Electrosynthesis of cyclopropane derivatives by a Perkin-type reaction

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Electrolysis of active methylene compounds at a Pt cathode in MeCN in the presence of vicinal dihaloalkanes leads to cyclopropane derivatives in yields up to 90 %. In the cases of CH-acids with low pK_a it is expedient to apply more active dihaloalkanes, while for CH-acids with higher pK_a the desired product yields may be raised using electrogenerated bases.

Key words: CH-acids; 1,2-dihaloalkanes; cyclopropanes; electrosynthesis; electroreduction; electrogenerated bases; azobenzene.

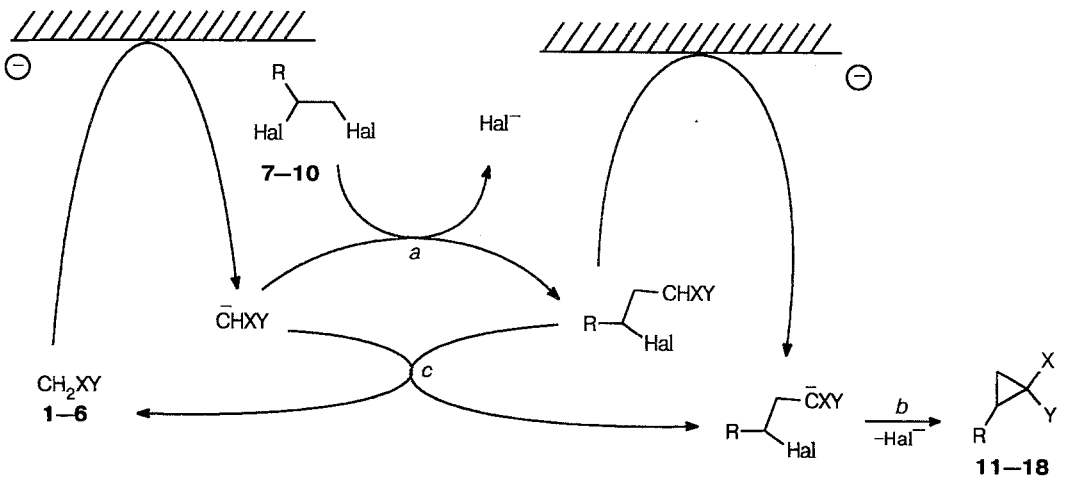
Previously we have reported[1] that during the cathodic electrolysis of active methylene compounds in 1,2-dichloroethane a Perkin-type reaction occurs to give 1,1-disubstituted cyclopropanes, though in some cases the yields are low. In the present work the factors controlling yields of cyclopropanes in this process have been investigated. Acetylacetone (**1**), malonodinitrile (**2**), ethyl esters of acetoacetic (**3**), cyanoacetic (**4**), and malonic (**5**) acids, and phenylacetonitrile (**6**) were used as CH-acids, and the vicinal dihaloalkanes used were 1,2-dichloroethane (**7**), 1,2-dibromoethane (**9**), 1,2-dichlorohexane (**8**), and 1,2-dibromohexane (**10**).

Results and Discussion

In an electrochemical variant of the Perkin reaction, the formation of cyclopropanes (**11**—**18**) can be described by Scheme 1, which is similar to the scheme we previously proposed.[1]

The electrode process includes the purely chemical stages *a* and *b* of the nucleophilic substitution of halogen atoms. Therefore, the nature of the dihaloalkane (the type of halogen and hydrocarbon fragment) can affect the whole process. Accordingly, we specifically investigated the interaction of electrogenerated anions of

Scheme 1



R = H: X = Y = Ac (**11**); X = Y = CN (**12**); X = Ac, Y = CO_2Et (**13**);
X = CN, Y = CO_2Et (**14**); X = Y = CO_2Et (**15**); X = Ph, Y = CN (**16**)
R = Bu: X = CN, Y = CO_2Et (**17**); X = Y = CO_2Et (**18**)

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Table 1. Reaction of $[CHXY]^-$anions obtained under conditions of cathodic diaphragm electrolysis of CH_2XY compounds (Pt-cathode, MeCN, Bu_4NBr, Q = 1 F mole^{-1}), with excess mono- and dihaloalkanes

Entry	Initial CH_2XY				Halide	Composition of resulting reaction mixture (%) (GLC)	
	Compound	X	Y	pK_a[2,3]		CH_2XY	Alkylation products*
1	**3**	Ac	CO_2Et	11	MeI	—	65
2					$BrCH_2CH_2Br$	39	18
3					$ClCH_2CH_2Cl$	36	8
4	**5**	CO_2Et	CO_2Et	15	MeI	10	85
5					$BrCH_2CH_2Br$	63	25
6					$ClCH_2CH_2Cl$	66	28
7					$BuCH(Br)CH_2Br$	29	9
8					$BuCH(Cl)CH_2Cl$	26	—
9	**6**	Ph	CN	21	MeI	95	—
10					$BrCH_2CH_2Br$	95	—
11					$ClCH_2CH_2Cl$	95	—

* Alkylation products are MeCHXY in the case of MeI, cyclopropane derivatives $\overset{\text{RCHCH}_2-\text{CXY}}{\underbrace{\qquad\qquad}}$ in the case of dihaloalkanes. Side products (difference from 100 %) — tar-like compounds with high boiling points, undetectable by GLC methods.

CH-acids with dihaloalkanes **7—10** without current. The initial CH-acids were subjected to cathodic diaphragm electrolysis (Q = 1 F mole^{-1}) to obtain a solution of the tetraalkylammonium salt of the corresponding CH-acid. Then the reaction mixture was treated with an excess of a halide.

The reaction of electrogenerated anions of CH-acids with an excess of strongly electrophilic MeI was selected as the reference reaction. It was believed that the analytical yields of the methylation products MeCHXY indicate the conversion of CH-acids into their anionic form (Table 1).

It is shown in Table 1 that ethyl acetoacetate **3** (entry *1*) undergoes complete conversion during electrolysis. The anion generated in this process is partially resinified, but most of it is methylated with MeI in 65 % yield. The anion of ethyl malonate **5** is more stable and gives the methylation product in 85 % yield (entry *4*). The formally incomplete conversion of ester **5** to the anion by electrolysis is most probably caused by partial protonation of this anion by the acidic components of the medium. Protonation of the anion intermediate dominates during electrolysis of phenylacetonitrile **6**, which is an active methylene compound with low acidity, and no methylation products of the corresponding anion were found in this case.

Vicinal dihaloalkanes **7—10** are less electrophilic than MeI (see Table 1). When they are involved, the process leads to cyclopropanes and is described by Scheme 1, except that the splitting of the C—H bond of the $RCH(Hal)CH_2CHXY$ intermediate occurs not electrochemically, but by the action of $[CHXY]^-$ (Scheme 1, stage *c*). The $RCH(Hal)CH_2CHXY$ type compounds being probable precursors of cyclopropanes were not detected in either of the experiments, but we noticed the formation of analogous intermediates in the electrosynthesis of four- and five-member alicycles.[4,5]

The formation of a three-membered cycle is accompanied by the substitution of two H atoms in the initial active methylene compound, therefore the yield of cyclopropane should be expected to be no more than half of the methyl derivative yield. In fact (see Table 1), the yields of cyclopropanes are much lower, and on the contrary, the amounts of the initial CH-acids in the reaction mixture (entries *2*, *3*, *5—8*) are 2.3—4.5 times higher than the stochiometric amounts which would be expected to form after stage *c* (see Scheme 1). This fact does not result from the ineffective conversion of CH-acid anions in their reactions with dihaloalkanes, since the addition of MeI to the catholyte after its treatment with dihaloalkanes does not result in the formation of the corresponding methyl derivatives. Therefore it can be assumed that protonation of the CH-acid anions competes with their reaction with dihaloalkanes, the latter themselves being able to serve as a proton source since their deprotonation is known to be a rather facile process and is widely used for the synthesis of alkenylhalides.

It is also clear from Table 1 that the mobility of the halogen atom in the dihaloalkane is important in the case of the relatively weak nucleophilic anion of acetoacetic ester **3**. With the more nucleophilic anion of malonic ester **5** the same dichloro- and dibromoalkanes give similar results. Taking malonic ester **5** as an example, the dependence of the cyclopropane yields on the type of dihaloalkane carbon fragment has been shown: in the case of sterically hindered 1,2-dihalocyclohexanes **9**, **10** the yield of cyclopropane derivatives is extremely low and high-boiling tar products are mainly formed.

Thus, cathode electrolysis of CH-acids with subsequent treatment of the catholyte with vicinal dihaloalkanes leads to cyclopropanes, though their yields are not high and decrease if sterically hindered dihaloalkanes are used.

Table 2. $E_{1/2}$ values (relative to Ag/0.1 *M* Ag^+) of the reduction waves of CH-acids **1—6** and vicinal dihaloalkanes **7—10** (rotating Pt-electrode, 0.1 *M* Bu_4NClO_4 solution in MeCN)

Compound	pK_a (for CH-acids)[2,3]	$-E_{1/2}$/V
CH_2Ac_2 (**1**)	9	1.33
$CH_2(CN)_2$ (**2**)	11	1.96
$AcCH_2CO_2Et$ (**3**)	11	PDBE*
$NCCH_2CO_2Et$ (**4**)	13	2.04
$CH_2(CO_2Et)_2$ (**5**)	15	PDBE*
$PhCH_2CN$ (**6**)	21	PDBE*
$ClCH_2CH_2Cl$ (**7**)	—	PDBE*
$BrCH_2CH_2Br$ (**8**)	—	1.84
$BuCH(Cl)CH_2Cl$ (**9**)	—	PDBE*
$BuCH(Br)CH_2Br$ (**10**)	—	1.94

* PDBE — potential of the discharge of base electrolite (more negative than −2.5 V).

Among other factors controlling cyclopropane yields is the relative feasibility of the reduction of the initial CH-acids **1—6** and vicinal dihaloalkanes **7—10**. The known data[6—9] on the voltamperometric investigation of similar compounds are not really comparable, because they were obtained under different conditions. So we tried to estimate the feasibility of the reduction of compounds **1—10** by determining the values of their cathode waves $E_{1/2}$ under standard conditions (rotating Pt disc electrode, 0.1 *M* Bu_4NClO_4 in MeCN) (Table 2).

It is clear from Table 2 that in some cases vicinal dihaloalkanes are reduced at potential values near (and even more negative than) those of the reduction of CH-acids, and in such cases the competitive reduction of dihaloalkanes can be a factor reducing the yield of the target products. However, the limited significance of the Table 2 data should be pointed out, because the results of the reduction of both CH-acids and haloalkanes on a Pt-electrode in a MeCN medium are poorly reproducible.

Results of the cathode electrolysis of the CH-acids **1—6** in the presence of dihaloalkanes **7—10** are given in Table 3 and Fig. 1. As was noted before, these data should be interpreted taking into account the data on the reactions of the CH-acid anions with dihaloalkanes in the absence of current (see Table 1) and voltamperometric data of the initial compounds (see Table 2).

The main factors reducing the cyclopropane yields can be considered to be the competitive reduction of the vicinal dihaloalkane to alkene (most characteristic in the case of CH-acids with high pK_a that are difficult to reduce) and resinification of the initial CH-acids during electrolysis (typical for CH-acids with low pK_a giving anions with low nucleophilicity, which slowly react with dihaloalkanes). In the first case some increase of the yield might be achieved by replace dibromoethane **8**

Table 3. Yield of cyclopropane derivatives $\underbrace{RCHCH_2}-CXY$ during the diaphragm amperostatic electrolysis (Pt-cathode, MeCN, Bu_4NBr, $Q \sim 2.2$ F $mole^{-1}$) of CH_2XY compounds (C = 0.125 *M*) in the presence of $RCH(Hal)CH_2Hal$

Entry	Initial CH_2XY				$RCH(Hal)CH_2Hal$				Products obtained	
	Compound	X	Y	Conversion (%)	Compound	R	Hal	*C/M*	Compound	Analytical yield* (%)
1	**1**	Ac	Ac	100	**7**	H	Cl	Electrolysis medium	**11**	13
2				100	**7**	H	Cl	1.0	**11**	0
3				100	**8**	H	Br	1.0	**11**	25
4	**2**	CN	CN	100	**7**	H	Cl	Electrolysis medium	**12**	13
5				100	**7**	H	Cl	1.0	**12**	0
6				100	**8**	H	Br	1.0	**12**	60
7	**3**	Ac	CO_2Et	83	**7**	H	Cl	Electrolysis medium	**13**	75
8				100	**7**	H	Cl	1.0	**13**	5
9				20	**8**	H	Br	1.0	**13**	12
10	**4**	CN	CO_2Et	90	**7**	H	Cl	Electrolysis medium	**14**	90
11				50	**7**	H	Cl	1.0	**14**	20
12				12	**8**	H	Br	1.0	**14**	12
13				80	**9**	Bu	Cl	1.0	**17**	0
14				45	**10**	Bu	Br	1.0	**17**	12
15	**5**	CO_2Et	CO_2Et	30	**7**	H	Cl	Electrolysis medium	**15**	30
16				38	**7**	H	Cl	1.0	**15**	38
17				12	**8**	H	Br	1.0	**15**	12
18				70	**9**	Bu	Cl	1.0	**18**	Traces
19				25	**10**	Bu	Br	1.0	**18**	8
20	**6**	Ph	CN	16	**7**	H	Cl	Electrolysis medium	**16**	16
21				25	**7**	H	Cl	1.0	**16**	25
22				0	**8**	H	Br	1.0	—	—

*The yield based on CH-acid used; it is close to the current yield. The main side processes: if the difference between the conversion and the yield is high, resinification; if the difference is small, competitive reduction of dihaloalkane.

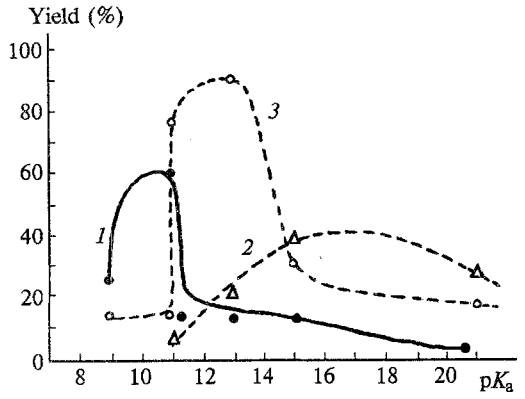

Fig. 1. Yield of cyclopropane derivatives $RCHCH_2-CXY$ *vs.* pK_a values of CH_2XY compounds (see Table 3) after their electrolysis (Q ~ 2.2 F mole^{-1}, 0.35 *M* Bu_4NBr) in the presence of 1,2-dihaloalkanes: 1.0 *M* $Br(CH_2)_2Br$ in MeCN (*1*); 1.0 *M* $Cl(CH_2)_2Cl$ in MeCN (*2*); in $Cl(CH_2)_2Cl$ medium (*3*).

with the more difficult to reduce dichloroethane **7** (see Table 3, entries *16*, *17*, *21*, *22*) and by carrying out the process in MeCN instead of excess dihaloalkane (entries *15*, *16*, *20*, *21*). Contrary to this, in the case of readily reduced CH-acids with low pK_a, that give anions with low nucleophilicity, it is expedient to apply the more active dibromoethane **8** (entries *2*, *3*, *5*, *6*). The dependence of the yield of cyclopropane derivatives on pK_a of the CH-acid used and on the electrolysis conditions is graphically demonstrated by Fig. 1. It is clear from Fig. 1 that in order to obtain cyclopropanes in maximum yield it is necessary to find the most appropriate dihaloalkane and its concentration in MeCN for every particular case. The yields of cyclopropanes **17** and **18** from 1,2-dichlorohexane **9** and 1,2-dibromohexane **10** are not high (entries *13*, *14*, *18*, *19*); the main reasons for this are not only the competitive reduction of these dihaloalkanes, but also the difficulty of the formation of the target products (see Table 1).

In order to suppress the competitive reduction of dihaloalkanes and to increase the current yield of cyclopropane derivatives we used a system with an electrogenerated base. According to the principles of the application of electrogenerated bases,[10] their precursors should undergo reduction more easily than CH-acids and dihaloalkanes. The anion intermediate formed by the electrogenerated base should deprotonate CH-acids, since it is a strong base. For the first time azobenzene[11] was used as a precursor, its anion-radical or dianion acting as the electrogenerated base[10,11] (the protonation of these species finally results in hydrazobenzene).

In our case azobenzene also proved to be an effective precursor of an electrogenerated base. The use of azobenzene allowed us to increase considerably the yields of cyclopropanes **13**—**15** starting from CH-acids **3**—**5** and 1,2-dibromoethane **8** (Table 4, Fig. 2).

CH-acids **1** and **2** have reduction potentials lower than or close to that of azobenzene (under the conditions of our experiment $E_{1/2}$ = −1.8 V rel. to Ag/0.1 *M* Ag^+), and the application of the latter as a precursor is not expedient. On the other hand, in the case of phenylacetonitrile **6** which is difficult to reduce and has low acidity, the corresponding cyclopropane **16** is obtained only in a 20 % yield. It is possible to assume that electrogenerated base arising during azobenzene reduction not only deprotonates the weak acids ($pK_a \geq 21$), but under the experimental conditions also enters other reactions, which compete with the target process (*e.g.*, the reaction with 1,2-dibromoethane **10** resulting in nitrogen heterocycles according to known data[12]).

Thus, some of the factors controlling the yields of cyclopropanes in the electrochemical variant of the Perkin reaction have been investigated. It was found that in the

Table 4. Yield of cyclopropane derivatives **11**—**16** during the cathodic electrolysis (Q = 2.2 F mole^{-1}) of CH_2XY compounds (C = 0.125 *M*) in the presence of 1,2-dibromoethane **8** (C = 1.0 *M*) and azobenzene (C = 0.125 *M*)

Initial CH_2XY				Products obtained	
Compound	X	Y	Conversion* (%)	Compound	Analytical yield* (%)
1	Ac	Ac	100 (100)	**11**	31 (25)
2	CN	CN	100 (100)	**12**	64 (60)
3	Ac	CO_2Et	90 (20)	**13**	85 (12)
4	CN	CO_2Et	90 (12)	**14**	85 (12)
5	CO_2Et	CO_2Et	80 (12)	**15**	80 (12)
6	Ph	CN	20 (0)	**16**	20 (0)

*In brackets — the data in the absence of azobenzene, taken from Table 3.

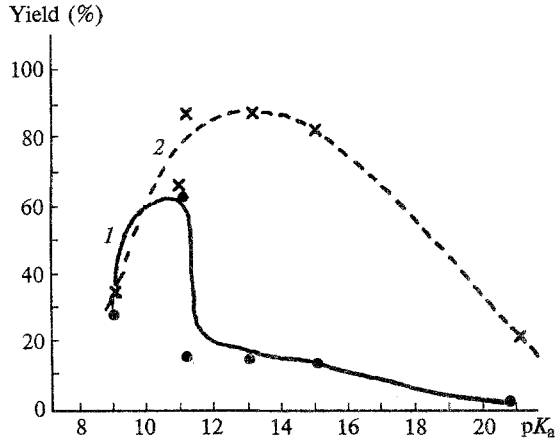

Fig. 2. Influence of equimolar additions of azobenzene on the results of CH_2XY electrolysis in the presence of 1,2-dibromoethane: without addition (curve *1*, Fig. 1)(*1*); with addition (*2*).

case of CH-acids with low pK_a, producing carbanions of low nucleophilicity, it is expedient to apply more active dihaloalkanes (*e.g.*, 1,2-dibromoethane). In the case of difficult to reduce CH-acids having high pK_a, the use of an electrogenerated base suppresses seccessfully the competitive reduction of the dihaloalkane to alkene. If the CH-acid anions are nucleophilic enough, 1,2-dichloroethane should be used since it is less disposed to electroreduction. Under the conditions studied, the application of other homologs of vicinal dihaloalkanes (*e.g.*, 1,2-dihalohexanes), containing less mobile secondary halogen atoms, leads to the target products in low yields.

Experimental

Voltamperometric measurements were carried out with the use of a P-5827M potentiostate and a revolving disc Pt-electrode (S = 0.239 cm^2, n = 1500 rev min^{-1}) in a glass cell with anode and cathode areas separated by a glass filter, and in an argon atmosphere. The standard electrode was Ag/0.1 M Ag^+, the counter electrode — carbon, the supporting electrolyte — a 0.1 M Bu_4NClO_4 solution in MeCN. Working concentrations of the depolarizer were (4—8) · 10^{-3} M.

The preparative electrolysis was carried out in diaphragmatic cell. The cathode was platinum foil (35 cm^2), previously stored in concentrated HNO_3, washed with distilled water, and annealed with a gas burner. The anode was a glasscarbon plate (2×10 mm), the supporting electrolyte — 0.35 M Bu_4NBr solution in MeCN, V of catholyte and anolyte — 35 and 25 mL respectively. 5 mmol of CH-acids **1—6** were added to the catholyte, and 2 mL of cyclohexane or 1-hexene (acceptors of the Br_2 generated) were added to the anolyte. The electrolysis was carried out at 20 °C, with intense magnetic stirring, and in a galvanostatic regime at I ~ 80 mA.

When anions of the CH-acids were electrogenerated to react with the alkylating agents, the samples of the catholyte (Q = 1 F mole^{-1}) were treated with excess MeI or dihaloalkanes **7—10** (~20 % of sample volume) and stored for 0.5 h.

When the CH-acids were electrolyzed in the presence of 40 mmol of dihaloalkanes **7—10**, 2.2 F of electricity per mole of the initial CH-acid were passed. The electrolysis of CH-acids in 1,2-dichloroethane medium has been described previously.[1] In some of the cases, 5 mmol of azobenzene were added to the catholyte.

To find out the composition of a catholyte, its samples were diluted with a five-fold volume of water, and the ether extract was analyzed by GLC (chromatograph Chrome-5, column 2.4 m, SE-30 on Chromatone). The yields of the electrolysis products and the residual amounts of the CH-acids were determined with the use of an inner standard, *i.e.*, 0.3 g of undecane or tridecane, introduced into the catholyte before the electrolysis.

The electrolysis products **11—18** were identified by their retention times using authentic samples, synthesized according to a known procedure.[13] The structures of the compounds were also confirmed by chromato-mass-spectrometry data.[1]

Ethyl-2-butyl-1-cyano-cyclopropanecarboxylate (17), a mixture of (*E,Z*)-isomers was obtained by the reaction of cyanoacetic ester **4** with 1,2-dibromohexane **10** under electrolysis conditions and also by the known procedure[13] using treatment with K_2CO_3 in DMSO. B.p. 119—120 °C (5 Torr), n_D^{20} 1.4492. ^{13}C NMR ($CDCl_3$), δ: 167.39 and 165.38 (C=O); 116.61 (CN); 62.13 (OCH_2); 33.52 and 30.91 (CH); 30.71 and 30.35 (CH_2Et); 29.68 and 25.60 (CH_2Pr); 24.80 and 22.59 (CH_2 cycle); 21.98 and 21.88 (CH_2Me); 19.07 and 17.45 (C); 13.81 and 13.61 (CH_3 of ethyl and butyl).

Diethyl-2-butylcyclopropane-1,1-dicarboxylate (18) was obtained by the reaction of malonic ester **5** with 1,2-dibromohexane **10** under electrolysis conditions and also by the known procedure[13] by treatment with K_2CO_3 in DMSO. B.p. 97—98 °C (1 Torr), n_D^{20} 1.4411. ^{13}C NMR ($CDCl_3$), δ: 170.32 and 168.08 (C=O); 61.06 and 60.97 (OCH_2); 34.07 (C); 30.93 (CH_2Et); 28.18 (CH_2Pr); 28.06 (CH); 22.17 (CH_2Me); 13.99, 13.88 and 13.73 (CH_3 of butyl and ethyl).

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References

1. A. A. Vasil'ev, V. I. Tatarinova, and V. A. Petrosyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 710 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 631 (Engl. Transl.)].
2. A. Gordon and R. Ford, in *The Chemist's Companion. A Handbook of Practical Data, Techniques, and References*, Wiley, New York, 1972.
3. O. A. Reutov, I. P. Beletskaya, K. P. Butin, *CH-Kisloty* [*CH-acids*], Nauka, Moscow, 1980, 247 p. (in Russian).
4. V. I. Tatarinova, A. A. Vasil'ev, and V. A. Petrosyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2646 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 2339 (Engl. Transl.)].
5. A. A. Vasil'ev, V. I. Tatarinova, and V. A. Petrosyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1381 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 1221 (Engl. Transl.)].
6. A. V. Bukhtiarov, V. N. Golyshin, A. P. Tomilov, and O. V. Kuz'min, *Zh. Obshch. Khim.*, 1988, **58**, 157 [*J. Gen. Chem. USSR*, 1988, **58**] (Engl. Transl.).
7. A. V. Bukhtiarov, V. N. Golyshin, A. P. Tomilov, and O. V. Kuz'min, *Zh. Obshch. Khim.*, 1988, **58**, 857 [*J. Jen. Chem. USSR*, 1988, **58** (Engl. Transl.)].
8. A. J. Fry, in *Synthetic Organic Electrochemistry*, Wiley, New York, 1989, 151.
9. In *Organicheskaya elektrokhimiya* [*Organic Electrochemistry*], Eds. M. Beizer and H. Lund, Khimiya, Moscow, 1988, **1**, 270 (Russ. Transl.).
10. In *Organicheskaya elektrokhimiya* [*Organic Electrochemistry*], Ed. M. Beizer and H. Lund, Khimiya, Moscow, 1988, **2**, 1003 (Russ. Transl.).
11. P. E. Iversen and H. Lund, *Tetrahedron Lett.*, 1969, 3623.
12. T. Troll and W. Elbe, *Electrochim. Acta*, 1977, **22**, 615.
13. N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, L. S. Surmina, and Z. A. Rashchupkina, *Zh. Org. Khim.*, 1983, **19**, 541 [*J. Org. Chem. USSR*, 1983, **19** (Engl. Transl.)].

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