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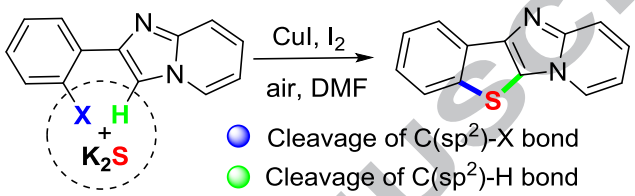

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Copper-catalyzed synthesis of benzo[*b*]thiophene-fused imidazopyridines via the cleavage of C-H bond and C-X bond

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ABSTRACT

A new and straightforward approach to synthesize benzo[*b*]thiophene-fused imidazopyridines has been developed by tandem cross-coupling reaction of K_2S with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines, which K_2S as sulfur source constructed double C-S bonds via the cleavage of C-H bond and C-X bond. In addition, the optical properties of a library of benzo[*b*]thiophene-fused imidazopyridines were for the first time fully characterized. Moreover, this synthetic strategy could be applied in preparation of benzo[*b*]thiophene-fused indoles.

Transition metal-catalyzed C-S bond cross-coupling reaction presents one of the most useful methods in the synthesis of natural products, pharmaceuticals, and materials.[1] In particular, the traditional coupling of C-X (X = Cl, Br, I, OTf) bonds with sulfides under metal-catalyzed conditions is of utmost importance in construction of C-S bond (Scheme 1, a).[2] Compared with the traditional coupling, the atom-economic sulfuration via C-H functionalization became known only until recently (Scheme 1, b).[3-8] In these methods, various sulfides such as disulfides,[4] thiols,[5] sodium sulfinates,[6] sulfonyl hydrazides[7] and arylsulfonyl chlorides[8] are needed as coupling partners for the reaction. However, despite their usefulness in forming C–S bonds, these methods have significant limitations, requiring either the implementation of metal–ligand combination or highly pre-functionalized precursors, suffering from difficulties in preparation of starting sulfur-containing materials.[9] Recently, we developed an efficient protocol for the synthesis of benzothiazoles via copper-catalyzed the traditional coupling and the oxidative coupling reaction from easily available potassium sulfide and *N*-benzyl-2-iodoanilines.[10] The nontoxic, odorless, and readily available metal sulfides should be a desired sulfur sources for the coupling partners. Encouraged by these results, we envisioned that the metal sulfides could be used to construct double C-S bonds, which the metal sulfides as sulfur source constructed double C-S bonds via the cleavage of C-H bond and C-X (X = Br or I) bond. (Scheme 1). To the best of our knowledge, the direct double sulfuration of C(sp^2)-X bond and C(sp^2)–H bond from metal sulfides as sulfur source has not been reported previously.

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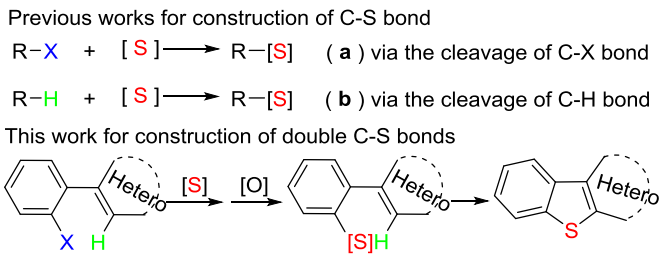
As an important class of heteroaromatic ring systems, benzo[*b*]thiophenes have found widespread application in many biologically active compounds and organic materials.[11] In addition, the derivatives of aza-heterocyclics have shown interesting biological activities and have been found in many drugs,[12] and they are also potentially used in material science as charge transporters.[13] With this background, we believe that fusion of such two classes of heterocycles into a single frame will have new and interesting properties. As a part of our continuous efforts for the synthesis of novel heterocycles containing benzo[b]thiophenes,[14] herein we wish to report an unexpected ligand-free inexpensive copper-catalyzed cascade reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with easily available potassium sulfide leading to novel benzothiophene-fused imidazopyridines.

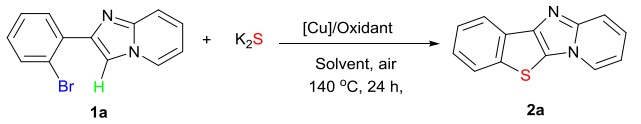


Scheme 1 Method for Construction of C-S Bond

In this work, 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**1a**) as the model substrate, was treated with K_2S to obtain the optimal reaction conditions, and the screening results are compiled in Table 1. Our investigation started by an attempted sulfuration of substrate **1a** with K_2S in DMF at 140 ^oC in the presence of CuI as the catalyst and air as the oxidant, and the desired product **2a** was isolated in 40% yield (entry 1). The product yield decreased to

21% when the reaction was performed under nitrogen atmosphere (entry 2), and increased to 59% when oxygen was used as the oxidant (entry 3). However, these results were not satisfactory. Subsequently, further investigation of other oxidants such as $PhI(OAc)_2$, DDQ, 1,4-benzoquinone, I_2 indicated that I_2 was superior to the others (entries 4−7). When the reaction was performed under nitrogen atmosphere, the yields of the target product **2a** decreased slightly (entry 8). Then, we explored other copper catalysts, such as CuBr and CuCl, but the product yields decreased slightly (entries 9−10). Other solvents such as DMSO and NMP were examined and showed lower efficiency (entries 11−12). Finally, relatively low yields were found when we reduced the amount of catalyst and oxidant or decreased temperature in the reaction (entries 13-16). Thus, the optimized reaction conditions were as follows: **1a** (0.3 mmol), K_2S (0.9 mmol), CuI (20 mol %), I_2 (0.3 mmol), in DMF (2 mL) under air atmosphere at 140 °C.

Table 1 Optimization of Reaction Conditions[a]

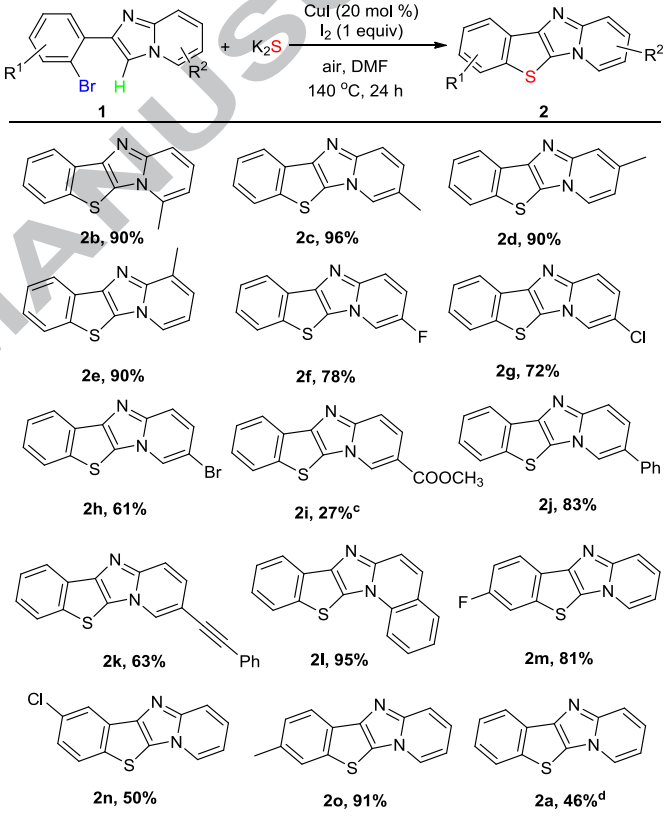


Entry	Catalyst	Oxidant	Solvent	Yield 2a (%)[b]
1	CuI	-	DMF	40
2[c]	CuI	-	DMF	21
3[d]	CuI	-	DMF	59
4	CuI	$PhI(OAc)_2$	DMF	73
5	CuI	DDQ	DMF	82
6	CuI	1,4-Benzoquinone	DMF	49
7	**CuI**	**I_2**	**DMF**	**96**
8[c]	CuI	I_2	DMF	88
9	CuCl	I_2	DMF	94
10	CuBr	I_2	DMF	90
11	CuI	I_2	DMSO	11
12	CuI	I_2	NMP	42
13[e]	CuI	I_2	DMF	87
14	-	I_2	DMF	8
15[f]	CuI	I_2	DMF	77
16[g]	CuI	I_2	DMF	56

[a] Reaction conditions: **1a** (0.3 mmol), K_2S (0.9 mmol), Cu salt (20 mol %), oxidant (0.3 mmol), solvent (2 mL), under air atmosphere in sealed Schlenk tube, at 140 °C, for 24 h. [b] Isolated yields. [c] Under nitrogen atmosphere. [d] Under oxygen atmosphere. [e] CuI (10 mol %). [f] Oxidant (0.15 mmol). [g] At 120 °C.

After the optimal reaction conditions were established, we then extended the substrate scope of the cyclization reaction. The results obtained under the optimized conditions are listed in Table 2. Initially, a various of imidazo[1,2-*a*]pyridines bearing substituents on pyridine rings were screened. The results demonstrated that both electron-withdrawing and donating groups were tolerated, and could smoothly transform into the desired products. Furthermore, a methyl group at different positions of the imidazo[1,2-*a*]pyridine did not obviously affect the efficiency and gave the desired products in 90-96% yield (**2b-2e**). It is noteworthy that the reactions of halo-substituted imidazo[1,2-*a*]pyridines proceed well and offered the halo-substituted products, which could be used for further modification (**2f-2h**). For example, bromo-substituted target product **2h** was obtained in 61% yield. Unluckily, the ester group substituted **2i** was obtained only in 27% yield. In addition, 2-(2-bromophenyl)-6-phenylimidazo[1,2-*a*]pyridine could react with K_2S and afford the expected product in 83% yield (**2j**). Importantly, 2-(2-bromophenyl)-6-(phenylethynyl)imidazo[1,2-a]pyridine and 2-(2-bromophenyl)imidazo[1,2-*a*]quinoline were also tolerated in this transformation generating corresponding **2k** and **2l** in 63% and 95% yield. Then, we also evaluated effects of the substituent on the benzene ring. Compared with the yields of unsubstituted **2a,** the desired products bearing the electron-withdrawing groups such as fluoro and chloro on the benzene rings, were obtained in a lower yields. However, **2o** well-tolerated under the same conditions and proceeded with superior efficiency. Finally, we investigated the effects of chloro substituents on 2-phenylimidazo[1,2-*a*]pyridine. As expected, moderate yield (46%) was observed when 2-(2-chlorophenyl)imidazo[1,2-*a*]pyridine was applied.

Table 2 Synthesis of Benzothiophene-fused Imidazopyridines[a,b].



[a] Reaction conditions: **1** (0.3 mmol), K_2S (0.9 mmol), CuI (20 mol %), I_2 (0.3 mmol), DMF (2 mL), under air atmosphere in sealed Schlenk tube, at 140 °C for 24 h. [b] Isolated yields. [c] DDQ instead of I_2. [d] 2-(2-Chlorophenyl)imidazo[1,2-*a*]pyridine was applied.

The successful synthesis of a small library of benzo[4',5']thieno[3',2':4,5]imidazo[1,2-*a*]pyridine and their π-expanded analogs gave us an excellent opportunity for measuring their photophysical properties for the first time. Among the benzo[*b*]thiophene-fused imidazopyridines presented here, **2l** was found to exhibit the highest fluorescence quantum yield. Substitution with a heavy atom (bromo-derivative **2h**), according to expectations, led to a further decrease in fluorescence intensity. The spectroscopic data collected for compounds **2a**, **2l**, **2h** and **2k** are shown in table 3, figure 1. Comparison of the properties of compounds **2a**, **2l** and **2h** with unsubstituted imidazo[1,2- *a*]pyridine (**IP**) led to a conclusion that fusion with a benzo[*b*]thiophene scaffold results in 30–40 nm and 39–46 nm

bathochromic shift of absorption and emission maxima, respectively. While, 70 nm bathochromic shift of emission maxima was found at **2k**.

Table 3 Spectroscopic Properties of Benzothiophene-fused Imidazopyridines [a]

Compd	Abs_{max} (nm)	ε ($\times10^{-3}$ M^{-1} cm^{-1})	$Emission_{max}$ (nm)	Stokes shift (cm^{-1})	Φ_{fl} [b]
IP[c]	318		376	4800	
2a	255	32.9	415	4640	0.311[d]
	348	9.06			
2l	249	37.2	421	4740	0.344[d]
	351	14.4			
2h	242	30.6	422	4240	0.026[e]
	259	30.4			
	358	8.43			
2k	299	42.7	446	1100	0.192[f]

[a] Measured in DCM. [b] Measured with quinine sulphate as a standard. [c] IP = unsubstituted imidazo[1,2-*a*]pyridine (data taken from ref. 15). [d] Excited at 344 nm. [e] Excited at 351 nm. [f] Excited at 305 nm.

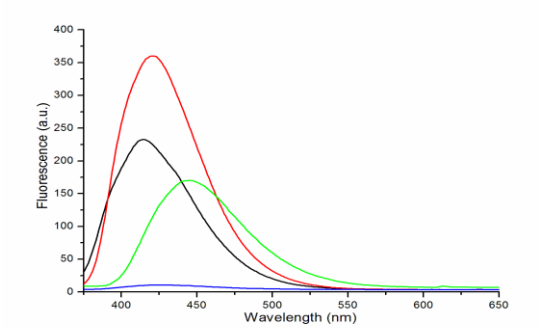
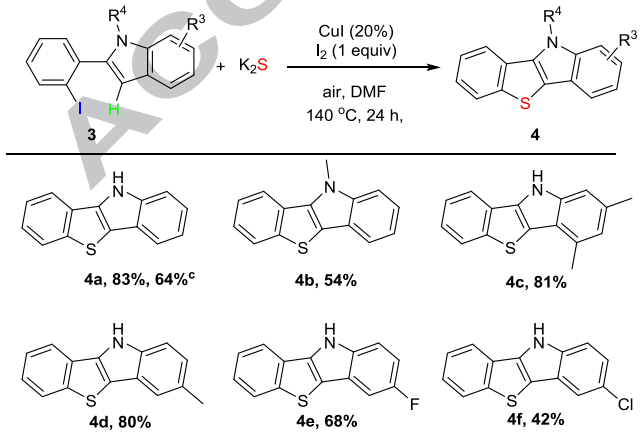


Figure 1 Normalized fluorescence (bottom) spectra of **2a** (black), **2l** (red), **2h** (blue) and **2k** (green) measured in DCM.

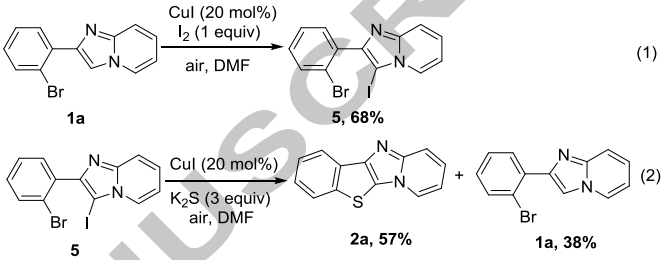
Considering indoles with widespread application in biological chemistry and material science,[16] we decided to further expand the synthetic strategy to preparation of benzo[*b*]thiophene-fused indoles. Fortunately, under similar reaction conditions, benzo[*b*]thiophene fused indoles **4** were obtained in 42−83% yield (Table 4).

Table 4 Synthesis of Benzo[b]thiophene-fused Indoles [a,b]



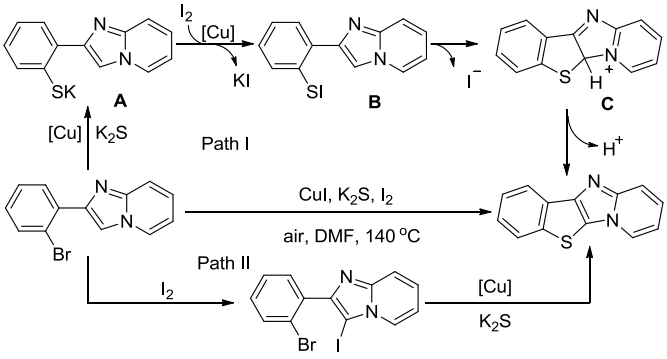
[a] Reaction conditions: **3** (0.3 mmol), K_2S (0.9 mmol), CuI (20 mol %), I_2 (0.3 mmol), DMF (2 mL), under air atmosphere in sealed Schlenk tube, at 140 °C for 24 h. [b] Isolated yields. [c] 2-(2-bromophenyl)-1H-indole was applied.

To elucidate the reaction mechanism, two control experiments were conducted (Scheme 2). First, iodinated product **5** was obtained in 68% in the reaction of **1a** with I_2 (1 equiv) and CuI (20 mol%) (Eq. 1). Then, the reaction of the iodinated product **5** with K_2S (3 equiv) was performed in the absence of I_2, and the target product **2a** (57%) together with deiodinated product **1a** (38%) were found (Eq. 2). These results suggested that iodinated product 5 should not be a dominating intermidate in this reaction because of the depressed yields. Furthermore, under the standard reaction conditions, the iodinated product **5** was not probed from crude reaction mixtures of the reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**1a**) with K_2S by using GC-MS analysis.



Scheme 2 Control Experiments.

According to the present results and previous reports[2-8], a reaction mechanism with two possible pathways for the cascade reaction that leads to the formation of the benzo[*b*]thiophene ring is shown in Scheme 3. For Path I, the copper catalyzed coupling reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with K_2S provides the intermediate **A** firstly. Then **A** reacts with I_2 to form an electrophilic species **B**, which can attack to imidazo[1,2-*a*]pyridine to give an intermediate **C**. Finally, the intermediate **C** gives the desired product via deprotonation. For Path II, the substrate 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine undergoes a iodination process firstly. Then, a copper-catalyzed double C-S bonds formation via Ullmann-type S-arylation takes place. Due to the lower yields of benzo[*b*]thiophene-fused imidazopyridines bearing electron-withdrawing groups on the ring of pyridine, the reaction Path I is more likely. However, the reaction Path II cannot be ruled out completely.



Scheme 3 Plausible Mechanism

In summary, we have demonstrated a novel copper-catalyzed coupling reaction to synthesize benzo[*b*]thiophene-fused imidazopyridines and benzo[*b*]thiophene-fused indoles, which are potentially used in biologically active compounds and organic materials. Efforts to extend the applications of the transformation in organic synthesis as well as screen for

biological activity of these types of compounds are currently underway in our laboratory.

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