Notes

Selective Removal of an *N*-BOC Protecting Group in the Presence of a *tert*-Butyl Ester and Other Acid-Sensitive Groups

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Received December 13, 1993 (Revised Manuscript Received March 8, 1994)

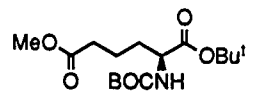
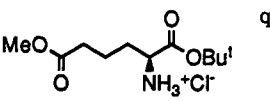
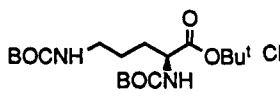
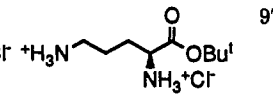
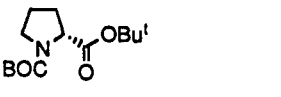
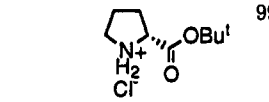
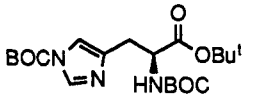
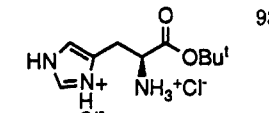
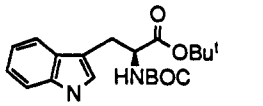
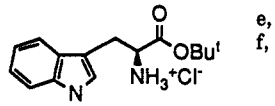
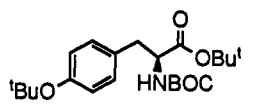
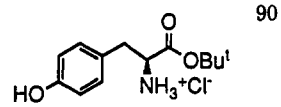
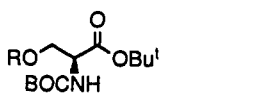
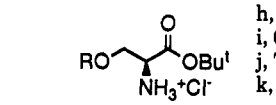
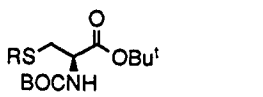
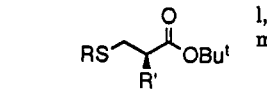
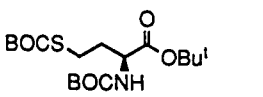
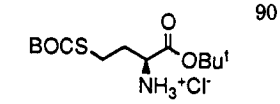
The selective removal of protecting groups is of critical importance in many synthetic sequences. The more selectively a protecting group can be removed, the more useful it becomes. We report here an efficient method for the selective removal of an *N*-BOC protecting group in the presence of a *tert*-butyl ester and several other common protecting groups.

During the course of earlier synthetic work,[1] it became necessary to remove an *N*-BOC while retaining a *tert*-butyl ester. Review of the literature revealed only one example of this transformation,[2] which we found to be slow and limited in scope. Examples of rapid *N*-BOC removal with dry HCl in ethyl acetate[3] are known, and we considered that this might give the desired selectivity. Treatment of *N*-BOC-aminoadipic acid *tert*-butyl ester derivative **1a** with a large excess of dry HCl in EtOAc for 3 h did indeed give the selective deprotection desired in 97% yield.[1] Further investigation established that as little as 500 mol % of a 1 M HCl in EtOAc solution would efficiently remove an *N*-BOC within 5 h at rt. In most cases, the product hydrochloride precipitated during the course of the reaction, possibly helping limit *tert*-butyl ester removal. The deprotection was carried out on a variety of *N*-BOC amino acid *tert*-butyl esters and derivatives, as shown in Table 1.

Each *tert*-butyl ester *N*-BOC amino acid derivative was treated under the same standard conditions, namely it was dissolved in a dry 1 M solution of HCl in EtOAc containing 500 mol % of HCl. The reaction mixture was stirred at rt until TLC indicated complete consumption of *N*-BOC *tert*-butyl ester 1. *S*- and *N*-BOC protected cysteine and homocysteine *tert*-butyl esters **1m** and **1n** were each treated with 1000 mol % of HCl to affect efficient cleavage of both the *S*- and *N*-BOC groups. In each case, amine hydrochloride product **2** was isolated either by filtration or after evaporation of the reaction mixture. Product hydrochlorides were usually analytically pure[4] and could be used without further purification.

Several results point out additional selectivity for this method. *tert*-Butyl ethers tyrosine **1g** and serine **1k** demonstrated the greater acid sensitivity of an aryl *tert*-butyl ether versus an alkyl *tert*-butyl ether. While the phenolic ether in tyrosine **1g** was completely cleaved within 2 h, the primary alcohol *tert*-butyl ether of serine **1k** survived almost quantitatively. The acid lability of the *S*-BOC group demonstrated with entry **1m** shows the BOC to be a versatile thiol protecting group, easily removed under basic or acidic conditions.[3] Loss of the *O*-trityl from serine entry **1j** was disappointing in light of the stability of the *tert*-butyl ether in **1k**. The *S*-trityl group on cysteine derivative **1l** did survive the deprotection conditions, contrasting differences between ether and thioether reactivity. We had hoped for some selectivity between the aryl and aliphatic *N*-BOC groups of histidine entry **1d**, but both were rapidly removed with only 500 mol % of HCl to give crystalline *tert*-butyl ester dihydrochloride

Table 1. Amino Acid *tert*-Butyl Ester Hydrochlorides 2 from *N*-BOC Substrates 1

entry	*N*-BOC *tert*-butyl esters 1	products 2	% yield
a			quant
b			97
c			99
d			93
e, f	 e, R = H f, R = CHO	 e, R = H f, R = CHO	e, 94 f, 92
g			90
h–k	 h, R = H j, R = trityl i, R = TBS k, R = Bu^t	 h, R = H j, R = H i, R = H k, R = Bu^t	h, 75 i, 60 j, 73 k, 92
l, m	 l, R = trityl m, R = BOC	 l, R = trityl, R' = NH_3^+ Cl^- m, R = H, R' = NH_3^+ Cl^-	l, 86 m, 97
n			90

(1) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.
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(4) Products were greater than 95% pure as judged by NMR spectroscopy, and typically gave correct C, H, and N analyses upon drying.

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product **2d**. Our investigation reveals that subtle differences in the stability of some common protecting groups toward acid cleavage can be used to synthetic advantage.

Experimental Section

Procedures for the Synthesis of *N*-BOC Amino Acid *tert*-Butyl Esters. In all examples, *N*-BOC protecting groups were introduced by the method of Ponnusamy.[5] All *tert*-butyl esters except for entries **1g** and **1k** were prepared using *N,N'*-diisopropyl-*O-tert*-butylisourea.[1] N^{i}-Formyltryptophan was obtained using the method of Ohno.[6] *N*-CBZ-serine and L-tyrosine were obtained by the method of Bergmann.[7] *O*-Tritylserine was prepared by the method of Zervas.[8] *S*-Tritylcysteine was synthesized according to Zervas.[8] L-Homocysteine was produced from L-methionine by the method of du Vigneaud.[9] NMR spectra were recorded at 300 MHz in $CDCl_3$ and *J* values are given in hertz.

***N,N'*-Bis-BOC-ornithine *tert*-butyl ester (1b)**: yield, 81% from ornithine; mp 80–82 °C; $[\alpha]^{25}_D$ +11.3° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 5.07 (br d, 1H, *J* = 7.8), 4.63 (m, 1H), 4.16 (t, 1H, *J* = 6.9), 3.14 (t, 2H, *J* = 6.0), 1.82–1.50 (m, 4H), 1.45 (s, 9H), 1.43 (s, 18H). Anal. Calcd for $C_{19}H_{36}N_2O_6$: C, 58.7; H, 9.3; N, 7.2. Found: C, 58.7; H, 9.7; N, 7.2.

***N*-BOC-proline *tert*-butyl ester (1c)**: yield, 81% from proline; $[\alpha]^{25}_D$ −50.5° (*c* 3.4, $CHCl_3$); ^{1}H NMR δ 4.12 (dd, 1H, *J* = 3.4, 8.9), 3.60–3.39 (m, 2H), 2.29–2.16 (m, 1H), 2.00–1.80 (m, 3H), 1.51 (s, 9H), 1.46 (s, 9H). Anal. Calcd for $C_{14}H_{26}NO_4$: C, 61.7; H, 9.6; N, 5.1. Found: C, 61.7; H, 9.6; N, 5.4.

N^{α},N^{τ}-Bis-BOC-histidine *tert*-butyl ester (1d): yield, 53% from histidine; mp 97–98 °C; $[\alpha]^{25}_D$ +17.8° (*c* 1.3, $CHCl_3$); IR 3880, 1750, 1710 cm^{-1}; NMR δ 7.98 (d, 1H, *J* = 0.8), 7.13 (s, 1H), 5.59 (br d, 1H, *J* = 8.4), 4.43 (dd, 1H, *J* = 2.9, 5.1), 3.00 (d, 2H, *J* = 5.2). Anal. Calcd for $C_{20}H_{34}N_3O_6$: C, 58.2; H, 8.3; N, 10.1. Found: C, 58.6; H, 8.2; N, 10.1.

(±)-N^{α}-BOC-tryptophan *tert*-butyl ester (1e): yield, 70% from tryptophan; mp 188–189 °C; ^{1}H NMR δ 7.49 (d, 1H, *J* = 7.8), 7.32 (d, 1H, *J* = 8.0), 7.07–7.01 (m, 2H), 6.99–6.96 (m, 1H), 4.08–4.05 (m, 1H), 3.10–3.03 (m, 1H), 2.98–2.92 (m, 1H), 1.32 (s, 18H). Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.6; H, 7.8, N, 7.8. Found: C, 66.9; H, 7.8; N, 7.9.

(±)-N^{i}-Formyl-N^{α}-BOC-tryptophan *tert*-butyl ester (1f): yield, 81% from (±)-N^{i}-formyltryptophan;[7] ^{1}H NMR δ 9.04 (s, 1H), 7.67–7.55 (m, 2H), 7.40–7.31 (m, 3H), 5.19–5.16 (m, 1H), 4.57–4.54 (m, 1H), 3.25–3.10 (m, 2H), 1.43 (s, 9H), 1.38 (s, 9H). Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.9; H, 7.3; N, 7.2. Found: C, 64.5; H, 7.4; N, 6.8.

***N*-BOC-*O-tert*-butyltyrosine *tert*-butyl ester (1g)**: yield, 42% from *N*-CBZ-tyrosine, by the method used for the synthesis of **1k**; $[\alpha]^{25}_D$ + 37.3° (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.10–6.89 (m, 4H), 5.01 (br d, 1H, *J* = 7.9), 4.43–4.40 (m, 1H), 2.99 (d, 2H, *J* = 6.1), 1.42 (s, 9H), 1.39 (s, 9H), 1.35 (s, 9H). Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.1; H, 9.0; N, 3.6. Found: C, 67.0; H, 9.0; N, 3.6.

***N*-BOC-serine *tert*-butyl ester (1h)**: yield, 56% from serine; mp 76–78 °C; $[\alpha]^{25}_D$ −20° (*c* 1.8, EtOH); ^{1}H NMR δ 5.40 (br s, 1H), 4.20 (br s, 1H), 3.84 (m, 2H), 2.55 (m, 1H), 1.45 (s, 9H), 1.40 (s, 9H). Anal. Calcd for $C_{12}H_{23}NO_5$: C, 55.2; H, 8.9; N, 5.6. Found: C, 55.2; H, 9.3; N, 5.6.

***N*-BOC-*O*-tert-butylserine *tert*-Butyl Ester (1k).** *N*-CBZ-serine (5.0 g, 25 mmol) was dissolved in 100 mL of dry dichloromethane. The solution was cooled to 0 °C and saturated with isobutylene, after which 1 mL of sulfuric acid was added and the reaction mixture was sealed at 0 °C and stirred at rt for 4 days. The reaction vessel was then carefully depressurized, and the mixture was washed with two 50-mL portions of saturated aqueous $NaHCO_3$ solution, dried, and evaporated. The residue of crude *N*-CBZ-*O-tert*-butylserine *tert*-butyl ester (6.73 g) was dissolved in dry methanol (50 mL), and to this solution were added BOC_2O (5 g, 23 mmol) and 0.6 g of 5% Pd/C. The mixture was stirred under an atmosphere of H_2 (balloon) overnight, after which it was filtered through Celite, evaporated, and chromatographed to give **1k** as a clear oil: 67% from L-serine; $[\alpha]^{25}_D$ +5.0° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 5.32 (br d, 1H, *J* = 8.8), 4.25 (dt, 1H, *J* = 8.7, 2.6), 3.76, (dd, 1H, *J* = 8.6, 2.7), 3.51 (dd, 1H, *J* = 8.6, 2.9), 1.58–1.18 (m, 27H). Anal. Calcd for $C_{16}H_{31}NO_5$: C, 60.5; H, 9.8; N, 4.4. Found: C, 60.3; H, 9.6; N, 4.1.

***N*-BOC-*S*-tritylcysteine *tert*-butyl ester (11)**: yield, 46% from cysteine; $[\alpha]^{25}_D$ +12.9° (*c* 2.6, $CHCl_3$); ^{1}H NMR δ 7.43–7.19 (m, 15H), 5.10 (d, 1H, *J* = 8.1), 4.22–4.19 (m, 1H), 2.52 (d, 1H, *J* = 4.5), 1.46 (s, 9H), 1.43 (s, 9H). Anal. Calcd for $C_{31}H_{37}NO_4S$: C, 71.6; H, 7.1; N, 2.7. Found: C, 72.0; H, 7.1; N, 2.8.

***N,S*-Bis-BOC-cysteine *tert*-butyl ester (1m)**: yield, 71% from cysteine; $[\alpha]^{25}_D$ +12.8° (*c* 1.7, $CHCl_3$); ^{1}H NMR δ 5.29 (d, 1H, *J* = 7.5), 4.45 (m, 1H), 3.20 (dd, 1H, *J* = 5.7, 14.5), 2.95 (dd, 1H, *J* = 3.9, 8.7), 1.50–1.41 (m, 27H). Anal. Calcd for $C_{17}H_{22}NO_6S$: C, 54.0; H, 8.2; N, 3.7. Found: C, 54.2; H, 8.1; N, 3.6.

***N,S*-Bis-BOC-homocysteine *tert*-butyl ester (1n)**: yield, 66% from homocysteine;[10] $[\alpha]^{25}_D$ +6.6° (*c* 0.9, $CDCl_3$); ^{1}H NMR δ 5.11 (br d, 1H, *J* = 4.0), 4.43–4.20 (m, 1H), 2.84–2.75 (m, 2H), 2.14–1.89 (m, 2H), 1.60–1.40 (m, 27H). Anal. Calcd for $C_{18}H_{33}NO_6S$: C, 55.1; H, 8.4; N, 3.5. Found: C, 55.4; H, 8.2; N, 3.6.

General Procedure for the Selective Removal of an *N*-Boc Group. The *N*-BOC amino acid ester (1 mmol) was dissolved in 500 mol % of a 1 M solution of HCl in ethyl acetate (prepared by bubbling dry HCl into dry ethyl acetate then diluting to 1 M with additional ethyl acetate). The reaction mixture was stirred at room temperature until the disappearance of starting material as determined by TLC (typically 3–5 h). At this time the precipitated product was isolated by filtration, or in the case of soluble products, the reaction mixture was evaporated in the cold and the residue crystallized by trituration with anhydrous ether, followed by filtration to isolate the product. In all cases, the crude isolated solid was greater than 95% pure, as determined by ^{1}H NMR in D_2O. All NMR spectra were recorded at 300 MHz in D_2O unless otherwise specified.

Ornithine *tert*-butyl ester dihydrochloride (2b): yield, 97% from **1b**; mp 195–196 °C; $[\alpha]^{25}_D$ +7.4° (*c* 1.4, H_2O); ^{1}H NMR δ 4.05 (t, 1H, *J* = 6.3), 3.05 (t, 2H, *J* = 7.5), 2.10–1.75 (m, 4H), 1.53 (s, 9H). Anal. Calcd for $C_9H_{22}N_2Cl_2O_2$: C, 41.3; H, 8.9; N, 10.7. Found: C, 41.1; H, 8.5; N, 10.7.

Proline *tert*-butyl ester hydrochloride (2c): yield, 99% from **1c**; mp 108–109 °C (lit.[10] mp 109–111 °C); $[\alpha]^{25}_D$ −31.6 (*c* 1.2, EtOH) [lit.[10] $[\alpha]$ −31.0° (*c* 2, EtOH)]; ^{1}H NMR δ 4.40–4.30 (m, 1H), 3.50–3.34 (m, 2H), 2.50–2.36 (m, 1H), 2.21–2.00 (m, 3H), 1.50 (s, 9H).

Histidine *tert*-butyl ester dihydrochloride (2d): yield, 93% from **1d**; mp 90 °C dec; $[\alpha]^{25}_D$ +19.1° (*c* 1.7, D_2O); ^{1}H NMR (DMSO) δ 8.51 (s, 1H), 7.20 (s, 1H), 4.13 (t, 1H, *J* = 6.2), 3.18 (d, 2H, *J* = 7.4), 1.18 (s, 9H). Anal. Calcd for $C_{15}H_{26}N_3ClO_4$: C, 42.3; H, 6.7; N, 14.7. Found: C, 42.6; H, 6.6; N, 14.2.

(±)-Tryptophan *tert*-butyl ester hydrochloride (2e): yield, 94% from **1e**; mp 212–213 °C dec [lit.[10] mp 214 °C dec]; ^{1}H NMR δ 7.51 (d, 1H, *J* = 8.0), 7.38 (d, 1H, *J* = 8.1), 7.15–7.11 (m, 2H), 7.04, (t, 1H, *J* = 7.4), 4.16 (t, 1H, *J* = 6.8), 3.28 (t, 2H, *J* = 7.0), 1.22 (s, 9H).

(±)-N^{i}-Formyltryptophan *tert*-butyl ester hydrochloride (2f): yield, 92% from **1f**; mp 164–165 °C dec; ^{1}H NMR δ 8.86 (br s, 1H), 7.48–7.45 (m, 2H), 7.31–7.26 (m, 3H), 4.20 (t, 1H, *J* = 7.1), 3.17 (d, 2H, *J* = 7.1), 1.17 (s, 9H). Anal. Calcd for $C_{16}H_{21}N_2O_3 \cdot H_2O$: C, 57.6; H, 6.6; N, 8.4. Found: C, 57.6; H, 6.3; N, 8.8.

Tyrosine *tert*-butyl ester hydrochloride (2g): yield, 90% from **1g**; mp >200 °C; $[\alpha]^{25}_D$ +4.5° (*c* 1.2, H_2O); ^{1}H NMR δ 7.01–6.73 (m, 4H), 4.02 (t, 1H, *J* = 6.7), 2.98 (d, 2H, *J* = 6.7), 1.24 (s, 9H). Anal. Calcd for $C_{13}H_{20}NClO_3$: C, 57.0; H, 7.3; N, 5.1. Found: C, 57.0; H, 7.4; N, 5.2.

Serine *tert*-butyl ester hydrochloride (2h): yield, 75% from **1h**; mp 111–113 °C; $[\alpha]^{25}_D$ −4.3° (*c* 1.8, EtOH); ^{1}H NMR δ 3.99–3.97 (m, 1H), 3.93 (dd, 1H, *J* = 12.4, 4.5), 3.84 (dd, 1H,

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J = 12.3, 3.4), 1.31 (s, 9H). Anal. Calcd for $C_7H_{16}NO_3 \cdot 0.5H_2O$: C, 40.7; H, 8.3; N, 6.8. Found: C, 40.9; H, 7.9; N, 7.2.

***O*-*tert*-Butylserine *tert*-butyl ester hydrochloride (2k)**: yield, 85% from **1k**; mp 149–150 °C; $[\alpha]^{25}_D$ −8.7° (*c* 1.4, H_2O); ^{1}H NMR δ 4.16 (dd, 1H, J = 3.4, 4.3), 3.90 (dd, 1H, J = 4.5, 10.4), 3.78 (dd, 1H, J = 3.4, 10.4), 1.55 (s, 9H), 1.20 (s, 9H). Anal. Calcd for $C_{11}H_{24}NClO_3$: C, 52.0; H, 9.5; N, 5.5. Found: C, 51.6; H, 9.2; N, 5.5.

***S*-Tritylcysteine *tert*-butyl ester hydrochloride (2l)**: yield, 86% from **1l**; characterized as the *N*-acetyl derivative. Compound **2l** (0.1 g, 0.2 mmol) was dissolved in 2 mL of pyridine. Acetic anhydride (0.5 mL) was added and the reaction mixture was stirred at rt for 2 h. The mixture was concentrated and the residue chromatographed to give ***N*-acetyl-*S*-tritylcysteine *tert*-butyl ester**: 0.079 g, 78%; mp 48–50 °C; $[\alpha]^{25}_D$ +6.0° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.46–7.20 (m, 15H), 5.93 (d, 1H, J = 7.7), 4.54 (m, 1H), 2.64 (dd, 1H, J = 5.4, 12.0), 2.49 (dd, 1H, J = 4.6, 12.0), 1.98 (s, 3H), 1.46 (s, 9H). Anal. Calcd for $C_{28}H_{31}NO_3S$: C, 72.8; H, 6.7; N, 3.0. Found: 72.6, 6.9, 3.1.

Cysteine *tert*-butyl ester hydrochloride (2m): yield, 94% from **1m**; mp 145–147 °C; $[\alpha]^{25}_D$ −17.2° (*c* 0.9, D_2O): ^{1}H NMR δ 4.30 (m, 1H), 3.20–3.00 (m, 2H), 1.52 (s, 9H). Anal. Calcd for $C_7H_{16}NClO_2S$: C, 39.3; H, 7.5; N, 6.5. Found: C, 39.4; H, 7.1; N, 6.3.

***S*-BOC-Homocysteine *tert*-butyl ester hydrochloride (2n)**: yield, 90% from **1n**; characterized as ***N*-acetyl-*S*-BOC-homocysteine *tert*-butyl ester** prepared by the procedure for **2l**: yield, 63% from **2n**; $[\alpha]^{25}_D$ +18.4° (*c* 0.7, $CDCl_3$); ^{1}H NMR δ 6.15 (d, 1H, J = 7.5), 4.51–4.44 (m, 1H), 2.15–2.04 (m, 1H), 1.98–1.85 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H). Anal. Calcd for $C_{15}H_{27}NO_5S$: C, 54.0; H, 8.1; N, 4.2. Found: C, 53.7; H, 7.9; N, 3.9.