

2,3-Dichloro-1-alkylpyrazinium tetrafluoroborates: the synthesis and reactions with nucleophiles

Gennady L. Rusinov, Pavel A. Slepukhin, Valerii N. Charushin* and Oleg N. Chupakhin

Institute of Organic Synthesis, Urals Branch of the Russian Academy of Sciences, 620219 Ekaterinburg, Russian Federation.
Fax: +7 3432 74 5191; e-mail: charushin@prm.uran.ru

10.1070/MC2001v011n02ABEH001381

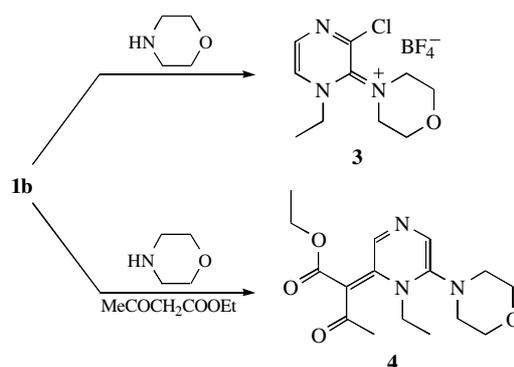
The alkylation of 2,3-dichloropyrazine with the Meerwein reagents $R_3O^+BF_4^-$ ($R = Me$ or Et) afforded 1-alkyl-2,3-dichloropyrazinium tetrafluoroborates, which were transformed into mono- or disubstitution products, while the reaction of these salts with 1,4-N,X-dinucleophiles resulted in fused heterocyclic systems.

The structural modification of pyrazines is of great interest for chemists since their derivatives, including fused pyrazines, are biologically active compounds.^{1–4} A common practice to modify the structure of pyrazines is the use of nucleophilic displacement reactions. In particular, nucleophilic substitution for chlorine atoms in 2,3-dichloropyrazine leading to fused pyrazines is well documented.^{5,6} The *ortho*-cyclisation based on the diaddition of bifunctional nucleophiles at C-2 and C-3 (C-5 and C-6) carbon atoms in *N*-alkylpyrazinium salts also seems to be a promising synthetic approach to fused pyrazines.^{7,8}

By the reactions of 2,3-dichloropyrazine with the Meerwein reagents $R_3O^+BF_4^-$ ($R = Me$ or Et) in CH_2Cl_2 at 20 °C, we first prepared 1-alkyl-2,3-dichloropyrazinium tetrafluoroborates **1a,b** (Schemes 1 and 2). Salts **1a,b** were expected to be highly reactive towards nucleophiles. Indeed, they are rather sensitive to water; therefore, dry aprotic solvents (for instance, acetonitrile) are required for handling **1a,b** to avoid their transformations into the corresponding 1-alkyl-3-chloropyrazin-2-ones. Because of the high reactivity of salts **1a,b**, we failed to find an appropriate solvent for their recrystallisation and remove impurities from **1a**, whereas salt **1b** gave satisfactory elemental analysis data.[†]

We supposed that salts **1a,b** exhibit an ambident character in respect to either nucleophilic addition at C-5 (C-6) or displacement reactions at C-2 (C-3) carbons.

Compounds **1a,b** were found to react easily with ammonia in MeCN at 20 °C affording 1-alkyl-3-chloro-2-iminopyrazine hydrotetrafluoroborates **2a,b**. Unlike 2-chloropyrazine reacting with ammonia to 2-aminopyrazine exclusively *via* the ANRORC mechanism (the Addition of Nucleophile at C-6–Ring Opening–Ring Closure),⁹ in the reactions of **1a,b** with ammonia the classical $S_N(AE)^{ipso}$ mechanism takes place, and no ANRORC products were observed (Scheme 1). This is evident from the ¹H and ¹³C NMR spectra of 1-alkyl-3-chloro-2-iminopyrazinium

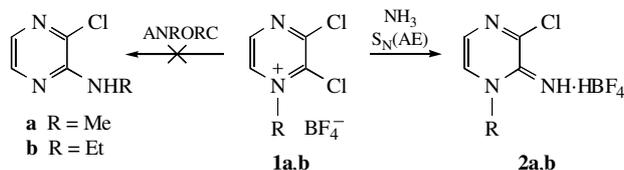


Scheme 2

hydrotetrafluoroborates **2a,b**.[‡] In particular, the signal of the NCH_2Me fragment in the ¹H NMR spectrum of **2b** is observed as a quartet at 4.19 ppm, while the methylene protons of the NCH_2Me group in 3-chloro-2-ethylaminopyrazine trifluoroacetate (reference compound) resonate at 3.45 ppm. Thus, the multiplicity of the C-6 resonance signal in the ¹³C NMR spectrum (double doublet of triplets) with the coupling constants $^1J_{C-6,H-6} = 192.5$ Hz, $^2J_{C-6,H-5} = 13.5$ Hz and $^3J_{C-6,NCH_2} = 4.5$ Hz provides unequivocal evidence for the structure of **2b**.

In a similar way the secondary morpholine reacts with 2,3-dichloropyrazinium salt **1b** to form monosubstitution product **3**[§] (Scheme 2); only minor quantities of the corresponding disubstitution product were observed in the ¹H NMR spectra of the reaction mixtures. Note that, when the same reaction of **1b** with morpholine was carried out in the presence of an excess of ethyl acetoacetate, *tele*-substitution product **4** was isolated from the complex reaction mixture (Scheme 2).

Although the yield of compound **4** was rather small (8%), a nucleophilic attack at the unsubstituted C-6 carbon resulting in the *tele*-substitution of a chloro atom at C-3 is a nice illustration of the ambident character of 1-alkyl-2,3-dichloropyrazinium salts. The structure of **4** was found by two-dimensional NMR. The



Scheme 1

[†] 2,3-Dichloro-1-ethylpyrazinium tetrafluoroborate **1b**. Triethyloxonium tetrafluoroborate (1.9 g, 10 mmol) was added to a solution of 2,3-dichloropyrazine (1.4 g, 10 mmol) in 10 ml of CH_2Cl_2 . The reaction mixture was stirred for 6 h at 20 °C. The crystals obtained were filtered off, washed with CH_2Cl_2 and dried in air to give 1.6 g (61%) of **1b**, mp 213–214 °C. ¹H NMR (CD_3CN) δ : 9.05 (br. d, 1H, 6-H, J 3.5 Hz), 8.83 (d, 1H, 5-H, J 3.5 Hz), 4.83 (q, 2H, NCH_2 , J 6.3 Hz), 1.61 (t, 3H, Me, J 6.3 Hz). Found (%): C, 27.22; H, 2.80; N, 10.68. Calc. for $C_6H_7BCl_2F_4N_2$ (%): C, 27.21; H, 2.66; N, 10.58.

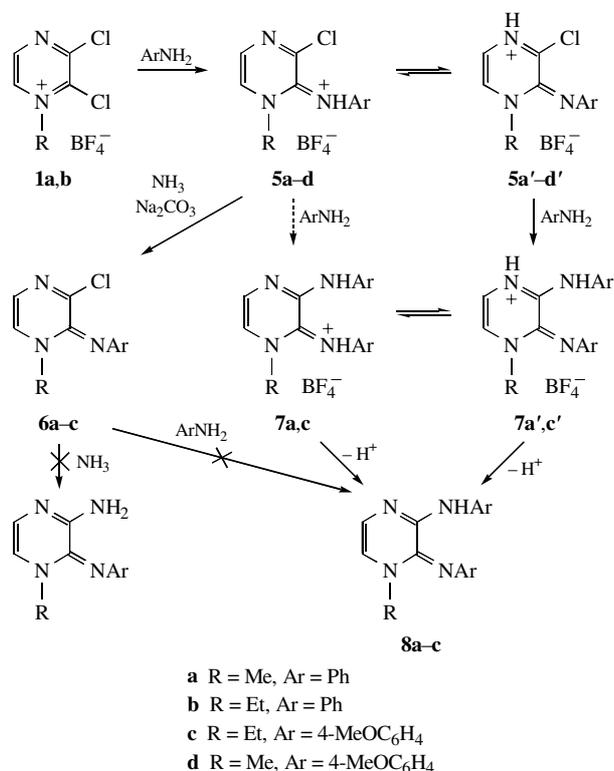
Compound **1a** was obtained analogously from 2,3-dichloropyrazine and trimethyloxonium tetrafluoroborate, yield 77%, mp 192–193 °C. ¹H NMR (CD_3CN) δ : 9.00 (br. d, 1H, 6-H, J 3.4 Hz), 8.80 (d, 1H, 5-H, J 3.4 Hz), 4.41 (s, 3H, NMe). Found (%): C, 23.00; H, 1.98; N, 10.49. Calc. for $C_5H_3BCl_2F_4N_2$ (%): C, 23.94; H, 2.01; N, 11.17.

[‡] 3-Chloro-1-ethylpyrazin-2-iminium tetrafluoroborate **2b**. Ammonia was added to a solution of 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1b** (0.300 g, 1.132 mmol) in 5 ml of MeCN. After stirring at room temperature for 10 min, the precipitated ammonium chloride was filtered off, followed by evaporation of the solvent. The residue was dissolved in MeCN and precipitated with diethyl ether to yield 3-chloro-1-ethylpyrazine-2-iminium tetrafluoroborate **2b**, 0.104 g (37%), mp 162–164 °C. ¹H NMR (CD_3CN) δ : 7.85 and 7.80 (2d, 2×1H, 6-H and 5-H, J 4.2 Hz), 6.5–9.0 (br. s, 2H, NH), 4.19 (q, 2H, NCH_2Me , J 7.3 Hz), 1.44 (t, 3H, NCH_2Me , J 7.3 Hz). ¹³C NMR ($[^2H_6]DMSO$) δ : 146.64 (m, C-2), 140.31 (dd, C-3, $^3J_{C-3,H-5} = 12.8$ Hz, $^3J_{C-3,NH} = 1.7$ Hz), 130.60 (ddt, C-6, $^1J_{C-6,H-6} = 192.5$ Hz, $^2J_{C-6,H-5} = 13.5$ Hz, $^3J_{C-6,NCH_2} = 4.5$ Hz), 128.65 (dd, C-5, $^1J_{C-5,H-5} = 197.9$ Hz, $^2J_{C-5,H-6} = 6.3$ Hz), 50.21 (tq, NCH_2 , $^1J = 141.5$ Hz, $^2J = 4.3$ Hz), 12.40 (qt, NCH_2Me , $^1J = 129.5$ Hz, $^2J = 3.7$ Hz). Found (%): C, 29.55; H, 3.95; N, 17.07. Calc. for $C_6H_6BClF_4N_3$ (%): C, 29.37; H, 3.70; N, 17.12.

Compound **2a** was obtained analogously from **1a** and ammonia; product **2a** was recrystallised from water. For **2a**: yield 83%, mp 148–149 °C. ¹H NMR (CD_3CN) δ : 7.84 and 7.77 (2d, 1H, 6-H and 5-H, J 4.2 Hz), 3.81 (s, 3H, NMe), 9.00–11.00 (br. s, 2H, NH). Found (%): C, 25.60; H, 3.32; N, 17.60. Calc. for $C_5H_7BClF_4N_3$ (%): C, 25.96; H, 3.05; N, 18.15.

signals in the ^1H and ^{13}C NMR spectra of **4**[¶] were assigned on the basis of ^1H – ^{13}C correlation spectroscopy, which also enabled us to establish the geometrical configuration of the ylidene substituent at C-2.

In the reactions of **1a,b** with arylamines in MeCN at 20 °C substitution of either one (**5a–d**, **6a–c**)^{††} or two (**7a–c**, **8a–c**)^{‡‡} chlorine atoms takes place (Scheme 3). In these transformations, proton transfer from the exocyclic amino group to N-4 of the



Scheme 3

[§] **3-Chloro-1-ethyl-2-(morpholin-4-yl)pyrazinium tetrafluoroborate 3**. Morpholine (0.260 ml, 3 mmol) was added dropwise to a solution of 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1b** (0.396 g, 1.5 mmol) in 5 ml of MeCN. After stirring at room temperature for 10 min, the precipitated morpholine hydrochloride was filtered off, MeCN was evaporated, and the residue was recrystallised from propan-2-ol to yield 3-chloro-1-ethyl-2-(morpholin-4-yl)pyrazinium tetrafluoroborate **3**, 0.258 g (55%), mp 124–125 °C. ^1H NMR ($[\text{D}_6]\text{DMSO}$) δ : 8.72 and 8.63 (2d, 2 \times 1H, 5-H and 6-H, J 3.9 Hz), 4.46 (q, 2H, NCH₂Me, J 7.2 Hz), 3.82 (t, 4H, CH₂OCH₂, J 4.8 Hz), 3.54 (t, 4H, CH₂NCH₂, J 4.8 Hz), 1.52 (t, 3H, Me, J 7.2 Hz). Found (%): C, 37.93; H, 4.69; N, 13.28. Calc. for C₁₀H₁₅BClF₄N₃O (%): C, 38.07; H, 4.79; N, 13.32.

[¶] **Ethyl 2-[1-Ethyl-6-(morpholin-4-yl)-1H-pyrazin-2-ylidene]-3-oxobutylate 4**. Morpholine (0.104 ml, 1.2 mmol) was added to a solution of ethyl acetoacetate (0.50 ml, 4 mmol) and 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1b** (0.106 g, 0.4 mmol) in 5 ml of MeCN. After stirring at room temperature for 10 min, the precipitated morpholine hydrochloride was filtered off, and the solvent was evaporated to dryness. The residue was separated by column chromatography on silica gel first with acetone and then with methanol to collect an orange fraction. Methanol was evaporated, and the product was recrystallised from *n*-octane. Yield 0.010 g (8%), mp 130–132 °C. ^1H NMR (CDCl₃) δ : 8.74 (s, 1H, H-3), 7.74 (s, 1H, H-5), 4.38 (q, 2H, NCH₂, J 7.0 Hz), 4.21 (q, 2H, OCH₂, J 7.1 Hz), 3.87 (t, 4H, CH₂OCH₂, J 4.6 Hz), 3.22 (t, 4H, CH₂NCH₂, J 4.6 Hz), 2.47 (s, 3H, COMe), 1.3–1.2 (m, 6H, 2Me). ^{13}C NMR (CDCl₃) δ : 190.28 (q, MeCO, 2J 5.9 Hz), 167.78 (t, COOCH₂, 3J 3.1 Hz), 154.52 (m, C-2, $^2J_{\text{C-2,H-3}}$ 12.6 Hz, $^3J_{\text{C-2,NCH}_2}$ 3.6 Hz), 150.25 (dd, C-3, $^1J_{\text{C-3,H-3}}$ 199.6 Hz, $^3J_{\text{C-3,H-5}}$ 10.0 Hz), 149.19 (m, C-6, $^2J_{\text{C-6,H-5}}$ 7.7 Hz), 127.59 (m, C-5, $^1J_{\text{C-5,H-5}}$ 188.9 Hz, $^3J_{\text{C-5,H-3}}$ 12.7 Hz), 98.61 [s, (MeCO)-(COOEt)C=], 66.16 (m, CH₂OCH₂, 1J 138.2 Hz), 59.11 (m, OCH₂Me, 1J 146.5 Hz, 2J 4.4 Hz), 52.78 (t, NCH₂Me, 1J 146.1 Hz), 51.32 [t, N(CH₂)₂, 1J 138.4 Hz], 29.83 (q, COMe, 1J 127.8 Hz), 14.99 (qt, 1J 128.9 Hz, 2J 3.6 Hz) and 14.58 (qt, 1J 126.6 Hz, 2J 2.5 Hz) (OCH₂Me and NCH₂Me). Found (%): C, 59.76; H, 7.56; N, 13.00. Calc. for C₁₆H₂₃N₃O₄ (%): C, 59.80; H, 7.21; N, 13.01.

pyrazine ring is an important step since the cationic structures like **5a–d** are undoubtedly more vulnerable for a nucleophilic attack at C-3 than the neutral species. Indeed, non-protonated iminopyrazine **6a–c** is unreactive towards arylamines and ammonia under similar conditions. A plausible way for substitution of the second chlorine atom at C-3 in protonated 2-iminopyrazines **5a–d** is presented in Scheme 3.

The reactions of **1a,b** with 1,4-N,X-dinucleophiles, such as *ortho*-phenylenediamine and *ortho*-aminophenol, in MeCN at 20 °C result in the formation of N-alkyl derivatives of diazaphenazine and diazaphenoxazine in good yields (Scheme 4).^{§§} Contrary to that, 6,7-difluoro substituted 1-ethylquinoxalium salts were found to react with bifunctional nucleophiles to give fused quinoxalines through the diaddition reaction at C-2 and C-3 carbons of the pyrazine ring instead of the replacement of two fluorine atoms.¹⁰

This work was supported in part by the US Civilian Research and Development Foundation (award no. REC-005).

^{††} **3-Chloro-1-methylpyrazin-2-[(4-methoxyphenyl)iminium] tetrafluoroborate 5d**. A solution of *para*-anizidine (0.098 g, 0.8 mmol) in 1.5 ml of MeCN was added to a solution of 2,3-dichloro-1-methylpyrazinium tetrafluoroborate **1a** (0.100 g, 0.4 mmol) in 1.5 ml of MeCN. The precipitate of *para*-anizidine hydrochloride obtained after stirring for 0.5 h was filtered off, the solvent was evaporated, and the residue was recrystallised from water to yield 1-methyl-3-chloropyrazine-2-(4-methoxyphenylimine) tetrafluoroborate, 0.116 g (86%), mp 129–130 °C. ^1H NMR ($[\text{D}_6]\text{DMSO}$) δ : 8.32 and 8.03 (2d, 2 \times 1H, 5-H and 6-H, J 4.1 Hz), 7.10 (m, 4H, Ar), 3.84 and 3.81 (2s, 2 \times 3H, NMe and OMe), 9–11 (br. s, 1H, NH). Found (%): C, 42.78; H, 3.71; N, 12.45. Calc. for C₁₂H₁₃BClF₄N₃O (%): C, 42.72; H, 3.58; N, 12.45.

Compound **5c** was obtained analogously, yield 86%, mp 102 °C. ^1H NMR ($[\text{D}_6]\text{DMSO}$) δ : 8.32 and 8.0 (2d, 2 \times 1H, 5-H and 6-H, J 4.0 Hz), 7.3–6.9 (m, 4H, Ar), 4.3 (q, 2H, NCH₂), 1.3 (t, 3H, Me). Found (%): C, 44.46; H, 4.36; N, 11.94. Calc. for C₁₃H₁₅BClF₄N₃O (%): C, 44.42; H, 4.30; N, 11.95.

3-Chloro-1-methylpyrazin-2-phenylimine 6a. A solution of aniline (0.018 g, 0.2 mmol) in 1.5 ml of MeCN was added to a solution of 2,3-dichloro-1-methylpyrazinium tetrafluoroborate **1a** (0.050 g, 0.2 mmol) in 1.5 ml of MeCN. The precipitate of aniline hydrochloride obtained after stirring for 0.5 h was filtered off, the solvent was evaporated, and the residue was recrystallised from aqueous 60% MeOH to yield 1-methyl-3-chloropyrazine-2-phenylimine **6a**, 0.017 g (39%), mp 106 °C. ^1H NMR (CDCl₃) δ : 7.1–6.7 (m, 7H, Ar, 5-H, 6-H), 3.42 (s, 3H, NMe). Found (%): C, 59.95; H, 4.39; N, 19.18. Calc. for C₁₁H₁₀ClN₃ (%) : C, 60.14; H, 4.59; N, 19.13.

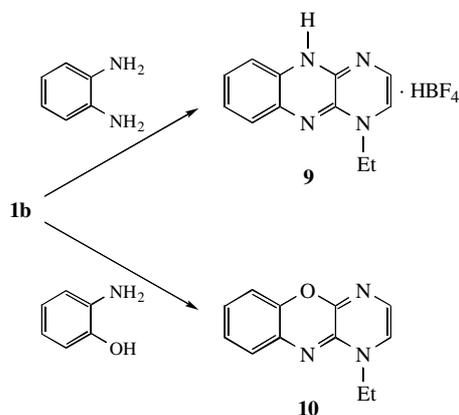
Compounds **6b,c** were prepared analogously. For **6b**: yield 75%, mp 64 °C. ^1H NMR (CDCl₃) δ : 7.10–6.7 (m, 7H, Ar, 5-H, 6-H), 3.91 (q, 2H, NCH₂, J 7.1 Hz), 1.362 (t, 3H, Me, J 7.1 Hz). Found (%): C, 61.43; H, 5.19; N, 17.77. Calc. for C₁₂H₁₂ClN₃ (%) : C, 61.67; H, 5.18; N, 17.98.

For **6c**: yield 94%, mp 109 °C. ^1H NMR (CDCl₃) δ : 7.1–6.7 (m, 6H, Ar, 5-H, 6-H), 3.91 (q, 2H, NCH₂Me, J 7.1 Hz), 3.78 (s, 3H, OMe) 1.34 (t, 3H, NCH₂Me, J 7.1 Hz). Found (%): C, 58.93; H, 5.62; N, 15.93. Calc. for C₁₃H₁₄ClN₃O (%) : C, 59.21; H, 5.35; N, 15.93.

^{‡‡} **1-Ethyl-3-phenylaminopyrazin-2-phenylimine 8b**. A solution of aniline (0.5 ml) in 3 ml of MeCN was added dropwise to a solution of 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1b** (0.265 g, 1 mmol) in 4 ml of MeCN, and the reaction mixture was stirred for 0.5 h. The precipitate of aniline hydrochloride was filtered off, and the solvent was evaporated. The residue was recrystallised from water, washed with an aqueous Na₂CO₃ solution, and dried in air to give 0.266 g (91%) of 1-ethyl-3-phenylpyrazine-2-phenyliminium **8b**, mp 118–119 °C. ^1H NMR (CDCl₃) δ : 8.70 (s, 1H, NH), 7.7–6.3 (m, 12H, Ar, 5-H and 6-H), 3.69 (q, 2H, NCH₂Me, J 7.2 Hz), 1.11 (t, 3H, NCH₂Me, J 7.2 Hz). Found (%): C, 74.41; H, 6.17; N, 19.46. Calc. for C₁₈H₁₈N₄ (%) : C, 74.46; H, 6.25; N, 19.30.

Compounds **8a,c** were obtained analogously. For **8a**: yield 83.6%, mp 122–123 °C. ^1H NMR (CDCl₃) δ : 8.90 (br. s, 1H, NH), 7.70–6.80 (m, 10H, Ar), 6.61 and 6.17 (2d, 2 \times 1H, 5-H and 6-H, J 4.8 Hz), 3.06 (s, 3H, NMe). Found (%): C, 73.72; H, 6.24; N, 20.12. Calc. for C₁₇H₁₆N₄ (%) : C, 73.89; H, 5.84; N, 20.27.

For **8c**: yield 73%, mp 126–127 °C. ^1H NMR ($[\text{D}_6]\text{DMSO}$) δ : 8.79 (s, 1H, NH), 7.70–6.30 (m, 10H, Ar, 5-H and 6-H), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.52 (q, 2H, NCH₂Me, J 7.1 Hz), 1.11 (t, 3H, NCH₂Me, J 7.1 Hz). Found (%): C, 68.63; H, 6.39; N, 15.63. Calc. for C₂₀H₂₂N₄O₂ (%) : C, 68.55; H, 6.33; N, 15.99.



Scheme 4

References

- 1 G. B. Barlin, in *The Chemistry of Heterocyclic Compounds*, eds. A. Wessberger and E. C. Taylor, Wiley Interscience, New York, 1982, vol. 41.
- 2 G. W. H. Cheesman and R. F. Cookson, in *The Chemistry of Heterocyclic Compounds*, eds. A. Wessberger and E. C. Taylor, Wiley Interscience, New York, 1979, vol. 35.
- 3 W. Kaim, *Angew. Chem.*, 1983, **95**, 201.
- 4 J. A. Maga, *Food Rev. Int.*, 1992, **8** (4), 479.
- 5 V. N. Charushin, M. G. Ponizovsky and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 1985, 1011 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1985, **21**, 839].
- 6 C. O. Okafor, *J. Heterocycl. Chem.*, 1981, **18**, 405.
- 7 V. N. Charushin, O. N. Chupakhin and H. C. van der Plas, *Adv. Heterocycl. Chem.*, 1988, **43**, 301.
- 8 O. N. Chupakhin, V. N. Charushin and A. I. Chernyshev, *Prog. NMR Spectroscopy*, 1988, **20** (2), 95.
- 9 P. J. Lont, H. C. van der Plas and A. J. Verbeek, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 949.
- 10 V. N. Charushin, G. A. Mokrushina, G. M. Petrova, G. G. Alexandrov and O. N. Chupakhin, *Mendeleev Commun.*, 1998, 133.

Received: 3rd October 2000; Com. 00/1707

9-Ethyl-6,9-diazaphendiazine tetrafluoroborate 9. A solution of **1b** (0.265 g, 1.0 mmol) in 2 ml of MeCN was added to a solution of *ortho*-phenylenediamine (0.216 g, 2 mmol) in 1 ml of MeCN. After 0.5 h, the precipitate of *ortho*-phenylenediamine hydrochloride was filtered off, and the solvent was evaporated. The residue was recrystallised from isopropanol. Yellow crystals were filtered off and dried in air to give 9-ethyl-6,9-diazaphendiazine tetrafluoroborate **9**, 0.092 g (31%), mp 225 °C. ¹H NMR ([²H₆]DMSO) δ: 6.90–6.70 (m, 4H, Ar), 6.42 and 6.31 (2d, 2×1H, 6-H and 5-H, *J* 5.2 Hz), 3.67 (q, 2H, NCH₂Me, *J* 7.2 Hz), 1.30 (t, 3H, NCH₂Me, *J* 7.2 Hz). Found (%): C, 47.96; H, 4.39; N, 18.46. Calc. for C₁₂H₁₃BF₄N₄ (%): C, 48.03; H, 4.37; N, 18.67.

9-Ethyl-6,9-diazaphenoxazine 10. A solution of *ortho*-aminophenol (0.218 g, 2 mmol) in 2 ml of MeCN was added to a solution of 2,3-dichloro-1-ethylpyrazinium tetrafluoroborate **1b** (0.530 g, 2 mmol) in 1 ml of MeCN. The solvent was evaporated, the residue was recrystallised from aqueous Na₂CO₃. The crystals were filtered off and dried in air to give 9-ethyl-6,9-diazaphenoxazine **10**, 0.376 g (88%), mp 108 °C. ¹H NMR (CDCl₃) δ: 6.74 (m, 4H, Ar), 6.22 and 6.13 (2d, 2×1H, 6-H and 5-H, *J* 4.7 Hz), 3.67 (q, 2H, NCH₂Me, *J* 7.1 Hz), 1.30 (t, 3H, NCH₂Me, *J* 7.1 Hz). Found (%): C, 67.35; H, 5.19; N, 19.44. Calc. for C₁₂H₁₁N₃O (%): C, 67.59; H, 5.20; N, 19.71.