Carbohydrate Research, 193 (1989) 283–287
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Zirconium(IV) chloride-catalyzed synthesis of 1,2-*trans*-1-thioglycopyranosides*

MARIE-ODILE CONTOUR, JACQUES DEFAYE, MARK LITTLE†, AND EMILE WONG
Département de Recherche Fondamentale, Laboratoire de Chimie des Macromolécules Végétales, Centre d'Études Nucléaires, 85 X, F-38041 Grenoble (France)

(Received January 17th, 1989; accepted for publication in revised form, May 4th, 1989)

The design of simple and efficient methods for the preparation of 1-thioglycoses and 1-thioglycosides is of interest since these derivatives find multiple uses in carbohydrate enzymology as inhibitors, nonmetabolizable inducers, model substrates, as well as stable ligands for affinity chromatography‡. More recently, 1-thioglycosides have been extensively used as glycoside donors in oligosaccharide synthesis[2].

Acid-mediated thiolysis of peracetylated sugars is, among other techniques[3], a well established route to the synthesis of 1-thioglycosides[4]. Lemieux and assoc.[5,6] first demonstrated the efficiency of this reaction by preparing several 1,2-*trans*-related ethyl 1-thioglycopyranosides with ethanethiol as solvent and zinc chloride as a nonprotonic acid catalyst. Several other catalysts have since been proposed and their choice was shown to be of importance in determining the anomeric ratio of products obtained[7].

Zirconium(IV) chloride was recently found to be an effective catalyst in thioglycosylation reactions, leading exclusively to peracetylated 1,2-*trans*-related 1-thioglycoses from the reaction of 1,2-*trans*-acetylated glycoses and thioacetic acid in dichloromethane[8]. Under the conditions described, the resulting thioglycose esters were stable and not subject to anomerization. This reaction scheme was simultaneously extended to the preparation of 1-thioglycosides, and 1,3,4,6-tetra-*O*-benzyl-β-D-fructofuranosyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside was obtained, together with its α,α-anomer, from the reaction of 1,3,4,6-tetra-*O*-benzyl-α,β-D-fructofuranose with 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranose under similar conditions, thus allowing the first synthesis of 1-thiosucrose[9]. How-

*Part XI in the series "Stereoselective thioglycoside synthesis", for part X, see ref. 1.
†Present address: Glaxo Inc., Five Moore Drive, Research Triangle Park, NC 27709, U.S.A.
‡For references in related fields, see ref. 1 and citations therein.

0008-6215/89/$ 03.50

ever, the expected difficulty in the anomeric control at C-2 of a ketohexofuranose derivative did not allow a proper evaluation of the scope of the reaction for the synthesis of 1-thioglycosides, on which this article reports.

In fact, when applied to the preparation of ethyl 1-thioderivatives of D-glucopyranose acetate starting from 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose and a twofold stoichiometric amount of ethanethiol in dichloromethane at 0°, the zirconium(IV) chloride-catalyzed thiolysis procedure was found to give rise exclusively to the corresponding 1,2-*trans*-related 1-thioglycoside. Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[5] was thus obtained in 74% yield. By contrast, when the same reaction was conducted at room temperature, a mixture of anomers was obtained, in which the 1,2-*cis*-related 1-thioglycoside, namely ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside[10], slightly preponderated. Formation of the latter compound obviously resulted from an anomerization of the β anomer, since a subsequent treatment in dichloromethane of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside in the presence of zirconium(IV) chloride at room temperature for 20 h yielded both anomers in a final 2:3 ratio of β- to α-anomer. This anomerization process is likely analogous to that of acetylated alkyl glycopyranosides on treatment with strong acids such as sulfuric acid, titanium tetrachloride, or boron trifluoride, and has already been reported with both last-named reagents for acetylated alkyl 1-thio-β-D-glucopyranosides[11–13]. Owing to the fact that the anomeric effect is less effective with 1-thioglycosides as compared to their *O*-glycosyl counterpart[14], the rate and extent of conversion, at equilibrium, to the axial anomer is as expected smaller, the equilibrium being reached after about 24 h for a ratio of α to β of 7:3. Both anomers were conveniently separated by crystallization or flash chromatography, or both.

Glycosyl chlorides are known to be formed when sugar esters are treated with chlorides of the groups III or IV elements in non- or weakly-polar media[15,16], and such an intermediate has already been proposed in the formation of 1,2-*trans*-1-thioglycose acetates from 1,2-*trans*-glycose acetates in dichloromethane with aluminium chloride as catalyst[17]. Accordingly, the zirconium(IV) chloride-catalyzed thiolysis of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in dichloromethane showed (^{13}C-n.m.r.) the presence of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride[18] after short reaction periods. Nevertheless, in the range of reaction time and with a molar excess of thiol as presently reported, glycopyranosyl chlorides could not be detected in the final reaction product.

This reaction scheme has been extended to the D-galactopyranose, D-mannopyranose, and D-xylopyranose series, and the results are reported in Table I, together with ^{13}C-n.m.r. characterizations in Table II. As expected, completion of the reaction went faster with 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose, and a 79% yield of ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside was reached after 7.5 h at −10°. An extended reaction time at higher temperatures (15 h at 20–25°) led to a mixture of anomers from which ethyl 2,3,4-tri-*O*-acetyl-1-thio-α-D-xylopyranoside was obtained after chromatographic purification. It is noteworthy , that

TABLE I

YIELD AND PHYSICAL CONSTANTS OF ETHYL PER-*O*-ACETYL-1-THIOGLYCOPYRANOSIDES

Ethyl per-O-acetyl-1-thio	R_F[a]	*Yield (%) Reaction conditions*[b]		*Characterization*				*Ref.*
				Found		*Lit.*		
		0°	*20°*	M.p. (°)	$[\alpha]_D^{20}$ (c, *chloroform*) *(degrees)*	*M.p. (°)*	$[\alpha]_D$ (c, *chloroform*) *(degrees)*	
α-D-Xylopyranoside	0.40		25		+155.5(2.24)			[c]
β-D-Xylopyranoside	0.32	79[d]	31	100.5–101.5 (Ethanol)	−86.3(0.5)	101	−83.5(0.5)	19
α-D-Galactopyranoside	0.27		32	108–108.5 (Ether–hexane)	+210.5(1.14)	108–109	+218(1.18)	20
β-D-Galactopyranoside	0.17	81	47	74.0–74.5 (Ether–hexane)	−8.8(2.28)	74–75	−8(2.1)	20
α-D-Glucopyranoside	0.31		38	91–93 (Ethanol)	+197(1.05)	95	+194(1.6)	21
β-D-Glucopyranoside	0.23	74	32	82–83 (Ethanol)	−26.7(1.05)	82.5–83	−28(0.9)	5
α-D-Mannopyranoside	0.5	43[e]	41	101–102 (Ethanol)	+98.7(0.9)	107–108	+104(0.8)	20

[a]In 1:1 (v/v) ether–hexane. [b]Reaction time 16 h, unless otherwise indicated. [c]Zemplén *O*-deacetylation yielded ethyl 1-thio-α-D-xylopyranoside, m.p. 104–105°, $[\alpha]_D$ +258° (*c* 0.5, water); lit.[22] m.p. 108–110°, $[\alpha]_D$ +269° (water). [d]Reaction time 7.5 h at −10°. [e]Reaction time 32 h at 0°.

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS (δ) FOR ETHYL PER-*O*-ACETYL-1-THIOGLYCOPYRANOSIDES

Ethyl per-O-acetyl-1-thio-	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
α-D-Xylopyranoside	81.2	68.9	70.0	68.5	58.4	
β-D-Xylopyranoside	83.6	69.9	72.4	68.7	65.5	
α-D-Galactopyranoside	82.0	69.0	68.0	66.5	68.0	61.8
β-D-Galactopyranoside	83.7	67.2	74.2	67.1	71.7	61.3
α-D-Glucopyranoside	81.7	68.7	70.7	67.6	70.6	61.9
β-D-Glucopyranoside	83.5	69.9	75.9	68.4	73.9	62.2
α-D-Mannopyranoside	88.9	71.4	67.8	65.4	71.2	61.7

1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose gave exclusively ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside, even after a prolonged treatment at room temperature. Therefore, these results indicate a facile route to alkyl 1,2-*trans*-related 1-thioglycosides, as well as to their corresponding 1,2-*cis*-related products, the *manno* derivative excepted, based solely upon control of the reaction temperature, and using zirconium(IV) chloride as a moderately hygroscopic and easily handled Lewis acid catalyst.

EXPERIMENTAL

General methods. — Melting points were measured in capillary tubes with a Büchi 535 apparatus and are corrected. Optical rotations were determined with a Jobin–Yvon (Paris) "Digital Micropolarimeter". ^{13}C-N.m.r. spectra were recorded with a Bruker WP200 spectrometer in (^{2}H)chloroform; chemical shifts are reported relative to the signal of tetramethylsilane in Table II. Reactions were monitored by t.l.c. on silica gel plates (Merck F-254, Darmstadt, Germany). Flash chromatography was carried out on columns of silica gel (Merck 60, 230–400 mesh). Gas chromatography was conducted in a Girdel 3000 Gas chromatograph, equipped with a flame-ionization detector and a wall-coated, open-tubular capillary column of SE-30 phase, and with N_2 as carrier gas.

*General procedure for the preparation of O-acetylated ethyl 1,2-*trans*-1-thioglycopyranosides.* — To a stirred solution of a 1,2-*trans*-per-*O*-acetylhexopyranose (5 g, 12.8 mmol; for D-*gluco*, see ref. 23, for D-*galacto*, ref. 24, and D-*manno*, ref. 25), in dichloromethane (175 mL) at 0°, was added 1 mol. equiv. of ethanethiol (0.95 mL, 12.8 mmol) and $ZrCl_4$ (2.8 g, 12 mmol). After 1 h, an additional equivalent of the thiol was added and the mixture stirred for further 15 h at 0°. The content was diluted with dichloromethane and the mixture successively washed with an ice-cold solution of water, saturated $NaHCO_3$, and water. The solution was dried (Na_2SO_4) and concentrated under reduced pressure at 40°. To the syrup was added the appropriate solvent listed in Table I to give the crystalline ethyl 1,2-*trans*-2,3,4,6-tetra-*O*-acetyl-1-thio-hexopyranosides listed in Table I.

The reaction temperature was not critical for the obtention of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside and ambient temperature could be used as well (see Table I). On the other hand, the preparation of ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside from 1,2,3,5-tetra-*O*-acetyl-β-D-xylopyranose[26] required the temperature to be kept at −10°, and the reaction time should not exceed 6.5 h.

When the same reaction was conducted at room temperature in the D-*gluco*, D-*galacto*, and D-*xylo* series, α and β anomers were obtained (Table I) which could be conveniently separated by flash chromatography (1:1, v/v, ether–hexane).

ACKNOWLEDGMENTS

Dr. Mark Little thanks the C.N.R.S. for a visiting postdoctoral research fellowship in the framework of the C.N.R.S.–N.S.F., U.S.–France Cooperative Science Program.

REFERENCES

1 J. DEFAYE, R. DARCY, A. GADELLE, A. GUILLIER AND T. O'SULLIVAN, *Carbohydr. Res.*, 192 (1989) 257–258.
2 P. FÜGEDI, P. J. GAREGG, H. LÖNN, AND T. NORBERG, *Glycoconjugate J.*, 4 (1987) 97–108, and references therein.
3 D. HORTON AND D. H. HUTSON, *Adv. Carbohydr. Chem.*, 18 (1963) 123–199.
4 R. J. FERRIER AND R. H. FURNEAUX, *Methods Carbohydr. Chem.*, 8 (1980) 251–253.
5 R. U. LEMIEUX, *Can. J. Chem.*, 29 (1951) 1079–1091.
6 R. U. LEMIEUX AND C. BRICE, *Can. J. Chem.*, 33 (1955) 109–119.
7 R. J. FERRIER AND R. H. FURNEAUX, *Carbohydr. Res.*, 52 (1976) 63–68.
8 J. DEFAYE, H. DRIGUEZ, E. OHLEYER, C. ORGERET, AND C. VIET, *Carbohydr. Res.*, 130 (1984) 317–321.
9 J. DEFAYE, H. DRIGUEZ, S. PONCET, R. CHAMBERT, AND M.-F. PETIT-GLATRON, *Carbohydr. Res.*, 130 (1984) 299–315.
10 E. PACSU AND E. J. WILSON, JR., *J. Am. Chem. Soc.*, 61 (1939) 1450–1454.
11 R. J. FERRIER, L. R. HATTON, AND W. G. OVEREND, *Carbohydr. Res.*, 6 (1968) 87–96.
12 B. ERBING AND B. LINDBERG, *Acta. Chem. Scand., Ser. B*, 30 (1976) 611–612.
13 D. T. CONNOLLY, S. ROSEMAN, AND Y. C. LEE, *Carbohydr. Res.*, 87 (1980) 227–239.
14 I. TVAROŠKA, *Chem. Zvesti.*, 38 (1984) 189–197.
15 R. U. LEMIEUX, *Methods Carbohydr. Chem.*, 2 (1963) 223–224.
16 R. I. SARYBAEVA, V. A. AFANAS'EV, G. E. ZAIKOV, AND L. S. SHCHELOKHOVA, *Usp. Khim.*, 46 (1977) 1395–1410; *Russ. Chem. Rev. (Engl. Transl.)*, 46 (1977) 722–730.
17 B. RAJANIKANTH AND R. SESHADRI, *Tetrahedron Lett.*, 28 (1987) 2295–2296.
18 K. BOCK AND C. PEDERSEN, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66.
19 M. GEHRKE AND W. KOHLER, *Ber. Dtsch. Chem. Ges.*, 64 (1931) 2696–2702.
20 J. FRIED AND D. E. WALZ, *J. Am. Chem. Soc.*, 71 (1949) 140–143.
21 E. PACSU AND E. J. WILSON, JR., *J. Am. Chem. Soc.*, 61 (1939) 1950–1956.
22 R. J. FERRIER, L. R. HATTON, AND W. G. OVEREND, *Carbohydr. Res.*, 6 (1968) 87–96.
23 M. L. WOLFROM AND A. THOMPSON, *Methods Carbohydr. Chem.*, 2 (1963) 211–215.
24 E. ERWING AND W. KOENIGS, *Ber. Dtsch. Chem. Ges.*, 22 (1889) 2207–2213.
25 C. S. HUDSON AND J. K. DALE, *J. Am. Chem. Soc.*, 37 (1915) 1280–1282.
26 W. E. STONE, *Am. Chem. J.*, 15 (1893) 653–656.