

Condensation of α -Amino Acid with Amine in the Absence of a Coupling Agent

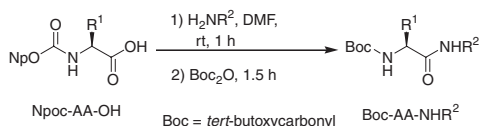
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Treatment of *N*-(4-nitrophenoxy-carbonyl)amino acid with an equimolar amount of amine in the absence of a coupling agent gave the corresponding α -amino acid amide in high yield.

4-Nitrophenyl *N*-substituted carbamate is known as a precursor of isocyanate¹ and is utilized in the synthesis of multi-substituted urea.² On the other hand, isocyanate reacts with some nucleophiles such as carboxamide³ and carboxylic acid⁴ to afford *N*-acylurea or carboxamide, respectively. From the above reports, we assumed that treatment of *N*-(4-nitrophenoxy-carbonyl)amino acid (Npoc-AA-OH) with amine generated 2-isocyanatocarboxylic acid, which, in turn, gave the corresponding *N*-carboxy anhydride (NCA) by its intramolecular cyclization. Since reaction of NCA with amine is reported,⁵ the corresponding α -amino acid amide will be obtained as a final product. In this communication, we wish to report that treatment of Npoc-AA-OH with amine gave the corresponding *tert*-butoxycarbonyl(Boc)-AA-NHR² in high to excellent yield after *tert*-butoxycarbonylation by the use of Boc₂O (Scheme 1). From the above reaction system, Npoc-AA-OH can be regarded as an acid component bearing a coupling agent. Generally, a certain coupling agent is used such as some carbodiimides,⁶ uroniums,⁷ and phosphoniums⁸ in amide formation. On the contrary, the condensation of Npoc-AA-OH with amine proceeds without a coupling agent, and this reaction system will be new methodology for amide formation of α -amino acids.

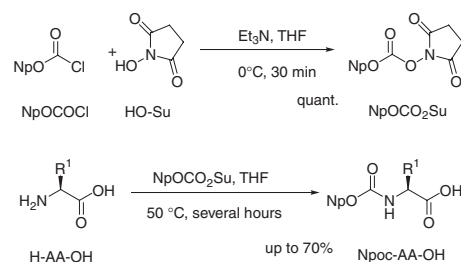


Scheme 1. Amide formation using Npoc-AA-OH.

Because Npoc-AA-OH was obtained only in slight yield when 4-nitrophenyl chloroformate, which was commonly purchased, was used as 4-nitrophenoxy-carbonyl agent under Shotten-Baumann's conditions, a new method for preparation of the starting materials was examined. After several attempts, it was found that *N*-(4-nitrophenoxy-carbonyloxy)succinimide (NpO-CO₂Su) was effective to increase the yields of Npoc-AA-OH (Scheme 2).

Most of Npoc-AA-OHs were obtained as crystals and could be purified by reprecipitation from ethyl acetate with hexane except for Npoc-Ile-OH, which was obtained as a viscous oil and was purified by chromatography on silica gel (CHCl₃:MeOH = 9:1). All Npoc-AA-OHs are stable at room temperature for three months and in a freezer at least for one year.

When Npoc-Phe-OH was treated with phenethylamine in some solvents at room temperature, all of the reaction mixture



Scheme 2. Preparation of Npoc-AA-OH.

Table 1. Solvent effect on amino acid amide formation using Npoc-Phe-OH

Run	Solvent	Time/h	Yield/%
1	DMF	1	85
2	THF	20	84
3	MeOH	24	63
4	CH ₂ Cl ₂	20	Not Detected

changed from colorless into yellow except that dichloromethane was used as solvent. It was found that Boc-Phe-NH(CH₂)₂Ph was obtained in high yield after *tert*-butoxycarbonylation using Boc₂O and the best result was given when DMF was used as solvent (Table 1, Run 1).

As shown in Table 2, several Npoc-AA-OHs were convert-

Table 2. Amino acid amide formation using Npoc-AA-OH

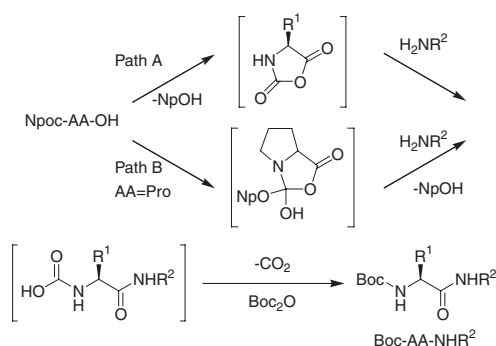
Run	AA	R ³	Yield/%
1	Leu	(CH ₂) ₂ Ph	98
2	Val	(CH ₂) ₂ Ph	88
3	Ile	(CH ₂) ₂ Ph	80
4	Ala	(CH ₂) ₂ Ph	67 (79) ^a
5	Gly	(CH ₂) ₂ Ph	46 (58) ^b
6	Asn(Trt) ^c	(CH ₂) ₂ Ph	78 (91) ^a
7	Ser(OBu')	(CH ₂) ₂ Ph	87
8	Trp	(CH ₂) ₂ Ph	97
9	Met	(CH ₂) ₂ Ph	88
10	Glu(OCH ₂ Ph)	(CH ₂) ₂ Ph	81
11	Pro	(CH ₂) ₂ Ph	56 (76)
12 ^d	Phe	CH ₂ CO ₂ Et	89
13 ^d	Trp	CH ₂ CO ₂ Et	88
14 ^d	Glu(OCH ₂ Ph)	CH ₂ CO ₂ Et	72

^aThe number in parentheses indicates the yield of Boc-AA-NH(CH₂)₂Ph when the reaction was performed in the presence of 1.0 equiv. of DIEA. ^bReaction time; 3 h. ^cTrt = trityl. ^dThe reaction was performed in the presence of 1.0 equiv. of triethylamine.

ed to the α -amino acid amide on treating with phenethylamine.⁹ In most cases, Boc-AA-NH(CH₂)₂Ph was obtained in high yield. However, the yields of Boc-AA-NH(CH₂)₂Ph were low in the reactions using some Npoc-AA-OHs (Runs 4–6). In these cases, an addition of diisopropylethylamine (DIEA) was effective to improve the yield of Boc-AA-NH(CH₂)₂Ph. Bender and Horner reported that 4-nitrophenyl *N,N*-disubstituted carbamate is hydrolyzed about 10⁶ times as slow as 4-nitrophenyl *N*-substituted carbamate¹ and hence it was suspected that no reaction using Npoc-Pro-OH proceeded. Boc-Pro-NH-(CH₂)₂Ph was, nevertheless, obtained in 56% yield and its yield was increased by addition of DIEA (Run 11). Reactions using H-Gly-OEt hydrogen chloride as the amino component in the presence of an equimolar amount of triethylamine were examined. In these cases, the corresponding dipeptides were also given in high yields (Runs 12–14). In the present reaction system, it might form by-product such as urea derivative (R²NHCO-AA-OH) and/or dipeptide (Boc-AA-AA-NHR²). However, since these by-products were not isolated, little amount of these by-products would be produced.

In the amide formation of α -amino acid, it is most important that the α -amino acid amide is obtained without racemization, so that a racemization check was made by HPLC. Peaks corresponding to H-Phe-NH(CH₂)₂Ph prepared from (*S*)-Npoc-Phe-OH were identified by comparison with *rac*-H-Phe-NH(CH₂)₂Ph standard run under identical conditions. Since (*S*)-H-Phe-NH(CH₂)₂Ph was detected in over 98% yield, the present reaction proceeded without racemization.¹⁰

The proposed reaction mechanism is outlined in Scheme 3. As pointed out before, 2-isocyanatocarboxylic acid, which is generated by Npoc-AA-OH on treatment with amine, cyclizes to give the corresponding NCA (Path A). Amine, in turn, attacks NCA to give Boc-AA-NHR² after evolution of carbondioxide and *tert*-butoxycarbonylation. However, the reaction using Npoc-AA-OH derived from imino acid, namely, proline, also proceeded, so that we should also assume an addition–elimination process (Path B).



Scheme 3. Proposed reaction pathways.

In conclusion, we have developed a condensation reaction of Npoc-AA-OH with amine in the absence of a coupling agent to form the amino acid amide without racemization.

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- General procedure for preparation of Boc-amino acid amide: To a DMF solution (2.0 mL) of Npoc-amino acid (0.2 mmol) was added 0.2 mmol of phenethylamine at room temperature. After stirring for 1 h, 0.22 mmol of Boc₂O was added to the resulted yellow solution for 1.5 h. DMF was removed under reduced pressure, organic materials were extracted with EtOAc. The organic layer was washed with 5% K₂CO₃ solution and brine, and the extract was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (CHCl₃:MeOH = 95:5 or 9:1) to give Boc-AA-NH(CH₂)₂Ph.
- Conditions; column, Sumichiral OA-4700 (Sumika Chemical Analysis Service, Ltd.) 1.0 mL/min of 98 to 90% hexane (EtOH containing 0.1% TFA) in 45 min; detection, 254 nm, retention time, (*S*)-form, 21.5 min; (*R*)-form, 22.7 min.