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An Efficient Electrochemical Method for Synthesis of (1*h*-1,2,4-triazol-3-ylthio)benzen-1,2-diol Derivatives

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ABSTRACT: *Electrochemical oxidation of catechols (**1a–c**) has been studied in the presence of 3-mercapto-1,2,4-triazole (**3**) as a nucleophile in water/acetonitrile (90/10) solutions. The results revealed that the quinones derived from catechols (**1a–c**) participate in the Michael addition reactions with anion of 3-mercapto-1,2,4-triazole (**3**) and are converted to the corresponding (1*H*-1,2,4-triazol-3-ylthio)benzen-1,2-diol derivatives (**4a–c**).* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:644–649, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20359

INTRODUCTION

Catechol is used in a variety of applications. It is used as a reagent for photography, dyeing fur, rubber and plastic production, and in pharmaceutical industry [1]. In addition, catechol derivatives play an important role in mammalian metabolism and many compounds of this type are known to be secondary metabolites of higher plants. In contrast, only 2 of more than 1800 examined antibiotics of microbial origin contain a catechol substructure. Therefore, the catechol derivatives are a promising group of compounds and are worthwhile for further investigation, which may lead to the discovery of selectively acting biodegradable agrochemicals having high human, animal, and plant compatibility [2]. Catechol itself and monosubstituted catechols (—OH, $-CH_3$, $-OCH_3$, —CHO, —COOH) are active in part against *Pseudomonas* and *Bacillus*, but not against *Penicillium* species. Caffeic acid is inhibitory to soil bacteria and fungi, but specific differences exist, whereas its methyl ester has more pronounced activity against *Bacillus* and *Pseudomonas* species. Hydroxychavicol inhibits a greater number of microorganisms including *Pseudomonas, Cladosporium*, and *Pythium* species. Many of flavonoids and catechol derivatives are also antimicrobial agents [3]. On the other hand, several members of the 1,2,4-triazole family have shown interesting biological properties, such as anti-allergic [4], antibacterial [5], and anti-HIV activity [6]. In addition, 1,2,4-triazoles are found to be in herbicides, fungicides, and dyes [7].

To synthesize compounds bearing 1,2,4-triazole and catechol moieties, we have investigated the electrochemical oxidation of catechols in the presence of 3-mercapto-1,2,4-triazole (**3**) as a nucleophile. The present work has led to the development of a facile and environmentally friendly reagent-less electrochemical method for synthesis of some new

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(1*H*-1,2,4-triazol-3-ylthio)benzen-1,2-diol derivatives at ambient conditions, with high-atomic economy and in undivided cell using graphite electrode.

RESULTS AND DISCUSSION

Cyclic voltammetry of a 2 mM solution of catechol (**1a**) in water/acetonitrile (90/10) solution containing 0.2 M acetate buffer (pH 5.5) shows one anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of catechol (**1a**) to *o*-benzoquinone (**2a**) and vice versa through a quasi-reversible two-electron process (Fig. 1, curve a). A peak current ratio (I_p^{Cl}/I_p^{Al}) of nearly unity, 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. It is noteworthy that the hydroxylation [8] or dimerization [9] reactions are too slow to be observed on the time scale of cyclic voltammetry. To get further support on the electrochemical oxidation of catechol (**1a**), the reaction was studied in the presence of 3-mercapto-1,2,4-triazole (**3**) as a nucleophile. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 2 mM solution of **1a** in the presence of 2 mM 3-mercapto-1,2,4-triazole (**3**). The voltammogram clearly exhibits an increase in anodic peak A_1 and a decrease in the cathodic peak C_1. For comparison, the cyclic voltammogram of a 2 mM solution of 3-mercapto-1,2,4-triazole (**3**) is shown in Fig. 1 (curve c).

The multicyclic voltammograms of **1a** in the presence of **3** are shown in Fig. 2. The voltammograms exhibit a relatively intense decrease in anodic peak current (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 probably due to the formation of a thin film of product at the surface of the electrode, inhibiting to certain extent the performance of electrode process [10].

Furthermore, it was observed that the height of the C_1 peak increased proportionally to the augmentation of potential sweep rate (Fig. 3, curves a–f). This confirms the reactivity of **2a** toward anion **3**. A similar situation was observed when the 3-mercapto-1,2,4-triazole (**3**) to **1a** concentration ratio is decreased. Moreover, the current function for the A_1 peak ($I_p^{Al}/v^{1/2}$) decreases slightly with an increasing scan rate (Fig. 3, curve g).

Controlled-potential coulometry was performed in an aqueous solution, containing 0.5 mmol (0.055 g) of **1a** and 0.5 mmol (0.051 g) of **3** at the potential of A_1 peak. The monitoring of electrolysis progress was carried out by cyclic voltammetry (Fig. 4). It is shown that, proportional to the advancement of coulometry, anodic peak A_1 decreases and disappear when the charge consumption becomes $2.3e^-$ per molecule of **1a**. These coulometry and voltammetry results allow us to propose an EC (electrochemical and chemical

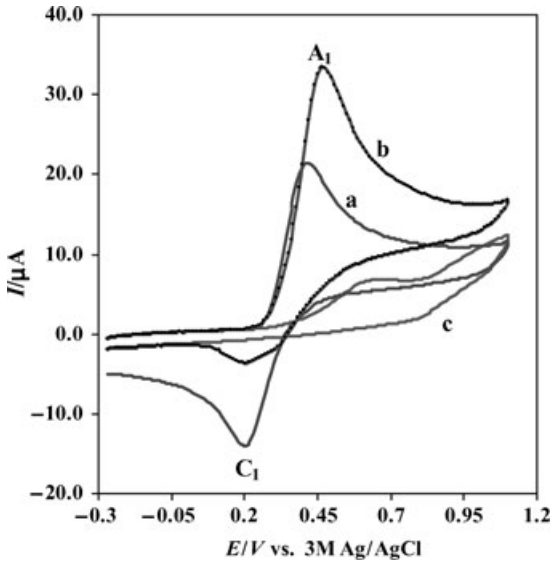


FIGURE 1 Cyclic voltammograms of 2 mM catechol (**1a**) in the absence (a) and presence (b) of 2 mM 3-mercapto-1,2,4-triazole (**3**) and (c) 2 mM 3-mercapto-1,2,4-triazole (**3**) alone, at glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (90/10) solution containing 0.2 M acetate buffer (pH 5.5). Scan rate: 50 mV s^{-1}; $t = 25 \pm 1°C$.

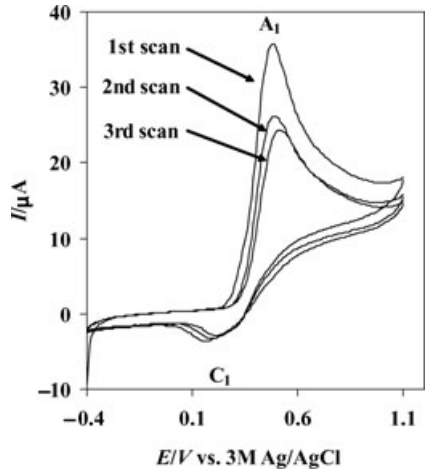


FIGURE 2 Multicyclic voltammograms of 2 mM catechol (**1a**) in the presence of 2 mM 3-mercapto-1,2,4-triazole (**3**), at glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (90/10) solution containing 0.2 M acetate buffer (pH 5.5). Scan rate: 50 mV s^{-1}; $t = 25 \pm 1°C$.

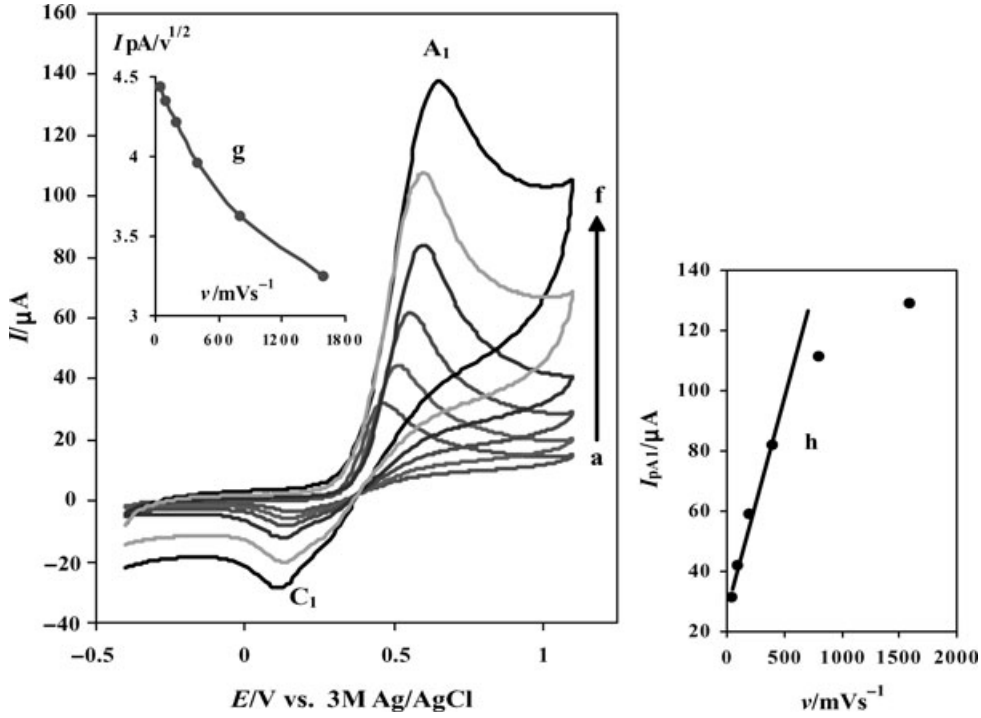


FIGURE 3 Typical voltammograms of 2.0 mM catechol (**1a**) in the presence of 2.0 mM 3-mercapto-1,2,4-triazole (**3**) in water/acetonitrile (90/10) solution containing 0.2 M acetate buffer (pH 5.5) at a glassy carbon electrode and at various scan rates. Scan rates from (a) to (f) are 50, 100, 200, 400, 800, and 1600 mV s^{-1}, respectively. Curve g: variation of peak current function ($I_p^{Al}/v^{1/2}$) versus the scan rate. Curve h: variation of peak current (I_p^{Al}) versus the scan rate. $t = 25 \pm 1°C$.

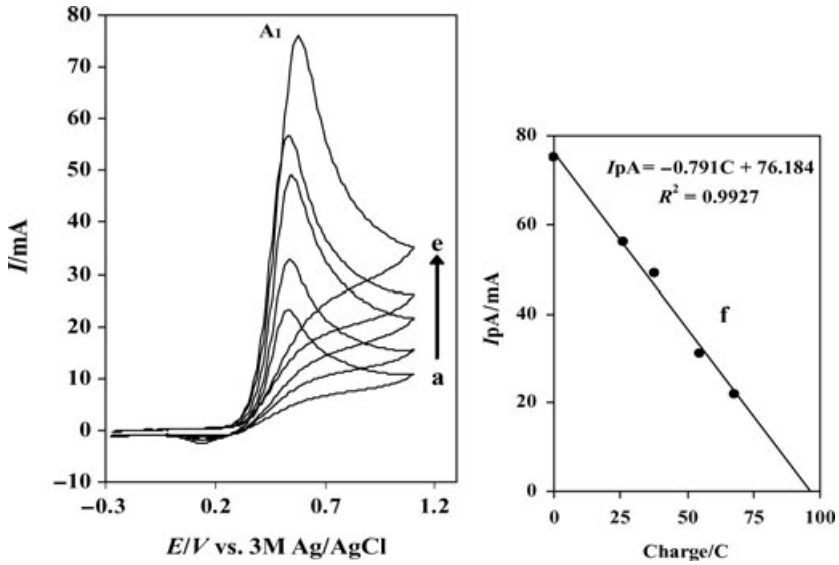
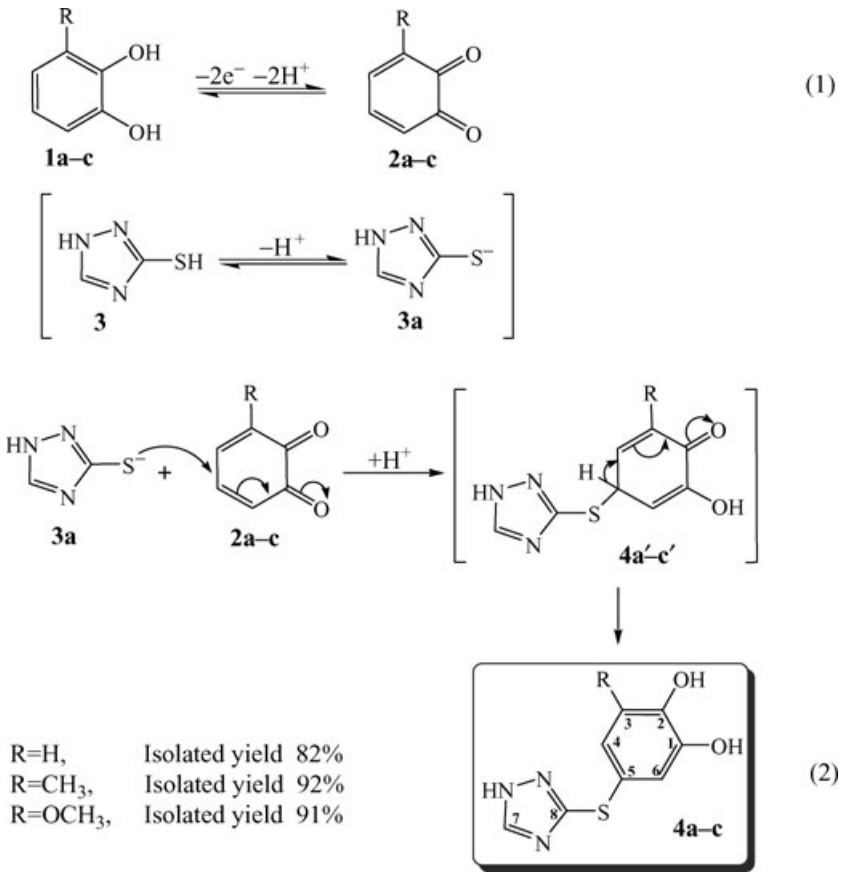


FIGURE 4 Cyclic voltammogram of 0.5 mmol catechol (**1a**) in the presence of 0.5 mmol 3-mercapto-1,2,4-triazole (**3**) in water/acetonitrile (90/10) solution containing 0.2 M actate buffer (pH 5.5) at a glassy carbon electrode during controlled-potential coulometry at 0.5 V versus 3M Ag\AgCl after the consumption of (a) 0, (b) 26, (c) 38, (d) 55, and (e) 68 C. (f) Variation of peak current (I_{pA1}) versus charge consumed. Scan rate 50 mV s^{-1}. $t = 25 \pm 1°C$.



SCHEME 1

reactions) mechanism [11] for the electrooxidation of **1a** in the presence of 3-mercapto-1,2,4-triazole (**3**) (Scheme 1).

According to our results, the Michael addition reaction of **3** to *o*-quinone (**2a**) (Eq. (2)) seems to occur much faster than other side reactions, leading to the product **4a**. The overoxidation of **4a** was circumvented during the preparative reaction because of the presence of mercaptotriazole group with electron-withdrawing character [12] on the catechol ring (Fig. 5) as well as the insolubility of the product in acetate buffer solution medium. The reason for anomalous increase in A_1 peak current, in the presence of 3-mercapto-1,2,4-triazole (**3**), is due to the presence of adsorption current in A_1 peak current arising from adsorption of mercapto-containing compounds on the surface of electrode (Fig. 3, curve h) [13].

The electro-oxidation of 3-methylcatechol (**1b**) and 3-methoxycatechol (**1c**) in the presence of **3** in acetate buffer solution proceeded in a similar way to that of **1a**. The presence of a methyl and methoxy groups at the C-3 position of **1b** and **1c**, respectively, probably causes *o*-benzoquinones derived from the oxidation of these catechols (**2b** and **2c**) to be attacked by **3** at the C-4 or C-5 positions to yield two types of products in each case (Fig. 6).

Spectroscopic characterization by ^{1}H NMR spectroscopy of crude products indicated the presence of singlet, relative to aromatic hydrogens ($\delta = 6.47$ and 6.42 ppm for **4b** and **4c**, respectively) at C-5, thus originating **4b** and **4c**. The addition to C-4 in the generation of more complex feature, once ortho hydrogens, would couple, which would result in a doublet with a coupling constant, J, of about 10 Hz. These results are consistent with the presence of two protons in the catechol ring of **4b** and **4c** in meta position [14]. Therefore, according to ^{1}H NMR results, we suggest that *o*-quinones **2b** and **2c** are attacked from C-5 position selectively by **3**, leading to the formation of the products **4b** and **4c**, respectively.

The Effect of pH

In acidic and neutral media, the voltammograms of catechol (**1a**) show one anodic (A_1) and a corresponding cathodic peak (C_1), with a peak current ratio (I_p^{Cl}/I_p^{Al}) of near unity. However, in basic

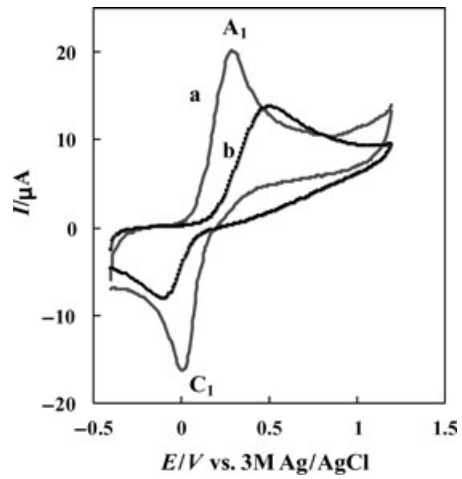


FIGURE 5 Cyclic voltammogram of (a) 1 mM 3-methylcatechol (**1b**), (b) saturated solution of obtained product (**4b**) at glassy carbon electrode in water/acetonitrile (45/55) solution containing 0.15 M sodium acetate, Scan rate: 100 mV s^{-1}; $t = 25 \pm 1°C$.

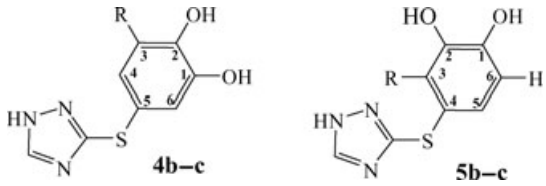


FIGURE 6 The structure of possible products in electrochemical oxidation of 3-methyl (R = CH_3) and 3-methoxycatechol (R = OCH_3) in the presence of 3-mercapto-1,2,4-triazole.

solutions, the peak current ratio (I_p^{Cl}/I_p^{Al} is less than unity and decreases with increasing pH and decreasing sweep rate [10c,11b]. This is related to the coupling of anionic or dianionic forms of catechols with *o*-benzoquinones (dimerization reaction) [9]. The rate of the coupling reaction is pH dependent and is enhanced by increasing pH. The oxidation of catechol (**1a**) in the presence of 3-mercapto-1,2,4-triazole (**3**) was studied at various pHs. The results showed that the peak current ratio (I_p^{Cl}/I_p^{Al}) decreases with increasing pH. This can be related to the deprotonation of 3-mercapto-1,2,4-triazole (**3**) and its subsequent activation toward a Michael addition. Thus, a solution of water/acetonitrile (90/10) mixture containing 0.2 M acetate buffer (pH 5.5) was employed as the most suitable solvent system for the synthesis of (1*H*-1,2,4-triazol-3-ylthio)benzen-1,2-diol derivatives mainly due to the decreased rate of the polymerization reaction of catechol and dimerization reaction of 3-mercapto-1,2,4-triazole (**3**) and the increased rate of the coupling reaction between 3-mercapto-1,2,4-triazole (**3**) and *o*-benzoquinone (**2a**).

EXPERIMENTAL

Apparatus and Reagents

Cyclic voltammetry was performed using a computerized 747 Metrohm polarograph and controlled-potential coulometry and preparative electrolysis were performed using a Behpajoh model BHP-2062 potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disk (1.8 mm diameter), and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and macroscale electrolysis was an assembly of eight graphite rods (8 mm diameter and 6 cm length), and a large platinum gauze constituted the counter electrode. The working electrode potentials were measured versus 3 M Ag\AgCl (graphite rods were obtained from Azar Electrode (Orumiyeh, Iran) and all other electrodes were obtained from Metrohm (Herisau, Switzerland)).

All chemicals (catechols and 3-mercapto-1,2,4-triazole) were reagent-grade materials, and sodium acetate and other solvents and reagents were of proanalysis grade; all of them were obtained from E. Merck (Darmstadt, Germany). These chemicals were used without further purification.

Electro-organic Synthesis of **4a–c**

A solution (about 100 mL) of acetate buffer (C = 0.2 M, pH 5.5) in water/acetonitrile (90/10) solution, containing 2 mmol of catechol (**1a–c**) and 2 mmol of 3-mercapto-1,2,4-triazole (**3**), was electrolyzed at 0.40 V versus 3 M Ag/AgCl, in an undivided cell. The electrolysis was terminated when the current decreased by more than 95%. The process was interrupted during the electrolysis, and the graphite anode was washed in acetone to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator for overnight. The precipitated solid was collected by filtration and was purified with column chromatography by using a dichloromethane–ethanol (20:80) mixture as eluent. After purification, the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.

*Characteristics of 4-(1H-1,2,4-Triazol-3-ylthio)-benzen-1,2-diol (***4a***).* mp 196–198°C (dec.); IR (KBr): 3405, 3112, 2921, 1584, 1515, 1474, 1374, 1333, 1287, 1274, 1211, 1080, 1027, 974, 870, 720, 629; ^{1}H NMR (300 MHz DMSO d_6) δ: 6.46 (s, 1H, C-6), 7.97–8.59 (m, 3H, C-3, C-4, and C-7), 10.05 (broad, 1H, −OH), 13.53 (broad, 1H, −OH), 13.82 (broad, 1H, −NH); ^{13}C NMR (300 MHz DMSO d_6)

δ: 116.3 (C-6), 125.1 (C-3), 131.2 (C-4), 145.1 (C-5), 146.8 (C-2), 147.6 (C-1), 148.6 (C-8), 150.5 (C-7); MS: *m/z* (%) 209 ($M^{+\cdot}$, 30.6), 141 (M-[$C_2H_2N_3$], 22.4), 101 (M-catechol, 100), 74 (32.6), 42 (42.8).

*Characteristics of 5-(1H-1,2,4-Triazol-3-ylthio)-3-methylbenzen-1,2-diol (***4b***).* mp 190–192°C (dec.); IR (KBr): 3528, 3118, 2848, 2684, 1570, 1474, 1406, 1376, 1281, 1215, 1036, 1004, 976, 869, 790, 714, 632; ^{1}H NMR (300 MHz DMSO d_6) δ: 2.22 (s, 3H, methyl); 6.47 (s, 1H, C-6); 8.47 (s, 1H, C-4); 8.67 (s, 1H, C-7); 9.81 (broad, 1H, —OH); 13.92 (broad, 1H, —OH); 14.20 (broad, 1H, —NH); ^{13}C NMR (300 MHz DMSO d_6) δ: 15.3 (methyl), 114.1 (C-6), 131.5 (C-4), 143.7 (C-3), 145.1 (C-5), 145.9 (C-2), 147.6 (C-1), 157.5 (C-8), 159.1 (C-7); MS: *m/z* (%) 223 ($M^{+\cdot}$, 69.4), 169 ([$C_8H_9O_2S$]$^{+\cdot}$, 18.4), 124 (M-[$C_2H_2N_3S$], 16.3), 101 (M-3-methylcatechol, 100), 74 (30.6), 42 (65.3).

*Characteristics of 5-(1H-1,2,4-Triazol-3-ylthio)-3-methoxybenzen-1,2-diol (***4c***).* mp 185–187°C (dec.); IR (KBr): 3412, 3265, 3108, 2852, 2680, 1626, 1545, 1467, 1438, 1384, 1344, 1283, 1193, 1087, 1003, 972, 879, 768, 693; ^{1}H NMR (300 MHz DMSO d_6) δ: 3.66 (s, 3H, methoxy); 6.42 (s, 1H, C-6); 8.3 (broad, 2H, C-4 and C-7); 9.8 (broad, 1H, —OH); 13.84 (broad, 2H, —OH and —NH); ^{13}C NMR (300 MHz DMSO d_6) δ: 61.8 (methoxy), 119.2 (C-4), 121.4 (C-6), 129.6 (C-2), 141.8 (C-5), 145.3 (C-8), 149.4 (C-1), 151.2 (C-7), 159.1 (C-3); MS: *m/z* (%) 239 ($M^{+\cdot}$, 18.4), 129 ([$C_4H_5N_3S$]$^{+\cdot}$57.1), 115 ([$C_3H_5N_3S$]$^{+\cdot}$, 100), 101 (M-3-methoxycatechol, 55.1), 74 (36.7), 42 (9).

CONCLUSIONS

The results of this work show that catechols are oxidized to their respective *o*-quinones. The quinones are then attacked by the anion of 3-mercapto-1,2,4-triazole (**3**). Contrary to Shahrokhian's report [15], final products are obtained via an EC mechanism, after consumption of only $2e^-$ per molecule of catechols (**1a–c**). The overall reaction mechanisms for anodic oxidation of catechols (**1a–c**) in the presence of **3** as nucleophile are presented in Scheme 1. According to our results, it seems that the Michael reaction of this nucleophile to *o*-quinones formed leads to the formation of new catechol derivatives as final products in good yield and purity.

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