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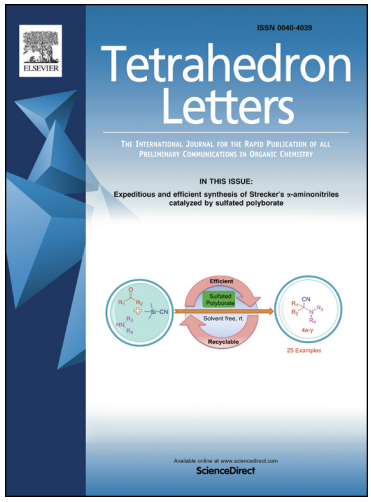

Practical Synthesis of Latent Disarmed *S*-2-(2-Propylthio)benzyl Glycosides for Interrupted Pummerer Reaction Mediated Glycosylation

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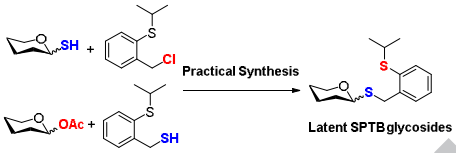

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Practical Synthesis of Latent Disarmed *S*-2-(2-Propylthio)benzyl Glycosides for Interrupted Pummerer Reaction Mediated Glycosylation

Yang Xu[a,1], Qian Zhang[a,1], Ying Xiao[a], Pinru Wu[a], Wei Chen[a], Zejin Song[a], Xiong Xiao[a], Lingkui Meng[a], Jing Zeng[a] and Qian Wan[a, b] *

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ABSTRACT

Practical synthetic methods to latent disarmed *S*-2-(2-propylthio)benzyl (SPTB) glycosides for interrupted Pummerer reaction mediated glycosylation have been discovered. Among them, both coupling reaction of PTB-Cl with glycosyl thiols and BF_3•OEt_2 promoted reaction of peracylated glycosides with PTB-SH produced peracylated SPTB glycosides in large scales and with high efficiency.

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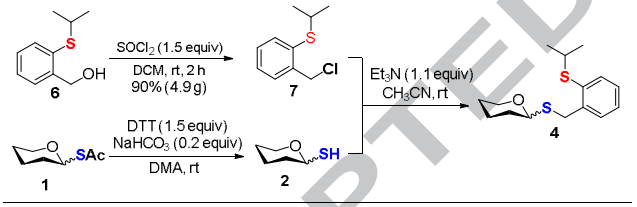
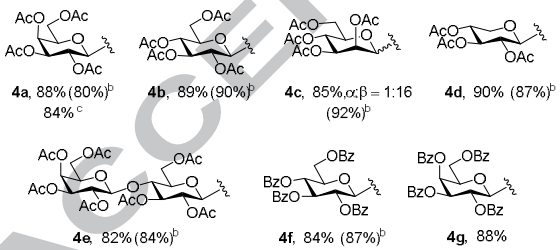
Although the vital functions of oligosaccharides and glycoconjugates in biological process have promoted the extraordinary achievements in oligosaccharides and glycoconjugates synthesis over the decades, the remaining challenges still encouraged the carbohydrate chemists to discover new glycosylation strategies.[1] Among those efforts, the development of glycosyl donors with novel anomeric leaving groups occupies an important niche. In addition to the traditional and widely used glycosyl donors,[2] several new types of glycosyl donors such as propargyl glycosides,[3] 3,3-difluoro-3*H*-indole-2-yl (OFox) glycosides,[4] *ortho*-alkynylbenzoyl/benzyl glycosides,[5] *S*-but-3-ynyl thioglycosides,[6] 4-*p*-methoxyphenyl-3-butenyl thioglycosides[7] and mannosyl 2,6-lactone[8] *etc.* have been successfully discovered and applied into the construction of glycosidic bonds in past ten years. Very recently, we have developed *O*-2-(2-propylsulfinyl)benzyl (OPSB) glycosides which were simply obtained from oxidation of corresponding latent *O*-2-(2-propylthio)benzyl (OPTB) glycosides as active glycosyl donors (Scheme 1a).[9] This new type of OPSB glycosyl donors could be efficiently activated with Tf_2O *via* an interrupted Pummerer reaction.[10] In addition, the intrinsic properties of OPTB and OPSB glycosides allows the successfully application of latent-active strategy[11] in oligosaccharide synthesis. Due to these *O*-benzyl glycosyl donors limited to "armed" and "super armed" glycosides,[12] we further discovered their *S*-analogues, *S*-2-(2-propylthio)benzyl (SPTB) glycosides and *S*-2-(2-propylsulfinyl)benzyl (SPSB) glycosides, as a new pair of latent-active donors (Scheme 1b).[13] This *O* to *S* replacement enabled the remote activation of corresponding disarmed glycosyl donors *via* interrupted Pummerer reaction. To further streamline the applicability of active SPSB glycosyl donors, herein, we reported practical synthetic methods to the latent disarmed *S*-2-(2-propylthio)benzyl (SPTB) glycosides.

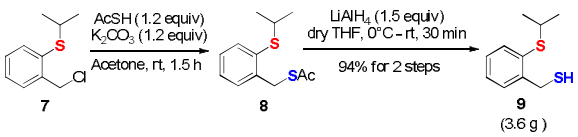
Scheme 1. Interrupted Pummerer reaction mediated glycosylation.





Scheme 2. Synthesis of disarmed SPTB glycosides by coupling of PTB-Cl with glycosyl thiols. [a] Yields of two steps reaction including selective deacetylation of **1** to form **2** and subsequent coupling with **7** , unless specified, the reactions were carried out in 0.1-0.5 mmol scale. [b] Yield of reaction with PTB-I in parentheses. [c] Yield with PTB-Cl in 1.5 grams scale synthesis. DTT = 1,4- dithiothreitol, DMA = dimethylacetamide.

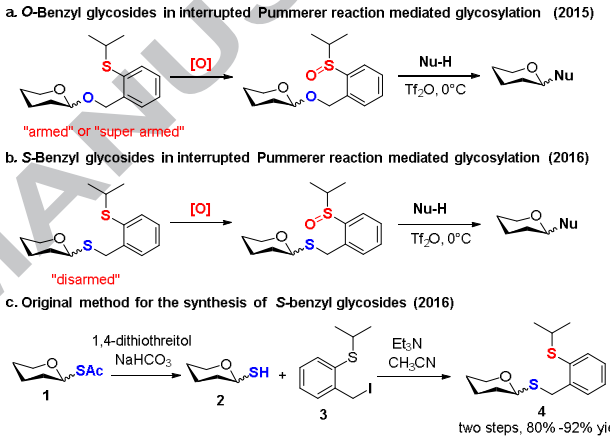
Original synthetic method to latent disarmed *S*-2-(2-propylthio)benzyl (SPTB) glycosides (**4**, Scheme 1c) involved two-step sequence: selective deacetylation of glycosyl thioacetates **1** to produce glycosyl thiols **2**[14] and subsequent coupling of **2** with 2-(2-propylthio)benzyl iodide (PTB-I, **3**).[13]



Although this procedure provided various SPTB glycosides in good yields, the instability of PTB-I limited its application especially in large scale synthesis. We then considered to replace PTB-I with more stable PTB-Cl **7** which was efficiently synthesized from 2-(2-propylthio)benzyl alcohol. It is much stable than PTB-I and could be kept for several months in fridge. The further coupling of compound **7** with glycosyl thiols **2** furnished SPTB glycosides **4a**-**e** in roughly equal efficiency to the reaction with PTB-I **3** (Scheme 2). The synthesis in gram-scale still offered **4a** in 84% yield. During the further reaction explorations, we found that glycosylation with peracetylated glycosyl donors sometimes led to intermolecular acetyl transfer byproducts.[13,15] These side reactions could be suppressed by changing the acetyl protecting group to benzoyl group.[15c-e] The perbenzoylated SPTB glycosides (**4f**, **4g**) could be obtained in good yields under the same reaction conditions.

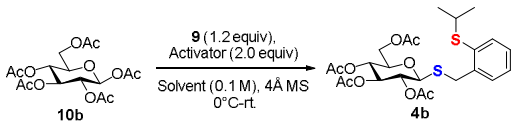
Scheme 3. Synthesis of PTB-SH **9**.

Although high efficiency was achieved in this protocol, one drawback is that some glycosyl thioacetates **1,** such as 2-aminoglucosyl thioacetate, mannosyl thioacetate and



rhamonnosyl thioacetate could not be obtained in good yields.[14] Thus, we considered to further improve the efficiency of the preparations by direct coupling of peracetylated glycosides **10** with 2-(2-propylthio)benzyl thiol (PTB-SH, **9**). First, PTB-SH was synthesized from PTB-Cl by thioacetylation and subsequent removal of acetate group by $LiAlH_4$ reduction. This two-steps protocol furnished PTB-SH in excellent yields even in multi-grams' synthesis (Scheme 3). It should be noted that deprotection of the acetate group under basic conditions led to low yields due to the formation of disulfide.

Table 1. Optimization of the coupling reaction conditions of **10b** with **9.**



Entry	Activator	Solvent	Time (h)	Yields (%)[a]
1	TMSOTf	DCM	4	63
2	BF_3•OEt_2	DCM	24	92
3	BF_3•OEt_2	MeCN	9	68
4	BF_3•OEt_2	toluene	9	84
5	BF_3•OEt_2	THF	9	-
6[b]	BF_3•OEt_2	DCM	24	94

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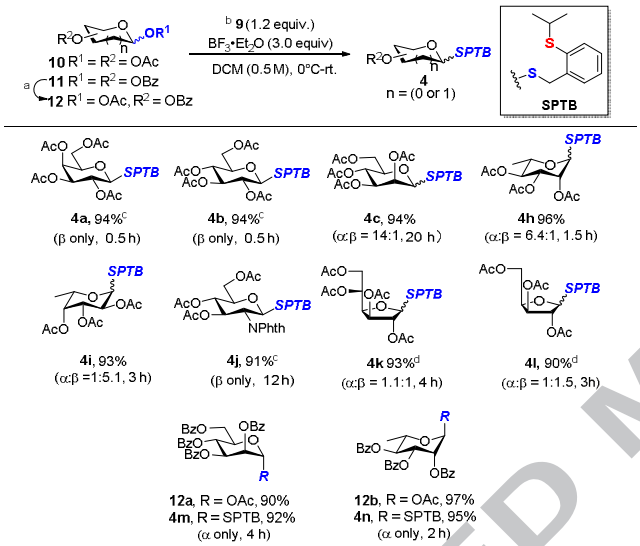
7[b,c]	BF_3•OEt_2	DCM	0.5	94

[a] Isolated yield
[b] 3.0 Equiv of BF_3·OEt_2 was used
[c] Concentration increased to 0.5 M

The coupling reaction of compound **10b** with PTB-SH **9** was then explored. TMSOTf promoted this reaction in DCM offered **4b** in moderated yield (Table 1, entry 1). Changing the activator from TMSOTf to BF_3•OEt_2 resulted in 92% yield, albeit requirement of much longer reaction time (entry 2). Screening of the solvents to MeCN, toluene or THF furnished diminished results (entries 3-5). Further increasing the amount of BF_3•OEt_2 didn't apparently accelerate the reaction speed (entry 6). Interestingly, carrying out the reaction in higher concentration (0.5M) largely shortened the reaction time to 0.5 h without affecting the reaction yield (entry 7).



Scheme 4. Synthesis of SPTB glycosides by coupling of PTB-SH with 1-*O*-acetyl glycosides. [a] Ac_2O (20.0 equiv), AcOH (10.0 equiv), H_2SO_4 (1.05 equiv), DCM, rt; [b] Unless specified, reactions were carried out in 50 mg scale. [c] Reactions were carried out in gram scale. [d] Reaction concentration was 0.1 M.

This optimized reaction conditions were applied to various peracylated glycosides, and the latent SPTB glycosyl donors were obtained in good to excellent yields (Scheme 4). The syntheses of **4a** and **4b** in gram-scale were achieved in excellent yield. The 6-deoxysugars **4h** and **4i** were prepared in high efficiency. Aminosugar **4j** was successfully produced in excellent yield in gram scales. Notably, the solvent concentration should be diluted to 0.1 M when producing pentose **4k** and **4l,** diminished yields were observed in high concentration due to side reactions in these two cases. It is worth noting that anomeric mixtures were obtained for 6-deoxysugars (**4h**, **4i**) and pentose (**4k**, **4l**). However, we didn't try to further optimize the reaction conditions to improve the anomeric selectivity, because it was found that the ratio of the anomeric mixture didn't affect the efficiency and selectivity in later interrupted Pummerer reaction mediated glycosylations.[13] Unfortunately, the reactions with peracetylated xylopyranose and lactose produced low yields.

The direct coupling of perbenzoylated glycosides **11** with PTB-SH **9** under above optimized conditions proceeded extremely slow and most of the starting materials **11** were recovered after 24h. These results implied that 1-*O*-benzoyl glycosides were much inert than corresponding 1-*O*-acetyl glycosides. Although further changing the solvent to dichloroethane (DCE) and increasing the reaction temperature[16] led to a full transformation of starting materials, a mixture of anomeric isomers containing unseperable unknown byproducts were obtained. To solve this problem, the anomeric benzoyl groups of **11a** and **11b** were transformed to acetyl groups to produce **12a** and **12b** in excellent yields. The coupling reactions of **9** with **12a/b** promoted by BF_3•OEt_2 under room temperature proceeded smoothly which offered perbenzoylated SPTB glycosides **4m** and **4n** in perfect yields.

In conclusion, we have reported practical synthetic methods to latent disarmed SPTB glycosides. According to these methods, the peracylated SPTB glycosides could be obtained efficiently either by direct coupling of **7** (PTB-Cl) with glycosyl thiols or by BF_3•OEt_2 promoted reaction of peracylated glycosides with **9** (PTB-SH). Both methods could offer the SPTB glycosides in large scales and in excellent yields. Comparatively speaking, the former method had broader substrates scopes which were only limited by the availability of thioacetates, while the later method was more direct albeit it was not suitable for pentopyranose and lactose. We believe that these methods would benefit those chemists who want to employ the interrupted Pummerer reaction mediated glycosylation in complex oligosaccharides and glycoconjugates synthesis. These methods are also helpful for other disarmed thioglycosides synthesis.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.01.006.

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Highlights:

- Two practical synthetic methods to disarmed SPTB glycosides are reported.
- Both methods can make SPTB glycosides in gram scale.
- Affords an easy access to various disarmed SPTB glycosides in high yields.

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