Heterocyclic Polyfluoro-compounds. Part 26.[1] Synthesis of 3,6-Bistrifluoromethyl-pyridazines and -dihydropyridazines

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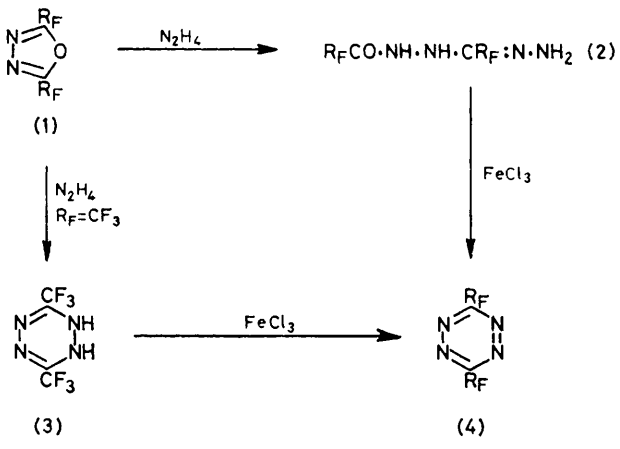
Bistrifluoromethyl-*s*-tetrazine reacts with styrene to yield 4-phenyl-3,6-bistrifluoromethyl-1,4-dihydropyridazine, with cyclohexene to give 3,8-bistrifluoromethyl-1,3a,4,5,6,7-hexahydrophthalazine, with 2,3-dimethylbut-2-ene to yield 4,4,5,5-tetramethyl-3,6-bistrifluoromethyl-4,5-dihydropyridazine and with norbornadiene to give, it is tentatively proposed, 2,5-bistrifluoromethyl-3,4-diazabicyclo[4.3.0]nona-1,4,8-triene, plus 3,6-bistrifluoromethylpyridazine. The last compound is formed by reaction of the tetrazine with acetylene, and 4-methyl- and 4,5-bistrimethylstannyl-3,6-bistrifluoromethyl-pyridazines are formed by reaction with propyne and with bistrimethylstannylacetylene, respectively.

Reaction of the tin compound with iodine and with chlorine yields 4,5-di-iodo- and -dichloro-3,6-bistrifluoromethylpyridazine, respectively, and the latter compound yields perfluoro-3,6-dimethylpyridazine with potassium fluoride.

Perfluoro-3,6-dimethylpyridazine rearranges photochemically in the vapour phase into perfluoro-2,5-dimethylpyrazine.

SINCE the report of Carboni and Lindsey of cycloaddition reactions of *s*-tetrazines to acetylenes and olefins, as a route to pyridazines (Scheme 1) such reactions have been

SCHEME 1

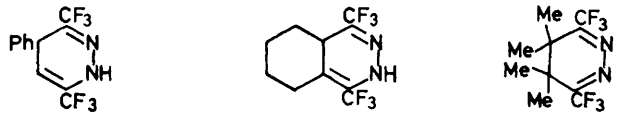


SCHEME 2

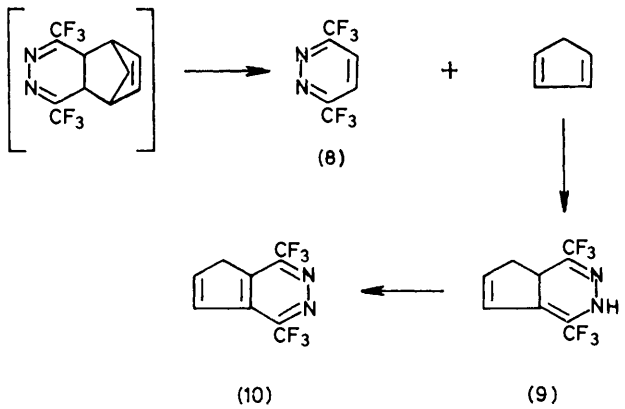
extensively studied.[2] Related reactions of bistrifluoromethyl-*s*-tetrazine have now been investigated as part of a study of routes to trifluoromethyl-substituted pyridazines.

The desired tetrazine had earlier been obtained pure only with difficulty and in poor yield by the reaction of tetrazinedicarboxylic acid with sulphur tetrafluoride.[3] Brown and his co-workers[4] described a number of examples of reactions of hydrazine in ethanol with the perfluoroalkyl oxadiazoles (1) [$(R_F)_2 = (C_2F_5)_2$; $(n\text{-}C_3F_7)_2$; and CF_3, C_3F_7]; oxidation of the products (2) of the last two with ferric chloride gave the tetrazines (4) in only 35 and 7% yield respectively. However, we found, surprisingly, that the bistrifluoromethyl analogue of (1) yields the dihydropyridazine (3), which is readily oxidised in 80% yield by anhydrous ferric chloride or nitrogen dioxide to bistrifluoromethyl-*s*-tetrazine (4; $R_F = CF_3$), a highly volatile, bright red crystalline solid, with a purple vapour (Scheme 2).

Vapour-phase photolysis of 3,6-bistrifluoromethyl-*s*-tetrazine gave trifluoroacetonitrile quantitatively. The tetrazine reacted rapidly with styrene to give (5), with



cyclohexene to give (6), and with 2,3-dimethylbut-2-ene to give (7). The initial adduct from norbornadiene was



SCHEME 3

apparently unstable, since 3,6-bistrifluoromethylpyridazine (8) was isolated, together with small amounts of an adduct (9), apparently derived from the cyclopentadiene

[1] Part 25, M. G. Barlow, D. E. Brown, and R. N. Haszeldine, *J.C.S. Perkin I*, 1978, 363.

[2] R. A. Carboni and R. V. Lindsey, *J. Amer. Chem. Soc.*, 1959, **81**, 4342. See, for example, J. Sauer and G. Heinrichs, *Tetrahedron Letters*, 1966, 4979, and P. L. Watson and R. N. Warrener, *Austral J. Chem.*, 1973, **26**, 1725, where much of the earlier work is cited.

[3] S. J. Weininger and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 2050.

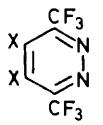
[4] H. C. Brown, H. J. Gisler, and M. T. Çheng, *J. Org. Chem.*, 1966, **31**, 781.

liberated, and readily oxidised to (10) (Scheme 3). It has been reported that tetrafluoroethyl-*s*-tetrazine (4) (R_F = CHF·CF_3) forms a bis-adduct by addition to both double bonds of norbornadiene,[2] but a related cleavage reaction when diphenyl-*s*-tetrazine reacts with 3,6-epoxy-3,6-dihydrotribenzocycloheptatrienone has recently been described.[5]

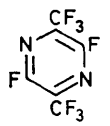
Acetylene reacts with bistrifluoromethyl-*s*-tetrazine to give the pyridazine (8), and propyne yields the expected 4-methylpyridazine. The pyridazine (11a), obtained by reaction with bistrimethylstannylacetylene provided a convenient source of 4,5-dihalogenopyridazines (11b) and (11c), since the trimethyltin groups could be readily cleaved by iodine or chlorine. Nucleophilic displacement of chlorine by fluorine in (11c) occurred readily with anhydrous potassium fluoride at 160 °C, yielding perfluoro-3,6-dimethylpyridazine (11d).

Bistrifluoromethyl-*s*-tetrazine is thus particularly reactive in cycloaddition reactions with olefins and acetylenes, where the tetrazine acts as the diene in a Diels–Alder reaction subject to inverse electron demand.

Pyridazine (11d) yielded pyrazine (12) upon vapour-phase irradiation in accord with other studies [6] of this type of photochemical rearrangement *via* unstable *para*-bonded isomers.



(11) a; X = $SnMe_3$
b; X = I
c; X = Cl
d; X = F



(12)

EXPERIMENTAL

Volatile materials were manipulated in a Pyrex vacuum system. Products were identified by elemental analysis, i.r. spectroscopy (Perkin-Elmer model 257), u.v. spectroscopy (Hilger and Watts Ultrascan or Unican SP 700), n.m.r. spectroscopy (Perkin-Elmer R10 or Hitachi–Perkin-Elmer model R 20A operating at 60.00 MHz for protons and 56.46 MHz for ^{19}F nuclei), mass spectrometry (A.E.I. model MS/902 at 70 eV), and g.l.c. (Pye 104 instrument). Molecular weights were obtained by mass spectrometry.

Preparation of 3,6-*Bis*(*trifluoromethyl*)-s-*tetrazine*.—2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole (20.4 g, 99 mmol), prepared by the method of Brown *et al.*,[7] was added dropwise with stirring to a solution of anhydrous hydrazine (38 ml) in 96% ethanol (37 ml) at 0 °C. After ½ h, the solution was adjusted to pH 6 with conc. hydrochloric acid, then dilute hydrochloric acid was added until crystallisation occurred. The product was washed with water, dried over P_2O_5, and sublimed at 0 °C *in vacuo* to give 3,6-*bistrifluoromethyl*-1,2-*dihydro*-s-*tetrazine* (6.6 g, 30 mmol, 30%) (Found: C, 22.1; H, 1.1; F, 52.1; N, 25.2%; *M*, 220.017 7. $C_4H_2F_6N_4$ requires C, 21.8; H, 0.9; F, 51.7; N, 25.5%; *M*, 220.018 2), as pale yellow needles, m.p. 126—127 °C, δ_F 8.4 p.p.m.,* and τ 2.13 (NH, $CDCl_3$ solution).

The dihydrotetrazine (5 g, 23 mmol) was passed *in vacuo* through a column loosely packed with anhydrous ferric chloride and the product was fractionated *in vacuo* to give 3,6-bistrifluoromethyl-*s*-tetrazine (4.0 g, 18 mmol, 80%) (Found: F, 52.3%; *M*, 218. Calc. for $C_4F_6N_4$: F, 52.3%; *M*, 218) as deep red plates with a purple vapour (3 mmHg at 22 °C), $\lambda_{max.}$ (vapour) 245 and 520 nm, δ_F 10.5 p.p.m.

Diels–Alder Reactions of 3,6-*Bistrifluoromethyl*-s-*tetrazine*.—(*a*) *With styrene*. To bistrifluoromethyl-*s*-tetrazine (80 mg, 0.37 mmol), kept at 0 °C *in vacuo*, was slowly admitted styrene as the vapour. The reaction, as indicated by the loss of red colour of the tetrazine was complete after 1 h and gave nitrogen (100%) and, after sublimation *in vacuo*, 4-*phenyl*-3,6-*bistrifluoromethyl*-1,4-*dihydropyridazine* (102 mg, 0.35 mmol, 95%) (Found: C, 49.0; H, 2.8; F, 38.6; N, 9.2%; *M*, 294. $C_{12}H_8F_6N_2$ requires C, 49.0; H, 2.7; F, 38.8; N, 9.5%; *M*, 294), as colourless crystals, m.p. 105 °C, $\nu_{max.}$ 3 323 (NH str), 1 653 w (C=N str), and 1 604 cm^{-1} (C=C str), δ_F 8.4 and 10.0 p.p.m. and τ 1.4 (NH), *ca.* 1.9 (C_6H_5), 3.68 (=CH, *J* 6 Hz), and 4.82 (CHPh, *J* 6 Hz).

(*b*) *With cyclohexene*. The tetrazine (0.49 g, 2.25 mmol) and cyclohexene (0.50 g) gave after 1 h, removal of unchanged cyclohexene, and sublimation *in vacuo*, 3,8-*bistrifluoromethyl*-1,3a,4,5,6,7-*hexahydrophthalazine* (0.54 g, 1.98 mmol; 88%) (Found: C, 44.2; H, 3.9; F, 41.5; N, 10.1%; *M*, 272. $C_{10}H_{10}F_6N_2$ requires C, 44.1; H, 3.7; F, 41.9; N, 10.3%; *M*, 272), as colourless crystals, m.p. 65 °C with $\nu_{max.}$ 3 320 (NH str) and 1 650 cm^{-1} (C=N str).

(*c*) *With* 2,3-*dimethylbut*-2-*ene*. The tetrazine (0.54 g, 2.48 mmol) and 2,3-dimethylbut-2-ene (0.8 g) gave after 2 weeks *in vacuo*, removal of the excess of the butene, and of nitrogen, and sublimation, 4,4,5,5-*tetramethyl*-3,6-*bistrifluoromethyl*-4,5-*dihydropyridazine* (0.62 g, 2.26 mmol, 91%) (Found: C, 43.7; H, 4.5; F, 41.6; N, 10.2%; *M*, 274. $C_{10}H_{12}F_6N_2$ requires C, 43.8; H, 4.4; F, 41.6; N, 10.2%; *M*, 274), as pale yellow crystals, m.p. 62—63 °C, $\nu_{max.}$ 1 460 cm^{-1} (C=N str), $\lambda_{max.}$ (Et_2O) 232 (ε 1 250) and 263 nm (700); δ_F 11.8 p.p.m. and τ 8.37.

(*d*) *With norbornadiene*. The tetrazine (85 mg, 0.39 mmol) and norbornadiene (35 mg, 0.38 mmol) were sealed *in vacuo*, and warmed slowly to room temperature overnight. 3,6-Bistrifluoromethylpyridazine (50 mg, 0.23 mmol, 59%) was removed *in vacuo* and identified by i.r. spectroscopy. The yellow residue (10 mg) was sublimed to give a compound tentatively identified as 2,5-bistrifluoromethyl-3,4-diazabicyclo[4.3.0]nona-1,4,8-triene, which upon storage was oxidised to orange crystals of 4,7-*bistrifluoromethyl*-5,6-*diazaindene* (Found: *M*, 254.027 6. $C_9H_4F_6N_2$ requires *M*, 254.027 7), m.p. 119—120 °C.

(*e*) *With acetylene*. The tetrazine (0.26 g, 1.19 mmol) was allowed to stand in an atmosphere of acetylene (200 mmHg) for 48 h, when 3,6-*bistrifluoromethylpyridazine* (0.20 g, 0.93 mmol, 79%) condensed at 0 °C as large colourless needles (Found: C, 33.5; H, 1.1; F, 52.6; N, 12.9%; *M*, 216. $C_6H_2F_6N_2$ requires C, 33.3; H, 0.9; F, 52.8; N, 13.0%; *M*, 216), m.p. 56.5 °C, with $\nu_{max.}$ 3 050w (CH str) and 1 590 cm^{-1}; δ_F 10.0 p.p.m. and τ 1.08.

(*f*) *With propyne*. The tetrazine (0.24 g, 1.10 mmol) and propyne (0.048 g, 1.20 mmol) sealed *in vacuo* at room temperature for 10 days gave 4-*methyl*-3,6-*bistrifluoromethylpyridazine* (0.23 g, 1.00 mmol, 91%) (Found: C, 36.9; H, 2.0; F, 49.1; N, 12.0%; *M*, 230. $C_7H_4F_6N_2$ requires C, 36.5; H, 1.7; F, 49.6; N, 12.2%; *M*, 230), as colourless crystals, m.p. 25 °C, with δ_F 11.1 and 13.3 p.p.m.; τ 1.37 (CH) and 6.58 (CH_3).

* Positive values to low field of external trifluoroacetic acid.

[5] T. Sasaki, K. Kanamatsu, K. Iizuka, and I. Ando, *J. Org. Chem.*, 1976, **41**, 1425.
[6] R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 1975, 1130.
[7] H. C. Brown, M. T. Cheng, L. J. Parcell, and D. Pilipovich, *J. Org. Chem.*, 1961, **26**, 4407.

(*g*) *With bis(trimethylstannyl)acetylene.* The acetylene (6.75 g, 19.2 mmol) and the tetrazine (4.26 g, 19.5 mmol) in diethyl ether (25 ml), sealed at 0 °C *in vacuo* for 2 days, gave a solid, which was separated, washed with a little dry carbon tetrachloride, and dried at the pump to give 3,6-*bistrifluoromethyl*-4,5-*bistrimethylstannylpyridazine* (8.08 g, 14.9 mmol, 78%) (Found: C, 26.6; H, 3.4; F, 20.9; N, 5.1. $C_{12}H_{18}F_6N_2Sn_2$ requires C, 26.6; H, 3.3; F, 21.1; N, 5.2%) as pale yellow cubes, m.p. 164—165 °C, with δ_F 16.5 p.p.m. and τ 8.73.

Photolysis of 3,6-*Bistrifluoromethyl*-s-*tetrazine.*—The tetrazine (50 mg, 0.23 mmol) irradiated at 254 nm in the vapour phase (6 mmHg) for 4 h gave a quantitative yield of nitrogen (0.23 mmol) and trifluoroacetonitrile (0.44 mg, 0.46 mmol).

Preparation of 4,5-*Di-iodo*-3,6-*bistrifluoromethylpyridazine.*— 3,6-Bistrifluoromethyl-4,5-bistrimethylstannylpyridazine (54 mg, 0.10 mmol) and iodine (49 mg, 0.19 mmol) in carbon tetrachloride (10 ml), sealed *in vacuo* and heated at 70 °C for 3 days, gave, after removal of the solvent *in vacuo*, a residue which was sublimed to give 4,5-*di-iodo*-3,6-*bistrifluoromethylpyridazine* (40 mg, 0.085 mmol, 85%) (Found, C, 15.7; I, 54.6%; *M*, 468. $C_6F_6I_2N_2$ requires C, 15.4; I, 54.2%; *M*, 468) as pale yellow crystals, m.p. 105 °C.

Preparation of 4,5-*Dichloro*-3,6-*bistrifluoromethylpyridazine.*—The tin-substituted pyridazine (6.7 g, 12.4 mmol) and chlorine (1.76 g, 25.0 mmol) in carbon tetrachloride (20 ml), were sealed *in vacuo* and warmed from −196 to −78 °C, and then slowly to room temperature over 4 days. The tube was then opened, material volatile at 0 °C removed *in vacuo*, and the residue was then fractionated *in vacuo* to give 4,5-*dichloro*-3,6-*bistrifluoromethylpyridazine* (2.91 g, 10.2 mmol, 82%) (Found: C, 25.2; Cl, 24.4; F, 39.5; N, 9.5%; *M*, 284. $C_6Cl_2F_6N_2$ requires C, 25.3; Cl, 24.9; F, 40.0; N, 9.8%; *M*, 284) as colourless cubic crystals, m.p. 60 °C, with $\lambda_{max.}$ (CCl_4 solution) 304 nm (ε 340) and δ_F 12.5 p.p.m.

Preparation of 4,5-*Difluoro*-3,6-*bistrifluoromethylpyridazine.*—4,5-Dichloro-3,6-bistrifluoromethylpyridazine (2.9 g, 10.2 mmol) and dry potassium fluoride (35 g), sealed in a 300 ml Pyrex tube and heated at *ca.* 160 °C for 4 days, gave, after fractionation *in vacuo*, 4,5-*difluoro*-3,6-*bistrifluoromethylpyridazine* (2.41 g, 9.6 mmol, 94%) (Found: C, 28.7; F, 60.3; N, 11.1%; *M*, 252. $C_6F_8N_2$ requires C, 28.6; F, 60.3; N, 11.1%; *M*, 252), as a colourless liquid which condensed at −24 °C, with δ_F 11.8 (CF_3) and −66.8 p.p.m. (CF).

Photochemical Rearrangement of 4,5-*Difluoro*-3,6-*bistrifluoromethylpyridazine* (With G. Lucas).—The title pyridazine (2.15 g, 8.5 mmol) and argon (100 mmHg), contained in a 20 l photochemical reactor with a water-cooled silica insert were irradiated with u.v. light (Hanovia U.V.S. 500 medium-pressure mercury lamp) for 90 h. Fractionation of the product *in vacuo* gave trifluoroacetonitrile (1.0 mmol) and a fraction (1.8 g) condensing at −95 °C, which was separated by g.l.c. (2 m SE30 at 80 °C) and shown to comprise mainly recovered starting material (*ca.* 40%) which was eluted last, then *perfluoro*-2,5-*dimethylpyrazine* (*ca.* 58%) (Found: C, 28.9%, *M*, 256. $C_6F_8N_2$ requires C, 28.6%; *M*, 252), as a colourless liquid with δ_F 9.0 (CF_3) and −3.5 (CF), together with trace amounts of a more volatile and unstable component (with *M* 252 by mass spectrometry) which was not identified. The chemical shift of ring fluorines in the pyrazine is similar to that observed for other perfluoro-2,5-dialkylpyrazines,[8] and the substantial CF_3–F coupling ruled out the 2,3-isomer.

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[8] R. D. Chambers, J. A. H. MacBride, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 1975, 396.