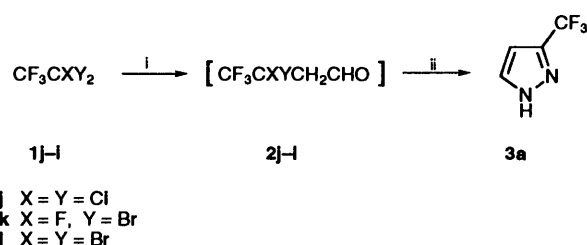


Scheme 2 Reagents and conditions: i, Ethyl vinyl ether, $\text{Na}_2\text{S}_2\text{O}_4/\text{NaHCO}_3$, MeCN, H_2O , 0°C ; ii, $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$, EtOH (or MeOH or MeCN/ H_2O), reflux



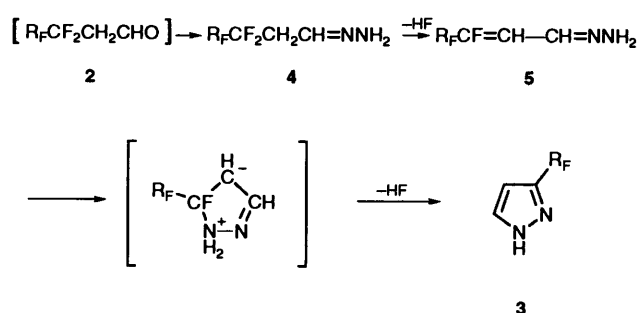
Scheme 3 Reagents and conditions: i, Ethyl vinyl ether, $\text{Na}_2\text{S}_2\text{O}_4/\text{NaHCO}_3$, MeCN, H_2O , 0°C ; ii, $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$, EtOH (or MeOH or MeCN/ H_2O), reflux

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 $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ 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 $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ 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 $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ 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.



Scheme 4

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 Me_4Si 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 $60\text{--}90^\circ\text{C}$. 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 $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ (5.52 g, 60 mmol) in ethanol (95%; 20 cm^3). The resultant reaction mixture was heated under reflux for 10 h and then cooled and diluted with water (40 cm^3). 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 $\text{Na}_2\text{S}_2\text{O}_4$ (3.48 g, 20 mmol) and NaHCO_3 (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 cm^3) and water (15 cm^3) at 0°C . After the mixture had been allowed to react for 0.5 h at this temperature, a solution of $\text{NH}_2\text{NH}_2\cdot\text{HOAc}$ (5.52 g, 60 mmol) in ethanol (10 cm^3) was added to it. The resultant reaction mixture was then heated under reflux for 10 h, cooled, diluted with water (30 cm^3) and extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) 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. $84\text{--}85^\circ\text{C}$; $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2900, 1470 and $1200\text{--}1100$; $\delta_{\text{H}}(\text{CDCl}_3)$ 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. $71\text{--}73^\circ\text{C}$ (Found: C, 30.2; H, 1.1; F, 56.5; N, 12.0. $\text{C}_8\text{H}_3\text{F}_7\text{N}_2$ requires C, 30.52; H, 1.28; N, 11.87; F, 56.33%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 1460, 1350 and $1200\text{--}1100$; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.65 (1 H, s) and 7.88 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ 4.0 (3 F, s), 33.1 (2 F, s) and 50.6 (2 F, s); m/z (rel. intensity) 236 (M^+ , 50), 217 ($\text{M}^+ - \text{F}$, 18), 117 ($\text{M}^+ - \text{C}_2\text{F}_5$, 100) and 69 (CF_3^+ , 10).

3-(Undecafluoropentyl)pyrazole 3c. M.p. $62\text{--}63^\circ\text{C}$ (Found: C, 28.3; H, 0.7; F, 62.2; N, 8.4. $\text{C}_8\text{H}_3\text{F}_{11}\text{N}_2$ requires C, 28.59; H, 0.90; N, 8.33; F, 62.18%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1700,

* $\text{R}_F = -[\text{CF}_2]_n\text{X}$, X = Cl, F.

1470, 1350 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.65 (1 H, s) and 7.88 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ 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 ($\text{M}^+ + 1$, 1), 336 (M^+ , 4), 317 ($\text{M}^+ - \text{F}$, 4), 117 ($\text{M}^+ - \text{C}_4\text{F}_9$, 100) and 69 (CF_3^+ , 20).

3-(Pentadecafluoroheptyl)pyrazole **3d**. M.p. 57–58 °C (Found: C, 27.2; H, 0.6; F, 65.25; N, 7.1. $\text{C}_{10}\text{H}_3\text{F}_{15}\text{N}_2$ requires C, 27.54; H, 0.69; F, 65.34; N, 6.42%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2900, 1700, 1630, 1470, 1350 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.67 (1 H, s) and 7.92 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ 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 ($\text{M}^+ - 1$, 10), 416 ($\text{M}^+ - \text{HF}$, 15), 117 ($\text{M}^+ - \text{C}_6\text{F}_{13}$, 100) and 69 (CF_3^+ , 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. $\text{C}_6\text{H}_3\text{N}_2\text{ClF}_6$ requires C, 28.54; H, 1.2; Cl, 14.04; F, 45.14; N, 11.09%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1630, 1470, 1350 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.69 (1 H, s) and 7.95 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ –9.8 (2 F, s), 30.1 (2 F, s) and 43.9 (2 F, s); m/z (rel. intensity) 252 (M^+ , 96.52), 254 (M^+ , 30), 233 ($\text{M}^+ - \text{F}$, 11), 217 ($\text{M}^+ - \text{Cl}$, 100) and 117 ($\text{M}^+ - \text{ClC}_2\text{F}_4$, 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. $\text{C}_8\text{H}_3\text{ClN}_2\text{F}_{10}$ requires C, 27.25; H, 0.86; N, 7.95%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 1460, 1350 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.65 (1 H, s) and 7.90 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ –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 ($\text{M}^+ - \text{Cl}$, 12) and 117 ($\text{M}^+ - \text{ClC}_2\text{F}_8$, 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. $\text{C}_{10}\text{H}_3\text{F}_{14}\text{ClN}_2$ requires C, 26.54; H, 0.67; N, 6.19; F, 58.77%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1460 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.67 (1 H, s) and 7.90 (1 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ –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 ($\text{M}^+ - \text{Cl}$, 17) and 117 ($\text{M}^+ - \text{ClC}_6\text{F}_{12}$, 100).

3,3'-(Octafluorobutane-1,4-diyl)dipyrazole **3h**. M.p. 209–210 °C (Found: C, 35.9; H, 1.7; N, 16.6. $\text{C}_{10}\text{H}_6\text{F}_8\text{N}_4$ requires C, 35.9; H, 1.8; N, 16.8%); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 1470, 1360, 1300 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.62 (2 H, s) and 7.86 (2 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ 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. $\text{C}_{12}\text{H}_6\text{F}_{12}\text{N}_4$ requires C, 33.20; H, 1.39; N, 12.99); $\nu_{\text{max}}(\text{KCl})/\text{cm}^{-1}$ 3100, 2910, 1470, 1360, 1310 and 1200–1100; $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$ 6.90 (2 H, s) and 7.89 (2 H, s); $\delta_{\text{F}}(\text{CD}_3\text{COCD}_3)$ 31.2 (4 F, s), 43.8 (4 F, s) and 44.8 (4 F, s); m/z (rel. intensity) 434 (M^+ , 32) and 117 (100).

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China.

References

- 1 R. Filler and Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Kodansha/Elsevier, New York, 1982; R. E. Bancs, *Organofluorine Compounds and Their Applications*, Ellis Horwood, Chichester, 1979; H. Fuchikami, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 775; H. Yoshioka, C. Takayama and N. Matsuo, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 809.
- 2 M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Ellis Horwood, New York, 1976; K. Tanaka, *J. Synth. Org. Chem. Jpn.*, 1990, **48**, 16, and refs. cited therein.
- 3 S. Ishii, K. Yagi, T. Umehara, M. Kudo, T. Nawamaki and S. Watanabe, *Jap P* 02,129,171/1990; *Chem. Abstr.*, 1990, **113**, 172014a; H. Shimotori, T. Ishii, H. Yamazaki, T. Kuwatsuka, Y. Yanase and Y. Tanaka, *GP* 3,713,744/1987; *Chem. Abstr.*, 1988, **108**, 112445d; I. G. Buntain, L. R. Hatton, D. W. Hawkins, C. J. Pearson and D. A. Roberts, *Eur P Appl.* 295,117/1988; *Chem. Abstr.*, 1990, **112**, 35845n; R. G. Micetic and R. B. Rastogi, *Can P* 1,130,808/1982; *Chem. Abstr.*, 1983, **98**, 72087e.
- 4 E. Okada, R. Masuda and M. Hojo, *Heterocycles*, 1992, **34**, 791; L. F. Lee, F. M. Schleppek, R. W. Schneider and D. H. Campbell, *J. Heterocycl. Chem.*, 1990, **27**, 243; B. J. Gaede and L. L. McDermott, *J. Heterocycl. Chem.*, 1993, **30**, 49 and refs. cited therein; R. J. Linderman and K. S. Kirolos, *Tetrahedron Lett.*, 1989, **30**, 2049; S. Portnoy, *J. Heterocycl. Chem.*, 1969, **6**, 223; J. R. Beck and F. L. Wright, *J. Heterocycl. Chem.*, 1987, **24**, 739.
- 5 Y. Kamitori, M. Hojo and R. Masuda, *J. Heterocycl. Chem.*, 1993, **30**, 389.
- 6 R. Fields and J. P. Tomlinson, *J. Fluorine Chem.*, 1979, **13**, 147; K. Tanaka and K. Mitsuhashi, *J. Synth. Org. Chem. Jpn.*, 1987, **45**, 269, and refs. cited therein.
- 7 J. Zhang, Z. Wang and Y. Shen, *J. Fluorine Chem.*, 1993, **61**, 17; G. Meazza and G. Zanardi, *J. Heterocycl. Chem.*, 1993, **30**, 365; S. Tajammal and A. E. Tipping, *J. Fluorine Chem.*, 1990, **47**, 45.
- 8 S. Iwata, J. Namekata, K. Tanaka and K. Mitsuhashi, *J. Heterocycl. Chem.*, 1991, **28**, 1971; Y. Kamitori, M. Hojo, R. Masuda, S. Ohara, K. Kawasaki and N. Yoshikawa, *Tetrahedron Lett.*, 1988, **29**, 5281; Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada and N. Yoshikawa, *J. Org. Chem.*, 1988, **53**, 519.
- 9 I. Ikeda, Y. Kogame and M. Okahara, *J. Org. Chem.*, 1985, **50**, 3640; M. D. Bargamova, S. M. Motsishkita and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2583; *Chem. Abstr.*, 1991, **114**, 122157z; M. Okahara, I. Ikeda and F. Nemoto, *Jap P* 6,277,370/1987; *Chem. Abstr.*, 1987, **107**, 134301k.
- 10 R. E. Banks and S. M. Hitchen, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1593.
- 11 Y. Kobayashi, H. Hamana, S. Fujino, A. Ohsawa and I. Kumadaki, *J. Org. Chem.*, 1979, **44**, 4930.
- 12 Y. Kobayashi, Y. Hanzawa, Y. Nakanishi and T. Kashiwagi, *Tetrahedron Lett.*, 1978, **19**, 1019.
- 13 W. Y. Huang, L. Lu and Y. F. Zhang, *Chin. J. Chem.*, 1990, 68; W. Y. Huang, L. Lu and Y. F. Zhang, *Chin. J. Chem.*, 1990, 281.
- 14 J. H. Atherton and R. Fields, *J. Chem. Soc. C*, 1968, 1507.

Paper 4/00817K

Received 10th February 1994

Accepted 18th April 1994