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A multi-component electro-organic synthesis of 2-amino-4*H*-chromenes

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ABSTRACT

Electrochemically induced multi-component condensation of resorcinol, malononitrile, and various aldehydes in propanol in an undivided cell in the presence of NaBr as an electrolyte results in the formation of 2-amino-4*H*-chromenes in good yields and short reaction time.

1. Introduction

2-Amino-4*H*-pyrans are an important class of heterocyclic compounds having important biological activities. During the last decade, such compounds had shown interesting pharmacological properties including antimicrobial,[1] antiviral,[2] mutagenicity,[3] antiproliferative,[4] sex pheromone,[5] antitumor,[6] cancer therapy,[7] and central nervous system activity.[8]

Several procedures for the preparation of 2-amino-4*H*-pyrans have been described.[9] Various catalysts such as piperidine,[10] morpholine,[11] CTACl (cetyltrimethylammonium chloride),[12] TEBA (triethylbenzylammonium chloride),[13] and alumina[14] have been used for this reaction, but all these methods require a long duration and high temperature.

Multi-component reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the diversity can be achieved simply by varying the reacting components.

Due to extensive research on the electrochemistry of organic compounds, electro-synthesis has become a useful method.[15] Additionally, electrochemical processes are beneficial from an environmental viewpoint because cleanly generated electricity acts as an oxidative and reductive agent in organic synthesis. Despite the significant synthetic potential and ecological advantages, the practical use of such procedures has often been limited on account of technical complexity and generally long processing times. Recently, we reported the preparation of quinazolinediones,[16] pyrroles,[17] and *cis*-isoquinolinic acids[18] via multi-component reactions, and benzofuran derivatives[19] via electrochemical synthesis. We now report a three-component (resorcinol **1**, malononitrile **2**, and aldehyde **3)** one-pot, electro-synthesis of 2-amino-4*H*-chromenes under mild conditions in propanol as solvent, in an undivided cell, in the presence of NaBr as the electrolyte (Tables 1 and 2, Scheme 1).

After screening several solvents, we found that dry propanol and a current density of 10 mA/cm^2 (I = 50 mA, electrode surface = 5 cm^2) promote the reaction of resorcinol **1**, malononitrile **2**, and benzaldehyde **3a** to afford 2-amino-3-cyano-4-phenyl-4*H*-chromene **4a**, efficiently (Table 1).

Encouraged by this success, we extended this reaction to a range of aldehydes **2b–h** under similar conditions to furnish the respective 2-amino-4*H*-chromenes **4b–h** in good yields. The results are summarized in Table 2.

We propose the following mechanism to account for the reaction. Alcohol deprotonation at the cathode leads to the formation of an alkoxide anion. Subsequent reaction between the alkoxide anion and malononitrile gives rise to a malononitrile anion. The

Table 1
Comparison of solvents and current on the reaction of resorcinol **1**, malononitrile **2**, and benzaldehyde **3a** to afford 2-amino-3-cyano-4-phenyl-4*H*-chromene **4a**[a]

Current (mA)	Electricity passed (F/mol)	Time (min)	Solvent	Yield[b] (%)
20	3	240	EtOH	60
50	2.8	90	EtOH	60
20	3	240	*n*-PrOH	80
50	2.8	90	*n*-PrOH	83

[a] For all reactions, 0.5 mmol of NaBr, an iron cathode (5 cm^2), a magnesium anode (5 cm^2), and room temperature were used.
[b] Isolated yields based on resorcinol.

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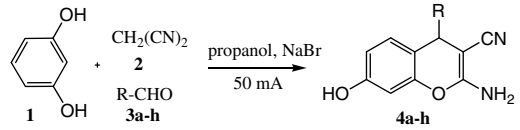
Table 2
Electrochemical condensation of resorcinol **1**, malononitrile **2**, and aldehydes **3** for the preparation of 2-amino-4*H*-chromenes **4**[a]

Product **4**[b]	R	Yield[c] (%)	Mp (°C)	Lit. mp (°C)
a	Ph	83	235–236	232–234[20a]
b	4-ClC_6H_4	85	163–164	161–162[9c]
c	4-$MeOC_6H_4$	80	111–112	112–114[9c]
d	4-FC_6H_4	85	187–189	–
e	4-BrC_6H_4	87	225–227	–
f	4-MeC_6H_4	90	182–184	185–187[20b]
g	Quinolin-2-yl	92	200–202	–
h	4-$MeO_2CC_6H_4$	86	231–233 dec.	233 dec.[20c]
i	2,4-$F_2C_6H_3$	80	219–221	221[20c]

[a] All reactions were run with resorcinol (0.110 g, 1 mmol), malononitrile (0.066 g, 1 mmol), 1 mmol of aldehyde, and 0.05 g (0.5 mmol) of NaBr in 25 mL of propanol at room temperature for 90 min.
[b] Prepared according to Scheme 1.
[c] Yields based on resorcinol.

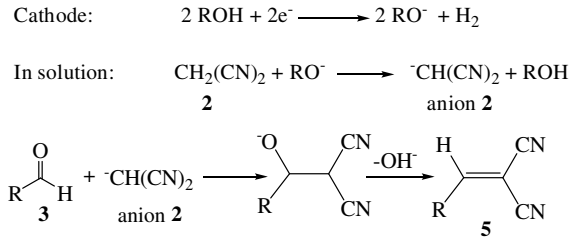


Scheme 1.

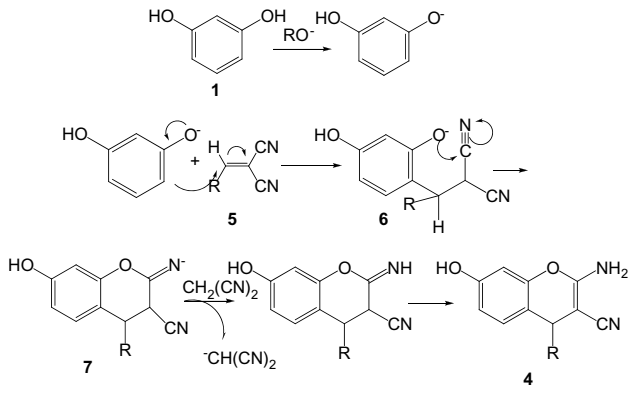
aldehyde **3** condenses with malononitrile anion **2** with elimination of hydroxide to afford 2-benzylidene-malononitrile intermediate **5** (Scheme 2).

Phenol C-alkylation gives the intermediate **6**, which cyclizes via nucleophilic attack of O^- on the cyano moiety to produce **7**. Finally, the products **4** are formed by protonation and rearrangement of **7** (Scheme 3).

In summary, we have described a practical, efficient, and simple electrocatalytic system for the preparation of 2-amino-4*H*-chromenes via a three-component cyclo condensation reaction of resorcinol, malononitrile, and aldehydes. The method has several advantages including high yields of products, easy experimental workup, and use of an undivided cell.



Scheme 2.



Scheme 3.

2. General electro-synthesis procedure for the preparation of 2-amino-4*H*-chromenes 4

A mixture of resorcinol (0.110 g, 1 mmol), malononitrile (0.066 g, 1 mmol), aldehyde (1 mmol), and NaBr (0.05 g, 0.5 mmol) in propanol (25 mL) was stirred and electrolyzed in an undivided cell equipped with an iron cathode (5 cm^2) and a magnesium anode (5 cm^2) at room temperature under a constant current density of 10 mA/cm^2 (I = 50 mA). After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane 1:1), the solvent was evaporated under reduced pressure, water (20 mL) was added to the reaction mixture, and the resulting solid was separated by filtration. The crude product was recrystallized from ethanol to afford pure product.

3. Spectral data for selected new products

3.1. 2-Amino-3-cyano-7-hydroxy-4-(4-fluorophenyl)-4*H*-chromene 4d

IR (KBr) (ν_{max}, cm^{-1}): 3426 (OH), 3222 (NH_2), 2192 (CN), 1651 (C=C vinyl nitrile), 1560 (C=C, aromatic). ^{1}H NMR (300 MHz DMSO-d_6,): δ_H 4.65 (s, 1H, H-4), 6.41 (d, 1H, J = 3, H-Ar), 6.47 (d, 1H, J = 6, H-Ar), 6.76 (d, 1H, J = 6, H-Ar), 6.89 (s, 2H, NH_2) 7.09–7.22 (m, 4H, H-Ar), 9.76 (s, 1H, OH). ^{13}C NMR (75 MHz DMSO-d_6,): δ_C 56.61, 102.67, 112.92, 113.93, 121.04, 129.64, 129.75, 130.32, 143.02, 149.25, 157.67, 159.80, 160.66, MS (70 eV) m/z (%): 282 (M^+, 20), 267 (M^+-NH_2, 10), 254 (35), 224 (20), 208 (35), 187 (100), 109 (25), 75 (25), 39 (20). Anal. Calcd for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.93; N, 9.92. Found: C, 68.00; H, 3.82; N, 9.81.

3.2. 2-Amino-3-cyano-7-hydroxy-4-(4-bromophenyl)-4*H*-chromene 4e

IR (KBr) (ν_{max}, cm^{-1}): 3440 (OH), 3336 (NH_2), 2188 (CN), 1645 (C=C vinyl nitrile), 1580 (C=C, aromatic). ^{1}H NMR (300 MHz DMSO-d_6,): δ_H 4.64 (s, 1H, H-4), 6.40 (d, 1H, J = 3, H-Ar), 6.46 (dd, 1H, J = 3, J = 9, H-Ar), 6.76 (d, 1H, J = 9, H-Ar), 6.92 (s, 2H, NH_2) 7.02–7.51 (m, 4H, H-Ar), 9.78 (s, 1H, OH). ^{13}C NMR (75 MHz DMSO-d_6,): δ_C 56.48, 102.69, 112.96, 113.53, 120.19, 120.97, 130.13, 130.35, 131.94, 146.22, 149.26, 157.74, 160.70. MS (70 eV) m/z (%): 342 (M^+ 30), 316 (15), 277 (10), 261 (20), 236 (10), 219 (20), 187 (100), 69(5), 75 (25), 39 (20). Anal. Calcd for $C_{16}H_{11}BrN_2O_2$: C, 56.00; H, 3.23; N, 8.16. Found: C, 55.89; H, 3.13; N, 8.03.

3.3. 2-Amino-3-cyano-7-hydroxy-4-(quinoline-2-yl)-4*H*-chromene 4g

IR (KBr) (ν_{max}, cm^{-1}): 3428 (OH), 3338 (NH_2), 2192 (CN), 1633 (C=C vinyl nitrile), 1560 (C=C, aromatic). ^{1}H NMR (300 MHz DMSO-d_6,): δ_H 4.65 (s, 1H, H-4), 6.39 (d, 1H, J = 3, H-Ar), 6.46 (d, 1H, J = 3, H-Ar), 6.49 (dd, 1H, J = 3, J = 9, H-Ar), 6.89 (s, 2H, NH_2), 7.09–7.22 (m, 6H, H-Ar), 9.70 (s, 1H, OH). ^{13}C NMR (75 MHz DMSO-d_6,) δ_C ppm 56.60, 102.64, 112.89, 113.99, 115.61, 115.89, 116.28, 116.58, 121.03, 129.65, 129.76, 130.36, 131.46, 131.57, 143.05, 149.25, 155.70, 157.60, 160.64. MS (70 eV) m/z (%): 315 (5), 282 (M^+-NH_2-OH, 10), 282 (60), 256 (15), 187 (100), 159 (16), 132 (17), 114 (17), 95 (20), 75 (26), 39 (25). Anal. Calcd for

$C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 71.26; H, 4.15; N, 13.23.

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