

Electrochemical Oxidation of 4-Methylcatechol in the Presence of β-Diketones

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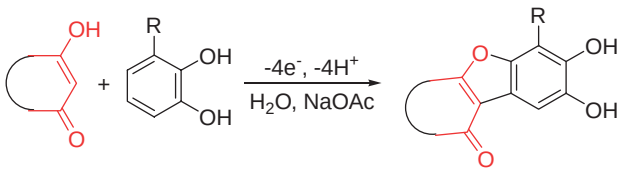
Received April 25, 2008; E-mail: nemat@basu.ac.ir

Electrochemical oxidation of 4-methylcatechol (**1**) in the presence of, benzoylacetone (**2**), dibenzoylmethane (**3**), 3-hydroxy-1*H*-phenalen-1-one (**4**), acetylacetone (**5**), dimedone (**6**), and 2-acetylcyclohexanone (**7**) as nucleophiles has been studied in detail by cyclic voltammetry and controlled-potential coulometry. The results indicate that the electrochemically generated quinone participates in Michael addition reaction with **2**–**7** via various mechanisms to produce new organic compounds. Furthermore, our studies show that the structure of intermediates play a crucial role in product selectivity under controlled-potential conditions. Various types of products were also obtained through the selective oxidation at the surface of a carbon electrode in an undivided cell.

Electrochemical oxidation is very mild and similar to enzymatic oxidation in biological systems. It often parallels the cytochrome P450-catalyzed oxidation in liver microsomes.[1] Since the electrode potential can be controlled over a wide range, a wide variety of electroorganic reactions are able to be designed in electrochemical synthesis. Also, the fact that the active species is formed at an interface donates some unique selectivities such as regio-, stereo-, and chemo-selectivities to these reactions.[2] Electrochemistry of catechols and their application in electrochemical synthesis is well known because of reversible oxidation of catechols and reactivity of generated *o*-quinones. Previously we have shown that electrochemically generated *o*-quinones are quite reactive and participate in various reactions.[3–9] Electrochemically generated C-3 substituted *o*-quinones attacked by β-diketones as nucleophiles via intermolecular Michael reaction, oxidation, and intramolecular addition to form corresponding benzofuran derivatives (Scheme 1).[10–16] Under the same conditions, final products of electrochemical oxidation of C-4 substituted catechols in the presence of nucleophiles is dependant on the nature of the substituents. Presence of a leaving group at the C-4 position cause formation of products similar to C-3 substituted catechol,[11] whereas the presence of a blocking group such as *t*-butyl inhibits its intramolecular addition and leads to the formation of different types of products.[17,18]

4-Methylcatechol is known as nonamine, a 4-alkylcatechol with biologic and therapeutic effects. It is a potent stimulator of nerve growth factor (NGF) synthesis and increases the NGF mRNA level of astroglial cells.[19] 4-Methylcatechol stimulates de novo synthesis of brain-derived neurotrophic factor (BDNF) in the infant rat brain,[20] increases the expression of Metallothionein mRNA in fetal mouse brain cells,[21] and protects neurons against experimental injury.[22] Also, contrary to our previous work the methyl group in C-4 position cannot act as a leaving group or blocking group.[17,18] Therefore, oxidation of 4-methylcatechol in the presence of nucleophiles with two acidic protons is complicated. This idea prompted us to investigate the electrochemical oxidation of 4-methylcatechol (**1**) in the presence of β-diketones **2**–**7**. We herein report the development of a procedure for one-pot, efficient, and selective syntheses of some new functionalized heterocycles and catechols.



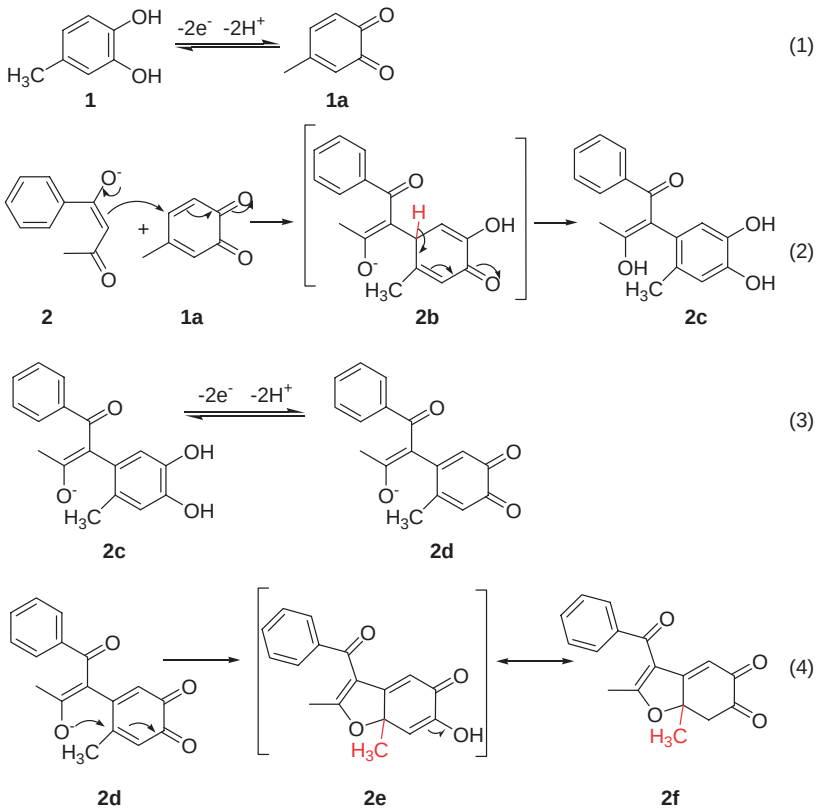
Scheme 1.

Results and Discussion

The electrochemical study of 1.0 mM solution of 4-methylcatechol (**1**) in a mixture of water/acetonitrile (80/20) containing sodium acetate solution (0.15 M) was performed using cyclic voltammetry (Figure 1, curve a). The voltammogram shows one anodic (A_1) and the corresponding cathodic peak (C_1) which correspond to the transformation of 4-methylcatechol (1) to the corresponding *o*-quinone (**1a**) and vice versa (Scheme 2, eq 1).[3–9]

Figure 1, curve b, shows a cyclic voltammogram of 1.0 M 4-methylcatechol (**1**) in the presence of 1 mM benzoylacetone (**2**) under the same conditions. In this case, the height of anodic peak (A_1) increases, cathodic peak (C_1) decreases, and a new cathodic peak (C_2) appears at lower potential. Anodic peak A_1 shifts to positive potential which can be due to formation of a thin film of product at the surface of the electrode inhibiting to a certain extent the performance of the electrode.[3–9] In this figure, curve c is the cyclic voltammogram of benzoylacetone (**2**). Figure 2 shows the effect of scan rate on the cyclic

Published on the web November 12, 2008; doi:10.1246/bcsj.81.1505



Scheme 2.

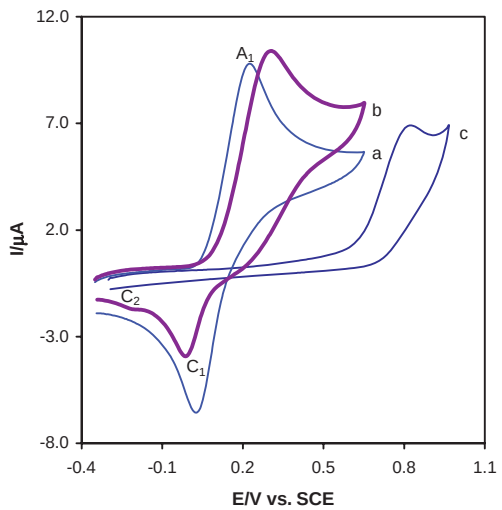


Figure 1. Cyclic voltammograms of 1.0 mM 4-methylcatechol: a) in the absence of benzoylacetone, b) in the presence of 1.0 mM benzoylacetone, and c) 1.0 mM benzoylacetone in the absence of 4-methylcatechol (**1**). Solvent system water/acetonitrile (80/20) solution containing 0.15 M sodium acetate. $t = 25\,^{\circ}C$, scan rate: 50 mV s^{-1}.

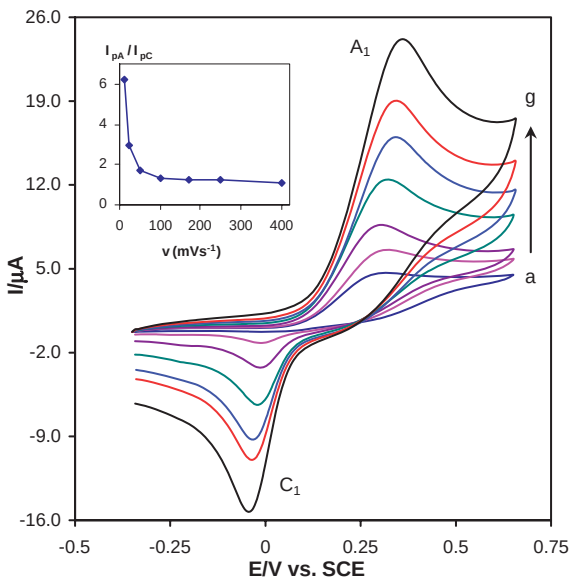


Figure 2. Cyclic voltammograms of 1.0 mM 4-methylcatechol in the presence of 1.0 mM benzoylacetone at various scan rates. Scan rates from a) to g) are: 10, 25, 50, 100, 170, 250, and 400 mV s^{-1}, respectively. Other conditions are the same as Figure 1. Inset: variation of peak current ratio versus scan rate.

voltammograms of 4-methylcatechol (**1**) in the presence of benzoylacetone (**2**).

It is seen that proportional to the augmentation of potential sweep rate, the height of the C_1 peak increases. In other words the peak current ratio (I_{pA1}/I_{pC1}) decreases with increasing scan rate (Figure 2, inset). Both cathodic peaks (C_1 and C_2) nearly disappear at very low scan rates, also cathodic peak C_2 disappears at high scan rates. A normalized cyclic voltammogram is obtained by dividing the cyclic voltammogram current by the square root of the scan rate. Multiple files at differ-

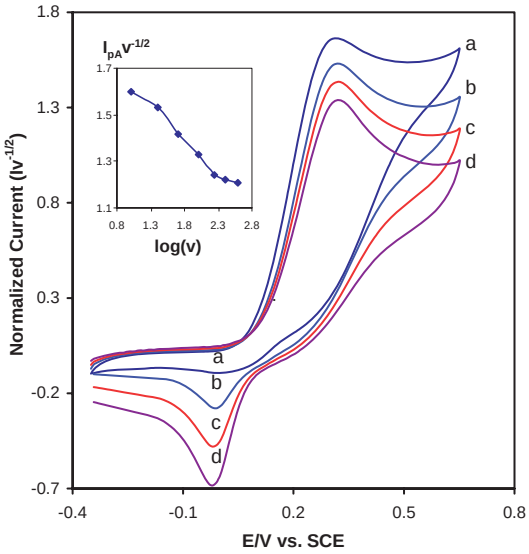


Figure 3. Normalized cyclic voltammograms at various scan rates. Scan rates from a) to d) are 10, 25, 50, and 100 mV s^{-1}. Other conditions are the same as Figure 2, inset variation of current function versus scan rate.

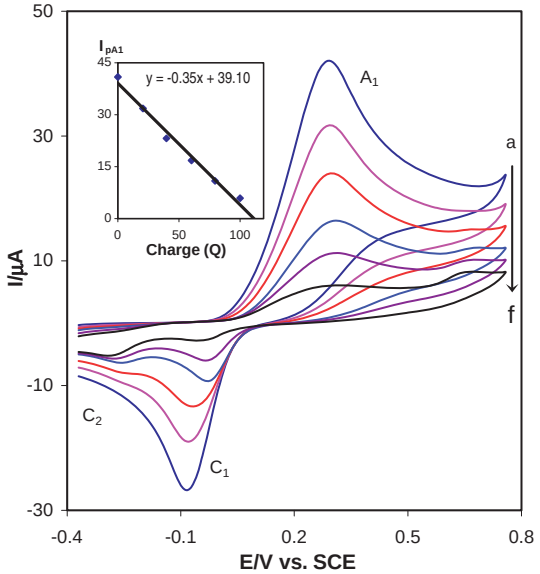
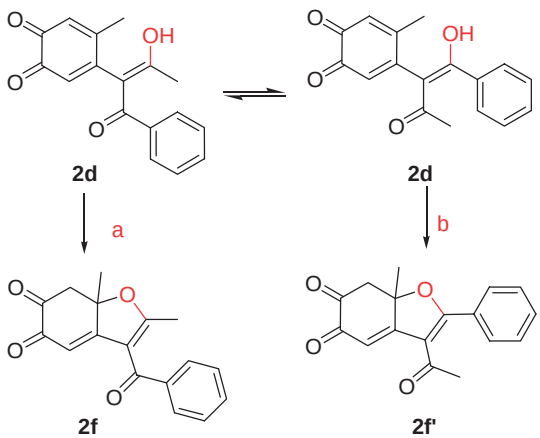


Figure 4. Cyclic voltammograms of 0.25 mmol 4-methylcatechol in the presence of 0.25 mmol benzoylacetone, at glassy carbon electrode during controlled-potential coulometry at 0.4 V versus SCE. After consumption of: (a) 0, (b) 20, (c) 40, (d) 60, (e) 80, and (f) 100 C. Inset: variation of peak current (I_{pA1}) versus charge consumed. Other conditions are the same as Figure 1.

ent scan rates can be normalized and overlaid for obtaining more information. Figure 3 shows normalized voltammograms of Figure 2, it is seen that proportional to the augmentation of potential sweep rate, the height of the normalized A_1 peak decreases and C_1 increases. On the other hand, the current function for the A_1 peak, ($I_{pa}v^{-1/2}$), decreases with increasing scan rate (Figure 3 inset).[23]

Decrease of peak C_1 in electrochemical oxidation of **1** in the presence of **2** is due to the participation of produced *o*-quinone (**1a**) in the following chemical reaction. Increase of normalized peak A_1 is due to immediate oxidation of intermediate **2c** that converts to its oxidized form **2d** because of its lower oxidation potential. *o*-Quinone **2d** can participate in fast intramolecular Michael reaction to give the final product **2f**. Owing to high reactivity of *o*-quinone **2d**, the height of peak C_2 which corresponds to its reduction disappears at very low scan rates. Controlled-potential coulometry (CPC) was performed in a cell containing 0.25 mmol of 4-methylcatechol (**1**) in the presence of 0.25 mmol of benzoylacetone (**2**). Cyclic voltammetric analysis was carried out during the coulometry (Figure 4) shows the progressive formation of a new cathodic peak (C_2) parallel to the disappearance of A_1 and C_1 peaks. All anodic and cathodic peaks disappear when the charge consumption becomes about $4e^-$ per molecule of 4-methylcatechol (**1**). Such a behavior is adopted as indicative of an ECEC mechanism.[10]

These observations allow us to propose the pathway in Scheme 2 for the electro-oxidation of 4-methylcatechol (**1**) in the presence of benzoylacetone (**2**). According to our results, it seems that the Michael addition of anion enolate **2** to **1a** (eq 2) is faster than other secondary reactions, leading to the **2c**. The oxidation of **2c** is easier than the oxidation of **1** by virtue of the presence of anion enolate **2** as an electron-donating group. Intramolecular Michael addition reaction is the last step (eq 4) and keto–enol rearrangement causes formation of final product **2f**.



Scheme 3.

As shown in Scheme 3 benzoylacetone (**2**) is an asymmetric β-diketone, this means that the intermediate **2d** can be attacked by either enolic hyroxy group to yield two isomeric products (Scheme 3, pathway a and b). However, spectroscopic data clearly shows that **2f** is the only product which is formed through pathway a.

Finally, the structure is further confirmed by single-crystal X-ray diffraction analysis that is shown in Figure 5.

The electro-oxidation of 4-methlycatechol (**1**) in the presence of dibenzoylmethane (**3**) and 3-hydroxy-1*H*-phenalen-1-one (**4**) proceeds in a similar way to that of benzoylacetone (**2**). The ^{1}H NMR results of the final products show a doublet–doublet pattern (δ 3.2 and 3.5, $J = 15$ Hz) and DEPT ($\theta = 3\pi/4$) indicates a methylene carbon for final products.[24,25] The overall reaction mechanism and the structure of final products **3f** and **4f** are shown in Scheme 4.

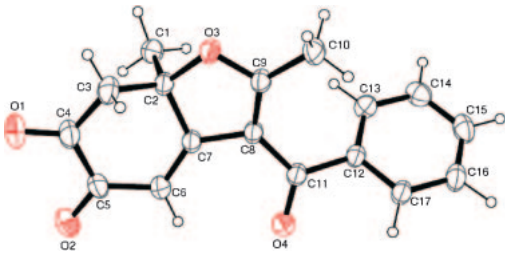
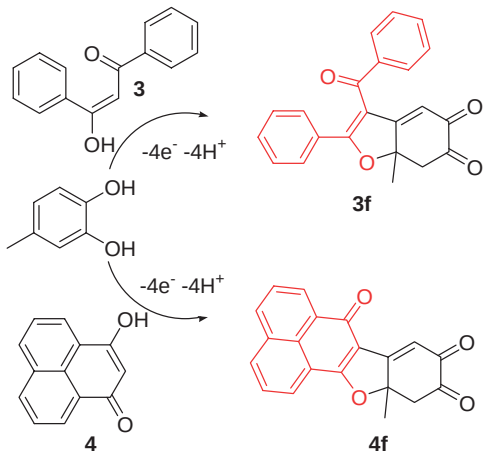


Figure 5. ORTEP depiction of compound **2f**.



Scheme 4.

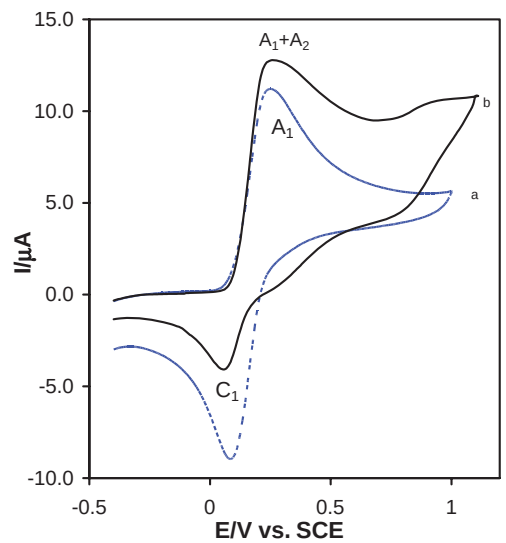
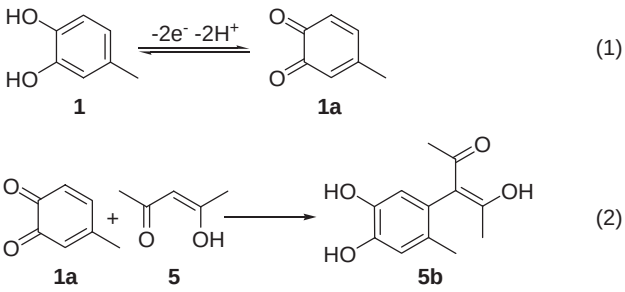
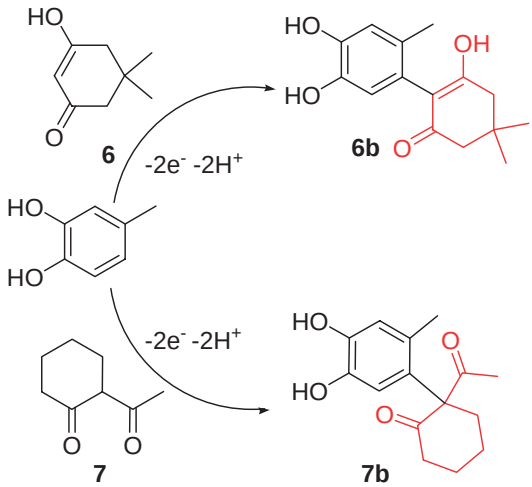


Figure 6. Cyclic voltammograms of 1.0 mM 4-methylcatechol (**1**): a) in the absence of acetylacetone (**5**), b) in the presence of 1.0 mM acetylacetone (**5**) in aqueous solution containing 0.10 M sodium acetate. $t = 25\,^{\circ}C$, scan rate: 50 mV s^{-1}.

Under the same conditions the electro-oxidation of 4-methylcatechol in the presence of acetylacetone (**5**) has been studied. Figure 6, curve b, shows the cyclic voltammogram obtained for a 1.0 mM solution of 4-methylcatechol (**1**) in the presence of 1.0 mM acetylacetone (**5**). Voltammetric studies show that the mechanism of reaction is ECEC but the oxidation potential of the intermediate is slightly more positive than 4-methylcatechol.



Scheme 5.



Scheme 6.

It was observed that during controlled-potential coulometry, proportional to the advancement of coulometry, the anodic peak A_1 decreases and anodic peak A_2 increases. Peak A_2 is related to oxidation of the catechol ring in **5b**. When peak A_1 disappears and peak A_2 reaches maximum value, the charge consumption becomes about $2e^-$ per molecule of **1**. These observations allow us to propose the pathway in Scheme 5 for the electro-oxidation of 4-methylcatechol in the presence of acetylacetone (**5**).

The electro-oxidation of 4-methlycatechol (**1**) in the presence of dimedone (**6**) and 2-acetylcyclohexanone (**7**) proceeded in a similar way to that of **5** (Scheme 6). CPC, IR, and NMR confirm existence of a catechol ring in the structure of final products **6b** and **7b**.

Contrary to previous cases, the over-oxidation of compounds **5b**, **6b**, and **7b** are more difficult than the oxidation of parent starting molecule **1** ($E_2 > E_1$) by virtue of the presence of the β-diketone **5–7** group with electron-withdrawing character on the catechol ring and therefore, the over-oxidation of these compounds was circumvented.

The dual behavior of β-diketones **2–7** is related to their acidity constants. In β-diketones **2–4** the presence of phenyl groups with electron-withdrawing character increase their acidity and anion fraction. While the presence of methyl or methylene groups with electron-donating character in **5–7** decrease the acidity,[26–28] their anion forms act as electron-donat-

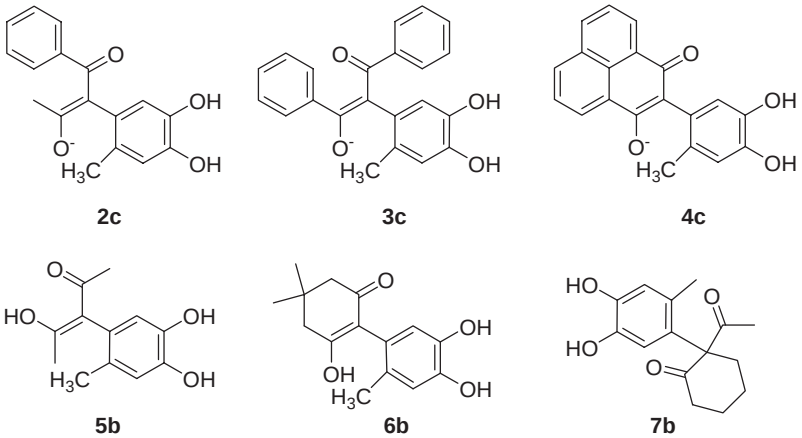
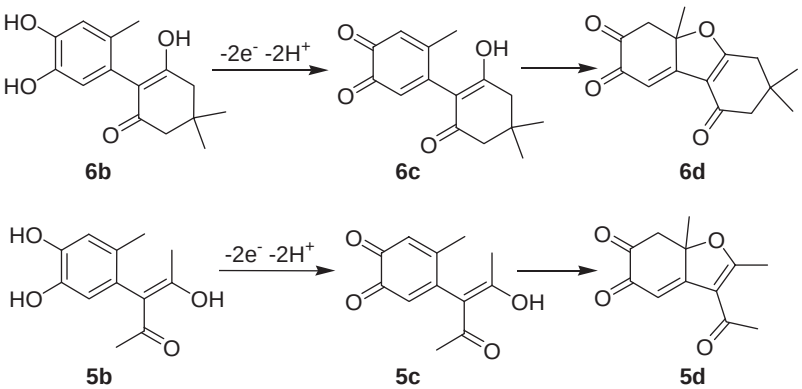


Figure 7. The structure of intermediates and final products.



Scheme 7.

ing groups, while in protonated form they are electron-withdrawing groups (Figure 7).

The over-oxidation (oxidation in more positive potentials) of **6b** leads to the formation of a four-electron product **6d** via an intramolecular Michael addition reaction, with structure similar to **2f–4f** (Scheme 7). In the case of **5b**, our attempts to separate and purify four-electron product **5d** were unsuccessful. This may be due to hydrogen bonding and less reactivity of hydroxy groups in compound **5c**. Contrary to **5b** and **6b**, compound **7b** has no acidic proton. Therefore, in over-oxidation of **7b**, we cannot obtain a four-electron product comparable to **2f–4f** or **6d**.

Conclusion

The results of this work show that 4-methylcatechol (**1**) is oxidized to its respective quinone. The overall reaction mechanisms for anodic oxidation of 4-methylcatechol (**1**) in the presence of β-diketones **2–7** are presented in Schemes 2–7. The electrochemically generated *o*-quinone is attacked by β-diketones via intermolecular Michael addition reaction. Oxidation potential of formed adduct is depend on the structure of the added β-diketone group. The oxidation potential of intermediates **2a**, **3a**, and **4a** are less than 4-methylcatechol (**1**) by virtue of the presence of anion enolates **2–4** as electron-donating groups. Their oxidation leads to formation of heterocycles **2f–4f** by consumption of $4e^-$ per molecule of **1** (ECEC mechanism). Conversely, the oxidation potential of adducts **5b**, **6b**, and **7b** are more than **1** by virtue of the presence of β-diketones **5–7** as electron-withdrawing groups. Therefore, electrochemical oxidation of **1** in the presence of **5–7**, leads to formation of compounds **5b–7b** as final products by consumption of $2e^-$ per molecule **1** (EC mechanism). Also our results show that in asymmetric β-diketones the reaction has good selectivity (specificity). Finally we derived various products with good yields and purity based on electrochemical oxidation in the controlled-potential condition as a selective and environmentally friendly method.

Experimental

Apparatus and Reagents. Reaction equipment is described in earlier articles.[4] All chemicals were reagent-grade materials, and Sodium acetate was of proanalysis grade. These chemicals were used without further purification.

Synthesis and Purification. In a typical procedure, solutions (ca. 80 mL) containing water or a suitable mixture of water/acetonitrile (Table 1) containing 0.1 M sodium acetate and 1.0 mmol of 4-methylcatechol (**1**) and β-diketones **2–7** (1 mmol) were 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 became more than 95%. At the end of electrolysis, 1 mL of acetic acid and 2.5 g of potassium chloride was added to the electrolyzed solutions and was placed in a refrigerator overnight. The precipitated

Table 1. Experimental Conditions for Synthesis and Purification of Products

Conversion	Applied potential[a)]/V	Synthesis solvent system	Isolated yield/%
1 → 2f	0.4	H_2O/AN (80/20)	86[b)]
1 → 3f	0.4	H_2O/AN (60/40)	89[b)]
1 → 4f	0.4	H_2O/AN (70/30)	77[b)]
1 → 5b	0.2	H_2O	92[c)]
1 → 6b	0.2	H_2O	82[c)]
1 → 6d	0.4	H_2O	51[b)]
1 → 7b	0.2	H_2O	68[c)]

a) Applied potential vs. SCE b) Crystallization solvent: hexane/ethyl acetate. c) Crystallization solvent: diethyl ether/chloroform.

solid was collected by filtration and then recrystallized by slow diffusion of hexane or diethyl ether vapor into ethyl acetate or chloroform respectively (Table 1). After recrystallization, products were characterized by: IR, ^{1}H NMR, ^{13}C NMR, MS, and X-ray. Table 1 shows the conditions and yield of isolated products.

Compounds Characteristics. 2f: Mp 158–161; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.74 (s, 3H), 3.13 (d, J = 15 Hz, 1H), 3.52 (d, J = 15 Hz, 1H), 6.14 (s, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 30.5, 51.5, 88.5, 114.2, 115.0, 128.7, 128.9, 133.5, 138.0, 171.3, 178.2, 182.4, 190.0, 190.6; MS (20 eV, EI): m/z (%): 283 (27), 282 (27), 254 (50), 241 (100), 240 (100), 239 (100), 225 (100), 212 (100), 211 (100), 197 (100), 183 (70), 165 (100), 152 (75), 115 (75), 105 (100), 77 (100), 43 (43); IR (KBr): ν = 3065, 2983, 2915, 1732, 1660, 1637, 1597, 1405, 1308, 1253, 949, 900, 740, 702. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-653923 for compound **2f**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

3f: Mp 181–183; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 3.54 (d, J = 14.4 Hz, 1H), 3.70 (d, J = 14.4 Hz, 1H), 6.22 (s, 1H), 7.32–7.40 (m, 3H), 7.46–7.54 (m, 5H), 7.79 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 51.4, 88.5, 112.9, 114.6, 128.3, 129.0, 129.1, 129.5, 129.7, 129.8, 133.2, 134.0, 137.4, 172.8, 174.3, 178.5, 190.9, 191.7; MS (20 eV, EI): m/z (%): 344 (25), 327 (20), 300 (65), 239 (18), 105 (100), 77 (100); IR (KBr): ν = 3059, 2972, 1773, 1653, 1536, 1393, 1248, 886, 734, 691.

4f: Mp 176–178; ^{1}H NMR (90 MHz, Acetone-d_6): δ 1.76 (s, 3H), 3.35 (d, J = 14.4 Hz, 1H), 3.49 (d, J = 14.4 Hz, 1H), 6.24 (s, 1H), 6.95–7.69 (m, 2H), 8.03–8.50 (m, 4H); MS (20 eV, EI): m/z (%): 316 (28), 301 (100), 283 (25), 255 (24), 196 (31), 149 (26), 69 (36), 55 (54), 43 (77); IR (KBr): ν = 2950, 1732, 1677, 1605, 1550, 1503, 1351, 1207, 1105, 896, 759.

5b: Mp 149–151; ^{1}H NMR (90 MHz, Acetone-d_6): δ 1.75 (s, 6H), 1.96 (s, 3H), 6.56 (s, 1H), 6.74 (s, 1H) 7.77 (br s, 2H), 16.63 (s, 1H); ^{13}C NMR (22.5 MHz, Acetone-d_6): δ 19.5, 24.0, 114.5, 118.4, 119.4, 128.5, 130.2, 144.5, 146.1, 192.3; MS (20 eV, EI): m/z (%): 222 (15), 204 (13), 179 (12), 161 (56), 137 (16), 115 (18), 69 (21), 43 (100); IR (KBr): ν = 3503, 3258, 1583, 1517, 1375, 1318, 1185, 972, 872, 814, 636.

6b: Mp 178–181; ^{1}H NMR (90 MHz, Acetone-d_6): δ 0.99 (s, 6H), 1.93 (s, 3H), 2.14 (s, 4H), 6.48 (s, 1H), 6.65 (s, 1H), 7.71 (br s, 3H); ^{13}C NMR (22.5 MHz, Acetone-d_6): δ 19.7, 28.3, 30.3, 47.7, 109.4, 118.2, 119.9, 124.4, 131.0, 143.9, 145.6, 184.7; MS (20 eV, EI): m/z (%): 262 (23), 244 (16), 188 (19), 124 (100), 83 (75), 78 (53), 56 (43), 39 (62); IR (KBr): ν = 3418, 2952, 1616, 1587, 1517, 1370, 1345, 1212, 1043, 1028, 865, 610.

6d: Mp 143–147; ^{1}H NMR (90 MHz, Acetone-d_6): δ 1.1 (s, 6H), 1.80 (s, 3H), 2.25 (s, 2H), 2.80 (s, 2H), 3.17 (d, J = 13 Hz, 1H), 3.41 (d, J = 13 Hz, 1H), 6.28 (s, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 27.2, 29.1, 30.8, 34.8, 50.7, 51.6, 77.3, 104.5, 108.6, 165.5, 170.2, 185.1, 192.4, 193.2; IR (KBr): ν = 2930, 1731, 1649, 1597, 1542, 1405, 1255, 1084, 900, 697.

7b: Mp 163–166; ^{1}H NMR (90 MHz, Acetone-d_6): δ 1.56–2.24 (m, 14H), 6.36 (s, 1H), 6.48 (s, 1H), 7.72 (br s, 2H); MS (20 eV, EI): m/z (%): 262 (24), 244 (18), 220 (100), 187 (50), 149 (83), 137 (65), 97 (35), 69 (48), 43 (67); IR (KBr): ν = 3424, 2940, 1725, 1701, 1653, 1608, 1503, 1289, 1195, 1101, 863.

We thank Professor Issa Yavari for helpful discussions, also financial support from the Research Affairs of Bu-Ali Sina University is gratefully acknowledged.

Supporting Information

Copies of ^{1}H, ^{13}C NMR, FTIR, and MS of all compounds **2f**–**4f**, **6d**, and **5b**–**7b**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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