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Iodine-Catalyzed Regioselective 2-Sulfonylation of Indoles with Sodium Sulfinates

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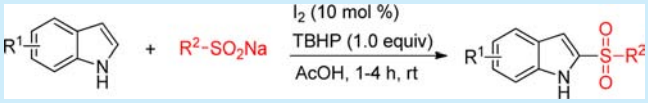
Supporting Information

ABSTRACT: Iodine-catalyzed selective 2-arylsulfonyl indole formation from indoles and sodium sulfinates is disclosed. Various substituted 2-arylsulfonyl indoles were obtained in one pot in the absence of metal catalyst at room temperature under air.



Organosulfones are important intermediates for agrochemicals, pharmaceuticals, and protecting and activating groups.[1] Among them, aryl sulfones have gained great attention due to their prominent drug activity, such as anti-HIV-1, antifungal, antibacterial, and antitumoral.[2] As a consequence, development of facile methods for aryl sulfones has stimulated considerable interest. The common methods for preparing aryl sulfones include oxidation of the corresponding aryl sulfides[3] or Friedel−Crafts sulfonylation of arenes with arenesulfonyl halides,[4] arenesulfonic acids,[5] or their derivatives[6] in the presence of a strong acid catalyst. In recent years, many efforts have been expended on developing sulfonylation reactions in the absence of strong acid. Among the various methods developed, palladium- or copper-catalyzed cross-coupling reaction of sodium arenesulfinates (or arenesulfonyl halides) with alkyl or aryl halides has proven to be an effective approach to prepare aryl sulfones, especially for unsymmetrical diaryl sulfones.[7,8] Besides aryl halides, aryl boronic acids[9] and diaryliodonium salts[10] also can be used as coupling reagents with or without metal catalyst. Direct sulfonylation via C−H functionalization can provide a shortcut for aryl sulfones.[11] Dong and co-workers developed a palladium-catalyzed direct sulfonylation of 2-aryl pyridines with arylsulfonyl chlorides.[12] However, direct sulfonylation of an aromatic C−H bond with less reactive sodium arenesulfinates is rare.

Indolyl aryl sulfones can be found in various drugs, such as SR 33805 oxalate, a Ca^{2+} antagonist with length-dependent Ca^{2+}-sensitizing properties in cardiac myocytes (Figure 1).[13] Indolyl aryl sulfones are generally prepared by oxidation of the corresponding arylthioindoles.[14] In recent years, alternative approaches have been developed for 3-arylsulfonyl indoles using aryl sulfonyl halides or aryl sulfonic acids as sulfonylation reagents.[15] Driver and co-workers developed an approach for 3-arylsulfonyl indoles via Rh-catalyzed sulfone group migration.[16] Meanwhile, a few approaches have also been developed for 2-arylsulfonyl indoles. The most used methods are oxidation of indolyl aryl sulfides or deprotonation and substitution reaction

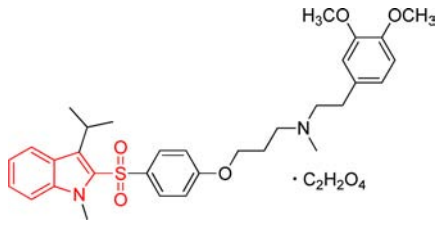


Figure 1. Structure of SR 33805 oxalate.

from indoles and aryl sulfonyl halides in the presence of butyllithium under anhydrous conditions.[17] Obviously, the later method is not suitable for indoles with active substituents. Thus, it is highly desirable to develop a general method with high selectivity and good functional group tolerance for 2-arylsulfonyl indoles. Herein, we describe an iodine-catalyzed regioselective sulfonylation of indoles with sodium sulfinates under mild conditions, affording 2-arylsulfonyl indoles in good to high yields.[18]

To achieve the best sulfonylation conditions, the reaction of indole (**1a**) with sodium benzenesulfinate (**2a**) was selected as the model reaction using *tert*-butyl hydroperoxide (TBHP, 1.0 equiv) as oxidant in acetic acid. In the absence of metal catalyst, various iodide-containing additives were investigated at room temperature under an air atmosphere. The desired product 2-(phenylsulfonyl)-1*H*-indole (**3a**) was obtained in good yield when 20 mol % of KI, *N*-iodosuccinimide (NIS), and tetrabutylammonium iodide (TBAI) were employed (Table 1, entries 1−3). The use of molecular I_2 (10 mol %) could further improve the reaction yield to 92% (entry 4). Other oxidants were also investigated and showed less efficiency (entries 5−9). The product was observed in 15% yield when oxygen was used as the sole oxidant (entry 9). Other organic solvents such as TFA, PivOH, toluene, and anisole were less effective for this

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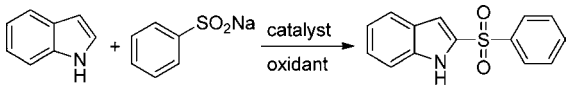
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	catalyst	oxidant	solvent	yield[b] (%)
1	KI	TBHP	AcOH	68
2	NIS	TBHP	AcOH	75
3	TBAI	TBHP	AcOH	60
4	I_2	TBHP	AcOH	92
5	I_2	TBP	AcOH	10
6	I_2	H_2O_2	AcOH	78
7	I_2	$K_2S_2O_8$	AcOH	54
8	I_2	Oxone	AcOH	55
9	I_2	O_2	AcOH	15
10	I_2	TBHP	TFA	4
11	I_2	TBHP	PivOH	50
12	I_2	TBHP	toluene	8
13	I_2	TBHP	anisole	6
14		TBHP	AcOH	0
15	I_2	TBHP	AcOH	91[c]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (0.1 mmol, for I_2 0.05 mmol), oxidant (0.5 mmol), solvent (1.0 mL), room temperature, 4 h under air. [b]GC yield based on **1a**. [c]Under Ar.

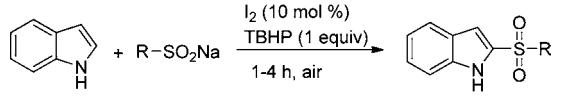
kind of reaction (entries 10−13). As a control experiment, no desired product **3a** was observed in the absence of I_2 catalyst (entry 14).

The scope of the sodium sulfinate substrates was investigated under the optimized conditions (Table 2). Various 4-substituted arylsulfinic acid sodium salts could smoothly react with **1a** to give 2-arylsulfonyl indoles in good to high yields (entries 2−5). Functional groups such as halogens, trifluoromethyl, and trifluoromethoxy could survive well under the optimized reaction conditions (entries 7−11). It should be noted that no cleavage of the C−halogen bond was observed. 2-(Naphthalen-2-ylsulfonyl)-1*H*-indole (**3l**) could be obtained in 81% when 2-naphthylsulfinic acid sodium salt (**2l**) was reacted with **1a** (entry 12). To our delight, besides aromatic sodium sulfinates, aliphatic sodium methanesulfinate (**2m**) also could couple with indole to give 2-(methylsulfonyl)-1*H*-indole (**3m**) in 90% yield (entry 13). It should be noted that the sulfonylation reaction occurred exclusively at the C-2 position of the indole ring in all cases.

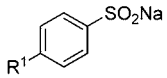
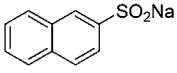
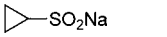
The influence of the substituents on the indole moiety was also evaluated (Table 3). Indoles bearing various substituents could smoothly couple with sodium benzenesulfinate (**2a**). When 3-methylindole was employed, the corresponding product **3n** was obtained in 84% yield (entry 1). Slightly higher yields could be obtained when the methyl group was located at C-4 and C-7 position in the indole ring (entries 2 and 3). The reaction yields decreased dramatically when 5-halogen substituted indoles were used as substrates (entries 5 and 6). However, better yields could be obtained when 4-halo and 5-halo indoles were used (entries 7−9). When the C-2 position of the indole ring was occupied by a methyl group, only a trace amount of C-3 sulfonylation product was observed (entry 10). Protected 1-methylindole (**1l**) also could couple with **2a** and gave lower yield than that of free indole (entry 11).

To gather more information, a control experiment was set up under the standard conditions. Competition reactions between styrene and indole with sodium benzenesulfinate were carried

Table 2. Sulfonylation of Indole (1a) with Sodium Sulfinates[a]



1a 2 3

entry	sodium sulfinate		product	yield[b] (%)
				
1	R^1 = H	**2a**	**3a**	83
2	R^1 = CH_3	**2b**	**3b**	85
3	R^1 = CH_2CH_3	**2c**	**3c**	88
4	R^1 = *iso*-propyl	**2d**	**3d**	71
5	R^1 = *tert*-butyl	**2e**	**3e**	74
6	R^1 = OCH_3	**2f**	**3f**	75
7	R^1 = F	**2g**	**3g**	71
8	R^1 = Cl	**2h**	**3h**	82
9	R^1 = Br	**2i**	**3i**	72
10	R^1 = CF_3	**2j**	**3j**	67
11	R^1 = OCF_3	**2k**	**3k**	51
12		**2l**	**3l**	81
13	CH_3SO_2Na	**2m**	**3m**	90
14	$CH_3CH_2CH_2SO_2Na$	**2n**	**3n**	35
15		**2o**	**3o**	65

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), I_2 (0.05 mmol), TBHP (0.5 mmol), AcOH (1.0 mL), room temperature, air, 1−4 h. [b]Isolated yield.

out under standard reaction conditions (Scheme 1). Vinyl sulphone can be obtained in 45% yield as determined by GC and GC−MS analysis. This means the mechanism might be similar to Nair's work, which using CAN as an oxidant.[19] Based on this, a plausible mechanism for the metal-free method to construct 2-arylsulfonyl indoles is illustrated in Scheme 2. As a first step, an oxygen-centered radical is generated by oxidation of sulfinate **1a** with TBHP. The oxygen-centered radical can be resonated to a sulphonyl radical. Addition of the sulphonyl radical with indole affords an intermediate radical **A**, which can be reacted with molecular iodine to form an intermediate **B** and an iodide radical. Elimination of intermediate **B** generates the desired product **3a** and releases HI, which can be reoxidized into iodide radical by TBHP. Combination of two iodide radicals regenerates molecular iodine. In the whole process, a catalytic amount of iodine is enough.

In summary, we have developed a simple method for 2-arylsulfonyl indoles from indoles and sodium sulfinates in the absence of metal catalyst. A catalytic amount of iodine acted as efficient promoter for this transformation, and the reaction could be finished in a couple of hours at room temperature. The direct sulfonylation reaction occurred exclusively at the C-2 position of the indole ring. Halogen other functional groups were well tolerated. This method afforded a novel alternative approach for the synthesis of biologically important hetero diaryl sulfones from sodium sulfinates.

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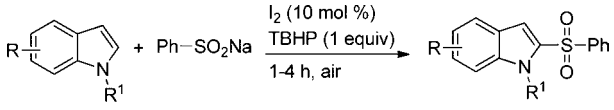
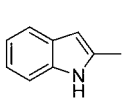
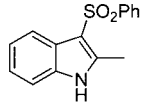
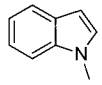
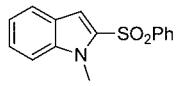
Table 3. Sulfonylation of Various Indoles with 2a[a]

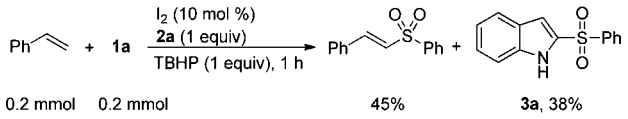


1 2a 3

entry	indole		product		yield[b] (%)
1	R = 3-Me	**1b**	**3p**		84
2	R = 4-Me	**1c**	**3q**		89
3	R = 7-Me	**1d**	**3r**		90
4	R = 5-MeO	**1e**	**3s**		89
5	R = 5-Cl	**1f**	**3t**		50
6	R = 5-Br	**1g**	**3u**		34
7	R = 4-Cl	**1h**	**3v**		75
8	R = 6-F	**1i**	**3w**		79
9	R = 6-Cl	**1j**	**3x**		65
10		**1k**		**3y**	trace
11		**1l**		**3z**	68

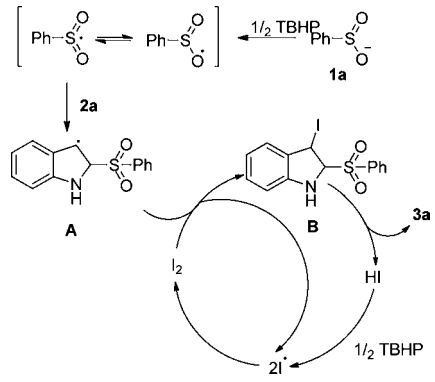
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1 mmol), I_2 (0.05 mmol), TBHP (1 equiv), AcOH (1.0 mL), room temperature, air, 1−4 h. [b]Isolated yield.

Scheme 1. Control Experiment[a]



[a]Yields were determined by GC analysis.

Scheme 2. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the 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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