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One-pot selective cleavage of prenyl carbamates using iodine in methanol followed by zinc

Jean-Michel Vatèle*

Laboratoire de Chimie Organique 1, UMR 5181 CNRS, Université Claude Bernard, CPE, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France

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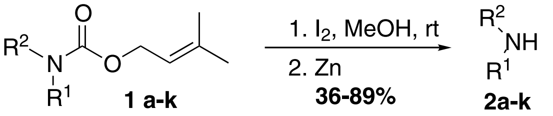
Abstract—The prenyloxycarbonyl (Preoc) moiety was efficiently removed from carbamates to provide the corresponding amines in good to excellent yields (63–88%) by using iodine in methanol followed by treatment of the resulting β-methoxyiodides by zinc powder. The reaction conditions are compatible with the presence of a number of functional groups such as Boc and Cbz carbamates, sulfides, double bonds, indoles and aromatic methyl ethers.

Amines, because of their high reactivity, must be protected before synthetic operations. Very often, these protecting groups have the function of negating the amine's basicity, a task realized by acylation. However, the deprotection of resulting amides or carbamates requires conditions that may damage the natural product or functionalities thereon. For these reasons, an impressive arsenal of amino protecting groups and of techniques of cleavage of these latter have been developed.[1] Nevertheless, because of the increasing complexity of the molecules synthesized and also only very few amino protecting groups have found wide applications, new protecting groups with modulated reactivity and new cleavage techniques of existing protecting groups are still needed.

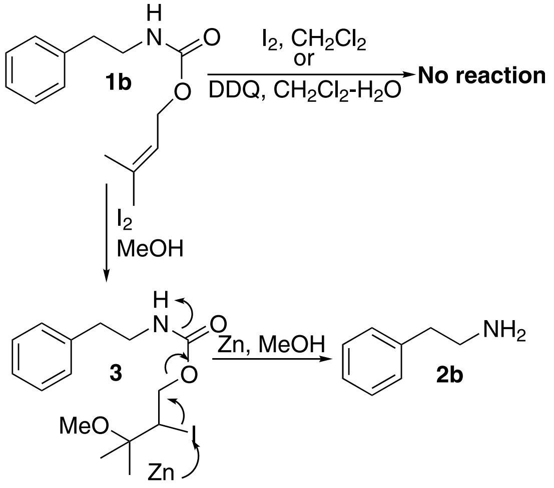
In an ongoing project aimed to develop the uses of prenyl group in the protection of alcohols and amines, we have recently reported that deprotection of prenyl ethers could be carried out chemoselectively, at room temperature, with iodine in dichloromethane or with dichlorodicyanoquinone (DDQ) in a mixture of dichloromethane and water.[2]

In this report, we wish to present a one-pot procedure for the cleavage of prenyl carbamates by first iodoetherification with iodine in methanol followed by reductive β-elimination with zinc (Scheme 1).

In preliminary experiments, the two protocols that we developed for the deprotection of prenyl ethers,[2] were tested for the cleavage of the carbamate derived from 2-phenylethylamine **1b**. In both cases, after stirring for 24 h at room temperature, the carbamate **1b** remained unchanged. In methanol, on the other hand, iodine



Scheme 1.



Scheme 2.

Keywords: amines; carbamates; iodine; deprotection; zinc.

* Fax: 33.4.72.43.12.14; e-mail: vatele@univ-lyon1.fr

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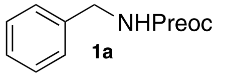
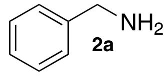
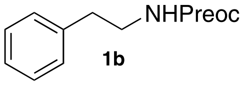
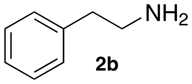
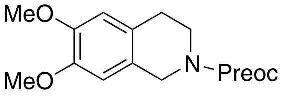
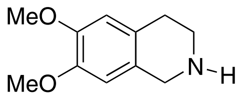
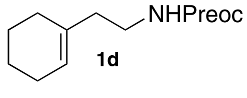
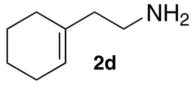
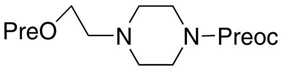
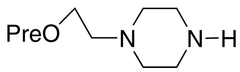
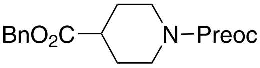
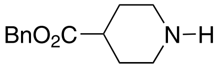
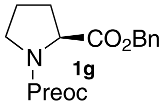
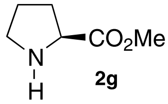
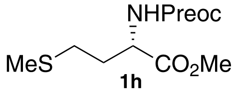
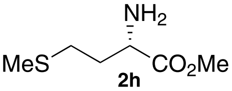
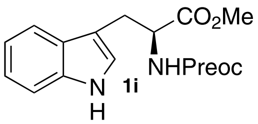
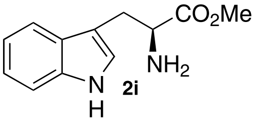
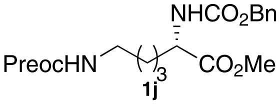
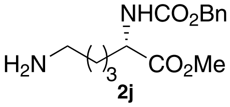
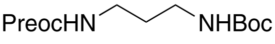
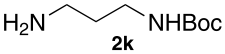
Table 1. One-pot deprotection of prenyl carbamates with I_2 in MeOH followed by Zn[a]

Entry	Substrate	Product	yield (%)
1	 **1a**	 **2a**	82
2	 **1b**	 **2b**	85
3	 **1c**	 **2c**	78
4	 **1d**	 **2d**	88
5	 **1e**	 **2e**	63
6	 **1f**	 **2f**	75
7	 **1g**	 **2g**	70
8	 **1h**	 **2h**	83
9	 **1i**	 **2i**	53
10	 **1j**	 **2j**	85
11	 **1k**	 **2k**	82

(a) Reaction conditions: I_2 (2 equiv), 7 h, r.t. then Zn (4 equiv), 30 min; entries 4 and 5: I_2 (4 equiv), Zn (8 equiv); entry 9: I_2 (2 equiv), 24 h, r.t.(without Zn).

reacted smoothly with **1b** to afford the β-methoxyiodide **3** (Scheme 2).

This compound bears a 2-haloalkoxycarbonyl system (a2d)[3] which is known to fragment easily in the presence of a metal.[4] Indeed, treatment of **3** with 2 equivalents of zinc in refluxing methanol for 30 min furnished the 2-phenylethylamine **2b** in 70% yield (not optimized).

In order to simplify the process, zinc was directly added to the reaction mixture containing the β-methoxyiodide **3**. This addition led almost instantaneously to the discoloration of the solution (ZnI_2 formation) with concomitant bubbling due to decarboxylation and heat formation. Thus, under the same reaction conditions, the liberation of the amine took place very readily without the need for heating. The reasons for the acceleration of the release of amine **1b** with zinc in the presence of iodine are uncertain. It is possible that iodine, present in the medium, transforms zinc into an active species, as it does with magnesium,[5] achieving its rapid oxidative insertion to the C–I bond.[6] It is admitted that magnesium halides initiate the formation of Grignard reagents,[7] zinc iodide, formed by reaction of zinc with iodine in excess, maybe play the same role in the formation of the organozinc intermediate.

In order to examine the generality of the method of prenyl carbamates deprotection, diversely functionalized prenyl carbamates[8] were prepared and the results of this study are presented in Table 1. As depicted in Table 1,[9,10] amines **2a–k** were obtained in acceptable to excellent yields (53–88%). Commonly used amino protecting groups such as Boc and Cbz groups are stable under our conditions of Preoc deprotection (entries 10, 11). In view of the oxidative nature of the medium,[11] deprotection of the methionine derivative (entry 8) emphasizes the mildness of the method. Compound **1d** bearing a double bond, in the presence of 4 equivalents of iodine and 8 equivalents of zinc, was deprotected in an excellent yield (88%, entry 4). As seen in entry 5, the N-Preoc group could be removed chemoselectively in the presence of a prenyl ether in an acceptable yield (63%). The release of the tetrahydroisoquinoline alkaloid **2c** occurred in good yield without affecting the two methoxy groups (entry 3). In the case of N-Preoc proline benzyl ester **1g**, removal of the carbamate happened with complete transesterification by methanol (entry 7). As no transesterication of the benzyl ester of the isonipecotic acid derivative **1f** was observed, in the same reaction conditions, we assume that the easy formation of the methyl ester **2g** is very likely the result of an intramolecular delivery of the methoxide anion to the carbonyl site of the ester by zinc, coordinated to the nitrogen of the pyrolidine ring of the proline derivative.[12] Surprisingly, in the presence of iodine in methanol, the liberation of the amine of N-Preoc-L-tryptophan methyl ester **2i** occurred directly after stirring for 24 h at room temperature (entry 9). In this case, the β-methoxyiodide intermediate was not seen by TLC. We have no mechanistic rationale to explain this result.

In summary, we have developed a mild and efficient method for the chemoselective deprotection of prenyl carbamates using zinc and iodine, two cheap reagents. Because of its simplicity and chemoselectivity, this procedure will undoubtedly extend the use of prenyl carbamates for the protection of a variety of amine compounds.[13]

References

1. (a) Kocienski, P. J. *Protecting Groups*; Thieme: Stuggart, 1994; Chapter 6; (b) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; 3rd ed., John Wiley and Sons Inc.: New York, 1999; Chapter 7.
2. (a) Vatèle, J.-M. *Synlett* **2001**, 1989–1991; (b) Vatèle, J.-M. *Synlett* **2002**, 507–509; (c) Vatèle, J.-M. *Tetrahedron* **2002**, *58*, 5689–5698.
3. Ho, T. L. *Heterocyclic Fragmentation of Organic Molecules*; Wiley: New York, 1993; p. 49.
4. For a good example of this fragmentation, see the deprotection of trichloroethylcarbamates: Mineno, T.; Choi, S.-R.; Avery, M. A. *Synlett* **2002**, 883–886 and references cited therein.
5. Rieke, R. D.; Sell, M. S. In *Handbook of Grignard Reagents*; Rakta, G. S.; Rakta, P. E., Eds.; Silverman, Marcel Dekker, 1996; p. 53.
6. Activation of zinc by iodine is precedented, see for example: (a) Palmer, M. H.; Reid, J. A. *J. Chem. Soc.* **1960**, 931–938; (b) Huo, S. *Org. Lett.* **2003**, *5*, 423–425.
7. Garst, J. F.; Ungvary, F. In *Grignard Reagents: New Developments*; Richey, H. G., Ed.; John Wiley, 2000; Vol. 7, p. 185.
8. Prenyl carbamates **1a–k** were prepared from the corresponding amines and prenyl *p*-nitrophenyl carbonate in the presence of a catalytic amount of DMAP.
9. All new compounds gave satisfactory physical and analytical data.
10. **Typical procedure for the cleavage of the N-Preoc of compound 1h**. To a solution of N-Preoc-L-methionine methyl ester **1h** (0.25 g, 0.9 mmol) in methanol (6 mL) was added, at room temperature, iodine (0.46 g, 1.8 mmol). After stirring 7 h, zinc[14] (0.24 g, 3.6 mmol) was added and the stirring was continued for 30 min. After evaporation to dryness, CH_2Cl_2 and saturated Na_2CO_3 solution were added and the formed precipitate and zinc in excess were filtered through a funnel. The aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to give pure L-methionine methyl ester as an oil (0.123 g, 83%). It was characterized as its hydrochloride salt: mp 145–149°C; $[\alpha]_D = +23.4$ (*c* 1.25, H_2O), (lit.[15] $[\alpha]_D = +25.2$ (*c* 5.1, H_2O); mp 147–150°C). ^1H NMR ($CDCl_3$, 200 MHz): 2.14 (s, 3H, Me), 2.29 (sextuplet, 2H, $J = 7.16$ and 6.33 Hz), 2.72 (t, 2H, $J = 7.16$ Hz), 3.88 (s, 3H), 4.34 (t, 1H, $J = 6.33$ Hz).^{13}C NMR ($CDCl_3$, 50 MHz): 14.4, 28.9, 29.2, 52.2, 54.2, 171.0.
11. For a study of the iodine oxidation of methionine, see: Young, P. R.; Hsieh, L. S. *J. Am. Chem. Soc.* **1978**, *100*, 7121–7122.
12. This Zn-mediated intramolecular transesterification is reminiscent of the intramolecular cleavage of phosphodiesters catalyzed by Zn(II) coordinated to amines: (a) Mollenveld, P.; Engbersen, J. F. J.; Reinhoudt, D. N. *Chem. Soc. Rev.* **2000**, *29*, 75–86; (b) Bonfà, L.; Gatos, M.; Mancin, F.; Teulla, P.; Tonellato, U. *Inorg. Chem.* **2003**, *42*, 3943–3949.
13. Until now, only one method to deprotect the N-Preoc group has been described: Lemaire-Audoire, S.; Savignac, M.; Pourcelot, G.; Genêt, J.-P.; Bernard, J.-M. *J. Mol. Cat. A: Chem.* **1997**, *116*, 247–258.
14. Aldrich Chemical Company, zinc dust <10 micron Catalog # 20,998-8.
15. Rachele, J. R. *J. Org. Chem.* **1963**, *28*, 2898.