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Letter

Copper(I)-Catalyzed Sulfenylation of 1,3-Dicarbonyl Substrates with Disulfides under Mild Conditions

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Jingnan Zhao^a Fan Yang^b Zongyi Yu^a Xiaofei Tang^a Yufeng Wu^a Cunfei Ma^a Qingwei Meng^{*a}

^a State Key Laboratory of Fine Chemicals, School of Chemical Engineering, Dalian University of Technology, Dalian 116024,

P. R. of China menggw@dlut.edu.cn

^b Dalian Institute of Chemical Physics, Chinese Academy of Sci-

ences, Dalian 116024, P. R. of China

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Abstract A copper(I) iodine catalyzed sulfenylation of 1,3-dicarbonyl substrates in the presence of MeCN is presented. Various β -keto esters and β -keto amide substrates can react with disulfides to afford their corresponding products in good to excellent yields. The notable features of this protocol include high atom economy, easy operation, mild reaction conditions, and excellent functional group tolerance.

Key words sulfenylation, disulfides, copper(1) iodide, $\beta\text{-keto}$ esters, MeCN

The formation of carbon-sulfur bonds represents an important step in organic synthesis, as well as in the pharmaceutical industry.1 Many chemists have devoted many efforts to the development of more efficient approaches to construct carbon-sulfur bonds avoiding the use of prefunctionalized reactants, expensive metal catalysts, and expensive sulfur agents.² In recent years, the direct sulfenylation via C-H functionalization has appeared to be an attractive powerful strategy for the preparation of complicated organosulfur compounds.³ α-Sulfenylation of carbonyl compounds is of particularly interest since these products have been applied in a variety of organic transformations.⁴ There were already some studies on asymmetric catalysis in this field. Jørgensen and co-workers described first enantioselective α -sulfenylation of β -ketoesters catalyzed by cinchona alkaloid derivative in 2005.⁵ Lately, chiral Ti(TADDOL) complexes for this transformation were achieved by Togni and co-workers. However, due to the use of moisture-sensitive sulfur reagents, an inert atmosphere is necessary for this catalytic system.⁶ In 2009, Zhu and co-workers reported sulfenylation of β -keto esters catalyzed by α, α -diaryl prolinol with excellent enantioselectivity and good yields.⁷



In 2013, a series of novel bifunctional quaternary phosphonium bromides were designed by Maruoka for the sulfenylation of β -keto esters under base-free phase-transfer conditions with high enantioselectivity (Scheme 1).⁸ The above methods generally involve using sulfur agents such as 1-(2,4-dinitrophenylsulfanyl)[1,2,4]triazole, ArSCl or *N*-(phenylthio)phthalimide, which comparatively lower the atom economy of the reaction.



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Most preferably, disulfides are regarded as ideal sulfurizing reagents, considering atom economy. To explore a sample sulfenylation of 1,3-dicarbonyl substrates procedure with high atom economy and mild conditions, we thus turned our attention to disulfides.

Initially, the reaction of 1-indanone-derived β -keto ester **1a** and diphenyl disulfide (**2a**) was examined in the dark. It was found that the addition of sodium iodide could catalyze the formation of the sulfenylation product, and **3a** was obtained in 32% yield (Table 1, entry 2). It is noteworthy that the reaction did not proceed completely in the absence of iodide (Table 1, entry 1), which suggested that iodide plays a key role in sulfenylation. These results promoted us to investigate various iodine sources including NaI, KI, TBAI, and Cul (Table 1, entries 2–5). Further investigation revealed that Cul exhibited much higher activity in promoting the formation of **3a** in the terms of efficiency and selectivity. Additional experiments at reducing the amount of Cul proved that the 20 mol% Cul loading was appropriate (Table 1).

 Table 1
 Optimization of Reaction Parameters for the Sulfenylation Reaction^a

CI	$\frac{CO_2Me}{1a} + \frac{S_3}{2a}$	catalyst solvent, r.t. C darkness	CO ₂ Me SPh
Entry	Catalyst (equiv)	Solvent	Yield of 3a (%) ^b
1	-	MeCN	N.R.
2	Nal (0.1)	MeCN	32
3	KI (0.1)	MeCN	N.R.
4	TBAI (0.1)	MeCN	N.R.
5	Cul (0.1)	MeCN	51
6	Cul (0.2)	MeCN	86
7	CuBr (0.1)	MeCN	N.R.
8	CuCl (0.1)	MeCN	N.R.
9	$[Cu(CH_3CN)_4]PF_6(0.1)$	MeCN	44
10	Cul (0.2)	toluene	N.R.
11	Cul (0.2)	xylene	N.R.
12	Cul (0.2)	CH_2CI_2	N.R.
13	Cul (0.2)	CHCl ₃	N.R.
14	Cul (0.2)	DMF	49
15	Cul (0.2)	THF	N.R.
16	Cul (0.2)	dioxane	N.R.
17	Cul (0.2)	EtOH	N.R.
18	Cul (0.2)	EtOAc	N.R.

^a Reaction conditions: **1a** (0.1 mmol), disulfide (0.06 mmol), and catalyst were stirred in 2 mL solvent at room temperature for a given time. ^b Determined by ¹H NMR analysis; N.R. = no reaction.

Next, the substrate scope was studied under the optimized reaction conditions for a variety of commercially available disulfides and 1,3-dicarbonyl substrates. As highlighted in Scheme 2, β -keto esters and β -keto amides can be sulfenylated under the developed reaction conditions. In the beginning, 1-indanone-derived β -keto ester **1a** was successfully reacted with disulfide 2a to give the respective 3a in 86% yield. Moreover, diphenyl disulfide bearing electrondonating groups such as methyl was well tolerated. The corresponding product 3c was obtained in good yield. The substitutions with fluoro and nitro did not affect the yields (**3b.e.f**). The reaction of heteroarvl disulfide **2d** also provided the product in good yield. Furthermore, a series of substituted 1,3-dicarbonyl substrates were examined, and the results are summarized in Scheme 2. Generally, the B-keto esters substituted with methyl, methoxy, and halogen reacted smoothly to provide the corresponding products in moderate yields (3i-m, 77-95% yields). Further substrate expansion to 1-tetralone-derived 1,3-dicarbonyl substrate and β -keto amide was also investigated, and the corresponding products were generated effectively (3n,o, 65% and 87% yield).

To further expand the utility of the reaction, we directed our efforts toward achieving a continuous-flow process. A dried 50 mL Schlenk tube equipped with a magnetic stir bar was charged with Cul (0.125 g, 20 mol%) and MeCN (10 mL). The mixture was stirred at 50 °C for 30 min. Then, the β -keto ester **1a** (0.5615 g, 2.5 mmol, 1.0 equiv) and **2a** was added. The HPLC pump used to deliver the solution was set to 1.0 mL min⁻¹ and was conveyed to the continuous-flow reactor through perfluoroalkoxyalkane (PFA) tubing (1/8 inch O.D.). Mixing occurred along the entire reactor channel (16.4 mL internal volume) and afforded **3a** in 82% yield (Scheme 3).

To gain insight into the reaction mechanism, we conducted control experiments as shown in Scheme 4. When employing PhSH as the sulfur agent instead of PhSSPh, no reaction was detected (Scheme 4, a).

Besides, when subjecting tetrakis(acetonitrile)copper(I) hexafluorophosphate and TBAI to the reaction, 61% yield was obtained (Scheme 4, b). Therefore, we speculated that the coordination of CuI with acetonitrile may be the key to promoting the reaction.

Plausible mechanistic processes were proposed as depicted in Scheme 5 based on the above results and considering previous works.⁹⁻¹⁴ The mechanism for this reaction proceeds via initial copper coordination to **1** and formed complex Cu(I) species **4**, which reacts with diphenyl disulfide to afford the PhSCu(I) species **6**. As reported previously,¹²⁻¹⁴ oxidation of the PhSCu(I) with oxygen regenerates the CuI catalyst and disulfide to close the catalytic cycle while also allowing both 'halves' of the disulfide to react.

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Scheme 2 Scope of the reaction



In summary, a sample and facile copper(I) iodide catalyzed system was developed for a direct sulfenylation of 1,3-dicarbonyl substrates with disulfides. Using disulfides as sulfurizing reagent, this approach enables the C-S bond coupling to occur effectively under relatively mild conditions. Additional advantages of this method include high atom economy and providing moderate to excellent yields of products with good scalability and simple experimental procedure. Further expansion of the synthetic utility and the application of this procedure in enantioselective synthesis is currently under investigation in our laboratories.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690221.

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Scheme 5 Proposed reaction mechanism

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