Convenient and versatile synthesis of 3-(polyfluoroalkyl)pyrazoles

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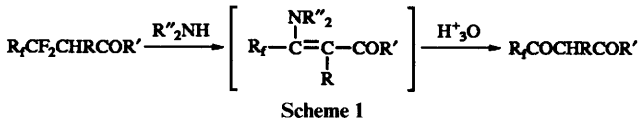
3-(Polyfluoroalkyl)pyrazoles **4** have been synthesized in excellent yields in a two-step sequence from polyfluoroalkyl iodides **1**. The synthesis consisted of the reaction of iodides **1** with enamines or enol ethers to give α-polyfluoroalkyl carbonyl derivatives **3** followed by treatment with hydrazine monohydrate. A practical one-pot synthesis of pyrazoles **4** directly from iodides **1** has also been developed and the reaction mechanism is discussed.

Many pyrazoles and their derivatives are known to be bioactive compounds which have applications as agricultural chemicals and medicines, but very few occur naturally.[1] For this reason, there is increasing interest in the development of a new procedure for the synthesis of pyrazoles and their derivatives.[2] Until now, however, there have been few syntheses of fluorine-containing pyrazoles. From a biological point of view, fluoro-substitution often confers unique properties on a molecule in terms of increased lipophilicity which, in turn, changes *in vivo* absorption and transport rates.[3] Therefore, much attention has recently been paid to the development of methodologies for the synthesis of fluorinated heterocycles.[4] 1,3-Dicarbonyl derivatives are versatile synthetic intermediates for the preparation of heterocyclic compounds. Similarly, fluorine-containing 1,3-dicarbonyl derivatives have been widely used to prepare trifluoromethyl or, more generally, perfluoroalkyl substituted heterocycles. In particular, trifluoromethylpyrazole derivatives are interesting compounds possessing high biological activities.[5] However, there are few examples of the preparation of heterocyclic compounds from α-polyfluoroalkyl carbonyl derivatives **3** in the literature. Here we describe the synthetic utility of compounds **3** for the preparation of 3-(polyfluoroalkyl)pyrazoles **4** in excellent yields.

Results and discussion

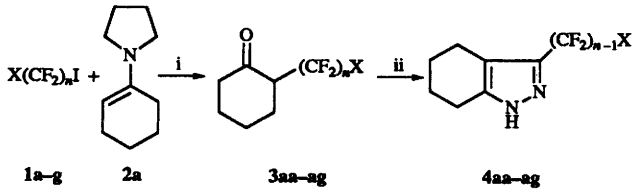
Our method is based on the observation of several groups who have reported that amines react with α-polyfluoroalkyl carbonyl derivatives to produce the intermediate, β-*N*-substituted α,β-unsaturated carbonyl derivatives, which undergo hydrolysis to yield 1,3-dicarbonyl derivatives upon treatment with acid solution (Scheme 1).[6] On the basis of this fact and the known



Scheme 1

generality of 1,3-dicarbonyl derivatives for the synthesis of pyrazoles by condensation with hydrazines,[7] it was expected that the direct reaction of α-polyfluoroalkyl carbonyl derivatives with hydrazine monohydrate would lead to the formation of polyfluoroalkylpyrazoles. In fact, it was found that if α-pentafluoroethylcyclohexanone **3aa** was allowed to react with 3.5 equiv. of hydrazine monohydrate in ethanol under reflux for 6 h, 3-trifluoromethyl-4,5,6,7-tetrahydroindazole **4aa** was obtained in 95% yield. The ^{19}F NMR spectrum of compound **4aa** revealed a single resonance at δ −15.5 and suggested a trifluoromethyl group (not a pentafluoroethyl group as in the starting material). The ^{13}C NMR spectrum showed the presence of a substituted pyrazole ring δ 114.2 (s, C-4), 141.3 (s, C-5) and 139.4 (q, J_{C-F} 34.4 Hz, C-3). The mass spectrum of **4aa** showed *m/z* 190 (M^+) and 162 ($M^+ - C_2H_4$). (See Experimental section.)

A series of α-polyfluoroalkylcyclohexanones **3aa–ag**, which were prepared conveniently from polyfluoroalkyl iodides **1a–g** and 1-pyrrolidin-1-ylcyclohex-1-ene **2a**,[8] were found to react smoothly with hydrazine monohydrate to give 3-polyfluoroalkyl-4,5,6,7-indazoles **4aa–ag** in ethanol under reflux (Scheme 2) in excellent yields as listed in Table 1. It should be pointed

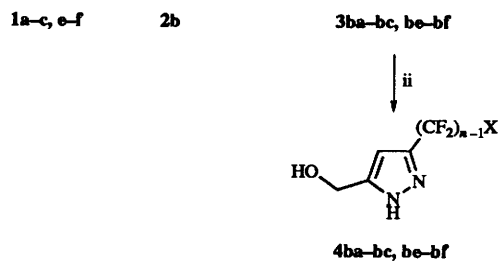


a X = F, *n* = 2
b X = F, *n* = 4
c X = F, *n* = 6
d X = F, *n* = 8
e X = Cl, *n* = 4
f X = Cl, *n* = 6
g X = Cl, *n* = 8

Scheme 2 *Reagents and conditions:* i, (a) hexane, UV, room temp.; (b) 40% H_2SO_4, room temp., 1 h; ii, $NH_2NH_2 \cdot H_2O$, EtOH, reflux

out that the polyfluoroalkyl group of the products is one carbon shorter than that of the starting materials.

Similarly, polyfluoroalkyl iodides **1a–c**, **1e** and **f** reacted with 2,2-dimethyl-4-methylidene-1,3-dioxolane **2b** to provide the corresponding ketones **3ba–bc**, **3be** and **bf**,[9] which were treated in turn with hydrazine monohydrate in refluxing ethanol to give 3-(polyfluoroalkyl) pyrazoles **4ba–bc**, **4be** and **bf** each with a hydroxymethyl functional group substituted at the C-5 position of the pyrazole ring as shown in Scheme 3.



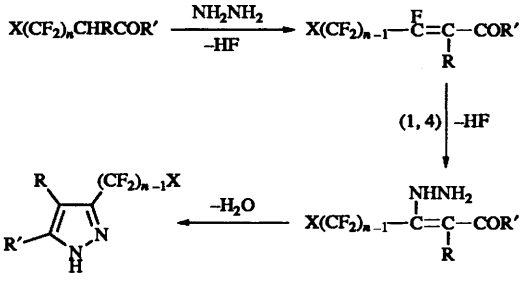
Scheme 3 *Reagents and conditions:* i, $Na_2S_2O_4$–$NaHCO_3$, MeCN–H_2O, 0 °C, 2 h; ii, $NH_2NH_2 \cdot H_2O$, EtOH, reflux

Table 1 Preparation of 3-(polyfluoroalkyl)pyrazoles **4**

Entry	R_fI or $I(CF_2)_nI$	t/h	Method[a]	Product[b]	Yield (%)[c]
1	**1a**	6	B	**4aa**	95
2	**1b**	5	B	**4ab**	90
3	**1c**	4	B	**4ac**	89
4	**1d**	4	B	**4ad**	93
5	**1e**	5	B	**4ae**	95
6	**1f**	5	B	**4af**	85
7	**1g**	6	B	**4ag**	88
8	**1a**	6	B	**4ba**	92
9	**1b**	5	A	**4bb**	72
10	**1c**	5	B	**4bc**	87
11	**1e**	6	B	**4be**	92
12	**1f**	6	B	**4bf**	90
13	**1a**	12	B	**4ca**	95
14	**1a**	14	A	**4ca**	90
15	**1a**	14	B	**4ca**	96[d]
16	**1b**	10	B	**4cb**	95
17	**1c**	12	B	**4cc**	96
18	**1d**	14	B	**4cd**	90
19	**1e**	12	B	**4ce**	92
20	**1e**	14	A	**4ce**	85
21	**1e**	12	B	**4ce**	88[e]
22	**1f**	14	B	**4cf**	94
23	**1f**	14	A	**4cf**	81
24	**1g**	14	A	**4cg**	84
25	**1h**	14	B	**4ch**	92
26	**1c**	10	A	**4dc**	65
27	**1d**	12	A	**4dd**	62
28	**1e**	8	A	**4de**	72
29	**1f**	9	A	**4df**	75
30	**1g**	10	A	**4dg**	68

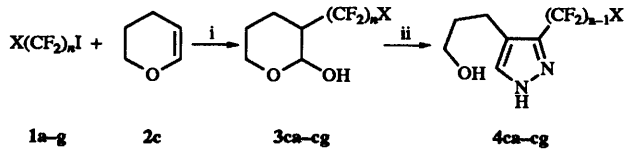
[a] See Experimental section. [b] All the products are hitherto unknown and are fully characterized by ^1H NMR, ^{19}F NMR, IR and mass spectroscopy and C, H, F, N elemental analyses. [c] Isolated yield based on **1** with method A and based on **3** with method B. [d] The reaction was carried out in MeOH. [e] The reaction was carried out in tetrahydrofuran.

The reaction of α-polyfluoroalkyl ketones with hydrazine monohydrate to give 3-(polyfluoroalkyl)pyrazoles could be considered to proceed as follows. The α-polyfluoroalkyl ketones release a hydrogen fluoride molecule in the presence of hydrazine monohydrate as the base to give the β-polyfluoroalkyl α,β-unsaturated ketones, which react with a further hydrazine again through an initial Michael reaction, followed by an elimination of a second hydrogen fluoride molecule, and then subsequent ring closure and aromatization to provide the 3-(polyfluoroalkyl)pyrazoles (Scheme 4).



Scheme 4

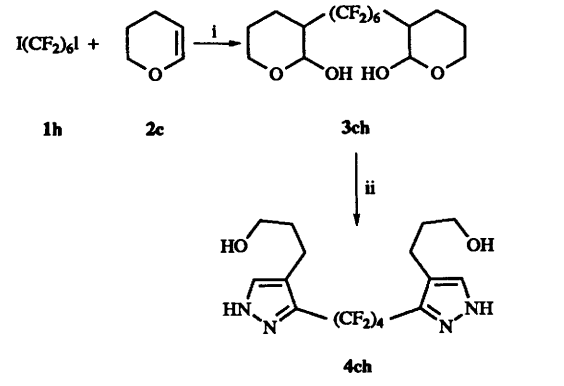
This reaction was also applied to a series of α-polyfluoroalkyl hemiacetals **3ca–cg**, which were prepared conveniently from polyfluoroalkyl iodides **1a–g** and 3,4-dihydro-2*H*-pyran **2c**.[10] Generally, a mixture of α-polyfluoroalkyl hemiacetals **3ca–cg** (10 mmol) and hydrazine monohydrate (35 mmol) was refluxed in ethanol for several hours and the mixture then worked up to give products **4ca–cg** in excellent yields (Scheme 5). The spectral



Scheme 5 *Reagents and conditions:* i, $Na_2S_2O_4$–$NaHCO_3$, MeCN–H_2O, 0 °C, 2 h; ii, NH_2NH_2·H_2O, EtOH, reflux

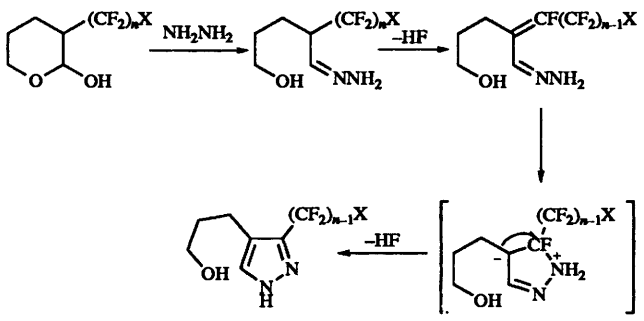
data of compounds **4ca–cg** indicated that the pyran ring was opened and a new pyrazole ring with a polyfluoroalkyl and a 3-hydroxypropyl group substituted at the C-3 and C-4 positions, respectively, was formed. Furthermore, the polyfluoroalkyl group of the product is one carbon shorter than that of the hemiacetal **3ca–cg**. For example, when α-pentafluoroethyl hemiacetal **3ca** was allowed to react with 3.5 equiv. of hydrazine monohydrate in ethanol under reflux for 12 h, 4-(3-hydroxypropyl)-3-trifluoromethylpyrazole **4ca** was obtained in 95% yield. The ^{19}F NMR spectrum of compound **4ca** revealed a single resonance at δ −16.5 and suggested a trifluoromethyl group (not a pentafluoroethyl group as in the starting material). The ^1H NMR spectrum showed the presence of an aromatic proton δ 7.73 (s). The ^{13}C NMR spectrum showed the presence of a substituted pyrazole ring δ 120.3 (s, C-4), 130.0 (s, C-5) and 140.1 (q, J_{C-F} 35.7 Hz, C-3). The mass spectrum of **4ca** showed *m/z* 194 (M^+) and 176 ($M^+ - H_2O$) (see Experimental section). In addition, it was found that solvents such as ethanol, methanol, acetonitrile and tetrahydrofuran did not have any significant effect on the reaction (entries 13–15 and 21) and the yields were not affected by the length of the polyfluoroalkyl chain in the cases examined so far (see Table 1). Based on the fact that the α-polyfluoroalkyl acetals **3ca–cg** were usually prepared in acetonitrile–water, tandem reactions of the polyfluoroalkyl iodide **1a–g**, first with 3,4-dihydro-2*H*-pyran **2c** in the presence of sodium dithionite and sodium hydrogen carbonate, followed by treatment of the resulting reaction mixture with hydrazine monohydrate were tested and proved to be effective, providing the expected 3-(polyfluoroalkyl)pyrazoles **4** in a convenient one-pot procedure (method A), and the yield was not lower than that of method B.

Interestingly, α,ω-diiodopolyfluoroalkane **1h** reacted with 2 equiv. of 3,4-dihydro-2*H*-pyran **2c** to give the dihemiacetal **3ch**, which was treated with 7.0 equiv. of hydrazine monohydrate to provide **4ch** in 92% yield in a one-pot procedure (Scheme 6).



Scheme 6 *Reagents and conditions:* i, $Na_2S_2O_4$–$NaHCO_3$, MeCN–H_2O, 0 °C, 2 h; ii, NH_2NH_2·H_2O, EtOH, reflux

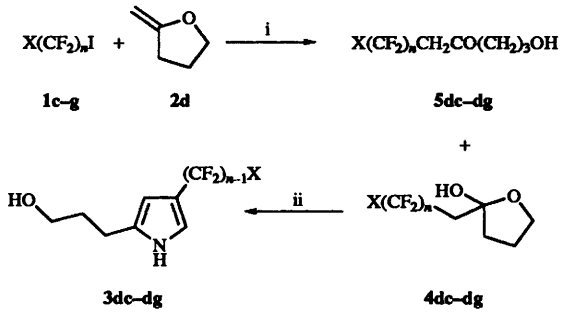
A possible mechanism for the reaction of α-polyfluoroalkyl hemiacetals **3ca–ch** with hydrazine monohydrate to give 3-(polyfluoroalkyl)pyrazoles **4ca–ch** is shown in Scheme 7. Reaction of α-polyfluoroalkyl hemiacetals with hydrazine



Scheme 7

monohydrate would result in the formation of a hydrazone intermediate. This could release a molecule of hydrogen fluoride to give the corresponding β-polyfluoroalkyl α,β-unsaturated hydrazone intermediate, which would undergo intramolecular nucleophilic addition, followed by a spontaneous elimination of a further molecule of hydrogen fluoride to provide 3-(polyfluoroalkyl)pyrazoles. This reaction mechanism is a little different from the above one and was supported by the fact that α-polyfluoroalkyl hemiacetals remained unchanged when treated with triethylamine in tetrahydrofuran at room temperature, but α-polyfluoroalkyl ketones gave the corresponding β-polyfluoroalkyl α,β-unsaturated ketones by elimination of a molecule of hydrogen fluoride under the same reaction conditions. This indicated that the hydrogen fluoride could not be eliminated at the first step of this reaction.

Although the reaction of polyfluoroalkyl iodide **1c–g** with 2-methylidenetetrahydrofuran **2d** [11] gave a tautomeric mixture of **3dc–dg** and **5dc–dg**,[12] it was reasonably expected that on treatment of these mixtures with hydrazine monohydrate, the corresponding 5-(3-hydroxypropyl)-3-(polyfluoroalkyl)-pyrazoles **4i–m** would be formed as the sole product in a one-pot procedure (Scheme 8) based on the above known facts.



Scheme 8 i, $Na_2S_2O_4$–$NaHCO_3$, $MeCN–H_2O$, 0 °C, 2 h; ii, NH_2-NH_2·H_2O, EtOH, reflux

In summary, a convenient method for the synthesis of new 3-polyfluoroalkyl substituted pyrazoles direct from polyfluoroalkyl iodides in a two-step sequence is described. The substitution pattern of the pyrazole ring can be altered simply by choosing the appropriate starting material. Both α-polyfluoroalkyl ketones and hemiacetals reacted with hydrazine monohydrate very well to give 3-(polyfluoroalkyl)pyrazoles in excellent yields. Furthermore, the simplicity of the two steps and the ready availability of the starting material make this a practical route. In addition, 3-(polyfluoroalkyl)pyrazoles could also be prepared conveniently from polyfluoroalkyl iodides in a one-pot procedure and their isolation is operationally straightforward since the product can often be collected directly from the reaction mixture by filtration after being diluted with water.

Experimental

Mps were uncorrected. ^1H NMR spectra were recorded on a Varian EM-360A, JEOL FX-90Q or Bruker AM300 spectrometer with Me_4Si (TMS) as an internal standard. ^{13}C NMR were recorded on a Bruker AM300 spectrometer. ^{19}F NMR spectra were obtained on a Varian EM-360L spectrometer with trifluoroacetic acid (TFA) (δ 0.00) as an external standard, downfield shifts were designated as negative. *J* Values are given in Hz. Infrared spectra were taken on a Shimadzu 440-IR spectrometer, and mass spectra were taken 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. α-Polyfluoroalkylcyclohexanones **3aa–3ag** were prepared according to ref. 8. 1-Hydroxy-3-polyfluoroalkylpropan-2-ones **3ba–bc**, **3be–bf** were synthesized according to ref. 9. α-Polyfluoroalkyl hemiacetals **3ca–ch** were prepared according to ref. 10. 2,2-Dimethyl-4-methylidene-1,3-dioxolane **2b** was prepared according to ref. 13. 2-Methylidenetetrahydrofuran **2d** was prepared according to ref. 11. The mixture of **3dc–dg** and **5dc–dg** was prepared according to ref. 12a.

General procedure for the preparation of 3-polyfluoroalkylpyrazoles. Method A: from polyfluoroalkyl iodides 1

A mixture of sodium dithionite (12 mmol) and sodium hydrogen carbonate (12 mmol) was added to a magnetically stirred solution of polyfluoroalkyl iodide **1** (10 mmol) and compound **2** (10 mmol) in acetonitrile (20 cm^3) and water (15 cm^3) at 0–5 °C. The mixture was stirred at that temperature for about 0.5 h and the progress of the reaction was monitored using ^{19}F NMR spectroscopy until the chemical shift corresponding to ICF_2 disappeared. Then hydrazine monohydrate (35 mmol) was added to it and the resulting reaction mixture was heated to reflux for several hours, cooled, diluted with water (40 cm^3) and then extracted with diethyl ether (2 × 50 cm^3). The combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on a silica gel column with light petroleum–ethyl acetate (8:2 v/v) as eluent or by recrystallization from ethanol–water.

Method B: from α-polyfluoroalkyl carbonyl derivatives 3

A solution of compound **3** (10 mmol) and hydrazine monohydrate (35 mmol) in ethanol (20 cm^3) was heated to reflux for several hours, cooled and then diluted with water (40 cm^3). The solid residue was collected by filtration and purified by recrystallization from ethanol–water to give 3-polyfluoroalkylpyrazoles **4**.

3-Trifluoromethyl-4,5,6,7-tetrahydroindazole 4aa.[15] Mp 125 °C (Found: C, 50.2; H, 4.7; F, 29.9; N, 14.9. $C_8H_9F_3N_2$ requires C, 50.53; H, 4.77; F, 29.97; N, 14.73%); ν(KCl)/cm^{-1} 3100, 2900, 1590, 1490, 1440, 1350, 1260, 1230 and 1110; δ_H(CD_3COCD_3–internal TMS) 1.78 (4 H, m), 2.56 (2 H, t, J_{H-H} 5.4) and 2.68 (2 H, t, J_{H-H} 5.4); δ_F(CD_3COCD_3–external TFA) −15.5 (s); δ_C(CD_3COCD_3) 20.5 (s), 21.4 (s), 22.9 (s), 23.4 (s), 114.2 (s, C-4), 123.7 (q, J_{C-F} 266.8, CF_3), 141.3 (s, C-5) and 139.4 (q, J_{C-F} 34.4, C-3); *m/z* (rel. intensity) 190 (M^+, 4%), 171 (8), 162 (100), 121 (13) and 69 (6).

3-Heptafluoropropyl-4,5,6,7-tetrahydroindazole 4ab. Mp 136–137 °C (Found: C, 41.2; H, 2.8; F, 45.85; N, 9.7. $C_{10}H_9F_7N_2$ requires C, 41.39; H, 3.13; F, 45.83; N, 9.65%); ν(KCl)/cm^{-1} 3100, 2910, 1590, 1490, 1445, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.79 (4 H, m), 2.56 (2 H, t, J_{H-H} 5.4) and 2.68 (2 H, t, J_{H-H} 5.4); δ_F(CD_3COCD_3–external TFA)

4.7 (3 F, s), 32.0 (2 F, s) and 50.0 (2 F, s); *m/z* (rel. intensity) 290 (M^+, 28%), 262 (37), 171 (10), 143 (22), 69 (59) and 57 (100).

3-Undecafluoropentyl-4,5,6,7,-tetrahydroindazole 4ac. Mp 110 °C (Found: C, 36.6; H, 2.0; F, 53.5; N, 7.1. $C_{12}H_9F_{11}N_2$ requires C, 36.94; H, 2.32; F, 53.56; N, 7.18%); ν(KCl)/cm^{-1} 3100, 2925, 1590, 1490, 1445 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.78 (4 H, m), 2.56 (2 H, t, J_{H-H} 5.5) and 2.68 (2 H, t, J_{H-H} 5.5); δ_F(CD_3COCD_3–external TFA) 4.2 (3 F, s), 31.9 (2 F, s), 45.5 (4 F, m) and 49.3 (2 F, s); *m/z* (rel. intensity) 390 (M^+, 21%), 362 (22), 171 (17), 143 (20), 121 (15), 69 (62) and 56 (100).

3-Pentadecafluoroheptyl-4,5,6,7-tetrahydroindazole 4ad. Mp 70–71 °C (Found: C, 34.4; H, 2.0; F, 58.0; N, 5.6. $C_{14}H_9F_{15}N_2$ requires C, 34.30; H, 1.85; F, 58.13; N, 5.71%); ν(KCl)/cm^{-1} 3100, 2910, 1595, 1490, 1450, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.78 (4 H, m) and 2.63 (4 H, m); δ_F(CD_3COCD_3–external TFA) 4.6 (3 F, s), 30.8 (2 F, s), 45.4 (8 F, m) and 49.8 (2 F, s); *m/z* (rel. intensity) 490 (M^+, 100%), 471 (23), 462 (62), 171 (67), 143 (53), 121 (28) and 69 (31).

3-(3-Chlorohexafluoropropyl)-4,5,6,7-tetrahydroindazole 4ae. Mp 133–134 °C (Found: C, 38.8; H, 2.7; Cl, 11.55; F, 37.1; N, 9.2. $C_{10}H_9ClF_6N_2$ requires C, 39.17; H, 2.96; Cl, 11.56; F, 37.17; N, 9.14%); ν(KCl)/cm^{-1} 3100, 2915, 1590, 1450 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.78 (4 H, m), 2.57 (2 H, t, J_{H-H} 5.4) and 2.70 (2 H, t, J_{H-H} 5.4); δ_F(CD_3COCD_3–external TFA) −9.4 (2 F, s), 31.7 (2 F, s) and 44.8 (2 F, s); *m/z* (rel. intensity) 306 (M^+, 49%), 308 (15), 278 (100), 280 (24), 271 (25), 171 (70), 143 (68) and 121 (65).

3-(5-Chlorodecafluoropentyl)-4,5,6,7-tetrahydroindazole 4af. Mp 108–109 °C (Found: C, 35.2; H, 2.0; Cl, 8.8; F, 46.85; N, 6.8. $C_{12}H_9ClF_{10}N_2$ requires C, 35.45; H, 2.23; Cl, 8.72; F, 46.72; N, 6.89%); ν(KCl)/cm^{-1} 3100, 2900, 1590, 1490, 1445 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.76 (4 H, m) and 2.62 (4 H, m); δ_F(CD_3COCD_3–external TFA) −8.5 (2 F, s), 32.8 (2 F, s), 44.0 (2 F, s), 44.7 (2 F, s) and 45.8 (2 F, s); *m/z* (rel. intensity) 406 (M^+, 68%), 408 (26), 378 (93), 380 (24), 371 (24), 171 (96), 143 (100) and 121 (46).

3-(7-Chlorotetradecafluoroheptyl)-4,5,6,7-tetrahydroindazole 4ag. Mp 68–70 °C (Found: C, 32.9; H, 1.5; Cl, 6.95; F, 52.8; N, 5.5. $C_{14}H_9ClF_{14}N_2$ requires C, 33.19; H, 1.79; Cl, 7.00; F, 52.50; N, 5.53%); ν(KCl)/cm^{-1} 3100, 2910, 1590, 1495, 1445 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.76 (4 H, m) and 2.62 (4 H, m); δ_F(CD_3COCD_3–external TFA) −8.5 (2 F, s), 30.5 (2 F, s), 43.4 (2 F, s) and 44.8 (8 F, m); *m/z* (rel. intensity) 506 (M^+, 58%), 508 (21), 478 (100), 480 (29), 471 (18), 171 (90), 143 (95) and 121 (43).

5-Hydroxymethyl-3-trifluoromethylpyrazole 4ba.[14] Mp 115–116 °C; ν(KCl)/cm^{-1} 3200, 2910, 1495, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 4.69 (2 H, s) and 6.50 (1 H, s); δ_F(CD_3COCD_3–external TFA) −15.2 (s); *m/z* (rel. intensity) 166 (M^+, 100%), 149 (18), 117 (32), 97 (20) and 69 (26).

3-Heptafluoropropyl-5-hydroxymethylpyrazole 4bb. Mp 112–114 °C (Found: C, 32.0; H, 1.7, F, 49.85; N, 10.3. $C_7H_5F_7N_2O$ requires C, 31.59; H, 1.89; F, 49.97; N, 10.53%); ν(KCl)/cm^{-1} 3200, 1490, 1360, 1240 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 4.69 (2 H, s) and 6.51 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.0 (3 F, s), 33.1 (2 F, s) and 50.6 (2 F, s); *m/z* (rel. intensity) 266 (M^+, 78%), 249 (19), 237 (33), 147 (100), 117 (29) and 97 (20).

5-Hydroxymethyl-3-undecafluoropentylpyrazole 4bc. Mp 202–203 °C (Found: C, 30.1; H, 1.5; F, 56.9; N, 7.9. $C_9H_5F_{11}N_2O$ requires C, 29.52; H, 1.38; F, 57.08; N, 7.65%); ν(KCl)/cm^{-1} 3200, 2915, 1495, 1350, 1245 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 4.69 (2 H, s) and 6.50 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.1 (3 F, s), 31.8 (2 F, s), 45.4 (4 F, m) and 49.2 (2 F, s); *m/z* (rel. intensity) 366 (M^+, 45%), 349 (13), 337 (25), 147 (100), 117 (14) and 97 (28).

3-(3-Chlorohexafluoropropyl)-5-hydroxymethylpyrazole 4be. Mp 118–119 °C (Found: C, 29.75; H, 1.7; Cl, 12.45; F, 40.7; N, 10.1. $C_7H_5ClF_6N_2O$ requires C, 29.75; H, 1.78; Cl, 12.55; F, 40.34; N, 9.91%); ν(KCl)/cm^{-1} 3200, 2910, 1490, 1345 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 4.66 (2 H, s) and 6.50 (2 H, s); δ_F(CD_3COCD_3–external TFA) −9.9 (2 F, s), 31.0 (2 F, s) and 44.3 (2 F, s); *m/z* (rel. intensity) 282 (M^+, 60%), 284 (25), 247 (15), 229 (24) and 147 (100).

3-(5-Chlorodecafluoropentyl)-5-hydroxymethylpyrazole 4bf. Mp 170–172 °C (Found: C, 28.2; H, 1.8; Cl, 9.8; F, 49.2; N, 7.7. $C_9H_5ClF_{10}N_2O$ requires C, 28.25; H, 1.32; Cl, 9.27; F, 49.66; N, 7.32%); ν(KCl)/cm^{-1} 3200, 2910, 1490, 1345 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 4.65 (2 H, s) and 6.52 (1 H, s); δ_F(CD_3COCD_3–external TFA) −8.6 (2 F, s), 32.8 (2 F, s), 44.0 (2 F, s), 44.7 (2 F, s) and 45.8 (2 F, s); *m/z* (rel. intensity) 382 (M^+, 36%), 384 (14), 365 (14), 347 (11), 147 (100) and 101 (28).

4-(3-Hydroxypropyl)-3-trifluoromethylpyrazole 4ca. Mp 85–87 °C (Found: C, 43.1; H, 4.5; F, 29.4; N, 14.4. $C_7H_9F_3N_2O$ requires C, 43.30; H, 4.67; F, 29.36; N, 14.43%); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1480, 1440, 1360 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.8), 3.61 (2 H, t, J_{H-H} 7.8) and 7.73 (1 H, s); δ_F(CD_3COCD_3–external TFA) −16.5 (3 F, s); δ_C(CD_3COCD_3) 20.2 (s), 34.3 (s), 120.3 (s, C-4), 123.6 (q, *J* 267.1, CF_3), 130.0 (s, C-5) and 140.1 (q, *J* 35.7, C-3); *m/z* (rel. intensity) 194 (M^+, 1%), 176 (100), 149 (69), 107 (23), 79 (11) and 69 (9).

3-Heptafluoropropyl-4-(3-hydroxypropyl)pyrazole 4cb. Mp 81–82 °C (Found: C, 36.9; H, 2.95; F, 44.95; N, 9.4. $C_9H_9F_7N_2O$ requires C, 36.75; H, 3.08; F, 45.21; N, 9.52%); ν_{max}(KCl)/cm^{-1} 3100, 2905, 1480, 1360 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.8), 3.62 (2 H, t, J_{H-H} 7.8) and 7.74 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.7 (3 F, s), 31.9 (2 F, s) and 50.0 (2 F, s); *m/z* (rel. intensity) 294 (M^+, 1%), 276 (100), 249 (54), 157 (23), 130 (17), 117 (6) and 69 (8).

4-(3-Hydroxypropyl)-3-undecafluoropentylpyrazole 4cc. Mp 61–62 °C (Found: C, 33.5; H, 2.2; F, 53.1; N, 6.9. $C_{11}H_9F_{11}N_2O$ requires C, 33.52; H, 2.30; F, 53.02; N, 7.11%); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1480, 1445, 1255 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.84 (2 H, m), 2.71 (2 H, t, J_{H-H} 7.6), 3.62 (2 H, t, J_{H-H} 7.6) and 7.74 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.2 (3 F, s), 30.4 (2 F, s), 45.2 (4 F, m) and 49.4 (2 F, s); *m/z* (rel. intensity) 394 (M^+, 4%), 376 (100), 349 (51), 180 (11), 157 (44), 137 (31), 130 (29), 117 (10) and 69 (18).

4-(3-Hydroxypropyl)-3-pentadecafluoroheptylpyrazole 4cd. Mp 78–79 °C (Found: C, 31.95; H, 1.8; F, 57.6; N, 5.7. $C_{13}H_9F_{15}N_2O$ requires C, 31.59; H, 1.84; F, 57.66; N, 5.67%); ν_{max}(KCl)/cm^{-1} 3100, 2905, 1480, 1365, 1260 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.81 (2 H, m), 2.66 (2 H, t, J_{H-H} 7.7), 3.60 (2 H, t, J_{H-H} 7.7) and 7.72 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.6 (3 F, s), 30.8 (2 F, s), 45.4 (8 F, m) and 49.8 (2 F, s); *m/z* (rel. intensity) 494 (M^+, 17%), 476 (100), 449 (24), 180 (15), 157 (68), 137 (39), 130 (26), 106 (18), 80 (29) and 69 (32).

3-(3-Chlorohexafluoropropyl)-4-(3-hydroxypropyl)pyrazole 4ce. Mp 68–70 °C (Found: C, 34.7; H, 2.75; Cl, 11.4; F, 36.55; N, 9.2. $C_9H_9ClF_6N_2O$ requires C, 34.80; H, 2.92; Cl, 11.41; F, 36.70; N, 9.02%); ν_{max}(KCl)/cm^{-1} 3100, 2905, 1485, 1445, 1360, 1265 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.8), 3.61 (2 H, t, J_{H-H} 7.8) and 7.73 (1 H, s); δ_F(CD_3COCD_3–external TFA) −9.8 (2 F, s), 30.1 (2 F, s) and 43.9 (2 F, s); *m/z* (rel. intensity) 310 (M^+, 2%), 312 (M^+, 1), 292 (100), 294 (36), 265 (30), 267 (10), 157 (31) and 137 (12).

3-(5-Chlorodecafluoropentyl)-4-(3-hydroxypropyl)pyrazole 4cf. Mp 67–69 °C (Found: C, 31.9; H, 2.2; Cl, 8.5; F, 46.2; N, 6.5. $C_{11}H_9ClF_{10}N_2O$ requires C, 32.17; H, 2.21; Cl, 8.63; F, 46.27; N, 6.82%); ν_{max}(KCl)/cm^{-1} 3100, 1900, 1480, 1345 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.81 (2 H, m), 2.68 (2 H, t, J_{H-H} 7.8), 3.62 (2 H, t, J_{H-H}) and 7.74 (1 H, s); δ_F(CD_3COCD_3–external TFA) −9.8 (2 F, s), 30.4 (2 F, s), 45.2

(4 F, m) and 49.5 (2 F, s); *m/z* (rel. intensity) 410 (M^+, 3%), 412 (M^+, 1), 392 (100), 394 (39), 365 (43), 367 (19), 157 (46), 137 (27), 130 (25), 117 (13), 85 (8) and 87 (3).

3-(7-Chlorotetradecafluoroheptyl)-4-(3-hydroxypropyl)pyrazole 4cg. Mp 90–91 °C (Found: C, 30.4; H, 1.7; Cl, 6.8; F, 52.2; N, 5.85. $C_{13}H_9ClF_{14}N_2O$ requires C, 30.58; H, 1.78; Cl, 6.94; F, 52.09; N, 5.49%); ν_{max}(KCl)/cm^{-1} 3100, 2904, 1464, 1345, 1260 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.8), 3.61 (2 H, t, J_{H-H} 7.8) and 7.72 (1 H, s); δ_F(CD_3COCD_3–external TFA) −8.2 (2 F, s), 30.7 (2 F, s), 43.6 (2 F, s) and 44.9 (8 F, m); *m/z* (rel. intensity) 510 (M^+, 3%), 512 (M^+, 1), 492 (100), 494 (18), 465 (36), 467 (15), 157 (68), 137 (39), 130 (27), 117 (11), 85 (14) and 87 (6).

1,4-Bis(4-hydroxypropylpyrazol-3-yl)-1,1,2,2,3,3,4,4,-octafluorobutane 4ch. Mp 185–187 °C (Found: C, 42.5; H, 4.0; F, 33.5; N, 12.3. $C_{16}H_{18}F_8N_4O_2$ requires C, 42.67; H, 4.03; F, 33.75; N, 12.44%); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1480, 1445, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.81 (4 H, m), 2.66 (4 H, t, J_{H-H} 7.7), 3.61 (4 H, t, J_{H-H} 7.7) and 7.73 (2 H, s); δ_F(CD_3COCD_3–external TFA) 29.1 (4 F, s) and 43.4 (4 F, s); *m/z* (rel. intensity) 451 (M^+ + 1, 100%), 450 (M^+, 4), 431 (23), 411 (30), 399 (51), 385 (47), 360 (22), 339 (27), 321 (31), 279 (26), 167 (50), 125 (45), 107 (64), 97 (26) and 81 (34).

5-(3-Hydroxypropyl)-3-undecafluoropentylpyrazole 4dc. Mp 99–101 °C (Found: C, 33.8; H, 2.2; F, 53.1; N, 6.9. $C_{11}H_9F_{11}N_2O$ requires C, 33.52; H, 2.30; F, 53.02; N, 7.11); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1450, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.86 (2 H, m), 2.72 (2 H, t, J_{H-H} 7.7), 3.68 (2 H, t, J_{H-H} 7.8) and 6.50 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.4 (3 F, s), 30.5 (2 F, s), 45.2 (4 F, m) and 49.4 (2 F, s); *m/z* (rel. intensity) 394 (M^+, 6%), 376 (100), 349 (51), 157 (53), 137 (34), 130 (30), 117 (10) and 69 (18).

5-(3-Hydroxypropyl)-3-pentadecafluoroheptylpyrazole 4dd. Mp 118–120 °C (Found: C, 31.5; H, 1.6; N, 5.4. $C_{13}H_9F_{15}N_2O$, C, 31.59; H, 1.84; N, 5.67%); ν_{max}(KCl)/cm^{-1} 3100, 2905, 1485, 1360 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.7), 3.66 (2 H, t, J_{H-H} 7.8) and 6.50 (1 H, s); δ_F(CD_3COCD_3–external TFA) 4.4 (3 F, s), 30.6 (2 F, s), 45.4 (8 F, m) and 49.8 (2 F, s); *m/z* (rel. intensity) 494 (M^+, 8%), 476 (6), 463 (33), 450 (100), 157 (12), 131 (6) and 69 (4).

3-(3-Chlorohexafluoropropyl)-5-(3-hydroxypropyl)pyrazole 4de. Mp 76–78 °C (Found: C, 34.6; H, 2.8; N, 8.8. $C_9H_9ClF_6N_2O$ requires C, 34.80; H, 2.92; N, 9.02%); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1450, 1350 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.67 (2 H, t, J_{H-H} 7.8), 3.66 (2 H, t, J_{H-H} 7.8) and 6.48 (2 H, s); δ_F(CD_3COCD_3–external TFA) −9.6 (2 F, s), 30.2 (2 F, s) and 44.0 (2 F, s); *m/z* (rel. intensity) 310 (M^+, 13%), 312 (4), 292 (7), 294 (2), 279 (34), 281 (11), 266 (100), 268 (58), 175 (15), 157 (65), 143 (24), 130 (27) and 81 (34).

3-(5-Chlorodecafluoropentyl)-5-(3-hydroxypropyl)pyrazole 4df. Mp 94–96 °C (Found: C, 32.3; H, 2.1; Cl, 8.65; F, 46.1; N, 6.95. $C_{11}H_9ClF_{10}N_2O$ requires C, 32.17; H, 2.21; Cl, 8.63; F, 46.27; N, 6.82%); ν_{max}(KCl)/cm^{-1} 3100, 2900, 1484, 1345 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.82 (2 H, m), 2.68 (2 H, t, J_{H-H} 7.8), 3.67 (2 H, t, J_{H-H} 7.8) and 6.48 (1 H, s); δ_F(CD_3COCD_3–external TFA) −9.8 (2 F, s), 30.4 (2 F, s), 45.4 (4 F, m) and 50.0 (2 F, s); *m/z* (rel. intensity) 410 (M^+, 16%), 412 (4), 392 (10), 394 (4), 379 (42), 381 (12), 366 (100), 368 (38), 175 (20), 157 (68), 137 (34), 143 (28), 130 (31) and 81 (39).

3-(7-Chlorotetradecafluoroheptyl)-5-(3-hydroxypropyl)pyrazole 4dg. Mp 110 °C (Found: C, 30.8; H, 1.6; Cl, 6.95; F, 52.4; N, 5.6. $C_{13}H_9ClF_{14}N_2O$ requires C, 30.58; H, 1.78; Cl, 6.94; F, 52.09; N, 5.49%); ν_{max}(KCl)/cm^{-1} 3100, 2905, 1485 and 1200–1100; δ_H(CD_3COCD_3–internal TMS) 1.85 (2 H, m), 2.88 (2 H, t, J_{H-H} 7.7), 3.60 (2 H, t, J_{H-H} 7.8) and 6.43 (1 H, s); δ_F(CD_3COCD_3–external TFA) −8.9 (2 F, s), 31.6 (2 F, s), 42.9 (2 F, s) and 44.0 (8 F, m); *m/z* (rel. intensity) 510 (M^+, 2%), 492 (4), 479 (100), 481 (21), 466 (90), 468 (33), 157 (25), 144 (10), 131 (13) and 81 (9).

Acknowledgements

We thank the National Natural Sciences of China for financial support.

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Paper 4/06753C
Received 4th *November* 1994
Accepted 20th *December* 1994