Carbohydrate Research, 73 (1979) 273–276

Note

Selective acetolysis of primary benzyl ethers

RONALD EBY, SUSAN J SONDHEIMER, AND CONRAD SCHUERCH

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210 (U.S.A.)

(Received June 16th, 1978; accepted for publication, August 1st, 1978)

The stepwise synthesis of oligosaccharides requires the preparation of sugar derivatives with both persistent and temporary blocking groups[1]. In many synthetic schemes, benzyl and allyl groups are used as persistent, and esters as temporary blocking groups[1–3]. To obtain the desired distribution of persistent and temporary substituents, a number of blocking and deblocking reactions are sometimes required. The conventional method of etherifying secondary hydroxyl groups without reaction with primary hydroxyl groups is to tritylate, etherify, and detritylate. Although this procedure is frequently satisfactory, we have found that it is often more convenient to benzylate completely and to debenzylate the primary position selectively by acetolysis. In individual cases, the starting materials may be more accessible, and the fully benzylated intermediate product may have better physical properties Usually, there are fewer reaction steps, and the reagents are less expensive. This reaction sequence has been successful with D-glucose, D-mannose, and D-galactose derivatives in the form of hemiacetal, glycoside, and orthoester. Primary benzyl ethers have been cleaved in the presence of secondary benzyl and allyl substituents.

The only difficulty we have encountered is in reproducing the reaction rates of the acid-catalyzed acetolysis. Apparently, slight variations in acidity are sufficient to markedly alter the rate. We have found that a careful monitoring of the reaction by ^{1}H-n.m.r. spectroscopy, in preference to t.l.c., gives satisfactory control. A peak appearing at δ 4.7–4.9 corresponds to two benzylic protons of benzyl acetate and a peak $\sim\delta$ 6.0 corresponds to H-1 of the α anomer. In the short reaction times used, we have not observed the β anomer. If the reaction is stopped before an excess of benzyl acetate appears, the desired product may usually be obtained in satisfactory purity for synthetic purposes.

During the course of this research, Ponpipom[4] published a report describing the synthesis of 1,2,6-tri-*O*-acetyl-3,4-di-*O*-benzyl-α-D-mannopyranose by the selective acetolysis of 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose in the same manner as described here. He also reported that the order of cleavage of the benzyl ethers by acetolysis of this compound is *O*-Bzl-6 > *O*-Bzl-4 > *O*-Bzl-3.

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were recorded with a Varian A-60-A spectrometer on solutions in chloroform-*d* with tetramethylsilane as the internal standard. The acetolysis reactions were recorded with acetic anhydride as the solvent and internal standard (δ 2.0). Optical rotations were determined with a Perkin–Elmer model 141 polarimeter with a jacketed 1-dm cell at 25°. Melting points were determined with a "Meltemp" instrument and are uncorrected.

Materials. — 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (Pfanstiehl Lab Inc.) was used as received. T.l.c. was performed on silica gel plates (2.5 × 7.5 cm) (Baker-flex 1B-F) with chloroform as eluent for the acetylated compounds and ether (U.S.P. grade) for the deacetylated compounds. The t.l.c. plates were examined either under a short-wavelength u.v. light or by spraying with 1:4 (v/v) sulfuric acid–ethanol and heating at 100°. Column chromatography was performed with Silica gel 60 (70–230 mesh, EM Labs. Inc.).

General acetolysis procedure. — The carbohydrate derivative (~1 g) was dissolved in acetic anhydride or 1:1 (v/v) acetic anhydride–acetic acid (anhydr.) (6–10 mL) at room temperature or by warming and then cooling to room temperature. A ^{1}H-n.m.r. spectrum was recorded on an aliquot of the mixture, and then 1–2% sulfuric acid (conc.) in acetic anhydride (4–5 drops) was added. ^{1}H-N.m.r. spectra were recorded at 5–10-min intervals in the region δ 5.0–10 until the ratio of anomeric proton to benzylic protons of benzyl acetate was 1:2. The reaction mixture was then poured into ice–water and stirred until all the acetic anhydride was hydrolyzed. The product was extracted with dichloromethane, and the extract was washed with water, saturated sodium hydrogencarbonate solution, and water, dried ($MgSO_4$ anhydr.), and evaporated to a syrup. In some cases, the acetyl compound could be crystallized directly; however, in most cases the product was noncrystalline and could only be purified by column chromatography on silica gel with chloroform as eluent. In most cases, deacetylation by refluxing in 10:1 (v/v) 1,4-dioxane–0.5M sulfuric acid for 3 h gave a more easily crystallizable product.

2,3,4-Tri-O-*benzyl*-D-*glucopyranose.* — 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (10 g) was dissolved in acetic anhydride (80 mL) and acetolyzed as just described to give 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α,β-D-glucopyranose, as a syrup, in a 95% yield. The product was dissolved in 10:1 (v/v) 1,4-dioxane–0.5M sulfuric acid and heated under reflux for 3 h. The solution was neutralized with sodium hydrogencarbonate and extracted with dichloromethane. The organic layer was washed with sodium hydrogencarbonate and water, dried (Na_2SO_4 anhydr.), and evaporated to a syrup. Chromatography on silica gel (2.5 × 30 cm) with chloroform gave 7.0 g of the diol (84%), which crystallized from chloroform–petroleum ether or aqueous ethanol to give 2,3,4-tri-*O*-benzyl-D-glucopyranose, m.p. 90–91°, $[\alpha]_D^{25}$ +19.0° (*c* 1, chloroform); lit.[5] m.p. 90–91°, $[\alpha]_D^{15}$ +19.6→18.8° (ethanol).

3,4,6-Tri-O-*benzyl*-D-*glucopyranose.* — 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose[6] (68.5 g) was benzylated with benzyl chloride (390 mL)

and potassium hydroxide (150 g) in toluene (300 mL) at reflux for 5 h. The product was processed as described by Zemplén *et al.*[5]. The tribenzyl orthoacetate could not be crystallized. However, deacetylation as described earlier gave 60 g of easily crystallized 3,4,6-tri-*O*-benzyl-D-glucopyranose (ether–hexane), m.p. 93–94.5°, $[\alpha]_D^{25}$ +70.2° (*c* 1, chloroform); lit.[7] m.p. 85–87°, $[\alpha]_{578}^{25}$ +71→65° (*c* 1, chloroform).

*Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside.* — 3,4,6-Tri-*O*-benzyl-D-glucopyranose (5 g) was dissolved in dry methanol containing 0.5% dry hydrogen chloride (50 mL). After 24 h the mixture was neutralized with aqueous sodium hydrogencarbonate, and the product extracted with dichloromethane. The organic phase was washed with water, dried (anhyd. $MgSO_4$), and evaporated to a syrup. The product could be crystallized from ether–petroleum ether to give 4.0 g, m.p. 74–76°, $[\alpha]_D^{25}$ +97.3° (*c* 1, chloroform); lit.[8] m.p. 96°, $[\alpha]_D^{23}$ +99.8° (*c* 1.15, chloroform).

2-O-Allyl-3,4-di-O-benzyl-D-glucopyranose. — Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.0 g) was allylated with allyl chloride (10 mL) and sodium hydride (2.0 g) (50% in mineral oil) in dry oxolane (tetrahydrofuran, 50 mL) at reflux for 3 h. The excess of hydride was removed with methanol and the solution evaporated to a syrup. Water was added and the product extracted with dichloromethane. The organic phase was washed with water, dilute hydrochloric acid, and water, dried ($MgSO_4$ anhydr.), and evaporated to a syrup. Purification on silica gel (2.5 × 30cm) with dichloromethane gave syrupy methyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (4.0 g), $[\alpha]_D^{25}$ +44.0° (*c* 1, chloroform); lit.[8] $[\alpha]_D^{25}$ +44.2° (*c* 1 59, chloroform). The methyl glucoside was acetolyzed as described earlier to give the noncrystalline 1,6-di-*O*-acetyl derivative, which was then deacetylated as described earlier to give, after silica gel chromatography with chloroform, 2.5 g of the title compound, m.p. 98–101° (ether–petroleum ether), $[\alpha]_D^{25}$ +31.5° (*c* 1, chloroform); lit.[9] m.p. 108–110°, $[\alpha]_D^{23}$ +32→27.6° (*c* 1, chloroform).

3,4-Di-O-benzyl-D-glucopyranose. — 3,4,6-Tri-*O*-benzyl-D-glucopyranose (1.0 g) was acetolyzed as described earlier, followed by deacetylation in 1,4-dioxane–0.5M sulfuric acid as described earlier. Chromatography on silica gel with ether (U.S.P.) gave 0.6 g, m.p. 119–121°, $[\alpha]_D^{25}$ +50.3° (*c* 1, chloroform); lit.[9] m.p. 120.5–122°, $[\alpha]_D^{23}$ +50.9° (*c* 1, chloroform).

2,3,4-Tri-O-benzyl-D-galactopyranose. — Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside[10] (1.0 g) was acetolyzed, and then deacetylated in 1,4-dioxane–0.5M sulfuric acid as described earlier. Chromatography on silica gel (1.0 × 10 cm) with chloroform gave 0.5 g, m.p. 72–74°, $[\alpha]_D^{25}$ +70.8° (*c* 1, chloroform); lit.[11] m.p. 70–71°, $[\alpha]_D^{25}$ +72.5° (*c* 0.8, ether).

1,2,6-Tri-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranose. — 3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose[12] (5.3 g) was acetolyzed as described earlier. The syrupy triacetate was crystallized from aqueous alcohol to give 3.6 g, m.p. 77–78°, $[\alpha]_D^{25}$ +31.9° (*c* 1, chloroform); lit.[4] m.p. 80–81.5°, $[\alpha]_D^{27}$ +32.5 ±0.6° (*c* 1.63, chloroform).

ACKNOWLEDGMENT

This research was supported by grant 1-RO1-AI-12509 of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Public Health Service, which is gratefully acknowledged.

REFERENCES

1 P. J. PFÄFFLI, S. H. HIXSON, AND L. ANDERSON, *Carbohydr. Res*, 23 (1972) 195–206.
2 R. EBY AND C. SCHUERCH, *Carbohydr. Res*, 50 (1976) 203–214.
3 R. U. LEMIEUX AND H. DRIGUEZ, *J. Am. Chem. Soc.*, 97 (1975) 4069–4075.
4 M. M. PONPIPOM, *Carbohydr. Res.*, 59 (1977) 311–317.
5 G. ZEMPLÉN, Z. CSÜRÖS, AND S. ANGYAL, *Ber.*, 70 (1937) 1845–1856.
6 N. K. KOCHETKOV, A. YA. KHORLIN, AND A. F. BOCHKOV, *Tetrahedron*, 23 (1967) 693–707.
7 G. EKBORG, B. LINDBERG, AND J. LÖNNGREN, *Acta Chem. Scand.*, 26 (1972) 3287–3292.
8 J. M. KÜSTER AND I. DYONG, *Justus Liebigs Ann. Chem*, 12 (1975) 2179–2189.
9 P. A. GENT AND R. GIGG, *Carbohydr. Res.*, 49 (1976) 325–333.
10 P N. AUSTIN, F. E. HARDY, J. G. BUCHANAN, AND J. BADDILEY, *J. Chem. Soc.*, (1965) 1419–1424.
11 R. GIGG AND C. D. WARREN, *J. Chem. Soc.*, (1965) 2205–2210.
12 N. E. FRANKS AND R. MONTGOMERY, *Carbohydr. Res.*, 6 (1968) 286–298.