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Annelation of perfluorinated heteroaromatic systems by 1,3-dicarbonyl derivatives

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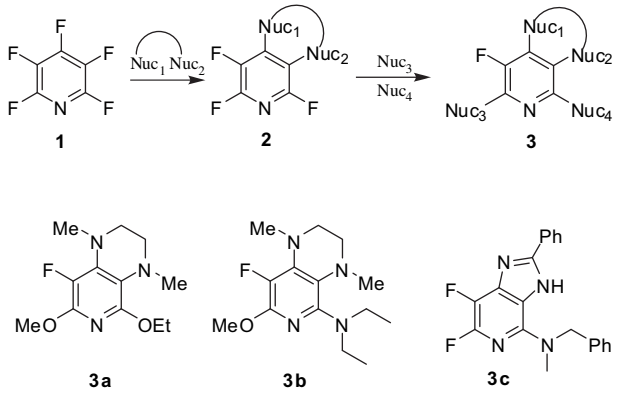
ABSTRACT

Reactions of various perfluorinated heteroaromatic substrates such as tetrafluoro-4-cyanopyridine, tetrafluoropyrazine and tetrafluoropyridazine with 1,3-dicarbonyl systems gave corresponding [5,6]-ring fused furo derivatives. Subsequent reactions of the [5,6] bicyclic scaffolds with nucleophiles gave some highly functionalised heteroaromatic systems.

1. Introduction

Heterocyclic chemistry is, of course, of central importance to the pharmaceutical industry and the majority of commercially important life-science products contain at least one heterocyclic sub-unit within their structures.[1,2] Functional heterocycles generally possess drug-like properties, such as a useful solubility profile, and their rigid structures may be accommodated by a wide variety of receptors leading to valuable biological activity. In order to further explore chemical space available for pharmaceutical applications, there is a continued demand for the development of new heterocyclic core scaffolds that have novel structures and bear functionality that may be readily transformed into focused libraries of analogues for bioassay and subsequent hit-to-lead medicinal chemistry development.

In a developing research programme, we have been exploring the chemistry of highly fluorinated heteroaromatic systems for the synthesis of a range of polyfunctional heterocyclic derivatives such as macrocycles,[3,4] glycosyl donors[5] and fluorinating agents.[6] In the context of polyfunctional heterocyclic synthesis for drug discovery[7] we have established that perfluoroheteroaromatic systems such as pentafluoropyridine may be used as core scaffolds for the synthesis of a range of highly functionalised heteroaromatic and ring fused polycyclic systems.[7–12] For example, reaction of pentafluoropyridine with various difunctional nucleophiles has provided rapid access to various [5,6]- and [6,6]-ring fused systems[8,11] as shown in Scheme 1. Reactions of pentafluoropyridine **1** occur selectively at the 4-position as this site is most activated towards nucleophilic attack[13] and subsequent cyclisation onto the less activated but geometrically accessible 3-position occurs to furnish the ring fused products **2**, which may react further to give functionalised systems **3**. We have developed analogous procedures for the synthesis of ring fused systems from tetrafluoropyridine derivatives,[12] tetrafluoropyridazine[14] and trifluoropyridazinone[15,16] providing an indication of the large range of synthetic opportunities that this strategy offers.



Scheme 1. Polyfunctional scaffolds from pentafluoropyridine **1**.

Our next goal was to expand the range of polycyclic scaffolds that could be accessed by this approach using difunctional nucleophiles derived from 1,3-dicarbonyl systems (Scheme 2), which would, in principle, provide bicyclic systems incorporating a furan ring.

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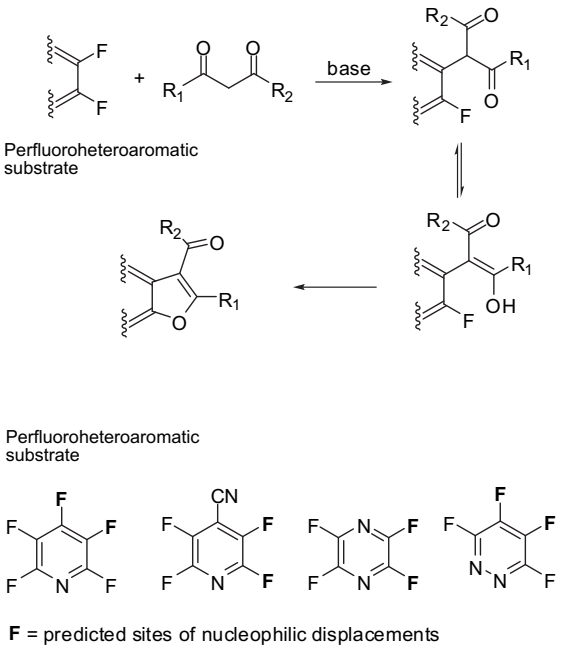


Scheme 2. Synthetic strategy for [5,6]-ring fused heterocyclic synthesis.

Facile routes to, for example, functionalised furo[2,3-*b*]pyridines are highly sought after because such compounds are useful in the search for pharmacologically active substances and are also parent systems for naturally occurring products such as furoquinolines and pterocarpans.[17]

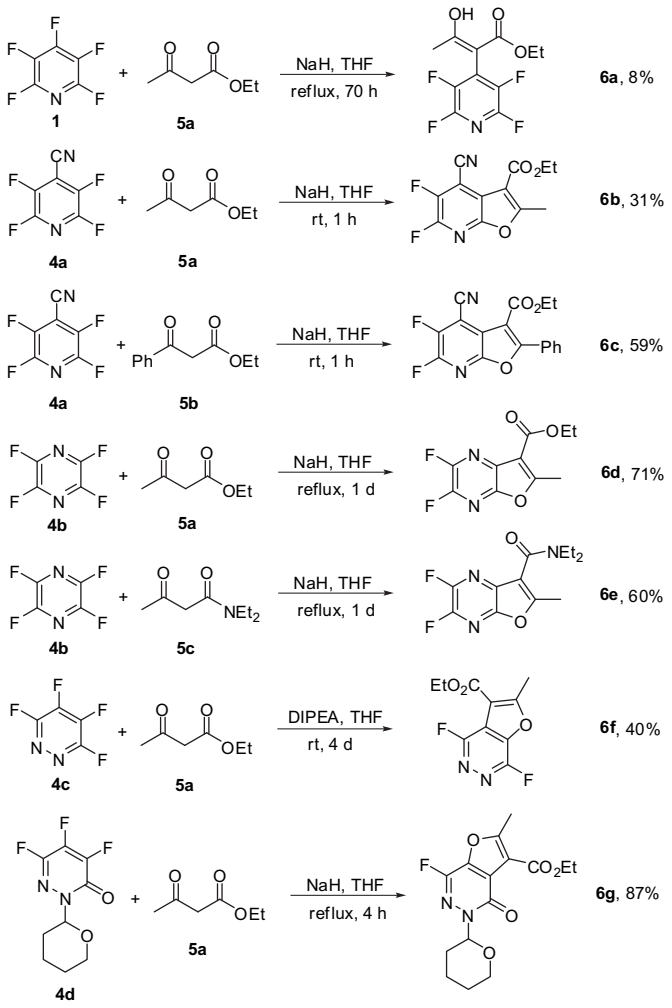
In this paper, we describe reactions between a variety of appropriate highly fluorinated heteroaromatic derivatives and representative 1,3-dicarbonyl substrates.

2. Results and discussion

Reactions between a variety of perfluoroheteroaromatic derivatives **1**, **4a**–**d** and representative 1,3-dicarbonyl substrates **5a**–**c** are collated in Scheme 3.

Reaction of ethyl acetoacetate **5a** with pentafluoropyridine **1** gave **6a** arising from substitution of fluorine at the 4-position but no cyclised product was observed even when strong bases such as LDA were added to the reaction mixture. Compound **6a** exists exclusively as the enol form in solution as determined by ^{1}H NMR spectroscopy in which the hydroxyl resonance occurs at 13.5 ppm whereas no R_3C–H resonance is observed. ^{19}F NMR analysis of the reaction mixture showed that the reaction gave **6a** in high yield but difficulties in purification led to a very low isolated yield.

Tetrafluorocyanopyridine **4a** reacts with ethyl acetoacetate **5a** and 3-oxo-3-phenyl-propionic acid ethyl ester **5b** to give the [5,6]-ring fused systems **6b** and **6c**, respectively, in moderate yield and the structure of **6b** was confirmed by X-ray crystallography (Fig. 1). The structure of **6b** indicates that the carbon nucleophile attacks the 3-position of the pyridine ring, which is strongly activated by the cyano group at the adjacent 4-position, as the first step of this process. The annelation step could, in principle, provide two products depending upon the site of ring closure whereby the oxygen nucleophile could attack the carbon atom of the cyano group in a process that is reminiscent of our earlier syntheses of pyrimidinopyridine systems[11] but, in this case, reaction occurs selectively at the 2-position to give **6b**. This regioselectivity reflects the attack of a 'hard' oxygen nucleophile at a 'hard' electrophilic site rather than at the relatively softer carbon centre of the cyano group and the formation of an aromatic furan ring being more favourable.



Scheme 3. Reactions of perfluoroheteroaromatic derivatives with 1,3-dicarbonyl systems.

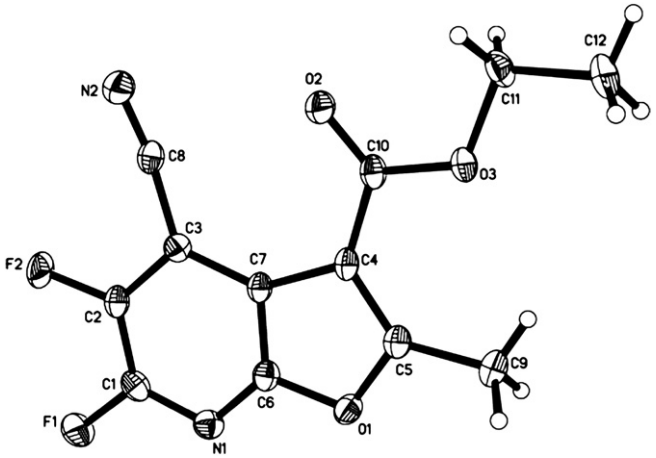


Figure 1. Molecular structure of **6b**.

The structures of **6d** and **6e**, derived from reaction of tetrafluoropyrazine **4b**, were confirmed by X-ray crystallography (Fig. 2).

Reaction of tetrafluoropyridazine **4c** with **5a** gave **6f** arising from attack of the dinucleophilic species at the 4- and 5-positions, consistent with the regioselectivity of nucleophilic aromatic

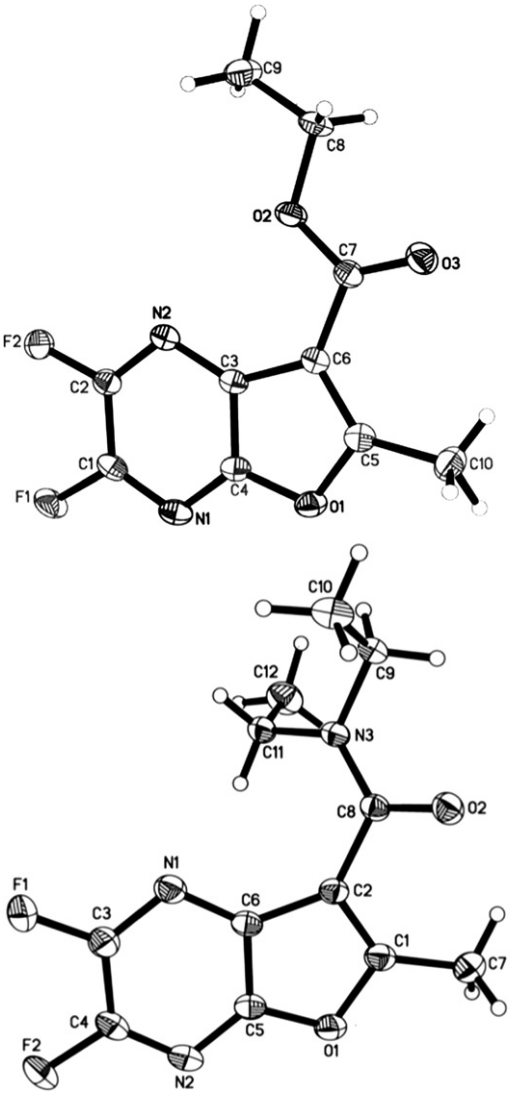


Figure 2. Molecular structures of **6d** (above) and **6e** (below).

substitution reactions established previously.[13] Protected pyridazinone **4d** gave **6g** following a similar reactivity profile to that established previously in which the 4-position is the site of initial nucleophilic substitution. The structure of **6g** was confirmed by X-ray crystallography (Fig. 3).

Each furo-fused ring system **6** possesses at least one fluorine atom attached to carbon that is activated towards nucleophilic attack and so we carried out reactions of representative annelated systems **6b**,**d**,**e** to provide an indication as to whether these systems could be utilised as scaffolds for array synthesis. Reactions of fused ring systems **6b**,**d**,**e** with representative nitrogen and oxygen nucleophiles are shown in Scheme 4.

Reaction of **6b** with lithium diethylamide gave **7**, the position of attack determined by a consideration of ^{19}F NMR data, in which one resonance was observed at −131.4 ppm consistent with fluorine located *meta* to ring nitrogen.

Furo[2,3-*b*]pyrazine **6d** gave products **8** and **9** arising from the substitution of the fluorine atoms located *para* to the furan ring carbon–carbon double bond upon reaction with sodium methoxide and diethylamine, respectively. Similarly, reaction of **6e** with diethylamine gave **10**. The regioselectivity of these processes may be explained by a consideration of the stability of the Meisenheimer intermediates (Scheme 5).

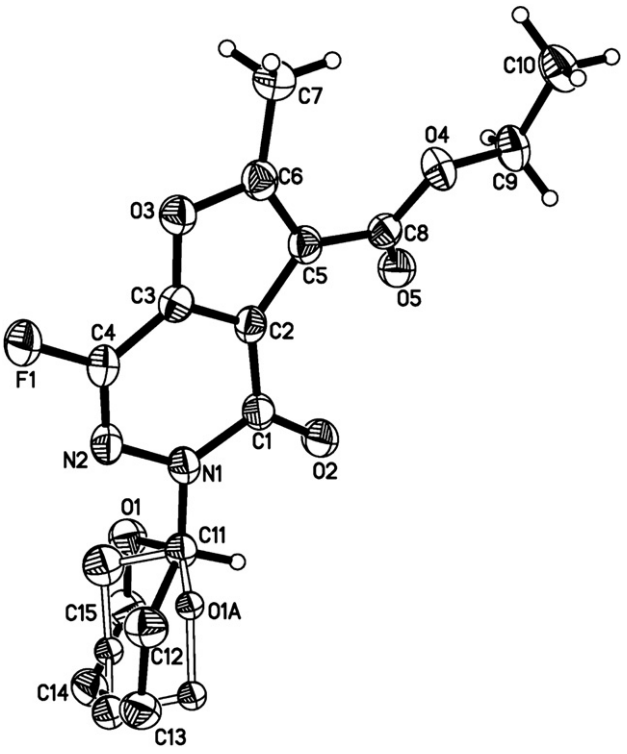
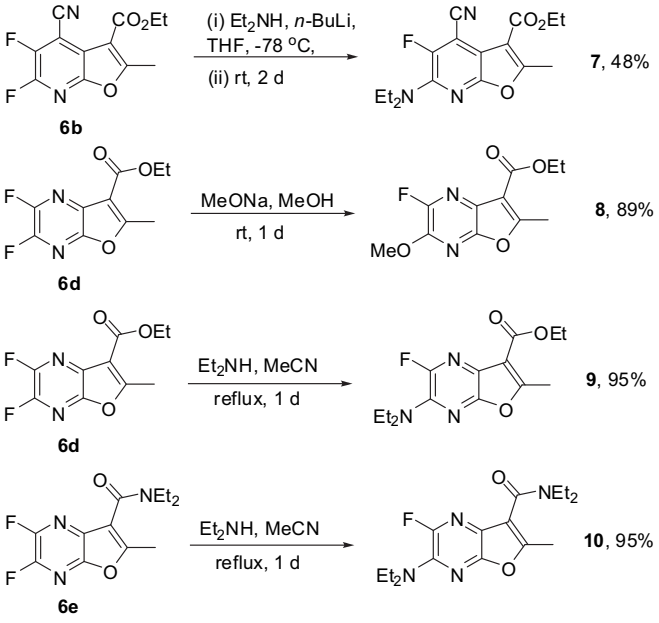


Figure 3. Molecular structure of **6g**.

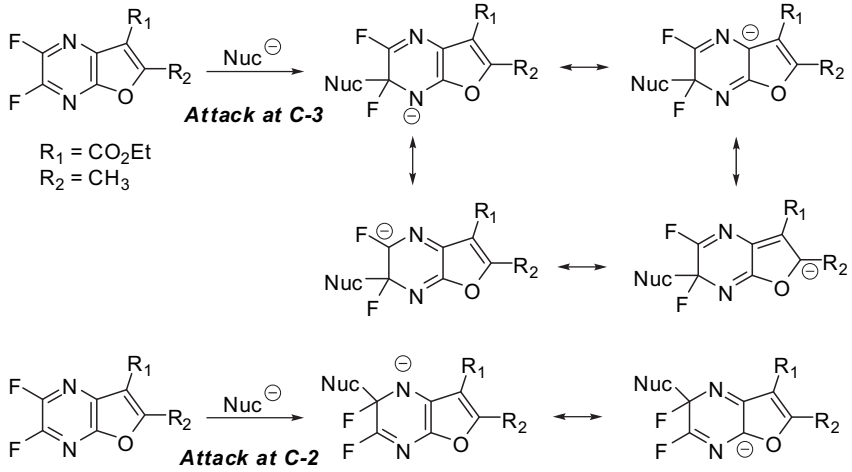


Scheme 4. Reactions of ring fused scaffolds with nucleophiles.

Reaction of nucleophiles at C-3 gives the more stable Meisenheimer intermediate in which the negative charge may be delocalised over both ring systems whereas this is not the case for attack of the nucleophile at C-2, leading to substitution at C-3.

3. Conclusions

Various [5,6]-ring fused furo-pyridine, pyrazine and pyridazine systems were synthesised by reaction of appropriate perfluorinated heteroaromatic substrates and 1,3-dicarbonyl derivatives providing a further illustration of the synthetic possibilities for heterocyclic



Scheme 5. Mechanism of nucleophilic substitution for furo-pyrazine derivatives.

synthesis using highly fluorinated heterocyclic starting materials. Regioselective functionalisations of the bicyclic systems were carried out and these give a further indication of the use of highly fluorinated scaffolds for analogue synthesis.

4. Experimental

4.1. General

All starting materials were obtained commercially. All solvents were dried using literature procedures.[18] NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian Mercury 400 operating at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR), respectively. Chemical shifts are given in parts per million and coupling constants are recorded in hertz, using tetramethylsilane and trichlorofluoromethane as internal standards. IR spectra were obtained using a Perkin Elmer 1600 Series FTIR using a Golden Gate attachment and analysed using GRAMS Analyst software. Mass spectra were recorded on a Thermoquest Trace GC–MS spectrometer (in EI mode), a Micromass LCT LC–MS spectrometer (in ES$^+$ mode) or a Waters ZQ mass spectrometer coupled to a Waters Acquity HPLC system (in ES$^{+/-}$ modes). Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by ^{19}F NMR spectroscopy. Column chromatography was carried out on silica gel.

4.2. Syntheses of [5,6]-ring fused systems

4.2.1. 3-Hydroxy-2-(2,3,5,6-tetrafluoro-pyridin-4-yl)-but-2-enoic acid ethyl ester ***6a****.* Sodium hydride (1.20 g, 30.0 mmol, 60% dispersion in mineral oil) was added to a stirred solution of pentafluoropyridine **1** (2.56 g, 15.0 mmol) and ethyl acetoacetate **5a** (3.90 g, 30 mmol) in dry THF (50 mL) and the reaction mixture was heated to reflux for 70 h, cooled, poured into water (50 mL) and extracted with dichloromethane (4×30 mL). Drying ($MgSO_4$) and evaporation gave a dark oil, which was distilled to give *3-hydroxy-2-(2,3,5,6-tetrafluoro-pyridin-4-yl)-but-2-enoic acid ethyl ester* **6a** (0.33 g, 8%) as a colourless oil; bp 32 °C, 0.50 mbar. Found: C, 47.6; H, 3.4; N, 5.0. $C_{11}H_9F_4NO_3$ requires: C, 47.3; H, 3.3; N, 5.0%; δ_H 1.21 (3H, t, $^3J_{HH}$ 7.1, CH_2CH_3), 1.94 (3H, s, CH_3), 4.22 (2H, q, $^3J_{HH}$ 7.1, CH_2), 13.52 (1H, br s, OH); δ_C 14.1 (s, CH_2CH_3), 20.1 (s, CH_3), 61.9 (s, CH_2), 89.6 (t, $^3J_{CF}$ 2.3, –C=), 128.4–128.8 (m, C-4), 140.4 (dm, $^1J_{CF}$ 257.3, C-3/C-5), 143.6 (dm, $^1J_{CF}$ 245.4, C-2/C-6), 170.0 ($COHCH_3$), 177.8 (s, C=O); δ_F −91.70 (2F, m, F-2), −140.12 (2F, m, F-3); *m*/*z* (EI$^+$) 279 ([M]$^+$, 78%), 43 (100%).

4.2.2. Ethyl 4-cyano-5,6-difluoro-2-methylfuro[2,3-b]pyridine-3-carboxylate ***6b****.* Ethyl acetoacetate **5a** (0.74 g, 5.68 mmol) and sodium hydride (0.27 g, 6.82 mmol, 60% dispersion in mineral oil) were added to dry THF (50 mL) under argon and stirred at rt for 1 h. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **4a** (1.0 g, 5.68 mmol) was added and the reaction mixture heated to reflux for 1 d. The reaction mixture was cooled, solvent evaporated and the residue redissolved in dichloromethane (50 mL). The mixture was poured into water (50 mL), further extracted with dichloromethane (3×50 mL), dried ($MgSO_4$) and evaporated to give the crude product as a brown solid (0.94 g). Purification by column chromatography on silica gel using *n*-hexane/ethyl acetate (3:1) as eluent gave *ethyl 4-cyano-5,6-difluoro-2-methylfuro[2,3-b]pyridine-3-carboxylate* **6b** (0.47 g, 31%) as a white solid; mp 91.8–93.3 °C. Found: C, 54.1; H, 3.0; N, 10.6. $C_{12}H_8F_2N_2O_3$ requires: C, 54.1; H, 3.0; N, 10.5%; R_f 0.5 (*n*-hexane/ethyl acetate, 3:1); δ_H 1.46 (3H, t, $^3J_{HH}$ 7.3, CH_2CH_3), 2.86 (3H, s, 3-CH_3), 4.52 (2H, q, $^3J_{HH}$ 7.3, CH_2); δ_C 14.6 (s, 3-CH_3), 15.0 (s, CH_2CH_3), 61.6 (s, CH_2CH_3), 106.0 (dd, $^2J_{CF}$ 14.9, $^3J_{CF}$ 3.8, C-4), 109.9–110.0 (m, C-3), 110.2 (d, $^3J_{CF}$ 4.8, CN), 116.1–116.2 (m, C-3*a*), 146.0 (dd, $^1J_{CF}$ 266.4, $^2J_{CF}$ 28.9, C-5), 148.0 (dd, $^1J_{CF}$ 247.5, $^2J_{CF}$ 17.3, C-6), 151.6 (dd, $^3J_{CF}$ 15.0, $^4J_{CF}$ 3.4, C-1*a*), 161.8 (s, C=O), 167.2 (d, $^5J_{CF}$ 4.4, C-2); δ_F −89.51 (1F, d, $^3J_{FF}$ 21.0, F-6), −138.36 (1F, d, $^3J_{FF}$ 21.0, F-5); *m*/*z* (EI$^+$) 266 ([M]$^+$, 36%), 193 ([M−$CO_2CH_2CH_3$]$^+$, 30%), 138 ([M−$C_6H_8O_3$]$^+$, 26%).

4.2.3. Ethyl 4-cyano-5,6-difluoro-2-phenylfuro[2,3-b]pyridine-3-carboxylate ***6c****.* 3-Oxo-3-phenyl-propionic acid ethyl ester **5b** (1.09 g, 5.68 mmol) and sodium hydride (0.27 g, 6.82 mmol, 60% dispersion in mineral oil) were added to dry THF (50 mL) under argon and stirred at rt for 1 h. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **4a** (1.0 g, 5.68 mmol) was added and the reaction mixture heated to reflux for 6 d. The reaction mixture was cooled to rt, solvent evaporated and the residue redissolved in dichloromethane (50 mL). The mixture was poured onto water (50 mL), extracted with dichloromethane (3×50 mL), dried ($MgSO_4$) and the solvent evaporated to yield the crude product as a brown oil (1.37 g). Purification by column chromatography on silica gel using *n*-hexane/ethyl acetate (7:1) as eluent gave *ethyl 4-cyano-5,6-difluoro-2-phenylfuro[2,3-b]pyridine-3-carboxylate* **6c** (1.1 g, 59%) as a white solid; mp 118.4–120.3 °C. Found: C, 62.2; H, 3.1; N, 8.5. $C_{17}H_{10}F_2N_2O_3$ requires: C, 62.2; H, 3.0; N, 8.5%; R_f 0.35 (*n*-hexane/

ethyl acetate, 7:1); δ_H 1.43 (3H, t, $^3J_{HH}$ 7.2, CH_3), 4.54 (2H, q, $^3J_{HH}$ 7.2, CH_2), 7.59–7.52 (3H, m, Ar H), 8.0–8.1 (2H, m, Ar H); δ_C 14.4 (s, CH_3), 62.1 (s, CH_2), 106.2 (dd, $^2J_{CF}$ 14.8, $^3J_{CF}$ 3.8, C-4), 109.3 (s, C-3), 110.1 (d, $^3J_{CF}$ 4.6, CN), 117.4 (d, $^3J_{CF}$ 5.3, C-3*a*), 127.4 (s, Ar C), 128.9 (s, Ar CH), 129.8 (s, Ar CH), 132.2 (s, Ar CH), 146.2 (dd, $^1J_{CF}$ 264.9, $^2J_{CF}$ 28.6, C-5), 148.6 (dd, $^1J_{CF}$ 247.0, $^2J_{CF}$ 16.8, C-6), 151.7 (dd, $^3J_{CF}$ 15.2, $^4J_{CF}$ 3.5, C-7*a*), 162.7 (d, $^5J_{CF}$ 4.6, C-2), 161.6 (s, C=O); δ_F −88.11 (1F, d, $^3J_{FF}$ 21.1, F-6), −137.90 (1F, d, $^3J_{FF}$ 21.1, F-5); *m*/*z* (EI^+) 328 ($[M]^+$, 84%), 283 ($[M-OCH_2CH_3]^+$, 100%).

4.2.4. Ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate ***6d***. Ethyl acetoacetate **5a** (2.56 g, 13 mmol) and sodium hydride (0.75 g, 19 mmol, 60% dispersion in mineral oil) were added to THF (250 mL) and stirred at rt for 2 h before the addition of tetrafluoropyrazine **4b** (1.5 g, 10 mmol). The reaction mixture was heated at reflux for 1 d. The reaction solvent was evaporated, added to water (40 mL), extracted with ethyl acetate (3×40 mL), dried ($MgSO_4$) and evaporated. Column chromatography on silica gel using *n*-hexane/ethyl acetate (4:1) as eluent gave *ethyl 2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate* **6d** (1.70 g, 71%) as a white solid; mp 98.9–102.4 °C. Found: C, 49.7; H, 3.4; N, 11.4. $C_{10}H_8F_2N_2O_3$ requires: C, 49.6; H, 3.3; N, 11.6%; R_f 0.4 (*n*-hexane/ethyl acetate, 4:1); δ_H 1.42 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3), 2.86 (3H, s, 6-CH_3), 4.43 (2H, q, $^3J_{HH}$ 7.2, CH_2); δ_C 14.5 (s, CH_2CH_3), 15.4 (s, CH_3), 61.5 (s, CH_2), 109.7 (s, C-7), 131.6 (dd, $^3J_{CF}$ 11.8, $^4J_{CF}$ 5.3, C-7*a*), 143.5 (dd, $^1J_{CF}$ 257.0, $^2J_{CF}$ 34.0, C-3), 146.5 (dd, $^1J_{CF}$ 245.9, $^2J_{CF}$ 28.2, C-2), 147.3 (dd, $^3J_{CF}$ 8.0, $^4J_{CF}$ 1.9, C-4*a*), 161.9 (s, C=O), 168.5 (d, $^5J_{CF}$ 5.4, C-6); δ_F −93.26 (1F, d, $^3J_{FF}$ 22.0, F-2), −95.61 (1F, d, $^3J_{FF}$ 22.0, F-3); *m*/*z* (EI^+) 242 ($[M]^+$, 44%).

4.2.5. N,N-Diethyl-2,3-difluoro-6-methylfuro[2,3-b]pyrazine-7-carboxamide ***6e***. *N,N*-Diethylacetoacetamide **5c** (4.40 g, 30 mmol) and sodium hydride (1.31 g, 30 mmol, 60% dispersion in mineral oil) were added to dry THF (400 mL) and stirred at rt for 2 h before the addition of tetrafluoropyrazine **4b** (2.07 g, 14 mmol). The reaction mixture was heated to reflux for 1 d. The reaction solvent was evaporated and water (40 mL) added to the residue. The aqueous phase was extracted with ethyl acetate (3×40 mL), dried ($MgSO_4$) and evaporated. Column chromatography on silica gel using *n*-hexane/ethyl acetate (4:1) as eluent gave *N,N-diethyl-2,3-difluoro-7-methylfuro[2,3-b]pyrazine-6-carboxamide* **6e** (2.04 g, 60%) as yellow crystals; mp 73–75 °C. Found: C, 53.7; H, 4.9; N, 15.4. $C_{12}H_{13}F_2N_3O_2$ requires: C, 53.5; H, 4.8; N, 15.6%; R_f 0.3 (*n*-hexane/ethyl acetate, 4:1); δ_H 1.04 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.17 (3H, t, $^3J_{HH}$ 7.0, CH_3), 2.56 (1H, s, 6-CH_3), 3.30 (2H, q, $^3J_{HH}$ 7.0, CH_2), 3.50 (2H, q, $^3J_{HH}$ 7.0, CH_2); δ_C 13.6 (s, CH_3), 14.3 (s, CH_3), 15.1 (s, 6-CH_3), 39.6 (s, CH_2), 43.3 (s, CH_2), 114.2 (s, C-7), 131.9 (dd, $^3J_{CF}$ 12.1, $^4J_{CF}$ 5.2, C-7*a*), 143.4 (dd, $^1J_{CF}$ 250.8, $^2J_{CF}$ 34.3, C-2), 147.2 (dd, $^1J_{CF}$ 240.4, $^2J_{CF}$ 29.3, C-3), 147.4 (s, C-4*a*), 147.6 (s, C-6), 161.4 (s, C=O); δ_F −95.80 (1F, d, $^3J_{FF}$ 25.3, F-2), −97.37 (1F, d, $^3J_{FF}$ 25.3, F-3); *m*/*z* (EI^+) 269 ($[M]^+$, 48%), 197 (100), 141 (18).

4.2.6. 4,7-Difluoro-2-methylfuro[2,3-d]pyridazine-3-carboxylic acid ethyl ester ***6f***. DIPEA (0.67 g, 5.17 mmol) and ethyl acetoacetate **5a** (0.25 g, 1.96 mmol) were added to a stirred solution of tetrafluoropyridazine **4c** (0.31 g, 2.05 mmol) in THF (10 mL). After 4 d at rt, the mixture was concentrated and partitioned between dichloromethane (3×10 mL) and water. The combined organic phases were dried and concentrated, and the residue purified by column chromatography on silica gel using *n*-hexane/ethyl acetate (1:1) as eluent to give *4,7-difluoro-2-methylfuro[2,3-d]pyridazine-3-carboxylic acid ethyl ester* **6f** (0.19 g, 40%) as a colourless oil. Found: C, 49.6; H, 3.4; N, 11.9. $C_{10}H_8F_2N_2O_3$ requires: C, 49.6; H, 3.3; N, 11.6%; R_f 0.3 (*n*-hexane/ethyl acetate, 1:1); ν_{max}/cm^{-1} 2988, 1719, 1615, 1587; δ_H 1.44 (3H, t, $^3J_{HH}$ 7.1, CH_2CH_3), 2.92 (3H, s, 2-CH_3), 4.44 (2H, q, $^3J_{HH}$ 7.1, CH_2); δ_C 14.2 (s, CH_3), 14.7 (s, 2-CH_3), 62.0 (s, CH_2), 109.1 (d, $^3J_{CF}$ 3.6, C-3), 119.1 (dd, $^2J_{CF}$ 35.4, $^3J_{CF}$ 5.9, C-3*a*), 141.8 (dd, $^2J_{CF}$ 28.6, $^3J_{CF}$ 10.1, C-1*a*), 152.2 (dd, $^1J_{CF}$ 241.0, $^4J_{CF}$ 3.9, C-4), 158.7 (dd, $^1J_{CF}$ 247.7, $^4J_{CF}$ 2.3, C-7), 161.0 (s, C=O), 168.2 (d, $^4J_{CF}$ 2.2, C-2); δ_F −76.5 (1F, d, $^5J_{FF}$ 33.5, F-4), −98.5 (1 F, d, $^5J_{FF}$ 33.5, F-7); *m*/*z* (EI^+) 242 ($[M]^+$, 49%), 214 (62), 197 (100), 170 (32).

4.2.7. Ethyl 7-fluoro-2-methyl-4-oxo-5-(tetrahydro-2H-pyran-2-yl)-4,5-dihydrofuro[3,2-d]pyridazine-3-carboxylate ***6g***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one **4d** (0.10 g, 0.43 mmol), ethyl acetoacetate **5a** (0.18 g, 1.28 mmol) and sodium hydride (0.033 g, 1.28 mmol, 60% dispersion in mineral oil) was heated at reflux in THF (10 mL) for 4 h. The mixture was concentrated and partitioned between dichloromethane (3×10 mL) and water. The combined organic phases were dried and concentrated, and purification by column chromatography using *n*-hexane/ethyl acetate (2:1) as eluent gave *ethyl 7-fluoro-2-methyl-4-oxo-5-(tetrahydro-2H- pyran-2-yl)-4,5-dihydrofuro[3,2-d]pyridazine-3-carboxylate* **6g** (0.12 g, 87%) as white crystals; mp 113–115 °C. Found C, 55.5; H, 5.3; N, 8.3. $C_{15}H_{17}FN_2O_5$ requires C, 55.6; H, 5.3; N, 8.6%; R_f 0.25 (*n*-hexane/ethyl acetate, 2:1); ν_{max}/cm^{-1} 2952, 1737, 1681, 1602, 1432, 1311, 1277, 1210, 1167, 1080; δ_H 1.41 (3H, t, $^3J_{HH}$ 7.7, CH_2CH_3), 1.50–1.70 (4H, m, CH_2), 2.00–2.20 (2H, m, CH_2), 2.72 (3H, s, 2-CH_3), 3.70–4.10 (2H, m, CH_2), 4.41 (2H, q, $^3J_{HH}$ 7.7, CH_2CH_3), 6.07 (1H, d, $^3J_{HH}$ 10.5, CH-O); δ_C 14.4 (s, CH_3), 14.5 (s, 2-CH_3), 23.2 (s, CH_2), 25.1 (s, CH_2), 29.2 (s, CH_2), 61.8 (s, CH_2CH_3), 69.0 (s, C-6′), 82.8 (s, C-2′), 113.9 (d, $^4J_{CF}$ 2.9, C-3), 124.2 (d, $^3J_{CF}$ 6.9, C-3*a*), 141.1 (d, $^2J_{CF}$ 34.2, C-7*a*), 142.4 (d, $^1J_{CF}$ 235.9, C-7), 156.4 (s, C-2), 161.9 (s, C=O), 164.7 (s, N–C=O); δ_F −105.4 (s); *m*/*z* (ES^+) 241 (100), 325 ($[MH]^+$, 5%), 347 ($[M+Na]^+$, 13%).

4.3. Reactions of ring fused scaffolds

4.3.1. 4-Cyano-6-diethylamino-5-fluoro-2-methylfuro[2,3-b]pyridine-3-carboxylic acid ethyl ester ***7***. *n*-Butyl lithium (0.83 mL, 1.32 mmol, 1.6 M in pentane) and diethylamine (0.10 g, 1.32 mmol) were added to THF (5 mL) at −78°C and the solution was stirred for 1 h before warming to rt. The solution was added to *ethyl 4-cyano-5,6-difluoro-2-methylfuro[2,3-b]pyridine-3-carboxylate* **6b** (0.35 g, 1.32 mmol) in THF (45 mL) and stirred at rt for 2 d. Solvent was evaporated and the residue redissolved in dichloromethane (50 mL). The mixture was poured onto water (50 mL), extracted with dichloromethane (3×50 mL), dried ($MgSO_4$) and solvent evaporated. Purification by column chromatography on silica gel using *n*-hexane/ethyl acetate (4:1) as eluent gave *4-cyano-6-diethylamino-5-fluoro-2-methylfuro[2,3-b]pyridine-3-carboxylic acid ethyl ester* **7** (0.20 g, 48%) as a yellow oil; ($[MH]^+$, 320.1406. $C_{16}H_{18}FN_3O_3$ requires: $[MH]^+$, 320.1405); R_f 0.3 (*n*-hexane/ethyl acetate, 4:1); δ_H 1.18 (6H, t, $^3J_{HH}$ 7.0, NCH_2CH_3), 1.37 (3H, t, $^3J_{HH}$ 7.3, OCH_2CH_3), 2.67 (3H, s, 2-CH_3), 3.50 (4H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 2.0, NCH_2), 4.40 (2H, q, $^3J_{HH}$ 7.3, OCH_2); δ_C 13.9 (s, $N(CH_2CH_3)_2$), 14.5 (s, 2-CH_3), 14.7 (s, OCH_2CH_3), 44.9 (d, $^4J_{CF}$ 6.3, $N(CH_2CH_3)_2$), 61.0 (s, OCH_2CH_3), 103.5 (d, $^2J_{CF}$ 19.2, C-4), 105.3 (s, CN), 109.3 (d, $^3J_{CF}$ 1.4, C-3*a*), 112.1 (d, $^4J_{CF}$ 1.9, C-3), 144.9 (d, $^2J_{CF}$ 9.6, C-6), 148.9 (d, $^1J_{CF}$ 262.0, C-5), 155.0 (d, $^4J_{CF}$ 2.4, C-7*a*), 161.8 (d, $^5J_{CF}$ 1.9, C-2), 163.0 (s, C=O); δ_F −131.43 (s); *m*/*z* (EI^+) 319 ($[M]^+$, 78%), 304 ($[M-CH_3]^+$, 100%), 290 ($[M-CH_2CH_3]^+$, 30%).

4.3.2. Ethyl 2-fluoro-3-methoxy-6-methylfuro[2,3-b]pyrazine-7-carboxylate ***8***. A solution of ethyl 2,3-difluoro-6-methylfuro[2,3-*b*]pyrazine-7-carboxylate **6d** (0.30 g, 1.2 mmol), and sodium methoxide (0.06 g, 1.2 mmol) in methanol (50 mL) was stirred at rt for 1 d. The reaction solvent was evaporated and the sample partitioned between ethyl acetate (3×40 mL) and water (40 mL). The organic layer was separated, dried ($MgSO_4$), evaporated and recrystallised from ethyl acetate to give *ethyl 2-fluoro-3-methoxy-6-methylfuro[2,3-b]pyrazine-7-carboxylate* **8** (0.27 g, 89%) as white needles; mp 159–160 °C. Found: C, 51.7; H, 4.3; N, 10.8. $C_{11}H_{11}FN_2O_4$

requires: C, 52.0; H, 4.4; N, 11.0%; δ_H 1.37 (3H, t, $^3J_{HH}$ 7.0, CH_3), 2.75 (3H, s, 6-CH_3), 4.03 (3H, s, OCH_3), 4.39 (2H, q, $^3J_{HH}$ 7.0, CH_3); δ_C 14.6 (s, CH_3), 15.1 (s, CH_3), 55.2 (s, OCH_3), 61.3 (s, CH_2), 109.6 (s, C-7), 125.0 (d, $^3J_{CF}$ 12.4, C-7*a*), 145.0 (d, $^2J_{CF}$ 30.5, C-3), 147.1 (d, $^1J_{CF}$ 248, C-2), 149.1 (s, C-4*a*), 162.7 (s, C-6), 164.3 (s, C=O); δ_F −91.90 (s); *m*/*z* (EI^+) 254.0 ($[M]^+$, 14%), 208 (100), 180 (82).

4.3.3. 3-(Diethylamino)-2-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate ***9***. Ethyl 2,3-difluoro-6-methylfuro[2,3-*b*]pyrazine-7-carboxylate **6d** (0.42 g, 1.7 mmol) and diethylamine (0.25 g, 3.4 mmol) in acetonitrile (50 mL) were stirred at reflux for 1 d. The reaction solvent was evaporated and partitioned between ethyl acetate (3×40 mL) and water (40 mL). The organic layer was separated, dried ($MgSO_4$), evaporated and recrystallised from ethyl acetate to give *3-(diethylamino)-2-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxylate* **9** (0.48 g, 95%) as yellow crystals; mp 43–45 °C. Found: C, 56.7; H, 6.2; N, 14.2. $C_{14}H_{18}FN_3O_3$ requires: C, 56.9; H, 6.1; N, 14.2%; δ_H 1.0–1.3 (9H, m, CH_3), 2.68 (3H, s, 6-CH_3), 3.4–3.6 (6H, m, CH_2); δ_C 13.8 (s, CH_3), 14.7 (s, CH_3), 15.0 (s, CH_3), 44.9 (s, CH_2), 61.0 (s, CH_2), 109.2 (s, C-7), 120.4 (d, $^3J_{CF}$ 11.1, C-7*a*), 141.0 (d, $^2J_{CF}$ 21.4, C-3), 148.3 (s, C-4*a*), 151.4 (d, $^1J_{CF}$ 196.6, C-2), 161.8 (s, C-6), 163.2 (s, C=O); δ_F −82.54 (s); *m*/*z* (EI^+) 295 ($[M]^+$, 52%), 280 (100), 249 (62).

4.3.4. 3-(Diethylamino)-N,N-diethyl-2-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxamide ***10***. *N*,*N*-Diethyl-2,3-difluoro-7-methylfuro[2,3-*b*]pyrazine-6-carboxamide **6e** (0.50 g, 1.9 mmol) and diethylamine (0.28 g, 3.8 mmol) in acetonitrile (40 mL) were stirred at reflux for 1 d. The reaction solvent was evaporated and the sample dissolved into ethyl acetate (3×40 mL) and water (40 mL). The ethyl acetate was separated, dried ($MgSO_4$), evaporated and recrystallised to give *3-(diethylamino)-N,N-diethyl-2-fluoro-6-methylfuro[2,3-b]pyrazine-7-carboxamide* **10** (0.56 g, 95%) as yellow crystals; mp 66–68 °C. Found: C, 59.4; H, 7.2; N, 17.2. $C_{16}H_{23}FN_4O_2$ requires: C, 59.6; H, 7.2; N, 17.4%; δ_H 1.0–1.3 (12H, m, CH_3), 2.41 (3H, s, 6-CH_3), 3.2–3.6 (8H, m, CH_2); δ_C 13.7 (s, CH_3), 13.8 (s, CH_3), 14.0 (s, CH_3), 14.3 (s, CH_3), 15.1 (s, CH_3), 39.6 (s, CH_2), 43.2 (s, CH_2), 44.7 (s, CH_2), 44.8 (s, CH_2), 113.7 (s, C-7), 120.8 (d, $^3J_{CF}$ 13.4, C-7*a*), 140.7 (d, $^2J_{CF}$ 25.9, C-3), 148.1 (d, $^1J_{CF}$ 244, C-2), 151.1 (s, C-4*a*), 154.1 (s, C-6), 162.5 (s, C=O); δ_F −83.54 (s); *m*/*z* (EI^+) 322 ($[M]^+$, 96%), 249 (100), 221 (94).

4.4. X-ray structures

Single crystal X-ray data were collected on Bruker Proteum-M (**6b** and **6d**) and SMART 6000 (**6e** and **6g**) diffractometers equipped with Cryostream (Oxford Cryosystems) nitrogen coolers at 120 K using graphite monochromated MoKα radiation (λ=0.71073 Å, ω-scan). 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-disordered non-hydrogen atoms were refined with anisotropic displacement parameters, non-disordered H-atoms were located on the difference map and refined isotropically.

Crystallographic data for structures **6b**, **6d**, **6e** and **6g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 753504–753507.

4.4.1. Crystal data for ***6b***. $C_{12}H_8F_2N_2O_3$, M=266.20, monoclinic, space group $P2_1/c$, a=112.7367(6), b=4.9712(2), c=18.2403(8) Å, β=105.90(4)°, U=1110.7(2) Å^3, $F(000)$=544, Z=4, D_c=1.592 mg m^{-3}, μ=0.138 mm^{-1}; 7702 reflections yielded 3049 unique data (R_{merg}=0.0951). Final $wR_2(F^2)$=0.1218 for all data (204 refined parameters), conventional $R_1(F)$=0.0506 for 1820 reflections with $I>2\sigma$, GOF=0.947.

4.4.2. Crystal data for ***6d***. $C_{10}H_8F_4N_2O_3$, M=242.18, triclinic, space group P-1, a=7.7365(4), b=8.3890(4), c=8.8129(5) Å, α=67.79(2), β=73.89(2), γ=76.26(2)°, U=503.05(5) Å^3, $F(000)$=248, Z=2, D_c=1.599 mg m^{-3}, μ=0.143 mm^{-1}. 4451 reflections yielded 2610 unique data (R_{merg}=0.0352). Final $wR_2(F^2)$=0.1119 for all data (186 refined parameters), conventional $R_1(F)$=0.0385 for 2249 reflections with $I>2\sigma$, GOF=1.041.

4.4.3. Crystal data for ***6e***. $C_{12}H_{13}F_2N_3O_2$, M=269.25, monoclinic, space group $P2_1/c$, a=8.0742(2), b=20.5408(6), c=7.8994(2) Å, β=109.89(1)°, U=1231.97(6) Å^3, $F(000)$=560, Z=4, D_c=1.452 mg m^{-3}, μ=0.121 mm^{-1}; 13,735 reflections yielded 3423 unique data (R_{merg}=0.0649). Final $wR_2(F^2)$=0.0973 for all data (224 refined parameters), conventional $R_1(F)$=0.0365 for 2522 reflections with $I>2\sigma$, GOF=1.045.

4.4.4. Crystal data for ***6g***. $C_{15}H_{17}FN_2O_5$, M=324.31, monoclinic, space group $P2/c$, a=11.1242(6), b=7.2292(4), c=18.7744(10) Å, β=94.35(2)°, U=1505.46(14) Å^3, $F(000)$=680, Z=4, D_c=1.431 mg m^{-3}, μ=0.116 mm^{-1}; 16,527 reflections yielded 3640 unique data (R_{merg}=0.0751). Final $wR_2(F^2)$=0.1098 for all data (264 refined parameters), conventional $R_1(F)$=0.0461 for 2095 reflections with $I>2\sigma$, GOF=1.047.

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