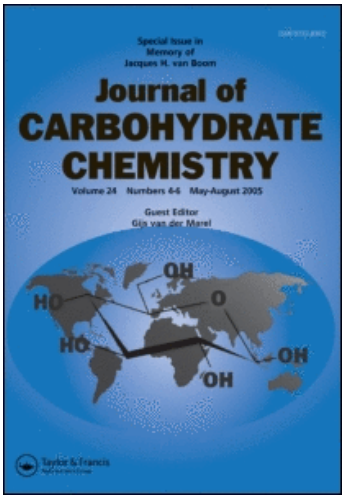

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Modified One-Pot Protocol for the Preparation of Thioglycosides from Unprotected Aldoses via *S*-Glycosyl Isothiouronium Salts

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Modified One-Pot Protocol for the Preparation of Thioglycosides from Unprotected Aldoses via *S*-Glycosyl Isothiouronium Salts

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An efficient one-pot protocol for the direct preparation of thioglycosides starting from unprotected reducing sugars via *S*-glycosyl isothiouronium salts is reported. In this one-pot methodology, $BF_3 \cdot OEt_2$ has been used as a general catalyst for both per-*O*-acetylation of sugars and conversion of sugar per-*O*-acetates into *S*-glycosyl isothiouronium salts, which was allowed to react with alkylating agents in the presence of a base to furnish thioglycosides in excellent yield.

Keywords Acetylation, Thioglycosides, One-pot, Stoichiometric, Aldoses, Thiourea, $BF_3 \cdot OEt_2$

INTRODUCTION

There has been explosive growth in the field of glycobiology in the last decade. Particular interest has been drawn to the complex carbohydrates, which play important roles in many biologic recognition events, including cell–cell adhesion, bacterial attachment, and viral infections.[1–4] In this context,

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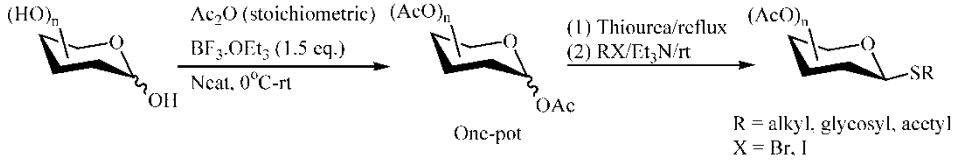
1-thiosugars have attracted considerable attention because of their close structural similarity to the natural *O*-glycosides. Due to the stability of thioglycosidic bond to enzymatic cleavage, thioglycosides have been considered as very promising candidates for the preparation of carbohydrate-based therapeutics.[5–9] Per-*O*-acetylated sugars and thioglycosides have found enormous applications in the field of synthetic carbohydrate chemistry, especially in the synthesis of oligosaccharides.[10–13] Among glycosyl donors, thioglycosides are widely used because of their high degree of stability in many organic reactions.

The most often employed approaches toward the synthesis of thioglycosides are the treatment of per-*O*-acetylated sugars with malodorous and toxic alkyl/aryl thiols or expensive alkyl/aryl thiotrimethylsilanes in the presence of a Lewis acid,[14–19] which often leads to the formation of anomerized products. Recently, we have emphasized the one-pot reaction protocol[20] for the preparation of acetylated thioglycosides directly from unprotected reducing sugars. However, the above-mentioned process had few limitations in the use of malodorous thiols and limited availability for carrying out a variety of reactions. As a result, we needed to develop a generalized reaction protocol for the preparation of a wide variety of thioglycosides without using malodorous and toxic thiols. Earlier, few reports appeared in the literature regarding the use of nonmalodorous thioglycoside donors in the glycosylation reactions, which involves the formation of *O*-methoxycarbonylphenyl thioglycoside from the corresponding glycosyl bromides and methylthiosalicylate.[21,22] However, a general method for the preparation of thioglycosides avoiding the use of the above-mentioned toxic thiols employs reaction of alkyl halides with *S*-glycosyl isothiouronium salts.[23–28] Conventionally, *S*-glycosyl isothiouronium salts are prepared from the reaction of thiourea with glycosyl halides, which are generally prepared from per-*O*-acetylated sugars. In practice, this environmentally safer preparation of per-*O*-acetylated thioglycosides from unprotected reducing sugars involves at least four steps consisting of (1) acetylation using excess acetic anhydride and pyridine or pyridine derivatives as solvent and activator despite their known toxicity and unpleasant odor, (2) bromination using HBr-AcOH, and (3) treatment of acetobromo sugar with thiourea followed by (4) the reaction of alkyl halide with the *S*-glycosyl isothiouronium salts, which require intermediate isolation and purification through conventional workup, causing the synthetic sequence to be tedious. Prompted by a recent report describing the reaction of glycosyl acetates with thiourea toward the formation of 1-thiosugars,[29] we have envisioned that the above-mentioned intermediate steps could be minimized by using a general catalyst for the acetylation and formation of *S*-glycosyl isothiouronium salts and reacting *S*-glycosyl isothiouronium salts produced in situ with alkylating agents in one-pot directly from free sugars. In the course of our ongoing thioglycoside syntheses using nonmalodorous reagents

in a minimum number of steps, we describe herein a modified one-pot protocol for the preparation of thioglycosides directly from unprotected reducing sugars.

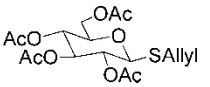
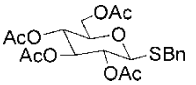
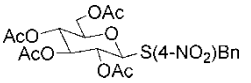
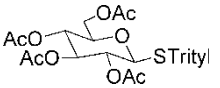
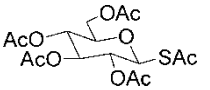
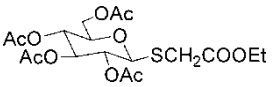
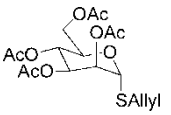
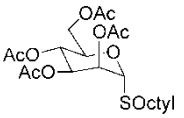
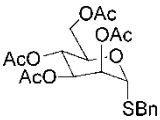
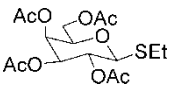
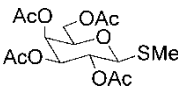
RESULTS AND DISCUSSION

To standardize the reaction protocol, $BF_3 \cdot OEt_2$ (1.5 mmol) was added to a well-stirred suspension of free sugar (1.0 mmol) in acetic anhydride (5.1 mmol) at rt. An exothermic reaction started immediately and a clear reaction mixture was obtained within a few minutes with a clean formation of per-*O*-acetylated sugar (TLC; hexane:EtOAc; 1:1). Reducing the quantity of $BF_3 \cdot OEt_2$ from 1.5 eq. to 1.0 eq. or 0.5 eq. led to a slow reaction, and the reaction was not complete even after 24 hr. After a series of experiments, it was optimized that use of 1.5 eq. of $BF_3 \cdot OEt_2$ and 1.02 eq. of acetic anhydride per hydroxy group of the free sugar produced excellent yield of per-*O*-acetylated products in a very fast and efficient manner. Although all acetylation reactions in milligram scale have been performed at rt, a cooling arrangement is required for the multigram scale to avoid the loss of reagents and decomposition of products due to overheating resulting from the exothermic reaction. After formation of the per-*O*-acetylated sugars using stoichiometric acetic anhydride, a small amount of CH_3CN was added to mobilize the thick syrupy mass of the sugar per-*O*-acetates. To the reaction mixture was added thiourea (2.0 eq.) and the reaction mixture was heated to 80°C for 15 min. TLC (EtOAc) showed complete conversion of sugar per-*O*-acetates to slower-moving *S*-glycosyl isothiouronium salts. The reaction mixture was cooled to rt and alkyl halides (1.5 eq.) were added to the reaction mixture followed by excess Et_3N. The above reaction mixture was allowed to stir at ambient temperature until *S*-glycosyl isothiouronium salts were consumed completely to a faster-moving component. After completion of the reaction as monitored by TLC (hexane: EtOAc 1:1), the solvent was evaporated and the resulting syrup was diluted with CH_2Cl_2 and washed with water, which on evaporation furnished pure alkyl thioglycoside in one-pot starting from free sugars. Following the similar reaction sequence, a series of alkyl and aralkyl 1,2-*trans*-1-thioglycosides were successfully synthesized starting from free sugars (Sch. 1, Table 1). Per-*O*-acetylated alkyl and aralkyl thioglycosides prepared from commonly



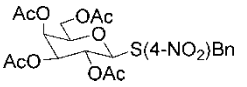
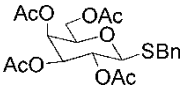
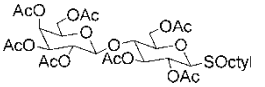
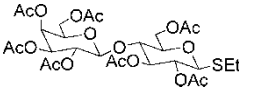
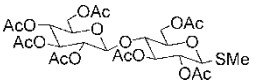
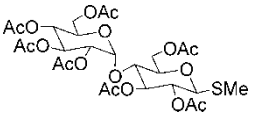
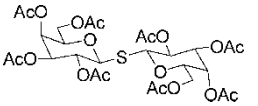
Scheme 1

Table 1: One-pot preparation of 1,2-*trans*-thioglycosides from unprotected reducing sugars via acetylation and formation of *S*-glycosyl isothiouronium salts.

Entry	Sugars (1)	Ac_2O (equiv)	Alkyl halides	Products (2)	Yield (%)	Ref.
a	D-glucose	5.1	Allyl bromide		92	(30)
b	D-glucose	5.1	Benzyl bromide		95	(30)
c	D-glucose	5.1	4-Nitro benzyl bromide		92	—
d	D-glucose	5.1	Trityl chloride		85	(27)
e	D-glucose	5.1	Acetic anhydride		95	(27)
f	D-glucose	5.1	Ethyl bromo acetate		92	(31)
g	D-mannose	5.1	Allyl bromide		90	(32)
h	D-mannose	5.1	Octyl bromide		90	(33)
i	D-mannose	5.1	Benzyl bromide		92	(34)
j	D-galactose	5.1	Ethyl bromide		95	(27)
k	D-galactose	5.1	Methyl iodide		90	(35)

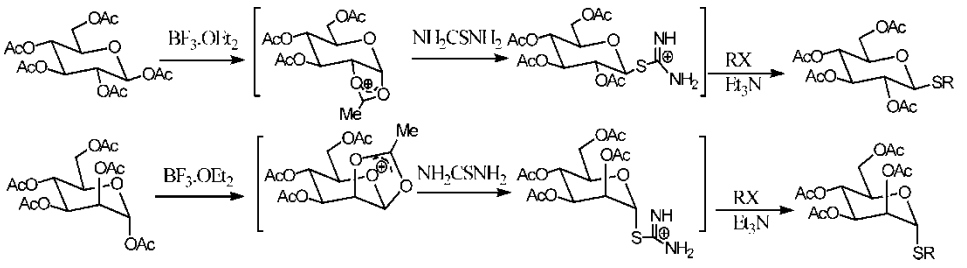
(*continued*)

Table 1: Continued.

Entry	Sugars (1)	Ac_2O (equiv)	Alkyl halides	Products (2)	Yield (%)	Ref.
l	D-galactose	5.1	4-Nitro benzyl bromide		95	(27)
m	D-galactose	5.1	Benzyl bromide		92	(30)
n	D-lactose	8.2	Octyl bromide		85	(36)
o	D-lactose	8.2	Ethyl bromide		90	(37)
p	D-cellobiose	8.2	Methyl iodide		85	(38)
q	D-maltose	8.2	Methyl iodide		92	(38)
r	D-galactose	5.1	Aceto bromo galactose		80	(39)

available sugars gave acceptable ^{1}H NMR and ^{13}C NMR spectra that matched data reported in the cited references. It is important to note that only single isomers of 1,2-*trans*-1-thioglycosides were obtained, which were confirmed from their NMR spectral data. This methodology has been further extended toward the synthesis of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 $\rightarrow$ 1)-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (Table 1, entry r) by reacting acetobromogalactose with D-galactosyl isothiouronium salt in the presence of Et_3N. Only a single β-linked disaccharide was isolated with no traces of formation of α-disaccharide, which was further confirmed from its NMR spectra that matched with the literature report.[39]

The exclusive formation of 1,2-*trans*-1-thioglycosides can be explained by considering the formation of 1,2-acyloxonium ions as the reaction intermediate as a result of neighboring group participation, which allows the approach of thiourea from one possible site to form 1,2-*trans*-*S*-glycosyl isothiouronium salts only. As *S*-glycosyl isothiouronium salts do not undergo anomerization



Scheme 2

as evident from the earlier report,[29] they always produce only a single isomer of 1,2-*trans*-1-thioglycosides on reacting with alkyl halides in the presence of a base (Sch. 2).

In summary, the present methodology offers a convenient one-pot protocol to prepare per-*O*-acetylated 1,2-*trans*-1-thioglycosides from the free sugars using a stoichiometric acetic anhydride and sequential thioglycosidation via *S*-glycosyl isothiouronium salt formation. This mild, operationally simple, one-pot reaction protocol for the preparation of thioglycosides directly from free sugars will certainly find application in oligosaccharide synthesis and carbohydrate-derived drug discovery programs. A series of thioglycosides prepared following the present protocol are under use in the oligosaccharide synthesis, which will be published in due course.

EXPERIMENTAL

General Methods

All the reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2 N H_2SO_4) sprayed plates in hot plate. Silica gel 230–400 mesh was used for column chromatography. FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon/Xenon (6 KV, 10 MA) as the FAB gas. ^1H and ^{13}C NMR was recorded on Brucker Advance DPX 200 MHz using TMS as internal reference. Chemical shift value is expressed in δppm. Elementary analysis was carried out on Carlo ERBA-1108 analyzer. Optical rotations were measured at 25°C on a Rudolf Autopol III polarimeter. Commercially available grades of organic solvents of adequate purity are used in many reactions.

Typical procedure for the preparation of 1,2-trans-1-thioglycosides

4-Nitrobenzyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (***2c***): A suspension of D-glucose (1.8 g, 10.0 mmol) in acetic anhydride (4.82 mL, 51.0 mmol)

was placed in an ice bath with continuous stirring. To the cold suspension of the reaction mixture was added $BF_3 \cdot OEt_2$ (1.9 mL, 15.0 mmol) at a time. An exothermic reaction started immediately and the reaction mixture was allowed to stir for 5.0 min. After completion of the per-*O*-acetylation (monitored by TLC; hexane:EtOAc 1:1), anhydrous CH_3CN (10.0 mL) was added to the reaction mixture followed by thiourea (1.52 g, 20.0 mmol) and the reaction mixture was placed on a preheated oil bath at 80°C for 15 min with constant stirring. After full consumption of the sugar per-*O*-acetates (as judged by TLC, EtOAc), the reaction mixture was cooled to rt. To the reaction mixture were added 4-nitrobenzyl bromide (3.24 g, 15.0 mmol) and Et_3N (5.0 mL) in succession and allowed to stir for 3 hr at ambient temperature. The solvent was evaporated and the resulting syrup was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude reaction product over SiO_2 using hexane-EtOAc (3:1) furnished pure 4-nitrobenzyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**2c**; 4.6 g; 92 %). Yellow oil. $[\alpha]_D^{25}$ -37° (*c* 1.0, $CHCl_3$); IR (Neat): 1752, 1522, 1348, 1225, 1042 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20–8.16 (d, $J = 8.5$ Hz, 2 H), 7.53–7.49 (d, $J = 8.5$ Hz, 2 H), 5.20–5.12 (t, $J = 9.0$ Hz each, 1 H), 5.10–5.0 (m, 2 H), 4.38 (d, $J = 8.0$ Hz, 1 H), 4.30–4.21 (dd, $J = 9.0$ and 4.5 Hz, 1 H), 4.18–4.10 (dd, $J = 12.0$ and 3.8 Hz, 1 H), 4.07–3.81 (dd, $J = 13.2$ Hz each, 2 H), 3.73–3.65 (m, 1 H), 2.10, 2.05, 2.03, 2.01 (4 s, 12 H); ^{13}C NMR ($CDCl_3$): δ 170.7, 170.3, 169.7 (2C), 147.6, 145.3, 130.3 (2C), 124.1 (2C), 82.2, 76.4, 73.9, 70.1, 68.6, 62.5, 33.1, 21.0, 20.9, 20.8 (2C); MS (FAB): m/z 500 [M + 1]; Anal. Calcd. for $C_{21}H_{25}NO_{11}S$ (499): C, 50.50; H, 5.04. Found: C, 50.25; H, 5.30.

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