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Electrocatalytic multicomponent cyclization of an aldehyde, malononitrile and a malonate into 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylate—the first one-pot synthesis of a cyclopropane ring from three different molecules

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Abstract—Electrolysis of an aldehyde, malononitrile and a malonate in an alcohol in an undivided cell in the presence of sodium acetate–sodium halide as a double mediatory system results in the formation of 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates in 40–60% yields.

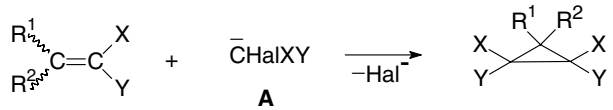
Cyclopropane is a basic structural element in a wide range of natural compounds and occupies a significant place in synthetic organic chemistry.[1] The cyclopropyl group is also a vital structural unit in many synthetic and naturally occurring compounds, exhibiting a wide spectrum of biological properties ranging from enzyme inhibition to herbicidal, antibiotic, antitumour and antiviral activities.[2,3] Insecticidal pyrethrins (derivatives of chrysanthemic acid) are perhaps the best known example of their use.[1] Thus, the prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.

Although the synthetic methods for cyclopropanes have long been documented, so far, all consist of two main groups: (1) intramolecular cyclization or, (2) interaction of two different molecules (addition of carbenes to olefins or Michael initiated ring closure (MIRC) are the best known examples of this type).[1,3] MIRC plays an important role in organic chemistry and many synthetic applications are described in the literature.[4]

The well-known MIRC leading to substituted cyclopropanes involves the addition of halogenosubstituted C–H acid anions (**A**), generated by the action of a base on the corresponding C–H acid (**AH**), to the conjugated activated olefins followed by cyclization with elimination of halide[5] (Scheme 1).

Anion (**A**) generation and its reactions with activated olefins have been accomplished in biphasic systems in the presence of a phase transfer catalyst.[6] The electrochemical reduction of dihalogeno substituted malonates followed by the addition of anion **A** (X=Y=COOR) to activated double bonds provides an improvement of this reaction scheme.[7]

The next essential step was to exclude halogen-containing organic compounds as initial reagents. Hence a novel electrochemical approach to functionally substituted cyclopropanes was performed by the electrolysis



X = COOR
Y = COOR, CN, C(O)NR$_2$
Hal = Br, I

Scheme 1.

Keywords: Electrolysis, Electrocatalytic transformation; Mediators; Aldehydes; Malononitrile; Malonate; Cyclopropanes.
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of alkylidenemalonates and malonate in an undivided cell in methanol in the presence of halides as mediators.[8]

The co-electrolysis of alkylidenecyanoacetic and malonic esters resulted in the stereoselective syntheses of (*E*)-isomers of trialkyl 3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates[9] (Scheme 2).

Recently, we accomplished the electrocatalytic transformation of alkylidenemalononitriles and malonate into dialkyl 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates[10] (Scheme 3).

It has also been found that tetracyanocyclopropanes, on electrolysis in alcohols in an undivided cell, were very easily attacked by alkoxide anions generated at the cathode to afford substituted 2-amino-4,4-dialkoxy-1,5-dicyano-3-azabicyclo[3.1.0]hex-2-enes[11] (Scheme 4).

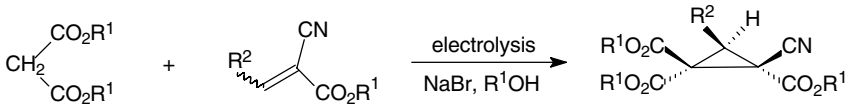
Combining these two methods, we accomplished the stereoselective electrocatalytic transformation of alkylidenemalononitriles and malononitrile into bicyclic pyrrolines containing a cyclopropane ring[12] (Scheme 5).

The next step of our research was a one-pot stereoselective electrocatalytic transformation of an aromatic aldehyde and malononitrile into bicyclic pyrrolines in the presence of the new double mediatory system NaOAc–NaBr[13] (Scheme 6).

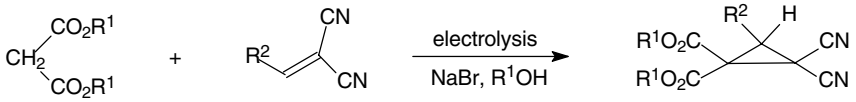
In the present study, we report our results on the one-pot, multicomponent electrocatalytic transformation of aldehydes **1a**–**i**, malononitrile and malonate into 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates **2a**–**i** in methanol in the presence of the double mediatory system sodium acetate–sodium bromide in an undivided cell, which to our knowledge is the first example of cyclopropane ring formation from three different molecules (Scheme 7, Table 1).

In the mediatory system, NaOAc acts as a catalyst for the Knoevenagel condensation of the aldehyde and malononitrile. When electricity was not passed, the aldehyde and malononitrile, in the presence of NaOAc, were condensed into alkylidenemalononitriles in a time less than half of that of the electrochemical reaction (30 min). Earlier NaOAc was used as a catalyst in the Perkin condensation[15] and in the Knoevenagel reaction.[13]

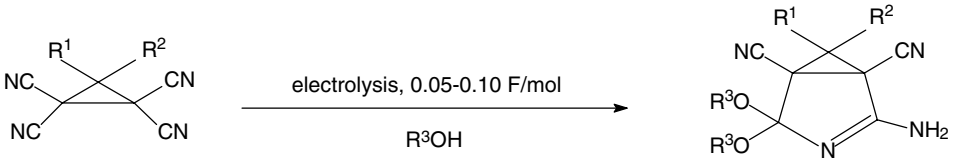
Taking into consideration the above results, the data on the mechanism of the electrocatalytic variant of the



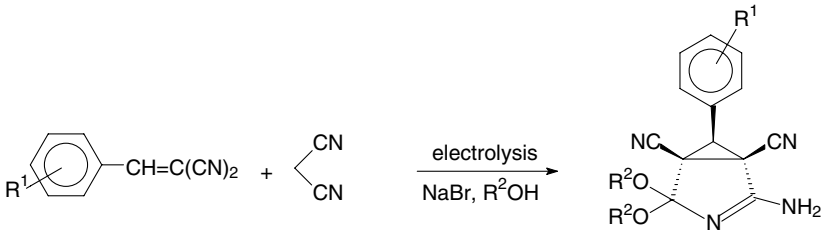
Scheme 2.



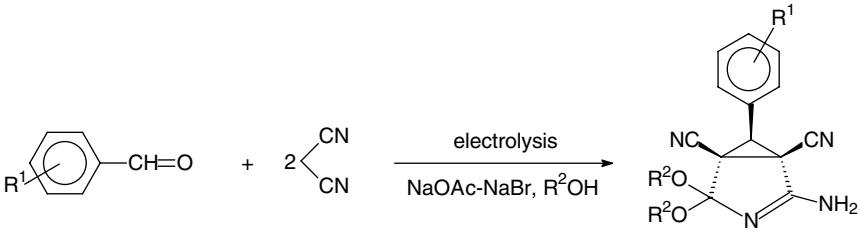
Scheme 3.



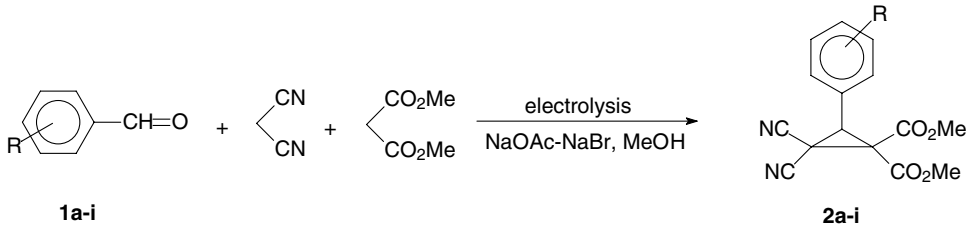
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

Table 1. Electrocatalytic transformation of an aldehyde, malononitrile and a malonate into 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates **2a**–**i**[a,14]

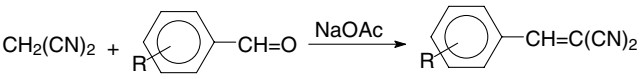
Aldehyde	R	Cyclopropane	Yield[b] (%)
1a[c]	H	**2a**	35
1a	H	**2a**	54
1a[d]	H	**2a**	41
1b	4-Me	**2b**	52
1c	4-MeO	**2c**	47
1d	2-MeO	**2d**	45
1e	4-Cl	**2e**	58
1f	2-Cl	**2f**	48
1g	4-Br	**2g**	46
1h	4-F	**2h**	63
1i	2-F	**2i**	46

[a] 12 mmol of malononitrile, 10 mmol of dimethyl malonate, 10 mmol of aldehyde, 5 mmol of NaBr, 5 mmol of NaOAc, 20 ml of methanol, Fe-cathode, C-anode, current density 100 mA/CM^2, 2.5 F/mol electricity passed at 0 °C.
[b] Isolated yields.
[c] 10 °C.
[d] Mediator: NaI–NaOAc.

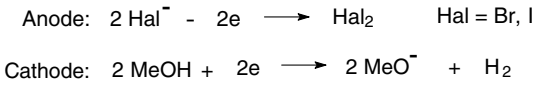
Wideqvist reaction[11] and the mechanism of electrocatalytic transformation of alkylidenemalononitriles and malonate into dialkyl 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates,[10] the following mechanism for the one-pot electrocatalytic transformation of an aldehyde, malononitrile and a malonate into 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates is suggested. Knoevenagel condensation of malononitrile and the aldehyde is catalyzed by NaOAc (Scheme 8).

The reactions occurring at the electrodes, are shown below (Scheme 9).

The formation of iodine or bromine at the anode is a well-known process and the corresponding halogen colour was observed at the anode when the electrolysis



Scheme 8.



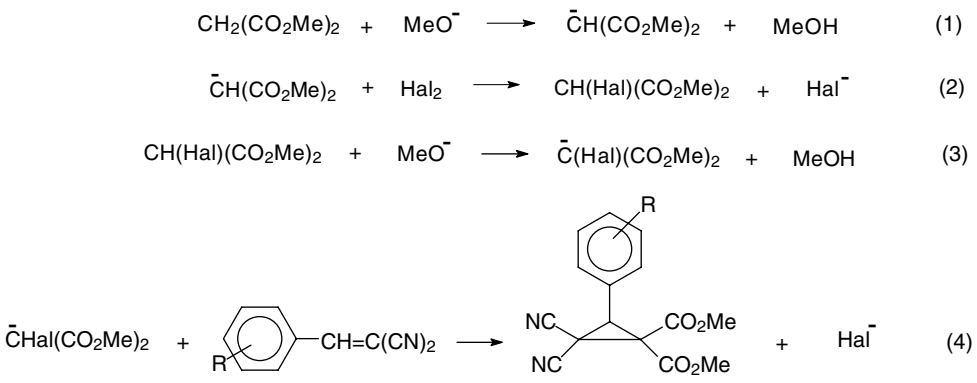
Scheme 9.

was conducted without stirring the reaction mixture. The evolution of hydrogen occurred at the cathode.

The reaction in solution between an alkoxide ion and malonate leads to the formation of a malonate anion. Halogenation of the malonate anion by the halogen generated at the anode, then the formation of the halogenomalonate anion, followed by the addition to the alkylidenemalonitrile gives rise to a 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate (Scheme 10).

Sodium bromide is more efficient as a mediator for the above process than sodium iodide. This result is directly related to the fact that the intermediate bromomalonate is a stronger CH acid than iodomalonate and thus the proton abstraction step with the formation of the halogenomalonate anion [Scheme 10, stage (3)] is faster in the case of bromomalonate.

Thus, the simple electrocatalytic system can produce under mild conditions one-pot electrocatalytic multicomponent transformations of an aldehyde, malononitrile and malonate into 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates **2a**–**i**. This process, to our knowledge, is the first example of cyclopropane ring formation from three different molecules.



Scheme 10.

Using classical organic chemistry, this transformation could only be accomplished as a three-step process comprising (i) Knoevenagel condensation of the aldehyde and malononitrile with formation of an alkylidenemalononitrile,[16] (ii) halogenation of the malonate[17] and, (iii) addition of the halogenomalonate to the double bond of the alkylidenemalononitrile followed by cyclization.[18]

This new electrochemical process is an efficient and convenient method for the synthesis of 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates. The procedure utilizes inexpensive reagents, simple equipment and an undivided cell, it is easily carried out and the work-up is not complicated.

To our knowledge this is also the first example using a multicomponent strategy for the synthesis of cyclopropanes.

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14. *General electrolysis procedure.* A solution of aldehyde (10 mmol), malononitrile (12 mmol), dimethyl malonate (10 mmol), sodium bromide (5 mmol) and sodium acetate (5 mmol) in methanol (20 ml) was electrolyzed in an undivided cell equipped with a C-anode and an Fe-cathode, a thermometer, external cooling and a magnetic stirrer under constant current density of 100 mA/cm^2 at 0 °C. At the end of the electrolysis, when 2.5 F/mol electricity had been passed, the dimethyl 3-substituted-2,2-dicyanocyclopropane-1,1-dicarboxylates were removed by filtration and washed with cold methanol. All compounds (**2a**–**i**) gave expected NMR spectra. For new compounds (**2d**,**g**,**h**), satisfactory elemental analyses were obtained. Mass-spectra (70 eV) were determined directly using Finningan MAT INCOS 50 spectrometer.

Dimethyl 3-(2-methoxyphenyl)-2,2-dicyanocyclopropane-1,1-dicarboxylate **2d**: mp 114–115 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.80$ (s, 3H, CH_3O), 3.84 (s, 1H, CH), 3.93 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 6.90–7.00 (m, 2H, Ar), 7.21 (d, 1H, Ar, $J = 7.8$), 7.33–7.44 (m, 1H, Ar); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 17.2$ (C), 36.9 (CH), 46.4 (C), 53.9 (CH_3O), 54.7 (CH_3O), 55.7 (CH_3O), 110.0 (CN), 111.1 (CH, Ar), 112.4 (CN), 115.8 (C, Ar), 120.7, 128.6, 131.3 (all CH, Ar), 158.2 (C–O, Ar), 162.0 (C═O), 163.7 (C═O). MS (70 eV) *m/z* (relative intensity %): 314 (M^+, 24), 282 (79), 255 (34), 239 (20), 223 (25), 181 (44), 59 (100). IR (KBr, cm^{-1}): *v* 2256, 1762, 1748, 1440, 1288. Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.93; H, 4.53; N, 8.69.

Dimethyl 3-(4-bromophenyl)-2,2-dicyanocyclopropane-1,1-dicarboxylate **2g**: mp 107–108 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3H, CH_3O), 3.93 (s, 1H, CH), 3.97 (s, 3H, CH_3O), 7.23 (d, 2H, Ar, $J = 8.4$), 7.53 (d, 2H, Ar, $J = 8.4$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 16.5$ (C), 36.6 (CH), 46.3 (C), 54.2 (CH_3O), 55.1 (CH_3O), 109.5 (CN), 111.6 (CN), 124.3 (C, Ar), 126.3 (C, Ar), 130.5, 130.5, 132.5, 132.5 (all CH, Ar), 161.4 (C═O), 163.3 (C═O). MS (70 eV) *m/z* (relative intensity %): 364 (M^+, 18), 362 (M^+, 22), 332 (41), 330 (38), 305 (39), 303 (38), 220 (83), 218 (75), 201 (65), 199 (76), 165 (60), 59 (100). IR (KBr, cm^{-1}): *v* 2252, 1756, 1748, 1440, 1272. Anal. Calcd for $C_{15}H_{11}BrN_2O_4$: C, 49.61; H, 3.05; Br, 22.00; N, 7.71. Found: C, 49.43; H, 3.01; Br, 21.79; N,7.58.

Dimethyl 3-(4-fluorophenyl)-2,2-dicyanocyclopropane-1,1-dicarboxylate **2h**: mp 126–127 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3H, CH_3O), 3.94 (s, 1H, CH), 3.98 (s, 3H, CH_3O), 7.11 (t, 2H, Ar, $J = 8.7$), 7.38 (dd, 2H, Ar, $J_1 = 5.1$, $J_2 = 8.7$); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 16.6$ (C), 39.6 (CH), 46.4 (C), 54.1 (CH_3O), 55.0 (CH_3O), 109.7 (CN), 111.7 (CN), 116.4 (d, CH, Ar, $^2J_{CF} = 22.9$), 123.2 (d, C, Ar, $^4J_{CF} = 3.5$), 130.9 (d, CH, Ar, $^3J_{CF} = 9.1$), 161.5 (C═O), 163.3 (d, CF, $J = 248.8$), 163.4 (C═O). MS (70 eV) *m/z* (relative intensity %): 302 (M^+, 12), 271 (67), 258 (44), 243 (50), 158 (100), 139 (90), 59 (91). IR (KBr, cm^{-1}): *v* 2256, 1760, 1740, 1512, 1436, 1236. Anal. Calcd for $C_{15}H_{11}FN_2O_4$: C, 59.61; H, 3.67; F, 6.29; N, 9.27. Found: C, 59.43; H, 3.58; F, 6.14; N, 9.19.

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