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Electrochemically enabled chemoselective sulfonylation and hydrazination of indoles†

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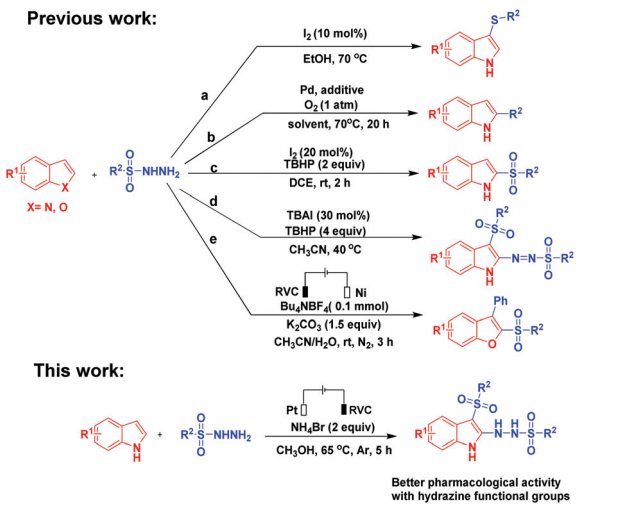
Environmentally benign electrochemically enabled chemoselective sulfonylation and hydrazination of C2,C3-unsubstituted indoles with arylsulfonyl hydrazide in the presence of ammonium bromide as a redox catalyst and electrolyte have been demonstrated in this work. Under mild electro-oxidation conditions, a series of indole hydrazination products with pharmacological activity were obtained. *In vitro*, the hydrazination products exhibited a better anti-cancer activity compared with the diazotization products. Further mechanistic studies showed that compound 3ae inhibits cell migration and tubulin aggregation in T-24 cells, thereby leading to cell apoptosis.

The indole moiety is probably the most common heterocycle in natural and pharmaceutical agents.[1] Substituted indole derivatives are considered "privileged structures" as they tend to combine with many receptors.[2] Since the development of synthetic chemistry, the functionalization and synthesis of indole derivatives have aroused much interest from synthetic organic chemists, and numerous effective methods for preparing indoles have been developed.[3] Unlike azo compounds that are widely used in the dyestuff industry, many marketed drugs, including isoniazid,[4] mildronate,[5] hydralazine,[6] and benserazide,[7] contain hydrazine functional groups. The hydrazine skeleton also exhibits a variety of bio-activities, such as anti-schistosomal,[8] anti-cancer,[9] anti-bacterial,[10] anti-inflammatory,[11] and anti-oxidant activities.[12] Therefore, introducing this group into the indole ring presents an attractive research direction, but only a few chemists have undertaken such an activity.

As a valuable synthon, sulfonylhydrazines have attracted much attention due to their different reactivities. They can be used as sulfonylation reagents[13] and transformed into various bioactive products.[14] Much attention has also been paid to the sulfonylation and sulfuration of indoles with sulfonylhydrazines. For example, Tian reported a sulfenylation reaction at the C-3 position of indoles with sulfonyl hydrazides through the I_2-catalysed cleavage of S–N and S–O bonds (Scheme 1, path a).[15] The palladium-catalyzed C-2 arylation of indoles and the I_2/TBHP-mediated C-2 sulfonylation of indoles with sulfonylhydrazines have also been reported (Scheme 1, paths b and c).[16] Tu *et al.* recently performed selective diazotization and sulfonylation of indoles through TBAI/TBHP-mediated oxidative reactions (Scheme 1, path d).[17] However, all these methods require the use of stoichiometric amounts of oxidants or transition metal catalysts. Organic electrosynthesis is an atom-economical and eco-friendly synthetic tool that realizes redox reaction *via* electron transfer and can be used to replace traditional oxidants.[18] This strategy has also been applied by Lei to achieve an electrochemical oxidative radical C–H sulfonylation of benzofuran.[19] Inspired by these studies



Scheme 1 Coupling reaction of indoles with sulfonyl hydrazides.

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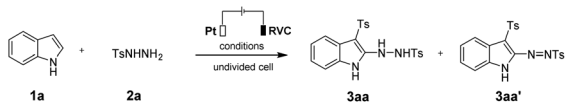
and our previous study on electrosynthesis,[20] we carried out the electrochemically initiated reaction between sulfonylhydrazines and indoles to obtain sulfonylation and hydrazination products under mild electro-oxidation conditions. These products are part of a new class of compounds with a better antitumor activity compared with traditional diazotization products.

We began our investigation with indole **1a** and *p*-toluenesulfonyl hydrazide **2a** as substrates. The effects of different reaction conditions on the reaction results, including the solvent, temperature, and electrolyte, were investigated by using the above model reaction. The results are shown in Table 1. In our previous work, ammonium iodide was used as an electrolyte to obtain high-yield products.[20] Therefore, we used iodide as an electrolyte for our current investigation. However, when using sodium iodide or potassium iodide as the electrolyte, the required product **3aa** was obtained in trace amounts (entries 1 and 2). A similar result was observed when using tetra-butylammonium iodide as the electrolyte, with ammonium iodide producing **3aa** with 40% yield (entries 3 and 4). Meanwhile, ammonium chloride did not show any progress (entry 5), and ammonium bromide produced **3aa** with a 80% yield (entry 6), and replacing ammonium bromide with tetra-butylammonium hexafluorophosphate and tetra-butylammonium bromide did not produce any product (entries 7 and 8). Different solvents, such as H_2O, CH_3CH_2OH, DMSO, and CH_3CN, were then examined under identical conditions. However, none of these solvents were identified as the best response option (entries 9 to 12). Therefore, with NH_4Br as the electrolyte, CH_3OH as the solvent, platinum as the anode, and reticulated vitreous carbon (RVC) as the cathode, the desired C–H sulfonylated **3aa** was obtained at a constant current of 20 mA in an undivided cell with a better yield.

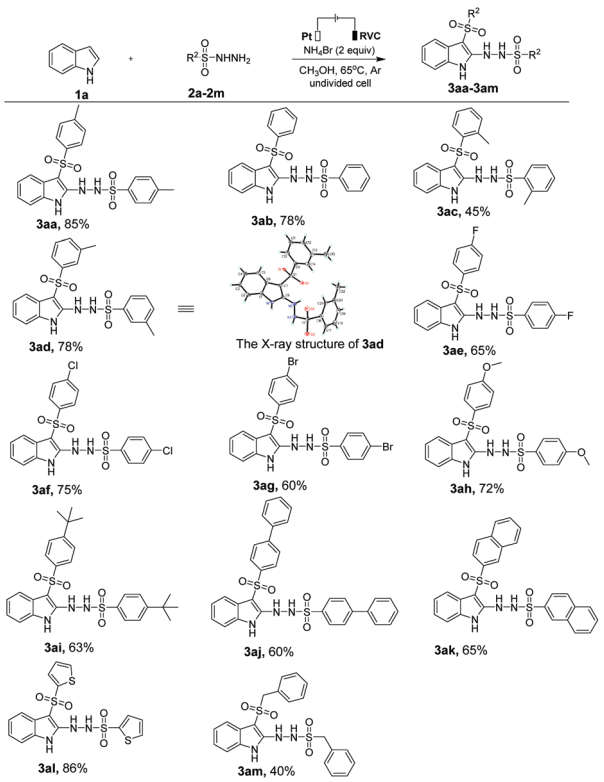
Table 1 Optimization of the reaction conditions[a,b]



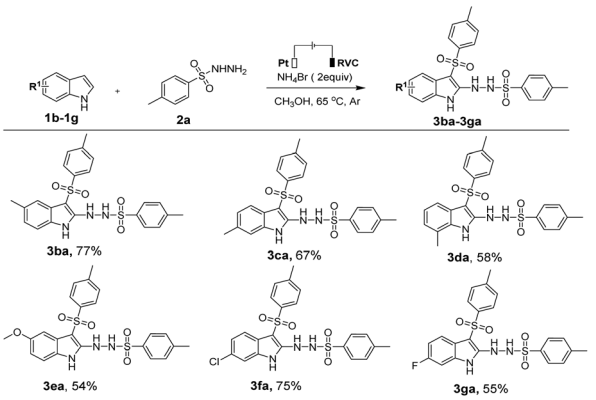
Entry	Electrolyte	Solvent	Yield[b] (%) 3aa	3aa′
1	NaI	CH_3OH	Trace	Trace
2	KI	CH_3OH	Trace	Trace
3	NH_4I	CH_3OH	40	15
4	*n*-Bu_4NI	CH_3OH	23	Trace
5	NH_4Cl	CH_3OH	0	0
6	NH_4Br	CH_3OH	85	0
7	*n*-Bu_4NBr	CH_3OH	Trace	0
8	*n*-Bu_4NPF_6	CH_3OH	0	0
9	NH_4Br	H_2O	20	0
10	NH_4Br	CH_3CN	30	0
11	NH_4Br	DMSO	0	0
12	NH_4Br	CH_3CH_2OH	Trace	0

[a] Reaction conditions: Pt plate as the anode (1 cm × 1 cm), reticulated vitreous carbon (RVC) as the cathode (100 PPI, 1 cm × 1 cm × 1.2 cm), undivided cell, constant current = 20 mA, **1a** (0.5 mmol), **2a** (1 mmol), electrolyte (2 equiv.), solvent (8 mL), under Ar at 65 °C for 5 h. [b] Isolated yields.

After establishing the optimal reaction conditions, we next subjected various aryl/heteroarylsulfonohydrazides **2b–2m** and indole **1a** to selective C3-sulfonylation and C2-hydrazination to obtain the corresponding products **3ab–3am** (Scheme 2). Benzene-sulfonylhydrazide as well as 2- and 3-methyl-benzenesulfonyl-hydrazide (**2b**, **2c**, and **2d**) reacted with **1a** to produce the products **3ab**, **3ac**, and **3ad** with 78%, 45%, and 78% yields, respectively. The product **3ac** was then characterized by X-ray diffraction. Similarly, electron donating substituents, such as 4-methoxy- and 4-*tert*-butylbenzenesulfonohydrazide (**2h** and **2i**), produced sulfonylation and hydrazination products **3ah** and **3ai** with 72% and 63% yields, respectively. Moreover, the benzenesulfonylhydrazides bearing halide substituents, including F, Cl, and Br, showed a good reaction efficiency, thereby generating the corresponding products with yields ranging from 60% to 75% (**3ae** to **3ag**). Notably, biphenylsulfonyl hydrazide (**2j**) formed the corresponding product **3aj** with a 60% yield, whereas naphthalene-2-sulfonohydrazide (**2k**) and thio-phene-2-sulfonylhydrazine (**2l**) showed a good reactivity with **1a** and obtained the corresponding products **3ak** and **3al** with 65% and 86% yields, respectively. Aliphatic sulfonylhydrazides were also suitable for this transformation. Phenylmethyl sulfonylhydrazine (**2m**) reacted with **1a** to generate the desired product **3am** in 40% yield.



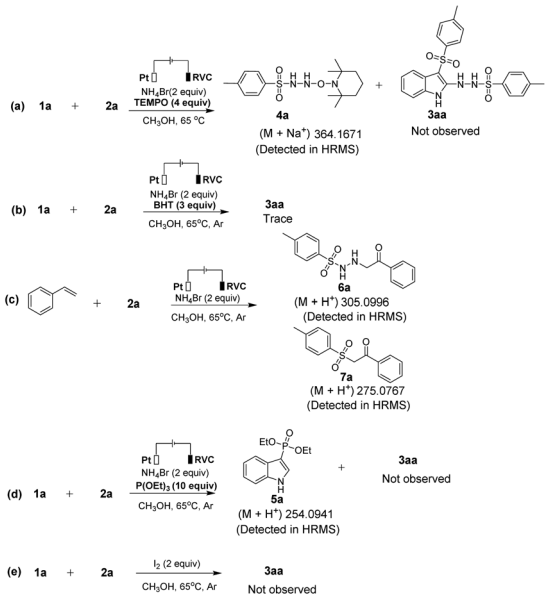
Scheme 2 Substrate scope of aryl/heteroarylsulfon yl hydrazides. Reaction conditions: Pt plate as the anode (1 cm × 1 cm), reticulated vitreous carbon (RVC) as the cathode (100 PPI, 1 cm × 1 cm × 1.2 cm), undivided cell, constant current = 20 mA, **1a** (0.5 mmol), **2** (1 mmol), electrolyte (2 equiv.), solvent (8 mL), under Ar at 65 °C for 5 h. Isolated yields.



Scheme 3 Substrate scope of indoles. Reaction conditions: Pt plate as the anode (1 cm × 1 cm), reticulated vitreous carbon (RVC) as the cathode (100 PPI, 1 cm × 1 cm × 1.2 cm), undivided cell, constant current = 20 mA, **1** (0.5 mmol), **2a** (1 mmol), electrolyte (2 equiv.), solvent (8 mL), under Ar at 65 °C for 5 h. Isolated yields.

To further study the substrate scope of this reaction, we investigated the substrate scope of indoles under standard conditions. As shown in Scheme 3, the indoles bearing electron-donating groups, such as 5-Me and 6-Me, demonstrated favorable reactivity and reaction efficiency with 77% and 67% yields, respectively (**3ba** and **3ca**). However, the indoles bearing 7-Me and 4-OMe groups produced the corresponding products with low yields (**3da** and **3ea**). In addition, the halide substituents, such as 4-chloro/fluoroindoles, can smoothly react with **2a** under optimized reaction conditions and produce the corresponding products **3fa** and **3ga** with 75% and 55% yields.

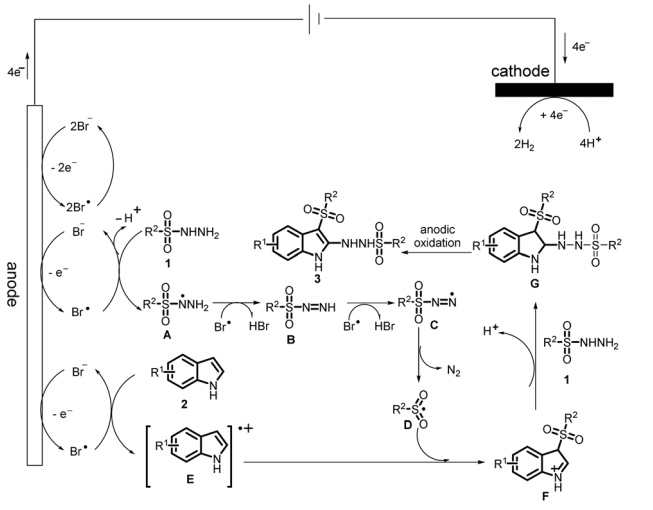
We performed some experiments to reveal the mechanism of this reaction (Scheme 4). When 4 equivalents of the radical scavenger TEMPO were added, the reaction between **1a** and **2a** did not proceed. The reaction mixture was analyzed by using HRMS which showed the presence of the TEMPO trapped radicals **4a** (Scheme 4, eqn (a)). When 3.0 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to the system, the product **3aa** was obtained only in trace amounts as expected (Scheme 4, eqn (b)). In addition, a reaction of hydrazide **2a** with styrene was performed under standard conditions (Scheme 4, eqn (c)) and the desired products **6a** and **7a** were detected by HRMS, the above results confirmed the radical mechanism. Furthermore, we added 10.0 equivalents of triethyl phosphite to the system to trap any radical intermediates. To our delight, the indole-phosphorylation product **5a** was obtained, which indicated that an indole radical was produced during the reaction (Scheme 4, eqn (d)).[21] Finally, a reaction of **1a** with **2a** was carried out in the presence of I_2, but the desired product **3aa** was not obtained, thereby suggesting that I_2 was not involved in the reaction and that the iodine radical was responsible for the oxidative coupling (Scheme 4, eqn (e)).



Scheme 4 Control experiments.

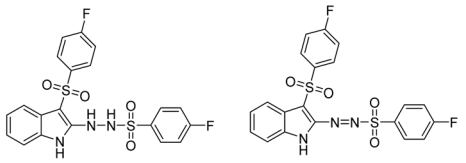
Based on the above experimental results and cyclic voltammetry experiments (Fig. S2†), we propose a reasonable reaction mechanism in Scheme 5. At the anode, bromine ions were oxidized to bromine radicals. Sulfonyl hydrazide **1** was oxidized by one molecule of bromine radical to produce the radical intermediate **A**. The radical **A** was further oxidized by the bromine radicals in two steps followed by the elimination of nitrogen to produce the sulfonyl radical **D**; this process was demonstrated by CV experiments. Similarly, indole **2** can be oxidized by the bromine radicals to produce the indole radical-cation intermediate **E**, which can undergo a radical coupling reaction with the sulfonyl radical **D** to produce the sulfonated indole intermediate **F**. The final nucleophilic addition and selective oxidative aromatization of the cation intermediate **F** leads to the formation of the sulfonated indole derivative **3**.[22] At the cathode, the protons are reduced to hydrogen to complete the reaction cycle.

Sulfonyl hydrazine compounds exhibit anti-tumor activities. To investigate the anti-tumor activity of these sulfonylation



Scheme 5 Proposed mechanism.

Table 2 IC_{50} (μM) values for compounds **3ae** and **3ae′**



	MGC-803	T-24	HepG-2	SK-OV-3	WI-38
3ae	20.7 ± 0.7	12.4 ± 1.4	15.3 ± 0.9	25.1 ± 2.3	>40
3ae′	38.9 ± 1.9	>40	26.8 ± 1.5	>40	>40
5-FU	35.2 ± 0.8	38.4 ± 1.1	>40	>40	>40

and hydrazination products, the *in vitro* cytotoxicities of compounds **3aa–3am** and **3ba–3ga** and those of the sulfonylation and diazotization product **3ae′** against four cancer cell lines (MGC-803, T-24, HepG-2, and SK-OV-3)[23] and one human normal cell line (WI-38) were screened by using the MTT assay with **5-FU** as a positive control. Interestingly, compound **3ae** demonstrated a higher *in vitro* anti-cancer activity to all cell lines compared with the sulfonylation and diazotization compound **3ae′**. This finding may be attributed to the better pharmacological activity of the sulfonyl hydrazide group compared with the sulfonyl diazo group. As shown in Table 2, compound **3ae** exhibited a favorable anti-cancer activity to the T-24 and HepG-2 cell lines with IC_{50} values of 12.4 ± 1.4 and 15.3 ± 0.9 μM, respectively. In addition, the inhibitory effect of compound **3ae** on tumor cells was more obvious than that on the human normal cell line WI-38.

Detailed studies *via* acid staining, intracellular ROS detecting, microfilament inhibition, and wound healing assay were carried out to further investigate the anti-cancer effects of compound **3ae** on T-24 cells. The Hoechst 33342 staining assay revealed that the compound **3ae** induced apoptosis in T-24 cells as shown in Fig. 1. In addition, treatment with **3ae** increased the intracellular calcium ion and ROS levels in T-24 cells (Fig. S3and S4†). Compound **3ae** also inhibited tubulin aggregation (Fig. S6†) and cell migration in T-24 cells (Fig. 2).

In summary, we developed a new metal- and oxidant-free method for synthesizing sulfonylation and hydrazination products. The versatility of the reaction was demonstrated by using various indoles and aryl/heteroarylsulfonyl hydrazides. Under mild electro-oxidation conditions, the indoles were selectively sulfonylated and hydrazinated to produce a new class of compounds with a better antitumor activity compared with traditional diazotization products. The reaction proceeds through a radical pathway as can be seen in the radical trapping experiment and CV studies. The *in vitro* cytotoxicities of all compounds against four cancer cell lines were screened by using the MTT assay with **5-FU** as a positive control. Compound **3ae** exhibited a higher *in vitro* anticancer activity to all cell lines compared with the sulfonylation and diazotization compound **3ae′**. Moreover, the preliminary analysis of the mechanism of action studies revealed that compound **3ae** inhibited cell migration and tubulin polymerization in T-24 cells, thereby leading to cell cycle apoptosis.

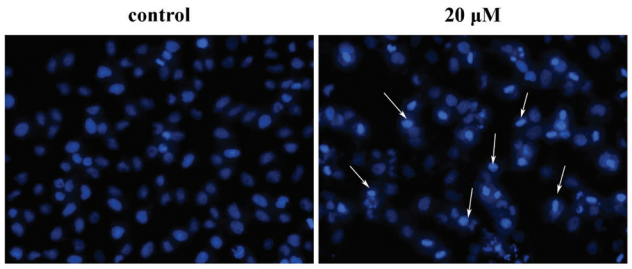


Fig. 1 Assessment of nuclear morphological changes *via* Hoechst 33342 staining in T-24 cells after 24 h.

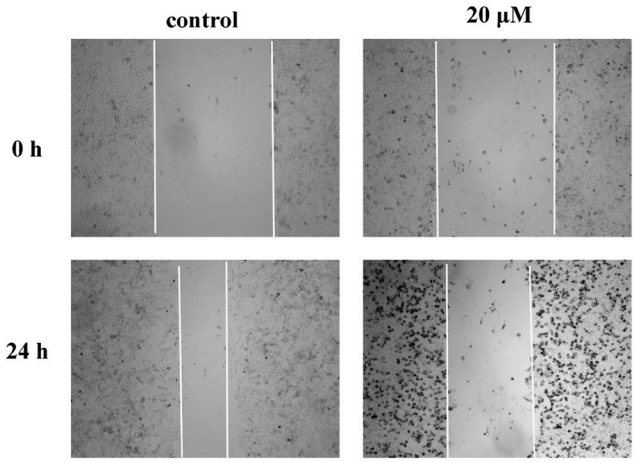


Fig. 2 Effect of compound **3ae** on the *in vitro* migration potential of T-24 prostate cancer cells.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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23 All cell lines in this article were purchased from the Shanghai Cell Bank of the Chinese Academy of Sciences.