Mendeleev Commun., 2001, 11(4), 152–153

Facile and general synthesis of pyrrolo[2,3-*b*]pyrazines *via* 2-(dicyanoylidene)-3-halopyrazines

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10.1070/MC2001v011n04ABEH001452

The ylidene group installation/ring annulation sequence was applied to the synthesis of pyrrolo[2,3-*b*]pyrazines starting from monocyclic and heterocyclic fused halopyrazines.

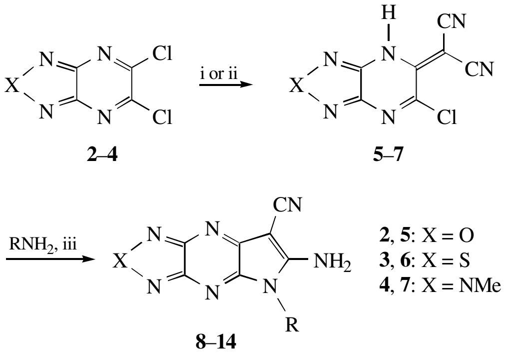
The synthesis and chemistry of pyrazine derivatives have attracted considerable attention in recent years because of their pharmacological and agrochemical properties.[1] Pratt and Keresztesy[2] published the pioneering work on reactions of 2,3-dichloroquinoxaline **1** with active methylene compounds, such as cyanoacetic acid esters, malononitrile (MN) and nitromethane, in the presence of potassium *tert*-butoxide in *tert*-butanol and on the transformations of the ylidene derivatives to benzo-fused pyrrolo[2,3-*b*]pyrazines. After this discovery, a meagre variety of reaction modifications has been made; however, the only starting pyrazine derivative, namely compound **1**, has been utilised.[3–5] Nevertheless, ylidenepyrazines are versatile precursors for organic syntheses.[6,7]

We described previously the preparation of polyhalopyrazines,[8] the synthesis of novel fused pyrazines by nucleophilic substitution of chlorine atoms[9–13] and unusual annulation of a furazan ring to pyrazine.[14] Polycyclic fused pyrazines were synthesised starting from 5,6-dichlorofurazano[3,4-*b*]pyrazine **2**.[15,16]

In a continuation of our work on polyfunctionalised pyrazines, we successfully adapted the Pratt facile ylidene group installation/ring annulation sequence to the synthesis of pyrrolo[2,3-*b*]pyrazines starting from monocyclic and heterocyclic fused halopyrazines.

The synthetic route to pyrrolo[2,3-*b*]pyrazines **8–14** involved the S_NAr[17] reaction of appropriate halopyrazines **2–4** with MN[18] in the presence of a base to ylidenic derivatives **5–7** and the subsequent treatment with primary amines (Scheme 1).

Ylidene derivative **5** was prepared in 42% yield by reaction of pyrazine **2** with MN in the presence of potassium *tert*-butoxide in *tert*-butanol at refluxing for 1 h according to the Pratt procedure.[2] In an attempt to develop a simpler and efficient synthesis of ylidene derivatives, a variety of reaction conditions were examined in the model reaction of **2** with MN. For instance, after treatment of **2** with a mixture of MN and NaOMe in methanol, a complex product mixture was obtained, which was difficult to separate. Compound **5** was isolated in 12% yield. Similar results were obtained with NEt_3 in place of potassium *tert*-butoxide. On the other hand, when the experiment was repeated with Na_2CO_3 in MeCN, **5** was obtained in 71% yield. The most successful chlorine displacement was achieved with MN in the presence of potassium carbonate in MeCN at 50 °C when compound **5** was obtained in 93% yield within 0.2 h. These conditions were successfully applied to the synthesis of other yliden pyrazines† in 75–95% yields (Scheme 1).



Scheme 1 *Reagents and conditions:* i, $MN/MeCN/K_2CO_3$; ii, H^+; iii, $PhCH_2NH_2/C_6H_6$–EtOH/reflux/1 h (70%).

All ylidenepyrazines thus prepared are new and the structures of the coloured products were characterised by usual spectroscopic methods‡ and compared with established literature data.[3,19,20] For example, the IR spectrum included a weak NH stretch band at 3000–3100 cm^{-1} and two sharp stretch bands at *ca.* 2170 and 2240 cm^{-1} due to nitrile groups. The EI MS diagnostic fragment at *m*/*z* (M^+ – HCN) was consistent with the presence of nitrile groups. In the ^{13}C NMR spectrum, two characteristic carbon signals of the ylidene moiety appeared at *ca.* 40 and *ca.* 140 ppm.

As shown in Scheme 1, ylidenepyrazines **5–7** subsequently reacted with primary amines such as (un)functionalised alkylamines and anilines in a mixture with benzene and ethanol at refluxing to afford pyrrolo[2,3-*b*]pyrazines **8–14**§ in good yields (Table 1). Weakly basic amines such as dinitroanilines and aminofurazans did not react with **5–7** due to their low nucleophilicity.

In an effort to avoid the isolation of the ylidene intermediate, we found that compounds **8–14** may be prepared by the one-pot treatment of halopyrazines **2–4** with MN in the presence of K_2CO_3 followed by cyclisation of the resulting salts with primary amines¶ using acetonitrile as a solvent. The yields of tricycles from the one-pot reaction were 90–95%.

All of the tricyclic compounds are novel heterocyclic systems. The ^{13}C NMR spectra of **8–14**‡ were consistent with the struc-

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† *General procedure for the preparation of ylidene pyrazines.* To a solution of malononitrile (0.01 mol) and K_2CO_3 (0.01 mol) in acetonitrile (50 ml) at room temperature the corresponding halopyrazine (0.01 mol) was added in a single portion with stirring. A dark-red mixture (the colour indicated the formation of an ylidene salt) was vigorously stirred at 50 °C for up to 1 h, until the complete consumption of the starting halopyrazine (according to TLC data). After removal of the solvent, chloroform (75 ml) and 10% H_3PO_4 (50 ml) were added to the residue and the mixture was vigorously stirred for 30 min. The organic phase was extensively washed with water, filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by recrystallisation from Pr^iOH as yellow to red crystals.

‡ All new compounds gave satisfactory spectroscopic and analytical results. For example, for **13**: ^1H NMR ([$^2H_6$]DMSO) δ: 2.42 (m, CMe), 4.34 (m, NMe), 5.48 (m, CH_2), 9.65 (br. s, NH), 10.08 (br. s, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 7.9 (C*Me*), 24.8 (NMe), 34.9 (CH_2), 63.6 (*C*C≡N), 113.2 (C≡N), 150.5, 150.7, 152.7, 153.3 (pyrazine ring), 151.0 (*C*Me), 151.1 (*C*CH_2), 163.1 (C–NH_2). IR (ν/cm^{-1}): 3135, 2226, 1679, 1550, 1490, 1460, 1185, 1016, 864. MS, *m*/*z*: 310 [M^+], 280 [M^+ – NO]. Found (%): C, 46.49; H, 3.30; N, 45.11. Calc. for $C_{12}H_{10}N_{10}O$ (%): C, 46.45; H, 3.25; N, 45.14.

§ *General procedure for the preparation of pyrrolo[2,3-*b*]pyrazines.* The corresponding ylidene pyrazine (0.01 mol), an amine (0.02 mol) or a mixture of the amine (0.01 mol) and triethylamine (0.01 mol), benzene (50 ml), and ethanol (50 ml) were refluxed with stirring for up to 2 h, until the complete consumption of the starting ylidenepyrazine was established by TLC. The solvents were removed, and the residue was washed with water and recrystallised from DMF.

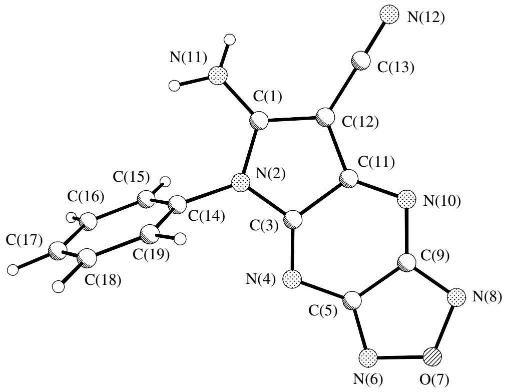
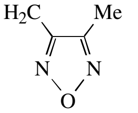
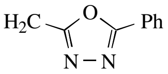
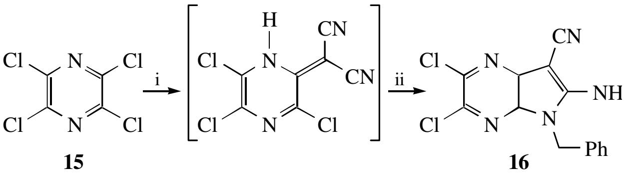


Figure 1 X-ray structure of **9**. Selected bond lengths (Å): C(1)–N(11) 1.303(3), C(1)–N(2) 1.381(2), C(1)–C(12) 1.415(3), N(2)–C(3) 1.375(2), C(3)–N(4) 1.289(2), C(3)–C(11) 1.487(2), N(4)–C(5) 1.374(2), C(5)–N(6) 1.306(3), C(5)–C(9) 1.431(3), N(6)–O(7) 1.384(2), O(7)–N(8) 1.395(2), N(8)–C(9) 1.311(3), C(9)–N(10) 1.370(3), N(10)–C(11) 1.316(2), C(11)–C(12) 1.409(3); selected bond angles (°): N(6)–C(5)–C(9) 109.85(18), C(5)–N(6)–O(7) 104.24(16), N(6)–O(7)–N(8) 112.50(14), C(9)–N(8)–O(7) 103.97(16), N(8)–C(9)–C(5) 109.44(18), C(1)–N(2)–C(14)–C(15) 77.2(3).

tures shown in Scheme 1. For each compound two quaternary pyrrole ring carbons, namely *C*–CN and C–NH$_2$, were discernible at *ca.* 63 and *ca.* 164 ppm, respectively. The IR spectra of these compounds exhibited a band at 2210 cm^{-1} typical of the nitrile group in fused 2-amino-3-cyanopyrroles.[3] The structural assignment was unequivocally confirmed by the X-ray crystallographic study of tricycle **9** (Figure 1).[††]

Table 1 Pyrrolo[2,3-*b*]pyrazines **8–14**.[‡]

Compound	X	R	Yield (%)	mp/°C
8	O	C_6H_{13}	85	227–228
9	O	Ph	93	320–322
10	O	$(CH_2)_4COOH$	73	>250 (decomp.)
11	S	Ad	81	299–301
12	S	CH_2Ph	89	>320
13	NMe		95	278–280
14	NMe		83	>320



15 **16**

Scheme 2 *Reagents and conditions*: i, MN/MeCN/K_2CO_3; ii, $PhCH_2NH_2$/MeCN/reflux/1 h (70%).

The similar ylidene group installation/ring annulation sequence was used for a synthesis of pyrrolo[2,3-*b*]pyrazine **16**[‡] starting from a monocyclic halopyrazine such as 2,3,5,6-tetrachloropyrazine **15** (Scheme 2).

In conclusion, the results demonstrate the efficiency and relative simplicity of the ylidene group installation/ring annulation sequence of *o*-dihalopyrazines for the formation of pyrrolo[2,3-*b*]pyrazine systems.

This work was supported by the Russian Foundation for Basic Research (grant no. 00-15-97359).

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Received: 15th March 2001; Com. 01/1778

[¶] *One-pot preparation of pyrrolo[2,3-*b*]pyrazines*. To a solution of malononitrile (0.01 mol) and K_2CO_3 (0.01 mol) in acetonitrile (50 ml) at room temperature the corresponding halopyrazine (0.01 mol) was added in a single portion with stirring. A dark-red mixture was vigorously stirred at 50 °C for up to 1 h (TLC monitoring). The suitable amine (0.011 mol) was added, and the mixture was refluxed with stirring for up to 2 h until the complete consumption of the intermediate was established by TLC. The solvents were removed, and the residue was washed with water and recrystallised from DMF.

[††] *Crystallographic data for* **9**: crystals of $C_{13}H_7N_7O$ at 298 K are monoclinic, space group *C*2/*c*, $a = 28.403(9)$ Å, $b = 6.621(3)$ Å, $c = 21.479(7)$ Å, $\beta = 131.14(3)°$, $V = 3042(2)$ Å^3, $Z = 8$, $M = 318.31$, $d_{calc} = 1.390$ g cm^{-3}, μ(MoKα) = 0.097 mm^{-1}, F(000) = 1312. Intensities of 3014 reflections were measured on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated MoKα-radiation ($\theta/\frac{5}{3}\theta$ scan technique, $\theta_{max} = 26°$) and 2956 independed reflections ($R_{int} = 0.0118$) were used in a further refinement. The structure was solved by the direct method and refined by full-matrix least squares against F^2 in the anisotropic approximation for non-hydrogen atoms. All the hydrogen atoms were located from the electron density Fourier difference synthesis and included in the refinement in an isotropic approximation. The refinement converged to $wR_2 = 0.1245$ and COF = 1.001 for all independed reflections [$R_1 = 0.0420$ was calculated against *F* for 1919 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using the SHELXTL software.[21] 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, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/88.