Polyhalogenated heterocyclic compounds. Part 44.[1] Reactions of perfluoro-(4-isopropylpyridine) with oxygen nucleophiles

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Dedicated to Otto Meth-Cohn on the Occasion of his 65th birthday

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Abstract

Reactions between perfluoro-(4-isopropyl pyridine) 1 and a variety of oxygen nucleophiles gave mono, di- and tri-alkoxylated systems depending on reaction conditions. The barrier to rotation for the perfluoro-isopropyl group in several pyridine systems was measured by ^{19}F n.m.r. saturation transfer experiments.

Keywords: Organofluorine, heterocyclic, nucleophilic substitution

Introduction

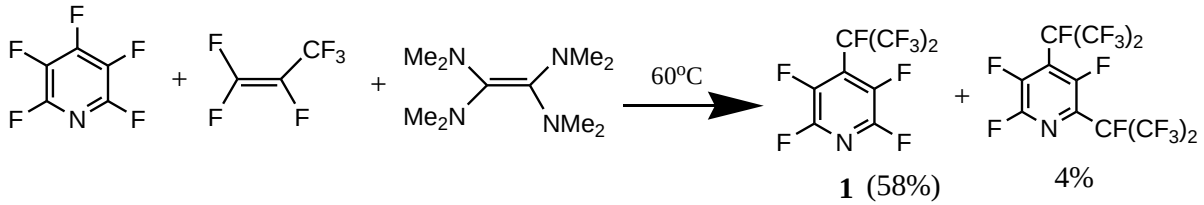
In earlier parts of this series,[1] we have described chemistry of a range of highly fluorinated heterocyclic systems including perfluoroalkylation reactions of fluoroheterocycles, which involve the trapping of perfluorinated carbanions. These carbanions are generated by addition of fluoride ion to fluoro-alkenes, and, therefore, in principle, a range of perfluoroalkylated heterocyclic derivatives may be obtained.[2,3] However, the development of the chemistry of perfluoro-(alkylheterocycles), which were first synthesised some time ago,[2] has been severely hampered by the lack of efficient isolation techniques for realistic large scale synthesis. Consequently, only a few examples of reactions involving perfluoro-(alkylheterocycles) have been reported[2,4,5] which include various novel photochemical rearrangements[6] and the formation of remarkably stable valence isomers.[7]

Recently, we reported new methodology[8] for the synthesis and isolation of perfluoro-(isopropylheterocycles), which allows efficient scale up. Consequently, a wider exploration of the chemistry of these systems is now feasible.

In general, there is continued interest in the introduction of perfluoroalkyl groups into organic molecules due to, for example, the modification of surface properties and the increased lipophilicity that such groups can impart upon a wide range of substrates. These effects are exemplified by the range of surfactants and textile treatment agents bearing perfluoroalkyl groups that are currently commercially available.[9] In particular, heterocyclic systems possessing perfluoroalkyl substituents (principally trifluoromethyl derivatives) are useful intermediates, for example, in the pharmaceutical and plant protection industries.[9] Such factors, therefore, provide a stimulus to explore the chemistry of perfluoroalkylated heterocyclic systems and consequently, in this paper, we report our studies concerning reactions of a model perfluoroalkylated heterocyclic system, perfluoro-4-isopropyl pyridine 1, with a range of oxygen nucleophiles.

Results and Discussion

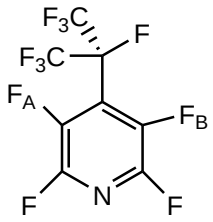
Following the procedures that we described previously,[8] 1 was synthesised in good yield, on a large scale, by reaction of pentafluoropyridine with hexafluoropropene using a tertiary amine, tetrakis-(dimethylamino)ethene (TDAE), as a catalyst to generate active fluoride ion (Scheme 1). The reaction was carried out *in the absence of solvent* making product isolation easy.



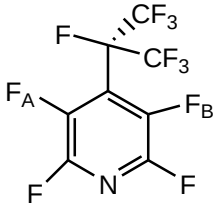
1 (58%) 4%

Scheme 1

The site of nucleophilic substitution was regioselective at the 4-position of the pyridine ring, consistent with earlier observations.[2] In this case, 1 gives a ^{19}F n.m.r. spectrum consisting of resonances at –74.4 (CF_3), -86.3 and –87.4 (*ortho*-F), -134.9 and –137.4 (*meta*-F) and –180.2ppm (CF). Significantly, restricted rotation of the perfluoroisopropyl group, between rotamers 1a and 1b (Scheme 2), gives rise to two signals, that appear as broad signals at room temperature, corresponding to each ring fluorine position (F_A and F_B).[10]



1a



1b

Scheme 2

Reaction of 1 with a series of alkoxide ions in an appropriate solvent (MeOH or THF) gave mono, di and tri alkoxylated products 2, 3 and 4 in ratios that depend on the reaction stoichiometry (Table 1).

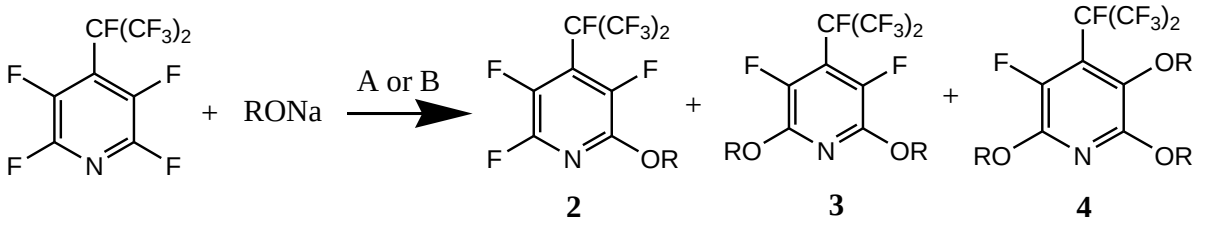
Nucleophilic substitution of fluorine by alkoxide occurs initially at the 2-position, as established by n.m.r. studies and consistent with literature data.[2] Disubstituted products 3 gave ^{19}F n.m.r. spectra which exhibited only one resonance corresponding to ring-fluorine, in the range –145 - -150 ppm, consistent with the presence of fluorine at the 3 and 5 positions and confirming the symmetrical nature of the 2,6-disubstituted pyridine system. Of course, if the second alkoxide nucleophilic substitution had occurred at the 5-position, two separate resonances corresponding to 3- and 6- ring fluorine atoms would have been observed, and this is clearly not the case here.

Alkoxy groups present in the 3 position in 4a and 4b further hinder rotation of the sterically demanding perfluoroisopropyl group and both rotamers, A and B, are observed in the ^{19}F n.m.r. spectrum of 4a and 4b even at room temperature.

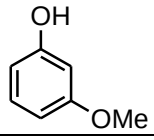
Coupling between the ring fluorine at the 5-position with the tertiary fluorine atom (CF-CF_3) is very large (approx. 94 Hz) in conformer B (Scheme 3) because, in this case, the two fluorine atoms can adopt a conformation which maximises 'through-space' interactions, whereas corresponding coupling is absent in conformer A.

Rates of exchange at various temperatures and the activation energies required for the rotation of the perfluoroisopropyl group between rotamers A and B were measured by ^{19}F n.m.r. saturation transfer experiments, involving irradiation of the resonance arising from the ring fluorine atom in 1, 4a and 4b.

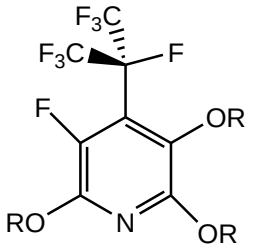
Table 1. Reactions of Perfluoroisopropyl-pyridine with Oxygen Nucleophiles



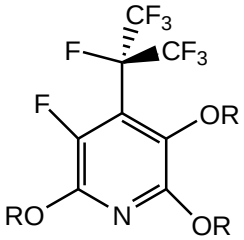
2 **3** **4**

Nucleophile ROH	Conditions	2 Yield (%)	3 Yield (%)	4 Yield (%)
KOH	A	2a, 61	-	-
CH_3OH	B	2b, 69	-	-
	C	2b, 6	3a, 66	-
	D*	-	-	4a, 75
$CH_3OCH_2CH_2OH$	B	2c, 38	3b, 8	-
	C	-	3b, 76	-
c-$C_6H_{11}OH$	B	2d, 64	3c, 8	-
	C	2d, 20	3c, 65	-
Ph-OH	B	2e, 66	-	-
	C	2e, 4	3d, 72	-
	D	-	-	4b, 27
	C	-	3e, 69	-

Conditions: A, KOH, *t*-BuOH, reflux, 24 h.
B, ROH (1.1 equiv.), Na or NaH, THF, reflux, 24 h.
C, ROH (2.2 equiv.), Na or NaH, THF, reflux, 24 h.
D, ROH (excess 10 equiv.), Na or NaH, THF (or MeOH*), reflux, 24 h.



Conformer A



Conformer B

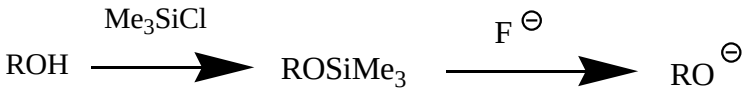
R = CH_3, **4a**, Ph, **4b**

Scheme 3

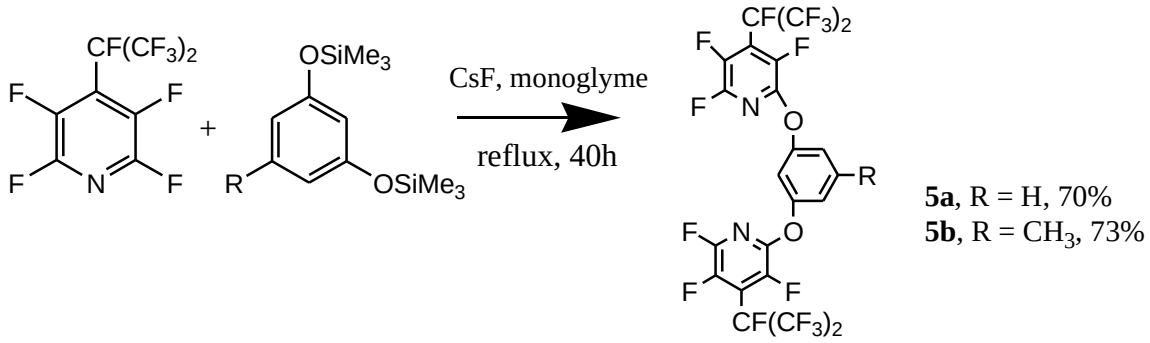
Activation energies for rotation of the perfluoroisopropyl group were calculated to be 100.3 kJ mol^{-1} for 4a, 81.0 kJ mol^{-1} for 4b and 35.7 $kJmol^{-1}$ for 1, reflecting the increased steric hindrance to rotation imparted by the methoxy and phenoxy groups compared to fluorine in this situation.

The studies outlined above demonstrate that 1 is a di- or tri-functional electrophile and, in principle, could be used as a 'building block' for the synthesis of a variety of supramolecular and polymer systems upon reaction with an appropriate di-nucleophile (e.g. a diol).

Reaction of 1 with the disodium salt of resorcinol gave largely intractable material. However, fluoride ion promoted desilylation methodology,[11] which allows the formation of alkoxide ions according to Scheme 4, was successful because, for example, reaction of 1,3-bis(trimethylsiloxy)benzene with 1 gave high yields of the dipyridyl system 5a (Scheme 5).



Scheme 4



Scheme 5

In summary, perfluoroisopropyl pyridine 1 reacts very efficiently with a range of mono- and di-functional oxygen nucleophiles. Extension of similar chemistry to the synthesis of a range of macrocyclic and polymeric systems will be described in future publications.

Experimental Section

General Procedures. All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem) 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 an internal standards. Mass

spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl -silicone) column. Elemental analyses were obtained on a 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 were determined by either ^{19}F-NMR or gas-chromatography on an Shimadzu GC8A system using an SE30 column. Distillation was performed using a Fischer Spaltrühr MS220 microdistillation apparatus. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063nm) and TLC analysis was performed on silica gel TLC plates.

Perfluoro-4-isopropylpyridine 1, 1,3-bis-(trimethylsilyloxy)benzene and 3,5-bis-(trimethylsilyloxy)-toluene were synthesised by literature procedures.[8, 12]

3,5,6-Trifluoro-2-hydroxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 2a. Under an atmosphere of dry nitrogen, potassium hydroxide (0.7 g, 12.5 mmol) was added to a solution of 1 (4.0 g, 12.5 mmol) in 2-methylpropanol (25 cm^3).and the mixture was stirred at reflux temperature for 24 h. Dilute HCl was added until the solution was pH 1 and the mixture was continuously extracted with dichloromethane, dried ($MgSO_4$), and evaporated to yield crude material (4.2 g). Column chromatography, using dichloromethane as the eluent, gave *2,3,5-tetrafluoro-6-hydroxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 2a(2.4 g, 61%) as a white solid; mp 88.9-89.3˚C; (Found C, 29.9; H, 0.4; N, 4.4. $C_8HF_{10}NO$requires C, 30.3; H, 0.3; N, 4.4%); δ_F (376 MHz) -71.3 (6F, m, CF_3), -86.8 and -87.8 (1F, m, 2-CF), -131.1 and -133.8 (1F, m, 5-CF), -141.6 and -144.8 (1F, m, 3-CF) and -176.4 (1F, m, 4-CF); δ_C (100 MHz) 95.5 (dsept, $^1J_{CF}$213.5, $^2J_{CF}$36.0, 4-CF), 120.7 (m, 4-C), 123.3 (qd, $^1J_{CF}$287.0, $^2J_{CF}$ 27.5, CF_3) and 140-150 (broad overlapping m, 2, 3, 5 and 6-C) ; m/z (EI$^+$) 317 (M^+, 50%), 289 (10), 249 (11), 220 (38), 198 (13), 170 (15), 69 (46).

Reactions of Perfluoro-isopropylpyridine with alkoxide nucleophiles

Reactions with Methoxide - General procedure

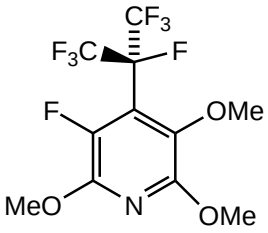
Under an atmosphere of dry nitrogen, 1 was added to a solution of sodium methoxide in methanol (20 cm^3)and the mixture was stirred at reflux temperature for 24 h before water (25 cm^3) was added. The mixture was continuously extracted with dichloromethane, dried ($MgSO_4$) and evaporated to yield crude material. The isolation of pure products was achieved by column chromatography, using hexane and dichloromethane (6:1) as the eluent.

2,3,5-Trifluoro-6-methoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 2b. Sodium methoxide (0.36 g, 6.5 mmol) and 1 (1.75 g, 5.5 mmol) gave crude product (1.9 g) which after column chromatography, afforded *2,3,5-trifluoro-6-methoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 2b(1.4 g, 69%) as a colourless liquid; bp 173-173.5˚C; (Found C, 32.3; H, 0.9; N, 4.2. $C_9H_3F_{10}NO$requires C, 32.6; H, 0.9; N, 4.2%); δ_H

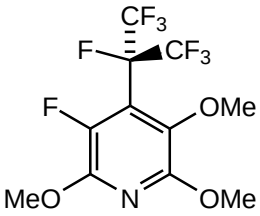
(399.9 MHz) 4.0 (s, CH_3); δ_F (376 MHz, at 25˚C) -75.1 (6F, m, CF_3), -91.2 and -92.4 (1F, m, 2-CF), -134.9 and -137.6 (1F, m, 5-CF), -146.9 and -150.1 (1F, m, 3-CF) and -179.9 (1F, m, 4-CF); δ_F (376 MHz at -39˚C) -75.1 (6F, m, -CF_3), -91.7 (1F, dd, $^3J_{FF}$ 21.8, $^5J_{FF}$ 30.4, 2-CF), -92.69 (1F, dd, $^3J_{FF}$ 23.3 $^5J_{FF}$ 29.4 , 2-CF), -138.4 (1F, dd, $^4J_{FF}$ 90.3, $^5J_{FF}$ 30.5, 5-CF), -135.7 (1F, m, 5-CF), -147.5 (1F, m, 3-CF), -150.6 (1F, dd, $^4J_{FF}$ 84.2, $^3J_{FF}$ 14.3, 3-CF), and -181.2 (1F, dd, $^4J_{FF}$ 84.5, $^4J_{FF}$ 74.1, 4-CF); δ_C (100 MHz) 55.2 (s, CH_3), 91.8 (dsept, $^1J_{CF}$214.4, $^2J_{CF}$36.2, 4-CF), 116.5 (dt, $^2J_{CF}$24.4, $^2J_{CF}$10.7, 4-C), 119.8 (qd, $^1J_{CF}$288.6, $^2J_{CF}$ 27.6, CF_3) and 144.0 -147.0 (broad overlapping m, 3 and 5-C) and 147.0 (broad overlapping m, 2 and 6-C); m/z (EI^+) 331 (M^+, 25 %), 302 (12), 169 (11), 92 (11), 69 (100).

3,5-Difluoro-2,6-dimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3a. Sodium methoxide (0.72 g, 13.1 mmol) and 1 (1.75 g, 5.5 mmol) gave crude material (2.2 g) which after column chromatography, afforded *3,5-difluoro-2,6-dimethoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 3a (1.44 g, 66%) as a yellow liquid; bp 217-8˚C; (Found C, 34.7; H, 1.6; N, 4.3. $C_{10}H_6F_9NO_2$ requires C, 34.9; H, 1.8; N, 4.1%); δ_H (399.9 MHz), 4.0 (s, 2-OCH_3); δ_F (376 MHz) -75.3 (6F, m, CF_3), -145.9 and -149.0 (1F, m, 3, 5-CF) and -179.9 (1F, m, 4-CF); δ_C (100 MHz) 54.2 (s, 2-OCH_3), 92.0 (dsept,$^1J_{CF}$213.3, $^2J_{CF}$35.5, 4-CF), 114.6 (dt, $^2J_{CF}$21.7, $^2J_{CF}$10.4, 4-C), 120.9 (qd, $^1J_{CF}$288.2, $^2J_{CF}$ 27.1, CF_3) 134-141 (broad overlapping m, 3-C) and 147.6 (m, 2 -C); m/z (EI^+) 343 (M^+, 30 %), 314 (10), 300 (14), 84 (10), 69 (100).

3-Fluoro-2,5,6-trimethoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4a. Sodium methoxide (4.1 g, 70 mmol) in methanol (15 ml) and 1 (2.0 g, 6.3 mmol) in methanol (5 ml) gave 3-fluoro-2,5,6-trimethoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4a (1.7 g, 75 %) as a colourless solid; mp 47-48 °C; (Found C, 37.4; N, 3.72; H, 2.71. $C_{11}H_9F_8NO_3$ requires C, 37.2; N, 3.90; H, 2.50%); δ_F -74.9 (6F, m, conformer B, CF_3), -75.1 (6F, m, conformer A, CF_3), -146.3 (1F, br s, conformer A, 5-F), -149.7 (1F, d, $^4J_{FF}$ 94.0 , conformer B, 5-F), -177.5 (1F, d, $^4J_{FF}$ 94.0 , conformer B, CF) and -182.0 (1F, s, conformer A, CF); d_C 53.9 (s, $C_{2,6}$-OCH_3), 60.5 (s, conformer A, C_3-OCH_3), 61.6 (s, conformer B, C_3-OCH_3), 92.2 (dsept, $^1J_{CF}$ 217.5, $^2J_{CF}$ 37.4, $CF(CF_3)_2$), 119.0 (m, 4-C), 120.3 (qd, $^1J_{CF}$ 280, $^2J_{FF}$ 27.7, $CF(CF_3)_2$), 133.3 (br s, conformer B, C_3-OMe), 135.3 (br s, conformer A, C_3-OMe), 135.4 (d, $^1J_{CF}$ 264, conformer A, C_5-F), 139.1 (d, $^1J_{CF}$ 264, conformer B, C_5-F), 146.5 (d, $^2J_{CF}$ 14, conformer A, C_6-OMe), 146.8 (d, $^2J_{CF}$ 14, conformer B, C_6-OMe), 150.0 (s, conformer B, C_2-OMe) and 152.4 (s, conformer A, C_2-OMe); d_H 3.76 (3H, s, C_3-OCH_3), 3.9 (6H, s, $C_{2,6}$-OCH_3); m/z (EI^+) 355 (M^+, 83%), 340 (100), 321 (33), 312 (80), 243 (55), 143, (29), 69 (42).



Conformer A



Conformer B

Reactions with Alkoxides - General procedure.

Under an atmosphere of dry nitrogen, sodium metal or sodium hydride (as a 60% dispersion in mineral oil) was added to a solution of the alcohol in THF (20 cm^3) and stirred until hydrogen evolution was complete. 1 was added to the solution which was stirred at reflux temperature for 24 h before water (25 cm^3) was added. The mixture was continuously extracted with dichloromethane, dried ($MgSO_4$) and evaporated to yield crude material. The isolation of pure products was achieved by column chromatography, using hexane and dichloromethane (6:1) as the eluent.

2,3,5-Trifluoro-6-methoxyethanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 2c. Sodium (0.13 g, 5.5 mmol), 1 (1.75 g, 5.5 mmol) and 2-methoxyethanol (0.42 g, 5.5 mmol) gave crude material (2.2 g) which after column chromatography afforded *2,3,5-trifluoro-6-methoxyethanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethylethyl)-pyridine* 2c (0.79 g, 38%) as a yellow oil; bp 256.8-257˚C; (Found C, 35.1; H, 1.9; N, 3.9. $C_{11}H_7F_{10}NO_2$requires C, 35.2; H, 1.9; N, 3.7%); δ_H(399.9 MHz), 3.4 (3H, s, CH_3), 3.8 (2H, dt, $^2J_{HH}$ 5.2, $^3J_{HH}$ 1.2, CH_3OCH_2), and 4.5 (2H, dt, $^2J_{HH}$ 5.2, $^3J_{HH}$ 1.2, CH_2), δ_F (376 MHz) -75.0 (6F, m, CF_3), -90.4 and -91.6 (1F, m, 2-CF), -133.4 and -136.1 (1F, m, 5-CF), -146.1 and -149.1 (1F, m, 3-CF) and -180.0 (1F, m, 4-CF); δ_C (100 MHz) 58.9 (s, CH_3), 67.3 (s, $-CH_2OCH_3$), 69.9 (s, CH_2), 91.6 (dsept, $^1J_{CF}$214.2, $^2J_{CF}$33.9, 4-CF), 116.4 (dt, $^2J_{CF}$24.4, $^2J_{CF}$12.9, 4-C), 119.9 (qd, $^1J_{CF}$281.6, $^2J_{CF}$ 27.6, CF_3) and 143.6-146.1 (broad overlapping m, 2, 3, 5 and 6-C); m/z (EI^+) 375 (M^+, 4 %), 318 (4), 69 (38).

3,5-Difluoro-2,6-dimethoxyethanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3b. Sodium (0.52 g, 22.1 mmol), 1 (1.75 g, 5.5 mmol) and 2-methoxyethanol (1.68 g, 22.0 mmol) gave crude material (2.5 g) which after column chromatography afforded *3,5-difluoro-2,6-dimethoxyethanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoro-methyl-ethyl)-pyridine* 3b (1.8g, 76%) as a clear liquid; bp >300˚C; (Found C, 39.0; H, 3.2; N, 3.2. $C_{14}H_{14}F_9NO_4$ requires C, 38.9; H, 3.2; N, 3.2%); δ_H (399.9 MHz), 3.4 (6H, s, CH_3), 3.7 (4H, dt, $^2J_{HH}$ 5.2, $^3J_{HH}$ 1.2, CH_3OCH_2), and 4.5 (4H, dt, $^2J_{HH}$ 5.2, $^3J_{HH}$ 1.2, CH_2); δ_F (376 MHz) -75.6 (6F, m, CF_3), -144.5 and -147.6 (1F, m, 3, 5-CF) and -180.3 (1F, m, 4-CF); δ_C (100 MHz) 59.1 (s, CH_3), 66.5 (s, CH_2OCH_3), 70.3 (s, CH_2), 91.9 (dsept, $^1J_{CF}$212.8, $^2J_{CF}$35.8, 4-CF), 114.8 (dt, $^2J_{CF}$22.1, $^2J_{CF}$11.1, 4-C), 119.9 (qd, $^1J_{CF}$288.6, $^2J_{CF}$ 28.7, CF_3), 134-140.0 (broad overlapping

m, 3 and 5-C) and 146.2 (broad overlapping m, 2 and 6-C); m/z (EI^+) 431 (M^+, 1 %), 59 (100).

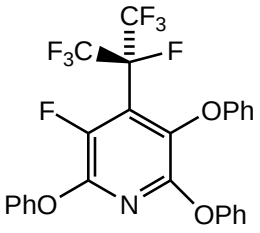
2,3,5-Trifluoro-6-cyclohexanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 2d. Sodium hydride (0.13 g, 5.3 mmol), 1 (1.75 g, 5.5 mmol) and cyclohexanol (0.55 g, 5.5 mmol) gave crude material (2.3 g), which after column chromatography afforded *2,3,5-trifluoro-6-cyclohexanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 2d (1.4 g, 64 %) as a colourless oil; bp >300˚C; (Found C, 41.8; H, 2.6; N, 3.5. $C_{14}H_{11}F_{10}NO$requires C, 42.1; H, 2.8; N, 3.5%); δ_H (399.9 MHz), 1.2-2.2 (10H, m, CH_2) and 5.0 (1H, tt, $^3J_{HH}$ 17.9, $^3J_{HH}$ 3.9, -OCH); δ_F (376 MHz) -75.3 (6F, m, CF_3), -90.8 and -91.9 (1F, m, 2-CF), -134.1 and -136.7 (1F, m, 5-CF), -147.5 and -150.6 (1F, m, 3-CF) and -180.0 (1F, m, 4-CF); δ_C (100 MHz) 23.6 (s, 3-C_{Hex}), 25.4 (s, 4-C_{Hex}), 31.4 (s, 2-C_{Hex}), 76.9 (s, 1-C_{Hex}), 91.9 (dsept, $^1J_{CF}$214.0, $^2J_{CF}$38.1, 4-CF), 116.4 (dt, $^2J_{CF}$22.5, $^2J_{CF}$9.2, 4-C), 119.9 (qd, $^1J_{CF}$288.7, $^2J_{CF}$ 27.6, CF_3) and 143.9 -146.5 (broad overlapping m, 2, 3, 5 and 6-C); m/z (EI^+) 399 (M^+, 1 %), 318 (22), 220 (10), 83 (64), 82 (87), 81 (18), 79 (13), 69 (17).

3,5-Difluoro-2,6-dicyclohexanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3c. Sodium hydride (0.26 g, 11.0 mmol), 1 (1.75 g, 5.5 mmol) and cyclohexanol (1.1 g, 11.0 mmol) gave crude material (2.9 g) which after column chromatography afforded *3,5-difluoro-2,6-dicyclohexanoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 3c (1.7g, 65%) as a white solid; mp 68.5-69.0˚C; (Found C, 49.8; H, 4.5; N, 2.8. $C_{20}H_{22}F_9NO_2$ requires C, 50.1; H, 4.6; N, 2.9%); δ_H (399.9 MHz), 1.2-2.0 (20H, m, C_6H_{10}) and 4.8 (2H, m, OCH); δ_F (376 MHz) -75.0 (6F, m, CF_3), -145.4 and -148.5 (1F, m, 3-CF) and -180.0 (1F, m, 4-CF); δ_C (100 MHz) 23.9 (s, 3-C_{Hex}), 25.5 (s, 4-C_{Hex}), 31.7 (s, 2-C_{Hex}), 75.8 (s, 1-C_{Hex}), 91.9 (dsept, $^1J_{CF}$212.8, $^2J_{CF}$35.7, 4-CF), 114.3 (dt, $^2J_{CF}$21.6, $^2J_{CF}$14.3, 4-C), 120.1 (qd, $^1J_{CF}$288.3 , $^2J_{CF}$ 27.7, CF_3), 130-140.0 (broad overlapping m, 3-C) and 145.9 (m, 2-C); m/z (EI^+) 479 (M^+, 6%), 316 (22), 315 (50), 83 (43), 82 (46), 81 (28), 79 (13), 69 (4).

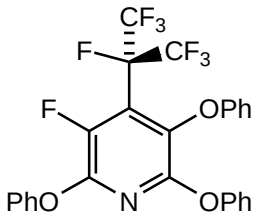
2,3,5-Trifluoro-6-phenoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 2e. Sodium (0.13 g, 5.5 mmol), 1 (1.75 g, 5.5 mmol) and phenol (0.52 g, 5.5 mmol) used gave crude material (2.6 g), which after column chromatography afforded *2,3,5-trifluoro-6-phenoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 2e (1.42 g, 66 %) as a colourless oil; bp 252.6-253.0˚C; (Found C, 42.5; H, 1.2; N, 3.5. $C_{14}H_5F_{10}NO$requires C, 42.7; H, 1.3; N, 3.6%); δ_H (399.9 MHz), 7.0-7.6 (m, Ar-H); δ_F (376 MHz) -75.5 (6F, m, CF_3), -88.6 and -89.6 (1F, m, 2-CF), -133.1 and -135.8 (1F, m, 5-CF), -142.0 and -145.0 (1F, m, 3-CF) and -180.1(1F, m, 4-CF); δ_C (100 MHz) 91.9 (dsept, $^1J_{CF}$214.3, $^2J_{CF}$36.2, 4-CF), 117.5 (m, 4-C), 119.9 (qd, $^1J_{CF}$292.7, $^2J_{CF}$ 27.1 Hz, CF_3), 120.9 (s, 2 and 6-C_{Ph}), 125.9 (s, 4-C_{Ph}), 129.8 (s, 3-C_{Ph}), 135-140.0 (broad overlapping m, 3 and 5-C), 143.8 (m, 6-C), 146.2 (m, 2-C) and 152.3 (s, 1-C_{Ph}); m/z (EI^+) 393 (M^+, 59 %), 365 (25), 364 (11), 296 (47), 276 (11), 269 (11), 205 (22), 196 (16), 77 (100), 69 (14).

3,5-Difluoro-2,6-diphenoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3d. Sodium (0.26 g, 11.7 mmol), 1 (1.75 g, 5.5 mmol) and phenol (1.1 g, 11.7 mmol) used gave crude material (3.1g) which after column chromatography afforded *3,5-difluoro-2,6-diphenoxy-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 3d (1.86 g, 72%) as a white solid; mp 45.1-45.8°C (Found C, 51.5; H, 2.1; N, 3.0. $C_{20}H_{10}F_9NO_2$ requires C, 51.4; H 2.1; N, 3.0%); δ_H (399.9 MHz), 7.0-7.4 (m, Ar-H); δ_F (376 MHz) -75.0 (6F, m, CF_3), -138.7 and -141.6 (1F, m, 3-CF) and -179.0 (1F, m, 4-CF); δ_C (100 MHz) 92.1 (dsept, $^1J_{CF}$213.6, $^2J_{CF}$35.8, 4-CF), 115.9 (dt, $^2J_{CF}$20.7, $^2J_{CF}$11.0, 4-C), 120.1 (qd, $^1J_{CF}$291.7, $^2J_{CF}$ 27.2, CF_3), 120.8 (s, 2 -C_{Ph}), 125.1 (s, 4-C_{Ph}), 129.2 (s, 3-C_{Ph})), 137-142.0 (broad overlapping m, 3-C), 145.3 (m, 2-C) and 152.3 (s, 1-C_{Ph}); m/z (EI^+) 467 (M^+, 58%), 362 (16), 346 (12), 243 (32), 180 (11), 177 (17), 77 (100).

3-Fluoro-2,5,6-phenoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4b. Sodium (2.6 g, 100 mmol), phenol (11.0 g, 110 mmol) and 1 (1.98 g, 6.2 mmol) *gave 3-fluoro-2,5,6-triphenoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine* 4b (0.91 g, 27 %) as a colourless solid; mp 47-48 °C; (Found C, 57.4; N, 2.6; H, 2.8. $C_{26}H_{15}F_8NO_3$ requires C, 57.6; N, 2.6; H, 2.8%); δ_F –71.5 (6F, s, conformer A, CF_3) –72.0 (6F, s, conformer B, CF_3), -136.2 (1F, s, conformer A, 5-F), –138.7 (1F, d, $^4J_{FF}$ 98.5, conformer B, 5-F), –174.5 (1F, d, $^4J_{FF}$ 98.5, conformer B, CF) and –178.3 (1F, s, conformer A, CF); d_H 6.4-7.4 (m, -C_6H_5); m/z (EI^+) 541 (M^+, 14%), 152 (12), 77 (100) and 51 (15).



Conformer A



Conformer B

3,5-Difluoro-2,6-bis-(3-methoxyphenoxy)-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3e. Sodium (0.26 g, 11.0 mmol), 1 (1.75 g, 5.5 mmol) and 3-methoxyphenol (1.36 g, 11.0 mmol) gave crude material (3.2 g) which after column chromatography afforded *3,5-difluoro-2,6-bis-(3-methoxyphenoxy)-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine* 3e(2.0 g, 69 %) as a white solid; mp 54.1-54.8°C; (Found C, 50.2; H, 2.7; N, 2.7 $C_{22}H_{14}F_9NO_4$ requires C, 50.1; H 2.7; N, 2.7%); δ_H (399.9 MHz), 3.7 (6H, s, CH_3), 6.6 (4H, m, 2 and 6-CH), 6.7 (2H, dd, $^3J_{HH}$ 8.4, 4-CH) and 7.2 (2H, t, $^3J_{HH}$ 8.4, 5-CH); δ_F (376 MHz) -75.6 (6F, m, CF_3), -138.5 and -141.5 (2F, m, 3-CF), -180.0 (1F, m, 4-CF); δ_C (100 MHz) 55.4 (s, CH_3), 92.2 (dsept, $^1J_{CF}$212.8, $^2J_{CF}$57.6, 4-CF), 106.9 (s, 5-C_{Ph}), 111.4 (s, 3-C_{Ph}), 112.9 (s, 1-C_{Ph}), 116.5 (dt, $^2J_{CF}$22.1, $^2J_{CF}$ 11.0, 4-C), 120.2 (qd, $^1J_{CF}$288.0, $^2J_{CF}$ 26.5, CF_3), 129.9 (s, 4-

C_{Ph}), 137-140.0 (broad overlapping m, 3-C), 145.2 (m, 2-C), 154.0 (s, 6-C_{Ph}) and 160.7 (s, 2-C_{Ph}); m/z (EI^+) 527 (M^+, 21%), 107 (20), 92 (67), 77 (100), 69 (17).

Silicon chemistry - General procedure

Under an atmosphere of dry nitrogen, the bis-silyl derivative was added to a solution consisting of caesium fluoride, 1 and monoglyme and heated to reflux for 40 h, before water (250 cm^3) was added. The mixture was continuously extracted into ether and dried ($MgSO_4$) and 1 present in the ether fraction was recovered by extraction into perfluorocyclohexane. The ether layer was evaporated to yield a crude product which was purified by recrystallisation from cyclohexane.

1,3-Bis[2,3,5-trifluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyrid-2-yloxy]benzene 5a. 1,3-Bis-(trimethylsilyloxy)benzene (1.8 g, 7.1mmol), caesium fluoride (2.5 g, 16.5 mmol), 1 (22.5 g, 70.5 mmol) and monoglyme (175 cm^3) gave *1,3-bis[2,3,5-trifluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyrid-2-yloxy]benzene* 5a (3.5 g, 70%); mp 138.0-138.4˚C; (Found C, 37.3; H, 0.5; N, 3.9. $C_{22}H_4F_{20}N_2O_2$ requires C, 37.3; H, 0.6; N, 3.9%); δ_H (399.9 MHz), 7.07 (1H, s, 2-CH), 7.14 (2H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 2.0, 4 and 6-CH), 7.50 (1H, t, $^3J_{HH}$ 8.4 , 5-CH); δ_F (376 MHz) -75.2 (12F, m, CF_3), -87.9 and -89.0 (2F, m, 2-CF), -132.8 and -135.3 (2F, m, 3-CF), -140.9 and -143.6 (2F, m, 5-CF), -180.3 (2F, m, 4-CF); δ_C (100 MHz) 91.9 (dsept, $^1J_{CF}$212.9, $^2J_{CF}$38.5, 4-CF), 114.6 (s, 2-$C_{Benzene}$), 118.0 (m, 4-C), 118.4 (s, 4-$C_{Benzene}$), 119.9 (qd, $^1J_{CF}$289.6, $^2J_{CF}$26.7, CF_3), 130.9 (s, 5-$C_{Benzene}$), 139.0 (broad overlapping m, 3 and 5-C), 145.8 (m, 2 and 6-C), 152.8 (s, 1 and 3-$C_{Benzene}$); m/z (EI^+) 708 (M^+, 5%), 323 (6), 273 (8), 69 (29).

1,3-Bis[2,3,5-trifluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyrid-2-yloxy]-5-methyl-benzene 5b. 3,5-Bis-(trimethylsilyloxy)-toluene(1.9 g, 7.1 mmol), caesium fluoride (2.5 g, 16.5 mmol), 1 (22.5 g, 70.5 mmol) and monoglyme (175 cm^3) gave *1,3-bis[2,3,5-trifluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyrid-2-yloxy]-5-methyl-benzene* 5b (3.7 g, 73%); mp 161-161.5˚C; (Found C, 38.0; H, 0.8; N, 3.9. $C_{23}H_6F_{20}N_2O_2$ requires C, 38.2; H, 0.8; N, 3.9%); δ_H (399.9 MHz), 2.4 (3H, s, CH_3), 7.1 (3H, m, Ar-H); δ_F (376 MHz) -76.2 (12F, m, CF_3), -90.8 and -91.9 (2F, m, 2-CF), -135.2 and -137.6 (2F, m, 3-CF), -143.8 and -146.4 (2F, m, 5-CF), -180.8 (2F, m, 4-CF); δ_C (100 MHz) 20.7 (s, CH_3), 92.1 (dsept, $^1J_{CF}$213.2, $^2J_{CF}$35.8, 4-CF), 111.2 (s, 2-$C_{Benzene}$), 116.7 (m, 4-C), 119.0 (s, 4-$C_{Benzene}$), 120.0 (qd, $^1J_{CF}$288.2, $^2J_{CF}$27.1, CF_3), 141.9 (s, 5-$C_{Benzene}$), 142.0-144.0 (broad overlapping m, 2, 3, 5 and 6-C), 153.6 (s, 1-$C_{Benzene}$); m/z (EI^+) 722 (M^+, 31%), 406 (41), 387 (39), 378 (21), 301 (18), 253 (18), 236 (16), 89 (24), 78 (13), 69 (30).

^{19}F n.m.r. Spin-saturation Transfer experiments

Spin saturation transfer experiments for 1, 4a and 4b were performed according to the method described in the literature. The percentage loss of spin coupled resonance upon saturation by irradiation at the radiofrequency corresponding to the resonances associated with ring-fluorine atoms in 1, 4a and 4b , rates of exchange and temperature are recorded in Table 2. A plot of

n k versus 1/T gave a straight line graph with gradient $-E_A/R$. T_1 values were determined in separate experiments using the inversion-recovery pulse sequence.
Perfluoro-4-isopropylpyridine 1 (35.7 $kJmol^{-1}$)

Temp / K	% Loss on Saturation	K / s^{-1}	1/T (x 10^{-3})	In k
236	65	1.95	4.24	0.67
233	52	1.31	4.29	0.27
228	39	0.78	4.39	-0.25
224	28	0.54	4.46	-0.62

3-Fluoro-2,5,6-trimethoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4a (100.3 $kJmol^{-1}$)

Temp / K	% Loss on Saturation	K / s^{-1}	1/T (x 10^{-3})	In k
267	52	0.55	3.75	-0.60
264	38	0.35	3.79	-1.04
261	23	0.19	3.84	-1.65
257	13	0.10	3.89	-2.29

3-Fluoro-2,5,6-phenoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine 4b(81.0 $kJmol^{-1}$)

Temp / K	% Loss on Saturation	K / s^{-1}	1/T (x 10^{-3})	In k
295	99	31.2	3.39	3.44
267	59	0.98	3.74	-0.20
263	43	0.54	3.81	-0.62
257	38	0.47	3.89	-0.76

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