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TMEDA-enabled regioselective sulfenylation of unprotected *N*-heterocycles *via* electrochemical sulfinyl radical generation†

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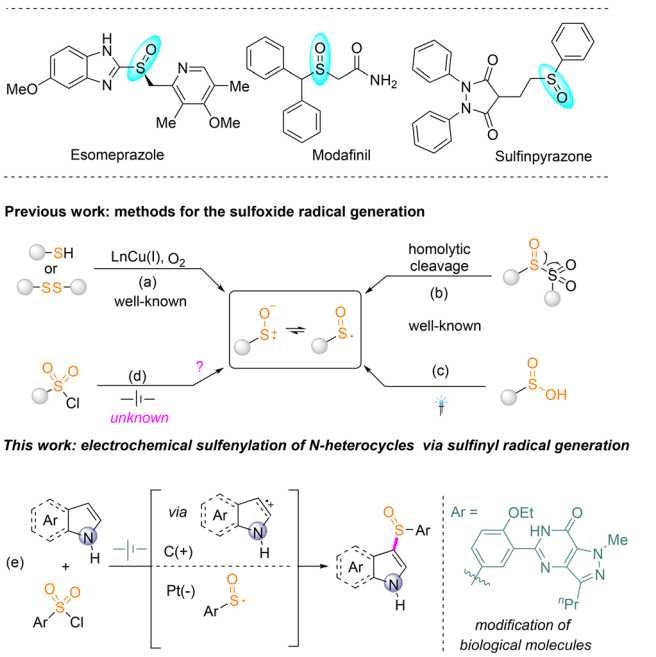
An electrochemical sulfenylation of unprotected *N*-heterocycles with a wide range of commercially available arylsulfonyl chlorides was developed. This protocol features the use of inexpensive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) serving as both a promoter and a base to tune the sulfenylation process, thus affording sulfenylated products in good yields with high regioselectivity. Importantly, TMEDA significantly lowers the oxidation potential of indole, thus avoiding the over-oxidation of indole.

Introduction

Sulfoxides, fundamental members of the sulfur-containing compounds, have unique structures and properties within sulfur chemistry.[1] The sulfoxide moiety is widely prevalent in various biologically active drugs, such as esomeprazole, modafinil and sulfinpyrazone, featuring sulfoxide frameworks (Scheme 1, top).[2] In addition, some well-designed chiral sulfoxides are often employed as ligands that can be coordinated with transition metals to achieve ideal enantioselectivity in synthetic chemistry.[3] In recent years, studies on the synthesis of sulfoxides have garnered increasing interest. Accordingly, several methods using various sulfur sources for sulfoxide synthesis have been well established.[4–6] Among them, direct oxidation of thiols or sulfides provides an approach to sulfoxides, but often have unpleasant odors, accompanied by the formation of over-oxidation products.[5] In these reports, with transition metal catalysis, the sulfinate anion (RSO^-) serving as a nucleophile can be further used to couple with suitable halogenated aromatic rings and their analogues to afford sulfoxides.[6] To address the abovementioned issues, odorless sulfinic acid or sulfenyl sulfone has become an ideal alternative for the synthesis of sulfoxides.[7] Additionally, from the viewpoint of the reaction pathway, only a handful of methods involving a sulfinyl radical have been developed to achieve this goal. For selected examples, Jang's group in 2016 investigated the aerobic oxidation of thiophenol with copper catalysis, in which sulfinyl radical generation was proposed for the subsequent synthesis of sulfinates and thiosulfonates (Scheme 1a).[7a] In 2021, Bi *et al.* disclosed a silver-catalyzed generation of sulfinyl radicals from sulfinyl sulfones, and further explored their radical addition/radical coupling with unsaturated hydrocarbons (Scheme 1b).[7b] In 2022, Wu and coworkers found that sulfinic acids under visible light irradiation could produce sulfinic radicals *via* a photochemical reduction process, which then underwent radical cross coupling with Hantzsch esters or



Scheme 1 Typical biologically active compounds and methods for sulfinyl radical generation.

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Meyer nitriles using NHC/photocatalysis to yield a number of sulfoxides (Scheme 1c).[7c] Noteworthy is that despite the advancements made in the past few years, a significant limitation is the requirement of hazardous compounds, starting materials with a noxious odor, toxic metal salts, and the use of expensive metal catalysts or photocatalysts for some well-designed reaction systems.[7]

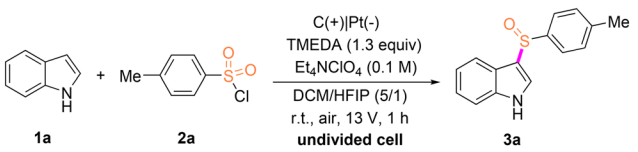
N-heterocyclic compounds, such as indoles and their analogues, generally have significant biological activity, and they are widely present in many natural products and synthetic drugs.[8,9] Over the past few decades, functionalization of indoles has recieved significant attention in synthetic chemistry.[10] However, electron-rich indoles, especially the C3–C–H bond, were often over-oxidized during the course of their functionalization.[11] To alleviate the negative effect, the N–H bond generally requires protection with an acyl, tosyl, Boc, Fomoc or alkyl group.[12] After this, removing the protecting group from the product not only leads to waste production, but also lowers the atom economy of the chemical process.[11,12] Therefore, it is highly urgent to develop an alternative methodology that is more environmentally friendly for indole functionalization.

Electro-organic synthesis as an environmentally benign technique has proven to be powerful in manipulating organic molecules.[13] In particular, the electrochemical transformation often proceeds under mild conditions, thus avoiding many undesired side reactions. We hypothesized that commercially available indoles would not need any other protection and could be selectively functionalized using the electrochemical method. Based on our understanding of the electrochemical synthesis, sulfonyl chlorides in theory can be employed to generate sulfinyl radicals *via* cathodic reduction (Scheme 1d). Hitherto, this design has not been realized in functionalizing the C3–C–H bond of unprotected indoles or some other *N*-heterocycles. As part of our ongoing effort in electro-organic synthesis, we here disclose a rare example of electrochemical generation of sulfinyl radicals from commercially available sulfonyl chlorides under mild conditions and its application in the regioselective sulfenylation of unprotected *N*-heterocycles, providing an approach to sulfenylated products (Scheme 1e). Remarkably, such an electrochemical method for sulfenylation has a significant advantage over the photocatalytic method, because the latter usually relies on precious iridium catalysts and designed N-heterocyclic carbene.[7c]

Results and discussion

Based on our recent studies on electro-organic synthesis,[14] we began to study the sulfenylation of indole **1a** with TsCl **2a** in an undivided cell by using a graphite carbon anode, a platinum cathode under constant voltage (13 V) and a mixture of anhydrous DCM and HFIP (v/v 5 : 1), and the results are summarized in Table 1. Using TMEDA as an additive and Et_4NClO_4 as an electrolyte, product **3a** was obtained in 76% yield (entry 1). A smaller amount of TMEDA led to the formation of **3a** in

Table 1 Optimization of reaction conditions[a,b]



Entry	Variation from the "standard conditions"	Yield (%)
1	None	76
2	No TMEDA	Trace
3	TMEDA (0.8 equiv.)	60
4	Et_4NClO_4 (0.05 M)	63
5	Et_4NBF_4 instead of Et_4NClO_4	66
6	$^nBu_4NClO_4$ instead of Et_4NClO_4	18
7	$^nBu_4NBF$, $^nBu_4NI$ instead of Et_4NClO_4	n.d.
8	GF as an anode	40
9	Pt as an anode	53
10	RVC as an anode	72
11	C as a cathode	n.d.
12	Ni form as a cathode	n.d.
13	MeCN instead of DCM	36
14	DCE instead of DCM	42
15	MeOH, DMF, DMSO instead of DCM	n.d.
16	No HFIP	Trace
17	No electric current	n.d.
18	Under N_2	74[c]

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.60 mmol, 2.0 equiv.), DCM (5 mL), HFIP (1 mL), TMEDA (0.39 mmol, 1.3 equiv.), Et_4NClO_4 (0.1 M), a carbon rod (Φ 6 mm), a platinum plate cathode (10 mm × 10 mm × 0.3 mm), 13 V, room temperature (r.t.), 1 h. [b] Isolated yields. [c] N_2. n.d. = not detected.

lower yields (entries 2 and 3). Using 0.05 M Et_4NClO_4, the model reaction only gave **3a** in 63% yield (entry 4). After testing several electrolytes, such as Et_4NBF_4, $^nBu_4NClO_4$, $^nBu_4NBF_4$ and $^nBu_4NI$, it was found that Et_4NClO_4 was the best one for this sulfenylation (entries 5–7). Replacing the carbon anode with GF, Pt, or RVC did not improve the yield of **3a** (entries 8–10). Next, the sulfenylation reaction of **1a** did not proceed when using carbon or Ni form as the cathode (entries 11 and 12). Using MeCN or DCE instead of DCM in the mixed solvent with HFIP resulted in a decrease in the isolated yield of **3a** (entries 13 and 14). Furthermore, mixed solvents containing MeOH, DMF or DMSO seemed to inhibit the occurrence of the sulfenylation process (entry 15). Remarkably, the presence of HFIP played a critical role in the sulfenylation of indole with TsCl (entry 16). In addition, no desired product **3a** was observed in the absence of electric current (entry 17). Interestingly, performing the model reaction under an N_2 atmosphere produced **3a** in 74% yield, indicating that the reaction is not very sensitive to air (entry 1 *vs.* entry 18). Finally, some common organic bases, including DMP, DABCO, TEA, TMEDA, and TPA, were screened under similar conditions. The results illustrate that TMEDA could promote the electrochemical sulfenylation of indole **1a** (Fig. 1).

After achieving the optimal conditions, we started to explore the generality of this electrochemical sulfenylation. As shown in Table 2, we first explored the scope of arylsulfonyl chlorides under the standard conditions. A series of arylsulfo-

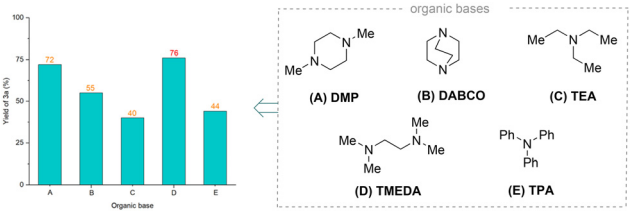
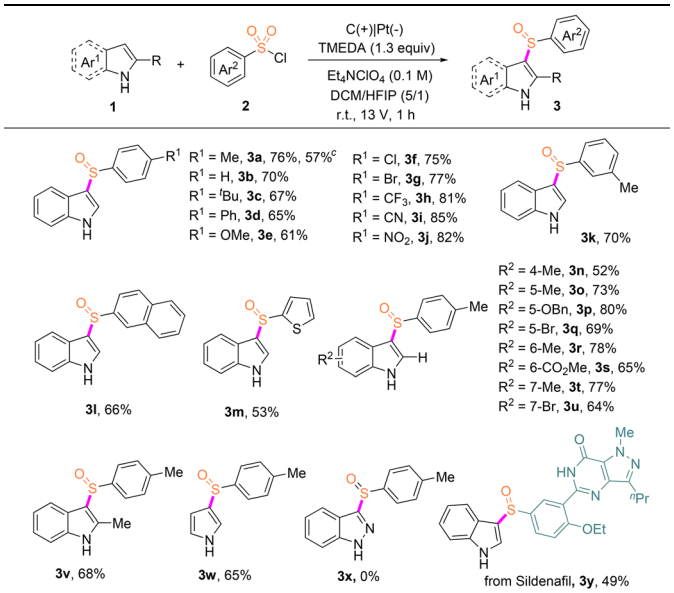


Fig. 1 Effect of the base on the electrochemical C3-sulfenylation of indole.

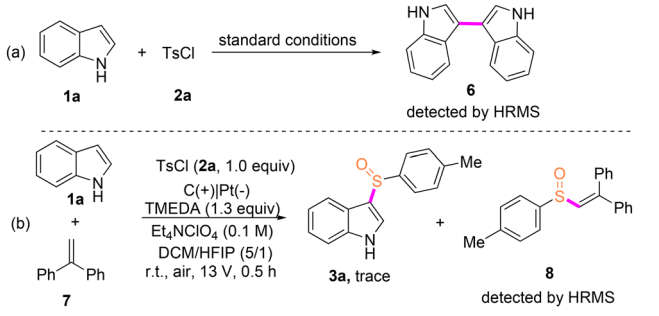
Table 2 Scope of the *N*-heterocycles and sulfonyl chlorides[a,b]



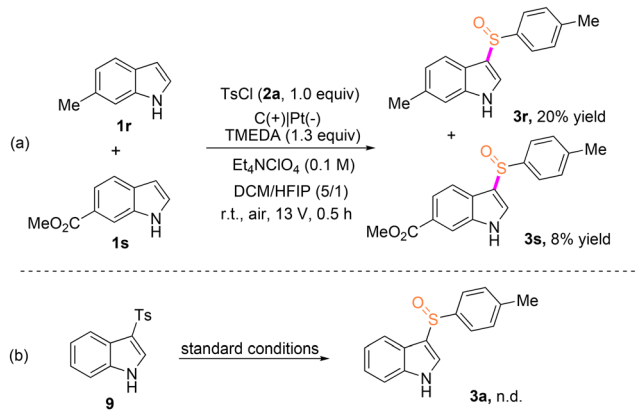
[a] Reaction conditions: **1** (0.30 mmol), **2** (0.60 mmol, 2.0 equiv.), DCM (5 mL), HFIP (1 mL), TMEDA (0.39 mmol, 1.3 equiv.), Et_4NClO_4 (0.1 M), a carbon rod (Φ 6 mm), a platinum plate cathode (10 mm × 10 mm × 0.3 mm), 13 V, room temperature, 1 h. [b] Isolated yields. [c] Gram-scale reaction.

nyl chlorides with *para*-substitution were reacted with indole **1a** to afford products **3** in varying yields. For instance, the reaction of sulfonyl chlorides containing Me, H, *t*-Bu, Ph, and OMe proceeded well to generate **3a–e** in 61–76% yields. Moreover, using sulfonyl chlorides having halogens led to the formation of **3f** and **3g** in 75% and 77% yields, respectively. In the case of sulfonyl chlorides bearing electron-withdrawing groups at the *para*-position, such as CF_3, CN and NO_2, the related products **3h–j** were obtained in good yields. The *meta*-Me-substituted substrate could react normally to give **3k** in 70% yield. Similarly, with a 2-naphthyl or 2-thiophenyl substitution, sulfenlyation products **3l** and **3m** were obtained in 66% and 53% yields, respectively. Next, we synthesized a series of substituted indoles and explored their compatibility under the optimal conditions. Introduction of a Me group at the C4-postion of indole resulted in the formation of **3n** in 52% yield. Moreover, we found that 5-Me-substitued indole reacted with **2a** to generate **3o** in 73% yield. Replacing the Me group with BnO and Br groups produced **3p** and **3q** in 80% and 69% yields, respectively. Similarly, it is found that incorporating an electron-rich group (Me) at the C6- or C7-position of indole can accelerate this sulfenylation process (**3r** *vs.* **3s**; **3t** *vs.* **3u**). We then tested the reaction of 2-methyl-1*H*-indole with **2a** under the optimal conditions, indicating that **3v** was obtained in a slightly decreasing yield. The newly established electrochemical method is also applicable to the C-3 sulfenylation of simple pyrrole, affording **3w** with a 65% isolated yield. Unfortunately, simple indazole did not work under similar conditions. Finally, a structurally valuable sulfonyl chloride derived from the bioactive sildenafil was synthesized and used in the reaction. The results indicate the cathodic reaction of this sulfonyl chloride with sulfinyl radicals still occurred to complete the sulfenylation of indole, although **3y** was formed in 49% yield.

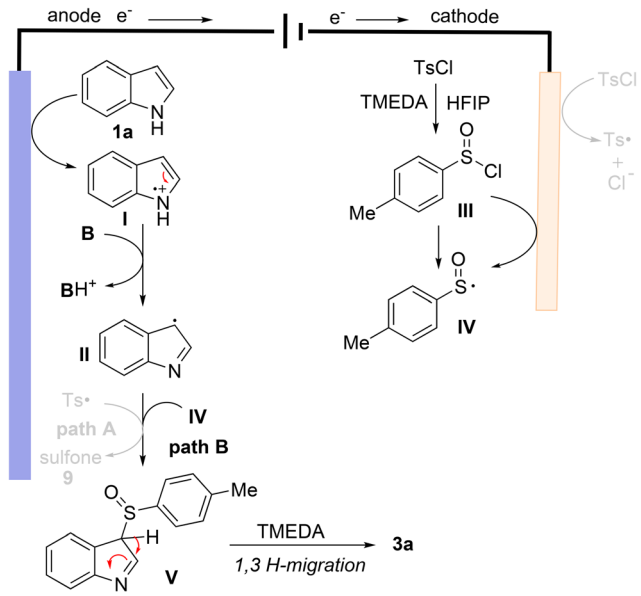
Next, several mechanistic experiments were carried out to understand the mechanism of the electrochemical sulfenylation reaction. First, related radical trapping experiments were performed, and observed the formation of the homo-coupling product of indole **6** using the HRMS method, further indicating the anodic oxidation of indoles to the corresponding radical intermediates (Scheme 2a). Finally, adding the radical scavenger 1,1-diphenylethylene to the reaction system led to the generation of the adduct product **8**, showing that a sulfinyl radical was generated at the cathode (Scheme 2b). In addition, the competition experiments involving the indoles with different substitutions and **2a** were carried out and the results showed that the sulfenylation reaction of electron-rich indole seemed to proceed faster than that of the electron- deficient one (Scheme 3a). Then, the Ts-substituted indole **9** was specifically synthesized and used in this control experiment under the optimized conditions, but product **3a** was not isolated. The experimental results show that the sulfonyl group in the by-products cannot be electrochemically reduced to the target product **3a** (Schemes 3b and 4). In addition, the CV experimental results show that TMEDA significantly lowers the oxidation potential of indole from 1.09 V to 0.97 V, thus avoiding the over-oxidation of indole. In addition, a reduction peak was observed at −1.16 V for methyl sulfonyl chloride **2a**, indicating the possible cathodic reduction to a sulfinyl radical. The oxidation potential of product **3a** is somewhat higher (1.43 V)



Scheme 2 Radical trapping experiments.



Scheme 3 Control experiments.



Scheme 4 Possible reaction mechanism.

than others, so it was relatively stable in this system (Fig. S4, see the ESI† for details).

Currently, there is no report on the electrochemical transformation of TsCl, especially acting as a sulfinic radical source for the functionalization of unprotected *N*-heterocycle. So, it is not easy to thoroughly figure out this process. Based on the above experimental results, a possible mechanism for the electrochemical sulfenylation of unprotected indole is depicted in Scheme 4. On one hand, indole **1a** at the anode was oxidized to yield cationic radical species **I**, which interacted with a base to afford radical intermediate **II**. On the other hand, TsCl was reduced to radical Ts$^{\bullet}$, which coupled with **II** to produce undesired sulfonylation product **9** (path A). Importantly, TsCl could be transformed to an unstable 4-methylbenzenesulfinic chloride **III**, and its generation could be supported by the trapping experiment of *p*-toluenesulfinic acid with HRMS (Fig. S7, see the ESI† for details). Furthermore, **III** underwent a cathodic reduction to afford intermediate **IV** (path B). Likewise, **IV** coupled with **II** to generate intermediate **V**, followed by 1,3-H migration with the assistance of a base such as TMEDA to deliver **3a**.

Conclusions

In conclusion, we have developed an electrochemical sulfenylation of unprotected *N*-heterocycles with commercially available arylsulfonyl chlorides as the cheap source of sulfinyl radicals. This electrochemical method not only effectively alleviates the undesired over-oxidation of N-heterocycles occurred in traditional chemical methods, but is also capable of synthesising functionalized indole and pyrrole derivatives. Mechanistic experiments disclose the dual roles of TMEDA in lowering the oxidation potential of indole and acting as a base to promote sulfenylation. Currently, extension of this electrochemical sulfenylation method to a more challenging molecular manipulation is underway in our laboratory.

Data availability

The data supporting the findings of this study are available within the article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

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