and the mixture was warmed to room temperature. Extractive workup of the reaction mixture with ether followed by Kugelrohr distillation gave imine (**7b**, 0.284 g, 78%, bath temperature 155 °C/0.18 mmHg).

Further extensions of the present methodology are now in progress in our laboratory.

Supplementary Material Available: Spectral data (IR, ^{1}H NMR) for **3**, **4**, and **7** (5 pages). Ordering information is given on any current masthead page.

Fluoride-Induced Formation and Ring Opening of Cyclic Sulfamates from Hydroxy Triflamides. Synthetic and Mechanistic Studies†

Terry A. Lyle,* Catherine A. Magill, and Steven M. Pitzenberger

Merck Sharp and Dohme Research Laboratories West Point, Pennsylvania 19486

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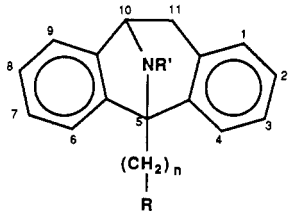
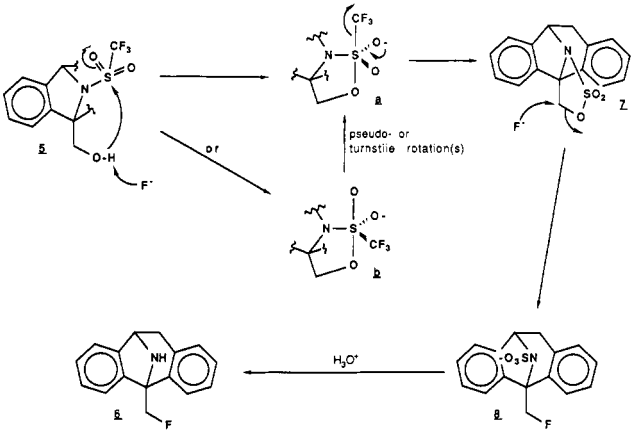
Introduction of fluorine into organic molecules has become an increasingly important field, particularly in the realm of biologically active compounds. Due to its modest steric requirements and unique electronic properties, fluorine has been extensively utilized in medicinal chemistry to influence the metabolism, bioactivity, and physical properties of pharmaceuticals.[1] Another rapidly expanding area of interest is the use of ^{18}F-labeled compounds as biological tools for imaging with use of Positron Emission Tomography (PET).[2] Due to its 110-min half-life, it is desirable to incorporate ^{18}F in the final or penultimate step of a reaction sequence as rapidly as possible. In the course of our efforts directed toward developing a method for the introduction of ^{18}F into the noncompetitive *N*-methyl-D-aspartate antagonist MK-801 (**1**),[3] we discovered an interesting series of reactions which provided a solution to the labeling problem as well as a potentially general method for the stereospecific synthesis of β- and γ-fluorinated secondary amines.



	n = 1		n = 2
1	R = R' = H (MK-801)	**10**	R = F R' = H
2	R = OH R' = H	**16**	R = OH R' = H
3	R = OSO_2CF_3 R' = H	**17**	R = OSO_2CF_3 R' = H
4	R = OSO_2CF_3 R' = SO_2CF_3	**18**	R = OSO_2CF_3 R' = SO_2CF_3
5	R = OH R' = SO_2CF_3		
6	R = F R' = H		
9	R = H R' = SO_2CF_3		

A common approach to ^{18}F labeling involves the displacement of reactive esters with fluoride in the latter stages of a reaction sequence.[4] In an attempt to use this method, the unprotected alcohol **2**[5] was treated with triflic anhydride and pyridine to afford the desired sulfonate ester **3**.[6a,7a] However, the reaction mixture contained a large amount of yellow polymeric material (presumably derived from the pyridine used as a base in the reaction)[8] which made purification impractical. A modified procedure utilizing an excess of triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine[8] was applied to the alcohol **2** with very different results. The products of the reaction were the bis-sulfonylated material **4**[6b,7a,d,e] and the trifluoromethanesulfonamide **5**[6b,9,7a,c,e] (68%) in a ratio of approximately 1:3. Presumably, the more hindered base is less effective in removing the sterically hindered hydroxyl proton, thus allowing preferential sulfonylation at nitrogen.

Scheme I



Quite unexpectedly, treatment of **5** with 0.21 M tetra-*n*-butylammonium fluoride in CH_3CN at 65 °C for 25 min, followed by brief exposure to aqueous acid, gave rise to the desired fluoro compound **6**[6b,9,7a-c] (71%). In order to elucidate the mechanism of this rather remarkable transformation, the following experiments were carried out. Treatment of **5** with this $(n\text{-Bu})_4N^+F^-$ solution at 22 °C produced a new product which was isolated by chromatography and shown to be the cyclic sulfamate **7**[6b,9,10] (54%) (Scheme I). The formation of this intermediate necessarily involves loss of the trifluoromethyl group from the triflamide, a process which is unprecedented to our knowledge. In order to examine further the reaction mechanism, the reaction was followed by ^{19}F NMR to determine the fate of the trifluoromethyl group. When two equivalents of the $(n\text{-Bu})_4N^+F^-$ solution were added to a solution of **5** in CD_3CN, the complete disappearance of the signal from the F_3CSO_2N group of **5** (s, −75.0 ppm, relative to $CFCl_3$) was noted within 2 min, and two new resonances had appeared in a 10:1 ratio: a doublet (78 Hz) at −78.3 ppm, corresponding to trifluoromethane[11] and a smaller triplet (12 Hz) at −79.1 ppm corresponding to CDF_3.[12] This indicates that the fluorinated product is initially a trifluoromethyl anion, and thus this reaction represents a sulfur-based version of the well-known haloform reaction of α-trihalomethyl ketones. When the triflamide **5** was treated with F^- at 65 °C and worked up with aqueous $NaHCO_3$, the fluoromethyl sulfamate **8**[7a] appeared to be the only product. It was smoothly converted to **6** upon exposure to aqueous

† Dedicated to the Memory of Professor Guido H. Daub, 1920-1984.

(1) (a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Elsevier Biomedical: *Amsterdam*, 1982. (b) Kollonitsch, J.; Patchett, A. A.; Marburg, S.; Maycock, A. L.; Perkins, L. M.; Doldouras, G. A.; Duggan, D. E.; Aster, S. D., *Nature (London)* **1978**, *274*, 906-908. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123-3197.

(2) Raichle, M. E. *Annu. Rev. Neurosci.* **1983**, *6*, 249-267.

(3) Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iverson, L. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104-7108.

(4) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658-664, and references therein.

(5) Presented at the 193rd Meeting of the American Chemical Society, Denver, CO; April 1987; ORGN 218.

(6) (a) Purified by preparative RP-HPLC. (b) Purified by silica gel chromatography.

(7) The following physical data were consistent with the assigned structure: (a) 300 MHz ^{1}H NMR. (b) 75 MHz ^{13}C NMR. (c) 282 MHz ^{19}F NMR. (d) Mass spectrum. (e) IR.

(8) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283-284.

(9) A satisfactory C, H, and N microanalysis was obtained for a purified sample.

(10) Mp 242-244 °C; ^{1}H NMR ($CDCl_3$) δ 5.19 (d, 8.9 Hz, HC-C_5), 5.38-5.41 (m, HC-C_5, H_{10}); IR 1360, 1185 (SO_2); M^+ = 299.

(11) *The Chemist's Companion*; Gordon, A. J., Ford, R. A. *John Wiley and Sons*: 1972.

(12) Jensen, H.; Schaumburg, K. *Mol. Phys.* **1971**, *22*, 1041-1054.

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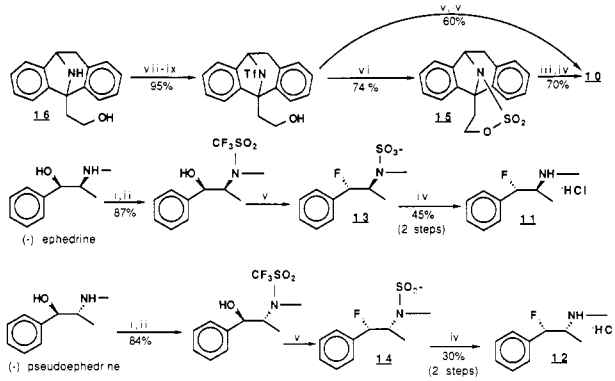
Scheme II[a]



[a] (i) TMS-imidazole/CH_2Cl_2; (ii) $(CF_3SO_2)_2O$/*t*-Bu_2Me-pyridine/CH_2Cl_2, 0 °C (H_3O^+ workup); (iii) *n*-$Bu_4N^+F^-/CH_3CN$, 70 °C, 20 min; (iv) 3.0 M HCl, 70 °C, 15 min; (v) *n*-$Bu_4N^+F^-/CH_3CN$, 70 °C, 60 min; (vi) NaH/THF reflux; (vii) TBDMS-Cl/imidazole/DMF; (viii) $(CF_3SO_2)_2O$/TEA/*t*-Bu_2Me-pyridine/CH_2Cl_2, 0 °C; (ix) TsOH/MeOH.

acid. The overall reaction pathway is summarized in Scheme I.

Reaction of tertiary sulfonamides with alkoxide under vigorous conditions normally results in cleavage of the S-N bond.[13] Indeed, when the triflamide derivative of MK-801 (**9**) is treated with sodium methoxide in refluxing acetonitrile, the only observed reaction is the slow removal of the sulfonyl group from nitrogen rather than loss of trifluoromethide. If this mechanism applied to the intramolecular reaction of the alkoxide oxygen with the sulfonyl group of **5**, one would not expect to observe the product **7** retaining the S-N bond. Therefore, it is likely that the intramolecular nature of the process as well as the stability of the trifluoromethide leaving group (pK_a = 25 for CHF_3)[14] leads to this unique observation. As shown in Scheme I, a transition state or intermediate involving a pentacoordinate sulfur should require that the incoming oxygen occupy an axial position of the trigonal bipyramid. Because the N and incoming O atoms are part of a five-membered ring, the N must occupy an equatorial position, thus giving rise to two possible isomers *a* and *b*. By the same token, the highly electronegative CF_3^- leaving group should occupy an axial position (isomer *a*) which would lead to the product **7**. Therefore if isomer *b* is formed first, it must isomerize to isomer *a* via pseudorotation or turnstile rotation.[15d]

To further define the scope of this reaction we have prepared the γ-fluoroamine **10**[6a,9,7a-c] and the acyclic β-fluoroamines **11**[6b,9,7a,c,d] and **12**[6b,9,7a,c,d] derived from (-)-ephedrine and (-)-pseudoephedrine, respectively (Scheme II). In these cases, transient protection of the hydroxyl groups as their silyl ethers was required in order to direct the sulfonation to nitrogen. In all cases, we have shown the intermediacy of cyclic sulfamates by the isolation of the acyclic (e.g., **13**[7a] and **14**[7a]) or cyclic sulfamate (e.g., **15**[6b,9,7a,e]) intermediates. In contrast to the previous syntheses in which **11** and **12** were obtained as a mixture of epimers at the carbon-bearing fluorine,[16] our methodology provides a stereospecific[17] route to these compounds which is also amenable to ^{18}F labeling. Attempts to convert the amino alcohol **16** to the triflate **17** by using triflic anhydride or to the cyclic sulfamate **15** by using sulfuryl diimidazole led only to azetidine formation. Also treatment of the disulfonylated material **18** with F^- caused elimination.

For preparative purposes, the cyclic sulfamates **7** and **15** may also be generated by treating the hydroxy triflamides with NaH in THF, thus avoiding the possibility of further reaction with F^-. Because **7** and **15** are stable, crystalline materials and give rise to the fluoro compounds **6** and **10** in a short period of time, they are currently being evaluated in radioactive labeling experiments for producing the ^{18}F analogues with encouraging initial results.[18]

In summary, the facile formation of cyclic sulfamates from hydroxy triflamides involving the unusual expulsion of CF_3^- has been documented. In this reaction, the trifluoromethanesulfonyl group serves as a protecting group for nitrogen as well as a means of activating the hydroxyl carbon toward nucleophilic attack. Until now, cyclic sulfamates have been relatively inaccessible.[19] We have also demonstrated the nucleophilic ring opening of these compounds to afford fluoroamines in a stereospecific manner.[20] This method provides an attractive addition to the existing synthetic methods for cyclic sulfamates and fluoroamines[16] and seems well suited for the requirements of ^{18}F labeling. In order to extend this methodology to primary amines, it is likely that transient protection of the triflamide N-H proton will be necessary.

Acknowledgment. We thank Dr. Paul Anderson for his support, interest, and encouragement during this work. We also thank Dr. Susan Britcher, Dr. Wayne Thompson, and Prof. Barry Trost for their comments, Dr. Samuel Graham for several helpful discussions, and Vera Finley for preparing the manuscript.

Supplementary Material Available: Selected spectral data (^1H NMR, ^{19}F NMR, ^{13}C NMR) for compounds **3-8** and **10-15** (2 pages). Ordering information is given on any current masthead page.

(13) Searles, S.; Nukina, S. *Chem. Rev.* **1959**, *59*, 1077-1103.
(14) Edgecombe, K. E.; Boyd, R. J. *Can. J. Chem.* **1984**, *62*, 2887-2891.
(15) For a discussion of nucleophilic displacement at sulfonyl centers, see: (a) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 156. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; McGraw Hill: 1985; pp 442-446. (c) White, E. H.; Linn, H. M. *J. Org. Chem.* **1987**, *52*, 2162-2166. (d) Schwoebel, A.; Kresze, G.; Perez, M. A. *Liebigs Ann. Chem.* **1985**, 72-77.
(16) (a) Alvernhe, G.; Lacombe, S.; Laurent, A.; Rousset, C. *J. Chem. Res. (Synop.)* **1983**, 246-247. (b) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771-777.
(17) The assigned stereochemistry is based on the assumed overall inversion at the benzylic carbon. Examination of the ^1H NMR of crude **11** and **12** indicates stereochemical homogeneity. In both cases, the diastereomer which would result from partial racemization at either chiral center could not be detected.
(18) Private communication from Dr. V. W. Pike, MRC Cyclotron Unit, Hammersmith Hospital, London.
(19) (a) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175-179. (b) Benson, G. A.; Spillane, W. J. *Chem. Rev.* **1980**, *80*, 151-186.
(20) This reaction resembles the nucleophilic fluoride opening of cyclic sulfates: cf. Tewson, T. J.; Soderlind, M. *J. Carbohydr. Chem.* **1985**, *4*, 529-543.

Reactions of Ammonium Salts with Butyllithium and with Lithium Hydride: New Routes to Fully Anhydrous Inorganic Lithium Complexes

Donald Barr, Ronald Snaith,* and Dominic S. Wright

University Chemical Laboratory
Cambridge CB2 1EW, U.K.

Robert E. Mulvey

Department of Pure & Applied Chemistry
Strathclyde University, Glasgow G1 1XL, U.K.

Kenneth Wade

Chemistry Department, Durham University
Durham DH1 3LE, U.K.

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Lithium halide complexes, $(LiHal{\cdot}xL)_n$, L = a nonmacrocyclic ligand, whether fully or partly ion-separated monomers, $Li(L)_x^+\cdots Hal^-$, or intact oligomers, $(LiHal)_n{\cdot}(xL)_n$,[1] often have understandably low melting points and good solubility in organic media. As such, their likely applications are as low-energy

(1) Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. A review of the structures of lithium compounds, including lithium halide complexes.

0002-7863/87/1509-7891$01.50/0