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A Sulfenylation Reaction: Direct Synthesis of 3-Arylsulfinylindoles from Arylsulfinic Acids and Indoles in Water

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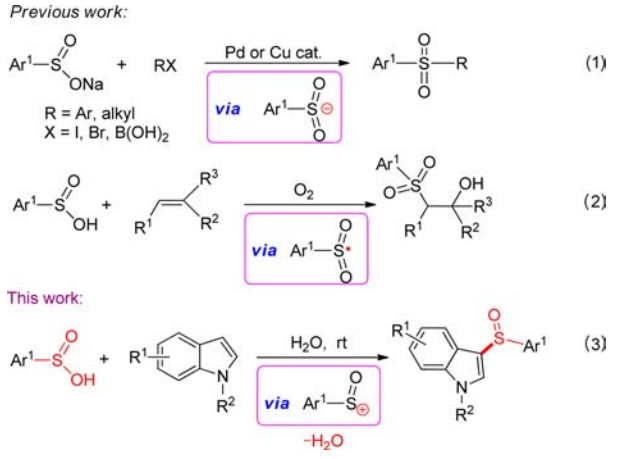
Supporting Information

ABSTRACT: A novel and efficient electrophilic sulfenylation of indoles with arylsulfinic acids is realized. The reaction utilizes readily available starting materials in water under catalyst- and additive-free conditions, providing an alternative and attractive approach to 3-arylsulfinylindoles with high yields. Preliminary mechanistic investigation suggested that the reaction is through an electrophilic substitution process.

Sulfoxides, one of the most valuable compounds, constitute the core motif of natural products,[1] materials,[2] and biologically significant molecules,[3] representative examples being the antiulcer agent esomeprazole[3a] and modafinil[3b] for narcolepsy. Furthermore, sulfoxides have been used in organocatalysis,[4] and as ligands in organometallic chemistry.[5] Despite their wide applicability, their direct synthesis remains a challenge. In general, sulfoxides are prepared by selective oxidation of the parent thioether[6] and the nucleophilic substitution of sulfinyl derivatives with organometallic reagents.[7] An advance in the synthesis of diaryl sulfoxides is Pd-catalyzed cross-coupling of sulfenate anions with aryl iodides and bromides.[8] Although some of these methods are popular and attractive, they still suffer from limitations in substrate scope, and multistep processes to reactants. Accordingly, development of straightforward, milder, and environmentally benign methods for the preparation of sulfoxides from easily available substrates is highly desirable.

Arylsulfinic acids (salts) are versatile and readily available intermediates in organic synthesis.[9] In recent years, much effort has been devoted toward developing sulfonylation reactions using sulfinic acids (salts) as sulfonylating agents. Among the reported methods, two different pathways have been developed to construct sulfones. First, transition-metal-catalyzed cross-coupling of sodium arenesulfinates with aryl halides and organoboronic acids has proven to be an effective approach to sulfones.[10] Arylsulfinic salts as the precursors of the sulfonyl anion reacted with a metal catalyst to form a key intermediate, sulfonyl-metal species (Scheme 1, eq 1). Second, addition of the sulfonyl radical to a carbon−carbon multiple bond provided an alternative for the preparation of functionalized aryl-sulfones.[11] For example, Lei and co-workers described a dioxygen-triggered oxidative radical reaction of aryl-sulfinic acids with alkenes leading to β-hydroxysulfones (Scheme 1, eq 2).[11a] Compared to the preparation of functionalized sulfones from arylsulfinic acids via the sulfonyl anions and radicals process, sulfinyl cations from arylsulfinic acids have never been used for the synthesis of sulfoxides and sulfones.

Scheme 1. Synthetic Application of Arylsulfinic Acids (Salts)



Herein, we present a novel strategy for the direct and highly efficient synthesis of 3-arylsulfinylindoles using arylsulfinic acids as electrophiles with indoles under metal- and additive-free conditions at ambient temperature in water (Scheme 1, eq 3). A preliminary mechanism revealed that an electrophilic substitution process was involved, and the arylsulfinyl cation

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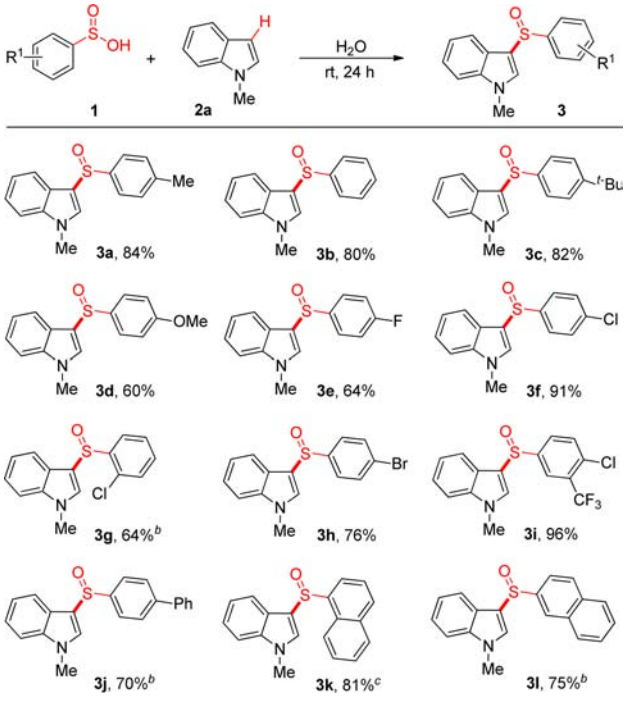
was found to be a stable and key intermediate by ESI-MS probe.

Treatment of *p*-tolylsulfinic acid (**1a**, 1.0 equiv) with 1-methylindole (**2a**, 1.0 equiv) in water at room temperature under air for 24 h afforded 1-methyl-3-(*p*-tolylsulfinyl)-indole (**3a**) in 45% yield (Table S1, entry 1, Supporting Information). The structure of **3a** was characterized by ^{1}H, ^{13}C NMR spectroscopy and HRMS and was confirmed by single-crystal X-ray diffraction analysis (see Supporting Information). Encouraged by this result, we optimized the reaction conditions to improve the product yield. To our delight, when the molar ratio of **1a**/**2a** was increased to 2:1, product **3a** was obtained in 84% yield (Table S1, entry 2). Then, various solvents were examined. The results indicated that organic solvents, such as tetrahydrofuran (THF), dioxane, ethanol, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and acetic acid, gave lower yields of **3a** (Table S1, entries 3−9). However, acetonitrile, dichloroethane (DCE), and nitromethane prohibited the reaction completely (Table S1, entries 10−12). After extensive additive, reaction time, and temperature screening, it turned out that the optimal parameters included being additive-free at room temperature for 24 h.

Having the optimized reaction conditions, the scope of this reaction with respect to the arylsulfinic acids was examined, shown in Scheme 2. The results indicated that the substituted arylsulfinic acids bearing methyl, *tert*-butyl, and methoxy on the aromatic rings reacted with 1-methylindole (**2a**) to afford the corresponding sulfenylation products in good yields (**3a**−**d**). Halogens on the arylsulfinic acids were well tolerated, providing good yields of products (**3e**−**i**), which are the potential substrates for further transition-metal-catalyzed functionalization. An obvious *ortho*-position effect was observed in the reaction (**3f** vs **3g**). It should be noted that the trifluoromethyl group (CF_3), as a useful structural motif in many biologically active molecules,[12] attached on the arylsulfinic acids afforded the corresponding product (**3i**) in excellent yield. More bulky 1,1′-biphenyl-, 1-naphthyl-, and 2-naphthylsulfinic acids also reacted with **2a** smoothly to offer the desired sulfoxides **3j**, **3k**, and **3l** in good yields.

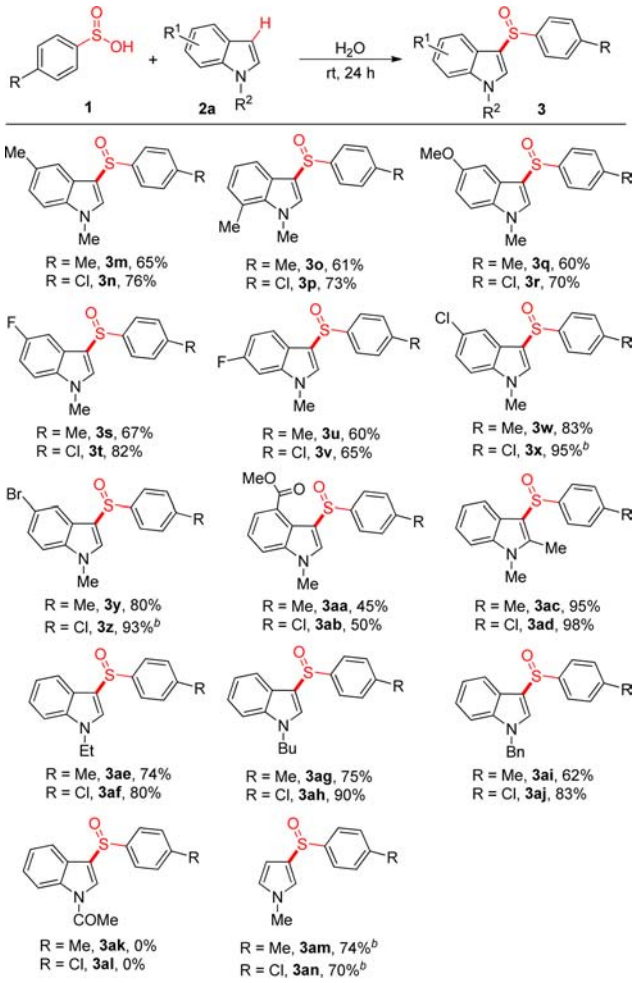
To further investigate the scope of indoles, various *N*-substituted indoles were treated with *p*-tolylsulfinic acid and *p*-chlorophenylsulfinic acid under optimized reaction conditions, and the results were summarized in Scheme 3. Both electron-donating and -withdrawing groups on the 4−7-positions of indole cores were tolerated, and the corresponding products (**3m**−**3aj**) were obtained in 45−98% yields. It is obvious that the more electron-poor indoles were less reactive and provided lower yields of the products (**3aa**, **3ab**). It is noteworthy that, by introducing a methyl group into the 2-position of the indole nucleus, almost quantitative yields were obtained (**3ac**, **3ad**). For *N*-substituted indoles, Et, Bu, and Bn substituents (**3ae**−**3aj**) proved to be suitable substrates, while COMe was inert (**3ak** and **3al**). These results clearly indicated that the sufficient electron density on the pyrrole ring of indole accelerates the

Scheme 2. Scope of Arylsulfinic Acids[a]



[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.25 mmol), H_2O (1.0 mL), at room temperature, 24 h, isolated yields of the products. [b]The reaction was performed at 70 °C for 24 h. [c]The reaction was performed in the mixture of acetic acid and water (1:1, 1.0 mL).

Scheme 3. Scope of Indoles[a]



[a]Reaction conditions: **1** (0.50 mmol), **2** (0.25 mmol), H_2O (1.0 mL), at room temperature, 24 h, isolated yields of the products. [b]The reaction was performed at 70 °C for 24 h.

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electrophilic substitution. It is well-known that indoles undergo electrophilic substitution at the 3-position, whereas pyrroles undergo the reaction at the 2-position.[13] Interesting, the sulfenylation reaction of electron-rich *N*-methylpyrrole with *p*-tolylsulfinic acid and *p*-chlorophenylsulfinic acid at 70 °C generated 3-substituted products **3am** and **3an** in good yields, which probably undergo a rearrangement from 2-sulfinylpyrroles to isomeric 3-sulfinylpyrroles,[14] and the structure of **3am** was confirmed by X-ray crystallographic analysis (Supporting Information).

To understand the reaction process, the model reaction was performed under an O_2 and Ar atmosphere instead of air. However, no improvement of this transformation was found, providing **3a** in 80% and 82% yields, respectively. The results demonstrated that a radical process might not be involved in the reaction, even though O_2, as a clean and environmental friendly radical initiator, was used in sulfonylation reactions.[11a,b] Electrospray ionization mass spectrometry (ESI-MS), as a soft MS ionization technique, promotes only a few fragmentation products and is also rapidly becoming the technique of choice for mechanistic studies and high-throughput screenings of homogeneous catalysis.[15] Considering the pivotal importance of characterizing the cationic species, we decided to take advantage of ESI-MS analysis on the model reaction of **1a** and **2a** to further probe the reaction mechanism. After the model reaction was stirred in water at room temperature for 2 h, an aliquot was withdrawn from the reaction mixture and directly analyzed by ESI-MS in positive ion mode. Several peaks with *m*/*z* signals characterized for cationic intermediates were trapped. On the analysis of the present *m*/*z* signals in Figure 1, structures of the cationic intermediates were proposed, assigned as **A**, **B**, and **C**.

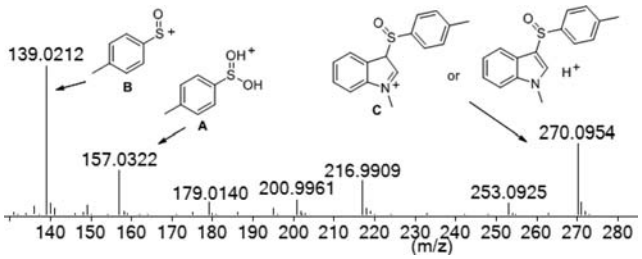
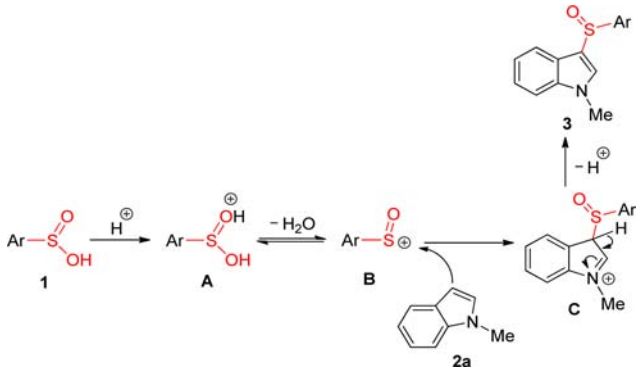


Figure 1. ESI-MS analysis for the reaction of **1a** and **2a**.

Scheme 4 describes a proposed reaction pathway for the formation of 3-arylsulfinylindoles based on the aforementioned results and isotope labeling experiment (see Supporting Information for detail), which is in agreement with an electrophilic substitution process. First, the reaction was initiated by a protonation of arylsulfinic acid (**1**) to form species **A** under acidic conditions. The formed **A** underwent a dehydration to release sulfinyl cation **B**. Subsequently, the intermediate **C** could be produced by a direct electrophilic substitution of an indole (**2a**) at the C-3 position. Finally, loss of a proton from **C** afforded product **3**.

Scheme 4. Proposed Reaction Mechanism



In summary, we have developed a highly attractive and operationally simple method to construct indol-3-yl aryl sulfoxides from readily available reactants. Notably, various substrates were employed in the reaction and the corresponding products were obtained in good to excellent yields under mild conditions. The novel method proceeded without any additional catalysts and additives and realized direct sulfenylation of indoles in water, which made this transformation sustainable and environmentally friendly. The preliminary mechanism revealed that an electrophilic substitution of the sulfinyl cation process was involved, determined by ESI-MS analysis. The unique transformation holds significant potential for application to a series of new organic reactions. Our further efforts in this area are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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