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A Facile Electrochemical Method for Synthesis of New Benzofuran Derivatives

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Abstract: Electrooxidation of 3-substituted catechols has been studied in the presence of dimedone in aqueous solution, using cyclic voltammetry and controlled-potential coulometry. The results indicate that the quinones derived from catechols participate in Michael addition reactions with dimedone to form the corresponding benzofuran derivatives (**6a**−**c**). We propose a mechanism for the electrode process. The efficient electrochemical synthesis of **6a**−**c** has been performed at carbon rod electrodes in an undivided cell using a constant current.

Because electrochemical oxidation very often parallels cytochrome P450 catalyzed oxidation in liver microsomes, it is interesting to study the anodic oxidation of catechols in the presence of a barbiturate or β-diketone to serve as a carbon-centered nucleophile. Because of the pharmacological uses of benzofurans their syntheses and pharmacological properties have been extensively investigated.[1−8] We have recently investigated the electrooxidation of 3,4-dihydroxybenzoic acid in the presence of 1,3-dimethylbarbituric acid and 1,3-diethyl-2-thiobarbituric acid as nucleophiles and described an efficient one-pot electrochemical method for the synthesis of some new benzofuro[2,3-*d*]pyrimidine derivatives.[9] In this work, the electrochemical oxidation of 3-substituted catechols (**1a**−**c**) has been studied in the presence of dimedone (**3**) as a carbon-centered nucleophile. The present work has led to the development of a facile one-pot galvanostatic method for the synthesis of new benzofuran derivatives (**6a**−**c**).

The electrochemical study of a 1 mM solution of catechol in an aqueous solution containing 0.15 M sodium acetate as supporting electrolyte, at a bare glassy carbon electrode, has been studied using cyclic voltammetry (Figure 1, curve a). The voltammogram shows one anodic (A_1) and corresponding cathodic peak (C_1), at 0.27 and 0.07 V, respectively, which correspond to the transformation of catechol (**1a**) to *o*-benzoquinone (**2a**) and vice versa within a quasireversible two-electron process (Scheme 1, eq 1). A peak current ratio (I_p^{C1}/I_p^{A1}) of near unity, particularly during the repetitive cycling of potential, can be considered as a criterion for the stability of *o*-quinone produced at the surface of electrode under the experimental conditions. In other words, any hydroxylation[10] or dimerization[11] reactions are too slow to be observed on the time scale of cyclic voltammetry. The oxidation of catechol (**1a**) in the presence of dimedone (**3**) as a nucleophile was studied in some detail. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 1 mM solution of **1a** in the presence of 1 equiv of dimedone (**3**). The voltammogram exhibits an increase in anodic peak current A_1 and the concomitant decrease of the cathodic counterpart of the anodic peak A_1. In this figure, curve c is the voltammogram of **3**. The voltammogram shows an irreversible process with an anodic peak A_2 at 0.96 V vs SCE.

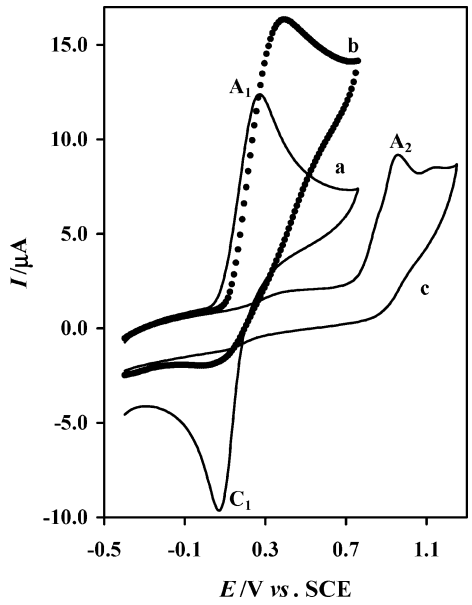

FIGURE 1. Cyclic voltammograms of 1 mM catechol (**1a**) (a) in the absence of dimedone (**3**), (b) in the presence of 1 mM dimedone (**3**); and (c) 1 mM dimedone (**3**) in the absence of catechol (**1a**) at a glassy carbon electrode (1.8 mm diameter) in aqueous solution. Supporting electrolyte 0.15 M sodium acetate; scan rate 100 mV s^{-1}; $T = 25 \pm 1$ °C.

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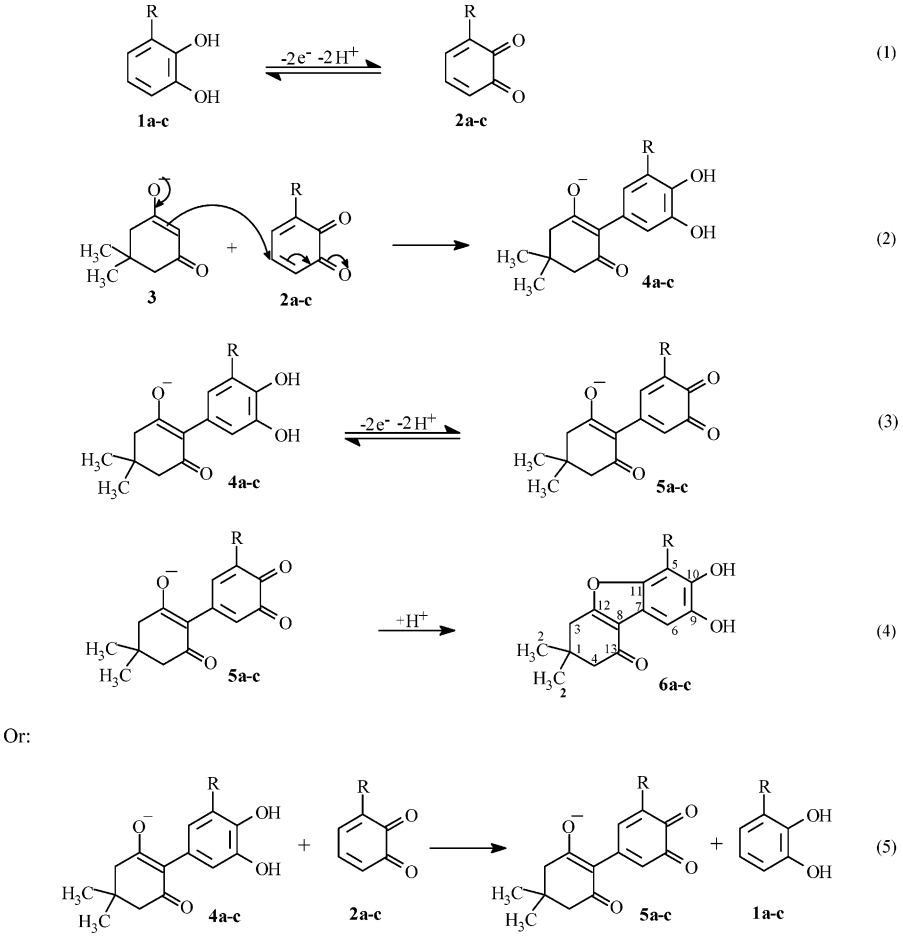
SCHEME 1



The multicyclic voltammetry of **1a** in the presence of **3** shows that, parallel to the shift of the A_1 peak in a positive potential direction, a new peak (A_0) appears as shoulder (Figure 2) in the second cycle. This new peak is related to electrooxidation of intermediate **4a**. The positive shift of the A_1 peak in the presence of **3** that was enhanced during the repetitive recycling of potential (Figure 2) and increasing dimedone (**3**) concentration is due to the formation of a thin film of product at the surface of the electrode, inhibiting to a certain extent the performance of electrode process.[11] In this figure, peak C_0 is the cathodic counterpart of A_0 and is related to the reduction of **5a**. Furthermore, it is seen that proportional to the increase in potential scan rate, the height of the C_1 peak of **1a** increases (Figure 3 curves a−d). A similar situation is observed when the dimedone (**3**) to **1a** concentration ratio is decreased. A plot of peak current ratio (I_p^{A1}/I_p^{C1}) versus scan rate for a mixture of catechol (**1a**) and dimedone (**3**) confirms the reactivity of **2a** toward **3**, appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Figure 3, curve e). On the other hand, the current function for the A_1 peak ($I_p^{A1}/v^{1/2}$) changes on increasing the scan rate, and such a behavior is consistent with the so-called ECEC mechanism.[12]

Controlled-potential coulometry was performed in aqueous solution containing 0.21 mmol of **1a** and 0.21 mmol of **3** at 0.40 V versus SCE. The electrolysis was monitored by cyclic voltammetry. It was observed that, proportional

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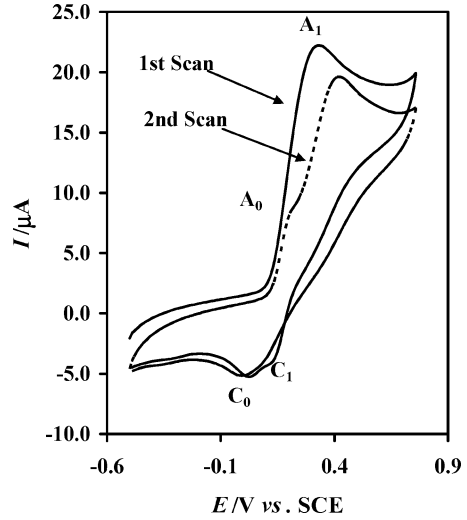

FIGURE 2. Multicyclic voltammograms of 1 mM catechol in the presence of 1mM dimedone, at a glassy carbon electrode, in sodium acetate solution (0.15 M); scan rate 250 mV s^{-1}; $T = 25 \pm 1$ °C.

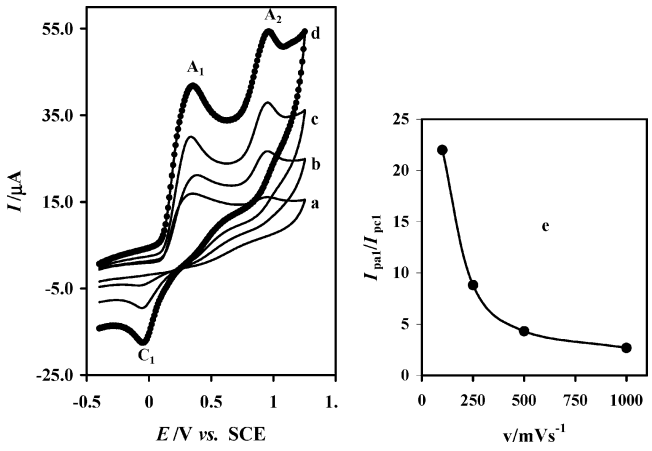

FIGURE 3. Typical voltammograms of 1 mM catechol (**1**) in water in the presence of 1 mM dimedone (**3**) at a glassy carbon electrode (1.8 mm diameter) and at various scan rates. Scan rates from (a) to (d) are 100, 250, 500, and 1000 mV s^{-1}, respectively. Supporting electrolyte 0.15 M sodium acetate. Curve e: variation of peak current ratio (I_p^{A1}/I_p^{C1}) versus scan rate. $T = 25 \pm 1$ °C.

to the advancement of coulometry, anodic peak A_1 decreases. All anodic and cathodic peaks disappear when the charge consumption becomes about 4 e^- per molecule of **1a**. These observations allow us to propose the pathway illustrated in Scheme 1 for the electrooxidation of **1a** in the presence of **3**.

According to our results, it seems that the Michael addition reaction of anion **3** to *o*-quinone (**2a**) (eq 2) is faster than the secondary reactions, leading to the intermediate **4a**. The oxidation of this compound (**4a**) is easier than the oxidation of the parent-starting molecule (**1a**) by virtue of the presence of an electron-donating group (Figure 2, peak A_0). It can be seen from the mechanism shown in Scheme 1 that as the chemical reaction (eq 2) occurs, **1a** is regenerated through homogeneous oxidation (eq 5) and hence can be reoxidized at the electrode surface. Thus, as the chemical reaction

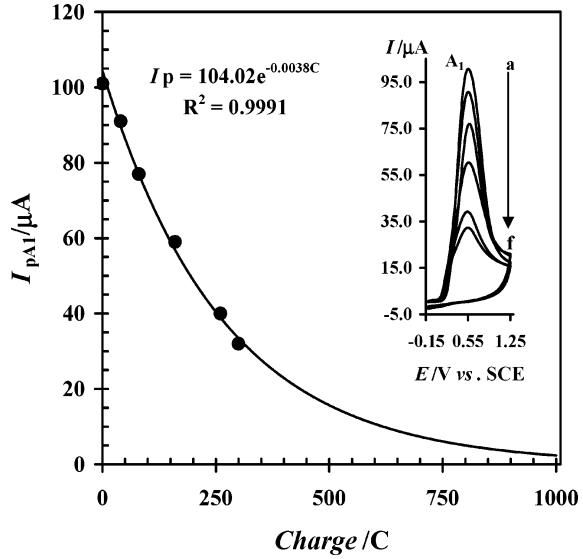

FIGURE 4. Variation of peak current I_p^{A1} versus charge consumed during constant-current coulometry. Inset: Cyclic voltammograms of 0.50 mmol catechol (**1**) in water in the presence of 0.50 mmol dimedone (**3**) at a glassy carbon electrode (1.8 mm diameter) during constant-current coulometry after consumption of (a) 0, (b) 40, (c) 80, (d), 160, (e) 260, and (f) 300 C. Supporting electrolyte 0.15 M sodium acetate; scan rate 100 mV s^{-1}; $T = 25 \pm 1$ °C.

takes place, the apparent number of electrons transferred increases from $n = 2$ to $n = 4$ electrons per molecule. The reaction product (**6a**) can also be oxidized at a lower potential than the starting compound **1a**. However, overoxidation of **6a** was circumvented during the preparative reaction because of the insolubility of the product in the water/sodium acetate solvent medium. Constant-current coulometry was performed in an aqueous solution containing 0.50 mmol of **1a** and 0.50 mmol of **3** under constant current density (2 mA/cm^2). The monitoring of electrolysis progress was monitored by cyclic voltammetry. It is shown that, proportional to the advancement of coulometry, anodic peak A_1 decreases (Figure 4).

A characteristic feature of the electrolysis is that low current density is required. The current efficiency and yield of product decrease with increasing current density. These observations can be explained by the occurrence of back reactions, such as the reduction of *o*-benzoquinones **2a** or **5a** on the platinum cathode and side reactions such as oxidation of nucleophile and/or solvent during constant current electrolysis in an undivided cell. In this work current density 2 mA/cm^2 is preferred.

The oxidation of **1b** and **1c** in the presence of **3** in a sodium acetate solution proceeds in a way similar to that of **1a**, but the existence of a methyl or methoxy group at the C-3 position of these compounds probably causes the related Michael acceptors (**2b** and **2c**) to be attacked by **3** at the C-4 and/or C-5 positions to yield two types of products in each case. However, according to ^{1}H NMR results,[13] we suggest that *o*-quinones **2b** and **2c** are selectively attacked from C-5 position by **3**, leading to the formation of the products **6b** and **6c**, respectively.

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The present results complete the previous reports on the anodic oxidation of some catechols.[1−11] The results of this work show that catechols are oxidized in water to their respective *o*-quinones. The quinones are then attacked by anion **3** to form benzofuran derivatives. The overall reaction mechanism for anodic oxidation of catechols in the presence of **3** as nucleophile is presented in Scheme 1. According to our results, the Michael addition leads to the formation of new benzofuran derivatives as final products, in good yields and purity.

Experimental Section

Apparatus and Reagents. Reaction equipment is described in an earlier paper.[14] All chemicals (catechols and dimedone) were reagent-grade materials, and sodium acetate was of pro-analysis grade. These chemicals were used without further purification.

Electroorganic Synthesis of 6a−c. A solution (ca. 80 mL) of sodium acetate in water (0.15 M) containing 2 mmol of catechols (**1a**−**c**) and dimedone (**3**) (2 mmol) was electrolyzed in an undivided cell equipped with graphite anode (an assembly of four rods, 6 mm diameter and 6 cm length) and a large platinum gauze cathode at 25 °C under constant current density of 2 mA/cm^2. The quantity of the electricity passed was determined using the exponential curve and related equation in Figure 4. The process was interrupted several times during the electrolysis, and the graphite anode was washed in acetone in order to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration, washed with water, and then recrystallized from a mixture of water/acetone. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. The isolated yields of **6a**−**c** before recrystallization are reported in Scheme 1. The crude products were pure by TLC.

Product 6a ($C_{14}H_{14}O_4$). Mp 289−291 °C. IR$_{(KBr)}$: 3480, 3160, 3048, 2920, 1639, 1582, 1515, 1458, 1437, 1332, 1308, 1279, 1248, 1183, 1120, 1102, 1043, 868, 815, 670, 616 cm^{-1}. ^{1}H NMR (90 MHz, DMSO-d_6): δ 1.05 (s, 6H); 2.32 (s, 2H); 2.80 (s, 2H); 6.96 (s, 1H); 7.19 (s, 1H); 9.16 (broad, 2H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 27.9, 34.6, 36.6, 51.8, 112.4, 113.4, 114.6, 115.3, 120.4, 147.9, 151.2, 167.8, 192.1. MS: *m*/*e* (relative intensity) 246(63.3), 190(83.4), 162(100), 134(10.2), 92(17.9), 69(24.3), 39-(18.4).

Product 6b ($C_{15}H_{16}O_4$). Mp 260−262 °C. IR$_{(KBr)}$: 3495, 3175, 3035, 2920, 1628, 1581, 1520, 1452, 1424, 1294, 1235, 1106, 1072, 1041, 1005, 892, 857, 813 cm^{-1}. ^{1}H NMR (90 MHz, DMSO-d_6): δ 1.06 (s, 6H); 2.24 (s, 3H); 2.33 (s, 2H); 2.84 (s, 2H); 7.09 (s, 1H); 8.51 (s, 1H); 9.40 (s, 1H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 9.0, 28.1, 35.0, 36.6, 51.6, 102.5, 108.1, 113.6, 114.8, 142.2, 143.5, 148.2, 168.7, 194.1. MS: *m*/*e* (relative intensity) 260(100), 204(99.8), 176(84.7), 147(14.1), 91(19.1), 83(13.2), 41(23.6).

Product 6c ($C_{15}H_{16}O_5$). Mp 289−291 °C. Mp 243−245 °C. IR$_{(KBr)}$: 3455, 3120, 3010, 2800, 1641, 1590, 1467, 1446, 1408, 1356, 1326, 1255, 1204, 1157, 1081, 1039, 1012, 913, 850, 826, 556 cm^{-1}. ^{1}H NMR (90 MHz, DMSO-d_6): δ 1.10 (s, 6H); 2.38 (s, 2H); 2.89 (s, 2H); 3.96 (s, 3H); 6.99 (s, 1H); 8.69 (s, 1H); 9.26 (s, 1H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 28.0, 34.8, 36.6, 51.5, 60.4, 99.9, 114.4, 114.8, 133.4, 136.1, 140.8, 145.0, 168.8, 193.8. MS: *m*/*e* (relative intensity) 262(100), 247(72.4), 219(20.4), 205(14.3), 191(12.1), 92(23.6), 78(36.5), 63(62.8).

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