

Convenient green preparation of dipeptides and primary amides via carbonic carboxylic anhydrides and asymmetric synthesis of memantine analogues as a candidate of anti-Alzheimer's medicine

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【Introduction】

The green chemistry meaning "the environment-conscious chemistry" is an attractive attention topic for the scientific technology because environmental pollution has become serious global issues. Since the Nobel Prize in Chemistry was won in the areas of the catalytic enantioselective reactions that were largely seen as a green chemistry in both 2001 (Knowles, Noyori, Sharpless) and 2005 (Chauvin, Grubbs, Schrock), they have made remarkable progress. In particular, development of organocatalysts and their application to asymmetric synthesis are considerable efforts. The intramolecular aldol reaction catalyzed by proline as an organocatalyst was firstly reported by Hajos,¹ and its intermolecular type was discovered by List.² Recently, effective approaches using peptide-derived organocatalyst for asymmetric reactions were also developed by many groups. α -Amino acids and their derivatives are commercially available chiral compounds and play an important role in the fields of chemical and biological researches.³ On the other hand, it is difficult to prepare the catalysts prepared from α -amino acid derivatives because of the problems such as protection of functional group, racemization or epimerization, side reaction, and low solubility in organic solvent.⁴ Development of catalytic synthetic method for chiral compounds have been strongly desired in terms of keeping green.

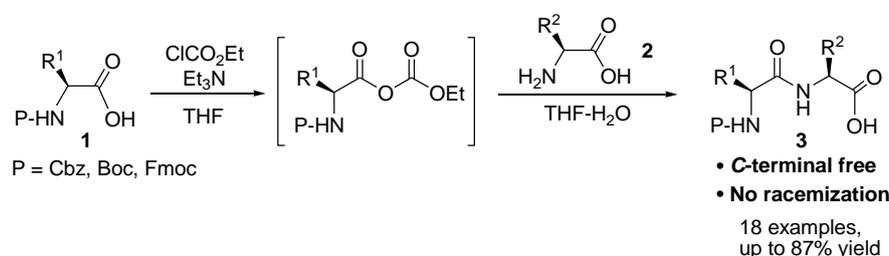
Under the background, we are aiming at development of green organic reactions and synthetic methods of the bioactive substances containing a chiral cyclopropane skeleton. Herein, the following two contents were presented; (I) convenient green preparation of dipeptides and primary amides via carbonic carboxylic anhydrides without racemization;⁵ (II) synthesis of memantine analogues containing a sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine.⁶

(I) Convenient green preparation of dipeptides and primary amides via carbonic carboxylic anhydrides without racemization

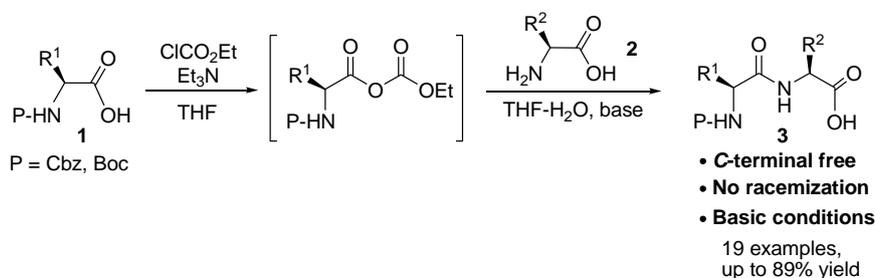
The amide group is one of the most important functional groups in organic chemistry. It is widely found in various compounds such as proteins, bioactive substances, drugs, and agrochemicals. So, development of convenient amidation has been a challenging subject in organic chemistry. So far, the convenient syntheses of various biological substances containing a chiral cyclopropane skeleton have been achieved in my group.⁷ In the process on the synthesis of cyclopropane amino acids which are α -amino acid derivatives containing a cyclopropane ring, preparation of primary amides as a key intermediate was succeeded by the reaction of the mixed carbonic carboxylic anhydride of carboxylic acids with aqueous ammonia solution. Generally, amides are prepared by reactions of activated carboxylic acids, such as acyl halides, acyl imidazole, mixed anhydrides, and esters with amines or by reductions of acyl azides and hydrazides.⁴ In particular, the mixed carbonic carboxylic

anhydrides prepared from the corresponding carboxylic acids are relatively stable and efficiently reactive with nucleophiles.⁸ I focused on advantageous property of the mixed carbonic carboxylic anhydride which is chemically more reactive with amines than alcohols, stable in water at low temperature, and prepared by simple procedure. Therefore, it would be expected that the mixed carbonic carboxylic anhydrides of carboxylic acids are easily condensed with the desired hydrophilic parts by the minimal use of protecting group.

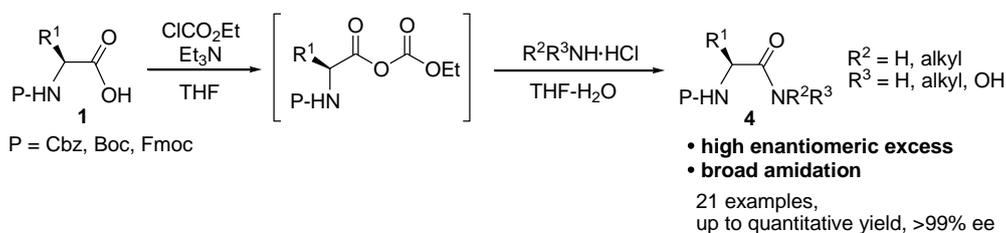
Dipeptides were obtained in high yields from the reaction of *N*-protected α -amino acids **1** with unprotected α -amino acids **2** via the corresponding mixed carbonic carboxylic anhydrides using ethyl chloroformate and triethylamine under neutral conditions (Scheme 1).^{5a} Unprotected α -amino acids **2** containing a hydrophilic side chain such as aliphatic alcohol, aromatic alcohol, thiol, carboxylic acid, and amide are also suitable as a nucleophile and were reacted with mixed carbonic carboxylic anhydrides under the basic conditions to afford the corresponding dipeptide in 66-96% yields (Scheme 2).^{5b} No racemization was observed by ¹H NMR analysis in my methods. Next, primary amidation of *N*-protected α -amino acids **1** with NH₄Cl in the presence of ethyl chloroformate and triethylamine gave the corresponding primary amides **4** in 74% to quantitative yields with 97->99% ee (Scheme 3).^{5c}



Scheme 1. Preparation of dipeptides without protection of C-terminal under neutral conditions



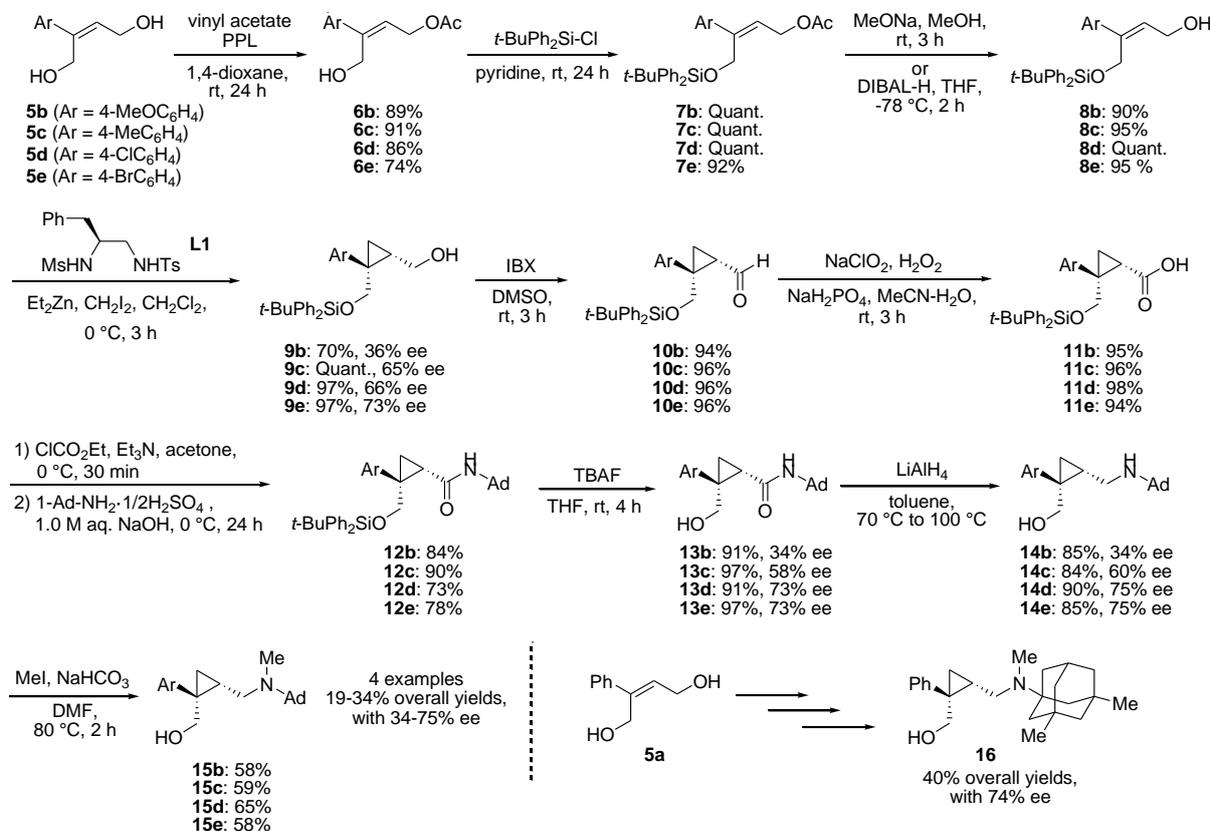
Scheme 2. Synthesis of dipeptides with unprotected α -amino acids **2** under basic conditions



Scheme 3. Primary amidation of *N*-protected α -amino acids **1** via the mixed carbonic carboxylic anhydrides

(II) Synthesis of memantine analogues containing a sigma-1 receptor activity as a candidate of anti-Alzheimer's medicine

The increase in degenerative brain diseases including Alzheimer's disease (AD) has become a social issue in the global aging and pathological elucidation about AD and urgent development of medicines for AD are demanded. Sigma receptor is established as the two subtypes sigma-1 and sigma-2 and has recently attracted attention as a new action site of therapeutic medicine for AD. It was reported that the sigma-1 receptor regulates protein folding/degradation, endoplasmic reticulum (ER)/oxidative stress, and cell survival through the molecular chaperone activity. The sigma-1 receptor is significantly influential in the homeostasis of tissue, which is incapable of repairing. Therefore, it is anticipated that the agonists activated by the sigma-1 receptor become the therapeutic agents of diseases caused by cell damage. Recently, it was reported by Marrazzo that (+)-(2*R*,3*S*)-4-(*N*-adamant-1-yl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol ((+)-AMMP) is a high affinity probe for the sigma receptors and that the methyl group of (+)-AMMP is important for the affinity on the sigma-1 binding site.⁹ We have just achieved convenient asymmetric synthesis of (+)-AMMP from (*Z*)-2-phenylbut-2-ene-1,4-diol **5a** via the following reactions¹⁰ such as (i) the regioselective acetylation using porcine pancreas lipase (PPL),¹¹ (ii) the catalytic enantioselective Simmons-Smith reaction in the presence of our developed chiral ligand which was prepared cheaply and easily from *L*-phenylalanine in five steps,¹² and (iii) the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.⁵ It is suggested that modification of (+)-AMMP on the benzene ring, and introduction of memantine (3,5-dimethyl-1-adamantan amine) instead of 1-adamantanamine moiety would provide the more efficient binding affinity to the sigma-1 receptor.



Scheme 4. Convenient asymmetric synthesis of memantine analogues via the three key reactions

I have achieved convenient enantioselective synthesis of (+)-AMMP analogues **15b-15e** containing a chiral cyclopropane skeleton in 19-34% overall yields from the corresponding 2-arylbut-2-ene-1,4-diols **5b-5e** with moderate to excellent ees via three key reactions. This synthetic route is more efficient and less expensive. Additionally, I have also succeeded in synthesizing memantine analogue **16** containing a chiral cyclopropane skeleton with 74% ee in 40% overall yield (Scheme 4).⁶

【Conclusion】

Convenient green preparation of dipeptides and primary amides via the corresponding mixed carbonic carboxylic anhydride has been succeeded.⁵ Furthermore, asymmetric syntheses of memantine analogues as a candidate of anti-Alzheimer's medicine have also achieved via the three key reactions.⁶

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