

## Green, catalyst-free, facile and one pot electrochemical synthesis of new bis-indoles from *p*- phenylenediamine oxidation in the presence of cyanoacetate derivatives

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### Abstract

Electrochemical oxidation of *p*- phenylenediamine has been investigated in the presence of methyl and ethyl cyanoacetate as a nucleophile in phosphate buffer solution mixed with ethanol (10/90 v/v) using cyclic voltammetry and controlled-potential coulometry methods. The results revealed that cyclohexa-2,5-diene-1,4-diimine derived from electro-oxidation of *p*- phenylenediamine participates in 1,4-Michael addition reactions with cyanoacetate derivatives. The formed adducts convert to the corresponding bis-indole derivatives via ECECCC (Electrochemical, chemical, chemical reactions) mechanism. In the present work, new bis-indoles were synthesized with high purity and good yields using controlled potential electrochemical oxidation at five graphite electrode in an undivided cell under mild conditions.

**Keywords:** Electrochemical oxidation; *p*- phenylenediamine; cyanoactate; Michael addition; ECECCC mechanism.

### 1. Introduction

Indole derivatives have been a topic of substantial research interest and continue to be one of the most active areas of heterocyclic chemistry, particularly due to their natural occurrence and pharmacological activities [1, 2]. Indoles are one of the most important nitrogen containing heterocyclic molecules, found extensively in biological system which play vital role in biochemical process. Indole alkaloids have been proved to be medicinally important natural compounds. Indole ring constitutes an important template for drug design such as the classical NSAIDs indomethacin and indoxole. Further Indole derivatives have been reported to possess promising biological activities including analgesic [3], antipyretic [4], antifungal [5], anti-inflammatory [6], anthelmintic [7], cardiovascular [8], anticonvulsant [9], antimicrobial [10] and selective COX-2 inhibitory activities [11]. According to the pharmacological and biological properties of indole derivatives, importance of green chemistry in organic synthesis, efficiency of the electrochemical synthesis method, facile and one-pot synthesis of new bis-indoles, the electro- oxidation of *p*- phenylenediamine has been studied by means of voltammetric methods in a phosphate buffer solution mixed with ethanol as a green and non-toxic solvent.

## 2. MATERIALS AND METHODS

### 2.1 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 (GC, 1.8 mm diameter) and a platinum disk was used as a counter electrodes (CE). The WE used in the controlled-potential coulometry was an assembly of 5 carbon rods, and a sheet platinum constituted the CE. The WE potentials were measured *vs.* Ag/AgCl. All electrodes were purchased from AZAR Electrode Company (Urmia, Iran). NMR spectra were recorded on a Bruker DRX-400 Advance Instrument (Germany). UV and IR spectra were recorded on a Shimadzu spectrophotometer (Tokyo, Japan). All the chemicals used were purchased from Merck Company (Germany). These chemicals were used without further purification.

### Typical Procedure for the electrochemical synthesis of bis-indoles (8a-8b)

In this procedure, 100 mL of water/ethanol (90:10 v:v) containing a 0.2 M phosphate buffer (pH 6) as the supporting electrolyte was pre-electrolyzed at 0.35 V *vs.* Ag/AgCl in an undivided cell. Subsequently, 1 mmol of *p*-phenylenediamine (**1a**) and 2 mmol of cyanoacetate (**3a** or **3b**) were added to the cell. Finally, the electrolysis was performed using 0.35 V *vs.* Ag/AgCl. The electrolysis was finished when the current decreased by more than 95%. The process was interrupted for six times during the electrolysis, and the carbon anode was washed in ethanol to reactivate it. At the end of electrolysis, the cell was placed in a refrigerator for one day. The precipitated solid was collected by centrifugation. The final product washed with mixture of ethanol and acetonitrile. After purification, the final product was characterized using the FT-IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and elemental analysis.

### 2,6-Diamino-1,5-dihydro-pyrrolo[2,3-*f*]indole-3,7-dicarboxylic acid dimethyl ester (8a)

Brown solid; Yield: 82%; Mp > 250 °C (decomposed); FT-IR (KBr, cm<sup>-1</sup>): 3280 (broad, NH<sub>2</sub> and NH), 2234 (CN), 1780 (C=O ester); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.13 (s, 3H, Methyl), 7.74 (s, 1H, aromatic), 8.12 (s, 2H, NH<sub>2</sub>, exchanged with D<sub>2</sub>O), 11.07 (broad, 1H, NH, exchanged with D<sub>2</sub>O); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 50.3, 101.4, 118.4, 120.3, 126.9, 138.7, 163; Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>: C, 55.63; H, 4.67; N, 18.53; Found: C, 55.59; H, 4.69; N, 18.54.

### 2,6-Diamino-1,5-dihydro-pyrrolo[2,3-*f*]indole-3,7-dicarboxylic acid dimethyl ester (8b)

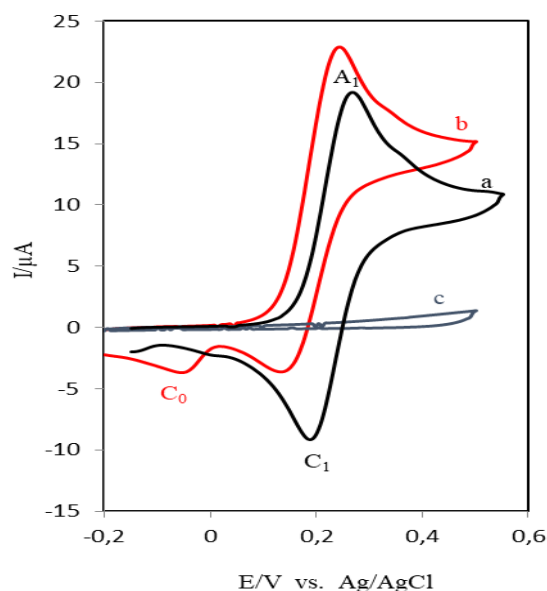
Gray solid; Yield: 80%; Mp > 250 °C (decomposed); FT-IR (KBr, cm<sup>-1</sup>): 3240 (broad, NH<sub>2</sub> and NH), 2228 (CN), 1764 (C=O ester); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.29 (t, 3H, Me), 4.1 (q, 2H, CH<sub>2</sub>), 7.72 (s, 1H, aromatic), 8.13 (s, 2H, NH<sub>2</sub>, exchanged with D<sub>2</sub>O), 11.07 (s, 1H, NH, exchanged with D<sub>2</sub>O); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 15.5, 51.1, 102.4, 119.7, 121.4, 127.3, 137.3, 163.6; Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>: C, 58.17; H, 5.49; N, 16.96; Found: C, 58.19; H, 5.48; N, 16.94.

## 3. Results and discussion

### Electro-oxidation of *p*-phenylenediamine (1a) in the presence of methyl cyanoacetate (3a)

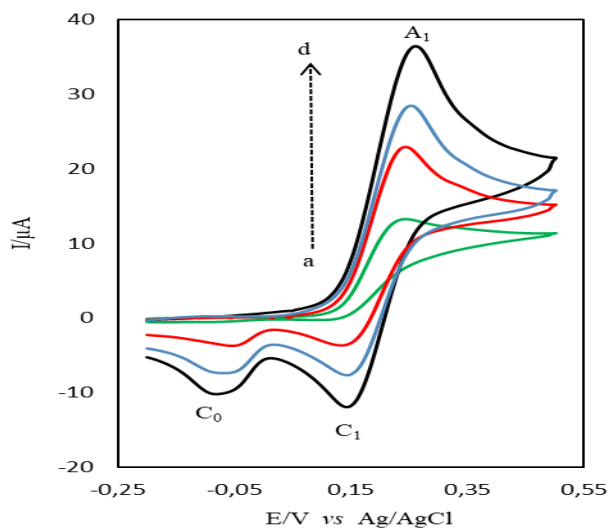
A cyclic voltammogram of a solution of 2 mM of *p*-phenylenediamine (**1a**) in a phosphate buffer solution (pH 6, 0.2 M) shows one anodic peak (A1) and a corresponding cathodic peak (C1), which represent the transformation of **1a** to cyclohexa-2,5-diene-1,4-diimine (**2a**) and vice versa within a quasi-reversible two-electron process [12-13] (Fig. 1, curve a). A peak current ratio (I<sub>pC1</sub>/I<sub>pA1</sub>) of nearly unity, particularly during recycling of the potential, can be

considered as a criterion for the stability of the cyclohexa-2,5-diene-1,4-diimine (**2a**) produced on the surface of the electrode under the optimum conditions. In other words, any side reaction such as hydrolysis [12] is too slow to be observed on the time scale of cyclic voltammetry. The electro-oxidation of *p*-phenylenediamine (**1a**) in the presence of methyl cyanoacetate (**3a**) was studied in detail. The electrochemical oxidation of **1a** in the presence of Methyl cyanoacetate (**3a**) as nucleophile was studied in detail. As can be seen, curve b (Fig. 1) shows the cyclic voltammogram recorded for solution of 2 mM of **1a** in the presence of 4 mM of **3a**. Under these optimum conditions, the cathodic counterpart of anodic peak  $A_1$  decreases and a new cathodic peak ( $C_0$ ) appears at potentials more with greater negative values than the cathodic peak ( $C_1$ ) is related to electrochemical reduction of intermediate **5a** to **4a**. In addition, curve c (Fig. 1) shows the cyclic voltammogram recorded for a solution of 2 mM of **3a** in the absence of **1a** (for comparison).



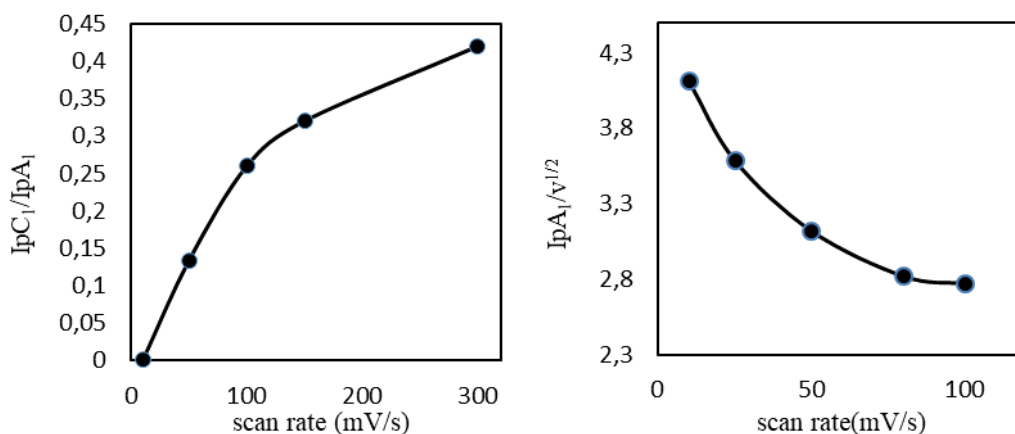
**Fig. 1** Cyclic voltammograms of 2 mM of *p*-phenylenediamine (**1a**) in the absence (a) and presence of 4 mM of methyl cyanoacetate (b) and that of a 2mM of methyl cyanoacetate in the absence of **1a** (c) at the glassy carbon electrode in a 0.2 M phosphate buffer solution (pH 6) mixed with ethanol (90:10 v:v) at a scan rate of 50 mV s<sup>-1</sup>.

It is observed that, proportional to the raise in the potential sweep rate and parallel with the decrease in height of  $C_0$ , the height of  $C_1$  increases (Fig. 2 curves a–d).



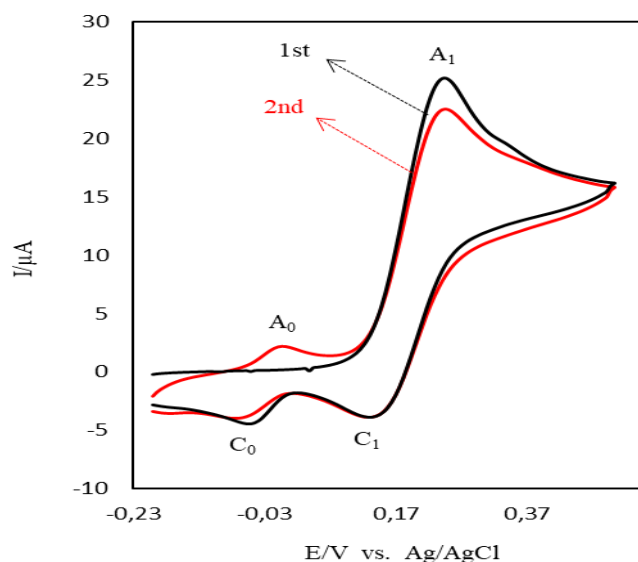
**Fig. 2** Typical voltammograms of 2 mM of *p*-phenylenediamine (**1a**) in the presence of methyl cyanoacetate at glassy carbon electrode, in a 0.2 M phosphate buffer solution (pH 6) mixed with ethanol (90:10 v:v) at various scan rates: a) 10, b) 25, c) 50 and d) 100 mV s<sup>-1</sup>.

In other words, the peak current ratios ( $I_{pC1}/I_{pA1}$ ) vs. potential sweep rate for a mixture of 2 mM of *p*-phenylenediamine (**1a**) and 4 mM of methyl cyanoacetate (**3a**) confirm the reactivity of **2a** towards methyl cyanoacetate (**3a**), appearing as an increase in  $I_{pC1}/I_{pA1}$  (Fig. 3) and a decrease in  $I_{pC0}/I_{pA0}$  (Fig. 2) at higher scan rates [14]. Moreover, the current function for the A1 peak ( $I_{pA1}/v^{1/2}$ ) decreases slightly with raise in the potential sweep rate (Fig. 3).

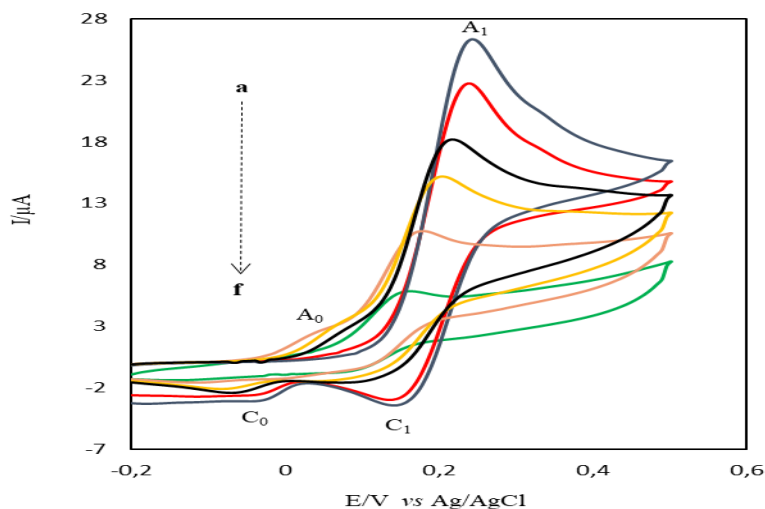


**Fig. 3** Variation of peak current ratio  $I_{pC1}/I_{pA1}$  and  $I_{pA1}/v^{1/2}$  versus scan rate for 2 mM of *p*-phenylenediamine in the presence of 4 mM of methyl cyanoacetate at various scan rates under optimum pH (pH 6).

Multi-cyclic voltammogram of *p*-phenylenediamine (**1a**) in the presence of methyl cyanoacetate (**3a**) shows that a new peak (A0) appears in the second cycle parallel to the positive shift of the A1 peak in a positive potential direction (Fig. 4). A0 corresponds to the electrochemical oxidation of intermediate **4a**. The electro-oxidation of this compound (**4a**) is easier than the electro-oxidation of the parent starting molecule *p*-phenylenediamine (**1a**) [15-17] due to the presence of an electron-donating group (enolat form of methyl cyanoacetate). After transformation of intermediate **5a-b** to **6a-b**, the latter can be attacked by another **3a-b** (Scheme 1). Then, NH<sub>2</sub> and OH groups of **6a-b** intermediate can be attached to CN groups and produce **8a-b** compound. These products (**8a-b**) are insoluble under the experimental conditions. On the other hand, the positive shift of the A1 peak in the presence of **3a** is due to the formation of a thin film of product on the electrode surface, which inhibits, to a certain extent, the performance of the electrode processes [14]. To overcome this problem, the glassy carbon electrode was polished with alumina powder after recording each cyclic voltammograms, in order to reactivate its surface. Electrolysis was performed under a constant potential (0.35 V) for 0.3 mmol of *p*-phenylenediamine (**1a**) in the presence of 0.6 mmol of methyl cyanoacetate (**3a**) in a 100mL mixed solution of phosphate buffer (0.2 M, pH 6) and ethanol (90:10, v:v). Figure 5 shows the cyclic voltammograms obtained for monitoring the electrolysis progress. It is clear that proportionally to the advancement of electrolysis anodic peak (A1) decreases, indicating the **1a** consumption and the occurrence of the desired reaction. The A1 peak disappeared when charge consumption was about 4e<sup>-</sup> per molecule of **1a**.

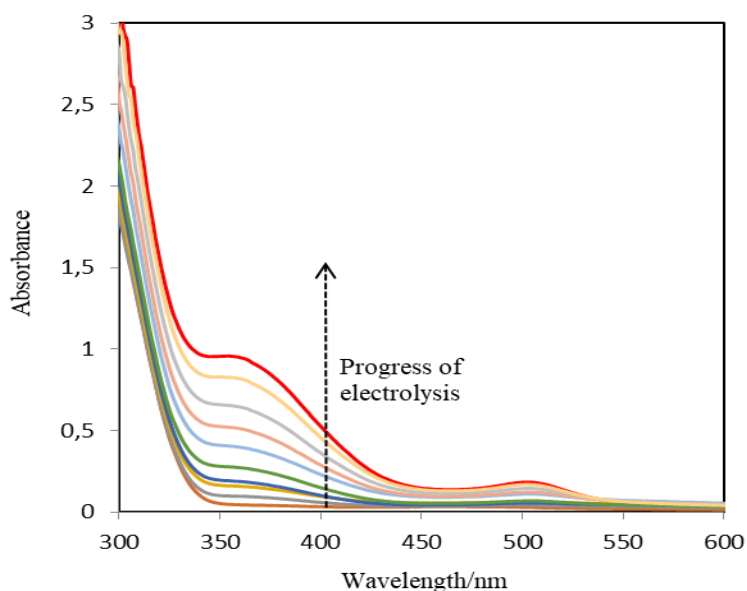


**Fig. 4** Multi-cyclic voltammograms of 2 mM *p*-phenylenediamine (**1a**) in the presence of 4 mM of methyl cyanoacetate, at glassy carbon electrode in 0.2 M phosphate buffer solution (pH 6) mixed with ethanol (90:10 v:v); scan rate: 50 mVs<sup>-1</sup>.



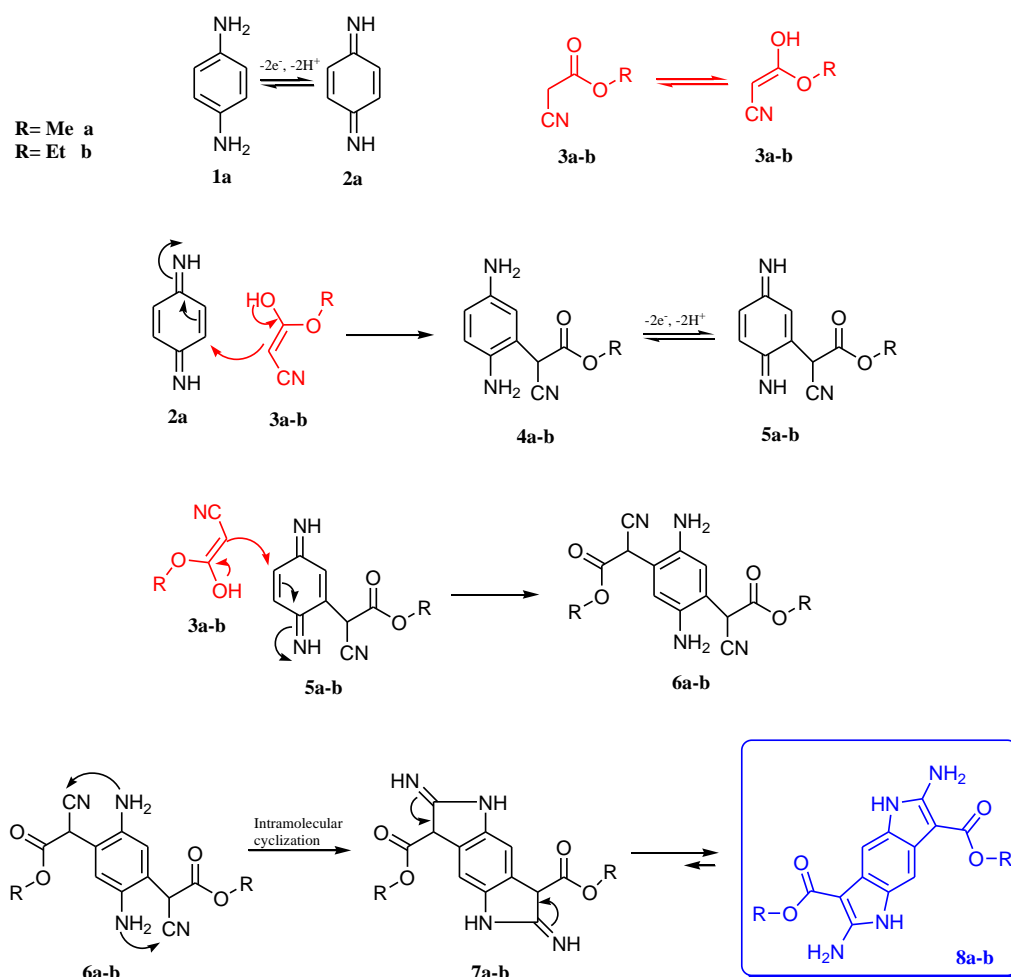
**Fig. 5** Cyclic voltammogram of 3 mM of *p*-phenylenediamine (**1a**) in the presence of 6 mM of methyl cyanoacetate at glassy carbon electrode in a 0.2 M phosphate buffer solution (pH 6) mixed with ethanol (90:10 v:v) during controlled-potential coulometry at 0.35 V vs. Ag/AgCl (scan rate: 50 mV s<sup>-1</sup>) Progress of electrolysis is associated with the decreased anodic peak (A1) current.

Beside, time-dependent absorption spectra of the mixture of 0.2 mmol of **1a** and 0.4 mmol of **3a** were collected during a electrolysis under 0.35 V vs. Ag/AgCl (Fig. 6). These spectra show that as the coulometry experiment is carried out, absorption peaks with  $\lambda_{\text{max}}$  at 356 and 490 nm appear and their height increase. These peaks relate to the produced **8a**.



**Fig. 6** Absorption spectra of the mixture of 2 mM of *p*-phenylenediamine (**1a**) and 4 mM of methyl cyanoacetate during electrolysis at 0.35 V vs. Ag/AgCl under optimum conditions.

These observations and the NMR spectroscopic and FT-IR data and elemental analysis allow to propose the *ECECCC* mechanism represented by [Scheme 1](#) for the electrochemical oxidation of *p*-phenylenediamine in the presence of cyanoacetate derivatives under above condition.



## Scheme 1 proposed mechanism

### Effect of pH

Electrosynthesis of **8b** was performed in the acidic, natural and basic media (pH: 3 to 9) and maximum amount of pure product was obtained at pH 6. Table 1 shows the pH value changes *versus* yield.

**Table 1.** Investigation of yield (**8a-b**) at various pH values

pH	3	4	5	6	7	8	9
Yield ( <b>8a</b> )	0%	21%	55%	82%	60%	40%	5%
Yield ( <b>8b</b> )	0%	22%	53%	80%	56%	41%	4%

## 4. Conclusion

The main goal of the present work was the electro-synthesis of new bis-indole derivatives *via* a facile, one-pot, catalyst-free, rapid and green path based on electro-oxidation of *p*-phenylenediamine in the presence of methyl and ethyl cyanoacetate. Cyclic voltammetry and coulometry under constant potential indicated that the electro-oxidation of *p*-phenylenediamine in the presence of cyanoacetates follows ECECCC mechanism, which are depicted in [Scheme 1](#). Four-electron process of the mentioned mechanism reaction (ECECCC) was confirmed by controlled potential coulometry results. Green and ecological synthesis, the use of electricity instead of catalyst, no need high temperature (reflux), as well as a one-pot process conducted under mild conditions are features of this study. Furthermore, this work introduces electrolysis as a “*powerful tool*” for the synthesis of new bis-indole derivatives.

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