

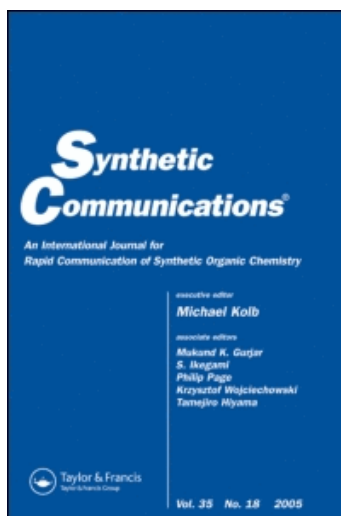
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Synthetic Communications

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Mohammed Boutayeb^a; Soufiane El Imadi^a; Mohammed Benchidmi^a; El Mokhtar Essassi^a; Nour-Eddine Es-Safi^a; Lahcen El Ammari^b

^a Laboratoire de Chimie Organique Hétérocyclique, Faculté des Sciences, Université Mohammed V, Rabat, Morocco ^b Laboratoire de Chimie du Solide Appliquée, Faculté des Sciences, Université Mohammed V, Rabat, Morocco

Online publication date: 17 June 2010

To cite this Article Boutayeb, Mohammed , Imadi, Soufiane El , Benchidmi, Mohammed , Essassi, El Mokhtar , Es-Safi, Nour-Eddine and Ammari, Lahcen El(2010) 'Synthesis of New Pyrazolo[1.5.4-*de*]quinoxalines', Synthetic Communications, 40: 14, 2130 — 2137

To link to this Article: DOI: 10.1080/00397910903219526

URL: <http://dx.doi.org/10.1080/00397910903219526>

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SYNTHESIS OF NEW PYRAZOLO[1.5.4-*de*]QUINOXALINES

Mohammed Boutayeb,¹ Soufiane El Imadi,¹
Mohammed Benchidmi,¹ El Mokhtar Essassi,¹
Nour-Eddine Es-Safi,¹ and Lahcen El Ammari²

¹Laboratoire de Chimie Organique Hétérocyclique, Faculté des Sciences,
Université Mohammed V, Rabat, Morocco

²Laboratoire de Chimie du Solide Appliquée, Faculté des Sciences, Université
Mohammed V, Rabat, Morocco

*New pyrazolo[1.5.4-*de*]quinoxaline derivatives were prepared by the action of 7-aminoindazole 1 on diethyl and dimethyl acetylene dicarboxylates. The structures of the obtained compounds and the direction of cyclization were investigated through a crystallographic study of compound 2. Further alkylation, hydrogenation, and bromination were also explored. The action of potassium thiocyanate on the obtained halo product led to a tetracyclic compound of 1.3-thiazolo[3.4-*a*]pyrazolo[1.5.4-*de*]quinoxaline series.*

Keywords: 7-Amino indazole; diethyl acetylene dicarboxylate; heterocyclization; hydrogenation; pyrazolo[1.5.4-*de*]quinoxaline

INTRODUCTION

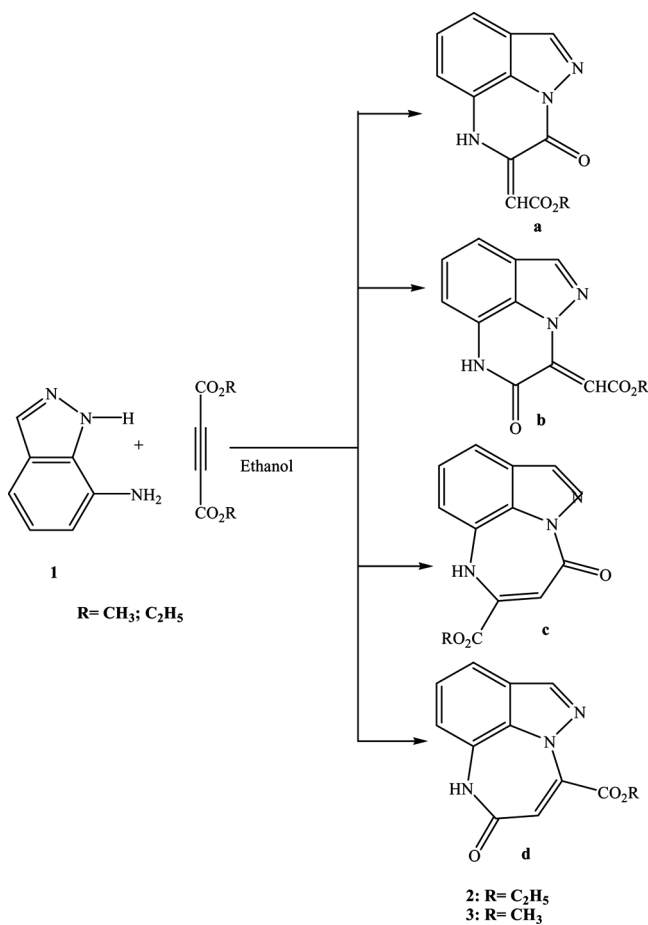
In previous works, we studied the condensation of 7-amino indazole **1** with 1,3-difunctional reagents and synthesized various heterocycles.^[1–7] Some of the obtained compounds were shown to possess psychotropic^[8] and anticancer properties.^[9] The interesting results prompted us to prepare new polycondensed systems by action of **1** with diethyl and dimethyl acetylene dicarboxylate.

RESULTS AND DISCUSSION

The action of 7-aminoindazole **1** on diethyl or dimethyl acetylene dicarboxylate in ethanol leads in each case to only one product, **2** and **3** respectively. Each of the obtained compounds could have one of the four expected structures, **a–d**. The quinoxalinic **a**, **b** or the benzodiazepinic **c**, **d** structures resulted respectively from a 1,2- or 1,3-condensation respectively (Scheme 1). The ¹H NMR spectra of the both synthesized compounds showed a signal located at 5.89–6.24 ppm corresponding to

Received May 5, 2009.

Address correspondence to Mohammed Benchidmi, Laboratoire de Chimie Organique Hétérocyclique, Faculté des Sciences, Université Mohammed V, Agdal. av. Ibn-Battouta, BP 1014, Rabat, Morocco. E-mail: b_chidmi@yahoo.fr



Scheme 1.

the vinylic proton. The more deshielded position of this proton signal compared to that of the benzodiazepinic structure^[1-6] allowed us to retain the quinoxalinic hypothesis. However, the obtained NMR results did not allow us to differentiate between the **a** and **b** propositions. This was achieved through a crystallographic study carried out on compound **2**, which showed us that the obtained compound was of **a** type with *Z* as stereochemistry of the double bond (Fig. 1).

The obtained structure could exist in two tautomeric **A** and **B** forms with the predominance of the form **A** because of the existence of an intramolecular hydrogen bond (Scheme 2).

As previously reported,^[10,11] this type of endo/exo cyclic tautomerism in the quinoxaline series engenders the enamine–methylene–imine equilibrium (Scheme 2). This prompted us to explore the reactivity of the synthesized compounds. Thus, reactions of alkylation, reduction, and bromination in addition to heterocyclization in the presence of potassium thiocyanate were investigated (Scheme 3).

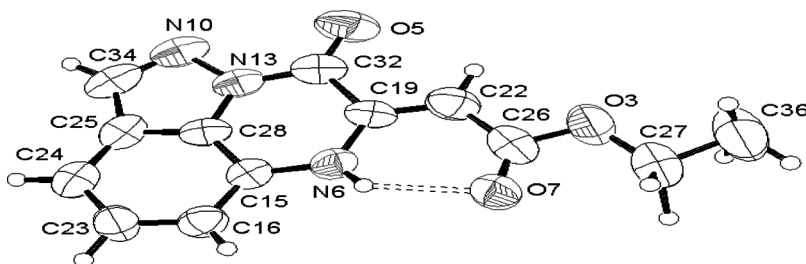
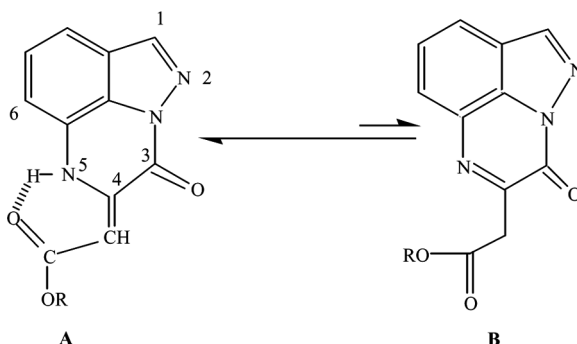


Figure 1.

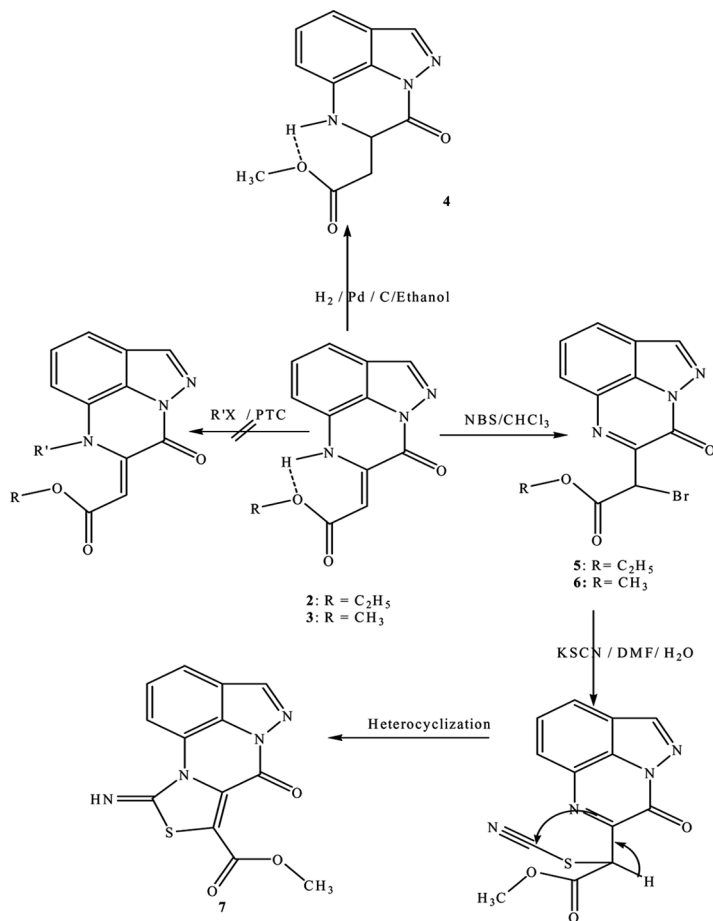
The alkylations of compounds **2** and **3** were investigated in the usual phase-transfer catalysis (PTC) conditions. However, the expected alkylated derivatives were not obtained, either in liquid–liquid or in solid–liquid conditions, and the parent compounds was unaltered. On the other hand, the catalytic hydrogenation of **3** under atmospheric pressure, in the presence of palladium on coal at 10% as catalyst, enabled us to isolate compound **4**, formed through the saturation of the double exo cyclic bond. This result was confirmed through ^1H NMR analysis by appearance of an ABX system corresponding to the protons in the α position of the carbonyl ester group and to the proton in position 4.

The halogenation of compounds **2** and **3** by N-bromosuccinimide led in each case to the formation of only one product, **5** and **6**, respectively (Scheme 3). The obtained compounds were identified through NMR and mass spectral (MS) analysis. The ^1H NMR of spectra of both compounds showed, in particular, the presence of a signal located at 5.97–6.06 ppm corresponding to the proton in the α position of the carbonyl ester group. The presence of the CHBr group in the molecule was confirmed through the observation of a signal around 44.41–44.33 ppm in the ^{13}C NMR spectra. Furthermore, the presence of the bromine atom was suggested by the characteristic isotopic cluster observed in their corresponding MS spectra at $m/z = 335, 337$ for compound **5** and $m/z = 321, 323$ for compound **6**.

The final reaction of compound **6** with thiocyanate in a water/dimethylformamide (DMF) (50/50) mixture and at room temperature allowed us to prepare a new tetracyclic compound **7**. Its structure was elucidated by comparison of its ^1H and



Scheme 2.



Scheme 3.

^{13}C NMR spectra with those of compound **6**. Thus, in the ^1H NMR spectrum, the presence of signals located at 3.87, 8.71, and 9.73 ppm—corresponding respectively to the methoxyl group, the indazolic proton, and the iminic proton^[12]—were observed. In the ^{13}C NMR spectrum, the signal corresponding to the aliphatic carbon in the α position of the carbonyl group was not observed in agreement with the proposed structure. This was finally corroborated through MS analysis, where a signal was observed at m/z 300, corresponding to the molecular ion of the formed compound.

From a mechanistic point of view, the formation of this new compound could be explained by the first nucleophilic substitution of the bromine atom by the thiocyanate ion, followed by a heterocyclization reaction, as shown in Scheme 3.

CONCLUSION

In this work, the condensation of 7-aminoindazole with diethyl and dimethyl acetylenedicarboxylate was used to prepare a new class of pyrazolo[1.5.4-*de*]quinoxalines.

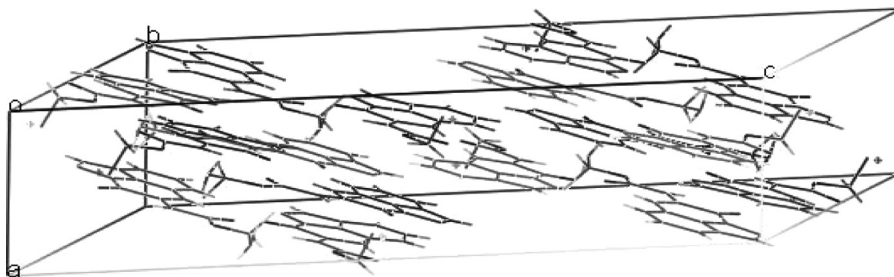


Figure 2. Molecules in the crystal parallel to the plane $(-4\ 0\ 6)$.

The obtained compounds were further submitted to bromination followed by nucleophilic substitution, leading to a new tetracyclic system of the thiazolo[3,4-*a*]pyrazolo[1,5,4-*de*]quinoxaline family. The crystallographic study of the obtained compounds showed that these molecules were planar (Fig. 2), suggesting their possible use as intercalating agents.

EXPERIMENTAL

Melting points were determined with a Büchi SMP-20 melting-point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX250 spectrometer (250.19 MHz ^1H ; 62.89 MHz ^{13}C) using tetramethylsilane (TMS) as internal standard. Multiplicities were determined by DEPT 135 sequence, chemical shifts are reported in parts per million (ppm), and coupling constants are reported in hertz (Hz). Splitting patterns were designated as s, singlet; d, doublet; and t, triplet. MS analyses were achieved on a Nermag R10-10C spectrometer using the electrospray ionization (EI) mode.

Synthesis of Ethyl and Methyl 2Z-(3-Oxo-1*H*-pyrazolo[1.5,4-*de*]quinoxalin-2(3*H*)-ylidene)ethanoate (2, 3)

Methyl or ethyl acetylene decarboxylate (7.5 mmol) was added to a solution consisting of 7.5 mmol of 7-aminoindazole **1** in 30 ml of ethanol. The mixture was refluxed for half an hour and then cooled down. The precipitated product was filtered and then recrystallized in ethanol.

Compound 2. Yield 65%, mp 154 °C (ethanol). ^1H NMR (CDCl_3), δ (ppm): 1.35 (t, $J = 7.2$ Hz, 3H), 4.27 (q, $J = 7.2$ Hz, 2H), 6.24 (s, 1H), 7.02–7.42 (m, 3H), 8.42 (s, 1H), 11.21 (broad s, 1H). ^{13}C NMR (CDCl_3), δ (ppm): 13.25 (CH_3), 59.47 (CH_2), 91.99 (CH), 109.75 (CH), 113.70 (CH), 122.68 (Cq), 123.21 (Cq), 125.55 (CH), 127.42 (Cq), 143.29 (CH), 150.73 (Cq), 168.83 (Cq), 176.43 (Cq). MS (IE): $m/z = 257$. CHN analysis (%): calculated: C: 60.70, H: 4.31, N: 16.33; found: C: 61.30, H: 4.33, N: 16.63.

Compound 3. Yield 65%, mp 124 °C (ethanol). ^1H NMR ($\text{DMSO}-d_6$), δ (ppm): 3.73 (s, 3H), 5.89 (s, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.46–7.54 (m, 2H), 8.70 (s, 1H), 11.17 (broad s, 1H). ^{13}C NMR ($\text{DMSO}-d_6$), δ (ppm): 51.58 (s, 3H), 90.56

(CH), 112.77 (CH), 115.41 (CH), 124.28 (Cq), 124.38 (Cq), 126.74 (CH), 128.81 (Cq), 145.31 (Cq), 145.35 (CH), 152.09 (Cq), 168.91 (Cq). MS (IE): m/z = 243. CHN analysis (%): calculated: C: 59.26, H: 3.73, N: 17.28; found: C: 60.21, H: 3.62, N: 18.00.

Synthesis of Methyl(3-oxo-2,3-dihydro-1*H*-pyrazolo[1.5.4-*de*]quinoxalin-2-yl)acetate (4)

Pyrazoloquinoxaline **3** (0.025 mol), palladium on coal at 10% (0.5 g), and ethanol (100 ml) were introduced into a hydrogenation reactor. The mixture was initially degassed and then put under atmosphere of hydrogen at normal pressure. When the reaction was finished (no more hydrogen consumption), the mixture was filtered and concentrated under vacuum. The obtained residue was recrystallized in xylol.

Yield 70%, mp 126–127 °C (xylol). ¹H NMR (CDCl₃), δ (ppm): 2.93–3.44 (m, 1H), 3.33–3.41 (m, 1H), 3.70 (s, 3H), 4.90 (m, 1H), 5.19 (broad s, 1H), 6.67 (dd, J = 6.7 and 1.3 Hz, 1H), 7.00–7.17 (m, 2H), 8.39 (s, 1H). ¹³C NMR (CDCl₃), δ (ppm): 37.92 (CH₂), 52.72 (CH), 56.63 (CH₃), 108.90 (CH), 110.00 (CH), 124.51 (CH), 126.34 (CH), 130.14 (Cq), 130.10 (Cq), 143.26 (Cq), 161.12 (Cq), 172.37 (Cq). MS (IE): m/z = 245.

Synthesis of Ethyl and Methyl Bromo(3-oxo-3*H*-pyrazolo[1.5.4-*de*]quinoxalin-2-yl)acetate (5, 6)

A mixture containing 4.1 mmol of pyrazoloquinoxaline **2** or **3** and 4.2 mmol of N-bromosuccinimide was refluxed in 30 ml of chloroform for an hour and then cooled down. The organic layer was washed two times with 20 ml of water and dried over calcium chloride. Chloroform was removed under vacuum, and the residue was recrystallized in ethanol.

Compound 5. Yield 65%, mp 211 °C (ethanol). ¹H NMR (CDCl₃), δ (ppm): 1.3 (t, J = 7.2 Hz, CH₃), 4.33 (q, J = 7.2 Hz, CH₂), 6.06 (s, CHBr), 7.60–8.12 (m, 3H), 8.61 (s, H). ¹³C NMR (CDCl₃), δ (ppm): 14.00 (CH₃), 44.33 (CHBr), 63.39 (CH₂), 126.98 (CH), 127.40 (CH), 129.84 (CH), 123.83 (Cq), 127.21 (Cq), 131.66 (Cq), 144.48 (CH), 148.63 (Cq), 158.95 (Cq), 169.94 (Cq). MS (IE): m/z = 335, 337.

Compound 6. Yield 70%, mp 196 °C (ethanol). ¹H NMR (CDCl₃), δ(ppm): 3.88 (s, CH₃), 5.97 (s, CHBr), 7.64–8.14 (m, 3H), 8.61 (s, H). ¹³C NMR (CDCl₃), δ(ppm): 44.41 (CHBr), 54.46 (CH₃), 127.00 (CH), 127.64 (CH), 130.32 (CH), 124.72 (Cq), 129.48 (Cq), 131.45 (Cq), 145.44 (CH), 148.76 (Cq), 159.29 (Cq), 170.92 (Cq). MS (IE): m/z = 321, 323.

Synthesis of 6-Imino-4-methoxycarbonyl-3-oxo[1.3]thiazolo[3.4-*a*]pyrazolo[1.5.4-*de*]quinoxalin (7)

Compound **6** (0.34 mmol) in 20 ml of DMF was added dropwise to 3.5 mmol of potassium thiocyanate in a 20 ml mixture of water/DMF (50/50) under magnetic agitation during 1.5 h at room temperature. After addition, agitation was maintained more than half an hour. The formed precipitate was dried and recrystallized in ethanol.

Yield 50%, mp 242 °C (ethanol). ^1H NMR (DMSO- d_6), δ (ppm): 3.87 (s, CH_3), 7.42–7.65 (m, 2H), 8.71 (s, 1H), 8.87 (m, 1H), 9.73 (s, 1H). ^{13}C NMR (DMSO- d_6): 53.83 (CH_3), 115.28 (CH), 126.04 (CH), 127.74 (CH), 117.44 (Cq), 124.05 (Cq), 128.11 (Cq), 130.97 (Cq), 144.80 (CH), 148.30 (Cq), 155.24 (Cq), 161.51 (Cq). MS (IE): m/z = 300. CHN analysis (%): calculated: C: 52.00, H: 2.69, N: 18.66; found: C: 51.76, H: 2.64, N: 19.50.

Crystallographic Data

The asymmetrical unit of the structure of the pyrazoloquinoxaline contains two almost identical plane molecules. The only notable difference between these molecules is the orientation of the final methyl, which is located in the plane of one molecule (Fig. 2) and almost perpendicular to the plane of the other. Figure 1 shows that each molecule is formed by three cycles plus a fourth, if one takes account of the intramolecular hydrogen bond. The molecules form layers parallel to the plane (–4 0 6) as showed in Fig. 2. The cohesion of the layers in the crystal is assured only by Van der Wals bonds, which explains the cleavage of these crystals.

Crystal data and structure refinement for pyrazolo quinoxaline. Empirical formula: $\text{C}_{26}\text{H}_{22}\text{N}_6\text{O}_6$; formula weight: 514.50; temperature: 293(2) K, wavelength: 0.71073 Å; crystal system monoclinic, C2/c; unit cell dimensions: $a = 7.055(3)$ Å, $b = 24.876(6)$ Å, $c = 27.650(2)$ Å and $\beta = 95.0330(10)$ deg. Volume: $4834(2)$ Å³; calculated density: 1.414 mg/mm^3 ; absorption coefficient: 0.103 mm^{-1} . $F(000)$: 2144. Full-matrix least-squares on F^2 . Data/restraints/parameters: 3033/0/431. Final R indices [$I > 2$ sigma (I)], $R1 = 0.1017$; $wR2 = 0.193$. R indices (all data) $R1 = 0.1293$; $wR2 = 0.2077$.

CCDC 736553 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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