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Direct Synthesis of Diastereomerically Pure Glycosyl Sulfonium Salts

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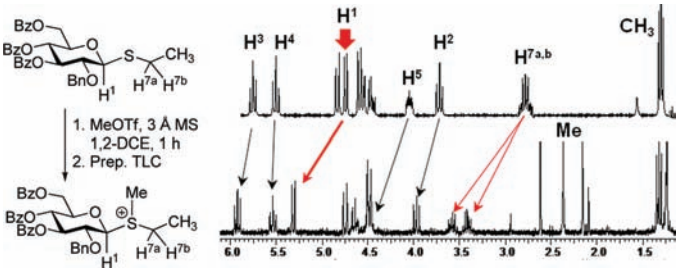
ABSTRACT



It is reported that stable glycosyl sulfonium salts can be generated via direct anomeric S-methylation of ethylthioglycosides. Mechanistically, this pathway represents the first step in the activation of thioglycosides for glycosidation; however, it can further allow for the synthesis and isolation of quasi-stable sulfonium ions, representing a new approach for studying these key intermediates.

Existing as the most abundant class of organic compounds, carbohydrates are involved in a myriad of life-sustaining and life-threatening processes.[1] While Nature flawlessly and repeatedly executes the glycosylation reaction to yield complex poly- and oligosaccharides,[2] chemical installation of the glycosidic linkage remains cumbersome, even with the aid of modern technologies.[3−8] In the past three decades, much effort has been dedicated to refining glycosylation reaction conditions.[9] However, enhancements resulting from this effort are still not sufficient to control the outcome of many glycosylations. Thioglycosides serve as a prime example of this, even though they have been one of the most studied and applied classes of glycosyl donors.[10] Among the various methodologies developed for thioglycoside activation, the alkylation pathway is commonly accessed utilizing the methylating reagent, MeOTf.[11] It is assumed that the reaction begins with the formation of a glycosyl sulfonium ion (Scheme 1), which is quickly converted into other reaction intermediates, such as an oxacarbenium ion, glycosyl triflate (or a combination thereof), and eventually a glycoside. While the latter stages of glycosylation have been extensively studied,[12−14] the first activation step has never been proven, nor has the postulated sulfonium ion intermediate of such glycosylation been isolated.

Since the pioneering studies by Schuerch et al.[15] and Sun et al.,[16] there has been an increased interest in the detailed investigation of anomeric sulfonium ions. Synthetic approaches to the formation of identifiable anomeric sulfonium ions, however, are indirect and often lack stereoselectivity, or the products are contaminated with other

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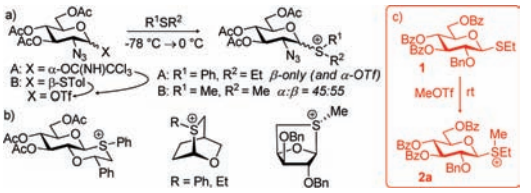
Scheme 1. Glycosidation of Thioglycosides

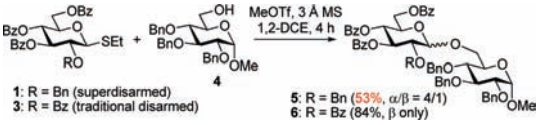
Scheme 2. Glycosyl Sulfonium Ions: (a) Obtained via Anomeric Triflate;[17,18] (b) Bicyclic Sulfonium Ions;[19−21] (c) Obtained via Direct Methylation of the Leaving Group (This Work)



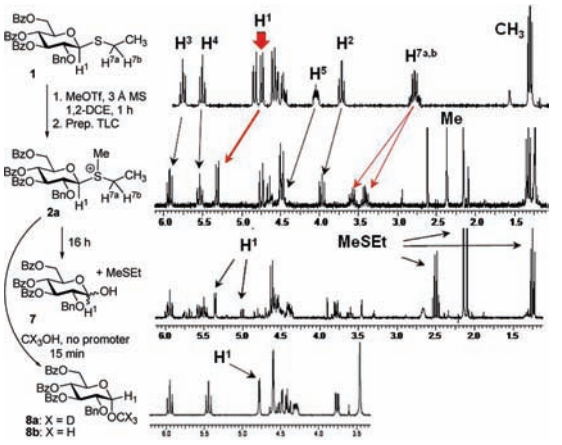
species (Scheme 2a).[17,18] The generation of bicyclic sulfonium ions, wherein the anomeric sulfur is tethered elsewhere to the sugar ring, has proven to be more stereoselective (Scheme 2b), but their preparation requires multiple synthetic steps.[19−22] Furthermore, unlike other classes of cyclic sulfonium salts (such as those used as enzyme inhibitors),[23] these anomeric reaction intermediates have been found to be relatively labile, existing mainly *in situ*,[24,25] and at low temperatures. Herein, we report a simple and direct method to generate anomerically pure sulfonium salts, such as **2a**, that can be isolated, characterized, and stored (Scheme 2c).

While expanding our investigations of the O-2/O-5 cooperative effect[26] to thioglycosides,[27,28] we noted that superdisarmed glycosyl donor **1** provided consistently lower yields in glycosylation in comparison to that of per-acylated glycosyl donor **3**.[11] Thus, the glycosylations

Scheme 3. Unexpectedly Low Yield of Disaccharide **5**



Scheme 4. Formation and Hydrolysis of Salt **2a** Monitored by 300 MHz ^{1}H NMR in $CDCl_3$



between standard glycosyl acceptor **4**[29,30] and glycosyl donors **1** or **3** (in the presence of MeOTf) were both quenched at 4 h. At this time, it was determined that the reaction between **3** and **4** was complete. However, the progress of the reaction between **1** and **4** was less clear, as there was a significant amount of acceptor **4** remaining, but none of glycosyl donor **1**, and so it too was quenched for further investigation. Upon analysis of the two reactions, it was found that disaccharide **5** (derived from glycosyl donor **1**), was only formed in 53% yield, whereas disaccharide **6**[31] (from **3**) was obtained in 84% yield (Scheme 3).

In further studying thioglycoside **1** in glycosylation, it was noticed that concomitant with the formation of disaccharide **5**, an unusually polar species also formed at the baseline of the TLC plate (ethyl acetate−toluene, 1/9, v/v; for comparison R_f(**1**) = 0.55). In a more polar TLC system (methanol−CH_2Cl_2, 1/9, v/v), the unknown compound was visualized as an elongated, yet well-defined, spot with an R_f spanning 0.40−0.55. In addition, when subjected to aqueous workup, it decomposed into the corresponding hemiacetal **7** (shown in Scheme 4). Based upon these findings, it was hypothesized that this unknown "baseline species" corresponded to anomeric glycosyl sulfonium salt **2a** (shown in Schemes 2 and 4), which was formed upon methylation of the thioethyl leaving group. Upon repeating the reaction between **1** and **4**, it was found that the reaction required an additional 2 h (6 h total) for the

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baseline spot (**2a**) to completely disappear/react; markedly improving the yield of disaccharide **5** to 87%.

We next reacted thioglycoside **1** with MeOTf in the absence of the glycosyl acceptor, which resulted in the near exclusive formation of the anticipated sulfonium salt **2a** (in about 1 h). The reaction mixture was then concentrated and purified by preparative TLC (acetone/CH_2Cl_2, 3.5/6.5, v/v). ^{1}H NMR and mass spectral analyses of the isolated product were consistent with those expected for ethylmethylsulfonium salt **2a**. In comparing the ^{1}H NMR spectra of **1** vs **2a** recorded at 300 MHz in $CDCl_3$ (depicted in Scheme 4), a downfield shift on a number of signals was noted. Most significantly, was that of the anomeric H^1 signal ($\Delta\delta$ = 0.59 ppm; while retaining β-configuration: $J_{1,2}$ = 9.9 Hz) and the $H^{7a,b}$ signal, which corresponds to the methylene protons of the leaving group ($\Delta\delta$ = 0.75 ppm). The appearance of a new singlet at 2.44 ppm was consistent with the newly acquired methylthio group. Several other downfield shifts were also noticed, including those of the H^2, H^3, and H^5 protons. The mass spectrum of **2a** exhibited an ion peak at m/z 641.2219 (calculated for $C_{37}H_{37}O_8S^+$, 641.2209).

A follow-up ^{1}H NMR spectrum recorded after 16 h revealed that salt **2a** had hydrolyzed completely, and the resulting mixture consisted of α/β-hemiacetal **7** and liberated ethylmethylsulfide (Scheme 4). On a side note, exposure of salt **2a** to methanol, gave rise to the exclusive formation of an α-methyl glucoside. Thus, attempts to record the spectrum in CD_3OD, gave rise to a follow-up spectrum (after 16 h) of **8a**, and the use of methanol in preparative TLC yielded **8b** as the sole product (spectrum shown in Scheme 4). It is noteworthy that the isolated **2a** yielded a similar glycosidation stereoselectivity to that obtained in reactions wherein **2a** was generated and allowed to react with glycosyl acceptor *in situ*.

We attribute the unusual stability of **2a**, to the electronic consequences resulting from the "superdisarming" (2-*O*-"nonparticipating alkyl"-3,4,6-tri-*O*-"electron-withdrawing acyl") protecting group motif.[26,28] This protecting group combination renders leaving group departure energetically unfavorable, as the resulting carbocation intermediate is incapable of achieving adequate stabilization.[32] Although this low-reactivity donor was initially developed to improve stereocontrol in the glycosylation reaction, it was subsequently found to be invaluable in the chemoselective introduction of a *trans*−*cis* or *cis*−*cis* oligosaccharide pattern, which was not directly accessible by the traditional armed−disarmed technique.[33] At present, it is this superdisarmed approach that has allowed us, for the first time, to detect, trap, and even isolate the key intermediates formed during the glycosidation of thioglycosides.

In our attempt to isolate other sulfonium salts, per-benzoylated (disarmed) thioglycoside **3** and its per-benzylated (armed) counterpart, were each treated with MeOTf. Other "superdisarmed" glycosyl donors equipped with sulfur-based leaving groups (including S-phenyl, S-tolyl, and S-benzoxazolyl) were also investigated for their potential ability to form sulfonium ions. Although all glycosyl donors underwent glycosidation in the presence of methyl triflate, salt formation was only nominally observed in the case of glycosyl donor **3**, whereupon isolation attempts as well as low temperature NMR monitoring were both unsuccessful.[31] These results made us believe that these intermediate sulfonium salts are significantly more reactive than ethylthioglycoside-derived salt **2a**.

Next, we decided to investigate the role that the (often overlooked) counteranion could be playing. To accomplish this task, we chose to generate a variety of "methylating promoters" *in situ*. Methyl iodide, which alone is too weak a promoter to activate *S*-ethyl glycosides, was chosen as the source of a methyl cation (Me^+). On the other hand, a series of commercially available silver salts (AgX, X = BF_4, PF_6, ClO_4, OTs, OMs, or NO_3) were chosen as the source of a counteranion, because these reagents alone *also* do not promote thioglycoside glycosidations. As silver compounds to readily undergo anion exchange with alkyl halides (such as MeI), we were then able to generate a series of new "methylating promoters" *in situ*.[34] Using these reagents, a range of sulfonium salts (each containing a different counteranion) could be generated in the absence of the glycosyl acceptor as follows. Thioglycoside **1** was stirred for 30 min with excess MeI (9 equiv), followed by the addition of the desired silver salt (Table 1) to generate the corresponding promoter. Accordingly, as the various sulfonium salts began to form, the precipitation of yellow AgI was noticed among the reactions between MeI and $AgBF_4$, $AgPF_6$, and $AgClO_4$, yielding sulfonium salts **2b**−**d** (entries 1−3), which were purified by preparative TLC. In the reactions between MeI and AgOTs, AgOMs, or $AgNO_3$, little-to-no AgI precipitate was observed, even after 16 h implying that no sulfonium salt was formed.

Interestingly, unlike the solitary H-1 signal seen at 5.31 ppm in the spectrum of **2a** (Scheme 4), the ^{1}H NMR spectra of sulfonium salts **2b**−**d** recorded at 300 MHz in $CDCl_3$ revealed the presence of two new downfield H-1 signals. As exemplified in the reaction between **1** and MeI/$AgClO_4$, the NMR spectrum of **2d** showed the new H-1 signals to be at 5.30 and 5.17 ppm (varies slightly for each counteranion), each having a coupling constant consistent with that of a β-glycoside (9.7 and 9.8 Hz, respectively). Additionally, these H-1 shifts could each be linked (via integration) to a different set of *S*-ethyl protons, and to a new singlet indicative of an

(32) Note: While per-acylated glycosyl donors (such as **3**) also suffer from an electron deficiency, the positive charge acquired upon leaving group departure can be better stabilized through acyloxonium ion formation. In fact, although a faint baseline spot could be also detected during the glycosidation of **3**, our attempts to isolate this species have been unsuccessful.

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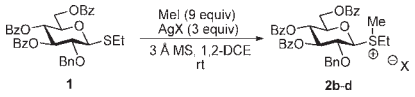
(34) Note: It should be noted that assuming the independent existence of such new MeX species is not entirely correct, as it is more likely that the methylation of the leaving group would occur concomitantly with counteranion exchange through a more complex transition state. Herein, however, it is referred to as such for the purpose of simplification. To verify that no reaction took place prior to the generation of the active promoter in situ, two glycosylations were attempted in the presence of MeI and separately in the presence of the silver salt (AgX), wherein no reactions were observed.

Table 1. Formation of β-Sulfonium Salts **2b**–**d** Using *in Situ* Generated Methylating Promoters



entry	AgX	promoter[34]	time	salt
1	$AgBF_4$	$MeBF_4$	0.5 h[a]	**2b**
2	$AgPF_6$	$MePF_6$	0.5 h[a]	**2c**
3	$AgClO_4$	$MeClO_4$	0.5 h[a]	**2d**

[a] Time at which significant amount of AgI formation was detected.

acquired methyl group (see the Supporting Information (SI)). Since rest of the signals remained overlapping we believe that these were diastereomeric β-sulfonium salts (**2d**[a] and **2d**[b], Figure 1), as has been previously documented.[17]

As an extension of our findings with β-sulfonium salt **2a**, we also attempted to synthesize its α-epimer (**2e**, Figure 1). Immediately, it became apparent that the reactivity of **2e** is much greater than that observed with its β-counterpart **2a**, and only small amounts of **2e** were detected. Interestingly, traceable **2e** could only be generated when utilizing the *in situ* generated promoters MeI/$AgBF_4$ and MeI/$AgPF_6$, and no salt was observed with MeOTf. The crude ^{1}H NMR spectra of **2e** revealed the presence of two new α-anomeric signals at around 6.21 and 6.31 ppm (see the SI). However, the spectrum indicated the presence of large amounts of the starting material and byproduct. Reinforcing these findings are the similar results found by both Yoshida and Boons, wherein β-sulfonium species were found to be more stable than their α-counterparts.[17,18]

We also found that when **1** was treated with dimethyl(methylthio)sulfonium triflate (DMTST),[35,36] it too gave rise to the baseline spot on TLC, indicative of a polar sulfonium species. When attempts were made to isolate this proposed thiomethylated salt (**2f**, Figure 1), this species was found to be less stable than its methylated analog **2a**. The ^{1}H NMR of purified compound **2f** recorded at 300 MHz in $CDCl_3$ contained a significant amount of hemiacetal **7**, but when a crude NMR of **2f** was acquired, a new H-1 peak could easily be identified at 6.45 ppm (see the SI). Although the spectrum remains unclear and will require further investigation we believe that the pyranose ring in **2f** may have undergone a conformational change,[37] as the NMR data was more indicative of a half-chair conformation.[38] Of further interest was that, upon treatment of **2f** with a large access of *p*-toluenethiol, the corresponding α-tolyl thioglycoside was obtained stereoselectively.

In conclusion, we believe that further investigation of quasi-stable reaction intermediates and expansion to

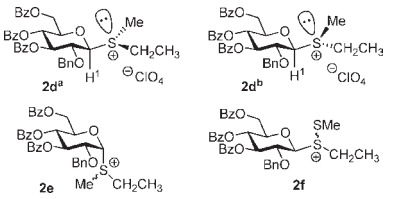


Figure 1. Structures of sulfonium salts **2d**[a], **2d**[b], **2e**, and **2f**.

studying the means by which these intermediates convert into glycoside products can contribute to understanding the reaction mechanisms of glycosylation. For instance, while Boons et al. found that the glycosidation of sulfonium salts results in excellent S_N2-like stereoselectivity,[17,19,39,40] several research groups have conversely encountered poor or unanticipated anomeric selectivities when dealing with these key intermediates. Yoshida et al. found that both the α- and β-sulfonium species fail to undergo the anticipated inversion.[18] Likewise, Woerpel et al. found an intramolecular glycosyl sulfonium species which also failed to yield an inverted product, giving, instead, a stereoselectivity arising from the predominance of the open cation (S_N1) pathway over a concerted (S_N2) displacement.[20,41] Thus, due to such experimental inconsistencies, we anticipate that the simple approach to glycosyl sulfonium ions described herein will aid in the investigation of traceable reaction intermediates in glycosylation. This discovery may also offer a reliable system for studying the controversial reaction mechanism by which anomeric sulfonium ions are displaced by nucleophiles. It is our belief that a carefully controlled reaction pathway will ultimately lead to the development of a highly stereocontrolled glycosylation. This study may ultimately impact areas outside of the glycosciences, as sulfonium salts of similar structural composition have been found to be valuable substrates[42,43] and reagents[44] in synthetic chemistry and represent valuable targets for computational studies.[45]

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Supporting Information Available. Experimental procedures, extended experimental data, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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