Cs$_2$CO$_3$-promoted cross-dehydrogenative coupling of thiophenols with active methylene compounds†

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A convenient and efficient $\alpha$-sulfonylation of carbonyl compounds has been achieved via the halogen-free Cs$_2$CO$_3$-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 $\alpha$-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, $\alpha$-sulfonylated carbonyl compounds are important intermediates for the synthesis of heterocycles,3 $\beta$-keto sulfones,4 $\alpha,\beta$-unsaturated carbonyl compounds,5 and others.6 Therefore, $\alpha$-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 $\alpha$-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)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 $\alpha$-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 $\alpha$-sulfonylation of carbonyl compounds (Fig. 1d).12 The coupling of thiols with active methylene compounds in the presence of CBr$_4$ has been reported by Liang and co-workers.12a Yadav and co-workers have reported $\alpha$-sulfonylation of monoketones in the presence of NCS.13 Recently, Hu, Lei and co-workers developed iodine-catalyzed oxidative coupling of 1,3-diketones with thiophenols using DTPB as the oxidant.12b Prabhu and co-workers developed a couple of $\alpha$-sulfonylations of monoketones or 1,3-diketones using K$_2$S$_2$O$_8$ or DMSO (in the presence of I$_2$) as the oxidant.12c–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 $\alpha$-sulfonylated carbonyl compounds might be formed through the CDC reaction of thiols with carbonyl compounds using O$_2$ as the oxidant in the presence of an inorganic base. Herein, we report an efficient halogen-free Cs$_2$CO$_3$-promoted $\alpha$-sulfonylation of active methylene compounds under air.

Fig. 1 Strategies for $\alpha$-sulfonylation of carbonyl compounds.
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 CH3CN in the absence of bases under air was carried out (entry 1). To our delight, when Cs2CO3 (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 N2, 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 Cs2CO3 was the optimal base. The increase or decrease of Cs2CO3 amount did not improve the yield (entries 10–14). Notably, the use of catalytic amounts of Cs2CO3 also led to the formation of 3aa in moderate yields (entries 13 and 14). Switching the solvent from CH3CN to THF, dioxane, DMSO, EtOH, or H2O decreased the yields (entries 13 and 14). Unfortunately, Cs2CO3 (0.4 mmol) in DMF (2 mL) stirring at room temperature under air was 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%).

Next, we turned our attention to aliphatic thiols. Unfortunately, ζ-sulfenylation of 1a with benzythiol or cyclohexythiol failed to give the desired 3at or 3au.

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 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.

Table 1 Optimization of reaction conditions.‡,b

| Entry | Base (equiv.) | Solvent | Yield of 3aa (%) |
|-------|--------------|---------|-----------------|
| 1     |              |         | 0               |
| 2     | Cs2CO3 (1)   | CH3CN   | 82              |
| 3‡    | Cs2CO3 (1)   | CH3CN   | Trace           |
| 4     | K2CO3 (1)    | CH3CN   | 65              |
| 5     | Na2CO3 (1)   | CH3CN   | 0               |
| 6     | NaOAc (1)    | CH3CN   | 0               |
| 7     | K3PO4 (1)    | CH3CN   | 45              |
| 8     | CsF (1)      | CH3CN   | 16              |
| 9     | Et3N (1)     | CH3CN   | <10             |
| 10    | Cs2CO3 (3)   | CH3CN   | 74              |
| 11    | Cs2CO3 (2)   | CH3CN   | 82              |
| 12    | Cs2CO3 (1.5) | CH3CN   | 75              |
| 13    | Cs2CO3 (0.5) | CH3CN   | 61              |
| 14    | Cs2CO3 (0.2) | CH3CN   | 48              |
| 15    | Cs2CO3 (1)   | THF     | 73              |
| 16    | Cs2CO3 (1)   | Dioxane | 50              |
| 17    | Cs2CO3 (1)   | DMSO    | 57              |
| 18    | Cs2CO3 (1)   | EtOH    | 25              |
| 19    | Cs2CO3 (1)   | H2O     | 0               |
| 20    | Cs2CO3 (1)   | DMF     | 98              |

‡ Reaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), base, solvent (1 mL), room temperature, open air, 6 h. ‡ Yield based on 1a was determined by 1H NMR analysis of crude products using an internal standard. ‡ The reaction was carried out under N2.

Table 2 Scope of thiols.‡,b

| Entry | R              | Yield (%) |
|-------|----------------|-----------|
| 3aa   | Br             | 93%       |
| 3ab   | Cl             | 62%       |
| 3ac   | F              | 93%       |
| 3ad   | Me             | 86% (79%) |
| 3ae   | f-Bu           | 87%       |
| 3af   | OH             | 50%       |
| 3ag   | NH2            | 53%       |
| 3ah   | Br             | 61%       |
| 3ai   | Cl             | 80%       |
| 3aj   | F              | 89%       |
| 3ak   | OMe            | 76%       |
| 3al   | Br             | 94%       |
| 3am   | Cl             | 72%       |
| 3an   | F              | 92%       |
| 3ao   | Me             | 76%       |
| 3ap   | Cl             | 64%       |
| 3aq   | Cl             | 73%       |
| 3ar   | Cl             | 58%       |
| 3as   | 95%            |           |

‡ Reaction conditions: 1a (0.4 mmol), 2a (0.8 mmol), and Cs2CO3 (0.4 mmol) in DMF (2 mL) stirring at room temperature under air for 6–12 h. ‡ Isolated yield based on 1a. ‡ The reaction was performed in a 4 mmol scale.
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, 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 Cs₂CO₃ under air was carried out, leading to the formation of disulfide 4a in quantitative yield (eqn (2)). The above results suggest that Cs₂CO₃ could increase the oxidation rate of thiols with dioxygen and disulfide was produced via a thyl radical homocoupling.\textsuperscript{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 Cs₂CO₃ failed to give 3aa (eqn (5)), which indicates Cs₂CO₃ is indispensable in this reaction.

According to the literatures and our observations, a plausible reaction mechanism is outlined in Scheme 2. Initially, thyl radical is generated from the autoxidation of thiol 2 in the presence of Cs₂CO₃ and dioxygen, and thyl radical undergoes homocoupling to produce disulfide 4.\textsuperscript{11j,14a,15,16} Meanwhile, active methylene compound 1 reacts with Cs₂CO₃ to form intermediate 5. Finally, the nucelophilic attack of the in situ-generated enolate 5 on disulfide 4 affords α-sulfenylated carbonyl compound 3.

**Conclusions**

In conclusion, we have developed the Cs₂CO₃-promoted cross-dehydrogenative coupling (CDC) of thiophenols with active methylene compounds, which provides a highly convenient and efficient protocol for the synthesis of α-sulfenylated 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.

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**Notes and references**

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