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Note

Removal of *O*-benzyl protecting-groups of carbohydrate derivatives by catalytic, transfer hydrogenation

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Wide use is made of the *O*-benzyl substituent as a protecting group in carbohydrate chemistry[1–3]. Its attractiveness stems from its stability both to acids and bases, as well as the fact that it may be removed under relatively mild conditions, *i.e.*, by catalytic[1–3] or chemical[3,4] hydrogenolysis, or by bromination–hydrolysis[3,5]. We have found that catalytic, transfer hydrogenation[6,7], a reaction used for the deprotection of peptide *N*-benzyl derivatives[7–9], provides an additional means for the removal of *O*-benzyl groups of carbohydrate derivatives. Because the reaction is highly efficient and experimentally facile, it may offer advantages over established methods in certain applications.

Catalytic, transfer hydrogenations generally employ palladium as the catalyst, and cyclohexene[6,7], cyclohexadiene[8], or formic acid[9] as the hydrogen donor. In the present study, a combination of palladium-on-charcoal and formic acid has been used. The benzyl ether in methanol containing 10% of formic acid was added under nitrogen to a suspension of 10% palladium-on-charcoal in the same mixed solvent. At the end of the reaction, the catalyst was filtered off, and the toluene formed by hydrogenolysis of the benzyl group(s) was removed by co-distillation with the solvent. By using one gram of the catalyst to 0.2–0.4 mmol of *O*-benzyl derivative, complete debenzylation was generally effected within one hour, judging from the results of periodic monitoring of the reaction mixture by thin-layer chromatography, and characterization of the crude product by n.m.r. spectroscopy.

Compounds that have been examined are listed in Table I, together with the products obtained. Several other types of protecting-group are represented, and it may be seen that *O*-benzylidene (as in **4**) and *O*-trityl (as in **7**) substituents are also readily removed under these conditions. As triphenylmethane was produced from **7**, and neither benzaldehyde nor benzyl alcohol was detected in the reaction mixture from **4**, these substituents were hydrogenolyzed, not hydrolyzed. An *O*-mesyl (as in **5**) and *O*-acyl (as in **3** and **7**) groups were unaffected, although the *tert*-butyldimethylsilyl substituent of **5** was removed.

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TABLE I

CATALYTIC, TRANSFER HYDROGENATION OF *O*-BENZYL AND OTHER DERIVATIVES

	Starting material	*Product*
1	2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose[a]	D-glucose
2	2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose	D-arabinose
3	1-*O*-Benzoyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[a]	1-*O*-benzoyl-α-D-glucopyranose
4	Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside[b]	methyl α-D-glucopyranoside
5	Methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside	methyl 4-*O*-mesyl-β-D-glucopyranoside
6	3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[c]	1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose
7	Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside	methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside

[a]Additional methanol was needed in order to bring the compound into solution. [b]When a solution of the compound was passed through a column of the catalyst (as in ref. 8) during 5 min, only ~10% debenzylation occurred. [c]During processing, the formic acid was removed by ion exchange.

During the reaction of 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**), ~5% of the 5,6-acetal groups were lost. This is not attributed solely to the acidity of the medium, because 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was unaffected in the same solvent for the same length of time, whereas it readily yielded 1,2-*O*-isopropylidene-α-D-glucofuranose when palladium-on-charcoal was introduced. Analogous behavior was shown by 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, although 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and its 6-acetate proved to be stable. Hence, the exocyclic acetal groups of these *gluco* and *allo* derivatives are highly labile in the presence of the catalyst. It is possible that, in the reaction of the 3-*O*-benzyl derivative **6**, the activity of the palladium following selective hydrogenolysis of the ether group was inadequate to cause ready removal of the 5,6-*O*-isopropylidene group.

Although the experimental conditions given were effective for the compounds examined, they are not necessarily optimal. The proportion of catalyst to substrate employed is probably suitable for most purposes, as several of the reactions were found to proceed far more slowly when only half of the recommended proportion of palladium-on-charcoal was used. Furthermore, the catalyst recovered immediately after complete debenzylation of **1** (in 1 h, with 1 g per 0.2 mmol, as already noted) had markedly lessened activity towards a second lot of **1**. In practice, however, in order to minimize the proportion of palladium used, it may be advisable to introduce the catalyst portionwise, while monitoring the progress of the reaction chromatographically. Cyclohexadiene was used as the hydrogen donor in some experiments, but appeared to offer no advantage over formic acid; for example, the reactions took much longer, and there was no improvement in selectivity between the *O*-benzyl

and *O*-benzylidene groups of **4**. We have not examined the effect of (*a*) solvents other than methanol, (*b*) other forms of palladium catalyst, or (*c*) changes in concentration and temperature.

EXPERIMENTAL

General. — Thin-layer chromatography (t.l.c.) was conducted on Eastman Chromagram sheets of silica gel with fluorescent indicator. N.m.r. spectra were recorded with a Varian HA-100 or a Bruker WH-90 spectrometer. The benzyl ethers and other starting materials were either available in our laboratory, or were prepared by well-known procedures. Formic acid (98–100%), analytical reagent grade, was obtained from British Drug Houses, Ltd. Palladium (10%) on activated charcoal was obtained from Aldrich Chemical Co.

Catalytic, transfer hydrogenation of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**4**). — In a representative experiment, methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (0.1 g) was dissolved in methanol (10 mL) containing 10% of formic acid. This solution was added to a stirred suspension of 10% palladium-on-charcoal (0.5 g) in the same solvent mixture (10 mL), maintained under a nitrogen atmosphere. One hour later, after periodic t.l.c. examination had indicated that the reaction was complete, the catalyst was filtered off, and successively washed with methanol and water, and the filtrates were combined and evaporated. The residue, dissolved in deuterium oxide (99.5%, 0.5 mL), afforded a p.m.r. spectrum indistinguishable from that of methyl α-D-glucopyranoside; no other products were detected.

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