Note

A practical synthesis of methyl 4-6-0-benzylidene-a- and -B-D-glucopyranoside

DAVID M. HALL

Department of Textile Engineering, Auburn University, Auburn, Alabama 36830 (U.S.A.) (Received April 28th, 1980; accepted for publication, May 20th, 1980)

Several methods have been published for the preparation of the title compounds, and a historical account thereof has already been given¹. The benzylidene acetal is usually the derivative of choice for protecting the 4- and 6-hydroxyl groups of Dglucosides during subsequent reactions of the remaining hydroxyl groups.

The benzylidene group is quantitatively removed by employing much milder conditions² than those used for the ethylidene group³, for example; however, the ethylidene acetal has heretofore been prepared in better yields³ than those reported for the benzylidene acetals. Consequently, a simpler method for preparing the benzylidene derivatives of methyl α - and β -D-glucoside in good yield was found desirable in order to make maximum use of the ease of removal of this group when preparing oligomers (related to cellulose) that might also contain other, somewhat labile substituents.

It has been found that the zinc chloride-benzaldehyde complex, first alluded to by Van Cleve¹ (who failed to recognize its significance), is a key intermediate in promoting the formation of high yields of the benzylidene acetal. Apparently, this catalyst complex does not form readily, or is poisoned, if the D-glucoside is added first to the reaction mix, and is then followed by the zinc chloride catalyst, and this may explain why variable yields of the acetal are sometimes obtained. It has further been found that pure materials and reagents are not necessary, that good yields may be obtained by using the benzaldehyde as received (but dried over Drierite), as well as the "practical grade" of methyl α - and β -D-glucoside, provided that they are essentially anhydrous, and that the zinc chloride employed need be neither reagent grade nor fused. Good results were obtained when lumps of dry, technical-grade zinc chloride were employed; use of this highly hygroscopic salt in large lumps, weighed by the difference method, lessens the amount of water sorbed by the catalyst before it can be added to the benzaldehyde (in which it quickly dissolves). The zinc chloridebenzaldehyde reaction is exothermic, thus aiding the dissolving process.

The reaction mixture is vigorously stirred for at least 15 min, to ensure maximum formation of the benzaldehyde-zinc chloride complex, resulting in the formation of

a milky, gelatinous paste; indeed, if proper care is exercised, some of the catalyst complex may even be precipitated. The D-glucoside is then added as rapidly as possible, with vigorous stirring, the viscosity of the solution decreasing during the addition. For the α -D-glucoside, the reaction mixture soon becomes clear, and remains so during the entire reaction; for the β -D-glucoside, the mixture thins out, and, after 15-30 min, the benzylidene acetal precipitates, and the solution again becomes difficult to stir.

Isolation of the acetal may be accomplished more simply than by previous methods. The reaction mixture is poured into a separatory funnel containing icewater and petroleum ether, and this mixture is vigorously shaken in order to remove zinc salts and unreacted D-glucoside, and precipitate the acetal as a fluffy, crystalline mass. Filtration, followed by washing with more water and petroleum ether, gives a product that has only a faint odor of benzaldehyde, and that after being air-dried, is pure enough for most further reactions, such as acetylation and benzylation. Virtually pure products are obtained after a single recrystallization from aqueous ethyl alcohol containing a small proportion of sodium hydrogencarbonate to remove any benzoic acid and traces of zinc salts. The steps of the synthesis outlined are both rapid and simple, in addition to providing excellent yields without the need for purified or special reagents. Furthermore, the compounds can be prepared in a single day, with a minimum of manipulations.

Use of the described zinc chloride-benzaldehyde catalyst system increased only marginally the yields (~10-15%) of 4,6-O-benzylidene-D-glucose, compared to that given by the method of Zervas⁴, probably owing to the fact that D-glucose is virtually insoluble in benzaldehyde. Both methyl α - and β -D-glucoside have somewhat greater solubility in benzaldehyde, and use of the isolation technique outlined herein for the D-glucosides facilitates easy and rapid recovery of the D-glucose acetals. The use of this catalyst system may find application to the synthesis of acetals of other aldoses and aldosides.

EXPERIMENTAL

General. — The methyl α - and β -D-glucosides were of "practical grade", and were dried over P₂O₅ in vacuo for several days before use. The benzaldehyde (NF grade) was dried over nonindicating Drierite (anhydrous calcium sulfate) for at least 24 h before use. The zinc chloride was granular, technical grade containing 95% of zinc chloride. Melting points were determined on a Nalge-Axelrod micro meltingpoint apparatus, and are corrected. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemical Engineering at Auburn University. Crude yields and the yield after at least one recrystallization are both reported.

Methyl 4,6-O-benzylidene- α -D-glucopyranoside. — With stirring, lump zinc chloride (45 g) was quickly added to dry benzaldehyde (155 mL). After 15–20 min, or when the mixture became a milky, gelatinous paste, methyl α -D-glucopyranoside

(45 g) was quickly added. Mechanical stirring was continued for 4 h, and the clear, syrupy mass was poured into a 1-L, separatory funnel containing ice-water (400 mL) and petroleum ether (400 mL). The mixture was vigorously shaken, and after a few minutes, the fluffy, crystalline mass obtained was filtered off, and alternately washed (4 times) with cold water (100 mL) and petroleum ether (100 mL). At this point, the crystals had only a faint odor of benzaldehyde, and yielded 57.5 g of air-dried product. The material can be used directly for further reactions, or obtained in virtually pure form by one recrystallization from 1:3 2-propanol-water containing sodium hydrogencarbonate (0.5 g), to give 52 g (80%) of fluffy needles, m.p. 166-167°, $[\alpha]_D^{25} + 108°$ (c 2, chloroform); lit.^{5,6} m.p. 166-167°, $[\alpha]_D^{20} + 110°$ (chloroform). *Anal.* Calc. for C₁₄H₁₈O₆: C, 59.6; H, 6.4. Found: C, 59.5; H, 6.4.

Methyl 4,6-O-benzylidene- β -D-glucopyranoside. — Methyl β -D-glucopyranoside was benzylidenated as for the α -D-glucoside. Zinc chloride (100 g), benzaldehyde (330 mL), and the β -D-glucoside (100 g) were allowed to react for 1 h after precipitation of the acetal had begun (usually, after 15–30 min), the viscous mass then being stirred only with difficulty. The air-dried product (110 g) may be used directly for further syntheses, or be recrystallized from 1:4 ethanol-water containing sodium hydrogencarbonate (0.5 g), to give 102 g (70%), m.p. 200–201°, $[\alpha]_D^{25} - 75^\circ$ (c 1, methanol); lit.^{5.6} values range from m.p. 194 to 208.5° and $[\alpha]_D - 75$ to -76° (methanol).

Anal. Calc. for C14H18O6: C, 59.6; H, 6.4. Found: C, 59.7; H, 6.4.

A further trial using zinc chloride (20 g), benzaldehyde (100 mL), and airdried methyl β -D-glucoside (20 g), gave 22 g of crude, and 19.5 g (67%) of oncerecrystallized, product.

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REFERENCES

- 1 J. W. VAN CLEVE, Carbohydr. Res., 17 (1971) 461-464.
- 2 D. J. BELL AND J. LORBER, J. Chem. Soc., (1940) 453-455.
- 3 D. M. HALL AND T. E. LAWLER, Carbohydr. Res., 16 (1971) 1-7.
- 4 L. ZERVAS, Ber., 64 (1930) 2289-2296.
- 5 A. N. DE BELDER, Adv. Carbohydr. Chem., 20 (1965) 219-302; Adv. Carbohydr. Chem. Biochem., 34 (1977) 179-241, and references cited therein.
- 6 M. E. EVANS, Carbohydr. Res., 21 (1972) 473-475.