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Regioselective Green Electrochemical Approach to the Synthesis of Nitroacetaminophen Derivatives

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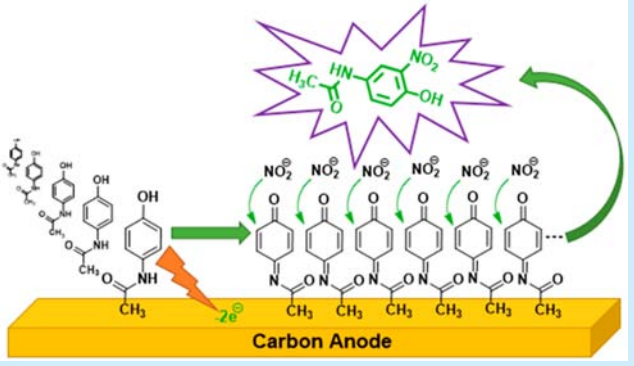
Supporting Information

ABSTRACT: A regioselective green synthesis of nitroacetaminophen derivatives was carried out by electrochemical oxidation of acetaminophen, *N*-(2-hydroxyphenyl)acetamide, and 1-(4-(4-hydroxyphenyl)piperazin-1-yl)ethanone in the presence of nitrite ion as a nucleophile. The present work has led to the development of a reagentless green and facile electrochemical method for the synthesis of some nitroacetaminophen derivatives.



Medical research shows that, when used in therapeutic doses, acetaminophen (**PAC**) is a safe drug. However, some adverse effects such as kidney and liver damage have been reported when overdosed.[1] In the presence of oxidizing enzymes such as cytochrome P-450, 5−10% of acetaminophen converts to *N*-acetyl-*p*-benzoquinone-imine (**PBQ**). This compound is a hepatotoxic agent, and its covalent bonding to the nucleic acids and proteins is responsible for the kidney and liver damage.[2] Under normal conditions, detoxification of this compound is carried out quickly by reaction with glutathione.[3] In overdose, however, the amount of cellular glutathione is insufficient to detoxify **PBQ**, resulting in the reaction of **PBQ** with cellular macromolecules, hepatocellular injury, and cell death. Based on this scientific reality, we chose to synthesize a more difficult-to-oxidize acetaminophen derivative. This may lead to minimization of the side effects of acetaminophen and improve the efficacy of the therapy. In order to achieve this objective, we decided to nitrate acetaminophen.

A literature survey indicated that only a few reports on the nitration of **PAC** have been published.[4] Nevertheless, these methods have some disadvantages such as heavy metal pollution, safety problems associated with overnitration, low yield, the use of strongly acidic media, and tedious workup. These disadvantages have encouraged us to develop electrochemical nitration of organic compounds. In this work, a green electrochemical method for the nitration of **PAC**, *N*-(2-hydroxyphenyl)acetamide (**OAC**), and 1-(4-(4-hydroxyphenyl)-piperazin-1-yl)ethanone (**APIP**) is reported. This method exhibits a high degree of regioselectivity toward the nitration of **PAC** and **OAC** compared with other nitration methods.

In an aqueous acetate buffer solution (c = 0.2 M, pH = 5.0), the cyclic voltammogram of **PAC** displays a quasi-reversible two-electron wave for the **PAC**/**PBQ** redox couple at $E_{1/2}$ 0.44 V (Figure 1, curve a).[3] At this pH value, the peak current ratio

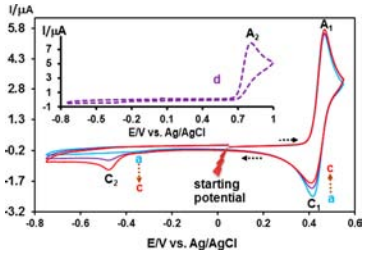


Figure 1. Cyclic voltammograms of **PAC** (1.0 mM): (a) in the absence, (b) in the presence of 20 mM, and (c) in the presence of 40 mM nitrite ion. (d) Cyclic voltammogram of NO_2^- (2.0 mM) at glassy carbon electrode, in acetate buffer solution (c = 0.2 M, pH = 5.0). Scan rate: 10 mV s^{-1}. Temperature = 25 ± 1 °C.

(I_{pC1}/I_{pA1}) is near 1, which shows that **PBQ** is stable on the time scale of cyclic voltammetry measurements. In the presence of nitrite ion, the current of cathodic peak C_1 (I_{pC1}) decreases and a new cathodic peak (C_2) appears at more negative potentials (−0.48 V vs Ag/AgCl). It was found that both I_{pC1}/I_{pA1} and I_{pC1}/I_{pC2} decrease with increasing nitrite ion concentration (Figure 1) as well as decreasing potential sweep rate.

The existence of a subsequent chemical reaction between **PBQ** and nitrite ion is supported by the following evidence:[5] (a) the decrease of I_{pC1}/I_{pA1}, (b) the increase of I_{pC1}/I_{pA1} with

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increasing scan rate, (c) the appearance of the cathodic peak C_2 at more negative potentials, (d) the increase of I_{pC1}/I_{pC2} with increasing scan rate, and (e) the decrease of I_{pC1}/I_{pA1} and I_{pC1}/I_{pC2} with increasing nitrite ion concentration.

Controlled-potential coulometry (CPC) was carried out in the same solution as used in Figure 1 containing both **PAC** and nitrite ion at 0.45 V versus Ag/AgCl to determine the number of transferred electrons per **PAC** molecule. Figure 2I displays

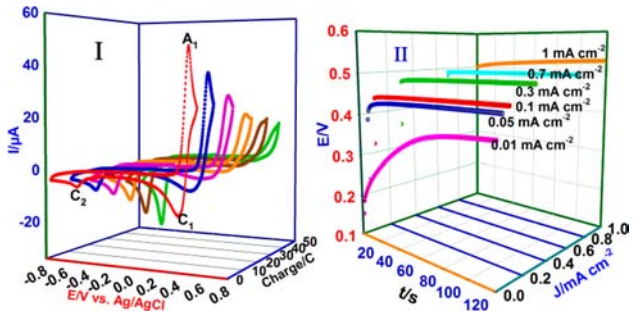
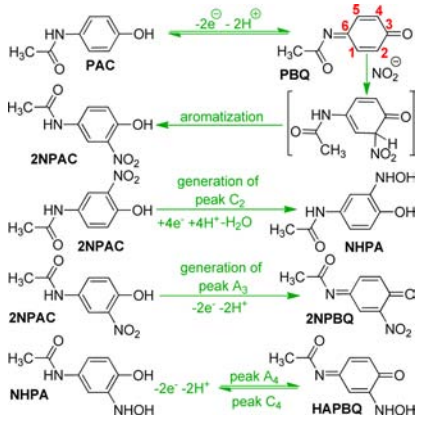


Figure 2. (I) Three-dimensional cyclic voltammograms of **PAC** (0.25 mmol) in the presence of NO_2^- (1 mmol) during controlled potential coulometry at 0.45 V versus Ag/AgCl after consumption of (a) 0, (b) 10, (c) 20, (d) 30, (e) 40, and (f) 50 C. Scan rate: 50 mV s^{-1}. (II) Potential−time diagram during constant current electrolysis for the above conditions. Electrode rotation rate: 1000 rpm. Other conditions are the same as for Figure 1.

the cyclic voltammograms of **PAC** in the presence of nitrite ion during the CPC. The voltammograms show that in parallel to the disappearance of peak A_1, the cathodic peak C_2 appears. The current of peak A_1 (I_{pA1}) becomes about zero with the transfer of about two electrons per molecule of **PAC**. The electrochemical evidence along with the spectroscopic data of the final product all point to 2-nitroacetaminophen (**2NPAC**), which would form according to the pathway shown in Scheme 1. The presence of the electron-withdrawing nitro group in the

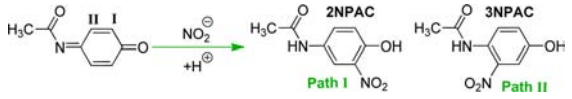
Scheme 1. Proposed Mechanism for Electrochemical Oxidation of PAC in the Presence of Nitrite Ion



structure of **2NPAC** causes the oxidation of the **2NPAC** to be more difficult than **PAC**. This feature ensured that the oxidation of **2NPAC** did not occur during the electrochemical oxidation of **PAC** at 0.45 V vs Ag/AgCl.

Accordingly, the cathodic peak C_2 pertains to the reduction of **2NPAC** to *N*-(4-hydroxy-3-(hydroxyamino)phenyl)-acetamide (**NHPA**) (Scheme 1).[6] **PBQ** is an asymmetric molecule that has two different sites, I and II, leading to two different chemical reactions between **PBQ** and nitrite ion (Scheme 2). However, single-crystal X-ray diffraction analysis of the synthesized compound[7] confirms regioselective formation of one isomer (**2NPAC**).

Scheme 2. Possible Nitration Compounds



The synthesis of **2NPAC** was also performed via the constant current electrolysis under the same conditions as described for controlled-potential electrolysis. Our data show that the highest yield (84%) was obtained at a current density of 0.1 mA/cm^2. In this current density, the electrode potential remained nearly constant at +0.45 V ($E_{1/2}$ of **PAC**/**PBQ** redox couple is +0.44 V), which is necessary for selective oxidation of **PAC** (Figure 2II) (see the Supporting Information). In order to investigate the electrochemical properties of **2NPAC**, cyclic voltammograms of a saturated solution of **2NPAC** in aqueous acetate buffer (pH = 5.0, c = 0.2 M) were recorded (Figure 3).

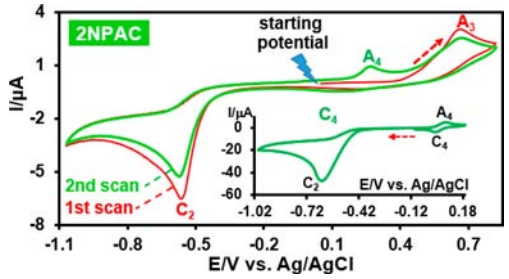


Figure 3. Cyclic voltammogram of first and second scans of **2NPAC** (saturated). In both cases, scan rate 10 mV s^{-1}. Inset: **2NPAC** (0.5 mM). Scan rate 100 mV s^{-1}. Other conditions are the same as for Figure 1.

Contrary to **PAC** (Figure 1), at the first cycle, the cyclic voltammogram of **2NPAC** shows an irreversible feature with an anodic peak (A_3) at 0.69 V vs Ag/AgCl, which belongs to the oxidation of **2NPAC** to 2-nitro-*N*-acetyl-*p*-benzoquinone-imine (**2NPBQ**), and the cathodic peak (C_2), which corresponds to the reduction of **2NPAC** to **NHPA** (Scheme 1). In the second cycle, the CV showed the new anodic (A_4) and cathodic peaks (C_4) which correspond to the oxidation of "*cathodically generated*" **NHPA** to 2-hydroxylamine-*N*-acetyl-*p*-benzoquinone-imine, **HAPBQ**, and vice versa (Scheme 1).[8] The latter peak (C_4) is clearer at the upper concentrations of **2NPAC**, with lower switching potential and also higher scan rates (Figure 3, inset).

In addition, in comparison with **PAC**, E_{pA3} is more positive than E_{pA1}. The result was predictable: the attachment of an electron-withdrawing group (EWG) to the phenyl ring increases the oxidation potential. This molecule (**2NPAC**) has more resistance to oxidation by cytochrome P-450 than **PAC**. The nitration reaction was also conducted by treating **PAC** with sodium nitrite according to a procedure described by Chiron and Gomez.[4d] Contrary to the electrochemical method (yield 85%), both **2NPAC** (yield 30%, mp = 158−160 °C) and 3-nitroacetaminophen (**3NPAC**) (yield 70%, mp = 217−219 °C) were isolated. We think that the regioselectivity observed

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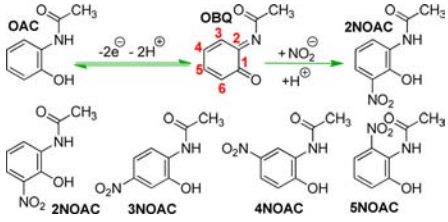
in electrochemical nitration of **PAC** may be due to the adsorption of electro-generated **PBQ** from the acetyl group on the surface of the carbon electrode (Figure 4).[9] In this manner, only site I is available for the nitration reaction.

Figure 4. Probable orientation of **PBQ** on the surface of the carbon electrode. The structure of **PBQ** has been optimized using MM2 calculations.

Electrochemical oxidation of **OAC** was also studied in the presence of nitrite ion. Since **OAC** shows the same electrochemical pattern as described for the electrochemical oxidation of **PAC** in the presence of nitrite ion (evidence a–e discussed previously), the electrochemical behavior of **OAC** is not reported here. The reaction mechanism for the electrochemical oxidation of **OAC** in the presence of nitrite ion is presented in Scheme 3.

Scheme 3. Reaction Mechanism for the Synthesis of 2NOAC

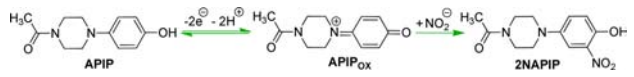


Since **2NOAC** has the same hydrogen-bonding pattern as **2NPAC**, the MS spectrum of it showed the same fragmentation pattern observed in **2NPAC** and confirmed that the nitro group is positioned *ortho* to the hydroxyl group. **OBQ** is an asymmetric molecule which has four different sites leading to four different products (Scheme 3). However, the presence of a triplet (1H) and two doublet of doublet (1H and 1H) peaks in the ^{1}H NMR spectrum of the isolated product does not comply with the structures of **3NOAC** and **4NOAC** and rejects the synthesis of these compounds during electrochemical oxidation of **OAC** in the presence of nitrite ion. Nitration of **OAC** by nitric acid in acetic anhydride was performed by King, who reported a melting point of 279–280 °C for **5NOAC**,[10] which is much higher than the observed melting point for the electrochemically nitrated **OAC** (228–230 °C). Therefore, these data confirm regioselective formation of **2NOAC**. The electrosynthesis of **2NOAC** was performed successfully using both controlled-potential and constant current electrolysis methods. The obtained yields were 68 and 64%, respectively.

Electrochemical nitration of **APIP** was also performed under the same conditions.[11] The reaction mechanism for the electrooxidation of **APIP** in the presence of NO_2^- is presented in Scheme 4. The yields of **2NAPIP** in both controlled-potential and constant current electrolysis methods were 78 and 75%, respectively (for more data, see the Supporting Information).

The NBO analysis was used for calculating the partial charge of each atom in the molecules investigated here at BP86/Def2-TZVPP level of theory. The natural charge of the carbons in

Scheme 4. Reaction Mechanism for the Synthesis of 2NAPIP



PBQ was found to vary in the order C4 < C2 < C1 < C5. According to these data, C5 and C1 sites are more appropriate sites for the nitration reaction. However, our experimental results confirm that the C2 is the reaction site and **2NPAC** was synthesized regioselectively by the anodic nitration of **PAC**. On the other hand, our computational studies show that the natural charge of the carbons in **OBQ** was found to vary in the order C6 < C3 < C4 = C5. These data show that C5 and C4 are more positive than other sites. However, our data confirm that the reaction site in electrochemical nitration of **OAC** is C6 (Scheme 3). The calculated Gibbs free energies of these compounds in the gas phase show that the **2NPAC** is 13.9 kcal/mol more stable than that of **3NPAC**. The relative stability of **2NPAC** is due to the formation of intramolecular hydrogen bonding between the OH and NO_2 groups. Our data also show that because of the formation of intramolecular hydrogen bonding between the hydroxyl and nitro groups the **2NOAC** is 9.7 kcal/mol more stable than that of **5NOAC**. In addition, calculations of the LUMO coefficients of **PBQ**, **OBQ**, and **APIP$_{ox}$** show that the LUMO coefficient of the carbon in the ortho position to the carbonyl carbon is larger than other carbons, which implies that a nucleophilic attack at this carbon should be favored.

According to these data, we conclude that the nature of the products that form (**2NPAC**, **2NOAC**, and **2NAPIP**) is influenced by the following parameters: (1) natural charge, (2) thermodynamic stability, (3) LUMO coefficient, and (4) electrode surface effects. However, we believe that the orientation of adsorbed **PBQ** and **OBQ** on the electrode surface plays an important role in the regioselective synthesis of these compounds and is the reason for the difference between chemical and electrochemical methods. In other words, the latter parameter has a significant effect on the regioselective nitration of **PAC** and **OAC** over other parameters such as natural bond orbital. Finally, in this work, electrochemistry was used as a powerful tool for organic synthesis.[12] The electrochemical nitration of **PAC** and **OAC** has two advantages over conventional methods. First, it is convenient to carry out and uses mild and green conditions with high atom economy (>99%). It proceeds at room temperature and in aqueous solution, without any catalysis, strong acids, or base and cosolvents. Second, in this method, the products were obtained regioselectively in high yields. **2NPAC** may lead to minimization of the side effects of acetaminophen and improve the efficacy of the therapy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01837.

Detailed experimental procedures and characterization data for all compounds; FT-IR, ^{1}H, ^{13}C NMR, and MS spectra of **2NPAC**, **2NOAC**, **3NPAC**, and **2NAPIP**; ORTEP view of X-ray crystal structure of **2NPAC**; TLC of **2NPAC**; calculated charge and LUMO coefficient for

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PBQ, **OBQ**, and **APIP$_{ox}$**; chemical structures of the possible nitrated compounds (PDF)
crystallographic data for **2NPAC** (CIF)

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Notes

The authors declare no competing financial interest.

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(7) Crystallographic data for the structure of **2NPAC** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC No. 1031158.
(8) A reviewer asked for evidence of the intermediacy of **NHPA** and **HAPBQ**. We reduced **2NPAC** electrochemically to the presumed hydroxylamine **NHPA**, which was reoxidized to the nitroso compound in a two-electron process by reversing the cell polarity. The nitroso compound could tautomerize rapidly to **HAPBQ** (see the Supporting Information for further details). We thank the reviewer for this helpful suggestion.
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