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Original article

A new approach for one-pot, green synthesis of new polycyclic indoles in aqueous solution

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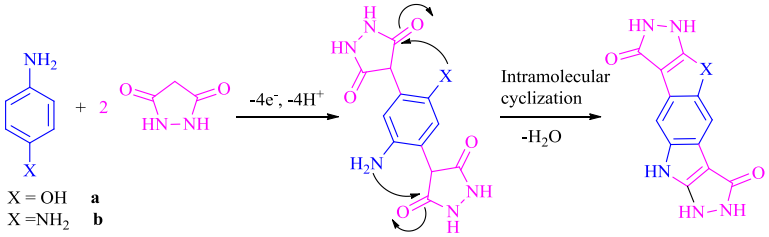
Graphical abstract



Electro-oxidation of phenylamine derivatives have been studied in the presence of pyrazolidine-3,5-dione as a nucleophile in phosphate buffer solution mixed with ethanol, using voltammetric and spectroscopic techniques.

ABSTRACT

Electro-oxidation of phenylamine derivatives (**1a-1b**) have been studied in the presence of pyrazolidine-3,5-dione (**3**) as a nucleophile in phosphate buffer solution mixed with ethanol, using voltammetric and spectroscopic techniques. The obtained results indicated that the oxidized form of phenylamines (**2a–2b**) participate in Michael addition type reactions with pyrazolidine-3,5-dione (**3**) and *via* ECECCCCC mechanisms convert to the corresponding new polycyclic indoles (**12a-12b**). In the present study, new polycyclic indole derivatives were synthesized with good yields and high purity using a facile, one-pot and environmentally friendly electrochemical method, without any chemical catalysts, toxic solvents and hard conditions.

Keywords:
Electro-oxidation
Phenylamine
Polycyclic indoles
Environmentally friendly
ECECCCCC mechanism

1. Introduction

The indole moiety is a privileged structural motif in many biologically active and medicinally valuable molecules [1, 2]. Polycyclic frameworks lead to relatively rigid structures that might be expected to show substantial selectivity in their interactions with enzymes or receptors [3]. Construction of polycyclic indoles usually requires multistep reactions [4]. The preparation of polyfunctional indoles is therefore an important research field. On the other hand, indole and its derivatives are found in molasses tar and coal tar [5]. Indole nucleus is also found in amino acids such as tryptophan, plant hormones, and certain important alkaloids [6], as well as in liver, pancreas [7], brain [8] and bile [9]. Furthermore, indole is a powerful anti-oxidant and appears to be especially effective against breast and cervical cancer because of its ability to increase the break-down of estrogen in the human body [10]. Electrochemistry has recognized as a high-powered tool to develop environmentally friendly processes [11, 12]. Graphite electrode may be regarded as a catalyst (non-toxic and safe) that is easily separated from the obtained product. Hence, it can be concluded that electro-synthesis is a green and safe waste approach for synthesis of various organic compounds. Over the last two years, electro-oxidation of phenylamine derivatives such as *p*-phenylenediamines, 4-aminophenols and 2-aminophenols have been studied in some details, in both the presence and absence of various compound, based on different electrochemical mechanisms [9, 13-15]. According to the wide applications of indole derivatives, complexity of chemical synthesis of polycyclic indoles and importance of green chemistry in the recent years, we encouraged to develop a facile, non-catalyst, easy handling, clean, safe waste, one-pot and fast method for the electrochemical synthesis of new polycyclic indoles. In this way, the electrochemical oxidation of phenylamine derivatives (**1a-b**) has been investigated in the presence and absence of pyrazolidine-3,5-dione (**3**) as a nucleophile under mild conditions (no heat, no reflux, no pressure and without any chemical catalyst) in a mixture of phosphate buffer solution with ethanol as a green medium.

2. Results and discussion

A cyclic voltammogram of 2 mmol/L of 4-aminophenol (**1a**) in a phosphate buffer solution (0.15 mol/L, pH 7.0) mixed with EtOH (70:30, v/v) shows one anodic (A1) and corresponding cathodic peak (C1), which are related to the transformation of 4-aminophenol (**1a**) to 4-iminocyclohexa-2,5-dienone (**2a**) and vice versa within a *quasi-reversible* 2e- process (Fig. 1, curve a). A peak current ratio (IpC1/IpA1) of nearly unity, particularly during the recycling of potential, can be considered as criteria for the stability of 4-iminocyclohexa-2,5-dienone (**2a**) formed at the surface of the working electrode (GC) under the optimum experimental conditions. In other words, any side reactions [9, 13-15] are too slow to be observed in the time scale of cyclic voltammetry. The electro-oxidation of 4-aminophenol (**1a**) in the presence of 3,5-pyrazolidinedione (**3**) was investigated in detail. As can be seen, curve b (Fig. 1) shows the cyclic voltammogram obtained for solution of 2 mmol/L of **1a** in the presence of 4 mmol/L of 3,5-pyrazolidinedione (**3**) as a nucleophile. Under experimental conditions, the cathodic counterpart of anodic peak A1 decreases and a new cathodic peak (C0) appears at potentials more negative than cathodic peak (C1) which is related to electrochemical reduction of intermediate **6a** to **5a**. Furthermore, in Fig. 1, curve c shows the cyclic voltammogram obtained for a solution of 2 mmol/L of 3,5-pyrazolidinedione (**3**) in the absence of 4-aminophenol (**1a**) under experimental condition for comparison. The same electrochemical behavior was seen (Fig. 1, curve d and e) for 1,4-diaminobenzene (**1b**) in the absence and presence of 3,5-pyrazolidinedione (**3**) in a phosphate buffer solution (0.15 mol/L, pH 6.0) mixed with EtOH (70:30 v:v).

The cyclic voltammograms of 2 mmol/L of 4-aminophenol (**1a**) in the presence of 4 mmol/L of 3,5-pyrazolidinedione (**3**) are shown in Fig. 2, at various scan rates. It can be seen that proportional to the raising of the scan rate in parallel with the decrease in the height of C0 peak (cathodic peak of intermediate), the height of the cathodic (C1) peak of 4-aminophenol (**1a**) increases. A similar situation is also seen when the pyrazolidinedione (**3**) to 4-aminophenol (**1a**) concentration ratio is decreased (data not shown). In other words, increasing current ratio IpC1/IpA1 with the increasing scan rate is a good indication of the reactivity of **3** toward 4-iminocyclohexa-2,5-dienone (**2a**).

Controlled-potential coulometry was carried out in phosphate buffer solution (0.15 mol/L, pH 7) mixed with EtOH (70:30, v/v), containing 0.5 mmol of 4-aminophenol (**1a**) and 1 mmol of 3,5-pyrazolidinedione (**3**), at 0.3 V *vs.* Ag/AgCl (3 mol/L) electrode. In the case of **1b**, coulometry was carried out in phosphate buffer solution with pH 6 mixed with ethanol containing 0.5 mmol of **1b** and 1 mmol of **3** at 0.3 V. The electro-synthesis progress was monitored by using cyclic voltammetry technique (Fig. 3). It is shown that, proportionally to the progress of coulometry, under constant potential, the anodic peak (A1) decreases and disappears when the charge consumption becomes about 4e− per molecule of **1b**, and the new anodic peak (A0) is related to the electrochemical oxidation of intermediate **5b** to **6b** (Scheme 1).

Regarding the results, it seems that the 1,4-Michael addition reaction of **3a** to **2a**, **b** is faster than the other side reactions and leads to the formation of intermediates **5a**, **b**. The oxidation of these compounds (**5a**, **b**) is easier than the oxidation of the parent-starting molecule **1a**, **b** by virtue of the presence of an electron-donating group [17-20]. Hence, **5a**, **b** can be oxidized on the surface of electrode and produces **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 **1a**, **b**. Then, 1,4-Michael addition reaction [21] of the second molecule of **3a** to **6a**, **b** is followed by two intramolecular cyclizations originating from two nucleophilic attacks of NH_2 and X to C=O groups. Finally, elimination of two molecules of H_2O leads to the final products **12a**, **b** (Scheme 1). According to the coulometric results, voltametric and spectroscopic data, the ECECCCCC electrochemical mechanism is proposed for the electrochemical oxidation of phenylamine derivatives (**1a**, **b**) in the presence of 3,5-pyrazolidinedione (**3**), under experimental optimum condition (Scheme 1).

3. Conclusions

The prominent features of this work such as the one-pot, simple electrochemical synthesis of polycyclic indole derivatives in aqueous/ethanol mixture instead of toxic solvents, at room temperature, high energy efficiency and using the graphite electrode as an electron source instead of toxic catalysts, are in accordance with the principle of green chemistry. Cyclic voltammetry, controlled-potential coulometry and spectroscopic data indicated that the electrochemical oxidation of phenylamine derivatives (**1a-1b**) in the presence of 3,5-pyrazolidinedione (**3**) were adopted with ECECCCCC mechanism (Scheme 1). Four-electron process of the electrochemical mechanism reaction was confirmed by coulometry, under constant potential data. In the present study, the obtained results explained that the electrochemistry can be applied as a green method for facile, high yield, safe waste, catalyst-free, rapid and one-pot synthesis of organic compounds, under mild conditions. In addition, this work introduces electrochemistry as a "powerful tool" for the synthesis of new supra heterocyclic compounds such as polycyclic indole derivatives.

4. Experimental

4.1. Apparatus and reagents

The reaction equipment was used as described in the Supporting information. All chemical materials were purchased from Merck (Darmstadt, Germany). These chemicals were used without further purification.

*4.2. Typical procedure for the chemical synthesis of pyrazolidine-3,5-dione (**3**)*

As an important starting material in this work, 3,5-pyrazolidinedione (**3**) was prepared according to the mechanism proposed by Metwally *et al.* (scheme 1) *via* cyclization of ethoxycarbonylacetohydrazide using sodium methoxide [16]. The spectroscopic data (^{1}H and ^{13}C NMR) and melting point confirmed synthesis of this compound (**3**), according to reference 16 (data not shown).

*4.3. Typical procedure for the electrochemical synthesis of indoles (**12a, 12b**)*

In the proposed method, 100 mL of phosphate buffer solution (0.15 mol/L) mixed with ethanol (80:20, v/v), as supporting electrolyte (in the case of **12a** pH 7 and **12b** pH 6), was pre-electrolyzed at the 0.3 V *vs.* Ag/AgCl in an undivided cell. Then, 0.2 mmol of 4-aminophenol (**1a**) or 1,4-diaminobenzene (**1b**) and 0.4 mmol of 3,5-pyrazolidinedione (**3**) were added to the electrochemical cell. Finally, the electrochemical synthesis under constant potential was performed using the 0.3 V *vs.* Ag/AgCl. The electrolysis was finished when the current decreased more than 95%. The process was interrupted several times during the electro-synthesis (for ensuring to complete the reaction), and the working electrodes (five carbon anodes) were washed in ethanol to reactivate (to clear the surface of working electrode from formed side products such as polymers). At the end of electrolysis, the electrochemical cell was placed in the refrigerator (T= 4±1 ^{o}C) for 24 h. The precipitated solid was collected by filtration and washed with warm etanol/acetonitrile (1:1, v/v) to separate the remained 4-aminophenol (**1a**) or 1,4-diaminobenzene (**1b**). Then, it was washed several times with cold water to more purification. After purification, the products (**12a** and **12b**) were characterized using FT-IR, mass spectroscopy (MS), elemental analysis (CHN), NMR.

4.4. Characterization of products

Compound **12a**: Yield: 83%. Mp> 260 °C (dec). FT-IR (KBr, cm^{-1}): 3417 (NH), 1660 (C=O, amide), 1570 and 1480 (C=C aromatic). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.63 (s, 2H, aromatic), 10.03 (s, broad, 2H, NH pyrazolidine ring), 10.52 (broad, 2H, NH, pyrazolidine ring), 11.28 (s, 2H, NH Phenylamine ring). ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.6, 112.2, 117.7, 122.6, 129.2, 166.6. MS (EI, *m/z*) (relative intensity): 269 (M+, 19), 186 (70), 156 (62), 108 (45), 54 (55). Anal. Calcd. for $C_{12}H_8N_6O_2$: C, 53.73; H, 3.01; N, 31.33. Found: C, 53.69; H, 3.07; N, 31.27.

Compound **12b**: Yield: 78%. Mp> 260 °C (dec). FT-IR (KBr, cm^{-1}): 3390 (NH), 1664 (C=O, amide), 1570 and 1443 (C=C aromatic). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (s, 1H, aromatic), 7.88 (s, 2H, aromatic), 10.04 (s, broad, 2H, NH Pyrazolidine ring), 10.38 (broad, 2H, NH, pyrazolidine ring), 11.24 (s, 1H, NH phenylamine ring). ^{13}CNMR (100 MHz, DMSO-d_6): δ 110.2, 110.3, 113.3, 117.6, 123.3, 124.6, 125.3, 131.5, 141.5, 143.3, 166.2, 166.9. MS (EI, *m/z*) (relative intensity): 270 (M+, 28), 187 (76), 161 (55), 94 (80), 54 (60). Anal. Calcd. for $C_{12}H_7N_5O_3$: C, 53.54; H, 2.62; N, 26.01. Found: C, 53.57; H, 2.57; N, 25.93.

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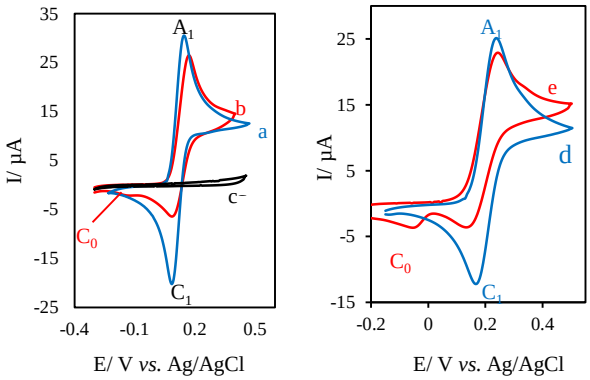


Fig. 1. Typical cyclic voltammograms of 2 mmol/L 4-aminophenol (**1a**) in the absence (a), in the presence of 4 mmol/L 3,5-pyrazolidinedione (b), that of a 2 mmol/L 3,5-pyrazolidinedione (**3**) in the absence of **1a** (c), cyclic voltammograms of 1,4-diaminobenzene (**1b**) in the absence (d) and in the presence of 4 mmol/L 3,5-pyrazolidinedione (e) at the glassy carbon electrode under experimental conditions at a scan rate of 50 mVs^{-1}.

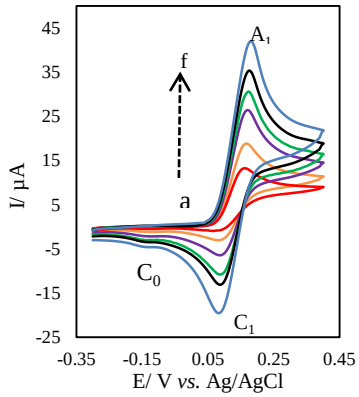


Fig. 2 Typical voltammograms of 2 mmol/L 4-aminophenol (**1a**) in the presence of 3,5-pyrazolidinedione (**3**) at the glassy carbon electrode, in 0.15 mol/L phosphate buffer solution (pH 7) mixed with ethanol (80:20 v:v) at different scan rates a) 10, b) 25, c) 50, d)80, e) 100 and f) 150 mVs^{-1}.

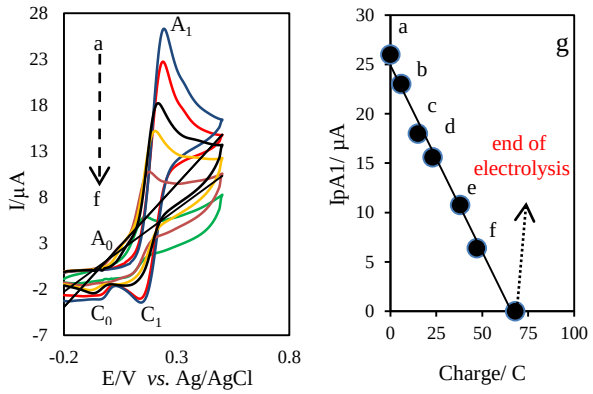
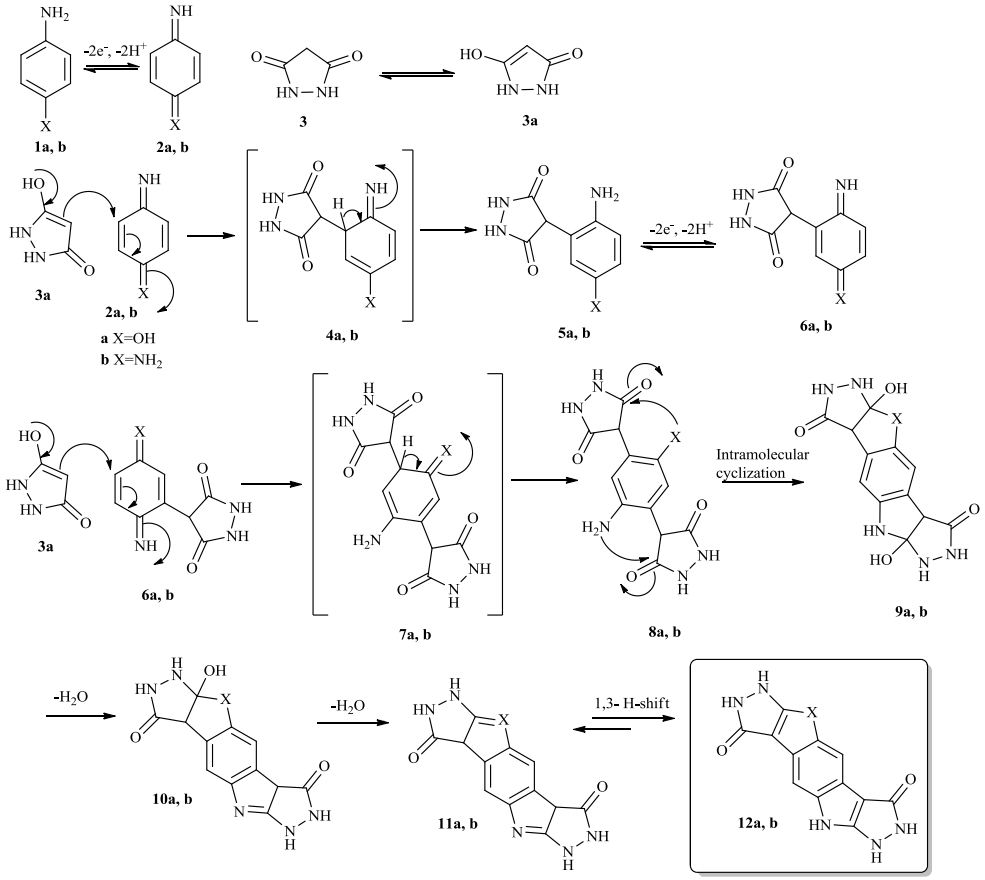
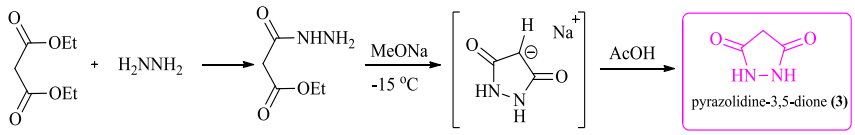


Fig. 3 Cyclic voltammogram of 0.2 mmol 1,4-diaminobenzene (**1b**) in the presenceof 0.4 mmol of 3,5-pyrazolidinedione (**3**), at glassy carbon electrode in 0.15 mol/L phosphate buffer solution (pH 6) mixed with ethanol (80:20, v:v) during controlled-potential coulometry at 0.3 V *vs.* Ag/AgCl (scan rate: 50 mV/s). After the consumption of a) 0, b) 6, c) 15, d) 23, e) 38 and f) 47 C. Progress of coulometry is associated with decreased anodic peak (A1) current. Curve g shows variation of anodic peak current (A1) versus charge consumed.



Scheme 1. Proposed mechanis.



Scheme 2. Synthesis of 3,5-pyrazolidinedione.