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COMMUNICATION

Electrochemical Regioselective Selenylation/Oxidation of *N*-Alkylisoquinolinium Salts via Double C(sp2)–H Bond Functionalization

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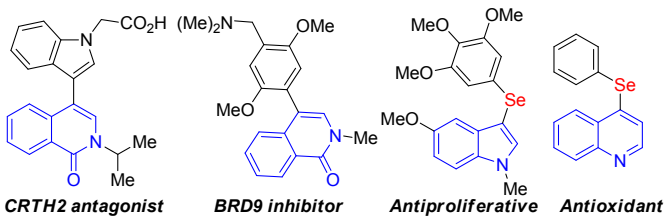
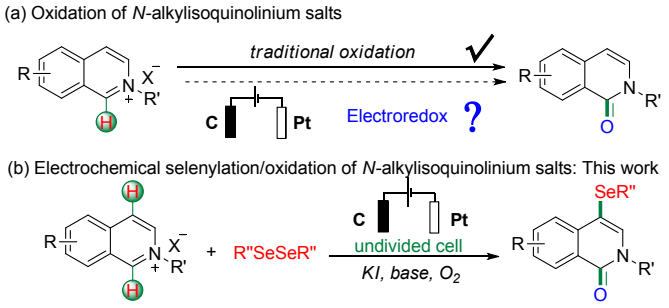
Abstract: An efficient, novel, and environmentally friendly electrochemical regioselective selenylation/oxidation of *N*-alkylisoquinolinium salts via double C(sp2)–H bond functionalization under undivided electrolytic conditions has been developed. A series of selenide isoquinolones were easily accessed through this sustainable and clean electrochemical system. The present protocol was further extended to afford selenide quinolones and 1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-ones. Furthermore, antiviral bioassays demonstrated that compound 3j exhibited excellent antiviral activity against tobacco mosaic virus (TMV), and its inhibition rate was up to 90%.

Isoquinolones are privileged building blocks and their characteristic structural are widely present in natural products, pharmaceuticals, and bioactive compounds. Also, isoquinolone derivatives exhibit powerful physiological functions, including antidepressant, antiulcer, antihypertensive agents, and in the treatment of asthma and tumors (Scheme 1).[1-2] Therefore, tremendous efforts have been devoted to the construction of isoquinolone derivatives. Direct oxidizing easily prepared isoquinolinium salts utilizing terminal oxidant such as $K_3Fe(CN)_6$ was considered as an important synthetic approach.[3] But these methods usually need to use excess expensive or hazardous oxidants, which makes the whole process cumbersome. Later on, some elegant catalytic oxidative functionalization of isoquinolines or isoquinolinium salts for the synthesis of isoquinolone have been documented.[4] However, the electrochemical generation of functionated isoquinolones through the anodic oxidation of *N*-alkylisoquinolinium salts have not been reported to date (Scheme 2a). Though it was a potential alternative and represented cleaned and more sustainable transformations.



Scheme 1 Biologically Active Natural Products and Drug Candidates

Indeed, organic electrochemistry is currently an increasingly important issue.[5] Owing to their replacement of oxidizing and reducing agents with electric current, electrochemical methods provide a reliable alternative to conventional methods under mild conditions.[6]



Scheme 2 Electrochemical Regioselective Selenylation/oxidation of *N*-Alkylisoquinolinium Salts

Organoseleno compounds are of great significance in the pharmaceutical industry, material sciences, and synthetic chemistry.[7] Particularly, recent studies have revealed that *N*-heterocyclic molecules equipped with selenyl-substituents show unique bioactivities and chemical properties (Scheme 1).[8] Undoubtedly, it is highly desirable to expand green synthetic methods for the introduction of selenium groups to the substituted heterocycles.[9] Herein, we reported an electrochemical regioselective selenylation/oxidation of *N*-alkylisoquinolinium salts via double C(sp2)–H bond

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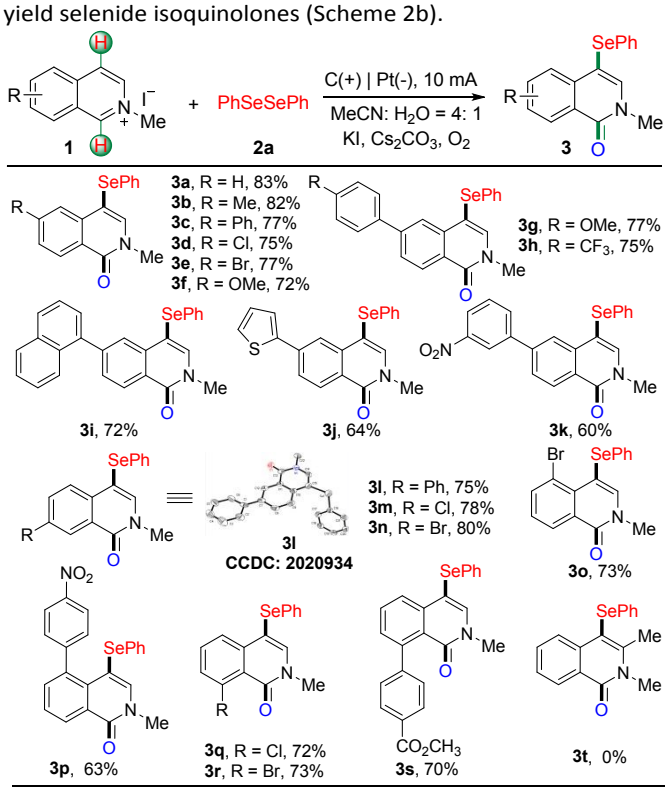
functionalization under undivided electrolytic conditions to yield selenide isoquinolones (Scheme 2b).



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.3 mmol), KI (1.5 mmol), Cs_2CO_3 (0.45 mmol), MeCN/H_2O = 4 mL/1 mL, O_2 atmosphere, 10 mA, r.t., 10 h. Isolated yield.
Scheme 3 Substrate Scope of *N*-Methylisoquinolinium Salts [a]

To explore optimal reaction conditions, we commenced the electrochemical selenylation/oxidation of isoquinolinium iodide salts (**1a**) with diphenyl diselenide (**2a**) in an undivided electrolytic cell under constant current (Tables S1 in the ESI). Initially, no desired product **3a** formation selecting KI as the electrolyte and MeCN/H_2O as the solvent under 10 mA constant current (Table S1, entry 1). To our delight, the reactions proceeded to achieve the selenylation/oxidation process when the bases such as Na_2CO_3, KH_2PO_4, K_2CO_3, and Cs_2CO_3 were added (Table S1, entries 2-5). Cs_2CO_3 was found to be the most efficient base for this transformation. A series of supporting electrolytes, such as KBr, NH_4I, *n*-Bu_4NI, *n*-Bu_4NBF_4, and Et_4NPF_6, showed lower efficiency compared to KI (15−66% yields, Table S1, entries 6-10). Subsequently, different kinds of solvents were screened with KI as the electrolyte and Cs_2CO_3 as the base under 10 mA constant current, and the cosolvent of CH_3CN/H_2O (v/v = 4/1) provided the highest yield (compare Table S1, entries 11−13). On the contrary, the cosolvent DMF/H_2O completely inhibited the transformation and no products were detected (Table S1, entry 12). To improve the yield of **3a**, the influence of atmosphere was surveyed. We conducted this electrochemical transformation at oxygen atmosphere instead of air atmosphere, resulting in higher yield of **3a** (Table S1, entry 14, 83%). Furthermore, changing the operating current (5 mA) led to decrease the product yield (Table S1, entry 15, 50%). Finally, control experiment showed that no desired product was generated without electricity (Table S1, entry 16).

With the establishment of the optimal reaction conditions (Table S1, entry 14), we turned our attention to investigate electronic and steric effects on electrochemical selenylation/oxidation with various *N*-alkylisoquinolinium iodide salts (Scheme 3). The substrates **1** bearing both electron-donating groups (-Me, -OMe, Ar, thienyl) and electron-withdrawing groups (-Cl, -Br) at the C-6 position provided good yields of the corresponding products **3b-3k**. The isoquinolinium salt with a substituent (−Ph, −Cl, −Br) at the C-7 position on the isoquinolin ring proceeded smoothly under the optimal reaction conditions, leading to the 1,4-bisfunctional products **3l**-**3n** in 75-80% yields. The structure of **3l** was verified by X-ray diffraction (CCDC 2020934). Next, the effects of C-5 and C-8 substituents on the isoquinolin ring were examined. It was found that substrates **1o**-**1s** all gave satisfactory results. We have also attempted to use C-3 substituted isoquinolinium salts as substrate, but failed to obtain the target product, which probably attributed to the large steric hindrance of **1t**.

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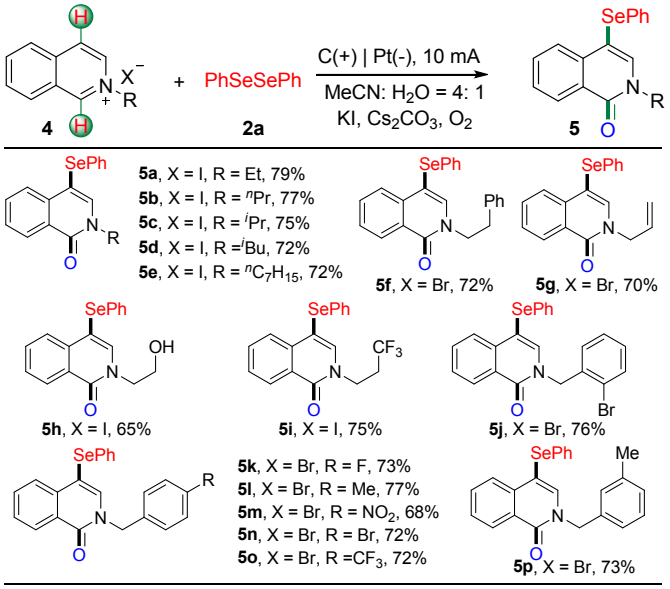
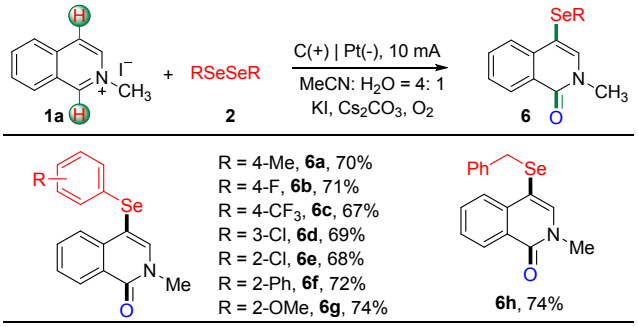


[a] Reaction conditions: **4** (0.3 mmol), **2a** (0.3 mmol), KI (1.5 mmol), Cs_2CO_3 (0.45 mmol), MeCN/H_2O = 4 mL/1 mL, O_2 atmosphere, 10 mA, r.t., 10 h. Isolated yield.
Scheme 4 Substrate Scope of *N*-Alkylisoquinolinium Salts [a]

Electrochemical selenylation/oxidation reaction was further surveyed with different alkyl substituted *N*-alkylisoquinolinium salts (Scheme 4). Substrates with linear and branched aliphatic substituents (**4a**−**4f**) produced target molecules in reasonable yields (72−79%). It is noteworthy that series of functional groups including alkenyl, hydroxy, and trifluoromethyl could be well tolerated (**5g**−**5i**). Subsequently, we turned our attention to extend the substrates **4j**-**4p**, in which the *N*-substituent contained various benzyl groups. Corresponding products **5j**-**5p** were afforded in good yields (68−77%) under the standard conditions.

The effects of different substituents of diselenides were investigated (Scheme 5). We discovered that a variety of functional groups on the aryl ring of the diphenyl diselenides were suitable under this electrochemical protocol, and the selenide isoquinolone derivatives could be generated in 67-74%

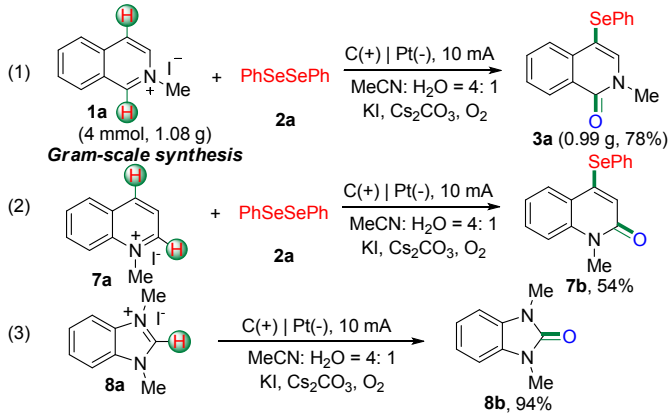
yields (**6a**–**6g**). Moreover, dibenzyl diselenide was also tolerated under the conditions, the corresponding product **6h** was obtained in 74% yield.



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.3 mmol), KI (1.5 mmol), Cs_2CO_3 (0.45 mmol), MeCN/H_2O = 4 mL/1 mL, O_2 atmosphere, 10 mA, r.t., 10 h. Isolated yield.

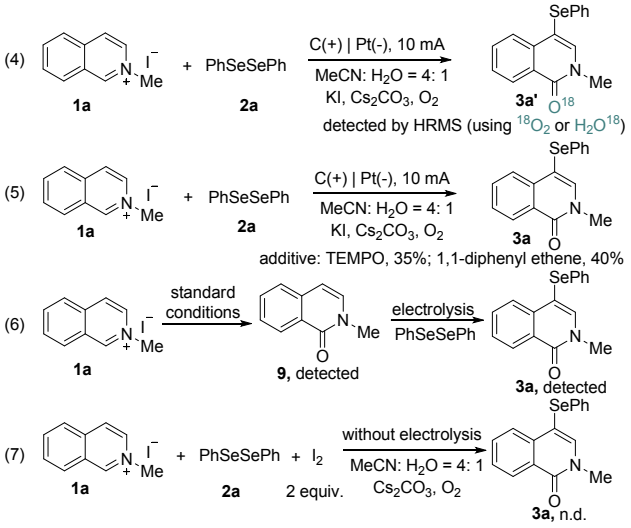
Scheme 5 Substrate Scope of Diselenides [a]

To prove the efficiency and practicability of electrochemical selenylation/oxidation reaction, we performed large-scale reaction using *N*-methylisoquinolinium salts **1a** as the substrate under the standard conditions. The selenide isoquinolones could still be accessed in 78% yield (eq. 1). In addition, this method could also be extended to prepare selenide quinolones. *N*-methylquinolinium salts **7a** underwent the similar selenylation/oxidation process to produce **7b** in moderate yield (eq. 2). Finally, we tried to oxidize 1,3-dimethyl-1*H*-benzo[*d*]imidazol-3-ium iodide **8a** via electrochemical synthesis. To our delight, the target product **8b** was obtained in 94% yield (eq. 3).



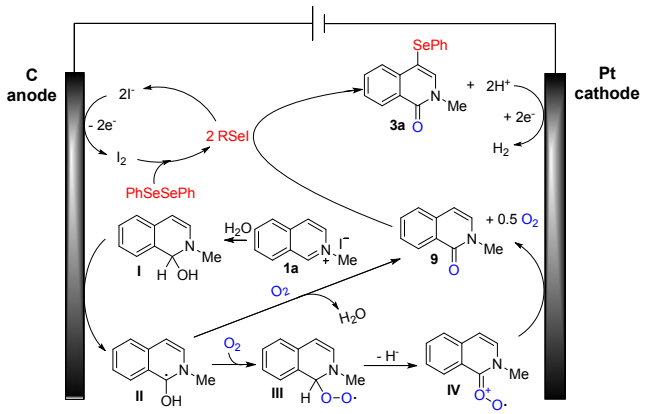
Scheme 6 Further Applications [a]

To gain further insights into the mechanism of this electrochemical 1,4-difunctionalization of isoquinolinium salts with diselenides, several control experiments were executed (Scheme 7). First, ^{18}O-labeling experiments were carried out. The ^{18}O-labeling product **3a'** was detected by HRMS whether using $^{18}O_2$ replaced common oxygen as atmosphere or using H_2O^{18} replaced H_2O (eq. 4), which suggested that oxygen atoms in carbonyl group of **3a** probably originated from molecular oxygen and water. In addition, yield of **3a** drop decreased when 2 equiv. of radical scavenger TEMPO and 1,1-diphenyl ethene was added to the electrocatalytic system (eq. 5), which showed a radical process involved in the transformation. To probe redox potential of substrates, three substrates (**1a**, **2a**, and KI) in MeCN were operated in cyclic voltammetry experiments (see ESI Figure S1). An oxidation peak of 2-methylisoquinolin-2-ium iodide (**1a**) was observed at 0.94 V (vs Ag/Ag+), which was lower than the oxidation potential of potassium iodide (at 1.13 V) and diphenyl diselenide (**2a**, at 1.81 V). These results indicated that **1a** and KI are oxidized preferentially at the anode. Furthermore, when isoquinolinium salt **1a** was reacted under the electrocatalytic conditions without diphenyl diselenide (**2a**), intermediate 2-methylisoquinolin-1(2*H*)-one **9** was formed. The intermediate **9** could further react with diphenyl diselenide (**2a**) to generate the final selenylation product (eq. 6). In order to illustrate the role of KI, we used I_2 instead of KI as the iodine source without electricity. No product **3a** was obtained (eq. 7). The results revealed that I_2 could not oxidize the isoquinolinium salts.



Scheme 7 Control Experiments

Based on the above control experiments and the literature reports,[4,9] a plausible reaction mechanism for the electrochemical 1,4-difunctionalization of isoquinolinium salts



Scheme 8 Plausible Mechanistic Pathway

has been proposed in Scheme 8. First, nucleophilic addition of H_2O to **1a** produces the intermediate **I,** which was oxidized at

the surface of anode to generate radical intermediate **II**. Probably, oxidation of radical intermediate **II** to **9** involved two pathways. First, the intermediate **II** was combined with molecular oxygen to form alkperoxide **III**, which underwent a proton loss to give oxygen-centered radical **IV**. Next, cleavage of the O−O bond in **IV** at cathode, intermediate **9** was obtained. Second, the intermediate **II** was directly oxidized by oxygen to form intermediate **9**. Meanwhile, direct anodic oxidation of I^- produced I_2, which reacted with diselenide **3a** to provide active species RSeI. Finally, RSeI was trapped by **9** to afford the product **3a** and two protons. Cathodic reduction of proton hydrogen render to the formation of hydrogen.

Finally, we also tested the antiviral activity of selenide isoquinolones (Table S3 and Figure S3 in the ESI). A half-leaf method was used to determine therapeutic effect against tobacco mosaic virus (TMV). It is gratifying to note that some compounds had shown good antiviral activity against TMV at a concentration of 500 μg mL^{-1}. Particularly, compound **3j** showed excellent inhibition effect on TMV, and its inhibition rate was up to 90%, which even exceeded that of the positive control (ningnanmycin, 64.1%). Further structural optimization and structure-activity relationship studies are in progress.

Conclusions

In conclusion, we have disclosed an efficient and environmentally friendly electrochemical regioselective 1,4-difunctionalization of isoquinolinium salts with diselenides. By this protocol, various selenide isoquinolones were accessed under undivided electrolytic conditions. In addition, the electrocatalytic system was successfully extended to synthesize selenide quinolones and 1,3-dimethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-ones. Importantly, selenide isoquinolones prepared by present method exhibited high fluorescence absorption and emission intensity, and good antiviral activity against tobacco mosaic virus. More in-depth studies of biological activity are ongoing and will be reported in near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Electrochemical Regioselective Selenylation/Oxidation of *N*-Alkylisoquinolinium Salts via Double C(sp2)–H Bond Functionalization

Xiang Liu,† Yajun Wang,† Dan Song, Yuhan Wang, and Hua Cao *

An efficient and environmentally friendly electrochemical regioselective selenylation/oxidation of N-alkylisoquinolinium salts via double C(sp2)–H bond functionalization has been developed.