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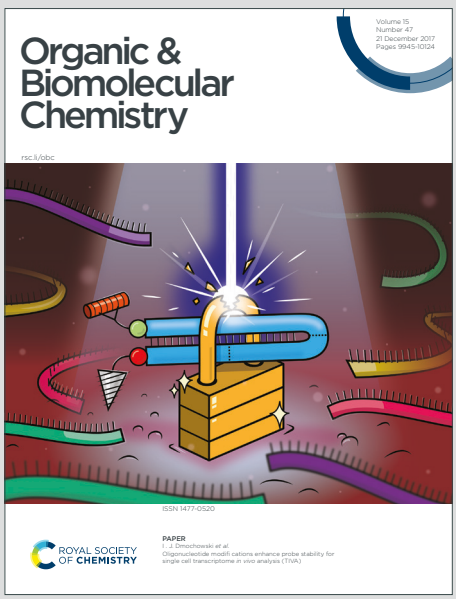

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Chemoselective Activation of Ethyl vs Phenyl Thioglycosides: One-pot Synthesis of Oligosaccharides

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Abstract:

Ethyl and phenyl thioglycosides are the two most common types of thioglycoside donors in carbohydragte chemistry, however, chemoselective activation of ethyl vs phenyl thioglycosides is very rare in the literature. In this work, ethyl thioglycosides could be readily activated with *N*-trifluoromethylthiosaccharin/TMSOTf system in the presence of phenyl thioglycosides carrying the same or even more arming protecting group pattern. Both armed and disarmed thioglycosides exhibited high chemoselectivity towards the promoter system. The chemoselective glycosylation was subsequently applied to one-pot synthesis, thus providing an efficient means to oligosaccharides.

Keywords: Thioglycoside; Chemoselective activation; *N*-trifluoromethylthiosaccharin; Glycosidation reaction; one-pot synthesis

Introduction

The construction of glycosidic bonds is the focal point in carbohydrate syntheses, and often requires exhaustive optimization of every parameter, such as leaving group, promoter and reaction temperature, with the target to achieve high yield and stereoselectivity.[1] A general glycosylation procedure is highly desirable but has not appeared yet. Thus, the development of new glycosylation methods and strategies are vital in carbohydrate chemistry in order to meet the intrinsic structural diversity of carbohydrates.[2] Unlike the glycosyl halide and glycosyl trichloroacetimidate donors, thioglycosides can serve not only as glycosyl donors but also as

glycosyl acceptors[3] due to the anomeric thioether group possessing great stability under a wide range of conditions for protecting group manipulation. As a result of their versatility, thioglycosides have often been used as key building blocks in the assembly of various complex oligosaccharides and have significantly improved synthetic efficiency. For example, a sulfated trisaccharide repeating unit of fucosylated chondroitin sulfate was synthesised efficiently in a one-pot manner with thioglycosides solely employed as the glycosyl donor.[4] More recently, thioglycosides were also used repeatedly as key building units in the synthesis of core trisaccharides derived from *Pseudomonas aeruginosa* O11 and *Staphylococcus aureus* type 5,[5] which are valuable structures for the development of carbohydrate vaccines and diagnostics. Undoubtedly, thioglycosides have proven and will continue to be one of the most versatile and frequently employed glycosyl donors.

Because of their inherent stability, reactivity tuning strategies to selectively activate one thioglycosyl donor over another are very attractive as they can offer flexible oligosaccharide sequencing. Such selective activation approaches of thioglycosides have been well documented in the literature, as reported in Wong's programmable one-pot synthesis[6] and Demchenko[7] and Bol's[8] work on superarmed donors. Extensive work in this area has been focused on controlling the reactivity of donors by choice of protecting group employed and induction of conformational change on glycosides.

On the other hand, selective activation of similarly protected thioglycosides through the exclusive use of leaving groups, remains relatively unexplored. There are a few reports of such a strategy used to chemoselectively activate thioglycosides. Boons and co-workers realised the effect of substituent size on the anomeric reactivity of thioglycoside donors by introducing a bulky dicyclohexylmethylthio group onto the anomeric position which had an adverse effect on its reactivity,[9] and ultimately led to a chemoselective glycosylation. Modulating the electronic properties of arylthio aglycons has also been explored. *p*-Acetamidophenyl thioglycosides can be selectively activated in the presence of electronically deactivated *p*-nitrophenyl thioglycosides, and the resulting disaccharide can subsequently be reduced and acetylated to give another *p*-acetamidophenyl thioglycoside for chain elongation.[10] Similarly, a series of *p*-substituted phenyl thioglycosides differing only in the aglycon substituents were also prepared and investigated towards donor differentiation,[11] and ultimately led to the design of a one-pot oligosaccharide synthesis.[12] Another relevant investigation carried out by Lahmann and co-workers focused on the reactivity of anomeric thioether groups, which led to a successful chemoselective activation of an ethyl thioglucoside in the presence of a *p*-

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bromophenyl thioglucoside.[13] Recently, orthogonal activation of glycosyl thioimidates and ethyl thioglycosides was also achieved using different types of activation conditions and applied successfully to an expeditious sequential synthesis of a hexasaccharide.[14]

Ethylthio and phenylthio groups are the most commonly employed leaving groups of choice and thus are the most widely used thioglycoside donors.[1a] It is the commercial availability of ethane thiol and thiophenol and the simplicity of preparation of such donors[15] that has popularized the use of ethyl and phenyl thioglycosides. Unfortunately, the selective activation of ethyl over phenylthioglycosides bearing similar protecting group patterns is scarcely seen in literature, even though it is strategically attractive and may add great value to the two most common thioglycoside donors. To the best of our knowledge, there is only one report on selective activation of anomeric ethylthio in the presence of phenylthio, in which an N^+-thiophilic reagent *O*-mesitylenesulfonylhydroxylamine was used to discriminate between an armed ethyl and armed phenyl thioglucoside.[16]

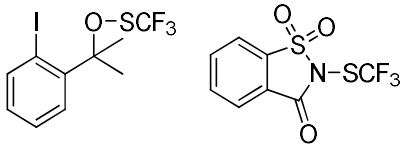
Albeit high stability, thioglycosides can be activated effectively by numerous promoters, but most of them, such as *N*-iodosuccinimide (NIS) plus a catalytic amount of protic acid or Lewis acid, may be too robust to be employed for chemoselective activation of anomeric ethylthio versus phenylthio groups. NIS in conjunction with TMSOTf was used recently to selectively activate ethyl thioglycosides with the same protecting group patterns,[17] in which a great disparity in reactivity between the two anomeric ethylthio groups was mediated by anomeric configuration and resulted in a successful chemoselective activation. However, the reactivity difference between ethyl and phenyl thioglycosides with the same protecting group patterns and anomeric configuration is subtle, and likely not sufficient to be discriminated by most promoter systems.

Results and Discussion

Two effective thioglycoside activation systems, both involving electrophilic trifluoromethylthiolating reagents[18] (Figure 1) have been developed recently in our laboratory.[19,20] A thioperoxide reagent **1** in combination with TMSOTf was first found to be a powerful thiophilic system, capable of activating different thioglycosides including armed and disarmed phenyl thioglycosides.[19] More recently, *N*-trifluoromethylthiosaccharin **2**, a more attractive reagent than **1** and most commonly used promoters in its ease of preparation and shelf stability, was used to activate a range of ethyl thioglycosides in the presence of a catalytic

amount of TMSOTf.[20] Upon activation, these thioglycosides underwent glycosidation reactions with various glycosyl acceptors in CH_2Cl_2 to give the desired disaccharides in good to very high yields. All reactions proceeded cleanly as a result of saccharin precipitating out of solution as a byproduct, thus minimising side product formation. In addition to CH_2Cl_2, participating solvents CH_3CN and Et_2O were also employed as cosolvents in order to determine their effect on the stereoselectivity of the glycosidation reactions (see Supporting Information).

Figure 1. Structures of thioperoxide **1** and *N*-trifluoromethylthiosaccharin **2**.



1 **2**

Interestingly, no activation of a disarmed phenyl thioglycoside was observed in the presence of **2**/TMSOTf, as reported in our previous communication.[20] Despite this low reactivity, we felt that we could turn it into an advantage. Hence, two successful chemoselective activations of disarmed ethyl thioglycoside donors in the presence of disarmed phenyl thioglycoside acceptors were achieved under the new activation condition.[20] Motivated by these results, we decided to pursue approaches to chemoselective glycosylations, and wish to report here *N*-trifluoromethylthiosaccharin **2** as an effective promoter for selective activation of anomeric ethylthio in the presence of phenylthio leaving groups. Its differentiating ability towards anomeric ethylthio vs phenylthio was also exploited in the design of an iterative one-pot oligosaccharide assembly.

Our initial investigation was to gain an insight into the observed chemoselectivity of an ethyl thioglycoside over a phenyl thioglycoside. As shown in Table 1, two sets of competition experiments were carried out with a view to compare the reactivity of disarmed (**3** vs **5**) and armed (**4** vs **6**) thioglucoside donors, respectively. The equimolar (1.1 eq.) mixture of ethyl and phenyl thioglycosides were treated with the new promoter system, i.e. **2** and TMSOTf, in the presence of one equivalent of glucosyl acceptor **7**. Both reactions were quenched after 40 minutes. The unreacted donors were recovered and their relative reactivity was determined by examination of the relative intensities of representative peaks on the ^{1}H NMR spectra. As displayed in Table 1, both thioglycoside pairs

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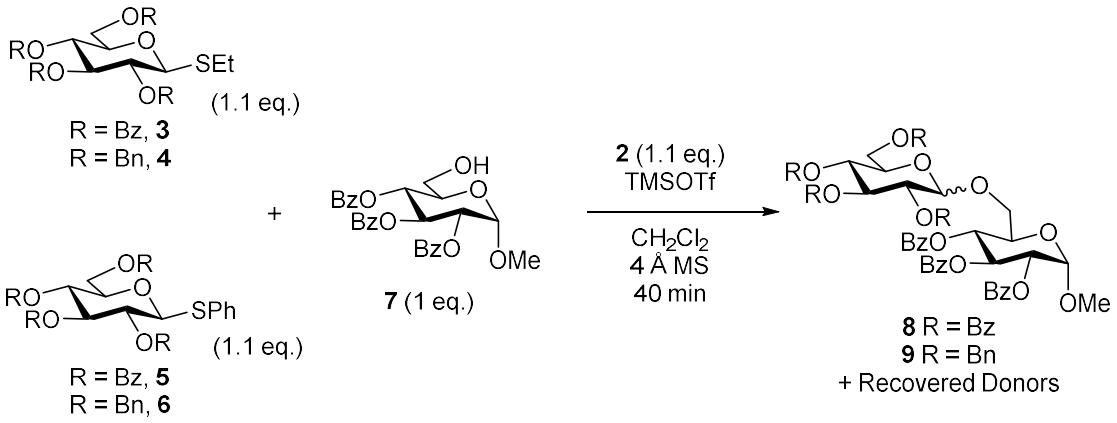
Table 1. Competitive glycosylation between ethyl and phenyl thioglucosides.



Entry	Donor **A**	Donor **B**	TMSOTf (eq.)	Temp (°C)	Yield[a] (α:β)	Recovery Ratio[b] (**A**:**B**)
1	**3**	**5**	1.0	0 °C to rt	63% (β only)	1 : 3
2	**4**	**6**	0.6	0 °C	81% (2:1)	1 : 12

[a]Calculated from isolated product mass following column chromatography. [b]Determined by integration of representative signals in the ^{1}H NMR; refers to the ratio of unreacted donors (donor **A** : donor **B**) after quenching.

demonstrated a significant difference in reactivity towards the new activation conditions. Both armed and disarmed ethyl thioglucoside donors could be preferentially activated with **2**/TMSOTf in the presence of the corresponding phenylthioglucoside donors. Although the recovery ratio for **3** and **5** may seem poor at first glance, this is a consequence of the lower reactivity of disarmed donors and the sluggish nature of this competitive reaction leading to incomplete conversion. Meanwhile, we were very pleased to observe the greater degree of selectivity for the armed donor **4** over **6** (Table 1, entry 2). Despite being the more reactive pair of the two, the armed donors showed a higher degree of selectivity under the present activation condition. Apparently, the preferential activation of ethyl over phenyl thioglycosides exhibited by the promoter stems from the higher nucleophilicity of the anomeric sulfur in the ethyl thioglycosides, and it is the extent of this promoter's influence that has made chemoselective activation and one-pot synthesis feasible (*vide infra*). The competitive experimental results indicated that *N*-trifluoromethylthiosaccharin-controlled selective activation could potentially serve as an invaluable extension to reactivity-based oligosaccharide synthetic strategies.

Encouraged by the above results, a series of thioglycoside donors and thioglycoside acceptors were then prepared in order to further explore the scope and generality of the new promoter system in selective activation of ethyl vs phenyl thioglycosides. Previous work[20] has shown disarmed ethyl thioglycosides donors could be effectively activated by promoter **2** in the presence of catalytic amounts of TMSOTf, with disarmed phenyl thioglycoside donors being relatively inert under the same activation conditions. This prompted us to test first the chemoselective activation between disarmed ethyl thioglycoside **3** and phenyl thioglycoside **12** (Table 2, entry 1). To our delight, the reaction proceeded smoothly under the action of promoter **2** and a stoichiometric amount of TMSOTf at room temperature, and the desired disaccharide **17** was isolated in very high yield.

Next, to validate the high selectivity observed above between armed thioglycosides **4** and **6**, phenyl thioglycoside **13** bearing a highly reactive protecting group pattern was selected as the acceptor to see if it could couple with ethyl thioglycoside **4** under similar reaction conditions (Table 2, entry 2). Hence, a mixture of **13** and **4** was treated with **2** and catalytic amount of TMSOTf at 0 °C, and as expected, the desired product **18** was formed in very good yield. This is a very promising result as it highlights the opportunities of performing such chemoselective glycosylation on other superarmed phenyl thioglycosides. Moreover, the unreacted phenyl thioglycoside **13** could be easily recovered and the yield was much higher based on the recovered material. It should be noted here that trace activation of **13** was also detected by TLC if the reaction time was prolonged.

We subsequently investigated the use of phenyl thiogalactosides **14** and **15** as acceptors, which represent typical equatorial and axial hydroxy groups, respectively (Table 2, entries 3 and 4). When a mixture of **4** and **14** was subjected to the above reaction conditions, the desired disaccharide **19** was efficiently obtained as an α/β mixture in 82% yield. It is worth noting that the α-stereoselectivity (α/β 5:1) observed in the formation of **19** was quite high for a normal glycosidation reaction without neighbouring group participation and solvent assistance etc. We speculated that the high stereoselectivity outcome could be attributed to the mildness of the activation conditions plus the relatively weak nucleophilicity of the acceptor.[21] Likewise, chemoselective activation of ethyl thioglycoside **4** in the presence of phenyl thioglycoside **15** was also successfully achieved under the same conditions, and the disaccharide **20** was produced again in very good yield (63%) and α-selectivity (α/β 3:1). Man*α*(1→2)Man oligomers are interesting structures for constructing multivalent systems mimicking high

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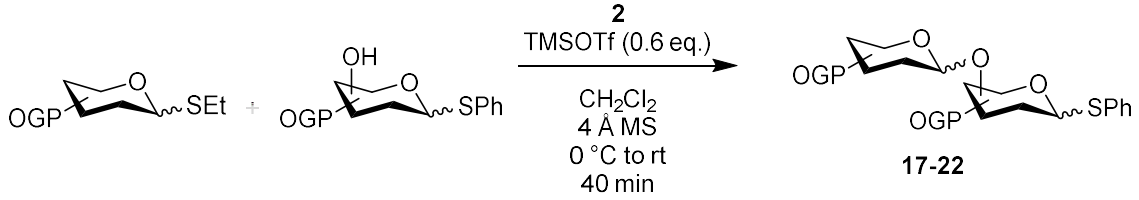
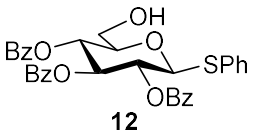
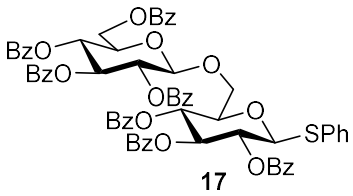
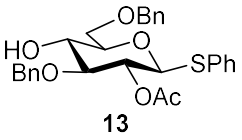
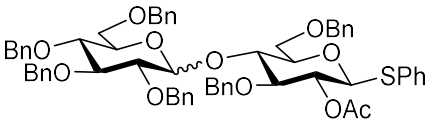
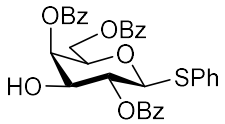
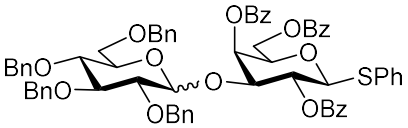
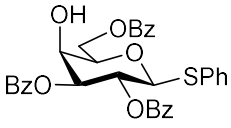
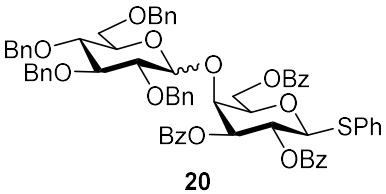
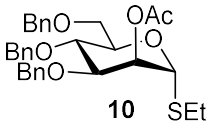
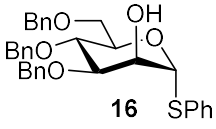
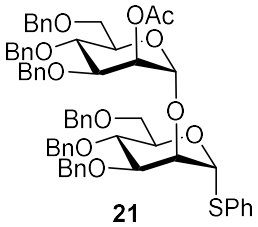
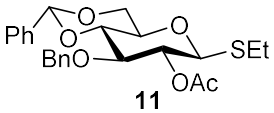
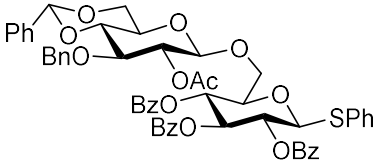
Table 2. Chemoselective activation of ethyl vs phenyl thioglycosides using **2**/TMSOTf.



Entry	Donor	Acceptor	Product	Yield	α/β[d]
1[a]	**3**	 **12**	 **17**	78%	β
2[b]	**4**	 **13**	 **18**	58%	1.5:1
3	**4**	 **14**	 **19**	82%	5:1
4	**4**	 **15**	 **20**	63%	3:1
5[b]	 **10** SEt	 **16** SPh	 **21**	59%	α
6[c]	 **11**	**12**	 **22**	73%	β

[a]1.0 eq. of TMSOTf added to reaction. [b]Temperature of reaction: 0 °C. [c]Temperature of reaction: -25 °C to -15 °C. [d] Determined by integration of representative signals in the ^{1}H NMR.

mannose interactions.[22] For this reason, ethyl thiomannosyl donor **10** and phenyl thiomannosyl acceptor **16** were also selected for the chemoselective activation with a view to construct oligomannosides in a highly efficient way. As shown in entry 5 in Table 2, the coupling of **10** with **16** also met with success under the same conditions producing the desired disaccharide **21** in 59% yield. It should be mentioned here that the reaction time was critical to eliminate unwanted activation of thioglycoside **16**.

To demonstrate the compatibility of acid-sensitive protecting groups with this new chemoselective glycosylation strategy, the 4,6-*O*-benzylidenated ethyl thioglycoside donor **11** was also prepared as the last example and reacted with phenyl thioglycoside **12**, as shown in entry 6 in Table 2. Again, upon treatment with promoter **2** and catalytic amounts of TMSOTf, the reaction led to the formation of the desired disaccharide **22** in very high yield. Slow dropwise addition of the solution of TMSOTf in CH_2Cl_2 at low temperature facilitated this chemoselective glycosylation. Conceivably, all the above disaccharides **17** - **22** could be used immediately as thioglycoside donors to construct more complex oligosaccharides, which, plus the ready availability of ethyl and phenyl thioglycosides, suggests that the present chemoselective glycosylation protocol may provide a convenient and efficient means to oligosaccharides.

The high degree of chemoselectivity in the above reactions led us to explore this selective glycosylation protocol further in the context of one-pot oligosaccharide chemistry. In addition, we would like to probe the question whether the present promoter system would be compatible with other commonly used promoters for thioglycoside activation, ideally those that can sequentially activate anomeric phenylthio leaving group in the same pot reaction. Possessing such compatibility would allow this new chemoselective glycosylation to be used as an extension to reactivity based one-pot oligosaccharide synthesis, thereby expanding further thioglycoside chemistry. For this purpose, ethyl thioglycoside **3**, phenyl thioglycoside **12** and methyl glycoside **7** were first chosen to undergo a sequential one-pot assembly, as illustrated in Scheme 1. Following the above chemoselective activation procedure, a mixture of thioglycosides **3** and **12** was first treated with thiosaccharin **2** in the presence of a stoichiometric amount of TMSOTf. Upon the complete conversion of donor **3** and the formation of disaccharide **17** as indicated by TLC, acceptor **7** and thioperoxide **1** were added successively into the mixture. It should be noted that thioperoxide **1**, belonging to the same family of trifluoromethylthiolating reagents as **2**,[18] was reported earlier to be capable of activating phenyl thioglycosides.[19] As expected, the desired trisaccharide **23** was produced in very good yield

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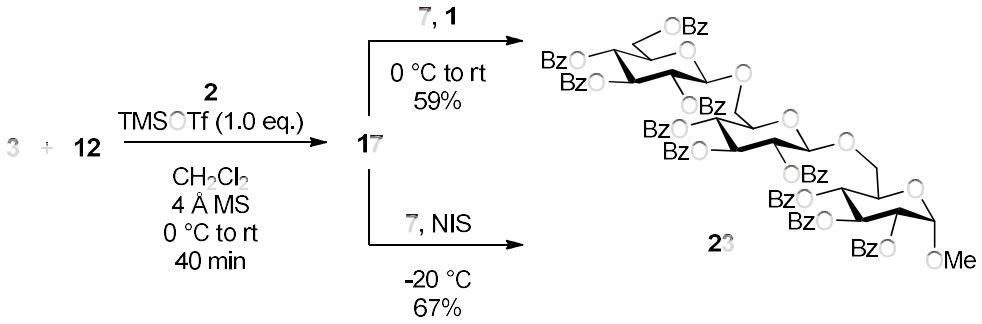
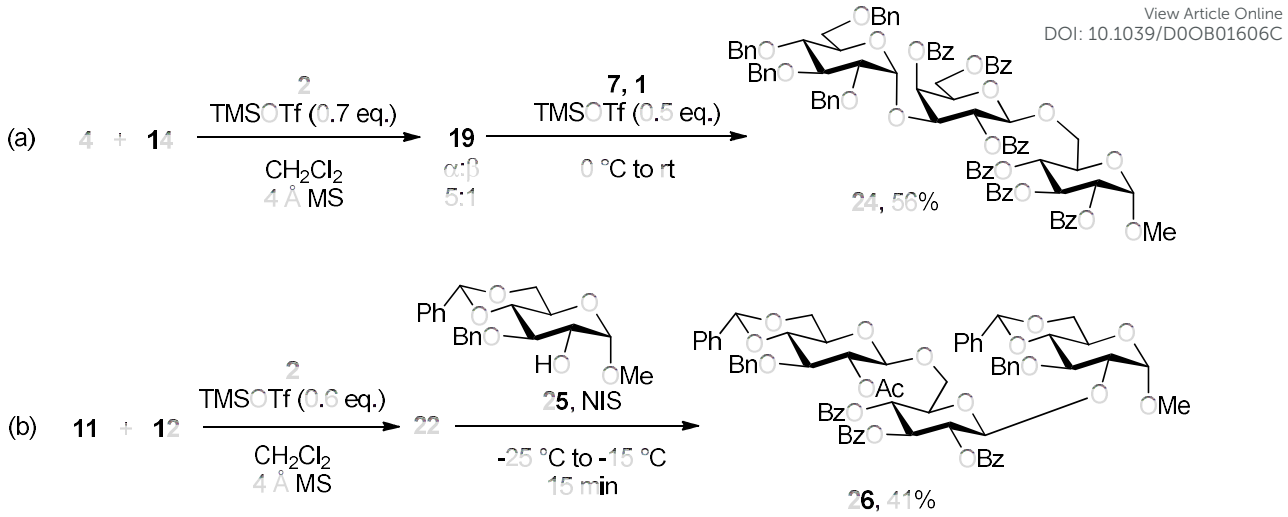
over two glycosidation steps. To further demonstrate the compatibility of the thiosaccharin system, NIS was also introduced instead of thioperoxide **1** into the above one-pot synthesis. Again, TLC indicated a clean reaction and the target trisaccharide **23** was produced smoothly in high overall yield. Here it is worth mentioning that the precipitation of saccharin in the first glycosidation step may be crucial to the success of the one-pot chemistry as insoluble saccharin could not interfere with the subsequent glycosidation step, thereby reducing the occurrence of side reactions. This sequential assembly involving chemoselective activation of ethyl vs phenyl thioglycosides thereby provides an attractive alternative in the synthesis of oligosaccharides.

Scheme 1. One-pot synthesis of trisaccharide 23.



To further demonstrate the effectiveness of the chemoselective glycosylation and the power of the one-pot synthesis, we proceeded to use **4**, **14**, **11** and **12** as thioglycosides in the one-pot synthesis of oligosaccharides. As shown in Scheme 2, coupling of thioglycosides **4** and **14** was first conducted under the above chemoselective activation conditions to generate disaccharide **19**, which was then activated by thioperoxide **1** in the presence of acceptor **7**, to give the desired trisaccharide **24** in 56% overall yield. Similarly, glycosylation of phenyl thioglycoside **12** with ethyl thioglycoside **11** was also carried out as part of the one-pot synthesis of trisaccharide **26**. Upon the formation of disaccharide **22** under thiosaccharin activation conditions, benzylidene-protected acceptor **25** and NIS were added successively into the reaction mixture. Fortunately, both benzylidene protecting groups survived under the current conditions containing catalytic amounts of TMSOTf and trisaccharide **26** was isolated in 41% overall yield.

Scheme 2. One-pot synthesis of trisaccharides **24** and **26**.



In conclusion, this investigation has demonstrated the power of *N*-trifluoromethylthiosaccharin **2** in the chemoselective activation of ethyl thioglycosides over phenyl thioglycosides in glycosylation reactions. The source of this differentiation stems from the higher nucleophilicity of the anomeric sulfur in the ethyl thioglycosides, and the extent of this preferential activation was applicable to both armed and disarmed ethyl thioglycosides. This reagent controlled chemoselective glycosylation was demonstrated through coupling of various ethyl thioglycoside donors and phenyl thioglycoside acceptors to give their corresponding disaccharides in good to high yields. Finally, the chemoselective glycosylation protocol was explored in the context of one-pot oligosaccharide chemistry with thiosaccharin **2** and thioperoxide **1** or NIS as promoters. Not only did we demonstrate the simplicity of the design and success of these oligosaccharide assemblies, but also the potential flexibility and future of thiosaccharin **2** with other common promoters. We believe that this straightforward chemoselective system will expand greatly thioglycoside chemistry and serve as an extension to reactivity-based one-pot oligosaccharide strategies.

Conflicts of interest

The authors state that there are no conflicts to declare.

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Ethyl thioglycosides could be selectively activated in the presence of phenyl thioglycosides carrying the same or even more arming protecting group pattern.