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ARTICLE TYPE

Regioselective Copper-Catalyzed Thiolation of Imidazo[1,2-a]pyridines: An Efficient C−H Functionalization Strategy for C−S Bond Formation

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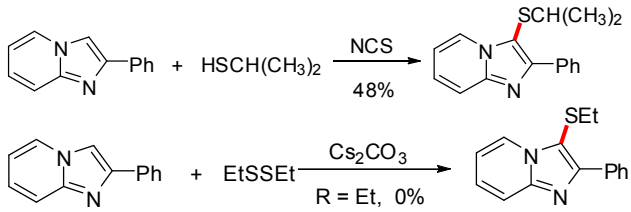
A highly regioselective C-H/S-H cross-coupling of imidazo[1,2-a]pyridines with thiols has been developed using molecular oxygen to form the C-3 sulfenated products in the presence of copper catalyst. It represents a simple process for the formation of C−S bonds to prepare thioether-decorated imidazo[1,2-a]pyridines. The reaction proceeds smoothly with a broad range of substrates to give imidazo[1,2-a]pyridines in good yields.

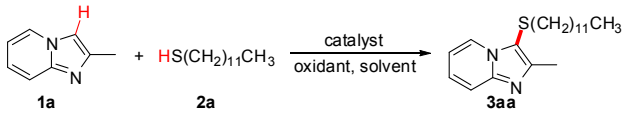
(Hetero)aryl thioether and their derivatives have been recognized as imperative building blocks for creating molecules of natural products, pharmaceutical interests, and functional materials.[1] Over the past decade, the formation of C-S bonds[2] to prepare (hetero)aryl thioether has emerged as a highly attractive and powerful strategy to construct complicated compounds. The traditional methods for the construction of (hetero)aryl thioether mainly involve condensation of thiols with aryl halides[3] and the reaction of aryl lithium or grignard reagents with sulfurated electrophiles.[4] However, these methods also faces some challenges: the transformation often requires harsh reaction conditions and the necessity to use prefunctionalized compounds, such as aryl halides, aryl lithium and Grignard reagents, thus adding steps and difficulties towards the formation of desired products. Hence, the development of a new process for the construction of (hetero)aryl thioether via direct C–H bond activation has drawn much attention in recent years. A number of transformation have been developed for the preparation of (hetero)aryl thioether via cross-coupling reactions using arenes,[5] such as benzene,[6] thiazoles,[7] imidazoheterocycles,[8] indoles,[9] azoles,[10] and 1,3,4-oxadiazoles.[11] Although several transformations have proven to be highly effective in such direct functionalization processes, the development of new transformation using molecular oxygen as oxidant [12] remains a significant challenge.

Recently, our group has reported metal-catalyzed C-H functionalization of imidazo[1,2-a]pyridine[13] which are known to exhibit interesting biological activities[14] and found to be key structural units in many pharmaceutically active compounds.[15] In this context, we hope to develop new catalytic transformations based on selective C-H functionalization of imidazo[1,2-a]pyridines to form C-S bonds. Indeed, this kind of C-S bonds formation has already been reported by Zhang etal. and Adimurthy et al. However, what is much less explored in the previous reaction systems is the reaction scope with aliphatic thiols. As a matter of fact, only one successful attempt with aliphatic thiol as a substrate was reported; and the reaction affords corresponding thioether with only 48% yield (Scheme 1). Hence, it is important to develop a new catalytic system that has a broader substrate scope. Herein, an efficient regioselective Cu(I) catalyzed C-H/S-H cross-coupling of imidazo[1,2-a]pyridines with (hetero)aryl and alkyl thiols to construct thioether-decorated imidazo[1,2-a]pyridines has been developed using molecular oxygen as the oxidant.



Scheme 1. Thiolation of Imidazo[1,2-a]pyridines

Table 1. Optimization of Reaction Conditions[a]

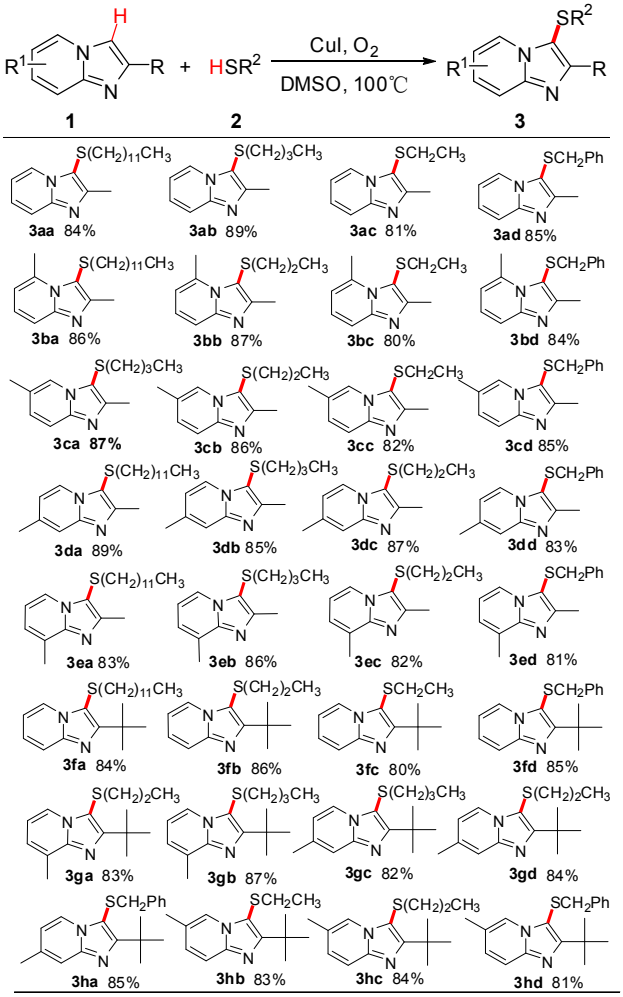


1a 2a 3aa

Entry	Catalyst	Oxidant	Solvent	T (□)	Yield(%)[b]
1	CuCl	TBHP	DMSO	100	61
2	CuBr	TBHP	DMSO	100	64
3	CuI	TBHP	DMSO	100	83
4	Cu_2O	TBHP	DMSO	100	40
5	CuCN	TBHP	DMSO	100	26
6[c]	CuI	O_2	DMSO	100	87(84)[d]
7	CuI	air	DMSO	100	53
8	CuI	$K_2S_2O_8$	DMSO	100	NP[e]
9	CuI	Oxone	DMSO	100	NP
10	CuI	BQ	DMSO	100	NP
11	CuI	O_2	DMF	100	86
12	CuI	O_2	Toluene	100	NP
13	CuI	O_2	dioxane	100	NP
14	CuI	O_2	DCE	100	NP
15	CuI	O_2	CH_3CN	100	NP
16	CuI	O_2	DMSO	120	82
17	CuI	O_2	DMSO	rt	NP

18	CuI	O_2	DMSO	80	71
19 [f]	-	O_2	DMSO	100	NP

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.2 mmol), catalyst (5 mol%), oxidant (1.0 mmol), solvent (3.0mL), rt-120 °C, 20 h; [b]GCyield; [c] O_2 or air (500 mL); [d] Isolated yield; [e] No produt; [f]The entry has been done without CuI..



[a] Isolated yields

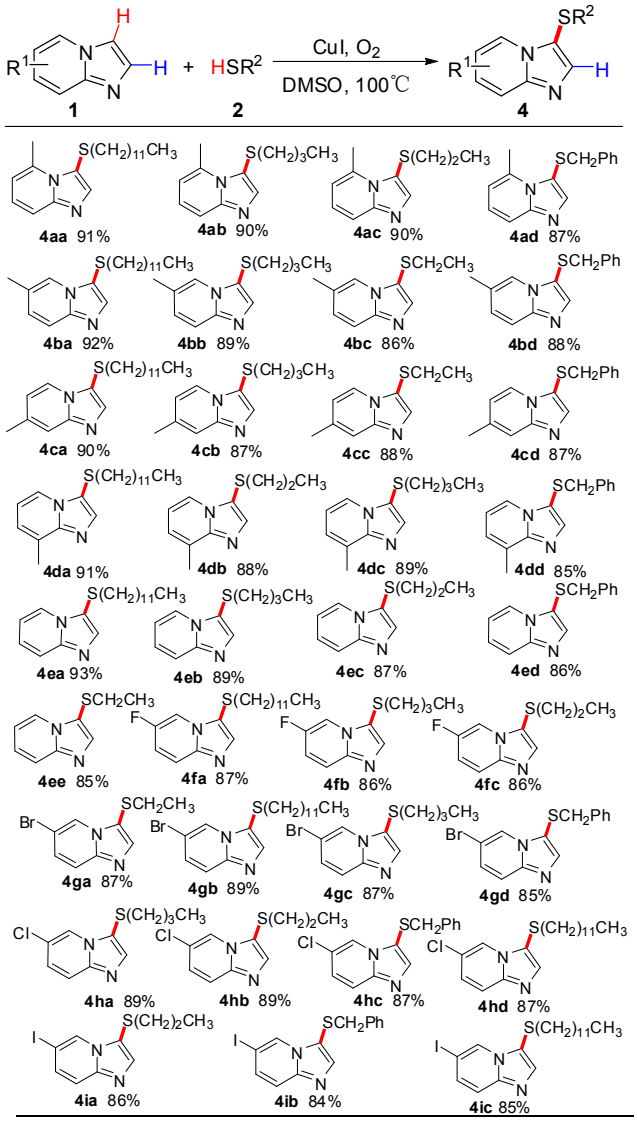
Scheme 2. CuI-Catalyzed Thiolation of Imidazo[1,2-a]pyridines[a]

The initial screening studies have been carried out using 2-methyl imidazo[1,2-a]pyridine **1a** and dodecane-1-thiol **2a** as model substrate to identify and optimize many different combinations of potential catalysts, oxidants, additives, solvents, and temperatures in order to achieve this goal. The key results are shown in Table 1. In the presence of 5 mol % of CuCl as a catalyst and 2 equiv of TBHP as an oxidant, DMSO as the solvent, the reaction carried out at 100 °C afforded the desired product **3aa** in 61% yield (Table 1, entry 1). Then various copper (I) salts, such as CuBr, CuI, Cu_2O, and CuCN, were also examined (Table 1, entries 2-5). To our delight, the desired product **3aa** was formed in 83% yield using CuI as a catalyst. Other oxidants, including O_2, air, $K_2S_2O_8$, oxone, and benzoquinone (BQ) were also tested (Table 1, entries 6-10). Unfortunately, $K_2S_2O_8$, oxone, and benzoquinone (BQ) were ineffective for this cross-coupling of **1a** with **2a**. Importantly, high isolated yield of product **3aa** could be obtained using molecular oxygen. Encouraged by this preliminary result, we then screened different solvents. Among then, DMSO and DMF showed good performances for this transformation while other solvents (toluene, dioxane, DCE, CH_3CN) were ineffective (Table 1, entries 11-15). The reaction totally fail at room temperature (Table 1, entries16-18). Notably, the desired product was not obtained in the absence of CuI. These results indicated that the copper catalyst should play a predominate role in this reaction. The experiments clearly demonstrated that the best way to proceed with the selective cross-coupling of **1a** and **2a** is by using CuI as the catalyst, O_2 as oxidants, and DMSO as solvent at 100 °C for 20h.

In a further set of experiments, the scope and generality of this process for the direct oxidative cross-coupling of imidazo[1,2-a] pyridines**1** and thiols **2** was investigated under the optimum reaction conditions. The results are summarized in Scheme 2. A series of primary thiols, such as dodecane-1-thiol, butane-1-thiol, propane-1-thiol,ethanethiol, and phenylmethane thiol, were examined. And the results showed that alkyl thiols can be efficiently converted to the corresponding cross-coupling products. Various substituted imidazo[1,2-a]pyridine derivatives reacted well with alkyl thiols. Different position substituted group on the pyridine or imidazole ring, having 2-CH_3, 2-$C(CH_3)_3$, 5-CH_3, 6-CH_3, 7-CH_3, 8-CH_3 substitution, were smoothly participated in this transformation to provide the corresponding imidazo[1,2-a]pyridines in good yields.

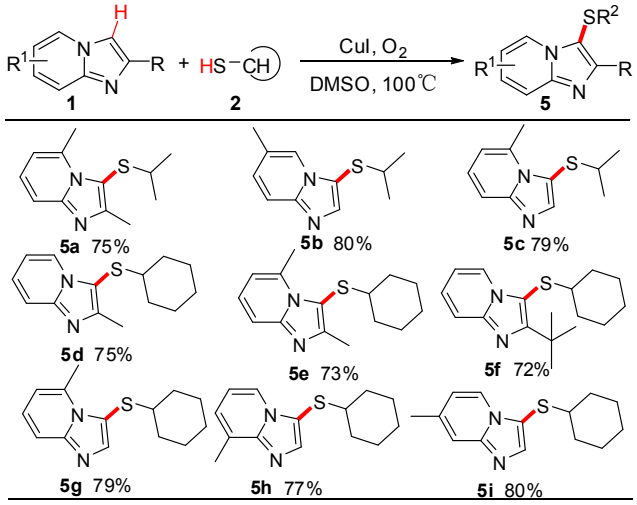
Subsequently, 2-unsubstituted imidazo[1,2-a]pyridines were also examined as the substrate with various thiols and the results are described in Scheme 3. To our delight, the reaction conditions were useful for a variety of 2-unsubstitutedimidazo[1,2-a]pyridines and the selective C-3 cross-coupling products were obtained in good to excellent yields. A variety of imidazo[1,2-a]pyridines with electron-donating methyl groups at the 5-, 6-, 7-, and 8- positions were smoothly sulfenated at the 3-position with thiols. It is also worth noting that the presence of halogen groups (F, Cl, Br, and I) at 5 position of the pyridine ring provided the corresponding selective C-3 sulfenated products in good yields. The present strategy showed high functional group tolerance in different position on the pyridine ring and led to a beneficial effect on the reaction outcome.

For further investigation, commercially available aliphatic secondary thiols were employed to explore the scope of the cross-coupling reaction under the optimized conditions. And the results are outlined in Scheme 4. Aliphatic secondary thiols, such aspropane-2-thiol and cyclohexane thiol, with imidazo[1,2-a]pyridines proceeded smoothly to afford the corresponding sulfenylated products in 72-80% yields. Notably, the selective C-3 sulfenated products were successfully obtained in moderate to good yields, when the reaction carried out using 2-unsubstitutied imidazo[1,2-a]pyridines as substrates with aliphatic secondary thiols. However, the desired sulfenated product was not formed using t-butylmercaptan as substrate probably due to steric hindrance of t-butyl group (Scheme 5). To our delight, the reaction of imidazo[1,2-a]pyrazine with 4-fluorobenzenethiol proceeded smoothly to afford the desired product **6a** in 87% yield (Scheme 6). All the results indicated that this strategy provided a wide range of substrates to form thioether-decorated imidazo[1,2-a]pyridines in good yields, which can be used to prepare potential biologically important molecules.



[a] Isolated yields

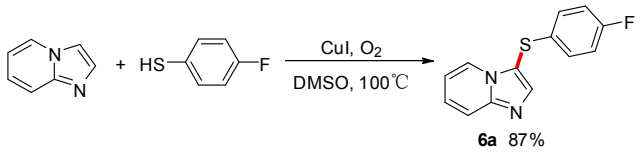
Scheme 3. Regioselective CuI-Catalyzed Thiolation of Imidazo[1,2-a]pyridines[a]



[a] Isolated yields

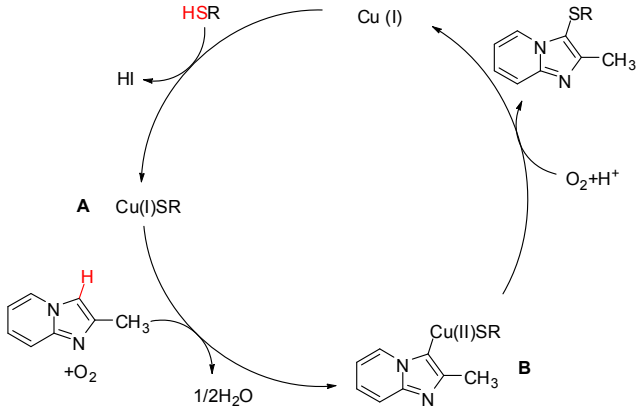
Scheme 4. Thiolation of Imidazo[1,2-a]pyrazines with Aliphatic Secondary Thiols[a]

Scheme 5. Thiolation of Imidazo[1,2-a]pyrazines with t-butylmercaptan



Scheme 6. Synthesis of **6a**

As mentioned in similar studies,[7f, 16] a plausible mechanism of this Cu-catalyzed direct C-H cross-coupling was depicted in Scheme 8. Initially, CuI reacts with **2** to give CuSR species A, which then would undergo a concerted metalation−deprotonation with imidazo[1,2-a]pyridines to form the intermediate **B**. Finally, intermediate **B** underwent reductive eliminati onto generate the cross-coupling product in the presence of molecular oxygenand released the Cu(I) catalyst.



Scheme 7. Proposed mechanism.

In summary, we have developed an efficient and highly regioselective CuI-catalyzed oxidative C-H/S-H cross-coupling of imidazo[1,2-a]pyridines with thiols by using O_2 as oxidant. This method provides a simple route for the synthesis of thioether-decorated imidazo[1,2-a]pyridines which are broadly applicable for the synthesis of biologically active molecules. The reaction proceeded with C-3-selectivity without the directing groups and showed a broad substrates cope in the C-H thiolation reaction. Owing to its high selectivity and broad substrate scope, this C-H thiolation reaction should be of high synthetic value. More synthetic applications of the present method are under investigation in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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