Efficient and Selective Cleavage of *t*-Butoxycarbonyl Group from Carbamates and Amides by $CeCl_3 \cdot 7H_2O$-NaI

J. S. Yadav,* B. V. Subba Reddy, K. Srinivasa Reddy

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91(40)7170512; E-mail: yadav@iict.ap.nic.in

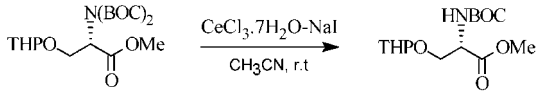
Received 31 October 2001

Abstract: A highly selective cleavage of the *t*-butoxycarbonyl group has been achieved in high yields using $CeCl_3 \cdot 7H_2O$-NaI in acetonitrile at ambient temperature under neutral conditions. This method is mild and compatible with a wide range of functional groups such as THP, TBDMS, TBDPS, trityl ethers, mono-BOC or Cbz protected amines, acetamide, sulfonamide and benzamide etc., present in the substrate.

Key words: cerium reagents, carbamates, amides, α-amino acids

The strategy of protection and deprotection of a functional group is frequently used in the multi-step synthesis of many complex natural products.[1] The *t*-butoxycarbonyl group is one of the most widely used amine-protective groups during the synthesis of amino acids, peptides and other biologically interesting molecules.[2] In addition, di-*t*-butylimidodicarbonates are very useful as phthalimide substitutes in Mitsunobu[3] and Gabriel-type processes[4] in the synthesis of several bio-active compounds and are found to be essential for the success of the reaction.[5a] However, the final stage of the chemical process requires their cleavage so as to regenerate the parent compounds. In consequence, several procedures have been reported for the selective cleavage of mono-BOC from di-BOC protected amides using strong acid catalysis.[6,7] However, many of these reagents or solvents used are corrosive or toxic, expensive and difficult to handle especially on large scale. In addition, some of these methods are of limited synthetic scope due to the lack of selectivity and incompatibility with other acid sensitive functional groups. Therefore, there is a need to develop a mild and efficient procedure for the removal of BOC group from *t*-BOC protected amides.

Lanthanide salts are unique Lewis acids[8] that are currently of great research interest. Among these catalysts cerium halides[9] are relatively non-toxic, readily available at low cost and are fairly stable to water. We wish to report that cerium(III)chloride-NaI is an efficient reagent system for the selective removal of mono-BOC from di-BOC protected amides under neutral conditions (Scheme 1).



Scheme 1

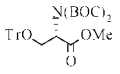
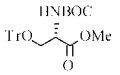
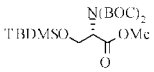
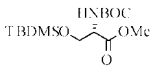
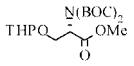
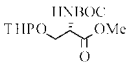
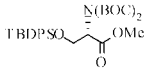
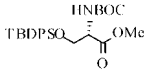
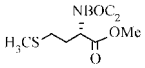
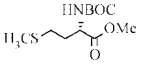
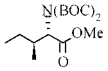
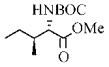
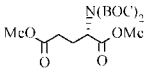
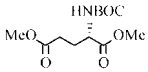
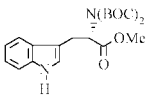
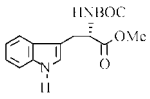
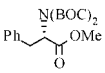
The cleavage was affected by equimolar ratio of $CeCl_3 \cdot 7H_2O$-NaI in acetonitrile at ambient temperature. The deprotection proceeded efficiently in high yields with high chemoselectivity. The combination of cerium(III) chloride with NaI selectively cleaved a *t*-butoxycarbonyl group from di-BOC protected amides leaving other functional groups intact. Such selectivity can be applied in synthetic sequences in which two BOC groups must be unmasked at different stages of the synthesis. This method is highly chemoselective for removal of a *t*-BOC group from di-BOC or BOC protected amides and carbamates without affecting the mono-BOC or Cbz protected amines. It should be noted that the $N(BOC)_2$ derivatives bearing α-stereogenic centres gave mono-BOC protected amines with complete retention of the original configuration.[10] Further, the removal of a *t*-BOC group from *N*-BOC protected acetamide, benzamide and sulfonamides was also achieved with high selectivity (entry f, g, k). The major advantage of this cleavage is in the selective removal of *t*-BOC group in the presence of highly acid sensitive trityl, TBDMS and THP ethers, which do not survive either in TFA or HBr in acetic acid.[6,7] Furthermore, the compatibility of this procedure is illustrated by the selective removal of *t*-BOC group without affecting mono-BOC or Cbz group and sulfonamide. In terms of selectivity and efficiency, this procedure is superior than reported methods where protic acids such as HCl, TFA and HBr are used. These reagents sequentially remove both BOC groups from di-BOC protected amides whereas mono-BOC protected amides survive under the present reaction conditions. The reactions are clean and complete with in 4–6.5 hours. Due to mild reaction conditions, a number of functional groups, albeit being capable of reacting with $CeCl_3 \cdot 7\ H_2O$, remain intact. There are many advantages in the use of cerium(III)chloride for this cleavage, which avoids the use of strongly acidic or basic conditions. In addition, this method does not require the use of expensive reagents or anhydrous solvents and no precautions need to be taken to exclude moisture from the reaction system. Thus, the present method is efficient and mild, tolerating a wide range of functional groups. As evident from the Table the acid sensitive protecting groups such as trityl, THP, TBDMS, TBDPS, BOC, Cbz group and sulfonamide are compatible with $CeCl_3 \cdot 7H_2O$-NaI in ace-

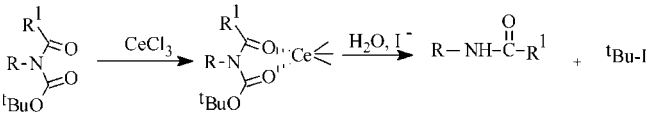
Synlett 2002, No. 3, 04 03 2002. Article Identifier:
1437-2096,E;2002,0,03,0468,0470,ftx,en;D21401ST.pdf.

ISSN 0936-5214

tonitrile at ambient temperature. The cleavage may be affected through the activation of carbonyl groups in the BOC protected amides by cerium(III)chloride resulting in the formation of oxonium ion which is attacked by I^- nucleophile to afford the corresponding amide and *t*-BuI as identified by spectral analysis (Scheme 2).

Table Selective Removal of BOC from BOC protected amides by $CeCl_3 \cdot 7\ H_2O$-Na^-

Entry	Substrate (**1**)	Product (**2**)	Time (h)	Yield (%)
a			4.5	91
b			4.0	89
c			5.0	93
d			6.0	95
e			4.0	85
f			4.0	83
g			5.0	87
h			6.0	91
i			6.5	92
j			6.0	91
k			6.5	85
l			4.5	95
m			6.0	89
n			6.0	91
o			10.0	–
p			12.0	–



Scheme 2

Finally, we have examined the possibility of $CeCl_3 \cdot 7\ H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. However best results were obtained with equimolar ratio of $CeCl_3 \cdot 7H_2O$-NaI. In the absence of NaI, the deprotection by $CeCl_3$ alone in acetonitrile at ambient temperature took longer to achieve complete conversion. This clearly indicates that the addition of 1 equivalent of NaI is crucial in the deprotection to obtain high yields of mono-BOC protected amines.

In summary, this paper describes a method for the selective removal of a single BOC group from di-BOC protected amides using a cheap and readily available reagent system that operates under neutral conditions thereby leaving acid- and base-labile protecting groups intact. The high levels of chemoselectivity in this process combined with a simple operation, high yields and ready availability of reagents will facilitate wider use of di-BOC protection in organic synthesis.

Acknowledgement

BVS and KSR thank CSIR, New Delhi for the award of fellowship.

References

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis, 3rd ed.*; John Wiley and Sons: New York, **1999**. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**.

(2) (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.

(3) (a) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900. (b) Koppel, I.; Koppel, J.; Degerback, F.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172.

(4) (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.

(5) (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.

(6) (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.

(7) (a) Allan, R. D.; Johnston, G. A.; Kazlauskas, R.; Tran, H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2983. (b) Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820. (c) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873.

(8) (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.

(9) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209. (b) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Cappa, A.; Marcantoni, E.; Sambri, L.; Orregiani, E. *J. Org. Chem.* **1999**, *64*, 5696. (c) Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. (d) Yadav, J. S.; Reddy, B. V. S. *Synlett* **2000**, 1275.

(10) **Experimental Procedure**: A mixture of di-BOC derivative (5 mmol), $CeCl_3 \cdot 7\ H_2O$ (5 mmol) and sodium iodide (5 mmol) in acetonitrile (10 mL) was stirred at ambient temperature for an appropriate time (Table). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4 and concentrated in vacuo, and the resulting product was purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate–hexane, 2:8) to afford pure mono-BOC protected amine. **Spectroscopic Data of 1a**: $[\alpha]_D^{25}$ = –38.2 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 18 H), 3.60 (dd, 2 H, *J* = 5.5, 13.6 Hz), 3.65 (s, 3 H), 5.38 (dd, 1 H, *J* = 5.5, 10.3 Hz), 7.28–7.42 (m, 15 H). **2a**: $[\alpha]_D^{25}$ = +11.3 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H), 3.38 (dd, 2 H, *J* = 5.5, 13.6 Hz), 3.75 (s, 3 H), 4.38 (m, 1 H), 5.35 (brd, NH, *J* = 8.0 Hz), 7.10–7.40 (m, 15 H). **1b**: $[\alpha]_D^{25}$ = –29.789 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.03 (s, 6 H), 0.85 (s, 9 H), 1.48 (s, 18 H), 3.67 (s, 3 H), 4.10 (dd, 2 H, *J* = 5.8, 13.7 Hz), 5.10 (dd, 1 H, *J* = 5.8 and 10.5 Hz). **2b**: $[\alpha]_D^{25}$ = +17.684 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.02 (s, 6 H), 0.84 (s, 9 H), 1.43 (s, 9 H), 3.75 (s, 3 H), 3.80 (dd, 1 H, *J* = 5.8, 13.7 Hz), 4.05 (dd, 1 H, *J* = 5.8, 13.7 Hz), 4.30 (m, 1 H), 5.23 (brd, NH, *J* = 7.8 Hz). **1d**: $[\alpha]_D^{25}$ = –11.8 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.03 (s, 9 H), 1.43 (s, 18 H), 3.62 (s, 3 H), 4.18 (dd, 2 H, *J* = 5.7, 13.8 Hz), 5.23 (dd, 1 H, *J* = 5.7, 10.3 Hz), 7.38–7.40 (m, 6 H), 7.58–7.65 (m, 4 H). **2d**: $[\alpha]_D^{25}$ = +14.2 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.0 (s, 9 H), 1.45 (s, 9 H), 3.78 (s, 3 H), 3.98 (dd, 2 H, *J* = 5.7, 13.8 Hz), 4.38 (m, 1 H), 5.32 (br d, NH, *J* = 8.3 Hz), 7.28–7.43 (m, 6 H), 7.5–7.63 (m, 4 H). **1h**: $[\alpha]_D^{25}$ = –35.57 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 18 H), 2.10 (s, 3 H), 2.43–2.60 (m, 4 H), 3.78 (s, 3 H), 5.05 (dd, 1 H, *J* = 9.0 and 4.5 Hz). **2h**: $[\alpha]_D^{25}$ = 24.3 (*c* 2.8, $CHCl_3$), (ref.[5] $[\alpha]_D^{25}$ = 24.6 (*c* 2.84, $CHCl_3$)). ^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 9 H), 1.78–1.90 (m, 2 H), 1.98 (s, 3 H), 2.41 (t, 2 H, *J* = 7.3 Hz), 3.65 (s, 3 H), 4.32–4.41 (m, 1 H), 5.23 (br s, NH). **1j**: $[\alpha]_D^{25}$ = +12.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, 3 H, *J* = 6.8 Hz), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.50 (s, 18 H), 2.42–2.50 (m, 1 H), 3.78 (s, 3 H), 4.48 (d, 1 H, *J* = 6.8 Hz). **2j**: $[\alpha]_D^{25}$ = –20.8 (*c* 1.1, MeOH) (ref.[5] $[\alpha]_D^{25}$ = –21.2 (*c* 1.1, MeOH)). ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, 3 H, *J* = 6.8 Hz), 0.90 (d, 3 H, *J* = 6.8 Hz), 1.50 (s, 9 H), 2.02–2.18 (m, 1 H), 3.75 (s, 3 H), 4.23 (m, 1 H), 4.95 (brs, NH). **1l**: $[\alpha]_D^{25}$ = –37.2 (*c* 2.15, $CHCl_3$), (ref.[5] $[\alpha]_D^{25}$ = –37.2 (*c* 2.15, $CHCl_3$)). ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 18 H), 2.18 (m, 1 H), 2.40 (m, 2 H), 2.45 (m, 1 H), 3.68 (s, 3 H), 3.75 (s, 3 H), 4.95 (dd, 1 H, *J* = 9.0 and 4.3 Hz). **2l**: $[\alpha]_D^{25}$ = +12.7 (*c* 2.00, $CHCl_3$), [ref.[5] $[\alpha]_D^{25}$ = +12.9 (*c* 2.00, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H), 1.90 (m, 1 H), 2.15 (m, 1 H), 2.39 (m, 2 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.40 (br s, 1 H), 5.15 (br s, NH). IICT Commun. No: 01/x/10.