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Selective Inhibition of Benzyl Ether Hydrogenolysis with Pd/C Due to the Presence of Ammonia, Pyridine or Ammonium Acetate[1]

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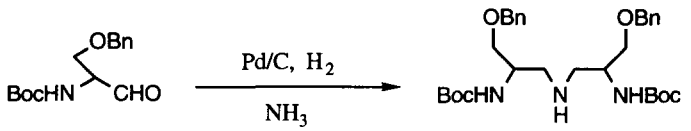
Abstract: *Ammonia, pyridine and ammonium acetate were found to be extremely effective as inhibitors of Pd/C catalyzed benzyl ether hydrogenolysis. While olefin, Cbz, benzyl ester and azide functionalities were hydrogenated smoothly, benzyl ethers were not cleaved in the presence of these additives.*

Highly selective deprotection methods are important in choosing useful combinations of protecting groups in organic synthesis. Benzyl ethers are widely used protective groups[2] chiefly because of their stability in a variety of reaction conditions, low cost, ease of formation, and removal by mild catalytic hydrogenolysis.[3] Although a number of catalysts have been employed for the hydrogenolysis of O-benzyl ethers, the selectivity of cleavage (or resistance) in the presence of other reducible functionalities within a molecule is usually poor.[2, 4]



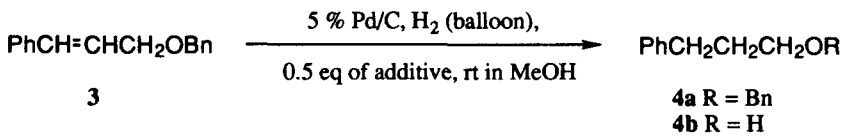
1 **2**

In the course of our investigations to establish novel synthetic routes to functional DTPA (diethylenetriamine pentaacetic acid) derivatives as effective MRI (magnetic resonance imaging) agents, we found that the O-benzyl ether of the Boc-aminoaldehyde **1** was not cleaved by reductive amination condition using 5 % Pd/C and ammonia in MeOH. In this communication, we wish to report that the addition of ammonia, pyridine or ammonium acetate causes quantitative inhibition of benzyl ether hydrogenolysis carried out at ambient pressure and temperature (5 % Pd/C, MeOH). Although several inhibitions of O-benzyl ether

hydrogenolysis in the presence of intramolecular amines have been reported[5], a solitary reference to use of n-butylamine as a basic nonaromatic amine additive for inhibition of O-benzyl ether hydrogenolysis (10 % Pd/C, 40 psi) has appeared as the conversion of 11-(benzyloxy)-1-undecene to benzyl n-undecylether .[5a]

As to the scope and limitation of the selective benzyl ether hydrogenolysis inhibition, the effects of ammonia, pyridine, ammonium acetate and ammonium chloride were first investigated in the reaction of 3-benzyloxy-1-phenyl-1-propene **3**. Although ammonium chloride did not indicate any inhibition, the benzyl ether hydrogenolysis was entirely hindered by the added 0.5 equivalent[6] of ammonia, pyridine[7] and ammonium acetate (Table 1).

Table 1. Effect of Additive on Pd/C Catalyzed Hydrogenolysis



3

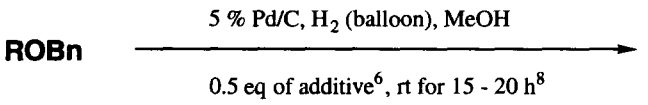
4a R = Bn
4b R = H

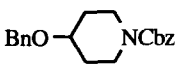
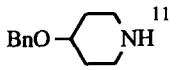
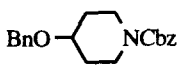
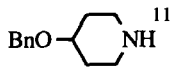
Additive	Product[a]	Yield (%)
None	(**4b**)[b]	100[c]
NH_3	(**4a**)[8,9]	**98**[d]
Pyridine	(**4a**)[8,9]	**98**[d]
NH_4OAc	(**4a**)[8,9]	**97**[d]
NH_4Cl	(**4b**)[b]	98[d]

[a]Reactions were completed within 30 min and all the products were identified by ^{1}H-NMR, ^{13}C-NMR and/or HRMS. [b]Commercially available (Aldrich). [c]By ^{1}H-NMR. [d]Isolated yield.

The present inhibition of benzyl ether hydrogenolysis can be applied to a variety of compounds which possess other reducible functionalities. Ammonia and ammonium acetate were chosen for their ease of removal from reaction mixture. The representative results of the 5 % Pd/C catalyzed hydrogenolysis of benzyl ethers with ammonia or ammonium acetate are shown in Table 2. These results indicate that ammonia and ammonium acetate can inhibit benzyl ether hydrogenolysis selectively in the presence of azide, Cbz and benzyl ester. In the case of Cbz-amino acids possessing a benzyl ether side chain, Cbz-Ser(Bn)-OH and Cbz-Thr(Bn)-OH, these conditions produced NH_2-terminal amino acids without cleavage of benzyl ether. The Cbz amino acids may be applied to the synthesis of peptides containing O-benzyl ether side chains without the use of Boc or Fmoc amino acids.

Table 2. Applications of NH_3 or NH_4OAc - Pd/C Combination to Other Reducible Functionalities



Entry	ROBn	Additive	Product[a]	Yield (%)[b]
1	$BnO(CH_2)_2OH$	NH_3	Recovery	99
2	$BnO(CH_2)_2N_3$	NH_3	$BnO(CH_2)_2NH_2$[10]	95
3	Boc-Ser(Bn)-OH	None	Boc-Ser-OH	94
4	Boc-Ser(Bn)-OH	NH_3	Recovery	99
5	Boc-Ser(Bn)-OH	NH_4OAc	Recovery	95
6	Cbz-Ser(Bn)-OH	None	H-Ser(Bn)-OH, Ser	40, 60[c]
7	Cbz-Ser(Bn)-OH	NH_3	H-Ser(Bn)-OH	97
8	Cbz-Thr(Bn)-OH	NH_3	H-Thr(Bn)-OH	93
9		NH_3		97
10		NH_4OAc		95
11	Boc-Ser(Bn)-OBn	NH_4OAc	Boc-Ser(Bn)-OH	96

[a]All the products were identified by ^{1}H-NMR, ^{13}C-NMR and /or HRMS. Commercially available (Aldrich, SIGMA and/or BACHEM CALIFORNIA) with the exception of entry 2, 9 and 10. [b]Isolated yield unless otherwise noted. [c]Partial removal of O-benzyl group was carried out and the ratio of O-benzylserine and serine was confirmed by ^{1}H-NMR.

Typically, the experimental procedure of 3-benzyloxy-1-phenyl-1-propene **3** with ammonium acetate was carried out as follows. After two vacuum / H_2 cycles to remove air from the reaction flask, the stirred mixture of **3** (1.00 mmol), 5 % Pd/C (20 mg) and 2M ammonia - MeOH (0.25 ml) in MeOH (5 ml) was hydrogenated at ordinary pressure and temperature for 16 h. The reaction mixture was filtered (celite cake), the filtrate was concentrated and the residue was partitioned between ether and water. The ethereal phase was washed with brine, dried ($MgSO_4$) and concentrated to provide 3-phenyl-1-propanol **4a** (97 %) as a sole product.

In conclusion, we have demonstrated the complete inhibition of O-benzyl ether hydrogenolysis in the presence of ammonia, pyridine or ammonium acetate. The advantages of this methodology are (1) its high selectivity of inhibition, (2) its mild experimental conditions and (3) the ease of the removal of additives. Further details on the scope and limitations of this useful methodology including the synthetic applications to aryl benzyl ethers[12] will be reported elsewhere in due course.

References and Note

1. This paper is dedicated to Professor Yoshifumi Maki for the occasion of his retirement from Gifu Pharmaceutical University on March, 1994.
2. Greene, T. W. and Wuts, P. G., *Protective Groups in Organic Synthesis*, 2nd ed., Wiley-Interscience, New York, **1991,** pp 47-53.
3. (a) Rylander, P. N., *Hydrogenation Methods*, Academic Press, New York, **1985**, pp 157-163. (b) *Idem.*, *Catalytic hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**, pp 271-279. (c) Freifelder, M., *Practical Catalytic Hydrogenation Techniques and Applications*, Wiley-Interscience, New York, **1971**, pp 398-413.
4. For example, (a) *Ibid*, *idem.*, pp 428-440. (b) Lee, B. H. and Miller, M. J., *J. Org. Chem.*, **1983**, *48*, 24.
5. For example, (a) Czech, B. P. and Bartsh, R. A., *J. Org. Chem.*, **1984**, *49*, 4077. (b) Pennings, M. L. M. and Reinhoudt, D. N., *J. Org. Chem.*, **1983**, *48*, 4043. (c) Fleet, G. W. J. and Smith, P. W., *Tetrahedron Lett.*, **1985**, *26*, 1469.
6. 0.1 equivalent also acceptable.
7. Under the reaction conditions described in reference 5a (10 % Pd/C, 40 psi of H_2), complete cleavage of the O-benzyl ether was found in the presence of even an equimolar amount of pyridine.
8. Reactions were completed within 30 min however these were allowed to stand for at least 15 h to prove the selectivity of the inhibition.
9. Akiyama, T., Hirofuji, H. and Ozaki, S., *Bull. Chem. Soc. Jpn.*, **1992**, *65*, 1932 and references cited therein.
10. Balderman, D. and Kalir, A., *Synthesis*, **1978**, 24 and references cited therein.
11. (a) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.42-1.59 (2H, m), 1.90-2.05 (2H, m), 2.59 (1H, dd, J = 3.0, 10.2 Hz), 2.63 (1H, dd, J = 3.0, 10.2 Hz), 3.08 (1H, t, J = 4.8 Hz), 3.12 (1H, t, J = 4.8 Hz), 3.40-3.54 (1H, m), 4.56 (2H, s), 7.20-7.41 (5H, m); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 32.85, 44.36, 69.41, 74.85, 127.34, 127.41. 128.26, 138.83; HREIMS *m/z* (obs.) 192.1386 (M^++1, 100 %), calc. for $C_{12}H_{18}NO$ 192.1388. (b) Warolin, C. and Schneider, R., *Eur. Pat. Appl.* 15817 (Appl. 79/6070, March 9, 1979).
12. When Boc-Tyr(Bn)-OH was used in the reaction described here (NH_3), the smooth cleavage of O-benzyl ether was observed (30 min, 89 %).

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