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Catalysis of Salicylaldehydes and Two Different *C*−*H* Acids with Electricity: First Example of an Efficient Multicomponent Approach to the Design of Functionalized Medicinally Privileged 2-Amino-4*H*-Chromene Scaffold

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Abstract: Electrochemically induced multicomponent transformation of salicylaldehydes and two different *C*−*H* acids in alcohols in an undivided cell in the presence of sodium bromide as an electrolyte results in the efficient and selective formation of diversely functionalized, medicinally privileged 2-amino-4*H*-chromene scaffolds in 65–86% yields. The developed electrocatalytic system affords the distinction between two *C*−*H* acids according to their reactivity, and offers an efficient approach to the 2-amino-4*H*-chromene scaffold with a predefined arrangement of desired substituents. The electrocatalytic multicomponent reaction smoothly proceeds with salicylaldehydes bearing both electron-donating and electron-withdrawing groups. Thus, fifteen previously inaccessible, close structural analogues of the tumor antagonists HA14-1 and MX58151 have been synthesized. The electrocatalytic process was found to be advantageous in terms of selectivity and yields compared to classic chemical base catalysis, and includes a remarkable mechanistic feature that is promising for the further development of 2-amino-4*H*-chromene chemistry. The application of this convenient electrocatalytic multicomponent method to the formation of medicinally relevant 2-amino-4*H*-chromenes is also beneficial from the viewpoint of diversity-oriented large-scale processes and represents a novel, facile and environmentally benign synthetic concept for multicomponent reaction strategy.

Keywords: *C*−*H* acids; chromenes; electrocatalysis; multicomponent reactions; salicylaldehydes

Introduction

In recent years the concept of "privileged medicinal structures or scaffolds"[1] has emerged as one of the guiding principles of the drug discovery process.[2] The structural analysis of 5120 commercially available drugs revealed that the half of them incorporated only 32 most frequently occurring molecular frameworks.[3] These privileged scaffolds commonly consist of a rigid hetero-ring system that assigns a well-defined orientation of appended functionalities for target recognition. In the light of this, the accessibility of convenient methods for the diversification of privileged scaffold functionalities impacts on the success in a search for potential drugs.

The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry.[4] One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials.[5] The rapid assembly of molecular diversity utilizing MCRs has received a great deal of attention, especially for the design and construction of elaborate heterocyclic frameworks possessing enhanced "drug-like" properties.[6] For example, the Hantzsch,[6c] Ugi,[6e,f] and Biginelli[7] multicomponent reactions are the methods of choice to prepare func-

tionalized 1,4-dihydropyridine, benzodiazepinedione, and dihydropyrimidine privileged scaffolds, respectively.

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. It is widely present in natural alkaloids, flavonoids, tocopherols, and anthocyanins.[8] Moreover, in recent years functionalized chromenes have played in ever-increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry.[9] Among the different types of chromene systems, 2-amino-4*H*-chromenes (or 2-amino-4*H*-benzo[*b*]pyrans) are of particular utility as they belong to privileged medicinal scaffolds serving for the generation of small-molecule ligands with highly pronounced spasmolytic, diuretic, anticoagulant, and antianaphylactic activities.[2b,d,10] The current interest in 2-amino-4*H*-chromene derivatives bearing a nitrile functionality arises from their potential application in the treatment of human inflammatory TNF-α-mediated diseases, such as rheumatoid and psoriatic arthritis, and in cancer therapy (Figure 1).[11]

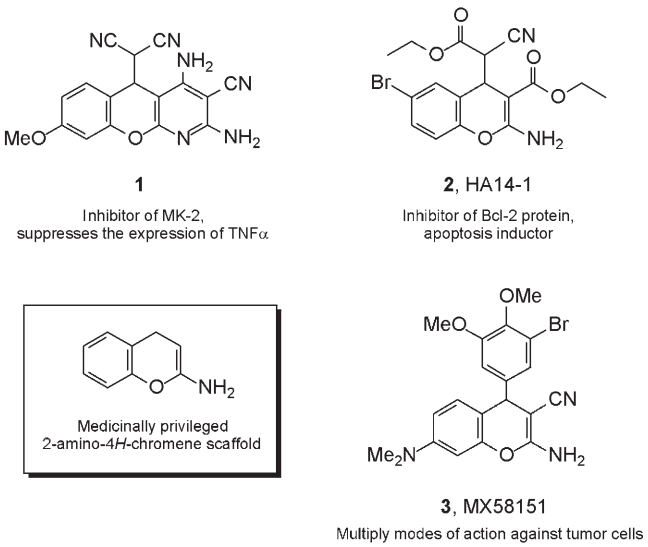
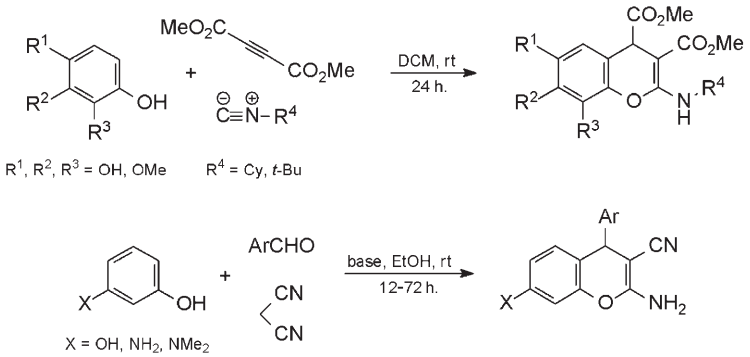


Figure 1. 2-Amino-4*H*-chromene as privileged medicinal scaffold.

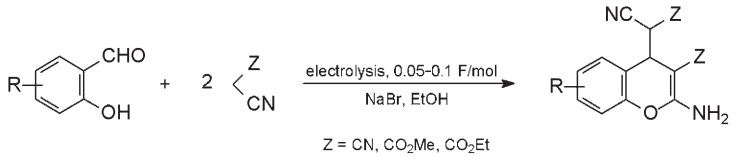
Thus, the corresponding cyano-functionalized benzopyranopyridine **1** originating from the 2-amino-4*H*-chromene scaffold was found to inhibit mitogen-activated protein kinase-activated protein kinase 2 (MK-2) and suppress the expression of TNF-α in U937 cells.[11a] In the case of cancer therapy, the tumor antagonist HA14-1 (**2**) and a family of related alkyl (4*H*-chromen-4-yl)cyanoacetates are a new class of small molecules that exhibit a binding activity for the surface pocket of the cancer-implicated Bcl-2 protein and induce apoptosis or programmed cell death in follicular lymphoma B cells and leukemia HL-60 cells.[11b,c] The 2-amino-3-cyano-4*H*-chromene MX58151 bearing a 3-bromo-4,5-dimethoxyphenyl substituent at the 4-position (**3**) represents a promising class of proapoptotic small-molecule agents with multiple action modes against the breast cancer cell line T47D, the lung cancer cell line H1299, and the colorectal cancer cell line DLD-1.[11d,e] It induces caspase-mediated apoptosis in tumor cells, and is about as potent as or slightly more potent than the commonly prescribed anticancer alkaloids vinblastine and paclitaxel in the caspase activation assay.[11e] Furthermore, compound MX58151 (**3**) might have an advantage for the treatment of the drug-resistant cancers as it retains activity in tumor cells resistant towards current antimitotic agents, taxanes (including Taxol and Taxotere), and *Vinca* alkaloids.[11d,e] The inhibition of tubuline polymerization and disruption of preformed endothelial cell capillary tubules constitute other significant activities of 2-amino-3-cyano-4-aryl-4*H*-chromenes of type **3** that can place them in the row of effective anticancer therapeutics with an analogous mode of action.[11e–g]

To the best of our knowledge, there are only two different multicomponent entries for the synthesis of substituted 2-amino-4*H*-chromene scaffold (Scheme 1).

The first multicomponent approach utilizes the reaction of alkyl isocyanides with dimethyl acetylenedi-



Scheme 1. Known MCR approaches to functionalized 2-amino-4*H*-chromenes.



Scheme 2. Electrocatalytic non-multicomponent synthesis of 2-amino-4*H*-chromenes.

carboxylate and either polyhydroxybenzenes or methoxyphenols, and affords certain 2-(alkylamino)-4*H*-chromenes in 80–90% yields.[12] The MCR proceeds under ambient conditions without any external activation, but requires 24 h of reaction time and allows for the use of starting phenols only with electron-donating hydroxy and/or methoxy substituents. Furthermore, the independent and selective variation of functional groups at the 3- and 4-positions of 2-amino-4*H*-chromene framework seems to be problematic through the method reported. The second type of MCR employs a three-component condensation of aromatic aldehydes and malononitrile with 3-aminophenols in the presence of equivalent quantities of piperidine[11d,e] or morpholine[13], or with resorcinol under catalysis with morpholine,[14] respectively. Although these processes provide with a wide variation of aryl substituents at the 4-position of the 2-amino-3-cyano-4*H*-chromene scaffold, they significantly suffer from moderate yields (generally 20–50%) and long reaction times (from 12 to 72 h). Moreover, this one-pot reaction does not proceed with phenols or 3-aminophenols bearing electron-withdrawing groups, e.g., halogens, which considerably limits the scope of accessible structures.[11d] Recently Shanthi et al. reported an analogous MCR of naphthols, isatin (as aldehyde equivalent) and malononitrile or alkyl cyanoacetates catalyzed by 20 mol% of indium(III) chloride.[15] This three-component condensation leads to corresponding 2-amino-4*H*-chromene scaffold with a fused isatin fragment in 65–90% reaction yields, but necessitates either reflux in acetonitrile for 2 h or microwave irradiation and fails with aminonaphthols. Furthermore, column chromatography is required for purification of the desired products. Therefore, each of the two known MCRs for the synthesis of medicinally privileged 2-amino-4*H*-chromenes has its merits, but the essence of facile and convenient multicomponent methodology that accounts for highly diverse reaction products is yet to be developed.

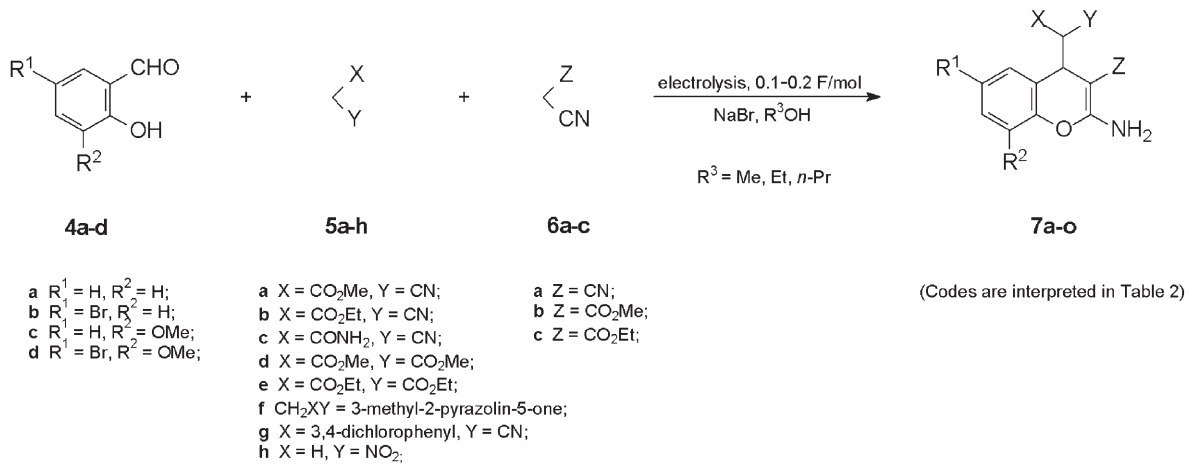
Results and Discussion

The advances in electrosynthesis in the last few decades have provided organic chemists with a new versatile synthetic device of great promise.[16] Despite the significant synthetic potential and ecological advantages of electrochemical methods, the practical usage of electrochemical procedure is often limited on account of its technical complexity and generally long processing times. In the course of our study on the electrochemical transformation of organic compounds, we have found a new type of electrochemical transformation, namely the electrocatalytic chain transformation of organic compounds induced by a catalytic amount of an electrogenerated base in an undivided cell.[17] In our recent preliminary communications we have reported a successful application of this facile electrocatalytic procedure, developed by us, to the non-multicomponent synthesis of a number of cyano-functionalized 2-amino-4*H*-chromenes starting from salicylaldehydes and two equivalents of either malononitrile or alkyl cyanoacetate (Scheme 2).[18]

The implication of the electrocatalysis in base-activated MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the facile electrocatalytic procedure. Considering our preliminary results on the electrocatalytic chain transformation of cyano-functionalized methylene compounds and salicyaldehydes as well as the certain biomedical applications of 2-amino-4*H*-chromene systems mentioned above, we were prompted to design a convenient and facile electrocatalytic MCR methodology for the synthesis of the 2-amino-4*H*-chromene scaffold that accounts for highly diverse reaction products and is based on an electrochemically induced reaction of salicylaldehydes with two different *C–H* acids.

In the present study we report our results on electrocatalytic multicomponent chain transformation of salicylaldehydes **4**, *C–H* acids **5** and necessarily cyano-functionalized *C–H* acids **6** into substituted 2-amino-4*H*-chromenes **7** under neutral and mild conditions by electrolysis in an undivided cell. The reaction is performed in alcoholic solvents in the presence of sodium bromide as an electrolyte (Scheme 3).

Our approach to the multicomponent design of 2-amino-4*H*-chromenes through the electrocatalysis of an alcoholic solution of salicylaldehyde and two different *C–H* acids has been guided by the following considerations: (a) since the electrolysis in an undivided cell allows for a very low and gradient current concentration of the base (alkoxide anions) generated at the cathode along with a neutral *pH* of the whole solution, the difference in acidity could provide for a successive participation of the *C–H* acids in a base-



Scheme 3. Electrocatalytic multicomponent transformation of salicylaldehydes and two different C-H acids into functionalized privileged 2-amino-4*H*-chromene scaffold.

promoted reaction cycle resulting in a selective formation of single 2-amino-4*H*-chromene product with a predefined arrangement of substituents; (b) in the case of non-multicomponent processes, the mild reaction conditions and the catalytic nature of the proposed electrochemical procedure accounted for superior reaction yields and selectivities in the formation of the corresponding 2-amino-4*H*-chromenes compared to known chemical methods. First, to evaluate the synthetic potential of the procedure proposed and to optimize the electrolysis conditions, the electrocatalytic multicomponent transformation of salicylaldehyde **4a**, methyl cyanoacetate **5a** and malononitrile **6a** was studied (Scheme 3, Table 1).

To our delight, the electrocatalysis of the alcoholic solutions of **4a**, **5a** and **6a** in an undivided cell in the presence of sodium bromide as an electrolyte led to the exclusive formation of methyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetate **7a**. The electrocatalytic system does distinguish the two *C*–*H* acids **5a** and **6a** according to their reactivity in the base-catalyzed process, and the more acidic malononitrile serves as a source for the 2-amino-3-cyano-4*H*-chromene framework while the less acidic methyl cyanoacetate gives rise to the corresponding 4-substituent of the 2-amino-4*H*-chromene **7a**. Excellent conversions of starting compounds were obtained under 10 mA cm^{-2} and 15 mA cm^{-2} current densities after 0.1 Fmol^{-1} had been passed. A current density of 10 mA cm^{-2} (I = 50 mA, electrodes surface 5 cm^2) was found to be optimal for the electrochemically induced chain process and allowed for the highest yield of 2-amino-4*H*-chromene **7a**. 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 lead to oligomerization of the starting material.

Table 1. Electrocatalytic transformation of salicylaldehyde **4a**, methyl cyanoacetate **5a** and malononitrile **6a** into methyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetate **7a**.[a]

I [mA]	Current density [mA cm^{-2}]	Time [min]	Alcohol	Electricity passed (Fmol^{-1})	Yield of **7a** [%][b]
5	1	320	EtOH	0.1	62
10	2	160	EtOH	0.1	66
20	4	80	EtOH	0.1	73
50	10	32	EtOH	0.1	85
75	15	22	EtOH	0.1	76
50	10	32	MeOH	0.1	74
50	10	32	*n*PrOH	0.1	82

[a] **4a** (10 mmol), **5a** (10 mmol), **6a** (10 mmol), NaBr (1 mmol), alcohol (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), 20 °C.

[b] Yield of isolated product obtained by filtration of the concentrated (from 20 mL to *ca* 4 mL) reaction mixture.

After electrolysis, 2-amino-4*H*-chromene **7a** was directly crystallized from the reaction mixture that was preliminarily concentrated to one fifth of its initial volume (4 mL) to ensure complete precipitation of the product.[19] As for the alcoholic solvent, electrolyses in MeOH, EtOH and *n*-PrOH lead to similar results, but the usage of EtOH is preferred when the product is isolated by direct filtration after the electrolysis according to the method described above.[20]

Under the optimal conditions (current density 10 mA cm^{-2}, 0.1 Fmol^{-1} passed, EtOH as solvent) the electrolysis of salicylaldehydes **4a**–**d**, *C*–*H* acids **5a**–**h** and necessarily cyano-functionalized *C*–*H* acids **6a**–**c** in an undivided cell affords substituted 2-amino-4*H*-chromenes **7a**–**n** in yields of 69–86% at ambient temperature over a 32 min reaction period (Table 2, entries 1–14). In the case of thee 4-(nitromethyl)-substituted 2-amino-4*H*-chromene **7o** obtained in 65%

Table 2. Electrocatalytic transformation of salicylaldehydes **4a–d**, *C–H* acids **5a–h** and *C–H* acids **6a–c** into 2-amino-4*H*-chromenes **7a–o**.[a]

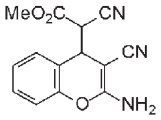
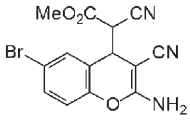
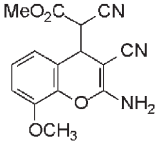
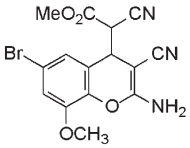
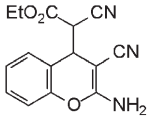
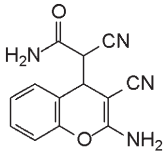
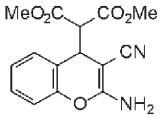
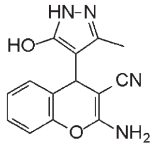
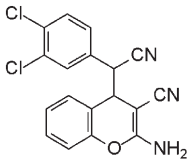
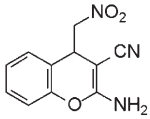
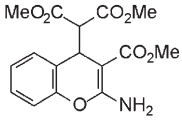
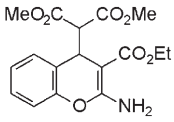
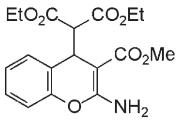
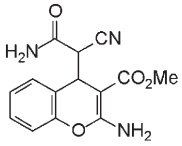
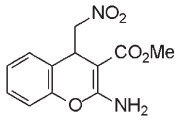
Entry	Aldehyde **4**	*C–H* acid **5**	*C–H* acid **6**	Electricity passed [Fmol^{-1}]	Product **7**	Yield [%][b]	Ratio of diastereoisomers[c]
1	**4a**	**5a**	**6a**	0.1	**7a** 	85	2:1
2	**4b**	**5a**	**6a**	0.1	**7b** 	69	2:1
3	**4c**	**5a**	**6a**	0.1	**7c** 	75	2:1
4	**4d**	**5a**	**6a**	0.1	**7d** 	72	2:1
5	**4a**	**5b**	**6a**	0.1	**7e** 	84	4:3
6	**4a**	**5c**	**6a**	0.1	**7f** 	73	1:1
7	**4a**	**5d**	**6a**	0.1	**7g** 	71	-
8	**4a**	**5f**	**6a**	0.1	**7h** 	86	-
9	**4a**	**5g**	**6a**	0.1	**7i** 	72	4:3
10	**4a**	**5h**[d]	**6a**	0.1	**7j** 	70	-
11	**4a**	**5d**	**6b**	0.1	**7k** 	83	-
12	**4a**	**5d**	**6c**	0.1	**7l** 	77	-

Table 2. (Continued)

Entry	Aldehyde **4**	*C*–*H* acid **5**	*C*–*H* acid **6**	Electricity passed [Fmol^{-1}]	Product **7**	Yield [%][b]	Ratio of diastereoisomers[c]
13	**4a**	**5e**	**6b**	0.1	**7m** 	81	-
14	**4a**	**5c**	**6b**	0.1	**7n** 	78	2:1
15	**4a**	**5h**[d]	**6b**	0.2	**7o** 	65	-

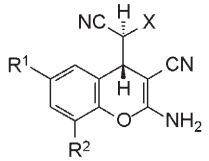
[a] **4a** (10 mmol), **5a** (10 mmol), **6a** (10 mmol), NaBr (1 mmol), EtOH (20 mL), iron cathode (5 cm^2), graphite anode (5 cm^2), current density 10 mA cm^{-2}, 20 °C.
[b] Yields of isolated products obtained by filtration of the concentrated (from 20 mL to *ca.* 4 mL) reaction mixtures.
[c] According to ^{1}H NMR data.
[d] 15 mmol of nitromethane (*C*–*H* acid **5h**) were used.

yield, a catalytic quantity of electricity of 0.2 Fmol^{-1} was required to achieve full conversion of the starting materials (Table 2, Entry 15). The developed electrocatalytic multicomponent transformation smoothly proceeds with salicylaldehydes bearing both electron-donating and electron-withdrawing groups (Table 2, entries 2–4). Furthermore, it allows for the selective and combined introduction of the wide range of *C*–*H* acid-borne functionalities, including medicinally promising nitrile, carboxylate and heterocyclic fragments, into the privileged 2-amino-4*H*-chromene scaffold.

According to ^{1}H and ^{13}C NMR analyses, the 2-amino-4*H*-chromenes **7a–f**, **7i** and **7n** thus obtained were mixtures of two diastereoisomers (Table 2, entries 1–6, 9 and 14). From a thermodynamic point of view, more abundant diastereoisomer should possess the (*S*,*S*)*-configuration in the case of **7a–e** and the (*R*,*S*)*-configuration in the case of **7i** and **7n**, respectively (Figure 2).[21]

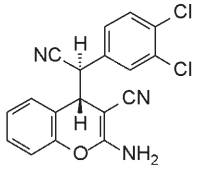
The conventional chemical approaches to the synthesis of 4*H*-chromene derivatives usually utilize the reaction of active methylene compounds with either aryl aldehydes and phenols, or salicylaldehydes in the presence of a necessarily required base, most notably piperidine.[11a,d,e,22] These reactions generally proceed with reasonable yields, often corresponding to those obtained under more sophisticated reaction conditions.[21,23] However, none of the chemical procedures that led to the 2-amino-4*H*-chromene scaffold through the one-pot condensation of salicylaldehydes with two different *C*–*H* acids have been reported so far. To provide a reference for the electrocatalytic MCR developed by us, we have studied the three-component condensation of salicylaldehyde **4a**, methyl cyanoacetate **5a** and malononitrile **6a** in the presence of catalytic and equimolar quantities of piperidine (Table 3).

Indeed, it was found that this chemical base-promoted process led to the formation of the desired 2-amino-4*H*-chromene **7a** along with a complete conversion of the starting compounds over a 32 min reaction period. Nevertheless, compare to electrocatalytic procedure it results in significantly lower reaction yields with the highest value of 49% obtained when as little as 1 mmol (10 mol.%) of piperidine was ap-

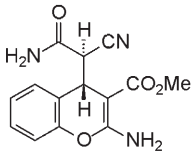


(*S*,*S*)*-**7a-e**

a R^1 = H, R^2 = H, X = CO_2Me;
b R^1 = Br, R^2 = H, X = CO_2Me;
c R^1 = H, R^2 = OMe, X = CO_2Me;
d R^1 = Br, R^2 = OMe, X = CO_2Me;
e R^1 = H, R^2 = H, X = CO_2Et;



(*R*,*S*)*-**7i**



(*R*,*S*)*-**7n**

Figure 2. Proposed configuration for more abundant diastereoisomers of **7a–e**, **7i** and **7n**.

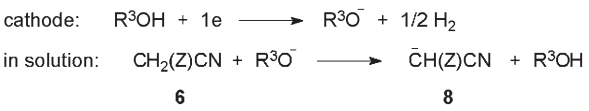
Table 3. Chemical transformation of salicylaldehyde **4a**, methyl cyanoacetate **5a** and malononitrile **6a** into methyl (2-amino-3-cyano-4*H*-chromen-4-yl)cyanoacetate **7a** in the presence of base.[a]

Base	Quantity of base [mmol]	Time [min][b]	Alcohol	Yield of **7a** [%][c]
Piperidine	1	32	EtOH	49
Piperidine	3	32	EtOH	44
Piperidine	5	32	EtOH	23
Piperidine	10	32	EtOH	18

[a] **4a** (10 mmol), **5a** (10 mmol), **6a** (10 mmol), alcohol (20 mL), 20 °C.
[b] Complete conversion of starting compounds is achieved after 20–25 min of reaction time.
[c] Yield of isolated product obtained by filtration of the concentrated (from 20 mL to *ca.* 4 mL) reaction mixture, ratio of diastereoisomers is 2:1.

plied. In all cases the ^{1}H NMR analysis of the reaction residues after the isolation of **7a** has revealed a complicated mixture of oligomeric by-products. As it follows from the obtained results, the MCR of salicylaldehydes with two different *C–H* acids is highly sensitive to the quantity of the base; and the mild and catalytic nature of the developed electrochemical process is an important feature that accounts for superior selectivity and reaction yields.

With the above results taken into consideration and the mechanistic data on the electrocatalytic chain cyclizations preliminary performed by us,[17,18] the following mechanism for the electrocatalytic multicomponent transformation of salicylaldehydes **4** and two different *C–H* acids **5** and **6** is proposed. The initiation step of the catalytic cycle begins with the deprotonation of a molecule of an alcohol at the cathode, which leads to the formation of an alkoxide anion and liberation of hydrogen gas. The subsequent reaction between the alkoxide anion and the strongest acid in the system (*C–H* acid **6**) gives rise to the anion **8**, directly or through equilibrium means (Scheme 4).



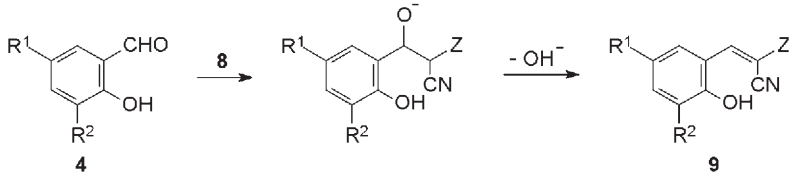
Scheme 4. Initiation step of electrocatalytic cycle and formation of C-H acid anion **8**.

The following processes in the solution represent a fairly complex pattern of equilibriums and cascade reactions. We believe that the general reaction route leading to 2-amino-4*H*-chromenes **7** under the described electrocatalytic conditions could be outlined as follows. First, Knoevenagel condensation of salicylaldehyde **4** and the anion **8** takes place with the elimination of a hydroxide anion and formation of adduct **9** (Scheme 5).[24]

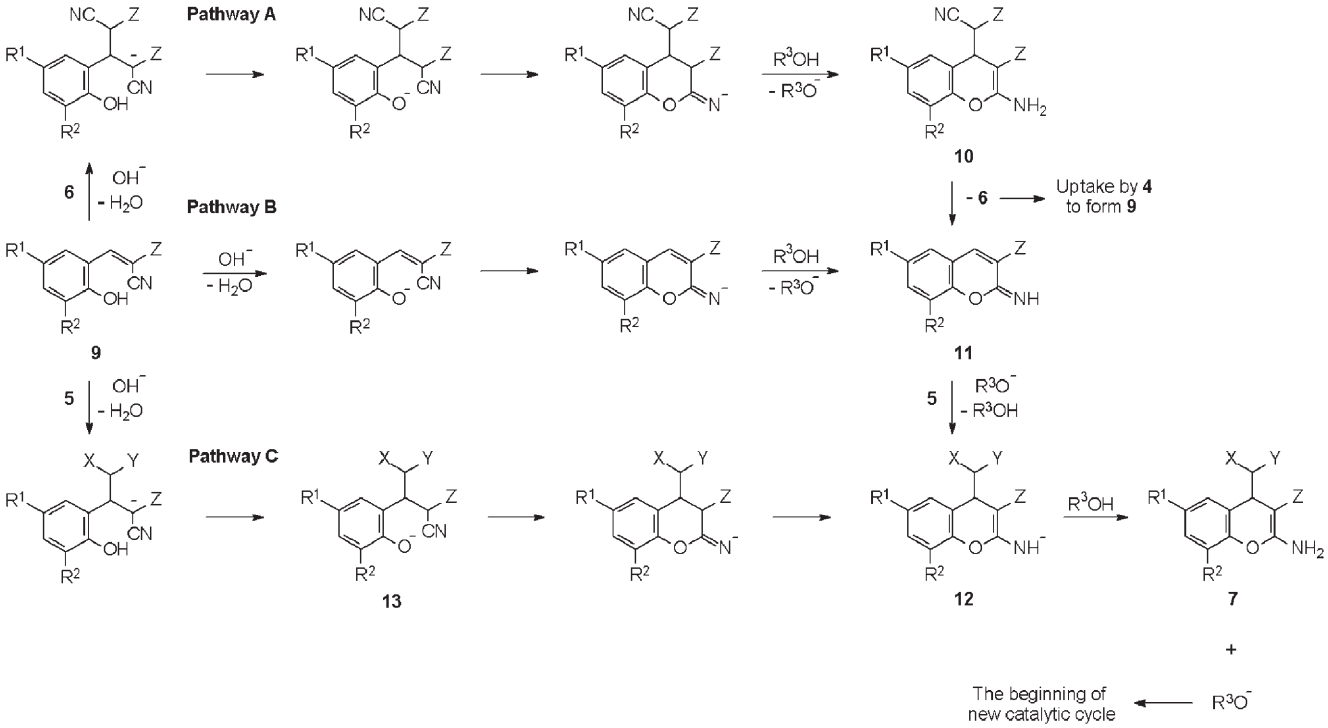
As confirmed by an additional electrocatalytic experiment,[25] the Knoevenagel condensation is not the fastest step on an overall way to **7**, so, it does not result in the full uptake of the salicylaldehyde **4** and *C–H* acid **6** from the system in the initial stage. Thus the presence of **4** and **6** in the solution should be taken into account for further mechanistic considerations.

Next, three reaction pathways are possible for Knoevenagel adduct **9** (Sheme 6).

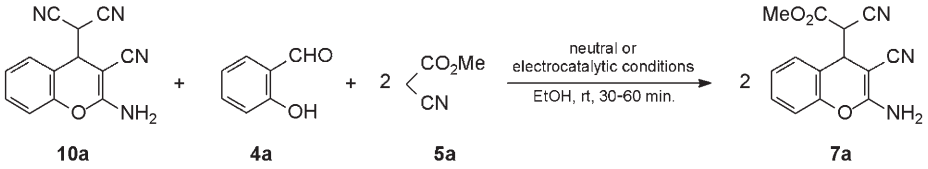
The hydroxide-promoted Michael addition of *C–H* acid **6** to the adduct **9** followed by intramolecular cyclization leads to corresponding 4*H*-chromene **10** (Pathway A). Although we were not able to detect compounds of type **10** in the solid products and reaction mixtures obtained after electrolysis, the contribution of pathway A in the whole process is not excluded. Recently, O'Callaghan et al. have noted that in alcoholic solution (2-amino-3-cyano-4*H*-chromen-4-yl)-malononitrile (**10a**, Z = CN) could exist in equilibrium with the corresponding 2-imino-2*H*-chromene-3-carbonitrile (**11a**) and malononitrile (**6a**) under certain reaction conditions.[22] If such an equilibrium exists in our case, the uptake of the stronger *C–H* acid **6** from the equilibrium by salicylaldehyde **4** could facilitate the base-promoted addition of weaker *C–H* acid **5** to 2-imino-2*H*-chromene **11**, which results in the full conversion of **10** into the desired 2-amino-4*H*-chromene **7** during the electrocatalytic process. To provide evidence for our suggestion, we have studied the reaction of (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **10a** obtained by a reported method[18a] with one equivalent of salicylaldehyde **4a** and two equivalents of methyl cyanoacetate **5a** (Scheme 7, Table 4).



Scheme 5. Knoevenagel condensation of salicylaldehyde **4** and anion **8** into adduct **9**.



Scheme 6. Possible catalytic pathways for the transformation of Knoevenagel adduct **9** into 2-amino-4*H*-chromene **7**.



Scheme 7. Exchange of substituent at 4-position of 2-amino-4*H*-chromene scaffold.

Table 4. Transformation of (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **10a**, salicylaldehyde **4a** and methyl cyanoacetate **5a** into methyl (2-amino-3-cyano-4*H*-chromen-4-yl)-cyanoacetate **7a** under neutral, electrocatalytic, and basic conditions.[a]

Conditions of the process	Time [min]	Alcohol	Yield of **7a** [%][b]
Neutral	60[e]	EtOH	55
Electrocatalysis[c]	32[e]	EtOH	72
Catalysis with piperidine[d]	32[f]	EtOH	-

[a] **10a** (5 mmol), **4a** (5 mmol), **5a** (10 mmol), alcohol (20 mL), 20 °C.
[b] Yield of isolated **7a** obtained by filtration of the concentrated (from 20 mL to *ca.* 4 mL) reaction mixture, ratio of diastereoisomers is 2:1.
[c] NaBr (1 mmol) as an electrolyte, iron cathode (5 cm^2), graphite anode (5 cm^2), current density 10 $mA\,cm^{-2}$, 0.1 $Fmol^{-1}$ passed.
[d] 1 mmol of piperidine.
[e] Complete conversion of starting compounds.
[f] 25% conversion of **10a**.

According to the obtained results, the process smoothly proceeds under neutral and electrocatalytic conditions giving rise to similar 55% and 72% yields of 2-amino-4*H*-chromene **7** over 60 and 32 min reaction periods, respectively (Table 4). Apart from the direct evidence for the possible contribution of mechanistic pathway A into the electrocatalytic multicomponent formation of **7** from salicylaldehydes **4** and two different *C*–*H* acids **5** and **6**, the transformation found offers a facile exchange of the substituent at the 4-position of corresponding 4*H*-chromene cycle for another nucleophilic fragment under mild reaction conditions – a promising synthetic opportunity in the design of functionalized 2-amino-4*H*-chromene scaffolds. Interestingly, the catalysis of the same mixture of **10a**, **4a** and **5a** at ambient temperature with piperidine does not lead to **7a** after 32 min of reaction time. Thus we believe that the studied MCR of **4**, **5** and **6** in the presence of piperidine (Table 3) does not imply the mechanistic pathway A for the formation of **7**, what could be a reason for lower reaction yields and

significant amounts of oligomeric by-products compared to the electrocatalytic version.

As for the pathway B (Scheme 6), it includes the hydroxide-promoted intramolecular cyclization of Knoevenagel adduct **9** into reactive 2-imino-2*H*-chromene **11**[22] with a subsequent base-promoted Michael addition of the weaker *C*–*H* acid **5** owing to the equilibrium considerations given above. The following protonation of the combined adduct **12** by a molecule of an alcohol leads to the formation of 2-amino-4*H*-chromene **7** with regeneration of an alkoxide anion. The contribution of pathway C into the overall mechanistic Scheme seems to be less probable, as it initially includes the addition of the anion of the weaker *C*–*H* acid **5** to **9** in the presence of the stronger *C*–*H* acid **6** (Scheme 6). Moreover, the pathway C does not imply any reason for the regioselective cyclization of preformed adduct **13** with the subsequent formation of 2-amino-4*H*-chromene **7** if it deals with *C*–*H* acid **5** bearing a nitrile functionality (**5a**–**c** and **5g**, Y = CN).

On the score of the obtained results, we conclude that the electrocatalytic MCR of salicylaldehydes with two different *C*–*H* acids proceeds through the concerted pathways A and B. It is conceivable that the joint action of pathways A and B under conditions of the electrocatalytic procedure is advantageous for the fast and selective assembly of the starting reagents into the privileged 2-amino-4*H*-chromene scaffold **7** compared to conventional catalysis with a chemical base. Moreover, the low current concentration of the alkoxide anions along with a neutral *pH* of the whole solution during the electrocatalytic process in an undivided cell affords superior reaction yields and less formation of oligomeric side products in this base-sensitive multicomponent chemistry of active methylene species bearing nitrile groups.

The last step of both pathways A and B includes the protonation of the combined adduct **12** by a molecule of an alcohol with the regeneration of the alkoxide anion (Scheme 6). The catalytic chain process then continues by the interaction of the alkoxide with the next molecule of the *C*–*H* acid **6** (Scheme 4). Therefore, under the conditions of the developed electrocatalytic process, the generation of even a single alkoxide anion at the cathode is theoretically sufficient for the total conversion of equimolar quantities of salicylaldehyde and two different *C*–*H* acids into the corresponding functionalized 2-amino-4*H*-chromene scaffold.

Conclusions

The simple electrocatalytic system can produce, under neutral and mild conditions, a fast and effective multicomponent transformation of salicylaldehydes and two different *C*–*H* acids into functionalized 2-amino-4*H*-chromenes in 65–86% yields. This novel electrocatalytic process offers a facile and convenient way to create diversely substituted medicinally privileged 2-amino-4*H*-chromene scaffold – the approved basis for the generation of small-molecule ligands with different biomedical properties including highly pronounced anticancer activities. Compared to known MCR protocols, the electrocatalytic multicomponent procedure represents the first efficient approach to the reliable design of diversely substituted 2-amino-4*H*-chromene scaffolds. Two different *C*–*H* acids are distinguished according to their reactivity in the electrocatalytic process which results in the selective formation of a single 2-amino-4*H*-chromene product with a predefined arrangement of desired substituents. Moreover, the reaction smoothly proceeds with salicylaldehydes bearing both electron-donating and electron-withdrawing groups, and allows for the selective and combined introduction of a wide range of medicinally promising functionalities into the privileged 2-amino-4*H*-chromene scaffold. Thus, fifteen previously inaccessible close structural analogues of the tumor antagonists HA14-1 and MX58151 have been obtained. The neutral conditions of the electrocatalytic procedure were found to be advantageous compared to conventional base catalysis, and afforded superior reaction yields in this base-sensitive MCR of active methylene species bearing a nitrile functionality. The reversibility of the formation of 2-amino-4*H*-chromenes **10** revealed during mechanistic investigations seems to be an important feature of the electrocatalytic system that is promising for the synthesis of novel types of functionalized 2-amino-4*H*-chromenes by exchange of the corresponding *C*–*H* acid residue in the 4-position of the 4*H*-chromene cycle for another nucleophilic species. The developed electrocatalytic multicomponent procedure utilizes facile equipment, an undivided cell, and requires simple and reasonable starting materials. It is easily carried out, and the reaction products are directly crystallized from the reaction mixture. Finally, the efficient electrocatalytic approach to the functionalized medicinally privileged 2-amino-4*H*-chromene scaffold represents an absolutely novel synthetic concept for multicomponent reactions, and allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of a facile electrocatalytic procedure. Therefore, this novel type of MCR brings us a step closer to the notion of "ideal synthesis".[26]

Experimental Section

General Rmarks

Instrumental details as well as spectral and analytical characterization of compounds **7a**–**o** are given in the Supporting

Information. 2-Amino-3-cyano-4*H*-chromen-4-yl)malononitrile (**10a**) was synthesized by a previously reported method.[18a]

Typical Electrolysis Procedure

A solution of salicylaldehyde (10 mmol), two different *C–H* acids (10 mmol each) and sodium bromide (0.1 g, 1 mmol) in the appropriate alcoholic solvent (20 mL) was electrolysed in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20 °C under a constant current density of 10 mA cm^{-2} (I = 50 mA, electrode squares 5 cm^2) until the catalytic quantity of electricity indicated in Table 2 was passed. After the electrolysis was finished, the reaction mixture was gently concentrated[19] to one fifth of its initial volume (*ca.* 4 mL) to crystallize the solid product, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (9:1, 2 mL), and dried under reduced pressure.

Transformation of 10a into 7a

Salicylaldehyde **4a** (0.61 g, 5 mmol) and methyl cyanoacetate **6a** (0.99 g, 10 mmol) were added to a suspension of **10a** (1.18 g, 5 mmol) in EtOH (20 mL). The resulting mixture was magnetically stirred in a 50-mL beaker for 60 min at 20 °C, or electrolysed in the presence of NaBr (0.1 g, 1 mmol) in an undivided cell equipped with a magnetic stirrer, a graphite anode and an iron cathode at 20 °C under a constant current density of 10 mA cm^{-2} (I = 50 mA, electrodes square 5 cm^2) until the catalytic quantity of electricity 0.1 Fmol^{-1} (32 min) was passed. Afterwards, the reaction mixture was gently concentrated[19] to one fifth of its initial volume (*ca.* 4 mL) to crystallize the solid product, which was then filtered out, twice rinsed with an ice-cold ethanol/water solution (9:1, 2 mL), and dried under reduced pressure. Yields of **7a** thus obtained are given in Table 4.

Acknowledgements

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