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Electron as potential and green catalyst in the multicomponent synthesis of pyrano[2,3-*d*]pyrimidine derivatives

Hojat Veisi*, Abbas Maleki, Yasaman Farokhzad

Department of Chemistry, Payame Noor University, 19395-4697 Tehran, Iran

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Abstract

An electroorganic reaction for the synthesis of7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives will be described, using an electrogenerated base of the anion of malonitrile or ethylcyanoacetate. This one-pot, three-component condensation of an aromatic aldehyde, barbituric acid and malonitrile or ethylcyanoacetatetakes place in ethanol in an undivided cell in the presence of tetrabutylammonium perchlorateas an electrolyte under mild conditions. This method has the advantages of high yields, wide application and employs an environmentally benign procedure.

Keywords: Electrochemistry; electrogenerated base; Pyrano[2,3-*d*]pyrimidine; multicomponent reaction; barbituric acid.

Introduction

Multicomponent reactions (MCRs) are significant in producing great level of diversity, as they allow more than two building units to be combined in practical synthesis, time-saving one pot operations, generate complex structures by formation of two or more bonds [1,2]. MCR scan dramatically reduce the generation of chemical waste and the cost of the starting materials [3-6]. Nitrogen and oxygen-containing heterocycles serve both as biomimetic and reactive pharmacophores due to their diverse therapeutic property thus playvital role in natural and synthetic organic chemistry [7,8]. Condensed uracils are important structural types in synthetic heterocyclic compounds of pharmaceutical interests. Pyrano[2,3-d]pyrimidines which are building blocks used to evaluate their antimicrobial activities and various derived natural products are also used as a drug for insomnia treatment [9]. Therefore, for the preparation of these complex molecules large efforts have been directed toward the synthetic manipulation of pyrano[2,3-d]pyrimidine derivatives. As a result, a number of reports which has appeared in the literature usually require forcing conditions, long reaction time, and complex synthetic pathways. Pyrano[2,3-d]pyrimidine synthesis was reported under various conditions such as microwave irradiation [10,11], ultrasonic irradiation [12], glycerol [13], sulfonic acid nanoporous silica (SBA-Pr-SO_3H) [14], diammonium

*Corresponding author: Hojat Veisi
Tel: +98 (838) 4227463, Fax: +98 (838) 4227463
E-mail: *hojatveisi@yahoo.com*

hydrogen phosphate (DAHP) [15], Zn[(L)proline]$_2$ and $H_{14}[NaP_5W_{30}O_{110}]$ [16], ionic liquids [17], Choline chloride. $ZnCl_2$ [18], L-proline [19] and DABCO [20]. Reported methods appearing in the literature usually require forcing conditions, long reaction time, create wastes, need complex synthetic pathway and involved organic solvents as well high energy to proceed. However, some of the reported methods for the synthesis of these products suffer from several drawbacks such as prolonged reaction times, low yields, harsh reaction conditions, the use of expensive reagents and catalysts, and tedious work-ups. Therefore, new, facile and highly efficient synthetic approaches to pyrano[2,3-d]pyrimidines are highly desirable.

Electrochemical organosynthetic methods have received significant attention because of their benefit to the environment. In these procedures, electricity acts as a 'green' oxidative and reductive agent [21,22]. The pronounced growth in organic electrochemistry over the last three decades has made electrosynthesis a very competitive method in modern organic chemistry [23]. Numerous electrochemical approaches have been developed for bond formation and functional group transformations [24].

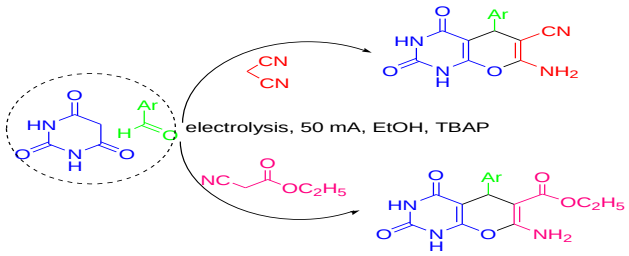
Experimental

Typical experimental procedure for the electrochemical synthesis of pyrano[2,3-d]pyrimidine products

A Mixture of an aldehyde (1 mmol), malonitrile or ethylcyanoacetate(1.1 mmol), barbituric acid (1 mmol), and TBAP (0.1 mmol, 0.035 g) (as the supporting electrolyte) in EtOH (15 mL) was electrolyzed in an undivided cell equipped with a magnetic stir bar, a graphite anode, and a Fe cathode, at 40 ºC at 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-layerchromatography. After the electrolysis was complete (30 min), the mixture was filtered, the solvent was evaporated under vacuum and the residue was purified by recrystallization from EtOH to furnish the desired product. All the products were characterized by spectroscopy and from physical data.

Results and discussion

Recently, it was found that chemical bases could be replaced with an electrogenerated base (EGB) to promote reactions in high yields [25]. Generally, electroorganic reactions proceed in good to excellent yields, with simple work-ups and do not require the use of harsh conditions such as high temperatures. To date, no reports have been published on the electrosynthesis of 7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives. Thus, In the continuation of our previous work on the development of new synthetic methodologies [26],we designed a convenient and facile multicomponent synthesis of 7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and methyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives based on the electrocatalytic transformation of barbituric acid, various aromatic aldehydes, and malonitrile or ethylcyanoacetate in an undivided cell.



Scheme 1. Electrochemical synthesis of pyrano[2,3-d]pyrimidines

Initially, to evaluate the synthetic potential of the proposed procedure and to optimize the electrolysis conditions, the electrochemical multicomponent condensation of benzaldehyde, ethylcyanoacetate, and barbituric acid to give ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate was investigated in EtOH in an undivided cell containing an iron electrode as the cathode and a graphite electrode as the anode at a constant current in the presence of tetrabutylammonium perchlorate (TBAP) as the electrolyte under various conditions.

As is shown in Table 1, a current density of 10 mA/cm^2 (I = 50 mA, electrode surface = 5 cm^2) and temperature of 40 ºC in EtOH was found to be optimum for the electrochemically induced chain process and afforded the highest yield of product (98%, entry 7). Increasing the current density up to 15 mA/cm^2 (I = 75 mA) resulted in a slight decrease in yield may be due to the activation of undesired electrochemical processes leading to the oligomerization of the starting material. In addition, to compare the electrochemical method with the chemical process, we used sodium metal as a catalyst (10 mol%) for the model reaction, however the desired product was not obtained with good yield.

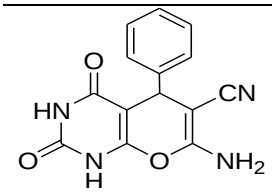
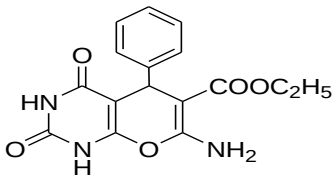
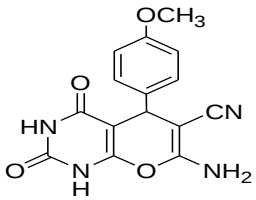
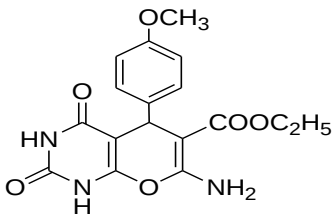
Table 1. Electrochemical transformation of benzaldehyde, ethylcyanoacetateandbarbituricacid into ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate[a]

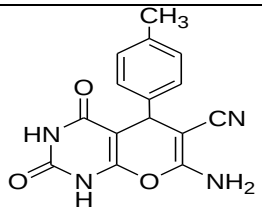
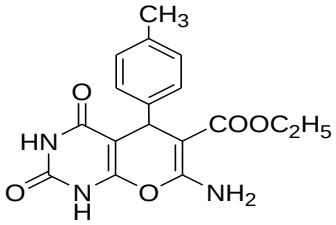
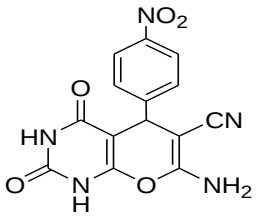
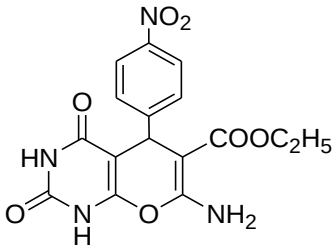
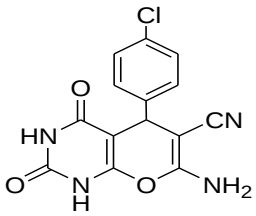
Entry	I (mA)	Current density (mA/cm^2)	Time (h)	Electricity passed (F/mol)	Catalyst	T (ºC)	Yield (%)[b]
1	10	2	3	1.11	-	25	35
2	50	10	3	5.59	-	25	60
3	100	20	3	11.18	-	25	55
4	5	1	2	0.37	-	40	45
5	10	2	2	0.74	-	40	60
6	25	5	2	1.86	-	40	85
7	50	10	0.5	0.93	-	40	98
8	75	15	1	2.79	-	40	90
9	-	-	3	-	Na	40	55

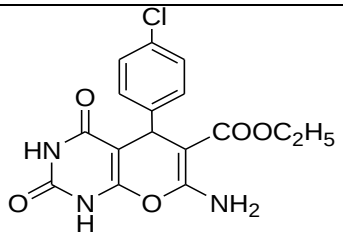
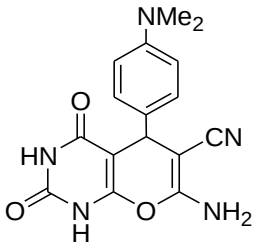
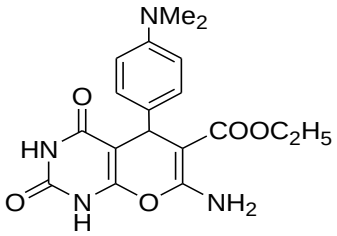
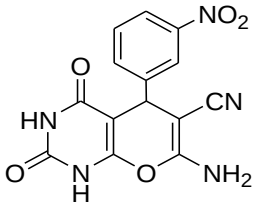
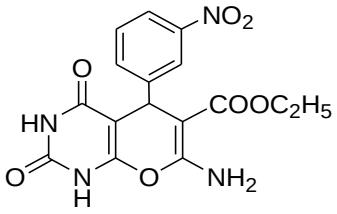
[a]General procedure: barbituric acid (1 mmol), benzaldehyde (1 mmol), ethylcyanoacetate (1.1 mmol), TBAP (0.1 mmol, 0.035 g), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2).
[b]Yield of isolated product.

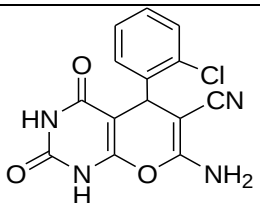
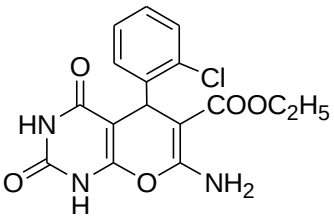
Under the optimum conditions (current density 10 mA/cm^2, 0.93 F/mol passed, 40 ºC, EtOH), the scope and generality of the reaction was explored. Different aryl aldehydes were reacted with barbituric acid and malonitrile or ethylcyanoacetateover a 30 minute reaction period, and the results are summarized in Table 2.Aldehydes containing electron-donating and electron-withdrawing substituents gave the corresponding products in good yields, and hence no electronic effects were observed in the reactions.

Table 2. Electrochemical synthesis of pyrano[2,3-d]pyrimidines[a]

Entry	Product	Yield (%)[b]	Mp (°C)	Mp (ºC) [Ref.]
1		96	206-208	205-207 [18]
2		98	208-210	206–210 [19]
3		96	280-282	279-280 [18]
4		98	294-296	290-293 [19]

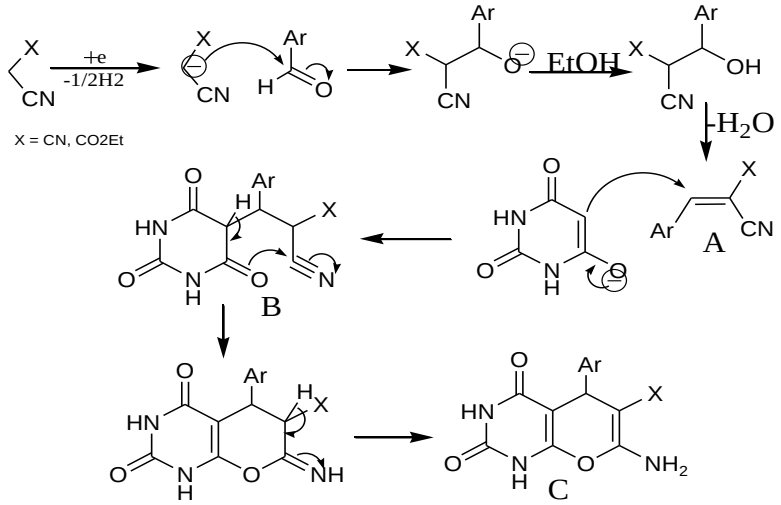
5		92	162-164	160-163 [18]
6		96	296-298	296-298 [19]
7		95	232-234	230-234[18]
8		96	286-288	289-293 [19]
9		95	242-244	242-244 [17]

10		96	>300	295-300 [19]
11		96	180-182	182-184 [18]
12		96	258–260	259–260 [19]
13		92	259-261	258-260 [18]
14		96	239-241	237-240 [18]

				
15		92	228-230	228-229 [13]
				
16		96	216-218	215-216 [19]

[a]General procedure: Barbituric acid (1 mmol), benzaldehyde (1 mmol), ethylcyanoacetate or malonitrile (1.1 mmol), TBAP (0.1 mmol, 0.035 g), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 30 min,40 ºC, 0.93 F/mol passed.
[b]Yield of isolated product

With the above results taken into consideration and the available mechanistic data on the electrochemically induced Henry and aldol reactions as well as the tandem Knoevenagel-Michael reaction, the mechanism for the preparation of the products is proposed in Scheme 2 [25]. Presumably, the electrogenerated base in the present case is the anion of malonitrile or ethylcyanoacetate, formed along with dihydrogen by the reduction of malonitrile or ethylcyanoacetateat the cathode [27,28]. Next, Knoevenagel condensation of the aldehyde with the anion of malonitrile or ethylcyanoacetatetakes place with the elimination of water and the formation of the corresponding intermediate **A**. Subsequent Michael addition of barbituric acid to the electron-deficient Knoevenagel adduct **A** followed by intramolecular cyclization of **B** and subsequent followed by totomerizationleads to the corresponding product **C**.



Scheme 2. Proposed mechanism for the preparation of pyrano[2,3-d]pyrimidines

The reaction at the anode is typical for the alcohol-electrolyte salt system. The anodic reaction does not participate in the process and has been discussed earlier [29].

Finally, to assess the present protocol with respect to other reported methods for the preparation of 7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives, the presented procedure was compared with some of the reported catalysts. From Table 3, it can be seen that present system exhibited higher conversions and yields compared to the other reported system.

Table 3. Comparison of the activity of different catalysts in the synthesis of pyrano[2,3-d]pyrimidines

Aldehyde	Catalyst	Reaction conditions	Yield (%)	[Ref.]
C_6H_5CHO	Electrolysis	EtOH, 40 °C, 30 min.	96	This study
	$[BMIm]BF_4$	90 °C, 180 min.	84	[17]
	Glycerol	80 °C, 60 min.	93	[13]
	$SBA\text{-}Pr\text{-}SO_3H$	140 °C, 5 min.	65	[14]
	Choline chloride.$ZnCl_2$	EtOH, 75 °C, 5 min.	96	[18]
4-ClC_6H_4CHO	Electrolysis	EtOH, 40 °C, 30 min.	95	This study
	$[BMIm]BF_4$	90 °C, 180 min.	92	[17]
	Glycerol	80 °C, 70 min.	91	[13]
	$SBA\text{-}Pr\text{-}SO_3H$	140 °C, 45 min.	30	[14]
	Choline chloride.$ZnCl_2$	EtOH, 75 °C, 2 min.	82	[18]

Conclusion

we have described a novel, efficient, and convenient electrochemical procedure for the synthesis of 7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile and ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate derivatives *via* a one-pot, three-component condensation of an aromatic barbituric acid, aldehydes and malonitrile orethylcyanoacetatein ethanol in an undivided cell and in the presence of tetrabutylammonium perchlorate as an electrolyte at 40 ºC. The key advantages of this method are the in situ generation of the base, the one-pot reaction, excellent yields under mild conditions, the avoidance of polluting or hazardous chemicals, the need for a base or pro-base, and involves an easy work-up procedure.

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