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LETTERS

A FACILE NEW METHOD FOR SELECTIVE DEPROTECTION OF *N*-(*tert*-BUTOXYCARBONYL)-PROTECTED CARBOXAMIDES WITH Yb(OTf)3 SUPPORTED ON SILICA GEL

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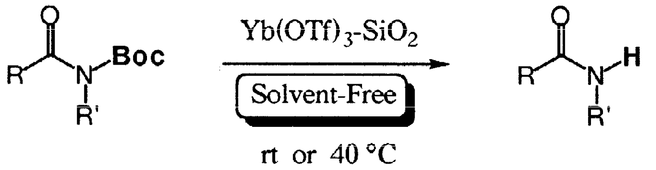
Abstract: A selective new method for the deprotection of *N*-Boc carboxamides was achieved by using $Yb(OTf)_3$ supported on silica gel under solvent-free conditions. © 1998 Elsevier Science Ltd. All rights reserved.

The *tert*-butoxycarbonyl (Boc) group is widely recognized as a convenient group for protecting a variety of amino compounds.[1] Classically, deprotection of the *N*-Boc group can be performed by the action of strong acids such as CF_3COOH and HCl,[1] and recently much milder reagents have been developed for this purpose.[2] In a closely related field of protection/deprotection of lactam amines, their carbamate intermediates are extensively employed in organic synthesis.[3] In a separate study of the synthesis of natural products,[4] we required an efficient method for the selective deprotection of *N*-Boc carboxamide derivatives. Toward this end, we were particularly interested in the characteristic Lewis acid nature of $Yb(OTf)_3$-SiO_2.[5] In this paper, we describe exactly how this reagent system is useful for the chemoselective deprotection of *N*-Boc carboxamides under solvent-free conditions (**Scheme 1**).[6]

Scheme 1



The results are summarized in **Table 1**.[7] A variety of *N*-Boc carboxamide derivatives were cleanly deprotected at room temperature or at 40 °C to the corresponding free amides in almost quantitative yields. Excellent chemoselectivity was observed for substrates containing a *N*-Cbz or a *N*-Boc amino group. The method is quite useful for the substrate having an acid-sensitive acetonide function. As exemplified in the last entries of the Table, *N*-Boc protected cyclic amine and pyrazole derivatives survived completely under these conditions. Although the present reactions were able to proceed in a heterogeneous phase in the presence of an organic solvent, they took longer than those using the solvent-free method, e.g., deprotection of *N*-Boc-acetanilide in refluxing CH_2Cl_2 completed after 4.5 h (98% yield).

In conclusion, we have developed a very simple and efficient procedure for the chemoselective deprotection of *N*-Boc carboxamides with $Yb(OTf)_3$-SiO_2 to the corresponding free amides under solvent-free conditions.[8] This method offers considerable advantages for use in organic synthesis in view of its simplicity, excellent yields, convenient work-up procedure, and very mild conditions involved.

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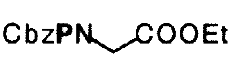
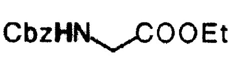
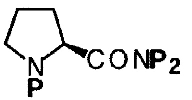
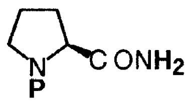
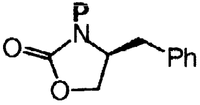
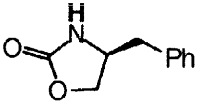
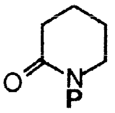
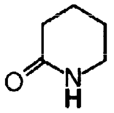
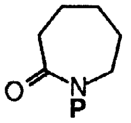
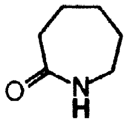
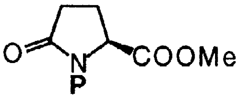
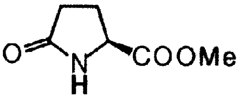
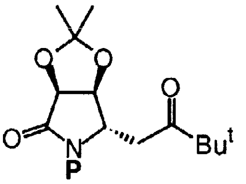
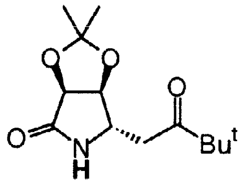
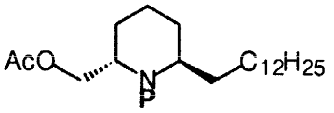
Table 1. Selective Deprotection of *N*-Boc-Protected Carboxamides with $Yb(OTf)_3$ / SiO_2 (P = Boc)^a

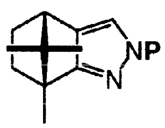
Substrate	Conditions	Product	Yield, %^{b}
	rt, 12 h		97
	40 °C, 1 h		99
$PhCH_2NPAc$	40 °C, 60 h	$PhCH_2NHAc$	99
PhNPAc	40 °C, 3 h	PhNHAc	98
	40 °C, 66 h		96
	40 °C, 2 h		100
	40 °C, 6 h		96

Substrate	Conditions	Product	Yield, %^{b}
	40 °C, 3 h		100
	40 °C, 3 h		100^c
	40 °C, 1 h		97

Unreactive substrates:



(40 °C, 24 h)



(40 °C, 24 h)

^{a} All reactions were performed using 9% $Yb(OTf)_3$-SiO_2 (400 mg / mmol). ^{b} Isolated yield. ^{c} No racemization was observed (specific rotation measurement was performed after reconversion to the starting *N*-Boc lactam).

General procedure: A mixture of the starting material (2 mmol) and 9% $Yb(OTf)_3$-SiO_2 (800 mg)[5] was suspended in 2 ml of CH_2Cl_2 and the solvent was removed *in vacuo.*[9] After standing at either room temperature or at 40 °C,[10] the product was extracted into ethyl acetate.[11] Concentration and purification by silica gel column chromatography or preparative TLC gave the corresponding free amide.

Acknowledgment. We thank Sumitomo Chemical Co., Ltd., for generously supplying Boc_2O.

References and Notes

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6. For related papers on the use of silica gel for deprotection of the *N*-Boc group, see: Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1471-1472; Siro, J. G.; Martín, J.; García-Navío, J. L.; Remuiñan, M. J.; Vaquero, J. J. *Synlett* **1998**, 147-148.
7. Satisfactory spectral data were obtained for all new compouds.
8. The use of $Yb(OTf)_3$ or SiO_2 separately as the reagent showed no synthetic value.
9. To dissolve the starting substrate, CH_2Cl_2 can be replaced with any solvent, e.g., AcOEt and THF.
10. During the reaction, carbon dioxide gas evolution was observed (positive $Ba(OH)_2$ test).
11. Due to the significant loss of $Yb(OTf)_3$ from the SiO_2 surface, recycling the catalyst was fruitless.