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Electroorganic Synthesis of New Benzofuro[2,3-*d*]pyrimidine Derivatives

Davood Nematollahi* and Hassan Goodarzi

Department of Chemistry, Faculty of Science, University of Bu-Ali-Sina, Hamadan, Iran

nemat@basu.ac.ir

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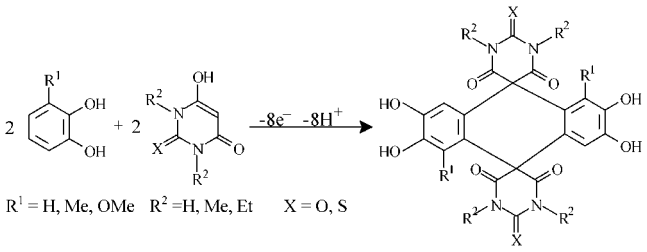
Abstract: Electrochemical oxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of 1,3-dimethylbarbituric acid (**2**) and 1,3-diethyl-2-thiobarbituric acid (**3**) as nucleophiles in aqueous solution has been studied using cyclic voltammetry and controlled-potential coulometry. The results indicate that **1** via Michael reaction under electro-decarboxylation reaction converts to benzofuro[2,3-*d*]pyrimidine derivatives (**6a**, **6b**). The electrochemical synthesis of **6a**, **6b** has been successfully performed in an undivided cell in good yields and purity.

Because electrochemical oxidation very often parallels the cytochrome P450 catalyzed oxidation in liver microsomes, it was interesting to study the anodic oxidation of catechols in the presence of the barbiturate as CH-acidic nucleophile. The barbiturates are of particular interest, since they are known to have hypnotic properties and they are used as long active on central nervous system.[1] In this direction, electrochemical oxidation of catechol and some of 3-substituted catechols in the presence of barbituric acids as nucleophiles have been investigated by others[2,3] and by us.[4,5] The results indicate formation of dispyropyrimidine derivatives (Scheme 1).

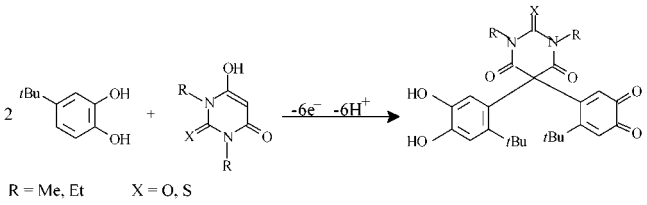
In addition, the preparation of spyropyrimidine derivatives via the electrooxidation of 4-*tert*-butylcatechol in the presence of barbituric acids has been recently reported by us[6] (Scheme 2).

On the other hand, because of the pharmacological uses of pyrimidines and benzofurans the syntheses and pharmacological properties of pyrimidine[7−14] and benzofuran[15−22] derivatives have been extensively investigated. To synthesis of compounds with benzofuro moiety on a pyrimidine ring, we have 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 a facile one-pot electrochemical method for synthesis of some new benzofuro[2,3-*d*]pyrimidine derivatives.

SCHEME 1



SCHEME 2



Cyclic voltammetry of a 2 mM 3,4-dihydroxybenzoic acid (**1**) in aqueous solution containing 0.15 M sodium acetate as supporting electrolyte shows one anodic (A_1) and corresponding cathodic peak (C_1), which corresponds to the transformation of 3,4-dihydroxybenzoic acid (**1**) to *o*-benzoquinone (**1a**) and vice-versa within a reversible two-electron process (Figure 1, curve a). A peak current ratio (I_p^{C1}/I_p^{A1}) of nearly unity, particularly during the repetitive recycling of potential, can be considered as criteria for the stability of *o*-quinone produced at the surface of electrode under the experimental conditions. In other words, any hydroxylation[23] or dimerization[24] reactions are too slow that to be observed in the time scale of cyclic voltammetry. The oxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of 1,3-dimethylbarbituric acid (**2**) as a nucleophile was studied in some detail. Figure 1 (curve b) shows the cyclic voltammogram

* To whom correspondence should be addressed. Fax: 0098−811−8272404.

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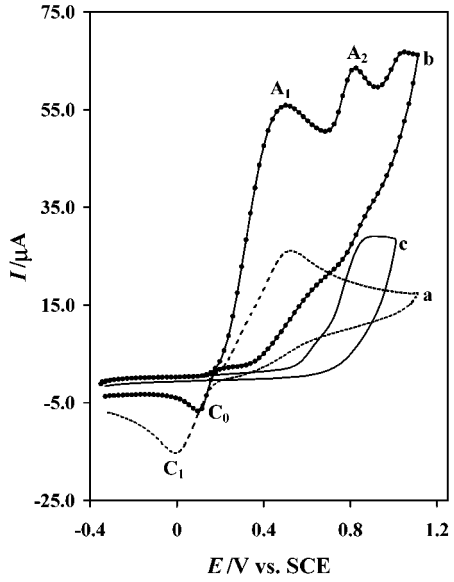

FIGURE 1. Cyclic voltammograms of 2 mM 3,4-dihydroxybenzoic acid: (a) in the absence, (b) in the presence of 2 mM 1,3-dimethylbarbituric acid, and (c) 2 mM 1,3-dimethylbarbituric acid in the absence of 3,4-dihydroxybenzoic acid, at glassy carbon electrode (5 mm diameter) in aqueous solution. Supporting electrolyte 0.15 M sodium acetate; scan rate: 50 m Vs^{-1}; $T = 25 \pm 1$ °C.

obtained for a 2 mM solution of **1** in the presence of 2 mM 1,3-dimethylbarbituric acid (**2**). The voltammogram exhibits two anodic peaks at 0.52 and 0.83 V versus SCE. The cathodic counterpart of the anodic peak A_1 disappears, and a new cathodic peak (C_0) is observed at less negative potential (0.11 V versus SCE). Comparison of voltammograms b and c reveals that the peak A_2 (curve b) corresponds to the oxidation of 1,3-dimethylbarbituric acid (**2**) or 1,3-dimethylbarbituric acid linked to 3,4-dihydroxybenzoic acid (**4a**). The multicyclic voltammetry of **1** in the presence of 1,3-dimethylbarbituric acid (**2**) shows that in the second cycle a new anodic peak (A_0) appears with an E_p value of 0.19 V versus SCE (Figure 2). This peak (A_0) is counterpart of cathodic peak C_0 and is related to the electrooxidation of intermediate **4a**. Furthermore, it is seen that proportional to the augmentation of potential sweep rate, parallel to the disappearance of peak C_0, the height of C_1 peak of **1** increases (Figure 3 curves a−d). A similar situation is observed when the 1,3-dimethylbarbituric acid (**2**) to **1** concentration ratio is decreased. A plot of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate for a mixture of 3,4-dihydroxybenzoic acid and 1,3-dimethylbarbituric acid confirms the reactivity of **1** toward 1,3-dimethylbarbituric acid (**2**), appearing as an increase in the height of the cathodic peak C_1 at higher scan rates. On the other hand, the current function for A_1 peak, ($I_p^{A1}/v^{1/2}$), changes with increasing the scan rate (Figure 3, inset), and such a behavior is adopted as indicative of ECEC mechanism.[4−6,22,25] Controlled-potential coulometry was performed in aqueous solution containing 5 mM of **1** and 5 mM of 1,3-dimethylbarbituric acid (**2**) at 0.60 V versus SCE. The monitoring of electrolysis progress was carried out by cyclic voltammetry (Figure 4). It is shown that, proportional to the advancement of coulometry, anodic

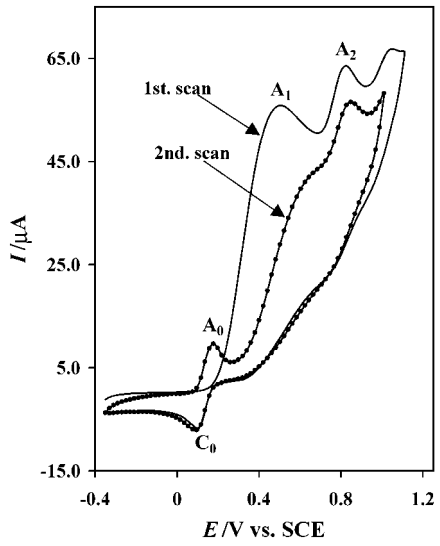

FIGURE 2. Multicyclic voltammograms of 2 mM 3,4-dihydroxybenzoic acid in the presence of 2 mM 1,3-dimethylbarbituric acid, at glassy carbon electrode (5 mm diameter) in aqueous solution. Supporting electrolyte 0.15 M sodium acetate; scan rate: 50 mVs^{-1}; $T = 25 \pm 1$ °C.

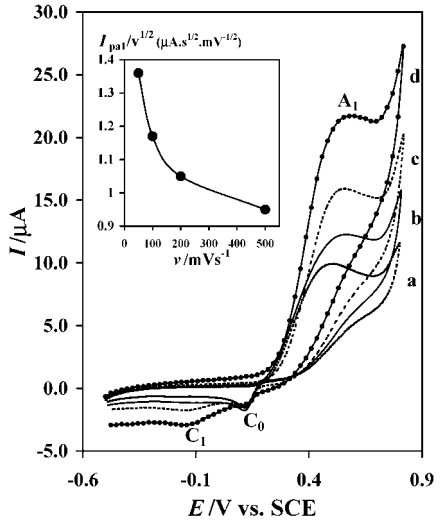

FIGURE 3. Typical voltammograms of 1 mM 3,4-dihydroxybenzoic acid in the presence of 1 mM 1,3-dimethylbarbituric acid at a glassy carbon electrode (2 mm diameter) and at various scan rates. Scan rates of a, b, c, and d are 50, 100, 200, and 500 mV $s^{-1,}$ respectively. Supporting electrolyte: 0.15 M sodium acetate. Inset: variation of peak current function ($I_p^{A1}/v^{1/2}$), versus scan rate. $T = 25 \pm 1$ °C.

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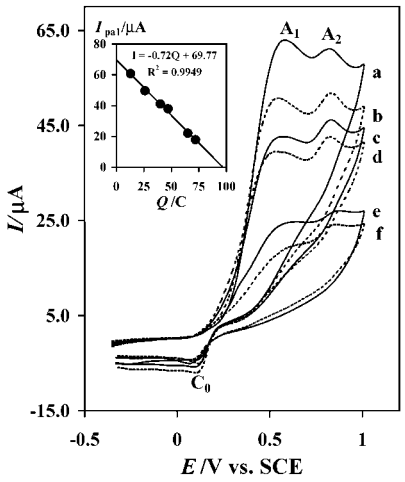


FIGURE 4. Cyclic voltammograms of 5 mM 3,4-dihydroxybenzoic acid in the presence of 5 mM 1,3-dimethylbarbituric acid in 50 mL of water, at a glassy carbon electrode (2 mm diameter) during controlled-potential coulometry at 0.60 V versus SCE. After consumption of (a) 13, (b) 26, (c) 40, (d), 47, (e) 65, and (f) 72 C. Inset: variation of peak current (I_{pa1}) versus charge consumed. Scan rate 50 mV s^{-1}; $T = 25 \pm 1$ °C.

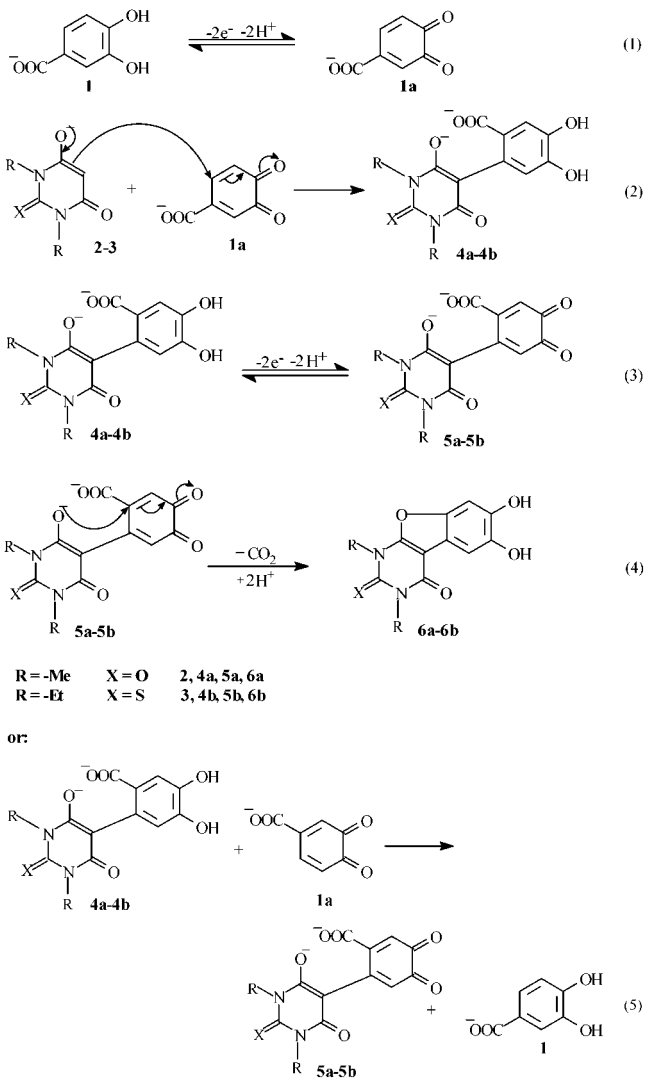
peak A_1 (as well as A_2) decreases. All anodic and cathodic peaks disappear when the charge consumption becomes about $4e^-$ per molecule of **1**. These observations allow us to propose the pathway in Scheme 3 for the electrooxidation of **1** in the presence of 1,3-dimethylbarbituric acid (**2**).

According to our results, it seems that the intermolecular (eq 2) and intramolecular (eq 4) 1,4-(Michael) addition reaction of anion enolate **2** to *o*-quinone **1a** is faster than other secondary reactions, leading to the intermediate **4a**. The oxidation of this compound (**4a**) is easier than the oxidation of parent starting molecule (**1**) by virtue of the presence of an electron-donating group that leads to the formation of **5a**. The intramolecular reaction (eq 4) was performed via a 1,4-(Michael) addition reaction followed by an electro-decarboxylation reaction. It can be seen from the mechanism shown in Scheme 3 that as the chemical reaction (eq 2) occurs, **1** is regenerated through homogeneous oxidation (eq 5) and hence can be reoxidized at the electrode surface. The reaction product **6a** can also be oxidized at a lower potential than the starting **1** compound. However, overoxidation of **6a** was circumvented during the preparative reaction because of the insolubility of the product in water/sodium acetate media.

The same results was obtained in electrooxidation of 3,4-dihydroxybenzoic acid (**1**) in the presence of 1,3-diethyl-2-thiobarbituric acid (**3**) (Scheme 3), and according to our results, the intermolecular (eq 2) and intramolecular (eq 4) 1,4-(Michael) addition reaction of anion enolate **3** to *o*-quinone **1a** leads to product **6b**.

It is well documented in literature that the electrooxidation of catechol, 3-substituted catechols, and 4-*tert*-butylcatechol, in the presence of 1,3-dimethylbarbituric acid (**2**) or 1,3-diethyl-2-thiobarbituric (**3**), will give the corresponding dispiropyrimidine,[2−5] spiropyrimidine,[6] or benzofuro[26] derivatives. In the case of 3,4-dihydroxybenzoic acid, the expected product via Michael reaction under the decarboxylation reaction therefore would be dispiro-

SCHEME 3



pyrimidine or benzofuro derivative. But, IR, ^{1}H NMR, and MS results did not agree with the structure of these compounds, but rather they indicate structure **6**.

The overall reaction mechanism for anodic oxidation of 3,4-dihydroxybenzoic acid in the presence of 1,3-diethyl-2-thiobarbituric acid as nucleophile is presented in Scheme 3. According to our results, it seems that the 1,4-(Michael) addition reaction of these nucleophiles to the *o*-quinone formed (eq 2 and 4) leads to the formation of new benzofuro[2,3-*d*]pyrimidine derivatives as final products, in good yields and purity (see Table 1).

Experimental Section

Apparatus and Reagents. Reaction equipment is described in an earlier paper.[5,6] All commercially obtained reagents were used without further purification.

Electroorganic Synthesis of Benzofuro[2,3-*d*]pyrimidine Derivatives (6a,b). In a typical procedure, 80 mL of sodium acetate solution in water (0.15 M) was preelectrolyzed at 0.60 V vs SCE, in an undivided cell; then, 2 mmol of 3,4-

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TABLE 1. Electroanalytical and Preparative Data

	peak potentials[a]/V (SCE)			
conversion	A_0	A_1	A_2	product yield, %
1 → 6a	0.19	0.52	0.83	80
1 → 6b	0.12	0.53	0.87	87

[a] Peak potentials were measured from cyclic voltammograms of 3,4-dihydroxybenzoic acid (2 mM) in the presence of 1,3-dimethylbarbituric acid (2 mM) and 1,3-diethyl-2-thiobarbituric acid (2 mM) recorded at 50 mV s^{-1}.

dihydroxybenzoic acid (**1**) and 1,3-dimethylbarbituric acid or 1,3-diethyl-2-thiobarbituric acid (2 mmol) were added to the cell. The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted several times during the electrolysis, and the graphite anode was washed in acetone in order to reactive it. At the end of electrolysis, a few drops of acetic acid were added to the solution, and the cell was placed in refrigerator overnight. The precipitated solid was collected by filtration and recrystallized from a mixture of chloroform−acetone solvent. After recrystallization, products were characterized by: IR, ^{1}H NMR, MS, and sulfur content.

Compound 6a ($C_{12}H_{10}N_2O_5$): Mp > 310 °C (dec). IR (cm^{-1}): 3380−3200 (br), 2900, 1700, 1640, 1530, 1455, 1307, 1200, 1120, 1070, 968, 870, 775, 740; ^{1}H NMR (90 MHz, DMSO-d_6): δ 3.23 (s, 6H), 7.02 (d, 2H), 914 (br s, 2H); MS (*m*/*z*) (relative intensity): 262 ([M]$^+$ 85.9), 205 (100), 190 (40.8) 162 (36.3) 106 (19.5), 69 (18.5).

Compound 6b ($C_{14}H_{14}N_2O_4S$). Mp > 310 °C (dec). IR (cm^{-1}): 3300 (br), 2900, 1650 (br), 1525, 1450, 1380, 1350, 1285, 1190, 1080, 1015, 950, 850, 780; ^{1}H NMR (90 MHz, DMSO d_6): δ 1.24 (t, 6H), 4.55 (q, 4H), 7.12 (d, 2H), 9.42 (br s, 2H); MS (*m*/*z*) (relative intensity): 306 ([M$^+$] 55.6), 219 (54.8), 191 (100), 163 (26.4), 83 (33.4); sulfur content: calculated for $C_{14}H_{14}N_2O_4S$, 10.45, found, 10.00%.

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