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Copper-Catalyzed Oxidative Reaction of β-Keto Sulfones with Alcohols via C−S Bond Cleavage: Reaction Development and Mechanism Study

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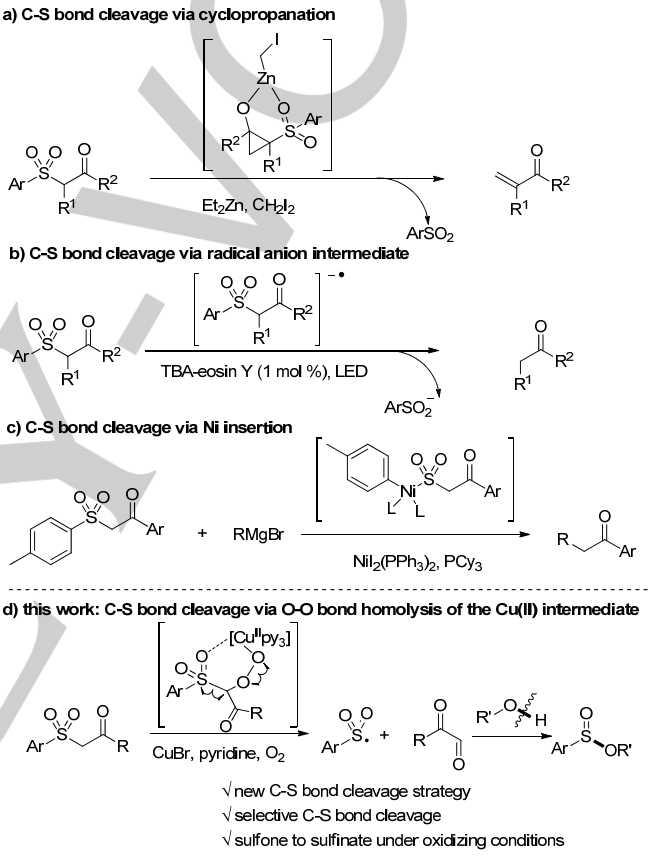
Dedication ((optional))

Abstract: A Cu-catalyzed cascade oxidative radical process of β-keto sulfones with alcohols has been achieved by using oxygen as an oxidant. In this reaction, β-keto sulfones were converted into sulfinate esters under the oxidative conditions via cleavage of C-S bond. Experimental and computational studies demonstrate that a new pathway is involved in this reaction, which proceeds through the formation of the key four-coordinated Cu(II) intermediate, O−O bond homolysis induced C−S bond cleavage and Cu-catalyzed esterification to form the final products. This reaction provides a new strategy to sulfonate esters and enriches the research contend of the C−S bond cleavage and transformations.

The activation and transformations of inert chemical bonds are fundamental scientific issues. Up to now the processes of C−H,[1] C−C,[2] C−N[3] and C−O[4] bond cleaving reactions catalyzed by transition metals have been well developed. In recent years, the C–S bond cleavage and transformations have become important in the petroleum industry and synthetic chemistry.[5] The most developed one in this area is insertion of a transition-metal into the C−S bond of organosulfur compounds, leading to the corresponding C–S bond cleavage.[6] Generation of a sulfur radical via the C−S bond homolysis in sulfones, sulfoxides or other compounds, also has been developed for another type of C−S bond cleavage.[7] Although significant advances have been made in the research of C−S bond cleavage during the past decades,[6-8] the development of catalytic, selective C−S bond cleavage reactions is still a challenging problem in organic chemistry.[9]

β-Keto sulfones[10] are attractive and powerful tools in organic synthesis, which could be easily converted into various classes of organic compounds via reactions on the methylene moiety or the carbonyl moiety.[11] However, there are few reports on the transformation of sulfonyl groups of β-keto sulfones.[12] In 2015, the Pandey group developed a Zn-promoted C−S bond cleavage of β-keto sulfones via cyclopropanation for the synthesis of α-methenyl ketones (Scheme 1a).[12a] Liu, Wu and co-workers also reported a photocatalytic C−S bond cleavage of β-keto sulfones with the radical anion as intermediate (Scheme 1b).[12b] The Li group developed a Ni-catalyzed Kumada coupling reaction between β-keto sulfones and Grignard reagents, which proceeded through the Ni insertion initiated C−S bond cleavage to give the modified aryl ketones as products (Scheme 1c).[12c] To the best of our knowledge, the transformation on sulfonyl group of β-keto sulfones to sulfinate compounds has never been reported until now. Herein, we report the first example on copper-catalyzed aerobic oxidative[13] C−S bond cleavage of β-keto sulfones to give sulfinate esters as the corresponding products (Scheme 1d). Our combined experimental and



Scheme 1. The C-S bond cleavage of β-keto sulfones.

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computational study aims to elucidate the factors that the transformation of sulfone into sulfinate under Cu-catalyzed oxidative conditions with O_2. A novel mechanism involving a key four-coordinated Cu(II) intermediate for this reaction is presented for this catalytic system. Furthermore, it should be mentioned that the transformation of sulfone into sulfinate ester[14] is conducted under oxidative conditions.

To determine the reaction parameters, benzenesulfonylacetone **1a** and 1-butanol **2d** were chosen as model substrates (Table 1). The initial combination of CuCl (10 mol %) and pyridine (1.0 equiv) in toluene was evaluated. The reaction did happen, however, to our surprise, an unpredictable sulfinate product **3ad** was detected in 12% yield under an oxygen atmosphere (entry 1). The reactions employing CuBr or $CuBr_2$ as the catalysts delivered the sulfinate product **3ad** in better yields (23% and 16%, respectively, entries 2 and 4). However, CuI gave a disappointing result since only a trace amount of the expected product was found (entry 3). A similar yield was found with benzene as solvent (entry 5), while (trifluoromethyl)-benzene provided an improved result (entry 8). Decreasing the amount of pyridine from 1.0 to 0.5 equiv, a slightly lower yield of product **3ad** was observed (entry 9). An improved yield was achieved by increasing the amount of pyridine to 2.0 equiv (36%, entry 10). Entries 11-13 of Table 1 showed that the concentration of the reaction mixture had an obvious effect on the outcome. The results clearly disclose that the use of 1.0 mL (trifluoromethyl)benzene was the best choice, affording a 43% yield (entry 12). Additional optimization using different amounts of CuBr catalyst was carried out, and the desired product was obtained in a dramatically higher yield when 20 mol % of CuBr was used (entry 14). The yield could be further increased to 62% when 4 Å molecular sieves were added into the reaction mixture (entry 15). Decreasing the reaction temperature from 90 °C to 70 °C, a lower chemical yield was found (46%, entry 16). Finally, control experiments carried out in the absence of either catalyst CuBr or ligand pyridine failed to give the target product (entries 17 and 18).

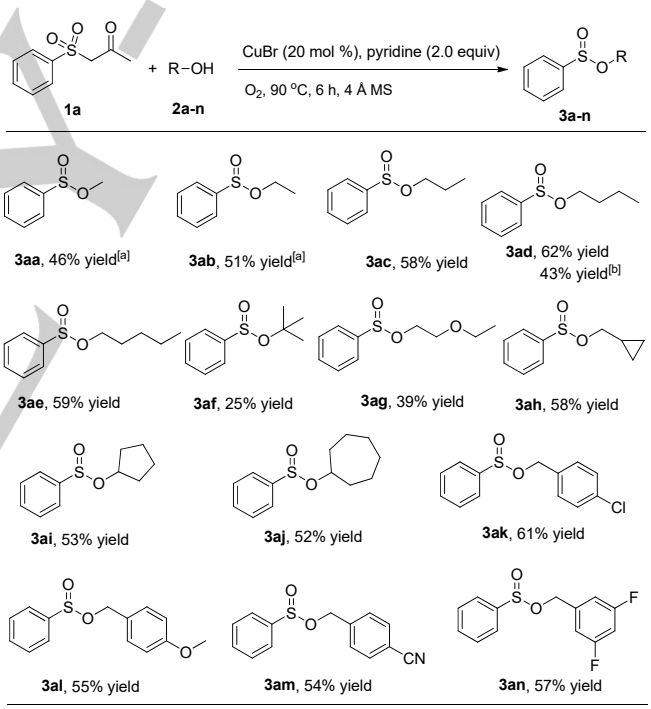
Table 1. Optimization of reaction conditions.[a]

1a **2d** **3ad**

Entry	Catalyst (mol %)	Pyridine (equiv)	Solvent (mL)	Yield (%)[b]
1	CuCl (10)	1.0	Toluene (2.0)	12
2	CuBr (10)	1.0	Toluene (2.0)	23
3	CuI (10)	1.0	Toluene (2.0)	<5
4	$CuBr_2$ (10)	1.0	Toluene (2.0)	16
5	CuBr (10)	1.0	Benzene (2.0)	22
6	CuBr (10)	1.0	Anisole (2.0)	13
7	CuBr (10)	1.0	PhF (2.0)	25
8	CuBr (10)	1.0	$PhCF_3$ (2.0)	28
9	CuBr (10)	0.5	$PhCF_3$ (2.0)	22
10	CuBr (10)	2.0	$PhCF_3$ (2.0)	36
11	CuBr (10)	2.0	$PhCF_3$ (0.5)	40
12	CuBr (10)	2.0	$PhCF_3$ (1.0)	43
13	CuBr (10)	2.0	$PhCF_3$ (4.0)	31
14	CuBr (20)	2.0	$PhCF_3$ (1.0)	54
15	CuBr (20)	2.0	$PhCF_3$ (1.0)	62[c]
16	CuBr (20)	2.0	$PhCF_3$ (1.0)	46[d]
17	–	2.0	$PhCF_3$ (1.0)	0
18	CuBr (20)	0	$PhCF_3$ (1.0)	0

[a] Reaction conditions: **1a** (0.25 mmol), **1d** (1.0 mmol), and the solvent, in a flask under O_2 balloon at 90 °C for 6 h. [b] Isolated yield based on **1a**. [c] 200 mg 4 Å molecular sieve was added. [d] at 70 °C.

We then investigated the reaction generality of alcohol substrates by using **1a** as the standard reacting partner (Scheme 2).

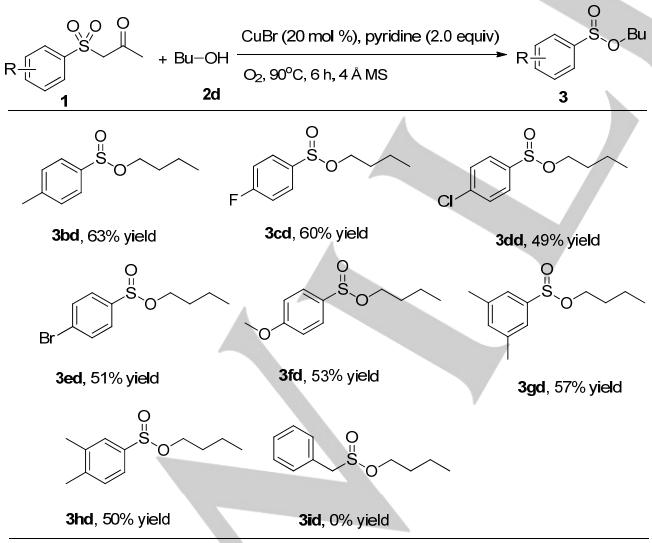


Scheme 2. Substrate scope study with variation of alcohols. (Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), CuBr (20 mol%), pyridine (2.0 equiv) and $PhCF_3$ (1.0 mL), in a flask under O_2 at 90 °C for 6 h. Isolated yields. [a] **2** (2.0 mmol) at 70 °C. [b] The yield from the reaction of 2.0 mmol of **1a**.)

Encouragingly, varieties of alcohols, such as aliphatic linear primary and tertiary alcohols, cyclic alcohols and benzyl alcohols were well accommodated to afford the corresponding sulfinate products in 25-62% isolated yields. In the case of aliphatic linear primary alcohols, high boiling alcohols, such as propanol **2c**, butanol **2d** and pentanol **2e**, could work well in this reaction giving rise to 58-62% yields (**3ac**-**ae**), while the reactions of methanol and ethanol afforded lower yields (**3aa**-**ab**). When the

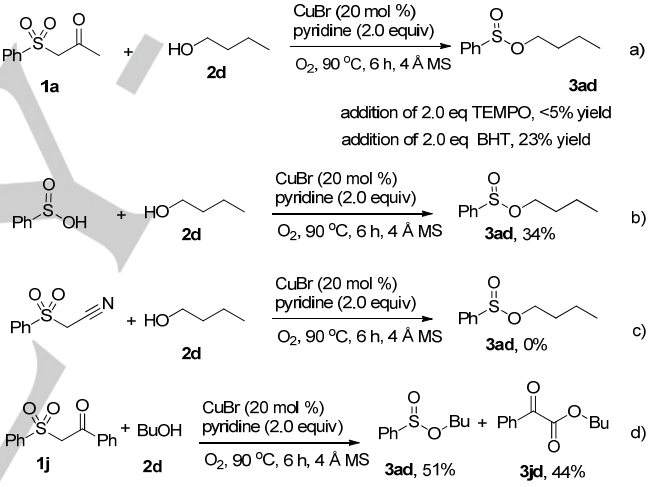
reaction scale of **1a** was increased from 0.25 mmol to 2.0 mmol, the reaction also proceeded smoothly, affording the corresponding product **3ad** in 43% yield. Notably, 2-ethoxyethanol was also well compatible with our reaction protocol resulting in 2-ethoxyethyl benzenesulfinate **3ag** with 39% isolated yield. Interestingly, the reaction of substrate with cyclopropyl substituent also proceeded smoothly, giving rising to **3ah** in 58% yield. In particular, the alcohol **2f** containing a bulky group still could work in this reaction, however a dramatically lower chemical yield was found (25%). This result clearly indicates that steric hindrance effects this Cu-catalyzed oxidative reaction. Remarkably, cyclic aliphatic alcohols were also effective substrates for this system, and provided sulfinic cyclic esters with moderate yields (**3ai**, **3aj**). Other benzyl alcohols (**2k-2n**) were found to be well suited to generate the products in moderate to good yields. Of particular importance was the tolerance of various substituents regardless of their electronegativity, generating the products in 54-61% yields.

Then, the generality of this Cu-catalyzed oxidative reaction with respect to butanol **2d** was examined for substituted arylsulfonylacetone (Scheme 3). Most of the examined arylsulfonylacetones were suitable substrates, and the transformation proceeded smoothly to afford the corresponding sulfinates in moderate isolated yield (49-63%, **3bd-hd**). It should be mentioned that the electronegativity of the substituents almost showed no effect on this process, even fluoro (**1c**) and methoxyl (**1f**) groups were well tolerated in this reaction. Quite notably, the substrates (**1g-1h**) with di-substituted aromatic ring still worked well in this reaction, and resulted in the expected sulfinate with 57% and 50% yield respectively. Finally, further scope examination was carried out with a benzyl group substrate, 1-(benzylsulfonyl)propan-2-one (**1i**). However, it could not be transformed to the corresponding sulfinate **3id** under current conditions.



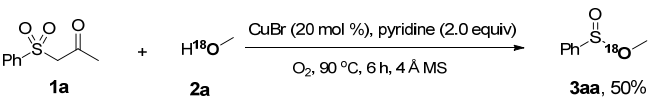
Scheme 3. Substrate scope study with variation of β-keto sulfone. (Reaction conditions: **1** (0.25mmol), **2** (1.0 mmol), CuBr (20 mol%), pyridine (2.0 equiv) and $PhCF_3$ (1.0 mL), in a flask under O_2 at 90 °C for 6 h. Isolated yields.)

To gain insight into this transformation mechanism, first of all, radical trapping experiments were carried out (Scheme 4a). When 2.0 equiv of TEMPO or BHT was added, the reaction was obviously suppressed, which implies that the radicals may be generated in the current copper-catalyzed aerobic oxidative reaction. Then, several control experiments were designed to further investigate the reaction mechanism. As shown in Scheme 4b, 34% yield of the sulfinate product was obtained when benzenesulfinic acid was examined in the current system, which implies that benzenesulfinic acid might be the active species in this transformation. The reaction with 2-(phenylsulfonyl)acetonitrile as substrate failed to give the desired product, which discloses the role of the carbonyl group not acting as the electron withdrawing group. We assign this to the inherent enol keto tautomerism of the carbonyl compound (Scheme 4c). In order to understand the transformation, we have chosen 1-phenyl-2-(phenylsulfonyl)ethanone **1j** as a substrate. Butyl 2-oxo-2-phenylacetate **3jd** was obtained in 44% yield under the standard conditions (Scheme 4d). Based on this result, arylsulfonylacetone carbonyl group is turned into the respective keto ester in the reaction.



Scheme 4. Control experiments.

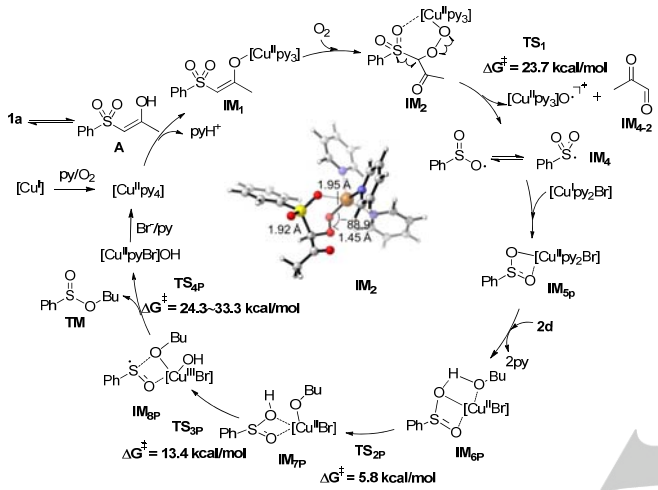
To clarify the direction of oxygen atom transfer in the reaction, an ^{18}O labelling experiment was designed and carried out with $Me^{18}OH$. Finally, the ^{18}O-labeled product **3aa'** was obtained in 50% yield (Scheme 5) proving the role of oxygen in the reaction.



Scheme 5. Isotope labelling experiment.

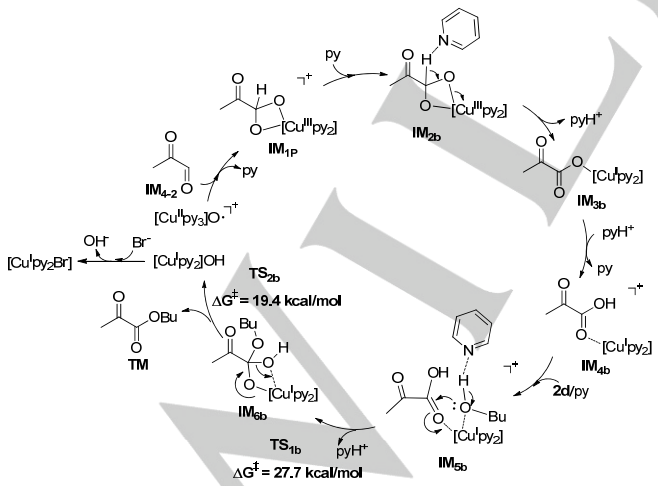
The possible reaction pathway of copper-catalyzed aerobic oxidative selective bond cleavage of β-keto sulfones to sulfonates is presented in Scheme 6. At first, β-keto sulfone went through an enol tautomerism process to form a hydroxyl group in β position. Then the catalyst attacked on the hydroxyl oxygen to replace the hydroxyl hydrogen and the pyridine ligand was removed simultaneously to generate intermediate **IM_1**. A six-membered ring of α-peroxo ketone (**IM_2**) was formed successively after O_2 attacks the α-carbon position. The O-O

and C-S bond cleavage of **IM_2** went through **TS_1** with an energy barrier of 23.7 kcal/mol, yielding **IM_3**. It was a concerted process for the cleavage of O-O and C-S bond of **IM_2**. **IM_3** is a weakly bonded complex of components, so it is easy to remove **IM_{1p}** to give **IM_4**. Subsequently, butanol (**1d**) was coordinated to the copper center of **IM_{5p}** to form the intermediate **IM_{6p}**. It is obvious that **IM_{6p}** went through an intramolecular hydrogen transfer process (**TS_{2p}**) with a low activation free energy barrier of 5.8 (12.4 for **TS_2**) kcal/mol to arrive **IM_{7p}** on the basis of the selected mulliken charges given in Figure S2. Finally, the product is obtained through the transfer of hydroxyl and alcohol oxygen group in the intermediate **IM_{8b}**.



Scheme 6. Proposed mechanism of the formation of sulfinate.

Beside the possible path for target product, a possible path for the other byproduct was also provided. The proposed mechanism for copper-catalyzed the transformation of the carbonyl to give the butyl 2-oxopropanoate **IM_{7b}** is presented in Scheme 7 and Figure S4.



Scheme 7. Proposed mechanism of product α-keto-ester

In conclusion, a copper-catalyzed aerobic oxidative selective bond cleavage of β-keto sulfones to sulfinates has been developed. The β-keto sulfones as a new type of sulfur containing coupling partner has been discussed by DFT calculation and control experiments. The DFT calculation discloses a novel O-O bond homolysis in copper(II)–peroxo complexes induced cleavage of C-S bond method. This fracture pattern enriches the knowledge of previous C-S bond cleavage. The detailed mechanistic study and further applications are ongoing in our laboratory.

Experimental Section

Typical procedure for Cu-catalyzed oxidative coupling reaction: Arylsulfonylacetones **1** (0.25 mmol), CuBr (0.05 mmol) and molecular sieve (200 mg) were added to a 25 mL schlenk tube under O_2 atmosphere, followed by addition of alcohols **2** (1.0 mmol), pyridine (0.5 mmol) and $PhCF_3$ (1.0 mL), The mixture was stirred at 90 ºC for 6 h, then filtered and the solid was washed with Et_2O. The organic solution was concentrated by rotary evaporator. Next, crude product was purified over a column of silica gel (eluant: petroleumether/ethylacetate) to afford the desired product **3**.

Acknowledgements ((optional))

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Keywords: Cu-catalyzed • C−S bond cleavage • aerobic oxidation • β-keto sulfones • DFT calculation

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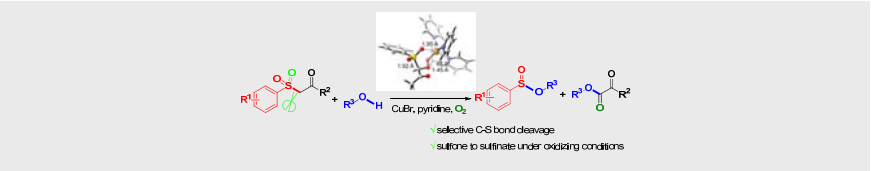

A Cu-catalyzed cascade oxidative radical process of β-keto sulfones with alcohols has been achieved by using oxygen as an oxidant. In this reaction, β-keto sulfones were converted into sulfinates ester under the oxidative conditions via selective cleavage of C-S bond. The mechanism has been investigated by experimental and computational studies.

Bingnan Du, Wenmin Wang, Yang Wang, Zhenghang Qi, Jiaqi Tian, Jie Zhou, Xiaochen Wang, Jianlin Han, Jing Ma,* Yi Pan*

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Copper-Catalyzed Oxidative Reaction of β-Keto Sulfones with Alcohols via C−S Bond Cleavage: Reaction Development and Mechanism Study