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N-Trifluoromethylthiosaccharin/TMSOTf: A New Mild Promoter System for Thioglycoside Activation

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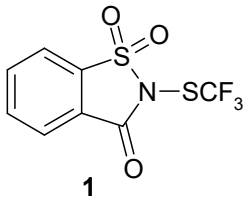
Abstract: For the first time, *N*-trifluoromethylthiosaccharin was used to activate thioglycosides in the presence of catalytic amounts of TMSOTf. The results show that the activated thioglycosides undergo glycosidation reactions with various glycosyl acceptors to give the corresponding glycosides in moderate to excellent yields. In addition, orthogonal activation of ethyl thioglycoside in the presence of phenyl thioglycoside was achieved under the above conditions.

Introduction

The first report of thioglycoside dates back more than a century ago[1] but new preparative and activation procedures are still emerging. The great interest in thioglycosides stems from their high stability under a wide range of conditions for protecting group manipulation and their survival under various activation conditions for other glycosyl donors. Anomeric thioether groups can thus act themselves as temporary protecting groups and therefore, are often used as glycosyl acceptors in glycosylation strategies. The compatibility of thioether with other leaving groups makes thioglycosides key building blocks in many oligosaccharide syntheses and greatly improves synthetic efficiency.[2] Such dependence on the stability of thioglycosides continues to be demonstrated in recent years. For example, the use of thioglycosides was central to a recent one-pot synthesis of a hexasaccharide intermediate, which was then triply glycosylated with a thiofucoside donor in one step to furnish the cancer-associated nonasaccharide KH-1 antigen.[3] Tumor-associated carbohydrate antigen RM2 derived from prostate cancer was also synthesized efficiently in one-pot manner with a series of thioglycosides as important building units.[4]

Undoubtedly, thioglycosides have proven and will continue to be one of the most versatile and frequently employed classes of sugar building blocks.[5] Albeit high stability, thioglycosides can be activated effectively under the action of different promoters, and as such serve widely as glycosyl donors. 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. The latter has become a valuable promoter for thioglycoside activation in the past decade. Several sulfinates in combination with Tf_2O have been developed as thioglycoside activators.[6] For example, *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT)/Tf_2O was used to promote the formation of β-mannosidic linkage in excellent yield and stereoselectivity.[6a] Both 1-benzenesulfinylpiperidine (BSP)/Tf_2O[6b] and Ph_2SO/Tf_2O[6c] also proved to be very powerful thiophilic promoter systems and could both activate disarmed thioglycosides. An important feature of these sulfinyl systems is their capacity to preactivate thioglycoside donors at low temperatures,[7] which allows a thioglycosyl donor to be activated prior to the addition of another thioglycosyl acceptor, regardless of their reactivity.[8] The success of this preactivation strategy has thus been utilized to design efficient one-pot synthesis strategies.[6d],[9] Numerous other organosulfur systems, such as Me_2S_2/Tf_2O,[10] *O*,*O*-dimethylthiophosphonosulfenyl bromide (DMTPSB)/AgOTf,[11] EtSNPhth/$TrB(C_6F_5)_4$,[12] *N*-(phenylthio)-ε-caprolactam/Tf_2O[13] and *N*-(*p*-methylphenylthio)-ε-caprolactam/TMSOTf[14] have also been developed for the activation of thioglycosides. At present, thioglycoside activation is a focus point in carbohydrate chemistry,[5] however, there is still a drive for finding more amenable and compatible promoters for oligosaccharide assembly. Recently, we reported an effective thioglycoside activation system, in which an organosulfur thioperoxide reagent in combination with TMSOTf was found to be able to activate both armed and disarmed thioglycoside donors.[15] A plausible reaction mechanism was also proposed for the activation process. As an extension of this work and part of our ongoing project on thioglycoside chemistry,[16] a more readily available organosulfur reagent was also developed as a thioglycoside promoter and reported here. Recently, a new electrophilic trifluoromethylthiolating reagent, *N*-trifluoromethylthiosaccharin **1** (Figure 1), was reported by Shen and his coworkers for the direct trifluoromethylthiolation of various nucleophiles such as alcohols, amines, thiols, and electron rich arenes.[17] This reagent is moisture and air stable and can be synthesized on a large scale.[18] We became curious whether this compound could also be used to activate thioglycoside donors.

Figure 1. Structure of *N*-Trifluoromethylthiosaccharin **1**



1

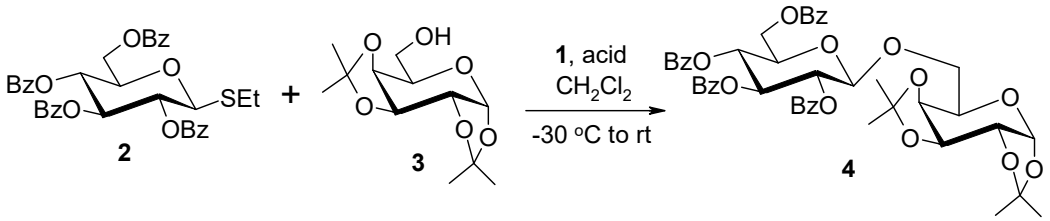
N-Trifluoromethylthiosaccharin

Hence, investigations towards thioglycoside activation with compound **1** were initiated. The results show that compound **1** is a mild and effective promoter for thioglycoside activation. Its usefulness is illustrated by a successful orthogonal activation of *S*-ethyl donors in the presence of *S*-phenyl donors, enabling the design of sequential glycosidation strategies in the future.

Results and Discussion

Based on our previous work,[15] compound **1** alone would unlikely activate thioglycosides. Indeed, when thioglucoside donor **2** was treated with **1** in the presence of 1,2:3,4-di-*O*-isopropylidiene galactopyranose **3**, no reaction was observed and **2** was not affected even after a prolonged reaction time (Table 1, entry 1). Hence, several common acids were tested in order to initiate the reaction, as shown in Table 1. Upon addition of Lewis acid $BF_3{\cdot}OEt_2$, the desired disaccharide **4** was produced but in relatively low yields (Table 1, entry 2). This result reassured that an additional acidic catalyst was needed to initiate the reaction. Brønsted acid TfOH was also used to initiate the reaction (Table 1, entry 3). As anticipated, the reaction proceeded well to give disaccharide **4** in much higher yield (67%). However, the reaction was undermined by heavy decomposition of thioglycoside **2** as detected by TLC. TMSOTf being less acidic than TfOH was then used together with **1** to promote the reaction, and to our delight, the glycosidation proceeded smoothly at -30 °C to generate **4** in a very high yield (Table 1, entry 4).

Table 1. Acid effect on **1**-mediated activation of thioglycoside



Entry	Acid	Yield (%)
1	-	-
2	$BF_3{\cdot}Et_2O$	46
3	TfOH	67
4	TMSOTf	74

With optimal conditions established, the next step was to assess the ability of *N*-trifluoromethylthiosaccharin **1** to activate a series of thioglucoside donors. Recently the reactivity of a series of α- and β-thioglucosyl donors bearing different protecting groups has been investigated in our laboratory and their reactivity differences have been exploited to design novel one-pot oligosaccharide synthesis strategies.[19] Thioglucosides **2** and **5-8** with disparity in reactivity from this series were then chosen to assess the capability of **1** to activate thioglycoside donors. The results are summarized in Table 2. All the reactions were cooled down to a low temperature and warmed up gradually with a strategy being to initiate the reaction at the lowest possible temperature to assess the donor reactivities under the present conditions. It is worth mentioning here that reaction conditions could have a great impact on reactivity of thioglycoside donors.[20] The reactions were monitored carefully by TLC and the temperature, at which the reactions were initiated, was recorded. Once initiated, the reaction mixture was slowly warmed up to the point where no acceptor remained, as determined by TLC, and was kept at that temperature for 30 minutes. The reactions were then ceased upon quenching by triethylamine. As expected, activation of donor **2** occurred smoothly under the above conditions to give disaccharide **10** in 74% yield in the presence of acceptor **9** (Table 2, entry 1). It is evident that the complete β-stereoselectivity in this glycosidation resulted from the assistance of the participating benzoyl group at the C-2 position of the donor **2**.

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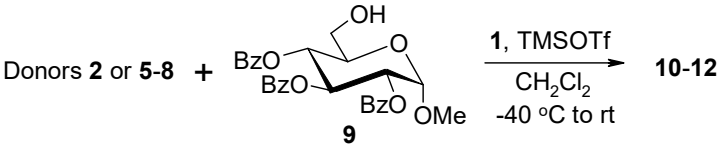
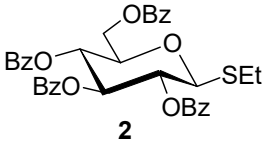
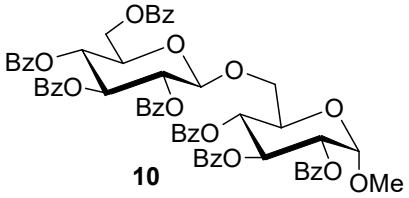
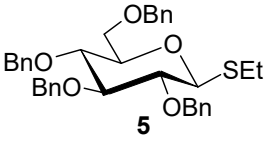
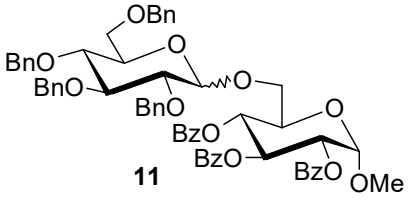
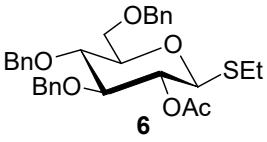
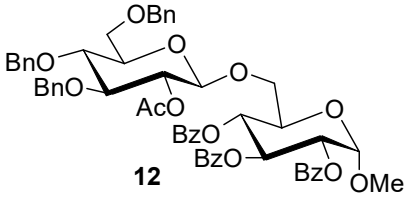
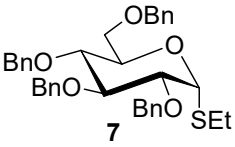
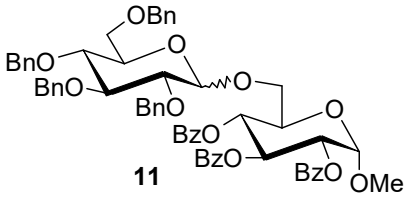
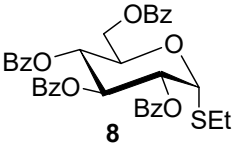
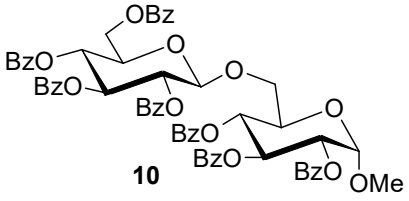
Table 2. Activation of donors **2** and **5-8** with *N*-Trifluoromethylthiosaccharin **1**/TMSOTf[a]



Entry	Donor	Product	Temp (°C)	Yield (%)[b]	α/β ratio[c]
1	 **2**	 **10**	-30	74	β only
2	 **5**	 **11**	-40	89	1:2
3	 **6**	 **12**	-40	90	β only
4	 **7**	 **11**	-40	86	1:1
5	 **8**	 **10**	-30	0	-

[a] Reaction conditions: donor (1.1-1.2 equiv), **9** (1.2 equiv), **1** (1.2 equiv), TMSOTf (0.6 equiv), under a N_2 atmosphere. [b] Isolated yield. [c] Determined by integration of the proton signals in the ^{1}H NMR spectrum after chromatographic purification.

The armed β-thioglucoside **5** being more reactive than donor **2**, was activated at a lower temperature (-40 °C) and coupled to acceptor **9** to generate the desired disaccharide **11** in 89% yield. All the glycosidation reactions in Table 2 were carried to completion and were clean with trace hydrolysis, which proceeded efficiently to form disaccharides in yields that are comparable to those in the literature.[10-14] Examination of the α/β composition of **11** gave an unexpected result, with the β-anomer being the predominant component of the mixture. We surmised that the influence of promoter **1** was at play. Investigation into the reaction mechanism in the future will be needed to explain the stereoselectivity. Next, a superarmed donor was prepared to demonstrate that it could undergo glycosidation under the new activation conditions. The 3,4,6-tri-*O*-benzyl-2-*O*-acetyl β-thioglucoside **6** was found to be a more reactive donor than the perbenzylated derivatives.[19],[21] This increase in reactivity was attributed to the *O*-2/*O*-5 cooperative effect.[22] Donor **6** was thus coupled with **9** under the action of **1** and catalytic amounts of TMSOTf. As anticipated, the reaction was initiated at -40 °C, and the desired disaccharide **12** was produced in excellent yield (90%) and β-only selectivity.

Following these promising results, the compatibility of this new system with α-thioglucoside donors was then tested. The fully benzylated α-donor **7**, being slightly less reactive than its counterpart **5**,[19] was successively activated under the same conditions at -40°C and coupled with **9** to produce disaccharide **13** in very high yield (86%) and α/β 1:1 selectivity (Table 2, entry 4). The result has indicated that anomeric configuration of thioglycosides can also have a bearing on reaction stereoselectivity. Apparently, these glycosidation reactions did not undergo simple S_N1 mechanism. To test the effectiveness of the new promoter system, the most unreactive α-thioglucoside **8** of the series was also subjected to the above conditions; surprisingly, no activation of this α-donor was observed (Table 2, entry 5). Donor **8** having an ester protecting group at 2-position and α-configured leaving group was predicted to have a negating effect on its reactivity,[19] but we had expected this disarmed donor to be activated by the new promoter. Despite no activation, this exceptionally low reactivity of **8** could potentially be exploited to design one-pot oligosaccharide synthesis where we could activate selectively its counterpart donor **2** in the presence of its derived thioglycosyl acceptor using the present new promoter system.

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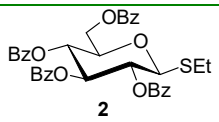
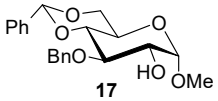
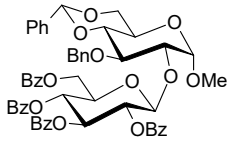
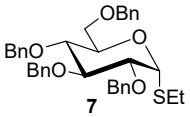
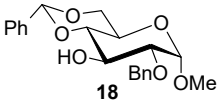
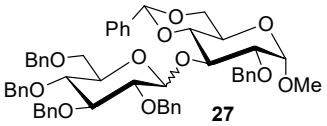
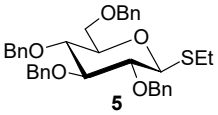
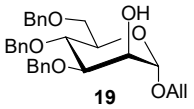
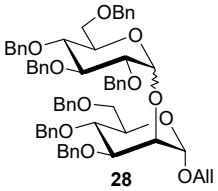
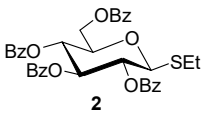
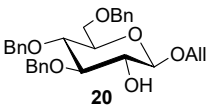
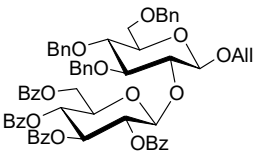
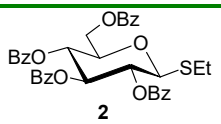
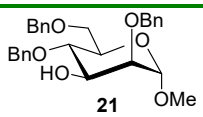
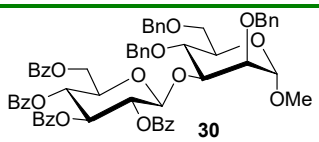
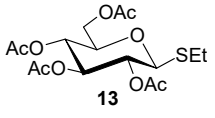
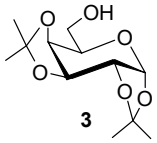
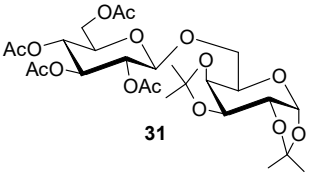
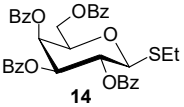
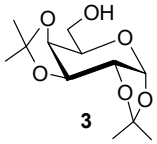
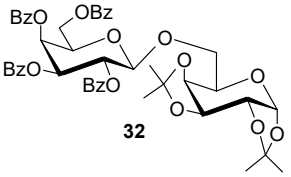
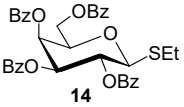
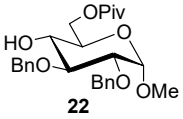
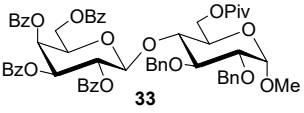
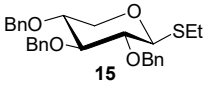
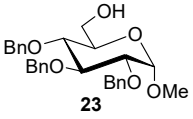
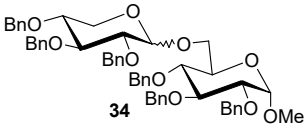
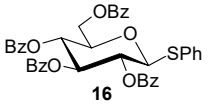
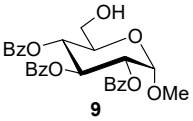
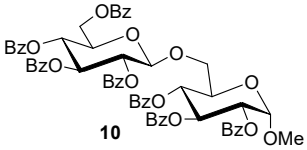
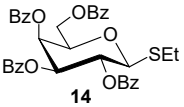
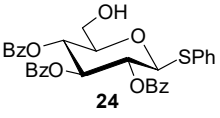
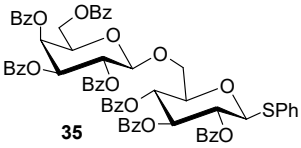
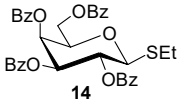
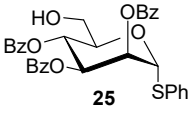
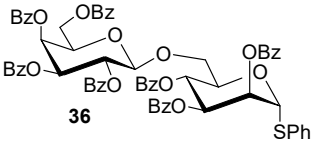
To further explore the scope and generality of the new promoter system for the activation of thioglycosides, we proceeded to use a wide range of thioglycosyl donors and other acceptors, as shown in Table 3. Based on the above results, all reactions were cooled down at -30 °C and slowly brought up to -10 °C and stirred at this temperature for 30 min. Under such conditions, the compatibility of the new system with sugars carrying different protecting groups was demonstrated. Acceptors with secondary hydroxyl groups were also used for the glycosylation reactions. Hence, acceptor **17** having a free hydroxyl group at the 2-position was glycosylated with donor **2** to give disaccharide **26** in 71% yield (Table 3, entry 1). Similarly, acceptor **18** having a secondary hydroxyl group was also reacted with α-donor **7** under the same conditions to furnish disaccharide **27** in very high yield (Table 3, entry 2). In both cases, the acid sensitive benzylidene group survived under the reaction conditions indicating the mildness of this new activation system. The mannosyl acceptor **19** was also coupled to donor **5** under the conditions to produce disaccharide **28** as an α/β mixture in 68% yield.

Table 3. Glycosidation reactions promoted by **1**/TMSOTf

Entry	Donor	Acceptor	Product	Yield (%)	α/β ratio
1	 **2**	 **17**	 **26**	71	β only
2	 **7**	 **18**	 **27**	87	1:1
3	 **5**	 **19**	 **28**	68	1.5:1
4	 **2**	 **20**	 **29**	74	β only

5	 **2**	 **21**	 **30**	70	β only
6	 **13**	 **3**	 **31**	48	β only
7	 **14**	 **3**	 **32**	69	β only
8	 **14**	 **22**	 **33**	77	β only
9	 **15**	 **23**	 **34**	75	1:2
10	 **16**	 **9**	 **10**	0	-
11	 **14**	 **24**	 **35**	73	β only
12	 **14**	 **25**	 **36**	72	β only

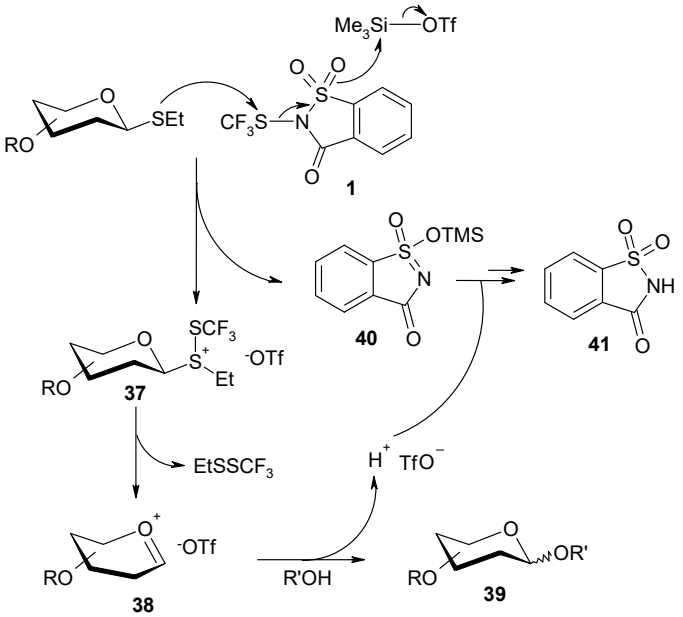
The β-configurated glucosyl acceptor **20**, together with donor **2**, was also subjected to the above reaction conditions, and expectedly, disaccharide **29** was produced smoothly in 74% yield (Table 3, entry 4). Another secondary alcohol **21** was also glycosylated with donor **2** under the same conditions to give the desired disaccharide **30** in 70% yield. The peracetylated thioglucoside **13** was also tested against the new promoter, and coupled with acceptor **3** (Table 3,

entry 6). Unfortunately, the desired disaccharide **31** was produced in low yield (48%), and the reaction was undermined by donor hydrolysis as detected by TLC. This indicated peracetylated thioglycosides would not be suitable for this glycosidation protocol. This result, however, conforms to the literature where peracetylated thioglycoside donors often preformed less efficiently, compared to perbenzoylated donors.[23] As such, the fully benzoylated thiogalactoside **14** was then used as donor and subjected to the glycosidation reactions with acceptors **3** and **22**, respectively, under the above activation conditions; as expected, the corresponding disaccharides **32** and **33** were generated in very good yields (Table 3, entries 7 and 8). Subsequently, the xylose-derived thioglycoside **15** was treated with the new promoter system in the presence of acceptor **23**, again the reaction proceeded smoothly to give the product **34** as an α/β mixture in 75% yield (Table 3, entry 9).

In addition to ethyl thioglycosides, we applied the glycosidation protocol to phenyl thioglycoside donors. Work by Lahmann et al.[24] quantified the reactivity difference between thioglycoside donors differing only in the aglycon moiety. An ethyl thioglycoside was reported to be more reactive than its corresponding phenyl thioglycoside, however, the reactivity difference between these donors was rarely exploited for one-pot strategies.[5i] That said, phenyl thioglucoside **16** was chosen to couple with acceptor **9** (Table 3, entry 10). To our surprise, the reaction failed to give any product under the same conditions and **16** was not affected even after a prolonged reaction time, i.e. no activation of donor **16** was observed. This was in sharp contrast with our previous organosulfur-mediated glycosidation reactions, in which phenyl thioglycosides could be readily activated with a thioperoxide in the presence of catalytic amounts of TMSOTf.[15] In spite of the extremely low reactivity of phenyl thioglycoside under the present conditions, we felt that we could turn it into an advantage. Hence, phenyl thioglucosyl acceptor **24**[25] was prepared and exposed, together with ethyl thiogalactoside **14**, to the above activation conditions; as expected, the orthogonal activation of ethylthio group in the presence of phenylthio group took place smoothly and gave rise to the disaccharide **35** in 73% yield (Table 3, entry 11). Obviously, **35** could be used immediately as glycosyl donor for further glycosidation reactions if necessary. Likewise, phenyl thiomannoside **25** remained also inactive under the present activation conditions, as shown in entry 12 in Table 3. The selective activation of ethyl thioglycoside **14** was readily attained in the presence of **25**, and disaccharide **36** was generated in

high yield, which could also serve as donor for further glycosidation reactions. The ready formation of **35** and **36** offered a preliminary suggestion that the new organosulfur system may well be employed to design thioglycoside-based one-pot oligosaccharide synthesis.

As could be summarized from the above results, *N*-trifluoromethylthiosaccharin **1** plus TMSOTf is a very mild and effective promoter and holds great potential in selective activation of thioglycosides with different reactivity. Although a thorough mechanistic investigation is pending, based on our previous work,[15] we proposed that the above glycosidation reactions proceed via the pathway outlined in Scheme 1. It is TMSOTf that enables thiosaccharin **1** to become a promoter as **1** alone cannot initiate the glycosidation reaction. The electrophilicity of **1** is enhanced in the presence of TMSOTf so that it can trifluoromethylthiolate the anomeric sulfur. The thioglycoside donor is then transformed into the sulfonium ion intermediate **37**, which subsequently collapses into an oxacarbenium ion **38** and ethyltrifluoromethyl disulphide ($EtSSCF_3$). Nucleophilic attack by an alcohol at the anomeric centre of **38** or other reactive



Scheme 1. Proposed mechanistic pathway for **1**/TMSOTf-promoted thioglycoside activation

intermediates, such as glycosyl triflate or acyloxonium ion in the case of neighbouring group participation, then gives the glycosidation product **39**. Meanwhile, thiosaccharin **1** is converted into saccharin after loss of SCF_3 group.

Conclusions

In conclusion, we have identified *N*-trifluoromethylthiosaccharin **1**, in the presence of catalytic amounts of TMSOTf, as a powerful reagent to activate a range of ethyl thiogylcosides with varying reactivity. Upon activation, these thioglycosides underwent glycosidation reactions with various glycosyl acceptors to give the desired disaccharides in good to very high yields. More interestingly, this new promoter system could selectively activate ethyl thioglycoside in the presence of phenyl thioglycoside with the same protecting group pattern. This orthogonal activation, in combination with our previous thioperoxide promoter system, can be readily utilized to design iterative one-pot oligosaccharide assembly, which is currently underway. Further investigation on the use of this new promoter system to achieve orthogonality within thioglycosides bearing different aglycon substituents is also in progress.

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Keywords: Thioglycoside activation; *N*-trifluoromethylthiosaccharin; Glycosidation reaction; Chemoselective glycosidation; Oligosaccharide

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