Tetrabutylammonium Iodide (TBAI) Catalyzed Electrochemical C–H Bond Activation of 2-Arylated *N*-Methoxyamides for the Synthesis of Phenanthridinones

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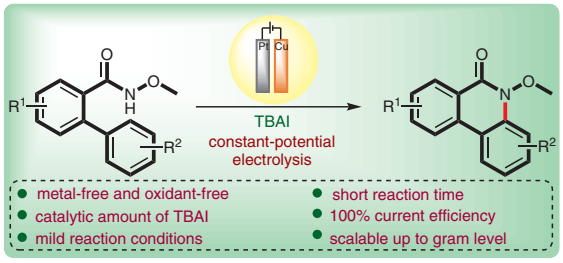


Received: 31.01.2021
Accepted after revision: 25.03.2021
Published online: 25.03.2021
DOI: 10.1055/a-1467-5585; Art ID: st-2021-b0038-l

Abstract An electrochemical method for the synthesis of phenanthridinones through constant-potential electrolysis (CPE) mediated by Bu_4NI (TBAI) is reported. The protocol is metal and oxidant free, and proceeds with 100% current efficiency. TBAI plays a dual role as both a redox catalyst and a supporting electrolyte. The intramolecular C–H activation proceeds under mild reaction conditions and with a short reaction time through electrochemically generated amidyl radicals. The reaction has been scaled up to a gram level, showing its practicability, and the synthetic utility and applicability of the protocol have been demonstrated by a direct one-step synthesis of the bioactive compound phenaglaydon.

Key words tetrabutylammonium iodide, phenanthridinones, amidyl radicals, electrochemistry, C–H bond activation, constant-potential electrolysis

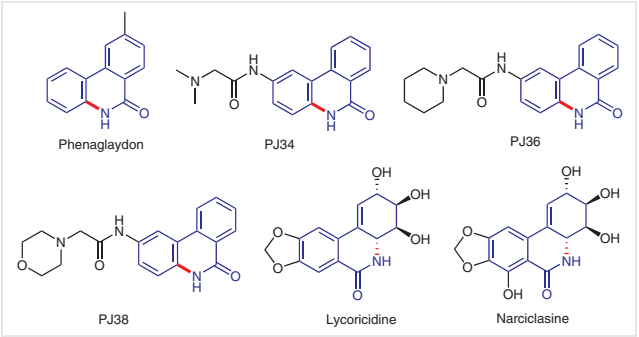


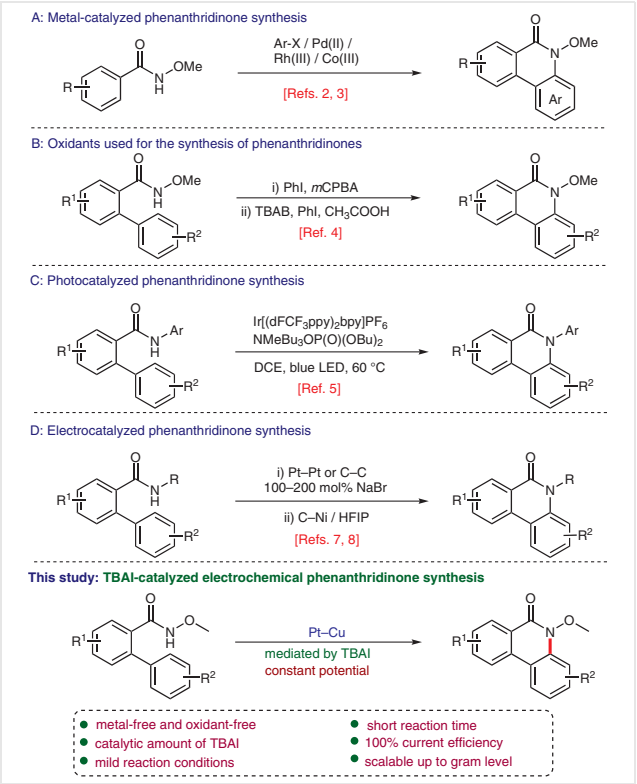
Figure 1 Examples of bioactive molecules having a phenanthridinone skeleton

Phenanthridinone scaffolds are present in many pharmaceutically active compounds[1] (Figure 1) that act as promising steroid surrogates. Moreover, phenanthridinones also show a broad range of other biological activities, including antiinflammatory, antimalarial, antibacterial, anti-HIV, immunosuppressant, and antitumor activities. In view of the unique properties of phenanthridinones, their syntheses have evinced constant research interest.

Of late, phenanthridinones have been synthesized from *N*-alkoxyamides by metal-catalyzed *ortho* arylation with arenes, arylboronic acids, or electron-rich aromatics, followed by intramolecular C–N bond formation (Scheme 1A).[2,3]

However, taking into account the limitations of these metal-catalyzed approaches and their negative impact on the environment, metal-free synthetic approaches have attracted increasing attention. Xue and co-workers[4] simultaneously developed two hypervalent iodine-catalyzed methods (Scheme 1B), and Moon et al.[5] described a photocatalyzed (Scheme 1C) approach to the synthesis of phenanthridinones through direct oxidative C–H aminations.

Being robust and environmentally benign, electrochemical C–H bond-activation reactions have attracted widespread attention in organic syntheses, where conventional metal-catalyzed reactions have been replaced by ones involving an electric current.[6] In 2018, Zeng and co-workers[7] reported a constant-current electrochemical method for the generation of amidyl radicals, which were employed in intramolecular C–H aminations to yield phenanthridin-6-ones (Scheme 1D). However, the reaction was limited to amides containing an *N*-acetyl or *N*-pivaloyl protecting group and it required the presence of a stoichiometric amount of NaBr as a mediator and, in special cases, Na_2CO_3 as an additive. Kehl et al. reported a synthesis of *N*-arylphenanthridin-6-ones by anodic N–C bond formation using directly generated amidyl radicals in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent (Scheme 1D).[8] In these electrochemical methods, deprotection of the synthesized



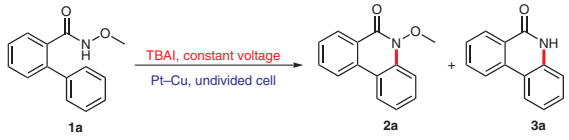
Scheme 1 Several synthetic routes towards phenanthridinones

phenanthridinones to yield the pharmaceutically active phenanthridin-6[5*H*]-one derivatives required additional steps involving conventional chemical methods.

By considering the fact that that iodine-based organic salts are good mediators as well as supporting electrolytes in electroorganic synthesis, we surmised that tetrabutylammonium iodide (TBAI) might be an ideal metal-free redox catalyst for the synthesis of phenanthridinones.[9] Furthermore, amides containing a simple methoxy directing group appeared to be suitable and simple alternatives to those containing pivaloyloxy or acetoxy groups previously used in this electrochemical transformation. On the basis of these ideas, we have developed a constant-potential electrolytic method for the synthesis of phenanthridinones through an intramolecular C–H amination of 2-aryl *N*-methoxyamides that uses a catalytic amount of TBAI as both a mediator and a supporting electrolyte.

Initially, *N*-methoxybiphenyl-2-carboxamide (**1a**) was chosen as the starting material to probe various reaction conditions for the envisioned intramolecular C–H amination reaction in an undivided cell (Table 1). To begin with, the reaction was carried out under constant-current conditions of 9 mA. We observed a decreased selectivity toward the desired product **2a**, as an appreciable amount of the demethoxylated product **3a** was obtained along with **2a** (Table 1, entry 1). It is well known that in all electrochemical reactions, the applied potential plays an important role by acting as the driving force for the reaction and also controls the selectivity toward the desired product.[10] Thus, controlled-potential electrolysis is considered to be more selective than controlled-current electrolysis. Bearing this in mind, to enhance selectivity toward **2a**, further optimizations were performed by using constant-potential electrolysis until 2 F mol^{-1} of electric charge was consumed. After optimization, a 92% yield of the desired product **2a** was obtained by constant-potential electrolysis at 2.5 V in the presence of 20 mol% of TBAI as the redox catalyst and DMF as the solvent at 70 °C (entry 2). It was noted that a further increase in the voltage affected the selectivity toward the desired product. Thus, lower yields of **2a** were obtained at voltages of 4.5 V (**2a**/**3a**: 36:64) and 5 V (**2a**/**3a**: 29:71). Screening of various redox catalysts revealed that TBAI gave the best yield (entries 5–7). An increase in the catalyst loading had little effect on the yield of **2a** (entry 8), whereas a decrease in the catalyst loading increased the duration of electrolysis (time required to achieve 2 F mol^{-1}), even though an appreciable yield of **2a** was still obtained (entry 9). Then, various solvents were examined and DMF was

Table 1 Optimization of the Reaction Conditions[a]

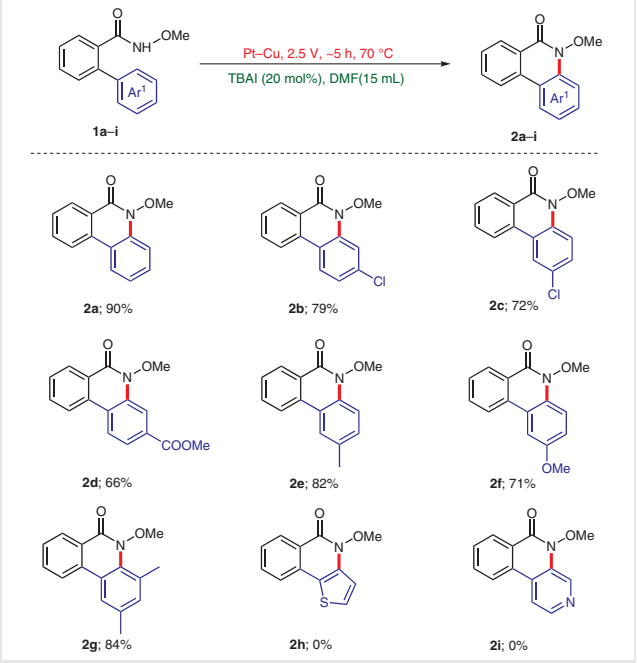


Entry	Variation from standard conditions	Yield[b] of **2b** (%)
1	constant current of 9 mA instead of a constant voltage of 2.5 V	70
2	–	92
3	4.5 V instead of 2.5 V	36
4	5 V instead of 2.5 V	29
5	TBAB instead of TBAI	86
6	Me_4NI instead of TBAI	66
7	KI instead of TBAI	70
8	25 mol% TBAI instead of 20 mol%	92
9	10 mol% TBAI instead of 20 mol%	84
10	MeCN instead of DMF	71
11	propylene carbonate instead of DMF	65
12	60 °C instead of 70 °C	76
13	80 °C instead of 70 °C	92
14	graphite anode instead of Pt	79
15	nickel cathode instead of Cu	71
16	no TBAI	nr
17	no electric current	nr

[a] Standard reaction conditions: **1a** (0.5 mmol), TBAI (20 mol%), DMF (15 mL), undivided cell, Pt plate anode and Cu plate cathode (each of dimensions 3 × 1.5 cm), 70 °C, 2.5 V, 2 F mol^{-1}.
[b] Determined by GC/MS; nr = no reaction.

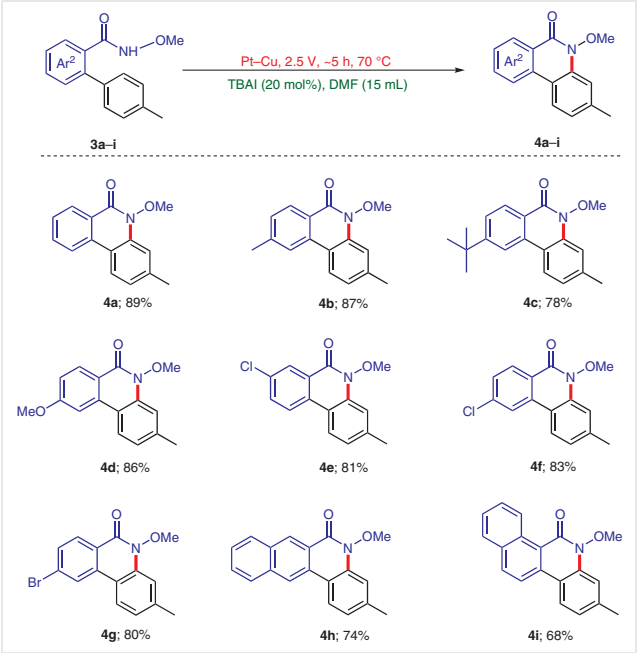
found to be optimal (entries 10 and 11). A lower temperature of 60 °C gave a lower yield due to a lower conversion, whereas a higher temperature of 80 °C did not affect the yield of **2a** (entries 12 and 13). Changing the electrode materials also adversely affected the yield and selectivity toward **2a** (entries 14 and 15). Note that the reaction progressed only in the presence of the redox catalyst, and that passage of an electric current was essential for the reaction to occur (entries 16 and 17).

With the optimized conditions in hand, we investigated the scope of the reaction for 2-arylated *N*-methoxyamides bearing various functionalities on the two phenyl rings. Initially, various substituents on Ar^1 were screened (Scheme 2). Electrochemical C–H amination of *N*-methoxybiphenyl-2-carboxamide (**1a**) gave phenanthridinone **2a** in 90% yield. Both electron-withdrawing and electron-donating substituents were tolerated and moderate to good yields of the corresponding phenanthridinones were obtained. Substrates with a weakly electron-withdrawing chloro group in the *para*- or *meta*-position gave the corresponding products **2b** and **2c** in yields of 79 and 72%, respectively. A stronger methoxycarbonyl group was also tolerated, giving **2d** in 66% yield. Substrates with an electron-donating methyl or methoxy group were successfully converted into the corresponding phenanthridinones **2e** and **2f**. Remarkably, a disubstituted amide was also converted into the corresponding product **2g** in good yield (84%). Unfortunately, heteroatom-bearing amides were stable to electrolysis and consequently did not yield corresponding phenanthridinones **2h** and **2i**.



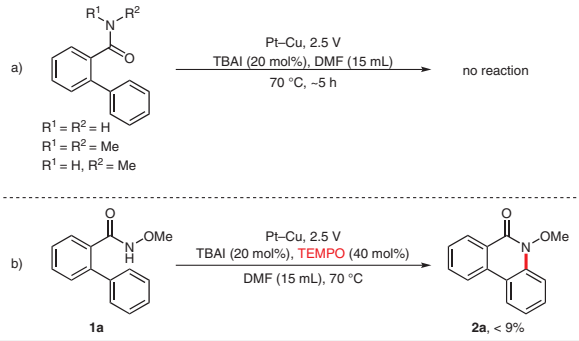
Scheme 2 Scope of *N*-methoxybenzamides **1a–i** with substituents on ring Ar^1. *Reagents and conditions*: *N*-methoxybenzamide **1a–i** (0.5 mmol), TBAI (20 mol%), DMF (15 mL), Pt and Cu electrodes, undivided cell, 2.5 V, 70 °C, ~5 h. Electrolyzed until 2 F mol^{-1} of electric charge was consumed. Yields of the isolated pure products are reported.

After monitoring the effect of substituents on the Ar^1 ring, we next focused our attention on the effect of substituents on the Ar^2 ring (Scheme 3). Substrates with Ar^2 bearing electron-donating or electron-withdrawing groups were easily converted into the corresponding products **4a–g** in good yields. Interestingly, substrates with Ar^2 bearing α- or β-*N*-methoxynaphthamide moieties were also successfully converted into the analogous phenanthridinones **4h** and **4i**.



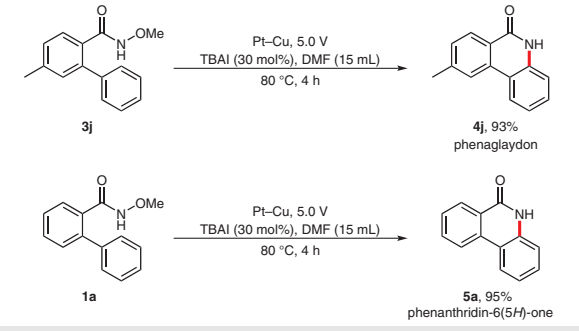
Scheme 3 Scope of *N*-methoxybenzamides **3a–i** with substituents on ring Ar^2. *Reagents and conditions*: *N*-methoxybenzamide **3a–i** (0.5 mmol), TBAI (20 mol%), DMF (15 mL), Pt and Cu electrodes, undivided cell, 2.5 V, 70 °C, ~5 h. Electrolyzed until 2 F mol^{-1} of electric charge was consumed. Yields of the isolated pure products are reported.

Subsequently, several control experiments were carried out under the standard reaction conditions (Scheme 4). We found that primary and tertiary amides did not undergo C–H amination to yield the corresponding products (Scheme 4a) and the starting materials were recovered. Only secondary amides bearing an N-OR group, for example an N-OMe group, were tolerated. We therefore concluded that an N–OMe group is necessary for the reaction to be viable. Further, to obtain insights into the reaction mechanism, the electrolysis was performed under standard conditions in the presence of 40 mol% of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical scavenger. Only a trace of product **2a** was isolated (Scheme 4b), indicating that the reaction proceeds by a radical mechanism.



Scheme 4 Control experiments

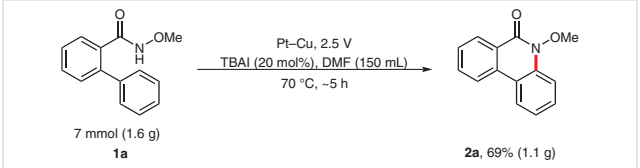
Next, we extended our electrochemical method to syntheses of the natural product phenaglaydon (**4j**) and phenanthridin-6(5*H*)-one (**5a**), a key intermediate in the synthesis of PJ34 (Scheme 5).[11] Unlike the method reported by Zeng and co-workers,[7] we have developed a direct single-step electrochemical method for the synthesis of the deprotected products by a slight modification of the standard procedure, in particular by altering the applied potential. Thus *N*-methoxy-5-methylbiphenyl-2-carboxamide (**3j**) was electrolyzed in the presence of 30 mol% of TBAI at 5.0 V for four hours to give the deprotected and demethoxylated product phenaglaydon (**4j**) directly in 93% yield. A similar protocol was followed in a synthesis of phenanthridin-6(5*H*)-one (**5a**) in 95% yield.



Scheme 5 Synthesis of biologically active phenanthridinones

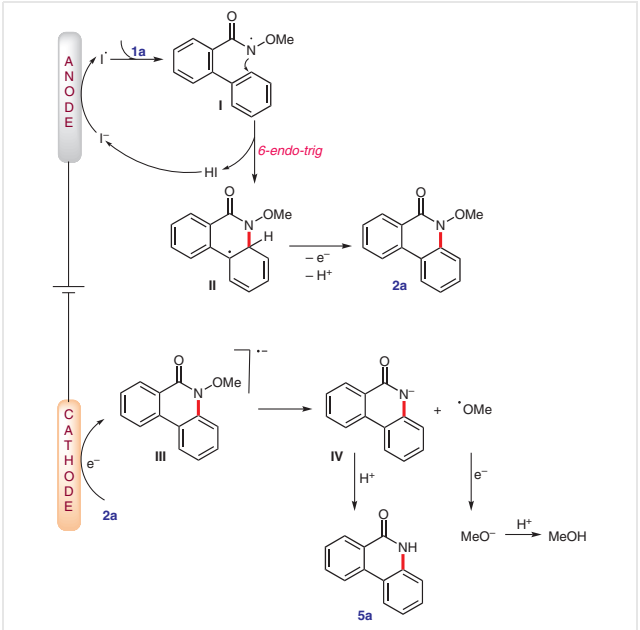
In an attempt to establish the practicality of the protocol, the electrochemical C–H amination of *N*-methoxybiphenyl-2-carboxamide (**1a**) was scaled up to a gram level, giving a 69% yield of 5-methoxyphenanthridin-6(5*H*)-one (**2a**) under the standard conditions, as shown in Scheme 6.

On the basis of the above observations and earlier reports in the literature,[7,8,12] a plausible reaction mechanism for the electrochemical reaction is proposed, as shown in Scheme 7. Initially, at the anode, electrochemical oxidation of the iodide ion leads to the formation of iodine radical that abstracts a hydrogen radical from the amide **1a** to form the amidyl radical intermediate **I**. This participates in a 6-*endo*-*trig* annulation to form the radical intermediate **II**



Scheme 6 Electrochemical gram-scale synthesis of 5-methoxyphenanthridin-6(5*H*)-one

with liberation of HI, which further undergoes oxidation to produce an iodide ion and H^+, continuing the catalytic cycle. Finally, the radical intermediate **II** undergoes rearomatization and is transformed into product **2a** by the loss of an electron and a proton. At a higher applied potential, **2a** acquires an electron from the cathode and is converted into a radical anion intermediate **III**, which undergoes cleavage to form anion **IV** and a methoxy radical. Finally, anion **IV** is protonated to form the demethoxylated product **5a**, and the methoxy radical eventually forms methanol.



Scheme 7 Plausible reaction mechanism

In conclusion, we have developed an efficient and operationally simple electrochemical method for the intramolecular C–H amination of 2-aryl *N*-methoxyamides for the syntheses of phenanthridinones.[13] The reaction proceeds through the formation of highly active amidyl radicals generated by the mediator TBAI. TBAI functions as both the electrocatalyst and the supporting electrolyte, thereby avoiding the need to use additional conducting salts. The reaction was performed by constant-potential electrolysis in an undivided cell containing a platinum anode and copper cathode with DMF as the solvent. This protocol exhibits 100% current efficiency with a broad substrate scope under

external oxidant- and transition-metal-free conditions. The practicability of the protocol was established by scaling up the reaction, and its synthetic utility was demonstrated by the direct synthesis of the bioactive compound phenaglaydon.

Conflict of Interest

The authors declare no conflict of interest

Funding Information

K.S. would like to thank the University Grants Commission of India (UGC) for providing a Senior Research Fellowship under the Basic Scientific Research (BSR) program vide No. [F.25-1/2014-15, F.7-227/2009 dt. 16th Feb, 2015]

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1467-5585.

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(13) **5-Methoxyphenanthridin-6(5*H*)-one[2d] (2a); Typical Procedure**

A 25 mL pear-shaped three-necked undivided cell equipped with Pt plate anode (30 × 15 mm) and a Cu plate cathode (30 × 15 mm) was charged with a solution of *N*-methoxybiphenyl-2-carboxamide (**1a**; 0.5 mmol, 113.6 mg) and TBAI (0.1 mmol, 36.9 mg) in DMF (15 mL). The cell was then connected to a regulated DC power supply, and constant-potential electrolysis was carried at 2.5 V and 70 °C until 2 F mol^{-1} electric charge was consumed (~5 h). The mixture was constantly stirred during the electrolysis. The resulting mixture was diluted with EtOAc and washed twice with H_2O. The organic layers were collected, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, PE–EtOAc (9.5:0.5)] to give a white solid; yield: 101.4 mg (90%); mp 102–104 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 8.1 Hz, 1 H), 8.28 (dd, *J* = 8.3, 4.0 Hz, 2 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H), 7.60 (q, *J* = 7.9, 7.4 Hz, 2 H), 7.41–7.32 (m, 1 H), 4.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 135.8, 133.0, 132.6, 130.0, 128.5, 128.1, 126.3, 123.2, 121.9, 118.6, 112.6, 62.7. GC/MS (EI, 70 eV): *m/z* (%) = 225.0 (39.0), 195.0 (100), 180.0 (28.7), 166.05 (58.2), 152.05 (16.0), 140.05 (28.6), 83.4 (13.7), 76.0 (13.2), 40.0 (13.9).

