An Improved Electrochemical Method for the Synthesis of Some Benzofuran Derivatives

Saied Saeed Hosseiny Davarani,[a] Nahid Mashkouri Najafi,[a] Somayyeh Ramyar,[a] Leila Masoumi,[a] and Mojtaba Shamsipur*,[b]

[a] *Department of Chemistry, Shahid Beheshti University; Tehran, Iran: and* [b] *Department of Chemistry, Razi University; Kermanshah, Iran.* Received December 15, 2005; accepted February 21, 2006

Electrochemical oxidation of catechol and some 3-substituted catechols (1a—c) has been studied in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (3) in aqueous solution using cyclic voltammetry and controlled-potential coulometry. The results indicate that the quinones derived from catechols (1a—c) participate in a Michael addition reaction with 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (3) with consumption of only two electrons per molecule of (1a—c) to from the corresponding benzoforans (10a—c). The electrochemical synthesis of benzofurans has been successfully performed at a carbon rod electrode and in an undivided cell with high yields and purity.

Key words cyclic voltammetry; catechol; 2-chloro-5,5-dimethyl-1,3-cyclohexanedione; electrochemical synthesis; benzofuran

Because of the broad pharmaceutical applications of benzofurans, the syntheses and pharmacological properties of benzofuran derivatives have been extensively investigated.[1—6] In this direction, it has been clearly shown that the synthesis of a wide variety of pharmaceutically important molecules derived from different catechol derivatives can be easily achieved at high purity and excellent yields by the electrochemical oxidation of catechols in the presence of the corresponding nucleophiles, *e.g.*, barbituric acid, acetylacetone, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and 2-mercaptopyridine.[7—10] The results indicated the formation of corresponding benzofuran derivatives *via* inter- and intramolecular Michael addition reactions, with consumption of four electrons per molecule of catechols.

In order to synthesize some novel benzofuran derivatives using a new method, we have investigated the electrochemical oxidation of catechols (**1a**—**c**) in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) as a nucleophile. Because this nucleophile (**3**) is a stronger CH-acid than dimedone (**d**)[9] and contains a Cl atom as a leaving group, the present work has led to the development of an environmentally friendly reagent-less electrochemical method for the facile one-pot synthesis of benzofuran derivatives (**10a**—**c**). This is done under ambient conditions in an undivided cell using carbon rod electrodes and with higher purity and better atomic economy when dimedone (**d**) is used as a nucleophile (Chart 1)[9] and *via* an EC mechanism with only about 2F charge consumption per each mol of **1a**—**c**.

Experimental

Apparatus and Reagents Cyclic voltammetry was performed using a computerized Metrohm voltametric analyzer model 747-VA. The controlled-potential coulometry and bulk electrolysis were performed using an Autolab model PGSTAT 20 potentiostal/galvanostat. The working electrode used in voltammetry experiments was a glassy carbon disc (1.8-mm diameter) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and bulk electrolysis was an assembly of four carbon rods (38 cm^2) and a large piece of platinum gauze constituted the counter electrode. The working electrode potentials were measured *versus* a 3 M Ag/AgCl reference electrode (carbon rods from Azar Electrode, Tabriz, Iran and all other electrodes from Metrohm).

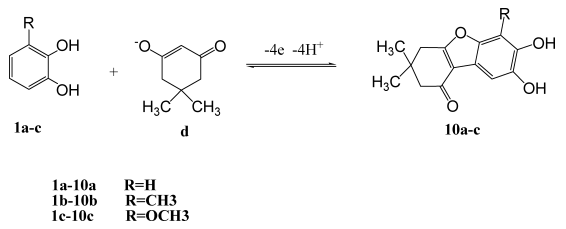

Chart 1

An IFS 66 Bruker FT-IR spectrometer, a QP-1100 EX Shimadzu mass spectrometer and a AQS-300MHz-Avance Bruker NMR spectrometer were used for recording different spectra.

Reagent grade 3-methylcatechol (Aldrich) and 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (Fluka) and all other chemicals such as catechol, 3-metoxycatechol, sodium acetate, acetonitrile, *etc.* (reagent and pro-analysis grades from Merck) were used as received.

Electro-organic Synthesis of (10a—c) In a typical procedure, 100 ml of 0.2 M sodium acetate solution was pre-electrolyzed at a chosen potential (see Table 1) in an undivided cell. Then, 1 mmol of catechol (**1a**) and 1 mmol of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) were added to the cell. The electrolysis was terminated when the decay of the current exceeded 95%. The process was interrupted during the electrolysis (due to the formation of a thin film of product at the surface of the electrode) and the glassy carbon anode was washed in acetone and reactivated by dissolving the precipitated product at the electrode surface. Despite the fact that almost all products were precipitated out during the electrolysis, at the end of that process a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The resulting precipitated solids were collected by filtration and recrystallized from a mixture of acetonitrile–ethylacetate; after recrystallization, the products were characterized by IR, ^{1}H-, ^{13}C-NMR and MS methods.

Characterization of 7,8-Dihydroxy-3,3-dimethyl-3,4-dihydro-2*H*-dibezofuran-1-one (10a, $C_{14}H_{13}O_4$) mp 289—291 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1})=3483, 3152, 3040, 2920, 1634, 1585, 1519, 1463, 1336, 1399, 1252, 1248, 1190, 1126, 1107, 1048, 873, 820, 654, 619. ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm)=1.05 (s, 6H), 2.32 (s, 2H), 2.80 (s, 2H), 6.96 (s, 1H), 7.19 (s, 1H), 9.16 (broad, 2H). ^{13}C-NMR (300 MHz, DMSO-d_6) δ (ppm)=27.9, 34.6, 36.6, 51.8, 112.4, 113.4, 114.6, 115.3, 120.4, 147.9, 151.2, 167.8, 191.2. MS: *m*/*e* (relative intensity) 246 (100), 190 (70), 162 (75), 134 (10.2), 92 (12), 69 (20), 39 (10).

Characterization of 7,8-Dihydroxy-3,3,6-trimethyl-3,4-dihydro-2*H*-dibenzofuran-1-one (10b, $C_{15}H_{15}O_4$) mp 260—262 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1})=3501, 3187, 2925, 1648, 1585, 1526, 1460, 1301, 1229, 1160, 1109, 1077, 1048, 1011, 895, 862, 819, 631. ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm)=1.07 (s, 6H), 2.241 (s, 3H), 2.35 (s, 2H), 2.87 (s, 2H), 7.08 (s, 1H), 8.46 (s, 1H), 9.38 (s, 1H). ^{13}C-NMR (300 MHz, DMSO-d_6): δ (ppm)=8.92, 27.98, 34.91, 36.74, 51.45, 102.21, 107.86, 113.23, 114.58, 141.96, 143.24, 147.89, 168.44, 193.80. MS: *m*/*e* (relative intensity) 260 (100), 243 (60), 204 (75), 176 (84), 147 (25), 91 (19), 83 (25), 39 (35).

* To whom correspondence should be addressed. e-mail: mshamsipur@yahoo.com

Characterization of 7,8-Dihydroxy-6-methoxy-3,3-dimethyl-3,4-dihydro-2*H*-dibenzofuran-1-one (10c, $C_{15}H_{15}O_5$) mp 289—291 °C. $IR_{(KBr)}$: ν_{max} (cm^{-1})=3453, 3120, 2956, 1645, 1528, 1450, 1328, 1261, 1224, 1159, 1087, 1043, 1002, 917, 854, 831, 791, 729, 634, 558. ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm)=1.10 (s, 6H), 2.38 (s, 2H), 2.89 (s, 2H), 3.96 (s, 3H), 6.99 (s, 1H), 8.69 (s, 1H), 9.26 (s, 1H). ^{13}C-NMR (300 MHz, DMSO-d_6): δ (ppm)=28.0, 34.8, 36.6, 51.5, 60.4, 99.9, 114.4, 114.8, 133.4, 136.1, 140.8, 145.0, 168.8, 193.8. MS: *m*/*e* (relative intensity)=276 (100), 220 (50), 205 (10), 192 (15), 146 (20), 92 (10), 78(20), 63 (30).

Results and Discussion

Cyclic voltammetry of a 2 mM solution of catechol (**1a**) in 0.2 M sodium acetate solution as supporting electrolyte shows one anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of (**1a**) to an *o*-quinone (**2a**) and *vice versa* through a quasi-reversible two-electron process (Fig. 1, curve a). A peak current ratio ($I_P^{C_1}/I_P^{A_1}$) of nearly unity, particularly during the repetitive recycling of potential, can be considered as a criterion for the stability of *o*-quinones produced at the surface of the electrode under the experimental conditions. In other words any hydroxylation[8,10—13] or dimerization[14,15] reaction is too slow to be observed on the time scale of cyclic voltammetry.

The oxidation of catechol (**1a**) in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) as a nucleophile was studied in detail, and the resulting cyclic voltammogram is shown in Fig. 1 curve b. As is obvious, in addition to A_1, the cyclic voltammogram exhibits a new anodic peak A_2 as well as a strong decrease in the cathodic peak C_1. It is interesting to note that, in the repeated cycling of the voltammogram (shown in Fig. 2), the second anodic peak A_2 disappeared while the peak A_1 shifted to more positive potentials. The observed changes in the cyclic voltammogram of catechol **1a** in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione is probably due to the formation of a thin film of product at the surface of the electrode, inhibiting the electrode performance, the extent of which increased during the repetitive cycling of the potential (Fig. 2)[7—10,15] In Fig. 1, curve c is the voltammogram of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) alone.

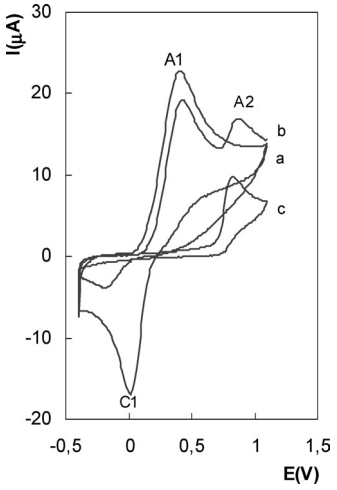

Fig. 1. Cyclic Voltammogram of 2.0 mM Catechol at Glassy Carbon Electrode in 0.2 M Sodium Acetate Solution: (a) in the Absence of 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione, (b) in the Presence of 2 mM 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione and (c) Cyclic Voltammogram of 2 mM 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione in the Absence of Catechol

Scan rate=100 mV s^{-1}, T=ambient temperature.

Furthermore, it was observed that proportional to augmentation of the potential scan rate, the C_1 peak current would be increased (Fig. 3). In fact, the increased peak current ratio ($I_P^{C_1}/I_P^{A_1}$) with scan rate for a mixture of catechol (**1a**) and 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) in 0.2 M sodium acetate solution (Fig. 3, curve g) confirms the reactivity of (**1a**) toward (**3**), appearing as an increase in the height of cathodic peak C_1 at higher scan rates. A similar situation is observed as the (**3**) to (**1a**) concentration ratio is decreased. Meanwhile, the peak current function for A_1 peak ($I_P^{A_1}/\nu^{1/2}$) decreases with increasing scan rate (Fig. 3 curve h), which is adapted as indication of an EC mechanism.[16] In this figure, the anodic peak A_2 could be related to the irreversible electro-oxidation of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**).

Controlled-potential coulometry was performed in 0.2 M of sodium acetate solution containing 0.5 mmol of each catechol (**1a**—**c**) and 0.5 mmol of 2-chloro-5,5-dimethyl-1,3-

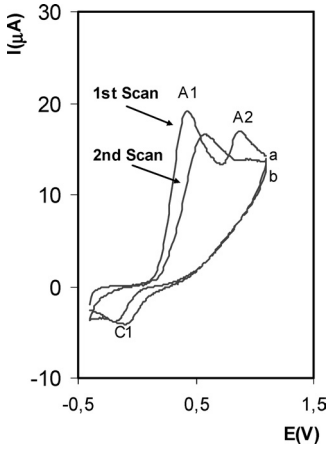

Fig. 2. Cyclic Voltammogram of 2 mM Catechol at Glassy Carbon Electrode in 0.2 M Sodium Acetate Solution: (a) in the Presence of 2 mM 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione (First Cycle), (b) in the Presence of 2.0 mM 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione (Second Cycle)

Scan rate=100 mV s^{-1}, T=ambient temperature.

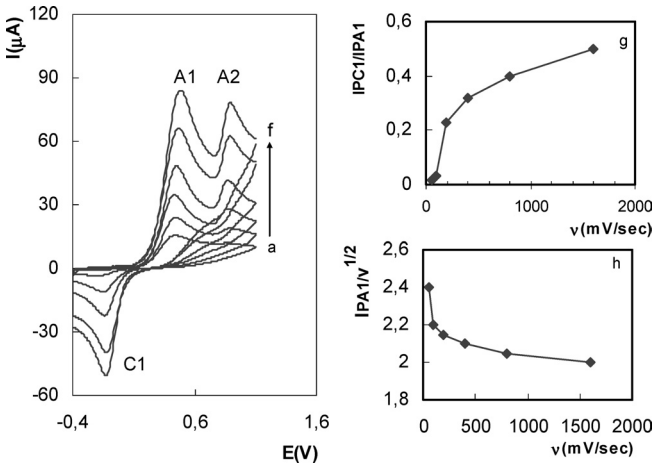

Fig. 3. Typical Cyclic Voltammograms of 2 mM Catechol (**1a**) in the Presence of 2 mM 2-Chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**), in 0.2 M Sodium Acetate Solution at a Glassy Carbon Electrode (1.8 mm Diameter) at Various Scan Rates

Scan rates from (a) to (f) are 50, 100, 200, 400, 800 and 1600 mV s^{-1}, respectively. (g) Variation of peak current ratio ($I_P^{A_1}/I_P^{C_1}$) *versus* scan rate. (h) Variation of peak current function for A_1 peak ($I_P^{A_1}/\nu^{1/2}$) *versus* scan rates. T=ambient temperature.

cyclohexanedione (**3**) at specified potentials *versus* 3 M Ag/AgCl (Table 1). The electrolysis progress was monitored by cyclic voltammetry and the results are summarized in Table 1. It was found that, proportional to the advancement of coulometry, the anodic peak decreases and disappears when the charge consumption becomes about $2e^-$ per molecule of (**1a**—**c**). In order to clearly demonstrate that the use of compound **3** instead of dimedone (**d**)[9] is the key success of the present effective transformation, the electrolyses of **1a**—**c** and dimedone were also carried out under the same experimental conditions, and the results are also included in Table 1. A comparison between the results given in Table 1 clearly indicates the improved yield and better atomic economy in the case of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) over that of dimedone (**d**).

Table 1. The Conditions and Results of Controlled Potential Electrolysis

Conversion	Applied potential (V *vs.* 3 M Ag/AgCl)	Product yield (%)	Consumed electricity (F/mol)
1a+**3b**→**10a**	0.40	66	2.23
1b+**3b**→**10b**	0.35	81	2.10
1c+**3b**→**10c**	0.35	80	2.15
1a+**d**→**10a**	0.40	58	4.35
1b+**d**→**10b**	0.35	70	4.23
1c+**d**→**10c**	0.35	67	4.25

The above mentioned coulometry and voltammetry results allow us to propose the pathways shown in Chart 2 for the electro-oxidation of catechol (**1a**) in the presence of 2-choloro-5,5-dimethyl-1,3-cyclohexanedione (**3**). According to our results, it seems that the 1,4-Michael addition reaction of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) to *o*-benzoquinones (**2a**—**c**) *via* Eq. 3 is faster than other side reactions, leading to the formation of **4a**—**c**, which are then converted to **5a**—**c**, during an elimination reaction and *via* removal of hydrogen chloride. Compounds **5a**—**c**, present in quinone methide form, are in equilibrium with their quinine (**6a**—**c**),[17,18] enol (**7a**—**c**) and enolate (**8a**—**c**) forms. Finally, the intramolecular Michael addition reaction of enolates (**8a**—**c**) will result in the formation of the final product (**10a**—**c**). Despite the fact that the anodic oxidation of **10a**—**c** was found to be more feasible than **1a**—**c** (see Fig. 4), the overoxidation of **10a**—**c** was circumvented during the preparative reaction because of the insolubility of the products in water/sodium acetate solution medium.

The existence of a methyl or methoxy group at the C-3 position of or 3-methylcatechol (**1b**) or 3-methoxycatechol (**1c**) would probably cause the Michael acceptors (**2c**) and (**2b**) to be attacked by the anion enolate of 2-chloro-5,5-dimethyl-1,3 cyclo hexanedione (**3**) at the C-4 or C-5 position to yield two other types of products (Chart 3).

The calculated[19] and experimental ^{13}C-NMR results of the

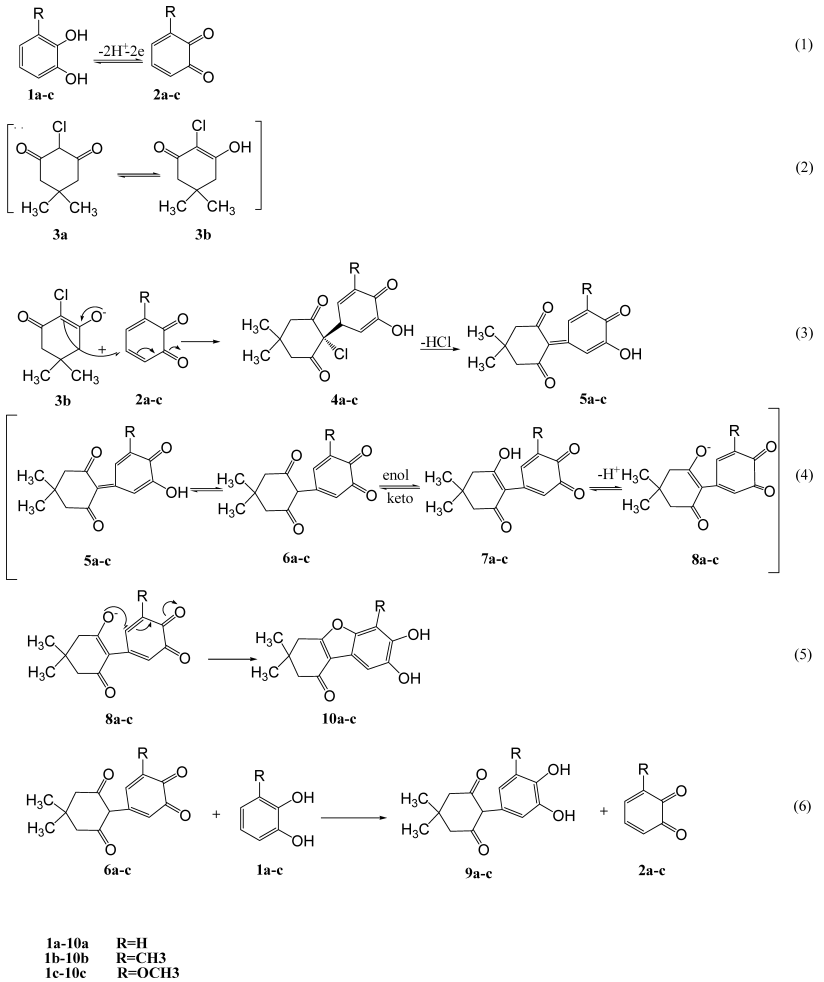

Chart 2

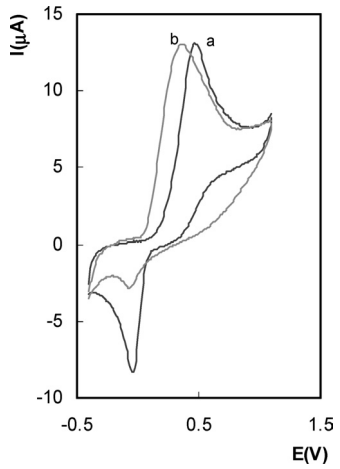

Fig. 4. Cyclic Voltammograms of (a) 2 mM Catechol (**1a**) and (b) 2 mM **10a**, at a Glassy Carbon Electrode in 0.2 M Sodium Acetate Solution Containing 45% by Acetonitrile Volume

Scan rate = 100 mV s^{-1}, T = ambient temperature.

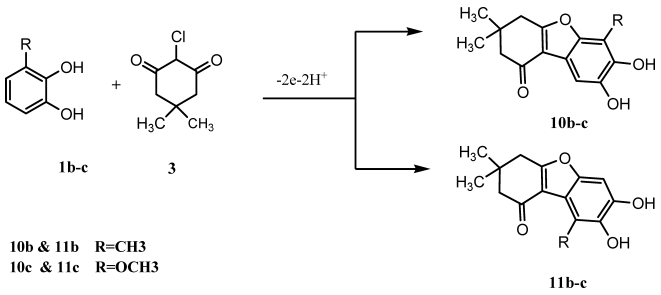

Chart 3

Table 2. Experimental and Calculated ^{13}C-NMR Data for Methyl Carbon in Catechol Ring

Type	^{13}C-NMR data
Experimental	8.9
Calculated for (**10b**)	8.6
Calculated for (**11b**)	12.9

methyl carbon in the catechol ring for the suggested possible structures are shown in Table 2. According to the ^{13}C-NMR results and ^{1}H-NMR results,[9,20] we suggest that *o*-benzoquinones **2b** and **2c** are selectively attacked from C-5 position by the anion enolate **3b** leading to the formation of products **10b** and **10c**, respectively.

Conclusion

The results of this work show that catechols are oxidized in solution to their respective *o*-quinones. The quinones are then attacked by the anion of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) to form benzofuran derivatives. The overall reaction mechanism for anodic oxidation of catechol in the presence of 2-chloro-5,5-dimethyl-1,3-cyclohexanedione (**3**) as a nucleophile is presented in Chart 1. The great advantage of the present work is development of a one-pot green electrolytic method for the synthesis of benzofuran derivatives (**10a**—**c**) as final products in good yield and purity, with only 2F charge consumption per each mol of catechols.

Acknowledgement Financial support from the research affairs of Shahid Beheshti University is gratefully acknowledged.

References and Notes

1) Kdieva M. G., Oganesyan E. T., *Chem. Heterocycl. Compd.* (Eng. Transl.), **33**, 1245—1258 (1997).
2) Tolmach E. L., Kudryavtsev A. B., Zheltov A. Ya., Stepanov B. I., *J. Org. Chem. USSR* (Eng. Transl.), **25**, 1594—1603 (1989).
3) Maeda S., Masuda H., Tokoroyama T., *Chem. Pharm. Bull.*, **42**, 2536—2545 (1994).
4) Zotova S. A., Korneeva T. M., Shvedov V. I., Fadeeva N. I., Leneva I. A, *Pharm. Chem. J.* (Eng. Transl.), **29**, 57—63 (1995).
5) Brown G. R., Foubister A. J., *Eur. J. Med. Chim.*, **27**, 723—727 (1992).
6) Abdel-Rahman A. H., Khalil A. M., Hanna A. M., *Bull. Chem. Farm.*, **136**, 262—265 (1997).
7) Nematollahi D., Goodarzi H., *J. Org. Chem.*, **67**, 5036—5039 (2002).
8) Nematollahi D., Rafiee M., *J. Electroanal. Chem.*, **566**, 31—37 (2004).
9) Nematollahi D., Habbibi D., Rahmati M., Rafiee M., *J. Org. Chem.*, **69**, 2637—2640 (2004).
10) Shamsipur M., Hosseiny Davarani S. S., Nasiri-Aghdam M., Namatollahi D., *Electrochim. Acta*, **51**, 3327—3331 (2006).
11) Papouchado L., Petrie G., Adams R. N., *J. Electroanal. Chem.*, **38**, 389—395 (1972).
12) Papouchado L., Petrie G., Sharp J. H., Adams R. N., *J. Am. Chem. Soc.*, **90**, 5620—5621 (1968).
13) Young T. E., Griswold J. R., Hulbert M. H., *J. Org. Chem.*, **39**, 1980—1982 (1974).
14) Nematollahi D., Rafiee M., Samadi-Maybodi A., *Electrochimica Acta*, **49**, 2495—2502 (2004).
15) Rayn M. D., Yueh A., Wen-Yu C., *J. Electrochem. Soc.*, **127**, 1489—1495 (1980).
16) Bard A. J., Faulkner L. R., "Electrochemical Methods," 2nd ed., Wiley, New York, 2001, pp. 497—500.
17) Iverson S. L., Qing Hu L., Vukomanovic V., Bolton J. L., *Chem. Res. Toxicol.*, **8**, 537—544 (1995).
18) Sugumaran M., Lipke H., *FEBS Lett.*, **155**, 65—68 (1983).
19) CS ChemDraw Ultra, Version 8.0, CambridgeSoft Corporation, 100 Cambridge Pork Drive, Cambridge.
20) Dean F. M., Sargent M. V., "Comprehensive Heterocyclic Chemistry," Vol. 4, Part 3, Chap. 10, ed. by Katritzky A. R., Rees C. W., Pergamon, New York, 1984, p. 561.