

Non-Catalyst, Fast, Simple and Green Synthesis of New Benzofuran Derivatives through Electrochemical Methods

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Abstract

For the purpose of synthesizing some new benzofuran derivatives, the electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) was accomplished in the presence of barbituric acids as nucleophiles in an aqueous phosphate buffer solution. The results show that electrogenerated quinone-imine (2a), participate in the reaction with barbiturics via the ECEC mechanism to construct the corresponding benzofuran derivatives (7a-b). The electro-synthesis of these compounds (7a-b) was performed profitably in an aqueous solution at carbon rod electrodes, without using any catalyst or toxic solvent and the products were finally produced in good yields and purity.

Keywords: Electro-oxidation; N, N, N', N'-Tetramethyl-benzene-1, 4-diamine; barbituric acid; carbon rod; Benzofuran.

Introduction

Benzo-fused heterocycles play important roles in both drug discovery and chemical biology (Appukkuttan et al., 2005). Benzofurans, Among benzoheterocycles containing an oxygen atom, are present in various biologically active molecules possessing, for example, antidepressant, antifungal, antibacterial, anti-inflammatory, antitumor, antiatherosclerotic, anticonvulsant and antipsychotic activity (Aslam et al., 2006; Kirilmis et al., 2008; Hayakawa et al., 2004; Wijngaarden et al., 1988; Mane et al., 2009; Malik et al., 1971; Dauzonne et al., 1995; Gfesser et al., 2005).

Respecting to the increase in the importance of green solvents in organic synthesis, development of more efficient and environmental friendly processes for chemical transformation is desired (Ojani et al., 2009). Therefore, it is interesting to study the synthesis of new benzofurans in phosphate buffer solution as a green solvent.

According to the pharmacological and biological activities benzofuran derivatives and importance of green solvents in recent century, the electrochemical oxidation of N,N,N',N'-

Tetramethyl-benzene-1,4-diamine (1a) has been investigated in the presence of barbituric acids (3a-b) under mild conditions in non-toxic solvents. As far as we know, the electrosynthesis of these new benzofurans has not been mentioned in the literature. In summary, we developed a simple, green, efficient, catalyst-free and fast method for the electro-organic synthesis of new benzofurans by the electrochemical oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine in the presence of (3a-b) in aqueous medium.

Materials and Methods

Apparatus and reagents

Cyclic voltammetric experiments were performed using a Metrohm Voltammetric Analyzer Model 747 (Herisau, Switzerland) and controlled-potential coulometry was performed using a Behpajoo model 2063 galvanostat/potentiostat (Isfahan, Iran). The working electrode (WE) used in the voltammetry experiments was a glassy carbon disc and platinum disk was used as a counter electrode (CE). The working electrode (WE) used in controlled-potential coulometry was an assembly of 6 carbon rods and a sheet platinum constituted the counter electrode (CE). The working electrode potentials were measured versus Ag/AgCl. All electrodes produced by AZAR Electrode Company (Urmia, Iran). The cell used was undivided type. NMR spectra were recorded on a Bruker DRX-400 spectrometer Advance Instrument. All chemicals materials were purchased from Merck (Darmstadt, Germany). These chemicals were used without further purification.

Typical method for the synthesis of new benzofurans (7a-b)

An aqueous solution of phosphate buffer (100 ml) (pH 7, 0.15 M) containing 0.2mmol of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) and 0.2mmol of barbituric (barbituric acid or thiobarbituric acid) was electrolyzed at 0.35 V versus the Ag/AgCl,(3M) in cell (undivided type) equipped with five carbon rods as the anodes and a sheet Pt cathode. The electrolysis was finished when the current decay became greater than 95%. The electro-oxidation was interrupted during electrolysis and the carbon anodes were washed in EtOH in order to reactivate it. At

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the end of electrolysis, the cell (undivided type) was placed in a cold chamber for 12h. The precipitated solid was collected by filtration, and it was washed several times with cold water to separate barbituric acids and N,N,N',N'-Tetramethyl-benzene-1,4-diamine remained. After this purification, the products (7a-b) were characterized using FT-IR, ¹H NMR, ¹³C NMR, Melting point (Mp) and elemental analysis (CHN).

Characterization of products

Benzo-furan derivative (7a), Yield:81%.Mp> 300 °C (decomposed). FT-IR (KBr, cm⁻¹): 3310 (NH), 1700 (C=O). ¹H NMR (400 MHz, DMSO-d₆): δ3.02 (s, 6H, Me), 3.18 (s, 6H, Me), 6.6 (d, 1H, aromatic), 6.77 (d, 1H, aromatic), 11.14 (s, 1H, NH), 11.63 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆): δ46.4, 47.1, 115.3, 117.6, 118.6, 120, 132.7, 134.6, 142.4, 153.4, 169.5, 170.7. Anal. Calcd. for C₁₄H₁₆N₄O₃: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.29; H, 5.61; N, 19.41.

Benzo-furan derivative (7b), Yield:79%.Mp> 300 °C (decomposed). FT-IR (KBr, cm⁻¹): 3318 (NH), 1690 (C=S). ¹H NMR (400 MHz, DMSO-d₆): δ2.91 (s, 6H, Me), 3.19 (s, 6H, Me), 6.53 (d, 1H, aromatic), 6.77 (d, 1H, aromatic). ¹³C NMR (100 MHz, DMSO-d₆): δ 45.3, 45.9, 113, 117.3, 119.7, 122.1, 132.3, 134.9, 141.4, 155.3, 169.7, 171.6. Anal. Calcd. for C₁₄H₁₆N₄O₂S: C, 55.25; H, 5.3; N, 18.41. Found: C, 55.23; H, 5.3; N, 18.42.

Results and Discussion

Electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the absence and presence of (3a) has been investigated by cyclic voltammograms in a buffer pH 7 (phosphate buffer, 0.15 M) as the supporting electrolyte. Typical cyclic voltammograms of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) are illustrated in Fig. 1. curve a (on the first anodic scan) one oxidation peak (A₁) was observed. In the contrary, on the reverse scan, a corresponding cathodic peak (C₁) was appeared. These well-defined anodic and cathodic peaks are corresponded to the oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) to (2a) and vice versa within a quasi-reversible two-electron process (Maleki et al., 2009; Nematollahi et al., 2010). The peak current ratio (I_{pC1}/I_{pA1}) is nearly equal with unity, which confirms the stability of (2a) produced at the surface of working electrode in the phosphate buffer solution. Side reactions such as hydroxylation or dimerization reactions are too slow on the time scale of the cyclic voltammetry (Ameri et al., 2014; Asghari et al., 2014). Cyclic voltammogram of 2mM of barbituric acid (3a) in the absence of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) was observable in the Fig. 1, curve c (for comparison). The electro-oxidation of 2mM solution of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2mM of barbituric acid (3a), as a nucleophile, was investigated by cyclic voltammograms. Fig. 1, curve b shows the cyclic voltammogram obtained for a 2 mM solution of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2 mM of (3a). The voltammograms exhibit two cathodic peaks C₁ and C₀.

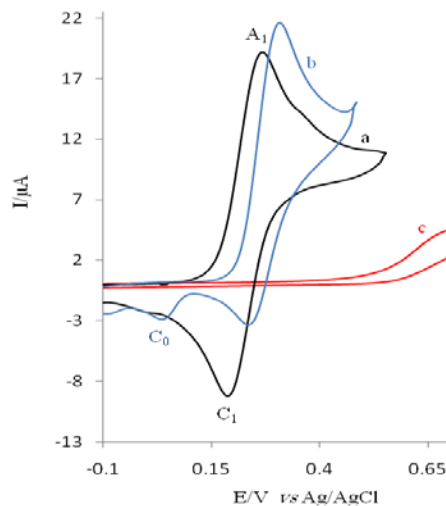


Fig. 1: Typical cyclic voltammograms of 2mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the absence (a), in the presence of 2mM barbituric acid (b), that of a 2mM barbituric acid in the absence of 1a (c) at the glassy carbon electrode in buffer solution pH 7 (0.15M phosphate buffer) at a scan rate of 50mVs⁻¹.

The cyclic voltammograms of N,N,N',N'-Tetramethyl-benzene-1,4-diamine in the presence of (3a) at different potential scan rates are shown in Fig. 2. It can be seen that proportional to the raising of the scan rate in parallel with the decrease in the height of (C₀) peak, the height of the cathodic peak (C₁) of (1a) increases. A similar situation is also observed when the (3a) to (1a) concentration ratio is decreased. On the other hand, increasing current ratio I_{pC1}/I_{pA1} with the increasing potential scan rate is a good indication of the reactivity of (3a) toward (2a).

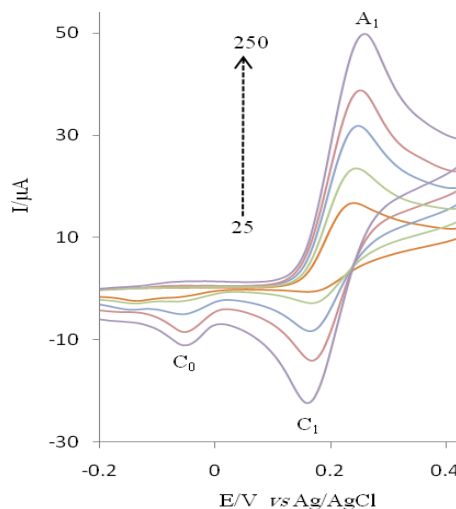


Fig. 2: Cyclic voltammograms of 2mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2mM barbituric acid (3a) at the glassy carbon electrode, in buffer solution pH 7 (0.15M phosphate buffer) at diverse scan rates a) 25, b) 50, c) 100, d) 150 and e) 250 mVs⁻¹.

In other words, the peak current ratios (I_{pC1}/I_{pA1}) and (I_{pC0}/I_{pC1}) versus scan rate for a mixture of 2mM of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) and 2mM of (3a) confirm the reactivity of (2a) towards barbituric acid (3a) for 1,4- Michael addition type reaction, appearing as an increase in the I_{pC1}/I_{pA1} (Fig. 3) and a decrease in the I_{pC0}/I_{pA0} (Fig. 3) at higher scan rates.

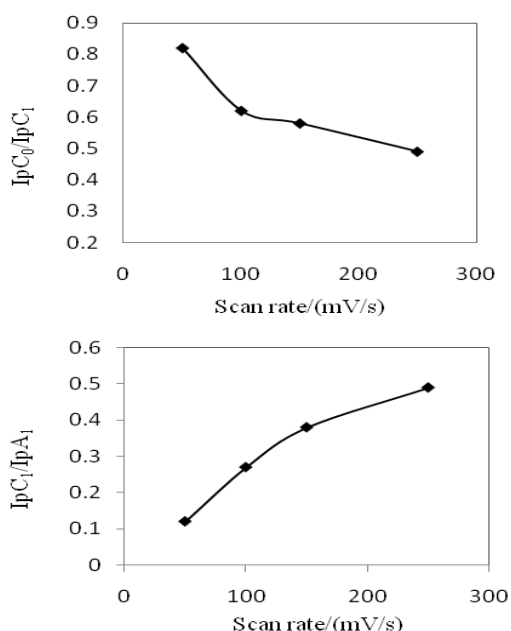


Fig. 3: Variation of peak current ratio I_{pC1}/I_{pA1} , I_{pC0}/I_{pC1} versus scan rate for 2mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2mM of (3a) at various potential sweep rates under experimental condition.

Second-cyclic voltammograms were recorded for 2 mM of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2 mM of barbituric acid (3a), and parallel to the positive shift of the A1 peak in a positive potential direction, a new anodic peak (A0) (that is related to the electrochemical oxidation of intermediate (5a) to (6a)) (Scheme 1) appeared with an E_p value less than the A1 peak potential in the second cycle (Fig. 4). This new peak The presence of an electron-donating group causes an easier oxidation of (5a) than its parent starting molecule N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) (Ameri et al., 2014; Asghari et al., 2014). The positive shift of the A1 peak in the presence of (3a), is probably due to the construction of a thin film of product at the surface of the electrode, inhibiting, to a certain extent, the performance of the electrode process (Nematollahi et al., 2007).

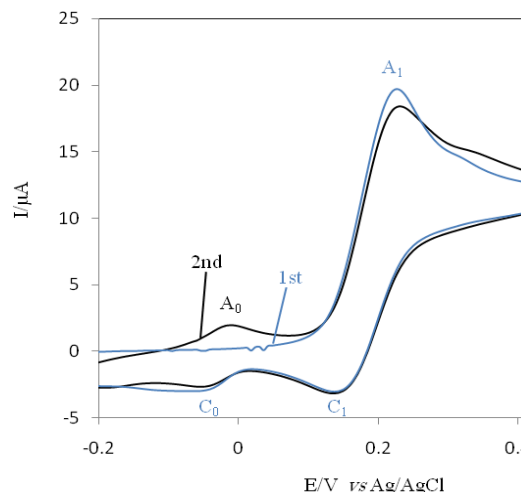


Fig. 4: Multi-cyclic voltammograms of 2mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2Mm (3a), at glassy carbon electrode under experimental condition; potential sweep rate: 50mVs⁻¹.

Controlled-potential coulometry was carried out in the phosphate buffer solution (pH=7.0, 0.15 M) containing 0.2mmol N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) and 0.2mmol of barbituric acid. In order to monitor the electrolysis progress and determination of the number of electrons transferred for each N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) molecule, the cyclic voltammetry was used during the electrolysis (Fig. 5). The electrolysis was finished when the decay of the current become more than 95% of its initial amount. According to our results, all anodic (A1 and A2) and cathodic (C1 and C2) peaks decrease and disappear when the charge consumption becomes 4e⁻ per molecule of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a), during the progress of coulometry. Regarding to our results, it seems that the 1,4-Michael addition-type reaction of (3a-b) to (2a) was faster than the other side-reactions and led to the formation of intermediates (5a-b). Electro-oxidation of these intermediate compounds (5a-b) is easier than electro-oxidation of the parent starting molecule N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) by virtue of the presence of an electron-donating group. Hence, intermediate (5a-b) can be oxidized on the electrode surface to produce intermediate (6a-b). This step causes the apparent numbers of transferred electrons to increase from the limit of n = 2 to n = 4 electrons per molecule of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a). Then the intramolecular conjugate addition reaction originating constructs a nucleophilic attack of enolate to the (6a-b) segment and the subsequent cyclization leads to the production of (7a-b) as the final products. According to cyclic voltammetry, coulometry and spectroscopic data, the ECEC mechanism (E: electrochemical and C: chemical) can be proposed for the electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of (3a-b) under experimental condition (Scheme 1).

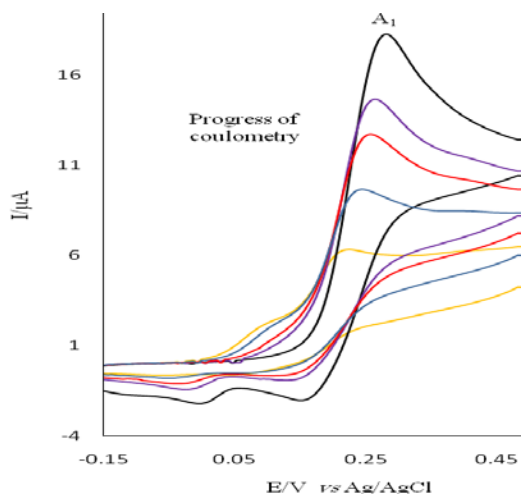
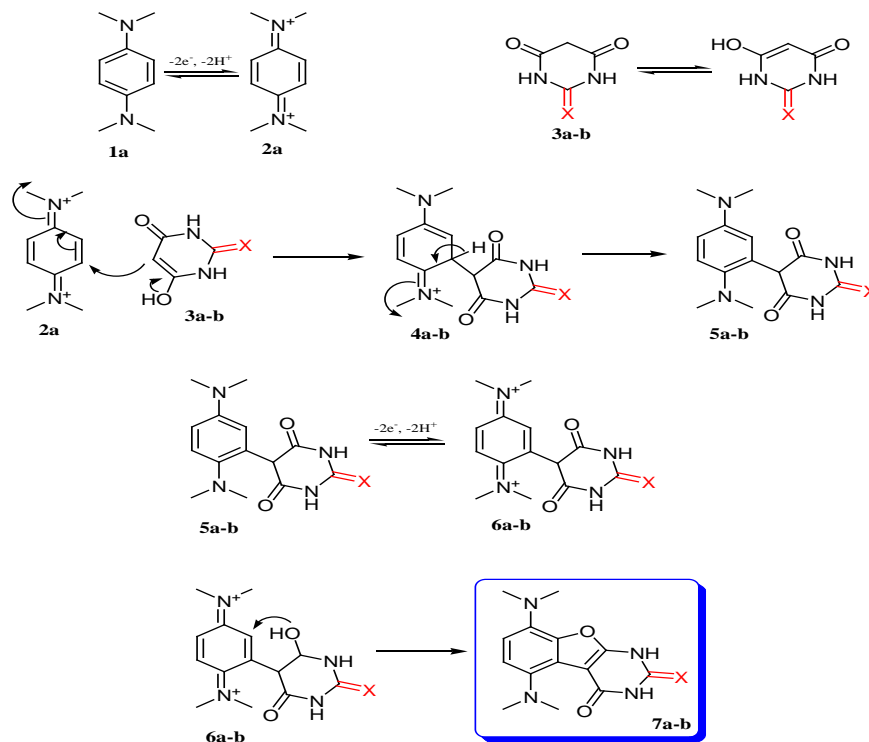


Fig. 5: Cyclic voltammogram of 0.2mmolN,N,N',N'-Tetramethylbenzene-1,4-diamine(1a) in the presence of 0.2mmol of (3a-b), at glassy carbon electrode in buffer solution pH 7 (0.15M phosphate buffer) during coulometry under constant potential at 0.35V vs.

Ag/AgCl (scan rate: 50 mVs⁻¹).Progress of coulometry is associated with decreased anodic peak (A1) current.

Effect of pH

For probing of pH value, electro-organic synthesis of product was performed at various pH ranges (3 to 9) and maximum amount of pure products (7a-b) were received at pH 7 value.



X = O 3a,4a,5a,6a,7a
X = S 3b,4b,5b,6b,7b

Figure 1: Proposed mechanism

Table 1- Investigation of pH

pH	3	4	5	6	7	8	9
Yield 7a (%)	0	5	20	48	81	42	8
Yield 7b (%)	0	5	18	48	79	40	7

Conclusion

The main target of the present work was the electro-synthesis of new benzofurans (7a-b) via a simple, fast, safe waste, catalyst-free, green and one-pot procedure. The electro-synthesis is based on electrochemical oxidation of N,N,N',N'-Tetramethylbenzene-1,4-diamine (1a) in the presence of barbituric acids (3a-b). Cyclic voltammetry and spectroscopic data showed that the electrochemical oxidation of N,N,N',N'-Tetramethylbenzene-1,4-diamine (1a) was adopted with ECEC mechanism (Scheme 1) in the presence of (3a-b).Four e- process of the electrochemical mechanism reaction was confirmed by controlled potential coulometry data. In this work, the results explained that the electrochemical synthesis can be applied as an excellent, green, facile and efficient method for synthesis of various organic compounds such as benzofurans. Also, the uses of electricity instead of catalysts and a one-step process under mild conditions are attractive features of this work.

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