Polyhalogenated heterocyclic compounds. Part 48.¹ Synthesis of perfluoroisopropyl-2,2′-bipyridyl derivatives

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Dedicated to Professor Charles Rees on the occasion of his 75th birthday
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Abstract
The synthesis of a highly halogenated 2,2′-bipyridyl system using organometallic methodology is reported.

Keywords: Heterocyclic, organofluorine, bipyridyl, polyhalogenated

Introduction
The chemistry of highly fluorinated bipyridyl derivatives remains relatively undeveloped. Earlier work from this laboratory includes synthesis of octafluoro-3,3′-bipyridyl by Ullman coupling of 3-chlorotetrafluoropyridine,² halogen exchange reactions, by heating octachloro-bipyridine derivatives with potassium fluoride at high temperature gave octafluoro-2,2′-bipyridyl³ and electrochemical reduction, involving the generation and coupling of perfluoropyridyl radical anions, gave octafluoro-4,4′-bipyridyl.⁴ So far as we are aware, these are the only synthetically realistic methods for the synthesis of these systems that have been reported,⁵ together with some studies of factors effecting the orientation of nucleophilic attack in perfluoro-3,3′-bipyridyl.²

In this paper, we report the synthesis of a 2,2′-bipyridyl derivative using organometallic methodology.

Results and Discussion
Perfluoroalkylation of pentafluoropyridine 1 was achieved by heating with hexafluoropropene and a catalytic amount of tetrakis(dimethylamino)ethylene (TDAE), following a procedure described earlier.⁶ Bromination of perfluoro-4-isopropylpyridine 2 by heating with hydrogen...
bromide and aluminium tribromide in an autoclave, proceeded efficiently to give the 2,6-dibromo pyridine derivative 3 in high yield. The subsequent reaction of 3 with n-butyl lithium in THF at low temperature afforded the lithio derivative 4 and then addition of one equivalent of the heterocycle 2, which is highly susceptible to nucleophilic attack, led to 2,2'-bipyridyl derivative 5 in moderate yield. (Scheme 1) However, we have not yet probed the factors that may lead to an increase in the yield of 5. Characterisation of 5 followed readily from elemental analysis, mass spectrometry and $^{19}$F n.m.r.

![Scheme 1](image)

**Scheme 1**
Reagents and Conditions
(i) CF3-CF=CF2, TDAE, 60oC; (ii) AlBr3 (2.2 equiv.), HBr (2.2 equiv.), 160oC, 48 h; (iii) n-BuLi (1.2 equiv.), THF, -78oC; (iv) 2, -78oC - r.t.; (v) NaOMe, MeOH, reflux, 24h

Bipyridyl derivative 5 is, of course, still very reactive towards nucleophiles. Heating 5 with sodium methoxide lead to the major product 6, in which the fluorine atom located ortho to ring nitrogen was substituted. This was deduced by the disappearance of the diagnostic resonance at –83.1 ppm, assigned to the ortho ring fluorine substituent in 4, in the $^{19}$F nmr spectrum.

In principle, nucleophilic attack on the perfluorinated ring could occur at sites both ortho and meta to the ring nitrogen which would lead to transition states approximating to 6a and 6b respectively. (Scheme 2)
Transition state 6b would be stabilised by delocalisation of the negative charge into the pyridine ring attached to the carbon atom para to the site of nucleophilic attack. However, the product 5 obtained indicates that the ortho/para activating influence of ring nitrogen is the dominant factor in these processes leading to preferential ortho substitution. Of course, the bromine atom could, in principle, be displaced because this substituent is also located ortho to ring nitrogen. However, replacement of the ortho fluorine is predominant because, in this case, the ‘hard’ oxygen nucleophile preferentially attacks the ‘harder’ carbon-fluorine bond rather than the ‘softer’ carbon-bromine bond, in line with previous findings.7

In summary, methodology for the preparation of bipyridyl derivatives in which a perfluoropyridyl lithium derivative is trapped by another equivalent of a perfluoropyridine has been established and many similar bis-heterocyclic systems, synthesised by analogous methodology, can be envisaged.

Experimental Section

General Procedures. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as an internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl -silicone) column. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions were determined by either 19F-NMR or gas-chromatography on a Shimadzu GC8A system using a SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. Column chromatography was
carried out on silica gel (Merck no. 109385, particle size 0.040-0.063nm) and TLC analysis was performed on silica gel TLC plates.

Perfluoro-4-isopropylpyridine 1, was synthesised by literature procedures. 6

2,6-Dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine (3). A Hastalloy autoclave was charged with aluminium bromide (34.1 g, 0.13 mol), 2 (19.2 g, 0.06 mol) and hydrogen bromide gas (10.2 g, 0.13 mol). The autoclave was heated at 160°C for 48 h. After cooling excess hydrogen bromide was neutralised by release into a sodium hydrogen carbonate solution. The autoclave was opened and ice/water was cautiously added to the solid contents. This mixture was then extracted with dichloromethane and the extracts were dried (MgSO4) and distilled under reduced pressure to give 2,6-dibromo-3,5-difluoro-4-(1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl)-pyridine 3 (21.6 g, 80%) as a colourless liquid; bp 56°C (4mmHg); (Found C, 21.8; N, 3.1. C8Br2F9N requires C, 21.8; N, 3.2%); δF –75.8 (6F, m, CF3), -103.7 and –105.8 (2F, br s, F-3), -180.0 (1F, m, CFCF3); δC 91.5 (dsept, 1JCF 216, 2JCF 36.0, CFCF3), 114.1 (dt, 2JCF 22.5, 3JCF 13.3, C-4), 119.7 (qd, 1JCF 289, 2JCF 27.1, CF3), 124.0 – 126.2 (br m, C-2), 148.0 – 155.0 (br m, C-3); m/z (EI+) 443 (M+, 33%), 441 (M+, 41%), 439 (M+, 48%), 343 (11), 341 (11), 324 (24), 322 (48), 320 (27), 212 (15), 193 (18), 162 (32), 124 (20), 69 (100).

2-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-lithiopyridine (4). A solution of n-butyllithium (3.5 cm³, 5.5 mmol of 1.6 M solution in hexanes) was added to a solution to 3 (2.0 g, 4.5 mmol) in tetrahydrofuran (25 cm³) at -78°C, with stirring, under an atmosphere of dry nitrogen.

2-{6-Bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl]-6-methoxy-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]pyridine (6). Under an atmosphere of dry nitrogen, sodium metal (0.02 g, 0.8 mmol) was added to methanol (20 cm³) and stirred until hydrogen evolution was complete. 5 (0.5 g, 0.8 mmol) was added to the solution which was stirred at reflux temperature for 24 h. Water (30 cm³) was added and the organic components were extracted into dichloromethane. The dichloromethane solution was dried (MgSO4) and evaporated to give a residue which after column chromatography, using hexane
and dichloromethane (4:1) as the eluent, gave 2-{6-bromo-3,5-difluoro-4-[1,2,2,2-tetrafluoro-1-
 trifluoromethyl-ethyl](2-pyridyl)}{3,5-difluoro-6-methoxy-4-[1,2,2,2-tetrafluoro-1-
(trifluoromethyl)ethyl]pyridine 6 (0.4 g, 79%) as a white solid; mp 79.8-81.6°C (Found: C, 30.3;
H, 0.4, N, 4.2. C_{17}H_{3}BrF_{18}N_{2}O requires C, 30.3; H, 0.5; N, 4.2%); δH 4.0 (s, CH3); δF –75.4 (12
F, m, CF3), -97.3 and −99.5 (1 F, br m, F-3), -115.2 and −119.6 (2 F, m, F-5,5′), -124.7 and –
127.1 (1 F, m, F-3′), -179.9 (2 F, m, CFCF3); m/z (EI+) 674 (M+, 48%), 672 (M+, 56%), 659 (11),
657 (11), 469 (16), 467 (17), 343 (11), 293 (15), 248 (20), 69 (100).

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