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Synthesis of quinazolin-4(*3H*)-ones via electrochemical decarboxylative cyclization of α-keto acids with 2-aminobenzamides

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ABSTRACT

Herein, an environmentally benign electrochemical protocol has been disclosed for the synthesis of quinazolin-4(3H)-one derivatives from readily available α-keto acids and 2-aminobenzamides. This decarboxylative cyclization process proceeds conveniently in the absence of any homogeneous metal catalysts, bases, or external oxidants. This protocol also features CO_2 by-products, mild reaction conditions (room temperature and air atmosphere), and a wide variety of substrate scope, including an array of 2,3-disubstituted quinazolinone products.

Introduction

The α-keto acids (α-oxocarboxylic acids), which play a crucial role in the energy-supplying biochemical processes, such as the Krebs cycle, have been utilized as versatile acylating agents in a plethora of acylation and cyclization reactions in the last decades. With extruded CO_2 as the byproduct, they are accredited to be greener acyl surrogates, compared with the traditionally used counterparts that usually employ stoichiometric activating reagents and lead to undesirable and toxic wastes. Therefore, their use in the synthesis of value-added chemicals has attracted considerable interest from the synthetic community. However, typically, to facilitate the decarboxylation process of α-keto acids, over stoichiometric amounts of oxidants are needed, which necessitates further development of more atom-economic reaction systems [1].

Electrochemical reactions enable the direct interaction between reactants and electrons, thereby bypassing the use of extra oxidants or reductants. This strategy has seen a renaissance in the field of organic synthesis, in the pursuit of more sustainable and environmentally benign synthetic protocols [2–5]. Historically, the Kolbe decarboxylative reaction should be one of the earliest examples of organic electrochemical reactions. However, it is very recently that more other types of electrochemical decarboxylative transformations were investigated, along with the revival of electrosynthesis [6–13]. More specifically, the electrochemical decarboxylation has been found efficient in activating α-keto acids and then transferring acyl groups in the acylation of heterocycles or cyclization reactions [14–18]. These electrochemical approaches not only promote the traditional reactions to be greener but also provide opportunities to achieve previously challenging transformations [19].

On the other hand, the quinazolinone skeleton is one privileged structure in numerous synthetic intermediates, natural alkaloids, and pharmaceuticals of biological and pharmacological activities, such as Methaqualone, Luotonin A, Rutaecarpine, Tryptanthrin, etc (Scheme 1). Consequently, considerable efforts have been made towards their efficient synthesis. Among the established methods, the most commonly used ones have been the fusion of readily available 2-aminobenzamides with aldehydes [20–23] or equivalents, such as alcohols [24–27], methyl arenes [28], amines [29–31], alkynes, CO plus aryl bromides [32], which can *in-situ* lead to similar reactive intermediates with aldehydes [33–37]. Although fruitful, these approaches still suffer from some of the following limitations: the use of stoichiometric or excess amounts of oxidants [38–43], such as TBHP (*tert*-butyl hydroperoxide), H_2O_2, $K_2S_2O_8$, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), in the presence of chemically unstable aldehydes (Scheme 1**a**); requirement for (noble) transition metal catalysts that might result in the contaminant of metal residue in products; high reaction temperature; excess amounts of bases and/or other additives that may lead to more wastes. Therefore, the development of other atom-economic strategies that can employ greener reactants and reagents is still of great significance in the field. As mentioned above, the α-keto acids have been applied as acyl suppliers in diverse reactions [1], and in some cases under electrochemical conditions [4]. However, an inspection into the

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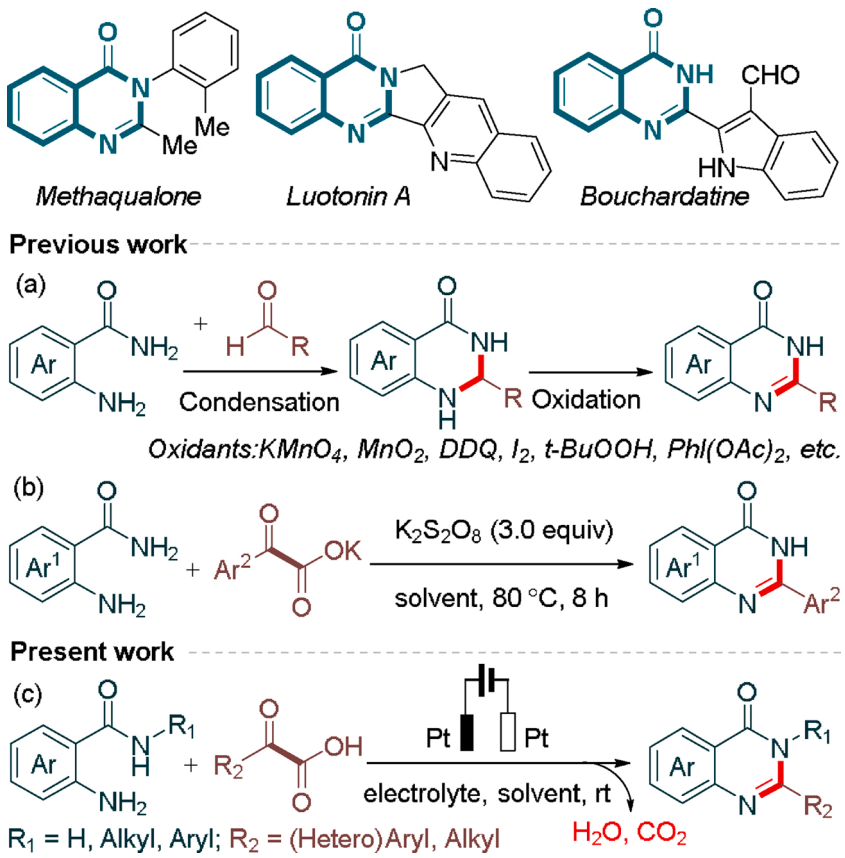
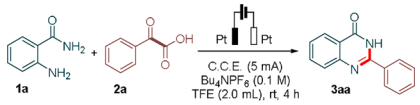


Scheme 1. Biologically active molecules containing the quinazoline-4(*3H*)-one skeleton; Methods for the construction of the quinazolin-4(*3H*)-one skeleton.

Table 1
Optimization of the reaction conditions [a].



Entry	Variations from the standard conditions	Yield [b]
1	None	90 %
2	reaction time: 6 h	56 %
3	CH_3CN	33 %
4	CH_3OH	32 %
5	HFIP	38 %
6	DMF	N.R.
7	DMSO	N.R.
8	Bu_4NBF_4 as electrolyte	85 %
9	Bu_4NClO_4 as electrolyte	73 %
10	Bu_4NAc as electrolyte	trace
11	C/Pt instead of Pt/Pt	40 %
12	C/C instead of Pt/Pt	29 %
13	Pt/GCE instead of Pt/Pt	84 %
14	GCE/C instead of Pt/Pt	trace
15	GCE/GCE instead of Pt/Pt	N.R.
16	I =3 mA	34 %
17	I =8 mA	35 %

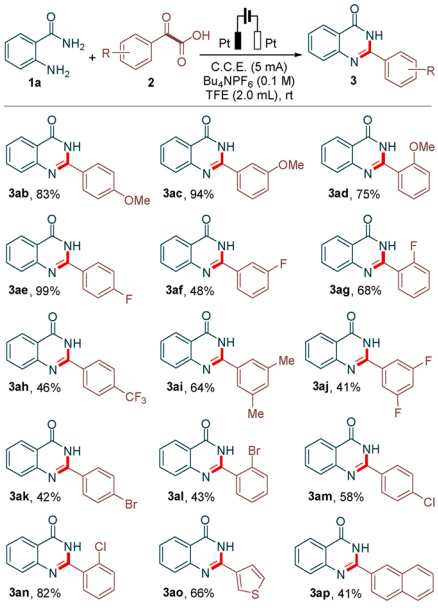
[a] Standard conditions: undivided cell, constant current =5 mA, **1a** (0.20 mmol) and **2a** (0.3 mmol, 1.5 equiv) in Bu_4NPF_6/TFE solution (0.1 M, 2.0 mL), room temperature for 4 h.
[b] Isolated yields.

literature data indicated that they have not been utilized in the synthesis of quinazolinone, except for one case where their potassium salts were used in the presence of $K_2S_2O_8$ (Scheme 1b) [44]. This situation inspired our following efforts [45–48], to activate the α-keto acids using electrochemical technology, and to realize the construction of quinazolinone under transition metal-, oxidant- and bases-free conditions (Scheme 1**c**) [49,50]. Such a strategy should be well consistent with the principles of green chemistry, in terms of atom economy, energy efficiency, catalysis, and safer chemicals and chemistry.

Results and discussion

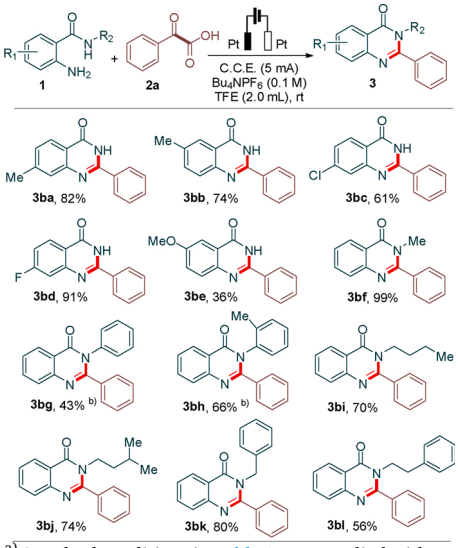
The investigation was initiated by exploring the reactions between 2-aminobenzamides **1a** and 2-oxo-2-phenylacetic acid **2a** (Table 1). The apparatus for electrochemical reaction consists of an undivided cell with a platinum (Pt) anode and a platinum (Pt) cathode. After extensive screening, the desired product **3aa** could be obtained in 90 % isolated yield, under the following conditions: constant current (I =5 mA), 2,2,2-trifluoroethanol (TFE) as solvent, Bu_4NPF_6 as electrolyte [Bu_4NPF_6/TFE (0.1 M, 2.0 mL)], room temperature for 4 h (Entry 1). Variations from these standard conditions would result in inferior outcomes. When the time was extended to 6 h, the yield would be reduced to 56 % (Entry 2), probably due to the electrolytic consumption of the product over time. Using different solvents, such as acetonitrile, methanol, or hexafluoroisopropanol (HFIP), could also lead to the formation of **3aa**, but the yields decreased significantly (around 35 %, Entries 3–5). When DMF or DMSO was used, the formation of **3aa** was fully suppressed (Entries 6, 7). When other quaternary ammonium salts were exploited as electrolytes, it was found that their counter anions played a critical role in this transformation. While the use of Bu_4NBF_4 and Bu_4NClO_4 led to decreased yields by 5 % and 17 %, respectively (Entries 8, 9), the presence of Bu_4NAc inhibited the reaction, affording only trace of the product (Entry 10). Using the graphite electrode instead of one platinum electrode, the yield of **3aa** fell to 40 % (Entry 11). Also, other electrode combinations, such as C/C, Pt/GCE (glassy carbon electrode), resulted in decreased yields or no reactivity. When the current was regulated to 3 mA or 8 mA, also, a substantial decrease in the yield was obtained

Table 2
Substrate scope of α-keto acids [a].



[a] Standard conditions in Table 1 were applied with extended reaction time (6 h).

Table 3
Substrate scope of 2-aminobenzamides [a].



[a] Standard conditions in Table 1 were applied with extended reaction time (6 h); [b] Et_4NPF_6 as the electrolyte.

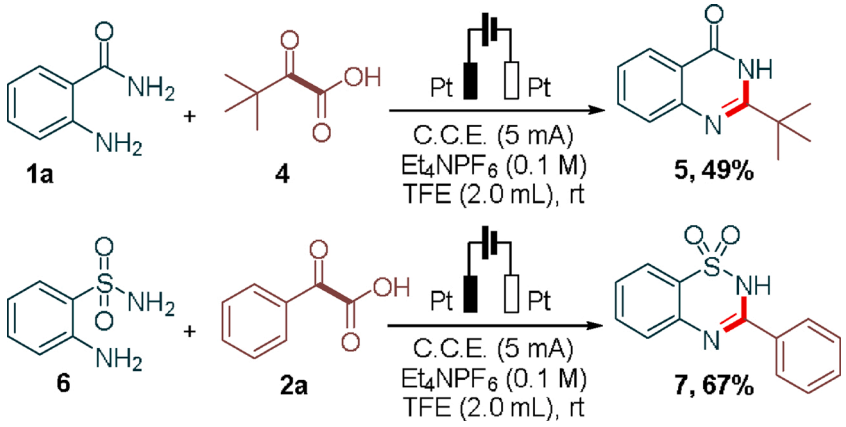
(Entries 16, 17).

After obtaining the optimal reaction conditions, we began to explore the substrate scope of this transformation.

First, 2-aminobenzamide **1a** was treated with a series of 2-(hetero) aryl α-keto acids. The results were illustrated in Table 2. As indicated, when the phenyl rings of α-keto acids were substituted by the electron-donating methoxy group, the transformations proceeded efficiently, regardless of the substitution pattern (*para*-, *meta*- or *ortho*-) of the starting materials. Correspondingly, **3ab**, **3ac** and **3ad** could be isolated in 83 %, 94 % and 75 % yields, respectively. The situation remained unchanged when a typical withdrawing substitution, the fluorine atom, was used. However, in this case, the divergence of isolated yields was much more obvious. While 2-(4-fluorophenyl)-2-oxoacetic acid led to the decarboxylative cyclization product **3ae** in 99 % yield. Its *meta*-substituted counterpart only afforded the corresponding product **3af** in 48 % yield. Disubstituted substrates, which also contained electron-donating or withdrawing groups, were also attempted to obtain **3ai** and **3aj** in moderate yields. It should be noted the bromine and chlorine atoms on the phenyl rings were well compatible with the reaction conditions. The obtained halide-substituted quinazolinones (**3ak-3an**) should be ready for further decoration, due to the diverse reactivity of aryl halides. Fortunately, the α-keto acids with hanging thiophen-3-yl and naphthalen-2-yl cycles were also competent to undergo this decarboxylative cyclization process, affording **3ao** and **3ap** in 66 % and 41 % yields, respectively.

The variations of 2-aminobenzamides were then explored (Table 3). In the beginning, the starting materials with different substitution on the phenyl rings were treated with **2a**. When methyl was at the 4- or 5-position of 2-aminobenzamides, the corresponding cyclization products **3ba** or **3bb** could be obtained in similar yields (82 %, 74 %). As anticipated, the halide atoms on 2-aminobenzamides were also compatible, leading to good to excellent yields of products. The reaction yield greatly decreased when 2-amino-5-methoxybenzamide was applied (**3be**, 36 %).

Then, 2-amino-*N*-substituted benzamides were used. In general, moderate to excellent yields could be obtained, no matter the substitution was aromatic or aliphatic groups. Therefore, an array of 2,3-disubstituted quinazolin-4(*3H*)-one products (**3bf-3bl**) were synthesized via this protocol. This should be the first time such compounds were accessed with α-keto acids as acyl surrogates, to the best of our knowledge. Specifically, while 2-amino-*N*-methylbenzamide was almost fully converted into the decarboxylative cyclization product **3bf** (99 %), its *N*-phenyl analogue showed much lower reactivity, affording the corresponding product **3bg** in only 43 % yield. When 2-amino-*N*-(o-tolyl) benzamide applied, 66 % of the product could be obtained. As for the

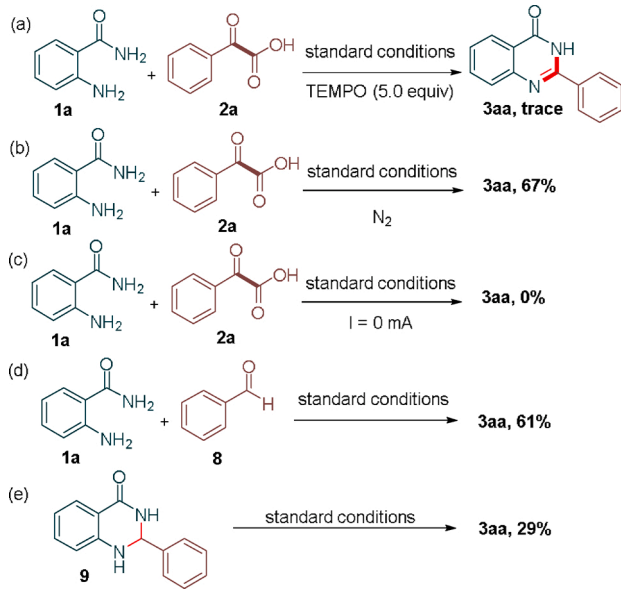


Scheme 2. Further exploration of the substrate scope.

Table 4
The function of electrosynthesis.

Entry	Variation from standard conditions	Yield [a]
1	5 mA, 1 h	14 %
2	5 mA, 1 h +0 mA, 2 h	15 %
3	5 mA, 2 h	33 %
4	5 mA, 2 h +0 mA, 2 h	35 %
5	5 mA, 3 h	50 %
6	5 mA, 3 h +0 mA, 2 h	51 %
7	5 mA, 4 h	90 %
8	5 mA, 4 h +0 mA, 2 h	90 %

[a] Isolated yields.



Scheme 3. Control experiments.

aliphatic substitutions, *n*-butyl, 3-isopentyl, benzyl, 2-phenylethyl were all competent for this transformation, affording products in moderate to good yields.

As shown in Scheme 2, 3,3-dimethyl-2-oxobutanoic acid **4** was also treated with **1a**, and 2-*tert*-butyl-substituted **5** could be obtained 49 % yield, initially confirming the effectiveness of this protocol in handling alkyl α-keto acids. After exploring the substrate scope of 2-aminobenzamide, we turned attention to its sulfonamide analogue. Under slightly-modified conditions, the electrocatalytic reaction between **6** and **2a** led to the decarboxylative cyclization product **7** in 67 % yield.

The mechanism of the reaction was explored by several control reactions. To study the function of current during this transformation, based on the optimal conditions, a series of control experiments were carried out (Table 4). The results showed the transformation from **1** and **2** to **3** was not feasible in the absence of the passing current, indicating its critical role in initiating this reaction.

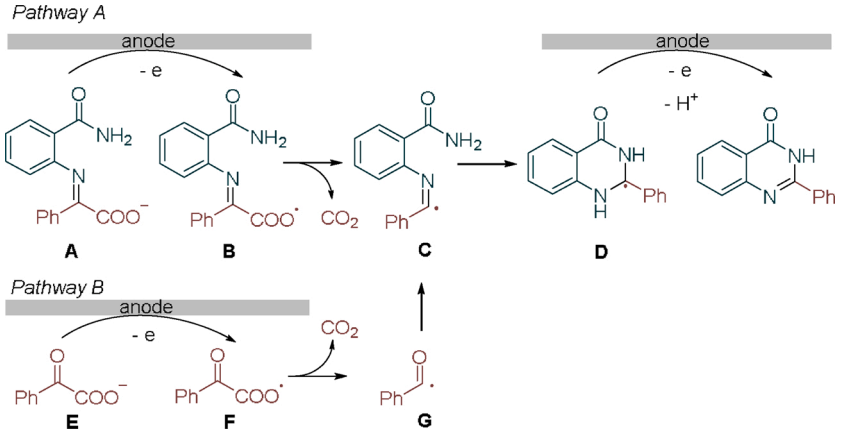
When 5.0 equiv of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO), a radical scavenger, was added into the standard reaction conditions, the formation of the desired product was almost halted (Scheme 3**a**), which implied the involvement of radical species during the reaction. When this experiment was completed under the protection of nitrogen, the yield of product was 67 % (Scheme 3b), which showed the oxidative process was feasible in the absence of air. The electricity was also identified to be critical to this transformation (Scheme 3c). The reaction between **1a** and benzaldehyde under standard conditions led to the formation of **3aa** in 61 % isolated yield (Scheme 3d). In addition, **9** could be oxidized to **3aa** in 29 % yield (Scheme 3e). These results indicated these two reactions might share similar reaction mechanisms/intermediates with the reaction using α-keto acids. Based on the above observations and previous reports, [14–18,49,50] two plausible mechanisms of this electrochemical cyclization were proposed, which were shown in Scheme 4. In Pathway A, the reaction was thought to be initiated by the condensation between 2-aminobenzamides and α-keto acids and the following deprotonation, which would generate carboxylate anion intermediate **A**. The carboxylate moiety then bound to the electrode surface and went through the anodic oxidation process to loss one electron and afford aroyloxy radical intermediate **B**, whose following decarboxylation would give **C**. Then, cyclization of this intermediate constructed the six-membered ring **D**. Finally, the anodic oxidation and deprotonation would occur once again to release the desired product. During this process, H_2 was released on the cathode via the consumption of the proton.

Conclusions

In summary, an efficient electrochemical protocol for the construction of quinazolin-4(*3H*)-one skeleton has been developed herein. Using α-keto acids as the acyl surrogate, an array of quinazolin-4(*3H*)-one derivatives could be accessed under metal catalyst, base, and external oxidant-free conditions at room temperature. This electrochemical methodology is expected to complement the existing methods in the construction of the privilege quinazolinone skeleton.

CRediT authorship contribution statement

Qing Tian: Investigation, Methodology. **Jinli Zhang:** Resources, Supervision. **Liang Xu:** Conceptualization, Writing - original draft. **Yu**



Scheme 4. Plausible reaction mechanism.

Wei: Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

We have no conflict of interest to declaration.

Acknowledgments

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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.mcat.2020.111345.

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