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Copper-catalyzed synthesis of 2-sulfenylindoles from indoline-2-thiones and aryl iodides

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ABSTRACT

A novel and efficient method for synthesis of 2-sulfenylindole *via* copper-catalyzed coupling reaction of indoline-2-thiones with aryl iodides has been developed. A series of N-substituted and N-free 2-sulfenylindole were obtained in high yields. Furthermore, the method was employed to synthesis of benzothieno[2,3-b]indoles from indoline-2-thiones with 1,2-diiodobenzene in the presence of CuI and $Pd(OAc)_2$ as catalysts.

Sulfenylindoles[1], categorized as significant derivatives of indoles, are broadly found in bioorganic and medicinal chemistry with application in drug discovery and development for the treatment of various diseases (Figure 1), such as HIV,[2] cancer,[3] vascular,[4] respiratory disorders,[5] heart disease,[6] and allergies.[7] Consequently, many efficient methods were developed for the synthesis of sulfenylindoles.[8] Among them, the direct sulfenylation of indoles is an efficient and common strategy.[9] Due to the nucleophilic of indoles, the thioethers can be easily introduce in the 3-position of indoles and a variety of sulenylating reagents such as sulfenyl halide,[10] disulfides,[11] thiols,[12] arylsulfonyl chorides,[13] arylsulfonyl hydrazides,[14] sulfonium salts,[15] sulfinic acids[16] were smoothly coupled with indoles to 3-sulfenylindoles. However, the synthesis of 2-sulfenylindole was limited applying this protocol. The classic method to 2-sulfenylindole was used acid-catalyzed rearrangement of 3-sulfenylindole[17] and the sulfenylation of 2-lithioindoles.[18] Recently, Cossy and coworkers have found TFA-promoted direct C-H sulfenylation at C2 position of non-protected indoles for the synthesis of 2-sulfenylindoles.[19] Nevertheless, these methods suffer from use of strong acids and strong bases, incompatible with various functional groups. Thus, it is highly desirable to provide efficient and facile strategy for the preparation of 2-sulenylindoles.

Indole-2-thiones are an efficient synthon to construct 2-sulfenylindoles.[20] However, they are commonly used to synthesize the 2-alkyl thiolester indoles. Herein, we would like to disclose a useful application of indole-2-thones for the production of 2-sufenylindoles (Scheme 1).

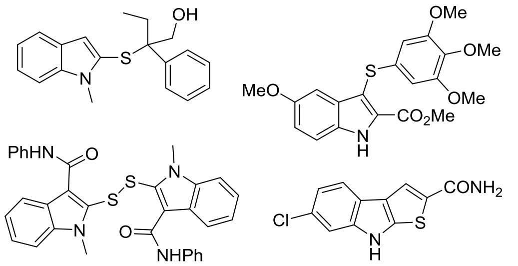
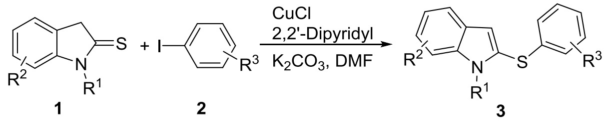


Figure 1 Representative examples of biologically active sulfenylindoles



Scheme 1 Method for preparation of 2-sulenylindoles

Initially, the coupling reaction of N-methylindoline-2-thione with iodobenzene was selected for optimization of reaction conditions, and the results are summarized in Table 1. Our investigation started by an attempted thiolation of N-methylindoline-2-thione with iodobenzene in DMF at 120 ^oC in the presence of CuI as the catalyst, and the desired product **3a** was isolated in 80% yield (entry 1). This result encouraged us to develop an efficient catalytic system to synthesize 2-sulfenylindoles from indoline-2-thiones and aryl iodides. A variety of copper catalysts, such as CuCl, CuBr, $Cu(OAc)_2$, $CuCl_2$, were screened and the results indicated that the catalyst of CuI is the best for this coupling reaction yet (entries 2-5). Without the copper catalyst, the desired product could not be isolated (entry 6). Subsequently, the effects of ligands were checked, and 2,2'-bipyridine was found to be an efficient ligand (entries 7-10). The effects of base (including K_3PO_4, KOAc, KF, and ^{t}BuOK) and solvent (including DMSO, CH_3CN and toluene) were examined. K_2CO_3 was found to give the best result and

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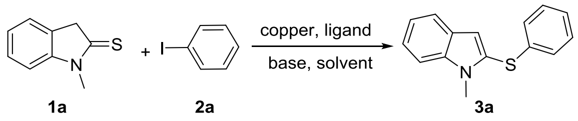
DMF was found to be the best solvent for the reaction (entries 11-17). Finally, the amount of catalyst and the reaction temperature were evaluated. Relatively low yields were found when the reaction carried out in 100 or 140 ^{o}C, and the yield of **3a** was the highest when using 10 mmol % loading of CuI and 20 mmol % of 2,2'-bipyridine (entries 18-20). Thus, the optimized reaction conditions were as follows: **1a** (0.3 mmol), **2a** (0.36 mmol), CuI (10 mmol %), 2,2'-bipyridine (20 mmol %), K_2CO_3 (0.9 mmol), in DMF (2 mL) at 120 ^{o}C.

Table 1 Optimization of reaction conditions[a]



Entry	Copper	Ligand	Base	Solvent	Yield (%)[b]
1	CuI		K_2CO_3	DMF	80
2	CuCl		K_2CO_3	DMF	81
3	CuBr		K_2CO_3	DMF	26
4	$Cu(OAc)_2$		K_2CO_3	DMF	70
5	$CuCl_2$		K_2CO_3	DMF	71
6	-		K_2CO_3	DMF	trace
7	CuCl	TEMDA	K_2CO_3	DMF	60
8	CuCl	2,2'-bipyridine	K_2CO_3	DMF	89
9	CuCl	1,10-phenanthroline	K_2CO_3	DMF	83
10	CuCl	L-proline	K_2CO_3	DMF	75
11	CuCl	2,2'-bipyridine	K_3PO_4	DMF	83
12	CuCl	2,2'-bipyridine	KOAc	DMF	79
13	CuCl	2,2'-bipyridine	KF	DMF	77
14	CuCl	2,2'-bipyridine	^{t}BuOK	DMF	77
15	CuCl	2,2'-bipyridine	K_2CO_3	DMSO	75
16	CuCl	2,2'-bipyridine	K_2CO_3	CH_3CN	86
17	CuCl	2,2'-bipyridine	K_2CO_3	Toluene	0
18[c]	CuCl	2,2'-bipyridine	K_2CO_3	DMF	83
19[d]	CuCl	2,2'-bipyridine	K_2CO_3	DMF	77
20[e]	CuCl	2,2'-bipyridine	K_2CO_3	DMF	80

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), Copper (10 mmol %), Ligand (20 mmol %), Base (3.0 equiv), Solvent (2 mL), 120 ^{o}C, N_2, 6 h.

[b] Isolated yield.

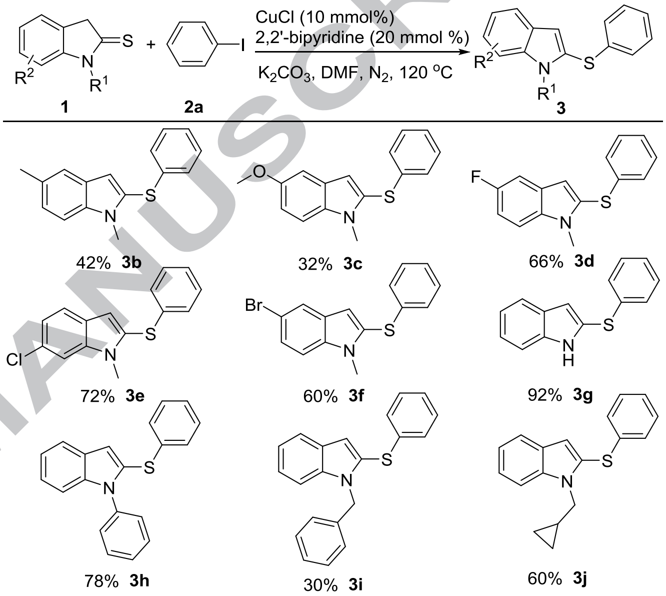
[c] Copper (20 mmol %), Ligand (40 mmol %).

[d] 100 ^{o}C.

[e] 140 ^{o}C.

With optimized the reaction conditions in hand, the coupling reaction of various indole-2-thiones with iodobenzene were investigated, and the results are summarized in Table 2. The N-methyl indole-2-thiones containing electron-donating substituents (Me and OMe) and electon-withdrawing substituents (F, Cl and Br) in the benzene ring were examined, and they all could tolerate the reaction conditions and give the corresponding 2-benylthioindoles. The electronic properties of substituents in the benzene ring exerted an obvious influence on the reaction. The electron-withdrawing groups substituted N-methyl indole-2-thiones showed higher activity than the electron-donating groups substituted N-methyl indole-2-thiones. Besides N-methyl indole-2-thione, N-free and other N-substituted groups (phenyl, benzyl and cyclopropylmethyl) were also involved. To our delight, non-protected 2-sulfenylindole **3g** given the perfect yield. However, the N-benzyl substituted 2-sulfenylindole **3i** only gain 30% yield. These results indicated that the steric effect of substituents is a main impact factor.

Table 2 Substrate scope for the reaction of indole-2-thiones **1** with iodobenzene **2a** [a,b].

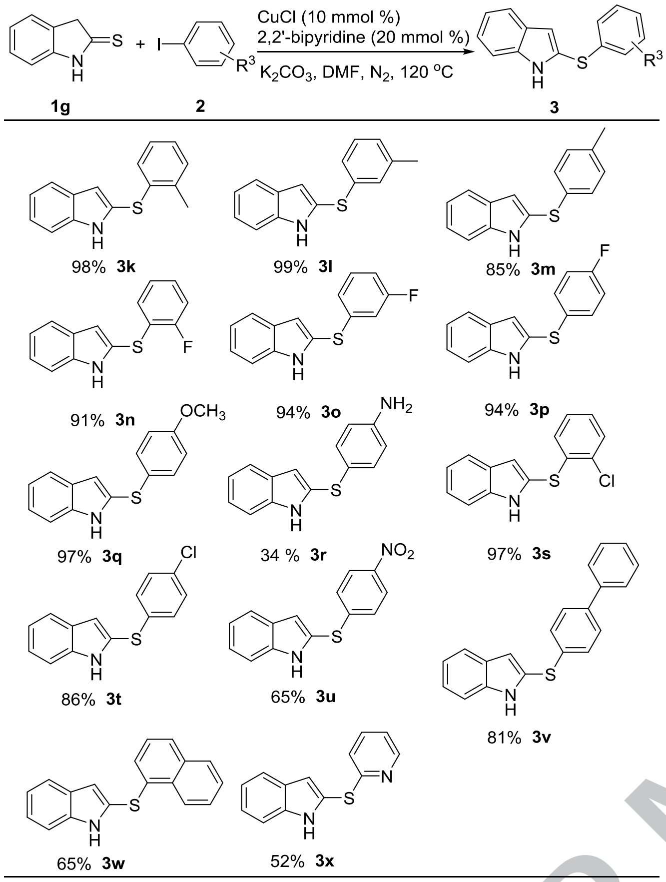


[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), CuCl (10 mmol %), 2,2'-bipyridine (20 mmol %), K_2CO_3 (3.0 equiv), DMF (2 mL), 120 ^{o}C, N_2, 6 h.

[b] Isolated yield.

We next examined the scope of various substituted iodobenzenes in order to accessing a variety of 2-arylsulfenylindoles（Table 3）. All of the substrates provided a good to excellent yields, showing good functional group tolerance. *o*-, *m*- or *p*-Methyl-iodobenzene all could efficiently react with indole-2-thione and afford 85-98% yields of the corresponding product respectively. Likewise, the *o*-, *m*- or *p*-Flour-iodobenzene all gave the corresponding product in perfect yields under standard reaction conditions. These results indicated the steric effects and electron effects of substituents shown a very limited influence on this reaction due to the inherent reactive activity of iodobenzene. Furthermore, the iodobenzene, bearing the electron-donating groups such as OMe and the electron-withdrawing groups such as Cl, NO_2 could give good to perfect yields. Importantly, π-extend 4-iodo-1,1'-biphenyl and 1-iodonaphthalene could performed with indole-2-thione and produce the desired product in 81% and 65% yield. In addition, the heterocyclic aryl substituted 2-(pyridin-2-ylthio)-1H-indole was afforded in 52% yield. Unfortunately, the bromobenzene could not efficiently react with indole-2-thione, and the 2-(phenylthio)-1H-indole was not observed under standard conditions.

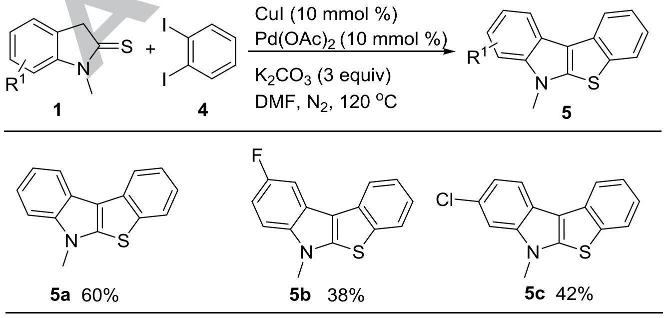
Table 3 Substrate scope for the reaction of indole-2-thiones **1g** with aryl iodides **2** [a,b].



[a] Reaction conditions: **1g** (0.3 mmol), **2** (0.36 mmol), CuCl (10 mmol %), 2,2'-bipyridine (20 mmol %), K_2CO_3 (3.0 equiv), DMF (2 mL), 120 °C, N_2, 6 h.
[b] Isolated yield.

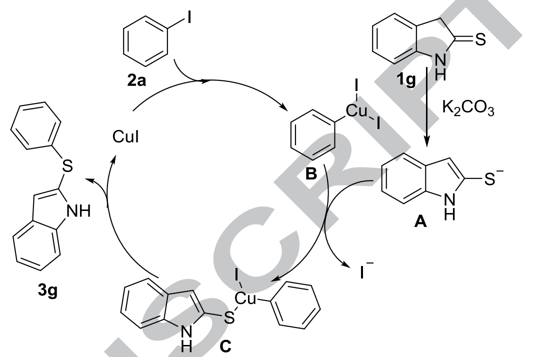
To further demonstrate the synthetic utility of this sulfenylation reaction, we applied this methodology to synthesis of a π-extend polycyclic benzothiophene fused indoles.[21] When the 1,2-diiodobenzene was chosen as the substrate in this coupling reaction, the corresponding sulfenylated products (benzothieno[2,3-b]indoles) should be produced. To our delight, the benzothieno[2,3-b]indoles could be obtained in moderate yield by copper- and palladium-catalyzed tandem coupling reaction (Table 4).

Table 4 Synthesis of benzo[b]thiophene-fused indoles [a,b]



[a] Reaction conditions: **1** (0.3 mmol), **4** (0.36 mmol), CuI (10 mmol %), $Pd(OAc)_2$ (10 mmol %), K_2CO_3 (3.0 equiv), DMF (2 mL), 120 °C, N_2, 24 h.
[b] Isolated yield.

Based on the present expermental results and the previous reported mechanism,[22] a proposed catalytic cycle for the formation of 2-sulfenylindoles from indoline-2-thiones and aryl halides is given in Scheme 2. First, the indole 2-thione is deprotonated by potassium carbonate to form a stabilized anion **A**. Then the anion **A** reacted with iodobenzene via copper-catalyzed coupling reaction and afford the desired product 2-sulfenylindole.



Scheme 2 Plausible mechanism

In summary, we have demonstrated a novel copper-catalyzed coupling reaction of indoline-2-thiones with aryl halides. This method provides an effective approach to synthesize N-substituted or N-free 2-sulfenylindoles, which are ubiquitous structural units in a number of biologically active componds. Furthermore, this strategy could extend to synthesize the π-extend polycyclic heterocyclic benzothiophene fused indoles. Further studies on the applications of this method are underway.

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Supplmentary Material

Supplementary data (experimental procedures and characterization data for all new compounds and copies of NMR spectra) associated with this article can be found, in the online version.

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Copper-catalyzed synthesis of 2-sulfenylindoles from indoline-2-thiones and aryl iodides

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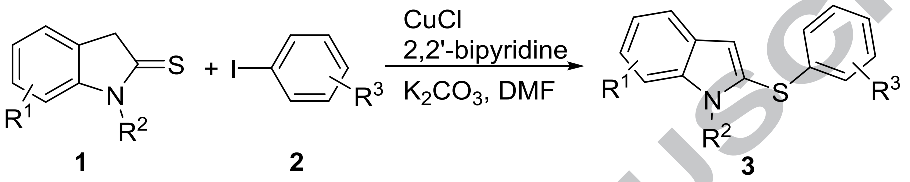

Highlights:

1). A novel and efficient method for synthesis of 2-sulfenylindoles;
2). Copper-catalyzed the formation of C-S bond;
3). Extend to synthesize benzothiophene fused indoles.