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Posted Date: 2 July 2024

doi: 10.20944/preprints202407.0182.v1

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Iodophor/H_2O_2 Mediated 2-Sulfonylation of Indoles and N-Methylpyrrole in Aqueous Phase

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Abstract: A convenient and efficient strategy for the preparation of 2-sulfonylindoles has been achieved through iodophor/H_2O_2-mediated 2-sulfonylation of indoles with readily available sulfonyl hydrazides in aqueous phase. Iodophor is commercially available and serves as the green catalyst and aqueous phase. A series of 2-sulfonylated products from indoles and *N*-methylpyrrole were synthesized in moderate yields in only 10 min. Control experiments were also conducted to reveal the mechanism. This method is environment friendly, easy to operate and suitable for a wide range of substrates.

Keywords: iodophor; 2-sulfonylation; indoles; sulfonyl hydrazides

1. Introduction

Indoles have emerged as a prominent structural motif in many natural products and pharmaceuticals [1–7]. Furthermore, the introduction of a sulfonyl moiety at the C2 position of the indole can often enhance its bioactivity [8,9]. In general, the C(2)–H sulfonylation of indoles has been the most straightforward way to synthesize 2-sulfonylindoles. However, in most of the literature, the sulfenylation of indoles often occurs at the C(3)–H position rather than the sulfonylation of C(2)–H [10–14]. And using the same strategy, 2-sulfenylindoles could be obtained when the C(3) position is occupied by substituents [15]. Thus, developing conditions for the direct synthesis of 2-sulfonylindoles is still a fascinating challenge. Over the past decade, numerous direct regioselective 2-sulfonylations of indoles with sodium sulfinate using molecular iodine and its salts as catalysts have been explored [16–20]. These reactions often require oxidants (e.g. TBHP and oxone) or promoters (e.g., TMSOTf). In 2017, Yu and co-workers developed an electrochemical 2-sulfonylation of 1*H*-indoles under chemical oxidant-free conditions, yielding various 2-sulfonylindoles in good to high yields [21]. In addition, *p*-toluenesulfonyl cyanide [22] and sulfonyl hydrazides [23,24] have also been used to construct 2-sulfonyl indoles. Especially sulfonyl hydrazides have proved to be environmentally friendly sulfur sources for the sulfonylation of indoles through the cleavage of their C–N bonds [25–30]. Iodophor is inexpensive, commercially available and not harmful to the environment. Therefore, choosing iodophor as a green catalyst and aqueous phase for 2-sulfonylation of indoles with sulfonyl hydrazides is highly desirable. In this context, we report a fast, mild and efficient iodophor catalyzed 2-sulfonylation of substituted indoles using 30% H_2O_2 solution as oxidant in aqueous phase. Furthermore, the synthetic strategy has the wide substrate scope with the high tolerance to various functional groups and steric hindrance in indoles and sulfonyl hydrazides.

2. Results and Discussion

The reaction of 1*H*-indole (**1a**, 0.5 mmol) and *p*-toluenesulfonyl hydrazide (**2a**, 1.0 mmol) was chosen as a model reaction for optimization, and the results are summarized in Table 1. Initially, the reaction was conducted with 1 equiv. H_2O_2 and 2 mL iodophor (0.04 mmol I_2) at 25 ℃ for 2 h, giving the desired product **3a** in only 28% yield (Table 1, entry 1). Moreover, 2-sulfonylation of indole could proceed rapidly, affording a similar yield of **3a** in 30% in only 10 min (Table 1, entry 2). Fortunately, increasing the amount of H_2O_2 solution (1 mL) further improved the reaction yield to 42% (Table 1, entry 3). Subsequently, a temperature range from 50 ℃ to 100 ℃ was investigated (Table 1, entries 4-8). The variations in temperature showed that 60 ℃ was optimal, giving 70% yield of **3a**. Reducing the I_2 loading to 0.02 mmol resulted in a significantly lower yield (35%) (Table 1, entry 9). In addition, an alternative 70% TBHP solution was employed as oxidant, showing less efficient (Table 1, entry 10). For cost and environmental reasons, 30% H_2O_2 solution was reduced by half for the oxidative 2-sulfonylation. A relatively low yield was obtained (Table 1, entry 11). Meanwhile, we attempted to optimize the reaction at 25 ℃ or 90 ℃, but only to result in lower yields of 38% and 32% respectively. Finally, the optimized reaction conditions are as follows: indole (**1a**) (0.5 mmol) with *p*-toluenesulfonyl hydrazide (**2a**) (1 mmol), H_2O_2 (1 mL) and iodophor (2 mL, 0.04 mmol I_2) at 60 ℃ for 10 min.

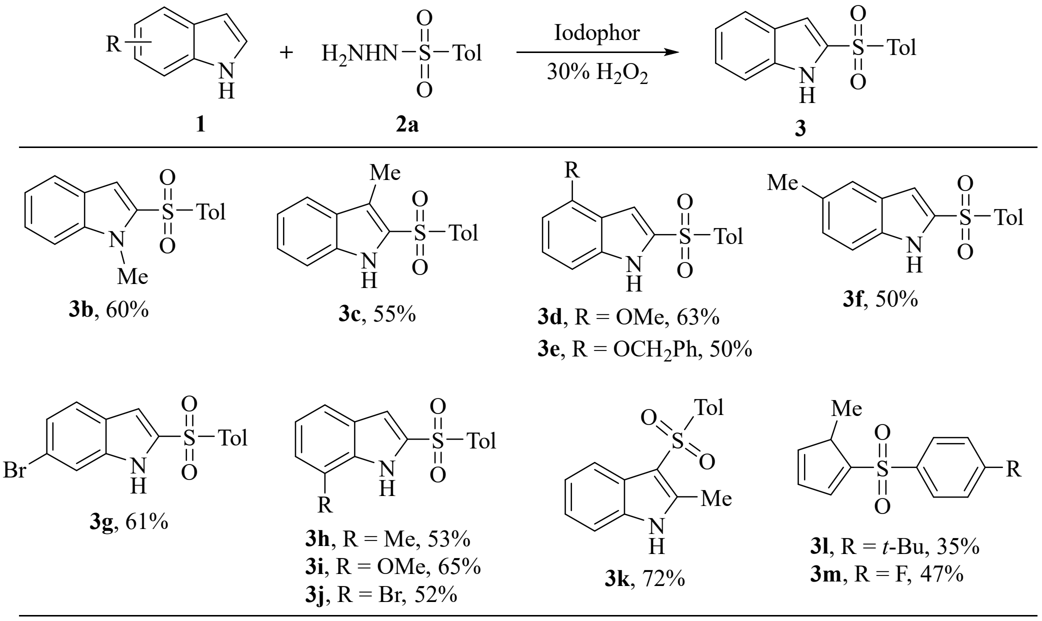
Table 1. Optimization of Reaction Conditions [1].

Entry	Oxidation	Iodophor (mL)	T (℃)	t (min)	Yield (%)[b]
1	H_2O_2 (1 equiv.)	2 (0.04 mmol I_2)	25	120	28
2	H_2O_2 (1 equiv.)	2 (0.04 mmol I_2)	25	10	30
3	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	25	10	42
4	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	50	10	45
5	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	60	10	70
6	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	80	10	50
7	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	90	10	40
8	H_2O_2 (1 mL)	2 (0.04 mmol I_2)	100	10	36
9	H_2O_2 (1 mL)	1 (0.02 mmol I_2)	25	10	35
10	TBHP (1 mL)	2 (0.04 mmol I_2)	60	10	55
11	H_2O_2 (0.5 mL)	2 (0.04 mmol I_2)	60	10	58
12	H_2O_2 (0.5 mL)	2 (0.04 mmol I_2)	25	10	38
13	H_2O_2 (0.5 mL)	2 (0.04 mmol I_2)	90	10	32

[1] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), iodophor (2 mL), H_2O_2 (1 mL), under air. [2] Isolated yields.

On the basis of optimal reaction conditions, the scope of sulfonyl indoles **1** and sulfonyl hydrazides **2** were investigated respectively. First, a series of aryl-substituted indoles with electron-donating substituents (Me, OMe and OCH_2Ph) were treated with benzenesulfonyl hydrazide (**2a**) to afford the corresponding products (**3b**~**3f**, **3h** and **3i**) in moderate yields (50%~65%). The results are summarized in Table 2. Among them, the substitution of OMe gave a slightly better reactivity than the other groups. In comparison, 6-bromo- and 7-bromo-indoles were employed to give the target products **3g** and **3j** in 61% and 52%, respectively. These results showed that the electronic effect of the substituents on the indole moiety has little significant impact on this synthetic method. Utilizing the same strategy, the 3-sulfonylation proceeded smoothly when the C-2 position was occupied by methyl, yielding the product **3k** in 72% yield. In addition，the 2-sulfonylation of *N*-methylpyrrole was also investigated. Generally, the 2-sulfonylation of *N*-methylpyrrole is conducted with reactive sulfur sources under harsh reaction conditions [20,31]. Fortunately, the 2-sulfonylation of *N*-methylpyrrole with 4-arylsulfonyl hydrazides could proceed smoothly, giving the corresponding products (**3l** and **3m**) in moderate yields. These results indicate that the synthetic strategy has a high tolerance to both electron-withdrawing groups and electron-donating groups of arylsulfonyl hydrazides **2**.

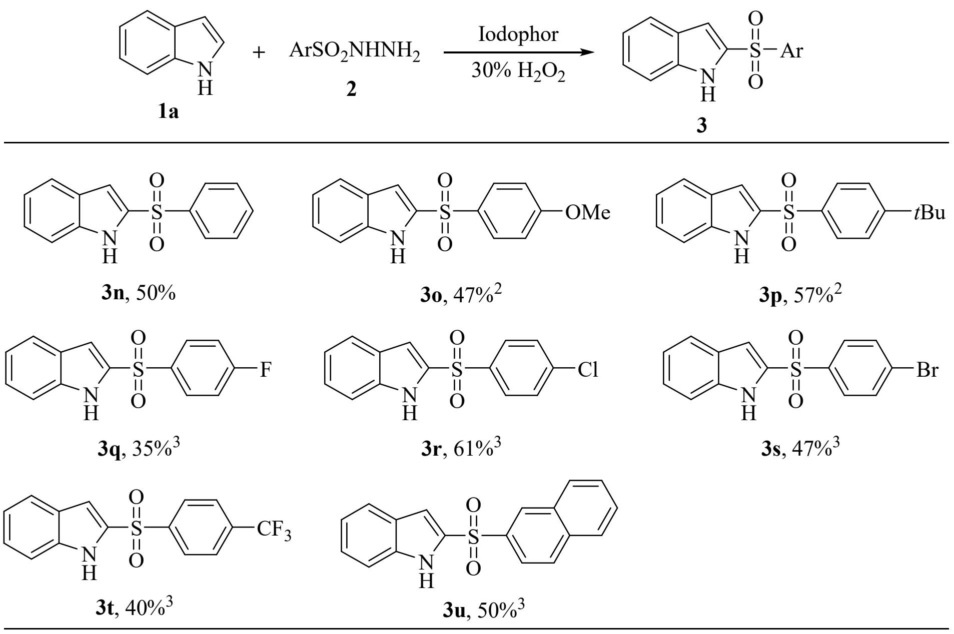
Table 2. Scope of indoles [1, 2].



[1] Reaction conditions: **1** (0.5 mmol), **2a** (1 mmol), iodophor (2 mL), H_2O_2 (1 mL), under air, 60 ºC, 10 min. [2] Isolated yield.

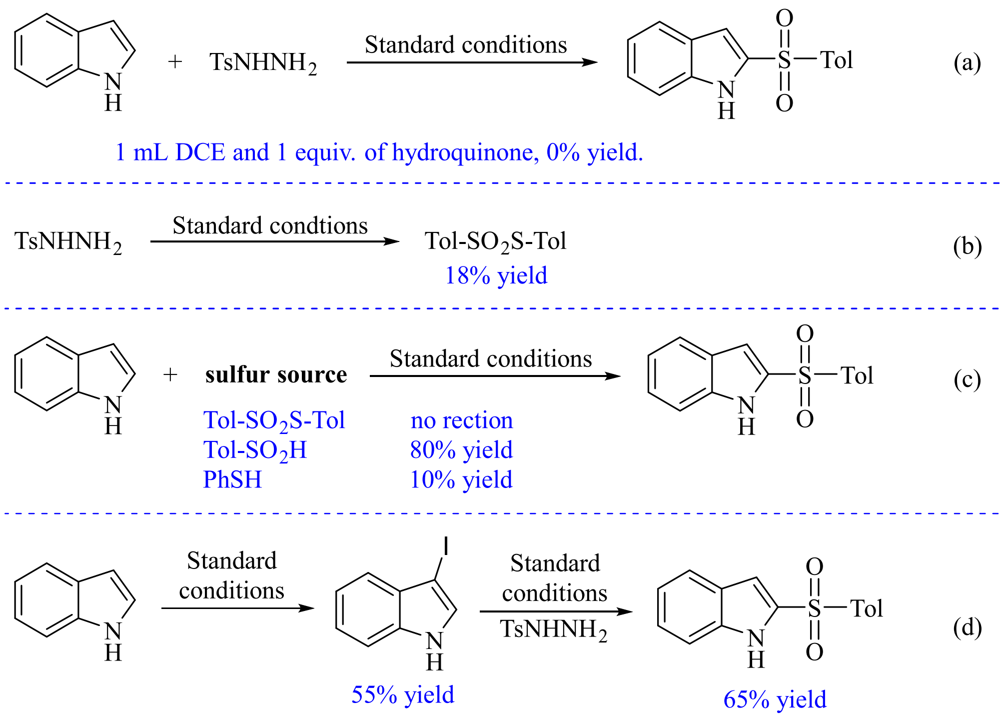
Subsequently, the scope of sulfonyl hydrazides was also evaluated (Table 3). It was disappointing that various substrates with functional groups such as methoxy, *t*-Bu, halogen and CF_3 in the aromatic rings were not applicable to the optimal reaction conditions. Only when benzenesulfonohydrazide was employed could the target product **3n** be obtained in 50% yield. The temperature was found to be crucial for the 2-sulfonylation of arylsulfonyl hydrazides. When the processes were carried out at 25 ℃, the corresponding products (**3o** ~ **3t**) were obtained in moderate yields. And as shown in Table 3, arylsulfonyl hydrazides bearing electron withdrawing groups showed better reactivity and gave the desired products in only 2 h, while the reaction of arylsulfonyl hydrazides with electron donating groups should proceed for 5 h to give the moderate yields. Naphthalene-2-sulfonohydrazide was also employed to afford the product **3u** in 50% yield.

Table 3. Scope of sulfonyl hydrazides [1].



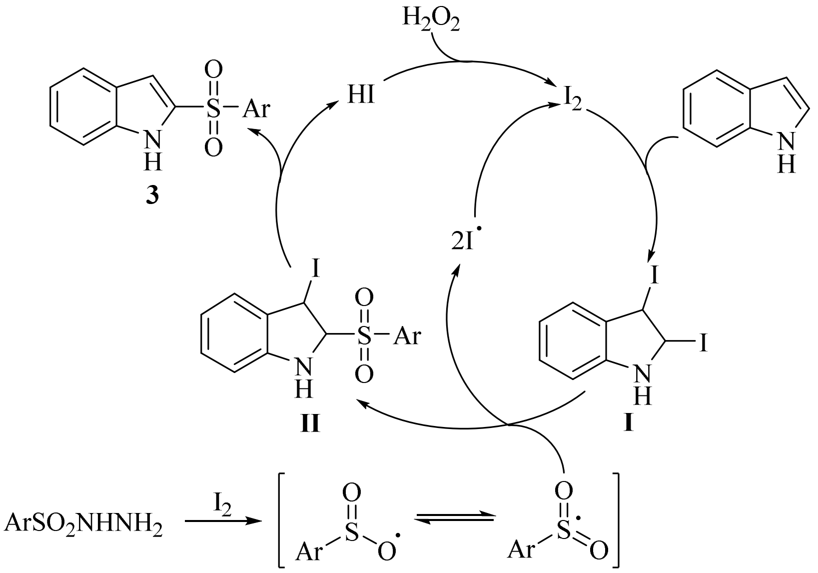
[1] Reaction conditions: **5a** (0.5 mmol), **2** (1 mmol), iodophor (2 mL), H_2O_2 (1 mL), under air, 60 ºC, 10 min. [2] Reaction time 2 h, 25 ℃. [3] Reaction time 5 h, 25 ℃.

To further understand the mechanism of this transformation, a series of control experiments were carried out. First, 1 equiv. of hydroquinone was used as a radical scavenger in the 2-sulfonylation of 1*H*-indole (**1a**) with *p*-toluenesulfonyl hydrazide (**2a**), and dichloroethane was also added to increase the solubility of hydroquinone. It was found that the reaction did not proceed, suggesting that the reaction is likely to be a radical process. Self-coupling of *p*-toluenesulfonyl hydrazide occurred in the absence of 1*H*-indole, giving the corresponding product S-*p*-tolyl 4-methylbenzenesulfonothioate in only 18%. Subsequently, S-*p*-tolyl 4-methylbenzenesulfonothioate was treated with 1*H*-indole and no product was detected. The results indicate that S-*p*-tolyl 4-methylbenzenesulfonothioate is not involved as an intermediate in 2-sulfonylation. When sodium 4-methylbenzenesulfinate and thiophenol were used as sulfur sources, the reaction proceeded to the 2-sulfonylated product in 80% and 10% yield, respectively. In the absence of *p*-toluenesulfonyl hydrazide, 1*H*-indole was iodinated by stoichiometric iodophor to give 3-iodo-1*H*-indole in 55% yield. In addition, 3-iodo-1*H*-indole could be further reacted with *p*-toluenesulfonyl hydrazide to give the 2-sulfonylated product (**3a**) in 65% yield. All of the above reactions were conducted under optimal reaction conditions (standard conditions).



Scheme 1. Control experiments.

Based on the results of control experiments and existing literature [18,19,23], a plausible mechanism for iodophor mediated 2-sulfonylation of indoles is illustrated in Scheme 2. Molecular iodine derived from iodophor is added to indole to form the important intermediate 2,3-diiodoindoline (**I**). Meanwhile, molecular iodine also rapidly activates *p*-toluenesulfonyl hydrazide to give the sulfonyl radical. Afterwards, the reaction of intermediate **I** with the sulfonyl radical leads to the formation of intermediate **II** and an iodine radical. Intermediate **II** undergoes a HI elimination to give the 2-sulfonylated product (**3**). And the molecule iodine in the catalytic system can be regenerated from the oxidation reaction of HI by H_2O_2 or coupling of two iodine radicals.



Scheme 2. Proposed mechanism for iodophor mediated 2-sulfonylation of indoles.

3. Materials and Methods

General methods

Unless otherwise stated, all reactions were carried out in Schlenk tubes. Melting points were determined using a melting point apparatus and are uncorrected. Chemicals were purchased commercially and were used without further purification. Column chromatography was performed on Qingdao Ocean Chemical silica gel (200 ~ 300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. High resolution mass spectrometry (HRMS) was performed on a Thermo Scientific LTQ or bitrap XL mass spectrometer, Thermo Fisher Q Exactive.

General procedure for iodophor/H_2O_2 mediated 2-sulfonylation of indoles and *N*-methylpyrrole

Indole **1a** (0.5 mmol) and benzenesulfonyl hydrazide **2a** (1.0 mmol) were placed in a sealed 10 mL reaction tube, 2 mL iodophor (0.04 mmol I_2) and 1 mL 30% H_2O_2 solution was added. Then the reaction proceeded at 60 ℃ for 10 min. After the reaction finished, saturated salt solution (10 mL) was used and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the organic solvent was evaporated on a rotatory evaporator. The crude was purified by flash chromatography on silica gel (PE/EtOAc) to give the corresponding products **3a.**

The characterization data of products

2-tosyl-1*H*-indole (3a) [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.43 (dd, *J* = 17.4, 7.6 Hz, 3H), 7.31-7.25 (m, 2H), 2.50 (s, 3H).

1-methyl-2-tosyl-1*H*-indole (3b) [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.32 -7.21 (m, 5H), 7.10 (t, *J* = 7.4 Hz, 1H), 3.77 (s, 3H), 2.33 (s, 3H).

3-methyl-2-tosyl-1*H*-indole (3c) [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36-9.08 (m, 1H), 7.86 (d, *J* = 5.7 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.33-7.27 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H).

4-methoxy-2-tosyl-1*H*-indole (3d) [23]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.32-7.24 (m, 4H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 2.41 (s, 3H).

4-(benzyloxy)-2-tosyl-1*H*-indole (3e) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.96 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.17 (s, 2H), 2.37 (s, 3H).

5-methyl-2-tosyl-1*H*-indole (3f) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (s, 1H), 7.90 (d, *J* = 16.1 Hz, 2H), 7.44 (s, 1H), 7.31 (dd, *J* = 8.3, 5.3 Hz, 3H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.11 (s, 1H), 2.43 (s, 3H), 2.40 (s, 3H).

6-bromo-2-tosyl-1*H*-indole (3g) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.25 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.54 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.11 (s, 1H), 2.38 (s, 3H).

7-methyl-2-tosyl-1*H*-indole (3h) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.02 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.18 (s, 1H), 7.10 (dd, *J* = 11.3, 7.2 Hz, 2H), 2.48 (s, 3H), 2.39 (s, 3H).

7-methoxy-2-tosyl-1*H*-indole (3i) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.03 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 3H), 7.16 (s, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 3.97 (s, 3H), 2.41 (s, 3H).

7-bromo-2-tosyl-1*H*-indole (3j) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.85 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 2.40 (s, 3H).

2-methyl-3-tosyl-1*H*-indole (3k) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.18 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.06 (dd, *J* = 15.7, 7.4 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H).

2-((4-(*tert*-butyl)phenyl)sulfonyl)-1-methyl-1*H*-pyrrole (3l) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.05 (dd, *J* = 4.0, 1.9 Hz, 1H), 6.78 (t, *J* = 2.2 Hz, 1H), 6.22-6.17 (m, 1H), 3.75 (s, 3H), 1.35 (s, 9H).

2-((4-fluorophenyl)sulfonyl)-1-methyl-1*H*-pyrrole (3m) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 – 7.79 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 6.93 (dd, *J* = 4.0, 1.9 Hz, 1H), 6.70 (t, *J* = 2.1 Hz, 1H), 6.09 (dd, *J* = 4.0, 2.6 Hz, 1H), 3.63 (s, 3H).

2-(phenylsulfonyl)-1*H*-indole (3n) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.36 (dd, *J* = 18.0, 8.4 Hz, 3H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 7.07 (t, *J* = 7.5 Hz, 1H).

2-((4-methoxyphenyl)sulfonyl)-1*H*-indole (3o) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 3.73 (s, 3H).

2-((4-(*tert*-butyl)phenyl)sulfonyl)-1*H*-indole (3p) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.51 (s, 1H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.22 (s, 1H), 7.16 (t, *J* = 7.1 Hz, 1H), 1.28 (s, 9H).

2-((4-fluorophenyl)sulfonyl)-1*H*-indole (3q) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.09 (s, 1H), 7.99 (dd, *J* = 10.4, 6.4 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.14 (dd, *J* = 15.8, 7.3 Hz, 4H).

2-((4-chlorophenyl)sulfonyl)-1*H*-indole (3r) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.50 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 3H), 7.41 (d, *J* = 6.0 Hz, 2H), 7.27-7.22 (m, 2H).

2-((4-bromophenyl)sulfonyl)-1*H*-indole (3s) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.32-7.25 (m, 1H), 7.12 (dd, *J* = 9.3, 4.6 Hz, 2H).

2-((4-(trifluoromethyl)phenyl)sulfonyl)-1*H*-indole (3t) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.95 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38-7.33 (m, 1H), 7.24 (d, *J* = 0.8 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H).

2-(naphthalen-2-ylsulfonyl)-1*H*-indole (3u) [23]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.89 (s, 1H), 8.59 (s, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.91 (s, 2H), 7.85 (d, J = 7.7 Hz, 1H), 7.61 (dt, J = 8.2, 7.1 Hz, 3H), 7.39 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.23 (s, 1H), 7.15 (t, J = 7.5 Hz, 1H).

4. Conclusions

In summary, we have developed an eco-friendly, fast and effective iodophor/H_2O_2-mediated 2-sulfonylation of indoles with readily available sulfonyl hydrazides in aqueous phase. Iodophor is commercially available and serves as the green catalyst and aqueous phase. In this approach, the 2-sulfonylation of indoles with sulfonyl hydrazides proceeded smoothly, yielding a series of 2-sulfonylated products in moderate yields in only 10 min. In addition, a series of control experiments were carried out to disclosed the radical reaction mechanism of 2-sulfonylation.

Author Contributions: Conceptualization, Y.L; methodology, Y.Y.; software, Y.Y.; validation, Y.Y. and Y.L.; formal analysis, J.H.; investigation, Y.Y.; resources, Y.L and Y.L.; data curation, Y.Y.; writing—original draft preparation, Y.L.; writing—review and editing, Y.L.; visualization, J. H.; supervision, J. H; project administration, Y.L.; funding acquisition, S.H., Y.L and Y.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Science and Technology Innovation Programme for Higher Education Institutions in Shanxi Province (No. 2021L137), Science and Technology Innovation Talents Program of Shihezi University (No. ZG010603), Innovation Development Program of Shihezi University (CXFZ202204) and the Fundamental Research Program of Shanxi Province (20210302124467).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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