ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 4582

Received 21st February 2014,
Accepted 16th March 2014

DOI: 10.1039/c4cc01353k

www.rsc.org/chemcomm

Copper-mediated S–N formation *via* an oxygen-activated radical process: a new synthesis method for sulfonamides†

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Copper-mediated direct S–N formation using readily available starting materials *via* an oxygen-activated radical process has been developed. This method provides a novel and direct approach for synthesis of sulfonamides under air conditions.

Sulfonamides that possess a wide range of biological activities have been widely used in the pharmaceutical industry.[1] The traditional methods for the synthesis of sulfonamides principally involve (1) reaction of amines with sulfonyl chlorides or sulfonic esters;[2a] (2) coupling of *N*-unsubstituted/*N*-monosubstituted sulfonamides with amines or organohalides;[2b] and (3) oxidation of sulfenamides.[2c] Although these methods are available and can be used to easily build the S–N bond, they are limited by their not readily available reactants, multistep reactions, strong oxidants and toxic derivatives. Transition metal-catalyzed reaction is a new strategy for the synthesis of sulfonamides.[3] In 2010, Taniguchi *et al.*[4] developed a method for copper-catalyzed synthesis of sulfonamides from thiols and amines under an oxygen atmosphere. Recently, Jiang *et al.*[5] reported on copper-catalyzed sulfonamide formation using sodium sulfinates and amines under an oxygen balloon. Using oxygen as an oxidant is favorable for green chemistry. However, limited substrate scope and restricted reaction conditions hinder the widespread application of oxygen as an oxidant. Thus, developing an efficient and versatile strategy for the synthesis of sulfonamides is necessary.

Dimethyl formamide (DMF) is a polar solvent that has been used as a precursor for $-NMe_2$, $-CONMe_2$, and –Me groups.[6] Among these reaction units, the decarbonylation of DMF as a source of $-NMe_2$ has elicited the attention of chemists.[7] In 2009, Chang *et al.*[8] developed a silver-mediated amination of benzoxazoles with DMF. Meanwhile, Wan *et al.*[9] introduced DMF as the source of the aminyl radical in the synthesis of amides.

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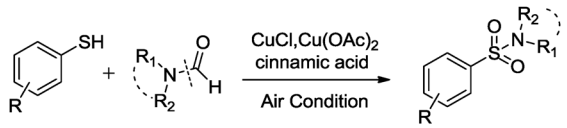
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc01353k



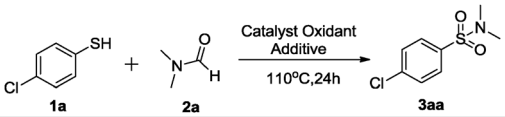
Scheme 1 Strategy for the synthesis of sulfonamides.

Based on increasing interest in thiols,[10] we report copper-mediated direct sulfonamide formation from thiols and formamides under air conditions (Scheme 1). To the best of our knowledge, this study is the first to use formamides as the N sources in the synthesis of sulfonamides.

4-Chlorothiophenol **1a** and DMF **2a** were used as the model substrates to optimize the reaction conditions. The results are summarized in Table 1.

The reaction was performed at 110 °C in the presence of CuCl (1 equiv.), $Cu(OAc)_2$ (1 equiv.) and benzoic acid (1 equiv.) (as an additive)

Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

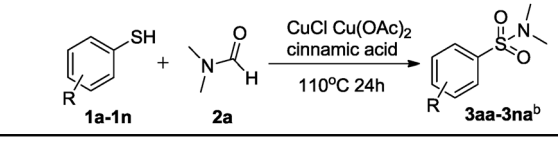
Entry	Copper salts (equiv.)	Oxidant (equiv.)	Additive (equiv.)	Yield[b] (%)
1	CuCl (1)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	81
2	CuI (1)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	15
3	CuBr (1)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	28
4	$CuCl_2$ (1)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	37
5	—	$Cu(OAc)_2$ (1)	Benzoic acid (1)	0
6	CuCl (2)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	78
7	CuCl (0.1)	$Cu(OAc)_2$ (1)	Benzoic acid (1)	Trace
8	CuCl (1)	$Cu(OAc)_2$ (1)	Cinnamic acid (1)	83
9	CuCl (1)	$Cu(OAc)_2$ (1)	L-Proline (1)	57
10	CuCl (1)	$Cu(OAc)_2$ (1)	L-Phenylalanine (1)	44
11	CuCl (1)	$Cu(OAc)_2$ (1)	CH_3COOH (2)	48
12	CuCl (1)	$Cu(OAc)_2$ (1)	H_2SO_4 (2)	37
13	CuCl (1)	$Cu(OAc)_2$ (1)	—	38

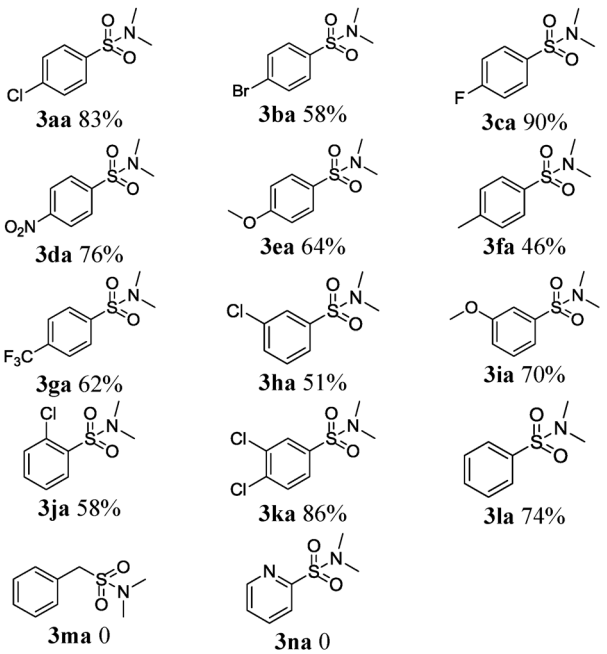
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 ml), copper salts, oxidant, additive under air conditions at 110 °C for 24 h. [b] Isolated yield.

under air conditions for 24 h. The desired product **3aa** was isolated in a yield of 81% (Table 1, entry 1). Then, different copper salts were introduced, among which CuCl showed the best activity (Table 1, entries 1–4). However, no desired product was obtained when no copper salt was added, implying that the Cu^{I} was necessary for the transformation (Table 1, entry 5). The amount of copper salt was also investigated, when 2 equiv. of CuCl was used, the yield slightly decreased to 78% (Table 1, entry 6). By contrast, only a trace amount of the product was obtained when 0.1 equiv. of CuCl was used (Table 1, entry 7). This result indicated that the stoichiometric amount of copper salt was essential for the fluent conversion. A series of additives was also examined (Table 1, entries 8 to 13). Only 38% yield of the product was obtained in the absence of acid (Table 1, entry 13), suggesting the importance of acid in the reaction. Cinnamic acid and benzoic acid proved to be better than other acids.[11] Moreover, $Cu(OAc)_2$ produced the best result among different oxidants.[12] The reaction time, temperature and solvent were also tested (see ESI,† Table S1). Thus, the optimal reaction conditions involved CuCl (1 equiv.)/$Cu(OAc)_2$ (1 equiv.)/cinnamic acid (1 equiv.) under air conditions.

With the optimal reaction conditions in hand, we then investigated the substrate scope of thiols. As shown in Table 2, the reaction proceeded smoothly with substrates containing electron-withdrawing groups and electron-donating groups in moderate to good yield (**3aa–3la**). In general, thiophenols bearing electron-donating groups produced lower yields. For example, when 4-methylthiophenol reacted with DMF under the optimal conditions, the isolated yield was 46% (**3fa**), whereas strong electron-withdrawing groups such as 4-CF_3 (**3ga**) and 4-NO_2 (**3da**) could produce products with yields of 62% and 76%, respectively. Halide groups (**3aa–3ca**, **3ka**) were all well tolerated and the corresponding products could be applied in further reactions. When 3,4-dichlorothiophenol was used, the desired product (**3ka**) was isolated in good yield. The steric effects had minimal influence on the transformation as confirmed by the higher yield facilitated by the 2-Cl substrate (**3ja**) than the 3-Cl substrate (**3ha**) (58% to 51%). However, neither the aliphatic thiol (**3ma**) nor the heterocyclic thiol (**3na**) was suitable for the smooth conversion. These results indicated that the aromatic groups were essential for the reaction.

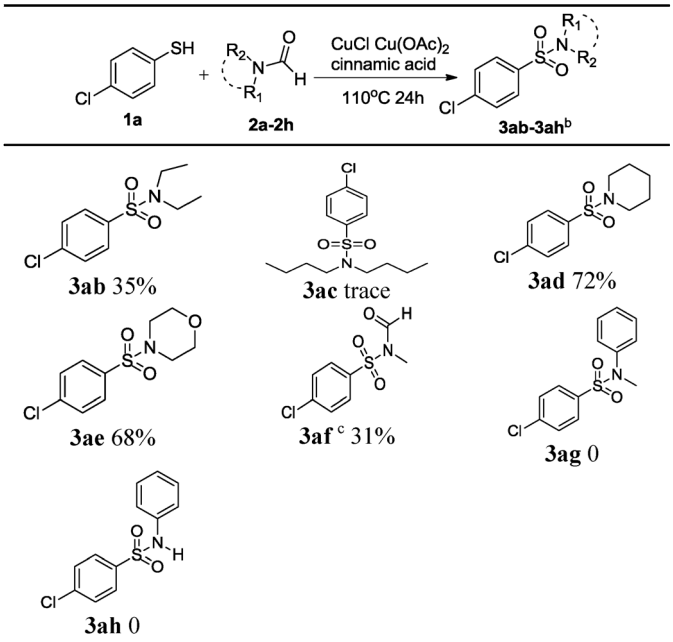
Table 2 Copper-mediated S–N formation by DMF and various thiols[a]





[a] Conditions: **1** (0.5 mmol), DMF (1.5 ml), CuCl (1 equiv.), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.) under air conditions at 110 °C for 24 h. [b] Isolated yield.

Table 3 Substrate scope of formamides with 4-chlorothiophenol[a]

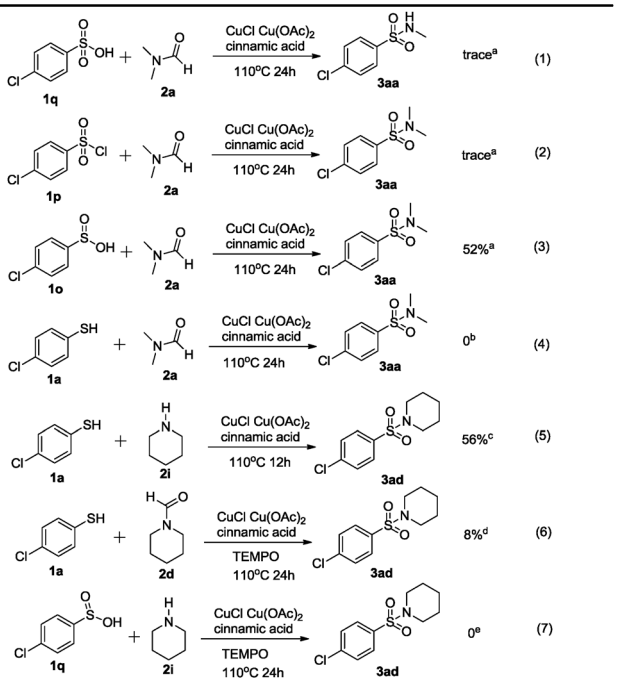


[a] Conditions: **1a** (0.5 mmol), **2** (1.5 ml), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.), CuCl (1 equiv.) under air conditions at 110 °C for 24 h. [b] Isolated yield. [c] **2f** (1 mmol), DMA (1.5 ml), 6 h.

A series of formamides was also examined to expand the synthetic utility of the protocol (Table 3). For *N*,*N*-disubstituted formamides, lower yields of products (**3aa** *vs.* **3ab** and **3ac**) were obtained as the carbon chain on the N atom increased. These results could be attributed to the larger steric hindrance on the N atom of formamides. Meanwhile, the formamides derived from cyclic amines produced higher yields (**3ad** and **3ae**) compared with those derived from linear amines. However, no desired product was obtained for the *N*-monosubstituted formamides. In addition, **3af** was isolated when *N*-methyl formamide reacted with **1a** through a dehydrogenation process. Besides, *N*-methylformanilide (**3ag**) and formanilide (**3ah**) did not provide good results. This finding could be attributed to the strong conjugation between the amide group and the phenyl ring that inhibited the decarbonylation of formamides.[9]

To gain further insights into the mechanism, a series of control experiments was carried out. The results are shown in Table 4. Only a trace amount of **3aa** was detected when 4-chlorobenzenesulfonic acid and 4-chlorobenzenesulfonyl chloride reacted with DMF under

Table 4 Investigation into the mechanism of reaction

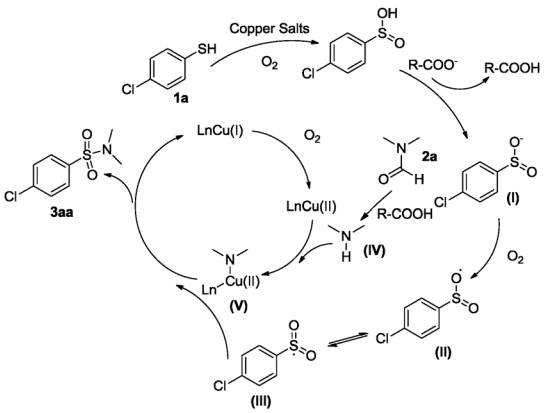


[a] Conditions: **1** (0.5 mmol), **2a** (1.5 ml), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.), CuCl (1 equiv.) under air conditions in 110 °C for 24 h. [b] Condition: under a N_2 atmosphere. [c] Conditions: **1a** (0.5 mmol), **2i** (1 mmol), DMA (1.5 ml), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.), CuCl (1 equiv.) under air conditions in 110 °C for 12 h. [d] Conditions: **1a** (0.5 mmol), **2d** (1.5 ml), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.), CuCl (1 equiv.), TEMPO (1.5 equiv.) under air conditions in 110 °C for 24 h. [e] Conditions: **1q** (0.5 mmol), **2i** (1 mmol), DMA (1.5 ml), $Cu(OAc)_2$ (1 equiv.), cinnamic acid (1 equiv.), CuCl (1 equiv.), TEMPO (1.5 equiv.) under air conditions at 110 °C for 24 h. Isolated yield.

the optimal conditions (Table 4, eqn (1) and (2)). However, the desired product produced a yield of 52% when 4-chlorobenzenesulfinic acid was used as the reactant (Table 4, eqn (3)). No desired product was detected when we changed the reaction atmosphere from air to nitrogen (Table 4, eqn (4)). These results suggested that benzenesulfinic acid may act as the intermediate formed by the oxidation of thiol under air conditions. Then, 56% yield of **3ad** was obtained when formamide was changed to amine (Table 4, eqn (5)). This result indicated that amine may be another intermediate obtained by the decarbonylation of formamide.

Furthermore, only a trace amount of the product was detected in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (Table 4, eqn (6) and (7)). This result implied that a radical step was involved in the reaction.

A plausible mechanism deduced according to the results above and recent publications[5,13] is presented in Scheme 2. First, thiol (**1a**) was oxidized to sulfinic acid with copper salts under air conditions, which was then transformed into the sulfinyl anion (**I**). The sulfinyl anion (**I**) was activated by oxygen *via* single electron transfer, providing an oxygen-centered radical (**II**) that could resonate with the sulfonyl radical (**III**). Meanwhile, Cu^{I} was oxidized to form Cu^{II} species by oxygen. Formamide (**2a**) was decarbonylated by the acid to form amine (**IV**), which could then coordinate with Cu^{II} species to form intermediate (**V**). Finally, the copper complex



Scheme 2 Proposed reaction mechanism.

(**V**) coupled with the sulfonyl radical (**III**) to generate the desired product **3aa** with the release of Cu^{I}.

In summary, we developed copper-mediated direct S–N bond formation from thiols and formamides. This protocol provides a novel and direct synthesis of sulfonamides from readily available starting materials *via* an oxygen-activated radical process. Further studies on the mechanism and related work are ongoing in our group.

The authors gratefully acknowledge financial support from the National Science Foundation of China (21025207).

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