



Electrocatalytic multicomponent assembling of aminouracils, aldehydes and malononitrile: An efficient approach to 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives

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Abstract: The electrocatalytic multicomponent transformation of 6-aminouracils, aromatic aldehydes and malononitrile in ethanol in an undivided cell in the presence of potassium bromide as an electrolyte leads to 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives in short reaction times (8–20 min) and in good to high yields (70–86 %).

Keywords: aldehyde; electrocatalytic transformation; multicomponent reactions; malononitrile; pyrido[2,3-*d*]pyrimidine; uracil.

INTRODUCTION

Uracil and its derivatives, such as pyrido[2,3-*d*]pyrimidines, have received considerable attention over the past years because of their biological activities, such as dihydrofolate reductase inhibiting,¹ antibacterial,² antiallergic,³ antimicrobial,⁴ tyrosine kinase inhibiting,⁵ anti-inflammatory,⁶ analgesic,⁷ calcium channel antagonists,⁸ antihypertensive,⁹ antitubercular,¹⁰ antileishmanial¹¹ and antifungal.¹²

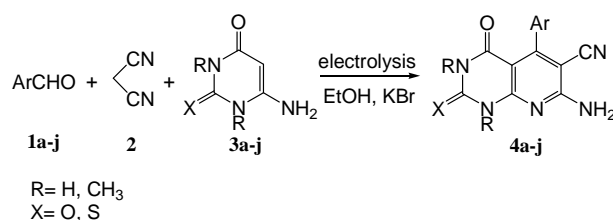
Several synthetic methodologies for the synthesis of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives have been reported.^{13–17} However, in spite of their potential utility, most of the reported synthetic methods suffer from limitations, such as the use of expensive catalysts, long reaction times, difficult work-up and commercial non-availability. Therefore, any new, facile and highly efficient synthetic approach to corresponding 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives is welcome.

In recent years, electrosynthetic, multicomponent reactions (EMCRs) have been used extensively to prepare biologically active compounds and have become an important area of research in organic, combinatorial, and medicinal

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chemistry.¹⁸ Due to electron transfer between the electrode and the substrate molecules, highly reactive intermediates are formed under mild conditions, thereby avoiding reductant or oxidant agents as well as acids, bases and related waste by-products. Thus, such methods could be one of the various fields in green chemistry.¹⁹

All these facts prompted the present design of a convenient and facile synthesis of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile compounds based on the electrochemically induced, multicomponent reaction of aromatic aldehydes, malononitrile and 6-aminouracils in an undivided cell without a base or any additive catalyst (Scheme 1).



Scheme 1. Synthesis of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives.

RESULTS AND DISCUSSION

During the course of the study on the electrochemical transformation of organic compounds,^{20,21} a new strategy was suggested for the synthesis of pyrido[2,3-*d*]pyrimidines by the combined electrolysis of aromatic aldehydes **1**, malononitrile **2** and 6-aminouracils **3** in alcohol in an undivided cell.

To optimize the reaction conditions, the three-component reaction of 4-chlorobenzaldehyde **1a**, malononitrile **2** and 6-aminouracil **3a** was investigated as a model reaction in an alcohol using an undivided cell containing a zinc electrode as the cathode and a Pt electrode as the anode in the presence of potassium bromide as the electrolyte. At first, the effects of solvent, temperature and current in the synthesis of **4a** were investigated (Table I). As indicated in Table I, excellent conversions of starting compounds were obtained after 0.16*F* of electricity had been passed. A current density 5 mA cm⁻² (*I* = 25 mA, electrode surface 5 cm²) in ethanol at 78 °C was found to be optimum for the electrochemically induced chain process and allowed for the highest yield (80 %) of **4a**. An increase in the current density up to 10 mA cm⁻² (*I* = 50 mA) resulted 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 oligomerization of the starting material.

Under the optimal conditions (current density 5 mA cm⁻², EtOH as solvent), the electrolysis of aromatic aldehydes **1a-j**, malononitrile **2** and 6-aminouracils

3a–j in an undivided cell at 78 °C gave rise to the corresponding 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile in 70–86 % yield (Scheme 1, Table II).

TABLE I. Electrocatalytic transformation of 4-chlorobenzaldehyde (**1a**, 1 mmol), malononitrile (1 mmol) and 6-aminouracil (1 mmol) into 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile (**4a**); KBr (0.1 mmol), alcohol (15 mL), zinc cathode (5 cm²), platinum anode (5 cm²)

Entry	Alcohol	<i>T</i> °C	<i>I</i> mA	Current density mA cm ⁻²	Time min	Electricity passed as parts of <i>F</i>	Yield %
1	EtOH	20	25	5	30	0.46	–
2	EtOH	60	25	5	30	0.46	–
3	EtOH	78	5	1	30	0.09	32
4	EtOH	78	10	2	15	0.09	78
5	EtOH	78	25	5	10	0.16	80
6	EtOH	78	50	10	5	0.16	70
7	MeOH	60	25	5	15	0.23	–
8	<i>n</i> -PrOH	97	25	5	15	0.23	75

TABLE II. Electrocatalytic multicomponent synthesis of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives (**4a–j**) under the optimized conditions; aromatic aldehyde (1 mmol), malononitrile (1 mmol), 6-aminouracil (1 mmol), KBr (0.1 mmol), ethanol (15 mL), zinc cathode (5 cm²), platinum anode (5 cm²), 78 °C

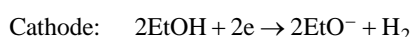
Compd.	Ar	R	X	Time min	Electricity passed as parts of <i>F</i>	Yield ^a %
4a	4-ClC ₆ H ₄	H	O	10	0.16	80
4b	4-OCH ₃ C ₆ H ₄	H	O	15	0.23	78
4c	3-NO ₂ C ₆ H ₄	H	O	10	0.16	85
4d	4-NO ₂ C ₆ H ₄	H	O	8	0.12	84
4e	4-ClC ₆ H ₄	H	S	12	0.19	82
4f	4-NO ₂ C ₆ H ₄	H	S	10	0.16	86
4g	4-ClC ₆ H ₄	CH ₃	O	20	0.31	71
4h	3-BrC ₆ H ₄	CH ₃	O	20	0.31	70
4i	3-NO ₂ C ₆ H ₄	CH ₃	O	20	0.31	76
4j	4-NO ₂ C ₆ H ₄	CH ₃	O	20	0.31	72

^aIsolated yields

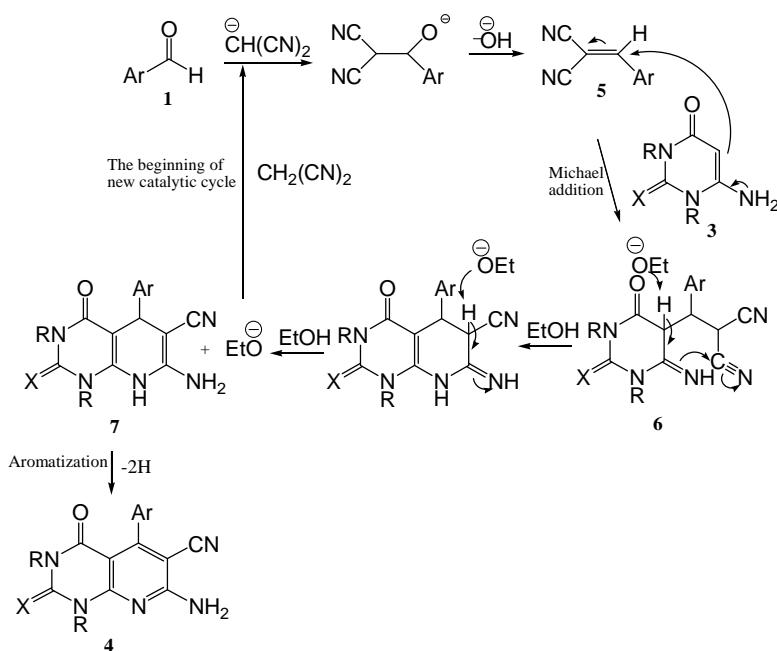
Taking into consideration the above results, the following mechanism for the electrocatalytic chain transformation of aromatic aldehydes **1**, malononitrile **2** and 6-aminouracils **3** into the corresponding 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile **4** is proposed.

As the initiation step of the catalytic cycle, the deprotonation of an ethanol molecule at the cathode leads to the formation of an ethoxide anion. The subsequent reaction in solution between the ethoxide anion and malononitrile gives rise to a malononitrile anion (Scheme 2). Then Knoevenagel condensation of the malononitrile anion with an aromatic aldehyde occurs in the solution with the

elimination of a hydroxide anion and formation of arylidene malononitrile **5**. The subsequent ethoxide-promoted Michael addition of 6-aminouracil **3** to electron deficient Knoevenagel adduct **5** followed by intramolecular cyclization and tautomerization of intermediate **6** leads to intermediate **7** with the regeneration of the ethoxide anion, which continues the catalytic chain process by interaction with the next molecule of malononitrile. The intermediate **7** is oxidized to afford the fully aromatized compound **4** (Scheme 3).



Scheme 2. Formation of ethoxide anion at the cathode.



Scheme 3. A proposed mechanism for the electrocatalytic transformation of aromatic aldehydes **1**, malononitrile **2** and 6-aminouracils **3** into the corresponding pyrido[2,3-*d*]pyrimidine **4**.

EXPERIMENTAL

General

All reagents were purchased from Merck or Fluka and used without further purification. Melting points were obtained in open capillary tubes and were measured on an Electrothermal IA 9100 apparatus. The IR spectra were recorded in KBr pellets on a Shimadzu FT-IR 8600 spectrophotometer. The ¹H- and ¹³C-NMR spectra were determined on a Bruker DRX-400 Avance instrument at 400 and 100 MHz, respectively.

The physical, analytical and spectral data for compounds **4a–j** are given in the Supplementary material to this paper.

*General procedure for electrochemical synthesis of pyrido[2,3-*d*]pyrimidines 4a–j*

A mixture of aromatic aldehyde (1 mmol), malononitrile (0.66 g, 1 mmol), 6-aminouracil (1 mmol), and KBr (0.1 g, 1 mmol) in EtOH (15 mL) was electrolyzed at 78 °C in an undivided cell equipped with a magnetic stirrer, a platinum anode and a zinc cathode under a constant current density of 5 mA cm⁻². The progress of the reaction was monitored by thin layer chromatography. After the electrolysis was finished, the mixture was filtered and the filter cake was washed twice with an ethanol/water (1:1) solution to yield pure products **4a–j**.

CONCLUSION

In conclusion, the electrocatalytic transformation of aromatic aldehydes, malononitrile and 6-aminouracils into the corresponding pyrido[2,3-*d*]pyrimidines, in comparison with conventional methods, has advantages, such as: *i*) *in situ* generation of base and the avoidance of pollution or hazardous chemicals or the addition of base or pro-base, *ii*) a very fast one-pot reaction in good to excellent yields under milder conditions, *iii*) the procedure utilizes inexpensive reagents, simple equipment and convenient work-up and *iv*) it is easily performed and is fully beneficial from the viewpoint of being an ecological method for organic syntheses and suitable for large-scale processes.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data of compounds **4a–j** are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

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ИЗВОД

ЕЛЕКТРОКАТАЛИТИЧКА ВИШЕКОМПОНЕНТНА РЕАКЦИЈА АМИНОУРАЦИЛА, АЛДЕХИДА И МАЛОНОНИТРИЛА: ЕФИКАСАН ПРИСТУП СИНТЕЗИ ДЕРИВАТА 7-АМИНО-ПИРИДО[2,3-*d*]ПИРИМИДИН-6-КАРБОНИТРИЛА

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Електрокаталитичком вишекомпонентном трансформацијом 6-аминоурацила, ароматичних алдехида и малонитрила у етанолу, у неподељеној ћелији у присуству калијум-бромида као електролита, добијени су деривати 7-амино-пиридо[2,3-*d*]пири-мидин-6-карбонитрила у кратком реакционом времену (8–20 min) у добром до високом приносу.

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