



Iodine-catalysed versatile sulfenylation of indoles with thiophenols: controllable synthesis of mono- and bis-arylthioindoles



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ABSTRACT

A versatile method for the synthesis of mono- and bis-arylthioindoles via I_2 catalysed direct oxidative sulfenylation of indoles with thiophenols (especially mercaptobenzoic acids) has been presented. This system features environmental friendliness, easy operation, and mild reaction conditions, and shows a broad functional group tolerance furnishing good to excellent yields.

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1. Introduction

The significance of sulfur-bearing indoles is well reflected in the myriad constructive and functional building blocks in medicinal chemistry, materials science and natural products.¹ Among a wide range of sulfur-modified indole derivatives known, the wide spectrum of therapeutic value of numerous sulfenylated indoles which constitutes a constant source of fascination, has been recently revealed to have dramatic effects on bacterial infection, HIV, cardiovascular diseases, cancer, affective and respiratory disorders, to name but a few,² since the discovery of 3-sulfenylindoles that can serve as an orally active inhibitor of 5-lipoxygenase in 1993.³

On account of the intriguing synthetic value and varying pronounced bioactivities of these compounds, the synthetic repertoire has currently enjoyed a resurgence of interest after the initial studies in 1980s,⁴ and resulted in the development of two major synthetic strategies. The first route is achieved by cyclization reactions of 2-alkynylanilines,⁵ *o*-ethenylaryl isocyanides,⁶ 2-(*gem*-dibromo(chloro)vinyl) anilines⁷ or phenylhydrazine hydrochloride,⁸ whereas the other method involves the direct sulfenylation of a pre-existing indole ring owing to its nucleophilic nature,^{9–16} using arylsulfenyl halides,^{4a,17c} diaryl disulfides,⁹ aryl-*N*-thioimides,¹⁰ aryl thiols,¹¹ arylsulfonfyl chlorides,¹² sulfonyl hydrazides,¹³ quinone mono-*O,S*-acetals,¹⁴ arylsulfonium salts¹⁵ and sulfinic acids¹⁶ as

sources of the sulfenylating agents. Nevertheless, many of these sulfur-transfer reagents are either difficult to prepare or air and moisture sensitive. Moreover, the existing methodologies frequently require harsh reaction conditions, excess additives and transition metal catalysts, suffer from a narrow substrate scope, or yield by-products unfriendly to the environment.

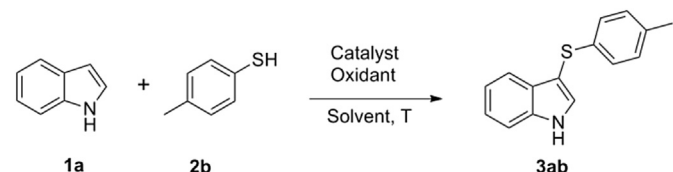
Although many methods have been successfully demonstrated to construct structurally diverse mono-sulfenyl indoles, synthesis of arylthioindoles having acidic proton functional groups (peculiarly CO_2H) has not been well documented to date.^{9g,11e} Moreover, methodologies that can accomplish double C–H sulfenylation in indoles at 2- and 3-positions have remained elusive. In the context of step- and atom-economy points of view in industrial and green chemistry, especially the low threshold residual tolerance of harmful ingredients for pharmaceuticals, there is a highly urgent demand for organic chemists to explore alternative sustainable processes for mono- and bis-arylthioindoles from simple and readily exploitable precursors under mild reaction conditions. To the best of our knowledge, there is no report on I_2 /TBHP catalyzed mono- and bis-sulfenylation of indoles with thiophenols. Herein, we detail an efficient and generally applicable methodology for the synthesis of diversely substituted mono- and bis-arylthioindoles. Unlike the previously reported sulfenylation of indoles with thiophenols, the protocol here has an extremely broad substrate scope, simple reaction conditions, and excellent yields. Notably, in this transformation, no metal salts, ligands or additives were added and without exclusion of air and moisture.

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2. Results and discussion

To acquire the optimized reaction conditions, the preliminary investigation was initiated from the model reaction of indole **1a** and *p*-toluenethiol **2b** in the presence of various iodo-containing catalysts and 1.05 equiv of *tert*-butyl hydroperoxide (TBHP). Pleasingly, I₂ (10 mol %) exhibited the best performance to produce the expected product **3ab**, 3-(*p*-tolylthio)-1*H*-indole, in 72% yield at 40 °C under air (Table 1, entry 2). Increasing the temperature to 60 °C caused an increase to 92% yield (Table 1, entry 5). The influence of the stoichiometric oxidant on the reaction system was subsequently assessed; nonetheless, better yield could not be obtained (Table 1, entries 6–8). Replacement of MeCN with other common solvents such as DMSO, MeOH and H₂O all decreased the reaction yield to varying degrees (Table 1, entries 9–11). By screening the catalyst loading, it was indicated that reducing the loading to 5 mol % gave rise to a much lower yield (Table 1, entry 12) and no product was formed without the presence of iodine catalyst (Table 1, entry 13).

Table 1
Optimization of reaction conditions for the synthesis of 3-(*p*-tolylthio)-1*H*-indole **3ab**^{a,b}



Entry	Catalyst	Oxidant	Solvent	T (°C)	Yield (%) ^b
1	NIS	TBHP	MeCN	40	70
2	I ₂	TBHP	MeCN	40	73
3	KI	TBHP	MeCN	40	13
4	TBAI	TBHP	MeCN	40	Trace
5	I ₂	TBHP	MeCN	60	92
6	I ₂	H ₂ O ₂	MeCN	60	78
7	I ₂	(NH ₄) ₂ S ₂ O ₈	MeCN	60	83
8	I ₂	DTBP	MeCN	60	Trace
9	I ₂	TBHP	DMSO	60	81
10	I ₂	TBHP	MeOH	60	63
11	I ₂	TBHP	H ₂ O	60	74
12 ^c	I ₂	TBHP	MeCN	60	71
13	—	TBHP	MeCN	80	—

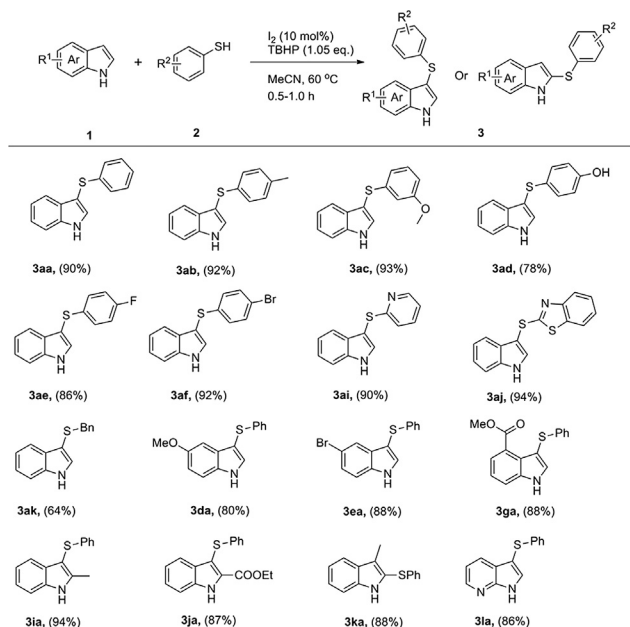
^a Reaction conditions: indole **1a** (0.50 mmol), *p*-toluenethiol **2b** (0.505 mmol), catalyst (10 mol %), oxidant (0.525 mmol), solvent (2.0 mL), open to air.

^b Isolated yield.

^c 5 mol % iodine was used.

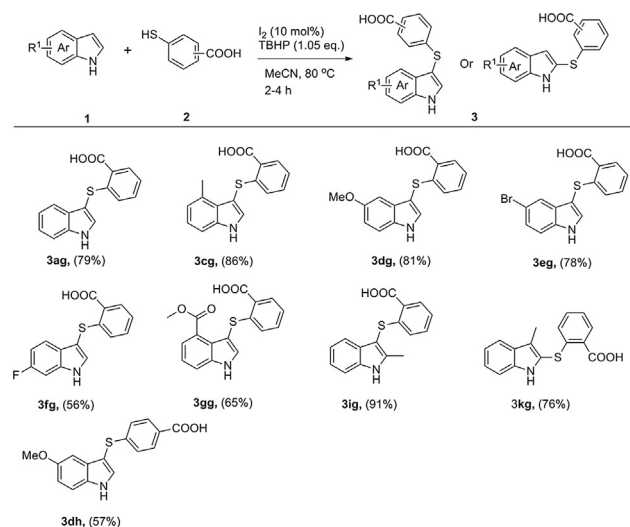
With the optimal reaction conditions in hand, a systematic investigation was conducted to evaluate the generality of the facile transformation. As outlined in Scheme 1, a vast variety of aryl- and heteroarylthiols smoothly underwent sulfenylation with indoles to generate structurally diverse thioethers in high yields with extremely high regioselectivity (Scheme 1, **3a–j**). In addition, sulfenylation reaction using benzyl mercaptan successfully took place under present catalytic conditions (Scheme 1, **3ak**). Indoles bearing functional groups such as alkoxy, halide and ester all displayed satisfactory tolerance to the protocol and provided corresponding products with good to excellent yields (Scheme 1, **3da–3ga**). Furthermore, we were delighted to disclose that high yields were also obtained from 7-aza-, 2- and 3-substituted indoles (Scheme 1, **3ia–3la**).

In the existing literature, very few synthetic pathways enabling the preparation of the sulfonylindoles using mercaptobenzoic acids as sulfur-transfer reagents were found because of the strong electron-withdrawing feature of carboxy group.^{9g,11e} Within this scenario, the optimized reaction conditions prompted us to validate a further useful application by reacting two sorts of



Scheme 1. Synthesis of monosulfonyl indoles^{a,b}.

mercaptobenzoic acids with various indoles to furnish the corresponding arylthioindoles. By comparing with previously reported results,^{9g,11e} it could be easily discerned that the new method not only considerably reduced the reaction time and temperature, but above all markedly increased the yield of the products. In particular, under our experimental conditions, methyl indole-4-carboxylate and 3-methylindole smoothly went through sulfenylation to afford the relevant derivatives in good yields (Scheme 2, **3gg**, **3kg**). Among the mercaptobenzoic acids tested, 4-mercaptobenzoic acid **2h** which exhibited worse reactivity compared with **3dg** could be explained mainly by taking into account the formation of different active species of mercaptobenzoic acids proposed by Li.^{11e}



Scheme 2. Scope of mercaptobenzoic acids^{a,b}.

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