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Communication

Electrochemical synthesis of 3-azido-indolines from amino-azidation of alkenes

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ABSTRACT

An electrochemical amino-azidation of 2-aminostyrene with sodium azide (NaN_3) was developed, which can be carried out smoothly in water under metal-free condition, affording a series of 3-azido indolines with high yields.

Organic azides are useful building blocks in chemical synthesis because of their remarkable biological activity as well as synthetic versatility. Moreover, azide derivatives have been incorporated into a lot of lead compounds designed in drug discovery [1–5]. As one typical kind of these species, β-azide amines are powerful precursors of nitrogen-containing molecules, which are employed in the mild and versatile copper-catalyzed “click” chemistry [6–8]. Therefore acquiring β-azide amine has attracted great attention during the past several decades.

Traditionally, simple β-azide amines are synthesized based on the ring opening of aziridine with NaN_3 (Scheme 1a) [9–13]. Recently, diverse β-azide amines were obtained by multistep processes, which involved haloamination of alkene followed by substitution with NaN_3 (Scheme 1b) [14–18]. With the request of green chemistry, minimizing synthetic steps and finding more milder transformations are highly desirable and much effort has been devoted by chemists. For instance, a direct amino-azidation of alkene catalyzed by copper from *N*-allyl urea and NaN_3 was reported by Chemler and co-worker in 2010 (Scheme 1c) [19]. However, the study mentioned above still existed some limitation, such as the need of metal. Therefore, there is still a great demand for the development of more green and sustainable approaches to produce this kind of product.

On the other hand, electrochemical synthesis, emerging as an environmentally friendly method, has been widely utilized in the construction of heterocyclic compounds [20–37], difunctionalization of olefins [38–45] and other functional molecules [46–58]. However, the direct electrochemical amino-azidolation of 2-aminostyrene with sodium azide has not been used for the synthesis of β-azide amines. With our ongoing interest in developing electrochemical synthesis and green methodology [59–70], as a consequence of the importance of azides in organic synthesis, we disclose a simple and efficient electrochemical amino-azidolation of 2-aminostyrene with sodium azide providing a facile route for the preparation of 3-azido-indolines in excellent yields.

At the outset of this investigation, a model reaction of 2-aminostyrene **1a** and sodium azide **2a** was performed in an undivided cell. Initially, n-Bu_4NI was employed as the electrolyte and CH_3CN as the solvent with a constant current of 10 mA. To our delight, the desired product **3a** was obtained in 35% yield (Table 1, entry 1). Afterwards, other electrolytes, such as NH_4I, n-Bu_4NBr, n-

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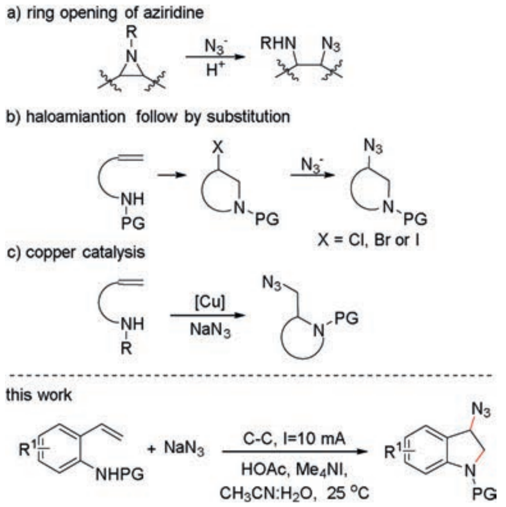
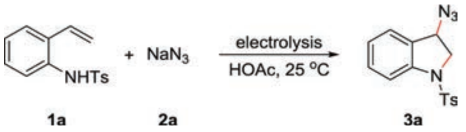


Scheme 1. Amino-azidation of alkenes.

$BuNClO_4$, n-$BuNBF_4$, NH_4PF_6 and Me_4NI, were examined in the reaction (entries 2 – 7). We found only iodine salts could promote this transformation, especially Me_4NI performed well in this reaction, giving the product **3a** in 83% yield. The screening of the different kinds of solvent showed that CH_3CN was the best solvent (entries 8 – 13). Moreover, the addition of water to this reaction could increase the yield of **3a,** perhaps due to the improvement of the solubility of NaN_3 in the presence of water (entry 14). Subsequently, the ratio of CH_3CN and H_2O was investigated. Changing the ratio of CH_3CN/H_2O to 5:1 could give the best result, that is, **3a** can be obtained in 95% (entries 14–16). Increasing the reaction temperature did not increase the yield of this transformation (entries 17 and 18). Finally, other types of electrodes were examined and the results indicated that the C|C electrodes was the best electrode in this reaction (entries 19 – 21). No product was observed without electricity, suggesting that the reaction driving force should be the electric energy.

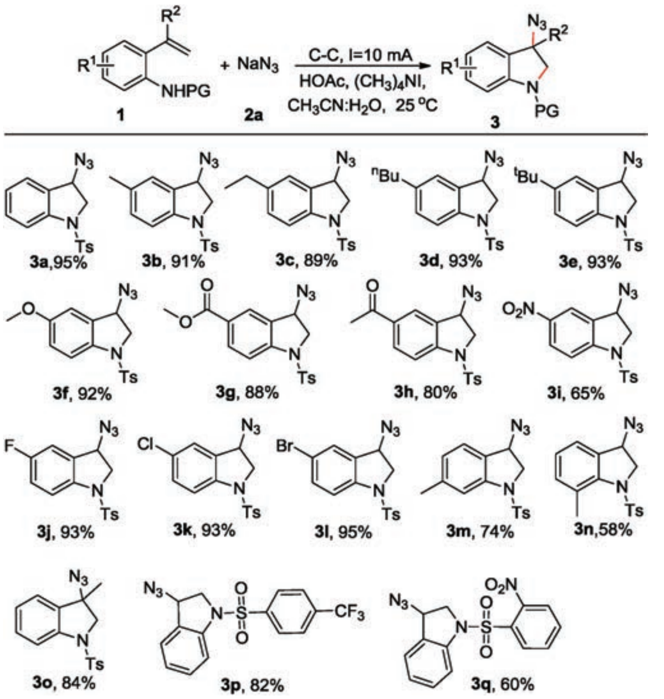
With the optimized conditions in hand, the scope of this reaction was investigated and the results were showed in Scheme 2. A variety of substituted 2-aminostyrene **1** were employed in this reaction. The styrenes bearing different groups could afford the amino-azidation products with good to excellent yields (Schemes 2 **3a**–**3o**). Electron-rich and electron-neutral substituted 2-aminostyrene on the phenyl ring were typically examined. In general, the substrates with electron-donating groups (R^1 = 5-Me, 5-Et, 5-n-Bu, 5-t-Bu, 5-OMe) on the phenyl ring gave higher yields than those bearing electron-withdrawing groups (R^1 = 5-COOMe, 5-COMe, 5-NO_2). Gratifyingly, halogen substituted aryl amines (R^1 = 5-F, 5-Cl, 5-Br) could perform well to

Table 1
Optimization of the reaction conditions[a].



Entry	Electrode	Electrolyte	Solvent	Yield (%)[b]
1	C|C	n-Bu_4NI	CH_3CN	35
2	C|C	NH_4I	CH_3CN	31
3	C|C	n-Bu_4NBr	CH_3CN	trace
4	C|C	n-$BuNClO_4$	CH_3CN	n.d.[c]
5	C|C	n-$BuNBF_4$	CH_3CN	n.d.
6	C|C	NH_4PF_6	CH_3CN	n.d.
7	C|C	Me_4NI	CH_3CN	83
8	C|C	Me_4NI	EtOH	15
9	C|C	Me_4NI	DCM	20
10	C|C	Me_4NI	DMF	n.d.
11	C|C	Me_4NI	DMSO	n.d.
12	C|C	Me_4NI	1,4-dioxane	trace
13	C|C	Me_4NI	toluene	n.d.
14	C|C	Me_4NI	CH_3CN:H_2O = 1:1	87
15	C|C	Me_4NI	CH_3CN:H_2O = 3:1	89
16	C|C	Me_4NI	CH_3CN:H_2O = 5:1	95
17[d]	C|C	Me_4NI	CH_3CN:H_2O = 5:1	93
18[e]	C|C	Me_4NI	CH_3CN:H_2O = 5:1	90
19[f]	Pt|C	Me_4NI	CH_3CN:H_2O = 5:1	69
20[g]	C|Pt	Me_4NI	CH_3CN:H_2O = 5:1	64
21[h]	Pt|Pt	Me_4NI	CH_3CN:H_2O = 5:1	78
23[i]	C|C	Me_4NI	CH_3CN:H_2O = 5:1	n.d.

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), HOAc (0.45 mmol), electrolyte (0.3 mmol), solvent (3 mL), 2.5 h, two carbon electrodes, and electrolyze at a constant current (10 mA) in an undivided cell.
[b] Isolated yield.
[c] n.d., not detected.
[d] Stirring at 35 °C.
[e] Stirring at 45 °C.
[f] C anode was replaced by Pt anode.
[g] C cathode was replaced by Pt cathode.
[h] Two platinum electrodes.
[i] Without the passage of electricity.

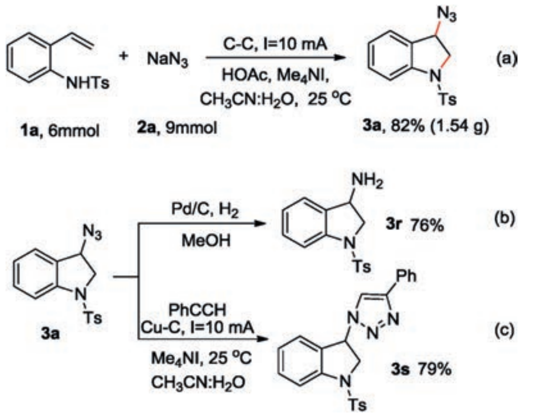


Scheme 2. Substrate scopes of 2-aminostyrenes. Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), HOAc (0.45 mmol), Me_4NI (0.3 mmol), $CH_3CN:H_2O$ = 5:1 (3 mL), two carbon electrodes, and electrolyze at the constant current of 10 mA in an undivided cell at 25 °C. Isolated yield.

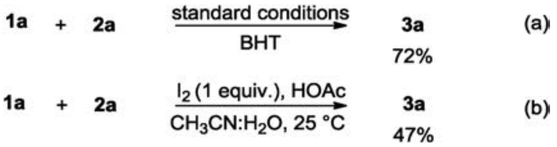
give the target products in excellent yields (**3j**, **3k** and **3l**, Scheme 2). Sterically encumbered 2-aminostyrenes (R^1 = 6-Me, 7-Me) were also explored and it was found that hindrance had a negative influence on the reaction (**3m** and **3n**, Scheme 2). It was noted that disubstituted alkene can be employed as the reaction substrate in this reaction. For instance, **1o** (R^2 = Me) could work well in the reaction to give the corresponding product in good yield (**3o**, Scheme 2). Moreover, 2-aminostyrenes with different *N*-protecting groups (PG = *p*-trifluoromethylbenzenesulfonyl, *o*-nitrobenzenesulfonyl) can also survived the reaction to afford the corresponding products **3p** and **3q** in 82% and 60% yields, respectively, as shown in Scheme 2.

In order to test the practicality and scalability of this developed method, we then scaled up this reaction (Scheme 3a). When 6.0 mmol of 2-aminostyrene was subjected to the reaction, corresponding product **3a** was obtained with a satisfactory yield of 82% (1.54 g), demonstrating the great potential of this method. Subsequently, some derivatizations based on the 3-azido-indolines can be obtained smoothly. For instance, **3a** was reduced to **3r** in methanol by using hydrogen with Pd/C electrodes, which could be exploited as a precursor of the other nitrogen-containing heterocycles (Scheme 3b). Besides, the click reaction of **3a** under electrochemical conditions gave the product **3s** in 79% yield (Scheme 3c), which is an impotrant moiety in the inhibitors of HCV NS3 protease [71].

To get insight into the reaction mechanism, some control experiments were performed (Scheme 4). When the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture, we did not observe the decrease of the reaction yield, which implied that there might be no radical intermediate involved in this reaction (Scheme 4a). The product **3a** could be obtained with 47% yield when 1 equiv. of I_2 was employed in the absence of other oxidants. This showed that I_2 could catalyze this transformation (Scheme 4b). However, the yield was low under the direct catalysis of molecular iodine. Perhaps the rate of the iodine addition to double bond is much faster than that of nucleophilic addition of aniline to the iodonium, resulting in the side reaction. Under electrochemical conditions, I^- was slowly oxidized to molecular iodine and the following formation of iodonium can be carried out slowly. In this way, the rate of iodonium formation can match that of annulation of nucleophilic addition, avoiding the side reaction.



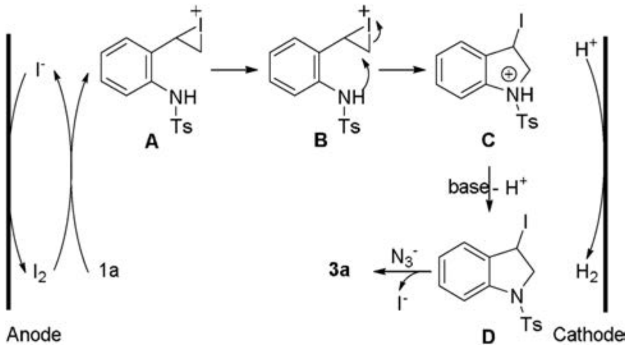
Scheme 3. Gram-scale synthesis and product transformations. Reaction conditions: (a) **1a** (6 mmol), **2a** (9 mmol), HOAc (9 mmol) and Me_4NI (6 mmol) in 60 mL $CH_3CN:H_2O$ = 5:1, 15 h, two carbon electrodes, and electrolyze at a constant current of 10 mA in an undivided cell at 25 °C. (b) **3a** (0.3 mmol), Pd/C (10 mmol%), MeOH (1.5 mL), 25 °C, 15 h. (c) **3a** (0.3 mmol), phenylacetylene (0.36 mmol), Me_4NI (0.3 mmol), $CH_3CN:H_2O$ = 5:1 (3 mL), 4 h, anode copper, cathode carbon bar, and electrolyze at a constant current of 10 mA in an undivided cell at 25 °C.



Scheme 4. Mechanism investigation.

Based on our mechanistic studies and the previous reports [72–77], a plausible mechanism involved an iodonium ion intermediate was proposed in Scheme 5. The transformation begins with the oxidation of I^- to I_2 at the anode. Subsequently, I_2 reacts with **1a** to give the intermediate **A**, then, the following nucleophilic addition leads to the formation of **C** and further deprotonation gives **D**, followed by the nucleophilic attack of azide to give the product **3a**.

In summary, we developed an effective electrochemical method for the synthesis of 3-azido-indolines. Compared with the previous methods, this process is environmentally friendly without any



Scheme 5. The proposed mechanism for the reaction.

metal or oxidizing agent. Moreover, this reaction tolerates a variety of functional groups with a broad scope of the reaction substrates. Further efforts are underway to develop electrochemical water-phase asymmetric synthesis in our group.

Declaration of competing interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.09.041.

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