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CuI-catalyzed thioarylation of active methylene compounds with in situ generated benzenethiols: Preparation of α-thioaryl-β-dicarbonyls and 4-thioaryl-5-pyrazolones

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ABSTRACT

In this paper, a one-step copper-catalyzed procedure for oxidative coupling of active methylene compounds including cyclic β-diketones, cyclic β-ketoesters and 5-pyrazolone with benzenethiols is described. Benzenethiols are in situ generated in the reaction mixture from aryl halides and thiourea as sulfur transfer reagent. α-Thioaryl compounds are obtained in excellent yields and in short reaction time *via* the process which is free from the foul smell of thiols.

1. Introduction

Sulfur functionalities are important building blocks in organic synthesis. They are important industrial compounds used in the agrochemicals, pharmaceutical and cosmetic industries as well as in the manufacture of polymers [1]. Among them, α-thioaryl-β-dicarbonyl compounds are extremely useful intermediates for the synthesis of heterocyclic compounds and pharmaceutical products [2]. For the formation of C–S bond between ketones and thiophenols, one of them need to be transformed to the corresponding electrophiles. Thus, traditional synthetic routes for preparation of these compounds can be divided into two categories: the nucleophilic substitution of α-halogenated ketones with thiophenols or disulfides [3] and the reaction of enolates with various sulfenylating reagents, such as sulfenamides [4], thiosulfonates [5], sulfuryl chloride [6], sulphenyl halides [7] and disulfides [8]. Since most electrophiles are directly or indirectly prepared from their corresponding nucleophiles, recently, efforts have been devoted toward the oxidative coupling between two nucleophiles. In this way, Tan et al. reported a new route to thioethers by reacting the sulfur nucleophiles with active methylene compounds in the presence of carbon tetrabromide [9]. Also, the iodine-catalyzed oxidative coupling between 1,3-diketones and thiophenols to afford β-dicarbonyl thioethers was recently described by Hu and co-workers [10].

Despite extensive efforts in the sulfenylation of indole [11] and imidazole [12] derivatives, less attention to date has been paid to the sulfenylation of dicarbonyl compounds.

In continuation of our research on C–S coupling reactions [13], herein, we report a novel method for odourless thioarylation of β-diketones and pyrazolones from aryl halides in the presence of sulfur transfer reagent. To our knowledge, there are no report describing the sulfenylation of active methylene compounds using aryl halides.

2. Results and discussion

The initial screening of the reaction conditions was conducted using 5,5-dimethylcyclohexane-1,3-dione (dimedone) (1.0 mmol) and 4-iodotoluene (2.0 mmol) in the presence of thiourea (2.6 mmol), C_2Cl_6 (1.5 mmol), CuI (20 mol%), DMAP (20 mol%) and Na_2CO_3 (2.0 mmol) at 120 °C. The reaction in DMSO afforded the desired product in 70% yield after 24 h (Table 1, entry 1). No better

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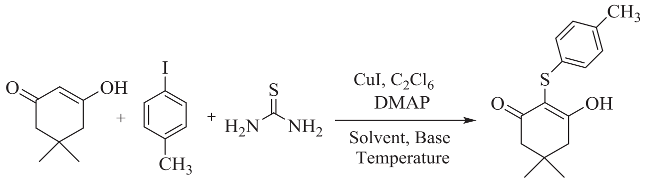
Table 1
Optimization of oxidative coupling reaction between dimedone (1.0 mmol) and 4-iodotoluene (2.0 mmol) under different conditions.



Entry	Catalyst (mol%)	Solvent	Base (2.0 mmol)	T (°C)	Time (h)	Yield (%)[a]
1	CuI (20)	DMSO	Na_2CO_3	120	24	70
2	CuI (20)	PEG-200	Na_2CO_3	120	24	45
3	CuI (20)	H_2O	Na_2CO_3	100	24	–
4	CuI (20)	Toluene	Na_2CO_3	reflux	24	–
5	CuI (30)	DMSO	Na_2CO_3	120	24	70
6	CuI (15)	DMSO	Na_2CO_3	120	24	41
7	CuI (10)	DMSO	Na_2CO_3	120	24	25
8	–	DMSO	Na_2CO_3	120	24	–
9	CuCl (20)	DMSO	Na_2CO_3	120	24	trace
10	$CuCl_2$ (20)	DMSO	Na_2CO_3	120	24	–
11	$Cu(OAc)_2$ (20)	DMSO	Na_2CO_3	120	24	–
12	$Cu(PPh_3)_3I$ (20)	DMSO	Na_2CO_3	120	24	55
13	CuI (20)	DMSO	K_2CO_3	120	24	75
14	CuI (20)	DMSO	Bu_3N	120	24	40
15	CuI (20)	DMSO	KOH	120	5	90
16	CuI (20)	DMSO	KOH (4.0)	120	15 min	93
17	CuI (20)	DMSO	KOH (4.0)	100	24	64
18	CuI (20)	DMSO	KOH (4.0)	130	15 min	93
19[b]	CuI (20)	DMSO	KOH (4.0)	120	24	–

[a] Isolated yield.
[b] The reaction was carried out in the absence of C_2Cl_6.

results were obtained, when the reaction was carried out in polyethylene glycol (PEG-200, 120 °C), H_2O (100 °C) or in refluxing toluene (Table 1, entries 2–4). Therefore, the subsequent reactions were performed in DMSO. No further yield improvement is achieved using higher concentration of ligand or/and substrates or increasing the catalyst loading. On the other hand, reducing the amount of CuI, greatly reduced the reaction yield (Table 1, entries 6 and 7). As expected, in the absence of catalyst, no product was formed (Table 1, entry 8). Performing the reaction in the presence of other Cu-catalysts such as CuCl, $CuCl_2$, $Cu(OAc)_2$ and $Cu(PPh_3)_3I$ showed that the appropriate choice of catalyst was CuI (Table 1, entries 9–12). Next, alternative bases such as K_2CO_3, Bu_3N, KOH were screened, however in these cases, KOH is the best, providing product in 93% isolated yield within 15 min (Table 1, entries 13–16). A temperature of 120 °C was found to be the optimal reaction temperature. Decreasing the temperature, resulted the product in lower yield (Table 1, entry 17) and higher temperature (Table 1, entry 18) did not have any significant effect on the conversion; The sulfenylation carried out at 100 and 130 °C, afforded 64% and 93% yields respectively. Finally, we observed that no sulfenylation product was detected in the absence of C_2Cl_6 (Table 1, entry 19).

We then applied the obtained optimized conditions (dicarbonyl compound (1.0 mmol), aryl halide (2.0 mmol), thiourea (2.6 mmol), C_2Cl_6 (1.5 mmol), CuI (20 mol%), DMAP (20 mol%) and KOH (4.0 mmol) in DMSO at 120 °C), for the reaction of different aryl iodides with active methylene compounds in the presence of sulfur transfer reagent. The results are summarized in Table 2.

The reactions of cyclic *β*-diketones (5,5-dimethylcyclohexane-1,3-dione and cyclohexane-1,3-dione), cyclic *β*-ketoesters (chromane-2,4-dione and 6-methyl-2*H*-pyran-2,4(3*H*)-dione) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one with iodobenzene proceeded smoothly in accordance with the optimized reaction conditions, affording the corresponding products in excellent yields. Electronically different aryl iodides were also proved to be very efficient and in these cases, the corresponding sulfenylated products were obtained in excellent yields (Table 2, entries 1–18). The aryl iodides functionalized with *ortho* substituents demonstrated viable reactivity, suggesting that steric factors on the arene group of halides do not apply a limitation for the product formation.

To further extend the substrate scope, various active methylene compounds such as malononitrile, methyl 2-cyanoacetate, ethyl 2-cyanoacetate, ethyl 3-oxobutanoate (Table 2, entries 19–22) were treated with *p*-iodoanisole under the optimized reaction conditions. However, with this substrate combination, the expected C–S bond formation did not occur and in all cases, the corresponding disulfide was formed as the sole product in the reaction mixture. Unexpectedly, when linear *β*-diketone such as pentane-2,4-dione was used as the coupling partners, no product was formed (Table 2, entry 23). The only difference between these structures (linear and circle) after the reaction with copper iodide is the formation of a six-membered chelate ring in linear structures that cannot be formed in the circles. But, it is not clear to us whether this difference is involved in the formation of cyclic products. As shown in entry 24 of Table 2, simple ketone enolates are not sufficiently reactive toward thioarylation by the use of our catalytic system; when acetophenone was allowed to react with *p*-iodoanisole under the optimized reaction conditions, no product was detected even after prolonged reaction time. After the successful application of this methodology for different aryl iodides, we studied the applicability of this catalytic system for the reaction of aryl bromides under the obtained optimized reaction conditions. As summarized in Table 3, couplings of different aryl bromides with cyclic *β*-diketones, cyclic *β*-ketoesters and pyrazolones for the preparation of desired products, found to be facile, generating high yields (Table 3, entries 1–13).

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