

Received: June 2, 1978

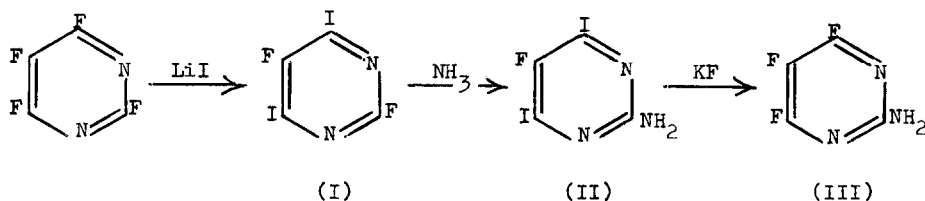
SHORT COMMUNICATION

Heterocyclic Polyfluoro-compounds. Part XXVIII [1]. Nucleophilic Substitution in 2,5-Difluoro-4,6-di-iodopyrimidine

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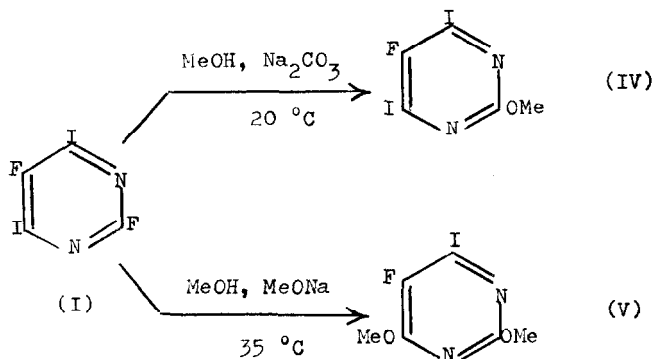
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The regiospecificity of nucleophilic attack on tetrafluoropyrimidine facilitates the synthesis of 4-substituted 2,5,6-trifluoropyrimidines [1-4], and 5-substituted 2,4,6-trifluoropyrimidines can be prepared from their trichloro-analogues via halogen-exchange reactions [5]. By contrast, no general method for the synthesis of 2-substituted 4,5,6-trifluoropyrimidines has been developed.



The need to obtain 2-amino-4,5,6-trifluoropyrimidine for work on the synthesis of fluorinated analogues of known drugs led us to attempt the sequence of reactions shown above, which exemplifies a potential general route to 2-substituted trifluoropyrimidines. 2,5-Difluoro-4,6-di-iodopyrimidine (I), prepared in 57.5% yield from tetrafluoropyrimidine and lithium iodide in DMF at 150 °C, was shown (i) to revert to the tetrafluoro-compound when heated with an alkali-metal fluoride, and (ii) to yield only a 2-amino-derivative (II) when treated with ammonia; however, an acceptable yield (50%) of tetrafluoropyrimidine could be obtained from the di-iodide only under forcing conditions (KF, 300 °C/36 h). Fluorination

of the di-iodoamine (II) under similar, though less severe, conditions (KF, 260 °C/24 h) gave only a brown intractable solid (m.p. >310 °C) of low fluorine content (2.7%). This failure to obtain either the desired product (III) or its immediate precursor, 2-amino-4,5-difluoro-6-iodopyrimidine, might seem best ascribed to step-growth polymerization of the amines involved at the high temperature used; other factors (one obvious possibility is homolysis of C-I bonds) must play a part, however, since application of the same fluorination technique to methoxy-compounds (IV) and (V) also gave only intractable dark-coloured products.



As shown above, treatment of 2,5-difluoro-4,6-diiodopyrimidine (I) with methanol under mild conditions leads to displacement of the 2-fluorine substituent, 5-fluoro-4,6-di-iodo-2-methoxypyrimidine being isolated in 71% yield (yields were not optimized); under more forcing conditions, 5-fluoro-4-iodo-2,6-dimethoxypyrimidine can be obtained in at least 85% yield. The orientation of nucleophilic attack on 2,5-difluoro-4,6-di-iodopyrimidine during its reactions with ammonia and methanol accords with current theories of anionic displacement of halogens from such systems.

#### EXPERIMENTAL

Unless stated otherwise, <sup>19</sup>F n.m.r. spectra were obtained with a Perkin-Elmer R10 instrument operating at 56.46 MHz; chemical shifts were measured relative to external CF<sub>3</sub>CO<sub>2</sub>H, bands to high field being designate positive.

Preparation of 2,5-Difluoro-4,6-di-iodopyrimidine (cf. ref. 3)

A mixture of tetrafluoropyrimidine (9.12 g, 60.0 mmol), anhydrous lithium iodide (20 g, 150 mmol), and dry dimethylformamide (25 cm<sup>3</sup>) was heated at 150 °C for 24 h in the absence of air in a Pyrex ampoule (250 cm<sup>3</sup>). The involatile product was extracted from the ampoule using ether (5 x 40 cm<sup>3</sup>) then water (5 x 40 cm<sup>3</sup>); the combined extracts were shaken with a saturated solution of sodium thiosulphate (100 cm<sup>3</sup>), then the ether layer was dried (MgSO<sub>4</sub>) and evaporated. The orange-white residue was recrystallized from methanol (with charcoal) to provide 2,5-difluoro-4,6-di-iodopyrimidine (12.7 g, 34.5 mmol, 57.5%) (Found: C, 13.3; N, 7.9. Calc. for C<sub>4</sub>F<sub>2</sub>I<sub>2</sub>N<sub>2</sub> : C, 13.1; N, 7.6%), m.p. 185 °C (lit. [3], 185 °C) possessing the correct <sup>19</sup>F n.m.r. properties.

Reactions of 2,5-Difluoro-4,6-di-iodopyrimidine

(a) With caesium fluoride

A mixture of caesium fluoride (dried in situ under a dynamic vacuum at 180 °C for 2 h), freshly-distilled sulpholane (50 cm<sup>3</sup>), and the di-iodopyrimidine (7.18 g, 19.5 mmol) was heated at 140 °C for 18 h in the absence of air in a Pyrex ampoule (250 cm<sup>3</sup>). Distillation of the liquid product afforded tetrafluoropyrimidine (0.28 g, 1.84 mmol, 10% based on starting material consumed), identified by i.r spectroscopy and g.l.c. analysis; 2,5-difluoro-4,6-di-iodopyrimidine (0.5 g, 1.36 mmol, 7% recovery) precipitated when the distillation residue was shaken with water.

(b) With potassium fluoride

An intimate, finely-ground mixture of anhydrous potassium fluoride (50.0 g, 862 mmol) and 2,5-difluoro-4,6-di-iodopyrimidine (6.00 g, 16.3 mmol) was heated at 300 °C for 36 h in the absence of air in a mild steel autoclave (300 cm<sup>3</sup>). Distillation of the volatile product gave tetrafluoropyrimidine (1.25 g, 8.22 mmol, 50%), identified by i.r. spectroscopy and g.l.c. analysis.

(c) With ammonia

A mixture of aqueous ammonia (25 cm<sup>3</sup>, d 0.880), dioxan (45 cm<sup>3</sup>), and 2,5-difluoro-4,6-di-iodopyrimidine (6.25 g, 17.0 mmol) was heated at 60 °C for 2 h. The white crystals which appeared when the reaction

mixture was allowed to cool to room temperature were isolated by filtration; more material precipitated when the filtrate was poured into water (100 cm<sup>3</sup>); the solids were combined, dried in vacuo over P<sub>2</sub>O<sub>5</sub>, and shown to be 2-amino-5-fluoro-4,6-di-iodopyrimidine (nc) (5.1 g, 14.0 mmol, 82%)(Found: C, 12.9; H, 0.9; N, 11.6. C<sub>4</sub>H<sub>2</sub>FI<sub>2</sub>N<sub>3</sub> requires C, 13.15; H, 0.6; N, 11.5%), m.p. 199-200 °C, δ<sub>F</sub> (94.1 MHz; 20% in HMPA) +38.5(s) p.p.m.

(d) With methanol

A mixture of 2,5-difluoro-4,6-di-iodopyrimidine (1.8 g, 4.9 mmol), anhydrous methanol (60 cm<sup>3</sup>), and dry sodium carbonate (0.25 g) was stirred at 20 °C for 10 h then poured into water (100 cm<sup>3</sup>) containing ice. The solid which precipitated was crystallized from light petroleum (b.p. 40-60 °C) to give 5-fluoro-4,6-di-iodo-2-methoxypyrimidine (nc) (1.33 g, 3.50 mmol, 71%)(Found: C, 15.8; H, 0.8; N, 7.1. C<sub>5</sub>H<sub>3</sub>FI<sub>2</sub>N<sub>2</sub>O requires C, 15.8; H, 0.8; N, 7.4%), m.p. 148-149 °C, δ<sub>F</sub> (15% soln. in Me<sub>2</sub>CO) +31.0(s) p.p.m.

(e) With sodium methoxide

A mixture of 2,5-difluoro-4,6-di-iodopyrimidine (6.0 g, 16 mmol), anhydrous methanol (35 cm<sup>3</sup>), dry ether (50 cm<sup>3</sup>), and sodium methoxide (1.6 g, 30 mmol), prepared at 0 °C, was heated at 35 °C for 7 h then poured into water (120 cm<sup>3</sup>). The material which precipitated was crystallized from light petroleum (b.p. 40-60 °C) to provide 5-fluoro-4-iodo-2,6-dimethoxypyrimidine (nc)(3.85 g, 13.6 mmol, 85%)(Found: C, 24.9; H, 2.2; N, 9.5. C<sub>6</sub>H<sub>6</sub>FIN<sub>2</sub>O<sub>2</sub> requires C, 25.35; H, 2.1; N, 9.9%), m.p. 116 °C, δ<sub>F</sub> (20% soln. in Me<sub>2</sub>CO) +66.5(s) p.p.m.

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- 5 R. E. Banks, D. S. Field, and R. N. Haszeldine, *J.Chem.Soc.(C)*, (1970) 1280. 2,4,6-Trifluoropyrimidine itself can be prepared by heating 2,4,6-trichloropyrimidine with anhydrous KF [see, for example, M. M. Boudakian, E. H. Kober, and E. R. Shipowski, *U.S.* 3,280,124 (1966)]; 5-chloro-2,4,6-trifluoropyrimidine can be obtained in the same manner starting from tetrachloropyrimidine (see, for example, ref. 2). For a review of the preparation and reactions of fluorinated pyrimidines and related heterocycles, see G. G. Yakobson, T. D. Petrova, and L. S. Kobrina, *Fluorine Chem. Rev.*, 7 (1974), 115.