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Reactions of 4-substituted tetrafluoropyridine derivatives with sulfur nucleophiles: S_NAr and annelation processes

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ABSTRACT

Reactions of model sulfur centred nucleophiles with 4-nitro-, 4-phenylsulfonyl- and 4-cyano-tetrafluoropyridine gave products arising from substitution of the nitro- and sulfonyl substituent or ring fluorine respectively. Ring fused products are formed upon reaction of 4-cyano-tetrafluoropyridine with mercapto-acetic acid ethyl ester.

1. Introduction

Perfluoroheteroaromatic derivatives such as pentafluoropyridine **1** have an extensive and growing chemistry that principally arises from nucleophilic aromatic substitution reactions of ring fluorine [1]. In principle, all five fluorine atoms attached to pentafluoropyridine may be displaced by a nucleophilic species and, indeed, this has been achieved in some cases [2] to provide ready access to highly functionalised heterocyclic systems from a structurally simple, inexpensive and readily handled starting material. Using this reactivity profile, we have recently been able to synthesise a variety of novel polyfunctional pyridine systems [3], macrocycles [4], glycosyl donors [5] and polycyclic scaffolds [6] by sequential regioselective displacement of fluorine from pentafluoropyridine **1** (Scheme 1). In particular, the relatively simple synthetic processes allow the preparation of a number of unusual heterocyclic scaffolds bearing multiple functionality which have found applications in parallel array synthesis in the life science industries [7].

Reactions of pentafluoropyridine **1** with nucleophiles occurs, in the vast majority of cases, to give products arising from regiospecific substitution of fluorine located *para* to ring nitrogen to give a range of 4-substituted tetrafluoropyridine systems **2**. Monosubstituted derivatives **2** are susceptible to further nucleophilic attack but the regioselectivity of these processes may be influenced by the nature of the substituent installed at the 4-position. In previous publications, we described reactions of various 4-substituted tetrafluoropyridine systems (**2**, X = NO_2, SO_2Ph, CN) with a range of nitrogen and oxygen centred nucleophiles that give a variety of polyfunctional pyridine systems and some [5,6]- and [6,6]-ring fused heterocyclic scaffolds [6]. Surprisingly, however, reactions of tetrafluoropyridine substrates **2** with sulfur nucleophiles have not been described previously and, in this paper, we report reactions of 4-nitro-, 4-phenylsulfonyl- and 4-cyano-tetrafluoropyridine **2a–c** with model alkyl and aryl sulfur centred nucleophiles such as ethanethiol **3** and thiophenol **4**.

2. Results and discussion

Reaction of 4-nitro-tetrafluoropyridine **2a** with either ethanethiol **3** or thiophenol **4** in the presence of sodium hydrogen carbonate in acetonitrile afforded complex mixtures of products arising from displacement of the nitro group along with several other unidentified products by ^{19}F and GCMS analysis. The large number of minor products made purification by column chromatography very difficult but major products **5** and **6** respectively could both be isolated in low yields. Reaction of the related 2-aminobenzenethiol **7** gave the corresponding 4-substituted product **8** derived from replacement of the 4-nitro substituent and the structure of **8** was confirmed unambiguously by X-ray

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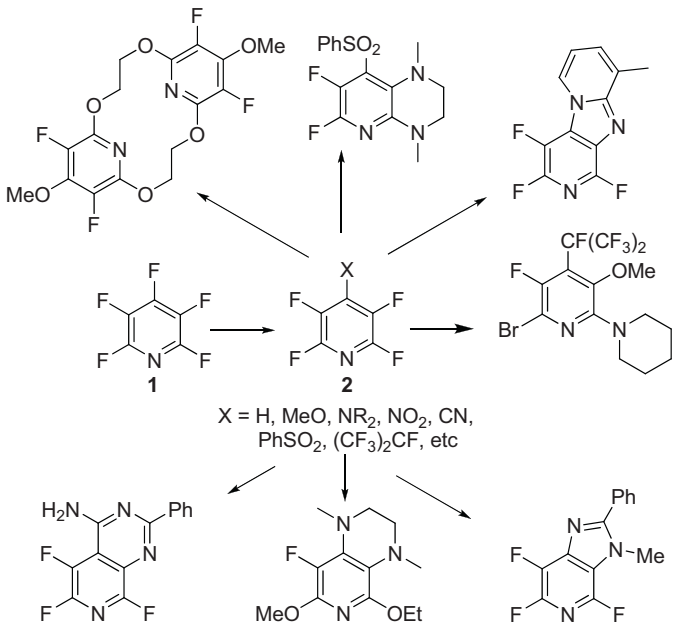
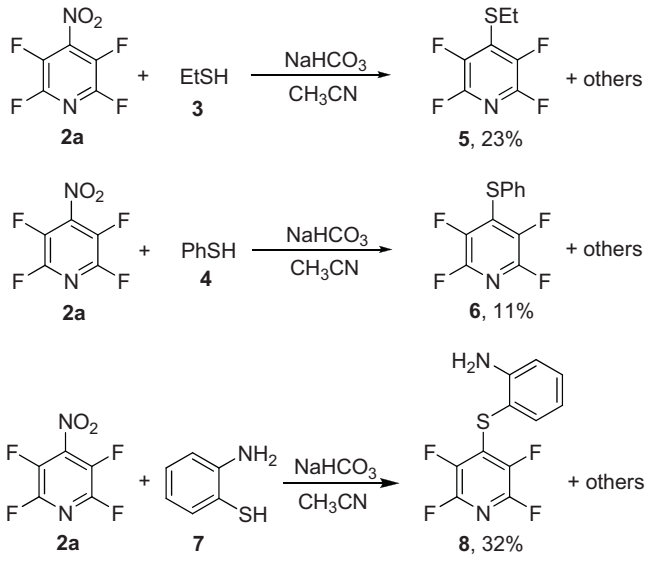


Scheme 1. Multi-substituted systems from pentafluoropyridine.

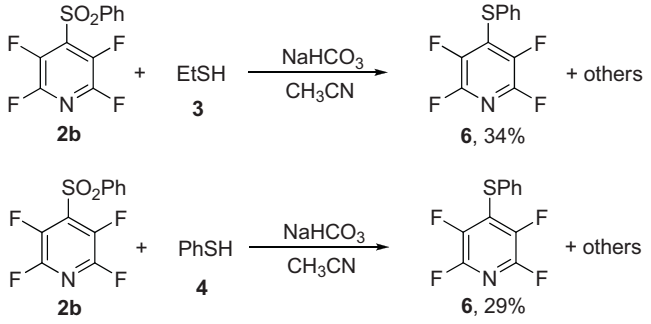
crystallography (Fig. 1). Comparison of ^{19}F NMR data of **5** and **6** with those obtained for **8** and by comparison with literature data [8] confirmed the structures of all major products (Scheme 2).

Therefore, reactions of **2a** with sulfur nucleophiles gave products arising from displacement of the labile nitro group that is attached to the highly activated 4-position of the pyridine ring rather than substitution of ring fluorine. It appears that the 'softer' sulfur nucleophiles prefer reaction with the softer carbon–nitro group bond rather than the 'harder' carbon–fluorine site, consistent with earlier observations concerning reactions of **2a** with relatively 'soft' amine nucleophiles [6c].

Similarly, reactions of 4-phenylsulfonyl-tetrafluoropyridine **2b** with ethanethiol **3** gave a complex mixture of products (Scheme 3) and the major isolated product was, surprisingly, the thiophenyl system **6**. This suggests that, in this case, ethanethiol **3** acts preferentially as a reducing agent, consistent with various single electron transfer reactions of ethanethiol described in the literature [9]. Reaction of thiophenol **4** with **2b** also gave **6**, most probably *via* a S_NAr process since thiophenol is not as powerful a reducing agent as ethanethiol. Product identity was confirmed by



Scheme 2. Reactions of 4-nitrotetrafluoropyridine **2a** with sulfur nucleophiles.



Scheme 3. Reactions of 4-phenylsulfonyl tetrafluoropyridine **2b** with sulfur nucleophiles.

comparison with literature data [8], in particular, ^{19}F NMR spectroscopy which shows two resonances at −91 and −137 ppm in a 1:1 ratio which are diagnostic of fluorine atoms located at 2- and 3-positions of highly fluorinated pyridine derivatives.

Reaction of 4-cyano-tetrafluoropyridine **2c** with one equivalent of either **3** or **4** gave product mixtures containing both the starting

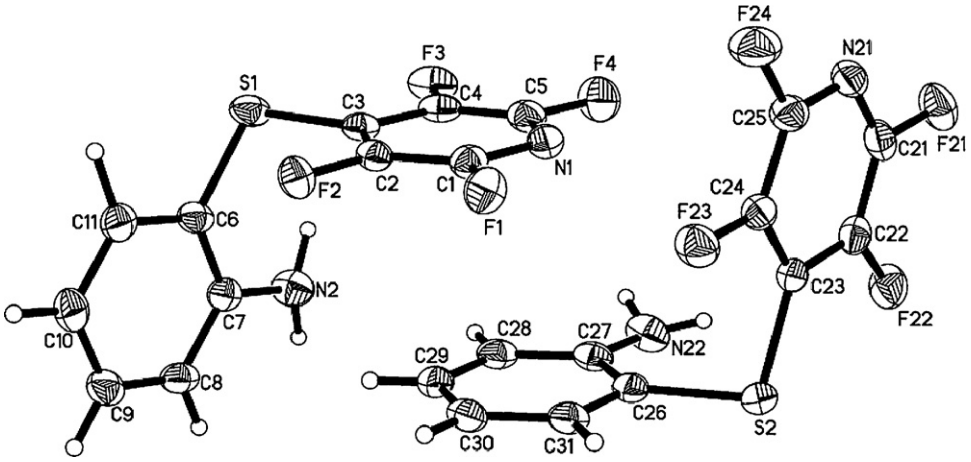
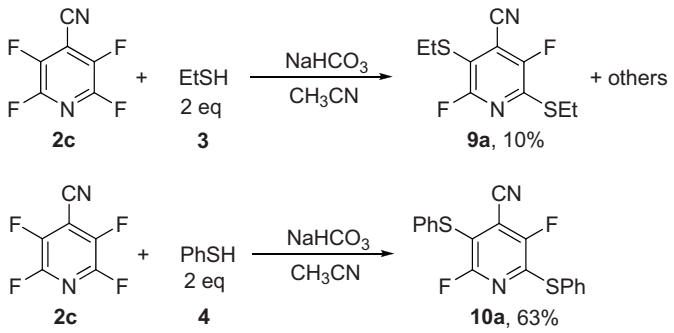


Fig. 1. Two independent molecules determined in the crystal structure of **8**.



Scheme 4. Reactions of 4-cyanotetrafluoropyridine **2c** with sulfur nucleophiles.

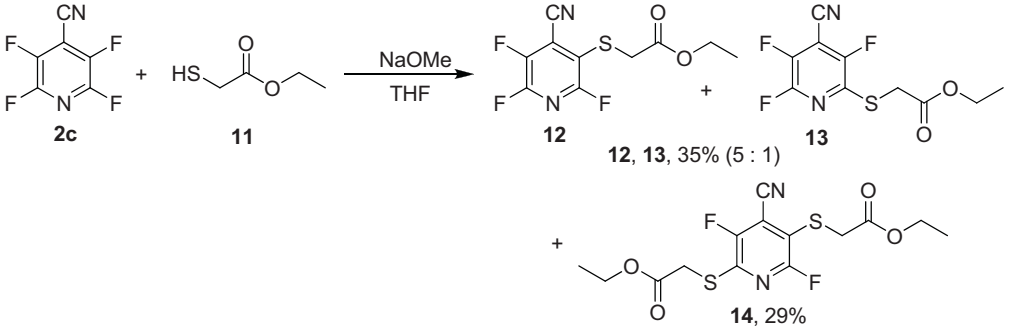
material and di-substituted products only. In order to purify and identify the disubstituted products, subsequent reactions involving reaction of two equivalents of ethanethiol **3** and thiophenol **4** gave **9a** and **10a** in 10% and 63% yields respectively (Scheme 4).

Mass spectrometry, microanalysis and ^{19}F NMR confirmed that product **9a** was a disubstituted system. The ^{19}F NMR spectrum showed two resonances at −64.9 and −119.0 ppm in a 1:1 ratio and, of the four possible disubstituted isomers **9a–d** (Fig. 2), two can be immediately discounted as we would expect only one resonance from structures **9c** and **9d**.

DFT calculations were carried out to obtain predicted ^{19}F NMR chemical shifts [10] for structures **9a** and **9b** and calculated and observed ^{19}F NMR shifts are listed in Table 1. The excellent agreement between the theoretical and observed shifts for **9a** confirms that the structure contains the sulfur substituents at the 3 and 6 positions. Furthermore, the data in Table 1 shows that **10a** is also a 3,6 isomer.

The reactions so far indicate that a trifluorocyanopyridine derivative bearing one alkyl sulfur substituent is more reactive than the tetrafluorocyanopyridine starting material, confirming the activating effect of sulfur substituents towards nucleophilic attack that has been noted previously [1b,8].

In order to confirm the regioselectivity of nucleophilic attack on **2c** by the first equivalent of sulfur nucleophile, reaction of **2c** with a less reactive system, ethyl 2-mercaptoacetate **11**, was studied. This reaction was carried out in the presence of sodium methoxide in THF and gave a mixture of three products **12**, **13** and **14** in a 5:1:2.5 ratio. The products and ratio were determined by ^{19}F NMR analysis of the crude product mixture (Scheme 5) and confirmed by calculated ^{19}F NMR data (Table 1). It was possible to separate the mono-substituted products **12** and **13** as a mixture from the disubstituted system **14**. This experiment indicates that the cyano group is highly activating towards sites *ortho* to itself and competes very efficiently with the activating effect of ring nitrogen towards adjacent sites in highly fluorinated heteroaromatic systems, consistent with earlier observations [6c].



Scheme 5. Reaction of 4-cyanotetrafluoropyridine **2c** with difunctional nucleophile ethyl 2-mercaptoacetate **11**.

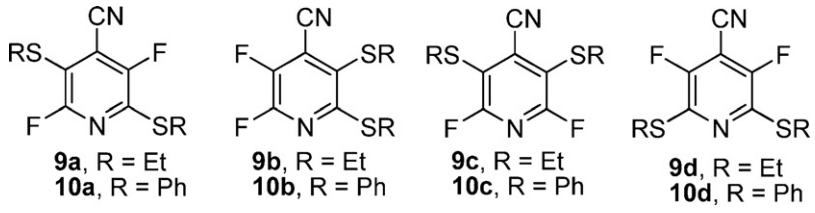
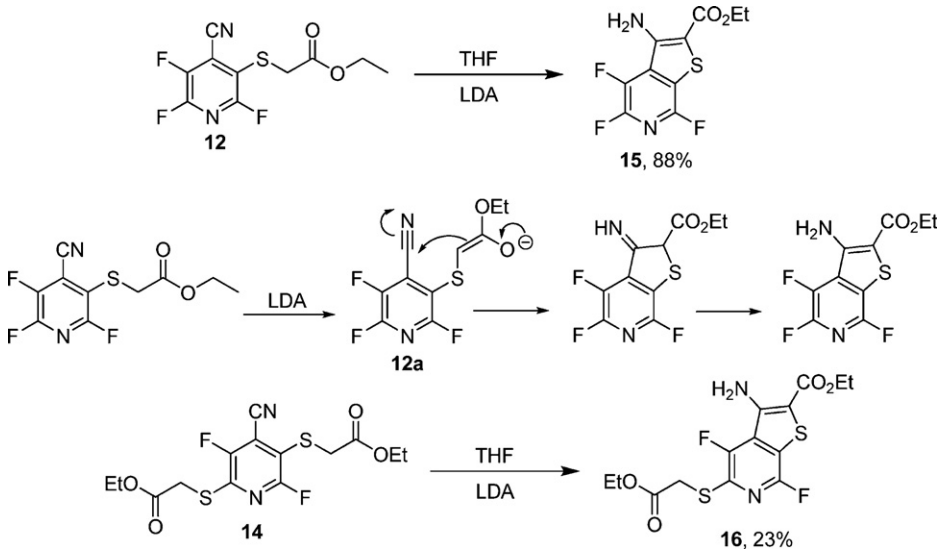


Fig. 2. Possible products, **9a–d**, **10a,b**.

Table 1
Observed and computed ^{19}F NMR data for **9**, **10** and **12–16**.

Product	Observed ^{19}F shifts	Geometry	Computed ^{19}F shifts
9a	−64.9 (F-2), −119.0 (F-5)	**9a**	−65.2 (F-2), −119.4 (F-5)
		9b	−82.7 (F-2), −136.2 (F-3)
10a	−62.6 (F-2), −118.0 (F-5)	**10a**	−67.4 (F-2), −109.0 (F-5)
		10b	−88.5 (F-2), −140.6 (F-3)
12	−63.0 (F-6), −81.8 (F-2), −135.5 (F-5)	**12**	−63.7 (F-6), −85.7 (F-2), −141.5 (F-5)
13	−86.0 (F-6), −116.5 (F-3), −137.6 (F-5)	**13**	−85.2 (F-6), −111.8 (F-3), −134.6 (F-5)
14	−64.4 (F-2), −118.9 (F-5)	**14**	−63.4 (F-2), −116.4 (F-5)
15	−71.7 (F-7), −100.5 (F-5), −158.1 (F-4)	**15**	−77.7 (F-7), −104.0 (F-5), −175.9 (F-4)
16	−71.4 (F-7), −137.3 (F-4)	**16**	−76.3 (F-7), −144.7 (F-4)



Scheme 6. Formation of fused ring systems, **15** and **16**.

Thioester **11** is, of course, a difunctional nucleophile and reaction of the mixture of monosubstituted products **12** and **13** obtained above with a strong base allowed the transformation of isomer **12** to the cyclised product **15** (Scheme 6) and this could be separated from unchanged **13**. The mechanism of this process is outlined in Scheme 6 and involves the formation of the enolate system **12a** and cyclisation by attack of the carbon nucleophile on the adjacent cyano group. The structure of **15** was confirmed by X-ray crystallography (Fig. 3). By an analogous procedure, disubstituted product **14** reacted with LDA to give cyclised system **16** in low yield (Scheme 6).

In summary, this study of reactions between several tetrafluoropyridine derivatives **2a–c** and model sulfur nucleophiles **3** and **4** shows that for systems where the 4-substituent is NO_2 or SO_2Ph, very complex mixtures of products are obtained in which the major products arise from nucleophilic substitution of the 4-substituent itself due to the lability of the substituents in S_NAr processes or, in the case of SO_2Ph, substituent reduction by appropriate electron donating sulfur nucleophiles. 4-Cyanotetrafluoropyridine **2c**, however, reacts with both ethanethiol **3** and thiophenol **4** to give systems with two sulfur containing substituents **9a** and **10a** respectively reflecting the activating effect of a sulfur substituent on S_NAr processes. Reaction of **2c** with difunctional nucleophile **11** followed by strong base allowed the syntheses of [5,6]-ring fused thieno-pyridine ring systems **15** and **16**. These processes further demonstrate the use of highly fluorinated heterocycles for the synthesis of polycyclic systems bearing multiple functionalities.

3. Experimental

3.1. General

Unless otherwise stated, commercially available reagents and solvents were used without purification. Dielectrically negative LC host MLC2038 was purchased from Merck and dielectrically positive LC host SY5225 was purchased from Chisso. An Innovative Technology Inc. Solvent Purification System fitted with a Metrohm 831 Karl Fischer Coulometric Titrator was used to dry THF (Fisher Scientific). Flash column chromatography was carried out using

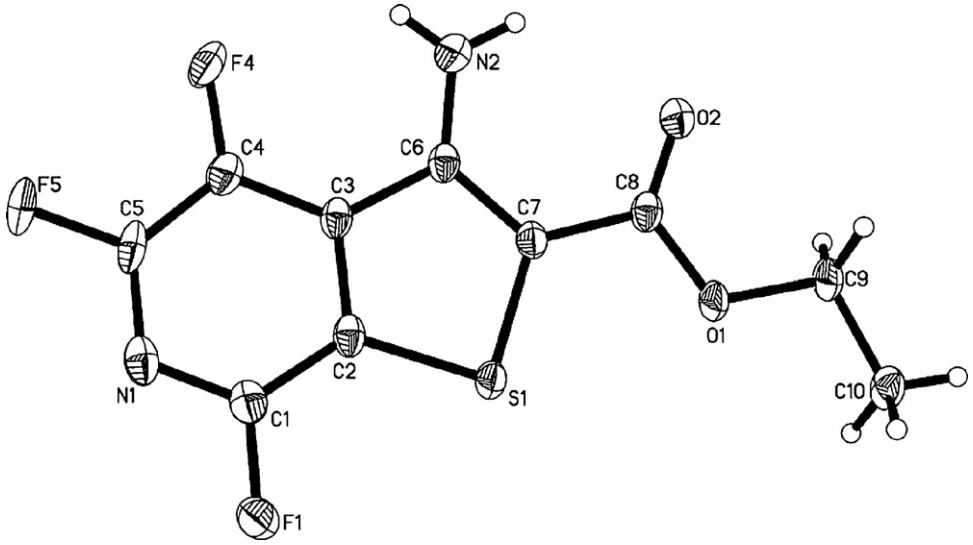


Fig. 3. Molecular structure of **15**.

Fluorochem Silicagel LC60A (40–63 μm). Proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Varian Inova-500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) or a Varian DD-700 (^{1}H NMR, 700 MHz; ^{13}C NMR, 176 MHz; ^{19}F NMR, 658 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.36 ppm; ^{19}F NMR, $CFCl_3$ at 0.00 ppm). ^{1}H, ^{13}C and ^{19}F spectroscopic data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and assignment. GC–MS analysis was performed using a Trace GC–MS device (Thermo-Finnigan Corporation) operating in electron impact ionisation (EI^+) mode. C, H and N analysis was calculated with an Exeter Analytical CE-440 Elemental Analyser.

3.1.1. X-ray crystallography

Single crystal X-ray data were collected on a Bruker SMART-CCD 6000 (compound **8**) and a Bruker Proteum-M (compound **15**) diffractometers equipped with Cryostream (Oxford Cryosystem) cooling devices at 120.0 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Both structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen non-disordered atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-874385 and 874386.

3.2. Reaction of 2,3,5,6-tetrafluoropyridine derivatives 2a–c with sulfur nucleophiles

3.2.1. General procedure

A mixture consisting of the 2,3,5,6-tetrafluoropyridine system, sulfur nucleophile, sodium hydrogen carbonate or sodium methoxide and acetonitrile or THF was stirred at rt or heated at reflux temperature as required. The solvent was evaporated and the residue redissolved in dichloromethane. The mixture was poured onto dil. hydrochloric acid (30 mL), extracted with dichloromethane (3× 50 mL), dried ($MgSO_4$) and the solvent evaporated to dryness to yield the crude product which was analysed by ^{19}F NMR analysis and GCMS. Purification by column chromatography on silica gel or recrystallisation gave isolated products.

3.2.2. Reactions of 4-nitro-2,3,5,6-tetrafluoropyridine 2a

3.2.2.1. With ethanethiol **3**. 4-Nitro-2,3,5,6-tetrafluoropyridine **2a** (0.42 g, 2.1 mmol), ethanethiol **3** (0.13 g, 2.1 mmol), sodium hydrogen carbonate (0.36 g, 4.3 mmol) and acetonitrile (75 mL) were stirred at rt for 2 d and, after purification of the crude product by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate), gave *4-(ethylsulfanyl)-2,3,5,6-tetrafluoropyridine* **5** (0.10 g, 22%) as a yellow oil; δ_F −92.14 (2F, m, F-2), −139.35 (2F, m, F-3); δ_H 3.22 (2H, q, $^3J_{HH}$ 6.5, CH_2), 1.36 (3H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 143.7 (dm, $^1J_{CF}$ 244.1, C-2), 141.1 (ddm, $^1J_{CF}$ 254.1, $^2J_{CF}$ 23.4, C-3), 131.7 (tt, $^2J_{CF}$ 17.3, $^3J_{CF}$ 3.0, C-4), 27.8 (t, $^4J_{CF}$ 5.3, CH_2), 15.3 (s, CH_3); *m*/*z* $(EI)^+$ 211 ($[M]^+$, 98%), 196 (40), 183 (100); as compared to literature data [8].

3.2.2.2. With thiophenol **4**. 4-Nitro-2,3,5,6-tetrafluoropyridine **2a** (0.42 g, 2.14 mmol), thiophenol **4** (0.24 g, 2.14 mmol), sodium hydrogen carbonate (0.36 g, 4.28 mmol) and acetonitrile (100 mL) were stirred at rt for 1 d and, after purification by column chromatography on silica gel (*n*-hexane), gave *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **6** (0.06 g, 11%) as a colourless oil; (found: $[M+H]^+$, 260.0153. $C_{11}H_5NF_4S$ requires: $[M+H]^+$ 260.0152); δ_F −91.01 (2F, m, F-2), −136.92 (2F, m, F-3); δ_H 7.25–7.45 (5H, m, ArH); δ_C 142.5 (dm, $^1J_{CF}$ 244.0, C-2), 140.0 (dm, $^1J_{CF}$ 257.3, C-3), 131.9 (s, Ar), 130.0 (tt, $^2J_{CF}$ 16.4, $^3J_{CF}$ 3.0, C-4), 128.6 (s, Ar), 128.5 (s, Ar), 128.1 (s, Ar); *m*/*z* $(EI)^+$ 259 ($[M]^+$, 100%), 239 (96), 77 (94); as compared to literature data [8].

3.2.2.3. With 2-aminothiophenol **7**. 4-Nitro-2,3,5,6-tetrafluoropyridine **2a** (0.65 g, 3.32 mmol), 2-aminothiophenol **7** (0.83 g, 6.63 mmol), sodium hydrogen carbonate (1.11 g, 13.27 mmol) and acetonitrile (150 mL) were heated at reflux for 5 d and, after purification by column chromatography on silica gel (5:1 *n*-hexane/ethyl acetate) and recrystallisation from *n*-hexane, gave *2-[(2,3,5,6-tetrafluoropyridin-4-yl)amino]thiophenol* **8** (0.29 g, 32%) as a yellow solid; mp 68.2–69.5 °C; (found: C, 48.2; H, 2.2; N, 10.3. $C_{11}H_6F_4N_2S$ requires: C, 48.2; H, 2.2; N, 10.2%); δ_F −91.25 (2F, m, F-2), −138.68 (2F, m, F-3); δ_H 7.53 (1H, d, $^3J_{HH}$ 7.5, ArH), 7.25 (1H, td, $^3J_{HH}$ 7.0, $^4J_{HH}$ 1.5, ArH), 6.76 (1H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.0, ArH), 6.75 (1H, td, $^3J_{HH}$ 7.5, $^4J_{HH}$ 1.0, ArH), 4.36 (2H, br s, NH_2); δ_C 149.4 (s, ArCS), 143.6 (dtm, $^1J_{CF}$ 248.1, $^2J_{CF}$ 14.5, C-2), 141.4 (ddm, $^1J_{CF}$ 258.7, $^2J_{CF}$ 21.0, C-3), 137.5 (s, Ar), 132.6 (s, Ar), 130.7 (m, C-4), 119.3 (s, Ar), 115.9 (s, Ar), 110.3 (s, Ar CNH_2); *m*/*z* (EI^+) 274 ($[M]^+$, 100%), 254 (86), 165 (10), 150 (12).

Crystal data for **8**: $C_{11}H_6F_4N_2S$, *M* = 272.24, triclinic, space group P−1, *a* = 7.3305(2), *b* = 12.1922(3), *c* = 12.2478(3) Å, α = 91.870 (1)°, β = 97.657(1)°, γ = 94.219(1)°, *U* = 1080.95(5) Å^3, *F*(0 0 0) = 552, *Z* = 4, D_c = 1.685 mg m^{-3}, μ = 0.336 mm^{-1}. 10,141 reflections were collected yielding 4692 unique data (R_{merg} = 0.020). Final w$R_2(F^2)$ = 0.01001 for all data (372 refined parameters), conventional $R_1(F)$ = 0.0365 for 3859 reflections with $I \geq 2\sigma$, GOF = 1.055.

3.2.3. Reactions of 2,3,5,6-tetrafluoro-4-(phenylsulfonyl)pyridine 2b

3.2.3.1. With ethanethiol **3**. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)pyridine **2b** (1.0 g, 3.44 mmol), ethanethiol **3** (0.21 g, 3.44 mmol), sodium hydrogen carbonate (0.58 g, 6.88 mmol) and acetonitrile (75 mL) were heated at reflux for 2 d and, after purification by column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) followed by preparative TLC (*n*-hexane), gave *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **6** (0.3 g, 34%) as a colourless oil; spectral data above.

3.2.3.2. With thiophenol **4**. 2,3,5,6-Tetrafluoro-4-(phenylsulfonyl)-pyridine **2b** (1 g, 3.44 mmol), thiophenol **4** (0.38 g, 3.44 mmol), sodium hydrogen carbonate (0.34 g, 4.0 mmol) and acetonitrile (150 mL) was heated at reflux for 4 d and, after purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate), gave *2,3,5,6-tetrafluoro-4-(phenylsulfanyl)pyridine* **6** (0.26 g, 29%) as a colourless oil; spectral data above.

3.2.4. Reactions of 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile 2c

3.2.4.1. With ethanethiol **3**. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **2c** (0.5 g, 2.84 mmol), ethanethiol **3** (0.18 g, 2.84 mmol), sodium hydrogen carbonate (0.48 g, 5.68 mmol) and acetonitrile (100 mL) were heated at reflux for 3 d to yield a crude product as a yellow oil (0.86 g) consisting of several major components by GCMS. Column chromatography on silica gel (6:1 *n*-hexane/ethyl acetate) gave a mixture of *2,5-difluoro-3,6-bis(ethylsulfanyl)isonicotinonitrile* **9a** (0.08 g, 10%) as a yellow oil; δ_F −64.89 (1F, d, $^5J_{FF}$ 29.3, F-2), −119.01 (1F, d, $^5J_{FF}$ 27.1, F-5); δ_H 3.19 (2H, q, $^3J_{HH}$ 7.5, CH_2), 3.01 (2H, q, $^3J_{HH}$ 7.5, CH_2), 1.39 (3H, t, $^3J_{HH}$ 7.5, CH_3), 1.29 (3H, t, $^3J_{HH}$ 7.5, CH_3); δ_C 158.5 (dd, $^1J_{CF}$ 237.5, $^4J_{CF}$ 2.4, C-2), 153.7 (dd, $^1J_{CF}$ 265.6, $^4J_{CF}$ 5.3, C-5), 148.7 (dd, $^2J_{CF}$ 20.1, $^3J_{CF}$ 15.3, C-6), 116.3 (dd, $^2J_{CF}$ 13.3, $^3J_{CF}$ 5.1, C-4), 114.2 (dd, $^2J_{CF}$ 41.5, $^3J_{CF}$ 3.4, C-3), 110.4 (d, $^3J_{CF}$ 4.3, CN), 29.9 (d, $^4J_{CF}$ 3.8, SCH_2), 24.5 (d, $^4J_{CF}$ 1.5, SCH_2), 15.2 (s, CH_3), 14.4 (s, CH_3); *m*/*z* (EI^+) 260 ($[M]^+$, 90%), 199 (100).

3.2.4.2. With thiophenol **4**. 2,3,5,6-Tetrafluoro-4-pyridinecarbonitrile **2c** (0.5 g, 2.84 mmol), thiophenol **4** (0.31 g, 2.84 mmol), sodium hydrogen carbonate (0.48 g, 5.68 mmol) and acetonitrile (100 mL) were stirred at rt for 12 d and, after purification by column chromatography on silica gel (4:1 *n*-hexane/ethyl acetate), gave *2,5-difluoro-3,6-bis(phenylsulfanyl)isonicotinonitrile* **10a** (0.63 g, 63%) as a yellow solid; mp 84.2–85.0 °C; (found: C, 60.6; H, 2.9; N, 7.8. $C_{18}H_{10}F_2N_2S_2$ requires: C, 60.8; H, 2.8; N, 7.9%); δ_F −62.61 (1F, d, $^5J_{FF}$ 27.1, F-2), −117.95 (1F, d, $^5J_{FF}$ 29.3, F-5); δ_H 7.55 (2H, m, ArH), 7.45 (5H, m, ArH), 7.32 (3H, m, ArH); *m*/*z* (EI$^+$) 356 ([M]$^+$, 97%), 109 (76), 77 (100).

3.2.4.3. With ethyl 2-mercaptoacetate **11**. 2,3,5,6-Tetrafluoropyridine-4-carbonitrile **2c** (1.0 g, 5.68 mmol), sodium methoxide (0.61 g, 11.36 mmol), ethyl 2-mercaptoacetate **11** (0.68 g, 5.68 mmol) and tetrahydrofuran (100 mL) were heated at reflux for 4 h to yield the crude product as a yellow oil (0.83 g). Purification by column chromatography on silica gel (1:1 *n*-hexane/ethyl acetate followed by 4:1 *n*-hexane/ethyl acetate) gave a mixture of *ethyl[(4-cyano-2,5,6-trifluoropyridin-3-yl)sulfanyl]acetate* **12** and *ethyl[(4-cyano-3,5,6-trifluoropyridin-2-yl)sulfanyl]acetate* **13** (0.55 g, 35%) as a yellow oil and in the ratio 5:1; **12**: δ_F −63.03 (1F, dd, $^3J_{FF}$ 29.3, $^4J_{FF}$ 11.3, F-6), −81.75 (1F, dd, $^5J_{FF}$ 22.6, $^4J_{FF}$ 11.3, F-2), −135.46 (1F, dd, $^3J_{FF}$ 27.1, $^5J_{FF}$ 20.3, F-5); *m*/*z* (EI$^+$) 276 ([M]$^+$, 66%), 203 (100); **13**: δ_F −85.95 (1F, dd, $^5J_{FF}$ 31.6, $^3J_{FF}$ 22.6, F-6), −116.45 (1F, dd, $^5J_{FF}$ 31.6, $^4J_{FF}$ 4.5, F-3), −137.61 (1F, dd, $^3J_{FF}$ 22.6, $^4J_{FF}$ 4.5, F-5); *m*/*z* (EI$^+$) 276 ([M]$^+$, 4%), 203 (16); and *(4-cyano-6-ethoxycarbonylmethylsulfanyl-2,5-difluoro-pyridin-3-ylsulfanyl)-acetic acid ethyl ester* **14** (0.30 g, 29%); δ_F −64.35 (1F, d, $^5J_{FF}$ 29.3, F-2), −118.85 (1F, d, $^5J_{FF}$ 29.1, F-5); **12**–**14** were used in subsequent reactions without further purification.

3.2.5. Synthesis of ethyl 3-amino-4,5,7-trifluorothieno[2,3-c]pyridine-2-carboxylate **15**

The mixture of **12** and **13** (5:1) (0.08 g, 0.29 mmol) obtained above was added to a solution of lithium di*iso*propylamide (0.32 mL, 0.58 mmol. 1.8 M) in dry tetrahydrofuran (200 mL) at −78 °C and stirred for 2 h. The reaction mixture was warmed to rt and stirred for 2 d, concentrated, poured into water (30 mL), extracted with dichloromethane (3× 50 mL) and dried ($MgSO_4$). The solvent was evaporated to dryness to yield a brown/yellow solid (0.12 g) consisting of one major component. Purification by preparative TLC on silica gel (4:1 *n*-hexane/ethyl acetate) gave *ethyl 3-amino-4,5,7-trifluorothieno[2,3-c]pyridine-2-carboxylate* **15** (0.07 g, 88%) as a yellow solid; (found: C, 43.7; H, 2.5; N, 10.2. $C_{10}H_7F_3N_2O_2S$ requires: C, 43.5; H, 2.5; N, 10.1%); mp 104.1–105.6 °C; δ_F −71.69 (1F, dd, $^5J_{FF}$ 29.3, $^4J_{FF}$ 11.3, F-7), −100.52 (1F, dd, $^3J_{FF}$ 20.3, $^4J_{FF}$ 13.5, F-5), −158.14 (1F, dd, $^5J_{FF}$ 31.6, $^3J_{FF}$ 20.3, F-4); δ_H 6.13 (2H, br s, NH_2), 4.32 (2H, q, $^3J_{HH}$ 7.0, CH_2), 1.33 (3H, t, $^3J_{HH}$ 7.0, CH_3); δ_C 163.2 (s, C=O), 147.9 (ddd, $^1J_{CF}$ 245.2, $^2J_{CF}$ 13.4, $^3J_{CF}$ 2.4, C-5), 144.6 (m, C-3), 143.4 (ddm, $^1J_{CF}$ 239.9, $^3J_{CF}$ 13.4, C-7), 137.5 (ddd, $^1J_{CF}$ 257.2, $^2J_{CF}$ 27.3, $^4J_{CF}$ 7.2, C-4), 131.7 (ddd, $^2J_{CF}$ 12.1, $^3J_{CF}$ 7.2, $^3J_{CF}$ 2.4, C-3*a*), 117.9 (dd, $^2J_{CF}$ 39.3, $^3J_{CF}$ 4.3, C-7*a*), 103.6 (s, C-2), 60.4 (s, CH_2), 13.3 (s, CH_3); *m*/*z* (EI$^+$) 276 ([M]$^+$, 50%), 230 (100).

Crystal data for **15**: $C_{10}H_7F_3N_2O_2S$, M = 276.24, monoclinic, space group C2/c, a = 20.319(1), b = 4.8461(2), c = 21.909(1) Å, β = 91.134(2)°, U = 2156.9(2) Å^3, F(0 0 0) = 1120, Z = 8, D_c = 1.701 mg m^{-3}, μ = 0.338 mm^{-1}. 11,148 reflections were collected yielding 3000 unique data (R_{merg} = 0.083). Final w$R_2(F^2)$ = 0.1274 for all data (191 refined parameters), conventional $R_1(F)$ = 0.0490 for 2431 reflections with $I \geq 2\sigma$, GOF = 1.003.

3.2.6. Synthesis of 3-amino-5-ethoxycarbonylmethylsulfanyl-4,7-difluoro-thieno[2,3-c]pyridine-2-carboxylic acid ethyl ether **16**

(4-Cyano-6-ethoxycarbonylmethylsulfanyl-2,5-difluoro-pyridin-3-ylsulfanyl)-acetic acid ethyl ester **14** (0.22 g, 0.59 mmol) and lithium di*iso*propylamide (1.3 mL, 2.34 mmol, 1.8 M) were added to dry THF (200 mL) under argon at −78 °C. The reaction mixture was stirred for 1 h before warming to rt and stirring for 17 h. The reaction mixture was concentrated, poured into water (30 mL), extracted with dichloromethane (3× 50 mL) and dried ($MgSO_4$). The solvent was evaporated to dryness to yield the crude product as a yellow oil (0.28 g) which consisted of one major component. Purification by column chromatography on silica gel using *n*-hexane/ethyl acetate (4:1) as elutant followed by recrystallisation from ethyl acetate gave *3-amino-5-ethoxycarbonylmethylsulfanyl-4,7-difluoro-thieno[2,3-c]pyridine-2-carboxylic acid ethyl ether* **16** (50 mg, 23%) as a yellow solid; mp 110.2–111.5 °C; (found: [M+H]$^+$ 377.0435. $C_{14}H_{14}N_2O_4F_2S_2$ requires: [M+H]$^+$, 377.0436); δ_F −71.35 (1F, d, $^5J_{FF}$ 31.6, F-7), −137.26 (1F, d, $^5J_{FF}$ 31.6, F-4); δ_H 6.20 (2H, br s, NH_2), 4.37 (2H, q, $^3J_{HH}$ 7.2, CH_2CH$_3$), 4.22 (2H, q, $^3J_{HH}$ 7.2, CH_2CH$_3$), 3.95 (2H, s, SCH_2), 1.39 (3H, t, $^3J_{HH}$ 6.8, CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.2, CH_2CH_3); δ_C 169.2 (s, C=O), 164.7 (s, C=O), 152.5 (d, $^1J_{CF}$ 238.0, C-7), 150.2 (dd, $^1J_{CF}$ 251.9, $^4J_{CF}$ 5.6, C-4), 145.6 (s, C-3), 134.2 (dd, $^2J_{CF}$ 22.5, $^3J_{CF}$ 13.4, C-5), 131.1 (s, C-2), 130.5 (dd, $^2J_{CF}$ 14.3, $^3J_{CF}$ 7.1, C-7*a*), 118.9 (d, $^2J_{CF}$ 41.4, C-3*a*), 62.1 (s, CH_2CH_3), 61.5 (s, CH_2CH_3), 32.7 (s, SCH_2), 14.6 (s, CH_2CH_3), 14.3 (s, CH_2CH_3); *m*/*z* (EI$^+$) 376 ([M]$^+$, 58%), 331 (16), 303 (100), 257 (42).

3.3. NMR calculations

All *ab initio*/DFT computations were carried out with the Gaussian 09 package. Optimisation of these geometries without symmetry constraints were carried out at the MP2/6-31G* level of theory. Calculated ^{19}F NMR shifts at the GIAO-B3LYP/6-311G* level were obtained from these MP2-optimised geometries using the $\delta(^{19}F) = 168.8 - \sigma(^{19}F)$ scale.

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