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Electrochemical Synthesis of Some 6-Amino-5-hydroquinone-1,3-dimethyluracil Derivatives: A Green, Simple and Efficient Strategy

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In order to synthesize some of new 6-amino-5-hydroquinone-1,3-dimethyluracil derivatives, the electrochemical oxidation of hydroquinones (**1a-c**) was carried out in the presence of 6-amino-1,3-dimethyluracil as a nucleophile in an aqueous phosphate buffer solution. The results show that electrogenerated *p*-benzoquinone moieties (**1a′-c′**) participate in the reaction with 6-amino-1,3-dimethyluracil via the EC mechanism to form the corresponding uracil derivatives (**3a-c**). The electrosynthesis of these compounds (**3a-c**) was performed successfully in an aqueous solution at carbon rod electrodes, without using any toxic reagents, catalyst or solvents and the products were finally produced in high yield and purity. The proposed method has a novel viewpoint in the synthesis of potential anticancer/antiviral uracil-base drugs.
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Dearomatization reactions have been widely recognized as a powerful tactic for the synthesis of complex molecules from simple aromatic substrates.[1–5] In this way, the controlled oxidation of arenes is very important for a substitution of different nucleophiles on the oxidized component.[6] This tactic can perform in organic synthesis with an electrochemical method like constant potential coulometry. The main benefits of using electrochemistry include high atom economy (conversion efficiency of the process) and reduction of waste generated by the several chemical processes as well as of the time and work required to carry them out.

In recent years, organic electrosynthesis has been known as a green methodology in organic chemistry.[7–10] Since electrons can be used as clean reduction reactants, it is possible to replace toxic and dangerous reagents[11–29] such as hypervalent iodine (exmp. $PhI(OAc)_2$, $PhI(TFA)_2$, F-$PhI(TFA)_2$),[30–32] $Pb(OAc)_4$,[33] oxone as the source of singlet oxygen,[34] $[\{(-)\text{-sparteine}\}_2Cu_2O_2]$ complex[35] and other reagents with an electric current. Essential reactions such as carbon-carbon, carbon-nitrogen, carbon-sulfur and carbon-oxygen bond formation and functional group interconversions[36] can be obtained from electron transfer.[37] These reactions in the electroorganic synthesis technique can be carried out at high selectivity, can reduce energy consumption, and can be carried at room temperature and without using of catalyst and toxic reagents.[38] Classical procedures of organic synthesis take place in organic solvents with low volatility, but electrochemical synthesis reactions can be performed in an aqueous medium without organic solvents[7] moreover, hydroalcoholic mixtures also are an excellent media to carry out electrosynthesis reactions.[39,40]

Due to the biological and environmental significance of hydroquinone such as application as antioxidant, production of dyes, pharmaceutical, cosmetics and photographic industries, the synthesis of hydroquinone derivatives is very important[41–43] and their redox system has been extensively studied.[44–47]

Uracil is one of the four nucleobases in the nucleic acid of RNA (ribonucleic acid) building block. Uracil derivatives are used as anticancer and antiviral drugs, pesticides and anti-photosynthetic herbicides.[48–54]

In the present study, we investigated a simple electrochemical method for the synthesis of new 6-amino-5-hydroquinone-1,3-dimethyluracil derivatives by the electrochemical oxidation of some hydroquinone moieties in the presence of 6-amino-1,3-dimethyluracil. The reaction was performed in an aqueous media and the target products were produced in excellent yield and purity that enables multiple transformations in the one-pot reaction sequence. Moreover, the reaction was carried out at room temperature and using any organic solvents and catalysts under green conditions. The other novelties of this work are the in situ production of quinone in the electrode interface area as an unsoluble reagent in the buffer solution media and replacing toxic and dangerous oxidizing reagents with electrons and reduce energy consumption of the reaction.

Experimental

Apparatus and reagents.—Cyclic voltammetry (CV), preparative electrolysis and controlled-potential coulometry were performed using a μ-AUTOLAB potentiostat/galvanostat model μIII AUTO 71174 connected to a Pentium IV personal computer through a USB electrochemical interface. The pH of the buffer solutions was adjusted using a pH-meter (Corning, Model 140) with a double junction glass electrode. The working and counter electrodes used in the voltammetry experiments were a glassy carbon disc electrode (0.031 cm^2 area) and a platinum wire electrode respectively. The working electrode used in controlled-potential coulometry and macroscale electrolysis was an assembly of tree ordinary carbon rods (9 mm diameter and 6 cm length). A large platinum gauze cylinder (10 cm^2 area) constituted the counter electrode. The potential of working electrode was measured versus Ag/AgCl (3.0 M KCl) electrode (all electrodes were from Azar Electrode Company). The glassy carbon electrode was polished with a polishing cloth before each measurement. The electrolysis was performed under a constant-potential condition in a cell with two compartments separated by an ordinary porous fritted glass diaphragm (a tube with 4 cm diameter). During electrolysis, a magnetic stirrer was used. The final products characterized using ^1H NMR, ^{13}C NMR, FT-IR spectroscopic techniques and CHNS analyzer. Fourier transform infrared (FT-IR) spectra were obtained using a Perkin-Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument spectrometer at 400 and 100 MHz in DMSO as a solvent in the presence of tetramethylsilane as internal standard.

The hydroquinones (hydroquinone, 2-methylhydroquinone and 2,3-dimethylhydroquinone) and 6-amino-1,3-dimethyluracil were reagent grade material and purchased from Merck chemical company. The NaH_2PO_4, Na_2HPO_4 and other acids and bases were of pro-analysis grade from Merck chemical company. These chemicals and solvents were used without further purification. All experiments were carried out at room temperature.

General procedure for the electroorganic synthesis of 6-amino-5-hydroquinone-1,3-dimethyluracil.—In a general procedure, phosphate buffer solution (pH 7.0, 0.1 M) containing of the 0.25 mmol of hydroquinones (**1a-c**) and 0.25 mmol of 6-amino-1,3-dimethyluracil (**2**) was electrolyzed at suitable potential (0.40, 0.39 and 0.37 V vs Ag/AgCl electrode for the **1a**, **1b** and **1c** respectively) in a divided cell. The progress of the reaction was monitored by the method of

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CV during the electrolysis. In order to reactive surface of the graphite anode, it washed occasionally in acetone. The electrolysis was terminated when the decay of current became more than 95% of its initial amount. At the end of electrolysis, the precipitated solid in its suspended form was collected by filtration and it was washed several times with water. Finally, for further purification, the products were recrystallized from ethanol.

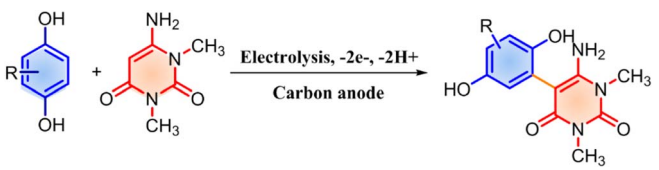
Characteristic of products.—*6-amino-5-(2,5-dihydroxyphenyl)-1,3-dimethyluracil (3a).*—Isolated in 96% yield as beige solid: m.p. > 300°C, decompose; FT-IR (KBr disc): 519.75, 569.61, 769.86, 972.85, 1227.68, 1262.50, 1387.38, 1424.55, 1466.04, 1546.88, 1616.40, 1641.94, 1679.75, 3258.22 cm^{-1}; ^1H NMR (DMSO, 400 MHz): 3.22 (s, 3H, N-CH_3), 3.46 (s, 3H, N-CH_3), 6.62 (d, 1H, J = 8.47 Hz, Ar-H), 7.18 (d, 1H, J = 8.47 Hz, Ar-H), 7.22 (s,1H, Ar-H), 9.03 (-NH_2, exchangeable hydrogens), 11.86 (-OH, exchangeable hydrogens); ^{13}C NMR (DMSO, 100 MHz): 27.77, 30.97, 91.18, 104.58, 111.46, 112.35, 124.99, 128.55, 145.54, 151.37, 153.27, 158.72; elemental analysis (CHNS) for $C_{10}H_8N_4O_3$: calcd: C 54.75, N 15.96, H 4.98; found: C 54.39, N 16.09, H 5.048.

6-amino-5-(2,5-dihydroxy-4-methylphenyl)-1,3-dimethyluracil (3b) and 6-amino-5-(2,5-dihydroxy-3-methylphenyl)-1,3-dimethyluracil (3b′).—Isolated in 94% yield as gray solid: m.p. >300°C, decompose; FT-IR (KBr disc): 515.79, 602.01, 710.59, 745.68, 771.62, 970.58, 1194.47, 1284.10, 1341.67, 1417.70, 1464.23, 1549.27, 1637.55, 1679.81, 2956.17, 3291.91 cm^{-1}; ^1H NMR (DMSO, 400 MHz): 2.21 (s, 3H, Ar-CH_3 (3b)), 2.42 (s, 3H, Ar-CH_3(3b′)), 3.25 (s, 6H, −NCH_3 (3b, 3b′)), 3.48 (s, 3H, −NCH_3 (3b)), 3.53 (s, 3H,−NCH_3 (3b′)), 6.46 (s, 1H, Ar-H (3b)), 7.09 (s, 2H, Ar-H, (3b, 3b′)), 7.29 (s, 1H, Ar-H, (3b′)), 8.93 (−NH_2, exchangeable hydrogens), 9.02 (-NH_2, exchangeable hydrogens), 11.27 (-OH, exchangeable hydrogens), 11.74 (−OH, exchangeable hydrogens); ^{13}C NMR (DMSO, 100 MHz): 16.71, 17.01, 27.32, 30.57, 30.89, 90.71, 91.25, 101.64, 103.68, 112.30, 112.63, 119.63, 121.73, 122.21, 124.31, 127.34, 128.03, 144.54, 145.08, 150.96, 151.02, 151.11, 152.86, 158.22, 158.33; elemental analysis (CHNS) for $C_{11}H_{10}N_4O_4$: calcd: C 56.31, N 15.15, H 5.45; found: C 56.87, N 14.89, H 5.478.

6-amino-5-(2,5-dihydroxy-3,4-dimethylphenyl)-1,3-dimethyluracil (3c).—Isolated in 95% yield as yellowish gray solid: m.p. >300°C, decompose; FT-IR (KBr disc): 423.53, 518.85, 612.58, 748.25, 979.96, 1084.66, 1212.88, 1285.09, 1336.61, 1448.07, 1547.99, 1611.32, 1642.10, 1687.57, 2954.77, 3418.82 cm^{-1}; ^1H NMR (DMSO, 400 MHz): 2.14 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 3.25 (s, 3H, N-CH_3), 3.56 (s, 3H, N-CH_3), 7.20 (s, 1H, Ar-H), 8.95 (-NH_2, exchangeable hydrogens), 11.09 (-OH, exchangeable hydrogens); ^{13}C NMR (DMSO, 100 MHz): 11.82, 13.98, 27.33, 30.93, 91.17, 101.35, 114.74, 118.01, 120.17, 121.27, 127.91, 144.64, 151.05, 158.29; elemental analysis (CHNS) for $C_{11}H_{10}N_4O_3$: calcd: C 57.72, N 14.42, H 5.88; found: C 57.91, N 14.51, H 5.989.

Results and Discussion

The electrochemical synthesis for the production of novel 6-amino-5-hydroquinone-1,3-dimethyluracil compounds was outlined in Scheme 1.



Scheme 1. The electrochemical synthesis of new 6-amino-5-hydroquinone-1,3-dimethyluracil.

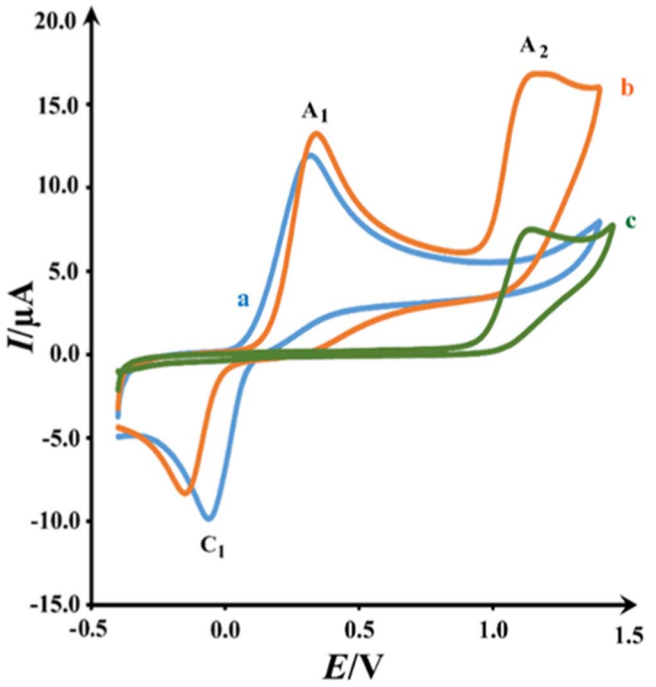


Figure 1. Cyclic voltammograms of 1.0 mM hydroquinone in the absence (a) and in the presence (b) of 1.0 mM 6-amino-1,3-dimethyluracil, and (c) 1.0 mM 6-amino-1,3-dimethyluracil singly. Conditions: glassy carbon electrode, phosphate buffer solution (pH 7.0, 0.1 M), scan rate = 100 mVs^{-1}, T = 25 ± 1°C.

Electrochemical oxidation of hydroquinone (1a) in the absence and presence of 6-amino-1,3-dimethyluracil (2).—*The cyclic voltammogram of 1.0 mM hydroquinone in the aqueous phosphate buffer solution (pH 7.0, 0.1 M) is shown in Fig. 1, curve **a**. In this condition, the voltammogram shows one anodic peak ($\mathbf{A_1}$) in the positive going scan and corresponding cathodic peak (C_1) in the negative going scan. These anodic and cathodic peaks represent the transformation of hydroquinone (**1a**) to *p*-benzoquinone (**1a′**) and vice versa within a quasi-reversible two electron process.[55] It is notable that the oxidation of hydroquinone to quinone is not a single electron transfer step (E reaction) and it is a series of electron transfer protonation reactions (ECEC, EECC or ECEEC) depending on the pH value.[56–58] The electrochemical oxidation of hydroquinone (**1a**) in the presence of 1.0 mM 6-amino-1,3-dimethyluracil (**2**) as a nucleophile was investigated in some details (Fig. 1, curve **b**). It shows that the current of cathodic peak C_1 counterpart of the anodic peak A_1 reduced and the current of the anodic peak counterpart of A_1 increased in the presence of **2**. Both these evidences confirm this fact that the *p*-benzoquinone (**1a′**) formed at the surface of the electrode is consumed by a chemical reaction with **2**. The cathodic shift potential of the peak C_2, when uracil derivative is present, is due to the change from a chemically reversible electron transfer reaction to a chemically irreversible reaction (Fig. 1, curve b), (last term of the Nernst equation is changing). The voltammogram exhibits two anodic peaks A_1 and A_2 and one cathodic peak C_1. Comparison of the voltammograms **b** and **c** reveals that the peak A_2 (curve **b**) corresponds to the oxidation of 6-amino-1,3-dimethyluracil (**2**). The Fig. 1, curve **c**, shows the cyclic voltammogram of 1.0 mM of **2** in the absence of hydroquinone under the optimum conditions. The positive shift of the A_1 peak in the presence of 2 (Fig. 1, curve b), which is enhanced during the repetitive recycling of potential (Fig. 2), confirms the quinones produced electrochemically at the electrode interface and then consumed during the reaction with 6-amino-1,3-dimethyluracil and led to the formation of the product **3**.

In the curves of **a**-**j** in Fig. 3 are shown the effect of different potential sweep rate on the cyclic voltammograms of 1.0 mM hydroquinone in the presence of 1.0 mM **2** at pH 7.0. It can be seen, upon increasing

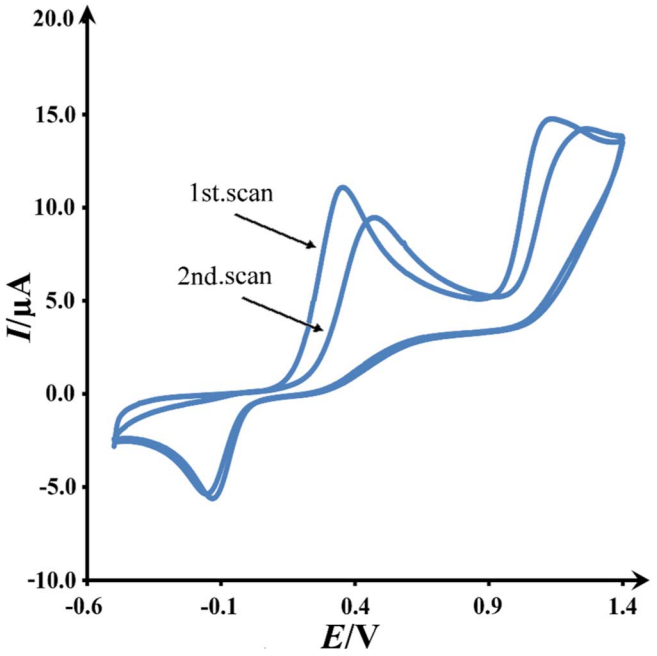


Figure 2. Multi-cyclic voltammograms of 1.0 mM hydroquinone in the presence of 1.0 mM 6-amino-1,3-dimethyluracil, at a glassy carbon electrode, in phosphate buffer solution (pH 7.0, 0.1 M); scan rate, 100 mVs^{-1}.

the potential sweep rate, the height of cathodic peak C_1 increases. The aforesaid increasing at higher scan rates is related to reducing the time needed for the chemical reaction of 6-amino-1,3-dimethyluracil (**2**) with *p*-benzoquinone (**1a′**). A similar situation is also observed when the concentration ratio of **2** to **1a** was decreased. Furthermore, the peak current ratio (I_p^{C1}/I_p^{A1}) slightly intensifies with increasing scan rates (Fig. 3, inset), which confirms a chemical reaction immediately after the electron transfer step.

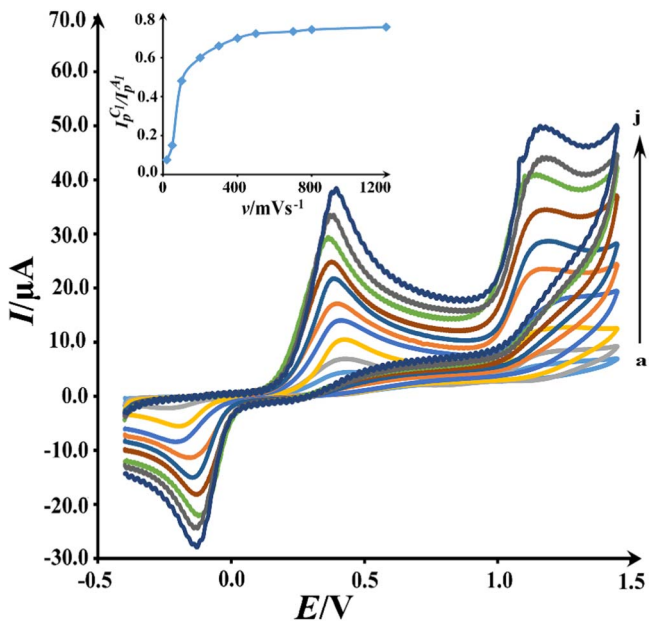


Figure 3. Typical cyclic voltammograms of 1.0 mM hydroquinone in the presence of 1.0 mM 6-amino-1,3-dimethyluracil at a glassy carbon electrode, in phosphate buffer solution (pH 7.0, 0.1 M). Scan rates from (a) to (j) are: 20, 50, 100, 200, 300, 400, 500, 700, 800 and 1200 mV s^{-1}, respectively. Inset: variation of peak current ratio (I_p^{C1}/I_p^{A1}) versus scan rate (ν). T = 25 ± 1°C.

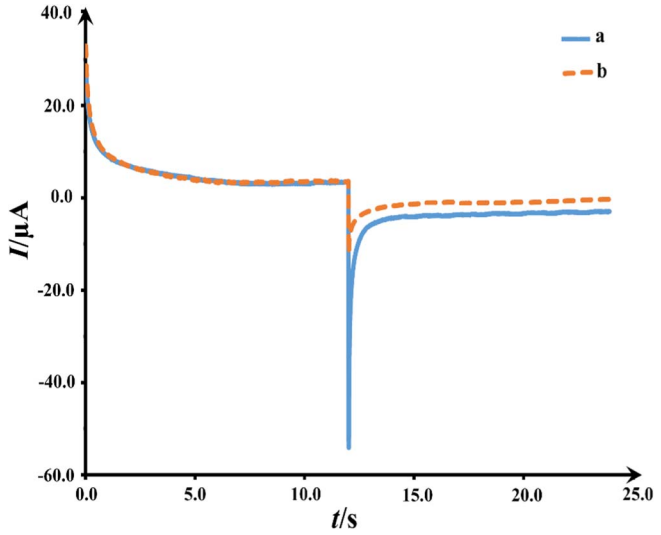
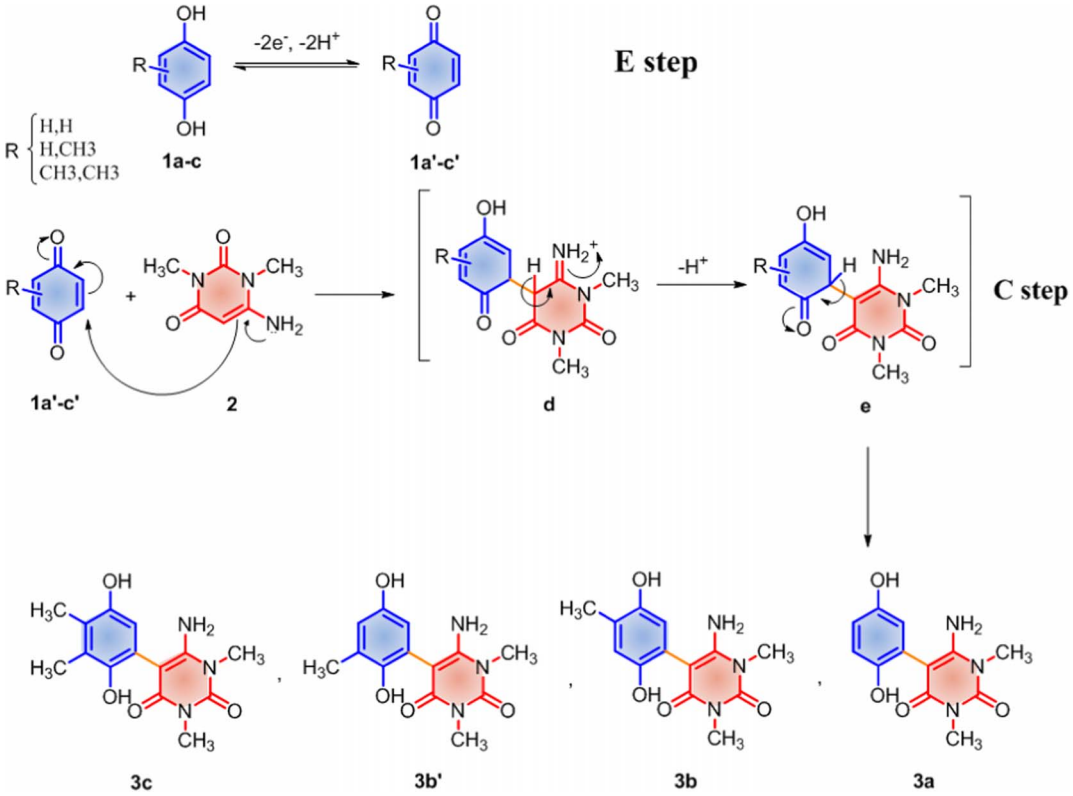


Figure 4. Double potential step chronoamperometry of 1.0 mM hydroquinone (a) in the absence of 1.0 mM 6-amino-1,3-dimethyluracil and (b) in the presence of 1.0 mM 6-amino-1,3-dimethyluracil, at a glassy carbon electrode in phosphate buffer solution (pH 7.0, 0.1 M). Pulse length, 12 s. The first potential step was from $E_0 = 0.00$ V to $E_1 = 0.40$ V and the second step from $E_1 = 0.40$ V to $E_2 = -0.14$ V vs. Ag/AgCl. T = 25 ± 1°C.

The determination of the existence of chemical reaction between electrochemically generated *p*-benzoquinone and 6-amino-1,3-dimethyluracil is also prove by the double potential step chronoamperometry. The curve **a** in Fig. 4, shows the double potential step chronoamperogram of **1a** in the absence of **2** that it is corresponding to an **E** mechanism, also, curve **b** in this Figure, shows double step chronoamperogram of **1a** in the presence of **2**. As can be seen in the figure, the currents of hydroquinone oxidation are equal in the absence and presence of **2**. While the current of the reduction of *p*-benzoquinone decreases in the presence of 6-amino-1,3-dimethyluracil. These behaviors adopt the EC mechanism (electrochemical-chemical reaction)[59,60] in the reaction between **1a** and **2** (Scheme 2).

In order to determine the effect of pH, behavior of the electrochemical oxidation of hydroquinone (**1a**) was studied in the absence and presence of 6-amino-1,3-dimethyluracil (**2**) in different pH values. A peak current ratio (I_P^{C1}/I_P^{A1}) of hydroquinone in acidic and neutral conditions is almost constant and near to unity particularly during recycling of the potential, which it is because of stability of *p*-benzoquinone produced at the surface of the electrode under the experimental conditions. In the other words, in a pH range of 3.0–7.0, the side reactions such as hydroxylation[61,62] or dimerization[63–65] are too slow to be observed on the time scale of cyclic voltammetry. In basic media (pH > 7.0), the peak current ratio (I_P^{C1}/I_P^{A1}) is less than unity and decreases with increasing the pH value. These variations can be related to the increasing of the acidic dissociation reaction of hydroquinone; consequently, the anionic forms of **1a** are produced in the reaction media. Therefore, the rate of the coupling reaction of the anionic or dianionic forms of hydroquinone with *p*-benzoquinones increases (dimerization side reactions).[65] Instead, in acidic solution, in the presence of 6-amino-1,3-dimethyluracil (**2**), **2** is inactive toward a Michael addition reaction with *p*-benzoquinone due to the protonation of the amino functional group. Accordingly, the peak current ratio (I_P^{C1}/I_P^{A1}) increases with decreasing of the pH values. This behavior is shown in Fig. 5 for pH values between 4.0 and 7.0. Thus, phosphate buffer solution with pH = 7.0 was selected as the optimum solution for this reaction.

Controlled-potential coulometry was carried out in the phosphate buffer solution (pH = 7.0, 0.1 M) containing 0.25 mmol hydroquinone and 0.25 mmol of 6-amino-1,3-dimethyluracil. In order to monitor the electrolysis progress and determination of the number of electrons



Scheme 2. Mechanism of the reaction.

transferred for each hydroquinone molecule, the cyclic voltammetry was used during the electrolysis (Fig. 6). The electrolysis was terminated when the decay of the current become more than 95% of its initial amount. According to our results, all anodic (A_1 and A_2) and cathodic (C_1) peaks decrease and disappear when the charge consumption becomes $2e^-$ per molecule of **1a**, during the progress of coulometry. The inset of Fig. 6 shows the number of coulombs consumption of this electrochemical reaction (ca. 48 C), that it is in accordance with the general mechanism proposed in Scheme 2.

All of the evidence in Experimental section such as cyclic voltammetry, controlled potential coulometry, double potential step

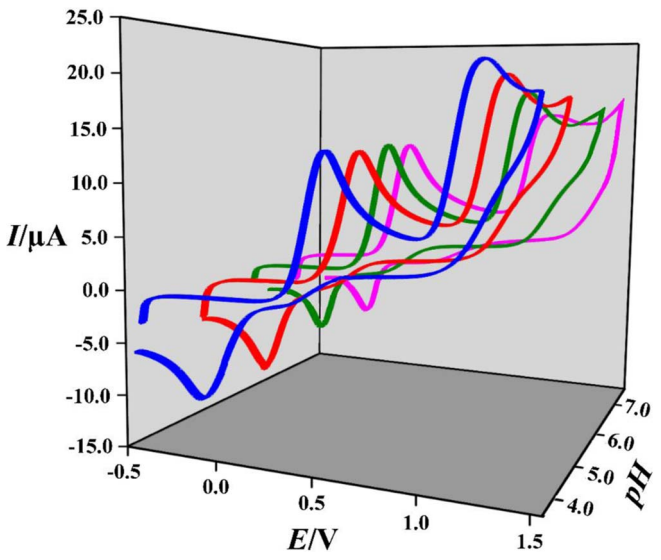


Figure 5. Cyclic voltammograms of 1.0 mM hydroquinone in the presence of 1.0 mM 6-amino-1,3-dimethyluracil at a glassy carbon electrode in phosphate buffer solution at various pH values (4.0, 5.0, 6.0 and 7.0); scan rate, 100 mVs^{-1}. T = 25 ± 1°C.

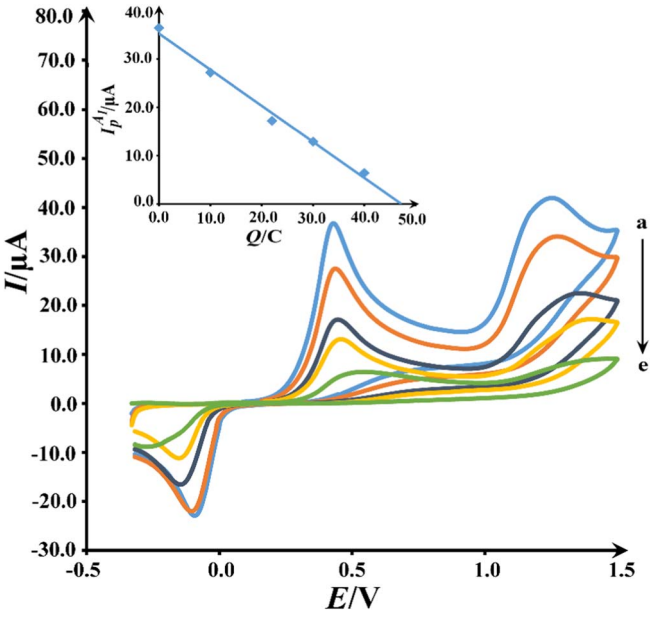


Figure 6. Cyclic voltammograms of 0.25 mmol hydroquinone in the presence of 0.25 mmol 6-amino-1,3-dimethyluracil, at a glassy carbon electrode during controlled potential coulometry at 0.40 V versus Ag/AgCl electrode, after consumption of: (a) 0, (b) 10, (c) 22, (d) 30 and (e) 40 C. Inset: Variation of peak current (I_p^{A1}) versus charge consumed during controlled potential Coulometry. Scan rate, 100 mV s^{-1}. T = 25 ± 1°C.

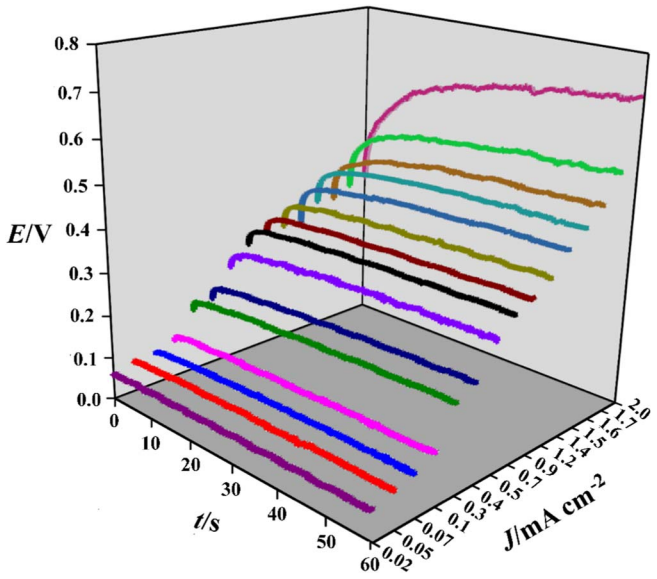


Figure 7. The potential-time diagram during constant current electrolysis of 0.25 mmol hydroquinone in the presence of 0.25 mmol 6-amino-1,3-dimethyluracil, at a glassy carbon electrode in phosphate buffer solution (pH 7.0, 0.1 M). Rotation rate: 1000 rpm. T = 25 ± 1°C.

chronoamperometry and also spectroscopic data of the isolated product, proved that the product **3a** is formed through anodic oxidation of hydroquinone and reaction with 6-amino-1,3-dimethyluracil; according to the pathway described in Scheme 2 (EC mechanism). In the first step (E), **1a′-c′** would be generated at the surface of the electrode, and in the second step (C step), these components participate as a Michael acceptor in a chemical reaction with 6-amino-1,3-dimethyluracil and produced the intermediate **d** in the solution. Then, **d** is rearranged and converts to the intermediate **e**. In the final step, the target products **3a-c** provide in the media of reaction from tautomerization of **e**. The products **3a-c** are insoluble in the phosphate buffer media and precipitate.

Furthermore, the synthesis of product **3a** was also performed via the constant-current electrolysis under the same conditions as described for controlled-potential coulometry. Due to the effect of current density on the yield and purity of the product, it was investigated in the range of 0.02 to 2.0 mA cm^{-2} at the same condition of electrolysis (0.25 mmol of hydroquinone and 0.25 mmol of 6-amino-1,3-dimethyluracil in phosphate buffer solution at pH = 7.0, 0.1 M and at room temperature). The effect of current density on the starting potential during constant-current electrolysis is shown in Fig. 7. Inasmuch as, in current density of 0.9 mA cm^{-2}, the generation potential is about 0.40 V and this potential is nearest amount to the oxidation potential of hydroquinone, only the hydroquinone can be oxidized with an acceptable rate while, **2** and/or product **3a** don't oxidize. Thus, the current density of 0.9 mA cm^{-2} was selected as an optimum value.

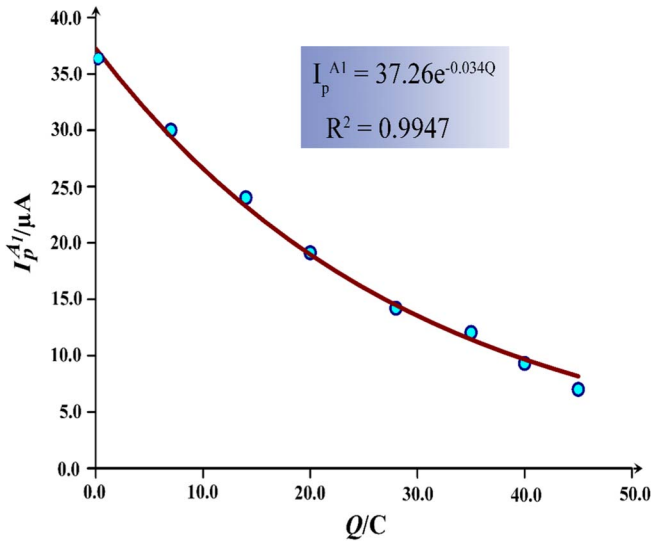


Figure 8. Variation of I_p^{A1} versus consumed charge during constant current electrolysis of 0.25 mmol hydroquinone in the presence of 0.25 mmol 6-amino-1,3-dimethyluracil at a glassy carbon electrode in phosphate buffer solution (pH 7.0, 0.1 M). Current density: 0.9 mA cm^{-2}.

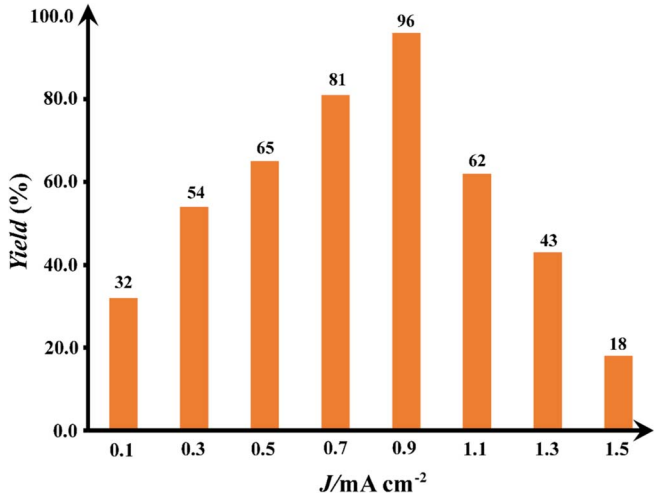


Figure 9. Effect of current density on the yield of product **3a**. Charge consumed 50 C.

To further investigation on galvanostatic studies, constant-current electrolysis was carried out in an aqueous phosphate buffer solution (pH = 7.0, 0.1 M) containing 0.25 mmol of **1a** and 0.25 mmol of **2**, under the 0.9 mA cm^{-2} as optimum current density, in a divided cell. The monitoring of the electrolysis progress was performed by cyclic voltammetry. The results show that, proportional to the advancement of coulometry, the current of anodic peaks A_1 and A_2 decrease. A nonlinear equation between I_p^{A1} and the charge consumed during the oxidation of hydroquinone in the presence of **2** has been found ($I_p^{A1} = 37.26e^{-0.034Q}$, $R^2 = 0.9947$) (Fig. 8).

The effect of current density on the yield of the reaction is shown in Fig. 9. In this study, the current density varied between 0.1 and 1.3 mA cm^{-2}, while the other parameters were kept constant. The results show that, with increasing the current density from 0.9 mA cm^{-2}, the yield of product decreases, because higher current density can cause the addition of side reactions.

Conclusions

The present study is the first reported work in the electrosynthesis of biologically significant products (**3a-c**) that have been produced directly and efficiently from the electrooxidation of hydroquinones (**1a-c**) and 6-amino-1,3-dimethyluracil (**2**). The reaction was carried out in water as a reaction media without using any toxic solvent, reagent or catalyst. This reaction was performed in the mild and green conditions at room temperature. Our results indicate that electrochemically generated of **1a′-c′** act as a Michael acceptor and then are attacked by **2** and after rearrangement convert to the target compounds (**3a-c**). The products obtained in high yield and purity through one-pot process and also, this procedure can lead to a minimization of the side reactions.

Acknowledgments

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