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# Stereoselective electrochemical transformation of alkylidenecyanoacetates and malonate into (*E*)-3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates

Michail N. Elinson,[a,*] Sergey K. Feducovich,[a] Zoya A. Starikova,[b] Olga S. Olessova,[a] Anatolii N. Vereshchagin[a] and Gennady I. Nikishin[a]

[a]*N.D. Zelinsky Institute of Organic Chemistry, Leninsky prospect 47, 117913 Moscow B-334, Russia*
[b]*A.N. Nesmeyanov Institute of Organoelement Compounds, ul. Vavilova 28, 117813 Moscow B-334, Russia*

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**Abstract**

Electrolysis of malonate and alkylidenecyanoacetates in alcohols in the presence of sodium bromide in an undivided cell results in the stereoselective formation of (*E*)-3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylates in 75–85% yields. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* electrochemical reactions; stereoselectivity; catalysis; cyclopropanes.

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 efficient agents in agriculture and medicine.[2] Furthermore, perhaps the best known example of their use, insecticidal pyrethrins are derivatives of cyclopropanoid chrysanthemic acid.[3]

There are known methods of synthesizing substituted cyclopropanes by the addition of halogenosubstituted CH acid anions (**A**) generated by the action of a base on the corresponding CH acid (**AH**) to conjugated activated olefins, followed by cyclization with elimination of halogen anion (Scheme 1).[4]

In recent years, both the method of 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 dihalogenosubstituted malonates and further successful addition of the anion (**A**, X = Y = COOR) to activated double bonds was an improvement in the development of this reaction scheme.[6]

* Corresponding author.

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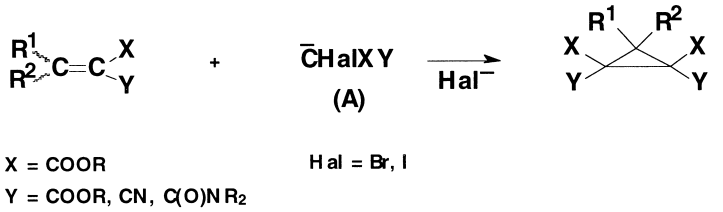
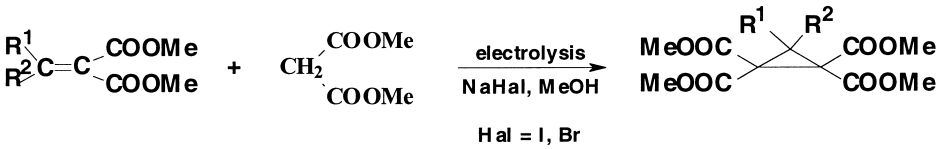


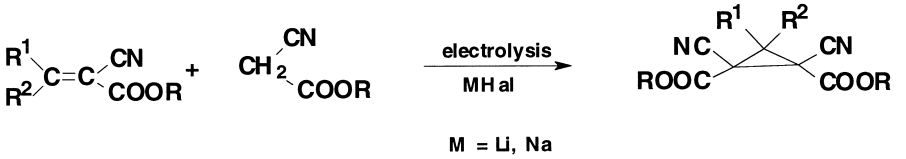

Scheme 1.

The next essential step was excluding 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 (Scheme 2).[7]




Scheme 2.

The same reaction scheme was also accomplished for the synthesis of substituted cyclopropanes by the co-electrolysis of alkylidenecyanoacetates and cyanoacetic ester (Scheme 3).[8]



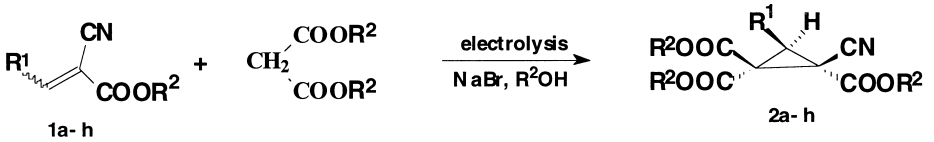

Scheme 3.

This communication deals with a new and unusual stereoselective electrochemical transformation of alkylidenecyanoacetates **1a**–**h** and malonate into (*E*)-3-substituted-2-cyanocyclopropane-1,1,2-tricarboxylates **2a**–**h** (Table 1).

Extra experiments have been performed to check the mechanism of the process. Decreasing the quantity of the electricity passed from 2.6 F/mol (exp. 1) to 1.0 and 0.5 F/mol resulted in decreasing the yield of **2a** from 85 to 38 and 16%, respectively. Under these conditions, 2-methyl-3-cyanopropane-1,1,3-tricarboxylate **3a** (mixture of diastereomers) was obtained as the main product in 36 and 57% yields.

Thus, the first step in the process of the indirect electrochemical transformation of alkylidenecyanoacetates and malonate into substituted cyclopropanes **2** is the electrochemically induced addition of malonate anion (**A**) to the activated double bond of alkylidenecyanoacetate with the formation of anion (**B**). Further halogenation of anion (**B**) with the halogen generated at anode and cyclization induced by the interaction with $R^2O^-$ anion result in the formation of the final product of the process, cyclopropane **2** (Scheme 4).

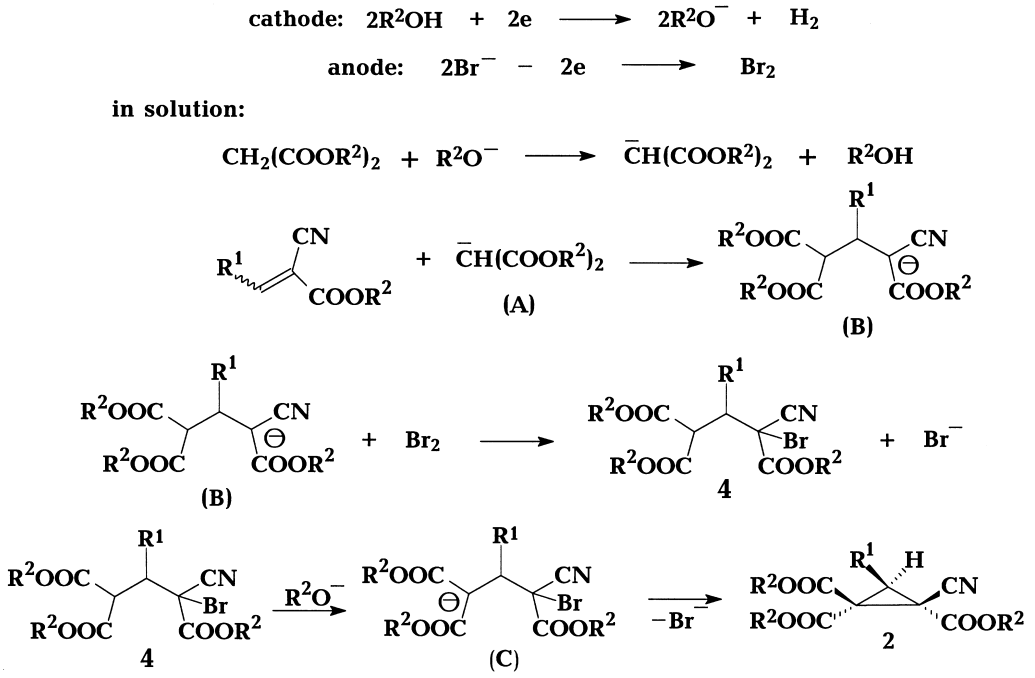
Table 1
Electrochemical synthesis of 3-substituted 2-cyanocyclopropane-1,1,2-tricarboxylates[a]




1a- h 2a- h

| N | Alkylidene-cyanoacetate | $R^1$ | $R^2$ | Mediator | Electricity passed, F/mol | Product, yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | Me | Me | NaBr | 2.6 | **2a**, 85 |
| 2 | **1b** | Et | Me | NaBr | 2.7 | **2b**, 78 |
| 3 | **1c** | Pr | Me | NaBr | 2.7 | **2c**, 75 |
| 4 | **1d** | *i*-Pr | Me | NaBr | 3.0 | **2d**, 74 |
| 5 | **1e** | Ph | Me | NaBr | 3.0 | **2e**, 78 |
| 6 | **1f** | Ph | Et | NaBr | 3.0 | **2f**, 82 |
| 7 | **1g** | 4-$MeOC_6H_4$ | Me | NaBr | 2.4 | **2g**, 85 |
| 8 | **1h** | 2-$ClC_6H_4$ | Me | NaBr | 3.0 | **2h**, 78 |

[a] Alkylidenecyanoacetate 10 mmol, malonate 10 mmol, mediator 7 mmol, 20 ml of alcohol, Fe-cathode, C-anode, current density 100 mA/cm$^2$, 5°C.
[b] Isolated yields.

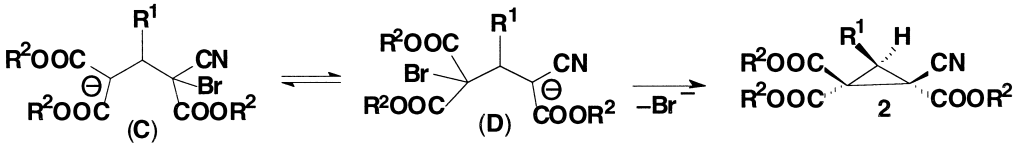



Scheme 4.

This new electrochemical reaction takes place with high stereoselectivity. In all experiments studied, only one of two possible isomeric cyclopropanes **2** was found by NMR spectroscopy. The structures of **2a** and **2e** were established by single crystal X-ray diffraction study.[9] Structures of **2b–d** and **2f–h** were confirmed by NMR spectroscopy using nuclear Overhauser effects.

The stereoselectivity of the process studied could be the result of the stereoselectivity of the halogenation step. Another explanation is connected with the difference in the rate of cyclization of two diastereomeric anions **C**. The interconversion of the two diastereomers of **C** may take place via protonation of anion **C**, then cathodic reduction of **4** into anion **B** and repeated halogenation.

Another possible reason for the stereoselectivity is $Br_T^+$ transfer mechanism[10] and formation of anion **D** directly from anion **C**. Further thermodynamically controlled cyclization of anion **D** should lead to the (*E*)-isomer of cyclopropane **2** (Scheme 5).




Scheme 5.

Earlier it has been found that the electrochemical cyclotrimerization of ethyl cyanoacetate in the presence of sodium bromide as mediator led stereoselectively to *trans* triethyl 1,2,3-tricyano-cyclopropane-1,2,3-tricarboxylate.[11]

*Experimental procedure*. A solution of alkylidenecyanoacetate (10 mmol), malonate (10 mmol) and NaBr (7 mmol) in methanol or ethanol was electrolyzed in an undivided cylindrical cell equipped with graphite anode and Fe–cathode at 5°C under constant current density 100mA/cm$^2$ until the quantity of the electricity indicated in Table 1 was passed. In some cases, the products were partially crystallized from the reaction mixture. The solvent was then removed and the reaction mixture was extracted with chloroform, washed with water and dried with $Na_2SO_4$. Chloroform was removed, and the product was then crystallized from the acetone–hexane mixture or isolated by distillation.[12]

Alkylidenecyanoacetates were obtained from cyanoacetate and corresponding aldehydes by Knoevenagel reaction.[13]

## Acknowledgements

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9. Crystal data for **2a**: $C_{11}H_{13}NO_6$, M = 255.22, monoclinic, space group $P2_1/n$, $a = 8.972(3)$ Å, $b = 15.159(7)$ Å, c = 9.732(4) Å, $\beta = 106.89$ (3)°, $V = 1266.5(9)$ Å$^3$, $Z = 4$, $D_C = 1.339$ g cm$^{-3}$. Crystal data for **2e**: $C_{16}H_{15}NO_6$, $M = 317.29$, rhombic, space group $P2_12_12_1$, $a = 9.715(5)$ Å, $b = 10.693(5)$ Å, $c = 15.013(8)$ Å, $V = 1559.9(14)$ Å$^3$, $Z = 4$, $D_C = 1.351$ g cm$^{-3}$. X-Ray diffraction experiments were carried out on CAD4 Enraf-Nonius (**2a**) and Siemens P3/PC (**2e**) difractometers ($T = 293$° K, graphite monochromated Mo-$K_‡$ radiation, $\theta_{max} = 25$°). The structures **2a** and **2e** were solved by direct methods and refined by the full-matrix least-squares technique on $F^2_{hkl}$ in the anisotropic approximation. H atoms were located from the difference Fourier synthesis and then refined isotropically. The final disperancy factors were $R_1 = 0.0580$ (1704 observed reflections), $wR_2 = 0.1278$ (for all 2226 reflections used in refinement) for **2a**, and $R_1 = 0.039$ (912 observed reflections), $wR_2 = 0.2348$ (for all 1547 reflections) for **2e**. All calculations were carried out with the complex of programs SHELXTL PLUS 5 (Sheldrick G.M. SHELXTL Version 5, Software Reference Manual, Siemens Industrial Automation, Inc., Madison, 1994).
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12. All new compounds (**2a**–**h**) gave expected NMR spectra, elemental analyses or exact mass measurements. **Trimethyl 3-methyl-2-cyanocyclopropane-1,1,2-tricarboxylate 2a**, mp 87–89°C, $^1$H NMR ($CDCl_3$): $\delta$ 1.45 (d, 3H, $CH_3$, $J = 6.1$ Hz), 2.67 (m, 1H, CH, $J = 6.1$ Hz), 3.70 (s, 3H, $CH_3O$), 3.79 (s, 6H, $CH_3O$). $^{13}$C NMR ($CDCl_3$): $\delta$ 9.57 (q), 31.04 (s), 31.77 (d), 47.02 (s), 53.61 (q), 53.75 (q), 54.38 (q), 112.64 (s), 163.22 (s), 164.43 (s), 164.90 (s). **Trimethyl 3-phenyl-2-cyanocyclopropane-1,1,2-tricarboxylate 2e**, mp 140–142°C, $^1$H NMR ($CD_3CN$): $\delta$ 3.70 (s, 3H, $CH_3O$), 3.79 (s, 3H, $CH_3O$), 3.88 (s, 3H, $CH_3O$), 3.96 (s, 1H, CH), 7.38 (m, 5H, $C_6H_5$). $^{13}$C NMR ($CDCl_3$): $\delta$ 30.57 (s), 39.55 (d), 47.72 (s), 53.45 (q), 53.65 (q), 54.54 (q), 112.37 (s), 128.48 (d), 128.67 (d), 128.78 (d), 129.32 (s), 162.69 (s), 164.27 (s), 164.86 (s).
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