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Synthesis of tetrahydropyrido- and pyrido-[1′,2′:1,2]imidazo[4,5-*b*]pyrazine derivatives

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ABSTRACT

Reactions of tetrafluoropyridazine with iminopiperidine and 2-aminopiccoline gave novel tetrahydropyrido- and pyrido-[1′,2′:1,2]imidazo[4,5-*b*]pyrazine heterocyclic frameworks respectively in high yields.

1. Introduction

Heterocyclic compounds have, of course, found many applications in all parts of the chemical industry and significantly impact on our daily lives as components of medicines, agrochemicals, natural products and commodity chemicals [1]. Consequently, there continues to be a demand for the development of effective methodology for the synthesis of structurally new heterocyclic architectures to unlock novel, valuable biological and physical properties, in particular, in the pharmaceutical industry [2–4]. The use of perfluoroheteroaromatic systems as precursors for the synthesis of novel polyfunctional heterocycles is emerging and an increasing variety of bi- and tricyclic heterocyclic structures that bear a range of functionality have been synthesised in our laboratories recently [5–10].

We were interested in expanding the use of perfluoroheteroaromatic derivatives as starting materials for the preparation of novel heterocyclic molecular architectures and focused on the possibility of synthesising derivatives of tetrahydropyrido- and pyrido-[1′,2′:1,2]imidazo[4,5-*b*]pyrazine **1** and **2** respectively (Scheme 1). Synthetic methodology for the preparation of tricyclic pyridoimidazopyrazine derivatives **1** and **2** has not been developed to any great extent and, consequently, the chemistry of such systems remains relatively unexplored. Indeed, only a few reports of the synthesis of a limited range of pyridoimidazopyrazine systems have appeared in the literature. Heating 2-amino-pyrazine-4-oxide with pyridine provides access to the non-functionalised tricyclic system **2** [11] whilst reaction of dichlorodicyanopyrazine with 2-aminopyridine derivatives gives access to a range of dicyano-pyridoimidazopyrazine products [12] whose electrochemical and fluorescent properties have been assessed [13]. However, these methods suffer from low yields, difficulties in the synthesis of the starting materials and do not permit the synthesis of pyridoimidazopyrazine analogues bearing a wider range of functionality.

In this paper, we report synthetic methodology for the preparation of pyridoimidazopyrazine systems from tetrafluoropyrazine. Reactions of tetrafluoropyrazine, a perfluorinated heteroaromatic system prepared by halogen exchange from the corresponding tetrachloropyrazine and potassium fluoride [14], with difunctional nucleophiles are rare and only a few examples of annelation processes have been reported from our laboratories previously [15].

2. Results and discussion

Tetrahydropyrido- and pyridoimidazolopyrazine scaffolds **3** and **4** were readily synthesised by heating tetrafluoropyrazine **5** with iminopiperidine **6** and 2-aminopicoline **7** respectively in

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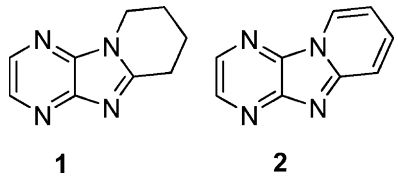


Scheme 1. Tetrahydropyrido- and pyrido-[1′,2′:1,2]imidazo[4,5-*b*]pyrazine frameworks **1** and **2**.

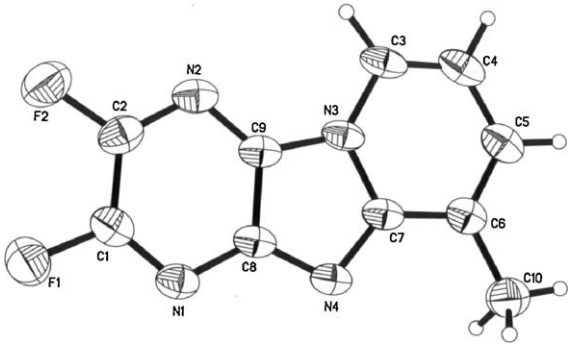


Fig. 1. Molecular structure of 2,3-difluoro-6-methylpyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazine **4**. Selected bond distances (Å): F1–C1 1.347(2); F2–C2 1.348(2); N1–C1 1.293(2); N1–C8 1.346(2); N2–C2 1.295(2); N2–C9 1.328(2); N4–C8 1.355(2); N4–C7 1.340(2).

acetonitrile in the presence of a base (Scheme 2). Both **3** and **4** were readily purified by crystallisation of the crude product mixture and the structures followed from NMR, mass spectrometry and elemental analysis. Additionally, the structure of **4** was confirmed by X-ray crystallography (Fig. 1).

Reactions of the tetrahydropyrido- and pyridoimidazolopyrazine scaffolds **3** and **4** with representative nitrogen and oxygen centred nucleophiles were studied in order to provide an indication of the reactivity of these systems towards nucleophilic attack and to establish the regioselectivity of such processes.

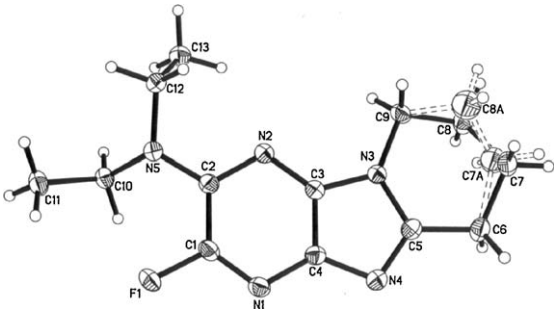


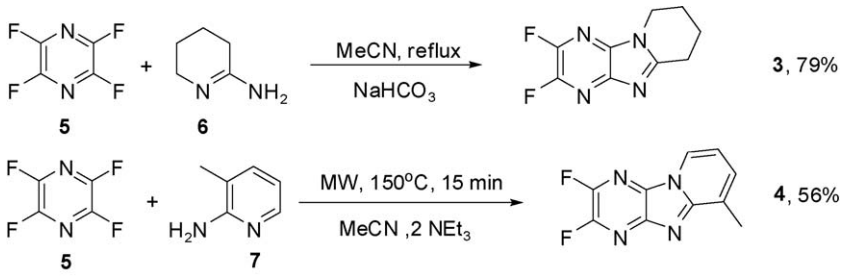
Fig. 2. Molecular structure of *N*,*N*-diethyl-3-fluoro-6,7,8,9-tetrahydropyrido[1′,2′:1,2]imidazo-[4,5-*b*]pyrazin-2-amine **8**. Selected bond distances (Å): F1–C1 1.357(1); N1–C1 1.300(1); N1–C4 1.348(1); N2–C3 1.331(1); N2–C2 1.342(1); N4–C4 1.377(1); N4–C5 1.326(1); N5–C2 1.376(1).

Reactions of **3** with diethylamine and sodium phenoxide gave **8**, whose structure was confirmed by X-ray crystallography (Fig. 2), and **9** respectively, where fluorine located at the 3-position is displaced selectively in both cases (Scheme 3).

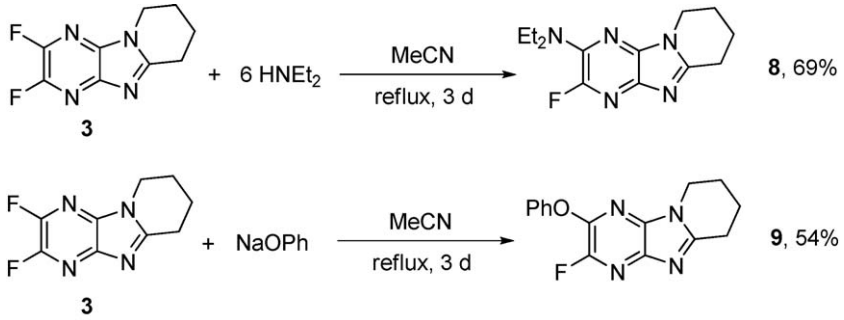
In contrast, reaction of **4** with diethylamine gave a mixture of products **10a** and **10b** in a 1:1 ratio by ^{19}F NMR analysis of the crude reaction mixture (Scheme 4). The structure of product **10a** was determined by X-ray crystallography (Fig. 3), confirming the regiochemistry of the nucleophilic substitution processes.

The regioselectivity of the nucleophilic aromatic substitution processes described above may be explained by a consideration of the relative stabilities of the intermediate Meisenheimer complexes (Scheme 5). Attack at the 3-position in **3** gives a more stable Meisenheimer intermediate in which the negative charge may be delocalised over both the conjugated 5- and 6-membered ring systems whereas this is not possible for corresponding attack at the 2-position.

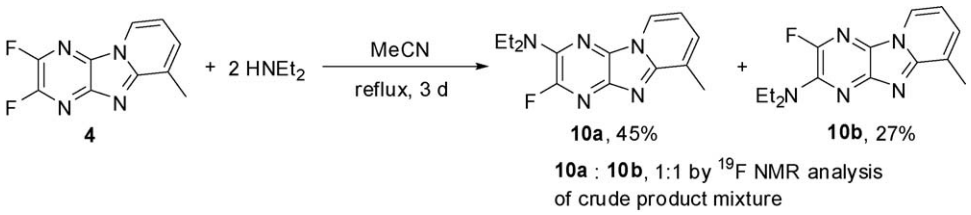
The most likely explanation for the lack of regioselectivity of the nucleophilic aromatic substitution reactions involving **4** as the substrate involves the significant aromaticity of the pyrido ring system in each Meisenheimer intermediate (Scheme 6).



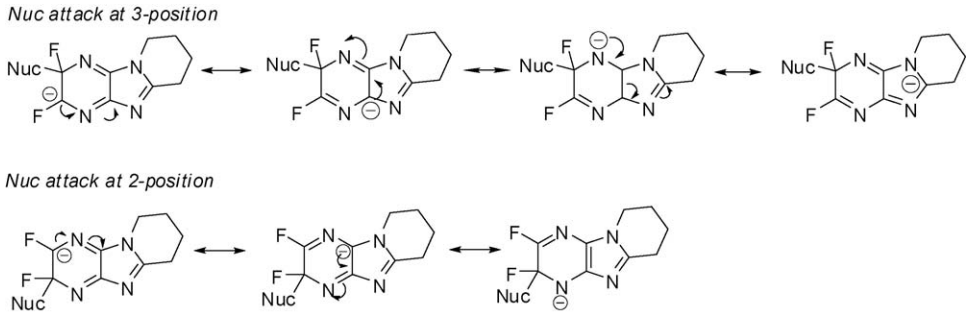
Scheme 2. Synthesis of tetrahydropyrido- and pyridoimidazolopyrazine scaffolds **3** and **4**.



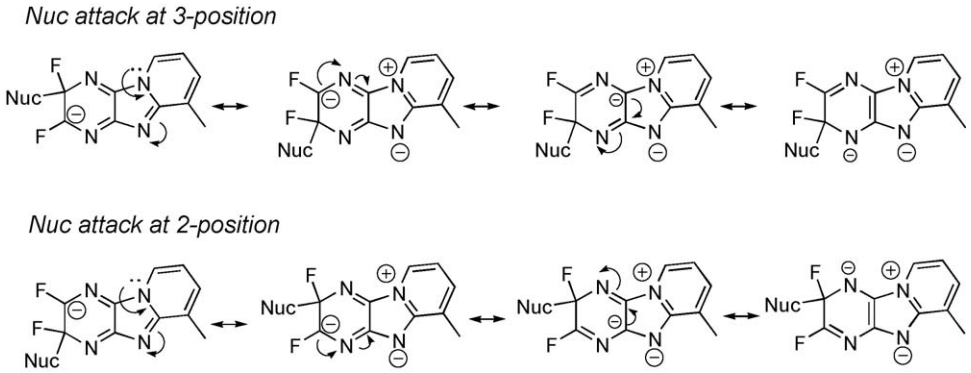
Scheme 3. Reactions of scaffold **3** with nucleophiles.



Scheme 4. Reaction of scaffold **4** with diethylamine.



Scheme 5. Meisenheimer intermediates in the nucleophilic aromatic substitution of **3**.



Scheme 6. Significant Meisenheimer intermediates in the nucleophilic aromatic substitution of **4**.

Charge delocalisation over the whole of the tricyclic ring system would break this aromaticity and so, in both cases, only delocalisation of the negative charge around the pyrazine ring occurs to any significant extent. Consequently, there is not a pronounced difference in the stabilities of the intermediates arising from nucleophilic attack at the 2- or 3-positions because the charge may not be efficiently delocalised over the whole of the tricyclic ring system in both cases and so a mixture of products is obtained.

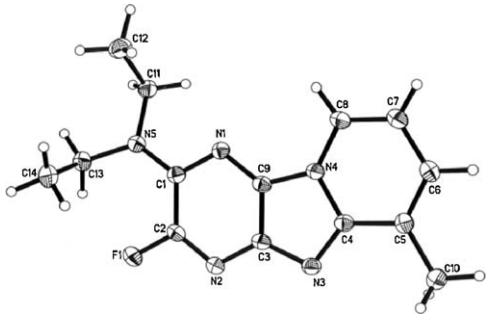


Fig. 3. Molecular structure of *N,N*-diethyl-2-fluoro-6-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-3-amine **10a**. Selected bond distances(Å): F1–C2 1.349(2); N1–C1 1.339(2); N1–C9 1.330(2); N2–C2 1.294(2); N2–C3 1.348(2); N3–C3 1.371(2); N3–C4 1.335(2); N5–C1 1.363(2).

The structures **4**, **8** and **10a** provide examples of how relatively minor changes in molecular shape affect molecular packing. As we observed previously [10], highly fluorinated heterocycles have a tendency to form anti-parallel stacks in the crystal and the nitrogen atoms of these heterocycles usually act as acceptors in intermolecular C–H...N interactions. Indeed, essentially planar molecules such as **4** in the crystal are linked into corrugated ribbons by double C–H...N contacts while π...π interactions between heterocycles bind the ribbons into the layers (Fig. 4a). Substitution of one fluorine atom in **4** by an NEt_2-group **10a** leaves the C–H...N intermolecular interactions intact and **10a** forms similar ribbons linked in pairs by π...π interactions in the crystal. However, the terminal methyl groups disturb the planarity of the molecules producing layers of double ribbons arranged in a herring-bone motif (Fig. 4b). Molecule **8** is not only even more non-planar than molecule **10a**, due to the presence of the tetrahydropyridine ring, but also lacks aromatic hydrogen atoms. As a result the packing of molecules of **8** in the crystal changes dramatically and isolated anti-parallel dimers which are linked together by a number of C(Me)–H...N contacts are observed in this case (Fig. 4c).

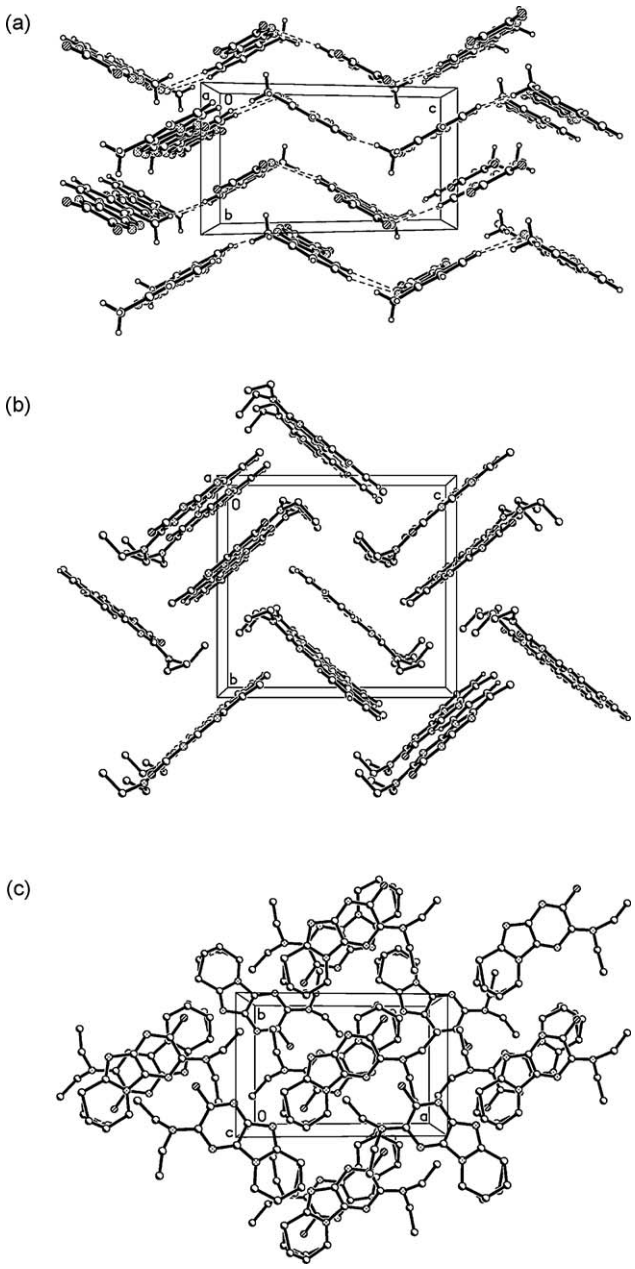


Fig. 4. (a) Corrugated layers in the structure **4**. (b) Double ribbons in the structure **10a**. (c) Dimers of molecules in the structure **8**.

In summary, novel polyfluorinated imidazolopyrazine scaffolds **3** and **4** may be synthesised in a one-step procedure from tetrafluoropyrazine providing further examples of annelation processes utilising mono-cyclic perfluorinated heteroaromatic systems as starting materials.

3. Experimental

3.1. General

All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated. ^{1}H, ^{13}C, ^{19}F, HSQC, COSY and HMBC NMR spectra were recorded on Bruker Avance-200, Varian-500 and Varian-700 spectrometers in the solvent stated. The ^{1}H NMR data were reported as follows: chemical shift (δ ppm), multiplicity (the peak integration; s, singlet; d, doublet; m, multiplet), J coupling constant (Hz). Elemental analyses were conducted on an Exeter Analytical Inc. CE-440 elemental analyser. All infra-red spectra were recorded using a FT-IR Perkin Elmer Spectrum RX1 machine. Mass spectra were recorded on a Thermo-Finnigan Trace instrument coupled with a Hewlett Packard 5890 series II Gas Chromatograph. Melting points were measured using a Gallenkamp melting point apparatus recorded at atmospheric pressure and are uncorrected. The progress of reactions was monitored by ^{19}F NMR. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230-400 mesh) and t.l.c. analysis was performed on silica gel t.l.c. plates.

3.2. Annelation reactions

3.2.1. 2,3-Difluoro-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine 3

A mixture of tetrafluoropyrazine (1.02 g, 6.7 mmol), 2-iminopiperidine hydrochloride (1.33 g, 9.9 mmol) and sodium hydrogen carbonate (3.31 g, 40 mmol) in acetonitrile (30 mL) was heated to reflux for 5 d. After cooling to rt, the reaction solvent was evaporated and water (40 mL) added. Extraction into DCM (3×40 mL), drying ($MgSO_4$), solvent evaporation and crystallisation from DCM gave *2,3-difluoro-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine* **3** (1.12 g, 79%) as a yellow solid; mp 144–146 °C (found: $[MH]^+$, 211.0792. $C_9H_8F_2N_4$ requires: $[MH]^+$, 211.0790); δ_H 1.97 (2H, m, CH_2), 2.05 (2H, m, CH_2), 3.06 (2H, m, CH_2), 4.13 (2H, m, CH_2); δ_C 19.9 (s, CH_2), 21.9 (s, CH_2), 26.1 (s, CH_2), 42.5 (s, C-5), 134.2 (d, $^{3}J_{CF}$ 10, C-9*a*), 140.3 (dd, $^{1}J_{CF}$ 210, $^{2}J_{CF}$ 33, C-2), 141.9 (dd, $^{1}J_{CF}$ 210, $^{2}J_{CF}$ 33, C-3), 142.1 (dd, $^{3}J_{CF}$ 12, $^{4}J_{CF}$ 4, C-4*a*), 154.7 (s, C-8*a*); δ_F −98.41 (1F, d, $^{3}J_{FF}$ 25, F-2), −100.38 (1F, d, $^{3}J_{FF}$ 27, F-3); m/z (EI^+) 210 ($[M]^+$, 100%), 182 (68), 154 (30).

3.2.2. 2,3-Difluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine 4

A mixture of tetrafluoropyrazine (1.50 g, 10 mmol), 2-amino-3-picoline (1.57 g, 15 mmol) and sodium hydrogen carbonate (3.32 g, 39 mmol) in THF (300 mL) was stirred at rt for 19 h. The reaction solvent was evaporated and water (40 mL) added. Extraction into ethyl acetate (3×40 mL), drying ($MgSO_4$), solvent evaporation and crystallisation from ethyl acetate gave *2,3-difluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine* **4** (1.04 g, 30%) as a brown solid; mp 213–215 °C (found: C, 54.4; H, 2.7; N, 25.5. $C_{10}H_6F_2N_4$ requires: C, 54.6; H, 2.8; N, 25.5%); δ_H 2.57 (3H, s, CH_3), 7.15 (1H, m, Ar-H), 7.61 (1H, m, Ar-H), 8.74 (1H, m, Ar-H); δ_C (d_6-DMSO) 18.5 (s, CH_3), 117.9 (s, C-6), 122.0 (s, C-5), 129.0 (s, C-7), 129.1 (m, C-4*a*), 132.1 (s, C-8), 140.2 (dd, $^{1}J_{CF}$ 377, $^{2}J_{CF}$ 35, C-3), 143.9 (m, C-9*a*), 144.1 (dd, $^{1}J_{CF}$ 374, $^{2}J_{CF}$ 31, C-2), 151.3 (s, C-8*a*); δ_F −89.52 (1F, d, $^{3}J_{FF}$ 27, F-2), −98.62 (1F, d, $^{3}J_{FF}$ 27, F-3); m/z (EI^+) 220 ($[M]^+$, 100%), 192 (6), 167 (2).

3.3. Reactions of scaffolds with nucleophiles

3.3.1. N,N-Diethyl-2-fluoro-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-3-amine 8

A mixture of **3** (0.30 g, 1.4 mmol) and diethylamine (0.63 g, 8.6 mmol) in acetonitrile (50 mL) was heated at reflux for 3 d. The reaction solvent was evaporated and water (40 mL) added. Extraction into ethyl acetate (3×40 mL), drying ($MgSO_4$), solvent evaporation and crystallisation from DCM gave *N,N-diethyl-2-fluoro-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-3-amine* **8** (0.26 g, 69%) as a yellow solid; mp 89–91 °C (found: C, 59.2; H, 6.9; N, 26.5. $C_{13}H_{18}FN_5$ requires: C, 59.3; H, 6.9; N, 26.6%); δ_H 1.15 (6H, t, $^{3}J_{HH}$ 7, CH_3), 2.06 (4H, m, CH_2), 3.00 (2H, m, CH_2), 3.48 (4H, m, CH_2), 4.03 (2H, m, CH_2); δ_C 13.7 (s, CH_3), 20.7 (s, CH_2), 22.5 (s, CH_2), 26.0 (s, CH_2), 41.7 (s, C-5), 44.8 (d, $^{4}J_{CF}$ 5.7, NCH_2), 135.5 (d, $^{3}J_{CF}$ 13.4, C-9*a*), 136.0 (s, C-4*a*), 140.8 (d, $^{2}J_{CF}$ 13.4, C-3), 145.79 (d, $^{1}J_{CF}$ 247, C-2), 151.03 (m, C-8*a*); δ_F −84.37 (s); m/z (ES^+) 264 ($[MH]^+$, 100%).

3.3.2. 2-Fluoro-3-phenoxy-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine 9

A mixture of **3** (0.30 g, 1.4 mmol) and sodium phenoxide (0.63 g, 8.6 mmol) in acetonitrile (50 mL) was heated at reflux for 3 d. The reaction solvent was evaporated and water (40 mL) added. Extraction into DCM (3 × 40 mL), drying ($MgSO_4$), solvent evaporation and crystallisation from hexane gave *2-fluoro-3-phenoxy-5,6,7,8-tetrahydropyrido[1′,2′:1,2]imidazo[4,5-b]pyrazine* **9** (0.22 g, 54%) as a white solid; mp 108–110 °C (found: C, 63.2; H, 4.6; N, 19.6. $C_{15}H_{13}FN_4O$ requires: C, 63.4; H, 4.6; N, 19.7%); δ_H 2.07 (4H, m, CH_2), 3.13 (2H, m, CH_2), 4.04 (2H, m, CH_2), 7.14–7.39 (5H, m, Ar-H); δ_C 20.8 (s, CH_2), 22.6 (s, CH_2), 26.5 (s, CH_2), 42.7 (s, C-5), 120.6 (s, C-2′), 125.4 (s, C-4′), 130.3 (s, C-3′), 134.9 (d, $^4J_{CF}$ 2, C-4*a*), 140.9 (d, $^3J_{CF}$ 12, C-9*a*), 143.5 (d, $^2J_{CF}$ 30, C-3), 149.0 (d, $^1J_{CF}$ 247, C-2), 154.9 (s, C-8*a*), 155.8 (d, $^4J_{CF}$ 2, C–O); δ_F −93.08 (s); *m*/*z* (EI$^+$) 284 ([M]$^+$, 90%), 255 (77), 206 (33).

3.3.3. N,N-Diethyl-2-fluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-3-amine 10a and N,N-diethyl-3-fluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-2-amine 10b

A mixture of **4** (200 mg, 0.9 mmol), diethylamine (140 mg, 1.8 mmol) and DIPEA (376 mg, 2.7 mmol) in THF (50 mL) was stirred at rt for 20 h and ^{19}F NMR analysis showed **10a** and **10b** in a 1:1 ratio. The THF was evaporated and the residue partitioned between DCM and brine. The organic layer was collected, dried ($MgSO_4$) and solvent evaporated to give a crude product (269 mg). Mass-directed auto-preparative HPLC purification gave *N,N-diethyl-2-fluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-3-amine* **10a** (56 mg, 45%) as a brown solid; mp 146–147 °C (found: C, 61.5; H, 5.9; N, 25.9. $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.28 (6H, t, $^3J_{HH}$ 7, CH_3), 2.67 (3H, s, CH_3), 3.64 (4H, q, $^3J_{HH}$ 6, CH_2), 6.82 (1H, m, Ar-H), 7.18 (1H, m, Ar-H), 8.37 (1H, m, Ar-H); δ_C 13.9 (s, CH_3), 17.3 (s, CH_3), 44.9 (d, $^4J_{CF}$ 6, CH_2), 111.8 (s, C-6), 121.1 (d, $^3J_{CF}$ 11, C-9*a*), 121.6 (s, C-5), 127.7 (s, C-7), 127.8 (s, C-8), 138.7 (d, $^4J_{CF}$ 6, C-4*a*), 143.6 (d, $^1J_{CF}$ 256, C-2), 144.7 (d, $^2J_{CF}$ 28, C-3), 145.9 (s, C-8*a*); δ_F −75.23 (s); *m*/*z* (ES$^+$) 274 ([MH]$^+$, 85%); and, *N,N-diethyl-3-fluoro-8-methylpyrido[1′,2′:1,2]imidazo[4,5-b]pyrazin-2-amine* **10b** (34 mg, 27%) as a yellow solid; mp 158–159 °C (found: C, 61.3; H, 5.9; N, 25.7. $C_{14}H_{16}FN_5$ requires: C, 61.5; H, 5.9; N, 25.6%); δ_H 1.30 (6H, t, $^3J_{HH}$ 7, CH_3), 2.68 (3H, s, CH_3), 3.68 (4H, q, $^3J_{HH}$ 6, CH_2), 6.85 (1H, m, Ar-H), 7.22 (1H, m, Ar-H), 8.33 (1H, m, Ar-H); δ_C 13.7 (s, CH_3), 17.3 (s, CH_3), 45.0 (d, $^4J_{CF}$ 6, CH_2), 111.6 (s, C-6), 121.7 (s, C-5), 126.9 (s, C-7), 128.3 (s, C-8), 130.3 (s, C-9*a*), 137.3 (d, $^3J_{CF}$ 15, C-4*a*), 140.6 (d, $^2J_{CF}$ 26, C-2), 147.2 (d, $^1J_{CF}$ 215, C-3), 149.9 (s, C-8*a*); δ_F −84.45 (s), *m*/*z* (ES$^+$) 274 ([MH]$^+$, 85%).

3.4. X-ray crystallography

Single crystal X-ray data for compounds **4**, **8** and **10a** were collected on a Bruker SMART-CCD 6000 diffractometer equipped with Cryostream (Oxford Cryosystem) cooling device at 120.0 K (**8** and **10a**) using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data for the compound **4** were collected at 250 K due to a phase transition, which takes place at about 200 K and proceeds with destruction of the crystal. All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL and Olex2 software. All non-hydrogen non-disordered atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. The hydrogen atoms of disordered ethylene group in molecule **8** were put in calculated positions and refined in riding mode. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-762827–762829.

Crystal data for **4**: $C_{10}H_6F_2N_4$, M = 220.19, monoclinic, space group P $2_1/n$, a = 11.0365(6), b = 7.0160(4), c = 13.1936(7) Å, β = 112.05(1)°, U = 946.88(9) Å^3, F(0 0 0) = 448, Z = 4, D_c = 1.545 mg m^{-3}, μ = 0.127 mm^{-1}. 9311 reflections were collected yielding 2516 unique data (R_{merg} = 0.059). Final $wR_2(F^2)$ = 0.0843 for all data (169 refined parameters), conventional $R(F)$ = 0.0380 for 1224 reflections with $I \geq 2\sigma$, GOF = 1.063.

Crystal data for **8**: $C_{13}H_{18}FN_5$, M = 263.32, monoclinic, space group P $2_1/n$, a = 11.2712(3), b = 7.6210(2), c = 14.9705(5) Å, β = 96.87(1)°, U = 1276.69(6) Å^3, F(0 0 0) = 560, Z = 4, D_c = 1.370 mg m^{-3}, μ = 0.097 mm^{-1}. 16002 reflections were collected yielding 3559 unique data (R_{merg} = 0.058). Final $wR_2(F^2)$ = 0.0984 for all data (253 refined parameters), conventional $R(F)$ = 0.0350 for 2921 reflections with $I \geq 2\sigma$, GOF = 1.127.

Crystal data for **10a**: $C_{14}H_{16}FN_5$, M = 273.32, orthorhombic, space group $P2_12_12_1$, a = 7.5730(2), b = 12.5894(3), c = 13.6232(3) Å, U = 1298.83(5) Å^3, F(0 0 0) = 576, Z = 4, D_c = 1.398 mg m^{-3}, μ = 0.099 mm^{-1}. 17010 reflections were collected yielding 2081 unique data (R_{merg} = 0.075). Final $wR_2(F^2)$ = 0.0934 for all data (245 refined parameters), conventional $R(F)$ = 0.0350 for 1860 reflections with $I \geq 2\sigma$, GOF = 1.102.

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