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Copper-catalyzed aerobic oxidation and cleavage/formation of C–S bond: a novel synthesis of aryl methyl sulfones from aryl halides and DMSO†

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With atmospheric oxygen as the oxidant, a novel copper(I)-catalyzed synthesis of aryl methyl sulfones from aryl halides and widely available DMSO is described. The procedure tolerates aryl halides with various functional groups (such as methoxy, acetyl, chloro, fluoro and nitro groups), which could afford aryl methyl sulfones in moderate to high yields. The copper-catalyzed aerobic oxidation and the cleavage/formation of C–S bond are the key steps for this transformation.

The synthesis of aryl (methyl) sulfones has attracted much attention due to their promising antibacterial, antifungal and antitumor activities.[1] For example, some aryl methyl sulfones (DuP-697, Rofecoxib and Etoricoxib, shown in Fig. 1) have been identified as very effective and specific cyclooxygenase-2 inhibitors.[2–4] Very recently, some investigations have also shown that aryl sulfones derivatives are potent inhibitors of several enzymes, such as HIV-1 reverse transcriptase, matrix metalloproteinase and γ-secretase.[5] In addition, aryl sulfones as synthetic intermediates could achieve particular transformations.[6] So far, various synthetic routes have been developed to synthesize aryl sulfones, mainly including the oxidation of sulfides,[7] the coupling reaction of arylboronic acids (or aryl halides) with sulfinic acid salts or arylsulfonyl chlorides,[8] the sulfonylation of arenes with arenesulfonic acids or arenesulfonyl halides and the reaction of Grignard reagents or organolithium compounds with sulfonate esters.[9] Some novel routes have been exploited in recent years as well.[10] As for the oxidiation methods, although numerous types of oxidation have been reported,[7] convenient and environmentally benign methods for the oxidation of sulfides or sulfoxides are still required. Air is a green, safe and economical oxidant. Using air as the oxidant still remains a challenge in this field.

In contrast to the development of catalytic C–O and C–N bond-forming method,[11] there have been fewer investigations on transition metal-catalyzed C–S bond formation.[12] Also, the majority of these investigations have mainly focused on the Pd(0)- or Ni(0)-catalyzed synthesis of aryl sulfides. Herein, we report an efficient method for the synthesis of aryl methyl sulfones from aryl halides and DMSO *via* copper-catalyzed aerobic oxidation and the cleavage/formation of C–S bonds (Scheme 1). Various aryl methyl sulfones could be obtained in moderate to good yields. To our knowledge, it is the first example of using atmospheric oxygen as the oxidant and widely available DMSO as the sulfur resource to prepare aryl methyl sulfones.

With iodobenzene (**1a**) and DMSO (**2a**) as substrates, the reaction parameters (catalysts, bases, ligand, solvents and temperature) were first examined. The obtained results are listed in Table 1. Under the same conditions, the catalytic activity of Cu(I) compounds is much higher than that of Cu(II) compounds (Table 1, entries 6–10). Among the examined catalysts (Cu_2O, CuBr, CuI, $Cu(OAc)_2$ and CuO), Cu_2O exhibits the best result and the isolated yield of phenyl methyl sulfone (**3a**) could reach 92% (Table 1, entry 6). With Cu_2O as the catalyst, some inorganic and organic bases ($K_3PO_4{\cdot}3H_2O$, K_2CO_3, Cs_2CO_3, KOH, DBU and *t*-BuOK) were further screened. The strong base KOH, especially *t*-BuOK, gave very good results (Table 1, entries 5 and 6), while weak bases $K_3PO_4{\cdot}3H_2O$, Cs_2CO_3 and DBU afforded quite poor ones (Table 1, entries 1, 3 and 4). Additionally, with K_2CO_3 as the base, or in the absence of the catalyst, strong base and ligand, no target product was obtained (Table 1, entries 2 and 13–15). These results clearly indicate that the catalyst, strong base and ligand are necessary for this transformation. Using $Cu(AcAc)_2$ (Cu(II) acetylacetonate) as the catalyst, **3a** was also obtained in 29% yield even without adding acetylacetone (Table 1, entry 20). If 1 equiv. of acetylacetone was added, the yield did not obviously change (Table 1, entry 21), indicating that acetylacetone only acts as the ligand (for details of ligands screening, see Supporting Information†). In addition, reaction temperature,

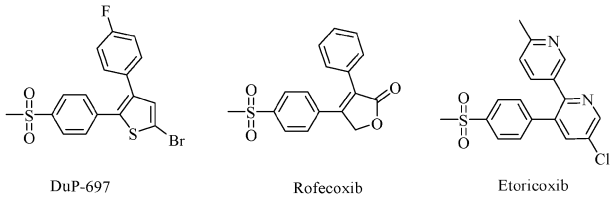

Fig. 1 Aryl methyl sulfones that are inhibitors.

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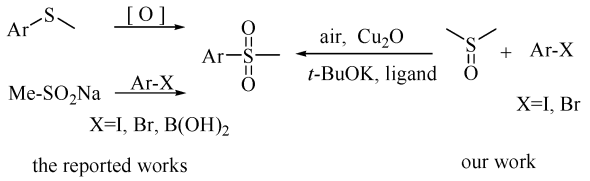
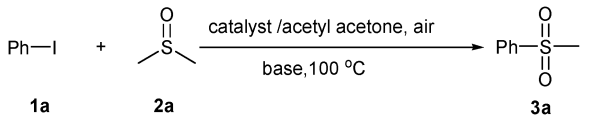
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds. See DOI: 10.1039/c2cc32964f



Scheme 1 Traditional methods *versus* our method.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	Cu_2O	$K_3PO_4·3H_2O$	DMSO	20
2	Cu_2O	K_2CO_3	DMSO	NR
3	Cu_2O	Cs_2CO_3	DMSO	<5
4	Cu_2O	DBU	DMSO	10
5	Cu_2O	KOH	DMSO	85
6	**Cu_2O**	***t*-BuOK**	**DMSO**	**96**
7	CuBr	*t*-BuOK	DMSO	86
8	CuI	*t*-BuOK	DMSO	82
9	$Cu(OAc)_2$	*t*-BuOK	DMSO	40
10	CuO	*t*-BuOK	DMSO	48
11	Cu_2O	*t*-BuOK	DMSO	40[c]
12	Cu_2O	*t*-BuOK	DMSO	70[d]
13	none	*t*-BuOK	DMSO	NR
14	Cu_2O	None	DMSO	NR
15	Cu_2O	*t*-BuOK	DMSO	NR[e]
16	Cu_2O	*t*-BuOK	DMSO : THF	83[f]
17	Cu_2O	*t*-BuOK	DMF	trace[g]
18	Cu_2O	*t*-BuOK	nitroethane	trace[h]
19	Cu_2O	*t*-BuOK	nitroethane	17[i]
20	$Cu(AcAc)_2$	*t*-BuOK	DMSO	29[e]
21	$Cu(AcAc)_2$	*t*-BuOK	DMSO	34
22	Cu_2O	*t*-BuOK	DMSO	NR[j]
23	CuO	*t*-BuOK	DMSO	NR[j]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 mL), ligand acetylacetone (1 equiv.), base (3 equiv.), catalyst (10 mol%) at 100 °C for 20 h. [b] Determined by GC. [c] For 10 h. [d] At 120 °C. [e] Without ligand. [f] Mix-solvent (2 mL, volume ratio 1 : 3). [g] DMSO (1 equiv.). [h] DMSO (1 equiv.). [i] DMSO (10 equiv.). [j] Under nitrogen atmosphere.

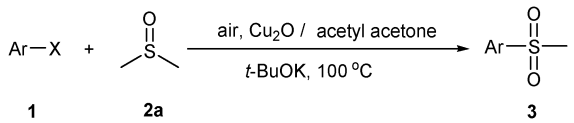
time and solvents have a significant effect on the yield of **3a**. For example, when the temperature was raised from 100 °C to 120 °C, the yield was decreased from 96% to 70% (Table 1, entries 6 and 12). Shortening the reaction time to 10 h led to only 40% yield (Table 1, entry 11). If the reaction was performed with pure DMF or nitroethane (2 mL) as the solvent and 1 equiv. of DMSO as the substrate, only a trace amount of **3a** was observed (Table 1, entries 17 and 18). Even with 10 equiv. of DMSO, the yield of **3a** was still very low (17%, Table 1, entry 19). Only when DMSO served as a substrate as well as the solvent could **3a** be obtained in high yields (Table 1, entries 6 and 16). Moreover, it is worth noting that **3a** was not formed at all if the reaction was conducted under a nitrogen atmosphere, even in the presence of Cu_2O (or CuO), *t*-BuOK, acetylacetone and DMSO as the solvent (Table 1, entries 22 and 23). Based on the catalytic results of Cu(I) and Cu(II) (Table 1, entries 6, 10, 22 and 23), it could be ruled out that the atmospheric oxygen is just needed to oxidize the catalytic amount of Cu(I) into Cu(II). It seems that the Cu-catalyzed aerobic oxidation is probably one of key steps for the formation of **3a**.

Under the optimized reaction conditions, we further studied the scope of the reaction with respect to aryl iodides and the results are summarized in Table 2. Aryl iodide derivatives bearing either an electron-withdrawing or electron-donating group reacted smoothly with **2a** to afford the corresponding products in moderate to high yields. Generally, substrates with electron-withdrawing groups were more reactive than those with electron-donating groups (Table 2, entries 2–11). Steric hindrance on the phenyl ring of aryl iodides has a significant influence on the transformation. For instance, **3c** could be obtained in 71% yield, while the yield of **3e** was only 43% (Table 2, entries 3 *vs.* 5). It is noteworthy that the iodobenzene derivatives with the *p*-acetyl- or chloro groups could also be successfully transformed into the corresponding target products (Table 2, entries 6 and 9). The results favor to broaden the application of the present method.

The reaction of aryl bromides with **2a** was further investigated. It was found that aryl bromides were also able to react with **2a** at 120 °C, affording the corresponding sulfones in moderate to good yields (Table 2, entries 15–20). In particular, the *beta*-bromostyrene, which has sp^2 C–Br bond, could also be converted into the desired product, although a higher reaction temperature and longer reaction time were required (Table 2, entry 20). Unlike other copper-catalyzed methodologies for the synthesis of aryl sulfones from sulfinic acid salts and aryl iodides, the present method could well achieve the conversion of aryl bromides.

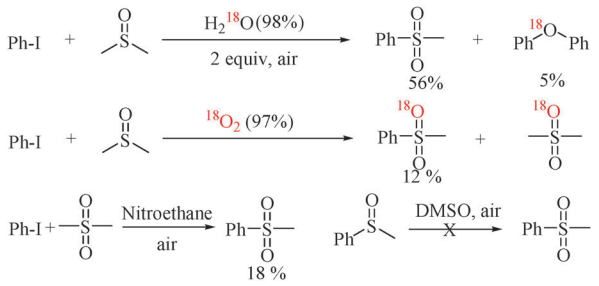
In order to probe the reaction mechanism, the isotopic labeling experiments with $H_2{}^{18}O$ and $^{18}O_2$ were performed (Scheme 2, for details of isotopic labeling experiments, see SI). The isotopic labeling studies demonstrated clearly that the additional oxygen atom of **3a** originated from molecular O_2

Table 2 Reactions of **2a** with various aryl halides[a]



Entry	Ar	X	1	3	Yield[b] (%)
1	Ar = Ph	**I**	**1a**	**3a**	92
2	Ar = *p*-MeO–C_6H_4	**I**	**1b**	**3b**	53
3	Ar = *p*-Me–C_6H_4	**I**	**1c**	**3c**	71
4	Ar = *m*-Me–C_6H_4	**I**	**1d**	**3d**	46
5	Ar = *o*-Me–C_6H_4	**I**	**1e**	**3e**	43
6	Ar = *p*-Acetyl–C_6H_4	**I**	**1f**	**3f**	52
7	Ar = *m*-F–C_6H_4	**I**	**1g**	**3g**	85
8	Ar = *p*-F–C_6H_4	**I**	**1h**	**3h**	95
9	Ar = *p*-Cl–C_6H_4	**I**	**1i**	**3i**	73
10	Ar = *p*-NO_2–C_6H_4	**I**	**1j**	**3j**	78
11	Ar = *o*-NO_2–C_6H_4	**I**	**1k**	**3k**	72
12	Ar = *o*-Et–C_6H_4	**I**	**1l**	**3l**	40
13	Ar = *p*-Et–C_6H_4	**I**	**1m**	**3m**	58
14	Ar = *p*-Ph–C_6H_4	**I**	**1n**	**3n**	67
15	Ar = Ph	**Br**	**1o**	**3a**	92
16	Ar = *p*-Et–C_6H_4	**Br**	**1p**	**3m**	65
17	Ar = 3,5-dimethyl–C_6H_3	**Br**	**1q**	**3o**	62
18	Ar = *p*-F–C_6H_4	**Br**	**1r**	**3h**	68
19	Ar = *p*-Cl–C_6H_4	**Br**	**1s**	**3i**	52
20	Ar = (*E*)-C_6H_4–CH=CH	**Br**	**1s**	**3p**	50[c]

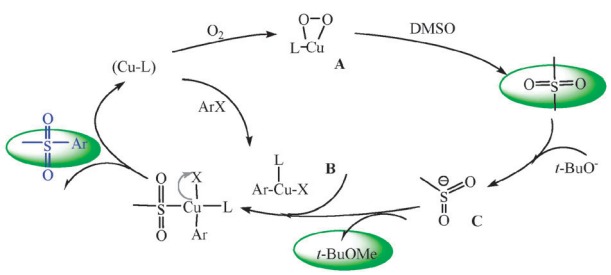
[a] Reaction conditions: as shown in Table 1, entries 15–20 at 120 °C. [b] Isolated yield. [c] At 130 °C for 36 h.



Scheme 2 Preliminary mechanistic studies.

instead of H_2O. Namely, the aerobic oxidation leads to the S=O bond formation of aryl methyl sulfones. Furthermore, under the standard conditions, it was found that the reaction of dimethyl sulfone with iodobenzene (**1a**) could afford the target product **3a** in 18% yield, while phenyl methyl sulfoxide could not be converted into **3a** at all (Scheme 2). In addition, we observed that aryl methyl sulfones were always formed together with dimethyl sulfone, but without aryl methyl sulfoxide in all of the synthetic experiments. Thus, we deduce that the formation of aryl methyl sulfones may undergo the oxidation of DMSO to dimethyl sulfone and the coupling reaction of dimethyl sulfone with Ar–X (*i.e.*, $MeSOMe + O_2 \rightarrow MeSO_2Me$, $Ar–X + MeSO_2Me \rightarrow ArSO_2Me$). In order to better understand the reaction mechanism, we separately examined the effect of the catalyst, ligand and base on the both processes. The results indicate that the oxidation process only needs the catalyst and ligand, while the base *t*-BuOK is necessary for the coupling reaction besides the catalyst and ligand (see ESI, Tables 2 and 3). In the synthetic experiment of **3a**, the by-product *t*-BuOMe was detected by GC-MS, but not EtSOMe. The *t*-BuO^- probably as the nucleophile plays a key role in the cleavage of the C–S bond. Based on the experimental results, a possible reaction mechanism was proposed in Scheme 3. O_2 and Ar–X are first activated by the ligand-catalyst to form intermediates **A** and **B**, respectively.[13,14] Then, the activated O_2 can oxidize DMSO to dimethyl sulfone. Under the nucleophilic attack of the *t*-BuO^-, the cleavage of the C–S bond of dimethyl sulfone generates reactive intermediate **C** (together with *t*-BuOMe), followed by the reaction with previously formed intermediate **B** to afford the desired aryl methyl sulfone with the release of the ligand-catalyst and X^- ions. The detailed mechanism needs to be studied further.

In conclusion, we have developed a novel method for the synthesis of aryl methyl sulfones from aryl halides and DMSO. The copper-catalyzed aerobic oxidation and the cleavage/formation of C–S bond play an important role in the formation of aryl methyl sulfones. Using the air, instead of toxic or expensive compounds, as the oxidant and Cu_2O as the catalyst mean the present synthetic route shows a potential application in organic and pharmaceutical synthesis.



Scheme 3 A plausible reaction mechanism.

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