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Catalytic Glycosylation with Glycosyl Thioimidate Donors

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A new class of glycosyl thioimidates, glycosyl *N*-phenyl-trifluorothioacetimidates, were prepared from the readily available glycosyl thiols in excellent yields. These imidates exhibited very good donor properties under the action of catalytic amounts of $BF_3{\cdot}Et_2O$, and the corresponding glycosidation products were formed in very good to excellent yields. Thus, the first catalytic glycosylations with glycosyl thioimidate donors were achieved.

Introduction

Glycoside bond formation is often the key step in most carbohydrate syntheses. Since the first historical glycoside syntheses by Michael[1] and Fischer,[2] followed by the seminal work of Koenigs and Knorr,[3] a very large number of glycosylation methods have been reported in the literature.[4] However, a general glycosylation procedure has not appeared yet, and even for the construction of a simple glycosidic bond, the optimization of every parameter, such as leaving group, promoter and glycosidation conditions, is sometimes crucial for achieving high yield and stereoselectivity. Thus, new glycosylation methods and strategies are still welcome in carbohydrate chemistry in order to meet the intrinsic structural diversity of carbohydrates.[5]

Among all the glycosylation methods developed to date, glycoside synthesis based on glycosyl imidates, particularly trichloroacetimidates, are probably the most popular and powerful. Glycosyl trichloroacetimidates,[6] introduced by Schmidt in 1980, exhibit outstanding donor properties and usually result in high product yields and high anomeric stereocontrol during glycosidation reactions.[7] In particular, they exhibit a great advantage in terms of the amount of the promoter used, as catalytic amounts of a promoter are usually sufficient to provide their high glycosyl donor properties, whereas other glycosyl donors, such as glycosyl halides and thioglycosides, generally require equimolar or even excess amounts of a promoter system. Needless to say, this catalytic characteristic is very important from the viewpoint of performing the glycosidation reaction on an industrial scale. Trichloroacetimidates have thus become one of the most widely used glycosyl donors in contemporary carbohydrate chemistry.

In 1983, Schmidt reported another type of glycosyl imidates, trifluoroacetimidates,[8] and investigated the glycosylating properties of a series of different *N*-substituted glycosyl trifluoroacetimidates, including the most common glycosyl *N*-phenyl-trifluoroacetimidates. As trichloroacetimidate analogues, trifluoroacetimidates could also be activated with catalytic amounts of promoters, and they have even shown advantages over trichloroacetimidates in the synthesis of some specific glycosides.[9] In the course of trichloroacetimidate glycosidation, a certain amount of an *N*-glycoside byproduct is occasionally produced by the glycosylation of trichloroacetamide liberated from the donor.[10] Particularly, this side reaction takes place when the acceptor is of low nucleophilicity or sterically hindered; however, this side reaction is diminished in trifluoroacetimidate glycosidation due to the lower N basicity and/or the presence of an N substituent.

With a view to expand the arsenal of catalytic glycosylation methods, and to carry forward the advantage of trifluoroacetimidate glycosylation, we present here a new class of glycosyl thioimidates as glycosylating agents, glycosyl trifluorothioacetimidates, which can be activated effectively with catalytic amounts of a promoter.

Results and Discussion

Glycosyl thioimidates are a class of glycosides bearing a $SCR_1{=}NR_2$ aglycon. Their preparation dates back to over 40 years ago,[11] and their use as glycosyl donors may date back to the early 1980s when Woodward et al. employed N-heterocyclic thioglycosides as glycosylating agents in the total synthesis of erythromycin.[12] Recently, the glycosyl donor properties of glycosyl thioimidates have been investigated extensively, most notably by Demchenko and cowork-

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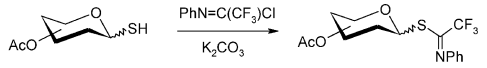
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

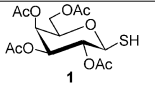
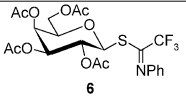
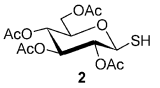
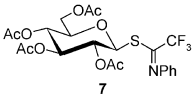
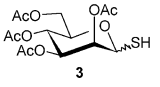
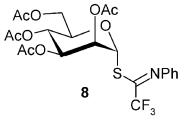
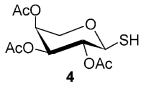
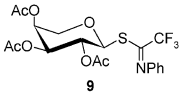
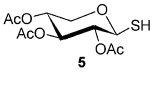
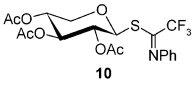
ers.[13] For instance, *S*-benzoxazolyl glycosides were employed as donors and activated with an excess amount of MeOTf or AgOTf in the synthesis of both 1,2-*trans* and 1,2-*cis* glycosides.[14] *S*-Thiazolyl glycosides have also proved to be efficient glycosyl donors under the activation of different promoter systems, providing the corresponding glycosides with various acceptors in high yields.[15] In addition, thioimidates have been utilized to develop rapid synthetic routes to oligosaccharides by incorporating different synthetic strategies, such as chemoselective activation and conventional armed–disarmed strategies.[16] As such, thioimidate donors hold great promise in carbohydrate chemistry. However, in all the reported thioimidate glycosidations, stoichiometric amounts of promoters were absolutely necessary. The common thiophilic reagents, NIS/catalytic TfOH, could not even initiate the glycosidation of *S*-thiazolyl donors, and the reaction could only be driven to completion by NIS/stoichiometric TfOH.[15] Therefore, it is of great interest to develop a new class of thioimidate donors that are readily activated by catalytic amounts of promoters.

Considering the above-mentioned advantage of trifluoroacetimidate donors, we speculated that glycosyl trifluorothioacetimidates may be activated in the presence of catalytic amounts of a Lewis acid, because the strong electron-withdrawing trifluoromethyl group could reduce the nucleophilicity of the liberated thioamide during activation. To verify this, we prepared a range of glycosyl *N*-phenyl-trifluorothioacetimidates **6**–**10**, as shown in Table 1, from the corresponding glycosyl thiols **1**–**5**. In practice, the thiols, such as galactosyl thiol **1** (Table 1, Entry 1), were treated with *N*-phenyl trifluoroacetimidoyl chloride and K_2CO_3 in acetone following the previous procedure[17] to give the desired glycosyl *N*-phenyl-trifluorothioacetimidates, such as compound **6**, in excellent yields. It is important to note that many glycosyl thiols are commercially available, or can be easily prepared by different procedures.[18] Moreover, both α- and β-glycosyl thiols are available;[19] they are quite stable and do not mutarotate even under basic conditions. Therefore, both α- and β-thioimidates could be readily prepared in this way. This will be conducive to future studies on the reactivity differences between α- and β-donors, and also to some specific cases in which only anomerically pure α- or β-donors can be used.

With the thioimidates in hand, their glycosylation properties were then investigated. As anticipated, activation of galactosyl thioimidate **6** with catalytic amounts of $BF_3{\cdot}Et_2O$ (0.1 equiv.) in the presence of methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**11**) gave rise to disaccharide **12** in 67% yield (Table 2, Entry 1). Glycosylation of **11** with glucosyl thioimidate **7** with promotion by catalytic amounts of $BF_3{\cdot}Et_2O$ (0.1 equiv.) also generated desired disaccharide **13** smoothly in very good yield. The complete 1,2-*trans* stereoselectivity observed in all the glycosidation reactions in this report is attributed to the assistance of the participating acetyl group at the C-2 position. The ready formation of **12** and **13** offered a preliminary suggestion that the present thioimidates may be another type of catalytically activated glycosylating agent. Indeed, all other investigated thioimidates **8**–**10** could be activated effectively under the same conditions, and the corresponding glycosidation products **13**–

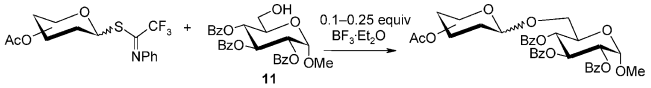
Table 1. Preparation of glycosyl *N*-phenyl-trifluorothioacetimidates.[a]

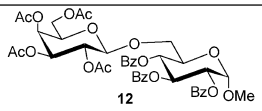
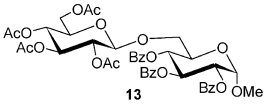
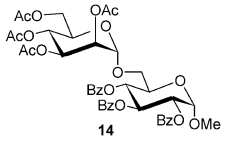
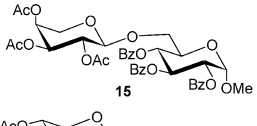
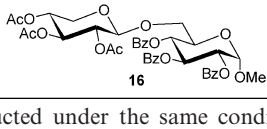


Entry	Substrate	Product	Yield [%][b]
1	 **1**	 **6**	96
2	 **2**	 **7**	98
3	 **3**	 **8**	60[c]
4	 **4**	 **9**	87
5	 **5**	 **10**	97

[a] All reactions were conducted under the same conditions; see Supporting Information for details. [b] Isolated yield following chromatography. [c] Yield of pure α-anomer.

Table 2. Catalytic glycosidations of thioimidates **6**–**10** with acceptor **11**.[a]



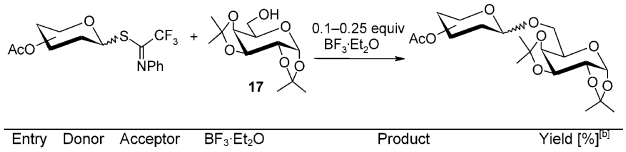
Entry	Donor	Acceptor	$BF_3{\cdot}Et_2O$	Product	Yield [%][b]
1	**6**	**11**	0.1 equiv.	 **12**	67
2	**7**	**11**	0.1 equiv.	 **13**	75
3	**8**	**11**	0.25 equiv.	 **14**	72
4	**9**	**11**	0.1 equiv.	 **15**	70
5	**10**	**11**	0.1 equiv.	 **16**	76

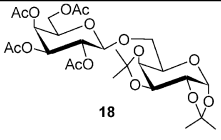
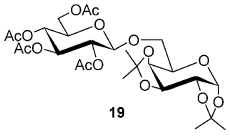
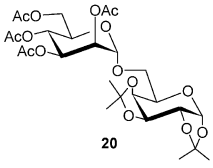
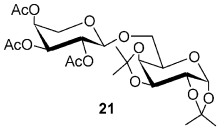
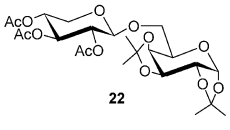
[a] All reactions were conducted under the same conditions; see Supporting Information for details. [b] Isolated yield following chromatography.

16 were produced in invariably good yields, as indicated in Table 2. Other common Lewis acids, such as TMSOTf and AgOTf, were also tested for the activation of all the thioimidates, but so far, $BF_3{\cdot}Et_2O$ has given the best results.

To further explore the glycosylating properties of this new class of thioimidates, we proceeded to use 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**17**) as the acceptor in the glycosidation reactions. Thus, reaction of donor **6** with **17** was conducted with $BF_3{\cdot}Et_2O$ (0.1 equiv.) as the promoter, and not unexpectedly, disaccharide **18** was produced in excellent yield (Table 3, Entry 1). Similarly, glycosidation of thioimidate **7** with **17** under the same conditions gave also the corresponding disaccharide **19** in almost quantitative yield (Table 3, Entry 2). In addition, excellent yields were also achieved for the glycosylation of **17** with thioimidate donors **8**, **9** and **10** under the present conditions, as shown in Table 3. These results, together with those in Table 2, are encouraging, as they demonstrate the feasibility of activating glycosyl thioimidates with catalytic amounts of promoters. Furthermore, the promising results suggest that these thioimidates could be applicable to more complex carbohydrate synthesis and may find their utility in modern carbohydrate chemistry.

Table 3. Catalytic glycosidations of thioimidates **6**–**10** with acceptor **17**.[a]



Entry	Donor	Acceptor	$BF_3{\cdot}Et_2O$	Product	Yield [%][b]
1	**6**	**17**	0.1 equiv.	 **18**	91
2	**7**	**17**	0.1 equiv.	 **19**	98
3	**8**	**17**	0.25 equiv.	 **20**	quant.
4	**9**	**17**	0.1 equiv.	 **21**	92
5	**10**	**17**	0.1 equiv.	 **22**	quant.

[a] All reactions were conducted under the same conditions; see Supporting Information for details. [b] Isolated yield following chromatography.

Conclusions

A new class of glycosyl thioimidates, glycosyl *N*-phenyltrifluorothioacetimidates, have been developed as glycosylating agents in this report. These thioimidates can be easily prepared from readily available glycosyl thiols in excellent yields and activated effectively with catalytic amounts of Lewis acid. To the best of our knowledge, this is the first report on catalytic activation of thioimidate donors. The availability, high stability and catalytic activation properties of this type of donor may render them a great use in carbohydrate synthesis. Studies on the application of this new glycosylation method to specific carbohydrate targets are in progress.

Supporting Information (see footnote on the first page of this article): General experimental procedures, as well as the characterization of all new compounds.

Acknowledgments

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