Photoinduced Electron-transfer Perfluoroalkylation of Aminopyridines with Perfluoroalkyl Iodides

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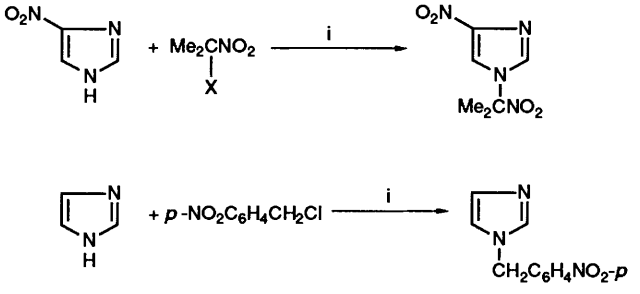
Irradiation of aminopyridines and perfluoroalkyl iodides results in perfluoroalkylation of the pyridine moieties. An electron-transfer mechanism is proposed.

Fluorine-containing heteroaromatic compounds, increasingly used in medicine and biochemistry,[1] are usually synthesized by cyclization of fluoro-containing substrates or more conveniently by direct perfluoroalkylation of the parent precursors.[2] Electron-rich heteroaromatic compounds, such as pyrrole, indole and imidazole have been perfluoroalkylated,[3] but there have been few reports of the direct perfluoroalkylation of pyridine and its derivatives.

Attempted perfluoroalkylation of the important aminopyridines[4] with bis(perfluoroalkanoyl) peroxides[5] as for pyridine, alkylpyridines and some hydroxypyridines was unsuccessful because of amide formation. Recently, Huang and Liu found that perfluoroalkyl groups could be introduced into the pyridine ring by the reaction of perfluoroalkyl iodides and 2-aminopyridine in the presence of rongalite; yields were low, however, except for alkylpyridines and pyridine itself.[6]

On the other hand, Adebayo *et al.*[7] and Beugelmans and Lechevallier[8] have reported that imidazoles react with alkyl halides when irradiated in the presence of K_2CO_3 to give the corresponding *N*-alkylated products by an $S_{RN}1$ mechanism (Scheme 1). Since, under similar conditions, we found that



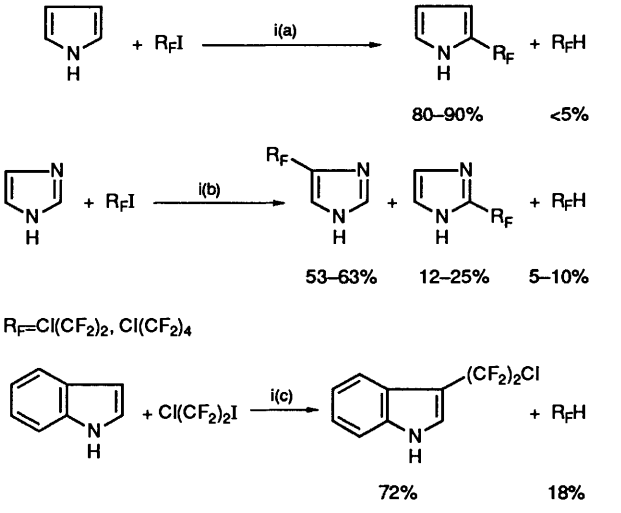
Scheme 1 *Reagents and conditions:* i, K_2CO_3, *hv*

perfluoroalkyl groups could be introduced into pyrrole, imidazole, and indole with perfluoroalkyl iodides to give *C*-alkylated, rather than *N*-alkylated derivatives (Scheme 2),[9] we have investigated the photoinduced perfluoroalkylation of aminopyridines with perfluoroalkyl iodides.

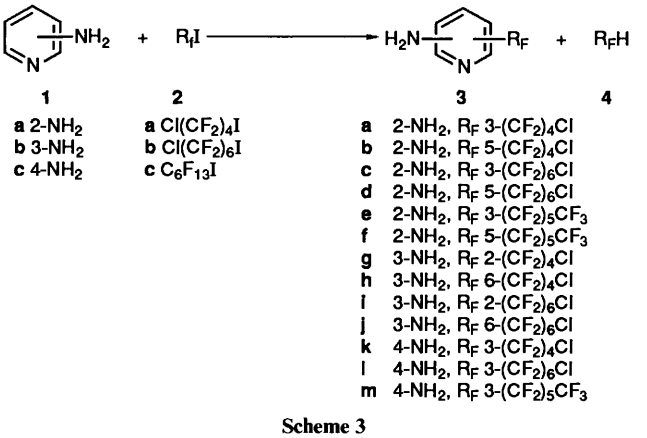
Results and Discussion

UV irradiation of mixtures of aminopyridines **1** and perfluoroalkyl iodides **2** in the presence of K_2CO_3 in dimethylformamide (DMF) for 8.5–20 h gave moderate to high yields of aminoperfluoroalkylpyridines **3** (see Scheme 3). The only by-product was R_FH **4** (20–30% yield on the basis of **1**), no diperfluoroalkylated products being formed. The reaction also proceeded without K_2CO_3, but more **1** was necessary in order to neutralize the HI produced.

The reaction temperature of the mixture of **1** and **2** when irradiated rose to 85 °C within *ca.* 0.5 h. The same mixture



Scheme 2 *Reagents and conditions:* i, Na_2CO_3, DMF, *hv* (a) 60 °C, 4 h; (b) 60 °C, 5 h; (c) 65 °C, 10 h



Scheme 3

when heated at 85 °C for some hours without irradiation gave no products, an indication that UV irradiation was essential to the reaction. The results are shown in Table 1.

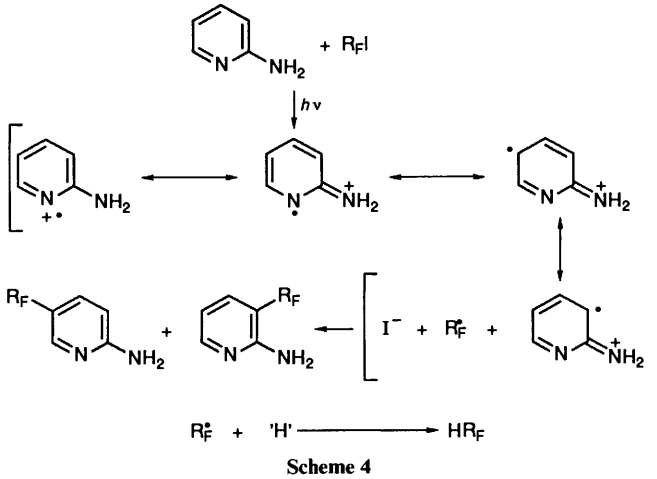
Since, as expected, **3** was an isomeric mixture, the ratio of products was judged by ^{19}F NMR spectrometry and the structures were characterized by ^1H NMR spectroscopy. It was found (see Table 1) that perfluoroalkylation always occurred at the *ortho*- or *para*-positions relative to the amino group of **1**. The yield of the reaction was greatly dependent upon the ratio of **1** to **2**, for example, it decreased from 75 to 38% when the ratio of **1a** to **2a** was reduced correspondingly from 1:3 to 1:1 (see Table 1). DMF was the most suitable solvent, although other solvents such as dimethyl sulfoxide (DMSO), acetonitrile and 1,4-dioxane could also be used for the reaction.

Table 1 Perfluoroalkylation of aminopyridines in the presence of K_2CO_3 at 85 °C by irradiation

Entry	1	2 (1:2)[a]	Reaction time/H	Total yield (%)[b]	Ratio of isomers (%)[c]
1	**a**	**a** (1:3)	8.5	75	25:75[d]
2	**a**	**a**	8.5	65	23:77[d]
3	**a**	**a** (1:1)	8.5	38	
4	**a**	**a**	8.5	20[e]	
5	**a**	**a**	8.5	0[f]	
6	**a**	**a**	8.5	10[g]	
7	**a**	**b** (1:3)	10	60	20:80[d]
8	**a**	**c**	11.5	56	22:78[d]
9	**b**	**a**	15	60	22:5:73[h]
10	**b**	**b**	12	65	30:7:63[h]
12	**c**	**a** (1:3)	20	50[i]	
13	**c**	**a**	20	37[i]	
14	**c**	**b**	12	40[i]	
15	**c**	**c**	25	42[i]	

[a] The ratio of **1** and **2** was 1:2 unless otherwise noted. [b] Isolated yield based on **1**. [c] Determined by ^{19}F NMR. [d] The ratio of 3- and 6-substituted products. [e] 20 mol% of *p*-DNB was added. [f] 20 mol% of di-*tert*-butylaminoxyl was added. [g] 20 mol% of hydroquinone was added. [h] The ratio of 2-, 4- and 6-substituted products. [i] The 3-substituted products.

Charge-transfer complexes can form between perfluoroalkyl iodides and amines,[10] the existence of which result in chemical-shift changes of the signal from $ICF_2 - R_f$ in the ^{19}F NMR spectrum.[11] In the present case, it was found that on reaction, of **1** and **2** in DMF, the CF_2I signals of **2**, were shifted upfield (*ca.* 3 ppm), an indication of charge-transfer complex formation. In order to confirm the reaction mechanism, inhibition studies were carried out. For example, addition of single-electron transfer scavengers, *p*-dinitrobenzene (*p*-DNB) and di-*tert*-butylaminoxyl or free radical inhibitor, hydroquinone, to the reaction mixtures suppressed significantly, or completely, the reaction (Entries 4–6 in Table 1). All the evidence presented, therefore, points to the reaction being a photoinduced single-electron transfer (SET) (see Scheme 4). The charge-transfer



Scheme 4

complex between **1** (using **1a** as an example) and **2** is photochemically stimulated to induce SET to generate the radical cation of **1** and a perfluoroalkyl radical; this is followed by mutual coupling to afford the product.[12] This scheme also explains the direction of perfluoroalkyl group attack on the pyridine ring of **1**. The by-product R_FH **4** may be ascribed to the hydrogen abstraction of $R_F^{\bullet}$ from the solvent.

Experimental

M.p.s are uncorrected. IR spectra were recorded on Carl Zeiss 75 Model and Schimadzu IR 440 Model instruments all in KBr pellets. ^1H NMR spectra were recorded on Varian 360A at 60 MHz and XL200 instruments with tetramethylsilane (TMS) as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360 spectrometer at 55.6 MHz and chemical shifts in ppm were positive for upfield shifts using $CFCl_3$ as internal standard. *J*-Values are given in Hz. Mass spectra were recorded on a Finnigan 4201 instrument. DMF was dried with CaH_2 before use.

Photoinduced Perfluoroalkylation of Aminopyridines with Perfluoroalkyl Iodide.—*2-Amino-3-(4-chloroactafluorobutyl)pyridine* **3a** *and 2-amino-5-(4-chlorooctafluorobutyl)pyridine* **3b**: *typical procedure.* Perfluoroalkyl iodide **2a** (7.25 g, 20 mmol) and K_2CO_3 (1.36 g, 10 mmol) were added to DMF (15 cm^3) in a Pyrex flask under a nitrogen atmosphere. The ^{19}F NMR spectrum showed a signal at δ 65.7 for ICF_2. Aminopyridine **1a** (0.94 g, 10 mmol) was added and after the mixture had been stirred for 5 min, the signal of ICF_2 shifted to δ 68.6 (2.9 ppm upfield). The system was connected to a solid-CO_2 cooler and then exposed, with stirring, to a high pressure mercury lamp (400 W) at a distance of 8 cm. The temperature rose to 85 °C within 0.5 h and carbon dioxide was released. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. After *ca.* 8.5 h, the reaction was complete. The by-product $Cl(CF_2)_4H$ was obtained (0.47 g, 20%) in the cooler. The mixture was then poured into water (40 cm^3), and extracted with dichloromethane (3 × 20 cm^3). The organic phase was washed with water (3 × 10 cm^3), dried ($MgSO_4$), and evaporated. The residue was subjected to column chromatography on silica gel using light petroleum–ethyl acetate (5:2) as eluent, to give the title compounds **3a** (0.5 g, 15%) and **3b** (1.60 g, 50%). **3a**: M.p. 50–52 °C, (Found: C, 32.9; H, 1.5; N, 8.55; F, 46.5. Calc. for $C_9H_5N_2ClF_8$: 32.88; H, 1.52; N, 8.52; F, 46.27); ν_{max}/cm^{-1} 3530, 3350, 1560 and 1195; $\delta_H(CDCl_3)$ 8.20 (1 H, d, *J* 4.8), 7.63 (1 H, d, *J* 8.0), 6.70 (1 H, dd, *J* 4.8 and 8.0) and 3.34 (2 H, s); $\delta_F(CDCl_3)$ 68.5 (2 H, s), 110.6 (2 F, s), 119.9 (2 F, s) and 121.8 (2 F s); *m/z* 331 (M^+ + 1, 28), 330 (M^+, 14), 328 (M^+, 25), 293 (M^+ − Cl, 29), 144 ($ArCF_2^+$ + 1, 100) and 143 ($ArCF_2^+$, 61). **3b**: M.p. 65–67 °C (Found: C, 33.2; H, 1.5; N, 8.6; F, 46.2. Calc. for $C_9H_5N_2ClF_8$: C, 32.88; H, 1.52; N, 8.52; F, 46.27); ν_{max}/cm^{-1} 3450, 3300, 1590, 1285 and 1200; $\delta_H([^2H_6]$-DMSO) 8.11 (1 H, d, *J* 2.0), 7.75 (1 H, dd, *J* 2.0 and 8.8), 6.54 (1 H, d, *J* 8.8) and 4.80 (2 H, s); $\delta_F([^2H_6]DMSO)$ 68.6 (2 F, s), 111.1 (2 F, s), 120.3 (2 F, s) and 121.8 (2 F, s); *m/z* 331 (M^+ + 1, 34), 330 (M^+, 12), 329 (M^+ + 1, 71), 328 (M^+, 64) and 143 ($ArCF_2^+$, 100).

2-Amino-3-(4-chlorododecafluorohexyl)pyridine **3c** *and 2-amino-5-(4-chlorododecafluorohexyl)pyridine* **3d**. **3c**: M.p. 54–56 °C (Found: C, 30.8; H, 0.9; N, 6.4; F, 53.1. Calc. for $C_{11}H_5N_2ClF_{12}$: C, 30.81; H, 1.17; N, 6.53; F, 53.21) ν_{max}/cm^{-1} 3530, 3320, 1580 and 1195; $\delta_H([^2H_6]DMSO)$ 8.19 (1 H, d, *J* 4.8), 7.60 (1 H, d, *J* 8.0), 6.70 (1 H, dd, *J* 4.8 and 8.0) and 3.35 (2 H, s); $\delta_F([^2H_6]DMSO)$ 69.1 (2 F, s), 110.3 (2 F, s), 120.7 (2 F, s), 121.7 (4 F, s) and 122.1 (2 F, s); *m/z* 431 (M^+ + 1, 38), 430 (M^+, 10), 429 (M^+ + 1, 100), 428 (M^+, 29) and 143 ($ArCF_2^+$, 8). **3d**: M.p. 88–90 °C (Found: C, 30.75; H, 1.1; N, 6.6; F, 53.7. Calc. for $C_{11}H_5N_2ClF_{12}$: C, 30.81; H, 1.17; N, 6.63; F, 53.21) ν_{max}/cm^{-1} 3450, 3300, 1610, 1285 and 1190; δ_H-($[^2H_6]DMSO$) 8.12 (1 H, d, *J* 2.0), 7.50 (1 H, dd, *J* 2.0 and 9.0), 6.50 (1 H, d, *J* 9.0) and 5.60 (2 H, br s); $\delta_F([^2H_6]DMSO)$ 69.1 (2 F, s), 110.4 (2 F, s), 120.8 (2 F, s) and 121.8 (6 F, s); *m/z* 430 (M^+, 3), 428 (M^+, 5), 393 (M^+ − Cl, 19), 144 ($ArCF_2^+$ + 1, 100), 143 ($ArCF_2^+$) and 100 ($C_2F_4^+$).

2-Amino-3-perfluorohexylpyridine **3e** *and 2-amino-5-perfluorohexylpyridine* **3f**. **3e**: M.p. 55–57 °C (Found: C, 31.9; H,

1.3; N, 6.7; F, 60.2. Calc. for $C_{11}H_5N_2F_{13}$: C, 32.05; H, 1.23; N, 6.80; F, 59.95); ν_{max}/cm^{-1} 3350, 3300, 1615 and 1200; $\delta_H([^2H_6]DMSO)$ 8.10 (1 H, d, *J* 5.0), 7.60 (1 H, d, *J* 8.5), 6.67 (1 H, dd, 5.0 and 8.5) and 3.40 (2 H, s); $\delta_F([^2H_6]DMSO)$ 75.7 (3 F, s), 110.4 (2 F, s), 121.6 (2 F, s) and 122.0 (6 F, s); *m/z* 412 (M^+, 25), 144 ($ArCF_2^+$ + 1, 100). **3f**: M.p. 86–88 °C (Found: C, 31.9; H, 1.25; N, 6.9; F, 60.0. Calc. for $C_{11}H_5N_2F_{13}$: C, 32.05; H, 1.23; N, 6.80; F, 59.95) ν_{max}/cm^{-1} 3400, 3320, 1620 and 1205; $\delta_H([^2H_6]DMSO)$ 8.02 (1 H, d, *J* 2.1), 7.42 (1 H, dd, *J* 2.1 and 6.6), 6.50 (1 H, d, *J* 6.6) and 4.61 (2 H, s); $\delta_F([^2H_6]DMSO)$ 75.3 (3 F, s), 110.6 (2 F, s), 121.3 (2 F, s) and 121.8 (6 F, s); *m/z* 412 (M^+, 19), 143 ($ArCF_2^+$, 100) and 69 (CF_3^+, 12).

3-*Amino*-2-(4-*chlorooctafluorobutyl*)*pyridine* **3g** *and* 3-*amino*-6-(4-*chlorooctafluoro*)*pyridine* **3b**. **3g**: M.p. 50–52 °C (Found: C, 32.9; H, 1.25; N, 8.55; F, 46.3. Calc. for $C_9H_5N_2ClF_8$: C, 32.88; H, 1.52; N, 8.52; F, 46.27) ν_{max}/cm^{-1} 3335, 3200, 1600, 1240 and 1180; $\delta_H(CDCl_3)$ 8.11 (1 H, d, *J* 5.0), 7.24 (1 H, d, *J* 7.8), 7.06 (1 H, dd, *J* 5.0 and 7.8) and 3.45 (2 H, br s); $\delta_F(CDCl_3)$ 68.0 (2 F, s), 110.9 (2 F, s), 119.4 (2 F, s) and 120.9 (2 F, s); *m/z* 331 (M^+ + 1, 13), 330 (M^+, 7), 329 (M^+ + 1, 42), 328 (M^+, 21), 293 (M^+ − Cl, 18) and 143 ($ArCF_2^+$, 100). **3h**: M.p. 68–70 °C (Found: C, 32.9; H, 1.25; N, 8.5; F, 46.1. Calc. for $C_9H_5N_2ClF_8$: C, 32.88; H, 1.52; N, 8.52; F, 46.27) ν_{max}/cm^{-1} 3380, 3210, 1590 and 1185; $\delta_H(CDCl_3)$ 8.13 (1 H, d, *J* 4.0), 7.42 (1 H, d, *J* 8.9), 7.02 (1 H, dd, *J* 4.0 and 8.9) and 4.38 (2 H, br s); $\delta_F(CDCl_3)$ 68.2 (2 F, s), 112.5 (2 F, s), 119.8 (2 F, s) and 121.4 (2 F, s); *m/z* 330 (M^+, 10), 329 (M^+ + 1, 23), 328 (M^+, 42), 293 (M^+ − Cl, 16), 143 ($ArCF_2^+$, 100) and 93 (Ar^+, 21). The 4-substituted product was detected by ^{19}F NMR but there was too small an amount to be isolated.

3-*Amino*-2-(4-*chlorododecafluorohexyl*)*pyridine* **3i** *and* 3-*amino*-6-(4-*chlorododecafluorohexyl*)*pyridine* **3j**. **3i**: M.p. 54–56 °C (Found: 30.8; H, 1.1; N, 6.7; F, 53.4. Calc. for $C_{11}H_5N_2ClF_{12}$: C, 30.81; H, 1.17; N, 6.53; F, 53.21) ν_{max}/cm^{-1} 3350, 3250, 1600 and 1200; $\delta_H(CDCl_3)$ 8.05 (1 H, d, *J* 5.5), 7.20 (1 H, d, *J* 7.5), 7.06 (1 H, dd, *J* 5.5 and 7.5) and 4.30 (2 H, br s); $\delta_F(CDCl_3)$ 68.2 (2 F, s), 110.4 (2 F, s), 119.8 (2 F, s) and 121.8 (6 F, s); *m/z* 430 (M^+, 10), 429 (M^+ + 1, 18), 428 (M^+, 31) and 143 ($ArCF_2^+$, 100). **3j**: M.p. 62–64 ° (Found: C, 30.7; H, 0.9; N, 6.4; F, 53.67. Calc. for $C_{11}H_5N_2ClF_{12}$: C, 30.81; H, 1.17; N, 6.53; F, 53.21) ν_{max}/cm^{-1} 3350, 3200, 1645 and 1205; $\delta_H(CDCl_3)$ 8.05 (1 H, d, *J* 3.5), 7.36 (1 H, d, *J* 8.8), 7.00 (1 H, dd, *J* 3.5 and 8.8) and 4.65 (2 H, s); $\delta_F(CDCl_3)$ 67.8 (3 F, s), 111.4 (2 F, s), 119.9 (2 F, s) and 121.6 (6 F, s); *m/z* 431 (M^+ + 1, 13), 430 (M^+, 11), 429 (M^+ + 1, 100), 393 (M^+ − Cl, 14), 143 ($ArCF_2^+$, 57). The 4-substituted product was detected by ^{19}F NMR spectroscopy but there was too small an amount to be isolated.

4-*Amino*-3-(4-*chlorooctafluorobutyl*)*pyridine* **3k**, 4-*amino*-3-(4-*chlorododecafluorohexyl*)*pyridine* **3l** *and* 4-*amino*-3-*perfluorohexylpyridine* **3m**. **3k**: M.p. 90–92 °C (Found: C, 32.75; H, 1.2; N, 8.4; F, 46.4. Calc. for $C_9H_5N_2ClF_8$: C, 32.88; H, 1.52; N, 8.53; F, 46.27) ν_{max}/cm^{-1} 3300, 3100, 1605, 1350 and 1200; $\delta_H(CDCl_3)$ 8.38–8.26 (2 H, m), 6.60 (1 H, d) and 4.85 (2 H, br); $\delta_F(CDCl_3)$ 68.8 (2 F, s), 109.6 (2 F, s), 120.3 (2 F, s) and 121.9 (2 F, s); *m/z* 330 (M^+, 9), 329 (M^+ + 1, 10), 328 (M^+, 24), 144 ($ArCF_2^+$ + 1, 100) and 143 ($ArCF_2^+$, 24). **3l**: M.p. 95–97 °C (Found: C, 30.6; H, 0.1; N, 6.4; F, 53.6. Calc. for $C_{11}H_5N_2ClF_{12}$: C, 30.81; H, 1.17; N, 6.53; F, 53.21) ν_{max}/cm^{-1} 3350, 3265, 1610, 1455 and 1200; $\delta_H(CDCl_3)$ 8.40–8.22 (2 H, m), 6.71 (1 H, d) and 4.78 (2 H, br s); $\delta_F(CDCl_3)$ 67.8 (2 F, s), 109.0 (2 F, s), 119.8 (2 F, s), 122.3 (6 F, s); *m/z* 430 (M^+, 17), 429 (M^+ + 1, 35), 428 (M^+, 20), 143 ($ArCF_2^+$, 100). **3m**: M.p. 92–94 °C (Found: C, 32.3; H, 1.35; N, 6.45; F, 59.7. Calc. for $C_{11}H_5N_2F_{13}$: C, 32.05; H, 1.23; N, 6.72; F, 59.95) ν_{max}/cm^{-1} 3455, 3350, 1605 and 1200; $\delta_H(CDCl_3)$ 8.20–8.06 (2 H, m), 6.72 (1 H, s) and 4.57 (2 H, s); $\delta_F(CDCl_3)$ 76.0 (3 F, s), 109.4 (2 F, s), 121.6 (2 F, s), 122.1 (6 F, s); *m/z* 413 (M^+ + 1, 6), 412 (M^+, 14), 143 ($ArCF_2^+$, 100) and 69 (CF_3^+, 4).

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