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Thioperoxide-Mediated Activation of Thioglycoside Donors

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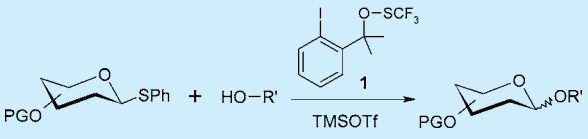
Supporting Information

ABSTRACT: Thioperoxide (**1**) in combination with trimethylsilyl trifluoromethanesulfonate (TMSOTf) provides a powerful thiophilic promoter system, capable of activating different thioglycosides. Both armed and disarmed thioglycosides were activated effectively in the presence of different glycosyl acceptors, giving glycosidation products in high to excellent yields. A plausible activation pathway was also proposed and supported by isolating side-products trifluoromethylphenyl disulfide (CF_3SSPh) and alkene (**42**).



Thioglycosides are frequently used as glycosyl donors in glycoside synthesis. Since the first report in 1909,[1] thioglycoside chemistry has been explored constantly and numerous protocols have been reported on their preparation and activation over the past century.[2] The advantage of thioglycosides lies in their great stability under a wide range of conditions for protecting group manipulation. Anomeric thioether groups can thus act themselves as temporary protecting groups. Therefore, thioglycosides can serve not only as glycosyl donors but also as glycosyl acceptors. This feature, combined with the tunable reactivity of thioglycosides, has often been exploited for the efficient synthesis of complex oligosaccharides.[3]

In general, thioglycosides can be activated by two types of promoters: one is via a halonium system and the other is via an organosulfur-based system. Among halonium systems, iodonium species generated typically by *N*-iodosuccinimide (NIS) in conjunction with a catalytic amount of protic acid or Lewis acid[4] were first reported in 1990 and since then have been widely used for activation of various thioglycosides. For example, different thioglycosides of great disparity in reactivity were all activated effectively with NIS/Lewis acid in the synthesis of carbohydrates present on the human embryonic stem cell surface.[5] Other variants of the iodonium system, such as IPy_2BF_4/triflic acid[6] and interhalogen compound/AgOTf,[7] were also found to be effective for glycosidation reactions of thioglycoside donors. Very recently, phenyl(trifluoroethyl)-iodonium triflimide, an air- and water-stable reagent, was also used to activate various thioglycosides.[8] In past decades, organosulfur compounds have also become valuable promoters for thioglycoside activation. In this respect, early studies were devoted to sulfonium or sulfenyl triflates, such as dimethyl-(methylthio)sulfonium triflate (DMTST), MeSOTf, and PhSOTf.[2] Recently, sulfinates in combination with Tf_2O have attracted significant attention as thioglycoside activators.[9] For example, the system *S*-(4-methoxyphenyl)benzenethiosulfinate (MPBT)/Tf_2O was capable of activating thioglycosides and promoting the formation of a challenging β-mannosidic linkage in excellent yield and stereoselectivity.[9a] Both 1-benzenesulfinylpiperidine (BSP)/Tf_2O[9b] and Ph_2SO/Tf_2O[9c] also proved to be a very powerful thiophilic promoter system and could both activate disarmed thioglycosides. Another similar sulfinyl system, benzenesulfinylmorpholine (BSM)/Tf_2O,[9d] was also employed to activate different thioglycosides. An important feature of these sulfinyl systems is their capacity to preactivate thioglycoside donors at low temperatures.[10] By virtue of preactivation,[11] one thioglycoside can be activated prior to addition of another thioglycoside acceptor regardless of their reactivity. Glycosylation reactions mediated by sulfinyl derivatives have thus been utilized to design an efficient one-pot synthesis.[9d] Other organosulfur systems, such as Me_2S_2/Tf_2O,[12] *O*,*O*-dimethylthiophosphonosulfenyl bromide (DMTPSB)/AgOTf,[13] EtSNPhth/TrB$(C_6F_5)_4$,[14] *N*-(phenylthio)-ε-caprolactam/Tf_2O,[15] and *N*-(*p*-methylphenylthio)-ε-caprolactam/TMSOTf,[16] have also been developed for the activation of thioglycosides. In addition, other conditions for thioglycoside activation, such as the use of $AgPF_6$,[17] visible light mediated activation,[18] and electrochemical oxidation,[19] have been reported recently. In view of the versatility of thioglycosides in carbohydrate chemistry, together with the advantage conferred by the organosulfur promoter system, we decided to pursue a new activation system for thioglycoside donors. We wish to report here a new organosulfur participating promoter system which can activate both armed and disarmed thioglycoside donors.

Recently, Shen et al. reported an electrophilic trifluoromethylthiolating reagent that could directly transfer the CF_3S group to various substrates including a series of enolate nucleophiles under very mild conditions.[20] Apart from its excellent performance in trifluoromethylthiolation, this reagent is also air and moisture stable. Initially the reagent was proposed as a hypervalent iodine structure, but very recently Buchwald et al. reinvestigated the structure and confirmed it

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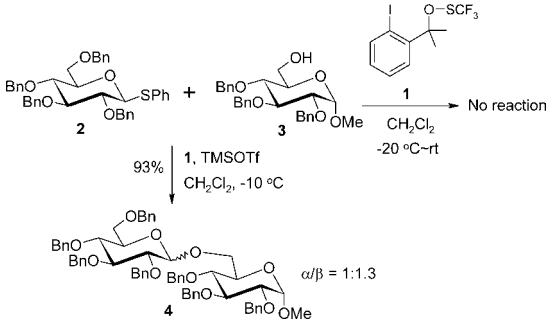
was the thioperoxide compound **1** (Scheme 1).[21] Although the reaction mechanism for trifluoromethylthiolation may have to

Scheme 1. Thioperoxide 1-Promoted Glycosidation of 2

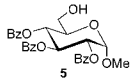
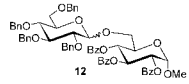
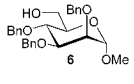
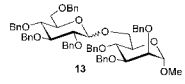
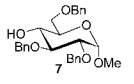
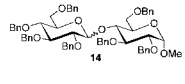
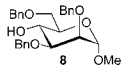
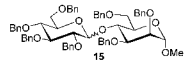
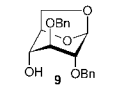
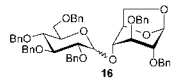
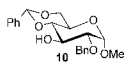
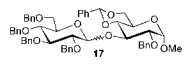
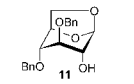
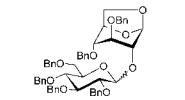


be revisited due to the structural revision, the chemical reactivity of the reagent was not affected at all. We speculated that this CF_3S-containing thioperoxide may also be used to activate thioglycoside donors. Also, if feasible, it would be interesting to find out how it would act as a promoter to activate thioglycosides with or without the assistance of a Lewis acid. Our initial efforts to test the activating ability of this reagent focused at first on armed[22] thioglycoside donors. Hence, the fully benzylated thioglucoside **2**[23] was first chosen as the donor and treated with **1** in the presence of glucosyl acceptor **3**[24] at low temperature (−20 °C) (Scheme 1). Unfortunately, no glycosidation reaction took place, and **2** was not affected even at rt and after a prolonged reaction time. We surmised that an additional catalyst would be needed to initiate the reaction as observed by Shen et al. in trifluoromethylthiolation of aryl or vinyl boronic acids and alkynes.[20] Hence, after a quick optimization of the reaction conditions, Lewis acid TMSOTf (0.6 equiv) was added to the above reaction, and to our delight, the glycosidation proceeded smoothly to generate the desired disaccharide **4** in excellent yield (93%). Although the stereoselectivity was low due to the absence of stereocontrol, the reaction was very clean except for the decomposition of the donor as indicated by TLC.

Encouraged by this result, a series of glycosyl acceptors were then prepared and subjected to glycosylation with donor **2** under the above same conditions as outlined in Table 1. Acceptors **5**[25] and **6**[26] having a primary hydroxyl group could also be glycosylated with **2** to give the corresponding disaccharides **12** and **13** in 88% and 89% yields, respectively (Table 1, entries 2 and 3). Acceptors **7**,[27] **8**,[27] and **9**[28] carrying a free hydroxyl group at the 4-position were also reacted with donor **2** under the same conditions, giving rise to the corresponding disaccharides **14**, **15**, and **16** in excellent yields (Table 1, entries 4, 5, and 6). Glycosylation of acceptors **10**[27] and **11**[29] possessing a free hydroxyl group at C-3 and C-2 also proceeded smoothly and led to the corresponding disaccharides **17** and **18** in 68% and 90% yield, respectively (Table 1, entries 7 and 8). These results clearly demonstrate that thioglycoside **2** could be activated effectively with thioperoxide **1** in the presence of TMSOTf, and the current activation conditions may find use in thioglycoside chemistry.

To further demonstrate the effectiveness of thioperoxide **1** for activation of thioglycosides, we prepared a range of different thioglycosides **19**−**25** and investigated their glycosylation property under the above conditions (Table 2).

Table 1. Activation of Donor 2 with Thioperoxide 1/TMSOTf

entry	donor	acceptor	product	yield (%)	α/β ratio[a]
1	**2**	**3**	**4**	93	1:1.3
2	**2**	 **5**	 **12**	88	1.6:1
3	**2**	 **6**	 **13**	89	1:1.2
4	**2**	 **7**	 **14**	97	1.3:1
5	**2**	 **8**	 **15**	90	1.3:1
6	**2**	 **9**	 **16**	93	1:1
7	**2**	 **10**	 **17**	68	2:1
8	**2**	 **11**	 **18**	90	1.6:1

[a]Determined by integration of proton signals in the ^{1}H NMR spectrum after chromatographic purification.

As anticipated, treatment of the similar armed thiogalactoside **19**[30] with **1** and catalytic amounts of TMSOTf in the presence of acceptor **3** afforded the desired disaccharide **26** as an α/β mixture in 87% yield (Table 2, entry 1). 4,6-Benzylidenated thioglucoside **20**[31] could also be activated under the same conditions to produce disaccharide **27** in 74% yield in the presence of acceptor **6** (Table 2, entry 2). Recently, an unusual reactivity pattern was observed for thioglycoside donors:[32] 3,4,6-tri-*O*-benzyl 2-*O*-acyl thioglycosides are even more reactive than armed perbenzylated derivatives, while 3,4,6-tri-*O*-acyl 2-*O*-benzyl thioglycosides are even less reactive than disarmed peracylated derivatives. These superarmed and -disarmed reactivities were attributed to the O-2/O-5 cooperative effect.[33] As another example, we decided to study the effect of the current activation conditions on the superarmed donor **21**.[34] Hence, coupling of **21** and acceptor **3** was conducted under the action of thioperoxide **1** and TMSOTf, not surprisingly, affording desired disaccharide **28** smoothly in excellent yield (Table 2, entry 3). The complete β-stereoselectivity observed in this glycosidation reaction and the following ones (vide infra) was attributed to the assistance of the participating acetyl or benzoyl group at the C-2 position.

To further examine the scope of the thioperoxide/TMSOTf system, we have also explored the disarmed thioglycoside donors, as shown in Table 2 (entries 4−9). Initially, experiments were run with conventionally disarmed thioglucoside **22**[35] and acceptor **3**. The reaction was clearly slower at −10 °C in comparison with the glycosidation of the above armed donors, although it proceeded well. More forcing reaction conditions were then investigated with the hope of

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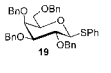
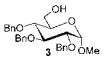
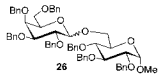
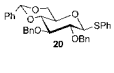
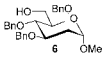
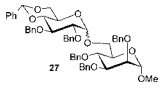
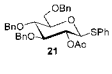
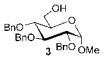
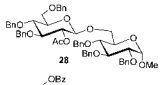
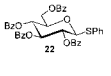
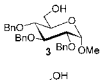
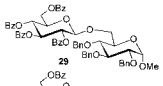
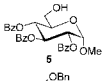
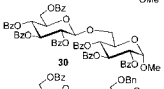
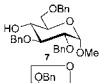
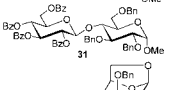
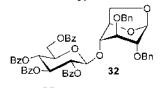
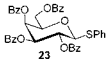
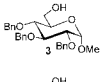
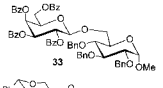
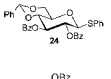
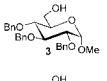
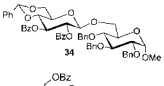
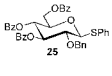
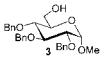
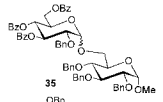
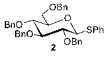
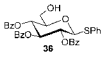
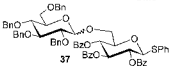
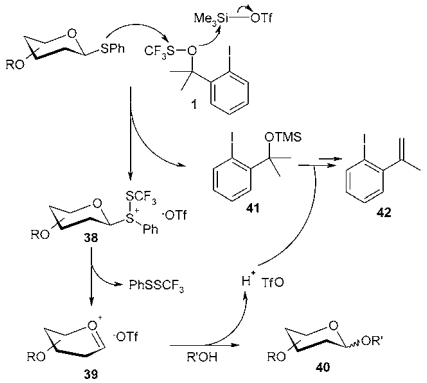
Table 2. Activation of Donors 19−25 and 2 with Thioperoxide 1/TMSOTf

entry	donor	acceptor	product	yield (%)	α/β ratio
1				87	1.5:1
2				74	3.2:1
3				94	β only
4				96	β only
5	**22**			92	β only
6	**22**			91	β only
7	**22**			86	β only
8				95	β only
9				82	β only
10				91	8.6:1
11				62	1.2:1

driving the reaction to completion within a relatively short period of time. Hence, the reaction temperature was raised to 0 °C and the amount of TMSOTf was increased to 1.5 equiv as well. As expected, under such conditions a clean reaction occurred within 2 h, and the glycosidation product **29** was obtained in almost quantitative yield (Table 2, entry 4). We speculated that apart from enhancing the reaction conditions the relatively large amounts of TMSOTf may also react with acceptor **3** to generate in situ the trimethylsilyl ether of **3** which possessed higher reactivity than the free hydroxyl group, thereby facilitating the glycosidation reactions.[36] To corroborate this, acceptor **3** was trimethylsilylated and subjected to glycosylation with **22** under the previous conditions (0.6 equiv of TMSOTf, −10 °C); as anticipated, the reaction proceeded smoothly and produced **29** in quantitative yield. The above slightly harsher conditions were then applied to activating all disarmed thioglycosides. We proceeded to use thioglucoside **22** as the donor and subjected it, together with acceptor **5**, to the conditions; fortunately, disaccharide **30** was also produced in excellent yield (Table 2, entry 5). Similarly, glycosylation of acceptors **7** and **9** with **22** gave also the corresponding disaccharides **31** and **32**, respectively, in very high yields (Table 2, entries 6 and 7). An excellent yield was also achieved for the coupling of thiogalactoside donor **23**[37] and acceptor **3** under the present conditions, as shown in Table 2. These results, together with those in Table 1, are very encouraging, as they clearly demonstrate the effectiveness of activating both armed and disarmed thioglycosides with the thioperoxide/TMSOTf system. Subsequently, coupling between donor **24**[38] and acceptor **3** was performed under the above-mentioned conditions; again, the reaction proceeded smoothly to give the desired *β*-linked disaccharide **34** in 82% yield (Table 2, entry 9). We reasoned that superdisarmed thioglycosides could also be activated with the thioperoxide/TMSOTf system, and indeed, as demonstrated by the glycosidation of donor **25**[39] with acceptor **3** (Table 2, entry 10), this proved to be the case. Activation of **25** with **1** and TMSOTf in the presence of **3** afforded disaccharide **35** in excellent yield. Finally, chemoselective activation of armed donor **2** in the presence of disarmed thioglycoside **36**[25] was also attempted under the previous milder conditions; as expected, disaccharide **37** was isolated in good yield (Table 2, entry 11).

The results summarized in Tables 1 and 2 clearly indicate that thioperoxide **1** can activate thioglycoside donors in a highly effective way in the presence of TMSOTf. Based on these results and mindful of earlier work by Shen and Buchwald et al. on the electrophilic trifluoromethylthiolation property of **1**, we proposed that the above glycosidation reactions proceed via the pathway outlined in Scheme 2.[40] Since thioperoxide **1** alone

Scheme 2. Proposed Mechanistic Pathway for Thioperoxide 1/TMSOTf-Promoted Thioglycoside Activation



cannot initiate the glycosidation reaction, it is very likely activated by TMSOTf to turn into a strong electrophile which could then activate thioglycoside by trifluoromethylthiolation of the anomeric sulfur. The thioglycoside donor is thereby transformed into the intermediate **38**, which subsequently collapses into an oxacarbenium ion **39** and trifluoromethylphenyl disulfide (CF_3SSPh). Nucleophilic attack by an alcohol at the anomeric center of **39** or other reactive intermediates, such as glycosyl triflate or acyloxonium ion in the case of neighboring group participation, then gives the glycosidation product **40**. Meanwhile, thioperoxide **1** breaks down after activation to form trimethylsilyl ether **41**, which undergoes an elimination reaction to give alkene **42**.[41] The mechanistic pathway was evidenced by isolating side-products disulfide CF_3SSPh and alkene **42**.

In conclusion, we have demonstrated that the air- and moisture-tolerant thioperoxide **1**, in the presence of TMSOTf, could act as a convenient and effective promoter of thioglycoside donors. The activation proceeds by the in situ activation of **1** with TMSOTf, which then serves to activate thioglycosides for glycoside bond formation. The activation protocol was successfully applied to a wide range of both armed and disarmed thioglycoside donors, and excellent yields were achieved for glycosylation of various acceptors. The next phase of this research will endeavor to explore the compatibility

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of the activation system with other glycosylation procedures as well as its application in complex glycoside synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for glycosidation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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