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## Selective N-debenzylation of amides with p-TsOH

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**Abstract**—*N*-Benzylamides were debenzylated efficiently with 4 equiv. of *p*-TsOH in refluxing toluene. Good to quantitative yields of the desired primary amides were obtained within 2–4 h from a wide variety of *N*-2,4-dimethoxybenzylamides. *N*-4-Methoxylbenzylamides and *N*-benzylamides were also debenzylated cleanly. In the case of *N*-2,4-dimethoxylbenzylamides, selective *N*-debenzylation was possible in the presence of *N*-Fmoc, *N*-*t*-BOC or *N*-trityl-protection. Protected amino acid amides survived these conditions without any detectable epimerization. © 2003 Elsevier Science Ltd. All rights reserved.

*N*-Benzyl groups are used in amine and amide protection or as handles for amine introduction in organic synthesis. However, they enjoy limited success because their removal is often difficult. The most commonly employed methods include acid hydrolysis in refluxing TFA<sup>1</sup> and hydrogenolysis with catalytic Pd/C.<sup>2</sup> Even under these conditions, their removal is not guaranteed. Strongly reducing conditions such as Na/NH<sub>3</sub>(l)<sup>3</sup> or Li with catalytic naphthalene<sup>4</sup> have been used or *t*-BuLi/ THF; O<sub>2</sub> can be employed in extreme conditions.<sup>5</sup> These harsh conditions can prevent the use of *N*-benzyl protecting groups for labile compounds.

Many attempts have been made to develop milder N-debenzylation conditions. 4-Methoxylbenzyl (MB), 2,4-dimethoxylbenzyl (DMB) and 2,4,6-trimethylbenzyl groups with increased acid sensitivity have been introduced. Nevertheless, the resultant benzyl cations are highly electrophilic. Alkylation of the starting material or the product are not uncommon. Addition of nucleophilic scavengers such as thioanisole<sup>6</sup> or anisole<sup>7</sup> is often necessary to suppress side reactions. N-MB and N-DMB but not N-benzyl groups can also be removed by oxidative N-debenzylation using CAN<sup>8,10</sup> or DDQ.<sup>9,10</sup> Obviously, oxidation sensitive starting materials are not compatible with these reagents.

Herein, we report the use of p-TsOH as a convenient and effective N-debenzylating agent. The application of this reagent is summarized in Table 1. The N-2,4-

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**Table 1.** Examples of N-debenzylation with p-TsOH in refluxing toluene



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dimethoxylbenzyl amides were synthesized by the reaction of the corresponding carboxylic acids with 2,4dimethoxylbenzylamine in the presence of DCC at ambient temperature in excellent yield. From entries 1-6, consisting of primary, secondary, tertiary, phenyl and styryl carboxyamides, *N*-debenzylation occurred smoothly with good to quantitative yields of the isolated primary amides. Even with the 1,2-diamide **2d**, a 65% yield of the desired product was isolated in spite of steric hindrance.

The optimum results were usually obtained when 0.3 M of the starting material was allowed to react with 4 equiv. of p-TsOH in refluxing toluene. Lower reaction temperature or the use of less p-TsOH led to inferior results.

When we applied this reagent to *N*-Fmoc-, *N*-*t*-BOC-, and *N*-trityl-protected amino acids, good to excellent yields of the desired amides were isolated. Both entries 7 and 8 report good yields of primary amides without any detectable racemization. The optical activities of **2g** and **2h** were  $[\alpha]_D^{19} = -4.02$  (*c* 1, MeOH) and  $[\alpha]_D^{25} =$ -25.42 (*c* 1, MeOH), respectively [lit.  $[\alpha]_D^{19} = -3.53$  (*c* 1, MeOH)<sup>11</sup> and  $[\alpha]_D^{25} = -25.8$  (*c* 1, MeOH),<sup>12</sup> respectively]. Both acid sensitive *t*-BOC- and base sensitive *N*-Fmocprotections survived the reaction conditions. Moreover, in the presence of *N*-trityl amide, selective *N*-debenzylation was possible as exemplified in **2i**. For both of the protected asparagine and glutamine, no epimerisation occurred and *N*-Fmoc and *N*-trityl protection remained intact.<sup>13</sup>

We then compared this method with two of the most commonly used *N*-debenzylation methods, i.e. acid hydrolysis in TFA/CH<sub>2</sub>Cl<sub>2</sub><sup>14</sup> and hydrogenolysis in catalytic Pd/C,<sup>15</sup> using *N*-benzyl-3-phenacylpropanamide **3a**, *N*-4-methoxybenzyl-3-phenacylpropanamide **3b** and *N*-2,4-dimethoxybenzyl-3-phenacylpropanamide **3c** as

 Table 2. Comparison of N-debenzylation methods



3c: X = 2,4-dimethoxy

S.M. <sup>a</sup>	Reagents (deprotection)	Temp.	Time (h)	Product 4 (yield %)
3a	5% Pd/C, H <sub>2</sub>	rt	11	0
3b	5% Pd/C, $H_2$	rt	6.5	7
3c	5% Pd/C, $H_2$	rt	4	19
3a	CF <sub>3</sub> CO <sub>2</sub> H (1.2 equiv.)/CH <sub>2</sub> Cl <sub>2</sub>	11	11	0
3b	CF <sub>3</sub> CO <sub>2</sub> H (1.2 equiv.)/CH <sub>2</sub> Cl <sub>2</sub>	11	6.5	4
3c	$CF_3CO_2H$ (1.2 equiv.)/ $CH_2Cl_2$	11	4	22
3a	p-TsOH (4.0 equiv.)/toluene	11	11	93
3b	<i>p</i> -TsOH (4.0 equiv.)/toluene	11	6.5	92
3c	<i>p</i> -TsOH (4.0 equiv.)/toluene	11	4	98

<sup>a</sup> S.M., starting material.

starting materials. The results are summarized in Table 2. Neither of the established methods was useful for **3a**, no product formation was observed even after prolonged reaction (20 h). This came as no surprise since there were literature reports that removal of N-benzyl groups can be sluggish in TFA and Pd/C-H<sub>2</sub>. On the other hand, p-TsOH afforded a 3% yield of 4 after 4 h, while the reaction was complete after 11 h with a 93% yield of the desired product. Some success was observed for starting material **3b**. After 4 h, 6 and 3% yields of the desired amide 4 were isolated using hydrogenolysis and acid hydrolysis, respectively, as the reactions were incomplete. In comparison, with p-TsOH, a 46% yield was obtained after 4 h with some starting material remaining, while the reaction was complete after 6.5 h. Similar results were obtained for 3c. After 4 h, the reactions using the first two methods were incomplete with 19 and 22% yields, respectively, while with p-TsOH, a 98% yield of the desired amide was obtained. Moreover, 6% of the reduced product (benzyl alcohol) was isolated from the hydrogenolysis mixture. This indicates that optimization of the hydrogenolysis conditions by extending the reaction time may be futile since it also increases the formation of the reduction product.

Using *N*-DMB-salicylamide **5** and *N*-DMB-5-phenyl-5hydroxypentamide **8** as model compounds, we compared *p*-TsOH against CAN and DDQ. With *N*-DMB-salicylamide **5** (Table 3), CAN failed to react after 20 h with 96% of starting material being recovered while DDQ afforded 85% of *N*-2,4-dimethoxylbenzoylsalicyamide **7**. In the case of *p*-TsOH, a 92% yield of salicylamide **6** was isolated cleanly after 2 h.

With *N*-DMB-5-phenyl-5-hydroxypentamide **8** as substrate (Table 4), CAN afforded 90% of the desired amide **9** in 20 h (<5% in 4 h) whereas DDQ gave 28% of **9** and 34% of the oxidized product **10** with 36% of recovered starting material. Obviously, DDQ oxidized



Reagents Temp. Time (h) Product (yield %) (deprotection) 7 6 p-TsOH (4.0 2 92 11 equiv.)/toluene 20 CAN (1.1 equiv.), rt CH<sub>3</sub>CN/H<sub>2</sub>O (1:1) DDQ (1.1 rt 2 85 equiv.)/CH2Cl2

<sup>a</sup> Recovered S.M. 96%.

## Table 4.



Reagents (deprotection)	Temp.	Time (h)	Product (yield %)	
			9	10
<i>p</i> -TsOH (4.0 equiv.)/toluene	11	2	93	_
CAN (1.1 equiv.), CH <sub>3</sub> CN/H <sub>2</sub> O (1:1)	rt	20	90	_
DDQ (1.1 equiv.)/CH <sub>2</sub> Cl <sub>2</sub>	rt	2	28	34 <sup>a</sup>

<sup>a</sup> Recovered S.M. 36%.

the benzyl alcohol as fast as the benzylamide. On the other hand, p-TsOH provided 93% of the desired amide 9 in just 2 h. No dehydration of the benzyl alcohol was observed.

From the results of Tables 3 and 4, we may conclude that DDQ is more sensitive to the oxidizability of the starting materials while CAN reacts more slowly. Obviously, these oxidants may not be applicable to *N*-benzylamides in contrast to *p*-TsOH.

In summary, a versatile and high yielding N-debenzylation method is described. It is applicable to a wide variety of N-2,4-dimethoxybenzylamides leading to reaction within 2–4 h. Under these reaction conditions, no epimerization of the protected amino acid amides was observed while N-Fmoc, N-t-BOC, and N-trityl protection remained unchanged. Dehydration of benzyl alcohol was also not observed. N-Benzyl- and N-4methoxybenzylamides may also be debenzylated in 11 and 6.5 h, respectively, while most methods failed. In general, it was more efficient than most reported Ndebenzylation methods including acid hydrolysis with TFA, hydrogenolysis with catalytic Pd/C and oxidation methods with DDQ and CAN. In the cases of oxidation or reduction sensitive starting materials, this new method could be very valuable. Apparently, it might be applicable to a wider variety of N-benzylamides.

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## References

- (a) Schlessinger, R. H.; Bebernitz, P. L.; Poss, A. Y. J. Am. Chem. Soc. 1985, 107, 1777; (b) Shimshock, S. S.; Waltermire, R. E.; Deshong, P. J. Am. Chem. Soc. 1991, 113, 8791.
- 2. Gigg, R.; Conant, R. Carbohydr. Res. 1982, 100, C5.
- (a) Ohgi, T.; Hecht, S. M. J. Org. Chem. 1981, 46, 1232;
   (b) Webster, F. X.; Millar, J. G.; Silverstein, R. M. *Tetrahedron Lett.* 1986, 27, 4941.
- 4. Alonso, E.; Ramon, D. J.; Yus, M. Tetrahedron 1997, 53, 14355.
- 5. Williams, R. M.; Kwast, E. Tetrahedron Lett. 1989, 30, 451.
- Wood, J. L.; Stoltz, B. M.; Dietrich, H. J. J. Am. Chem. Soc. 1995, 117, 10413.
- Wood, J. L.; Stoltz, B. M.; Goodman, S. N. J. Am. Chem. Soc. 1996, 118, 10656.
- Overman, L. E.; Osawa, T. J. Am. Chem. Soc. 1985, 107, 1698.
- 9. Mori, S.; Iwakura, H.; Takechi, S. *Tetrahedron Lett.* 1988, 29, 5391.
- Buenadicha, F. L.; Bartolame, M. T.; Aguirre, M. J.; Avendano, C.; Sollhuber, M. *Tetrahedron: Asymmetry* 1998, 9, 483.
- 11. Gayathri, K.; Gopi, H. N.; Babu, V. V. S. Indian J. Chem., Sect. B 1998, 37, 151.
- 12. Eberle, A.; Fauchere, T. L.; Tesser, G. I.; Schwyzer, R. *Helv. Chim. Acta* **1975**, *58*, 2106.
- Pietta, P. G.; Cavallo, P.; Marshall, G. R. J. Org. Chem. 1971, 36, 3966.
- 14. Brooke, G. M.; Mohammed, S.; Whiting, M. C. Chem. Commun. 1997, 1511.
- 15. Rigby, J. H.; Gupta, V. Synlett 1995, 547.