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Direct Synthesis of Diastereomerically Pure Glycosyl Sulfonium Salts

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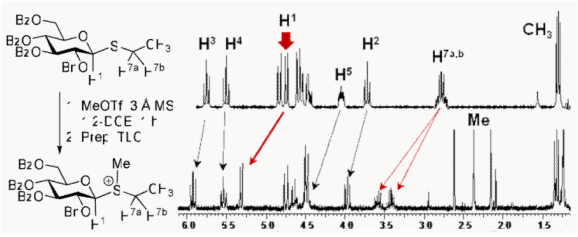
Abstract



It is reported that stable glycosyl sulfonium salts can be generated via direct anomeric *S*-methylation of ethylthio glycosides. 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] Amongst 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), eventually leading to 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 species

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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.

(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 between standard glycosyl acceptor **4**[29,30] and glycosyl donors **1** and **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. Subsequently, upon analysis of the two glycosylation 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 addition, when investigated 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 work-up, it decomposed into the corresponding hemiacetal **7** (shown in Scheme 4). Being significantly more polar than all other reaction components (including **7**), and finding it susceptible to hydrolysis, 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) in order for the baseline spot (**2a**) to completely disappear/react. Resultantly, disaccharide **5** was isolated in a significantly improved yield of 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 the residue was 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 its 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, our initial attempt to record the spectrum in CD_3OD, gave rise to a follow up spectrum (recorded after 16 h) showing the exclusive

formation of methyl(D_3) α-glucoside **8a**. Likewise, if compound **2a** was handled in the presence of methanol used as a co-solvent for the preparative TLC, the corresponding α-methyl glucoside **8b** was isolated 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*-"non-participating 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 also 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 (3 equiv.) in the presence of molecular sieves, in 1,2-dichloroethane at rt. While the armed thioglycoside did not yield a sulfonium salt, the less reactive disarmed glycosyl donor **3** showed nominal signs of sulfonium salt formation. However, all efforts made to isolate this per-benzoylated sulfonium salt were unsuccessful, as were attempts to detect this species using low temperature NMR monitoring.[31] 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 glycosylation in the presence of methyl triflate, no salt formation was observed. These results made us believe that these intermediate sulfonium salts are significantly more reactive than ethylthio glycoside-derived salt **2a**.

Next, we decided to investigate the role that the (often overlooked) counter-anion 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 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 counteranion, because these reagents alone *also* do not promote thioglycoside glycosidations. Exploiting the known affinity of 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 counter-anion) 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). However, it should be noted that in the reactions between MeI and AgOTs, AgOMs or $AgNO_3$, little-to-no AgI precipitate was observed, even after 16 h (Table 1, entries 4-6). It therefore followed that in these cases no sulfonium salt was formed, as the anion exchange did not occur. At this point, sulfonium salts **2b-d** were purified by preparative layer chromatography and subsequent NMR spectra were recorded.

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 ppm and 5.17 ppm (varies slightly for each counter-anion), and to each have a coupling constant consistent with that of a *β*-glycoside (9.7 Hz 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 acquired methyl group (see the SI). Furthermore, while there was splitting seen for the H-1 protons and the leaving group protons, the rest of the signals remained overlapping. This led us to believe that these were diastereomeric β-sulfonium salts (**2d^a** and **2d^b**, Figure 1), as this occurrence has been documented previously.[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 by-products. 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]

In order to further investigate the ability of glycosyl donor **1** to form a “stable” cationic species, we screened other common thioglycoside promoters that could potentially form a detectable *β*-sulfonium salt. As a result, it was 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 CDCl3 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). Interestingly, unlike the H-1 signal seen in the NMR spectrum of methylated salt **2a**, the H-1 signal of donor **2f** was much more deshielded and displayed a significantly smaller coupling constant ($J_{1,2}$ = 4.5 Hz). Upon first glance, it seemed as though the thiomethylated leaving group had anomerized. Soon after however, other peculiarities were noticed, such as the unusually small coupling constants of H-3 ($J_{2,3} = J_{3,4}$ = 5.3 Hz) and the 0.88 ppm downfield shift of H-2. This led us to believe that the pyranose ring in **2f** was no longer residing in a $^4C_1$ chair conformation,[37] but may have undergone a conformational change, as the NMR data was more indicative of a half-chair conformation.[38] Of further interest, was that upon treatment of **2f** with 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 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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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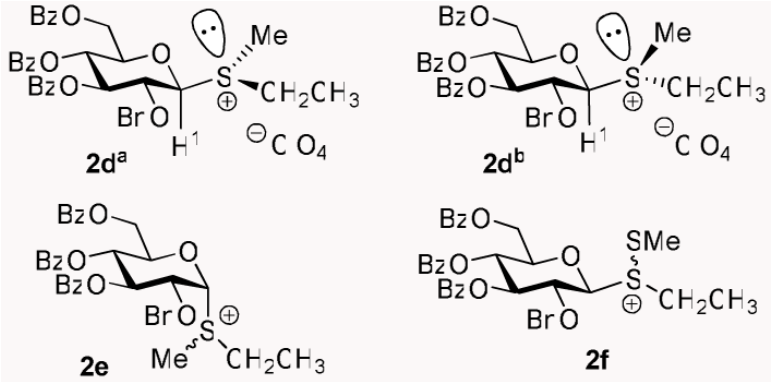
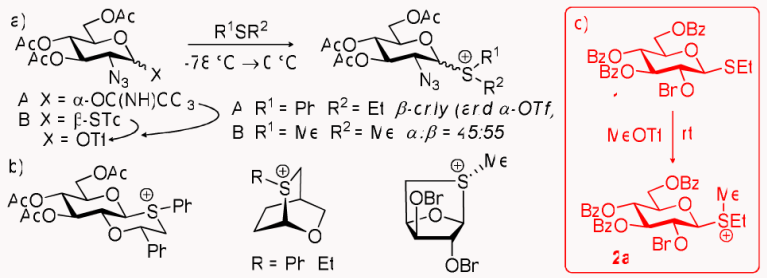


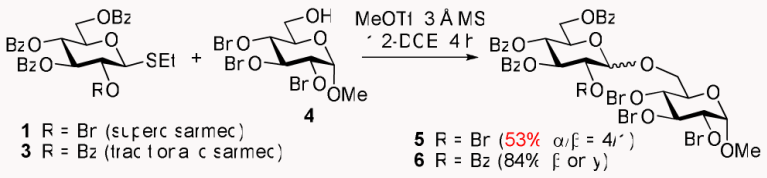
Figure 1.
Structures of sulfonium salts **2d**[a], **2d**[b], **2e** and **2f**.

Scheme 1.
Glycosidation of thioglycosides

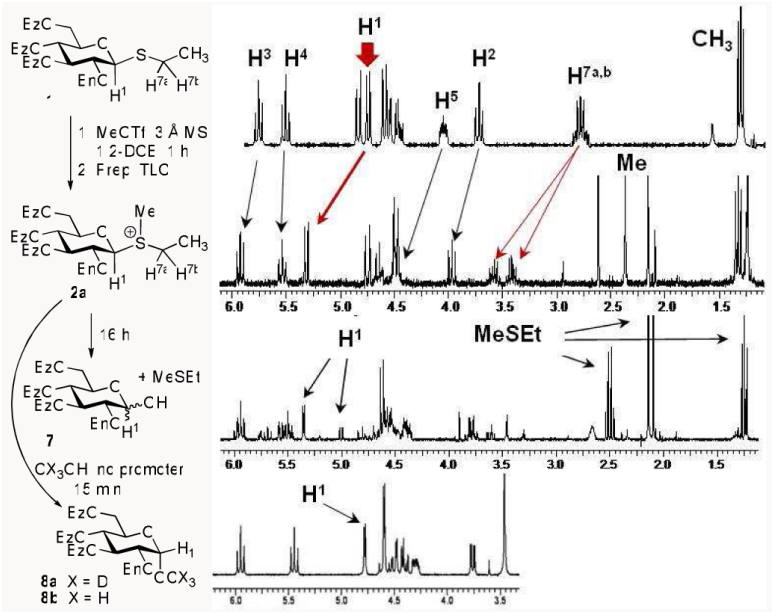


Scheme 2.

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).



Scheme 3.
Unexpectedly low yield of disaccharide **5**.

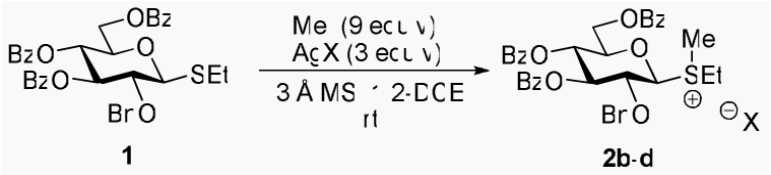


Scheme 4.

Formation and hydrolysis of salt **2a** monitored by 300 MHz ^{1}H NMR in $CDCl_3$.

Table 1

Formation of β-sulfonium salts **2b-d** using *in situ* generated methylating promoters.



entry	AgX	promoter34	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**
4	AgOTs	MeOTs	16 h	none
5	AgOMs	MeOMs	16 h	none
6	$AgNO_3$	$MeNO_3$	16 h	none

[a]–time at which significant amount of AgI formation was detected