

Unusual reaction of aryldiazoacetates with enamines: highly effective synthesis of γ -ketoesters

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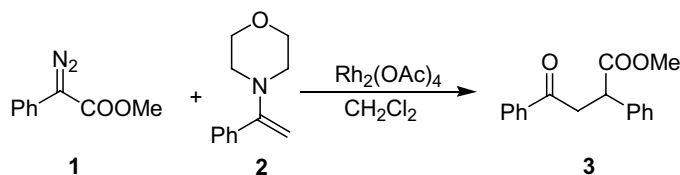
Abstract—The reaction of aryldiazoacetates with enamines catalyzed by copper and rhodium complexes provided γ -ketoesters in good yields. Careful analysis of the crude reaction mixture revealed a substituted enamine as the primary product, which was hydrolyzed over silica gel to give a γ -ketoester as the final product. A reaction mechanism involving nucleophilic addition of an enamine to a metal carbene and subsequent hydrogen transfer was proposed.

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Transition metal catalyzed decomposition of diazo compounds and consequent transformations have constituted various synthetic useful reactions in the past decades.¹ Cyclopropanation of olefins with diazo compounds have been extensively studied. Wenkert reported the cyclopropanation of enol ether with diazo compounds catalyzed by copper salts provided oxycyclopropanes.² However the reaction of enamines with ethyl diazoacetate (EDA) in the presence of cuprous chloride or silver oxide unexpectedly gave α -diazo- β -aminoester in good yield.³ The reaction was probably proceeded via a nucleophilic addition of EDA to iminium cation formed by isomerization of enamine under the reaction conditions. On the other hand Wang et al. studied the addition of EDA to enamine catalyzed by *N*- α -(4-chlorophenyl)isobutyl-(salicylaldimino)copper complex and obtained the aminocyclopropane product in 12% yield.⁴ Muck and Wilson reported the addition of diazomethane to enamine catalyzed by cuprous chloride gave ami-

nocyclopropane derivatives in good yields.⁵ In the absence of transition metal catalysts, the addition of EDA to enamines could provide either dihydro pyrazoles or azo coupling products depending on the structure of the enamine.⁶ In this paper we report an unusual reaction of aryldiazoacetates with enamines catalyzed by copper and dirhodium complexes leading to γ -ketoesters in good yields.

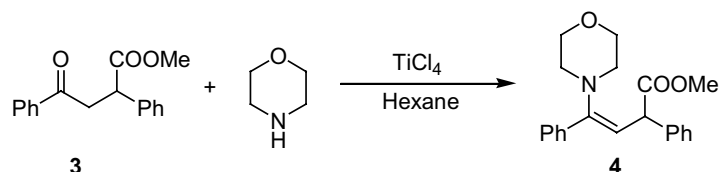
Reaction of methyl phenyldiazoacetate (**1**) with *N*-(1-styryl)morpholine (**2**) in the presence of 1 mol% Rh₂(OAc)₄ afforded a white solid after flash chromatography over silica gel (Scheme 1). This product was unambiguously confirmed as methyl 4-oxo-2,4-diphenylbutanoate (**3**) by combination of ¹H NMR, ¹³C NMR and mass spectral analyses.⁷ None of the expected aminocyclopropane product was found after careful examination of the reaction mixture. It is known that aminocyclopropane is stable even under acidic



Scheme 1.

Keywords: Enamine; Diazo compound; Catalysis; γ -Ketoesters; Dirhodium tetraacetate; Copper salt.

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Scheme 2.

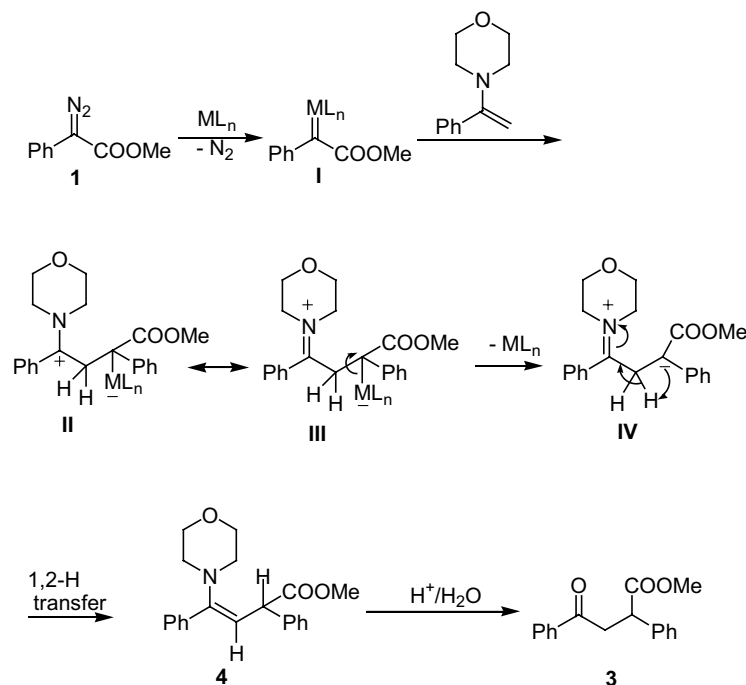
conditions.⁸ Accordingly, the product **3** could not be formed via the decomposition of an aminocyclopropane intermediate.

Analysis of the crude reaction mixture with ^1H NMR revealed only very weak signals assigned for **3**. Instead, another compound was found to be the major component in the reaction mixture, which provided the following ^1H NMR spectrum: 7.36–7.19 (m, 10H), 5.08 (d, $J=10.4\text{Hz}$, 1H), 4.18 (d, $J=10.4\text{Hz}$, 1H), 3.87–3.78 (m, 2H), 3.71–3.65 (m, 2H), 3.63 (s, 3H), 3.10–2.96 (m, 2H), 2.83–2.74 (m, 2H). Its IR spectrum revealed two strong absorption bands at 1731.38 and 1615cm^{-1} , indicating existence of a carbonyl group and a double bond. According to these data this compound was assigned as an enamine (**4**). Further attempt to purify and characterize **4** was unsuccessful due to its unstable property. Thus a control test was carried out to verify the structure of **4**. Treatment of **3** with morpholine in the presence of TiCl_4 gave a crude product, which provided identical ^1H NMR and IR spectra with **4** obtained above (Scheme 2).

Alonso and Fernandez reported apparent vinyl C–H insertion in the reaction of vinyl ether with diazomalones and suggested an addition–elimination mechanism through highly polarized zwitterionic intermediates.⁹ Doyle et al. suggested a similar explanation, in which

a competitive hydrogen transfer step was proposed.¹ Davies et al. also suggested the involvement of zwitterionic intermediates in rhodium-catalyzed reaction of vinyl diazoacetates with electron-rich dienes.¹⁰ Based on these suggestions and our present experiment results, a possible mechanism for the reaction of enamine with phenyldiazoacetate was proposed (Scheme 3). Nucleophilic addition of enamine to highly electron-deficient metal carbene (**I**) produced a zwitterionic intermediate (**II**). The developed positive charge at the carbon could be stabilized efficiently by nitrogen atom through resonance structure (**III**). The hydrogen transfer occurred with complete preference over the competitive cyclopropanation process and provided enamine **4**, which was hydrolyzed over silica gel to give γ -ketoester **3** as the final product.

Several copper complexes were also tested as the catalyst in the reaction of **1** with **2** and the results were summarized in Table 1. The reaction did not occur in the absence of a catalyst (entry 1). In addition to $\text{Rh}_2(\text{OAc})_4$, the copper (II) salts are also highly effective catalysts for this transformation. Even cuprous iodide, a catalyst with low catalytic activity for decomposition of diazo compounds, could afford **3** in the moderate yield (entry 7). It was noticeable that copper catalysts were found to be less effective than $\text{Rh}_2(\text{OAc})_4$ for the reaction involv-



Scheme 3.

Table 1. Reaction of **1** with **2** catalyzed by copper and dirhodium complexes^a

Entry	ML _n	Mol (%)	Time (h)	Yield (%) ^b
1	None	NA ^c	24	0
2	Rh ₂ (OAc) ₄	1	0.5	63
3	Cu(hfacac) ₂ ^d	1	0.5	59
4	Cu(hfacac) ₂	3	0.5	64
5	Cu(hfacac) ₂	3	0.5	75 ^e
6	Cu(OTf) ₂ ^f	3	1	60
7	CuI	3	10	50

^aThe reactions were carried out with 1 mmol **1** and 1 mmol **2** in refluxing dichloromethane.

^bIsolated yield after column chromatography.

^cNot applicable.

^dCu(hfacac)₂ = bis-hexafluoroacetoacetato copper (II).

^e1.5 mmol enamine was used in this case.

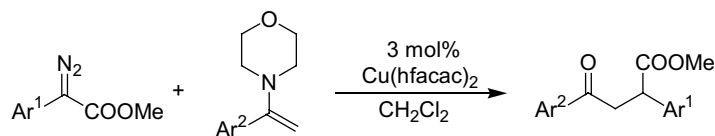
^fCu(OTf)₂ = copper (II) bis-trifluoromethanesulfonate.

ing phenyldiazoacetate.¹¹ The ratio of enamine to diazo compound also played an important role for the yield of the final product. Increasing the amount of enamine from 1 to 1.5 equiv could improve the chemical yield from 64% to 75% (entries 4 and 5), probably due to the decomposition of a small amount of enamine **2** under the reaction conditions.

Though many efficient methods have been developed to prepare α - and β -ketoesters, the available synthetic routes leading to γ -ketoesters are deficient. The γ -ketoester **3** had been prepared by conjugate addition of cyanide to chalcone or by 1,3-dipolar addition of α -diazoketone to olefins followed by a consequent acid catalyzed hydrolysis.¹² The present method via direct addition of aryldiazoacetates to enamines is more convenient and efficient for the preparation of **3** as well as other γ -ketoesters. The lower price of Cu(hfacac)₂ than Rh₂(OAc)₄ makes it the preferred catalyst for this reaction. Several aryldiazoacetates were examined in the reaction with enamines (Scheme 4) and the results were summarized in Table 2.

Moderate to excellent yields were obtained for the most of tested aryldiazoacetates and enamines. However *N*-1-(2-methoxystyryl)morpholine gave low yield of the product, presumably due to its intensified steric hindrance.

In conclusion we have discovered an unusual reaction of aryldiazoacetates with enamines leading to γ -ketoesters in good yields. A reaction mechanism involving nucleophilic addition of an enamine to a metal carbene and subsequent hydrogen transfer was proposed. Further studies are under the way to elucidate the scope and limitation of this reaction and to develop a catalytic asymmetric synthesis of γ -ketoesters.

**Scheme 4.****Table 2.** The catalytic addition of aryldiazoacetates to enamines^a

Entry	Ar ¹	Ar ²	Yield (%) ^b
1	4-Br-C ₆ H ₄	Ph	85
2	1-Naphthyl	Ph	77
3	2-Naphthyl	Ph	83
4	2-Thiophenyl	Ph	56
5	Ph	4-MeO-C ₆ H ₄	80
6	Ph	2-MeO-C ₆ H ₄	33

^aThe reactions were carried out with 1 mmol aryldiazoacetate, 1.5 mmol enamine and 0.03 mmol Cu(hfacac)₂ in refluxing dichloromethane.

^bIsolated yield after column chromatography.

Acknowledgements

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