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Electrocatalytic one-pot multicomponent assembly of aldehydes, 2,4-dihydro-3*H*-pyrazol-3-ones and kojic acid

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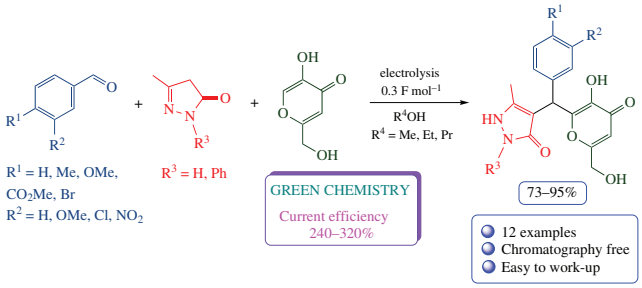
Electrocatalytic transformation of aldehydes, 2,4-dihydro-3*H*-pyrazol-3-ones and kojic acid in alcohols occurs in an undivided cell in the presence of sodium halides, selectively affording substituted 4-{[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-ones in 73–95% yields and with 240–320% current efficiency. The multicomponent process provides a facile and efficient way to the new type of systems with heterocyclic moieties separated by aryl-substituted C-spacer. The product structure has been confirmed by X-ray diffraction data.



Keywords: electrocatalysis, multicomponent process, tandem reaction, aldehydes, 2,4-dihydro-3*H*-pyrazol-3-one, kojic acid.

In the last few decades, organic electrochemistry has become a new useful method with important synthetic and ecological advantages.[1] Nevertheless, the practical application of electrochemical reactions is typically limited by their technical complexity and long processing time. In our investigation in this area, we have found a new type of transformation, namely electrocatalytic chain assembly of organic molecules induced by an electrogenerated base as a catalyst in undivided cell.[2] We have applied this procedure to the synthesis of pharmacologically relevant 2-amino-4*H*-chromene derivatives.[3] The use of a simple undivided electrochemical cell makes this method suitable for large-scale processes due to its catalytic mechanism and the employment of electricity as a cheap and environmentally responsible factor. The method is promising for initiation of base-activated multicomponent reactions (MCRs), since it combines synthetic virtues of the MCR strategy as well as the ecological benefits and convenience of electrocatalytic procedure.[4]

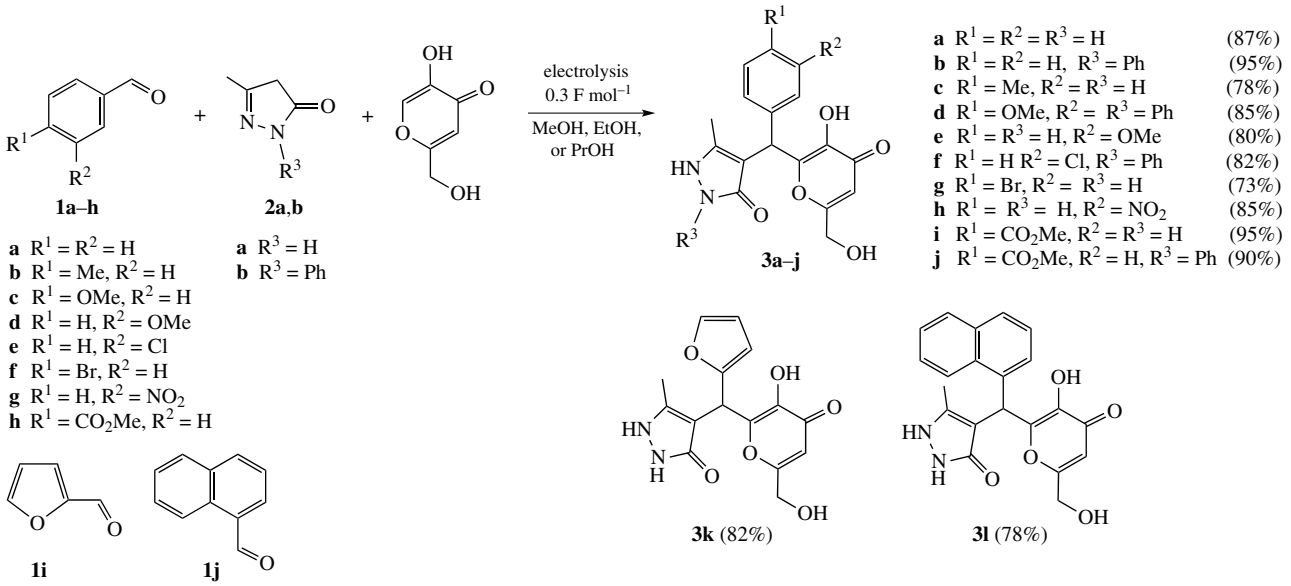
Heterocycles represent key structural components for medicinal chemistry[5] and are found in numerous bioactive molecules such as enzymes, vitamins and natural products as well as serve as constituents of pharmaceuticals with antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, antiallergic, anti-HIV and anticancer activity.[6] Among the pharmacologically relevant nitrogen heterocycles, functionally substituted pyrazolinone scaffold has attracted special attention.[7,8] Thus, the first truly synthetic pain reliever Antipyrin is an *N*-methyl derivative of 3-methyl-1-phenyl-3-pyrazolin-5-one and represents an approved nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic activities.[9] Numerous 4-substituted 3-methyl-2-pyrazolin-5-ones are known as neuroleptics.[10]

On the other hand, kojic acid, or 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, is a fungal methabolite produced, for example, by *Aspergillus oryzae* in the rice fermentation process[11,12] and used as a chelation agent as well as an inhibitor of pigment formation in the area of food and cosmetics.[13] Kojic acid derivatives possess anticonvulsant,[14] anti-inflammatory[15] and anti-HIV activities[16] as well as are known as inhibitors of oxidases,[17] tyrosinase[18] and aminopeptidase.[19] The introduction of both medicinally privileged pyrazolinone and kojic acid scaffolds into one molecule can combine and enhance their pharmacological activity.

We have realized some electrochemicaly induced multicomponent transformations of carbonyl compounds and different CH-acids.[20] Here we report a new selective electrocatalytic multicomponent assembly of aldehydes **1a–j**, 2,4-dihydro-3*H*-pyrazol-3-ones **2a**,**b** and kojic acid into earlier unknown substituted 4-{[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-ones **3a–l** in alcoholic media in an undivided cell (Scheme 1 and Table 1).

First, to evaluate the synthetic potential of the procedure and to optimize the electrolysis conditions, the multicomponent assembly of benzaldehyde **1a**, 2,4-dihydro-3*H*-pyrazol-3-one **2a** and kojic acid was investigated (see Table 1).

Data in Table 1 indicate, that the current density 5 mA cm^{-2} (*i.e.* I = 25 mA with electrodes area 5 cm^2) and the temperature near to the solvent boiling point appear to be optimal and result in the highest yield of product **3a** (entry 4, 87% with current efficiency 290%). An increase in the current density up to 10 mA cm^{-2} (I = 50 mA) leads to a decrease in both the current efficiency and the substance yield. A decrease in the current density to 2 mA cm^{-2} corresponding to I = 10 mA also diminished both the current efficiency and the product yield, likely due to the insufficient initiation of the electrochemically induced chain reaction.



Scheme 1

Table 1 Electrocatalytic multicomponent assembly of benzaldehyde **1a**, 2,4-dihydro-3*H*-pyrazol-3-one **2a** and kojic acid.[a]

Entry	Solvent	*T*/°C	*I*/mA	Current density/ mA cm^{-2}	*t*/min	Electricity passed/ F mol^{-1}	Yield of **3a** (%)[b]	Current efficiency (%)
1	MeOH	25	25	5	64	0.2	12[c]	60
2	MeOH	65	25	5	64	0.2	53	265
3	MeOH	65	25	5	96	0.3	81	270
4	EtOH	78	25	5	96	0.3	87	290
5	EtOH	78	25	5	128	0.4	84	210
6	*n*-PrOH	97	25	5	96	0.3	78	260
7	EtOH	78	10	2	240	0.3	73	243
8	EtOH	78	50	10	48	0.3	68	227
9	EtOH	78	50	10	64	0.4	82	205
10	EtOH[d]	78	25	5	96	0.3	81	270

[a] Undivided cell, iron cathode (5 cm^2), graphite anode (5 cm^2), benzaldehyde **1a** (5 mmol), 2,4-dihydro-3*H*-pyrazol-3-one **2a** (5 mmol), kojic acid (5 mmol), NaBr (1 mmol) and alcohol (20 ml). [b] Isolated yield. [c] ^{1}H NMR yield. [d] NaI used as an electrolyte.

Under the optimized conditions, benzaldehydes **1a–j**, 2,4-dihydro-3*H*-pyrazol-3-ones **2a**,**b** and kojic acid were transformed into the corresponding products **3a–l** in 73–95% yields with current efficiency 243–317%.† After the electrolysis was completed, for all the runs the reaction mixture was concentrated to one fifth of its initial volume, the solid product was crystallized, filtered off, rinsed twice with an ice-cold ethanol–water and dried *in vacuo*. The structure of new compounds **3a–l** was confirmed by ^{1}H, ^{13}C NMR and IR spectroscopy, mass spectrometry and elemental analysis (see Online Supplementary Materials). The structure of product **3a** was additionally confirmed by X-ray diffraction data (Figure 1).‡

With all these data in hand and taking into consideration the mechanism of multicomponent tandem Knoevenagel–Michael reaction,[21] we proposed the following mechanism for the electrocatalytic multicomponent assembly reaction (Scheme 2, compounds **1a** and **2a** in ethanol are taken as an example). The first step of this electrochemically induced process is the deprotonation of ethanol at the cathode, affording ethoxide anion. Its reaction with 2,4-dihydro-3*H*-pyrazol-3-one **2a** results in 2-pyrazolin-5-one anion **A**, which reacts in the solution with benzaldehyde **1a** with elimination of hydroxide anion and formation of the Knoevenagel adduct **4**.[22] Finally, the hydroxide

† *General procedure for synthesis of compounds* **3a–l**. A solution of aldehyde (5 mmol), appropriate 2,4-dihydro-3*H*-pyrazol-3-one (5 mmol), kojic acid (5 mmol) and sodium bromide (0.1 g, 1 mmol) in ethanol (20 ml) was subjected to electrolysis in an undivided cell with a magnetic stirrer, graphite anode and iron cathode at 78 °C under a constant current density of 5 mA cm^{-2} (I = 25 mA, electrodes area 5 cm^2) until the catalytic quantity of 0.3 F mol^{-1} of electricity was passed. Then the reaction mixture was concentrated to one fifth of its initial volume (to *ca.* 4 ml) and chilled to 0 °C. The crystallized solid product was filtered off, rinsed twice with ice-cold ethanol–water (8 : 2, 4 ml) and dried *in vacuo*.

*4-{[3-Hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](phenyl)-methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one* **3a**. Yield 1.43 g (87%), mp 226–227 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.87 (s, 3H, Me), 4.22 (s, 2H, CH$_2$), 5.49–5.72 (m, 2H, CH, OH), 6.33 (s, 1H, CH), 7.12 (d, 2H, 2CH^{Ar}, ^3J 7.3 Hz), 7.20 (t, 1H, CH^{Ar}, ^3J 7.3 Hz), 7.29 (t, 2H, 2 CH^{Ar}, ^3J 7.3 Hz), 8.98 (br s, 1H, OH), 9.68–11.76 (br. s, 2H, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.1, 36.9, 59.6, 99.4, 109.1, 126.4, 127.7 (2C), 128.4 (2C), 138.2, 140.2, 141.5, 150.8, 159.8, 167.3, 173.7. MS, *m*/*z* (%): 328 (100) [M$^+$], 251 (8), 231 (55), 227 (87), 185 (67), 157 (22), 128 (68), 109 (31), 77 (55), 29 (67). IR (KBr, ν/cm^{-1}): 3383, 3225, 3032, 2903, 1621, 1583, 1500, 1446, 1206, 702. Found (%): C, 62.05; H, 4.86; N, 8.45. Calc. for $C_{17}H_{16}N_2O_5$ (%): C, 62.19; H, 4.91; N, 8.53.

‡ *Crystal data for* **3a**. $C_{17}H_{16}N_2O_5 \cdot 2C_2H_6O$, triclinic, space group $P\bar{1}$, a = 7.4689(19), b = 8.235(2) and c = 17.198(4) Å, α = 79.683(6), β = 89.451(6) and γ = 83.594(6)°, V = 1034.2(5) Å^3, Z = 2, T = 120 K, μ(MoKα) = 0.102 mm^{-1}, d_{calc} = 1.350 g cm^{-3}, 12152 reflections measured (4.82° ≤ 2θ ≤ 56.56°), 5103 unique (R_{int} = 0.0852, R_σ = 0.1188), which were used in all calculations. The final R_1 was 0.0572 [$I > 2\sigma(I)$] and wR_2 was 0.1270.

CCDC 1965816 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

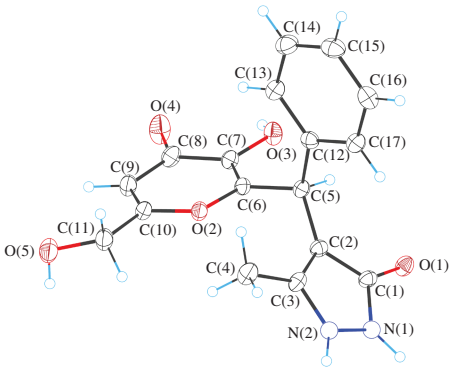
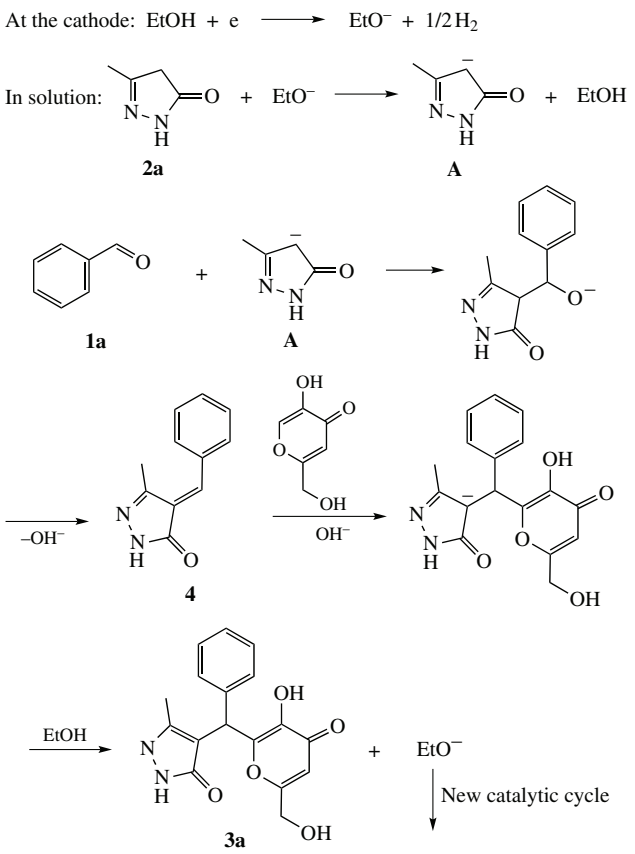


Figure 1 Molecular structure of compound **3a**. Thermal ellipsoids are drawn at a 50% probability level.

anion-promoted Michael addition of kojic acid to the electron deficient Knoevenagel adduct **4** affords product **3a** with regeneration of ethoxide anion. The reaction of the latter with the next molecule of **2a** continues the catalytic cycle.

The reaction at the anode is typical of the system alcohol–NaBr, does not take part in the electrochemically induced process and has been already discussed.[3(*b*)]

In summary, this new one-pot electrochemically induced multicomponent process is simple and efficient way to the earlier unknown substituted 4-{[3-hydroxy-6-(hydroxymethyl)-4-oxo-4*H*-pyran-2-yl](aryl)methyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-ones. The products contain 1,2-dihydro-3*H*-pyrazol-3-one and kojic acid moieties separated by aryl-substituted C-spacer, and can be promising compounds for biomedical applications, such as anticonvulsant, anti-AIDS and anti-inflammatory remedies. The synthetic procedure utilizes simple equipment, an undivided cell and available starting compounds, it is easily carried out and the product isolation is not complicated, which makes this method suitable for environmentally benign diversity-oriented large-scale processes, including creation of new potential drug libraries.



Scheme 2

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.031.

References

1 (*a*) *Organic Electrochemistry: Revised and Expanded*, 5th edn., eds. O. Hammerich and B. Speiser, CRC Press, Boca Raton, FL, 2015; (*b*) M. Yan, Y. Kawamata and P. S. Baran, *Angew. Chem., Int. Ed.*, 2018, **57**, 4149; (*c*) G. I. Nikishin, M. N. Elinson and I. V. Makhova, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1716.
2 M. N. Elinson, S. K. Feducovich, T. L. Lizunova and G. I. Nikishin, *Tetrahedron*, 2000, **56**, 3063.
3 (*a*) 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**, 591; (*b*) M. N. Elinson, A. N. Vereshchagin, Yu. E. Anisina, S. K. Krymov, A. N. Fakhrutdinov and M. P. Egorov, *Mendeleev Commun.*, 2019, **29**, 581.
4 (*a*) M. N. Elinson, A. N. Vereshchagin and F. V. Ryzhkov, *Chem. Rec.*, 2016, **16**, 1950; (*b*) M. N. Elinson, A. N. Vereshchagin, Yu. E. Anisina, A. S. Goloveshkin, I. E. Ushakov and M. P. Egorov, *Mendeleev Commun.*, 2018, **28**, 372; (*c*) M. N. Elinson, A. N. Vereshchagin, Y. E. Anisina, A. S. Goloveshkin, I. E. Ushakov and M. P. Egorov, *Russ. Chem. Bull., Int. Ed.*, 2018, **67**, 1695 (*Izv. Akad. Nauk, Ser. Khim.*, 2018, 1695).
5 P. Arora, V. Arora, H. S. Lamba and D. Wadhwa, *Int. J. Pharm. Sci. Res.*, 2012, **3**, 2947.
6 A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones and O. Fadeyi, *Org. Biomol. Chem.*, 2016, **14**, 6611.
7 R. H. Wiley and P. F. Wiley, *Pyrazolones, Pyrazolidones, and Derivatives*, Interscience Publishers, New York, 1964.
8 J. Elguero, in *Comprehensive Heterocyclic Chemistry II*, 2nd edn., eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon, Oxford, 1996, vol. 3, pp. 1–75.
9 R. N. Brogden, *Drugs*, 1986, **32** (4 Suppl.), 60.
10 L. D. Wise, D. E. Butler, H. A. DeWald, D. M. Lustgarten, I. C. Pattison, D. N. Schweiss, L. L. Coughenour, D. A. Downs, T. G. Heffner and T. A. Pugsley, *J. Med. Chem.*, 1987, **30**, 1807.
11 R. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 1046.
12 S. Parvez, M. Kang, H.-S. Chung, C. Cho, M.-C. Hong, M.-K. Shin and H. Bae, *Phytother. Res.*, 2006, **20**, 921.
13 S. Shafiquzzaman, in *New and Future Developments in Microbial Biotechnology and Bioengineering. Pennicillium System Properties and Applications*, eds. V. G. Gupta and S. Rodrigues-Couto, Elsevier, 2018, pp. 69–94.
14 M. D. Aytemir, E. Septioğlu, and U. Çaliş, *Arzneim. Forsch.*, 2010, **60**, 22.
15 H. S. Rho, S. M. Ahn, D. S. Yoo, M. K. Kim, D. H. Cho and J. Y. Cho, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6569.
16 R. Tanaka, H. Tsujii, T. Yamada, T. Kajimoto, F. Amano, J. Hasegawa, Y. Hamashima, M. Node, K. Katoh and Y. Takebe, *Bioorg. Med. Chem.*, 2009, **17**, 5238.
17 G. A. Burdock, M. G. Soni and I. G. Carabin, *Regul. Toxicol. Pharmacol.*, 2001, **33**, 80.
18 G. Karakaya, A. Türe, A. Ercan, S. Öncül and M. D. Aytemir, *Bioorg. Chem.*, 2019, **88**, 102950.
19 S. Ansorge, U. Bank, K. Nordhoff, M. Taeger and F. Striggow, *US Patent 2007/0037752 A1*, 2007.
20 M. N. Elinson, E. O. Dorofeeva, A. N. Vereshchagin, R. F. Nasybullin and M. P. Egorov, *Catal. Sci. Technol.*, 2015, **5**, 2384.
21 M. N. Elinson, V. M. Merkulova, A. I. Ilovaisky, F. Barba and B. Batanero, *Electrochim. Acta*, 2011, **56**, 8219.
22 S. Patai and Y. Israeli, *J. Chem. Soc.*, 1960, 2025.

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