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Note

One-pot synthesis of per-*O*-acetylated thioglycosides from unprotected reducing sugars☆

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Abstract—A sequential per-*O*-acetylation and thioglycosidation of unprotected reducing sugars using a stoichiometric quantity of acetic anhydride and alkyl- or arylthiols is reported. These reactions, which are catalyzed by $BF_3{\cdot}OEt_2$, together constitute an efficient one-pot method for the synthesis of acetylated thioglycosides.

Keywords: Acetylation; Thioglycosides; One-pot; Stoichiometric; Unprotected sugars; $BF_3{\cdot}OEt_2$

There has been an explosive growth is the field of glycobiology in the last decade. Particular attention has been paid to complex carbohydrates, which play important roles in many biological recognition events including cell–cell adhesion, bacterial attachment, and viral infections.[1,2] Progress in the synthesis of complex oligosaccharides has been directly related to the development of new glycosylation methods. Per-*O*-acetylated sugars and thioglycosides have found enormous application in the synthetic carbohydrate chemistry especially in the synthesis of oligosaccharides.[3,4] Among glycosyl donors, thioglycosides are widely used because of their high degree of stability to many reaction conditions.

The method most often employed for the synthesis of thioglycosides is the treatment of per-*O*-acetylated sugars with alkyl/arylthiols or alkyl/aryl thiotrimethylsilanes in the presence of a Lewis acid.[5–7] An alternate method for the preparation of thioglycosides employs *S*-glycosylisothiourea derivatives generated from glycosyl halides.[8,9] Conventionally, preparation of thioglycosides from free sugars is achieved in two steps. The first step involves the per-*O*-acetylation of free sugars using an excess of acetic anhydride in the presence of a Lewis acid catalyst or pyridine and pyridine derivatives, which are toxic. This reaction requires a work-up consisting of neutralization of excess reagents and purification of the product prior to the next step. The second step involves the nucleophilic substitution of the anomeric acetate group by a thiol in the presence of a Lewis acid. Recently, two reports appeared in the literature that deal with the per-*O*-acetylation of free hexoses using a stoichiometric quantity of acetic anhydride catalyzed by $Cu(OTf)_2$[10] or iodine[11] and sequential substitution of anomeric acetate group to the thioglycosides in the presence of $BF_3{\cdot}OEt_2$ or excess iodine and hexamethyldisilane. In this context, it would be useful to employ an economical and convenient catalyst, which would promote both the per-*O*-acetylation as well as thioglycosylation steps in one-pot. To avoid the use of excess acetic anhydride and other toxic catalysts like pyridine and to shorten the synthesis of thioglycosides, we envisioned that the use of a stoichiometric quantity of acetic anhydride in the presence of $BF_3{\cdot}OEt_2$ followed by addition of a thiol would result in a one-pot preparation of acetylated thioglycosides. In an earlier report, $BF_3{\cdot}OEt_2$ has been used as a catalyst for acetylation of free hemiacetals and subsequent one-pot conversions to glycosyl bromides.[12] In this report, we describe an efficient one-pot preparation of per-*O*-acetylated thioglycosides from

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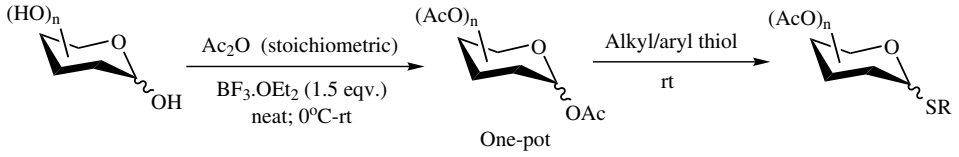


Scheme 1. One-pot sequential per-*O*-acetylation and thioglycosidation of unprotected sugars.

unprotected reducing sugars mediated by $BF_3{\cdot}OEt_2$ (Scheme 1).

To standardize the reaction protocol, $BF_3{\cdot}OEt_2$ (1.5 mmol) was added to a well-stirred suspension of D-glucose (1.0 mmol) in acetic anhydride (5.1 mmol) at room temperature. An exothermic reaction started immediately and a clear reaction mixture was obtained within few minutes with a clean formation of per-*O*-acetylated D-glucose (as detected by TLC). Reducing the quantity of $BF_3{\cdot}OEt_2$ from 1.5 equiv to 1.0 or 0.5 equiv led a slower reaction, which was not complete even after 24 h. After a series of experiments, it was observed that use of 1.5 equiv of $BF_3{\cdot}OEt_2$ and 1.02 equiv of acetic anhydride per hydroxy group of the free sugar produced excellent yield of per-*O*-acetylated products in a very fast and efficient reaction. Following similar reaction conditions, a series of monosaccharides, disaccharides, and trisaccharides have been successfully per-*O*-acetylated using a stoichiometric quantity of acetic anhydride within few minutes. All per-*O*-acetylated products of reducing sugars were obtained as a mixture of anomers that matched to authentic samples, which were prepared as previously reported.[13]

After the successful outcome of the per-*O*-acetylation of free sugars using stoichiometric acetic anhydride, we turned our attention to a one-pot synthesis of thioglycosides from reducing sugars, which proceeded via the per-*O*-acetylated sugars formed in situ. In contrast to conventional per-*O*-acetylation, where an excess of acetic anhydride is used and neutralization followed by work-up and purification is essential before the second step, in our method, the use of stoichiometric acetic anhydride and the $BF_3{\cdot}OEt_2$ already present in the reaction mixture allows a sequential per-*O*-acetylation–anomeric thiolysis to proceed in one-pot, without the need for the addition of more promoter. Therefore, after the complete per-*O*-acetylation of the free sugars (monitored by TLC), the alkyl or arylthiols (1.5 mmol/mmol of free sugar) were added and the reaction mixture was allowed to stir for the appropriate time (Table 1) to furnish thioglycosides. Following a similar reaction sequence, a series of aryl and alkyl thioglycosides were synthesized in a very efficient manner. Per-*O*-acetylated thioglycosides prepared from commonly available sugars gave acceptable ^1H NMR and ^{13}C NMR spectra that matched data reported in the cited references. In most of the cases, a single isomer, the 1,2-*trans*-thioglycoside, was obtained, which is due to the neighboring group participation of the acetyl group at C-2, followed by the attack of thiol. In the case of L-rhamnose monohydrate, a mixture of α- and β-thioglycosides were obtained after column chromatography, the ratio of which was determined by comparing the integration of resonances in the ^1H NMR spectrum. Although on a milligram scale, all acetylation reactions can be performed at room temperature, on a multigram scale it is necessary to cool the reaction mixture to avoid the loss of reagents and decomposition of products due to overheating that results from the exothermic reaction.

In summary, the present methodology offers a convenient way to prepare per-*O*-acetylated thioglycosides from the free sugars in one-pot using a stoichiometric acetic anhydride acetylation and sequential thiolysis. We feel this mild and operationally simple reaction protocol for the preparation of thioglycosides directly from free sugars will certainly find application in oligosaccharide syntheses.

1. Experimental

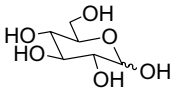
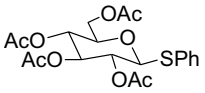
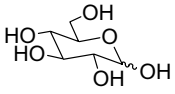
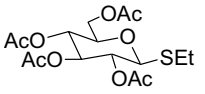
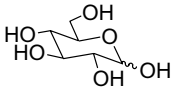
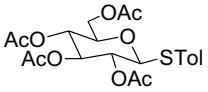
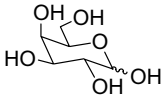
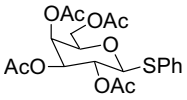
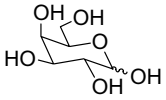
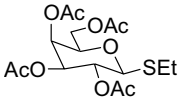
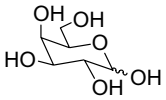
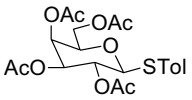
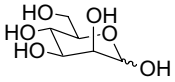
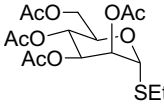
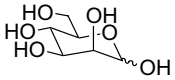
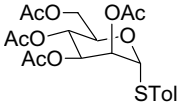
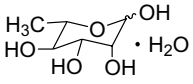
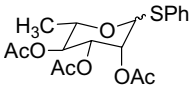
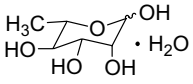
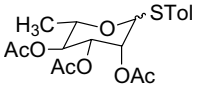
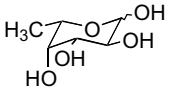
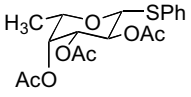
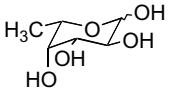
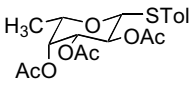
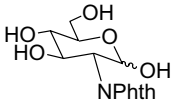
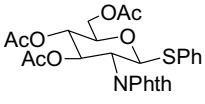
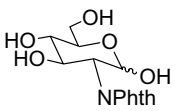
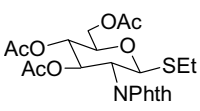
1.1. General methods

General methods were same as used previously.[14]

1.2. Typical experimental protocol for the preparation of per-*O*-acetylated thioglycosides: phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (2d)

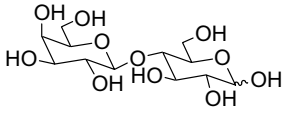
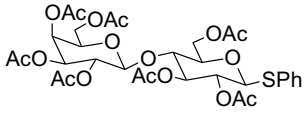
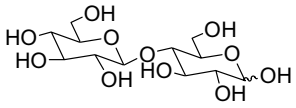
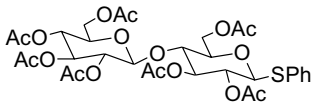
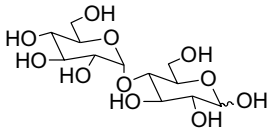
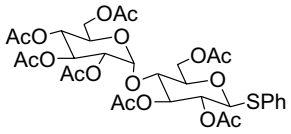
A suspension of D-galactose (1.8 g, 10.0 mmol) in Ac_2O (4.82 mL, 51.0 mmol) was placed in an ice bath with continuous stirring. To this cold suspension was added $BF_3{\cdot}OEt_2$ (1.9 mL, 15.0 mmol) in one portion. An exothermic reaction started immediately and the mixture was allowed to stir for 5.0 min. After completion of the reaction (as indicated by TLC, hexane–EtOAc 1:1), thiophenol (1.6 mL; 15.6 mmol) was added and the reaction mixture was allowed to stir for another 5 h. The reaction was quenched by addition of aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude reaction product by column chromatography on silica gel using hexane–EtOAc (3:1) as the eluant furnished pure phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**2d**), which could be crystallized from

Table 1. $BF_3{\cdot}OEt_2$ catalyzed sequential per-*O*-acetylation and thioglycosidation of free sugars for the preparation of thioglycosides in one-pot[a]

Entry	Sugars (**1**)	Thiols	Products (**2**)	Time (h)	Yield[b] (%)	Ref.
a		PhSH		5	90	7
b		EtSH		4	85	16
c		*p*-MePhSH		5	90	10
d		PhSH		5	90	15
e		EtSH		3.5	80	16
f		*p*-MePhSH		4	85	10
g		EtSH		4	80	5
h		*p*-MePhSH		4.5	75	10
i		PhSH		4	75 α/β 4:1	17
j		*p*-MePhSH		4	70 α/β 4:1	10
k		PhSH		4	80	18
l		*p*-MePhSH		4	75	10
m		PhSH		5	80	19
n		EtSH		5	85	6

(*continued on next page*)

Table 1 (*continued*)

Entry	Sugars (**1**)	Thiols	Products (**2**)	Time (h)	Yield[b] (%)	Ref.
o		PhSH		6	75	20
p		PhSH		6	70	20
q		PhSH		6	75	20

[a] All reactions were conducted at room temperature.
[b] Isolated yield.

Et_2O–hexane (3.9 g, 90%); mp 80–81 °C; $[\alpha]_D^{25}$ +14 (*c* 2.0, $CHCl_3$); lit.:[15] viscous oil; $[\alpha]_D^{25}$ +11.86 (*c* 1.6, $CHCl_3$).

Acknowledgments

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