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Short communication

N-Halogeno compounds. Part 14. "Transfer fluorination" of quinuclidine using F-TEDA-BF_4 (Selectfluor™ reagent): laboratory synthesis of *N*-fluoroquinuclidinium salts not requiring the use of elemental fluorine ☆

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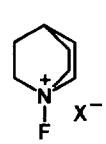
Abstract

N-Fluoroquinuclidinium tetrafluoroborate (**1b**) has been prepared in excellent yield by "transfer fluorination" of quinuclidine with 1-chloromethyl-4-fluoro-1,4-diazoniab*icyclo*[2.2.2]octane bis(tetrafluoroborate) (F-TEDA BF_4, Selectfluor™ reagent), which will also effect *N*-fluorination of pyridine and 2,4,6-trimethylpyridine.

Keywords: *N*-halogeno compounds; Quinuclidine; Synthesis

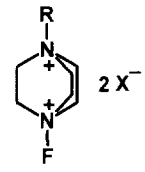
1. Introduction

N-Fluoroquinuclidinium (NFQN) salts (**1**), particularly the triflate (**1a**) and its less expensive tetrafluoroborate analogue (**1b**) (the fluoride **1c** is hygroscopic), are easily handled, site-selective electrophilic fluorinating agents useful for the fluorination of carbanions [1–3]. In our limited experience, highly basic (charge-localized) carbanions give better yields of C–F products with NFQN salts than with the equally user-friendly but more powerful "F^+" transfer reagents based on triethylenediamine (F-TEDA salts, **2**). Hitherto, the possibility of widespread use of this advantage has been virtually precluded by the lack of NFQN salts commercially [1] and the unwelcome prospect in many laboratories of having to undertake their own in-house synthesis using fluorine [1,2]. The present report explains how these disadvantages have been overcome.



(1)

X = (a) $CF_3SO_3^-$ (TfO^-)
(b) BF_4^-
(c) F^-



(2)

2. Results and discussion

In keeping with the order of fluorinating power F-TEDA-BF_4 (**2**; R = CH_2Cl, $X^- = BF_4^-$) > NFQN-T (**1a**) > *N*-fluoropyridinium triflate (NFP-T (**3**; Y = H, $X^- = TfO^-$)) > *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTMP-T (**3**; Y = Me, $X^- = TfO^-$)) established through practical experience of the use of these *N*-fluoroammonium salts in C–F bond synthesis (see, for example, Refs. [2–4]), and also confirmed by electrochemical measurements [5] [2], transfer

☆ Part 13: Banks and Sharif [1].

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[1] Small quantities produced at UMIST have been made available through Fluorochem Ltd. (Glossop, UK).

[2] Note that the recent criticism of basing reactivity orders of electrophilic fluorinating agents of the N–F class on electrochemical measurements [6] will be rebutted soon [7].

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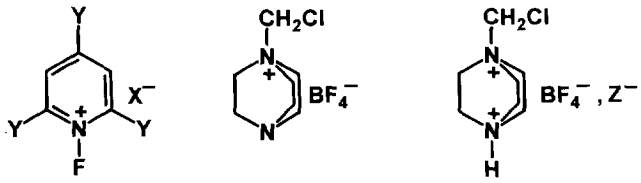
of "F^+" from F-TEDA-BF_4 to the tertiary nitrogen sites in quinuclidine, pyridine and 2,4,6-trimethylpyridine has been shown to occur rapidly and exothermically in acetonitrile (initially at ambient temperature). Reactions were followed by NMR analysis (^{13}C, ^1H, ^{19}F) and found to be complete within 10 min.



(3) (4) (5) $Z^- = HSO_4^-$ (6) $Z^- = Cl^-$

Preparative experiments were carried out only with quinuclidine. *N*-Fluoroquinuclidinium tetrafluoroborate (**1b**) and the F-TEDA-BF_4 residue 1-chloromethyl-4-aza-1-azoniabi*cyclo*[2.2.2]octane tetrafluoroborate (**4**) were obtained quantitatively, and separated using chromatography or by conventional solvent extraction following the addition of sulphuric or hydrochloric acid to convert **4** to its 4-azonia derivatives (**5** or **6**, respectively). Since F-TEDA-BF_4 (Selectfluor™ reagent (**2**; $R = CH_2Cl$, $X^- = BF_4^-$)) is readily available in commercial quantities [3], the synthesis of *N*-fluoroquinuclidinium tetrafluoroborate can now be achieved without having to handle fluorine.

No attempt was made to develop preparative procedures for "F^+" transfer from F-TEDA-BF_4 to ring nitrogen in pyridine or 2,4,6-trimethylpyridine because both of the *N*-fluoropyridinium tetrafluoroborates formed (**3**; Y = H or Me, $X = BF_4^-$) are available commercially (see, for example, Ref. [8]). Note, however, that while formation of the trimethyl compound appeared to proceed smoothly (reactions were followed by ^1H and ^{19}F NMR analysis), the parent *N*-fluoropyridinium ion (in **3**; Y = H) suffered decomposition in unidentified secondary reactions, presumably associated with proton abstraction from position C-2 [9].

3. Experimental details: preparation of N-fluoroquinuclidinium tetrafluoroborate (1b)

3.1. Fluorine-transfer procedure

Using standard glassware filled with dry nitrogen, a solution of commercial (Air Products) 1-chloromethyl-4-fluoro-1,4-diazoniabi*cyclo*[2.2.2]octane bis(tetrafluoroborate) (**2**; $R = CH_2Cl$, $X^- = BF_4^-$; 7.71 g, 21.75 mmol) in HPLC-grade acetonitrile (Aldrich; 30 cm^3) was added slowly but continuously to a stirred solution of quinuclidine (Aldrich; 2.42 g, 21.8 mmol) in the same solvent (20 cm^3). The exothermic reaction which commenced immediately proceeded to completion within 10 min, according to ^1H NMR analysis of the reaction mixture; nevertheless, the mixture was stirred at room temperature for 2 h before the solvent was removed under reduced pressure to provide a white solid (10.01 g, 99%), shown by NMR analysis to be an equimolar mixture of *N*-fluoroquinuclidinium tetrafluoroborate (**1b**) and 1-chloromethyl-4-aza-1-azoniabi*cyclo*[2.2.2]octane tetrafluoroborate (**4**).

3.2. Separation of products

3.2.1. Chromatographic

A sample (2.0 g) of a 1:1 molar mixture of **1b** and **4** produced by transfer fluorination was subjected to dry column flash chromatography (DCFC) on dry silica (Art. 7736 Kieselgel 60H, Merck; dried at 120 °C in air for 24 h) eluted with successive portions (15 cm^3) of CH_2Cl_2–Me_2CO (1:1 v/v; 2:5 v/v Et_2O–Me_2CO works equally well and eliminates the use of a chlorocarbon). Spectroscopically pure (^1H, ^{19}F and ^{13}C NMR [1,2]) *N*-fluoroquinuclidinium tetrafluoroborate (**1b**; elution monitored iodimetrically [1] using starch–iodide paper) eluted first, and was recovered (Rotavapor) and dried (as a solution in AnalaR acetone, with $MgSO_4$; 24 h), to provide analytically pure material (0.91 g). Anal. found: C, 38.9; H, 5.9; N, 6.5. $C_7H_{13}BF_5N$. Calc.: C, 38.75; H, 6.0; N, 6.5%, m.p. 183–185 °C (literature [1], 180–185 °C). Subsequent elution gave 1-chloromethyl-4-aza-1-azoniabi*cyclo*[2.2.2]octane tetrafluoroborate (**4**) (1.02 g), m.p. 132 °C (literature [10], 132 °C), with correct NMR parameters [10].

3.2.2. Via salt formation

A solution of 96% sulphuric acid (0.55 g, 5.3 mmol) in AnalaR acetone (55 cm^3) was added dropwise to a vigorously stirred solution of a 1:1 molar mixture (2.0 g, 8.4 mmol) of **1b** and **4** in the same solvent (50 cm^3) under dry nitrogen at room temperature. The white solid which precipitated was recovered by filtration, washed with AnalaR acetone (3×15 cm^3), dried in vacuo, and identified by elemental analysis and NMR spectroscopy as 1-chloromethyl-4-hydro-1,4-diazoniabi*cyclo*[2.2.2]octane hydrogen sulphate tetrafluoroborate (**5**; nc) (1.4 g, 4.0 mmol). Anal. found: C, 24.1; H, 4.6; N, 8.3; S, 8.8. $C_7H_{16}BClF_4N_2SO_4$ requires C, 24.3; H, 4.6; N, 8.1; S, 9.2%), m.p. (decomp.) 185 °C. NMR δ_H (300 MHz; Me_4Si ref.; soln. in D_2O), 3.95 (m, $3 \times CH_2NH^+$), 4.19 (m, $3 \times CH_2$), 5.50 (s, CH_2Cl) p.p.m., δ_F (188.8 MHz; CF_3CO_2H ext. ref.; same soln.) −72.50 (s, BF_4^-) ppm. Addition of diethyl ether (50 cm^3) to the filtrate caused a white solid to precipitate; this was washed with a 1:1 v/v mixture of dry diethyl ether and AnalaR acetone (3×30 cm^3), dried in vacuo, and identified by NMR spectroscopy (^1H, ^{19}F) as *N*-fluoroquinuclidinium tetrafluoroborate (**1b**) (0.88 g, 4.15 mmol).

The sulphuric acid can be replaced by hydrochloric acid, as illustrated by the large-scale separation described below.

[3] From Air Products and Chemicals Inc., 7201 Hamilton Boulevard, Allentown, PA 18195-1501, USA, or Air Products PLC, European Technology Group, Chineham, Basingstoke, Hampshire RG24 0FE, UK.

3.2.3. Large-scale procedure

A yellowish, dry 1:1 molar mixture (31.36 g; analysed by NMR spectroscopy, soln. in D_2O) of *N*-fluoroquinuclidinium tetrafluoroborate (**1b**) and 1-chloromethyl-4-aza-1-azoniabi*cyclo*[2.2.2]octane tetrafluoroborate (**4**) was prepared by evaporating to dryness (Rotavapor) a solution obtained by adding quinuclidine (6.02 g, 52.5 mmol) in dry acetonitrile (50 cm^3) dropwise (15 min) to a warm (50 °C), well-stirred solution of F-TEDA-BF_4 (99% pure, 2.80 mmol F^+ g^{-1}; 19.59 g, 54.8 mmol) in the same solvent (400 cm^3); an atmosphere of dry nitrogen was maintained throughout, and the reaction mixture was stirred at room temperature for 1 h before the solvent was removed.

The yellow mixture of **1b** and **4** was dissolved in HPLC-grade acetone (200 cm^3), and the stirred solution treated dropwise (30 min) with concentrated hydrochloric acid (61 mmol HCl) dissolved in acetone (20% v/v conc. HCl; 25 cm^3). The pale yellow solid which precipitated was recovered by filtration, washed with acetone (2×100 cm^3), then dried in vacuo at room temperature and shown by mass balance (yield: 15.37 g; theor., 14.96 g) and NMR analysis (^1H, ^{19}F; no NFQN-BF_4 (**1b**) was detected) to be essentially pure 1-chloromethyl-4-hydro-1,4-diazoniabi*cyclo*[2.2.2]octane chloride tetrafluoroborate (**6**; nc). The filtrate and washings were concentrated by evaporation (down to 40 vol.%) then mixed with diethyl ether (2×50 cm^3) to cause the precipitation of pale yellow *N*-fluoroquinuclidinium tetrafluoroborate (**1b**); this was washed with several portions of dry diethyl ether to provide NMR-pure, though still pale yellow, material (10.88 g (50.2 mmol, 96% yield) after being dried in vacuo at room temperature).

References

[1] R.E. Banks and I. Sharif, *J. Fluorine Chem., 55* (1991) 207.

[2] R.E. Banks, R.A. Du Boisson, W.D. Morton and E. Tsiliopoulos, *J. Chem. Soc., Perkin Trans. 1,* (1988) 205.

[3] G.S. Lal, US Patent 5 233 074 (to Air Products and Chemicals Inc.), 1993; *Chem. Abs., 120* (1994) 30546w.

[4] R.E. Banks, S.N. Mohialdin-Khaffaf, G.S. Lal, I. Sharif, and R.G. Syvret, *J. Chem. Soc., Chem. Commun.,* (1992) 595; R.E. Banks, N.J. Lawrence and A.L. Popplewell, *J. Chem. Soc., Chem. Commun.,* (1994) 343; T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada and K. Tomita, *J. Am. Chem. Soc., 112* (1990) 8563.

[5] A.G. Gilicinski, G.P. Pez, R.G. Syvret and G.S. Lal, *J. Fluorine Chem., 59* (1992) 157.

[6] K. Sudlow and A.A. Woolf, *J. Fluorine Chem., 66* (1994) 9.

[7] G.P. Pez et al., in preparation.

[8] *Chem. Eng. News,* (January 31, 1994) 46.

[9] T. Umemoto and G. Tomizawa, *J. Org. Chem., 54* (1989) 1726.

[10] R.E. Banks, I. Sharif and R.G. Pritchard, *Acta Cryst., C49* (1993) 492.