Green synthesis of various medicine analogues containing α-amino acids or dipeptides without racemization or epimerization under the extremely mild conditions

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【Introduction】

Medicines are metabolized and these chemical structures are changed after being taken in bodies. The formation of reactive intermediates such as electrophiles and free radicals often induces various toxicities against the bodies. So much research about the reactive metabolites has been done so far. It is important to exclude the by-produced reactive metabolites from pharmaceuticals in the manufacturing stages because they cause a variety of toxicities.[1] Furthermore, various efforts in development of new medicines include reducing the amount of chemical waste, saving energy, and minimizing the amount of used and discharged hazardous substances. Green chemistry is defined as "Technology that designs a process for producing chemical products while minimizing the use and generation of hazardous or environmentally polluting substances".[2] The United States of America awards the "Green Chemistry Presidential Award" for companies and scientists who have successfully contributed to green chemistry every year. For example, *Eastman* won the Green Chemistry Award for development of the enzyme-based esterification in 2009.[3] The methods includes milder reaction conditions and less amount of solvents and by-products than conventional synthetic ones.

Although amidation in pharmaceutical synthesis often involves the reaction of active acyl chlorides with amines, acyl chlorides are usually unstable in water and it is necessary to avoid moisture during the reaction. The use of *N*, *N*-dicyclohexylcarbodiimide (DCC) as an alternative condensing agent is not cheap and introduces difficulties with respect to workup. We have recently reported convenient syntheses of dipeptides and primary amides via mixed carbonic carboxylic anhydrides.[4] Herein, I describe eco-friendly, economical, and convenient synthesis of various medicine analogues containing α-amino acids or dipeptides without racemization or epimerization using amidation via corresponding mixed carbonic carboxylic anhydrides under the extremely mild conditions. The following two contents are presented: (I) Synthesis of acetaminophen analogues containing α-amino acids and fatty acids for inhibiting hepatotoxicity,[5] (II) Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions.[6]

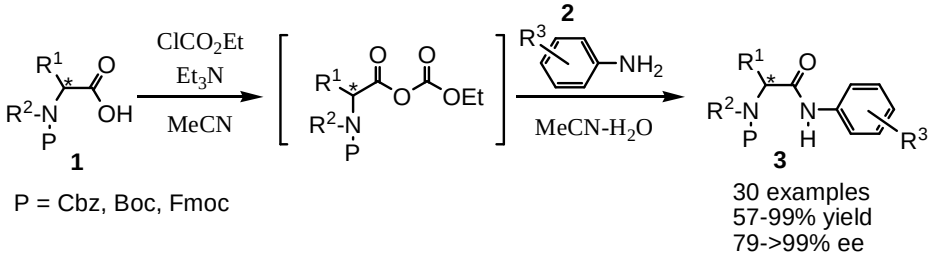
(I) Synthesis of acetaminophen analogues containing α-amino acids and fatty acids for inhibiting hepatotoxicity[5]

Acetaminophen is a popular antipyretic analgesic medicine that has a weaker anti-inflammatory properties and lower incidence of side effects than nonsteroidal anti-inflammatory drugs (NSAIDs). However, it is well known that acetaminophen causes severe hepatotoxicity due to the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) upon overdose. NAPQI accumulates, binds to intracellular macromolecules, and causes hepatocellular necrosis.[7] So, I replaced the acetyl group of acetaminophen with bulkier α- amino acids in order to construct the corresponding NAPQI analogues which would be less susceptible to nucleophilic attack by intracellular macromolecules.

Furthermore, Zygmunt et al. have recently reported that the physiological action of acetaminophen is very similar to

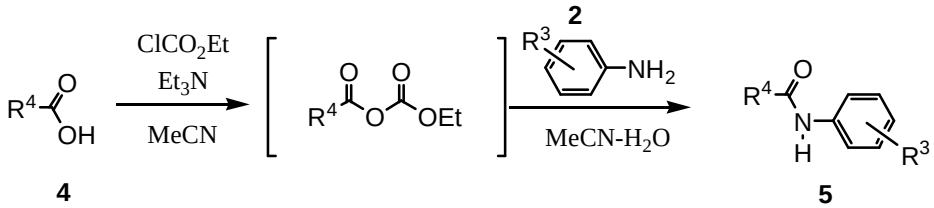
that of *N*-(4-hydroxyphenyl)arachidonamide (AM404).[8] AM404 has a strong agonistic action in $TRPV_1$, which is an ion channel, and affects the cannabinoid CB_1 receptor. These receptors are also involved with pain and thermoregulatory systems and have received considerable attention as analgesic and anti-inflammatory therapeutic targets in recent years.[9] Therefore, acetaminophen analogues of various fatty acids are quite interesting as AM404 analogues.

I initially examined the condensation of *N*-protected α-amino acids **1** with various anilines **2** for synthesis of the corresponding acetaminophen analogues **3**. The reaction of *N*-protected α-amino acid **1** with 4-aminophenol, 4-ethoxyaniline, and 4-ethoxyaniline proceeded via the corresponding mixed carbonic carboxylic anhydride in the presence of $ClCO_2Et$ and Et_3N under the neutral conditions to afford **3** in 57-99% yields with 79->99% ee (Scheme 1).



Scheme 1. Synthesis of acetaminophen analogues **3** containing α-amino acids **1**

Next, I synthesized various AM404 analogues **5** from various fatty acids **3** and anilines **2**. The reactions of **3** with 4-ethoxyaniline and 4-aminophenol via the mixed carbonic acid carboxylic anhydrides gave the corresponding AM404 analogues **5** in 76-99% yields (Scheme 2). The stability at 0℃ and 22℃ after 240 h by analysed by 2D TLC and ^1H NMR spectra, and no change was observed. Although unsaturated fatty acids are usually sensitive in air and at rt, it was found that the synthesized AM404 analogues **5** were relatively stable.

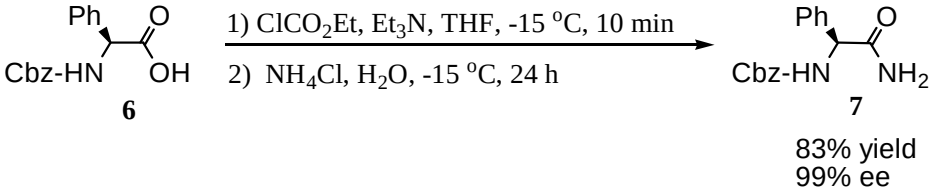


Scheme 2. Synthesis of AM404 analogues **5** containing fatty acids **4**

(II) Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions[6]

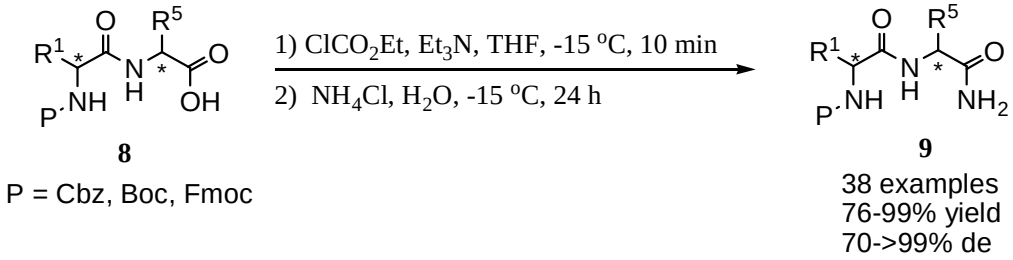
Recently, peptide medicines have attracted much attention due to the realization of oral administration, targeting of biomolecules in cells, and low side effects compared with antibody medicines. Although amidation is most important in peptide synthesis, it makes problems such as utilization of a large amount of expensive condensation agent and generation of a large amount of waste.[10] In addition, linkage of amino acids in high yields would be a significant research because of easy racemization. Cysteine, histidine, and phenylglycine are more susceptible to racemize than the other amino acids. In particular, synthesis of peptides containing phenylglycine remains a challenging task because it has been reported that phenylglycine easily causes racemization about 60 times compared with alanine.[11]

I optimized the reaction conditions for the primary amidation of Cbz-L-Phg-OH **6** without racemization. The preparation of Cbz-L-Phg-NH_2 **7** was accomplished in 83% yield with 99% ee when the reaction times for the activation and the amidation at -15 ^oC were 10 min and 24 h, respectively (Scheme 3).



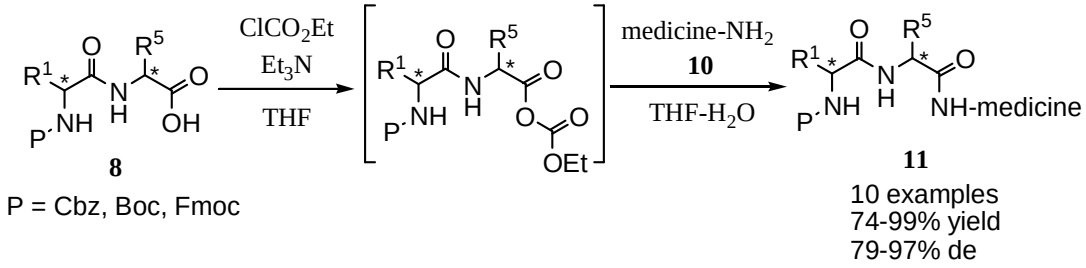
Scheme 3. Primary amidation of Cbz-L-Phg-OH **6**

Next, I tried to synthesize various primary amides **9** from the corresponding dipeptides **8** without epimerization. The amidation of the dipeptides **8** combined with various α-amino acids proceeded to obtain **9** in 76-99% yields with 70->99% de (Scheme 4).



Scheme 4. Preparation of primary amides **9** derived from various dipeptides **8**

Subsequently, various dipeptides-containing medicine analogues **11** were obtained by condensation of the dipeptides **8** with the amino group-substituted medicines **10** such as 4-aminophenol, dopamine, amantazine, (±)-rimantadine, and memantine in 74-99% yields with 79-97% de (Scheme 5).



Scheme 5. Synthesis of various medicine analogues **11** containing dipeptides **8**

【Conclusion】

I have synthesized acetaminophen analogues **3** in 57-99% yields and AM404 analogues **5** in 76-99% yields by using the convenient and economical procedure. These analogues would be useful *p*-aminophenol donors and are expected to act as novel antipyretic analgesics like acetaminophen. Various amides were obtained in high to excellent yields with excellent enantioselectivities after purification by silica gel column chromatography, by using $ClCO_2Et$ and Et_3N under the mild conditions. In particular, both of the activating agents ($ClCO_2Et$ and Et_3N) are relatively inexpensive and the by-products obtained by our efficient method are triethylamine hydrochloride, carbon dioxide, and the corresponding

alcohols, which are relatively environmentally benign. Although amidations via activated carboxylic acids are usually carried out under anhydrous conditions, it is quite unique that the reaction of the activated carbonic carboxylic anhydride smoothly proceeded in aqueous organic solvent to afford the corresponding amides. My synthetic method is also characterized by no racemization and low levels of by-product formation.

In addition, various dipeptides **9** were prepared in 76-99% yields with 70->99% de. Then, the various dipeptides-containing medicine analogues **11** were synthesized in 74-99% yields with 79-97% de. I have also succeeded green and economical synthesis of various dipeptides **9** and dipeptides-containing medicine analogues **11** in aqueous THF at -15 ℃ via the mixed carbonic carboxylic anhydrides by the activation of the corresponding carboxylic acids **8**. It is noted that the results were obtained by precisely controlling the reaction temperature during the activation of the corresponding carboxylic acids **8**. Furthermore, the dipeptides-containing medicine analogues **11** are expected to be useful donors of peptide medicines.

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