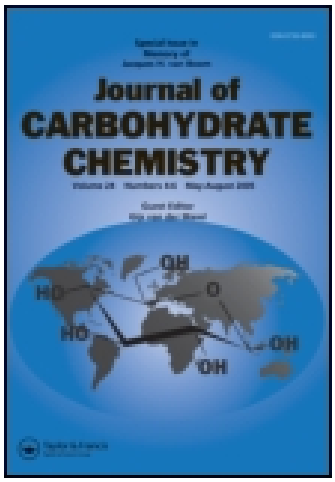

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Synthesis of Tetra-*O*-acetyl-1-thio-α-D-glucopyranose by Reaction of Tetra-*O*-acetyl-α-D-glucopyranosyl Bromide with *N*,*N*-Dimethylthioformamide

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ABSTRACT

A reaction system was found to prepare tetra-*O*-acetyl-1-thio-D-glycopyranose in both α and β-forms. Methanolysis of the adduct prepared from the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with *N*,*N*-dimethylthioformamide afforded the corresponding tetra-*O*-acetyl-1-thio-D-glucopyranose with an anomer ratio α/β of 52:48 in 98% yield. The anomer mixture was easily separated by column chromatography to obtain the product of α-form. This synthetic method is very convenient to proceed by one-pot reaction under ordinary conditions.

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INTRODUCTION

Tetra-*O*-acetyl-1-thio-D-glucopyranose is usually prepared by the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with thiourea followed by hydrolysis in alkaline solution of the isothiouronium bromide. This method gives tetra-*O*-acetyl-1-thio-β-D-glucopyranose selectively.[1] In a preceding paper,[2] we reported that the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with thioacetamide instead of thiourea gives an adduct identified as 2-(tetra-*O*-acetyl-D-glucopyranosylthio)ethaniminium bromide, methanolysis of which affords tetra-*O*-acetyl-1-thio-β-D-glucopyranose. This method also gives tetra-*O*-acetyl-1-thio-β-D-galactopyranose, tetra-*O*-acetyl-1-thio-α-D-mannopyranose, hepta-*O*-acetyl-1-thio-β-lactose, hepta-*O*-acetyl-1-thio-β-maltose or hepta-*O*-acetyl-1-thio-β-cellobiose starting with tetra-*O*-acetyl-D-glycopyranosyl bromide or chloride.

The reaction of acylated sugar affords generally per-*O*-acetyl-1,2-*trans*-glycoside owing to the participation of a neighboring acyl group.[3,4] Utilizing this characteristic a variety of per-*O*-acetyl-1,2-*trans*-1-thioglycoses have been successfully prepared, but it is generally difficult to prepare per-*O*-acetyl-1,2-*cis*-1-thiosugars by this method in a good yield.[4] Since the work of P. Brigl[5] that reported the preparation of tetra-*O*-acetyl-1-thio-α-D-glucopyranose from 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose, some attempts for synthesis of 1,2-*cis*-1-thioglycose have been explored using, for example, alkyl or benzyl xanthates[6] and thioacetic acid.[7–10] It was also reported that tetra-*O*-acetyl-1-thio-α-D-glucopyranose is prepared through the reaction of the phenylmercury(II)thio derivative of tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-glucopyranose with hydrogen sulfide.[11]

In the course of our investigations, we found that a modification of our method,[2] in which *N*,*N*-dimethylthioformamide is used, gives an anomeric mixture of tetra-*O*-acetyl-1-thio-D-glucopyranoses, from which the α-anomer can be readily separated.

RESULTS AND DISCUSSION

Initially, the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with *N*,*N*-dimethylthioformamide instead of thioacetamide under anhydrous conditions was not successful. As described previously,[2] the starting materials (tetra-*O*-acetyl-α-D-glucopyranosyl bromide and *N*,*N*-dimethylthioformamide in this case) are soluble in a warm nonpolar organic solvent (e.g., benzene), but the thioiminium salt is barely soluble. K. Hattori[12] and Y. Kobayashi[13] reported that thioiminium salts can be prepared from the reaction of alkyl or aryl halides with *N*,*N*-dimethylthioformamide, so we reexamined our reaction under modified conditions. As a result, it was found that the reaction takes place if a slight amount of water is present, at approximately 100°C. The reaction system was estimated to contain ca. ~0.2% of water. The product was mainly *N*,*N*-dimethyl(tetra-*O*-acetyl-D-glucopyranosylthio)methaniminium bromide as indicated by FAB-MS data; the fragment positive ion peaks of *m*/*z* 420 ($[M - Br^-]^+$) and 331 (pyranosyl ring cation) (Figure 1) and the negative ion peaks of *m*/*z* 578, 580, 582 ($[M + Br^-]^-$) and 363 (glucosylthiolate anion) and 79, 81 (Br^-) were clearly observed (Figure 2). The methanolysis of the thioiminium salt gave an anomeric mixture of tetra-*O*-acetyl-1-thio-D-glucopyranose with the anomer

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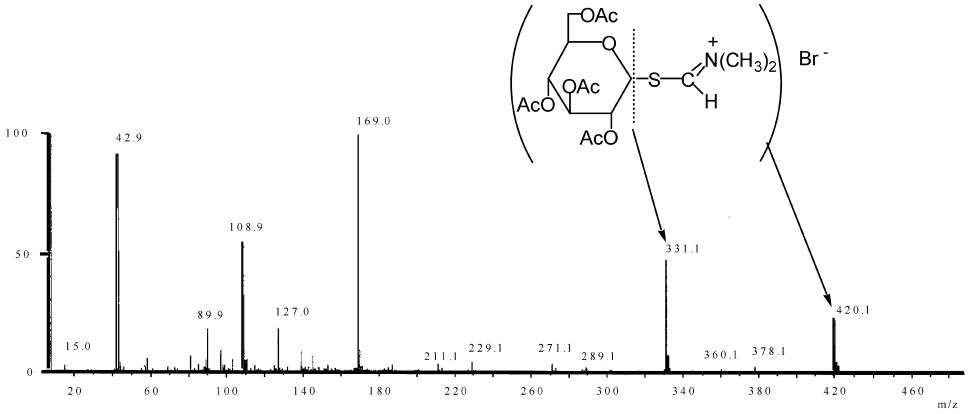

Figure 1. FAB spectrum (positive ion mode) of thioiminium salt from tetra-*O*-acetyl-α-D-glucopyranosyl bromide with *N*,*N*-dimethylthioformamide.

ratio of α:β = 52:48 in 98% yield. This anomer mixture was easily separated by column chromatography.

Little is known about the effect of a slight amount of water in these reactions. It was reported that the anomeric mixture of pyridinium bromide derivatives obtained from the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide in pyridine is 1:1.[14,15] Although the effect of moisture was not mentioned, the anomer ratio of the product

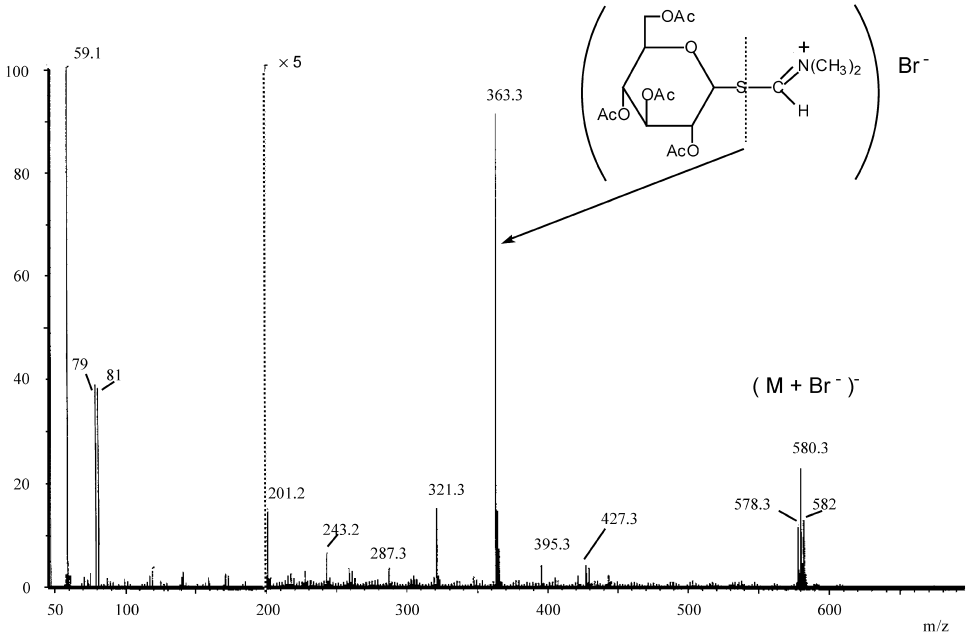

Figure 2. FAB spectrum (negative ion mode) of thioiminium salt from tetra-*O*-acetyl-α-D-glucopyranosyl bromide with *N*,*N*-dimethylthioformamide.

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varied with the concentration of tetra-*O*-acetyl-α-D-glucopyranosyl bromide in pyridine.[15] This reaction is probably a first example of the reaction which is not affected by the participation of neighboring groups in the absence of a catalyst.

The present method was unsuccessful when tetra-*O*-benzyl-α-D-glucopyranosyl chloride instead of bromide was used. The present method gave a similar result by using *N*,*N*-dimethylthioacetamide instead of *N*,*N*-dimethylthioformamide and, therefore, this reaction is considered to require a tertiary thioamide. The use of primary or secondary thioamides gives a different result from that of tertiary thioamide. Primary or secondary thioamides react with tetra-*O*-acetyl-α-D-glucopyranosyl bromide under completely anhydrous conditions to give exclusively tetra-*O*-acetyl-1-thio-β-D-glucopyranose. On the other hand, the reaction system containing a slight amount of water affords an anomeric mixture of the product, but the content of α-form product is rather low (20 $\sim$ 30%).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with a JEOL GX-400 instrument using tetramethylsilane as a standard. FAB MS spectra were recorded by direct inlet probe with a JEOL MS 700 instrument using glycerin as a matrix and Xe as a reaction gas. Chemical ionization mass spectra were recorded by direct inlet probe with a JEOL JMS-AMII 150 instrument using trimethylmethane as a reaction gas. Optical rotation was determined with a Horiba SEPA-200 polarimeter at 20°C. HPLC analysis (RI monitor) was accomplished by using a Senshu Pak silica-3301-N column (8 × 300 mm, Senshu Kagaku Co. Ltd.), with hexane and ethanol (9:1) as an eluent at a flow rate of 1.5 mL/min.

General method. Freshly prepared tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.5 mmol, 1.03 g) and *N*,*N*-dimethylthioformamide (2.6 mmol, 0.23 g) were stirred mechanically under an argon stream at approximately 100°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, and the precipitated product was separated and purified by silica gel chromatography (benzene–chloroform, 9:1). The products are tetra-*O*-acetyl-1-thio-α-D-glucopyranose (0.46 g, 51%) and tetra-*O*-acetyl-1-thio-β-D-glucopyranose (0.42 g, 47%) as a colorless syrup.

Tetra-*O*-acetyl-1-thio-α-D-glucopyranose. R_f 0.59 (benzene:chloroform 9:1); mp 93–94°C (Lit. 92–93°C[7]); $[\alpha]_D^{20}$ + 171° (Lit. + 168°[7]) (*c* 0.8, chloroform); ^{1}H NMR (chloroform-*d*): δ 1.91 (d, 1H, $J_{1,SH}$ 5.77 Hz, SH), 4.11 (dd, 1H, $J_{5,6a}$ 2.20, $J_{6a,6b}$ 12.50 Hz, H-6a), 4.30 (dd, 1H, $J_{5,6b}$ 4.12, $J_{6a,6b}$ 12.50 Hz, H-6b), 4.44 (ddd, 1H, $J_{5,6a}$ 2.20, $J_{5,6b}$ 4.12, $J_{4,5}$ 10.16 Hz, H-5), 5.03 (dd, 1H, $J_{1,2}$ 5.77, $J_{2,3}$ 9.89 Hz, H-2), 5.07 (dd, 1H, $J_{3,4}$ 9.89, $J_{4,5}$ 10.16 Hz, H-4), 5.39 (dd, 1H, $J_{3,4}$ 9.89, $J_{2,3}$ 9.89 Hz, H-3), 5.94 (dd, 1H, $J_{1,SH}$ 5.77, $J_{1,2}$ 5.77 Hz, H-1); ^{13}C NMR (chloroform-*d*): δ 61.6 (C-6), 68.9 (C-4), 69.9 (C-3), 70.3 (C-2), 77.1 (C-5), 77.2 (C-1), CIMS: *m*/*z* 365 (M + 1).

Tetra-*O*-acetyl-1-thio-β-D-glucopyranose. R_f 0.62 (benzene:chloroform 9:1); mp 113–114°C (Lit. 115°C[1]); $[\alpha]_D^{20}$ + 11° (*c* 1.0, chloroform); ^{1}H NMR (chloroform-*d*):

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δ 2.32 (d, 1H, $J_{1,SH}$ 9.61 Hz, SH), 3.73 (ddd, 1H, $J_{5,6a}$ 2.20, $J_{5,6b}$ 4.94, $J_{4,5}$ 9.75 Hz, H-5), 4.13 (dd, 1H, $J_{5,6a}$ 2.20, $J_{6a,6b}$ 12.36 Hz, H-6a), 4.25 (dd, 1H, $J_{5,\ 6b}$ 4.94, $J_{6a,6b}$ 12.36 Hz, H-6b), 4.55 (dd, 1H, $J_{1,\ SH}$ 9.61, $J_{1,\ 2}$ 9.61 Hz, H-1), 4.98 (dd, 1H, $J_{1,2}$ 9.61, $J_{2,3}$ 9.34 Hz, H-2), 5.11 (dd, 1H, $J_{3,4}$ 9.61, $J_{4,5}$ 9.75 Hz, H-4), 5.20 (dd, 1H, $J_{3,4}$ 9.61, $J_{2,3}$ 9.34 Hz, H-3); ^{13}C NMR (chloroform-*d*): δ 62.0 (C-6), 68.1 (C-4), 73.5 (C-2), 73.6 (C-3), 76.3 (C-5), 78.7 (C-1), CIMS: *m/z* 365 (M + 1).

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