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Stereoselective electrocatalytic transformation of arylidene- or alkylidenemalononitriles and malonate into alkyl (1*R*,5*R*,6*R*)* 6-substituted 5-cyano-4,4-dialkoxy-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylates

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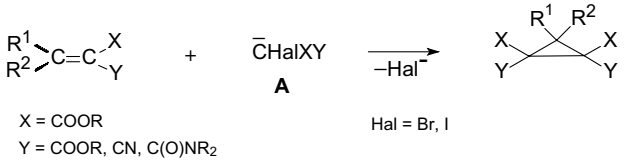
Abstract—Electrolysis of arylidene- or alkylidenemalononitriles and malonate in alcohol in an undivided cell in the presence of sodium halide as mediator results in the stereoselective formation of alkyl (1*R*,5*R*,6*R*)* 6-substituted 5-cyano-4,4-dialkoxy-2-oxo-3-azabicyclo[3.1.0]hexan-1-carboxylates in 50–70% yields.

Cyclopropane derivatives occupy a significant place in synthetic organic chemistry.[1] Their structural and reactivity features have found widespread application in the synthesis of natural products. Cyclopropanecarboxylic acid derivatives play an important role as effective agents in agriculture and medicine.[2] Insecticidal pyrethrins (derivatives of cyclopropanoid chrysanthemic acid) are perhaps the best known examples of their use.[3]

A well-known method for the synthesis of substituted cyclopropanes involves addition of halogeno-substituted C–H acid anions (**A**), generated by the action of a base on the corresponding C–H acid (**AH**), to conjugate activated olefins followed by cyclisation with elimination of a halogen anion (Scheme 1).[4]

Both anion **A** generation and its reactions with activated olefins have been accomplished in biphasic systems in the presence of a phase transfer catalyst.[5] Electrochemical reduction of dihalogeno-substituted malonates followed by the addition of the anion



Scheme 1.

(**A**, X = Y = COOR) to activated double bonds provides an improvement in this reaction.[6]

The next essential step was to exclude halogen-containing organic compounds as initial reagents. The new electrochemical approach to functionally substituted cyclopropanes was performed by the electrolysis of alkylidenemalonates and malonate in an undivided cell in methanol in the presence of halides as mediators.[7,8]

The co-electrolysis of alkylidenecyanoacetic and malonic esters carried out within the framework of this approach resulted in the stereoselective synthesis of (*E*)-isomers of trialkyl 3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates[9] (Scheme 2).

It has also been found that tetracyanocyclopropanes, being electrolysed in alcohols in an undivided cell, are

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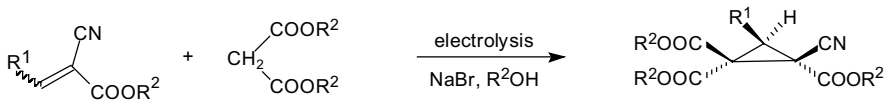
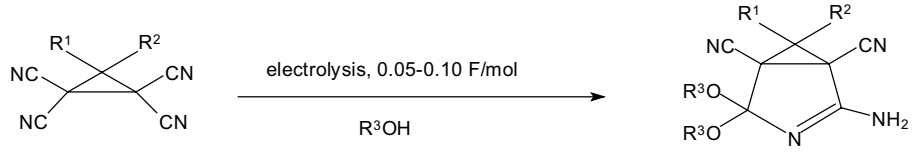


Scheme 2.



Scheme 3.

very easily attacked by alkoxide anions generated at the cathode and result in the transformation into substituted 2-amino-4,4-dialkoxy-1,5-dicyano-3-azabicyclo-[3.1.0]hex-2-enes[10] (Scheme 3).

Combining the last two methods, we have recently reported a procedure for the stereoselective electrocatalytic transformations of arylidenemalononitriles and malononitrile into bicyclic pyrrolines containing cyclopropane ring[11] (Scheme 4).

In the present study we report our results on the stereoselective electrocatalytic transformations of arylidene- or alkylidenemalononitriles **1a**–**g** and malonate into bicyclic pyrrolidones **2a**–**h**, in alcohols, in the presence of sodium halide as a mediator (Table 1, Scheme 5).[12]

This electrochemical reaction takes place with high stereoselectivity. In all experiments, only one of the two possible isomers of bicyclic pyrrolidones **2a**–**h** was found by NMR spectroscopy. The structures of **2a** and **2f** were established by single-crystal X-ray diffraction studies.[13]

In **2a** and **2f**, the R^1-substituent and the pyrrolidone ring are in trans positions relative to the cyclopropane ring. From the point of view of the least steric hindrance, all other bicyclic pyrrolidones **2b**–**e**,**g**,**h** should have similar structures (see Fig. 1).

Taking into consideration the above results, the data on the mechanism of the electrocatalytic variant of the Wideqvist reaction,[10] and the mechanism of the stereoselective electrocatalytic transformation of arylidenemalononitrile and malononitriles into (1*R*,5*S*,6*R*)*-6-aryl-2-amino-4,4-dialkoxy-1,5-dicyano-3-aza-bicyclo-

Table 1. Stereoselective electrocatalytic transformation of arylidene- or alkylidenemalononitriles **1a**–**g** and malonate into bicyclic pyrrolidones **2a**–**h**[a]

Nitrile	R^1	R^2	Mediator	Bicyclic pyrrolidone	Yield[b] (%)
1a	Ph	Me	NaBr	**2a**	69
1a	Ph	Me	NaI	**2a**	53
1b	4-MeC_6H_4	Me	NaBr	**2b**	58
1c	4-$MeOC_6H_4$	Me	NaBr	**2c**	45
1d	4-ClC_6H_4	Me	NaBr	**2d**	67
1e	Me	Me	NaBr	**2e**	69
1f	Et	Me	NaBr	**2f**	73
1g	*n*-Pr	Me	NaBr	**2g**	57
1a	Ph	Et	NaBr	**2h**	62

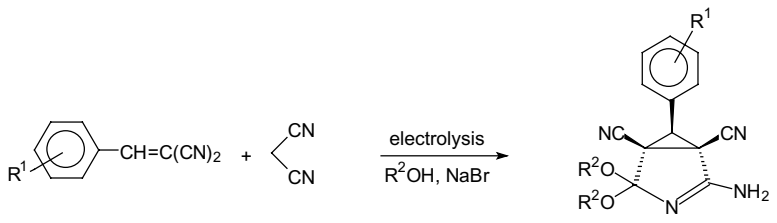
[a] 10 mmol of arylidene- or alkylidenemalononitrile **1a**–**g**, 10 mmol of malonate, 5 mmol of mediator, 20 mL of alcohol, Fe-cathode, C-anode, current density 100 mA/cm^2, 2.5 F/mol electricity passed at 10 °C.

[b] Isolated yields.

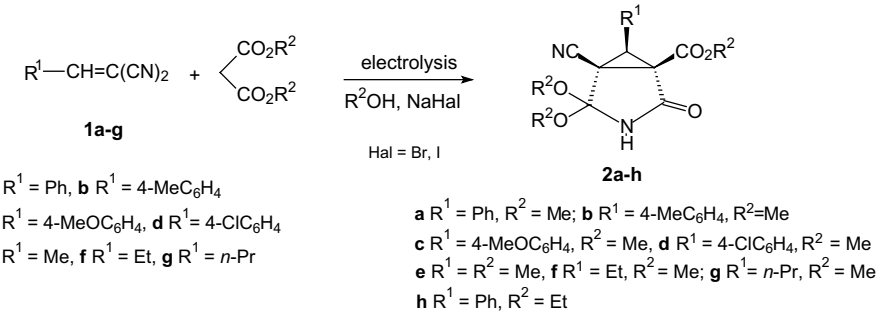
[3.1.0]hex-2-enes,[11] the following mechanism for the stereoselective electrocatalytic transformation of arylidene- or alkylidenemalononitriles **1a**–**g** and malonate into bicyclic pyrrolidones **2a**–**h** is proposed. The reactions at the electrodes, which take place during the process, are shown below (Scheme 6).

The formation of iodine or bromine at the anode is a well-known process and the corresponding colour was observed at the anode when the electrolysis was conducted without stirring the reaction mixture whilst evolution of hydrogen occurred at the cathode.

Reaction in solution between the alkoxide ion and malonate leads to the formation of the malonate ion as the



Scheme 4.



Scheme 5.

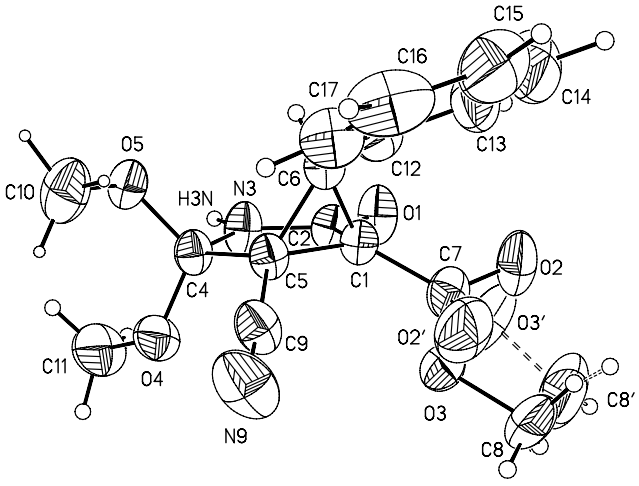
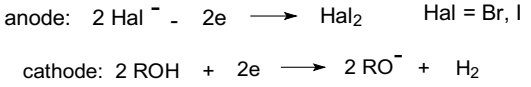


Figure 1. The general view of **2a** molecular structure in representations of atoms by thermal ellipsoids.



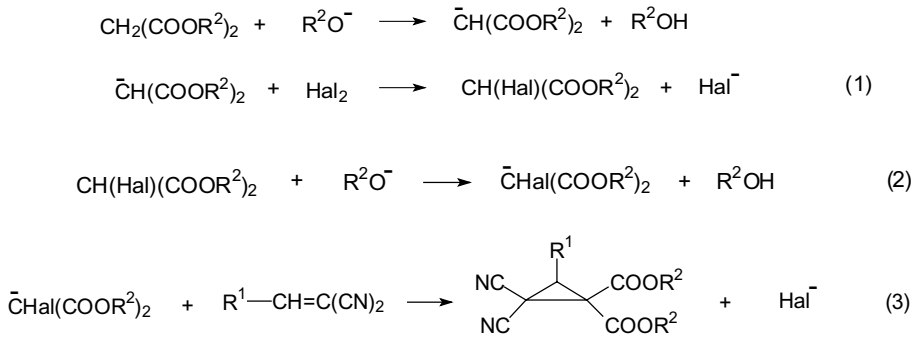
Scheme 6.

general result of the cathodic process. Halogenation of the malonate anion by the halogen generated at the anode, formation of the halogenomalonate anion, followed by the addition of the latter to arylidene- or alkylidenemalonitrile gives rise to the 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate (Scheme 7).

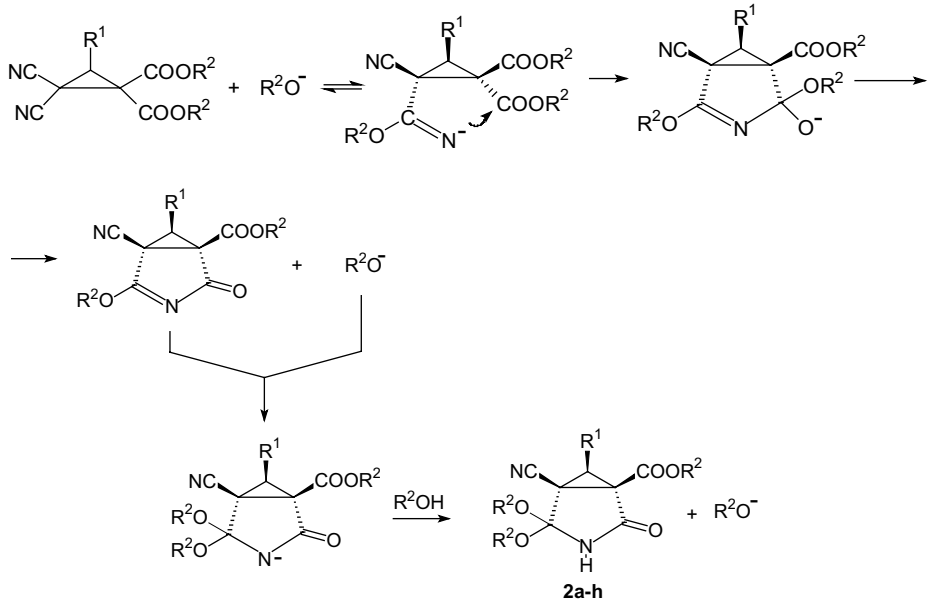
The stereoselective formation of **2a**–**h** is a result of the chain electrocatalytic mechanism shown in Scheme 8, which takes place as the successive addition of two R^2OH molecules to the intermediate 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate initiated by an R^2O^- ion and includes the regeneration of the R^2O^- anion at the last stage, which continues the catalytic chain process by interaction with the next molecule of the substrate.

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 formation of the halogenomalonate anion (Scheme 7, stage 2) is faster in the case of bromomalonate. The stereoselectivity of the process could be the result of the stereoselectivity of the alkoxide anion attack on CN-group. This attack takes place on the sterically less hindered CN group, which is in a trans position to the R^1 substituent.

Thus, this simple electrocatalytic system can produce, under mild conditions, a direct 'one-pot' stereoselective transformation of arylidene- or alkylidenemalononitriles and malonates into bicyclic pyrrolidones **2a**–**h** in high yields. Using classical organic chemistry, this transformation could only be accomplished as a three-step process comprising (i) halogenation of malonate,[14]



Scheme 7.



Scheme 8.

(ii) addition of halogenomalonate to the double bond of the arylidene- or alkylidenemalononitrile followed by cyclisation,[15] (iii) reaction of 3-substituted 2,2-dicyanocyclopropane-1,1-dicarboxylate obtained in a step (ii) with alkoxide ions in alcohols. The last reaction is novel and unknown in organic chemistry. Thus, this new electrochemical process is an efficient and convenient stereo- selective method for the synthesis of bicyclic pyrrolidones containing a cyclopropane ring. The procedure utilises inexpensive reagents, simple equipment and an undivided cell, it is easily carried out and the work-up is not complicated.

Acknowledgements

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12. *General electrolysis procedure*: A solution of arylidene- or alkylidenemalononitrile (10 mmol), malonate (10 mmol), and a mediator (5 mmol) in alcohol (20 mL) was electrolysed in an undivided cell equipped with a C-anode and Fe-cathode, a thermometer, external cooling and with magnetic stirring under a constant current density of 100 mA/cm^2 at 10 °C. At the end of the electrolysis (2.5 F/mol electricity) the bicyclic pyrrolidones were usually crystallised directly from the reaction mixture and were then filtered off. The additional portion of bicyclic pyrrolidones was isolated from the residue of the reaction mixture according to the following procedure. The solvent was removed, and the residue was extracted with chloroform, washed with water and dried over Na_2SO_4. Chloroform was removed and the residue was crystallised from methanol.
All new compounds (**2a**–**h**) gave expected NMR spectra and elemental analyses.
Methyl (1*R*,5*R*,6*R*)* 5-cyano-4,4-dimethoxy-2-oxo-6-phenyl-3-azabicyclo[3.1.0]hexan-1-carboxylate (**2a**): mp 110–112 °C; ^{1}H NMR ($CDCl_3$): δ 3.29 (s, 1H, CH), 3.46 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 7.35 (s, 1H, NH), 7.40 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 31.66 (C), 39.87 (CH), 43.51 (C), 50.17 (OCH_3), 51.66 (OCH_3), 53.00 (OCH_3), 106.64 [$C(OMe)_2$], 112.82 (CN), 128.36, 128.45, 128.79, 129.21 (C_6H_5), 162.06 (NC═O), 167.21 (OC═O); IR (KBr): ν_{max} 2256, 1760, 1708.
Methyl (1*R*,5*R*,6*R*)* 5-cyano-4,4-dimethoxy-6-(4-methylphenyl)-2-oxo-3-azabicyclo[3.1.0]hexan-1-carboxylate (**2b**): mp 127–129 °C; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3),

3.25 (s, 1H, CH), 3.47 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 7.20 (d, 2H, J = 8 Hz, Ar), 7.38 (d, 2H, J = 8 Hz, Ar), 7.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 21.18 (CH_3), 31.75 (C), 39.82 (CH), 43.98 (C), 50.26 (OCH_3), 51.81 (OCH_3), 53.15 (OCH_3), 106.79 [$C(OMe)_2$], 112.98 (CN), 126.26, 128.49, 129.59, 138.95 (Ar), 161.82 (NC=O), 167.14 (OC=O); IR (KBr): ν_{max} 2252, 1760, 1728.

Methyl (1*R*,5*R*,6*R*)* 5-cyano-4,4-dimethoxy-6-methyl-2-oxo-3-azabicyclo[3.1.0]hexan-1-carboxylate (**2e**): mp 150–151 °C; ^{1}H NMR ($CDCl_3$): δ 1.58 (d, 3H, J = 7 Hz, CH_3), 2.15 (q, 1H, J = 7 Hz, CH), 3.42 (s, 3H, CH_3O), 3.48 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 6.35 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 10.54 (CH_3), 31.95 (CH), 32.37 (C), 42.90 (C), 49.91 (CH_3O), 51.68 (CH_3O), 53.28 (CH_3O), 106.41 [$C(OMe)_2$], 112.87 (CN), 162.51 (NC=O), 167.27 (OC=O); IR (KBr); ν_{max} 2248, 1744, 1724.

Methyl (1*R*,5*R*,6*R*)* 5-cyano-4,4-dimethoxy-6-ethyl-2-oxo-3-azabicyclo[3.1.0]hexan-1-carboxylate (**2f**): mp 144–146 °C; ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 3H, J = 7 Hz, CH_3), 1.79 (m, 1H, CH_2), 1.89 (m, 1H, CH_2), 1.95 (m, 1H, CH), 3.40 (s, 3H, CH_3O), 3.47 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 7.63 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.35 (CH_3), 19.17 (CH_2), 31.56 (C), 38.56 (CH), 42.95 (C), 49.92 (CH_3O), 51.45 (CH_3O), 53.25 (CH_3O), 106.40 [$C(OMe)_2$], 112.94 (CN), 162.58 (NC=O), 167.47 (OC=O); IR (KBr): ν_{max} 2248, 1748, 1720.

13. Crystal data for **2a**: $C_{16}H_{16}N_2O_5$, M = 316.31, space group $C2/c$, a = 18.691(9) Å, b = 15.080(6) Å, c = 13.292(7) Å, β = 121.390(3)°, V = 3198.2(2) Å^3, Z = 8, D_C = 1.314 g cm^{-3}.
Crystal data for **2f**: $C_{12}H_{16}N_2O_5$, M = 268.27, space group $P2_1/c$, a = 7.7817(7) Å, b = 10.5320(9) Å, c = 16.6245(14) Å, β = 101.490(2)°, V = 1335.2(2) Å^3, Z = 4, D_C = 1.335 g cm^{-3}.
Crystallographic data for **2a** and **2f** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 262938 and CCDC 262939. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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