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An Improvement in the Preparation of Some Carbohydrate Benzylidene Acetals

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Abstract

Carbohydrate benzylidene and *p*-methoxybenzylidene acetals are easily prepared by treatment of various sugar derivatives with either benzaldehyde diethyl acetal or *p*-methoxybenzaldehyde diethyl acetal, respectively, in refluxing chloroform containing camphorsulfonic acid.

Benzylidene acetals are useful protecting, and reactive, groups in carbohydrate chemistry.[1] The preferred method of preparation generally involves treatment of the appropriate carbohydrate with benzaldehyde/zinc chloride, but procedures utilizing benzaldehyde dimethyl or diethyl acetal and an acid catalyst are also commonly employed. A recent paper[2] describing the preparation of a carbohydrate benzylidene derivative by using such a benzaldehyde acetal in dichloromethane prompts us to report on our own, more extensive, studies.

Treatment of methyl α-D-galactopyranoside with benzaldehyde/zinc chloride according to Hall's procedure[3] for the corresponding D-glucoside gave variable yields of the desired methyl 4,6-*O*-benzylidene-α-D-galactoside. The use of benzaldehyde dimethyl acetal[4] as an alternative reagent improved the yield of the desired benzylidene acetal considerably (74%), but the experimental procedure was still unattractive (heating in dimethylformamide at 100° under a stream of nitrogen gas). However, when methyl α-D-galactopyranoside was subjected to benzaldehyde diethyl acetal and a trace of camphorsulfonic acid in *chloroform* at reflux, the desired methyl 4,6-*O*-benzylidene-α-D-galactoside was obtained essentially pure and in good yield. Similarly, methyl β-D-galactopyranoside, methyl α-D-glucopyranoside and methyl β-D-glucopyranoside all gave their corresponding 4,6-*O*-benzylidene derivatives when subjected to the benzaldehyde acetal in chloroform at reflux. Not unexpectedly, methyl α-D-mannopyranoside could *not* be converted into the desired methyl 4,6-*O*-benzylidene-α-D-mannoside (here the dimethylformamide procedure *is* superior[4]), presumably owing to the solubility of this monobenzylidene derivative in chloroform

[1] Gelas, J., *Adv. Carbohydr. Chem. Biochem.*, 1981, **39**, 71.
[2] Åkerfeldt, K., and Bartlett, P. A., *Carbohydr. Res.*, 1986, **158**, 137.
[3] Hall, D. M., *Carbohydr. Res.*, 1980, **86**, 158.
[4] Patroni, J. J., Stick, R. V., Skelton, B. W., and White, A. H., *Aust. J. Chem.*, 1988, **41**, 91.

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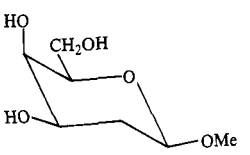
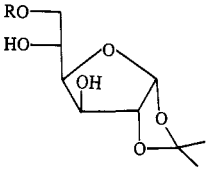
(only the products of further benzylidenation, namely the methyl 2,3 : 4,6-di-*O*-benzylidene-α-D-mannosides, were ever formed in amount). In all cases, completion of the reaction was indicated by disappearance of the insoluble starting material. Neutralization (solid potassium carbonate) of the reaction mixture, followed by filtration and evaporation of the filtrate, gave an essentially pure product suitable for subsequent transformations. Occasionally, particularly on large-scale reactions, some of the liberated ethanol was removed by distillation to ensure completion of reaction.

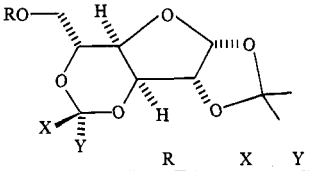


(1)



(2) R = H

(4) R = $SiPh_2Bu^t$



	R	X	Y
(3)	H	Ph	H
(5)	$SiPh_2Bu^t$	H	Ph

Apart from the simple methyl glycosides described above, several other carbohydrate derivatives were converted into their benzylidene derivatives. The deoxy sugar (1) was easily transformed into the known methyl 4,6-*O*-benzylidene derivative, but the triol (2) gave only a modest yield of the 3,5-*O*-benzylidene derivative (3). However, the silyl derivative (4) smoothly gave the 3,5-*O*-benzylidene derivative (5),* and these last two reactions have been commented upon recently.[2] As well, methyl α-D-glucopyranoside, methyl α-D-galactopyranoside and the deoxy sugar (1) all gave the expected 4,6-*O*-*p*-methoxybenzylidene derivatives when treated with *p*-methoxybenzaldehyde diethyl acetal, and methyl α-D-mannopyranoside gave a high yield of methyl 2,3 : 4,6-di-*O*-*p*-methoxybenzylidene-α-D-mannosides. In contrast, D-glucose and D-mannitol showed essentially no reaction with the benzaldehyde acetal in chloroform, and this limits the method to substrates which have *some* solubility in chloroform.

Experimental

Experimental details have been given previously.[5]

General Benzylidenation Procedure

The carbohydrate starting material was powdered by hand and added to chloroform (5 ml per mmol) containing the appropriate benzylidene diethyl acetal (1·4 mol. equiv.) and camphorsulfonic acid (50 mg). The mixture was then heated at reflux until all of the solid had dissolved (1–2 h; for chloroform-soluble starting materials, the progress of the reaction could be easily monitored by t.l.c.; for large-scale preparations and some of the substrates it was advantageous to remove the liberated ethanol by distillation, a constant reaction volume being maintained by the addition of fresh chloroform). T.l.c. of the chloroform solution then generally indicated the formation of the desired product, and powdered potassium carbonate (5 g) was added, followed by a further period (0·5 h) of stirring and heating. Filtration of the hot solution and removal of solvent from the filtrate gave a solid which was generously washed with hexane (to remove the excess benzaldehyde acetal) to leave the essentially pure product. A small sample of the product was then purified by recrystallization.

• The catalyst used here was pyridinium *para*-toluenesulfonate.

[5] Patroni, J. J., Skelton, B. W., Stick, R. V., and White, A. H., *Aust. J. Chem.*, 1980, 33, 987.

*Specific Compounds**

Methyl 4,6-*O*-benzylidene-α-D-galactoside.[a,b] M.p. 169–171° (EtOH/light petroleum; lit.[6] 170–172°), $[\alpha]_D^{20}$ +159° (lit.[6] +166·5°).

Methyl 4,6-*O*-*para*-methoxybenzylidene-α-D-galactoside.[b] M.p. 141–143° (EtOH; lit.[7] 139–141°), $[\alpha]_D^{20}$ +128° (lit.[7] +120°).

Methyl 4,6-*O*-benzylidene-β-D-galactoside.[a,b] M.p. 198–200° (EtOH/light petroleum; lit.[8] 200°), $[\alpha]_D^{20}$ −33·0° (lit.[8] −35·1°).

Methyl 4,6-*O*-benzylidene-α-D-glucoside.[b] M.p. 163–164° (EtOAc; lit.[9] 164–165°), $[\alpha]_D^{20}$ +113° (lit.[9] +117·5°).

Methyl 4,6-*O*-para-methoxybenzylidene-α-D-glucoside.[b] M.p. 199–200° (EtOAc; lit.[7] 194°), $[\alpha]_D^{20}$ +93·7° (*c*, 1·5 in dimethylformamide; lit.[7] +97·4°).

Methyl 4,6-*O*-benzylidene-β-D-glucoside.[b] M.p. 201–203° (EtOAc; lit.[9] 199–201°), $[\alpha]_D^{20}$ −61·0° (lit.[9] −62·3°).

Methyl 2,3 : 4,6-di-*O*-benzylidene-α-D-mannosides.[a–c] M.p. 182–183° (MeOH; lit.[10] 180–181°), $[\alpha]_D^{20}$ 0·0° (lit.[10] 0°). M.p. 96–98° (MeOH; lit.[10] 96–98°), $[\alpha]_D^{20}$ −58·0° (lit.[10] −61°).

Methyl 2,3 : 4,6-di-O-para-*methoxybenzylidene*-α-D-mannoside.[b,c] M.p. 160–161° (MeOH),[d] $[\alpha]_D^{20}$ −3·0° (Found: C, 64·3; H, 6·1. $C_{23}H_{26}O_8$ requires C, 64·2; H, 6·1%). ^{1}H n.m.r. (80 MHz) δ 5·58, s, ArCH; 6·23, s, ArCH. ^{13}C n.m.r. (20·1 MHz) δ 102·1, ArCH; 103·1, ArCH.

Methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*lyxo*-hexoside (67%).[e] M.p. 199–202° (CH_2Cl_2/light petroleum; lit.[11] 200–204°), $[\alpha]_D^{20}$ −42·5° (lit.[11] −40·5°).

Methyl 2-deoxy-4,6-O-para-*methoxybenzylidene*-β-D-lyxo-*hexoside* (76%).[e] M.p. 189–190° (Pr^i_2O/EtOH), $[\alpha]_D^{20}$ −48·0° (Found: C, 60·8; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). ^{1}H n.m.r. (80 MHz) δ 5·54, s, ArCH. ^{13}C n.m.r. (20·1 MHz) δ 101·1, 101·4 (C 1, ArCH).

3,5-*O*-(*S*)-Benzylidene-1,2-*O*-isopropylidene-α-D-glucose (3) (54%).[e] M.p. 147–150° (EtOAc/light petroleum; lit.[12] 151–152°), $[\alpha]_D^{20}$ +22·3° (lit.[12] +23·9°).

3,5-*O*-(*R*)-Benzylidene-6-*O*-t-butyldiphenylsilyl-1,2-*O*-isopropylidene-α-D-glucose (5). $[\alpha]_D^{20}$ +38·0° (lit.[2] +36·8°).

Acknowledgment

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* Superscript letters identify the following conditions.

[a] Ethanol was removed by distillation.

[b] The crude product, obtained in near-quantitative yield, was essentially pure by t.l.c.

[c] 2·7 mol. equiv. of the benzaldehyde diethyl acetal were used.

[d] Only one diastereoisomer, assigned the (*R*,*R*)-2,3 : 4,6-di-*O*-para-methoxybenzylidene configuration,[4] was obtained pure.

[e] The crude product was obtained as a mixture (t.l.c.), and the required compound was isolated in the yield indicated.

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[12] Van Cleve, J. W., Inglett, G. E., and Tjarks, L. W., *Carbohydr. Res.*, 1985, **137**, 259.