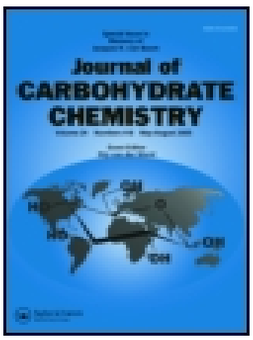

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Mechanism investigations of the activation process of *S*-2-[(propan-2-yl)sulfinyl]benzyl (SPSB) glycosides

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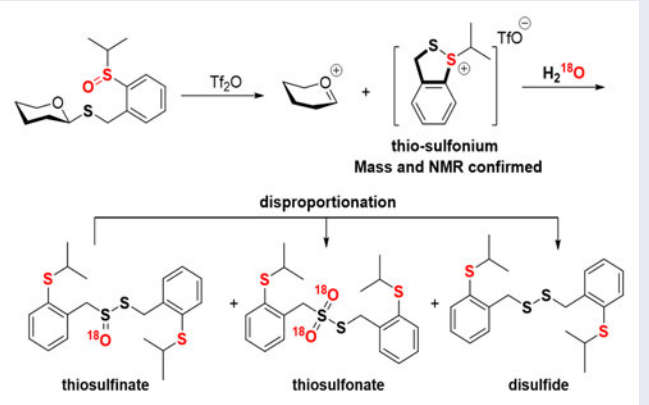
ABSTRACT

In our recently developed interrupted Pummerer reaction mediated (IPRm) glycosylation with *S*-2-[(propan-2-yl)sulfinyl] benzyl (SPSB) glycosides as glycosyl donors, the anomeric leaving groups were recovered in the forms of thiosulfinate, disulfide and thiosulfonate. These products were presumed to be obtained by the hydrolysis and disproportionation of a cyclic thio-sulfonium intermediate. In this study, mass spectrometry and ^{1}H NMR studies were carried out which confirmed that the cyclic thio-sulfonium intermediate exists. Further ^{18}O isotopic labeling reactions revealed that the cyclic thio-sulfonium ion was hydrolyzed to thiosulfinate which further disproportionated to disulfide and thiosulfonate. This study clarifies the activation process of the SPSB glycosides involved glycosylation reactions.

GRAPHICAL ABSTRACT



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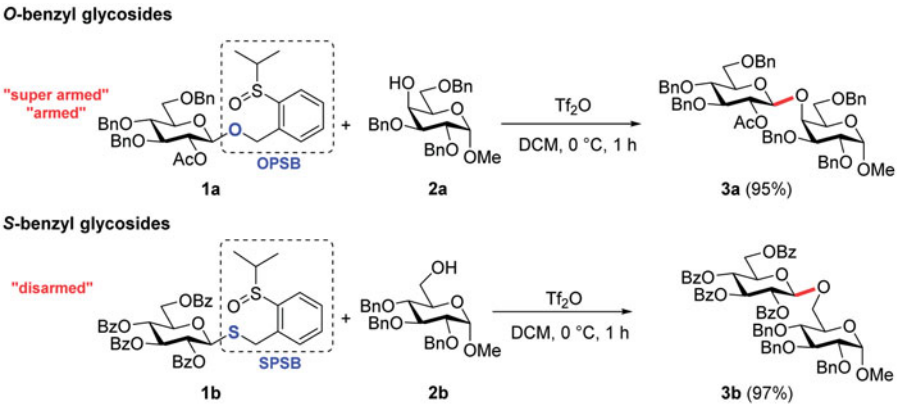
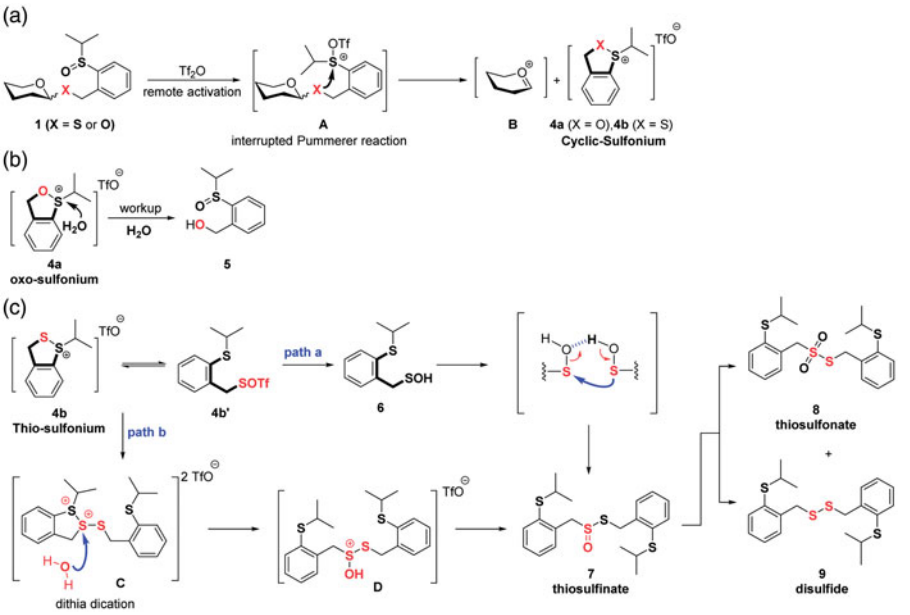


Scheme 1. Selected glycosylation reactions with OPSB and SPSB glycosyl donors.

Introduction

Sulfoxides have long been widely used in chemical synthesis but were not introduced in carbohydrate chemistry as glycosyl donors until the 1980s by Kahne and co-workers.[1] Since then, activation of glycosyl sulfoxides has become one of the most powerful methods for construction of glycosidic bonds.[2–4] However, the commonly used glycosyl sulfoxide donors always incorporated the sulfinyl groups at the anomeric position which sometimes resulted in instability problems. Recently, we have developed two kinds of new sulfoxide donors with sulfinyl groups located at a site remote to the anomeric position: *O*-2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycosides (**1a**) applicable for armed and super-armed glycosides[5–7] and *S*-2-[(propan-2-yl)sulfinyl]benzyl (SPSB) glycosides (**1b**) suitable for dis-armed glycosides (see Scheme 1).[8–10] These two sulfoxide donors exhibited high efficiency in the construction of glycosidic bonds especially in the synthesis of complex oligosaccharides and glycoconjugates, due to their comparative stability and the ability to employ latent-active glycosylation strategies. We have successfully synthesized a series of bioactive phenylethanoid glycosides[5,11] and we are currently working on the total synthesis of complex macrolide resin glycosides using these glycosyl donors.[12]

A proposed simplified activation pathway of *O*/*S*-PSB donors is illustrated in Scheme 2 (eq a). The initial step is the activation of phenyl sulfoxide by Tf_2O to form a transient intermediate **A**. The attack of the benzylic oxygen or sulfur atom on the cationic sulfur atom *via* an interrupted Pummerer reaction (IPR) pathway yields oxocarbenium ion **B** and cyclic sulfonium intermediate **4a** or **4b**. In these glycosylation reactions with OPTB glycosides, the *O*-2-[(propan-2-yl)sulfinyl]benzyl group was transformed to 2-[(propan-2-yl)sulfanyl]benzyl alcohol **5** (Scheme 2b), while the glycosylation reaction with SPSB glycosides delivered the *S*-2-[(propan-2-yl)sulfinyl]benzyl group to thiosulfinate **7**, thiosulfonate **8** and disulfide **9**. Thiosulfonate **8** and disulfide

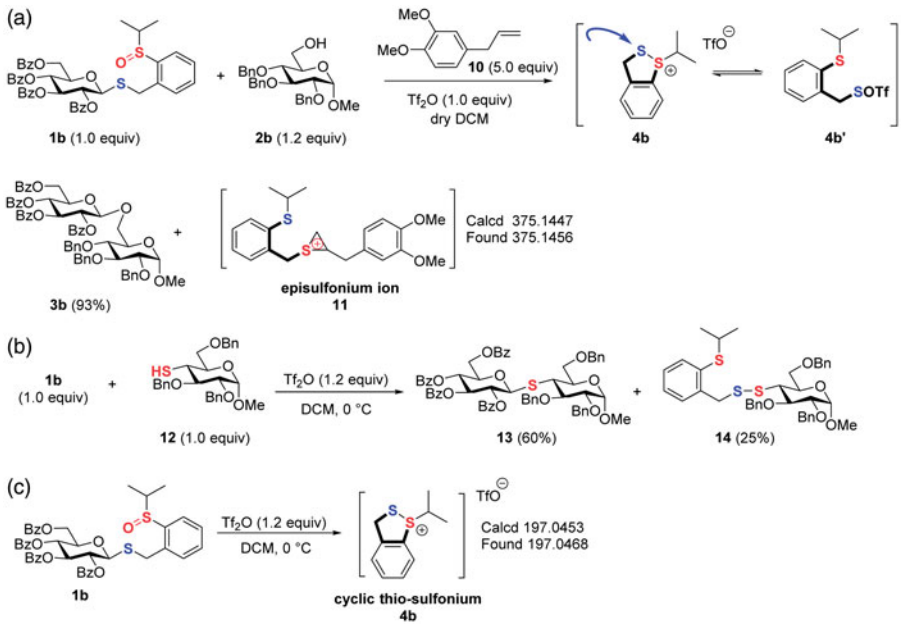


Scheme 2. Proposed mechanism for activation of OPSB and SPSB glycosyl donors.

9 were always isolated in nearly a 1:1 ratio (Scheme 2c). We have demonstrated that cyclic oxo-sulfonium ion **4a** was hydrolyzed to furnish **5** (PSB-OH) during the work-up process.[13] Despite high structural similarity of thio-sulfonium ion **4b** and oxo-sulfonium ion **4a**, the further transformation of **4b** during the glycosylation and work-up process is much more complex than that of **4a**. In our original research paper,[8] we have proposed two plausible pathways to generate thiosulfinate **7**, thiosulfonate **8** and disulfide **9**. Herein, we describe our further studies on the formation and transformation of **4b** based on MS, NMR, and isotopic labeling studies.

Results and discussion

The thiosulfonium **4b** and sulfenyl triflate **4b′** were proposed as key in situ generated electrophiles during the activation of remote sulfoxide. When an electrophile scavenger **10**, 4-allyl-1, 2-dimethoxybenzene (ADMB), was added to the glycosylation reaction between **1b** and **2b** under the standard reaction conditions, the desired disaccharide **3b** was obtained in excellent yield and the glycosidic bond generation was not disturbed by addition of **10**. In addition, an episulfonium ion **11** was detected in this reaction by high resolution mass spectrometry (Scheme 3a). The coupling of SPSB glycoside **1b** and thiosugar **12** in a one-pot procedure provided thio-disaccharide **13** in moderate yield (Scheme 3b). This result indicated that the electrophilic **4b** and **4b′** were much less active than the well-known phenyl sulfenyl triflate (PhSOTf) and can be orthogonal with thioglycoside.



Scheme 3. Capture the cyclic thio-sulfonium ion intermediate.

Meanwhile, electrophilic **4b** or **4b′** could be trapped by nucleophilic thiol **12**. Consequently, an asymmetric disulfide **14** was isolated in 25% yield. Upon exposure of the SPSB glycoside **1b** alone to Tf_2O, the resulting reaction mixture was subjected directly to MS detection. A peak at 197.0468 (m/z) was observed. It was a match to the calculated molecular weight (197.0453) of **4b** (Scheme 3c). This observation suggested that **4b** was very likely to be generated in the reaction system and it was quite stable. However, the presence of sulfenyl triflate **4b′** could not be excluded based on the aforementioned experiments.

In our previous studies,[8] it was found that activation of sulfoxide **15** with Tf_2O followed by quenching with water also furnished thiosulfinate **7**, thiosulfonate **8** and disulfide **9** with similar isolated yields. This phenomenon indicated that the activation of SPSB glycosides and sulfoxide **15** might form the same intermediate **4b** (Figure 1(a)). Later, this speculation was confirmed by the observation of MS peak at 197.0477 (m/z). The activation of asymmetric sulfoxide **15** with Tf_2O in CD_2Cl_2 at 0 ˚C was measured by ^1H NMR (Figure 1(b)). It was found that a clean and single compound was presented in the NMR tube after 30 min activation (Figure 1(e)). The ^1H NMR spectra showed that the signal of isopropyl proton moved downfield from 2.86 ppm (H_a) and 3.28 ppm (H_a') respectively to 3.97 ppm (H_a''), and the signal of benzylic proton moved downfield from 3.72 (H_b) ppm and 3.95 ppm (H_b') respectively to 4.98 ppm (H_b''). These results suggested that isopropyl group in the intermediate was linked to a sulfur atom with a

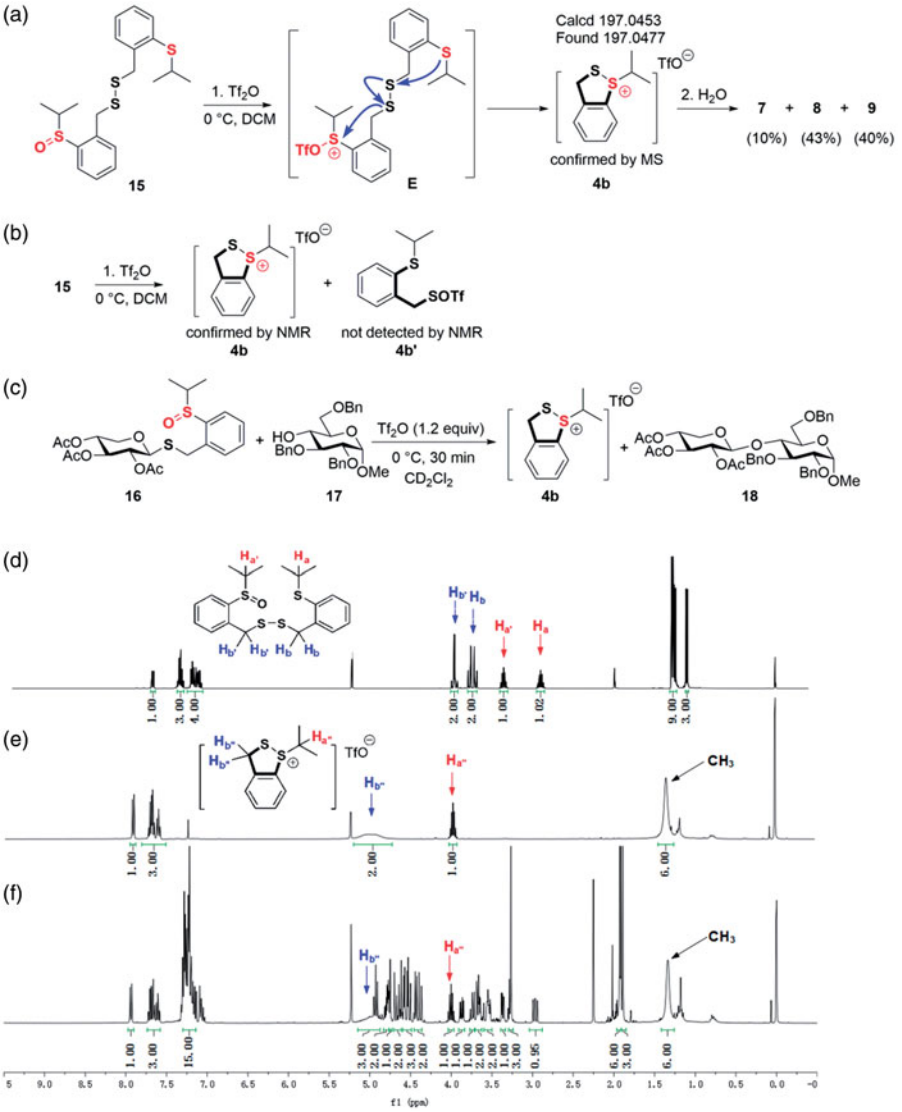
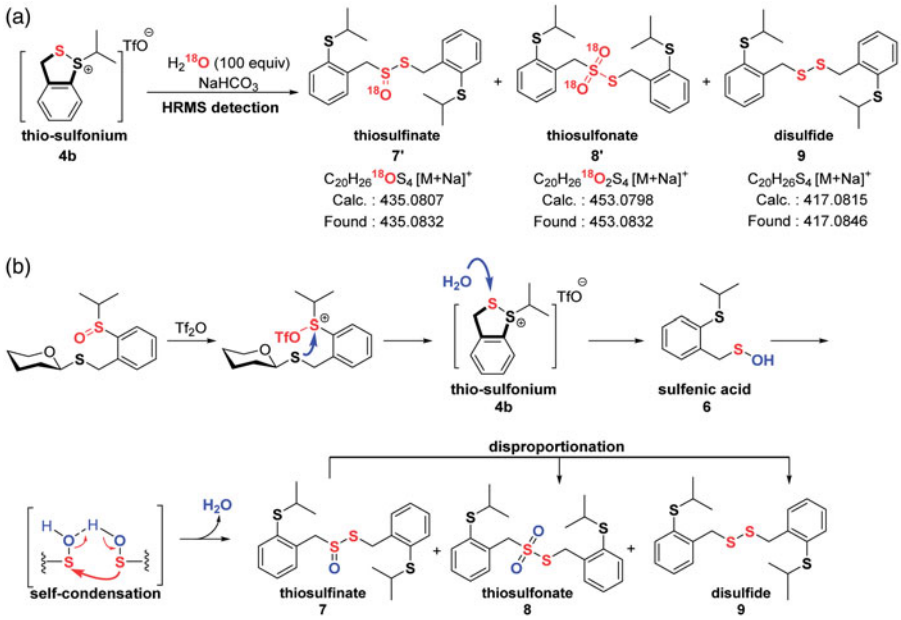


Figure 1. NMR study on cyclic thio-sulfonium ion intermediate **4b**: (a) Alternative pathway to generate **4b** from sulfoxide **15** (b) Activation of **15** in CD_2Cl_2 leads to **4b**; (c) IPRm glycosylation of **16** with **17** (d) ^{1}H NMR spectrum of sulfoxide **15**; (e) ^{1}H NMR spectrum of cyclic thiol-sulfonium **4b**; (f) ^{1}H NMR spectrum of glycosylation of **16** with **17**.

positive charge and the structure of the intermediate was most likely to be stable cyclic thio-sulfonium **4b**.[14] At this stage, the presence of reactive sulfenyl triflate **4b′** in quantities detected by ^{1}H NMR could be excluded definitively. Additionally, a ^{1}H NMR spectrum of coupling reaction between SPSB glycoside **16** and acceptor **17** was measured. In this experiment, all the signals of **4b** were clearly found in the spectrum of the reaction mixture. Consequently, we could conclude that the leaving group SPSB was transferred to a stable cyclic thio-sulfonium intermediate **4b** after activation.



Scheme 4. (a) Quenching of the thio-sulfonium intermediate **4b** with $H_2{}^{18}O$; (b) Outline of activation of SPSB glycoside.

Having confirmed the existence of the cyclic thio-sulfonium **4b** in the glycosylation reactions, we then commenced to determine the transformation process from the intermediate **4b** to thiosulfinate **7**, thiosulfonate **8** and disulfide **9**. To this end, $H_2{}^{18}O$ was introduced as an isotopic labeling reagent to quench the intermediate. HRMS analysis of the reaction mixture revealed the formation of the thiosulfinate **7′**, thiosulfonate **8′** and disulfide **9**. Among them, it was found that almost all the oxygen atoms of thiosulfinate **7′** and thiosulfonate **8′** had been labeled by ^{18}O.[15] This result indicated that thiosulfinate and thiosulfonate were generated by hydrolysis of the cyclic thio-sulfonium intermediate **4b**. Considering that the thiosulfonate **8** and disulfide **9** were always isolated in a 1:1 ratio and thiosulfinate essentially prior to disproportionation,[16–19] it was reasonable to deduce that these two compounds were produced from thiosulfinate **7** by disproportionation. This disproportionation reaction was observed upon standing of the thiosulfinate **7**. The isotopic labeling of thiosulfinate **7** also implied that H_2O attacked the benzylic sulfur atom of intermediate **4b** to produce sulfenic acid **6**. Then, a self-condensation of acid **6** possibly occurred to form thiosulfinate **7** (Scheme 4a).[16,20]

Finally, based on the above observations, we concluded that, in the glycosylation reaction with SPSB glycosides, the SPSB leaving group was transformed to cyclic thio-sulfonium ion **4b** upon activation with Tf_2O through an interrupted Pummerer reaction pathway. This intermediate might further hydrolyze to sulfenic acid **6** which underwent self-condensation to

produce thiosulfinate **7**. Further disproportionation of thiosulfinate **7** generated thiosulfonate **8** and disulfide **9**. The NMR, HRMS and isotopic labeling studies provided substantial evidence for the existence of the cyclic thio-sulfonium ion intermediate and its hydrolysis process, which clarified the activation mode of SPSB glycosides (Scheme 4b).

Experimental section

General experimental methods

NMR spectra were recorded on Bruker AM-400 spectrometer (400 MHz) and Bruker Ascend TM-600 spectrometer (600 MHz), and the ^{1}H and ^{13}C NMR chemical shifts were referenced to the solvent or solvent impurity peaks for $CDCl_3$ at δ H 7.24 and δ C 77.23, CD_2Cl_2 at δ H 5.23 and δ C 54.00 High resolution mass spectras were recorded on a Bruker micro TOF II spectrometer using electrospray ionization (ESI). All reagents and solvents were of pure analytical grade. Thin layer chromatography (TLC) was performed on silica-gel-coated TLC plates (Yantai Chemical Industry Research Institute) and revealed with either a UV lamp ($\lambda_{max} = 254$ nm) or by spraying with 10% H_2SO_4 (10% H_2SO_4 in ethanol) and subsequent charring by heating. Column chromatography was performed using silica gel (Qingdao Marine Chemical Inc., China).

Materials

Prior to running the glycosylation reactions, all reagents except Tf_2O and those with low boiling point (<180 °C) were dried by repeated azeotropic removal of water using toluene and a rotary solvent purifier. Trifluoromethanesulfonic anhydride (Tf_2O) was purchased from Adamas and TCI. $H_2{}^{18}O$ was purchased from *J&K* Scientific. Other reagents were purchased from Adamas or Acros Company.

Detection of the cyclic thio-sulfonium ion intermediate 4b by activation of asymmetric sulfoxide 15

The asymmetric sulfoxide **(15)** (12 mg, 0.030 mmol) was dissolved in CD_2Cl_2 (0.6 mL) at 0 °C, followed by addition of Tf_2O (6.0 μL, 0.036 mmol), after 30 min, the ^{1}H NMR, ^{13}C NMR spectrum and HMQC were acquired. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.91 (1H, d, $J = 8.0$ Hz), 7.73-7.56 (3H, m), 4.98 (2H, brs), 3.97 (1H, h, $J = 6.4$ Hz), 1.34 (6H, brs). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 143.0, 134.8, 131.1, 128.6, 128.2, 127.5, 59.8, 45.8, 17.5 (low-intensity multiplet). HRMS calcd for $C_{10}H_{13}S_2$ $[M]^+$ 197.0453, found 197.0477.

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