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Tracking the leaving group in the remote activation of *O*-2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycoside

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ABSTRACT

In our recently developed interrupted Pummerer reaction mediated glycosylation with *O*-2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycosides as glycosyl donors, the anomeric leaving group was recovered as a benzyl alcohol which didn't affect the glycosylation efficiency. To investigate the mechanism of the occurrence of this alcohol, an ^{18}O isotopic labeling reaction was carried out to track the leaving group. It was found that the benzyl alcohol was generated during the aqueous work up process from an inactive cyclic oxo-sulfonium ion intermediate. It was also proved that H_2O prefer to attack the sulfur atom position during the hydrolysis of the intermediate.

1. Introduction

Glycosylation plays the key role in carbohydrate chemistry and glycobiology. Development of efficient glycosylation strategies is the core of chemical synthesis of oligosaccharides and glycoconjugates [1]. Over the past century, a lot of efficient glycosylation methods have been developed [2]. Most of these methods focus on the discovery of glycosyl donors, such as traditional used glycosyl halides [3a,b], thioglycosides [3c-e], glycosyl sulfoxides [3f,g] and sulfones [3h], glycosyl imidates and thioimidates [3i-l], glycosyl orthoesters [3m], glycosyl phosphates [3n] and phosphites [3o], and recently developed 3,3-difluoro-3*H*-indole-2-yl (OFox) glycosides [3p,q], *ortho*-alkynylbenzoyl (Abz) glycosides [3r,s], *S*-but-3-ynyl thioglycosides [3t], mannosyl 2,6-lactone [3u], *ortho*-(*para*-methoxyphenylethynyl)phenyl (MPEP) glycosides [3v] and so on. Despite great advantages of these donors, some of them have poor stability, which were either decomposed quickly or incompatible with other reaction conditions in the complex oligosaccharide and glycoconjugate synthesis. Normally, these unstable glycosyl donors need to be freshly prepared or transformed from their precursors before glycosylation, consequently, increased the complexity of the synthesis. In contrast, *O*-alkyl glycosyl donors have great stability, which were able to tolerate most conditions for glycosylation and functional group transformation. However, these glycosyl donors were seldom discovered due to the possibility of releasing the *O*-alkyl leaving group as an alcohol nucleophile which interrupted the desired glycosylation reaction [4]. Therefore, the existing successful examples were always attempted to trapping the anomeric oxygen atom of the leaving group in a ring closure mode upon activation, in most cases, upon remote activation [5] to avoid the formation of extra alcohol. For example, Fraser-Reid employed *n*-pentenyl group as anomeric leaving group which was transformed to tetrahydrofuran after activation with NBS (Scheme 1a) [6]; Kim and coworkers developed an O-glycosylation method with the leaving group released in the form of lactone (Scheme 1b) [7]; Hotha and coworkers activated propargyl glycosides with $AuCl_3$ and the leaving group was found to be isomerized to cyclopropanone (Scheme 1c) [8]; Very recently, Yu et al. reported a latent-active glycosylation strategy by applying *ortho*-(methyltosylaminoethynyl)benzyl glycosides as glycosyl donors, in this method, the leaving group underwent an intramolecular cyclization reaction to form 1*H*-isochromene (Scheme 1d) [9].

Recently, we have developed a novel latent-active glycosylation

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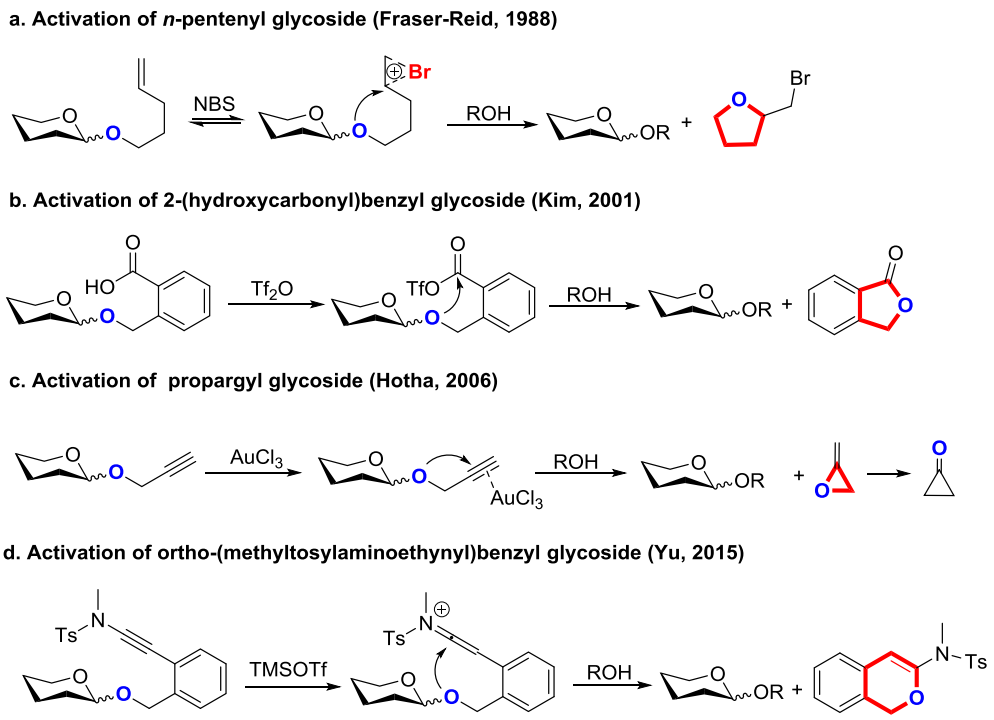


Scheme 1. Selected examples of transglycosylation *via* remote activation.

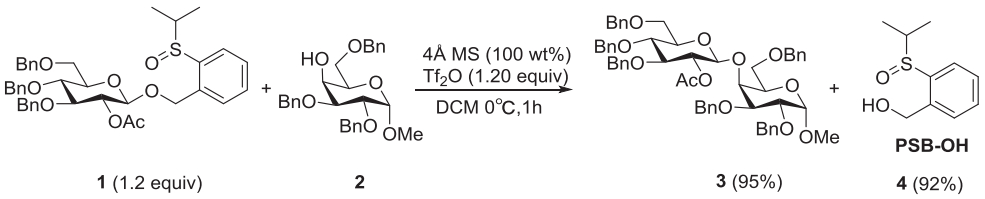
strategy by employing *O*-2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycosides as glycosyl donors. Upon remote activation of the sulfoxide group of the leaving group, the glycosylation proceeded smoothly and exhibited broad applicability in oligosaccharide and glycoconjugate syntheses [10]. Interestingly, unlike the above mentioned transglycosylation reactions, the leaving group in this reaction was recovered in alcohol form, *i.e.* 2-[(propan-2-yl)sulfinyl]benzyl alcohol (**4**, PSB-OH). Obviously, this alcohol didn't affect the glycosylation efficiency. For example, in the glycosylation reaction depicted in Scheme 2, the disaccharide **3** formed in 95% yield accompanied with 92% yield of recovered PSB-OH **4** (Scheme 2). This unusual phenomenon promoted us to further study the reaction mechanism by tracking the leaving group, aimed to reveal the rationale behind.

2. Results and discussion

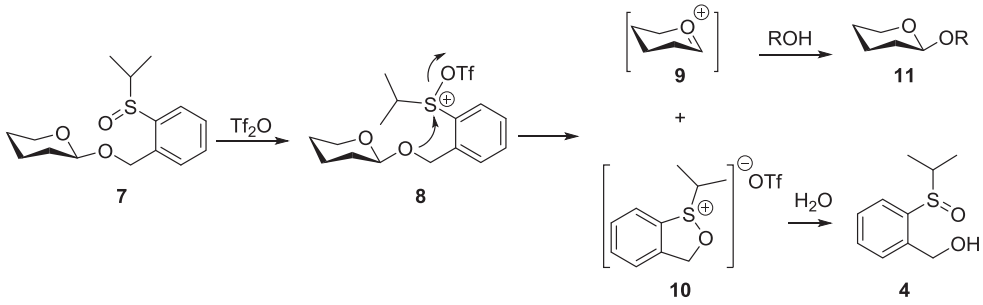
Since PSBOH didn't competed with the glycosyl acceptors to affect the glycosylation reactions, we hypothesized that this alcohol was produced during the aqueous quenching process rather than generated in the activation and glycosylation step. We have demonstrated that the PSB glycosides participated glycosylation reaction passed through interrupted Pummerer reaction mechanism [10a,b], in which, the activation of the sulfoxide group led to the intramolecular cyclization to form the oxocarbenium **9** and cyclic oxo-sulfonium ion **10**. We speculated that this cyclic oxo-sulfonium ion has certain stability in the reaction system, however, when quenching the reaction with water, it hydrolyzed quickly to generate PSB-OH **4** (Scheme 3).

To verify this hypothesis, an isotopic labeling experiment was carried out. First, OPSB glycoside **1** was activated by Tf_2O in DCM at 0 °C for 1 h. After that, $H_2^{18}O$ was added to quench the reaction (Scheme 4). Interestingly, the cyclic oxo-sulfonium **10** was detected by high-resolution MS during the activation step. This observation proved that the oxo-sulfonium ion **10** was really existed and it was stable enough in the reaction system until further hydrolysis. After addition of $H_2^{18}O$, PSB-OH **13** was then isolated in 95% yield. Most importantly, mass spectrometry confirmed that one of the oxygen atom of PSB-OH **13** was fully labeled by ^{18}O. These results clearly indicated that PSBOH was produced by hydrolysis during work-up process. It is also explained that why the generation of extra alcohol didn't affect the efficiency of the glycosylation reaction. However, we neither observed the oxocarbenium ion **14** by mass spectrometry nor isolated its hydrolyzed product **12**, possibly due to the high reactivity of this super-armed oxocarbenium ion, which decomposed quickly underwent complex pathways.

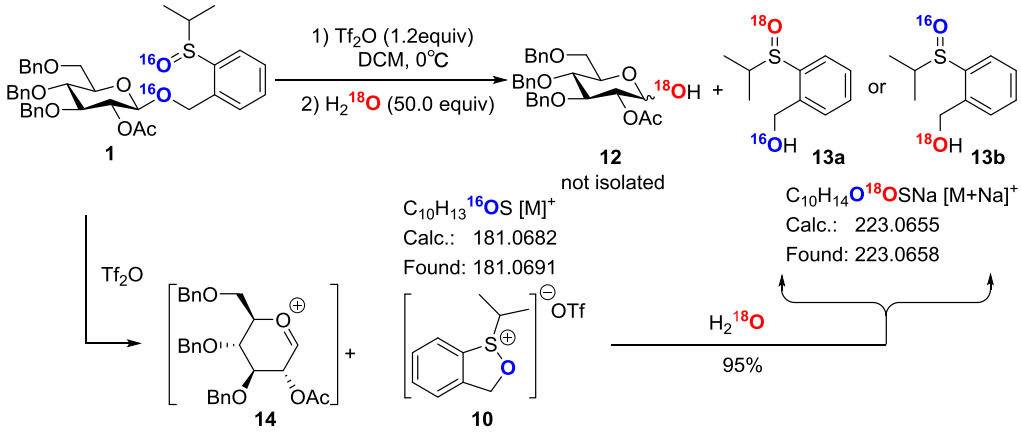
Although it was confirmed that one of the oxygen atom of PSB-OH **13** was isotopic labeled, we didn't know which oxygen atom was labeled in this stage. Thus, several reduction conditions were examined to reduce the sulfoxide group to thioether (Table 1). Among the tested conditions, thiosalicylic acid (TSA)/I_2 [11] produced the best result which generated 2-[(propan-2-yl)sulfanyl]



Scheme 2. Recovery of leaving group in an interrupted Pummerer reaction mediated glycosylation.

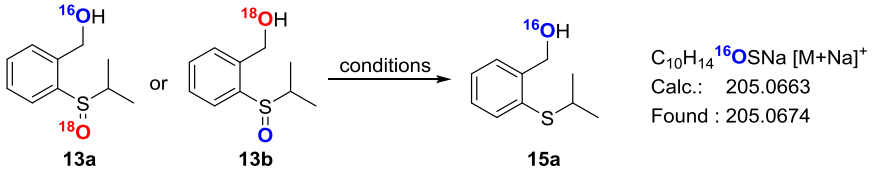


Scheme 3. Proposed mechanism for the interrupted Pummerer reaction mediated glycosylation.



Scheme 4. Results of quenching the glycosylation reaction with $H_2^{18}O$.

Table 1
Reduction of the sulfoxide group of PSBOH.



Entry	Conditions	Yield[a]
1	TSA (2.0 equiv), I_2 (0.1 equiv), DCM, rt, 4 h	94%
2	$NaBH_4$ (1.2 equiv), I_2 (2.0 equiv), THF, rt, 1 h	70%
3	$LiAlH_4$ (2.0 equiv), THF, rt	49%

[a] Isolated yield; TSA = thiosalicylic acid.

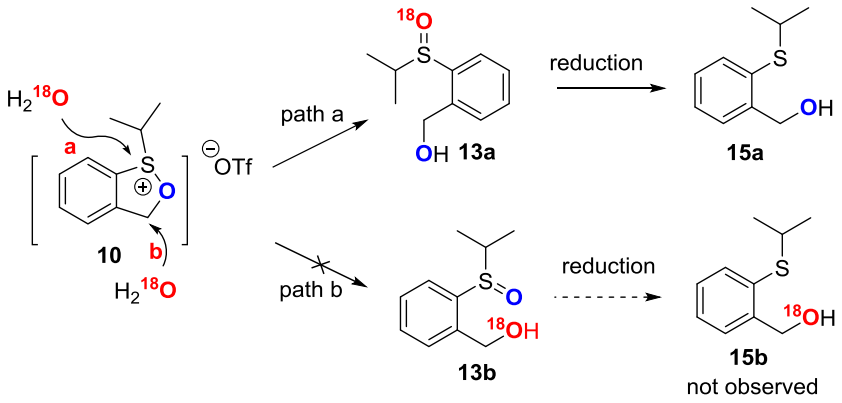
benzyl alcohol **15a** (PTB-OH) in excellent yield, while $NaBH_4/I_2$ [12] and $LiALH_4$ reduced the sulfoxide in moderate yields. It is worth noting that ^{18}O atom was not observed in PTB-OH **15a** generated by these conditions. These observations clearly indicated that the ^{18}O atom was labeled on the sulfoxide group to give **13a**. Furthermore, the isotopic labeling of sulfoxide group was also implied that the $H_2^{18}O$ attacked the sulfur atom (Scheme 5, path a) rather than the benzylic position (Scheme 5, path b) during the hydrolysis of the cyclic oxo-sulfonium ion **10**.

In conclusion, we investigated the mechanism of OPSB glycosides involved interrupted Pummerer reaction mediated glycosylation. Through tracking the leaving groups with isotopic labeling reaction, it was revealed that the recovered PSB-OH in this type of reaction was generated by hydrolysis in the aqueous workup step. This is the reason why extra alcohol generated from the leaving group by the reaction didn't compete with the glycosyl acceptors to affect the glycosylation efficiency. In addition, it was also proved that H_2O preferred to attack the sulfur atom in cyclic sulfonium ion **10** during the hydrolysis.

3. Experimental

3.1. General methods

NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz), and the ^1H 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. High resolution mass spectra were recorded on a Bruker



Scheme 5. Possible pathway for the hydrolysis of **10.**

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 (λ_{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), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden).

3.2. 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 evaporator at 28 °C. Solvents for reactions were dried on an Innovative Technologies Pure Solv400 solvent purifier. Trifluoromethanesulfonic anhydride (Tf_2O) was purchased from Adamas. $H_2^{18}O$ was purchased from J&K Scientific. Other reagents were purchased from Adamas or Acros Company.

3.3. Isotopic labeling reaction with $H_2^{18}O$

A solution of 2-[(propan-2-yl)sulfinyl]benzyl 3,4,6-tri-*O*-benzyl-2-acetyl-β-D-glucopyranoside **1** (100.0 mg, 0.15 mmol) in dry DCM (1.5 mL) was stirred at 0 °C for 10 min, then Tf_2O (30.0 μL, 0.18 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, and then quenched by addition of $H_2^{18}O$ (0.15 mL, 7.5 mmol). The mixture was stirred for another 10 min and diluted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated. Finally, the residue was purified by flash column chromatography (petroleum-EtOAc 1:2) to give 2-[(propan-2-yl) (^{18}O)sulfinyl] benzyl alcohol **13a** (28.2 mg, 95% yield) as colorless oil. Rf = 0.2 (petroleum-EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.47 (1H, m), 7.27–7.20 (3H, m), 4.60 (1H, dd, *J* = 2.8, 13.2 Hz), 4.51 (1H, dd, *J* = 2.8, 12.8 Hz), 3.37 (1H, s), 2.92–2.81 (1H, m), 1.01–0.97 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.8, 131.4, 129.8, 128.4, 126.3, 62.4, 54.3, 17.4, 14.2. HRMS calc. for $C_{10}H_{14}O^{18}OS$ $[M+Na]^+$: 223.0655, found: 223.0658.

3.4. Reduction reactions of PSB-OH

3.4.1. Method 1

A solution of 2-[(propan-2-yl) (^{18}O)sulfinyl]benzyl alcohol **13a** (15.0 mg, 0.08 mmol), TSA (35.0 mg, 0.15 mmol) and I_2 (2.0 mg, 0.01 mmol) in DCM (0.28 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc and washed with saturated $Na_2S_2O_3$, $NaHCO_3$, brine, the organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography (petroleum-EtOAc 3:1) to give 2-[(propan-2-yl)sulfanyl] benzyl alcohol **15a** (12.8 mg, 94% yield) as colorless oil.

3.4.2. Method 2

To a solution of 2-[(propan-2-yl) (^{18}O)sulfinyl]benzyl alcohol **13a** (20.0 mg, 0.10 mmol) and I_2 (51.0 mg, 0.20 mmol) in dry THF (2.0 mL) was added $NaBH_4$ (5.0 mg, 0.1 mmol). The resulting solution was stirred at room temperature. After 0.5 h, the suspension was quenched by saturated $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated, and purified by flash column chromatography (petroleum-EtOAc 3:1) to give 2-[(propan-2-yl)sulfanyl]benzyl alcohol **15a** (12.7 mg, 70% yield) as colorless oil.

3.4.3. Method 3

$LiAlH_4$ (9.5 mg, 0.26 mmol) was added to a solution of 2-[(propan-2-yl) (^{18}O)sulfinyl]benzyl alcohol **13a** (25.0 mg, 0.13 mmol) in 1.3 mL THF and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, and the aqueous NaOH solution was added. The residue was filtered through Celite and extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, concentrated, and purified by silica gel column chromatography (petroleum-EtOAc 3:1) to give 2-[(propan-2-yl)sulfanyl]benzyl alcohol **15a** (11.4 mg, 49% yield) as colorless oil.

3.5. 2-[(Propan-2-yl)sulfanyl]benzyl alcohol 15a (PTB-OH)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.37 (2H, m), 7.25–7.23 (2H, m), 4.77 (2H, d, *J* = 6.4 Hz), 3.40–3.33 (1H, m), 2.39 (1H, t, *J* = 6.4 Hz), 1.28 (6H, d, *J* = 6.4 Hz). HRMS calc. for $C_{10}H_{14}OS$ $[M+Na]^+$: 205.0663, found: 205.0674.

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