## Catalyst-free, facile, one-pot and safe waste synthesis of new benzofurans *via* electrochemical methods under *ECEC* mechanism

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#### Abstract

The electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) is carried out in the presence of cyanoacetates (3a–c), as nucleophiles, in a phosphate buffer solution (0.2 M, pH 7) mixed with EtOH using voltammetric methods. The results indicate that quinone-imine 2a derived from N,N,N',N'-Tetramethyl-benzene-1,4-diamine participates in a 1,4-Michael-type addition reaction with cyanoacetate derivatives form the new benzofuran derivatives (7a–c) in good yields and with high purities using a simple, catalyst-free, clean, fast and one-pot electrochemical method using six carbon electrodes.

Keywords: Electro-oxidation; N,N,N',N'-Tetramethyl-benzene-1,4-diamine; Catalyst-free; Michael-type addition; Benzofuran

#### INTRODUCTION

Benzofurans have attracted considerable interest because of their presence in natural products, biologically active compounds, and other molecules of pharmaceutical interest <sup>[1, 2]</sup>. Benzofuran heterocycles are the key components found in a variety of natural products. Recently, benzofuran derivatives attracted natural product researchers due to their valuable biological activities including anticancer, antimicrobial, immunomodulatory, antioxidant and anti-inflammatory properties <sup>[3-8]</sup>.

On the other hand, as green organic synthesis is getting more important, development of more efficient and environmental friendly processes for chemical transformation is desired <sup>[9]</sup>. Therefore, it is more beneficial to study the electro-synthesis of new benzofurans in mix of ethanol and phosphate buffer solution as a safe waste solvent.

Considering the wide properties of benzofurans and importance of green chemistry in recent years, the electrooxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) has been investigated the presence of cyanoacetate derivatives (3a-3c) under mild conditions (room temperature, no pressure and catalyst-free) in non-toxic solvent. This has led to the synthesis of new benzofurans using a facile, fast, catalyst-free and safe waste procedure.

### METHOD

#### Apparatus and reagents

Cyclic voltammetric experiments were performed using a Metrohm Voltammetric Analyzer Model 747 (Herisau, Switzerland) and a controlled-potential coulometry was performed using а Behpajooh model 2063 galvanostat/potentiostat (Isfahan, Iran). The working electrode (WE) used in the voltammetry experiments was a glassy carbon disc (GC, 2 mm diameter) and platinum disk (2 mm diameter) was used as a counter electrodes (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 were from AZAR Electrode Company (Urmia, Iran). The cell used was an undivided type. NMR spectra were recorded on a Bruker DRX-400 Advance Instrument. All the chemicals materials were purchased from Merck (Darmstadt, Germany). Those chemicals were used without any further purification.

# Typical procedure for the electrosynthesis of new benzofurans (7a-c)

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An aqueous solution of phosphate buffer (90 ml) (pH 7, 0.2 M) was mixed with EtOH (10 mL) containing 0.5 mmol of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) and 0.5 mmol of cyanoacetate (3a-3c) was electrolyzed at 0.25 V versus the Ag/AgCl, in an undivided cell equipped with six carbon rod as the anodes and a Pt cathode. The electrolysis was terminated when the current decay became greater than 95%. The oxidation was interrupted during electrolysis and the carbon anodes were washed in EtOH in order to reactivate it.At completion of electrolysis, the cell was placed in a refrigerator overnight. The precipitated solid was collected by centrifugation and it was washed several times with warm EtOH to separate the cyanoacetates and N,N,N',N'-Tetramethyl-benzene-1,4-diamine remained. After these washings, the products were sufficiently purified for characterizing. The products were characterized using FT-IR, 1H NMR, 13C NMR, Melting point (Mp) and elemental analysis (CHN).

#### Characterization of products

benzofuran derivative (7a), Yield: 78%. Mp: 184 °C. FT-IR (KBr, cm-1): 2220 (CN), 1515, 1370. 1H NMR (400 MHz, DMSO-d6):  $\delta$  2.93 (s, 6H, Me), 3.14 (s, 6H, Me), 3.87 (s, 3H, OMe), 6.64 (d, 1H, aromatic), 6.80 (d, 1H, aromatic). 13C NMR (100 MHz, DMSO-d6):  $\delta$  43.7, 46.2, 50.5, 59.3, 111.4, 118.7, 123.7, 126.1, 132.9, 135.2, 153.2, 160.4. Anal. Calcd. for C14H17N3O2: C, 64.85; H, 6.61; N, 16.2. Found: C, 64.81; H, 6.62; N, 16.17.

Benzofuran derivative (7b), Yield: 76%. Mp: 203 °C. FT-IR (KBr, cm-1): 2227 (CN), 1535 and 1390. 1H NMR (400 MHz, DMSO-d6): δ 1.39 (t, 3H, Me), 2.91 (s, 6H, Me), 3.12 (s, 6H, Me), 4.12 (q, 2H, CH2), 6.52 (d, 1H, aromatic), 6.76 (d, 1H, aromatic). 13CNMR (100 MHz, DMSO-d6): δ 14, 43.3, 43.9, 50.4, 59, 110.2, 117.1, 125.3, 129.7, 132.7, 134.5, 154.8, 160. Anal. Calcd. for C15H19N3O2: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.93; H, 7.05; N, 15.36.

Benzofuran derivative (7c), Yield: 82%. Mp: 177 °C. FT-IR (KBr, cm-1): 2230 (CN), 1560 and 1402. 1H NMR (400 MHz, DMSO-d6):  $\delta$  1.95 (s, 3H, Me), 2.9 (s, 6H, Me), 3.1 (s, 6H, Me), 6.48 (d, 1H, aromatic), 6.85 (d, 1H, aromatic). 13CNMR (100 MHz, DMSO-d6):  $\delta$  12.7, 42.3, 49.3, 55.7, 110.4, 117.3, 119.7, 122.1, 132, 134.6, 149.4, 162.6. Anal. Calcd. for C14H17N3O: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.15; H, 7.09; N, 17.25.

#### RESULTS

A cyclic voltammogram of 2 mM N,N,N',N'-Tetramethylbenzene-1,4-diamine (1a) in phosphate buffer solution (0.2 M, pH 7) mixed with EtOH (90:10, v:v) shows one anodic peak (A1) and the corresponding cathodic peak (C1) related to the transformation of N,N,N',N'-Tetramethyl-benzene-1,4diamine (1a) to 2a and vice versa within a quas-reversible two-electron process (Fig. 1, curve a). A peak current ratio (IpC1/IpA1) of nearly unity, particularly during the recycling of the potential, can be considered as a criterion for the stability of 2a produced on the surface of the electrode under the experimental conditions <sup>[10, 11]</sup>. The above results indicate that any side reactions is too slow to be observed on the time scale of cyclic voltammetry. The electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of cyanoacetates (3a-3b) was investigated in details. Fig. 1, curve b shows the cyclic voltammogram obtained for a 2 mM solution of N,N,N',N'-Tetramethyl-benzene-1,4diamine (1a) in the presence of 2 mM of 3a. The voltammograms exhibit two cathodic peaks C1 and C0. Also, curve c is related to 2 mM solution of 3a in the absence of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (for comparison).



**Figure 1:** Typical cyclic voltammograms of 2 mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the absence (a), in the presence of 2 mM methyl cyanoacetate (b), that of a 2 mM 3a in the absence of 1a (c) at the glassy carbon electrode in 0.2 M phosphate buffer solution (pH 7) mixed with EtOH (90:10 v:v) at a scan rate of 50 mVs-1.

In addition, it is observed that proportional to the augmentation of potential sweep rate and parallel to the decrease in height of C0, the height of C1 peak increases (Fig. 2 curves a–d). A similar condition is observed when the cyanoacetate to N,N,N',N'-Tetramethyl-benzene-1,4-diamine concentration ratio is decreased



**Figure** 2: Typical voltammograms of 2 mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2mM 3a at the glassy carbon electrode, in 0.2M phosphate buffer solution (pH 7) mixed with EtOH (90:10 v:v) at different scan rates a) 25, b) 50, c) 100 and c) 150 mVs-1.

In other words, the peak current ratios (IpC1/IpA1) and (IpC0/IpC1) versus scan rate for a mixture of 2 mM of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) and 2 mM of 3a confirm the reactivity of 2a towards cyanoacetates (3a-3c) for 1,4- Michael addition type reaction, appearing as an increase in the IpC1/IpA1 (Fig. 3) and a decrease in the IpC0/IpA0 (Fig. 3) at higher scan rates.





**Figure 3:** Variation of peak current ratio IpC1/IpA1, IpC0/IpC1 versus scan rate for 2 mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2 mM of 3a at various scan rates of under experimental optimum condition.

In Fig. 4, multi-cyclic voltammogram of 2 mM of 1a in the presence of 2 mM of methyl cyanoacetate (3a) was observed. As observed, in the second cycle, a new peak A0 was appeared. A0 peak corresponds to the electrochemical oxidation of intermediate 5a to 6a, and C0 peak is related to the electrochemical reduction of 6a to 5a.



**Figure 4**: multi-cyclic voltammograms of 2 mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of 2 mM 3a, at glassy carbon electrode under experimental optimum condition; scan rate: 100 mVs-1.

Coulometry under constant potential was performed in a phosphate buffer solution (0.2 M, pH 7) mixed with EtOH (90:10 v:v) containing 2 mM of 1a and 2 mM of 3a at 0.25 V versus Ag/AgCl. The coulometry progress was monitored using cyclic voltammetry (Fig. 5). As it can be seen, proportional to the decrease in the heights of the A1 and C1 peaks, product was created. All the anodic and cathodic peaks decreased and disappeared when the charge consumption became 4e- per molecule of 1a. At the end of coulometry, all voltammograms disappeared. With regard to the results, it seems that the 1,4-Michael addition-type reaction of 3a-c to 2a was faster than the other side-reactions and led to the formation of intermediates 5a-c. electro-oxidation of these compounds (5a-c) is easier than electro-oxidation of the

parent starting molecule 1a by virtue of the presence of an electron-donating group <sup>[12-14]</sup>. Hence, 5a–c can be oxidized on the electrode surface to produce 6a–c. This step causes the apparent numbers of transferred electrons to increase from the limit of n = 2 to n = 4 electrons per molecule of 1a. Then the intramolecular conjugate addition reaction originating from a nucleophilic attack of enolate to the 6a-c segment and the subsequent cyclization leads to the production of 7a–c as the final products. According to the coulometric, voltammetric, and spectroscopic data, the ECEC mechanism can be proposed for the electrochemical oxidation of 1a in the presence of 3a-c under experimental optimum condition (Scheme 1).



R= OMe 3a,4a,5a,6a,7a R= OEt 3b,4b,5b,6b,7b R= Me 3c,4c,5c,6c,7c Scheme 1 proposed mechanism



**Figure 5:** Cyclic voltammogram of 2 mM N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presenceof 2 mM of 3a, at glassy carbon electrode in 0.2 M phosphate buffer solution (pH 7) mixed with EtOH (90:10 v:v) during controlled-potential coulometry at 0.25 V vs. Ag/AgCl (scan rate: 50 mVs<sup>-1</sup>). Progress of coulometry is associated with decreased anodic peak (A1) current.

#### Effect of pH

For investigation of pH value, electro-synthesis was performed at various pH values (from 3 to 9) and maximum amount of pure products (7a-c) were obtained at pH 7.

| Table 1: investigation of pH |   |    |    |    |    |    |    |
|------------------------------|---|----|----|----|----|----|----|
| рН                           | 3 | 4  | 5  | 6  | 7  | 8  | 9  |
| Yield 7a (%)                 | 0 | 8  | 22 | 55 | 78 | 46 | 12 |
| Yield 7b (%)                 | 0 | 7  | 20 | 51 | 76 | 42 | 12 |
| Yield 7c (%)                 | 0 | 10 | 28 | 58 | 82 | 43 | 10 |

## CONCLUSION

The main target of the present experiment was the electrochemical synthesis of new benzofuran derivatives (7ac) via a facile and clean synthetic path, based on electrooxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of cyanoacetate derivatives (3a-3c). Voltammetry, controlled-potential coulometry and spectroscopic data indicated that the electro-oxidation of N,N,N',N'-Tetramethyl-benzene-1,4-diamine (1a) in the presence of cyanoacetates (3a-3c) was adopted with ECEC mechanism (Scheme 1). In this experiment, the results explained that the electrochemistry can be applied as an useful method for safe waste, simple and efficient synthesis of benzofuran derivatives. Furthermore, the use of electricity instead of catalyst and a one-step process conducted under mild conditions are attractive features of this work.

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