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1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate): An Electrophilic Fluorinating Agent

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Abstract: 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), NFTh, is a electrophilic fluorinating that can be used to fluorinate aromatic rings, olefins, dienol acetates and enol ethers. When NFTh is reacted with an active methylene compound in the presence of $ZnCl_2$, the corresponding mono- or di-fluoro derivative can be isolated.

During the past decade considerable attention has been focused on new and safe methods for introducing fluorine into organic compounds.[1] This interest has been due to the profound effect the fluorine has on a compound's physical properties and biological activity.[2] We have introduced N-fluoropyridinium pyridine heptafluorodiborate, NFPy, as a reagent to selectively transfer fluorine under mild conditions to the reactive sites of activated olefins (e.g. enol esters, silyl enol esters, and enamides) and N-fluorobenzenesulfonimide, NFSi, as a highly versatile and inexpensive source of electrophilic fluorine for the halogenation of anions and enolic compounds.[3] Zupan's recent publications on electrophilic fluorinating agents has prompted us to communicate our investigation into the chemistry of 1-fluoro-4-hydroxy-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate), NFTh, **1**.[4]

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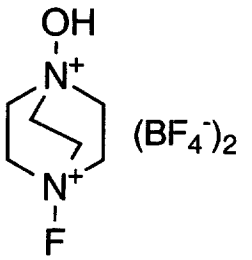

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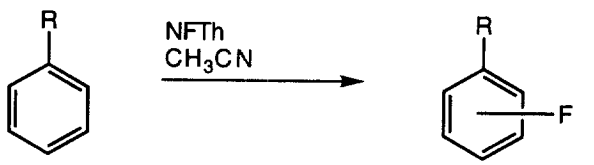
NFTh is conviently prepared by fluorinating (10% F_2/N_2, 2 equivalent) an acetonitrile solution (0.1 M) of 1,4-diazabicyclo[2.2.2]octane N-oxide, boron trifluoride (1.25 equivalents), and tetrafluoroboric acid (1 equivalent) at 0°C.[5,6] After evaporation of the solvent, the solids were washed with 1,2-dimethoxyethane and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), **1**, was isolated in 75% yield as a white solid that decomposes at 125°C.[7] The reagent requires no special glassware or handling for fluorination reactions.

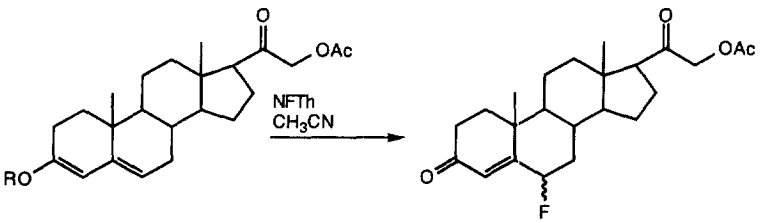
A survey of the reactions of NFTh indicate that it is capable of introducing fluorine to the reactive position of an aromatic ring, across a stabilized carbon-carbon double bond, or to the activated site of an electron-rich olefin (e.g. dienol acetates or silyl enol ethers). In the presence of a Lewis acid, NFTh can be used to convert active methylene compounds into their corresponding mono- or di-fluoro derivatives.

Treatment of electron rich aromatics with NFTh in acetonitrile affords the corresponding fluoroaromatics in good yield. Acetanilide, **2**, reacts with NFTh at 40°C in acetonitrile to yield a 2:1 mixture of *ortho*- to *para*-fluoroacetanilide. Similarily, the less reactive phenylurethane, **3**, affords the same mixture of fluorinated products in 88% yield and anisole reacts with NFTh at room temperature give a 1:2.4 mixture of 1- to 4-fluoroanisole in 83% yield.



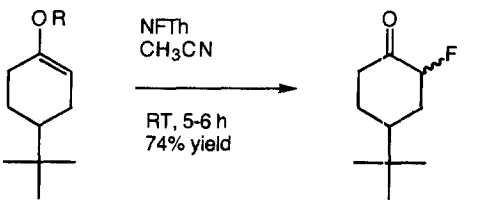
2	R = NHAc	40°C, 6 h	84% yield	o / p = 2 : 1
3	R = $NHCO_2Et$	80°C, 6 h	88% yield	o / p = 1 : 2.3
4	R = OCH_3	20°C, 5 h	83% yield	o / p = 1 : 2.4

Fluorine can be introduced selectively into the 6-position of steroids by employing a dienol derivative. The reaction of the dienol acetate derived from 4-pregnen-21-ol-3,20-dione acetate, **5**, with NFTh at room temperature yields the expected 6-fluoro steroid. The corresponding methyl dienol ether, **6**, can also be fluorinated with NFTh in 72% yield.



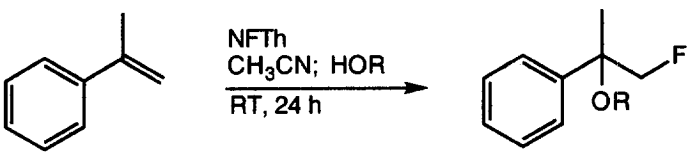
5	R = Ac	25°C, 15 min	89% yield	α / β = 1 : 2.2
6	R = CH_3	25°C, 6 h	72% yield	α / β = 1 : 2.4

We have found that enol acetates, enol ethers and trimethylsilyl enol ethers also react efficiently with NFTh in acetonitrile to afford α-fluoro ketones. Treating 1-acetoxy-4-tertbutylcyclohexanone, **7**, with 1-fluoro-4-hydroxy-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) at room temperature affords a 74% yield of a 1:1.2 ratio of *cis*- to *trans*-2-fluoro-4-tertbutylcyclohexanone. The corresponding ethyl enol ether, **8**, and trimethylsilyl enol ether, **9**, can also be fluorinated with NFTh to yield the fluoro-cyclohexanone.



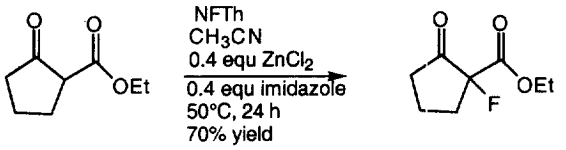
7	R = Ac	74% yield	cis / trans = 1 : 1.2
8	R = Et	43% yield	cis / trans = 12.8 : 1
9	R = TMS	44% yield	cis / trans = 9.8 : 1

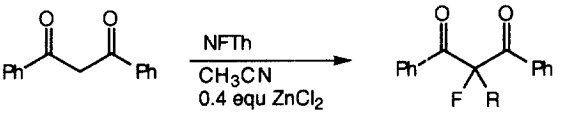
1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), **1**, is capable of introducing fluorine across a stabilized carbon-carbon double bond to give fluoro ethers or alcohols The reaction of an α-methyl styrene with NFTh in acetonitrile/water afforded 1-fluoro-2-hydroxy-2-phenylpropane, **10**, in 71% yield. When methnaol was mixed with acetonitrile and used as the reaction solvent, NFTh fluorinated a-methyl styrene to give 1-fluoro-2-methoxy-2-phenylpropane, **11**.



10 R = H 71% yield
11 R = CH_3 85% yield

In the presence of the Lewis acid, $ZnCl_2$, and an amine, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), **1**, can be used to convert active methylene compounds into their corresponding mono- or di-fluoro derivatives. The mono-fluoro diketone predominates when the fluorinating agent is limited to one equivalent and imidazole is used as the amine component. Di-fluorination is accomplished with an excess of NFTh and collidine as the accompaning base.





1 equ NFTh, 0.4 equ imidazole, 50°C, 24 h 92% yield, R = H / F = 6.2 : 1

2 equ NFTh, 1 equ collidine, 50°C, 48 h 68% yield, R = F

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[7] Compound **1**: ^{1}H NMR (D2O): d 5.0 (m, 6H), 4.6 (m, 6H); ^{13}C NMR (D2O): d 61.6 (d, J=15.5 Hz), 62.3 (d, J=6.2 Hz); ^{19}F (D2O): d 41 (1F), -150 (8F). Anal. Calcd for $C_6H_{13}B_2F_9N_2O$: C, 22.40; H, 4.07; N, 8.70; B, 6.72. Found: C, 22.69; H, 4.25; N, 8.80; B, 6.39.