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ORIGINAL PAPER

Electrochemical study of catechols in the presence of 2-thiazoline-2-thiol: application to electrochemical synthesis of new 4,5-dihydro-1,3-thiazol-2-ylsulfanyl-1,2-benzenediol derivatives

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Abstract Electrochemical oxidation of catechols (**1a–d**) has been studied in the presence of 2-thiazoline-2-thiol (**3**) as a nucleophile in aqueous solution, using cyclic voltammetry and controlled potential coulometry. The results indicate that the quinones derived from catechols (**1a–d**), participate in Michael addition reactions with 2-thiazoline-2-thiol and via an EC mechanism pathway, convert to the corresponding catechols derivatives (**4a–d** and **4′d**). The electrochemical synthesis of compounds (**4a–d** and **4′d**) has been successfully performed at a carbon rod electrode and in an undivided cell with good yield and high purity. The products have been characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

Keywords Electrochemical synthesis · EC mechanism · Catechol · 2-Thiazoline-2-thiol

1 Introduction

From the point of view of green chemistry, using electrosynthesis methods has important advantages. Clean synthesis, use of electricity as energy instead of oxidative reagents, use of aqueous media instead of organic solvents, one step reactions, operation at room temperature and pressure, technical feasibility, and especially high atom economy are among preeminent green advantages [1]. Electrosynthesis can lead to efficient and sometimes unexpected synthesis of compounds, which cannot be easily prepared by conventional organic synthesis [2].

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Other work has shown that the 2-thiazoline-2-thiol [3, 4] is an antithyroid agent that strongly reduces the thyroid hormone level. Synthesis of these hormones is catalyzed in vivo by thyroid peroxidase. The interaction of these drugs with molecular iodine and its effect on peroxidase activity is the reason of the antithyroid effect for these drugs [5, 6]. Lagorce et al. [7] showed that series of the pyridine, pyrimidine or pyrazine derivatives of 2-thiazoline-2-thiol have shown antithyroid effects. Moreover thiols, as one of the intercellular reducing agents, generally protect biological systems against oxidative and/or cofactors for intercellular enzymatic anti-oxidation functions [1]. Catechols can be oxidized electrochemically to *o*-quinones. These are quite reactive and can be attacked by a variety of nucleophiles, such as a 4-hydroxy-methyl-2(1*H*)quinolone [8], 4,6-dihydroxy-2-methyl pyrimidine [9], barbituric acid [10], methanol [11] and some other nucleophiles [12–14]. Also, there are some reports for the electrosynthesis of thioethers from catechols and mercapto compounds [15–18]. The electrochemical behavior of catecholamines has been investigated in some other reports [19–21].

Regarding the parallel oxidation of catecholamines in the mammalian central nervous system and this process occurs in the human body [22], we decided to study catechol, 3-methoxycatechol, 3-methylcatechol and 4-methylcatechol in the presence of 2-thiazolinze-2-thiol as a nucleophile.

2 Experimental

2.1 Methods

Cyclic voltammetry (CV) was performed using a μAutolab potentiostat/galvanostat type III. Controlled-potential coulometry was performed using an Autolab potentiostat/

galvanostat model 30 and 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 platinum wire was used as the counter electrode (CE). The WE used in controlled-potential coulometry and macro scale 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 working electrode potentials were measured versus the Ag|AgCl|KCl(3 M) as a reference electrode (All electrodes were obtained from Metrohm). NMR spectra were recorded on a Bruker DRx-300 Avance Instruments. IR spectra were recorded on a Bruker IFS-66 FT-IR 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.

2.2 Materials

Chemicals (catechol, 3-methoxycatechol, 4-methylcatechol and 2-thiazoline-2-thiol) were reagent-grade and phosphate salts were of pro-analysis grade from E. Merck and 3-methylcatechol was reagent-grade from Acros. These chemicals were used without further purification. All experiments were carried out at room temperature.

2.3 Electro-organic synthesis of **4a–d** and **4′d**

In a typical procedure, 100 mL mixture of water/acetonitrile (95/5) containing total phosphates (KH_2PO_4/K_2HPO_4) 0.15 M as the buffer (pH 7.2) and supporting electrolyte was pre-electrolyzed at the potential mentioned in Table 1 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 using the same potential, as mentioned in Table 1.

Initially the current density was 2 mA cm^{-2} and the electrolysis was terminated once the current decreased by more than 95%. The process was interrupted several times during the electrolysis and the carbon anode was washed in acetone in order 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 by using IR, ^{1}H NMR, ^{13}C NMR and MS.

2.4 Characteristics of the products

4-(4,5-Dihydro-1,3-thiazol-2-ylsulfanyl)-1,2-benzenediol (**4a**): m.p. > 250 °C. IR (KBr) ν (cm^{-1}): 3166, 1659, 1551, 1487, 1255, 1117, 1001. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.27 (t, $^3J_{HH}$ = 8.10 Hz, 2H, CH_2), 4.17 (t, $^3J_{HH}$ = 8.10 Hz, 2H, CH_2), 6.75–6.96 (m, 3H, arom), 9.36 (s, 1H, OH), 9.53 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 34.46, 65.94, 116.55, 117.53, 123.10, 127.86, 146.10, 148.33, 167.61. MS (70 eV) m/z (relative intensity): 226 (100), 207 (37), 167 (48), 141 (25), 119 (60), 64 (25), 45 (70).

4-(4,5-Dihydro-1,3-thiazol-2-ylsulfanyl)-5-methyl-1,2-benzenediol (**4b**): m.p. 179–180 °C. IR (KBr) ν (cm^{-1}): 3274, 1565, 1513, 1428, 1289, 1003. ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.29 (t, $^3J_{HH}$ = 8.10 Hz, 2H, CH_2), 4.21 (t, $^3J_{HH}$ = 8.10 Hz, 2H, CH_2), 6.83 (s, 1H, arom), 7.10 (s, 1H, arom), 8.40 (broad, 2H, OH). ^{13}C NMR (75 MHz, Acetone-d_6) δ (ppm): 19.53, 34.10, 65.70, 117.31, 117.73, 123.39, 134.98, 143.30, 147.88, 167.42. MS (70 eV) m/z (relative intensity): 241 (85), 194 (88), 154 (73), 124 (62), 78 (18), 59 (56), 43 (100).

5-(4,5-Dihydro-1,3-thiazol-2-ylsulfanyl)-3-methoxy-1,2-benzenediol (**4c**): m.p. 150–153 °C. IR (KBr) ν (cm^{-1}): 3391, 2936, 1659, 1089. ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm): 3.28 (t, $^3J_{HH}$ = 8.10, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.17 (t, $^3J_{HH}$ = 8.10, 2H, CH_2), 6.68 (m, 2H, CH), 9.06 (broad, 2H, OH). ^{13}C NMR (75 MHz, Acetone-d_6) δ (ppm): 34.45, 56.54, 65.95, 111.47, 116.88, 117.11, 137.15, 146.31, 148.72, 167.63. MS (70 eV) m/z (relative intensity): 256 (100), 226 (29), 197 (12), 171 (12), 140 (22), 119 (24), 97 (18), 69 (14), 47 (46), 31 (32).

Mixture of 5-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-3-methyl-1,2-benzenediol (**4d**) and 4-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-3-methyl-1,2-benzenediol (**4′d**): m.p. 165–168 °C. IR (KBr) ν (cm^{-1}): 3471, 2924, 2850, 1639, 1615, 1556, 1460, 1380, 1283, 1224, 1200, 1126, 1002. ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm): 2.22 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.25–3.32 (m, 4H, CH_2), 4.17–4.23 (m, 4H, CH_2),

Table 1 Electroanalytical and preparative data

Conversion	Applied potential vs. Ag|AgCl|KCl(3M)/V	Purification	Product yield[a] (%)
1a → **4a**	0.25	Washing in water	81
1b → **4b**	0.15	Washing in water	91
1c → **4c**	0.10	Washing in water	74
1d → (**4d**:**4′d**)	0.15	Washing in water	87[b] (50:50)

[a] Isolated yield

[b] Yield is related to the mixture of two isomers

6.76 (d, $^3J_{HH}$ = 8.28 Hz, 1H, arom), 6.92 (s, 1H, arom), 6.98 (s, 1H, arom), 7.01 (d, $^3J_{HH}$ = 8.28 Hz, 1H, arom), 8.33 (broad, 4H, OH). ^{13}C NMR (75 MHz, Acetone-d_6) δ (ppm): 14.42, 15.88, 34.96, 35.01, 66.55, 113.43, 118.49, 120.36, 120.90, 126.10, 129.29, 130.52, 130.63, 144.99, 145.41, 146.81, 147.92, 168.49, 168.86. MS (70 eV) m/z (relative intensity): 240 (100), 181 (26), 154 (25), 119 (35), 97 (25), 78 (32), 59 (62), 41 (87).

Crystal data for 4-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-3-methyl-1,2-benzenediol (**4′d**): $C_{10}H_{11}NO_2S_2$: M_w = 241.32, space group triclinic, P $\bar{1}$, a = 5.547 (2) Å, b = 8.489 (4) Å, c = 11.916 (5) Å, α = 97.98 (3)°, β = 90.81 (3)°, γ = 103.38 (3)°, V = 540.0 (4) Å ^{3}, Z = 2, D_c = 1.484 mg/m^3, F (000) = 252, crystal size 0.40 × 0.30 × 0.30 mm^3, radiation Mo Kα (λ = 0.71073 Å), teta range for data collection 1.73–29.19°. Intensity data were collected at 293 K with a STOE IDPS II two-circle diffractometer and employing ω-scanning technique, in the range $-7 \leq h \leq 6$, $-11 \leq k \leq 10$, $-16 \leq l \leq 16$. The structure was solved by direct methods [23] and refined an F^2 by full-matrix least squares using the X-STEP32 program package [24] giving a final R_1 = 0.0532 and wR_2 = 0.1409.

3 Results and discussion

The electrochemical oxidation of catechols (**1a–d**) in the presence of 2-thiazoline-2-thiol (**3**) undergoes a smooth 1:1 addition reaction in water medium at ambient temperature to produce 4- or 5-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1,2-benzenediols (**4a–d** and **4′d**). Cyclic voltammetry of 1 mM catechol (**1a**) in water/acetonitrile (95/5) solution containing 0.15 M phosphate buffer (pH 7.2), shows one anodic (A_1) and a corresponding cathodic peak (C_1), which is related to the transformation of catechol (**1**) to *o*-benzoquinone (**2**) and vice versa through a quasi-reversible two-electron process (Fig. 1, curve a).

A peak current ratio (Ip^{C1}/Ip^{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 electrode surface. In other words, any hydroxylation [25] or dimerization [26] reactions are too slow to be observed on the time scale of the cyclic voltammetry. Then the electrochemical oxidation of catechols (**1**) was studied in the presence of 2-thiazoline-2-thiol (**3**) as a nucleophile. Figure 1 (curve b) shows the cyclic voltammogram obtained for a 1 mM catechol (**1a**) in the presence of 1 mM 2-thiazoline-2-thiol (**3**). The cyclic voltammogram of 1 mM 2-thiazoline-2-thiol (**3**) is shown in Fig. 1, curve c, for comparison.

The multi-cyclic voltammograms of **1a** in the presence of **3** are shown in Fig. 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 a thin film of product at the electrode surface [27].

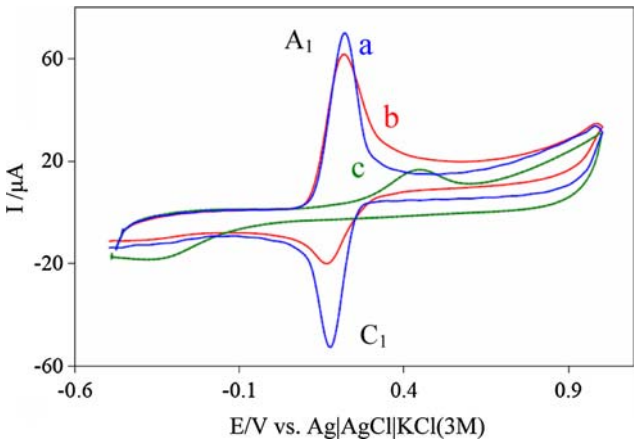


Fig. 1 Cyclic voltammograms of 1 mM catechol (**1a**) in the absence (a) and in the presence (b) of 1 mM 2-thiazoline-2-thiol (**3**) and 1 mM 2-thiazoline-2-thiol (**3**) in the absence of catechol (c) at a glassy carbon electrode (1.8 mm diameter), in phosphate buffer (pH 7.2, C = 0.15 M); scan rate = 100 mV s^{-1}; room temperature

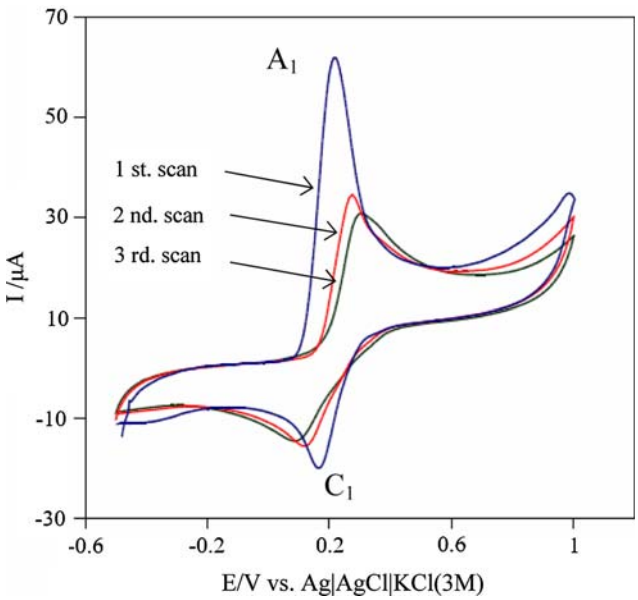


Fig. 2 Multi-cycle voltammograms of 1 mM catechol (**1a**) in the presence of 2-thiazoline-2-thiol (**3**), at glassy carbon electrode (1.8 mm diameter) in water/acetonitrile (95/5) containing 0.15 M phosphate buffer (pH 7.2); scan rate = 100 mV s^{-1}; room temperature

Voltammograms of 1 mM **1a** in the presence of 1 mM **3** at different scan rates are shown in Fig. 3. The height of the cathodic peak (C_1) increases proportionally to the augmentation of potential sweep rate (Fig. 3, curves a–i). Moreover, the peak current ratio (Ip^{C1}/Ip^{A1}) increases slightly with increasing scan rate (Fig. 3, curve j).

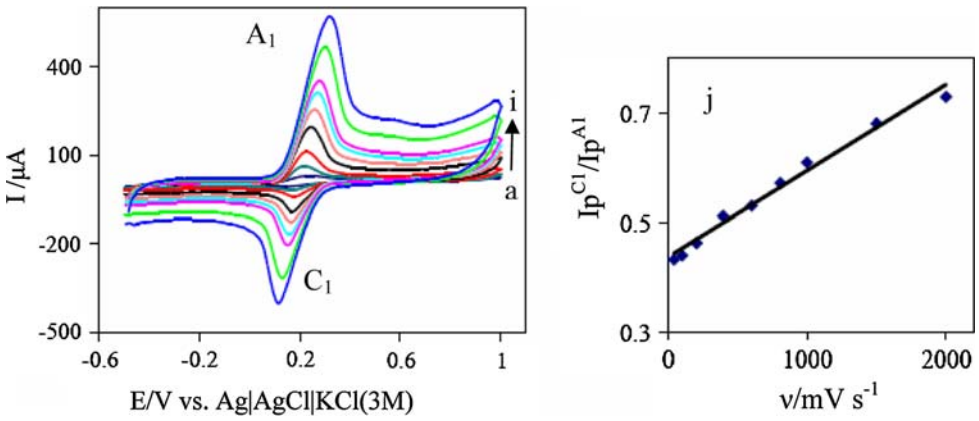


Fig. 3 Typical voltammograms of 1 mM catechol (**1a**) in the presence of 1 mM 2-thiazoline-2-thiol (**3**) in water/acetonitrile (95/5) containing 0.15 M phosphate buffer (pH 7.2) at glassy carbon electrode (1.8 mm diameter) and at various scan rates. Scan rates from (a) to (i) are: 50, 100, 200, 400, 600, 800, 1000, 1500, 2000 mV s^{-1}. (j) Variation of peak current ratio (Ip^{C1}/Ip^{A1}) versus scan rate; room temperature

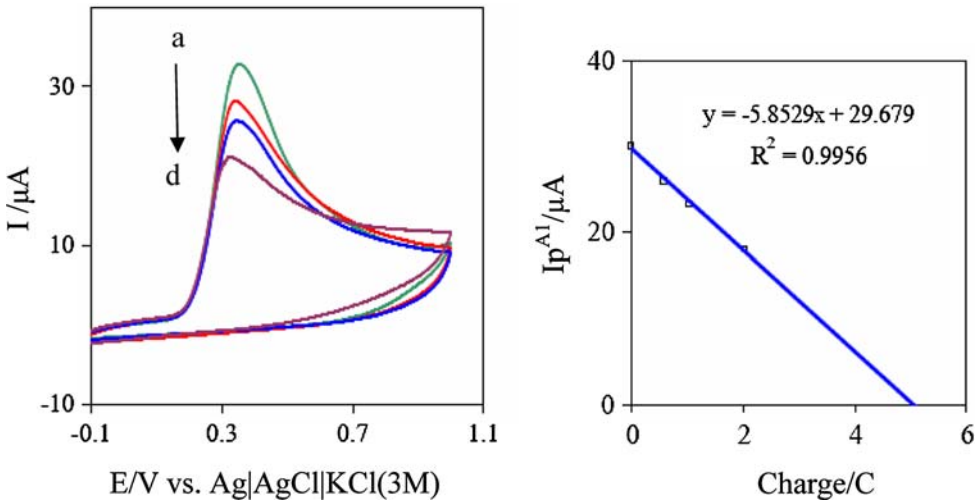
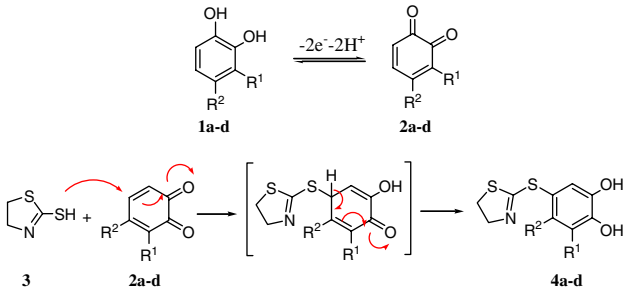


Fig. 4 Cyclic voltammograms of 0.025 mmol catechol (**1a**) in the presence of 0.025 mmol 2-thiazoline-2-thiol (**3**) in water/acetonitrile (95/5) solution containing 0.15 M phosphate buffer (pH 7.2) at glassy carbon electrode during controlled-potential coulometry at 0.25 V vs. Ag|AgCl|KCl(3 M) after the consumption of (a) 0, (b) 0.6, (c) 1.05, (d) 2.03 Coulombs. (e) Variation of peak current (I_p^{A1}) vs. charge consumed; scan rate = 50 mV s^{-1}; room temperature

Controlled potential coulometry was performed in a water/acetonitrile (95/5) solution containing 0.025 mmol of **1a** and 0.025 mmol of **3**. Considering the closeness of oxidation potential peaks of **1a** and **3** (Fig. 1) to minimize the oxidation of 2-thiazoline-2-thiol (**3**) and hence achieving higher selectivity, we applied 0.25 V versus Ag|AgCl|KCl(3 M) in both the coulometry and preparative synthesis processes. Monitoring of electrolysis was carried out by cyclic voltammetry (Fig. 4).

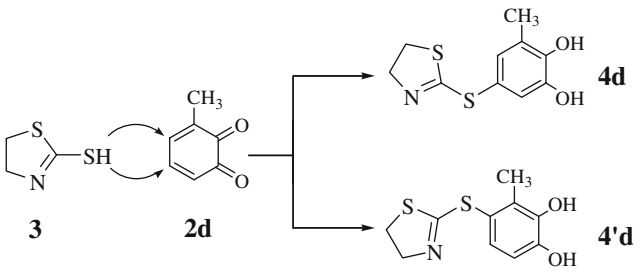
The anodic peak A_1 decreased and disappeared when the charge consumption became about $2e^-$ per molecule of **1a**. These coulometry and voltammetry results allowed us to propose an EC mechanism [28] for the electrooxidation of catechols in the presence of 2-thiazoline-2-thiol (Scheme 1). It was observed that when a methyl group is presented in the C-3 position, two products can result. This may be due to the attack of the nucleophile with high activity to either the C-4 or C-5 position (Scheme 2). Further investigation confirmed the suggestion using ^{1}H NMR results and single crystal X-ray diffraction analysis (Fig. 5). Moreover, among the different catechol derivatives which were synthesized using this technique, only 3-methyl derivatives showed the same phenomenon. The



Compound	R^1	R^2
a	H	H
b	H	CH_3
c	OCH_3	H
d	CH_3	H

Scheme 1 Proposed mechanism for the electrooxidation of catechols (**1a-d**) in the presence of 2-thiazoline-2-thiol (**3**)

percentage of each isomer was calculated from ^{1}H NMR spectrum according to the intensities of peaks appearing in the aromatic region (6.7–7.1).



Scheme 2 Possible products for the electrooxidation of 3-methylcatechol (**1d**) in the presence of 2-thiazoline-2-thiol (**3**)

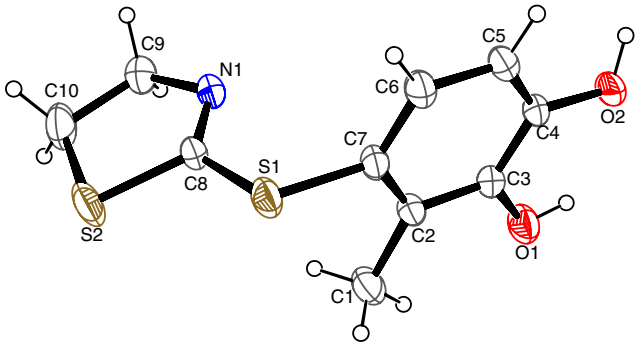


Fig. 5 ORTEP diagram of **4'd**

4 Conclusions

Catechols are oxidized in water to their respective *o*-quinones. The quinones are then attacked by nucleophile (**3**) to form 4- or 5-(4,5-dihydro-1,3-thiazol-2-ylsulfanyl)-1,2-benzenediol derivatives (**4a-d** and **4′d**). The reaction mechanism for anodic oxidation of catechols (**1**) in the presence of (**3**) is presented in Scheme 1 and 2.

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References

1. Nematollahi D, Tammari E (2005) J Org Chem 70:7769
2. Fotouhi L, Heravi MM, Nematollahi D (2006) Tetrahedron Lett 47:8553
3. Thomes JC, Comby F, Lagorce JF, Buxeraud J, Raby C (1992) Jpn J Pharmacol 58:201
4. Beyssen ML, Lagorce JF, Cledat D, Buxeraund J (1999) J Pharm Pharmacol 51:745
5. Roy G, Mugesh G (2006) Bioinorg Chem Appl 2006:1
6. Aizawa T, Yamada T (1981) Clin Exp Pharmacol Physiol 8:215
7. Lagorce JF, Comby F, Rousseau A, Buxeraud J, Raby C (1993) Chem Pharm Bull (Tokyo) 41:1258
8. Bayandori Moghaddam A, Kobarfard F, Fakhari AR, Nematollahi D, Hoseiny Davarani SS (2005) Electrochim Acta 51:739
9. Fakhari AR, Nematollahi D, Bayandori Moghaddam A (2005) J Electroanal Chem 577:205
10. Nematollahi D, Tammari E (2005) Electrochim Acta 50:3648
11. Nematollahi D, Golabi SM (2000) J Electroanal Chem 481:208
12. Nematollahi D, Goodarzi H (2002) J Org Chem 67:5036
13. Nematollahi D, Habibi D, Rahmati M, Rafiee M (2004) J Org Chem 69:2637
14. Hoseiny Davarani SS, Nematollahi D, Shamsipur M (2007) Heteroatom Chem 18:644
15. Tammari E, Mirazi N, Nematollahi D (2006) Mendeleev Commun 5:285
16. Fotouhi L, Mosavi M, Heravi MM, Nematollahi D (2006) Tetrahedron Lett 47(48):8553
17. Fotouhi L, Nematollahi D, Heravi MM, Tammari E (2006) Tetrahedron Lett 47(11):1713
18. Shahrokhian S, Hamzehloei A (2003) Electrochem Commun 5(8):706
19. Chen SM, Peng KT (2003) J Electroanal Chem 547:179
20. Zhao H, Zhang Y, Yuan Z (1997) Anal Chim Acta 354:343
21. Hernandez P, Sanchez I, Paton F, Hernandez L (1998) Talanta 46:985
22. Chen SM, Lin KC (2002) J Electroanal Chem 523:93
23. Sheldrick GM (1997) SHELX97. Program for crystal structure solution and refinement. University of Göttingen, Germany
24. Stoe & Cie, X-STEP32, Version 1.07b: Crystallographic package; GmbH:Darmatadt, Germany, 2000
25. Papouchado L, Petrie G, Adams RN (1972) J Electroanal Chem 38:389
26. Nematollahi D, Rafiee M, Samadi-Meyboi A (2004) Electrochim Acta 49:2495
27. Bard AJ, Faulkner LR (2001) Electrochemical methods, 2nd edn. Wiley, New York, p 497
28. Nematollahi D, Rahchamani RA (2002) J Electroanal Chem 520:145