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Chemoselective Inhibition of the Hydrogenolysis of the MPM Protective Group for Phenolic Hydroxy Functions Using a Pd/C-pyridine Catalyst

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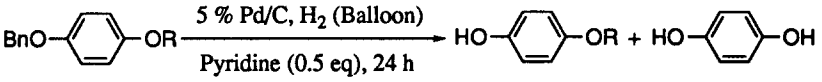
Abstract: *A convenient method for the selective hydrogenation of phenolic benzyl ether, Cbz, benzyl ester, nitro and olefin functions distinguishing from the MPM (4-methoxybenzyl) protective group for the phenolic hydroxy groups was accomplished by the addition of pyridine to the Pd/C-catalyzed reduction system.* Copyright © 1996 Elsevier Science Ltd

Although benzyl groups are widely used as excellent protecting groups for hydroxy functions, the lack of chemoselectivity between the benzyl groups and other sensitive functional groups toward Pd-catalyzed hydrogenation is a serious problem.[1] Recently, one of us disclosed that addition of ammonia , pyridine or ammonium acetate to a Pd/C catalyzed reduction system strongly inhibited the hydrogenolysis of an aliphatic benzyl ether with smooth hydrogenation of other reducible functions such as olefin, Cbz, benzyl ester and azide.[2] However, the benzyl protecting group of aryl ethers is promptly deprotected under the same conditions. Therefore, the selective inhibition is not applicable to the hydrogenolysis of phenolic benzyl ethers.[2,3] To the best of our knowledge, there is only one method for the chemoselective inhibition of the hydrogenolysis of phenolic benzyl ethers. Davis *et al.* reported that a sterically crowded 2,4-dimethylbenzyl protecting group resisted Pd/C-catalyzed hydrogenolysis.[4] We continuously investigated an applicable procedure for chemoselective inhibition of the hydrogenolysis of a benzyl-type protective group for phenolic hydroxy functions. This paper describes the selective hydrogenation between the 4-methoxybenzyl (MPM) protective group and other susceptible functions to Pd/C-catalyzed reduction using a heterogeneous Pd/C-pyridine combination.

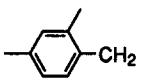
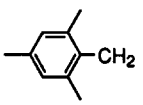
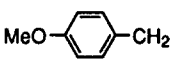
We first investigated the effectiveness of pyridine in chemoselective hydrogenolysis of **1**,[5] which possesses both phenolic benzyl ether and substituted benzyl ethers within the molecule, with 5 % Pd/C at ordinary hydrogen pressure (balloon) and temperature. As indicated in Table 1, hydrogenolysis of the substituted benzyl groups (R = 2,4-dimethylbenzyl, 2,4,6-trimethylbenzyl, and MPM) of **1** was depressed (see: the ratio between **2** and **3** in Table 1) by the addition of 0.5 equivalent of pyridine, respectively, even though the benzyl protection of **1** was hydrogenated smoothly in each case.[2,3] Throughout the course of the

reaction, hydrogenolysis of the 2,4,6-trimethylbenzyl group and the MPM group was completely blocked by the addition of pyridine even after 24 h (Entry 3 and 4). Even if pyridine was not added to the reaction mixture, the sterically bulky 2,4,6-trimethylbenzyl group was hydrogenated very slowly, showing only 11 % hydrogenolysis in 24 h (Entry 3). However, the deprotection method for the 2,4,6-trimethylbenzyl group is limited to the use of TFA (trifluoroacetic acid).[6] Therefore, the more commonly used MPM protection was chosen for further investigation because of the easy deprotection under a variety of conditions such as DDQ or CAN oxdation,[7] treatment with TFA,[8] reduction with $NaBH_3CN$–$BF_3(OEt_2)$[9] and Pd/C catalytic hydrogenation.[7]

Table 1. The Product Distributions after 24 h for the Hydrogenolysis



1 **2** **3**

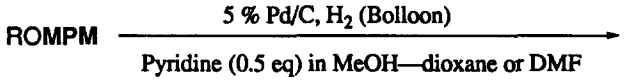
Entry	R	Products ratio[a,b] 2 : 3
1	Bn	17 : 83 (0 :100)
2		90 : 10 (60 :40)
3		100 : 0 (89 :11)
4		100 : 0 (49 :51)

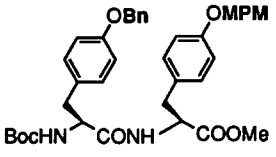
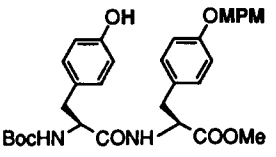
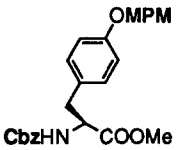
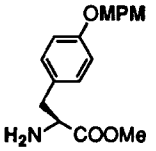
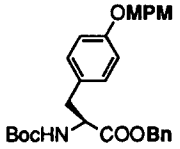
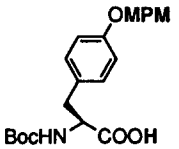
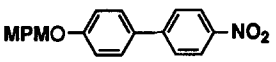
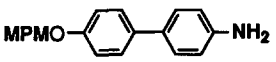
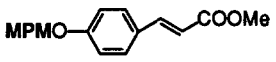
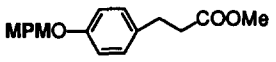
[a]Reactions were followed by TLC scanner (Shimadzu CS-9000). [b]The products ratios in parenthesis were obtained without pyridine.

The hydrogenation of several phenolic MPM ethers coexisting with phenolic *O*-benzyl **4**, Cbz **6**, benzyl ester **8**, nitro **10**, or olefin **12** functions within a molecule was demonstrated.[10] As shown in Table 2, the novel techniques selectively inhibited the hydrogenolysis of the MPM group but smoothly hydrogenated *O*-benzyl ether,[11] Cbz,[12] benzyl ester, nitro and olefin functions. The selectively hydrogenated products **5**, **7**, **9**, **11** and **13** were obtained in excellent isolated yields. Although the reactions of **4**, **6** and **8** were completed within 1—2.5 h, the MPM group remained intact even after 24 h (entry 1—3). Control experiment of the dipeptide **4** indicated that, under standard 5 % Pd/C hydrogenolysis conditions without the addition of pyridine,

both benzyl and MPM groups were deprotected to the corresponding Boc-Tyr-Tyr-OMe in 78 % yield.

Table 2. Chemoselective Inhibition of the Hydrogenolysis of MPM Ethers[10]



Entry	Substrate (ROMPM)	Reaction time (h)	Product	Yield (%)[c]
1	 **4**	24[a]	 **5**	96
2	 **6**	24[b]	 **7**	86
3	 **8**	24[a]	 **9**	95
4	 **10**	1	 **11**	94
5	 **12**	2	 **13**	96

[a]Reaction was completed within 1 h by TLC scanner (Shimadzu CS-9000). [b]Reaction was completed within 2.5 h by the TLC scanner.
[c]Isolated yield.

In conclusion, employment of a Pd/C-pyridine combination as a catalyst is a very useful method for the selective removal of phenolic *O*-benzyl, Cbz and benzyl ester protecting groups and for the selective reduction of nitro and olefin functions in the hydrogenation of phenols protected with the MPM group. These discriminatory results are apparently attributable to the effect of pyridine. The MPM group could be extensively applied to chemoselective hydrogenation as a protecting group for phenolic hydroxy functions.[13] Further study of the scope and limitations concerning the optimization and applications of this methodology is under way.

REFERENCES AND NOTES

1 (a) Green, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 2nd ed., 1991; pp. 47-53 and 156-158. (b) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; pp. 157-163. (c) *Idem. Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979, pp. 271-279. (d) Freifelder, M. *Practical Catalytic Hydrogenation Techniques and Applications*; Wiley-Interscience: New York, 1971, pp. 398-413 and 428-440.

2 Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.

3 (a) McPhee, W. D.; Erickson, E. S. *J. Am. Chem. Soc.* **1946**, *68*, 624. (b) Czech, B. P.; Bartsh, R. A. *J. Org. Chem.* **1984**, *49*, 4077.

4 Davis, R.; Muchowski, J. M. *Synthesis* **1982**, 987.

5 Satisfactory analytical data were obtained for all new compounds.

6 Young, S. D.; Tamburini, P. P. *J. Am. Chem. Soc.* **1989**, *111*, 1933.

7 Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021 and references cited therein.

8 White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736.

9 Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961.

10 *General procedure*: a mixture of the substrate (ROMPM, 1 mmol), 5 % Pd/C (10 weight % of the substrate) and pyridine (0.5 mmol) in MeOH—dioxane (1 :1) or DMF (20 ml) was hydrogenated (balloon) at r.t. for an appropriate time or 24 h. The reaction mixture was filtered through a cellulose acetate syringe filter (pore size 0.45 μm) or celite pad and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with dil. $KHSO_4$ soln. (not for product **11**) and water and evaporated to give a product. The product was purified with silica gel column chromatography if necessary.

11 We previously reported[2] the smooth cleavage of *O*-benzyl protection of Boc-Tyr(Bn)-OH under the hydrogenolysis condition with a Pd/C-ammonia system (30 min, 89 %).

12 Under the hydrogenolysis condition without pyridine, reasonably selective removal of the Cbz protecting group of **6** was also observed due to the effect of the amino group of the product **7**.

13 Horita *et al.* reported[7] that the selective removal of an aliphatic *O*-benzyl protection in the presence of a MPM protective group for aliphatic hydroxy functions was achieved with hydrogenolysis over W-4 Raney nickel, although a large excess amount of catalyst was required to complete the reaction.

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