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

Arpal Pal[a], Naga D. Koduri[a] ,Zhiguo Wang[a], Erika Lopez Quiroz[a], Alexandra Chong[a], Matthew Vuong[a], Nisha Rajagopal[a], Michael Nguyen[a], Kenneth P. Roberts[a], and Syed R. Hussaini[a*]

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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 enanminones when reacted with α-diazodiesters, α-diazoketoesters, α-diazodiketones, α-diazoketoamides, α-diazoesteramides, 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 larvicicidal[17] 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]

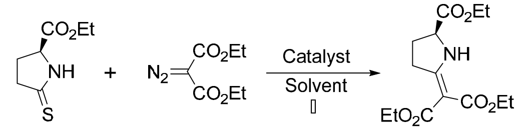
A variety of methods are available for the synthesis of enaminones.[10-14] Among the reported methods, the Eschenmoser sulfide contraction (ESC) reaction has been used extensively for the construction of enaminones.[14, 25, 26] However, the ESC reaction suffers from significant drawbacks. The preparation 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, $Rh_2(OAc)_4$ 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 $Rh_2(OAc)_4$.[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

11) failed to completely consume **1a** in 26 hours. The use of CuCl, CuBr and CuI gave reduced yields (Table 1, entries 12 14) and **1a** did not undergo complete conversion into **3aa**. When anhydrous $CuSO_4$ was used, only 15% conversion **1a** into **3aa** was observed (Table 1 entry 15). Use of (IPr)CuCl and CuTC did not improve the yield (Table 1, entries 16 and 17) and $Cu(acac)_2$ showed scarce conversion of **1a** into **3aa** (Table 1, entry 18).

Table 1: Optimization of Reaction Conditions^{a}



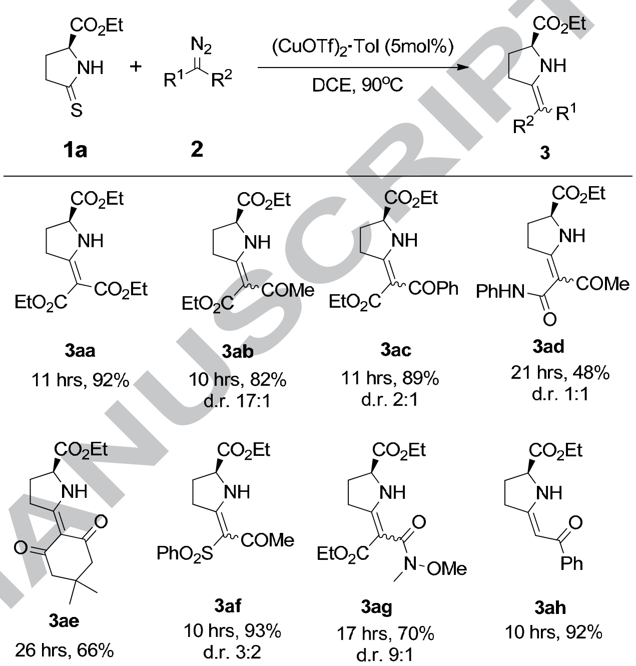
1a **2a** **3aa**

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1.^{b}	$Cu(OTf)_2$	Benzene	26	40
2.^{b}	$Cu(OTf)_2$	DCB	26	60
3.^{c}	$Cu(OTf)_2$	DCE	26	72
4.^{c}	$(CuOTf)_2$·Tol	Benzene	19	67
5.^{c}	$(CuOTf)_2$·Tol	Toluene	18	70
6.^{c}	$(CuOTf)_2$·Tol	DCB	12	74
7.^{c}	**$(CuOTf)_2$·Tol**	**DCE**	**11**	**92**
8.^{d}	$(CuOTf)_2$·Tol	DCM	26	<1
9.^{b}	$Cu(CH_3CN)_4BF_4$	DCE	26	15
10.^{b}	$Cu(CH_3CN)_4BF_4$	DCB	26	66
11.^{b}	$Cu(CH_3CN)_4PF_6$	DCE	26	30
12.^{b}	CuCl	DCE	26	49
13.^{b}	CuBr	DCE	26	39
14.^{b}	CuI	DCE	26	41
15.^{b}	$CuSO_4$	DCE	26	15
16.^{b}	(IPr)CuCl	DCE	26	50
17.^{b}	CuTC	DCE	26	24
18.^{b}	$Cu(acac)_2$	DCE	26	trace

^{a}All reactions were performed in a pressure vessel under an argon atmosphere. Reaction conditions: **1a** (0.2 mmol), **2a** (0.26 mmol), catalyst (5 mol%) in 2.0 ml solvent at 90°C. ^{b}Determined by ^{1}H NMR with reference to **1a**. ^{c}Isolated yield. ^{d}Reaction carried out at 50°C; DCE = 1,2-dichloroethane; DCB = 1,2-dichlorobenzene.

With the optimized reaction conditions in hand (Table 1, entry 7), we next examined six different classes of acceptor/acceptor-substituted diazo compounds– α-diazodiesters, α-diazoketoesters, α-diazodiketones, α-diazoketoamides, α-diazoesteramides and α-diazoketosulfones (Table 2) in this reaction. These diazo compounds when reacted with thiolactam **1a**, gave corresponding enaminones in moderate to excellent yields (48–93%) (Table 2). The reaction of α-diazo acetophenone **2h** with **1a** also afforded the enaminone **3ah** in 92% yield without the addition of any triphenylphosphine. The same transformation with Ru(II) requires 5 equivalents of PPh_3.[35] Formation of **3ag** is also noteworthy as we are aware of only four reports of enaminones containing Weinreb amides.[40-43]

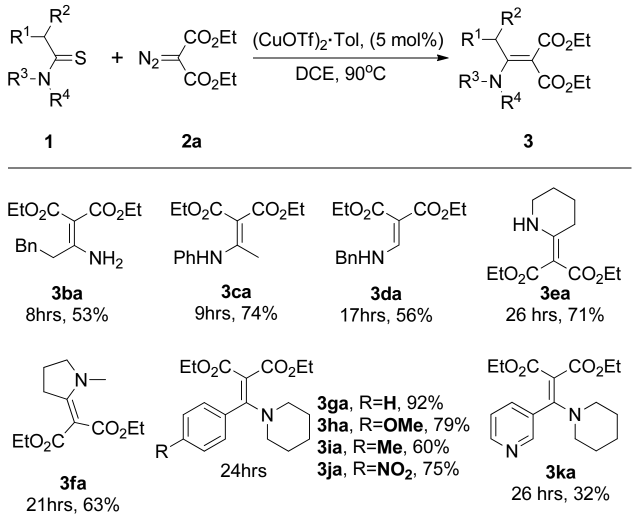
Table 2. Copper-Catalyzed Coupling Reaction of **1a** with Acceptor/Acceptor-Substituted Diazo Compounds



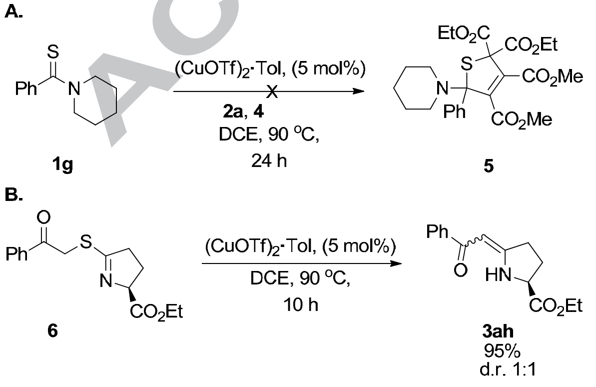
The diastereoselectivity was also probed for this coupling reaction. Only a single diastereomer **3ah** was obtained when **2h** was used. Such selectivity has been observed before and is explained as a result of the greater stability of the *Z* isomer.[14] The exposure of other differently substituted diazo compounds to the reaction conditions provided mixtures of diastereomers (**3ab**–**3ad**, **3af** and **3ag**). The selectivity observed in the case of **3ab**, **3ac** and **3ag** is similar to the ones observed in Eschenmoser type reactions. Various explanations have been postulated for such selectivity.[14, 44]

Next, we explored the scope of this copper-catalyzed coupling reaction with various thioamides (Table 3). Primary, secondary and tertiary thioamides were all converted into the corresponding enaminones in moderate to excellent yields (32–92%). Both cyclic (**3fa**, **3ea**) and acyclic positioned thioamides are viable substrates in this coupling reaction. The reaction also shows excellent chemoselectivity. The α-diazocarbonyl compounds, in the presence of copper catalysts, are known to undergo N H insertion, C H insertion and Buchner reactions.[1] While evaluating the substrate scope, N H insertion, C H insertion or Buchner reaction products were never observed. Such selectivity is suspected to be due to higher nucleophilicity of sulfur compared to other functional groups and the highly electrophilic nature of the copper carbene generated from Cu(I) triflate.[1] Table 3 (**3da**) also shows the first example of a metal-catalyzed coupling of a thioformamide and a diazo compound for the formation of an enaminone.

Table 3. Copper-Catalyzed Coupling Reaction of Differently Substituted Thioamides

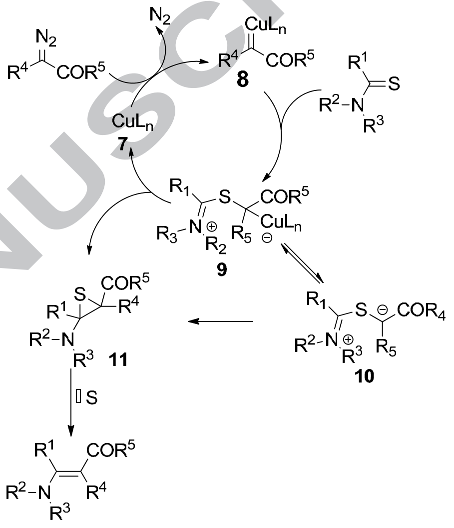


Thioethers are known to form when acceptor-only diazo compounds react with thioamides in the presence of Ru(II) catalysts. This suggests that ylides are present in this reaction.[34, 35] We attempted to trap the intermediate thiocarbonyl ylide. However, the reaction of **1g** and **2a** in the presence of a dipolarophile **4** (DMAD; dimethylacetylenedicarboxylate) did not yield cycloadduct 5 (Scheme 1A), and only **3ga** was obtained. Unlike the Ru(II) catalysts,[35] with Cu(I)OTf, the reaction of **1a** with **2h** only gave the enaminone **3ah** (Table 2), and formation of thioimino ether **6** was not observed (Scheme 1B). This suggests that, with Cu(I)OTf, the extrusion of sulfur is not occurring just due to simple thermal activation. Furthermore, the thioimino ether **6** could be converted into the enaminone **3ah** under the reaction conditions (Scheme 1B). These results support the hypothesis that copper(I) triflate catalyzes the extrusion of sulfur in this reaction. Although rarely reported, similar metal and acid catalyzed -sulfur extrusions have been observed with zinc, nickel, BF$_3$ and TFA in the Eschenmoser sulfide contraction reaction.[14, 45-47]



Scheme 1. Mechanistic Experiments

On the basis of these experimental observations and our previous studies,[34, 35] a mechanism is proposed for this copper-catalyzed coupling reaction (Scheme 2). The reaction of a copper complex with α-diazocarbonyl compounds generates the copper-carbene complexe **8**. The nucleophilic attack of thioamide to the copper-carbene complex gives the copper-associated sulfur ylide **9**. The metal-free ylide **10** can be obtained by the dissociation of copper from **9**. Both the metal associated ylide **9** and the metal free ylide **10** can undergo electrocyclization to form episulfide **11**. Copper(I) triflate assists in the formation of episulfide **11** and the subsequent extrusion of sulfur to provide enaminones. Mechanistic studies have been planned to test the validity of the proposed mechanism.



Scheme 2. Proposed Mechanism for Enaminone Formation

In conclusion, we have successfully developed an unprecedented copper-catalyzed cross-coupling reaction of thioamides with α-diazocarbonyl compounds for the synthesis of enaminones.[48] This reaction has a diverse substrate scope. It also represents the synthesis of enaminones containing the Weinreb amide, thioformamide, and sulfone functionalities which can further broaden the synthetic application of this reaction. We have also discovered a new catalytic reactivity of copper(I) triflate that enables the extrusion of sulfur from thioimino ether. Currently, we are working on the utilization of donor/acceptor-substituted diazo compounds and ester diazoacetates in this coupling reaction.

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Supplementary data

Experimental procedures, spectroscopic data and ^{1}H and ^{13}C spectra.

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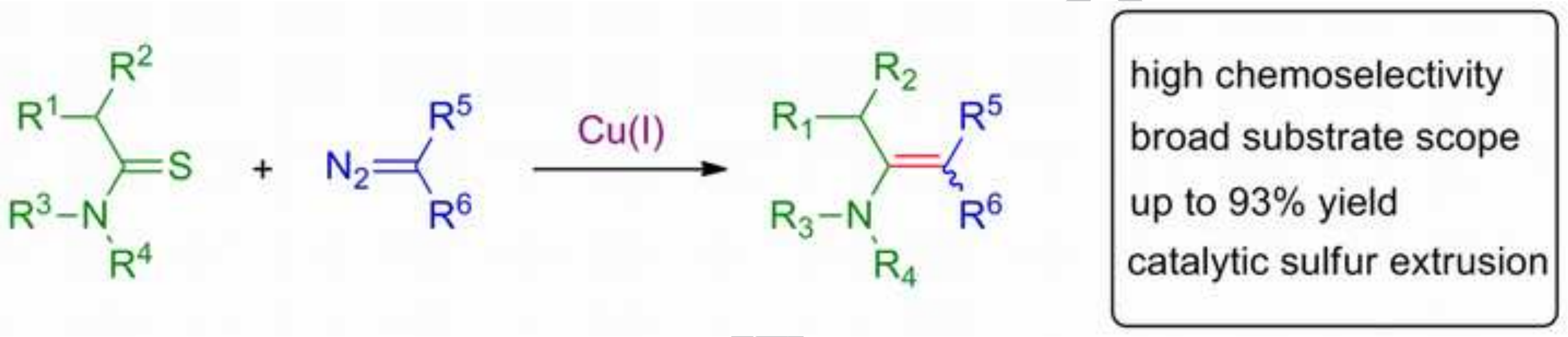
48. General experimetal for the synthesis of enaminones: 5 mol% (CuOTf)2.Tol complex was weighed in a screw capped reaction vial. The vial was purged with argon. A solution of thioamide (0.2 mmol) in 1.0 ml dry 1,2-dichloroethane was transferred to a vial containing a diazo compound (0.26 mmol). The well mixed solution of thioamide and diazo compound was added to the vial containing the catalyst. The vials containing the starting materials were washed twice with 0.5 ml of dry 1,2-dichloroethane and the contents were transferred to the reaction vial. The reaction mixture was heated at 90˚C. Once the reaction was complete (as observed by the TLC analysis), the solvent was evaporated, and the crude product was purified by the silica gel column chromatography.

***Graphical Abstract**



high chemoselectivity
broad substrate scope
up to 93% yield
catalytic sulfur extrusion

***Highlights**

- First report of copper-catalyzed coupling of thioamides and diazo compounds for the synthesis of enaminones
- Thioformamide and primary, secondary and tertiary thiomamides can undergo this reaction
- Acceptor/acceptor and acceptor-only substituted diazo compounds are coupling viable partners
- Catalytic extrusion of sulfur is reported