Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 30 Jun 2011.Version of record first published: 27 May 2011.

To cite this article: A. Makhloufi , M. Baitiche , M. Merbah & D. Benachour (2011): Synthesis of New Quinoxaline Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:23, 3532-3540

To link to this article: http://dx.doi.org/10.1080/00397911.2010.519091

Synthetic Communications®, 41: 3532–3540, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.519091

SYNTHESIS OF NEW QUINOXALINE DERIVATIVES

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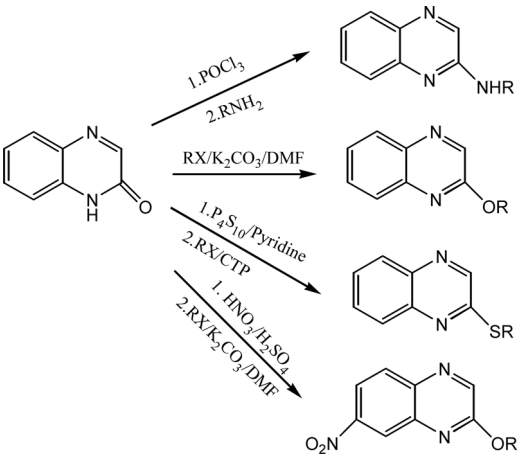
GRAPHICAL ABSTRACT



Abstract *New quinoxaline derivatives were prepared by the reaction of 2-hydroxyquinoxaline* ***1*** *and alkyl or alkylaminoalkyl halides in dimethylformamide using potassium carbonate as a base. The hydroxyl group was readily converted into a thiol function by treatment with phosphorus pentasulfide and/or Lawesson's reagent in pyridine, and the subsequent alkylation of the thiol group was carried out under phase-transfer catalyst conditions. Chlorination of* ***1*** *was carried out with phosphorus oxychloride. Branching of alkylamino side chains to the 2-OH, 2-SH, and 2-Cl quinoxalines resulted in the synthesis of several compounds. Synthesis and alkylation of 2-hydroxy 7-nitroquinoxaline are also reported.*

Keywords Alkylation; aminoalkylation; chlorination; quinoxalines; thiation

Received January 22, 2010.
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INTRODUCTION

Nitrogen-containing heterocyclic compounds are desirable structural units for both chemists and biochemists. Quinoxaline compounds have important pharmacological activities, such as the following: imidazoquinoxalines have been reported as antiviral agents,[1] pyrazoloquinoxalines showed relatively high antibacterial activity,[2] quinoxaline-1,4-di-*N*-oxides were used for treatment of tuberculosis,[3] pyrimido[4,5-b]quinoxaline is known to be a antihypertensive and blood platelet antiaggregating agent,[4] and some quinoxaline derivatives have cytotoxic effects on human cancer cell lines,[5,6] and are commercially important as agrochemicals,[7] herbicides,[8] and amebicides.[9] Different analogs of quinoxalines have been prepared by alkylation. The presence of an alkyl group with nitrogen or sulfur atoms as a side chain on an quinoxaline ring is an important factor for biological activities,[10] so within the frame of our ongoing research in such chemosensitizers, we intended to prepare new derivatives belonging to these series.

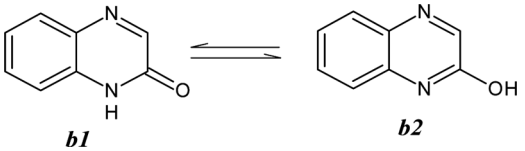
Alkylation reactions were carried out by nucleophilic substitution through alkyl halides. It is well established that the 2-hydroxyquinoxaline exists in two tautomeric forms, *b1* and *b2* (Fig. 1). This enolic equilibrium, which is a very slow process in a neutral medium, can be catalyzed by bases or acids.[11] By considering a reactional medium made of N,N-dimethylformamide (DMF)/potassium carbonate (K_2CO_3), the enolic form *b1* will prevail and consequently its reaction with the alkylating agents will be favored, thus giving mainly alkoxy products compared to the N-alkylated ones.[12] Previously, these conditions have shown to be very efficient when using quinolines.[13]

According to previous works, chlorination of similar heterocycles is made by acting thionyle chloride ($SOCl_2$) on the hydroxylated form, but it seems that this way of preparing chlorinated heterocyclic compounds usually gives poor yields. In this situation, the reaction with phosphorus oxychloride ($POCl_3$) was more effective.[14]

A large number of aromatic heterocyclic amines are prepared by direct reaction of primary amines on the chlorinated compound. The conditions of the reaction depend on the nucleophilic power of the amine and its volatility.[15]

The conversion of a carbonyl group into a thione is a classical reaction. It can be carried out either under the effect of sulfur at high temperature or by an oxygen/sulfur exchange under the action of phosphorus decasulfide or Lawesson's reagent in solvents such as pyridine, diglyme, or dioxane.[16] Greater yields were observed with the latter method, which is why this was taken as the basis for the thiation reaction of the initial product.

Sulfides are known for their biological properties,[17] and bringing more modifications to the main skeleton by adding segments on the sulfur atom seems very



b1 *b2*

Figure 1. Tautomeric forms of 2-hydroxyquinoxaline.

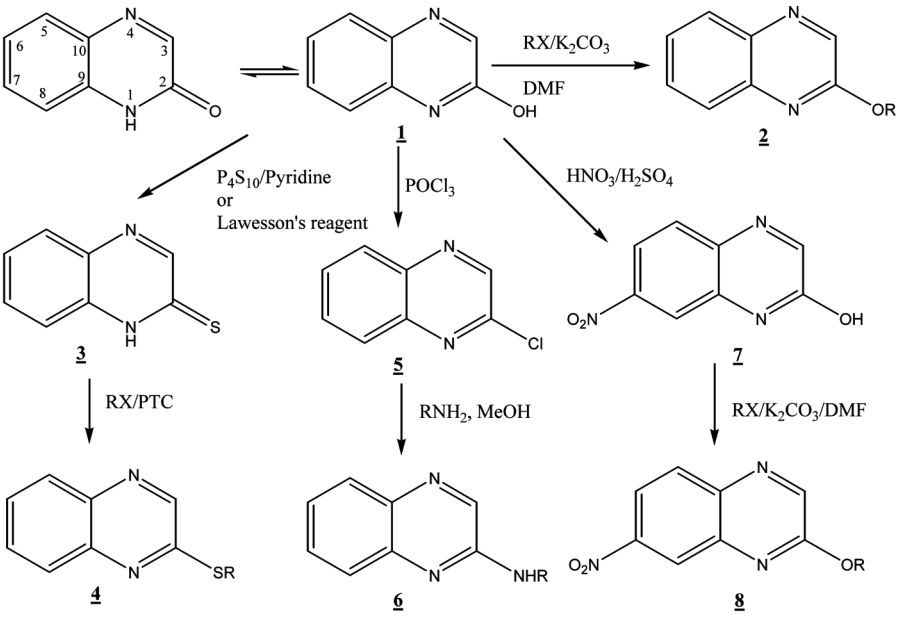
interesting. Alkylation reactions were carried out on previously prepared 2-thiol-quinoxaline. We note that because of the poor yields of the alkylation reactions when using the classical method of preparing 2-thioalkylatedquinoxalines, the phase-transfer catalysis (PTC) procedure was adopted, which overcomes this deficiency.[18]

Based on the fact that the presence of a nitro group on an aromatic heterocyclic compound may bring some new and interesting biological properties,[19] a nitration reaction was at tempted on the initial product. For this, the nitration reaction was carried out by the direct action of nitric acid in concentrated sulfric acid medium onto the initial compound at 0 °C,[11] and the resulting product was subjected to alkylation reactions according to the classical method.

RESULTS AND DISCUSSION

At first, 2-hydroxyquinoxaline **1** was used as the starting material. With the aim to obtain the O-alkyl derivatives **2**, a mixture of **1** and alkyl or alkylaminoalkyl halides was heated at 80 °C in dimethylformamide (DMF) in the presence of potassium carbonate for 5 h.

On the one hand, the 2-thioquinoxaline **3** was prepared by treating **1** with phosphorus pentasulfide or with Lawesson's reagent in pyridine. The yields were respectively 75% and 60%. Alkylation of the thione gave 2-alkylthioquinoxaline derivatives **4**. The reaction was carried out under PTC conditions at 110 °C for 24 h with tetrabutylammonium bromide (TBAB) as a dispersing agent.



R= ethyl (a), methyl (a'), piperidinoethyl (b), pyrrolidinoethyl (c), morpholinoethyl (d), dimethylaminoethyl (e)
(a, a': X=Br); (b, c, d, e: X=Cl)

Figure 2. Scheme showing the main chemical synthetic pathways.

Table 1. Chemical and physical data

Compd	Reaction time (h)	Yield (%)	Mp (°C)	λmax (nm/EtOH)	Wave number (cm^{-1})	^{1}H NMR (solvent/TMS), δ (ppm), J (Hz)
1	–	–	273	242, 282, 346	3076(υ_{CHar}), 1698($\upsilon_{C=O}$), 1642($\upsilon_{C=N}$), 1538($\upsilon_{C=C}$)	(DMSO) 11.50(s, broad, OH), 8.12(s, 1 H, $C_3\underline{H}$), 7.73(smr, 1H, $C_8\underline{H}$), 7.51(m, 1H, $C_5\underline{H}$), 7.27(m, 2H, $C_6\underline{H}C_7\underline{H}$)
2a	6	64	64	224, 242, 324	3062(υ_{CHar}), 2978($\upsilon_{CHalkyl}$), 1578($\upsilon_{C=C}$), 1036(υ_{C-O-C})	($CDCl_3$) 8.45(s, 1 H, $C_3\underline{H}$), 8.00(smr, 1H, $C_8\underline{H}$), 7.83(m, 1H, $C_5\underline{H}$), 7.80(m, 1H, $C_6\underline{H}$), 7.55(m, 1H, $C_7\underline{H}$), 4.54(qd, 2H, OCH_2, J = 7.1), 1.48(t, 3H, CH_3, J = 7.2)
2b	6	30	63.7	288, 324, 336	3062(υ_{CHar}), 2938-2922($\upsilon_{CHalkyl}$), 1582($\upsilon_{C=C}$), 1228(υ_{C-N}), 1032(υ_{C-O-C})	(DMSO) 8.40(s, 1H, $C_3\underline{H}$), 8.00(smr, 1H, $C_8\underline{H}$), 7.70 (m, 3H, C_5H, $C_6\underline{H}$, $C_7\underline{H}$), 4.50(t, 2H, J = 5.9, $OC\underline{H}_2$), 3.30(m, 4H), 2.70 (t, 2H, J = 5.9), 1.50(m, 6H)
3	**4**	70	211	225, 254, 408	3076(υ_{CHar}), 1611($\upsilon_{C=S}$), 1577($\upsilon_{C=C}$)	($CDCl_3$) 8.74(s, 1H, $C_3\underline{H}$), 7.93(d, 1H, $C_8\underline{H}$, J = 1.24), 7.62 (m, 1H, $C_5\underline{H}$), 7.44(m, 2H, $C_6\underline{H}$,$C_7\underline{H}$).
4b	24	46	oil	238, 262, 358	3042(υ_{CHar}), 2934($\upsilon_{CHalkyl}$), 1229(υ_{C-N}), 1088 (υ_{C-S-C})	($CDCl_3$) 8.10(s, 1H, $C_3\underline{H}$), 7.50(m, 4H, $C\underline{H}_{aromatic}$), 3.50(smr, 6H), 2.90(m, 2H, $NC\underline{H}_2$), 1.80(m, 6H, $C\underline{H}_{2cycle}$)
4c	24	48	oil	238, 262, 358	3045(υ_{CHar}), 2932($\upsilon_{CHalkyl}$), 1220(υ_{C-N}), 1088(υ_{C-S-C})	($CDCl_3$) 8.08(s, 1H, $C_3\underline{H}$), 7.49(m, 4H, $C\underline{H}_{Aromatic}$), 3.61(smr, 2H, $C\underline{H}_2N$), 3.30(smr, 4H, $NC\underline{H}_2$), 3.07(m, 2H, $SC\underline{H}_2$), 2.10(m, 4H, $NC\underline{H}_2C\underline{H}_2$)
4d	24	47	oil	238, 262, 358	3045(υ_{CHar}), 2933($\upsilon_{CHalkyl}$), 1220(υ_{C-N}), 1170(υ_{C-O-C}), 1088 (υ_{C-S-C})	($CDCl_3$) 8.15(s,1H, $C_3\underline{H}$), 7.49(smr, 4H, $C\underline{H}_{aromatic}$), 3.86(t, 4H, $OC\underline{H}_2$), 3.30(smr, 8H, $NC\underline{H}_2C\underline{H}_2O + SC\underline{H}_2C\underline{H}_2N$)
4e	24	41	202	238, 262, 358	3066(υ_{CHar}), 2922($\upsilon_{CHalkyl}$), 1020–1025(υ_{C-N}), 1088 (υ_{C-S-C})	($CDCl_3$) 8.04(s, 1H, $C_3\underline{H}$), 7.47 (smr, 3H, $C\underline{H}_{aromatic}$), 7.35(d, 1H, $C_8\underline{H}$, J = 5.26), 3.35 (smr, 4H, $SC\underline{H}_2C\underline{H}_2N$), 2.96(smr, 6H, $N(C\underline{H}_3)_2$)
5	3	60	50	242, 282, 346	758 (υ_{C-Cl}) diparition of ($\upsilon_{C=O}$) at 1698	($CDCl_3$) 8.80(s, 1H, $C_3\underline{H}$), 8.07(smr, 2H, $C\underline{H}_{aromatic}$), 7.82 (m, 2H, $C\underline{H}_{aromatic}$), $O\underline{H}$ at 11.50 ppm is absent.
6b	3	60	60	212, 248, 372	3200($\upsilon_{NHsecondary\ amine}$)	($CDCl_3$) 8.22(s, 1H, $C_3\underline{H}$), 7.82(m, 1H, C_8-$\underline{H}$,), 7.65 (m, 1H, C_5H, J = 6.91), 7.53(m, 1H, $C_6\underline{H}$), 7.34 (m, 1H, $C_7\underline{H}$), 3.71(smr, 4H), 3.57(q, 2H, $NC\underline{H}_2$, J = 5.45), 2.64(t, 2H, $C\underline{H}_2N$, J = 6.21), 2.48 (m, 4H, $NC\underline{H}_{2cycle}$)
6c	3	54	90	212, 244, 374	3250($\upsilon_{NHsecondary\ amine}$)	($CDCl_3$) 8.22(s, 1H, $C_3\underline{H}$), 7.86(m, 1H, $C_8\underline{H}$,), 7.67(m, 1H, $C_5\underline{H}$), 7.53(m, 1H, $C_6\underline{H}$), 7,35(m, 1H, $C_7\underline{H}$), 3.63(m, 2H, $NC\underline{H}_2$), 2.79(m, 2H, $C\underline{H}_2N$), 2.56(smr, 4H, $NC\underline{H}_2$CH2), 1.77(smr, 4H, $NCH_2C\underline{H}_2$)

(*Continued*)

Table 1. Continued

Compd	Reaction time (h)	Yield (%)	Mp (°C)	λmax (nm/EtOH)	Wave number (cm^{-1})	^{1}H NMR (solvent/TMS), δ (ppm), J (Hz)
6d	3	52	82	216, 250, 374	3200($\upsilon_{NHsecondary\ amine}$)	($CDCl_3$) 8.18(s,1H, $C_3\underline{H}$), 7.82(m, 4H, $C\underline{H}_{aromatic}$), 3.84(m, 4H), 7.53(m, 8H)
7	7	70	292	238, 270, 328	1481($\upsilon_{asN=O}$), 1338($\upsilon_{sN=O}$)	(DMSO) 8.25(s, 1H, $C_3\underline{H}$), 8.13(m, 2H, $C_5\underline{H}$&$C_6\underline{H}$), 7.30(m, 1H, $C_8\underline{H}$)
8a	6	30	151	238, 260, 326	1500($\upsilon_{asN=O}$), 1364 ($\upsilon_{sN=O}$), 1114($\upsilon_{C\text{-}O\text{-}C}$)	(DMSO) 8.91(s, 1H, $C_3\underline{H}$), 8.62 (s, 1H), 8.45(dd, 1H, J = 2.5–9.16), 7.8(d, 1H, J = 9.1), 4.66(q, $2H_{alkyl}$, J = 7), 1.51(t, $3H_{alkyl}$, J = 7)
8a′	6	70	217	238, 270, 326	1504($\upsilon_{asN=O}$), 1346($\upsilon_{s\ N=O}$), 1014($\upsilon_{C\text{-}O\text{-}C}$)	(DMSO) 8.50(s, 1H, $C_3\underline{H}$), 8.40(d, 1H, J = 9.52), 8.21 (s, 1H), 7.80 (dd, 1H, J = 2.7–9.24), 3.66 (s, $3H_{alkyl}$, $C\underline{H}_3$)

Table 2. ^{13}C NMR chemical shifts

Compound	^{13}C NMR (solvent) δ (ppm)
1	(DMSO) 154.876 (C_2); 151.531 (C_3); 131.978 (C_5); 131.765 (C_{10}); 130.689 (C_7); 128.717 (C_8); 123.198 (C_9); 115.669 (C_6);
2a	($CDCl_3$) 139.83, 130.028, 128.94, 127.16, 126.38, 62.32 ($O\underline{C}H_2$), 14.35 ($OCH_2\underline{C}H_3$)
3	($CDCl_3$) 174.931 (C_2=S); 155.807 (C_3); 131.651 (C_5); 135.306 (C_{10}); 131.365 (C_7); 128.746 (C_8); 125.705 (C_9); 116.117 (C_6);
4d	($CDCl_3$) 152.55 (C_2); 141.09 (C_3); 139.75 (C_{10}); 136.26 (C_9); 131.54 (C_5); 128.57 (C_6); 126.12 (C_7); 125.25 (C_8); 64.62 (CH_2O); 57.56 (CH_2N); 53.24 (NCH_2); 36.25 (SCH_2);
4e	($CDCl_3$) 153.94 (C_2); 143.54 (C_3); 141.45 (C_{10}); 137.83 (C_9); 131.21 (C_5); 129.43 (C_8); 127.28 (C_6); 127.28 (C_7); 56.35 [$\underline{C}H_2N$ & $N(\underline{C}H_3)_2$]; 43.31 ($S\underline{C}H_2$).
5	($CDCl_3$) 147.21 (C_2); 145.22 (C_3); 144.84 (C_9); 144.80 (C_{10}); 141.8 (C_9); 140.8 (C_5); 140.4 (C_7); 128.11 (C_8).
6d	($CDCl_3$) 151.75 (C_2); 140.09 (C_3); 139.48 (C_{10}); 135.48 (C_9); 130.73 (C_5); 127.67 (C_8); 125.09 (C_7); 124.17 (C_8); 63.72 ($\underline{C}H_2O$); 56.80 ($\underline{C}H_2N$); 52.16 ($N\underline{C}H_2$); 35.13 ($\underline{C}H_2$).
7	(DMSO) 160.04 (C_2); 152.88 (C_7); 148.86 (C_9); 144.96 (C_3); 129.01 (C_{10}); 128.19 (C_5); 122.69 (C_8); 121.88 (C_6).

On the other hand, chlorination of **1** with phosphorus oxychloride gave 2-chloroquinoxaline **5** in good yield. Because of its high reactivity, **5** reacts easily with amino derivatives to form the 2-alkylaminoquinoxalines **6**.

The 2-hydroxy 7-nitroquinoxaline **7** is obtained with good yield (75%) when 2-hydroxyquinoxaline **1** reacts with nitric acid in the sulfuric acid. Alkylation of **7** was realized under the same conditions as those used for **1**.

Synthetic pathways are schematised in Fig. 2.

Chemical data of these compounds are gathered in Tables 1 and 2.

According to Table 1, the O-alkylated isolated products have different yields. We note a raised value for the ethyl group (64%) as compared with that obtained with the piperidinoethyl motive (30%). Large side chains are favorable for steric hindrance. The aminoalkyl halides react less quickly with the 2-hydroxyquinoxaline and require longer reaction times. The thioalkylation reaction yields are boarding the 45% for the aminoalkyl halides series used. It would be interesting to use a simple alkyl halide of smaller size to compare the reactivity as was done with O-alkylated compounds. For amination reactions, the yields are increased. The chlorine atom is mobile toward nucleophilic reagents such as amines. The yields of the alkylation reaction of the nitrated product were different. We observed a bigger value for the ethyl group than for the methyl one. Even there, the chain size plays an important role in reactivity.

EXPERIMENTAL

Different techniques are used for spectroscopic characterization. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 1000 spectrophotometer. NMR spectra were recorded on a Brücker Advance 200 spectrometer with tetramethylsilane (TMS) used as internal standard. Melting points were determined on a Büchi B540 apparatus.

2-Alkoxyquinoxalines 2

In a round-bottomed flask, a mixture of **1** (5 mmol) and potassium carbonate (5 mmol) was dissolved in 15 ml of DMF at 80 °C under continuous stirring. Then, the alkyl halide (5 mmol) was dropwise added to the solution and heated at 80 °C for 6 h. The obtained product **2** was poured into the water. The precipitated was filtered and purified by recrystallization from ethanol.

2-Quinoxalinethiol 3

2-Hydroxyquinoxaline **1** (4 mmol) was added to a solution of phosphorus pentasulfide (4.5 mmol) in pyridine (30 ml) under vigorous stirring under reflux at 80 °C for 4 h. The precipitated product in water was filtered and purified by recrystallization from ethanol.

2-Alkylthioquinoxalines 4

A mixture of 2-quinoxalinethiol (3 mmol), alkyl halide (3 mmol), tetrabutylammonium bromide (3 mmol) in toluene (30 ml), and 50% aqueous potassium hydroxide (15 ml) were refluxed at 110 °C for 24 h. The oily crude product was extracted from the dried organic layer and purified by column chromatography in ethyl acetate/methanol (7:3) system.

2-Alkylaminoquinoxalines 6

A mixture of 2-hydroxyquinoxaline (10 mmol) and phosphorus oxychloride (30 ml) was heated at 80 °C for 3 h to produce 2-chloroquinoxaline **5**, which was converted into **6** by addition of amine in the presence of MeOH (1.5 ml). The crude product was precipitated in aqueous KOH (10%), filtered, and purified by column chromatography using petroleum ether/ethyl acetate (1:1) system.

2-Hydroxy 7-Nitroquinoxaline 7

Nitric acid (0.6 ml) was added dropwise to a solution of 2-hydroxyquinoxaline (5 mmol) in sulfuric acid (6 ml) with stirring at room temperature for 7 h. The crude product was precipitated in crushed ice, filtered, and purified by recrystallization in MeOH/water.

Alkylation of **7** was carried out in the same manner as for **1**.

ACKNOWLEDGMENT

The authors are thankful to ANDRS (Agence Nationale pour le Développement de la Recherche en Santé) for supporting this work.

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