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Copper-Catalyzed Domino Synthesis of Sulfur-Containing Heterocycles Using Carbon Disulfide as a Building Block

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Abstract. In this paper, we describe the successful development of an efficient domino method for the synthesis of C-3 sulfenylated imidazo[1,2-*a*]pyridine derivatives applying carbon disulfide as a readily available, cheap and easy-to-handle building block. Most importantly, a single copper catalyst mediates two type reactions and three chemical bonds are formed in a one-pot organic transformation. The developed method provids an attractive alternative approach to various potentially bioactive sulfur-containing heterocycles, and will find broad applicability in organic synthesis and pharmaceutical chemistry.

Keywords: domino; heterocycle; sulfur; copper; carbon disulfide

Introduction

The replacement of multistep chemical transformations with domino reactions that strive for atom economy is having a significant impact on the synthesis of pharmaceutical intermediates and fine chemicals.[1] A quantum jump in efficiency can be achieved by using a single catalyst to conduct more than one chemical transformation in a single synthetic process. In recent years, there has been a growing interest in the field of transition-metal-catalyzed tandem processes for the formation of C-C and C-heteroatom bonds.[2] To date, copper-catalyzed Ullmann-type coupling reactions for the formation of C-N, C-O, and C-C bonds have been well explored and studied.[3] However, the methods available for C-S bond formation, especially in a domino process, are rather limited because of the propensity of thiols to undergo oxidative dimerization and their affinity for transition metals, resulting in a decrease in catalytic efficiency.[4] Additionally, when designing a sequential cascade reaction, it is often necessary to consider the compatibility of the catalyst with the residual materials (other catalysts, intermediates, additives and solvents) from the preceding steps.[5] Thus, it is challenging and highly desirable to develop efficient methods for the formation of C-S bonds in a one-pot organic transformation, using a single catalyst to mediate two or more reactions.[6]

2-Thio-substituted benzothiazoles are an important class of sulfur-containing compounds possessing various excellent medicinal and biological activities,[7] including heat shock protein-90 (HSP) inhibitor **A**,[8] Cathepsin-D inhibitor **B**,[9] avarol-3′-thiobenzothizole **C**,[10] and PPAR receptor activator **D**[11] (Fig. 1a). Consequently, the development of efficient approaches to 2-thio-substituted benzothiazoles continues to be one of the most attractive research areas in organic chemistry. Additionally, the imidazo[1,2-*a*]pyridine skeleton is the core unit of many biological molecules and commercially available drugs, such as **E** (zolpidem; used to treat insomnia),[12] **F** (minodronic acid; to treat osteoporosis),[13] **G** (olprinone; used to treat heart failure), **H** (zolimidin; used to treat peptic ulcer),[14] and **I** (GSK812397; a potent noncompetitive CXCR4 receptor antagonist)[15] (Fig. 1b). Recently, significant progress has been made in the discovery of efficient methods for the synthesis and functionalization of imidazo[1,2-*a*]pyridines.[16] We envisaged that combining the frameworks of 2-thio-substituted benzothiazoles and imidazo[1,2-*a*]pyridine might yield valuable substrates for the synthesis of biologically active compounds with different structural features from the two units separately (Fig. 1c). Therefore, we set out to

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synthesize this new kind of sulfur-containing heterocycle, which might possess medicinal and biological activity.

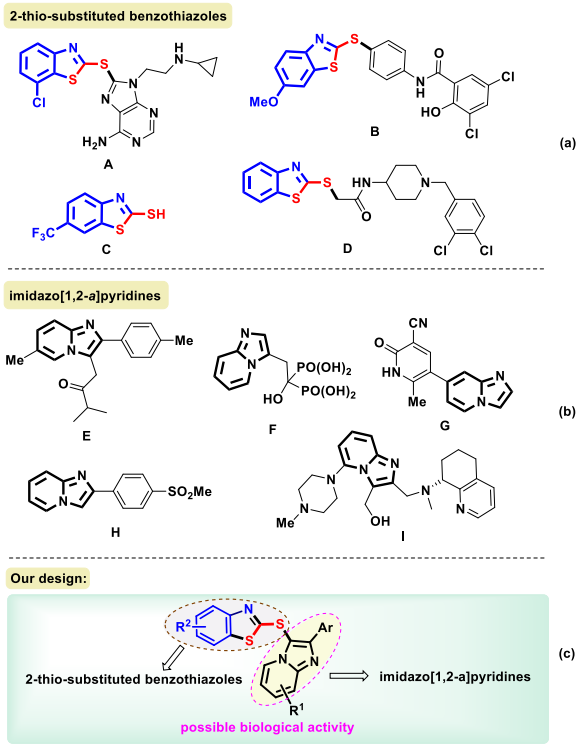


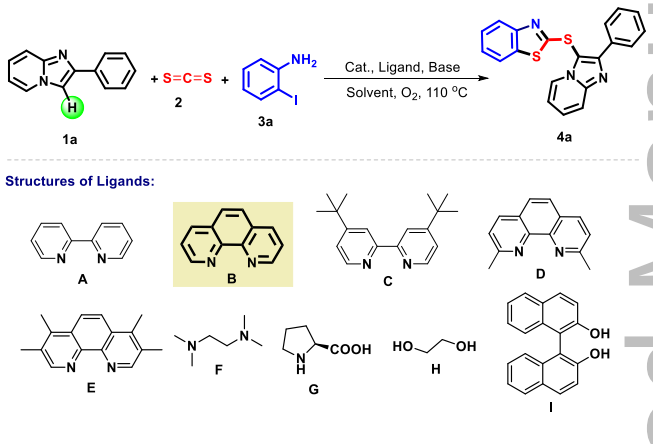
Figure 1. Bioactive molecules containing 2-thio-substituted benzothiazoles and imidazo[1,2-*a*]pyridine frameworks.

Carbon disulfide is an important and readily available chemical raw material, which has been widely used in the synthesis sulfur-containing compounds. However, using carbon disulfide in transition-metal-catalyzed C-S bond forming reactions is rare.[17] In 2011, the Ma group reported an elegant copper-catalyzed Ullmann-type reaction for the synthesis of 2-*N*-substituted benzothiazoles using carbon disulfide as a building block.[17b] In 2011, Xi's group developed a highly efficient method for the synthesis of 2-mercaptobenzothiazole derivatives via base-promoted tandem reaction of o-haloanilines and carbon disulfide.[17c] In 2013, Xi and co-workers also developed an efficient copper-catalyzed approach to diaryl thioethers using carbon disulfide as a cheap and sulfide surrogate.[17d] However, challenges still remain, and it is highly desirable to develop more efficient transition-metal-catalyzed strategies for the synthesis of sulfur-containing compounds using carbon disulfide as a building block.

In recent years, the direct functionalization of inert C–H bonds by copper complexes has emerged as an economical and environmentally friendly alternative to traditional palladium-catalyzed C-H activation, considering the abundance, low toxicity and cost efficiency of copper catalysts.[18] In 2006, Yu et al. reported pioneering work on the copper-mediated C-H thiolation of 2-phenylpyridine with thiols and disulfides.[18i] Since then, significant progress has been made in developing Csp2-H thiolation, since it affords a new strategy for the formation of C–S bonds.[19] However, strategies for the construction of C-S bonds via C-H bond functionalization in a one-pot transformation using a single catalyst to mediate two or more reactions have not been extensively studied.[20] On the other hand, as an inexpensive and low-toxic organic solvent, DMSO (dimethyl sulfoxide) has been widely used in synthetic organic chemistry, particularly as an oxidant in Kornblum oxidation,[21] Swern oxidation,[22] and formal C–H activation.[23] Arising from our ongoing research interest in the synthesis of sulfur-containing molecules,[24] herein we report a new copper-catalyzed domino method for the synthesis of sulfur-containing heterocycles using carbon disulfide as a readily available, cheap and easy-to-handle building block via Ullmann-type coupling and C-H functionalization.

Results and Discussion

Table 1. Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Base	Ligand	Yield [b] (%)
1	CuI	DMSO	K_2CO_3	None	46
2	CuI	DMSO	Cs_2CO_3	None	30
3	CuI	DMSO	DBU	None	52
4	CuI	DMSO	DBN	None	26
5	CuI	DMSO	Et_3N	None	Trace
6	CuI	DMSO	Pyridine	None	Trace
7	CuI	DMSO	DABCO	None	10
8	CuBr	DMSO	DBU	None	46
9	$CuCl_2$	DMSO	DBU	None	31
10	$Cu(OAc)_2$	DMSO	DBU	None	42
11	None	DMSO	DBU	None	N.D.
12	CuI	DMF	DBU	None	55
13	CuI	Toluene	DBU	None	Trace
14	CuI	NMP	DBU	None	9
15	CuI	DMSO	DBU	**A**	73
16	CuI	DMSO	DBU	**B**	79
17	CuI	DMSO	DBU	**C**	68
18	CuI	DMSO	DBU	**D**	52
19	CuI	DMSO	DBU	**E**	57
20	CuI	DMSO	DBU	**F**	32
21	CuI	DMSO	DBU	**G**	26

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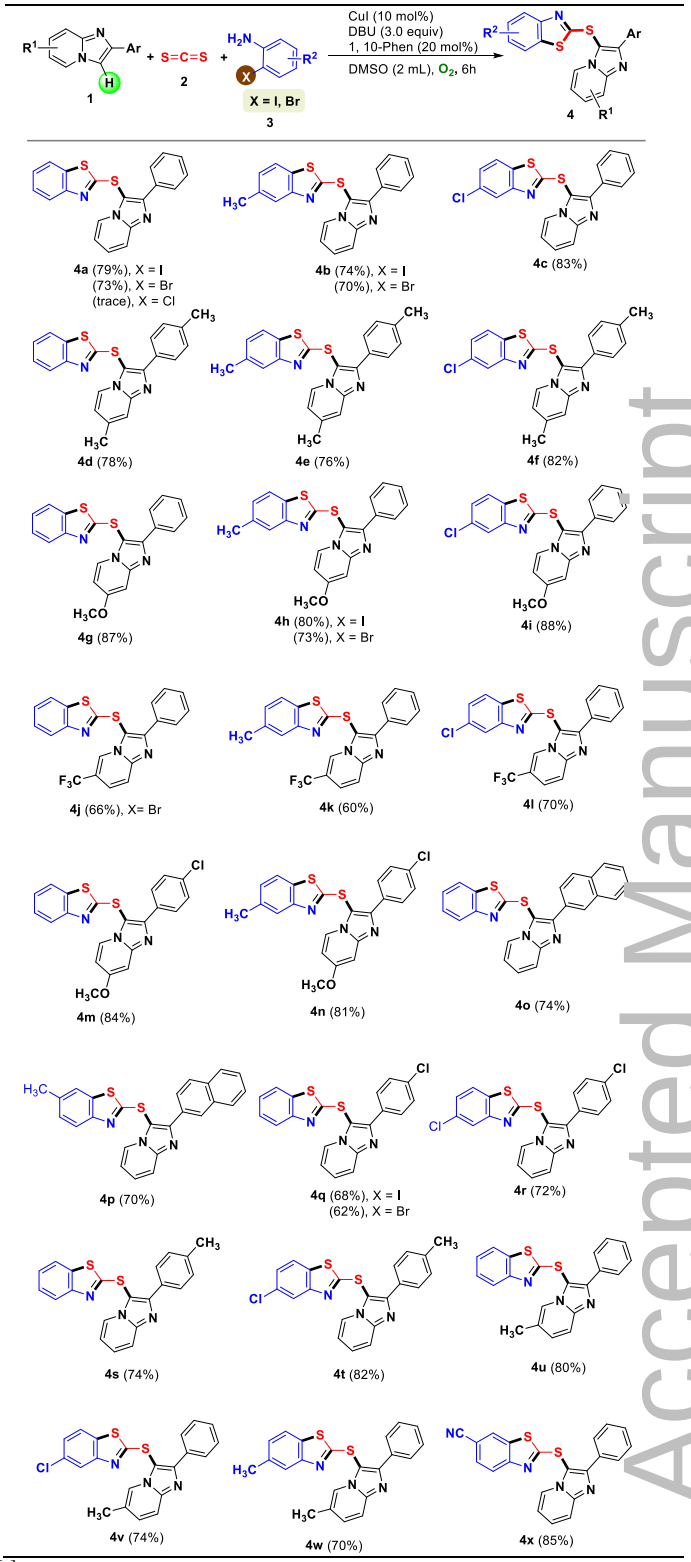
22	CuI	DMSO	DBU	**H**	42
23	CuI	DMSO	DBU	**I**	Trace
24	CuI	DMSO	DBU	**B**	79[c]
25	CuI	DMSO	DBU	**B**	74[d]
26	CuI	DMSO	DBU	**B**	7%[e]
27	CuI	DMSO	DBU	**B**	37%[f]

[a] Reaction conditions: Under oxygen atmosphere, **1a** (0.2mmol), **2** (0.6 mmol), **3** (0.3 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), base (0.6 mmol), solvent (2 mL), at 110°C for 6 h. N.D. = not detected.
[b] Isolated yield.
[c] At 120 °C.
[d] At 100 °C.
[e] Under N_2 atmosphere.
[f] Under air atmosphere.

Initially, 2-phenylimidazo[1,2-*a*]pyridine (**1a**), carbon disulfide (**2**), and 2-iodoaniline (**3a**) were chosen as the model substrates to optimize the reaction conditions, including the catalysts, solvents, bases, ligands, and the reaction temperature under O_2 atmosphere. As shown in Table 1, seven bases, including K_2CO_3, Cs_2CO_3, DBU, DBN, Et_3N, pyridine, and DABCO, were tested in DMSO in the presence of 0.1 equiv. of CuI at 110°C (entries 1-7), and DBU provided the highest yield of 52% (entry 3). We investigated various copper catalysts (compare entries 3, 8-10), and CuI was found to be the most effective (entry 3). It should be noted that no desired product was obtained without a copper catalyst (entry 11). Next, we screened various solvents, including toluene, DMF, NMP, and DMSO, and DMSO was found to be the best choice (compare entries 3, 12–14). Various ligands were investigated to further optimize the efficiency of this transformation, and 1,10-phen (1,10-phenanthroline) (**B**) showed the highest activity (compare entries 3, 15–23). Furthermore, different reaction temperatures were tested and the yield of the target product was maximized at 110°C (compare entries 3, 24, and 25). Finally, control experiments indicated that oxygen is crucial for this domino reaction (compare entries 16, 26–27).

Table 2. Copper-catalyzed domino synthesis of C-3 sulfenylated imidazo[1,2-*a*]pyridine derivatives[a],[b]



[a] Reaction conditions: Under oxygen atmosphere, imidazo[1,2-*a*]pyridines **1** (0.2 mmol), carbon disulfide **2** (0.6 mmol), *o*-haloanilides **3** (0.3 mmol), CuI (0.02 mmol), 1,10-Phen (0.04 mmol), DBU (0.6 mmol), DMSO (2 mL), at 110°C for 6 h. Unless otherwise noted, all products were obtained from *o*-iodoanilines.
[b] Isolated yield.

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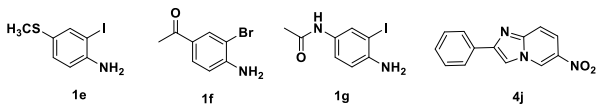
The scope of this copper-catalyzed domino synthesis of C-3 sulfenylated imidazo[1,2-a]pyridine derivatives from the reactions of substituted imidazo[1,2-*a*]pyridines (**1**) and carbon disulfide (**2**) with *o*-haloanilines (**3**) was investigated using optimized conditions (0.1 equiv of CuI as the catalyst, 0.02 equiv. of 1,10-phen as the ligand, 3 equiv. of DBU as the base in DMSO under oxygen atmosphere). To our delight, most of the substrates provided the corresponding products in moderate to good yields. The structure of the products were unambiguously confirmed by the single crystal X-ray diffraction study of compound (**4j**). Among the substituted *o*-haloanilides, *o*-iodoacetanilines showed slight higher reactivity compared to *o*-bromoaniline derivatives (**4a**, **4b**, **4h**, and **4q**). Unfortunately, *o*-chloroaniline was a poor substrate and only a trace amount of the product was obtained (**4a**). *o*-Haloanilides containing electron-withdrawing groups showed higher reactivity compared to ones containing electron-donating groups. Further investigation with respect to the substituent groups in imidazo[1,2-*a*]pyridines, the substrates bearing electron-withdrawing group such as chlorine and trifluoromethyl or electron-donating group such as methyl and methoxy were found to show no obvious difference in this transformation. In addition, the copper-catalyzed cascade transformations above were able to tolerate some functional groups such as C-Cl bonds, methyl groups, and ethers, affording opportunities for further modifications. However, other substituents such as NO_2, NHCOMe, COMe and SMe were not compatible in the present transformation, no desired products were obtained under the standard conditions, even at a high temperature (Scheme 1). Further exploration on the scopes and limits of the synthetic application are in progress. The structures of the products were unambiguously confirmed by the single crystal X-ray diffraction of compounds **4j** (Figure 2). [25]



Scheme 1. Unsuccessful substrates for the domino process.

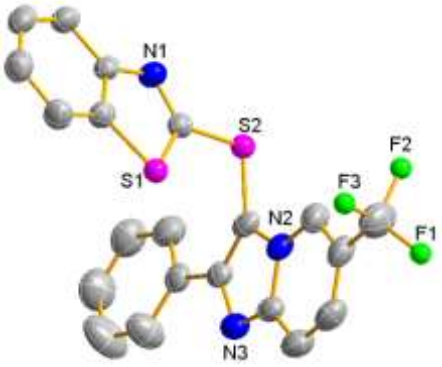


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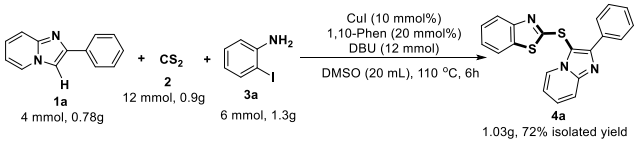
Figure 2. X-ray structure of **4j**.

Furthermore, we investigated whether gram-scale applications are feasible to the developed synthetic method. To our delight, the present reaction could afford 1.03 g of **4a** under the standard conditions, with no significant loss of it efficiency (Scheme 2).



Scheme 2. Synthesis of **4a** on a Gram Scale.

In order to gain more information about this copper-catalyzed domino reaction, several preliminary control experiments were carried out as shown in Scheme 2. When the reaction of **3a** with **2** was carried out under standard conditions, an 89% yield of 1,2-bis(benzo[*d*]thiazol-2-yl)disulfane (**6**) was obtained (Scheme 3a). Treatment of benzo[*d*]thiazole-2-thiol (**5**) under standard conditions afforded 1,2-bis(benzo[*d*]thiazol-2-yl)disulfane (**6**) in 93% yield (Scheme 3b). Notably, treatment of benzo[*d*]thiazole-2-thiol (**5**) with imidazo[1,2-*a*]pyridine (**1a**) under the standard conditions gave the desired product **4a** in 91% yield, which suggests that benzo[*d*]thiazole-2-thiol **5** might be a key intermediate in this transformation (Scheme 3c). However, treatment of 1,2-bis(benzo[*d*]thiazol-2-yl)disulfane (**6**) with imidazo[1,2-*a*]pyridine (**1a**) under the standard conditions only afforded the corresponding (**4a**) in 6% yield (Scheme 3d). These results indicates a competition reaction between 2-mercaptobenzothiazoles with imidazo[1,2-*a*]pyridines and 2-mercaptobenzothiazoles with itself. Also, when the reaction of (**5**) with (**1a**) in the absence of either CuI or oxygen resulted in no conversion (Scheme 3c and 3e) Treatment of **3a** with **2** in the absence of CuI under the standard conditions gave a messy TLC, and only a trace amount of **5** was detected, which indicates that CuI plays an indispensable role in this transformation (Scheme 3f).

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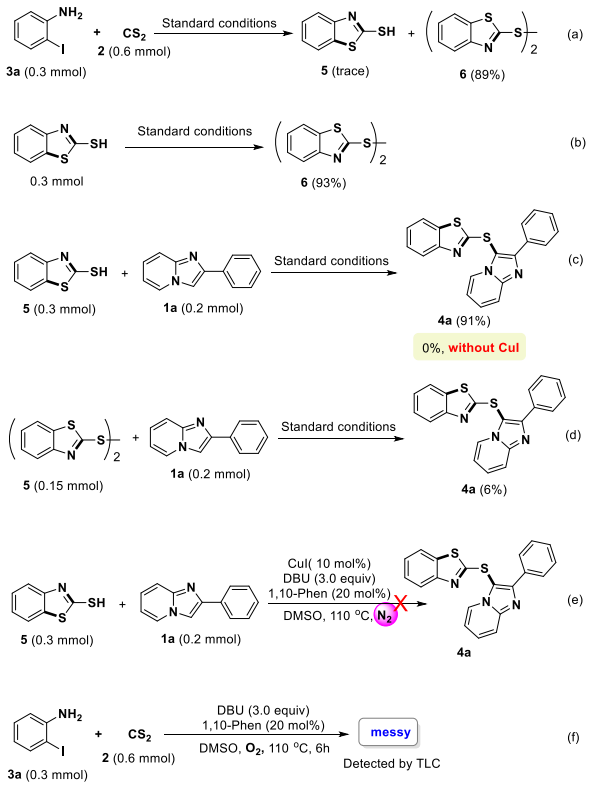
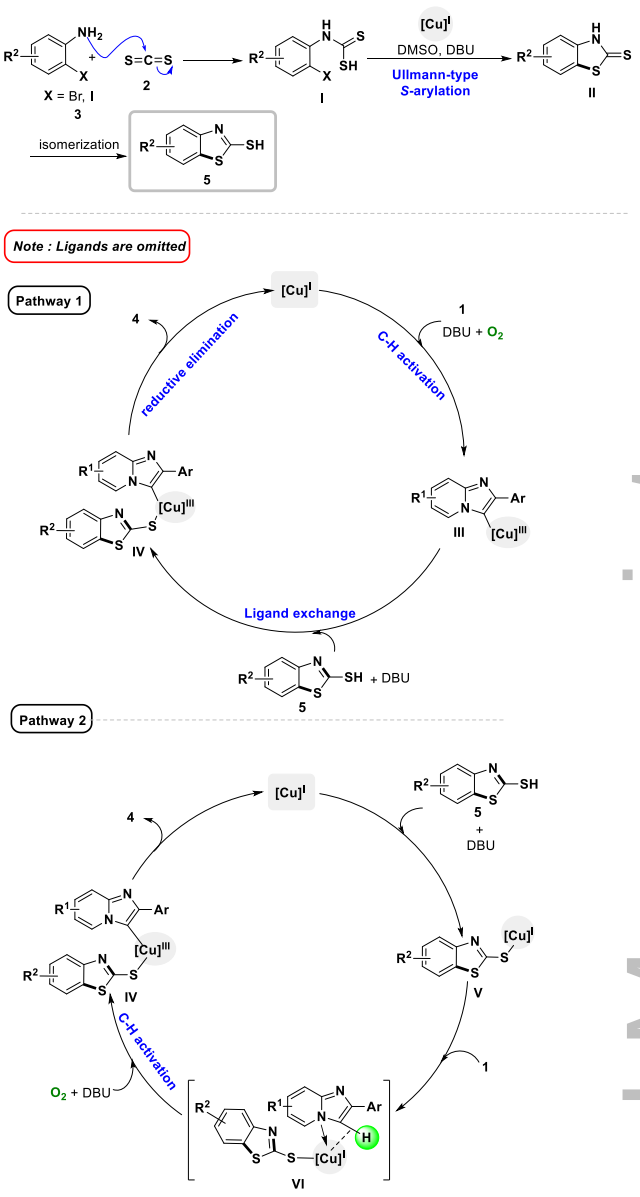


Scheme 3. Control experiments.

Based on the aforementioned preliminary experimental results and in accordance with previous reports[26] two plausible pathways for this present reaction are proposed (Scheme 4). Initially, nucleophilic addition of *o*-haloanilides with carbon disulfide (**2**) leads to *o*-halocarbamodithioic acid (**I**), which subsequently undergoes copper-catalyzed intramolecular *S*-arylation, affording (**II**). Isomerization of (**II**) forms intermediate (**5**). In pathway 1, the Cu-imidazo[1,2-*a*]pyridine complex (**III**) is initially formed through C-H activation. Subsequently, complex (**III**) reacts with **5** in the presence of DBU and ligand exchange gives another complex, **IV**. Finally, reductive elimination gives thr desired sulfenylated product **4**. In pathway 2, the Cu-thiolate complex (**V**) is initially generated in the presence of the copper catalyst and DBU. Treatment of complex (**V**) with the imidazo[1,2-*a*]pyridines (**1**) also gives the same intermediate (**IV**) with the assistance of DBU and O_2.



Scheme 4. Two possible mechanisms for the domino transformation

Conclusion

In summary, a copper-catalyzed tandem process has been initially developed for the formation of C-3 sulfenylated imidazo[1,2-*a*]pyridine derivatives using readily available, cheap and easy-to-handle carbon disulfide as a building block. Most attractively, in this process three chemical bonds were formed in a one-pot organic transformation using a single copper catalyst. We anticipate that this strategy will open a new avenue for the synthesis of sulfur-containing heterocycles and may also find broad applicability in pharmaceutical chemistry and synthetic organic chemistry. Further investigation of the detailed mechanism and the studies on the bioactivities of these compounds are ongoing in our laboratory.

Experimental Section

General procedure for the synthesis of compounds 4: A 25 ml Schlenk tube equipped with a magnetic stirring bar was charged with imidazo[1,2-*a*]pyridines **1** (0.2 mmol), *o*-haloanilides **3** (0.3 mmol), CuI (3.8 mg, 0.02 mmol), and 1,10-Phen (7.2 mg, 0.04 mmol). The tube was evacuated twice and backfilled with oxygen, then carbon disulfide **2** (36 μL, 0.6 mmol), and DBU (90 μL, 0.6 mmol) were added to the tube under an oxygen atmosphere. The tube was sealed with an oxygen balloon and then the mixture was allowed to stir at 110°C for 6 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The residue was purified with chromatography column on silica gel (gradient eluent of EtOAc/petroleum) ether to give the corresponding products **4**.

Acknowledgements

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FULL PAPER

Copper-Catalyzed Domino Synthesis of Sulfur-Containing Heterocycles Using Carbon Disulfide as a Building Block

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