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Copper-Catalyzed Chemoselective Cross-Coupling Reaction of Thioamides and α -Diazocarbonyl Compounds: Synthesis of Enaminones

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The development of operationally simple and cost-effective methods for C–C bond formation reactions are highly important in pharmaceutical, agrochemical and material research. In this article we describe the first copper-catalyzed cross-coupling reaction of thioamides with acceptor/acceptor-substituted and acceptor-only substituted α -diazocarbonyl compounds to yield enaminones. The reaction shows broad substrate scope in terms of thioamides and diazocarbonyl compounds. Primary, secondary and tertiary thioamides all give enaminones when reacted with α -diazodiesteres, α -diazoketoesters, α -diazodiketones, α -diazoketoamides, α -diazooesteramides, α -diazoketosulfones and α -diazomonoketones.

Enaminone
Copper
Heterocycle
Diazocarbonyl compounds
Cross-coupling

Introduction

Copper-catalyzed reactions of diazocarbonyl compounds contribute to a number of valuable transformations in organic synthesis.^{1–8} Numerous methods are known for the construction of C–C and C–X (X= N, O, S and Si) bonds using copper-carbenoids.¹ Despite these significant advances, the copper-catalyzed cross-coupling reaction of thioamides and α -diazocarbonyl compounds for the synthesis of enaminones have never been reported.⁹ Here, for the first time, we disclose the synthesis of enaminones via a copper-catalyzed chemoselective cross-coupling of thioamides and α -diazocarbonyl compounds.

Enaminones are versatile synthetic intermediates in organic chemistry.^{10–14} They are widely used for the construction of heterocycles and pharmaceutically active compounds.^{10–14} Enaminones are also found to exert anticonvulsant,¹⁵ proteasome inhibition,¹⁶ molluscicidal and larvicidal¹⁷ activities. Because of their importance, the development of new and efficient methods for the synthesis of enaminones is an active area of research.^{18–24}

A variety of methods are available for the synthesis of enaminones.^{10–14} Among the reported methods, the Eschenmoser sulfide contraction (ESC) reaction has been used extensively for the construction of enaminones.^{14, 25, 26} However, the ESC reaction suffers from significant drawbacks. The preparation of suitable α -bromocarbonyl compounds can be difficult. The ESC also requires a long time for completion.^{27–30} Furthermore, the ESC method is unsuccessful in coupling sterically hindered thioamides with α -halocarbonyl compounds.^{14, 31} Modified versions of the ESC reaction have emerged to overcome these shortcomings.^{14, 26} One such reaction is the Rh(II) and the Ru(II)-catalyzed coupling of thioamides with α -diazocarbonyl groups.^{14, 32–34} One problem associated with the Rh(II) and the Ru(II)-

catalyzed versions of this reaction is the competing formation of the homocoupled products.³⁵ Another issue is that, in the coupling of thioamides with the monocarbonyl diazo compounds, the reaction stops at the thioether stage. A large excess of thiophile is needed to convert the thioethers into enaminones.³⁵ There are also no reports of the coupling of the thioformamides and diazo compounds for the formation of enaminones. Coupling with thioformamides could provide disubstituted enaminones that are useful intermediates in natural product synthesis.³⁶ Furthermore, Rh₂(OAc)₄ and Ru(II)-catalysts used in transformation are more expensive than common Cu catalysts that have been used in the generation of copper carbenoids.¹ To address these challenges, we tested selected copper catalysts (Table 1). Copper is not a precious metal, and many copper catalysts are better in avoiding dimerization reactions than Rh₂(OAc)₄.³ Copper catalysts also have a broad tolerance of functional groups present on substrates.³⁷

Results and discussion

We initiated our studies with the screening of copper catalysts for the coupling of thiolactam **1a** and diazoester **2a** (Table 1). All catalysts shown in Table 1 are known to generate copper carbenoids from acceptor-substituted diazo compounds.^{1, 38, 39} We tested Cu(OTf)₂ (5 mol%) as a catalyst in benzene at 90 °C and monitored the progress of the reaction up to 26 hours. However, the reaction did not undergo complete conversion into the product and starting materials remained (Table 1, entry 1). A higher yield of **3aa** was obtained when 1,2-dichloroethane was used as the solvent (Table 1, compare entries 1–3). The best yield of **3aa** (92%) was obtained when the reaction was carried out with (CuOTf)₂·Tol in 1,2-dichloroethane (Table 1, entry 7). Other electrophilic copper catalysts (Table 1, entries 9, 10 and

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