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Full Paper

One-pot Synthesis of New Benzofurane-Chatecholamine Derivatives by Electrochemical Method

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Abstract-The electrochemical oxidation of some catechols has been studied in the presence of N-phenylacetoacetamide in aqueous sodium phosphate buffer (pH=7), using cyclic voltammetry and controlled-potential coulometry. All the catechol derivatives were converted into benzofuran derivatives through a Michael-type addition reaction of N-phenylacetoacetamide to anodically generated *o*-quinones. The electrochemical syntheses benzofuran derivatives of were successfully performed in one pot in an undivided cell using an environmentally friendly method .

Keyword- Electrochemical Synthesis, Benzofuran, Chatecholamines

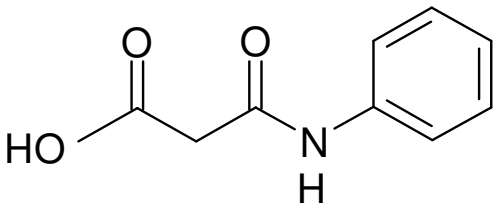
1. INTRODUCTION

Catechols are well known in biological systems often as a reactive center of electron transfer in the structure of many natural compounds [1,2]. In recent years, medicinal properties of benzofuran derivatives have been widely investigated and were shown to be effective as antioxidant, antitumor [3] anti-depressant [4] antifungal [5] anti-hypertensive, and cytotoxic [6]. They are also potent and selective oxytocin antagonists [7] the search for new molecules with anti-oxidant properties is a very active domain of research, since they

can protect the human body from free radicals and retard the progress of many chronic diseases. A number of synthetic compounds such as flavonoids and phenolic compounds, quinazolinones [8] thiazoles [9] and benzothiophene [10] benzufuranes [11] and chatecholamines [12] have also been extremely exploited for anti-oxidants activity. The above observation stimulated our interest to synthesize a series of compounds containing catechol- benzofurane ring system associated with amine moiety.

Previously it has been shown that catechols can be oxidized electrochemically to *o*-quinones. The formed quinones are quite reactive and can be attacked by a variety of nucleophiles such as: 4-hydroxycoumarin [13,14], 4-hydroxy-6-methyl-2-pyrone [15], barbituric acids [16-19], benzensulfinic acid [20,21] and were converted to the corresponding coumestan [13-15] pyrimidine [16-19] and sulfone derivatives [20-21] respectively.

This idea leads to study of electrochemical oxidation of benzenediols (a-c) in the presence of N-phenylacetoacetamide (scheme 1) as a nucleophile. To the best of our knowledge, the electrosynthesis of such compounds has not yet been reported in the literature. Here the development of an environmentally friendly method for one-pot, efficient synthesis of some new benzofuran derivatives in high yield and purity using undivided cell is reported.



N-phenylacetoacetamide (3)

Scheme 1. Structural formula of N-phenylacetoacetamide

2. EXPRIMENTAL

2.1. Apparut and Reagents

Cyclic voltammetry (CV) and preparative electrolysis were performed using a Behpajooh potentiostat/galvanostat and Zonner potentiostate. The working electrode (WE) used in the voltammetry experiment was a glassy carbon disc(1.8 mm diameter, 2.5 mm^2 area) and platinum wire was used as the counter electrode (CE). The WE used in mini scale electrolysis was an assembly of two carbon rods (8 mm diameter and 4 cm length, 25 cm^2 area) and a

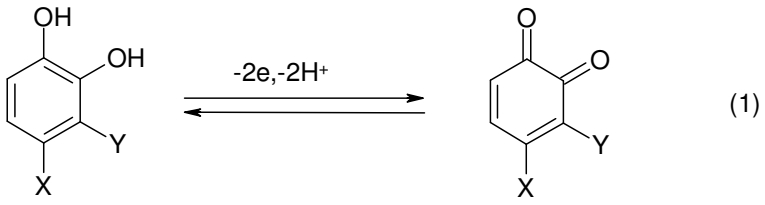
large platinum plate (2×2 cm^2) constituted the CE. The potentials were measured versus Ag/AgCl/KCl (3 M) as a reference electrode.

2.2. Electroorganic synthesis of 5a–c

In a typical procedure, 50 ml of an aqueous solution containing 0.2 M phosphate buffer, c=0.2 M, pH=7.0) in an undivided cell, subsequently, 1 mmol each of catechol (1a–c) and 3 (1 mmol) were added to the cell. The electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted during the electrolysis and the carbon anode was washed in acetone in order to re-active 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 overnight. The resulting precipitate was filtered and washed with water. All products were characterized using IR, ^{1}HNMR, ^{13}CNMR and elemental analysis [29].

3. RESULTS AND DISSCUSSION

A cyclic voltammogram of a solution of 1.0 mM 4-methylcatechol in water containing phosphate buffer (pH 7, c=0.2 M) shows one anodic peak (A1) and the corresponding cathodic peak (C1), which represent transformation of 4-methyl catechol 1a to 4-methyl-*o*-benzoquinone 2a within a quasi-reversible two-electron process [22] (Scheme 2, Fig. 1, curve a). A peak current ratio (I_p^{C1}/ I_p^{A1}) of nearly unity can be considered as a criterion for the stability of 4-methyl-*o*-benzoquinone 2a produced at the surface of electrode under the experimental conditions, particularly during recycling of the potential.



(1)

(1a-1c) (2a-2c)

X=CH3 Y=H 1a,2a,3a,4a
X=H Y=CH3 1b,2b,3b,4b
X=H Y=H 1c,2c,3c,4c

Scheme 2. Electroxidation reaction of substituted catechols

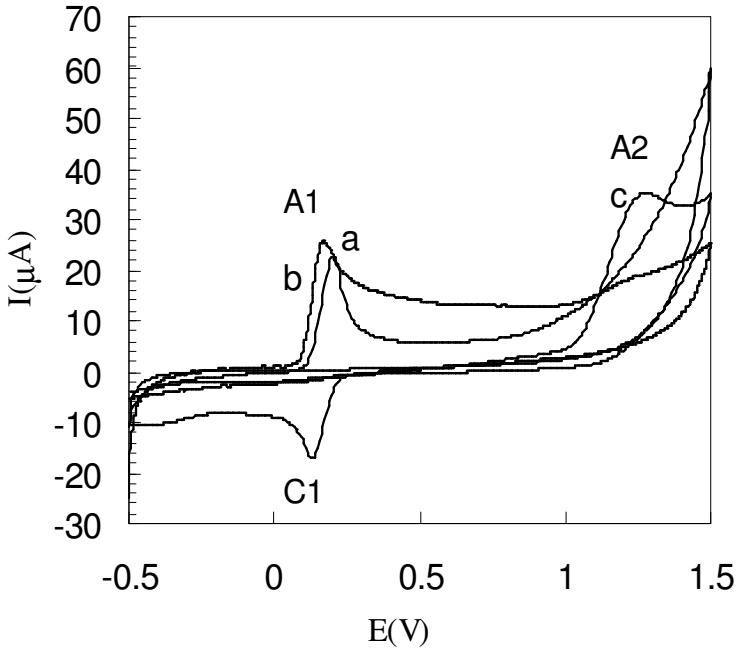
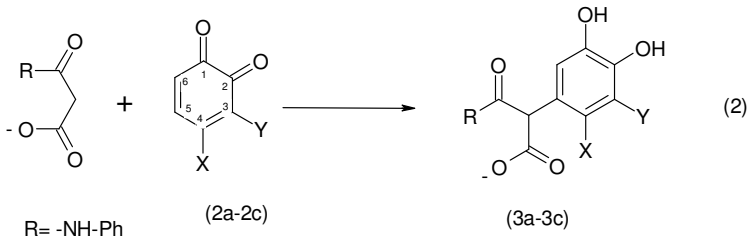


Fig. 1. Cyclic voltammograms of 1 mM 4-methylcatechol(1a): (a) in the absence, (b) in the presence of 1 mM N-phenylacetoacetamide (3) and (c) 1 mM N-phenylacetoacetamide (3) in the absence of 4-methylcatechol, at glassy carbon electrode in phosphate buffer (C=0.20 M, pH 7.2) scan rate: 50 mV s^{-1}; t =25±1 ^{o}C

Thus, any side reactions such as hydroxylation [23] dimerization [24] or radical formation [25–27] are too slow to be observed on the time scale of cyclic voltammetry. Study of the oxidation of catecholes 1a in the presence of N-phenylacetoacetamide (3) shows that the voltammogram for 1a (1.0 mM) in the presence of N-phenylacetoacetamide (1.0 mM) 3a (Fig. 1, curve b) exhibits an anodic peak (A1) and their relative cathodic peak (C1) for oxidation reduction of 1a to 2a, respectively. In the presence of 3, A1 peak shifted to positive potential and a new irreversible peak correspond to formation of new product of 3a formed. Under this condition, the cathodic counterpart of the anodic peak disappears, which indicates the reactivity of electrochemically generated benzoquinone 2a toward 3a (scheme 3) while curve c is the voltammogram of 3 in the absence of 1.

Furthermore, it can be seen that proportional to increase of the potential sweep rate, height of the cathodic C1 peak increases (Fig. 2). A plot of peak ratio (I_p^C /I_p^A) versus scan rate for a mixture of 1a and 3 leads to an increase in height of the cathodic peak C at higher scan rates. On the other hand, with increasing the scan rate, the current function for the anodic A peak (I_p^A /$\nu^{1/2}$) decreased and such behavior is adopted as indicative of an ECEC mechanism [28].



Scheme 3. Michael-type addition reaction of acetoacetanilid with substituted catechols

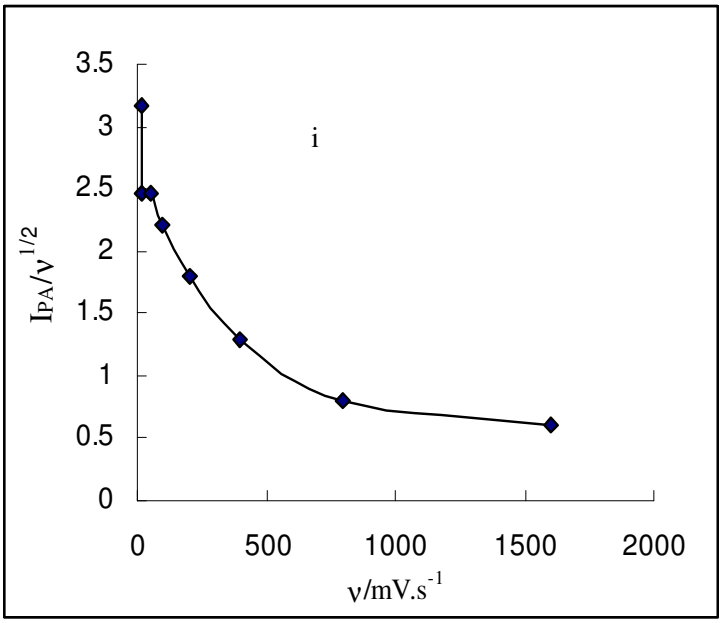


Fig. 2. Typical voltammograms of 1 mM 4-methylcatechol (1a) in the presence of 1 mM acetoacetanilide (3) in 0.2 M aqueous acetate buffer (pH 7.2) solution at a glassy carbon electrode (1.8mm diameter) and various scan rates. Scan rates from (a) to (h) are: 20, 50, 100, 200, 400, 800 and 1600 mV s^{-1}, respectively. Inset h: variation of peak current function (I_P^{C1}/I_P^{A1}) *vs.* scan rate. Curve i: variation of the peak current function ($I_P^{A1}/\nu^{1/2}$) t=25±1 ^oC

Controlled-potential coulometry was performed in an aqueous solution of 1 mmol of 1a and 1 mmol of 3 which contains 0.2 M phosphate buffer (pH 7), at a potential 0.2 V versus Ag/AgCl. The progress of electrolysis was monitored by cyclic voltammetry. It is shown that proportional to the advancement of coulometry, anodic peak A1 decreases and disappears

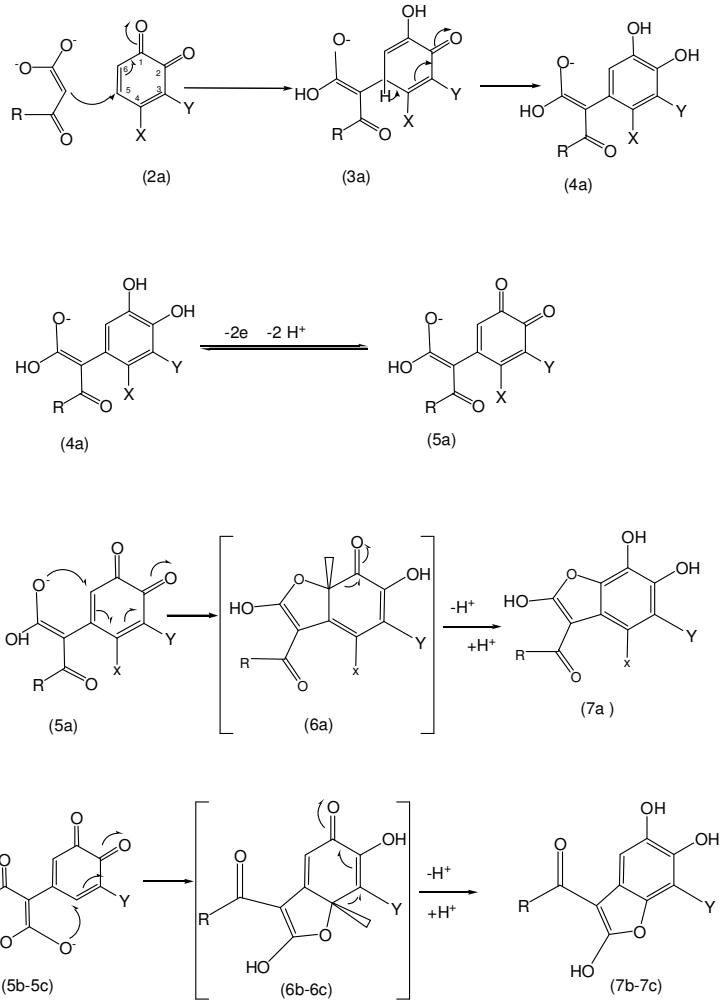
when the charge consumption became about 4e-per molecule of 1a. These observations allowed us to propose the following mechanism (Scheme 4).

According to our results, it is seems that the 1,4-Michael addition reaction of 3 to *o*-quinone (1a) (Eq. 2) is much faster than other secondary reactions, leading presumably to the intermediate (4a). The oxidation of this compound (4a) is easier than oxidation of the parent starting molecule (1a) by virtue of presence of an electron-donating group. Intramolecular cyclization of 4a followed by elimination of one molecule of H_2O leads to 5a. The electrooxidation of 1b and 1c in the presence of 3 as a nucleophile in phosphate buffer solution proceeded in a manner similar to that of 1a, but based on product spectral analysis, it seems that the 7b and 7c are the main products. IR, 1HNMR, 13CNMR spectra and elemental analysis supported the structure and aromaticity of products.

In conclusion the results of this work show that benzenediols (1a-c) are oxidized to their respective quinones. The quinones are then attacked by anion of 3 via intermolecular Michael addition reaction (Scheme 3). According to our results, it seems that the Michael reaction of this nucleophile to electro generated benzoquinones leads to the formation of new benzofuran derivatives as final products, with high atom economy, good yields and purity in one-pot manner. All products were characterized using IR, ^{1}HNMR, ^{13}CNMR and elemental analysis. The obtaine results are as follows:

3-(N-phenylacetamide)-2,6,7-trihydroxy-4-methyl-benzofurane (7a): Yield (88%) mp:256-258°C. IR(KBr) υ(cm^{-1}): 3400, 1680, 1620, 1305, 1100, 970, 831, 705cm^{-1}. ^{1}NMR(300MHz,DMSO-d6) δ(ppm):2.69 (s,3H), 6.62 (s,2H), 7.13 (s,1H), 7.25 (s,1H), 7.34(t,2H),7.39(t,1H)7.61(d,2H),8.21(s,1H). ^{13}CNMR (75 MHz, DMSO-d6)δ (ppm): 201.8, 134.6, 134.5, 134.1, 133.7, 132.2, 132, 130.8, 129.2, 128.7, 127.8, 126.2, 125.9, 122.9, 120.2, 116.7, 114.5, 50.4, 49.8, 49.3, 48. 5,22.3. Anal. Calcd for C 16H 13N O5 : C, 64.21; H, 4.39; N 4.68; O,26.72. Found C, 64.11; H,4.26; N,4.42; O,26.51. 3-(N-phenylacetamide)-2,5,6-trihydroxy-7-methyl-benzofurane (7b): Yield (85%) mp. 244-246°C.IR(KBr) υ(cm^{-1}): 3400, 1679, 1617, 1305, 1115, 970, 840, 700cm^{-1}. ^{1}NMR(300MHz,DMSO-d6) δ (ppm): 2.41 (s,3H), 6.52(s,2H), 6.68(s,1H), 7.11(s,1H), 7.30(t,2H), 7.36(t,1H), 7.57(d,2H), 8.12(s,1H). ^{13}CNMR(75 MHz, DMSO-d6) δ (ppm): 200.9, 135.5, 134.9, 134.1, 133.2, 132.3, 131.8, 130.9, 129.9, 128.8, 127.5, 126.6, 125.59, 121.9, 120.3, 116.2, 0.5, 50.1,50, 47.3, 21.4.
Anal. Calcd for $C_{16}H_{13}N O_5$: C, 64.21 H, 4.39; N, 4.68; O, 26.72. Found C, 64.18; H, 4.22; N, 4.47; O, 26.59 . 3-(N-phenylacetamide) -2,5,6-trihydroxy-benzofurane (7c): Yield (87%) mp: 248-250°C. IR(KBr) υ (cm^{-1}): 3400, 1675, 1615, 1302, 1112, 980, 835, 710 cm^{-1} ^{1}NMR (300MHz,DMSO-d6)δ (ppm): 6.7(s,1H), 6.69 (s,1H), 7.04 (s,1H), 7.20 (s,1H), 7.28(t,2H), 7.32(t,1H), 7.57(d,2H), 8.39(s,1H)^{13}CNMR(75 MHz, DMSO-d6) δ(ppm) : 200.8, 136.8, 136.3, 134.7, 133.9, 132.0, 131.9, 131.1, 130.8, 129.8, 126.4, 125.5, 124.5, 122.7, 120.5,

50.4, 50.3, 50.2, 48.8. Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.14; H, 3.89; N,4.91; O,28.03. Found: C, 62.98; H,3.69; N,4.78; O,27.96.



Scheme 4. Proposed mechanism for the electrooxidation of substituted catechols in the presence of acetoacetanilide

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