One-Pot Synthesis of Highly Conjugated Benzofuran Derivatives Based on Electrochemical Oxidation of Benzenediols in the Presence of Dibenzoylmethane

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Received December 2, 2006; accepted March 14, 2007

Electrochemical oxidation of benzenediols (1—4) has been studied in the presence of dibenzoylmethane (5) as a nucleophile using cyclic voltammetry and controlled-potential coulometry. The results indicate that the electrochemically generated quinones participate in Michael addition reaction with 5 *via* various mechanisms to produce new benzofuran derivatives. We derived various products based on electrochemical oxidation in the controlled potential condition, at carbon electrode without toxic reagents in an undivided cell and ambient condition.

Key words   benzofuran; electrochemical synthesis; cyclic voltammetry; benzenediol; dibenzoylmethane

Catechols are a promising group of compounds worthwhile for further investigation, which may lead to the discovery of selective acting, biodegradable agrochemicals having high human, animal and plant compatibility.[1,2] Also, heterocycles, particularly those containing oxygen or nitrogen atoms in the ring, are important building blocks for natural products and pharmaceutical reagents. In recent years, medicinal properties of benzofuran derivatives have been investigated widely and were shown to be effective as antitumor,[3] anti-depressant,[4] antifungal[1,5] anti-hypertensive, and cytotoxic.[6] They are also potent and selective oxytocin antagonists,[7] PDE5 inhibitor for treatment of erectile dysfunction,[8] and H$_3$ receptor antagonists.[9] Thus, development of efficient methods to functionalize heterocycles is critical for synthetic chemistry and we thought that synthesis of organic compounds with both structures of catechol and benzofuran would be interest from the point of view of pharmaceutical properties. This idea prompted us to investigate the electrochemical oxidation of benzenediols (1—4) in the presence of dibenzoylmethane (5) as a nucleophile. We herein report the development of procedure for one-pot, efficient, and regioselective synthesis of some benzofuran derivatives with high conjugation by electro-oxidation of benzenediols in the presence of 5.

Results and Discussion

The electrochemical study of 1 mM solution of catechol (1) in a 50% mixture of water/acetonitrile solution has been performed using cyclic voltammetry (Fig. 1, I, curve a). The voltammogram shows one anodic (A$_1$) and corresponding cathodic peak (C$_1$) which correspond to the transformation of 1 to *o*-quinone (1a) and *vice versa* (Chart 1, Eq. 1).[10,11] Figure 1, I, curve b, shows cyclic voltammogram of 1 mM of 1 in the presence of 5 in the same conditions. In this condition, the height of cathodic peak (C$_1$) decreased and a new cathodic peak (C$_2$) appeared at a lower potential. Decreasing of C$_1$ is due to the arriving of 1a in following chemical reaction. The positive shift of the A$_1$ peak in the presence of 5 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.[10,11] In this figure, curve c is the cyclic voltammogram of 5. Furthermore, proportional to the augmentation of potential sweep rate, the peak current ratio (I_{pa}/I_{pc}) in-
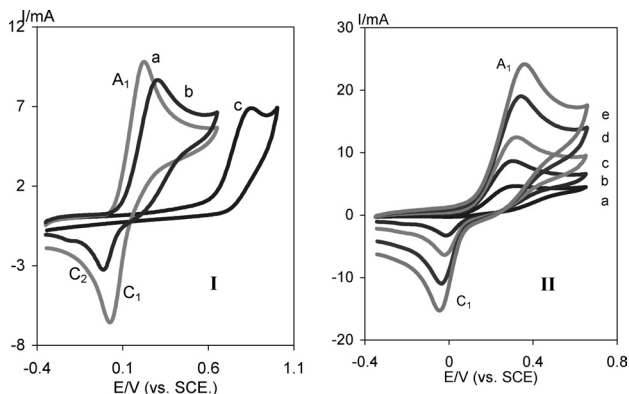
Fig. 1.   (I) Cyclic Voltammograms of 1 mM Catechol (1): a) in the Absence of Dibenzoylmethane (5), b) in the Presence of 1 mM 5 and c) 1 mM 5 in the Absence of 1

Scan rate: 50 mV s^{-1}.

(II) Voltammograms at Various Scan Rates

Scan rates from a) to e) are: 10, 50, 100, 250 and 400 mV s^{-1}, respectively. Solvent system 50% mixture of water/acetonitrile solution containing 0.10 M sodium acetate. t=25 °C.
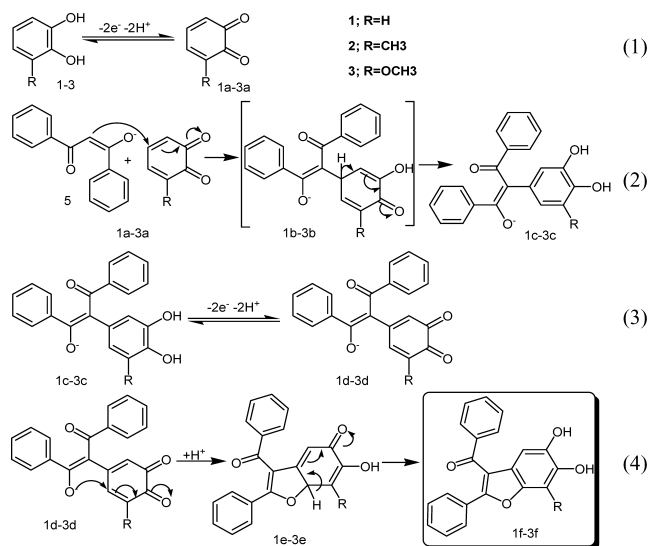
Chart 1

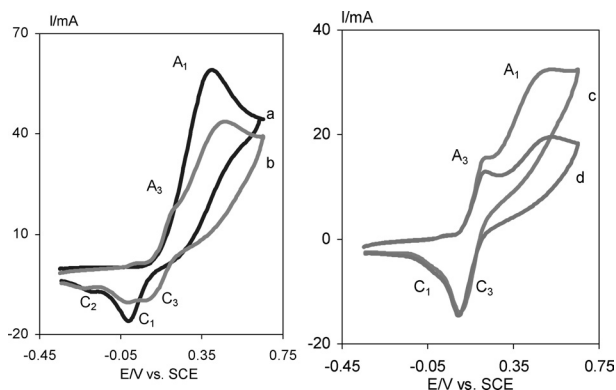* To whom correspondence should be addressed.   e-mail: nemat@basu.ac.ir

Fig. 2. Voltammograms of 0.20 mmol Catechol (**1**) in the Presence of 0.20 mmol Dibenzoylmethane (**5**), during Coulometry at 0.40 V *versus* SCE after Consumption of: a) 0, b) 25, c) 55 and d) 75 °C

Scan rate 50 mV s^{-1}. Other conditions are as same as Fig. 1.

Chart 2

creases (Fig. 1, II). A similar situation is observed when the **5** to **1** concentration ratio is decreased.

On the other hand, the current function for the A$_1$ peak, ($I_{pa}/v^{1/2}$), decreases on increasing the scan rate and such a behavior is adopted as indicative of an ECEC mechanism.[12] Also, proportional to the augmentation of sweep rate, the height of the C$_2$ peak decreases. This peak disappears in very high or low scan rates. Controlled-potential coulometry was performed in a cell containing 0.2 mmol of **1** and 0.2 mmol of **5**. Cyclic voltammetric analysis was carried out during the coulometry shows the progressive formation of new anodic peak (A$_3$) and its cathodic counterpart (C$_3$) parallel to the disappearance of A$_1$ peak, this peak (A$_3$) is related to the transformation of intermediate **1c** to **1d** (Chart 1). Also, C$_2$ peak decreased parallel to decrease in the height of C$_3$. This peak can be related to the over-reduction of **1c**. All anodic and cathodic peaks disappear when the charge consumption becomes about 4e$^-$ per molecule of **1** (Fig. 2).

These observations allow us to propose the pathway in Chart 1 for the electro-oxidation of **1**—**3** in the presence of **5**. According to our results, it seems that the Michael addition of anion enolate **5** to **1a** (Eq. 2) is faster than other secondary reactions, leading to the **1c**. The oxidation of **1c** is easier than the oxidation of **1** by virtue of the presence of an electron-donating group. The intramolecular Michael addition reaction is last step (Eq. 4) to formation of benzofuran derivative **1f** as a final product. The over-oxidation of **1f** was circumvented during the preparative reaction because of the more difficult oxidation of it.[10] The electro-oxidation of 3-methlycatechol (**2**) and 3-methoxycatechol (**3**) in the presence of **5** proceeded in a similar way to that of **1**.

The presence of a methyl or methoxy group at the C-3 position of **2a** and **3a** could mean that the corresponding *o*-quinones could be attacked by the anion of **5** at either or both C-4 and C-5 positions to yield two isomeric products. However, the comparison of experimental and calculated,[13] ^{1}H- and ^{13}C-NMR data showed formation of **2f** and **3f**, respectively. In the case of **3**, also, we obtained a novel quinone methide type compound **3j** *via* intermolecular Michael addition of anion **3** to the *o*-quinone **3d**, reoxidation of adduct **3h** and tautomeric conversion of *o*-quinones **3i** to *p*-quinone methide **3j** (Chart 2). The extension of π-conjugation is driving force of conversion of **3i** to **3j**.[14]
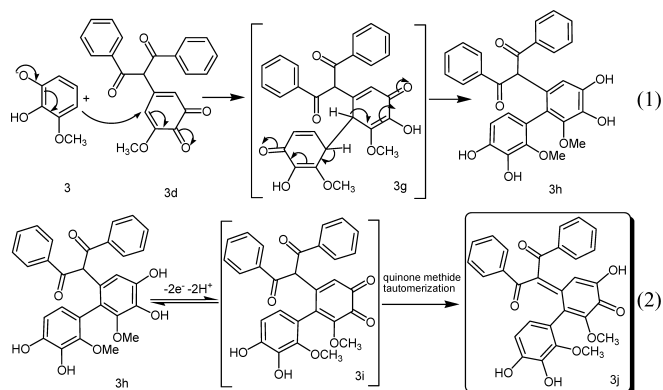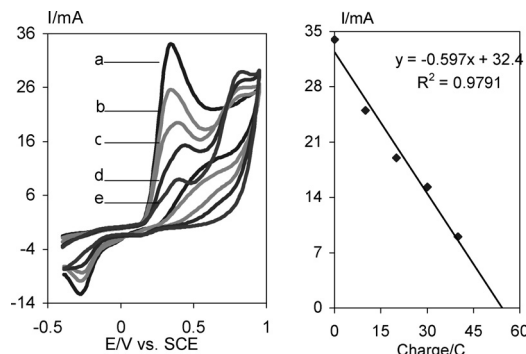

Fig. 3. Cyclic Voltammograms of 0.25 mmol 2,5-Dihyroxybenzoic (**4**) Acid in the Presence of 0.25 mmol Dibenzoylmethane (**5**) during Controlled Potential Coulometry at 0.45 V *versus* SCE after Consumption of: a) 0, b) 10, c) 20, d) 30 and e) 40 °C

Scan rate 50 mV s^{-1}. Other conditions are as same as Fig. 1.

Under the same conditions the electro-oxidation of 2,5-di-hydroxybenzoic acid (**4**) in the presence of **5** has been studied. Figure 3, curve a, shows the cyclic voltammogram obtained for a 0.25 mmol solution of **4** in the presence of 0.25 mmol **5**. It was observed that, proportional to the advancement of coulometry, the anodic peak A$_1$ decreases and a new anodic peak (A$_2$) appears and its current increases. Peak A$_2$ is related to irreversible oxidation of benzofuran **4e**. The irreversibility character of this peak indicates that there is no hydroquinone ring in the structure of final product (**4e**). Hydroquinone rings show a reversible or quasi-reversible behavior.[11] Peak A$_1$ disappears and peak A$_2$ reaches to a maximum value when the charge consumption becomes about 2e$^-$ per molecule of **4**. These observations allow us to propose the pathway in Chart 3 for the electro-oxidation of **4** in the presence of **5**.

The Michael addition of anion enolate **5** to *p*-quinone **4a** (Eq. 2) leading to the **4c**. The ring-chain tautomerism[15] and the removal of a water molecule from **4d** (dehydration) are the last steps (Eq. 3) to formation of benzofuran derivative **4e** as a final product. The over-oxidation of **4e** was circumvented during the preparative reaction because of the more difficult oxidation of **4e**.[11] The electro-oxidation of **4** in the presence of **5** is considered to involve the Michael acceptor **4a** could be attacked at positions C-2, C-4 or C-5 to yield three isomeric products. However, the comparison of experimental and calculated,[13] ^{1}H- and ^{13}C-NMR data showed for-
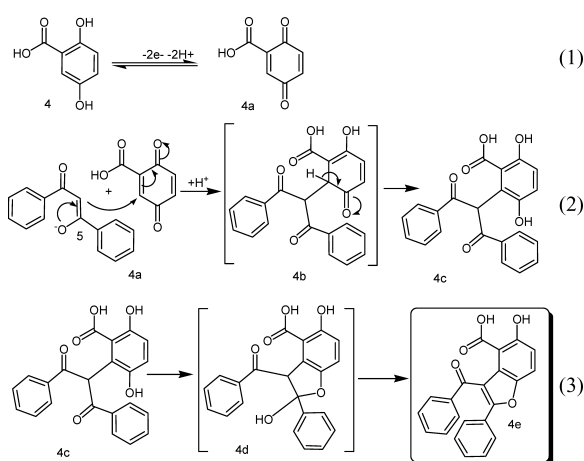
Chart 3

Table 1. Electroanalytical and Preparative Data

Compound	Applied potential (*vs.* SCE)	Melting point (°C)	Product yield (%)
1f	0.40	179—181	84
2f	0.45	175—177	92
3f	0.45	174—177	30
3j	0.45	231—232	32
4e	0.40	177—179	93

mation of **4e**.

The results of this work show that benzenediols (**1**—**4**) are oxidized to their respective quinones. The quinones are then attacked by anion of **5** *via* intermolecular Michael addition reaction. We observed diversity in their behavior of formed adducts in next steps (Charts 1—3). The overall reaction mechanisms for anodic oxidation of benzenediols (**1**—**4**) in the presence of **5** are presented in Charts 1—3. According to our results, it seems that the Michael reaction of this nucleophile to Electrogenerated benzoquinones leads to the formation of new benzofuran derivatives as final products, with high atom economy, good yields and purity in one-pot manner.

Experimental

Apparatus and Reagents Reaction equipment is described in an earlier article.[10] All chemicals were reagent-grade materials, and Sodium acetae was of proanalysis grade. These chemicals were used without further purification.

Synthesis of Products In a typical procedure, a solution (*ca.* 80 ml) of 0.1 M sodium acetate in water/acetonitrile (50/50) containing 1 mmol of benzenediols (**1**—**4**) and dibenzoylmethane (**5**) (1 mmol) was electrolyzed in an undivided cell equipped with carbon anode (an assembly of four rods, 6 mm diameter and 6 cm length) and a large platinum gauze cathode at the chosen potential (Table 1). The electrolysis was terminated when the decay of the current become more than 95%. At the end of electrolysis, the electrolyzed solution was added to an aqueous solution (*ca.* 200 ml) containing acetic acid (1%) and potassium chloride (2.5 g), and was placed in a refrigerator overnight. The precipitated solid was collected by filtration and then has been recrystallized by slow diffusion of *n*-hexane vapor into ethyl acetate solution.

Compounds Characterization (5,6-Dihydroxy-2-phenylbenzofuran-3-yl)(phenyl)methanone (**1f**): IR (KBr, v cm^{-1}): 3551, 3189, 1611, 1460, 1400, 1311, 1130, 915, 746, 697. ^{1}H-NMR (90 MHz, acetone-d_6) δ: 4.8

(broad, 2H), 6.9—8.2 (m, 12H). ^{13}C-NMR (125 MHz, acetone-d_6) δ: 98.5, 106.1, 117.1, 121.1, 128.7, 129.2, 129.3, 129.9, 130.3, 133.8, 139.1, 144.1, 146.1, 149.4, 156.8, 192.6. MS (relative intensity): 330 (79), 253 (24), 105 (100), 77 (62).

(5,6-Dihydroxy-7-methyl-2-phenylbenzofuran-3-yl)(phenyl)methanone (**2f**): IR (KBr, v cm^{-1}): 3500, 3210, 1648, 1600, 1361, 1161, 891, 686. ^{1}H-NMR (90 MHz, acetone-d_6) δ: 2.3 (s, 3H); 6.8—8.2 (m, 11H). ^{13}C-NMR (125 MHz, acetone-d_6) δ: 8.9, 107.4, 110.5, 118.5, 120.7, 127.0, 128.0, 129.3, 129.5, 133.0, 133.4, 136.0, 137.7, 143.6, 148.2, 152.2, 192.4. MS (relative intensity): 344 (49), 223 (81), 147 (42), 105 (100), 77 (78).

(5,6-Dihydroxy-7-methoxy-2-phenylbenzofuran-3-yl)(phenyl)methanone (**3f**): IR (KBr v cm^{-1}): 3380, 1623, 1599, 1573, 1446, 1373, 1341, 1080, 909, 695. ^{1}H-NMR (90 MHz, acetone-d_6) δ: 3.8 (s, 3H); 6.7—8.1 (11H). ^{13}C-NMR (22.5 MHz, acetone-d_6) δ: 56.2, 96.5, 111.0, 117.7, 119.4, 125.9, 127.3, 128.3, 128.8, 129.0, 129.3, 130.1, 132.9, 134.1, 136.4, 140.9, 142.6, 191.7. MS (relative intensity): 360 (49), 223 (24), 105 (100), 77 (83).

3-(3,4-Dihydroxy-2-methoxyphenyl)-4-(1,3-dioxo-1,3-diphenylpropan-2-ylidene)-6-hydroxy-2-methoxycyclo hexa-2,5-dienone (**3j**): IR (KBr v cm^{-1}): 3499, 1643, 1601, 1483, 1410, 1371, 1262, 1066, 906, 696. ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 3.8 (s, 3H); 4.2 (s, 3H); 6.2 (s, 1H); 7.2—7.8 (12H). ^{13}C-NMR (125 MHz, CDCl$_3$) δ: 55.2, 55.4, 97.6, 106.5, 114.6, 119.7, 122.1, 128.1, 128.7, 129.9, 133.7, 134.6, 137.4, 149.5, 151.4, 152.2, 154.7, 155.4, 184.8, 192.1. MS (relative intensity): 468 [M−OMe+H][16,17] (100), 422 (15), 105 (80), 77 (78), 51 (22).

3-Benzoyl-5-hydroxy-2-phenylbenzofuran-4-carboxylic Acid (**4e**): IR (KBr v cm^{-1}): 3058, 1732, 1676, 1490, 1194, 893, 830, 697. ^{1}H-NMR (300 MHz, acetone-d_6) δ: 4.8 (s, 1H), 7.0—8.2 (m, 12H), 11.2 (broad 1H). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 103.6, 115.7, 116.9, 117.7, 119.1, 127.2, 128.8, 129.9, 130.2, 133.0, 130.2, 138.8, 147.8, 155.2, 160.7, 164.6, 170.8, 192.2. MS (relative intensity): 358 (22), 339 (100), 314 (18), 254 (21), 236 (27), 105 (100), 77 (100).

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