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Synthesis of [2,3-*b*]thieno- and furoquinoxalines by the S_N^H and S_N^{ipso} reactions of 2-substituted quinoxalines with acetophenones

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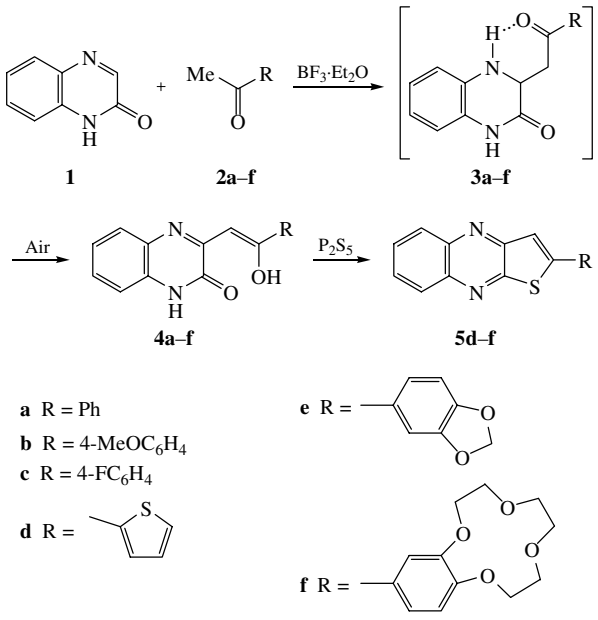
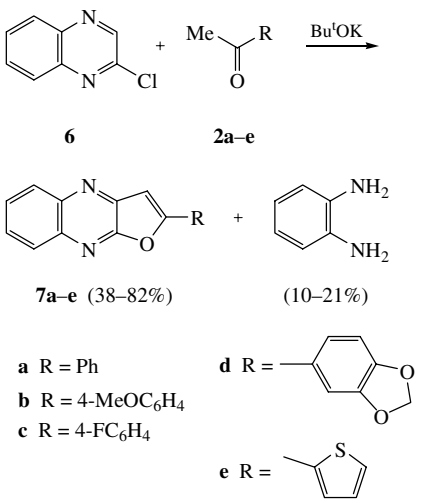
The treatment of quinoxalin-2-one with acetophenones in the presence of boron trifluoride gives 3-(2-hydroxy-2-R-vinyl)-quinoxalin-2-ones, which can be transformed into [2,3-*b*]thienoquinoxalines by reactions with P_2S_5.

Quinoxalines are of interest because some natural compounds bearing the quinoxaline skeleton exhibit high biological activity, *e.g.*, echinomycine and triostine. Condensed quinoxalines are important quinoxaline derivatives by virtue of their structural,[1] biological[2–4] and medical[5] specialties. The main stage of the two-step synthesis of such compounds is condensation of 1,2-phenylenediamine with 1,2,4-tricarbonyl compounds, which can be transformed into furo- and thienoquinoxalines.[6,7] Here we consider the nucleophilic substitution of hydrogen (S_N^H),[8,9] which was successfully used for the synthesis of condensed heterocyclic systems.[10–12] It was applied to the modification of 2-substituted quinoxalines by acetophenones and the design of [2,3-*b*]thieno- and furoquinoxalines.

Reactions of quinoxalin-2-one **1** with acetophenones afford the direct C–C coupling of heterocyclic and acetophenone fragments. Boron trifluoride is a perfect activating agent in the reaction. On the one hand, it promoted enol formation and, on the other hand, enhanced quinoxaline ring electrophilicity owing to complex formation. According to modern concepts in the S_N^H chemistry, the first stage of reaction is the formation of σ^H adducts **3a–f**. However, our attempts to detect them by both TLC and UV spectroscopy failed but the reaction resulted in the products of nucleophilic substitution of hydrogen in a quinoxaline ring obtained by the smooth aromatization of adducts **3a–f** (Scheme 1). This points to the fact that intermediates **3** are unstable and/or exist in a small concentration due to the fast conversion of **3** into **4**.† To our mind, the ready oxidation of σ^H adducts **3a–f** is due to the tendency to fix a preferred conformation for oxidation in which the oxidized bond tends to be located in the ring plane, as shown in Scheme 1. In this case, the oxidizing aromatization of this intermediate proceeds either with the starting quinoxalinone or with air oxygen assistance. The first way should be excluded because the yields of products **4a–f** are higher than 50%. Moreover, the rate of the reaction and the yields of products did not increase while an excess (2 equiv.) of quinoxaline **1** was put into the reaction mixture. Oxidation of σ^H adducts occurred most likely by the action of oxygen dissolved in solvents. This fact was confirmed by the experiment under anaerobic conditions (argon atmosphere) using a degassed solvent. The presence of two characteristic absorption bands at 415 and 440 nm in the UV spectrum of product **4a** makes it possible to perform the UV determination of absorbance depending on the duration of oxidation. An attempt to detect the formation of **4a** by UV spectroscopy using a degassed solvent failed. The introduction of another oxidant



Scheme 1



Scheme 2

(*e.g.*, $FeCl_3$) increases the reaction rate and does not affect the yield of the product.

Products **4a–f** were converted into corresponding thienoquinoxalines **5** according to a commonly used procedure[13] by treatment with phosphorous pentasulfide in pyridine (Scheme 1).‡

As for furo[2,3-*b*]quinoxalines, they can be obtained from compounds **4** according to the well-known reaction.[6] We propose another way to **7**, which consists in the reactions of 2-chloroquinoxaline with acetophenones (Scheme 2).§

Taking into account the tendency of 1,4-diazines to a double nucleophilic attack on two neighbouring carbons,[5,10] 2-chloroquinoxaline **6** is a good starting material for the synthesis of condensed heterocyclic systems. Note that its chemistry was presented essentially to *ipso*-substitution of halogens. For example, replacement of the chlorine atom by treatment of **6** by enols was described previously.[14,15] We found that the reaction of 2-chloroquinoxaline with enols generated from acetophenones appears in the presence of Bu^{t}OK to be a tandem of S_N^H and S_N^{ipso} processes leading to furoquinoxalines **7** with moderate yields (Scheme 2). In addition to the main product, 1,2-phenylenediamine was isolated in 10–21% yield. In our opinion, *o*-phenylenediamine forms as a result of destruction of an intermediate product of a nucleophilic attack of two acetophenone molecules on the C(2) and C(3) atoms of quinoxaline. In order to confirm

† Column and flash chromatography was performed using Lancaster silica gel (230–400 mesh) and CH_2Cl_2–MeOH as an eluent. All melting points were measured on a Boetius melting point apparatus. Elemental analyses were performed on a Carlo Erba 1108 CHNO Analyzer. The ^{1}H NMR spectra were recorded on a Bruker DRX 400 spectrometer with TMS as an internal standard. Starting quinoxalin-2-one **1** and 2-chloroquinoxaline **6** were obtained according to published procedures.[16,17]

General procedure for the preparation of 3-(2-hydroxy-2-arylvinyl)-1H-quinoxalin-2-ones **4a–f**. Acetophenone **2a–f** (0.68 mmol) was added to a suspension of quinoxalin-2-one **1** (100 mg, 0.68 mmol) in the mixture of methanol (3 ml) and boron trifluoride etherate (1 ml), and resulted mixture was stirred for 3 h at room temperature. Next, it was diluted with water (2 ml) and neutralised with saturated $NaHCO_3$. The precipitate obtained was filtered off and recrystallised from EtOH.

3-(2-Hydroxy-2-phenylvinyl)-1H-quinoxalin-2-one **4a**: yield 108 mg (60%), mp 260 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 13.67 (s, 1H, NH), 12.05 (s, 1H, OH), 7.98–8.00 (m, 2H, Ar), 7.52–7.61 (m, 4H, Ar), 7.13–7.16 (m, 3H, Ar), 6.83 (s, 1H, CH). Found (%): C, 72.36; H, 4.44; N, 10.37. Calc. for $C_{16}H_{12}N_2O_2$ (%): C, 72.71; H, 4.58; N, 10.60.

3-[2-Hydroxy-2-(4-methoxyphenyl)vinyl]-1H-quinoxalin-2-one **4b**: yield 102 mg (51%), mp 277–280 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 13.60 (s, 1H, NH), 11.99 (s, 1H, OH), 7.97–7.99 (m, 2H), 7.47–7.48 (m, 1H), 7.05–7.15 (m, 5H), 6.79 (s, 1H, CH), 3.85 (s, 3H, OMe). Found (%): C, 68.97; H, 4.84; N, 9.37. Calc. for $C_{17}H_{14}N_2O_3$ (%): C, 69.39; H, 4.76; N, 9.52.

3-[2-Hydroxy-2-(4-fluorophenyl)vinyl]-1H-quinoxalin-2-one **4c**: yield 85 mg (44%), mp 251–252 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 13.62 (s, 1H, NH), 12.05 (s, 1H, OH), 8.05–8.08 (m, 2H, Ar), 7.52–7.54 (m, 1H, Ar), 7.34–7.37 (m, 2H, Ar), 7.13–7.15 (m, 3H, Ar), 6.80 (s, 1H, CH). Found (%): C, 67.98; H, 3.94; N, 9.52. Calc. for $C_{16}H_{11}N_2O_2F$ (%): C, 68.09; H, 3.92; N, 9.92.

3-[2-Hydroxy-2-(thien-2-yl)vinyl]-1H-quinoxalin-2-one **4d**: yield 120 mg (65%), mp 270–272 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 13.26 (s, 1H, NH), 12.02 (s, 1H, OH), 7.89–7.91 (m, 2H), 7.47–7.48 (m, 1H), 7.22–7.24 (m, 1H), 7.11–7.14 (m, 3H), 6.68 (s, 1H, CH). Found (%): C, 61.97; H, 3.84; N, 10.17. Calc. for $C_{14}H_{10}N_2O_2S$ (%): C, 62.22; H, 3.73; N, 10.37.

3-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)vinyl]-1H-quinoxalin-2-one **4e**: yield 136 mg (66%), mp 281–283 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 13.55 (s, 1H, NH), 12.00 (br. s, 1H, OH), 7.60–7.62 (m, 1H), 7.46–7.50 (m, 2H), 7.30–7.32 (m, 1H), 7.11–7.13 (m, 2H), 7.03–7.05 (m, 1H), 6.74 (s, 1H, CH), 6.14 (s, 2H, CH_2). Found (%): C, 65.93; H, 3.84; N, 8.87. Calc. for $C_{17}H_{12}N_2O_4$ (%): C, 66.23; H, 3.92; N, 9.09.

3-[1-Hydroxy-2-(2-oxoquinoxalin-3-yl)vinyl]benzo-12-crown-4 **4f**: yield 148 mg (53%), mp 241–242 °C. ^{1}H NMR ([$^2H_6$]DMSO): 13.63 (s, 1H, NH), 11.99 (br. s, 1H, OH), 7.68–7.65 (m, 1H), 7.62–7.63 (m, 1H), 7.47–7.48 (m, 1H), 7.13–7.17 (m, 4H), 6.78 (s, 1H, CH), 4.13 (s, 4H, CH_2), 3.71–3.75 (m, 4H, CH_2), 3.61–3.63 (m, 4H, CH_2). Found (%): C, 63.89; H, 5.61; N, 6.65. Calc. for $C_{22}H_{22}N_2O_6$ (%): C, 64.39; H, 5.37; N, 6.82.

‡ *General procedure for the preparation of 2-arylthieno[2,3-b]quinoxalines* **5d–f**. A mixture of **4d–f** (0.5 mmol), phosphorus pentasulfide (1 mmol), and pyridine (2 ml) was refluxed for 8 h. After cooling to room temperature, the reaction mixture was diluted with water (4 ml) and the precipitate obtained was filtered off. The crude product was subjected to column chromatography (silica gel 40/60) using CH_2Cl_2 as an eluent to give pure **5d–f**.

2-(2-Thienyl)thieno[2,3-b]quinoxaline **5d**: yield 82 mg (61%), mp 200–201 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.14–8.19 (m, 2H), 7.94 (s, 1H), 7.84–7.92 (m, 4H), 7.29 (dd, 1H, *J* 3.7 Hz, *J*′ 5 Hz). Found (%): C, 62.48; H, 2.95; N, 10.20. Calc. $C_{14}H_8N_2S_2$ (%): C, 62.69; H, 3.00; N, 10.45.

2-(3,4-Methylenedioxyphenyl)thieno[2,3-b]quinoxaline **5e**: yield 98 mg (64%), mp 252–254 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.13–8.18 (m, 2H), 8.1 (s, 1H), 7.85–7.90 (m, 2H), 7.71 (d, 1H, *J* 1.8 Hz), 7.48 (dd, 1H, *J* 8 and 1.8 Hz), 7.12 (d, 1H, *J* 8 Hz), 6.17 (s, 2H). Found (%): C, 66.65; H, 3.23; N, 8.76. Calc. for $C_{17}H_{10}N_2O_2S$ (%): C, 66.66; H, 3.29; N, 9.15.

3-(Thieno[2,3-b]quinoxalin-2-yl)benzo-12-crown-4 **5f**: yield 77 mg (38%), mp 172–174 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.14–8.19 (m, 2H), 8.13 (s, 1H), 7.86–7.89 (m, 2H), 7.74 (d, 1H, *J* 2.3 Hz), 7.58 (dd, 1H, *J* 2.3 and 8.4 Hz), 7.23 (d, 1H, *J* 8.4 Hz), 4.21–4.29 (m, 4H), 3.73–3.77 (s, 4H), 3.63 (s, 4H). Found (%): C, 64.22; H, 4.61; N, 6.71. Calc. for $C_{22}H_{20}N_2O_4S$ (%): C, 64.71; H, 4.94; N, 6.86.

§ *General procedure for the preparation of 2-arylfuro[2,3-b]quinoxaline* **7a–e**. A solution of acetophenone (0.61 mmol) in THF and Bu^{t}OK (205 mg, 1.8 mmol) was added portionwise to a solution of 2-chloroquinoxaline (100 mg, 0.61 mmol) in THF (20 ml) for three days with vigorously stirring. After addition of reagents, stirring was continued for a day at room temperature. The solvent was evaporated to dryness. The residue was dissolved in water. The obtained solution was neutralised with dilute HCl and extracted with $CHCl_3$ (3×5 ml). The combined extracts were dried over $CaCl_2$, and the solvent was evaporated to give a crude product. Recrystallization from ethanol gave analytically pure **7a–e**.

2-Phenylfuro[2,3-b]quinoxaline **7a**: yield 123 mg (82%), mp 261–263 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.16–8.20 (m, 3H), 8.10–8.12 (m, 1H), 7.93 (s, 1H), 7.83–7.85 (m, 2H), 7.61–7.66 (m, 3H). Found (%): C, 77.88; H, 4.03; N, 11.21. Calc. for $C_{16}H_{10}N_2O$ (%): C, 78.01; H, 4.12; N, 11.40.

2-(4-Methoxyphenyl)furo[2,3-b]quinoxaline **7b**: yield 90 mg (53%), mp 204 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.10 (d, 2H, *J* 9.0 Hz), 8.06–8.18 (m, 2H), 7.79–7.82 (m, 2H), 7.74 (s, 1H), 7.19 (d, 2H), 3.88 (s, 3H). Found (%): C, 73.98; H, 4.43; N, 10.01. Calc. $C_{17}H_{12}N_2O_2$ (%): C, 73.91; H, 4.32; N, 10.10.

2-(4-Fluorophenyl)furo[2,3-b]quinoxaline **7c**: yield 77 mg (48%), mp 209 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.22 (dd, 2H, J_{HH} 9.0 Hz, J_{HF} 5.4 Hz), 8.16–8.18 (m, 1H), 8.01–8.11 (m, 1H), 7.90 (s, 1H), 7.81–7.86 (m, 2H), 7.50 (dd, 2H, J_{HH} 9.0 Hz, J_{HF} 11.8 Hz). Found (%): C, 72.58; H, 3.33; N, 10.01. Calc. for $C_{16}H_9N_2OF$ (%): C, 72.71; H, 3.42; N, 10.60.

2-(3,4-Methylenedioxyphenyl)furo[2,3-b]quinoxaline **7d**: yield 100 mg (57%), mp 217 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.16–8.18 (m, 1H), 8.10–8.13 (m, 1H), 7.71–7.77 (m, 2H), 7.63 (dd, 1H, *J* 8.1 and 1.6 Hz), 7.47 (d, 1H, *J* 1.6 Hz), 7.14 (s, 1H), 6.98 (d, 1H, *J* 8.1 Hz), 6.10 (s, 2H). Found (%): C, 70.18; H, 3.43; N, 9.41. Calc. for $C_{17}H_{10}N_2O_3$ (%): C, 70.31; H, 3.52; N, 9.72.

2-(Thien-2-yl)furo[2,3-b]quinoxaline **7e**: yield 58 mg (38%), mp 219 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.14–8.18 (m, 1H), 8.05–8.09 (m, 1H), 8.04 (dd, 1H, *J* 1.1 and 3.8 Hz), 8.00 (dd, 1H, *J* 1.1 and 5.0 Hz), 7.79–7.85 (m, 2H), 7.67 (s, 1H), 7.37 (dd, 1H, *J* 3.8 and 5.0 Hz). Found (%): C, 66.68; H, 3.13; N, 11.01. Calc. $C_{14}H_8N_2OS$ (%): C, 66.71; H, 3.22; N, 11.10.

this reaction pathway, we carried out a blank test. The stirring of a THF solution of 2-chloroquinoxaline and an excess of Bu^tOK for two days did not result in the destruction of the quinoxaline ring.

Thus, readily available 2-substituted quinoxalines can be used for the synthesis of fused quinoxalines by the combination of S_N^H and S_N^{ipso} reactions.

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