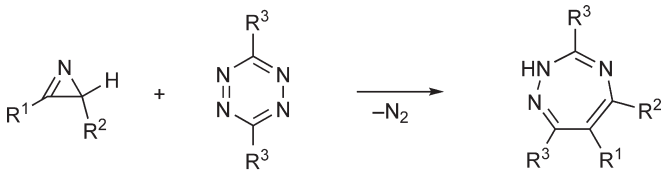
Scheme 297

4.3.6.3 Seven-membered Rings

4.3.6.3.1 Heteroatoms in the 1,2,4-positions

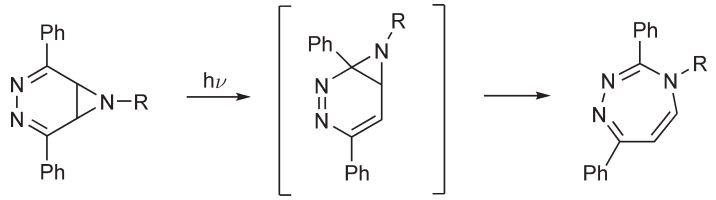
Fully-unsaturated 2*H*-1,2,4-triazepines **690** are formed by the cycloaddition of 1-azirines **688** to 1,2,4,5-tetrazines **689** (**Scheme 298**). The initial product rearranges by a 1,5-hydrogen shift to give **690** <1974TL2303>.

The 4*H*-1,2,4-triazepine system **692** can be prepared via a photochemical rearrangement of 3,4,7-triaza-2,4-norcaradienes **691** (**Scheme 299**) <1976TL2459>.



688 **689** **690**

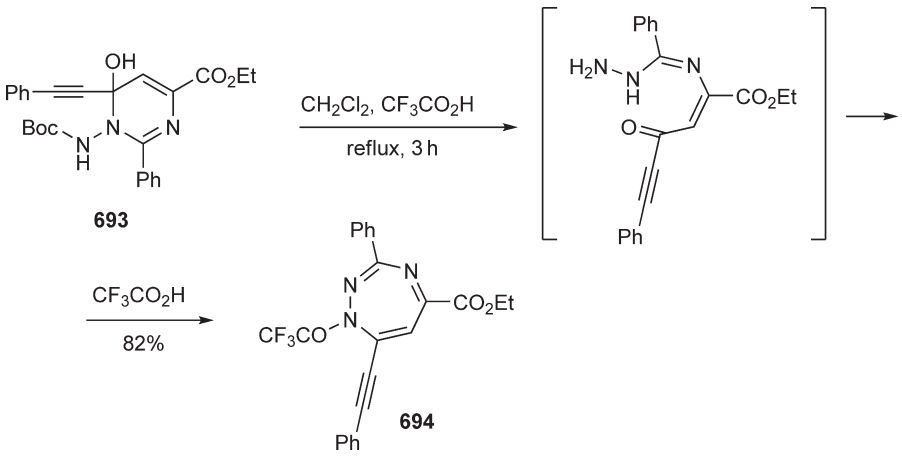
Scheme 298



691 **692**

Scheme 299

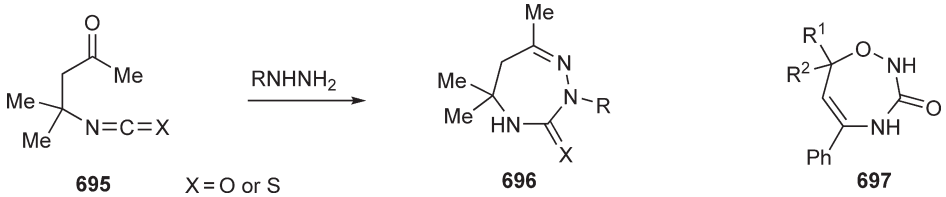
The alkynyl-substituted trifluoroacetyltriazepine **694** has been prepared in high yield via ring expansion of the six-membered ring precursor **693** (**Scheme 300**) <2005JOC3307, CHEC-III(13.14.6.1)414>.



693 **694**

Scheme 300

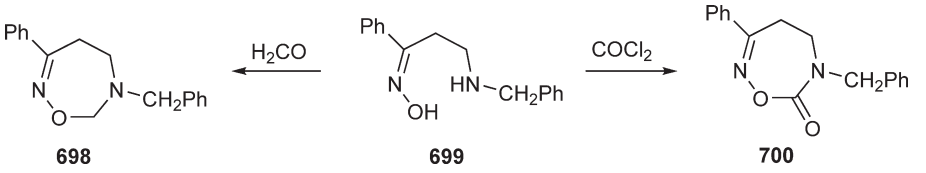
The -functionalized isocyanate **695** (X = O) reacts with methylhydrazine to give **696** <1977S756>, and **695** (X = S) reacts with both alkylhydrazines and unsubstituted hydrazine to give the same ring system **696** (X = S) (**Scheme 301**).



695 X = O or S **696** **697**

Scheme 301

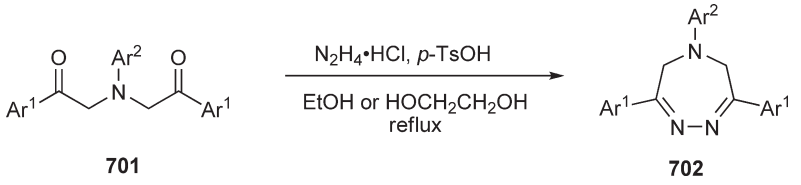
3-Oxo-1,2,4-oxadiazepines **697** have been prepared by the reaction of hydroxyurea with some ,-unsaturated ketones <1975TL2979>. *syn*--(Benzylamino)propiophenone oximes (e.g., **699**) react with phosgene to give the 7-oxo-1,2,6-oxadiazepines **700** <1975CB3387>, and with formaldehyde to give **698** (**Scheme 302**) <1980CB3373>.



Scheme 302

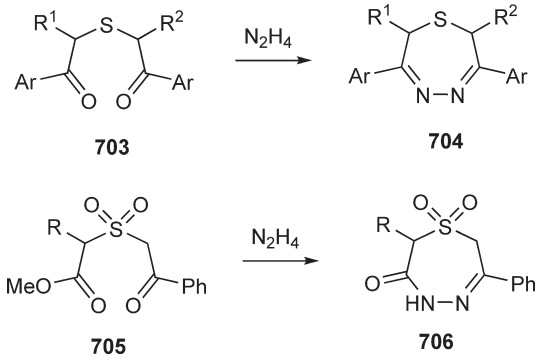
4.3.6.3.2 Seven-membered rings with heteroatoms in the 1,2,5-positions

The reaction of *N,N*-bis(phenacyl)anilines **701** with hydrazine hydrochloride in EtOH or ethylene glycol under reflux leads to the formation of 1,2,5-triazepines **702** (**Scheme 303**) <2007JHC133, CHEC-III(13.15.7.1)454>.



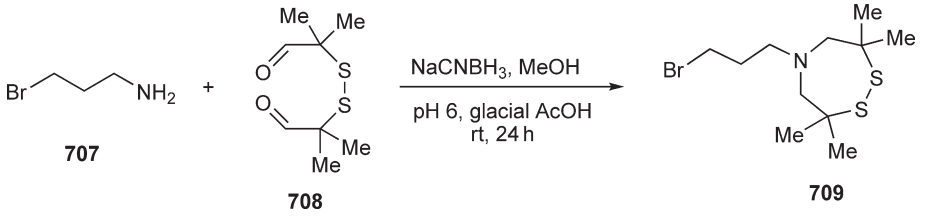
Scheme 303

The sulfides **703** and sulfones **705** react with hydrazine to give products **704** and **706** (**Scheme 304**) <1970JHC431, 1972T2307>.



Scheme 304

The fully-saturated 5-(3-bromopropyl)-3,3,7,7-tetramethyl[1,2,5]perhydrodithiazepine **709** has been prepared via the reductive amination of 2-[(1,1-dimethyl-2-oxoethyl)disulfanyl]-2-methylpropanal **708** with 3-bromopropylamine **707** in the presence of $NaCNBH_3$ (**Scheme 305**) <2001BML1859, CHEC-III(13.15.7.6)459>.

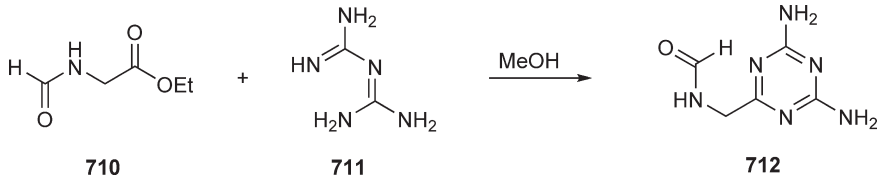


Scheme 305

4.3.7 Three Heteroatoms in the 1,3,5-Positions

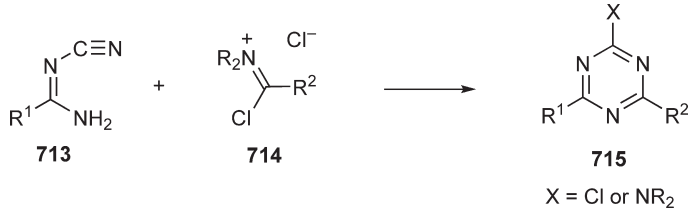
4.3.7.1 *s*-Triazines

Biguanidines react with lactones, amides, *ortho* esters, esters, acid anhydrides, and acid chlorides to produce a wide range of 6-substituted 2,4-diamino-1,3,5-triazines <CHEC-III(9.03.9.2.1)236>; for example, *N*-formylglycine ethyl ester **710** and biguanide **711** condense smoothly in methanolic solution to afford the triazine derivative **712** (**Scheme 306**) <2003OL2067>. Biguanidines with carbodiimides, isothiocyanates, and ketones give corresponding melamines, thiones, and dihydro derivatives, respectively.



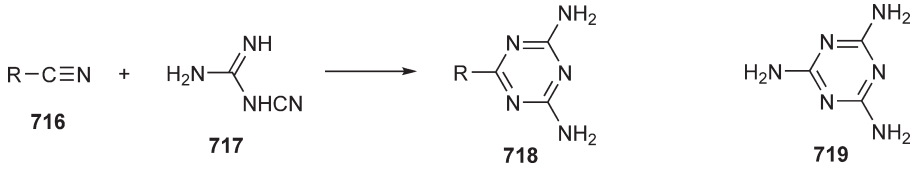
Scheme 306

The condensation of *N*-cyanoamidines **713** with chloromethylene-iminium salts **714**, prepared *in situ* from the respective amides R^2CONR_2 and PCl_3, provides an efficient, convenient route to many 1,3,5-triazines **715** (**Scheme 307**) <1980S841, 1981AJC623>.



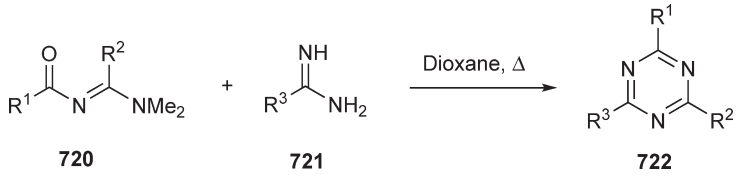
Scheme 307

A convenient synthetic approach to 2,4-diaminotriazines utilizes the addition reactions of nitriles **716** with dicyandiamide **717** (also called cyanoguanidine) as shown in **Scheme 308** <CHEC-III(9.03.9.2.1)236, 1996JOC6371>. The self-condensation reaction of dicyandiamide **717** is used for the preparation of melamine **719**.



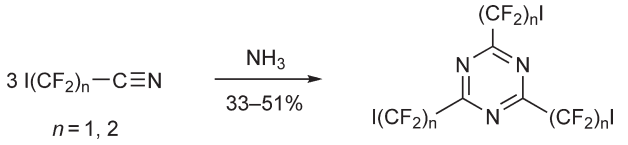
Scheme 308

Cyclizations of acylamidines **720** with amidines **721** or guanidines in aprotic solvents give *s*-triazines **722** bearing three different substituents (**Scheme 309**) <1995JOC8428>.



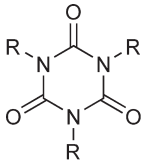
Scheme 309

Cyclotrimerization of nitriles is a well-known route to 1,3,5-triazines <CHEC-III(9.03.9.6.2)245>. The reaction is of value for preparing the symmetrical derivatives only. Nevertheless, many important triazines, such as cyanuric chloride, are made in this way. Various perfluoralkyl-substituted 1,3,5-triazines (e.g. **Scheme 310**) have been prepared using this approach <2003JOC4410, 1997JOC9070, 2004JOC198>.

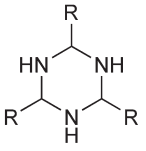


Scheme 310

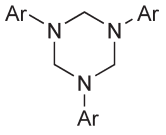
Trimerization of imidates is a valuable route to 1,3,5-triazines <CHEC-III(9.03.9.5.3)244>. Imidates can be considered as activated nitriles and cyclotrimerize more readily. Most symmetrical 2,4,6-trialkyl-1,3,5-triazines are easily formed, although large alkyl substituents may give rise to steric hindrance <1961JOC2778>. Symmetrical isocyanurates **723** are readily available from isocyanates, RNCO; catalysts include tertiary amines, phosphines and sodium methoxide. Aldehydes RCHO and ammonia give hexahydro-1,3,5-triazines **724**, known as aldehyde ammonias <1973JOC3288>; formaldehyde and aryl amines give analogous N-substituted triazines **725** <2004JFC(125)1273>.



723



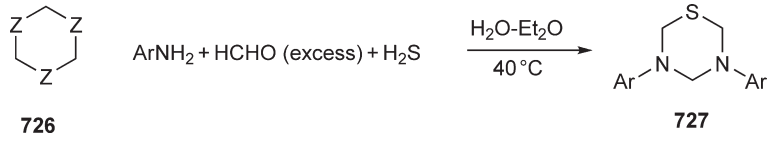
724



725

4.3.7.2 Compounds Containing O or S Atoms

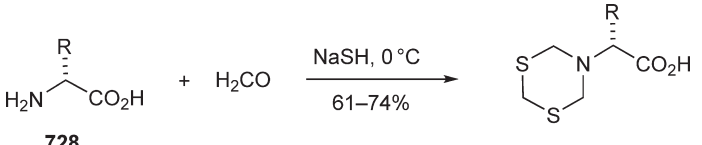
1,3,5-Trioxanes **726** (Z = O) are trimers of aldehydes or ketones formed by acid-catalyzed condensations of the monomers. 1,3,5-Trithiane **726** (Z = S) is prepared by passing H_2S through formaldehyde and hydrochloric acid <1943OSC(2)610>. The reaction of formaldehyde and H_2S with amines affords the corresponding thiadiazines **727** (**Scheme 311**) <2003RCB1817, CHEC-III(9.09.9.3)511>.



726 **727**

Scheme 311

A common method for the preparation of 1,3,5-dithiazines consists of the reaction of aldehydes and primary amines in the presence of H_2S (or HS) <CHEC-III(9.10.3)558>. For example, dithiazines **729** have been prepared by treatment of basic aqueous solutions of L-amino acids **728** with formaldehyde and NaSH (**Scheme 312**) <2002OL4129>.

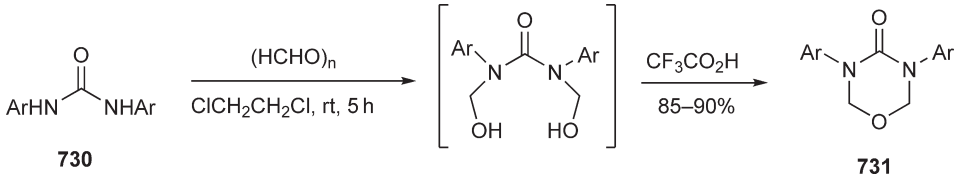


728 **729**

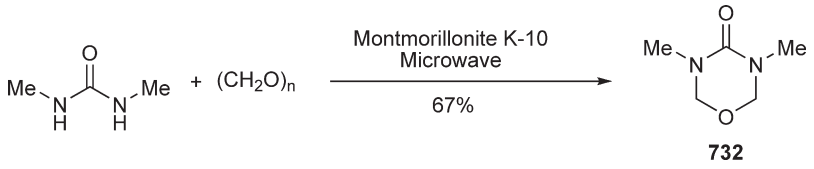
R = H, alkyl, aryl

Scheme 312

Treatment of *N,N*-diaryl ureas **730** (without activating groups on the aromatic ring), with paraformaldehyde in the presence of trifluoroacetic acid, furnishes the corresponding 3,5-diaryl-5,6-dihydro-2*H*-1,3,5-oxadiazin-4(3*H*)-ones **731** in high yields (**Scheme 313**) <1996SC3217, CHEC-III(9.09.9.1)486>. Likewise, 4-oxo-oxadiazine **732** was prepared using microwave irradiation in the presence of Montmorillonite K-10 (**Scheme 314**) <1999JCM392>.

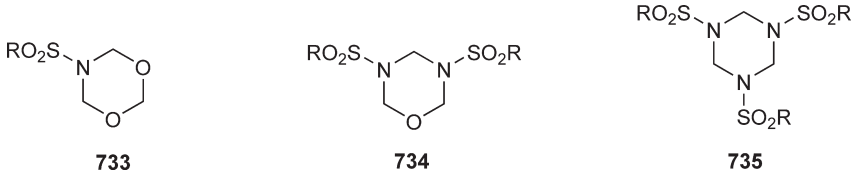


Scheme 313



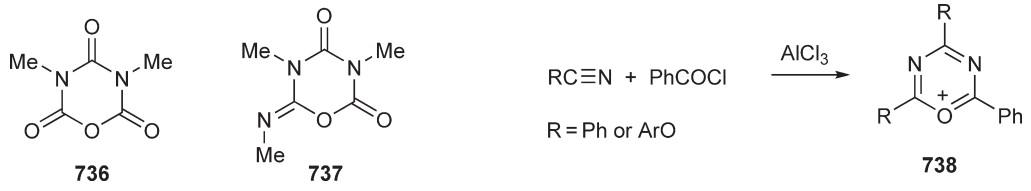
Scheme 314

Sulfonamides RSO_2NH_2 react with formaldehyde to give *N*-sulfonyl-1,3,5-dioxazines **733**, -1,3,5-oxadiazines **734** or -1,3,5-triazines **735** according to the relative quantities of reactants used <1975J(P1)772>.



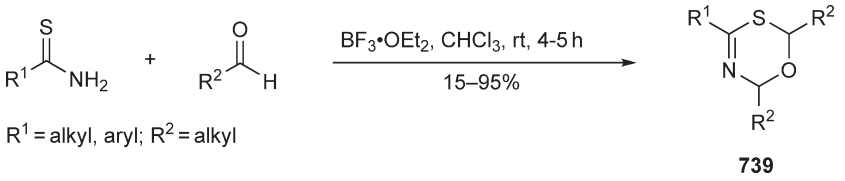
Trimerization of methyl isocyanate (MeNCO) in the presence of tri-*n*-butylphosphine gives a 1,3,5-oxadiazine **736** <1973CRC(277)795>. In the presence of carbon dioxide, the reaction leads to the 1,3,5-oxadiazinimine **737** derived from CO_2 (1 mol eq.) and the isocyanate (2 mol eq.) <1974BSF1497>.

Benzoyl chloride condenses with benzonitrile or aryl cyanates in the presence of aluminum trichloride to give 1,3,5-oxadiazinium salts **738** (**Scheme 315**) <1967CB3736>.



Scheme 315

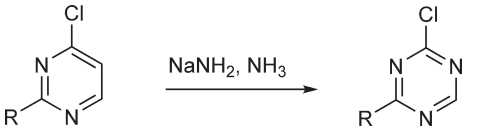
Oxathiazines **739** have been prepared by the condensation of thioamides with aliphatic aldehydes in the presence of BF_3•OEt_2 (**Scheme 316**) <2004HAC175>.



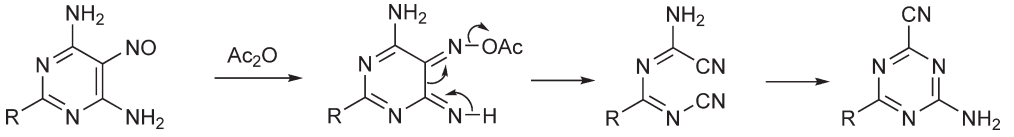
Scheme 316

4.3.7.3 Synthesis from Heterocyclic Precursors

2-Substituted 4- or 5-halopyrimidines with sodium amide in liquid ammonia give 4-methyl-1,3,5-triazines (**Scheme 317**); the reaction is general and yields are good; cf., the related conversion of 6-substituted 2-bromopyridines into pyrimidines (Section 4.3.3.3.4). 4-Amino-5-nitrosopyrimidines are converted into 1,3,5-triazines by acetic anhydride or phosphorus oxychloride (**Scheme 318**). 1,3,5-Triazines can be obtained from 1,3,5-oxadiazinium cations (Section 3.2.1.6.1.3).

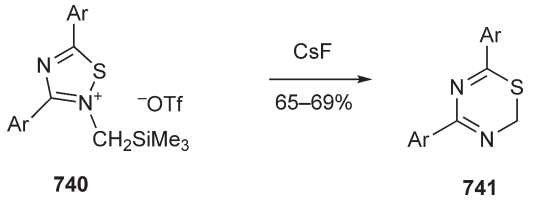


Scheme 317



Scheme 318

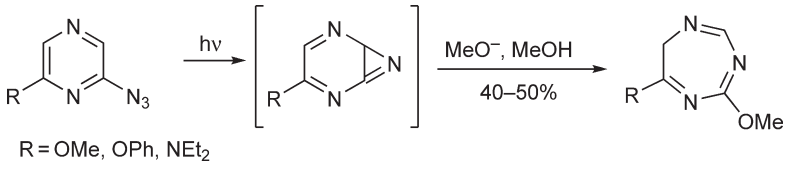
The desilylation of 3,5-diaryl-1,2,4-thiadiazolium salts **740** with CsF results in ring expansion to afford substituted 2*H*-1,3,5-thiadiazines **741** in moderate yield (**Scheme 319**) <1999J(P1)1709, CHEC-III(9.09.10.2)514>.



Scheme 319

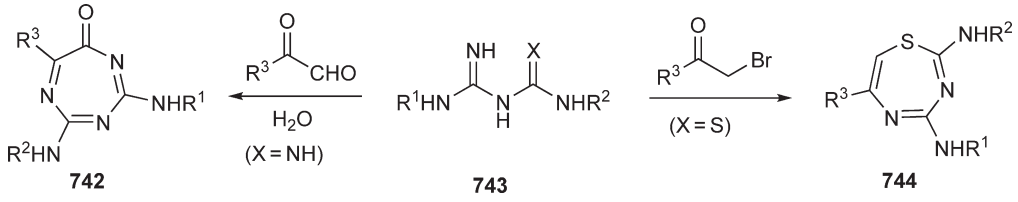
4.3.7.4 Seven-membered Rings

Irradiation of azido-substituted pyrazines or pyrimidines bearing strong electron-donating substituents, in the presence of a base, such as MeONa or diethylamine, results in ring expansion with formation of 1,3,5-triazepines (e.g., **Scheme 320**) <1990CC723, 1984J(P1)1719, CHEC-III(13.16.10)517>.



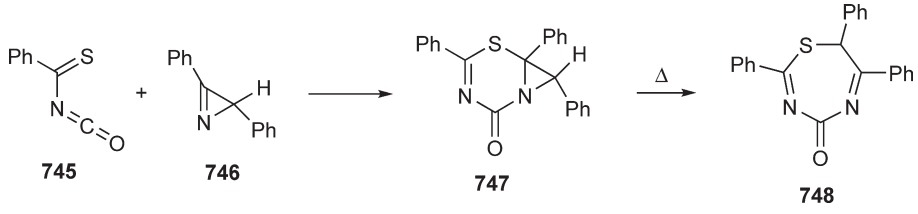
Scheme 320

Cyclocondensation of biguanidines **743** (X = NH) with -oxoaldehydes gives triazepinones **742** in moderate yields, whereas reaction of **743** (X = S) with -bromo ketones results in formation of thiadiazepines **744** (**Scheme 321**) <CHEC-III(13.16.9.3)511>.



Scheme 321

The 1,3,5-thiadiazepine **748** has been prepared by the thermal rearrangement of the [4 + 2] cycloadduct **747** of the azirine **746** and thiobenzoyl isocyanate **745** (**Scheme 322**) <1974JOC3763>.

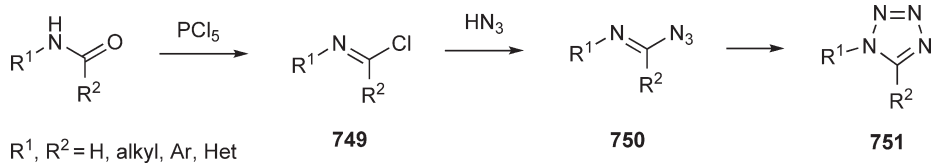


Scheme 322

4.3.8 Four or More Heteroatoms

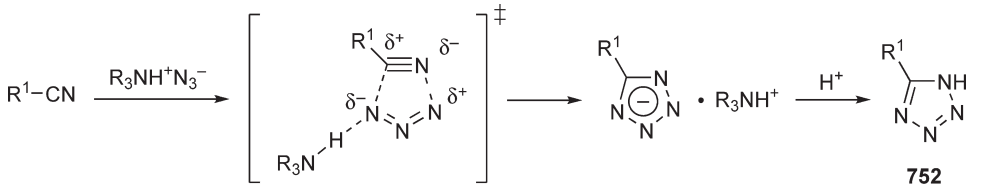
4.3.8.1 Five-membered Rings

1,5-Disubstituted tetrazoles **751** are most often prepared by the cyclization of imidoyl azides **750**. The traditional method for generation of imidoyl azides **750** consists of treating the appropriate imidoyl chlorides **749** with HN_3 or NaN_3 (**Scheme 323**); numerous other methods for the synthesis of imidoyl azides and their cyclization to tetrazoles have also been reported <CHEC-III(6.07.9.1)371>.



Scheme 323

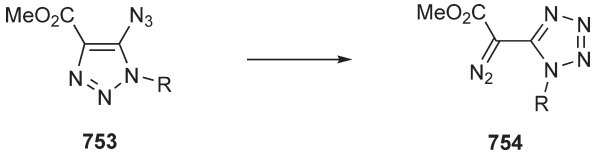
The reaction of nitriles with ammonium azide and alkylammonium azides in dipolar aprotic solvents remains the main procedure for the synthesis of 1*H*-tetrazoles **752** (**Scheme 324**). This method affords tetrazole derivatives with substituents of various character attached to the endocyclic carbon. This procedure has been used in the syntheses of various complex organic molecules <2003CHE1317, 2005T7002, 2006CHE469, 2002HCA2847, 2003RCR143>. Theoretical and experimental investigations <2000CHE759> show that the limiting stage of the process is 1,3-dipolar cycloaddition of alkylammonium azides to nitriles (**Scheme 324**). The rate of the process considerably grows with increasing electron-withdrawing properties of the substituents R^1, and also under high pressure. However, due to the low activation entropy of the cycloaddition, in most cases a reasonable yield (5080%) of 1*H*-tetrazoles is obtained by prolonged (840 h) heating of the reagents at 100160° <2000CHE759, CHEC-III(6.07.9.2)383>.



R^1 = H, Ar, Het, alkyl; R^2 = alkyl

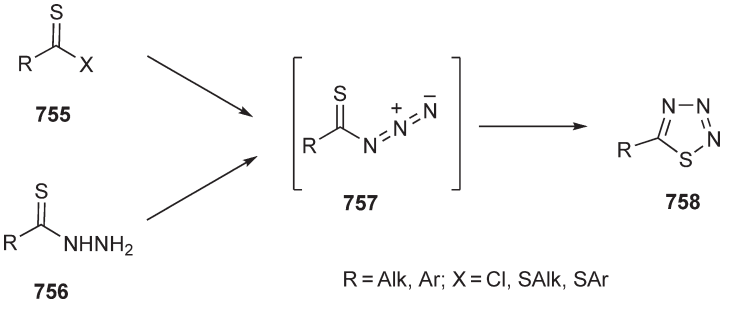
Scheme 324

Most transformations of other azoles into tetrazoles involve azido substituents; for example, 5-azido-1,2,3-triazoles **753** with a CO_2Me group at C(4) rearrange at 5070°C in organic solvents into the 5-diazoester substituted tetrazoles **754** (**Scheme 325**) <1998J(P2)785>. For a comprehensive review on the preparation of tetrazoles from transformations of other heterocycles see <1998JPR687>.



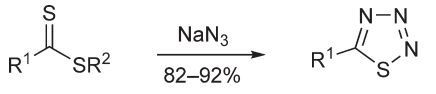
Scheme 325

The 5-substituted 1,2,3,4-thiatriazoles **758** are prepared by the generation of intermediate azidothiocarbonyl compounds **757** followed by 1,5-electrocyclic reaction (**Scheme 326**). The intermediate compounds **757** have never been isolated; they can be generated by treatment of derivatives of thiohydrazides **756** with either nitrous acid or with arenediazonium salts, and in reactions of thiophosgene (or dithiocarboxylates) **755** (X = Cl, SR) with either sodium- or trimethylsilyl azide (**Scheme 326**) <CHEC-III(6.09.9.1)471>. For example, thiatriazoles **760** can be prepared in high yields by the reaction of or *S*-thioacyl dithiophosphates **759** with sodium azide (**Scheme 327**) <2002J(P1)1271>.



R = Alk, Ar; X = Cl, SAlk, SAr

Scheme 326

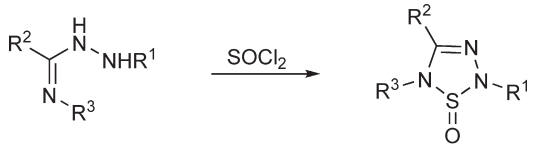


759 **760**

R^1 = Alk, Ar, Het; R^2 = Alk, $P(S)(CH_2O)_2OMe$

Scheme 327

2,5-Dihydro-1,2,3,5-thiatriazole 1-oxides **762** are prepared by the reaction of amidrazones **761** with thionyl chloride in the presence of a base (**Scheme 328**) <1989JHC205, 1990J(P2)1619, 2003PS1433, CHEC-III(6.10.9.2)492>.

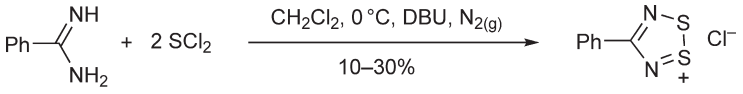


761 **762**

R^1 = Ar, COR, Ts; R^2 = Ar, CO_2Et; R^3 = Alk, Ar

Scheme 328

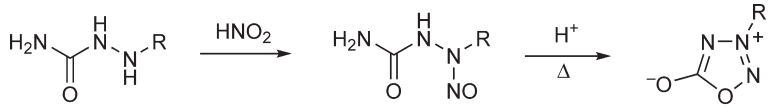
Amidines react with sulfur dichloride or disulfur dichloride in the presence of base to produce the dithiadiazolium chlorides, as illustrated by the preparation of 4-phenyl-1,2,3,5-dithiadiazolium chloride **763** (**Scheme 329**) <1989CC1134, CHEC-III(6.11.8.1)507>.



763

Scheme 329

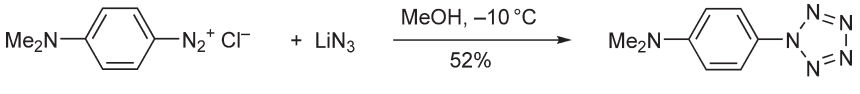
1,2,3,4-Oxatriazole derivatives are usually prepared by the cyclization of *N*-nitrosohydrazines as illustrated by the synthesis of 3-alkyl-1,2,3,4-oxatriazolium-5-olates **764** from semicarbazides via nitrosation (**Scheme 330**) <CHEC-III (6.08.9)431>.



764

Scheme 330

1-Arylpentazoles can be prepared by reaction of aryldiazonium salts with azide anion <1985AG515>. For example, a relatively stable 1-(4-dimethylaminophenyl)pentazole **765** precipitates as pale yellow plates from a solution of *p*-dimethylaminobenzenediazonium chloride and lithium azide in methanol (**Scheme 331**) <CHEC-III(6.18.6)753>.

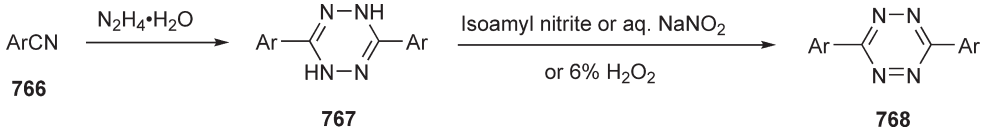


765

Scheme 331

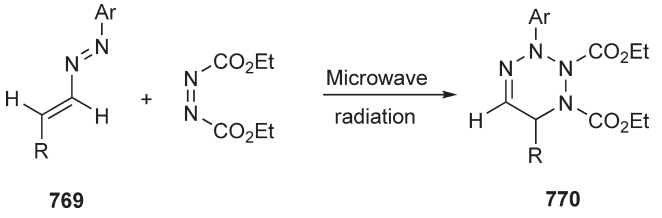
4.3.8.2 Six-membered Rings

Most of the preparations of the tetrazine ring are based on cyclocondensations of nitriles with hydrazines or hydrazones <CHEC-III(9.12.6)652>. For example, numerous 1,4-dihydrotetrazines **767** were prepared by reacting the corresponding nitriles **766** with hydrazine hydrate. Further oxidation of dihydrotetrazines **767** with isoamyl nitrite or nitrous acid or hydrogen peroxide gave the fully-conjugated compounds **768** (**Scheme 332**) <2003T4761, 2004NJC387>.



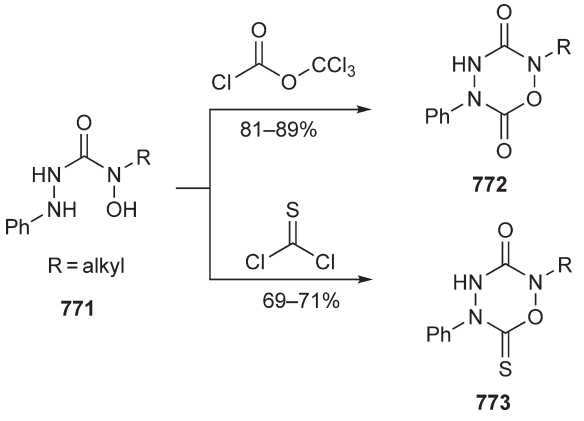
Scheme 332

1,2,3,6-Tetrahydro-1,2,3,4-tetrazines **770** have been prepared via hetero DielsAlder reactions of 1,2-diaza-1,3-butadienes **769** with diethyl azodicarboxylate (**Scheme 333**) <1999JOC6297, CHEC-III(9.13.9)729>.



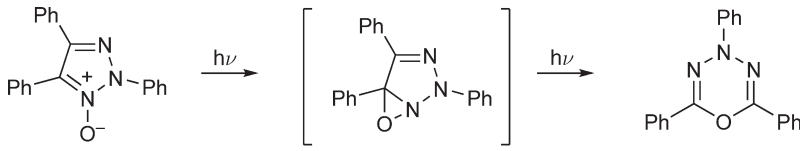
Scheme 333

1,2,4,5-Oxatriazine-3,6-diones **772** and 6-thioxo-1,2,4,5-oxatriazin-3-ones **773** have been prepared by cyclic carbonylation of 1,4-disubstituted 4-hydroxysemicarbazides **771** with diphosgene or thiophosgene, respectively (**Scheme 334**) <2002HCO321, CHEC-III(9.14.8.2.3)773>.



Scheme 334

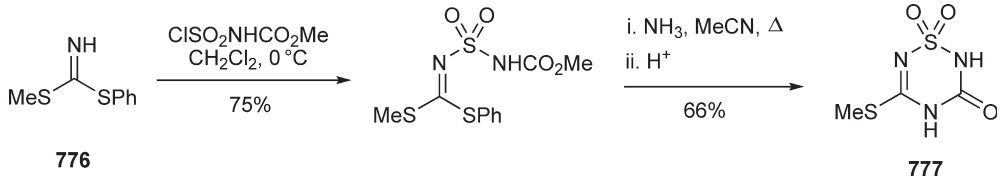
Photolysis of 2,4,5-triphenyl-1,2,3-triazole 1-oxide **774** gives the triphenyl-1,3,4,5-oxatriazine **775** in high yields (**Scheme 335**) <1980AJC2447>.



774 775

Scheme 335

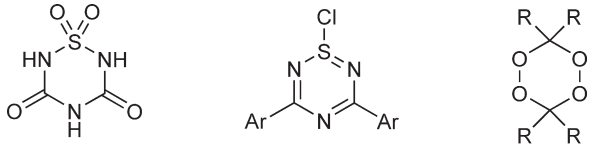
1,2,4,6-Thiatriazine 1,1-dioxides (e.g., **777**) can be prepared from the dithioimidocarbonate **776** (**Scheme 336**) <1996H(43)2199, CHEC-III(9.14.8.2.3)774>. There has been particular interest in *N*-alkyl-1,2,4,6-thiatriazine 1,1-dioxides because of their herbicidal, fungicidal, and histamine H_2-antagonist activity <1987S170>.



776 777

Scheme 336

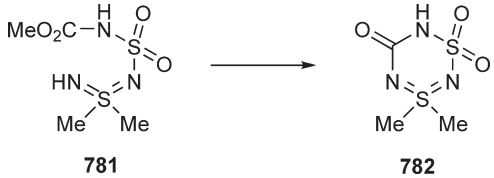
Sulfonyl diisocyanate gives the thiatriazine **778** on treatment with ammonia <1958CB1200>. A convenient and versatile reaction leading to aryl derivatives of 1-chloro-1,2,4,6-thiatriazine **779** involves heating an arylamidine with trichlorocyclotrithiazene, $(NSCl)_3$, in refluxing acetonitrile <1985JA1346>.



778 779 780

Ketones and hydrogen peroxide give 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes **780** <1980JCM35, 2002RMC113, CHEC-III(9.14.8.3)775>.

The sulfonylsulfur diimide **781** cyclizes to the 1,3,2,4,6-dithiatriazine **782** on heating in DMF <1971AGE264> (**Scheme 337**).



781 782

Scheme 337

4.4
Synthesis of Bicyclic Ring Systems Without Ring Junction Heteroatoms

Material in this chapter is arranged firstly by the number of heteroatoms in the heterocyclic ring, secondly by the orientation of the heteroatoms to the fused ring (usually benzenoid), and finally by the size of the heterocyclic ring.

4.4.1 Synthesis by Substituent Introduction and Modification

Most benzo-fused heterocyclic systems are constructed from a substituted benzene by synthesis of the heterocyclic ring. Similarly most bicyclic heterocycles with heteroatoms in both rings commence with a monoheterocycle and build on the second heterocycle. However, substituent modification and, to a lesser extent, substituent introduction are also important, particularly in the later stages of a synthesis, and we now survey available methods for this.

4.4.1.1 In the Heterocyclic Ring

The reactivity of heterocyclic rings is modified but not radically changed by benzo- or hetero-ring fusion. We therefore refer readers to the appropriate sections dealing with the analogous monocyclic rings:

1. pyrroles, furans and thiophenes (Section 4.2.3.2);
2. pyridines (Section 4.2.4.1);
3. azoles (Section 4.3.1.2);
4. azines (Section 4.3.1.3).

Benzo-ring fusion tends to facilitate reaction: it reduces the loss of resonance energy in nonaromatic transition states and intermediates.

4.4.1.2 In the Benzene Ring

Again, the reactivity of a benzene ring, although modified, is not radically changed by hetero-ring fusion. The reactivity sections of this book have dealt with the reactions of fused benzene rings and we refer now to those sections.

Since thiophene, pyrrole, and furan are more readily attacked by electrophiles than is benzene, in the corresponding benzo-fused heterocycles attack generally, but not invariably, occurs in the heterocyclic ring (Section 3.3.3.2.1).

Conversely in benzopyridines and benzazines, electrophilic attack usually occurs in the benzene ring (Section 3.2.3.2).

Benzazoles occupy an intermediate position, but in most cases electrophilic attack occurs in the benzene ring (Section 3.3.3.2.1).

4.4.2 One Heteroatom Adjacent to a Ring Junction

4.4.2.1 Three- and Four-Membered Rings

4.4.2.1.1 Three-membered rings

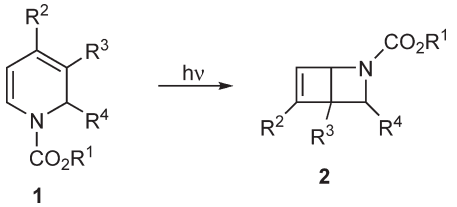
Fused-ring three-membered heterocycles fall into three classes:

1. In the majority of cases the fused ring is saturated or partially saturated: the synthetic methods utilized for the corresponding nonfused systems apply.
2. Compounds of the benzene oxide and benzene imide types are tautomeric with, and generally exist predominantly as, the seven-membered oxepin and azepine rings (see Sections 2.5.5.2 and 3.5.2.2). For arene oxides and related derivatives see <CHEC-III(1.04.2.5)243>.
3. True fused-ring oxirenes and thiirenes are known only as intermediates (see <CHEC-III(1.04.3)289>).

4.4.2.1.2 Four-membered rings

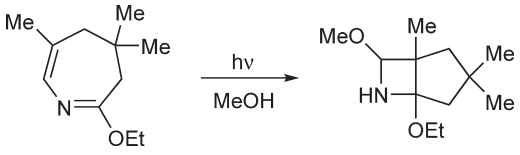
1. Azetidines, azetidinones. Synthetic routes to penicillins <CHEC-III(2.03.11)213>, cephalosporins <CHEC-III(2.02.6.3)135>, and other fused azetidines <CHEC-III(2.04.9)269> are described in the cited CHEC-III chapters.

   Photochemically induced valence bond isomerism of other heterocycles is a useful method for the preparation of fused azetidines <CHEC-III(2.04.10)286>. Ring contraction of 1,2-dihydropyridines **1** is a convenient route to 2-azabicyclo[2.2.0]hex-5-enes **2** (**Scheme 1**) <2001JOC1805, 2001JOC1811, 2005JOC590>, and **Scheme 2** illustrates the conversion of a seven-membered ring into a 4,5-fused derivative <1971JOC1934>. Benzazetidines **3** are available by ring contraction as shown in **Scheme 3** <1980CC471>. Another convenient approach to benzazetine derivatives **5** consists of intramolecular iodoamination of *o*-(acylamino)styrene derivatives **4** (**Scheme 4**) <2005BCJ886>.

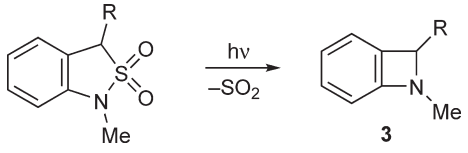


1 **2**

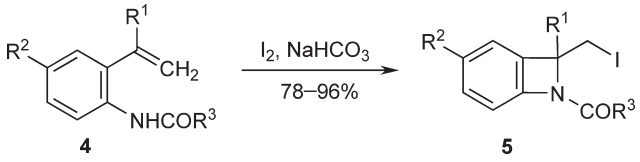
Scheme 1



Scheme 2

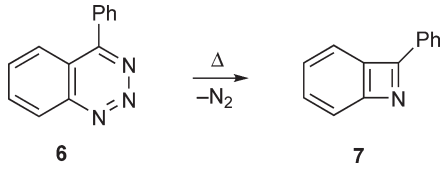


Scheme 3

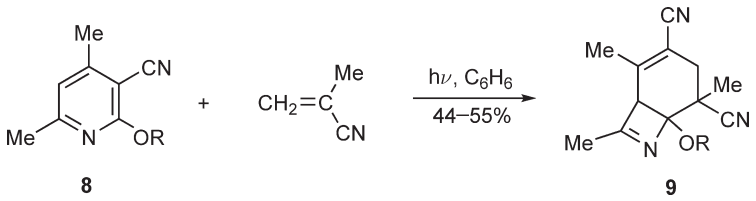


Scheme 4

2. Benzazetes **7** are obtained by thermolysis of 1,2,3-benzotriazines **6** (**Scheme 5**) <1975J(P1)45>. Photocycloaddition of 2-alkoxy-3-cyanopyridines **8** with methylacrylonitrile yields a bicyclic [2 + 2] cycloadduct intermediate followed by rearrangement to give product **9** in moderate yield (**Scheme 6**) <1996CC1349>.

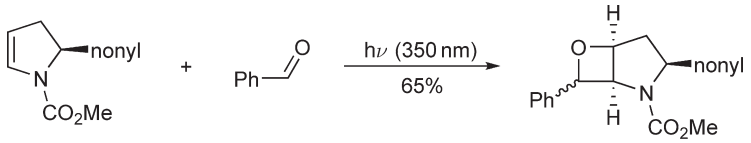


Scheme 5



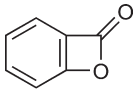
Scheme 6

3. The synthesis of fused oxetane derivatives *via* the Paterno-Bchi cycloaddition of carbonyls and alkenes is discussed in detail in <CHEC-III(2.06.9)372>; a representative example is shown in **Scheme 7** <2001CEJ4512>. See also Sections 3.3.1.8.3 and 3.4.1.10.5 for the preparation of fused oxetanes and azetdines by [2 + 2] cycloaddition reactions. Benzoxetan-2-one **10** has been prepared in an argon matrix by CO_2 loss from phthaloyl peroxide <1973JA4061>.
4. The preparation of fused thietane derivatives is discussed in <CHEC-III(2.08.9)442>.



endo : *exo* > 4.5:1

Scheme 7

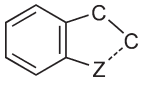


10

4.4.2.2 Five-Membered Rings

4.4.2.2.1 Survey of syntheses for indoles, benzofurans, and benzothiophenes

We deal successively with methods to construct the Z–C(2) (**11**), the ring–C(3) (**12**), the C(2)C(3) (**13**) and the ring–Z (**14**) bonds, and methods from other heterocycles. **Table 1** gives an overview of the most important methods for preparing these compounds.



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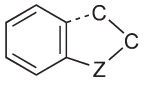

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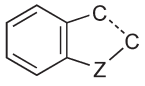
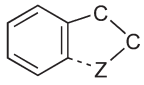


13



14

Table 1 Important ring syntheses for indoles, benzo[*b*]furans, benzo[*b*]thiophenes, and their derivatives

Ring	*Synthesis type*	*Synthesis name*	*Section*
Indoles	**11**	Nenitzescu	4.4.2.2.2.3
	11	Reissert	4.4.2.2.2.4
	11	LeimgruberBatcho	4.4.2.2.2.4
	12[a]	Fischer	4.4.2.2.3.1
	12	Bischler	4.4.2.2.3.3
	12	Gassman	4.4.2.2.3.4
	13	Madelung	4.4.2.2.4.1
	12	Heck cyclization	4.4.2.2.3.5
	14	HemetsbergerKnittel	4.4.2.2.5
Benzo[*b*]furans and benzo[*b*]thiophenes	**11**		4.4.2.2.2.4, 4.4.2.2.2.5
	12		4.4.2.2.3.2, 4.4.2.2.3.3, 4.4.2.2.3.4
	13		4.4.2.2.4.2
Indolines and analogues	**11**		4.4.2.2.2.1
Indoxyls	**12**		4.4.2.2.3.4
Oxindoles	**11**		4.4.2.2.2.2
	12	Brunner	4.4.2.2.3.7
Indolenines	**12**[a]	Fischer	4.4.2.2.3.1
Isatins	**12**		4.4.2.2.3.8

[a]Classified under type **12** from the point of view of precursors although mechanistically should strictly be type **11** for the indole ring-forming step.

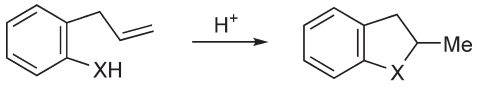
4.4.2.2.2 Ring closure by formation of Z-C(2) bond

1. Indolines **16** (Z = NH) and their S- and O-analogues can be prepared from -substituted -phenylethyl bromides **15** which cyclize spontaneously, on heating or on treatment with alkali (**Scheme 8**).

   The intramolecular addition of the heteroatom to a suitably disposed double bond is the basis of a variety of ring syntheses (**Scheme 9**). The cyclization of *o*-allylphenols to 2,3-dihydrobenzofurans **17** **18** (X = O) frequently accompanies the Claisen rearrangement of allyl aryl ethers, and is promoted by acid catalysis <1968JCC1837> or by transition metals, e.g., **Scheme 10** <2005TL1237, 2006SL1278, CHEC-III(2.07.7.1)554>. 2,3-Dihydrobenzothiophenes <1966JOC413> and 2,3-dihydrobenzoselenophenes <1967ZOR597> have been obtained through analogous

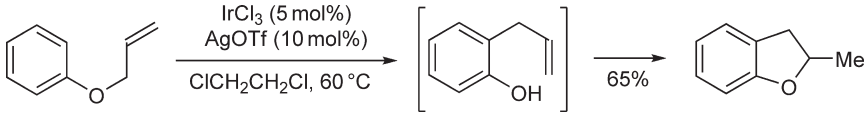
15 16

Scheme 8



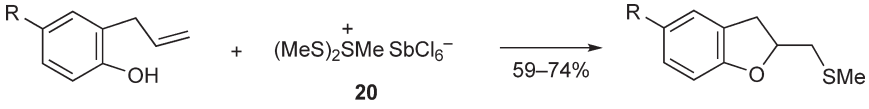
17 18

Scheme 9



Scheme 10

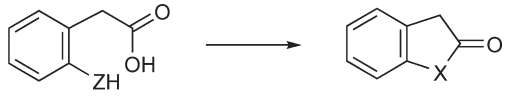
cyclizations **17** **18** (X = S, Se). *o*-Allylanilines can be converted into indolines **17** **18** (X = NH) <1961JA3319>. The employment of nonprotic electrophiles in a similar cyclization, as illustrated by the reaction of *o*-allylphenols **19** with methyl(bismethylthio)sulfonium salt **20** leading to 2,3-dihydrobenzofurans **21** (**Scheme 11**), leaves a useful point of departure for further transformations <1981J(P1)3106>.



19 R = H, Me, Cl, NO_2 **20** **21**

Scheme 11

2. Oxindoles **23** (Z = NH) and the corresponding S- and O-heterocycles are formed by spontaneous cyclization of acids of type **22** (**Scheme 12**).

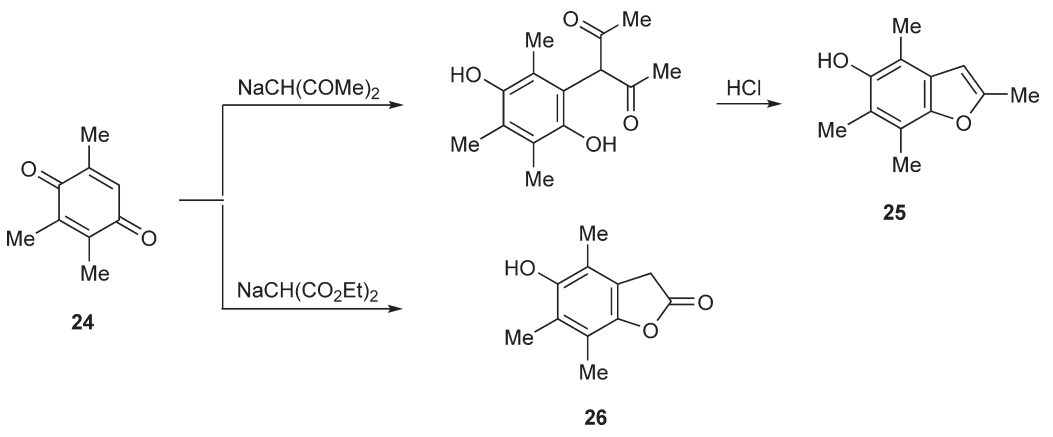


22 **23**

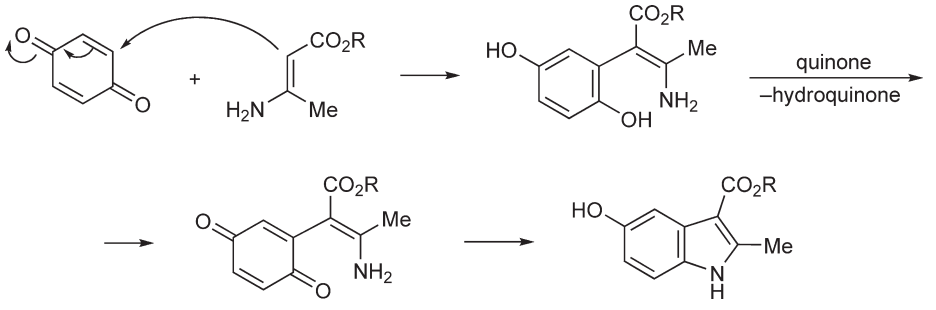
Scheme 12

3. The addition of -keto carbanions to *p*-quinones **24** having at least one unoccupied nuclear position provides syntheses of benzo[*b*]furans **25** and benzo[*b*]furanones **26** (**Scheme 13**) <1940JA133>. In the Nenitzescu indole synthesis, a quinone is reacted with a -aminocrotonate (e.g. **Scheme 14**) or similar enamine derivatives <CHEC-III(3.03.6)315, 1996JOC9055, 2005JME635, 2001JOC4457>. The use of 1,1-diamines, e.g., **27**, allows direct preparation of 2-aminoindole derivatives such as the system **28** in modest yields (**Scheme 15**) <2005S2414>. This approach has been employed in the preparation of an extended set of related 2-aminoindoles for evaluation as inhibitors of human 5-lipoxygenase <2006JME4327>.
4. Fully aromatic derivatives result from the cyclizations of compounds of type **29** or of equivalents which can be constructed in a variety of ways, and are often not isolated.

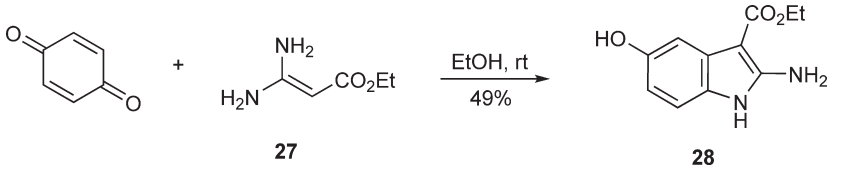
   Amino groups in precursors **29** are frequently derived from nitro groups. In the Reissert indole synthesis, *o*-nitrotoluene undergoes Claisen condensation with oxalic ester to yield the pyruvic ester **30**. When this is reduced with Zn-AcOH the corresponding amino derivative spontaneously cyclizes to the 2-ethoxycarbonylindole **31**



Scheme 13

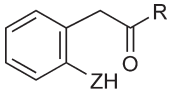


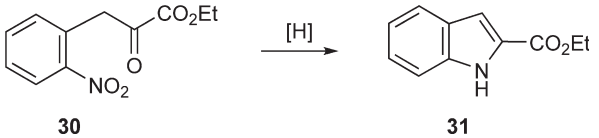
Scheme 14



Scheme 15

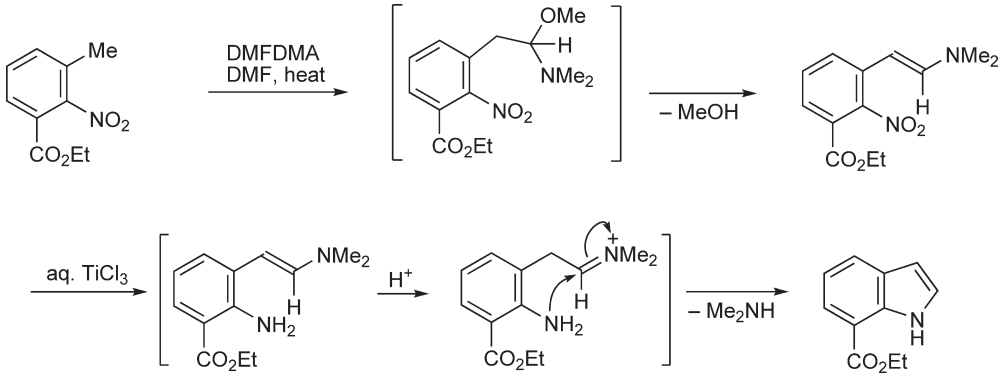
(**Scheme 16**) <1963OS(43)40>. Numerous examples of similar reductive cyclizations of appropriate nitroarenes leading to derivatives of indole are discussed in CHEC-III <CHEC-III(3.03.2)284>.





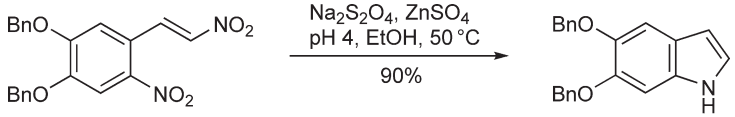
Scheme 16

The LeimgruberBatcho indole synthesis depends on the acidity of methyl groups *ortho* to aromatic nitro to allow introduction of the future indole -carbon as an enamine and thence the synthesis of pyrrole-ring-unsubstituted indoles (**Scheme 17**). Condensation with hot dimethylformamide dimethyl acetal (DMFDMA) leads to an enamine; the condensation can be enhanced by microwave irradiation <CHEC-III(3.03.5)300>. Subsequent reduction of the nitro group, usually in acid conditions, leads directly to the hetero-ring-unsubstituted indole probably *via* a C-protonated amino-enamine. The LeimgruberBatcho reaction has been employed for the preparation of various indoles, for example, ethyl 6-aminoindole-7-carboxylate <1996JOC1155>, 6-chloro-5-fluoroindole <2004SC2295>, 6-fluoroindole <2006EJO2956>, masked 5-formylindole <2005JHC137>, pyrrolo[2,3-*b*]xanthone system <2005SC2695>, indole possessing a Weinreb amide moiety at C(4) <1996TL3067>, and 6-iodo-4-trifluoromethylindole <2002T3605, CHEC-III(3.03.5)300>.



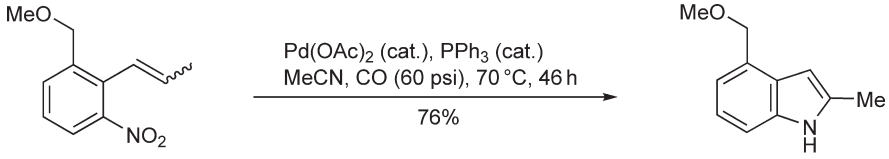
Scheme 17

Reductive cyclization of nitrostyrene precursors has also proven to be a useful route to 5,6-dihydroxyindole and its derivatives, as illustrated by the efficient preparation of the system **32** (**Scheme 18**) <1999S793>. A general synthetic approach to indoles involves a palladium-catalyzed reductive cyclization of 2-nitrostyrenes <1997JOC5838>. This procedure was used in the synthesis of several natural products, e.g., 4-(methoxymethyl)-2-methylindole **33** (**Scheme 19**), a constituent of a *tricholoma* species <1999JOC9731, CHEC-III(3.03.2)282>.



32

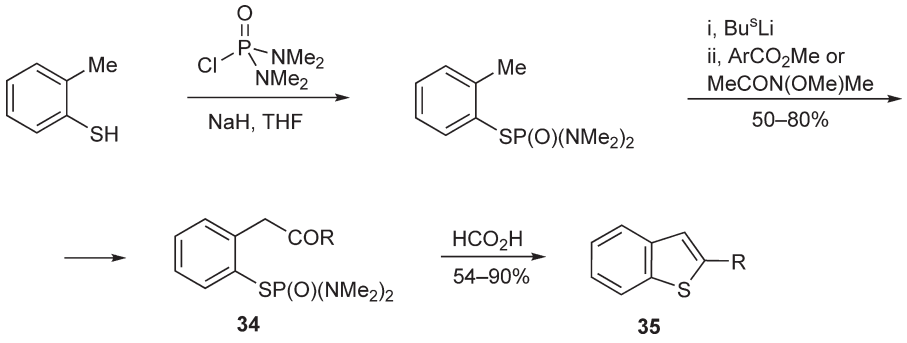
Scheme 18



33

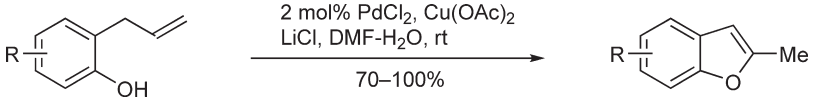
Scheme 19

2-Methyl- and 2-aryl-substituted benzo[*b*]thiophenes **35** can be synthesized in three steps starting from *o*-toluenethiol; this involves the intramolecular addition of thiols, produced by acid hydrolysis, to the carbonyl group in the intermediate product **34** followed by dehydration as the final step (**Scheme 20**) <1991JHC173>.

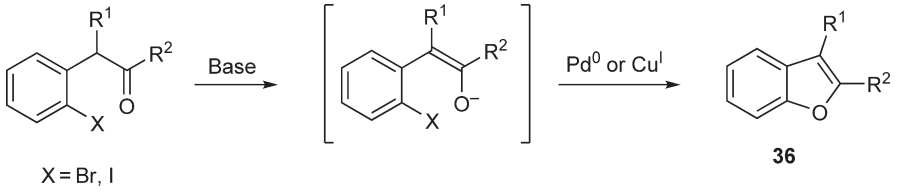


Scheme 20

The cyclization of *o*-allyl- or -vinyl-phenols into benzo[*b*]furans can be effected by palladium catalysts <CHEC-III(3.07.5.1)546>. A convenient method involves Pd(II)-catalyzed oxidative cyclization of 2-allylphenols (**Scheme 21**) <1998JOM(560)163>. Intramolecular O-arylation with enolates using palladium <2006T11513> or copper <2005JOC6964> catalysts gives benzofurans **36** in good to excellent yields (**Scheme 22**). Benzothiophenes can be prepared by a similar Pd(0)-catalyzed cyclization of the analogous thio-enolates generated from the appropriate thio-ketones <2006T11513>.

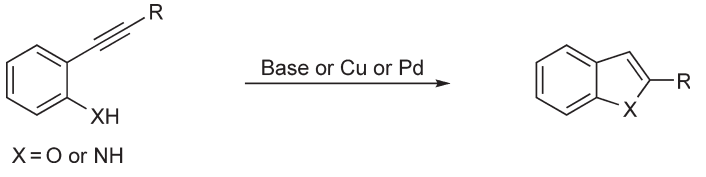


Scheme 21

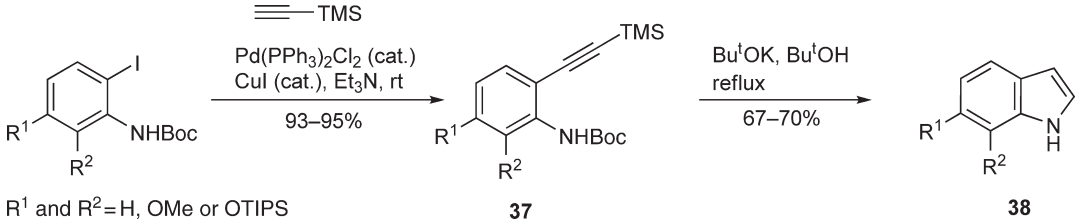


Scheme 22

5. A general and convenient route to 2-substituted benzofurans <CHEC-III(3.07.5.1)545> or indoles <CHEC-III(3.03.2)278> is based on intramolecular annulation of 2-alkynylphenols or 2-alkynylanilines (**Scheme 23**), which are in turn readily available *via* alkynylaryl cross-coupling reactions. In a representative example, base-induced cyclization of the precursors **37** with concomitant elimination of the TMS-moiety affords the indoles **38** in good yields (**Scheme 24**) <1997JOC6507>.

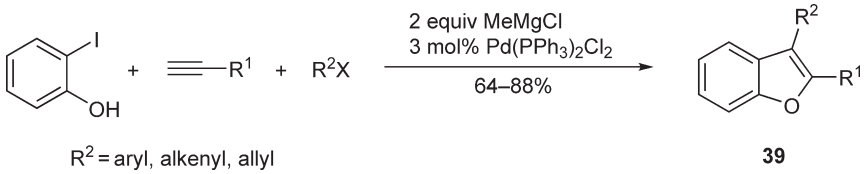


Scheme 23



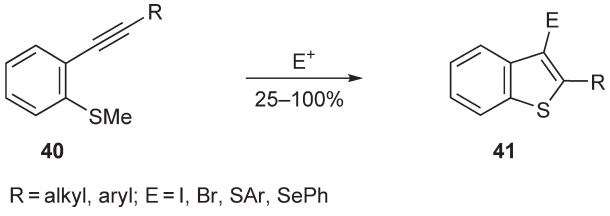
Scheme 24

The cross-coupling reactions can be combined with catalytic cyclization of 2-alkynylphenols in a one-pot, multi-component coupling procedure leading to 2,3-disubstituted benzofurans **39** as shown in **Scheme 25** <CHEC-III (3.07.5.1)545, 2001CC1594>.



Scheme 25

The electrophile-induced cyclization of 2-ethynylaryl sulfides **40** provides a general approach to 3-substituted benzo[*b*]thiophenes **41** (**Scheme 26**) <2002JOC1905, 2005JOC9985, CHEC-III(3.11.2.1.5)855>. A similar cyclization induced by halogen or selenium electrophiles has also been used for the preparation 3-substituted benzo[*b*]furans from 2-alkynylphenols or 2-alkynylphenol ethers <1999SL1432, 2005EJO3334, 2005JOC10292>.

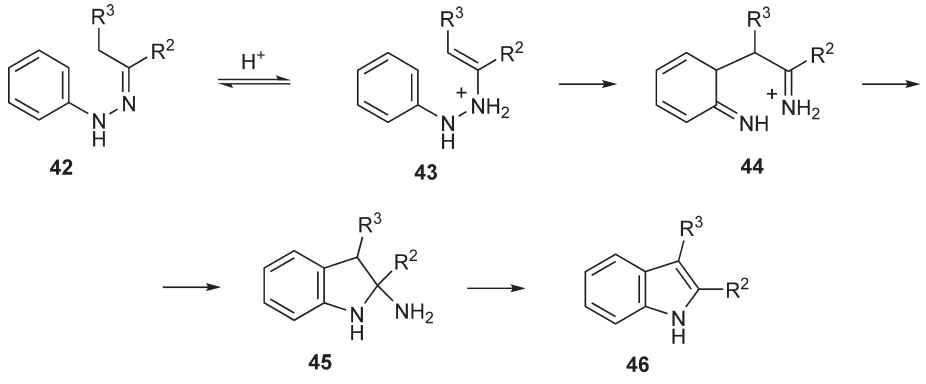


Scheme 26

For ring closure of an *o*-substituted azide on to a double bond see Section 3.3.3.4.3.

4.4.2.2.3 Ring closure by formation of ringC bond

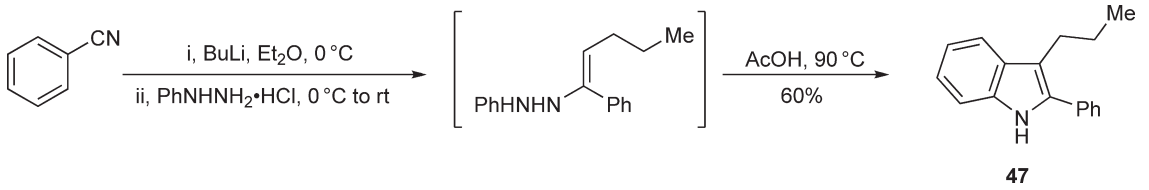
4.4.2.2.3.1 The Fischer indole synthesis. The Fischer acid-catalyzed conversion of an *N*-arylhydrazone **42** into an indole is one of the most powerful and versatile methods for the preparation of indoles <CHEC-III(3.03.6)306, 1993OPP607>. The mechanism involves a [3,3] sigmatropic Claisen-type rearrangement of a protonated enehydrazine tautomer **43** to give intermediate **44**, which spontaneously cyclizes by loss of ammonia, probably *via* indoline **45**, to an indole **46** (**Scheme 27**). For unsymmetrical ketones, two isomeric indoles are possible and the general result is that the indole derived from the more stable (usually the more highly substituted) enehydrazine is formed.



Scheme 27

The Fischer cyclization is very versatile in terms of the functional groups which can be tolerated at positions 2 and 3, and in the aromatic ring. The reaction is somewhat retarded by strong electron-withdrawing groups, but even nitroaryl hydrazones can be cyclized under appropriate conditions <1997T8853>. A variety of protonic and Lewis acids can be used to effect the cyclization.

Several modern adaptations of the Fischer indole synthesis have been devised, employing solid phase <2005TL911> or dendrimer <1996PNA10012> supported ketones, as well as immobilized hydrazines <2003CC1822> or hydrazones <2004AGE224>. A microwave-assisted Fischer indolization has also been reported <2004TL8831, 2005EJO3672>. A one-pot approach features construction of hydrazones by treatment of nitriles with organometallic reagents, followed by introduction of hydrazines, and final cyclization to the target indoles, giving, for example, the product **47** (**Scheme 28**) <CHEC-III(3.03.6)308>.

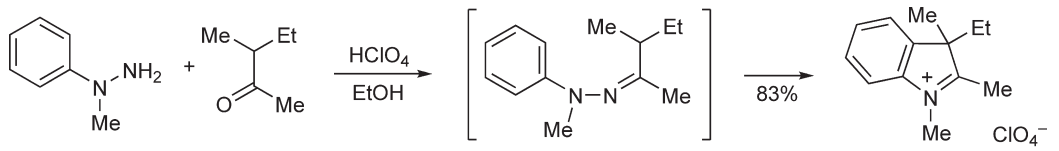


47

Scheme 28

The ketone component can be replaced by cyclic enol ethers, which react with phenylhydrazines to give phenylhydrazones, as has been demonstrated by a large-scale synthesis of 5-fluorohomotryptophol derivatives from 4-fluorophenylhydrazine hydrochloride and tetrahydropyran <1997OPD300>. The Grandberg modification of the Fischer synthesis involves the use of an acetal as the ketone equivalent <2001T1041>.

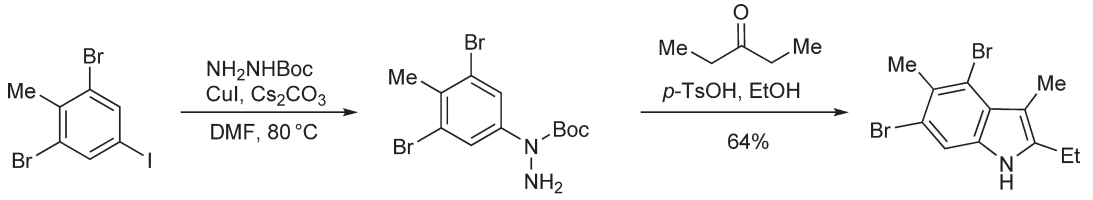
The use of branched ketones enables preparation of 3*H*-indolium salts as illustrated by the synthesis of product **48** (**Scheme 29**) <2000JHC1571>. The hydrazine components can also be generated from anilines in a one-pot variant of this route <2004JHC103>.



48

Scheme 29

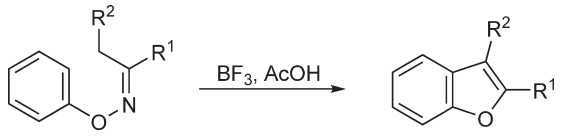
Other variations involve transition metal-catalyzed generation of the required hydrazones <CHEC-III(3.03.6)309>. In a representative example, the iodoarene derivative **49** was converted to the intermediate **50**, which was thereafter subjected to Fischer conditions rendering the indole **51** in a good overall yield (**Scheme 30**) <2004JOC3336>.



49 **50** **51**

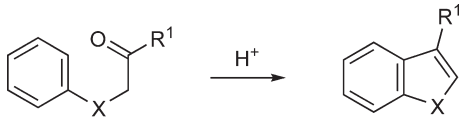
Scheme 30

4.4.2.2.3.2 Benzofurans. A route similar to the Fischer indole synthesis, for the preparation of benzofurans from *o*-aryloximes, is exemplified in **Scheme 31** <1967TL2867>.



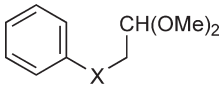
Scheme 31

4.4.2.2.3.3 Bischler indole synthesis and related methods for O- and S-analogues. The Bischler synthesis of indoles is the acid catalyzed cyclization of -arylamino ketones **52** (X = NR) shown in **Scheme 32** <1892CB2860>. -Aryloxy and -arylthio ketones **52** can be cyclized similarly to benzo[*b*]furans **53** (X = O) <1900LA(312)237> and benzo[*b*]thiophenes **53** (X = S) <1970JCC2621>, respectively. Concurrent migrations of groups occur from position 3 to position 2, especially under vigorous conditions. To obtain indoles <1981JOC778>, benzo[*b*]furans, and benzo[*b*]thiophenes <1971T1253> unsubstituted at positions 2 and 3, the cyclization of the acetals **54** (X = NR, O, S) by polyphosphoric acid catalysis is used.



52 X = NR, O, S **53**

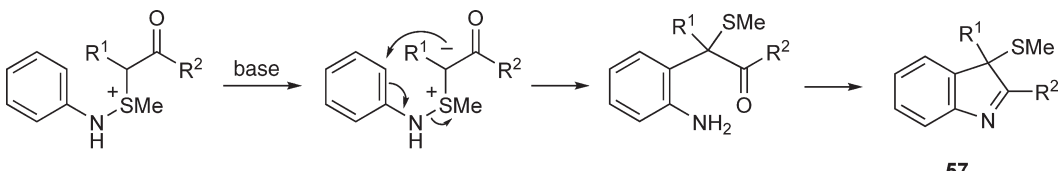
Scheme 32



54

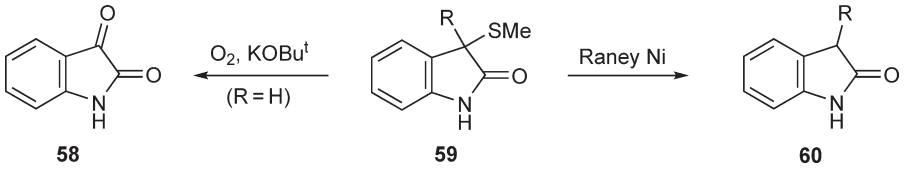
The classical Bischler reaction has received relatively little attention in comparison with other methods for indole synthesis because of the harsh reaction conditions that it requires. The milder modifications involve the use of lithium bromide as a catalyst <2005T77> and a procedure under microwave irradiation conditions <2006SL91>.

4.4.2.2.3.4 Gassman synthesis of indoles and benzo[*b*]furans. The Gassman synthesis of indoles depends on a sigmatropic rearrangement to generate the ring-carbon bond. An *N*-chloroaniline reacts with a -keto sulfide to form a sulfonium salt **55**; this is deprotonated to an ylide **56** which then rearranges and cyclizes to **57**; desulfurization then gives an indole (**Scheme 33**) <1974JA5512>. Likewise, an -ethoxycarbonyl sulfide **55** (R^2 = OEt) in place of the -keto sulfide leads *via* **59** to an oxindole **60** or isatin **58** (**Scheme 34**) <1980JCR(S)347>. This synthetic approach has been extended to benzo[*b*]furans **61** (**Scheme 35**) <1975SC325>.

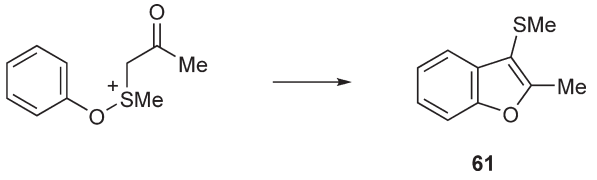


55 **56** **57**

Scheme 33

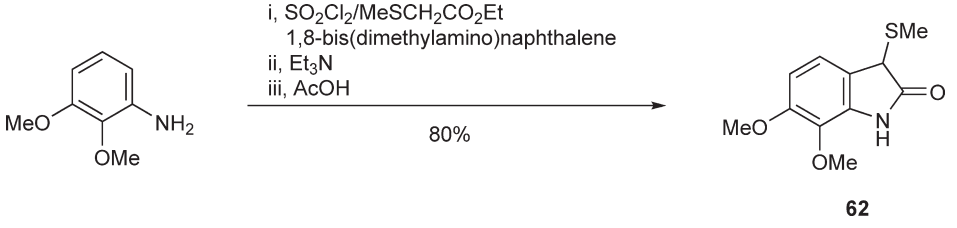


Scheme 34



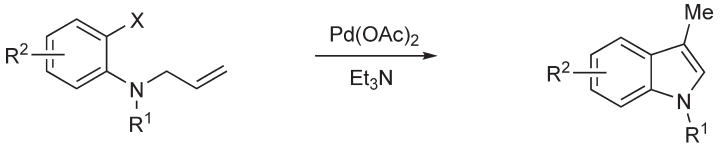
Scheme 35

The Gassman synthesis has been utilized for preparation of a 6,7-dihydroxyoxindole unit of the natural product paraherquamide A *via* the key intermediate product **62** (**Scheme 36**) <1996JOC8696, CHEC-III(3.03.6)312>.



Scheme 36

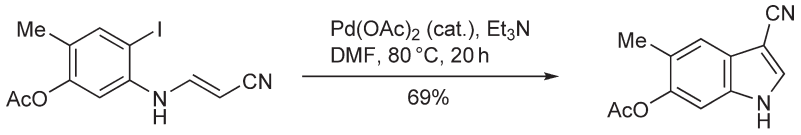
4.4.2.2.3.5 Indole synthesis by intramolecular Heck reaction. The intramolecular Heck cyclization of *N*-allyl-*o*-haloanilines is an effective route to the synthesis of indole derivatives <CHEC-III(3.03.4)293>. The reaction was initially carried out using $Pd(OAc)_2$, Ph_3P, and triethylamine <1980JOC2709>. An examination of alternative bases found CH_3CO_2Na and Na_2CO_3 to be preferable in some cases <1987TL5291>. A water-soluble phosphine ligand that permits mild cyclization conditions was introduced <1992SL715>. The reaction presumably requires regeneration of palladium(0) *in situ* to maintain the catalytic cycle, which involves oxidative addition at the aryl halogen bond. The reaction proceeds by 5-*exo-trig* cyclization *via* indolinylmethylpalladium and *exo*-methyleneindoline intermediates. The latter are sometimes isolated <1993J(P1)1941>. The reaction is applicable to both ring- and N-substituted indoles (**Scheme 37**) <1991JOC3048, 1992TL8011, CHEC-III(3.03.4)293>.



X = Br, I; R^1 = H, SO_2Me, etc.; R^2 = H, OMe, NO_2, etc.

Scheme 37

The intramolecular Heck reaction and similar transition metal-catalyzed cyclizations are commonly used in organic synthesis as illustrated by the preparation of 3-cyanoindole **63** (**Scheme 38**) <2004BMC2867>. Similar Heck cyclizations have also been employed in the syntheses of tryptophan derivatives <1996T14975>. Solid phase protocols based



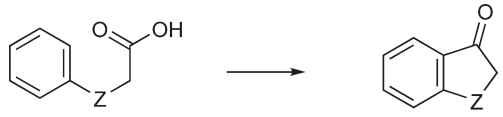
63

Scheme 38

on Heck reactions providing access to indole-3-carboxylates <2002JCO191> or indole-2-carboxylates <2002CC210> are also available.

Intramolecular Heck reactions have proved to be useful for asymmetric synthesis of various 3,3-substituted oxindoles <1998JA6488>, 3-alkyl-3-aryloxindoles <2003JA6261>, in the construction of the skeleton of the antitumor antibiotic CC-1065 <1998CEJ1554>, as well as other 1,2-dihydro-3*H*-benzo[*e*]indoles <2002JOC8958>. A strategy based on this type of annulation involving generation of the precursors by a four-component reaction between acrylic aldehydes, 2-bromoanilines, carboxylic acids, and isocyanides has also appeared <2006TL4683>.

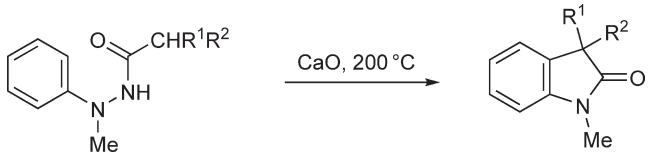
4.4.2.2.3.6 Indoxyls and their analogues. Indoxyls and their oxygen and sulfur analogues **65** (Z = NH, O, S) are prepared by the cyclization of anilino-, phenoxy-, and phenylthio-acetic acids **64**, respectively, with phosphonium anhydride <1989JOC1144> (for Z = NH), P_2O_5 (for Z = O), and H_2SO_4 (for Z = S) (**Scheme 39**).



64 Z = NH, O, S **65**

Scheme 39

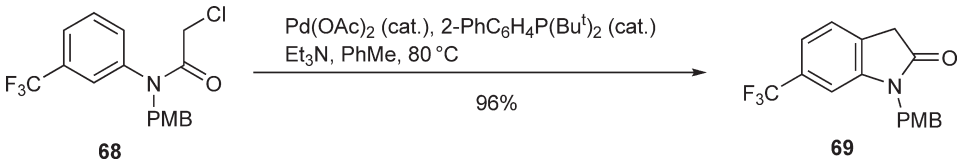
4.4.2.2.3.7 Oxindoles. Under much more forcing conditions than those used to convert hydrazones in the Fischer indole synthesis, phenylhydrazides **66** give oxindoles **67** (Brunner synthesis) (**Scheme 40**).



66 **67**

Scheme 40

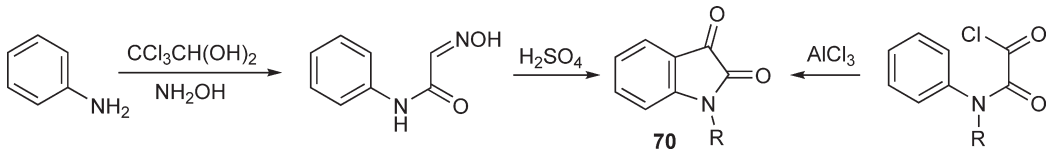
Palladium-catalyzed annulation of -chloroacetanilides provides a general approach to oxindoles, as exemplified by the conversion of the substrate **68** into the product **69** (**Scheme 41**) <2003JA12084, CHEC-III(3.03.4)297>.



68 **69**

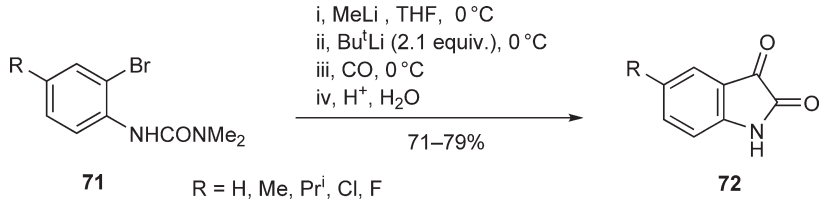
Scheme 41

4.4.2.2.3.8 Isatins. Intramolecular acylation is involved in both syntheses of isatins **70**, as shown in **Scheme 42** <1975AHC (18)1>.



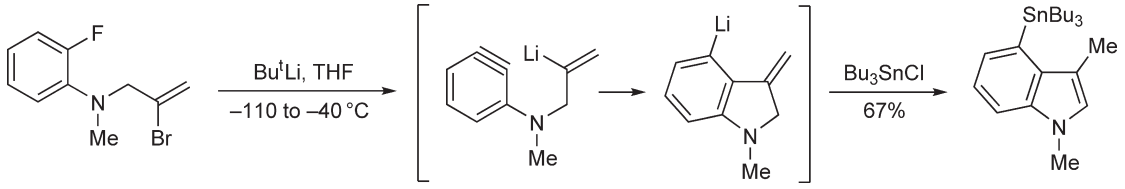
Scheme 42

A set of isatins **72** have been prepared by a route involving dilithiation of the starting ureas **71**, followed by introduction of carbon monoxide, which serves as a source for the carbon atom at the 3-position (**Scheme 43**) <2003S2047, CHEC-III(3.03.11)334>.

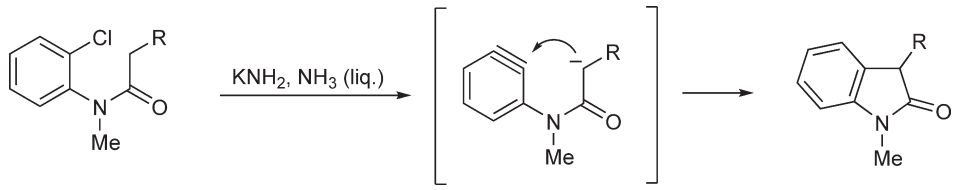


Scheme 43

4.4.2.2.3.9 Reaction *via* arynes. The intramolecular addition of a carbanion to an aryne has been applied to the synthesis of indoles (e.g., **Scheme 44**) <2002CEJ2034, CHEC-III(3.03.4)297> and oxindoles (**Scheme 45**) <1963JOC1>.

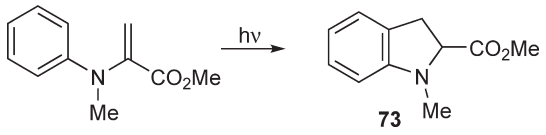


Scheme 44

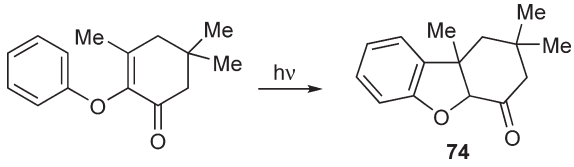


Scheme 45

4.4.2.2.3.10 Photochemically mediated cyclizations. These have been used to produce oxindoles <1980JA3646>, indolines **73** (**Scheme 46**) <1980T1757>, and 2,3-dihydrobenzofurans **74** (**Scheme 47**) <1978JA2150>.



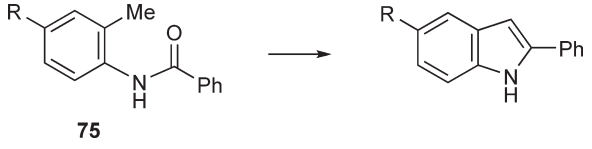
Scheme 46



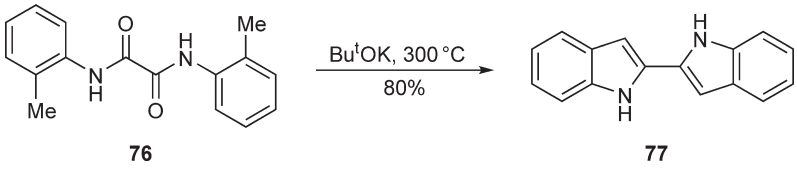
Scheme 47

4.4.2.2.4 Ring closure by formation of C(2)C(3) bond

4.4.2.2.4.1 C(3) as nucleophile. The Madelung synthesis of indoles from *N*-acyl-*o*-toluidines **75** (**Scheme 48**) originally necessitated heating with sodamide at 250°C; however, the stronger bases *n*-butyllithium or lithium diisopropylamide (LDA) cause reaction at 20°C <1981JOC4511>. The Madelung cyclization is sometimes a useful approach to indoles lacking sensitive functional groups <CHEC-III(3.03.3)288>. For example, heating of the diamide **76** with potassium *t*-butoxide provides the method of choice for the preparation of 2,2-biindolyl **77** (**Scheme 49**) <1995T5631>. The Madelung approach has also been used for synthesis of fused 2-methylindole derivatives <2002TL4707>, whereas a modified form involving cyclization of amides derived from (2-aminophenyl)acetonitrile has been adapted to solid phase <2002TL5189>.

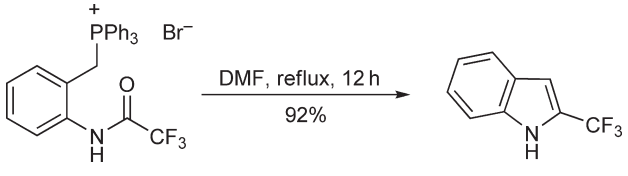


Scheme 48



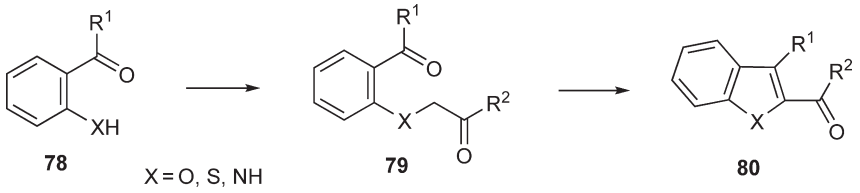
Scheme 49

The ring closure involving an intramolecular Wittig reaction is exemplified by **Scheme 50** <CHEC-III(3.03.3)288, 1996J(P1)1261>.

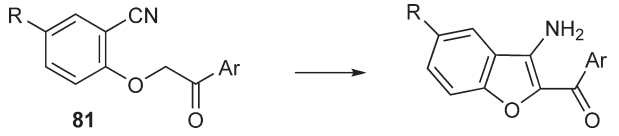


Scheme 50

4.4.2.2.4.2 C(2) as nucleophile. These include useful ring syntheses for benzo[*b*]-fused compounds. The sequence **78 79 80** (**Scheme 51**) has been extensively applied to obtain benzo[*b*]furans <1948JCS2254>, benzo[*b*]thiophenes <1931LA(488)259>, and less frequently, indoles <1927JCS1937>. Corresponding nitriles (e.g., **81**) afford 3-amino derivatives (**Scheme 52**).

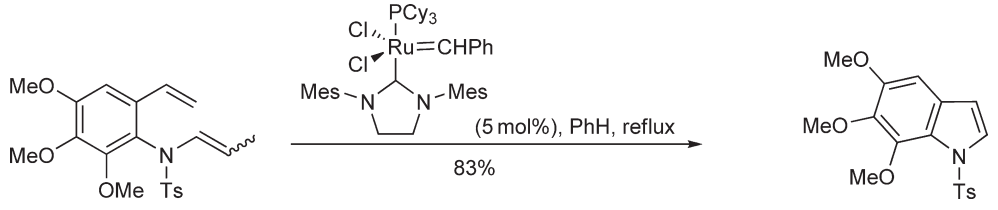


Scheme 51

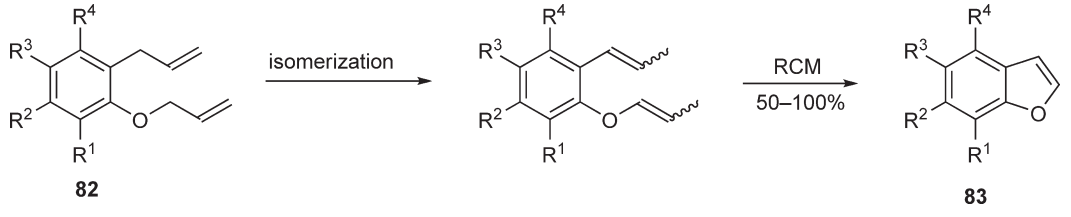


Scheme 52

4.4.2.2.4.3 Transition metal-catalyzed cyclizations. The ring-closing metathesis reaction (RCM) has been utilized in the indole ring construction as illustrated in **Scheme 53** <2006JOC4255, CHEC-III(3.03.3)289>. Likewise, highly substituted benzofurans **83** have been synthesized from the corresponding substituted 1-allyl-2-allyloxybenzenes **82** using a ruthenium-mediated C- and O-allyl isomerization followed by ring-closing metathesis (**Scheme 54**) <2005T7746, CHEC-III(3.07.5.1)546>.

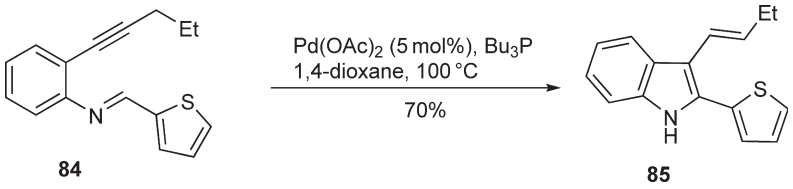


Scheme 53



Scheme 54

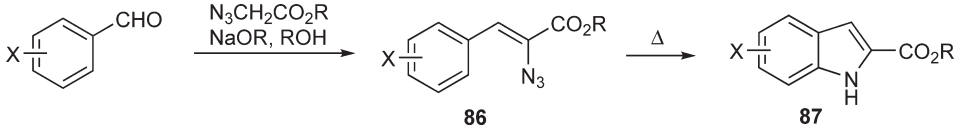
Palladium-catalyzed intramolecular cyclization of the imine **84**, which is available from the corresponding *o*-alkynylaniline and thiophene-2-carboxaldehyde, affords the indole **85** (**Scheme 55**). Several other related indoles have been prepared in this manner by varying the aldehyde or *o*-alkynylaniline components <2000JA5662, CHEC-III (3.03.3)288>.



Scheme 55

4.4.2.2.5 Ring closure by formation of ringZ bond

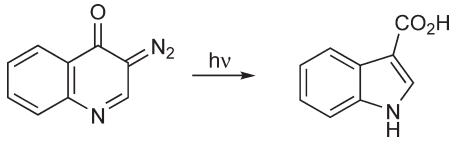
The HemetsbergerKnittel indole synthesis (**Scheme 56**) requires simple and readily available starting materials, tolerates a number of useful functional groups, and often proceeds in good overall yields <CHEC-III(3.03.2)275>. The standard procedure involves condensation of a benzaldehyde with an alkyl azidoacetate in the presence of a base, and subsequent cyclization of the resulting azidocinnamates **86** to the corresponding alkyl indole-2-carboxylate **87** by a thermally induced nitrene insertion (**Scheme 56**). A mechanistically related formation of indoles featuring nitrene insertion has been reported to occur upon thermolysis of phenyl azirines <2006JA10589>.



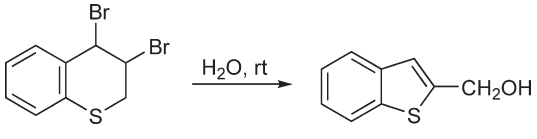
Scheme 56

4.4.2.2.6 From other heterocycles

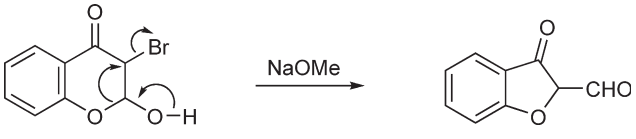
Preparations from six-membered rings by reactions analogous to those known for acyclic compounds are illustrated by the Wolff rearrangement (**Scheme 57**) and analogues of the Meerwein rearrangement shown in **Scheme 58** <1972J(P1)787> and **Scheme 59** <1975JHC981>.



Scheme 57

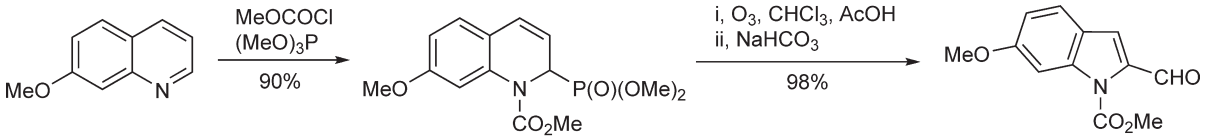


Scheme 58



Scheme 59

The quinoline **88** has been transformed into the intermediate **89**, which was subsequently ring-opened by ozonolysis, followed by base-induced ring closure to the indole-2-carboxaldehyde **90** (**Scheme 60**) <2002TL5295>. Several useful 4-substituted indoles have also been prepared by ring-contraction of *N*-alkyl-5-aminoisoquinolinium salts with the system $NaHSO_3/Na_2SO_3$ <2000JHC1293, CHEC-III(3.03.10)333>.



88 **89** **90**

Scheme 60

4.4.2.3 Six-Membered Rings

4.4.2.3.1 Survey of synthetic methods for quinolines, benzo[*b*]pyrans, and their derivatives

The important methods involve ring closure of *o*-substituted anilines and phenols (type **91**) and cyclization of *o*-unsubstituted aniline, etc., derivatives (type **92**). Additionally, cycloadditions and transformations from other heterocycles are considered. **Table 2** gives an overview of the important methods for preparation of derivatives of these types.

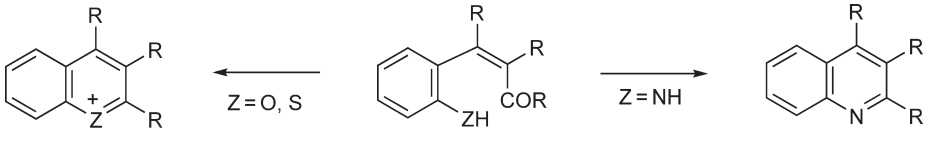
91 **92**

Table 2 Important ring syntheses for quinolines, benzo[*b*]pyrans, benzo[*b*]thiins, and their derivatives

Ring	*Synthesis type*	*Synthesis name(s)*	*Section*
Quinolines	**91**	Friedlȍnder, Pfitzinger	4.4.2.3.2.1 (a, b)
	92	Skraup, Doebner-von Miller, Baeyer, Riehm	4.4.2.3.3.2
Quinolones	**91**	Camps	4.4.2.3.2.2
	92	-Keto ester	4.4.2.3.3.1 (a)
Tetrahydroquinolines	**92**		4.4.2.3.3.3 (a)
Benzo[*b*]pyryliums	**91**		4.4.2.3.2.1 (c)
Coumarin, and chromones	**91**	Kostanecki-Robinson	4.4.2.3.2.1 (d)
Coumarins	**92**	von Pechmann	4.4.2.3.3.1 (b)
Chromones	**92**	Simonis	4.4.2.3.3.1 (b)
Chromans and tetrahydrobenzothiins	**92**		4.4.2.3.3.3 (a)

4.4.2.3.2 Ring closure of *o*-substituted anilines or phenols

4.4.2.3.2.1 From or *via* *o*-substituted cinnamoyl derivatives. *ortho*-Substituted benzenes of type **93** (Z = O, S, NH) can undergo ring closure (**Scheme 61**). Amines of type **93** (Z = NH), which usually cyclize spontaneously, are often prepared *in situ* by reduction of nitro compounds, e.g., *o*-nitrocinnamic acid with $(NH_4)_2S$ gives 2-quinolone.

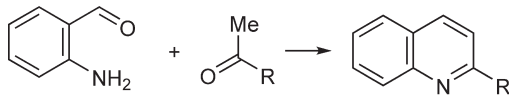


93

Scheme 61

Important reactions that involve an aldol reaction to form the intermediate **93** *in situ* include:

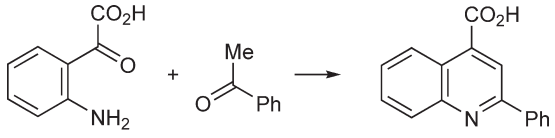
a. The Friedlȍnder synthesis of quinolines **94** from *o*-amino benzaldehydes and ketones (**Scheme 62**) <CHEC-III (7.03.3.3)129>. A convenient modified procedure employs the more stable *o*-aminobenzylalcohols in the presence of oxidants as starting compounds <2001CC2576, 2004TL6029>.



94

Scheme 62

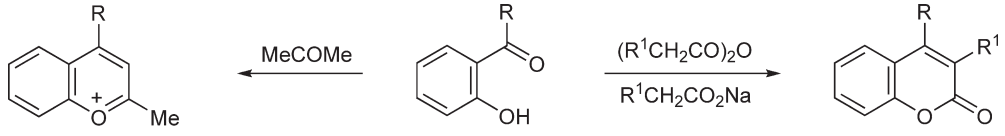
b. The Pfitzinger synthesis of quinoline-4-carboxylic acids (e.g., **96**) from a ketone and isatinic acid **95** (obtained *in situ* from isatin) (**Scheme 63**) <1986JPR100, 2004TL5473>.



95 **96**

Scheme 63

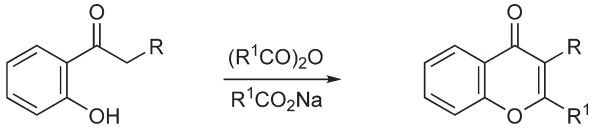
c. The preparation of benzopyrylium ions **97** from ketones and *o*-acylphenols **98** (**Scheme 64**) <CHEC-III(7.08.31.1)673>.



97 **98** **99**

Scheme 64

d. The KostaneckiRobinson synthesis which leads to coumarins **99** (**Scheme 64**) or chromones **100** (**Scheme 65**) <CHEC-III(7.08.16.2)580>.



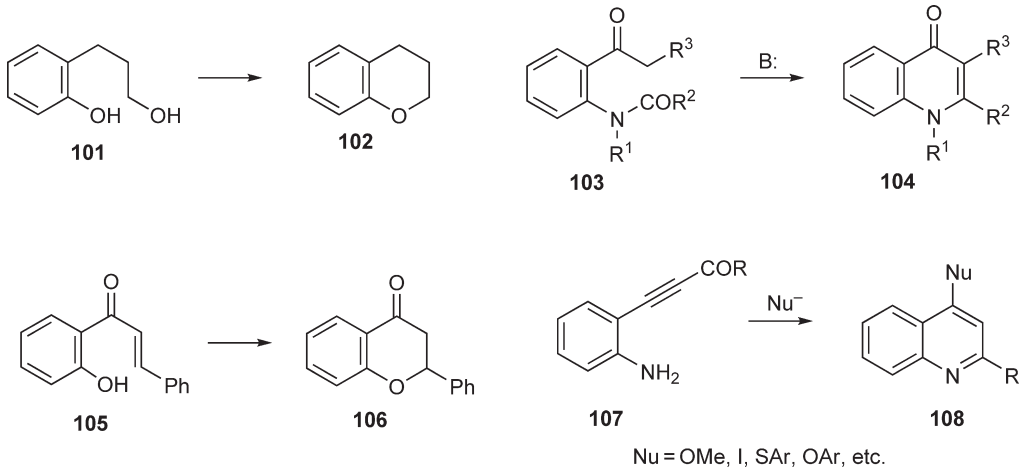
100

Scheme 65

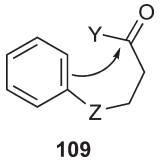
4.4.2.3.2.2 From other *o*-substituted benzenes. Standard reactions of aliphatic chemistry can be applied; for example, chroman **102** can be prepared by ring closure of **101**. 4-Quinolones result from the Camps reaction (**103** **104**), and flavonone **106** is prepared by cyclization of **105**. The nucleophile-induced cyclization of suitably substituted *o*-alkynylanilines **107** provides a general synthetic approach to quinolines **108** (**Scheme 66**) <CHEC-III(7.05.2.1)219, 1999OL1977, 1999T13233>. Similar cyclizations of *o*-alkynylphenols lead to the formation of coumarins <CHEC-III(7.08.14.2)568>.

4.4.2.3.3 Formation of a CC bond by reaction of a multiple bond with a benzene ring

These reactions involve electrophilic attack on a benzene ring, which is activated by the heteroatom Z as in **109**.

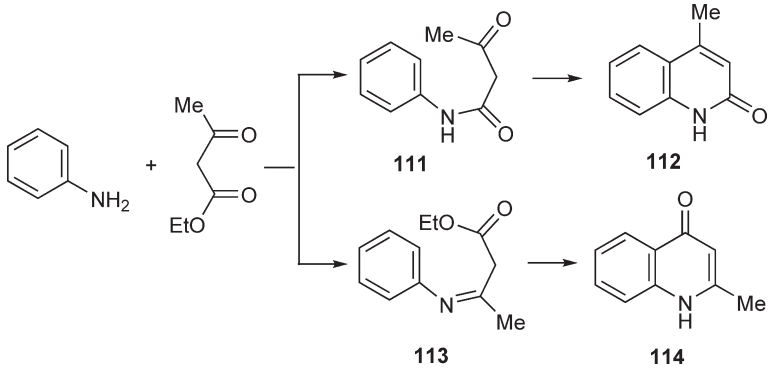


Scheme 66



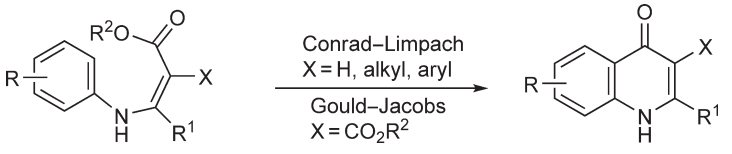
4.4.2.3.3.1 Quinolones, benzopyrones, and benzothiinones.

a. Anilines and -keto esters **110** give either Schiffs bases **113** at 20°C or at 100°C the more slowly forming but more stable amides **111**. Cyclization of the amide **111** with H_2SO_4 at 100°C yields 2-quinolone **112**, whereas the Schiffs base **113** is converted into 4-quinolone **114** at 280°C (**Scheme 67**).



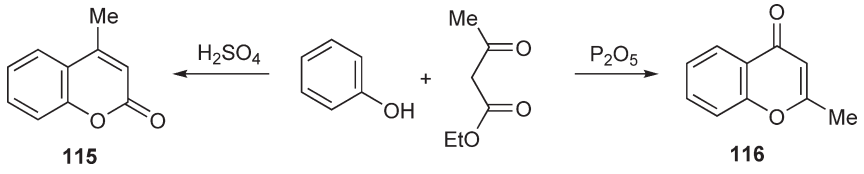
Scheme 67

The frequently used synthesis of 4-quinolinones is the ConradLimpach cyclization <1955OSC593> and its modification due to Gould and Jacobs (**Scheme 68**) <1992T7373>.



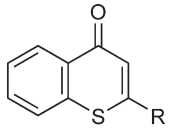
Scheme 68

b. Phenols and -keto esters give either coumarins **115** (von Pechmann reaction <CHEC-III(7.08.14.2)560>) or chromones **116** (Simonis reaction <CHEC-III(7.08.16.2)585>) under the conditions indicated (**Scheme 69**). In modified form the Pechmann reaction can be carried out in refluxing toluene catalyzed by zinc and iodine <2002TL8583> or W/ZrO_2 <2001SC3603>, or under solvent-free conditions in the presence of *p*-TsOH <2001CL110>, titanium(IV) chloride <2005TL3501>, bismuth(III) chloride <2005S1231>, WellsDawson heteropolyacid ($H_6P_2W_{18}O_{62}$ñ24H_2O) <2004TL8935>, indium(III) chloride <2002TL9195>, samarium(III) nitrate hexahydrate <2004TL7999>, sulfamic acid (H_2NSO_3H) <2004SL1909>, and zirconium(IV) chloride <2004SC3997>. The Simonis reaction can also be promoted by microwave irradiation <2005JOC2855>.



Scheme 69

c. Thiophenols and -keto esters give benzothiinones **117** <CHEC-III(7.10.4.3.5)904, 1996JME1975, 2004JME4268>.

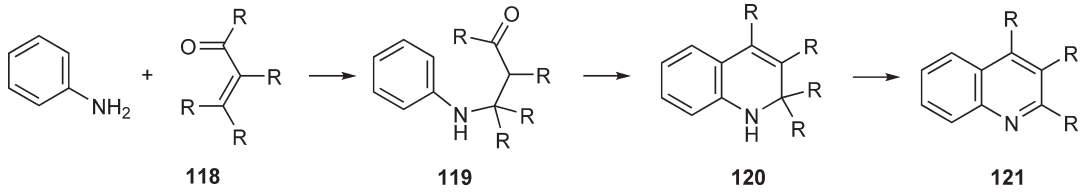


4.4.2.3.3.2 Quinolines. In the reactions listed in **Table 3**, Michael addition of a primary aromatic amine to an ,-unsaturated aldehyde or ketone **118** (prepared *in situ*) gives **119** which is followed by cyclization and oxidation of the intermediate dihydroquinoline **120** to a quinoline **121** (**Scheme 70**).

Table 3 Formation of quinolines from anilines

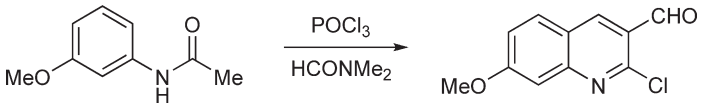
Name of reaction	*Starting materials*	*Catalyst*	*Initerrnediate carbonyl compound*	*Oxidizing agent*
Skraup	Glycerol	H_2SO_4	CH_2═CHCHO	As_2O_5, $ArNO_2$,[a] or *m*-$NO_2C_6H_4SO_3H$
Doebner-von Miller	RCHO and RCH_2CHO	$ZnCl_2HCl$	RCH═CRCHO	ArN═CHR[b]
Baeyer	RCHO and RCH_2COR	HCl, 20°C	RCH═CRCOR	ArN═CHR[b]
Riehm	RCOR and RCH_2COR	HCl, 200°C	R_2C═CRCOR	None (RH lost from product)[c]

[a]Nitro compound corresponding to the amine.
[b]Schiff's base from RCHO and amine.
[c]Dihydroquinolines, e.g., **120** (R = Me), can be isolated.

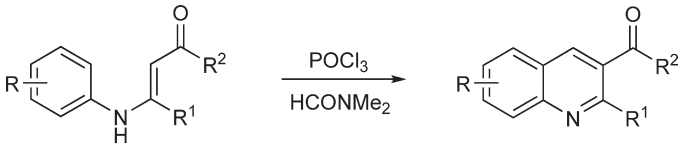


Scheme 70

Acylanilines react with the VilsmeierHaack reagent ($POCl_3$DMF) to give quinolines in good yield (e.g., **Scheme 71**) (for a review see <1993H(35)539>). Reaction of the Vilsmeier reagent with the vinylogous enamides **122** gives quinolines **123** (**Scheme 72**) <1983TL517, 2003JOC3966, CHEC-III(7.05.2.2)248>.



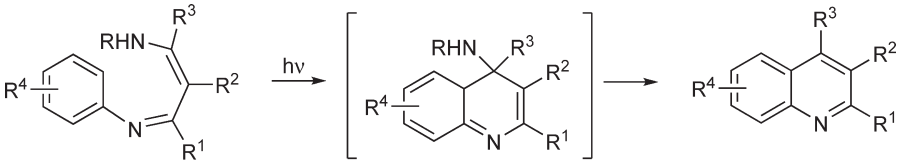
Scheme 71



122 **123**

Scheme 72

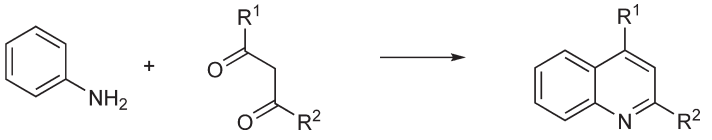
Photochemical cyclization of unsaturated imines **124** gives quinolines **125** in excellent yields (**Scheme 73**) <1993TL5321, 1996JOC7195, CHEC-III(7.05.2.1.3)234>.



124 **125**

Scheme 73

The Combes synthesis of quinolines (**Scheme 74**) has been reviewed <1992KGS1011>.



Scheme 74

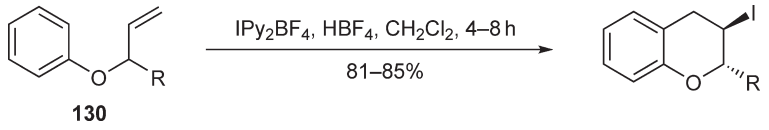
4.4.2.3.3.3 Partially-saturated rings. Ring closure of compounds of types **126, 128, 133, 135**, and **137** can give a wide variety of partially-saturated rings.

a. Tetrahydroquinolines, chromans, and tetrahydrobenzothiins **127** result from **126** (Y = OH, OR, OTs, or halogen) and from reactions of type **128** **129** (**Scheme 75**).

126 **127** **128** **129**

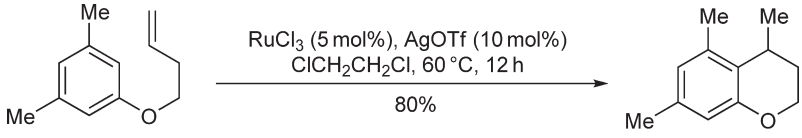
Scheme 75

The cyclizations of unsaturated precursors **128** can be induced by an electrophile or by a transition metal catalyst as illustrated by the iodonium ion promoted cyclization of allyloxybenzenes **130** (**Scheme 76**) <2004JA3416> and the preparation of 4,5,7-trimethylchroman **132** from **131** using a $RuCl_3$/AgOTf catalytic system (**Scheme 77**) <2004OL581, CHEC-III(7.08.11.1.2)517>.



130

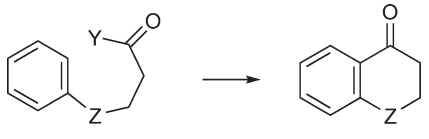
Scheme 76



131 132

Scheme 77

b. Dihydro-4-quinolones, chromanones, or dihydrobenzothiinones **134** are obtained from **133** (Y = halogen, OH, OR, or NR_2) (**Scheme 78**).

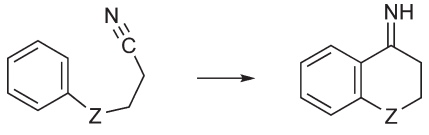


133 **134**

Y = halogen, OH, OR, NR_2

Scheme 78

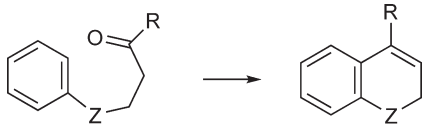
c. Imino derivatives **136** are formed by the cyclization of nitriles **135** (**Scheme 79**).



135 **136**

Scheme 79

d. 1,2-Dihydroquinolines and benzopyrans **138** can be made from **137** (**Scheme 80**).

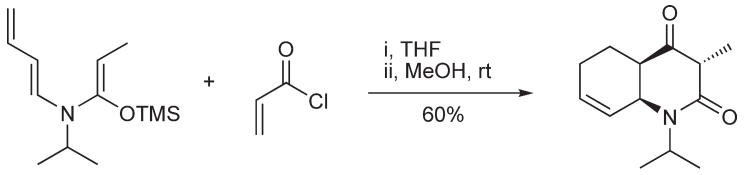


137 **138**

Scheme 80

4.4.2.3.4 Synthesis *via* cycloaddition reactions

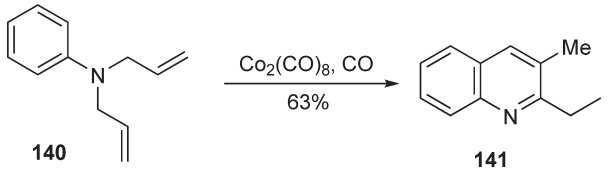
Intramolecular DielsAlder reactions can simultaneously form both rings as illustrated by the cascade [4 + 2] cycloaddition-acylation reaction leading to the tetrahydroquinoline dione **139** (**Scheme 81**) <1996T11643, CHEC-III(7.05.2.2.2)272>.



139

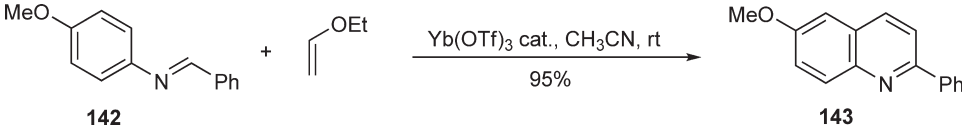
Scheme 81

Diallylaniline **140** is converted exclusively into 2-ethyl-3-methylquinoline **141** when heated with a catalytic amount of $Co_2(CO)_8$ under an atmosphere of CO (**Scheme 82**) <2003JOC3563>. A [4 + 2] cycloaddition of *N*-arylaldimines **142** with vinyl ethers catalyzed by ytterbium(III) triflate affords quinoline derivatives **143** in good yields (**Scheme 83**) <1995S801, CHEC-III(7.05.2.2.2)260>.



140 **141**

Scheme 82

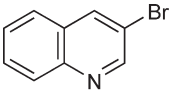


142 **143**

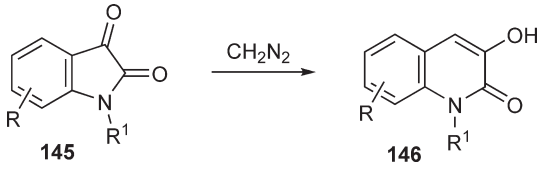
Scheme 83

4.4.2.3.5 Synthesis from other heterocycles

Indoles with dibromocarbene are ring-expanded to 3-bromoquinolines **144** and benzofurans behave analogously (Section 3.3.1.7.1). Isatins **145** with diazomethane form 3-hydroxy-2-quinolones **146** (**Scheme 84**).



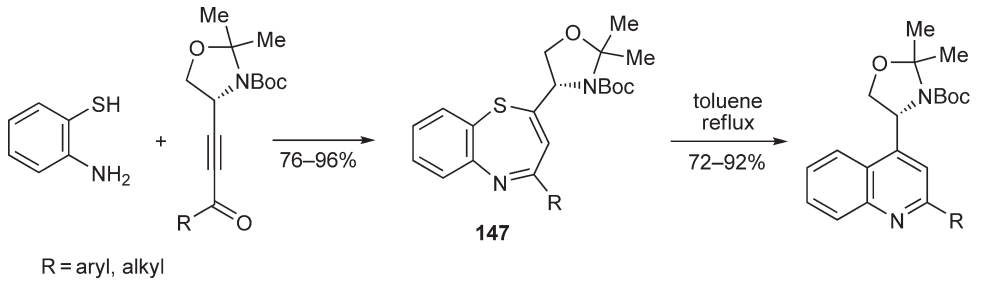
144



145 **146**

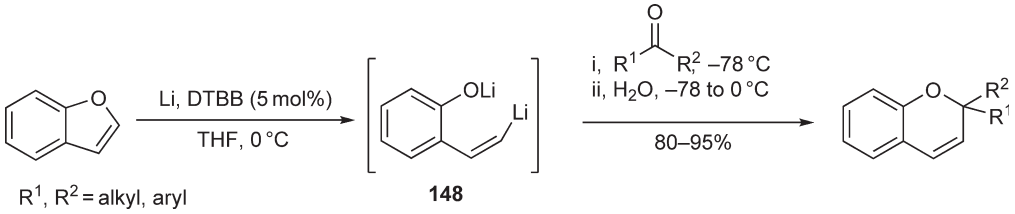
Scheme 84

A sulfur extrusion reaction can lead to quinolines after an initial cyclocondensation producing the intermediate seven-membered ring compound **147** (**Scheme 85**) <2000SL595>. A similar reaction affords 2-trifluoromethyl-4-formyl derivatives <1997T641, CHEC-III(7.05.3.5)298>.



Scheme 85

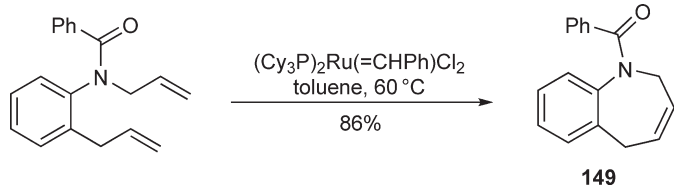
Selective ring opening of benzofuran with lithium, in the presence of a catalytic amount of 4,4-di(*tert*-butyl)diphenyl (DTBB), forms the (*Z*)-dilithiated species **148**, which upon addition of a ketone or aldehyde forms 2*H*-chromenes (**Scheme 86**) <2001EJO2809, CHEC-III(7.08.3.3)444>.



Scheme 86

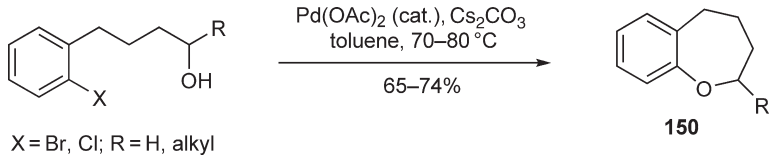
4.4.2.4 Seven-Membered and Larger Rings

Classical ring closures (of the FriedelCrafts, Dieckmann, etc., types) can be applied to benzazepine synthesis <1974AHC(17)45>. Particularly useful are approaches to benzazepines based on transition metal-catalyzed cyclizations <CHEC-III(13.01.6)10>, as illustrated by the synthesis of 1-benzazepine derivative **149** in high yield by Ru-catalyzed ring-closing metathesis with Grubbs I catalyst (**Scheme 87**) <2005JOC1545>.



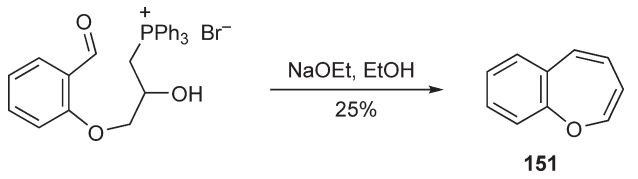
Scheme 87

The Pd-catalyzed cyclization of 2-halogen-substituted -hydroxyalkylbenzenes is a useful method for the synthesis of 1-benzoxepanes **150** (**Scheme 88**) <2000JA12907, CHEC-III(13.02.7.1)55>.



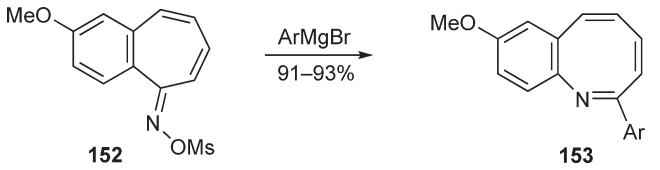
Scheme 88

The synthesis of the benzoxepin **151** involves an intramolecular Wittig reaction (**Scheme 89**) <1968JOC2590>.



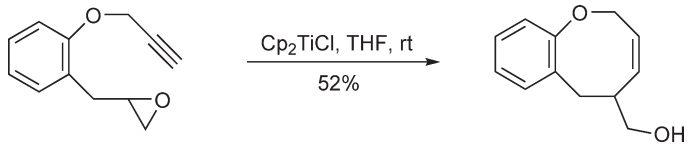
Scheme 89

2-Arylated 1-benzazocines **153** are prepared *via* Beckmann rearrangement of 5*H*-benzocyclohepten-5-one oxime mesylates **152** in dry toluene using aryl Grignard reagents to induce rearrangement in the absence of a protic agent (**Scheme 90**) <2006TL4721, CHEC-III(14.01.5.4)30>.



Scheme 90

Titanocene-promoted radical cyclizations provide access to various benzoxocines as exemplified in **Scheme 91** <2006TL1599, CHEC-III(14.02.9.6)68>.

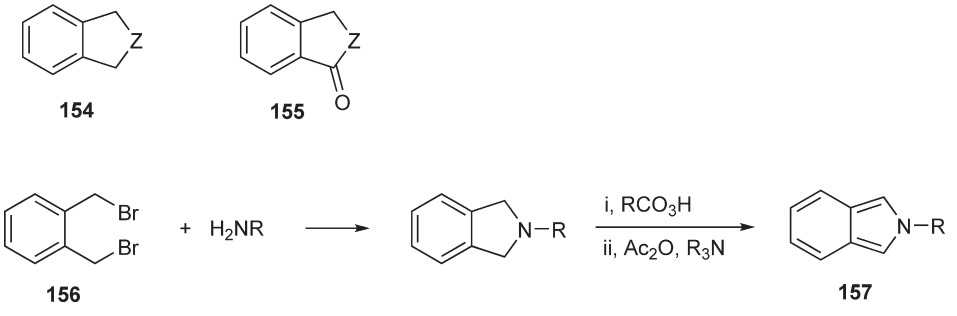


Scheme 91

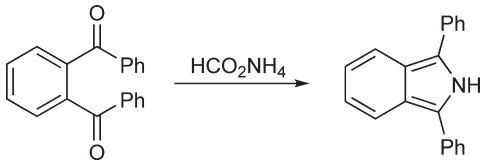
4.4.3 One Heteroatom Not Adjacent to a Ring Junction

4.4.3.1 Five-Membered Rings: Isoindoles and Related Compounds

1. Compounds of types **154** and **155** can be prepared from *o*-disubstituted benzenes by standard reactions. Thus, 2-alkyl- <1988CZ85> and 2-aryl-2*H*-isoindoles **157** <1987CZ155> are prepared from 1,2-bis(bromomethyl)benzene **156** *via* Polonovsky elimination of dihydroisoindole *N*-oxides in acetic anhydride/triethylamine (**Scheme 92**). The application of this type of ring formation to ene-1,4-dione systems utilizes a reducing agent as illustrated in **Scheme 93** <1965CC272>.

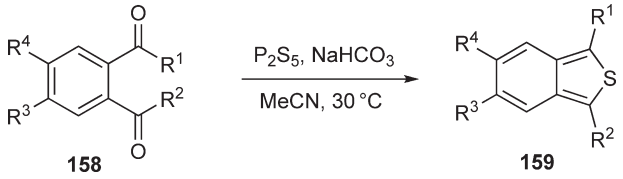


Scheme 92

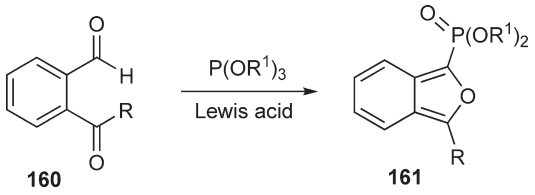


Scheme 93

o-Diaroyl- and *o*-bis(trimethylacetyl)-benzenes **158** with P_2S_5 in the presence of $NaHCO_3$ afford benzo[*c*]thiophenes **159** stabilized by aryl or *t*-butyl groups at the 1- and 3-positions (**Scheme 94**) <1990PS(54)209, 1990S670, see also 1993CC172>. Likewise, dialkyl benzo[*c*]furanyl derivatives **161** have been prepared by the cyclization of appropriate precursors **160** (**Scheme 95**) <2006S4124, CHEC-III(3.07.6)552>.

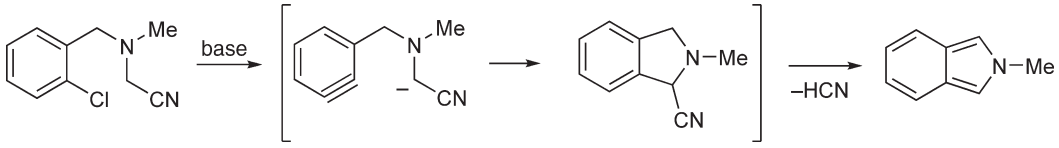


Scheme 94



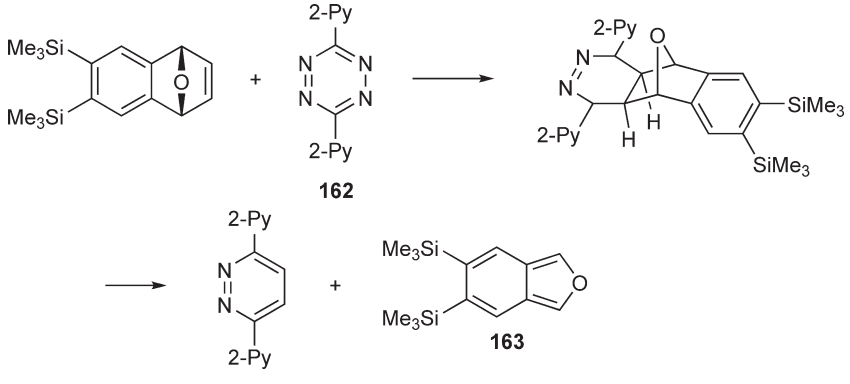
Scheme 95

2. A versatile isoindole synthesis (**Scheme 96**) proceeds through intramolecular carbanion addition to an aryne and subsequent aromatization by base-promoted elimination of hydrogen cyanide <1977T2255>.



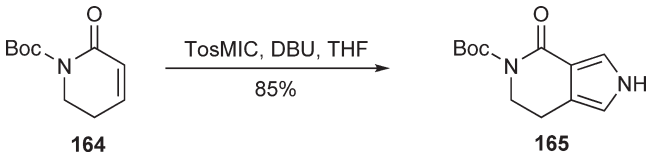
Scheme 96

A broadly applicable synthesis of benzo[*c*]furans by Warrener relies on DielsAlder/retro DielsAlder reactions with *s*-tetrazines. Using this methodology with 3,6-di(pyridin-2-yl)-*s*-tetrazine **162** the generation of an isolable 5,6-(bistrimethylsilyl)benzo[*c*]furan **163** has been achieved (**Scheme 97**) <2002T9413, CHEC-III(3.07.6)551>.



Scheme 97

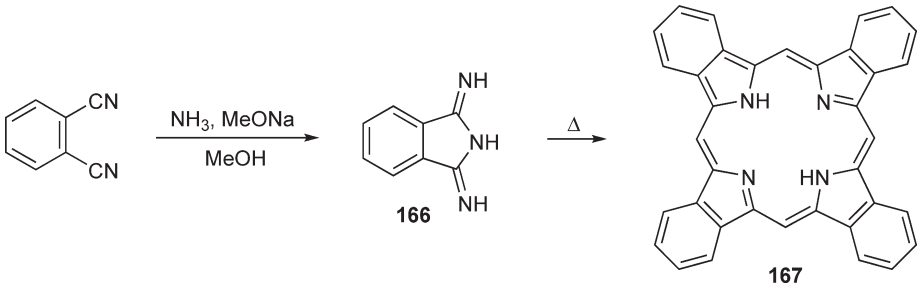
3. The versatile van Leusen pyrrole synthesis (Section 4.2.3.3.4) is also useful for the preparation of fused pyrrole derivatives, for example, **165**, which is obtained in good yield upon treatment of the lactam **164** with *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of DBU (**Scheme 98**) <2003BML1939>. This method has also been used in the construction of isoindole derivatives <1997H(45)1989, CHEC-III(3.03.9)327>.



164 **165**

Scheme 98

4. The isoindole ring is present in the phthalocyanines (e.g., **167**) and a common method for their synthesis is from 1,3-diiminodihydroisoindole **166** which is prepared by cyclization of *o*-phthalonitrile (**Scheme 99**) <1991JOC82, B-2003MI17-61>.



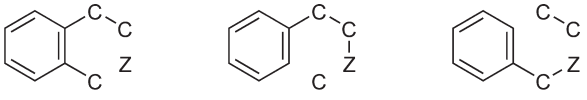
166 **167**

Scheme 99

4.4.3.2 Six-Membered Rings

4.4.3.2.1 Overview of ring syntheses of isoquinolines, benzo[*c*]pyrans, and their derivatives

We deal successively with methods corresponding to disconnections of types **168, 169**, and **170**. Important methods are summarized in **Table 4**.



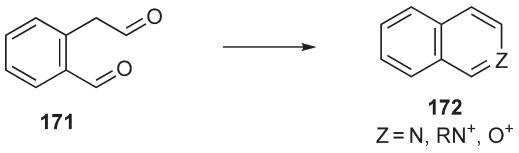
168 **169** **170**

Table 4 Important ring syntheses for isoquinolines, benzo[*c*]pyrans, and derivatives

Ring	*Synthesis type*	*Synthesis name(s)*	*Section*
Isoquinolines	**168**	–	4.4.3.2.2
	169	PictetGams	4.4.3.2.3.2
	170	PomeranzFritsch	4.4.3.2.4
3,4-Dihydroisoquinolines	**169**	BischlerNapieralski	4.4.3.2.3.1
Tetrahydroisoquinolines	**169**	PictetSpengler	4.4.3.2.3.2
Benzo[*c*]pyrylium salts	**168**	–	4.4.3.2.2
Isochromenes	**168**	–	4.4.3.2.2

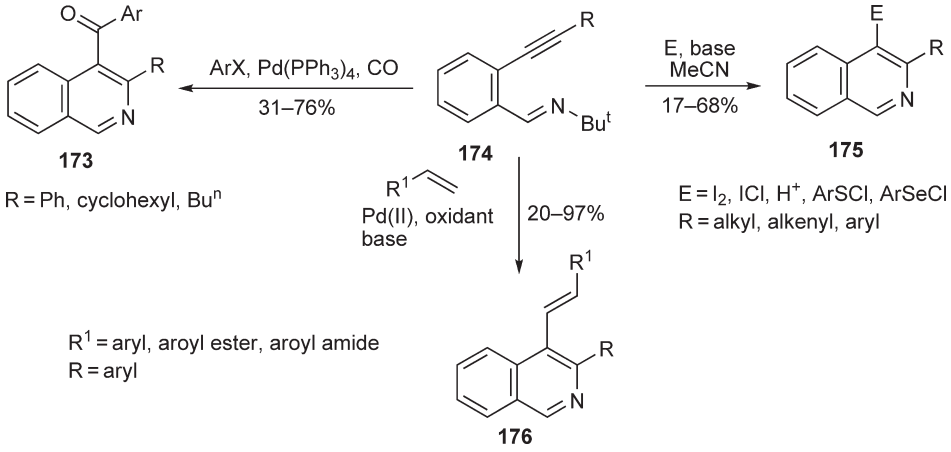
4.4.3.2.2 Ring closure of an *o*-disubstituted benzene

Homophthalaldehyde **171** gives isoquinoline, isoquinoline 2-oxide, 3,4-benzopyrylium salts, and 2-alkyl- and 2-aryl-isoquinolinium salts **172** by reaction with NH_3, NH_2OH, H^+, or RNH_2, respectively (**Scheme 100**).



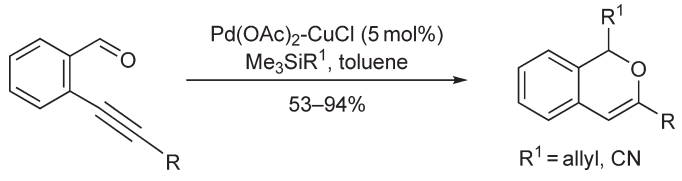
Scheme 100

Various cyclizations of alkynylbenzaldimines (e.g., **174**) are particularly useful in the synthesis of isoquinolines as summarized in **Scheme 101** <CHEC-III(7.05.2.1)221>. The use of electrophiles and base yields 3,4-disubstituted isoquinolines **175** <2002JOC3437> whereas the palladium-catalyzed carbonylation affords 4-aroylquinolines **173** <2002JOC7042>. Cyclization followed by Heck reaction gives rise to 4-alkenyl substituted isoquinolines **176** (**Scheme 101**) <2002TL3557>.



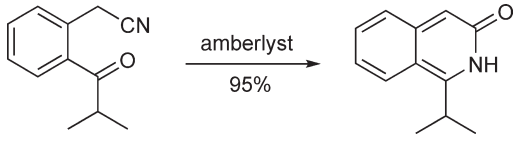
Scheme 101

1*H*-Isochromenes are best prepared by similar cyclizations of 2-alkynylbenzyl alcohols or 2-allylbenzaldehydes <CHEC-III(7.08.6.1)459>; a representative example is shown in **Scheme 102** <2005T11322>.



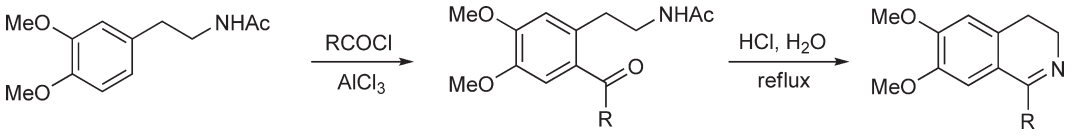
Scheme 102

The cyclization of 2-acylphenylacetonitriles under acidic conditions affords 1-substituted 2*H*-isoquinolin-3-ones in high yield as exemplified in **Scheme 103** <2004JHC979>.



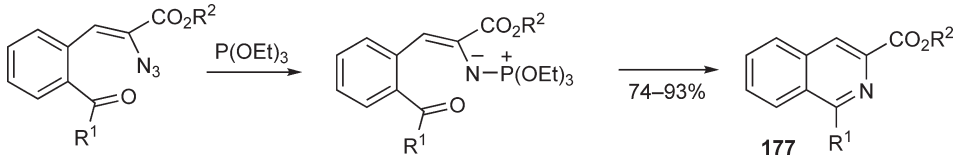
Scheme 103

Cyclizations of *o*-formyl or *o*-acylderivatives of -phenethylamine give 3,4-dihydroisoquinolines (**Scheme 104**) <1988H(27)2403>.



Scheme 104

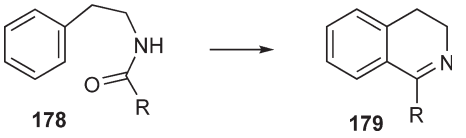
Nitrogen ylide cyclization gives isoquinolines **177** as shown in **Scheme 105** <1987J(P1)921> (see also <1998J(P1) 807, CHEC-III(7.05.2.1)231>).



Scheme 105

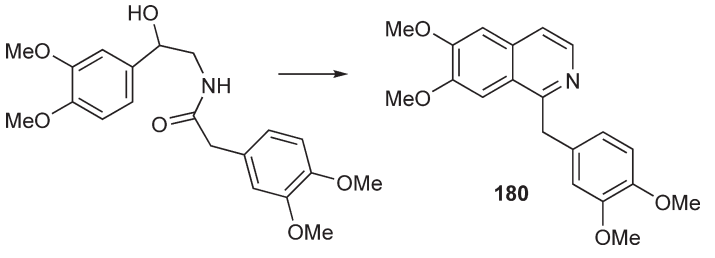
4.4.3.2.3 From a -phenethylamine

1. In the BischlerNapieralski synthesis of 3,4-dihydroisoquinolines **179** from *N*-acylated 2-phenethylamines **178** (**Scheme 106**), the amide carbonyl group is condensed with a benzene ring using acid catalysis (e.g., P_2O_5, $POC1_3$, H_3PO_4–P_2O_5). Electron-releasing substituents in the *meta* position generally facilitate reaction, but in the *para* position they can inhibit cyclization. *m*-Substituted phenethylamides form mainly 6-substituted dihydroisoquinolines.



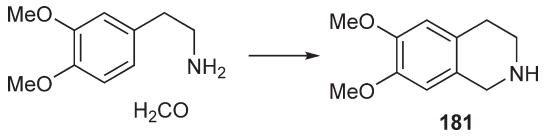
Scheme 106

2. PictetGams preparation of isoquinolines from *N*-acylated 2-hydroxyphenethylamines, e.g., the synthesis of papaverine **180** (**Scheme 107**), utilizes similar conditions.

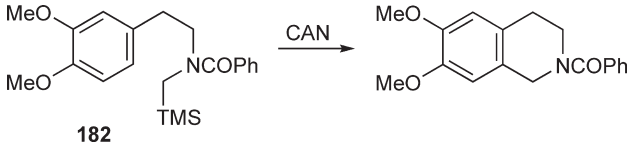


Scheme 107

3. A Mannich-type reaction is used in the PictetSpengler synthesis of tetrahydroisoquinolines **181** (**Scheme 108**) <CHEC-III(7.05.2.2)250>. Indoles similarly give -carbolines (Section 3.3.1.5.7.4). A variation of the PictetSpengler reaction involves the oxidative cyclization of **182** using ceric ammonium nitrate (CAN) (**Scheme 109**) <1998JOC860>.

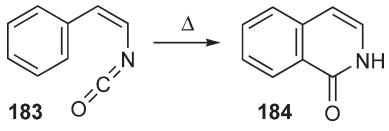


Scheme 108



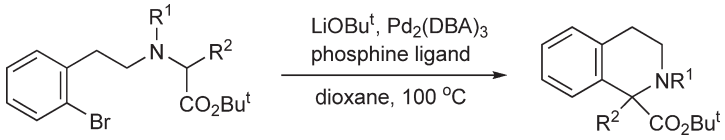
Scheme 109

4. Styryl isocyanates **183**, readily available by Curtius rearrangement of cinnamoyl azides, undergo thermal or Friedel Crafts cyclization to 1-isoquinolones **184** (**Scheme 110**).



Scheme 110

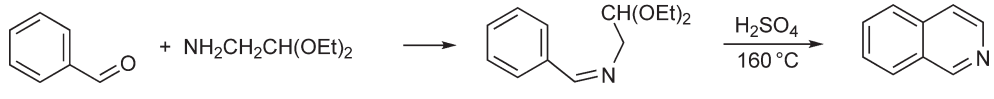
5. The Pd-catalyzed cyclization of appropriate 2-phenethylamine derivatives is a commonly used approach to the isoquinoline system as illustrated by **Scheme 111** <2002JOC465, CHEC-III(7.05.2.1)234>.



Scheme 111

4.4.3.2.4 From a benzylimine

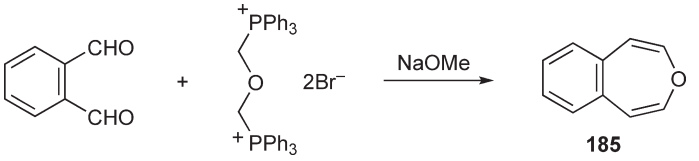
The PomeranzFritsch synthesis of isoquinolines is illustrated by **Scheme 112**. See Section 3.3.1.5.6 for a related synthesis of a thienotetrahydropyridine.



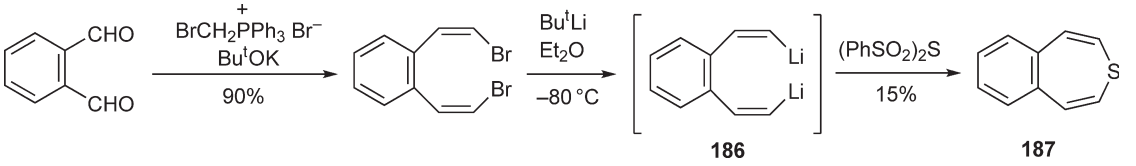
Scheme 112

4.4.3.3 Seven-Membered and Larger Rings

3-Benzoxepin **185** can be synthesized as shown in **Scheme 113** <1966CB634>. The benzothiepin **187** can be obtained by the reaction of an electrophilic sulfur reagent with (*Z*,*Z*)-*o*-bis(-lithiovinyl)benzene **186** which is derived in two steps from *o*-phthalaldehyde (**Scheme 114**) <2003CPB1283, CHEC-III(13.03.9.2)127>.

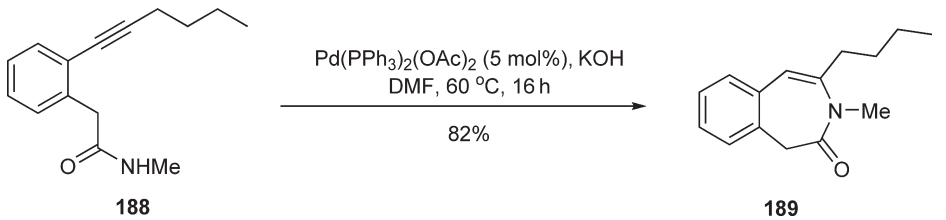


Scheme 113



Scheme 114

Various benzazepines can be prepared by transition-metal-catalyzed cyclizations <CHEC-III(13.01.6)10>; for example, a palladium-catalyzed intramolecular hydroamidation with the alkyne **188** affords the 3-benzazepinone **189** (**Scheme 115**) <2006TL3811>.

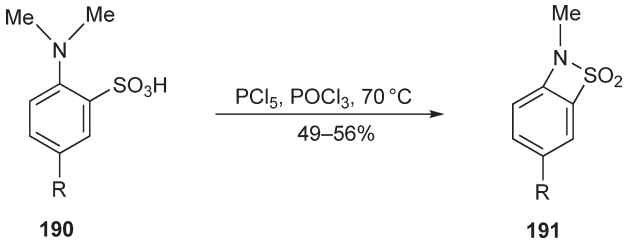


Scheme 115

4.4.4 Two Heteroatoms 1,2 to a Ring Junction

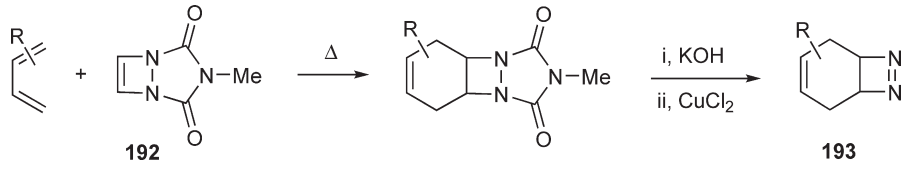
4.4.4.1 Four-Membered Rings

A convenient synthesis of benzo[*c*]-1,2-thiazetidine 1,1-dioxides (1,2-benzosultams) **191** is based on a demethylative intramolecular cyclization of the sulfonic acid **190** (**Scheme 116**) <1998JOC2348, CHEC-III(2.15.8.2.2)755>.



Scheme 116

Various fused derivatives of 1,2-diazetidines **193** can be prepared *via* cycloaddition reactions of the dienophile **192** (**Scheme 117**) (also see Section 4.3.2.2.1) <2001OL3185, CHEC-III(2.13.9.4.2)675>.

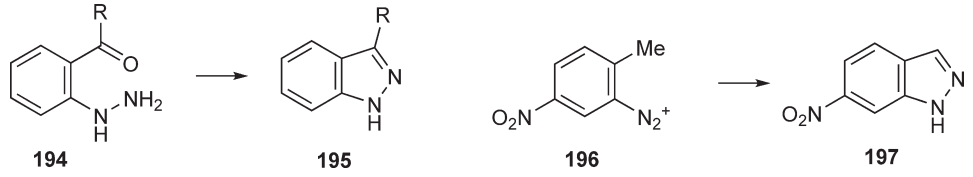


Scheme 117

4.4.4.2 Five-Membered Rings

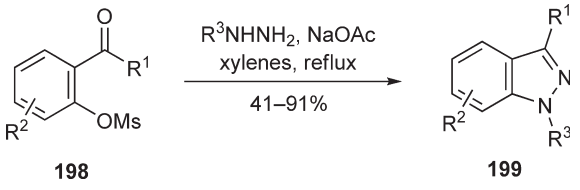
4.4.4.2.1 Indazoles

Indazoles **195** are formed by spontaneous cyclization of *o*-acylphenylhydrazines **194**. Certain *o*-toluenediazonium salts (e.g. **196**) cyclize spontaneously to indazoles **197** (**Scheme 118**); yields are good when the methyl group is activated by an *ortho* or *para* electron-withdrawing group.



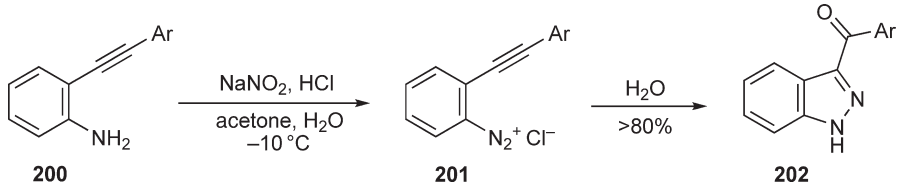
Scheme 118

A versatile and efficient synthesis of 3-substituted-1*H*-indazoles **199** is based on the generation and subsequent cyclization of the intermediate hydrazones from aryl mesylates **198** and hydrazines (**Scheme 119**) <1999S588, CHEC-III(4.01.9.1.2)94>.



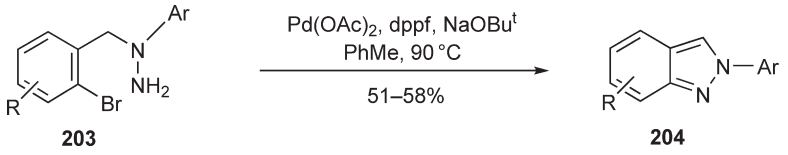
Scheme 119

Cyclization of *ortho*-(arylethynyl)benzene diazonium salts **201**, prepared from alkynyl anilines **200**, affords indazoles **202** (**Scheme 120**) <2003TL5453>.



Scheme 120

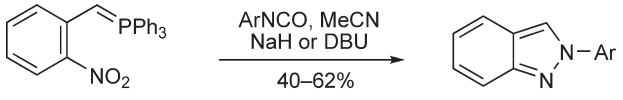
Intramolecular palladium-catalyzed cyclization reactions are commonly used to synthesize indazole derivatives <CHEC-III(4.01.9.1.1)72>. For example, *N*-Aryl-*N*-(*o*-bromobenzyl)hydrazines **203** participate in a palladium-catalyzed intramolecular amination reaction to give 2-aryl-2*H*-indazoles **204** (**Scheme 121**) <2000OL519>.



203 **204**

Scheme 121

Reaction of 2-nitrobenzyl triphenylphosphonium ylide **205** with aryl isocyanates affords 2-aryl-2*H*-indazoles **206** (**Scheme 122**) <2000TL9893>.

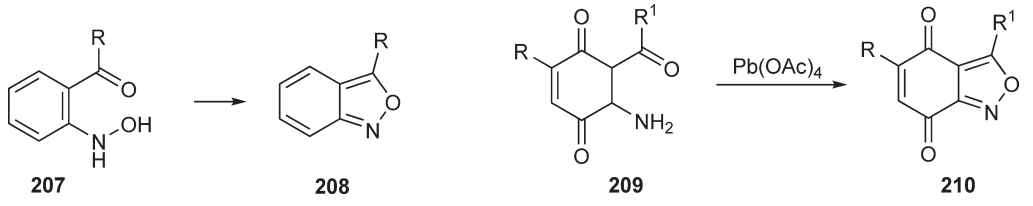


205 **206**

Scheme 122

4.4.4.2.2 Anthranils, benzisothiazoles, and saccharins

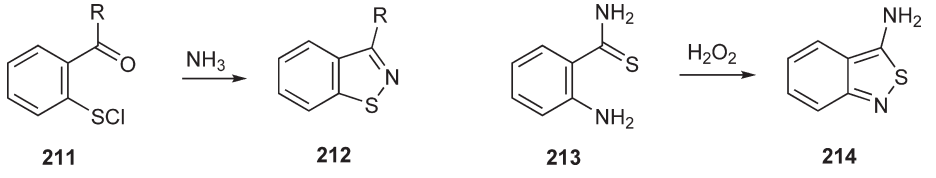
1. Anthranils **208** are formed by spontaneous cyclization of *o*-acylphenylhydroxylamines **207**, which are prepared by reduction of the corresponding nitro compounds. Treatment of the -amino ketone **209** with lead tetraacetate gives the anthranil **210** (**Scheme 123**). For similar cyclizations leading to other 3,4-fused isoxazoles see the related chapter of CHEC-III <CHEC-III(4.03.9.1)425>.



207 **208** **209** **210**

Scheme 123

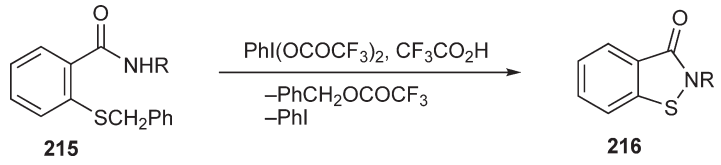
2. Benz[*d*]isothiazoles **212** are prepared from sulfenyl chlorides **211**, and their benz[*c*] isomers **214** result from the H_2O_2 oxidation of *o*-aminothiobenzamides **213** (**Scheme 124**). Iminobenzodithioles equilibrate thermally with benzisothiazolethiones (Section 3.4.1.2.4).



211 **212** **213** **214**

Scheme 124

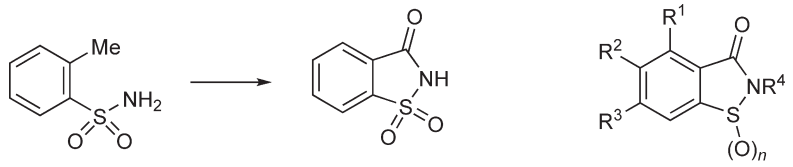
Treating *N*-aryl-2-(benzylthio)benzamides **215** with [bis(trifluoroacetoxy)iodo]benzene containing TFA results in an interrupted Pummerer-type reaction to give 2-aryl-1,2-benzisothiazolo-3(2*H*)-ones **216** (**Scheme 125**) <2001H(55) 1231, CHEC-III(4.05.9.1)596>.



215 216

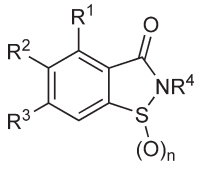
Scheme 125

3. Saccharin **218** is obtained by $KMnO_4$ oxidation of *o*-methylbenzenesulfonamide **217** (**Scheme 126**). Various *N*-alkylsaccharins **219** (n = 2) and *N*-alkyl-1,2-benzisothiazolin-3-one *S*-oxides **219** (n = 1) are conveniently prepared in moderate to good yields by the reaction of *N*-alkyl(*o*-methylarene)sulfonamides with (diacetoxyiodo)benzene in the presence of iodine under irradiation with a tungsten or mercury lamp <1999T14885, CHEC-III(4.05.9.1.2)599>.



217 218 219

Scheme 126

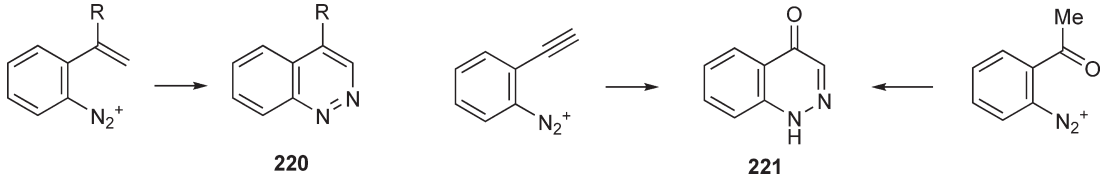


219

4.4.4.3 Six-Membered Rings

4.4.4.3.1 Cinnolines

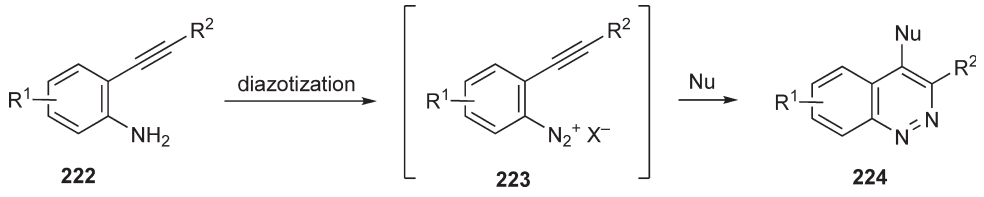
o-Alkenyl-, *o*-alkynyl-, and *o*-acyl-diazonium ions cyclize spontaneously to give cinnolines **220** or cinnolones **221** (**Scheme 127**) <CHEC-III(8.01.9.2.1)77>.



220 221

Scheme 127

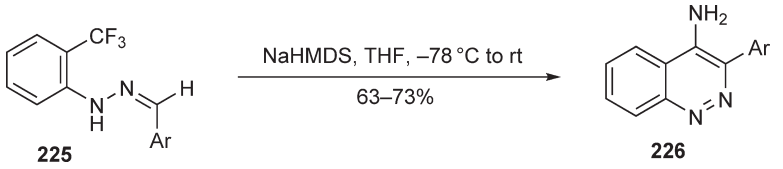
Particularly useful is a synthetic approach utilizing the diazotization of *o*-alkynylanilines **222** followed by cyclization of intermediate diazonium salts **223** (the Richter method) (**Scheme 128**) <CHEC-III(8.01.9.2.1)78>. In this reaction a nucleophile attacks the C(1) of the alkyne moiety in the diazonium intermediate **223**, allowing substitution in the C(4) position of the cinnoline **224**. Classically, water was used as the attacking species in the Richter reaction but more recently chloride and bromide nucleophiles have been successfully utilized <1995LA775, 2004T7983>.



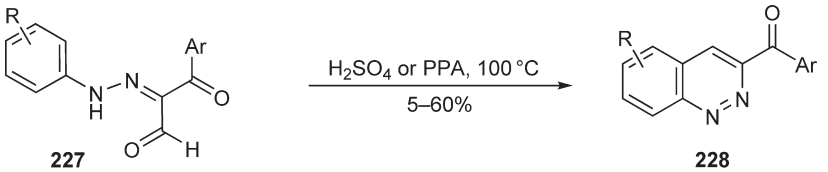
222 223 224

Scheme 128

Many useful procedures employ the cyclization of arylhydrazones, as illustrated by the preparation of 3-arylcinnolin-4-amines **226** from *o*-trifluoromethylphenyl hydrazones **225** (**Scheme 129**) <1999TL5111> and the synthesis of 3-benzoylcinnolines **228** *via* acid catalyzed cyclization of 3-oxo-3-aryl-2-arylhydrazonopropanals **227** (**Scheme 130**) <2001T1609>.



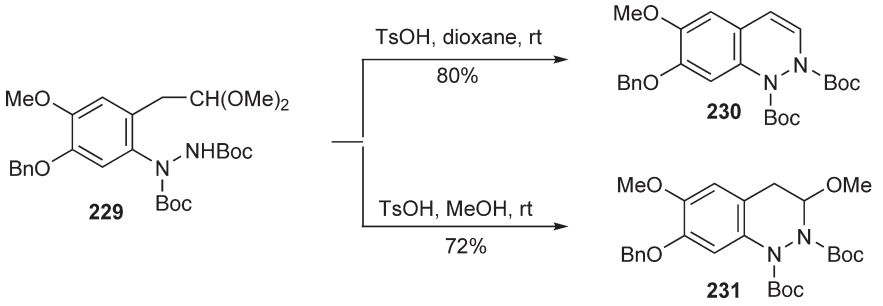
Scheme 129



Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl
R = H, 6-MeO, 6-NO_2, 5-Cl, 7-Cl

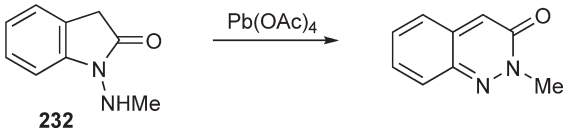
Scheme 130

1,2-Dihydrocinnoline derivative **230** can be synthesized from the [2-(2,2-dimethoxyethyl)phenyl]hydrazine **229** *via* acid-catalyzed cyclization in dioxane. When methanol is used as solvent a 3-methoxy-1,2,3,4-tetrahydrocinnoline **231** is formed (**Scheme 131**) <1995LA1303>.

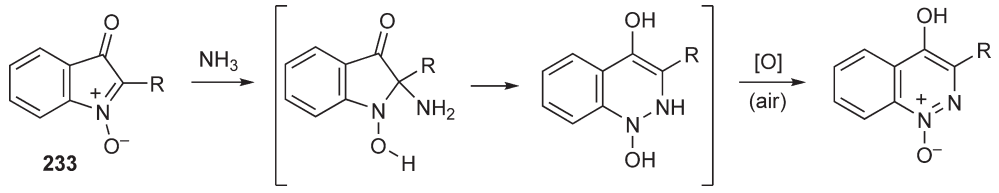


Scheme 131

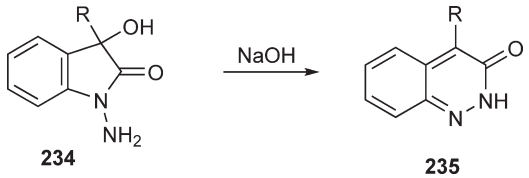
Preparations of cinnolines by expansion of five-membered heterocycle rings include the oxidation of *N*-aminooxindoles **232** (**Scheme 132**) <1988JHC847>, the treatment of isatogens **233** with ammonia (**Scheme 133**), and the base-catalyzed conversion of 1-aminodioxindoles **234** into cinnolin-3-ones **235** (**Scheme 134**) <1960JA4634>. Additional examples of the synthesis of cinnolines by transformation of another ring are available in CHEC-III <CHEC-III(8.01.10)85>.



Scheme 132



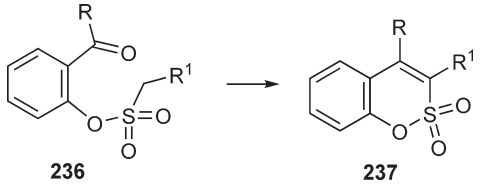
Scheme 133



Scheme 134

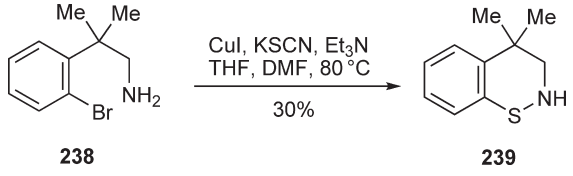
4.4.4.3.2 Rings containing O or S atoms

1,2-Benzoxathiin 2,2-dioxides **237** can be prepared from 2-acylphenols by reaction with a sulfonyl chloride, $R^1CH_2SO_2Cl$, followed by base-catalyzed cyclization of the sulfonate ester **236** (**Scheme 135**). For additional examples of the synthesis of 1,2-benzoxathiin 2,2-dioxides see CHEC-III <CHEC-III(8.10.9.3.5)719>.



Scheme 135

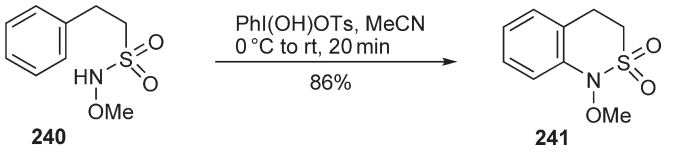
A variety of methods exist for the formation of fused 1,2-thiazines *via* the construction of an SN bond by nucleophilic attack of nitrogen onto a sulfur bearing a leaving group <CHEC-III(8.07.9.2.1)543>. For example, the reaction of aryl bromide **238** with potassium thiocyanate in the presence of copper(I) iodide and triethylamine affords benzothiazine **239**, although in low yield (**Scheme 136**) <2000JOC8152>.



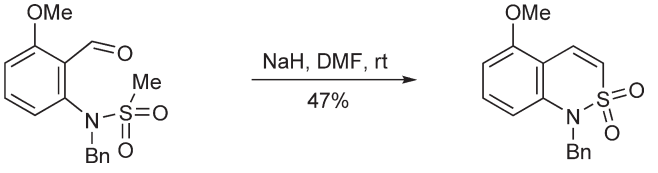
Scheme 136

Oxidative CH amination has been applied to the synthesis of a variety of 1,2-thiazine 1,1-dioxides <CHEC-III (8.07.9.2.2)545>; for example, the reaction of *N*-methoxy(2-arylethane)sulfonamide **240** with [hydroxyl(tosyloxy) iodo]benzene affords benzenesulfonamide **241** under mild conditions in excellent yield (**Scheme 137**) <2003OBC1342>.

Intramolecular methanesulfonamide anion alkylation and aldol condensation reactions have been employed for the synthesis of 2,1-benzothiazine 2,2-dioxides (e.g. **Scheme 138**) <1994TL2911, CHEC-III(8.07.9.2.4)549>.

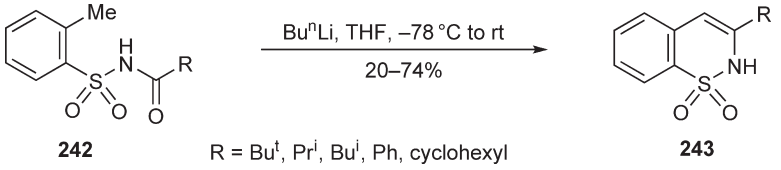


Scheme 137



Scheme 138

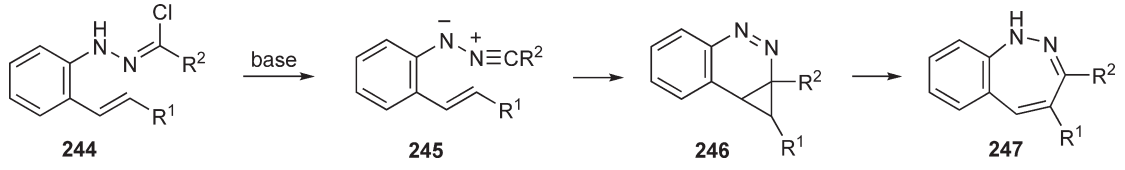
Directed *ortho*-methyl lithiation/cyclization of *N*-acyl-*o*-toluenesulfonamides **242** provides a convenient approach to the synthesis of 1,2-benzothiazine 1,1-dioxides **243** *via* creation of the bond between C(3) and C(4) (**Scheme 139**) <1999CPB1730>. The best yields of cyclization products are achieved when the R group on the amide **242** is bulky.



Scheme 139

4.4.4.4 Seven-Membered Rings

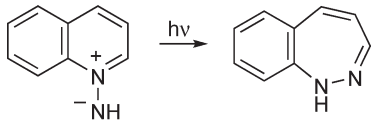
In an intramolecular 1,3-dipolar reaction, the nitrilimines **245**, generated by the reaction of the hydrazoyl chlorides **244** with triethylamine at 80°C, cyclize to give 1*H*-1,2-benzodiazepines **247** (**Scheme 140**) <1979S380>. At 20°C using silver carbonate as a base, the intermediate cyclopropa[*c*]cinnolines **246** can be isolated; these intermediates rearrange *via* ring expansion and hydrogen migration to give the benzodiazepines **247** <1981JOC1402>.



Scheme 140

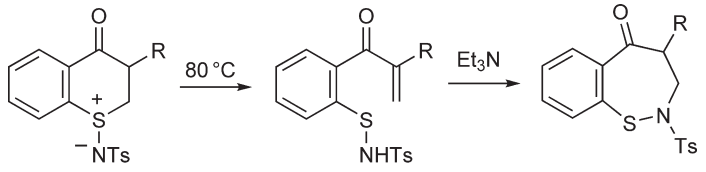
The photolysis of quinoline *N*-imides **248** (which are in equilibrium with their dimers) gives 1*H*-1,2-benzodiazepines **249** (**Scheme 141**) <1977JOC1856>. Reactions of this type have also provided routes to pyrido-, thieno-, and furo-1,2-diazepines <1979CPB2183, 1979H(12)471>.

N-Tosylsulfimines, e.g., **250**, are converted into 1,2-benzothiazepines **252** by triethylamine (**Scheme 142**). In the absence of base the intermediate **251** can be isolated <1981J(P1)1037>. 1,2-Benzothiazepine 1,1-dioxides **254** are prepared by ring expansion of the 1,2-benzoisothiazole derivatives **253** upon treatment with 1-diethylamino-1-propyne (**Scheme 143**) <1996T3339, CHEC-III(13.07.4.2)241>.



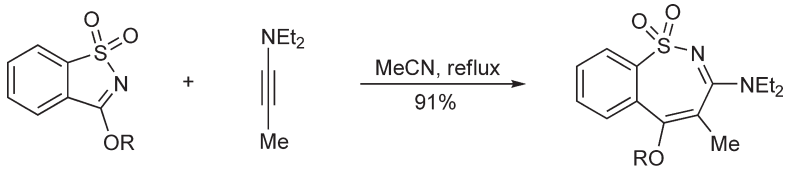
248 249

Scheme 141



250 251 252

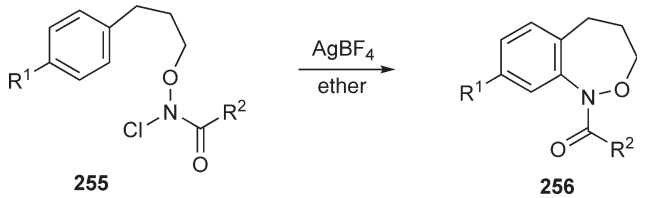
Scheme 142



253 254

Scheme 143

N-Acyl-1,3,4,5-tetrahydro-2,1-benzoxazepines **256** are synthesized from the *N*-chloro derivatives **255** (**Scheme 144**). The reaction proceeds *via* initial *ipso* attack followed by 1,2-carbon migration <1984J(P1)2255, 1990T7247>.



255 256

Scheme 144

4.4.5 Two Heteroatoms 1,3 to a Ring Junction

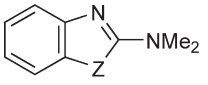
4.4.5.1 Five-Membered Rings

4.4.5.1.1 Ring closure of an *o*-disubstituted benzene or hetarene

1. *o*-Hydroxy-, *o*-mercapto-, and *o*-amino-anilides **257** (Z = O, S, NH) cyclize (e.g., by heating at 150°C or refluxing with acid) to benzoxazoles <CHEC-III(4.04.9.3)524>, benzothiazoles <CHEC-III(4.06.9.6.2)694>, and benzimidazoles <CHEC-III(4.02.9.1)286> **258** (Z = O, S, NH), respectively (**Scheme 145**). The anilides are often prepared and cyclized *in situ* by heating the corresponding *o*-substituted anilines with a carboxylic acid, anhydride, acid chloride, ester, nitrile, amidine, etc. *o*-Substituted anilines with the phosgeneiminium chloride $Cl_2C{=}NMe_2{}^+Cl$ give benzoxazoles, benzothiazoles, and benzimidazoles **259** containing a 2-dimethylamino substituent <1973AGE806>. Other *ortho*-disubstituted heterocycles react similarly, providing entry into a large number of ring-fused systems, including purines (Traube synthesis).

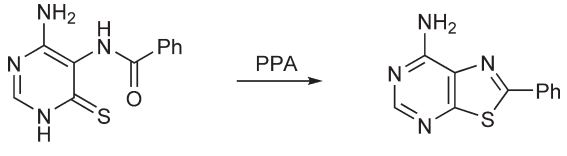
257 **258**

Scheme 145



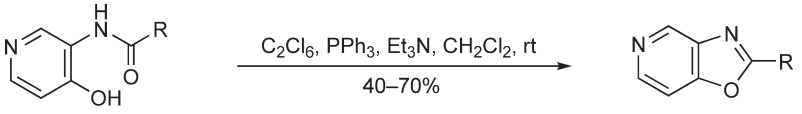
259 (Z = O, S, NR)

Similar methods lead to ring closure on a variety of other ring systems. The substituted pyrimidinethione **260** with polyphosphoric acid formed the thiazolo[5,4-*d*]pyrimidine **261** (**Scheme 146**) <1965JOC1916>. The cyclization of *N*-acylated aminopyridinols such as **262** affords oxazolopyridines **263** (**Scheme 147**) <2005TL9001, CHEC-III(4.04.9.3)524>.



260 **261**

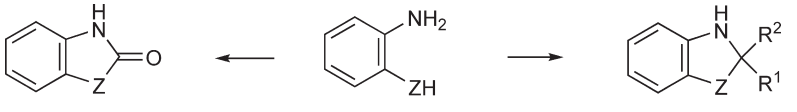
Scheme 146



262 **263**

Scheme 147

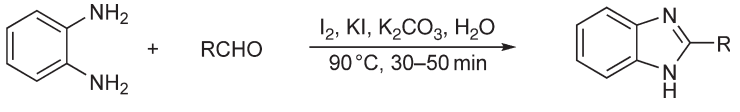
2. Benzoxazolones, benzothiazolones, and benzimidazolones **264** are prepared by the reaction of carbonic acid derivatives [$CO(OEt)_2$, $COCl_2$ or $ClCO_2Et$] with the corresponding *o*-substituted anilines **265** (**Scheme 148**).



264 **265** **266**

Scheme 148

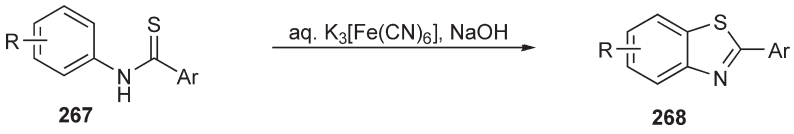
3. If an aldehyde, ketone, or *gem*-dihalo compound is used in place of the carbonic acid derivative, the corresponding nonaromatic compound **266** is formed (**Scheme 148**). In the reaction of aldehydes, the nonaromatic intermediate **266** can be oxidized *in situ* to the respective aromatic heterocycle using I_2 <2006TL795>, as exemplified by **Scheme 149**, $K_3Fe(CN)_6$ <2005SC2395>, atmospheric oxygen <2004H(63)2769>, or other mild oxidants <CHEC-III(4.02.9.2.1)300>.



Scheme 149

4.4.5.1.2 Other methods

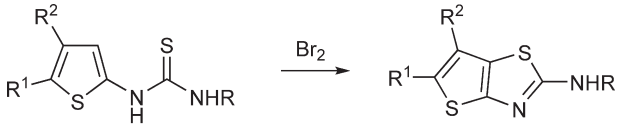
Oxidative CS bond formation converts thioanilides into benzothiazoles (the JacobsonHugershoff synthesis) <CHEC-III(4.06.9.6.1)692>. Various oxidants (e.g., I_2, Br_2, or $SOCl_2$) can be used; for example, the synthesis of benzothiazoles **268** involves oxidative cyclization of an arylthioamide **267** on an unsubstituted *ortho* position, using potassium ferricyanide in a basic medium (**Scheme 150**) <1999J(P1)1437>. This method has been applied to the synthesis of various benzothiazoles, including analogues of kuanoniamine A <2004OBC3039>. Hypervalent iodine reagents (e.g., DessMartin periodinane) are particularly efficient as oxidants in the Jacobson cyclization and are also applicable to solid-phase synthesis <2006JOC8261>.



267 **268**

Scheme 150

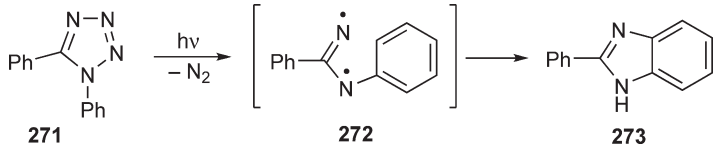
Similar cyclization can be applied for preparation of other ring systems. The 2-thienylthioureas **269** with bromine in acetic acid give the thieno[3,2-*d*]thiazole **270** (**Scheme 151**) <1978JHC81>. Pyrazolo[3,4-*d*]thiazoles are formed similarly.



269 **270**

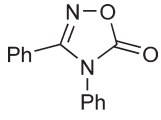
Scheme 151

Nitrene-like intermediates can lead to CN bond formation and thus to imidazole derivatives. 1,5-Diphenyltetrazole **271** fragments to **272**, which is trapped intramolecularly to form **273** (**Scheme 152**) (also see Section 3.4.1.2.1). Photolysis of the oxadiazole **274** also gives the intermediate **272** and thus **273** (Section 3.4.3.12.2).



271 **272** **273**

Scheme 152

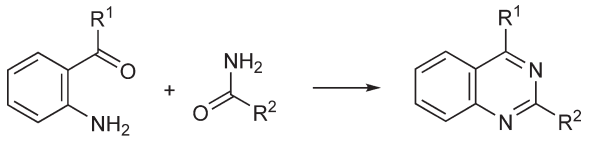


274

4.4.5.2 Six-Membered Rings

4.4.5.2.1 Quinazolines and azinopyrimidines by cyclization procedures

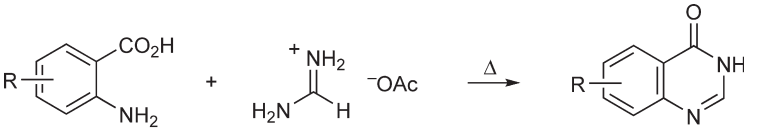
The usual precursor is an appropriately *ortho*-disubstituted benzene <CHEC-III(8.02.9.2.1)204>. Thus, quinazolines **276** can be prepared by the reaction of *o*-acylanilines **275** (R = alkyl) with amides (**Scheme 153**). Heating anthranilic acid with amides or amidines yields 4-quinazolinones <CHEC-III(8.02.9.2.1)215>; for example, the 2-unsubstituted



275 276

Scheme 153

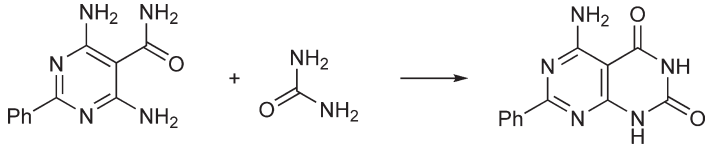
4(3*H*)-quinazolinones **279** are best prepared by heating anthranilic acids **277** with formamidine acetate **278** in an alcohol solvent (**Scheme 154**) <2004S429, 2005JME744, 2005OPD440, 2006BML1633>.



277 278 279

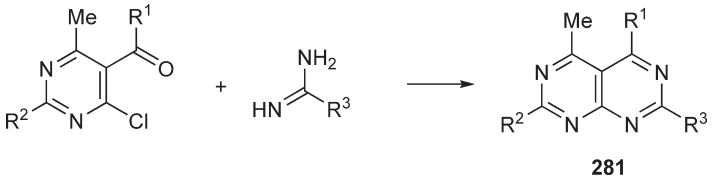
Scheme 154

The synthesis of pyrimidopyrimidines (e.g. **280** and **281**) <CHEC-III(10.19.2.4.3)1020>, pyrimidopyridazines (e.g. **282**) <CHEC-III(10.19.2.2.2)994>, and pteridines (e.g. **283**) <CHEC-III(10.18.9.1)934> is illustrated in **Schemes 155158**. Additional examples are given in the appropriate chapters of CHEC-III. In addition to the syntheses that resemble those of quinazolines from anthranilic acid, the high reactivity of the 4-chlorine in a pyrimidine to nucleophiles is exploited (e.g., **Scheme 156**).



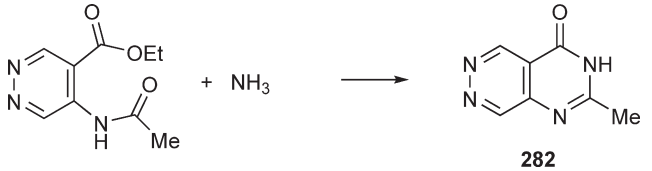
280

Scheme 155



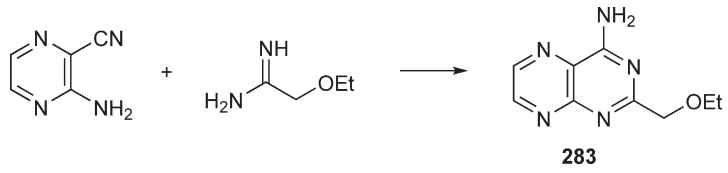
281

Scheme 156



282

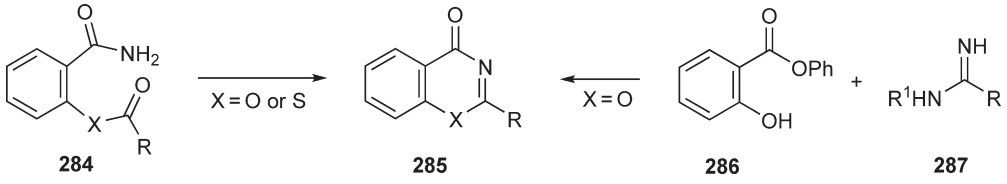
Scheme 157



Scheme 158

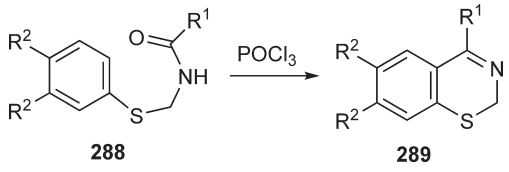
4.4.5.2.2 Rings containing O or S atoms

1,3-Benzoxazin-4-ones **285** (X = O) are made by the cyclization of *O*-benzoylsalicylamides **284** (X = O) or reactions between phenyl salicylates **286** and benzamidines **287** (**Scheme 159**). The first method has wide applicability, and when 2-acylmercaptobenzamides **284** (X = S) are used 1,3-benzothiazin-4-ones **285** (X = S) are obtained <1967BSF4441>.

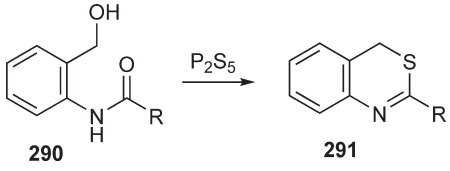


Scheme 159

2*H*-1,3-Benzothiazines **289** are available through a BischlerNapieralski-type cyclization of amides **288** (**Scheme 160**) <1977ACH(92)317>. The amide **290** can be cyclized to benzothiazine **291** with phosphorus pentasulfide (**Scheme 161**).

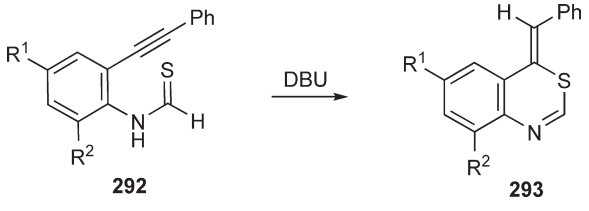


Scheme 160



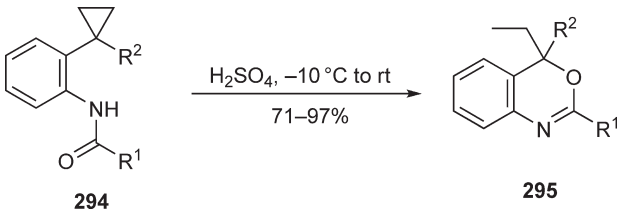
Scheme 161

N-(2-Phenylethynylaryl)methanethioamides **292** undergo 6-*exo-dig* cyclization to yield (*Z*)-4-benzylidene-4*H*-3,1-benzothiazines **293** (**Scheme 162**) <2003SL2231, CHEC-III(8.08.9.6)594>.



Scheme 162

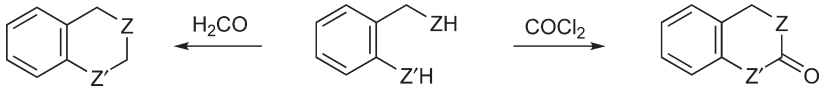
The intramolecular rearrangement of *N*-acyl-2-cyclopropylanilines **294** on treatment with sulfuric acid gives substituted 4*H*-3,1-benzoxazines **295** in high yields (**Scheme 163**) <CHEC-III(8.05.9.4)430>. *N*-Acylamino-2-alkenylbenzenes, in which the double bond of the alkyl chain is conjugated with the benzene ring, undergo a similar rearrangement <2003CHE794>.



294 **295**

Scheme 163

Saturated derivatives of types **296** and **298** can be made from the *o*-tolyl precursor **297** as shown in **Scheme 164**.



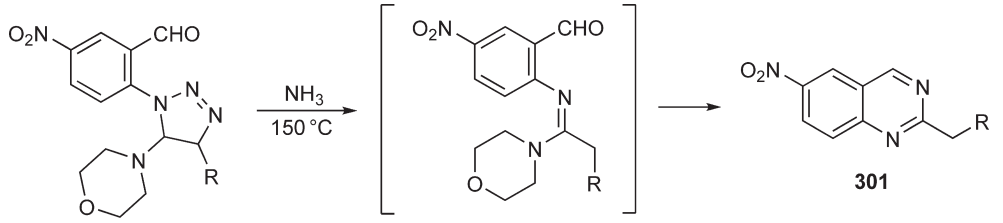
296 **297** **298**

Scheme 164

4.4.5.2.3 From other heterocycles

N-Alkylbenz[*d*]isoxazolium cations undergo base-catalyzed ring expansion to 1,3-benzoxazines (Section 3.4.3.12.3). Benzoxazinones are obtained by heating 3-acylanthranils (Section 3.4.3.4.4) or acylating anthranils (Section 3.4.1.8.6).

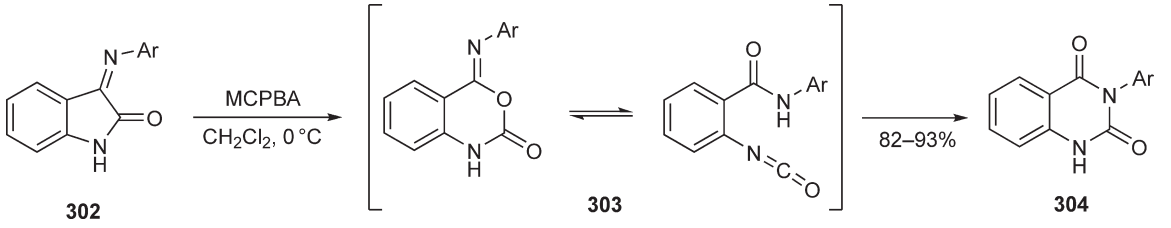
2-Substituted quinazolines **301** have been prepared by treatment of dihydrotriazolines **299** with ammonia, in a process which involves initial thermal ring opening to an amidine **300**, and cyclocondensation of the ammonia with the amidine and carbonyl groups (**Scheme 165**) <1999J(P1)421, CHEC-III(8.02.10.2)228>.



299 **300** **301**

Scheme 165

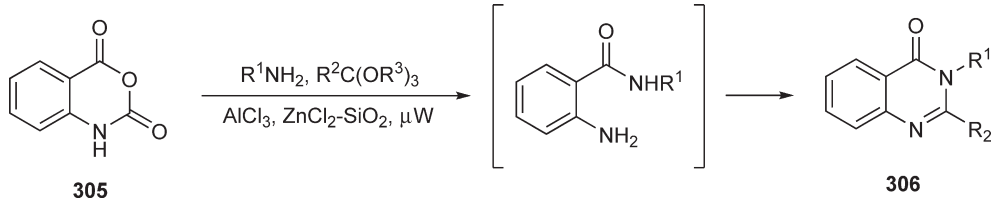
3-Aryl-2,4-quinazolinediones **304** can be prepared from 3-arylimino-2-indolinones **302** by oxidation with *m*-chloroperbenzoic acid at 0°C (**Scheme 166**) <2000TL5265>. The reaction proceeds through benzoxazinone and isocyanate intermediates **303** <CHEC-III(8.02.10.2)229>.



302 **303** **304**

Scheme 166

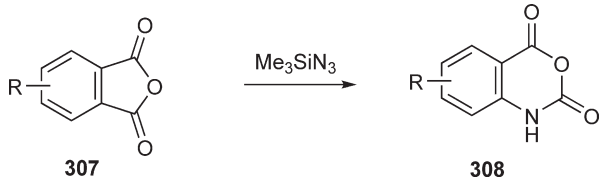
The 2,3-disubstituted 4(3*H*)-quinazolinones **306** are often prepared by reaction of amines with isatoic anhydride **305** <CHEC-III(8.02.9.2.1)219> as exemplified by **Scheme 167** <2005SC279>.



305 **306**

Scheme 167

The reaction of phthalic anhydrides **307** with trimethylsilyl azide affords 1,3-benzoxazine-2,4-diones **308** in good yield (**Scheme 168**) <1995OPP651, 1998JOC6797, CHEC-III(8.05.10)444>.



307 **308**

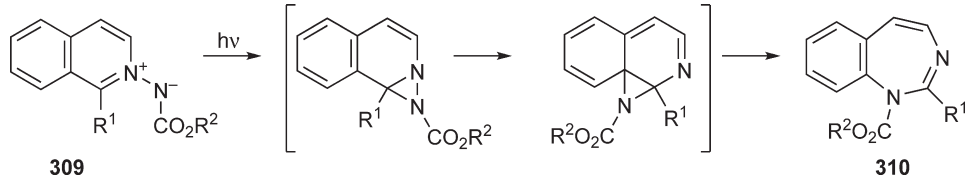
Scheme 168

4.4.5.3 Seven-Membered Rings

Benzoxazepines are obtained photochemically from quinoline 1-oxides (Section 3.2.3.12.5.4).

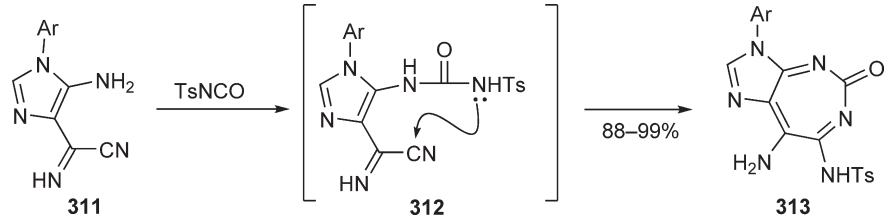
4.4.5.3.1 Seven-membered rings with heteroatoms 1,3 to a ring junction

The fully-unsaturated 1,3-benzodiazepine **310** is formed by a photoreaction of the 1-substituted isoquinoline *N*-imide **309** (**Scheme 169**) <1980CPB2602>. The same principle has been applied to prepare thieno-, furo-, and pyrrolo-fused 1,3-diazepines <1980CC454, 1981CPB1539>. The imidazolo-fused 1,3-benzodiazepin-2-ones **313** can be prepared by the reaction of 5-amino-4-(cyanoformimidoyl)imidazoles **311** with tosyl isocyanate. The mechanism of this reaction includes a 7-*exo-dig* cyclization of intermediates **312** followed by a Dimroth rearrangement to give the thermodynamic products **313** (**Scheme 170**) <1996JHC855, CHEC-III(13.05.9.2.2)174>.



309 **310**

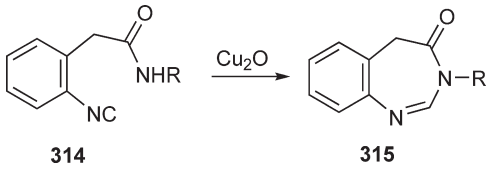
Scheme 169



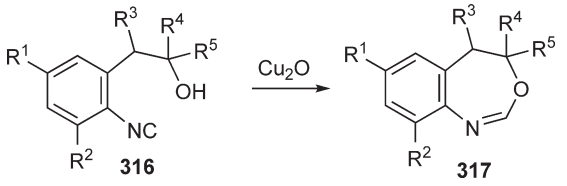
311 **312** **313**

Scheme 170

1,3-Benzodiazepin-4-ones **315** have been synthesized by the Cu_2O-catalyzed cyclization of **314**; the competing route to indoles is disfavored by bulky R groups (**Scheme 171**) <1979TL1039>. Likewise, the copper-catalyzed insertion of isocyanides **316** into the OH bond of alcohols provides a high-yielding route to 4,5-dihydro-3,1-benzoxazepines **317** (**Scheme 172**) <1978TL2087>.

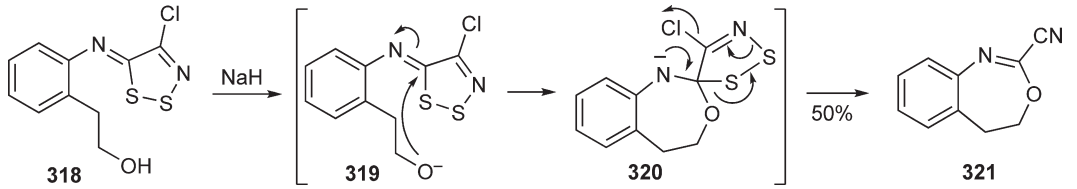


Scheme 171



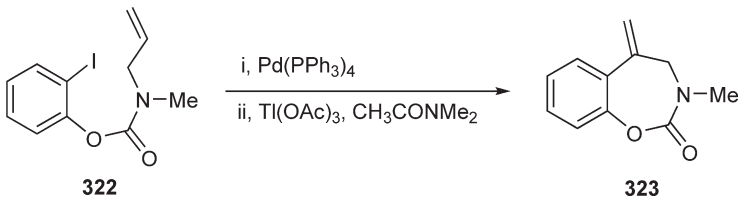
Scheme 172

Heating the alcohol **318** and NaH in THF affords the 3,1-benzoxazepine **321** in moderate yield. This reaction proceeds *via* intramolecular nucleophilic attack by the alkoxide on the exocyclic imino group in **319**, followed by expulsion of S_2 and Cl in the dithiazole intermediate **320** to afford **321** (**Scheme 173**) <1997SL704, CHEC-III (13.08.4.1)247>.



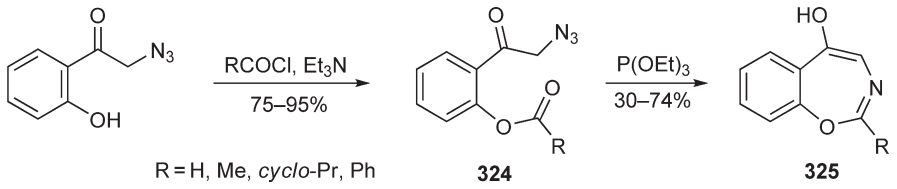
Scheme 173

The cyclization of aryl iodide **322** with a Pd(0) catalyst and thallium acetate provides a convenient approach to the 1,3-benzazepinone system **323** (**Scheme 174**) <1998ICA123, CHEC-III(13.08.4.1.3)249>.



Scheme 174

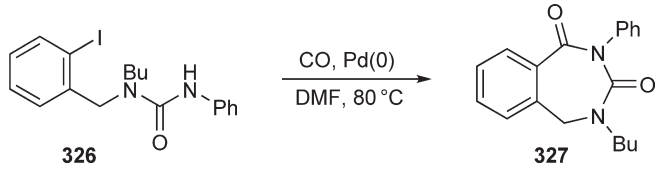
The fully-unsaturated 1,3-benzoxazepine system **325** can be obtained by intramolecular aza-Wittig reaction of the esters **324** induced by triethyl phosphite (**Scheme 175**) <1990S455, 1992CC81>.



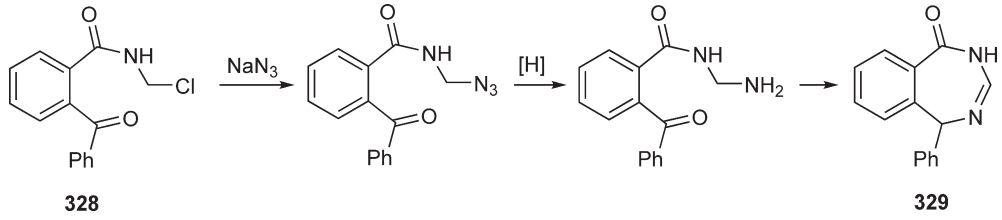
Scheme 175

4.4.5.3.2 Seven-membered rings with heteroatoms 2,4 to a ring junction

Carbonylation of **326** using a Pd(0) catalyst under CO atmosphere affords 2,4-benzodiazepin-1,3-dione **327** (**Scheme 176**) <1999TL2623, CHEC-III(13.05.9.2.5)175>. Treatment of **328** as shown in **Scheme 177** gives 2,4-benzodiazepin-1-one **329** <1975JHC903>.

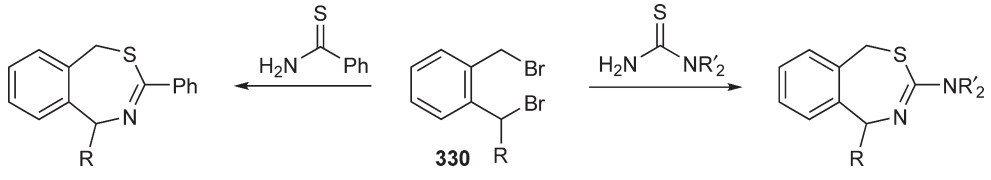


Scheme 176



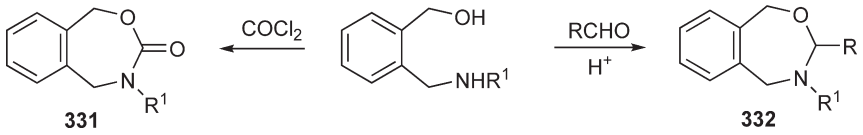
Scheme 177

The reaction of 1,4-dihalo compounds (e.g., *o*-xylyl dibromides **330**) with thioureas or thioamides can lead to 2,4-benzothiazepines (**Scheme 178**) <1975CPB1764, 1977HCA2872>. *o*-Chloromethylbenzoyl halides similarly give 2,4-benzothiazepin-5-ones and 4-bromobutyryl chloride gives the 1,3-benzothiazepin-4-one system.



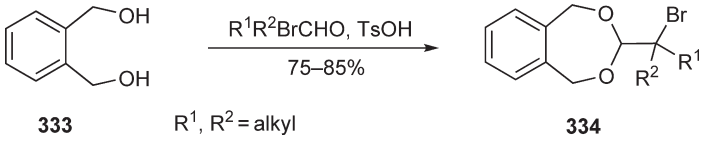
Scheme 178

One-pot reactions involving successive nucleophilic attack by oxygen and nitrogen on a 1,1-bis-carbon electrophile (e.g., phosgene or an aldehyde) are used in the synthesis of 2,4-benzoxazepine systems **331** and **332** (**Scheme 179**) <1972JHC1209, 1975FES773>.

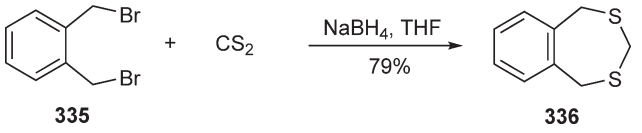


Scheme 179

Reaction of 1,2-benzenedimethanol **333** with aldehydes or related compounds gives 1,5-dihydro-3*H*-2,4-benzodioxepins **334** as exemplified in **Scheme 180** <2001TL3183, CHEC-III(13.11.11.2)361>. The analogous benzodithiepin system **336** can be prepared by the reaction of 1,2-benzenedimethanethiol with methylene iodide in the presence of base or from the dibromide **335** and CS_2 as shown in **Scheme 181** <2000OL1133, CHEC-III(13.11.9.4)356>.



Scheme 180

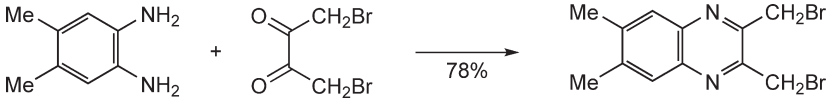


Scheme 181

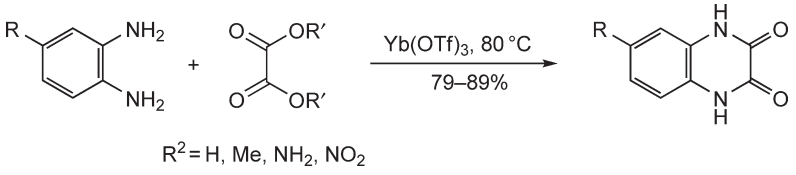
4.4.6 Two Heteroatoms 1,4 to a Ring Junction

4.4.6.1 Quinoxalines and Azinopyrazines

Condensation of 1,2-diaminobenzenes with 1,2-dicarbonyl compounds provides the most practical approach to quinoxalines <CHEC-III(8.03.9.1)307>, as exemplified by **Scheme 182** <1995JOC8283> and **Scheme 183** <2004SC1349>.

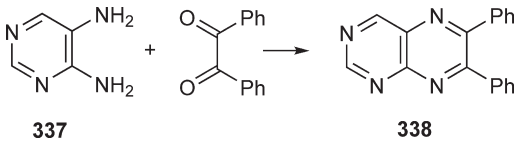


Scheme 182



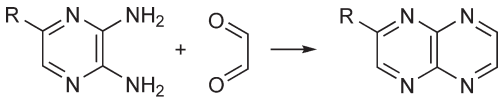
Scheme 183

Heterocyclic *o*-diamines react analogously, as in the preparation of pteridines (e.g., **338**) by condensation of a 5,6-diaminopyrimidine **337** with a 1,2-dicarbonyl compound (**Scheme 184**) <CHEC-III(10.18.9.1)934> and pyrazinopyrazines (e.g., **340**) from *o*-pyrazinediamines **339** and glyoxal (**Scheme 185**) <CHEC-III(10.19.2.5.3)1044, 2004OL2007, 2005BML3241>.



337 338

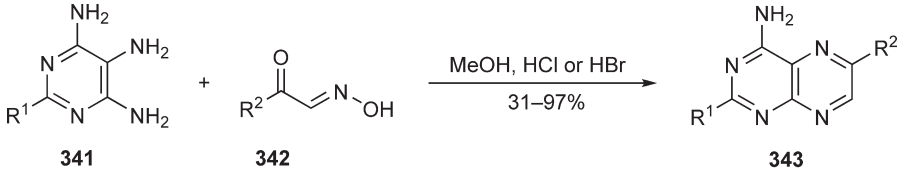
Scheme 184



339 340

Scheme 185

The condensation of a 5,6-diaminopyrimidine **337** with nonsymmetrical 1,2-dicarbonyl compounds commonly affords mixtures of isomeric products. By converting an aldehyde into its oxime, the reactivity difference in -dicarbonyl compounds can be magnified to afford single products in condensation reactions. Based on this approach, the regioselective, one-step synthesis of 2,6-disubstituted 4-aminopteridines **343** from 2-substituted 4,5,6-triaminopyrimidines **341** and -ketoaldoximes **342** has been achieved (**Scheme 186**) <1997TL6835, CHEC-III(10.18.9.1)934>. The oxime methodology has also been used in a large study of inhibitors of nitric oxide synthase <1999JME4108>.



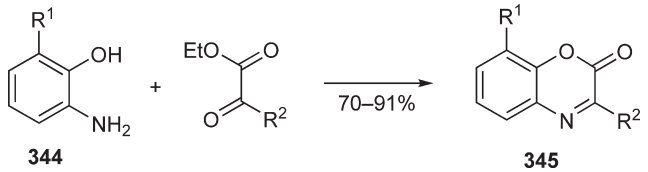
341 342 343

R^1 = H, NH_2, SMe, Ph; R^2 = Me, Et, CH_2Cl, CH_2Br, Ph, *p*-Tol

Scheme 186

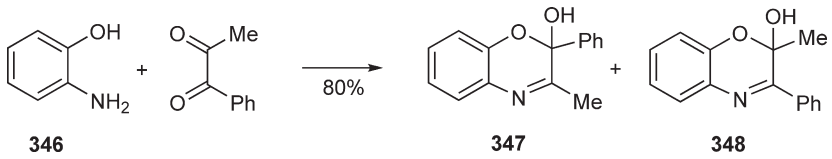
4.4.6.2 1,4-Benzoxazines and 1,4-Benzothiazines

1,4-Benzoxazines are commonly prepared from 2-aminophenols by reaction with 1,2-dielectrophiles <CHEC-III(8.06.9.3.1) 493>. For example, the aminophenol **344** reacts with -ketoesters to give **345** (**Scheme 187**) <1961CB1664>, which is probably the result of initial rapid imine formation followed by lactonization. The reaction of **346** and 1-phenyl-1,2-propanedione affords a mixture of the isomeric compounds **347** and **348** in a 3:2 ratio (**Scheme 188**) <1999M1481>.



344 345

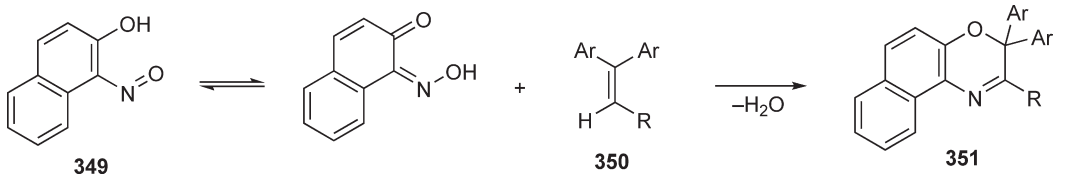
Scheme 187



346 347 348

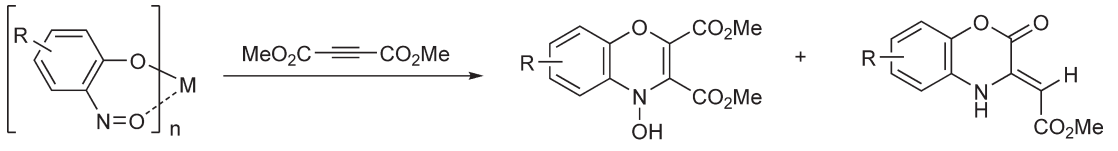
Scheme 188

[4 + 2] Cycloadditions have also been used to form benzoxazines <CHEC-III(8.06.9.3.1)493>. The reactants are typically an alkene such as **350** and a 1-nitroso-2-naphthol **349** (the tautomeric form of a 1,2-benzoquinone monoxime) (**Scheme 189**) <1981TL3945>; microwave heating was found to improve yields of this process <2004SC315>. A similar, but metal-catalyzed cycloaddition of a 2-nitrosophenolate **352** with DMAD gives two isomeric products **353** and **354** (**Scheme 190**) <1995JCM454>.



349 **350** **351**

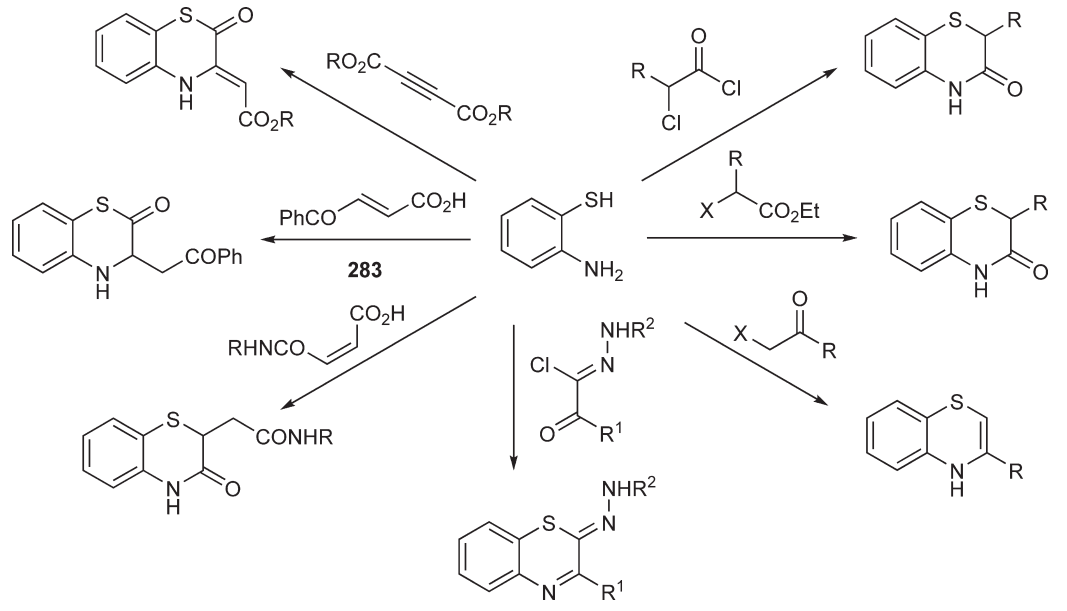
Scheme 189



352 **353** (30–70%) **354** (20–35%)

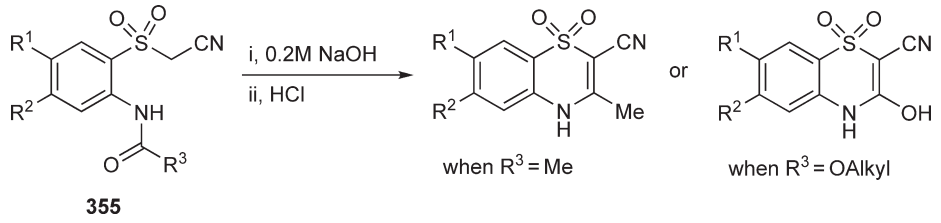
Scheme 190

1,4-Benzothiazines can be obtained from 2-aminothiophenols by their reactions with appropriate dielectrophiles, e.g., 2-chloroacyl chlorides <1990EJM403>, 2-haloesters <2003JME3670>, -haloketones <1999T7915>, iminochloroketones <1997H(45)1183>, maleic acid amides <1986T2731>, and acetylenedicarboxylates <2003T4785> as illustrated in **Scheme 191** <CHEC-III(8.09.9.3)658>.



Scheme 191

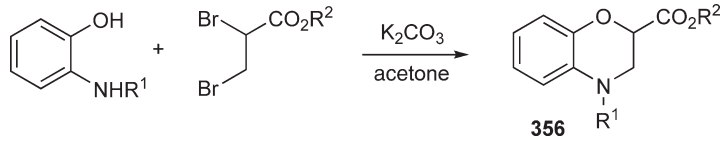
4*H*-1,4-Benzothiazine 1,1-dioxides can be synthesized from sulfones (e.g., **355**) by base-induced cyclization as exemplified in **Scheme 192** <2005BMC141, CHEC-III(8.09.9.1.3)653>.



355

Scheme 192

Dihydro-1,4-benzoxazines (e.g., **356**) are prepared from 2-aminophenol and its *N*-substituted derivatives with 1,2-dihalides under basic conditions as illustrated in **Scheme 193** <CHEC-III(8.06.9.3.2)496>.



356

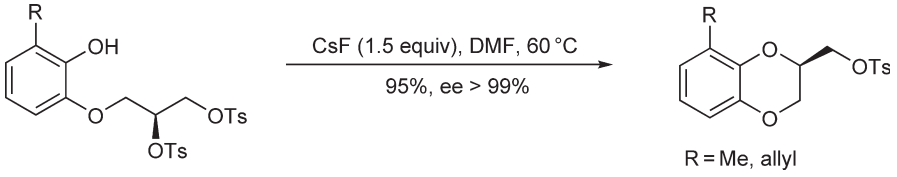
Scheme 193

4.4.6.3 Rings Containing Oxygen and/or Sulfur Atoms

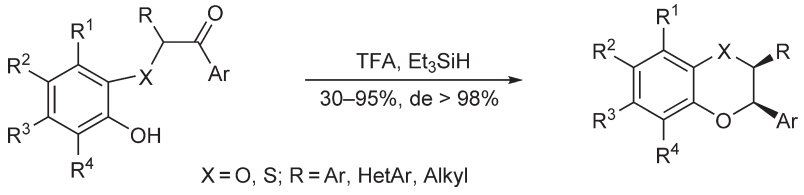
The monobenzo-fused derivatives of 1,4-dioxin **357** (Y = Z = O), 1,4-oxathiin **357** (Y = O, Z = S), and 1,4-dithiin **357** (Y = Z = S) can all be prepared by base-catalyzed reaction between the appropriate 1,2-disubstituted benzene and an -haloethanal ketal *via* an intermediate 2-alkoxy-2,3-dihydro derivative **358** <1967ZC152>.

357 Y, Z = O or S **358**

Other general routes to benzo-fused derivatives of 1,4-dioxanes, 1,4-oxathianes, and 1,4-dithianes make use of anions or dianions of the appropriate 1,2-disubstituted benzene as exemplified by **Scheme 194** <2001ASC95> and **Scheme 195** <2003OL685, CHEC-III(8.12.9.1)882>.

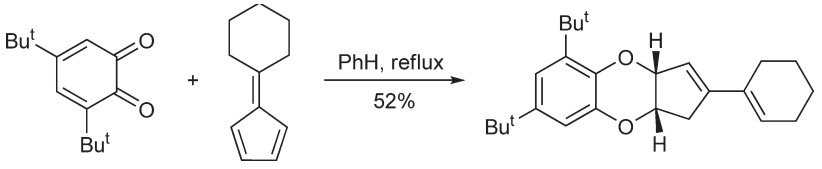


Scheme 194



Scheme 195

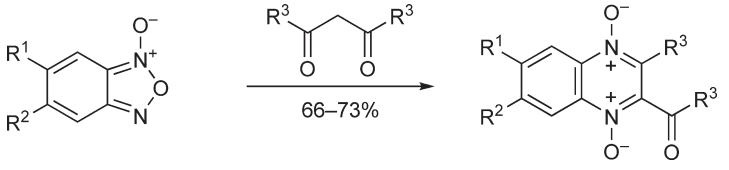
An alternative approach to the synthesis of 1,4-benzodioxanes involves DielsAlder addition reactions of alkenes across the quinone function of 1,2-benzoquinones, e.g., **Scheme 196** <1996T4029, 1999T11017, CHEC-III (8.12.9.1.4)887>.



Scheme 196

4.4.6.4 Synthesis from Heterocyclic Precursors

Initial nucleophilic attack and ring opening are involved in the conversion of benzofuroxans into quinoxaline di-*N*-oxides by treatment with imines, enamines, carbonyl compounds, and active methylene compounds (the Beirut reaction, also see Section 3.4.1.10.1); a representative example is shown in **Scheme 197** <2003EJM791, 2005H(65) 1589, CHEC-III(8.03.10)313>.

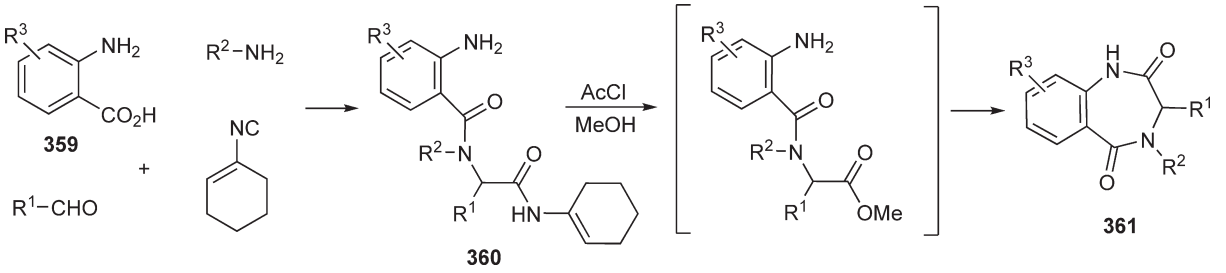


Scheme 197

4.4.6.5 Seven-Membered Rings with Two Heteroatoms 1,4 to a Ring Junction

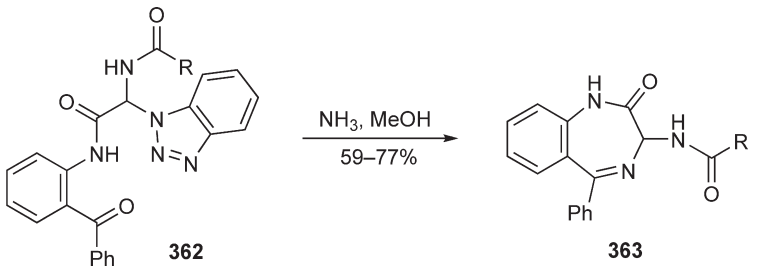
4.4.6.5.1 1,4-Benzodiazepines

A particularly important route to 1,4-benzodiazepine-2,5-diones **361** is based on ring-closure of precursors **360** prepared from anthranilic acids **359** using the Ugi reaction, a 4-component process that allows considerable structural diversity to be introduced in a combinatorial fashion (**Scheme 198**) <1996JA2574, 1996JOC8935, CHEC-III(13.06.9.1)202>. The convenience of this procedure is further enhanced by using resin-bound isocyanides <2002OL1167, 2002TL4083>.



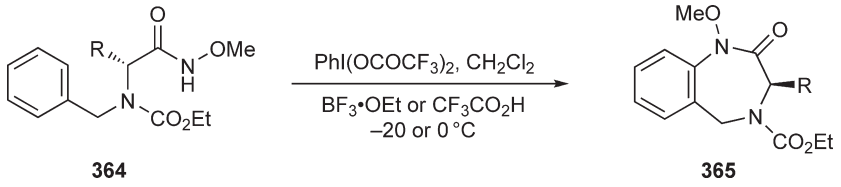
Scheme 198

3-Amino-2,3-dihydrobenzo-1,4-diazepine-2-ones **363** are obtained in good yield by cyclization of -amidobenzotriazoles **362** in a saturated solution of ammonia in methanol (**Scheme 199**) <1995JOC730, 2001M747, 2003JOC2844, CHEC-III(13.06.9.1.6)208>. In this reaction the synthetically versatile benzotriazole moiety offers an effective and convenient leaving group that facilitates ring-closure.



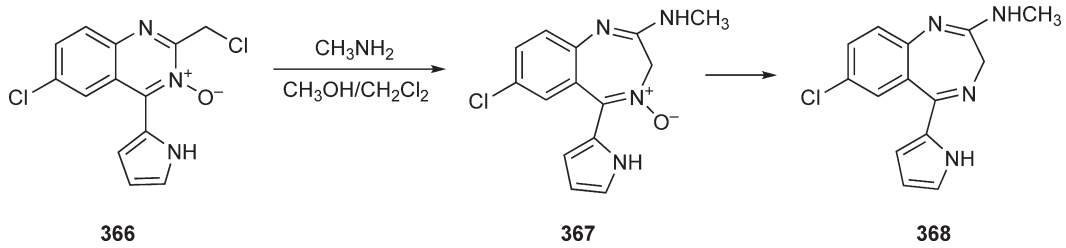
Scheme 199

The oxidation of *N*-alkoxyamides (e.g., **364**) with [bis(trifluoroacetoxy)iodo]benzene provides an efficient route to 1,4-benzodiazepine derivatives **365** under mild conditions (**Scheme 200**) <2005JOC2256>. This cyclization has been used to prepare synthetic precursors to the antitumor antibiotic (±)-DC-81 <2003T7103, 2005JOC2256>.



Scheme 200

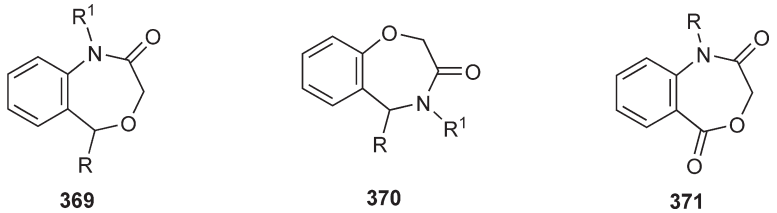
Addition of methylamine to the 2-position of the quinazoline *N*-oxide **366** results in a ring-expansion to give the 1,4-benzodiazepine *N*-oxide **367**, which can be further reduced with Raney nickel to afford the HIV Tat antagonist **368** (**Scheme 201**) <1995BMC391, CHEC-III(13.06.10.2)224>.



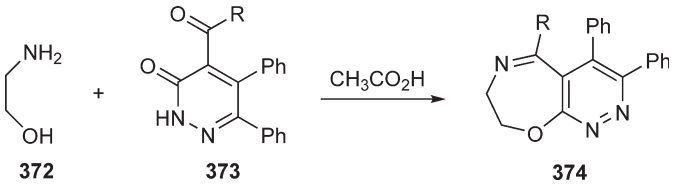
Scheme 201

4.4.6.5.2 1,4- and 4,1-Benzoxazepines, 1,4- and 1,5-benzothiazepines, and 1,4-benzodioxepins

o-Aminobenzyl alcohols are used as precursors to 4,1-benzoxazepin-2-ones **369** <1965FES323>, *o*-hydroxybenzylamines give 1,4-benzoxazepin-3-ones **370** <1966JHC237, 1971JOC305>, and anthranilic acids give 4,1-benzoxazepine-2,5-diones **371**. For example, compounds **370** are obtained by the reaction of *o*-hydroxybenzylamines with bromoacetic esters <1971JOC305>.

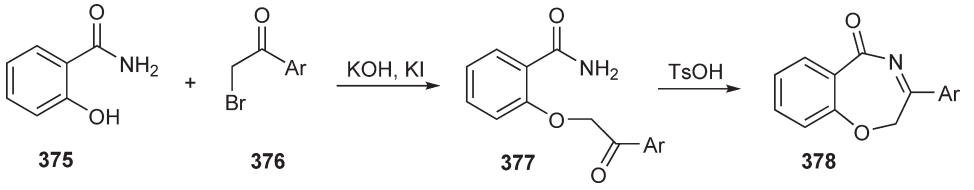


The reaction of 2-aminoethanol **372** with ketones **373** affords the pyridazino-oxazepine **374** (**Scheme 202**) *via* intermediate formation of the corresponding enamines <2003PS199, CHEC-III(13.09.9.1)273>.



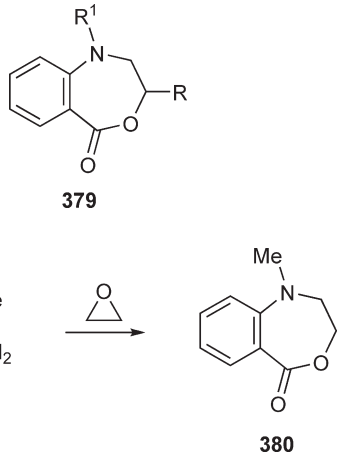
Scheme 202

Alkylation of the salicylamide **375** with aryl bromomethyl ketones **376**, followed by the acid-mediated cycloconden-sation of intermediates **377** under DeanStark reflux conditions give the oxazepinones **378** in high yield (**Scheme 203**) <2002BML2367, CHEC-III(13.09.9.1)272>.



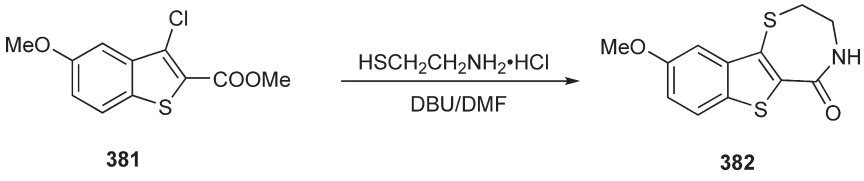
Scheme 203

Anthranilic acids and esters with halohydrins give the 4,1-benzoxazepin-5-one system **379** <1975BSF(2)283>. *o*-Methylaminobenzamide with ethylene oxide gives **380** (**Scheme 204**) <1966JOC4268>.



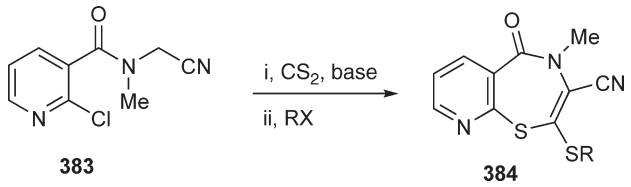
Scheme 204

The 1,4-benzothiazepin-5-one **382** is easily obtained in a one-pot reaction of **381** with cysteamine-HCl in the presence of base (**Scheme 205**) <1996JOC6060, CHEC-III(13.09.9.2)279>.



Scheme 205

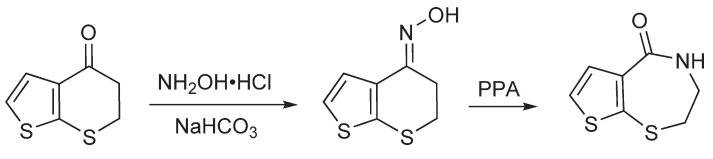
The aminonitrile **383** can be condensed with carbon disulfide and base, leading to an intermediate dithiocarboxylate, which undergoes intramolecular substitution. After alkylation of the remaining thiolate function, pyridothiazepinones **384** are formed (**Scheme 206**) <1998EJO1237>.



383 **384**

Scheme 206

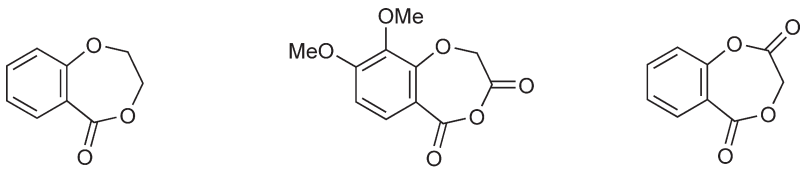
The reaction of oxime **385** with polyphosphoric acid results in ring expansion *via* Beckmann rearrangement leading to the fused 1,4-benzothiazepine derivative **386** (**Scheme 207**) <1997JHC921, CHEC-III(13.09.10.2)286>.



385 **386**

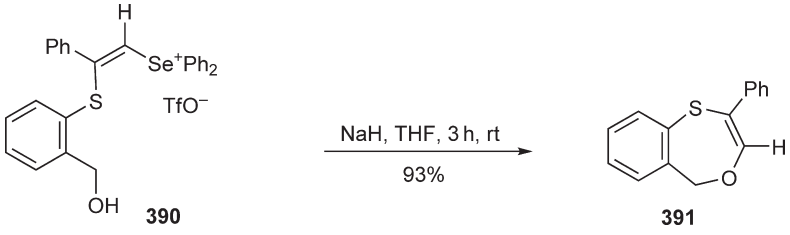
Scheme 207

The reaction of sodium salicylate and 2-chloroethanol gives 5*H*-1,4-benzodioxepinone **387** <1975BSF(2)277>. The dicarbonyl compound **388** is prepared by heating 2-carboxy-5,6-dimethoxyphenoxyacetic acid in acetic anhydride. Dicarbonyl compound **389** is prepared from chloroacetylsalicylic acid.



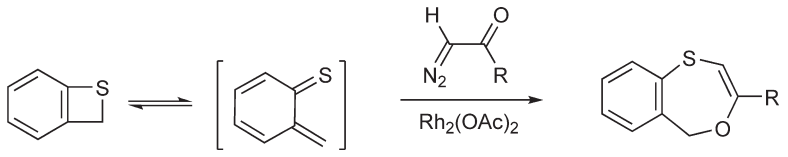
387 **388** **389**

Alkenylselenonium salts **390** undergo cyclization on treatment with sodium hydride to provide a useful approach to benzoxathiepins **391** (**Scheme 208**) <2000JOC8893, CHEC-III(13.12.8.2)374>. Benzoxathiepins have also been prepared by the reaction of 2*H*-1-benzothiete with diazo compounds in the presence of rhodium acetate (**Scheme 209**) <1995TL6047, CHEC-III(13.12.9)377>.



390 **391**

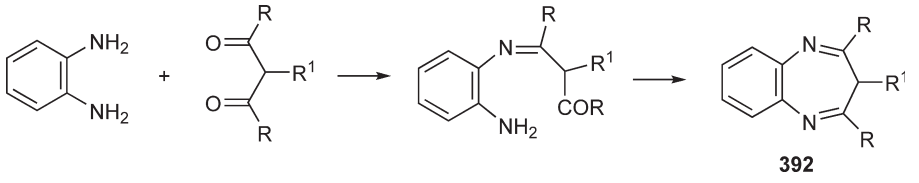
Scheme 208



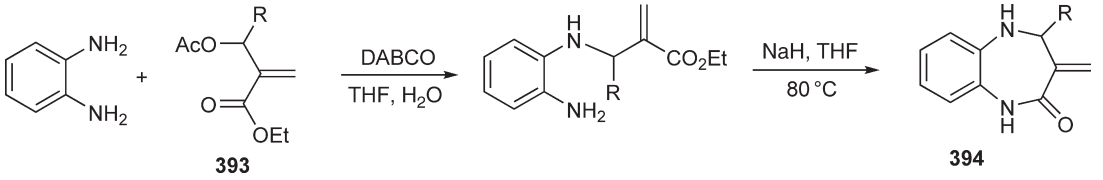
Scheme 209

4.4.6.6 Seven-Membered Rings with Two Heteroatoms 1,5 to a Ring Junction

1,5-Benzodiazepines **392** are generally prepared from the appropriately *o*-disubstituted benzene (e.g., *o*-phenylenediamine) and a 1,3-bis carbon electrophile (**Scheme 210**) <CHEC-III(13.06.9.2)217>. For example, acetylated derivatives of BaylisHillman adducts **393** derived from ethyl acrylate and aromatic or heteroaromatic aldehydes readily react with *o*-phenylenediamine under the influence of base to provide 1,4-benzodiazepin-2-ones **394** in good overall yields (**Scheme 211**) <2006S4205>.

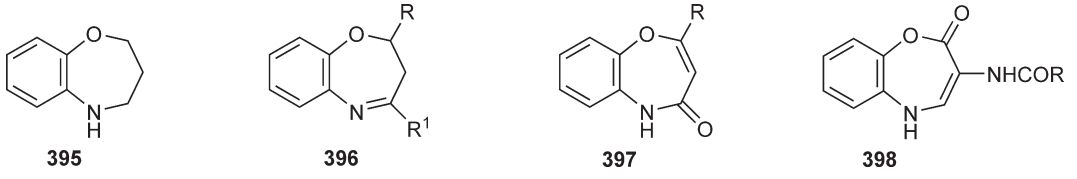


Scheme 210

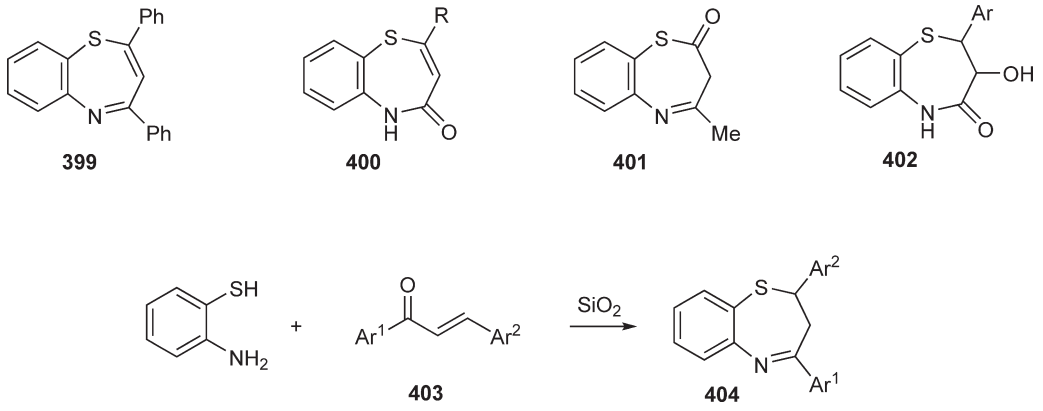


Scheme 211

1,4-Benzoxazepines are prepared similarly from *o*-aminophenols <CHEC-III(13.09.0.1)217>. 2-Aminophenol with 1,3-dibromopropane gives 1,4-benzoxazepine **395** and 3-chloropropionyl chloride gives the analogous 4-oxo derivative. Similarly ,-unsaturated ketones give **396**, -keto esters give **397**, and 1,3-oxazolidin-5-ones give **398**.

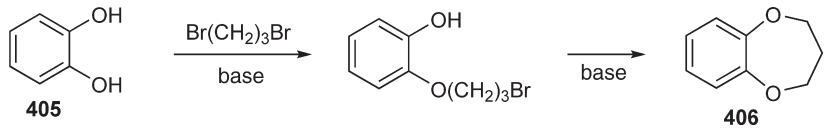


In a similar fashion, 2-aminothiophenol can be reacted with 1,3-bis-carbon electrophiles to give various types of 1,5-benzothiazepine <CHEC-III(13.09.9.2)279>. Thus, 1,3-diphenylpropynone gives **399**, reaction with -keto esters gives products of type **400**, reaction with diketene gives **401**, and reaction with methyl 3-arylglycidates gives **402**. The reaction of *o*-aminothiophenol with chalcones **403** gives 1,4-benzothiazepines **404** in excellent yield under solvent-free conditions in the presence of silica gel (**Scheme 212**) <2004SC1783, CHEC-III(13.09.9.2)280>.



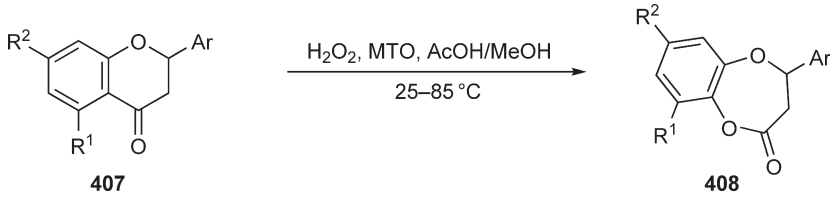
Scheme 212

The major routes to 3,4-dihydro-2*H*-1,5-benzodioxepins **406** employ catechol **405** as starting compound (**Scheme 213**) and are applicable to a wide range of substituted derivatives. The 3-oxo derivative can be prepared *via* the reaction of catechol with chloroacetonitrile <1975CJC2279>.



Scheme 213

The BaeyerVilliger oxidation of flavanones **407** using methyltrioxorhenium (MTO) catalyst affords 1,5-benzodioxepin-2-ones **408** in excellent yields (**Scheme 214**) <CHEC-III(13.09.9.2)279, 2001TL5401, 2003TL4823>.

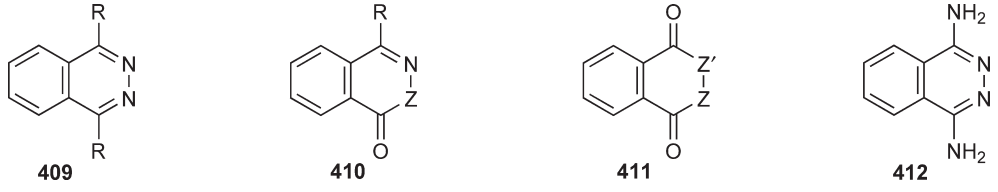


Scheme 214

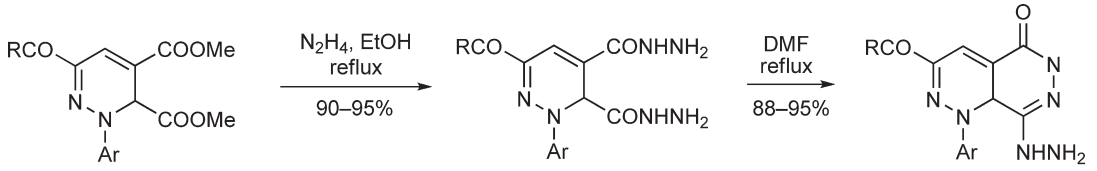
4.4.7 Two Heteroatoms 2,3 to a Ring Junction

4.4.7.1 Six-Membered Rings

o-Diacylbenzenes with hydrazine form phthalazines **409**. Monoxo compounds of type **410** result from *o*-acylbenzoic acids and hydrazine or hydroxylamine, and dioxo derivatives **411** from phthalic acid derivatives with N_2H_4, NH_2OH, or H_2O_2. Phthalodinitrile is converted by methanolic hydrazine into 1,4-diaminophthalazine **412** <1968JHC111>.

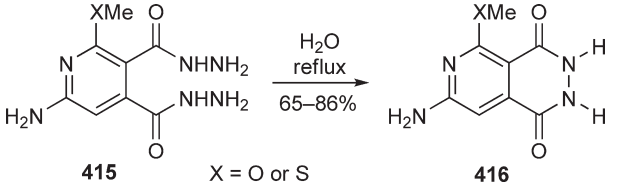


Many other [*c*]-fused pyridazines have been prepared similarly. The condensation of a pyridazine-2,3-dicarboxylic acid derivatives **413** with hydrazine gives rise to 8-hydrazinopyridazino[4,5-*c*]pyridazines **414** (**Scheme 215**) <2001S1861, 2004JHC647, CHEC-III(10.19.2.1.3)982>. Pyrido[3,4-*d*]pyridazine derivative **416** is obtained similarly from azaphthalohydrazide **415** (**Scheme 216**) <1997T8225, CHEC-III(8.01.9.1.2)73>. Pyridazine-3,4-dicarbonitrile **417** with hydrazine gives the diamino heterocycle **418** (**Scheme 217**) <1967JHC393>.



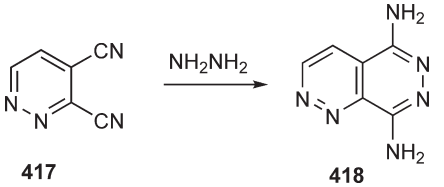
413 **414**

Scheme 215



415 X = O or S **416**

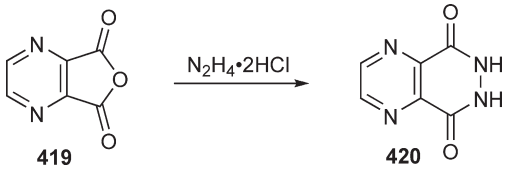
Scheme 216



417 **418**

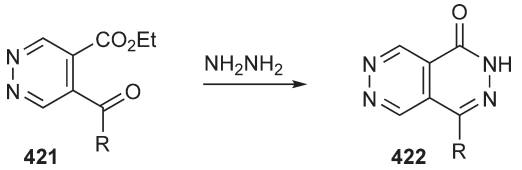
Scheme 217

Pyrazino[2,3-*d*]pyridazine-5,8-dione **420** can be prepared from pyrazine-2,3-dicarboxylic acid anhydride **419** (**Scheme 218**). Likewise, the reaction of a pyridazine-4,5-dicarboxylic acid derivative with hydrazine is the most convenient approach to pyridazino[4,5-*d*]pyridazines <2000TL2863, CHEC-III(10.19.2.1.3)984>; a related synthesis of pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones **422** from ethyl 5-acylpyridazine-4-carboxylates **421** is shown in **Scheme 219** <1979M365>.



419 **420**

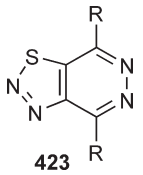
Scheme 218



421 **422**

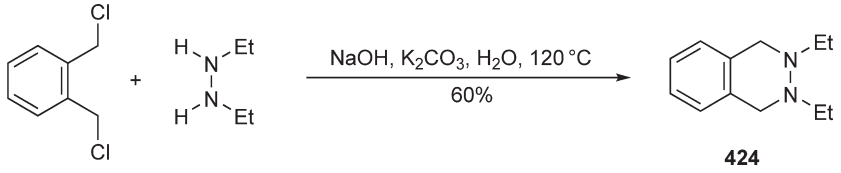
Scheme 219

The 1,2,3-thiadiazolo[4,5-*d*]pyridazines **423** are prepared similarly from the appropriate thiadiazoles <1976JHC301>.



423

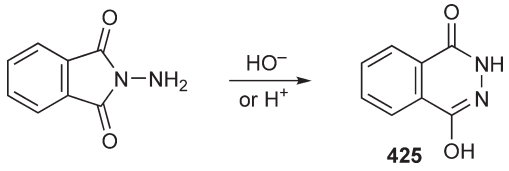
Tetrahydrophthalazines (e.g., **424**) and analogues can be made as indicated in **Scheme 220** <2006JOC135, CHEC-III(8.01.9.2.2)83>.



424

Scheme 220

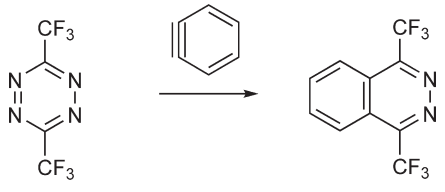
2-Aminophthalimide when heated with dilute alkali or acid is rearranged into 4-hydroxyphthalazin-1(2*H*)-one **425** (**Scheme 221**) <1955JCS852>.



425

Scheme 221

Various fused pyridazine derivatives can be prepared by the inverse-electron-demand DielsAlder cycloadditions of 1,2,4,5-tetrazines with a wide range of alkynes and alkenes <CHEC-III(8.01.10.3)88>. For example, 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **426** cycloadds to benzyne giving a quantitative yield of 1,4-bis(trifluoromethyl)phthalazine **427** (**Scheme 222**) <1987AGE332>.

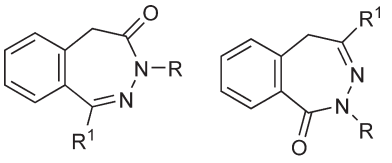


426 **427**

Scheme 222

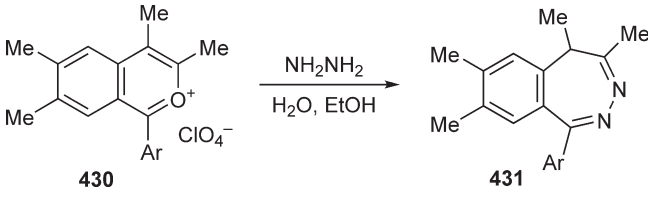
4.4.7.2 Seven-Membered Rings

Reactions of appropriate carbonyl precursors with hydrazine have been used to obtain compounds such as 3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones **428** and 2,5-dihydro-1*H*-2,3-benzodiazepin-l-ones **429** <1967AHC(8)21>.



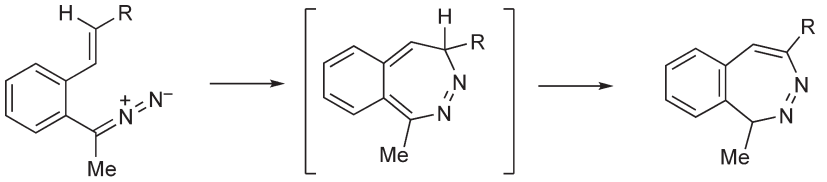
428 429

Reaction of 2-benzopyrylium perchlorate **430** with hydrazine gives 1-aryl-5*H*-2,3-benzodiazepines **431** (**Scheme 223**) <CHEC-III(13.04.10.3)155, 2001MI243>. 1*H*-2,3-Benzodiazepines **433** <1994J(P1)3149, CHEC-III(13.04.9.2)150> and analogous thienodiazepines <1980J(P1)1718> are obtained from electrocyclic reaction of diazo derivatives **432** (**Scheme 224**).



430 431

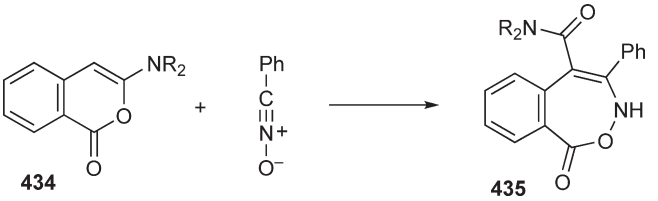
Scheme 223



432 433

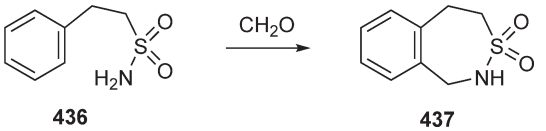
Scheme 224

The 2,3-benzoxazepin-l-one system **435** is prepared by the reaction of benzonitrile oxide with the benzopyranone **434** (**Scheme 225**) <1980J(P1)846>. The intramolecular sulfonamidomethylation of **436** by reaction with formaldehyde affords tetrahydro-3,2-benzothiazepine 3,3-dioxide **437** (**Scheme 226**) <1976CC470>.



434 435

Scheme 225



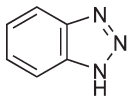
436 437

Scheme 226

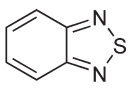
4.4.8 Three or More Heteroatoms

4.4.8.1 Five-Membered Heterocyclic Rings

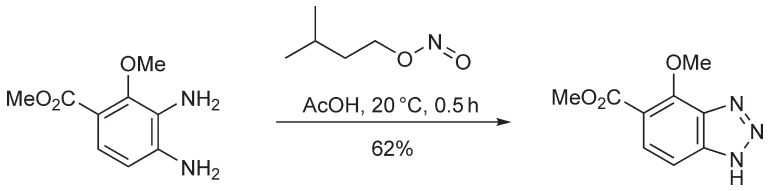
o-Phenylenediamine is readily converted by HNO_2 into 1,2,3-benzotriazole **438** and by $SOCl_2$ into 2,1,3-benzothiadiazole **439**. Best synthetic methods for the preparation of 1,2,3-benzotriazoles are summarized in the related section of CHEC-III <CHEC-III(5.01.11.2)140>; most important procedures are based on the reactions of substituted *o*-phenylenediamines with nitrous acid or nitrites as illustrated by **Scheme 227** <2006JME4762>. Likewise, the annulated thiadiazoles are commonly synthesized by the reaction of sulfur electrophiles with appropriate 1,2-diamines (e.g., **Scheme 228**) <1999JA10281, 2004BML5045, CHEC-III(5.09.9.2)550>.



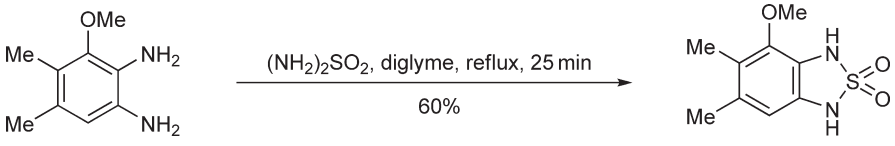
438



439

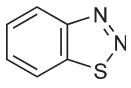


Scheme 227

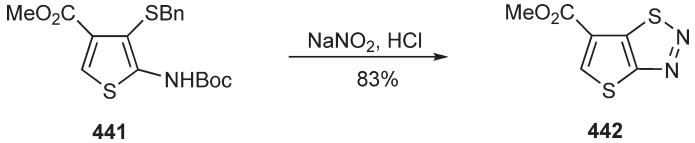


Scheme 228

The most common method for the preparation of 1,2,3-benzothiadiazoles (e.g., **440**) is the diazotization of 2-aminobenzenethiol or its derivatives <CHEC-III(5.07.11.3)483>. This method has been extended to include heterocyclic derivatives; thus the *tert*-butyloxycarbonyl (Boc)-protected derivative of 2-aminothiophene **441** can be converted into the thienothiadiazole **442** on treatment with sodium nitrite in HCl in high yield (**Scheme 229**) <1999JHC761>.



440



441 **442**

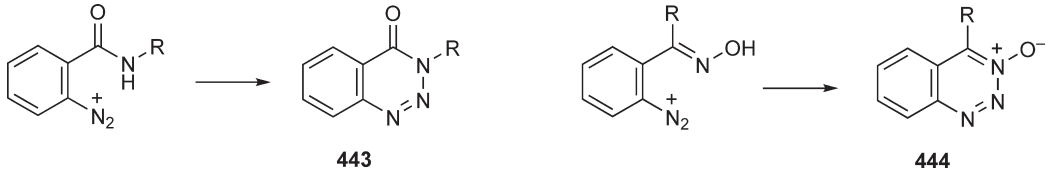
Scheme 229

Benzofurazans can be obtained by the benzazole rearrangement (Section 3.4.3.2.4).

4.4.8.2 Six-Membered Heterocyclic Rings

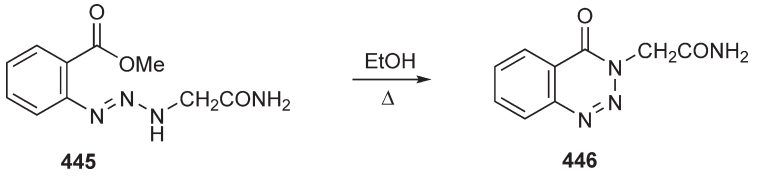
4.4.8.2.1 Three heteroatoms in the 1,2,3-positions

1. 1,2,3-Benzotriazines can be prepared by methods of the type illustrated for **443** and **444** (**Scheme 230**) <CHEC-III (9.01.9)76>, which resemble those used for the synthesis of cinnolines (cf. Section 4.4.4.3.1).

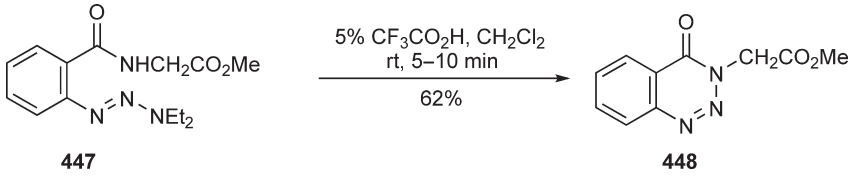


Scheme 230

Convenient procedures are based on the cyclization of the suitably *ortho*-substituted phenyltriazenes <CHEC-III (9.01.9)74>. For example, 1,2,3-benzotriazin-4-one **446** was obtained from 3-(carbamoylmethyl)-1-(2-alkoxycarbonyl) phenyltriazenes **445** by heating in a minimum volume of ethanol (**Scheme 231**) <1996JOC210>. A similar cyclization of **447** under acidic conditions affords the benzotriazine **448** (**Scheme 232**) <2004JCO38>.

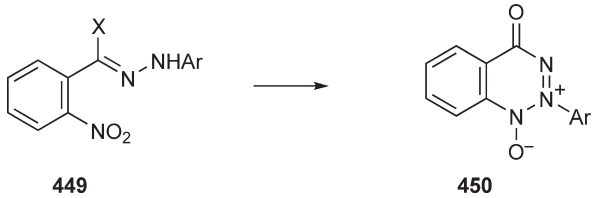


Scheme 231



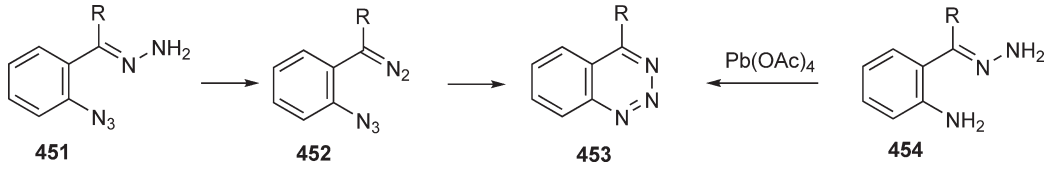
Scheme 232

2-Nitrobenzaldehyde arylhydrazones with a halogen give compounds **449** (X = Hal), which on treatment with base form 2-aryl-4-oxido-1,2,3-benzotriazinium betaine 1-oxides **450** (**Scheme 233**) <1974JOC2710>.



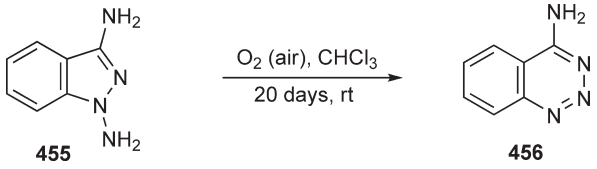
Scheme 233

Oxidation of 2-azidophenyl ketone hydrazones **451** affords the 2-azidophenyldiazoalkanes **452**, which can be cyclized thermally to 1,2,3-benzotriazines **453**. Similarly, 2-aminophenyl ketone hydrazones **454** give 1,2,3-benzotriazines **453** on oxidation with lead tetraacetate (**Scheme 234**) <1975J(P1)31>.



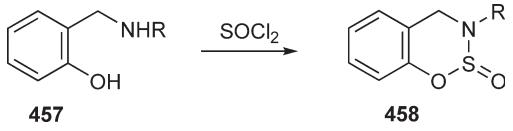
Scheme 234

Slow autoxidation in chloroform solution transforms 1,3-diaminoindazole **455** into 4-amino-1,2,3-benzotriazine **456** (**Scheme 235**) <2001CHE567, CHEC-III(9.01.10)79>.

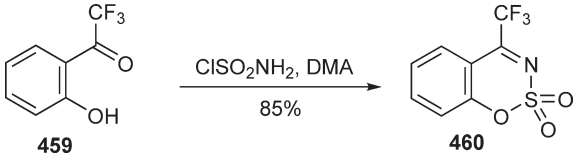


Scheme 235

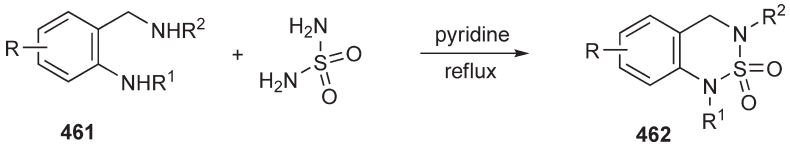
2. 1,2,3-Benzoxathiazine and 2,1,3-benzothiadiazine derivatives are usually prepared by the reaction of electrophilic sulfur reagents with *ortho*-substituted phenols and anilines; thus, **458** results from **457** with $SOCl_2$ (**Scheme 236**), **460** was prepared from *o*-acylphenol **459** (**Scheme 237**) <CHEC-III(9.10.9.2)555, 2005JA15391>, and the thiadiazine ring of **462** was constructed from diamine **461** by treatment with sulfamide (**Scheme 238**) <2001JME1847, 2003BMC367, 2004BML5045, CHEC-III(9.7.9.2.3)394>.



Scheme 236

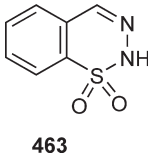


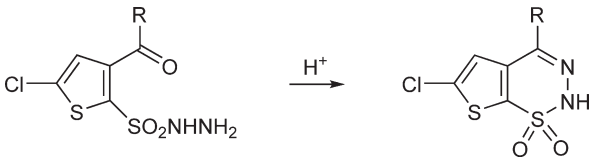
Scheme 237



Scheme 238

1,2,3-Benzothiadiazine 1,1-dioxides (e.g., **463**), which are cyclic sulfonylhydrazides, are prepared by the cyclization of appropriate arylhydrazides as exemplified in **Scheme 239** <CHEC-III(9.04.9.1)294>.

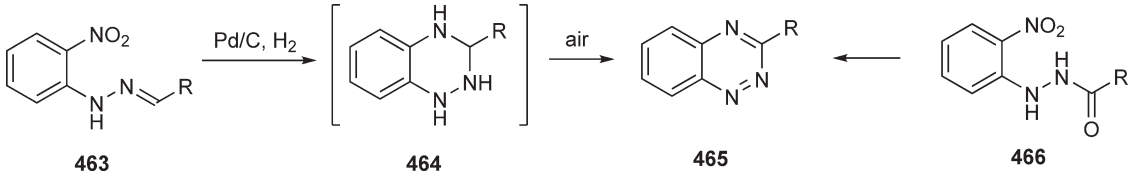




Scheme 239

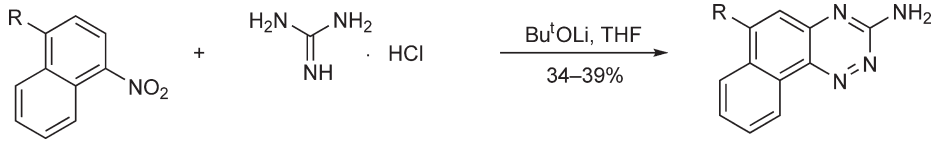
4.4.8.2.2 Three heteroatoms in the 1,2,4- or 1,3,4-positions

4.4.8.2.2.1 1,2,4-Benzotriazines. Reduction of 2-nitrophenylhydrazones **463** or similar hydrazides **466** gives 1,2-dihydro-1,2,4-benzotriazines **464** (**Scheme 240**). In most cases the initial dihydro compounds **464** are oxidized by air or potassium ferricyanide to the aromatic 1,2,4-benzotriazines **465** <1997J(P1)3107, 1999JHC589, CHEC-III (9.02.7.4)177>.

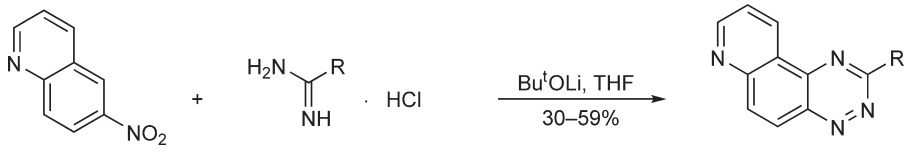


Scheme 240

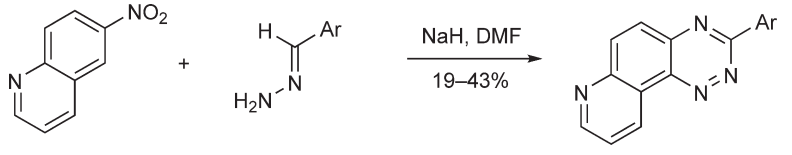
A series of condensed 1,2,4-triazines have been obtained from nitroarenes and guanidines or other *N*-nucleophiles as exemplified in **Schemes 241243** <1999JOC3361, 2002J(P1)696, 2006RCB1243, CHEC-III(9.02.7.1)158>. The key step in these reactions involves nucleophilic displacement of hydrogen *ortho* to a nitro group by the action of the *N*-nucleophile followed by intramolecular cyclization to the 1,2,4-triazine system.



Scheme 241

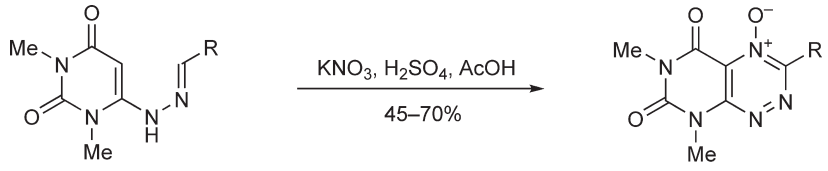


Scheme 242

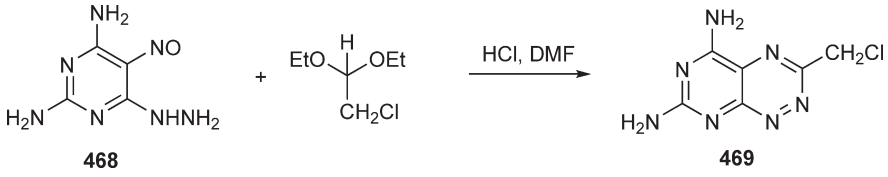


Scheme 243

Condensed 1,2,4-triazines can be obtained by the cyclization of hydrazones (e.g., **467**) with nitronium or nitrosonium cations as exemplified by **Scheme 244** <1999M819, CHEC-III(9.02.7.3.2)174>. Similar pyrimidotriazines (e.g., **469**) can be made by the reaction of 2,4-diamino-6-hydrazino-5-nitrosopyrimidine **468** with 1,1-diethoxy-2-chloroethane (**Scheme 245**) <2003BML2895>.

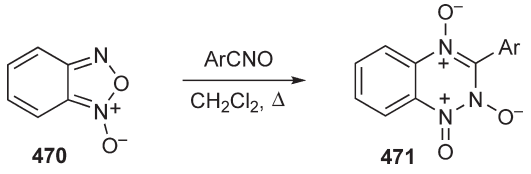


Scheme 244



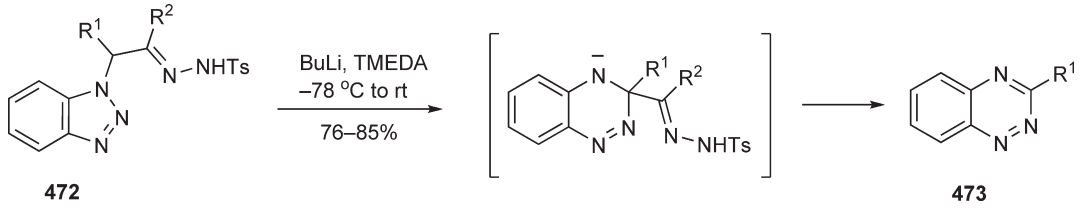
Scheme 245

Reaction of benzofuroxan **470** with nitrile oxides affords 1,2,4-benzotriazine 1,2,4-trioxides **471** (**Scheme 246**) <1989CC986>; this ring expansion is similar to the Beirut reaction (see Section 4.4.6.4).



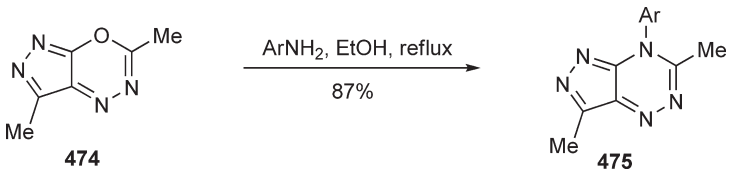
Scheme 246

Lithiation of -(benzotriazol-1-yl)-substituted tosylhydrazones **472** with butyllithium initiates the ring-opening and ring-closure reactions leading to 1,2,4-benzotriazines **473** (**Scheme 247**) <1997SC3963, CHEC-III(9.02.8.1)180>.



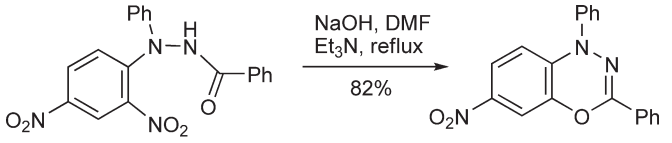
Scheme 247

The 1,3,4-oxadiazine ring in the pyrazolo[4,3-*e*][1,3,4]oxadiazine **474** is transformed into the 1,2,4-triazine **475** when treated with a primary arylamine (**Scheme 248**) <2002IJB664, CHEC-III(9.02.8.1)180>.



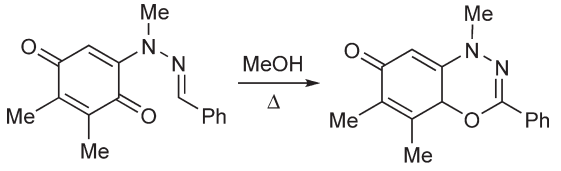
Scheme 248

4.4.8.2.2.2 Six-membered rings containing O or S atoms. 1,3,4-Benzoxadiazines (e.g., **477**) are prepared in high yields by ring closure of the suitably *ortho*-substituted phenylhydrazides (e.g., **476**) with displacement of NO_2 or halogen as exemplified in **Scheme 249** <1980JOC3677>. In a related approach, bicyclic 1,3,4-oxadiazinones **479** are obtained by briefly heating the hydrazino-1,4-benzoquinones **478** in methanol (**Scheme 250**) <2000T5137, CHEC-III (9.08.8.1)428>. Routes to 1,2,4-benzoxadiazines **482** involve the cyclization of nitrosoimine intermediates **481**, which can be generated by oxidation of *N*-arylamidoximes **480** (**Scheme 251**).



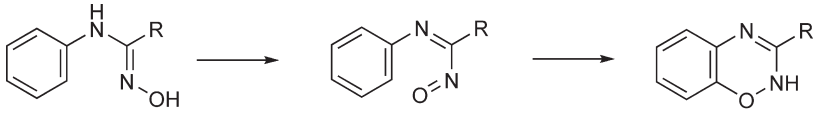
476 **477**

Scheme 249



478 **479**

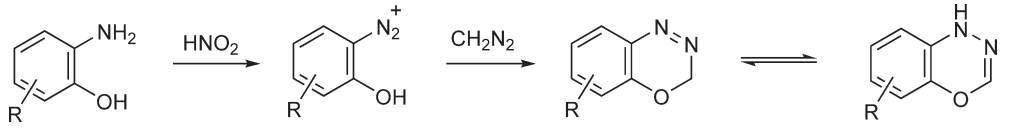
Scheme 250



480 **481** **482**

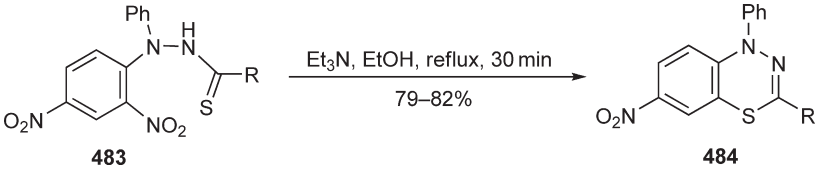
Scheme 251

Diazotization of 2-aminophenols followed by reaction with diazomethane gives 1,3,4-benzoxadiazines (**Scheme 252**); the initially formed 2*H*-isomers readily tautomerize to the more stable 4*H*-isomers <1970CB331>.



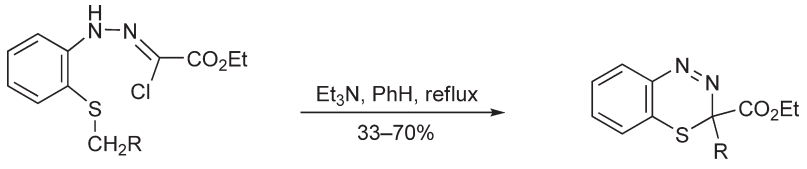
Scheme 252

1,3,4-Benzothiadiazines **484** are prepared by cyclization of **483** (**Scheme 253**) <1980JOC3677>, and similar heterocycles **486** result from cyclization of the chlorohydrazones **485** with triethylamine (**Scheme 254**) <1981J(P1) 2245>.



483 **484**

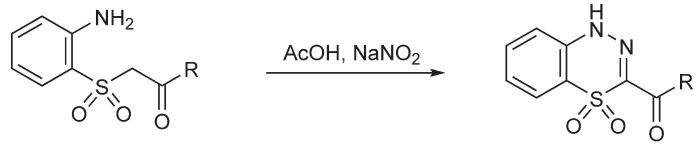
Scheme 253



485 486

Scheme 254

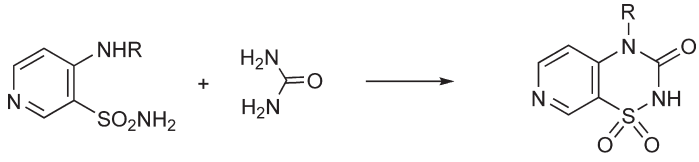
The cyclization of the *ortho*-substituted aniline **487** with acetic acid and sodium nitrite affords 4,1,2-benzothiadiazin-3-carboxylate 4,4-dioxides **488** *via* diazonium salt intermediates (**Scheme 255**) <1996JHC347, CHEC-III(9.08.8.1)429>.



487 488

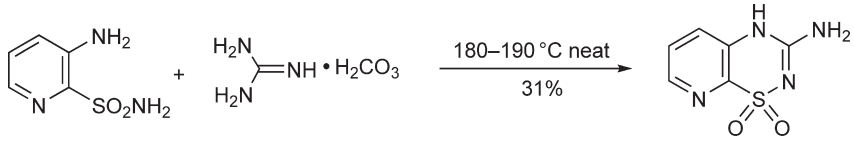
Scheme 255

Reaction of pyridine-derived aminosulfonamides **489** and **491** with urea or guanidine gives access to the fused 1,2,4-thiadiazine 1,1-dioxides **490** (**Scheme 256**) and **492** (**Scheme 257**), respectively <1999T5419, 2002JME90, CHEC-III (9.05.9.2.3)331>.



489 490

Scheme 256



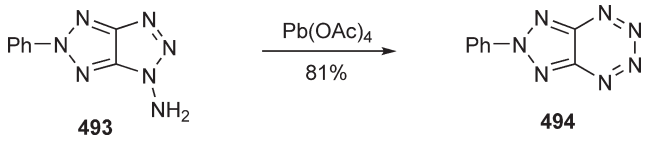
491 492

Scheme 257

4.4.8.2.3 Four heteroatoms

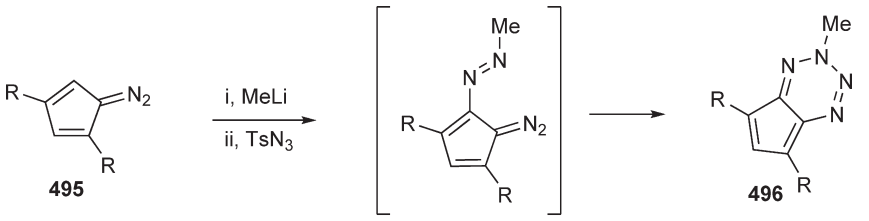
The triazolo-fused 1,2,3,4-tetrazine **494** was obtained in good yield on oxidation of 1-amino-5-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,3-triazole **493** with lead tetraacetate (**Scheme 258**) <1988CC1608>. Fused 1,2,3,4-tetrazines **496** were prepared *via* reaction of diazocyclopentadienes **495** with methyllithium, followed by a diazo transfer using tosyl azide, as shown in **Scheme 259** <1994CB1479, CHEC-III(9.13.9.2.1)730>.

The benzotetrazine oxides **498** have been prepared from *ortho*-(*t*-butylazoxy)anilines **497**, *via* nitration with N_2O_5 or NO_2BF_4 (**Scheme 260**) <2002EJO2342, 2002RCB1841, 2002RCB1849>.



493 494

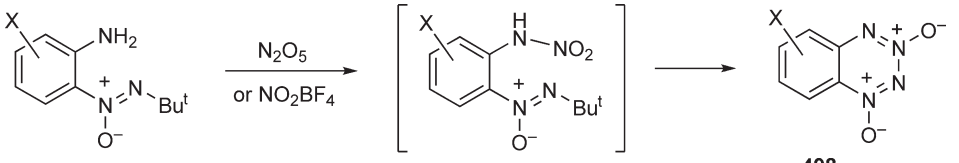
Scheme 258



495 496

R = H or Bu^t

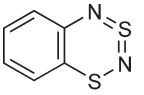
Scheme 259



497 X = Br or NO_2 498

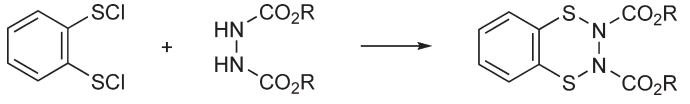
Scheme 260

The benzodithiadiazine **499** is formed by the ring closure of PhN═S═NSCl <1983CC73>.



499

1,2-Hydrazinedicarboxylates with 1,2-disulfenyl chlorides give 1,4,2,3-benzodithiadiazines (**Scheme 261**) <1974CB771>.

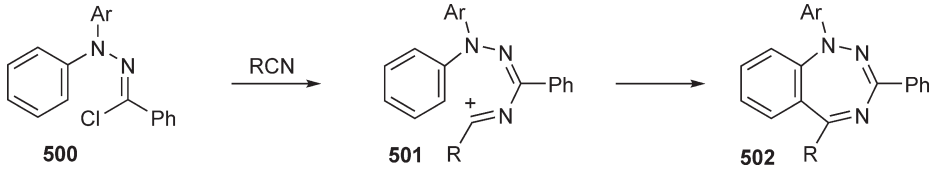


Scheme 261

4.4.8.3 Seven-Membered and Larger Rings

4.4.8.3.1 Heteroatoms 1,2,4 to a ring junction

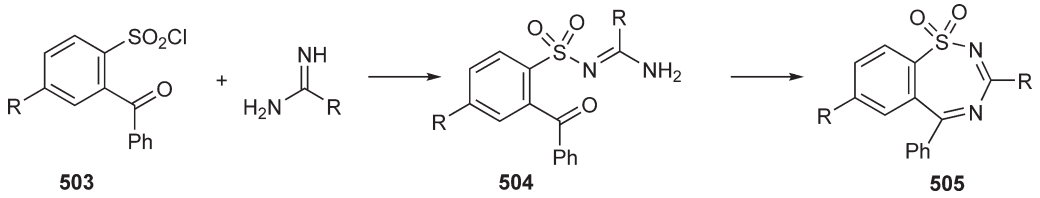
1*H*-1,2,4-Benzotriazepines **502** can be prepared by reaction of hydrazidoyl chlorides **500** with cyano compounds *via* the nitrilium salt **501** (**Scheme 262**) <1974T195>.



500 501 502

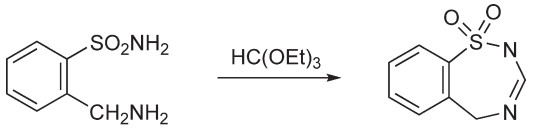
Scheme 262

2-Benzoylarenesulfonyl chlorides **503** with amidines, guanidine, or *S*-alkylthioureas give arenesulfonyl derivatives **504** (R = Ph, NH_2 or SMe), which cyclize on heating to 1,2,4-benzothiadiazepine 1,1-dioxides **505** (**Scheme 263**) <1968JHC719>.

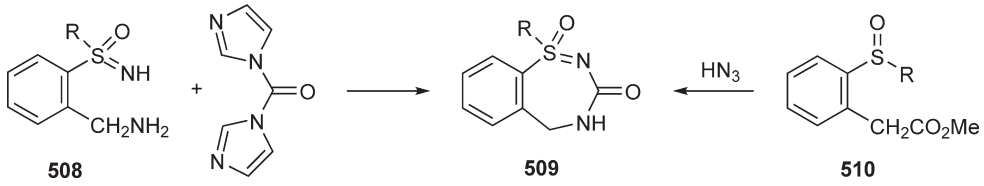


Scheme 263

2-Aminomethylsulfonamide **506** with ethyl orthoformate gives the 1,2,4-benzothiadiazepine **507** (**Scheme 264**) <1960JA1594>, and **509** is prepared from the sulfoximide **508** with *N*,*N*-carbonyldiimidazole <1972CB2575>. The cyclic sulfoximides **509** are also prepared from **510** with hydrazoic acid (**Scheme 265**) <1972CB2575>.

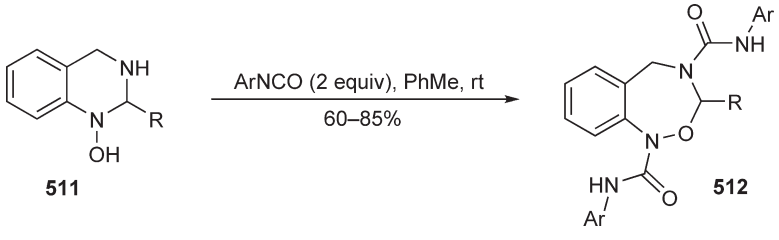


Scheme 264



Scheme 265

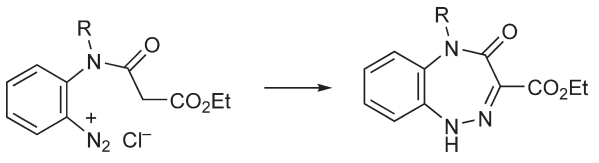
Quinazolyl-1-ols **511** react with aryl isocyanates to give the corresponding 6-oxa-5,8-diazabenzocycloheptenes **512** (**Scheme 266**) <2004TL8973, CHEC-III(13.14.7.2.2)422>.



Scheme 266

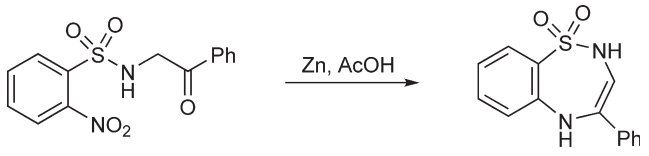
4.4.8.3.2 Heteroatoms 1,2,5 to a ring junction

1*H*-4,5-Dihydro-1,2,5-benzotriazepin-4-ones **514** can be prepared by cyclization of the diazonium salts **513** (**Scheme 267**) <1968T6395>.



513 514

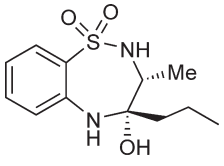
Scheme 267



515 516

Scheme 268

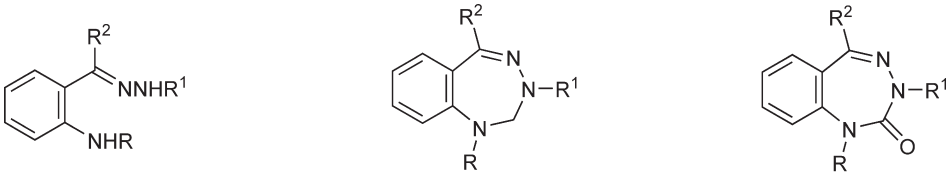
The 1,2,5-benzothiadiazepine 1,1-dioxide **516** and its 3,4-dihydro analogue have been prepared by the reaction of 2-nitrobenzenesulfonyl chloride with -aminoacetophenone to give **515** followed by reductive cyclization using Zn in acetic acid (**Scheme 268**) <1979JHC835>. A similar reductive cyclization with H_2 and Pd on carbon has been employed in the synthesis of the 1,2,5-benzothiadiazepine **517** <2004T3349, CHEC-III(13.15.8.4)472>.



517

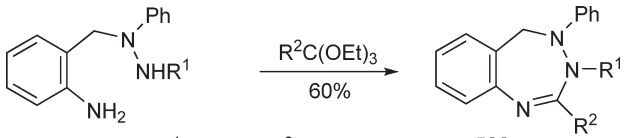
4.4.8.3.3 Heteroatoms 1,3,4 to a ring junction

The hydrazones or semicarbazones of 2-aminoaryl ketones **518** react with paraformaldehyde to give the 2,3-dihydro-1*H*-1,3,4-benzotriazepine **519** <1970BCJ135>, and with ethyl chloroformate to give the 2-oxo analogue **520** <1974JPS838>. Compounds of type **520** can also be prepared by the reaction of 2-aminoaryl ketones with ethoxycarbonylhydrazine.



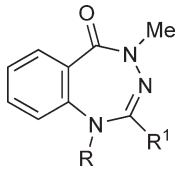
518 519 520

1-[(2-Aminophenyl)methyl]-1-phenylhydrazines **521**, prepared from phenylhydrazine and 2-nitrobenzyl chloride, readily cyclized with triethyl orthoacetate and with orthopropionate to give the 4,5-dihydro-3*H*-1,3,4-benzotriazepines **522** (**Scheme 269**) <1985JHC1105>. 2-Aminobenzoyl hydrazides have similarly been used in the preparation of 1,3,4-benzotriazepin-5-ones **523** by reaction with ortho esters <1976JOC2732, 1976JOC2736>.



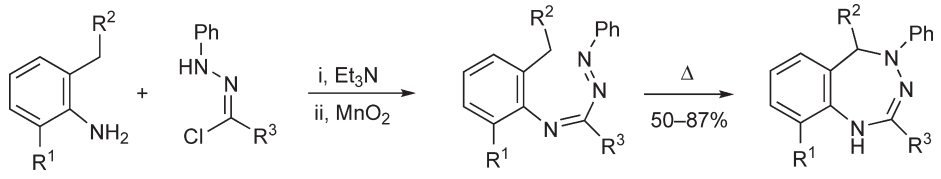
521 R^1 = H, Me; R^2 = Me, Et 522

Scheme 269



523

Arylazoarylimines **526**, with a methyl or ethyl group *ortho* to the imine function (prepared by oxidation with manganese dioxide of arylaminohydrazones from anilines **524** and chlorohydrazones **525**), undergo thermal intramolecular cyclization in refluxing xylene catalyzed by DABCO to give the 1*H*-4,5-dihydro-1,3,4-benzotriazepines **527** in good yields (**Scheme 270**) <1986JHC1795>.

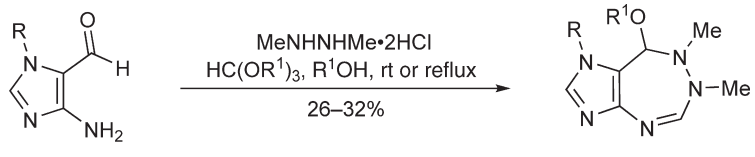


524 **525** **526** **527**

R^1 = Me, Et; R^2 = H, Me; R^3 = H, CN, CO_2Me

Scheme 270

The imidazo[4,5-*e*]triazepines **529** were synthesized in a single-pot reaction of 4-amino-1-benzylimidazole-5-carbaldehyde **528** with 1,2-dimethylhydrazine dihydrochloride and trimethyl or triethyl orthoformate using the corresponding alcohol as the solvent (**Scheme 271**) <2004JME1044, 2004NN263, CHEC-III(13.14.7.1.1)419>.

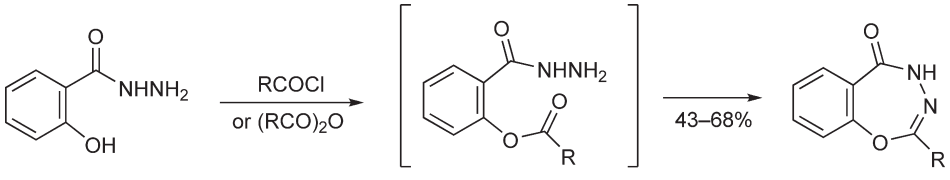


528 **529**

R = $PhCH_2$, 4-$MeOC_6H_4CH_2$; R^1 = Me or Et

Scheme 271

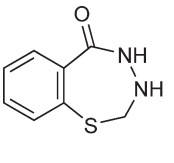
Treatment of salicylic hydrazide in toluene with an acid chloride, carboxylic acid anhydride, or orthoester, in the presence of an equimolecular amount of methanesulfonic acid gives the 1,3,4-benzoxadiazepin-5-ones **531**, *via* the *O*-acylation intermediates **530** (**Scheme 272**) <1992S929>.



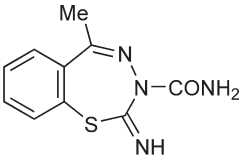
R = H, Me, Pr^i, Ph, CH_2Cl, CO_2Et **530** **531**

Scheme 272

2-Mercaptobenzoylhydrazide with formaldehyde gives **532** <1953JOC1380> and *o*-thiocyanatoacetophenone with semicarbazide gives **533** <1979JCM395>.



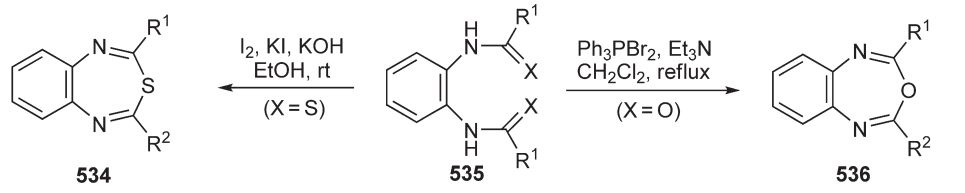
532



533

4.4.8.3.4 Heteroatoms 1,3,5 to a ring junction

Intramolecular cyclization of bis(amides) **535** (X = O) on treatment with Ph_3PBr_2 in the presence of triethylamine gives the corresponding benzoxadiazepines **536** in yields of 52-74% (**Scheme 273**) <1988M1279>. Similarly, reaction of bis (thioureas) **535** (X = S) using iodine affords in 6879% yields the benzothiadiazepines **534**, existing predominantly as exocyclic bis(imino) tautomers <2004MI773, CHEC-III(13.16.9.1.2)503>.



534 ($R^1 = R^2 = NHBu^t$, arylamino)

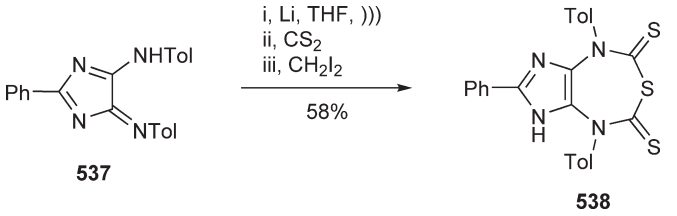
535

536 (R^1, R^2 = Me, Ph, 4-BrC_6H_4)

Scheme 273

Sonication of (imino)imidazole **537** in the presence of lithium followed by treatment with CS_2 and quenching with diiodomethane affords imidazolo-fused thiadiazepinedithione **538** (**Scheme 274**) <1999H763, CHEC-III(13.16.9.5)516>.

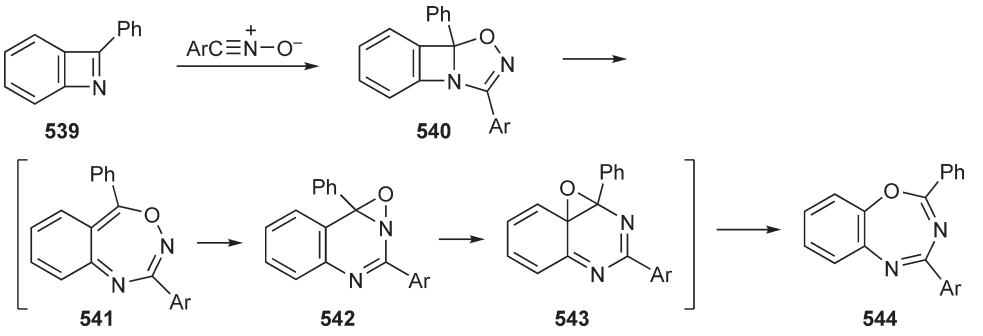
2-Phenylbenzazete **539** with nitrile oxides gives labile adducts **540** which rearrange to the 1,3,5-benzoxadiazepines **544**, probably *via* **541**, **542**, and **543** (**Scheme 275**) <1975CC740>.



537

538

Scheme 274



539

540

541

542

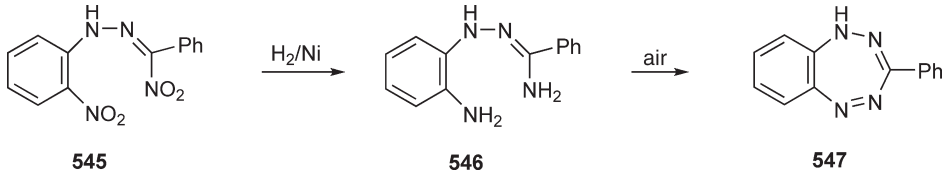
543

544

Scheme 275

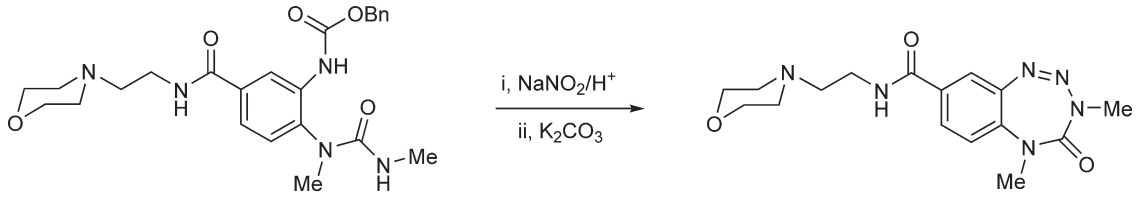
4.4.8.3.5 Four or more heteroatoms

The 1,2,4,5-benzotetrazepine **547** is produced in good yield by the oxidative ring closure of **546** (**Scheme 276**) or directly by the action of zinc and aqueous sodium hydroxide on **545** <1955CB1284>. The highly water-soluble tetrazepinone **549** was prepared by the cyclization of **548** (**Scheme 277**) <2000BML2325, CHEC-III(13.17.7.8)549>.



545 **546** **547**

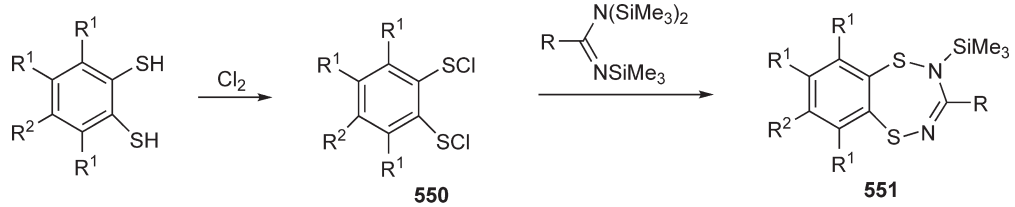
Scheme 276



548 **549**

Scheme 277

1,5,2,4-Dithiadiazepines **551** were synthesized by the cyclocondensation reaction of **550** as shown in **Scheme 278** <1997IC4772, CHEC-III(13.17.7.4)547>.

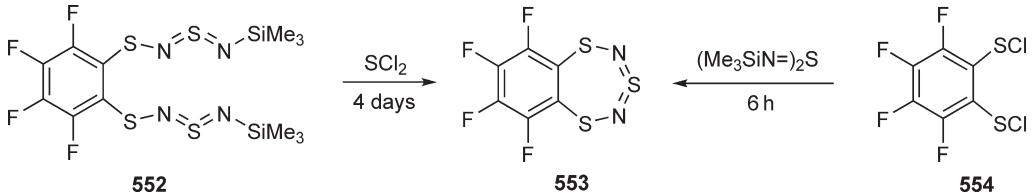


550 **551**

R^1, R^2 = H, Me, Cl; R = Ph, Tol

Scheme 278

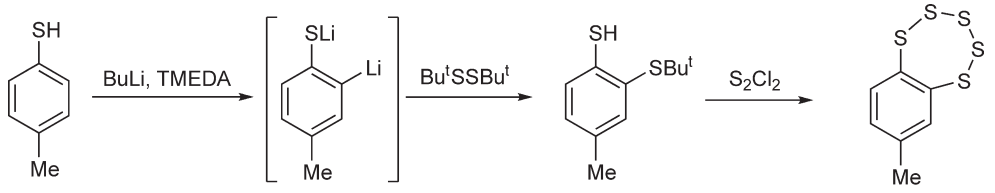
The synthesis of 1,3,5,2,4-trithiadiazepine **553** was realized by two methodsfrom the bis(trimethylsilazane) derivatives **552** and from the disulfenyl chloride **554** (**Scheme 279**) <CHEC-III(13.17.7.11)551>.



552 **553** **554**

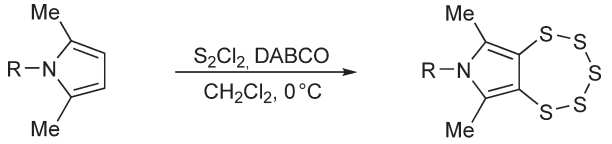
Scheme 279

Aromatic and heteroaromatic fused pentathiepins, e.g., **555**, can be prepared by reactions of S_2Cl_2 with vicinal dithiols or their derivatives as exemplified in **Scheme 280** <1985JA3871, 1995JA7261, CHEC-III(13.17.7.14)556>. Treatment of *N*-substituted 2,5-dimethylpyrroles **556** or indoles with an equilibrated mixture of S_2Cl_2 and DABCO at 0°C affords pentathiepinopyrroles **557** in moderate yields (**Scheme 281**) <2005OBC3496, 2005OL5725, 2009ARK(i) 129>.



555

Scheme 280

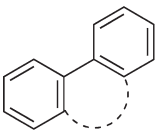


556 R = Me, Et, Pr, Pr^i, Bn **557**

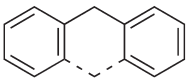
Scheme 281

4.5 Synthesis of Tri- and Polycyclic Ring Systems Without Ring Junction Heteroatoms

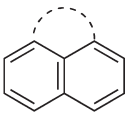
The arrangement of the material in this chapter follows closely that for the bicyclic analogues: it is ordered first by the mutual relationship of the fused rings, second by the number of heteroatoms, and finally by the size of the heterocyclic ring. We define adjacent as in **1** and nonadjacent fused rings as in **2**. Rings of type **3** form a class of *peri*-annulated heterocyclic systems.



1



2



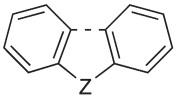
3

4.5.1 Two Adjacent Fused Rings, One Heteroatom

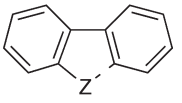
4.5.1.1 Five-membered Heterocyclic Ring

4.5.1.1.1 Overview of synthetic methods for carbazoles, dibenzofurans, and dibenzothiophenes

Most of the important methods involve C–C (**4**) or C–Z (**5**) bond formation and these two classes are considered in turn. There are a variety of miscellaneous methods.



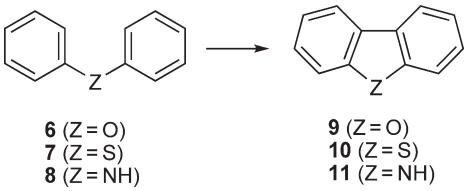
4



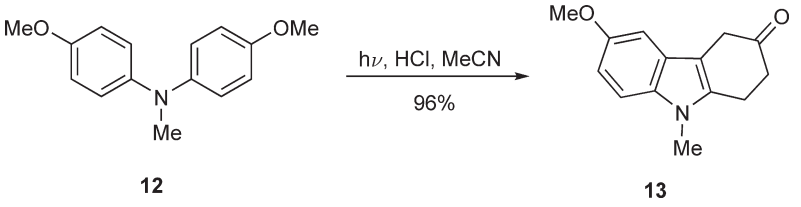
5

4.5.1.1.2 Formation of CC bond

1. The photochemically initiated cyclizations of diphenyl ethers to dibenzofurans **6** **9** <1975AJC1559, 1975S532>, diphenyl sulfides to dibenzothiophenes **7** **10** <1975S532>, and diarylamines to carbazoles **8** **11** (**Scheme 1**) <1966CC272, 1966TL661, 1996J(P1)669> normally require the presence of an oxidizing agent such as iodine or oxygen. Photocyclization of *N*-alkyl-(*p*-methoxyphenyl)anilines in the presence of aqueous hydrochloric acid affords tetrahydrocarbazolones, as illustrated by the conversion of the diarylamine **12** into the system **13** (**Scheme 2**) <2002CC270, CHEC-III(3.03.4)299>.

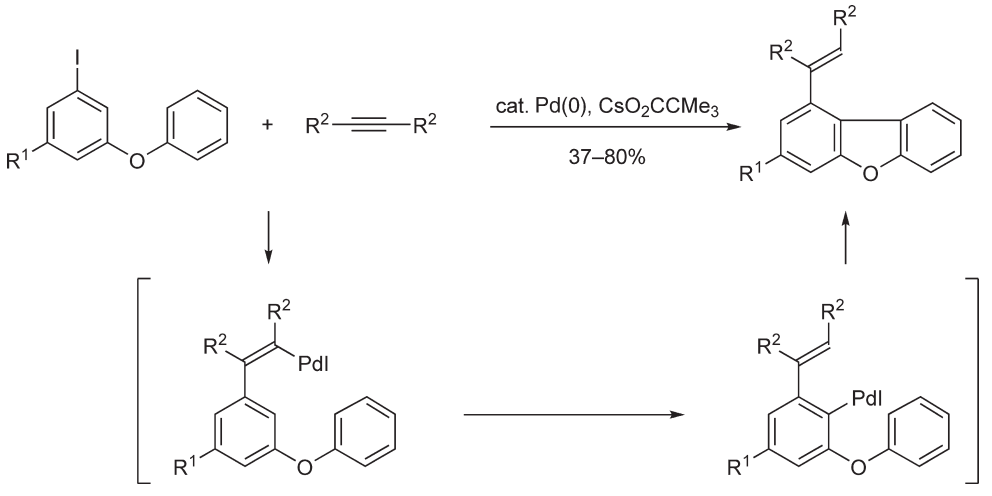


Scheme 1



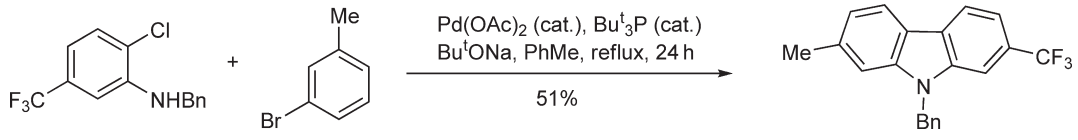
Scheme 2

The oxidative ring closure of diphenyl ethers to dibenzofurans **6** **9** is also catalyzed by palladium(II) acetate <1975JOC1365, 1976J(P1)1236>, as is that of diphenylamines to carbazoles <1975JOC1365, 1986CPB2672, 1992J(P1)3439, 1994TL1695>. Substituted dibenzofurans as well as carbazoles can be prepared by palladium-catalyzed cross-coupling of alkynes and appropriately substituted aryl iodides <CHEC-III(3.07.5.2)548>. These reactions proceed by carbopalladation of the alkyne, heteroatom-directed migration of palladium from a vinyl to the adjacent aryl position, and ring closure via intramolecular arylation (**Scheme 3**) <2006JOC5340>.



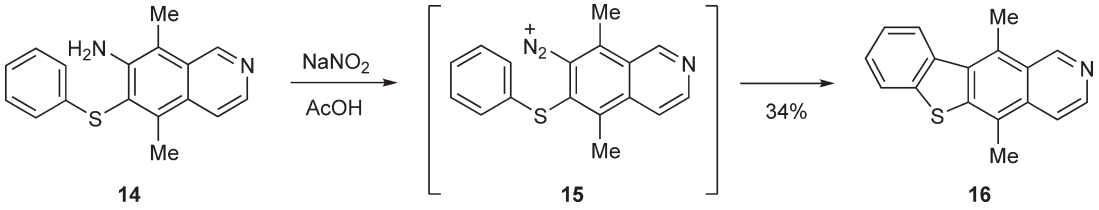
Scheme 3

o-Iododiarylamines on treatment with $Pd(OAc)_2$ also yield carbazoles <1984T1919>. This approach has been extended to a one-pot palladium-catalyzed sequential amination and CH activation procedure exemplified in **Scheme 4** <2002CC2310, CHEC-III(3.03.6)316>.



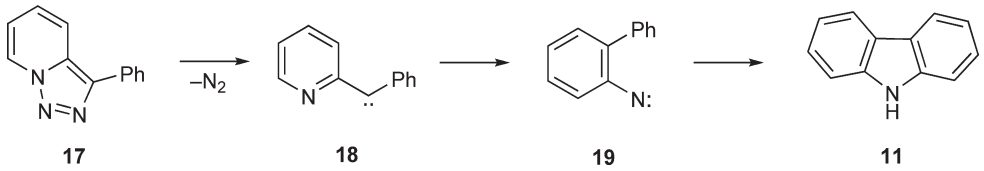
Scheme 4

2. Dibenzofurans **9** <1981BCJ2374>, dibenzothiophenes **10** <1996T3953>, and N-substituted carbazoles <1952JCS2276> are formed by spontaneous Pschorr-type cyclization of appropriate diazonium salts. For example, the diazonium salt **15**, derived from aminoisoquinoline **14**, undergoes cyclization to afford 6-thiaellipticine **16** (**Scheme 5**) <1996CC2711, CHEC-III(3.11.2.3.4)883>.



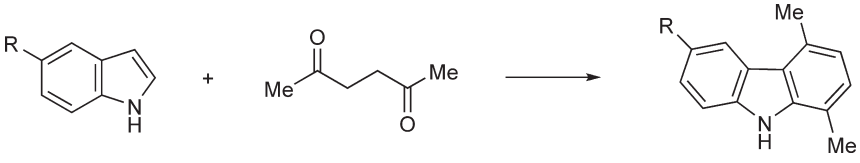
Scheme 5

3. Carbazoles are prepared by the GraebeUllmann synthesis: 1-arylbenzotriazoles on pyrolysis yield carbazoles <1956JCS1076>, see Section 3.4.1.2.1. Pyrolysis of 3-phenyltriazolo-pyridine **17** is more complex, ultimately providing carbazole **11** *via* **18** and **19** (**Scheme 6**) <1975JA7467>.



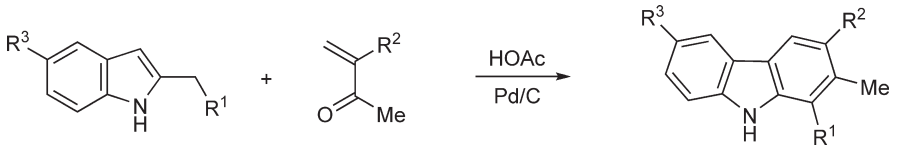
Scheme 6

4. Substituted carbazoles are made by acid-catalyzed condensation of indoles with 2,5-hexanedione (**Scheme 7**) <1987CPB425, 1990H(31)401>.



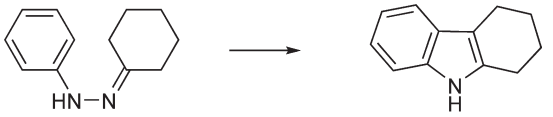
Scheme 7

Indoles with 2-substituents such as methyl or benzyl are cyclized with enones to carbazoles in acetic acid in the presence of Pd/C. This reaction involves electrophilic addition at C(3) and aromatization (**Scheme 8**) <1988T5215>.



Scheme 8

5. The Borsche synthesis of tetrahydrocarbazoles **21** is a special case of the Fischer indole synthesis in which cyclohexanone phenylhydrazones **20** are used as the starting materials (**Scheme 9**) (see, e.g., <2009BML4110>).

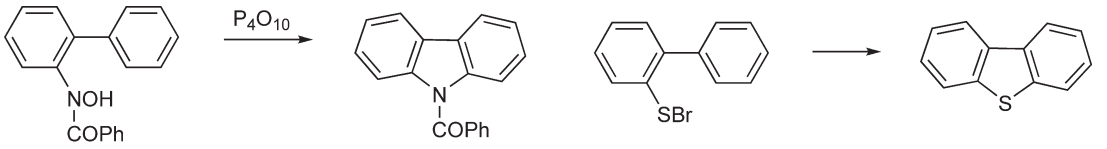


20 **21**

Scheme 9

4.5.1.1.3 Formation of CZ bond

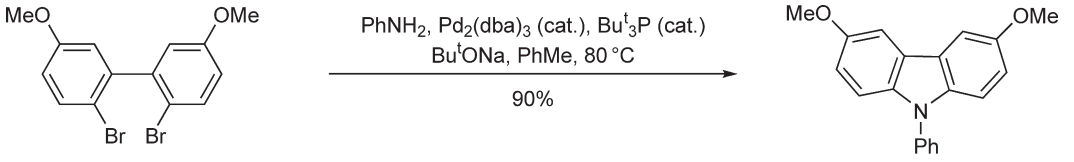
Electrophilic attack by the *ortho* heteroatom of biphenyl derivatives is involved in the conversions **22** **23** <1982JOC3585> and **24** **25** (**Scheme 10**) <1962JOC4111>.



22 **23** **24** **25**

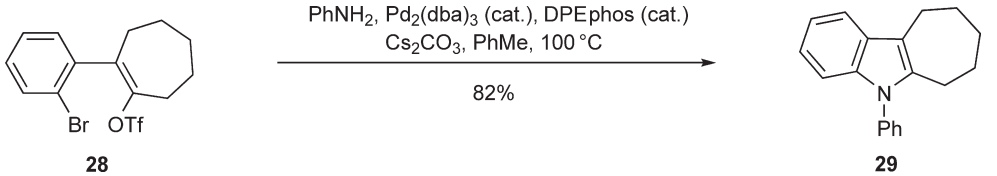
Scheme 10

Several routes to carbazoles featuring formation of two CN bonds rely on transition metal-catalyzed amination reactions <CHEC-III(3.03.8)326>. Such a methodology has been employed in the conversion of the biphenyl **26** into the carbazole **27** (**Scheme 11**). Variation of the amine and biphenyl components allowed preparation of a series of carbazole derivatives bearing either electron-withdrawing or releasing substituents <2003AGE2051>. Likewise, the triflate **28** could be efficiently transformed into a similar tricyclic system **29** by amination with aniline (**Scheme 12**) <2005AGE4036>.



26 **27**

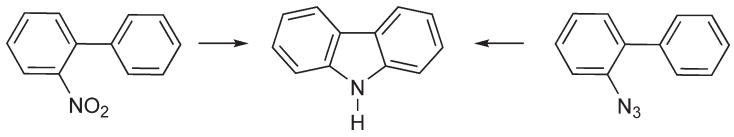
Scheme 11



28 **29**

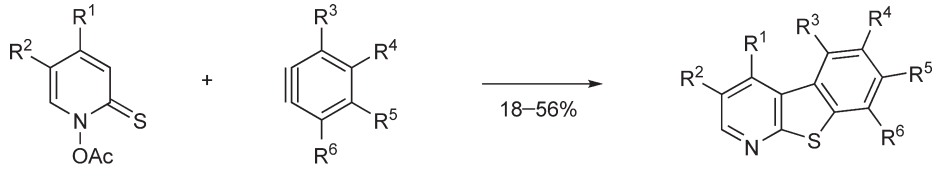
Scheme 12

A variety of pyrrole ring-closure reactions are conveniently formulated as proceeding *via* nitrene-type intermediates. Pyrolysis of *o*-nitrobiphenyls with iron(II) oxalate <1961T80>, or reduction under milder conditions with triethyl phosphite <1965JCS4831> or tris(trimethylsilyl) phosphite <1979TL375>, leads to the carbazole, as does the pyrolysis or photolysis of 2-azidobiphenyls (**Scheme 13**) <1975JA6193>.



Scheme 13

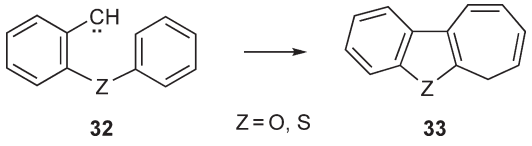
O-Acyl derivatives of thiohydroxamic esters (Barton esters) react with benzynes to afford a tricyclic thiophene ring system; thus the pyridine derivative **30** gives benzo[4,5]thieno[2,3-*b*]pyridines **31** (**Scheme 14**) <2002JOC3409, CHEC-III(3.11.3.3)900>.



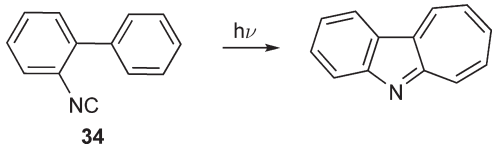
Scheme 14

4.5.1.1.4 Miscellaneous methods

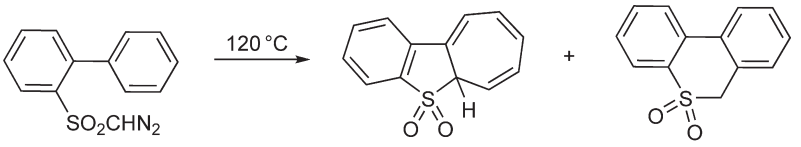
Intramolecular attack of the carbenes **32** provides benzo[*b*]cyclohepta[*d*] furans and thiophenes **33** (**Scheme 15**). Photolysis of 2-biphenyl isocyanide **34** (**Scheme 16**) <1972JOC3571> and thermolysis of 2-biphenylsulfonyl diazomethane **35** (**Scheme 17**) <1972CC893> also result in the formation of ring expanded products.



Scheme 15



Scheme 16

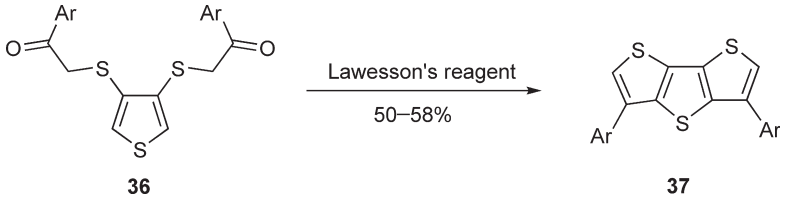


35

Scheme 17

The extrusion of sulfur from phenothiazine and thianthrene, leading to carbazole <1975CJC2293> and dibenzothiophene <1937RTC627>, respectively, is effected by thermolysis in the presence of copper bronze.

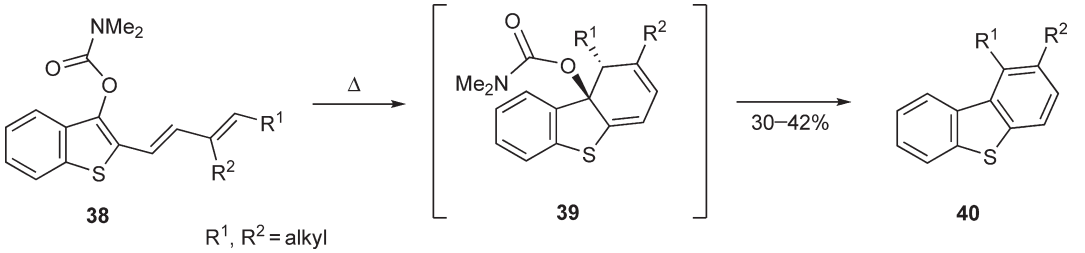
Treatment of diketones **36** with Lawessons reagent affords dithienothiophenes **37** (**Scheme 18**) <2004TL3405, CHEC-III(3.11.2.3.6)885>.



36 37

Scheme 18

Electrocyclization of benzothiophenes **38** affords intermediates **39** which eliminate carbamic acid to give dibenzothiophenes **40** (**Scheme 19**) <1999CC541, CHEC-III(3.11.6.6)885>.



38 39 40

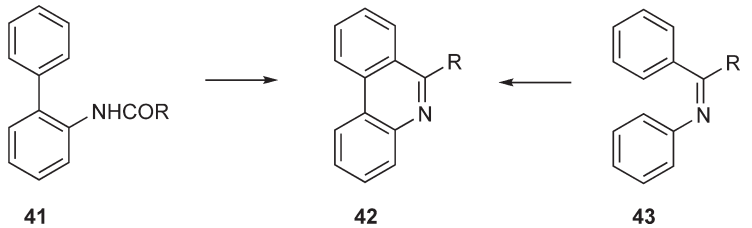
R^1, R^2 = alkyl

Scheme 19

4.5.1.2 Six-membered Rings

Phenanthridines and related systems are obtained by the following methods:

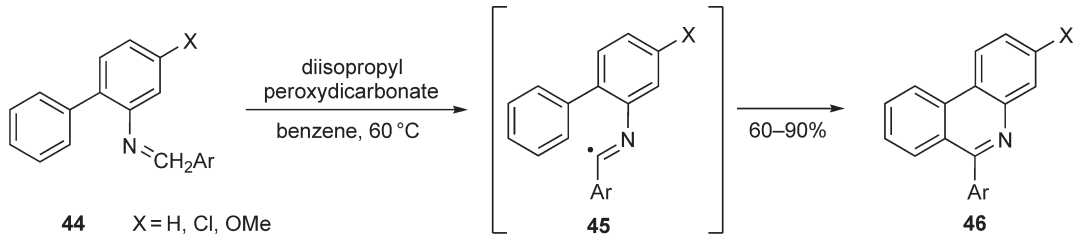
1. Cyclodehydration of acylated 2-aminobiphenyls **41** **42** (**Scheme 20**).



41 42 43

Scheme 20

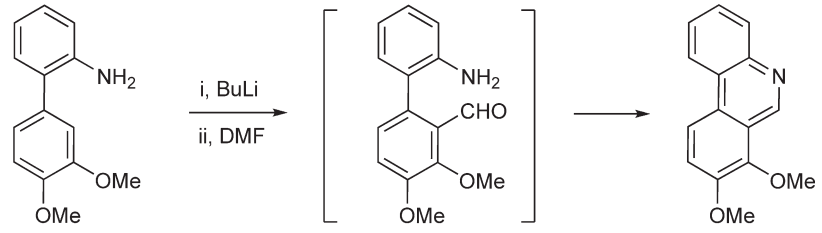
2. Photochemical dehydrogenation of azomethines **43** **42** (**Scheme 20**); dihydro compounds are initially formed and aromatization is effected with either oxygen or iodine. Phenanthridine formation by this method is improved by the presence of BF_3 <1988TL5213>.
3. Radical cyclization of 2-arylidenaminodiphenyls **44** leading to phenanthridines **46**, possibly *via* radical intermediates **45** (**Scheme 21**) <1985S107>.



44 X = H, Cl, OMe **45** **46**

Scheme 21

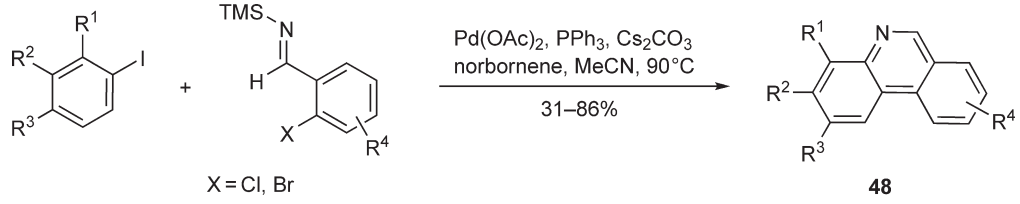
4. Intramolecular cyclization of 2-amino-2-formyldiphenyls (e.g., **47**) obtained *in situ* from the corresponding 2-lithium derivatives (**Scheme 22**), cf. Section 3.4.3.4.4.



47

Scheme 22

5. Various Pd-catalyzed cyclizations, which provide a convenient route to phenanthridine and related systems, e.g., <2009AGE572, 2009AGE6713, CHEC-III(7.05.2)222>. For example, palladium-catalyzed domino direct arylation/N-arylation affords phenanthridines **48** in generally high yields (**Scheme 23**) <2009AGE6713>.



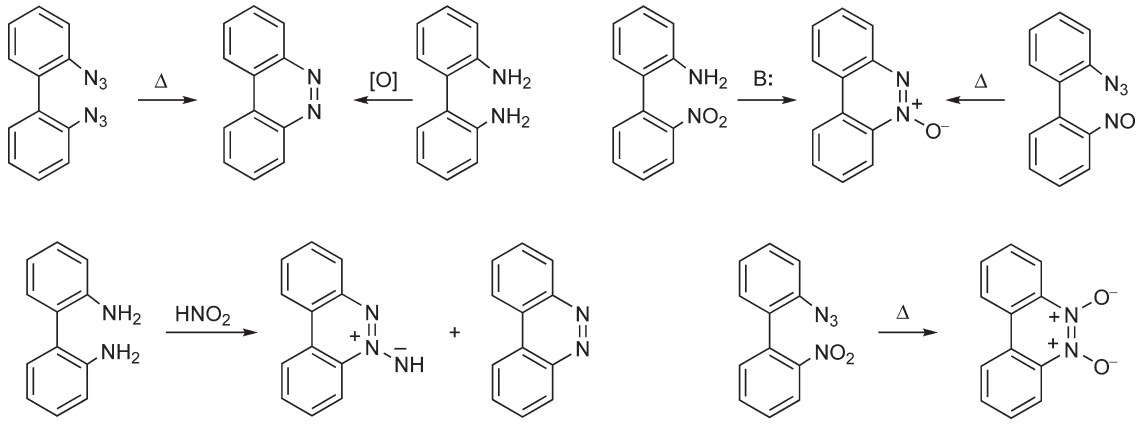
X = Cl, Br **48**

Scheme 23

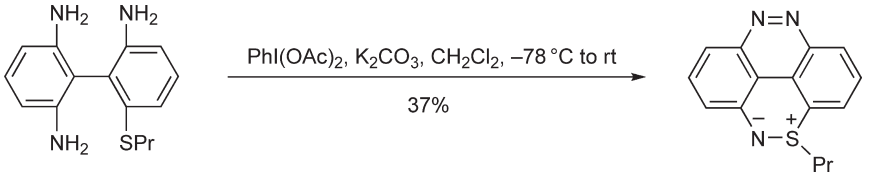
4.5.2 Two Adjacent Fused Rings, Two Heteroatoms

Benzo[*c*]cinnoline derivatives of different oxidation levels are prepared by N–N bond formations from suitable 2,2-disubstituted biphenyls as outlined in **Scheme 24**.

Benzo[*c*]cinnolines have been conveniently prepared by the cyclization of symmetrically disubstituted 2,2-diaminobiphenyls using iodobenzene diacetate as the oxidant <1996J(P1)83, CHEC-III(8.01.9.1)72>. A similar oxidation of 2,2,6-triamino-6-propylthiobiphenyl **49** afforded a new tetracyclic ring system **50** (**Scheme 25**) <2000JOC6388>.

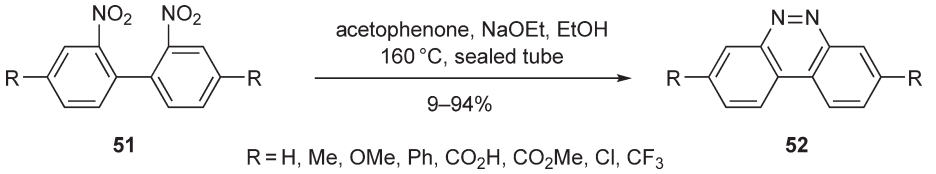


Scheme 24



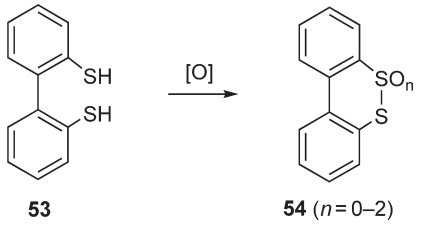
Scheme 25

In the synthesis of symmetrically 3,8-disubstituted benzo[*c*]cinnolines **52** from the corresponding 4,4-disubstituted 2,2-dinitrobiphenyls **51**, acetophenone has been used as reductant in a basic solution (**Scheme 26**); 2-nitroso-2-hydroxylaminobiphenyls are assumed to be intermediates in this reaction <2004JOC7720, CHEC-III(8.01.9.1)73>.

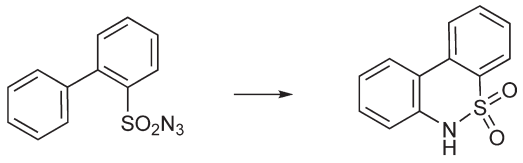


Scheme 26

Dibenzo[1,2]dithiins **54** are prepared by oxidation of appropriate dithiols **53** and related starting materials (e.g., **Scheme 27**). Dibenzo[1,2]thiazine dioxide **56** is obtained by thermolysis of the azide **55** (**Scheme 28**) <1969JA1219>.



Scheme 27

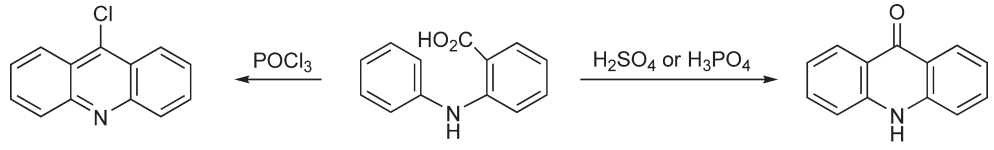


55 56

Scheme 28

4.5.3 Two Nonadjacent Fused Rings, One Heteroatom

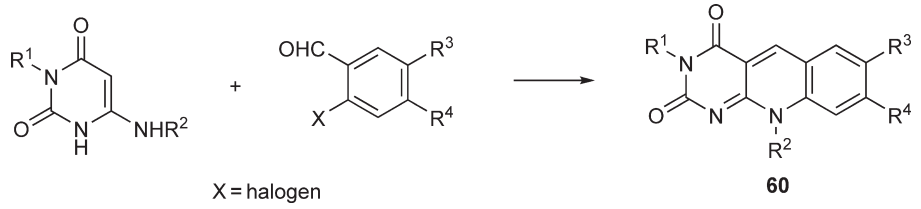
1. *o*-Anilinobenzoic acid **58** gives 9-chloroacridine **57** and acridone **59** under the conditions indicated in **Scheme 29**.



57 58 59

Scheme 29

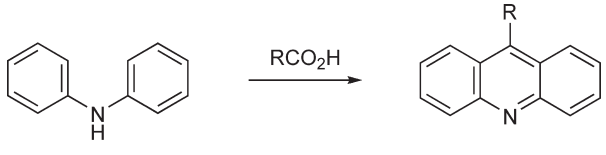
In **Scheme 30**, an aminouracil reacts with an *o*-halobenzaldehyde as 1,3-bis electrophile to provide a simple preparation of 5-deazaflavins **60** <1982CC1085>.



60

Scheme 30

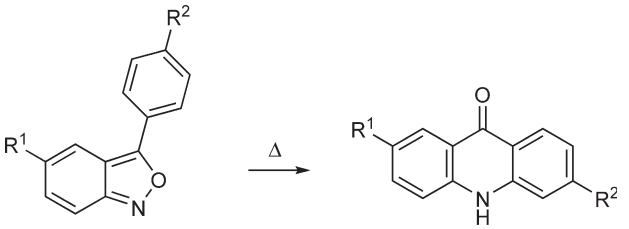
2. In the Bernthsen synthesis, diphenylamine **61** and carboxylic acids form 9-substituted acridines **62** (**Scheme 31**).



61 62

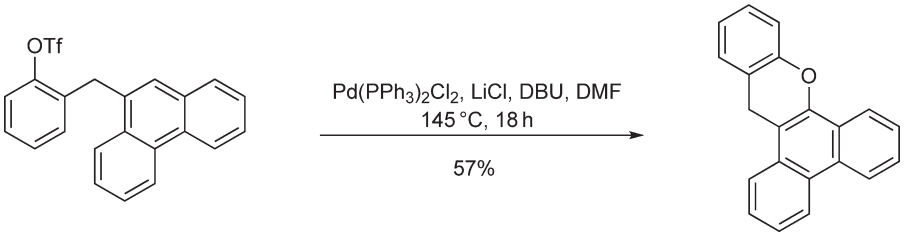
Scheme 31

3. 3-Arylanthranils **63** give acridones **64** on thermolysis (**Scheme 32**) or on nitrous acid treatment (Section 3.4.3.4.2).
4. Synthetic approaches to xanthenes (9*H*-dibenzo[*b*,*e*]pyrans) most commonly involve cyclizations creating new CO bonds (e.g., **Scheme 33**) <2002T5927> or new CC bonds (e.g., **Scheme 34**) <2001SC877, CHEC-III(7.08.7)467>.
5. The preparation of xanthones (9*H*-dibenzo[*b*,*e*]pyran-9-ones) is illustrated by **Schemes 35** and **36** <1997SL1081, 2005OL4273, CHEC-III(7.08.19)600>.

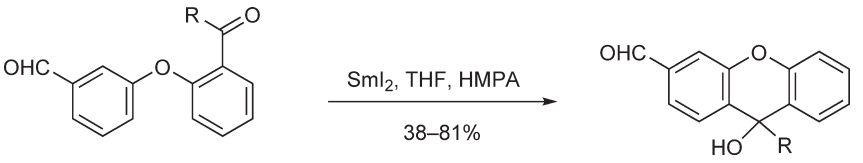


63 **64**

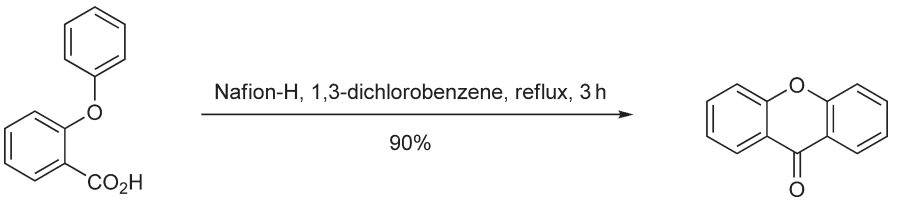
Scheme 32



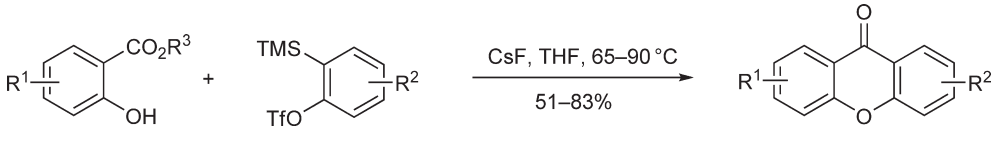
Scheme 33



Scheme 34



Scheme 35

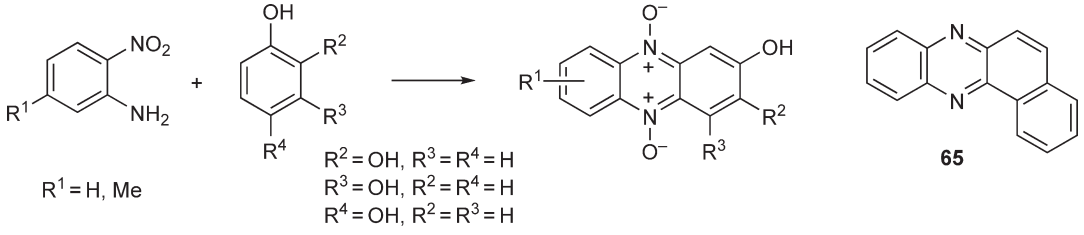


Scheme 36

4.5.4 Two Nonadjacent Fused Rings, Two Heteroatoms

4.5.4.1 Phenazines

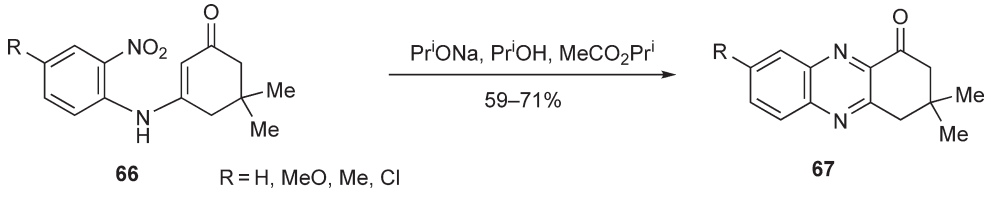
Phenazines can be obtained from *o*-nitrodiphenylamines by reduction or from *o*-aminodiphenylamines by oxidative techniques. Phenazine 5,10-dioxides are prepared by the Beirut reaction (see Section 4.4.6.4) using hydroquinone <CHEC-III(8.03.11.7)319>, and they can also be synthesized by treatment of *o*-nitroanilines with dihydroxybenzenes (e.g., **Scheme 37**) <1995M1217>.



Scheme 37

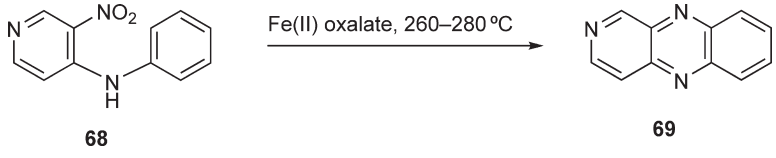
o-Phenylenediamine with *o*-quinones gives phenazines; thus, -naphthoquinone yields **65**.

Cyclization of nitroanilinocyclohexenones **66** gives 3,4-dihydrophenazin-1(2*H*)-ones **67** in generally good yields (**Scheme 38**) <1982S852>.



Scheme 38

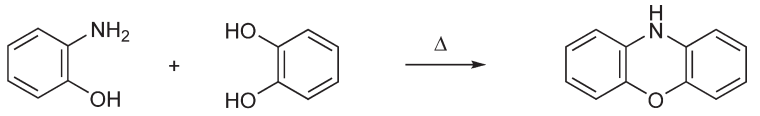
o-Nitroanilinopyridines, e.g., **68**, are cyclized to pyrido[2,3-*b*]- or -[3,4-*b*]-quinoxalines **69** by reduction with iron(II) oxalate (**Scheme 39**) <1974J(P1)1965>.



Scheme 39

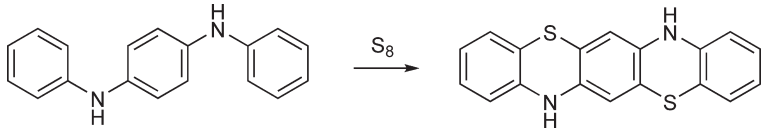
4.5.4.2 Phenoxazines and Phenothiazines

Traditional routes to phenoxazines (e.g., **72**) include the thermolysis of 2-aminophenol **70** and catechol **71** (**Scheme 40**) or catechol and ammonia. Phenothiazines are prepared by heating diphenylamines with sulfur as exemplified in **Scheme 41** <1985AXC1062, CHEC-III(8.09.9.2)655>. 2-Hydroxy- (or mercapto-) 2,4-dinitrodiphenylamines **73** cyclize to phenoxazines (or phenothiazines) in the presence of base by elimination of nitrous acid. These reactions are complicated by Smiles-type rearrangements of the amines **73** so that mixtures of isomeric products **74** and **75** are obtained (**Scheme 42**).

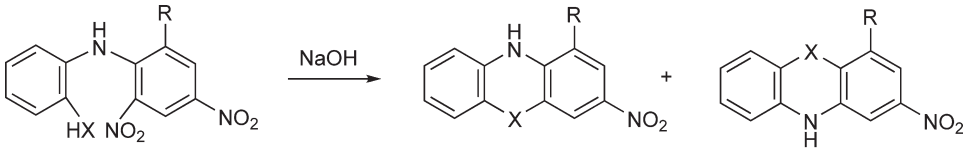


70 71 72

Scheme 40



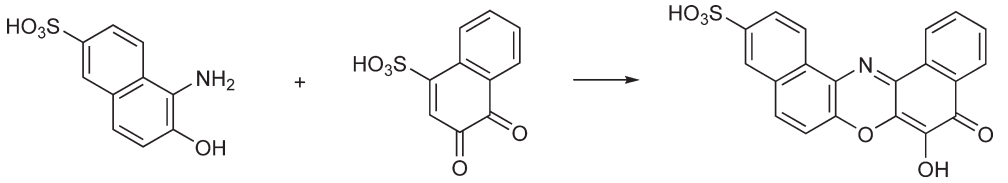
Scheme 41



73 X = O or S 74 75

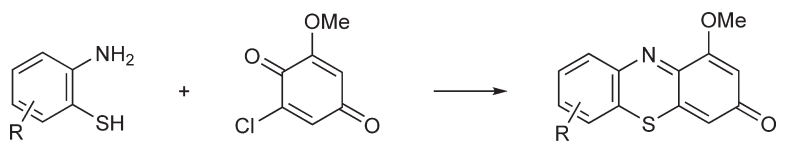
Scheme 42

Phenoxazin-3-ones and phenothiazin-3-ones can be prepared by condensation of 2-aminophenols or -thiols with quinones. Alizarin Green G **78**, for example, is obtained from **76** and **77** (**Scheme 43**). Similarly, 2-aminothiophenols and 6-chloro-2-methoxy-1,4-benzoquinone **79** afford phenothiazin-3-ones **80** (**Scheme 44**). *o*-Aminophenols react with quinones to give phenoxazonium salts, e.g., **81** (**Scheme 45**).



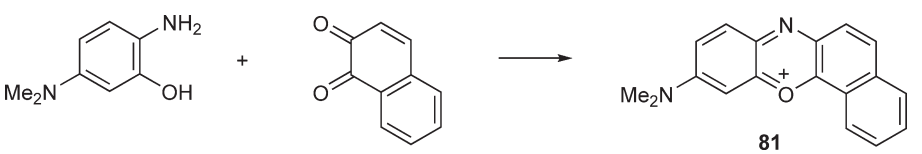
76 77 78

Scheme 43



79 80

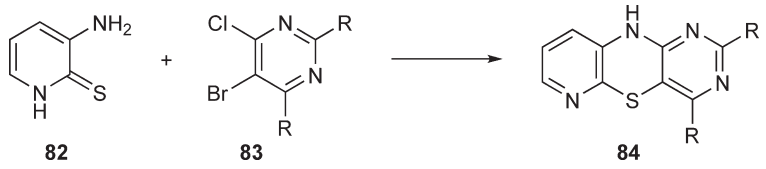
Scheme 44



81

Scheme 45

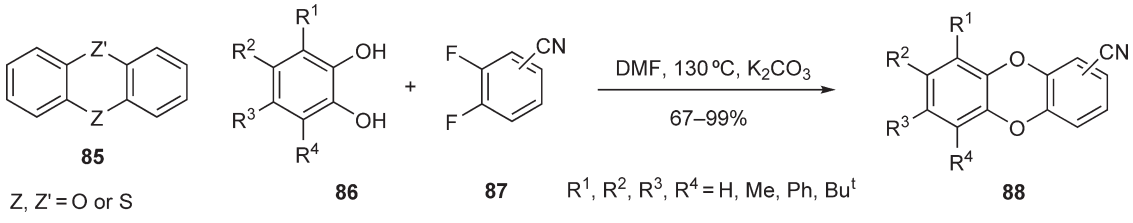
The triazaphenothiazine **84** is prepared by the reaction of 3-aminopyridine-2-thione **82** with the dihalopyrimidine **83** (**Scheme 46**).



Scheme 46

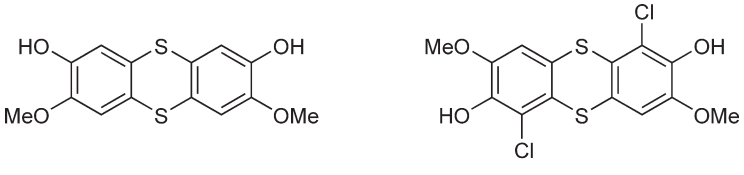
4.5.4.3 Dibenzo[1,4]dioxin, Phenoxathiin, and Thianthrene

Dibenzo[*b*,*e*][1,4]dioxin (oxanthrene) **85** (Z, Z = O) is prepared by heating 2-chlorophenol, potassium carbonate, and copper <1957JA1439>. Cyanooxanthrenes **88** were quantitatively prepared from catechols **86** by nucleophilic displacement of fluoride from 2,3- and 3,4-difluorobenzonitriles **87** (**Scheme 47**) <1999CL479, 2001NJC379, CHEC-III (8.12.9.1.1)882>.



Scheme 47

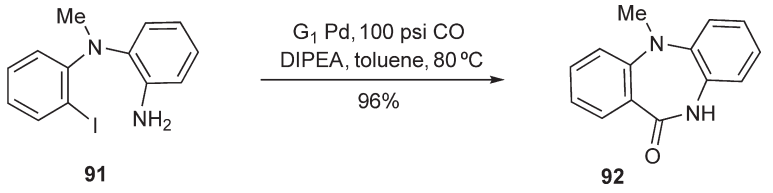
A general route to phenoxathiins **85** (Z = O, Z = S) utilizes the reaction of diphenyl ethers with sulfur. One route to thianthrene **85** (Z, Z = S) involves reaction of sulfur monochloride with benzene over aluminum chloride. Likewise, *o*-methoxyphenol reacts with sulfur dichloride to give, depending on the rate of addition of the reactant, 2,8-dihydroxy-3,7-dimethoxythianthrene **89** or 1,6-dichloro-2,7-dihydroxy-3,8-dimethoxythianthrene **90** <1997JCM272>.



4.5.4.4 Dibenzodiazepins, Dibenzoxepins, and Dibenzothiepins

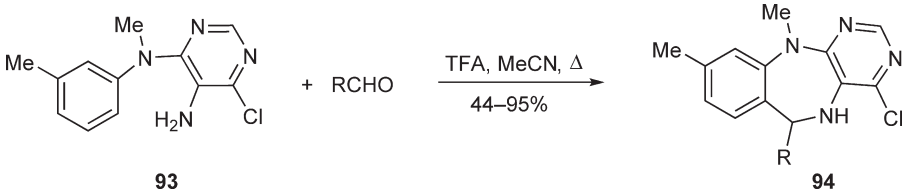
The carbonylation of N^1-(2-iodophenyl)-N^1-methylbenzene-1,2-diamine **91**, catalyzed by Pd complexed to a silica-based dendrimer ligand (G_1), provided 5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one **92** in excellent yield (**Scheme 48**) <2005JA14776, CHEC-III(13.06.9.1.8)211>.

A trifluoroacetic acid-catalyzed PictetSpengler reaction between the N,N-disubstituted aniline **93** and aromatic or aliphatic aldehydes afforded fused 1,4-benzodiazepines **94** in high yields after stirring at reflux in acetonitrile for 1648 h (**Scheme 49**). Electron-deficient aromatic aldehydes provided the best yields of **94**, attributed to facile imine formation, while ketones were uniformly unreactive <2006T2563, CHEC-III(13.06.9.1.8)212>.



91 **92**

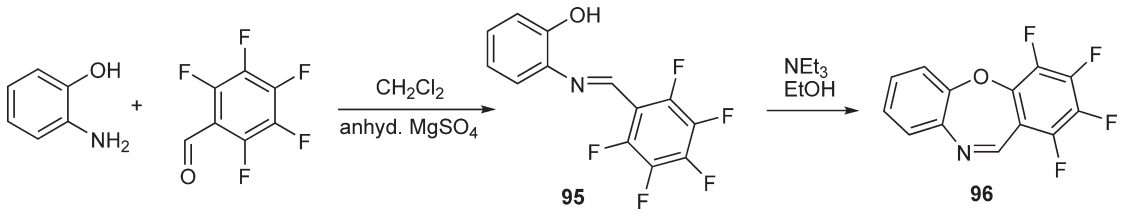
Scheme 48



93 **94**

Scheme 49

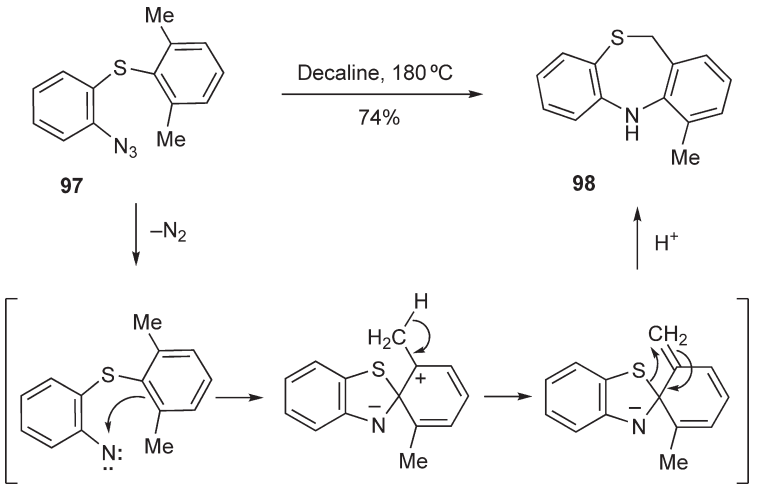
1,2,3,4-Tetrafluorodibenzo[*b*,*f*][1,4]oxazepine **96** was prepared by the cyclization of imine **95** in the presence of an excess of triethylamine (**Scheme 50**) <2002JFC(115)91, CHEC-III(13.09.9.1.4)274>.



95 **96**

Scheme 50

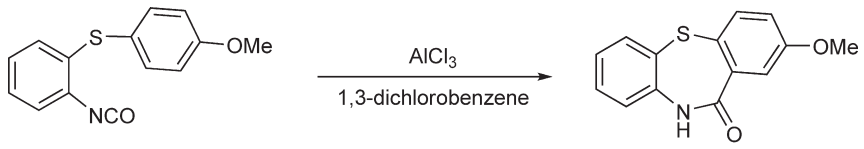
5,11-Dihydro-4-methyldibenzo[*b*,*e*][1,4]thiazepine **98** was prepared in high yield by the thermolysis of 2-azido-2,6-dimethyldiphenyl sulfide **97** *via* the mechanism outlined in **Scheme 51** <1970CC233>. The isomeric [*b*,*f*][1,4] thiazepine was not detected in this reaction.



97 **98**

Scheme 51

The dibenzo[1,4]thiazepinone **100** was obtained by treatment of isocyanate **99** with aluminum chloride (**Scheme 52**) <1999JME2235, CHEC-III(13.09.9.2.4)285>.



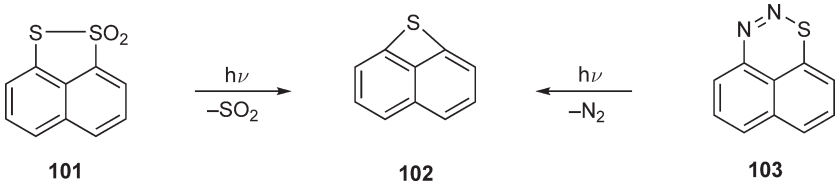
99 **100**

Scheme 52

4.5.5 *peri*-Annulated Heterocyclic Systems

Due to proximity effects, *peri*-cyclizations leading to this type of heterocycle have some special features (for reviews see <1966CRV567, 1990AHC(51)1, 2008AHC(95)1>). Thus, when five-membered and especially six-membered *peri*-rings are formed, cyclization occurs much more readily than in the case of *ortho*-disubstituted arenes with similar structures. At the same time cyclizations involving the formation of four- or seven-membered *peri*-rings proceed with greater difficulty since they demand considerable bond distortions.

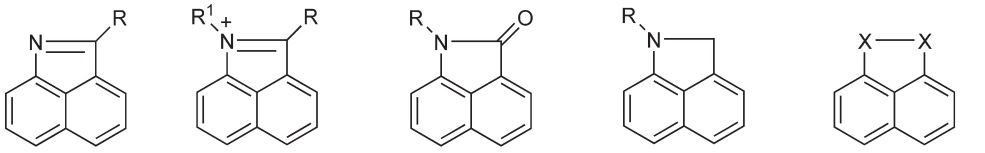
Naphtho[*b*,*c*]thiete **102** was obtained with high yield as a stable compound on photolysis of **101** or **103** (**Scheme 53**). Nitrogen and oxygen analogues of **102** are unstable, but can in some instances be trapped.



101 **102** **103**

Scheme 53

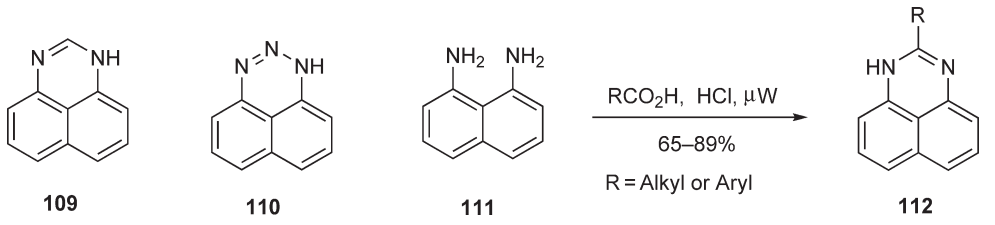
The cyclization of *peri*-aminonaphthoyl compounds allows the preparation of three main types of benzo[*c*,*d*]indoles **104106**. 1,2-Dihydrobenzo[*c*,*d*]indoles **107** are unstable and easily autooxidized to **106**. Naphtho[1,8-*c*,*d*]dichalcogenols **108** were obtained in good yield on treatment of 1,8-dilithionaphthalene with sulfur, selenium, or tellurium.



104 **105** **106** **107** **108** (X = S, Se, Te)

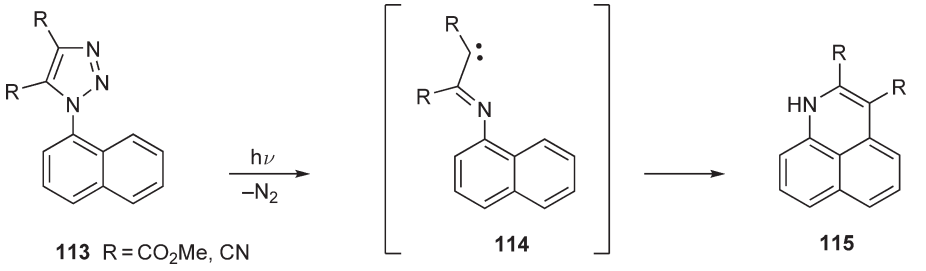
Syntheses of perimidine **109** <CHEC-III(8.02.9.3)222> and naphtho[1,8-*d*,*e*]triazine **110** <CHEC-III(9.01.11.4)82> derivatives usually start from 1,8-diaminonaphthalene by procedures which are quite similar to the synthesis of benzimidazoles and benzotriazoles from 1,2-diaminobenzene <1995AQ151>. For example, 2-alkyl and 2-arylperimidines **112** can be readily obtained in good yield by heating carboxylic acids with 1,8-naphthalenediamine **111** under microwave conditions (**Scheme 54**) <2005ASJ2411>.

Intramolecular carbenoid and nitrenoid insertions are also quite effective for the preparation of *peri*-condensed heterocycles. Thus, photolysis of 1-naphthyl-1,2,3-triazoles **113** leads to benzo[*d*,*e*]quinolines **115**, possibly *via* carbene intermediate **114** (**Scheme 55**) <1987J(P1)413>. Similarly, on photolysis or thermolysis of 8-azido-1-arylazonaphthalenes **116** naphtho[1,8-*d*,*e*]triazine derivatives **117** are formed along with *N*-aryliminobenzo[*c*,*d*]indazoles **118** (**Scheme 56**) <1978JOC2508, 1982JOC1996>.



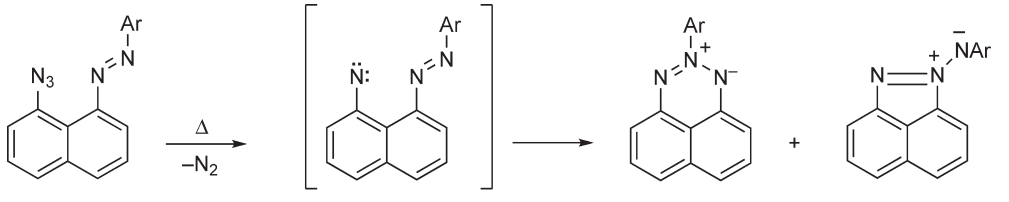
109 110 111 112

Scheme 54



113 R = CO_2Me, CN 114 115

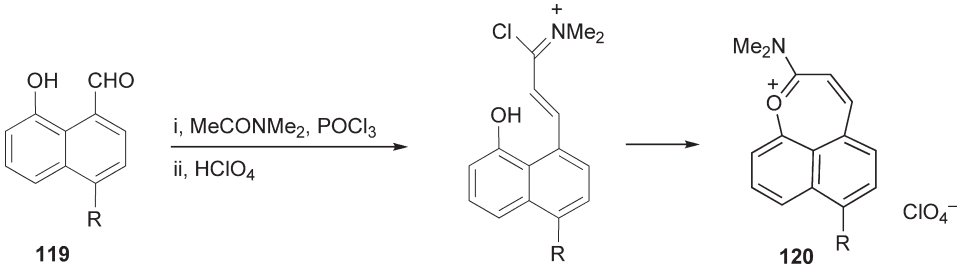
Scheme 55



116 117 118

Scheme 56

2-Dimethylaminonaphtho[*b,c*]oxepinium salts **120** have been obtained from hydroxynaphthalenes **119** in accordance with **Scheme 57** <1990AHC(51)1>.

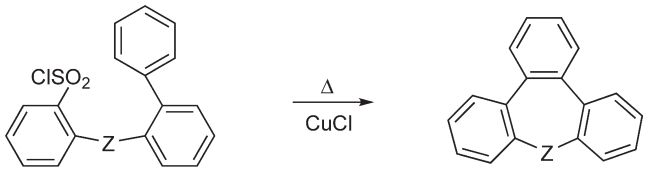


119 120

Scheme 57

4.5.6 Three Fused Rings

The tribenzo[*b,d,f*]oxepin **122** (Z = O) is made from the biphenyl-2-yl ether **121** (Z = O), and the thio analogue **122** (Z = S) is prepared similarly (**Scheme 58**) <1965T1299>.



121 Z = O, S **122**

Scheme 58

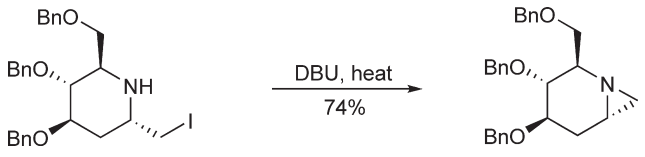
4.6 Synthesis of Fused Ring Systems with Ring Junction Heteroatoms

This chapter considers the formation of rings containing one or more N or S atoms at a ring junction. For nitrogen, this is possible with the retention of a three-coordinate neutral, or four-coordinate positively charged, nitrogen atom. We consider successively the formation of small (three- or four-membered) rings with such a feature, five-membered and then six-membered rings with one ring junction N atom, and finally rings containing two ring junction N atoms.

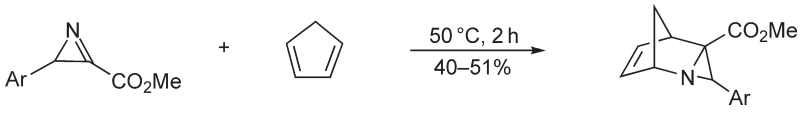
A very large number of these systems with ring junction heteroatoms exist, and this number is constantly increasing. Only illustrative examples of the preparation of such systems can be given here. The synthetic methods for the formation of this type of heterocycle can be usefully classified as follows: (1) various cyclocondensations between the corresponding heterocyclic derivatives and bifunctional units, (2) intramolecular cyclizations of electrophilic, nucleophilic, or (relatively rare) radical type, (3) cycloadditions, (4) intramolecular oxidative coupling, (5) intramolecular insertions, (6) cyclization of open-chain predecessors, and (7) various reactions (quite often unusual) which are specific for each type of system. Examples given below illustrate all these cases.

4.6.1 Formation of Three- or Four-Membered Rings with One N Atom at a Ring Junction

A systematic review of synthetic approaches to fused azirines is provided in CHEC-III <CHEC-III(1.02.3.2)116>. One of the most common routes to aziridines of this type involves a cyclization *via* nucleophilic attack of a nitrogen on an exocyclic sp^3-hybridized carbon as exemplified in **Scheme 1** <2003TL7997, 2003TA1969>. Another general approach to fused azirines involves DielsAlder reactions of carboxylate-substituted 2*H*-azirines (e.g., **Scheme 2**) <1997S271, 1998J(P1)2969, 2005S555, CHEC-III(1.02.3.2.2)121>.

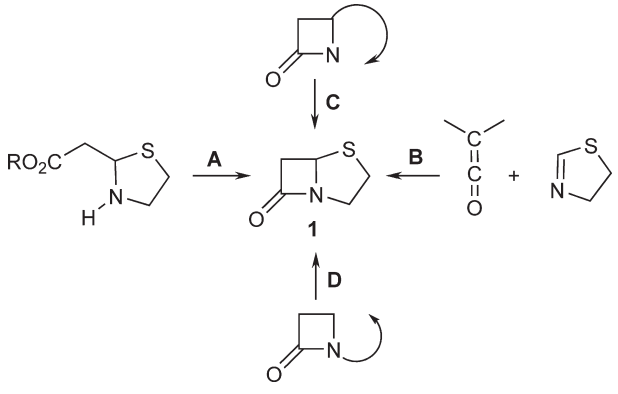


Scheme 1



Scheme 2

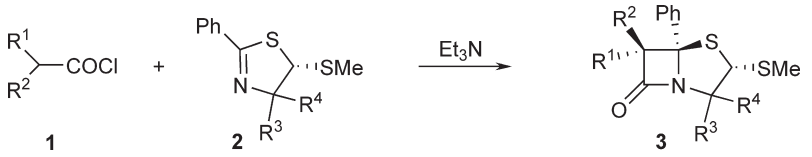
Various strategies (**AD**) for the synthesis of penams **1**, the backbone of penicillins, are schematically outlined in **Scheme 3**. The oldest approaches to the penam skeleton from acyclic precursors were based on the azetidinone ring closure from β-amino acid precursors (strategy **A**) and the [2 + 2] cycloaddition of ketenes or enolates to imines (strategy **B**). Most of the modern total syntheses of nonnatural penams and penems make use of chiral preformed β-lactams including appropriate side-chains and substituents, for fused ring cyclization with the desired stereochemistry (strategies **C** and **D**) <CHEC-III(2.03.9)209, 2003T7631, 2004ACR592>.



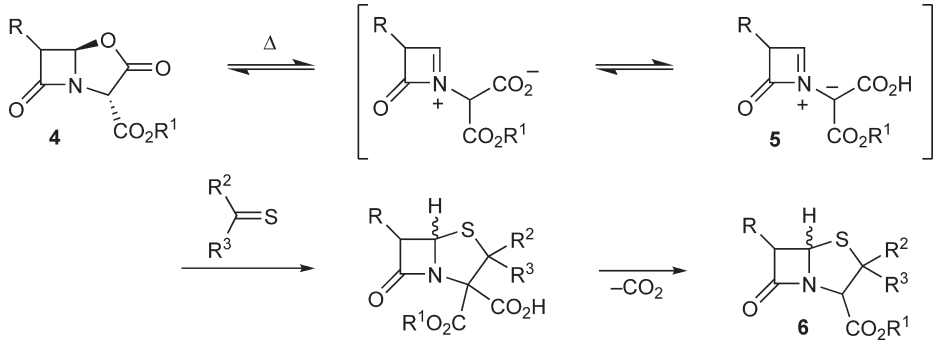
Scheme 3

Use of the Staudinger reaction <CHEC-III(2.01.3.10.11)73> is exemplified by the synthesis of substituted penam derivatives **3** from 4,5-dihydro-1,3-thiazole **2** and either dichloroacetyl chloride (**1**; $R^1 = R^2 = Cl$) or azidoacetyl chloride (**1**; $R^1 = N_3$, $R^2 = H$) (**Scheme 4**).

The synthesis of penams **6** from oxazolidinones **4** via the carboxylated azomethine ylide intermediates **5** is outlined in **Scheme 5** <CHEC-III(2.03.10)212, 2001J(P1)1281, 2004OL2781, 2005PAC2033>.



Scheme 4



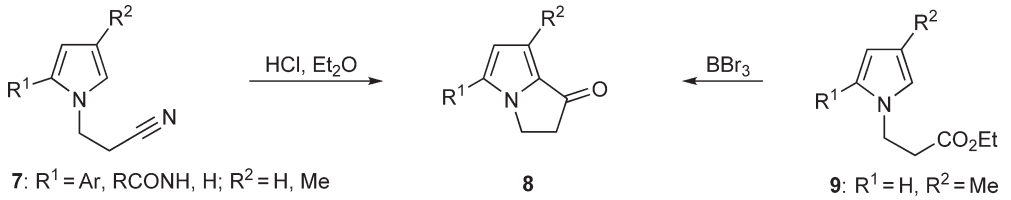
Scheme 5

4.6.2 Formation of a Five-Membered Ring with One N Atom at a Ring Junction

4.6.2.1 No Other Heteroatoms

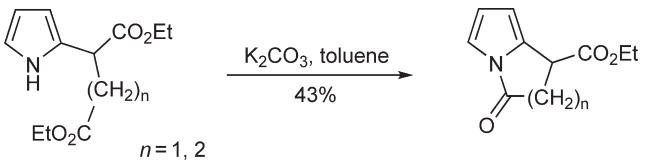
4.6.2.1.1 [55] Systems

Various intramolecular cyclizations are widely used to prepare this type of heterocycle <CHEC-III(11.01.7)15>. Intramolecular acylation has been used frequently <1984AHC(37)1>. Particularly useful is the HoubenHoesch cyclization of 2-substituted 1--cyanoethylpyrroles **7** <1966JA1305, 2003JIC851> or their ester analogues **9** <1995HCA1511, 2002T10407> leading to 1-oxo-2,3-dihydropyrrolizines **8** in good yields (**Scheme 6**) <CHEC-III (11.01.7.1)16>.



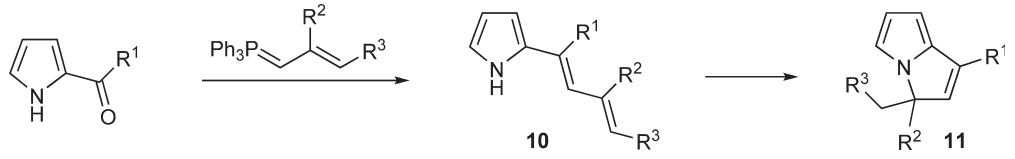
Scheme 6

Intramolecular alkylation of suitably substituted pyrroles and indoles gives pyrrolizinones (n = 1) in moderate yields (e.g., **Scheme 7**) <1980J(P1)97, 2004TL6587, CHEC-III(11.01.7.4)23>.



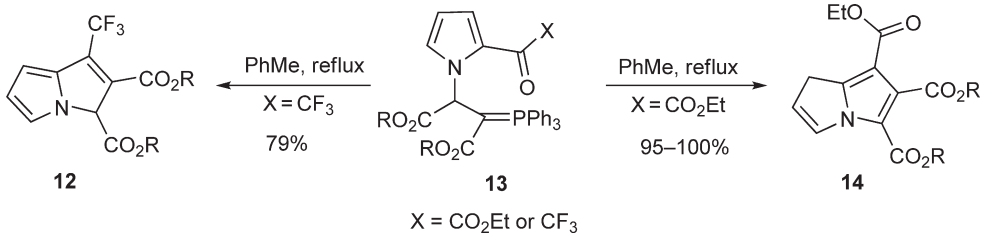
Scheme 7

2-Acylpyrroles react with allylphosphoranes to give pyrrolizines **11** *via* butadiene **10**, which can be isolated and cyclized subsequently (**Scheme 8**) <1966JOC2912>.



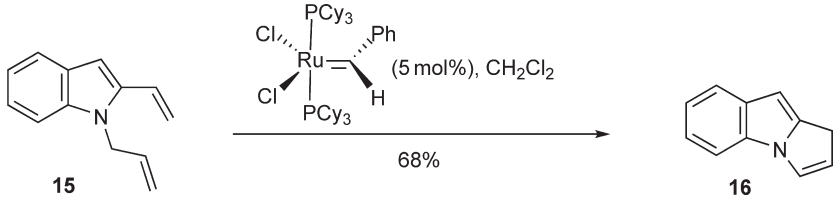
Scheme 8

Intramolecular Wittig reaction of keto-stabilized ylides **13** takes place in refluxing toluene leading to the 1*H*-dihydropyrrolizines **14** in the case of -ketocarboxylic derivatives (X = CO_2Et) <2001T5873>, while trifluoroacetyl ylide **13** (X = CF_3) affords exclusively the 3*H*-dihydropyrrolizine **12** (**Scheme 9**) <2006ARK(x)55, CHEC-III(11.01.7.2)19>.



Scheme 9

1*H*-Dihydropyrrolizine **16** was obtained from **15** by ring-closing metathesis using commercial first generation Grubbs catalyst (**Scheme 10**) <2002TL4765, CHEC-III(11.01.7.2)21>.

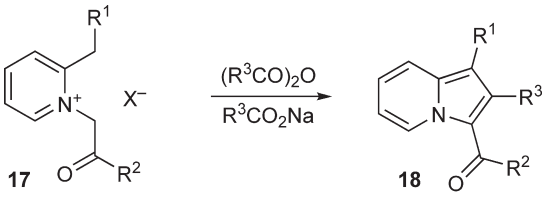


Scheme 10

4.6.2.1.2 [56] Systems

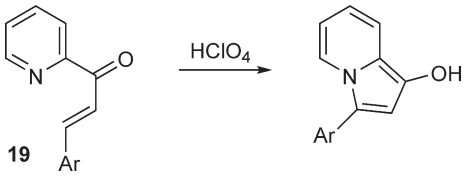
2-Substituted indolizines **18** are formed in Chichibabin reactions of 1-[alkyl(aryl)carbonylmethyl]-2-alkylpyridinium halides **17** (**Scheme 11**) <1972AJC1003>. Various modifications of this method are used for the preparation of many other pyrrolo[1,2-*a*]azines and pyrrolo[1,2-*a*]azoles. Indolizines can also be made by intramolecular Michael additions, e.g., by the cyclization of 2-acylpyridine **19** (**Scheme 12**).

The 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient alkenes and alkynes provides a general approach to indolizines <CHEC-III(11.09.6.1)370>; a representative example is shown in **Scheme 13**. This reaction can be applied to the synthesis of 3-unsubstituted indolizines **22** using *N*-(carboxymethyl)pyridinium halides **20** which undergo decarboxylation upon cycloaddition <2000S1733>. The reaction is performed using electron-deficient alkenes **21** together with a mild oxidant such as MnO_2 to obtain the fully conjugated product (**Scheme 14**).

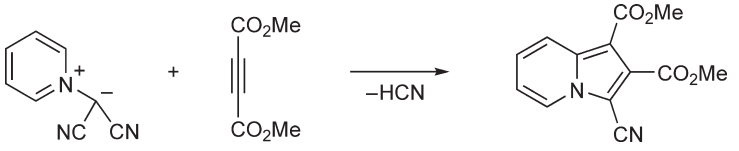


R^1, R^2 = H, Me, Ph; R^3 = Me, Et, Ph

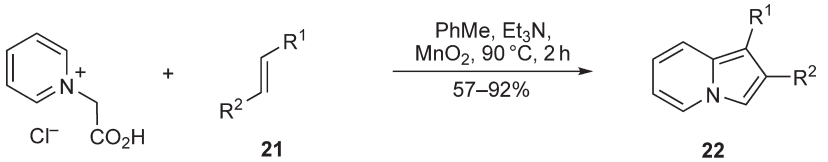
Scheme 11



Scheme 12



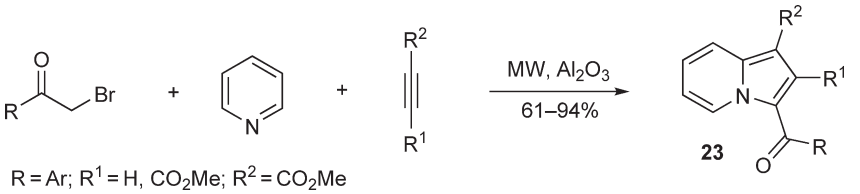
Scheme 13



R^1 = CO_2Et, CN; R^2 = CO_2Et, H, Ph

Scheme 14

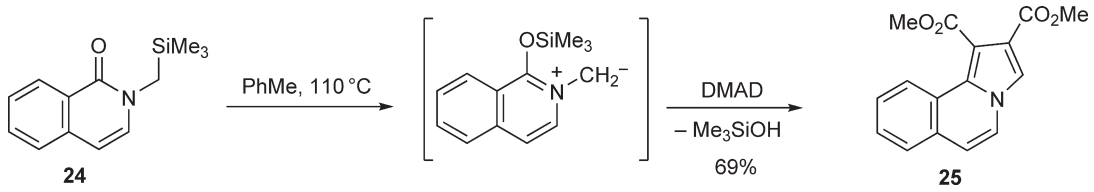
A related method for the synthesis of the indolizine skeleton is represented by a three-component reaction between -bromo ketones, pyridine, and ethyl propiolate or diethyl acetylenedicarboxylate. These reagents, under microwave irradiation and catalysis by basic alumina, afford a good variety of 3-aroyl indolizines **23** (**Scheme 15**) <2003OL435>.



R = Ar; R^1 = H, CO_2Me; R^2 = CO_2Me

Scheme 15

Another variation of this procedure is provided by the use of *N*-(silylmethyl)isoquinolin-1-one **24**, which through 1,4-silatropy and subsequent 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate affords the indolizine **25** (**Scheme 16**) <2003S1398, CHEC-III(11.09.6.1)371>.

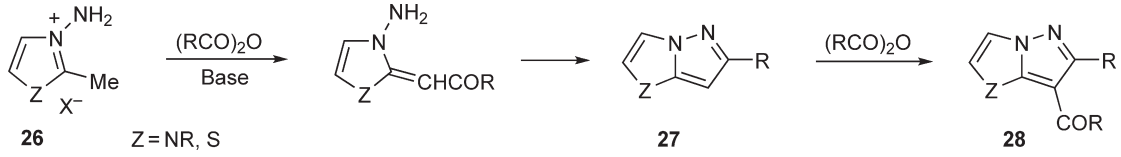


Scheme 16

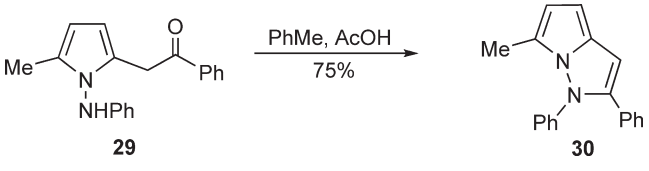
4.6.2.2 One Additional Heteroatom

4.6.2.2.1 Pyrazolo-fused systems

Cyclization of an N-amino group with an α-methyl substituent in *N*-aminoazinium salts or in N-aminoazoles is one of the frequently used routes to pyrazolo-fused systems <1993AHC(53)85, CHEC-III(11.04.9.1)155>. Thus, *N*-amino-imidazolium and -thiazolium salts **26** on heating with anhydrides in the presence of a base are cyclized to give the pyrazoloazoles **27** that are then acylated under the reaction conditions leading to the final products **28** (**Scheme 17**). Likewise, the amino pyrrole **29** undergoes an acid-catalyzed intramolecular condensation to give the 3*H*-pyrrolo[1,2-*b*] pyrazole **30** ring system in good yield (**Scheme 18**) <1998JOC9131, CHEC-III(11.02.2.4)47>

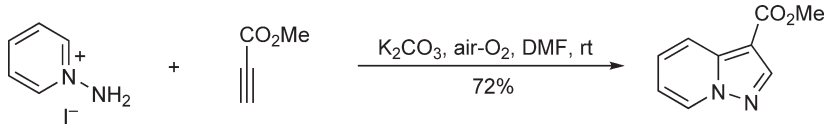


Scheme 17



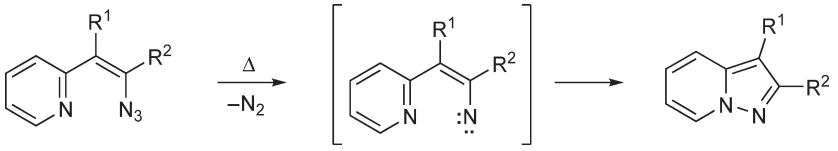
Scheme 18

The 1,3-dipolar cycloaddition of *N*-aminopyridinium derivatives with electron-deficient alkenes and alkynes is the most widely used approach to the [56] pyrazolo-fused systems as exemplified in **Scheme 19** <2001JME2691, CHEC-III(11.10.2.7)416>.



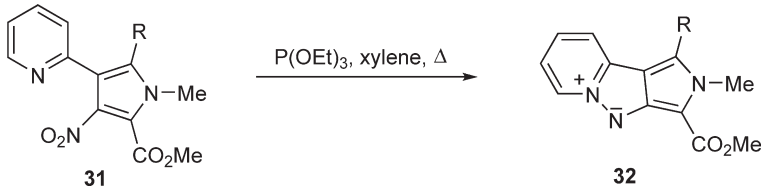
Scheme 19

Another synthetic methodology of growing importance is based on the cyclization of a transient nitrene, most often generated by thermolysis of an azido group as depicted in **Scheme 20** <2000BML1767, 2003T9001, 2004JHC531, CHEC-III(11.10.2.7)418>.



Scheme 20

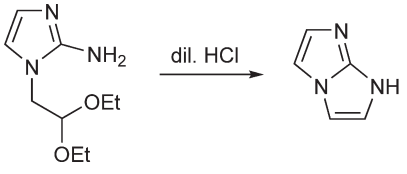
The 2-substituted pyridines **31** with triethyl phosphite yield the pyrrolopyrazoles **32** (**Scheme 21**) <1979JOC622>.



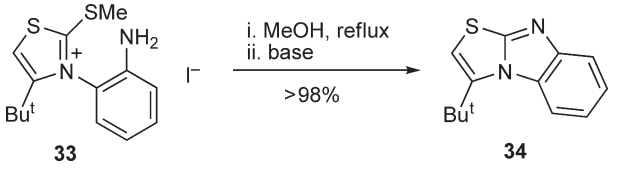
Scheme 21

4.6.2.2.2 Imidazo-fused systems

Many syntheses of imidazo-fused systems involve cyclization of amino-substituted heterocycles (or their tautomers), suitably substituted at an adjacent ring position. This provides a convenient route to imidazo[2,1-*b*]thiazoles, imidazo[1,2-*a*]imidazoles (**Scheme 22**), imidazo[1,2-*b*]pyrazoles, imidazo[1,5-*a*]imidazoles, and imidazo[1,5-*c*]thiazoles. Similarly, the thiazolium salt **33** easily undergoes the cyclization resulting in thiazolo[3,2-*a*]benzimidazoles **34** after a subsequent basic treatment (**Scheme 23**) <2005MOL327, CHEC-III(11.04.9.1.1)152>.

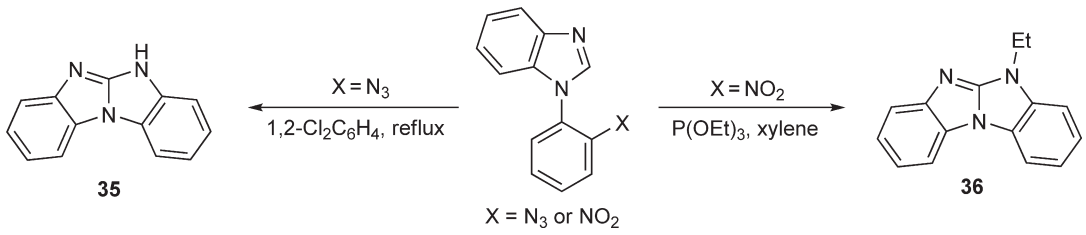


Scheme 22



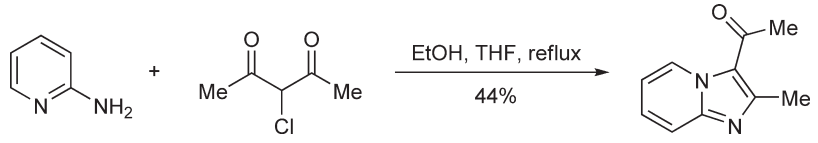
Scheme 23

Tetracyclic benzimidazo[1,2-*a*]benzimidazoles **36** and **35** were prepared by deoxygenation of 1-(2-nitrophenyl) benzimidazole with triethyl phosphite and thermal decomposition of 1-(2-azidophenyl) benzimidazole, respectively (**Scheme 24**) <2000PJS168, CHEC-III(11.04.9.1.1)153>.



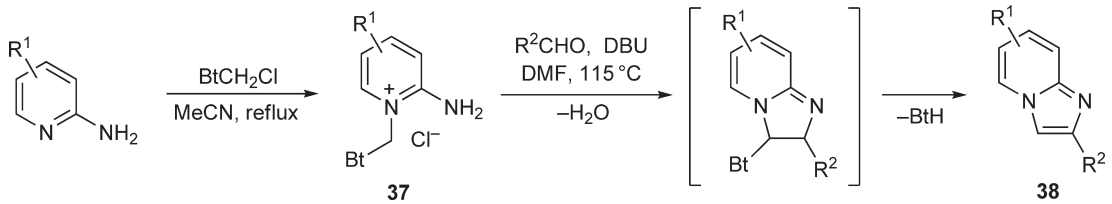
Scheme 24

The most common approach to the [5-6] imidazo-fused systems involves the cyclocondensation of 2-aminopyridine with an -halo carbonyl compound as exemplified in **Scheme 25** <2004BML2245, CHEC-III(11.10.6.7.1)463>.



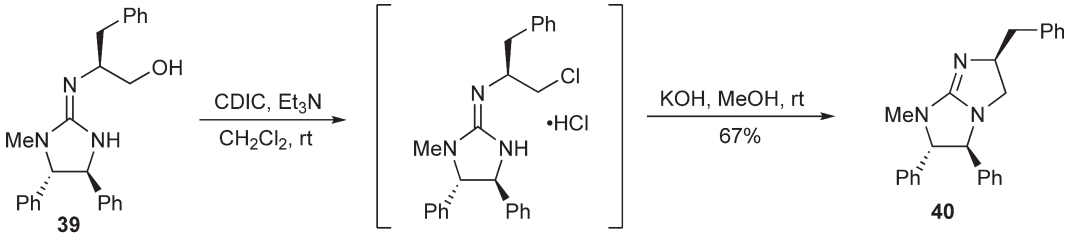
Scheme 25

An efficient synthesis of derivatives **38** is based on the reaction of 2-amino-1-[-benzotriazol-1-ylmethyl] pyridinium chlorides **37** with aldehydes in the presence of DBU as a base (**Scheme 26**) <2000JOC9201, CHEC-III (11.10.6.7.1)465>.



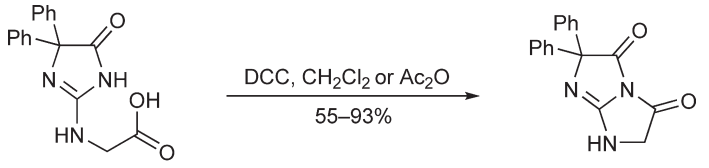
Scheme 26

The 2,3,5,6-tetrahydro-imidazo[1,2-*a*]imidazole system **40**, a bicyclic guanidine, has been prepared by treatment of the 2-(2-hydroxyethylimino)imidazolidine **39** with 2-chloro-1,3-dimethylimidazolium chloride (CDIC) (**Scheme 27**) <2000JOC7779, CHEC-III(11.04.9.1.4)159>.



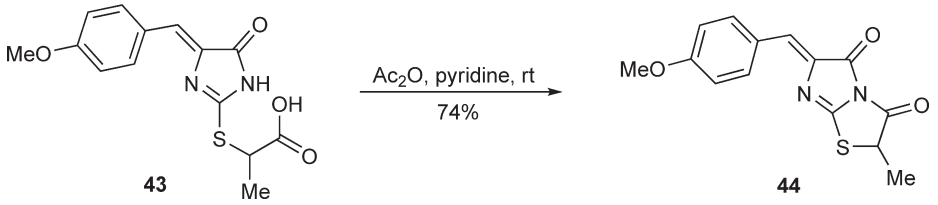
Scheme 27

The lactamization of *N*-(5,5-diphenyl-4-oxo-2-imidazolyl)glycine **41** to 6,6-diphenyl-1,6-dihydroimidazo[1,2-*a*]imidazole-3,5-dione **42** (**Scheme 28**) and the conversion of 2-thioacetic acid derivative **43** into the respective imidazo[2,1-*b*]thiazole-3,5-dione **44** can be induced by treatment with DCC or acetic anhydride (**Schemes 28** and **29**) <1997AP85, 2000PHA429, 2001JST(597)73, CHEC-III(11.04.9.1.4)159>.



41 **42**

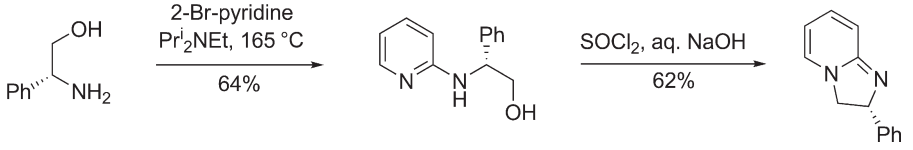
Scheme 28



43 **44**

Scheme 29

The preparation of partially-saturated [5-6] imidazo-fused systems is exemplified by **Scheme 30** <2004JA12226, CHEC-III(11.10.6.7.2)468>.



Scheme 30

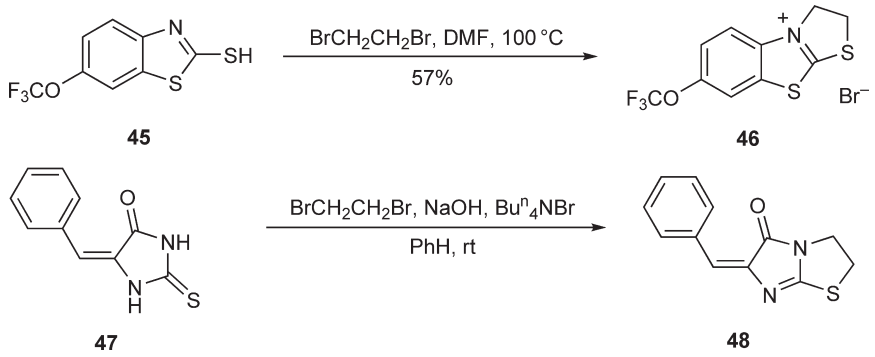
4.6.2.2.3 Thiazolo-fused systems

The usual precursor to the thiazolo-fused systems is a cyclic thioamide or its tautomeric form <CHEC-III(11.04.9.3.2)176>. A convenient approach to the synthesis of bicyclic [5-5] systems, e.g., the tricyclic thiazolium salt **46** and 2,3-dihydroimidazo[2,1-*b*]thiazol-5-one **48**, involves the N,S-dialkylation of appropriate precursors **45** and **47** with 1,2-dihaloalkanes (**Scheme 31**) <1999JMC2828, 2002EJC777>.

The thiazole-2-thiones **49** with an α-halo ketone give the intermediates **50** which are cyclized by strong acid to the thiazolo[2,3-*b*]thiazolium salts **51** (**Scheme 32**) <1977HC(30)1>. A wide variety of [5,5]-fused systems have been prepared in this way.

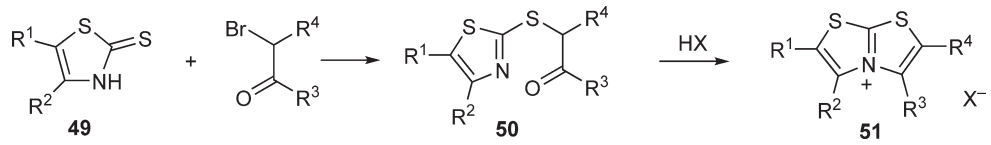
The (1-methylimidazol-2-yl)thioglycolic acid **52** can be converted into the ring-fused mesoionic system **53** by reaction with acetic anhydride (**Scheme 33**) <1979JOC3803>. The thioether **54** with ethanolic sodium ethoxide gives the 3-benzylthiazolo[3,2-*a*]benzimidazole **55** (**Scheme 34**).

Palladiumcopper-catalyzed heterocyclization provides a useful approach to thiazolo-fused systems <CHEC-III(11.04.9.1.4)162> as illustrated by the synthesis of substituted thiazolo[3,2-*a*]benzimidazoles **57** from 2-propargylmercapto benzimidazole **56** *via* a tandem Sonogashira cross-coupling with iodoaryls and a subsequent exocyclic heterocyclization (**Scheme 35**) <2004TL5747>.



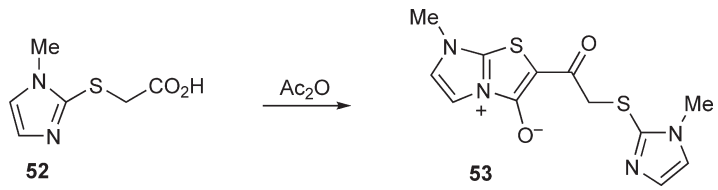
45 46 47 48

Scheme 31



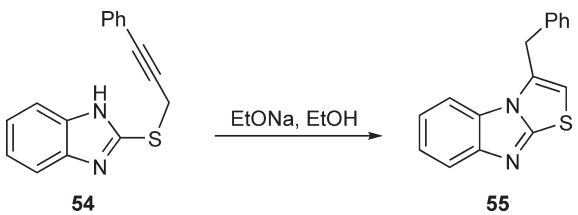
49 50 51

Scheme 32



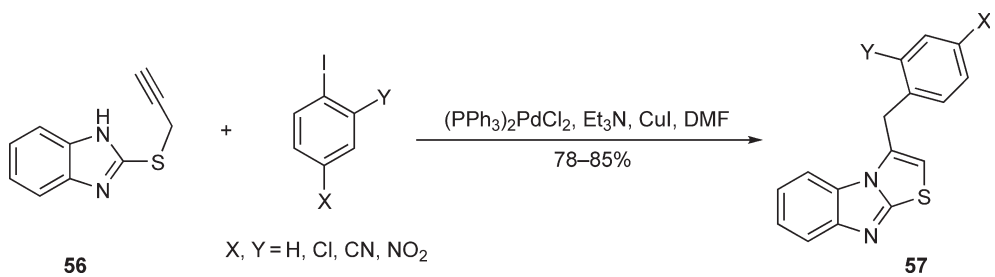
52 53

Scheme 33



54 55

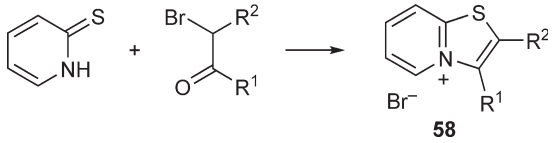
Scheme 34



56 57

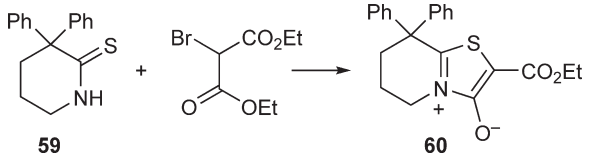
Scheme 35

Six-membered ring cyclic thioamides react with -halo ketones to give the thiazolo[3,2-*a*]pyridinium system, e.g., **58** (**Scheme 36**). A similar reaction of **59** affords the thioisomnchnone **60** (**Scheme 37**) <2001J(P1)2055, CHEC-III (11.10.8.2)487>.



58

Scheme 36



59 **60**

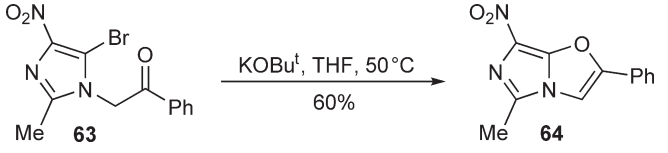
Scheme 37

4.6.2.2.4 Oxazolo- and isoxazolo-fused systems

Cyclic amides can be used like the thioamides of the previous section. 1-(2-Chloroethyl)imidazolidine-2-one **61** with potassium hydroxide affords the tetrahydroimidazo[2,1-*b*]oxazole **62** (**Scheme 38**) <1957JA5276>. The bicyclic imidazo[2,1-*b*]oxazole **64** can be prepared by the cyclization of **63** (**Scheme 39**) <1999H1081>. A similar methodology was applied to the synthesis of oxazolo[3,2-*a*]benzimidazole **66** by heating 2-chloro-1-phenacylbenzimidazole **65** with sodium benzoate in DMF (**Scheme 40**) <2001CHE1179, CHEC-III(11.04.9.1.1)151>.

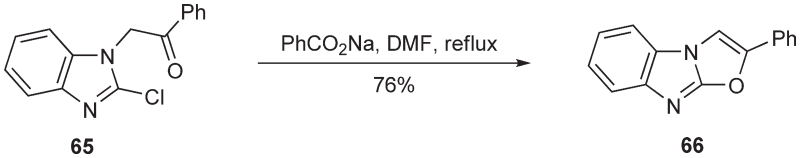
61 **62**

Scheme 38



63 **64**

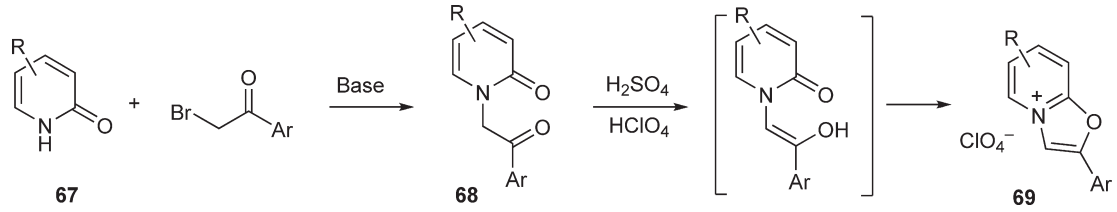
Scheme 39



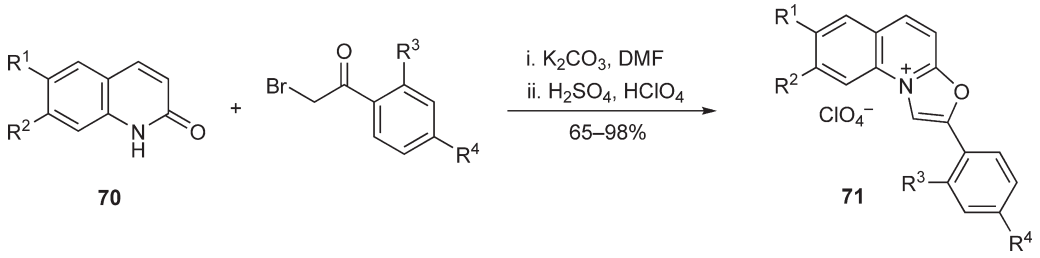
65 **66**

Scheme 40

The most efficient route to the cationic oxazolo[3,2-*a*]pyridine ring system **69** relies on the cyclocondensation of N-phenacyl-2-pyridones **68** obtained by alkylation of 2-pyridones **67** (**Scheme 41**) <1967JHC66, CHEC-III(11.10.7.8) 479>. The use of this method is exemplified by the preparation of tricyclic oxazolo[3,2-*a*]pyridines **71** from the corresponding quinolin-2(1*H*)-ones **70** (**Scheme 42**) <2003H131>.

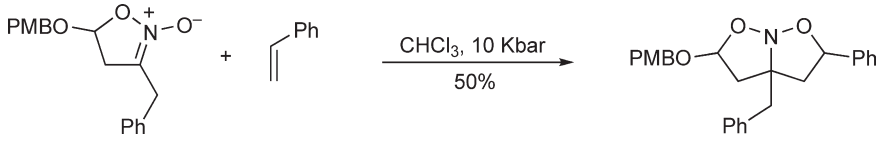


Scheme 41



Scheme 42

Perhydropyrrolo[1,2-*b*]isoxazoles result from 1,3-dipolar cycloaddition of cyclic *N*-oxides with alkenes (e.g., **Scheme 43**) <2001EJO553, CHEC-III(11.04.9.3.1)168>.

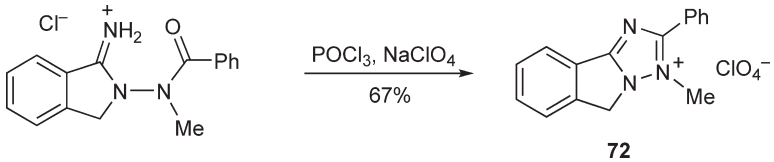


Scheme 43

4.6.2.3 Two Other Heteroatoms

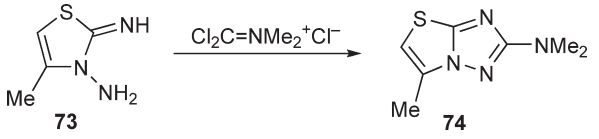
4.6.2.3.1 1,2,4-Triazolo[*b*]-, 1,2,4-thiadiazolo[*b*]-, and 1,3,4-thiadiazolo[*b*]-fused systems

Many syntheses of pyrrolo-fused bicyclic [5–5] systems of this type start from pyrrole derivatives and involve formation of the ring containing three heteroatoms, as illustrated by preparation of the 1,2,4-triazole derivative **72** (**Scheme 44**) <CHEC-III(11.03.9.1)117, 2002CHE1019>.



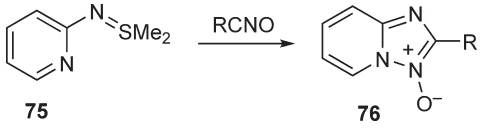
Scheme 44

The 1,2-diamino-4-methylthiazole **73** with phosgeniminium chloride gives the thiazolo[3,2-*b*][1,2,4]triazole derivative **74** (**Scheme 45**) <1973AGE806>. Reaction of the sulfimide **75** with nitrile oxides forms [1,2,4]triazolo[1,5-*a*]pyridine 3-oxides **76** in good yields (**Scheme 46**). This method is applicable to analogous pyrimidines and pyrazines <1976J(P1)2166, 1978BCJ563>.



73 **74**

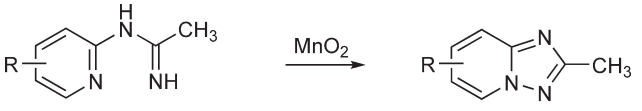
Scheme 45



75 **76**

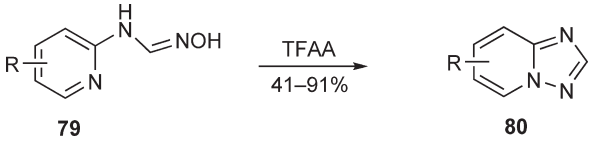
Scheme 46

The [1,2,4]triazolo[1,5-*a*]pyridine system is usually constructed by the closure of the triazole ring either by oxidative formation of the NN bond or by condensation of the N-aminopyridine derivatives <CHEC-III(11.13.9.14)617>. Various compounds **78** were obtained by the oxidation of the amidine **77** with MnO_2 (**Scheme 47**) <2003IJB2901, 2005ARK(xiii)21>. A dehydrative cyclization by treatment of formamidoximes **79** with trifluoroacetic anhydride (TFAA) has been used in the synthesis of **80** (**Scheme 48**), which are key building blocks in the preparation of DPP (IV) inhibitors <2005EJO3761, 2006JME3614>.



77 **78**

Scheme 47

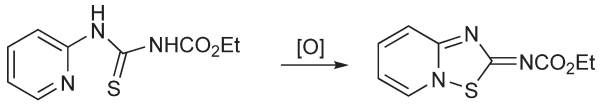


79 **80**

R = 3-,4-,5-, or 6-Me; 3-,5-, or 6-Br; 3-I; 5-COOMe

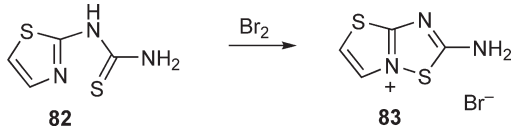
Scheme 48

[1,2,4]-Thiadiazolo[2,3-*a*]pyridine derivatives are commonly prepared by oxidative cyclization of their N-2-pyridyl thiourea precursors (e.g., **81**, **Scheme 49**) using sulfuryl chloride <1996H2657>, bromine <2003K576>, potassium hexacyanoferrate(III) <2003JHC261>, or air under heating <2000CSC687, CHEC-III(11.13.9.7)607>. Similarly, bromine oxidation of 2-thiazolylthiourea **82** gives the 2-aminothiazolo[3,2-*b*][1,2,4]thiadiazolylium bromide **83** (**Scheme 50**) <1971JPR1148>.



81

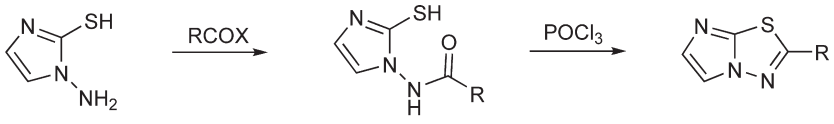
Scheme 49



82 83

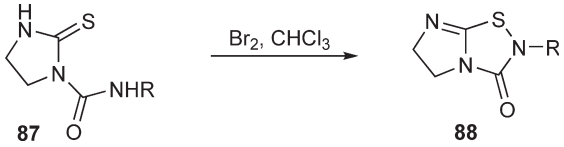
Scheme 50

Reaction of an amino-substituted heterocyclic thiol such as **84** with acylating agents gives compounds **85**, which are cyclized by $POCl_3$ to form the respective imidazo[2,1-*b*][1,3,4]thiadiazoles **86** (**Scheme 51**) (for a review see <1998CHE1003>). Bromine oxidation of the cyclic thiourea **87** forms 2,3,5,6-tetrahydroimidazo[1,2-*d*][l,2,4]thiadiazol-3-ones **88** (**Scheme 52**) <1973JPR539>.



84 85 86

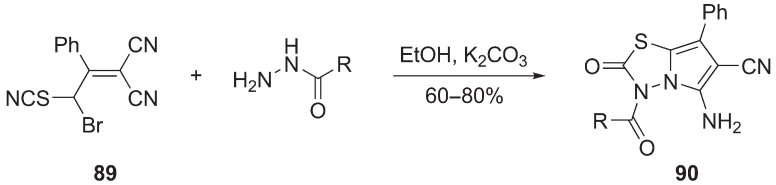
Scheme 51



87 88

Scheme 52

The 1,3,4-thiadiazolo[*b*]-fused system can be conveniently prepared by intramolecular bis-annulation procedures <CHEC-III(11.03.9.5)124>; for example, pyrrolothiadiazolines **90** are prepared by condensation between hydrazides and compound **89** (**Scheme 53**) <1998JPR676>.

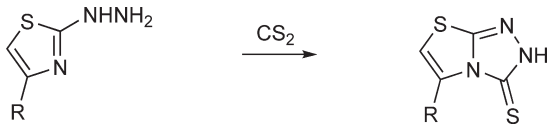


89 90

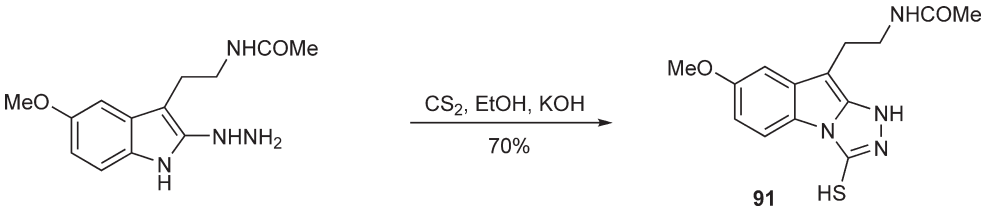
Scheme 53

4.6.2.3.2 1,2,4-Triazolo[*c*]- and 1,2,4-thiadiazolo[*c*]-fused systems

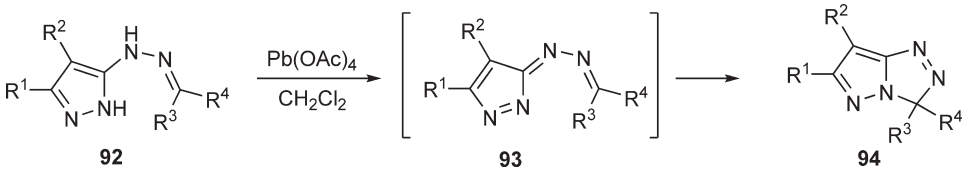
-Hydrazino nitrogen heterocycles are readily converted into 1,2,4-triazolo[*b*]-fused systems, as exemplified by **Scheme 54** <1971JOC10>. A similar approach has been used for the synthesis of triazoloindole derivative **91** (**Scheme 55**) <2005BMC1847, CHEC-III(11.03.9.1)117>. Oxidation of the 2-pyrazolyl hydrazones **92** with lead tetraacetate gives, *via* azines **93**, the 3*H*-pyrazolo[5,1-*c*]-1,2,4-triazoles **94** (**Scheme 56**) <1979TL1567>.



Scheme 54

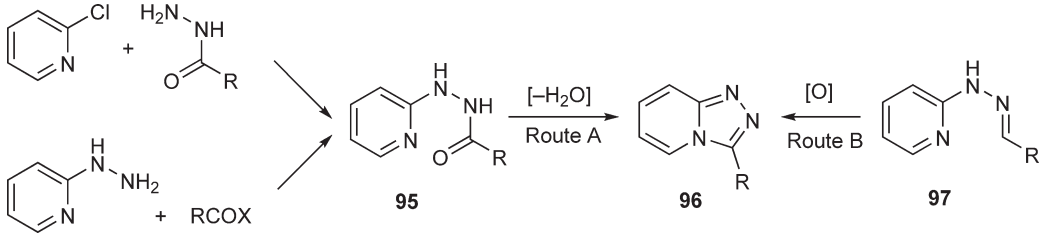


Scheme 55



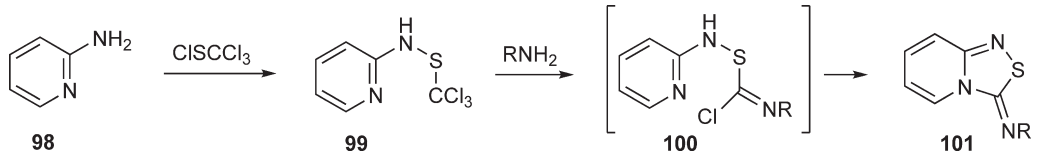
Scheme 56

Most preparations of the 1,2,4-triazolo[3,4-*a*]pyridines **96** can be divided into two distinct routes (**Scheme 57**): a condensation pathway (route A) and an oxidative cyclization starting from the corresponding hydrazone (route B) <CHEC-III(11.13.9.13)611>. The condensation route A usually requires the isolation of the intermediate hydrazides **95** followed by cyclization induced by heat <2005EJM155, 2005JME5001> or by a dehydrating agent such as $POCl_3$ <2003IJB1746> or Ph_3PCl_2/Et_3N <2005BML2129>. The oxidative cyclization of the hydrazones **97** (route B) can be promoted by Br_2 <2002TA821, 2004NN567>, $PhI(OAc)_2$ <2002SC2377>, chloramine T <2004JCR145>, $Pb(OAc)_4$ <2005TA2927>, $CuCl_2$ <2005T5942>, or other oxidants <CHEC-III(11.13.9.13)612>.



Scheme 57

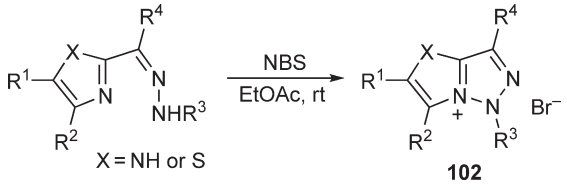
Trichloromethanesulfenyl chloride converts 2-aminopyridine **98** into the sulfenamide **99** which with an aromatic amine cyclizes to **101**, probably *via* the intermediate **100** (**Scheme 58**) <1975JOC2600>.



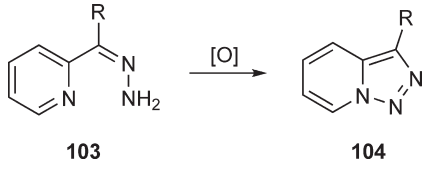
Scheme 58

4.6.2.3.3 1,2,3-Triazolo[*c*]-fused systems

An example of the synthesis of a 1,2,3-triazolo[*c*]-fused system **102** by the oxidative N–N bond formation is shown in **Scheme 59**. Nickel peroxide as oxidizing agent has advantages over NBS or lead tetraacetate <1991T2851>. Likewise, the 1,2,3-triazolo[1,5-*a*]pyridine derivatives **104** are generally prepared by oxidation of the hydrazones **103** using MnO_2 <2002ARK(x)52, 2004T5785, 2005OBC3905> or hypervalent iodine reagents (**Scheme 60**) <2000SC417, CHEC-III (11.13.9.12)609>.



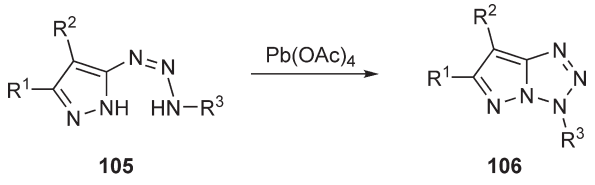
Scheme 59



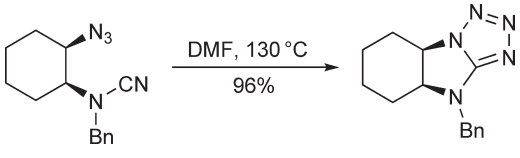
Scheme 60

4.6.2.4 Three Other Heteroatoms: Fused Tetrazoles

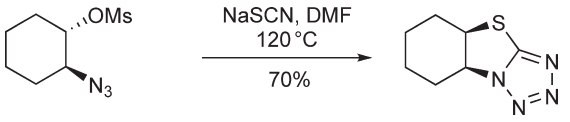
Compounds of type **106** are readily available by intramolecular dehydrogenation of appropriate triazenopyrazoles **105** (**Scheme 61**) <1987CB1375>. A general approach to the fused tetrazole system is provided *via* intermolecular [3 + 2] cycloadditions of the azide group with the activated nitrile functionality present in cyanamides, thiocyanates, and cyanates as illustrated in **Schemes 6264** <CHEC-III(11.08.7.4)358, 2001OL4091>.



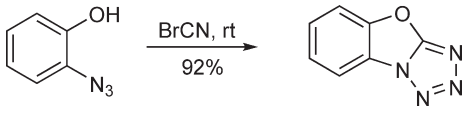
Scheme 61



Scheme 62



Scheme 63



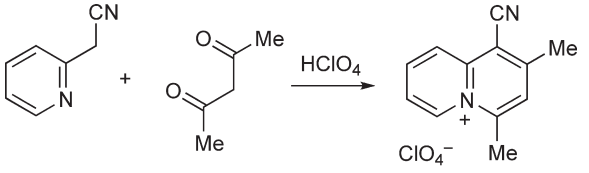
Scheme 64

Fused tetrazoles with three unsubstituted nitrogens arise by cyclizations of azides; see Sections 2.2.5.3, 2.4.5.4, 3.2.3.6.4, and 3.4.1.2.3.

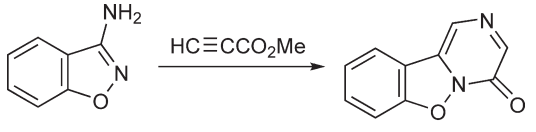
4.6.3 Formation of a Six-Membered Ring with One N Atom at a Ring Junction

4.6.3.1 Ring Formation Using a Three-Atom Fragment

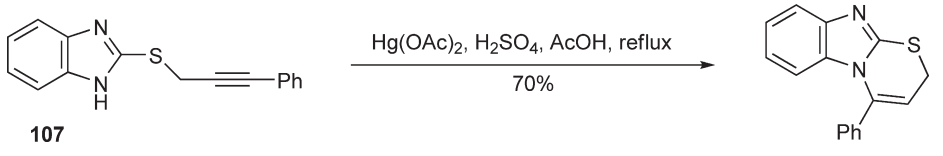
Six-membered rings are formed by the reaction of a three-carbon fragment with an aza heterocycle containing any of (1) an α-alkyl, (2) an α-amino, or (3) a potential α-mercapto group (e.g., **107**). Examples of routes (1), (2), and (3), respectively, are shown in **Schemes 65** <1975KGS530>, **66** <1972CB794>, and **67** <1976S189>. A related cyclization on the pyridine N atom is represented by the synthesis of benzo[*c*]quinolizine derivatives **109** *via* benzo[*c*] quinolizinium salts **108** as intermediates (**Scheme 68**) <2002JOC2082, CHEC-III(12.01.9.1)24>.



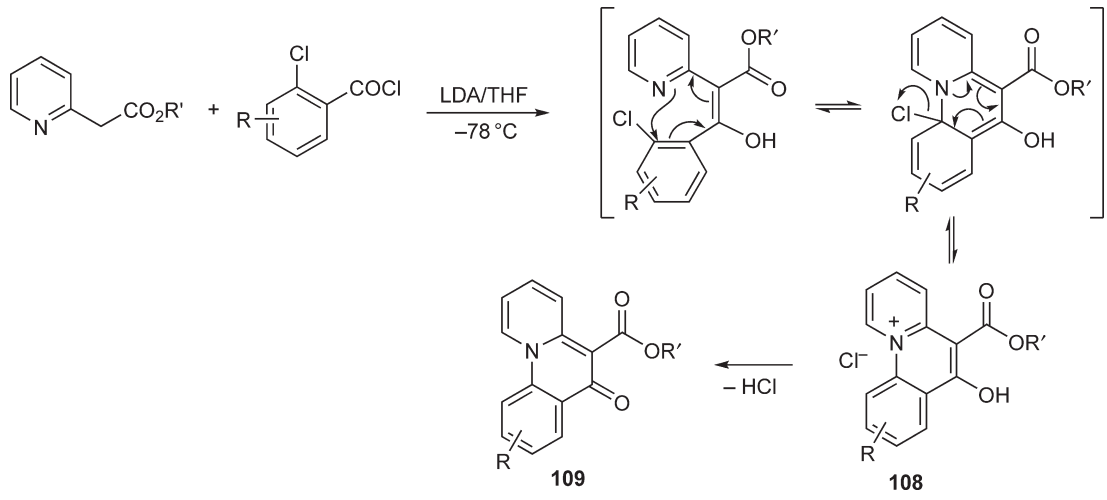
Scheme 65



Scheme 66

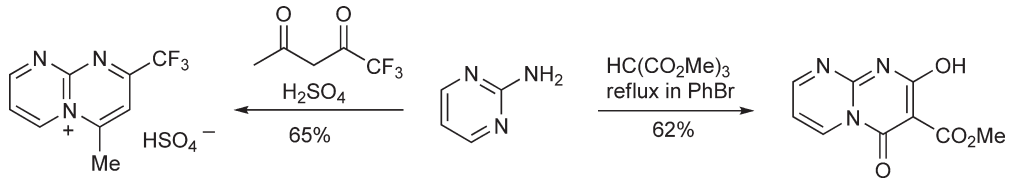


Scheme 67

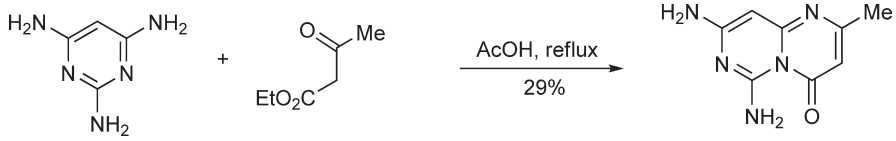


Scheme 68

Reactions of this type have been used extensively for the preparation of diazinodiazines as exemplified in **Schemes 69** <1999JHC237, 2002JFC(118)135, CHEC-III(12.04.2.6.5)282> and **70** <1999JOC634, CHEC-III(12.04.2.6.6)287>.

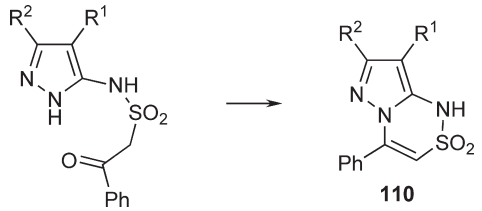


Scheme 69

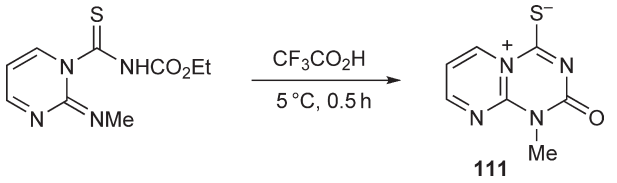


Scheme 70

Methods analogous to those described above, but using a CCS or CNC three-atom fragment, are illustrated by the syntheses of compound **110** (**Scheme 71**) and the fused 1,3,5-triazine mesomeric betaine **111** shown in **Scheme 72**.



Scheme 71

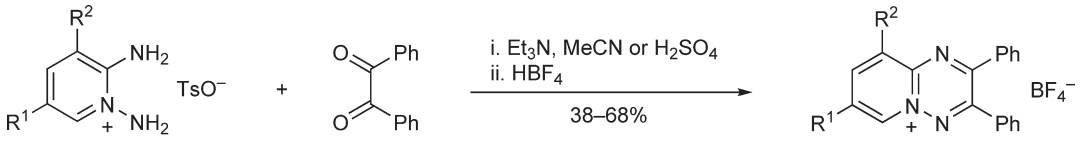


111

Scheme 72

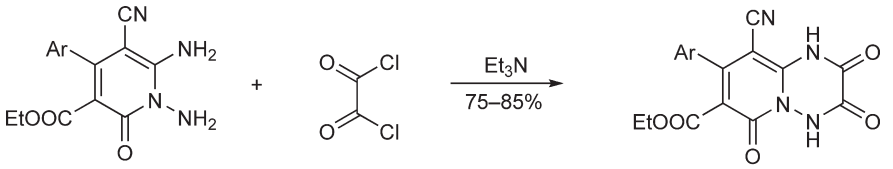
4.6.3.2 Ring Formation Using a Two-Atom Fragment

Pyrido[1,2-*b*][1,2,4]triazinium salts **113** can be obtained from **112** with benzil in the presence of either base <2001CPH77> or sulfuric acid (**Scheme 73**) <2003ARK(xiv)155>. In an analogous reaction, 1,2-diaminopyridines **114** are transformed into 2,3,6-trioxopyridotriazines **115** by treatment with oxalyl chloride in the presence of triethylamine (**Scheme 74**) <1998SC3331, CHEC-III(12.03.2.4.4)237>.



112 113

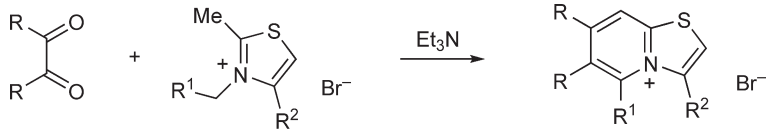
Scheme 73



114 Ar = Ph, 4-ClC6H4, 4-NO2C6H4 115

Scheme 74

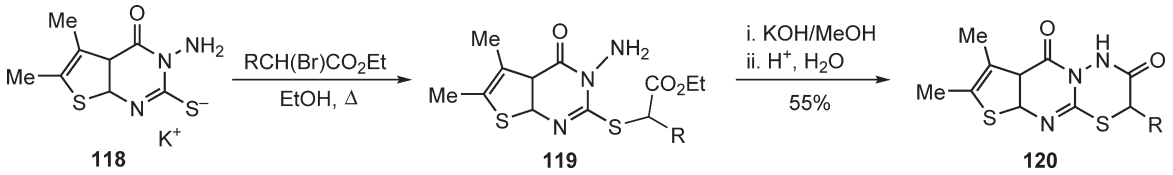
2-Methylthiazolium salts **116** with 1,2-dicarbonyl compounds give thiazolo[2,3-*b*]pyridinium salts **117** (**Scheme 75**) <1986JHC1889>.



116 117

Scheme 75

The reaction of the tetrahydrothieno[2,3-*d*]pyrimidine-2-thiolate **118** with -bromoesters results in the formation of **119** which can be cyclized to products **120** by treatment with alkali followed by acidification (**Scheme 76**) <2000JHC1161, CHEC-III(12.06.10.1.3)334>.

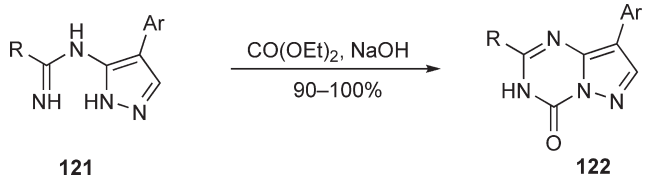


118 119 120

Scheme 76

4.6.3.3 Ring Formation Using a One-Atom Fragment

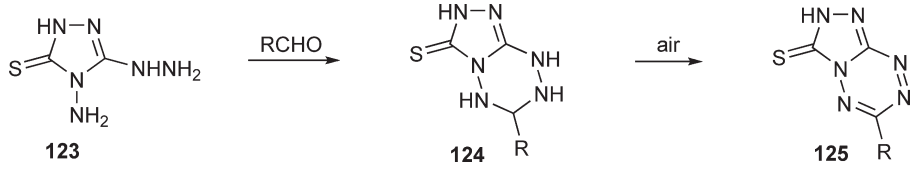
A ring-closure reaction of amidine-containing pyrazoles **121** can be effected by treatment with diethyl carbonate under basic conditions to afford products **122** in almost quantitative yields (**Scheme 77**) <2000JME449, 2003BMC4093, CHEC-III(11.17.6.3.5)798>.



121 122

Scheme 77

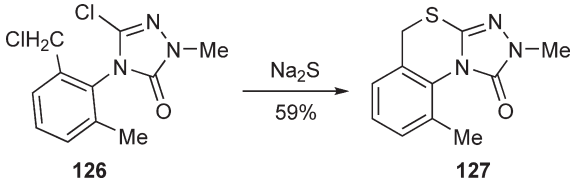
4-Amino-3-hydrazino-1,2,4-triazoline-5-thione **123** and aldehydes form unstable products **124**, which are readily oxidized by air to deeply colored tetrazines **125** (**Scheme 78**). This is a sensitive method for determining aldehydes <1970JCS(D)1719>.



123 124 125

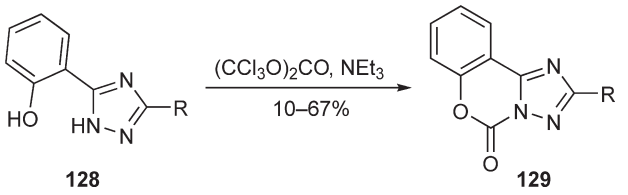
Scheme 78

Other syntheses of this type are exemplified by the conversion of **126** to **127** by treatment with sodium sulfide (**Scheme 79**) <2004T4361, CHEC-III(11.16.6.1.2)711>, the synthesis of the tricyclic [1,2,4]triazolo[1,5-*c*][1,3]benzoxazine **129** by reaction of the triazolylphenol **128** with bis-trichloromethyl carbonate (**Scheme 80**) <1995JME2196, CHEC-III(11.16.6.1)710>, and the preparation of indolo[2,1-*c*]benzo[1,2,4]triazine derivatives **131** by diazotization of 2-amino-1-aryltetrahydroindoles **130** followed by an intramolecular coupling of the diazonium group with the aryl moiety (**Scheme 81**) <2003H2519, CHEC-III(11.14.8.4)638>.

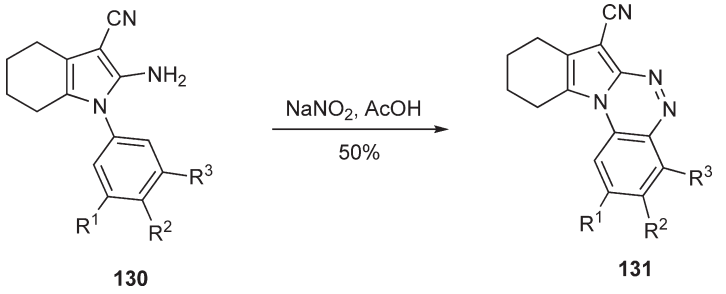


126 127

Scheme 79



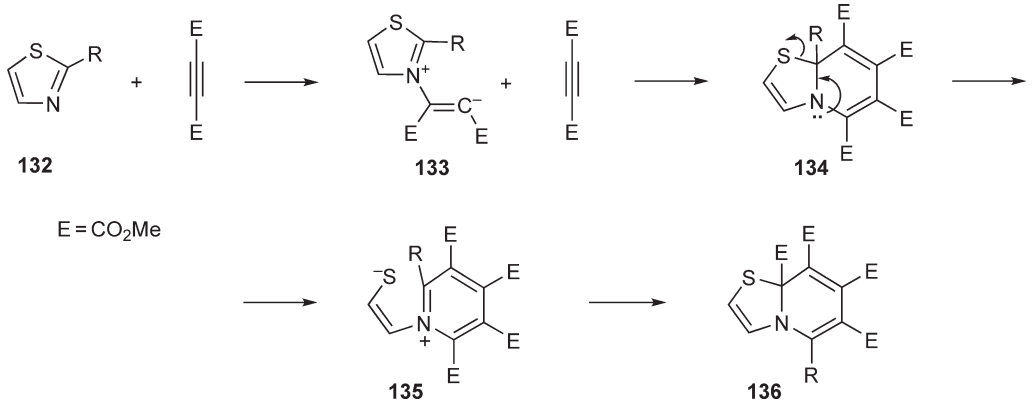
Scheme 80



Scheme 81

4.6.3.4 Cycloaddition and Ring Transformation Reactions

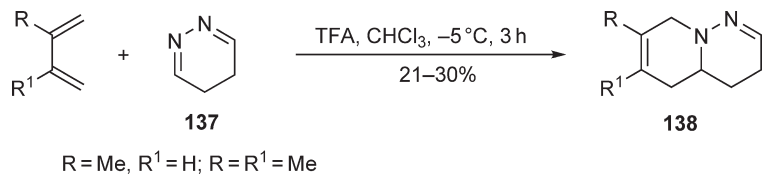
1,4-Dipolar cycloadditions lead to six-membered rings. Rearrangements may be encountered. Thiazole or 2-methylthiazole **132** (R = H and Me) with DMAD forms an initial 1,4-dipolar species **133**. Reaction of **133** with a second molecule of DMAD gives a 1:2 adduct, presumably **134**. Ring opening to **135**, followed by cyclization in the alternative mode, results in **136** (**Scheme 82**) <1978AHC(23)263>. For the similar reactions of pyridine with DMAD and pyridazine with maleic anhydride, see Section 3.2.1.3.7.



Scheme 82

DielsAlder type [4 + 2] cycloadditions of 4,5-dihydropyridazine **137**, prepared *in situ* from its trimer, with 2-methyl- and 2,3-dimethyl-1,3-butadienes afford the tetrahydropyrido[1,2-*b*]pyridazines **138** in relatively low yields (**Scheme 83**) <1997CEJ1588, CHEC-III(12.02.2.5.4)90>.

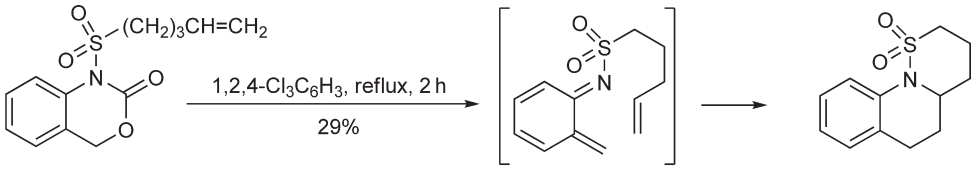
Heating 1,3-benzoxazino derivative **139** in boiling 1,2,4-trichlorobenzene gives hexahydrothiazino[2,3-*a*]quinoline **140** *via* initial decarboxylation followed by an intramolecular [4 + 2] cycloaddition reaction (**Scheme 84**) <1996J(P1) 1809, CHEC-III(12.02.2.5.5)91>.



137 **138**

R = Me, R^1 = H; R = R^1 = Me

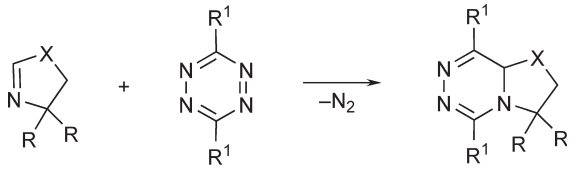
Scheme 83



139 **140**

Scheme 84

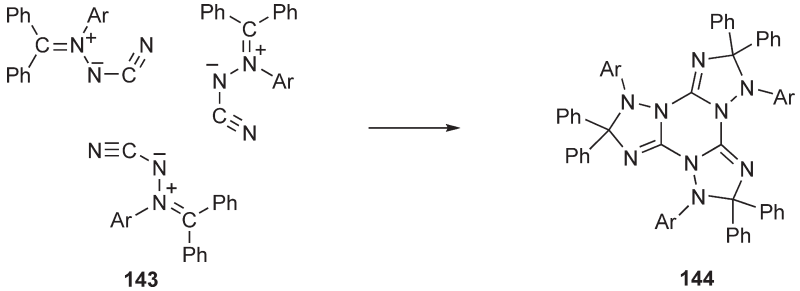
DielsAlder reaction of oxazolines and thiazolines **141** with tetrazines yields bicyclic compounds **142** (**Scheme 85**) <1984AP(317)237>.



141 X = O, S **142**

Scheme 85

Triaryl-*N*-cyanoazomethine imines **143** are trimerized on heating to **144** (**Scheme 86**) *via* a succession of three 1,3-dipolar cycloadditions, the third being intramolecular <1980AGE906>.

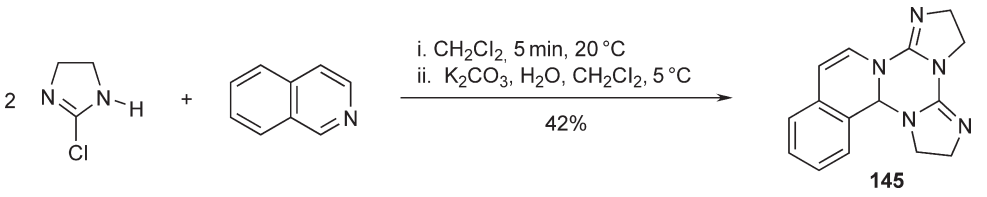


143 **144**

Scheme 86

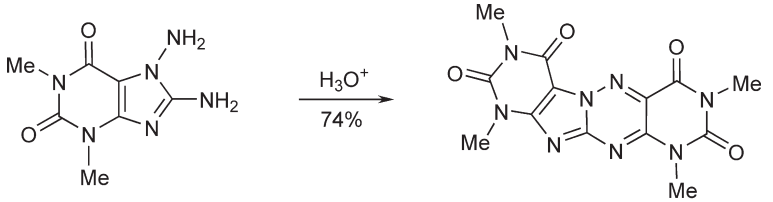
Mixed trimerization of heterocyclic compounds is a potentially valuable route to fused systems, e.g., isoquinoline with 2-chloro-4,5-dihydroimidazole affords **145** (**Scheme 87**) <1981S154>.

7,8-Diaminotheophiline **146** is transformed on heating with acids into tetracycle **147** (**Scheme 88**) <1987CPB4031>.



145

Scheme 87



146 147

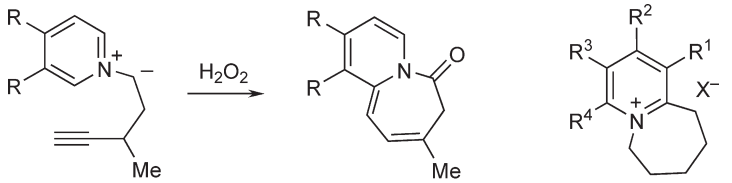
Scheme 88

4.6.3.5 Other Methods

Azole aldehydes with an -NH group dimerize (Section 3.4.3.4.4). Cyclic N^+N links can be formed using nitrene intermediates (Section 3.4.3.4.2).

4.6.4 Formation of a Seven-Membered Ring with One N Atom at a Ring Junction

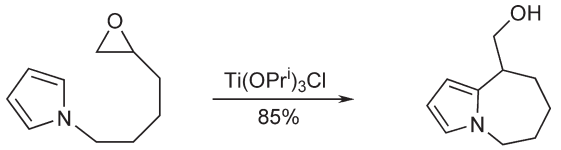
Ylide **148** is cyclized by 30% aqueous hydrogen peroxide to afford the pyrido[1,2-*a*]azepines **149** (**Scheme 89**) <1991HCA1095>. The pyrido[1,2-*a*]azepinium system **150** is obtainable by intramolecular free radical cyclization of 5-(1-pyridinio)-pentyl iodide <1991T4077>.



148 149 150

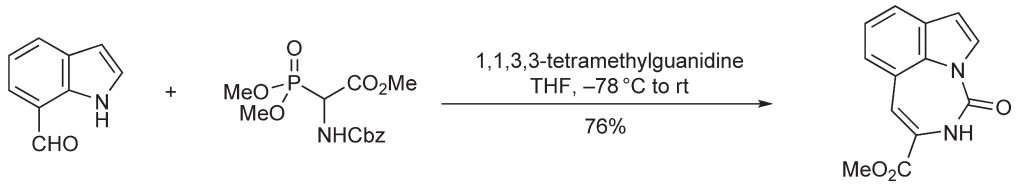
Scheme 89

Pyrrolo[1,2-*a*]azepines occur in a number of natural products and compounds of biological interest. The pyrroloalkyl epoxide **151** is cyclized to the alcohol **152** by $Ti(OPr^i)_3Cl$ (**Scheme 90**) <1987JOC819>. Preparation of 1,3-diazepine based systems is exemplified in **Schemes 91** <2002JOC6256, CHEC-III(13.05.9.2.3)175> and **92** <1997T15895, CHEC-III(13.05.9.1.1)169>.

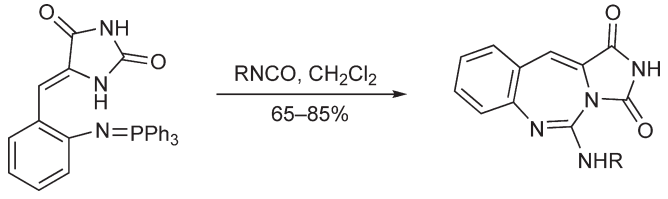


151 152

Scheme 90



Scheme 91

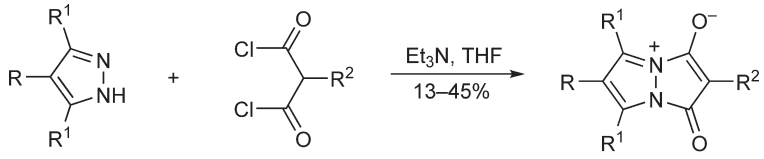


Scheme 92

4.6.5 Two Nitrogen Atoms at a Ring Junction

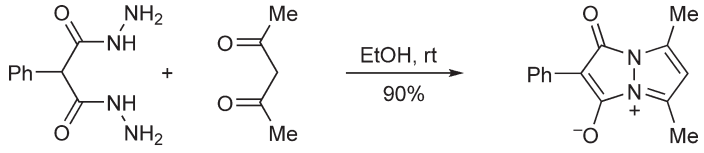
4.6.5.1 Five-Membered Rings

A wide variety of methods for the synthesis of these compounds are available <CHEC-III(12.10.10)401>; the following examples are intended only to be illustrative. Pyrazoles **153** react with reactive malonic acid derivatives, e.g., dichlorides in the presence of triethylamine, yielding pyrazolo[l,2-*a*]pyrazole cross-conjugated betaines **154** (**Scheme 93**) <1980JA3971, 1994JOM(481)109>. Likewise, treatment of malonic acid dihydrazide **155** with a 1,3-diketone in ethanol at room temperature provides **156** in good yield (**Scheme 94**) <2005JHC287>.



153 **154**

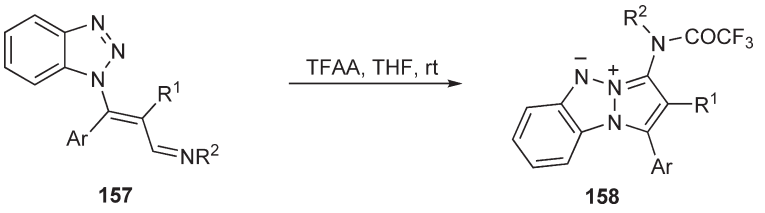
Scheme 93



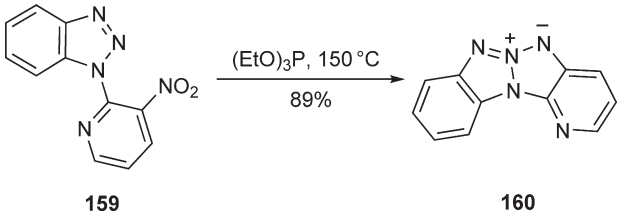
155 **156**

Scheme 94

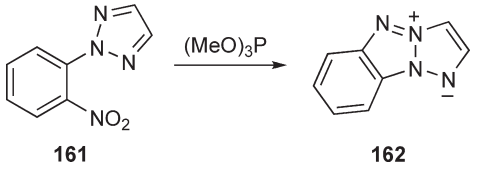
Treatment of imines **157** with trifluoroacetic anhydride affords triazapentalene derivatives **158** (**Scheme 95**) <2003TL7507>. Compound **159** treated with triethyl phosphite in refluxing xylene provides **160** in high yield (**Scheme 96**) <2005AGE7089>. Likewise, the [1,2,3]triazolo[2,1-*a*]benzotriazole (2,3-benzo-1,3a,4,6a-tetraazapentalene) system **162** is obtained by an electrophilic attack of singlet nitrene, generated by heating the corresponding nitrophenyl triazole **161** with trimethyl phosphite, on the triazole nitrogen (**Scheme 97**) <1998JOC3352, CHEC-III (12.10.10.4)404>.



Scheme 95

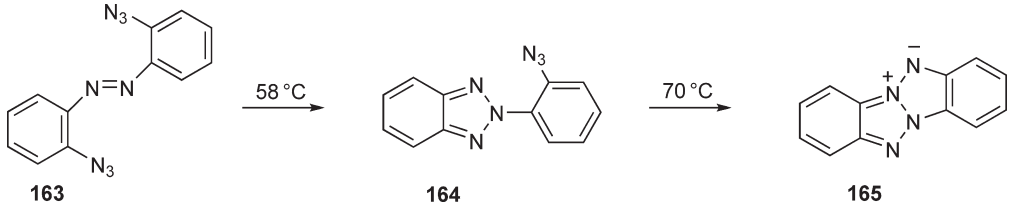


Scheme 96



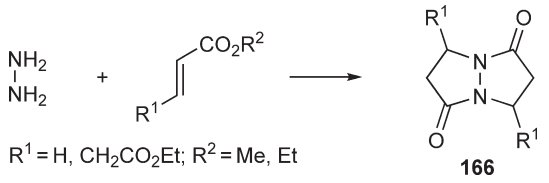
Scheme 97

Heating 2,2-diazidoazobenzene **163** at 58°C forms **164**; at 70°C a second ring closure gives the tetraazapentalene **165** (**Scheme 98**) <1967JA2618>.

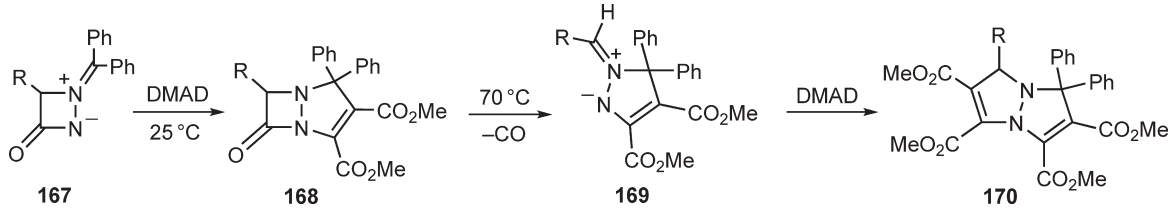


Scheme 98

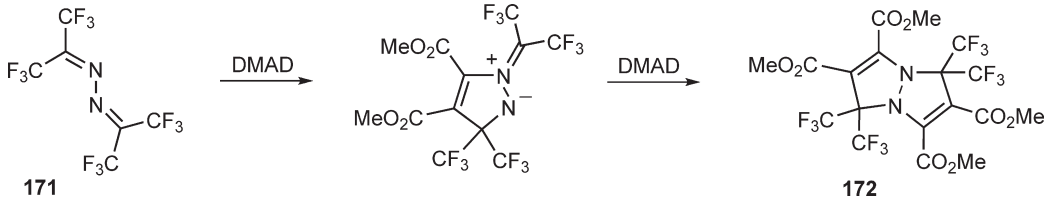
Pyrazolo[1,2-*a*]pyrazole systems **166** can be obtained by the reaction of hydrazine with acrylic esters (**Scheme 99**) <2001J(P2)243, CHEC-III(12.10.12.1)406>. The betaines **167** reacts with dimethyl acetylenedicarboxylate to give products **168** which easily undergo thermal fragmentation to **169** followed by another cycloaddition to form **170** (**Scheme 100**) <1981JA7743>. Criss-cross addition of azines, e.g. **171**, also involves two successive 1,3-dipolar cycloadditions to give pyrazolo[1,2-*a*]pyrazoles, e.g., **172** (**Scheme 101**) <1976S349>.



Scheme 99



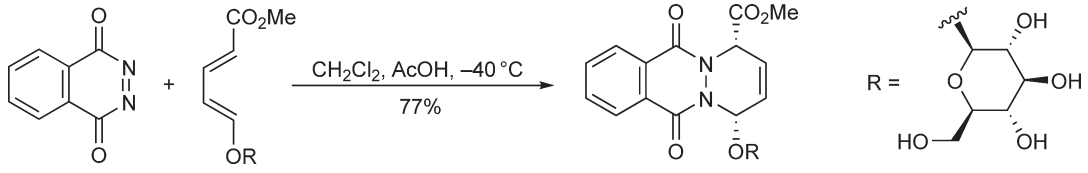
Scheme 100



Scheme 101

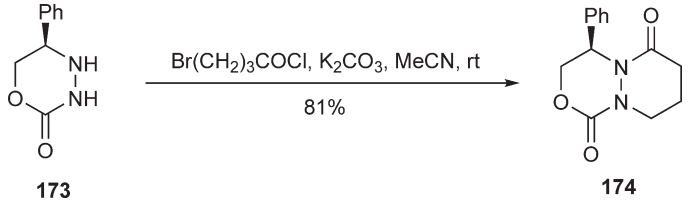
4.6.5.2 Six-Membered Rings

The aza DielsAlder reaction is a useful and well-established method for synthesis of pyridazino[1,2-*a*]pyridazines <CHEC-III(12.10.14.1)459>; an example is shown in **Scheme 102** <1994TL3397>.



Scheme 102

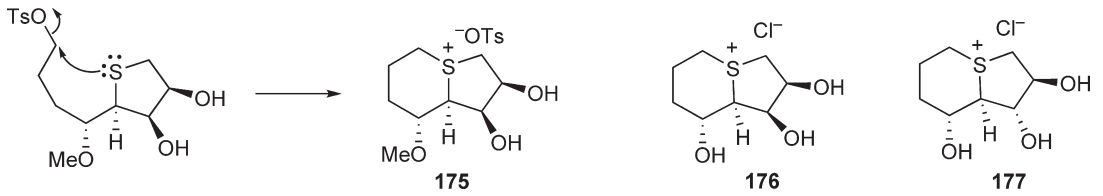
The condensation of 1,3,4-oxadiazinan-2-one derivative **173** with bromobutyryl chloride under classical basic conditions gives bicyclic derivative **174** (**Scheme 103**) <1998TL8081, CHEC-III(12.10.14.2)460>.



Scheme 103

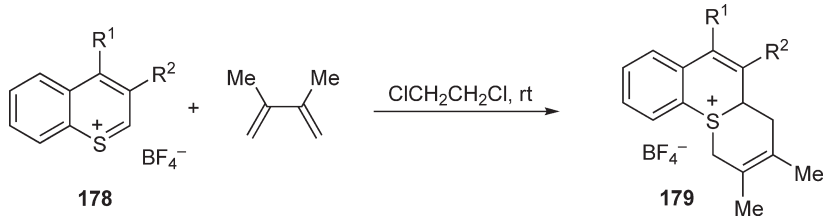
4.6.6 Sulfur at a Ring Junction

Preparations of bicyclic sulfonium ions (e.g., **175**) utilize intramolecular alkylation of the tosylate precursor as exemplified in **Scheme 104** <1996TA2567>. A sulfonium ion analogue **176** of swainsonine <2006CAR1685> and an analogue **177** of epi-swainsonine <2006JOC1262> were synthesized using a similar approach <CHEC-III(12.11.2.1.2)491>.



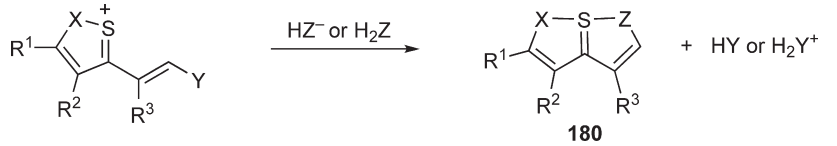
Scheme 104

The benzo-fused bicyclic sulfonium salts **179** can be prepared *via* [4 + 2] cycloaddition reactions of 2-thianaphthylium ions **178** with various butadienes (e.g., **Scheme 105**) <CHEC-III(12.11.2.1.2)488, 1996J(P1)2227>.



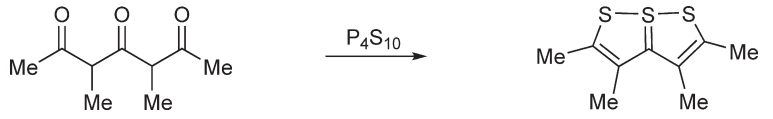
Scheme 105

Numerous synthetic methods for triheterapentalenes **180** (X and Z = O, S, Se, or NR) are discussed in CHEC-III (12.11.6)488; illustrative examples are shown in **Schemes 106110**. The method of **Scheme 106** has been widely used; X can be S or NMe; Y = OMe, SMe, or NMe_2; Z = O, S, Se, or NR. For related syntheses see Section 3.4.3.3.4.

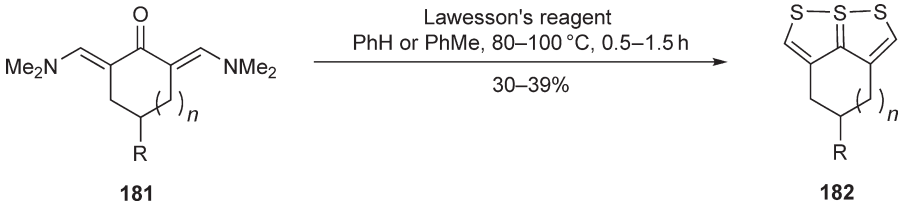


X = S or NMe; Y = OMe, SMe or NMe_2, and Z = S, Se, O, or NR

Scheme 106



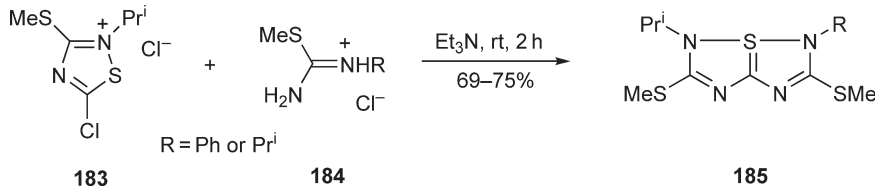
Scheme 107



Scheme 108

1,6,6a^4-Trithiapentalenes are obtained from 1,3,5-triketones with P_2S_5 <CHEC-III(12.11.6.3)518>, e.g., **Scheme 107**. A similar preparation of 3,4-bridged trithiapentalenes **182** is based on the thiolation of keto dienamines **181** using Lawessons reagent (**Scheme 108**) <2001SL1129>.

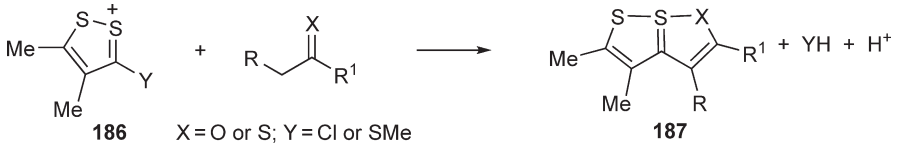
5-Chloro-3-methylthio-1,2,4-thiadiazol-2-ium chlorides **183** are useful precursors to a variety of thiapentalene systems <2003HAC95>. The treatment of **183** with *S*-methyl isothioureas **184** generated the corresponding 1,6,6a^4-thia-1,3,4,6-tetraazapentalenes **185** (**Scheme 109**).



183 **184** **185**

Scheme 109

1,2-Dithiolylium cations carrying a leaving group at the 3-position **186** react with active methylene compounds to give products **187** in which X = O or S (**Scheme 110**) <1980AHC(27)151>.



186 X = O or S; Y = Cl or SMe **187**

Scheme 110

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* Indicates that this is a reference to the synthesis of either a specific compound or a group of compounds

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JOURNAL ABBREVIATIONS

CHEC-I, CHEC-II and CHEC-III refer to the first, second and third editions of Comprehensive Heterocyclic Chemistry, respectively.

AC(R)	*Ann. Chim. (Rome)*
ACA	*Acta Chem. Scand., Ser. A*
ACB	*Acta Chem. Scand., Ser. B*
ACH	*Acta Chim. Acad. Sci. Hung.*
ACR	*Acc. Chem. Res.*
ACS	*Acta. Chem. Scand.*
AF	*Arzneim.-Forsch.*
AG	*Angew. Chem.*
AGE	*Angew. Chem., Int. Ed. Engl.*
AJC	*Aust. J. Chem.*
AK	*Ark. Kemi*
ALD	*Aldrichimica Acta*
ALE	*Anal. Lett.*
ANA	*Anal. Chim. Acta*
ANY	*Ann. N. Y. Acad. Sci.*
AP	*Arch. Pharm. (Weinheim, Ger.)*
APC	*Appl. Catal. A*
AQ	*An. Quim.*
ARB	*Ann. Rep. Prog. Chem., Sect. B*
ARK	*Arkivoc*
ASC	*Adv. Synth. Catal.*
ASJ	*Asian J. Chem.*
AX	*Acta Crystallogr.*
AXB	*Acta Crystallogr., Sect. B*
AXC	*Acta Crystallogr., Sect. C*
AXE	*Acta Crystallogr., Sect. E*
BAP	*Bull. Acad. Pol. Sci., Ser. Sci. Chim.*
BCJ	*Bull. Chem. Soc. Jpn.*
BKC	*Bull. Korean Chem. Soc.*
BMC	*Bioorg. Med. Chem.*
BML	*Bioorg. Med. Chem. Lett.*
BSB	*Bull. Soc. Chim. Belg.*
BSF	*Bull. Soc. Chim. Fr.*
C	*Chimia*
CAR	*Carbohydr. Res.*
CB	*Chem. Ber.*
CC	*Chem. Commun. [J. Chem. Soc., D / J. Chem Soc., Chem. Commun.*
CCA	*Croat. Chem. Acta*
CCC	*Collect. Czech. Chem. Commun.*
CCR	*Coord. Chem. Rev.*
CEJ	*Chem. Eur. J.*
CEN	*Chem. Eng. News*
CEO	*CrystEngComm*
CHE	*Chem Heterocycl. Compd. (Engl. Transl.)*
CHI	*Chirality*
CIL	*Chem. Ind. (London)*
CJC	*Can. J. Chem.*
CL	*Chem. Lett.*
CM	*Chem. Mater.*
COR	*Curr. Org. Chem.*
CPB	*Chem. Pharm. Bull.*
CPH	*Chem. Phys.*
CPL	*Chem. Phys. Lett.*
CRB	*C. R. Acad. Sci. II*
CRC	*C. R. Hebd. Seances Acad. Sci., Ser. C*
CRV	*Chem. Rev.*
CS	*Chem. Scr.*
CSC	*Cryst. Struct. Commun. Acta Cryst.*
CSR	*Chem. Soc. Rev.*
CSY	*Curr. Org. Synth.*
CZ	*Chem.-Ztg.*
DOK	*Dokl. Akad. Nauk SSSR*
DP	*Dyes Pigments*
EAC	*Electrochim. Acta*
EJC	*Egypt. J. Chem.*
EJI	*Eur. J. Inorg. Chem.*
EJM	*Eur. J. Med. Chem.*
EJO	*Eur. J. Org. Chem*
FES	*Farmaco Ed. Sci.*
G	*Gazz. Chim. Ital.*
GC	*Green Chem.*
GEP	*Ger. Pat.*
H	*Heterocycles*
HAC	*Heteroatom Chem.*
HC	*Chem. Heterocycl. Compd.*
HCA	*Helv. Chim. Acta*
HCO	*Heterocycl. Commun.*
IC	*Inorg. Chem.*
ICA	*Inorg. Chim. Acta*
IJB	*Ind. J. Chem., Sect. B*
IJY	*Indian J. Phys.*
IZV	*Izv. Akad. Nauk SSSR, Ser. Khim.*
J(F1)	*J. Chem. Soc., Faraday Trans. 1*
J(P1)	*J. Chem. Soc., Perkin Trans. 1.*
J(P2)	*J. Chem. Soc., Perkin Trans. 2*
JA	*J. Am. Chem. Soc.*
JAM	*J. Am. Soc. Mass Spectrom.*
JBS	*J. Braz. Chem. Soc.*
JC	*J. Comput. Chem.*
JCA	*J. Chem. Soc., A*
JCB	*J. Chem. Soc., B*
JCC	*J. Chem. Soc., C*
JCD	*J. Chem. Soc., Dalton Trans.*
JCF	*J. Chem. Soc., Faraday Trans.*
JCH	*J. Chromatogr.*
JCI	*J. Chem. Inf. Comput. Sci.*
JCM	*J. Chem. Res. (S)*
JCO	*J. Comb. Chem.*
JCP	*J. Chem. Phys.*
JCS	*J. Chem. Soc.*
JCX	*J. Chem. Crystallogr.*
JFA	*J. Agric. Food Chem.*
JFC	*J. Fluorine Chem.*
JGU	*J. Gen. Chem. USSR (Engl. Transl.)*
JHC	*J. Heterocycl. Chem.*
JIC	*J. Indian Chem. Soc.*
JLC	*J. Liq. Chromatogr.*
JMC	*J. Mater. Chem.*
JME	*J. Med. Chem.*
JMM	*J. Mol. Model.*
JMOA	*J. Mol. Catal. A.*
JMOB	*J. Mol. Catal., B*
JMT	*J. Mol. Struct. Theochem*
JOC	*J. Org. Chem.*
JOM	*J. Organomet. Chem.*
JPC	*J. Phys. Chem.*
JPCA	*J. Phys. Chem. A*
JPO	*J. Phys. Org. Chem.*
JPR	*J. Prakt. Chem.*
JPS	*J. Pharm. Sci.*
JSP	*J. Mol. Spectrosc.*
JST	*J. Mol. Struct. (Theochem.)*
K	*Crystallogr. Rep.*
KFZ	*Khim. Farm. Zh.*
KGS	*Khim. Geterotsikl. Soedin.*
LA	*Leibigs Ann. Chem.*
M	*Monatsh. Chem.*
MC	*Mendeleev Commun.*
MI	*Miscellaneous references — see full reference list*
MM	*Macromolecules*
MOL	*Molecules*
MP	*Mol. Phys.*
MR	*J. Magn. Reson.*
MRC	*Magn. Reson. Chem.*
MRO	*Mini-Rev. Org. Chem.*
NAT	*Nature (London)*
NJC	*New. J. Chem.*
NN	*Nucleosides, Nucleotides Nucleic Acids*
OBC	*Org. Biomol. Chem.*
OL	*Org. Lett.*
OM	*Organometallics*
OMR	*Org. Magn. Reson.*
OMS	*Org. Mass. Spectrom.*
OPD	*Org. Process Res. Dev.*
OPP	*Org. Prep. Proced. Int.*
OR	*Org. React.*
OS	*Org. Synth.*
OSC	*Org. Synth. Coll. Vol.*
PAC	*Pure Appl. Chem.*
PC	*personal communication*
PCP	*Phys. Chem. Chem. Phys.*
PHA	*Pharmazie*
PHC	*Prog. Heterocycl. Chem.*
PJC	*Pol. J. Chem.*
PJS	*Pak. J. Sci. Ind. Res.*
PMH	*Phys. Methods Heterocycl. Chem.*
PNA	*Proc. Natl. Acad. Sci. U.S.A.*
PS	*Phosphorus, Sulfur Silicon Relat. Elem.*
PTR	*Pteridines*
RCB	*Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
RCM	*Rapid Commun. Mass Spectrom.*
RCR	*Russ. Chem. Rev. (Engl. Transl.)*
RJC	*Russ. J. Gen. Chem. (Engl. Transl.)*
RJE	*Russ. J. Electrochem.*
RJO	*Russ. J. Org. Chem. (Engl. Transl.)*
RMC	*Mini Rev. Med. Chem.*
RRC	*Rev. Roum. Chim.*
RSQM	*Rev. Soc. Quim. Mex.*
RTC	*Recl. Trav. Chim. Pays-Bas Belg.*
S	*Synthesis*
SA	*Spectrochim. Acta*
SAA	*Spectrochim. Acta, Part A*
SC	*Synth. Commun.*
SCI	*Science*
SL	*Synlett*
SM	*Synth. Met.*
SP	*Sci. Pharm.*
SPL	*Spectrosc. Lett.*
SR	*Sulfur Rep.*
SSN	*Solid State Nucl. Magn. Reson.*
STC	*Struct. Chem.*
SUL	*Sulfur Lett.*
T	*Tetrahedron*
TA	*Tetrahedron: Asymmetry*
TCA	*Theor. Chim. Acta*
TFS	*Trans. Faraday Soc.*
TL	*Tetrahedron Lett.*
ZC	*Z. Chem.*
ZFA	*Z. Anorg. Allg. Chem.*
ZFK	*Zh. Fiz. Khim.*
ZK	*Z. Kristallogr. NCS*
ZNA	*Z. Naturforsch., Teil A*
ZOB	*Zhurnal Obshchei Khimii.*
ZOR	*Zhumal Organicheskoi Khimii.*
ZPK	*Zh. Prikl. Khim.*