

*Full Paper*

## **Green Electrosynthesis of Pyrano[2,3-*d*]Pyrimidinones at Room Temperature**

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**Abstract-** Electrocatalytic transformation of barbituric acid, aldehyde and malononitrile in ethanol in an undivided cell in the presence of potassium bromide as an electrolyte results in the formation of substituted pyrano[2,3-*d*]pyrimidinones at room temperature in 65-85% yields. The progress and completeness of electrolysis were monitored by cyclic voltammetry (CV). The voltammograms were recorded with  $\mu$ Autolab FRA2 Potentiostat-Galvanostat. A three-electrode system was used with a platinum rod as working electrode, a GC electrode as the counter electrode and an Ag/AgCl as the reference electrode. The structure of products was characterized by FT-IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy. In this electrosynthesis, the first step is electrochemical that follows by chemical reaction. Therefore the proposed mechanism is EC.

**Keywords-** Pyrano[2,3-*d*]pyrimidinones, Malononitrile, Barbituric acid, Electrocatalytic transformation, Cyclic voltammetry

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### **1. INTRODUCTION**

There is a continuous widespread interest in the synthesis of pyrano-pyrimidinones because of the diverse biological properties associated with this system. Compounds with

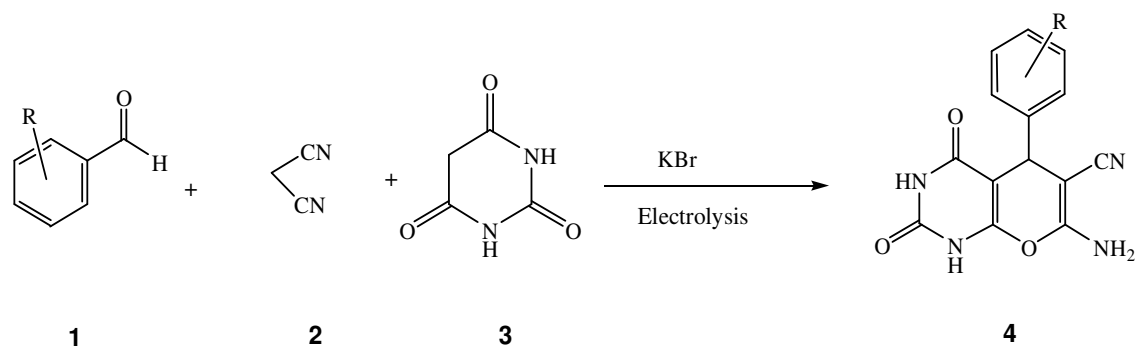
such annulated uracils have antitumor, antibacterial, antihypertensive, hepatoprotective, cardiogenic, vasodilator, bronchodilators and antiallergic activities and some of them exhibit antimalarial, antifungal, analgesics and herbicidal properties [1-5].

In spite of frequent reports for synthesis of similar compounds using classic methods [6-12], there are only a few reports for the synthesis of 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones in which aromatic aldehyde, malononitrile with barbituric acid have been reacted under either traditional thermal condition or microwave irradiation [13-15]. In contrast of their potential utility, there are disadvantages for most of these methods due to long reaction time, low yields, harsh reaction conditions, unrecoverable catalyst or solvent and effluent pollution.

One of the most important strategies can be used to overcome such problems is performing these reactions by electrochemical methods. Electro organic reactions proceed generally smoothly with easy work-up and do not require the use of harsh conditions such as high temperatures and expensive reagents [16-22].

Recently, Elinson et al. [23] reported an efficient approach to electrocatalytic preparation of *N*-alkyl barbiturates with malononitril and aryl aldehydes at relatively high temperature (78 °C). In spite of acceptable performance, this method suffers from high reaction temperature limitation.

To the best of our knowledge, there are no report on: a) electrocatalytic transformation of barbituric acid, aldehyde and malononitrile to 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones at room temperature and b) determining reaction time by using cyclic voltammetry (CV). Therefore, in this research, we wish to report, for the first time, the electrocatalytic chain procedure for the preparation some of these compounds in the environmentally-friendly reactor (without toxic catalyst) via electrolysis of three-component mixture in the undivided electrochemical cell (Fig. 1.) at room temperature and introduce of two alternative methods for determining reaction time.



**Fig. 1.** Electrocatalytic transformation of barbituric acid, aldehyde and malononitrile

## 2. EXPERIMENTAL

### 2.1. Reagents and equipments

All reagents were purchased from Merck and Fluka and used without further purification. Melting points were obtained in open capillary tubes and were measured on an Electro-thermal IA 9100 apparatus. IR spectra were recorded on KBr pellets on a Shimadzu FT-IR 8600 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined on a Bruker 500 DRX Avance instrument at 400 and 100 MHz. The voltammograms were recorded with  $\mu\text{Autolab}$  FRA2 Potentiostat-Galvanostat apparatus. A three-electrode system was used with a platinum rod as working electrode, a GC electrode as the counter electrode and an Ag/AgCl as the reference electrode (Autolab).

### 2.2. Typical electrolysis procedure

A solution of an appropriate aromatic aldehydes (2 mmol), barbituric acid (2 mmol), malononitrile (2 mmol) and KBr (0.1 mmol) in ethanol (15 mL) and water (15 mL) was electrolyzed in an undivided cell with a magnetic stirrer, an iron cathode and graphite anode (Autolab) at room temperature under a constant current density of  $20\text{ mA cm}^{-2}$  ( $I = 100\text{ mA}$ , electrodes square  $5\text{ cm}^2$ ) until the catalytic quantity of electricity was passed. On completion of reaction, monitored by CV, the reaction mixture was removed from electrolytic cell. The solid separated was filtered and washed with cold ethanol to obtain the pure products. Physical, analytical and spectroscopic characterization data of the synthesized compounds are given below.

## 3. RESULT AND DISCUSSION

### 3.1. Optimization of electrosynthesis

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic transformation of 3-nitrobenzaldehyde **1a**, barbituric acid and malononitrile to 7-amino-6-cyano-5-(3-nitrophenyl)-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones (**4a**) was studied in ethanol and water in an undivided cell containing an iron cathode electrode as cathode and graphite anodes at constant current in the presence of an electrolyte. After that, the effect of current and electrolyte was examined.

As is indicated in Table 1, the current density  $20\text{ mA cm}^{-2}$  ( $I=100\text{ mA}$ , electrodes surface  $5\text{ cm}^2$ ) in an undivided cell containing an iron cathode and graphite as anodes at room temperature were found to be optimal for the electrochemically induced chain process and allowed for the highest substance yield of 7-amino-6-cyano-5-(3-nitrophenyl)-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones (**4a**, 79%). An increase in the current density up to  $50\text{ mA cm}^{-2}$  ( $I=250\text{ mA}$ ) results in a slight decrease of the reaction yield, that may be

connected with the activation of undesired direct electrochemical processes leading to oligomerization of starting material. A decrease in the current density to  $10 \text{ mA cm}^{-2}$  ( $I=50 \text{ mA}$ ) also led to the decrease the substance reaction yields, more likely due to the insufficient initiation of the electrochemically induced chain reaction in this case.

Also, for determining the end of electrochemical transformation, three strategies were employed: i) monitoring by T.L.C. ii) Electrical charge-Time plot iii) Cyclic Voltammetry (CV)

Thin layer chromatographic investigation of reaction mixture showed that after 20 min. process stopped, approximately.

**Table 1.** Electrocatalytic transformation of 3-nitrobenzaldehyde, barbituric acid, malononitrile to 7-amino-6-cyano-5-(3-nitrophenyl)-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones (4a)<sup>a</sup> at optimum conditions

Entry	I (mA)	Current density (mA/cm <sup>2</sup> )	Electricity passed (F/mol)	Time (min)	Yield of 4a <sup>b</sup> (%)
1	50	10	0.31	20	38
2	75	15	0.47	20	42
3	100	20	0.62	20	79
4	125	25	0.77	20	34
5	250	50	1.55	20	40

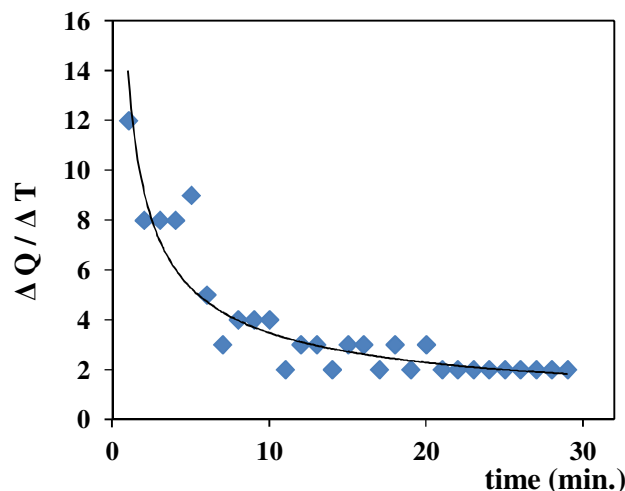
<sup>a</sup> 3-nitro benzaldehyde (2 mmol) (**1a**), barbituric acid (2 mmol) (**2a**), malononitrile (2 mmol), KBr (1 mmol), EtOH (15 mL) and water (15 mL), iron cathode (5 cm<sup>2</sup>), graphite anode (5 cm<sup>2</sup>), r.t., current density 5 mA cm<sup>-2</sup>.

<sup>b</sup> Yield of isolated product (isolated by filtration of reaction mixture).

Fig. 2 shows the variation of electrical charge (Q) during electrolysis process. As can be seen, the  $\Delta Q/\Delta t$  (C/min.) ratio decreases with time exponentially and after about 22 minute, this decreasing occurs very slowly. Therefore this time is the end of electrolysis.

In order to confirm our finding about the end of reaction time, cyclic voltammetric experiments were used. In the first step, the voltammograms of barbituric acid, benzaldehyde and malonitrile in KBr (all in ethanol-water solution) were recorded, separately. After that, the voltammograms of this reactants mixture and electrolytic cell content after 22 minute were recorded. All of these investigations perform at three-electrode system (Ag-AgCl as

reference, Glassy carbon as counter and Pt rod as working electrode). Fig. 3 shows that after 22 min., the wave at 0.5 V remarkably diminishes. This anodic wave is related to barbituric acid [24] and disappearing of this wave is an acceptable clue for relatively complete consumption of barbituric acid.



**Fig. 2.** Variation of  $\Delta Q/\Delta t$  ratio with  $t$  during the electrolysis

Under the optimal conditions ( $I=100$  mA, current density  $20$  mA  $\text{cm}^{-2}$ , time 22 min, KBr as electrolyte) the electrolysis of barbituric acid (**1**), aryl aldehyde (**2**) and malononitrile (**3**) in ethanol and water in an undivided cell resulted in the formation of corresponding substituted products (**4a–j**) in 65-85 % yields. All the products are known and were identified by comparison of their physical (mp) and spectroscopic data (IR and  $^1\text{H}$  or  $^{13}\text{C}$  NMR) with those reported (Table 2) [25].

### 3.2. Spectral data

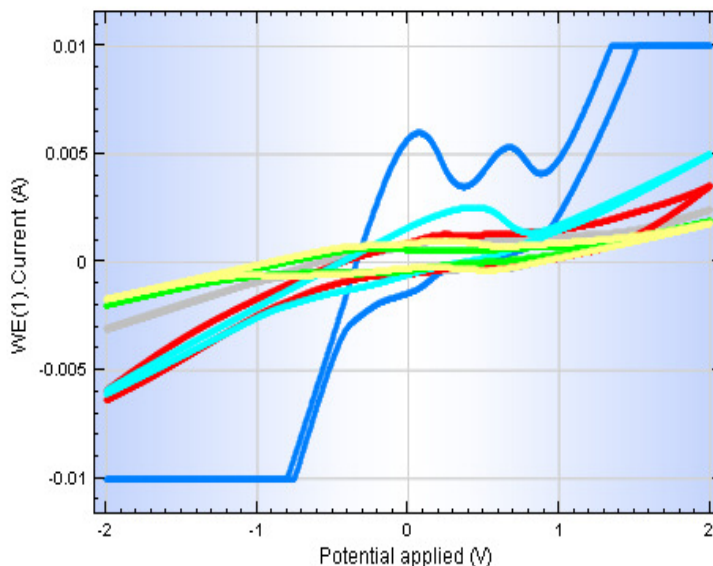
The spectroscopic data of 7-amino-6-cyano-5-(3-nitrophenyl)-5H-pyrano[2,3-d]pyrimidinone (**4a**) present in Fig. 4. These results confirm structure of mentioned product. The spectroscopic studies on the other products summarized in the next part.

#### 3.2.1. 7-amino-6-cyano-5-(3-nitrophenyl)-5H-pyrano[2,3-d]pyrimidinone (**4a**)

Light yellow solid; yield 70%; mp 267-270 °C; IR (KBr):  $\nu = 3415, 3311, 3178, 3078, 2193, 1689, 1677$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 4.48 (s, 1H, H-5), 7.29 (brs, 2H,  $\text{NH}_2$ ), 7.62 (t, 1H,  $J$  8.0 Hz, Ar), 7.75 (d, 1H,  $J$  7.2 Hz, Ar), 8.07 (s, 1H, Ar), 8.35 (d, 1H,  $J$  8.0 Hz, Ar), 11.12 (s, 1H, NH), 12.16 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 35.9, 58.1, 88.0, 119.4, 122.4, 122.5, 130.4, 134.9, 146.8, 148.2, 149.9, 153.0, 158.3, 163.9 ppm.

### 3.2.2. 7-amino-6-cyano-5-(2-chloro)-5H-pyrano[2,3-d]pyrimidinone (4c)

White solid; yield 70 %; mp 240-242°C; IR (KBr)  $\nu$  = 3519, 3313, 3171, 3008, 2827, 2200, 1713, 1662  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 4.73 (s, 1H, H-5), 7.17 (br s, 2H,  $\text{NH}_2$ ), 7.22-7.29 (m, 3H, Ar), 7.38 (d, 1H,  $J$  7.6 Hz, Ar), 11.07 (s, 1H, NH), 12.11 (br s, 1H, NH);  $^{13}\text{C}$  NMR (100MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 33.7, 57.7, 88.0, 119.2, 128.4, 128.9, 130.0, 132.4, 136.2, 141.2, 150.0, 153.2, 158.3, 162.8 ppm.



**Fig. 3.** Cyclic voltammogram of a) primary mixture of reactants (blue) b) barbituric acid (turquoise) c) electrolyzed mixture after 22 min. (red) d) benzaldehyde (yellow) e) malonitrile (green) f) KBr in ethanol-water solution at Pt rod working (gray), Glassy carbon as counter and Ag-AgCl as reference electrode and scan rate 100 mV/S

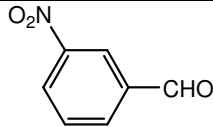
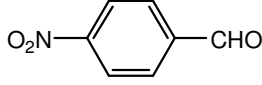
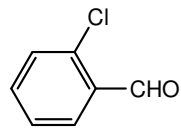
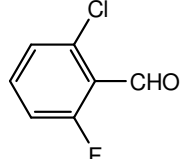
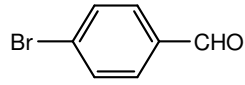
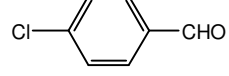
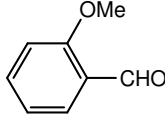
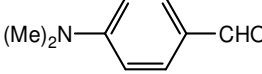
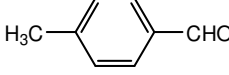
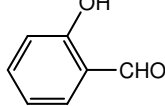
### 3.2.3. 7-amino-6-cyano-5-(2-chloro-6-fluorophenyl)-5H-pyrano[2,3-d]pyrimidinone (4d)

Light yellow solid; yield 86 %; mp 250-252°C; IR (KBr)  $\nu$  = 3425, 3342, 3172, 3056, 2941, 2200, 1710, 1683, 1639  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 4.96 (s, 1H, H-5), 7.19 (brs, 2H,  $\text{NH}_2$ ), 7.29-7.35 (m, 3H, Ar), 11.12 (s, 1H, NH), 12.14 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 30.0, 56.5, 87.1, 115.7, 119.2, 125.8, 127.4, 128.7, 129.9, 134.2, 149.9, 153.2, 159.1, 162.7 ppm.

### 3.2.4. 7-amino-6-cyano-5-(4-chlorophenyl)-5H-pyrano[2,3-d]pyrimidinone (4f)

White solid; yield 77 %; mp 232-234 °C; IR (KBr): 3394, 3211, 3085, 2842, 2194, 1710, 1662  $\text{cm}^{-1}$ .

**Table 2.** Electrosynthesis of 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones<sup>a</sup>

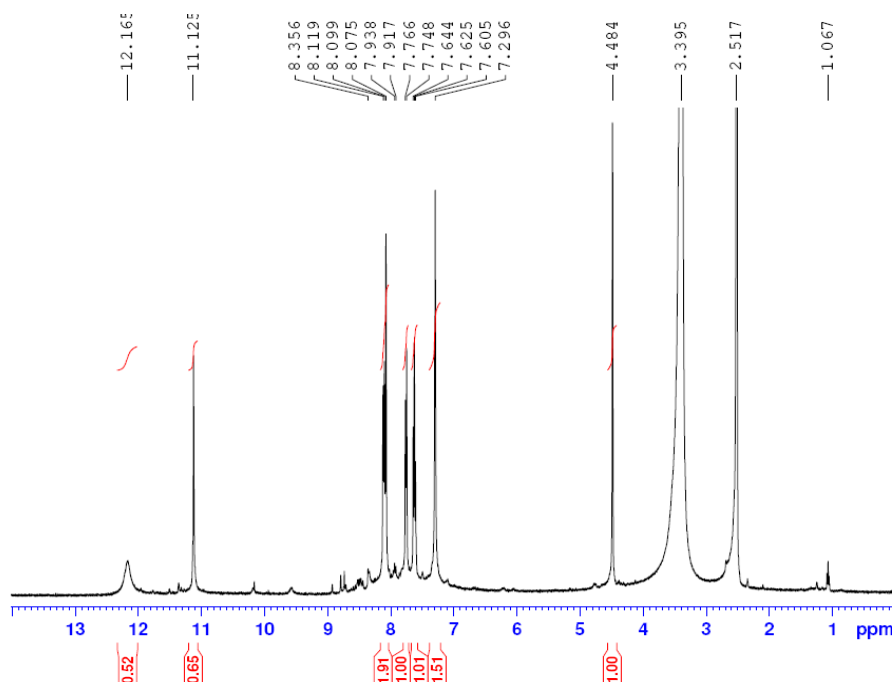
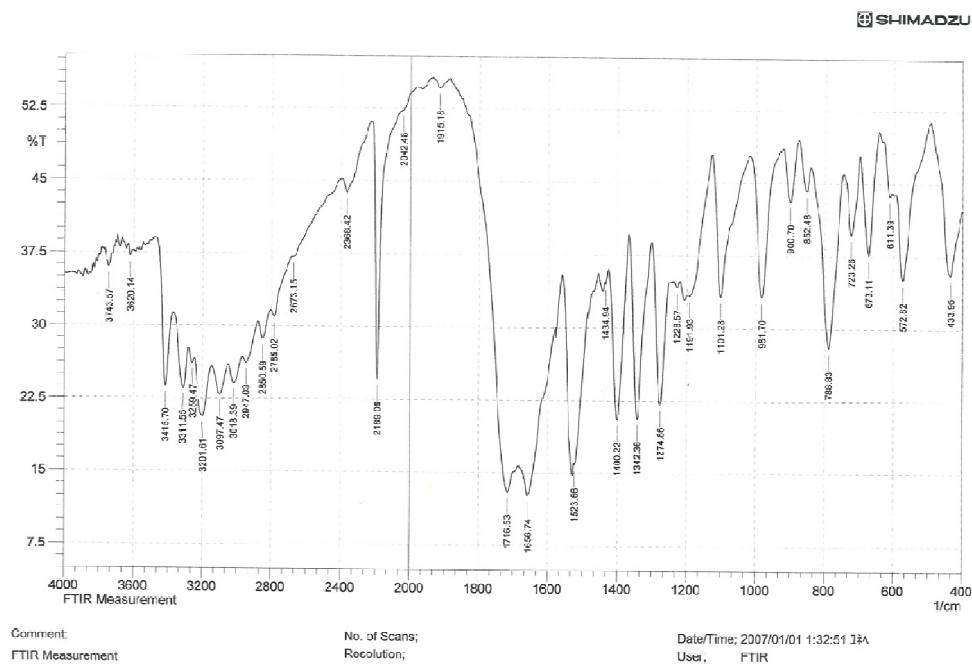
Entry	Aldehyde	Product	Yield <sup>b</sup> (%)	mp (°C)	
				Found	Reported [25]
1		4a	79	267-270	268-270
2		4b	73	238-240	239-240
3		4c	70	240-242	-
4		4d	85	250-252	-
5		4e	78	226-228	227-229
6		4f	77	232-234	-
7		4g	69	172-174	-
8		4h	65	207-210	-
9		4i	75	175-178	-
10		4j	80	162-163	-

<sup>a</sup>Aryl aldehyde (2 mmol) (**1a**), barbituric acid (2 mmol) (**2a**), malononitrile (2 mmol), KBr (1 mmol), EtOH (15 mL) and water (15 mL), iron cathode (5 cm<sup>2</sup>), graphite anode (5 cm<sup>2</sup>), r.t., current density 5 mA cm<sup>-2</sup>

<sup>b</sup> Yield of isolated product (isolated by filtration of reaction mixture)

### 3.2.5. 7-amino-6-cyano-5-(2-methoxyphenyl)-5*H*-pyrano[2,3-*d*]pyrimidinone (4g)

Yellow solid; yield 69%; mp 172-175 °C; IR (KBr): 3357, 3205, 3070, 2839, 2217, 1731, 1668 cm<sup>-1</sup>.



**Fig. 4.** Spectral data of 7-amino-6-cyano-5-(3-nitrophenyl)-5H-pyrano[2,3-d]pyrimidinone (4a)



## 3.2.6. 7-amino-6-cyano-5-(4-dimthylaminophenyl)-5H-pyrano[2,3-d]pyrimidinone (4h)

Yield: 65% mp: 207-210 °C; IR (KBr): 3521, 3454, 3197, 3074, 2918, 2202, 1730, 1683, 1649, 1610 cm<sup>-1</sup>.

## 3.2.7. 7-amino-6-cyano-5-(4-methylophenyl)-5H-pyrano[2,3-d]pyrimidinone (4i)

Yield: 75% mp: 175-178 °C; IR (KBr): 3413, 3193, 3022, 2725, 2200, 1719, 1689, 1650 cm<sup>-1</sup>.

## 3.2.7. 7-amino-6-cyano-5-(2-hydroxyphenyl)-5H-pyrano[2,3-d]pyrimidinone (4j)

Yield: 80% mp: 160-163 °C; IR (KBr): 3398, 3075, 2227, 1730, 1657, 1662, 1602 cm<sup>-1</sup>.

### 3.3. Proposed Mechanism

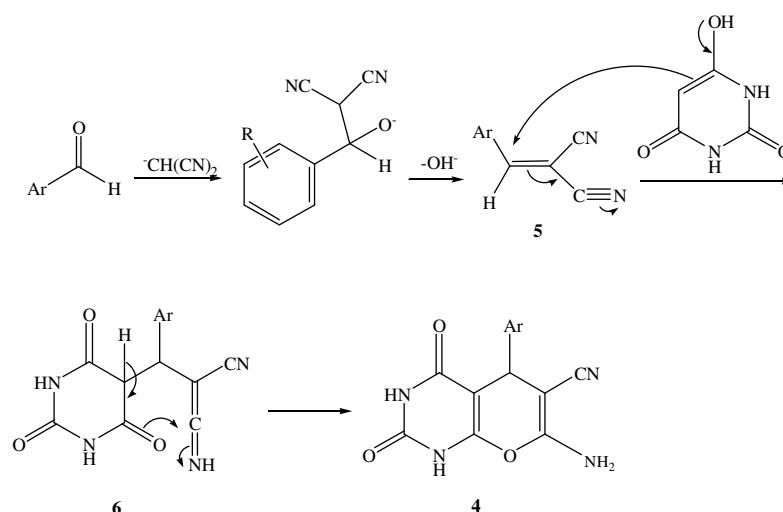
Taking into consideration the above results and the data [18] on the mechanism of the electrocatalytic chain transformation of cyclic 1,3-diketones, isatins and malononitrile into substituted spiro[(4*H*-chromene)-4,3-oxindoles] the following mechanism for the electrocatalytic chain transformation of aryl aldehyde, barbituric acids and malononitrile into 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones is proposed.

As the initiation step of the catalytic cycle, the deprotonation of an alcohol at the cathode leads to the formation of alkoxide anion. The subsequent reaction in solution between alkoxide anion and malononitrile gives rise to malononitrile anion (Fig. 5).



**Fig. 5.** Initial step in electrosynthesis of products

Then Knoevenagel condensation of malononitrile anion with arylaldehyde takes place in the solution with elimination of hydroxide anion and formation of corresponding arylidene malononitrile (5). The subsequent Michael addition of barbituric acid to electron deficient Knoevenagel adduct 5 followed by intramolecular cyclization leads to corresponding 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones (4) (Fig. 6).



**Fig. 6.** Proposed mechanism for electrocatalytic transformation

#### 4. CONCLUSION

In conclusion, the simple electrocatalytic system can produce, under mild conditions, a fast and selective transformation of barbituric acid, aldehyde and malononitrile into 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidine-(1H,3H)-2,4-diones under room temperature in good yields. The time of reaction termination was studied by three methods: i) monitoring by T.L.C ii) Electrical charge-Time plot. iii) Cyclic voltammetric investigation for the first time.

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#### REFERENCES

- [1] E. M. Griva, S. Lee, C. W. Siyal, D. S. Duch, and C. A. Nichol, *J. Med. Chem.* 23 (1980) 327.
- [2] G. L. Anderson, J. L. Shim, and A. D. Broom, *J. Org. Chem.* 41 (1976) 1095.
- [3] M. M. Ghorab, and A. Y. Hassan, *Phosphorus, Sulfur, Silicon Related Elem.* 141 (1998) 251.
- [4] D. Heber, C. Heers, and U. Ravens, *Pharmazie* 48 (1993) 537.
- [5] J. Davoll, J. Clarke, and E. F. Eislager, *J. Med. Chem.* 15 (1972) 837.
- [6] S. Gao, C. H. Tsai, C. Tseng, and C. F. Yao, *Tetrahedron* 64 (2008) 9143.

- [7] A. G. E. Amr, A. M. Mohamed, S. F. Mohamed, N. A. Abdelhafez, and A. E. G. Hammam, *Bioorg. Med. Chem.* 14 (2006) 5481.
- [8] M. M. Heravi, B. Baghernezhad, and H. A. Oskooie, *J. Chinese Chem. Soc.* 55 (2008) 659.
- [9] D. N. Bobrov, and V. I. Tyvorskii, *Tetrahedron* 66 (2010) 5432.
- [10] O. M. Ahmed, M. A. Mohamed, R. R. Ahmed, and S. A. Ahmed, *Europ. J. Med. Chem.* 44 (2009) 3519.
- [11] J. M. Khurana, B. Nand, and P. Saluja, *Tetrahedron* 66 (2010) 5637.
- [12] T. H. Al-Tel, *Europ. J. Med. Chem.* 45 (2010) 5724.
- [13] Y. Gao, S. J. Tu, T. Li, X. Zhang, S. Zhu, F. Fang, and D. Shi, *Synth. Commun.* 34 (2004) 1295.
- [14] M. N. Elinson, V. M. Merkulova, A. I. Ilovaisky, F. Barba, and B. Batanero, *Electrochim. Acta* 56 (2011) 8219.
- [15] D. Nematollahi, E. Mehdipour, A. Zeinodini-Meimand, A. Maleki, *Tetrahedron Lett.* 51 (2010) 6447.
- [16] A. N. Vereshchagin, M. N. Elinson, E. O. Dorofeeva, T. A. Zaimovskaya, N. O. Stepanov, S. V. Gorbunov, P. A. Belyakov, and G. I. Nikishin, *Tetrahedron* 68 (2012) 1198.
- [17] M. N. Elinson, V. M. Merkulova, A. I. Ilovaisky, A. O. Chizhov, P. A. Belyakov, Y. F. Barba, and B. Batanero, *Electrochim. Acta* 55 (2010) 2129.
- [18] M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, D. V. Demchuk, P. A. Belyakov, Y. N. Ogibin, and G. I. Nikishin, *Electrochim. Acta* 53 (2008) 8346.
- [19] M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, R. F. Nasybullin, S. V. Gorbunov, and G. I. Nikishin, *Electrochem. Commun.* 8 (2006) 1567.
- [20] M. Boominathan, M. Nagaraj, S. Muthusubramanian, and R. V. Krishnakumar, *Tetrahedron* 67 (2011) 6057.
- [21] M. N. Elinson, A. I. Ilovaisky, A. S. Dorofeev, V. M. Merkulova, N. O. Stepanov, F. M. Miloserdov, Y. N. Ogibin, and G. I. Nikishin, *Tetrahedron* 63 (2007) 10543.
- [22] L. Fotouhi, M. M. Heravi, A. Fatehi, and K. Bakhtiari, *Tetrahed. Lett.* 48 (2007) 5379.
- [23] M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya, and G. I. Nikishin, *Mendel. Commun.* 21 (2011) 122.
- [24] D. Nematollahi, and M. Hesari, *Microchem. J.* 70 (2001) 7.
- [25] S. Balalaie, S. Abdolmohammadi, H. R. Bijanzadeh, and A. M., Amani, *Mol. Divers.* 12 (2008) 85.