Pergamon

Tetrahedron Letters 41 (2000) 7013–7016

TETRAHEDRON LETTERS

Deprotection of *N*-*tert*-butoxycarbonyl (Boc) groups in the presence of *tert*-butyl esters

Linus S. Lin,* Thomas Lanza Jr., Stephen E. de Laszlo, Quang Truong, Theodore Kamenecka and William K. Hagmann

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Received 21 April 2000; revised 30 June 2000; accepted 6 July 2000

Abstract

Deprotection of Boc groups in the presence of *tert*-butyl esters was achieved by using concentrated H_2SO_4 (1.5–3.0 equiv.) in *t*BuOAc or $MeSO_3H$ (1.5–3.0 equiv.) in *t*BuOAc:CH_2Cl_2 (4:1 v/v). The yields ranged from 70 to 100% for a variety of amino acid and dipeptide substrates.

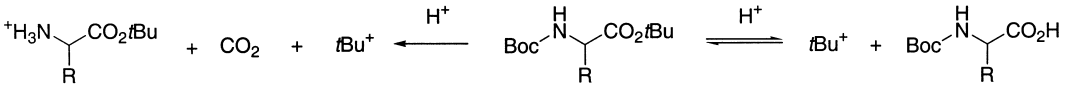
Keywords: amino acids and derivatives; deblocking; protecting groups.

N-*tert*-Butoxycarbonyl (Boc) and *tert*-butyl ester are among the most utilized protecting groups in organic syntheses, and they serve a critical role in amino acid and peptide chemistry.[1,2] While there is no reliable procedure for the selective deprotection of *tert*-butyl esters in the presence of Boc, Rapoport and co-workers reported that a Boc group can be selectively removed by treatment with 1 M HCl in EtOAc.[3a] This protocol works well for a variety of amino acid substrates, especially if the product crystallizes out of the reaction mixture, which presumably helps to prevent further deprotection of the *tert*-butyl ester group. Thus, when a phenylalanine substrate was subjected to the standard conditions,[3a] it afforded 78% yield of the desired amino ester in one experiment (1.8 mmol scale), but in another experiment (16 mmol scale), the material collected by filtration consisted of a 3:1 mixture of the amino ester and the Boc-protected amino acid as a result of *tert*-butyl ester removal (54% combined yield).

We then examined the mechanisms of the deprotection of Boc and *tert*-butyl esters. It is highly likely that the removal of Boc is an irreversible process due to protonation of the amine product and loss of CO_2. In contrast, the deprotection of the *tert*-butyl ester should be reversible under acidic conditions (Scheme 1). Indeed, *tert*-butyl esters are generally prepared under acid-catalyzed conditions in the presence of a *t*-Bu^+ source (e.g. isobutylene,[1,2] *t*BuOAc,[2] *t*-butanol,[4] etc.). Based on this analysis, we have discovered a simple procedure for the deprotection of Boc groups in the presence of *tert*-butyl esters, which is reported herein.

* Corresponding author. Tel: 732 594-8391; fax: 732 594-5790; e-mail: linus_lin@merck.com

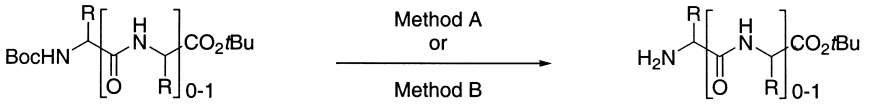
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01203-X



Scheme 1.

Thus, in a typical experiment,[5] the substrate was dissolved (or suspended) in *t*BuOAc (0.2 to 0.5 M), and concentrated H_2SO_4 was added (1.5 equiv.) (Method A). The reaction was stirred at room temperature until complete consumption of the starting material (2 to 16 h, an additional 0.5 to 1.5 equiv. of concentrated H_2SO_4 may be necessary). After the reaction mixture was neutralized by addition of saturated $NaHCO_3$, the product was extracted with EtOAc. Concentration afforded the product as the free amine (> 95% purity by NMR).[6] Alternatively, $MeSO_3H$ (1.5 to 3 equiv.) can be used in the place of concentrated H_2SO_4 with CH_2Cl_2 added as a co-solvent (4:1 v/v) (Method B). Under the latter conditions, the starting material and the product are more likely to remain in solution during the course of the reaction, and may offer advantages in some cases. As summarized in Table 1, these conditions work well for a variety of amino acid and dipeptide substrates. The yields range from good to excellent in all the cases studied. It is also noteworthy that a number of common nitrogen-protecting groups remain intact under these conditions.

Table 1



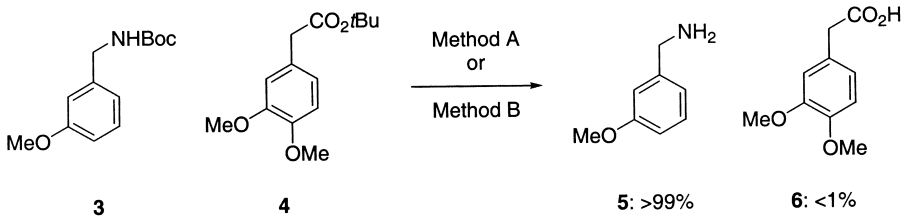
1a-h **2a-h**

Method A: conc H_2SO_4 (1.5-3.0 eq), *t*BuOAc, rt, 2-16 h

Method B: $MeSO_3H$ (1.5-3.0 eq), *t*BuOAc/CH_2Cl_2 (4:1), rt, 2-16 h

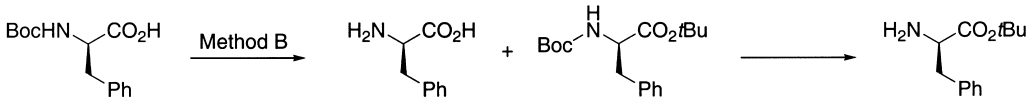
Entry	Substrate	Structure	Method	Isolated yield (%) of amino ester **2a-h**
1	*N*-Boc-(L)-Phe-O*t*Bu	**1a**	A	81
2	N_α-Boc-N_δ-Alloc-(L)-Orn-O*t*Bu	**1b**	A	75
3	N_α-Boc-N_δ-Cbz-(L)-Orn-O*t*Bu	**1c**	A	80
4	*N*-Boc-4(*R*)-acetoxy-(L)-Pro-O*t*Bu	**1d**	B	92
5	*N*-Boc-3(*R*)-phenyl-β-Ala-O*t*Bu	**1e**	A	70
6	*N*-Boc-3(*R*)-phenyl-β-Ala-O*t*Bu	**1e**	B	76
7	2-(BocNHCH$_2$CH$_2$)-5-Cl-PhCO$_2$*t*Bu	**1f**	A	77
8	*N*-Boc-(L)-Val-(L)-Pro-O*t*Bu	**1g**	A	100
9	*N*-Boc-(L)-Phe-(L)-Phe-O*t*Bu	**1h**	A	96

The effectiveness of this new protocol was also examined in a competition experiment. Thus, a mixture of **3** and **4** was subjected to the standard conditions (Methods A and B, respectively), and the reaction was followed by HPLC (Scheme 2). After 20 h at room temperature, >99% of **3** was converted to the free amine **5**, and <1% of the acid **6** was detected under either conditions.



Scheme 2.

For mechanistic considerations, BocPhe **7** was subjected to the standard reaction conditions (Method B), and the course of the reaction was followed by HPLC. After 15 min, a rapid formation of BocPheO*t*Bu **1a** was observed along with PheO*t*Bu **2a** and Phe **8** as their methanesulfonic acid salts, and only the latter precipitated out from the reaction mixture (determined by NMR after isolation) (Scheme 3). At 4 h, a more significant amount of PheO*t*Bu (**2a**) was observed at the expense of **1a**. After 20 h at room temperature, **2a** and **8** were the only products observed by HPLC and LC–MS.[7] These results suggest that acid-catalyzed equilibration between carboxylic acids and *t*BuOAc is a rapid process, and the mechanism in Scheme 1 is likely to operate under these conditions. It is worth noting, however, that the extent of ester exchange remains unknown.



Reaction time	**7** : **8** : **1a** : **2a**
0.25 h	54 : 28 : 16 : 2
4 h	5 : 63 : 13 : 19
20 h	0 : 73 : 0 : 27

Scheme 3.

In a related study, Fmoc-Ala-HMPB-resin, Fmoc-Ala-Wang-resin and Fmoc-Ala-chlorotrityl-resin were treated with *t*BuOAc:CH_2Cl_2:$MeSO_3H$ (80:20:1, 1 g resin/5 mL solvent mixture). In each case, a 1:1 mixture of Fmoc-Ala-O*t*Bu and Fmoc-Ala-OH was obtained (rt, 16 h). Although not synthetically useful, these results also demonstrate that ester exchange is a facile process under these acid-catalyzed conditions.

In comparison with concentrated H_2SO_4 or $MeSO_3H$, neither trifluoroacetic acid nor concentrated HCl was found to be effective for the removal of Boc groups in the presence of *tert*-butyl esters. Alternative solvents were also studied (e.g. HCO_2tBu, $ClCH_2CO_2tBu$, and

$AcCH_2CO_2tBu$). Among them, only HCO_2tBu performed well, but it is significantly more expensive than *t*BuOAc. Finally, EtOAc was compared side by side with *t*BuOAc using **1a** as a substrate, and a much lower yield was obtained (15 to 20% less).

In summary, we have developed a convenient and efficient procedure for the removal of Boc in the presence of *tert*-butyl esters. It has the advantage of using commercial reagents[8] and ease of scale-up,[9] and it is also effective for peptide substrates. The yields are good to excellent for a number of amino acid and dipeptide substrates.

Acknowledgements

We wish to thank Mr. Henry Murillo and Ms. Amy Bernick for LC–MS measurements.

References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed.; John Wiley & Sons: New York, 1991.
2. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd Ed.; Springer-Verlag: Berlin, 1994.
3. (a) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216. (b) For the use of HCl/dioxane in solid-phase applications, see: Hruby, V.; Tamaki, M.; Han, G. *Abstracts of Papers*; 219th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington DC, 2000; ORG 140. Two other isolated cases were reported in the context of total synthesis. See: Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110,* 1630 (TBSOTf/lutidine; K_2CO_3/MeOH); Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1991**, *47*, 5835 (TsOH/MeOH).
4. Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345.
5. All substrates were purchased commercially or prepared by literature procedures.
6. Spectra of new compounds. Compound **1d** (mixture of two rotamers): ^{1}H NMR (500 MHz, CD_3OD) δ 5.28–5.20 (1H, m), 4.26–4.18 (1H, m), 3.68–3.60 (1H, m), 3.58–3.50 (1H, m), 2.46–2.34 (1H, m), 2.21–2.12 (1H, m), 2.04 (3H, s), 1.48/1.47 (9H, s), 1.46/1/44 (9H, s); ES-MS: calculated for $C_{16}H_{27}NO_6$, 329; found: *m*/*e* 330 ($M+H^+$). Compound **2d**: ^{1}HNMR (500 MHz, CD_3OD) *δ* 5.30–5.24 (1H, m), 4.18–4.00 (1H, m), 3.43–3.36 (1H, m), 3.16–3.08 (1H, m), 2.36–2.28 (1H, m), 2.20–2.12 (1H, m), 2.04 (3H, s), 1.49 (9H, s); ES-MS: calculated for $C_{11}H_{19}NO_4$, 229; found: *m*/*e* 230 ($M+H^+$).
7. The final ratio did not change significantly after 1 week, suggesting conversion of Phe (**8**) to PheO*t*Bu (**2a**) is slow under these conditions, which may be attributed to poor solubility of **8**.
8. HCl in EtOAc is not commercially available.
9. The reaction has been performed on 50 mg to 30 g scale with reproducible results.