The reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione with hydrazines: a re-investigation

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(Received June 16, 1992; accepted February 9, 1993)

Abstract

The reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione with hydrazine (N_2H_4) in boiling ethanol gives 3,5-bis(trifluoromethyl)pyrazole but reaction with *N*-aryl or *N*-aroyl hydrazines gives the 1-aryl- or 1-aroyl-3,5-bis(trifluoromethyl)-4,5-dihydro-5-hydroxypyrazoles, as shown by NMR and mass spectra, in contrast to a previous report.

Introduction

During a programme of synthesis of (trifluoromethyl)heterocycles for medicinal and pH sensor applications [1], 3,5-bis(trifluoromethyl)pyrazole (**4a**) and its 1-substituted analogues were required. Preparation of the parent compound **4a** has been reported to have been carried out by reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1**) with hydrazine (**2a**) under various conditions [2–4] and by dipolar cycloaddition of 2-diazo-1,1,1-trifluoroethane with 3,3,3-trifluoropropyne [5]. Synthesis of 1-aryl and 1-aroyl-3,5-bis(trifluoromethyl)pyrazoles **4b–e** has hitherto only been claimed by Claire *et al.* [2] by reaction of substituted hydrazines **2b–e** with diketone **1** in boiling ethanol. Since it is difficult to rationalise the spectroscopic data reported [2] with the aromatic pyrazole claimed, and in view of our observations [1] that treatment of heteroarylhydrazines with 1,1,1-trifluoropentane-2,4-dione sometimes affords only the partial condensation products, i.e. the 5-hydroxy-4,5-dihydropyrazoles, a re-investigation of the reaction of **1** with hydrazines **2a–e** was undertaken.

Results and discussion

Treatment of 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1**) with an equimolar amount of hydrazine hydrate in refluxing ethanol gave, as predicted, 3,5-bis(trifluoromethyl)pyrazole (**4a**) as volatile white crystals with a distinctive odour. The ^{1}H NMR spectrum was consistent with an aromatic pyrazole structure. The 4-H atom gives a resonance at δ 6.95, which is slightly broadened by coupling to ^{19}F. Only one ^{19}F NMR signal was evident for **4a**, owing to rapid site exchange of the NH proton. The electron-impact mass spectrum of this pyrazole showed an abundant molecular ion at *m/z* 204, with no evidence of ions at higher mass (e.g. *m/z* 218 for the hydroxydihydropyrazole structure).

However, the ^{1}H NMR spectra of the heterocycles formed from **1** and the substituted hydrazines **2b–e** showed no signal in the region expected for the 4-H atom of an aromatic pyrazole (δ 5.8–δ 7.2) [1, 6]. Claire *et al.* [2] also report no signals in this region but claim that 4-H resonates at $\delta \sim 3.6$; no integral or multiplicity data were given. The extensive study by Tensmeyer and Ainsworth [6] of substituent effects on the chemical shifts in pyrazoles does not support this assignment. In our work, the signals in the region δ 3–δ 4 comprised two doublets, the integral of each doublet corresponding to one proton. The coupling constants between these doublets were >14 Hz, typical values for geminal coupling. Thus these signals can be assigned to a prochiral CH_2 group in an asymmetric environment. Broad resonances due to OH were also observed. On the basis of these data, the hydroxydihydropyrazole structures **3b–e** are proposed, rather than the pyrazoles **4b–e** claimed [2].

The electron-impact (EI) mass spectra of the 5-hydroxydihydropyrazoles **3c–e** at 70 eV ionisation energy revealed abundant molecular ions. The molecular ion of **3b** was present in the EI spectrum only at 1% abundance, but abundant ions were observed at *m/z* 326 (M) in the chemical ionisation (CI) spectrum and at *m/z* 327 (M+H) in the positive ion fast atom bom-

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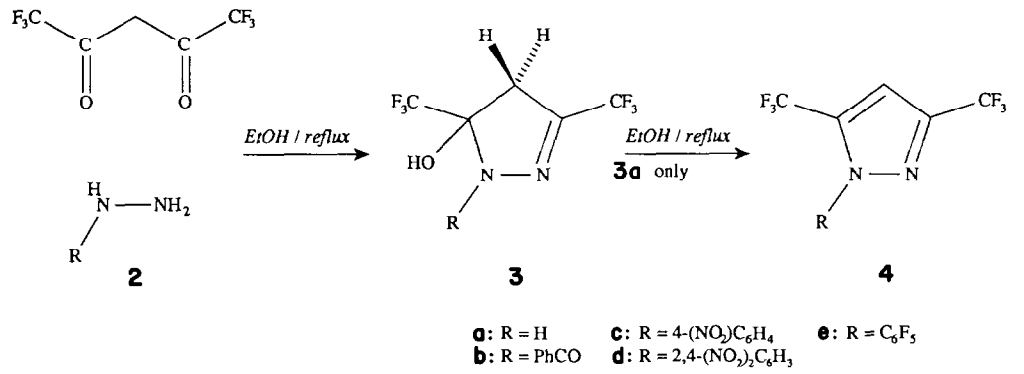

Scheme 1. Reaction of hydrazines with 1,1,1,5,5,5-hexafluoropentane-2,4-dione in boiling ethanol.

bardment (FAB) spectrum. Dehydration was not favoured (giving M-18) but loss of $\cdot CF_3$ gave highly abundant peaks at (M − 69) in all cases. The reported interpretation [2] of similar data, representing the ions at highest mass as molecular clusters of (pyrazole + H_2O), should be regarded as unlikely under EI conditions.

Experimental

^1H NMR spectra were obtained at 270 MHz and 400 MHz using JEOL GX270 and JEOL EX400 spectrometers, respectively (solvent, $CDCl_3$; internal standard, $SiMe_4$). The ^{19}F NMR spectrum was obtained at 84.25 MHz using a JEOL FX90Q spectrometer (solvent, H_2O/phosphate buffer pH 7.3; external standard, $NaPF_6$ in phosphate buffer pH 7.3). Low-resolution EI, CI (isobutane) and FAB and high-resolution EI mass spectra were furnished by a VG 7070 spectrometer, whereas a ZAB-E instrument gave the high-resolution FAB spectrum. Solvents were evaporated under reduced pressure, except where noted.

3,5-Bis(trifluoromethyl)pyrazole (4a)

1,1,1,5,5,5-Hexafluoropentane-2,4-dione (**1**) (4.16 g, 20 mmol) was added to hydrazine hydrate (**2a**) (1.2 g, 24 mmol) in ethanol (50 ml). The mixture was boiled under reflux for 18 h and allowed to cool. The solvent was distilled off carefully at atmospheric pressure. The residue was distilled at atmospheric pressure. The distillate, in dichloromethane, was dried (anhydrous $MgSO_4$) and filtered and the solvent evaporated to give **4a** (1.04 g, 25%) as white crystals, m.p. 69–70 °C (lit. [2] m.p. 71–72 °C). ^1H NMR (270 MHz) δ: 6.95 (br s, 1H, 4-H); 11.97 (br, 1H, NH) ppm. ^{19}F NMR δ: +10.92 (s, 6F, 2×CF_3) ppm. MS (EI) *m/z*: 204 (M); 185; 154; 69.

1-Benzoyl-3,5-bis(trifluoromethyl)-4,5-dihydro-5-hydroxypyrazole (3b)

1,1,1,5,5,5-Hexafluoropentane-2,4-dione (**1**) (300 mg, 1.44 mmol) was added to benzoyl hydrazide (**2b**) (136 mg, 1 mmol) in ethanol (50 ml). The mixture was boiled under reflux for 5 h and allowed to cool. The solvent was evaporated to give **3b** (315 mg, 96%) as a white solid, m.p. 82–84 °C (lit. [2] m.p. 84–85 °C claimed for pyrazole **4b**). ^1H NMR (270 MHz) δ: 3.38 (d septet, 1H, J_{H-H} = 19.5 Hz, J_{H-F} = 1.5 Hz, pyrazole 4-H); 3.56 (br d, 1H, J_{H-H} = 19.5 Hz, pyrazole 4-H); 6.43 (br s, 1H, OH); 7.47 (*c.* t, 2H, J = 7.5 Hz, Ar 3,5-H_2); 7.59 (tt, 1H, J = 7.5 Hz, J = 1.3 Hz, Ar 4-H); 7.86 (*c.* d, 2H, J = 7.5 Hz, Ar 2,6-H_2) ppm. MS (EI) *m/z*: 326 (M, 1%); 105 (PhCO, 100%). MS (CI) *m/z*: 326 (M). MS (FAB; +ve ion) *m/z*: 327.0599 (M + H) ($C_{12}H_9F_6N_2O_2$ requires: 327.0568).

3,5-Bis(trifluoromethyl)-4,5-dihydro-5-hydroxy-1-(4-nitrophenyl)pyrazole (3c)

The dione **1** (300 mg, 1.44 mmol) was added to 4-nitrophenylhydrazine (**2c**) (200 mg, 1.3 mmol) in ethanol (50 ml). The mixture was boiled under reflux for 3 h and allowed to cool. The solvent was evaporated to give **3c** (410 mg, 92%) as a yellow solid, m.p. 105–106 °C (lit. [2] m.p. 105–108 °C claimed for pyrazole **4c**). ^1H NMR (270 MHz) δ: 3.42 (d septet, 1H, J_{H-H} = 19.6 Hz, J_{H-F} = 1.5 Hz, pyrazole 4-H); 3.74 (br d, 1H, J_{H-H} = 19.6 Hz, pyrazole 4-H); 5.75 (br, 1H, OH); 7.60 (d, 2H, J = 9.4 Hz, Ar 2,6-H_2); 8.12 (d, 2H, J = 9.4 Hz, Ar 3,5-H_2) ppm. MS (EI) *m/z*: 343 (M); 274 (100%); 228. Analysis: Found: C, 38.70; H, 2.03; N, 12.50%. $C_{11}H_7F_6N_3O_3$ requires: C, 38.48; H, 2.06; N, 12.25%.

3,5-Bis(trifluoromethyl)-4,5-dihydro-1-(2,4-dinitrophenyl)-5-hydroxypyrazole (3d)

The dione **1** (208 mg, 1.0 mmol) was added to 2,4-dinitrophenylhydrazine (**2d**) (260 mg, 1.3 mmol) in ethanol (60 ml). The mixture was boiled under reflux for 5 h and allowed to cool. Evaporation of the solvent gave a gum which was extracted with methanol. Evap-

oration of the methanol gave **3d** (300 mg, 77%) as a viscous orange oil which crystallised on standing to an orange–yellow solid, m.p. 81–83 °C (lit. [2] m.p. 82–83 °C claimed for pyrazole **4d**) ^{1}H NMR (400 MHz) δ: 3.06 (d, 1H, J=14.6 Hz, pyrazole 4-H); 3.18 (d, 1H, J=14.6 Hz, pyrazole 4-H); 5.1 (br, 1H, OH); 8.04 (d, 1H, J=9.5 Hz, Ar 6-H); 8.40 (dd, 1H, J=9.5 Hz, J=2.4 Hz, Ar 5-H); 9.14 (d, 1H, J=2.4 Hz, Ar-3-H) ppm. MS, (EI) *m/z*: 388.0179 (M) ($C_{11}H_6F_6N_4O_5$ requires: 388.0242); 291.0327 ($M-CF_3CO\cdot$) ($C_9H_6F_3N_4O_4$ requires: 291.0341).

3,5-Bis(trifluoromethyl)-4,5-dihydro-5-hydroxy-1-(pentafluorophenyl)pyrazole (3e)

The dione **1** (300 mg, 1.44 mmol) was added to pentafluorophenylhydrazine (**2e**) (198 mg, 1.0 mmol) in ethanol (50 ml). The mixture was boiled under reflux for 5 h and allowed to cool. The solvent was evaporated to give **3e** (355 mg, 91%) as colourless prisms, m.p. 61–62 °C (lit. [2] m.p. 60–62 °C claimed for pyrazole **4e**). ^{1}H NMR (400 MHz) δ: 3.32 (br d, 1H, J=18.9 Hz, pyrazole 4-H); 3.59 (dq, 1H, J_{H-H}=18.9 Hz, J_{H-F}=1.5 Hz, pyrazole 4-H); 6.13 (br s, 1H, OH) ppm. MS (EI) *m/z*: 388.0099 (M) ($C_{11}H_3F_{11}N_2O$ requires: 388.0070); 319 (100%); 299.

Conclusions

Whereas condensation of hydrazine (**2a**) with 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**1**) in boiling ethanol gives the aromatic pyrazole **4a**, treatment of this dione with more hindered and less nucleophilic aryl- and acyl-hydrazines gives only the partial condensation products, the 4,5-dihydro-5-hydroxypyrazoles **3b–e**. A previous report [2] of the formation of the 1-substituted pyrazoles **4b–e** must be regarded as erroneous. The conditions required to effect the dehydration **3b–e** → **4b–e** are under investigation.

Acknowledgements

The authors thank Dr Sarah K. Branch (University of Bath) for help with the ^{19}F NMR spectrum, Dr J.A. Ballantine and the S.E.R.C. Mass Spectrometry Centre (University College, Swansea) for the high-resolution FAB mass spectrum and Professor S.P. Singh (Kurukshetra University, India) for helpful discussions. This work has been taken in part from the undergraduate B. Pharm. project of A.K.H. and was supported in part by S.E.R.C.

References

1 S.P. Singh, D. Kumar, Savita and M.D. Threadgill, *Indian J. Chem., 31B* (1992) 233.
2 P.P.K. Claire, P. Coe, C.J. Jones and J.A. McCleverty, *J. Fluorine Chem., 51* (1991) 283.
3 S. Trofimenko, *J. Am. Chem. Soc., 89* (1967) 3165.
4 D.H. O'Brien and C.-P. Hrung, *J. Organomet. Chem., 27* (1971) 185.
5 J.H. Atherton and R. Fields, *J. Chem. Soc. C,* (1968) 1507.
6 L.G. Tensmeyer and C. Ainsworth, *J. Org. Chem., 31* (1966) 1878.