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Metal-free, iodine-catalyzed regioselective sulfenylation of indoles with thiols

Shanli Yi, Meichao Li *, Weimin Mo, Xinquan Hu, Baoxiang Hu, Nan Sun, Liqun Jin, Zhenlu Shen *

College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China

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ABSTRACT

An iodine-catalyzed regioselective sulfenylation of indoles in the presence of DMSO has been presented. Various indoles can react with aryl thiols or alkyl thiols to afford their corresponding 3-sulfenylindoles in good to excellent yields. The notable features of this protocol include easy operation, metal-free reaction conditions, and excellent functional group tolerance.

The formation of C–S bonds represents a key step in general organic synthesis as well as in the pharmaceutical industry and in material science.[1] Consequently, the development of efficient strategies for the formation of C–S bonds has stimulated considerable interest. In recent years, the direct sulfenylation via C–H functionalization has emerged as a highly attractive and powerful strategy to construct complicated organosulfur compounds.

The substituted indole is widespread in a large number of natural products and is extremely significant in medicinal chemistry.[2] The development of general protocol for 3-sulfenylindoles formation has received significant attention because of their therapeutic value in the treatment of cancer,[3] HIV,[4] allergies,[5] heart disease,[6] and bacterial infection.[7] During the synthetic efforts, two major synthetic strategies have been developed in the preparation of 3-sulfenylindoles. The first route is achieved by cyclization reactions of *o*-ethenylaryl isocyanides,[8] 2-alkynylanilines,[9] phenylhydrazine hydrochloride[10] or 2-(*gem*-dibromovinyl) anilines,[11] whereas the other protocol involves the direct sulfenylation of indoles.[12–20] A variety of sulfenylating reagents have been shown as the reaction partners such as O,S-acetals,[12] arylsulfenyl halides,[13] aryl-*N*-thioimides,[14] sulfonyl hydrazides,[15] sulfinic acids,[16] arylsulfonium salts,[17] arylsulfonyl chlorides,[18] disulfides,[19] and thiols.[20] However, these reported sulfenylation reactions all have some drawbacks: (i) some of them should be catalyzed by $VO(acac)_2$, $FeCl_3$, $MgBr_2$, $PdCl_2$, CuI, $CeCl_3$, or other metal catalysts; (ii) some of them need excess additives or harsh reaction conditions, and suffer from a narrow substrate scope; (iii) many of these sulfenylation reagents either need for moisture-free reaction conditions or are difficult to obtain. It should be noted that although most of sulfenylation reagents showed excellent activities in sulfenylation reactions of indoles, they have to be prepared from thiols or disulfides frequently. On the other hand, thiols and disulfides have been utilized as attractive starting materials for sulfenylation reactions due to their ready availability. The main disadvantage of using disulfide as the sulfenylating reagent is that disulfides should be synthesized from thiols via the oxidative coupling reaction. This protocol means an additional operation step and low atom economics. Therefore, there is a growing demand to develop an efficient and metal-free method for synthesis of 3-sulfenylindoles from indoles. Obviously, directly using thiols as sulfenylating reagents for the reaction is most preferred.

Recently, molecular iodine has attracted much attention as a metal-free, inexpensive, non-toxic, and readily available catalyst for various organic transformations. Especially, iodine has been known as an important oxidation catalyst for the C–S cross-coupling reactions.[21] Herein, we report a new efficient protocol for the synthesis of 3-sulfenylindoles based on direct C–H bond functionalization of indoles with thiols to form C–S bonds using I_2 as the catalyst and DMSO as the oxidant. It is worth mentioning that not only aryl thiols but also alkyl thiols are successfully applied in the sulfenylation reaction under present catalytic conditions. Indeed, DMSO has already been utilized in the sulfenylation of indoles with thiols in the presence of NaOH.[21i] However,

* Corresponding authors. Tel.: +86 571 88320416; fax: +86 571 88320103.
E-mail addresses: limc@zjut.edu.cn (M. Li), zhenlushen@zjut.edu.cn (Z. Shen).

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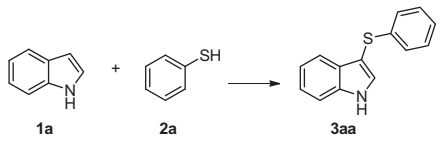
sulfenylation reactions using aliphatic thiols or *N*-methylindole as substrates were not successful under reported catalytic conditions.

In order to achieve the optimized conditions, the sulfenylation of indole (**1a**) with thiophenol (**2a**) was selected as the model reaction. Then, systematic investigation has been conducted. As outlined in Table 1, the influence of different solvents was studied. Among them, 1,2-dichloroethane showed good performance for this transformation while other solvents such as methanol, ethyl acetate, acetonitrile, toluene, hexane, and H_2O were low in effectiveness (entries 1–7). To our surprise, the reaction almost did not proceed when DMSO was used as the solvent (entry 8). Subsequent attempt on reducing the amount of catalyst and oxidant was found to be negative to the reaction (entries 9–11). Notably, the desired product was not obtained in the absence of iodine (entry 9). These results indicated that iodine should play a predominate role in this reaction. In the absence of DMSO, 16% conversions of **1a** was achieved under air atmosphere with 5 mol% of iodine (entry 12). Meanwhile, under oxygen and nitrogen atmosphere the conversions of **1a** were 18% and 5%, respectively (entries 13 and 14). It was deducible that the oxygen could promote this sulfenylation to a certain extent. When the reaction time was extended from 3 h to 8 h, the conversion of **1a** did not increase obviously at 40 °C (entry 15).

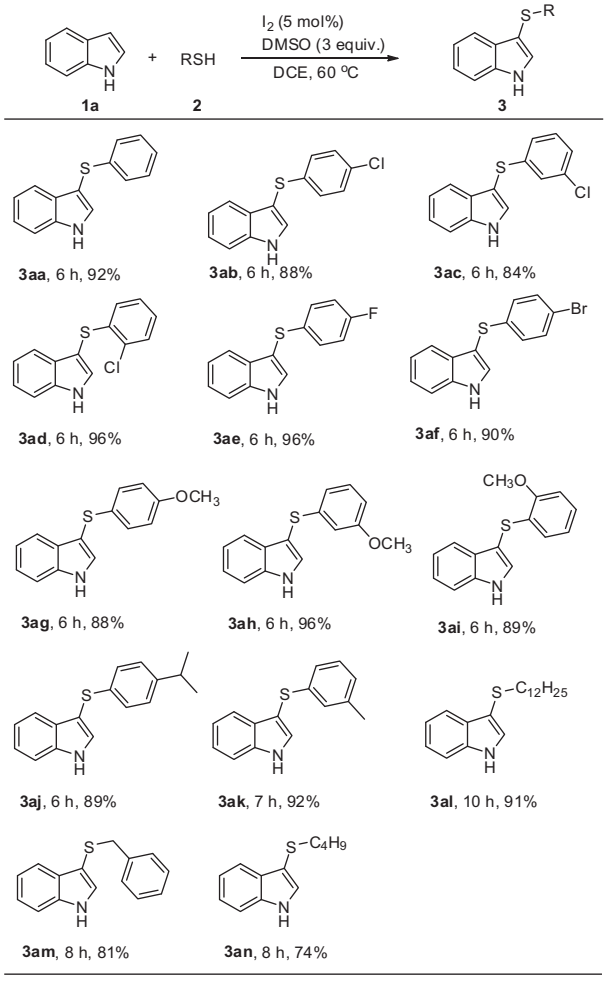
Then the effect of reaction temperature was further examined (entries16–19). The reaction carried out at 60 °C led to the formation of the 3-sulfenyl indole (**3aa**) in a higher conversion of **1a** (entry 17). 98% Conversion of **1a** and 98% selectivity to **3aa** could be obtained when the reaction time was prolonged to 6 h (entry 18). By contrast, a significant decrease in the conversion of **1a** was observed when the reaction was performed at room temperature (entry 16). Although **1a** could be converted completely at 80 °C in 3 h, the selectivity to **3aa** was dropped to 88% (entry 19). Some by-products could be observed, and a small amount of bis-sulfenylation product was detected. Thus, we chose 5 mol% of I_2 in the presence of 3.0 equiv of DMSO in 1,2-dichloroethane at 60 °C as the optimal reaction conditions.

Table 1
Optimization on reaction conditions[a]



Entry	I_2 (mol%)	DMSO (equiv)	*T* (°C)	Solvent	Time (h)	Conv.[b,c] (%)	Select.[c] (%)
1	5	3	40	CH_3OH	3	29	96
2	5	3	40	EtOAc	3	62	99
3	5	3	40	CH_3CN	3	72	95
4	5	3	40	Toluene	3	48	98
5	5	3	40	Hexane	3	Trace	—
6	**5**	**3**	**40**	**DCE**	**3**	**87**	**99**
7	5	3	40	H_2O	3	8	98
8	5		40	DMSO	3	Trace	—
9	0	3	40	DCE	3	N.R.	—
10	3	3	40	DCE	3	55	99
11	5	1.5	40	DCE	3	66	99
12	5	0	40	DCE	3	16	98
13[d]	5	0	40	DCE	3	18	96
14[e]	5	0	40	DCE	3	5	95
15	5	3	40	DCE	8	93	98
16	5	3	rt	DCE	3	67	99
17	5	3	60	DCE	3	94	99
18	**5**	**3**	**60**	**DCE**	**6**	**98**	**98**
19	5	3	80	DCE	3	>99	88

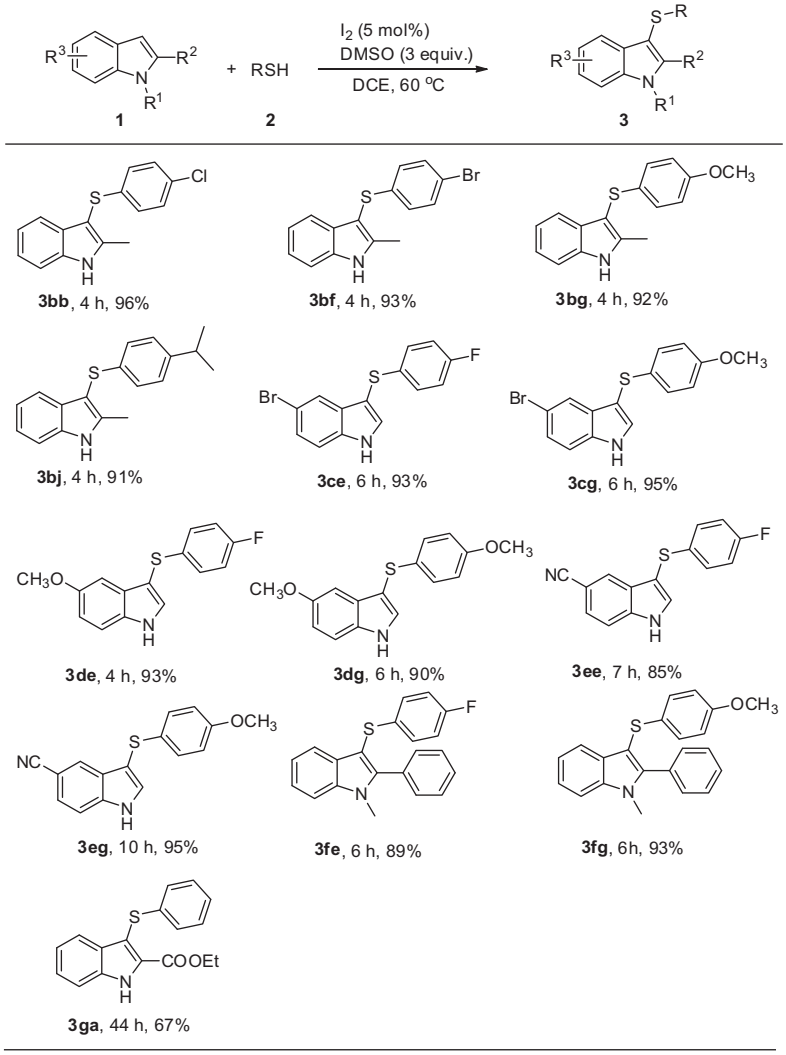
[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), solvent (5 mL).
[b] Conversion of indole.
[c] Determined by GC with area normalization method.
[d] Under oxygen atmosphere.
[e] Under nitrogen atmosphere.



Scheme 1. Reaction of indole (**1a**) with various thiols. The reactions were carried out with 2 mmol of **1a**, 2 mmol of thiols, 5 mol% of I_2, and 6 mmol of DMSO in 10 mL of DCE at 60 °C. Yield of isolated product 74–96%.

In an endeavor to expand the scope of the methodology, the reactivities of various thiol derivatives were investigated. The results in Scheme 1 demonstrate that most of the thiols tested underwent smooth transformations to afford the corresponding 3-sulfenylindoles in good to excellent yields (**3aa**–**3an**).[22] The reaction tolerated various thiophenols bearing electrondonating (Me, OMe, isopropyl) and withdrawing groups (F, Cl, Br) in ortho, meta and para positions. The electronic effect and steric effect did not play great important roles in the isolated yield of the desired product (**3ab**–**3ak**). We were delighted to disclose that similar sulfenylation reactions, using aliphatic thiols including 1-dodecanethiol, benzyl mercaptan, and 1-butanethiol as sulfenylating agents, were also performed successfully under present reaction conditions (**3al**–**3an**).

Having established the scope with respect to the thiol moiety, subsequently, we turned our attention to the indole derivatives. The reactions of various indoles with different coupling partners proceeded in excellent yields (**3bb**–**3fg**, Scheme 2). 2-Methylindole could react with para-substituted thiophenols steadily, and the isolated yields of corresponding 3-(arylthio)-2-methylindoles were higher than 90% (**3bb**–**3bj**). The presence of an electron donating group (OMe) and electron withdrawing groups (Br, CN) on the benzene ring of indoles did not prevent the smooth formation of

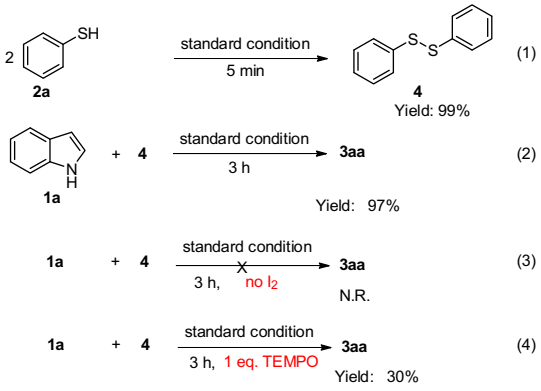


Scheme 2. Scope of indole derivatives. The reactions were carried out with 2 mmol of **1**, 2 mmol of **2**, 5 mol% of I_2, and 6 mmol of DMSO in 10 mL of DCE at 60 °C. Yield of isolated product 67–96%.

the expected products (**3ce**–**3eg**). In addition, no steric hindrance was observed even when a phenyl group was introduced in the C-2 position of indoles (**3fe** and **3fg**). However, when 2-carbethoxylindole was used as the substrate, only 67% yield of sulfenylation product **3ga** could be obtained even the reaction time was prolonged to 44 h.

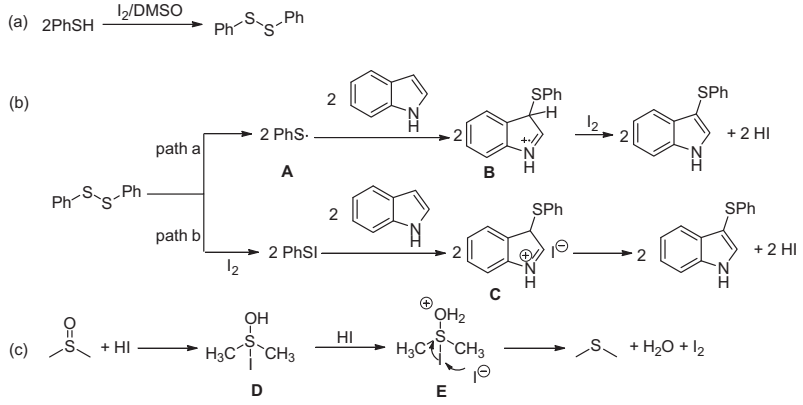
To gain some insight into the possible reaction mechanism, several control experiments were then carried out (Scheme 3). I_2/DMSO is well known to oxidize thiols into disulfides.[23] Thiophenol (**2a**) could be converted to 1,2-diphenyldisulfane (**4**) completely in the presence of 5 mol% of I_2 and 3 equiv of DMSO at 60 °C in 5 min (Eq. 1). The sulfenylation of indole (**1a**) with **4** could be successfully catalyzed by I_2 in the presence of DMSO (Eq. 2), implying **2a** might be converted to **4** firstly in the iodine-catalyzed sulfenylation of **1a** with **2a**. As blank reaction of **1a** and **4** without iodine catalyst could not afford any product (Eq. 3), we thought iodine played an important role in this reaction. When stoichiometric radical-trapping reagent TEMPO was added into the reaction of **1a** and **4**, the yield of **3aa** reduced from 97% to 30% (Eq. 4), indicating that this transformation might proceed via a radical pathway.

According to the literatures and our observations, a plausible reaction mechanism for 3-sulfenylation of indole has been proposed (Scheme 4). Initially, disulfide is generated from thiol in



Scheme 3. Control experiments for mechanism studies. Standard reaction conditions: **1a** or **2a** (2 mmol), **4** (1 mmol), I_2 (0.1 mmol), DMSO (6 mmol), DCE 10 mL, 60 °C. Yield of **3aa** was determined by GC internal standard method.

the presence of I_2 and DMSO (Scheme 4a).[23] Subsequently, thio radical **A** is formed from disulfide. The radical **A** reacts with indole giving intermediate **B**,[17a] which loses hydrogen atom to release the product 3-sulfenylindole (Scheme 4b, path a). However, multiple pathways may be involved in this transformation. As references



Scheme 4. Proposed reaction mechanism.

reported,[17b,19b,20f,20h] disulfide can react with I_2 to produce PhSI, which attack on the C-3 position of indole to produce intermediate **C**. **C** is deprotonated, and the desired product 3-sulfenylindole is generated (Scheme 4b, path b). Then HI produced in path a or path b reacts with DMSO to form intermediate **D**. Protonation of **D** gives intermediate **E**, which is nucleophilic attacked by I^- on the iodide atom to regenerate I_2 and release dimethylsulfane and H_2O (Scheme 4c).

In conclusion, we have successfully applied the I_2/DMSO system, a metal-free catalytic oxidation system, for the regioselective sulfenylation of indoles with thiols to the corresponding 3-sulfenylindoles. Under the optimal reaction conditions, a variety of indoles can react with aryl thiols or alkyl thiols to afford their corresponding 3-sulfenylindoles in good to excellent yields, with excellent functional group tolerance. The features of this protocol for the synthesis of 3-sulfenylindoles are easy operation and metal-free reaction conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.073.

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22. Typical procedure for sulfenylation of indoles (Scheme 1, **3aa**): A sealed tube (90 mL) equipped with magnetic stirring bar was charged with 0.234 g of indole (**1a**, 2 mmol), 0.220 g of thiophenol (**1b**, 2 mmol), 0.468 g of DMSO (6 mmol, 3 equiv), 25.4 mg I_2 (0.1 mmol, 5 mol%) and 10 mL of DCE. Then the tube was placed in an oil bath, which was preheated to 60 °C. The mixture was stirred for 6 h until starting material was complete consumed as monitored by TLC. The reaction mixture was washed by H_2O (10 mL × 3) to remove excess of DMSO and then organic layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel to afford 92% isolated yield of **3aa** as a white solid. ^{1}H NMR ($CDCl_3$): δ = 8.43 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.32–7.28 (m, 1H), 7.21–7.16 (m, 3H), 7.15–7.11 (m, 2H), 7.06–7.09 (m, 1H). ^{13}C NMR (125 MHz, CDCl3): δ = 139.2, 136.5, 130.7, 129.1, 128.7, 125.9, 124.8, 123.1, 121.0, 119.7, 111.6, 102.9. MS (EI): m/z 224.96 (M^+).

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