Polyhalogenated heterocyclic compounds. Part 43. Reactions of 4-lithio-2,6-dibromo-3,5 difluoro pyridine

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Dedicated to Gurnos Jones on the occasion of his 70th birthday
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Abstract

4-Lithio-2,6-dibromo-3,5-difluoropyridine (2), readily prepared from 2,4,6-tribromo-3,5 difluoropyridine 1, reacts with a range of electrophiles to give various functionalised pyridine derivatives. A subsequent X-ray crystallographic study of 2,6-dibromo-3,5-difluoro(4-pyridyl) methylphenyl ketone 3e shows an unusual solid state lattice packing arrangement.

Keywords: Lithium-halogen exchange, polyhalogenated heterocycles, lithio-2,6-dibromo-3,5-difluoro pyridine

Introduction

The use of a variety of per-halogenated heterocyclic system in the preparation of many commercially significant plant protection agents and fibre reactive dyes, continues to provide a stimulus for the synthesis of novel polyhalogenated heterocyclic derivatives and the subsequent development of their chemistry.

Whilst an extensive chemistry of perfluoro- and per-chloro-fluoro heterocyclic systems has emerged, studies concerning the synthesis and chemistry of per-bromo-fluoro heterocycles are relatively scarce. However, in an earlier paper in this series, we demonstrated that 2,4,6-tribromo-3,5-difluoro pyridine 1 was a synthetically useful "building block" that could be used for the preparation of a wide range of polyhalogenated heterocyclic derivatives upon reaction with a range of hard and soft nucleophiles. In an effort to exploit the organometallic chemistry of 1, we demonstrated, in a preliminary experiment, that debromo-lithiation occurs exclusively at

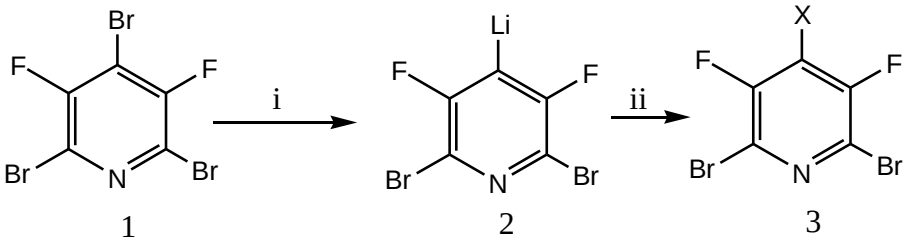
the 4-position and that the organolithium species 2 that is generated may be trapped by allyl bromide.

In this paper, we report further reactions of the lithio-pyridine 2 with electrophiles and, subsequently, an unusual X-ray crystal structure of a pyridyl-arene derivative prepared by such a process.

Results and Discussion

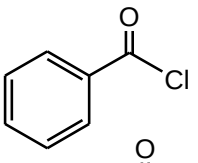
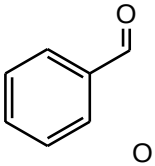
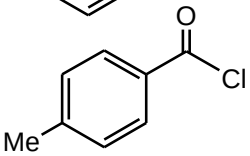
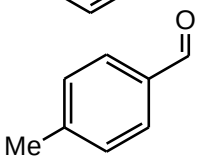
Organolithium derivative 2 is readily generated by clean reaction of 1 with *n*-BuLi in diethylether at low temperature. De-bromometallation occurs exclusively at the 4 position, because the carbanionic carbon atom in 2 is stabilised by the presence of two *ortho* fluorine substituents, rather than only one *ortho* fluorine atom in the case of substitution of the 2 position. Trapping of the lithium derivative 2 by a range of electrophiles occurs readily upon warming the ethereal solution to room temperature, giving the desired products 3. (Table)

Table 1. Reactions of 4-Lithio-2,6-dibromo-3,5-difluoro-pyridine

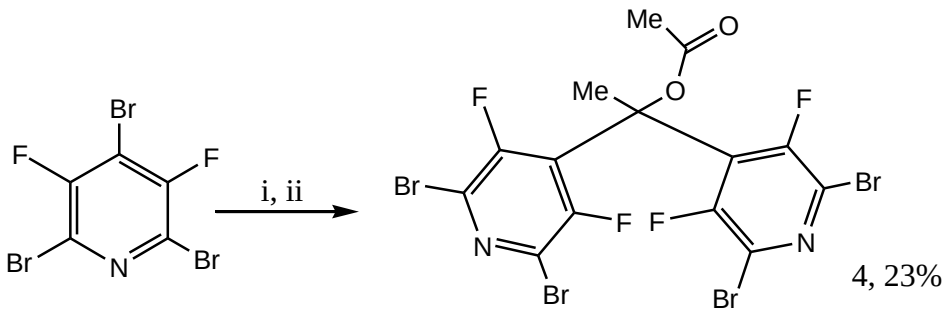


1 2 3

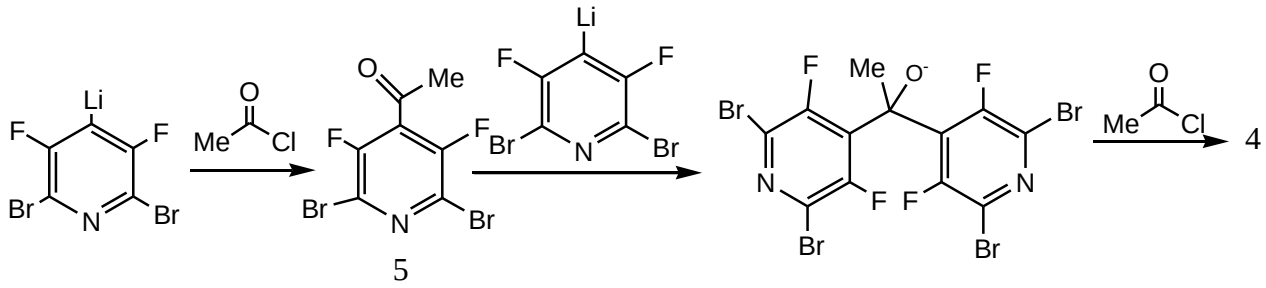
Reagents and Conditions: i. *n*-BuLi, Et_2O, -78°C; ii. electrophile, -78°C to r.t.

Electrophile	X	Yield (%)
H_2O	H	3a, 100
Me_3SiCl	Me_3Si	3b, 85
CO_2	COOH	3c, 35
		3d, 57
		3e, 77

In contrast, reaction of 2 with acetyl chloride gave the bi-pyridyl derivative 4, even when a deficiency of acetyl chloride was used as the electrophilic species. A mechanism for this process is given in Scheme and indicates that intermediate ketone 5 is more reactive than acetyl chloride due to the presence of the highly electron withdrawing pyridyl ring adjacent to the carbonyl group in this system.



Reagents and Conditions: i. *n*-BuLi, Et_2O, -78°C; ii. CH_3COCl, -78°C to r.t.



Scheme 1. Reaction of 1 with acetyl chloride.

A similar process involving a perfluoroheterocyclic lithiated system was reported by Coe during the course of this work.

In summary, 2 may be trapped by a range of electrophiles leading to various products depending on the electrophilic system, thus extending the synthetic utility of perbromo-fluoro heterocycles such as 1.

X-Ray crystallography

A single crystal of 3e was grown that was suitable for X-ray crystallography. We expected to observe significant face-to-face π-π interaction between the electron poor pyridine ring and the relatively electron rich aryl ring, as is observed in many systems involving a combination of highly fluorinated aromatic derivatives and hydrocarbon aromatic systems. However, as shown in Figs. 1 and 2, the molecules in the crystal form stacks along the *a* direction that are arranged in a herring bone configuration in which the pyridine subunits adopt an edge-to-face

configuration with the aromatic ring of the adjacent molecule. Furthermore, at first sight, it appears that face-to-face π-π interactions between adjacent pyridine rings is occurring but the calculated interplanar distance (3.68A) is too large for any such interaction to be significant. Consequently, the crystal structure observed is probably due to the adoption of the most favourable stacking arrangement and the minimisation of unfavourable electron pair interactions.

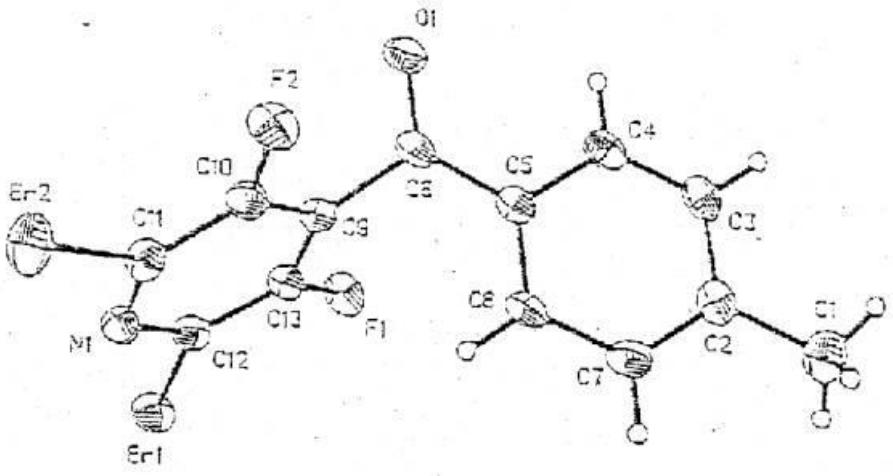


Figure1. X-ray crystal structure of 2,6-dibromo-3,5-difluoro(4-pyridyl) methylphenyl ketone 3e.

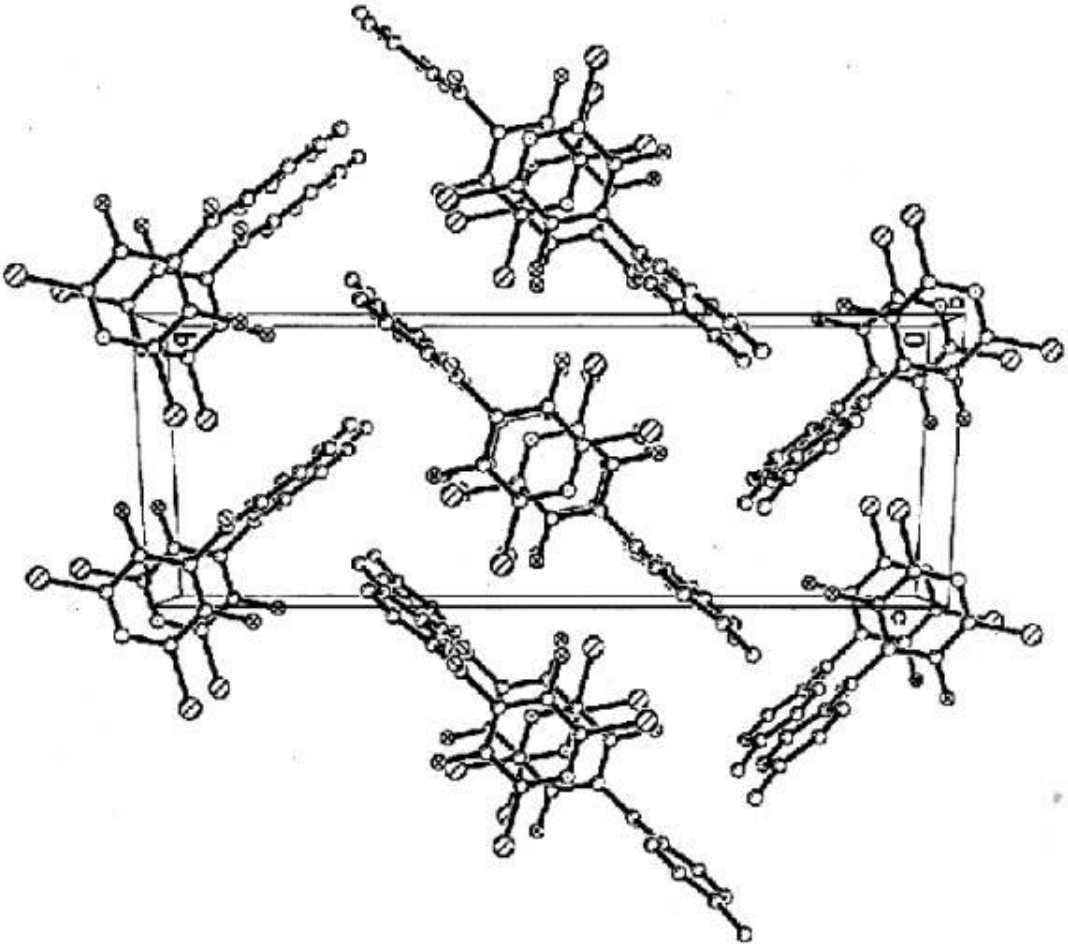


Figure 2. Crystal stacking arrangement of 2,6-dibromo-3,5-difluoro(4-pyridyl) methylphenyl ketone 3e.

Experimental Section

General Procedures. All solvents were dried before use by literature procedures. NMR spectra were recorded on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards and deuteriochloroform as solvent, unless otherwise stated. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Coupling constants are given in Hz. Mass spectra were recorded a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer using KBr plates while elemental analyses were obtained on either a Perkin-Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was performed on silica gel (Merck no. 1-09385) and TLC analysis was performed on silica gel TLC plates (Merck).

2,4,6-Tribromo-3,5-difluoropyridine was synthesised according to the literature procedure.

Generation and reactions of 4-lithio-2,6-dibromo-3,5-difluoro-pyridine. General procedure
A three necked flask, equipped with a low temperature thermometer, a drying tube and flushed with dry nitrogen, was charged with 2,4,6-tribromo-3,5-difluoropyridine and diethyl ether. The mixture was cooled to -78ºC before *n*-butyllithium (1.6 M solution in hexanes) was added. The resulting solution, which gradually turned yellow in colour, was stirred at -78ºC for 90 min. ^{19}F NMR analysis of the crude mixture indicated complete conversion of the starting material to 4-lithio-2,6-dibromo-3,5-difluoropyridine; δ_F-89.7 (s). The electrophile was added to the cool solution and the mixture was allowed to warm to rt overnight. Addition of water, followed by extraction by dichloromethane (3 x 20 mL), drying (MgSO4) and evaporation gave the crude product. Purification of the functional pyridine derivative was accomplished by column chromatography on silica gel, recrystallisation or vacuum sublimation, as indicated.

2,6-Dibromo-3,5-difluoropyridine (3a). 2,4,6-Tribromo-3,5-difluoropyridine (1.0 g, 2.84 mmol), *n*-butyllithium (1.9 mL, 3.55 mmol), diethyl ether (15 mL) and water (10 mL) gave, after sublimation, *2,6-dibromo-3,5-difluoropyridine3a* (0.55 g, 71%)as a white solid; mp 110 - 111ºC; (Found: C, 22.2; N, 5.0; H, 0.4; Br, 58.3; F, 13.7, $C_5HBr_2F_2N$ requires: C, 22.2; N, 5.1; H, 0.3; Br, 58.6; F 13.9%); δ_C 113.7 (t, 2JCF 23.9, C-4), 122.6 (X part of ABX, C-2), 155.4 (dd, 1JCF 270.5, 3JCF 4.9, C-3); δ_H 7.31 (t, 3JHF 6.3),δ_F-109.53 (d, 3JFH 7.1); m/z (EI) 271 (M, 56%), 273 (M, 100), 275 (56), 274 (5%).

2-(2,6-dibromo-3,5-difluoro-4- trimethylsilyl-pyridine (3b). 2,4,6 Tribromo 3,5-difluoropyridine(1.0 g, 2.84 mmol), *n*-butyllithium (1.9 mL, 3.55 mmol), diethyl ether (15 mL) and chlorotrimethylsilane (0.38 g, 3.5 mmol) gave, after column chromatography on silica gel using diethyl acetate-hexane (1:1) as eluant, *2-(2,6-dibromo-3,5-difluoro-4-trimethylsilylpyridine* 3b(0.82 g, 85%); mp 86 -88ºC; (Found: C, 27.8; H, 2.6; N, 3.4. $C_8H_9Br_2F_2NSi$ requires C, 27.8; H, 2.60; N, 4.05%); δ_C 0.66 (s, CH3), 122.4 (X part of ABX system, C-2), 127.4 (t, ^{2}JCF 33.6, C-4), 158.5 (dd, ^{1}JCF 257, ^{3}JCF 8.4, C-3); δ_H 0.36 (s); δ_F-99.7 (s); m/z (EI) 347 (M, 24), 345 (M, 47), 343 (25), 77 (100%).

2,6-Dibromo-3,5-difluoropyridine-4-carboxylic acid (3c). 2,4,6-Tribromo-3,5-difluoropyridine (0.4 g, 1.14 mmol), diethyl ether (15 mL), *n*-butyllithium (0.76 mL, 1.42 mmol) and carbon dioxide gas (passed through the solution for 2 h), gave, after the aqueous layer was acidified and extracted with ether, *2,6-dibromo-3,5-difluoropyridine-4-carboxylic acid* 3c(0.12 g, 35%) as white crystals; mp 154 - 156ºC; (Found: C, 22.8; N, 4.1; H, 0.3. $C_6HBr_2F_2NO_2$ requires C, 22.7; N, 4.4; H, 0.3%); δ_C 106.4 (t, 2JCF 24.2, C-4), 123.4 (X part of ABX system, C-2), 152.6 (dd, 1JCF 270.4, 3JCF 3.9, C-3), 159.1 (s, COOH); δ_H 6.26 (bs, COOH); δ_F-110.56 (s); m/z (EI) 316 (M, 100), 272 (M+COOH, 100%).

2,6-Dibromo-3,5-difluoro(4-pyridyl) phenyl ketone (3d). 2,4,6-Tribromo-3,5-difluoropyridine (1.0 g, 2.84 mmol), *n*-butyllithium (1.9 mL, 3.55 mmol), diethyl ether (15 mL) and benzoyl chloride (0.61 g, 4.32 mmol) gave, after purification by column chromatography using dichloromethane-hexane (1:4) as eluant and recrystallisation from hexane, *2,6-dibromo-3,5-difluoro(4-pyridyl) phenyl ketone* 3d(0.61 g, 57%) as a white solid; (Found: C, 38.2; N, 3.6; H, 1.4. $C_{12}H_5Br_2F_2NO$ requires C, 38.2; N, 3.7; H, 1.3%); δ_C 123.3 (X part of an ABX system, C-2),

126.24 (m, C-4), 129.5 (s, C-*ortho*), 130.3 (s, C-*meta*), 134.9 (s, C-*ipso*), 135.9 (s, C-*para*), 152.1 (dd, 1JCF 266.3,[3]JCF 3.9, C-3), 184.5 (s, C=O); δ_H 7.5-7.7 (m, Ar-H); δ_F-112.24 (s); m/z (EI) 375 (M, 7%), 377 (M, 14), 379 (M, 7).

2,6-Dibromo-3,5-difluoro(4-pyridyl) 4-methylphenyl ketone (3e). 2,4,6-Tribromo-3,5-difluoropyridine (1.0 g, 2.84mmol), *n*-butyllithium (1.9 mL, 3.55 mmol), diethyl ether (15mL) and *p*-toluoyl chloride (0.66 g, 4.26 mmol) gave, after recrystallisation, *2,6-dibromo-3,5-difluoro(4-pyridyl) 4-methylphenyl ketone* 3e (0.85 g, 77%); mp 145 -146ºC; (Found: C, 39.9; H, 1.8; N, 3.6, $C_{13}H_7Br_2F_2NO$ requires C, 39.9; H, 1.7; H, 4.0%); δ_C 26.9 (s, CH_3), 123.3 (X part of an ABX system, C-2), 126.5 (t, [2]JCF 21.4, C-4), 130.1 (s, C-*ortho*), 130.3 (s, C-*meta*), 132.3 (s, C-C=O), 147.2 (s, C-CH_3), 152.0 (dd, [1]JCF 258, 3JCF 1.9, C-3), 184 (s, C=O); δ_h 1.36 (3 H, s, CH3), 7.28 and 7.60 (4 H, AB, J_{AB} 8.4, Ar-H); δ_F-112.28 (s); m/z (EI) 389 (M, 4%), 391 (M, 8), 393 (4), 119 (100), 91 (55), 65.(52).

1,1-Bis(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate (4). 2,4,6-Tribromo-3,5-difluoropyridine (1.0 g, 2.84 mmol), *n*-butyllithium (1.9 mL, 3.55 mmol), diethyl ether (15 mL) and acetyl chloride (0.33 g, 4.26 mmol) gave, after column chromatography using dichloromethane-hexane (1:3 v/v) as eluant, *1,1-bis(2,6-dibromo-3,5-difluoro-4-pyridyl)ethyl acetate* 4 (0.41 g, 23%); mp 158 -160ºC; (Found: C, 27.0; H, 1.2; N, 4.2, $C_{14}H_6Br_4F_4N_2O_2$ requires C, 26.6; H, 0.95; N, 4.4%); δ_C 21.4 (s, $COCH_3$), 26.9 (s, CH_3), 78.14 (s, C-O), 124.3 (X part ABX system, C-2), 128.5 (m, C-4), 153.1 (d, 1JCF 267, C-3), 168.5 (s, C=O);δ_H 2.16 (3H, s, OCOCH3), 2.34 (3H, s, C-CH_3); δ_F-108.05 (s); m/z (EI) 629 (M - H, 0.4), 627 (0.3), 632 (0.2), 587 (5.2), 43 (100%); CI- 569 (M - $OCOCH_3$, 100%).

X-ray Crystallography

Crystal data for 2,6-dibromo-3,5-difluoro(4-pyridyl) methylphenyl ketone 3e. $C_{13}H_7Br_2F_2NO$, M=391.02, monoclinic, space group P $2_1/c$, a = 7.4899(15), b=22.206(4), c=8.6648(17) Å, β =113.35(3)º, U=1323.1(5)Å^3, F(000) =752, Z=4, D_c = 1.963 mg m^{-3}, μ =6.14 mm^{-1} (Mo-Kα , λ=0.71073 Å), T = 120.0(1)K. 19375 reflections (1.83 $\leq\theta\leq$30.36º) were collected on a Bruker SMART-CCD diffractometer (ω-scan, 0.3º/frame) yielding 3736 unique data (R_{merg} = 0.071). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software.[8] All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were placed at calculated positions and refined using the 'riding'-mode. Final $wR_2(F^2)$ =0.0758 for all data (172 refined parameters), conventional R (F) = 0.0302 for 3082 reflections with I ≥2s , GOF = 1.047. The largest peak on the residual map is 0.49 a/Å^3.

The plane of the carbonyl group in molecule 3e is almost parallel to the plane of heterocycle(corresponding dihedral angle is -10.0º) whilst the dihedral angle between the plane of C=O group and the plane of Ph-ring is -67.2º. The molecules in the stacks are connected by their centres of symmetry and the heterocycles of adjacent molecules overlap with interplanar

distances of 3.68 and 3.45Å. Also there are short intermolecular contacts BrO 3.054Å connecting the stacks in *c*-direction.

Acknowledgements

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