Carbohydrate Research, 123 (1983) 157–159
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Partial benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

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(Received May 21st, 1983; accepted for publication, June 18th, 1983)

Partially benzylated monosaccharides are widely used as intermediates for stepwise synthesis of oligosaccharides. In a previous paper[1], partial benzylation of methyl 4,6-*O*-benzylidene-α- and -β-D-glucopyranoside was reported. This communication describes partial benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) with benzyl bromide in the presence of barium oxide.

During the past decade, two publications have appeared on the partial benzylation of **1**. One concerned monobenzylation with benzyl bromide in *N,N*-dimethylformamide in the presence of silver oxide, reported by Borén *et al.*[2]; they isolated methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**3**) in 36% yield by crystallization from the reaction mixture, and fractional recrystallization. However, no decision could be made as to the order of the relative reactivity of the hydroxyl groups, because of the unknown ratio of **3** to methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**4**), and a low yield of **3**.

The other study on this monobenzylation, reported by Indian chemists[3], used benzyl bromide in dimethyl sulfoxide in the presence of sodium hydride, giving methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**2**) (20% yield) and **4** (66% yield), with a trace of **3**. The physical constants reported for the **4** obtained by them are, however, quite different from the values for the compound prepared[4] by benzylation of methyl 4,6-*O*-benzylidene-2,3-*O*-(dibutylstannylene)-α-D-mannopyranoside. A reinvestigation of the foregoing partial benzylation of **1** was clearly necessary.

Partial benzylation of **1** with 1.2 mol. equiv. of benzyl bromide in *N,N*-dimethylformamide in the presence of barium oxide and barium hydroxide yielded **2** (10%), **3** (16%), **4** (66%), and **1** (8%), as shown by quantitative t.l.c. Monobenzylation of **1** by the method of Borén *et al.*[2] with benzyl bromide and silver oxide in *N,N*-dimethylformamide gave a mixture of **2** (10%), **3** (55%), **4** (19%), and **1** (16%), as detected by t.l.c. When **1** was treated with 0.84 mol. equiv. of benzyl bromide in dimethyl sulfoxide in the presence of sodium hydride, as described[3], the reaction mixture was found to consist of **2** (65%), **3** (16%), **4** (7%), and **1** (12%) by t.l.c. analysis.

0008-6215/83/$ 03.00

The molar ratios of the reaction products suggest that, in benzylation in the presence of barium oxide, OH-3 is more reactive than OH-2. Under the same conditions, it was shown[1] that the reactivity of the hydroxyl groups is OH-2 > OH-3 for methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, and OH-3 > OH-2 for the β anomer. From the foregoing findings, it seems that the *cis*-OR substituent activates the adjacent equatorial hydroxyl group in benzylation in the presence of barium oxide. The order of the reactivity of the hydroxyl groups in benzylation in the presence of silver oxide is OH-2 >OH-3.

The order of the reactivity of the hydroxyl groups in benzylation in the presence of sodium hydride may be OH-2 > OH-3. However, the quite high yield of the dibenzyl ether **2** suggests that the benzylation occurs very rapidly, and that this method is not suitable for achieving a selective reaction. The reverse order in benzylation in the presence of sodium hydride was found by the Srivastavas[3]. They indicated that the 3-benzyl ether migrates faster than the 2-benzyl ether in t.l.c., and the physical constants they reported for the 3-benzyl ether are very similar to those previously given[2] for the 2-benzyl ether; in contrast, we found that the 2-benzyl ether moves faster than the 3-benzyl ether in t.l.c., and the physical constants for the 3-benzyl ether are quite different from those described by Nashed[4] for the 2-benzyl ether. It is therefore obvious that the discrepancy as regards the order of reactivity is actually attributable to wrong assignments of **3** and **4**.

EXPERIMENTAL

For general methods, see refs. 1 and 5.

Monomolar benzylation. (a) In the presence of barium oxide. — A solution of D-mannoside **1** (2 g) in *N*,*N*-dimethylformamide (20 mL) was stirred with benzyl bromide (1.03 mL, 1.2 mol. equiv.), barium oxide (2.5 g), and barium hydroxide octahydrate (1 g) for 20 h in the dark at room temperature.

(b) In the presence of silver oxide. — The D-mannoside **1** (2 g) was benzylated with silver oxide (4 g) and benzyl bromide (1.03 mL, 1.2 mol. equiv.) in *N*,*N*-dimethylformamide (20 mL) for 48 h in the dark at room temperature, as described by Borén *et al.*[2].

(c) In the presence of sodium hydride. — The D-mannoside **1** (149 mg) was treated with benzyl bromide (53 μL, 0.8 mol. equiv.) in dimethyl sulfoxide (0.75 mL) in the presence of sodium hydride (150 mg) for 2 h at room temperature, as described by the Srivastavas[3].

The reaction products obtained by these three methods were individually fractionated by chromatography on silica gel into three components (other than the starting material).

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**2**) was obtained as a syrup: $[\alpha]_D^{18}$ +26.7° (*c* 2.2, chloroform); R_L 0.95 (9:1 benzene–acetone) and 0.84 (3:2 hexane–ethyl acetate); p.m.r. (in $CDCl_3$): δ 7.32 (m, 15 H,

3 Ph), 5.58 (s, 1 H, PhC*H*), 4.75 and 4.68 (2 s, 5 H, 2 PhCH_2, H-1), and 3.28 (s, 3 H, OCH_3).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.60; H, 6.56.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**3**) crystallized from ethanol, m.p. 44–46°, $[\alpha]_D^{21}$ +2.9° (*c* 1.0, chloroform); R_F 0.66 (9:1 benzene–acetone or 3:2 hexane–ethyl acetate); lit.[2] m.p. 42–44°, $[\alpha]_D$ +2° (*c* 1.0, chloroform); p.m.r. (in $CDCl_3$): δ 7.37 (m, 10 H, 2 Ph), 5.55 (s, 1 H, PhC*H*), 4.70 (s, 3 H, PhCH_2, H-1), 3.33 (s, 3 H, OCH_3), and 2.55 (broad s, 1 H, OH).

Treatment of **3** with benzoyl chloride gave methyl 3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside as a syrup; $[\alpha]_D^{10}$ −42.1° (*c* 1.7, chloroform); p.m.r. (in $CDCl_3$): δ 5.60 (s, 1 H, PhC*H*), 5.53 (q, 1 H, $J_{2,3}$ 2, $J_{3,4}$ 10 Hz, H-3), 4.73 (s, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.58 (s, 2 H, PhCH_2), and 3.40 (s, 3 H, OCH_3).

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**4**) was obtained as a syrup; $[\alpha]_D^{20}$ +38.8° (*c* 1.8, ethanol); R_F 0.44 (9:1 benzene–acetone), 0.42 (3:2 hexane–ethyl acetate); lit.[4] $[\alpha]_D^{25}$ +38.3° (*c* 1, ethanol), lit.[6] $[\alpha]_D$ +38° (ethanol); p.m.r. (in $CDCl_3$): δ 7.5–7.2 (m, 10 H, 2 Ph), 4.38 (s, 1 H, PhC*H*), 5.0–4.6 (broad d, 3 H, PhCH_2, H-1), 3.36 (s, 3 H, OCH_3), and 2.83 (broad s, 1 H, OH). The p.m.r. spectrum ($CDCl_3$) (lit.[4]) showed δ 7.5–7.25 (Ph), 4.86 and 4.70 (q, 2 H, PhCH_2), and 3.37 (s, 3 H, OCH_3).

Benzoylation of **4** afforded methyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside as a syrup; $[\alpha]_D^{18}$ −51.6° (*c* 1.3, chloroform); lit.[4] $[\alpha]_D^{25}$ −52.9° (*c* 1, chloroform); p.m.r. (in $CDCl_3$): δ 5.63 (s, 1 H, PhC*H*), 5.57 (q, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 3.5 Hz, H-2), 4.80 (d, 1 H, H-1), 4.70 (s, 2 H, PhCH_2), and 3.35 (s, 3 H, OCH_3). The p.m.r. spectrum ($CDCl_3$) (lit.[4]) showed δ 5.59 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.4 Hz, H-2), and 4.82 (d, 1 H, H-1).

ACKNOWLEDGMENT

The authors thank Mr. O. Kato, Iatron laboratories, Inc., for the quantitative t.l.c.

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