Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2011, **21**, 122–124
Mendeleev Communications

Electrocatalytic multicomponent assembling of aldehydes, *N*-alkyl barbiturates and malononitrile: an efficient approach to pyrano[2,3-*d*]pyrimidines

Michail N. Elinson,*[a] Alexey I. Ilovaisky,[a] Valentina M. Merkulova,[a] Tatiana A. Zaimovskaya[b] and Gennady I. Nikishin[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: + 7 499 135 5328; e-mail elinson@ioc.ac.ru*
[b] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2011.04.002

Electrochemically induced multicomponent reaction of aldehydes, *N*-alkyl barbiturates and malononitrile in alcohols in an undivided cell leads to substituted pyrano[2,3-*d*]pyrimidines in 70–80% substance yields and 700–800% current yields.

The discovery of novel synthetic methodologies to facilitate the preparation of complex organic compounds is a pivotal focal point of research activity in the field of modern organic chemistry. One approach to address this challenge involves the development of multicomponent reactions (MCR). Such a strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent and atom efficient nature.[1,2] In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[3] Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in heterocyclic MCR methodology and, according to current synthetic requirements, ecologically pure multicomponent procedures are particularly welcome.

Pyrano[2,3-*d*]pyrimidines have received considerable attention over the past years due to their wide range of the diverse pharmacological action such as antitumor,[4,5] cardiotonic,[6] hepatoprotective,[7] antihypertensive[7] and antibronchitic[8] activity.

The general procedures for the preparation of pyrano[2,3-*d*]-pyrimidines usually include the reaction of benzylidenemalononitriles with barbituric acids in the presence of base catalysts,[9,10] or in ionic liquids,[11] or under microwave irradiation.[12] The more complex example of their synthesis from aldehydes, malononitrile and *N*,*N*′-dialkyl barbiturates is also known. Thus, reaction of benzaldehyde and malononitrile in distilled water at 80 °C for 3 h resulted in benzylidenemalononitrile. Further, *N*,*N*′-dimethylbarbiturate was added into the same reaction vessel and continuing heating at 80 °C for additional 8.5 h afforded corresponding pyrano-[2,3-*d*]pyrimidine.[13] As to our knowledge the only one multicomponent procedure with using special equipment and microwave irradiation for the synthesis of two substituted pyrano-[2,3-*d*]pyrimidines from aldehydes, malononitrile and *N*-alkyl barbiturates is described.[14] Thus, the all known procedures for the synthesis of pyrano[2,3-*d*]pyrimidine system are worth of note, although MCR methodology was not still widely developed in its construction.

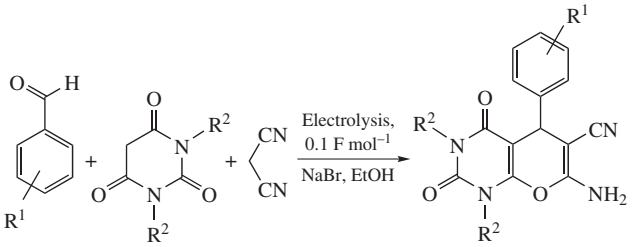
Here, we report our results on electrocatalytic multicomponent transformation of aldehydes, *N*,*N*′-dialkylbarbiturates and malononitrile into substituted pyrano[2,3-*d*]pyrimidines in an undivided cell in alcohols in the presence of sodium bromide as electrolyte (Scheme 1, Table 1). The present study is a continuation of our recent investigations on electrolytic chain transformations of aldehydes and CH-acids.[15–18]

Table 1 Electrocatalytic transformation of aldehyde **1d**, *N*,*N*′-dimethylbarbituric acid **2a** and malononitrile into pyrano[2,3-*d*]pyrimidine **3d**.[a]

Alcohol	*T*/°C	*I*/mA	Current density/ mA cm^{-2}	*t*/min	Electricity passed/ F mol^{-1}	Yield of **3d** (%)[b]
EtOH	20	25	5	32	0.1	38
EtOH	78	25	5	32	0.1	81
EtOH	78	25	5	48	0.15	78
EtOH	78	15	3	54	0.1	75
EtOH	78	50	10	16	0.1	73
EtOH	78	50	10	24	0.15	70
MeOH	60	25	5	32	0.1	55
PrOH	97	25	5	32	0.1	73

[a] 5 mmol of **1d**, 5 mmol of **2a**, 5 mmol of malononitrile, 0.5 mmol of NaBr, 20 ml of alcohol, iron cathode (5 cm^2), graphite anode (5 cm^2). [b] Yield of isolated product.

First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the assembling of 4-chlorobenzaldehyde **1d**, *N*,*N*′-dimethylbarbituric acid **2a** and malononitrile into 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-



1a–h **2a**,**b** **3a–j**

1a R^1 = H
1b R^1 = 4-Me
1c R^1 = 4-MeO
1d R^1 = 4-Cl
1e R^1 = 2-Cl
1f R^1 = 3-Br
1g R^1 = 4-F
1h R^1 = 4-NO_2

2a R^2 = Me
2b R^2 = Et

3a R^1 = H, R^2 = Me, 71%
3b R^1 = 4-Me, R^2 = Me, 75%
3c R^1 = 4-MeO, R^2 = Me, 73%
3d R^1 = 4-Cl, R^2 = Me, 81%
3e R^1 = 2-Cl, R^2 = Me, 79%
3f R^1 = 3-Br, R^2 = Me, 75%
3g R^1 = 4-F, R^2 = Me, 77%
3h R^1 = 4-NO_2, R^2 = Me, 73%
3i R^1 = 2-Cl, R^2 = Et, 76%
3j R^1 = 4-F, R^2 = Et, 73%

Scheme 1

1,3,4,5-tetrahydro-2,4-dioxo-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile **3d** was carefully studied (Table 1).

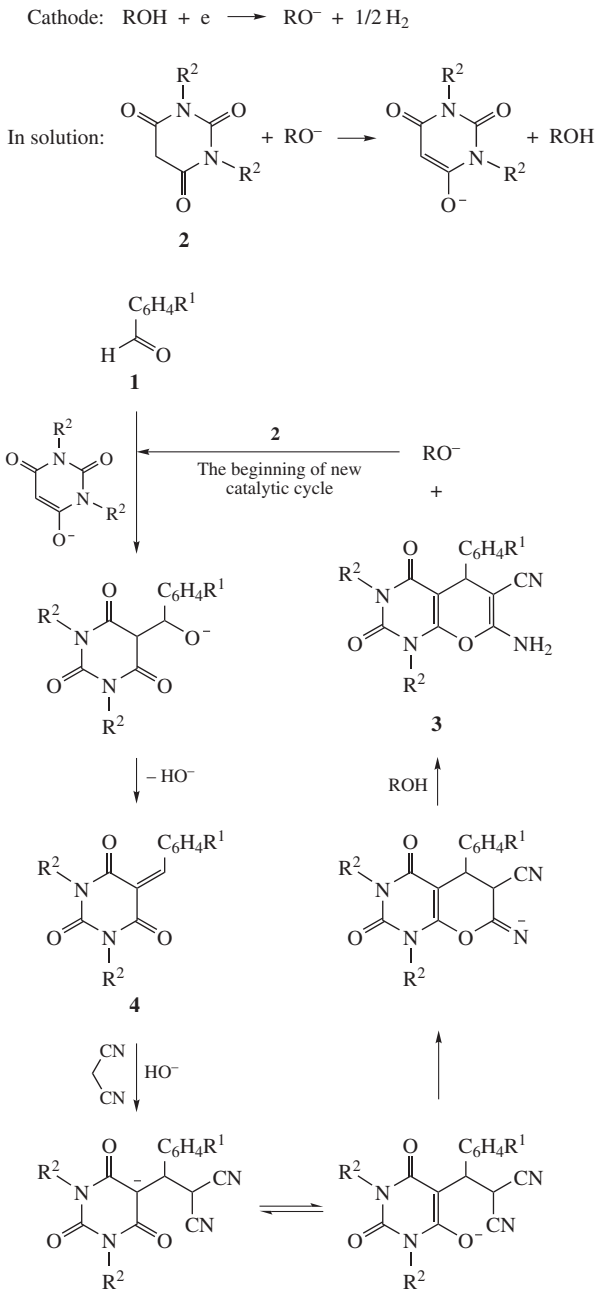
The current density 5 mA cm^{-2} (I = 25 mA, electrodes surface 5 cm^2) was found to be the optimum and provided the highest yield (81%) of the product **3d** in ethanol at 78 °C. Raising of current density up to 10 mA cm^{-2} (I = 50 mA) results in a slight decrease of the yield, what may be caused by acceleration of undesired direct electrochemical processes leading to oligomerization of the reactants. The low yield and insufficient conversion of starting compounds were observed when electrolysis was carried out at 20 °C.

Among alcohols tested, EtOH is preferable in view of easy isolation of reaction products by simple filtration after electrolysis.

Under the optimal conditions thus found (current density 5 mA cm^{-2}, 0.1 F mol^{-1} passed, EtOH as a solvent, 78 °C), the electrolysis of aldehydes **1a**–**h**, barbituric acids **2a**,**b** and malononitrile in ethanol at 78 °C in an undivided cell gives rise to corresponding pyrano[2,3-*d*]pyrimidines **3a**–**j** in 71–81% substance yields and 710–810% current yields in ~30 min reaction period (Scheme 1).†

Taking into consideration the above results and the data on the mechanisms of electrocatalytic chain cyclizations of tetracyanocyclopropanes[19] and mechanism of the electrocatalytic chain transformation of aldehydes and C–H acids,[15–18,20] the following mechanism for the electrocatalytic chain transformation of aldehydes **1**, barbituric acids **2** and malononitrile into pyrano[2,3-*d*]-pyrimidines **3** is proposed (Scheme 2). As the initiation step of the catalytic cycle, deprotonation of an alcohol at the cathode leads to formation of alkoxide anion. Its subsequent reaction in solution with barbituric acid **2** gives rise to barbituric acid anion. Then Knoevenagel condensation of aldehyde **1** with barbituric acid anion takes place in the solution with the elimination of hydroxide anion and formation of the corresponding 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **4**.[21] The subsequent hydroxide-promoted Michael addition of malononitrile to electron-deficient Knoevenagel adduct **4** followed by intramolecular cyclization results in corresponding pyrano[2,3-*d*]pyrimidine **3** with regeneration of alkoxide anion at the last step, which continues the catalytic chain process by the interaction with the next molecule of barbituric acid. Thus, the generation of even single alkoxide anion at the cathode is theoretically sufficient for total conversion of equimolar quantities of aldehyde, barbituric acid and malononitrile into corresponding pyrano[2,3-*d*]pyrimidine system.

In conclusion, the simple electrocatalytic system can produce, under neutral and mild conditions, a fast (~30 min) and selective multicomponent transformation of aldehydes, barbituric acids and malononitrile into 7-amino-1,3-dialkyl-5-aryl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitriles in 70–80% substance yields and 700–800% current yields. This novel electrocatalytic chain process opens an efficient and convenient way to



Scheme 2

cyanofunctionalized pyrano[2,3-*d*]pyrimidines – the promising compounds for the different biomedical applications. The procedure requires simple equipment and an undivided cell; it is easily carried out and is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes. This efficient electrocatalytic protocol represents novel synthetic concept for multicomponent reactions strategy and allows one to combine the synthetic virtues of conventional MCR with ecological benefits and convenience of facile electrocatalytic procedure proposed; therefore, makes the MCR strategy a step closer to a notion of 'ideal synthesis'.[22]

This work was supported by the Presidential Scholarship Program for State Support of Leading Science Schools of the Russian Federation (project no. 4945.2010.3).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.04.002.

† *General procedure.* A solution of benzaldehyde **1** (5 mmol), *N*,*N*′-dialkylbarbituric acid **2** (5 mmol), malononitrile (0.33 g, 5 mmol) and sodium bromide (0.05 g, 0.5 mmol) in ethanol (20 ml) was electrolyzed in an undivided cell equipped with a magnetic stirrer, reflux condenser, a graphite anode and an iron cathode at 78 °C under a constant current density of 5 mA cm^{-2} (I = 25 mA, electrodes square 5 cm^2) until the catalytic quantity of 0.1 F mol^{-1} of electricity was passed. After the electrolysis was finished, the solution was filtered to isolate the solid product **3**, which was then twice rinsed with an ice-cold ethanol/water solution (9:1, 5 ml), and dried under reduced pressure. For **3i**,**j**, after the electrolysis was finished, the solution was evaporated to dryness, the residue was then rinsed with an ice-cold ethanol/water solution (9:1, 3 ml) and filtered to isolate the solid product **3**, which was washed with ice-cold ethanol/water solution (9:1, 3 ml), diethyl ether (5 ml) and dried under reduced pressure.

For characteristics of **3a**–**j**, see Online Supplementary Materials.

References

1 R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471.
2 L. Weber, *Drug Discovery Today*, 2002, **7**, 143.
3 L. A. Thompson, *Curr. Opin. Chem. Biol.*, 2000, **4**, 324.
4 E. M. Grivaky and S. Lee, *J. Med. Chem*., 1980, **23**, 327.
5 J. A. Valderrama, P. Colonelli, D. Vásquez, M. F. González, J. A. Rodríguez and C. Theoduloz, *Bioorg. Med. Chem.*, 2008, **16**, 10172.
6 D. Heber, C. Heers and U. Ravens, *Pharmazie*, 1993, **48**, 537.
7 S. Furuya and T. Ohtaki, *Eur. Pat. Appl.* EP 608565, 1994.
8 M. C. Bagley, D. D. Hughes, M. C. Lubinu, E. A. Merrit, P. H. Taylor and N. C. O. Tomkinson, *QSAR Comb. Sci.*, 2004, **23**, 859.
9 Yu. A. Sharanin and G. V. Klokol, *Zh. Org. Khim.*, 1984, **20**, 2448 (in Russian).
10 F. Seeliger, S. T. A. Berger, G. Y. Remennikov, K. Polborn and H. Mayr, *J. Org. Chem.*, 2007, **72**, 9170.
11 J. Yu and H. Wang, *Synth. Commun*., 2005, **35**, 3133.
12 Y. Gao, S. Tu, T. Li, X. Zhang, S. Zhu, F. Fang and D. Shi, *Synth. Commun*., 2004, **34**, 1295.
13 A. Shaabani, S. Samadi and A. Rahmati, *Synth. Commun.*, 2007, **37**, 491.
14 I. Devi, B. S. D. Kumar and P. J. Bhuyan, *Tetrahedron Lett.*, 2003, **44**, 8307.
15 M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, R. F. Nasybullin, S. V. Gorbunov and G. I. Nikishin, *Electrochem. Commun.*, 2006, 1567.
16 M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, R. F. Nasybullin, S. V. Gorbunov, F. M. Miloserdov, N. O. Stepanov and G. I. Nikishin, *Tetrahedron Lett*., 2006, **47**, 7629.
17 M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, R. F. Nasybullin, S. V. Gorbunov, F. M. Miloserdov and G. I. Nikishin, *Eur. J. Org. Chem.*, 2006, 4335.
18 M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov, A. I. Ilovaisky, S. K. Feducovich, P. A. Belyakov and G. I. Nikishin, *Adv. Synth. Catal.*, 2008, **350**, 59.
19 M. N. Elinson, S. K. Feducovich, T. L. Lizunova and G. I. Nikishin, *Tetrahedron*, 2000, **56**, 3063.
20 D. A. White, *J. Electrochem. Soc.*, 1977, **124**, 1177.
21 S. Patai and Y. Israeli, *J. Chem. Soc.*, 1960, 2025.
22 P. A. Wender, S. T. Handy and D. L. Wright, *Chem. Ind. (London)*, 1997, 765.

Received: 15th December 2010; Com. 10/3642