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Synthesis of tetrahydropyrido[2,3-*b*]pyrazine scaffolds from 2,3,5,6-tetrafluoropyridine derivatives

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Abstract—Reactions between *N*,*N*′-dimethylethylene diamine and a range of 2,3,5,6-tetrafluoropyridine derivatives provided ready access to the corresponding tetrahydropyrido[2,3-*b*]pyrazine systems if the substituent located at the 4-position of the pyridine ring was either hydrogen or an electron withdrawing substituent. In contrast, the presence of electron donating substituents at the 4-position made the formation of ring-fused products much more difficult. The two-step sequential nucleophilic substitution procedures from pentafluoropyridine gave convenient and adaptable methodology for the synthesis of polyfunctional tetrahydropyrido[2,3-*b*]pyrazine scaffolds of interest to the life science discovery arenas.

1. Introduction

Strategies for the synthesis of novel families of polysubstituted heterocyclic systems of readily variable molecular architecture are of increasing importance in the life science industries,[1,2] due to the surprisingly high proportion of commercially important pharmaceutical and plant protection products that are based upon a small heterocyclic ring 'core scaffold' or 'privileged structure'.[3–5] In particular, the human genome project has given medicinal chemists valuable information about the structural characteristics of many receptor sites[6,7] and low molecular weight biologically active heterocyclic molecules offer great possibilities for the discovery of new chemical entities for potential lead optimisation.

Consequently, many strategies for the synthesis of heterocyclic analogues, such as parallel,[8] rapid analogue[1,2] and diversity orientated[9,10] syntheses, are being developed to unearth new polyfunctional heterocyclic systems for drug development. Essentially, a heterocyclic 'core scaffold' must bear several reactive sites that may be readily functionalised in a controlled manner in high yield and regioselectivity. Unfortunately, however, many highly functionalised pyridine systems, for example, are difficult to access due to the inherent low reactivity of heteroaromatic systems towards electrophilic attack.

In recent publications,[11,12] we described the use of highly fluorinated pyridine systems as scaffolds for the synthesis of [6,6] ring-fused bicyclic nitrogen heterocyclic derivatives. Perfluorinated pyridine systems are highly reactive towards nucleophilic attack[13,14] due to the presence of several electronegative fluorine substituents and a sequence of nucleophilic aromatic substitution reactions has allowed us to synthesise various phenylsulfonyl-tetrahydropyrido[2,3-*b*]-pyrazine systems (Scheme 1). Pentafluoropyridine **1** reacts with sodium phenylsulfinate to give **2** arising from regioselective substitution of the fluorine atom located at the 4-position.[13,14] Reaction of **2** with an appropriate diamine leads selectively to the desired tetrahydropyrido[2,3-*b*]pyrazine scaffold **3** by substitution at the 2-position of the pyridine ring followed by intramolecular ring closure at the geometrically accessible 3-position (Scheme 1). In this case, the strong electron withdrawing phenylsulfonyl group activates the pyridine ring towards further nucleophilic attack allowing annelation to proceed efficiently. Reaction of scaffold **3** with nucleophiles gave products **4** arising from the displacement of the phenylsulfonyl substituent.

To increase the molecular diversity of functional heterocyclic systems accessible by this new approach, we must first establish the effect of the substituent attached at the 4-position on the reactivity of pyridine systems **5** towards further

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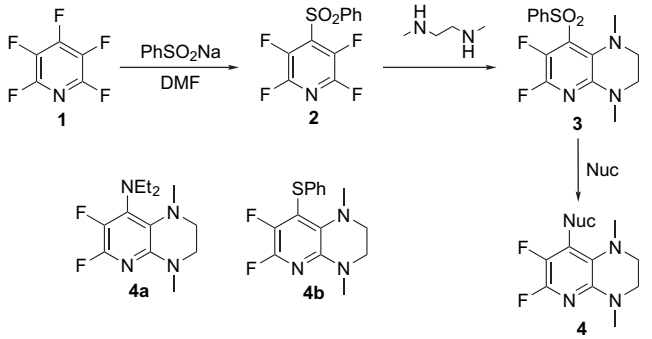
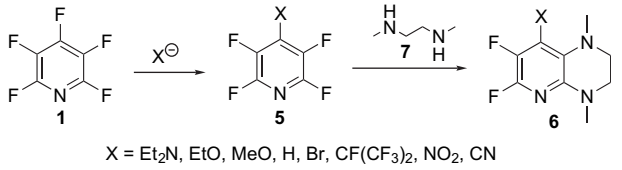


Scheme 1. General approach to tetrahydropyridopyrazines from pentafluoropyridine.

nucleophilic substitution and annelation processes and to gauge the compatibility of functional groups for the synthesis of polyfunctional systems **6** (Scheme 2).



Scheme 2. Strategy for the synthesis of functional scaffolds.

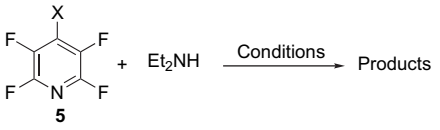
Products **5** are, of course, electron deficient aromatic ring systems and further nucleophilic substitution should, in principle, occur readily. However, perhaps surprisingly, relatively few studies concerning reactions of 2,3,5,6-tetrafluoropyridine derivatives **5** that systematically explore the effects of the 4-substituent upon the regiochemistry of nucleophilic substitution have been reported. For example, the synthesis of 2,4,6-trimethoxypyridine derivatives from 4-methoxy-2,3,5,6-tetrafluoropyridine was recorded by Banks[15] and a variety of reactions between perfluoro-4-*iso*-propyl pyridine and various nucleophiles were surveyed recently.[16] In this paper, we report our studies concerning reactions of various 2,3,5,6-tetrafluoropyridine derivatives **5** (X=H, MeO, EtO, Et_2N, *i*-PrNH, Br, $CF(CF_3)_2$, CN and NO_2) to assess the influence of the substituent at the 4-position upon reactions with a model amine, *N*,*N*-diethylamine, and a diamine, *N*,*N*′-dimethylethylene diamine, in order to establish regioselectivity of further nucleophilic substitution processes, the types of functionality that may be present on the perfluorinated pyridine ring that would permit subsequent annelation reaction to proceed and, consequently, the scaffolds that may be realistically accessed by this strategy.

2. Results and discussion

Reactions between a range of 2,3,5,6-tetrafluoropyridine derivatives **5** bearing a substituent at the 4-position (X=Et_2N, EtO, MeO, H, Br, CN and NO_2) and diethylamine are summarised in Table 1.

In each case the pyridine derivative **5** and amine were heated together in either acetonitrile or THF at reflux temperature until ^{19}F NMR spectroscopic analysis of the reaction mixture indicated high conversion to products. Excess diethylamine could be removed either by the addition of Amberlite resin to the crude reaction mixture or by column chromatography. The regiochemistry of the nucleophilic substitution reactions were determined by ^{19}F NMR spectroscopic analysis using arguments discussed previously.[12]

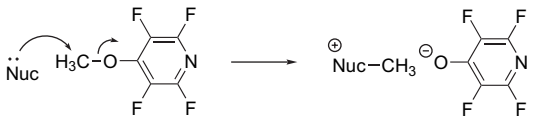
Table 1. Reactions of tetrafluoropyridine systems with diethylamine



X	Product(s), yield (%)	X	Products(s), yield (%)
5a, NEt_2	**6a**, 63	**3**, SO_2Ph*[a]	**6g**, 38
5b, NH^iPr	**6b**, 26	**5g**, $CF(CF_3)_2$*[b]	**6h**, 92
5c, OMe	**6c**, 93	**5h**, NO_2	**6i**, 35 + **6j** **6i** : **6j**, 2 : 1
5d, OEt	**6d**, 63		
5e, H	**6e**, 68		**6k**, 50
5f, Br	**6f**, 61	**5i**, CN	**6l**, 17

[a] Ref. 11.
[b] Ref. 16.

The results outlined in Table 1 indicate that substitution reactions of most of the tetrafluoropyridine derivatives (X=Et_2N, EtO, H and Br) occur selectively at sites *ortho* to the ring nitrogen. However, 4-methoxy pyridine derivative **5c** gave only 4-pyridinol salt **6c** upon reaction with diethylamine, arising from nucleophilic displacement of the methyl group by the amine nucleophile, rather than ring fluorine displacement because, in this case, the electron deficient pyridine group acts as a good leaving group (Scheme 3).



Scheme 3.

In contrast, the related ethoxy pyridine **5d** gives only **6d** arising from displacement of ring fluorine and this is a reflection of the much slower rate of attack of nucleophiles at methylene sites compared to methyl,[17] allowing nucleophilic aromatic substitution to compete very effectively in this case.

4-Nitropyridine derivative **5h** gives a mixture of products **6i** and **6j** arising from substitution of fluorine *ortho* to nitrogen and the nitro group, respectively. This is perhaps not surprising given the high lability of nitro groups in nucleophilic aromatic substitution processes, a property that has been used to great effect in many synthetic procedures.[18]

Consequently, we conclude that of the systems studied, only the 4-methoxy pyridine system is an unsuitable substrate for related annelation reactions and, with these results in hand, we studied reactions between *N*,*N*′-dimethylethylene diamine **7** and the tetrafluoropyridine derivatives **5** (Table 2).

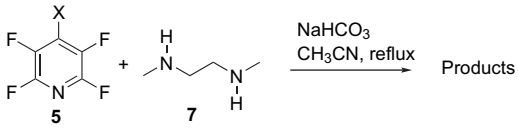
Substituents located at the 4-position that are electron donating (**5a**, Et_2N and **5d**, EtO) do not give ring-fused products even after prolonged heating in acetonitrile and the only products obtained after work up using aqueous hydrochloric acid were those arising from nucleophilic substitution of the fluorine atom located *ortho* to pyridine ring nitrogen **8a** and **8b**. These experiments demonstrate that a pyridine ring bearing two electron donating substituents (two amino or amino and alkoxy) are too deactivated under the conditions employed towards nucleophilic attack at the desired, relatively less activated 3-position, despite the presence of three fluorine atoms on the heterocyclic ring. Tetrafluoropyridine **5e**, however, gave annelated product **8c** upon heating with **7** in acetonitrile.

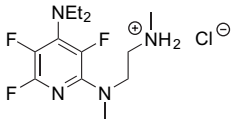
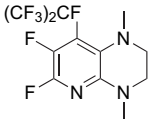
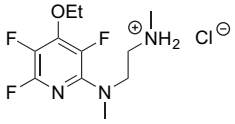
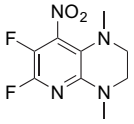
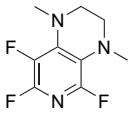
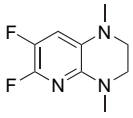
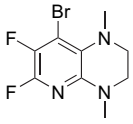
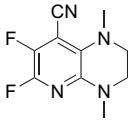
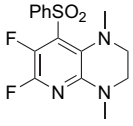
The presence of an electron withdrawing group, such as Br, $(CF_3)_2CF$, SO_2Ph or CN, at the 4-position allows high yields of tetrahydropyrido[2,3-*b*]pyrazine scaffolds **8d–f** and **8i** to be synthesised. In these cases, the heterocyclic ring is still sufficiently activated towards nucleophilic attack upon initial substitution by the diamine allowing the annelation to occur. Compound **8f** is obtained as a mixture of rotamers (Scheme 4), which can be observed by ^{19}F NMR spectroscopy and resemble similar perfluoro-4-*iso*-propylpyridine derivatives.[16]

In contrast, 4-nitro pyridine **5h** gave a mixture of bicyclic products **8g** and **8h** in a ratio of 1:1, the latter formed by displacement of the nitro group, as we would have expected from the results obtained using diethylamine shown in Table 1. The structures of the tetrahydropyrido[2,3-*b*]pyrazines followed from NMR spectroscopic data and analysis by X-ray crystallography.

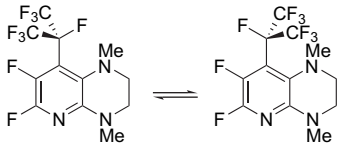
The molecular structures of the tetrahydropyridopyrazines **8d**,**8e**,**8f** and **8i** show some common features. In particular, all the piperazine rings adopt an envelope conformation in which one of the carbon atom deviates out of the plane of the other atoms of the bicyclic system (Fig. 1a). Both piperazine nitrogen atoms in all compounds are in the plane of the pyridine rings, but one of them is planar while the other has a pyramidal bond configuration. This conformation difference results in the difference of corresponding N–C(pyridine) bond lengths (typically 1.36 Å for the planar nitrogen atom and 1.42 Å for the pyramidal nitrogen). All these molecules exhibit a stacking arrangement of some sort in the crystals where they form dimers with a parallel layout of heterocyclic systems (**8d**, **8e**, **8f** and **8i**; Fig. 1b).

Table 2. Synthesis of tetrahydropyrido[2,3-*b*]pyrazine scaffolds



X	Product(s), yield (%)	X	Products(s), yield (%)
5a, NEt_2	 **8a**, 15 After aq HCl work up	**5g**, $CF(CF_3)_2$	 **8f**, 40
5d, OEt	 **8b**, 23 After aq HCl work up	**5h**, NO_2	 **8g**, 46 +  **8h**, 20
5e, H	 **8c**, 66		
5f, Br	 **8d**, 20	**5i**, CN	 **8i**, 90
3, SO_2Ph*[a]	 **8e**, 20		

[a] Ref. 11.



Scheme 4. Rotamers of **8f**.

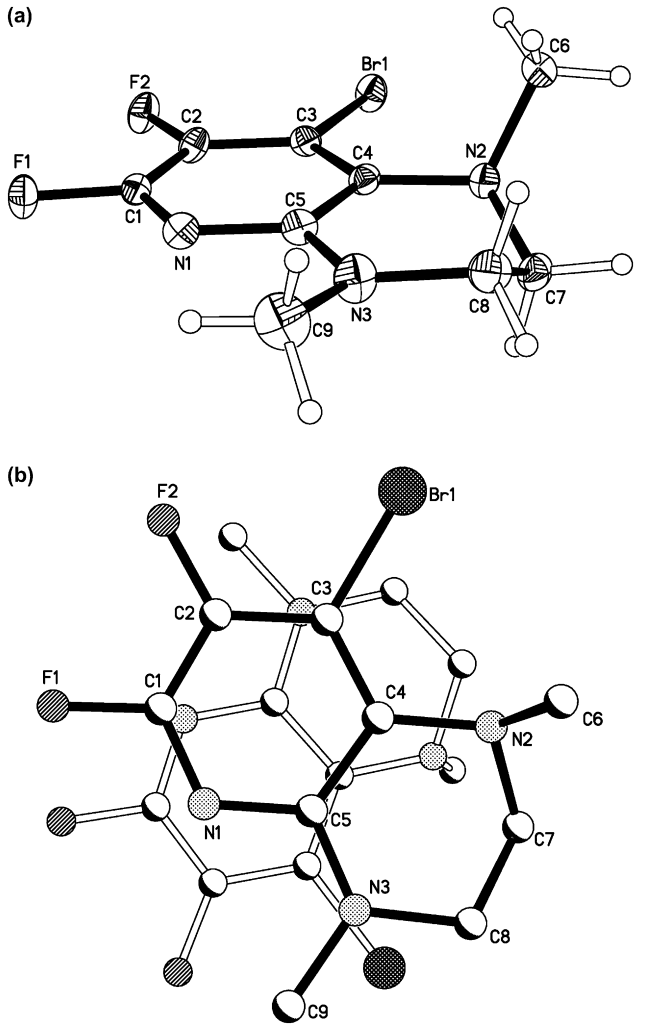


Figure 1. (a) Molecular structure of **8d**; (b) dimeric arrangement of the molecules **8d** in the crystal (hydrogen atoms omitted for clarity).

The mutual orientation and degree of overlapping of the adjacent molecules in dimers and stacks in these crystals varies depending on the substituents present in the pyridine rings, steric and packing effects.

In summary, our general strategy for the synthesis of polyfunctional heterocyclic ring-fused scaffolds from highly fluorinated pyridine precursors, is most effective when the substituent located at the 4-position is a strong electron withdrawing group (Br, $(CF_3)_2CF$, SO_2Ph or CN) that is also not itself highly labile towards nucleophilic attack. Reactions of these polyfunctional scaffolds will be described in due course.

3. Experimental

3.1. General

All starting materials were obtained commercially (Sigma–Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR experiments and coupling constants are given in hertz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry service, Swansea, U.K. Elemental analyses were obtained on either a Perkin–Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck No. 1-09385, 230-400 mesh) and TLC analysis was performed on silica gel TLC plates.

3.2. General procedure—purification using Amberlite resin

A solution of diethylamine in THF was added dropwise to the pyridine derivative at room temperature over 30 min and the resulting mixture was heated at reflux temperature for 2 days. Amberlite resin (0.50 g) was added with stirring at room temperature for 30 min, the solution was then filtered and the solvent evaporated. Purification by reduced pressure distillation yielded product.

3.2.1. N^2,N^2,N^4,N^4-Tetraethyl-3,5,6-trifluoropyridine-2,4-diamine 6a. Diethylamine (6.96 g, 9.0 mmol), **5a** (1.945 g, 8.8 mmol) and THF (20 ml) gave N^2,N^2,N^4,N^4-tetraethyl-3,5,6-trifluoropyridine-2,4-diamine **6a** (1.520 g, 63%) as a colourless liquid; bp 85 °C, 0.6 mbar; (Found C, 56.7; H, 7.4; N, 15.1. $C_{13}H_{20}F_3N_3$ requires C, 56.7; H, 7.3; N, 15.3%); δ_H 1.13 (3H, t, $^3J_{HH}$ 7.2, 2-NCH$_2$*C*H$_3$), 1.15 (3H, t, $^3J_{HH}$ 7.2, 4-NCH$_2$*C*H$_3$), 3.29 (2H, qt, $^3J_{HH}$ 7.2, $^5J_{HF}$ 1.5, 4-N*C*H$_2$CH$_3$), 3.36 (2H, qd, $^3J_{HH}$ 7.2, $^5J_{HF}$ 1.5, 2-N*C*H$_2$CH$_3$); δ_C 13.6 (s, 2-NCH$_2$*C*H$_3$), 13.8 (s, 4-NCH$_2$*C*H$_3$), 44.3 (d, $^4J_{CF}$ 4.5, 2-N*C*H$_2$CH$_3$), 46.4 (t, $^4J_{CF}$ 4.5, 4-N*C*H$_2$CH$_3$), 131.7 (dd, $^1J_{CF}$ 240.4, $^2J_{CF}$ 19.2, C-5), 137.7 (m, C-4), 139.2 (dd, $^1J_{CF}$ 240.4, $^3J_{CF}$ 6.9, C-3), 142.2 (ddd, $^2J_{CF}$ 19.2, $^3J_{CF}$ 6.9, $^4J_{CF}$ 4.4, C-2), 146.0 (dd, $^1J_{CF}$ 240.4, $^2J_{CF}$ 19.2, C-6); δ_F −94.73 (1F, dd, $^3J_{FF}$=$^5J_{FF}$=26.0, 6-F), −146.11 (1F, d, $^5J_{FF}$ 26.0, 3-F), −165.05 (1F, d, $^3J_{FF}$ 26.0, 5-F); *m*/*z* (EI$^+$) 276 (M$^+$+1, 43), 275 (M$^+$, 100), 261 (55), 260 (89), 246 (72), 233 (29), 232 (92), 230 (28), 216 (62), 202 (57), 188 (68), 72 (46), 29 (52).

3.2.2. N^2,N^2-Diethyl-3,5,6-trifluoro-N^4-isopropylpyridine-2,4-diamine 6b. Diethylamine (7.907 g, 108.1 mmol), **5b** (2.017 g, 9.7 mmol) and THF (15 ml) gave N^2,N^2-diethyl-3,5,6-trifluoro-N^4-isopropylpyridine-2,4-diamine **6b** (0.668 g, 26%) as a colourless oil; bp 91 °C, 2.9 mbar; (Found: C, 55.3; H, 6.8; N, 16.1. $C_{12}H_{18}F_3N_3$ requires C, 55.2; H, 6.9; N, 16.1%); δ_H 1.13 (6H, t, $^3J_{HH}$ 6.8, NCH$_2$*C*H$_3$), 1.22 (6H, d, $^3J_{HH}$ 6.8, HNCH(*C*H$_3$)$_2$), 3.35 (4H, qt, $^3J_{HH}$ 6.8, $^5J_{HF}$ 1.5, N*C*H$_2$CH$_3$), 3.89 (1H, br s, *NH*CH(CH$_3$)$_2$), 4.04 (1H, sex t, $^3J_{HH}$ 6.8, $^5J_{HF}$ 1.5, HN*C*H-(CH$_3$)$_2$); δ_C 13.8 (s, NCH$_2$*C*H$_3$), 24.2 (s, HNCH(*C*H$_3$)$_2$), 44.1 (d, $^4J_{CF}$ 4.3, NH*C*H$_2$CH$_3$), 46.2 (t, $^4J_{CF}$ 4.3, HN*C*H-(CH$_3$)$_2$), 127.0 (dd, $^1J_{CF}$ 235.2, $^2J_{CF}$ 21.7, C-5), 134.1 (dd, $^1J_{CF}$ 235.2, $^3J_{CF}$ 7.3, C-3), 135.2 (dt, $^2J_{CF}$ 21.7, $^3J_{CF}$ 7.3, C-4), 140.9 (ddd, $^2J_{CF}$ 21.7, $^3J_{CF}$ 7.3, $^4J_{CF}$ 4.3, C-2), 145.7 (ddd, $^1J_{CF}$ 235.2, $^2J_{CF}$ 21.7, $^4J_{CF}$ 4.3, C-6); δ_F −94.73 (1F,

t, $^{3/5}J_{FF}$ 26.3, F-6), −157.92 (1F, d, $^{5}J_{FF}$ 26.3, F-3), −173.76 (1F, d, $^{3}J_{FF}$ 26.3, F-5); *m/z* (EI$^+$) 261 ([M]$^+$, 75%), 247 (24), 246 (100), 232 (33), 218 (79), 202 (22), 190 (32), 176 (83), 72 (31).

3.2.3. 4-Ethoxy-*N*,*N*-diethyl-3,5,6-trifluoropyridin-2-amine 6d. Diethylamine (1.694 g, 23.2 mmol), **5d** (2.006 g, 10.3 mmol) and THF (15.0 ml) gave 4-ethoxy-*N*,*N*-diethyl-3,5,6-trifluoropyridin-2-amine **6d** (1.612 g, 63%) as a colourless oil; bp 62 °C, 3.3 mbar; (Found: C, 52.9; H, 6.1; N, 11.4. $C_{11}H_{15}F_3N_2O$ requires C, 53.2; H, 6.1; N, 11.3%); δ_H 1.15 (6H, t, $^{3}J_{HH}$ 7.1, NCH$_2$*CH*$_3$), 1.42 (3H, t, $^{3}J_{HH}$ 7.1, OCH$_2$*CH*$_3$), 3.40 (4H, qd, $^{3}J_{HH}$ 7.1, $^{5}J_{HF}$ 1.5, N*CH*$_2$CH$_3$), 4.38 (2H, qt, $^{3}J_{HH}$ 7.1, $^{5}J_{HF}$ 1.5, O*CH*$_2$CH$_3$); δ_C 13.8 (s, NCH$_2$*CH*$_3$), 15.6 (s, OCH$_2$*CH*$_3$), 44.1 (s, N*CH*$_2$CH$_3$), 70.0 (t, $^{4}J_{CF}$ 3.5 O*CH*$_2$CH$_3$), 129.5 (dd, $^{1}J_{CF}$ 241.9, $^{2}J_{CF}$ 18.6, C-5), 137.2 (dd, $^{1}J_{CF}$ 241.9, $^{3}J_{CF}$ 7.0, C-3), 141.6 (ddd, $^{2}J_{CF}$ 18.6, $^{3}J_{CF}$ 7.0, $^{4}J_{CF}$ 3.5, C-2), 145.3 (ddd, $^{1}J_{CF}$ 241.9, $^{2}J_{CF}$ 18.6, $^{4}J_{CF}$ 3.5, C-6), 145.3 (dt, $^{2}J_{CF}$ 18.6, $^{3}J_{CF}$ 7.0, C-4); δ_F −91.74 (1F, t, $^{3/5}J_{FF}$ 26.6, F-6), −155.32 (1F, d, $^{3}J_{FF}$ 26.6, F-3), −172.15 (1F, d, $^{5}J_{FF}$ 26.6, F-5); *m/z* (EI$^+$) 248 ([M]$^+$, 89%), 233 (90), 219 (35), 205 (63), 203 (28), 191 (54), 188 (32), 177 (100), 175 (34), 149 (33), 148 (52).

3.3. General procedure—standard workup

Diethylamine and sodium hydrogen carbonate (0.24 g, 2.84 mmol) were added to acetonitrile (20 ml) under argon. The 2,3,5,6-tetrafluoropyridine derivative was added and the resulting solution refluxed at 90 °C until ^{19}F NMR indicated complete conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured onto water (50 ml), extracted with dichloromethane (3×50 ml), dried ($MgSO_4$) and the solvent evaporated to dryness to yield a crude product, which was purified by column chromatography on silica gel.

3.3.1. 2,3,5,6-Tetrafluoro-pyridin-4-olate-diethyl-ammonium 6c. A solution of diethylamine (4.031 g, 55.1 mmol) in THF (25 ml) was added to **5c** (4.872 g, 27.0 mmol) at room temperature over 30 min; the resulting mixture was heated at reflux temperature for 20 h before water (50 ml) was added. The mixture was filtered and recrystallised from DMSO to give 2,3,5,6-tetrafluoro-pyridin-4-olate-diethyl-ammonium **6c** (6.031 g, 93%) as a white crystalline solid; mp 220–222 °C; (Found: C, 45.0; H, 5.1; N, 11.6. $C_9H_{12}F_4N_2O$ requires C, 45.0; H, 5.0; N, 11.7%); δ_H 1.71 (6H, t, $^{3}J_{HH}$ 7.2, NCH$_2$*CH*$_3$), 2.93 (2H, q, $^{3}J_{HH}$ 7.2, N*CH*$_2$CH$_3$), 8.90 (br s, NH$_2$); δ_C 11.0 (s, NCH$_2$*CH*$_3$), 41.5 (s, N*CH*$_2$CH$_3$), 136.0 (dm, $^{1}J_{CF}$ 231.3, C-3), 144.8 (dm, $^{1}J_{CF}$ 231.3, C-2), 158.9 (m, C-4); δ_F −103.87 (2F, m, F-2), −173.55 (2F, m, F-3); *m/z* (EI$^+$) 167 (100), 138 (21), 119 (59), 100 (21), 93 (35).

3.3.2. *N*,*N*-Diethyl-3,5,6-trifluoropyridin-2-amine 6e. Diethylamine (0.48 g, 6.62 mmol), **5e** (1 g, 6.62 mmol), sodium hydrogen carbonate (0.56 g, 6.62 mmol) and acetonitrile (20 ml) gave a brown oil (1.0 g). Purification by column chromatography on silica gel (10:1 *n*-hexane/ethyl acetate) gave *N*,*N*-diethyl-3,5,6-trifluoropyridin-2-amine **6e** (0.92 g, 68%) as a colourless oil; ([M+H]$^+$ 205.0947, $C_9H_{11}N_2F_3$ requires [M+H]$^+$ 205.0947); δ_F −93.44 (1F, t, $^{3}J_{FF}$ 31.6, F-6), −135.20 (1F, dd, $^{3}J_{FF}$ 31.6, $^{4}J_{FF}$ 11.3, F-5), −156.20 (1F, dd, $^{4}J_{FF}$ 24.8, $^{5}J_{FF}$ 6.8, F-3); δ_H 7.17 (1H, dt, $^{3}J_{HF}$ 11.2, $^{3}J_{HF}$ 8.0, H-4), 3.44 (4H, qd, $^{3}J_{HH}$ 7.2, CH$_2$), 1.17 (6H, t, $^{3}J_{HH}$ 7.2, CH$_3$); δ_C 144.5 (dd, $^{1}J_{CF}$ 229.1, $^{2}J_{CF}$ 14.1, C-6), 143.1 (ddd, $^{1}J_{CF}$ 251.2, $^{3}J_{CF}$ 5.3, $^{4}J_{CF}$ 1.9, C-3), 141.9 (m, C-2), 134.3 (ddd, $^{1}J_{CF}$ 248.2, $^{2}J_{CF}$ 32.4, $^{3}J_{CF}$ 5.4, C-5), 116.4 (ddd, $^{2}J_{CF}$ 25.2, $^{2}J_{CF}$ 19.8, $^{3}J_{CF}$ 3.8, C-4), 44.3 (d, $^{4}J_{CF}$ 5.8, CH$_2$), 13.8 (s, CH$_3$); *m/z* (EI$^+$) 204 ([M]$^+$, 79), 189 ([M−CH$_3$]$^+$, 100), 175 ([M−CH$_2$CH$_3$]$^+$, 64), 161 ([M−(CH$_2$)$_2$CH$_3$]$^+$, 100).

3.3.3. 4-Bromo-*N*,*N*-diethyl-3,5,6-trifluoropyridin-2-amine 6f. Diethylamine (0.21 g, 2.84 mmol), **5f** (0.65 g, 2.84 mmol), sodium hydrogen carbonate (0.24 g, 2.84 mmol) and acetonitrile (20 ml) gave a brown oil (0.78 g). Purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave 4-bromo-*N*,*N*-diethyl-3,5,6-trifluoropyridin-2-amine **6f** (0.49 g, 61%) as a colourless oil; ([M+H]$^+$ 283.0050, $C_9H_{10}N_2F_3Br$ requires [M+H]$^+$ 283.0052); δ_F −90.45 (1F, t, $^{3}J_{FF}$ 27.1, F-6), −130.80 (1F, dd, $^{3}J_{FF}$ 29.3, $^{4}J_{FF}$ 9.0, F-5), 151.47 (1F, dd, $^{4}J_{FF}$ 24.8, $^{5}J_{FF}$ 6.8, F-3); δ_H 3.45 (4H, qd, $^{3}J_{HH}$ 7.2, $^{4}J_{HF}$ 2.0, CH$_2$), 1.19 (6H, t, $^{3}J_{HH}$ 7.2, CH$_3$); δ_C 144.5 (ddd, $^{1}J_{CF}$ 231.0, $^{2}J_{CF}$ 14.8, $^{4}J_{CF}$ 2.3, C-6), 141.6 (m, C-2), 141.2 (ddd, $^{1}J_{CF}$ 251.6, $^{3}J_{CF}$ 6.1, $^{4}J_{CF}$ 3.5, C-3), 133.3 (ddd, $^{1}J_{CF}$ 248.2, $^{2}J_{CF}$ 33.9, $^{3}J_{CF}$ 1.6, C-5), 111.7 (ddd, $^{2}J_{CF}$ 24.8, $^{2}J_{CF}$ 19.4, $^{3}J_{CF}$ 5.4, C-4), 44.4 (d, $^{4}J_{CF}$ 6.1, CH$_2$), 13.8 (s, CH$_3$); *m/z* (EI$^+$) 282 ([M]$^+$, 40), 267 ([M−CH$_3$]$^+$, 100).

3.3.4. *N*,*N*-Diethyl-3,5,6-trifluoro-4-nitropyridin-2-amine 6i. Compound **5h** (0.5 g, 2.55 mmol), diethylamine (0.19 g, 2.55 mmol), sodium hydrogen carbonate (0.21 g, 2.55 mmol) and acetonitrile (175 ml) gave a brown oil (0.55 g), which contained **6i** and diethyl-(2,3,5,6-tetrafluoro-pyridin-4-yl)-amine[19] **6j**; δ_F −94.90 (2F, m, F-2), −156.64 (2F, m, F-3); *m/z* (EI)$^+$ 222 ([M]$^+$, 26), 207 ([M−CH$_3$]$^+$, 86), 179 ([M−(CH$_2$)$_2$CH$_3$]$^+$, 99) in the ratio 2:1 by ^{19}F NMR. Purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) gave *N*,*N*-diethyl-3,5,6-trifluoro-4-nitropyridin-2-amine **6i** (0.22 g, 35%) as an orange oil; ([M]$^+$ 249.0718, $C_9H_{10}N_3F_3O_2$ requires [M]$^+$ 249.0720); δ_F −85.35 (1F, m, F-6), −147.54 (1F, dd, $^{3}J_{FF}$ 31.6, $^{4}J_{FF}$ 13.5, F-3), −166.50 (1F, dd, $^{3}J_{FF}$ 24.8, $^{4}J_{FF}$ 11.3, F-5); δ_H 3.50 (4H, qd, $^{3}J_{HH}$ 7.0, $^{5}J_{HF}$ 2.0, CH$_2$), 1.21 (6H, t, $^{3}J_{HH}$ 7.0, CH$_3$); δ_C 143.2 (ddd, $^{1}J_{CF}$ 233.6, $^{2}J_{CF}$ 12.9, $^{4}J_{CF}$ 1.9, C-6), 140.6 (m, C-2), 137.2 (m, C-4), 133.3 (dm, $^{1}J_{CF}$ 265.1, C-5), 124.7 (ddd, $^{1}J_{CF}$ 260.4, $^{2}J_{CF}$ 36.3, $^{3}J_{CF}$ 2.9, C-3), 43.4 (d, $^{4}J_{CF}$ 6.3, CH$_2$), 12.5 (s, CH$_3$); *m/z* (EI)$^+$ 249 ([M]$^+$, 66), 234 ([M−CH$_3$]$^+$, 100), 220 ([M−CH$_2$CH$_3$]$^+$, 8), 203 ([M−CH$_3$NO$_2$]$^+$, 77), 160 ([M−NO$_2$CH$_3$CH$_2$N]$^+$, 75).

3.3.5. 2-(Diethylamino)-3,5,6-trifluoroisonicotinonitrile 6k. Compound **5i** (1.0 g, 5.68 mmol), diethylamine (0.41 g, 5.68 mmol), sodium hydrogen carbonate (0.48 g, 5.68 mmol) and acetonitrile (175 ml) gave a yellow oil (0.87 g). Purification by column chromatography on silica gel (1:1 *n*-hexane/dichloromethane) gave 2-(diethylamino)-3,5,6-trifluoroisonicotinonitrile **6k** (0.65 g, 50%) as a yellow oil; ([M+H]$^+$ 230.0901. $C_{10}H_{10}N_3F_3$ requires [M+H]$^+$ 230.0900); δ_F −88.14 (1F, m, F-6), −130.48 (1F, dd, $^{3}J_{FF}$ 33.8, $^{4}J_{FF}$ 11.3, F-5), −153.41 (1F, dd, $^{4}J_{FF}$ 24.8, $^{5}J_{FF}$ 9.0, F-3); δ_H 3.49 (4H, qd, $^{3}J_{HH}$ 7.0, $^{5}J_{HF}$ 2.0, CH$_2$),

1.21 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 143.2 (dd, $^1J_{CF}$ 216.5, $^2J_{CF}$ 12.4, C-6), 142.7 (m, C-3), 140.5 (m, C-2), 131.6 (dd, $^1J_{CF}$ 260, $^2J_{CF}$ 33.9, C-5), 107.0 (s, CN), 102.5 (m, C-4), 43.4 (d, $^4J_{CF}$ 5.8, CH_2), 12.5 (s, CH_3); *m/z* (EI^+) 229 ($[M]^+$, 19), 214 ($[M-CH_3]^+$, 82), 186 ($[M-NCH_2CH_3]^+$, 100); and 2,3-(bisdiethylamino)-5,6-difluoroisonicotinonitrile **6l** (0.27 g, 17%) as a yellow oil; ($[M+H]^+$ 283.1730, $C_{14}H_{20}N_4F_2$ requires $[M+H]^+$ 283.1729); δ_F −74.68 (1F, d, $^3J_{FF}$ 31.6, F-6), −132.58 (1F, d, $^3J_{FF}$ 31.6, F-5); δ_H 3.49 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.5, CH_2), 3.06 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 1.0, CH_2), 1.21 (6H, t, $^3J_{HH}$ 7.0, CH_3), 1.02 (6H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 153.6 (d, $^1J_{CF}$ 240.0, C-6), 143.0 (d, $^1J_{CF}$ 232.3, C-5), 141.9 (m, C-2), 118.1 (d, $^3J_{CF}$ 34.4, C-3), 114.2 (m, C-4), 110.7 (m, CN), 47.4 (d, $^4J_{CF}$ 2.4, CH_2), 43.1 (d, $^4J_{CF}$ 5.8, CH_2), 12.7 (s, CH_3), 12.6 (s, CH_3); *m/z* (EI^+) 282 ($[M]^+$, 71), 267 ($[M-CH_3]^+$, 100), 253 ($[M-CH_2CH_3]^+$, 10), 239 ($[M-CH_2CH_2CH_3]^+$, 53).

3.4. Annelation reactions

3.4.1. General procedure. *N,N′*-Dimethylethylene diamine **7** and sodium hydrogen carbonate were added to acetonitrile (400 ml) under argon. The pyridine derivative was added and the solution heated to reflux until ^{19}F NMR indicated high conversion of starting material. The reaction mixture was cooled to room temperature, the solvent evaporated and the residue redissolved in dichloromethane. The mixture was poured into 1 M hydrochloric acid (150 ml), extracted with dichloromethane (2×100 ml), dried ($MgSO_4$) and evaporated to give a crude product. Purification by recrystallisation, sublimation under vacuum or column chromatography on silica gel gave the ring-fused product.

3.4.1.1. 2-[[4-(Diethylamino)-3,5,6-trifluoropyridin-2-yl](methyl)amino]-*N*-methylethanaminium chloride 8a. Compound **7** (1.44 g, 20 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol), **5a** (2.22 g, 10 mmol) and acetonitrile (400 ml) gave a brown oil (1.1 g). Purification by recrystallisation from ethyl acetate gave 2-[[4-(diethylamino)-3,5,6-trifluoropyridin-2-yl](methyl)amino]-*N*-methylethanaminium chloride **8a** (0.5 g, 15%) as beige crystals; mp 122.8–123.1 °C; (Found: C, 47.6; H, 6.8; N, 17.0. $C_{13}H_{22}ClF_3N_4$ requires: C, 47.8; H, 6.7; N, 17.2%); δ_F −95.08 (1F, t, $^3J_{FF}$ 25.2, F-2), −145.03 (1F, d, $^3J_{FF}$ 23.4, F-3), −162.34 (1F, d, $^3J_{FF}$ 25.2, F-5); δ_H 9.78 (2H, br s, NH_2), 3.69 (2H, t, $^3J_{HH}$ 6.7, NCH_2CH_2NH), 3.35 (2H, q, $^3J_{HH}$ 7.0, NCH_2CH_3), 3.24 (2H, t, $^3J_{HH}$ 6.7, NCH_2CH_2NH), 3.08 (3H, d, $^3J_{HH}$ 4.3, NCH_3), 2.80 (3H, s, $CH_3N(Ar)CH_2$), 1.17 (3H, t, $^3J_{HH}$ 7.0, NCH_2CH_3); δ_C 145.9 (dd, $^1J_{CF}$ 225.2, $^2J_{CF}$ 15, C-6), 143.0 (m, C-4), 139.0 (dd, $^1J_{CF}$ 245.6, $^3J_{CF}$ 10.8, C-3), 138.3 (m, C-2), 132.0 (dd, $^1J_{CF}$ 244.5, $^2J_{CF}$ 31.2, C-5); *m/z* (EI^+) 270 ($[M-HF]^+$, 34), 246 ($[M-CH_2NHCH_3]^+$, 100), 179 ($[M-(CH_3)_2CH_2N]^+$, 82).

3.4.1.2. 2-[(4-Ethoxy-3,5,6-trifluoropyridin-2-yl)(methyl)amino]-*N*-methylethanaminium chloride 8b. Compound **7** (1.76 g, 20 mmol), **5d** (1.95 g, 10 mmol), sodium hydrogen carbonate (3.36 g, 40 mmol) and acetonitrile (400 ml) gave an off-white solid (1.34 g). Purification by recrystallisation from dichloromethane gave 2-[(4-ethoxy-3,5,6-trifluoropyridin-2-yl)(methyl)amino]-*N*-methylethanaminium chloride **8b** (0.70 g, 23%) as a white solid; mp 139.0–141.2 °C; (Found: C, 43.8; H, 5.7; N, 13.8. $C_{11}H_{17}N_3ClF_3O$ requires: C, 44.1; H, 5.7; N, 14.0%); δ_F −91.60 (1F, t, $^3J_{FF}$ 25.5, F-6), −152.70 (1F, d, $^3J_{FF}$ 29, F-5), −168.80 (1F, d, $^4J_{FF}$ 24.6, F-3); δ_H 9.67 (2H, br s, NH_2), 4.42 (2H, q, $^3J_{HH}$ 6.8, CH_2CH_3), 3.80 (2H, t, $^3J_{HH}$ 6.8, NCH_2), 3.22 (2H, t, $^3J_{HH}$ 6.0, NCH_2), 3.15 (3H, d, $^3J_{HH}$ 4.0, NCH_3), 2.77 (3H, t, $^3J_{HH}$ 5.6, NH_2CH_3) 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C146.0 (m, C-2), 145.5 (dd, $^1J_{CF}$ 232.6, $^2J_{CF}$ 10.6, C-6), 141.7 (m, C-4), 138.0 (dd, $^1J_{CF}$ 249.0, $^3J_{CF}$ 5.7, C-3), 131.0 (dd, $^1J_{CF}$ 249.7, $^2J_{CF}$ 31.6, C-5), 70.4 (t, $^4J_{CF}$ 3.4, NCH_2), 48.3 (s, $NCH_2CH_2NH_2$), 47.0 (s, OCH_2), 39.2 (d, $^4J_{CF}$ 9.6, NCH_3), 33.3 (s, NCH_3), 15.8 (s, OCH_2CH_3); *m/z* (EI^+) 244 ($[M-HFCl]^+$, 2), 219 ($[M-CH_2NH_2CH_3Cl]^+$, 43), 191 ($[M-CH_2CH_2CH_2NH_2CH_3Cl]^+$, 88).

3.4.1.3. 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 8c. Compound **7** (1.17 g, 13.2 mmol), **5e** (1 g, 6.62 mmol), sodium hydrogen carbonate (2.23 g, 26.5 mmol) and acetonitrile (175 ml) gave a purple-black solid (1.23 g). Purification by column chromatography on silica gel (2:1 *n*-hexane/ethyl acetate) gave 6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **8c** (0.87 g, 66%) as a red solid, mp 30 °C; ($[M+H]^+$ 200.0994, $C_9H_{11}N_3F_2$ requires $[M+H]^+$ 200.0994); δ_F −108.05 (1F, s, F-6), −160.50 (1F, s, F-7); δ_H 6.42 (1H, m, H-8), 3.41 (2H, br s, CH_2), 3.17 (2H, br s, CH_2), 2.96 (3H, br s, CH_3), 2.73 (3H, br s, CH_3); δ_C 142.0 (dd, $^1J_{CF}$ 220.4, $^2J_{CF}$ 15.2, C-6), 141.0 (d, $^3J_{CF}$ 13.7, C-3*b*), 135.9 (dd, $^1J_{CF}$ 238.6, $^2J_{CF}$ 28.6, C-7), 130.2 (s, C-2*b*), 107.8 (d, $^2J_{CF}$ 21.8, C-8), 48.3 (s, CH_2), 48.2 (s, CH_2), 39.2 (s, CH_3), 36.7 (s, CH_3); *m/z* (EI^+) 199 ($[M]^+$, 100), 184 ($[M-CH_3]^+$, 56), 169 ($[M-(CH_3)_2]^+$, 16).

3.4.1.4. 8-Bromo-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 8d. Compound **7** (0.73 g, 8.73 mmol), **5f** (1.0 g, 4.37 mmol), sodium hydrogen carbonate (1.47 g, 17.47 mmol) and acetonitrile (400 ml) gave a brown solid (0.48 g). Purification by column chromatography on silica gel (1:1 ethyl acetate/*n*-hexane) gave *8-bromo-6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **8d** (0.24 g, 20%) as yellow crystals; mp 76.2–77.0 °C; (Found: C, 39.1; H, 3.7; N, 15.0; $C_9H_{10}N_3BrF_2$ requires: C, 39.0; H, 3.6; N, 15.2%); δ_F −94.67 (1F, d, $^3J_{FF}$ 26.7, F-6), −152.39 (1F, d, $^3J_{FF}$ 26.7, F-7); δ_H 3.37 (2H, t, $^3J_{HH}$ 5, CH_2), 3.12 (3H, s, CH_3), 3.06 (2H, t, $^3J_{HH}$ 5, CH_2), 2.73 (3H, s, CH_3); δ_C 145.9 (dd, $^1J_{CF}$ 228.7, $^2J_{CF}$ 15.6, C-6), 145.3 (dd, $^3J_{CF}$ 15.6, $^4J_{CF}$ 1.2, NCN), 133.8 (dd, $^1J_{CF}$ 241.6, $^2J_{CF}$ 31.6, C-3), 126.4 (dd, $^3J_{CF}$ 5.8, $^4J_{CF}$ 2.2, BrC*C*N), 117.8 (dd, $^2J_{CF}$ 16.3, $^3J_{CF}$ 5.0, CBr), 48.1 (s, CH_3), 43.3 (s, CH_2), 42.90 (s, CH_3), 36.6 (s, CH_2); *m/z* (EI^+) 277 ($[M]^+$, 96), 262 ($[M-CH_3]^+$, 72), 183 ($[M-CH_3Br]^+$, 26), 168 ($[M-C_2H_6Br]^+$, 22).

3.4.1.5. 6,7-Difluoro-1,4-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 8f. Compound **7** (1.23 g, 14 mmol), **5g** (2.02 g, 6.33 mmol), sodium hydrogen carbonate (1.24 g, 14.8 mmol) and acetonitrile (30 ml) gave a yellow-brown solid (1.2 g). Purification by recrystallisation from *n*-hexane gave *6,7-difluoro-1,4-dimethyl-8-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **8f** (0.98 g, 40%) as yellow needle-like crystals, which darken upon exposure to light and as a mixture of rotamers;

mp 57.9–58.5 °C; (Found: C, 39.3; H, 2.7; N, 11.5. $C_{12}H_{10}N_3F_9$ requires: C, 39.2; H, 2.7; N, 11.2%; δ_F (major rotamer) −74.88 (6F, br m, CF_3), −94.44 (1F, $^3J_{FF}$ 27, F-6), 155.65 (1F, sex, $^5J_{FF}$ 27, F-7), −179.66 (1F, s, $(CF_3)_2CF$); δ_F (minor rotamer) −70.77 (6F, s, CF_3), −92.47 (1F, d, $^3J_{FF}$ 33, F-6), −156.80 (1F, d, $^4J_{FF}$ 44, F-7), −168.43 (1F, d, $^4J_{FF}$ 88, $(CF_3)_2CF$); δ_H 3.47 (2H, br s, CH_2), 3.13 (3H, s, CH_3), 2.97 (2H, br m, CH_2), 2.63 (3H, s, CH_3); δ_C 147.6 (dd, $^1J_{CF}$ 183.1, $^2J_{CF}$ 13.8, C-6), 147.2 (d, $^3J_{CF}$ 11.1, NCN), 132.4 (dm, $^1J_{CF}$ 200.7, C-7), 128.5 (s, CFC*C*N), 120.8 (qd, $^1J_{CF}$ 230.0, $^2J_{CF}$ 22.5, CF_3), 119.9 (m, C-8), 92.0–96.0 (m, *C*F$(CF_3)_2$), 47.1 (s, CH_2), 45.7 (d, $^5J_{CF}$ 5.7, 1-NCH_3), 43.2 (s, CH_2), 37.4 (s, 4-NCH_3); *m/z* (EI^+) 368 ($[MH]^+$, 34), 367 ($[M]^+$, 100), 352 ($[M-CH_3]^+$, 90), 325 ($[M-C_2H_4N]^+$, 49), 263 ($[M-C_4H_9N_2F]^+$, 89), 69 ($[CF_3]^+$, 32), 42 ($[C_2H_4N]^+$, 53).

3.4.1.6. 6,7-Difluoro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine 8g. Compound **7** (0.58 g, 6.63 mmol), **5h** (0.65 g, 3.32 mmol), sodium hydrogen carbonate (1.11 g, 13.27 mmol) and acetonitrile (150 ml) gave a red oily solid (1.04 g). Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate) gave *6,7-difluoro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine* **8g** (0.37 g, 46%) as dark red crystals; mp 79.4–80.9 °C; (Found: C, 44.3; H, 4.1; N, 22.9; $C_9H_{10}N_4F_2O_2$ requires: C, 44.3; H, 4.1; N, 23.0%); δ_F −99.61 (1F, d, $^3J_{FF}$ 24.6, F-6), −170.43 (1F, d, $^3J_{FF}$ 23.7, F-7); δ_H 3.42 (2H, t, $^3J_{HH}$ 4.2, CH_2), 3.26 (2H, t, $^3J_{HH}$ 5.0, CH_2), 3.08 (3H, s, CH_3), 2.78 (3H, s, CH_3); δ_C 144.0 (dd, $^3J_{CF}$ 14.5, $^4J_{CF}$ 2.1, C-3), 142.7 (dd, $^1J_{CF}$ 226.4, $^2J_{CF}$ 13.3, C-6), 136.5 (dm, $^2J_{CF}$ 12.5, C-8), 127.8 (dd, $^1J_{CF}$ 252.7, $^2J_{CF}$ 33.9, C-7), 122.1 (dd, $^3J_{CF}$ 5.3, $^4J_{CF}$ 3.1, C-2), 49.3 (s, CH_2), 45.5 (s, CH_2), 42.0 (s, CH_3), 37.2 (s, CH_3); *m/z* (EI^+) 244 ($[M]^+$, 100), 214 ($[M-(CH_3)_2]^+$, 8), 198 ($[M-NO_2]^+$, 34); and, **8h** (0.14 g, 20%); spectral data consistent with the literature data.[12]

3.4.1.7. 6,7-Difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine-8-carbonitrile 8i. Compound **7** (0.67 g, 7.57 mmol), **5i** (0.66 g, 3.79 mmol), sodium hydrogen carbonate (1.27 g, 15.14 mmol) and acetonitrile (175 ml) gave a yellow-black solid. The solid was filtered through a silica plug and recrystallisation from ethyl acetate/*n*-hexane gave *6,7-difluoro-1,4-dimethyl-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-8-carbonitrile* **8i** (0.76 g, 90%) as bright yellow crystals; mp 128.0–128.8 °C; (Found: C, 53.6; H, 4.5; N, 25.2; $C_{10}H_{10}N_4F_2$ requires: C, 53.6; H, 4.5; N, 25.0%); δ_F −104.75 (1F, d, $^3J_{FF}$ 22.6, F-6), −156.79 (1F, d, $^3J_{FF}$ 22.9, F-7); δ_H 3.40 (2H, m, CH_2), 3.39 (2H, m, CH_2), 3.30 (3H, s, CH_3), 3.05 (3H, s, CH_3); δ_C 142.6 (dd, $^3J_{CF}$ 15.5, $^4J_{CF}$ 3.0, C-4*a*), 141.3 (dd, $^1J_{CF}$ 223.6, $^2J_{CF}$ 13.9, C-6), 134.7 (dd, $^1J_{CF}$ 250.4, $^2J_{CF}$ 31.5, C-7), 133.5 (dd, $^3J_{CF}$ 4.4, $^4J_{CF}$ 2.4, C-8*a*), 113.4 (d, $^3J_{CF}$ 4.8, CN), 94.3 (dm, $^2J_{CF}$ 14.9, C-8), 49.7 (s, CH_2), 46.2 (s, CH_2), 42.8 (s, CH_3), 37.4 (s, CH_3); *m/z* (EI^+) 224 ($[M]^+$, 100), 209 ($[M-CH_3]^+$, 52), 194 ($[M-(CH_3)_2]^+$, 8).

3.5. X-ray crystallography

The data were collected on a Bruker SMART CCD 6K (**8a** and **8i**), 1K (**8f**) and Bruker Proteum M CCD (**8d**) at 120 K using graphite monochromated Mo Kα radiation (λ=0.71073 Å). All structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were found in the difference Fourier maps and refined isotropically (structures **8a**, **8f**) or were placed in calculated positions and refined using a 'riding model' (structures **8d** and **8i**). Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 636370–636373. The structures of **8e** and **8h** have been described in the previous papers.[11,12]

*Crystal data for **8a***: $C_{13}H_{22}ClF_3N_4$, M=326.80, orthorhombic, space group $Pna2_1$, a=9.1534(3), b=31.9807(9), c=5.3121(1) Å, U=1555.02(7) Å^3, $F(000)$=688, Z=4, D_c=1.396 mgm^{-3}, μ=0.276 mm^{-1}. 16,451 reflections ($2.31\leq\theta\leq29.99°$), 4538 unique data (R_{merg}=0.0250). Final $wR_2(F^2)$=0.0877 for all data (279 refined parameters), conventional $R_1(F)$=0.0336 for 4277 reflections with $I\geq2\sigma$, GOF=1.095.

*Crystal data for **8d***: $C_9H_{10}BrF_2N_3$, M=278.11, monoclinic, space group $C2/c$, a=9.8077(3), b=15.1523(5), c=14.1039(5) Å, β=101.77(1)°, U=2051.9(1) Å^3, $F(000)$=1104, Z=8, D_c=1.801 mgm^{-3}, μ=4.005 mm^{-1}. 7616 reflections ($2.51\leq\theta\leq29.00°$), 2656 unique data (R_{merg}=0.0202). Final $wR_2(F^2)$=0.0752 for all data (136 refined parameters), conventional $R_1(F)$=0.0261 for 2329 reflections with $I\geq2\sigma$, GOF=1.178.

*Crystal data for **8f***: $C_{12}H_{10}F_9N_3$, M=367.23, monoclinic, space group $P2_1/c$, a=6.9634(5), b=13.5908(10), c=14.8672(11) Å, β=92.12(1)°, U=1406.0(2) Å^3, $F(000)$=736, Z=4, D_c=1.735 mgm^{-3}, μ=0.190 mm^{-1}. 12,100 reflections ($2.03\leq\theta\leq25.99°$), 2756 unique data (R_{merg}=0.055). Final $wR_2(F^2)$=0.1638 for all data (257 refined parameters), conventional $R_1(F)$=0.0792 for 2141 reflections with $I\geq2\sigma$, GOF=1.180.

*Crystal data for **8i***: $C_{10}H_{10}F_2N_4$, M=224.22, monoclinic, space group $P2_1/n$, a=6.9196(1), b=14.5749(2), c=9.7248(1) Å, β=90.64(1)°, U=980.71(2) Å^3, $F(000)$=464, Z=4, D_c=1.519 mgm^{-3}, μ=0.123 mm^{-1}. 12,644 reflections ($2.52\leq\theta\leq29.00°$), 2608 unique data (R_{merg}=0.0519). Final $wR_2(F^2)$=0.1141 for all data (183 refined parameters), conventional $R_1(F)$=0.0379 for 2194 reflections with $I\geq2\sigma$, GOF=1.020.

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