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Electrochemical synthesis of 6-amino-5-(3,4-dihydroxyphenyl) pyrimidine

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Abstract

Electrochemical oxidation of several catechols is studied in the presence of 4(6)-aminouracil (**3a**) and 6-amino-1,3-dimethyl uracil (**3b**) as nucleophiles in aqueous solution using cyclic voltammetry and controlled-potential coulometry. The results reveal that quinones derived from catechols participate in Michael additions with **3a** and **3b** to give the corresponding catecholamine derivatives via an electron transfer followed by chemical reaction (EC) mechanistic pathway in good yields and purities.

Keywords: Cyclic voltammetry; Electrochemical synthesis; Catechol; 4(6)-Amino uracil; Catecholamine; 6-Amino-1,3-dimethyl uracil

1. Introduction

Pyrimidines represent a broad class of compounds which have received considerable attention due to their wide range of biological activities.[1–6] Several patents have been reported on the preparation of these heterocycles, derivatives of which are useful as bronchodilators,[7,8] vasodilators,[3,4] antiallergic,[7–9] antihypertensive,[10] and anti cancer[7,8] agents. Catecholamines have been found in many plants and their synthesis is regulated by stress conditions.[11] They are widely used in pharmaceutical preparations. They can be oxidized chemically to *o*-quinone derivatives, and in mammals they are known to function as neurotransmitters with glycogen mobilizing ability.[12]

The importance of uracil derivatives and catecholamines prompted us to synthesize a number of these compounds from catechols and amino uracils. We have investigated the electrochemical oxidation of catechols **1a**–**c** in the presence of uracils **3a** and **3b** as nucleophiles. The present work has led to the development of a facile and environmentally friendly reagent-less electrochemical method for the synthesis of catecholamine derivatives **5a**–**f** under ambient conditions and in a two-compartment cell using a graphite electrode with high atomic economy.

The cyclic voltammogram of a 2 mM solution of catechol **1a** in 0.2 M sodium acetate solution as supporting electrolyte shows an anodic (A_1) and a corresponding cathodic peak (C_1), which correspond to the transformation of **1a** to *o*-quinone **2a** and vice versa within a quasi-reversible two electron reaction (Fig. 1, curve a). A peak current ratio (I_P^{C1}/I_P^{A1}) of nearly unity, particularly during the repetitive recycling of potential, can be considered a criterion for the stability of the *o*-quinones produced at the surface of the electrode under the experimental conditions. In other words, any hydroxylation[13–20]or dimerization[21–23] reaction is too slow to be observed on the cyclic voltammetry time-scale.

The oxidation of catechol **1a** in the presence of 6-amino-1,3-dimethyluracil (**3b**) as nucleophile was studied in detail, (Fig. 1, curve b). In this cyclic voltammogram, the cathodic

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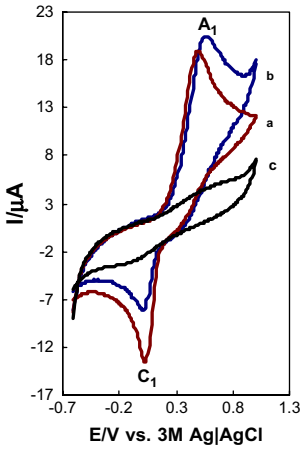


Fig. 1. Cyclic voltammogram of 2 mM catechol (**1a**): (a) in the absence of 6-amino-1,3-dimethyluracil (**3b**), (b) in the presence of 2 mM 6-amino-1,3-dimethyluracil. (c) Cyclic voltammogram of 2 mM 6-amino-1,3-dimethyluracil (**3b**) in the absence of catechol, at the glassy carbon electrode, in 0.2 M sodium acetate solution. Scan rate: 100 mV s^{-1}, T = ambient temperature.

counterpart of the anodic peak A_1 was decreased strongly due to the reactivity of the formed *o*-quinone (**2a**) at the surface of the electrode with 6-amino-1,3-dimethyluracil (**3b**).[24–27]

An increase in the A_1 peak current may be due to accumulative current from catechol and the nucleophile. The positive shift of the A_1 peak and negative shift of the C_1 peak in the presence of 6-amino-1,3-dimethyluracil are probably due to the formation of a thin film of product at the electrode surface, inhibiting to a certain extent, the performance of the electrode process that was enhanced during the repetitive cycling of the potential (Fig. 2).[13,20,28]

Furthermore, it can be seen that, the C_1 peak current increases proportionally to the augmentation of the potential scan rate. In other words, the peak current ratio

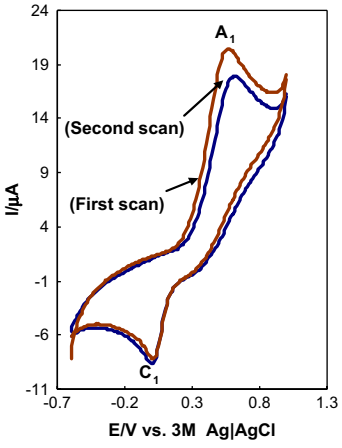


Fig. 2. Cyclic voltammogram of 2 mM catechol: (a) in the presence of 2 mM 6-amino-1,3-dimethyluracil (first cycle), (b) in the presence of 2 mM 6-amino-1,3-dimethyluracil (second cycle), at the glassy carbon electrode, in 0.2 M sodium acetate solution. Scan rate: 100 mV s^{-1}, T = ambient temperature.

(I_P^{C1}/I_P^{A1}) versus scan rate for a mixture of catechol (**1a**) and 6-amino-1,3-dimethyluracil (**3b**) in 0.2 M sodium acetate solution, confirms the reactivity of *o*-quinone (**2a**) with 6-amino-1,3-dimethyluracil (**3b**),[24–27] appearing as an increase in the height of the cathodic peak C_1 at higher scan rates (Fig. 3, curve g). A similar situation was observed when **3b** to **1a** concentration was decreased. On the other hand, the peak current function for the A_1 peak ($I_P^{A1}/v^{1/2}$) decreased on increasing the scan rate (Fig. 3, curve h) and such behavior is indicative of an electron transfer followed by chemical reaction (EC) mechanism.[15] Controlled-potential coulometry was performed in 0.2 M sodium acetate solution, containing 0.5 mmol of **1a** and 0.5 mmol of 6-amino-1,3-dimethyluracil (**3b**) at 0.35 V versus 3 M Ag/AgCl. The electrolysis progress was monitored by cyclic voltammetry (Fig. 4). It was observed that, proportional to the advancement of coulometry, the anodic peak (A_1) decreases. All anodic and cathodic peaks will disappear when the consumption equals about $2e^-$ per molecule of **1a**. These observations allow us to propose the pathways in Scheme 1 for the electro-oxidation of catechol (**1a**) in the presence of 6-amino-1,3-dimethyluracil (**3b**).

Similar results were observed for the oxidation of **1b** and **1c** in the presence of 6-amino-1,3-dimethyluracil (**3b**), and for **1a–c** in the presence of 4(6)-aminouracil (**3a**). The successful synthesis of the target materials (**5a–f**) was established via IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and MS spectroscopic methods, the results of which are given in Section 2.

The presence of methyl and methoxy groups at C-3 of **1b** and **1c**, respectively, probably causes the *o*-benzoquinone derived from the oxidation of catechols **2b** and **2c** to be attacked by **3a** and **3b** at C-4 or C-5 to yield two types of

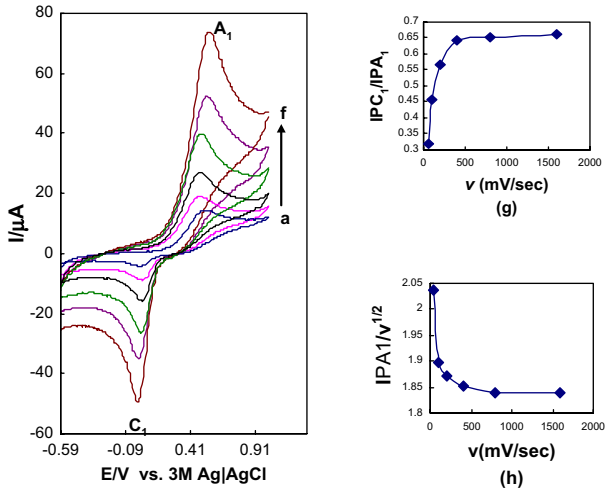


Fig. 3. Typical cyclic voltammograms of 2 mM catechol (**1a**) in the presence of 2 mM 6-amino-1,3-dimethyluracil (**3a**), in 0.2 M sodium acetate solution at the glassy carbon electrode (1.8 mm diameter) at various scan rates. Scan rates from (a) to (f) are 50, 100, 200, 400, 800, and 1600 mV s^{-1}, respectively. (g) Variation of peak current ratio (I_p^{C1}/I_P^{A1}) versus scan rate. (h) Variation of peak current function for the A_1 peak ($I_P^{A1}/v^{1/2}$) versus scan rate. T = ambient temperature.

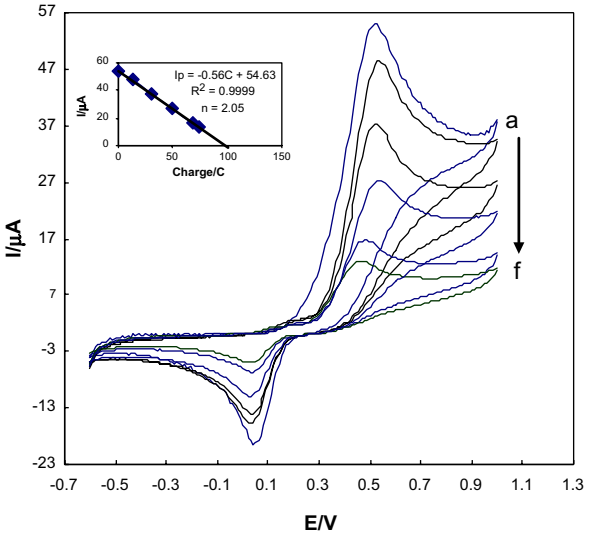
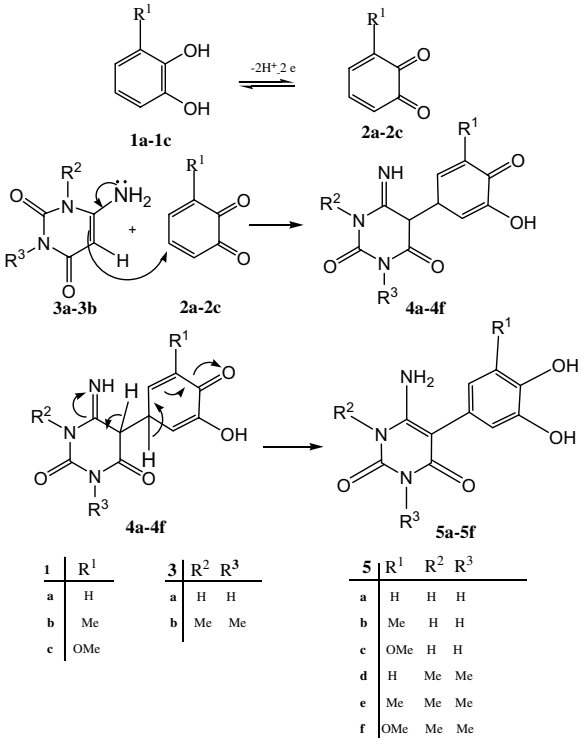


Fig. 4. Cyclic voltammograms of 0.5 mM catechol (**1a**) in the presence of 0.5 mM 6-amino-1,3-dimethyluracil (**3b**), at a glassy carbon electrode during controlled-potential coulometry at 0.35 V versus 3 M Ag/AgCl. After the consumption of: (a) 0, (b) 13.1, (c) 31, (d) 50, (e) 68, (f) 75 C. Inset: Variation of peak current (I_P^{41}) versus charge consumed. Scan rate: 100 mV s^{-1}, T = ambient temperature.



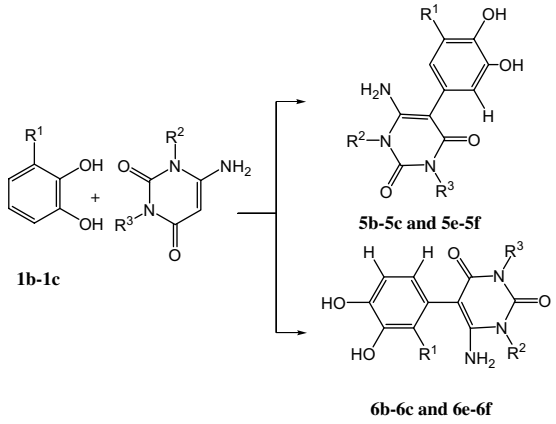
1	R^1
a	H
b	Me
c	OMe

3	R^2	R^3
a	H	H
b	Me	Me

5	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	OMe	H	H
d	H	Me	Me
e	Me	Me	Me
f	OMe	Me	Me

Scheme 1.

products in each case (Scheme 2). Spectroscopic characterization by ^{1}H NMR revealed the presence of singlets, due to the C-5 aromatic hydrogens ($\delta = 6.36$ and 6.47, $\delta = 6.25$ and 6.28, $\delta = 6.36$ and 6.46, and $\delta = 6.25$ and 6.26 ppm for **5b**, **5c**, **5e**, and **5f**, respectively). Addition to C-4 would lead to the generation of more complex features,



Scheme 2.

in the ^{1}H spectra. The *ortho* and *meta* hydrogens would couple, which would result in a doublet with a coupling constant '*J*' of about 10 Hz. These results would be consistent with the presence of two adjacent protons on the catechol ring of **6b**, **6c**, **6e** and **6f**.[29] Therefore, according to ^{1}H NMR results we suggest that *o*-quinones **2b** and **2c** are attacked at C-5 selectively by **3a** and **3b**, leading to the formation of products **5b**, **5c**, **5d** and **5f**, respectively.

In conclusion, the results of this work show that catechols are oxidized in solution to their respective *o*-quinones. The quinones are then attacked by 4(6)-aminouracil (**3a**) or 6-amino-1,3-dimethyluracil (**3b**) to form catecholamine derivatives (Table 1). The advantage of the present work is the development of a one-pot electrolytic method for the synthesis of catecholamine derivatives **5a**–**f** in good yields and purities, with 2e$^-$ consumption per molecule of catechol.

2. Apparatus and reagents

Cyclic voltammetry was performed using a computerized 747 Metrohm polarograph. The controlled-potential (potenstiostat) coulometry and controlled-potential (potentiostat) preparative electrolysis were carried out with a Zahrner pp-200 Potentiostat/galvanostat. The working electrode used in the voltammetry experiments was a glassy carbon disc (2.5 mm^2 area), and a platinum wire was used as the counter electrode. The working electrode was used in the controlled-potential coulometry and macro scale electrolysis was an assembly of four graphite rods (25 cm^2

Table 1
Electroanalytical and preparative data

Product	Applied potential (V) 3 M Ag/AgCl	Yield (%)
5a	0.35	86
5b	0.30	88
5c	0.30	84
5d	0.35	91
5e	0.30	94
5f	0.30	90

area) and a large surface platinum gauze constituted the counter electrode (graphite rods from Azar Electrode, Urmieh, Iran and all other electrodes from Metrohm). The working electrode potentials were measured versus 3 M Ag/AgCl.

3-Methyl catechol was reagent grade material from Acros. All other chemicals were reagent or pro-analysis grade materials from Merck. These chemicals were used without any further purification.

2.1. General procedure for the electro-organic synthesis of **5a–f**

Sodium acetate (100 ml of 0.2 M) solution was pre electrolyzed at the chosen potential (see Table 1) in a two-compartment cell. Next, 2 mmol of catechol **1a–c** and nucleophile **3a**, **3b** were added to the cell. Initially the current density was 2 mA/cm^2 and the electrolysis was terminated when the decay of the current became more than 95%. The process was interrupted during electrolysis (due to the formation of a thin film of product at the surface of the electrode) and the graphite anode was washed in acetone and polished to reactivate it. At the end of electrolysis, a few drops of acetic acid were added to the solution and the cell was placed in a refrigerator overnight. The precipitated solid was collected by filtration and after washing with hot water and drying, the solid products were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and MS.

2.1.1. 6-Amino-5-(3,4-dihydroxyphenyl)pyrimidine-2,4(1H,3H)-dione (**5a**, $C_{10}H_9N_3O_4$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3496, 3441, 3248, 2882, 1724, 1592, 1550, 1446, 1372, 1113, 772, 708. ^{1}H NMR (300 MHz DMSO-d_6): δ 5.57 (s, 2H, NH_2), 6.45 (d, $J = 6$ Hz, 1H, aromatic), 6.61 (s, 1H, aromatic), 6.70 (d, $J = 6$ Hz, 1H, aromatic), 8.78 (s, 1H, OH), 8.82 (s, 1H, OH), 10.07(s, 1H, NH), 10.33 (s, 1H, NH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 115, 119, 122, 123, 144, 145, 150, 151, 163. Anal. Calcd for $C_{10}H_9N_3O_4$ (235.196): C, 51.07; H, 3.68; N, 17.87. Found: C, 51.18; H, 3.74; N, 17.89. MS, *m*/*z* (%): 235 (M$^+$, 100), 189 (10), 147 (25), 122 (10), 103 (10), 63 (20), 43 (90).

2.1.2. 6-Amino–5-(3,4-dihydroxy-5-methylphenyl)-pyrimidine-2,4(1H,3H)-dione (**5b**, $C_{11}H_{11}N_3O_4$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3458, 3353, 1721, 1634, 1389, 1579, 1313, 972, 752, 672, 592. ^{1}H NMR (300 MHz DMSO-d_6): δ 2.09 (s, 3H, methyl), 5.54 (s, 2H, NH_2), 6.36 (s, 1H, aromatic), 6.47 (s, 1H, aromatic), 8.09 (s, 1H, OH), 9.08 (s, 1H, OH), 10.02 (s, 1H, NH), 10.30 (s, 1H, NH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 16.1, 88.63, 116.45, 123.01, 124.24, 124.44, 142.45, 144.93, 150.45, 151.81, 163.58. Anal. Calcd for $C_{11}H_{11}N_3O_4$ (249.223): C, 53.01; H, 4.45; N, 16.86. Found: C, 53.07; H, 4.42; N, 16.91. MS, *m*/*z* (%): 249 (M$^+$, 100), 231 (45), 205 (45), 188 (25), 163 (50), 117 (20), 77 (25), 43 (91).

2.1.3. 6-Amino-5-(3,4-dihydroxy-5-methoxyphenyl) pyrimidine-2,4(1H,3H)-dione (**5c**, $C_{11}H_{11}N_3O_5$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3401, 1698, 1621, 1596, 1512, 1392, 1207, 1085. ^{1}H NMR (300 MHz DMSO-d_6): δ 3.70 (s, 3H, methoxy), 5.61 (s, 2H, NH_2), 6.25 (s, 1H, aromatic), 6.28 (s, 1H, aromatic), 8.14 (s, 1H, OH), 8.79 (s, 1H, OH), 10.03 (s, 1H, NH), 10.32 (s, 1H, NH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 56.09, 88.75, 106.76, 112.52, 122.92, 133.29, 145.94, 148.51, 150.44, 151.86, 163.49. Anal. Calcd for $C_{11}H_{11}N_3O_5$ (265.222): C, 49.81; H, 4.18; N, 15.84. Found: C, 49.77; H, 4.15; N, 15.79. MS, *m*/*z* (%): 265 (M$^+$, 100), 249 (15), 221 (5), 205 (25), 177 (20), 151 (10), 84 (15), 43 (89).

2.1.4. 6-Amino-5-(3,4-dihydroxyphenyl)-1,3-dimethyl-pyrimidine-2,4(1H,3H)-dione (**5d**, $C_{12}H_{13}N_3O_4$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3435, 3334, 3232, 1696, 1641, 1585, 1381, 1272, 1088, 780, 730. ^{1}H NMR (300 MHz DMSO-d_6): δ 3.12 (s, 3H, methyl), 3.32 (s, 3H, methyl), 6.03 (s, 2H, NH_2), 6.44 (d, $J = 8$ Hz, 1H, aromatic), 6.58 (s, 1H, aromatic), 6.72 (d, $J = 8$ Hz, 1H, aromatic) 8.81 (s, 1H, OH), 8.84 (s, 1H, OH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 28.05, 30.45, 89.30, 116.13, 119.50, 122.81, 124.78, 144.62, 145.55, 151.35, 152.24, 161.08. Anal. Calcd for $C_{12}H_{13}N_3O_4$ (263.249): C, 54.75; H, 4.98; N, 15.96. Found: C, 54.81; H, 5.02; N, 15.99. MS, *m*/*z* (%): 263 (M$^+$, 100), 206 (25), 189 (25), 150 (60), 122 (25), 81 (10), 58 (75).

2.1.5. 6-Amino-5-(3,4-dihydroxy-5-methylphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5e**, $C_{13}H_{15}N_3O_4$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3476, 3416, 1693, 1648, 1596, 1314, 1200, 1017, 771, 608. ^{1}H NMR (300 MHz DMSO-d_6): δ 2.10 (s, 3H, methyl), 3.12 (s, 3H, methyl), 3.37 (s, 3H, methyl), 6.02 (s, 2H, NH_2), 6.36 (s, 1H, aromatic), 6.46 (s, 1H, aromatic), 8.12 (s, 1H, OH), 9.10 (s, 1H, OH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 16.0, 27.5, 29.9, 89.03, 116.2, 123.4, 124.1, 142.2, 144.6, 150.8, 151.7, 160.5. Anal. Calcd for $C_{13}H_{15}N_3O_4$ (277.27): C, 56.31; H, 5.45; N, 15.15. Found: C, 56.29; H, 5.45; N, 15.17. MS, *m*/*z* (%): 277 (M$^+$, 100), 220 (25), 203 (25), 191 (25), 164 (50), 136 (50), 77 (20), 57 (70), 30 (30).

2.1.6. 6-Amino-5-(3,4-dihydroxy-5-methoxyphenyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5f**, $C_{13}H_{15}N_3O_5$)

Mp >270 °C; IR (KBr) (ν_{max} cm^{-1}): 3419, 3336, 3248, 1693, 1638, 1587, 1519, 1332, 1213, 1095, 1031, 849, 778, 674. ^{1}H NMR (300 MHz DMSO-d_6): δ 3.33 (s, 3H, methyl), 3.38 (s, 3H, methyl), 3.70 (s, 3H, methoxy), 6.08 (s, 2H, NH_2), 6.25 (s, 1H, aromatic), 6.26 (s, 1H, aromatic), 8.19 (s, 1H, OH), 8.82 (s, 1H, OH). ^{13}C NMR (75.4 MHz DMSO-d_6): δ 28.05, 30.44, 56.09, 89.66, 107.15, 112.81, 123.85, 133.56, 146.13, 148.78, 151.36, 152.26, 161.00. Anal. Calcd for $C_{13}H_{15}N_3O_5$ (293.27): C, 53.24; H, 5.15; N, 14.33. Found: C, 53.29; H, 5.18; N, 14.35. MS, *m*/*z*

(%): 293 (M^+, 100), 207 (20), 180 (50), 151 (20), 136 (10), 78 (10), 58 (85), 32 (50).

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