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New fluoride ion reagent from pentafluoropyridine

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Dedicated to our colleague and close friend, Prof. Dick Chambers, on the occasion of his 70th birthday.

Abstract

A new nucleophilic fluorinating agent, derived from reaction of dimethylaminopyridine (DMAP) with pentafluoropyridine, has been synthesised and assessed in various carbon–fluorine bond forming processes.

Keywords: Fluorination; Fluoride ion; Nucleophilic fluorinating agents; Pentafluoropyridine

1. Introduction

Development of efficient carbon–fluorine bond forming methodology that enables the selective fluorination of systems which are involved in the latter stages of target molecule synthesis remains an important goal in organofluorine chemistry [1,2]. The increasing importance of fluorinated systems in healthcare, plant protection and high technology products [1] stimulates research in this field and a number of fluorinating agents [3–6] have been studied extensively to meet the varying demands of both academia and industry.

Fluorinating agents that are sources of nucleophilic fluoride ion have been the subject of great development due to the ready availability of several fluoride salts and a wide variety of systems bearing halogen, nitro and sulfonate ester groups that are useful substrates for both aliphatic and aromatic nucleophilic substitution processes. Many fluoride ion reagents [6], such as the alkali metal fluorides [7,8], ammonium salts [9,10] and hydrogen fluoride/amine systems [11–13] have been developed but, in many cases, the low solubility, harsh reaction conditions required and the difficulty of isolating products from the aprotic solvent media employed, offers considerable scope for improvement for wider synthetic application.

Reaction of tertiary amines with perfluorinated alkenes gives ammonium fluoride salts (Scheme 1) which, once formed in situ, catalyse oligomerisation of the fluoroalkene substrate [14]. However, reaction of a tertiary amine with a perfluorinated system, such as pentafluoropyridine, that is susceptible towards nucleophilic attack [15,16] but is not oligomerised in the presence of fluoride ion (Scheme 1), would provide access to fluoride ion reagents that may be useful for carbon–fluorine bond forming reactions.

In this paper, we describe the synthesis and application of a new fluorinating agent from a tertiary amine and pentafluoropyridine. Whilst related fluoride salts have been synthesised from reactions between tertiary amines and either hexafluorobenzene [17] or pentafluoropyridine [18], the viability of using such systems for carbon–fluorine bond formation has not been assessed.

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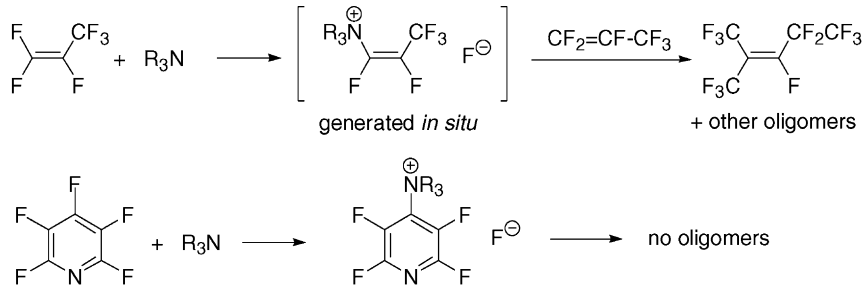
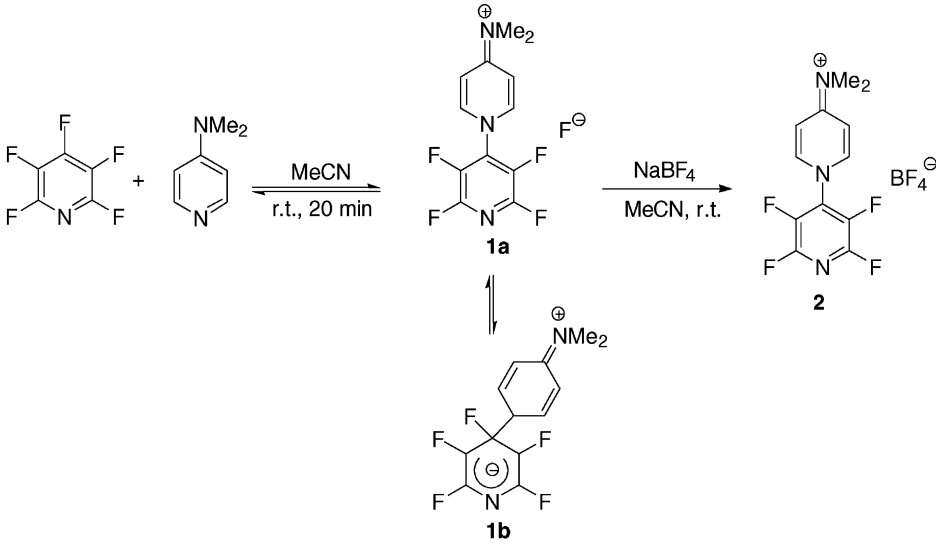


Scheme 1.



Scheme 2.

2. Results and discussion

After initial experiments involving reactions between pentafluoropyridine and a variety of 4-substituted pyridine derivatives (R–C_5H_4N; R = H, Me, OMe, NH_2), we found that reaction between pentafluoropyridine and strongly nucleophilic dimethylaminopyridine (DMAP) in acetonitrile after stirring at room temperature for several minutes gave a yellow precipitate, which we attribute to either a fluoride salt **1a** or the σ-bonded system **1b** (Scheme 2). Due to difficulties in isolating the highly hygroscopic fluoride salt **1**, we sought to synthesise a more stable salt by counter anion exchange for identification purposes. Consequently, a slurry of sodium tetrafluoroborate was added to the reaction mixture and the stable tetrafluoroborate salt **2** was isolated, purified and characterised by X-ray crystallography (Fig. 1), supporting the suggested structure of the analogous fluoride salt **1a**, although fluoride abstraction from **1b** would also lead to salt **2**. Overall, therefore, substitution of fluorine located at the 4-positon of pentafluoropyridine by the dimethylaminopyridine nucleophile occurs selectively, in accordance with well-established principles [15,16]

Cations and anions in **2** are located in special positions at the 2-fold axes and the two aromatic rings of the cation are twisted relative to each other (the torsion angle of C2–C3–N2–C4 is 64.2(1)°). In the crystal, ion pairs of 2-form layers perpendicular to the (0 1 0) direction.

The potential of using **1** as a nucleophilic fluorinating reagent was determined in reactions with a short series of model halogenated substrates in which the leaving group is attached to a variety of sp^2 and sp^3 hybridised carbon sites (Table 1). The halogenated substrates were added to a slurry of **1** in acetonitrile and, after stirring overnight with heating if necessary, the yields of fluorinated products were obtained by quantitative ^{19}F NMR with reference to a known mass of 1,4-difluorobenzene. In all cases, fluorination of the substrate occurred and fluorinated products were obtained in modest-good yields.

The low yield of 1-fluorooctane from 1-bromooctane was attributed to the formation of oct-1-ene, which could be identified by GC/MS, and formed by fluoride ion promoted elimination of hydrogen bromide. A further yield-limiting process was found to be reaction of the electrophilic substrate with free DMAP, generated by fluoride ion attack on **1**. For example, in a separate experiment we confirmed that reaction of 1-bromooctane with DMAP in acetonitrile, under the same reaction conditions as those used for fluorination, resulted in the formation of 4-(dimethylamino)-1-octylpyridinium bro-

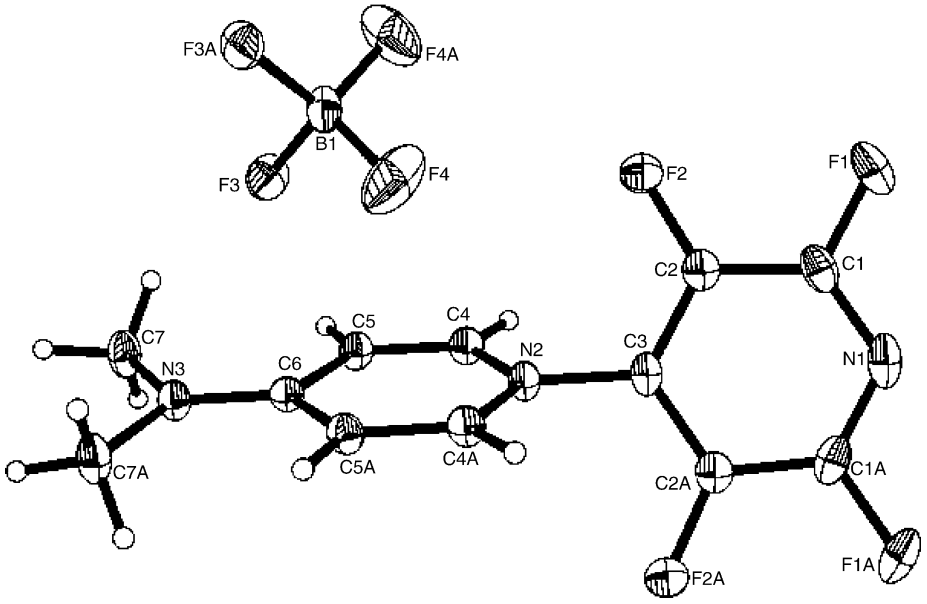
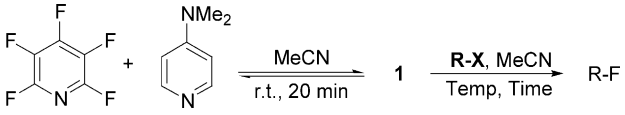
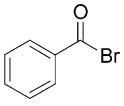
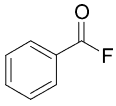
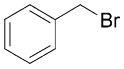
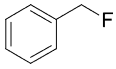
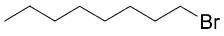
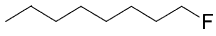
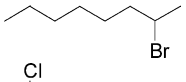
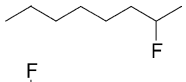
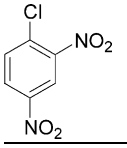
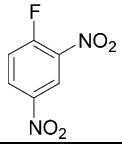


Fig. 1. X-ray structure of **2**.

Table 1
Fluorination of organo-halides using **1**

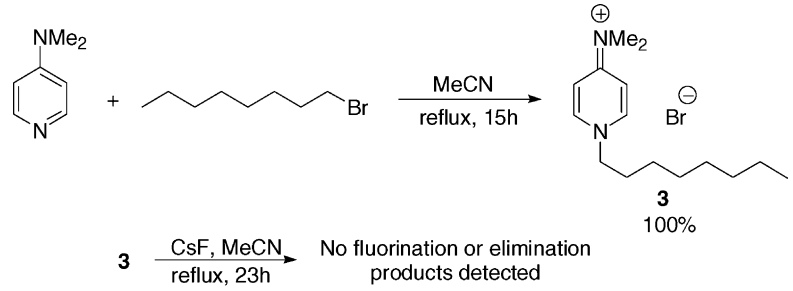


R-X	R-F	Temperature (°C)	Time (h)	Yield (%)
		Reflux	17	57[a]
		20	1	53[b]
		Reflux	24	47[b]
		Reflux	17	10[a]
		20	18	72[b]

[a] Reaction mixture heated upon addition of pentafluoropyridine, halogenated substrate added when reflux attained.
[b] DMAP and pentafluoropyridine alowed to react for 5 min at 20 °C prior to addition of halogenated substrate and heating if neccessary.

mide **3** in quantitative yield (Scheme 3). Pyridinium groups are, of course, good leaving groups and may be susceptible towards nucleophilic attack by fluoride ion. However, reaction of **3** with anhydrous caesium fluoride in refluxing acetonitrile gave no fluorinated products, as observed by NMR and GC techniques, indicating that alkylation of the electrophilic substrate by DMAP effectively removes the substrate from the fluorination process.

Reaction of **1** with 1-bromooctane was carried out in a range of solvents without any significant increase in yield from that achieved in acetonitrile (Table 2). An exception to this was the use of DMF, which gave a slight increase in the yield of fluorinated product. However, acetonitrile is probably the most effective reaction medium for these processes because of the well-known difficulties of isolating products from DMF in the longer term.



Scheme 3.

Table 2
Fluorination of 1-bromooctane in different solvents

Solvent	1-Fluorooctane (%)
Ethylene glycol	0
DCM	19
THF	23
Toluene	24
MeCN	31
DMF	37

3. Conclusions

In summary, therefore, a new nucleophilic fluorinating reagent, derived from reaction of dimethylaminopyridine with pentafluoropyridine has been prepared. A short series of fluorination reactions established that the fluoride salt **1** is a reasonably efficient fluorinating agent, although the relatively low solubility of the salt **1** in acetonitrile limits the fluorinating ability of the system. Related pyridine/DMAP type fluoride ion reagents would have to be more soluble in organic solvents before such fluorinating agents can be considered to approach the utility of more established sources of fluoride ion.

4. Experimental

All starting materials were obtained commercially (Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S n.m.r. spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. In ^{19}F NMR spectra, upfield shifts are quoted as negative and coupling constants are given in Hz. Mass spectra were recorded on either a VG 7070E spectrometer or a Fissons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. 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. Single crystal data were collected on a Bruker SMART-CCD 6000 diffractometer ((-scan, 0.3°/frame) at 120.0(2) K using graphite monochromated Mo K(radiation ((= 0.71073 Å). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXL software.

4.1. 4-(Dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl) pyridinium tetrafluoroborate 2

A two-necked flask equipped with a condenser, magnetic stir bar, septa and inert gas inlet was charged with DMAP (2.41 g, 20 mmol) and MeCN (40 mL), followed by pentafluoropyridine (3.38 g, 20 mmol). After stirring for 20 min at 20 °C, a pale yellow solution and thick light yellow precipitate had formed. The reaction mixture was filtered using Schlenk techniques and washed twice with portions of cold MeCN. A pale yellow solid was isolated and slurried with MeCN (40 mL). Sodium tetrafluoroborate (2.20 g, 20 mmol) was added, resulting in the almost immediate dissolution of the pale yellow solid to form a yellow solution from which a white solid slowly precipitated. After stirring overnight, the solution was filtered and the solvent was evaporated to yield the crude product as a yellow solid (2.68 g). Recrystallisation from acetonitrile gave 4-(dimethylamino)-1-(2,3,5,6-tetrafluoropyridin-4-yl)pyridinium tetrafluoroborate **2** (1.22 g, 17%) as colourless crystals; mp >250 °C; (Found: C, 39.7; H, 2.8; N, 11.4. $C_{12}H_{10}BF_8N_3$ requires C, 40.1; H, 2.8; N, 11.7%); δ_H (DMSO) 3.34 (6H, s, N(CH_3)$_2$), 7.35 (2H, d, $^3J_{HH}$ 7.6, Ar-H), 8.39 (2H, d, $^3J_{HH}$ 7.6, Ar-H); δ_F (DMSO) −88.7 (2F, m, F-2), −147.0 (2F, m, F-3), −148.7 (4F, s, B-F_4^-); δ_C (DMSO) 40.6 (s, N(CH_3)$_2$), 108.6 (s, (NMe$_2$)C-*C*), 131.0 (m, N$^+$-*C*-CF), 137.8 (dd, $^1J_{CF}$ 263, $^3J_{CF}$ 38, N$^+$-C-*C*F), 141.2 (s, N$^+$-*C*H), 142.8 (dt, $^1J_{CF}$ 245, $^3J_{CF}$ 16, N-*C*F), 156.6 (s, N-*C*-CH); *m*/*z* (EI$^+$) 272 (M$^+$, 100%). Suitable crystals were obtained for X-ray diffraction by slow evaporation of their MeCN solution.

Crystal data for **2**:[1] $C_{12}H_{10}BF_8N_3$, M = 359.04, monoclinic, space group C2/c, *a* = 7.9938(8), *b* = 22.540(2), *c* = 7.8484(5) Å,(= 103.46(4)°, *U* = 1375.3(2) Å^3, *F*(000) = 720, *Z* = 4, D_c = 1.734 mg m^{-3}, (= 0.181 mm^{-1}. 4976 reflections (1.81 ≤ (≤ 27.5°) were collected yielding 1568 unique data (R_{merg} = 0.023). Final $wR_2(F^2)$ = 0.1201 for all

[1] CCDC contains the supplementary crystallographic data for this paper. These data can be viewed free of charge via http://www.ccdc.cam.ac.uk/cont/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

Table 3
Fluorination reactions of fluoride ion source 1

Substrate	Quantity	Product (δ_F)	Temperature (°C)	Time (h)	Yield (%)
PhCOBr	1.29 mL, 10 mmol	PhCOF (+18)	Reflux	17	57[a]
$PhCH_2Br$	1.15 mL, 10 mmol	$PhCH_2F$ (−204)	20	1	13[b]
n-$C_8H_{17}Br$	1.80 mL, 10 mmol	n-$C_8H_{17}F$ (−217)	Reflux	24	20[b]
$CH_3CHBrC_6H_{13}$	1.80 mL, 10 mmol	$CH_3CHFC_6H_{13}$ (−171)	Reflux	17	10[a]
2,4-Dinitrochlorobenzene	1.99 g, 10 mmol	2,4-Dinitrofluorobenzene (−108)	20	18	64[b]

[a] Reaction mixture heated upon addition of pentafluoropyridine, halogenated substrate added when reflux attained.
[b] DMAP and pentafluoropyridine allowed to react for 5 min at 20 °C prior to addition of halogenated substrate and heating if neccessary.

data (132 refined parameters), conventional $R(F) = 0.0416$ for 1344 reflections with $I \geq 2($, GOF = 1.065.

4.2. Fluorination reactions – general procedure

A two-necked round-bottom flask was equipped with a condenser, magnetic stir bar, septa and inert gas inlet. The flask was charged with DMAP (1.22 g, 10 mmol) and acetonitrile (20 mL). Depending on the substrate, one of two procedures was then followed (see Yield entries in Table 3):

(i) When the DMAP had dissolved, pentafluoropyridine (1.69 g, 10.0 mmol) was added via a syringe and the mixture was heated to reflux. A yellow solution formed immediately on mixing and within a five-minute period a thick yellow precipitate had formed that dissolved at reflux. Halologenated substrate (10 mmol) was then added via a syringe as soon as reflux temperature had been attained and the reaction was stirred at reflux until the reaction was complete.
(ii) When the DMAP had dissolved, pentafluoropyridine (1.69 g, 10.0 mmol) was added via a syringe and the mixture was left to stir for five minutes at 20 °C. A yellow solution formed immediately on mixing and within the five-minute period a thick yellow precipitate had formed. Halogenated substrate (10 mmol) was then added via a syringe and the reaction was stirred at the desired temperature until the reaction was complete.

Quantitative ^{19}F NMR using 1,4-difluorobenzene as an internal standard allowed determination of yields of fluorinated products by integration to the internal standard with reference to literature data. Substrates, quantities used, ^{19}F NMR shifts of products formed, reaction conditions and yields are collated in Table 3.

4.3. 4-(Dimethylamino)-1-octylpyridinium bromide **3**

A two-necked flask equipped with a condenser, magnetic stir-bar, septa and inert gas inlet was charged with DMAP (1.22 g, 10 mmol) and MeCN (10 mL) followed by 1-bromooctane (1.80 mL, 10 mmol) when the DMAP had fully dissolved. The reaction was heated to reflux and left to stir for 15 h. Evaporation of the solvent on a rotary evaporator gave 4-(dimethylamino)-1-octylpyridinium bromide **2** (3.15 g, 100%) as a very pale yellow hygroscopic solid; (Found: C, 56.8; H, 8.5; N, 9.1. $C_{12}H_{27}BrN_2$ requires C, 57.1; H, 8.6; N, 8.9); δ_H 0.83 (3H, t, $^3J_{HH}$ 7.0, CH_3), 1.23 (10H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.84 (2H, m, $^3J_{HH}$ 7.0, $N^+CH_2CH_2$), 3.25 (6H, s, $N(CH_3)_2$), 4.31 (2H, t, $^3J_{HH}$ 7.5, N^+CH_2), 7.03 (2H, d, $^3J_{HH}$ 7.5, $N(CH_3)_2CH$), 8.46 (2H, d, $^3J_{HH}$ 8.0, N^+CH);*m/z* (ES^+) 235 (M^+, 100%).

4.4. Attempted reaction of **3** with caesium fluoride

A two necked flask was charged with **3** (2.70 g, 8.6 mmol) and anhydrous CsF (1.45 g, 9.5 mmol) in a glove box. The flask was removed from the glove box and a condenser and inert gas inlet were attached. MeCN (10 mL) was added and the flask was stirred at 20 °C. A pale yellow solution resulted and, after stirring overnight, ^{19}F NMR showed that no reaction had occurred. The reaction was then heated to reflux for 23 h but no fluorinated products were observed by ^{19}F NMR analysis. The volatile fractions were then removed by vacuum transfer to yield a colourless liquid, which was shown by GC analysis to be MeCN only.

4.5. Screening of solvents for fluorination reactions

A six-flask Radley's Carousel reactor was purged with argon and five of the flasks were charged with DMAP (1.22 g, 10 mmol), followed by the appropriate solvent (40 mL). The condenser head was connected to a glycol/water recirculating cryostat at −10 °C. When the DMAP had dissolved and the head had cooled (−8 °C indicated), pentafluoropyridine (1.69 g, 10 mmol) was added, and the reaction mixture was stirred rapidly for five minutes. All reactions showed the expected yellow/orange colouration, except for the flask containing ethylene glycol which remained colourless. 1-Bromooctane (1.80 mL, 10 mmol) was added and the reactions were heated to reflux for 20 h. Analysis by quantitative NMR, using 1,4-difluorobenzene as the reference, gave the yields of 1-fluorooctane as indicated in Table 2.

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