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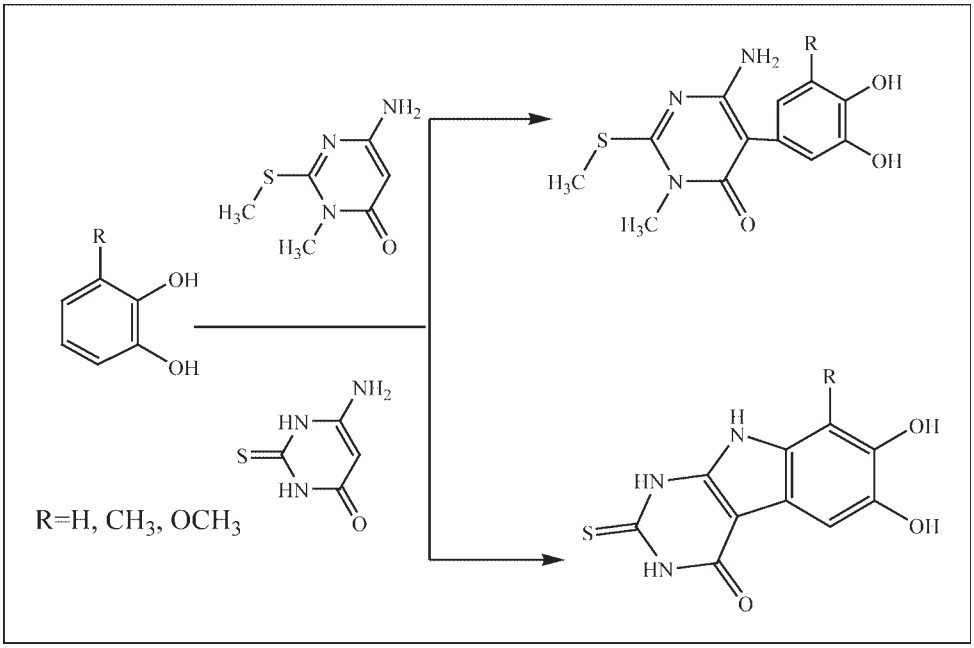
Received December 30, 2008
DOI 10.1002/jhet.231
Published online 21 December 2009 in Wiley InterScience (www.interscience.wiley.com).



Electrochemical oxidations of catechols have been studied in the presence of 6-amino pyrimidine derivatives as nucleophiles in aqueous solution using cyclic voltammetry. The efficient electro-organic synthesis of products has been successfully performed at carbon rod electrodes in an undivided cell under controlled potential conditions in good yield and purity.

J. Heterocyclic Chem., **47**, 40 (2010).

INTRODUCTION

Pyrimidine and its derivatives are attracting the attention of an increasing number of synthetic organic chemists because of their broad range of biological activity and medicinal importance [1,2]. Numerous reports delineate the antitumor [3], antiviral [4], antioxidant [5], antifungal [6], and hepatoprotective [7], activities of these compounds. Therefore, large efforts for the preparation of these molecules have been directed toward the synthetic manipulation of uracils [8]. The importance of pyrimidine derivatives prompted us to synthesis a number of these compounds from catechols and thiouracils. We have investigated the electrochemical oxidation of catechols (**1a**–**1c**) in the presence of 6-amino pyrimidine derivatives (**3a**, **3b**) as nucleophiles. This work has led to the development of a facile and environmentally friendly electrochemical method for synthesis of pyrimidine derivatives (**5a**–**5c**) and uracil derivatives (**8d**–**8f**).

RESULTS AND DISCUSSION

Cyclic voltammetry of 2 m*M* solution of catechol (**1a**) in 0.2*M* sodium acetate solution containing 10% acetonitrile 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 electrons reaction (Fig. 1, curve a). A peak current ratio (I_P^{C1}/I_P^{A1}) of nearly unity can be considered as a criterion for the stability of *o*-quinones (**2a**) produced at the surface of the electrode under the experimental conditions [9,10]. In other words, any hydroxylation [11,12], dimerization

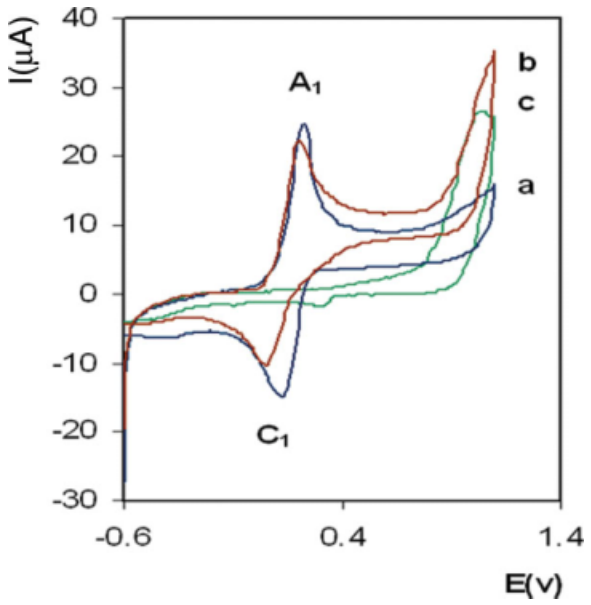


Figure 1. Cyclic voltammogram of 2 m*M* catechol (**1a**): (a) in absence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**), (b) in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one, (c) cyclic voltammogram of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) in the absence of catechol, at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 mVs^{-1}, T = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

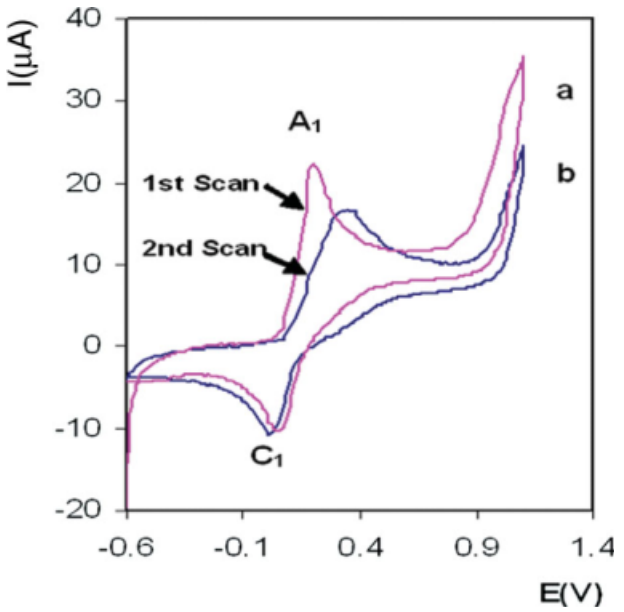


Figure 2. Cyclic voltammogram of 2 m*M* catechol: (a) in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (first cycle), (b) in the presence of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (second cycle), at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 mV s^{-1}, T = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

[13,14], or radical cations formation [15–18] are too slow to be observed on the time scale of cyclic voltammetry.

To get further support on the electrochemical oxidation of catechol (**1a**), it was studied in the presence of **3a** as a nucleophile. Curve b in Figure 1 shows the cyclic voltammogram obtained for a 2.0 m*M* solution of **1a** in the presence of 2.0 m*M* **3a**. The voltammogram exhibits decreasing in cathodic counterpart (C_1) of anodic peak (A_1). This is due to the reactivity of **1a** with **3a**. The cyclic voltammogram of 2.0 m*M* of **3a** is shown in Figure 1 curve c, for comparison.

The multicyclic voltammogram of **1a** in the presence of 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) are shown in Figure 2. In this figure, the second scan exhibits a relatively intense decrease in anodic peak current A_1 together with a potential shift in a positive direction. The decrease in A_1 peak current and positive shift of this peak are probably due to the formation of a thin film of product at the surface of the electrode inhibiting to a certain extent the performance of electrode process [19,20].

Furthermore, it was observed that the height of the C_1 peak increased proportional to augmentation of potential scan rate (Fig. 3, curve a–f). This confirms the reactivity of **2a** toward **3a**. A similar situation was observed when **3a**/**1a** concentration ratio is decreases. Moreover, the current function for A_1 peak ($I_P^{A1}/v^{1/2}$) decreases slightly with increasing scan rate (Fig. 3, curve g).

Controlled-potential coulometry was performed in an aqueous solution containing 0.5 mmol of **1a** and 0.5 mmol of **3a** at the potential of A_1 peak. At the end of coulometry, it was specified that charge consumption per molecules of **1a** becomes about $2e^-$.

The coulometry and voltammetry results allow us to propose an EC mechanism[16,17] for the electro-oxidation of **1a** in the presence of **3a** (Scheme 1). According to our results, the Michael addition reaction of **3a** to *o*-quinone (**2a**) [eq. (2)] seems to occur much faster than other side reactions, which leads to the product **5a**. The overoxidation of **5a** was circumvented during the preparative reaction because of the almost insolubility of the product in acetate buffer solution medium.

The electro-organic synthesis of **5b** and **5c** has been performed using oxidation of **1b** and **1c** in the presence of **3a** as described for **5a** (Table 1).

The electro-oxidation of catechol (**1a**) in the presence of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one (**3b**) as a nucleophile was studied by cyclic voltammetry and controlled-potential coulometry in 0.2*M* sodium acetate solution containing 10% acetonitrile too. Figure 4, curve b, shows the cyclic voltammogram obtained for a 2.0 m*M*

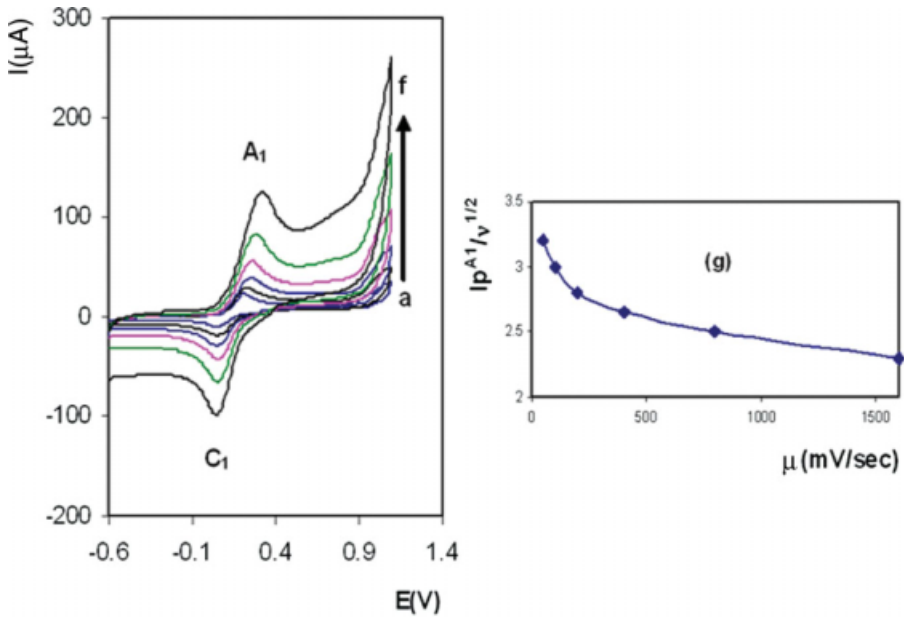
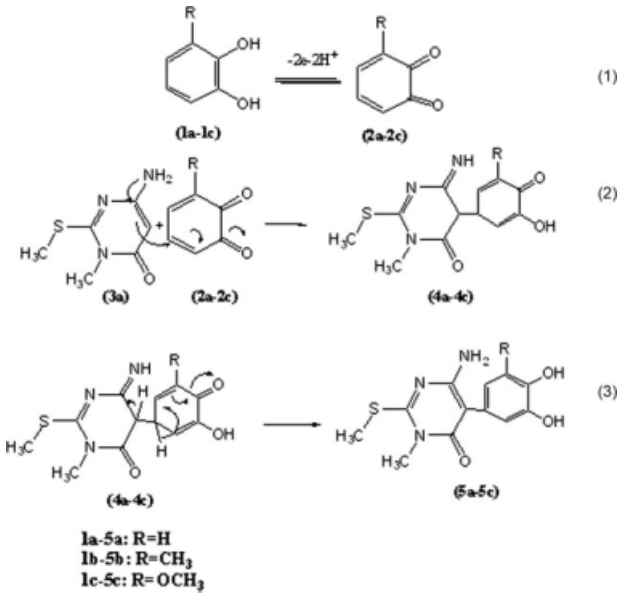


Figure 3. Typical cyclic voltammogram of 2 m*M* catechol (**1a**) in the presence of 2 m*M* 6-amino-1-methyl-2-(methyl)2-(methylthio)pyrimidin-4(1*H*)-one (**3a**) in 0.2*M* sodium acetate solution containing 10% acetonitrile at a glassy carbon electrode (1.8-mm diameter) at various scan rate. Scan rate from (a) to (f) are 50, 100, 200, 400, 800, and 1600 mV s^{-1}, respectively. (g) Variation of peak current ratio ($I_P^{A1}/v^{1/2}$) *versus* scan rate, T = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

solution of **1a** in the presence of 2.0 m*M* **3b**. The voltammogram clearly exhibits an increase in anodic peak A_1 and a decrease in the cathodic peak C_1. This is due to the reactivity of **2a** with **3b**. For comparison, the cyclic voltammogram of 2.0 m*M* solutions of catechol (**1a**) and **3b** are shown in Figure 4, curves a and c, respectively.

The possible reason for the observed large increase in the $\mathbf{A_1}$ peak current could be the oxidation of

Scheme 1



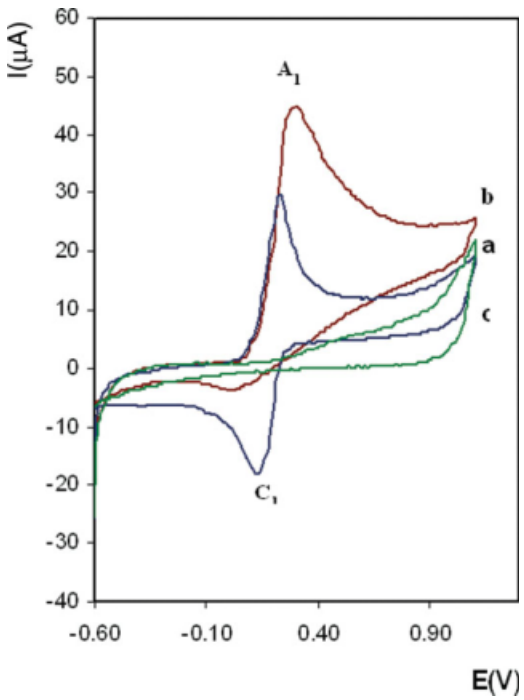
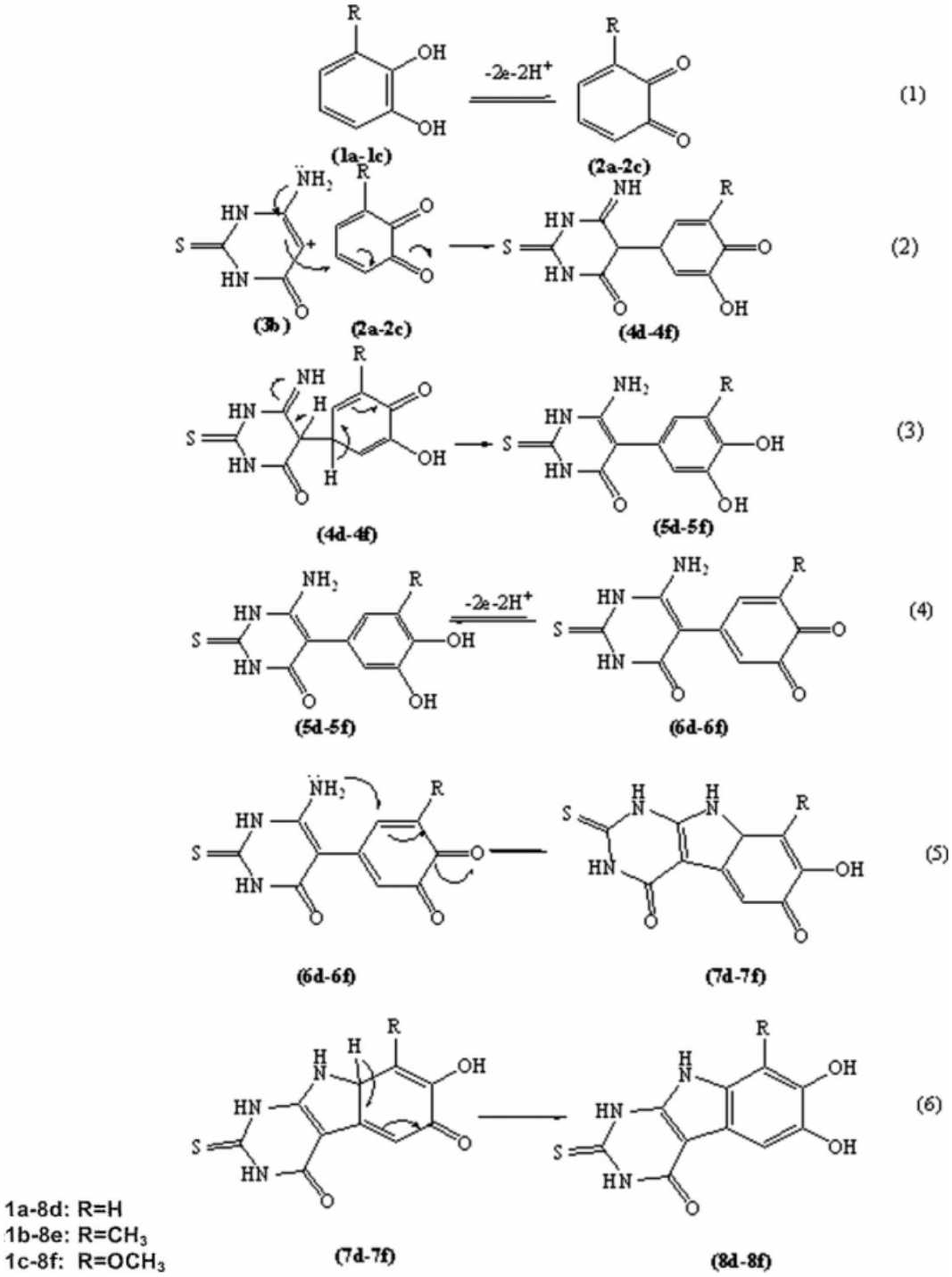


Figure 4. Cyclic voltammogram of 2 m*M* catechol (**1a**): (a) in the absence of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one (**3b**), (b) in the presence of **3b**, (c) cyclic voltammogram of 2 m*M* 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1H)-one (**3b**) in the absence of catechol, at glassy carbon electrode, in 0.2*M* sodium acetate solution containing 10% acetonitrile. Scan rate: 100 mV s^{-1}, T = ambient temperature. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2



intermediate **5c** at a potential close to that of the starting catechol. This oxidation is due to solubility of the **5c** in the reaction medium. The most important differences between this and previous cases are the large increase in the A_1 peak current (Fig. 4, curve b) and the number of transferred electrons during controlled-potential coulometry.

The results demonstrate that contrary to the previous cases, the consumed charge is about $4e^-$ per molecule of catechol (**1a**). This is related to two two-electron transfer processes [eqs. (1) and (4) in Scheme 2]. The coulometry, voltammetry, and NMR results allow us to propose an ECEC mechanism [21–24], indicated in

Scheme 2 for the electro-oxidation of catechol (**1a**) in the presence of **3b**.

CONCLUSIONS

In conclusion, the results of this work show that catechols (**1a–1c**) are oxidized to their respective *o*-benzoquinone (**2a–2c**). The formed *o*-benzoquinones are attacked by nucleophiles **3a** and **3b** to form final products **5a–5c** and **8d–8f**. We observed an interesting diversity in the electro-oxidation mechanism and products of catechols (**1a–1c**) in the presence of (**3a**, **3b**). In the cases of **1a–1c** in the presence of **3a**, the final products **5a–5c** are pyrimidine derivatives that were obtained after consumption of $2e^-$ per molecule **1a**, **1b**, and **1c**. In the case of **1a–1c** in the presence of **3b**, the final products **8d–8f** are uracil derivatives that were obtained after consumption of $4e^-$ per molecule **1a–1c**, *via* intermolecular and intramolecular Michael addition reactions. The overall mechanism for anodic oxidation of catechols (**1a–1c**) in the presence of **3a** and **3b** are presented in Schemes 1 and 2. These mechanisms show a good diversity in anodic oxidation of **1a–1c** in the presence of **3a** and **3b**.

EXPERIMENTAL

Chemical and solutions. Catechol derivatives were reagent-grade materials, sodium acetate, and other solvents were of proanalysis grade (all from E. Merck). These chemicals were used without further purification. The stock solution of catechols was prepared daily.

Electrode and electrochemical instrument. A cyclic voltammetry was performed using a micro-Autolab type III potentiostat/galvanostat and millimole scale electrolysis was performed using a pp-200 Zahrner potentiostat/galvanostat. The working electrode used in voltammetry experiments was a glassy carbon disc (2.7 mm^2 area) and a platinum wire was used as the counter electrode. The working electrode used in controlled-potential coulometry and millimole scale electrolysis was assembly of three carbon rods (27 cm^2 area) and large platinum gauze constituted the counter electrode. The working electrode potentials were measured *versus* 3*M* Ag/AgCl reference electrode (carbon rods from Azar electrode and other electrodes from Metrohm).

Bruker IFS-66 FTIR spectrometer, Shimadzu QP 1100-EX mass spectrometer operating at an ionization potential of 70 eV, and Bruker DRX-300 AVANCE NMR spectrometer were used for recording different spectra.

Electrochemical synthesis of 5a–c and 8d–f. In a typical procedure, 100 mL of 0.2*M* sodium acetate solution containing 10% acetonitrile was pre-electrolyzed at mentioned potential (Table 1) *versus* 3*M* Ag/AgCl in an undivided cell. Then 2 mmol of catechols (**1a–1c**) and 2 mmol of nucleophiles (**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 the electrolysis and the graphite anode was washed in acetone 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 purified by washing with hot water (Table 1).

Table 1

Electro-analytical and preparative data.

Conversion	Applied potential (V) *vs.* (Ag/AgCl)	Yield (%)	Consumed charge (C)	Time of electrolysis (h)
1a–5a	0.3	68	98.1	16.3
1b–5b	0.3	72	97.8	16.2
1c–5c	0.3	69	98.2	16.4
1a–8d	0.25	64	196.2	33.4
1b–8e	0.25	67	196.8	33.1
1c–8f	0.25	62	196.5	33.8

Characteristics of products

6-Amino-5-(3,4-dihydroxyphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5a). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3438, 3324, 3225, 2931, 1635, 1590, 1537, 1505, 1418, 1359, 1223, 1092, 845. ^{1}H NMR (DMSO-d_6): δ = 3.30 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 5.86 (s, 2H, NH_2), 6.31 (d, *J* = 8Hz,1H, Ar—H), 6.45 (s, 1H, Ar—H), 6.59 (d, *J* = 10Hz, 1H, Ar—H), 8.16 (s, 1H, OH), 8.79 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.6, 29.9, 95.1, 106.1, 111.7, 124.2, 133.3, 146.0, 148.6, 158.0, 159.8, 160.8 ppm; MS, m/z (%): 279 (M^+, 100), 230 (10), 171 (40), 126 (30), 110 (50), 83 (46), 63 (50), 47 (90). *Anal*. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.48; H, 4.73; N, 14.98.

6-Amino-5-(3,4-dihydroxy-5-methylphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5b). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3445, 3157, 2930, 1636, 1516, 1411, 1359, 1298, 1204, 1093, 1036, 906, 860. ^{1}H NMR (DMSO-d_6): δ = 2.09 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 5.78 (s, 2H, NH_2), 6.42 (s, 1H, H-Ar), 6.53 (s, 1H, H-Ar), 8.11 (s, 1H, OH), 9.09 (s, 1H, OH) ppm. ^{13}C NMR (DMSO-d_6): δ = 14.6, 16.5, 29.9, 95.1, 115.7, 123.5, 124.3, 124.5, 142.4, 145.0, 158.0, 159.7, 160.9 ppm; MS (EI, 70 eV): m/z (%) = 293 (M^+, 100), 243 (5), 171 (25), 124 (50), 105 (20), 88(50), 57 (55), 41 (50). *Anal*. Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23 H, 5.15; N, 14.31. Found: C, 53.18; H, 5.18; N, 14.31.

6-Amino-5-(3,4-dihydroxy-5-methoxyphenyl)-3-methyl-2-(methylthio)pyrimidin-4(3H)-one (5c). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3456, 1636, 1583, 1523, 1388, 1251, 1041, 998, 844, 800, 578. ^{1}H NMR (DMSO-d_6): δ = 3.21 (s, 3H, OCH_3), 3.49 (s, 3H, CH_3), 3.71 (s, 3H, CH_3) 5.86 (s, 2H, NH_2), 6.33 (s, 1H, H-Ar), 6.62 (s, 1H, H-Ar), 8.35 (s, 1H, OH), 9.85 (s, 1H, OH) ppm.^{13}C NMR (DMSO-d_6): δ = 19.3, 23.4, 29.9, 90.2, 105.7, 121.4, 125.2, 145.4, 153.2, 157.2, 159.9, 161.0, 163.4 ppm; MS (EI, 70 eV): m/z (%) = 309 (M^+, 100), 236 (10), 171 (12), 140 (32), 88(25), 57 (30), 41 (50). *Anal*. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.47 H, 4.89; N, 13.58. Found: C, 50.46; H, 4.89; N, 13.60.

2,3-Dihydro-6,7-dihydroxy-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8d). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3415, 3343, 3173, 1639, 1566, 1481, 1450, 1366, 1309, 1201, 864.

^{1}H NMR (DMSO-d_6): δ = 5.03 (s,1H, NH), 639 (s, 1H, H-Ar), 6.70 (s, 1H, H-Ar), 7.20 (s, 1H, NH), 8.38 (s, 1H, NH), 9.37 (s, 1H, OH), 9.41 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6): δ = 81.1, 106.4, 108.6, 112.3, 129.3, 144.9, 145.1, 161.0, 162.4, 163.0 ppm; MS (EI, 70 eV): m/z (%) = 249 (M^+, 80), 221 (25), 210 (25), 182(90), 155(10), 128 (10), 85 (30), 68 (100), 41 (55). *Anal*. Calcd for $C_{10}H_7N_3O_3$ S: C, 48.19; H, 2.83; N, 19.25. Found: C, 48.22; H, 2.85; N, 19.75.

2,3-Dihydro-6,7-dihydroxy-8-methyl-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8e). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3464, 3367, 2928, 1633, 1505 1452, 1361, 1297, 1228, 1033, 804. ^{1}H NMR (DMSO-d_6) δ = 2.17 (s, 3H, CH_3), 5.01 (s, 1H, NH), 6.94 (s, 1H, H-Ar), 7.28 (s, 1H, NH), 8.22 (s, 1H, NH), 8.86 (s, 1H, OH), 9.97 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6) δ = 14.6, 81.2, 105.7, 113.9, 117.3, 118.0, 128.2, 142.6, 144.9, 161.1, 162.4 ppm; MS (EI, 70 eV): m/z (%) = 263 (M^+, 100), 223 (15), 196 (75), 150 (10), 124 (25), 85 (30), 68 (60), 41 (100). *Anal*. Calcd for $C_{11}H_9N_3O_3$ S: C, 50.18; H, 3.44; N, 15.96. Found: C, 50.17; H, 3.45; N, 15.97.

2,3-Dihydro-6,7-dihydroxy-8-methoxy-2-thioxo-1H-pyrimido[4,5-b]indol-4(9H)-one (8f). Mp > 270°C; IR (KBr) (ν_{max} cm^{-1}): 3435, 3336, 3339, 2924, 1659, 1565, 1463, 1394, 1278, 1020, 768. ^{1}H NMR (DMSO-d_6) δ = 2.93 (s, 3H, OCH_3), 4.91 (s, 1H, NH), 6.11 (s, 1H, H-Ar), 6.68 (s, 1H, NH), 7.88 (s, 1H, NH), 8.35 (s, 1H, OH), 10.31 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6) δ = 59.6, 91.5, 108.2, 121.4, 128.9, 132.2, 150.9, 152.6, 158.5, 166.3, 170.1 ppm; MS (EI, 70 eV): m/z (%) = 279 (M^+, 93), 251 (70), 223 (15), 157 (50), 140 (30), 110 (27), 60 (80), 41 (100). *Anal*. Calcd for $C_{11}H_9N_3O_4S$: C, 47.31; H, 3.25; N, 15.05. Found: C, 47.29; H, 3.26; N, 15.06

Acknowledgment. This work was supported by the Research Affairs, Shahid Beheshti University.

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