ONE-POT CONVERSION OF N-BENZYLOXYCARBONYL GROUP INTO N-TERT-BUTOXYCARBONYL GROUP

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Summary: An efficient one-pot two stage transformation of the N-Z group into the N-t-Boc group was carried out under the neutral conditions.

N-Benzyloxycarbonyl (Z) and N-*tert*-butoxycarbonyl (*t*-Boc) groups are the most common amino protecting groups used for the syntheses of amino acids, aminosugars, alkaloids, and peptides.¹ Since these groups exhibit contrasting chemical stabilities against acids and bases, choice of either Z or *t*-Boc amino protective group plays a key role in the planning of a synthetic strategy. If these groups can be exchanged under neutral conditions, it would serve an useful tool from the synthetic point of view. In the previous paper, we reported a conversion of the *t*-Boc group into the Z group via a silylcarbamate, but the converse of this transformation was unsuccessful.² As an answer to this problem, we wish to present two practical methods in this paper.

Usually, hydrogenation conditions catalyzed by Pd-C are used for the removal of N-Z group. We have found that the presence of di-*tert*-butyl dicarbonate (Boc₂O) in the above reaction gives the corresponding N-*t*-Boc compound.³ Moreover, the same transformation is possible by the use of triethylsilane (Et₃SiH)^{2b} and Boc₂O in the presence of a catalytic Pd(OAc)₂ (EtOH as the solvent).⁴

RNHCO₂CH₂Ph (Z) RNHCO₂-*t*-Bu (*t*-Boc)

The typical experimental procedures of these methods is as follows. (i) H₂/Pd-C system (method A): A solution of N-Z-valine methyl ester (100 mg, 0.36 mmol), Boc₂O (106 µl, 0.46 mmol) and 5% Pd-C (20 mg) under a hydrogen atmosphere (1 atm) in 5 ml of MeOH was stirred at room temperature for 5 h. The reaction mixture was filtered and evaporated under a reduced pressure to give an oily residue. Chromatography on SiO₂ (elution with Et₂O/hexane=1/4) gave the N-*t*-Boc valine methyl ester (82.5 mg) in 95% yield. (ii) Et₃SiH/Pd(OAc)₂ system (method B): To a dark suspension of Et₃SiH (304 µl, 1.90 mmol), Boc₂O (261 µl, 1.14 mmol), Pd(OAc)₂ (22 mg, 0.1 mmol), and triethylamine (42 µl, 0.3 mmol) in 5 ml of EtOH at room temperature was added dropwisely a solution of N-Z-proline methyl ester (249mg, 0.95 mmol) in 3 ml of EtOH under nitrogen. After stirring for 15 h, the reaction mixture was filtered and concentrated in vacuo. The residue was chromatographed on SiO₂ (elution with Et₂O/hexane =1/4) to give N-*t*-Boc proline



^aReaction conditions for method A and B: A; H₂/5% Pd-C, Boc₂O, MeOH, room temperature: B; 2 equiv Et₃SiH/cat. Pd(OAc)₂, cat. Et₃N, Boc₂O, EtOH, room temperature.^bAll products were fully characterized by the spectroscopic methods. ^cIsolated yield. ^dThe reaction using method B proceeded very slowly and resulted in the recovery of the starting material. ^eHori, K.; Ohfune, Y. to be published. ¹Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041.

methyl ester (204 mg, 94% yield). As summarized in Table I, the N-Z group was replaced with the N-*t*-Boc group in high yields. These reactions proceed chemoselectively in the presence of other acid sensitive groups (entries 6 and 7). It should be noted that the benzyl ether group in entry 8 was stable under the method B and the *t*-Boc compound was obtained exclusively.⁶ It is proposed that the conversion using method B proceeds through the following 3 step sequence of reactions; (1) formation of triethylsilyl carbamate, (2) liberation of amine by ethanolysis, and (3) reaction of the resulting amine with Boc₂O. However, the detailed mechanism is not clear at this time. Thus, practical methods for the interconversion of these important amino protecting groups have been demonstrated.⁷

References:

- 1. Greene, T. W. Protective Groups in Organic Chemistry; John Wiley & Sons: New York, 1981, p 232.
- (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. (b) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, *27*, 3753.
- One-pot conversion of the azide group into the N-t-Boc group using hydrogenation conditions in the presence of Boc₂O was recently studied: S. Saito, to be published. We thank Prof. S. Saito, Okayama University, for informing us of their results prior to publication.
- 4. The use of other solvents, such as MeOH, resulted in a decomposition of the reagent. Decrease in reaction rate and yields was observed by the use of other protic solvent.
- 5. We thank Dr. Kimura and Mr. Nishio, Peptide Institute Inc., for providing a sample in entry 5.
- 6. The presence of a sulfur group in the substrate is noted as limitation of these reactions. For example, treatment of N-Z-methionine methyl ester using method B gave a trace amount of its corresponding N-t-Boc compound.
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