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A domino electro-oxidative synthesis of 3,3′-bis(indolyl)methane nanoparticles

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Abstract An effective route for electro-oxidative synthesis of 3,3′-bis(indolyl)methane nanoparticles has been described via a domino multi-component reaction between various alcohols and indole derivatives in an undivided cell under constant potential conditions in CH_3CN at room temperature. The mechanistic aspect of this electro-oxidative condensation has also been studied by UV–Vis spectra and cyclic voltammograms. The nanostructure of the products has been confirmed by scanning electron microscopy.

Graphical abstract
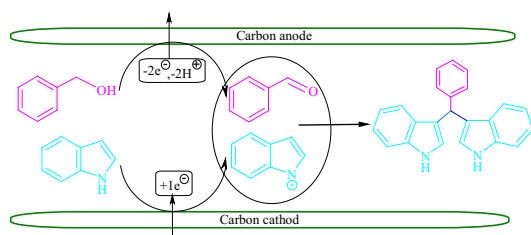
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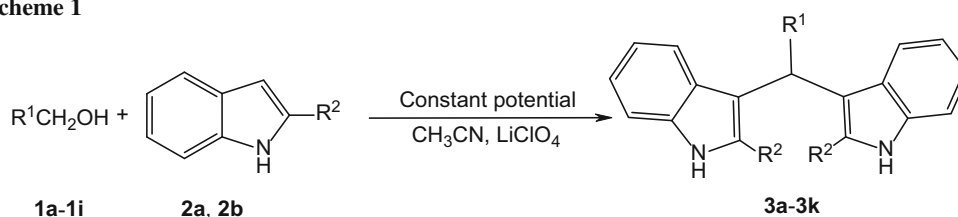
Introduction

Indole and its derivatives have attracted so much interest in the recent century owing to their extensive biological activities [1]. Bis(indolyl)methanes (BIMs) are one of the most important groups of indole derivatives that are found in cruciferous plants and marine sources [2]. These compounds have shown different pharmaceutical activities such as anticancer [3], antihyperglycemic, antiviral, and antimicrobial [4], and antioxidant [5] properties. They are also known as a promoter of estrogen metabolism [6] and induce apoptosis in human cancer cells [7]. Therefore, the synthesis of these moieties has received much attention during the last years.

A simple and direct method for the synthesis of BIMs is the condensation of indole with the carbonyl groups. In this manner, the reaction of indole with aldehydes or ketones produces azafulvenium salts that react further with a second indole molecule to form bis(indolyl)methanes [8]. On the basis of this general protocol, various Bronsted acids [9, 10], protic acids [11–13], Lewis acids [14–19], heterogeneous acidic catalysts [20–23], ionic liquids [24–26], and N-haloorganocatalysts [27, 28] have been applied for this synthesis. Although a vast range of procedures has been utilized for BIM preparation via the condensation of indoles with carbonyls, reports of oxidative condensation of alcohols with indoles are rare [29, 30].

In spite of the applicability of the reported protocols, most of them suffer from one or more drawbacks including long reaction times, low yields of products, harsh reaction conditions, and use of expensive and/or toxic catalysts and solvents. Therefore, there is still a strong demand for a mild, clean, and highly efficient procedure for one-pot multi-component transformations for BIM synthesis.

Electrochemical organo-synthetic methods have received significant attention because of their benefit to the

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Scheme 1

R^1CH_2OH + [indole] R^2 $\xrightarrow[\text{CH}_3\text{CN, LiClO}_4]{\text{Constant potential}}$ [product]

1a-1i   **2a**, **2b**   **3a-3k**

environment. In these procedures, cleanly generated electricity acts as a "green" catalyst. Among electrochemical synthesis of various organic compounds reported in the literature [31–36], few are dependent on electro-catalytic multi-component condensations [37–39].

Nanosized organic compounds have been prepared through different methods in which organic compounds are first synthesized and then can be transformed into nanosized particles using modern high technology such as ultrahigh pressure rapid expansion of supercritical solutions (RESS) system [40] and hydrocortisone using supercritical antisolvent with enhanced mass transfer [41]. Direct synthesis of nanosized organic compounds is a rarely used method.

On the basis of our research activity about indole derivatives [42–47], we herein report a mild and efficient procedure for the one-pot domino electro-oxidative condensation of alcohols **1a**–**1i** and indoles **2a**, **2b** via controlled-potential coulometry in an undivided cell, in the presence of LiClO$_4$ as electrolyte in CH$_3$CN at room temperature to yield the nanoparticles of the corresponding 3,3′-di(indolyl)methanes **3a**–**3k** (Scheme 1).

Results and discussion

The electrochemical study of 1 mmol solution of 4-chlorobenzyl alcohol (**1e**) in CH$_3$CN containing 0.05 g LiClO$_4$ at a glassy carbon electrode was performed by cyclic voltammetry (Fig. 1). The voltammogram shows one anodic peak (A$_1$) and one cathodic peak (C$_1$) at 2.0 and −0.6 V versus SCE which correspond to the oxidation of 4-chlorobenzyl alcohol (**1e**) to 4-chlorobenzaldehyde (Scheme 2A) and the reduction of anodically generated 4-chlorobenzaldehyde from 4-chlorobenzyl alcohol (**1e**), respectively.

Controlled-potential coulometry was applied in a solution containing 1 mmol of 4-chlorobenzyl alcohol (**1e**) at the potential of peak A$_1$. Monitoring of the electrolysis progress was carried out by TLC and cyclic voltammetry (Fig. 2). It was observed that, proportional to the advancement of coulometry, the height of A$_1$ decreases. The anodic peak A$_1$ disappears when the charge
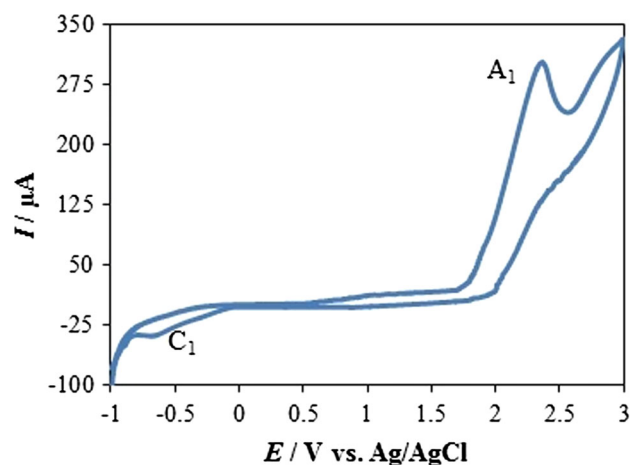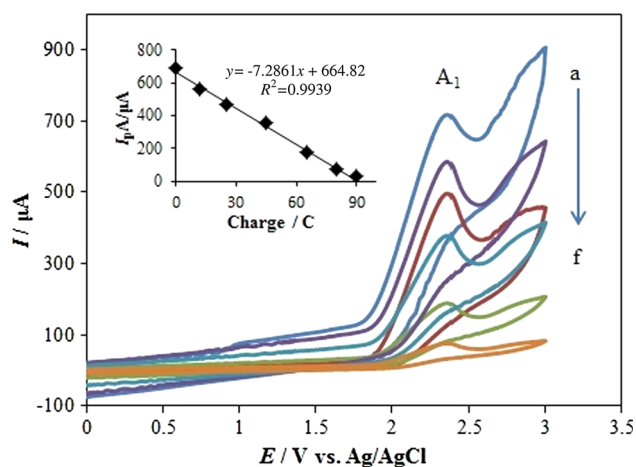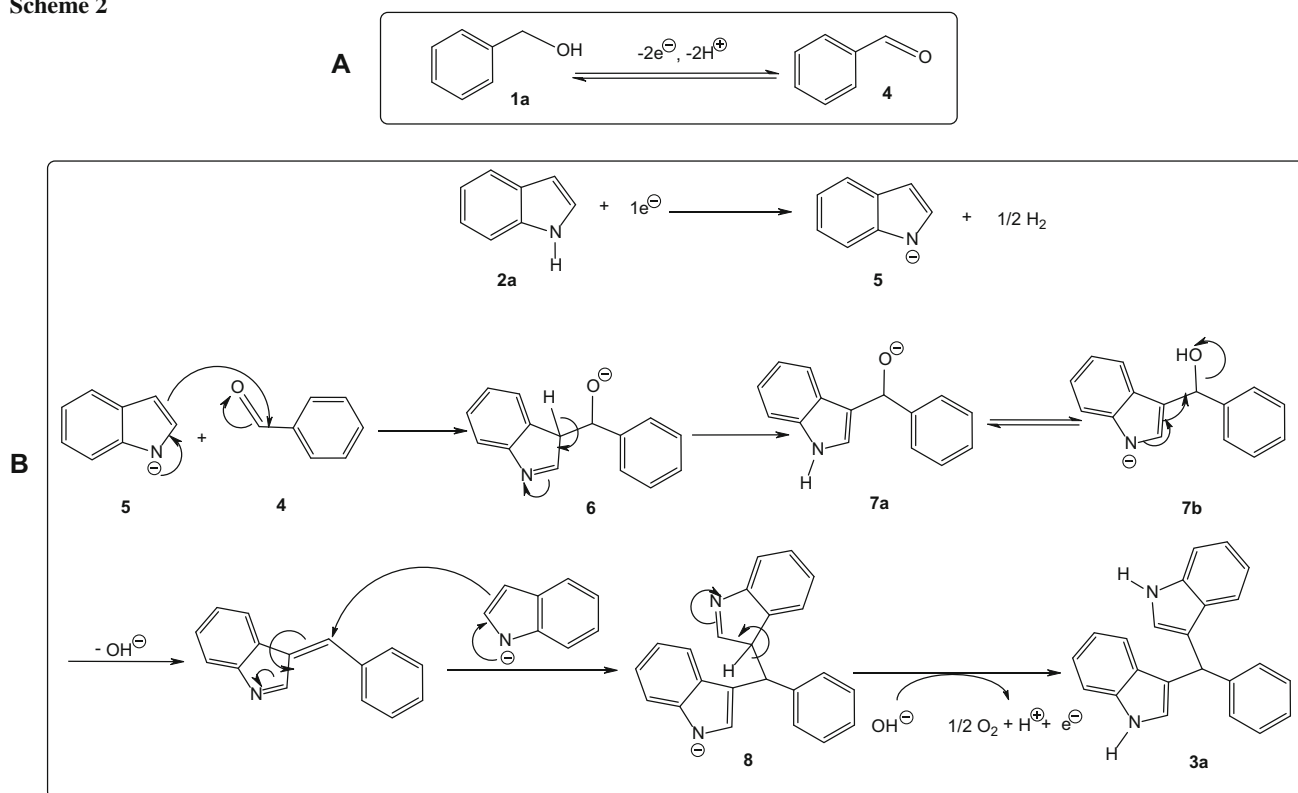

Fig. 1 Cyclic voltammogram of 1 mmol of 4-chlorobenzyl alcohol (**1e**) at the glassy carbon electrode, in CH$_3$CN (40 cm^3) containing 0.05 g LiClO$_4$ at the scan rate of 100 mV s^{-1}

consumption reaches about 2e$^-$ per molecule of **1e** (Fig. 2, inset). This number of electrons confirms the oxidation of 4-chlorobenzyl alcohol (**1e**) to 4-chlorobenzaldehyde.

In the next step, electro-condensation was followed by the addition of indoles **2a**, **2b** to the reaction cell alternatively. Voltammetric behaviors of 1 mmol 4-chlorobenzaldehyde (curve 3a), 2 mmol indole (**2a**) (curve 3b), and 1 mmol 4-chlorobenzyl aldehyde in the presence of 2 mmol indole (**2a**) (curve 3c), are shown in Fig. 3. The cyclic voltammogram observed for indole indicated one anodic peak (A$_1$) and one cathodic peak (C$_1$) at 1.25 and −0.87 V, respectively (curve 3b), that are related to the oxidation and reduction of indole, respectively. The voltammogram for 4-chlorobenzaldehyde in the presence of indole (**2a**) (curve 3c) shows two anodic peaks (A$_2$, A$_3$) and one cathodic peak (C$_3$). The new peak couple (A$_3$/C$_3$) corresponds to the reaction between 4-chlorobenzaldehyde in the presence of indole (**2a**). The negative shift of peak A$_2$ in the presence of 4-chlorobenzaldehyde is due to the reactivity of the electrochemically generated product **3e** which has formed a thin film on the surface of the electrode.
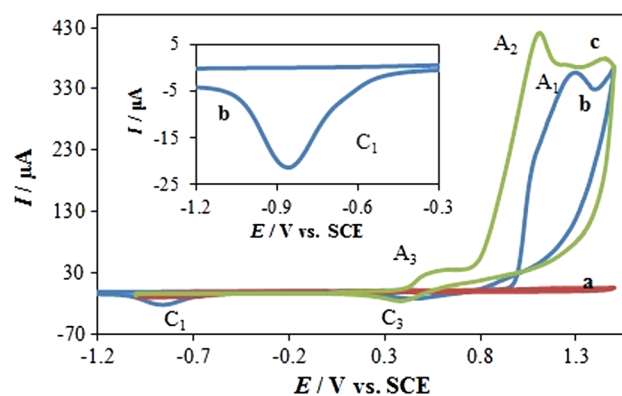
Controlled-potential coulometry was performed in a CH$_3$CN solution (40 cm^3) containing 4-chlorobenzaldehyde (1 mmol) in the presence of indole (**2a**, 2 mmol) at −0.9 V versus SCE. Electrolysis progress was monitored

Scheme 2

Fig. 2 Cyclic voltammograms of 1 mmol 4-chlorobenzyl alcohol (1e) at the glassy carbon electrode, in CH$_3$CN (40 cm^3) containing 0.05 g LiClO$_4$, during controlled-potential coulometry at 2.0 V versus SCE. After consumption of: *a* 0, *b* 10, *c* 25, *d* 45, *e* 65, and *f* 80 C. *Inset* variation of peak current I_p versus charge consumed at the scan rate 100 mVs^{-1}

Fig. 3 Cyclic voltammograms of: *a* 4-chlorobenzaldehyde (1 mmol), *b* indole (2 mmol), *c* a mixture of 4-chlorobenzaldehyde/indole (1/2 mol ratio) at the glassy carbon electrode in acetonitrile (40 cm^3) containing 0.05 g LiClO$_4$ with the scan rate of 100 mV s^{-1}

by cyclic voltammetry and TLC (Fig. 4). As Fig. 4 shows, proportional to the advancement of coulometry, the cathodic peak (C$_1$) decreases and disappears when the charge consumption reaches about 1e$^-$ per molecule of

indole. These observations allow us to propose the mechanism illustrated in Scheme 2.

Additionally, the effect of the scan rate on the electrochemical behavior of 4-chlorobenzaldehyde in the presence of indole (2a) was investigated (Fig. 5). It can be observed that proportional to the augmentation of potential sweep rate, the height of peak C$_3$ increases. On the other hand, the current function for peak A$_2$ ($I_p^{A_2}/v^{1/2}$), changes only
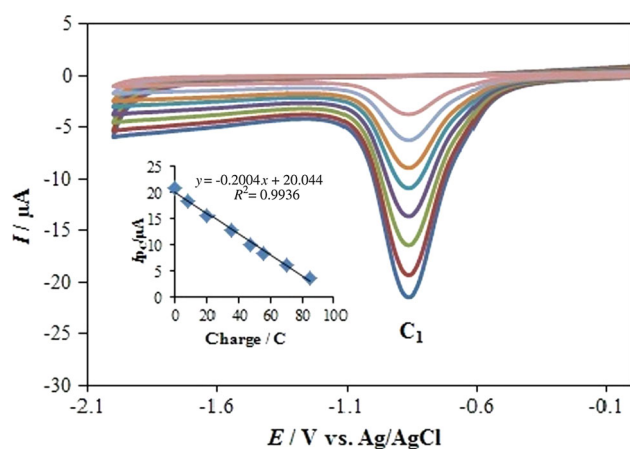
Fig. 4 Cyclic voltammograms of 2 mmol indole (**2a**) at the glassy carbon electrode, in CH_3CN (40 cm^3) containing 0.05 g LiClO$_4$, during controlled-potential coulometry at −0.9 V versus SCE, after consumption of: *a* 0, *b* 20, *c* 40, *d* 70, *e* 95, *f* 120, *g* 150, and *h* 180 C. *Inset* variation of peak current $I_p^{C_1}$ versus charge consumed at the scan rate 100 mVs^{-1}
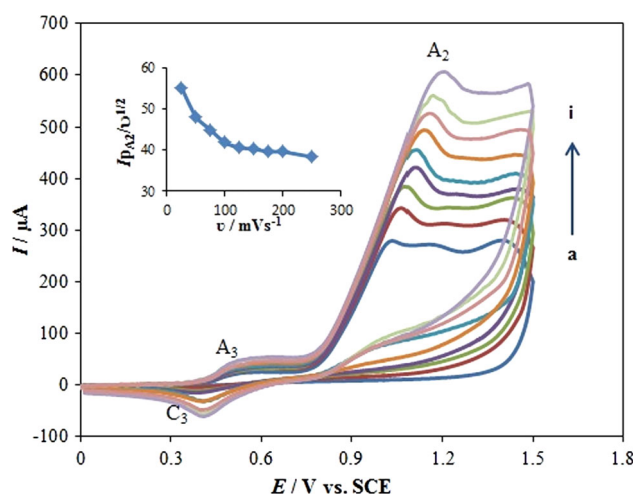
Fig. 5 Typical voltammograms of a mixture of 4-chlorobenzaldehyde (1 mmol) in the presence of indole (**2a**) (2 mmol) at the glassy carbon electrode, in CH_3CN (40 cm^3) containing 0.05 g LiClO$_4$, at different scan rates (*a → i*): 25, 50, 75, 100, 125, 150, 200, 250, 300 mV s^{-1}. *Inset* variation of peak current function ($I_p^{A_2}/v^{1/2}$) vs. scan rate

slightly with the increase in scan rate (Fig. 5, inset). Such behavior is taken as indicative of an EC mechanism [48, 49].

Subsequently, oxidative condensation reaction between various alcohols and indole derivatives was performed. All the tests were carried out in a domino condition in which, at the first step, alcohols were added to the cell where they electro-oxidized to their corresponding aldehyde. Electro-condensation was followed by the addition of indoles to the reaction cell alternatively. The prepared products and reaction conditions are summarized in Table 1.

According to Table 1, benzyl alcohol (**1a**) and its electron-donating derivatives *p*-methyl-, *p*-methoxy-, and *o*-hydroxybenzyl alcohols (**1b**–**1d**) and also electron-deficient *p*-chloro-, *p*-nitro-, and *o*-nitro derivatives (**1e**–**1g**) react with indole (**2a**) in high yields. The results confirmed the regioselectivity in electro-oxidation; as in the case of *o*-hydroxybenzyl alcohol (**1d**), any oxidation of its hydroxyl moiety was observed (Table 1, entry 4). In order to survey the efficacy of the method, the domino electro-oxidative condensation of 1-propanol (**1h**) as an aliphatic alcohol model and cinnamyl alcohol (**1i**) as an example of an allylic derivative were also performed with indole successfully (Table 1, entries 8, 9). The study also revealed the slower condensation of aliphatic alcohol with indole rather than this reaction between allylic alcohol and indole. It may depend on the greater reactivity of allylic alcohols. 2-Methylindole (**2b**), as another indolic alternative was also utilized for the domino electro-oxidative condensation with *p*-methyl and *p*-chlorobenzyl alcohols. The results (Table 1, entries 10, 11) confirm obtaining the corresponding 3,3′-di(indolyl)methanes successfully. The high yields of the reactions present the domino-cascaded electro-oxidative condensation method as an efficient and eco-friendly protocol as a multi-component condensation reaction.

The SEM image of 3,3′-bis(1*H*-indol-3-yl)-(4-chlorophenyl)methane (**3e**) shown in Fig. 6, reveals that the nanoparticle morphology has been created. The average diameter of the nanoparticles of **3e** is 35–50 nm.

Coulometry, voltammetry, and structural observations allow us to propose the pathway shown in Scheme 2 for the electrochemical synthesis of di(indolyl)methane derivatives **3a**–**3k**.
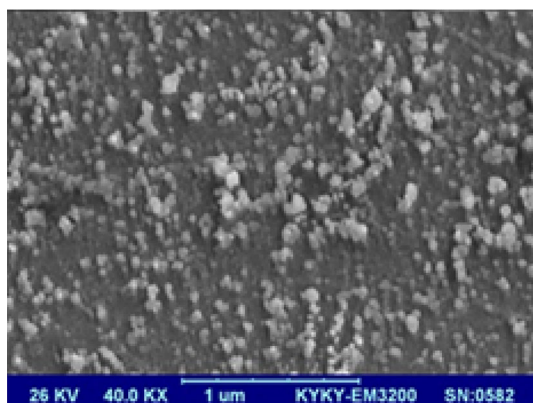
Although the comprehensive mechanism of the reaction is not known, the following rationalization may be worthwhile to explain the product (**3a**) formation (Scheme 2). In the first step of the domino reaction (Scheme 2A), the oxidation of benzyl alcohol (**1a**) at the anode yields benzaldehyde (**4**). By the further addition of indole (**2a**) to the reaction medium (Scheme 2B), indole anion **5** was created via cathodic electron absorbance. Nucleophilic attacks of **5** to the carbonyl moiety of **4** yield intermediate **6**. This intermediate stabilizes with an H-shift and converts to intermediates **7a** and **7b**. Releasing the hydroxyl anion, along with a nucleophilic attack of another indole anion **5**, gives rise to intermediate **8**. Finally, the protonation of **8** by the in situ produced H$^+$ form hydroxyl oxidation at the anode followed by rearrangement creates product **3a**.

In order to further survey the illustrated mechanism, time-dependent absorption spectra of a mixture of 4-chlorobenzaldehyde (1 mmol) and indole (**2a**) (2 mmol) in CH_3CN (40 cm^3) containing 0.05 g LiClO$_4$ were collected during a controlled-potential coulometry experiment (Fig. 7). These spectra show that, as the coulometry experiment proceeds, absorption peaks with a λ_{max} at 500 nm appears and its height

Table 1 Electro-oxidative synthesis of di(indolyl)methane derivatives **3a–3k** via the reaction of alcohols **1a–1i** with indoles **2a**, **2b**

Entry	R^1	R^2	Product	Yield[a]/%	Observed m.p./°C	Lit. m.p./°C
1	C_6H_5	H	**3a**	90	121–123	123–125 [19]
2	p-MeC_6H_4	H	**3b**	90	97–99	95–97 [23]
3	p-$MeOC_6H_4$	H	**3c**	85	190–192	190–192 [19]
4	o-HOC_6H_4	H	**3d**	70	256–258	259-261 [20]
5	p-ClC_6H_4	H	**3e**	85	74–76	78–80 [21]
6	p-$NO_2C_6H_4$	H	**3f**	75	229–231	229–223 [19]
7	o-$NO_2C_6H_4$	H	**3g**	60	106–108	112–114 [20]
8	C_3H_7	H	**3h**	60	78–79	77–79 [42]
9	$C_6H_5CH=CH$	H	**3i**	90	96–98	92–94 [42]
10	p-MeC_6H_4	CH_3	**3j**	85	173–175	174–176 [24]
11	p-ClC_6H_4	CH_3	**3k**	90	146–147	145–147 [42]

[a] Isolated yields

Fig. 6 The SEM image of 3,3′-bis(1H-indol-3-yl)(4-chlorophenyl)-methane (**3e**)

Fig. 7 Absorption spectra of the mixture of 4-chlorobenzaldehyde and indole (**2a**) during controlled-potential coulometry at −0.9 V vs. SCE in CH_3CN containing 0.05 g $LiClO_4$. After consumption of: 0, 20, 40, 70, 95, 120, and 150 C. *Inset* absorption spectra of 1 m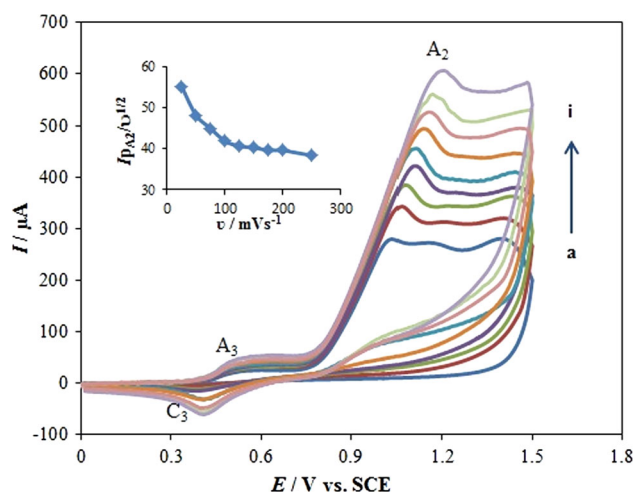mol/CH_3CN (40 cm^3) of (I) 4-chlorobenzaldehyde, (II) indole (**2a**), and (III) 3,3′-bis(1H-indol-3-yl)(4-chlorophenyl)methane (**3a**)

increases. This peak belongs to $n \rightarrow \pi^*$ absorption of product **3e**. The bands between 300 and 400 nm also relate to $\pi \rightarrow \pi^*$ transitions of the highly conjugated BIM **3e**. Growth of the peak intensity during the time interval, which is a proof of the product formation, could be a confirmation for the proposed mechanism depicted in Scheme 2.

According to the above observations, the presented mechanism is quite substantive. The CV spectra affirm the key role of the electrosynthetic protocol for BIM preparation under the above-mentioned conditions.

Conclusion

In conclusion, the cascaded electro-oxidative domino condensation of alcohols and indoles to afford the corresponding 3,3′-bis(indolyl)methanes has been performed. This direct environmentally friendly electrosynthesis of nanosized 3,3′-bis(indolyl)methanes via multi-component condensation shows highlighted advantages over conventional chemistry, such as (a) in situ generation of the nano-sized products without further preparation procedures; (b) avoidance of using a Lewis, Bronsted, and/or protic acid catalyst; (c) a one-pot domino MCR affording excellent yields under mild conditions, and (d) avoiding the use of polluting or hazardous chemicals and toxic reagents. These noteworthy points make the method a green, convenient, and efficient method in organic transformations.

Experimental

Electrochemical measurements were performed by an electrochemical system analyzer (Sama Instruments, Iran). The working electrode used in the voltammetry

experiments was a glassy carbon disc (1.8 mm^2 area) and platinum wire was used as a counter electrode. The working electrode used in controlled-potential coulometry and macroscale electrolysis was an assembly of three carbon rods (8 mm diameter and 4 cm length) and a large platinum gauze (3×3 cm^2) constituted the counter electrode. The working potentials have been measured versus standard calomel electrode (SCE) as a reference electrode (all electrodes were obtained from Azar Electrode, Urmia, Iran). Melting points were determined using a Stuart Scientific SMP2 capillary apparatus. IR spectra were recorded from KBr discs on Shimadzu IR-435. ^{1}H NMR spectra were recorded with a Bruker DRX-500 spectrometer. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. Preparative layer chromatography (PLC) carried out on 20×20 cm^2 plates, coated with a 1 mm layer of Merck silica gel PF$_{254}$, prepared by applying the silica as slurry and drying in air. The scanning electron microscope (SEM, model Σ-IJMA) was used to characterize the nano-structures. The alcohols, indoles, and solvents were purchased from Merck, Aldrich, and Alfa Aesar and used without further purification.

General procedure for the domino electro-oxidative condensation of indoles with alcohols

A 40 cm^3 acetonitrile solution of alcohols **1a–1i** (1 mmol) in LiClO$_4$ (0.05 g) was electrolyzed at the 2.0 V versus SCE. After completion of the electro-oxidation of alcohols to their corresponding aldehydes, indoles **2a**, **2b** (2 mmol) were added and electrolyzed at −0.9 V versus SCE. In the two mentioned stages, electrosynthesis reactions were done in an undivided cell equipped with graphite rods as the cathode and Pt-anode at room temperature. The electrolysis was terminated when the current decreased by more than 95 %. A magnetic stirrer was employed during the electrolysis. The process was interrupted several times during the electrolysis and the graphite rod was washed in acetone in order to reactivate it. After completion of the electro-condensation, the solvent was evaporated and the resulting crude product was purified by preparative thin-layer chromatography on silica gel (eluent: *n*-hexane–EtOAc, 4:1) to afford 3,3′-di(indolyl)methanes **3a–3k**. All the products were characterized by comparison of their melting points and also spectroscopic data (IR, ^{1}H NMR and mass spectra) with those of the authentic samples in literature.

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