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# Electrochemical Synthesis of Quinazolinones by the Metal-Free and Acceptor-Free Dehydrogenation of 2-Aminobenzamides

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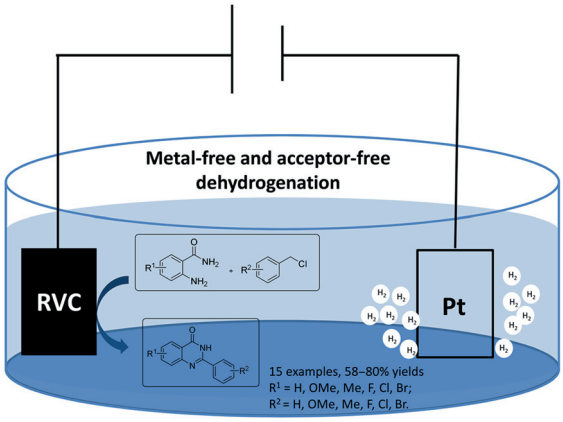


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**Abstract** An efficient approach has been developed for the construction of quinazolin-4(3*H*)-ones by the selective anodic dehydrogenative oxidation/cyclization of benzylic chlorides and 2-aminobenzamides. The method features acceptor-free and metal-free dehydrogenation of amines to imines; a subsequent intermolecular addition provides the products in moderate to good yields.

**Key words** quinazolinones, electrochemical synthesis, aminobenzamides, benzylic chlorides, metal-free

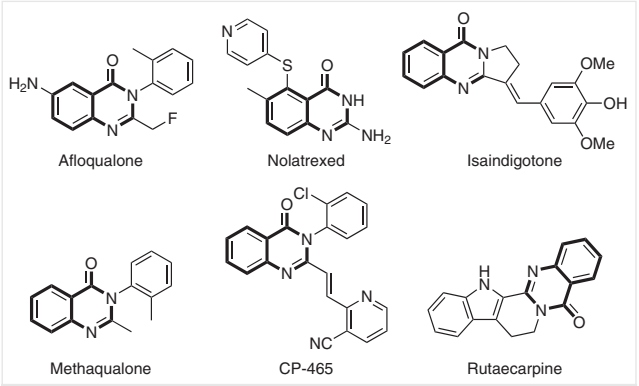


**Figure 1** Selected examples of biologically active quinazolinones

Quinazolinones are an important class of nitrogen-containing heterocyclic compounds, widely present in natural products[1] and pharmaceutical agents that present diverse biological activities, such as antibacterial,[2] antiviral,[3] anti-inflammatory,[4] and antitumor activities[5] (Figure 1). Because of the wide range of applications of quinazolinones, much effort has been devoted to the exploration of efficient methods for their construction.

2-Aminobenzamide has been widely used as a precursor for preparing quinazolinones. In conventional methods, quinazolinones are commonly prepared through coupling of 2-aminobenzamide with aldehydes,[6] carboxylic acids,[7] or acyl halides.[8] However, these methods involve harsh conditions or require substrates that are not readily available. Some recent studies have resulted in the development of methods to overcome these drawbacks. A cascade reaction of 2-aminobenzamides with benzylic alcohols gave the desired quinazolinones in good yields under catalysis by transition metals.[9] In the presence of the $I_2$/DMSO catalytic system, ketones as substrates coupled with 2-aminobenzamide to provide the desired quinazolinones.[10] Li and coworkers reported a valuable synthesis of quinazolinones through the cross-coupling of methylarenes with 2-aminobenzamide promoted by DTBP/TsOH.[11] However, these transformations rely on catalysis by transition metals and oxidation by stoichiometric quantities of oxidants, both of which are environmentally unfriendly. Therefore, it is still highly desirable to develop green methods for the synthesis of quinazolines.

Acceptor-free dehydrogenation is considered an important synthetic approach in terms of atom economy and environmental effects.[12] The functionalization of amines by acceptor-free dehydrogenation has attracted widespread recent attention, and several methods based on catalysis by precious transition metals such as Ir,[13] Ru,[14] or Os[15] have been developed. However, the high cost and toxicity of precious transition metals cannot be ignored.



 
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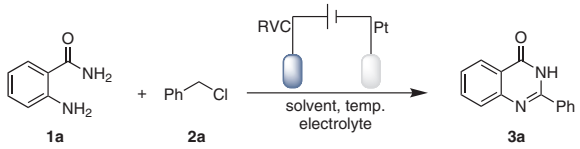
**Table 1** Optimization of the Synthesis of 2-Phenylquinazolin-4(3*H*)-one (**3a**)[a]




| Entry | Solvent | Constant current (mA) | Temp (°C) | Yield (%)[b] |
|---|---|---|---|---|
| 1[c] | $H_2O$–1,4-dioxane (1:1) | 10 | 90 | 36 |
| 2 | $H_2O$–1,4-dioxane (1:1) | 10 | 90 | 52 |
| 3[d] | $H_2O$–1,4-dioxane (1:1) | 10 | 90 | 44 |
| 4 | MeCN–$H_2O$ (1:1) | 10 | 90 | 33 |
| 5 | $H_2O$ | 10 | 90 | 0 |
| 6 | EtOH | 10 | 90 | 0 |
| 7 | MeCN | 10 | 90 | 80 |
| **8** | **MeCN** | **10** | **80** | **80** |
| 9 | MeCN | 10 | 70 | 45 |
| 10 | MeCN | 7.5 | 80 | 45 |
| 11 | MeCN | 15 | 80 | 54 |
| 12[e] | MeCN | 10 | 80 | 76 |

[a] Reaction conditions: RVC anode (100 PPI, 1 × 1 × 1.2 cm), Pt plate cathode (1 × 1 cm), undivided cell, constant current: 10 mA, **1a** (0.5 mmol), **2a** (0.6 mmol), $Bu_4NBF_4$ (10 mol%), solvent (6 mL), 80 °C, 6 h.
[b] Isolated yield.
[c] No electrolyte.
[d] 10% $Et_4NBF_4$ was used.
[e] Under Ar (1 atm).

Organic electrosynthesis is an environmentally friendly synthetic strategy due its use of electrons as redox reagents. The application of organic electrosynthesis in acceptor-free dehydrogenation recently attracted our attention.[16] In this respect, an anodic oxidation sequence of alcohols/aldehydes/benzyl ethers with *ortho*-aminobenzamides has been applied in the preparation of quinazolinones.[17] Furthermore, in our previous work, we reported an electrochemical metal-free synthesis of quinazolinones by coupling of alkenes with 2-aminobenzamides.[18] We therefore speculated the N-substituted 2-aminobenzamides might undergo dehydrogenation/cyclization through electrocatalytic anodic oxidation. Here, we report an electrochemical synthesis of quinazolinones by coupling of 2-aminobenzamides and halides in one pot.

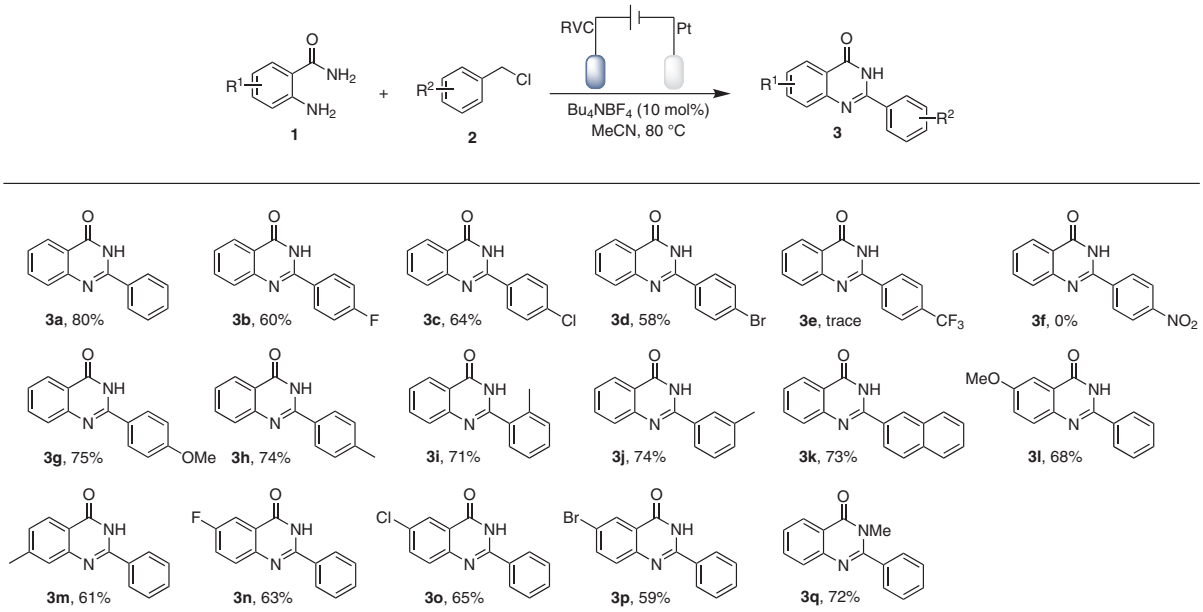
Initially, the reaction of 2-aminobenzamide (**1a**) and benzyl chloride (**2a**) in $H_2O$–1,4-dioxane (1:1) with reticulated vitreous carbon (RVC) as the anode and Pt as the cathode in an undivided cell at a constant current of 10 mA provided quinazolone **3a** in 36% yield (Table 1, entry 1). Delighted with this result, we then optimized the reaction conditions, and the results of our optimization study are summarized in Table 1. The addition of an electrolyte led to a significant increase in yield; $Bu_4NBF_4$ was found to be the best electrolyte, and gave **3a** in 52% yield (entries 2 and 3). Among various solvents examined, MeCN was found to be optimal, providing an 80% yield (entries 2 and 4–7). When the temperature was decreased to 80 °C, the yield of **3a** remained at 80%, whereas a lower yield was obtained at 70 °C (entries 8 and 9). Increasing or decreasing the constant current reduced the yield markedly, providing **3a** in yields of 54 and 45%, respectively (entries 10 and 11). When the reaction of **1a** and **2a** was carried out under an argon atmosphere, it proceeded smoothly to form quinazolinone **3a** in 76% yield (entry 12). Finally, the optimal conditions were identified as MeCN as solvent, containing $Bu_4NBF_4$ as an electrolyte, with RVC as the anode and Pt as the cathode, in an undivided cell at a constant current of 10 mA, and at 80 °C.

With the optimal reaction conditions in hand, we investigated the scope of the 2-aminobenzoamides and halides (Scheme 1). The presence of various halogens on the benzene ring of the benzylic chloride led to a slight drop in yield, and quinazolones **3b–d** were obtained in yields of 58–64%. Unfortunately, benzylic chlorides with highly electron-deficient substituents ($CF_3$ or $NO_2$) failed to give the corresponding quinazolinones **3e** and **3f**. When benzylic chlorides bearing electron-donating methoxy or methyl groups on the benzene ring were used, products **3g–j** were obtained in yields of 71–75%. 2-(Chloromethyl)naphthalene (**2k**) reacted smoothly, generating quinazolinone **3k** in 73% yield. 2-Aminobenzoamides bearing various substituents, such as methoxy, methyl, or halo groups, gave the corresponding products **3l–p** in moderate yields of 59–68%. 2-(Methylamino)benzamide also gave the desired product **3q** in 72% yield.

To demonstrate the practicability and scalability of this protocol, we carried out an acceptor-free and metal-free dehydrogenation of 2-aminobenzamide at an 8 mmol scale under the standard condition, giving **3a** in 70% yield (Scheme 2).

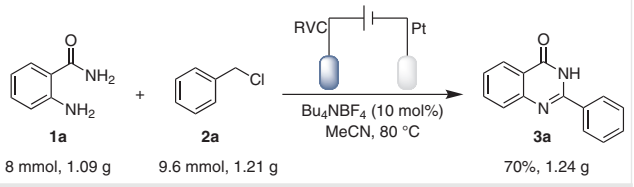
To explore the reaction mechanism, control experiments were performed. When the reaction of **1a** and **2a** was conducted in MeCN with 10 mol% $Bu_4NBF_4$ at 80 °C without electrolysis, only trace amounts of **3a** and **5a** were detected by GC/MS, and **4a** was obtained in 50% yield, indicating that **4a** is a key intermediate (Scheme 3, eq. 1). Electrolysis of **4a** under the standard conditions gave **3a** in 90% yield (Scheme 3, eq. 2).

The reaction was then examined by cyclic voltammetry (CV) (Figure 2). An oxidation peak was observed for the reaction of **1a** at $E_p$ = +1.155 V vs. SCE, in the region of 0.0–3.0 V vs. Ag/AgCl, while this peak was markedly weakened (Figure 2, curve b).[17a] The cyclic voltammogram for the reaction of **2a** showed an oxidation peak at $E_p$ = +2.567 V (Figure 2, curve c). However, a mixture of **1a** and **2a** showed an oxidation peak at $E_p$ = +1.155 V with a slightly decrease in the catalytic current (Figure 2, curve d). These results indicate that **1a** and **2a** are not directly oxidized at the anode to par-




**Scheme 1** Synthesis of 2-substituted quinazolinones **3a–q**. *Reagents and conditions*: RVC anode (100 PPI, 1 × 1 × 1.2 cm), Pt plate cathode (1 × 1 cm), undivided cell, constant current: 10 mA, **1** (0.5 mmol), **2** (0.6 mmol), $Bu_4NBF_4$ (10 mol%), MeCN (6 mL), 80 °C, 6 h. Isolated yield are reported.

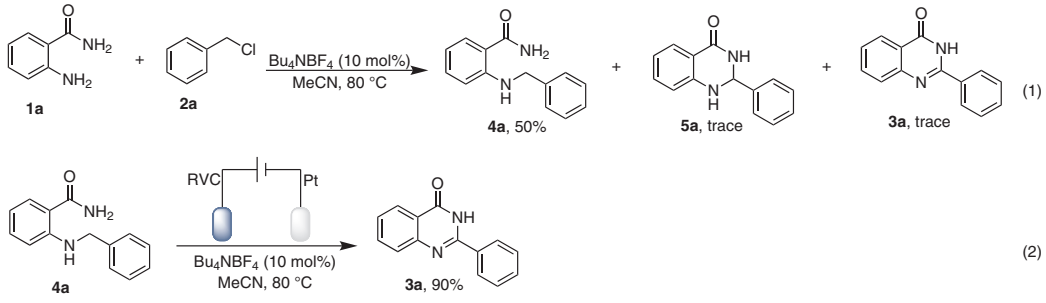
ticipate in the reaction. To clarify the mechanism of the reaction, a CV study of the coupling product **4a** was carried out, and the result showed a slightly higher oxidation potential than that of **1a** (Figure 2, curve e), but with an additional marked increase in the catalytic current; this provided further confirmation that **4a** is an intermediate in this electrocatalytic cascade reaction.




**Scheme 2** Synthesis of **3a** on a gram scale

Based on the above results, a plausible mechanism for the formation of quinazolinones was proposed (Scheme 4). The coupling of **1a** and **2a** generates an intermediate **4a** that loses an electron to the anode surface to generate the cationic radical **A**. After release of a proton, intermediate **A** is transformed into radical **B**. Further anodic oxidation of **B** produces imine **C**, and subsequent intramolecular cyclization gives **5a**. Finally, **3a** is formed through anodic oxidation of **5a**. Protons are reduced to hydrogen at the cathode to complete the cycle.

In conclusion, an efficient electrocatalytic cascade reaction of 2-aminobenzamides and benzylic chlorides has been developed that provides quinazolin-4(3*H*)-ones in moderate to good yields.[19] For this approach, a mechanism involving an acceptor-free dehydrogenation of amines to imines promoted by electrocatalytic anodic oxidative has been proposed.




**Scheme 3** Controlled reactions for exploring the reaction mechanism

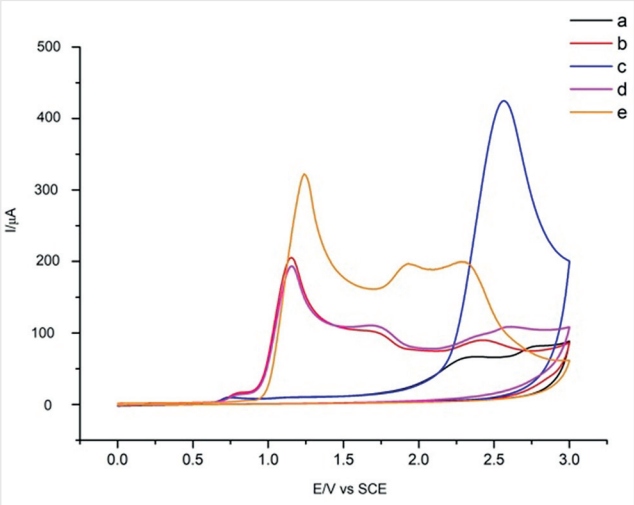
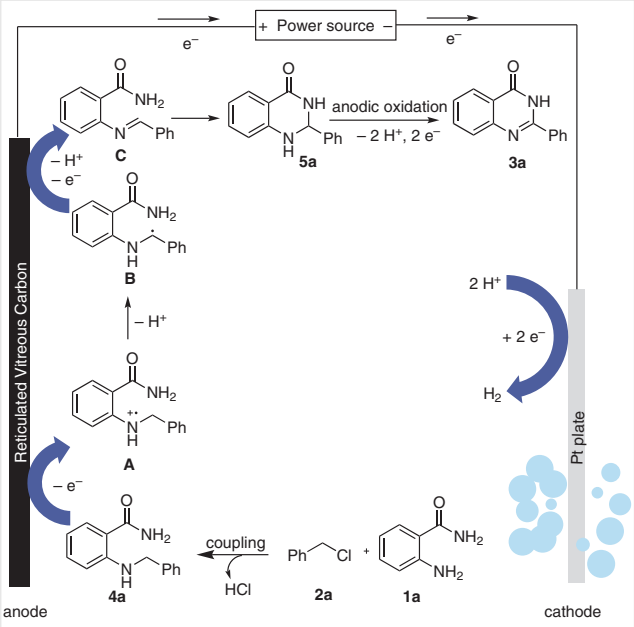



**Figure 2** Cyclic voltammograms of reactants and their mixtures in 0.01 M $Bu_4NBF_4$/MeCN on a glassy carbon disk working electrode (diameter: 3 mm) with a Pt disk and Ag/AgCl (MeCN) as the counter and reference electrode, respectively, at a scan rate of 100 mV/s. (a) Background, (b) *o*-aminobenzamide, (c) benzyl chloride, (d) *o*-aminobenzamide + benzyl chloride, (e) 2-(benzylamino)benzamide.




**Scheme 4** Plausible mechanism

## Funding Information

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707248.

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(19) **Quinazolinones 3a–q; General Procedure**

A mixture of the appropriate 2-aminobenzamide **1** (0.5 mmol), benzylic chloride **2** (0.6 mmol), and $Bu_4NBF_4$ (10 mol%) was placed in a 25 mL three-necked round-bottomed flask equipped with a condenser, an RVC (100 PPI) anode, and a Pt plate (1 × 1 cm) cathode. The flask was opened to air and MeCN (6 mL) was added. Electrolysis was carried out at 80 °C (oil-bath temperature) at a constant current of 10 mA until the substrate was completely consumed (TLC). The mixture was then cooled to rt, and the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc–PE).

**2-Phenylquinazolin-4(3*H*)-one** (**3a**)

White solid; yield: 88.8 mg (80%); mp 233–235 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.52 (s, 1 H), 8.22–8.12 (m, 3 H), 7.84–7.77 (m, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.53 (qt, *J* = 11.0, 5.2 Hz, 4 H). $^{13}$C NMR (101 MHz, DMSO): δ = 162.80, 152.84, 149.28, 135.09, 133.26, 131.90, 129.12, 128.30, 128.03, 127.09, 126.39, 121.51.

**2-(4-Fluorophenyl)quinazolin-4(3*H*)-one** (**3b**)

White solid; yield: 72.0 mg (60%); mp 240–242 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.57 (s, 1 H), 8.25 (dd, *J* = 8.8, 5.6 Hz, 2 H), 8.15 (d, *J* = 6.4 Hz, 1 H), 7.84 (t, *J* = 6.8 Hz, 1 H), 7.73 (d, *J* = 8.1 Hz, 1 H), 7.55–7.50 (m, 1 H), 7.39 (t, *J* = 8.8 Hz, 2 H). $^{13}$C NMR (100 MHz, DMSO): δ = 162.69, 151.86, 149.11, 135.15, 130.85 (d, *J* = 9.3 Hz), 130.10, 129.66 (d, *J* = 3.2 Hz), 127.92, 127.11, 126.32, 121.32, 116.11 (d, *J* = 22.0 Hz).

**2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3c)**

White solid; yield: 81.9 mg (64%); mp 295.5–298 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.61 (s, 1 H), 8.21 (d, *J* = 8.7 Hz, 2 H), 8.16 (d, *J* = 7.9 Hz, 1 H), 7.85 (t, *J* = 6.9 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.6 Hz, 2 H), 7.54 (t, *J* = 7.5 Hz, 1 H). $^{13}$C NMR (100 MHz, DMSO): δ = 163.04, 152.10, 149.31, 137.04, 135.45, 132.29, 130.37, 129.44, 128.27, 127.55, 126.62, 121.72.