


 Cite this: *RSC Adv.*, 2017, **7**, 39758

Received 20th June 2017

Accepted 8th August 2017

DOI: 10.1039/c7ra06904a

rsc.li/rsc-advances

Cs₂CO₃-promoted cross-dehydrogenative coupling of thiophenols with active methylene compounds†

 Qian Chen, *^{ab} Xiaofeng Wang,^a Chunxiao Wen,^a Yulin Huang,^a Xinxing Yan^a and Jiekun Zeng^a

A convenient and efficient α -sulfonylation of carbonyl compounds has been achieved *via* the halogen-free Cs₂CO₃-promoted cross-dehydrogenative coupling (CDC) of thiophenols with active methylene compounds using air as the oxidant under mild conditions. This transformation provides a straightforward route to the construction of carbon–sulfur bonds with wide functional group compatibility, which produces α -sulfonylated carbonyl compounds in up to 95% yield.

The development of new methods to construct carbon–sulfur bonds has been of particular interest due to the wide applications of organosulfur compounds in biological chemistry and organic synthesis.^{1,2} Among them, α -sulfonylated carbonyl compounds are important intermediates for the synthesis of heterocycles,³ β -keto sulfones,⁴ α, β -unsaturated carbonyl compounds,⁵ and others.⁶ Therefore, α -sulfonylation of carbonyl compounds is highly desirable, and a variety of useful synthetic methods have been well documented. The traditional preparation of this class of compounds mainly relies on the use of pre-functionalized substrates including: (1) nucleophilic substitution of α -halogenated carbonyl compounds with thiols⁷ (Fig. 1a) or disulfides⁸ (Fig. 1b); and (2) the reactions of carbonyl compounds with thio sources such as sulphenyl halides, disulfides, sulfonothioates, sulfenamides, and *N*-(phenylthio)disulfides, sulfonothioates, sulfenamides, and *N*-(phenylthio)

succinimide (Fig. 1c).⁹ However, these methods are limited because the corresponding starting materials are high-cost and/or temperature- or moisture-sensitive. Thus, the development of a convenient and efficient protocol for the synthesis of α -sulfonylated carbonyl compounds remains a challenge.

The cross-dehydrogenative coupling (CDC) reactions are powerful methods in organic synthesis that can avoid the use of pre-functionalized substrates.¹⁰ The CDC reactions involving thiols have attracted much attention because this strategy represents more straightforward, efficient, and atom-economic to construct carbon–sulfur and sulfur–heteroatom bonds.¹¹ The oxidative CDC has also been applied to α -sulfonylation of carbonyl compounds (Fig. 1d).¹² The coupling of thiols with active methylene compounds in the presence of CBr₄ has been reported by Liang and co-workers.^{12a} Yadav and co-workers have reported α -sulfonylation of monoketones in the presence of NCS.^{12b} Recently, Hu, Lei and co-workers developed iodine-catalyzed oxidative coupling of 1,3-diketones with thiophenols using DTPB as the oxidant.^{12c} Prabhu and co-workers developed a couple of α -sulfonylations of monoketones or 1,3-diketones using K₂S₂O₈ or DMSO (in the presence of I₂) as the oxidant.^{12d–f} However, the current oxidative coupling protocols requires the use of halogenated reagents and/or strong oxidants. In this regard, seeking greener oxidants for this CDC reaction is still a significant issue. Molecular oxygen as the greener and more sustainable oxidant has been widely used in organic synthesis.¹³ Moreover, inorganic bases have been well utilized for carbon–sulfur and sulfur–heteroatom bond forming reactions.¹⁴ With these backgrounds, we envisioned that α -sulfonylated carbonyl compounds might be formed through the CDC reaction of thiols with carbonyl compounds using O₂ as the oxidant in the presence of an inorganic base. Herein, we report an efficient halogen-free Cs₂CO₃-promoted α -sulfonylation of active methylene compounds under air.

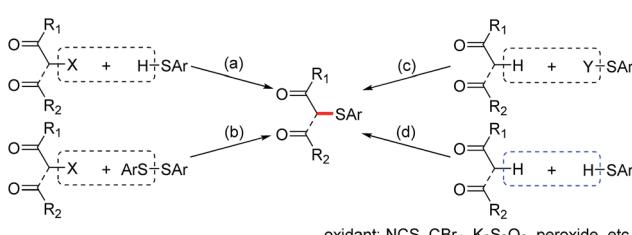


Fig. 1 Strategies for α -sulfonylation of carbonyl compounds.

^aSchool of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China. E-mail: qianchen@gdut.edu.cn; Fax: +86 20 3932 2235; Tel: +86 20 3932 2231

^bKey Laboratory of Functional Molecular Engineering of Guangdong Province, South China University of Technology, Guangzhou 510640, China

† Electronic supplementary information (ESI) available: General information and copies of ¹H and ¹³C NMR spectra. See DOI: 10.1039/c7ra06904a



The reaction conditions were tested by using a model reaction of acetylacetone **1a** with 4-bromo-thiophenol **2a** in solvents under air atmosphere at room temperature, and the results were shown in Table 1. Initially, no reaction occurred when the reaction of **1a** with **2a** in CH_3CN in the absence of bases under air was carried out (entry 1). To our delight, when Cs_2CO_3 (1 equiv.) was added, the reaction proceeded smoothly to afford the desired product 3-(4-bromophenylthio)pentane-2,4-dione **3aa** in 82% yield (entry 2). When the reaction of **1a** with **2a** was carried out under N_2 , only trace amounts of **3aa** were detected (entry 3). This result demonstrates that the reaction involved an aerobic oxidative cross-coupling. We then turned to screen other bases (entries 4–9), and found that Cs_2CO_3 was the optimal base. The increase or decrease of Cs_2CO_3 amount did not improve the yield (entries 10–14). Notably, the use of catalytic amounts of Cs_2CO_3 also led to the formation of **3aa** in moderate yields (entries 13 and 14). Switching the solvent from CH_3CN to THF, dioxane, DMSO, EtOH, or H_2O decreased the yield of **3aa** (entries 15–19), while the use of DMF afforded the desired product in 98% yield (entry 20). It is noteworthy that disulfide **4a**, which was generated *via* an aerobic oxidative homocoupling of thiol **2a**,^{14a} was observed in all cases under air.

We then set out to explore the generality of the CDC reaction of thiols with active methylene compounds. We first applied the optimized conditions to the coupling of various thiols **2** with

Table 1 Optimization of reaction conditions^{a,b}

Entry	Base (equiv.)	Solvent	Yield of 3aa (%)
1		CH_3CN	0
2	Cs_2CO_3 (1)	CH_3CN	82
3 ^c	Cs_2CO_3 (1)	CH_3CN	Trace
4	K_2CO_3 (1)	CH_3CN	65
5	Na_2CO_3 (1)	CH_3CN	0
6	NaOAc (1)	CH_3CN	0
7	K_3PO_4 (1)	CH_3CN	45
8	CsF (1)	CH_3CN	16
9	Et_3N (1)	CH_3CN	<10
10	Cs_2CO_3 (3)	CH_3CN	74
11	Cs_2CO_3 (2)	CH_3CN	82
12	Cs_2CO_3 (1.5)	CH_3CN	75
13	Cs_2CO_3 (0.5)	CH_3CN	61
14	Cs_2CO_3 (0.2)	CH_3CN	48
15	Cs_2CO_3 (1)	THF	73
16	Cs_2CO_3 (1)	Dioxane	50
17	Cs_2CO_3 (1)	DMSO	57
18	Cs_2CO_3 (1)	EtOH	25
19	Cs_2CO_3 (1)	H_2O	0
20	Cs_2CO_3 (1)	DMF	98

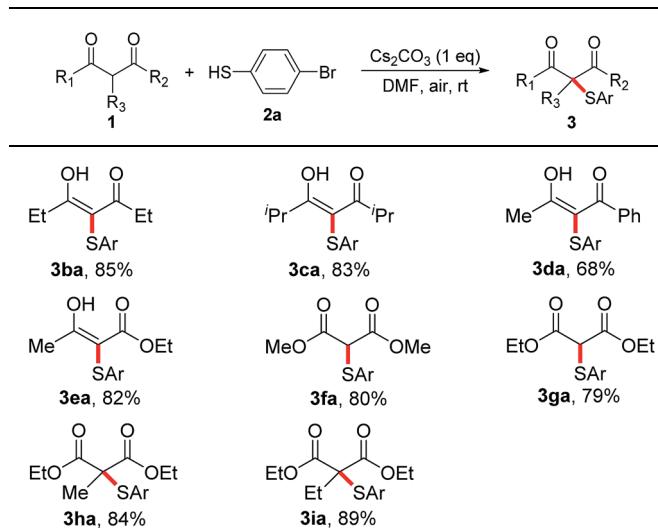
^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base, solvent (1 mL), room temperature, open air, 6 h. ^b Yield based on **1a** was determined by ^1H NMR analysis of crude products using an internal standard. ^c The reaction was carried out under N_2 .

acetylacetone **1a** (Table 2). Pleasingly, the results showed that thiophenol substrates bearing different groups such as electron-withdrawing halogen groups (Br, Cl and F) and electron-donating groups (alkyl, OMe, OH and NH₂) at the *para*, *meta* or *ortho* or at both positions of aromatic rings, as well as the bulky 2-naphthalenethiol, were all well tolerated. The corresponding **3aa**–**3as** were isolated in moderate to excellent yields, indicating that the electronic and steric effects were not evident in this reaction. The scale-up reaction was also attempted. When we increased the scale of the reaction from 0.4 to 4 mmol, the yield of **3ad** only slightly decreased (from 86% to 79%). We then turned our attention to aliphatic thiols. Unfortunately, α -sulenylation of **1a** with benzylthiol or cyclohexylthiol failed to give the desired **3at** or **3au**.

Next, the coupling of 4-bromo-thiophenol **2a** with a variety of active methylene compounds **1** under the optimized conditions was examined, and the results are illustrated in Table 3. 1,3-Diketones bearing methyl, ethyl, isopropyl and phenyl groups were all applicable to the CDC reaction, leading to the formation of **3ba**–**3da** in 68–85% yields. When ethyl acetoacetate was employed, the reaction also proceeded smoothly to afford **3ea** in 82% yield. In addition, dialkyl malonates were also well tolerated, and the desired products **3fa** and **3ga** were obtained in good yields. We then turned to α -sulenylation of monosubstituted malonates, and the reaction of **2a** with α -alkylmalonates led to the corresponding **3ha** and **3ia** in 84% and 89% yield, respectively.

Table 2 Scope of thiols^{a,b}

^a Reaction conditions: **1a** (0.4 mmol), **2** (0.8 mmol), and Cs_2CO_3 (0.4 mmol) in DMF (2 mL) stirring at room temperature under air for 6–12 h. ^b Isolated yield based on **1a**. ^c The reaction was performed in a 4 mmol scale.

Table 3 Scope of active methylene compounds^{a,b}

^a Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol), and Cs_2CO_3 (0.4 mmol) in DMF (2 mL) stirring at room temperature under air for 6–12 h. ^b Isolated yield based on **1**.

the yield of **3aa** reduced from 93% to 0% and 17%, respectively (eqn (1)), suggesting that this transformation might proceed *via* a radical pathway. In consideration of the generation of disulfides in all cases, the reaction of thiol **2a** with Cs_2CO_3 under air was carried out, leading to the formation of disulfide **4a** in quantitative yield (eqn (2)). The above results suggest that Cs_2CO_3 could increase the oxidation rate of thiols with dioxygen and disulfide was produced *via* a thiyl radical homocoupling.^{14a,15} In addition, the reaction of **1a** with disulfide **4a** under the standard conditions gave **3aa** in good yields regardless of the presence of air (eqn (3) and (4)), which demonstrates that disulfide might be an intermediate in the CDC reaction. Moreover, the reaction of **1a** with **4a** in the absence of Cs_2CO_3 failed to give **3aa** (eqn (5)), which indicates Cs_2CO_3 is indispensable in this reaction.

According to the literatures and our observations, a plausible reaction mechanism is outlined in Scheme 2. Initially, thiyl radical is generated from the autoxidation of thiol **2** in the presence of Cs_2CO_3 and dioxygen, and thiyl radical undergoes homocoupling to produce disulfide **4**.^{11j,14a,15,16} Meanwhile, active methylene compound **1** reacts with Cs_2CO_3 to form intermediate **5**. Finally, the nucleophilic attack of the *in situ*-generated enolate **5** on disulfide **4** affords α -sulfonylated carbonyl compound **3**.

Conclusions

In conclusion, we have developed the Cs_2CO_3 -promoted cross-dehydrogenative coupling (CDC) of thiophenols with active methylene compounds, which provides a highly convenient and efficient protocol for the synthesis of α -sulfonylated carbonyl compounds with wide functional group compatibility under mild conditions. To the best of our knowledge, this finding is the first example of aerobic CDC reaction of thiols with carbonyl compounds. We envision that the reaction mode outlined here will have potential applications in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

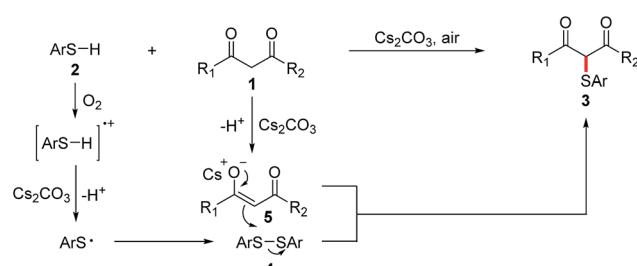
Acknowledgements

This work was supported by the Science and Technology Planning Project of Guangdong Province (No. 2015A020211026 and 2017A010103044), 100 Young Talents Programme of Guangdong University of Technology (220413506), and the Open Fund of the Key Laboratory of Functional Molecular Engineering of Guangdong Province (2016kf07, South China University of Technology).

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Scheme 1 Mechanistic studies.



Scheme 2 Proposed mechanism.

To gain more insight into the mechanism of the CDC reaction, a series of control experiments were conducted (Scheme 1). When radical scavenger BQ and BHT was introduced into the reaction,



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