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SHORT COMMUNICATION

Heterocyclic Polyfluoro-compounds. Part XXIV.¹ Synthesis and Some Reactions of 3-Chloro-2,5,6-trifluoro- and 3,5-Dichloro-2,6-difluoro-4-iodopyridine

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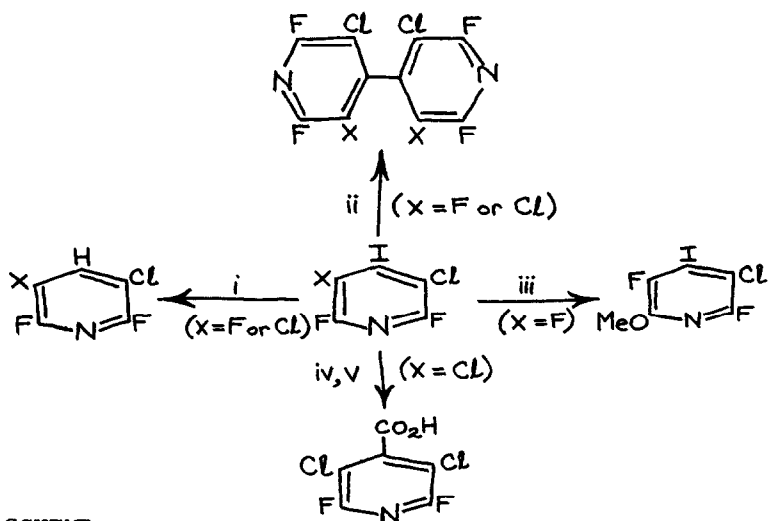
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Summary

3-Chlorotrifluoro- and 3,5-dichlorodifluoro-4-iodopyridine, easily procured by treatment of 3-chlorotetrafluoro- and 3,5-dichlorotrifluoro-pyridine, respectively, with sodium iodide, yield the corresponding 4,4'-bipyridyls when heated with copper and their 4-H analogues when reduced with sodium iodide in DMF. 3,5-Dichlorodifluoroisonicotinic acid can be prepared via lithium-iodine exchange between 3,5-dichlorodifluoro-4-iodopyridine and butyl-lithium.

Results

Treatment of pentafluoropyridine with sodium iodide in hot dimethylformamide under anhydrous conditions provides easy access to tetrafluoro-4-iodopyridine, a useful intermediate in synthesis [2]. Application of this nucleophilic I-for-F exchange to the appropriate chlorofluoropyridines produces 3-chlorotrifluoro- and 3,5-dichlorodifluoro-4-iodopyridine (yields >60%) for exploitation in halogenopyridine synthesis, as exemplified in the Scheme



SCHEME

Reagents: i, NaI-DMF, 155-164 °C; ii, Cu, ca. 200 °C; iii, NaOMe-MeOH, 0-20 °C; iv, n-BuLi-Et₂O, -20 to -10 °C; v, CO₂, then 2M-HCl aq.

EXPERIMENTAL

3-Chlorotetrafluoro- and 3,5-dichlorotrifluoro-pyridine were prepared by heating pentachloropyridine with potassium fluoride [3]. N.m.r. spectra were recorded with a Perkin-Elmer R10 instrument operating at 56.46 (¹⁹F) or 60 MHz (¹H); chemical shifts to high field are designated negative.

3-Chloro-2,5,6-trifluoro-4-iodopyridine. - The original experiment [2] was repeated on a larger scale [30.05 g (162 mmol) of 3-chlorotetrafluoropyridine, 65.0 g of anhydrous sodium iodide, and 20 cm³ of dimethylformamide at 155 °C for 18 h], to give 3-chlorotetrafluoropyridine (6.37 g, 34.3 mmol, 21% recovery), 3-chloro-2,5,6-trifluoropyridine (1.22 g, 7.28 mmol, 6% based on 3-ClC₅F₄N consumed) [Found: C, 36.1; H, 0.8; N, 8.1%; \underline{M}^{\dagger} , 167 (³⁵Cl, 100% peak). Calc. for C₅HClF₃N: C, 35.8; H, 0.6; N, 8.4%; \underline{M} , 167.5], b.p. 71 °C at 99 mmHg, with correct n.m.r. parameters [4], 3-chloro-2,5,6-trifluoro-4-

iodopyridine (23.49 g, 80.03 mmol, 63%), m.p. 45-46 °C, identified spectroscopically (i.r. and n.m.r. [2]), and 3,3'-dichloro-2,2',5,5',6,6'-hexafluoro-4,4'-bipyridyl (1.91 g, 5.74 mmol, 9%) (Found: C, 36.2; N, 8.1. $C_{10}Cl_2F_6N_2$ requires C, 36.0; N, 8.4%), m.p. 59-60 °C, b.p. 85 °C at 0.3 mmHg, δ_F (20% soln. in acetone) +3.7 (2-,2'-F), -10.9 (6-,6'-F), and -64.0 (5-,5'-F) p.p.m.

3,5-Dichloro-2,6-difluoro-4-iodopyridine.- The above experiment was repeated with 60.0 g (297 mmol) of 3,5-dichlorotrifluoropyridine, sodium iodide (120 g), and dimethylformamide (40 cm³) at 180 °C for 18 h, to provide 3,5-dichlorotrifluoropyridine (3.40 g, 16.8 mmol, 6% recovery), 3,5-dichloro-2,6-difluoropyridine (1.80 g, 9.78 mmol, 3.5% based on 3,5-Cl₂C₅F₃N consumed) (Found: C, 32.7; H, 0.7; N, 7.5. Calc. for C₅HCl₂F₂N: C, 32.6; H, 0.5; N, 7.6%), m.p. 48-49 °C, with correct n.m.r. parameters [4], 3,5-dichloro-2,6-difluoro-4-iodopyridine (56.68 g, 182.8 mmol, 65%) (Found: C, 19.6; N, 4.6%; M^+ , 309 (³⁵Cl, 100% peak). C₅Cl₂F₂IN requires C, 19.35; N, 4.5%; M , 310], m.p. 86-87 °C (isolated finally by sublimation at 60 °C and 0.3 mmHg), δ_F (20% soln. in acetone) +9.2 p.p.m., and 3,3',5,5'-tetrachloro-2,2',6,6'-tetrafluoro-4,4'-bipyridyl (0.17 g, 0.46 mmol, <1%) (Found: C, 33.0; N, 7.7%. C₁₀Cl₄F₄N₂ requires C, 32.8; N, 7.7%), m.p. 119-120 °C (isolated by sublimation at 90 °C and 0.3 mmHg).

Reactions of 3-Chloro-2,5,6-trifluoro-4-iodopyridine.- Reactions with (a) sodium iodide in dimethylformamide, (b) methanolic sodium methoxide at 0 °C, and (c) copper at 200 °C were carried out as described for tetrafluoro-4-iodopyridine [2], to yield: (a) 3-chloro-2,5,6-trifluoropyridine (52%); (b) 3-chloro-2,5-difluoro-4-iodo-6-methoxypyridine (88%) (Found: C, 23.8; H, 1.0; N, 4.6%. C₆H₃ClF₂INO requires C, 23.6; H, 1.0; N, 4.6%), m.p. 43-44 °C (purified by sublimation at 35 °C and 0.4 mmHg), δ_F (25% soln. in acetone) +4.3 (2-F) and -40.6 (5-F) p.p.m. ($J_{2,5}$ 27 Hz); and (c) 3,3'-dichloro-2,2',5,5',6,6'-hexafluoro-4,4'-bipyridyl (59%).

Reactions of 3,5-Dichloro-2,6-difluoro-4-iodopyridine.-

Reactions with (a) sodium iodide in dimethylformamide (at 164 °C), (b) copper (at 190 °C), and (c) n-butyl-lithium (in ether only) followed by carbon dioxide were carried out as described for tetrafluoro-4-iodopyridine [2], to yield: (a) 3,5-dichloro-2,6-difluoropyridine (26%); (b) 3,3',5,5'-tetrachloro-2,2',6,6'-tetrafluoro-4,4'-bipyridyl (78%); and (c) 3,5-dichloro-2,6-difluoropyridine-4-carboxylic acid (78%) (Found: C, 31.8; H, 0.7; N, 6.4%. $C_6HCl_2F_2NO_2$ requires C, 31.6; H, 0.4; N, 6.1%), m.p. (dec.) 208 °C.

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