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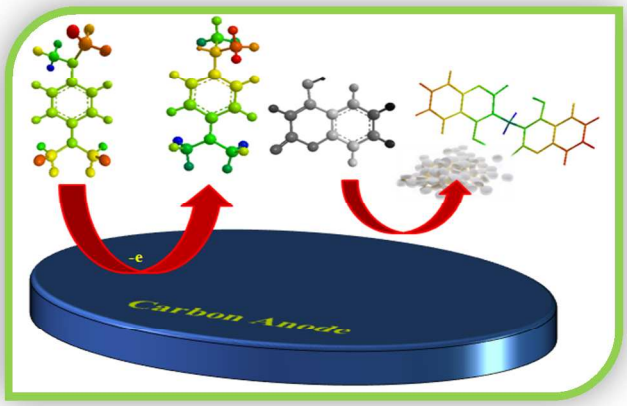

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Electrochemically induced cross-dehydrogenative coupling (*CDC*) reaction. An efficient electrochemical method for the synthesis of dicoumarols†

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Electrochemical synthesis of dicoumarols as anticoagulant drugs was carried out by the electrochemical oxidation of *N,N,N',N'*-tetramethyl-1,4-phenylenediamine in the presence of 4-hydroxycoumarin derivatives. Electrochemically generated radical cation participates in cross-dehydrogenative coupling (*CDC*) reaction with 4-hydroxycoumarins. The present work has led to the development of a facile catalyst-less, one-pot and environmentally friendly method under ambient conditions using a carbon electrode.

Introduction

Dicoumarol is an anticoagulant drug that functions as a vitamin K antagonist.[1] It is metabolized from coumarin in the sweet clover by molds, such as *penicillium nigricans* and *penicillium jensi* and is considered to be a fermentation product and mycotoxin.[2] Coumarin was used as early as 1000 *A.D* as medicinal plant extract according to Persian literature.[3] After that, numerous reports were published about anti-proliferative and antitumor activities of coumarin and its derivatives such as 7-hydroxycumarin by interfering with mitotic spindle microtubule function.[4] Dicoumarol was synthesized via a Knoevenagel-Michael reaction between 4-hydroxycoumarin and formaldehyde or aromatic aldehydes, which allows attachment of a second 4-hydroxycoumarin molecule through the linking carbon of the aldehyde, to the 3-position of the first 4-hydroxycoumarin molecule, to give the semi-dimer the motif of the drug class.[5]

Formation of *C-C* bonds is one of the most important reactions in organic synthesis. The direct coupling of two *C-H* bonds is the most efficient method for constructing *C-C* bonds.[10] Transition metals, iron, Li and other alkali metals made a significant contribution to develop a series of synthetic method to form *C-C* bond directly from two *C-H* bonds under oxidative conditions.

This mechanism was characterized as cross-dehydrogenative-coupling (*CDC*).[6] The biological importance of this drug prompted us to develop a facile and one-pot electrochemical method for the synthesis of dicoumarols. Therefore, the development of an efficient method for the synthesis of dicoumarol derivatives, that overcome the drawbacks of reported methods, would be appreciable. To the best of our knowledge, there is only two reports on electrochemical synthesis of dicoumarol.[7] These objects prompted us to investigate the electrochemical oxidation of *N,N,N',N'*-tetramethyl-1,4-phenylenediamine (**TMPD**) (Wurster's reagent) in the presence of 4-hydroxycoumarin (**1a**), 4-hydroxy-6-methylcoumarin (**1b**) and 4-hydroxy-6-methylpyron (**1c**). Finally, we have discovered an easy and one-pot electrochemical method for the synthesis of dicoumarol derivatives (**3a-3c**) in the high yield and purity, using an environmentally friendly method. From green chemistry and waste management viewpoints, dicoumarol was synthesized via catalyst-less electrochemically *CDC* mechanism. Therefore, this method minimizes metallic catalyst consumption as a great pollutant and on the other hand, catalyst recycling cost decreases particularly.

Results and discussion

Cyclic voltammogram of **TMPD** in water (phosphate buffer, c = 0.2 M, pH = 3.0)/ethanol mixture (70/30, v/v) is shown in Fig. 1 curve a. In this condition, voltammogram exhibits two anodic (A_1 and A_2) in the positive-going scan and two cathodic peaks (C_1 and C_2) in the negative-going scan. Anodic peaks A_1 and A_2

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† *Electronic Supplementary Information (ESI) available: ^{1}H NMR ,^{13}C NMR, FT-IR, MS of **3a-3c**. See DOI: 10.1039/b000000x/*

are correspond to the transformation of **TMPD** to radical cation (**TMPD**$^{\cdot+}$) and **TMPD**$^{\cdot+}$ to dication (**TMPD**$^{++}$), respectively, within two successive quasi-reversible one-electron processes (Scheme 1). Obviously, cathodic peaks C_2 and C_1 are related to the reduction of **TMPD**$^{++}$ to **TMPD**$^{\cdot+}$ and **TMPD**$^{\cdot+}$ to **TMPD**, respectively.[8]

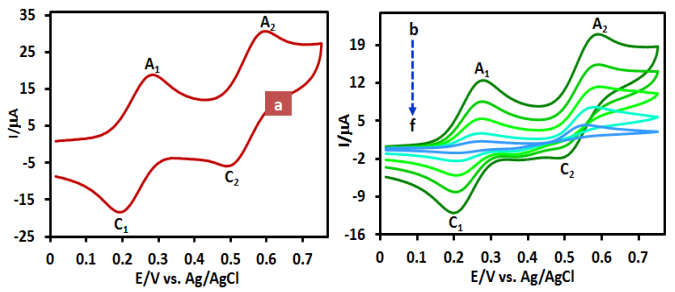
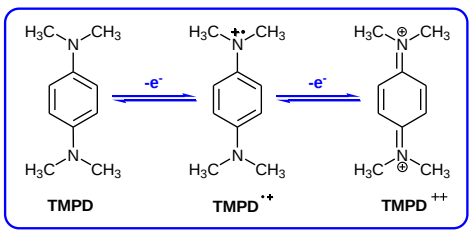


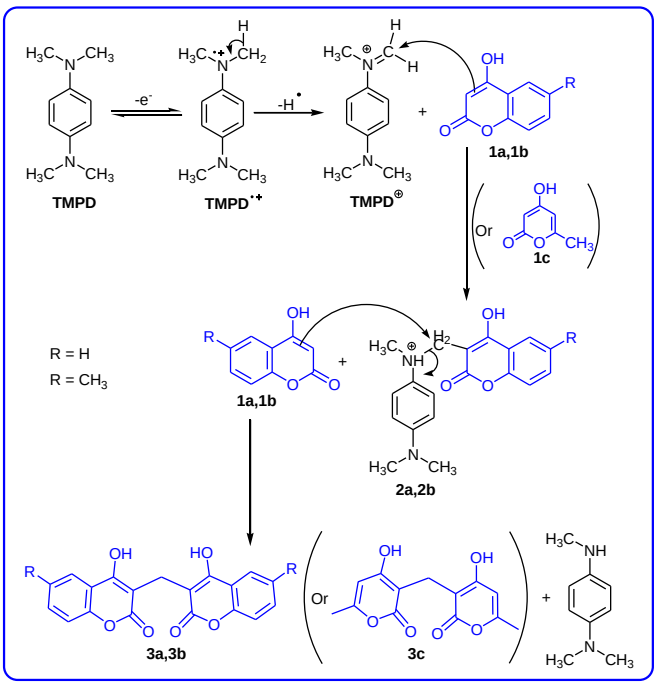
Fig. 1. Cyclic voltammograms of **TMPD** at a glassy carbon electrode in water (phosphate buffer, c = 0.2 M, pH = 3.0)/ethanol (70/30) mixture. Scan rate from a to f are 1000, 500, 250, 100, 25 and 5 mV s^{-1}. t = 25 ± 1 °C.

The effect of potential scan rate on the cyclic voltammogram of **TMPD** was also studied. It is seen that, upon decreasing the potential scan rate, the peak current ratios I_{pC1}/I_{pA1} and I_{pC2}/I_{pA2}) decrease, which is indicative of the presence of a following chemical reaction (such as hydroxylation) after the electron transfer step.[9] It also should be noted that, the effect of potential scan rate on the I_{pC2}/I_{pA2} is more than I_{pC1}/I_{pA1}. These data is consistent with the higher reactivity of **TMPD**$^{++}$ compared with that of **TMPD**$^{\cdot+}$. The peak current ratios (I_{pC1}/I_{pA1} and I_{pC2}/I_{pA2}) are also dependent to pH of the solution. Our data show that, I_{pC1}/I_{pA1} and I_{pC2}/I_{pA2} decrease with increasing pH. These data also indicate that I_{pC2}/I_{pA2} is more sensitive to pH than I_{pC1}/I_{pA1} so that, the cathodic peak C_2 disappears in basic solutions. This confirms instability of **TMPD**$^{++}$ compared with that of **TMPD**$^{\cdot+}$.



Scheme 1. Electrochemical Oxidation of **TMPD**.

Preparative scale electrolyses were performed in a mixture of phosphate buffer (c = 0.2 M, pH = 3.0)/ethanol (70/30, v/v), containing **TMPD** (0.5 mmol) and **1a** (1.0 mmol) in an undivided cell at the first peak potential. The reaction product was isolated and identified as dicoumarol (**3a**) (yield 95%) (Scheme 2). The formation of this compound is explained as follows: oxidation of **TMPD** at 0.25 V (vs. Ag/AgCl), by loss of an electron, affords the corresponding radical cation (**TMPD**$^{\cdot+}$), which further converts to hydrogen radical and the cation **TMPD**$^{+}$. Subsequent intramolecular attack of **1a** to **TMPD**$^{+}$ gives intermediate **2a**. In acidic media, **2a** undergoes direct S_N2 substitution[11] by the second molecule of **1a** to afford the final product (**3a**). This work has been extended with the use of **1b** and **1c** as a substrate and related semi-dimer products have been reported.



Scheme 2. Proposed Mechanism for the Electrochemical Oxidation of **TMPD** in the Presence of **1a-1c**.

Galvanostatic Studies

Constant current electrolysis was performed for improving applicability of the procedure. To take the high product yield, some affecting electrosynthesis factors must be optimized. In this direction, applied current density, charge passed and electrode material were investigated by setting all parameters to be constant and optimizing one each time. Among the electrochemical parameters for the synthesis of organic compounds, the current density is one of the most important factors influencing the yield and purity. This factor can also play an important role in determining the dominant reaction at the surface of electrode. In this work, the current density varied from 0.05 to 1.20 mA/cm^2, while the other parameters (temperature = 298 K, charge passed = 50 C, **TMPD**, 0.5 mmol and **1a** 1.0 mmol) are kept constant. The highest product yield was obtained at current density of 1.0 mA/cm^2 (Fig. 2, part I.). The formation of **TMPD**$^{++}$ (two electron oxidation) at higher current densities and its participation in Michael addition reaction cause a decrease in the product yield. The product yield also depends on the amount of charge passed, as shown in Figure 2, part II. The effect of charge passed was studied in the range of 10-60 C (theoretical amount is 50 C). As is shown, the product yield decreases with increasing charge passed from theoretical amount. This may be due to the over-oxidation of **3a** after

consumption of **1** F mol^{-1}**.** All variables (anode = carbon, current density = 1.0 mA/cm^2, temperature = 298 K, **TMPD**, 0.5 mmol and **1a**, 1.0 mmol), except the amount of charge passed, were kept constant. The effect of anode material (carbon, platinum and gold) on the yield of **3a** was also studied. Our data show that carbon is a suitable anode for the synthesis of **1a**. The similar results are obtained by repeating the same experiments for **1b** and **1c**.

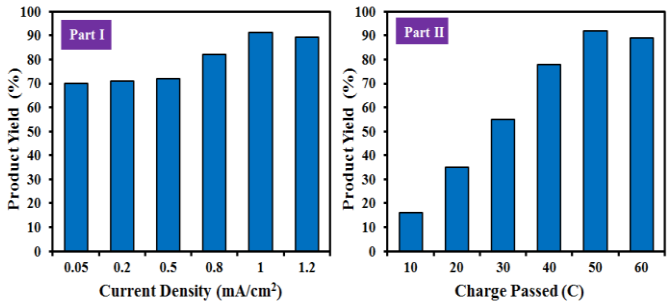


Fig. 2. Effect of current density and charge passed on the yield of **3a**.

Conclusion

The results of this work show that **TMPD** is oxidized to its respective radical cation. The formed radical cation via the cross-dehydrogenative-coupling (*CDC*) converts to dicoumarol (**3a**) in good yield and high purity without any metal catalysts. The prominent features of this paper, the synthesis of valuable compounds in aqueous/ethanol mixture instead of toxic solvents, room temperature conditions, high energy efficiency and using the electrode as an electron source instead of toxic reagents, are in accord with the principle of green chemistry.

Experimental

The working electrode used in the voltammetry experiments was a glassy carbon disc (1.8 mm^2 area) and platinum wire was used as counter electrode. The working electrode used in controlled-potential coulometry and macro-scale electrolysis was carbon plate (148 cm^2) and large steel gauze constitutes the counter electrode. The working electrode potential was measured versus Ag/AgCl. The electrochemical oxidations were performed under constant-current condition in a simple cell equipped with a magnetic stirrer. *N,N,N',N'*-tetramethyl-1,4-phenylenediamine, 4-hydroxycoumarin, ethanol, phosphoric acid and phosphate salts were reagent-grade materials and obtained from commercial sources. These chemicals were used without further purification. The glassy carbon electrode was polished using alumina slurry (from Iran Alumina Co.). Reaction equipment is described in an earlier article.[10] For more details see ESI†.

Electroorganic synthesis of 3a-3c

A solution of phosphate buffer (c = 0.2 M, pH = 3.0)/ethanol (70/30 v/v) mixture, containing **TMPD** (0.5 mmol) and **1a**, **1b** or **1c** (1.0 mmol), was electrolyzed in an undivided cell by potentiostatic method at first peak potential or galvanostatic method at current density 1.0 mA/cm^2. The electrolysis was terminated when the consumed charge equals to 52 C. At the end of the electrolysis, the precipitated solid was collected by filtration and washed with water/ethanol mixture (50/50 v/v). The products were characterized by: MS, FTIR, ^{1}H NMR and ^{13}C NMR (see **ESI**†).

3,3'-Methylenebis(4-hydroxy-2*H*-chromen-2-one) or dicoumarol (**3a**)

Creamy–white crystalline powder (yield 95%). mp = 286−289 °C (dec) (Lit. 289-292).[11a] ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 2H, methylene), 7.34 (m, 4H, aromatic), 7.59 (t, J =7.6, 2H, aromatic), 7.91 (d, J =7.6, 2H, aromatic); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.3, 102.2, 116.0, 116.8, 123.3, 123.8, 131.6, 151.8, 162.4, 163.6; IR (KBr, cm^{-1}): 770, 1110, 1309, 1349, 1454, 1601, 1628, 1651, 2612, 2729, 3067, 3436; MS (EI) (*m/z*) (relative intensity): 336 [M]$^+$ (83), 290 (7), 215 (67), 187 (44), 175 (27), 162 (82), 121 (100), 65(63).

4-Hydroxy-3-((4-hydroxy-6-methyl-2-oxo-2H-chromen-3-yl) methyl)-6-methyl-2H-chromen-2-one (**3b**)

Creamy–white powder (yield 90%). mp = 273–275 °C (dec.) (Lit. 273-275).[11a,11b] ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 6H, methyl), 3.77 (s, 2H, methylene), 7.24 (d, J = 8.4, 2H, aromatic), 7.39 (d, J = 8.4, 2H, aromatic), 7.71 (s, 2H,aromatic); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.3, 20.4, 102.2, 115.8, 116.4, 123.0, 132.6, 133.1, 150.0, 164; IR (KBr, cm^{-1}): 816, 916, 1106, 1211, 1282, 1332, 1447, 1504, 1581, 1659, 2925, 3061, 3432; MS (EI) *m/z* (relative intensity): 364 [M]$^+$ (85), 318 (11), 290 (3), 255 (3), 229 (58), 202 (32), 176 (69), 135 (100), 106 (30), 72 (32), 51 (15). Anal. calcd for $C_{21}H_{16}O_6$: C, 69.23; H, 4.43%. Found: C, 69.16; H, 4.60.

4-Hydroxy-3-((4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)methyl)-6-methyl-2H-pyran-2-one (**3c**)

Black crystalline powder (yield 80%). mp = 245-247 °C (dec.) (Lit. 250-251).[11c] ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 6H, methyl), 3.33 (s, 2H, methylene), 5.96 (s, 2H, aromatic), 11.1 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.2, 19.1, 99.3, 100.3, 159.7, 165.0, 165.6. IR (KBr, cm^{-1}): 525, 991, 1076, 1175, 1238, 1578, 1681, 2672, 2926, 3087, 3439. MS (EI) *m/z* (relative intensity): 264 [M]$^+$ (100), 221 (14), 179 (85), 151 (50), 111 (21), 85 (42), 55 (18). Anal. calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%. Found: C, 58.93; H, 4.67.

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