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# The first electrocatalytic stereoselective multicomponent synthesis of cyclopropanecarboxylic acid derivatives

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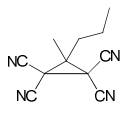
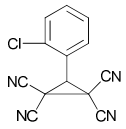
The one-pot electrocatalytic domino transformation of aldehydes and two different C-H acids – alkyl cyanoacetate and dialkyl malonate in the presence of sodium bromide–sodium acetate as a double mediatory system in alcohol in an undivided cell (simple beaker) results in stereoselective formation of trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates in 52–87% yields. This protocol uses group-assisted purification (GAP) chemistry in which the pure products were simply isolated by filtration from the reaction mixture. Developed electrocatalytic process allows to obtain multigramme-scale amount of trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates.

## Introduction

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, antiviral and antidopamine activities.[2,3] Cyclopropanecarboxylic acid derivatives are successfully used in agriculture and medicine.[4,5] It has recently been found that substituted 1,1,2,2-tetracyanocyclopropanes inhibit RGS-proteins (regulators of G-protein signaling)[5a] and protein autosplicing and used for the treatment of tuberculosis.[5b]



RGS Inhibitor



Inhibitor of protein autosplicing

Though the methods of cyclopropanes synthesis have been documented a long time ago, all of them 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 most known examples of this type).[6] The well-known method of MIRC synthesis of substituted cyclopropanes involves addition of halosubstituted C-H acid anions, generated by the treatment of the corresponding C-H acid with base, to the conjugated activated olefins followed by cyclization with elimination of halogen anion.[7]

Electrosynthesis is a competitive method of modern organic chemistry.[8a] The importance of electrochemical synthesis can hardly be overestimated because of its great and, in some cases, unique possibilities for performing various transformations of organic compounds.[8b]

The next essential step in the cyclopropane ring construction was electrochemical modification, which was performed with C-H acids instead of halogenated ones and using halogen, generated *in situ* on a mediatory system in an undivided cell (Fig. 1).[9]

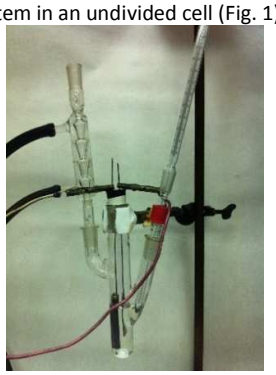
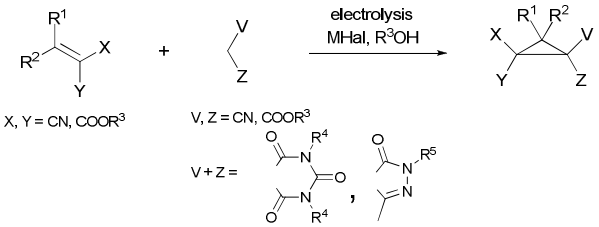


**Fig. 1** Undivided three-necked cell

This modification allowed to create a novel approaches to the synthesis of substituted cyclopropanes: 1) electrolysis of activated olefins (alkylidenemalonates,[10a] alkylidencyanoacetates[10b] or alkylidenemalononitriles[10c,d]) and C-H acids (malonic esters[10b,d], cyanoacetic esters,[10e] malononitrile[10c]) including heterocyclic C-H acids (barbituric acids[11a] and pyrazoline-5-ones[11b]), Scheme 1;




**Scheme 1** Electrolysis of activated olefins and C-H acids

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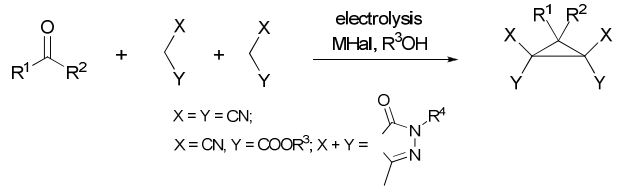
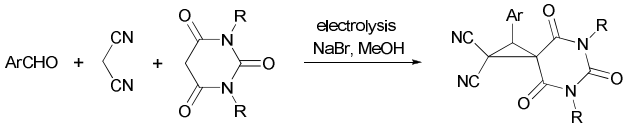
2) electrolysis of carbonyls and two equivalents of C-H acids,[12] Scheme 2; 3) electrolysis of carbonyls and two different C-H acids (electrocatalytic multicomponent synthesis of cyclopropanes), Scheme 3.[13]




**Scheme 2** Electrolysis of carbonyls and C-H acids




**Scheme 3** Electrocatalytic multicomponent synthesis of cyclopropanes

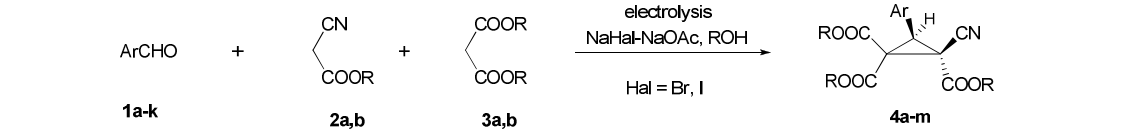
## Results and discussion

In the present study, we report the first electrocatalytic stereoselective multicomponent synthesis of cyclopropanes *via* one-pot electrolysis of aromatic aldehydes, alkyl cyanoacetates and dialkyl malonates in the presence of mediator in an undivided cell. In order to find optimal conditions, the electrolysis of benzaldehyde **1a**, methyl cyanoacetate **2a** and dimethyl malonate **3a** in methanol was selected as a model reaction (Scheme 4, Table 1).

Our regular electrocatalytic transformations were usually carried out in an undivided three-neck cell (Fig. 1). However, there are problems with stirring in case of formation of insoluble products or large-scale electrolyses. To resolve this problem in the present study we used simple beaker as an undivided cell (Fig. 2).

As it follows from our results, the proposed electrocatalytic process was carried out at one stage by co-electrolysis of benzaldehyde, methyl cyanoacetate and dimethyl malonate in the presence of NaBr as mediator passing 3.0 F/mol electricity. In all cases, high conversion of benzaldehyde **1a** and methyl cyanoacetate **2a** was observed. Optimal temperature of the process is 0 °C. The yield decreases with the raise of temperature up to 10 °C (Table 1, entry 2), most likely due to various side oligomerization processes, which are typical for cyanoacetic derivatives in the presence of bases.[14] Temperature lowering to –10 °C (entry 3) also leads to yield drop. In this case methyl benzylidenecyanoacetate (the product of benzaldehyde and methyl cyanoacetate condensation) was detected in the reaction mixture by NMR spectroscopy (25%).

The use of NaBr–NaOAc mediatory system resulted in increasing the yield of cyclopropane **4a** from 43 up to 72% (entry 5). In double mediatory system, NaOAc is a catalyst of Knoevenagel condensation of aldehyde and methyl cyanoacetate. In the absence of electricity, benzaldehyde and methyl cyanoacetate under the action of NaOAc undergo condensation into the corresponding methyl benzylidenecyanoacetate **5** during 30 min.




**a** Ar = $C_6H_5$, **b** Ar = 2-$CH_3C_6H_4$, **c** Ar = 3-$CH_3C_6H_4$, **d** Ar = 4-$CH_3C_6H_4$, **e** Ar = 4-$CH_3OC_6H_4$, **f** Ar = 4-$FC_6H_4$, **g** Ar = 3-$BrC_6H_4$, **h** Ar = 2-$NO_2C_6H_4$, **i** Ar = 3-$NO_2C_6H_4$, **j** Ar = 4-$NO_2C_6H_4$, **k** Ar = 3-Py

**a** R = Me, **b** R = Et

**a** Ar = $C_6H_5$, R = Me; **b** Ar = $C_6H_5$, R = Et; **c** Ar = 2-$CH_3C_6H_4$, R = Me; **d** Ar = 3-$CH_3C_6H_4$, R = Me; **e** Ar = 4-$CH_3C_6H_4$, R = Me; **f** Ar = 4-$CH_3OC_6H_4$, R = Me; **g** Ar = 4-$FC_6H_4$, R = Me; **h** Ar = 3-$BrC_6H_4$, R = Me; **i** Ar = 2-$NO_2C_6H_4$, R = Me; **j** Ar = 3-$NO_2C_6H_4$, R = Me; **k** Ar = 4-$NO_2C_6H_4$, R = Me; **l** Ar = 4-$NO_2C_6H_4$, R = Et; **m** Ar = 3-Py, R = Me

**Scheme 4** Electrocatalytic stereoselective multicomponent synthesis of trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates **4a–m**.

**Table 1** Electrocatalytic stereoselective multicomponent transformation of benzaldehyde **1a**, methyl cyanoacetate **2a** and dimethyl malonate **3a** into trimethyl (2*R**,3*R**)-2-cyano-3-phenylcyclopropane-1,1,2-tricarboxylate **4a**[a]

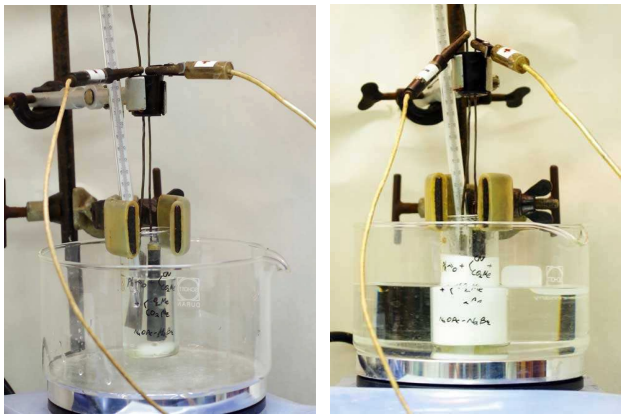
| Entry | Mediator | Premixing time at rt (min) | Electicity passed (F $mol^{-1}$) | Time of the electrolysis (min) | Temperature of the electrolysis (°C) | Yield of **4a** (%)[b] | Current efficiency (%) |
|---|---|---|---|---|---|---|---|
| 1 | NaBr | 0 | 3.0 | 144 | 0 | 43 (65)[c] | 29 |
| 2 | NaBr | 0 | 3.0 | 144 | 10 | (44)[c] | |
| 3 | NaBr | 0 | 3.0 | 144 | -10 | (26)[c] | |
| 4 | NaBr | 0 | 3.5 | 168 | 0 | 41 (60)[c] | 23 |
| 5 | NaBr-NaOAc | 0 | 3.0 | 144 | 0 | 72 | 48 |
| **6** | **NaBr-NaOAc** | **15** | **3.0** | **144** | **0** | **84** | **56** |
| **7** | **NaBr-NaOAc** | **30** | **3.0** | **144** | **0** | **87** | **58** |
| 8 | NaI-NaOAc | 30 | 3.0 | 144 | 0 | 72 | 48 |

[a] 50 ml beaker. Benzaldehyde **1a** (15 mmol, 1.59 g), methyl cyanoacetate (15 mmol, 1.49 g), dimethyl malonate (15 mmol, 1.98 g), NaHal (5 mmol, 0.41 g), NaOAc (5 mmol), methanol (35 mL), iron cathode (5 $cm^2$), graphite anode (5 $cm^2$), current density 100 mA/$cm^2$ [b] Isolated cyclopropane. [c] The yields given in parenthes were determined from $^1$H NMR spectroscopic and GLC data.

**Table 2** Electrocatalytic stereoselective multicomponent transformation of aromatic aldehydes **1a–k**, alkyl cyanoacetates **2a,b** and malonic esters **3a,b** into trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates **4a–m**[a]

| Entry | Aldehyde | Ar | R | Electricity passed (F mol$^{-1}$) | Time of the electrolysis (min) | Product | Yield of **4** (%)[b] | Current efficiency (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$ | Me | 3.0 | 144 | **4a** | 86 | 57 |
| 2[c] | **1a** | $C_6H_5$ | Me | 3.5 | 530 | **4a** | 87 | 50 |
| 3 | **1a** | $C_6H_5$ | Et | 3.0 | 144 | **4b** | 74 | 49 |
| 4 | **1b** | 2-$CH_3C_6H_4$ | Me | 3.2 | 154 | **4c** | 72 | 45 |
| 5 | **1c** | 3-$CH_3C_6H_4$ | Me | 3.2 | 154 | **4d** | 75 | 47 |
| 6 | **1d** | 4-$CH_3C_6H_4$ | Me | 3.0 | 144 | **4e** | 78 | 52 |
| 7 | **1e** | 4-$CH_3OC_6H_4$ | Me | 3.5 | 168 | **4f** | 85 | 49 |
| 8 | **1f** | 4-$FC_6H_4$ | Me | 3.2 | 154 | **4g** | 82 | 51 |
| 9 | **1g** | 3-$BrC_6H_4$ | Me | 3.0 | 144 | **4h** | 87 | 58 |
| 10 | **1h** | 2-$NO_2C_6H_4$ | Me | 3.2 | 154 | **4i** | 65 | 41 |
| 11 | **1i** | 3-$NO_2C_6H_4$ | Me | 3.3 | 158 | **4j** | 67 | 41 |
| 12 | **1j** | 4-$NO_2C_6H_4$ | Me | 3.2 | 154 | **4k** | 64 | 43 |
| 13 | **1j** | 4-$NO_2C_6H_4$ | Et | 3.0 | 144 | **4l** | 66 | 44 |
| 14 | **1k** | 3-Py | Me | 3.3 | 158 | **4m** | 52 | 32 |

[a] 50 ml beaker. Aldehyde **1** (15 mmol), alkyl cyanoacetate **2** (15 mmol), malonic ester **3** (15 mmol), NaBr (5 mmol, 0.51 g), NaOAc (5 mmol, 0.41 g), alcohol (35 mL). Premixing for 30 min at rt then electricity was passed at 0 °C (the conversion of starting material was checked by GLC), iron cathode (5 cm$^2$), graphite anode (5 cm$^2$), current density 100 mA/cm$^2$. [b] Isolated cyclopropane. [c] Scale of electrolysis: **1a** (50 mmol), **2a** (50 mmol), **3a** (50 mmol), NaBr (5 mmol, 0.51 g), NaOAc (5 mmol, 0.41 g), methanol (50 ml).



**a** **b**

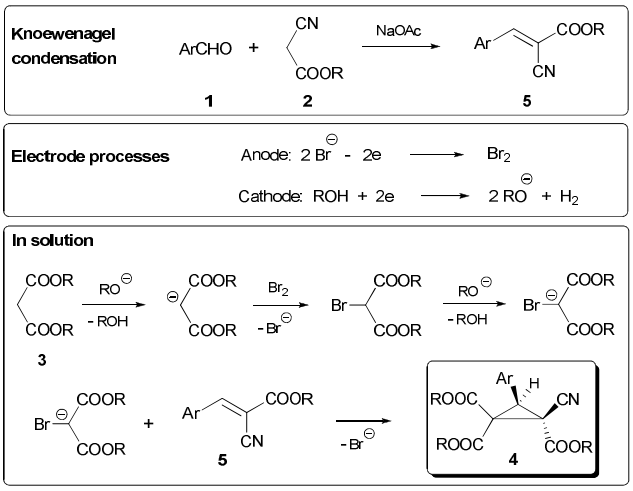
**Fig. 2 a)** Start point of domino process, **b)** reaction mixture after premixing (the white precipitate is methyl benzylidenecyanoacetate **5**).

We have established that a 30 min stirring of benzaldehyde **1a**, methyl cyanoacetate **2a** and malonate **3a** in methanol in the presence of NaBr–NaOAc at ambient temperature followed by cooling down to 0 °C resulted in the formation of precipitate of methyl benzylidenecyanoacetate **5** (Fig. 2). Subsequent passing of electricity at 0 °C affords the cyclopropane **4a** in 87% yield (Table 1, entry 7), which was isolated without chromatography and recrystallization by simple filtration from reaction mixture. NaBr–NaOAc is more efficient mediatory system than NaI–NaOAc for the studied electrocatalytic process (Table 1, entry 8).

Under the optimal conditions the electrocatalytic stereoselective multicomponent transformation of an aldehydes **1a–k**, alkyl cyanoacetates **2a,b** and a malonates **3a,b** afforded the corresponding trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates **4a–m** in 52–86% substance yields and 32–58% current efficiency (Scheme 4, Table 2).

The developed process is scalable. Thus, 30 min stirring of benzaldehyde, methylcyanoacetate and dimethylmalonate (50 mmol of each) in the presence of NaBr–NaOAc (5 mmol of each) in methanol at rt followed by passing electricity (3.5 F/mol, until complete conversion of starting material controlled by GLC) at 0 °C afforded 13.8 g (87%) of **4a** in 8 h 50 min (Table 2, entry 2).

In the NMR spectra of **4a–m** only a single set of signals was present, indicating stereoselective formation of a single isomer in the electrocatalytic process. The structure of **4a** was previously confirmed by a single-crystal X-ray diffraction study.[10b] An appropriate mechanism of the chemical-electrocatalytic domino process is outlined in Scheme 5.




**Scheme 5** Mechanism of the electrocatalytic stereoselective multicomponent synthesis of cyclopropanes **4**.

Knoevenagel condensation of alkyl cyanoacetate and aromatic aldehyde is catalyzed by NaOAc, and afforded alkyl arylidenecyanoacetate **5**.[15a] Reactions at electrodes are standard for the applied mediatory system and lead to the formation of bromine at the anode and the deprotonation of alcohol at the cathode with the evolution of hydrogen. The reaction in solution between an alkoxide ion and malonate leads to the formation of a malonate anion. Bromination of the malonate anion,[16] then the formation of the bromomalonate anion followed by the addition to olefin **5** stereoselectively give rise to trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylate **4**.[17]

## Conclusions

To summarize, we have performed one-pot electrocatalytic stereoselective domino synthesis of the trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates from aromatic aldehydes (bearing both electron-donating and electron-withdrawing groups in all positions) alkyl cyanoacetates and dialkyl malonates in the presence of sodium bromide–sodium acetate as a double mediatory system in alcohol in a beaker. In double mediatory system, NaOAc is a catalyst of the chemical process (Knoevenagel condensation of aldehyde and methyl cyanoacetate), and NaBr is a mediator of the electrocatalytic transformation between arylidenecyanoacetate formed *in situ* and malonate under constant current mode in alcohol.

Using classical organic chemistry, this transformation can only be accomplished as a three-step process comprising: 1) Knoevenagel condensation of an aldehyde and alkyl cyanoacetate with formation of an alkylidenecyanoacetate,[15] 2) halogenation of the malonate[16] and 3) addition of the halogenated malonate to the double bond of the alkylidenecyanoacetate followed by cyclization.[17]

This new electrocatalytic process is an efficient and convenient method for the synthesis of trialkyl (2*R**,3*R**)-3-aryl-2-cyanocyclopropane-1,1,2-tricarboxylates. The techniques for electrolysis and isolation of the desired compounds are simple and convenient to use both under laboratory conditions and in large-scale apparatus.

## Acknowledgements

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