



Cite this: RSC Adv., 2017, 7, 37739

Received 22nd July 2017
 Accepted 25th July 2017

DOI: 10.1039/c7ra08086g
rsc.li/rsc-advances

Photocatalytic direct C–S bond formation: facile access to 3-sulfenylindoles via metal-free C–3 sulfenylation of indoles with thiophenols†

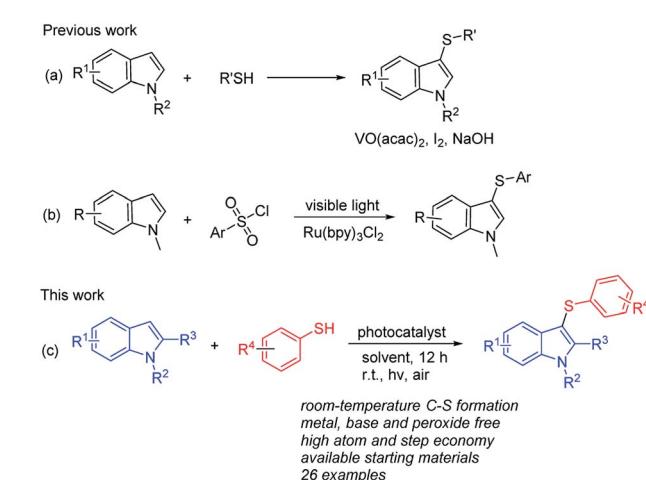
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An efficient and convenient photocatalytic direct C–3 sulfenylation of indoles with thiophenols has been developed for the construction of 3-sulfenylation. This protocol employs thiophenols as the sulfenyling agents, inexpensive rose bengal as the photocatalyst, and shows mild conditions, readily available starting materials, high atom and step atom economy, and environmental advantages. The representative method provides a straightforward approach for C–S bond formation, and has potential applications in the chemical and pharmaceutical industries.

Introduction

3-Substituted indoles compose an important skeleton in natural products, agrochemicals, and functional materials.¹ More specifically, 3-sulfenylindoles have been explored for their therapeutic worth in many fields, such as anti-bacterial infection² and anti-allergy agents.³ Because of the importance of such compounds, numerous synthetic approaches of 3-sulfenylindoles have been successfully established in previous literature.^{4–5} Importantly, direct functionalization of indoles at the C–3 position is a valuable approach for the effective preparation of 3-sulfenylindoles. So far, a variety of sulfenyling agents such as arylsulfonyl halides,⁶ arylsulfonyl chlorides,⁷ sulfonyl hydrazides,⁸ diaryl disulfides,⁹ *N*-thiophthalimides,¹⁰ *O*,*S*-acetals,¹¹ arylsulfonium salts,¹² sulfinic acids,¹³ Bunte salts,¹⁴ and thiols¹⁵ have also been employed for C3-sulfenylation of indoles. Although many 3-sulfenylindoles can be obtained using these methods, most of the reactions mentioned above suffered from one or more drawback such as stringent conditions (transition metals ($\text{VO}(\text{acac})_2$),^{16a} iodine,^{7c} strong base,^{16b,c} high temperature or extreme low temperature^{16d}) and unavailable starting materials (Scheme 1a). Therefore, the development of simple and efficient procedures for the acquisition of 3-sulfenylindoles from easily available starting materials under mild conditions continues to attract the interest of organic chemists because of the remarkable application value of the target products.

For the past several years, more and more chemists gave their attentions to the photocatalytic organic reaction for the synthesis of useful products.¹⁷ The metal complexes ($[\text{Ru}(\text{bpy})_3]^{2+}$, *fac*- $[\text{Ir}(\text{ppy})_3]^{+}$) and organic dyes (eosin Y, rose bengal) have been explored in photocatalytic radical reaction. Zheng's group successfully developed a visible light mediated C–3 sulfenylation of indole derivatives using $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ as the photocatalyst (Scheme 1b).^{7b} Herein, we wish to present a simple and efficient synthesis method for the direct sulfenylation of indoles with various thiophenols in the presence of inexpensive and environmentally friendly photocatalyst under air conditions (Scheme 1c). The present protocol provides a convenient and highly attractive approach to a variety of 3-sulfenylindoles in good to excellent yields, and does not require any metal catalyst, base, or peroxide oxidants.



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† Electronic supplementary information (ESI) available. See DOI: [10.1039/c7ra08086g](https://doi.org/10.1039/c7ra08086g)

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Scheme 1 Synthesis of 3-thioindole with different pairs.



Results and discussion

We started our investigation of light-mediated indole sulfenylation reaction using 1-methyl-1*H*-indole (**1a**) and 4-methylbenzenethiol (**2a**) as the model substrates in the presence of 1 mol% Ru(phen)₃Cl₂ in CH₃CN. The reaction was carried out open to air, under irradiation with a 5 W compact 415 nm lamp. The desired product 3-((4-methylphenyl)thio)-1-methyl-1*H*-indole (**3aa**) was obtained in 47% yield after 12 h (Table 1, entry 1). Inspired by this result, systematic investigation has been conducted to enhance the efficiency of the reaction. Initial attempt on changing photocatalysts was found to be effective to enhance the yield of **3aa**, and using rose bengal as the photocatalyst led to significant improvement by giving **3aa** with 77% yield (Table 1, entries 2–5). Next, a number of solvents were screened, such as DMF, DMSO, toluene, CH₂Cl₂ and EtOH (Table 1, entries 6–10). To our delight, **3aa** was obtained in 85% yield in CH₂Cl₂ after 12 h (Table 1, entry 9). No product was formed in the absence of photocatalysts (Table 1, entry 11). Furthermore, no product is produced when additional 1 eq. base was added (Table 1, entry 12). To our delight, **3aa** was obtained in 78% yield with 10 W 415 nm lamp after 12 h (Table 1, entry 13). When the reaction was performed on

nitrogen or vacuum atmospheres (Table 1, entries 14 and 15), no desired product **3aa** was formed. Further control experiment indicated that no reaction took place at all in the absence of light, which clearly showed that photoinduced irradiation was necessary for this transformation (Table 1, entry 16). Gram scale reaction was performed under the optimized reaction conditions to afford the **3aa** in 72% isolated yields.

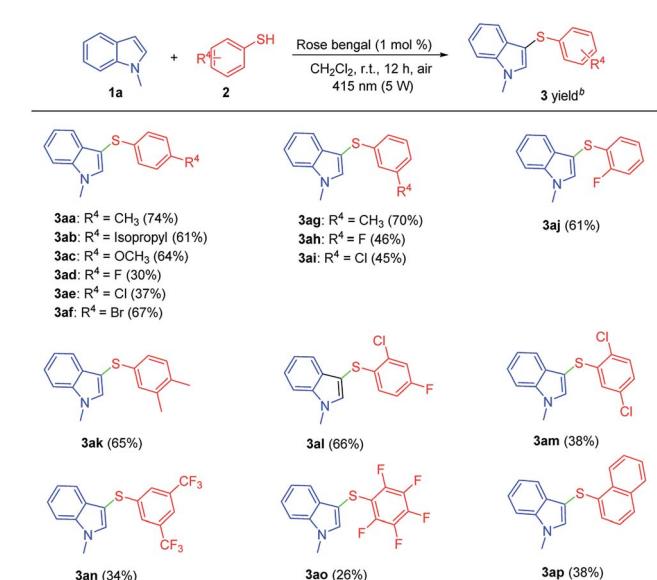
Under the optimized reaction conditions, the scope of the substrates was investigated. Firstly, the reactions of 1-methyl-1*H*-indole (**1a**) with a variety of thiophenols (**2**) were examined and the results were shown in Scheme 2. Thiophenols bearing an electron-donating group or an electron-withdrawing group at *p*-, *m*-, *o*-position reacted smoothly to give the corresponding products in moderate yields **3aa**–**3aj**. However, the electron-withdrawing group on thiophenols afforded lower yields, which attributed to the worse activities of the corresponding thiyl radical intermediates. Moreover, some difunctionalities substituent thiophenols such as 3,4-dimethylbenzenethiol (**2k**), 2-chloro-4-fluorobenzenethiol (**2l**), 2,5-dichlorobenzenethiol (**2m**) were compatible with this reaction leading to the products **3ak**–**3am**, which are the potential substrates for further transformations. Notably, 3,5-bis(trifluoromethyl)benzenethiol (**2n**) and 2,3,4,5,6-pentafluorobenzenethiol (**2o**) were suitable for this reaction, with the desired products obtained in moderate yields (**3an**, **3ao**). Moreover, as expected, 2-naphthalenethiol (**2p**) was also tolerated in this process to afford desired product **3ap** obtained in 38% yield.

The scope of the indoles substrates is also crucial for the extensive utility of this direct sulfenylation of indoles transformation (Scheme 3). The listed results demonstrate that various indole derivatives (**1**) reacted smoothly with 4-methylbenzenethiol (**2a**) to afford the corresponding 3-sulfenyliindoles

Table 1 Selected optimization studies^a

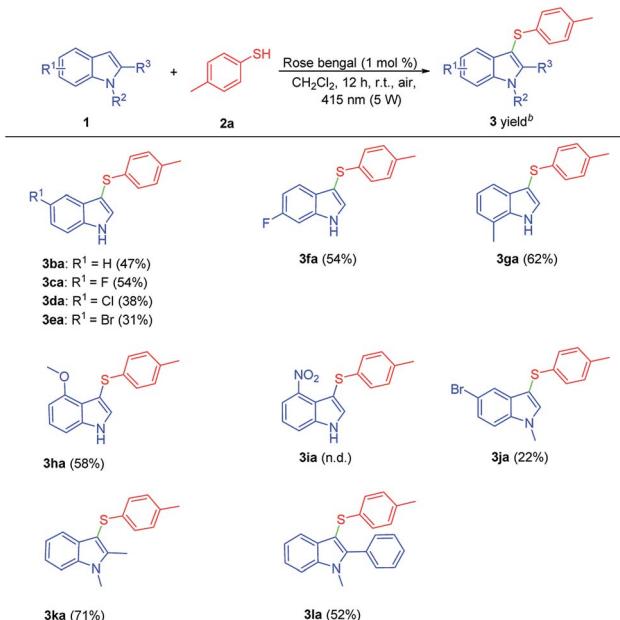
Entry	Photocatalyst	Solvent	Yield ^b (%)
1	Ru(phen) ₃ Cl ₂	CH ₃ CN	47
2	<i>fac</i> -Ir(ppy) ₃	CH ₃ CN	35
3	Eosin B	CH ₃ CN	13
4	Eosin Y	CH ₃ CN	11
5	Rose bengal	CH ₃ CN	77
6	Rose bengal	DMF	18
7	Rose bengal	DMSO	Trace
8	Rose bengal	Toluene	68
9	Rose bengal	CH ₂ Cl ₂	85
10	Rose bengal	EtOH	50
11	—	CH ₂ Cl ₂	n.d.
12 ^c	Rose bengal	CH ₂ Cl ₂	n.d.
13 ^d	Rose bengal	CH ₂ Cl ₂	78
14 ^e	Rose bengal	CH ₂ Cl ₂	n.d.
15 ^f	Rose bengal	CH ₂ Cl ₂	n.d.
16 ^g	Rose bengal	CH ₂ Cl ₂	n.d.
17 ^h	Rose bengal	CH ₂ Cl ₂	72

^a Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), catalyst (1 mol%), solvent (2.0 mL), open to air under a 5 W 415 nm lamp at room temperature for 12 h. ^b GC yields based on **1a** with *n*-dodecane as an internal standard. ^c Reaction condition was added 1 eq. K₂CO₃. ^d under 10 W 415 nm lamp promoted. ^e under nitrogen atmosphere. ^f in a vacuum. ^g in the dark. ^h The reaction was performed with **1a** (10 mmol), **2a** (12 mmol), rose bengal (1 mol%), in 5 mL CH₂Cl₂, open to air under a 5 W 415 nm lamp at room temperature for 12 h.



Scheme 2 Substrate scope of thiophenols. ^aAll reactions were performed with **1a** (0.10 mmol), **2** (0.12 mmol), and rose bengal (1 mol%) in 2.0 mL of CH₂Cl₂, open to air under a 5 W 415 nm lamp at room temperature for 12 h. ^bIsolated yields (based on **1a**).



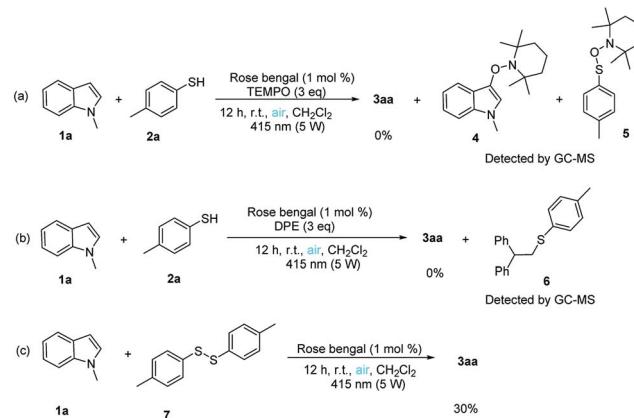


Scheme 3 Substrate scope of indoles. ^aUnless otherwise noted, all reactions were performed with **1** (0.10 mmol), **2a** (0.12 mmol), and rose bengal (1 mol%) in 2.0 mL of CH_3CN , open to air under a 5 W 415 nm lamp at room temperature for 12 h. ^bIsolated yields (based on **1a**).

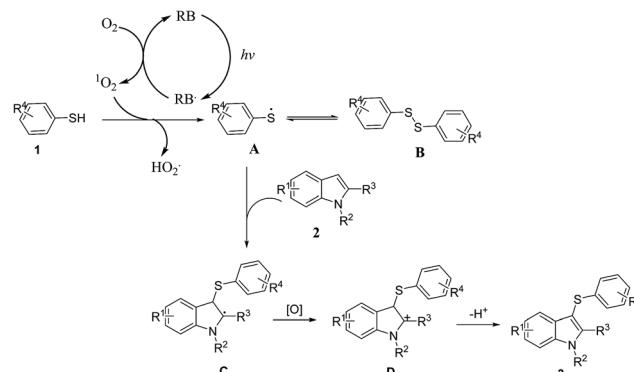
(3) in good yields (Scheme 3). Either electron-withdrawing group or electron-donating group at C-4, C-5, C-6, C-7 position of indoles were reacted with **2a** smoothly to give the corresponding products in moderate to good yields **3ba**–**3ha**. However, 4-nitro-1*H*-indole (**1i**) failed to react with **2a** and no desired product was detected. 5-Bromo-1-methyl-1*H*-indole (**1j**) with **2a** was examined, providing **3ja** in 22% yield. Satisfactorily, 1,2-dimethyl-1*H*-indole (**1k**) and 1-methyl-2-phenyl-1*H*-indole (**1l**) were also underwent the reaction with **2a** to afford the desired products **3ka** and **3la** in 71% and 52% yields.

Several control experiments were conducted to gain more insight into the mechanism of this unique reaction and the results are presented in Scheme 4. When 3 equivalents of 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) or 1,1-diphenylethylene (DPE), a radical scavenger, were added to the reaction, no desired product **3aa** obtained, however, we detected 1-methyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-1*H*-indole (**4**), 2,2,6,6-tetramethyl-1-((*p*-tolylthio)oxy)piperidine (**5**) and (2,2-diphenylethyl)(4-methylphenyl)sulfane (**6**) by GC-MS (Scheme 4a and b). Moreover, when 1-methyl-1*H*-indole reacted with disulfides (**7**) under standard conditions, the corresponding product **3aa** was obtained in 30% yields (Scheme 4c).

On the basis of above results, a possible mechanism is proposed in Scheme 5.^{9b,c} First, rose bengal (RB) is excited under light irradiation to produce its excited state species RB^* , which interacts with O_2 to generate $^1\text{O}_2$ via the energy transfer. In this process, the excited state RB^* returns to its ground state (RB).¹⁸ Subsequently, the generated $^1\text{O}_2$ abstracts a hydrogen atom from thiophenol **1** to afford the thiophenol radical **A**. Next, the resulting thiophenol radical **A** interacts with **2** to produce the radical intermediate **C**. Finally, **C** is oxidized to the intermediate **D**,



Scheme 4 Mechanistic studies.



Scheme 5 Proposed mechanism.

which affords the product **3** via deprotonation. Aerobic oxygen probably plays a crucial role to complete the photoredox cycle by oxidation of the RB radical anion to the ground state (Table 1, entries 14 and 15).¹⁸

Conclusions

In conclusion, we have successfully accomplished attractive strategy for direct assembly of 3-sulfenylindoles *via* photocatalytic direct C-3 sulfenylation of indoles with thiophenols at mild conditions. A variety of indoles and thiophenols have been efficiently transformed to structurally diverse products at room temperature. The reaction uses an inexpensive and readily available organic dye, rose bengal as the photocatalyst and air as the terminal oxidant. Moreover, no heavy-metal waste was generated during the process. It is a practical and environmentally-benign protocol that could prove useful to the chemical and pharmaceutical industries.

Experimental

General information

Melting points were measured using a melting point instrument and are uncorrected. ^1H and ^{13}C NMR spectra were



recorded on a 400 MHz NMR spectrometer. IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. GC-MS data were obtained using electron ionization. HRMS was conducted on a high-resolution mass spectrometer. TLC was performed using commercially available 100–400 mesh silica gel plates (GF254). The photoreaction instrument (WPTEC-1020L) was purchased from WATTCAS, China. Unless otherwise noted, purchased chemicals were used without further purification.

General procedure for the synthesis of 3-sulfenylindoles derivatives

A mixture of indoles (0.10 mmol), benzenethiols (0.12 mmol), and rose bengal (1 mol%) was stirred in CH_2Cl_2 (2.0 mL) under a 5 W 415 nm lamp in the photoreaction instrument at room temperature for 12 h. After completion of the reaction (monitored by TLC), water (10 mL) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were then dried over MgSO_4 , filtered, and then concentrated in vacuum. The residue was purified by flash chromatography on silica gel to give the desired product (using the mixture of petroleum ether and ethyl acetate as eluents).

Acknowledgements

We are grateful to the National Natural Science Foundation of China (21602031 and 21662002), the Advanced Innovation Research Teams Project of Jiangxi Province (20133BCB24011), and the Jiangxi Natural Science Foundation (20171BAB203010, 20141BBG70070 and 20151BAB203011).

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