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Transition-metal- and oxidant-free directed anodic C−H sulfonylation of N,N-disubstituted anilines with sulfinates†

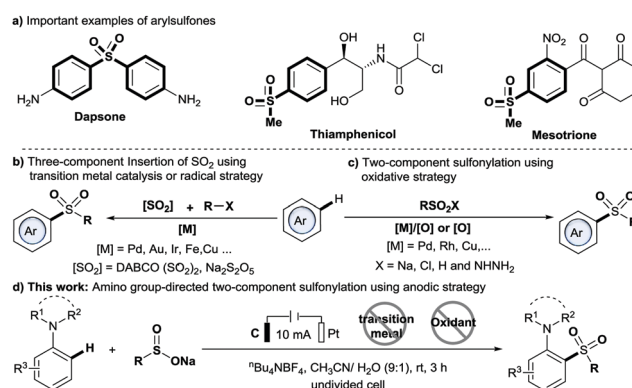Yan-Chen Wu,[a] Shuai-Shuai Jiang,[a] Shu-Zheng Luo,[a] Ren-Jie Song*[a] and Jin-Heng Li [ID] *[ab]

A new, practical directed anodic C−H sulfonylation of N,N-disubstituted anilines with sodium sulfinates for producing o- or p-amino arylsulfones and diarylsulfones is described. Employing the anodic strategy, the reaction proceeds efficiently under mild (room temperature) and transition-metal- and chemical oxidant-free conditions, and enables the formation of C−S bonds via directed activation of ortho- or para-C−H bond to the amino group with broad substrate scope and excellent site selectivity.

Arylsulfones are recognized as an important class of organic molecule because they have unique biological activity and wide applications ranging from chemical to physical.[1,2] For example, dapsone is a preferred drug for leprosy (Scheme 1a).[3] Traditionally, methods for the synthesis of arylsulfones generally proceed by means of Friedel–Crafts-type sulfonation or oxidation of sulfides.[4,5] In recent years, C–H sulfonylation reactions using either the C–H activation or the radical strategy have been developed (Scheme 1b and c).[6–10] Particularly, the directed C–H activation strategy has attracted much attention due to its high atom and step economies as well as excellent site selectivity, which has been widely applied in C–H sulfur dioxide insertion reactions (Scheme 1b) and oxidative C–H sulfonylation (Scheme 1c). However, most of these methods require expensive noble transition metal catalysts, stoichiometric amounts of oxidants and/or relatively high temperature. Thus, the development of new, efficient strategies toward arylsulfone derivatives under mild, metal-free and chemical oxidant-free conditions is appealing.

Electrochemical synthesis has become a powerful tool in organic synthesis due to its safety and sustainability.[11] Importantly, the electrochemical strategy has been applied to C–H

functionalization, albeit with the majority involving the use of transition metal catalysis. In 2018, Lei and co-workers reported an electrochemical direct oxidative C–H sulfonylation of (hetero)-arenes using sulfonyl hydrazides as sulfonylating agents.[12] Very recently, Waldvogel and co-workers reported a novel metal- and reagent-free electrochemical strategy for the synthesis of arylsulfones by direct sulfonylation of phenols with sodium sulfinates.[13] However, the method is limited by the requirement of special highly substituted phenols to achieve excellent regioselectivity. To our knowledge, methods for directed sulfonylation of anilines using the electrochemical method have never been reported. Herein, we report a new anodic C–H sulfonylation of N,N-disubstituted anilines with sodium sulfinates for producing o- or p-amino arylsulfones and diarylsulfones (Scheme 1d). The method enables the regiospecific construction of the C–S bond under mild and transition-metal- and chemical oxidant-free conditions, and provides a practical and sustainable tool to access the valuable C,S-coupling products from common reaction components: N,N-disubstituted anilines and sodium sulfinates.

By utilizing $^{n}Bu_4NBF_4$ as the electrolyte and CH_3CN/H_2O as co-solvents, the directed anodic C–H sulfonylation between 4-methoxy-N,N-dimethylaniline (1a) and sodium 4-chlorobenzenesulfinate (2a) was performed, affording the desired C,S-coupling

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Scheme 1 Important sulfones and C−H sulfonylation.

Table 1 Screening of optimal reaction conditions[a]

Entry	Variation from the standard conditions	Yield (%)
1	None	91
2	5 mA instead of 10 mA, 6 h	90
3	15 mA instead of 10 mA, 1.5 h	83
4	$^{n}Bu_4NBr$ instead of $^{n}Bu_4NBF_4$	85
5	$LiClO_4$ instead of $^{n}Bu_4NBF_4$	62
6	CH_3OH/H_2O (9 : 1) instead of $MeCN/H_2O$ (9 : 1)	67
7	Without H_2O	Trace
8	Without MeCN	26
9	C(+)|C(−) instead of C(+)|Pt(−)	75
10	Pt(+)|C(−) instead of C(+)|Pt(−)	85
11	Under Ar	88
12	No electric current	0
13[b]	None	71
14[c]	No $^{n}Bu_4NBF_4$, HFIP : H_2O (9 : 1) as solvent	27

[a] Reaction conditions: carbon rod anode, platinum plate cathode, constant current = 10 mA, **1a** (0.3 mmol), **2a** (4 equiv.), $^{n}Bu_4NBF_4$ (0.1 mmol), CH_3CN/H_2O (9.0 mL/1.0 mL), room temperature under air atmosphere for 3 h. [b] **1a** (1 g, 6.6 mmol) for 18 h, 13% of **1a** was recovered. [c] By-product 2,6-bis((4-chlorophenyl)sulfonyl)-4-methoxy-N,N-dimethylaniline (**4aa**) was isolated in 12% yield.

product **3aa** in a 91% yield under 10 mA constant current for 3 h in an undivided cell (a three-necked round-bottomed flask) equipped with a carbon rod anode and a platinum plate cathode (entry 1; Table 1). Changing the operating current of this transformation resulted in a decrease in yield (entries 2 and 3). Control experiments showed that the reaction had less reactivity when using $^{n}Bu_4NBr$ or $LiClO_4$ as the electrolyte (entries 4 and 5). The yield decreased sharply to 67% using $MeOH/H_2O$ instead of CH_3CN/H_2O (entry 6). We found that H_2O was necessary to increase the solubility of the salts (entry 7). However, use of water alone as the medium led to diminishing yield (entry 8). Two other electrode material combinations were screened, which proved use of graphite rod as the anode and platinum plate as the cathode to be the best choice (entry 1 versus entries 9, 10). The method showed no apparent sensitivity to oxygen and therefore could be performed under air atmosphere conditions (entry 11). The reaction could not take place under no electric current condition (entry 12). Notably, the synthetic potential of this reaction was then evaluated by performing a 6.6 mmol (1 g) scale reaction, giving 1.64 g of **3aa** (71% yield) after 18 h (entry 13). The reaction could also give **3aa** in 27% yield under Waldvogel's condition, and give by-product 2,6-bis((4-chlorophenyl)sulfonyl)-4-methoxy-N,N-dimethylaniline (**4aa**) in 12% yield.

We then investigated the substrate scope of the reaction by varying the substituents of the aryl and alkyl sulfinates, and the results are summarized in Table 2. Sulfinate derivatives **2b–f** with different functional groups, such as electron-donating groups (R^1 = Me, OMe) and electron-withdrawing groups (R^1 = Br, CN)
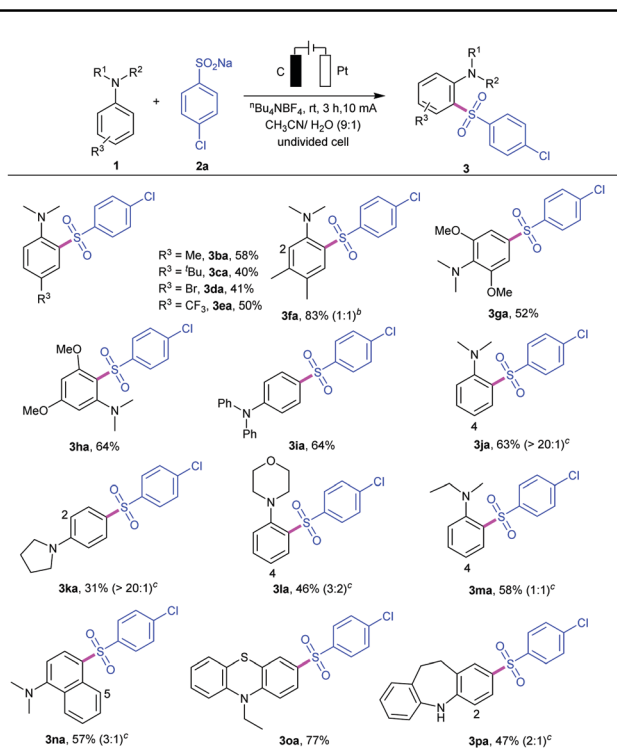
on the *para*-site of aryl ring, were suitable for this electrooxidative C–H sulfonylation and furnished the desired sulfonyl aniline in moderate to excellent yields (**3ab–af**). The position of the substituents on the aryl ring had a minor effect on the efficiency of this transformation. For instance, *meta*- or *ortho*-substituted sulfinates **2g** and **2h** proceeded smoothly to give the corresponding products **3ag** and **3ah** in 62% and 72% yields, respectively. To our delight, sodium naphthalene-2-sulfinate **2i** was compatible with the current conditions and gave the corresponding sulfonyl aniline **3ai** in 62% yield. Subsequently, we also examined the reactivity of di- or trisubstituted sulfinates **2j–k**, and the results showed that they could be successfully reacted with aniline **1a** (products **3aj** and **3ak**). Notably, 2,3-dihydrobenzofuranyl, heterocyclic thienyl and 3-pyridyl sulfinates could work well in the reaction to provide the corresponding heterocyclic products **3al–3an** in 61–83% yields. Moreover, alkyl sulfinates, including sodium methanesulfinate **2n**, sodium 3-methoxy-3-oxopropane-1-sulfinate **2o** and sodium cyclopropanesulfinate **2p**, could be applied under this condition, providing the corresponding sulfones **3ao–aq** in moderate yields.

To examine the synthetic utility of this electrooxidative arylsulfonylation protocol, the scope of N,N-disubstituted anilines **1** was also investigated (Table 3). A series of N,N-disubstituted anilines can be tolerated regardless of the electronic and steric effects. For example, *para*-substituted anilines **1b–e** bearing both electron-donating groups (R^3 = Me, *tert*-butyl) and electron-withdrawing groups (R^3 = Br, CF_3) led to sulfonyl

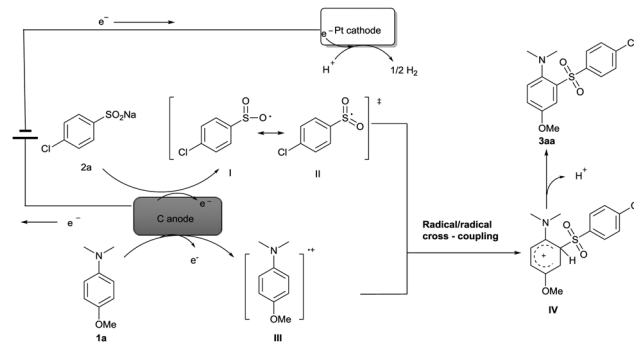**Table 2** Variation of the sulfinate (**2**)[a]

[a] Reaction conditions: carbon rod anode, platinum plate cathode, constant current = 10 mA, **1a** (0.3 mmol), **2a** (4 equiv.), $^{n}Bu_4NBF_4$ (0.1 mmol), CH_3CN/H_2O (9.0 mL/1.0 mL), room temperature under air atmosphere for 3 h.

Table 3 Variation of the N,N-disubstituted anilines (1)[a]

Scheme 2 Possible reaction mechanism.

[a] Reaction conditions: carbon rod anode, platinum plate cathode, constant current = 10 mA, **1a** (0.3 mmol), **2a** (4 equiv.), ^{n}Bu$_4$NBF$_4$ (0.1 mmol), CH$_3$CN/H$_2$O (9.0 mL/1.0 mL), room temperature under atmosphere for 3 h. [b] This compound is obtained as a mixture of regioisomers that could not be separated by standard chromatography. [c] This compound could be separated by standard chromatography; for details, see ESI.

anilines **3ba–3ea** in 40–58% yields. Asymmetric disubstituted aniline **1f** could react with sodium 4-chlorobenzenesulfinate **2a**, giving a mixture of products **3fa** in 83% yield. Moreover, symmetrical disubstituted anilines **1g** and **1h** were also amenable to this protocol, affording the reasonable products **3ga** and **3ha** in 52% and 64% yields, respectively. A survey of aniline derivatives with different aromatic groups and alkyl groups substituted at the nitrogen atom showed reactivity with sulfinate **2a**. In addition, N,N-dialkyl-substituted anilines, such as N,N-dimethylaniline **1j**, N-phenyl heterocyclic amines **1k–l**, and N-ethyl-N-methylaniline **1m**, were also tolerated but led to lower yields. It was observed that, in most cases, this electrooxidative sulfonylation reaction occurred predictably at the ortho- and para-positions with respect to the amino substituent. The ortho- and para-amino arylsulfones were obtained at the same time, and the site selectivity may be controlled by the steric hindrance effect. Notably, N,N-dimethylnaphthalen-1-amine **1n** was also suitable for this transformation (product **3na**).[14] As we expected, C4,C5-sulfonated products can be separated under the same catalytic system. This methodology could also be applied to some drug structure derivatives. For example, the reaction of 10-ethyl-10H-phenothiazine (**1o**) gave the desired product **3oa** in 67% yield, and iminodibenzyl (**1p**) also showed good reactivity, affording the C2- and C4-sulfonated product **3pa** in 47% yield

under the same reactions. Phenothiazine derivatives have been reported to be a class of antipsychotics and iminodibenzyl is an important class of pharmaceutical intermediates for synthesis of specific analgesic and antipsychotic agents.

Based on the experiments, CV results (see ESI†) and previous reports,[15,16] a possible mechanism for the electrochemical oxidative direct sulfonylation of anilines is proposed in Scheme 2. Firstly, sodium 4-chlorobenzenesulfinate **2a** is oxidized at the anode to give the oxygen-centered radical **I**, and the oxygen-centered radical resonates to the more stable sulfonyl radical **II**. At the same time, 4-methoxy-N,N-dimethylaniline **1a** might also be oxidized by the carbon anode to generate a radical cation **III**. C–S bond was likely to be formed from the radical/radical cross-coupling between radical cation **III** and sulfonyl radical **II**, and finally resulted in the desired product **3aa** after a deprotonation process. At the cathode, the co-solvent H$_2$O could be reduced to give hydrogen gas during the reaction.

In conclusion, we have established a general protocol to couple N,N-disubstituted anilines with aryl, heteroaryl and alkyl sulfinates in the absence of any transition metal catalyst promoted by electrochemical means at room temperature using undivided electrochemical cells. A broad range of aryl and hetero-aryl sulfones could be constructed under this catalyst system and this method tolerated many functional groups. Importantly, the reaction conditions were compatible with some drug structure derivatives. Further efforts to understand the electro-chemical oxidative reaction mechanism are currently underway in our laboratory.

Conflicts of interest

The authors declare no conflict of interest.

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