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PAPER
Jason B. Benedict et al
The role of atropisomers on the photo-reactivity and fatigue of diarylethene-based metal–organic frameworks

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Convenient KI-Catalyzed Regioselective Synthesis of 2-Sulfonylindoles Using Water as Solvent

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Abstract: A convenient procedure is developed for the preparation of 2-sulfonylindoles from indoles and sodium sulfinates catalyzed by KI in water. This environmentally benign 2-sulfonylation of indoles proceeds efficiently under mild conditions, affording the products with high regioselectivity and in moderate to good yields.

Keywards: 2-Sulfonylation, Indole, Sodium sulfinate, Potassium iodide, Catalysis.

The indole nucleus is ubiquitous in a wide range of natural products, pharmaceuticals and fine chemicals, and consequently, much attention has been paid to the synthesis of substituted indoles.[1] 2-Sulfonylindoles are a significant class of indole compounds due to the sulfonyl moiety can enhance the biological activity of these compounds[2] and also serve as useful vehicles for the development of new strategies and tactics for synthesis.[3] Recently, using sodium sulfinates as sulfur-containing reagents for a direct regioselective synthesis of 2-sulfonylindoles has attracted considerable attention. Deng and co-workers in 2014 first reported on the facile 2-sulfonylation of indoles catalyzed by molecular iodine using indoles, sodium sulfinates and oxidant TBHP in AcOH (Scheme 1, a).[4] Then, Kuhakarn's group demonstrated the regioselective 2-sulfonylation of indoles from indoles and sodium sulfinates mediated by I_2 in MeOH (Scheme 1, b).[5] Zhang and co-workers just reported the new contribution on the selective synthesis of 2-sulfonylindoles and 3-sulfonylindoles, and they found that in the presence of catalyst NH_4I combined with oxidant TBHP, a regioselective 2-sulfonylation of indoles was reached (Scheme 1, c).[6] The above new approaches for synthesis of 2-sulfonylindoles have some advantages over previous methods, such as simple, efficient, direct, regioselective and giving good yields. However, these new methods were not effective in water. Therefore, an exploration of more environmentally benign protocol for synthesis of 2-sulfonylindoles using water as solvent is highly desirable. Herein, we wish to report a convenient 2-sulfonylation of indoles with sodium sulfinates and Oxone® in water using KI as catalyst (Scheme 1, d). To the best of our knowledge, this regioselective 2-sulfonylation of indoles in water has not been reported before.

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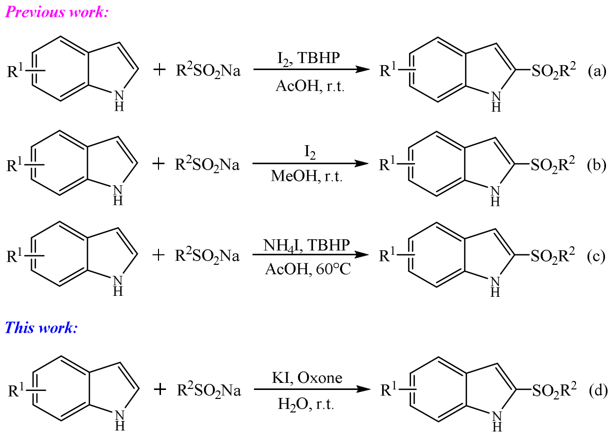

Scheme 1 Methods for the 2-sulfonylation of indoles

The catalytic utilization of molecular iodine and its salts in organic synthesis is increasing in importance, with growing interest in the development of environmentally benign synthetic transformations.[7] Due to the ease of handling, low toxicity, commercial availability and mild reactivity, especially the metal-like behavior of iodine, a number of recent studies have demonstrated the utility of iodine catalysis as an efficient and powerful tool for the formation of carbon-carbon and carbon-heteroatom bonds.[8] In order to explore the possibility for the regioselective 2-sulfonylation of indoles in water, we first checked the reaction of indole **1a**, sodium phenylsulfinate **2a** and KI in water at room temperature, and after long time stirring, only the substrate **1a** was recovered in near quantitatively. Then, a water-soluble oxidant Oxone® ($2KHSO_5$-$KHSO_4$-K_2SO_4) was added in and the suspension was stirred for a short time, the desired product, 2-(phenylsulfonyl)-1*H*-indole **3a** was fortunately obtained as sediment. Encouraged by the result, the 2-sulfonylation of 1.0 equiv of **1a** in water with **2a** and Oxone® in the presence of KI at room temperature over 1 h was optimized (Table 1). It is obvious that the amount of oxidant has the influence on the yield and the most suitable amount of it for the reaction is 2.5 equiv (Table 1, entries 1-6). The optimal amounts of **2a** and KI were then evaluated, 1.5 equiv for **2a** and 0.2 equiv for KI proving to be the best choices consequently (entries 4, 7-14). Other iodine-containing iodides such as NaI, NH_4I and Et_4NI were all effective in the reaction, resulting in the similar yields (entries 4, 15-17). Some oxidants such as *m*CPBA, TBHP and H_2O_2 were also checked under the optimal reaction conditions; however, besides *m*CPBA gave a poor yield, other two were not active in the reaction (entries 18-20). As the control experiment, it was found that in the absent of Oxone® or KI, no desired product **3a** was observed (entries 21-22). In order to explore the mechanism, a radical scavenger, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), was added in the reaction. It is clear that when more TEMPO was added, the yield decreased sharply, meaning the reaction may undergo a radical pathway (entries 23-29).[5]

Based on the extensive screening process, we arrived at the optimal reaction conditions. Next, the 2-sulfonylation of 1.0 equiv of a number of indoles **1** with 1.5 equiv of several sodium sulfinates **2** and 2.5 equiv of Oxone® in the presence of 0.2 equiv of KI in water at room temperature over 1 h was investigated, and a series of corresponding 2-sulfonylindoles **3** were afforded. The results are summarized in Table 2.

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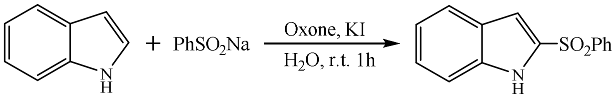
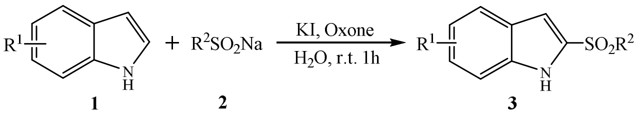
Table 1 Optimization of the 2-sulfonylation of indoles catalyzed by KI

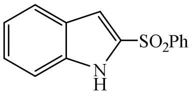


Entry	$PhSO_2Na$ (equiv)	KI (equiv)	Oxone® (equiv)	TEMPO (equiv)	Yield (%)[a]
1	1.5	0.2	1.2	-	35
2	1.5	0.2	2.0	-	53
3	1.5	0.2	2.3	-	74
4	1.5	0.2	2.5	-	74
5	1.5	0.2	2.7	-	76
6	1.5	0.2	3.0	-	59
7	1.0	0.2	2.5	-	62
8	2.0	0.2	2.5	-	74
9	3.0	0.2	2.5	-	70
10	4.0	0.2	2.5	-	47
11	1.5	0.1	2.5	-	49
12	1.5	0.3	2.5	-	72
13	1.5	0.5	2.5	-	74
14	1.5	1.0	2.5	-	72
15	1.5	NaI (0.2)	2.5	-	74
16	1.5	NH_4I (0.2)	2.5	-	76
17	1.5	Et_4NI (0.2)	2.5	-	68
18	1.5	0.2	*m*CPBA (2.5)	-	30
19	1.5	0.2	TBHP (2.5)	-	0
20	1.5	0.2	H_2O_2 (2.5)		0
21	1.5	0.2	-	-	0
22	1.5	-	2.5	-	0
23	1.5	0.2	2.5	0.2	58
24	1.5	0.2	2.5	0.5	52
25	1.5	0.2	2.5	1.0	43
26	1.5	0.2	2.5	2.0	37
27	1.5	0.2	2.5	3.0	29
28	1.5	0.2	2.5	5.0	19
29	1.5	0.2	2.5	6.0	17

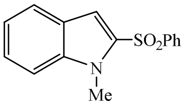
[a] Isolated yields.

Table 2 2-sulfonylation of indoles catalyzed by KI [a,b]

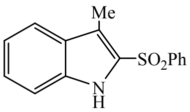




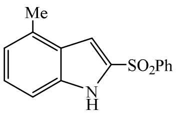
3a, 74%



3b, 56%



3c, 52%



3d, 52%

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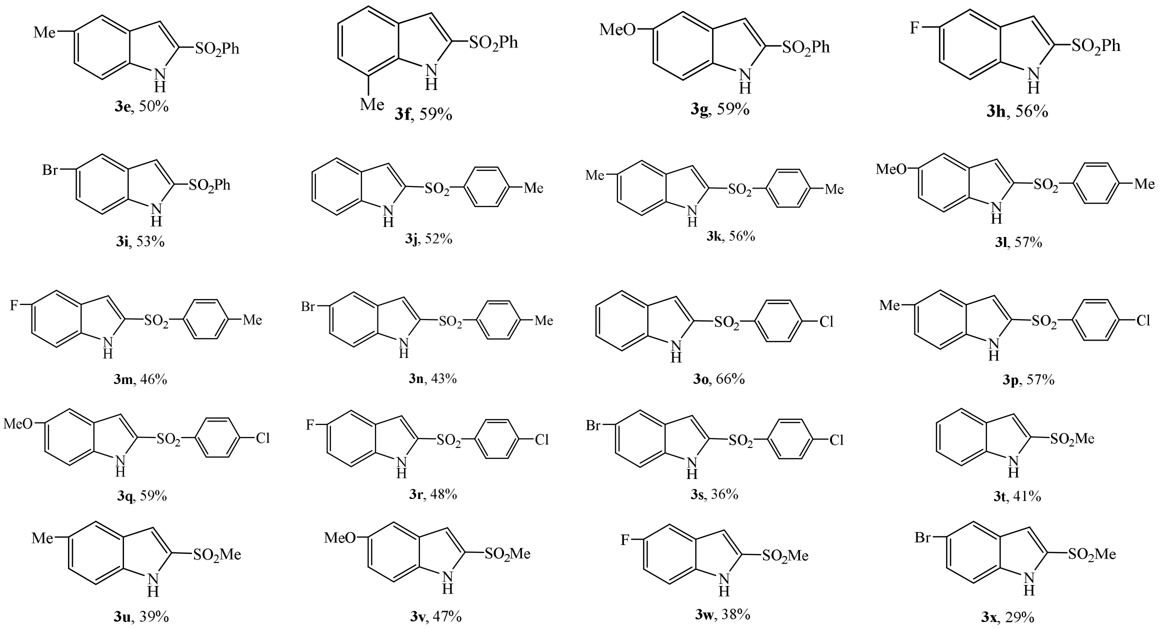


3e, 50% **3f**, 59% **3g**, 59% **3h**, 56%

3i, 53% **3j**, 52% **3k**, 56% **3l**, 57%

3m, 46% **3n**, 43% **3o**, 66% **3p**, 57%

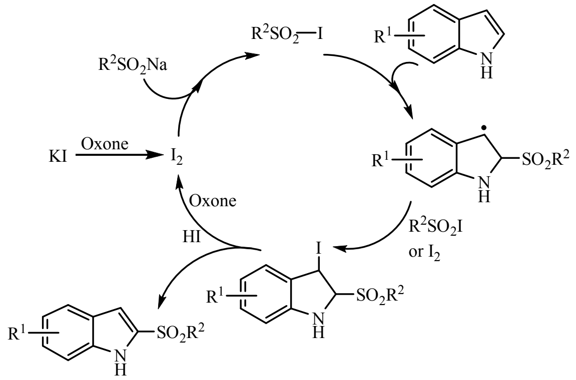
3q, 59% **3r**, 48% **3s**, 36% **3t**, 41%

3u, 39% **3v**, 47% **3w**, 38% **3x**, 29%

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Oxone® (0.5 mmol), KI (0.04 mmol) in water (3mL), stirred at r.t. for 1 h. [b] Yield of the isolated product **3**.

As shown in Table 2, the KI-catalyzed 2-sulfonylation was compatible with the studied indoles when they reacted with sodium phenylsulfinate **2a**, affording the corresponding 2-sulfonylindoles **3a**-**3i** in good yields. It is obvious that the substituents on indole ring, whether they were electron-donating (methyl and methoxy) or electron-withdrawing (fluoro and bromo) groups, usually had no significant influence on the yields. In the similar manner, 2-methylindole was checked; however, only the corresponding 3-sulfonylindole[6] was obtained with much poor yield. 5-Nitrolindole was also examined in the reaction, but no product was observed. To investigate the scope of sodium sulfinates, indole **1a** and 5-substituent indoles **1e**, **1g-1i** were used as the representatives of indoles to react with sodium *p*-toluenesulfinate **2b** and sodium *p*-chlorophenylsulfinate **2c**, respectively. Similarly, the reaction proceed smoothly in water and gave the corresponding 2-sulfonylindoles **3j**-**3s** in yields ranging from 36-66%. From the results it seems that the electron-donating groups on indole ring led to higher yields than those with electron-withdrawing groups. Sodium methylsulfinate **2d,** an aliphatic sulfinate, can also react with indoles; however, the given yields were somewhat lower then aromatic sulfinates.

According to the above results and control experiments, similar to literatures,[4-6] a plausible radical addition mechanism catalyzed by KI is supported in Scheme 2. Thus, KI is first oxidized by Oxone® to form molecular iodine, the fresh molecular iodine reacts quickly with sodium sulfinate to produce the active sulfonyl iodide.[9] Then, a radical addition of the sulfonyl iodide on indole occurs and generates an intermediate. Finally, a HI elimination takes place to provide the 2-sulfonylindole. Meanwhile, the molecular iodine can be re-generated *via* the oxidation of HI by oxidant.



Scheme 2 Proposed mechanism for KI-catalyzed 2-sulfonylation of indoles

In summary, we have developed a convenient procedure for preparation of 2-sulfonylindoles from indoles and sodium sulfinates catalyzed by KI in water at room temperature. This regioselective 2-sulfonylation of indoles using water as solvent is an environmentally benign protocol, which has mild reaction conditions and simple procedure. Furthermore, this reaction will extend the application scope of inorganic iodides in organic synthesis.

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Graphical abstract

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