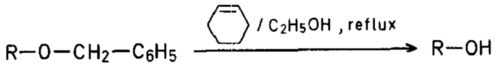
# Facile Cleavage of Benzyl Ethers by Catalytic Transfer Hydrogenation

Stephen HANESSIAN*, Teng Jiam LIAK[1], Benoit VANASSE[2]

Departement of Chemistry, University of Montreal, Montreal, Quebec, Canada, H3C 3V1

Benzyl ethers are among the most useful in the repertoire of *O*-protecting groups in synthetic organic chemistry[3], primarily because of their ease of formation, inherent stability, and the variety of methods available for regenerating the hydroxy groups(s)[4]. Frequently however, problems associated with compatibility and in particular, slow debenzylation arise when multiple functionality is present. We have found that *O*-benzyl ethers (**1**) can be efficiently cleaved by hydrogenolysis under catalytic transfer hydrogenation[5], using 20% palladium hydroxide on carbon[6] and cyclohexene as the hydrogen donor (Scheme).



$$R{-}O{-}CH_2{-}C_6H_5 \xrightarrow[\text{cyclohexene}\,/\,C_2H_5OH\text{, reflux}]{20\%\ Pd(OH)_2/C/} R{-}OH$$

**1** **2**

Although the technique in general has been used for de-*N*-benzylation in the peptide series[7] (palladium on carbon, formic acid, or 1,4-cyclohexadiene), applications in the *O*-benzyl series are sparse[5,8]. Palladium hydroxide on carbon[6] is a neutral, non-pyrophoric catalyst which has been effectively used as a hydrogenation catalyst for a variety of functional groups[9]. Its use in conjunction with transfer hydrogenation conditions presents definite advantages for small and moderately large scale operations. The Table lists several types of benzyl ethers in the carbohydrate series that were debenzylated. A noteworthy case is the selective removal of two benzyl ethers in the presence of a benzylidene acetal (entry 1). Such selectivity cannot be achieved under normal hydrogenation conditions[10] or under the recently reported transfer hydrogenation utilizing 10% formic acid as hydrogen donor[8]. Esters (acetates, benzoates, sulfonates, etc), ethers (methoxyethoxymethyl, methoxymethyl, tetrahydropyranyl, *t*-butyldimethylsilyl, etc), acetal, and glycosidic groups are unaffected. Solvolysis was not observed in the cases studied and multiple cleavage of axial and equatorial benzyl ethers takes place. Debenzylation of nucleoside benzyl ethers (entry 8) is particularly interesting because of the recorded difficulties in catalytic debenzylation in this series[11]. The favorable catalyst/substrate ratio, the neutral conditions (compare Ref.[7,8]), the compatibility of the conditions with the presence of a variety of other commonly used protecting groups, and the efficacy of the process should enhance its practice in the cleavage of one or more benzyl ethers in a variety of compounds.

### De-*O*-benzylation; General Procedure:

The benzyl ether **1** (1 mmol) is dissolved in ethanol (8 ml) and cyclohexene (4 ml), 20% palladium hydroxide on carbon[6] (1:10 or 2.5:10 catalyst/substrate by weight) is added and the suspension is stirred under reflux for the required period of time (T.L.C. monitoring). The catalyst is removed by filtration and the filtrate is processed by evaporation to dryness and crystallization of the product **2** directly or by chromatography on silica gel (Table).

*We thank the Natural Sciences and Engineering Council of Canada and le Ministère de l'Education du Québec for financial assistance. We also thank Dr. C. Battistini, Farmitalia-Carlo Erba for informing us of his work pertaining the removal of* N-*benzyloxycarbonyl group by catalytic transfer hydrogenation.*

Received: August 8, 1980
(Revised form: December 1, 1980)

---

[1] Post-doctoral associate.

[2] Summer undergraduate research participant.

[3] See for example, L. S. Hegedus, L. G. Wade, Jr., *Compendium of Organic Synthetic Methods*, Vol. III, John Wiley & Sons, New York, 1977, and previous volumes.
C. B. Reese in *Protective Groups in Organic Chemistry*, J. F. Mc Omie, Ed., Plenum Press, New York, 1973, p. 95.

[4] For some examples, see: (catalytic hydrogenation), (a) C. M. McCloskey, *Advan. Carbohydr. Chem.* **12**, 137 (1957).
(b) H. G. Fletcher, Jr., *Methods Carbohydr. Chem.* **2**, 386 (1963).
(Sodium/ethanol), (c) N. Prentice, L. S. Cuendet, F. Smith, *J. Am. Chem. Soc.* **78**, 4439 (1956).
(Sodium/liquid ammonia), (d) E. J. Reist, V. J. Bartuska, L. Goodman, *J. Org. Chem.* **29**, 3725 (1974).
(Acetic anhydride, acetic acid, $H^{\oplus}$, acetolysis), (e) R. Allerton, H. G. Fletcher, Jr., *J. Am. Chem. Soc.* **76**, 1757 (1954).
(f) G. M. Tener, H. G. Khorana, *J. Am. Chem. Soc.* **79**, 436 (1957).
(g) S. J. Angyal, M. H. Randall, M. E. Tate, *J. Chem. Soc.* **1967**, 919.
(Bromine, sulfolane), (h) J. N. BeMiller, R. E. Wing, C. Y. Meyers, *J. Org. Chem.* **44**, 1661 (1979).
For organosilane reagent combinations and other recent methods of de-*O*-alkylation, see S. Hanessian, Y. Guindon, *Tetrahedron Lett.* **21**, 2305 (1980); and references cited therein.

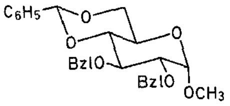
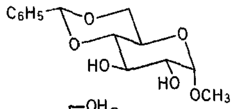
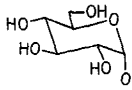
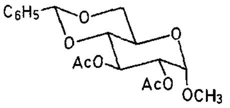
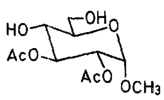
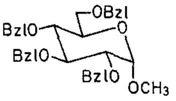
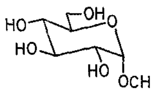
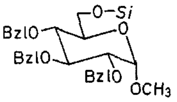
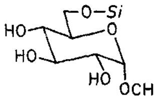
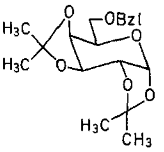
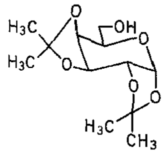
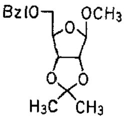
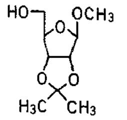
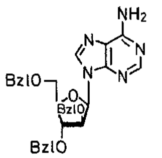
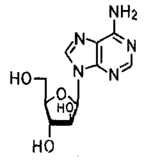
[5] For a review, see G. Brieger, T. J. Nestrick, *Chem. Rev.* **74**, 567 (1974).

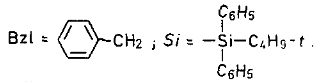
[6] W. M. Pearlman, *Tetrahedron Lett.* **1967**, 1663.

[7] See for example, B. El Amin et al., *J. Org. Chem.* **44**, 3442 (1979).
A. Felix et al., *J. Org. Chem.* **43**, 4194 (1978), and references cited therein.

0039-7881/81/0532-0396 $ 03.00

**Table.** Cleavage of Benzyl Ethers by Catalytic Transfer Hydrogenation [20% $Pd(OH)_2/C$, ethanol, cyclohexene, reflux]

| Benzyl ether 1[a] | Alcohol 2[b] | Ratio catalyst: substrate | Reaction time [h] | Yield[c] [%] | m.p. [°C] | |
|---|---|---|---|---|---|---|
| | | | | | found | reported |
|  |  | 1:10 | 2 | 75 | 166–169° | 166–169°[12] |
| |  | 2.5:10 | 2 | >98 | 168–170° | 169–171°[13] |
|  |  | 2.5:10 | 2 | >98[d] | syrup | syrup[14] |
|  |  | 1:10 | 2 | >98 | 168–170° | 169–171°[13] |
|  |  | 2.5:10 | 2.5 | >98 | 116–117° | 117–118°[15] |
|  |  | 2.5:10 | 2 | >98 | syrup | syrup[16] |
|  |  | 2.5:10 | 2 | >98 | syrup | syrup[17] |
|  |  | 2.5:10 | 2 | >98 | 254–256° | 257°[18] |

[a] 

$Bzl = C_6H_5CH_2$ ; $Si = -\overset{C_6H_5}{\underset{C_6H_5}{Si}}-C_4H_9\text{-}t$ .

[b] All crystalline products were compared with authentic samples (mixture mp.). Syrups were characterized by N.M.R. and $[\alpha]_D$ data.

[c] Yield of pure, isolated product.

[d] Treatment with benzaldehyde/zinc chloride gave the crystalline benzylidene derivative; m.p. 108–110 °C; Ref. [13], m.p. 108–110 °C.

---

[8] After this work was completed a report describing the removal of O-benzyl groups in carbohydrate derivatives was published, see V. S. Rao, A. S. Perlin, *Carbohydr. Res.* **83**, 175 (1980). The conditions call for a large excess of 10% Pd/C (1 g/0.2 mmol of substrate) in the presence of 10% formic acid as the hydrogen donor in methanol.

[9] We have successfully used this catalyst for the cleavage of O-benzylidene acetals O-benzyl and trityl ethers, N-benzyloxycarbonyl groups, and for the reduction of olefinic linkages and halides.

[0] See however, A. L. Fink, G. W. Hay, *Can. J. Chem.* **47**, 841 (1969).

[1] See for example, C. P. J. Glaudemans, H. G. Fletcher, Jr., *J. Org. Chem.* **28**, 3004 (1963); as cited in ref. 2d in this paper.

[2] N. K. Richtmyer, *Methods Carbohydr. Chem.* **2**, 107 (1963).

[3] E. Pacsu, *Methods Carbohydr. Chem.* **2**, 107 (1963).
E. Fischer, *Ber. Dtsch. Chem. Ges.* **26**, 2406 (1893).

[4] A. Nowakowski, Z. Mroczkowski, *Comptes Rend.* **48**, 461 (1944).

[5] S. Hanessian, P. Lavallée, *Can. J. Chem.* **53**, 2975 (1975).

[6] O. T. Schmidt, *Methods Carbohydr. Chem.* **2**, 318 (1963).

[7] N. J. Leonard, K. L. Carraway, *J. Heterocycl. Chem.* **3**, 485 (1966).

[8] W. W. Lee, A. Benitez, L. Goodman, B. R. Baker, *J. Am. Chem. Soc.* **82**, 2648 (1960).