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Regioselective electrochemical cascade C–H sulfonylation–bromination of indolizines to access difunctionalized indolizines†

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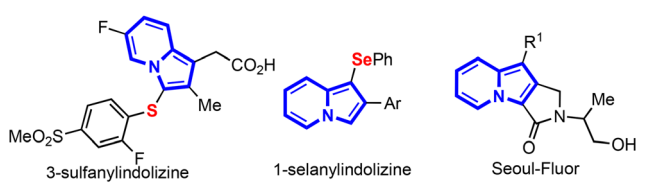
Regioselective electrochemical C–H sulfonylation–bromination between indolizines, sodium sulfinates, and KBr has been established in an undivided cell, in which KBr serves as both the brominating agent and electrolyte. This consecutive C3–H sulfonylation and C1–H bromination protocol enables the synthesis of difunctionalized indolizine derivatives under catalyst- and oxidant-free conditions. Moreover, electrochemical C–H sulfonylation–thiocyanation/selenylation/thiolation of indolizines was realized *via* a two-step process. This protocol features excellent regioselectivity and environmentally friendly electrolysis.

The past two decades have witnessed the flourishing development of electrochemical organic synthesis. As an environmentally friendly, practical, and selectivity tunable synthetic method, electrochemistry has been recognized as a powerful and sustainable tool in various organic transformations.[1,2] Recently, electrochemical C–H sulfonylation[3] and bromination reactions[4] have been well established. However, to the best of our knowledge, research studies on highly selective electrochemical C–H sulfonylation and halogenation at different sites of the same parent molecule are very rare, although this strategy will simultaneously introduce both sulfonyl and halogen groups into a parent molecule.

Indolizines are privileged scaffolds owing to their biological activities and fluorescence properties in synthetic pharmaceuticals and materials science (Scheme 1).[5,6] As a consequence, several methods for the preparation of functionalized indolizines have been developed.[7] Among these cases, selective C–H functionalization is regarded as an ideal strategy for the modification of indolizine rings due to no need for prefunctionalization of precursors and a higher atom- and step-economy.[8] Traditionally, C–H functionalization mainly occurs at the C3 position; for example, we have realized a variety of C3–H thiolation, dicarbonylation, carboxamidation, dithiocarbamation, and disulfuration reactions (Scheme 2a, eqn (1)).[9] In addition, we have also discovered selective C3–H and C1–H dithiolation and electrochemical diselenylation to introduce two of the same group into indolizines (Scheme 2a, eqn (2)).[10] However, introducing two different functional groups *via* selective C3–H and C1–H difunctionalization is challenging and vary rare. Very recently, we have successfully implemented an electrochemical phosphorothiolation and 1,4-S → C phospho-Fries rearrangement to access phosphorothiolated and mercapto-phosphono substituted indolizines (Scheme 2a, eqn (3)).[11] This success inspired us to further explore the selective C3–H and C1–H difunctionalization of indolizines. As part of our continuous interest in indolizines and electrochemistry,[12] we report herein a regioselective electrochemical C–H sulfonylation–bromination from indolizines, sodium sulfinates, and KBr to efficiently incorporate a sulfonyl and a Br atom at the C3 and C1 sites, respectively. Notably, KBr serves as both the brominating agent and electrolyte (Scheme 2b).

To investigate the regioselective electrochemical C–H sulfonylation–bromination, our initial study started with 2-phenylindolizine **1a** and sodium *p*-toluenesulfonate **2a** as model substrates. Gratefully, when electrolysis was carried out using KBr as the electrolyte, Cs_2CO_3 and S_8 as additives, and MeCN/H_2O (v/v = 4/1) as the co-solvent, 65% yield of the selective sulfony-



Scheme 1 Biologically active molecules and the fluorescent core skeleton.

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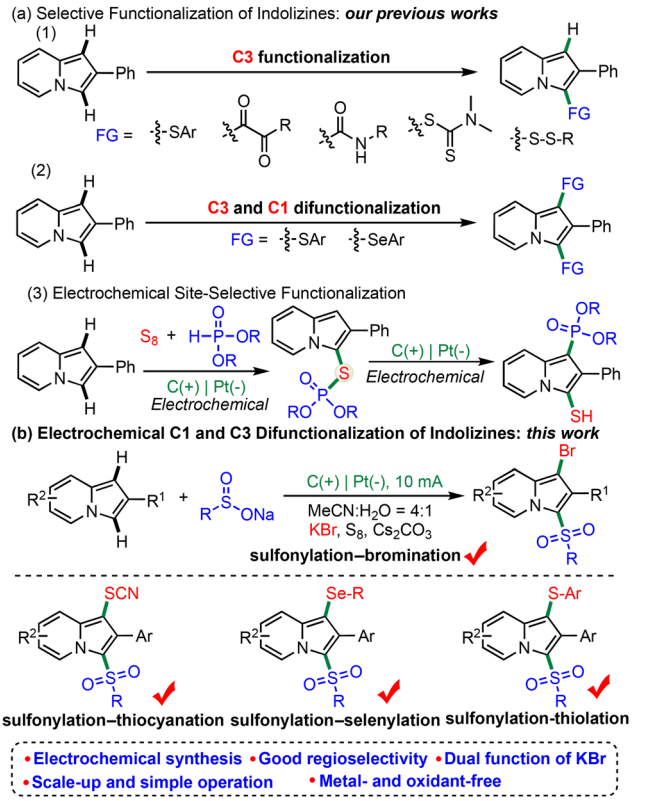
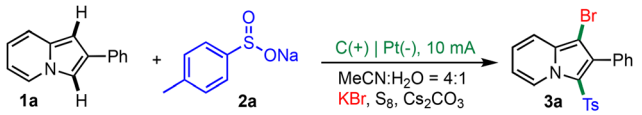


Scheme 2 Selective C–H functionalization of indolizines.

lation–bromination product **3a** was afforded at 10 mA constant current in 10 h (Table 1, entry 1). Further exploration revealed that the electrolyte was sensitive to the transformation, and almost no target product **3a** was detected when $^{n}Bu_4NBr$ was used instead of KBr as the electrolyte (entry 2). The reaction

Table 1 Optimization of the reaction conditions[a]

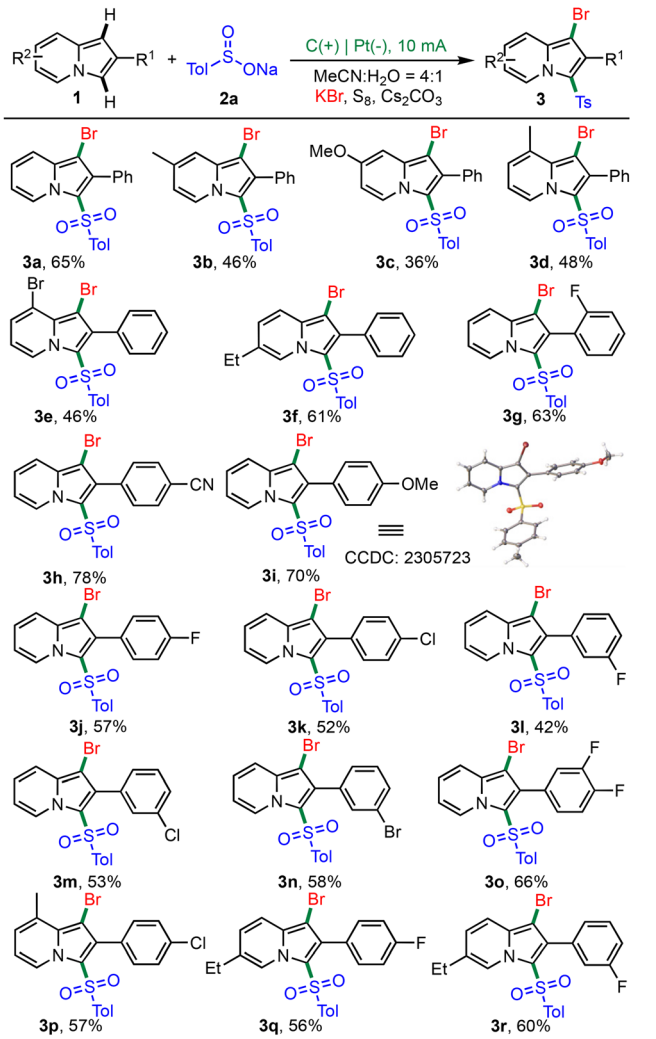


Entry	Deviation from standard conditions	**3a**/yield[b] (%)
1	None	65
2	$^{n}Bu_4NBr$ instead of KBr	—
3	Et_3N instead of Cs_2CO_3	18
4	DBU instead of Cs_2CO_3	27
5	K_2CO_3 instead of Cs_2CO_3	38
6	DMF/H_2O as the solvent	26
7	THF/H_2O as the solvent	21
8	Constant current = 15 mA	32
9	Constant current = 8 mA	37
10	No Cs_2CO_3	56
11	No S_8	—
12	No electricity	—

[a] Reaction conditions: vitreous carbon plate anode, platinum plate cathode, constant current = 10 mA, **1a** (0.3 mmol), **2a** (2 equiv.), electrolyte (1.2 mmol), base (1 equiv.), S_8 (2.5 equiv.), solvents (5.0 mL, v/v = 4 : 1), undivided cell, r.t., 10 h. [b] Isolated yield.

proceeded to achieve the cascade C–H functionalization when other bases such as Et_3N, DBU, and K_2CO_3 were added (entries 3–5). Cs_2CO_3 was found to be the most efficient base for this transformation. Subsequently, reaction solvents were screened. MeCN/H_2O as the solvent gave the best result compared to DMF/H_2O and THF/H_2O (entries 6 and 7). Furthermore, when the current was increased to 15 mA or reduced to 8 mA, a reduced yield of **3a** was observed (entries 8 and 9). The reaction provided **3a** in 56% yield without the addition of Cs_2CO_3 (entry 10). Moreover, product **3a** was not detected in the absence of S_8 or electricity, which illustrated that both are crucial for the transformation (entries 11 and 12).

After optimizing the electrolysis conditions, we then turned our attention to exploring the substrate scope of this electrochemical C–H sulfonylation–bromination of indolizines. Various indolizine derivatives were first evaluated under the optimal conditions, and the results are shown in Scheme 3. 2-Phenylindolizines with substituents such as –Me, –OMe, –Et,



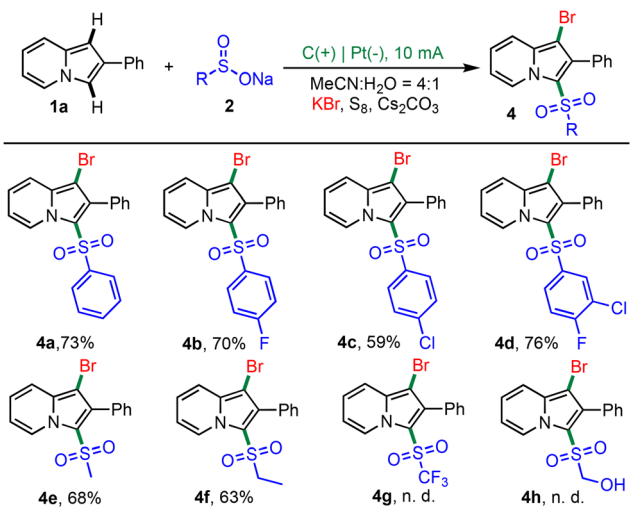
Scheme 3 Substrate scope of indolizines. Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), KBr (1.2 mmol), Cs_2CO_3 (0.3 mmol), S_8 (0.75 mmol), MeCN/H_2O = 4 mL/1 mL, 10 mA, r.t., 10 h. Isolated yield.

and –Br on the pyridine ring smoothly delivered the dual C–H functionalization products **3b–3f** in 36–61% yields. When the *ortho*-substituent of the phenyl in 2-phenylindolizine was occupied by the electron-withdrawing group –F, the reactions provided the desired product **3g** in 63% yield. Next, the effect of the substituent at the *para* position of the phenyl in 2-phenylindolizines was examined. The 2-phenylindolizines bearing substituents such as –OMe, –F, –Cl, –CN, and $-CF_3$ at the *para* position offered the corresponding products **3h–3k** in 52–78% yields. The structure of product **3i** was determined by single-crystal X-ray analysis (CCDC number: 2305723†). When the substituents (–F, –Cl, and –Br) occupied the *meta* position, it was found that the reactivity was slightly affected, furnishing the functional indolizine products **3l–3n** in 42–58% yields. Notably, 2-(4-fluoro-3-methylphenyl)indolizine was also found to be effective for the electrochemical C–H sulfonylation–bromination (**3o**). In addition, disubstituted indolizines were tolerated in this electrochemical reaction as well, giving the expected sulfonylated–brominated indolizine derivatives **3p–3r** in acceptable yields.

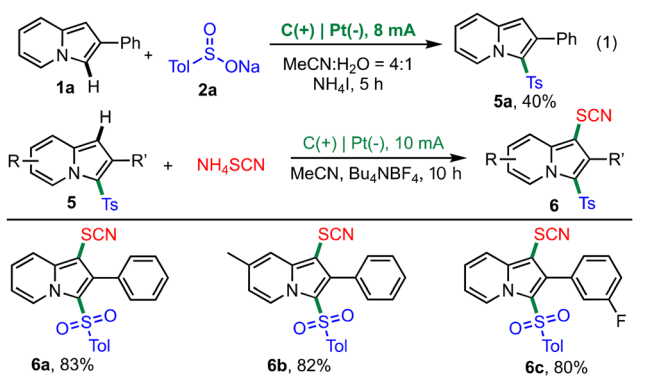
Next, the scope of the reaction with respect to the sodium sulfinate reactants was investigated with 2-phenylindolizine as the substrate (Scheme 4). Under the optimized conditions, the electroneutral substrate sodium benzenesulfinate allowed the preparation of product **4a** in 73% yield. Meanwhile, satisfactory yields of the target products could also be obtained for the substrates bearing electron-withdrawing substituents including sodium 4-fluorobenzenesulfinate, sodium 4-chlorobenzenesulfinate, and even sodium 3-chloro-4-fluorobenzenesulfinate (**4b–4d**). Moreover, aliphatic sulfinates such as sodium methanesulfinate and sodium ethanesulfinate proved to be suitable reaction partners, providing the desired sulfonylbrominated indolizines in 63–68% yields (**4e** and **4f**). However, sodium trifluoromethanesulfinate and sodium hydroxymethanesulfinate did not convert to the desired products (**4g** and **4h**).

Encouraged by the above success, we wondered whether diverse functional groups such as –SCN, –SeR, and –SR could be selectively introduced into indolizines.[12a,13] If possible, it would widely expand the applications of this electrochemical C3–H and C1–H difunctionalization protocol. However, we did not detect the desired products when 2-phenylindolizine **1a**, sodium *p*-toluenesulfonate **2a**, and NH_4SCN were used under the optimal electrochemical conditions. Interestingly, this aim could be realized *via* a two-step process. Electrochemical selective C3–H sulfonylation occurred first, which gave the C3-sulfonated indolizine **5a** (Scheme 5, eqn (1)). C3-sulfonated indolizines further underwent electrochemical C1–H thiocyanation to furnish the products **6**. For example, a variety of indolizines led to the formation of sulfonylation–thiocyanation products **6a–6c** in good yields (Scheme 5). This strategy was extended to the electrochemical synthesis of the sulfonylation–selenylation products **7a–7c** and they were obtained in excellent yields (Scheme 6). The diaryl diselenide and dialkyl diselenide were both efficient coupling partners. Moreover, diaryl disulfide could also participate in the electrochemical selective sulfonylation–thiolation, providing the desired product **7d** in 81% yield.

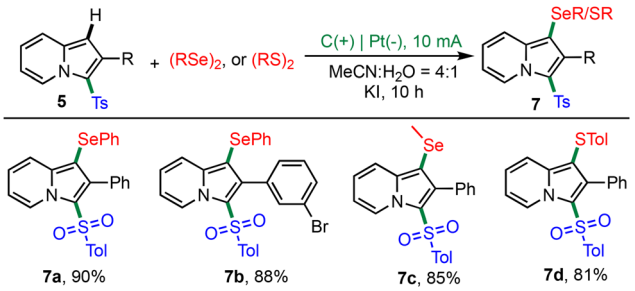
In addition, a scale-up reaction of **1a** and **2a** was performed in an undivided cell, resulting in the generation of the difunctional indolizine derivative **3a** in 61% isolated yield (Scheme 7, eqn (2)). To gain insights into the mechanism of the electrochemical C–H sulfonylation–bromination of indolizines, control experiments and cyclic voltammetry (CV) tests were carried out (Schemes 7 and 8). First, 3-sulfonylated indolizine **5a** was detected *via* electrochemical cross-coupling reactions between 2-phenylindolizine **1a** and sodium sulfinate **2a** (Scheme 5, eqn (1)). The 3-sulfonylated indolizine **5a** further underwent the electrochemical C–H bromination to afford the final difunctionalized product **3a** in 81% yield, which indicated that **5a** was likely to be an effective intermediate in the reaction (Scheme 7, eqn (3)). Meanwhile, we also noticed that the desired product **3a** could not be observed in the absence of



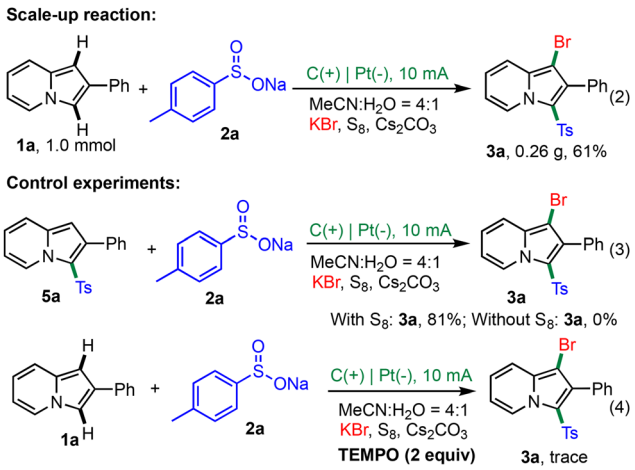
Scheme 4 Substrate scope of sodium sulfinates. Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), KBr (1.2 mmol), Cs_2CO_3 (0.3 mmol), S_8 (0.75 mmol), MeCN/H_2O = 4 mL/1 mL, 10 mA, r.t., 10 h. Isolated yield.



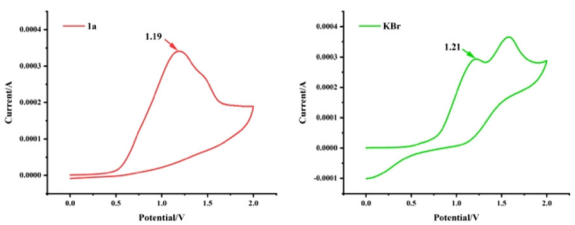
Scheme 5 Electrochemical selective sulfonylation–thiocyanation of indolizines. Reaction conditions: **5** (0.2 mmol), NH_4SCN (0.6 mmol), Bu_4NBF_4 (0.8 mmol), MeCN = 5.0 mL, 10 mA, r.t., 10 h. Isolated yield.



Scheme 6 Electrochemical selective sulfonylation–selenylation/thiolation of indolizines. Reaction conditions: **5** (0.2 mmol), $(RSe)_2$ or $(RS)_2$ (0.6 mmol), KI (0.8 mmol), $MeCN/H_2O$ = 4 mL/1 mL, 10 mA, r.t., 10 h. Isolated yield.



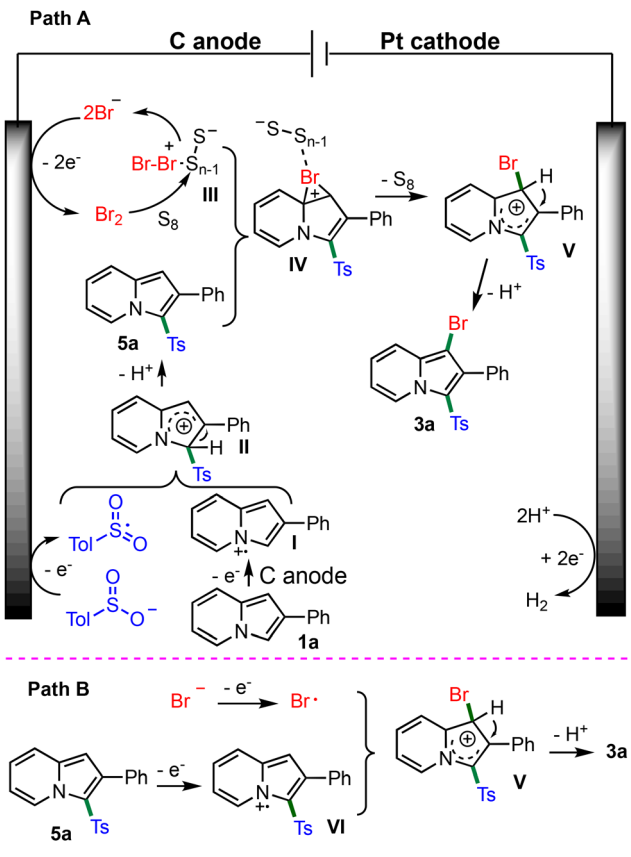
Scheme 7 Scale-up reaction and mechanistic experiments.



Scheme 8 CV experiments.

S_8 or electric current, which confirmed the important role of S_8 and electric current in the bromination reaction (Table 1, entry 11 and eqn (3)). Moreover, the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) inhibited the model reaction completely (Scheme 7, eqn (4)). This suggested that the reaction possibly proceeded *via* a radical pathway. Finally, we explored the redox behavior of 2-phenylindolizine **1a**, *p*-toluenesulfinate **2a**, and KBr by CV to understand the possible mechanism. The oxidation peaks of **1a** and **2a** were observed at 1.19 V and 1.20 V, respectively.[8b] The very close oxidation potentials between **1a** and **2a** likely induced the radical–radical cross-coupling reaction. Meantime, KBr showed an oxidation peak at 1.22 V. Thus, **1a** and **2a** exhibited a lower oxidation potential and were preferentially oxidized at the anode.

Based on the experimental results and literature reports,[4a,8b,13] two plausible reaction mechanisms for the electrochemical C–H sulfonylation–bromination of indolizines were proposed, as shown in Scheme 9. In path A, *p*-toluenesulfinate **2a** first loses one electron at the anode to generate a sulfonyl radical. 2-Phenylindolizine **1a** is also oxidized at the anode to produce the radical species **I**. Subsequently, the radical–radical cross-coupling reaction between the sulfone radical and radical species **I** gives the intermediate **II**, which undergoes deprotonation to provide 3-sulfonylated indolizine **5a**. On the other hand, Br_2 was formed *via* the electrochemical oxidization at the anode. The formed Br_2 was quickly captured by S_8 to give the complex **III**,[14] which further reacted with 3-sulfonylated indolizine **5a** to yield the active bromonium ion intermediate **IV**. Next, a ring-opening reaction occurred to give the intermediate **V**, which was followed by deprotonation to give the final product **3a**. In path B, 3-sulfonyl indolizine **5a** was generated according to path A. The electrochemical oxidation of **5a** to its corresponding radical cation **VI** occurs; meanwhile the bromine radical is formed at the anode. Then the radical cation **VI** and the bromine radical undergo "radical–radical" coupling to give the intermediate **V**. Finally, product **3a** was obtained *via* the deprotonation of intermediate **V**.



Scheme 9 Proposed mechanism pathways.

Conclusions

In conclusion, we have demonstrated an environmentally friendly electrochemical regioselective C–H sulfonylation–bromination from indolizines and sodium sulfinates with readily available KBr as the halogenating agent and electrolyte. This selective electrochemical sulfonylation–bromination protocol allows for the construction of difunctionalized indolizine derivatives under catalyst- and oxidant-free conditions. Moreover, electrochemical C–H sulfonylation–thiocyanation/selenylation/thiolation of indolizines was also achieved *via* a two-step process. Finally, a series of control experiments and CV examinations were conducted to clarify the reaction mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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