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# Electrochemical synthesis of quinazolinone *via* I<sub>2</sub>-catalyzed tandem oxidation in aqueous solution†

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The development of protocols for synthesizing quinazolinones using biocompatible catalysts in aqueous medium will help to resolve the difficulties of using green and sustainable chemistry for their synthesis. Herein, using I<sub>2</sub> in coordination with electrochemical synthesis induced a C–H oxidation reaction which is reported when using water as the environmentally friendly solvent to access a broad range of quinazolinones at room temperature. The reaction mechanism strongly showed that I<sub>2</sub> cooperates electrochemically promoted the oxidation of alcohols, then effectively cyclizing amides to various quinazolinones.

The N-heterocycles are key core structures that form the basis of many pharmaceutical, agrochemical and natural products.<sup>1</sup> Among them, quinazolinones are an important motif in several biologically relevant pharmacophores,<sup>2</sup> such as methaqualone which is famous for its effective sedative and hypnotic effects, luotonin A which is a quinazolinone alkaloid with anti-inflammatory effects, and erlotinib which is an anti-tumour agent, and all these compounds contain a quinazolinone bond in their backbone (Fig. 1).<sup>3</sup>

Due to their advantageous structures quinazolinones have been widely explored in numerous syntheses.<sup>4</sup> The classical method involves condensation of aldehydes and *o*-amino-benzamides to give amination intermediates, which then undergo oxidation to yield the final quinazolinone product.<sup>5</sup> Another strategy is to use more benign and readily available alcohols as starting materials.<sup>6</sup> The reaction takes place through a two-step oxidation pathway, where the alcohols are first oxidized to aldehydes, followed by coupling with *o*-aminobenzamides. The catalyst needs to demonstrate high activity and selectivity as the reaction involves dehydrogenation of both the C–H and N–H bonds in one pot. In 2018, Sarma and co-workers<sup>7</sup> demonstrated that a magnetically recoverable iron oxide-carbon dot nano-composite was an effective catalyst for cyclooxidative tandem synthesis of quinazolinones in aqueous medium using alcohols as starting materials. Furthermore, annulation reactions of *o*-aminoaryl acids may be the most employed strategies, which include the condensation of *o*-aminoaryl acids with amides,

nitriles, or acid derivatives plus a nitrogen source.<sup>8</sup> Moreover, the synthesis of quinazolinone involving transition metal catalysed reactions of *o*-haloarylamides with nitriles, or amines<sup>9</sup> and reaction of *o*-halogenated aryl acid with amides<sup>10</sup> have been explored (Scheme 1).

Although the above approaches solved a lot of practical problems, there are still some limitations such as long reaction time, high temperature and by-products. Hence, development of greener, atom economic, synthetic approaches for the preparation of quinazolinones from inexpensive and easily available starting materials under relatively mild conditions is desirable. On one hand, electrochemical-induced direct functionalization has gained significant attention from the synthetic chemistry community due to it being environmentally friendly, and requiring mild conditions, and low-energy irradiation.<sup>11</sup> With electrons as the oxidizing/reducing agent, organic electro-synthesis could offer appropriate alternatives to traditional oxidation or reduction reactions. For example, Zhao and co-workers<sup>12</sup> reported an efficient electrochemical-induced C–H methylation of electron-rich aromatics *via* a three-component cross-coupling strategy. On the other hand, the non-metallic

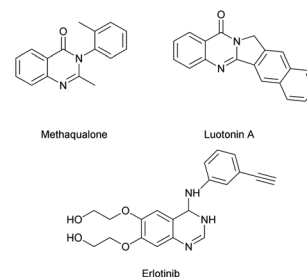


Fig. 1 Bioactive compounds containing quinazolinone skeleton.

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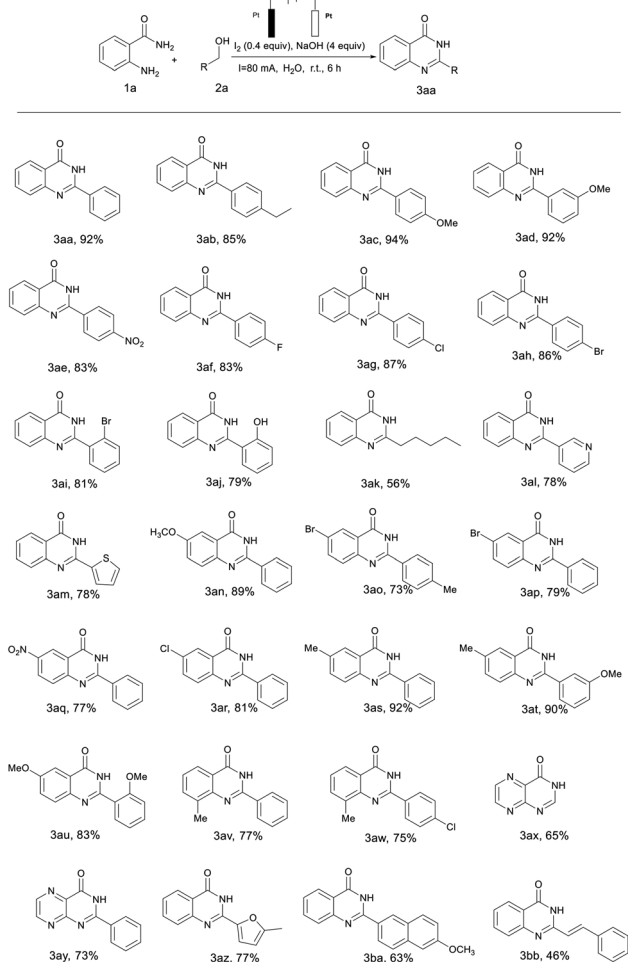
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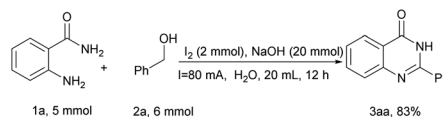


Table 2 Synthesis of quinazolinones from benzyl alcohols and *o*-aminobenzamides<sup>a,b</sup>



<sup>a</sup> Standard Conditions: undivided cell, Pt anode, Pt cathode, **1a** (0.5 mmol), **2a** (0.6 mmol),  $I_2$  (0.2 mmol), NaOH (2 mmol) in  $H_2O$  (3 mL),  $I = 80$  mA at room temperature for 6 h. <sup>b</sup> Isolated yield.

with excellent yields of 79–94% (Table 2, **3ab–3aj**). Because of the stability of the electron donor to intermediates and free radical electrons, it was found that the yield of electron-donating substrates (–Et, –OMe) was slightly higher than that of electron-withdrawing substrates (–NO<sub>2</sub>, –F, –Cl, –Br, –OH). The highest yield of 94% was obtained with 4-methoxybenzyl alcohol whereas the lowest yield was 79% with 2-hydroxybenzyl alcohol (Table 2, **3ac** and **3aj**). It was obvious that heterocyclic alcohols such as pyridinyl, thienyl and methylfuran were well-tolerated in this catalytic system with 78% and 77% yields (Table 2, **3al**, **3am** and **3az**). Notably, long-chain aliphatic alcohols also yielded a corresponding product, but the yield was dramatically lower than that of aromatic alcohols (Table 2, **3ak**). Furthermore, highly catalytic activities were found in transformations of naphthalenemethanol to the corresponding products (Table 2, **3ba**). When alkenyl alcohol was employed



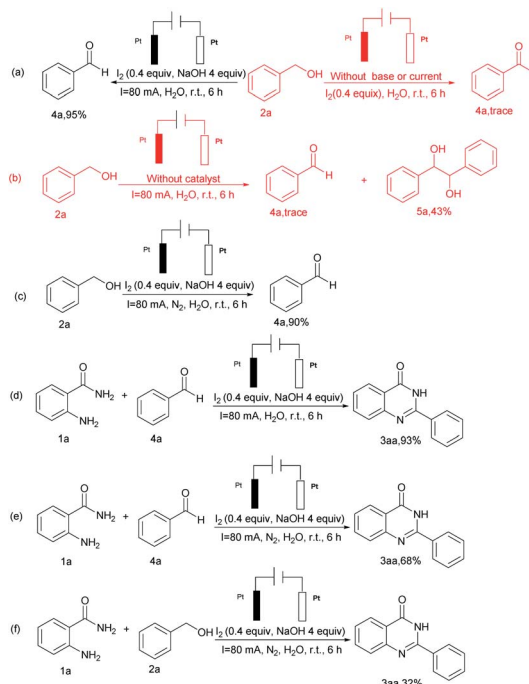
Scheme 2 Gram-scale experiment.

under the same reaction conditions, the product formed only had a 46% yield (Table 2, **3bb**).

Subsequently, the substrates of *o*-aminobenzamide were also expanded (Table 2, **3an–3aw**). Similar to the observation with the alcohol substitution compounds, *o*-aminobenzamides with electron-donating groups (–Me, –OMe) gave relatively higher reactivity than those with electron-withdrawing groups (–NO<sub>2</sub>, –F, –Cl, –Br). Whereas when heterocyclic amides were used as the starting substrates, yields of 65% and 73% of the corresponding products were also obtained (Table 2, **3ax** and **3ay**).

In order to demonstrate the practicality of this method, the gram-scale preparation of **1a** (5 mmol) and **2a** (6 mmol) with  $H_2O$  (20 mL) under the optimized reaction conditions was performed as shown in Scheme 2, which gave the desired product **3aa** with an 83% yield (1.47 g). This reveals that the new procedure has significant advantages over many current methods for further practical applications.

To exclude the possibility of other reaction pathways, some control experiments were performed (Scheme 3). Firstly, benzyl alcohol **2a** effectively gave benzaldehyde **4a** using aerobic oxidation reactions under standard conditions. In contrast, the absence of either base or current lead to the production of trace amounts of benzaldehyde, furthermore, the lack of catalyst lead to the formation of **5a** (Scheme 3 a and b) with a yield of 43%.



Scheme 3 Control experiments of alcohol oxidation and synthesis of **3aa**.



Nevertheless, the yield of **4a** was reduced to 90% when nitrogen was substituted for air (Scheme 3c). Then, the reaction of **1a** and **4a** under the standard conditions effectively gave **3aa** with a high yield of 93% (Scheme 3d), whereas the reaction of *o*-aminobenzamide under a nitrogen atmosphere, resulted in **3aa** with a yield of 68% and 32% (Scheme 3e and f).

To gain an understanding of the reaction mechanism, cyclic voltammetry (CV) was then conducted (Fig. 2). Using H<sub>2</sub>O as the solvent, a glass electrode as the working electrode, platinum wire as the opposite electrode, and SCE as the reference electrode with a 0.1 V s<sup>-1</sup> scanning rate. By comparing curves c, f

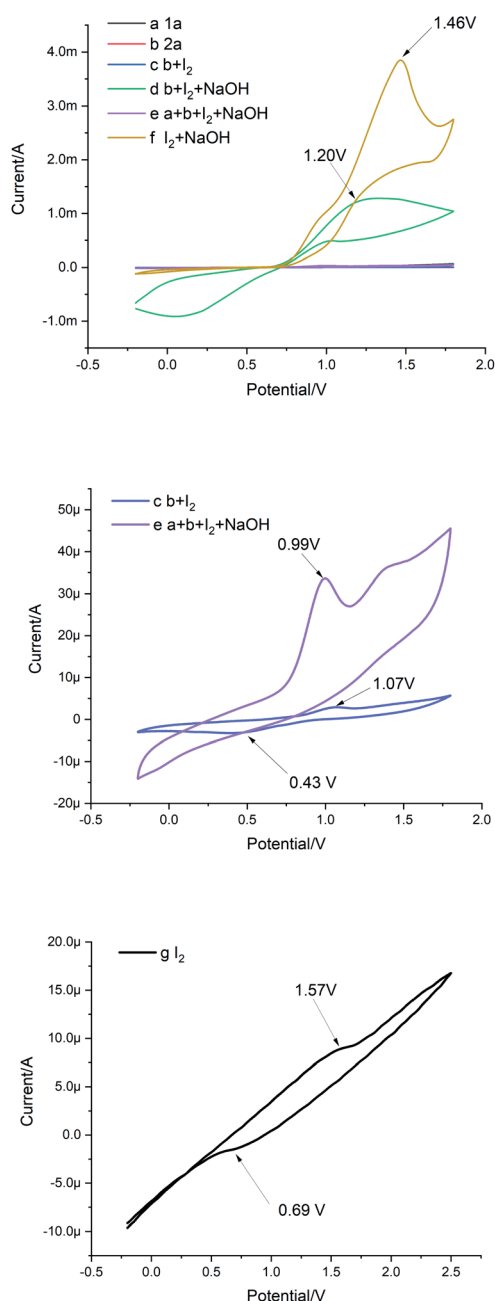
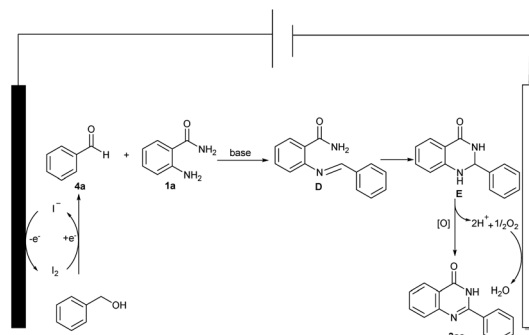


Fig. 2 Cyclic voltammetry measurements were performed at room temperature with standard three electrode systems.

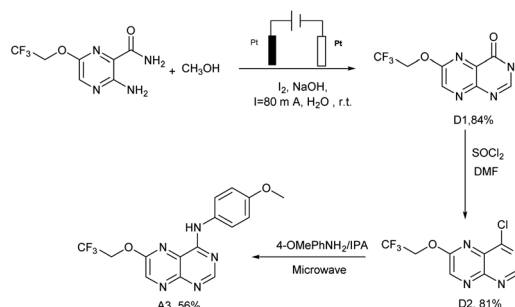


Scheme 4 Proposed mechanism for this transformation.

and g, it was observed that the onset potential of the I<sub>2</sub> oxidation shifted from 1.57 to 1.07 V vs. SCE in the presence of substrate **2a**, which was more than that in the presence of NaOH, indicating that I<sub>2</sub> was more likely to react with **b** than disproportionated with NaOH (Fig. 2, curves c, f and g). However, a reduction peak appears in b at 0.43 V, and the reduction peak of I<sub>2</sub> was 0.69 V, indicating that I<sup>-</sup> is still carrying out the reduction reaction in the presence of b (Fig. 2, curve c and g). Interestingly, the addition of **1a** and NaOH further decreases the onset potential of I<sub>2</sub> complex oxidation to 0.99 V vs. SCE (Fig. 2, curve e). In contrast, the oxidation potential increased when NaOH was added individually, and this may be evidence that NaOH does not interact with **2a** and I<sub>2</sub> (Fig. 2, curve d).

By considering the whole of the experimental findings, a plausible mechanistic pathway for the formation of compound **3aa** is outlined in Scheme 4. First of all, benzyl alcohol **2a** is first oxidized to benzaldehyde **4a** by I<sub>2</sub>, which is generated *in situ* on the anode.<sup>6a,18</sup> The iodine undergoes cathodic reduction by regenerating the iodide ion for the catalytic cycle. Next, **4a** can readily react with **1a** to obtain the imine **D**, imine **D** is then converted to **E** in the presence of a base, and thus **E** oxidizes and dehydrogenates to give the desired product **3aa**.<sup>19</sup> Finally, H<sup>+</sup> removed from **E** combines with O<sub>2</sub> to form H<sub>2</sub>O at the cathode.<sup>20</sup>

Lots of nuclear nitrogen heterocycles, such as pteridine which is a widely existing aromatic compound, similar to quinazolines, which are tyrosine kinase inhibitors, which have good specificity and inhibitory activity on tumour cells. It is



Scheme 5 Synthesis of *N*-(4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy) pteridin-4-amine (**A3**).



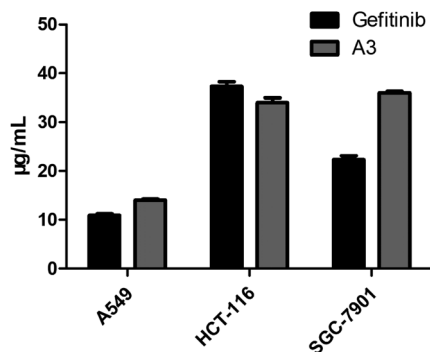


Fig. 3 *In vitro* inhibitory data of target compounds against A549, HCT-116 and SGC-7901 cell line.

thought that many fluorine-containing drugs have been widely used in clinical situations. The introduction of fluorine atoms and fluorine-containing groups into drugs can improve the clinical efficacy of drugs and reduce their side effects. Based on this, the electrocatalytic system was applied to the synthesis of the structure of the trexine and the synthesis of gefitinib analogues. For example, *N*-(4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy)pteridin-4-amine A3 was synthesized from 3-amino-6-(2,2,2-trifluoroethoxy) pyrazine-2-carboxamide with a yield of 56% (see Scheme 5). The compounds were then tested using the MTT assay and the results are shown in Fig. 3. The A3 inhibited human non-small-cell lung carcinoma cells, A549, human colon cancer cells, HCT-116, and human gastric cancer cells, SGC-7901 to different degrees. As shown in Fig. 3, the results showed that the IC<sub>50</sub> value of A3 in HCT116 cells (IC<sub>50</sub> = 14.79 µg mL<sup>-1</sup> in A549 cells, IC<sub>50</sub> = 34.52 µg mL<sup>-1</sup> in HCT116 cells, IC<sub>50</sub> = 36.44 µg mL<sup>-1</sup> in SCG-7901 cells) was just surpassed by that of gefitinib.

## Conclusions

In summary, it is demonstrated that simple and commercially available I<sub>2</sub> could be used as an electrocatalyst for the selective oxidation of a range of activated C–H bonds in alcohols. It is also demonstrated that I<sub>2</sub> together with electrochemistry is a mild catalyst to efficiently promote C–H oxidation reactions. Oxidative tandem cyclization is of importance in the synthesis of heteropolycyclic skeletons and has a high atom economy. Furthermore, use of both electrocatalysis as a reaction process and water as a green solvent was consistent with the concept of green synthesis. This catalytic protocol avoids using toxic reagents and shows a broad substrate scope, providing consistently good yields of quinazolinones under constant current at room temperature for 6 h. Further extension of this electrochemical protocol to the synthesis of other heterocycles is underway.

## Experimental section

### General procedure (for Tables 1 and 2)

To a dried 10 mL quartz tube equipped with 80 mA current was added benzamide (0.5 mmol), alcohol (0.6 mmol), I<sub>2</sub> (0.2

mmol), NaOH (2.0 mmol) and water (3 mL). The mixture was stirred at room temperature for 6 h in a 80 mA circuit. After the reaction was completed the solution containing the crude product was concentrated under vacuum, and the residue was purified by column chromatography on a silica gel (petroleum ether/ethyl acetate = 3/1) to give the target product as a white solid.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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