

**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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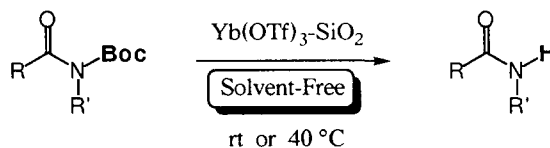
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Abstract: A selective new method for the deprotection of *N*-Boc carboxamides was achieved by using Yb(OTf)₃ supported on silica gel under solvent-free conditions. © 1998 Elsevier Science Ltd. All rights reserved.

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 CF₃COOH 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-SiO₂.⁵ 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 CH₂Cl₂ 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-SiO₂ 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.

Table 1. Selective Deprotection of *N*-Boc-Protected Carboxamides with Yb(OTf)₃/SiO₂ (P = Boc)^a

Substrate	Conditions	Product	Yield, % ^b	Substrate	Conditions	Product	Yield, % ^b
	rt, 12 h		97		40 °C, 3 h		100
	40 °C, 1 h		99		40 °C, 3 h		100 ^c
	40 °C, 60 h		99		40 °C, 1 h		97
	40 °C, 3 h		98	Unreactive substrates: (40 °C, 24 h) (40 °C, 24 h)			
	40 °C, 66 h		96				
	40 °C, 2 h		100				
	40 °C, 6 h		96				

^a All reactions were performed using 9% Yb(OTf)₃-SiO₂ (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-SiO₂ (800 mg)⁵ was suspended in 2 ml of CH₂Cl₂ 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.

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References and Notes

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- Satisfactory spectral data were obtained for all new compounds.
- The use of Yb(OTf)₃ or SiO₂ separately as the reagent showed no synthetic value.
- To dissolve the starting substrate, CH₂Cl₂ can be replaced with any solvent, e.g., AcOEt and THF.
- During the reaction, carbon dioxide gas evolution was observed (positive Ba(OH)₂ test).
- Due to the significant loss of Yb(OTf)₃ from the SiO₂ surface, recycling the catalyst was fruitless.