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Synthesis of α-Fluorosulfonate and α-Fluorosulfonamide Analogues of a Sulfated Carbohydrate

Latifeh Navidpour, Wallach Lu, and Scott D. Taylor*

Department of Chemistry, University of Waterloo, 200 University Avenue West, Waterloo, Ontario, Canada, N2L 3G1

s5taylor@sciborg.uwaterloo.ca

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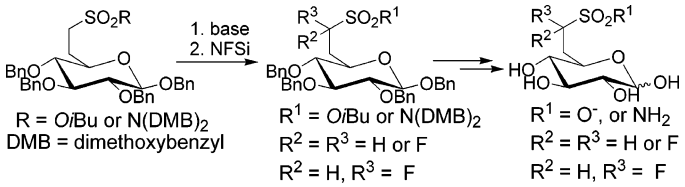
ABSTRACT



The first synthesis of sulfonamide and sulfonate analogues of a sulfated carbohydrate in which the ester oxygen of the sulfate is replaced with a CHF or CF_2 group is reported. This was accomplished by electrophilic fluorination of the protected sulfonate and sulfonamide precursors.

Sulfated carbohydrates play key roles in numerous biological functions such as viral cell recognition, cell−cell interactions, blood clotting, inhibition, and promotion of tumor growth to name but a few.[1a,b] The sulfation of carbohydrates is accomplished by a class of enzymes known as sulfotransferases which transfer a sulfate group from 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to the hydroxyl group of the carbohydrate.[1b] Another class of enzymes, the sulfatases, remove the sulfate groups.[2] Inhibitors and probes of these enzymes would be very useful as tools for studying how these enzymes work in conjunction to control the sulfation state of carbohydrates, which is essential to understanding the role these enzymes have in regulating certain biological processes. One approach to the design of inhibitors of the sulfatases is to prepare nonhydrolyzable analogues of sulfated carbohydrates such as replacing the ester oxygen of the sulfate moiety with a CH_2, CHF, or CF_2 unit. This approach has been used extensively to obtain phosphonate-based inhibitors of phosphatases.[3,4] We recently demonstrated that the CF_2 group can be used as a stable replacement for the bridging oxygen in estrone sulfate in that the CF_2 sulfonate is a good competitive inhibitor of steroid sulfatase and was approximately 10-fold more potent than its nonfluorinated analogue.[5] Since both the fluorinated and nonfluorinated estrone sulfate analogues have pK_a values that are far below physiological pH we reasoned that their difference in potency was due to the fluorines interacting with residues in the active site perhaps by fluorine H-bonding with His-290, which is believed to act as a general acid during the cleavage of the S−O bond.[5] The active site in sulfatases is highly conserved,[6] which suggests that carbohydrate sulfate analogues in which the ester oxygen is replaced with a CF_2 or CFH group might also be effective inhibitors of sulfatases that act upon sulfated carbohydrates. However, the synthesis of such compounds presents certain challenges. Benzylic α-fluorinated sulfonates, such as the estrone sulfate analogue mentioned above, can be readily prepared by electrophilic fluorination (EF) of the α-carbanions of their neopentyl-protected sulfonate precursors with *N*-fluorobenzene sulfonimide (NFSi).[7a−d] These reactions generally proceed well because the in situ generated carbanion is stabilized by the protected sulfonate group as

(1) (a) Toida, T.; Chaidedgumjorn, A.; Linhardt, R. J. *Trends Glycosci. Glycotech.* **2003**, *15*, 29. (b) Honke., K.; Taniguchi, N. *Med. Res. Rev.* **2002**, *22*, 637.

(2) Hanson, S. R.; Best, M. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5736.

(3) Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(4) Blackburn, G. M. *Chem. Ind.* **1981**, 134.

(5) Lapierre, J.; Ahmed, V.; Chen, M.-J.; Ispahany, M.; Guillemette, J. G.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 151.

(6) Ghosh, D. *Methods Enzymol.* **2005**, *400*, 273.

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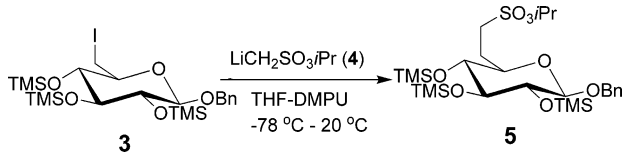
well as the phenyl ring. Indeed, EF usually works best on "acidic" substrates in which the resulting carbanion is stabilized by two adjacent electron withdrawing groups (EWG's) and the vast majority of these reactions are performed on such substrates.[8] There are only a few examples in the literature describing the electrophilic difluorination of less acidic substrates[8,9] and this has never been reported for sulfonates in which the resulting carbanion is not stabilized by an additional EWG as would be the case with a carbohydrate sulfonate as substrate. This letter describes the results of our preliminary investigations into the preparation of α-fluorinated sulfonate and sulfonamide analogues of a sulfated carbohydrate by electrophilic fluorination. We report that this approach can be used to prepare both the mono- and difluorinated derivatives. In addition, we demonstrate stereochemistry of the monofluorinated sulfonate can be controlled to a certain degree by the counterion of the base used to generate the carbanion. Finally, we show that this methodology can also be used to prepare the corresponding α-fluorinated sulfonamide carbohydrates.

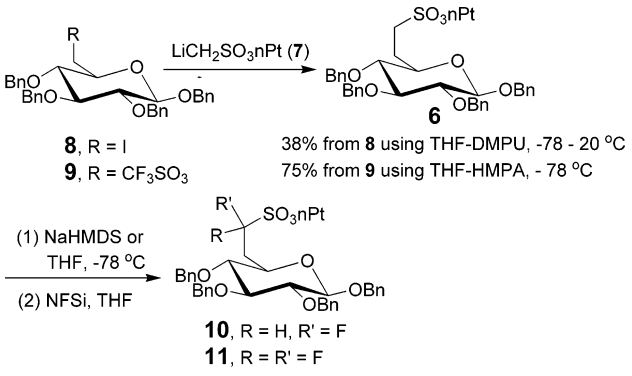
To our knowledge only a single report has appeared in the literature describing the synthesis of a pyranoside sulfonate in which the ester oxygen of the corresponding sulfate is replaced with a methylene group. This was achieved by Musicki and Widlanski, who reacted the 6-iodo carbohydrate derivative **3** with lithiated isopropyl methanesulfonate (**4**) in the presence of DMPU in THF to give carbohydrate sulfonate **5** in 57% yield (Scheme 1).[10] We wished to prepare

Scheme 1. Widlanski Synthesis of Sulfonate **5**



pyranoside sulfonate **6** (Scheme 2) and use it as a model system for our investigations. Compound **6** is the protected sulfonate analogue of glucose-6-sulfate, a component of mucus glyceroglucolipids and a substrate for *Helicobacter pylori* glycosulfatase.[11] We anticipated that **6**c ould be readily constructed from iodo carbohydrate **8**[12] using Widlanski's sulfonation procedure and that the benzyl and neopentyl protecting groups would be compatible with our EF conditions yet would be easily removed under neutral conditions at the end of the synthesis. However, reacting lithiated neopentyl (nPt) methanesulfonate (**7**) with compound **8** under Widlanski's conditions gave sulfonate **6** in only a 38% yield. Berkowitz and co-workers have shown that the phosphonate analogue of **6** can be prepared in good yield by reacting triflate **9** with lithiated diethyl methanephosphonate in THF/HMPA at −78 °C.[13] Employing these conditions with compounds **7** and **9**, carbohydrate sulfonate **6** was obtained in 75% yield.

Scheme 2. Synthesis of Sulfonates **6**, **10**, and **11**



Electrophilic difluorination of **6** was initially attempted with use of conditions similar to those we developed for the difluorination of benzylic sulfonates.[7a−d] Thus, 2.5 equiv of Na HMDS in THF was added to **6** at −78 °C in THF. The mixture was stirred for 2 h and then 3.3 equiv of *N*-fluorobenzene sulfonimide (NFSi) in THF was added, the mixture was stirred for 1 h at −78 °C, and then the reaction was warmed to rt and then stirred for a further 16 h. ^{19}F NMR analysis of the crude reaction product indicated that, although peaks corresponding to the mono- and difluorinated products **10** and **11** (Scheme 2) were evident, many other products were formed and compounds **10** and **11** were formed in very low yields. Further studies revealed that the fluorination reaction proceeded quite readily within the first 30 min but significant decomposition occurred upon warming the reaction mixture or with prolonged reaction times. Nevertheless, it was found that by maintaining the reaction at −78 °C and subjecting **6** to 2.5 equiv of KHMDS for just 15 min and then adding 3.0 equiv of NFSi dropwise over 15 min and reacting for an additional 15 min the reaction was cleaner and compounds **10** and **11**, which could be separated by chromatography, were isolated in 18% and 52% yields, respectively.

Before further EF studies were undertaken deprotection of the sulfonate moiety in compounds **10** and **11** was examined. Subjecting **11** to LiBr in refluxing butanone[7a] for 48 h resulted in less than 50% deprotection and in the case of compound **10** very little deprotection was achieved in this time frame. Roberts et al. have described the removal of neopentyl groups from sulfonates using tetramethyl ammonium chloride in DMF at 160 °C.[14] However, this also proceeded very slowly.

(7) (a) Kotoris, C.; Chen, M-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052. (b) Chen, M-J.; Taylor, S. D. Te*trahedron Lett.* **1999**, *40*, 2669. (c) Liu, S.; Dockendorf, C.; Taylor, S. D. *Org. Lett.* **2001**, *3*, 1571. (d) Leung, C.; Lee, J.; Meyer, N.; Jia, C.; Grzyb, J.; Liu, S.; Hum, G.; Taylor, S. D. *Bioorg. Med. Chem.* **2002**, *10*, 2309.

(8) Taylor, S. D.; Kotoris, C.; Hum, G. H. *Tetrahedron* **1999**, *55*, 12431.

(9) Konas, D. W.; Coward, J. K. *Org. Lett.* **1999**, *1*, 2105.

(10) Musicki, B.; Widlanski, T. S. *J. Org. Chem.* **1990**, *55*, 4231.

(11) Slomiany, B. L.; Murty, V. L.; Piotrowski, J.; Grabska, M.; Slomiany, A. *Am. J. Gastroenterol.* **1992**, *87*, 1132.

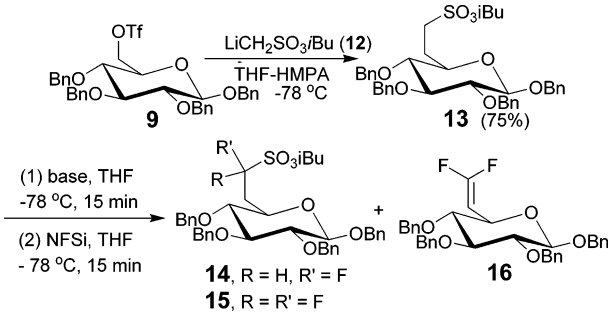
(12) Berkowitz, D. B.; Eggen, M-J.; Shen, Q.; Sloss, D. G. *J. Org. Chem.* **1993**, *58*, 6174.

(13) Berkowitz, D. B.; Bose, M.; Pfannestiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498.

(14) Roberts, J. C.; Gao, H.; Gopalsomy, A.; KongsJahju, A.; Patch, R. J. *Tetrahedron Lett.* **1997**, *38*, 335.

Due to the difficulties associated with removing the neopentyl group, we decided to examine the isobutyl moiety as a sulfonate protecting group since it is easier to remove.[15] Reaction of lithiated isobutyl methanesulfonate (**12**) with carbohydrate **9** gave sulfonate **13** in 75% yield (Scheme 3).

Scheme 3. Synthesis of Carbohydrates **14** and **15**



Treatment of **13** with 2.0 equiv of base at −78 °C in THF for 15 min followed by the addition of 2.5 equiv of NFSi and stirring at −78 °C for 15 min gave a mixture of mono-, **14**, and difluorinated, **15**, products (entries 1−4 in Table 1).

Table 1. Electrophilic Fluorination of **13** with Various Bases and *N*-Fluorobenzenesulfonimide

entry	base	yield of **14**[d]	yield of **15**
1	NaHMDS[a]	23 (1:21)	31
2	KHMDS[a]	4 (1:9)	31
3	LiHMDS[a]	20 (4:1)	4
4	BuLi[a]	52 (5.3:1)	17
5	NaHMDS[b]	59 (1:7.2)	12
6	NaHMDS[c]	17	48

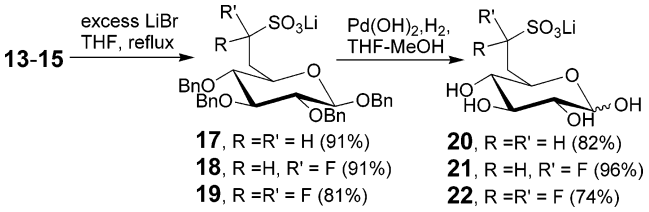
[a] 2.0 equiv of base, 2.5 equiv of NFSi. [b] 1.2 equiv of base, 1.5 equiv of NFSi. [c] 3.0 equiv of base, 3.5 equiv of NFSi. [d] Shown in parentheses is the ratio of the downfield diastereomer (δ −177) to the upfield diastereomer (δ −183) as determined by ^{19}F NMR.

With NaHMDS as base, **14** and **15** were obtained in yields of 23% and 31%. With KHMDS, **14** and **15** were obtained in 31% and 4% yields, respectively. With LiHMDS, the overall yield was low with the monofluorinated product predominating. With *n*-BuLi, the monofluoro product **14** dominated and was obtained in a 52% yield. In all cases compound **14** was formed as a mixture of diastereomers as determined by ^{19}F NMR. Interestingly, the stereochemical outcome of the fluorination reaction was dependent upon the cation of the base. When lithium was the cation (LiHMDS and *n*-BuLi) formation of the downfield diastereomer at δ −177 was favored (5.3:1 with *n*-BuLi). However, when Na or K was the cation, formation of the upfield diastereomer at δ −183 was favored (21:1 with NaHMDS). The best yield of **14** was obtained by reacting **13** with 1.2 equiv of NaHMDS and 1.5 equiv of NFSi, which gave **14** in a 59% yield favoring the upfield diastereomer in a ratio of 7:1, which also shows that the de is dependent upon the concentration of base. The best yield of difluorinated compound **15** was obtained with 3.0 equiv of Na HMDS and 3.5 equiv of NFSi, which gave **15** in a 48% yield.

^{19}F NMR analysis of the crude reaction products from all of the above reactions indicated that one particular byproduct was sometimes formed in substantial amounts. The amount of this byproduct increased as the amount of base and NFSi increased above 1 equiv, if the reaction times were prolonged, or if the temperature was allowed to warm above −78 °C after the addition of NFSi. This byproduct was isolated and found to be compound **16** (Scheme 3). Once **15** is formed, the β-proton is acidic enough to be removed by the base and elimination of SO_2 and isobutoxide occurs. This result may account, at least in part, for our difficulty in obtaining **15** in yields greater than 48%.

Deprotection of the sulfonate group in compounds **13**−**15** was achieved by treating them with an excess of LiBr in refluxing THF for several hours, which gave sulfonates **17**−**19** in 81−91% yield (Scheme 4). Removal of the benzyl

Scheme 4. Deprotection of **13**−**15**



groups with $Pd(OH)_2/H_2$ gave carbohydrate sulfonates **20**−**22** in 74−96% yield. The de of compound **21** did not change significantly from that of compound **14**.[16]

We recently reported that the α,α-difluoromethyl sulfonamide analogue of estrone sulfate is also a good inhibitor of steroid sulfatase.[17] Therefore, we decided to examine whether the sulfonamide equivalents of compounds **20**−**22** could be constructed. We recently demonstrated that α-fluorosulfonamides can be prepared by EF of bis(dimethoxybenzyl)-protected sulfonamides.[18] α,α-Difluoroalkyl sulfonamides were best obtained by treating the sulfonamide with 1.3 equiv of *n*-BuLi or *n*-BuK in the presence of 5 equiv of HMPA followed by 1.5 equiv of NFSi at −78 °C in THF and then

(15) Xie, M.; Widlanski, T. S. *Tetrahedron Lett.* **1996**, *37*, 4443.

(16) We were unable to obtain the crystal structure of the monofluorinated diastereomers and therefore we were unable to determine their absolute stereochemistry, which makes rationalizing the effect of the counterion on the stereochemistry very difficult. In contrast to the significant number of theoretical and synthetic studies on α-carbanions of sulfones, studies related to α-carbanions of sulfonate esters and sulfonamides are scarce. As with the sulfones, many factors may affect their structure and reactivity patterns such as negative hyperconjugation, complexation of the cations with the sulfonate group or carbanion, π−cation and cation−solvent interactions, differences in the sizes of the cations, etc. For a discussion on the structure of α-carbanions of sulfones see: Raabe, G.; Gais, H-J.; Fleishhauer, *J. J. Am. Chem. Soc.* **1996**, *118*, 4622 and references therein.

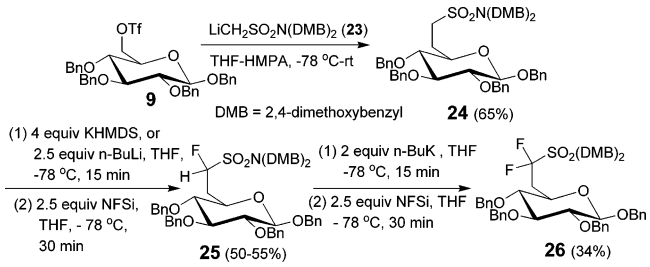
(17) Liu, Y.; Ahmed, V.; Hill, B.; Taylor, S.D. *Org. Biomol. Chem.* **2005**, *3*, 3329.

(18) Hill, B.; Liu, Y.; Taylor, S. D. O*rg. Lett.* **2004**, *6*, 4285.

warming to rt. The purified monofluoro derivatives, which were obtained in yields of 41−69%, were subjected to the same conditions which gave the difluoro compounds in modest yields.[18]

Sulfonamide carbohydrate **24** was obtained in a 65% yield by reacting triflate **9** with the lithium salt of *N*,*N*-bis(2,4-dimethoxybenzyl)methane sulfonamide (**23**).[19] The conditions described above for monofluorination of less complex alkyl sulfonamides[18] were not suitable for sulfonamide **24** since a large number of byproducts formed upon warming the reaction to rt. After some experimentation it was found that the monofluoro sulfonamide **25** could be isolated in 50−55% yield by treating **24** with 4 equiv of KHMDS or 2.5 equiv of *n*-BuLi at −78 °C, stirring for 15 min, and then adding 2.5 equiv of NFSi and reacting at −78 °C for 15−30 min (Scheme 5). The reaction with KHMDS produced exclusively compound **25** while the reaction with *n*-BuLi also produced about 10% difluorinated compound **26**, which could be separated by careful chromatography. ^{19}F NMR revealed that the stereoselectivity was not affected by the cation as both KHMDS and *n*-BuLi gave the same diastereomer in very high de (95−96%).[16]

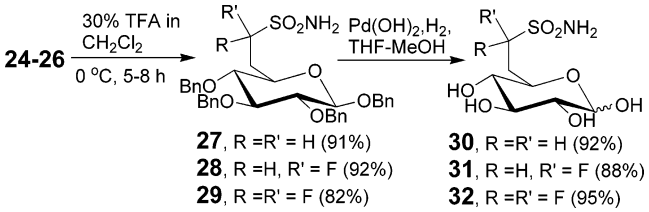
Scheme 5. Electrophilic Fluorination of **24**



We were unable to obtain even modest amounts (>15%) of compound **26** directly from **24** and converting pure **25** to **26** proved to be challenging. Nevertheless, after considerable experimentation we were able to obtain **26** from **25** in a modest 34% yield by briefly treating **25** with *n*-BuK at −78 °C followed by reaction with 2.5 equiv of NFSi for 30 min.[20]

Deprotection of the sulfonamide moiety in **24**−**26** was achieved in excellent yields (82−91%) with TFA in CH_2Cl_2 (Scheme 6). Further deprotection of the hydroxyl groups in primary sulfonamides **27**−**29** by hydrogenolysis gave carbohydrate sulfonamides **29**−**32** in 88−95% yields.

Scheme 6. Deprotection of **23**−**25**



In summary, the first synthesis of the CHF and CF_2 sulfonate and sulfonamide analogues of a sulfated carbohydrate is reported. This was accomplished by EF of the protected sulfonate and sulfonamide precursors. To the best of our knowledge, this is the first example of an EF of an unactivated sulfonate. The stereochemistry of the monofluorosulfonates was dependent upon the counterion of the base but this was not the case with the monofluorosulfonamides. Knowledge of the absolute stereochemistry of these compounds would be helpful in determining the origin of the effect of the counterion on the stereochemistry of these reactions and we are in the process of preparing other monofluorinated carbohydrate sulfonates and sulfonamides that we anticipate will be more amenable to X-ray crystallographic studies. Further studies on applying this methodology to the synthesis of α-fluorinated sulfonate and sulfonamide analogues of other biologically relevant sulfated carbohydrates are also in progress. Also worthy of note is the use of reagent **23** to prepare the first CH_2 sulfonamide analogue of a sulfated carbohydrate. Reports describing the synthesis of an alkyl sulfonamide via a nucleophilic substitution reaction using a monolithiated methane sulfonamide are rare.[21] Reagent **23** may prove to be very useful as a general reagent for preparing compounds bearing a primary sulfonamide moiety, an important pharmacophore in medicinal chemistry.

Acknowledgment. This work was supported by a Natural Sciences and Engineering Research Council (NSERC) of Canada Discovery grant to S.D.T.

Supporting Information Available: Preparation procedures and characterization data for **6**, **10**, **11**, and **13**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See the Supporting Information for the synthesis of reagent **23**.

(20) We did not detect compound **16** as a byproduct in these reactions. However, ^{19}F NMR analysis of the crude reaction products suggested a byproduct resulting from the attack of the carbanion on the sulfur of NFSi may have formed. This side reaction was shown to occur during the fluorination of other alkyl sulfonamides (see ref 18).

(21) (a) Eisleb, *Chem. Ber.* **1941**, *74*, 1433. (b) Klein, U.; Sucrow, W. *Chem. Ber.* **1977**, *110*, 161.