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| Journal: | *RSC Advances* |
| Manuscript ID: | RA-COM-08-2014-008251.R2 |
| Article Type: | Communication |
| Date Submitted by the Author: | 06-Oct-2014 |
| Complete List of Authors: | Veisi, Hojat; Payame Noor University,<br>Lotfi, Shahram; PNU,<br>Maleki, Abas; PNU,<br>Omrani, Zahra; PNU, |
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# Electrogenerated base-promoted synthesis of 5-aryl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones by multicomponent assembling of barbituric acid, aldehydes and Meldrum's acid at room temperature

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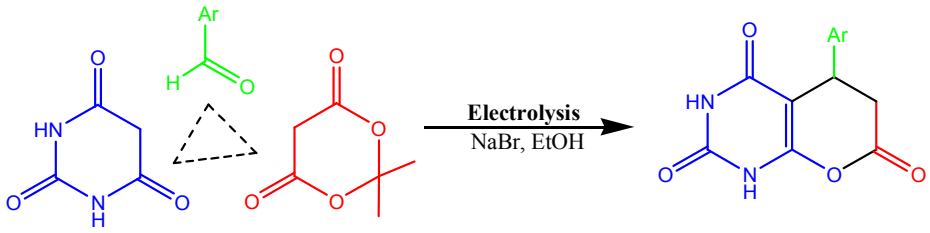
**Abstract:** An electrochemical strategy to the synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones is described, using an electrogenerated base of the anion of barbituric acid in a one-pot, three component condensation of an aromatic aldehyde, Meldrum's acid and barbituric acid in ethanol in an undivided cell and in the presence of sodium bromide as an electrolyte at room temperature. This protocol has the advantages of high yields, wide application scope and an environmental benign procedure.

**Keywords:** Electrochemical, Electrogenerated base, Pyrano[2,3-d]pyrimidine-2,4,7-triones, Multicomponent reaction, Meldrum's acid

Pyrimidinone derivatives form a class of important heterocycles with a wide range of biological[1] and pharmaceutical properties.[2] They display anti-tumor action; in the treatment of B16 melanoma and P388 leukemia[3] or antagonize cell proliferation and induce cell differentiation by inhibiting (a nontelomeric) endogenous reverse transcriptase.[4] Pyrimidine derivatives are of interest due to their wide range of biological activities.[5] The synthesis of naturally occurring molecules containing a uracil ring provides significant synthetic challenges.[6] The development of clinically useful anticancer (5-fluorouracil)[7] and antiviral drugs (AZT, DDI, BVDU)[8-10] has renewed the interest in the synthetic manipulation of uracils.[11] Many substances that have a uracil moiety in the skeleton of an organic molecule show antitumor, antibacterial, bronchodilator, antihypertensive, cardiotonic, hepatoprotective, and antiallergic activities; some of them also exhibit antimalarial, analgesic, antifungal, and herbicidal properties.[12-19]

Electrosynthesis offers chemists many novel and versatile synthetic protocols. Advantages include high material utilization, the use of mild reaction conditions, decreased energy requirement, ease of control of the reaction, less hazardous processes as a result of reduced waste production, and the ability to perform wide range of precisely tunable oxidation and reduction reactions.[20,21] Pronounced growth of investigations in organic electrochemistry during last three decades has made electrosynthesis one of the most competitive methods of modern organic chemistry.[22] Numerous electrochemical approaches have been developed for bond formations and functional group transformations.[23]

The multi-component reactions (MCRs) have been employed for preparing compound libraries by virtue of straightforward reaction condition, atomic economy, high bond forming efficiency and great diversity generating potential.[24] Methods of organic transformations based on electrochemically induced MCRs involving carbonyl compounds have been extensively developed.[25] To date, just one report have been published on the synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones via a three-component reaction of an aromatic aldehyde, Meldrums acid, and barbituric acid in the presence of $K_2CO_3$ that limited due to hazardous conditions of microwave irradiation.[25] To continue our work on the electrochemical multi-component synthesis of heterocyclic compound library,[27] herein we shall report an electrogenerated base of the anion of ethanol in a one-pot, three component condensation of an aromatic aldehyde, Meldrum's acid and barbituric acid for the fabrication of 5-aryl-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-triones in an undivided cell (Scheme 1).




**Scheme 1.** Electrochemical synthesis of 5-aryl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones.

Initially, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrochemical multicomponent condensation of 3-nitrobenzaldehyde, Meldrums acid, and barbituric acid into 5-(3-nitrophenyl)-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones in EtOH in an undivided cell containing an iron electrode as cathode and a graphite electrode as anode at constant current in the presence of sodium bromide as an electrolyte was studied at room temperature. As it is indicated in Table 1, the current density 10 mA/cm$^2$ (I = 50 mA, electrode surface 5 cm$^2$) in EtOH was found to be the optimum one for the electrochemically induced chain process and afforded the highest yield of product (97%). The current density increase up to 15 mA/cm$^2$ (I = 75 mA) results in a slight decrease of the reaction yield, which may be connected with the activation of undesired direct electrochemical processes possible under these conditions and leading to the oligomerization of the starting material. In addition, to compare the electrochemical method with the chemical one, we used sodium metal as a catalyst (10 mol%) for the model reaction, but the desired product was not observed.

**Table 1**

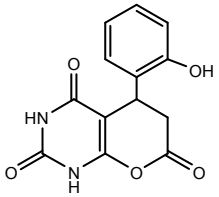
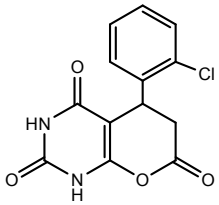
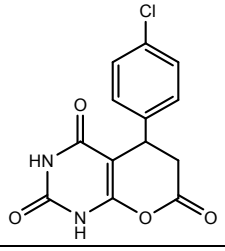
Electrochemical transformation of 3-nitrobenzaldehyde, Meldrum's acid and barbituric acid into the corresponding 5-(3-nitrophenyl)-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones.[a]

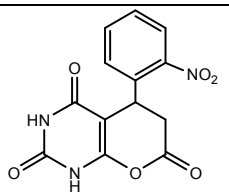
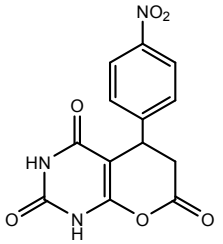
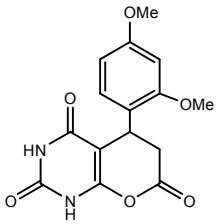
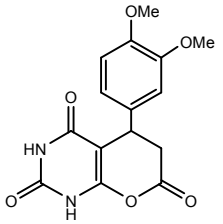
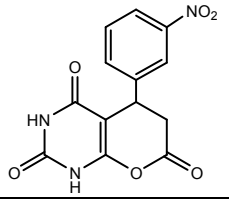
| Entry | I(mA) | Current density ($mA/cm^2$) | Time (min) | Electricity passed (F/mol) | Catalyst | Solvent | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | 5 | 1 | 360 | 1.11 | - | EtOH | 40 |
| 2 | 10 | 2 | 360 | 2.22 | - | EtOH | 45 |
| 3 | 20 | 4 | 360 | 4.47 | - | EtOH | 75 |
| 4 | 30 | 6 | 360 | 6.71 | - | EtOH | 82 |
| 5 | 40 | 8 | 360 | 8.95 | - | EtOH | 90 |
| 6 | 50 | 10 | 240 | 7.46 | - | EtOH | 97 |
| 7 | 75 | 15 | 240 | 11.19 | - | EtOH | 90 |
| 8 | - | - | 240 | - | Na | EtOH | 0 |

[a]General procedure: Barbituric acid (1 mmol), 3-nitrobenzaldehyde (1 mmol), Meldrum's acid (1 mmol), NaBr (0.1 mmol), ethanol (20 mL), iron cathode (5 $cm^2$), graphite anode (5 $cm^2$), room temperature.
[b]Yield of isolated product.

Under the optimal conditions, the scope and generality of the reaction was explored. A variety of aryl aldehydes were investigated to react with Meldrum's acid and barbituric acid, and the results are summarized in Table 2. It was found that the aromatic aldehydes with both electron-withdrawing and donating groups, in reaction with other starting materials, had excellent isolated yields.

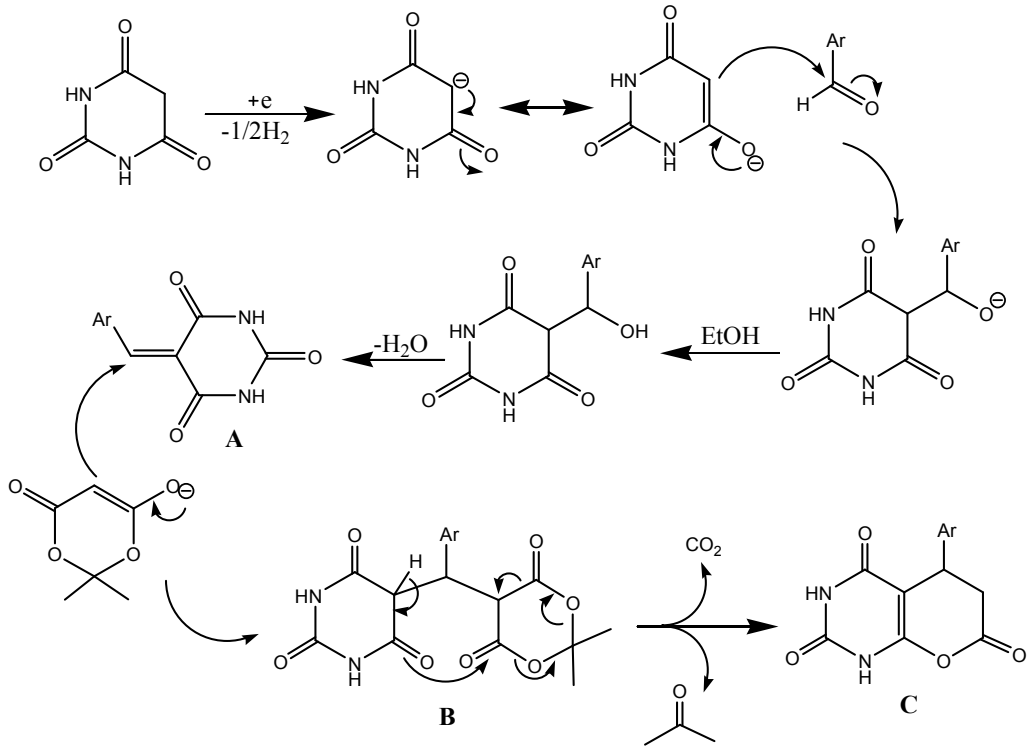
**Table 2**
Electrochemical synthesis of 5-aryl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones.[a]

| Entry | Product | Electricity passed (F $mol^{-1}$) | Yield (%)[b] | Mp (°C) | Mp (ºC) (lit. 26) |
|---|---|---|---|---|---|
| 1 |  | 7.46 | 96 | 290-292 | 292 |
| 2 |  | 7.46 | 95 | 241-242 | 240 |
| 3 |  | 7.46 | 97 | 280-281 | 282 |

| | | | | | |
|---|---|---|---|---|---|
| 4 |  | 7.46 | 90 | 219-221 | 218-220 |
| 5 |  | 7.46 | 95 | 246-248 | 248-250 |
| 6 |  | 7.46 | 94 | 231-233 | 235-237 |
| 7 |  | 7.46 | 92 | 276-278 | 277 |
| 8 |  | 7.46 | 97 | 271-273 | 273 |

[a]General procedure: Barbituric acid (1 mmol), aldehyde (1 mmol), Meldrum's acid (1 mmol), NaBr (1 mmol), ethanol (20 mL), iron cathode (5 $cm^2$), graphite anode (5 $cm^2$), current density 10 $mA/cm^2$, 4 hours at room temperature.
[b]Yield of isolated product.

Taking the above results into consideration, the following proposed mechanism for the preparation of the related products is depicted in Scheme 2.[28] We presume that the electrogenerated base in the present case is the anion of barbituric acid, formed along with dihydrogen by the reduction of barbituric acid at the cathode.[29] Then, Knoevenagel condensation of aldehyde, with the barbituric acid anion takes place in the solution with the elimination of water and the formation of the corresponding intermedate **A**. The subsequent electrogenerated base-promoted Michael addition of Meldrum's acid to the electron-deficient Knoevenagel adduct **A**. Cyclization of **B** via a translactonization reaction leads to liberation of an acetone molecule and a molecule $CO_2$ and also produced the final product **C.**




**Scheme 2.** Proposed mechanism for the preparation of 5-aryl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones.

In conclusion, we have described a novel, efficient, convenient and electrochemical procedure to the synthesis of 5-aryl-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-triones via one-pot, three component condensation of an aromatic aldehyde, Meldrum's acid and barbituric acid in ethanol in an undivided cell and in the presence of sodium bromide as an electrolyte at room temperature. The key advantages of this method are the in situ generation of base, a one-pot reaction in excellent yields under milder conditions, avoidance of polluting or hazardous chemicals or the addition of base or pro-base, and involves an easy work-up procedure.

## Experimental

*Typical experimental procedure for electrochemical synthesis of pyrano[2,3-d]pyrimidine-2,4,7-triones derivatives*

A mixture of aromatic aldehydes (1 mmol), Meldrum's acid (1 mmol), barbituric acid (1 mmol), and NaBr (0.1 g, 1 mmol) in EtOH (20 mL) was electrolyzed in an undivided cell equipped with a magnetic stirrer, a graphite anode, and an Fe cathode at room temperature under a constant current density of 10 mA/cm$^2$ (I = 50 mA, electrode surface 5 cm$^2$). The progress of the reaction was monitored by thin layer chromatography. The reaction time was in all the cases about 4 h. After electrolysis was finished, the mixture was filtered, then rinsed twice with an ice-cold ethanol/water solution (9:1, 5 mL), and

dried under reduced pressure. All the products were characterized by spectroscopy and from physical data.

*Analytical data for selected compound (Table 2, entry 6)*
*5-(2',4'-dimethoxyphenyl)-5,6-dihydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione:*

Mp 231-233 ºC; IR (KBr) ($\nu_{max}$, $cm^{-1}$): 3410, 3298, 2992, 1722, 1691, 1582, 1498, 1443, 1365, 1269, 1171, 1032 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 200 MHz, δ ppm): 3.30 (d, 2H, $CH_2$), 3.85 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 4.55 (t, 1H, CH), 6.65-7.61 (m, 3H, Ph), 11.02 (s, 1H, NH), 11.15 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz, δ ppm ): 164.8, 163.6, 151.2,152.0,144.6, 135.6, 129.1, 114.6, 107.5, 104.9, 91.6,57.2(OCH3), 56.8 (OCH3), 27.5, 20.4. Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.80%. Found: C, 56.35; H, 4.54; N, 8.78%

**Acknowledgments.** We are thankful to Payame Noor University (PNU) for partial support of this work.

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# Graphical Abstract

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