Synthesis of fused quinoxalines

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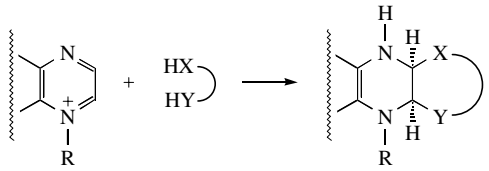
10.1070/MC2002v012n02ABEH001560

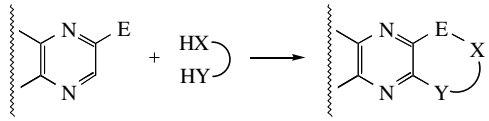
The intramolecular cyclization of NH and N-alkyl quaternary salts of 2-quinoxaline-2-carboxaldehyde hydrazones affords pyrazolo-[3,4-*b*]quinoxalines in good yields.

The idea to use tandem nucleophilic addition reactions at two neighbouring C=N bonds of an azine ring for construction of condensed aza heterocycles has been successfully applied to pyrazines and their aza and benzo analogues.[1–5] Indeed, the *ortho*-cyclization of 1-alkyl-1,4-diazinium salts with bifunctional nucleophiles is an efficient synthetic approach to condensed pyrazines, quinoxalines, pyrido[2,3-*b*]pyrazines and pteridines in which the pyrazine ring is fused with five- and six-membered heterocycles (Scheme 1).[1,2]



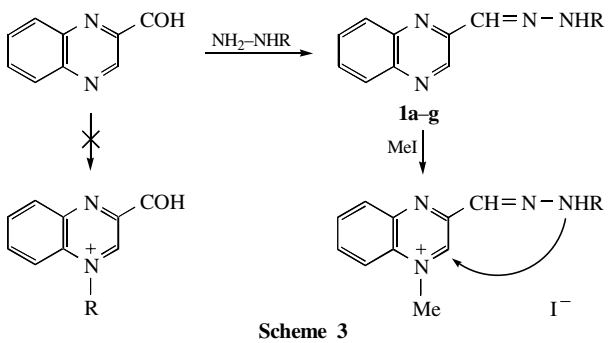
Scheme 1

Another approach to condensed aza heterocycles is based on a nucleophilic reaction at the C=N bond of an azine ring in combination with a nucleophilic attack at the *exo*-cyclic electrophilic centre (Scheme 2). This approach was illustrated by the reaction of 6-carbonyl-substituted 1,2,4-triazines with hydrazines.[6] In this paper, we report on a new methodology for the synthesis of fused quinoxalines from quinoxaline-2-carboxaldehyde.



Scheme 2

Attempts to perform a cyclization reaction between quinoxaline-2-carboxaldehyde and hydrazines without activation of the quinoxaline moiety were unsuccessful. We also failed to obtain N-alkyl quaternary salts by reacting quinoxaline-2-carboxaldehyde with methyl iodide or triethyloxonium tetrafluoroborate (the Meerwein reagent). Therefore, it was suggested to obtain fused quinoxalines in two steps: (i) condensation of quinoxaline-2-carboxaldehyde with hydrazines resulting in corresponding hydrazones **1a**–**g**; (ii) quarternization of quinoxalines **1a**–**g** with methyl iodide followed by an intramolecular nucleophilic attack of NH of the side-chain hydrazone moiety at the activated C=N bond of the pyrazinium cation (Scheme 3).



Scheme 3

Hydrazones **1a**–**g** prepared according to standard procedures† were subjected to N-alkylation with methyl iodide. It was expected that both nitrogen atoms of the pyrazine ring, N-1 and N-4, might be alkylated with methyl iodide. Indeed, the quaternization‡ of quinoxaline-2-carboxaldehyde *N*,*N*-dimethylhydrazone **1a** (a model compound incapable of a further intramolecular cyclization) gave a mixture of two quaternary salts **2a** and **3a** in

† *A common synthetic procedure for quinoxalin-2-carboxaldehyde hydrazones* **1a**–**g**. A solution of 1.0 g (6.2 mmol) of quinoxaline-2-carboxaldehyde in 15 ml of ethanol was added gradually to a solution of 6.2 mmol of hydrazine (or hydrazine hydrochloride) in 10 ml of water for 3–5 min with stirring at 60–70 °C. After stirring for additional 3–5 min, the reaction mixture was cooled to room temperature to give a hydrazone precipitate, which was filtered off and recrystallised.

1a: 66% (from water), mp 78–79 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.18 (s, 6H, NMe_2), 7.33 (s, 1H, CH=N), 7.6–7.8 (m, 2H, H-6, H-7), 7.9–8.0 (m, 2H, H-5, H-8), 9.28 (s, 1H, H-3). ^{13}C NMR ([$^2H_6$]DMSO) δ: 41.90 (qq, Me, $^1J_{C,H}$ 137.0 Hz, $^3J_{C,Me}$ 3.03 Hz), 126.95 (dm, CH=N, $^1J_{C,H}$ 166.0 Hz), 127.94, 128.51, 129.66 (m, C-5, C-6, C-7, C-8), 140.09 (ddd, C-4a, $^3J_{C,CH}$ 10.6 Hz, $^3J_{C,CH}$ 10.3 Hz, $^2J_{C,CH}$ 5.4 Hz), 141.37 (dd, C-8a, $^3J_{C,CH}$ 9.0 Hz, $^2J_{C,CH}$ 5.8 Hz), 142.56 (dd, C-3, $^1J_{C,H}$ 185.0 Hz, $^3J_{C,CH}$ 3.5 Hz), 153.33 (dd, C-2, $^2J_{C,CH}$ 9.4 Hz, $^2J_{C,CH}$ 6.2 Hz). Found (%): C, 51.9; H, 4.2; N, 30.0. Calc. for $C_{11}H_{12}N_4$ (%): C, 51.95; H, 3.89; N, 30.28.

1b: 75% (from aqueous ethanol), mp 210–212 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.85–7.35 (m, 5H, Ph), 7.70–7.90 (m, 2H, H-6, H-7), 7.90–8.10 (m, 2H, H-5, H-8), 8.01 (s, 1H, CH=N), 9.51 (s, 1H, H-3), 11.91 (s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 112.78 (d, C-3′, $^1J_{C,H}$ 160.6 Hz), 120.32 (dm, C-5′, $^1J_{C,H}$ 160.7 Hz, $^3J_{C,CH}$ 7.4 Hz), 128.36, 128.74, 128.94 and 130.14 (C-5, C-6, C-7, C-8), 129.13 (ddd, C-4′, $^1J_{C,H}$ 158.9 Hz, $^3J_{C,CH}$ 8.0 Hz, $^2J_{C,CH}$ 1.7 Hz), 134.38 (dd, CH=N, $^1J_{C,H}$ 166.4 Hz, $^3J_{C,CH}$ 3.7 Hz), 140.64 (ddd, C-4a, $^3J_{C,CH-3}$ 9.4, $^2J_{C,CH-6}$ 5.8 Hz, $^3J_{C,CH-5}$ 5.8 Hz), 141.37 (dd, C-8a, $^3J_{C,CH-7}$ 8.7 Hz, $^2J_{C,CH-8}$ 5.7 Hz), 142.90 (dd, C-3, $^1J_{C,H}$ 186.3 Hz, $^3J_{C,CH}$ 4.0 Hz), 143.91 (m, C-1′), 149.68 (dd, C-2, $^2J_{C,CH}$ 9.4 Hz, $^2J_{C,CH}$ 6.6 Hz). Found (%): C, 72.5; H, 4.7; N, 22.5. Calc. for $C_{15}H_{12}N_4$ (%): C, 72.56; H, 4.87; N, 22.57.

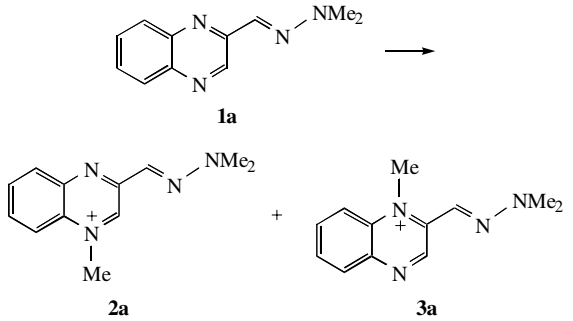
1c: 75% (from aqueous ethanol), mp 220–221 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.37 (s, 3H, Me), 7.04–7.22 (m, 4H, *p*-C_6H_4), 7.60–7.81 (m, 2H, H-6, H-7), 7.88–8.01 (m, 2H, H-5, H-8), 7.92 (s, 1H, CH=N), 9.45 (s, 1H, H-3), 11.09 (s, 1H, NH). Found (%): C, 73.5; H, 5.1; N, 21.1. Calc. for $C_{16}H_{14}N_4$ (%): C, 73.26; H, 5.38; N, 21.36.

1d: 87% (from acetic acid), mp 338–340 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.30–4.60 (br. s, 1H, COOH), 7.30 (d, 2H, H-2′, H-6′), 7.72–7.87 (m, 2H, H-6, H-7), 7.80 (d, 2H, H-3′, H-5′), 7.98–8.11 (m, 2H, H-5, H-8), 8.10 (s, 1H, CH=N), 9.50 (s, 1H, H-3), 11.5 (s, 1H, NH). Found (%): C, 65.8; H, 4.1; N, 19.1. Calc. for $C_{16}H_{12}N_4O_2$ (%): C, 65.70; H, 4.14; N, 19.17.

1e: 63% (from acetic acid), mp 255–256 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.35 (d, 2H, H-2′, H-6′), 7.76–7.89 (m, 2H, H-6, H-7), 8.00–8.12 (m, 2H, H-5, H-8), 8.16 (d, 2H, H-3′, H-5′), 8.20 (s, 1H, CH=N), 9.50 (s, 1H, H-3), 11.80 (s, 1H, NH). Found (%): C, 61.3; H, 3.7; N, 23.7. Calc. for $C_{15}H_{11}N_5O_2$ (%): C, 61.43; H, 3.78; N, 23.88.

1f: 70% (from aqueous ethanol), mp 96–98 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.00 (d, 3H, NMe), 7.40 (s, 1H, H-3), 7.58–7.75 (m, 2H, H-6, H-7), 7.81–8.99 (m, 2H, H-5, H-8), 8.40 (d, 1H, NH), 9.20 (s, 1H, CH=N). Found (%): C, 64.8; H, 5.2; N, 29.6. Calc. for $C_{10}H_{10}N_4$ (%): C, 64.50; H, 5.41; N, 30.09.

1g: 72% (from aqueous ethanol), mp 91–92 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.50 (d, 2H, CH_2Ph), 7.20–7.40 (m, 5H, Ph), 7.60 (s, 1H, H-3), 7.65–7.79 (m, 2H, H-6, H-7), 7.87–8.02 (m, 2H, H-5, H-8), 8.90 (t, 1H, NH), 9.20 (s, 1H, CH=N). Found (%): C, 73.1; H, 5.4; N, 20.9. Calc. for $C_{16}H_{14}N_4$ (%): C, 73.26; H, 5.38; N, 21.36.

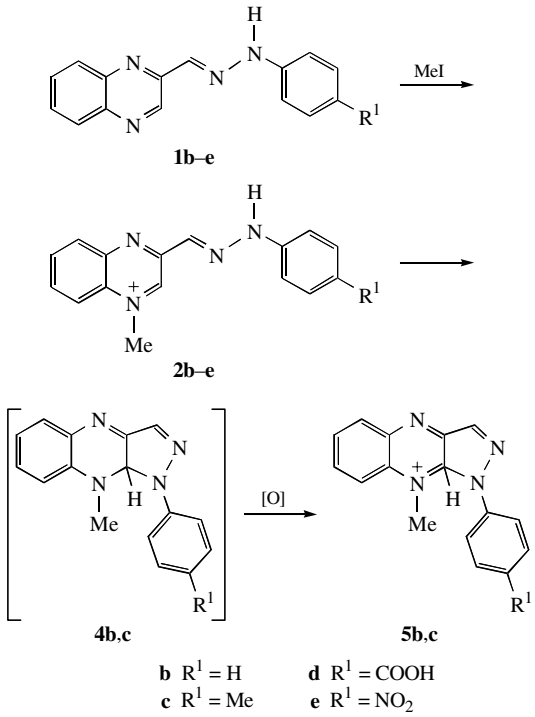


Scheme 4

the ratio 4:1 (^{1}H NMR data).

The quaternization of quinoxalines **1b**,**c** with methyl iodide in DMSO proceeds more selectively to result in the formation of $N_{(4)}$-quaternary salts **2b**,**c**. Salts **2b**,**c** undergo a spontaneous intramolecular nucleophilic attack leading to σ^H-adducts **4a**,**b** followed by their oxidation into pyrazolo[3,4-*b*]quinoxalines **5b**,**c**. This two-step reaction can be regarded as intramolecular nucleophilic substitution of hydrogen (S_N^H).[7] Indeed, the elimination of hydrogen is facilitated by atmospheric oxygen, as it takes place in many other S_N^H reactions.[7] In case of phenylhydrazones **1d**,**e** bearing electron-withdrawing groups (COOH, NO_2) at the *para*-position, the nucleophilic character of NH of the hydrazone moiety is insufficient to cause the S_N^H process; therefore, only the N_4-methylation reaction takes place affording quaternary salts **2d**,**e** (Scheme 5).

Evidence for the structure of pyrazoloquinoxalines **5b**,**c** is provided by ^{1}H and ^{13}C NMR data.§ The X-ray diffraction analysis of compound **5b** revealed that the pyrazoloquinoxaline system is planar and the methyl group is attached to the quaternary nitrogen, while the phenyl group is not coplanar with the tricyclic system due to hindrance caused by the N-methyl substituent (Figure 1).¶



Scheme 5

In N-alkyl-substituted quinoxalin-2-carboxaldehyde hydrazones **1f**,**g** the nucleophilic character of NH is enhanced, and the intramolecular reaction can be carried out on reflux in aqueous ethanol in the presence of a few drops of sulfuric acid to afford

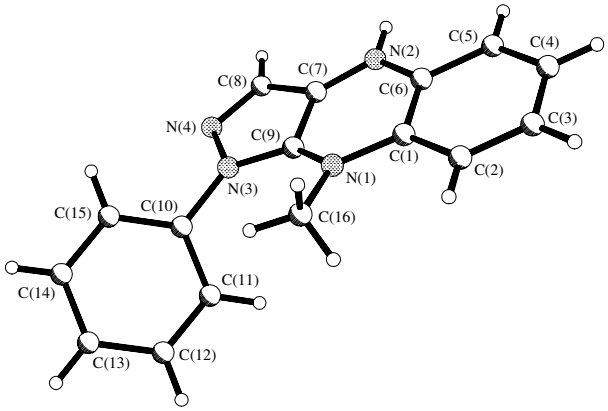


Figure 1 Molecular structure of pyrazolo[3,4-*b*]quinoxalinium iodide **5b**.

‡ *Quaternization of quinoxalin-2-carboxaldehyde phenylhydrazones* **1a–e** *with methyl iodide*. A solution of the corresponding quinoxalin-2-carboxaldehyde phenylhydrazone (2 mmol) in 2 ml of DMSO and 2 ml of methyl iodide was heated in water bath at 40–50 °C and refluxed for 3 h. The precipitate obtained after cooling the reaction mixture to room temperature was filtered off, washed with diethyl ether, dried in air and recrystallised to give either quinoxalinium salts **2d**,**e** or pyrazolo[3,4-*b*]-quinoxalinium salts **5b**,**c**. Attempts to isolate individual salts **2a** and **3a** derived from quaternization of quinoxaline **1a** with methyl iodide by recrystallization were unsuccessful.

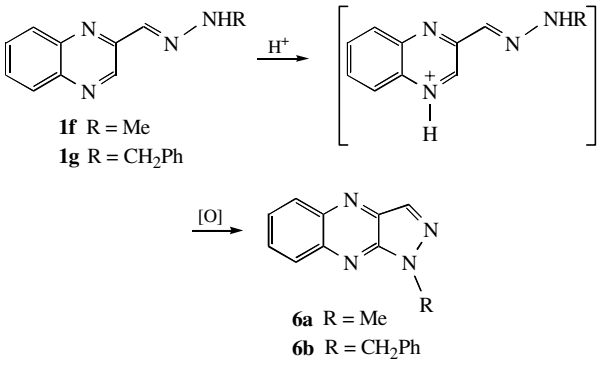
2d: 65% (from AcOH–DMSO), mp 360–362 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.0 (br. s, 1H, COOH), 4.70 (s, 3H, N$^+$Me), 7.48 (d, 2H) and 7.93 (d, 2H, *p*-C_6H_4), 8.11–8.59 (m, 4H, H-5, H-6, H-7, H-8), 8.23 (s, 1H, CH=N), 10.0 (s, 1H, H-3), 11.98 (s, 1H, NH). Found (%): C, 46.7; H, 3.4; N, 12.6. Calc. for $C_{17}H_{15}N_4O_2I$ (%): C, 47.02; H, 3.47; N, 12.90.

2e: 67% (from AcOH–DMSO), mp 314–315 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.79 (s, 3H, N$^+$Me) 7.56 (d, 2H, H-2′, H-6′), 8.16–8.28 (m, 2H, H-3′, H-5′), 8.16–8.59 (m, 4H, H-5, H-6, H-7, H-8), 8.31 (s, 1H, CH=N), 10.13 (s, 1H, H-2), 12.26 (s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 45.60 (dd, N$^+$Me, $^1J_{C,H}$ 146.1 Hz, $^3J_{C,CH}$ 4.6 Hz), 113.25 (ddd, C-2′, C-6′, $^1J_{C,H}$ 166.4 Hz, $^3J_{C,CH}$ 5.7 Hz, $^2J_{C,CH}$ 2.4 Hz), 119.53, 133.79, 134.03 and 136.79 (C-5, C-6, C-7, C-8), 125.83 (dd, C-3′, C-5′, $^1J_{C,H}$ 167.6 Hz, $^3J_{C,CH}$ 4.6 Hz), 129.73 (m, C-8a), 130.15 (dd, CH=N, $^1J_{C,H}$ 171.3 Hz, $^3J_{C,CH}$ 5.1 Hz), 141.16 (dm, C-2, $^1J_{C,H}$ 197.7 Hz), 140.73 (tt, C-4′, $^2J_{C,H}$ 9.6 Hz, $^3J_{C,CH}$ 3.4 Hz), 144.01 (m, C-4a), 148.82 (m, C-1′), 151.46 (dd, C-3, $^3J_{C,CH}$ 7.5 Hz, $^2J_{C,CH}$ 4.3 Hz). Found (%): C, 44.1; H, 3.3; N, 16,4. Calc. for $C_{16}H_{14}N_5O_2I$ (%): C, 44.16; H, 3.24; N, 16.09.

§ **5b**: 62% (from water), mp 206–208 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.19 (s, 3H, N$^+$Me), 7.70–7.88 (m, 5H, Ph), 8.20–8.78 (m, 4H, H-5, H-6, H-7, H-8), 9.61 (s, 1H, CH=N). ^{13}C NMR ([$^2H_6$]DMSO) δ: 38.65 (q, N$^+$Me, $^1J_{C,H}$ 146.3 Hz), 117.77, 130.32, 132.59 and 137.83 (C-5, C-6, C-7, C-8), 127.86 (dm, $^1J_{C,H}$ 166.1, C-2′, C-6′), 129.7 (m, C-8a), 130.06 (ddd, C-3′, C-5′, $^1J_{C,H}$ 165.4 Hz, $^3J_{C,CH}$ 6.1 Hz, $^2J_{C,CH}$ 3.1 Hz), 131.26 (dm, C-4′, $^1J_{C,H}$ 163.5 Hz, $^3J_{C,CH}$ 7.2 Hz), 132.97 (m, C-9a), 137.59 (m, C-1′), 140.31 (dd, C-4a, $^2J_{C,CH}$ 5.4 Hz, $^3J_{C,CH}$ 9.7 Hz), 140.34 (d, C-3, $^1J_{C,H}$ 204.8 Hz), 145.79 (d, C-3a, $^2J_{C,CH}$ 11.0 Hz). Found (%): C, 49.4; H, 3.4; N, 14.2. Calc. for $C_{16}H_{14}N_4I$ (%): C, 49.38; H, 3.62; N, 14.20.

5c: 71% (from water), mp 304–305 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.83–1.92 (m, 3H, MePh), 4.18 (s, 3H, N$^+$Me), 7.58 (d, 2H), and 7.74 (d, 2H, *p*-C_6H_4), 8.17–8.78 (m, 4H, H-5, H-6, H-7, H-8), 9.6 (s, 1H, CH=N). Found (%): C, 50.8; H, 3.5; N, 14.0. Calc. for $C_{17}H_{15}N_4I$ (%): C, 50.77; H, 3.76; N, 13.93.

¶ *Crystallographic data for* **5b**: crystals of $C_{16}H_{13}N_4I$ are monoclinic at 293 K, space group *Cc*, a = 6.689(3), b = 33.689(15), c = 7.224(3) Å, β = 112.416(10)°, V = 1504.9(12) Å^3, Z = 4, M = 389.21, d_{calc} = 1.713 g cm^{-3}, μ(MoKα) = 2.126 cm^{-1}, F(000) = 760. Intensities of 3863 reflections were measured with a Smart 1000 CCD diffractometer at 293 K [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 62°$], and 2476 independent reflections (R_{int} = = 0.0260) were used in further refinement. The absorption correction was carried out semiempirically from equivalents. The structure was solved by the heavy atom method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The positions of the hydrogen atoms were calculated geometrically and refined in a ridding model. The refinement converged to wR_2 = 0.0899 and GOF = 0.984 for all independent reflections [R_1 = 0.0395 was calculated against F for 1912 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/106.



Scheme 6

pyrazolo[3,4-*b*]quinoxalines **6a**,**b** in good yields (Scheme 6).†† In this case, the pyrazine ring is activated by N-protonation; indeed, no reaction was observed without an acid.

†† *Intramolecular cyclization of quinoxalin-2-carboxaldehyde alkylhydrazones* **1f**,**g** *into pyrazolo[3,4-*b*]quinoxalines* **6a**,**b**. A few drops of sulfuric acid were added to a solution of quinoxalin-2-carboxaldehyde alkylhydrazone (2 mmol) in 10 ml of ethanol and 10 ml of water to adjust pH 2, and the reaction mixture was refluxed for 4 h. The precipitate obtained after cooling and neutralization of the reaction mixture was filtered off and recrystallised to give pyrazolo[3,4-*b*]quinoxalines **6a**,**b**.

6a: 75% (from aqueous ethanol), mp 129–130 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.18 (s, 3H, NH*Me*), 7.80 (tm, 2H), 7.91 (tm, 2H, H-6, H-7), 8.11 and 8.20 (2dd, 2×2H, H-5, H-8), 8.66 (s, 1H, CH=N). ^{13}C NMR ([$^2H_6$]DMSO) δ: 33.76 (q, Me, $^1J_{C,H}$ 140.4 Hz), 127.55, 128.05, 129.65 and 130.64 (C-5, C-6, C-7, C-8), 132.71 (d, C-3, $^1J_{C,H}$ 197.0 Hz), 136.34 (d, C-3a, $^1J_{C,H}$ 10.11 Hz), 140.33 (ddd, C-4a, $1J_{C,H}$ 9.88 Hz, $^2J_{C,CH}$ 5.52 Hz, $^2J_{C,CH}$ 1.23 Hz), 140.61 (dd, C-8a, $^1J_{C,H}$ 10.11 Hz, $^2J_{C,CH}$ 5.52 Hz), 141.45 (m, C-9a). Found (%): C, 65.3; H, 4.5; N, 30.4. Calc. for $C_{10}H_8N_4$ (%): C, 65.21; H, 4.38; N, 30.42.

6b: 80% (from aqueous ethanol), mp 113–114 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.80 (s, 2H, CH_2Ph), 7.25–7.35 (m, 5H, Ph), 7.80–8.00 (m, 2H, H-6, H-7), 8.15–8.31 (m, 2H, H-5, H-8), 8.82 (s, 1H, CH=N). Found (%): C, 73.7; H, 4.3; N, 21.2. Calc. for $C_{16}H_{12}N_4$ (%): C, 73.83; H, 4.65; N, 21.52.

Although several approaches to the synthesis of pyrazolo-[3,4-*b*]quinoxalines have been described in the literature,[8–10] we believe that the above two-steps procedure involving condensation of the carbonyl group ring with hydrazines (to introduce a nucleophilic fragment into a side-chain of pyrazines) followed by intramolecular S_N^H reaction at the activated C=N bond is a promising methodology for the synthesis of fused 1,4-diazines.

This work was supported by the US Civilian Research and Development Foundation (award no. REC-005) and the Russian Foundation for Basic Research (grant no. 01-03-96456a).

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Received: 28th January 2002; Com. 02/1886