A Facile Electrochemical Method for the Synthesis of 5-Phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol Derivatives

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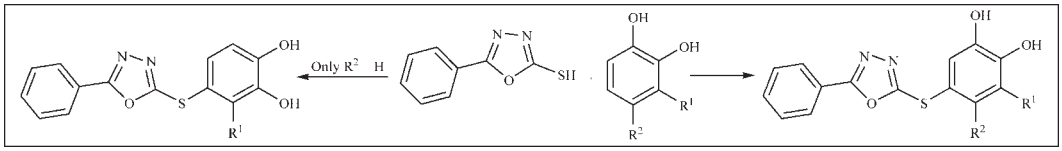

Electrochemical oxidation of catechols to corresponding *o*-quinones was successfully performed in aqueous solution by electrolysis at the controlled potentials. Quinones derived from catechols, participate in Michael addition reactions with 5-phenyl-1,3,4-oxadiazole-2-thiol and *via* EC mechanism, converted to corresponding 5-phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol derivatives (**4** and **4′**). The products have been characterized using IR, ^{1}H NMR, ^{13}C NMR, X-ray, and mass spectral data.

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INTRODUCTION

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds. Some material applications of 1,3,4-oxadiazole derivatives lie in the field of liquid crystals [1]. 1,3,4-Oxadiazole derivatives are also among the most widely used electron-conducting and hole-blocking materials in organic light-emitting diodes [2]. Substituted 1,3,4-oxadiazoles are associated with many types of biological properties [3–5]. The 2-aryl-5-(substituted)-1,3,4-oxadiazoles have been reported to show antibacterial [6,7], antifungal [8], anti-inflammatory [9,10], and hypoglycemic [7] activity. Catechols can be oxidized electrochemically to *o*-quinones. *O*-quinones derived from catechols are quite reactive and can be attacked by nucleophiles [11–15]. Regarding the importance of 1,3,4-oxadiazole derivatives in biological systems and following our previous works [16–19], we have reported the simple electrochemical method for the synthesis of some novel 1,3,4-oxadiazole derivatives from catechols and 5-phenyl-1,3,4-oxadiazole-2-thiol in this work.

RESULTS AND DISCUSSION

The electrochemical oxidation of catechols (**1a–d**) in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) undergoes a smooth 1:1 addition reaction in water medium at an ambient temperature to produce 5-phenyl-1,3,4-oxadiazol-2-ylthio-benzene-1,2-diol (**4** and **4′**). Cyclic voltammetry (CV) of 1 m*M* 4-methylcatechol (**1a**) in water/acetonitrile (95/5) solution containing 0.15*M* phosphate buffer (pH 7.2) shows one anodic (A_1) and corresponding cathodic peak (C_1), which is related to the transformation of 4-methylcatechol (**1a**) to *o*-benzoquinone (**2a**) and *vice versa* through a quasi-reversible two-electron process (Fig. 1, curve I).

A peak current ratio (I_P^{C1}/I_P^{A1}) of nearly one, particularly during the repetitive recycling of 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 [20] or dimerization [21] reactions are too slow to be observed on the time scale of the CV. Then, the electrochemical oxidation of catechols (**1**) was studied in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) as a nucleophile. Figure 1 (curve II) shows the cyclic voltammogram obtained for a 1 m*M* 4-methylcatechol (**1a**) in the presence of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**). The cyclic voltammogram of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) is shown in Figure 1, curve III, for comparison.

The multicyclic voltammograms of **1a** in the presence of **3** are shown in Figure 2. The voltammograms exhibit a relatively intense decrease in anodic peak (A_1) together with some potential shift in a positive direction. The positive shift of the A_1 peak in the presence of **3** is due to the formation of thin film of product at the surface of the electrode in the experimental condition [22].

Characteristics of the products are shown in Table 1. It can be observed that when methyl and methoxy groups are presented in C-3 position, two products are formed. This could be due to nucleophilic attack at either the C-4 or C-5 position. Further investigations

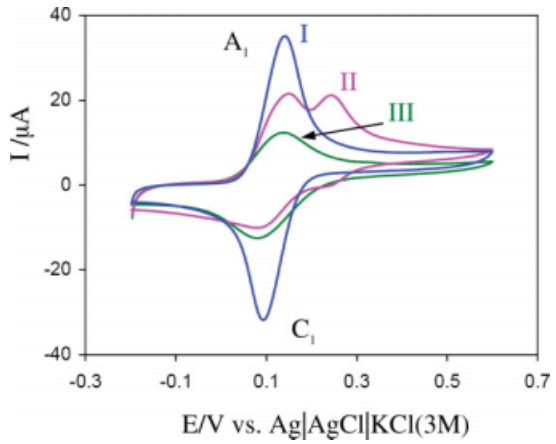


Figure 1. Cyclic voltammograms of 1 m*M* 4-methylcatechol (**1a**) in the absence (I) and in the presence (II) of 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) and 1 m*M* 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**) in the absence of 4-methylcatechol (III) at a glassy carbon electrode (1.8 mm diameter), in phosphate buffer (pH 7.2, $C = 0.15M$); scan rate: 100 mV s^{-1}; room temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

confirmed the suggestion using ^{1}H NMR results and single crystal X-ray diffraction analysis (Fig. 3).

The percentage of each isomer was calculated from the ^{1}H NMR spectrum according to the intensity of peaks that are observed in both aliphatic and aromatic regions.

These voltammetry and spectral results allowed us to propose an EC mechanism [23] for the electrooxidation of catechols in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (Scheme 1).

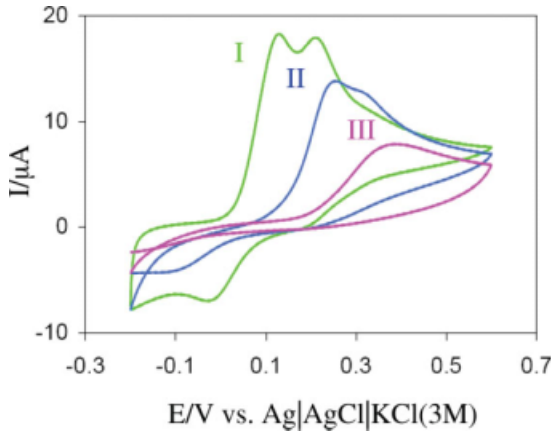
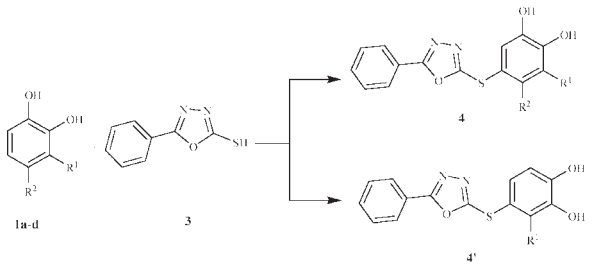


Figure 2. Multicycle voltammograms of 1 m*M* 4-methylcatechol (**1a**) in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**), at glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (95/5) containing of phosphates (KH_2PO_4/K_2HPO_4) as the buffer and supporting electrolyte (pH 7.2, $C = 0.15M$), scan rate: 100 mV s^{-1}; room temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1

The electrochemical synthesis of products (**4** and **4′**).



Entry	R^1	R^2	%Product yield[a](**4**:**4′**)
a	H	Me	94
b	H	H	82
c	OCH_3	H	91 (75:25)
d	CH_3	H	93 (32:68)

[a] Isolated yield.

EXPERIMENTAL

Apparatus and reagents. Cyclic voltammetry was performed using μAutolab potentiostat/galvanostat type III. Preparative analysis was carried out using an EG&G PAR A Model 174 A potentiostat/galvanostat. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc (1.8 mm diameter), and the platinum wire was used as the counter electrode (CE). The WE used in macroscale electrolysis was an assembly of three carbon rods (8 mm diameter and 4 cm length) and a large platinum gauze (3 × 3 cm^2) constituted the CE. The WE potentials were measured *versus* the Ag|AgCl|KCl (3*M*) as a reference electrode (all electrodes were obtained from Azar electrode, Urmia, I. R. Iran). NMR spectra were recorded on a Bruker DRx-300 Avance Instruments. IR spectra were recorded on a Bruker IFS-66 FTIR Spectrophotometer. Mass spectra were obtained using a QP-1100EX Shimadzu GC-MS (EI at 70 eV). Melting points of the products were obtained using an electrothermal melting point model 9200.

Chemicals (catechol, 3-methoxycatechol, 4-methylcatechol, and 5-phenyl-1,3,4-oxadiazole-2-thiol) were reagent-grade, and phosphate salts were of pro-analysis grade from E. Merck and

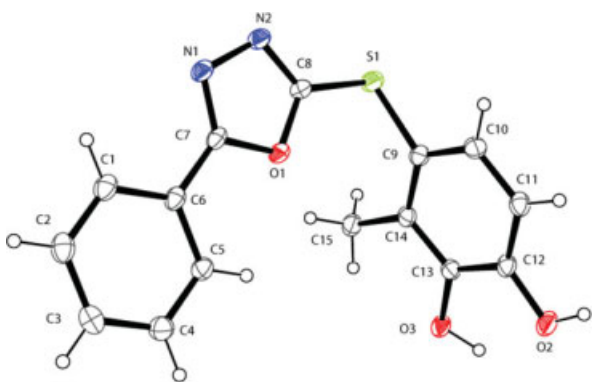
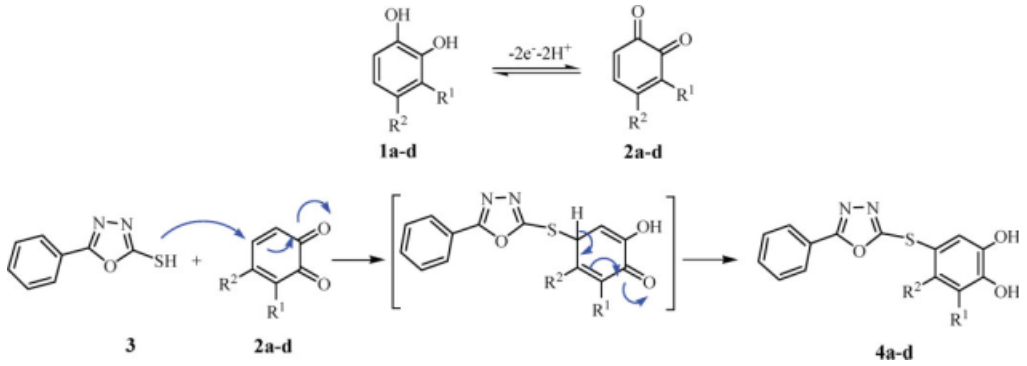


Figure 3. ORTEP structure of **4′d**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 1. Proposed mechanism for the electrooxidation of catechols in the presence of 5-phenyl-1,3,4-oxadiazole-2-thiol (**3**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



3-methylcatechol was reagent-grade from Acros. These chemicals were used without further purification. All experiments were carried out at room temperature.

Electroorganic synthesis of products. In a typical procedure, 100 mL mixture of water/acetonitrile (95/5) containing phosphates (KH_2PO_4/K_2HPO_4) as the buffer and supporting electrolyte (pH 7.2, $C = 0.15M$) was preelectrolyzed at the potential mentioned in Table 2 in an undivided cell. Subsequently, 2 mmol of catechols (**1a–d**) and 2 mmol of nucleophile (**3**) were added to the cell. Finally, the electrolysis was performed at the same potential.

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 carbon anode was washed in acetone to reactivate it. At the end of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and then was washed several times with distilled water. After purification, products were characterized using IR, ^{1}H NMR, ^{13}C NMR, X-ray, and Mass spectral data.

Characteristics of the products. ***4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-5-methylbenzene-1,2-diol (4a).*** m.p. 205–207°C. IR (KBr) ν (cm^{-1}): 3443, 2924, 1709, 1608, 1583, 1555, 1472, 1420, 1364, 1292, 1224, 1197. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.29 (s, 3H, CH_3), 6.81 (s, 1H, CH), 7.07 (s, 1H, CH), 7.58 (m, 3H, CH), 7.87 (m, 2H, CH), 9.42 (broad, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 20.08, 113.00, 118.55, 123.08, 123.43, 126.76, 129.90, 132.50, 133.80, 144.55, 148.63, 163.71, 165.76. MS (70 eV) *m*/*z* (relative intensity): 301 (5), 178 (30), 145 (30), 124 (63), 77 (100), 39 (60).

4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)benzene-1,2-diol (4b). m.p. 164–166°C. IR (KBr) ν (cm^{-1}): 3447, 2924, 1603, 1550, 1477, 1434, 1358, 1277, 1253, 1187, 1150. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.84 (d, $^3J_{HH} = 8.22$ Hz, 1H, CH), 7.01 (d, $^3J_{HH} = 8.22$ Hz, 1H, CH), 7.07 (s, 1H, CH), 7.57 (m, 3H, CH), 7.88 (m, 2H, CH), 9.62 (broad, 2H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 114.21, 117.10, 121.64, 123.40, 126.51, 126.81, 129.91, 132.57, 146.76, 148.34, 163.83, 165.88. MS (70 eV) *m*/*z* (relative intensity): 287 (10), 178 (55), 145 (30), 110 (70), 77 (100), 51 (55).

Mixture of 5-(5-phenyl-1,3,4-oxadiazol-2-ylthio)-3-methoxybenzene-1,2-diol (4c) 4-(5-phenyl-1,3,4-oxadiazol-2-ylthio)-3-methoxybenzene-1,2-diol (4′c). m.p. 175–178°C. IR (KBr) ν (cm^{-1}): 3367, 2937, 1600, 1551, 1503, 1472, 1341, 1293, 1196, 1088. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.68 (d, $^3J_{HH} = 8.40$ Hz, 1H, CH), 6.80 (s, 1H, CH), 6.83 (s, 1H, CH), 6.98 (d, $^3J_{HH} = 8.40$ Hz, 1H, CH), 7.56 (m, 6H, CH), 7.87 (m, 4H, CH), 9.34 (broad, 4H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.59, 61.00, 108.67, 110.03, 112.28, 113.76, 115.55, 123.42, 125.69, 126.72, 126.80, 129.91, 132.56, 137.03, 139.92, 146.91, 149.27, 150.32, 163.66, 165.62, 165.91. MS (70 eV) *m*/*z* (relative intensity): 317 (20), 178 (40), 140 (100), 97 (50), 77 (75), 43 (60).

5-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-3-methylbenzene-1,2-diol (4d). m.p. 180–181°C. IR (KBr) ν (cm^{-1}): 3062, 2924, 1591, 1550, 1514, 1471, 1414, 1349, 1266, 1189. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.12 (s, 3H, CH_3), 6.94 (br s, 2H, CH), 7.59 (m, 3H, CH), 7.88 (m, 2H, CH), 8.91 (broad, 1H, OH), 9.77 (broad, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm):16.26, 113.40, 118.94, 123.42, 126.50, 126.84, 127.77, 129.94, 132.59, 146.08, 146.28, 163.88, 165.90. MS (70 eV) *m*/*z* (relative intensity): 300 (30), 178 (32), 145 (75), 124 (36), 77 (100), 51 (48).

4-(5-Phenyl-1,3,4-oxadiazol-2-ylthio)-3-methylbenzene-1,2-diol (4′d). m.p.178–180°C. IR (KBr) ν (cm^{-1}): 3077, 2660, 1608, 1552, 1479, 1353, 1290, 1213, 1178. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.28 (s, 3H, CH_3), 6.75 (d, $^3J_{HH} = 8.29$ Hz, 1H, CH), 7.07 (d, $^3J_{HH} = 8.29$ Hz, 1H, CH), 7.56 (m, 3H, CH), 7.87 (m, 2H, CH), 8.74 (broad, 1H, OH), 9.98 (brod, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.52, 113.83, 114.46, 126.82, 127.83, 129.62, 132.47, 132.56, 144.95, 148.22, 165.67, 165.89. MS (70 eV) *m*/*z* (relative intensity): 300 (22), 178 (38), 124 (42), 77 (100), 39 (43).

Crystal data for (4′d) $C_{15}H_{12}N_2O_3S_1$, $M_w = 300.34$: space group monoclinic, $P2_1/a$, $a = 8.3924(6)$ Å, $b = 18.4381(15)$ Å, $c = 9.7245(6)$ Å, $\beta = 111.713(5)°$, $V = 1398.00(17)$ $Å^{-3}$:

Table 2

Applied potentials for the synthesis of products.

Conversion	Applied potential (*V*) *vs.* Ag|AgCl|KCl (3*M*)
1a → **4a**	0.15
1b → **4b**	0.2
1c → (**4c**:**4′c**)	0.10
1d → (**4d**:**4′d**)	0.15

$Z = 4$, $D_c = 1.427$ mg/m^3: $F(000) = 624$, crystal size = 0.20 mm × 0.16 mm × 0.12 mm, radiation Mo Kα ($\lambda = 0.71073$ Å), theta range for data collection 2.21°–29.28°. Intensity data were collected at 298 K with a STOE IDPS II two-circle diffractometer and using ω-scanning technique, in the range of $-11 \leq h \leq 10$, $-25 \leq k \leq 24$, $-13 \leq l \leq 13$. The structure was solved by direct methods [24] and refined an F^2 by full-matrix least squares using the X-STEP32 program package [25] giving a final $R_1 = 0.0684$, $wR_2 = 0.1520$ for $I > 2\sigma$ (I) reflections.

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