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Electrochemically induced chain transformation of salicylaldehydes and alkyl cyanoacetates into substituted 4*H*-chromenes

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Abstract—Electrolysis of salicylaldehydes and alkyl cyanoacetates in ethanol in an undivided cell in the presence of sodium bromide results in the formation of substituted alkyl 2-amino-4-(1-cyano-2-alkoxy-2-oxoethyl)-4*H*-chromene-3-carboxylates in 85–95% yields.

The chromene (or benzopyran) moiety often appears as an important structural component in both biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols and anthocyanins.[1] Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of biomedicinal chemistry.[2] The current interest in 4*H*-chromene derivatives bearing a nitrile functionality arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis, and of cancer therapy. Thus, the corresponding (4*H*-chromen-4-yl)malononitriles were found to inhibit mitogen-activated protein kinase-activated protein kinase 2 (MK-2) and suppress the expression of the TNFα in U937 cells.[3] In the case of cancer therapy, substituted alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of cancer implicated Bcl-2 protein and induce apoptosis or programmed cell death in tumor cells.[4]

The condensation of salicylaldehyde derivatives with active methylene compounds in the presence of ammonium acetate, pyridine, or piperidine usually leads to coumarins,[5] or coumarin imines, which can be hydrolyzed to coumarins.[5c]

Nevertheless, synthetic approaches to the corresponding 4*H*-chromen-4-yl derivatives are known and employ the reaction of salicylaldehydes with alkyl cyanoacetates catalyzed by ammonium acetate,[6] aluminum oxide,[7] molecular sieves 3 Å[8] or by potassium exchanged layered zirconium phosphate under solvent-free conditions.[9] The catalysis with ammonium acetate requires careful temperature control (5–10) °C to ensure product selectivity and the yields of the desired product are in the range of 40–80%.[6] The application of solid phase catalysis using aluminum oxide[7] or the molecular sieves 3 Å[8] is more convenient and results in the formation of the corresponding 4*H*-chromene derivatives in 50–85% yields. The best yields (70–95%) of the corresponding substituted 4*H*-chromenes were reported for the reaction of salicylaldehydes with alkyl cyanoacetates using potassium exchanged layered zirconium phosphate catalyst under the solvent-free conditions, but this method requires long reaction times (2–15 h) and a 60 °C reaction temperature.[9]

Due to the extensive research on the electrochemistry of organic compounds over the last three decades, electrosynthesis has become a useful method in modern organic chemistry.[10] Additionally, electrochemical processes are beneficial from the viewpoint of environmentally benign organic synthesis as electricity is the most ecologically

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Keywords: Electrocatalysis; Electrolysis; Electrocatalytic transformation; Salicylaldehydes; Alkyl cyanoacetates; 4*H*-chromenes.

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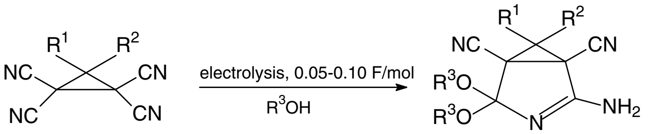
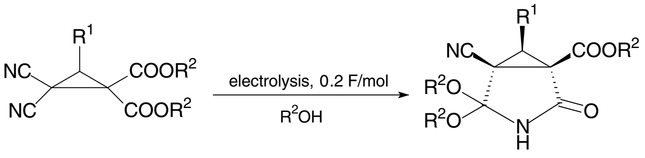


Scheme 1.



Scheme 2.

Table 1. Electrocatalytic transformation of salicylaldehyde **1a** and methyl cyanoacetate **2a** into 4*H*-chromene **3a**[a,b,14]

I (mA)	Time (min)	Electricity passed (F/mol)	Yield (%)[c]
250	30	0.47	68
125	30	0.23	75
50	30	0.09	95
20	30	0.04	79

[a] 10 mmol of salicylaldehyde **1a**, 20 mmol of methyl cyanoacetate, 1 mmol of NaBr, 20 ml of EtOH, Fe-cathode (5 cm^2), C-anode (5 cm^2), 20 °C.

[b] Melting point **3a**: 121–123 °C, lit. melting point 120–122 °C.[7] The ratio of diastereoisomers was 2:1 (according to NMR data in DMSO-d_6).

[c] Isolated yields.

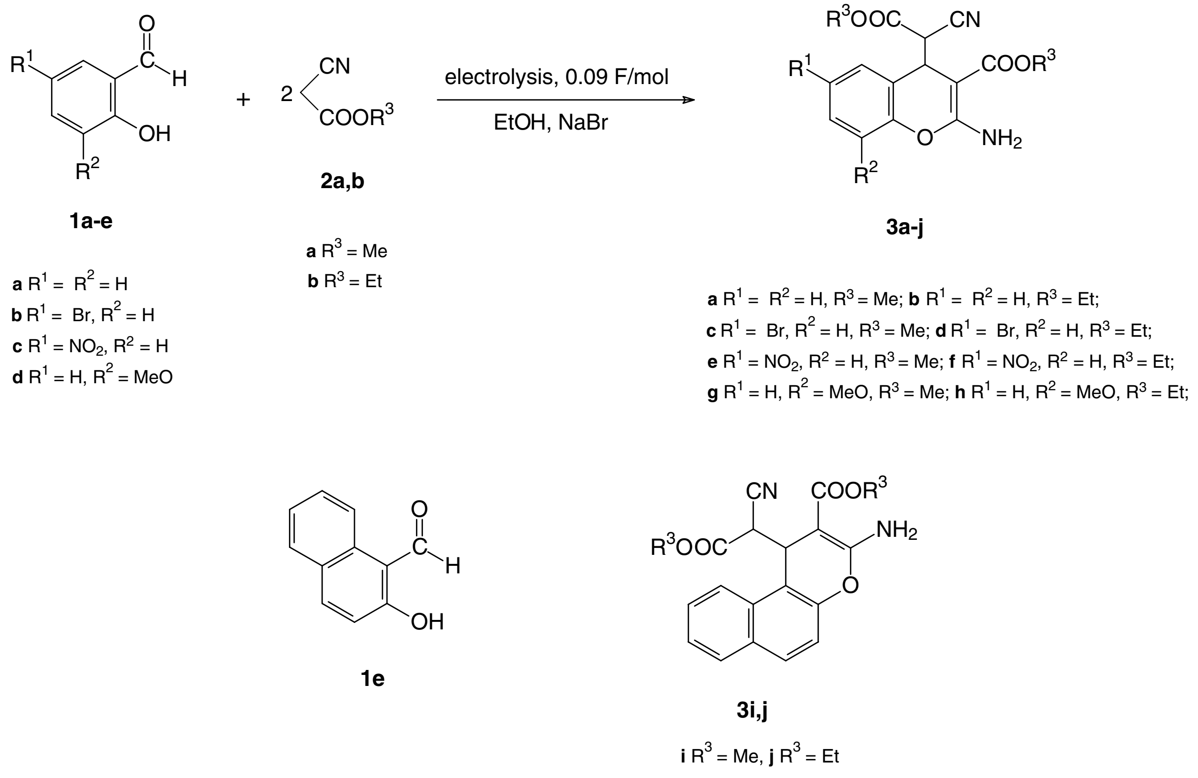
Table 2. Electrocatalytic transformation of substituted salicylaldehydes **1a**–**e** and alkyl cyanoacetates **2a**,**b** into 4*H*-chromenes **3b**–**j**[a,14]

Aldehyde	Alkyl cyanoacetate	4*H*-Chromene	Yield, %[b]	Ratio of isomers[c]	Mp °C found	Mp °C reported
1a	**2b**	**3b**	91	2:1	141–143	142–143[6]
1b	**2a**	**3c**	93	3:2	126–127	—
1b	**2b**	**3d**	88	2:1	107–108	104–105[6]
1c	**2a**	**3e**	85	3:2	155–156	156[9]
1c	**2b**	**3f**	87	5:2	134–135	—
1d	**2a**	**3g**	84	2:1	156–157	150–153[7]
1d	**2b**	**3h**	89	2:1	125–126	126–127[6]
1e	**2a**	**3i**	85	7:2	150–152	—
1e	**2b**	**3j**	83	2:1	127–128	—

[a] 10 mmol of salicylaldehyde, 20 mmol of alkyl cyanoacetate, 1 mmol of NaBr, 20 ml of EtOH, Fe-cathode (5 cm^2), C-anode, (5 cm^2), 20 °C.

[b] Isolated yields.

[c] According to ^{1}H NMR data in DMSO-d_6.



Scheme 3.