Trifluoromethanethiolate Ion. Part 3.[1] Reactions with Tetrafluoropyridazine and Tetrafluoropyrimidine

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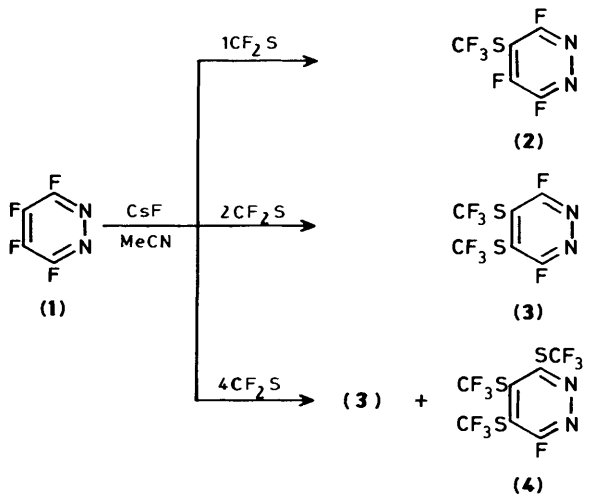
Reactions of tetrafluoropyridazine (**1**) with gaseous thiocarbonyl difluoride or its liquid trimer, *viz.* bis(trifluoromethyl) trithiocarbonate, in the presence of caesium fluoride yield, selectively, 3,4,6-trifluoro-5-trifluoromethylthiopyridazine (**2**) or 3,6-difluoro-4,5-bis(trifluoromethylthio)pyridazine (**3**) depending on the reactant ratio; with an excess of the CF_3S^- ion source a small amount of 3-fluoro-4,5,6-tris(trifluoromethylthio)pyridazine (**4**) was formed. The reactions of tetrafluoropyrimidine (**5**) proceeded unselectively to give mixtures of 2,4,5-trifluoro-6-trifluoromethylthiopyrimidine (**6**), 2,4-difluoro-5,6-bis(trifluoromethylthio)pyrimidine (**7**), 2,5-difluoro-4,6-bis(trifluoromethylthio)-pyrimidine (**8**), and in some cases 5-fluoro-2,4,6-tris(trifluoromethylthio)pyrimidine (**9**). The new trifluoromethylthio derivatives of pyridazine and pyrimidine have been characterized by b.p., ^{19}F n.m.r., and m.s. data.

In preceding papers[1,2] the new trifluoromethanethiolate ion, generated in a reversible addition of fluoride ion to thiocarbonyl difluoride or its trimer, *viz.* bis(trifluoromethyl) trithiocarbonate, was shown to react with pentafluoropyridine to give trifluoromethylthio substituted fluoropyridines. We now report the extension of the application of the trifluoromethanethiolate ion to the nucleophilic substitutions of tetrafluoropyridazine and tetrafluoropyrimidine.

Tetrafluoropyridazine is known to be more reactive than pentafluoropyridine, and the most easily substituted fluorine atoms are those at C-4 and C-5.[3] The fluoride ion promoted reactions with perfluoroalkenes occur readily at 20—80 °C to give perfluoroalkyl substituted derivatives.[4,5] The reaction between tetrafluoropyridazine (**1**), gaseous thiocarbonyl difluoride, and caesium fluoride proceeded smoothly in acetonitrile at −10 °C to give a high yield of either 3,4,6-trifluoro-5-trifluoromethylthiopyridazine (**2**) or 3,6-difluoro-4,5-bis(trifluoromethylthio)pyridazine (**3**) depending on the reactant ratio. The substitution of the second fluorine for the trifluoromethylthio group evidently proceeds much slower than the first one. This allows compounds (**2**) and (**3**) to be obtained with high selectivity by reacting (**1**) with one or two moles of thiocarbonyl difluoride, respectively.

Similarly, when bis(trifluoromethyl) trithiocarbonate, $(CF_3S)_2C{=}S$, was used as a precursor of the CF_3S^- anion, the selective preparations of (**2**) or (**3**) were easily achieved by the use of the appropriate ratio of the reactants.

The attempted syntheses of tetrakis(trifluoromethylthio)-pyridazine failed. The reaction of tetrafluoropyridazine (**1**) with an excess of bis(trifluoromethyl) trithiocarbonate in acetonitrile gave the disubstituted pyridazine (**3**) as the main product together with a small amount of 3-fluoro-4,5,6-tris(trifluoromethylthio)pyridazine (**4**) but no tetrasubstituted product was found. A similar run in sulpholane gave exclusively (**3**). The prolonged reaction of (**3**) with $(CF_3S)_2C{=}S$ in sulpholane at 100 °C resulted in the formation of polymeric material from which no individual compound could be isolated. Also, attempts to oxidise (**3**) with chromium(VI) oxide in sulphuric acid[1] were unsuccessful; no reaction occurred at 20 °C but at slightly increased temperature total decomposition took place to give water-soluble products.

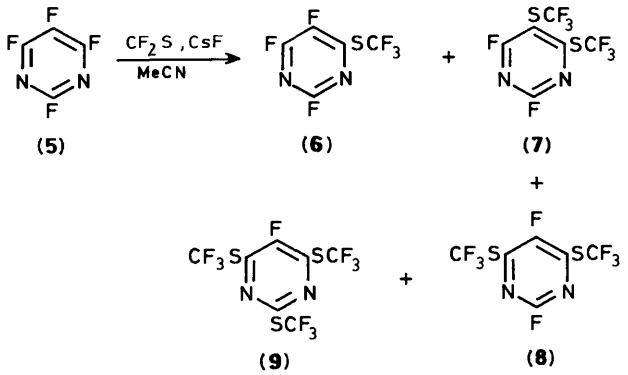


Scheme 1.

In contrast to tetrafluoropyridazine (**1**), but as in similar reactions involving perfluorocarbanions,[6] no selectivity was observed in the reactions of the CF_3S^- anion with tetrafluoropyrimidine (**5**). These reactions, in general, give four compounds: 2,4,5-trifluoro-6-trifluoromethylthiopyrimidine (**6**), 2,4-difluoro-5,6-bis(trifluoromethylthio)pyrimidine (**7**), 2,5-difluoro-4,6-bis(trifluoromethylthio)pyrimidine (**8**), and 5-fluoro-2,4,6-tris(trifluoromethylthio)pyrimidine (**9**). No tetrasubstituted pyrimidine was found.

The reaction of equimolar amounts of tetrafluoropyrimidine (**5**) and gaseous thiocarbonyl difluoride, however, resulted mostly in monosubstitution yielding (**6**); a large amount of (**5**) remained unchanged and a number of minor products were formed. With a 1:4 ratio of (**5**):CF_2S, compounds (**7**), (**8**), and (**9**) were formed in the ratio 1.1:1.8:1. When bis(trifluoromethyl) trithiocarbonate was used as a source of the CF_3S^- anion, only compounds (**6**) and (**7**) were obtained in variable amounts depending on the ratio of the substrates.

Structures of the new trifluoromethylthio derivatives of pyridazine and pyrimidine were elucidated from elemental



Scheme 2.

analyses, mass spectra, and by close agreement of the ^{19}F n.m.r. data with those reported for perfluoroalkyl substituted fluorodiazines[7] and trifluoromethylthio substituted pyrimidines.[8] However, no n.m.r. data were obtained for the tris(trifluoromethylthio) substituted pyrimidine, in which the steric requirements and the orientation in the similar reactions of (**5**) with hexafluoropropene[6] indicate structure (**9**) as the most probable one.

Experimental

B.p.s were determined in capillaries (Sivoloboff) and are uncorrected.[19]F N.m.r. spectra were recorded with a Bruker WM 250 FT spectrometer. Chemical shifts are upfield from internal CCl_3F. Mass spectra were obtained with an Analytical GCMS System LKB 2091. G.l.c. separations were performed using a 3.5 m × 4 mm column for analytical work and 3.5 m × 10 mm column for preparative work, both columns packed with Chromosorb G coated with 3% silicon oil SE-52. Solvents and all equipment were carefully dried before use. Caesium fluoride was dried at 200 °C for at least 72 h. The experimental technique used is described in detail in the preceding paper.[1]

Preparation of 3,4,6-*Trifluoro*-5-*trifluoromethylthiopyridazine* (**2**).—(*a*) Gaseous thiocarbonyl difluoride (15 mmol; initial pressure 350 Torr) was introduced during 40 min to a vigorously stirred solution of tetrafluoropyridazine (**1**) (2 g, 13 mmol) in acetonitrile (8 ml) in the presence of caesium fluoride (0.5 g, 3.3 mmol) during which addition the reaction temperature was maintained at −10 °C. The reaction mixture was further stirred at 20 °C for 1.5 h, then poured into water and extracted with CH_2Cl_2 (30 ml). The extract was washed with water and dried ($CaCl_2$). The residue obtained after removal of the solvent was shown by g.l.c. to consist of a single product (2.7 g, 88.8%) identified as 3,4,6-*trifluoro*-5-*trifluoromethylthiopyridazine* (**2**), colourless liquid, b.p. 167 °C (Found: C, 25.6; F, 48.7; N, 12.1; S, 13.65. $C_5F_6N_2S$ requires C, 25.65; F, 48.7; N, 11.95; S, 13.7%); δ_F(250 MHz; $CDCl_3$) 39.0 (3 F, t, *J* 6.1 Hz, CF_3), 72.3 (1 F, dm, *J* 32.5 Hz, 6-F), 94.7 (1 F, dd, *J* 26.1 and 32.5 Hz, 3-F), and 110.9 (1 F, ddq, *J* 26.1, 14.6, and 6.1 Hz, 4-F) p.p.m.; *m*/*z* 234 (M^+, 100%).

(*b*) To a vigorously stirred suspension of caesium fluoride (0.3 g, 2 mmol) in a solution of tetrafluoropyridazine (**1**) (2 g, 13 mmol) in acetonitrile (10 ml) at −5 °C was added dropwise a solution of bis(trifluoromethyl) trithiocarbonate, $(CF_3S)_2C{=}S$, (1.1 g, 4.5 mmol, equiv. of 13.5 mmol of CF_2S) in acetonitrile (5 ml) during 1 h. When the reaction mixture had been further stirred at 20 °C for 1 h the reaction mixture was worked up as in (*a*). Vacuum distillation gave g.l.c.-pure compound (**2**) (2.2 g, 72.3%).

Preparation of 3,6-*Difluoro*-4,5-*bis*(*trifluoromethylthio*)*pyridazine* (**3**).—(*a*) Gaseous thiocarbonyl difluoride (160 mmol, initial pressure 750 Torr) was treated during 4 h with tetrafluoropyridazine (**1**) (12.2 g, 80 mmol) and caesium fluoride (2.3 g, 15 mmol) in acetonitrile (50 ml) at −10 °C followed by stirring overnight at 20 °C. The reaction mixture was poured into water, extracted with CH_2Cl_2 (3 × 30 ml), and the extract was dried ($CaCl_2$). The residue obtained after removal of the solvent was shown by g.l.c. to consist of a single product. Vacuum distillation gave 3,6-*difluoro*-4,5-*bis*(*trifluoromethylthio*)*pyridazine* (**3**) (20.7 g, 82%) as a yellow viscous liquid, b.p. 200 °C, 100—103 °C/22 Torr (Found: C, 22.9; F, 48.1; N, 9.0; S, 20.4. $C_6F_8N_2S_2$ requires C, 22.8; F, 48.05; N, 8.85; S, 20.3%); δ_F(250 MHz; $CDCl_3$) 38.4 (6 F, CF_3) and 72.4 (2 F, 3-F, and 6-F) p.p.m.; *m*/*z* 316 (M^+, 100%).

(*b*) Bis(trifluoromethyl) trithiocarbonate (2.2 g, 9 mmol; equiv. of 27 mmol CF_2S), tetrafluoropyridazine (**1**) (2 g, 13 mmol), and caesium fluoride (0.5 g, 3.3 mmol) were allowed to react in acetonitrile (15 ml) at −5 °C and worked up as described for the preparation of (**2**) to give compound (**3**) (2.5 g, 61%) as the only product.

Attempted Preparations of Tetrakis(*trifluoromethylthio*)*pyridazine*.—(*a*) Bis(trifluoromethyl) trithiocarbonate (4.6 g, 18.7 mmol; equiv. of 56 mmol CF_2S), tetrafluoropyridazine (**1**) (2 g, 13 mmol), and caesium fluoride (0.5 g, 3.3 mmol) were allowed to react in acetonitrile (15 ml) at −5 °C as described above followed by stirring overnight at 20 °C. Vacuum distillation (92—98 °C/12 Torr) gave a mixture (2.9 g, 69% overall) of compound (**3**) (89%) and 3-*fluoro*-4,5,6-*tris*(*trifluoromethylthio*)*pyridazine* (**4**) (11%). Compound (**4**) was isolated by preparative g.l.c. as a yellow viscous liquid, b.p. 222 °C (Found: C, 21.2; F, 47.6; N, 6.9; S, 24.3. $C_7F_{10}N_2S_3$ requires C, 21.1; F, 47.7; N, 7.0; S, 24.2%); δ_F(250 MHz; $CDCl_3$) 38.0 (3 F, d, *J* 15.3 Hz, CF_3), 38.3 (3 F, s, CF_3), 40.6 (3 F, s, CF_3), and 72.6 (1 F, q, *J* 15.3 Hz, 3-F) p.p.m.; *m*/*z* 398 (M^+, 100%).

(*b*) A similar run in sulpholane gave compound (**3**) (2.5 g, 61%) as the only product.

(*c*) 3,6-Difluoro-4,5-bis(trifluoromethylthio)pyridazine (**3**) (2 g, 6.3 mmol), bis(trifluoromethyl) trithiocarbonate (2.5 g, 10 mmol; equiv. of 30 mmol CF_2S), and caesium fluoride (0.5 g, 3.3 mmol) in sulpholane (10 ml) were stirred in a sealed glass tube at 100—105 °C for 40 h. The reaction mixture was poured into water, extracted with CH_2Cl_2, and the extract was dried ($CaCl_2$). Evaporation of the solvent gave a black tar (3.6 g) from which no distillable product was isolated. The attempted isolation of a product by vacuum sublimation also failed.

Reactions of Tetrafluoropyrimidine (**5**) *with Thiocarbonyl Difluoride*.—(*a*) Gaseous thiocarbonyl difluoride (14 mmol; initial pressure 410 Torr), tetrafluoropyrimidine (**5**) (2 g, 13 mmol), and caesium fluoride (0.5 g, 3.3 mmol) were stirred in acetonitrile (10 ml) at −10 °C and worked up as described for the reaction with (**1**). The residue obtained after removal of the solvent (3.4 g) was shown by g.l.c. to be a complex mixture. The two main components appearing in the ratio 1:1.3 were separated by preparative g.l.c. and identified, respectively, as unchanged (**5**) and 2,4,5-*trifluoro*-6-*trifluoromethylthiopyrimidine* (**6**), a colourless liquid, b.p. 133 °C (Found: C, 25.7; F, 48.6; N, 12.6; S, 13.7. $C_5F_6N_2S$ requires C, 25.65; F, 48.7; N, 11.95, S, 13.7%); δ_F(250 MHz; $CDCl_3$) 38.0 (3 F, s, CF_3), 44.1 (1 F, d, *J* 27.0 Hz, 2-F), 74.0 (1 F, d, *J* 20.1 Hz, 4-F), and 151.4 (1 F, ddq, *J* 27.0, 20.1, and 2.2 Hz, 5-F) p.p.m.; *m*/*z* 234 (M^+, 100%).

(*b*) Thiocarbonyl difluoride (52 mmol; initial pressure 700 Torr), tetrafluoropyridazine (**5**) (2 g, 13 mmol), and caesium fluoride (0.8 g, 5.3 mmol) were allowed to react in acetonitrile (10 ml) at −10 °C as in (*a*) followed by stirring overnight at 20 °C. A brown oil (3.85 g) obtained after work-up of the

reaction mixture consisted of three main compounds in the ratio 1.1:1.8:1 (in order of increasing g.l.c. retention time). These compounds were separated from the tar by vacuum distillation and isolated by preparative g.l.c. to give, respectively, pure 2,4-*difluoro*-5,6-*bis*(*trifluoromethylthio*)*pyrimidine* (**7**), a colourless liquid, b.p. 170—171 °C (Found: C, 22.6; F, 48.2; N, 8.9; S, 20.2. $C_6F_8N_2S_2$ requires C, 22.8; F, 48.1; N, 8.9; S, 20.3%); δ_F(250 MHz; $CDCl_3$) 35.2 (1 F, s, 2-F), 40.3 (3 F, s, CF_3), 41.2 (3 F, d, *J* 6.1 Hz, CF_3), and 48.5 (1 F, 4-F) p.p.m.; *m*/*z* 316 (M^+, 100%); 2,5-*difluoro*-4,6-*bis*(*trifluoromethylthio*)*pyrimidine* (**8**), colourless liquid, b.p. 180—181 °C (Found: C, 22.9; F, 40.0; N, 9.0; S, 20.1); δ_F(250 MHz; $CDCl_3$) 38.0 (6 F, s, CF_3), 45.4 (1 F, d, *J* 30.5 Hz, 2-F), and 131.8 (1 F, d, *J* 30.5 Hz, 5-F) p.p.m.; *m*/*z* 316 (M^+, 100%); and 5-*fluoro*-2,4,6-*tris*(*trifluoromethylthio*)*pyrimidine* (**9**), yellow liquid, b.p. 206—207 °C (Found: C, 21.0; F, 47.7; N, 6.9; S, 24.4. $C_7F_{10}N_2S_3$ requires C, 21.1; F, 47.7; N, 7.0; S, 24.2%); *m*/*z* 398 (M^+, 100%).

Reactions of Tetrafluoropyrimidine (**5**) with *Bis*(*trifluoromethyl*) *Trithiocarbonate*.—(*a*) A solution of bis(trifluoromethyl) trithiocarbonate (1.1 g, 4.5 mmol; equiv. of 13.5 mmol CF_2S) in acetonitrile (5 ml) was added dropwise during 1 h to a vigorously stirred mixture of tetrafluoropyrimidine (**5**) (2 g, 13 mmol), caesium fluoride (0.3 g, 2 mmol), and acetonitrile (10 ml) at −5 °C. The reaction mixture was additionally stirred at 20 °C for 1 h, poured into water, and worked up as usual. Vacuum distillation gave a mixture which was found by g.l.c. to consist of the unchanged (**5**) (20.6%), monosubstituted pyrimidine (**6**) (49.7%), and disubstituted pyrimidine (**7**) (29.7%).

(*b*) Bis(trifluoromethyl) trithiocarbonate (4.6 g, 18.7 mmol; equiv. of 56 mmol CF_2S), tetrafluoropyrimidine (**5**) (2 g, 13 mmol), and caesium fluoride (0.3 g, 2 mmol) were allowed to react as in (*a*) followed by stirring overnight at 20 °C to give, after distillation, a mixture (2 g) of compounds (**6**) and (**7**) in a 1:3.5 ratio.

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