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MICROREVIEW

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# Synthetic Methodologies for the Preparation of β-Amino Thiols

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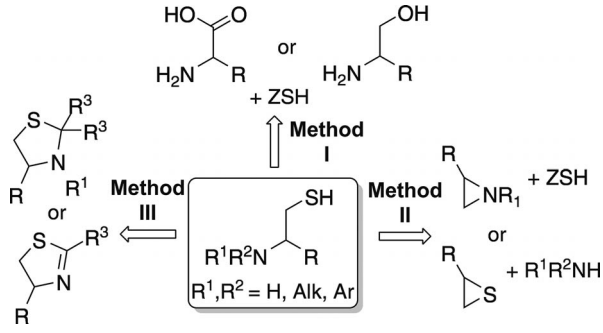
**Keywords:** Synthetic methods / Ring opening / Nitrogen heterocycles / Sulfur heterocycles / β-Amino thiols

β-Amino thiols are an important class of bifunctional compounds that have found various applications in many areas of chemistry. This microreview highlights the synthetic methods judged to be the most efficient and general for their preparation.

## Introduction

A β-amino thiol is a bifunctionalized compound containing a basic amino function and an acidic thiol function, linked by a two-carbon alkyl chain. These compounds have found various applications in many areas, including synthetic and medicinal chemistry, catalysis and materials chemistry. Their versatility is mainly due to the nucleophilicities of the two heteroatoms (potential to act as *N*- or *S*-nucleophiles or as *N,S*-binucleophiles), as well as their ability to chelate metals. Some β-amino thiols (i.e., cysteine, cysteamine, penicillamine) are naturally occurring compounds and are involved in important biological processes. They are constituents of complex molecules of biological interest, natural (e.g. glutathione, coenzyme A) or unnatural. The commonest applications of β-amino thiols include their use as enzyme inhibitors,[1] radioprotective agents,[2] intermediates for the synthesis of biologically active compounds (in particular in peptide synthesis),[3] and as convenient precursors for various *N,S*-heterocycles (e.g. thiazolines,[4] thiazolidines,[5] thiomorpholines,[6] thiazepines[7]). More recently, 2-amino thiols and their thioether derivatives have been used as ligands in organometallic catalysis.[8]

In spite of the importance of this class of compounds, their syntheses have, to the best of our knowledge, never been reviewed. In this microreview we have attempted to make a selection of synthetic methods, judged to be efficient and general, for the preparation of β-amino thiols. Syntheses starting either from α-amino acids or from β-amino alcohols through the introduction of sulfur nucleophiles, from five-membered *N,S*-heterocycles, or based on opening of an aziridine or thiirane ring with a sulfur or a nitrogen nucleophile, respectively, are described, as well as recent methodologies using new convenient sulfur reagents (Scheme 1). Only structures containing a free thiol function have been selected, whereas the amine function can be primary, secondary or tertiary. Cited references are restricted to journals, reviews, and books, and mainly cover the last two decades. With this contribution we hope to offer chemists a practical guide for the preparation of these β-amino thiols.




Scheme 1.

## Syntheses from α-Amino Acids or β-Amino Alcohols (Method I)

Some of the starting amino alcohols are commercially available, but they can also be obtained from α-amino acids, by reduction, or by other synthetic methods. In many examples, enantiopure amino thiols have been obtained from naturally occurring α-amino acids. The key step of this method is the replacement of the hydroxy group of the amino alcohol by a sulfanyl group. This can be done by transformation of the OH function into a better leaving group (e.g., tosylate,[9] mesylate,[10] halide[11]) and subsequent nucleophilic substitution ($S_N2$) with a sulfur nucleophile. This latter can be also introduced directly by a Mitsunobu reaction.[12,10b]

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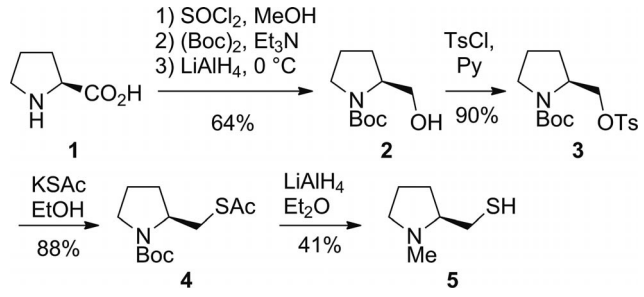
**By Nucleophilic Substitution**

Gibson et al. synthesized the *N*-methylproline thiol **5** (Scheme 2) starting from L-proline (**1**). In three steps – esterification, nitrogen protection and reduction – the α-amino acid was transformed into *N*-Boc-prolinol. Activation of the hydroxy group as a tosylate and subsequent nucleophilic substitution with potassium thioacetate afforded the *N*-Boc proline thioacetate **4**, which was reduced to the desired product with lithium aluminium hydride.[9] Some tertiary β-amino thiols were obtained from (*S*)-valine (**6**, Scheme 3). After dibenzylation, reduction and Swern oxidation to produce an *N*,*N*-dibenzylamino aldehyde, additions of aryl or alkylmagnesium bromides to the carbonyl group proceeded with high diastereoselectivities to afford various β-amino alcohols.




Scheme 2.

The dibenzylamino group was transformed into a cyclic amine by *N*-deprotection and *N*-dialkylation with a dibromoalkane. *O*-Mesylation of the amino alcohol, followed by displacement of the mesylate with thioacetate and then by reduction of the thioester, afforded the tertiary β-amino thiol **10** (Scheme 3).[10a] The OH→SH transformation takes place with retention of the configuration, because two $S_N2$ reactions are involved, via an aziridinium ion.

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*Vincent Reboul obtained his PhD (1996) under the direction of Dr. C. Thal at ICSN (CNRS/Gif-sur-Yvette), working on organoiron complexes. He spent a year and a half in a postdoctoral position in the laboratory of Professor R. Holton, at Florida State University (Tallahassee), being involved in the total synthesis of taxol. In 1998 he obtained his present position as Assistant Professor, at the University of Caen, in P. Metzner's group. He joined A.-C. Gaumont's group in 2008. His scientific interests include all aspects of asymmetric synthesis with organosulfur chemistry.*

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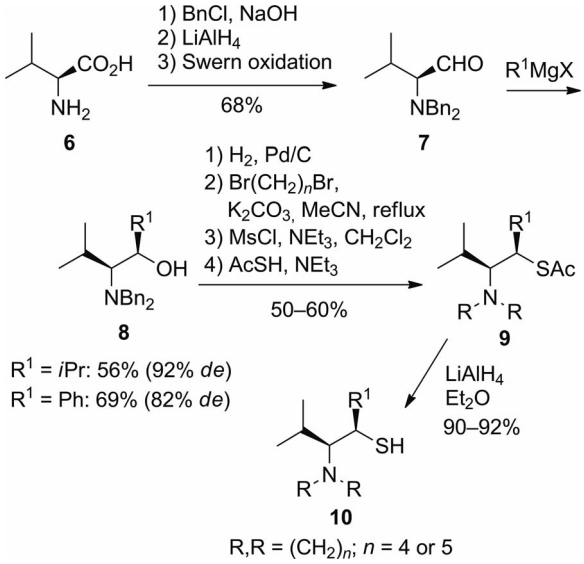
*Jocelyne Levillain was born in Saint-Lô (France) in 1963. She studied chemistry at the University of Caen and in 1994 completed her Ph.D thesis under the supervision of Dr. M. Vazeux. After postdoctoral work at the Royal College of Surgeons in Ireland with Professors K. Nolan and D. Fitzgerald, she returned to Caen at the University as "Maitre de Conférences" J. L. Ripoll's group, working on flash vacuum thermolysis. In 2001 she joined the group of Professor A.-C. Gaumont, and she is now involved in the chemistry of chiral ionic liquids.*

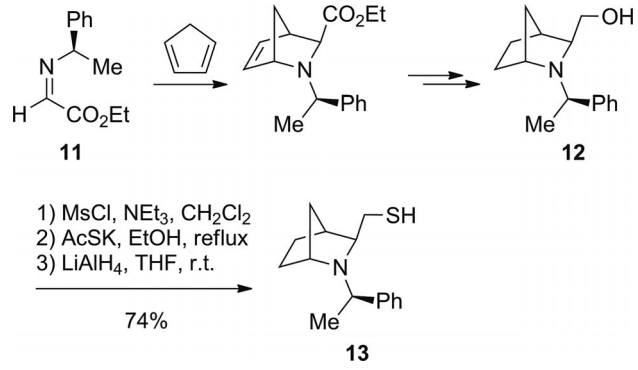
*Annie-Claude Gaumont was born in 1964 in Vannes (Morbihan, France). She studied chemistry at the University of Rennes (France). In 1991 she joined the research group of Dr. J.M. Denis, graduating with her PhD degree. She had postdoctoral experience as a research associate with Professor J. M. Brown at the University of Oxford (U.K.). She returned to the University of Rennes as a CNRS researcher and in 2001 moved to Caen (Normandy), where she was promoted Professor of Organic Chemistry. Her group research interests mainly focus on phosphorus and sulfur chemistry in catalysis (ligands) and synthesis (preparation of new building blocks) and development of new media for catalysis (ionic liquids, supported phases such as SILP).*



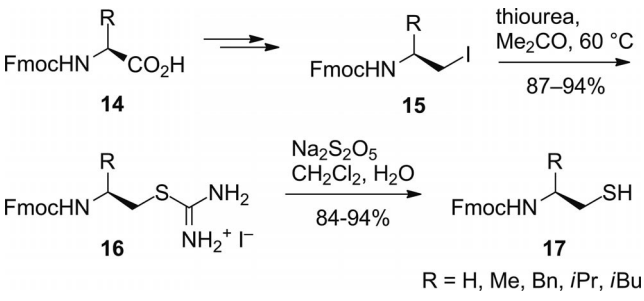

Scheme 3.

2-Azabornylmethanol **12** (Scheme 4) was prepared in three steps including an aza-Diels–Alder reaction and then transformed into its amino thiol analogue **13** by mesylation, nucleophilic substitution with potassium thioacetate and reduction of the thioester to the corresponding thiol.[10e]



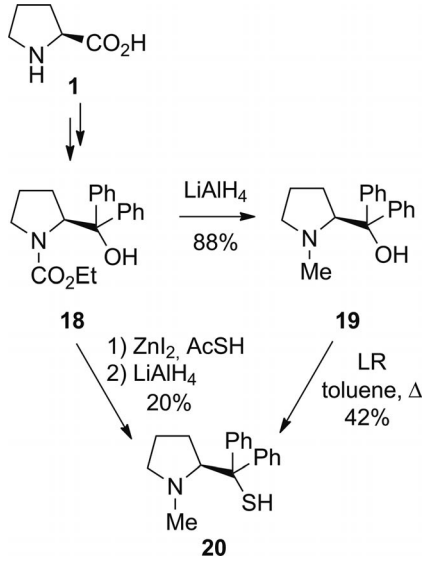

Scheme 4.

In some examples, *N*-protected amino acids have been transformed into the corresponding 2-amino-substituted alkyl bromides or iodides,[11] which have then been converted into amino thiols via isothiouronium salts. *N*-Fmoc amino acids **14** (Scheme 5) were transformed in this way by reduction into alcohols, substitution with iodide (under Mitsunobu conditions) and treatment with thiourea. The resulting isothiouronium salts **16** were then hydrolysed with aqueous sodium pyrosulfite solution, leading to the desired *N*-Fmoc 2-amino thiols **17**.[11c]




Scheme 5.

Gibson synthesized the amino thiol **20** (Scheme 6), with two phenyl substituents α to the sulfanyl group, from proline for application as a chiral catalyst in additions of diethylzinc to aldehydes.[13] The use of a tertiary thiol group, more resistant to autoxidation to disulfides, improved the enantioselectivity of the reaction relative to that achieved with primary thiol derivatives. The transformation of the tertiary alcohol into the corresponding thiol involves a nucleophilic substitution of first order ($S_N1$). This was performed by two methods: either with thioacetic acid in the presence of zinc diiodide and subsequent thioester→thiol reduction, or directly by use of the Lawesson reagent (LR, Scheme 6). In both cases, low yields were obtained.




Scheme 6.

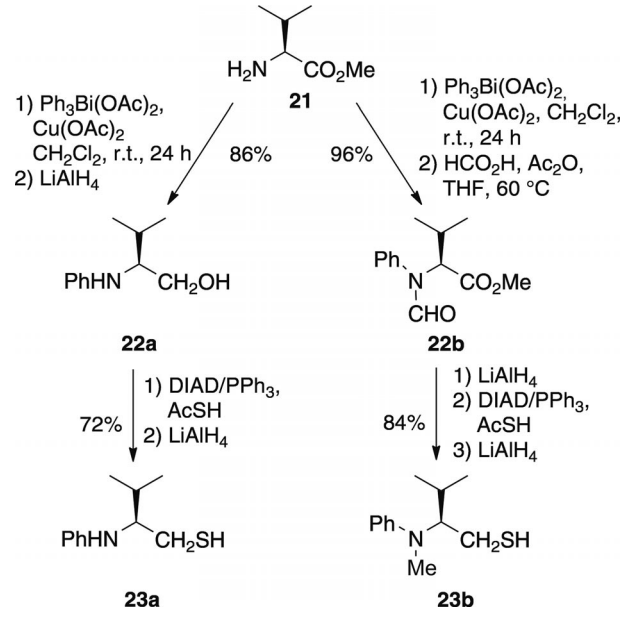
## By Mitsunobu Reaction

The sulfur nucleophile could also be introduced into a β-amino alcohol through a Mitsunobu reaction with use of thioacetic acid in the presence of the diisopropyl diazodicarboxylate/triphenylphosphane (DIAD/$Ph_3P$) system. Anderson, starting from (*S*)-valine methyl ester (**21**, Scheme 7), prepared a series of secondary and tertiary β-amino thiols **23** by this method for applications in asymmetric catalysis.[12] Various substituents were introduced on the nitrogen atom prior to the Mitsunobu reaction. Two examples of these syntheses are given in Scheme 7.[12a]

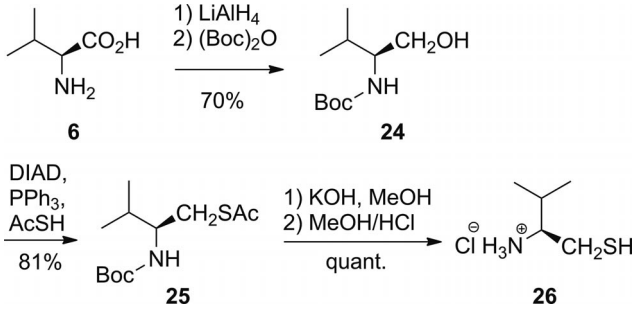
In another example, the primary amino thiol **26** (Scheme 8) was obtained from L-valine, which was transformed in three steps into the *N*-Boc β-amino thioacetate **25** and then deprotected to give the product **26** as its hydrochloride salt.[12b]

Although general, these methods all have one main drawback: their reaction sequences are too long, due to the pro-




Scheme 7.




Scheme 8.

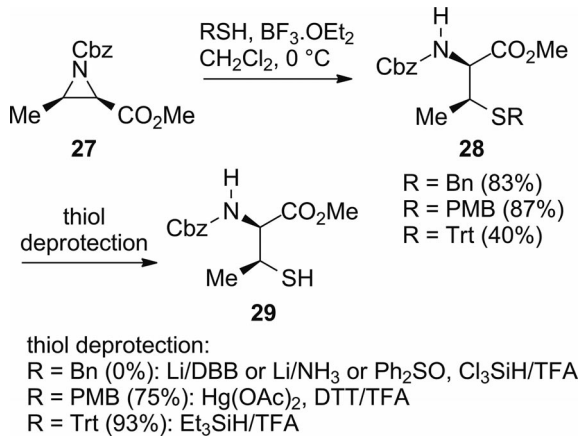
tection and deprotection steps necessary to obtain free amino and sulfanyl functions. In the case of the Mitsunobu reaction, the main problem is the difficult treatment and purification process due to the formation of triphenylphosphane oxide and hydrazine dicarboxylate from the $Ph_3P$/DIAD reagents.

## Syntheses by *N*- or *S*-Heterocycle Ring Opening (Method II)

### Ring Opening of Aziridines

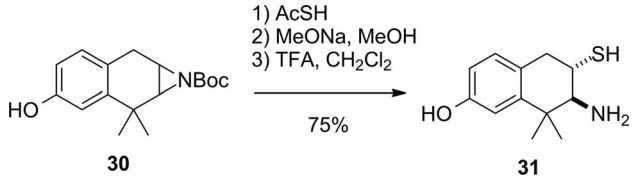
The method consists of the opening of an aziridine with an appropriate *S*-nucleophile and subsequent cleavage of both thiol and amine protecting groups to afford the 2-amino thiol. Rosenthal et al. described the first example in which an aziridine was opened with $H_2S$.[14] The choice of the *S*-nucleophile is important, because the thiol deprotection, depending on the nature of the protective group and the reaction conditions, is not trivial.

As an example, to synthesize *N*-protected β-methylcysteine **29** (Scheme 9), *N*-carboxybenzyl-protected aziridines **27** were opened with various thiol nucleophiles. Different deprotecting conditions were required in each case.[15] The best overall yield was obtained with *p*-methoxy-thiophenol (PMBSH).



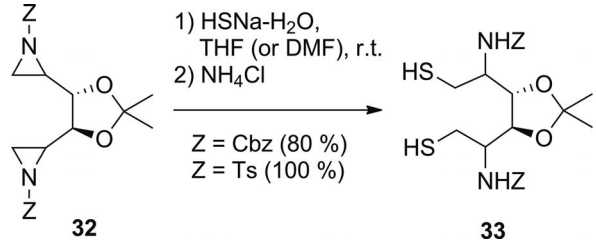

Scheme 9.

To synthesize the potent biologically active tetraline-derived amino thiol **31** (Scheme 10), the *N*-Boc-protected aziridine **30** was ring-opened with thioacetic acid. The deprotection of the thiol function was achieved with sodium methoxide. *N*-Boc was removed with trifluoroacetic acid.[16]




Scheme 10.

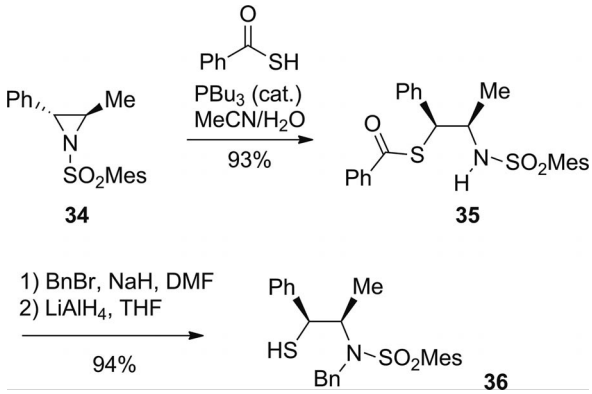
*N*-Tosyl- or *N*-carboxybenzyl-protected chiral bis-aziridines **32** (Scheme 11) prepared from D-mannitol were treated with sodium hydrosulfide to afford the corresponding *N*-protected bis(amino thiols) **33** in good yield.[17]




Scheme 11.

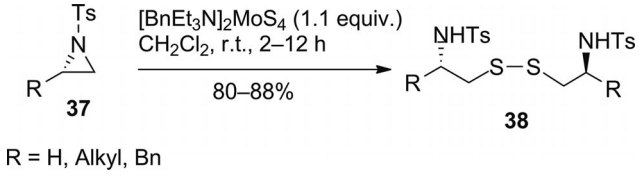
*N*-Sufonylmesityl amino thiol **36** (Scheme 12), derived from norephedrine, was also synthesized via an aziridine and used as a sulfur analogue of the Abiko–Masamune chiral auxiliary.[18] The aziridine **34** was opened with thiobenzoic acid, and the thiol deprotection was achieved by reduction of the thioester with $LiAlH_4$.



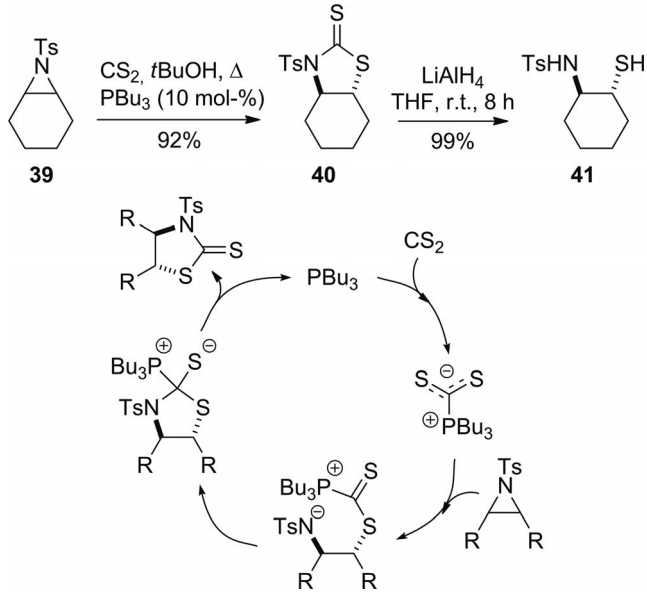

Scheme 12.

A direct route to 2-sulfonamido disulfides based on the opening of *N*-tosylaziridines **37** (Scheme 13) with benzyltriethylammonium tetrathiomolybdate was developed.[19] The method might also be useful for accessing the corresponding 2-amino thiols, because several known procedures to reduce disulfides to thiols are available in the literature.




Scheme 13.

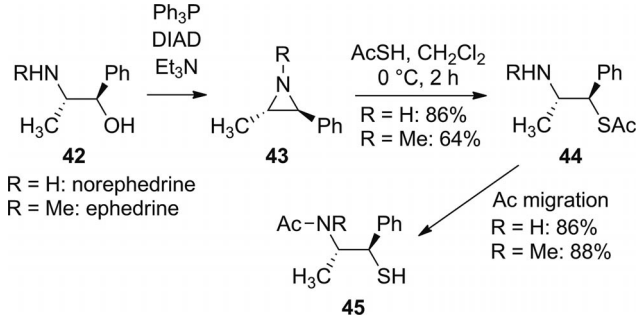
The reactions between *N*-tosyl-substituted aziridines **39** (Scheme 14) and carbon disulfide, catalysed by tributylphosphane, led to thiazolidine-2-thiones, which could be reduced to the *N*-protected amino thiols **41** by $LiAlH_4$.[20] It was proposed by the authors that the phosphane could attack $CS_2$ to form a zwitterion, which would react with the aziridine to give a ring-opened intermediate. Subsequent




Scheme 14.

cyclisation of this would give the thiazolidinethione heterocycle.

Nonactivated[21] or unprotected aziridines[22] can also be used. However, when unprotected aziridines were opened with potassium thioacetate, the extraction of the resulting amino thiols from the aqueous solutions after hydrolysis of the thioesters was difficult and poor yields were obtained. Aziridines **43** (Scheme 15), derived from (1*R*,2*S*)-(–)-norephedrine and (1*R*,2*S*)-(–)-ephedrine, were synthesized by use of the Mitsunobu reaction and were then opened with thioacetic acid. In situ migration of the acetyl group from the sulfur to the nitrogen atom occurred, leading to enantiopure *N*-acetyl amino thiols **45**. The stereochemistry at C-1 remained unchanged because the two consecutive reactions took place with inversion of configuration.[23]

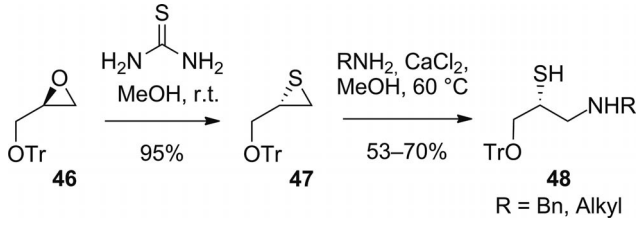



Scheme 15.

## Ring Opening of Thiiranes

Another route to aminoethanethiols is the ring opening of thiiranes (episulfides) with amines.[24] It is usually necessary to prepare the episulfide, however, because only very few are commercially available. It is worth noting is that it is difficult to obtain primary 2-amino thiols in this way, because the use of ammonia provokes undesired polymerization.

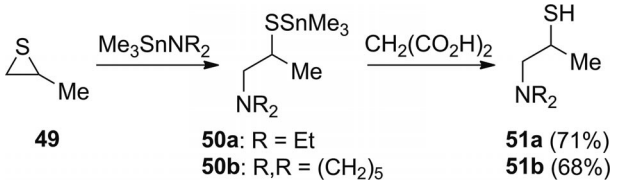
Lemaire et al. chose this method to prepare various aminoethanethiol trityl ether ligands for asymmetric catalysis.[25] Chiral enantiopure episulfide **46** (Scheme 16) was prepared from the appropriate epoxide and thiourea and then opened in a totally regioselective manner by attack of various primary amines at the less hindered carbon.




Scheme 16.

Taddei et al. described the ring opening of thiiranes with $Me_3SnNR_2$. The resulting products **50** (Scheme 17) possess trimethyltin substituents on their sulfur atoms.[26] Deprotection was achieved by treatment with malonic acid, leading to tertiary 2-amino thiols **51** in good overall yields.

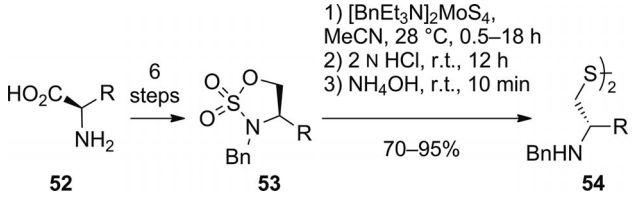
  




Scheme 17.

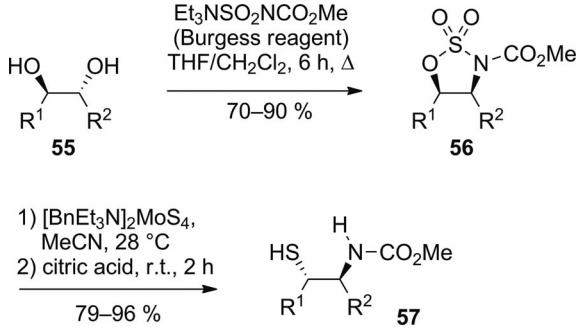
### Ring Opening of Sulfamidates

Chandrasekaran et al. used nucleophilic ring opening of sulfamidates with $[BnNEt_3]_2MoS_4$ (benzyltriethylammonium tetrathiomolybdate) to prepare β-amino thiols[27] and amino disulfides.[28] Cyclic sulfamidates were first prepared from α-amino acids in six steps (Scheme 18). After treatment with the sulfur reagent and subsequent hydrolysis, various secondary amino disulfides **54** were obtained in good yields.[28] With use of *N*-protected sulfamidates (*N*-Boc, *N*-PMB or *N*-Fmoc derivatives) the amino disulfides were directly incorporated into peptides.




Scheme 18.

Another series of sulfamidates were prepared from 1,2-diols **55** (Scheme 19) and the Burgess reagent. In these cases, treatment with $[BnNEt_3]_2MoS_4$ and hydrolysis with saturated aqueous citric acid solution led with high yields to β-amino thiols **57** (as their carbamate derivatives) with a wide variety of structures, including enantiopure amino thiols (Scheme 19, Table 1).[27]




Scheme 19.

Table 1. Synthesis of β-amino thiols **57** from sulfamidates and tetrathiomolybdate (selected examples).[27]

| Entry | Product | $R^1$ | $R^2$ | Yield [%] |
|---|---|---|---|---|
| 1[a] | **57a** | Bn | H | 88 |
| 2[a] | **57b** | *i*Pr | H | 87 |
| 3[b] | **57c** | *n*-$C_6H_{13}$ | H | 92 |
| 4[a] | **57d** | Me | Me | 79 |
| 5[b] | **57e** | Et | Et | 95 |
| 6[b] | **57f** | $CO_2Et$ | Ph | 93 |

[a] From enantiopure diols. [b] From racemic diols.

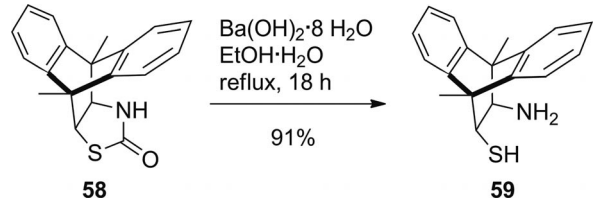
## Syntheses from Five-Membered *N,S*-Heterocycles (Method III)

Five-membered-ring *N,S*-heterocycles such as thiazolidines and thiazolines (or their derivatives) can be hydrolysed to afford 2-amino thiols.

### Thiazolidinones and Thiazolidines

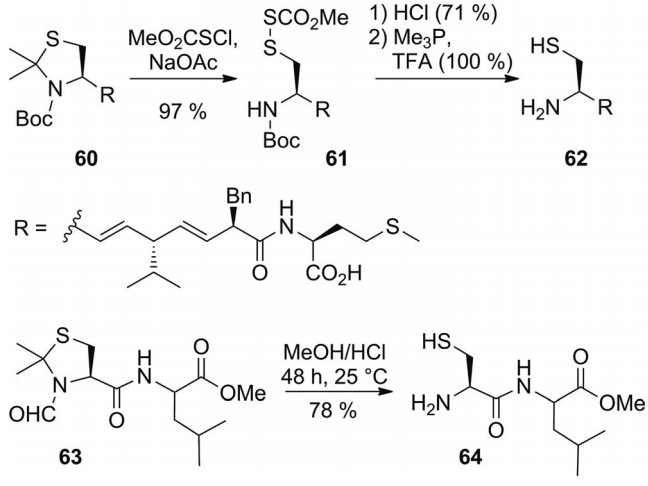
Thiazolidine and thiazolidinone heterocycles are often synthesized from 2-amino thiols as their protected forms. They can be opened and hydrolysed to regenerate the free thiol and amine functions.

As an example, 2-thiazolidinone **58** (Scheme 20) afforded the "roofed" amino thiol **59** on hydrolytic ring cleavage with barium hydroxide.[29]




Scheme 20.

*N*-Boc thiazolidine **60** (Scheme 21) was used as a protected amino thiol moiety in the synthetic transformation of cysteine into the new farnesyl transferase inhibitor **62**.[30] At the end of the synthesis, deprotection of the *N*-Boc thiazolidine **60** was achieved in three steps: ring opening by treatment with a mixture of methoxycarbonylsulfenyl chloride/sodium acetate in acetic acid, amine deprotection by acidic hydrolysis and thiol deprotection by treatment with trimethylphosphane and trifluoroacetic acid (Scheme 21). In another example, dipeptide **64** (Scheme 21), containing



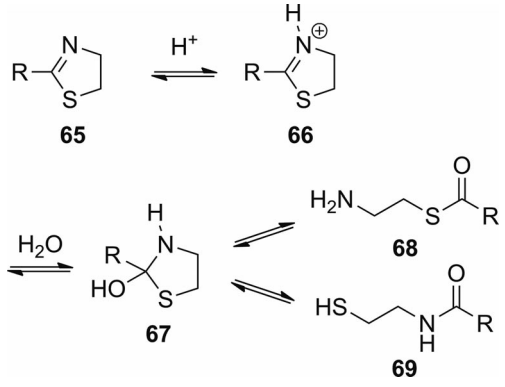

Scheme 21.

an amino thiol moiety, was obtained by starting from cysteine, via a *N*-formylthiazolidine cycle.[31] Deprotection of **63** was achieved in a methanolic HCl solution. The *N*-Boc thiazolidine protected form was also used by Nicolaou et al. in the synthesis of thiostrepton.[32]

### Thiazolines and Thiazolinium Salts

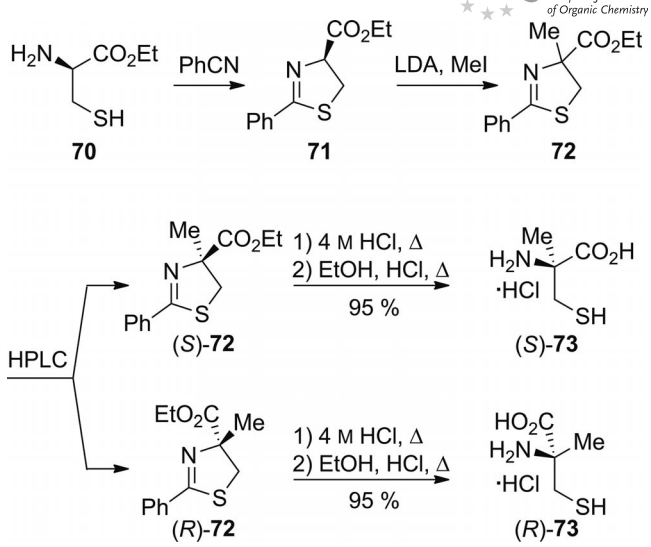
The ring opening of thiazolines by acidic hydrolysis was a subject of study as early as 1959,[33] presumably because of the presence of the thiazoline heterocycle in many biologically active natural compounds. After protonation, the mechanism involves the attack of water on the thiazolinium salt **66** (Scheme 22), leading to 2-hydroxythiazolidine intermediate **67**, which then give *S*-acyl or *N*-acyl 2-amino sulfanyl derivatives **68** or **69**, depending on the conditions used.




Scheme 22.

The hydrolysis of thiazolines has not commonly been used as a method to access amino thiols and only isolated cases have been reported in the literature. As an example, in the synthesis of 2-amino-2-deoxy-3-thio-mannose, the thiazoline ring was used as a protected form of amino and thiol groups.[34,35] The authors reported the remarkable resistance of the thiazoline ring to strong acids: with use of aqueous trifluoroacetic acid, at room temperature, the acetamido-thiol was obtained. Handrick et al. prepared 2-amino thiols for applications as antiradiation drugs by hydrolysis of 2-phenylthiazolines under acidic conditions.[36] One application of the hydrolysis of thiazolines to afford amino thiols was the modification of the structure of cysteine by introduction of a new substituent α to the carboxyl group. The conversion of L-cysteine ester **70** (Scheme 23) into 2-methylcysteine derivative **73** was achieved by the formation of thiazoline **71**, followed by its methylation at the 4-position and subsequent acidic hydrolysis. Both optically pure enantiomers of 4-methylthiazoline **72** could be obtained upon HPLC separation and led after acidic hydrolysis to the corresponding methylcysteines (*R*)-**73** and (*S*)-**73** (Scheme 23).[37]

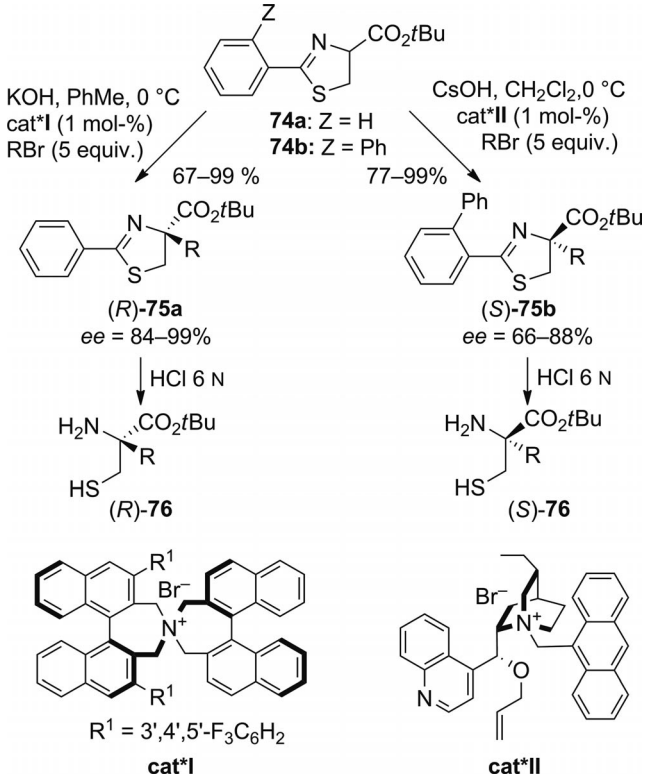
Bergeron et al. applied the same method to a thiazoline containing a 2-(3-hydroxypyridyl) system instead of a phenyl group as the substituent in the 2-position.[38] The asymmetric syntheses of (*S*)- and (*R*)-*N*-Fmoc-*S*-trityl-α-




Scheme 23.

methylcysteine were achieved by use of (1*R*)- and (1*S*)-2,10-camphorsultam, respectively, as chiral auxiliaries.[39] These in turn were introduced through amide formation with the 2-phenyl thiazoline derived from cysteine. The methylation at the α-position to the chiral amido group was highly diastereoselective.

Kim et al. reported an enantioselective version of the method to access directly optically active 4-substituted cysteine derivatives. Thiazolines **74** (Scheme 24) were prepared from cysteine and were then alkylated in their 4-positions




Scheme 24.

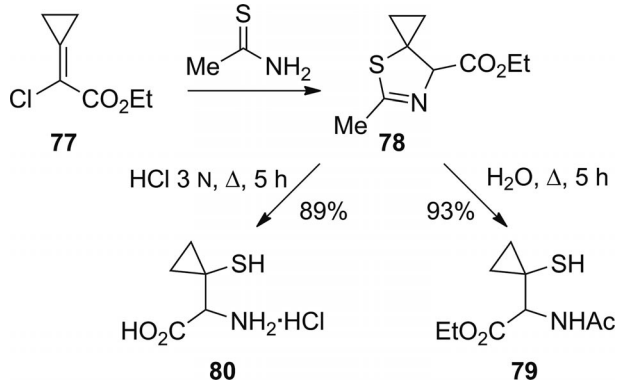
  

under asymmetric phase-transfer catalysis (PTC) conditions with alkyl, allyl, propargyl and benzyl halides. Through the use of two different chiral PTC catalysts (cat*I or cat*II) with thiazolines **74a** and **74b**, respectively, alkylcysteines (*R*)-**76** and (*S*)-**76** were both accessible (after acidic hydrolysis) with high enantioselectivities (Scheme 24, Table 2).[40]

Table 2. Catalytic enantioselective alkylation of thiazolines **74** (selected examples).[40]

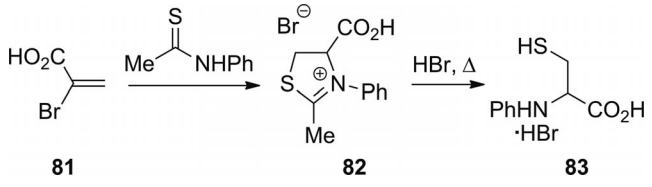
| Entry | Starting thiazoline | R | Catalyst | Yield [%] | % *ee* (config.) |
|---|---|---|---|---|---|
| 1 | **74a** | allyl | Cat*I | 68 | 96 (*R*) |
| 2 | **75a** | allyl | Cat*II | 90 | 87 (*S*) |
| 3 | **74a** | propargyl | Cat*I | 67 | 97 (*R*) |
| 4 | **75a** | propargyl | Cat*II | 92 | 68 (*S*) |
| 5 | **74a** | Bn | Cat*I | 90 | 99 (*R*) |
| 6 | **75a** | Bn | Cat*II | 99 | 84 (*S*) |

4-Cyclopropyl-substituted thiazoline **78** (Scheme 25) was prepared from α-chloro α,β-unsaturated carboxylic ester **77** and thioacetamide. Aqueous hydrolysis of **78** afforded the corresponding *N*-acyl-2-amino thiol **79**, whereas acidic hydrolysis afforded the desired amino thiol **80** (Scheme 25), a restrained analogue of penicillamine with a cyclopropyl substituent instead of the *gem*-dimethyl system α to the thiol function.[41]




Scheme 25.

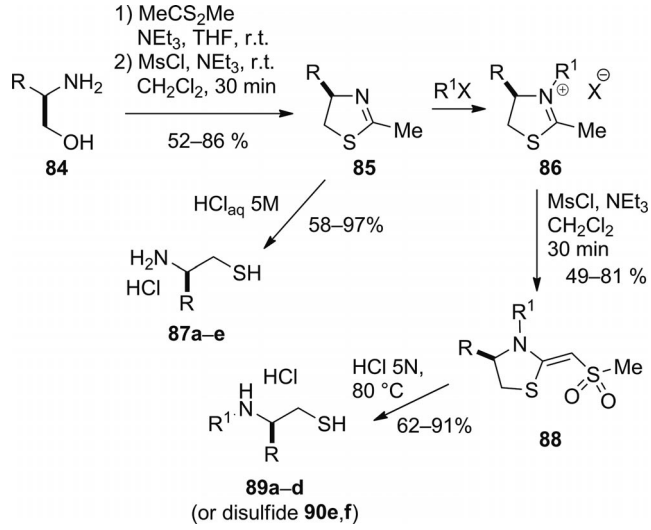
In a similar manner the thiazolinium salt **82** (Scheme 26) was prepared from α-bromoacrylic acid (**81**) and *N*-phenylthioacetamide and hydrolysed under acidic conditions to afford the secondary amino thiol **83**.[42]




Scheme 26.

One paper described the basic hydrolysis of 2-mercaptothiazoline to afford cysteamine hydrochloride.[43]

Some of us have recently developed an efficient method to prepare both primary and secondary 2-amino thiols with a wide range of structures, via thiazoline[44] or thiazolinium salts,[45] respectively (Scheme 27, Table 3). The starting materials are β-amino alcohols (most of them enantiopure) and methyl dithioacetate, which is a convenient and easy accessible source of sulfur. The numbers of steps to transform amino alcohols **84** into amino thiols were smaller than with other methods: three steps for the primary 2-amino thiols **87**[44] (Table 3, Entries 1–5) and five steps for the secondary 2-amino thiols **89**[45a] (Table 3, Entries 6–9). This was possible through the combination of sulfur introduction and amino group protection in one thioacylation step and through the deprotection of both amino and thiol functions by acidic hydrolysis of the *N*,*S*-heterocycle. It was shown for one example (with R = H, $R^1$ = Me) that the acidic hydrolysis of thiazolinium salt **86a** proceeded very slowly (3 days) and led mainly to the disulfide, whereas the corresponding thiazolidine **88a** hydrolysed more rapidly (2 h), leading cleanly to amino thiol **89a**. Thus, to prepare secondary amino thiols, thiazolidines were used as the hydrolysis substrates instead of thiazolinium salts. Although the atom economy in this methodology is rather low, it enables access to various amino thiols through easy variation of the substituents on the heterocycle and the *N*-alkylating agent. In the case of prolinol, which is a secondary amino




Scheme 27.

Table 3. Synthesis of primary β-amino thiols **87** from thiazolines **85** and of secondary β-amino thiols **89** from thiazolidines **88** (selected examples).

| Entry | Product | R | $R^1$ | Yield [%] | Ref. |
|---|---|---|---|---|---|
| 1 | **87a** | *i*Pr | H | 58 | [44] |
| 2 | **87b** | Bn | H | 81 | [44] |
| 3 | **87c** | Ph | H | 94 | [44] |
| 4 | **87d** | $CH_2OH$ | H | 81 | [44] |
| 5 | **87e** | $CO_2H$ | H | 94 | [44] |
| 6 | **89a** | H | Me | 98 | [45a] |
| 7 | **89b** | H | Bu | 91 | [45a] |
| 8 | **89c** | H | allyl | 60 | [45a] |
| 9 | **89d** | H | $CH_2CO_2H$ | 71 | [45a] |
| 10 | **90e** | *i*Pr | Me | 83 | [45a] |
| 11 | **90f** | $CO_2H$ | Me | 62 | [45a] |

Table 4. Syntheses of β-amino thiols (selected examples).

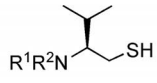
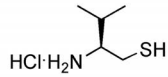
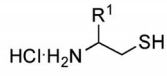
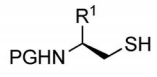
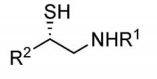
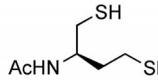
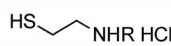
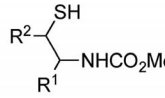
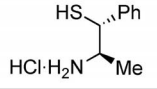
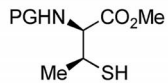
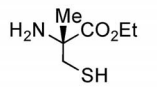
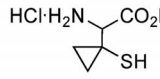
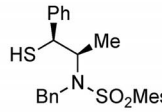
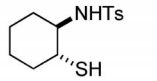
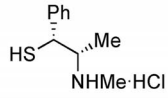
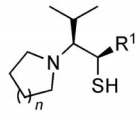
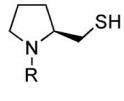
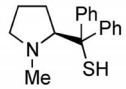
| Product | Structure variation | Method | Starting material [a] or [b] | Sulfur source [a] or [b] | Steps | Overall yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
|  | $R^1 = H$, $R^2 = Ph$ | **I**, Mitsunobu-type react. | (*S*)-valine[a] | AcSH[a] | 4 | 62 | [12a] |
| | $R^1 = R^2 = Ph$ | | | | 5 | 44 | |
| | $R^1 = Me$, $R^2 = Ph$ | | | | 5 | 68 | |
| | $R^1 = R^2 = Bn$ | **I**, Mitsunobu-type react. | (*S*)-valinol[a] | AcSH[a] | 3 | 74 | [12a], [10b] |
|  | – | **I**, Mitsunobu-type react. | (*S*)-valine[a] | AcSH[a] | 5 | 57 | [12b] |
| | – | **III** | (*S*)-valinol[a] | $MeCS_2Me$[b] | 3 | 29 | [44] |
|  | $R^1$ = Et, *i*Pr, *i*Bu, *t*Bu, Bn, Ph, $CO_2H$, $CH_2OH$ | **III** | β-amino alcohol[a] | $MeCS_2Me$[b] | 3 | 25–78 | [44] |
|  | $R^1$ = H, Me, *i*Pr, *i*Bu, Bn, Ph, $(CH_2)_4NHZ$, $(CH_2)_2CO_2Bn$ PG = Fmoc, $CO_2Bn$ | **I**, $S_N2$ via iodide | β-amino iodide[b] | thiourea[a] | 2 | 60–75 | [11c] |
|  | $R^1$ = Bu, Bn, $(CH_2)_2Ph$, CH(Me)Ph $R^2 = CH_2OTrt$ | **II** | amine ($R^1NH_2$)[a] | thiirane[b] | 1 | 50–70 | [25] |
|  | – | **III** | L-methioninol[a] | $MeCS_2Me$[b] | 3 | 62 | [44] |
|  | R = Me, Bu, Bn, Allyl, $CH_2CO_2H$ | **III** | 2-methylthiazoline[a] | | 3 | 26–51 | [45a] |
|  | $R^1$ = H, Me, Et, Pr $R^2$ = Me, Et, Pr, *i*Pr, *n*-$C_6H_{11}$, *sec*-Bu, *i*Bu, Bn, $(CH_2)_2Ph$ | **III** | sulfamidate[b] | $(BnNEt_3)_2MoS_4$[b] | 1 | 78–96 | [27] |
|  | – | **III** | *D*-Norephedrine [a] | $MeCS_2Me$[c] | 3 | 20 | [44] |
|  | PG = PMB | **II** | aziridine[b] | PMBSH[b] | 2 | 65 | [15] |
| | PG = Trt | **II** | aziridine[b] | TrtSH[a] | 2 | 37 | [15] |
|  | – | **III** | Ethyl cysteine·HCl[a] | | 7 | 49 | [37] |
|  | – | **III** | 2-chloro-2-cyclopropyl[b] | $MeC(S)NH_2$[a] | | 65 | [41] |
|  | – | **II** | aziridine[b] | PhC(O)SH[a] | 3 | 87 | [18] |
|  | – | **II** | aziridine[b] | $CS_2$[a] | 2 | 91 | [20] |

Table 4. *(Continued)*.

| Product | Structure variation | Method | Starting material [a] or [b] | Sulfur source [a] or [b] | Steps | Overall yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
|  | – | **II** | aziridine[b] | $H_2S$[a] | 2 | 61 | [21b] |
|  | $R^1$ = Ph, *i*Pr<br>*n* = 1, 2 | **I,** $S_N2$ via a mesylate | (*S*)-valine[a] | AcSH[a] | 8 | 17–26 | [10a] |
| | $R^1$ = H<br>*n* = 2 | **I,** Mitsunobu-type react. | (*S*)-valinol[a] | AcSH[a] | 3 | 56 | [12a] |
|  | R = H (as hydrochloride) | **III** | L-proline[a] | $MeCS_2Me$[b] | 3 | 54 | [45a] |
| | R = Me | **I,** $S_N2$ via a tosylate | L-proline[a] | AcSK[a] | 6 | 21 | [9] |
| | R = Fmoc | **I,** $S_N2$ via a iodide | β-amino iodide[b] | thiourea[a] | 2 | 72 | [11c] |
|  | – | **I,** $S_N1$ | L-proline[a] | Lawesson reagent[a] | 4 | 25 | [13] |

[a] Commercially available. [b] Not commercially available.

alcohol, this methodology enables the formation of prolinethiol in only three steps.[45a] In cases in which amino disulfides **90** are obtained (Table 3, Entries 10–11), reduction should offer access to the corresponding 2-amino thiols, as in cases described above, through ring opening by $[BnNEt_3]_2MoS_4$ (see Schemes 13 and 18).

## Conclusion

This contribution constitutes the first review on available synthetic methods for the preparation of β-amino thiols. Syntheses starting from α-amino acids or β-amino alcohols through the introduction of sulfur nucleophiles or from five-membered-ring *N,S*-heterocycles have been described, as well as others based on ring-opening reactions. The first methodology, although general, tends to require many protection and deprotection steps (of the hydroxy, amino and sulfanyl groups), making the reaction sequences rather long. The second methodology mainly involves aziridines or episulfides as substrates for ring opening with sulfur or nitrogen nucleophiles, respectively. Very few of these substrates are commercially available, and their synthesis in various structures represents a drawback to the use of this method as a general one for the preparation of β-amino thiols. On the other hand, the ring opening of sulfamidates with benzyltriethylammonium tetrathiomolybdate appears to be a general and efficient method, thanks to the easy access to a large variety of cyclic substrates (from amino acids or from 1,2-diols) and to the sulfur reagent, which does not requires *S*-deprotection at the end of the sequence. The methodology via thiazoline intermediates, which uses β-amino alcohols and methyl dithioacetate, as a convenient source of sulfur, as the starting materials is also general. It enables both primary and secondary β-amino thiols to be obtained by step-economic reaction sequences.

Until now, cysteine and cysteamine (widely commercially available) were the amino thiols mainly used in most of the synthetic applications. We hope that this review, which reveals the various synthetic methods existing in the literature for the preparation of β-amino thiols and the variety of accessible structures, will contribute to spread the applications of these compounds through greater molecular diversity.

Table 4 compiles a list of the most widely encountered β-amino thiols and the methods so far reported for their preparation.

## Acknowledgments

Much of this work has been performed at the Institute of Chemistry (INC3M FR 3038) and was financially supported by the Ministère de la Recherche et des Nouvelles Technologies (grant to G. M.), the Centre National de la Recherche Scientifique (CNRS), the Région Basse-Normandie and the European Union (FEDER funding).

[1] See, for examples: a) T. D. Ocain, D. H. Rich, *Biochem. Biophys. Res. Commun. Biochem. Biophys.* **1987**, *145*, 1038–1042; b) T. D. Ocain, D. H. Rich, *J. Med. Chem.* **1988**, *31*, 2193–2199; c) W. W.-C. Chan, *Biochem. Biophys. Res. Commun. Biochem. Biophys.* **1983**, *116*, 297–302; d) D. L. Bienvenue, B. Bennett, R. C. Holz, *J. Inorg. Biochem.* **2000**, *78*, 43–54; e) L. Martin, F. Cornille, P. Coric, B. P. Roques, M. C. Fournié-Zaluski, *J. Med. Chem.* **1998**, *41*, 3450–3460; f) J. D. Park, D. H. Kim, *J. Med. Chem.* **2002**, *45*, 911–918; g) H. Chen, B. P. Roques, M.-C. Fournié-Zaluski, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1511–1516.

[2] See, for examples: a) C. P. K. Schumacher, Y. Robbe, M.-T. Sicart, G. Subra, R. Delard, J.-B. Dubois, *Il Farmaco* **1998**, *53*, 118–124; b) G. R. Handrick, E. R. Atkinson, F. E. Granchelli, R. J. Bruni, *J. Med. Chem.* **1965**, *8*, 7632–766; c) G. R. Handrick, E. R. Atkinson, *J. Med. Chem.* **1966**, *9*, 558–562; d) E. Chiotellis, C. I. Stassinopoulou, A. Varvarigou, H. Vavouraki, *J. Med. Chem.* **1982**, *25*, 1370–1374; e) P. Auzeloux, J. Papon, R. Pasqualini, J.-C. Madelmont, *J. Med. Chem.* **2001**, *44*, 1116–1121.

[3] a) D. Hesek, M. Toth, V. Krchnak, R. Fridman, S. Mobashery, *J. Org. Chem.* **2006**, *71*, 5848–5854; b) A. F. Spatola, A. L. Bettag, *J. Org. Chem.* **1981**, *46*, 2393–2394; c) L. Hu, H. Zhu, D. Du-Ming, J. Xu, *J. Org. Chem.* **2007**, *72*, 4543–4546; d) S. J. deSolms, E. A. Guliani, S. L. Graham, K. S. Koblan, N. E. Mosser, S. D. Kohl, A. I. Oliff, D. L. Pompliano, E. Rands, T. H. Scholz, C. M. Wiscount, J. B. Gibbs, R. L. Smith, *J. Med. Chem.* **1998**, *41*, 2651–2656; e) D. Ramos, P. Rollin, W. Klaffke, *J. Org. Chem.* **2001**, *66*, 2948–2956; f) S. Mourtas, C. Katakalou, A. Nicolettou, C. Tzavara, D. Gatos, K. Barlos, *Tetrahedron Lett.* **2003**, *44*, 179–182; g) E. M. Gordon, J. D. Godfrey, N. G. Delaney, M. M. Asaad, D. Von Langen, D. W. Cushman, *J. Med. Chem.* **1988**, *31*, 2199–2211; h) L. Badolo, M. Gelbcke, J. Dubois, M. Hanocq, *Pharmazie* **1998**, *53*, 15–19.

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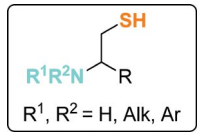
A practical method for the preparation of β-amino thiols is presented. This important class of compounds has various applications in many areas of chemistry. The present review reveals efficient and general methods for their synthesis reported in the literature, as well as the variety of accessible structures.






**Keywords:** Synthetic methods / Ring opening / Nitrogen heterocycles / Sulfur heterocycles / β-Amino thiols