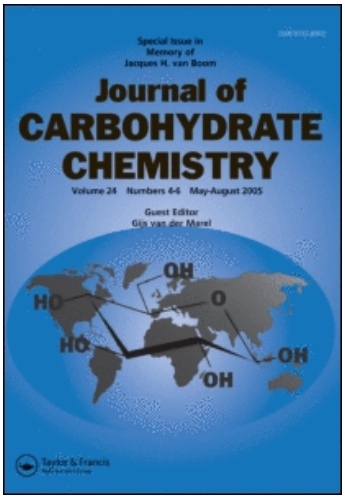

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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Online publication date: 21 August 2002

To cite this Article Fujihira, Takayoshi , Chida, Mitsutaka , Kamijo, Haruo , Takido, Toshio and Seno, Manabu(2002) 'NOVEL SYNTHESIS OF 1-THIOGLYCOPYRANOSES VIA THIOIMINIUM SALTS', Journal of Carbohydrate Chemistry, 21: 4, 287 — 292
To link to this Article: DOI: 10.1081/CAR-120013495
URL: http://dx.doi.org/10.1081/CAR-120013495

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JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 21, No. 4, pp. 287–292, 2002

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ABSTRACT

Methanolysis of a glycosylthioiminium salt, which was prepared from the reaction of acetohalogenosugar with thioacetamide, afforded the corresponding per-*O*-acetylated 1,2-*trans*-1-thioglycose in good yield after fractional crystallization. This synthetic method is very convenient in operation and proceeds without loss of acetyl groups, as the reaction is carried out under mild and neutral conditions.

Key Words: Synthesis; 1-Thioglycopyranose; Thioamide; Iminium salt

INTRODUCTION

1-Thioglycopyranoses are used as starting materials for the synthesis of various 1-thioglycosides; for example, glucosinolates,[1] carbohydrate clusters[2] and alkyl thioglycosides.[3] The 1-thioglycosides are useful as stable glycosyl donors for the synthesis of oligosaccharides.[4] Tetra-*O*-acetyl-1-thio-D-glucopyranose is usually prepared by alkali hydrolysis of the *S*-glucopyranosyl isothiouronium bromide[5] prepared from the reaction

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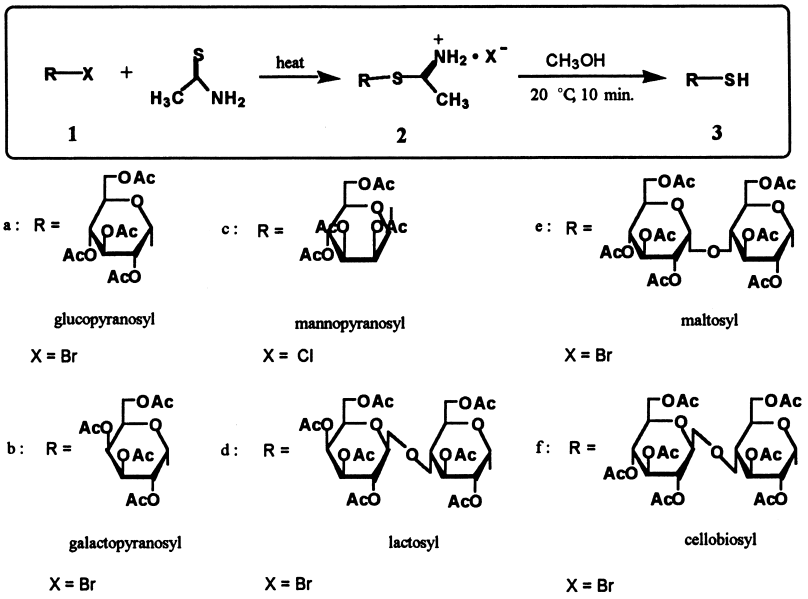
DOI: 10.1081/CAR-120013495 0732-8303 (Print); 1532-2327 (Online)

of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with thiourea. Other 1-thioglycoses are also prepared by similar methods.[1,7–10] It should be noted that, in the reaction with thiourea, the prolonged time required for decomposition of the thioisouronium salt brings about gradual hydrolysis of acetyl groups.[5] Very recently, the conversion of *S*-glycosyl isothiourea derivatives into thioglycosides without loss of acetyl groups was reported.[11]

We recently described the preparation of 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)ethaniminium bromide from the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with thioacetamide.[6] It was found in a subsequent study that the glycosylthioiminium salt affords tetra-*O*-acetyl-1-thio-β-D-glucopyranose by methanolysis. In this paper we report on this novel, simple and effective method for the synthesis of per-*O*-acetylated 1,2-*trans*-1-thioglycoses, including disaccharides.

RESULTS AND DISCUSSION

Per-*O*-acetylated glycopyranosyl bromides **1a** and **1b** were synthesized by the literature procedure[7] and other glycopyranosyl bromides **1d–1f** were similarly prepared.[8] Tetra-*O*-acetyl-β-D-mannopyranosyl chloride **1c** is commercially available. According to the method previously described,[6] 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylthio)ethaniminium bromide **2a** is prepared from tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a** and thioacetamide in a melt state without solvent or under reflux in dry benzene. As this thioiminium salt was gradually hydrolyzed in the presence of moisture in air, the glycosylthioiminium salt, which is an adduct of acetohalogenosugar and thioacetamide, was predicted to be easily decomposed by the addition of a nucleophilic reagent. It was found that **2a** was decomposed by the addition of methanol for a short time (ca. 10 min.) at 20°C to give tetra-*O*-acetyl-1-thio-β-D-glucopyranose. This synthetic method is applicable to other sugars **1b–1f** (see Scheme 1). In the case of monosaccharides **1a–1c**, freshly prepared and dried (anhydrous conditions) acetohalogenosugar and thioacetamide were stirred just above the melting temperature (ca. 120°C) in a dry nitrogen or argon stream. Although the starting materials (acetohalogenosugar and thioacetamide) were soluble in a warm nonpolar organic solvent (e.g., benzene), the reaction products were barely soluble. The products are mainly the thioiminium salts **2a–2c** as indicated by FAB-MS data; the fragment ion peaks of *m/z* 406 ($[M\text{-}Br^-]^+$) and 331 (pyranosyl ring cation) were clearly observed.[6] In the case of disaccharides **1d–1f**, the reaction was complete (the reaction mixture became solid and viscous) in approximately 3 h under reflux conditions in a small amount of dry benzene to give glycosylthioiminium salts. The reaction intermediates from disaccharides are presumed to be thioiminium salts as with monosaccharides, although their formation could not be detected by FAB-MS under the present reaction conditions. Side reactions such as the amino-carbonyl reaction were minimized under these conditions. When the reaction of disaccharides was carried out without solvent at an elevated temperature, the amino-carbonyl reaction proceeded to give products of higher melting points. From this result, we decided to include a small amount of dry benzene as a solvent in these cases (see Experimental). As shown in Table 1, per-*O*-acetylated 1,2-*trans*-1-thioglycoses synthesized from monosaccharides are tetra-*O*-acetyl-1-thio-β-D-glucopyranose **3a** (yield 89%), tetra-*O*-acetyl-1-thio-β-D-galactopyranose **3b** (97%) and tetra-*O*-acetyl-1-thio-α-D-mannopyranose **3c** (98%), and from disaccharides, hepta-*O*-acetyl-1-thio-β-lactose **3d** (75%), hepta-*O*-acetyl-1-thio-β-mal-



Scheme 1. Synthesis of per-*O*-acetylated 1,2-*trans*-1-thioglycopyranoses.

tose **3e** (73%) and hepta-*O*-acetyl-1-thio-β-cellobiose **3f** (76%). In the methanolysis of **2e** the yield of **3e** deposited from the methanol solution was 44%.

^{1}H NMR coupling constants from 9.6 Hz to 9.9 Hz for H-1 of reducing terminal, except for **3c**, were observed for the methanolysis products. Measurements of ^{1}H and ^{13}C NMR of **3b** were carried out on viscous precipitates after methanol was distilled off, as the crystallization was difficult (Tables 1 and 2). Also, the molecular weights of these products (**3a–3f**) were measured by chemical ionization mass spectrometry, the fragment ion peaks of *m/z* 365 (M + 1) and 331 (pyranose ring cation) were observed in the case of monosaccharides (**3a–3c**) and the fragment ion peaks of *m/z* 653 (M + 1) and 619 and 332 (pyranose ring cation) were observed in the case of disaccharides (**3d–3f**). From these results, it was confirmed that per-*O*-acetylated 1,2-*trans*-1-thioglycoses were obtained by the present method.

This reaction is considered to proceed in a similar way as the reaction using thiourea. Glycosylthioiminium salt **2** is formed by the reaction of the acetohalogenosugar with thioacetamide by an S_N2 type reaction and undergoes nucleophilic attack by methanol to give per-*O*-acetylated 1,2-*trans*-1-thioglycose. In the reaction using *d*-methanol, the formation of the product **3** having a deuteriated thiol group was observed. Furthermore, evolution of hydrogen bromide was detected in this reaction and suggests the formation of acetonitrile.[6]

The reaction temperature must to be monitored carefully in the preparation of glycosylthioiminium salts by this method in order to avoid the amino-carbonyl side reaction. It is necessary for the reaction temperature to be lower than the melting point of thioacetamide (ca. 114°C) and higher than the melting points of acetohalogenosugar. The progress of the side-reaction may be detected by observing a change in color of the reaction mixture; from initial yellow to orange color, and finally brown.

Table 1. Methanolysis[a] Glycosylthioiminium Salts **2** and Physical Properties of 1-Thioglycose **3**

Sugar **1**	Acetylated R	X	Reaction Temp. of **2** (°C)	Yield (%) of **3**	mp (°C) [Ref.]	^{1}H NMR[b] (δ, ppm) H-1 of Red. Terminal	Form of **3**	CI-MS[c] (M + 1)
a	Glucopyranosyl	Br	120	89	114 ~ 115 [115][5]	4.55 ($J_{1,2}$ = 9.61 Hz)	β	365
b	Galactopyranosyl	Br	120	97	syrup [syrup][9][d]	4.55 ($J_{1,2}$ = 9.90 Hz)	β	365
c	Mannopyranosyl	Cl	120	98	159 ~ 160 [syrup][10]	4.89 ($J_{1,2}$ = 1.29 Hz)	α	365
d	Lactosyl	Br	reflux[e]	75	81 ~ 82 [syrup][12]	4.54 ($J_{1,2}$ = 9.90 Hz)	β	653
e	Maltosyl	Br	reflux[e]	73 (44)[f]	153 ~ 154 [149 ~ 152][12]	4.59 ($J_{1,2}$ = 9.88 Hz)	β	653
f	Cellobiosyl	Br	reflux[e]	76	208.5 ~ 209.5 [209 ~ 212][13]	4.51 ($J_{1,2}$ = 9.90 Hz)	β	653

[a]Methanolysis temp.: 20°C.
[b]TMS standard in $CDCl_3$.
[c]Gas: isobutane.
[d]mp 86.5 ~ 88.0°C (by purifying for analytical purposes).
[e]Solvent: dry benzene.
[f]Yield deposited in methanolysis.

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Table 2. ^{13}C NMR Chemical Shift Data of 1-Thioglycose **3**

	Chemical Shift (δ, ppm, $CDCl_3$)											
3	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
a	78.7	73.5	73.6	68.1	76.3	62.0						
b	79.1	70.8	71.5	67.2	74.9	61.4						
c	76.3	71.6	72.0	65.2	76.9	62.6						
d	78.5	73.9	73.5	70.7	77.2	58.5	101.1	69.1	71.0	66.6	62.2	60.8
e	78.2	74.3	76.1	72.6	76.5	63.0	95.6	69.9	69.3	67.9	68.6	61.4
f	78.5	73.7	73.2	76.7	77.2	61.5	100.8	71.5	67.7	72.0	72.9	62.1

The reaction of acetohalogenosugars with thiourea affords stable thioisouronium salts, from which per-*O*-acetylated 1,2-*trans*-1-thioglycoses are derived by alkali hydrolysis. However, the time required for alkali hydrolysis can result in loss of acetyl groups and careful treatment of pH adjustment is always necessary to obtain a good yield. In the present synthetic method using thioacetamide instead of thiourea, the resulting thioiminium salts are easily decomposed even with alcohol, and per-*O*-acetylated 1,2-*trans*-1-thioglycoses are obtained without loss of acetyl groups and also tedious pH adjustment. Furthermore, per-*O*-acetylated 1,2-*trans*-1-thioglycoses are purified by fractional crystallization from a chilled alcohol solution without the need for separation by column chromatography. In conclusion, the procedure described here is a convenient method to prepare per-*O*-acetylated 1,2-*trans*-1-thioglycose in good yield under mild and neutral conditions.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded with a JEOL GX-400 instrument using tetramethylsilane as a standard. Chemical ionization mass spectra were recorded by direct inlet probe with a JEOL JMS-AMII 150 instrument using isobutane as a reaction gas.

General method (3a–3c). Freshly prepared and dried (anhydrous conditions) acetohalogenosugar (2.5 mmol) and thioacetamide (2.7 mmol, 0.2 g) were stirred mechanically under argon at approximately 120°C for 5 min. Dry methanol (20 mL) was added after cooling to 20°C, and the mixture was stirred for about 10 min (until the solid dissolved). Solvent was evaporated under reduced pressure, a slight amount of methanol was added again, and the mixture cooled to −18°C. The product separated by fractional crystallization was filtered and dried.

For the disaccharides (**3d–3f**), the first step of the reaction was carried out as follows. Freshly prepared and dried acetohalogenosugar (2.5 mmol) and thioacetamide (2.7 mmol, 0.2 g) in dry benzene (below 5 mL) were stirred mechanically at reflux temperature (ca. 82°C) for 3 h under argon. Molecular sieves (4 Å) were included in this reaction mixture in order to maintain anhydrous conditions. Dry methanol (20 mL) was added after cooling to 20°C, and the mixture was stirred for about 10 min (until the solid dissolved). Solvent was evaporated under reduced pressure, and a slight

amount of methanol was added again and the mixture cooled to −18°C. The product separated by fractional crystallization was filtered and dried.

ACKNOWLEDGMENT

We thank Ms. Fujita for measurements of NMR spectra.

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Received July 9, 2001
Accepted April 4, 2002