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One-Pot Synthesis of Quinazolin-4(3*H*)-ones through Anodic Oxidation and the Related Mechanistic Studies

Liu Cao,[a] Hengrui Huo,[a] Haipeng Zeng,[a] Yu Yu,[a] Dengfu Lu [a]* and Yuefa Gong [a]*

[a] School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Rd., Wuhan, Hubei, 430074, China
E-mail: dlu@hust.edu.cn; gongyf@hust.edu.cn

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Abstract: A metal-free and oxidant-free method for the one-pot preparation of quinazolin-4(*3H*)-ones enabled by electrochemical oxidation is described. Together with 2-aminobenzamides, a variety of aldehydes were successfully applied to an acid-catalyzed annulation and direct anodic oxidation cascade, affording structurally diverse quinazoline-4(*3H*)-ones in good to excellent yields. Additionally, certain alcohols can be directly applied instead of the corresponding aldehydes to achieve the same final products with the assistance of an electrolysis mediator (TEMPO). The reaction mechanism was carefully examined and the results strongly suggest that the direct and indirect oxidation go through different pathways. As an efficient and environmentally friendly access to a broad range of quinazolin-4(*3H*)-ones, the synthetic utility of this method was demonstrated by gram-scale operation, as well as the preparation of bioactive mackinazolinone and truncated erlotinib.

Keywords: Quinazoline-4(3*H*)-ones; Annulation; Anodic oxidation; Indirect electrolysis; Oxidation mechanism

Introduction

Quinazolin-4(3*H*)-ones are important nitrogen-containing heterocyclic scaffolds.[1] Both naturally occurring and synthetic quinazolin-4(3*H*)-ones have been shown to exhibit a wide range of pharmacological and biological activities, including antibacterial, anti-infective, anti-inflammatory, and antitumor properties (Figure 1).[2] For these reasons, their preparation has attracted extensive research interests, and several elegant methods have been developed in the recent decade.[3] The representative synthetic routes include: (i) Pd-catalyzed cyclocarbonylation of 2-haloanilines with imidoyl chlorides[4] or trimethyl orthoformate;[5] (ii) transition metal-catalyzed cascade reactions of amidine salt with 2-haloaryl carbonyl compounds;[6,7] (iii) amidation of benzoxazinones with arylamines;[8] (iv) reduction/cyclization sequence of 2-nitrobenzamides with carbonyl compounds;[9] and (v) cyclization/oxidation cascade of 2-aminobenzamides with aldehydes[10], benzyl alcohols[10b, 11] or ortho esters.[12]

Among these methods, the cyclization/oxidation sequence of 2-aminobenzamides with aldehydes or benzyl alcohols were the most applied. However, the prevailing strategies generally require either stoichiometric amount of hazardous oxidants or transition-metal catalysts (when benign oxidants were used), as well as elevated temperatures and extended reaction times (Scheme 1a). It is still highly desirable to establish a more efficient, mild, yet environment-friendly approach to structurally diverse quinazolin-4(3*H*)-ones.

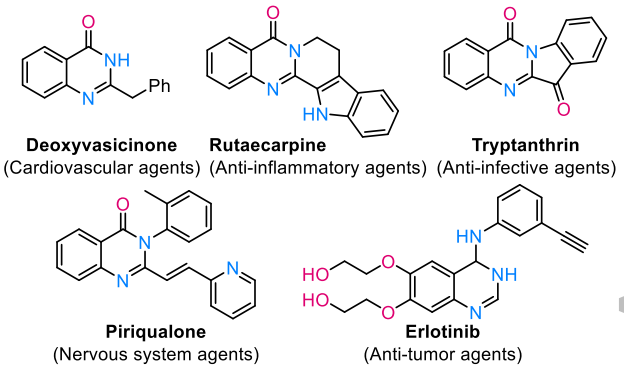

Figure 1. Biologically Active Quinazoline-4(3*H*)-ones.

With electrons as the oxidizing/reducing agent, organic electrosynthesis could offer appropriate alternatives to traditional oxidation or reduction reactions.[13] Electrochemical dehydrogenation[14] and cross-dehydrogenative coupling reactions[15] have achieved prominent developments in recent years.

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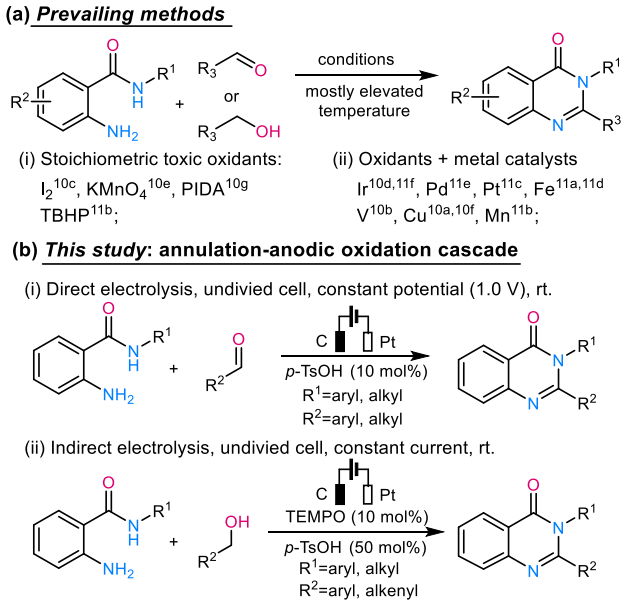
Not only do they avoid the use of excess oxidants, but also emit hydrogen gas as the sole byproduct, not to mention the electrolysis is typically carried out at ambient temperature. In sum, electrosynthesis complies well with the criteria of green chemistry. Herein, we report a metal-free and oxidant-free approach for the uniform synthesis of diversified quinazolin-4(3*H*)-ones via electrochemical dehydrogenation of 2,3-dihydro-quinazolin-4(*1H*)-ones, which are formed in situ through an acid-catalyzed annulation between 2-aminobenzamides and aldehydes (Scheme 1b (i)). In addition, based on the *N*-oxyl radicals mediated anodic oxidation reaction of alcohols,[16] an oxidation-cyclization-dehydrogenation cascade that started directly with an alcohol and a 2-aminobenzamide was also achieved with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as a redox mediator (Scheme 1b (ii)).

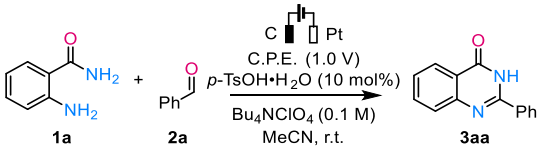


Scheme 1. Reported Methods and Current Studies on the Synthesis of Quinazoline-4(3*H*)-ones

Results and Discussion

We began our study with the reaction of 2-aminobenzamides **1a** and benzaldehyde **2a** (Table 1). The electrochemical setup consists of an undivided cell[17] equipped with a graphite (C) anode and a platinum plate (Pt) cathode. After careful screening of reaction conditions, the optimal results were obtained under controlled potential electrolysis (C.P.E., 1.0 V) with *p*-TsOH•H_2O (10 mol%) as an acid catalyst and Bu_4NClO_4 as the electrolyte (0.1 M solution in MeCN) (Table 1). Under these conditions, the desired 2-phenylquinazolin-4(3*H*)-one (**3aa**) was isolated in 93% yield after 1.5 h (entry 1). Several other organic solvents were investigated, but the results were not as good. The reaction in EtOH or EtOH/MeCN (v/v 1:1 mixture) under otherwise the same conditions resulted in slightly lower yields (entries 2, 3), and only 68% of **3aa** was isolated when the reaction was performed in CF_3CH_2OH (entry 4). Interestingly, an acid catalyst was shown to be critical (entry 5) and its acidity also plays a subtle role in the reaction performance. Strong acids like CF_3CO_2H and triflic acid were competent catalysts (entries 6, 7), while weaker acids such as AcOH or a NaH_2PO_4/Na_2HPO_4 buffer (pH = 4.4) led to inferior yields (entries 8, 9). Additionally, several supporting electrolytes were also assessed. No product was detected when the electrolysis was performed in a $LiClO_4$/MeCN solution, whereas a lower yield was obtained in Bu_4NBF_4/MeCN (entries 10, 11). As an excellent redox mediator, TEMPO, however, does not show noticeable accelerating effect under the optimal reaction conditions (90% yield, 1.5 h, entry 12).

Table 1. Optimization of the Reaction Conditions.[a)]



entry	Variations from the standard conditions	Time (h)	Conv./Yield (%)[b,c)]
1	none	1.5	99/93
2	EtOH as solvent	5.5	99/81
3	MeCN:EtOH=1:1 as solvent	3	99/86
4	CF_3CH_2OH as solvent	12	99/68
5[d)]	In the absence of TsOH	18	30/18
6	CF_3CO_2H instead of TsOH	3	99/84
7	TfOH instead of TsOH	1.5	99/89
8	AcOH instead of TsOH	13	40/23
9	pH = 4.4 buffer[e)]	16	79/60
10	$LiClO_4$ as electrolyte	2	99/<5
11	Bu_4NBF_4 as electrolyte	2	80/69
12	TEMPO was added (10 mol%)	1.5	99/90

[a)]Standard conditions: undivided cell, controlled potential (1.0 V), **1a** (0.20 mmol), **2a** (0.30 mmol), *p*-TsOH•H_2O (10 mol %) in a 0.1 M Bu_4NClO_4 solvent mixture (8.0 mL) at room temperature, 2.2 F; [b)]Determined by ^1H NMR analysis with an internal standard; [c)]Isolated yield; [d)]constant current 5 mA; [e)]NaH_2PO_4/Na_2HPO_4 buffer.

With the optimal conditions in hand, the substrate scope of this transformation was then evaluated as shown in Table 2. 2-Aminobenzamides **1b-1g** with different substituents on the amide nitrogen were first tested with the standard procedure. Both electron-rich and electron-deficient aryl groups, as well as *n*-butyl group, are tolerated, furnishing **3ba-3ga** in 65% to 86% yields (entry 1). Electron-rich amides generally shows better reactivity. Next, the reaction between 2-amino-*N*-phenylbenzamide **2b** and a series of aldehydes were performed. Aromatic aldehydes with various substituents or heterocycles behave consistently, giving desired quinazolin-4(3*H*)-one

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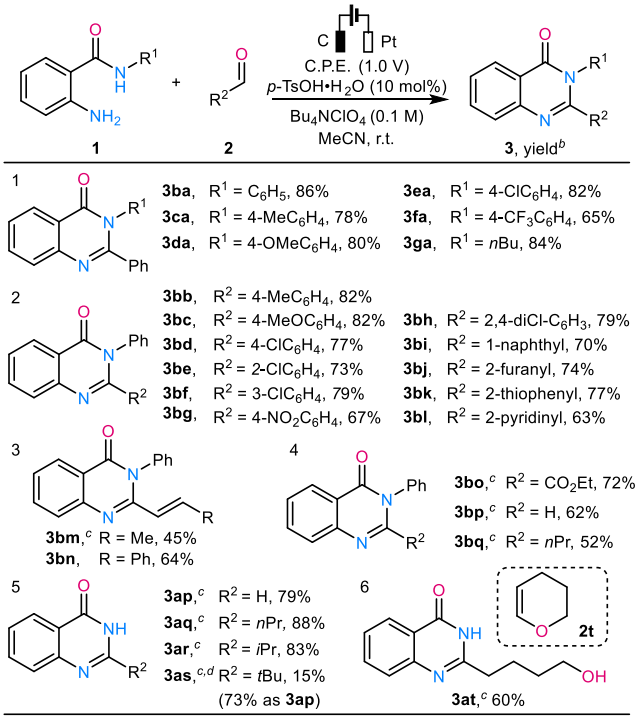
3bb-**3bl** in satisfactory yields (entry 2). Crotonate and cinnamaldehyde were tolerated with this method, albeit the corresponding products **3bm** and **3bn** were obtained in lower yields (entry 3). In addition, ethyl glyoxylate, formaldehyde and butyraldehyde were also suitable reaction partners with **1b**, however, only afforded the products in moderate yields, probably because the cyclization step were less efficient (entry 4). Improved conversions and yields were achieved when aliphatic aldehydes were applied with a simple 2-aminobenzamide **1a** (entry 5). Unexpectedly, when pivalaldehyde was used, the *tert*-butyl group was eliminated during the electrolysis to generate **3ap** as the major product, presumably through a radical or cation fragmentation.[18] Gratifyingly, 3,4-dihydro-2*H*-pyran **2t** was also proven compatible with this method, providing **3at** in decent yield (entry 6), which is a key intermediate in the synthesis of mackinazolinone.[19]

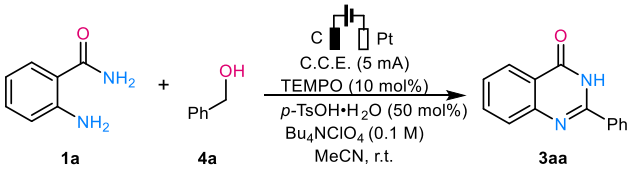
Table 2. Substrate Scope of the Direct Electrolysis.[a)]



[a)]General conditions: undivided cell, controlled potential (1.0 V), **1** (0.20 mmol), **2** (0.30 mmol) and *p*-TsOH•H_2O (0.02 mmol) in a Bu_4NClO_4/MeCN solution (0.1 M, 8.0 mL) at room temperature for 1.5 h (2.2-3.5 F); [b)]Isolated yield; [c)]Reation was stirred for 3 h before electrolysis; [d)]**3ap** was isolated as the major product.

Since aldehydes are highly reactive to oxidants and nucleophiles and thus usually difficult to preserve, we envisaged that the substrate scope of this transformation could be expanded to the corresponding alcohols, which could serve as stable precursors of aldehydes. 2-Aminobenzamide **1a** and benzyl alcohol **4a** were selected as the model substrates to validate this hypothesis (Table 3). The initial attempts with direct electrolysis setup turned to be incapable of promoting this oxidation/annulation/dehydrogenation cascade, perhaps due to the high oxidation potential of benzyl alcohol, as well as the competing and non-productive oxidation of 2-aminobenzamide.

Table 3. Optimization of the Reaction Conditions with Alcohol as a Starting Material.[a)]



entry	Variations from the standard conditions	yield (%)[b)]
1	none	91
2	Without TEMPO	N.D.[c]
3	TEMPO was reduced to 5 mol%	38
4	*p*-TsOH•H_2O was reduced to 30 mol%	71
5	*p*-TsOH•H_2O was reduced to 10 mol%	31
6	Constant current (10 mA)	55
7	Constant current (20 mA)	30
8	Controlled potential (1.0 V)	27
9	Controlled potential (2.0 V)	72

[a)]Standard conditions: undivided cell, constant current = 5 mA (j_{anode} ≅ 0.42 mA·cm^{-2}), **1a** (0.20 mmol), **2a** (0.40 mmol), *p*-TsOH•H_2O (0.5 equiv.) in a Bu_4NClO_4/MeCN solution (0.1 M, 8.0 mL) at room temperature for 14.5 h (5.8 F); [b)]Isolated yield; [c)]N.D. = Not detected.

To address these challenges, we resorted to indirect electrooxidation, which applies a redox active agent as a mediator. This agent readily loses its electron(s) on the anode and then its oxidation form oxidizes the substrate through chemical processes, completing the catalytic circle.[20] To our delight, after introducing an *N*-oxyl radical TEMPO as the redox-mediator and meanwhile increasing the amount *p*-TsOH•H_2O to 50 mol%, the desired cascade reaction underwent smoothly to afford 2-phenylquinazolin-4(3*H*)-one **3aa** in excellent yield (entry 1). Notably, the reaction hardly proceeded when the electrolysis was performed without TEMPO, and lowering its loading led to dramatic yield dropping (entries 2, 3). In this process, acid played a critical role in protecting **1a** from being oxidized to decomposition products. Thus, lowering the amount of *p*-TsOH•H_2O clearly led to declining yields (entries 4, 5). Additionally, it seemed that maintaining a proper current density was helpful, as increasing the current to either 10 or 20 mA caused inferior yields (entries 7, 8). Furthermore, electrolysis under controlled potentials was also inspected. A constant potential of 1.0 or 2.0 V (vs Ag/Ag+) failed to provide better results (entries 9, 10).

Having established the reaction conditions, the scope of alcohols was subsequently explored (Table 4). First, an array of benzylic alcohols were tested together with 2-aminobenzamide **1a**. All these reactions went smoothly, forming corresponding

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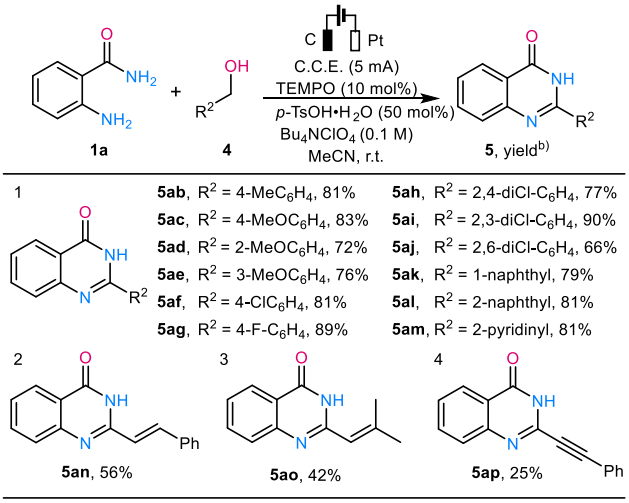
products **5ab-5am** in good to excellent yields (entry 1). Other than that, both cinnamyl alcohol and prenol readily participated to give products **5an** and **5ao** in moderate yields (entries 2 & 3). As for 3-phenyl-2-propyn-1-ol, only 25% yield of product **5ap** was obtained under these conditions (entry 4), presumably because the phenylpropionaldehyde generated from the oxidation was unstable under acidic conditions. Unfortunately, saturated alcohols are not applicable to this cascade procedure, possibly because they can hardly be chemically oxidized by $TEMPO^+$ salt under the reaction conditions.

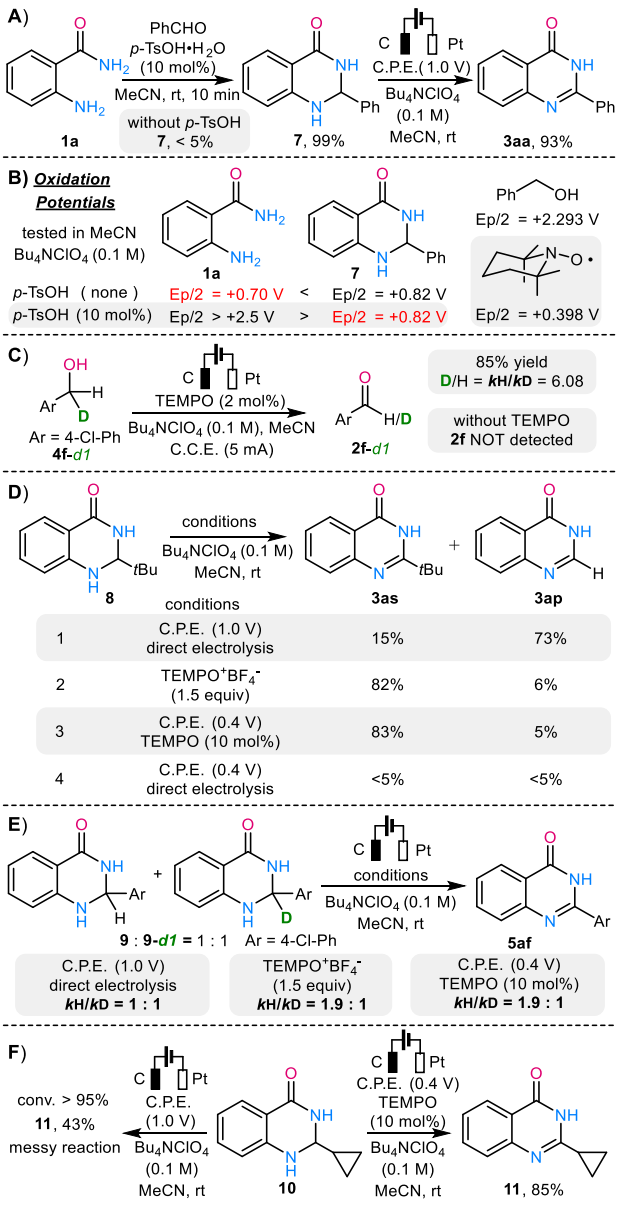
Table 4. Substrate Scope of the Indirect Electrolysis.[a)]



[a)]General conditions: undivided cell, constant current = 5 mA (j_{anode} ≈ 0.42 mA·cm^{-2}), **1a** (0.2 mmol), **4** (0.4 mmol), *p*-TsOH•H_2O (0.1 mmol) in a Bu_4NClO_4/MeCN solution (0.1 M, 8.0 mL) at room temperature for 16.5 h (5.8 F); [b)]Isolated yield.

To gather evidence for a mechanistic hypothesis of this annulation/anodic oxidation reaction, a series of control experiments and electrochemical analysis were carried out, and the results are summarized in Scheme 2 & Figure 2. Firstly, the cyclization between **1a** and benzaldehyde is significantly accelerated by *p*-TsOH•H_2O (10 mol%), and the quantitatively obtained product **7** could be oxidized to 2-phenylquinazolin-4(3*H*)-one **3aa** under direct electrolysis (C.P.E., 1.0 V) in excellent yield (Scheme 2A). The similar results obtained in one-pot (Table 1, entry 1) and stepwise procedures suggest that the aldehyde participated reactions may simply go through a stepwise acid-promoted cyclization and direct anodic oxidation sequence.

On the other hand, when the electrolysis is performed with alcohols as a starting material, the requirement for a redox catalyst and a higher loading of *p*-TsOH•H_2O might imply the involvement of different reaction mechanisms. To better understand the reactivity and selectivity, the oxidation potentials of substrates, intermediate and catalyst were tested, respectively, in MeCN with Bu_4NClO_4 as the electrolyte (0.1 M) and Ag/Ag^+ as the reference electrode. First, benzylic alcohol demands a rather high potential (Ep/2 = 2.29 V vs Ag/Ag^+) to be oxidized directly on the anode, followed by intermediate **7** (0.82 V) and starting material **1a** (0.70 V). This data explains why the desired reaction doesn't proceed when performed under direct electrolysis (C.P.E., 1.0V) without TEMPO, which has an oxidation potential as low as 0.398 V (Scheme 2B). Interestingly, when the reaction media was acidified with *p*-TsOH•H_2O (10 mol%), the oxidation potential of **1a** increased drastically, while that of **7** remained unchanged. This result suggests that the acid not only promotes the cyclization step, but also prevents **1a** from being directly oxidized. Next, the simple oxidation of a mono-deuterated benzyl alcohol **4f**-d_1 was examined under the reaction conditions. A primary kinetic isotope effect (KIE, *k*H:*k*D = 6.08) was observed when TEMPO (2 mol%) served as a catalyst, while no aldehyde was detected in the absence of TEMPO (Scheme 2C), proving the alcohol oxidation to be a typical TEMPO-mediated indirect electrolysis process.



Scheme 2. Mechanistic Related Control Experiments

Even with the above observations, it still remains unclear that whether TEMPO also plays a role in the second dehydrogenation step, which has been proven feasible under direct electrolysis (C.P.E., 1.0 V). In order to address this problem, we utilized several special substrates as mechanistic probes. In the reaction of pivalaldehyde, a *tert*-butyl eliminated **3ap** was isolated as the major product along with desired one **3as** through direct electrolysis (Table 2, entry 5). Therefore, we examined the reaction of 2-*tert*-butyl dihydroquinazolinone **8** under different conditions (Scheme 2D). Notably, **8** can be oxidized by 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoro borate ($TEMPO^+BF_4^-$) (1.5 equiv.) and the chemical oxidation predominately afford the dehydrogenation product **3as**, with only trace amount of fragmentation product **3ap**. Essentially the same products distribution was observed when the anodic oxidation was performed with TEMPO (10 mol%) as a mediator (C.P.E., 0.4 V). As a reference, in the absence of TEMPO, the oxidation doesn't occur at this potential. Next, a 50% deuterium-labeled dihydroquinazolinone **7** was also employed to further understand the mechanistic nuances (Scheme 2E). No distinct KIE was observed when the oxidation was conducted under direct electrolysis (controlled potential, 1.0 V, *k*H:*k*D ≈ 1.0–1.1), while the chemical oxidation by $TEMPO^+BF_4^-$ evidently favors the non-deuterated isotopomer (*k*H:*k*D = 1.9). When the reaction was carried out at lower potential (C.P.E., 0.4 V), TEMPO (10 mol%) was proven indispensable, and a similar KIE with the chemical oxidation (*k*H:*k*D = 1.9) was determined. These two sets of control experiments strongly suggest the second oxidation step is catalytically controlled by TEMPO when an appropriate potential was applied. In addition, as the C–H cleavage is an essential step in the TEMPO mediated oxidation, we proposed to examine the reaction of cyclopropyl dihydroquinazolinone **10** under both direct and indirect electrolysis to verify if this event went through tandem single electron transfer events or a concerted two-electron pathway (Scheme 2F). The direct electrolysis led to several non-identifiable side products along with the dehydrogenation product **11**, whereas the TEMPO-catalyzed one was decisively more selective and furnished **11** as the sole product in 85% yield.

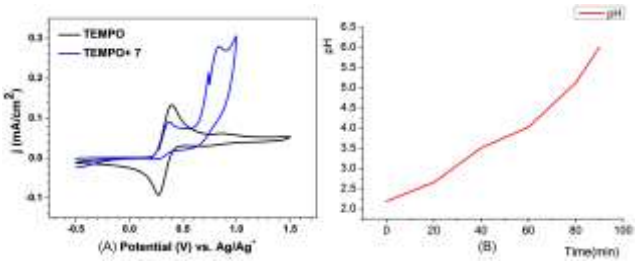
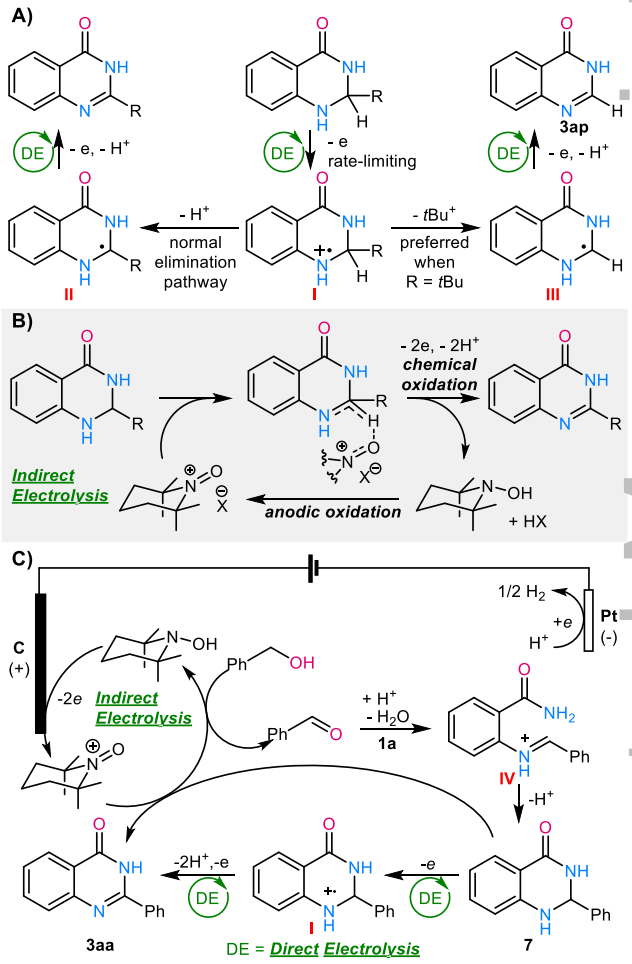


Figure 2. The Cyclic Voltammograms and the pH Trend.

Furthermore, the voltammograms of TEMPO were recorded in the presence and absence of 2-phenyl dihydroquinazolinone **7**, respectively (Figure 2A). The addition of intermediate **7** (Ep/2 = 0.82 V vs Ag/Ag^+) resulted in the disappearance of the reduction wave in the voltammogram. These data may serve a direct evidence that dihydro-quinazolinone **7** is oxidizable by the in situ formed $TEMPO^+$ salt. Moreover, the pH of the reaction process was monitored by a pH meter and the increasing value suggested that the protons generated from anodic oxidation were seemingly reduced on cathode to release H_2 throughout the reaction (Figure 2B).



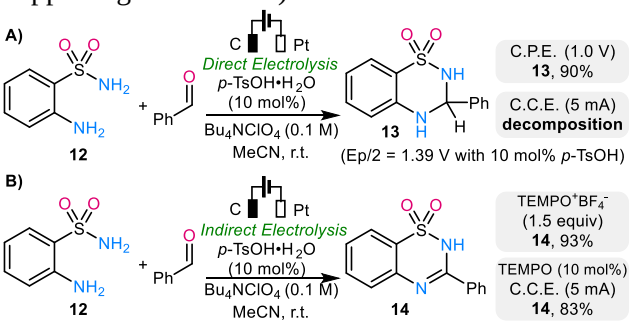
Scheme 3. Plausible Reaction Mechanism.

Based on these observations above, we propose a plausible mechanistic working hypothesis as illustrated in Scheme 3. In the direct electrolysis scenario, the first electron transfer should occur on the nitrogen atom, resulting an amine radical cation species **I**. In most cases, this radical cation eliminates a proton to form a more stable radical intermediate **II**,[21] and further loses one electron and a proton to afford the final product. When a *tert*-butyl group is present, a more stable tertiary carbocation would be preferentially eliminated to generate radical **III**, which then leads to **3ap**. The missing isotope effect

in the direct oxidation of **7**, in turn, suggested that the elimination step may take place promptly once the amine radical cation was formed (Scheme 3A). On the other hand, there are mechanistic differences between the indirect and direct electrolysis processes. Since the TEMPO-mediated oxidation reactions of alcohols are already well-documented in literature,[22] the mechanistic discussion here will be focused on the second oxidation step. In the TEMPO-mediated case, the suppression of the *tert*-butyl elimination product, together with a certain isotope effect, suggest the oxidation proceeds through a C–H bond cleavage, which is involved in the rate-limiting step. According to the mechanism of alcohol and amine oxidation,[23] we believe that the $TEMPO^+$ salt oxidizes the dihydroquizolinone in a similar concerted two-electron pathway, without generating radical or radical cation species (Scheme 3B). This hypothesis is also supported by the highly selective oxidation of **10**, which bears an adjacent cyclopropyl group.

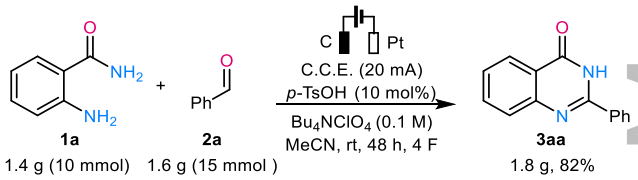
Overall, taking the benzyl alcohol participated indirect electrolysis as an example, the proposed reaction process is summarized in Scheme 3C. 2,2,6,6-Tetramethylpiperidin-1-ol easily loses two electrons and two protons on the anode at relatively low potential (above 0.4 V). The resulting $TEMPO^+$ species serves as a potent chemical oxidant, converting benzylic alcohols to benzaldehydes, which would then rapidly cyclize with 2-aminobenzamides **1a** to form dihydroquizolinone **7** under the catalysis of *p*-TsOH. Next, compound **7** could be oxidized by the catalytically regenerated $TEMPO^+$ salt. However, the direct electrolysis pathway cannot be ruled out, especially when potential is above 0.82 V. In the virtual reaction processes, both pathways are possible, depending on the reaction conditions.

After examining the mechanistic differences between direct and indirect electrolysis, we decided to re-investigate the unsuccessful or less efficient substrates in the direct electrolysis. The reaction of 2-aminobenzenesulfonamide **12** used to stop at the aminal stage (C.P.E., 1.0 V). It turned out **13** requires a relatively high potential (1.39 V vs Ag/Ag^+) under the reaction conditions to be oxidized to a radical cation, probably due to the strongly electron-withdrawing nature of the sulfonamide group. However, if a constant current (5 mA) was applied, **13** was oxidized unselectively to decomposition products (Scheme 4A). Fortunately, this oxidation was made possible by using $TEMPO^+BF_4^-$ (1.5 equiv.) as a chemical oxidant, offering the desired product **14** in excellent yield. Additionally, the constant current electrolysis (5 mA) in the presence of catalytic amount of TEMPO was also proven to be effective [24] to afford **14** in comparable yield (Scheme 4B). Furthermore, we also re-evaluated a few substrates that suffered unsatisfactory yields in Table 2 (**3fa**, **3be**, **3bg**, **3bi** and **3bl**), an average 10% yield bump was observed when TEMPO (10 mol%) was used as an mediator under constant current electrolysis (C.C.E. 5 mA, for details, see the Supporting Information)



Scheme 4. The Reaction of 2-Aminobenzenesulfonamide**.**

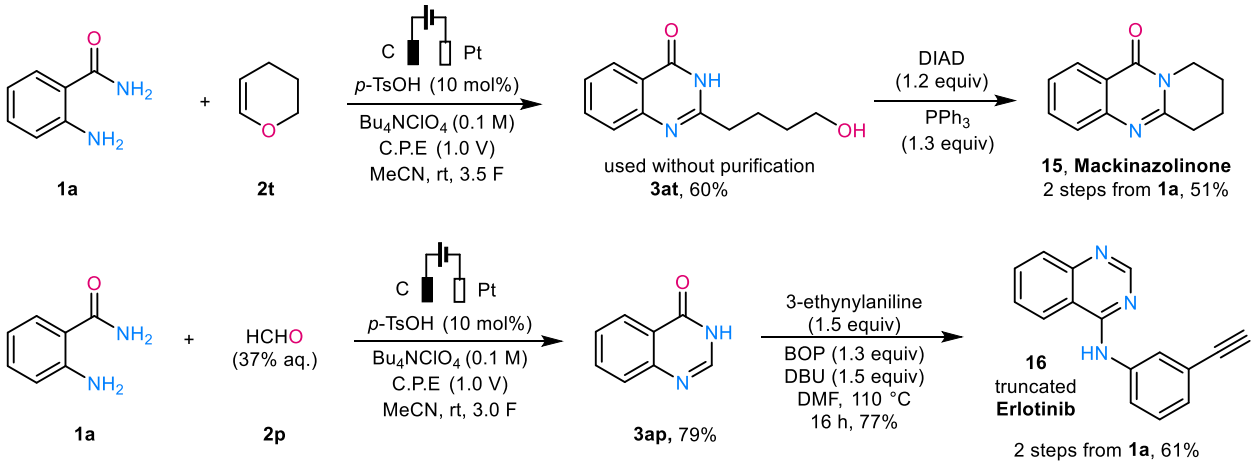
To verify the synthetic utility of our method, the reaction of **1a** and **2a** was performed on 10 mmol scale. Product **3aa** was smoothly produced using a constant current (20 mA) in 82% yields (Scheme 5), which is a proven useful *β*-glucuronidase inhibitor[25]. Next, we successfully applied this method to the one-pot synthesis of mackinazolinone **15** in 51% overall yield. Moreover, *N*-(3-ethynylphenyl) quinazolin-4-amine **16**, which is a truncated version of an anti-cancer drug Erlotinib (Figure 1), was obtained in 61% yield over two steps (Scheme 6).



Scheme 5. Gram-Scale Synthesis of **3aa.**

Conclusion

In summary, we have developed a metal-free and oxidant-free method for the synthesis of quinazolin-4(3*H*)-ones by combining acid-catalyzed annulation and direct electrochemical dehydrogenation with 2-aminobenzamides and aldehydes as starting materials. The analogous reaction can also be achieved with 2-aminobenzamides and benzyl alcohol in one-pot, through TEMPO-mediated indirect anodic oxidation/cyclization/dehydrogenation cascade. Meticulous mechanistic studies reveal that different mechanisms are involved in the direct and indirect electrolysis. Direct anodic oxidation is presumably initiated by a single electron transfer from nitrogen atom to anode to form a radical cation intermediate, while TEMPO mediated indirect electrolysis possibly goes through a concerted hydride transfer. A variety of quinazolin-4(3*H*)-ones including biologically active molecules could be readily prepared with these two procedures under mild and environmentally benign conditions. Further application of the electrochemical dehydrogenation strategy in organic synthesis is underway in our laboratory.



Scheme 6. Synthetic Applications of this Annulation/Anodic Oxidation Cascade.

Experimental Section

General procedure A for the eletrochemical synthesis of quinozolinones from 2-aminobenzamide and aldehyde. To an oven-dried 10 mL test tube charged with a magnetic stir bar, a graphite anode (6.0 mm graphite rod), a platinum plate (1 cm × 1 cm × 0.1 cm) cathode and a Ag/Ag^+ reference electrode were added a 2-aminobenzamide **1** (0.20 mmol), an aldehyde **2** (0.30 mmol), *p*-TsOH·H_2O (3.4 mg, 0.02 mmol), and an electrolyte solution (Bu_4NClO_4 in MeCN, 0.1 M, 8.0 mL). The electrolysis was carried out at room temperature under a constant potential (1.0 V vs Ag/Ag^+) until complete consumption of the substrate **1** and 2,3-dihydroquinazolin-4(1*H*)-one which is produced by annulation (monitored by TLC). The reaction mixture was concentrated *in vacuo*. The residue was purified through silica gel column chromatography with petroleum ether (PE)/ethyl acetate (EtOAc) as eluent to give the desired product **3**.

2-Phenylquinazolin-4(3*H*)-one (**3aa**) was prepared through the reaction of benzaldehyde, 2-aminobenzamide according to general procedure A. Compound **3aa** was isolated through a silica gel column chromatography (PE: EtOAc from 5:1 to 2:1) as a white solid (40 mg, 93% yield, m.p. 234–235 °C) which is a known compound[10c] and the characterization data are in accordance with the literature; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (br, s, 1H), 8.21 – 8.17 (m, 3H), 7.87 – 7.83 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.63 – 7.51 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.7, 152.8, 149.2, 135.1, 133.2, 131.9, 129.1, 128.2, 128.0, 127.1, 126.3, 121.5.

The characterization data of other products **3** included in Table 2 are described in the *Supporting Information*.

General procedure B for the eletrochemical synthesis of quinozolinones from 2-aminobenzamide and benzyl alcohol. To an oven-dried 10 mL test tube charged with a magnetic stir bar, a graphite anode (6.0 mm graphite rod), a platinum plate (1 cm × 1 cm × 0.1 cm) cathode were added 2-aminobenzamide **1a** (27 mg, 0.20 mmol), benzyl alcohol **4** (0.40 mmol), TEMPO (3.1 mg, 0.02 mmol), *p*-TsOH·H_2O (8.6 mg, 0.05 mmol), electrolyte solution (Bu_4NClO_4 in MeCN, 0.1 M, 8.0 mL). The electrolysis was carried out at room temperature under a constant current (5 mA), as more corresponding benzaldehyde was generated (monitored by TLC, around 4 h, 1.5 F), the other portion of *p*-TsOH·H_2O (8.6 mg, 0.05 mmol) was added. Then the electrolysis was continued until complete consumption of the substrate **1a** 2,3-dihydroquinazolin-4(1*H*)-one which is produced by annulation (monitored by TLC). The reaction mixture was concentrated *in vacuo*, and the residue was purified through silica gel chromatography with PE/EtOAc as eluent to give the desired product **5**.

2-(*p*-tolyl) Quinazolin-4(3*H*)-one (**5ab**) was prepared according to procedure B through the reaction of *p*-tolylmethanol and 2-aminobenzamide. Compound **5ab** was isolated through a silica gel column chromatography (PE: EtOAc from 5:1 to 2:1) as a white solid (38 mg, 81% yield, m.p. 239–241 °C) which is a known compound[10c] and the characterization data are in accordance with the literature; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (br, s, 1H), 8.16 (d, J = 7.6 Hz, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.86–7.82 (m 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.54–7.50 (m, 1H), 7.36 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8, 152.7, 149.3, 141.9, 135.0, 130.4, 129.6, 128.1, 127.9, 126.8, 126.3, 121.4, 21.5.

The characterization data of other products included in Table 4 are described in the *Supporting Information*.

General procedure for gram-scale synthesis of 3aa.

The gram-scale electrolysis was conducted in 50 mL round-bottom flask using a graphite anode (6.0 mm graphite rod), and a platinum plate (2 cm × 2 cm × 0.1 cm) cathode and a constant current of 20 mA (j_{anode} =1.67 mA·cm^{-2}). The cell was charged with 2-aminobenzamide **1a** (1.35 g, 10 mmol), benzaldehyde (1.5 g, 15 mmol), *p*-TsOH·H_2O (172 mg, 1 mmol), electrolyte solution (Bu_4NClO_4 in MeCN, 0.1 M, 50 mL), the electrolysis was carried out at room temperature for 36 h. After completion, the precipitate in solution was collected by filtration. Recrystallization in ethanol and filtration afforded the first batch of **3aa** (1.53 g, 69%). The filtrates were then concentrated *in vacuo*, purified though column chromatography to provide additional **3aa** (0.27g, 13%).

Synthetic applications

Mackinazolinone (15). To an oven-dried 10 mL reaction tube charged with a magnetic stir bar, a graphite anode (6.0 mm graphite rod), a platinum plate (1 cm × 1 cm × 0.1 cm) cathode and a Ag/Ag^+ reference electrode were added 2-aminobenzamide (135 mg, 1.0 mmol), 3,4-dihydro-2*H*-pyran (92 uL, 1.2 mmol), *p*-TsOH·H_2O (34 mg, 0.2 mmol), electrolyte solution (Bu_4NClO_4 in MeCN, 0.1 M, 8.0 mL). The reaction mixture was stirred for 2 h at room temperature, then the electrolysis was carried out at room temperature under a controlled potential of (1.0 V vs Ag/Ag^+) until complete consumption of the substrate (electricity = 3.5 F). Then diisopropyl azodicarboxylate

(222 mg, 1.1 mmol) and triphenylphosphine (315 mg, 1.3 mmol) was added to the above reaction mixture. The reaction mixture was stirred at room temperature and monitored by TLC. After completion, the mixture was concentrated *in vacuo*, and the residue was purified through silica gel chromatography (PE:EtOAc = 5:1) to give product **15** (111 mg, 85%, m.p. 88–91 °C) which is a known compound[26] and the characterization data are in accordance with the literature; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 2.01 – 1.93 (m, 2H), 1.93 – 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 153.9, 146.3, 133.2, 125.6, 125.3, 125.1, 119.4, 41.3, 30.9, 21.1, 18.3.

***N*-(3-ethynylphenyl)quinazolin-4-amine (16).** Quinazolin -4(3*H*)-one (**3ap**) was prepared through the reaction of formaldehyde, 2-aminobenzamide according to general procedure A. To an oven-dried 10 mL reaction tube charged with a stir bar were added **3ap** (150 mg, 1.0 mmol), BOP (CAS NO. 56602-33-6, 575 mg, 1.3 mmol,), 3-Aminophenyl-acetylene (140 mg, 1.5 mmol), DMF (2 mL), then DBU (230 mg, 1.5 mmol) was added drop-wise. The reaction mixture was stirred at 110 °C for 16 h and then cooled down, 20 mL water was added, the organic layer was extracted with EtOAc (20 mL) and collected organic phase was washed with brine (15 mL × 3), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and then purified through silica gel chromatography (PE:EtOAc = 5:1) to afford the **16** as a pale yellow solid (189 mg, 77% yield, m.p. 179–181 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.70 (s, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 8.02 – 7.97 (m, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 4.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 154.8, 150.1, 140.0, 133.6, 129.4, 128.3, 127.2, 126.8, 125.4, 123.4, 123.2, 122.3, 115.6, 84.0, 81.1; IR ν_{max} (neat)/cm^{-1}:3495, 3310, 3212, 2923, 2106, 1621, 1578, 1540, 1442, 1390, 767, 677; HRMS (ESI/FT-ICR, m/z): calcd for $C_{16}H_{11}N_3Na^+$ [M + Na]$^+$ 268.0845, found. 268.0845.

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[17] Usually a reaction tube charged with a stir bar. For the reaction set-up details and images, see the Supporting Information.

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FULL PAPER

One-Pot Synthesis of Quinazolin-4(3*H*)-ones through Anodic Oxidation and the Related Mechanistic Studies

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Liu Cao, Hengrui Huo, Haipeng Zeng, Yu Yu, Dengfu Lu* and Yuefa Gong*