Carbohydrate Research, 115 (1983) 254–258
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A simple preparation of aromatic 1-thioglycosides

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(Received July 19th, 1982; accepted for publication, November 10th, 1982)

1-Thioglycosides are an important class of sugar derivative. They are employed as inhibitors of enzymes[1], in affinity chromatography[2], and in synthesis for temporary protection of the anomeric centre[3] and for preparation of glycosides[4,5].

Synthesis of acylated aromatic 1-thioglycosides is most often accomplished by the reaction of acylglycosyl halides with thiols in the presence of strong bases, *e.g.*, sodium methoxide[6,7], sodium hydride[8], and alkali hydroxides and carbonates[9–11]; yields are in the range of 20–80%. The strong bases used to generate thiolate anions may cause deacylation, thus necessitating inconvenient acetylation of the reaction products[6,7,12].

Condensation of peracylated sugar derivatives with aromatic thiols in the presence of protic or Lewis acids[13] is less popular; moderate yields and the formation of anomeric 1-thioglycosides[14] are the main drawbacks. Boron trifluoride etherate appears to be the most effective catalyst of this reaction[15]. Alkylation of 1-thio sugar derivatives with alkyl halides[13] and the aforementioned reaction of peracylated sugars with aliphatic thiols are the most common methods for the synthesis of aliphatic 1-thioglycosides.

We now describe a simple and effective method of synthesis of peracetylated aromatic 1-thioglycosides based on the reaction of peracetylglycosyl bromides with aromatic thiols ($pK_a \sim 5$–7) in the presence of triethylamine. Thus, the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**) with aromatic thiols (10% molar excess) in acetonitrile in the presence of 2 molar equivalents of triethylamine at room temperature afforded the corresponding aryl 1-thio-β-D-glucopyranoside tetra-acetates (**2**–**7**) in essentially quantitative yield (t.l.c.) within 0.5–1 h. The yields and properties of these compounds isolated by direct crystallisation are recorded in Table I. Acetylated aryl 1-thio-β-D-galactopyranosides **8** and **9** were synthesised in an analogous manner from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide.

This reaction is not applicable for the synthesis of aliphatic 1-thioglycosides from the less acidic ($pK_a \sim 10$–11) aliphatic thiols. Thus, treatment of **1** with ethanethiol for 48 h in the presence of triethylamine gave traces (t.l.c.) of peracetylated

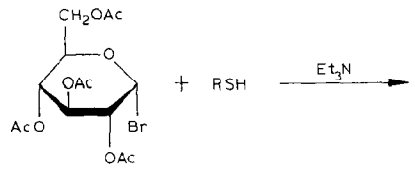
0008-6215/83/$ 03.00

TABLE I

YIELDS AND PROPERTIES OF AROMATIC THIOGLYCOSIDES

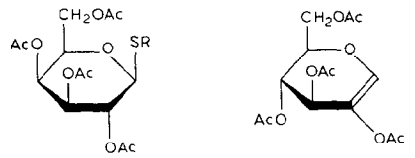
Compound	Yield (%)	M.p. (degrees)	$[\alpha]_D^{20}$ [a] (degrees)	Literature data		
				M.p. (degrees)	$[\alpha]_D^{20}$ [a] (degrees)	Ref.
3	72	182–184[b]	−35	185–186	−33	16
4	81	108–111[b]	−23	113	−25	11
5	79.5	115–117[b]	−17 −41 (toluene)	118	−40.1 (toluene)	17
6	64	95–97[b]	−27	101–102	−28.1	11
7	77	113–115[b]	−19	118	−21	11
8	88	155–157[b]	−8	158–159	−7	6
9	82	69–73[c]	+4	70.5	+5	18

[a]In chloroform, unless otherwise stated (*c* 1.2–1.7). [b]Crystallised from ethanol. [c]Crystallised from ether–hexane.



1

2 R = 3-ClC$_6$H$_4$
3 R = 4-O$_2$NC$_6$H$_4$
4 R = 4-ClC$_6$H$_4$
5 R = Ph
6 R = 4-MeOC$_6$H$_4$
7 R = 4-MeC$_6$H$_4$



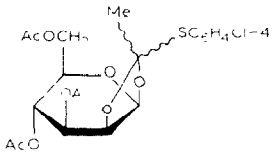
8 R = 4-O$_2$NC$_6$H$_4$
9 R = Ph

10

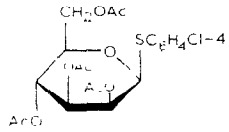
ethyl 1-thio-D-glucopyranoside and the isomeric 1,2-thio-orthoester, the main component being 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**10**, isolated in 56% yield).

The reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide at 37° for 20 h with 1.5 molar equivalents of 4-chlorothiophenol in acetonitrile in the presence of 4 equivalents of triethylamine gave a mixture of isomeric 1,2-thio-orthoesters **11** and the thiomannoside **12**; the *endo*-Me isomer of **11** and **12** had identical R_F values and could not be separated by chromatography. Therefore, the reaction

mixture was treated with mercuric bromide in aqueous acetone to convert **11** into more-polar hydrolysis products[19]. Subsequent column chromatography afforded 40.5% of a mixture (~9:1) of **12** and its α anomer (^{1}H- and ^{13}C-n.m.r. data) from which **12** was isolated in 34% yield by crystallisation.



11



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The use of triethylamine as a base is advantageous for preparation of peracetates of aromatic 1-thioglycosides, as complications due to deacetylation of the reaction products are avoided.

EXPERIMENTAL

Acetonitrile was distilled from P_2O_5 and then from CaH_2. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Melting points were determined with a Kofler apparatus and are uncorrected. ^{1}H-N.m.r. spectra were recorded with Varian DA-60-IL (^{1}H, 60 MHz) and Bruker WM-250 (^{1}H, 250 MHz; ^{13}C, 62.89 MHz) instruments for solutions in $CDCl_3$ with tetramethylsilane as the internal standard. Column chromatography was performed on Silica Gel L (100/250 μm, CSSR) with gradient elution benzene → ether. Solutions were concentrated *in vacuo* at 40°.

3-Chlorophenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**2**). — To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**1**; 820 mg, 2 mmol) in acetonitrile (4 mL) were added triethylamine (0.56 mL, 4 mmol) and 3-chlorothiophenol (0.25 mL, 2.2 mmol). The mixture was kept for 1 h at ambient temperature, diluted with chloroform (50 mL), and washed with water (3 × 50 mL), the organic layer was evaporated, and the residue was crystallised from ethanol to give **2** (670 mg, 70.5%), m.p. 87–89°, $[\alpha]_D^{20}$ −26° (*c* 1.2, chloroform). ^{1}H-N.m.r. data (60 MHz): δ 1.96, 1.98, 2.04, 2.05 (4 s, 12 H, 4 Ac), and 7.18–7.53 (m, 4 H, aromatic).

Anal. Calc. for $C_{20}H_{23}ClO_9S$: C, 50.58; H, 4.88; Cl, 7.46; S, 6.75. Found: C, 50.75; H, 4.90; Cl, 7.37; S, 6.67.

Compounds **3**–**9** (Table 1) were obtained in an analogous manner.

The reaction of **1** *with ethanethiol and triethylamine.* — A mixture of **1** (820 mg, 2 mmol), ethanethiol (0.17 mL, 2.2 mmol), and triethylamine (0.56 mL, 4 mmol) in acetonitrile (4 mL) was kept for 48 h at ambient temperature, diluted with chloroform (50 mL), and washed with water (3 × 50 mL), and the organic layer was evaporated. The residue was subjected to column chromatography to give **10** (370 mg, 56%), m.p. 55–57° (from ether–hexane), $[\alpha]_D^{20}$ −33° (*c* 0.5, chloroform), −17

(*c* 1.15, ethanol); lit.[20] m.p. 61°, $[\alpha]_D^{20}$ −20° (ethanol). ^{1}H-N.m.r. data (60 MHz): δ 2.03 (s, 3 H, Ac), 2.09 (s, 9 H, 3 Ac), 4.26–4.55 (m, 3 H, H-4,6,6'), 5.23 (m, 1 H, H-5), 5.55 (d, 1 H, $J_{3,4}$ 4 Hz, H-3), and 6.62 (s, 1 H, H-1).

4-Chlorophenyl 2,3,4,6-tetra-O-*acetyl-1-thio-β-*D-*mannopyranoside* (**12**). — To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide [obtained[21] from 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (1.04 g, 2.67 mmol)] in acetonitrile (7 mL) were added 4-chlorothiophenol (580 mg, 4 mmol) and triethylamine (1.5 mL, 10.7 mmol), the mixture was kept for 20 h at 37°, diluted with chloroform (100 mL), and washed with water (3 × 100 mL), and the organic layer was evaporated. The residue was dissolved in acetone (10 mL), and water (2 drops) and mercuric bromide (360 mg, 1 mmol) were added. The precipitate was filtered off, the filtrate was evaporated, and the residue was chromatographed to give a chromatographically homogeneous syrup (510 mg, 40.5%), $[\alpha]_D^{20}$ −49° (*c* 1.9, chloroform). The ^{13}C-n.m.r. spectrum contained, *inter alia*, signals at δ 85.3 and 76.6 (C-1 and C-5 of **12**), and 85.6 and 69.3 (C-1 and C-5 of the α anomer of **12**) in a ratio of ~9 : 1. Crystallisation occurred during several days, and recrystallisation from ether–hexane gave **12** (430 mg, 34%), m.p. 99–102°, $[\alpha]_D^{20}$ −73.5° (*c* 1.2, chloroform). N.m.r. data: ^{1}H (250 MHz), δ 1.99, 2.05, 2.10, 2.21 (4 s, 12 H, 4 Ac), 3.72 (m, 1 H, $J_{5,6}$ 2.5, $J_{5,6'}$ 6.5 Hz, H-5), 4.17 (dd, 1 H, $J_{6,6'}$ 12.5 Hz, H-6), 4.29 (dd, 1 H, H-6'), 4.92 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 5.07 (dd, $J_{3,2}$ 3.5, $J_{3,4}$ 10 Hz, 1 H, H-3), 5.28 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 5.66 (dd, 1 H, H-2), 7.29, 7.47 (2 d, 4 H, *J* 8.5 Hz, aromatic); ^{13}C, δ 85.3 (C-1), 76.6 (C-5), 71.8 (C-3), 70.5 (C-2), 66.0 (C-4), 62.8 (C-6), 20.5, and 20.4 (Ac).

Anal. Calc. for $C_{20}H_{23}ClO_9S$: C, 50.58; H, 4.88; Cl, 7.46; S, 6.75. Found: C, 50.61; H, 4.96; Cl, 7.24; S, 6.72.

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