Organic LETTERS

Letter

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Synthesis of α,α-Disulfenylated Aldehydes via Oxidative Transformation of Tertiary Amines

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Supporting Information

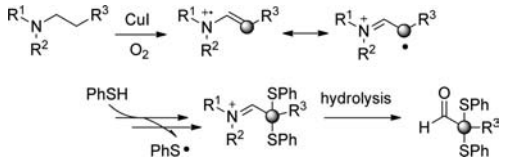
ABSTRACT: A method for the copper-catalyzed regioselective β-functionalization of tertiary amines with thiophenols has been developed. The control experiments and primary studies show that a thiyl radical is involved in the reaction, and the method provides a novel and direct approach to synthesize C(sp^3)−S bonds without a directing group under ligand-free conditions.

Tertiary amine derivatives are widespread in natural products and are therefore important in the pharmaceutical industry. The functionalization of tertiary amines has become an enduring challenge that attracts much interest from organic chemists. The direct α-functionalization of tertiary amines was developed as an efficient and conventional way to synthesize tertiary amine derivatives.[1] To synthesize α-functionalized tertiary amines, well-accepted methods involved either the formation of iminium intermediates oxidized by various oxidants or the activation of the C−H bond adjacent to an N atom by transition metals.[2] More recently, a method utilizing α-amino radical intermediates formed through single-electron transfer by photoredox catalysts was developed for this transformation.[3]

Compared to the extensive studies of the α-position of tertiary amines, β-functionalized tertiary amines are mostly limited by their relatively inert C−H bonds. To date, three major approaches to synthesize β-functionalized tertiary amines have been developed: (1) transition-metal-catalyzed selective β-position functionalization using ligand control or four-membered-ring cyclometalation complexes;[4] (2) nuclephilic enamines used as starting materials or key intermediates followed by reactions with appropriate electrophiles;[5] and (3) the novel enamine cation radical generated by CAN oxidants or photoredox catalysts as a novel synthetic pathway.[6] Recently, the Seidel group reported a redox-neutral strategy for amine β-functionalization under metal-free conditions.[7] These methods are efficient and useful for the β-functionalization of tertiary amines, but in most cases, access to the compounds requires multiple steps and indirect pathways. Furthermore, precious transition-metal catalysts such as palladium or ruthenium are often required. Therefore, the direct, convenient, and selective transformation of aliphatic C−H bonds remains a challenge. Based on recent studies on C(sp^3)−S coupling[8] and our interest in thiophenols,[9] we report a copper-catalyzed direct and selective β-sulfenylation of aliphatic tertiary amines through a radical pathway to obtain α,α-disulfenylated aldehydes that have emerged as versatile reagents in cyclization reactions (Scheme 1).[10,11]

Our initial intention was to oxidize 4-chlorothiophenol (**1a**) to the corresponding sulfinic acid with a copper salt in air in the presence of a tertiary amine. This could be achieved in low yield

Scheme 1. Radical Pathway for the Synthesis of β-Functionalized Tertiary Amines



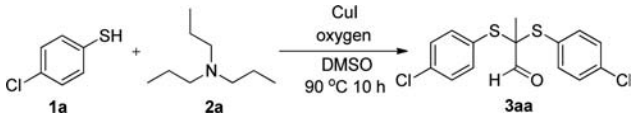
with pyridine as base. To our surprise, treatment of **1a** with copper(I) iodide in DMSO in air at 90 °C afforded 2,2-bis[(4-chlorophenyl)thio]propanal (**3aa**) in 61% yield (Table 1, entry 1). To confirm the structure of **3aa**, single-crystal X-ray analysis was performed (see the Supporting Information). A series of experiments were then examined to optimize the reaction conditions, as shown in Table 1.

First, different catalysts were tested; copper catalysts showed catalytic activities for the reaction (Table 1, entries 1−4), and CuI was found to be the most efficient, whereas iron catalysts or no catalyst could not afford the desired product (Table 1, entries 5 and 6). Using a 20 mol % amount of catalyst resulted in 34% yield (Table 1, entry 8), and increasing the amount of catalyst resulted in a slightly higher 63% yield (Table 1, entry 9). Next, we investigated the influence of solvent; most solvents such as toluene and CH_3CN were not effective at producing high yields for this reaction (Table 1, entries 10−14), and DMF was the only solvent that could produce the desired product (Table 1, entry 15). Peroxide oxidants were unsuitable for the reaction (Table 1, entries 16 and 17), and the nitrogen-protected experiment resulted in no product formation, which indicates that oxygen is essential for the oxidation (Table 1, entry 7). Thus, we performed the reaction in an oxygen atmosphere, and the product was isolated in a higher yield (Table 1, entry 18). Moreover, other factors such as temperature, reaction time, and additive were also investigated (see the Supporting Information). Therefore, the optimal reaction conditions involved treatment of thiophenol (**1**) with tertiary amine (**2**) in a 1:2 ratio in DMSO at

Received: October 4, 2015
Published: October 12, 2015

DOI: 10.1021/acs.orglett.5b02876
Org. Lett. 2015, 17, 5488−5491

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst[b]	oxidant	solvent	yield[c] (%)
1	CuI	air	DMSO	61
2	CuCl	air	DMSO	52
3	CuBr	air	DMSO	55
4	$CuCl_2$	air	DMSO	49
5	$FeCl_2$	air	DMSO	NR
6		air	DMSO	NR
7[d]	CuI	air	DMSO	NR
8[e]	CuI	air	DMSO	34
9[f]	CuI	air	DMSO	63
10	CuI	air	CH_3CN	trace
11	CuI	air	toluene	NR
12	CuI	air	dioxane	NR
13	CuI	air	H_2O	NR
14	CuI	air	THF	NR
15	CuI	air	DMF	55
16	CuI	TBHP	DMSO	NR
17	CuI	H_2O_2	DMSO	NR
18	**CuI**	**O_2**	**DMSO**	**72**

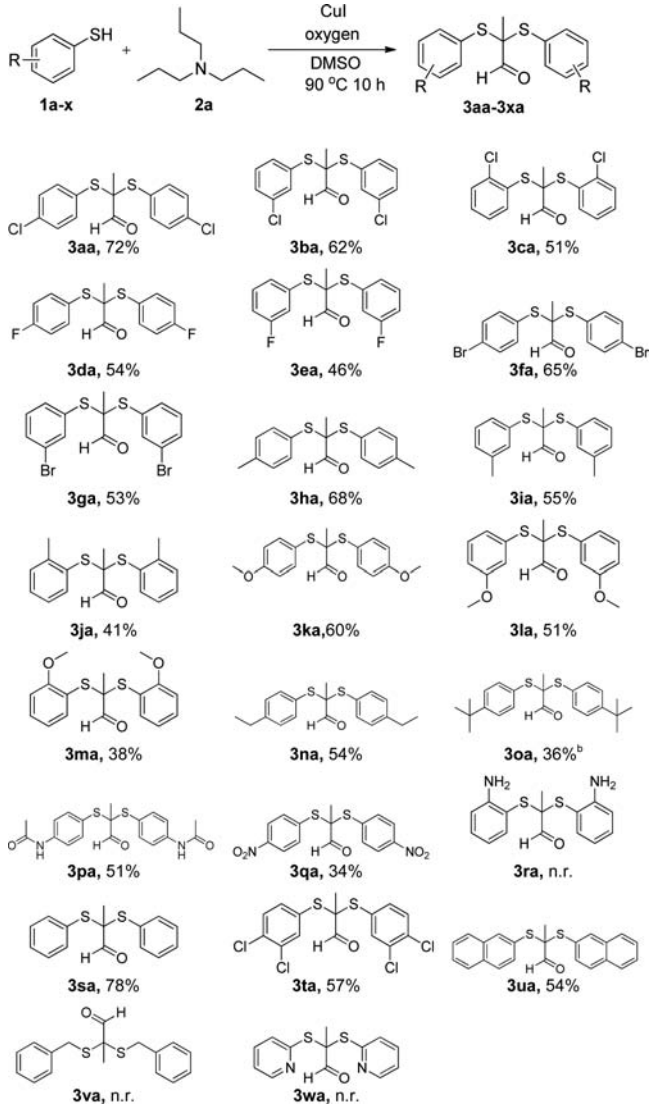
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (50 mol %), and solvent (1.5 mL) under air atmosphere at 90 °C for 10 h. [b]Other Cu(II) salts are reported in the Supporting Information. [c]Isolated yields. [d]Under N_2 atmosphere. [e]20 mol % of CuI was used. [f]100 mol % of CuI was used.

90 °C and catalyst by CuI (50 mol %) in an oxygen atmosphere for 10 h.

With the optimal reaction conditions determined, we then investigated the substrate scope of thiophenol (**1**) with tripropylamine (**2a**) as shown in Scheme 2. Both electron-donating and electron-withdrawing substituents were well-tolerated to produce aldehydes in moderate to good yields. For the strong electron-withdrawing group, 4-NO_2, the desired product was isolated in 34% yield (**3qa**). Notably, steric hindrance had a strong effect on the reaction. For example, for the methoxy-substituted thiols, the yields of the corresponding aldehydes decreased significantly as substitution changed from *para* to *meta* to *ortho* (**3ka**, **3la**, **3ma**). Similar reactivity patterns of chloro-substituted thiols were also observed (**3aa**, **3ba**, **3ca**). Furthermore, when the thiophenol (**3sa**) wa used directly, the product was isolated in a higher yield than when reactants containing substituents were used. Moreover, the halide substituents (Br, Cl, F) including *para*, *meta*, and *ortho* derivatives were all accessible to allow for the formation of the corresponding aldehydes, which could then be applied to further reactions. To our delight, the disubstituted thiophenols were also well-tolerated under these reaction conditions, and **3ta** was obtained in 57% yield. Moreover, naphthyl, benzyl, and heterocycle substituents were also examined (**3ua**, **3va**, **3wa**), and the results showed that the thionaphthol (**3ua**) was suitable for reaction under the conditions, whereas the benzyl (**3va**) and heterocycle (**3wa**) substituents did not lead to product formation. These results indicated that aromatic thiols are essential for the formation of the C−S bond.

Next, we examined the reactions of different tertiary amines with 4-chlorothiophenol (**1a**) as shown in Table 2. The results clearly showed that various aliphatic tertiary amines are suitable

Scheme 2. Substrate Scope of Thiophenol with Tripropylamine[a]

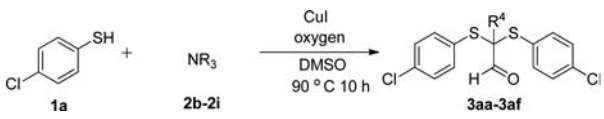


[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), CuI (50 mol %), and DMSO (1.5 mL) under oxygen balloon at 90 °C for 10 h. Isolated yields. [b]Reaction for 16 h.

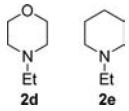
for the C−S coupling. Surprisingly, **3aa** was isolated in good yield when triallylamine (**2b**) instead of tripropylamine (**2a**) was used as a reactant. This result revealed that the saturated bond in the aliphatic tertiary amine might convert to an unsaturated bond during the reaction. When triethylamine (**2c**) was used as a short carbon chain, the desired product (**3ab**) was obtained in 75% yield, which is higher than the yield obtained when long carbon chains were used. Notably, the product **3ab** as the key reactant has been applied for the synthesis of *β*-lactams like thienamycin.[12] Moreover, we also chose amines with different R groups, such as *N*-ethylmorpholine (**2d**) and *N*-ethylpiperidine (**2e**), as reactants, and the product **3ab** was isolated in yields of 64% and 69%, respectively. This outcome indicates that the C−S bond was previously formed at the terminal *β*-position with less steric hindrance. We also tested other long-carbon-chain amines, and the yields of the aldehydes decreased as the carbon chain length increased on the tertiary amines (**3ac**, **3ad**, **3ae**). However, when a branched tertiary amine (**2i**) was

DOI: 10.1021/acs.orglett.5b02876
Org. Lett. 2015, 17, 5488−5491

Table 2. Substrate Scope of Tertiary Amines with 4-Chlorothiophenol[a]



entry	2, R	3, R^4	yield (%)
1	**2b**, allyl	**3aa**, Me	59
2[b]	**2c**, Et	**3ab**, H	75
3	**2d**, see below	**3ab**, H	64
4	**2e**, see below	**3ab**, H	69
5	**2f**, *n*-Bu	**3ac**, Et	54
6	**2g**, *n*-pentyl	**3ad**, *n*-Pr	43
7[c]	**2h**, *n*-hexyl	**3ae**, *n*-Bu	35
8	**2i**, isopentyl	**3af**, *i*-Pr	n.r.



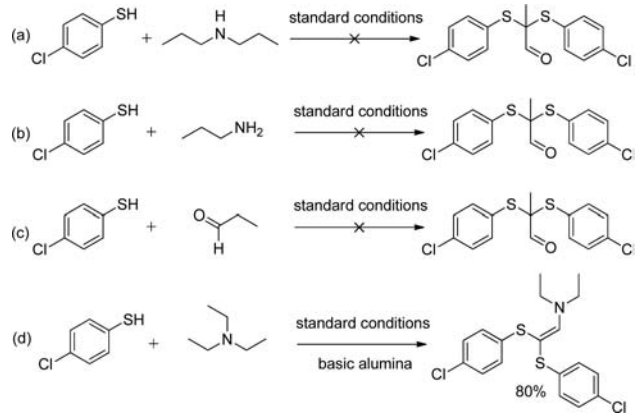
[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), CuI (50 mol %), and DMSO (1.5 mL) under oxygen balloon at 90 °C for 10 h, unless otherwise noted. Isolated yields. [b]Cooled to room temperature after the reaction, then added silica gel for 10 h. [c]Reaction for 16 h.

used, no desired product was obtained. These results indicated that steric hindrance greatly impacts this reaction.

To explore the reaction mechanism, radical-trapping experiments have been performed.[13] First, 2 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a radical inhibitor was added to the standard reaction conditions, and less than 10% yield of **3aa** was obtained. We isolated the TEMPO adduct with thiophenol in 27% yield. No desired product was isolated when 2 equiv of butylated hydroxytoluene (BHT) was used. The oxidation of the BHT product was obtained in 75% yield. From these results, we believe that a radical pathway is involved in the reaction process.

To gain insight into the reaction mechanism, a series of control experiments were performed as shown in Scheme 3. First, when

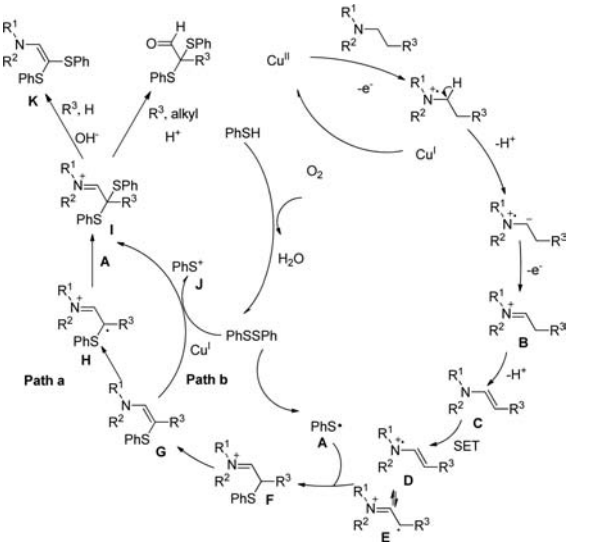
Scheme 3. Control Experiments To Determine the Reaction Mechanism



tertiary amines were replaced by the corresponding primary and secondary amine (Scheme 3a,b), the desired product was not obtained. These results indicate that tertiary amines are necessary for the reaction to proceed. According to previous reports,[14] copper–oxygen systems are efficient for the formation of aldehydes decomposed from tertiary amines, so we used propanal instead of tripropylamine as the source of aldehyde under standard conditions, but **3aa** was not detected (Scheme 3c). These results illustrate that the formation of the C–S bond occurred prior to the formation of the aldehyde. When the reaction between triethylamine and thiophenol was treated with basic alumina, the enamine product was isolated in good yield (Scheme 3d). On the basis of this result, it is likely that aldehydes are converted from enamines hydrolysis.

On the basis of the control experiments and previous reports[15] on the β-functionalized tertiary amines, a plausible mechanism is proposed in Scheme 4. Initially, the thiophenol is oxidized to a

Scheme 4. Proposed Mechanism



disulfide, which can produce the thiol radical **A** and thiol cation **J**. Moreover, the copper–oxygen species are used as single-electron-transfer agents, and imine intermediate **B** is formed from the tertiary amine. Enamine **C** is then generated after a deprotonation process. Next, the cationic radical species **D** and **E** are produced through single-electron transfers. Once the radical intermediates **A** and **E** are formed, a radical coupling reaction occurs to form the monosulfenylated ion **F**. After a deprotonation process, enamine intermediate **G** is produced. Two possible pathways are involved in the next stage. Path a proceeds via another radical process as follows: A different cationic radical species **H** is produced through single-electron transfer from **G**, and **H** coupling with thiol radical **A** generates the disulfenylated ion **I**. Path b is also reasonable because the disulfide could coordinate with Cu^I to generate thiol cation **J**.[16] Then, **J** acting as an electrophile could react with enamine intermediate **G** to form the disulfenylated ion **I**. Finally, the intermediate **I** is hydrolyzed to form the final aldehyde product under acidic conditions. It is worth noting that when the R^3 group is hydrogen, enamine product **K** is reasonably generated under alkaline conditions as confirmed in our control experiment.

In conclusion, we have developed a novel and efficient method for the synthesis of aldehyde derivatives using copper-catalyzed C(sp^3)–S coupling. This transformation shows the ideal β-selectivity of aliphatic tertiary amines under ligand- and additive-free conditions. Although aliphatic thiols are limited under the reaction system, various aromatic thiols and tertiary amines are suitable, and the corresponding aldehydes of potential value are isolated in moderate to good yields. Moreover, a series of control experiments and radical-trapping experiments confirm that a

DOI: 10.1021/acs.orglett.5b02876
Org. Lett. 2015, 17, 5488–5491

radical procedure is involved in the reaction process. Further mechanistic studies and determination of the application of this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02876.

X-ray data for **3aa** (CIF)

Experimental details, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21327010 and 21372199) for financial support.

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DOI: 10.1021/acs.orglett.5b02876
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