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RESEARCH ARTICLE

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Electrochemical Decarboxylative Addition of *N*-Aryl Glycines to Enaminones: Access to C3-Aminomethyl Chromones

Siyang Han,[a],[b] Chengcheng Fang,[a],[b] Yaoge Zhang,[a],[b] Sifeng Li,*[a],[c] Min Huang,[a] Taimin Wang,[a] Baigang An*[b] and Bin Cheng*[a],[b]

[a] S. Han, C. Fang, Y. Zhang, Dr. S. Li, Prof. Dr. M. Huang, Dr. T. Wang, Prof. Dr. B. Cheng
Institute of Marine Biomedicine, Shenzhen Polytechnic University
Shenzhen 518055, China
E-mail: ifulfill@szpu.edu.cn; chengbin@szpu.edu.cn

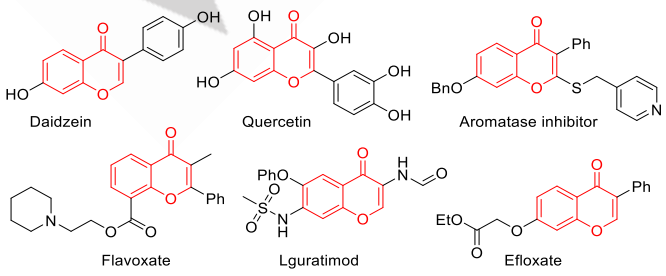
[b] S. Han, C. Fang, Y. Zhang, Prof. Dr. B. An
School of Chemical Engineering, University of Science and Technology Liaoning
Anshan 114051, China
E-mail: bgan@ustl.edu.cn

[c] Dr. S. Li
Institute of Critical Materials for Integrated Circuits, Shenzhen Polytechnic University
Shenzhen 518055, China
E-mail: ifulfill@szpu.edu.cn

Abstract: An electrochemical decarboxylative addition of *N*-substituted glycines to enaminones has been developed and conducted under oxidant-, catalyst-, and light-free conditions in acetonitrile at room temperature by using electron as the traceless oxidant, which provided a green approach to C3-aminomethyl chromones. The resulting products were formed through radical addition/oxidation/cyclization or electrophilic addition/cyclization pathway and could act as valuable building blocks to construct polysubstituted pyrimidine derivatives.

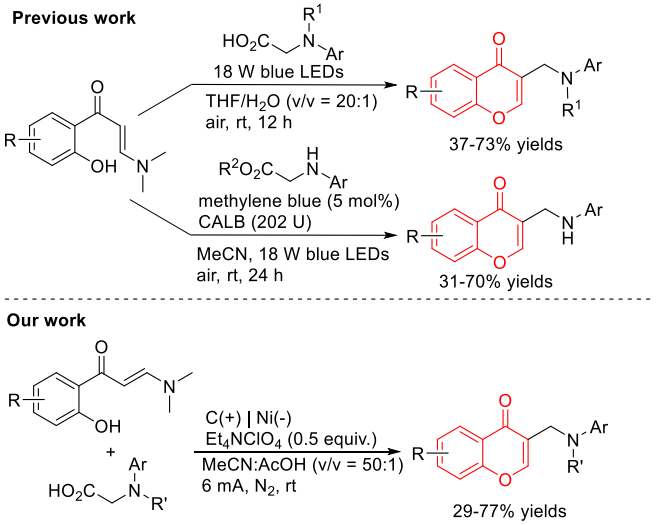
Introduction

Chromone, also referred to as benzo-γ-pyrone, is a highly significant structural motif found in natural products,[1] pharmaceuticals,[2] and compounds with diverse optical applications,[3] which has continuously captured the attention of biochemists and chemists. Over the years, many efforts have been developed to synthesize various valuable chromone derivatives.[4] Particularly, the synthesis of C3-functionalized chromones has garnered continuing attention due to their unique bioactivities[5] (Scheme 1). Among them, the utilization of *o*-hydroxyphenyl enaminone as the starting material has emerged as an efficient strategy.[6]



Scheme 1 C3-Functionalized chromones in natural products and drugs

Selecting enaminones as the precursors of chromone skeletons, except for the example of installing cyano group at the C2-position of chromones,[7] a vast range of carbon-based fragments such as aryl,[8] alkyl,[9] alkynyl,[10] alkenyl,[11] indolyl,[12] furyl,[13] di/trifluoromethyl,[14] and aminomethyl[15] have been successfully introduced at the C3-position. In 2022, Zhu, Xie, and Le developed a blue light-induced decarboxylative cascade cyclization reaction of *o*-hydroxyphenyl enaminones with *N*-arylglycines in the absence of photosensitizers and additives (Scheme 2).[15a] Subsequently, they updated this photocatalysis strategy with Methylene Blue as the photocatalyst, using Lipase B *Candida antarctica* (CALB) to *in situ* generate *N*-arylglycines from *N*-arylglycine esters.[15b] Furthermore, *N*-substituted glycines have also been confirmed as eligible aminomethyl moieties in electrosynthesis.[16] Continuing our interest in *N*-aryl glycines,[16a] herein we will disclose an approach to access C3-aminomethyl chromones using electron as the traceless oxidant under mild conditions.

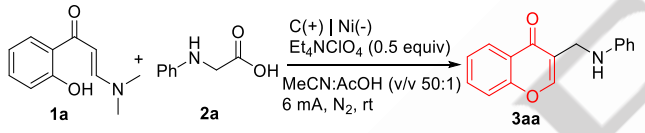


Scheme 2 Previous work and our work on the synthesis of 3-aminomethyl chromones from enaminones

Results and Discussion

Initially, a model electrochemical reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)-2-propen-1-one (**1a**) with *N*-phenyl glycine (**2a**) was first investigated. The major parameters of additive, electrolyte, cathode, and solvent were scrutinized when it was settled under a constant current of 6 mA under nitrogen at room temperature (Table 1). After thorough optimization, it was found that the desired transformation proceeded best in an undivided cell equipped with a graphite anode and a nickel cathode in MeCN with Et_4NClO_4 as the electrolyte and acetic acid as the additive (entry 1), which afforded **3aa** in 77% yield with releasing carbon dioxide, hydrogen, and dimethylamine as the by-products. However, a decrease in AcOH loading resulted in a significant reduction in yield (entries 2 and 3), while using excess AcOH completely blocked the aminomethylation (entry 4). The utilization of electrolytes such as $^nBu_4NBF_4$, $^nBu_4NPF_6$, or $^nBu_4NClO_4$, (entries 5–7) and cathode materials such as iron, zinc, and platinum (entries 8–10) led to a dramatic decrease in reaction efficiency. A decreased yield was afforded under air (entry 11), suggesting that the involvement of oxygen may contaminate the reaction. Screening solvents indicated that DMF and DMSO prohibited the reaction thoroughly (entries 13 and 14), while DCE gave an inferior result (entry 12).

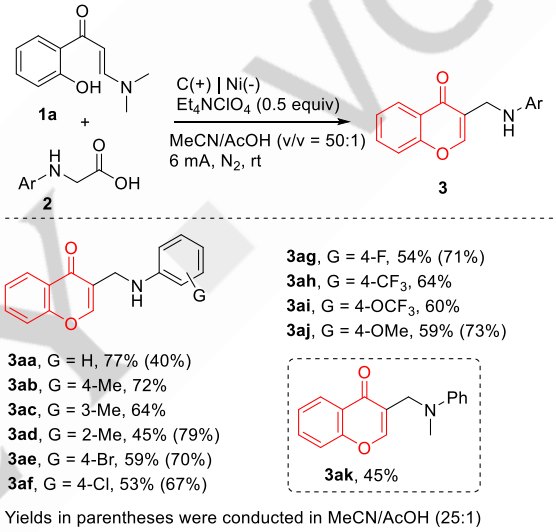
Table 1. Optimization of reaction conditions[a]



Entry	Variation from standard reaction conditions	Time (h)	Yield (%) [b]
1	None	6	77
2	MeCN/AcOH (100:1)	6	70
3	MeCN/AcOH (25:1)	6	40
4[c]	MeCN/AcOH (9:1)	6	trace
5	$^nBu_4NBF_4$ instead of Et_4NClO_4	3.5	71
6	$^nBu_4NPF_6$ instead of Et_4NClO_4	5	11
7	$^nBu_4NClO_4$ instead of Et_4NClO_4	3	35
8	Fe used as cathode instead	3	74
9	Zn used as cathode instead	3	30
10	Pt used as cathode instead	3	66
11	Under air	3	42
12	DCE/AcOH (50:1)	10	22
13	DMF/AcOH (50:1)	10	trace
14	DMSO/AcOH (50:1)	10	trace

[a] Reaction condition: graphite anode, nickel cathode, **1a** (0.2 mmol), **2a** (0.6 mmol), AcOH (100 μL), and Et_4NClO_4 (0.1 mmol) were dissolved in acetonitrile (5 mL), and the mixture was then stirred at 6 mA and room temperature under nitrogen for the indicated time. [b] Isolated yield. [c] Chromone was isolated.

Once the optimal reaction condition was established, a range of *N*-aryl glycines were subjected to this electrochemical reaction system to evaluate its applicability (Scheme 3). It was found that *N*-aryl glycines with different substituents on the phenyl ring such as Me, Br, Cl, F, OCF_3, CF_3, and OMe all proceeded well (**3ab**–**3aj**). Obvious steric effect could be observed from methyl-substituted substrates (**3ab**–**3ad**) and halo-substituted (e.g., Br and Cl) ones were tolerated (**3ae** and **3af**), which could be used for further derivatization. It should be noticed that the extra addition of AcOH could boost yields in most cases, probably because AcOH can suppress the inner salt form of glycines or stabilize the radical intermediates. In addition, *N*-methyl-*N*-phenylglycine was also tolerated in this electrochemical transformation and afforded **3ak** in 45% yield.



Scheme 3 The scope of *N*-aryl glycines

Then, the scope of *o*-hydroxyphenyl enaminones was also investigated (Scheme 4). It was observed that the substrates with distinct substituents (e.g., Me, Br, Cl, F, and OMe) on phenyl moiety gave diminished yields (**3ba**–**3ia**), and the more groups attached on phenyl moiety (**3ba** *vs.* **3ca**; **3ea** *vs.* **3fa**; **3ha** *vs.* **3ia**), the lower yields were isolated. Unfortunately, the strong electron-withdrawing group (NO_2) tethered enaminone could only provide trace amount of desired product **3ja**.

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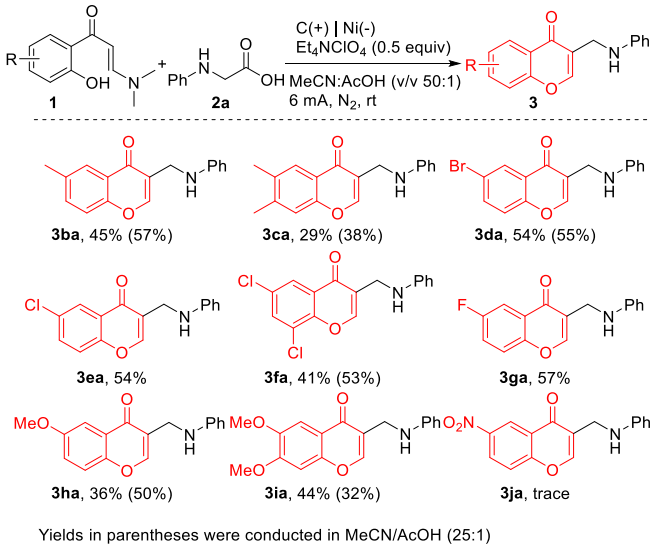
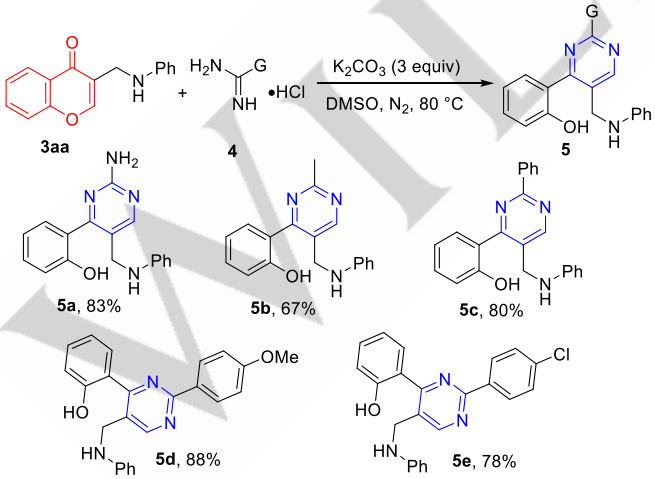


Yields in parentheses were conducted in MeCN/AcOH (25:1)

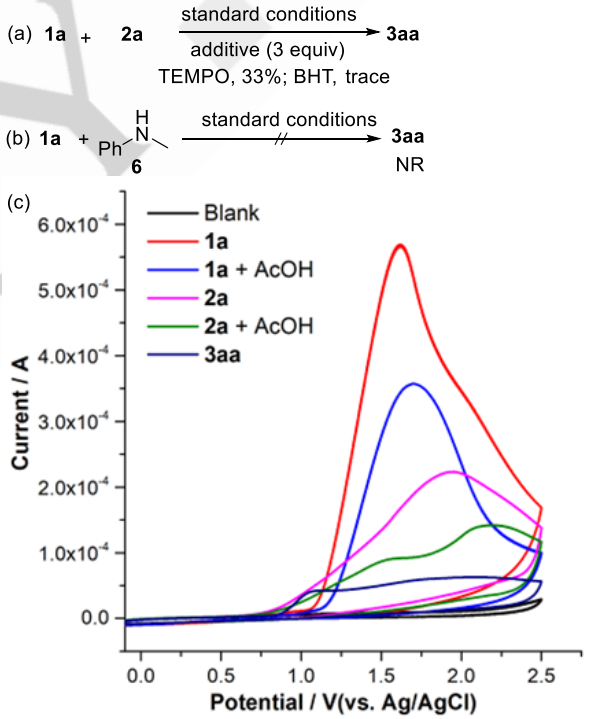
Scheme 4 The scope of *o*-hydroxyphenyl enaminones

To demonstrate the utility of C3-aminomethyl chromones, compound **3aa** was treated with readily available N–C=N synthons such as guanidine or amidines **4** in DMSO in the presence of potassium carbonate under nitrogen. Encouragingly, **3aa** reacted smoothly with **4**, offering aminomethyl pyrimidines **5** *via* a sequence of ring-opening-closure reaction at 80 °C (Scheme 5). Diverse pyrimidine products were obtained in moderate to good yields when guanidine (**5a**), methyl amidine (**5b**), and aryl amidines (**5c**–**5e**) were used. These results indicated that the C3-aminomethyl chromones can act as valuable building blocks to construct pyrimidine derivatives decorated with phenol and aryl aminomethyl groups, which would expand the pyrimidine library of potential bioactivities.



Scheme 5 Derivatization of C3-aminomethylated chromones

To elucidate the reaction mechanisms, several control experiments and cyclic voltammetry (CV) experiments were manipulated to probe the electron transfer/oxidation processes and the redox potentials of the substrates. As shown in Figure 1a, when equivalents of radical scavengers were added as additives, the butylated hydroxytoluene (BHT) resulted in dramatically reduced yield while the 2,2,6,6-tetramethyl piperidinyl-1-oxide (TEMPO) afforded decreased yield. Possibly, TEMPO can act as an alternative oxidant in the case of TEMPO.[17] These results implied that this electrochemical decarboxylative annulation presumably contains a radical pathway. Furthermore, the replacement of **2a** with *N*-methyl aniline **6** led to the failure of the desired product **3aa** (Figure 1b), suggesting that the decarboxylation is crucial to form the hypothetical aminomethylene radical. The CV diagrams in Figure 1 indicated that the involvement of AcOH to enaminone **1a** and *N*-phenyl glycine **2a** resulted in higher starting oxidative voltages (from 1.07 V to 1.14 V for **1a**; from 0.91 V to 0.96 V for **2a**) and higher oxidation peak potentials (from 1.64 V 1.72 V for **1a**; from 1.92 V to 1.49V and 2.09 V for **2a**), but lower catalytic current. These results implied that the treatment of AcOH may suppress the oxidation processes. Interestingly, the addition of AcOH to **2a** produced two distinct oxidation peaks (1.49 V and 2.09 V), suggesting that **2a** probably underwent anodic oxidation twice to deliver active intermediates during electrolysis. Moreover, the product **3aa** began to be oxidized at approximately 0.88 V and reached an oxidation peak at 1.04 V, implying that the annulation product was oxidized more easily on the anode compared to the substrates.

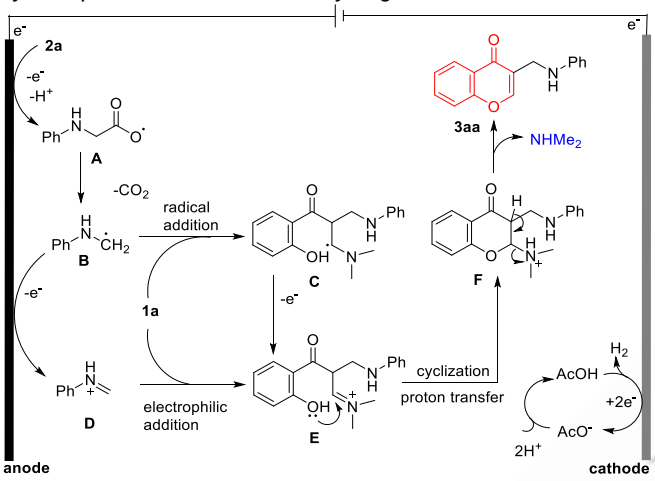


Cyclic voltammetry studies were conducted in a solution of $^{n}Bu_4BF_4$ in MeCN (0.01 M, 5 mL), 0.05 V/s. **1a** (0.2 mmol), **2a** (0.6 mmol), **3aa** (0.2 mmol), and AcOH (100 μL) were used respectively.

Figure 1 Control experiments and CV experiments

With inspiration from literature reports[16a,16b,16d] and mechanistic studies, a plausible reaction mechanism was proposed (Scheme 6). The *N*-phenyl glycine **2a** undergoes sequential anodic oxidation and deprotonation to form a carboxyl radical **A**, which then discharges carbon dioxide to generate the

primary carbon radical **B**. The radical addition of **B** to **1a** gives rise to radical **C**, and then it can afford iminium intermediate **E** *via* further anodic oxidation process. Alternatively, intermediate **B** may undergo further anodic oxidation to give cation intermediate **D**, which combines enaminone **1a** via electrophilic addition to yield iminium **E**. Then, the intramolecular cyclization of intermediate **E** initiated by the nucleophilic addition of OH group to imine cation delivers intermediate **F**. Finally, the C–N bond cleavage of **F** generates the desired product C3-aminomethyl chromone **3aa** accompanying with the elimination of dimethylamine. Simultaneously, the cathodic reduction of hydrion produces the molecular hydrogen.



Scheme 6 Proposed mechanism

Conclusion

In conclusion, we have successfully developed an electrochemical tandem reaction of *N*-aryl glycines with *o*-hydroxyphenyl enaminones to synthesize C3-aminomethyl chromones under oxidant- and catalyst-free conditions, by utilizing electrons as the traceless oxidant. Mechanism studies showed this transformation involved a radical addition/oxidation/cyclization or electrophilic addition/cyclization pathway. Moreover, the products could act as valuable building blocks to construct polysubstituted pyrimidine derivatives with potential bioactivities.

Experimental Section

General Procedure: Enaminone **1** (0.2 mmol, 1 equiv.), *N*-aryl glycine **2** (0.6 mmol, 3.0 equiv.), Et_4NClO_4 (0.1 mmol, 0.5 equiv.), acetic acid (100 μL), and MeCN (5.0 mL) were added into a 10 mL tube equipped with a stir bar. The tube was equipped with a graphite plate (20 mm × 10 mm × 2 mm) anode and a nickel plate (20 mm × 10 mm × 0.2 mm) cathode, and the two electrodes were then submerged in the solution for 10 mm. The reaction mixture was then stirred and electrolyzed at a constant current of 6 mA at room temperature for 3.5 h. After the completion of the reaction as monitored by TLC, the resulting mixture was poured into saturated $NaHCO_3$ (5 mL) before extracting with ethyl acetate (3 × 10 mL). The combined organic phases were washed with saturated brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated to give a residue, which was purified by silica gel column to provide the desired products.

Supporting Information

The authors have cited additional references within the Supporting Information.[18]

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: chromone • enaminone • *N*-aryl glycine • aminomethylation • electrochemical decarboxylation

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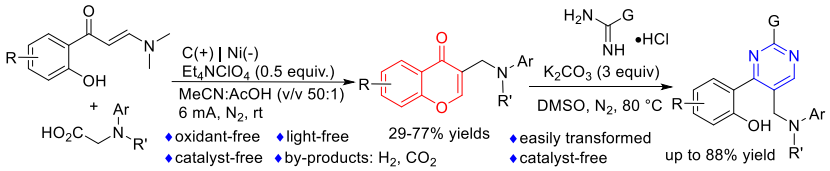

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