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Electroorganic Synthesis of Catecholthioethers

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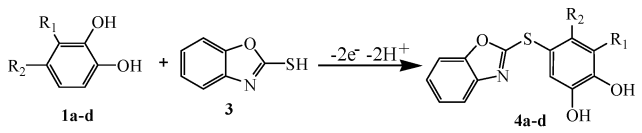

R1= H ,	R2= H	**1a,2a,4a**	Isolated Yield = 51%
R1= H ,	R2= CH_3	**1b,2b,4b**	Isolated Yield = 65%
R1= H ,	R2= *t*-Bu	**1c,2c,4c**	Isolated Yield = 68%
R1= OCH_3,	R2= H	**1d,2d,4d**	Isolated Yield = 55%

It is demonstrated that *o*-quinones, generated by the electrochemically driven oxidation of the catechols (**1a**−**d**) at physiological pH, are rapidly scavenged by 2-mercaptobenzoxazole (**3**) to give related catecholthioethers (**4a**−**d**) via an EC electrochemical mechanism pathway. The electrochemical syntheses of **4a**−**d** have been successfully performed in one-pot in ambient conditions and in an undivided cell using an environmentally friendly method with high atom economy.

Thiols, as one of the intercellular reducing agents, generally protect biological systems against oxidative and inflammatory stress by serving as radical scavengers and/or cofactors for intracellular enzymatic anti-oxidation functions.[1] The existence of sulfhydryl thiols (RSH) in biological media, such as human physiological liquids, makes their investigations very interesting, particularly from their anti-oxidation and/or pro-oxidation properties when they attach to cellular species. Picklo and coworkers showed that the ability of catecholthioethers to cause oxidative damages in vitro is not based simply upon the reduction potential, but rather reflects a complex relationship among structures of the parent catechol and thio adduct. The neurotoxicity of these adducts may be due to direct oxidative damage or possibly mitochondrial impairment.[2] Their studies also indicated that the structure of the individual catecholthioether, rather than E_{red}, is a major determinant in predicting oxidative damage and, on the other hand, demonstrated that catecholthioethers can possess pro-oxidant activities.[2] Therefore, with the aim of investigating electrooxidation of catechols in the presence of a thiol, and synthesis of a new class of catecholthioether compounds, as well as investigation of electrochemical oxidation potential of these new catecholthioethers, we investigated the electrooxidation of some catechols in the presence of 2-mercaptobenzoxazole (**3**) and synthesized new catecholthioethers in aqueous solutions with high atomic economy in ambient conditions and in undivided cell using a graphite electrode.

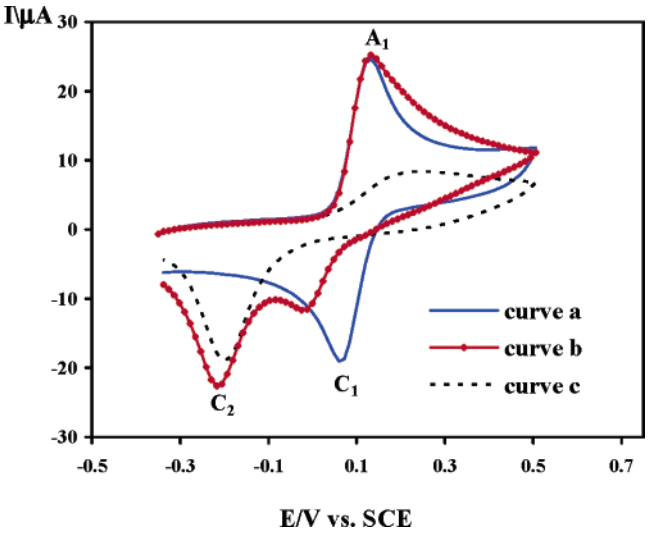

FIGURE 1. Cyclic voltammograms of 1 mM 4-*tert*-butylcatechol (**1c**). (a) In the absence and (b) in the presence of 1 mM 2-mercaptobenzoxazole (**3**), (c) 1 mM 2-mercaptobenzoxazole (**3**) in the absence of 4-*tert*-butylcatechol (**1c**) at glassy carbon electrode in water/acetonitrile (80/20) solution containing 0.2 M phosphate buffer (pH = 7.2). Scan rate: 200 mV s^{-1}; t = 25 ± 1 °C.

Cyclic voltammetry of 1 mM 4-*tert*-butylcatechol (**1c**) in water/acetonitrile (80/20) solution containing 0.2 M phosphate buffer (pH = 7.2) shows one anodic (A_1) and corresponding cathodic (C_1) peak which corresponds to the transformation of 4-*tert*-butylcatechol (**1c**) to its related *o*-benzoquinone (**2c**) and vice versa within a quasireversible two-electron process (Figure 1, curve a).[3] 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*-benzoquinone **2c** under the experimental conditions. In other words, any hydroxylation[4] or dimerization[3,5] reactions are too slow to be observed in the time scale of cyclic voltammetry. The oxidation of 4-*tert*-butylcatechol (**1c**) in the presence of 2-mercaptobenzoxazole (**3**) as nucleophile was studied in some detail. Figure 1, curve b, shows the cyclic voltammogram obtained for a 1 mM solution of **1c** in the presence of 1 mM 2-mercaptobenzoxazole (**3**). The voltammogram exhibits one anodic peak at 0.14 V versus SCE and two cathodic peaks (C_1 and C_2). In this figure, curve c is the voltammogram of 2-mercaptobenzoxazole (**3**) in

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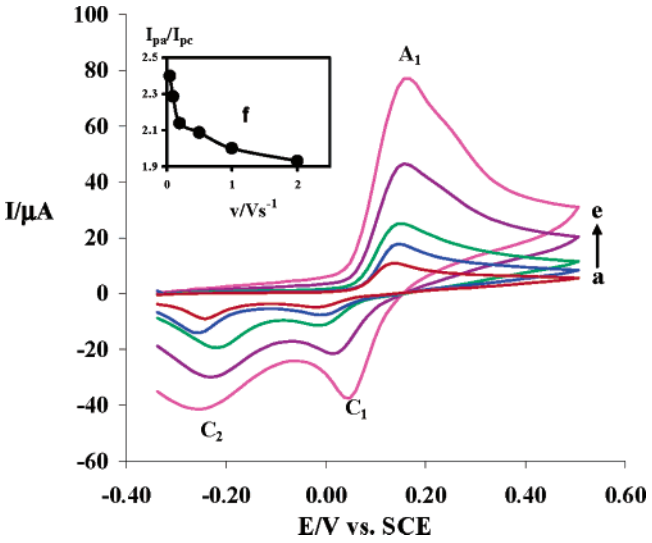

FIGURE 2. Typical cyclic voltammograms of 1 mM 4-*tert*-butylcatechol (**1c**) in the presence of 1 mM 2-mercaptobenzoxazole (**3**) at a glassy carbon electrode in water/acetonitrile (80/20) solution containing 0.2 M phosphate buffer (pH = 7.2) Scan rates from (a) to (e) are: 50, 100, 200, 500, and 1000 mV s^{-1}, respectively. (f) Variation of peak current ratio (I_p^{A1}/I_p^{C1}) versus scan rate; $t = 25 \pm 1$ °C

the same condition and in the absence of 4-*tert*-butylcatechol (**1c**). The cathodic peak that can be seen in both curves b and c at −0.2 V versus SCE is a well-defined peak corresponding to reduction of product of dimerization of 2-mercaptobenzoxazole (**3**).[6] The negative shift of the C_1 and C_2 peaks in the presence of **3** is probably 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.[7]

Furthermore, it is seen that, proportional to the augmentation of potential sweep rate, the height of the C_1 peak of **1c** increases (Figure 2, curves a−e). A similar situation is observed when the concentration ratio of the 2-mercaptobenzoxazole (**3**) to **1c** is decreased. A plot of peak current ratio (I_p^{A1}/I_p^{C1}) versus scan rate for a mixture of 4-*tert*-butylcatechol (**1c**) and 2-mercaptobenzoxazole (**3**) confirms the reactivity of **2c** toward 2-mercaptobenzoxazole (**3**), appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Figure 2, curve f). Such an electrochemical and cyclic voltammetry behavior is adopted as indicative of EC mechanism (Scheme 1).[7a,b,8]

Considering closeness of oxidation potential peaks of 4-*tert*-butylcatechol (**1c**) and 2-mercaptobenzoxazole (**3**) (Figure 1), to minimize the oxidation of 2-mercaptobenzoxazole (**3**) and hence achieving higher selectivity, we applied 0.10 V potential versus SCE in both coulometry

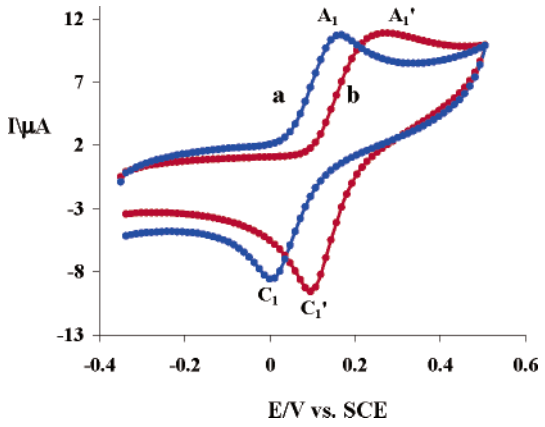

FIGURE 3. Cyclic voltammogram of (a) 1 mM 4-*tert*-butylcatechol (**1c**), (b) 1 mM obtained product (**4c**) at glassy carbon electrode in water/acetonitrile (50/50) solution containing 0.2 M phosphate buffer (pH = 7.2). Scan rate: 50 mV s^{-1}; $t = 25 \pm 1$ °C.

and preparative synthesis processes. Wittstock and coworkers reported that the main product in oxidation of 2-mercaptobenzoxazole (**3**) is bis(benzoxazolyl) disulfide.[9] To determine electrochemical efficiency, controlled potential coulometry of 4-*tert*-butylcatechol (**1c**) in the presence of 2-mercaptobenzoxazole (**3**) was performed at 0.10 V versus SCE. On the basis of obtained results, the electrochemical efficiency is 75%.

The preparative synthesis was performed in potentiostatic condition by oxidation of 4-*tert*-butylcatechol (**1c**) in the presence of 2-mercaptobenzoxazole (**3**) at 0.10 V versus SCE potential on a graphite rode anode electrode in an undivided cell. More detail is described in the Experimental Section.

According to our results, it seems that the 1,4-(Michael) addition reaction of **3** to *o*-quinone **2c** is faster than secondary reactions, leading to the product **4c**. The oxidation of this compound (**4c**) is harder than the oxidation of the parent-starting molecule (**1c**) by virtue of the presence of an electron-withdrawing group (Figure 3).

The existence of a methoxy group in **1d** probably causes the Michael acceptor **2d** to be attacked by 2-mercaptobenzoxazole (**3**) at the C-4 or C-5 positions to yield two types of products (**4a** and **5d**) in each case (Scheme 2). In this connection, the ^{1}H NMR spectrum of the obtained product indicates two singlet peaks for aromatic protons in the catechol ring (6.80 and 6.91 ppm) that are in agreement with the existence of two protons in the catechol ring in the meta positions.[10] Therefore, according to ^{1}H NMR results we suggest that *o*-quinone **2d** is attacked in C-5 position by **3** leading to the formation of **4d**.

From the point of view of green chemistry, use of the electrosynthesis method has some important advantages. Clean synthesis, use of electricity as energy instead of oxidative reagents, use of aqueous media (80% water) instead of organic solvents, one-step reaction, work in

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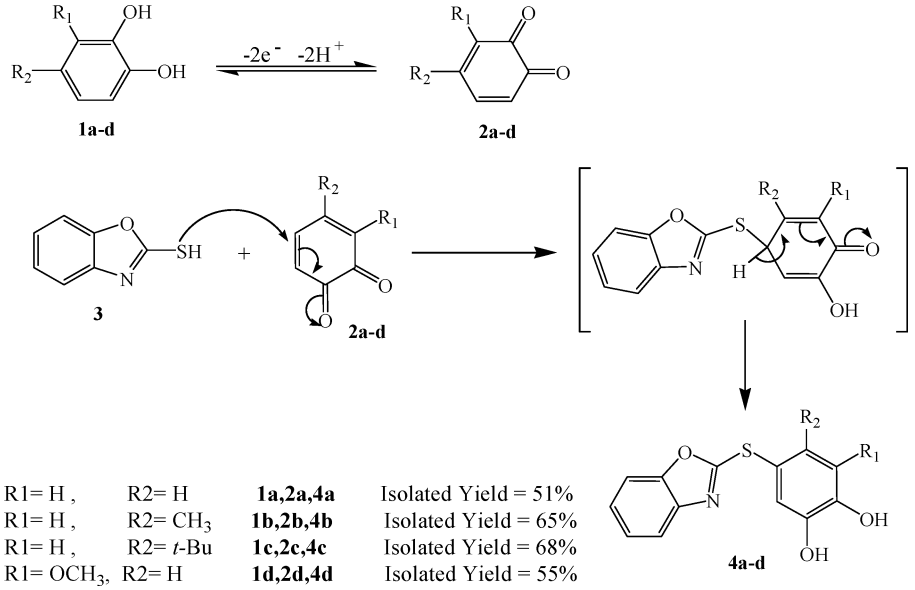
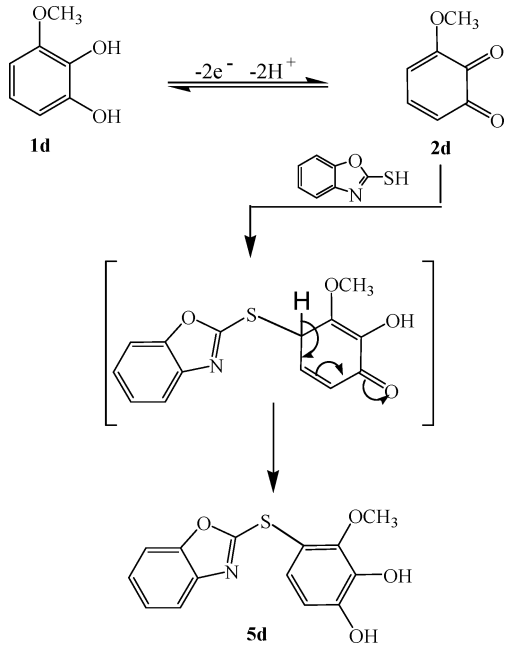
SCHEME 1



SCHEME 2



room temperature and pressure, technical feasibility, and especially dramatically high atom economy (>99%) are of preeminent green advantages.

Conclusion

The results of this work show that catechol derivatives are oxidized to their respective *o*-quinone. The formed *o*-quinone is attacked by 2-mercaptobenzoxazole (**3**) to form catecholthioethers (**4a**−**d**). The overall reaction mechanism for anodic oxidation of some catechols in the presence of 2-mercaptobenzoxazole (**3**) is presented in Scheme 1. According to our results, it seems that the Michael addition reactions of this nucleophile to formed *o*-quinone lead to the formation of new and unique catecholthioether derivatives (**4a**−**d**) as final products.

Experimental Section

Apparatus and Reagents. Reaction equipment is described in an earlier article.[7c] All chemicals (catechols, 2-mercaptobenzoxazole, and acetonitrile) were reagent-grade materials, and phosphate salts were of pro-analysis grade. These chemicals were used without further purification.

Electroorganic Synthesis of 4a−d. In a typical procedure, a solution (ca. 80 mL) of phosphate buffer solution in water/acetonitrile (80/20) (0.2 M, pH = 7.2) containing 1 mmol of catechols (**1a**−**d**) and 2-mercaptobenzoxazole (**3**) (1 mmol) was electrolyzed in an undivided cell equipped with a carbon anode (an assembly of four rods, 6-mm diameter, and 6-cm length) and a large platinum gauze cathode at 0.1 V versus SCE, at 25 °C. The electrolysis was terminated when the current decayed to 5% of its original value. The process was interrupted during the electrolysis for washing the graphite anode in acetone to activate it. At the end of electrolysis, the precipitated solid was collected by filtration and then was recrystallized in acetonitrile. After recrystallization, products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. The isolated yields of **4a**−**d** after recrystallization are reported in Scheme 1.

4-(Benzo[*d*]oxazol-2-ylthio)benzene-1,2-diol (4a) ($C_{13}H_9NO_3S$). mp 125−126 °C. ^{1}H NMR, δ (90 MHz DMSO d_6): 6.92−7.52 (m, aromatic), 9.54 (broad, −OH). ^{13}C NMR, δ (90 MHz DMSO d_6): 110.2, 113.8, 116.6, 118.5, 122.0, 124.4, 124.6, 126.8, 141.4, 146.2, 148.0, 151.3, 165.5. IR$_{(KBr)}$: 743, 809, 907, 1002, 1097, 1137, 1218, 1240, 1277, 1358, 1430, 1450, 1494, 1517, 1592, 3068, 3459 cm^{-1}. MS: *m/e* (relative intensity); 259 ($M^{+\bullet}$, 100), 198 (11.2), 170 (12.2), 153 (22.4), 141 (20.4), 119 (10.2), 91 (17.3), 63 (28.6), 39 (28.6).

4-(Benzo[*d*]oxazol-2-ylthio)-5-methylbenzene-1,2-diol (4b) ($C_{14}H_{11}NO_3S$). mp 198−200 °C. ^{1}H NMR, δ (90 MHz DMSO d_6): 2.23 (s, 3H, $-CH_3$), 6.85 (s, 1H, aromatic), 7.2 (m, 3H, aromatic), 7.5 (m, 2H, aromatic), 9.3 (broad, 2H, −OH). ^{13}C NMR, δ (300 MHz DMSO d_6): 20.1, 110.7, 113.3, 118.5, 118.9, 123.6, 124.7, 125.0, 134.1, 141.9, 144.5, 148.6, 151.7, 164.0. IR$_{(KBr)}$: 641, 745, 815, 869, 1003, 1096, 1134, 1236, 1270, 1354, 1380, 1424, 1454, 1496, 1599, 3078, 3427, 3523 cm^{-1}. MS: *m/e* (relative intensity); 273 ($M^{+\bullet}$, 100), 240 (72.9), 222 (18.6), 194 (30.5), 166 (78), 108 (23.7), 91 (22.0), 65 (35.6), 39 (54.2).

4-(Benzo[*d*]oxazol-2-ylthio)-5-tert-butylbenzene-1,2-diol (4c) ($C_{17}H_{17}NO_3S$). mp 168−171 °C. ^{1}H NMR, δ (90 MHz DMSO d_6): 1.24 (s, 9H, *-tert*-butyl), 7.06−7.52 (m, 6H, aromatic), 9.5 (broad, 2H, −OH). ^{13}C NMR, δ (90 MHz DMSO d_6): 31.4, 34.0, 110.2, 112.0, 115.8, 118.6, 122.3, 124.4, 124.6, 141.9, 142.6, 144.9, 145.9, 151.5, 163.4. IR$_{(KBr)}$: 651, 744, 811, 859, 961, 1099, 1138, 1213, 1240, 1291, 1364, 1416, 1456, 1501, 1597, 2866,

2963, 3013, 3506 cm^{-1}. MS: *m/e* (relative intensity); 315 ($M^{+\bullet}$, 77.5), 300 (100), 152 (55.1), 91 (28.6), 63 (12.2), 39 (20.4).

5-(Benzo[*d*]oxazol-2-ylthio)-3-methoxybenzene-1,2-diol (4d) ($C_{14}H_{11}NO_4S$). mp 157−159 °C. ^1H NMR, δ (90 MHz DMSO d_6): 3.75 (s, 3H, $-OCH_3$), 5.46 (broad, OH), 6.80 (s, 1H, aromatic), 6.91 (s, 1H, aromatic), 7.22 (m, 2H, aromatic), 7.46 (m, 2H, aromatic). ^{13}C NMR, δ (300 MHz DMSO d_6): 56.6, 110.7, 110.9, 113.6, 116.6, 119.0, 124.9, 125.1, 137.3, 141.9, 146.9, 149.2, 151.7, 164.1. $IR_{(KBr)}$: 679, 743, 810, 1000, 1095, 1109, 1132, 1203, 1217, 1237, 1298, 1332, 1356, 1452, 1511, 1605, 2841, 2940, 2995, 3040, 3510 cm^{-1}. MS: *m/e* (relative intensity); 289 ($M^{+\bullet}$, 100), 202 (10.2), 171 (22.4), 152 (12.2), 128 (12.3), 85 (19.4), 63 (20.4), 39 (42.8).

Supporting Information Available: Copies of ^1H, ^{13}C NMR, FTIR, and MS of compounds **4a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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