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

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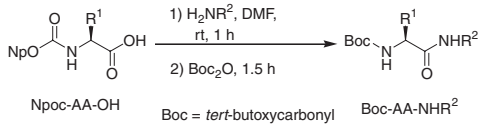
Treatment of *N*-(4-nitrophenoxycarbonyl)amino acid with an equimolar amount of amine in the absence of a coupling agent gave the corresponding α-amino acid amide in high yield.

4-Nitrophenyl *N*-substituted carbamate is known as a precursor of isocyanate[1] and is utilized in the synthesis of multisubstituted urea.[2] On the other hand, isocyanate reacts with some nucleophiles such as carboxamide[3] and carboxylic acid[4] to afford *N*-acylurea or carboxamide, respectively. From the above reports, we assumed that treatment of *N*-(4-nitrophenoxycarbonyl)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-NHR^2 in high to excellent yield after *tert*-butoxycarbonylation by the use of Boc_2O (Scheme 1). From the above reaction system, Npoc-AA-OH can be regarded as an acid component bearing a coupling agent. Generally, a certain coulping agent is used such as some carbodiimides,[6] uroniums,[7] and phosphoniums[8] 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.

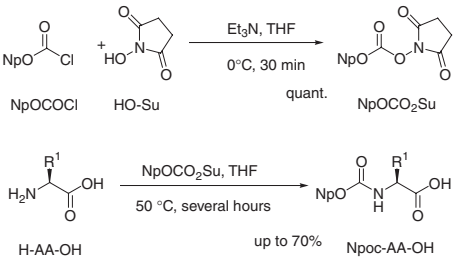


Scheme 1. Amide formation using Npoc-AA-OH.

Because Npoc-AA-OH was obtained only in slight yield when 4-nitrophenyl chloroformate, which was commonly purchased, was used as 4-nitrophenoxycarbonyl 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-nitrophenoxycarbonyloxy)succinimide (NpO-CO_2Su) 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 ($CHCl_3$: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 changed from colorless into yellow except that dichloromethane was used as solvent. It was found that Boc-Phe-NH(CH_2)$_2$Ph was obtained in high yield after *tert*-butoxycarbonylation using Boc_2O and the best result was given when DMF was used as solvent (Table 1, Run 1).



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_2Cl_2	20	Not Detected

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

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

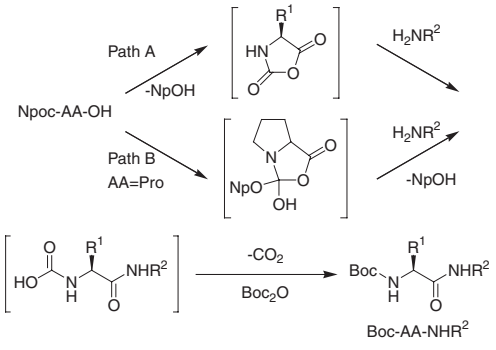
Run	AA	R^3	Yield/%
1	Leu	$(CH_2)_2Ph$	98
2	Val	$(CH_2)_2Ph$	88
3	Ile	$(CH_2)_2Ph$	80
4	Ala	$(CH_2)_2Ph$	67 (79)[a]
5	Gly	$(CH_2)_2Ph$	46 (58[b])[a]
6	Asn(Trt)[c]	$(CH_2)_2Ph$	78 (91)[a]
7	Ser(OBu^t)	$(CH_2)_2Ph$	87
8	Trp	$(CH_2)_2Ph$	97
9	Met	$(CH_2)_2Ph$	88
10	Glu(OCH_2Ph)	$(CH_2)_2Ph$	81
11	Pro	$(CH_2)_2Ph$	56 (76)
12[d]	Phe	CH_2CO_2Et	89
13[d]	Trp	CH_2CO_2Et	88
14[d]	Glu(OCH_2Ph)	CH_2CO_2Et	72

[a]The number in parentheses indicates the yield of Boc-AA-NH(CH_2)$_2$Ph when the reaction was performed in the presence of 1.0 equimolar of DIEA. [b]Reaction time; 3 h. [c]Trt = trityl. [d]The reaction was performed in the presence of 1.0 equimolar amount of triethylamine.

ed to the α-amino acid amide on treating with phenethylamine.[9] In most cases, Boc-AA-NH$(CH_2)_2$Ph was obtained in high yield. However, the yields of Boc-AA-NH$(CH_2)_2$Ph 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$(CH_2)_2$Ph. Bender and Hormer reported that 4-nitrophenyl *N*,*N*-disubstituted carbamate is hydrolyzed about 10^6 times as slow as 4-nitrophenyl *N*-substituted carbamate[1] and hence it was suspected that no reaction using Npoc-Pro-OH procceded. Boc-Pro-NH-$(CH_2)_2$Ph 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 (R^2NHCO-AA-OH) and/or dipeptide (Boc-AA-AA-NHR^2). 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$(CH_2)_2$Ph prepared from (*S*)-Npoc-Phe-OH were identified by comparison with *rac*-H-Phe-NH$(CH_2)_2$Ph standard run under identical conditions. Since (*S*)-H-Phe-NH$(CH_2)_2$Ph 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-NHR^2 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.

References and Notes

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9 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 Boc_2O 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% K_2CO_3 solution and brine, and the extract was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC ($CHCl_3$:MeOH = 95:5 or 9:1) to give Boc-AA-NH$(CH_2)_2$Ph.

10 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.

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