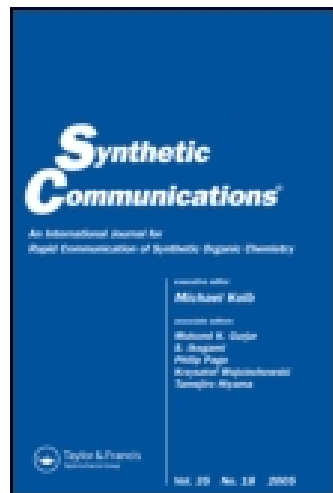


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A New Protocol for Selective Deprotection of N - tert -Butoxycarbonyl Protective Group (t -Boc) with Sn(OTf)₂

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A New Protocol for Selective Deprotection of *N*-*tert*-Butoxycarbonyl Protective Group (*t*-Boc) with Sn(OTf)₂[#]

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ABSTRACT

A simple and efficient method for the selective removal of *N*-Boc group by employing tin(II) trifluoromethanesulfonate [Sn(OTf)₂] in CH₂Cl₂ or solvent-free conditions was developed. The scope of this procedure is explored for the deprotection of a variety of amines, including amino acid derivatives.

Key Words: *N*-*tert*-butoxycarbonyl group; Deprotection; Tin(II)-trifluoromethane sulfonate; Solvent-free.

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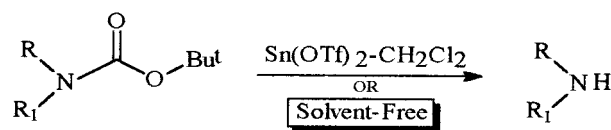
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The need of developing selective and mild methods for the protection and deprotection of functional groups with high selectivity, is still one of the most important manipulations in organic synthesis. The *tert*-butoxycarbonyl (*t*-Boc) group is extensively used as a convenient group for the protection of amine and amide NH groups due to its stability to basic and mildly acidic conditions and its ease of removal under specific conditions.^[1] Classically, removal of the *t*-Boc group can be accomplished by the action of acid trifluoroacetic acid (TFA) either neat or in combination with CH₂Cl₂.^[2] Deprotection with other mineral acids has been reported.^[3] In some instances Lewis acids have been used, e.g., BF₃·OEt₂.^[4] Less frequently, non-acidic conditions have been developed.^[5] In some cases, such as with electron rich substrates, thermolytic conditions can be used.^[6]

During the course of our investigations directed towards the total synthesis of natural products containing a proline-ring system,^[7] we had the opportunity to examine the selective removal of a *t*-Boc group. Toward this end, we were particularly interested in the nature of tin(II)trifluoromethanesulfonate Sn(OTf)₂. Literature reports have demonstrated that this reagent is widely used primarily for the generation of tin(II) enolates for stereoselective Aldol and Michael reactions.^[8] In this article, we describe our findings on the utility of this reagent for the selective deprotection of *N*-Boc derivatives under mild conditions (Sch. 1).

In order to study the generality of the present method we examined the deprotection of different substrates. The results are illustrated in Table 1. A variety of *N*-Boc derivatives were cleanly deprotected in CH₂Cl₂ at room temperature in 2 h. This method overcomes many of the disadvantages associated with Lewis acids developed so far, e.g., some of them are restricted to *sec*-*N*-Boc amines, require longer reaction times or reflux temperatures. The salient features of our method are that the reaction proceeds efficiently in high yield at room temperature within a short period of time, side products formation is minimized, and the work-up procedure is easy. Notably, esters (*tert*-butyl or methyl), ether linkages, base-sensitive groups present in the molecule, were found to be



Scheme 1.

Deprotection of (*t*-Boc) with Sn(OTf)₂

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Table 1. Removal of Boc group from different *N*-Boc derivatives.

Entry	Substrate 1	Product 2 ^a	Yield (%) ^b
1			90
			88
2			92
3			91
4			87
5			92
6			89
7			95

^aAll products gave satisfactory analytical and ¹H NMR spectroscopic data.^[9]^bYields of pure isolated products.

resistant under the conditions employed. *N*-Boc derivatives bearing “ α ” stereogenic centers afford the corresponding amines with full retention of configuration (specific rotation measurement was performed after reconversion to the starting *N*-Boc derivative).^[9] Finally, removal of *t*-Boc in the presence of *N*-Cbz was achieved with a high degree of selectivity.

To reduce the employment of ecologically suspected solvents, we have also carried out the similar cleavage of **1a** under solvent-free con-



ditions. For example, neutral Al_2O_3 used as solid support at room temperature for 4 h gave the corresponding amine **2a** in almost quantitative yield (88%). Among various mineral supports examined, such as alumina, clay, silica, etc., alumina was found to give the best results.

PROCEDURE (I)

To a solution of *N*-Boc derivative (**1a**) (0.458 g, 2.0 mmol) in anhydrous CH_2Cl_2 (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer under N_2 atmosphere, was added $\text{Sn}(\text{OTf})_2$ (832 mg, 2.0 mmol) in portions at 0°C . The suspension was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC; eluent: EtOAc:hexane, 9:1 v/v), it was neutralized with aqueous NaHCO_3 solution and the product was extracted with EtOAc (2×15 mL). The organic phase was separated, dried (Na_2SO_4), the mixture filtered and the solvent was removed in vacuo to afford the crude product which was purified by column chromatography (ethyl acetate/hexane, 9:1 v/v) to afford **2a** (0.116 g), in 90% yield.

PROCEDURE (II)

Solvent-free conditions: neutral alumina (2.0 g) is added to substrate (**1a**) (0.458 g, 2.0 mmol), and $\text{Sn}(\text{OTf})_2$ (832 mg, 2.0 mmol) that is dissolved in a minimum amount of dichloromethane (2–3 mL). After evaporation of the solvent,^[10] the dry powder is mixed thoroughly using a vortex mixer and the reaction mixture is kept at room temperature for 4 h. The product is extracted into ethyl acetate (2×5 mL). The combined organic phases were washed with aqueous NaHCO_3 , brine, dried (Na_2SO_4) and the solvent was removed in vacuo to afford the crude product **2a** (0.113 g) in 88% yield.

In summary, this method offers considerable advantages for use in organic synthesis in view of its simplicity, excellent yield, short reaction period, and mild conditions involved.

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9. **Selected analytical data:** compounds **1a**, **1b**, **2a**, **2f** isolated as amine hydrochloride salts. **1a**: $[\alpha]_D = -45.0^\circ$ (c 0.53, CHCl₃), ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.85–2.05 (m, 4H), 3.38–3.60 (m, 2H), 3.75 (s, 3H), 4.16–4.36 (m, 1H). **1b**: $[\alpha]_D = -49.5^\circ$ (c 3.4, CHCl₃), ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 1.50 (s, 9H), 1.81–1.98 (m, 3H), 2.15–2.30 (m, 2H), 3.38–3.58 (m, 2H), 4.10 (dd, 1H, *J* = 3.4, 8.9). Anal. calcd. for C₁₄H₂₆NO₄: C, 61.7; H, 9.6; N, 5.1. Found: C, 61.5; H, 9.6; N, 5.2. **2a**: m.p. 68–70°C (lit.^[11] m.p. 69–71°C); $[\alpha]_D = -31.0$ (c 0.5, H₂O), lit.^[11] $[\alpha]_D = -33 \pm 2^\circ$ (c 0.5, H₂O). **2b**: m.p. 108–109°C (lit.^[13] m.p. 109–111°C); $[\alpha]_D = -30.0$ (c 1.2, EtOH), lit.^[12] $[\alpha]_D = -31.0^\circ$ (c 2.0, EtOH), Anal. calcd. for C₉H₁₇NO: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.0; H, 10.6; N, 8.7. **2c**: m.p. 58–59°C (lit.^[11] m.p. 57–60°C); **1d**: $[\alpha]_D = +13.5$ (c 1.0, CHCl₃), ¹H NMR (CDCl₃) δ 1.45 (s, 9H), 3.54–3.70 (m, 2H), 3.95–4.01 (m, 2H), 4.72–4.88 (bs, 1H), 5.12–5.31 (m, 2H), 5.75–5.94 (m, 1H), 7.22–7.35 (m, 5H). **2d**: $[\alpha]_D = +24.5$ (c 1.0, CHCl₃). Anal. calcd. for C₁₁H₁₅NO;



C, 74.5; H, 8.5; N, 7.9. Found: C, 75.0; H, 8.2; N, 7.5. **1f**: $[\alpha]_D = +9.0^\circ$ (c 1.0, CHCl_3), $^1\text{H NMR}$ (CDCl_3): δ 1.44 (s, 9H), 1.50–1.81 (m, 6H), 3.11–3.27 (m, 2H), 3.75 (s, 3H), 4.18–4.31 (m, 1H), 4.78 (bs, 1H, exchangeable with D_2O), 5.05 (bs, 1H), 5.08 (s, 2H), 7.22 (s, 5H). **2f**: m.p. 116–118°C (lit. m.p. 117–118°C); Anal. calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_4$: C, 61.2; H, 7.5; N, 9.5. Found: C, 61.5; H, 7.8; N, 9.2. $[\alpha]_D = +14.5^\circ$ (c 1.0, H_2O), lit. $[\alpha]_D = +15.5^\circ$ (c 2.0, H_2O), Coggins, J.; Demayo, R.; Benoiton, N.L. *Can. J. Chem.* **1970**, *48*, 385. **1g**: $^1\text{H NMR}$ (CDCl_3): δ 1.65 (s, 9H) 6.53 (d, 1H), 7.12–7.33 (m, 2H), 7.46–7.48–57 (m, 2H), 8.10 (d, 1H). **2g**: m.p. 53–55°C (lit.^[11] m.p. 52–54°C).

10. To dissolve the starting substrate, CH_2Cl_2 can be replaced with any solvent, e.g., THF and CH_3CN . During the reaction, carbon dioxide gas evolution was observed [positive $\text{Ba}(\text{OH})_2$ test].
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