Direct Synthesis of 3-(Fluoroalkyl)pyrazoles from Polyfluoroalkyl Aldehydes

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3-(Fluoroalkyl) pyrazoles 3 have been synthesized in excellent yields by reaction of various fluoroalkyl aldehydes with NH₂NH₂+HOAc under mild conditions. It appears that the reaction involves the formation of a hydrazone intermediate, followed by elimination of hydrogen halide and intramolecular nucleophilic addition. A practical one-pot synthesis of 3-(fluoroalkyl) pyrazoles from polyfluoroalkyl iodides 1 has also been developed.

It is well recognized that the regioselective replacement of hydrogen in an aromatic or heterocyclic system by a fluoroalkyl group may have profound influence on the biological and physical properties of such molecules. As a result, considerable efforts have been devoted to the development of methodologies for the synthesis of fluorine-containing heterocycles,² and fluoroalkylpyrazoles are compounds possessing high biological activities as herbicides, fungicides, insecticides, analgesics, antipyretics and antiinflammatories.³ This, therefore, has led to the development of a few general, but somewhat limited, methods for their synthesis. Among them, the cyclocondensation of fluorinated α,β-unsaturated carbonyl derivatives or 1,3-dicarbonyl derivatives with hydrazines 4 and hydrazones 5 is the most widely used method, which, however, leads to the formation of a mixture of isomers. Another route for the synthesis of fluoroalkylpyrazoles is the 1,3-dipolar cycloaddition of fluoroalkyl substituted 1,3-dipoles,6 as well as fluoroalkyl substitued dipolarophiles.7 Recently, the condensation of trifluoroacetaldehyde hydrazones with glyoxals to give trifluoromethylpyrazoles has been described.⁸ In addition, perfluorinated olefins ⁹ or acetylenes, ¹⁰ phosphorus-containing 11 and oxygen-containing 12 polycyclic compounds have been employed for the preparation of polyfluorinated pyrazoles. Fluoroalkyl iodides 1 reacted with ethyl vinyl ether to give fluoroalkyl aldehydes 2.13 We describe here the use of 2 to synthesize the hitherto unknown 3-(fluoroalkyl)pyrazoles 3.

Results and Discussion

In the presence of sodium dithionite and sodium hydrogen carbonate, fluoroalkyl iodides 1 reacted with ethyl vinyl ether to afford fluoroalkyl aldehydes 2 in high yields. (Scheme 1). When 2 was allowed to react directly with hydrazine monohydrate, however, the corresponding fluoroalkylpyrazole 3 was not formed. This failure might be due to the instability of 2 under such strong basic conditions, which thus prompted us to try a direct synthesis of 3 by the reaction of 2 with hydrazine acetic acid instead of hydrazine monohydrate. When 2 was treated with NH₂NH₂·HOAc, a very mild and clean reaction took place yielding 3-(fluoroalkyl)pyrazoles 3. Generally, a mixture of fluoroalkyl aldehyde 2 (ca. 20 mmol, which was prepared from the corresponding fluoroalkyl iodide 1 without purification) and NH₂NH₂·HOAc (60 mmol) was refluxed in ethanol for several hours and the mixture worked up to give product 3. Spectral data of 3 indicated the presence of an alkyl group one carbon shorter than that of the aldehyde 2. The results obtained are summarized in Table 1. Changing the solvent from ethanol to methanol or acetonitrile had no significant effect on the reaction (entries 7 and 8). The fact that fluoroalkyl aldehyde 2 was usually prepared in acetonitrile/water from the fluoroalkyl

$$X[CF_2]_n I$$
 $\stackrel{i}{\longrightarrow}$ $[X[CF_2]_n CH_2 CHO]$ $\stackrel{ii}{\longrightarrow}$ N

1a-g 2a-g 3a-g

a $X = F$, $n = 2$
b $X = F$, $n = 4$
c $X = F$, $n = 6$
d $X = F$, $n = 8$
e $X = CI$, $n = 8$
f $X = CI$, $n = 6$
g $X = CI$, $n = 8$

Scheme 1 Reagents and conditions: i, Ethyl vinyl ether, Na₂S₂O₄/NaHCO₃, MeCN, H₂O, 0 °C; ii, NH₂NH₂·HOAc, EtOH (or MeOH or MeCN/H₂O), reflux

Table 1 Synthesis of 3-(fluoroalkyl)pyrazoles 3

Entry	$R_f CF_2 I$ or $I(CF_2)_m I$	Time (<i>t</i> /h)	Method a	Products b	Yield (%)°
1	la	8	В	3a	91
2	1b	8	Α	3b	85
3	1c	9	Α	3c	90
4	1c	10	В	3c	93
5	1d	9	Α	3d	91
6	1e	8	Α	3e	86
7	1e	8	Α	3e	82 d
8	1e	8	Α	3e	85°
9	1e	10	В	3e	92
10	1f	10	Α	3f	90
11	1f	10	В	3f	92
12	1g	10	Α	3g	93
13	1ĥ	12	Α	3h	90
14	1h	10	В	3h	94
15	1i	12	Α	3i	94
16	1j	9	В	3a	96
17	1k	10	В	3a	92
18	11	9	В	3a	60

^a See Experimental. ^b All new products are fully characterized by ¹H NMR, ¹⁹F NMR, IR, MS and elemental analyses. ^c Isolated yield, based on 1. ^d The reaction was carried out in MeOH. ^e The reaction was carried out in acetonitrile.

iodide 1 led us to test a straightforward conversion of fluoroalkyl iodide into the corresponding 3-(fluoroalkyl)-pyrazoles 3 in a one-pot procedure. This avoided the troublesome experimental procedure for the separation of the fluoroalkyl aldehydes, especially when low boiling fluoroalkyl iodides were employed. The one-pot synthesis of 3-(fluoroalkyl)-pyrazoles from fluoroalkyl iodides consisted of stirring a

Scheme 2 Reagents and conditions: i, Ethyl vinyl ether, Na₂S₂O₄/NaHCO₃, MeCN, H₂O, 0.°C; ii, NH₂NH₂-HOAc, EtOH (or MeOH or MeCN/H₂O), reflux

$$CF_3CXY_2 \xrightarrow{i} [CF_3CXYCH_2CHO] \xrightarrow{ii} N$$

$$1J-I \qquad 2J-I \qquad 3a$$

$$X = Y = CI$$

$$k \quad X = F, \quad Y = Br$$

$$1 \quad X = Y = Br$$

Scheme 3 Reagents and conditions: i, Ethyl vinyl ether, Na₂S₂O₄/NaHCO₃, MeCN, H₂O, 0 °C; ii, NH₂NH₂·HOAc, EtOH (or MeOH or MeCN/H₂O), reflux

mixture of sodium dithionite, sodium hydrogen carbonate, fluoroalkyl iodide and ethyl vinyl ether in acetonitrile/water at 0 °C for ca. 1 h. Then a solution of NH₂NH₂·HOAc in ethanol was added and the resultant reaction mixture was refluxed for several hours. Work-up and recrystallization provided the desired 3-(fluoroalkyl)pyrazole in excellent yields, as listed in Table 1. The one-pot procedure (method B) gave slightly better yields. All products present very similar spectral characteristics consistent with the proposed structure 3. Yields reported in Table 1 were overall yields based on polyfluoroalkyl iodides 1.

Furthermore, α,ω -fluorinated dialdehydes **2h**, **i** or α,ω -perfluoroalkylene diiodides **1h**, **i**, in a one-pot procedure, also reacted smoothly with NH₂NH₂·HOAc to give the corresponding products **3h**, **i** in high yields (Scheme 2). In addition, fluoroalkyl aldehydes **2j**-l, from the reaction of perhalogeno-fluoroethanes **1j**-l and ethyl vinyl ether, also reacted with NH₂NH₂·HOAc to give 3-(trifluoromethyl)pyrazole **3a** in a one-pot procedure (Scheme 3). This constitutes an improved method for the synthesis of 3-(trifluoromethyl)pyrazole compared with the reported one. ¹⁴

A possible mechanism for the transformation of fluoroalkyl aldehydes 2 to 3-(fluoroalkyl)pyrazoles 3 is shown in Scheme 4.* Reaction of 2 with hydrazine acetic acid would give, first, a hydrazone intermediate 4 and this upon release of hydrogen fluoride would afford the intermediate 5. Intramolecular nucleophilic addition by 5 followed by elimination of a further molecule of hydrogen fluoride would provide 3-(fluoroalkyl)pyrazoles 3.

In summary, a convenient synthesis of new 3-(fluoroalkyl)-pyrazoles is described. The simplicity of the experimental procedures, the utilization of the crude fluoroalkyl aldehydes 2, the ready availability of the starting material and the high yields obtained make this route a practical one. Furthermore, 3-(fluoroalkyl)pyrazoles can also be prepared conveniently in a one-pot procedure, from fluoroalkyl iodides 1. In addition, isolation of 3 is straightforward since the product can often be filtered off after dilution of the reaction mixture with water.

*
$$R_F = -[CF_2]_n X, X = Cl, F.$$

$$\begin{bmatrix} R_F C F_2 C H_2 C H O \end{bmatrix} \longrightarrow R_F C F_2 C H_2 C H = NNH_2 \xrightarrow{HF} R_F C F = C H - C H = NNH_2$$

$$2 \qquad \qquad 4 \qquad \qquad 5$$

$$= \begin{bmatrix} R_F & C & H & H & H & H \\ R_F & C &$$

Further synthetic utility of the fluoroalkyl aldehydes for the synthesis of other heterocycles is under investigation.

Experimental

M.p.s were determined using a Büchi apparatus and are uncorrected. 1H NMR spectra were recorded on a Varian EM-360A spectrometer with Me₄Si as an internal standard. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (δ 0.00) as an external standard, downfield shifts were designated as negative. IR spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra on a Finnigan 4021 GC/MS/ DC instrument. All reactions were monitored routinely with the aid of ^{19}F NMR spectroscopy.

All chemicals and reagents were of analytical grade and were used without further purification. Light petroleum refers to the fraction boiling in the range 60–90 °C. Polyfluoroalkyl aldehydes 2 were prepared according to ref. 13.

General Procedures for the Preparation of 3-(Fluoroalkyl)-pyrazoles 3.—Method A. The crude fluoroalkyl aldehyde 2 (ca. 20 mmol, which was not purified further) was added to a stirred solution of NH₂NH₂·HOAc (5.52 g, 60 mmol) in ethanol (95%; 20 cm³). The resultant reaction mixture was heated under reflux for 10 h and then cooled and diluted with water (40 cm³). The solid residue was filtered off and recrystallized from light petroleum to give 3-(fluoroalkyl)pyrazole 3.

Method B. With magnetic stirring, a mixture of Na₂S₂O₄ (3.48 g, 20 mmol) and NaHCO₃ (1.68 g, 20 mmol) was added to the solution of fluoroalkyl iodide 1 (20 mmol), ethyl vinyl ether (1.44 g, 20 mmol), acetonitrile (20 cm³) and water (15 cm³) at 0 °C. After the mixture had been allowed to react for 0.5 h at this temperature, a solution of NH₂NH₂·HOAc (5.52 g, 60 mmol) in ethanol (10 cm³) was added to it. The resultant reaction mixture was then heated under reflux for 10 h, cooled, diluted with water (30 cm³) and extracted with diethyl ether. The combined extracts were dried (Na₂SO₄) and evaporated and the residual solid product was purified by recrystallization from light petroleum to give 3-(fluoroalkyl)pyrazole 3.

3-(Trifluoromethyl) pyrazole 3a. M.p. 84–85 °C; $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2900, 1470 and 1200–1100; $\delta_{\text{H}}(\text{CDCl}_3)$ 6.70 (1 H, s), 6.92 (1 H, s) and 7.74 (1 H, s); $\delta_{\text{F}}(\text{CDCl}_3)$ –15.6 (s); m/z (rel. intensity) 136 (M⁺, 100).

3-(Heptafluoropropyl) pyrazole **3b**. M.p. 71–73 °C (Found: C, 30.2; H, 1.1; F, 56.5; N, 12.0. $C_6H_3F_7N_2$ requires C, 30.52; H, 1.28; N, 11.87; F, 56.33%); $\nu_{\rm max}(KCl)/{\rm cm}^{-1}$ 3100, 1460, 1350 and 1200–1100; $\delta_{\rm H}({\rm CD_3COCD_3})$ 6.65 (1 H, s) and 7.88 (1 H, s); $\delta_{\rm F}({\rm CD_3COCD_3})$ 4.0 (3 F, s), 33.1 (2 F, s) and 50.6 (2 F, s); m/z (rel. intensity) 236 (M⁺, 50), 217 (M⁺ – F, 18), 117 (M⁺ – C_2F_5 , 100) and 69 (CF₃⁺, 10).

3-(*Undecafluoropentyl*) *pyrazole* **3c**. M.p. 62–63 °C (Found: C, 28.3; H, 0.7; F, 62.2; N, 8.4. $C_8H_3F_{11}N_2$ requires C, 28.59; H, 0.90; N, 8.33; F, 62.18%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1700,

1470, 1350 and 1200–1100; $\delta_{\rm H}({\rm CD_3COCD_3})$ 6.65 (1 H, s) and 7.88 (1 H, s); $\delta_F(CD_3COCD_3)$ 4.3 (3 F, s), 33.0 (2 F, s), 45.6 (4 F, s) and 49.6 (2 F, s); m/z (rel. intensity) 337 (M⁺ + 1, 1), 336 (M⁺, 4), 317 (M⁺ - F, 4), 117 (M⁺ - C₄F₉, 100) and 69 $(CF_3^+, 20).$

3-(Pentadecafluoroheptyl) pyrazole 3d. M.p. (Found: C, 27.2; H, 0.6; F, 65.25; N, 7.1. C₁₀H₃F₁₅N₂ requires C, 27.54; H, 0.69; F, 65.34; N, 6.42%); $v_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2900, 1700, 1630, 1470, 1350 and 1200–1100; $\delta_H(CD_3COCD_3)$ 6.67 (1 H, s) and 7.92 (1 H, s); $\delta_F(CD_3COCD_3)$ 4.2 (3 F, s), 32.0 (2 F, s), 45.5 (8 F, m)and 49.3 (2 F, s); m/z (rel. intensity) 436 $(M^+, 1)$, 435 $(M^+ - 1, 10)$, 416 $(M^+ - HF, 15)$, 117 (M^+) C₆F₁₃, 100) and 69 (CF₃⁺, 18).

3-(3-Chloro-1,1,2,2,3,3-hexafluoropropyl)pyrazole **3e**. M.p. 66-68 °C (Found: C, 28.45; H, 1.3; Cl, 14.1; F, 45.0; N, 11.15. C₆H₃N₂ClF₆ requires C, 28.54; H, 1.2; Cl, 14.04; F, 45.14; N, 11.09%); $v_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1630, 1470, 1350 and 1200– 1100; $\delta_{H}(CD_{3}COCD_{3})$ 6.69 (1 H, s) and 7.95 (1 H, s); $\delta_{\rm F}({\rm CD_3COCD_3}) = 9.8 \, (2 \, {\rm F, s}), 30.1 \, (2 \, {\rm F, s}) \, {\rm and} \, 43.9 \, (2 \, {\rm F, s}); \, m/z$ (rel. intensity) 252 (M^+ , 96.52), 254 (M^+ , 30), 233 ($M^+ - F$, 11), 217 (M^+ – Cl, 100) and 117 (M^+ – ClC₂F₄, 42).

3-(5-Chloro-1,1,2,2,3,3,4,4,5,5-decafluoropentyl) pyrazole 3f. M.p. 52-54 °C (Found: C, 27.1; H, 0.75; N, 8.1. C₈H₃ClN₂F₁₀ requires C, 27.25; H, 0.86; N, 7.95%); $v_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 1460, 1350 and 1200–1100; $\delta_{\rm H}({\rm CD_3COCD_3})$ 6.65 (1 H, s) and 7.90 (1 H, s); $\delta_{\rm F}({\rm CD_3COCD_3}) = 8.4$ (2 F, s), 33.0 (2 F, s), 43.9 (2 F, s), 44.7 (2 F, s) and 45.8 (2 F, s); m/z (rel. intensity) 352 (M⁺, 6), 354 $(M^+, 2)$, 317 $(M^+ - Cl, 12)$ and 117 $(M^+ - ClC_4F_8, 100)$.

3-(7-Chloro-1,1,2,2,3,3,4,4,5,5,6,6,7,7-tetradecafluoroheptyl)pyrazole 3g. M.p. 52-53 °C (Found: C, 26.3; H, 0.5; N, 6.4; F, 58.7. C₁₀H₃F₁₄ClN₂ requires C, 26.54; H, 0.67; N, 6.19; F, 58.77%); $v_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1460 and 1200–1100; $\delta_{H}(CD_{3}COCD_{3})$ 6.67 (1 H, s) and 7.90 (1 H, s); $\delta_{F}(CD_{3}COCD_{3})$ -8.6 (2 F, s), 30.5 (2 F, s), 43.4 (2 F, s) and 45.0 (8 F, m); m/z(rel. intensity) 452 (M^+ , 10), 454 (M^+ , 4), 417 (M^+ – C1, 17) and $117 (M^+ - ClC_6F_{12}, 100)$.

3,3'-(Octafluorobutane-1,4-diyl) dipyrazole 3h. M.p. 209-210 °C (Found: C, 35.9; H, 1.7; N, 16.6. C₁₀H₆F₈N₄ requires C, 35.9; H, 1.8; N, 16.8%); $v_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 1470, 1360, 1300 and 1200–1100; $\delta_{H}(CD_{3}COCD_{3})$ 6.62 (2 H, s) and 7.86 (2 H, s); $\delta_{\rm F}({\rm CD_3COCD_3})$ 32.0 (4 F, s) and 45.4 (4 F, s); m/z (rel. intensity) 334 (M⁺, 5) and 117 (100).

3,3'-(Dodecafluorohexane-1,6-diyl)dipyrazole 3i. M.p. 177-178 °C (Found: C, 33.15; H, 1.1; N, 12.8. $C_{12}H_6F_{12}N_4$ requires C, 33.20; H, 1.39; N, 12.99); $\nu_{max}(KCl)/cm^{-1}$ 3100, 2910, 1470, 1360, 1310 and 1200–1100; $\delta_{\rm H}({\rm CD_3COCD_3})$ 6.90 (2 H, s) and 7.89 (2 H, s); $\delta_{\rm F}({\rm CD_3COCD_3})$ 31.2 (4 F, s), 43.8 (4 F, s) and 44.8 $(4 \text{ F}, \text{ s}); m/z \text{ (rel. intensity)} 434 \text{ (M}^+, 32) \text{ and } 117 \text{ (100)}.$

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