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Desulfurative Fluorination Using Nitrosonium Tetrafluoroborate and Pyridinium Poly(Hydrogen Fluoride) [1]

Chentao York, G. K. Surya Prakash,* George A. Olah*

Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles,CA 90089-1661, USA

Abstract: Nitrosonium tetrafluoroborate in conjunction with pyridinium poly(hydrogen fluoride) has been found to be excellent desulfurative fluorination reagent. In $NO^+BF_4^-$/PPHF system, *mono*-fluorides and *gem*-difluordes have been obtained in high yields from the corresponding phenylsulfides and dithiolane derivatives, respectively.

Introduction

Selective introduction of fluorine into organic compounds is important since selectively fluorinated organic compounds have unique biological and physical properties.[2] Desulfurative fluorination is one of the useful fluorination methods[3] in forming carbon-fluorine bonds by the cleavage of carbon-sulfur bonds.[4] In desulfurative fluorination, a combination of oxidative reagent and HF or HF-base complex is used for the conversion of thio groups to fluorine such as in the conversion of phenylthiol glycoside to glycosyl fluoride,[5] dithiolanes to *gem*-difluorides[6,7,8] and aryldithiocarboxylic acid esters to trifluoromethylarenes.[9,10,11,12] The oxidative reagents most frequently used are 1,3-dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromosuccinimide (NBS).[5-12] A drawback with DBH or NBS is that the *in situ* formed BrF is also capable of side reactions such as bromination of electron-rich aromatic rings.[6,7,10,12] Moreover, the reaction with DBH or NBS necessitates the removal of imides formed in the reaction and any unreacted haloamides, usually by chromatographic methods.[8]

In previous papers we described the use of nitrosonium tetrafluoroborate and pyridinium poly (hydrogen fluoride) complex ($NO^+BF_4^-$/PPHF) as a new fluorinating reagent for the conversion of ketoximes to geminal difluorides,[13] and diarylacetylenes to diaryltetrafluoroethanes.[14] In continuation of our work, we would now wish to report that $NO^+BF_4^-$/PPHF reagent is also suitable for the oxidative desulfurative fluorination of phenyl sulfides and dithiolane derivatives.

Results and Discussion

Phenyl sulfides are easily prepared from ketones or aldehydes by two steps in a one-pot improved procedure.[15] The carbonyl compounds react with phenylthiol under boron trifluoride monohydrate catalysis and the intermediate mixed acetal is subsquently reduced with triethylsilane. The resulting phenyl sulfides are readily fluorinated with $NO^+BF_4^-$/PPHF. The corresponding fluorides were obtained in high yields (see Table 1).

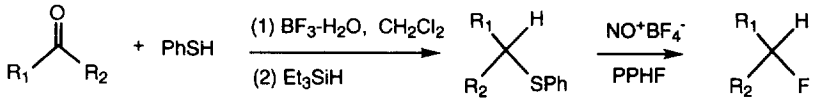
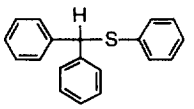
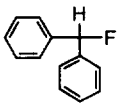
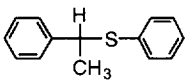
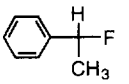
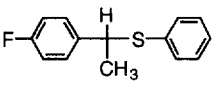
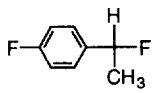
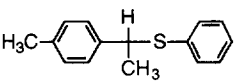
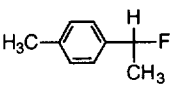
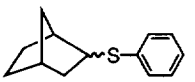
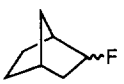


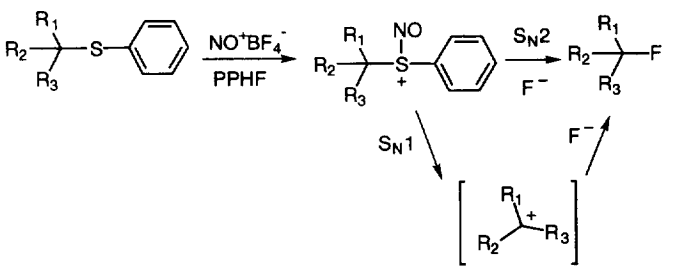
Table 1. Fluorination of phenyl sulfides using $NO^+BF_4^-$/PPHF

Substrate	Product	Yield (%)[a]
		79
		89
		92
		81
		84

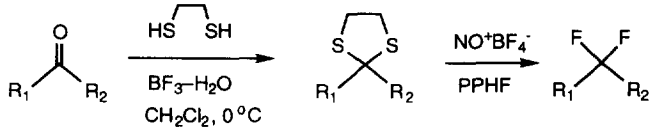
(a) Isolated yield of pure products.

The possible mechanism of desulfurative fluorination of phenyl sulfides using $NO^+BF_4^-$ and PPHF reagent is proposed in Scheme 1. Sulfonium ion is formed by the attack of NO^+ on to sulfur. The fluorides are obtained through nucleophilic substitution by F^- in a S_N2 (or S_N1) pathway. However, the reaction was found to have limitations. In the case of phenyl cyclohexyl sulfide, only low yield of fluorocyclohexane was obtained.

Scheme 1



1,3-Dithiolane derivatives undergo similar facile reaction with $NO^+BF_4^-$/PPHF to give the corresponding *gem*-difluoro compounds. The CF_2 moiety is isosteric with an ether oxygen and has significance in biological chemistry. Since 1,3-dithiolanes are prepared readily from the corresponding aldehydes or ketones and 1,2-ethanedithiol,[16] the overall two-step process represents a convenient method to convert aldehydes and ketones to *gem*-difluorides.

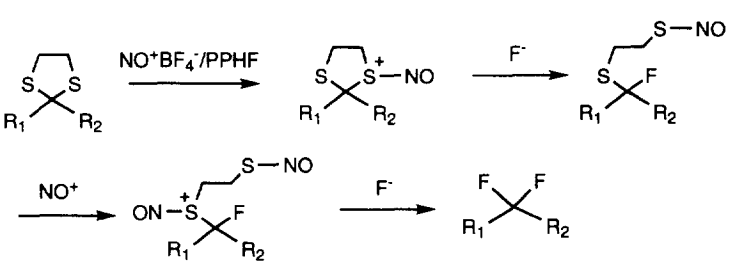


Under very mild conditions geminal difluorides were obtained in high yields (Table 2). $NO^+BF_4^-$/PPHF reagent is also suited to aromatic substituents containing even strongly electron releasing groups, such as three methyls, or methoxy. With these electron rich systems the use of DBH or NBS/PPHF as fluorinating reagents results in brominated aromatic ring byproducts.[6]

The used work-up procedure in our reactions is advantageous. The reaction mixture upon dilution CH_2Cl_2 forms two layers. The top PPHF layer is easily separated. The bottom CH_2Cl_2 layer containing the product is passed through neutral Al_2O_3 column. This procedure also prevents the otherwise exothermic reaction which would arise between PPHF and Al_2O_3.[6] Moreover, this procedure is highly suitable for the isolation of diaryldifluoromethanes, which are otherwise easily hydrolyzed to parent ketones under aqueous work-up process.[6]

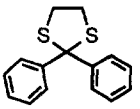
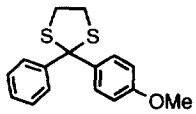
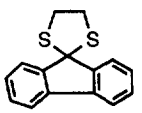
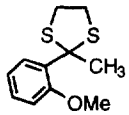
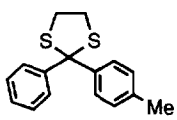
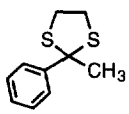
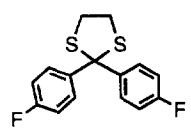
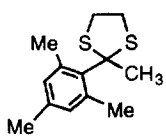
In scheme 2, the mechanism for desulfurative fluorination of 1,3-dithiolane derivatives using $NO^+BF_4^-$/PPHF is proposed. The NO^+ ion again reacts with the sulfur resulting in a nitrososulfonium ion. The subsequent nucleophilic displacement of the nitrososulfonium by fluoride ion from HF-Py complex results in the carbon fluorination.

Scheme 2



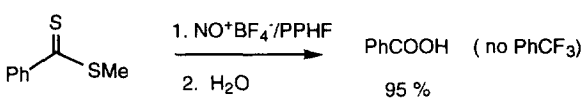
The reported method is not applicable for the fluorination of dialkyl dithiolanes, as they undergo oxidative cleavage to the corresponding parent ketones under the reaction conditions.

Table 2. Fluorination of dithiolane derivatives using $NO^+BF_4^-$/PPHF

Substrate	Yield of Product (%)*	Substrate	Yield of Product (%)*
	95		89
	92		85
	95		92
	96		71

* Isolated yield of pure products.

The $NO^+BF_4^-$/PPHF reagent was also attempted for the conversion of aryldithiolcarboxylic acid esters to corresponding aryltrifluoromethanes. However, with the reagent system we obtained only carboxylic acids instead of trifluoromethanes. The reason may be that the nitrosonium ion is not a strong enough oxidizing reagent to effect the desired transformation.



Conclusion

In summary, $NO^+BF_4^-$/PPHF reagent system is a useful alternative reagent for the desulfurative fluorination of phenyl sulfides and dithiolane derivatives to the corresponding *mono*-fluorides or *gem*-difluorides, respectively, in high yields.

Experimental

General information ^1H and ^{13}C and ^{19}F NMR spectra were obtained at 200 MHz, 50.31 MHz and 188.22 MHz, respectively, on a Varian VXR 200 NMR spectrometer. The ^{19}F NMR chemical shifts are reported in ppm from $FCCl_3$ (δ 0.0). Mass spectra were obtained on a Hewlett Parkard 5890 Series II mass spectrometer at an ionization potential of 70 eV. $NO^+BF_4^-$ is commercially avalible and was purchased from Adrich Co. Pyridinium Poly(hydrogen fluoride) was prepared by condensing the needed amount of anhydrous hydrogen

fluoride at -78 °C into plastic vessel containing pyridine in a well-ventilated hood (CAUTION: proper precaution must be used while handling anhydrous hydrogen fluoride[17]). It is also commercially available from Aldrich.

Preparation of phenyl sulfides and dithiolanes: The dithiolanes and phenyl sulfides were prepared from the corresponding ketones and aldehydes, by the literature procedures.[6,15,16]

General procedure of fluorination of dithiolanes using $NO^+BF_4^-$/PPHF: The 1,3-dithiolane of benzophenone (0.258g, 1 mmol) dissolved in 2mL CH_2Cl_2 was added dropwise to a solution of $NO^+BF_4^-$ (0.26g, 2.2 mmol) and 60% PPHF (1 mL) in 5mL CH_2Cl_2, in a 25mL plastic bottle at 0 °C under dry nitrogen atmosphere. The mixture was stirred at room temperature for 1h. Upon dilution with 20mL CH_2Cl_2 the solution formed two layers. The bottom layer was separated from the top PPHF layer and passed through short column packed with Al_2O_3 (5g) and anhydrous $MgSO_4$ (2g). The collected CH_2Cl_2 solution was rotavaped under reduced pressure. The product was further purified, if necessary, by column chromatography on silica gel with pentane eluent, to give 0.193g of diphenyldifluromethane.[18] ^{1}H NMR δ 7.2 (m, aromatic), 7.5 (m, aromatic); ^{19}F NMR δ -89 (m); MS 204 (80), 183 (20), 127 (100), 77(10).

General procedure of fluorination of phenyl sulfides using $NO^+BF_4^-$/PPHF: The procedure is similar to that described above using 1.2 equiv. of $NO^+BF_4^-$ instead of 2.2 equivalents.

The spectroscopic data of the prepared fluoro drivatives are summarized below with the relevant literature references.

1-Fluoro-1,1-diphenylmethane:[19] ^{19}F NMR δ -163 ($^2J_{H\text{-}F}$ = 48Hz); MS 186(95), 185(100), 165(50), 109(50), 83(20).

1-Fluoro-1-phenylethane:[19] ^{1}H NMR δ 1.60 (3H, dd, $^3J_{H\text{-}H}$ = 6.4 Hz, $^3J_{H\text{-}F}$= 24 Hz), 5.55 (1H, dq, $^3J_{H\text{-}H}$ = 6.4 Hz, $^2J_{H\text{-}F}$= 48 Hz), 7.45 (5H, br); ^{19}F NMR δ –167.50 (sex, $^3J_{H\text{-}F}$= 24 Hz, $^2J_{H\text{-}F}$ = 48 Hz); MS 124 (50), 109 (100), 77 (20).

1-Fluoro-1-(p-fluorophenyl)ethane: ^{1}H NMR δ 1.59 (3H, dd, $^3J_{H\text{-}H}$ = 6.6 Hz, $^3J_{H\text{-}F}$= 23Hz), 5.57 (1H, dq, $^3J_{H\text{-}H}$ = 6.6Hz, $^2J_{H\text{-}F}$= 47 Hz), 7.30 (4H, br.); ^{19}F NMR δ –114 (m), –165.1 (sex, $^3J_{H\text{-}F}$= 23Hz, $^2J_{H\text{-}F}$ = 47 Hz); MS 142 (20), 127 (100), 101 (10), 77 (5).

1-Fluoro-1-(p-tolyl)ethane: ^{1}H NMR δ 1.67 (3H, dd, $^3J_{H\text{-}H}$ = 5.7 Hz, $^3J_{H\text{-}F}$= 23.7 Hz), 2.4 (3H), 5.60 (1H, dq, $^3J_{H\text{-}H}$ = 5.7Hz, $^2J_{H\text{-}F}$= 40.6Hz), 7.35 (4H, br.); ^{19}F NMR δ –165.4 (sex, $^3J_{H\text{-}F}$= 23.7 Hz, $^2J_{H\text{-}F}$ = 40.6 Hz); MS 138 (30), 123 (100), 103 (10), 77 (10).

2-Fluoro-2-norbornane:[20] ^{19}F NMR δ –160 (m), MS 114 (10), 99 (10), 85 (20), 68 (100).

9,9-Difluorofluorene:[18] mp 37-43 °C; ^{1}H NMR δ 7.4 (m); ^{19}F NMR δ -110 (s); MS 202 (100), 183 (50), 101 (5).

Difluoro-1-phenyl-1-(*p*-tolyl)methane: ^{1}H NMR δ 2.4 (3H, s), 7.5 (5H, m); ^{13}C NMR δ 137.8 (t, J = 2.8 Hz),136.9, 134.8(t, J = 28 Hz), 129.7, 128.9, 128.3, 125.75 (t, J = 5.6 Hz), 125.72 (t, J = 5.6 Hz), 120.8 (t, J = 241 Hz); MS 218 (100), 203 (80), 183 (10), 141 (70), 127 (50), 77(10).

Difluorophenyl-di-(*p*-fluorophenyl)methane:[8] ^{13}C NMR δ 133.4 (dt, J = 2.5 Hz, J' = 19 Hz), 132.4 (d, J = 6.0 Hz), 128 (dt, J = 3.5 Hz, J' = 5.7 Hz), 120 (t, J = 161 Hz), 115.44 (d, J =14.7 Hz); ^{19}F NMR δ -86.7 (s), -111 (m); MS 240 (80), 221(20), 201 (10), 145 (100).

Difluoro-1-phenyl-1-(*o*-anisyl)methane: ^{1}H NMR δ 3.8 (3H, s), 7.2 (9H, m); ^{19}F NMR δ -87.3, MS 234(80), 157(100), 127(50), 77(50).

1, 1-Difluoro-1-(*o*-anisyl)ethane: ^{1}H NMR δ 2.0 (3H, t, *J* = 20Hz), 3.9 (3H, s), 7.0 (4H, m); ^{13}C NMR 131, 126 (t, *J* = 8.5Hz), 121.3 9t, *J* = 201.2 Hz), 55.6, 24.6 (t, *J* = 29 Hz); ^{19}F NMR -87.7 (q, *J* = 18.8 Hz); MS 172 (80), 157 (82), 127 (60), 109 (100).

1,1-Difluoro-1-phenylethane:[21] ^{19}F NMR δ -87.9 (q, *J* =18.2 Hz), MS 142 (30), 127 (100), 77 (10).

1,1-Difluoro-1-(2,4,6-trimethylphenyl)methane:[6] ^{1}H NMR δ 2.42 (3H,s), 2.43 (6H,s), 6.86 (2H,s), 6.94 (H, t, *J* = 54 Hz); ^{19}F NMR δ -111.5 (*J* = 54 Hz); MS 170 (80), 155 (60), 119 (100), 91 (40).

Acknowledgment

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