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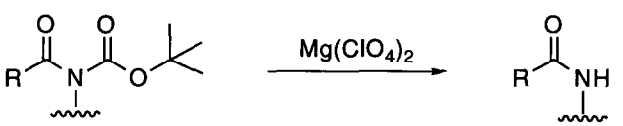
A Highly Selective Protocol for the Deprotection of BOC-Protected Amides and Carbamates

Jeffrey A. Stafford*, Marcus F. Brackeen, Donald S. Karanewsky, and Nicole L. Valvano
Glaxo Research Institute
5 Moore Drive
Research Triangle Park, NC 27709

Abstract: A BOC-protected amide or carbamate undergoes mild and selective deprotection by treatment with catalytic $Mg(ClO_4)_2$ in acetonitrile. Simple BOC-protected amines are not affected by these conditions.

The BOC (t-butyloxycarbonyl) group is widely used for the protection of amine and amide NH groups due its stability to mildly acidic and basic conditions and its ease of removal under specific conditions.[1] Removal of the BOC group is achieved by treatment with a strong acid (e.g., trifluoroacetic acid, HCl/acetic acid, etc.).[1] While these methods of BOC deprotection are undoubtedly extremely useful, a compound that possesses other acid-sensitive functionality can be compromised by these procedures. In this communication we describe our findings that a BOC-protected amide (or carbamate) can be selectively deprotected by treatment with catalytic $Mg(ClO_4)_2$ in acetonitrile. This procedure is highly specific for compounds of general structure **1** and leaves simple BOC-protected amines untouched.

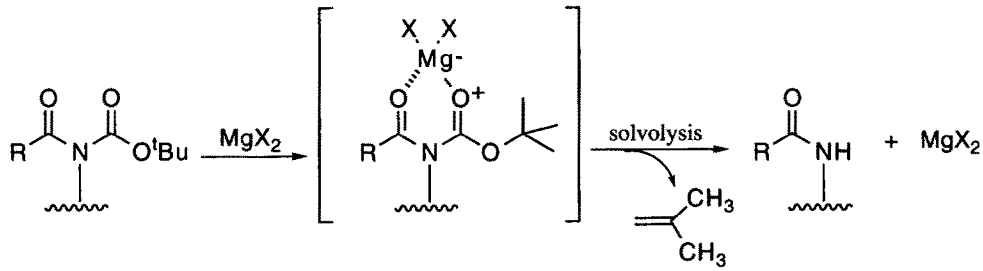


1

In order to explore the generality of the present method we examined the deprotection on a number of substrates.[2] In particular, we studied the deprotection of t-butylimidodicarbonates, a class of compounds that has received considerable attention as phthalimide substitutes in Mitsunobu[3] and Gabriel-type processes,[4] and more recently in the area of amino acid chemistry.[5] The data are summarized in the Table.[6] The deprotection of both *N*-benzyl-di-t-butylimidodicarbonate and $(BOC)_2$-Phe-OCH_3 proceeded smoothly to give only the *mono*protected amines in excellent yields (entries 1 and 2). Of particular note within this class is the selective deprotection of $(BOC)_2$-β-t-butylaspartate (entry 3). The β-t-butyl ester of the amino acid was left unharmed by this new method, a result that might be difficult to achieve using the existing methods of BOC deprotection.[7]

The scope of the present method is further illustrated by the selective deprotection of the cytosine base analogue (entry 5).[8] With respect to the reaction rate, it appears that reaction times are generally longer when there are competing Lewis basic sites and/or other chelating groups on the molecule. The long time required for the 3,4-dimethoxyphenethylamine derivative (entry 6) is perhaps due to competitive chelate formation by the catechol ether moiety. Indeed, when the two methoxy groups were removed (entry 7) a faster reaction rate was observed. No attempt was made to determine the dependency of rate or yield on the amount of Lewis acid catalyst. Finally, it appears that neither the nature of the nitrogen atom nor the nature of the flanking carbonyl group interferes with the deprotection. For example, the amide carbonyl can be conjugated to an aromatic ring (entry 8) without affecting the reaction's rate or yield. Furthermore, a BOC group attached to a relatively non-basic anilide-type nitrogen also undergoes the present reaction (entry 9).

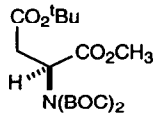
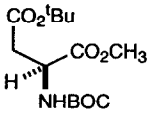
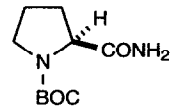
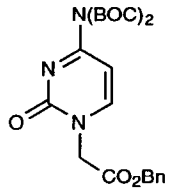
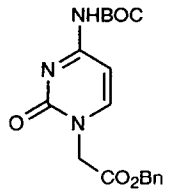
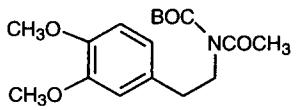
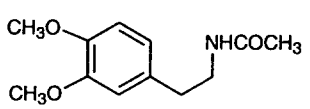
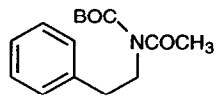
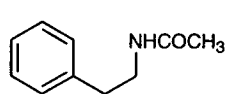
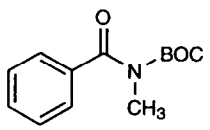
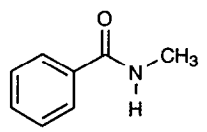
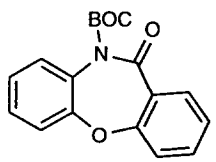
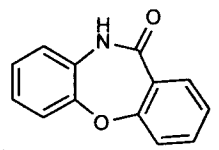
We propose that the mechanism for this reaction occurs by initial formation of a six-membered chelate between the mildly Lewis acidic $Mg(ClO_4)_2$[9] and the *N*-acyl-t-butyl carbamate. Solvolytic loss of the t-butyl group takes place to provide the deprotected compound.[10] In accord with this mechanism, a di-t-butylimidodicarbonate (entry 1) undergoes loss of only one carbamate group due to the inability of the product t-butyl carbamate to form a six-membered ring chelate. We were unsuccessful in our attempts to deprotect either BOC-prolinamide (entry 4) or BOC-Phe-OBn, further evidence that a simple BOC-protected amine is unchallenged by these reaction conditions.[11]



The following procedure is representative: To a stirring solution of *N*-benzyl-di-t-butyliminodicarbonate (614 mg, 2 mmol) in CH_3CN (5 mL) was added $Mg(ClO_4)_2$[12] (89 mg, 0.4 mmol). The solution was warmed to 50 °C and stirred for 3 hr, at which time TLC analysis indicated complete consumption of starting material. The solution was cooled to rt and partitioned between ether and 1M H_3PO_4. The organic layer was washed with brine. The combined aqueous layers were extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the product as a colorless solid (413 mg, 99%). Anal. calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.47; H, 8.30; N, 6.71.

In summary, we have described a simple, mild, and highly specific protocol for the deprotection of BOC-protected amides and carbamates. The need to protect an amide or carbamate NH is often encountered in the context of multistep organic synthesis, and we believe that the present procedure will find use in situations requiring an extremely mild and selective deprotection strategy.

Table. $Mg(ClO_4)_2$-catalyzed deprotection of BOC-amides and carbamates.

Entry	BOC-amide (carbamate)	Product	Temp.	Time	Yield (%)
1	$PhCH_2N(BOC)_2$	$PhCH_2NHBOC$	50 °C	3 h	99
2	$(BOC)_2$-Phe-OCH_3	BOC-Phe-OCH_3	rt	16 h	97
3			rt	16 h	99
4		—	80 °C	6 h	—
5			rt	72 h	82
6			50 °C	48 h	85
7			50 °C	12 h	98
8			50 °C	20 h	99
9			50 °C	4 h	99

Acknowledgements

The authors wish to thank Drs. Paul L. Feldman and Mukund M. Mehrotra for helpful discussions during the course of this work.

References and Notes

1. (a) Greene, T.W. and Wuts, P G M. *Protective Groups in Organic Synthesis*; 2nd ed.; Wiley: New York, 1991; p 403, pp 327-30 (b) Carpino, L.A. *Acc. Chem. Res* **1973**, *6*, 191, ref 12.
2. (a) BOC-amides and $(BOC)_2$-amino acid esters were prepared according to the procedure described by Davidsen and coworkers· Davidsen, S.K.; May, P D.; Summers, J.B *J. Org Chem* **1991**, *56*, 5482 (b) The *N*-benzyl-di-t-butylimidodicarbonate was prepared according to the procedure of Carpino, ref. 4a.
3. (a) For a recent, comprehensive review of the Mitsunobu reaction, see· Hughes, D.L. *Org. React.* **1992**, *42*, 335. (b) Grehn, L ; Ragnarsson, U. *Coll. Czech. Chem. Commun.* **1988**, *53*, 2778. (c) Koppel, I.; Koppel, J ; Degerbeck. F.; Grehn, L.; Ragnarsson, U. *J. Org Chem.* **1991**, *56*, 7172. (d) *N*-sulfonyl-t-butylcarbamates (e.g. $BOCNHSO_2R$) have also been used in the Mitsunobu reaction. See, for example: Henry, J.R.; Marcin, L.R ; McIntosh, M C.; Scola, P.M ; Harris, G.D.; Weinreb, S.M. *Tetrahedron Lett* **1989**, *30*, 5709, Campbell, J.A.; Hart, D.J *J. Org. Chem* **1993**, *58*, 2900
4. (a) Carpino, L.A. *J Org. Chem.* **1964**, *29*, 2820. (b) Gibson, M.S., Bradshaw, R W *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919 (c) Ragnarsson, U.; Grehn, L *Acc. Chem. Res.* **1991**, *24*, 285. (d) Di-t-butylimidodicarbonate has been alkylated with π-allyl palladium complexes: Connell, R.D.; Rein, T., Åkermark, B.; Helquist, P *J. Org. Chem.* **1988**, *53*, 3845.
5. (a) Gunnarsson, K ; Grehn, L.; Ragnarsson, U *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 400 (b) Carpino, L A ; Mansour, E.M.E ; El-Faham, A. *J Org. Chem.* **1993**, *58*, 4162.
6. Unless noted all reactions were conducted with 0.2 equiv. $Mg(ClO_4)_2$ in acetonitrile (0.5 M), except entry 7, which was done in THF. All yields refer to isolated, pure products having proper spectral and/or analytical data.
7. Åkermark, Helquist, and coworkers have reported the partial deprotection of simple *N*-alkyl-di-t-butylimidodicarbonates with trifluoroacetic acid (TFA) [4d]
8. The authors thank Ms Kathryn L. Reed for providing a sample of the cytosine derivative
9. Other Lewis acids that were investigated include $MgCl_2$, $Mg(OTf)_2$, and $Zn(OTf)_2$. All these acids promoted the monodeprotection of *N*-benzyl-di-t-butylimidodicarbonate in excellent yields. Additionally, $Zn(OTf)_2$ selectively monodeprotected $(BOC)_2$-β-t-butylaspartate (entry 3) in 99% yield, also leaving the t-butyl ester intact. We preferred $Mg(ClO_4)_2$ due to its relative cost, the absence of a nucleophilic counterion, its good solubility in CH_3CN, and its ease of removal from the organic phase by a single extraction with aqueous acid
10. Both *N*-methoxycarbonyl-*N*-methylbenzamide and *N*-benzyloxy-*N*-methylbenzamide were inert to treatment with 0.2 equiv. $Mg(ClO_4)_2$ in CH_3CN at 50 °C, a consequence of the inability of these compounds to solvolyze with loss of a methyl or benzyl cation, respectively.
11. BOC-prolinamide was inert to treatment with 0.5 equiv. $Mg(ClO_4)_2$ in refluxing CH_3CN
12. Purchased from Aldrich Chemical Co. (cat.# 22, 228-3) In the presence of highly oxidizable groups $Mg(ClO_4)_2$ can represent an explosion hazard. We did not encounter any hazardous situations during the course of this study, however, reasonable precautions should be taken when using this reagent.

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