

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

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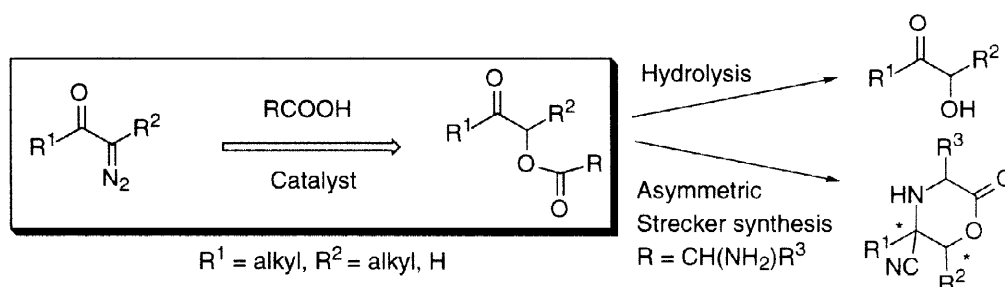
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Abstract

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.

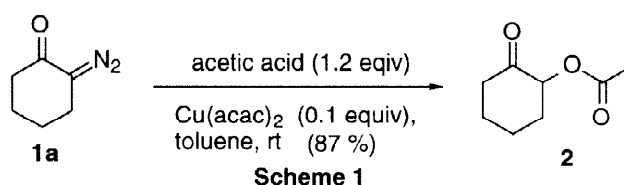
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α -Acyloxyketone is a plausible precursor for the construction of the α -hydroxyketone moiety of biologically important natural products such as cortisone steroids and ketoses.[1-3] Recently, we have exemplified the utility of the α -[(1-amino)acyloxy]ketones 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



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 $\text{Cu}(\text{acac})_2$ -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 $\text{Cu}(\text{acac})_2$, CuCl , and CuSO_4 effectively catalyzed the insertion at room temperature to afford **2** in 87, 77 and 64% yields, respectively.[14] Thus, the $\text{Cu}(\text{acac})_2$ catalyst was found to be superior to other catalysts with respect to both the yields and the reaction conditions.

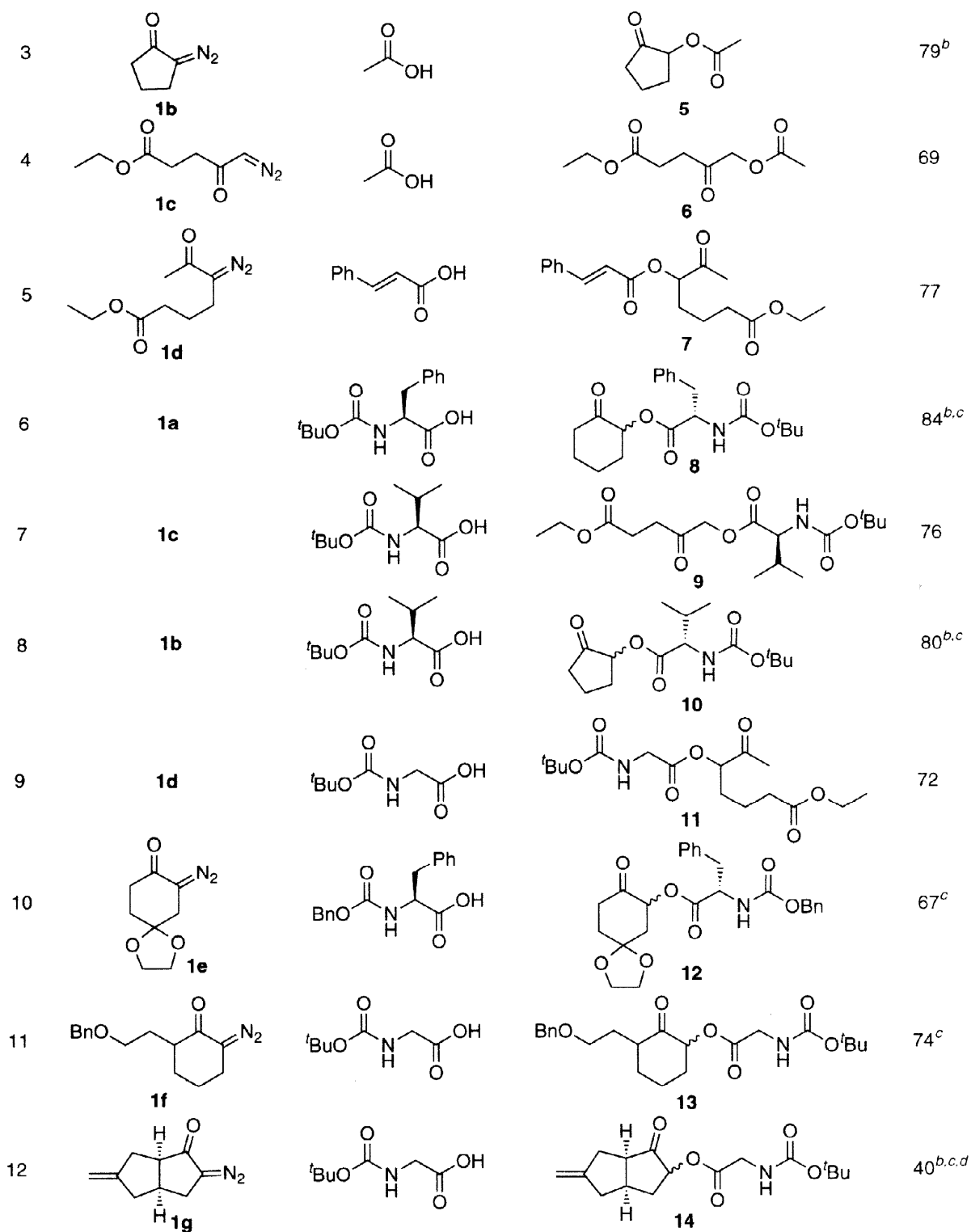


On the basis of the model study, we applied $\text{Cu}(\text{acac})_2$ -catalyzed insertion reactions to various combinations of diazoketones and carboxylic acids (Table 1). Most of the diazoketones reacted with a nearly stoichiometric amount of a carboxylic acid at room temperature to give the corresponding 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).

Table 1. $\text{Cu}(\text{acac})_2$ -catalyzed insertion reaction

Entry	Diazo Compound	Carboxylic Acid	Product	Yield ^a (%)
1	1a			78
2	1a			74

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 $\text{Cu}(\text{acac})_2$ 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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References and Notes

- [1] Wolfrom ML, Waisbrot SW, Brown RL. *J. Am. Chem. Soc.* 1942;64:2329.
- [2] Wolfrom ML, Thompson A, Evans EF. *J. Am. Chem. Soc.* 1945;67:1793.
- [3] Fenselau C. *Steroid Reactions*. Djerassi C., editor. San Francisco: Holden-Day, 1963:537-591.
- [4] Ohfuné Y, Horikawa M. *J. Syn. Org. Chem. Jpn.* 1997;55:982.
- [5] Ohfuné Y, Nanba K, Takada I, Kan T, Horikawa M, Nakajima T. *Chirality* 1997;9:459.
- [6] Horikawa M, Nakajima T, Ohfuné Y. *Synlett* 1997:253.
- [7] Moon S-H, Ohfuné Y. *J. Am. Chem. Soc.* 1994;116:7405.
- [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.
- [9] Erickson JLE, Dechary JM, Kesling MR. *J. Am. Chem. Soc.* 1951;73:5301.
- [10] Sumner T, Ball LE, Platner J. *J. Am. Chem. Soc.* 1959;73:5301.
- [11] Ye T, McKervey MA. *Chem. Rev.* 1994;94:1091.
- [12] Kirmse W. *Carbene Chemistry: Second Edition*. Blomquist AT, Wasserman H, editors. New York: Academic Press. 1971:407-449.
- [13] A few examples using CuCl_2 , $\text{Cu}(\text{OAc})_2$, and copper powder were reported. See references 1, 9, and 10.
- [14] The yields using other catalysts are as follows; $\text{Rh}_2(\text{OAc})_4$ (44%, room temperature), $\text{Cu}(\text{OAc})_2$ (74%, 70 °C), $\text{Cu}(\text{salen})$ (65%, 70 °C), CuI (64%, 70 °C), $\text{Ni}(\text{OAc})_2$ (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 $\text{Cu}(\text{acac})_2$ -catalyzed insertion reaction. To a mixture of Boc-L-phenylalanine (318 mg, 1.2 mmol) and $\text{Cu}(\text{acac})_2$ (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.