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O- and *N*-Sulfations of Carbohydrates Using Sulfuryl Imidazolium Salts

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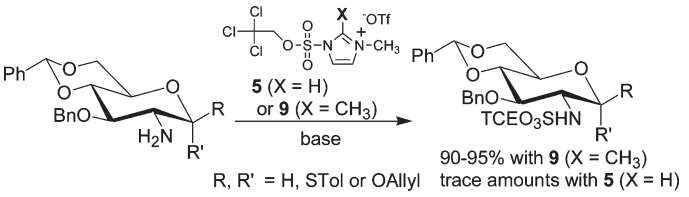

A series of sulfuryl imidazolium salts (SISs) were prepared and examined as reagents for incorporating trichloroethyl-protected sulfate esters into carbohydrates. The SIS that contained a 1,2-dimethylimidazolium moiety (SIS **9**) proved to be a superior sulfating compared to SISs bearing no alkyl groups or bulkier alkyl groups on the imidazolium ring. Difficult *O*-sulfations that required prolonged reaction times and a large excess of the SIS bearing a 1-methylimidazolium group (SIS **5**) were achieved in high yield using less than half the amount of SIS **9** in less time. Certain *N*-sulfated compounds that were practically inaccessible using SIS **5** were obtained in excellent yield using SIS **9**.

Introduction

Biomolecules bearing one or more sulfate groups, such as sulfated carbohydrates, nucleosides, steroids, and proteins, have been known for many years and have been found to play important roles in a wide range of crucial biochemical processes. Consequently, new and improved methods for preparing sulfated biomolecules and their derivatives are of some importance. Organosulfates have traditionally been prepared by treating their nonsulfated precursors with a sulfating agent such as a sulfur trioxide−amine complex, chlorosulfuric acid, or similar reagents. The sulfation step is usually carried out at or near the end of the synthesis to minimize purification and stability issues associated with the highly polar and acid-sensitive sulfates. However, if the target, such as carbohydrates, contains multiple reactive groups but only one or a select few require sulfation then intensive protecting group manipulation is required at the end of the synthesis which can result in reduced yields.[1] It has been known for many years that the synthesis of organosulfates would be considerably improved if the sulfate group(s) could be introduced at an early stage in the synthesis as a protected, neutral sulfodiester(s).[2,3] However, the sulfate protecting groups that were initially designed for this purpose had little impact on multistep organosulfate syntheses mainly because of difficulties encountered with their introduction and/or removal.[2−5] More recently, two additional sulfate protecting groups, with properties that make this approach to organosulfate syntheses much more attractive have been reported.[6−8] We introduced one of these new sulfate protecting groups, the 2,2,2-trichloroethyl (TCE) group, in order to prepare aryl sulfates that could not be obtained using the traditional methodology.[6] The TCE-protected sulfate group is incorporated using reagent **1** and is readily removed under mild conditions using Zn or Pd/C in the presence of ammonium formate (Scheme 1). Since our initial report, this has become the most widely used sulfate

(1) For examples, see: (a) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E.; Palmacci, E. R.; Seeberger, P. H. *Chem. Eur. J.* **2003**, 140. (b) Nicolaou, K. C.; Bockovich, N. J.; Carcanague, D. R. *J. Am. Chem. Soc.* **1993**, *115*, 8843. (c) Singh, K.; Fernandez-Mayoralas, A.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1994**, 775. (d) Lubineau, A.; Lemoine, R. *Tetrahedron Lett.* **1994**, *35*, 8795. (e) Stahl, W.; Sprengard, U.; Kretzschmar, G.; DSchmidt, D. W.; Kunz, H. *J. Prakt. Chem.* **1995**, *337*, 441.

(2) Penney, C. L.; Perlin, A. S. *Carbohydr. Res.* **1981**, *93*, 241.

(3) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *38*, 7243.

(4) Karst, N. A.; Islam, T. F.; Linhardt, R. J. *Org. Lett.* **2003**, *5*, 4839.

(5) Karst, N. A.; Islam, T. F.; Avci, F. Y.; Linhardt, R. J. *Tetrahedron Lett.* **2004**, *45*, 6433.

(6) Liu, Y.; Lien, I. F. F.; Ruttgaizer, S.; Dove, P.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 209.

(7) Simpson, L. S.; Widlanski, T. S. *J. Am. Chem. Soc.* **2006**, *128*, 1605.

(8) Ethyl sulfite esters have also been used recently for preparing organosulfates. However, further optimization is required for this procedure to be of general utility. See: Huiber, M.; Manuzi, A.; Rutjes, P. J. T.; van Delft, F. L. *J. Org. Chem.* **2006**, *71*, 7473.

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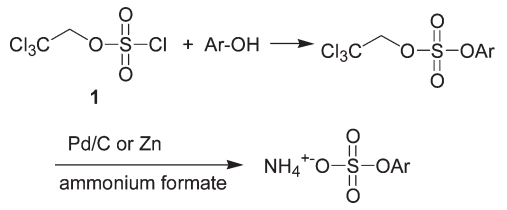
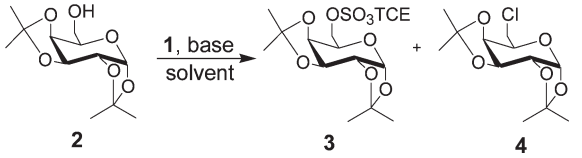
SCHEME 1. Introduction and Deprotection of TCE-Protected Arylsulfate Esters



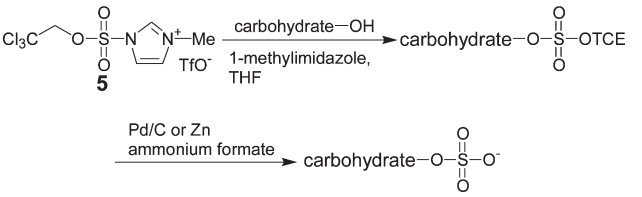
SCHEME 2. Byproduct Produced from the Reaction of Carbohydrate 2 with Reagent 1



protecting group and has been used to prepare a broad range of sulfated compounds.[9a−j]

Our interest in sulfated biomolecules lies primarily in the synthesis and study of sulfated carbohydrates, a class of compounds that play key roles in important biological processes such as blot clotting, cell adhesion, and cell−cell communication to name but a few.[10] However, we encountered problems when reagent **1** was used for preparing certain sulfated carbohydrates. For example, the synthesis of compound **3** from monosaccharide **2** proceeded in modest yield due to the formation of chloro sugar **4** as a byproduct (Scheme 2).[11] To solve this problem, we prepared reagent **5**, a new class of sulfating agent and the first known example of a sulfuryl imidazolium salt (SIS) (Scheme 3).[11] Using reagent **5**, TCE-protected sulfate esters could be introduced into monosaccharides in high yield and withstand many of the conditions that are commonly employed during the synthesis of complex carbohydrates.[11] The sulfate group can be deprotected in high yields under very mild conditions using Zn or Pd/C and ammonium formate.[6,11] Although SIS **5** works well for most sulfations it does have some limitations. The sulfations must be carried out in THF as **5** is poorly soluble in less polar solvents such as CH_2Cl_2 and chloroform. In THF, its stability is limited and so for certain difficult sulfations, which can take 24−48 h to complete, **5** must be replenished during the reaction and, therefore, a considerable excess of **5** is sometimes required for high yields.[11] Consequently we wish to design SISs with improved stability, solubility, and sulfating properties. Toward this end, we report the synthesis and sulfating properties of a series of sulfuryl imidazolium salts. We demonstrate that by

SCHEME 3. Sulfation of Carbohydrates Using Reagent 5



making a minor modification to the imidazolium ring of **5**, a more efficient sulfating agent can be obtained and certain sulfo-protected compounds that were inaccessible or challenging to obtain using reagent **5** can now be readily prepared.

Results and Discussion

We anticipated that the solubility, stability, and sulfating properties of SIS **5** could be altered by introducing alkyl groups on the imidazolium ring. Toward this end, we prepared a series of SISs, all of which contained the TCE group yet had different alkyl groups at the 2- and 3-positions of the imidazolium ring. The tetrafluoroborate counterion was also examined. In most cases, the synthesis of these compounds was readily achieved by reacting reagent **1** with the appropriate imidazole derivative to give compounds **6**−**8** (Table 1). Reaction of **6**−**8** with methyl triflate or trimethyl- or triethyloxonium tetrafluoroborate gave the SISs usually in very good yield (Table 1). When the product precipitated out of the reaction mixture pure SISs were obtained simply by filtration. It is possible that precipitation during the reaction is required to drive SIS formation since SISs **14**, **16**, and **17** did not precipitate out of the reaction mixture irrespective of the solvent used (diethyl ether, THF, CH_2Cl_2) and did not go to completion even after extended reaction times. Attempts to selectively precipitate out the SISs **14**, **16**, and **17** using apolar solvents such as hexane or pentane were unsuccessful as a semisolid was formed which consisted of both the starting material and product. In general, SISs having the triflate counterion were obtained in higher yields than those having a tetrafluoroborate counterion. In one instance, we were unable to obtain the BF_4^- salt (compound **14** which did not precipitate during the reaction), yet the corresponding TfO^- salt (compound **11**) was readily obtained. Several of us encountered strong allergic reactions when we attempted to prepare and isolate the TfO^- analogues of compounds **15**−**17**, and so these triflate salts were not pursued any further. All of the SISs that were obtained in pure form were white powders and could be stored at 4 °C for months without any detectable decomposition. Unlike compound **5**, all of these SISs exhibited good solubility in less polar solvents such as methylene chloride and chloroform. SISs **12**, **13**, and **15**, which had the BF_4^- counterion, were poorly soluble in THF. ^{1}H NMR analysis of solutions of the SISs in $CDCl_3$ revealed no detectable decomposition even after several days.

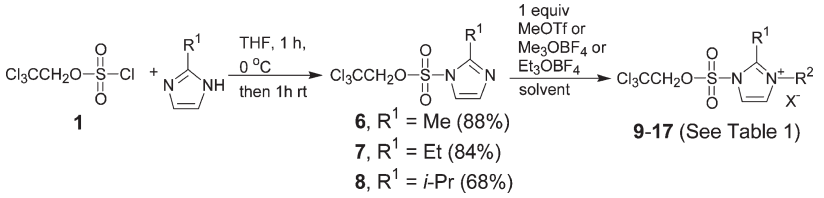
We chose carbohydrate **18** as a model substrate to test the sulfating ability of the above SISs because we had previously found that sulfation of the 4-OH was challenging using reagent **5**. In THF, 8.0 equiv of sulfating agent **5** and 8.5 equiv of 1-methylimidazole (1-MeIm) added over a 48 h period were required to obtain a 76% yield of carbohydrate **19**. The yield (56%) was even poorer in CH_2Cl_2 possibly due to the very limited solubility of **5** in this solvent. To evaluate the new SISs, compound **18** was reacted with

(9) (a) Bunschoten, A.; Kruijtzer, J. A. W.; Ippel, J. H.; de Haas, C. J. C.; van Strijp, J. A. G.; Kemmink, J.; Liskamp, R. M. J. *Chem. Commun.* **2009**, 2999. (b) Li, X. S.; Robertson, L. W.; Wehmler, H. J. *Chem. Cent. J.* **2009**, *3*, 5. (c) Ali, A. M.; Hill, B.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 3583. (d) Chen, J.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 1682. (e) Lu, C. P.; Ren, C. T.; Wu, S. H.; Chu, C. Y.; Lo, L. C. *ChemBioChem* **2007**, *8*, 2187. (f) Furstner, A.; Domostoj, M. M.; Scheiper, B *J. Am. Chem. Soc.* **2006**, *128*, 8087. (g) Yamaguichi, T.; Fukada, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755. (h) Furstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620. (i) Ahmed, V.; Ispahany, M.; Ruttgaizer, S.; Guillemette, G.; Taylor, S. D. *Anal. Biochem.* **2005**, *340*, 80. (j) Gunnarsson, G. T.; Riaz, M.; Adams, J.; Desai, U. R. *Bioorg. Med. Chem.* **2005**, 1783.

(10) Toida, T.; Chaidedgumjorn, A.; Linhardt, R. J. *Trends Glycosci. Glycotech.* **2003**, *15*, 29.

(11) Ingram, L. J.; Taylor, S. D. *Angew. Chem., Int. Ed. Engl.* **2006**, 3503.

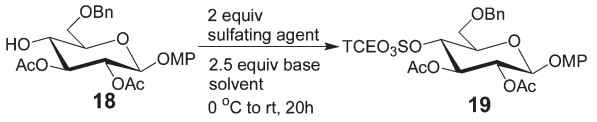
TABLE 1. Preparation of Sulfuryl Imidazolium Salts 9−13 and 15



compd	R^1	R^2	X^-	% yield
9	Me	Me	TfO^-	99[a]
10	Et	Me	TfO^-	98[a]
11	iPr	Me	TfO^-	85[a]
12	Me	Me	BF_4^-	85[b]
13	Et	Me	BF_4^-	79[b]
14	iPr	Me	BF_4^-	ND[d]
15	Me	Et	BF_4^-	81[c]
16	Et	Et	BF_4^-	ND[d]
17	IPr	Et	BF_4^-	ND[d]

[a]Solvent: dry diethyl ether. [b]Solvent: dry THF. [c]Solvent: dry CH_2Cl_2. [d]ND = not determined. Mixture of starting material and product as semisolids was obtained.

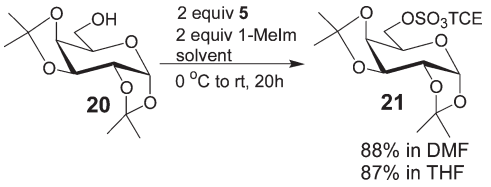
TABLE 2. Sulfation of Carbohydrate 18 with Reagents 5 and 9−13 and 15



entry	SIS	base	solvent	% yield of **19**
1	**5**	1-MeIm	DMF	35
2	**9**	1,2-dMeIm	THF	65
3	**9**	1,2-dMeIm	CH_2Cl_2	80
4	**9**	1-Me-2-*i*PrIm	CH_2Cl_2	53
5	**9**	1,2-dMeIm	DMF	40
6	**10**	1-Me-2-EtIm	THF	18
7	**10**	1,2-dMeIm	THF	58
8	**10**	1-Me-2-EtIm	CH_2Cl_2	21
9	**10**	1,2-dMeIm	CH_2Cl_2	68
10	**11**	1-Me-2-*i*PrIm	THF	18
11	**11**	1,2-dMeIm	THF	54
12	**11**	1-Me-2-*i*PrIm	CH_2Cl_2	30
13	**11**	1,2-dMeIm	CH_2Cl_2	66
14	**12**	1,2-dMeIm	CH_2Cl_2	79
15	**13**	1-Me-2-EtIm	CH_2Cl_2	38
16	**13**	1,2-dMeIm	CH_2Cl_2	78
17	**15**	1-Et-2-MeIm	CH_2Cl_2	45
18	**15**	1,2-dMeIm	CH_2Cl_2	75

2 equiv of SIS in the presence of 2.5 equiv of base in various solvents for 20 h, the reaction was stopped, whether or not it was complete, and the yield of **19** was determined after purification (Table 2). For SISs **9**−**11**, higher yields were obtained in CH_2Cl_2 compared to THF. We were unable to evaluate SISs **12**−**15** in THF due to their limited solubility in this solvent. SISs **9** and **12**, which bear a 1,2-dimethylimidazolium group, gave good yields using 1,2-dimethylimidazole (1,2-dMeIm) as the base (entries 3 and 14). The counterion (TfO^- or BF_4^-) had no effect on yield. Low yields were obtained when the SIS contained an ethyl or isopropyl moiety at the 2-position of the imidazolium group (SISs **10**, **11**, and **13**) but only if these reactions were performed using a base (1-methyl-2-isopropylimidazole (1-Me-2-*i*-PrIm) or 1-methyl-2-ethylimidazole (1-Me-2-EtIm)) that was the same as the leaving group of the respective SISs (entries 6, 8, 10, 12, and 15). However, if these reactions were performed using 1,2-dMeIm as base then the yields improved considerably (entries 7, 9, 11, 13, and 16). ^{1}H NMR studies in $CDCl_3$ revealed that just 1 equiv of 1,2-dMeIm rapidly displaced the 1-Me-2-EtIm or 1-Me-2-*i*PrIm from SISs **10** and **11** within minutes, thus forming SIS **9** in situ which is a better sulfating agent. Even after several hours, ^{1}H NMR provided no evidence that the reverse reaction back to SISs **10** and **11** was occurring, indicating that SIS **9** is more stable than SISs **10** and **11** possibly due to steric hindrance between the ethyl or isopropyl group at the 2-position and the sulfonate moiety and methyl group. We also found that a reduced yield of **19** was obtained using SIS **9** and 1-Me-2-*i*PrIm in CH_2Cl_2 as the base (entry 4), revealing that the low yields encountered with SISs **10**, **11**, and **13** with 1-Me-2-*i*PrIm or 1-Me-2-EtIm may in part be due to the added imidazole derivative itself, which may be acting as a general base during the reaction. It is possible that there is greater steric crowding at the transition state of the reaction with SISs **10**, **11**, and **13** and 1-Me-2-*i*PrIm or 1-Me-2-EtIm than with SISs **9** or **12** and 1,2-dMeIm. SIS **15**, which differs from SIS **12** only by the presence of an ethyl rather than methyl group on one of the nitrogens, gave lower yields than SIS **12** (entry 14) when 1-ethyl-2-methyl imidazole (1-Et-2-MeIm) was used as base but almost the same yield when 1,2-dMeIm was used as base (entries 17 and 18), again suggesting that the 1-Et-2-MeIm group in SIS **15** was exchanging with 1,2-dMeIm. We also examined DMF as a solvent for SISs **5** and **9**, but low yields were obtained (entries 1 and 5).

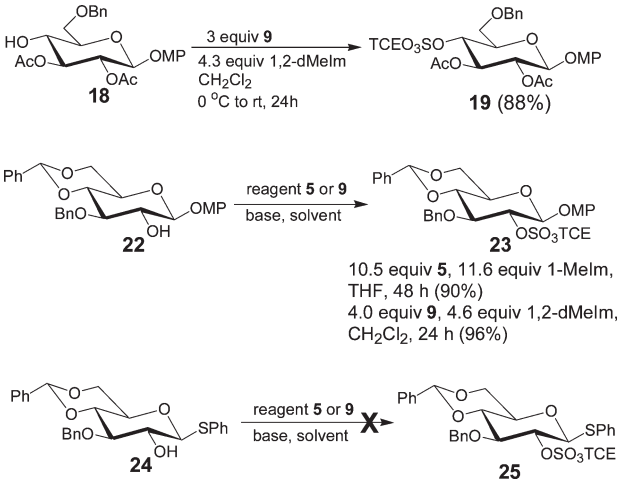
SCHEME 4. Sulfation of Carbohydrate 20 in DMF and THF



However, we found that DMF can be used as a solvent for less challenging sulfations. For example, 1:2,3:4-di-*O*-isopropylidene galactose (**20**) is sulfated with 2 equiv of reagent **5** and 2 equiv of 1-MeIm in very good yields in either THF or DMF (Scheme 4).

Since SIS **9** can be readily prepared in very high yield and the best yields in Table 1 were obtained with this compound, we decided to use this reagent for subsequent studies. Further studies with SIS **9** and carbohydrate **18** revealed that an 88% yield of **19** could be obtained in 24 h using just 3 equiv of reagent **9** and 4.3 equiv of 1,2-dMeIm in CH_2Cl_2 (Scheme 5). We had previously prepared carbohydrate **23** in 90% yield after subjecting compound **22** to 10.5 equiv of SIS **5** and 11.6 equiv of 1-MeIm for 28 h in THF (Scheme 5).[11]

SCHEME 5. Sulfation of Carbohydrates 18, 22, and 24 with Reagents 5 and/or 9

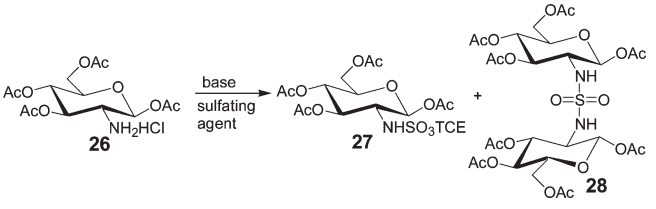


However, when 4 equiv of SIS **9** and 4.6 equiv of 1,2-dMeIm in CH_2Cl_2 were used, carbohydrate **23** was obtained in a 96% yield after just 24 h. Performing the reaction under the same conditions in THF gave a 40% yield of **23** with unreacted **22** still remaining after 24 h, demonstrating that these reactions can be subject to a significant solvent effect. A complex mixture of products was obtained when we attempted to sulfate compound **24**, which is the STol analogue of **22**, with either SIS **5** or **9**, and we were unable to isolate the desired sulfated compound **25**. This was unexpected since we had previously reported the sulfation of the 4-OH of *p*-tolyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-1-thio-β-D-glucopyranoside in high yield using reagent **5**.[11] It is possible that upon sulfation of compound **24** intramolecular displacement of the TCE sulfate group by the sulfur atom occurs resulting in the formation of a reactive episulfonium ion.

Since *N*-sulfation is a common feature in heparin-like glycosaminoglycans, we also examined the ability of SISs to *N*-sulfate glycosamines. Recently, Chen and Yu reported the synthesis of compound **27** (Table 3) in 82% yield by the addition of a solution of compound **26** and 3 equiv of Et_3N in DMF over 1 h to a solution of 6 equiv of reagent **1** and 1 equiv of DMAP in DMF.[9d] The best yield of **27** that we were able to obtain using these conditions was 45%, and half of the product was always dimer **28**, a byproduct not mentioned in Chen and Yu's original report (entry 1, Table 3). We performed this reaction under these conditions numerous times, and in each instance **27** and **28** were formed in 40−45% yield. Performing the reaction under the same conditions in methylene chloride gave exclusively dimer **28** in a 70% yield. Attempts to prepare compound **27** using SIS **9** also gave disappointing results with the best yield of **27** being only 29% when performing the reaction with 6.0 equiv of **9** in the presence of 3.5 equiv of 1,2-dMeIm in methylene chloride (entry 3, Table 3). Performing the reaction in DMF gave a lower yield (entry 4), though in neither case was dimer **28** formed probably because a stronger base such as Et_3N is necessary for elimination of trichloroethanol from **27** which leads to dimer formation. Performing the reaction with 4 equiv of SIS **9** and 1,2-dMeIm in the presence of 1 equiv of Et_3N or in pyridine with 1 equiv of Et_3N gave only trace amounts of the desired product.

To determine whether other carbohydrates would undergo *N*-sulfation more readily than carbohydrate **26**, we examined carbohydrates **29** and **30** as substrates (Table 4) which were prepared as stable free amines. Subjecting **29** to reagent **1** and the conditions of Chen and Yu[9d] did not result in the formation of *N*-sulfated product **31**, although dimer

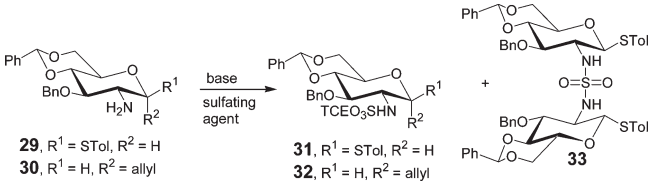
TABLE 3. *N*-Sulfation of Carbohydrate 26



entry	reagent (equiv)	base (equiv)	solvent	% yield of **27**	% yield of **28**
1	**1** (6)	Et_3N (3.5) DMAP (1)	DMF	45[a]	45[a]
2	**1** (6)	Et_3N (3.5) DMAP (1)	CH_2Cl_2	0[a]	70[a]
3	**9** (6)	1,2-dMeIm (3.5)	CH_2Cl_2	29[b]	0[b]
4	**9** (6)	1,2-dMeIm (3.5)	DMF	18 [b]	0[b]
5	**9** (6)	Et_3N (2.5)	CH_2Cl_2	0[c]	68[c]
6	**9** (4)	Et_3N (1) 1,2-dMeIm (4)	CH_2Cl_2	trace	trace
7	**9** (4)	Et_3N (1)	pyridine	trace	trace

[a] **26** and NEt_3 (3.5 equiv) in solvent (0.1 M wrt **26**) were added at 0 °C over 1 h to a solution of **1** (6.0 equiv) and DMAP (1.0 equiv) in solvent (2.0 M wrt **1**). [b] 1,2-dMeIm (3.5 equiv) followed by **9** (6.0 equiv) were added to **26** in solvent (0.05 M). [c] Et_3N (2.5 equiv) followed by **9** (3.0 equiv) were added to **26** in CH_2Cl_2 (0.15 M). Additional **9** (3.0 equiv) was added after 12 h.

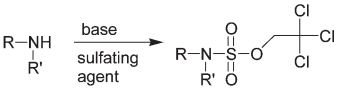
TABLE 4. *N*-Sulfation of Carbohydrates 29 and 30



entry	substrate	reagent (equiv)	base (equiv)	solvent	% yield of **31** or **32**	% yield of **33**
1	**29**	**1** (6)	Et_3N (3.5) DMAP (1)	DMF	0[a]	70[a]
2	**29**	**5** (2)	1-MeIm (2.5)	THF	trace[b]	0[b]
3	**29**	**5** (6)	1-MeIm (4)	THF	trace[b]	0[b]
4	**29**	**5** (6)	1-MeIm (4)	CH_2Cl_2	trace[b]	0[b]
5	**29**	**9** (6)	1,2-dMeIm (4)	THF	94[b]	0[b]
6	**29**	**9** (6)	1,2-dMeIm (4)	CH_2Cl_2	95[b]	0[b]
7	**30**	**1** (2)	1,2-dMeIm (4)	THF	60[c]	NA[d]
8	**30**	**5** (6)	1-MeIm (4)	THF	9[b]	NA[d]
9	**30**	**9** (4)	1,2-dMeIm (4)	THF	94[b]	NA[d]

[a]A solution of **29** and Et_3N (3.5 equiv) in DMF (0.1 M wrt **29**) was added dropwise over 1 h to a solution of **1** and DMAP (1.0 equiv) in DMF (1.8 M wrt **1**). [b]**5** or **9** was added to a solution of 1-MeIm or 1,2-dMeIm and **29** or **30** in THF (0.23 M) at 0 °C. The reaction was gradually warmed to rt, 8−16 h. [c]Compound **1** was added to a solution of 1,2-dMeIm and **30** in THF (0.23 M) at 0 °C. The reaction was gradually warmed to rt, 8 h. [d]NA: not applicable.

TABLE 5. Sulfation of Amines 34−37

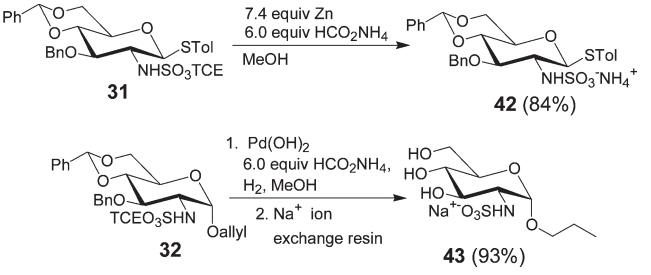


substrate	reagent (equiv)	product	% yield[a]
34 (R′ = H, R = cyclohexyl)	**9**	**38**	99
	5	**38**	13
35 (R′ = H, R = benzyl)	**9**	**39**	95
	5	**39**	14
36 (R′ = Me, R = butyl)	**9**	**40**	90
37 (R = R′ = $-(CH_2)_5-$)	**9**	**41**	98

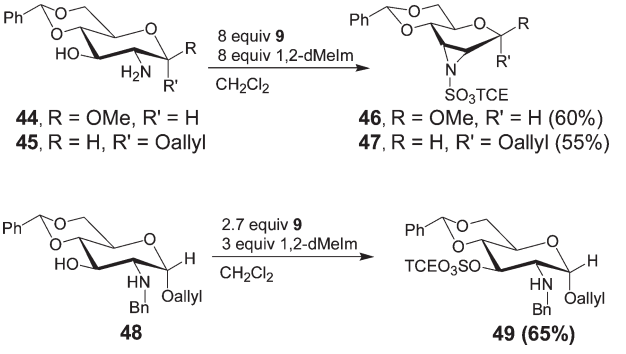
[a]THF (0.23 M), 2.5 equiv of 1-MeIm or 1,2-dMeIm, and 2.0 equiv of **5** or **9**, 8−14 h.

33 was isolated in a 70% yield (entry 1). Sulfations using reagent **5** and 1-MeIm were also unsuccessful in that a complex mixture of products were formed (as determined by TLC) and only trace quantities of the desired product **31** was formed under a variety of conditions (entries 2−4). However, subjecting **29** to 6 equiv of reagent **9** and 4 equiv of 1,2-dMeIm in either THF or CH_2Cl_2 gave compound **31** in a 94−95% yield (entries 5 and 6). Reaction of **30** with 2 equiv of reagent **1** in the presence of 4 equiv of 1,2-dMeIm resulted in complete consumption of **30** within 6 h; however, product **32** was isolated in only a 60% yield (entry 7). Similarly, sulfation of carbohydrate **30** with reagent **5** gave only 9% of the desired product **32**, while STS **9** under the same conditions gave carbohydrate **32** in a 94% yield (entries 8 and 9). This difference in reactivity between SISs **5** and **9** is not limited to just carbohydrate *N*-sulfations. Sulfation of amines **34** and **35** with reagent **9** gave the desired sulfated products **38** and **39** in excellent yields, while very poor yields were obtained using reagent **5** (Table 5). *N*-Sulfation of secondary amines with reagent **9** also proceeded in very high yields (Table 5). We do not have a clear understanding as to why SISs **5** and **9** behave so differently with amines. A reaction between the amino group and

SCHEME 6. Deprotection of Carbohydrates 31 and 32



SCHEME 7. Reaction of Carbohydrates 44, 45, and 48 with Reagent 9



SIS **5** may be taking place such as attack of the amino group at the 2-position of SIS **5** or deprotonation of the proton at C-2 of SIS **5**.[12]

The sulfate group in carbohydrate **31** was deprotected to give carbohydrate **42** in 84% yield using Zn/ammonium formate, while carbohydrate **32** was completely deprotected using $Pd(OH)_2$, H_2, and ammonium formate (Scheme 6) to give carbohydrate **43** in a 93% yield.

We also attempted to disulfate carbohydrates **44** and **45** using reagent **9** (Scheme 7). These reactions proceeded

(12) We were unable to examine the behavior of SIS **5** with amines by NMR since SIS **5** is poorly soluble in $CDCl_3$.

slowly, and a considerable excess of the SIS was required before all of the **44** and **45** were consumed. Moreover, none of the desired disulfated products were isolated, but instead aziridines **46** and **47** were obtained in 55−60% yields. Surprisingly, reaction of the N-benzyl derivative of **45**, compound **48**, with 2.7 equiv of reagent **9** gave the *O*-sulfated product **49** in a 65% yield, and no *N*-sulfated, disulfated, or sulfated aziridine product was formed even after the addition of a considerable excess of the sulfating agent (Scheme 7).

Conclusions

In conclusion, we have prepared a series of sulfuryl imidazolium salts (SISs) and examined them as reagents for incorporating TCE-protected sulfate esters into carbohydrates. We demonstrated that by incorporating a methyl group at the 2-position of the imidazolium ring a more efficient sulfating agent, SIS **9** was obtained. *O*-Sulfations that required prolonged reaction times and a large excess of the original SIS, compound **5**, were more readily achieved using SIS **9**. Certain *N*-sulfated compounds that that were practically inaccessible using SIS **5** could be obtained in excellent yield using SIS **9**. We expect that this next generation of sulfating agent will find widespread use in the preparation of sulfated carbohydrates and other organosulfates.

Experimental Section

Representative Procedure for the Preparation of Compounds 6−8 (Table 1, Compound 6). To a solution of 2-methylimidazole (5.9 g, 0.072 mol, 3.60 equiv) in dry THF (40 mL) at 0 °C was added dropwise a solution of reagent **1** (5.0 g, 0.02 mol, 1.0 equiv) in THF (50 mL). The reaction was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 1 h. The reaction mixture was filtered, the residue was washed with THF, and the filtrate was concentrated under vacuum. The crude residue was purified by flash chromatography (33:67 EtOAc/hexanes) to give **6** as a white solid (5.2 g, 88%): mp 53−55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H, H_{imi}), 6.94 (s, 1H, H_{imi}), 4.65 (s, 2H, CH_2), 2.67 (s, 3H, $CH_{3\text{-imi}}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 128.2, 120.1, 91.7, 80.0, 14.9; HRMS (EI^+) calcd for $C_6H_7Cl_3N_2O_3S$ $(M)^+$ 291.9243, found 291.9244.

Representative Procedure for the Preparation of Sulfuryl Imidazolium Triflate Salts (Table 1 Compound 9). To a solution of compound **6** (4.4 g, 15 mmol, 1.0 equiv) in dry Et_2O (70 mL) at 0 °C was added methyl triflate (1.8 mL, 15 mmol, 1.0 equiv) dropwise . The reaction was stirred for 3 h at 0 °C during which time a white precipitate formed. The mixture was filtered. The filter cake was washed with cold ether, and the filtrate was cooled to − 20 °C and filtered. This second precipitate was washed with cold ether and then combined with the first precipitate, which afforded compound **9** as a white solid (6.8 g) in 99% yield. We have prepared compound **9** in batches up to 75 g in excellent yield. We typically store compound **9** at 4 or −20 °C and have never detected any decomposition even after 6 months. We have also stored reagent **9** on the benchtop at room temperature for a month and not detected any decomposition: ^{1}H NMR (300 MHz, CD_3OD) δ 8.09 (d, 1H, J = 2.1 Hz, H_{imi}), 7.74 (d, 1H, J = 1.8 Hz, H_{imi}), 5.35 (s, 2H, CH_2), 3.92 (s, 3H, $CH_{3\text{-imi}}$), 2.91 (s, 3H, $CH_{3\text{-imi}}$); ^{13}C NMR (75 MHz, CD_3OD) δ 148.6, 123.52, 120.8, 120.4 (q, J_{CF} = 316.5 Hz, CF_3), 91.6, 82.0, 35.3, 10.5; ^{19}F NMR (282 MHz, CD_3OD) δ −79.8; HRMS (+ESI) calcd for $(M - OTf)^+$ $C_7H_{10}Cl_3N_2O_3S^+$ 306.9478, found 306.9469.

Representative *O*-Sulfation Using Reagent 9 (Scheme 5, Compound 23). To carbohydrate **22** (0.200 g, 0.431 mmol) in dry dichloromethane (2.7 mL) at 0 °C was added 1,2-diMeIm (0.100 g, 1.0 mmol) followed by reagent **9** (0.400 g, 0.874 mmol). The reaction was gradually brought to rt and stirred for 16 h. Analysis by TLC indicated remaining starting material; thus, additional 1,2-diMeIm (0.100 g, 1.0 mmol) and sulfating agent **9** (0.4 g, 0.874 mmol) were added. The reaction was stirred for an additional 8 h, diluted with dichloromethane (1.0 mL), and quenched with water (1.0 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to a brown crude oil. Purification by flash chromatography (25:75 EtOAc/hexanes) afforded **23** as a white solid (0.278 g, 96%): mp 105−107 °C; $[\alpha]^{25}_D$ = −34.6 (*c* 1.0, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (ddd, 1H, $J_{5,6ax}$ = 9.7, $J_{5,4}$ = 9.5, $J_{5,6eq}$ = 5.0 Hz, H5), 3.80 (s, 3H, CH_3), 3.86 (dd, 1H, $J_{6eq,6ax} = J_{6ax,5}$ = 10.4 Hz, $H6_{ax}$), 3.88 (dd, 1H, $J_{4,5} = J_{4,3}$ = 9.2 Hz, H4), 3.98 (dd, 1H, $J_{3,4} = J_{3,2}$ = 9.1 Hz, H3), 4.43 (dd, 1H, $J_{6eq,6ax}$ = 10.5, $J_{6eq,5}$ = 5.0 Hz, $H6_{eq}$), 4.68, 4.71 (AB, 2H, J = 11.1 Hz, CH_2CCl_3), 4.85 (m, 1H, H2), 4.87, 5.01 (AB, 2H, J = 11.2 Hz, CH_2Ph), 5.02 (d, 1H, $J_{1,2}$ = 7.8 Hz, H1), 5.61 (s, 1H, CHPh), 6.85−6.88 (m, 2H, ArH), 7.06−7.09 (m, 2H, ArH), 7.33−7.50 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 66.2, 66.30, 74.6, 77.9, 79.9, 81.2, 83.9, 92.6, 99.9, 101.4, 114.6, 118.8, 125.9, 127.9, 128.1, 128.1, 128.3, 128.3, 128.3, 128.4, 129.1, 136.6, 137.1, 150.2, 156.0; HRMS (EI^+) m/z = 674.0546, $C_{29}H_{29}Cl_3O_{10}S$ requires 674.0547.

Representative *N*-Sulfation Using Reagent 9 (Compound 32, Table 4, Entry 9). To a solution of **30** (0.10 g, 0.252 mmol) in THF (1.1 mL, 0.23 M) at 0 °C was added 1,2-dMeIm (0.06 g, 0.62 mmol) followed by reagent **9** (0.460 g, 1.01 mmol). The reaction was stirred at 0 °C, gradually warmed to room temperature by allowing the ice bath to melt, and then stirred overnight. After 14 h, the mixture was applied directly to a silica gel column. Flash chromatography (33:67 EtOAc/hexanes) gave pure **32** as an amorphous white solid (0.144 g, 94%): $[\alpha]^{25}_D$ = +71.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (br-ddd, 1H, $J_{2,NH} = J_{2,3}$ = 8.8 Hz, $J_{2,1}$ = 3.4 Hz, H2), 3.73−3.94 (m, 4H, H3, H4, H5, $H6_{ax}$), 4.08 (dd, 1H, $J_{H,H}$ = 12.6, 6.4 Hz, OCH_2-$CHCH_2$), 4.25 (dd, 1H, $J_{H,H}$ = 12.6, 5.5 Hz, OCH_2CHCH_2), 4.32 (dd, 1H, $J_{6eq,6ax}$ = 9.9 Hz, $J_{6eq,5}$ = 4.3 Hz, $H6_{eq}$), 4.58, 4.62 (AB, 2H, J = 10.8 Hz, CH_2CCl_3), 4.76, 4.99 (AB, 2H, J = 11.5 Hz, CH_2Ph), 5.00 (br-d, $J_{NH,2}$ = 8.8 Hz, NH), 5.15 (d, 1H, $J_{1,2}$ = 3.7 Hz, H1), 5.27−5.37 (m, 2H, OCH_2CHCH_2), 5.62 (s, 1H, CHPh), 5.88−6.01 (m, 1H, OCH_2CHCH_2), 7.28−7.52 (m, 10H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.8, 62.7, 68.8, 69.0, 75.0, 75.5, 78.3, 82.8, 92.9, 96.9, 101.37, 118.8, 126.0, 128.0, 128.2, 128.3, 128.6, 129.1, 132.9, 137.1, 137.7; HRMS (ESI^+) m/z = 608.0665, $C_{25}H_{29}NO_8Cl_3S$ (M + H) requires 608.0679.

***p*-Tolyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-deoxy-2-sulfoxyamino-1-thio-β-D-glucopyranoside (42).** To a suspension of ammonium formate (0.083 g, 1.3 mmol) in HPLC-grade MeOH (1.3 mL, 1.0 M) was added **31** (0.15 g, 0.22 mmol) followed by zinc dust (0.1 g, 1.55 mmol). The reaction was stirred for 7 h at room temperature, at which point no starting material was detected using TLC. The reaction was filtered through Celite and concentrated to crude product. Flash chromatography (20:4:1 CH_2Cl_2/MeOH/NH_4OH) afforded a white solid, which was lyophilized (3×) from water to yield **42** as a white powder (0.105 g, 84%): $[\alpha]^{25}_D$ = −78.0 (c 0.85, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.01 (dd, 1H, $J_{2,3} + J_{2,1}$ = 17.1 Hz, H2), 3.39−3.46 (m, 1H, H5), 3.65 (dd, 1H, $J_{6ax,6eq} + J_{6ax,5}$ = 10.2 Hz, $H6_{ax}$), 3.71 (dd, $J_{4,5} + J_{4,3}$ = 18.3 Hz, H4), 4.20 (dd, 1H, $J_{6eq,6ax}$ = 10.2, $J_{6eq,5}$ = 5.1 Hz, $H6_{eq}$), 4.39 (dd, $J_{3,4} = J_{3,2}$ = 8.5 Hz, H3), 4.74 (d, 1H, J = 11.5 Hz, 1/2 CH_2Ph), 4.97 (d, 1H, J = 11.5 Hz, 1/2 CH_2Ph), 5.59 (d, 1H, J = 9.1 Hz, H1), 5.66 (s, 1H, CHPh), 5.76 (s, 1H, NH), 7.14−7.40 (m, 18 H, 14 ArH + NH_4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.1, 59.8, 68.5. 68.9, 74.0, 78.9, 81.7, 87.0, 100.6, 126.4, 126.4, 127.4, 128.2, 128.3, 128.5, 130.0, 131.2, 131.8, 138.3, 140.1; HRMS (ESI^-) m/z = 542.1306, $C_{27}H_{28}NO_7S_2$ requires 542.1307.

Propyl 2-Deoxy-2-sulfoxyamino-α-D-glucopyranoside (43). To a solution of compound **42** (61 mg, 0.1 mmol) in MeOH

(2 mL) was added ammonium formate (38 mg, 0.6 mmol) and the mixture stirred until all of the ammonium formate dissolved. $Pd(OH)_2$ (20 mg, 33 wt %) was added and the mixture stirred over an atmosphere of H_2 (balloon) for 16 h. The mixture was filtered through Celite and the filtrate concentrated. The filtrate was dissolved in MeOH and concentrated again, and this was repeated two more times. The residue was dissolved in MeOH (2 mL), 10 mg of $Pd(OH)_2$ was added, and the mixture was stirred over an atmosphere of H_2 (balloon) for 16 h. The mixture was filtered through Celite and the filtrate concentrated. The residue was dissolved in water and passed through a small Dowex 50 Na^+ ion-exchange column which gave compound **43** as a white powder (28 mg, 93%): $[\alpha]^{25}_D = +89.3$ (*c* 1.4, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 0.81 (t, 3H, $J = 7.4$ Hz, CH_3), 1.52 (m, 2H, CH_2CH_3) 3.11 (dd, 1H, $J_{1,2} = 3.0$ Hz, $J_{2,3} = 10.2$ Hz, H2), 3.53 (m, 7H, H3, H4, H5, H6, H6′, OCH_2-), 5.01 (d, 1H, $J_{1,2} = 3.0$ Hz, H1); ^{13}C NMR (125 MHz, D_2O) δ 10.0, 22.1, 57.8, 60.6, 70.1, 70.2, 71.5, 71.6, 97.2; HRMS (ESI^-) $m/z = 300.0753$, $C_9H_{18}NO_8S$ requires 300.0755.

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Supporting Information Available: Experimental procedures and characterization data for all novel compounds except compounds **6**, **9**, **23**, **32**, **42**, and **43**. ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.