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An Efficient Synthesis of α -Acyloxyketone by Cu(acac)₂-Catalyzed Insertion Reaction of α -Diazoketone to Carboxylic Acid.

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Abstract

An efficient insertion reaction of α -diazoketone to various carboxylic acids was achieved by using Cu(acac)₂ as a catalyst. Treatment of the diazo compound with a carboxylic acid (1.2 equiv) in the presence of Cu(acac)₂ (0.1 equiv) at room temperature afforded the corresponding ketoester in good yield. Various kinds of functional groups were tolerated under the reaction conditions. © 1998 Elsevier Science Ltd. All rights reserved.

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 α -Acyloxyketone is a plausible precursor for the construction of the α -hydroxyketone moiety of biologically important natural products such as cortisone steroids and ketoses.[1-3] Recently, we have exemplified the utility of the α -[(1-amino)acyloxy]ketones in the synthesis of optically active α,α -disubstituted α -amino acid via an intramolecular asymmetric Strecker synthesis.[4-7] In this case, the starting ketones were prepared by esterification of an α -ketol with an α -amino acid or mono-esterification of a *vic*-diol followed by oxidation. In the present circumstances, these methods incurred problems which are represented by resistance of the hydroxy group of the α -ketol to the esterification with an α -amino acid and by the



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difficulty in the mono-esterification to the requisite position of the vic-diol.[8] To explore an alternative method for the synthesis of α -[(1-amino)acyloxy)]ketones, we envisaged the application of an insertion reaction of α -diazoketone to carboxylic acid. However, the previous papers were only focused on the synthesis of α -acetyloxy- or phenacyloxyketone. [2, 9-12] Moreover, its general application has not been extensively studied. We report herein a Cu(acac),-catalyzed insertion reaction which is quite effective for the synthesis of not only α -[(1-amino)-acyloxy)]ketones but also various kinds of acyloxyketones.

The insertion reaction without any metal-catalyst usually required a large excess of the carboxylic acid, in some cases used as the solvent, and high temperature.[3] It is expected that the use of a metal-catalyst would enable milder the reaction conditions. However, the feasibility has been tested only in a few cases.[13] These facts led us to survey a variety of catalysts using the reaction of **1a** and acetic acid as a model system (Scheme 1). Among the catalysts, we found that Cu(acac), CuCl, and CuSO₄ effectively catalyzed the insertion at room temperature to afford 2 in 87, 77 and 64% yields, respectively.[14] Thus, the Cu(acac), catalyst was found to be superior to other catalysts with respect to both the yields and the reaction conditions.



On the basis of the model study, we applied Cu(acac)-catalyzed insertion reactions to various combinations of diazoketones and carboxylic acids (Table 1). Most of the diazoketones reacted with a nearly stoichiometric amount of a carboxylic acid at room temperature to give the corresponding acyloxyketones in good yield, except the diazoketones **1b**,g with a five-membered ring which required warming to 70 °C (entries 3,8, and 12).[15] It is noted that the insertions always proceeded in a highly chemoselective manner at the diazo group of the diazoketones; other functional groups, such as ester, phosphate, ketone, β -keto ester, C-C double bond, and ketal groups were tolerated (entries 1-5).

Entry	Diazo Compound	Carboxylic Acid	Product	Yield ^a (%)
1	1a	(EtO) ₂ R OH		78
2	1a	о о вио ОН		74

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continued from Table 1



^{*a*} The reaction was carried out using carboxylic acid(1.2 equiv) and Cu(acac)₂ (0.1 equiv) in toluene at room temperature for 1 h. ^{*b*} The reaction was carried out at 70°C for 1 h. ^{*c*} A 1:1 mixture of diastereomers was obtained. ^{*d*} An α , β -unsaturated enone was obtained as a by-product in 43% yield.

The usefulness of the present method is highlighted by the successful syntheses of acyclic and cyclic α -[(1-amino)acyloxy]ketones (entries 6-12). For example, Boc-L-Phe was smoothly inserted to **1a** or **1d** in the presence of Cu(acac)₂ to give the corresponding esters **8** and **11**, respectively (entries 6 and 9). Benzyloxycarbonyl (Z) group was also compatible as represented in the synthesis of **12** (entry 10).

In conclusion, we have demonstrated the synthesis of various types of α -acyloxyketones by the Cu-catalyzed insertion reaction. The present method would be highly advantageous for the synthesis of α -acyloxyketones in view of its simple operation, mild reaction conditions, and easy availability of the starting diazoketones.[11,16,17]

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- [8] For example, the hydroxyketones corresponding to 1c,e,f did not form α -acyloxyketones with Boc-amino acids using EDCI in the presence of DMAP.
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- [13] A few examples using CuCl₂, Cu(OAc)₂ and copper powder were reported. See references 1, 9, and 10.
- [14] The yields using other catalysts are as follows; Rh₂(OAc)₄ (44%, room temperature), Cu(OAc)₂ (74%, 70 °C), Cu(salen) (65%. 70 °C), CuI (64%, 70 °C), Ni(OAc)₂ (76%, 70 °C), none (0%, 70 °C).
- [15] 2-Cyclopentenone was a by-product due to a 1,2-hyride shift. Its yield was increased when the reaction was carried out at room temperature.
- [16] Typical procedure for the Cu(acac)₂-catalyzed insertion reaction. To a mixture of Boc-L-phenylalanine (318 mg. 1.2 mmol) and Cu(acac)₂ (26.2 mg, 0.1 mmol) in toluene (3 mL) was added, dropwisely, 2-diazocyclohexanone 1a (124 mg. 1 mmol) in toluene (3 mL) at room temperature. The mixture was stirred at the same temperature for 1 h and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give 8 (303 mg, 84%) as a colorless oil.
- [17] By the present method, 8 was prepared on 20 g scales.