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Ceric ammonium nitrate (CAN) mediated esterification of *N*-Boc amino acids allows either retention or removal of the *N*-Boc group

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Abstract—Reaction of *N*-Boc amino acids with ceric ammonium nitrate in an alcohol as the solvent at room temperature resulted in the esterification of *N*-Boc amino acids with Boc group retention. When the reaction was conducted at reflux temperature, esterification was accompanied with simultaneous removal of the Boc group. Both reactions gave the desired products in good yields.
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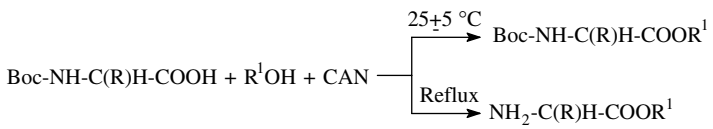
Esters of *N*-*tert*-butoxycarbonyl (Boc) amino acids are widely used in peptide chemistry and in preparing several chiral auxiliaries such as β-amino alcohols, oxazolidinones,[1] and α-amino aldehydes.[2] *N*-Boc amino esters can be prepared either from amino esters by reacting with di-*tert*-butyl dicarbonate (diBoc), or from *N*-Boc amino acids by esterification. Both methods are unsatisfactory. In the first method, the reaction with diBoc requires alkaline conditions in which the ester group is not stable, although in some cases weaker bases can be used but these require longer reaction times, and the yields are moderate. In the second method, commonly used esterification protocols involving reaction with an alcohol in the presence of acid catalysts such as, HCl, H_2SO_4, thionyl chloride, PTSA, etc. cannot be used since the Boc group is unstable in acidic conditions.[3]

Presently, *N*-Boc amino esters are often prepared from *N*-Boc amino acids using expensive dehydrating agents such as carbodiimides[4,5] or unsafe reagents such as alkyl halides,[6,7] diazomethane,[8,9] or chloroformates.[10] Thus there is a need for simple alternative methods for the esterification of *N*-Boc amino acids. This paper describes one such simple and inexpensive method.

Recently, Pan et al. reported that phenylacetic acids and oleic acid react with alcohols in the presence of ceric ammonium nitrate (CAN) to give esters.[11] Earlier, Hwu et al. had shown that CAN removes the Boc group from amines, alcohols, and thiols.[12] These reports prompted us to study the effect of CAN on alcoholic solutions of *N*-Boc amino acids expecting to obtain esters with simultaneous removal of the Boc group. However, contrary to the expectation, we obtained *N*-Boc amino esters in good yield and no removal of the Boc group was observed. Although the reaction solution was acidic (pH = 2) throughout, the Boc group was retained. Further, and interestingly, when the reaction was conducted at higher temperature, esterification was accompanied by the removal of the Boc group (Scheme 1). Thus, CAN mediated reaction of *N*-Boc amino acids with alcohols offers a simple and inexpensive alternative method for preparing the corresponding esters with either retention or removal of the Boc group.



Scheme 1.

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The procedure is illustrated by a typical example. CAN (10.6 mmol) was added to a solution of *N*-Boc alanine **1a**, (10.6 mmol) in dry methanol (20 mL) and the mixture stirred at 25 ± 5 °C until the starting material disappeared (TLC) (24 h). EtOAc (50 mL) and water (20 mL) were added and the mixture stirred. The organic layer was separated, washed with water (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromato- graphy to give *N*-Boc alanine methyl ester **2a**, in 83% yield as a colorless oil (Table 1). To remove the *N*-Boc group, the methanolic solution containing CAN (10.6 mmol) and **1a** (10.6 mmol) was refluxed for 24 h. The solvent was removed in vacuo and the residue was purified by column chromatography to give alanine methyl ester **3a** (Table 2) (82%) as a colorless oil.

When the initial solution was made neutral, neither esterification nor Boc removal took place. At temperatures below 25 ± 5 °C, esterification was incomplete even after 48 h. At 40 °C and above, esterification was accompanied with partial removal of the Boc group. When the CAN concentration was varied, it was found that with 0.5 equivalents, esterification was incomplete and with 1.5 equivalents, there was no significant increase in the rate or yield of esterification but removal of the Boc group was observed even at room temperature.

The generality of the method was examined by studying various *N*-Boc amino acids (Tables 1 and 2). In most cases, except ornithine (Tables 1 and 2, entry 10), treatment of methanolic solutions of *N*-Boc amino acids with CAN at 25 ± 5 °C and at reflux temperature, gave the corresponding *N*-Boc amino esters and N-deprotected amino esters, respectively, in high yields. Aspartic acid (Tables 1 and 2, entry 6), being a dicarboxylic acid, gave a diester. The products **2** and **3** were analyzed for their stereochemical integrity and no racemization was found to have occurred during the reaction. A similar conclusion was drawn by Hwu et al. in their studies on the removal of the *N*-Boc group from amino acids using CAN.[12]

Table 1. Esterification of *N*-Boc amino acids by CAN in methanol at room temperature

Entry	Starting material **1**	Product **2**[a]	Yield (%)[b]
1	Boc-Ala-OH **1a**	Boc-Ala-OMe **2a**	83
2	Boc-Gly-OH **1b**	Boc-Gly-OMe **2b**	78
3	Boc-Leu-OH **1c**	Boc-Leu-OMe **2c**	38
4	Boc-Phe-OH **1d**	Boc-Phe-OMe **2d**	76
5	Boc-Tyr-OH **1e**	Boc-Tyr-OMe **2e**	62
6	Boc-Asp-OH **1f**	Boc-Asp(OMe)-OMe **2f**	80
7	Boc-Asn-OH **1g**	Boc-Asn-OMe **2g**	77
8	Boc-Trp-OH **1h**	Boc-Trp-OMe **2h**	51
9	Boc-Pro-OH **1i**	Boc-Pro-OMe **2i**	77
10	Boc-Orn-OH **1j**	Boc-Orn-OMe **2j**	38
11	Boc-isonipecotic acid **1k**	Boc-isonipecotic-OMe **2k**	80

[a] The HPLC and ^{1}H NMR data of the isolated products were identical to those of authentic samples.
[b] Isolated yield.

Table 2. Esterification and Boc deprotection of *N*-Boc amino acids by CAN in methanol at reflux temperature

Entry	Starting material (**1**)	Product (**3**)[a]	Yield (%)[b]
1	Boc-Ala-OH **1a**	H-Ala-OMe **3a**	82
2	Boc-Gly-OH **1b**	H-Gly-OMe **3b**	80
3	Boc-Leu-OH **1c**	H-Leu-OMe **3c**	47
4	Boc-Phe-OH **1d**	H-Phe-OMe **3d**	52
5	Boc-Tyr-OH **1e**	H-Tyr-OMe **3e**	57
6	Boc-Asp-OH **1f**	H-Asp(OMe)-OMe **3f**	82
7	Boc-Asn-OH **1g**	H-Asn-OMe **3g**	78
8	Boc-Trp-OH **1h**	H-Trp-OMe **3h**	47
9	Boc-Pro-OH **1i**	H-Pro-OMe **3i**	73
10	Boc-Orn-OH **1j**	H-Orn-OMe **3j**	42
11	Boc-isonipecotic acid **1k**	Isonipecotic-OMe **3k**	74

[a] The HPLC and ^{1}H NMR data of the isolated products were identical to those of the authentic samples.
[b] Isolated yield.

Table 3. Esterification of Boc-Ala-OH with alcohols using CAN at room temperature

Entry	Alcohol	Product **4**[a]	Yield (%)[b]
1	*n*-PrOH	Boc-Ala-O-*n*-Pr **4a**	83
2	*i*-PrOH	Boc-AlaO-*i*-Pr **4b**	73
3	*t*-BuOH	Boc-Ala-O-*t*-Bu **4c**	No reaction
4	BzOH	Boc-Ala-OBz **4d**	65

[a] The HPLC and ^{1}H NMR data of the isolated products were identical to those of authentic samples.
[b] Isolated yield.

Esterification was also studied using other alcohols (Table 3). *n*-Propanol (entry 1) reacted with **1a** in the presence of CAN to afford an *n*-propyl ester **4a** in 83% yield. Isopropanol (entry 2), afforded a lower yield of ester **4b** (72%), while with *tert*-butanol (entry 3) there was no esterification even after 48 h. Benzyl alcohol (entry 4) afforded only a 65% yield of benzyl ester **4d**. These results show that the CAN mediated esterification is influenced by steric factors.

In conclusion, the use of CAN affords a simple and useful method for the conversion of *N*-Boc amino acids to *N*-Boc amino esters, which are difficult to prepare. Further, the method is also useful for converting *N*-Boc amino acids to their esters with simultaneous removal of the Boc group.

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