



Rapid microwave-assisted deprotection of *N*-Cbz and *N*-Bn derivatives

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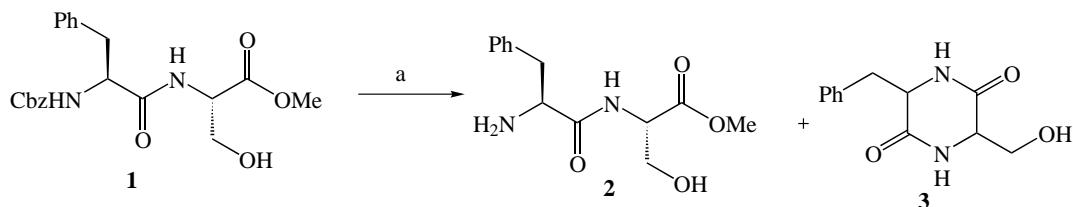
Abstract—Catalytic-transfer hydrogenation in *iso*-propanol under microwave irradiation has been performed to rapidly deprotect *N*-Cbz and *N*-Bn derivatives. The method is particularly suitable for the synthesis of short peptides and can also be carried out on supported molecules. The rapid cleavage of chiral molecules derived from (*S*)-1-phenylethylamine can be very useful for asymmetric synthesis of nitrogen containing compounds. © 2001 Elsevier Science Ltd. All rights reserved.

The benzyl carbamate (Cbz) and the benzyl (Bn) protective groups are very popular for amines.¹ This success depends on the easy and selective procedures for removal, based on catalytic hydrogenation, catalytic-transfer hydrogenation and other reducing reactions.² Although catalytic-transfer hydrogenation is a more efficient deprotection procedure than catalytic hydrogenation, it has not been largely used as it must be carried out in high boiling solvents for relatively long times with potential damage of particularly sensitive organic compounds.^{2,3}

Following a recent report on the influence of microwave on the catalytic hydrogenation of double bonds,⁴ we found that amino groups, protected as Cbz or Bn, can be deprotected in few minutes by microwave-assisted-transfer hydrogenation with Pd/C in *i*-PrOH as the solvent and HCOONH₄ as the hydrogen donor.

Dipeptide **1** was employed to find the best reaction conditions. This product could be deprotected using Pd/C and HCOONH₄ in boiling toluene for 5 h, or with cyclohexene in boiling MeOH for 12 h. In both cases the desired product was always obtained together with 20–40% of diketopiperazine **3** (Scheme 1).⁵

On this reaction, different kinds of catalysts, hydrogen donors, solvents and microwave conditions were tested to find the best results. The reactions were carried out in an unmodified domestic microwave oven following the so called MORE (microwave organic reaction enhancement) techniques.⁴ The reactions were carried out in an Erlenmeyer flask covered with a filter funnel to prevent spillage during the experiments. Moreover, a beaker with water was placed in the oven together with the reaction flask to modulate the microwave energy input into the hydrogenation mixture.



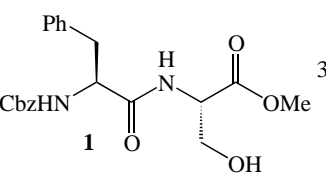
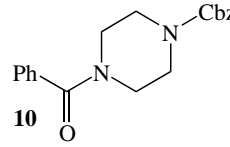
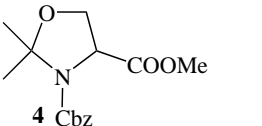
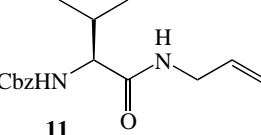
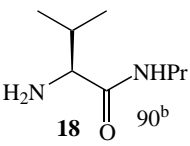
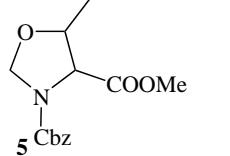
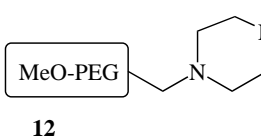
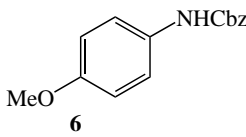
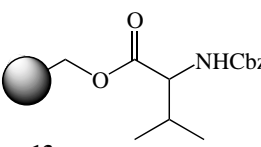
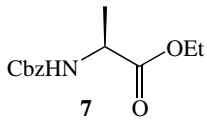
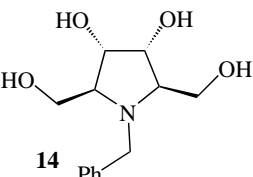
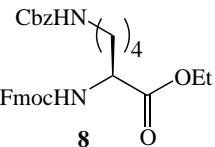
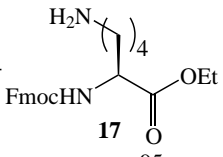
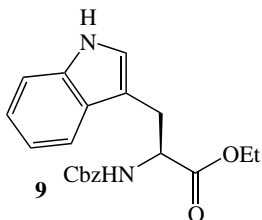
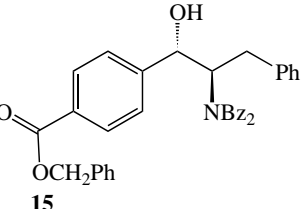
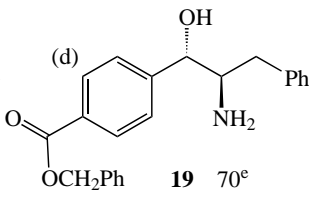
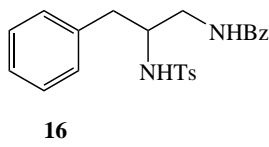
Scheme 1. (a) Pd/C (10%), HCOONH₄, toluene, reflux for 5 h or Pd/C (10%), cyclohexene MeOH 1/1, reflux for 12 h.

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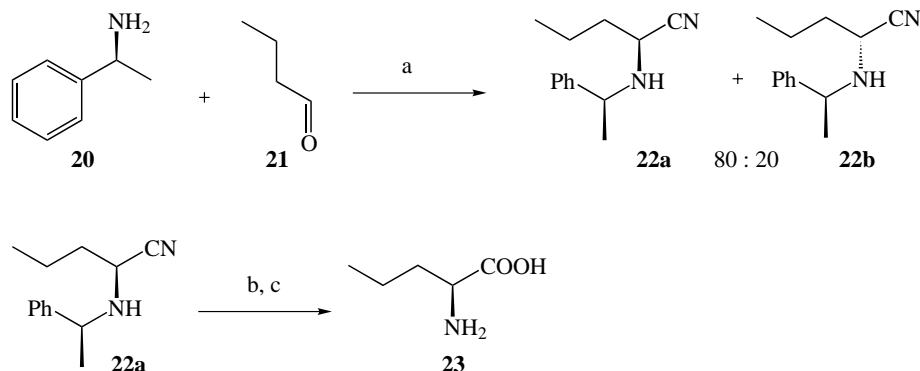
Pd/C and HCOONH_4 were the best choice whereas *i*-PrOH resulted in the better compromise between a safe and a high yielding solvent. In fact, when ethylene glycol was used (bp 198°C)⁴ and the flask was exposed to microwaves for 2 min, the solvent did not reach the boiling point and the deprotection of **1** was complete according to TLC analysis. Unfortunately the yield of

isolated **2** was not very high (60–65%) as the separation of the NH_2 -free dipeptide from the polar ethylene glycol was difficult. On the other hand, when *i*-PrOH was used (bp 82°C), complete deprotection occurred together with boiling of the solvent. To reduce the risk of the presence of solvent vapors inside the oven we operated as follows: the product was dissolved⁶ with

Table 1. Deprotection of different *N*-Cbz and *N*-Bn derivatives

Substrate	n. of cycles	yield of the free amine (%) ^a	Substrate	n. of cycles	yield of the free amine (%) ^a
 1	3	95 ^b	 10	5	93
 4	3	93 ^b	 11	8	 18 90 ^b
 5	5	90 ^b	 12	8	95
 6	3	95 ^c	 13	8	95
 7	4	90 ^b	 14	3	90
 8	4	 17 95			
 9	5	90 ^b	 15	(d)	 19 70 ^e
			 16	(d)	95

a) Yields determined on the product, recovered after filtration and evaporation of the solvent, that resulted pure at ^1H NMR analysis (300 MHz). b) The absence of racemisation was controlled as described in ref. 8. c) Yields related to the corresponding hydrochloride. d) These products were deprotected using a microwave organic synthesis apparatus (Synthewave 402, Prolabo) doing a single cycle of 20 min with 30 W of power (75°C). e) Yields of product isolated by column chromatography.



Scheme 2. (a) NaCN, AcOH, MeOH, rt, 24 h; (b) MeOH, dry HCl, 2 h, followed by LiOH, MeOH, H₂O, 16 h; (c) HCOONH₄, Pd/C, *i*-PrOH, MW (600 W), eight cycles of 1 min of irradiation and 1 min of rest.

i-PrOH in the flask and HCOONH₄ (4 equiv.) and Pd/C 10% (5% in weight respect to the substrate) added. The flask was irradiated for 1 min at 600 W and the deprotection monitored by TLC. If starting material was present, additional cycles of 1 min at 600 W followed by at least 1 min of rest were applied until no trace of the starting material was present at TLC analysis. In the case of compound **1**, deprotection was complete after three cycles. Compound **2** was isolated in high yield (95%) after filtration of the catalyst and evaporation of the solvent. No trace of diketopiperazine **3** was observed at the TLC analysis.

To explore the scope of the microwave acceleration, the hydrogenolysis of different substrates was investigated. The results shown in Table 1 demonstrate that the procedure can be successfully applied to different kinds of substrates. Compounds **4–11** afforded the deprotected amine always in yield higher than 90%. In the presence of allylic groups (**11**) hydrogenolysis of the Cbz occurred together with hydrogenation of the double bond. In the presence of *N*-Fmoc groups (as in the case of doubly protected lysine **8**) we observed that, after four cycles (1 min irradiation and 1 min of rest), Cbz was completely removed and Fmoc was not deprotected. Nevertheless when *N*-FmocProOMe was submitted to ten cycles of irradiation and rest we observed 10% of deprotection.⁷ The microwave-assisted deprotection was also fully compatible with enantiomerically pure amino acids and peptides as no racemization was observed in amines derived from compounds **1**, **4**, **5**, **7**, **9** and **11**.⁸ Finally, deprotection can be successfully carried out also on substrates supported on MeO-PEG (MW 5000) **12** and even on a Wang-type resin **13**. In this last case, after eight cycles we did not observe cleavage from the resin.⁹

The ammonium formate catalytic-transfer hydrogenation accelerated by microwaves can be also applied to the deprotection of benzyl amines. The procedure was particularly useful for compound **14**¹⁰ that gave a polar polyhydroxy pyrrolidine in 5 min (three cycles) after the simple work-up. This procedure was also compatible with tosyl and even with benzyl esters as demonstrated by selective deprotection of compound **15**.

Finally, the procedure was successfully applied to the cleavage of the benzyl group in a chiral compound obtained by reaction of (*S*)-1-phenethylamine (**20**).

For example, Strecker reaction¹¹ of **20** with butanal (**21**) gave compound **22** in 75% yield as a mixture of diastereoisomers (80:20) that can be simply separated by column chromatography. The major isomer, (1*S*,2*S*)-2-(1-phenylethylamino)butyronitrile (**22a**) was transformed¹² into enantiomerically pure (*L*)-norvaline **23** in 75% yield.¹³ (Scheme 2)

In conclusion, a mild, simple and short method for deprotection of nitrogen using microwave irradiation in solution has been developed and its potential has been demonstrated. The application of this methodology to more complex syntheses on polymeric support is currently under investigation in our laboratory.

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References

- Kocienski, P. J. In *Protecting Groups: Thieme Foundations of Organic Chemistry Series*; Enders, D.; Noyori, B.; Trost, B. M., Eds.; Thieme: Stuttgart, 1994.
- Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed; J. Wiley & Sons: New York, 1991; p. 335.
- Rajagopal, S.; Anwer, M. K.; Spatola, A. F. In *Peptides: Design, Synthesis and Biological Activity*; Basava, C.; Anantharamaiah, G. M., Eds.; Birkhauser: Boston, 1994; Chapter 2, p. 11.
- Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746.
- Falorni, M.; Satta, M.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2389.
- Insoluble products can be solubilized in *i*-PrOH irradiating with microwaves the flask (600 W for 1 min) before adding HCOONH₄ and the catalyst.

7. Atherton, E.; Bury, C.; Sheppard, R. C.; Williams, B. *J. Tetrahedron Lett.* **1979**, 20, 3041.
8. The absence of racemization was done by ^{19}F NMR of the (*S*)-MTPA amides formed with amines derived from compounds **4**, **5**, **7**, **9**, and **11**. For amines derived from **1**, **14**, **15** and **16**, the control was done directly by ^1H NMR (300 MHz).
9. Ammonium formate catalytic-transfer hydrogenation has been reported to remove peptides from a Merrifield-type resin. See: Anwer, M. K.; Spatola, A. F. *Tetrahedron Lett.* **1981**, 22, 4369.
10. Esposito, A.; Taddei, M. *Tetrahedron Lett* **1998**, 39, 6543.
11. (a) Duthaler, R. O. *Tetrahedron* **1994**, 50, 1539; (b) Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, 48, 5369; (c) Inaba, T.; Fujita, M.; Ogura, K. *J. Org. Chem.* **1991**, 56, 1274.
12. Kempson, J.; Pattenden, G. *Synlett* **1999**, 11, 533–536.
13. Compound **23** showed optical rotation data comparable with those reported in: Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, 110, 1547.