Synthesis of a series of trifluoromethylazoles and determination of pK_a of acidic and basic trifluoromethyl heterocycles by ^{19}F NMR spectroscopy

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Trifluoroacetylation at the 5-position of 3,4-dihydro-2*H*-pyran and the 3-position of 4,5-dihydrofuran, followed by treatment with hydrazine, gave 3-(3-trifluoromethyl-1*H*-pyrazol-4-yl)propanol and 2-(3-trifluoromethyl-1*H*-pyrazol-4-yl)ethanol, respectively. In the latter case, an intermediate dimer was isolated. Isomeric 2-(3-trifluoromethyl-1*H*-pyrazol-5-yl)ethanol was formed by reaction of hydrazine with 6-benzyloxy-1,1,1-trifluorohex-3-yn-2-one and deprotection. Reaction of 3-benzyloxypropylamine with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole, followed by deprotection, afforded 3-[3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazol-4-yl]propanol. A series of 2-trifluoromethyl-1*H*-benzimidazoles and 2-trifluoromethyl-3*H*-imidazopyridines were prepared by condensation of the appropriate *ortho*-arenediamine with trifluoroacetic acid. Analysis of the ^{19}F NMR spectra of the trifluoromethylazoles and of 3-trifluoromethylpyridine in aqueous solution at different pHs enabled determination of pK_a values. All the compounds evaluated had one or more pK_a between 1 and 13, except the triazole. Several compounds were identified as having potential use in measuring pH in biological media by ^{19}F NMR spectroscopy.

A large number of pyrazoles and derived heterocycles have found use[1] as therapeutic agents and as agrochemicals. Trifluoromethyl heterocycles are also of considerable interest in these areas[2] on account of the acid-strengthening/base-weakening electronic effects of incorporation of the trifluoromethyl group and in view of the increased lipophilicity of compounds bearing this functionality. As part of a programme of synthesis and evaluation of trifluoromethyl heterocycles for medicinal and pH sensor applications,[3,4] we required pyrazoles and 1,2,4-triazoles with one or more trifluoromethyl groups on the heterocycle, and also carrying an ω-hydroxyalkyl function for later attachment to various moieties, such as 2-nitroimidazole,[5] to permit biological targeting to specific tissue or cell types.

Of the methods available for the synthesis of N-unsubstituted pyrazoles, those involving condensation of hydrazine with 1,3-diketones and with α,β-acetylenic ketones are among the more widely used.[6] Clearly, the range of pyrazoles that can be prepared by both methods is limited to those where the substrate is readily synthetically accessible and, in the latter case, to 4-unsubstituted pyrazoles. We[4] and others[7] have recently reported the synthesis of 3,5-bis(trifluoromethyl)-pyrazole from 1,1,1,5,5,5-hexafluoropentane-2,4-dione but all attempts to alkylate this 1,3-diketone at C-3, leading to 4-substituted 3,5-bis(trifluoromethyl)pyrazoles, were unsuccessful. For our series of target pyrazoles, with ω-hydroxyalkyl substituents, there is an additional requirement for introduction or appropriate protection of the hydroxy group.

In planning the synthesis of 3-(3-trifluoromethyl-1*H*-pyrazol-4-yl)propanol **3** and 2-(3-trifluoromethyl-1*H*-pyrazol-4-yl)ethanol **8**, where the ω-hydroxyalkyl group is at the 4-position of the pyrazole, we recognised that the trifluoroacetyldihydropyran **2** and the trifluoroacetyldihydrofuran **6**, respectively, contain the correct carbon skeleton and a masked 1,3-diketone for condensation with hydrazine. Furthermore, this condensation would reveal the required ω-hydroxyalkyl function as a leaving group, thus obviating the need for earlier introduction and possible protection of the hydroxy group.

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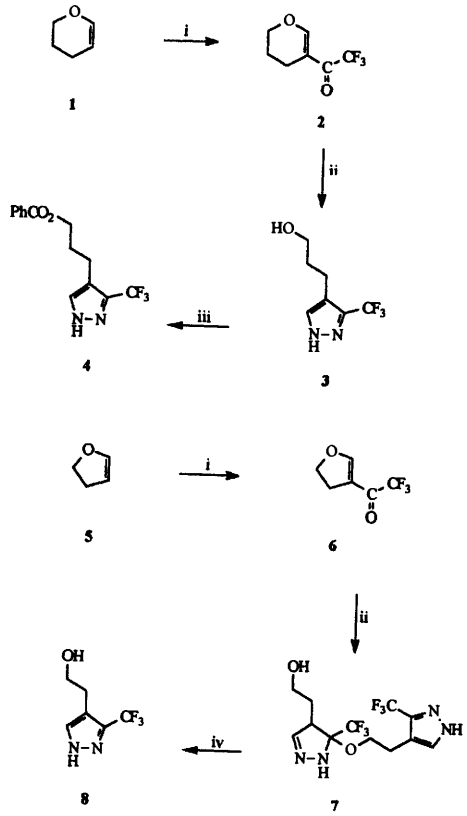
Dihydropyran **1** and dihydrofuran **5** were trifluoroacetylated using trifluoroacetic anhydride and pyridine in dichloromethane, as shown in Scheme 1. The yields in these first steps were



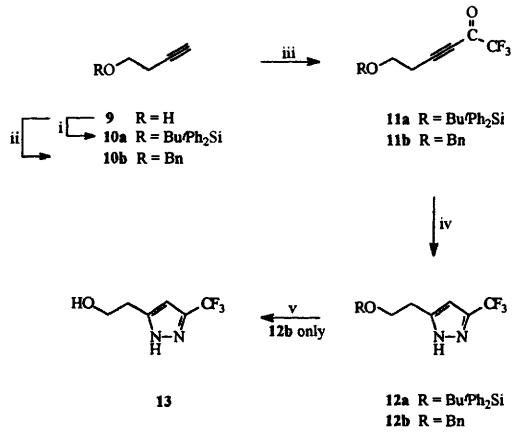
Scheme 1 *Reagents:* i, $(CF_3CO)_2O$, pyridine, CH_2Cl_2; ii, N_2H_4, EtOH; iii, BzCl; iv, HCl, EtOH

notably higher than those reported by Hojo *et al.*[8] for the same procedure. Treatment of **2** with hydrazine in boiling ethanol effected the condensation with concomitant exposure of the

3-hydroxypropyl group, as predicted. The trifluoromethylpyrazolylpropanol **3** was isolated in 96% overall yield from **1**. To ensure that the ω-hydroxy group could be derivatised without interference from the pyrazole, the corresponding benzoate ester **4** was formed in the usual way. Since this work was carried out, Tang and Hu[9] have reported the synthesis of **3** by addition of the expensive iodopentafluoroethane across the enol ether of **1**, in the presence of sodium dithionite, and treatment of the pentafluoroethyltetrahydropyran with hydrazine.

In contrast, treatment of the five-membered ring homologue **6** with hydrazine did not give the expected pyrazolylethanol **8** directly. Under essentially the same conditions as above, a virtually quantitative yield of the dimer **7** was formed. In this dimer, one molecule of the fully condensed aromatic pyrazolylethanol has intercepted another molecule where the elimination of water from the intermediate is not complete, although the detailed mechanism of the formation of **7** is not clear. It is particularly noteworthy that no material could be isolated where solvent ethanol, rather than the pyrazolylethanol, has reacted as the incoming nucleophile, despite the much higher concentration of the former. The dimer **7** readily formed the target pyrazolylethanol **8** upon reflux in the presence of a trace of acid. In a control experiment, it was demonstrated that **8** was not converted to the dimer **7** under the condensation conditions, indicating that **7** had not been formed from two molecules of **8**.

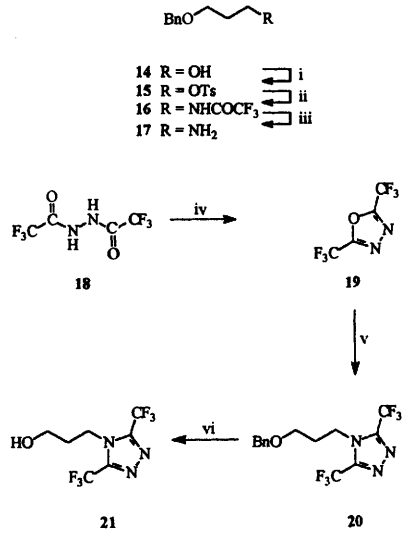
In the approach to the 3,5-disubstituted pyrazole **13**, ring formation from hydrazine and an α,β-acetylenic ketone was investigated, as shown in Scheme 2. In this case, it was not



Scheme 2 *Reagents:* i, Bu^{t}Ph$_2$SiCl, imidazole, DMF; ii, BnBr, NaH, DMF; iii, BuLi, $CF_3CO_2CH_2CF_3$, THF; iv, N_2H_4, EtOH; v, H_2, Pd–C, $HClO_4$, MeOH

possible to design a process in which the hydroxyalkyl group was revealed during the condensation and it was necessary to assemble an appropriate trifluoromethyl ketone containing the alcohol, possibly in a protected form. But-3-ynol **9** was protected as its *tert*-butyldiphenylsilyl ether **10**, essentially by the method of Delorme *et al.*[10] This allowed formation of the acetylenic carbanion by treatment with butyllithium at low temperature. Addition of trifluoroethyl trifluoroacetate as the electrophile afforded the *tert*-butyldiphenylsilyl-protected acetylenic trifluoromethyl ketone **11a** in 95% yield. Other electrophilic trifluoroacetylating agents, such as trifluoroacetic anhydride, ethyl trifluoroacetate and ethyl trifluorothioacetate, were considerably less effective. Condensation of this ketone **11a** with hydrazine formed the *tert*-butyldiphenylsilyl-protected pyrazol-5-ylethanol **12a** in virtually quantitative yield. Unexpectedly, it proved impossible to remove the silyl protecting group with fluoride using conditions under which the product pyrazolylethanol **13** could be isolated. Repetition of the sequence using *O*-benzyl protection was more successful. The alcohol **9** was benzylated, essentially by the method of Johnson *et al.*,[11] to give the ether **10b**. As before, formation of the acetylenic anion and trifluoroacetylation (trifluoroethyl trifluoroacetate) gave the ketone **11b** in very high yield. Condensation with hydrazine in boiling ethanol afforded the protected 3,5-disubstituted pyrazole **12b**. Now, exposure of the hydroxy group was effected by hydrogenation under acidic conditions to afford the target trifluoromethylpyrazolylethanol **13** with the substituents in the desired 3,5-arrangement.

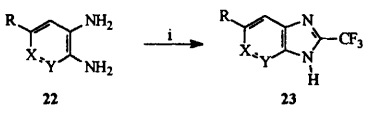
The most common routes for preparation of 1,2,4-triazoles are thermal condensation of an acylhydrazide with a (thio)-amide (the Pellizzari reaction)[12] and condensation of a diacylamine with hydrazine (the Einhorn–Brunner reaction).[13] However, the symmetry of the target compound, the 3,5-bis(trifluoromethyl)triazolylpropanol **21**, and the need for a functionalised substituent at the 4-position, suggested that condensation of an appropriately protected ω-hydroxyalkyl primary amine with an *N*,*N*′-diacylhydrazine, or its equivalent, would be a more efficient route. Scheme 3 shows the route



Scheme 3 *Reagents:* i, TsCl, KOH, Et_2O; ii, CF_3CONH_2, KOBu^t, THF, NaI; iii, NaOH, MeOH; iv, P_2O_5, heat; v, **17**, MeOH; vi, H_2, Pd–C, $HClO_4$, EtOH

adopted. 3-Benzyloxypropylamine **17** was synthesised in three steps from the commercially available mono-*O*-benzyl protected propane-1,3-diol **14**. Activation of the alcohol as the toluene-*p*-sulfonate **15** was achieved using toluene-*p*-sulfonyl chloride (TsCl) in the presence of powdered potassium hydroxide. Substitution with the anion derived from trifluoroacetamide served to introduce the nitrogen atom, giving the amide **16**. Selective hydrolytic deprotection under basic conditions afforded the required *O*-benzyl-protected hydroxypropylamine **17** in 58% overall yield from **14**. In a modification of the technique used by Reitz and Finkes,[14] 1,2-bis(trifluoroacetyl)hydrazine **18** was cyclised to form the oxadiazole **19** in good yield by dehydration with phosphorus pentoxide at high temperature. Although the condensation of this normally reactive heterocycle **19** with the amine **17** proceeded only in moderate yield to form **20**, subsequent deprotection by hydrogenolysis under acidic conditions was efficient, affording the target 3-[3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazol-4-yl]propanol **21** in 39% yield from the amine **17** and in 23% overall yield in five steps from **14**.

Scheme 4 shows the preparative route developed for synthesis of the 2-trifluoromethylimidazopyridines **23a,b** and the 2-trifluoromethylbenzimidazoles **23c,d**. The former pair of compounds were selected as being potentially water-soluble. The benzimidazoles were designed to carry two inequivalent sets of



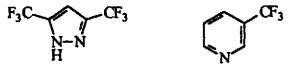
22 **23**

a R = H, X = N, Y = CH
b R = H, X = CH, Y = N
c R = F, X = Y = CH
d R = F_3C, X = Y = CH

Scheme 4 *Reagent:* i, CF_3CO_2H

fluorine atoms with different sensitivities of chemical shift to pH. In benzimidazole **23d**, the chemical shift of the 5-trifluoromethyl group should be sufficiently insensitive to pH for it to act as an internal chemical shift standard. Prolonged treatment of the pyridinediamines **22a,b** with boiling trifluoroacetic acid gave mixtures of regioisomeric acylaminopyridines, along with small amounts of the cyclised products **23a,b**, as shown by ^1H and ^{19}F NMR spectroscopy. Cyclisation was completed at 200 °C in a Kugelrohr apparatus, with sublimation of the target imidazopyridines **23a,b**. The benzimidazoles **23c,d** were formed by similar condensations, also in excellent yields.

The effect of pH on the ^{19}F NMR chemical shift (δ_F) of the trifluoromethyl heterocycles **3**, **8**, **13**, **21**, **23a,b**, **24** and **25** was then measured with the aim of measuring pK_a values and identifying compounds in which δ_F was highly sensitive to pH in the physiological range. Compound **24** was available in the laboratory[4] and compound **25** was obtained commercially. The benzimidazoles **23c,d** were not sufficiently soluble in aqueous media to permit these measurements to be made.



24 **25**

Pyrazole has an acidic pK_a = 14.18, as reported by Elguero *et al.*[15] who used UV spectroscopic methods. This group also studied the acid-strengthening effects of electron-withdrawing groups on pyrazoles, with 3-trifluoromethyl-5-methylpyrazole having pK_a = 12.33, while the second trifluoromethyl group, as in 3,5-bis(trifluoromethyl)pyrazole **24**, increased the acidity even more markedly (pK_a = 7.51). Similar but more pronounced effects are seen for the sequential incorporation of nitro groups.[16] Fig. 1(*a*) shows the δ_F–pH relationship for 3-(3-trifluoromethyl-1*H*-pyrazol-4-yl)propanol **3**, while Fig. 1(*b*) shows that for the lower homologue, 2-(3-trifluoromethyl-1*H*-pyrazol-4-yl)ethanol **8**. As expected, these compounds have very similar pK_a values (12.1 and 12.0, respectively). Moving the ω-hydroxyalkyl substituent to the 5-position, as in 2-(3-trifluoromethyl-1*H*-pyrazol-5-yl)ethanol **13**, had a slight acid-weakening effect, giving pK_a = 12.8. For the 3,5-bis(trifluoromethyl)-1*H*-pyrazole **24** [Fig. 1(*d*)], the pK_a was determined to be 7.55, closely in agreement with the reported value.[15] These results place the mono(trifluoromethyl)pyrazoles well outside the useful range for measurement of pH in biological systems but the pK_a of **24** is highly appropriate. All four trifluoromethylpyrazoles **3**, **8**, **13** and **24** gave simple sigmoidal curves with good sensitivity of chemical shift to changes in pH, with $\Delta\delta_F$ (the total changes in chemical shift across the whole pH range) being in the range 2.09 to 2.33 ppm for the mono(trifluoromethyl)pyrazoles and 1.47 ppm for the bis(trifluoromethyl)-pyrazole. As expected, formation of the anions at higher pHs caused the signals to move upfield.

In contrast, the ^{19}F chemical shift of the analogous 3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole **21** was virtually independent of pH in the range pH 0.0 to 9.5, as shown in Fig. 2. As this compound cannot be a heterocyclic acid, unlike the pyrazoles, no studies were made under more alkaline conditions. Thus, either the corresponding triazolium cation has δ_F identical to that of the unionised triazole or, more likely, the pK_a of the compound is <0.0.

The relationships of δ_F to solution pH for the isomeric 2-trifluoromethylimidazopyridines **23a,b** both approximated closely to double sigmoidal curves (Fig. 3), indicating two ionisation events for each compound with different pK_a values. The principal ionisation event for 2-trifluoromethyl-3*H*-imidazo[4,5-*c*]pyridine **23a**, loss of the imidazole N–H proton with the neutral molecule acting as an acid, occurs at pK_a = 8.78. There is also an ionisation event at pK_a = *ca.* 3.5, probably corresponding to protonation of the neutral molecule at the pyridine nitrogen. The former event causes greater change in chemical shift than the latter ($\Delta\delta_F$ 1.0 and $\Delta\delta_F$ 0.1, respectively). The curve for 2-trifluoromethyl-3*H*-imidazo[4,5-*b*]pyridine **23b** is similar in shape. The pK_a values are 6.92 and *ca.* 2.2, representing the acidic and basic ionisations, respectively. The fact that the principal pK_a of this compound lies well within the physiological pH range makes it an attractive candidate lead compound for measurement of pH in biological systems, although the $\Delta\delta_F$ is relatively small (0.55 ppm). For comparison, the analogous 2-trifluoromethylbenzimidazole has been reported[17] to have pK_a = 8.13, as measured spectroscopically, but it was too insoluble to allow investigation by ^{19}F NMR spectroscopy.

Finally, commercially available 3-trifluoromethylpyridine **25** was investigated. As shown in Fig. 4, this compound gave a simple sigmoidal curve with pK_a measured as 2.67 and $\Delta\delta_F$ = 1.0 ppm. Clearly, this represents protonation at the pyridine nitrogen but the basicity of **25** is much reduced by incorporation of the electron-withdrawing trifluoromethyl group (*cf.* 3-methylpyridine pK_a = 5.68)[18] which is apparently similar in effect to a chlorine atom (3-chloropyridine pK_a = 2.84).[18]

In conclusion, syntheses of four trifluoromethylpyrazoles, one trifluoromethyl-1,2,4-triazole, two trifluoromethylbenzimidazoles and two trifluoromethylimidazopyridines have been achieved. Studies of the effect of solution pH on the ^{19}F NMR chemical shift have revealed sensitivity of δ_F to the state of ionisation of the trifluoromethyl heterocycles and hence to the solution pH. Three compounds, **23a,b** and **24**, have been identified as having pK_a close to the physiological range and therefore as having potential for use in a non-invasive method of measuring pH in biological systems by ^{19}F NMR spectroscopy. In all the compounds examined, the trifluoromethyl group acts in two roles; reporter of the state of ionisation and acid-strengthener/base-weakener. Further development of the lead compounds will involve incorporation of appropriate functional groups to permit attachment of biological targeting moieties and to 'fine-tune' the pK_a.

Experimental

Experiments were conducted at ambient temperature, unless otherwise noted. Solutions in organic solvents were dried with anhydrous magnesium sulfate. NMR spectra were obtained of solutions in deuteriochloroform (unless otherwise noted), using tetramethylsilane as chemical shift standard for ^1H (at 400 and 270 MHz) and ^{13}C (at 100 MHz). An external $CF^{35}Cl_3$ signal from fluorotrichloromethane was used for ^{19}F spectra (at 376 and 84.6 MHz). THF refers to dry tetrahydrofuran and brine refers to saturated aqueous sodium chloride. Solvents were evaporated under reduced pressure, except where noted. The stationary phase for chromatography was silica gel. A Kugelrohr apparatus was used for distillations and sublimations. Bps refer to the temperature of the Kugelrohr oven. Mps are uncorrected. A Corning 240 pH meter with a 3.7 mm, pH 0–14 Russell CLSCH11/1m electrode was used for the pH measurements. Compound **24** was prepared as described previously by us.[4]

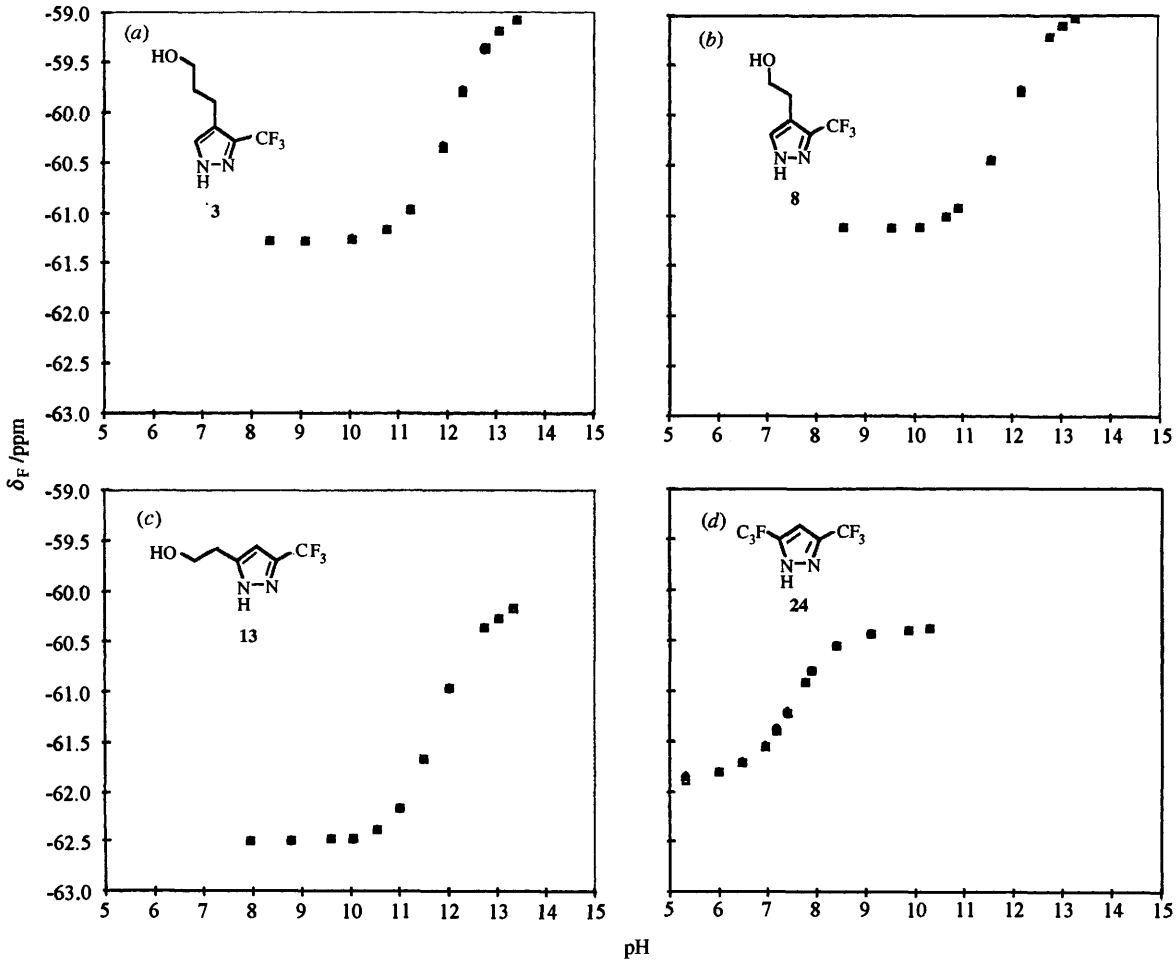


Fig. 1 δ_F–pH Relationships for the trifluoromethylpyrazoles (*a*) **3**, (*b*) **8**, (*c*) **13** and (*d*) **24**

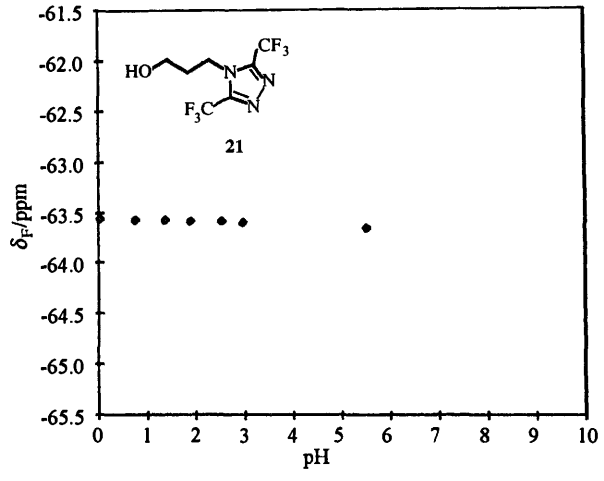


Fig. 2 δ_F–pH Relationship for the bis(trifluoromethyl)-4*H*-1,2,4-triazole **21**

5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran 2

Trifluoroacetic anhydride (17.9 g, 85 mmol) was added dropwise at 10 °C to 3,4-dihydro-2*H*-pyran **1** (5.00 g, 59 mmol) and pyridine (1.57 g, 20 mmol) in dichloromethane (40 cm^3) and the mixture was stirred for 18 h at ambient temperature. The mixture was washed twice with water and with saturated aqueous sodium hydrogen carbonate and was dried. Distillation gave 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran **2** (10.84 g, 97%) as a colourless liquid: bp_{20} 95–100 °C (lit.,[8] bp_{10} 64.6 °C); $\delta_H(D_2O)$ 1.96 (2 H, br quintet, *J* 6 Hz, 3-H_2), 2.34 (2 H, t, *J* 6 Hz, 4-H_2), 4.21 (2 H, t, *J* 6 Hz, 2-H_2), 7.83 (1 H, s, 6-H); δ_F −70.37 (s); *m/z* (EI) 180 (M, 29%), 111 (M − CF_3, 100).

3-(3-Trifluoromethyl-1*H*-pyrazol-4-yl)propanol 3

The pyran **2** (1.0 g, 5.5 mmol) was heated under reflux with hydrazine hydrate (0.83 g, 16 mmol) in ethanol (3 cm^3) for 3 h. Distillation gave 3-(3-trifluoromethyl-1*H*-pyrazol-4-yl)propanol **3** (1.09 g, 99%) as a white solid: $bp_{0.4}$ 160 °C; mp 84–85 °C (lit.,[9] mp 85–87 °C); $\delta_H(D_2O)$ 1.79 (2 H, quintet, *J* 7 Hz, $CH_2CH_2CH_2$), 2.62 (2 H, t, *J* 7.3 Hz, pyrazole-CH_2), 3.59 (2 H, t, *J* 6.3 Hz, CH_2O), 7.66 (1 H, s, pyrazole 5-H); δ_F −61.31 (s) (HRMS: found M + H^+, 195.0745. $C_7H_{10}F_3N_2O$ requires *M* + H^+, 195.0745).

3-(3-Trifluoromethyl-1*H*-pyrazol-4-yl)propyl benzoate 4

Benzoyl chloride (540 mg, 3.9 mmol) was added dropwise over 15 min to the pyrazolylpropanol **3** (500 mg, 2.6 mmol) and triethylamine (5.2 g, 51.5 mmol) in dichloromethane (20 cm^3) at 0 °C and the mixture was allowed to warm to ambient temperature over 16 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (2 M, five times) and brine and was dried. Chromatography (ethyl acetate–hexane, 1 : 1) of the evaporation residue gave the *ester* **4** (620 mg, 81%) as large white plates, mp 46–46.5 °C; δ_H 2.09 (2 H, quintet, *J* 7 Hz, $CH_2CH_2CH_2$), 2.80 (2 H, t, *J* 7.6 Hz, pyrazole-CH_2), 4.38 (2 H, t, *J* 6.1 Hz, CH_2O), 7.44 (2 H, br t, *J* 8 Hz, Ph 3,5-H_2), 7.54 (1 H, s, pyrazole 5-H), 7.56 (1 H, br t, *J* 8 Hz, Ph 4-H), 8.03 (2 H, br d, *J* 8 Hz, Ph 2,6-H_2); δ_F −61.30 (s); *m/z* (CI) 299 (M + H, 100%), 176 (M − $PhCO_2H$, 48), 105 (29) (HRMS: found M + H^+, 299.1007. $C_{14}H_{14}F_3N_2O_2$ requires *M* + H^+, 299.1007).

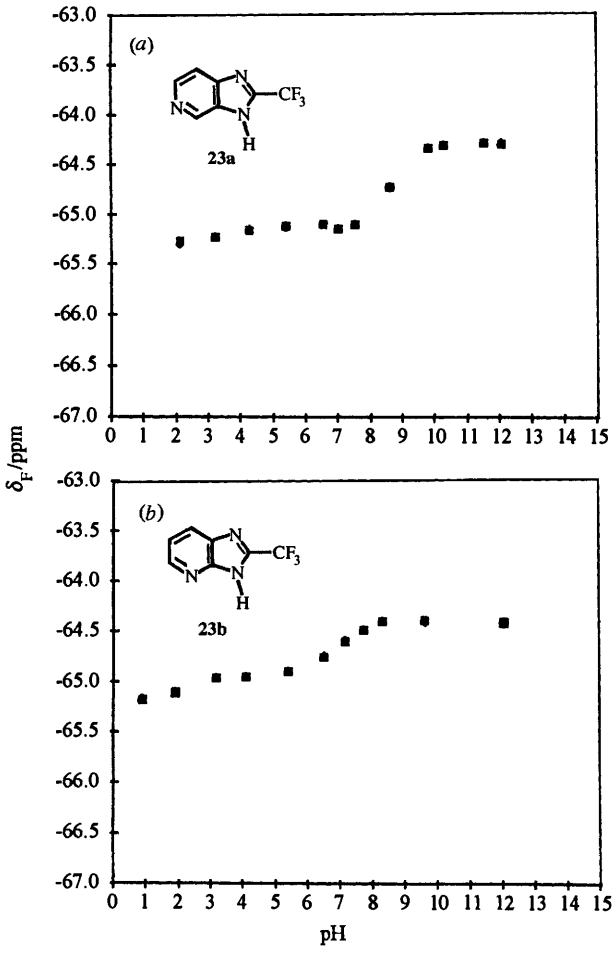


Fig. 3 δ_F–pH Relationships for 2-trifluoromethyl-3*H*-imidazol[4,5-*c*]-pyridines (*a*) **23a** and (*b*) **23b**

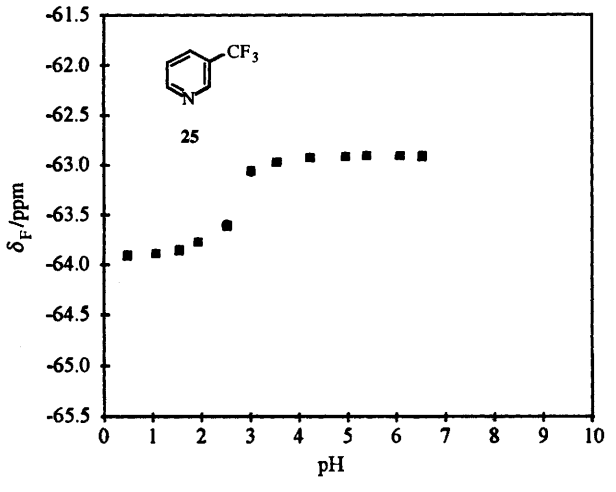


Fig. 4 δ_F–pH Relationship for 3-trifluoromethylpyridine **25**

3-Trifluoroacetyl-4,5-dihydrofuran 6

Trifluoroacetic anhydride (22.5 g, 107 mmol) was added dropwise with cooling to 2,3-dihydrofuran **5** (5.00 g, 71 mmol) and pyridine (1.88 g, 24 mmol) in dichloromethane (40 cm^3) and the mixture was stirred for 18 h. Distillation gave 3-trifluoroacetyl-4,5-dihydrofuran **6** (9.72 g, 82%) as a colourless liquid, bp_{20} 95–100 °C (lit.,[8] $bp_{10.5}$ 48.5 °C); δ_H 2.98 (2 H, tq, J_{H-H} 9.8, J_{H-F} 0.6 Hz, 4-H_2), 4.68 (2 H, t, J_{H-H} 9.8 Hz, 5-H_2), 7.64 (1 H, q, J_{H-F} 1.5 Hz, 2-H); δ_F −73.88 (br s); δ_C 26.93 (s, 4-C), 74.01 (s, 5-C), 114.37 (s, 3-C), 116.62 (q, J_{C-F} 190 Hz, CF_3), 163.84 (q, J_{C-F} 5 Hz, 2-C), 176.08 (q, J_{C-F} 36 Hz, C=O); *m/z* (EI) 166 (M + H, 45%), 97 (M − CF_3, 100) (HRMS: found M + H^+, 166.0239. $C_6H_5F_3O_2$ requires *M* + H^+, 166.0242).

2-{4,5-Dihydro-5-trifluoromethyl-5-[2-(3-trifluoromethyl-1*H*-pyrazol-4-yl)ethoxy]-1*H*-pyrazol-4-yl}ethanol 7

The furan **6** (1.0 g, 6.0 mmol) was heated under reflux with hydrazine hydrate (0.30 g, 6.0 mmol) in ethanol (13 cm^3) for 3 h. Evaporation of the solvent gave the *title compound* **7** (1.08 g, 99%) as a white solid, mp 84–85 °C; ν_{max}(Nujol)/cm^{-1} 3300, 3180, 1170; δ_H 1.82 (1 H, m) and 1.93 (1 H, m) (dihydropyrazole-CH_2), 2.79 (2 H, t, *J* 6.8 Hz, pyrazole-CH_2), 3.31 (1 H, br t, *J* 7 Hz, dihydropyrazole 4-H), 3.71 (2 H, t, *J* 6.8 Hz, pyrazole-CH_2CH_2O), 3.73 (2 H, m, dihydropyrazole-CH_2CH_2OH), 4.94 (3 H, 2 × NH + OH), 6.82 (1 H, s, dihydropyrazole 3-H), 7.67 (1 H, s, pyrazole 5-H); δ_F −82.57 (3 F, s, dihydropyrazole-CF_3), −62.20 (3 F, s, pyrazole-CF_3); δ_C 27.60 (s, CH_2), 28.36 (s, CH_2), 49.49 (s, dihydropyrazole 4-C), 60.92 (s, CH_2), 62.95 (s, CH_2), 92.93 (q, J_{C-F} 31 Hz, dihydropyrazole 5-C), 117.52 (s, pyrazole 4-C), 123.70 (q, J_{C-F} 268 Hz, CF_3), 125.68 (q, J_{C-F} 281 Hz, CF_3), 131.36 (s, CH), 140.95 (q, J_{C-F} 37 Hz, pyrazole 3-C), 146.30 (s, CH) (HRMS: found M + H^+, 361.1099. $C_{12}H_{15}F_6N_4O_2$ requires *M* + H^+, 361.1099).

2-(3-Trifluoromethyl-1*H*-pyrazol-4-yl)ethanol 8

Compound **7** (1.00 g, 2.8 mmol) was heated under reflux with hydrochloric acid (9 M, 0.05 cm^3) in ethanol (12 cm^3) for 16 h. The solvent and reagent were evaporated to give 2-(3-*trifluoromethyl*-1H-*pyrazol*-4-*yl*)*ethanol* **8** (990 mg, 99%) as a pale yellow solid, mp 90–91 °C; δ_H[$(CD_3)_2SO$] 2.65 (2 H, br t, *J* 7 Hz, pyrazole-CH_2), 3.54 (2 H, t, *J* 7 Hz, CH_2O), 4.9 (1 H, br, OH), 7.78 (1 H, br s, pyrazole 5-H); δ_F[$(CD_3)_2SO$] −59.66 (s); *m/z* (EI) 180 (M, 30%), 159 (M − CH_2OH, 100) (HRMS: found M, 180.0515. $C_6H_7F_3NO$ requires *M*, 180.0510).

6-*tert*-Butyldiphenylsilyloxy-1,1,1-trifluorohex-3-yn-2-one 11a

Butyllithium (2.5 M in hexanes; 13 cm^3, 32.4 mmol) was added to 4-*tert*-butyldiphenylsilyloxybut-1-yne **10a**[10] (10.0 g, 32.4 mmol) in THF (50 cm^3) at −78 °C and the mixture was stirred at this temperature for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (7.00 g, 35.7 mmol) in THF (60 cm^3) was added, followed immediately by boron trifluoride–diethyl ether (5.65 g, 40 mmol), and the mixture was stirred at −78 °C for 90 min. Saturated aqueous ammonium chloride (18 cm^3) was added and the mixture was allowed to warm to ambient temperature. The THF was evaporated and the residue, in diethyl ether, was washed with water and twice with brine and dried. Evaporation of the solvent gave the *ketone* **11a** (12.43 g, 95%) as a colourless viscous oil; δ_H 1.06 (9 H, s, Bu^t), 2.72 (2 H, t, *J* 6.3 Hz, $CH_2C{\equiv}C$), 3.85 (2 H, t, *J* 6.3 Hz, CH_2O), 7.3–7.7 (10 H, 2 × Ph-H_5); δ_F −78.63 (s) (HRMS: found M + H^+, 405.1498. $C_{22}H_{24}F_3O_2Si$ requires *M* + H^+, 405.1498).

6-Benzyloxy-1,1,1-trifluorohex-3-yn-2-one 11b

Butyllithium (2.5 M in hexanes; 18 cm^3, 45 mmol) was added to 4-benzyloxybut-1-yne **10b**[11] (7.2 g, 45 mmol) in THF (100 cm^3) at −78 °C and the mixture was stirred at this temperature for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (9.7 g, 50 mmol) in THF (70 cm^3) was added, followed immediately by boron trifluoride–diethyl ether (8.5 g, 60 mmol) and the mixture was stirred at −78 °C for 90 min. Saturated aqueous ammonium chloride (30 cm^3) was added and the mixture was allowed to warm to ambient temperature. The THF was evaporated and the residue, in dichloromethane, was washed with water and twice with brine and dried. Evaporation of the solvent gave the *ketone* **11b** (11.13 g, 97%) as a pale yellow oil; δ_H 2.80 (2 H, t, *J* 6.6 Hz, $CH_2C{\equiv}C$), 3.69 (2 H, t, *J* 6.6 Hz, OCH_2CH_2), 4.58 (2 H, s, $PhCH_2O$), 7.30–7.35 (5 H, m, Ph-H_5); δ_F −78.65 (s) (HRMS: found M − H, 255.0633. $C_{13}H_{10}F_3O_2$ requires *M* − H, 255.0633).

5-(2-*tert*-Butyldiphenylsilyloxyethyl)-3-trifluoromethyl-1*H*-pyrazole 12a

The ketone **11a** (378 mg, 0.93 mmol) was heated under reflux with hydrazine hydrate (73 mg, 0.93 mmol) in ethanol (2.2 cm^3) for 90 min. The evaporation residue, in dichloromethane, was dried and the solvent was evaporated to give the *pyrazole* **12a** (385 mg, 99%) as a colourless oil; δ_H 1.06 (9 H, s, Bu^t), 2.88 (2 H, t, *J* 5.7 Hz, pyrazole-CH_2), 3.89 (2 H, t, *J* 5.7 Hz, CH_2O), 6.33 (1 H, s, pyrazole 4-H), 7.3–7.7 (10 H, m, 2 × Ph-H_5); δ_F −62.31 (s); δ_C 19.01 (s, CMe_3), 26.74 (s, 3 × CH_3), 28.44 (s, pyrazole-CH_2), 62.53 (s, CH_2O), 102.69 (s, pyrazole 4-C), 121.44 (q, J_{C-F} 268 Hz, CF_3), 127.80 (s, 2 × Ph 3,5-C_2), 129.89 (s, 2 × Ph 4-C), 132.83 (s, 2 × Ph 1-C), 135.41 (s, 2 × Ph 2,6-C_2), 142.87 (q, *J* 37 Hz, pyrazole 3-C), 143.28 (s, pyrazole 5-C) (HRMS: found M + H^+, 419.1767. $C_{22}H_{26}F_3N_2OSi$ requires *M* + H^+, 419.1767).

5-(2-Benzyloxyethyl)-3-trifluoromethyl-1*H*-pyrazole 12b

The ketone **11b** (500 mg, 1.95 mmol) was boiled under reflux with hydrazine hydrate (153 mg, 1.95 mmol) in ethanol (4.6 cm^3) for 1 h. The evaporation residue, in dichloromethane, was dried and the solvent was evaporated to give the *pyrazole* **12b** (480 mg, 91%) as a pale yellow oil; δ_H 2.91 (2 H, t, *J* 5.9 Hz, pyrazole-CH_2), 3.68 (2 H, t, *J* 5.9 Hz, OCH_2CH_2), 4.51 (2 H, s, $PhCH_2O$), 6.33 (1 H, s, pyrazole 4-H), 7.2–7.4 (5 H, m, Ph-H_5); δ_F −62.35 (s); δ_C 25.96 (s, pyrazole-CH_2), 68.31 (s, OCH_2), 73.21 (s, OCH_2), 102.33 (s, pyrazole 4-C), 121.46 (q, J_{C-F} 268 Hz, CF_3), 127.75 (s, Ph 2,6-C_2), 127.91 (s, Ph 4-C), 128.48 (s, Ph 3,5-C_2), 137.44 (s, Ph 1-C), 142.66 (q, J_{C-F} 39 Hz, pyrazole 3-C), 143.02 (s, pyrazole 5-C) (HRMS: found M + H^+, 271.1058. $C_{13}H_{14}F_3N_2O$ requires *M* + H^+, 271.1058).

2-(3-Trifluoromethyl-1*H*-pyrazol-5-yl)ethanol 13

The benzyl protected compound **12b** (320 mg, 1.2 mmol) and perchloric acid (60% in water, 0.01 cm^3) in methanol (4.0 cm^3) and THF (1.0 cm^3) were treated with hydrogen in the presence of palladium on charcoal (10%, 100 mg) for 70 min. The mixture was filtered through Celite and the solvent was evaporated from the combined filtrate and methanol washings. Recrystallisation of the residue from chloroform–ethanol gave 2-(3-*trifluoromethyl*-1H-*pyrazol*-5-*yl*)*ethanol* **13** (200 mg, 94%) as a white solid; mp 85–86 °C; $\delta_H[(CD_3)_2CO]$ 2.98 (2 H, dt, *J* 0.5, 5.7 Hz, pyrazole-CH_2), 4.12 (2 H, t, *J* 5.7 Hz, CH_2O), 6.40 (1 H, br s, pyrazole 4-H); δ_F −61.83 (br s) (HRMS: found M, 180.0541. $C_6H_7F_3N_2O$ requires *M*, 180.0510. Found M − CH_2O, 150.0436. $C_5H_5F_3N_2$ requires *M* − CH_2O, 150.0404).

3-Benzyloxypropyl toluene-*p*-sulfonate 15

3-Benzyloxypropanol **14** (7.61 g, 46 mmol) was stirred with powdered potassium hydroxide (2.60 g, 46 mmol) and toluene-*p*-sulfonyl chloride (8.73 g, 46 mmol) in dry diethyl ether (50 cm^3) for 6 h. Powdered potassium hydroxide (2.0 g, 36 mmol) was added and stirring continued for a further 2.5 h. The mixture was filtered and the filtrate was washed twice with water and dried. The solvent was evaporated to give 3-*benzyloxypropyl toluene*-p-*sulfonate* **15** (13.3 g, 91%) as white crystals, mp < 25 °C; δ_H 1.88 (2 H, quintet, *J* 6.1 Hz, $CH_2CH_2CH_2$), 2.45 (3 H, s, CH_3), 3.52 (2 H, t, *J* 6.0 Hz, $BnOCH_2$), 4.19 (2 H, t, *J* 6.2 Hz, $TsOCH_2$), 4.43 (2 H, s, $PhCH_2O$), 7.25–7.35 (7 H, m, Ph-H_5 + Tol 3,5-H_2), 7.82 (2 H, d, *J* 8.3 Hz, Tol 2,6-H_2); *m/z* (CI) 321 (M + H, 17%), 181 (9), 155 (10), 91 (100).

***N*-(3-Benzyloxypropyl)-2,2,2-trifluoroacetamide 16**

Potassium *tert*-butoxide (770 mg, 6.9 mmol) was added to trifluoroacetamide (780 mg, 6.9 mmol) in THF (20 cm^3), followed by the tosylate **15** (2.0 g, 6.2 mmol) and sodium iodide (50 mg). The solution was stirred for 4 h and was then cooled to 0 °C. Diethyl ether (20 cm^3) and water (10 cm^3) were added and the mixture was acidified to pH 1 by addition of hydrochloric acid, the layers were separated and the organic phase was washed twice with water and once with brine. The solution was dried and the solvent was evaporated to give the *amide* **16** (1.67 g, 97%) as a pale yellow oil; ν_{max}(liquid film)/cm^{-1} 3350, 1715, 1170; δ_H 1.87 (2 H, m, $CH_2CH_2CH_2$), 3.50 (2 H, m, CH_2N), 3.66 (2 H, t, *J* 5.4 Hz, $BnOCH_2$), 4.45 (2 H, s, $PhCH_2O$), 7.34 (5 H, m, Ph-H_5); δ_F −76.71 (s). This material was used immediately without further characterisation.

3-Benzyloxypropylamine 17

The amide **16** (1.60 g, 5.8 mmol) was heated under reflux with sodium hydroxide (1.00 g, 50 mmol) in methanol (40 cm^3) for 4 h. The solvent was evaporated. The residue, in diethyl ether, was washed with saturated aqueous sodium hydrogen carbonate and dried. The solvent was evaporated and the residue was distilled to give the primary amine **17** (630 mg, 66%) as a colourless liquid, $bp_{0.6}$ 85–90 °C (lit.,[19] $bp_{0.75}$ 93.5 °C); δ_H 1.43 (2 H, br, NH_2), 1.75 (2 H, quintet, *J* 6.2 Hz, $CH_2CH_2CH_2$), 2.82 (2 H, t, *J* 6.8 Hz, CH_2N), 3.55 (2 H, t, *J* 6.2 Hz, $BnOCH_2$), 4.51 (2 H, s, $PhCH_2O$), 7.33 (5 H, m, Ph-H_5).

2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole 19

1,2-Bis(trifluoroacetyl)hydrazine **18** (6.94 g, 31 mmol) was mixed intimately with phosphorus pentoxide (15 g) and the mixture was covered with a further layer of phosphorus pentoxide (10 g). The mixture was heated to 300 °C in a distillation apparatus and the volatile materials were condensed in a trap at −78 °C. The distillate was redistilled (Kugelrohr) from calcium hydride to give the oxadiazole **18** (4.01 g, 74%) as a colourless liquid, bp 65 °C (lit.,[14] bp 65 °C); δ_F −65.34 (s).

3,5-Bis(trifluoromethyl)-4-(3-benzyloxypropyl)-4*H*-1,2,4-triazole 20

The oxadiazole **19** (371 mg, 1.8 mmol) was added dropwise to 3-benzyloxypropylamine **17** (300 mg, 1.8 mmol) in methanol (0.6 cm^3) at 0 °C over 5 min. The mixture was heated under reflux for 9 d. Distillation gave the *triazole* **20** (270 mg, 42%) as a colourless liquid, $bp_{0.6}$ 150–155 °C; δ_H 2.12 (2 H, m, $CH_2CH_2CH_2$), 3.57 (2 H, t, *J* 5.5 Hz, $BnOCH_2$), 4.38 (2 H, t, *J* 8.2 Hz, NCH_2), 4.51 (2 H, s, $PhCH_2O$), 7.30 (5 H, m, Ph-H_5); δ_F −62.80 (s) (HRMS: found M + H^+, 354.1041. $C_{14}H_{14}F_6N_3O$ requires *M* + H^+, 354.1041).

3-[3,5-Bis(trifluoromethyl)-4*H*-1,2,4-triazol-4-yl]propanol 21

The benzyloxypropyltriazole **20** (200 mg, 570 μmol) in ethanol (2.5 cm^3) and perchloric acid (60% in water, 0.01 cm^3) were stirred under an atmosphere of hydrogen with palladium on charcoal (10%, 30 mg) for 29 h. The catalyst was removed by filtration through Celite. Sodium hydrogen carbonate (1.0 g) was added to the combined filtrate and ethanol washings and the mixture was stirred for 1 h. The mixture was filtered and the solvent was evaporated from the filtrate to give the *alcohol* **21** (140 mg, 94%) as a white solid, mp < 25 °C; $\delta_H(D_2O)$ 2.14 (2 H, m, $CH_2CH_2CH_2$), 3.74 (2 H, t, *J* 5.8 Hz, CH_2O), 4.48 (2 H, t, *J* 7.9 Hz, NCH_2); δ_F −63.49 (s) (HRMS: found M + H^+, 264.0720. $C_7H_8F_6N_3O$ requires *M* + H^+, 264.0720).

2-Trifluoromethyl-3*H*-imidazo[4,5-*c*]pyridine 23a

3,4-Diaminopyridine **22a** (1.00 g, 9.2 mmol) was heated under reflux in trifluoroacetic acid (10 cm^3) for 2 d. Evaporation of excess reagent and sublimation (200 °C, 0.1 Torr) gave 2-trifluoromethyl-3*H*-imidazo[4,5-*c*]pyridine **23a** (1.71 g, 98%) as a white solid, mp 159–161 °C (lit.,[20] mp 290–291 °C) (Found: C, 44.70; H, 2.12; N, 22.10. $C_7H_4F_3N_3$ requires C, 44.93; H, 2.15; N, 22.46%); $\delta_H[(CD_3)_2SO]$ 7.98 (1 H, d, *J* 6.6 Hz, 7-H), 8.27 (1 H, d, *J* 6.6 Hz, 6-H), 9.25 (1 H, s, 4-H), 14.2 (1 H, br, NH); $\delta_C[(CD_3)_2SO]$ 114.32 (s, 7-C), 120.91 (q, J_{C-F} 270 Hz, CF_3), 129.42 (m, 2-C), 133.35 (s, 6-C), 142.15 (s, 4-C), 154.02 (br, C_q) (the signal for one quaternary carbon was not observed); $\delta_F[(CD_3)_2SO]$ −63.60 (s) (HRMS: found M, 187.0364. $C_7H_4F_3N_3$ requires *M*, 187.0357).

2-Trifluoromethyl-3*H*-imidazo[4,5-*b*]pyridine 23b

2,3-Diaminopyridine **22b** (1.00 g, 9.2 mmol) was heated under reflux in trifluoroacetic acid (10 cm^3) for 2 d. Evaporation of excess reagent and sublimation (200 °C, 0.1 Torr) gave 2-*trifluoromethyl*-3H-*imidazo*[4,5-b]*pyridine* **23b** (1.67 g, 97%) as a yellow solid, mp 240–241 °C; $\delta_H[(CD_3)_2SO]$ 7.48 (1 H, dd, *J* 8.4, 4.8 Hz, 6-H), 8.29 (1 H, br d, *J* 8.1 Hz, 7-H), 8.59 (1 H, dd, *J* 4.8, 1.5 Hz, 5-H), 14.6 (1 H, br, NH); $\delta_C[(CD_3)_2SO]$ 119.07 (q, J_{C-F} 271 Hz, CF_3), 119.59 (br, 6,7-C_2), 142.73 (q, J_{C-F} 44 Hz, 2-C), 145.76 (s, 5-C) (signals due to the quaternary carbons at 3a and 7a were not observed); $\delta_F[(CD_3)_2SO]$ −63.65 (s) (HRMS: found M, 187.0353. $C_7H_4F_3N_3$ requires *M*, 187.0357).

5-Fluoro-2-trifluoromethyl-1*H*-benzimidazole 23c

4-Fluorobenzene-1,2-diamine **22c** (1.00 g, 7.9 mmol) was heated under reflux in trifluoroacetic acid (10 cm^3) for 5 d. Evaporation of excess reagent and sublimation (200 °C, 12 Torr) yielded 5-fluoro-2-trifluoromethyl-1*H*-benzimidazole **23c** (1.56 g, 95%) as a white solid, mp 174–175 °C (lit.,[21] mp 219–220 °C) (Found: C, 46.80; H, 1.93; N, 13.50. $C_8H_4F_4N_2$ requires C, 47.07; H, 1.98; N, 13.72%); $\delta_H[(CD_3)_2SO]$ 7.28 (1 H, dt, *J* 9.2, 2.1 Hz, 6-H), 7.56 (1 H, br d, *J* 8.9 Hz, 7-H), 7.79 (1 H, m, 4-H), 14.2 (1 H, br, NH); $\delta_F[(CD_3)_2SO]$ −63.20 (s, CF_3), −116.79 (br m, 5-F) (HRMS: found M^+, 204.0321. $C_8H_4F_4N_2$ requires *M*, 204.0311).

2,5-Bis(trifluoromethyl)-1*H*-benzimidazole 23d

4-(Trifluoromethyl)benzene-1,2-diamine **22d** (1.00 g, 5.68 mmol) was heated under reflux in trifluoroacetic acid (10 cm^3) for 5 d. Evaporation of excess reagent and sublimation (150 °C, 10 Torr) afforded 2,5-bis(trifluoromethyl)-1*H*-benzimidazole **23d** (1.24 g, 89%) as a white solid, mp 159–161 °C (lit.,[22] 198–199 °C) (Found: C, 42.60; H, 1.55; N, 11.10. $C_9H_4F_6N_2$ requires C, 42.54; H, 1.59; N, 11.02%); $\delta_H[(CD_3)_2SO]$ 7.72 (1 H, dd, *J* 8.8, 1.8 Hz, 6-H), 7.95 (1 H, d, *J* 8.4 Hz, 7-H), 8.16 (1 H, br s, 4-H), 14.3 (1 H, br, NH); $\delta_F[(CD_3)_2SO]$ −63.44 (s, 2-CF_3), −59.72 (br s, 5-CF_3) (HRMS: found M, 254.0254. $C_9H_4F_6N_2$ requires *M*, 254.0279).

Studies on the effect of pH on ^{19}F NMR chemical shift

The heterocycles (*ca.* 2 mg) were dissolved in aqueous buffers (*ca.* 1 cm^3) of various compositions and pHs. The ^{19}F NMR spectra of samples (0.6 cm^3) were acquired using a JEOL EX400 spectrometer. An external reference (the $CF^{35}Cl_3$ signal in fluorotrichloromethane in deuteriochloroform) was used before and after each determination but no drift was noted. The chemical shifts were found to be independent of the composition of the inorganic buffers and independent of the concentrations of the buffers and trifluoromethylheterocycle in the range 100 to 400 mM for the buffer and 5 to 20 mM for the trifluoromethyl heterocycles. The effect of temperature was insignificant in the range 25 to 37 °C, so spectra were recorded routinely at 25 °C. Each determination of δ_F was performed in triplicate for each pH value. The pHs of the solutions containing the test compound, the buffer and 5% D_2O were measured immediately before the NMR experiments, using a pH meter with an electrode suitable for small volumes. 132K Data points were used in each NMR data acquisition to ensure high digital resolution (*ca.* 0.4 Hz per data point).

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References

1 J. Elguero, *Pyrazoles and their Benzo Derivatives*, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5, p. 291; B. J. Gaede and L. L. McDermott, *J. Heterocycl. Chem.*, 1993, **30**, 49.
2 X.-Q. Tang and C.-M. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2161; M. Schlosser, *Tetrahedron*, 1978, **34**, 3; J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
3 S. P. Singh, D. Kumar, Savita and M. D. Threadgill, *Indian J. Chem., Sect. B*, 1992, **31**, 233; B. G. Jones, S. K. Branch, M. D. Threadgill and D. E. V. Wilman, *J. Fluorine Chem.*, 1995, **74**, 221.
4 M. D. Threadgill, A. K. Heer and B. G. Jones, *J. Fluorine Chem.*, 1993, **65**, 21.
5 T. C. Jenkins, M. A. Naylor, P. O'Neill, M. D. Threadgill, S. Cole, I. J. Stratford, G. E. Adams, E. M. Fielden, M. J. Suto and M. J. Steir, *J. Med. Chem.*, 1990, **33**, 2603; L. M. Cobb, J. Nolan and S. A. Butler, *Br. J. Cancer*, 1990, **62**, 915; R. El Gamoussi, M. D. Threadgill, M. Prade, I. J. Stratford and M. Guichard, *Cancer Chemother. Pharmacol.*, 1993, **31**, 277; M. Scobie and M. D. Threadgill, *J. Org. Chem.*, 1994, **59**, 7008; R. J. Hodgkiss, J. Parrick, M. Porssa and M. R. L. Stratford, *J. Med. Chem.*, 1994, **37**, 4352; K. Ramalingam, N. Raju, P. Nanjappan and D. P. Nowotnik, *Tetrahedron*, 1995, **51**, 2875; E. O. Aboagye, A. D. Lewis, A. Johnson, P. Workman, M. Tracy and I. M. Huxham, *Br. J. Cancer*, 1995, **72**, 312; D. H. Swenson, B. H. Laster and R. L. Metzger, *J. Med. Chem.*, 1996, **39**, 1540.
6 L. C. Behr, R. Fusco and C. H. Jarboe, *Pyrazoles, pyrazolines, indazoles and condensed rings*, Interscience, New York, 1967; R. H. Wiley and P. E. Hexner, *Org. Synth.*, 1963, Coll. Vol. IV, 351; K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 1946, 953; R. J. Linderman and K. S. Kirrollos, *Tetrahedron Lett.*, 1989, **30**, 2049; B. Jiang, Y. Y. Xu and J. Yang, *J. Fluorine Chem.*, 1994, **67**, 83.
7 O. Renn, L. M. Venanzi, A. Marteletti and V. Gramlich, *Helv. Chim. Acta*, 1995, **78**, 993; P. P. K. Claire, P. L. Coe, C. J. Jones and J. A. McCleverty, *J. Fluorine Chem.*, 1991, **51**, 283.
8 M. Hojo, R. Masuda, S. Sakaguchi and M. Tagakawa, *Synthesis*, 1986, 1016.
9 X.-Q. Tang and C.-M. Hu, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1039.
10 D. Delorne, Y. Girard and J. Rokech, *J. Org. Chem.*, 1986, **54**, 3635.
11 W. S. Johnson, K. Wiedhaup, S. F. Brady and G. L. Olson, *J. Am. Chem. Soc.*, 1974, **96**, 3979.
12 M. Pesson, S. Dupin and M. Antoine, *Bull. Soc. Chim. Fr.*, 1962, 1364.
13 M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 1952, 3418.
14 D. B. Reitz and M. J. Finkes, *J. Heterocycl. Chem.*, 1989, **26**, 225.
15 J. Elguero, G. I. Yranzo, J. Laynez, P. Jiménez, M. Menéndez, J. Catalán, J. L. G. de Paz, F. Anvia and R. W. Traft, *J. Org. Chem.*, 1991, **56**, 3942.
16 J. W. A. M. Janssen, C. G. Kruse, H. J. Koeners and C. L. Habraken, *J. Heterocycl. Chem.*, 1973, **10**, 1055.
17 J. Elguero, A. Fruchier, N. Jagerovic and A. Werner, *Org. Prep. Proced. Int.*, 1994, **26**, 35.
18 *CRC Handbook of Chemistry and Physics*, ed. R. C. Weast, CRC Press Inc., Cleveland, 1978, p D148.
19 W. P. Utermohlen, *J. Am. Chem. Soc.*, 1945, **67**, 1505.
20 W. T. Smith and E. C. Steinle, *J. Am. Chem. Soc.*, 1953, **75**, 1292.
21 L. R. Mandel, C. C. Porter and F. A. Kuehl, *J. Med. Chem.*, 1970, **13**, 1043.
22 *Br. Pat.*, 1 114 199, 1968.

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