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Title	Development of Novel Carboxylation Reactions Using Gaseous Carbon Dioxide : α -Amino Acid Synthesis via α -Amino Metal Species [an abstract of dissertation and a summary of dissertation review]
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Degree Grantor	北海道大学
Degree Name	博士(薬科学)
Dissertation Number	甲第11420号
Issue Date	2014-03-25
Doc URL	https://hdl.handle.net/2115/55808
Rights(URL)	https://creativecommons.org/licenses/by-nc-sa/2.1/jp/
Type	doctoral thesis
File Information	Chen_Jianyang_abstract.pdf, 論文内容の要旨



学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称 博士（薬科学） 氏 名 陳 建 揚

学 位 論 文 題 名

Development of Novel Carboxylation Reactions Using Gaseous Carbon Dioxide: α -Amino Acid Synthesis via α -Amino Metal Species

（二酸化炭素ガスを用いた新規カルボキシル化反応の開発： α -アミノ金属種を経由する α -アミノ酸の化学合成）

Carbon dioxide (CO_2) is an ideal carbon feedstock for organic synthesis due to its abundance, low cost, low toxicity, and ease of handling. The reaction of carbon nucleophiles with CO_2 is serving as one of the most efficient processes to afford carboxylic acids and their derivatives. Among them, the synthesis of α -amino acids through CO_2 incorporation is especially attractive since α -amino acids have been found broad application in both bio- and organic chemistry. The most direct approach to α -amino acids is α -carboxylation of amine derivatives (e.g., alkyl amines and α -amino stannanes) with CO_2 . However, these methods employed organolithium reagents for the generation of α -amino carbanions, followed by the carboxylation with CO_2 to produce α -amino acids. Applicability of these methods is relatively narrow because strongly basic organolithium reagents are incompatible with many functional groups. Therefore, the generation of α -amino carbanions under mild conditions is highly desirable. For this purpose, I developed the following three carboxylation reactions to synthesize α -amino acids from imine equivalents, which can be easily synthesized from the corresponding aldehydes.

1. One-pot synthesis of α -amino acids using TMS-SnBu₃

Since an imine and CO_2 both behave as electrophiles, umpolung on imino carbon is crucial to synthesize α -amino acids from imine equivalents via α -carboxylation with CO_2 . Therefore, I considered the use of α -stannyl anion, which is known to react with imine so that the resulting α -amino stannane would act as a nucleophile towards CO_2 after Sn-metal exchange. Thus, a one-pot synthesis of α -amino acids from *N*-Boc- α -amido sulfones (*N*-Boc-imine precursors) was designed. After considerable experimentation, the one-pot carboxylation from α -amino sulfones via imines and α -amino stannanes was achieved. In the presence of CsF (5.0 eq) and TMS-SnBu₃ (1.1 eq), various types of α -aryl- α -amino sulfones underwent carboxylation smoothly in DMF solvent at 100 °C under 10 atm of CO_2 pressure affording the corresponding α -amino acid derivatives in up to 88% yield. This one-pot process consisted of three sequential steps (imine formation, stannylation, and carboxylation). For each step, CsF works as a different role, such as a base, silane activator, and stannane activator. This transformation should be a complementary method to Strecker amino acid synthesis because readily available and relatively nontoxic CO_2 can be employed as a C1 unit instead of toxic HCN. However, several limitations still existed: (1) potentially toxic TMS-SnBu₃ was utilized, (2) only α -aryl- α -amino sulfones were applicable, (3) harsh reaction conditions (100 °C and 10 atm of CO_2 pressure) were necessary to induce efficient carboxylation. These limitations promoted me to carry out further

exploration of this one-pot reaction.

2. One-pot synthesis of α -amino acids using PhMe₂Si-Bpin

In order to overcome the above-mentioned limitations, I investigated other less toxic and more reactive bismetal reagents without toxic organotin moieties. As a result, PhMe₂Si-Bpin was found to mediate the one-pot reaction as well. By using it, further condition screening revealed the best conditions: in the presence of CsF (5.0 eq), PhMe₂Si-Bpin (1.1 eq), and *p*-TsOH H₂O (20 mol%), various α -amino sulfones were carboxylated to produce the corresponding α -amino acid derivatives in DMF solvent at room temperature under 5 atm of CO₂ pressure. Compared to the previous system using TMS-SnBu₃, toxic organotin reagents could be avoided, and the yields of α -amino acids were generally higher. In addition, substrate scope was expanded to tolerate both α -aryl and α -alkenyl- α -amino sulfones, which is a big advantage of replacement with PhMe₂Si-Bpin. Moreover, milder reaction conditions (room temperature and 5 atm of CO₂ pressure) were achieved. Addition of a catalytic amount of protic additive plays a crucial role in silylation step. α -Isobutyl- α -amino acid ester obtained by this one-pot procedure was successfully transformed into several useful α -amino acids within two steps. Furthermore, without purification by silica gel column chromatography, the products were obtained as (*R*)-1-phenethylamine salt forms, which would then provide optically active phenyl glycine after recrystallizations.

3. Synthesis of α -amino acids using manganese(0)

Although one-pot reactions using TMS-SnBu₃ and PhMe₂Si-Bpin have been developed; however, there are still some problems to solve, for example: (1) bismetal reagents are relatively expensive and difficult to prepare, (2) high CO₂ pressure, such as 10 atm and 5 atm, is required. Therefore, more efficient carboxylation using commercially available and inexpensive reagents under ambient CO₂ atmosphere is highly desirable.

A new strategy was envisioned to synthesize α -amino acids through CO₂ incorporation using *N*-acyl-*N*,*O*-acetals, which are easily prepared from the corresponding aldehydes. Various parameters of this new carboxylation reaction were examined. The optimal reaction conditions were eventually decided: by using BF₃ Et₂O (5.0 eq), Mn powder (3.0 eq), and LiCl (4.0 eq), the carboxylation of various aryl substrates having both electron-donating and electron-withdrawing groups proceeded smoothly in THF solvent at 0 °C under 1 atm of CO₂ atmosphere, affording the desired α -amino acid derivatives in up to 88% yield. The used reagents (Mn powder, BF₃ OEt₂, and LiCl) are commercially available and inexpensive, which provides high potential for practical use for the synthesis of α -amino acids. LiCl is considered to promote the generation of the organomanganese intermediate and enhance its nucleophilicity toward CO₂ by forming RMnCl LiCl complex. Compared to the precedent examples of reductive carboxylation, 1 atm of CO₂ atmosphere is sufficient. After the removal of protecting groups on the nitrogen atom, free α -amino acids were successfully obtained.

In summary, three carboxylation reactions have been successfully developed to synthesize α -amino acids via α -amino metal species. The one-pot reactions were made possible by using a combination of CsF and a bismetal reagent, such as TMS-SnBu₃ or PhMe₂Si-Bpin. Furthermore, the Mn-mediated reductive carboxylation proceeded efficiently even under 1 atm of CO₂ pressure.