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Electrochemical synthesis of 5,6-dihydroxy-2-methyl-1-benzofuran-3-carboxylate derivatives

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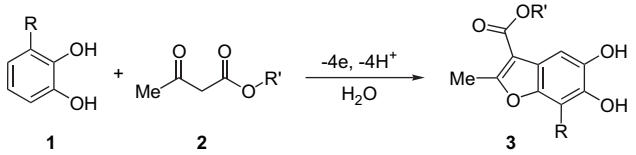
Abstract—Electrochemical oxidation of catechols (**1a–c**) has been studied in the presence of methyl acetoacetate (**2a**) and ethyl acetoacetate (**2b**) as nucleophiles in aqueous solution using cyclic voltammetry and controlled-potential coulometry. The results indicate that the quinones derived from catechols (**1a–c**) participate in Michael addition reactions with **2a** and **2b** to form the corresponding benzofuran derivatives (**3a–f**). The electrochemical synthesis of **3a–f** has been successfully performed in an undivided cell in good yield and purity. The oxidation mechanism was deduced from voltammetric data and by coulometry at controlled potential. The products have been characterized after purification by IR, ^{1}H NMR, ^{13}C NMR, MS, and single crystal X-ray diffraction.

1. Introduction

In nature's collection of biologically active heterocycles benzofuran derivatives[1] constitute a major group. They are usually important constituent of plant extracts used in medicinal chemistry for their various biological activities, including insecticidal, traditional medicine, antimicrobial, and antioxidant properties.[2] The most common synthetic strategy employed for benzofuran synthesis is the annulation of a furan ring onto a preexisting benzene ring through Sonogashira coupling followed by palladium-catalyzed cyclization[3] or through benzannulation onto a preexisting furan ring.[4] Numerous benzofuran-containing natural products have been efficiently synthesized according to these methods. One of the prime principles of green chemistry is to develop an alternative reaction medium, which is the basis for the development of many cleaner chemical technologies and electrochemical synthesis in water. With due attention to our experiences on electrochemical oxidation of catechols in the presence of nucleophiles,[5] we used electrochemical oxidation of catechols in the presence of ethyl acetoacetate and methyl acetoacetate in water medium and synthesis of new benzofurans from β-diketones.

2. Results and discussion

The electrochemical oxidation of catechol (**1**) in the presence of methyl acetoacetate or ethyl acetoacetate (**2**) undergoes a smooth 1:1 addition reaction in water medium at ambient temperature to produce 5,6-dihydroxy-2-methyl-1-benzofuran-3-carboxylate derivatives (**3**) (Scheme 1).



1	R
a	H
b	Me
c	OMe

2	R'
a	Me
b	Et

3	R	R'	%Yield of 3
a	H	Me	60
b	Me	Me	70
c	OMe	Me	55
d	H	Et	65
e	Me	Et	72
f	OMe	Et	60

Scheme 1.

Cyclic voltammetry of 2 mM catechol (**1a**) in phosphate buffer (pH 7.2, C=0.15 M) shows one anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of catechol (**1a**) to *o*-benzoquinone (**4a**) and vice versa within a quasi-reversible two-electron process (Fig. 1, curve a). A peak current ratio ($I_P^{C_1}/I_P^{A_1}$) of nearly

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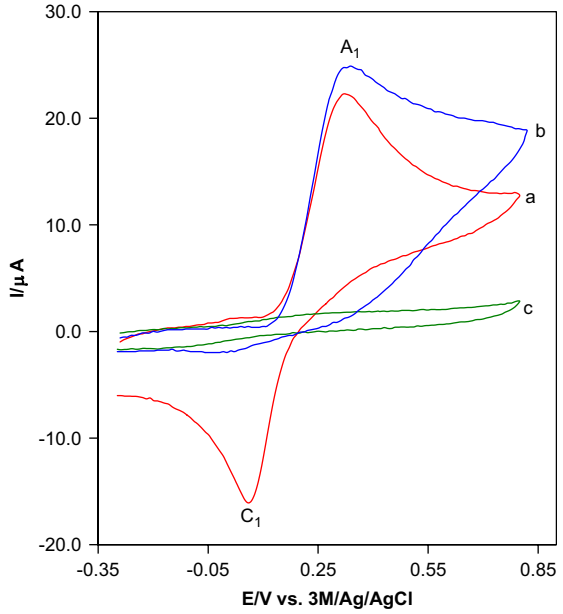

Figure 1. Cyclic voltammograms of 2 mM catechol in the absence (a) and presence of 2 mM ethyl acetoacetate (b) and 2 mM ethyl acetoacetate in the absence of catechol (c), at a glassy carbon electrode (1.8 mm diameter) in phosphate buffer (pH 7.2, C=0.15 M); scan rate: 100 mV s^{-1}; t=25±1 °C.

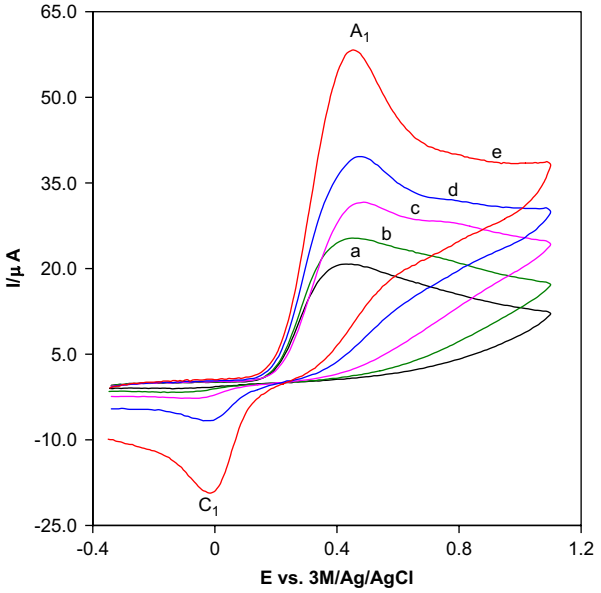

Figure 2. Typical voltammograms of 2 mM catechol in the presence of 2 mM ethyl acetoacetate, at a glassy carbon electrode (1.8 mm diameter) and at various scan rates in phosphate buffer (pH 7.2, C=0.15 M); scan rates from (a) to (e) are: 50, 100, 200, 400, 800 mV s^{-1}, respectively. t=25±1 °C.

unity, particularly during the repetitive recycling of the potential, can be considered as a criterion for the stability of *o*-benzoquinone produced at the surface of electrode under the experimental conditions. In other words, any hydroxylation[6] or dimerization[7] reactions are too slow to be observed on the time scale of the cyclic voltammetry. The oxidation of catechol (**1a**) in the presence of ethyl acetoacetate (**2b**) as a nucleophile was studied in some detail. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 2 mM solution of **1a** in the presence of 2 mM ethyl acetoacetate. The voltammogram exhibits one anodic peak at 0.35 V versus 3 M Ag/AgCl electrode and the cathodic counterpart of anodic peak (C_1) disappears. In this figure, curve c is the voltammogram of 2 mM ethyl acetoacetate (**2b**).

It is seen that, proportional to the augmentation of the potential sweep rate, the height of cathodic peak increases (Fig. 2). A similar situation is observed when the concentration ratio of ethyl acetoacetate (**2b**) to (**1a**) decreased. The current function for the anodic peak, $I_P^{A_1}/v^{1/2}$, changes with increasing scan rate. On the other hand, a plot of the peak current ratio ($I_P^{C_1}/I_P^{A_1}$) versus the scan rate for a mixture of catechol and ethyl acetoacetate (**2b**) shows an increase in the height of the cathodic peak (C_1) at higher scan rates. Such behavior is adopted as indicative of an ECEC mechanism.[8] Controlled-potential coulometry was performed in an aqueous solution containing 0.25 mmol of **1a** and 0.25 mmol of ethyl acetoacetate (**2b**) at 0.40 V versus 3 M Ag/AgCl electrode. The electrolysis progress was monitored by using cyclic voltammetry (Fig. 3). It is shown that, proportional to the advancement of coulometry, the anodic peak (A_1) decreases and disappears when the charge consumption becomes about 4e^- per molecule of **1a**. These observations allowed us to propose the pathway in Scheme 2 for the electrochemical oxidation of **1a** in the presence of ethyl acetoacetate (**2b**).

According to our results, it is clear that the 1,4-Michael addition reaction of anion enolate (**5**) to *o*-quinone (**4**) (Eq. 2) is much faster than other secondary reactions, leading presumably to the intermediate (**7**). The oxidation of this compound (**7**) is easier than oxidation of the parent starting molecule (**1**) by virtue of the presence of an electron-donating group. The reaction product (**3**) can also be oxidized at a lower potential than the starting compound **1**. However, overoxidation of **3** was circumvented during the preparative reaction because of the insolubility of the product in the water/phosphate solvent medium (Scheme 2).

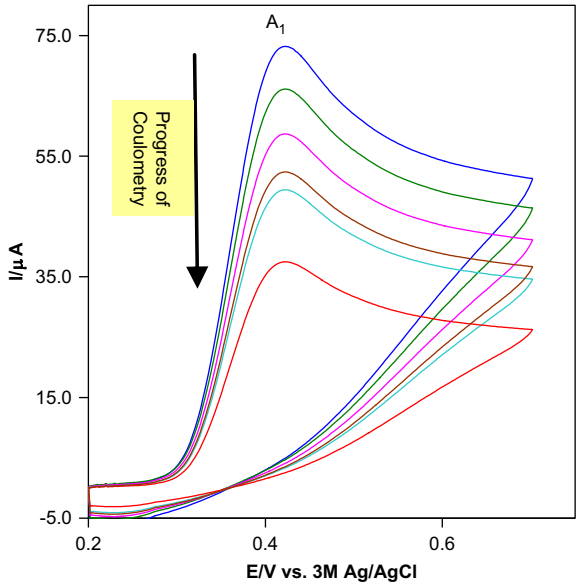

Figure 3. Cyclic voltammograms of 0.25 mmol catechol in the presence of 0.25 mmol ethyl acetoacetate in phosphate buffer (pH 7.2, C=0.15 M), at a glassy carbon electrode (1.8 mm diameter) during controlled-potential coulometry at 0.40 V versus 3 M Ag/AgCl electrode. Scan rate 100 mV s^{-1}; t=25±1 °C.