# *N*-Halogeno compounds. Part 13. *N*-Fluoroquinuclidinium salts — synthesis and use as electrophilic fluorinating agents*†

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## Abstract

A convenient one-pot method has been developed for the preparation of the easily handled electrophilic fluorinating agent *N*-fluoroquinuclidinium triflate from quinuclidine, lithium triflate and fluorine. The corresponding trifluoroacetate, heptafluoro-n-butyrate and tetrafluoroborate salts were procured in a two-step fashion by adding the appropriate sodium salts to acetonitrile solutions of *N*-fluoroquinuclidinium fluoride. Site-specific fluorination of phenylmagnesium bromide (to PhF), diethyl sodio(phenyl)malonate [to $PhCF(CO_2Et)_2$], 2-nitropropan-2-yl-lithium [to $Me_2CFNO_2$], 1-morpholinocyclohexene [to $\overline{CH_2(CH_2)_3CHFC}{=}O$], phenol (to 2- and 4-$FC_6H_4OH$ + 1,4-$F_2C_6H_3OH$) and sodium benzenesulphinate (to $PhSO_2F$) was achieved using these new *N*-fluoroquinuclidinium salts.

## Introduction

Interest in electrophilic fluorinating agents of the N—F class continues to mount [2], as revealed by the steady rate of publication of information concerning both new [3] and established reagents [4, 5].

Several such reagents, notably *N*-fluoroquinuclidinium fluoride, *N*-fluoro-*N*-alkyl-*p*-toluensulphonamides (Barnette reagents) and *N*-fluoropyridinium salts (Umemoto reagents), including the recent Allied-Signal modification '*N*-fluoropyridinium pyridine heptafluorodiborate', are available commercially**; clearly, however, the search continues for an 'ideal' N—F reagent or group of reagents in which the fluorinating power can be adjusted through simple structural modification. Here we describe in detail [1] studies aimed at eliminating problems associated with the use of *N*-fluoroquinuclidinium fluoride (**1**; $X^- = F^-$) arising from its marked hygroscopicity and insolubility problems [2a].

*Dedicated to Prof. Dr mult. Dr h.c. Alois Haas (Ruhr-Universität, Bochum) on the occasion of his 60th birthday.

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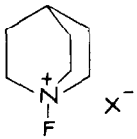


(1) $X^- = F^-$, $CF_3SO_3^-$ ($TfO^-$), $BF_4^-$, $CF_3CO_2^-$ or $n\text{-}C_3F_7CO_2^-$

## Experimental

*Spectroscopic analysis*

Details of the instruments used have been given previously [2a]. $^{19}F$ NMR (84.6 MHz) chemical shift values were determined using trifluoroacetic acid (TFA) as the external reference; positive values refer to downfield absorptions.

*Preparation of* N-*Fluoroquinuclidinium salts*

*(a) Triflate (1; $X^- = CF_3SO_3^-$)*

*(i) In a closed system* — Using exactly the same apparatus and techniques employed previously to prepare *N*-fluoroquinuclidinium fluoride from quinuclidine and fluorine in a closed glass vacuum system [2a], neat fluorine (0.95 g, 25 mmol) at 15–20 mmHg pressure was passed during 5.5 h into a de-gassed, vigorously stirred, cold (−35 °C) solution of quinuclidine (2.38 g, 21.4 mmol) and lithium triflate (3.34 g, 21.4 mmol) in HPLC grade (Aldrich) acetonitrile (200 $cm^3$) which had been prepared and transferred to the reaction vessel under strictly anhydrous conditions (dry-box techniques). After the excess of fluorine had been pumped out of the apparatus via a trap packed with granular potassium iodide, the reactor was allowed to warm to room temperature and its contents filtered to remove the finely-divided lithium fluoride which had precipitated. Evaporation of the filtrate (Rotavapor) left a white solid, which was dissolved in the minimum quantity of AnalaR acetone, reprecipitated by the slow addition of dry ethyl acetate, recovered by filtration, dried under vacuum and shown by spectroscopic methods {$\delta_F$(TFA) (soln. in $D_2O$) + 134.5 (br.s; $FN^+$), 0.0 (s; $CF_3SO_3^-$) ppm; the $^1H$ NMR spectrum was virtually identical with that of *N*-fluoroquinuclidinium fluoride [2a]; *m/z* 130 [$(M-OTf)^+$, 100%]} and elemental analysis (Found: C, 34.6; H, 4.6; F, 27.1; N, 4.9; S, 11.2%. Calc. for $C_8H_{13}F_4NO_3S$: C, 34.4; H, 4.7; F, 27.2; N, 5.0; S, 11,5%) to be *N*-fluoroquinuclidinium triflate (5.26 g, 18.85 mmol, 88%), m.p. (decomp.), 266–268 °C.

*(ii) In a flow system* — Using the apparatus employed previously to fluorinate aqueous solutions of ureas [6] except that no cold traps were employed, fluorine diluted with nitrogen (*ca.* 10% $F_2$ by volume) was bubbled slowly through a cold (−35 °C) vigorously stirred solution of quinuclidine (11.63 g, 104.7 mmol) and lithium triflate (16.34 g, 104.8 mmol) in dry acetonitrile (150 $cm^3$) until the exit gas gave a strong positive test for the

halogen (KI paper). The reaction mixture was filtered then worked up as described in (i) above, to give *N*-fluoroquinuclidinium triflate (25.03 g, 89.7 mmol, 86%) (Found: C, 34.6; H, 4.6; F, 27.1; N, 4.9; S, 11.2%. Calc. for $C_8H_{13}F_4NO_3S$: C, 34.4; H, 4.7; F, 27.2; N, 5.0; S, 11.5%), identical spectroscopically ($^1H$, $^{19}F$ NMR; IR) with the material obtained using a closed system [(i) above] or by treating *N*-fluoroquinuclidinium fluoride with trimethylsilyl trifluoromethanesulphonate [1].

The preparation was repeated on twice the scale [21.9 g quinuclidine (197 mmol) and 30.8 g lithium triflate (197 mmol) in 350 $cm^3$ acetonitrile (500 $cm^3$ reactor) at −35 °C; 1:9 (v/v) $F_2$:$N_2$ blend passed at the rate of 200 $cm^3$ $min^{-1}$] to give, after purification as before, 47.2 g (165 mmol, 85%) of *N*-fluoroquinuclidinium triflate with a correct elemental composition (C, H, F, N), m.p. (decomp.), 266–268 °C.

*(b) Trifluoroacetate (1; $X^- = CF_3CO_2^-$)*

A cold (−78 °C), vigorously stirred solution of quinuclidine (1.65 g, 14.9 mmol) in trichlorofluoromethane (200 $cm^3$) containing powdered molecular sieve (5 Å, 0.5 g to scavenge any HF formed) was exposed to fluorine at < 20 mmHg pressure in a closed reactor [2a] until uptake of the halogen ceased (*ca.* 5 h). After removal of unreacted fluorine (pumped out via a KI trap), a solution of sodium trifluoroacetate (2.01 g, 14.8 mmol) in dry acetonitrile (50 $cm^3$) was injected into the reactor, which was then allowed to warm to −40 °C *in vacuo* (dynamic pumping) to remove much of the trichlorofluoromethane (collected for recycling in a −196 °C trap). The remaining solution was warmed to 20 °C, filtered to remove sodium fluoride and the molecular sieve, and evaporated (Rotavapor). The white residue was purified by dissolution in AnalaR acetone and reprecipitation with dry ethyl acetate, then dried under vacuum to provide hygroscopic *N*-fluoroquinuclidinium trifluoroacetate (nc) (2.60 g, 10.7 mmol, 72%) (Found: C, 44.7; H, 5.7; F, 31,1; N, 5.8%. Calc. for $C_9H_{13}F_4NO_2$: C, 44,4; H, 5.35; F, 31.3; N, 5.8%), m.p. 162–164 °C; $\delta_F$(TFA) (soln. in $CH_3CN$) + 133.5 (br.s; $FN^+$), + 2.0 (s; $CF_3CO_2^-$) ppm; *m/z* 130 [$(M - CF_3CO_2)^+$, 12%], 111 ($C_7H_{13}N^+$, 80%).

*(c) Heptafluorobutyrate (1; $X^- = n\text{-}C_3F_7CO_2^-$)*

Reaction (b) was repeated with 1.69 g (15.2 mmol) quinuclidine, and sodium heptafluoro-n-butyrate (3.58 g, 15.2 mmol) in acetonitrile (100 $cm^3$) was added in the second stage instead of sodium trifluoroacetate. The same work-up procedure gave a markedly hygroscopic sample of *N*-fluoroquinuclidinium heptafluoro-n-butyrate (2.46 g, 7.2 mmol, 47%), m.p. 142–144 °C; $\delta_F$(TFA) (soln. in $CH_3CN$) + 134.0 (br.s; $FN^+$), − 3.2 (t, $^4J_{FF}$ 9 Hz; $CF_3$), − 39.7 (q, $^4J_{FF}$ 9 Hz; $CF_3CF_2CF_2$), − 49.0 (s; $CF_3CF_2CF_2$) ppm (rel. int. 1:3:2:2); *m/z* 111 ($C_7H_{13}N^+$, 100%), with an unsatisfactory carbon and fluorine analysis (Found: C, 35.6; H, 3.7; F, 40.1; N, 3.7%. Calc. for $C_{11}H_{13}F_8NO_2$: C, 38.5; H, 3.8; F, 44.3; N, 4.1%).

*(d) Tetrafluoroborate (1; $X^- = BF_4^-$)*

After the preparation of *N*-fluoroquinuclidinium fluoride as in reaction (b) [using 1.19 g (10.7 mmol) of quinuclidine in 200 $cm^3$ of $CFCl_3$], sodium tetrafluoroborate (1.17 g, 10.7 mmol) in 100 $cm^3$ acetonitrile was added in the second stage. The same work-up procedure provided *N*-fluoroquinuclidinium tetrafluoroborate (nc) (1.46 g, 6.7 mmol, 63%) (Found: C, 39.0; H, 6.3; $BF_4^-$, 39.6; $F^+$, 8.6%. Calc. for $C_7H_{13}BF_5N$: C, 38.75; H, 6.0; $BF_4^-$, 40.0; $F^+$, 8.75%), m.p. 180–185 °C; $\delta_F$(TFA) (soln. in $CH_3CN$) + 134.0 (br.s; $FN^+$), −73.5 (s; $BF_4^-$) ppm; *m/z* 130 ($C_7H_{13}NF^+$, 100%).

*Site-specific electrophilic fluorinations with N-fluoroquinuclidinium salts*

Reactions involving phenylmagnesium bromide, diethyl sodio(phenyl)malonate, 2-nitropropan-2-yl-lithium and 1-morpholinocyclohexene were carried out as described previously in studies employing *N*-fluoroquinuclidinium fluoride as the source of electrophilic fluorine [2a]. The rest are described below. All the products are well-known compounds, and their identities were established by comparison of their NMR spectra ($^1H$ and $^{19}F$) with those of authentic samples.

*(a) Phenol*

*N*-Fluoroquinuclidinium triflate (0.30 g, 1.7 mmol) was added to a solution of phenol (0.15 g, 1.59 mol) in 20% aqueous sodium hydroxide solution at room temperature. An exothermic reaction occurred immediately, the mixture becoming yellow. The product was extracted with dichloromethane (2 × 10 $cm^3$), and the combined extracts were dried ($MgSO_4$), filtered and evaporated (Rotavapor). The residue was shown by $^{19}F$ NMR analysis to contain 2- and 4-fluorophenol and 2,4-difluorophenol in an approximate molar ratio of 1:1:1. Using the triflate signal present in the spectrum as an internal reference, quantitative conversion of the *N*-fluoroquinuclidinium salt to the fluorophenols was shown to occur.

In a second experiment, a slurry of *N*-fluoroquinuclidinium triflate (0.89 g, 3.19 mmol) in dry THF was added slowly to a solution of sodium phenolate in cold (−10 °C) THF [prepared by adding a 60% dispersion of NaH (5.8 mmol) in oil to PhOH (0.30 g, 3.19 mmol) in THF (10 $cm^3$) under $N_2$ at 20 °C]. The reaction mixture (which turned brown) was stirred under $N_2$at room temperature for 30 min, then diluted with diethyl ether (50 $cm^3$) before being washed with 0.5 M oxalic acid (20 $cm^3$), 10% aqueous potassium hydrogen carbonate (20 $cm^3$) and saturated brine (20 $cm^3$) (in that order), dried ($MgSO_4$) and evaporated under reduced pressure. NMR spectroscopic analysis ($^1H$ and $^{19}F$) of the residue (0.06 g, 0.54 mmol, 17%) revealed it to be a *ca.* 1:2 mixture of 2- and 4-fluorophenol (authentic samples of which were used for comparison).

*(b) Sodium benzenesulphinate*

Using a 5-mm o.d. NMR tube as a reaction vessel, *N*-fluoroquinuclidinium triflate (0.15 g, 0.54 mmol) was added to dry commercial (BDH) sodium

benzenesulphinate (0.08 g, 0.54 mmol) in HPLC grade (Aldrich) acetonitrile (1 $cm^3$). A reaction occurred immediately and a clear solution formed. NMR spectroscopic analysis revealed that complete consumption of the *N*-fluoro compound had occurred (no absorption in the region of + 135 ppm) with the formation of benzenesulphonyl fluoride in 94% yield (by comparison of the relative intensities of the $^{19}F$ absorptions assignable to benzenesulphonyl fluoride and the triflate anion at $\delta_F$(TFA) + 142.5 and 0.0 ppm respectively). An analytically pure (C, H, F, S) sample of *p*-toluenesulphonyl fluoride, obtained as a by-product from the conversion of *N*-t-butyl-*p*-toluenesulphonamide to its *N*-fluoro derivative with fluorine [7] as described by Barnette [8], showed a singlet in its $^{19}F$ NMR spectrum at + 143.7 ppm ($CDCl_3$ soln.).

## Results and discussion

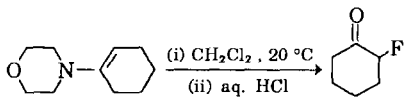
The problem of the hygroscopicity of *N*-fluoroquinuclidinium fluoride (**1**; $X^- = F^-$), has been solved by replacing the fluoride with triflate (trifluoromethanesulphonate) (to give **1**; $X^- = CF_3SO_3^-$) or tetrafluoroborate (to give **1**; $X^- = BF_4^-$). The former anion switch can be made by treating isolated *N*-fluoroquinuclidinium fluoride with trimethylsilyl triflate in dry acetonitrile (full details are given in ref. 1); however, it is much more convenient and less expensive simply to pass a 1:9 (v/v) fluorine–nitrogen blend into cold (−35 °C) acetonitrile containing an equimolar mixture of quinuclidine and lithium triflate. This one-pot procedure, conducted using a standard Pyrex reaction vessel and stirrer, provides pure *N*-fluoroquinuclidinium triflate in at least 85% yield and has been conducted several times on a 50-g (product) scale without mishap.

*N*-Fluoroquinuclidinium trifluoroacetate (**1**; $X^- = CF_3CO_2^-$), heptafluoro-n-butyrate (**1**; $X^- = n\text{-}C_3F_7CO_2^-$) and tetrafluoroborate (**1**; $X^- = BF_4^-$) have been synthesised by adding the appropriate sodium salts in acetonitrile to freshly prepared solutions of *N*-fluoroquinuclidinium fluoride in chlorotrifluoromethane [2a] (*i.e.* the fluoride **1** was not isolated). The respective yields were 72, 47 and 63% of analytically pure material, except in the case of the heptafluorobutyrate which was markedly hygroscopic. More recent work on the preparation of *N*-fluorotetrafluoroborates from 1,4-diazabicyclo[2.2.2]octane [9] indicates that the one-pot procedure used to obtain *N*-fluoroquinuclidinium triflate should be applicable to the preparation of the corresponding tetrafluoroborate (**1**; $X^- = BF_4^-$).

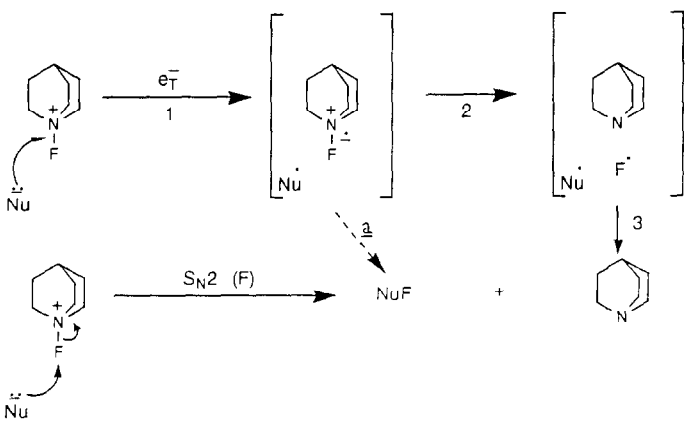
All four new *N*-fluoroquinuclidinium salts are high-melting white solids. Each of them rapidly oxidises aqueous iodide ion to iodine, and shows $^+NF$ resonance in the $\delta_F$(TFA) range + 133.5 to + 135.5 ppm, like *N*-fluoroquinuclidinium fluoride. The seemingly non-hygroscopic (though very water-soluble) trifluoromethanesulphonate and tetrafluoroborate can be handled 'normally', but the trifluoroacetate and heptafluorobutyrate are hygroscopic — the latter markedly so — and are best manipulated using dry-box techniques, like the fluoride [2a].

TABLE 1

Site-specific electrophilic fluorination with *N*-fluoroquinuclidinium salts (**1**)

| Reaction[a] | Salt used and yield (%)[b] of product(s) | | | | |
|---|---|---|---|---|---|
| | $F^-$ [2a] | $CF_3SO_3^-$ | $CF_3CO_2^-$ | $C_3F_7CO_2^-$ | $BF_4^-$ |
| $PhMgBr \xrightarrow[20\ °C]{Et_2O^c} PhF$ | 26 | 26 | – | – | – |
| $PhC(CO_2Et)_2^-Na^+ \xrightarrow[-10\ to\ 20\ °C]{THF^c} PhCF(CO_2Et)_2$ | 56 | 52 | – | – | – |
| $Me_2CNO_2^-Li^+ \xrightarrow[0\ to\ 20\ °C]{MeOH^d} Me_2CFNO_2$ | 47[e] | 72[e] | 56[e] | 61[e] | 50[e] |
| $PhSO_2Na \xrightarrow[20\ °C]{MeOH^d} PhSO_2F$ | – | 94[e] | – | – | – |
| $PhOH \xrightarrow{NaOH\ aq.^d}$ 2-$FC_6H_4OH$, 4-$FC_6H_4OH$, 2,4-$F_2C_6H_3OH$ (1:1:1) | – | 100[e] | – | – | – |
|  | 43 | 58[e] | 67[e] | 88[e] | 62[e] |

[a]1:1 Molar ratios of N–F: substrate were employed.
[b]Isolated yields unless stated otherwise.
[c]Suspension of the N–F reagent used.
[d]Solution of the N–F reagent used.
[e]Yield estimated by GLC and $^{19}F$ NMR analysis (using internal standards).




[a]Note that if steps 2 and 3 of the SET pathway merge, the question of the release of fluorine atom does not arise; neither does the onset of an $S_{RN}1$ process.

Scheme 1.

Site-selective fluorinations carried out with the new salts are summarized in Table 1, together with details for the prototypical fluoride [2a]; note that no effort was made to optimise yields. The yield of 2-fluorocyclohexanone achieved with *N*-fluoroquinuclidinium heptafluoro-n-butyrate seems to indicate some influence of the counteranion on the reaction outcome. This is a possible feature which we have not investigated, as is the effect of solvent character. Hopefully, research groups interested in the synthesis of C–F bonds in much more complicated molecules than our model substrates will choose to utilise one or more of these *N*-fluoroquinuclidinium salts, and so provide further information on their behaviour as fluorinating agents.

On a practical note, one of the drawbacks to using *N*-fluoroquinuclidinium fluoride is that it is not perceptibly soluble in tetrahydrofuran, chlorinated solvents (*e.g.* $CH_2Cl_2$), acetone, DMSO or hydrocarbons, and not very soluble in acetonitrile. By contrast, *N*-fluoroquinuclidinium triflate is noticeably soluble in acetonitrile, acetone and DMSO, as well as being very soluble in water, methanol, ethanol and trifluoroacetic acid (as is the fluoride salt [2a]). In addition, the tetrafluoroborate, trifluoroacetate and heptafluorobutyrate are soluble in acetonitrile, acetone and hydroxylic solvents.

No effort has been made to probe the mechanism of '$F^+$' transfer to anionic carbon (or sulphur in sodium benzenesulphinate). As with perfluoro-*N*-fluoropiperidine [5], reactions may proceed either via concerted displacements on the fluorine of the $FN^+$ moiety or through an SET process (see Scheme 1 for the general case of a charged substrate). Not that the conversion of a sulphinate salt to the corresponding sulphonyl fluoride with an N–F reagent appears to be novel. Studies on the mechanism and synthetic scope of this reaction are in progress.

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