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## Note

# Formylation as a side-reaction in glycosidation: formation of benzyl 2,3,4-tri-*O*-benzyl-6-*O*-formyl-β-D-glucopyranoside

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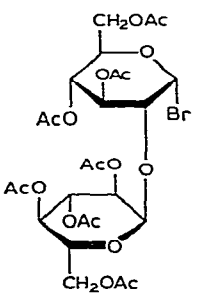
Hough and Lewis[1] reported an unexpected formylation in an attempted glycosidation reaction in which *N*,*N*-dimethylformamide was used as solvent. We now describe another case of such a reaction.

In an attempted synthesis[2] of α-D-Glc*p*-(1→2)-α-D-Glc*p*-(1→6)-D-Glc, the branching part of some native dextrans[3], hepta-*O*-acetyl-α-kojibiosyl bromide[4] (**1**) was treated with benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside[5] (**2**) under halide-ion catalyzed conditions[6] with dichloromethane–*N*,*N*-dimethylformamide as solvent. No condensation between **1** and **2** was observed at room temperature, even after 2 weeks. Instead, benzyl 2,3,4-tri-*O*-benzyl-6-*O*-formyl-β-D-glucopyranoside (**3**) was formed (70% yield). The structure of **3** was proved by its p.m.r. spectrum (a sharp singlet at δ 7.97, characteristic of formates[7]) and by an independent synthesis of **3** *via* formylation[8] of **2** with (chloromethylene)dimethylammonium chloride[9]. No trace of **3** could be detected when **2** was treated with tetraethylammonium bromide (**4**), ethyldi-isopropylamine (**5**), and 4Å molecular sieve in a mixture of dichloromethane and *N*,*N*-dimethylformamide, and **1** was recovered (82%) when it was stirred with **4**, **5**, and 4Å molecular sieve in the same solvent. Both **4** and **5** were found to be essential for formylation to occur.



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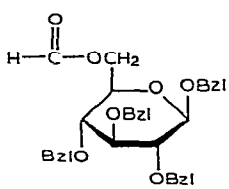

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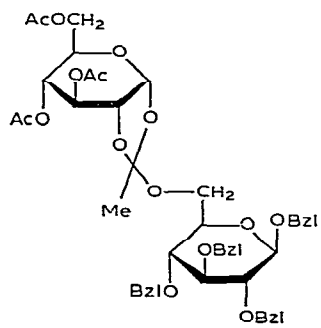

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Under identical conditions, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[10] and **2** yielded **6** with no traces of **3**. Orthoester synthesis *via* halide-ion catalysis was reported first by Lemieux and Morgan[11], and more recently, using tributylstannylidene-activated aglycons, by Ogawa and Matsui[12].

It is thought that, in this formylation, the first step is epimerization (at a reasonable rate) at C-1 of **1** (containing a non-participating group[13] at position 2), yielding the more-reactive β-bromo derivative which then, together with *N*,*N*-dimethylformamide, induces a Vilsmeier-type formylation of **2**, instead of functioning as a glycosylating agent.

## EXPERIMENTAL

Melting points were measured on a Kofler hot-stage and are uncorrected. T.l.c. was performed on pre-coated layers of silica gel containing fluorescent indicator (Merck). Detection was effected with ultraviolet light or by charring with 50% sulfuric acid. Silica gel (according to Stahl) was used for column chromatography. Benzene–methanol (100 : 3) was used for both t.l.c. and column chromatography. P.m.r. spectra were recorded for solutions in $CDCl_3$ (internal $Me_4Si$) with a Jeol MH-100 instrument at 100 MHz. I.r. spectra were recorded with a Perkin–Elmer 238 spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter at room temperature.

*Hepta-O-acetyl-α-kojibiosyl bromide* (**1**). — A solution of α-kojibiose octaacetate[14,15] (5.0 g) in acetic acid (50 ml) was treated with 40% hydrogen bromide in acetic acid (50 ml), and the mixture was kept at 4° for 1 h and then at room temperature for 2 h. A solution of the reaction mixture in chloroform (200 ml) was washed successively with ice–water (3 × 50 ml), aqueous sodium hydrogen carbonate (3 × 50 ml), and ice–water (3 × 50 ml), and dried ($Na_2SO_4$). Evaporation of the solvent left a colourless syrup which crystallized immediately upon addition of ether (30 ml), to give **1** (4.8 g, 93%), m.p. 146–147°, $[\alpha]_D$ +218.5° (*c* 1.2, chloroform); lit.[4] m.p. 141–142°, $[\alpha]_D^{25}$ +243° (*c* 0.7, acetone).

*Anal.* Calc. for $C_{26}H_{35}BrO_{17}$: C, 44.64; H, 5.04. Found: C, 44.79; H, 4.86.

*Benzyl 2,3,4-tri-O-benzyl-6-O-formyl-β-D-glucopyranoside* (**3**). — (*a*) A mixture of **1** (2.39 g, 3.42 mmol), benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**2**; 0.95 g, 1.75 mmol), **4** (0.72 g, 3.42 mmol), **5** (0.6 ml, 3.42 mmol), 4Å molecular sieve (1.5 g), dichloromethane (8 ml), and *N*,*N*-dimethylformamide (1.5 ml) was stirred at room temperature for 7 days. The mixture was diluted with chloroform (20 ml), filtered, and washed with water (3 × 10 ml). The resulting syrup was chromatographed on silica gel (50 g), to give **3** (0.70 g, 70.0%), m.p. 100–102°, $R_F$ 0.70. Recrystallization from cyclohexane gave **3** as fine needles, m.p. 102–103°, $[\alpha]_D$ +1.1° (*c* 1.60, chloroform); $\nu_{max}^{CCl_4}$ 1735 $cm^{-1}$ (C=O). P.m.r. data: δ 3.4–3.6 (m, 4 H, H-2,3,4,5), 4.15–5.02 (m, 11 H, H-1,6,6′, 4 C*H*$_2$-Ph), 7.24–7.36 (m, 20 H, aromatic protons), and 7.98 (s, 1 H, *H*-C=O).

*Anal.* Calc. for $C_{35}H_{36}O_7$: C, 73.92; H, 6.38. Found: C, 74.27; H, 6.61.

(*b*) A solution of **2** (300 mg) in dichloromethane (2 ml) was treated with freshly prepared (chloromethylene)dimethylammonium chloride[9] (~0.5 g) at room temperature for 3 h. The mixture was then diluted with dichloromethane (20 ml), washed with water (20ml), dried ($Na_2SO_4$), and concentrated. The residual syrup crystallized spontaneously, to give crude **3** (290 mg, 93%), $R_F$ 0.70. Recrystallization from cyclohexane (3 ml) afforded pure **3** (230 mg), m.p. 101–102.5°, $[\alpha]_D$ +0.6° (*c* 1.36, chloroform). The p.m.r. spectrum was identical to that described in (*a*).

*3,4,6-Tri-O-acetyl-α-D-glucopyranose 1,2-(1,2,3,4-tetra-O-benzyl-β-D-glucopyranose-6-yl orthoacetate*) (**6**). — A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (700 mg, 1.70 mmol), **2** (370 mg, 0.68 mmol), **4** (755 mg, 3.59 mmol), **5** (0.3 ml, 1.72 mmol), 4Å molecular sieve (3 g), dichloromethane (10 ml), and *N,N*-dimethylformamide (5 ml) was stirred at room temperature for 4 days, during which 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (650 mg), **4** (380 mg), and **5** (0.3 ml) were added to the mixture. T.l.c. then indicated almost complete disappearance of **2**. The mixture was diluted with dichloromethane (100 ml), filtered, washed with water (2 × 10 ml), dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on silica gel (70 g, pretreated[16] with ammonium hydroxide), to give a colourless, homogeneous syrup (0.47 g). Trituration with hexane gave solid **3** (380 mg, 64%), $R_F$ 0.56. Recrystallization from ether–hexane afforded **3**, m.p. 78–81°, $[\alpha]_D$ +8.4° (*c* 1.22, chloroform). P.m.r. data: $\delta$ 1.71 (s, 3 H, orthoacetate *endo*-Me[11,17]), 1.98–2.14 (m, 9 H, 3 AcO), 3.4–6.2 (m, 21 H, 5 $CH_2$-Ph and skeleton protons), 5.7 (d, $J$ ~5 Hz, 1 H, H-1), and 7.2–7.4 (m, 20 H, aromatic protons).

*Anal.* Calc. for $C_{48}H_{54}O_{15}$: C, 66.20; H, 6.20. Found: C, 66.05; H, 6.28.

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