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Electrooxidative Metal-free Dehydrogenative α-Sulfonylation of 1-*H*-Indole with Sodium Sulfinates

Mei-Lin Feng, Long-Yi Xi, Shan-Yong Chen* and Xiao-Qi Yu*[a]

Abstract: An electrochemical α-sulfonylation of 1-*H*-indole with arenesulfinates has been developed. A variety of indoles underwent this sulfonylation smoothly at room temperature under metal- and chemcial oxidant-free conditions, affording indolyl aryl sulfones in good to high yields. This reaction tolerates a variety of functional groups including halides, cyclopropyl, ether, ester and aldehyde. It can be applied to the syntheis of biologically active 5-HT6 modulators.

Introduction

Organic electrosynthesis, which employs electrons as reagents, presents an attractive alternative to traditional chemical processes in a large apart owing to the fact that the former uses less chemical reagents and generates less waste than the latter. Dehydrogenative coupling serves as a step- and atom-economical method for building complex molecules. The combination of electrolysis and dehydrogenative coupling provides a new strategy for green organic synthesis. Therefore, electrooxidative dehydrogenative coupling has gained increasing interest in recent years.[1] In spite of these breakthroughs, electrooxidative dehydrogenative coupling was mainly applied to constructing C-N or C-C bonds.[2] Reports on C-S formation through electrooxidative dehydrogenative coupling are especially rare.[3]

The heteroaromatic sulfone moiety exists widely in medicinally active compounds, such as enzyme inhibitors,[4] antagonists,[5] and antimicrobial agents.[6] Among them, indolyl aryl sulfones have gained great attention due to their prominent biological activity, such as serving as 5-HT6 modulators,[7] HIV-1 non-nucleoside reverse transcriptase inhibitor,[8] Ca^{2+} antagonists in cardiac myocytes,[9] canabinoid receptor angonisists(Figure 1).[10] 3-sulfonylindoles are traditionally prepared by oxidation of the corresponding arylthioindole.[11] Direct sulfonylation of indoles with aryl sulfonyl halides or aryl sulfonic acids is an alternative approach for 3-sulfonylindoles.[12] It is well-known that the C3-position of indoles has priority in functionalization over the C2-position. Literature methods for the installation of the sulfur moiety at the C2-position of indoles often involve multistep synthesis and the use of highly dangerous alkyllithium reagents.[13] Recent limited examples afford an alternative method for the synthesis of 2-sulfonylindoles. However, excess of oxidants and large amounts of acid were required, which limit their application in large scale preparation.[14] Herein we report a novel electrooxidative dehydrogenative coupling strategy to exclusively generate 2-sulfonylindoles in good to high yields using only a catalytic amount of TBAI and acetic acid without toxic reagents under mild conditions.

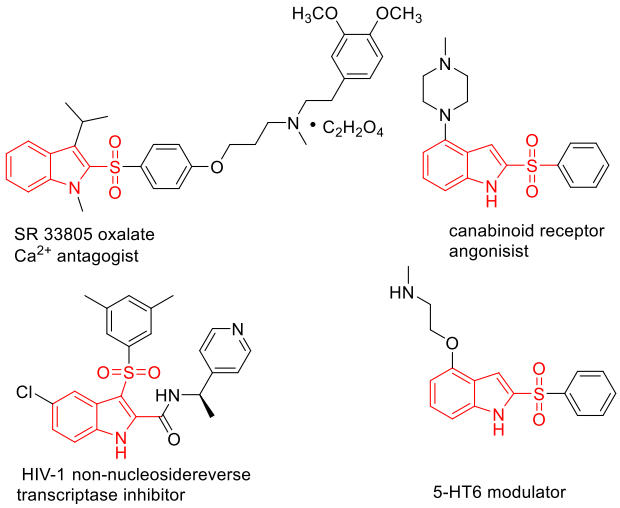

Figure 1. Examples of biologically active indolyl aryl sulfones.

Results and Discussion

1-*H*-indole (**1a**) and sodium benzenesulfinate (**2a**) were chosen to optimize reaction conditions. Initially, these two starting materials were treated in a solution of TBAI (tetrabutylammonium iodide) and acetic acid in CH_3CN/H_2O (1:1) mixture solvent in an undivided cell equipped with a pair of Pt foil electrodes (0.25 cm^2 each) under a constant current (10 mA) at room temperature. After stirring for 8 h, indole transformed completely and product **3a** was obtained in a yield of 69% (Table 1, entry 1).The structure was confirmed by single-crystal X-ray diffraction studies (Figure 2). [15] When $LiClO_4$ was used as the supporting electrolyte instead of TBAI, no obvious product formation was observed (Data not shown), suggesting that TBAI is not only a supporting electrolyte but also a catalyst. Changing the current or increasing the amount of TBAI did not improve the efficiency (Entries 2-4). We thought the low efficiency may result from the oxidation of indole at high potential. Then we turned our attention to performing this reaction under a constant potential. After optimizing the potential we found that 1.5 V (*vs* Ag/AgCl) gave the best result, affording the product in 81% yield (Entries 5-7). We further found the amount of TBAI can be reduced by half (Entry 8 *vs* entries 7-9). Other iodide catalysts, such as NaI and KI were sluggish (Entries 10-11). Attempts to reduce the amounts of acetic acid or sulfinate as well as changing the solvent were not successful. Finally, we found that the yield increased to 92% when half volume of the mixture solvent was used.

We monitored the reaction using ^1H NMR and found that the yield of **3a** increased with time and the maximum appeared at about 8 h (Figure 3).

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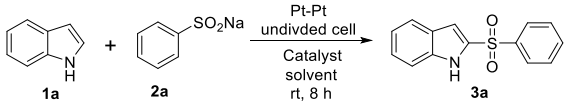
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst (mol %)	Solvent	Currency Potential	Yiled [%][b]
1	TBAI (40)	CH_3CN/H_2O	10 mA	69
2	TBAI(40)	CH_3CN/H_2O	5 mA	35
3	TBAI(80)	CH_3CN/H_2O	10 mA	66
4[c]	TBAI(40)	CH_3CN/H_2O	10 mA	56
5	TBAI(40)	CH_3CN/H_2O	1.5 V	81
6	TBAI(40)	CH_3CN/H_2O	1 V	65
7	TBAI(40)	CH_3CN/H_2O	2.5 V	81
8	TBAI(20)	CH_3CN/H_2O	1.5 V	81
9	TBAI(10)	CH_3CN/H_2O	1.5 V	15
10	NaI(20)	CH_3CN/H_2O	1.5 V	20
11	KI(20)	CH_3CN/H_2O	1.5 V	39
12[d]	TBAI(20)	CH_3CN/H_2O	1.5 V	76
13[e]	TBAI(20)	CH_3CN/H_2O	1.5 V	70
14	TBAI(20)	H_2O	1.5 V	trace
15	TBAI(20)	Ionic liquid[f]	1.5 V	trace
16[g]	TBAI (20)	CH_3CN/H_2O	1.5 V	67
17[h]	TBAI (20)	CH_3CN/H_2O	1.5 V	92

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), acetic acid (0.5 mmol), CH_3CN (4 mL), H_2O (4 mL), Ag/AgCl as the reference electrode at room temperature, 8 h. [b] Isolated yield. [c] 0.75 mmol of **2a**. [d] Acetic acid (0.6 mmol). [e] Acetic acid (0.3 mmol). [f] 1-Butyl-3-methylimidazolium tetrafluoroborate. [g] 1.5 equiv of **2a** (0.45 mmol). [h] CH_3CN (2 mL), H_2O (2 mL).

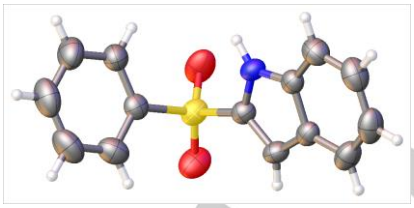


Figure 2. X-ray structure of the product **3a**.

The optimal reaction conditions were then applied to various indoles as summarized in Table 2. A variety of indoles bearing electron-donating or electron-withdrawing groups underwent smoothly, affording the corresponding products in moderate to good yields. When C2-position of the indole ring was occupied, only trace of 3-indoyl sulfone was detected (**3f**), indicating that this electrochemical oxidative sulfonylation was highly selective for the C2-position. This reaction tolerates a variety of functional groups including halides, ether, ester and aldehyde (**3g**-**3l, 3o** and **3p**). Halogen-containing indoles gave indolyl aryl sulfones in moderate yields, providing opportunity for further functionalization (**3g**-**3l**). It is well-known that aldehyde group is hardly kept in a chemical oxidation. While, aldehyde functional group survived in this process (**3o**), showing electrochemical oxidation has its unique advantage over current chemical process.

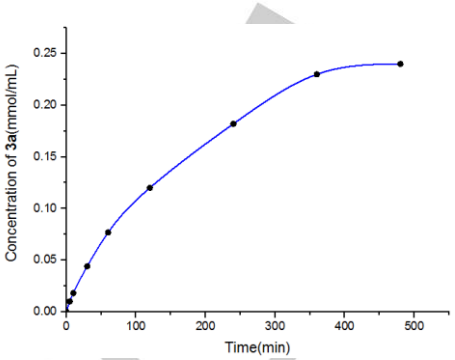
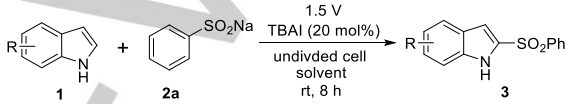
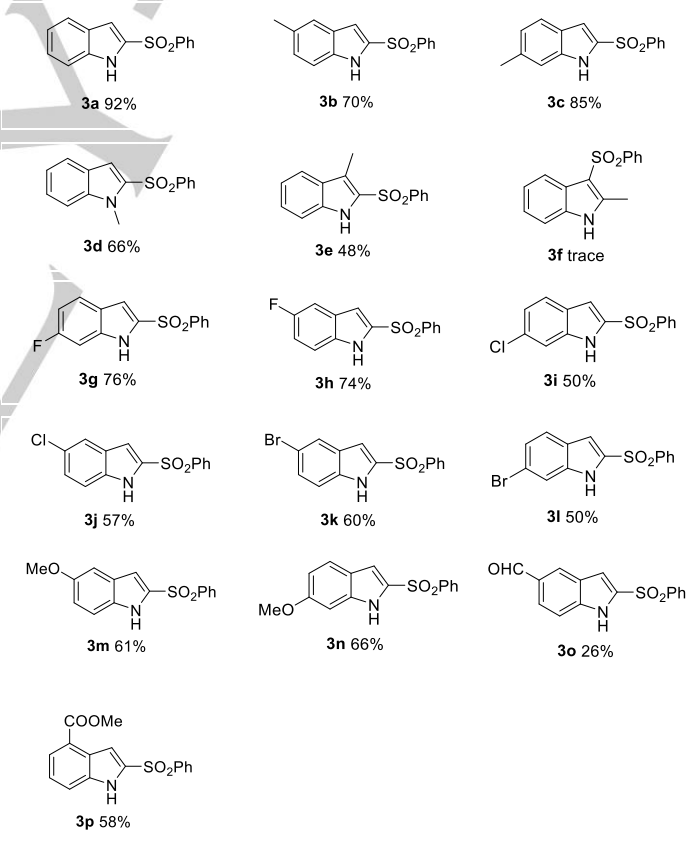


Figure 3. Concentration profile of **3a** during the electrolysis process.

Table 2. The scope of indole substrates.[a]



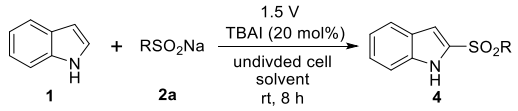


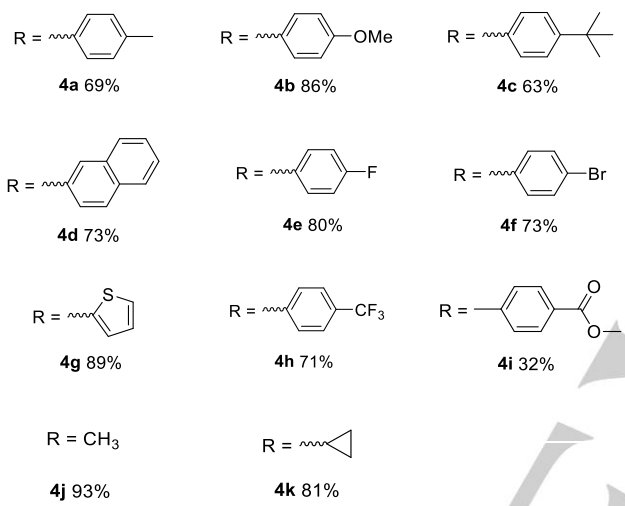
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), TBAI (0.06 mmol), acetic acid (0.5 mmol), CH_3CN (2 mL), H_2O (2 mL), Pt foil electrodes (0.25 cm^2 each), Ag/AgCl as the reference electrode, constant potential (1.5 V *vs* Ag/AgCl), undivided cell, air, room temperature, 8h. Isolated yield.

Several sodium arenesulfinates containing weak electron-withdrawing and electron-donating functionalities were also evaluated. Most of the tested substrates afforded the

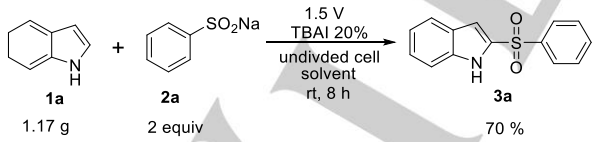
corresponding products in good to excellent yields. Functional groups such as halides, ester and cyclopropyl could survive well under the standard reaction condition (Table 3, **4e**, **4f**, **4i** and **4k**). Sodium 2-naphthalenesulfinate and sodium 2-thiophenesulfinate also gave indolyl aryl sulfones in good yields (**4d** and **4g**). In addition, alkyl sulfinate, such as methyl and cyclopropyl underwent smoothly, affording the corresponding indolyl alkyl sulfones in excellent yields (**4j** and **4k**). Sodium trifluoromethanesulfinate and sodium 4-nitropheny sulfinate did not undergo this transformation (date not shown).

Table 3. The scope of sulfinates.[a]





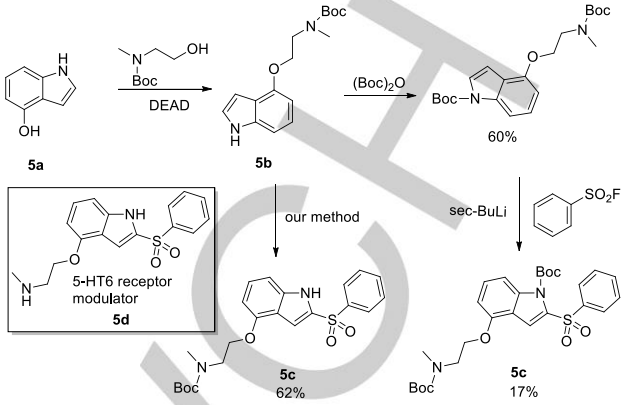
A gram scale reaction was conducted to assess the scalability of this electrochemical sulfonylation under standard condition in a beaker (Scheme 1). Indolyl aryl sulfone **3a** was obtained in 70% yield, which was only slightly decreased in comparison with that of a smaller scale.



[a] Reaction conditions: **1a** (10 mmol), **2a** (20 mmol), TBAI (20 mol%), acetic acid (16 mmol), CH_3CN (66 mL), H_2O (66 mL), Pt foil electrodes (1.5 cm^2 each), Ag/AgCl as the reference electrode, constant potential (1.5 V vs Ag/AgCl), undivided cell, air, room temperature, 36h. Isolated yield.

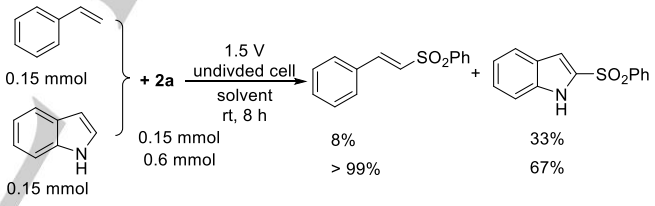
Scheme 1. Gram scale synthesis of **3a**. [a]

To demonstrate the utility of this electrochemical sulfonylation, we applied it to prepare biologically active molecules. Compound **5d** can serve as the 5-HT6 receptor modulator. The reported method to prepare **5d** requires the protection of the amino group on the indole ring and the use of a dangerous reagent *sec*-BuLi. [16] Even so, only 10% yield of **5c** was obtained (based on **5b**). In our method, **5b** was directly sulfonylated with sodium benzene sulfinate, affording **5c** in 62% yield. This method avoids the protection step and the use of dangerous reagents.



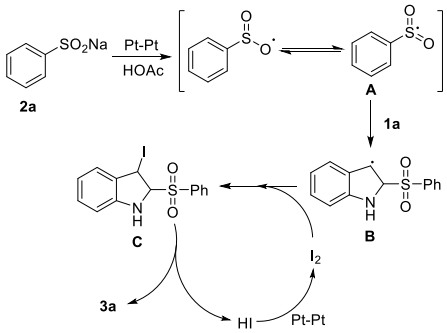
Scheme 2. Electrochemical synthesis of the precursor of **5d**.

It has been known that unsaturated system can be sulfonylated through a radical process. [17] To gain insight into the mechanism, competition reactions between styrene and indole with sodium benzene sulfinate were carried out. Vinyl sulfone and indolyl sulfone were isolated in 8% and 33% yields respectively using **2a** as the limiting reagent. However, the yield of vinyl sulfone was high up to 99% in the presence of excess **2a** (Scheme 3). We suspected that a sulfonyl radical might be involved.



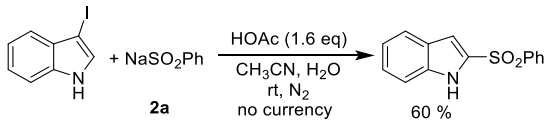
Scheme 3. Competition reactions.

Based on the above experimental results and literatures, [14] a possible mechanism was outlined in Scheme 4. Firstly, sulphonyl radical **A** is directly generated from sulfinate through electrolysis in the presence of acetic acid.[18] And then the addition of the sulphonyl radical to indole affords an intermediate radical **B**. This radical is stabilized by the p-π conjugation, which is responsible for the selectivity for the C2-position. The reaction of **B** with I_2 generated through electrolysis at the anode affords intermediate **C**. Lastly, the elimination of HI gives the product **3a**. [19] Protons are reduced at the cathode to release H_2.

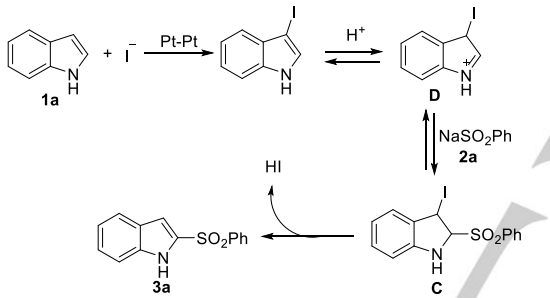


Scheme 4. Proposed radical mechanism.

On the other hand, during the process, we observed the formation of 3-iodo-1*H*-indole (see Supporting information), which could react with azole nucleophiles to afford 2-(azol-1-yl)indoles according to a previous report by Beaulieu.[20] Therefore, we suspected that sodium benzenesulfinate also reacted with 3-iodo-1H-indole in the same mode. The reaction of **1a** with **1b** did give product **3a** in 60% yield by stirring the mixture under nitrogen atmosphere without electricity (Scheme 5). We further observed the formation of 3-iodo-1*H*-indole in the absence of **2a** during electrolysis. Based on the above results, another possible mechanism was proposed (Scheme 6). The iodogenation of indole gives 3-iodo-1*H*-indole during the electrolysis. Subsequent protonation of 3-iodo-1*H*-indole affords a cationic intermediate **D**, [20] which then interacts with nucleophilic **2a** and gives intermediate **C**. The release of HI furnishes the desired product **3a**.



Scheme 5. The reaction of 3-iodo-1H-indole with **2a**.



Scheme 6. Another possible mechanism.

Conclusions

In conclusion, we have developed an electrochemical α-sulfonylation of 1-*H*-indoles with sodium sulfinates under metal- and chemical oxidant-free conditions. This reaction tolerates a variety of functional groups including halides, ether, ester and aldehyde. This transformation can be applied to the synthesis of biologically active 5-HT6 modulators. In comparison with the current chemical synthesis, this sulfonylation have great advantages including step-economy, good efficiency and avoiding the use of highly dangerous reagents.

Experimental Section

The electrochemical sulfonylation of 1a with 2a: The electrolysis was carried out in a one-compartment cell. Pt foils (0.25 cm^2 each) were chosen as the electrodes and an Ag/AgCl served as the reference electrode. To a one-compartment cell were added **1a** (0.3 mmol), **2a** (0.6 mmol), n-$(Bu)_4NI$ (0.06 mmol) acetic acid (0.5 mmol), CH_3CN (2 mL), H_2O (2 mL). The solution was electrified under a constant potential of 1.5 V (*vs* Ag/AgCl) at room temperature under air atmosphere. After electrolysis for 8 hours, electrodes were removed. A saturated $Na_2S_2O_3$ solution (30 mL) and ethyl acetate (30 mL) were added to the resulted mixture. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 30 mL). The combined organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed through silica gel eluting with ethyl acetate/hexanes to give the product.

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Keywords: electrochemical oxidation • sulfonylation • electrolysis • indolyl sulfone • dehydrogenative coupling

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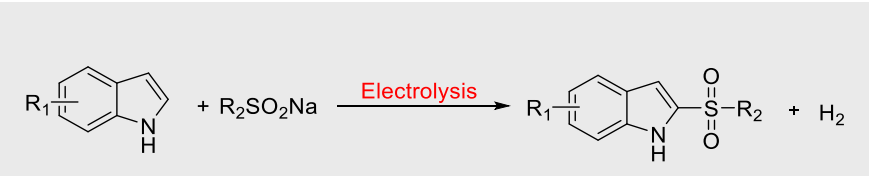

Electrochemical α–Sulfonylation of indoles: An electrochemical α-sulfonylation of 1-*H*-indole with arenesulfinates was developed. A variety of indoles underwent this sulfonylation smoothly at room temperature under metal-free conditions, affording 2-indolyl sulfones in good to high yields. This reaction tolerates a variety of functional groups including halides, cyclopropyl, ether, ester and aldehyde.

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Metal-free Electrochemical α-Sulfonylation of 1-*H*-indole with Arenesulfinates