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COMMUNICATION

Electrochemical Decarboxylative C3 Alkylation of Quinoxalin-2(1*H*)-ones with *N*-Hydroxyphthalimide Esters

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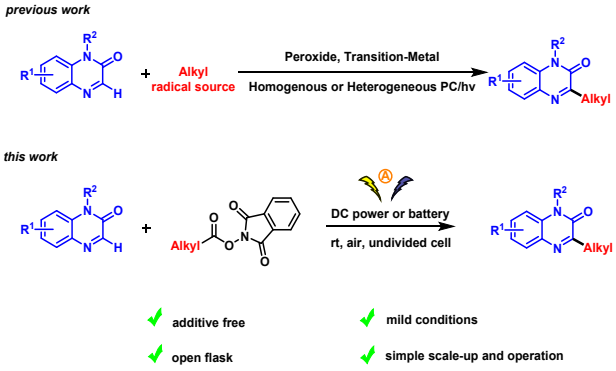
Kaikai Niu,[a] Lingyun Song,[a] Yanke Hao,[a] Yuxiu Liu[a] and Qingmin Wang*[a,b]

We have developed a protocol for electrochemical decarboxylative C3 alkylation of a wide range of quinoxalin-2(1*H*)-ones under metal- and additive-free conditions. *N*-Hydroxyphthalimide esters derived from chain, cyclic, primary, secondary, and tertiary carboxylic acids with a broad scope proved to be suitable substrates. This operationally simple protocol performed in an undivided cell under constant-current conditions is suitable for late-stage functionalization of quinoxalin-2(1H)-ones. The reactions can even be carried out with a 3 V battery as a power source, which demonstrates that organic electrosynthesis can be accomplished without the need for specialized equipment.

New methods and strategies for the direct functionalization of quinoxalin-2(1*H*)-ones[1] and other *N*-heterocycles[2] can greatly fulfill the demand of high-throughput drug screening.[3] The direct C3 alkylation of quinoxalin-2(1*H*)-ones has played a prominent role in this context owing to the utility of C3 alkylated quinoxalin-2(1*H*)-ones as versatile drug candidates.[4] Quinoxalin-2(1*H*)-ones alkylated at C3 have traditionally been synthesized by reactions of 1,2-diaminobenzene derivatives with alkyl-substituted keto esters or acids.[5] In recent years, substantial effort has been devoted to developing methods for direct C3 alkylation of quinoxalin-2(1*H*)-ones[6]. Most of these methods involve addition reactions of alkyl radicals generated from their precursors by means of radical initiators (Scheme 1). However, despite many attempts to improve the practicality and efficiency of these methods, most of them require stoichiometric amounts of oxidants,[7] metal catalysts,[8] or photocatalysts.[9] Therefore, greener and more sustainable methods for direct C3 alkylation of quinoxalin-2(1*H*)-ones would be desirable.

We speculated that electrochemistry could serve this purpose. Electrochemistry, which is a powerful and economical way of forging new chemical bonds, uses electrons as a clean, renewable reagent.[10] The past few years have witnessed booming interest in organic electrosynthesis, and various electrochemical reactions that form C–C,[11] C–N,[12] C–O,[13] and C–S[14] bonds under mild conditions have been reported. Inspired by this elegant work, we have now developed an electrochemical protocol for decarboxylative C3 alkylation of quinoxalin-2(1*H*)-ones with *N*-hydroxyphthalimide (NHP) esters, which are prepared in one step from the corresponding carboxylic acids and served as excellent alkyl radical precursors (Scheme 1).[15]



Scheme 1. Strategies for direct C3 alkylation of quinoxalin-2(1*H*)-ones by means of a radical intermediate.

We commenced our investigation by using 1-methylquinoxalin-2(1*H*)-one (1a) and NHP ester 2a as model substrates to optimize the reaction conditions (Table 1). We were pleased to find that when we used graphite plates as electrodes, dimethylacetamide (DMA) as the solvent, $^{n}Bu_4NBF_4$ as the electrolyte, and a current density of 5 mA/cm^2, desired product 3aa could be obtained in 85% yield by ^{1}H NMR spectroscopy and 92% isolated yield after 12 h under an air atmosphere (entry 1). When we shortened the reaction time, the yield decreased (entries 2 and 3). Decreasing or increasing the current density also lowered the yield (entries 4–7). Evaluation of different solvents revealed that DMA was the best choice (entries 8–10). In addition, control experiments indicated that the current and the electrolyte were essential for this reaction and that it was unaffected by air (entries 11–13). The structure of 3aa was unambiguously confirmed by X-ray analysis (Scheme 2).

[a] *State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China. E-mail: wangqm@nankai.edu.cn*
[b] *Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China*
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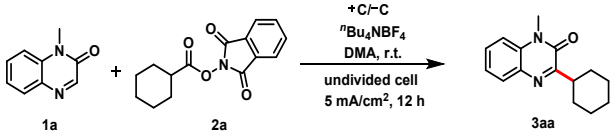
Table 1. Optimization of the reaction conditions[a]



1a 2a 3aa

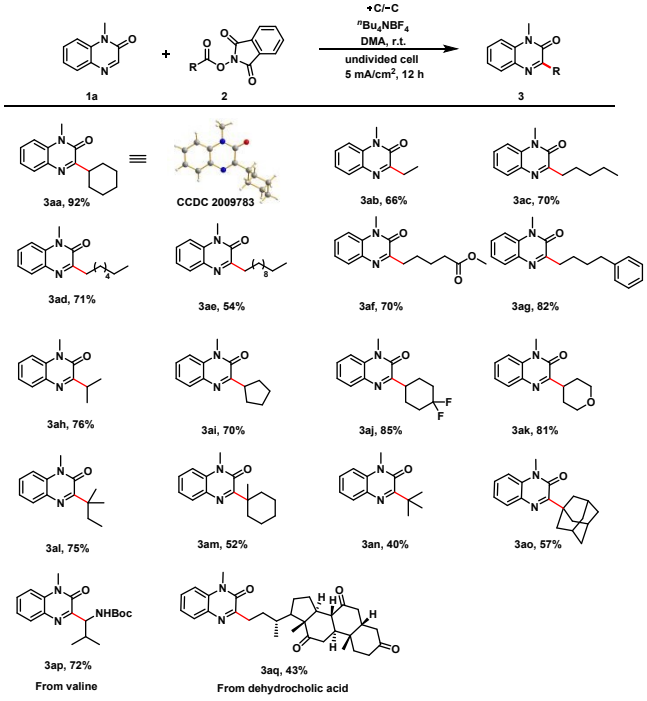
Entry	Variation from standard conditions	Yield[b] (%)
1	none	85 (92[c])
2	1.5 h	13
3	4.5 h	31
4	3 mA/cm^2	62
5	8 mA/cm^2	74
6	10 mA/cm^2	72
7	15 mA/cm^2	15
8	MeCN as solvent	34
9	DMSO as solvent	43
10	DMF as solvent	53
11	No electricity	0
12	No electrolyte	0
13	Under Air	87

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (2.0 equiv), DMA (5 mL), undivided cell with two graphite electrodes (each 1.0 × 1.0 cm^2), room temperature (r.t.), 5 mA/cm^2, 12 h. [b]Yields were determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [c]Isolated yield.

Having optimized the conditions, we investigated the scope of the reaction with respect to the NHP ester (Scheme 2). To our delight, a wide range of chain, cyclic, primary, secondary, and tertiary NHP esters proved to be suitable substrates (**3aa–3ao**). Included were some heterocyclic substrates, which gave products **3aj** and **3ak**. Furthermore, NHP esters derived from valine and dehydrocholic acid were also acceptable, affording **3ap** and **3aq** and suggesting that this method is applicable to other amino acids and natural products.

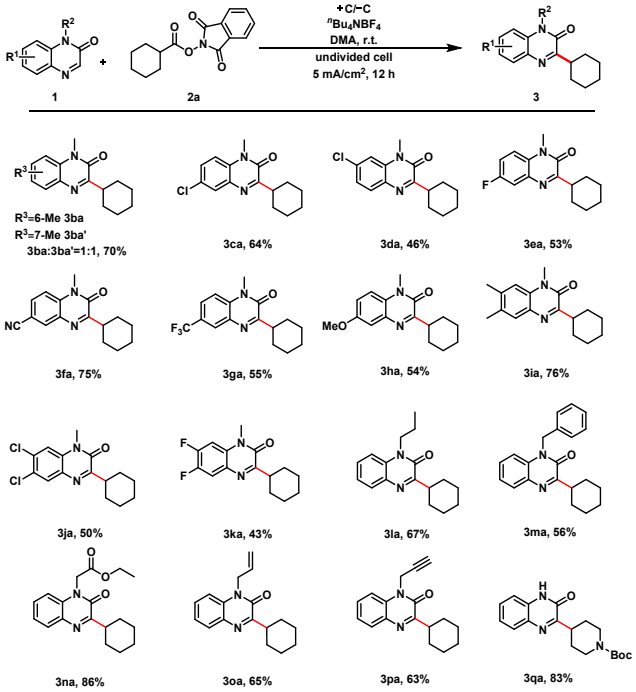
We also investigated the scope with respect to the quinoxalin-2(1*H*)-one (Scheme 3). Substrates **1** bearing various substituents on the aromatic ring (methyl, chloro, fluoro, cyano, methoxy, and trifluoromethyl) reacted smoothly with **2a** under the optimal conditions to produce the corresponding products (**3ba–3ka**) in moderate to good yields. Furthermore, in addition to 1-methylquinoxalin-2(1*H*)-ones, quinoxalin-2(1*H*)-ones bearing an ^{n}propyl, benzyl, or ethoxycarbonylmethylene group on the nitrogen were also suitable substrates, providing **3la–3na**, respectively. It is worth noting that sensitive allyl and alkyne groups were also retained under the reaction conditions (**3oa** and **3pa**). In addition, **3qa** could be synthesized from the corresponding substrate with an unprotected nitrogen atom on the quinoxalin-2(1*H*)-one moiety.

Scheme 2. Substrate scope with respect to the NHP ester[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (2.0 equiv), DMA (5 mL), undivided cell with two graphite electrodes (each 1.0 × 1.0 cm^2), room temperature (r.t.), 5 mA/cm^2, 12 h. Isolated yields are provided.

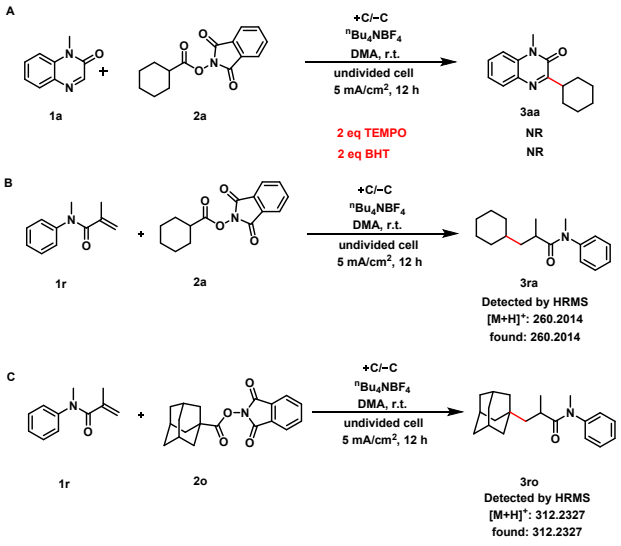
Scheme 3. Substrate scope with respect to the quinolin-2(1*H*)-one[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), ^{n}Bu$_4$NBF$_4$ (2.0 equiv), DMA (5 mL), undivided cell with two graphite electrodes (each 1.0 × 1.0 cm^2), room temperature (r.t.), 5 mA/cm^2, 12 h. Isolated yields are provided.

Having explored the substrate scope, we turned our attention to the mechanism (Scheme 4). First, when 2.0 equiv of a radical inhibitor, TEMPO (2,2,6,6-Tetramethylpiperidinooxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol), was added to the standard reaction mixture (Scheme 4A), alkylation was completely suppressed. When *N*-phenylmethacrylamide (**1r**) was subjected to electrolysis with NHP esters **2a** and **2o** under the standard conditions, radical addition products **3ra** and **3ro** were detected by high-resolution mass spectrometry[16] (Scheme 4B, 4C). These results indicate that this reaction probably proceeded via a radical pathway. Furthermore, cyclic voltammetry showed that the reduction potentials of substrates **1a** and **2a** were −1.67 and −1.23 V (vs. SCE), respectively; that is, **2a** was more easily reduced than **1a** at the surface of the cathode (Figure 1).[1a] The reduction peak of **2a** indicates a reductive pathway for alkyl radical generation.

Scheme 4. Mechanistic studies



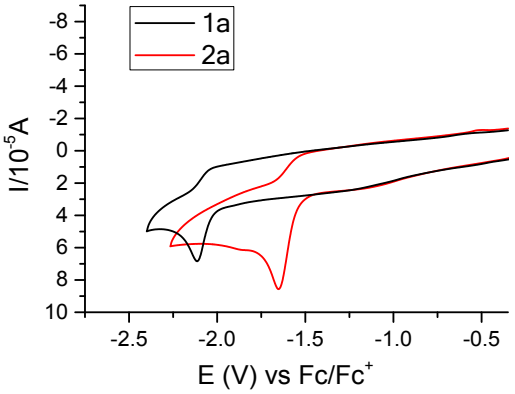
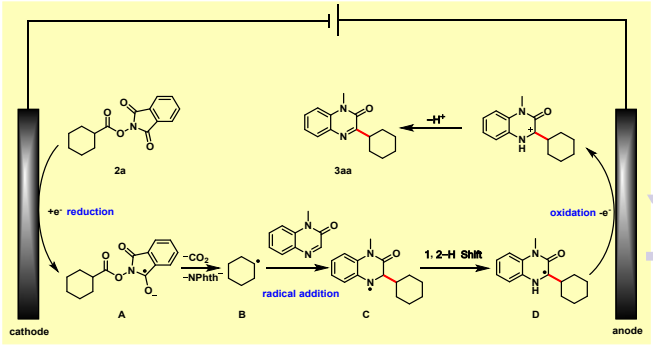


Figure 1. Cyclic voltammograms of **1a** and **2a** in 0.1 M $^{n}Bu_4NPF_6$/MeCN at a scan rate of 100 mV/s. The reduction potentials versus an aqueous SCE ($E^{1a/1a^-}$ = −1.67 V; $E^{2a/2a^-}$ = −1.23 V) were calibrated by the addition of ferrocene (Fc) as an internal standard; $E_{(Fc/Fc+)}{}^{0}$ = 0.424 V vs SCE.[17]

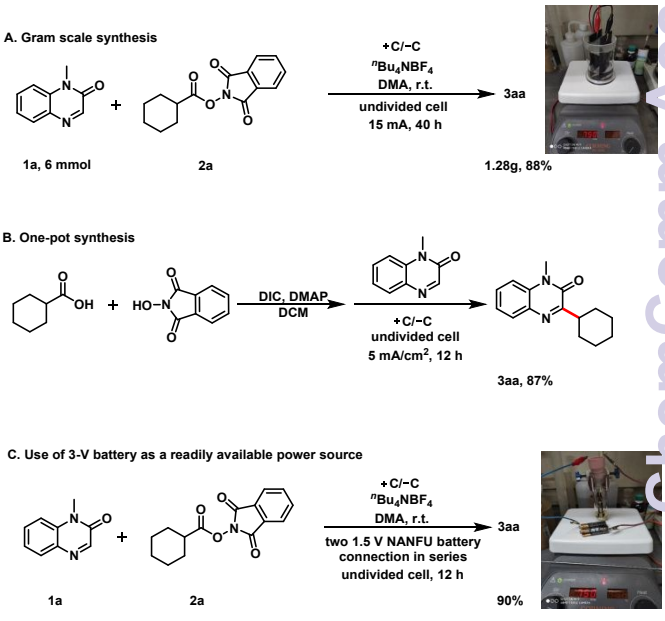
On the basis of literature reports, a proposed mechanistic pathway for this electrochemical decarboxylative C3 alkylation is depicted in Scheme 5. Initially, single-electron reduction of NHP ester **2a** at the cathode generates radical anion **A**, which then undergoes N–O bond cleavage followed by decarboxylation to give corresponding alkyl radical **B**. This reactive species adds to the quinoxalinone to furnish nitrogen-centered radical **C**. Next, a 1,2-H shift gives carbon-centered radical **D**, which undergoes single-electron oxidation at the anode, followed by deprotonation, to give product **3aa**.

Scheme 5. Proposed mechanism



To verify the practicality of this protocol, we carried out a scaled-up reaction. Specifically, when 6.0 mmol of 1-methylquinoxalin-2(1*H*)-one (**1a**) was allowed to react with NHP ester **2a** under the standard condition, **3aa** was isolated in 88% yield, indicating no loss in efficiency (Scheme 6A). In addition, the reaction could be carried out in one pot, without separation of the NHP ester (Scheme 6B). Finally, in a further test of the robustness of this electrochemical reaction, we performed it using a 3 V battery and obtained a 90% yield of **3aa** (Scheme 6C).

Scheme 6. Practicality of the electrochemical method



Conclusions

In conclusion, we have developed a protocol for metal- and additive-free electrochemical decarboxylative C3 alkylation of quinoxalin-2(1*H*)-ones with NHP esters, and we demonstrated its practicality, scalability, and operational simplicity. We believe that this protocol has potential utility for pharmaceutical derivatization and other industrial applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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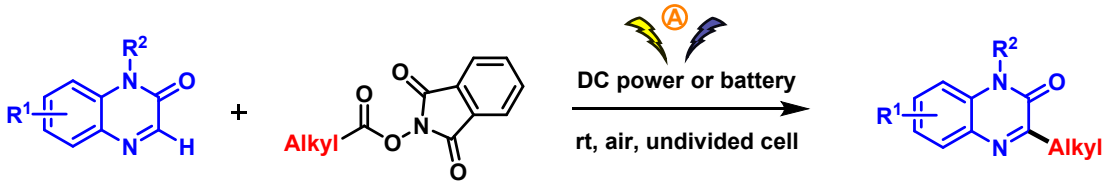

✓ additive free ✓ mild conditions

✓ open flask ✓ simple scale-up and operation

Electrochemical decarboxylative C3 alkylation of a wide range of quinoxalin-2(1*H*)-ones under metal- and additive-free conditions was reported.