1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Salts: a Novel Family of Electrophilic Fluorinating Agents[1]

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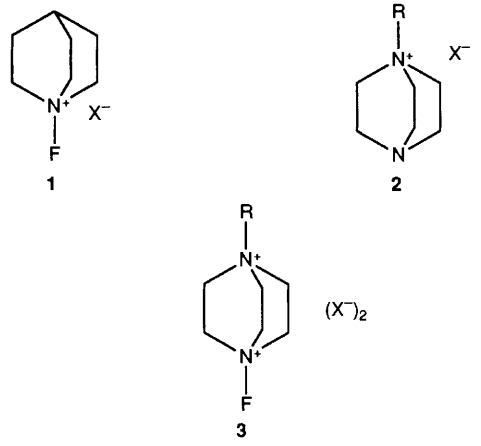
Members of a new series of solid, easily handled, storable, transportable, commercially viable, site-selective electrophilic fluorinating agents of the $^+$N–F class (tradenamed Selectfluor reagents) have been synthesized *via* direct fluorination of monoquaternary salts of 1,4-diazabicyclo[2.2.2]octane.

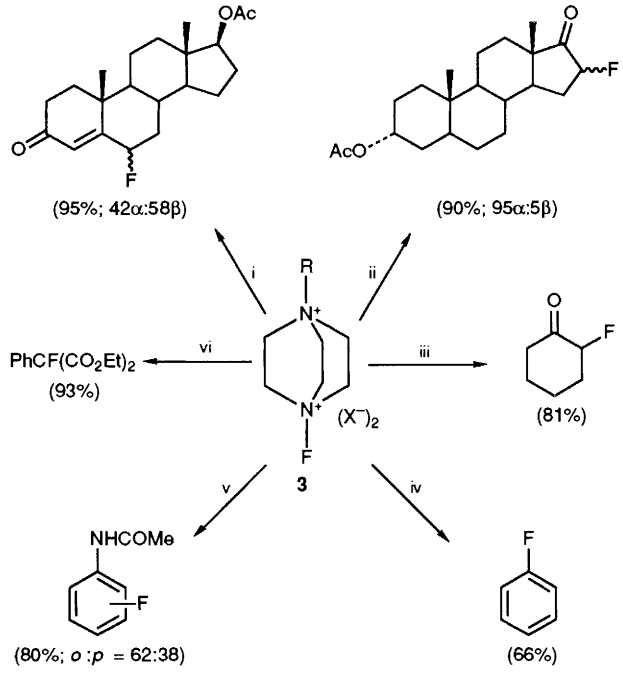
Unremitting interest worldwide in site-selective fluorination (including ^{18}F placement) of biologically-active molecules[2,3] has heightened demand for more generally acceptable (less aggressive, non-explosive, less toxic, inexpensive) electrophilic fluorinating agents[4] than perchloryl fluoride,[5] O–F reagents (CF_3OF, $CsSO_4F$),[4–6] xenon difluoride[7] or fluorine itself.[8] Of late, the search for an ideal 'F^+' transfer agent has centred on N–F compounds,[9] with the result that *N*-alkyl-*N*-fluoro-*p*-toluenesulfonamides (Barnette reagents), *N*-fluoroquinuclidinium fluoride and trifluoromethanesulfonate (triflate, TfO^-) (Banks reagents) **1** and certain *N*-fluoropyridinium salts (Umemoto reagents), including a modification of the prototypical tetrafluoroborate,[10] are now commercially available.

Direct fluorination of 1,4-diazabicyclo[2.2.2]octane and its monoquaternary salts **2** has been studied with the objective of producing electrophilic fluorinating agents that are just as easy and safe to use as *N*-fluoroquinuclidinium salts **1**[11] but more powerful. This simple strategy of incorporating a second quaternized bridgehead nitrogen into the ring system proved extremely successful, for not only did it produce the desired effect, but also it enabled the fluorinating power to be 'tuned' through variation in the electronegativity of the quaternizing group R.

Attempts to prepare 1,4-difluoro-1,4-diazoniabicyclo-[2.2.2]octane difluoride **3** (R = F; X^- = F^-) or ditriflate **3** (R = F; X^- = TfO^-) *via* passage, respectively, of neat fluorine at approximately 20 mmHg pressure into cold (−78 °C) trichlorofluoromethane containing 1,4-diazabicyclo[2.2.2]octane,[12] or fluorine–nitrogen blends into cold (−20 to −40 °C) solutions of the same substrate in acetonitrile containing lithium triflate at atmospheric pressure, proved unsatisfactory [*cf.* ref. 11 the successful syntheses of **1** (X^- = F^- or TfO^-)]. However, fluorination of monoquaternary salts **2** (R = Me, CH_2Cl, or CF_3CH_2; and X^- = TfO^- or BF_4^-, for example) in the presence of lithium triflate or sodium tetrafluoroborate, as appropriate, proceeded smoothly in cold acetonitrile to give high yields (87–95% after purification) of the corresponding 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts **3** (R = Me, CH_2Cl or CH_2CF_3; X^- = TfO^- or BF_4^-). The structures of these new fluoroammonium salts were established by elemental (C, H, F, N) and spectroscopic analyses [notably ^{1}H, ^{13}C, ^{19}F; δ$^+$NF (CF_3CO_2H) values (D_2O solutions) fall in the range from +124 to +127.5 (*cf.* ref. 11*a*, *N*-fluoroquinuclidinium salts of from +133.5 to +135.5)], and X-ray crystallography [$^+$N–F distance in **3** (R = CH_2Cl; X^- = BF_4^-) = 1.37(2) Å;[13] *cf.* ref. 13 **1** (X^- = TfO^-) 1.406 Å]; they are white, freeflowing, virtually non-hygroscopic, crystalline, high-melting solids [*e.g.* **3** (R = CH_2Cl; X^- = BF_4^-) 190 °C;[14] **3** (R = Me; X^- = TfO^-) 220–221 °C (decomp.)] that are soluble in polar solvents [H_2O, Me, MeCN and dimethylformamide (Me_2SO attacks them)], liberate iodine rapidly from acidified (HCl) aqueous acetonic potassium iodide, hence they can be assayed (1 mol $^+$NF ≡ 1 I_2),[11] oxidize bromide ion to bromine at room temperature, and, though stable towards cold aqueous mineral acids, are decomposed by cold aqueous sodium hydroxide. Conventional methodology provides easy access to the monoquaternary salts **2** used as precursors of the Selectfluor reagents **3** {*e.g.* 1,4-diazabicyclo[2.2.2]octane + MeCl + $NaBF_4$ (or LiOTf) in MeCN at 20 °C → **2**, R = Me, X^- = BF_4^- (or TfO^-), in 98% (or 86%) yield, after purification}.

1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts **3** smoothly and selectively fluorinate a variety of substrates with





Scheme 1 *Reagents and conditions*: i, testosterone enol diacetate, MeCN, 15 min at 25 °C (R = CH_2Cl, X^- = BF_4^-); ii, androsterone enol diacetate, MeCN, 2 h at 25 °C (R = CH_2Cl, X^- = BF_4^-); iii, 1-morpholinocyclohex-1-ene, CH_2Cl_2, 20 °C (R = CH_2CF_3, X^- = TfO^-); iv, PhMgBr, 25 °C, 2 h, Et_2O (R = CH_2Cl, X^- = TfO^-); v, PhNHCOMe, refluxing MeCN, 15 min (R = CH_2Cl, X^- = BF_4^-); vi, sodio derivative of diethyl phenylmalonate, tetrahydrofuran–dimethylformamide (2:1), 25 °C, 30 min (R = Me, X^- = TfO^-). Reactant ratios = 1:1 molar. Yields refer to isolated products.

overt or masked carbanionic character, as exemplified in the fluorination reactions of Scheme 1. Steroids, in the form of the appropriate enol acetates are rapidly and selectively fluorinated at room temperature giving the 6- or 16-fluoro compounds in high yields, the latter also with very high stereoselectivity ($\alpha:\beta = 95:5$). In this application they are far more effective than the other available $^{+}$N–F reagents.[4,10,11] Highly-stabilized carbanions such as the sodium salt of diethyl phenylmalonate give fluoro derivatives in high yields, but the reagents appear to be less effective with more reactive carbanion systems such as ketone-derived metal enolates. Grignard reagents are smoothly converted to the corresponding monofluoro compounds.

Within the Selectfluor reagent series there is greater ease of 'F^{+}' transfer as the electronegativity of the quaternary group R increases. For example, with **3** where R = CH_2CF_3 and X^- = TfO^-, in wet acetonitrile there is 72% conversion of anisole to an approximately 1:1 mixture of *o*- and *p*-fluoroanisole in 5 h at 40 °C. With the *N*-chloromethyl (**3**: R = CH_2Cl; X^- = TfO^-) and *N*-methyl (**3**: R = Me; X^- = TfO^-) analogues, the reaction proceeds to the same extent under otherwise identical conditions in 6 and 13 h, respectively. In consonance with the stratagem on which the discovery of reagents of type **3** was based, *N*-fluoroquinuclidinium salts **1** have been found to be noticeably less reactive than salts of type **3** towards many types of substrate. Thus, fluorination of anisole at 40 °C in wet acetonitrile is imperceptible (gas chromatographic analysis) even after 24 h.

The Selectfluor salts comprise a highly reactive, yet remarkably stable, family of selective electrophilic fluorinating agents. Investigations aimed at uncovering further applications of these new reagents are in progress.

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