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Synthesis of α-Fluorosulfonamides by Electrophilic Fluorination

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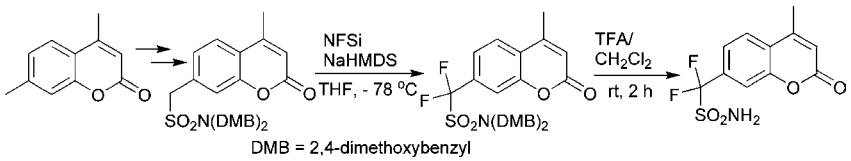
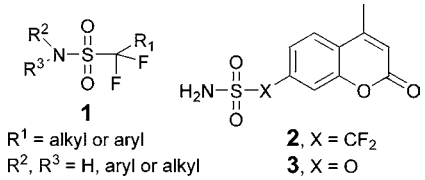
ABSTRACT



α-Fluorosulfonamides were prepared by electrophilic fluorination of tertiary sulfonamides using *N*-fluorobenzenesulfonimide as fluorinating agent and utilizing the dimethoxybenzyl group (DMB) as a new sulfonamide protecting group. Removal of the DMB group with TFA/CH_2Cl_2 gave primary and secondary α-fluorosulfonamides.

The sulfonamide moiety is one of the most important pharmacophores in medicinal chemistry, and numerous bioactive agents bear this functionality.[1] Included in this class of compounds are α-fluorosulfonamides which have been shown to have herbicidal and antiinflammatory activity, some of which are used commercially.[2a−d] The introduction of fluorines α to the sulfonamide results in a linear acidity increase of 1.47 pK_a units per fluorine as well as a significant increase in lipophilicity.[3] Both of these features can have a significant impact on biological activity.[2a−c] Biological studies on α-fluorinated sulfonamides have focused mainly on fluoromethane sulfonamides (F_3CSO_2NRR or HF_2CSO_2-NRR). α-Alkyl or α-aryl α-fluorosulfonamides, of general structure **1**, have received less attention possibly due to a lack of a facile method for their preparation.



Our interest in the synthesis of α-fluorosulfonamides stemmed from our desire to prepare benzylic α,α-difluorosulfonamides, such as compound **2**, to test as reversible inhibitors of the enzyme estrone sulfatase (ES) and as probes to test mechanisms proposed for the irreversible inhibition of this therapeutically significant enzyme by sulfamates, such as compound **3**.[4] Here we report that compound **2**, as well as other primary, secondary, and tertiary sulfonamides of type **1**, can be prepared by electrophilic fluorination of α-carbanions of protected sulfonamides.

We previously reported that α,α-difluorosulfonates can be prepared by electrophilic fluorination of α-carbanions of sulfonate esters using *N*-fluorobenzene sulfonamide.[5a−c] Therefore, we envisioned preparing α,α-difluorosulfonamides by electrophilic fluorination of α-carbanions of sulfonamides. We initiated our studies on model tertiary sulfonamides **7** and **8** in which the sulfonamide was protected with the benzyl or *p*-methoxybenzyl (PMB) groups, two

(1) Bowman, W. C.; Rand, M. J. *Textbook of Pharmacology*, 2nd ed.; Blackwell: London, 1979; Chapter 34.

(2) (a) Moore, G. G. I.; Harrington, J. K. *J. Med. Chem.* **1975**, *18*, 386−391. (b) Trepka, R. D.; Harrington, J. K.; McConville, J. W.; McGurran, K. T.; Mendel, A.; Pauly, D. R.; Robertson, J. E.; Waddington, J. T. *J. Agric. Food Chem.* **1974**, *22*, 1111−1119. (c) Trepka, R. D.; Harrington, J. K.; Robertson, J. E.; Waddington, J. T. *J. Agric. Food Chem.* **1970**, *18*, 1176−1177. (d) Harrington, J. K.; Robertson, J. E.; Kvam, D. C.; Hamilton, R. R.; McGurran, K. T.; Trancik, R. J.; Swingle, K. F.; Moore, G. G. I.; Gerster, J. F. *J. Med. Chem.* **1970**, *22*, 137.

(3) Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094−1098.

(4) Compound **3** and other aryl sulfamates are potent irreversible inhibitors of ES. For a discussion on the mechanism of inhibition of ES by sulfamates, see: Ahmed, S.; Owen, C. P.; James, K.; Patel, C. K.; Sampson, L. *J. Steroid Biochem. Mol. Biol.* **2002**, *80*, 429−440.

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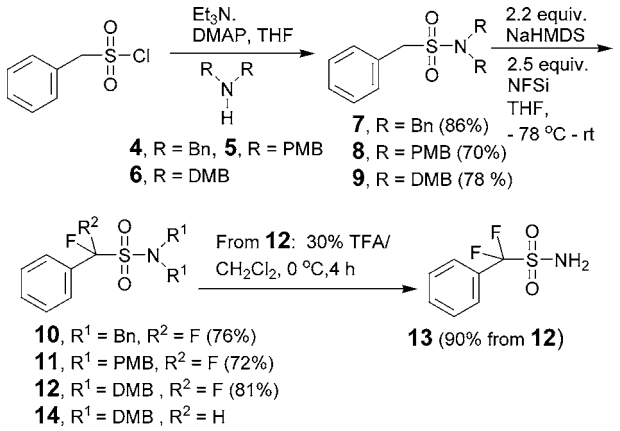
Scheme 1



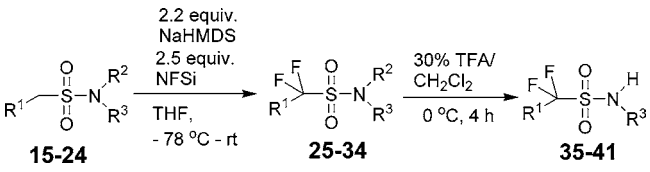
moieties that have been used to protect sulfonamides.[6] Compounds **7** and **8** were prepared in yields of 86 and 70% by reacting benzylsulfonyl chloride with 1.2 equiv of the secondary amines **4** and **5** in the presence of 1.2 equiv of Et_3N and cat. DMAP in THF (Scheme 1). The one-step fluorination procedure that we developed for the fluorination of sulfonates[5a] was used for the fluorination of **7** and **8**. Thus, 2.2 equiv of NaHMDS was added to a solution of the sulfonamide containing 2.5 equiv of *N*-fluorobenzenesulfonimide (NFSi) in THF at −78 °C, stirred for 2 h, followed by warming to rt. This gave the desired difluorinated compounds **10** and **11** in 76 and 72% yields, respectively. However, conditions that are typically used to remove benzyl protecting groups from sulfonamides ($Pd(OH)_2$, 45 psi H_2 in MeOH[6b]) failed with **10** with only 4% of the desired product **13** being formed after 2 days. The PMB group is typically removed using 50% TFA/CH_2Cl_2 in about 12 h at room temperature.[6a] However, even after being subjected to 80% TFA/CH_2Cl_2 for 15 h, only 30% of **11** was converted into **13**. Due to the difficulties in removing these groups, we decided to examine the 2,4-dimethoxybenzyl moiety (DMB) as a sulfonamide protecting group. Although never before used for sulfonamide protection, we anticipated that the DMB group would be more readily removed than the benzyl and PMB groups. Thus, reaction of benzylsulfonyl chloride with bis-2,4-dimethoxybenzylamine, **6**,[7] in the presence of DMAP in THF gave sulfonamide **9** in 78% yield. Fluorination of **9** gave fluorosulfonamide **12** in 81% yield. In this case, deprotection of **12** was readily achieved in 4−5 h using 30% TFA/CH_2Cl_2 at 0 °C to give **13** in an excellent yield of 90%. Therefore, the DMB group was used for all subsequent studies.

The fluorination reaction was found to be dependent upon the base and cation. Fluorination of **9** using the above procedure but with *n*-BuLi or LDA yielded mainly monofluorinated product **14** in 39 and 59% yield, respectively. LiHMDS gave 69% **12** and 12% **14** while NaHMDS and KHMDS gave exclusively difluoro product in yields of 81 and 90%, respectively. The yield increases with the size of the cation. This may be due to the larger cations being less strongly bound to the anion.

Using the above procedure, a variety of tertiary benzylic sulfonamides bearing the DMB group (Table 1, **15**−**21**) were fluorinated in good to excellent yield as did the *N*,*N*-dimethylsulfonamide **22**. We also examined the TBS group as a protecting group using *N*-TBS-*N*-methyl- and *N*-TBS-*N*-phenylsulfonamides **23** and **24** as model substrates. In the case of **24**, the TBDMS group was partially removed during the fluorination reaction yielding 24% and 58% of both protected, **34**, and deprotected, **41**, products, respectively. However, the TBS group in methyl derivative **23** was retained during the fluorination reaction and gave the desired product **33** in a 67% yield. Deprotection of DMB-protected compounds **25**−**31** using 30% TFA/CH_2Cl_2 proceeded smoothly in most cases giving primary (**35**−**39**) or secondary (**40** and **41**) sulfonamides in good to excellent yields, the exception being the 4-Me derivative (**38**) which gave the desired product in 56%. The TBS group from **33** was removed in 87% yield using 1 N HCl in THF.

Dianions of secondary sulfonamides have been α-alkylated in good yield by subjecting the sulfonamides to 2 equiv of *n*-BuLi at −78 °C, warming to 0 °C for 1 h followed by the addition of 1 equiv of an electrophile at − 78 °C.[8] However, electrophilic fluorination of secondary sulfonamides **42** and

Table 1. Synthesis and Deprotection of Benzylic α,α-difluorosulfonamides **25**−**34**



substrate[a]	% yield **25**−**34**	% yield **35**−**41**
15 (R^1 = 4-BrPh, R^2 = R^3= DMB)	84 (**25**)	92 (**35**, R^3 = H)
16 (R^1 = 4-IPh, R^2, R^3 = DMB)	86 (**26**)	86 (**36**, R^3 = H)
17 (R^1 4-NO_2Ph, R^2 = R^3 = DMB)	65 (**27**)	91 (**37**, R^3 = H)
18 (R^1 = 4-MePh, R^2 = R^3 = DMB)	76 (**28**)	56 (**38**, R^3 = H)
19 (R^1 = 3-BrPh, R^2 = R^3 = DMB)	92 (**29**)	82 (**39**, R^3 = H)
20 (R^1 = Ph, R^2 = DMB, R^3 = Me)	65 (**30**)	90 (**40**, R^3 = Me)
21 (R^1 = Ph, R^2 = DMB, R^3 = Ph)	75 (**31**)	96 (**41**, R^3 = Ph)
22 (R^1 = Ph, R^2 = R^3 = Me)	69 (**32**)	na[b]
23 (R^1 = Ph, R^2 = TBS, R^3 = Me)	67 (**33**)	87 (**40**, R^3 = Me)[c]
24 (R^1 = Ph, R^2 = TBS, R^3 = Ph)	24 (**34**)[d]	58 (**41**, R^3 = Ph)[e]

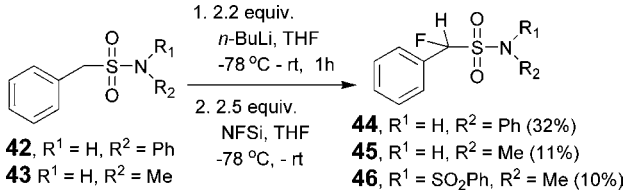
[a] Sulfonamides **15**−**21** were prepared by reacting the sulfonyl chlorides with secondary amines **6**, *N*,*N*-methyl-2,4-dimethoxybenzylamine, or *N*,*N*-phenyl-2,4-dimethoxybenzylamine in the presence of DMAP and or Et_3N in THF. Sulfonamides **23** and **24** were prepared by reacting *N*-methyl- or *N*-phenylbenzylsulfonamide with KH and 18-C-6 followed by the addition of TBDMSCl. See the Supporting Information for details. [b] na = not applicable. [c] Deprotection achieved using 1 N HCl/THF [d] Loss of the TBS group occurred during fluorination. [e] Formed during fluorination reaction.

(5) (a) Leung, C.; Lee, J.; Meyer, N.; Jia, C.; Grzyb, J.; Liu, S.; Hum G.; Taylor, S. D. *Bioorg. Med. Chem.* **2002**, *10*, 2309−2323. (b) Liu, S.; Dockendorf, C.; Taylor, S. D. *Org. Lett.* **2001**, *3*, 1571−1574. (c) Kotoris, C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052−8057.

(6) (a) Morris, J.; Wishka, D. G. *J. Org. Chem.* **1991**, *56*, 3549−3556. (b) Burlingham, B. T.; Widlanski, T. S. *J. Am. Chem. Soc.* **2001**, *123*, 2937−2945.

(7) Katrizky, A. R.; Zhao, X.; Hitchings, G. J. *Synthesis* **1991**, 703−708.

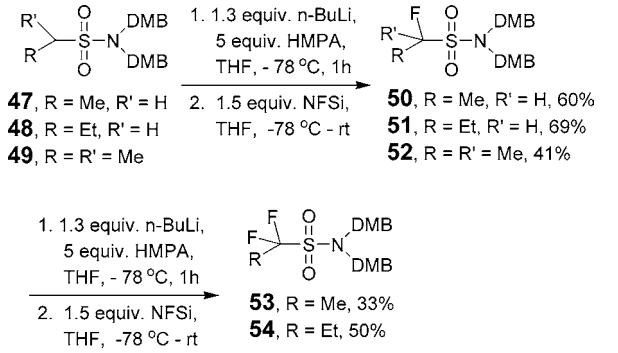
Scheme 2



43 under these conditions (2.2 equiv of *n*-BuLi, 2.5 equiv of NFSi) gave only monofluorinated products **44** and **45** and in low yield (Scheme 2).[9] In the case of the methyl derivative we were also able to isolate compound **46** which resulted from the attack of the amide anion on the sulfur of NFSi and partly account for the low yields of these reactions. Addition of HMPA or employing other bases, even in considerable excess, did not result in an increase in the yield of any fluorinated products. Therefore, the most effective route to α-fluoro secondary sulfonamides appears to be protection of the secondary sulfonamides followed by fluorination and deprotection (e.g., compounds **40** and **41**, Table 1).

We also examined the fluorination of nonbenzylic tertiary sulfonamides using ethyl, propyl and isopropyl derivatives **47**−**49** as model substrates (Scheme 3). Fluorination of

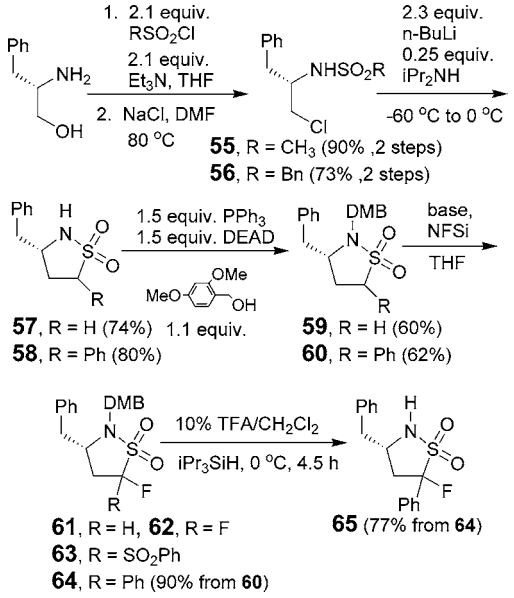
Scheme 3



ethylsulfonamide **47** employing the one-step procedure using NaHMDS, KHMDS, or *n*-BuLi was unsuccessful. However, when the reaction was performed in the presence of 1.2 equiv of *n*-BuLi, 2.5 equiv of NFSi, and 5 equiv of HMPA, the monofluorinated product **50** could be obtained in a respectable 60% yield (Scheme 3). Applying these conditions to *n*-propylsulfonamide **48**, the monofluorinated product **51** was obtained in 69% yield. However, under these conditions, the isopropyl compound **52** was obtained in only a 14% yield. Nevertheless, the yield of **52** could be improved to 41% by adding 2.2 equiv of *t*-BuOK. Fluorination of the purified monofluoro species **50** and **51** using the same procedure gave the difluoro products **53** and **54** in 33% and 50% yields,

(8) For example see: Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700−1703.

Scheme 4



respectively (Scheme 3). This approach to difluorination is similar to that taken by Differding, who also found it necessary to purify and then fluorinate the monofluoro products during the synthesis of α,α-difluoroalkyl phosphonates using NFSi.[10]

Electrophilic fluorination of cyclic sulfonamides (sultams) was examined using compounds **59** and **60** as model systems, which were prepared using a procedure recently described by Lee et al. (Scheme 4).[11] For the nonbenzylic sultam **59**, electrophilic fluorination using the conditions described above for the monofluorination of alkyl sulfonamides gave compound **61** in just 18% yield, as well as trace amounts of the difluoro compound **62**. A byproduct was also isolated in 10% yield, which was identified as compound **63** and resulted from the reaction of the carbanion with the sulfur of NFSi.[12] Using 1.2 equiv of LDA as base, we were able to obtain monofluoro product **61** in a 25% yield; however, the amount of byproduct **63** increased also to 14%. Fluorination of the benzylic cyclic sulfonamide **60** using 2.0 equiv of NaHMDS, 2.2 equiv of NFSi, in THF at −78 °C to rt, proceeded smoothly giving the monofluoro product **64** in a 90% yield as a mixture of diastereomers (ratio: 1:1.7). Deprotection using our usual conditions gave sultam **65** in a low 22% yield. However, by using 10% TFA and adding the cation scavenger, $^{i}Pr_3SiH$, the yield of **65** was increased to 77%.

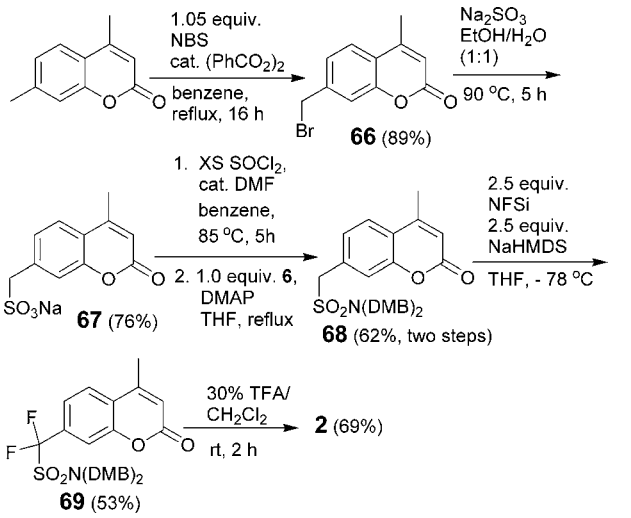
(9) Under these conditions, except using MeI as electrophile, we could readily α-methylate secondary sulfonamides in 60−70% yields.

(10) Differding, E.; Duthaler, R. O.; Kreiger, A.; Ruegg, G. M.; Schmit, C. *Synlett* **1991**, 395−396.

(11) Lee, J.; Zhong, Y.-L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175−4177.

(12) A comparison of the ^{19}F NMR of compound **63** with the ^{19}F NMR's obtained from the crude reaction mixtures from the fluorination of compounds **47** and **48** suggested that similar byproducts were formed during the fluorination of **47** and **48**. However, we were unable to isolate these byproducts in pure form to confirm this. These results may account for the lower yields obtained with the alkyl derivatives compared to the benzylic derivatives.

Scheme 5



Finally, compound **2** was prepared according to Scheme 5. 4,7-Dimethylchromen-2-one was selectively brominated at the 7-methyl group to give **66** in 89% yield using NBS. Conversion of bromide to the sulfonate **67** was achieved in 76% yield using sodium sulfite. Treatment of **67** with $SOCl_2$/cat. DMF and reaction of the resulting sulfonyl chloride with amine **6** gave sulfonamide **68** in a 62% yield. Subjecting **68** to 2.5 equiv of NaHMDS and NFSi at − 78 °C gave difluoro compounds **69**. Unlike our previous fluorination of benzylic sulfonamides, the best yield for the fluorination was achieved by keeping the reaction at − 78 °C. Warming to room temperature resulted in a decrease in yield due to an increase in unidentified byproducts. Finally, deprotection of **69** using TFA/CH_2Cl_2 gave **2** in a 69% yield.[13]

In summary, a variety of α-fluorosulfonamides have been prepared by electrophilic fluorination of α-carbanions of sulfonamides using NFSi as fluorinating agent. Benzylic sulfonamides are generally fluorinated in higher yields than nonbenzylic sulfonamides. To our knowledge, this is the first report describing the electrophilic fluorination of sulfonamides. We expect that this procedure will be very useful for the preparation of new fluorinated sulfonamides with useful biological properties. Also of note is the first use of the DMB group as a protecting group for sulfonamides. This group is stable to base and nucleophiles yet is readily removed under very mild conditions. We expect that the DMB group will find widespread use as a protecting group for sulfonamides in general.

Acknowledgment. This work was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada. We also thank Merck-Frosst Canada & Co. for financial support and the Government of Ontario for a Premiere's Research Excellence Award to S.D.T.

Supporting Information Available: Preparation procedures and characterization data for **2** and **7**−**69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Inhibition studies with compound **2** and ES will be reported elsewhere.