A convenient synthesis of new 1-pyrazolylquinoxalin-2-one derivatives from 1,5-benzodiazepine-2-thione

Mohamadou Lamine Doumbia, Rachid Bouhfid, Noureddine Hamou Ahabchane, and El Mokhtar Essassi*

Laboratoire de Chimie Organique Hétérocyclique, Pôle de compétences Pharmacochimie, Faculté des Sciences, Av. Ibn Batouta BP 1014, Rabat, Marocco

E-mail: emessassi@yahoo.fr

Abstract
New pyrazole-, 1,3,4-oxadiazole-, and 1,2,4-triazole- conjugated pyrazolylquinoxalines were synthesized from 4-phenyl-1,5-benzodiazepine-2-thione. The identification of these compounds was carried out using $^1$H- and $^{13}$C- NMR, IR, and mass spectrometry.

Keywords: 1,5-Benzodiazepine, quinoxalines, 1,3,4-oxadiazole, 1,2,4-triazole

Introduction
The interest aroused by quinoxaline chemistry is based essentially on the different applications of these compounds in various fields. It is well known that the quinoxaline derivatives are used as dyes to detect metals and anions.$^{1,2}$ They are also used as agrochemicals,$^3$ anti-virals,$^4$ anti-microbials,$^5$ and for the treatment of tuberculosis,$^6$ and human cancer cell lines,$^7$ and herbicides.$^8$ We have continued our investigations and prepared new quinoxaline derivatives in the hope that they may possess various pharmacological activities. According to some reviews,$^{9-15}$ quinoxaline derivatives have been prepared by several methods. We describe here the synthesis of new quinoxaline derivatives, using 4-phenyl-1,5-benzodiazepine-2-thione, 1, as starting material.

Result and Discussion
The pyrazolylquinoxaline derivatives 9, 10, and 12 described in this paper are prepared by the approach outlined in Schemes 2 and 3. The key step of these syntheses is based on the reactivity of the pyrazolyl-quinoxaline 6 towards triethyl orthoformate, carbon disulfide, or methyl isocyanate in presence of potassium hydroxide, to give the products 9, 10 and 12. In a previous
paper,\textsuperscript{16} we reported that 4-phenyl-1,5-benzodiazepine-2-thione, 1, reacts with hydrazine to give 3-N-(2-aminophenyl-amino)-5-phenylpyrazole 2 (Scheme 1). The reaction of 2 with diethyl acetylenedicarboxylate, 3, in ethanol under stirring at room temperature afforded ethyl 2-(2-ethoxy-2-oxoethyl)-1-(3-phenyl-1H-pyrazol-5-yl)-2,3-dihydro-1H-benzimidazole-2-carboxylate, 5 (resulting from the attack of the NH\textsubscript{2} and NH groups of 2 on the triple bond of 3) and 3-ethoxycarbonylmethylene-2-oxo-l-[3(5)-phenylpyrazol-5(3)-yl]-1,2,3,4-tetrahydroquinoxaline, 4, in good yield. There exists a tautomeric equilibrium between the enamine form A and the methyleneimine form B as shown in Scheme 1. The identification of compounds 4 and 5 was carried out using \textsuperscript{1}H- and \textsuperscript{13}C- NMR, IR, and mass spectrometry.

\begin{equation}
\text{Scheme 1}
\end{equation}

The proton nuclear magnetic resonance spectrum of 4 in DMSO-d\textsubscript{6} revealed signals due to vinyl and methylene protons at $\delta$ 5.62 and 3.93 ppm respectively, and the integral ratio of the two signals was 1.2:1 suggesting predominance of the tautomer A. On the other hand, the \textsuperscript{13}C- NMR also exhibited vinyl and methylene carbon signals respectively at $\delta$ 85.8 and 39.6 ppm in accord with this tautomeric equilibria.

In the \textsuperscript{1}H NMR spectrum of product 5 in CDCl\textsubscript{3}, the methylene hydrogens linked to C\textsubscript{2} appeared as an AB system at $\delta$ 2.98 and 2.65 ppm with $J$=16 Hz. The \textsuperscript{13}C- NMR spectrum showed the carbon of this methylene group at $\delta$ 41.8 ppm. The mass spectrum of 5 taken in the desorption chemical ionization mode, showed the molecular peak m/z at 421, which helps confirm the structure of the product. It is interesting to note that compound 4, obtained in a good
yield, possesses several reaction centers, and therefore it may be used as a precursor in the synthesis of more elaborate quinoxaline derivatives.

In relation to the above target compounds, we found that compound 4 was converted easily into the 3-hydrazidomethylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline, 6, by reaction with an excess of hydrazine hydrate in ethanol under 3 hours reflux (Scheme 2).

Scheme 2

The structure of 6 was established on the basis of its $^1$H- and $^{13}$C- NMR, IR, and mass spectral data. The infrared (IR) absorption band of the hydrazido group was observed at 1673 cm$^{-1}$ which is much lower than the ester carbonyl group. In the $^1$H NMR spectrum the signals relating to vinyl and methylene protons were observed at $\delta$ 5.75 and 3.73 ppm respectively. Furthermore, the $^{13}$C NMR also showed the co-existence of tautomer forms — the signals corresponding to the vinyl and methylene carbon appeared at $\delta$ 88.1 and 39.0 respectively. In addition, compound 6 was found to be a useful key intermediate, leading to novel pyrazole, 1,2,4-triazole- conjugated quinoxalines.

The reaction of compound 6 with triethyl orthoformate and triethyl orthoacetate in ethanol furnished exclusively 3-(N-ethoxymethylene)hydrazidomethylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline, 7, and 3-(N-(1-ethoxyethylene) hydrazidomethylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline, 8, respectively (Scheme 2),
the structures of which were attributed on the basis of their spectral data (\(^1\)H-, \(^{13}\)C- NMR, IR, and mass spectra). Further refluxing of 7 in \(N, N\)-dimethylformamide induced cyclization leading to product 9 3-(5-oxo-3-pyrazolin-4-yl)-2-oxo-1(3(5)-phenylpyrazol-5(3)-yl)-1,2-dihydro-quinoxaline (Scheme 2). In contrast, the cyclization did not occur when compound 8 was heated under reflux under the same reaction conditions. Presumably, owing to steric hindrance by the methyl group, this cyclization route cannot be realized. The structure of compound 9 was assumed satisfactorily on the basis of its spectral data. The \(^1\)H NMR spectrum of 9 in DMSO-\(d_6\) exhibits a signal due to the 3-H of the pyrazolone ring at 8.45 ppm, in accord with the structure assigned.

Various 1,3,4-oxadiazoles\(^{17-19}\) and 1,2,4-triazoles\(^{20}\) have been tested as herbicidal, fungicidal, bactericidal, antihistaminic, and plant-growth-regulatory agents. Accordingly, we undertook the synthesis of new 1-pyrazolylquinoxalines possessing 1,3,4-oxadiazolylmethylene and triazolylmethylene groups in the 3-position in order to test their activities.

Starting from compound 6 by a one-pot reaction with carbon disulfide in the presence of potassium hydroxide in water, we have prepared 3-(5-thioxo-4,5-(dihydro-1,3,4-oxadiazol-2-yl)methylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline, 10 (Scheme 3), whose structure was elucidated by means of spectroscopic data.

![Scheme 3](image)

The infrared spectrum of compound 10 showed no SH absorption band, but exhibited the C=S absorption band at 1160 cm\(^{-1}\). The \(^1\)H- NMR spectrum of 10 in DMSO-\(d_6\) revealed signals
corresponding to the vinyl and methylene protons at δ 6.01 and 4.42 ppm respectively. These data are consistent with the structure of 10, the vinyl and methylene protons of the aromatized 1,3,4-oxadiazole compounds being observed at lower magnetic field.21

Moreover, when methyl isothiocyanate reacted with 6 under reflux in dioxane, the corresponding thiosemicarbazide 11 was obtained. This later compound was heated under reflux in water, in the presence of potassium hydroxide. The dehydration led to 3-(4-methyl-3,4 dihydro-3-thioxo-2H-1,2,4-triazol-5-yl)methylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline, 12 (Scheme 3). The structure of compound 12 was confirmed on the basis of its 1H-, 13C- NMR, IR, and mass spectral data. The infrared spectrum of 12 showed the C=S absorption band at 1270 cm⁻¹, the mass spectrum (DCI/NH₃) exhibited a major peak at m/z = 416 (MH⁺), and the 1H NMR revealed, in addition to the signals due to vinyl and methylene protons at δ 6.08 and 4.37 ppm, respectively, a signal corresponding to the methyl group at 3.52 ppm. It has been noticed that these spectral data are consistent with the dihydrotriazole ring for the same reasons invoked for the compound 12.21

In conclusion, we describe in this paper the synthesis of new heterocyclic conjugated quinoxalines using the 4-phenyl-1,5-benzodiazepine-2-thione, 1, as starting material.

### Experimental Section

**General Procedures.** Melting points were determined on a Büchi Tottoli apparatus and are uncorrected. Spectra were recorded using the following instruments: IR, Perkin-Elmer 577 (KBr disks); NMR, Bruker AC 250 spectrometer, 250 MHz for 1H- and 62.89 MHz for 13C), chemical shifts δ are given in ppm downfield from TMS internal standard; MS (DCI/NH₃) VARIAN MAT 311 A spectrophotometer. RT denotes room temperature.

**Synthesis of 3-ethoxycarbonylmethylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline (4) and ethyl 2-(2-ethoxy-2-oxoethyl)-1-(3-phenyl-1H-pyrazol-5-yl)-2,3-dihydro-1H-benzimidazole 2-carboxylate (5).** To a solution of 215 (10² mole) in 100 mL of EtOH, 1.5 equiv. of diethyl acetylenedicarboxylate, 3, was added slowly. The mixture was stirred at RT for 1 hour. The product 4 precipitated as yellow needles, which were collected by filtration. The filtrate was evaporated and the resulting crude material was chromatographed over silica gel column using 20:80 ethyl acetate: hexane as eluent to give an additional quantity of 4 and product 5. Product 4: 90% yield, m.p. 154-156°C; IR (KBr): 3291 cm⁻¹ (NH); 1726 cm⁻¹ (C=O); 1H- NMR (DMSO-d₆): 1.30 (3H, t, J = 7 Hz); 3.93 (2H, s, C₃-CH₂); 4.18 (2H, q, J = 7 Hz); 5.62 (1 H, s, C₃=CH); 6.58 and 6.61 (1H, s, C₄-H); 6.67-7.86 (9H , m, H_Ar); 11.18 (1H, s, N₄H); 13.78 and 13.87(1H, s, NHpyrazole). 13C NMR (DMSO-d₆) δ 13.9, 14.2, 39.4, 59.2, 60.4, 85.0, 100.7, 115.6, 125.0, 127.3, 128.5, 144.4, 155.1, 155.5, 166.9, 166.9. MS (DCI/NH₃), m/z 375 [MHH⁺]. Anal. Calcd for C₂₁H₁₈N₄O₃: C, 67.37; H, 4.85; N, 14.96%. Found: C, 67.23; H, 4.79; N, 15.06%. Product 5: 10% yield, m.p. 130-132°C; IR (KBr): 3331 cm⁻¹ (NH); 1721 cm⁻¹.
(C=O); 1H- NMR (CDCl3): 0.93 (3H, t, J = 7 Hz); 1.20 (3H, t, J = 7 Hz); 2.65 (1 H, d, J = 16 Hz); 2.98 (1H, d, J=16 Hz); 3.71 (2H, q, J = 7 Hz); 3.86 (2H, q, J = 7 Hz); 6.49 (1 H, s, C4-H); 6.77-7.42 (9H, m, C6-H, HAr); 11.56 (1H, s, NHbenzimidazole); 13.81 (1H, s, NHpyrazole); 13C NMR (CDCl3): 13.7; 14.0; 41.8; 61.3; 62.8; 104.2; 117.5; 129.4; 130.3; 151.0; 170.9; 171.6. MS (DCI/NH3): m/z 421 [MH]+. Anal. Calc. for C22H24N6O3: C, 65.70; H, 5.75; N, 13.33. Found: C, 65.76; H, 5.69; N, 13.38%.

2-(3-Oxo-4-(3-phenyl-1H-pyrazol-5-yl)-3,4-dihydroquinoxalin-2(1H)-yldiene)-acetohydrazide (6). A solution of 4 (10−2 mole) and hydrazine hydrate (10−1 mole) in 80 mL of EtOH was heated under reflux for 3 h. The colorless product 6 precipitated and was collected by filtration. Evaporation of the filtrate gave an additional quantity of 6. An analytically pure sample was obtained by washing with hot EtOH several times. Yield 90%, m.p. 249-251°C. IR (KBr) 3296 cm−1 (NH2), 1673 cm−1 (C=O); 1H NMR (DMSO-d6): 3.73 (2H, s, C3-CH2); 4.36 (2H, br, s); 5.75 (1 H, s, C3=CH); 6.48 and 6.51 (1 H, s, C4-H); 6.80-7.85 (9H, m, mAr, m); 9.27 (1H, s, CONHNH2); 11.18 (1H, s, NH); 13.78 (1H, s, NHpyrazole). 13C NMR (DMSO-d6): 38.7, 88.1, 100.6, 114.4, 125, 125.9, 126.9, 128.4, 130.0, 131.5, 133.9, 138.4, 146.2, 153.6, 156.4, 167.4. MS (DCI/NH3): m/z: 361 [MH]+. Anal. Calc. for C19H16N7O2 C, 63.32; H, 4.48; N, 23.32. Found: C, 63.26; H, 4.54; N, 23.28%.

3-(N-Ethoxymethylene)hydrazidomethylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline (7) and 3-[2-{2-(1-ethoxyethylidene)hydrazino]-2-oxoethylidene]-2-oxo-1-(3(5)phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline (8). A solution of 6 (10−2 mole) and 20 mL of the appropriate ortho-ester in 100 mL of EtOH was heated under reflux for 3h. When triethyl orthoformate was employed, yellow needles of 7 precipitated during the reaction, and were collected by filtration. The filtrate was evaporated to provide an additional quantity of product 7. The analytically pure sample was obtained by washing with hot EtOH several times. Yield 80%, m.p. 234-236°C. IR (KBr, cm−1) 3279 (NH), 1680 (C=O). 1H- NMR (DMSO-d6): 1.27 (3H, t, J = 7 Hz), 3.76 (2H, s, C3-CH3), 4.14 (2H, q, J = 7 Hz), 5.74 (1 H, s, C3=CH), 6.11 (1H, s); 6.50 (1 H, s, C4-H); 6.81-7.84 (9H, m, mAr); 9.27 (1H, s, NH); 10.80 (1 H, s, NH); 11.97 (H, s, NH); 13.76 and 13.87 (1H, s, NHpyrazole). 13C- NMR (DMSO-d6): 14.0, 15.3, 28.9, 62.3, 66.7, 88.2, 100.8, 100.9, 114.7, 125.0, 125.7, 128.5, 128.7, 130.1, 133.7, 153.6, 156.5, 165.3. MS (DC/NH3), m/z 417 [MH]+. Anal. Calc. for C22H20N6O3: C, 63.45; H, 4.84; N, 20.18. Found: C, 63.53; H, 4.80; N, 20.25%. When triethyl orthoacetate was used, the solvent was evaporated off to afford yellow needles of 8, which were collected by filtration and washed several times with hot EtOH to give an analytically pure sample. Yield 80%, m.p. 173-175°C; IR (KBr) 3227 cm−1 (NH); 1675 cm−1 (C=O); 1H NMR (DMSO-d6): 1.22 (3H, t, J = 7 Hz); 1.97 (3H, s); 3.83 (2H, s, C3-CH2); 4.08 (2H, q, J = 7 Hz); 5.94 (1H, s, C3=CH); 6.48 and 6.52 (1 H, s, C4-H); 6.84-7.85 (9H, m, mAr); 10.04 (1H, s, NH); 10.11 (1 H, s, NH); 11.92 (1H, s, NH); 13.75 and 13.85 (1H, s, NHpyrazole). 13C NMR (DMSO-d6): 14.0; 14.6; 15.29; 39.0; 61.4; 64.1; 88.5; 100.8; 114.6; 125.0; 125.5; 127.3; 128.5; 130.1; 131.5; 153.7; 155.9; 156.4; 164.4; 165.0; 169.6; 169.8; MS (DCI/NH3): m/z: 431 [MH]+. Anal. Calc. for C23H22N6O3: C, 64.17; H, 5.15; N, 19.52. Found: C, 64.11; H, 5.21; N, 19.62%. 
3-(5-Oxo-3-pyrazolin-4-yl)-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2-dihydroquinoxaline (9).

A solution of 7 (10⁻³ mole) in dimethylformamide (100 mL) was heated at reflux for 20 h in an oil bath at 160-180°C. Thereafter the solvent was evaporated off and the resulting crude material was chromatographed on a silica gel column (eluent, 30:70 ethyl acetate: hexane) to give an analytically pure compound was chromatographed on a silica gel column (eluent, 30:70 ethyl acetate: hexane) to give an analytically pure sample. Yield 70%. m.p. 253-255°C. IR (KBr, cm⁻¹): 1680 (C=O), 1640 (C=N), 1160 (C=S). MS (FAB, m/z): 434 [MH]+. Anal. Calcd for C₂₀H₁₄N₆O₂: C, 64.86; H, 3.57; N, 20.88. Found: C, 64.76; H, 3.88; N, 22.62%.

3-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline (10). To a solution of 6 (2x10⁻³ mole) and 1.5 equiv. of KOH in 30 mL of H₂O, 10 mL of CS₂ was added slowly. The reaction mixture was heated at reflux for 1 h. Product 10 precipitated as a yellow powder and was purified over a silica gel column using 20:80 ethyl acetate: hexane as eluent to give an analytically pure sample. Yield 70%. m.p. 253-255°C. IR (KBr, cm⁻¹): 1680 (C=O), 1640 (C=N), 1160 (C=S). MS (FAB, m/z): 371 [MH]+. Anal. Calcd for C₂₀H₁₄N₆O₂: C, 64.86; H, 3.57; N, 20.88. Found: C, 64.76; H, 3.88; N, 22.62%.

Synthesis of the thiosemicarbazide (11). A suspension of 6 (2x10⁻³ mole) and an equimolar amount of methyl isothiocyanate in 70 mL of dioxane was heated at reflux for 1 h: 11 precipitated as a yellow product. Trituration with hot ethanol afforded an analytically pure sample in 80% yield, m.p. 227-229°C. IR (KBr, cm⁻¹): 3300 (NH), 1670 cm⁻¹ (C=O), 1221 cm⁻¹ (C=S). ¹H NMR (DMSO-d₆): 2.87 and 2.89 (3H, d, J = 4.5 Hz), 3.84 (2H, s, C₂=CH₂), 5.80 (1H, s, C₃=CH), 6.52 and 6.55 (1H, s, C₄=CH), 6.87-7.85 (9H, m, Ar), 7.88 (1H, q, J = 4.5 Hz, CSNMe), 9.21 (1H, s, NH), 9.41 (1H, s, NH), 9.80 (1H, s, NH), 11.69 (1H, s, NH), 13.74 (1H, s, NH), 13.88 (1H, s, NH). ¹³C NMR (DMSO-d₆): 30.6, 30.8, 87.2, 39.72, 100.6, 111.5, 125.0, 125.9, 128.5, 128.7, 130.3, 131.5, 131, 156.1, 167.7, 181.9, 182.4. MS (DCI/NH₃), m/z: 434 [MH]+. Anal. Calc. for C₂₁H₁₉N₇O₃S: C, 58.19; H, 4.42; N, 22.62. Found: C, 58.08; H, 4.49; N, 22.70%.

3-(4-Methyl-3,4-dihydro-3-thioxo-2H-1,2,4-triazol-5-yl)methylene-2-oxo-1-(3(5)-phenylpyrazol-5(3)-yl)-1,2,3,4-tetrahydroquinoxaline (12). A suspension of the thiosemicarbazide 11 (0.5x10⁻³ mol) and 1.5 equiv. of KOH in 30 mL of H₂O was heated under reflux for 1 h to precipitate the product 12 as a yellow powder. This was collected by filtration and purified over a silica gel column using 10:90 ethyl acetate: hexane as eluent to give an analytically pure sample. Yield 80%, m.p. 302-304°C. IR (KBr cm⁻¹): 3128 (NH), 3066 (NH), 3015 (NH), 1680 (C=O), 1270 (C=S). ¹H-NMR (DMSO-d₆) 3.47-3.50 (3H, s); 4.37 (2H, s, C₃=CH₂); 6.08 (1H, s,
C_3=CH); 6.53 and 6.56 (1H, s, C_4-H); 6.88-7.84 (9H, m, H_Ar); 10.21 (1H, s, NH); 13.72 (1H, s, NH); 13.76 (1H, s, NH); 13.81 (1H, s, NH); 14.01 (1H, s, NH). 13^C NMR (DMSO-d_6): 29.4, 30.2, 39.8, 81.1, 100.7, 114.9, 125.0, 127.3, 128.5, 129.1, 133.8, 134.7, 156.2, 165.6. MS (DCI/NH_3): m/z 416 [MH]^+. Anal. Calc. for C_{21}H_{17}N_7OS: C, 60.71; H, 4.12; N, 23.60%. Found: C, 60.69; H, 4.07; N, 23.67%.

Acknowledgements

The authors would like to acknowledge the financial support provided by the ministry ESRSFC of the Moroccan Government (Pôle de Compétences Pharmacochimie).

References