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N-Halogeno compounds. Part 16. Perfluoro-[N-fluoro-N-(4-pyridyl)acetamide] – a new site-selective electrophilic fluorinating agent [1]

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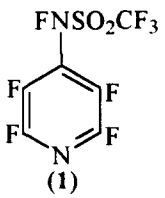
Abstract

Perfluoro-[*N*-fluoro-*N*-(4-pyridyl)acetamide] (**2**), prepared via direct fluorination of the sodium salt (**4**) of perfluoro-[*N*-(4-pyridyl)-acetamide], readily fluorinates diethyl sodio(phenyl)malonate [$\rightarrow PhCF(CO_2Et)_2$], 1-morpholinocyclohexene ($\rightarrow$ 2-fluorocyclohexanone), anisole ($\rightarrow$ 2- and 4-FC_6H_4OMe), and phenol ($\rightarrow$ 2- and 4-FC_6H_4OH) under mild conditions. The sodium salt precursor (**4**) of this side-chain N-F reagent (**2**) is easily made from pentafluoropyridine via the trifluoroacetylation of its 4-amino derivative or, more directly, by treating it with two equivalents of the monosodium salt of trifluoroacetamide.

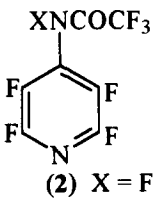
Keywords: *N*-Halogeno; Electrophilic fluorination; Fluoropyridines; *N*-Fluoroacetamides

1. Introduction

N-Fluorocarboxamides have received scant attention as site-selective electrophilic fluorinating agents [1]. Having prepared perfluoro-[*N*-fluoro-*N*-(4-pyridyl)methanesulfonamide] (**1**) [2] in order to make available an F^+ delivery agent virtually as potent, but more attractive to prepare (especially from a hazards viewpoint) [2a], as the powerful DesMarteau sulfonimide $(CF_3SO_2)_2NF$ [3], we decided to utilize the sodium salt fluorination procedure involved in the synthesis of **1** in an effort to procure its carboxamido analogue **2**. Previously [4], direct fluorination of the parent amide (**3**) had not proved possible.



(1)



(2) X = F
(3) X = H
(4) X = Na

[1] Part 15: R.E. Banks and M.K. Besheesh, *J. Fluorine Chem.*, *76* (1996) 161.

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2. Results and discussion

Conversion of pentafluoropyridine to perfluoro-[*N*-fluoro-*N*-(4-pyridyl)acetamide] (**2**) has been achieved as outlined in Scheme 1. The key intermediate is the sodium salt (**4**) of perfluoro-[*N*-(4-pyridyl)acetamide], which can be procured by two routes, A and B, the former being the more direct. Fluorination of **4** in cold (-35 °C) acetonitrile was carried out using neat fluorine at 10–20 mmHg pressure, but there seems no reason why it cannot be achieved with a fluorine–nitrogen blend (10% F_2 by volume; cf. Ref. [5]). Note, however, that even with the excellent control of ingress of moisture which working with a vacuum fluorinator [6] allows, it proved impossible to obtain a sample of **2** free from its N–H analogue **3**; the best result achieved was production of approx. 80% pure material {assayed by ^{19}F NMR spectroscopy and by iodometric NF estimation ($2I^- + >NF \rightarrow I_2 + F^- + >N^-$ [7])}. This situation parallels that found in work on the synthesis of the sufonyl analogue (**1**) of **2** by fluorination of the sodium salt 4-CF_3SO_2N-(Na)C_5F_4N [2].

The structure of **2**, seemingly the first perfluorinated *N*-fluorinated secondary carboxamide to be reported, was clearly established by NMR (^{19}F, ^{13}C) spectroscopic examination of its mixture with its N–H analogue (**3**). Like other

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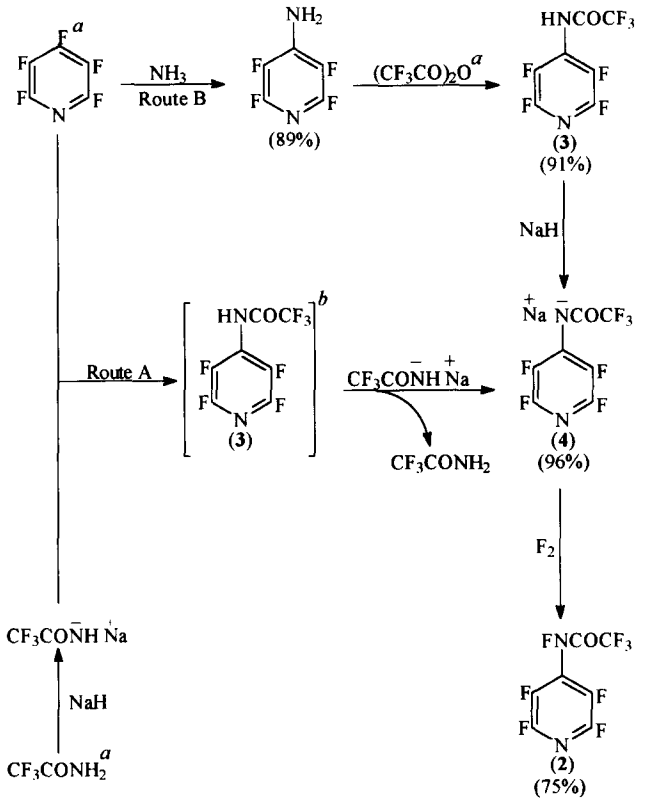


Scheme 1. [a] Available commercially. [b] Not isolated but converted in situ to 2 by the second molar equivalent of $CF_3CONHNa$ used in the reaction with C_5F_5N (cf. Ref. [2a]).

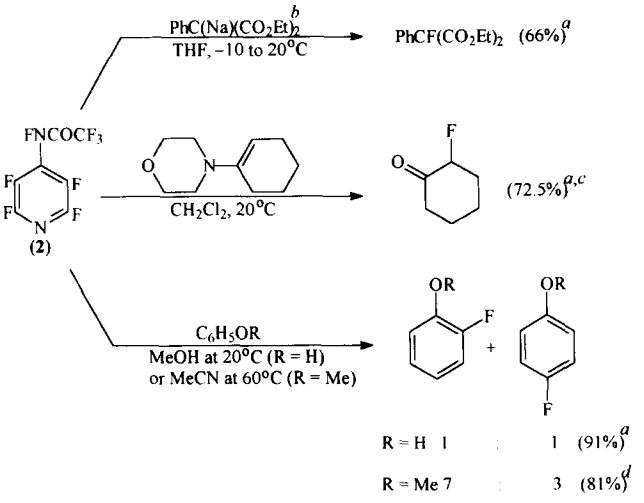
secondary *N*-fluoroamides [8–10], the NF absorption appeared at low field (136.0 ppm) relative to CF_3CO_2H.

The ease of electrophilic fluorination of the electron-rich species diethyl sodio(phenyl)malonate, 1-morpholinocyclohexene, phenol, and anisole observed using impure **2** (see Scheme 2) were in keeping with expectations. However, much further work would be required to enable its relative utility compared with other electrophilic fluorinating agents of the NF class to be established. Such work might usefully include a study of the seemingly unknown pentafluorophenyl analogue $C_6F_5NFCOCF_3$, which would be cheaper to prepare and of a similar order of reactivity.

3. Experimental details

3.1. Spectroscopic analysis

NMR Spectra were recorded with Perkin–Elmer instruments [R34 (220 MHz) for ^1H; R32 (84.6 MHz for ^{19}F] and a Bruker AC-300 spectrometer (75.5 MHz; ^{13}C) using standard references (^1H, ext. Me_4Si; ^{19}F, ext. CF_3CO_2H; ^{13}C, D_2O lock and ext. Me_4Si); positive values are assigned to absorptions downfield of these. Mass spectra were obtained with AEI MS902 (EI and CI, at 70 eV) and Kratos MS50 (FAB) machines, and IR spectra were recorded using a Perkin–Elmer DE783 spectrophotometer.



Scheme 2. [a] Product yields are based on the NMR-determined N-F content of the fluorinating agent (**2**) (see text). [b] Prepared from $PhCH(CO_2Et)_2 + NaH$ in THF [6]. [c] Isolated after an aqueous acid (1M-HCl) work-up procedure [6]. [d] The parent acetamide **3** was isolated in ca. 80% yield.

3.2. Starting materials

Pentafluoropyridine was prepared in 85% yield by heating commercial pentachloropyridine (Fluorochem) with anhydrous potassium fluoride [11] and converted to 4-aminotetrafluoropyridine with aqueous ammonia as described earlier [12], except that the reaction was improved (by an easier technique and an improved product yield) by carrying it out in an open vessel with tetrahydrofuran as a co-solvent. Thus a mixture of C_5F_5N (60.1 mmol), 0.880 NH_3 aq (25 cm^3), and THF (50 cm^3) was heated under reflux (24 h, not optimized) to give 53.4 mmol (89% yield) of analytically pure (C, H, F, N) 4-$H_2NC_5F_4N$, m.p. 82–83 °C (Ref. [12], 83.5–84.0 °C). Trifluoroacetamide, prepared from commercial (Fluorochem) trifluoroacetic acid by the classical route $CF_3CO_2H \rightarrow CF_3CO_2Et \rightarrow CF_3CONH_2$ [13], was converted to its monosodium salt by heating it with sodium hydride (reactant ratio 1.0: 1.0) in dry THF under N_2 at −10 °C; simple removal of the solvent in vacuo after the reaction mixture had been stirred at room temperature for 2 h gave an acceptably pure sample of $CF_3CONHNa$ (Found: C, 18.2; H, 0.8; F, 42.1; N, 10.7%. Calc. for C_2HF_3NNaO: C, 17.8; H, 0.7; F, 42.2; N, 10.4%), δ_F (in acetone-d_6) 2.2 (s, CF_3), δ_C (same soln.) 117.9 (q, $^1J_{CF}$ 294.5 Hz), 161.5 (q, $^1J_{CF}$ 37.8 Hz; CO), δ_H (same soln.) 7.3 (br. s) ppm, *m/z* 136 [$(M+H)^+$, 20%], 116 [$(M-F)^+$, 8%], 69 (CF_3^+, 100%), a hygroscopic solid which was used immediately.

3.3. Perfluoro-[N-(4-pyridyl)acetamide] (3)

Commercial (Flurorochem) trifluoroacetic anhydride (7.6 g, 36.1 mmol) was added slowly to a cold (0 °C) stirred solution of 4-aminotetrafluoropyridine (6.0 g, 36.1 mmol) in trifluoroacetic acid (80 cm^3) under dry nitrogen. The reaction mixture was heated under reflux for 5 h, cooled to 20 °C,

evaporated (Rotavapor) and the pale cream residue crystallized from light petroleum (b.p. 80–100 °C) to give long off-white needles of perfluoro-[*N*-(4-pyridyl)acetamide] (**3**; n.c.) (6.65 g, 25.4 mmol, 70%) (Found: C, 32.2; H, 0.3; F, 50.8; N, 10.8. $C_7HF_7N_2O$ requires C, 32.1; H, 0.4; F, 50.8; N, 10.7%), m.p. 86–87 °C; λ_{max} (KBr disc) 3300 (s; N–H str.), 1745 (C=O str.) cm^{-1}, δ_H (in $CDCl_3$) 9.2 (br.s), δ_F (same soln.) 3.2 (s; CF_3), −13.5 (m; 2-, 6-F), −67.0 (m; 3-, 5-F), δ_C (same soln.) 116.5 (q, $^1J_{CF}$ 293.6 Hz; CF_3), 128.0 (m; C4), 138.5 (m; C2, C6), 145.0 (m; C3, C5,), 154.9 (q, $^2J_{CF}$ 41.9 Hz; CO) ppm, *m/z* (EI, CI) 263 [$(M+1)^+$, 2%], 262 (M^+, 100%).

A superior yield (91%) of **3** was achieved by repeating the above reaction under anerobic conditions in a sealed Pyrex tube. The trifluoroacetic anhydride (36.15 mmol) was condensed, in vacuo, into a cold (−196 °C) Rotaflo tube (approx. 250 cm^3) containing a de-gassed solution of pentafluoropyridine (36.15 mmol) in trifluoroacetic acid (50 cm^3); the tube was closed, placed in an explosion-proof cabinet and, after it had warmed to room temperature, heated at 70 °C for 5 h. The pale-cream crude amide (**3**), recovered by evaporation (Rotavapor) of the reaction product, was purified by standard techniques (treatment of its solution in hot diethyl ether with decolorising charcoal etc.) to give pure white crystalline material (32.8 mmol) with the correct spectroscopic (IR, NMR) characteristics.

3.4. Perfluoro-[N-(4-pyridyl)-N-(sodio)acetamide]

3.4.1. From perfluoro-[N-(4-pyridyl)acetamide]

A solution of the amide (**3**; 5.0 g, 19.1 mmol) was added dropwise for 30 min. to sodium hydride (0.5 g, 20.8 mmol) suspended in stirred THF (20 cm^3) under dry nitrogen. The mixture was stirred at 20 °C for 1 h then at 50 °C for 2 h before the excess of sodium hydride was removed (filtration) under N_2 and the THF solution evaporated under vacuum. The hygroscopic white solid residue (5.5 g, 18:3 mmol, 96%) was analysed and found to be pure perfluoro-[*N*-(4-pyridyl)-*N*-(sodio)acetamide] (**4**; n.c.) (Found: C, 29.4; F, 46.8; N, 9.8. $C_7F_7N_2NaO$ requires C, 29.6; F, 46.8; 9%), m.p. 215 °C (decomp.), λ_{max} (KBr disc) 1780 cm^{-1} (s, C=O str.), δ_F [soln. in $(CD_3)_2CO$] 4.0 (s; CF_3), −18.2 (m; 2-, 6-F), −74.2 (m; 3-, 5-F), δ_C [same soln.] 119.9 (q, $^1J_{CF}$ 28-6.2 Hz; CF_3), 137.5 (m; C2, C6), 144.95 (m; C3, C5), 146.0 (m; C4), 160.0 (q, $^2J_{CF}$ 33.8 Hz; CO) ppm.

3.4.2. Directly from pentafluoropyridine

Using dry-box (N_2) techniques, a solution of pentafluoropyridine (1.8 g, 10.65 mmol) in dry THF (50 cm^3) was poured into a Pyrex Rotaflo tube (approx. 200 cm^3) containing a freshly prepared sample of the monosodium salt of trifluoroacetamide (2.9 g, 21.5 mmol). The mixture was degassed (−196 °C; three freeze-pump-thaw cycles), and the tube was closed and heated at 60 °C (whilst being shaken gently in a vertical position behind a blast screen) for 24 h. The product was washed out of the tube with dry THF, filtered to remove sodium fluoride, the solvent was removed (Rotavapor) and the solid residue freed from trifluoroacetamide (by sublimation at 75 °C in vacuo), leaving a pure sample (by IR and ^{19}F NMR analysis) of perfluoro-[*N*-(4-pyridyl)-*N*-(sodio)acetamide] (**4**; 2.2 g, 7.75 mmol, 73%).

3.5. Perfluoro-[N-fluoro-N-(4-pyridyl)acetamide]

Using a virtually all-glass vacuum fluorination apparatus of the type described previously and fitted with an unjacketed Pyrex reactor (approx. 250 cm^3) [6], a cold (−35 °C), degassed, vigorously stirred solution of freshly prepared perfluoro-[*N*-(4-pyridyl)-*N*-(sodio)acetamide] (**4**) (2.2 g, 7.75 mmol) in HPLC-grade acetonitrile (200 cm^3; Aldrich) was continuously treated with neat fluorine at 10–20 mmHg pressure until consumption of the halogen appeared to have ceased (6.5 h). After residual fluorine had been pumped away (via a KI scrubber [6]), the yellowish reaction mixture was warmed to room temperature, filtered under dry nitrogen to remove sodium fluoride [0.28 g (after being dried in vacuo at 20 °C), 6.7 mmol, 86%], and the filtrate evaporated in vacuo. The noticeably hygroscopic, pale yellow, semi-solid residue was identified by ^{19}F NMR analysis as a 79:18 mixture (by comparison of the CF_3 signals) of perfluoro-[*N*-fluoro-*N*-(4-pyridyl)acetamide] (**2**; n.c.) and the parent N–H compound **3**; the purity of the N–F compound **2** was shown to be 80% by iodometric assay (titration against $Na_2S_2O_4$ aq of the iodine liberated instantaneously when 0.50 g of the semi-solid product mixture was added to an excess of KI in 10% aqueous Me_2CO at 20 °C). The following NMR data were extracted from the spectra of the mixture of **2** and **3** (soln. in CD_3CN): δ_F 136.0 (broadened s; NF), 2.0 (s; CF_3), −14.5 (m; 2-, 6-F), −91.0 (m; 3-, 5-F), δ_C (same soln.) 121.3 (q, $^1J_{CF}$ 298.5 Hz; CF_3), 139.7 (m; C2, C6; CO), 145.6 (m; C3, C5), 148.0 (m; C4), 169.35 (q, $^2J_{CF}$ 42 Hz) ppm.

3.6. Electrophilic fluorinations using a ca. 80:20 (molar) mixture of 2 and 3

3.6.1. Diethyl phenylmalonate and 1-morpholinocyclohexene

These fluorinations were carried out on a roughly 5 mmol scale exactly as described in Ref. [6] for work with *N*-fluoroquinuclidinium fluoride. The results are shown in Scheme 2; the products were identified by NMR (^1H, ^{19}F) and MS techniques.

3.6.2. Phenol

A reaction occurred immediately when the impure N–F reagent **2** (0.5 g, 1.7 mmol of **2**) was added to a solution of phenol (0.16 g, 1.7 mmol) in anhydrous methanol (the reaction solution turned yellow). The reaction mixture was degassed at −196 °C (three freeze-pump-thaw cycles) and left in a sealed Pyrex tube (approx. 100 cm^3) overnight at 20 °C before it was concentrated (20 cm^3 of MeOH was removed)

and treated dropwise with dry diethyl ether (30 cm^3) until no more perfluoro-[*N*-(4-pyridyl)acetamide] (**3**; identified by ^1H and ^{19}F NMR analysis) precipitated. The N–H compound (**3**) was removed by filtration and the filtrate evaporated to yield an oily approximately 1:1 mixture (91% yield) of 2- and 4-fluorophenol (identified by ^1H and ^{19}F NMR spectroscopy). The product yield was determined by ^{19}F NMR analysis of the crude reaction product (prior to removal of MeOH), using the CF_3 signal of **3** as the internal standard.

3.6.3. Anisole

A solution of an approximately 80:20 molar mixture of **2** and **3** containing 1.8 mmol of the former (by ^{19}F NMR analysis) and anisole (0.19 g, 1.76 mmol) in dry acetonitrile (20 cm^3) contained in a Pyrex Rotaflo tube (approx. 100 cm^3) was cooled to −196 °C, de-gassed, allowed to warm to 20 °C, in vacuo, then heated at 60 °C overnight behind a stout blast screen (standard precaution for sealed glass vessel). The clear reaction product was diluted with dry diethyl ether, filtered to remove the perfluoro-[*N*-(4-pyridyl)acetamide] (**3**; 0.38 g, 1.45 mmol after being dried) which precipitated, and the filtrate evaporated (Rotavapor) to give a roughly 70:30 mixture (by ^{19}F NMR analysis) of 2- and 4-fluoroanisole (0.18 g, 1.42 mmol, 81% based on anisole).

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