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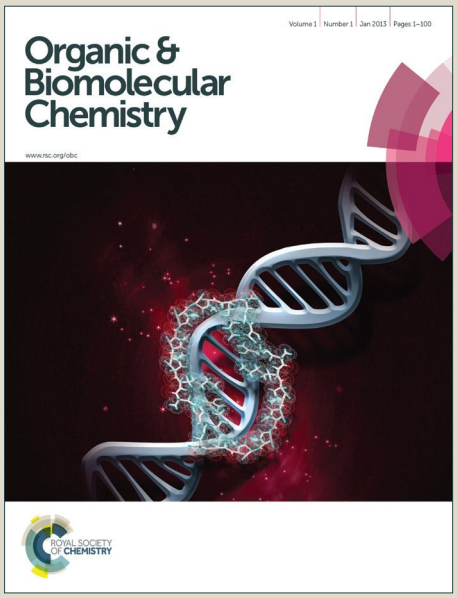


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ARTICLE TYPE

# Byproduct Promoted Regioselective Sulfenylation of Indoles with Sulfinic Acids

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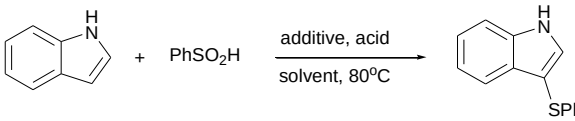
**An unprecedented method to synthetise 3-sulfenylindoles is demonstrated via byproduct promoted sulfenylation of indoles with sulfinic acids in the absence of external catalyst. The reaction selectively afforded structurally diverse indole thioethers in good to excellent yields in 1,2 - dichloroethane at 80 °C.**

The indole moiety is an important unit because of its presence in many bioactive relevant molecules, such as colchicines, combretastatin A-4, indolyl-3-glyoxamide D-24851 and 2-aryl-3-arylcarbonylindole.[1] Developing efficient synthetic approaches to construct differently substituted indole derivatives is one of the most exciting topics in organic synthesis.[2] Among them, the direct carbon-hydrogen bond functionalization is a more convenient method for the formation of carbon-carbon and carbon-heteroatom bonds on indole rings.[3] In this regard, the sulfenylation of indoles has been developed for the synthesis of 3-sulfenylindoles, some of which are important drugs assessed in several disease areas, including bacterial infection, cancer, HIV, obesity, heart diseases and allergies.[4] Various sulfenylating agents such as sulfonium salts,[5] quinone mono-O,S-acetals, [6]sulfonyl hydrazides,[7] sulfinates,[8] disulfides,[9] sulfenyl halides,[10] N-thioimides,[11] thiols[12] and arylsulfonyl chlorides[13] were smoothly coupled with indoles. However, many of these sulfenylating agents are impractical due to the accessibility, substrate compatibility, stability. Moreover, many reported sulfenylation reactions of indoles frequently require catalysts, harsh reaction conditions or excess sulfenylating agents. Therefore, a new general and flexible approach for the sulfenylation of indoles is still necessary.

Sulfinic acids are readily accessible and they have been employed to form sulfones which have versatile applications in medicinal chemistry.[14] Moreover, sulfinic acids can be reduced to disulfides ,which are conventional sulfenylating agents. So we envisioned that sulfinic acids might serve as potential sulfenylating agents to couple with indoles under certain reaction conditions. To our knowledge, there are no examples describing the sulfenylation of indoles using sulfinic acids as potential sulfenylating agents. Herein we report an efficiend synthesis of 3-sulfenylindoles via byproduct promoted sulfenylation of indoles with sulfinic acids in the absence of external catalysts.

To get the optimized reaction conditions, several Brønsted acids (10 mol%) were examined in the model reaction of indole **1a** with benzenesulfinic acid **2a** using tetrabutylammonium iodide as additive in 1,2 - dichloroethane at 80 °C. To our delight, TsOH was identified as the acid of choice, which promoted the formation of 3-sulfenylindole **3a** in 69% yield (Table 1, entry 1). Nevertheless, the yield decreased dramatically when replacing tetrabutylammonium iodide with sodium iodide or potassium iodide (Table 1, entries 5 and 6). A number of common solvents were examined, but no better yield was obtained. (Table 1, entries 7-15). A high yield was obtained when the loading of Tetrabutylammonium iodide was increased to 1.2 equivalent (Table 1, entriy 16). Further efforts to increase the yield of 3-sulfenylindole **3a** by increasing the loading of TsOH to 0.2 equivalent resulted in a higher yield 98% (Table 1, entriy 17).

**Table 1**. Optimization of Reaction Conditions [a]




**1a** **2a** **3a**

| Entry | Solvent | Additive (eq) | Acid(eq) | Yield(%) |
|---|---|---|---|---|
| 1 | DCE | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 69 |
| 2 | DCE | n-$Bu_4NI$ (1.0) | HCl (0.1) | 47 |
| 3 | DCE | n-$Bu_4NI$ (1.0) | TfOH (0.1) | 63 |
| 4 | DCE | n-$Bu_4NI$ (1.0) | $H_2SO_4$ (0.1) | 55 |
| 5 | DCE | NaI (1.0) | TsOH (0.1) | 23 |
| 6 | DCE | KI (1.0) | TsOH (0.1) | 11 |
| 7 | MeCN | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 27 |
| 8 | $MeNO_2$ | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 14 |
| 9 | Toluene | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 38 |
| 10 | DMA | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 43 |
| 11 | DMSO | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 40 |
| 12 | DMF | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 43 |
| 13 | Dioxane | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 32 |
| 14 | EtOH | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 30 |
| 15 | $H_2O$ | n-$Bu_4NI$ (1.0) | TsOH (0.1) | 40 |
| 16 | DCE | n-$Bu_4NI$ (1.2) | TsOH (0.1) | 87 |
| **17** | **DCE** | **n-$Bu_4NI$ (1.2)** | **TsOH (0.2)** | **98** |

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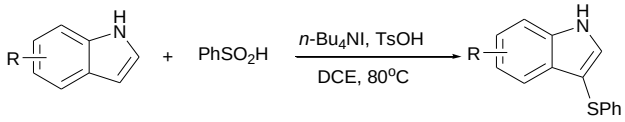
[a] Reaction conditions: indole **1a** (0.20 mmol), benzenesulfinic acid **2a** (0.24 mmol), additive , acid, solvent (1.0 mL), 80 °C (oil bath), 12 h. [b] Isolated yield.

Encouraged by our preliminary findings, we investigated the substrate scope for the sulfenylation of indoles with benzenesulfinic acid (**2a**). Under the optimized reaction conditions, a number of indoles bearing either electron-withdrawing groups (Cl, Br, $NO_2$, and $CO_2Me$) or electron-donating groups (Me, Ph, and OMe) on the N-1, C-2, C-4, C-5 or C-6 positions of the indole rings, were transformed into their corresponding 3-phenylthioindoles in good to excellent yields (table 2). Lower yields was obtained when strong electron withdrawing groups, like a carbomethoxy group or nitro group, were present at the C-5 position in the indole (table 2, entries 8 and 9).

**Table 2**. Regioselective Sulfenylation of Indoles with benzenesulfinic Acid (**2a**) [a]



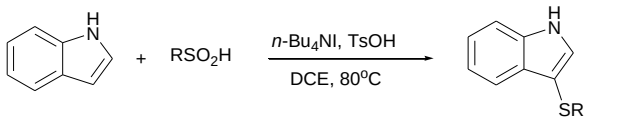

**1** **2a** **3a-j**

| Entry | **1** (R) | **3** | Yield (%)b |
|---|---|---|---|
| 1 | **1a** ( H) | **3a** | 98 |
| 2 | **1b** (1-Me) | **3b** | 99 |
| 3 | **1c** (2-Me) | **3c** | 87 |
| 4 | **1d** (2-Ph) | **3d** | 93 |
| 5 | **1e** (4-Br) | **3e** | 95 |
| 6 | **1f** (5-Br) | **3f** | 98 |
| 7 | **1g** (5-OMe) | **3g** | 90 |
| 8 | **1h** (5-$CO_2$Me) | **3h** | 86 |
| 9 | **1i** (5-$NO_2$) | **3i** | 70 |
| 10 | **1j** (6-Cl) | **3j** | 97 |

[a] Reaction conditions: indole **1** (0.20 mmol), benzenesulfinic acid **2a** (0.24 mmol), *n*-$Bu_4NI$ (0.24 mmol), TsOH (0.040 mmol), DCE (1.0 mL), 80 °C (oil bath), 12 h. [b] Isolated yield.

Next, we examined the reactivity of various sulfinic acids toward indole (**1a**) (Table 3). A range of arylsulfinic acids smoothly reacted with indole **1a** to give the corresponding 3-arylthioindoles in good to excellent yields (table 3, entries 1-9). It is noteworthy that both electon-withdrawing and electron-donating groups were introduced into the sulfenylation product by employing arylsulfinic acid bearing such groups on the aromatic ring. Furthermore, alkylsulfinic acids also could smoothly react with indole **1a** to give the corresponding 3-alkylthioindoles, and as expected, lower yieldes were given for the sulfenylation of indoles with these less reactive sulfinic acids (table 3, entries 10-12).

**Table 3**. Regioselective Sulfenylation of Indole (**1a**) with Sulfinic Acids [a]

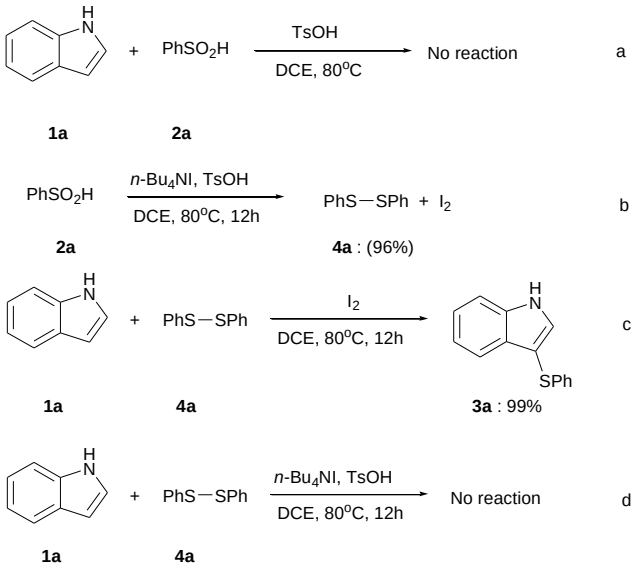



**1a** **2** **3k-v**

| Entry | **2** (R) | **3** | Yield (%) |
|---|---|---|---|
| 1 | **2b** (3-$O_2NC_6H_4$) | **3k** | 92 |
| 2 | **2c** (4-$O_2NC_6H_4$) | **3l** | 96 |
| 3 | **2d** (4-$FC_6H_4$) | **3m** | 83 |
| 4 | **2e** (4-$ClC_6H_4$) | **3n** | 90 |
| 5 | **2f** (4-$BrC_6H_4$) | **3o** | 89 |
| 6 | **2g** (4-$IC_6H_4$) | **3p** | 88 |
| 7 | **2h** (4-$MeC_6H_4$) | **3q** | 94 |
| 8 | **2i** (4-$MeOC_6H_4$) | **3r** | 84 |
| 9 | **2j** (2-naphthyl) | **3s** | 96 |
| 10 | **2k** (Me) | **3t** | 80 |
| 11 | **2l** $(CH_2)_7CH_3$ | **3u** | 70 |
| 12 | **2m** $CH_2Ph$ | **3v** | 77 |

[a] Reaction conditions: indole **1a** (0.20 mmol), Sulfinic acid **2** (0.24 mmol), *n*-$Bu_4NI$ (0.24 mmol), TsOH (0.040 mmol), DCE (1.0 mL), 80 °C (oil bath), 12 h. [b] Isolated yield.

During these reactions, we observed that the colors of mixtures were purple (Table 1,2 and 3), So we speculated that there was iodine produced. To gain insight into the reaction mechanism, four control experiments were set up under various reaction conditions. No reaction occurred upon treatment of indole **1a** with benzenesulfinic acid **2a** in the absence of tetrabutylammonium iodide (Scheme 1, a). Under the optimized reaction conditions, benzensulfinic acid was reduced into diphenyldisulfane **4a** in 96% yield, while iodide ion was oxidized into iodine (scheme 1, b). In the presence of 1.2 equivalents iodine, indole **1a** smoothly reacted with diphenyldisulfane **4a** to




**Scheme 1** Control Experiments

give the corresponding 3-phenylthioindole **3a** in 99% yield (scheme 1, c). No reaction occurred upon treatment of indole **1a** with diphenyldisulfane **4a** in the optimized reaction conditions

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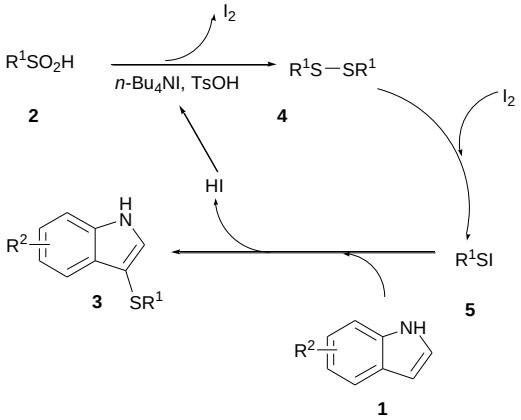
(Scheme 1, d).

On the basis of the above experimental results and previous relevant mechanistic studies,[9] we proposed the reaction pathway depicted in Scheme 2. Initially, diphenyldisulfane (**4**) is generated from sulfinic acid **2** in the presence of TsOH and *n*-$Bu_4NI$. Then **4** reacts with $I_2$ to give the sulfenyl iodide **5**, which is attacked by **1** to give thioether **3** and HI. HI react with **2** to give **4** and regenerate iodine to promoted the reaction continually.




**Scheme 2** Proposed Reaction Pathway

## Conclusions

In summary, we have developed an unprecedented method to synthesise 3-arylthioindoles and 3-alkylthioindoles from indoles and sulfinic acids. In the presence of 10 mol% TsOH and 1.2 equivalent *n*-$Bu_4NI$ , a range of aryl- and alkylsulfinic acids smoothly underwent sulfenylation with indoles to give structurally diverse indole thioethers in good to excellent yields. The byproduct $I_2$ acted as an efficient catalyst for this kind of transformation.

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [spectral data for all reported compounds]. See DOI: 10.1039/b000000x/

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