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Electrocatalytic multicomponent assembling of aldehydes, 4-hydroxycoumarin and malononitrile: An efficient approach to 2-amino-5-oxo-4,5-dihydropyrano(3,2-*c*)chromene-3-carbonitrile derivatives

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ABSTRACT

2-Amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile derivatives are obtained in excellent yields by a simple, mild and efficient procedure by an electrocatalytic multicomponent chain transformation of aryl aldehydes, 4-hydroxycoumarin and malononitrile under neutral and mild conditions by electrolysis in an undivided cell in the presence of sodium bromide as an electrolyte.

1. Introduction

The electrosynthetically 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 chemistry [1].

Due to the electron transfer between an electrode and the substrate molecules, the formation of highly reactive intermediates is achieved under mild conditions, avoiding reductive or oxidant agents as well as acids, bases and related waste by-products so that it can be one of the various fields in green chemistry [2].

Pyrano [3,2-*c*]chromene derivatives are a class of important heterocycles with a wide range of biological properties, such as spasmolytic, diuretic, anticoagulant, anti-cancer, and anti-anaphylactic activity [3].

Many methods with different conditions have been reported. Some of these compounds have been already prepared in the presence of piperidine [4], diammonium hydrogen phosphate (DAHP) [5], K_2CO_3 under microwave irradiation [6], $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ [3], MgO [7], tetrabutylammonium bromide (TBAB) [8], DBU [9], and 3-hydroxypropanaminium acetate (HPAA) [10].

However, some of these protocols require long reaction times, multi-step reactions and complex synthetic pathways and afford products with only modest yields. Therefore, the introduction of milder, faster and more ecofriendly methods, accompanied with higher yields, are needed.

Here, we report the successful synthesis of pyrano [3,2-*c*]chromene derivatives via the direct addition of various aromatic aldehydes, malononitrile and 4-hydroxycoumarin only with an electrochemical cell and without base or any additive catalyst, in green media.

The structural evaluation studies of the compounds were performed with various experimental techniques, such as IR, mass, ^1H and ^{13}C NMR spectroscopies. Notably, in examining their synthetic performance, it has been

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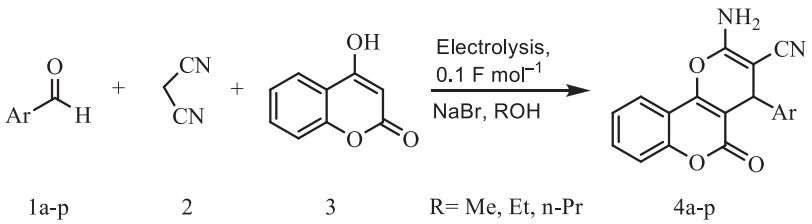


Scheme 1.

shown that this method is capable of promoting organic synthesis of pyrano [3,2-*c*]chromene derivatives in environmentally friendly conditions.

2. Experimental

2.1. Typical experimental procedure for electrocatalytic synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives

A mixture of aryl aldehyde (10 mmol), malononitrile (12 mmol), 4-hydroxycoumarin (10 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 iron cathode at 25 °C under a constant current density of 10 mA/cm^2 [electrodes square 5 cm^2], until the catalytic quantity of 0.1 F/mol of electricity was passed. 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.

2.2. Analytical data for the selected compounds

2.2.1. 2-Amino-5-oxo-4-(2,5-dimethoxyphenyl)-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4l, Entry 12)

m.p.: 238–240 °C, ^{1}H NMR (DMSO-d$_6$, 500 MHz, δ ppm): 3.63 (s, 3H, CH$_3$), 3.64 (s, 3H, CH$_3$), 4.64 (s, 1H, CH), 6.66 (d, *J* = 2.3 Hz, 1H, Ar), 6.76–6.79 (m, 1H, Ar), 6.90 (d, *J* = 8.8 Hz, 1H, Ar), 7.25 (s, 2H, NH$_2$), 7.43 (d, *J* = 8.25 Hz, 1H, Ar), 7.46 (t, *J* = 7.5 Hz, 1H, Ar), 7.67 (t, *J* = 7.5 Hz, 1H, Ar), 7.89 (d, *J* = 7.7 Hz, 1H, Ar); ^{13}C NMR (DMSO-d$_6$, 125 MHz, δ ppm): 55.2, 56.4, 56.8, 103.1, 112.2, 112.9, 113.1, 115.7, 116.4, 119.2, 122.2, 124.5,125, 131.9, 132.6, 151.5, 152.0, 153.1, 153.9, 158.5, and 159.4; IR (KBr, cm^{-1}): 3403–3322(NH$_2$), 3192 (CH aromatic), 2195 (C≡N), 1708(C=O), MS (EI, 70 eV) *m*/*z* (%) =376 (M$^+$, 23), 361 (14), 345 (42), 279 (100), 239 (26), 215 (13), and 121 (24) (Table 2).

2.2.2. 2-Amino-5-oxo-4-o-tolyl-4,5-dihydropyrano[3,2-c]chromene-3- carbonitrile (4n, Entry 14)

m.p.: 262–266 °C, ^{1}H NMR (DMSO-d$_6$, 500 MHz, δ ppm): 2.48 (s, 3H, CH$_3$), 4.73 (s, 1H, CH), 6.90–7.20 (m, 4H, Ar), 7.34 (s, 2H, NH$_2$), 7.41 (d, *J* = 8.3 Hz, 1H, Ar), 7.46 (t, *J* = 7.6 Hz, 1H, Ar), 7.67 (t, *J* = 7.25, 1H, Ar), 7.89 (d, *J* = 7.8 Hz, 1H, Ar); ^{13}C NMR (DMSO-d$_6$, δ ppm125 MHz): 19.0, 57.9, 104.5, 122.8, 116.4, 119.1, 122.3, 124.6, 126.6, 123.6, 126.7, 127.8, 130.0, 132.7, 135.2, 142.2, 152.0, 153.4, 157.7, 159.5; IR (KBr, cm^{-1}): 3400- 3283 (NH$_2$), 3179 (CH aromatic), 2202 (C≡N), 1709 (C=O), MS (EI, 70 eV) *m*/*z* (%) = 330 (M$^+$, 18), 249 (24), 240 (17), 239 (100), 121 (21).

3. Results and discussion

Our investigations of the electrocatalytic multicomponent chain transformation of aryl aldehydes, 4-hydroxycoumarin and malononitrile into 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile derivatives under neutral and mild conditions by electrolysis in an undivided cell began with the optimization of the reaction conditions. The synthetic pathway is shown in Scheme 1.

Table 1 lists the representative data obtained for the synthesis of 2-amino-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **4a** from benzaldehyde **1a**, malononitrile **2** and 4-hydroxycoumarin **3** under various experimental conditions. The reaction is performed in alcoholic solvents in the presence of sodium bromide as an electrolyte. The reaction mixture was stirred at room temperature and the progress was monitored by TLC.

Various current quantities were applied under the mentioned conditions. Excellent conversions of the starting materials were obtained under 10 mA/cm^2 current densities after 0.1 F/mol of electricity had passed. The current density of 10 mA/cm^2, *I* = 50 mA, electrode surface

Table 1
Optimization of reaction conditions for synthesis of 2-amino-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile at room temperature.

Entry	*I* (mA)	Current density (mA/cm^2)	Time (min)	Catalyst	Solvent	Electricity passed (F/mol)	Yield (%)
1	5	1	375	–	EtOH	0.1	62
2	10	2	190	–	EtOH	0.1	70
3	20	4	87	–	EtOH	0.1	82
4	50	10	35	–	EtOH	0.1	92
5	75	15	25	–	EtOH	0.1	80
6	50	10	35	–	MeOH	0.1	80
7	50	10	35	–	*n*-PrOH	0.1	83
8	–	–	35	Na	EtOH	–	0

5 cm^2 were found to be the optimal conditions for the electrochemically induced chain process and allowed the highest yield of **4a**. An increase in the current density up to 15 mA/cm^2 (I = 75 mA) resulted in a slight decrease in the reaction yield, and may be a result of the activation of the undesired direct electrochemical processes that led to the oligomerization of the starting material.

In addition, various solvents were employed for the aforementioned reaction and high conversion (92%) was observed using ethanol at room temperature for 35 min under aerobic conditions.

In order to compare the electrocatalytic method with the chemical one, we used sodium metal as a catalyst (10 mol%) for the preparation of **4a**, but the desired product was not observed.

We can see in Table 1 that the electrocatalytic method has some advantages over other chemical methods: it is green and environmentally friendly, and the catalyst is produced and consumed in the reaction medium.

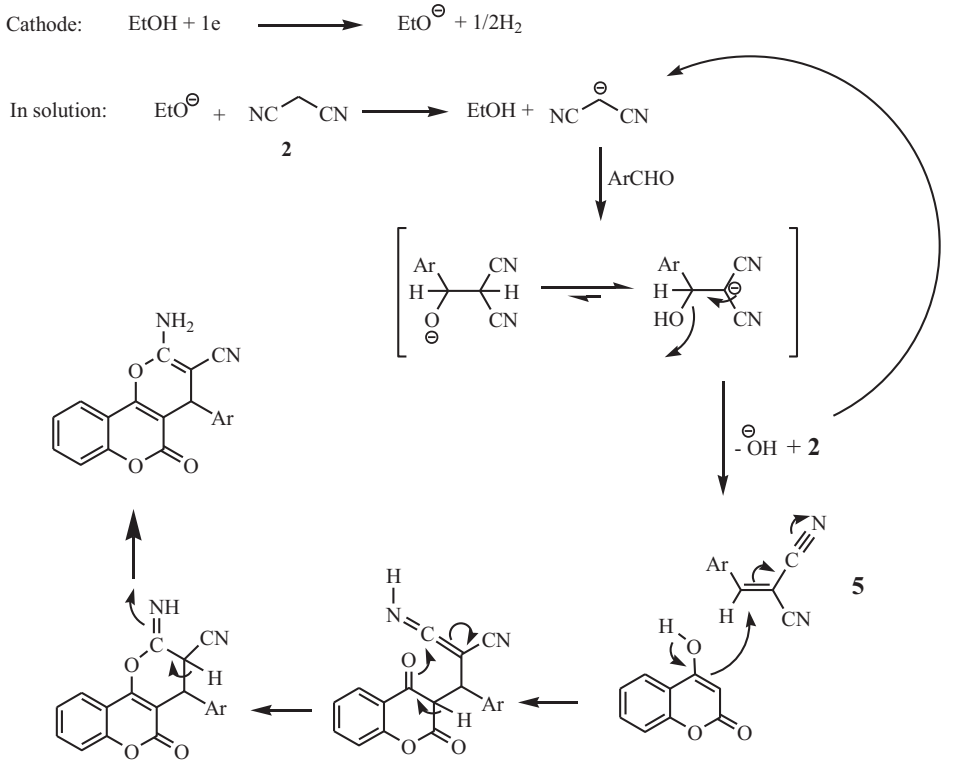
With a reliable set of conditions in hand, we also probed the scope and generality of the reaction of several aryl aldehydes with malononitrile and 4-hydroxycoumarin for the synthesis of 2-amino-5-oxo-4,5-dihydropyrano(3,2-c)chromene-3-carbonitrile derivatives (Table 2, **4a–p**).

As shown in Table 2, the products were obtained in excellent yields. 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
Electrocatalytic multicomponent synthesis of 2-amino-5-oxo-4,5-dihydropyrano(3,2-*c*)chromene-3-carbonitrile derivatives under optimized conditions.

Entry	Aldehyde	Product	Yield (%)	M.p. (°C)	Reference
1	Ph	**4a**	92	255–257	256–258 [11]
2	4-$NO_2C_6H_4$	**4b**	93	257–262	258–260 [11]
3	3-$NO_2C_6H_4$	**4c**	93	260–264	262–264 [11]
4	4-ClC_6H_4	**4d**	90	265–267	263–265 [11]
5	2,4-$Cl_2C_6H_4$	**4e**	90	258–260	257–259 [11]
6	2,3-$Cl_2C_6H_4$	**4f**	90	285–289	287–289 [11]
7	2,6-$Cl_2C_6H_4$	**4g**	90	298–301	299–301 [11]
8	4-OHC_6H_4	**4h**	90	262–265	264–266 [11]
9	4-FC_6H_4	**4i**	90	277–284	278–282 [9]
10	4-$OCH_3C_6H_4$	**4j**	90	241–243	240–242 [8]
11	2-$OCH_3C_6H_4$	**4k**	90	234–237	236–238 [9]
12	2,5-$(OCH_3)_2C_6H_4$	**4l**	90	238–240	247–248 [9]
13	3-$OCH_3C_6H_4$	**4m**	90	240–243	242–244 [9]
14	2-$CH_3C_6H_4$	**4n**	90	262–266	264–265 [9]
15	4-$CH_3C_6H_4$	**4p**	90	262–265	265–267 [9]

The proposed mechanism for the preparation of the related products is depicted in Scheme 2. As the initiation step of the catalytic cycle, deprotonation of an alcohol at the cathode leads to the formation of the alkoxide anion [12]. Its subsequent reaction in solution with malononitrile gives rise to the malononitrile anion. Then, Knoevenagel condensation of aldehyde, **1**, with the malononitrile anion takes place in the solution with the elimination of water



Scheme 2. Proposed mechanism for preparation 2-amino-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile derivatives.

and the formation of the corresponding α-cyanocinnamonitrile derivatives **5**. The subsequent hydroxide-promoted Michael addition of 4-hydroxycoumarin to the electron-deficient Knoevenagel adduct **5** followed by intramolecular cyclization results in the corresponding products **4**, with regeneration of the alkoxide anion as the last step, which continues the catalytic chain process by the interaction with the next molecule of malononitrile.

4. Conclusion

In conclusion, we have described the synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile derivatives in excellent yields by a simple and efficient procedure under neutral and mild conditions in the presence of sodium bromide as an electrolyte. The key advantages of this method are the very short reaction time, high yields, simple workup, and non-chromatographic purification of products. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified within green chemistry.

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