# Pyrido[3,2-b][1,4]oxazine and pyrido[2,3-b][1,4]benzoxazine systems from tetrafluoropyridine derivatives

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**Abstract**

Pyrido[3,2-b][1,4]oxazine and pyrido[2,3-b][1,4]benzoxazine systems were synthesised by annelation reactions involving highly fluorinated pyridine derivatives and nitrogen and oxygen centred difunctional nucleophiles by sequential regioselective nucleophilic aromatic substitution processes.

**Keywords**: organofluorine chemistry; perfluoroaromatic; nucleophilic aromatic substitution; tetrafluoropyridine; pyrido[3,2-b][1,4]oxazine; pyrido[2,3-b][1,4]benzoxazine.

## 1. Introduction

In a series of publications, a strategy of utilising highly fluorinated heteroaromatic substrates [1a,b] for the synthesis of a range of functional polycyclic scaffolds with applications in parallel synthesis programmes within the drug discovery arena [1c-f] has developed. For example, penta- and tetra-fluoropyridine derivatives have been used as substrates in annelation reactions involving reaction with appropriate difunctional nucleophiles to give various tetrahydro-pyridopyrazine [2], imidazopyridine [3], dipyridoimidazole [4], furopyridine [5] and thienopyridine systems [6] that are very difficult heterocyclic scaffolds to access by conventional reported methodologies.

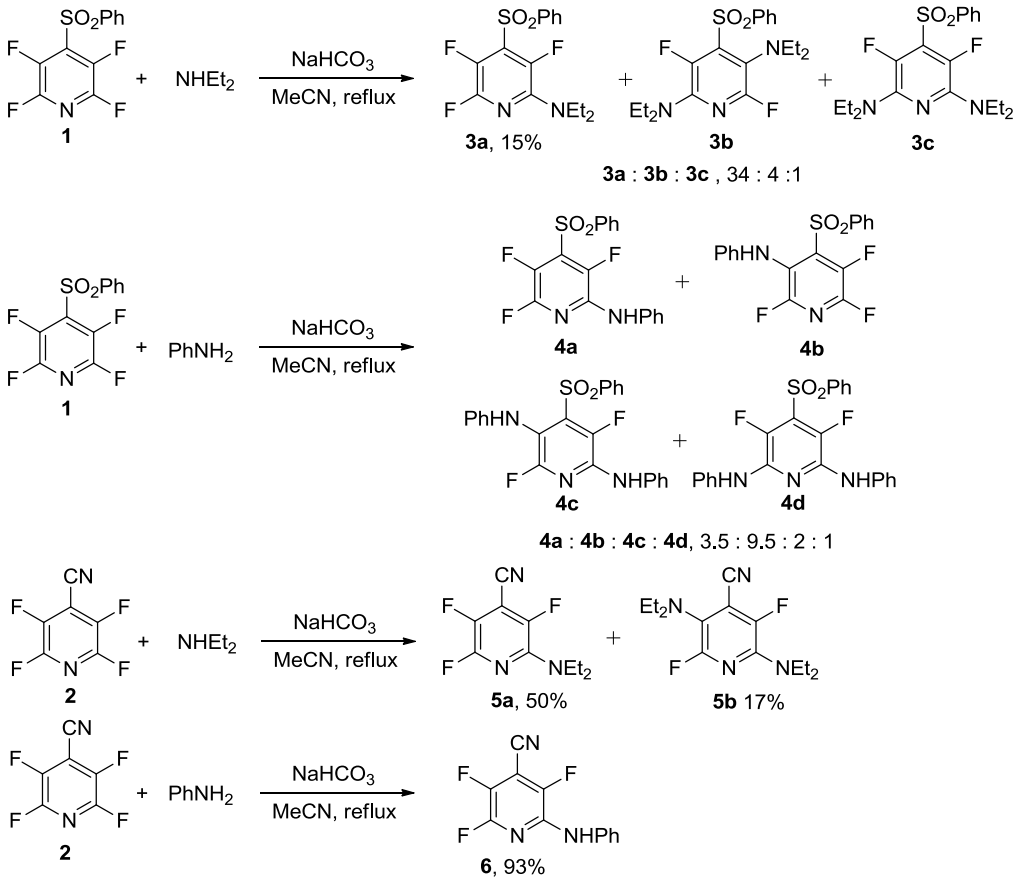
In this paper, we describe a short series of processes involving reaction of nitrogen and oxygen-centred difunctional nucleophiles and 4-phenylsufolnyl- and cyano-tetrafluoropyridine for the synthesis of novel fluorinated pyrido[3,2-b][1,4]oxazine and pyrido[2,3-b][1,4]benzoxazine heterocycles.

## 2. Results and discussion

Initially, model reactions of 4-phenylsulfonyl tetrafluoropyridine **1** and 4-cyano tetrafluoropyridine **2** with representative aliphatic and aryl nitrogen centred nucleophiles were performed before annelation reactions were attempted in order to determine the regioselectivity of $S_NAr$ processes of these systems. Since the nitrogen centre in N,O-centred difunctional nucleophiles can be expected to be more nucleophilic than oxygen sites in appropriate conditions, this would determine the regioselectivity of subsequent annelation processes. Reactions of **1** and **2** with diethylamine have been reported previously [2c] but these results are included here again for clarity (Scheme 1).

The regioselectivity of reactions of **1** with nitrogen centred nucleophiles (Scheme 1) depends on the nature of the substrates involved. Diethylamine gave products **3a-c** arising from predominant *ortho*-

substitution whereas aniline, a softer nucleophile, gave products **4a-d** arising from a modest preference for substitution at the softer *meta*-fluorine site, which is still sufficiently activated towards nucleophilic attack by the presence of the adjacent phenylsulfonyl group. From these two experiments, only product **3a** could be separated from the product mixtures while all other products were identified by diagnostic $^{19}F$ NMR shift data. Resonances of fluorine atoms *ortho* to ring nitrogen typically appear in the -66 - -96 ppm range while *meta* fluorine occur between -135 - -155 ppm. Mono- and di-substituted products were further characterised by mass spectrometry.

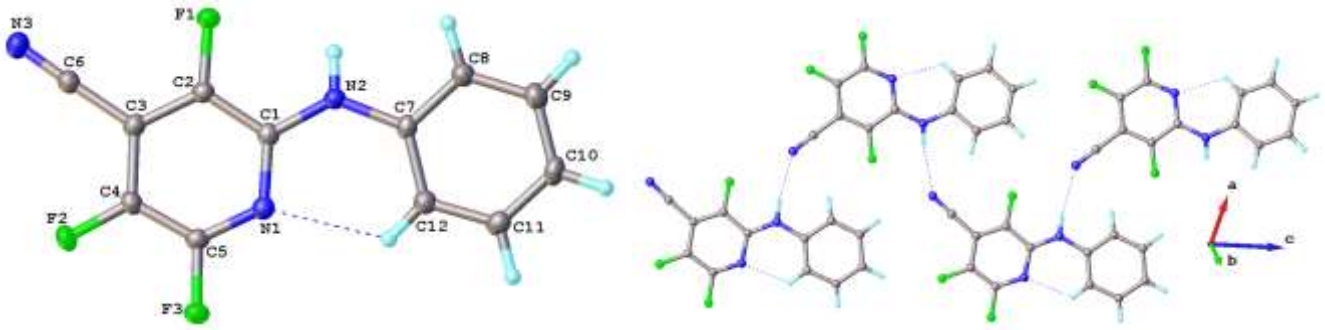



**Scheme 1**. Reactions of **1** and **2** with monofunctional nitrogen nucleophiles

Corresponding reaction of **2** with diethylamine and aniline gave products arising from initial substitution *ortho* to ring nitrogen in both cases (Scheme 1). All products could be isolated due to the less complex product mixtures formed and the structure of **6** was confirmed by X-ray crystallography (Fig. 1).

Crystal **6** (Fig. 1) contains two virtually identical planar (within 0.13Å) crystallographically independent molecules. The planar configuration of the molecule is probably augmented by a weak intramolecular C(Ph)-H…N(Py) (C…N 2.923(2)Å, C-H…N 120(1)°) hydrogen bond. The molecules are linked together by N-H…N (cyano-) (N…N 3.211(2) and 3.223(2)Å, N-H…O 170(2) and 164(1)° for two independent molecules respectively) hydrogen bonds in zig-zag chains along the [001] direction. The weak direction specific C-H…F contacts (C…F 3.146(2) and 3.524(2)Å, the corresponding C-H…F angles 133(1) and 156(1)°) exist between the adjacent chains. Extensive π…π interactions (the shortest interatomic contact is C5…C27(1-x,1-y,1-z) 3.253(2)Å) between aromatic rings of the molecules, belonging to neighbouring layers, complete the 3D framework of the intermolecular interactions in **6**.

These few reactions (Scheme 1) indicate the range of products that may be obtained by $S_NAr$ processes of highly activated polyfluoropyridine substrates, the outcomes of which depend on the nature of both the nucleophile and substrate used.

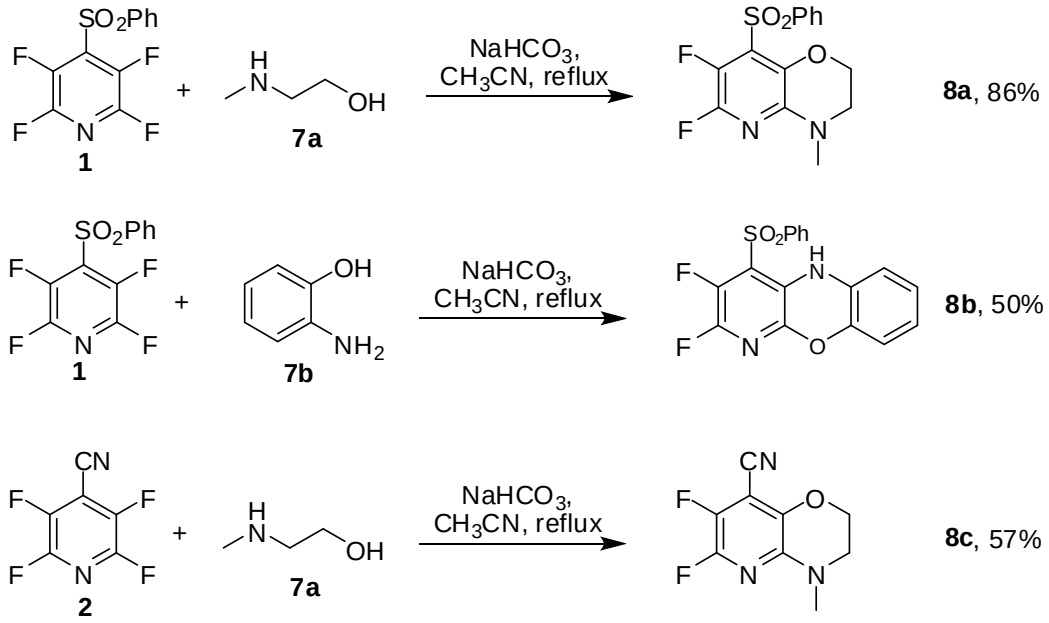



a b

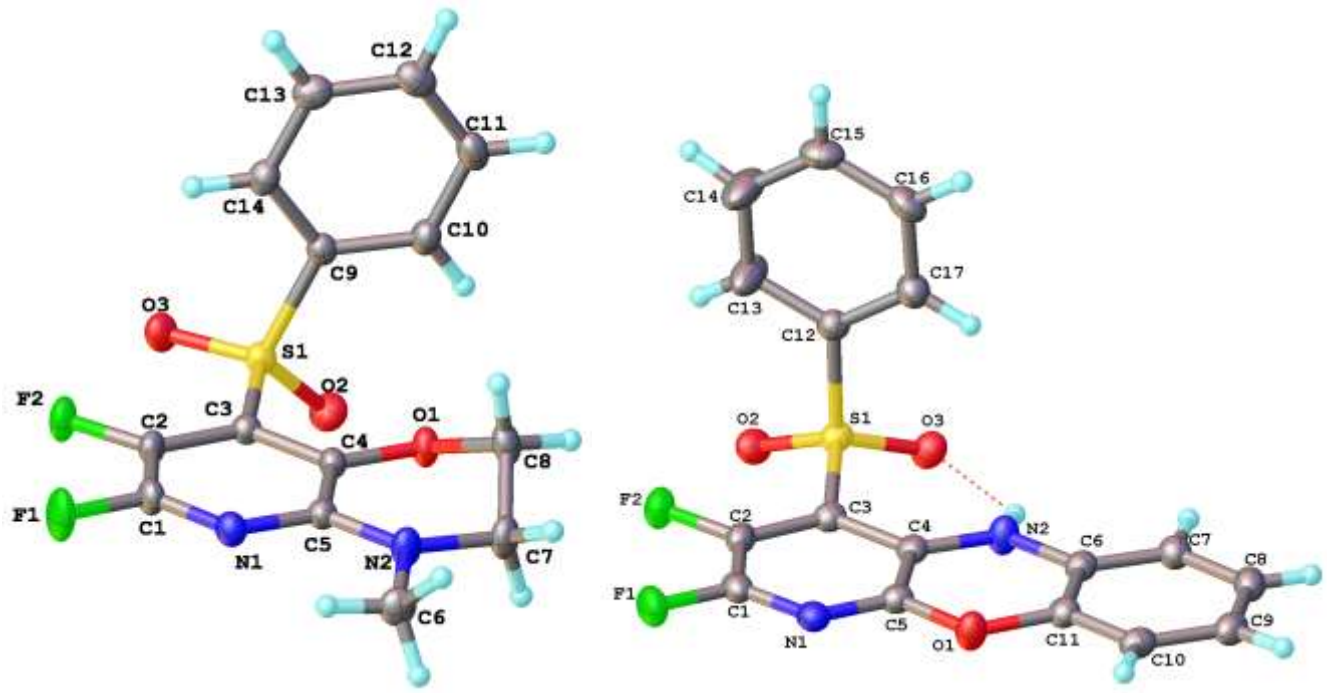
**Fig 1**. One of the independent molecules of **6** (a) and the H-bonded chain in structure **6** (b)

With these model results in hand, reaction of **1** and **2** with representative N,O-difunctional nucleophiles were carried out (Scheme 2). *N*-Methyl ethanolamine **7a** gave high yields of oxazine systems **8a** and **8b**

upon reaction with **1** and **2** respectively due to initial reaction of the more nucleophilic nitrogen atom at the 2-position, consistent with results outlined in Scheme 1, followed by ring closure at the geometrically accessible adjacent site. In addition, reaction of 2-aminophenol **7b** gave **8b** due to initial attack at the *meta*-position by the nitrogen nucleophile, again consistent with model reactions involving aniline described in Scheme 1. All polycyclic products **8a-c** were isolated and characterised by X-ray crystallography (Fig. 2, 3).

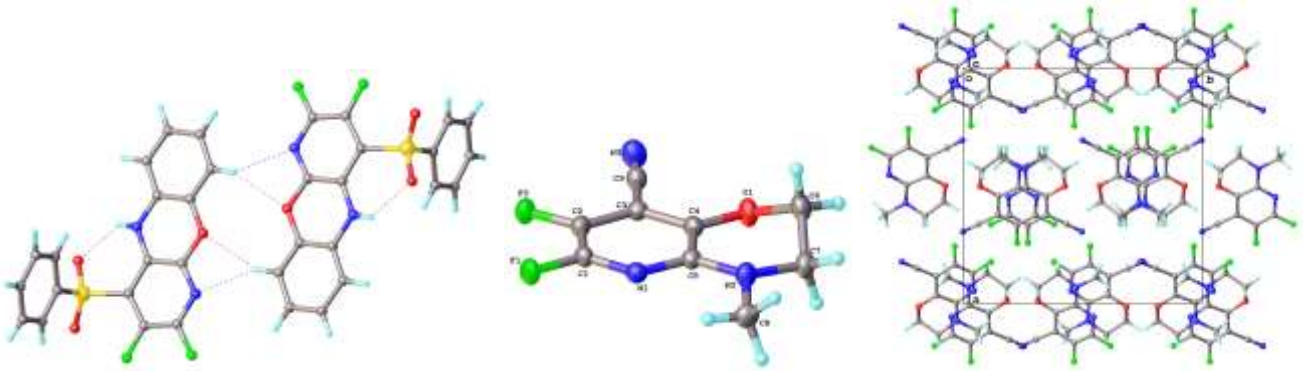



**Scheme 2.** Reactions of **1** and **2** with bifunctional nucleophiles




a b

Fig.2 Molecular structures of **8a** (a) and **8b** (b).



a b c

Fig.3 Centrosymmetrical dimer in structure **8b** (a); one of the independent molecules **8c** (b) and columns in structure **8c** (c)

Aromatic fragments of molecule **8a** (Fig. 2) are almost perpendicular to each other and the molecules in the crystal are linked together by π…π interactions. In contrast to similar π…π interactions in structure **6,** corresponding interactions in **8a** occur between identical aromatic systems: Ph/Ph and Py/Py. Mutual perpendicular orientations of aromatic fragments in structures **8a** and **8b** differ slightly (torsion angles C(4)C(3)S(1)C(Ph) are equal to -65.0(1) and -89.4(2)° respectively) probably due to the presence of an intramolecular hydrogen bond N-H…O in **8b** (N…O 2.720(2)Å, N-H…O 133(2)°). Only the planar aromatic ring systems participate in π…π interactions in structure **8b** (the shortest corresponding interatomic distance is O1…O1(1-x,-y,1-z) 3.240(3)Å) while the Ph-rings are shifted relative to each other and do not overlap. A possible reason for such a shift is the presence of two unusual bifurcated C(1)-H…O(1)/N(1) (C…O 3.530(2)Å, C-H…O 156(1)°; C…N 3.452(2)Å, C-H…N 151(1)°) intermolecular contacts that link two adjacent molecules into centrosymmetrical dimers (Fig. 3).

Similarly to **6**, structure **8c** also contains two almost identical crystallographically independent molecules. In this case the only difference between the molecules is the orientation of the methyl groups, reflecting a non-identical crystal environment of the two molecules. In the absence of strong hydrogen bonds, the packing of molecules **8c** in the crystal is dominated by π…π interactions between the heteroaromatic ring systems (the shortest corresponding interatomic contacts are N1…C4(-x,1-y,1-z) 3.502(2) and N11…C12 (x,1.5-y, -0.5+z) 3.404(2)Å) and these interactions link the molecules in columns along the [001] direction (Fig. 3).

In summary, pyrido[3,2-b][1,4]oxazine and pyrido[2,3-b][1,4]benzoxazine systems, whose identity was determined unambiguously by X-ray crystallography, can be accessed by annelation reactions of highly fluorinated pyridine derivatives and appropriate N,O-difunctional nucleophiles, further extending the use of polyfluorinated heteroaromatic substrates for the synthesis of unusual polyfunctional heterocyclic ring systems.

## 3. Experimental

### 3.1 General

All starting materials were obtained commercially and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz ($^{1}$H n.m.r.), 376 MHz ($^{19}$F n.m.r.) and 100 MHz ($^{13}$C n.m.r.) with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by 1H-1H COSY and 1H-13C HETCOR experiments and coupling constants are given in Hz. Mass spectra were recorded on a VG 7070E spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. 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. Column chromatography was carried out on silica gel (230-400 mesh) and t.l.c. analysis was performed on silica gel t.l.c. plates. Reactions of **1** and **2** with diethylamine were reported previously [2c].

### 3.2 Reactions with Aniline

#### 3.2.1 Reaction of 1 with aniline

A mixture consisting of aniline (1.6 g, 17.2 mmol), sodium hydrogencarbonate (2.89 g, 34.4 mmol), 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **1** (1.0 g, 3.44 mmol) and acetonitrile (100 mL) was heated at reflux temperature. Over the course of the reaction 7 extra equivalents of aniline (2.24 g, 24.08 mmol) were added. The reaction mixture was cooled to rt, solvent evaporated and the residue dissolved in DCM (10mL). The mixture was poured into 1.0 M hydrochloric acid (20 mL), extracted with DCM (3 x 50 mL), dried ($MgSO_4$) and solvent evaporated to give a brown oil (3.0 g) consisting of four major components in the ratio **4a** : **4b** : **4c** : **4d**, 3.5 : 9.5 : 2 : 1 by $^{19}$F NMR and GCMS analysis which could

not be separated; *3,5,6-trifluoro-N-phenyl-4-(phenylsulfonyl)pyridine-2-amine* **4a**; $\delta_F$ -88.62 (1F, dm, $^3J_{FF}$ 31.6, F-6), -138.47 (1F, dm, $^3J_{FF}$ 31.6, F-5), -153.34 (1F, dm, $^4J_{FF}$ 27.1, F-3); *m/z* (EI)$^+$ 364 ([M]$^+$, 84), 77 (100); *2,5,6-trifluoro-N-phenyl-4-(phenylsulfonyl)pyridine-3-amine* **4b**; $\delta_F$ -66.56 (1F, dd, $^3J_{FF}$ 31.6, $^5J_{FF}$ 13.2, F-5), -96.74 (1F, dd, $^4J_{FF}$ 23.7, $^5J_{FF}$ 13.2, F-2), -139.00 (1F, dd, $^3J_{FF}$ 31.6, $^4J_{FF}$ 23.7, F-6); *m/z* (EI)$^+$ 364 ([M]$^+$, 96), 77 (100); *3,6-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,5-diamine* **4c**; $\delta_F$ -70.29 (1F, d, $^5J_{FF}$ 31.6, F-6), -138.20 (1F, d, $^5J_{FF}$ 31.6, F-3); *m/z* (EI)$^+$ 437 ([M]$^+$, 100), 77 (66); and, *3,5-difluoro-N,N-diphenyl-4-(phenylsulfonyl)pyridine-2,6-diamine* **4d**; $\delta_F$ -74.15 (s); *m/z* (EI)$^+$ 437 ([M]$^+$, 100), 417 (12), 77 (76).

### 3.2.2 Reaction of 2 with aniline

By a similar process to above, aniline (3.17 g, 34 mmol), sodium hydrogencarbonate (0.48 g, 5.68 mmol), 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile **2** (0.5 g, 2.84 mmol) and acetonitrile (100 mL), after purification of the crude product (1.0 g) by column chromatography on silica gel using 3:1 *n*-hexane/ethyl acetate as elutant followed by recrystallisation from ethyl acetate, gave *2-anilino-3,5,6-trifluoroisonicotinonitrile* **6** (0.66 g, 93%) as orange crystals; mp 204.5 - 205.5°C (Found: C, 57.7; H, 2.4; N, 17.0. $C_{12}H_6N_3F_3$ requires: C, 57.8; H, 2.4; N, 16.9%); $\delta_F$ ($d_6$-acetone) -87.96 (1F, dd, $^3J_{FF}$ 32.0, $^5J_{FF}$ 22.0, F-6), -134.61 (1F, dd, $^3J_{FF}$ 31.0, $^4J_{FF}$ 9.0, F-5), -148.75 (1F, dd, $^4J_{FF}$ 22.0, $^5J_{FF}$ 9.2, F-3); $\delta_H$ ($d_6$-acetone) 7.55 (2H, d, $^3J_{HH}$ 7.6, H-2'), 7.39 (2H, t, $^3J_{HH}$ 7.6, H-3'), 7.16 (1H, t, $^3J_{HH}$ 7.0, H-4'), 6.69 (1H, br s, NH); *m/z* (EI$^+$) 248 ([M-H]$^+$, 100%), 77 (94).

## 3.3 Annelation reactions

### 3.3.1 *6,7-Difluoro-3,4-dihydro-4-methyl-8-(phenylsulfonyl)-2H-pyrido[3,2-b][1,4]oxazine* 8a

By a similar process to above, 2-methylaminoethanol **7a** (0.50 g, 6.67 mmol), sodium hydrogen carbonate (1.12 g, 13.3 mmol), 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **1** (0.97 g, 3.33 mmol) and acetonitrile (200 mL), after purification by column chromatography on silica gel using 1:3 *n*-hexane/ethyl acetate as elutant followed by several recrystallisations from DCM, gave *6,7-difluoro-3,4-dihydro-4-methyl-8-(phenylsulfonyl)-2H-pyrido[3,2-b][1,4]oxazine* **8a** (0.94 g, 86%) as yellow crystals, mp 177.2 - 178.5°C (Found: C, 51.4; H, 3.7; N, 8.9. $C_{14}H_{12}N_2F_2O_3S$ requires: C, 51.5; H, 3.7; N, 8.6%); $\delta_F$ -96.96 (1F, d, $^3J_{FF}$ 27.1, F-6), -159.44 (1F, d, $^3J_{FF}$ 27.1, F-7); $\delta_H$ 8.06 (2H, dm, $^3J_{HH}$ 7.2, H-2'), 7.65 (1H, tt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.2, H-4'), 7.54 (2H, tm, $^3J_{HH}$ 7.2, H-3'), 4.18 (2H, t, $^3J_{HH}$ 4.5, $CH_2$), 3.44 (2H, t, $^3J_{HH}$ 4.5, $CH_2$), 3.03 (3H, s, $NCH_3$); $\delta_C$ 144.7 (dd, $^1J_{CF}$ 230.2, $^2J_{CF}$ 16.8, C-6), 141.7 (dd, $^3J_{CF}$ 14.9, $^4J_{CF}$ 2.7, C-4*a*), 141.4 (s, C-1'), 134.4 (s, C-2'), 134.3 (m, C-8), 131.5 (dd, $^1J_{CF}$ 255.1, $^2J_{CF}$ 32.6, C-7), 129.2 (s, C-3'), 128.3 (s, C-4'), 126.4 (d, $^3J_{CF}$ 10.3, C-8*a*), 64.4 (s, $NCH_2$), 47.0 (s, $OCH_2$), 36.4 (s, $CH_3$); *m/z* ($EI^+$) 326 ($[M]^+$, 100%), 311 (8), 185 (18).

### 3.3.2 *2,3-Difluoro-4-(phenylsulfonyl)-5H-pyrido[2,3-b][1,4]benzoxazine* **8b**

By a similar process to above, 2-aminophenol **7b** (0.75 g, 6.87 mmol), sodium hydrogencarbonate (1.15 g, 13.7 mmol), 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine **1** (1.0 g, 3.44 mmol) and acetonitrile (200 mL), after purification by column chromatography on silica gel using 2:1 *n*-hexane/ethyl acetate as elutant, gave *2,3-difluoro-4-(phenylsulfonyl)-5H-pyrido[2,3-b][1,4]benzoxazine* **8b** (0.62 g, 50%) as orange crystals; mp >220 °C (decomposes) (Found: C, 56.7; H, 2.8; N, 7.7. $C_{17}H_{10}N_2SO_3F_2$ requires: C, 56.7; H, 2.8; N, 7.8%); $\delta_F$ -103.27 (d, $^3J_{FF}$ 22.2, F-2), -146.62 (d, $^3J_{FF}$ 22.9, F-3); $\delta_H$ 8.30 (1H, br s, NH), 8.03 (2H, dm, $^3J_{HH}$ 8.8, H-2'), 7.74 (1H, tt, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.2, H-4'), 7.62 (2H, tm, $^3J_{HH}$ 8.0, H-3'), 6.89 (1H, td, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar), 6.80 (1H, td, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar), 6.75 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.6, Ar), 6.59 (1H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, Ar); $\delta_C$ 144.2 (d, $^3J_{CF}$ 3.9, C-4*a*), 142.1 (dd, $^1J_{CF}$ 234.8, $^2J_{CF}$ 17.5, C-2), 142.3 (s, Ar), 140.3 (s, Ar), 137.3 (dd, $^1J_{CF}$ 258.0, $^2J_{CF}$ 28.5, C-3), 135.3 (s, C-1'), 128.8 (s, C-3'), 127.9

(d, $^{5}J_{CF}$ 2.2, C-2'), 127.2 (s, C-4'), 126.8 (d, $^{3}J_{CF}$ 4.6, C-8*a*), 125.7 (s, Ar), 123.9 (s, Ar), 119.8 (d, $^{2}J_{CF}$ 14.5, C-4), 116.6 (s, Ar), 114.9 (s, Ar); *m/z* ($EI^{+}$) 360 ($[M]^{+}$, 100%), 219 (80).

### 3.3.3 *6,7-Difluoro-4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-8-carbonitrile* 8c

By a similar process to above, 2-methylaminoethanol **7a** (0.85 g, 11.36 mmol), sodium hydrogencarbonate (1.91 g, 22.72 mmol), tetrafluoro-4-pyridinecarbonitrile **2** (1.0 g, 5.68 mmol) and acetonitrile (175 mL), after purification by column chromatography on silica gel using 2:1 *n*-hexane/ethyl acetate as elutant, gave *6,7-difluoro-4-methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-8-carbonitrile* **8c** (0.68 g, 57%) as yellow crystals; mp 79.1 - 80.7°C (Found: C, 51.2; H, 3.4; N, 19.8. $C_9H_7N_3F_2O$ requires: C, 51.2; H, 3.3; N, 19.9%); $\delta_F$ -97.60 (1F, d, $^{3}J_{FF}$ 22.9, F-6), -155.35 (1F, d,$^{3}J_{FF}$ 22.9, F-7); $\delta_H$ 4.39 (2H, t, $^{3}J_{HH}$ 4.6, $CH_2$), 3.49 (2H, t, $^{3}J_{HH}$ 4.8, $CH_2$), 3.08 (3H, s, $CH_3$); $\delta_C$ 143.5 (dd, $^{1}J_{CF}$ 215.3, $^{2}J_{CF}$ 13.4, C-6), 141.4 (dd, $^{3}J_{CF}$ 15.3, $^{4}J_{CF}$ 2.3, C-4*a*), 139.2 (dd, $^{3}J_{CF}$ 5.4, $^{4}J_{CF}$ 1.5, C-8*a*), 134.0 (dd, $^{1}J_{CF}$ 255.8, $^{2}J_{CF}$ 32.4, C-7), 109.9 (d, $^{3}J_{CF}$ 4.2, CN), 99.5 (dd, $^{2}J_{CF}$ 15.2, $^{3}J_{CF}$ 4.2, C-8), 65.3 (s, $CH_2$), 47.1 (s, $CH_2$), 36.2 (s, $CH_3$); *m/z* ($EI^{+}$) 211 ($[M]^{+}$, 100%), 196 (91), 182 (60), 156 (37), 128 (50).

## 3.4 X-Ray crystallography

All X-ray single crystal data were collected on a Bruker SMART CCD 6000 diffractometer (graphite monochromator, λMoKα, λ =0.71073Å) equipped with Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats at the temperature of 120.0(2)K. All structures were solved by direct methods and refined by full-matrix least squares on $F^2$ for all data using SHELXTL software [7]. All non-disordered non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. Crystal data and parameters of refinement are listed in Table 1. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 990353-990356.

Table 1. Crystal data and parameters of refinement of the structures **6** and **8a-c**.

| Compound | **6** | 8a | 8b | 8c |
|---|---|---|---|---|
| Empirical formula | $C_{12}H_6F_3N_3$ | $C_{14}H_1F_2N_2O_3S$ | $C_{17}H_{10}F_2N_2O_3S$ | $C_9H_7F_2N_3O$ |
| Formula weight | 249.20 | 326.32 | 360.33 | 211.18 |
| Crystal system | Triclinic | Triclinic | Triclinic | Monoclinic |
| Space group | P-1 | P-1 | P-1 | $P2_1/c$ |
| a, Å | 8.8617(2) | 7.5733(1) | 5.1225(7) | 15.1139(4) |
| b, Å | 9.9871(2) | 9.2075(1) | 11.1001(17) | 15.1334(4) |
| c, Å | 12.4080(3) | 10.7750(2) | 13.6789(19) | 7.7728(2) |
| α, ° | 76.814(1) | 84.59(1) | 99.733(6) | 90 |
| β, ° | 73.813(1) | 76.49(1) | 100.341(6) | 96.82(1) |
| γ, ° | 79.227(1) | 67.47(1) | 102.043(6) | 90 |
| Volume | 1017.83(4) Å$^3$ | 674.82(2) | 730.85(18) | 1765.27(8) |
| Z | 4 | 2 | 2 | 8 |
| $D_{calc}$, Mg/m$^3$ | 1.626 | 1.606 | 1.637 | 1.589 |
| μ, mm$^{-1}$ | 0.140 | 0.279 | 0.266 | 0.137 |
| F(000) | 504 | 336 | 368 | 864 |
| Reflections collected | 11988 | 7912 | 7744 | 15643 |
| Independent reflections, $R_{int}$ | 5363, 0.0344 | 3568, 0.0140 | 3809, 0.0287 | 4921, 0.0343 |
| Data / restraints / parameters | 5363 / 0 / 373 | 3568/0/235 | 3809/0/266 | 4921/0/328 |
| Goodness-of-fit on $F^2$ | 1.018 | 1.075 | 0.992 | 0.946 |
| Final $R_1$ indices [I>2σ(I)] | 0.0376 | 0.0327 | 0.0401 | 0.0418 |
| Final $wR_2$ indices (all data) | 0.1075 | 0.095 | 0.1151 | 0.1193 |

## 4. Acknowledgements

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## 5. References

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