Pergamon

Tetrahedron Letters 43 (2002) 1549–1551

TETRAHEDRON LETTERS

Indium-mediated facile cleavage of the *t*-butoxycarbonyl group from di-*t*-butylimidodicarbonate

J. S. Yadav,* B. V. S. Reddy, K. Srinivasa Reddy and K. Bhaskar Reddy

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

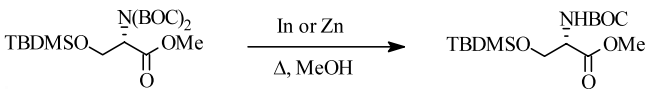
Received 27 July 2001; revised 6 December 2001; accepted 14 December 2001

Abstract—Di-*t*-butylimidodicarbonates are selectively and efficiently deprotected to the corresponding mono-BOC protected amines in high yields using indium or zinc metal in refluxing methanol. Simple BOC and CBz protected amines are unaffected by these conditions.

Protection of amines with appropriate protecting groups plays an important role in multi-step synthesis and also in peptide synthesis. Among various amine-protecting groups, carbamate protecting groups are widely used during the synthesis of amino acids, peptides and other natural products.[1] The *t*-butoxycarbonyl group is one of the most frequently used amine-protecting groups in organic synthesis due to its chemical stability to basic and mildly acidic conditions and its ease of removal under specific conditions. Further, di-*t*-butylimidodicarbonates are very useful as phthalimide substitutes in Mitsunobu[2] and Gabriel-type processes[3] in the synthesis of several bioactive molecules and are found to be essential for the success of the reaction.[4] However, the final stage of the chemical process frequently requires their cleavage so as to regenerate the parent compounds. Generally, the removal of the *t*-BOC group is achieved by strong acid catalysis.[5,6] However, most of these procedures are of limited synthetic scope due to lower selectivity for e.g. the removal of both BOC groups by conc. HCl[6a] or HBr[6b] and incompatibility with other acid sensitive functional groups.[5,6] Therefore, the development of a neutral alternative would extend the scope of the di-BOC protective group in peptide synthesis.[7] Recently, metal mediated reactions have attracted much interest in organic synthesis because of their high reactivity, stability and selectivity. Particularly, indium metal has gained more popularity,[8] owing to its unique reactivity and stability in aqueous media. However, there are no reports on the partial deprotection of di-*t*-butylimidodicarbonate using indium or zinc metal. In the course of our studies on the synthesis of biologically interesting compound sphingosine, we required the selective removal of the *t*-butoxycarbonyl group from *N*-BOC protected carbamates and sulfonamides in the presence of THP, trityl, TBDMS and TBDPS ethers.

In this report we describe a new and efficient procedure for the selective removal of the *t*-butoxycarbonyl group from *N*-BOC protected carbamates using indium or zinc metal under mild and neutral conditions (Scheme 1).

The cleavage of di-BOC protected amides was effected by indium metal in methanol at reflux temperature. This method is highly selective for cleavage of the *t*-BOC group from *N*-BOC protected cabamates and leaves simple BOC protected amines unaffected. The deprotection of *t*-butylimidodicarbonates proceeded smoothly to give exclusively mono-BOC protected amines in excellent yields. Such selectivity can be applied in synthetic sequences in which two BOC groups must be unmasked at different stages of the synthesis. It should be noted that the $N(BOC)_2$ derivatives bearing α-stereogenic centers gave the mono-BOC protected amines with complete retention of the original configuration.[9] The removal of *t*-BOC from a *N*-BOC protected sulfonamide was achieved with high selectivity (Table 1, entry m). There are many advantages in the use of indium metal for this cleavage which



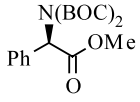
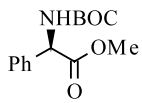
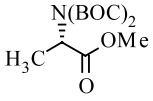
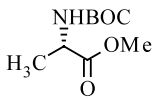
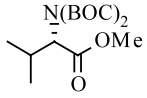
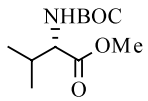
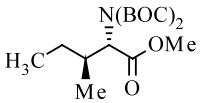
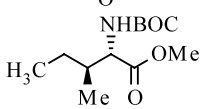
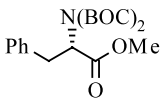
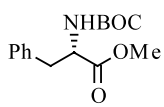
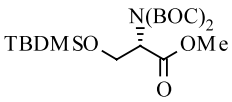
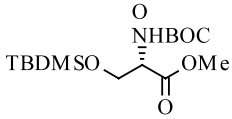
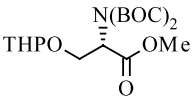
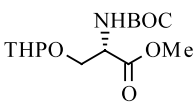
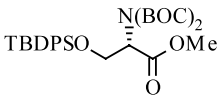
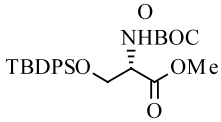
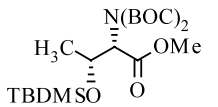
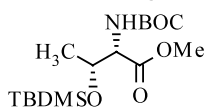
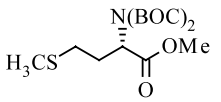
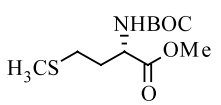
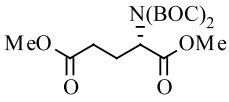
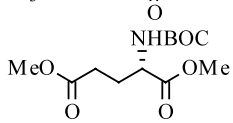
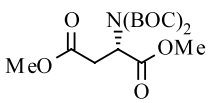
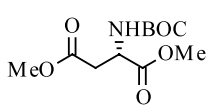
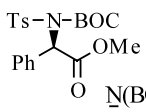
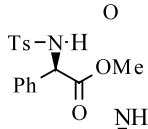
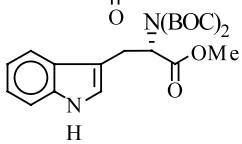
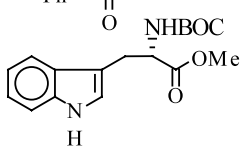
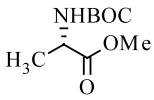
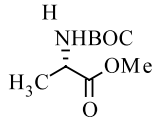
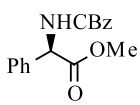
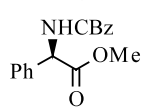
Scheme 1.

Keywords: indium; carbamates; sulfonamides; α-amino acids.

* Corresponding author. E-mail: yadav@iict.ap.nic.in

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02374-7

Table 1. Metal-mediated conversion of di-BOC to mono-BOC

Entry	Substrate (1)	Product (2)	Zinc		Indium	
			Time (h)	Yield (%)	Time (h)	Yield (%)
a)			15	90	20	92
b)			20	92	30	90
c)			18	85	20	89
d)			22	80	24	87
e)			20	83	23	85
f)			24	87	24	90
g)			21	80	22	83
h)			20	89	18	87
i)			17	85	20	89
j)			20	78	22	85
k)			18	90	20	92
l)			16	88	18	90
m)			18	87	20	90
n)			20	80	20	85
o)			--	--	--	--
p)			--	--	--	--

include the selective removal of a mono-*t*-BOC group from di-*t*-BOC protected carbamates and sulfonamides in the presence of other acid sensitive functional groups. Another advantage of this procedure is the selective removal of a *t*-BOC group in the presence of highly acid sensitive protecting groups such as THP, TBDMS and trityl ethers who do not survive TFA or conc. HCl. Other functional groups such as esters, carbamates, ethers and olefins are unaffected by these conditions. Furthermore, the compatibility of this procedure is illustrated by the selective removal of the *t*-BOC group without affecting mono-BOC, CBz and sulfonamides. In terms of efficiency and selectivity, this procedure is superior to the reported methods where protic acids such as TFA, conc. HBr and HCl are used. These reagents sequentially remove both BOC groups from di-BOC protected amides whereas mono BOC protected amines survive under the present reaction conditions. It is of interest to note that both *t*-BOC and ester groups were hydrolyzed when the reaction was carried out with 2 equiv. of sodium hydroxide in methanol at ambient temperature. Similarly, 2 equiv. of sodium metal in methanol or sodium methoxide also cleaved both acid and amine protective groups. In contrast, indium metal in methanol being a mild base (pH of the reaction media approximately 7.2) selectively cleaved mono-BOC from di-*t*-BOC protected amides leaving both acid and base labile functional groups intact.

The results illustrated in Table 1 indicate the scope and generality of the reaction with respect to various *t*-BOC protected amino acids. Similar results were also obtained with zinc metal in refluxing methanol (Table 1). The use of metal grade zinc powder makes the procedure inexpensive and offers advantages over existing methods. Finally, mono-*t*-BOC and CBz protected amines are unaffected under similar conditions (entries o and p). This procedure has strengthened the utility of di-BOC protection in organic synthesis, which allows application in peptide synthesis.

In conclusion, we have demonstrated a novel and highly efficient protocol for the selective removal of the *t*-BOC group from *N*-BOC protected amides using indium or zinc metal under mild conditions. Due to its high chemoselectivity, efficiency and simplicity, this method may find wide applications in solid-phase peptide synthesis.

Acknowledgements

B.V.S., K.S.R. and K.B.R. thank CSIR New Delhi for the award of fellowships.

References

1. (a) Kocienski, P. J. *Protective Groups*; Thieme Verlag: Stuttgart, New York, 1994; p. 192; (b) Greene, T. W.; Wutts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p. 327.
2. (a) Koppel, I.; Koppel, J.; Degerback, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172; (b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709; (c) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900.
3. (a) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919; (b) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.
4. (a) Kokotos, G.; Padron, J. M.; Martin, T.; Gibbons, W. A.; Martin, V. S. *J. Org. Chem.* **1998**, *63*, 3741; (b) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054; (c) Sugawara, N.; Stevens, E. S.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7044.
5. (a) Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1988**, 53; (b) Brosse, N.; Pinto, M.-F.; Gregoire, B. J. *Tetrahedron Lett.* **2000**, *41*, 205; (c) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873.
6. (a) Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820; (b) Allan, R. D.; Johnston, G. A.; Kazlauskas, R.; Tran, H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2983; (c) Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 245.
7. (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.
8. (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149; (b) Cintas, P. *Synlett.* **1995**, 1087; (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. M. *Tetrahedron Lett.* **2000**, *41*, 2663; (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, G. S. K. K. *Tetrahedron Lett.* **2000**, *41*, 2695.
9. *Experimental procedure:* A mixture of *t*-butyl imidodicarbonate (5 mmol), indium or zinc powder (10 mmol) in methanol (15 ml) was stirred under reflux for an appropriate time. After complete conversion, as indicated by TLC, the solvent was removed under reduced pressure, diluted with water (15 ml) and extracted with ethyl acetate (2×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate:hexane, 2:8) to afford mono-BOC protected amines. Spectral data for compound **1c**: $[\alpha]_D^{25}=12.8$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.88 (d, 3H, $J=6.8$ Hz), 1.18 (d, 3H, $J=6.8$ Hz), 1.50 (s, 18H), 2.42–2.50 (m, 1H), 3.78 (s, 3H), 4.48 (d, 1H, $J=6.8$ Hz). Compound **2c**: $[\alpha]_D^{25}=-20.8$ (*c* 1.1, MeOH); (lit.,[4] $[\alpha]_D^{25}=-21.2$ (*c* 1.1, MeOH); ^1H NMR ($CDCl_3$): δ 0.85 (d, 3H, $J=6.8$ Hz), 0.90 (d, 3H, $J=6.8$Hz), 1.50 (s, 9H), 2.02–2.18 (m, 1H), 3.75 (s, 3H), 4.23 (m, 1H), 4.95 (brs, NH). Compound **1j**: $[\alpha]_D^{25}=-35.57$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.48 (s, 18H), 2.10 (s, 3H), 2.43–2.60 (m, 4H), 3.78 (s, 3H), 5.05 (dd, 1H $J=9.0$, 4.5 Hz,). Compound **2j**: $[\alpha]_D^{25}=24.3$ (*c* 2.8, $CHCl_3$); (lit.,[4] $[\alpha]_D^{25}=24.6$ (*c* 2.84, $CHCl_3$).; ^1H NMR ($CDCl_3$): δ 1.33 (s, 9H), 1.78–1.90 (m, 2H), 1.98 (s, 3H), 2.41 (t, 2H, $J=7.3$ Hz), 3.65 (s, 3H), 4.32–4.41 (m, 1H), 5.23 (brs, NH). Compound **1k**: $[\alpha]_D^{25}=-37.02$ (*c* 2.15, $CHCl_3$) (lit.,[4] $[\alpha]_D^{25}=-37.2$) (*c* 2.15, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.50 (s, 18H), 2.18 (m, 1H), 2.40 (m, 2H), 2.45 (m, 1H), 3.68 (s, 3H), 3.75 (s, 3H), 4.95 (dd, 1H, $J=9.0$, 4.3 Hz). Compound **2k**: $[\alpha]_D^{25}=+12.7$ (*c* 2.00, $CHCl_3$), (lit.,[4] $[\alpha]_D^{25}=+12.9$) (*c* 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.40 (s, 9H), 1.90 (m, 1H), 2.15 (m, 1H), 2.39 (m, 2H), 3.65 (s, 3H), 3.70 (s, 3H), 4.30 (bs, 1H), 5.15 (brs, NH).