Synthetic Communications[®], 35: 745–750, 2005 Copyright © Taylor & Francis, Inc. ISSN 0039-7911 print/1532-2432 online DOI: 10.1081/SCC-200050387



Efficient Synthesis of γ-Keto Esters from Enamines and EDA

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Abstract: The reaction of enamines with ethyl diazoacetate (EDA) catalyzed by dirhodium and copper complexes provided γ -keto esters in good yields. The influences of catalyst, reaction solvent, temperature, and structure of enamines on this transformation were investigated.

Keywords: Enamines, ethyl diazoacetate (EDA), catalysis, γ -keto esters

 γ -Keto esters are important intermediates for preparation of a large number of heterocyclic compounds such as pyrroles, furans, lactones, β -lactam antibiotics, isoquinolines, lactonic sex pheromones, and alkoxythiophenes.^[1] The efficient synthesis of γ -keto esters has been the goal of numerous research efforts. Zercher et al. developed a zinc-mediated chain extension reaction to prepare γ -keto esters from β -keto esters.^[2] Ballini et al. reported one-pot synthesis of γ -keto esters from nitroalkanes and α , β -unsaturated ketones or esters.^[3] Nakamura et al. developed a palladium-catalyzed acylation of

Received in Japan 15 October 2004

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siloxycyclopropanes to prepare γ -keto esters in good yield.^[4] Parker et al. reported a conjugate aroylation reaction of α,β -unsaturated ester gave γ -keto esters.^[5] Reissig et al. studied the addition of methyl diazoacetate to enol silyl ethers and obtained the siloxycyclopropanecarboxylate, which underwent a fluoride-catalyzed rearrangement to give γ -keto esters in a moderate to good yield.^[6] Although these methods were successfully used to prepare a lot of γ -keto esters with diversified structures, many of them suffered from drawbacks such as the requirement of harsh conditions, employment of expensive chemicals, tedious procedure, and low yields.

Recently we found an unusual, highly effective synthesis of 2-aryl- γ -keto esters from aryldiazoacetates and enamines.^[7] This new discovery suggested a new, general synthetic route to γ -keto esters via the catalyzed reaction of the enamines with diazo carbonyl compounds. In this paper we report the reaction of ethyl diazoacetate (EDA) with a variety of enamines leading to γ -keto esters in good yields.

The reaction of N-(1-styryl)morpholine (1a) with ethyl diazoacetate (EDA) catalyzed by $Rh_2(OAc)_4$ provided ethyl 4-oxo-4-phenylbutanoate (2a) in 47% yield. Furthermore a variety of copper complexes were tested as catalysts and the results were summarized in Table 1. The property of the copper complex showed profound effect on the yield. The Cu(hfacac)₂ was found to be the best catalyst concerning the yield and catalytic activity.

| | N_2 O $Et + Ph$ N O $Catalyst PhF$ Ph $COOEt$ 1a $2a$ | | | | |
|-------|--|---------|----------|----------------|--|
| Entry | Catalyst | Mol (%) | Time (h) | Yield $(\%)^b$ | |
| 1 | None | 0 | 24 | 0 | |
| 2 | $Rh_2(OAc)_4$ | 1 | 2 | 47 | |
| 3 | CuI | 3 | 1 | 10 | |
| 4 | $Cu(OTf)_2^c$ | 3 | 2 | 52 | |
| 5 | $Cu(acac)_2$ | 3 | 1 | 69 | |
| 6 | $Cu(hfacac)_2^d$ | 3 | 0.5 | 72 | |
| 7 | CuPF ₆ | 3 | 1.5 | 29 | |

Table 1. Catalytic reaction of EDA with N-(styryl)morpholine $(1a)^a$

^{*a*}The reactions were carried out with 1 mmol EDA and 1.5 mmol enamine in refluxing fluorobenzene.

^bIsolated yields after column chromatography.

 c Cu(OTf)₂ = copper (II) bis(trifluoromethanesulfonate).

 d Cu(hfacac)₂ = bis(hexafluoroacetylacetonate) copper (II).

Synthesis of γ -Keto Esters

| | $N_2 = 0$ Et + Ph N O - | 3 mol% Cu(hfacac) ₂ PhF Ph | Ph COOEt | |
|-------|-------------------------|---|----------------|--|
| | 1a | | 2a | |
| Entry | T (°C) | Time (h) | Yield $(\%)^b$ | |
| 1 | 0 | 2 | 64 | |
| 2 | 25 | 1 | 65 | |
| 3 | 40 | 0.5 | 71 | |
| 4 | 80 | 0.5 | 72 | |

Table 2. Reaction of EDA with N-(styryl)morpholine (1a) at different temperature^a

^{*a*}The reactions were carried out with 1 mmol EDA, 1.5 mmol enamine and 0.03 mmol Cu(hfacac)₂ in fluorobenzene.

^bIsolated yield after column chromatography.

The screen of several frequently used solvents for diazo decomposition revealed that fluorobenzene and dichloroethane afforded higher chemical yield than did other solvents such as benzene, toluene, and dichloromethane.¹ The influence of temperature on the yield was also investigated and the results were summarized in Table 2. The reaction occurred even in zero degrees to provide **2a** in 64% yield and higher chemical yield could be achieved in refluxing fluorobenzene.

After careful examination of the effects of other reaction factors, the optimum reaction conditions for this transformation were identified as following: slow addition of EDA (1.0 equiv.) to a stirred refluxing fluorobenzene solution of enamine (1.5 equiv) and Cu(hfacac)₂ (3 mol%) under an argon atmosphere. The scope of the reaction was explored with a variety of enamines and the results were summarized in Table 3. In most cases γ -keto esters were obtained in good yields. The substituents on the 4-position of the phenyl ring showed neglectable effects on this reaction (Table 3, entries 1–5). 2-Substituted enamines (**1f** and **1g**) were able to react with EDA, providing corresponding γ -keto esters in moderate yields. The enamine **1h** derived from β -naphthyl methyl ketone gave lower yield of product, presumably due to its intense steric hindrance. The enamine **1i** prepared from dialkyl ketone also afforded low yield of product and a reasonable explanation of the result could not be achieved at the present time.

In the reaction of enamines with aryldiazoacetate, we found that the reaction proceeded via a 1,2-proton transfer step to form substituted enamines as transient intermediates, which were hydrolyzed over silica gel

¹The yields of **2a** obtained in different solvents: $ClCH_2CH_2Cl$, 70%; CH_2Cl_2 , 52%; benzene, 62%; PhF, 72%; toluene, 38%.

| N ₂ | $\int_{O}^{O} Et + \frac{R^2}{R^1} + \frac{R^2}{R^1} = 1$ | $\frac{3 \text{ mol}\%}{\text{Cu(hfacac)}_2} \qquad R^1$ PhF, reflux | ² OEt |
|----------------|---|--|------------------|
| Entry | Enamines | γ -Keto Esters ^b | Yield $(\%)^c$ |
| 1 | | | 72 |
| 2 | MeO Ib | MeO 2b OEt | 76 |
| 3 | | Br $2c$ OEt | 72 |
| 4 | | CI 2d OEt | 71 |
| 5 | | O ₂ N 2e OEt | 71 |
| 6 | | | 65 |
| 7 | | | 56 |
| 8 | | | 45 |
| 9 | \downarrow^{0}_{N} \downarrow^{1}_{N} | | 45 |

Table 3. Synthesis of γ -keto esters from enamines and EDA.^{*a*}

"The reactions were carried out with 1 mmol EDA, 1.5 mmol enamine and ^bAll products were fully characterized by ¹H NMR, ¹³C NMR, HRMS, and

elemental analysis.

^cIsolated yields after column chromatography.



Scheme 1. The proposed reaction pathways.

to give γ -keto esters as final products.^[7] In the reaction of enamine **1a** with EDA, analysis of the crude reaction mixture with ¹H NMR and IR spectra allowed us to identify undoubtedly an enamine intermediate **3** (Scheme 1).² The results implied the generality of 1,2-proton transfer mechanism in the transition metal catalyzed reactions of enamines with diazo compounds.

In conclusion, we have developed a facile and efficient synthetic route to γ -keto esters *via* the catalyzed reaction of enamines with EDA. The distinct advantages of this methodology are the ease of preparation of enamines, the simple reaction procedure, and the good yields. Further efforts are under way to expand the scope of enamines and diazo compounds as well as to explore the synthetic utilities of this reaction.

Typical Experimental Procedure

To a round-bottomed flask equipped with a stirrer and an additional funnel under argon atmosphere, was charged N-(styryl)morpholine (**1a**) (0.284 g, 1.5 mmol), Cu(hfacac)₂ (14.3 mg, 0.03 mmol), and fluorobenzene (3 mL). The reaction solution was heated in an oil bath and kept refluxing. The addition funnel was charged with a solution of EDA (0.114 g, 1 mmol) in fluorobenzene (4 mL), which was added dropwise to the reaction solution over 20 minutes. The reaction mixture was refluxed for an additional 30 minutes. After the solvent was evaporated under vacuum, the crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 10:1) over silica gel to give ethyl 4-oxo-4-phenylbutanoate (**2a**) as a light yellow oil (0.149 g, 72% yield). IR (KBr): 1732, 1687 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.99 (d, J = 6.8 Hz, 2 H), 7.57 (t, $J_1 = 8.0$ Hz, $J_2 = 9.6$ Hz, 1 H), 7.46 (t, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz, 2 H), 4.16 (q, J = 7.6 Hz, 2 H), 3.31 (t, $J_1 = 7.6$ Hz, $J_2 = 5.2$ Hz, 2 H), 2.75

²Characteristic spectral peaks of enamine **3**: ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, J = 5.6 Hz, 2 H), 7.11 (t, J = 7.2 Hz, 1 H), 7.06 (t, $J_1 = 14.4$ Hz, $J_2 = 8.8$ Hz, 2 H), 4.75 (t, J = 7.2 Hz, 1H, -C=CH), 4.16 (q, J = 7.2 Hz, 2 H), 3.75 (m, 4 H), 2.95 (d, J = 7.2 Hz, 2H, $-CH_2-COOEt$), 2.76 (m, 4 H), 1.26 (t, J = 7.2 Hz, 3 H); IR (film): 1733 cm⁻¹ (s, -CO-OEt), 1595 cm⁻¹ (s, -C=C-).

(t, $J_1 = 7.6$ Hz, $J_2 = 5.2$ Hz, 2 H), 1.26 (t, J = 7.6 Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ 198.4, 173.2, 136.8, 133.5, 128.9, 128.3, 0.96, 33.7, 28.6, 14.5 ppm. HRMS (EI⁺) calcd. for C₁₂H₁₄O₃: 206.0944; found 206.0943. Anal. calcd. for C₁₂H₁₄O₃: C, 69.88; H, 6.84. Found: C, 70.68; H, 7.05.

ACKNOWLEDGMENTS

Financial supports from the National Natural Science Foundation of China (Project number 20472061) and Suzhou University (Project number Q4109308) are gratefully acknowledged.

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