Protecting Groups

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Introduction of 2,2,2-Trichloroethyl-Protected Sulfates into Monosaccharides with a Sulfuryl Imidazolium Salt and Application to the Synthesis of Sulfated Carbohydrates**

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Sulfated polysaccharides are widespread in nature. These compounds are implicated in a wide variety of important biological processes such as blood clotting, cell adhesion, and cell–cell communication.[1] However, detailed characterization of their specific biological roles has proved very challenging. One reason for this is that the synthesis of even relatively small sulfated oligosaccharides still remains a considerable challenge. The current approach to their synthesis involves first protecting the hydroxy groups in the monosaccharide building blocks. The hydroxy groups that bear the sulfate groups in the final product are protected in a manner orthogonal to those that are not sulfated. After assembly of the oligosaccharide, the hydroxy groups to be sulfated are deprotected. These groups are then sulfated, usually with a sulfur trioxide–amine or –amide complex, following which all other protecting groups are removed to give the desired product.[2] There are several drawbacks to this approach. First, intensive manipulation of protecting groups is required at the end of the synthesis. Second, the sulfated products are highly polar and can be difficult to purify and manipulate for subsequent deprotections. Finally and most significantly, good yields of the sulfation reactions can be difficult to attain especially when multiple sulfations are necessary. Such difficulties can potentially be removed and/or diminished by the introduction of the sulfate groups at the monosaccharide stage as protected sulfate diesters; this strategy would avoid the need for selective hydroxy deprotections and sulfations at the end of the synthesis. Although this alternative approach could be highly effective in the synthesis of sulfated carbohydrates, it has received little attention, most probably because of the difficulties in developing protecting groups for sulfate monoesters. Perlin and Penney used phenyl chlorosulfate to introduce phenyl-protected sulfate groups into monosaccharides.[3] However, no further reports on the use of this protecting group in the synthesis of sulfated monosaccharides or higher carbohy-

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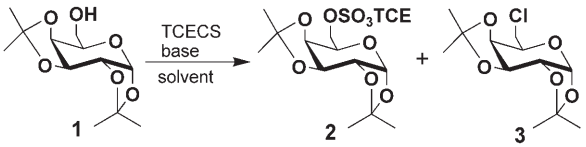
drates have appeared in the literature, possibly owing to low or variable yields during removal of the phenyl group. Proud et al. later introduced the trifluoroethyl (TFE) group as a protecting group for sulfated carbohydrates,[4] but there are two disadvantages to this approach. TFE was introduced by treating sulfate monoesters with trifluorodiazoethane, a reagent that must be freshly prepared and is highly toxic and potentially explosive. Moreover, its removal requires somewhat harsh conditions, that is, refluxing with KO*t*Bu/HO*t*Bu. Karst et al. recently demonstrated that deprotection of the sulfate groups proceeds in low or moderate yields when using fully protected disaccharides as substrates.[5]

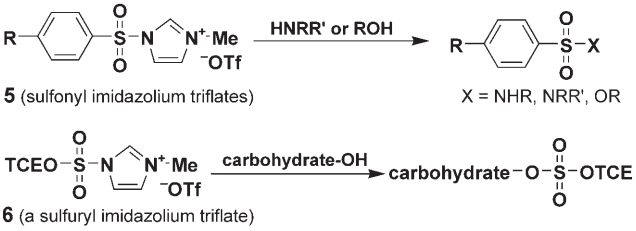
Recently, we described the use of the 2,2,2-trichloroethyl (TCE) group as the first protecting group developed for aryl sulfates.[6] The TCE-protected sulfate esters were prepared in a single step by the reaction of phenols with 2,2,2-trichloroethyl chlorosulfate (TCECS) in the presence of triethylamine. The resulting protected sulfates were stable to a variety of conditions, but were readily deprotected in excellent yields under neutral conditions with Pd/C–ammonium formate or zinc–ammonium formate. These studies prompted us to examine the TCE group as a protecting group for sulfated carbohydrates. Herein we describe the first synthesis of a sulfuryl imidazolium salt, an entirely new class of sulfating agents. We demonstrate that this reagent is highly effective for introducing TCE-protected sulfates into carbohydrates. We also show that the TCE group can be removed in excellent yields and that this group shows outstanding potential as a valuable tool for the synthesis of sulfated carbohydrates.

Incorporation of the TCE-protected sulfate group into carbohydrates was first examined with diisopropylidene-D-galactose (**1**) as a model substrate. Reaction of **1** with TCECS under a wide variety of conditions generally gave the desired product **2** in very low yields (Scheme 1);[7] the dominant product was often chlorosugar **3**. In an attempt to decrease the amount of chloride-displacement product, the reactions were performed in the presence of



Scheme 1. Reaction of **1** with TCECS.

various silver salts. After some experimentation, it was found that the reaction of **1** in the presence of AgCN, Et_3N, and 4-dimethylaminopyridine (DMAP) in THF gave the desired product **2** in approximately 50% yield. However, **3** still accounted for a significant proportion of the products (Scheme 1). Moreover, applying these conditions to other monosaccharides such as benzyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**4**) gave little or no sulfodiester product. Nevertheless, these results suggest that the desired compounds could be formed in good yield if a highly reactive sulfating agent that did not liberate a nucleophilic species such as chloride ion could be developed. O'Connell and Rapoport reported the synthesis of aryl sulfonamides and sulfonates with highly reactive sulfonyl imidazolium triflates **5**

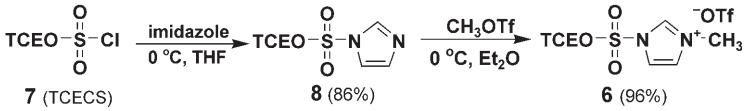


5 (sulfonyl imidazolium triflates)

6 (a sulfuryl imidazolium triflate)

Scheme 2. Sulfonyl and sulfuryl imidazolium triflates.

(Scheme 2).[8] These reagents were particularly useful for preparing sterically hindered sulfonates and sulfonamides, as well as certain primary sulfonates that were difficult to prepare with sulfonyl chlorides owing to the formation of alkyl chloride by-products. On the basis of these studies, we anticipated that sulfuryl imidazolium triflate[9] **6** would be a highly effective sulfating agent and would be particularly useful for introducing TCE-protected sulfate esters into carbohydrates (Scheme 2). Although sulfuryl imidazolium salts have never been reported, we found that **6** was readily constructed. Reaction of TCECS (**7**)[6] with imidazole gave sulfuryl imidazole **8** in 86% yield (Scheme 3). Reaction of **8**



7 (TCECS) **8** (86%) **6** (96%)

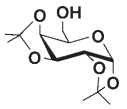
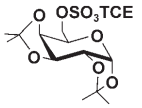
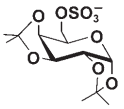
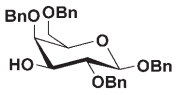
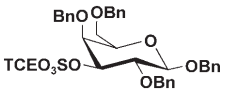
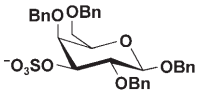
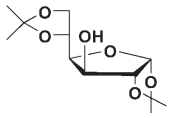
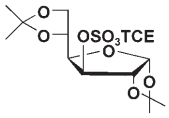
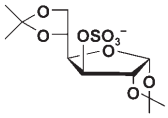
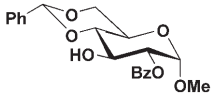
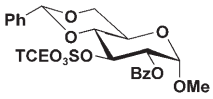
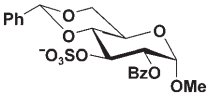
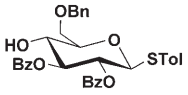
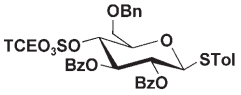
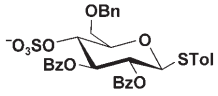
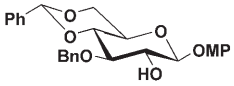
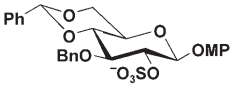
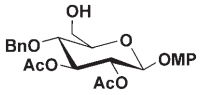
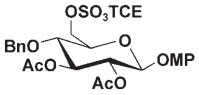
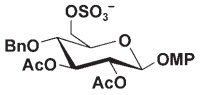
Scheme 3. Synthesis of sulfuryl imidazolium triflate **6**.

with methyl triflate in dry diethyl ether resulted in the precipitation of **6**, which was isolated in almost quantitative yield by filtration of the reaction mixture (Scheme 3).[10] No further purification of **6** was necessary. Imidazolium salt **6** is stable and does not require storage under an inert atmosphere. It can be stored at room temperature for weeks or at −20 °C for months without any detectable decomposition.

Imidazolium salt **6** was treated with a variety of monosaccharides that bear an array of hydroxy protecting groups in the presence of *N*-methylimidazole (NMI) in THF (Table 1). In most cases, primary and secondary hydroxy groups were sulfated in good to excellent yields by subjecting them to **6** (2.0–4.7 equiv) and NMI (2.5–6.0 equiv) in THF at room temperature for 16–48 h.[10] In the case of **12**, 10.5 equivalents of **6**, 11.6 equivalents of NMI, and 72 h were required to allow 90% yield. The presence of NMI was essential for all the reactions. Other bases (Et_3N, Hünig base, pyridine, 2,6-lutidine, piperidine) were considerably less effective.

The TCE group was removed from **2** and **14**–**19** in very good yields by employing zinc–ammonium formate in methanol (Table 1).[10] Apart from the presence of $ZnCl_2$, $(HCO_2)_2Zn$, and NH_4Cl, the crude material was essentially

Table 1: Synthesis of TCE-protected sulfocarbohydrates with **6** and deprotection of the sulfate group with Zn–HCO_2NH_4.

	Substrate		Sulfodiester product	Protection yield[a,b] [%]		Deprotected product	Deprotection yield[b,h] [%]
1		**2**		87[c]	**20**		99
4		**14**		94[c]	**21**		94
9		**15**		90[c]	**22**		97
10		**16**		94[d]	**23**		96
11		**17**		91[e]	**24**		96
12		**18**		90[f]	**25**		91
13		**19**		81[g]	**26**		94

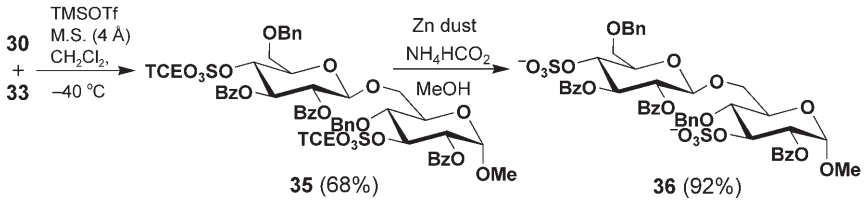
[a] All reactions were conducted with the carbohydrate (0.22–0.26 M) in THF. [b] Yield of isolated pure product. [c] 2 equiv **6**, 2.5 equiv NMI. [d] 4.7 equiv **6**, 5.3 equiv NMI. [e] 4.3 equiv **6**, 5.2 equiv NMI. [f] 10.5 equiv **6**, 11.6 equiv NMI. [g] 3.7 equiv **6**, 6 equiv NMI. [h] HCO_2NH_4 (6 equiv), Zn dust (7.6 equiv), carbohydrate (0.1 M) in MeOH. Bn = benzyl, Bz = benzoyl, MP = *p*-methoxyphenyl, Tol = *p*-tolyl.

pure. These impurities were easily removed by passing the product through a short column of silica with CH_2Cl_2/MeOH/NH_4OH (20:4:1) as eluent. Deprotection studies were also performed with Pd/C–ammonium formate; however, the yields were slightly lower than those with Zn.

Preliminary studies indicate that the TCE-protected sulfates are stable to many of the conditions commonly encountered in carbohydrate chemistry (Table 2).[10] Selective 6-O-debenzylation and acetylation of **14** with $ZnCl_2$/AcOH/Ac_2O gave **27** in 95% yield. Subjection of **27** to catalytic NaOMe in MeOH gave the deacetylated product **28** in 85% yield. Benzylidene ring opening of **16** with either TfOH (Tf = trifluoromethanesulfonyl) or $PhBCl_2$ in the presence of Et_3SiH gave **29**, which bears a free 4-OH group, or **30**, which bears a free 6-OH group, in 96% and 87% yield, respectively. Complete cleavage of the benzylidene group of **16** was obtained in 94% yield with TsOH (Ts = *p*-toluenesulfonyl). Subjection of **17** to *N*-bromosuccinimide (NBS) in acetone/water gave **32**, with a free anomeric OH group, in 74% yield. Reaction of **32** with trichloroacetonitrile in the presence of catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the trichloroacetimidate **33** in 80% yield. Attempts to remove the benzyl group in **19** selectively with H_2 and Pd catalyst, without affecting the TCE-protected sulfate group, were unsuccessful. However, the benzyl group in **19** was selectively cleaved to give **34** in 91% yield by irradiation with a 250-W lamp in the presence of NBS and $CaCO_3$.[11]

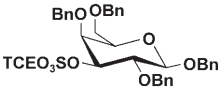
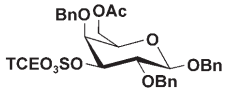
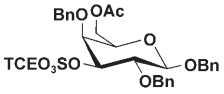
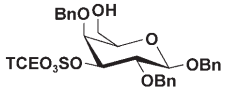
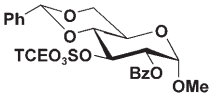
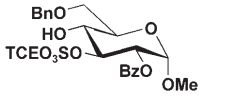
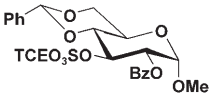
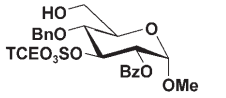
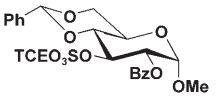
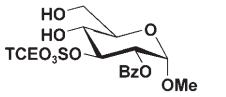
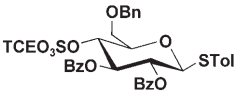
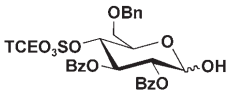
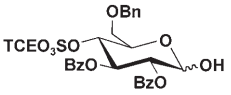
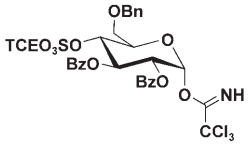
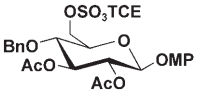
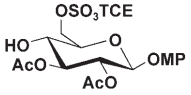
As mentioned earlier, Karst et al. removed the TFE moiety from sulfate groups in fully protected disaccharides with low to moderate yields.[5] We anticipated that this would not be an issue with the TCE group as it is removed under very mild conditions. To illustrate this, **30** was coupled to **33** (Scheme 4) in the presence of TMSOTf (TMS = trimethylsilyl) to give disaccharide **35** in 68% yield (unoptimized). Deprotection of **35** with zinc–ammonium formate gave the sulfo-deprotected product **36** in 92% yield (Scheme 4).[10]

In summary, the first synthesis of a sulfuryl imidazolium salt **6** is reported. This compound represents a new class of highly potent sulfating agents.[12] Compound **6** was very effective in introducing TCE-protected sulfates into monosaccharides. The TCE-protected sulfates were stable to many of the reaction conditions commonly encountered in carbo-



Scheme 4. Glycosylation and TCE cleavage. M.S. = molecular sieves.

Table 2: Cleavage of selected hydroxy protecting groups from TCE-protected sulfocarbohydrates.

	Substate		Product	Yield [%][a]
14		27		95[b]
27		28		85[c]
16		29		96[d]
16		30		87[e]
16		31		94[f]
17		32		74[g]
32		33		80[h]
19		34		91[i]

[a] Yield of isolated pure product. [b] $ZnCl_2$ (3.7 equiv), $AcOH/Ac_2O$, 3 h. [c] NaOMe (0.16 equiv) in MeOH, 3 h. [d] TfOH (3.4 equiv), Et_3SiH (3.0 equiv), 4-Å molecular sieves, −78 °C, CH_2Cl_2, 1 h. [e] $PhBCl_2$ (3.4 equiv), Et_3SiH (3.0 equiv), 4-Å molecular sieves, −78 °C, CH_2Cl_2, 1 h. [f] TsOH (0.1 equiv), CH_2Cl_2/MeOH, 45 °C, 16 h. [g] NBS (3.0 equiv), acetone/H_2O, 0 °C, 20 min. [h] DBU (0.2 equiv), Cl_3CCN (16 equiv), −40→−10 °C, CH_2Cl_2, 3 h. [i] NBS (3.5 equiv), $CaCO_3$ (5 equiv), CCl_4/H_2O, 250-W incandescent lamp.

hydrate chemistry. Deprotection of the sulfate group with zinc–ammonium formate proceeded in outstanding yields. This methodology should have a significant impact on the synthesis of sulfated carbohydrates. More studies on the scope of this methodology and its application to the synthesis of complex sulfated oligosaccharides are in progress and will be reported in due course.

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[7] The initial intention of Proud et al.[4] was to use TCE protection. Although they anticipated that the TCE group would be easily removed under very mild conditions using Zn/HOAc, they reported that the yields of TCE-protected sulfated monosaccharides with unspecified reagents and reaction conditions were very poor. Therefore, the TFE group was examined. However, the reaction of 2,2,2-trifluoroethylchlorosulfate with carbohydrates proceeded in poor yields and gave a number of unspecified by-products, hence the use of trifluorodiazoethane. We found that deprotection of the TCE-protected sulfocarbohydrates described herein with Zn–HOAc results in the formation of desulfated products.
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[9] Although the terms sulfonyl and sulfuryl are often used interchangeably, we designated **6** a sulfuryl imidazolium salt. We use the term sulfuryl to differentiate it from sulfonyl imidazolium salts, which is the term used by O'Connell and Rapoport to describe their sulfonating agents.[8]
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[12] We have also prepared the TFE, phenyl, and other analogues of **6**. Their synthesis and sulfating properties will be reported elsewhere.

