Electrochemical carbonylation of 2,2-dibromo-1-carbomethoxy-1-methylcyclopropane

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Direct and indirect electrochemical reductive carbonylation of 2,2-dibromo-1-carbomethoxy-1-methylcyclopropane involving Ni^{II} ions and CO was studied in an MeCN—benzene (3 : 1) mixture in the presence of *n*-PrOH and Et_2NH. 2-Bromo-1-carbomethoxy-1-methylcyclopropane with *cis*-configuration of substituents is formed upon direct carbonylation in the case of *n*-propanol, while ester or amide of 1-carbomethoxy-1-methylcyclopropanecarboxylic acid are obtained in the other cases. In the presence of amine, the direct electrochemical carbonylation occurs under milder conditions and results in a different ratio of stereoisomeric products.

Key words: electrochemistry, carbonylation, dibromocyclopropane, nickel tetracarbonyl.

Functionally substituted cyclopropanes exhibit high biological activity and find various applications in practice. At the present time, methods for functionalization of cyclopropanes are being developed along with search for new active cyclopropane derivatives. Hirao and coworkers have recently suggested[1,2] a convenient method for synthesis of derivatives of cyclopropanecarboxylic acid by reductive carbonylation of *gem*-dibromocyclopropanes in DMF involving nickel tetracarbonyl. We studied a similar process of direct and indirect electrochemical carbonylation of 2,2-dibromo-1-carbomethoxy-1-methylcyclopropane.

Experimental

^1H NMR spectra of compounds **1** and **2** in CCl_4 were recorded on a Bruker WM-250 instrument (working frequency 250 MHz) with $SiMe_4$ as a standard. IR spectra of compounds **2** in Vaseline oil were recorded on a UR-20 instrument. Dipolar moments of compounds **2a** and **2b** were determined in benzene at 25 °C by the procedure presented in Ref. 3.

2,2-Dibromo-1-carbomethoxy-1-methylcyclopropane (DBCP) was synthesized by the known procedure[4] and purified by vacuum distillation. Acetonitrile was purified by triple distillation over phosphoric anhydride. $Ni(BF_4)_2 \cdot 6H_2O$ was used without additional purification. Polarograms were recorded on a PU-1 polarograph. Capillary parameters were the following: m = 0.17 mg s^{-1} and t_1 = 0.5 s. An 0.1 *N* solution of Bu_4NBr was used as a supporting electrolyte under polarographic conditions. Measurements were carried out at 25 °C. Potentials are presented relative to bottom mercury with a potential of −0.5 V relative to SCE.

Upon direct carbonylation, preparative electrolysis was performed by a B5-70 power-supply source in a galvanostatic regime (I = 0.3 A) in an electrolyzer without a diaphragm. A working solution 100 mL in volume was prepared by dissolution of $Ni(BF_4)_2$ (0.001 mol), dibromocyclopropane (0.018 mol), diethylamine or *n*-propanol (0.045 mol), and tetrabutylammonium bromide (0.01 mol) in a acetonitrile—benzene (3 : 1) mixture. Electrolysis was performed using a Ni anode (S = 10 cm^2) and a Pb cathode with the working surface area of 50 cm^2. To remove dissolved oxygen and saturate the solution with carbon monoxide, the latter was bubbled through the solution at atmospheric pressure for 30 min before electrolysis. The process was carried out with a continuous flow of carbon monoxide and vigorous stirring of the reaction mixture. In each case, the amount of electricity passed through the solution was 0.98 A h. After completion of the electrolysis, an excess of nickel tetracarbonyl was removed from the solution by evacuation followed by distilling off the solvent. The residue obtained was treated with diethyl ether (3×30 mL). After distilling off the ether, the carbonylation product was purified by vacuum distillation. Stereoisomers were separated by column chromatography (silica gel, hexane—ether, 1 : 2). Reaction products were identified by ^1H NMR and IR spectroscopies.

Upon indirect carbonylation of DBCP, a solution of nickel tetracarbonyl was obtained by preliminary electrolysis in an acetonitrile—benzene (3 : 1) mixture according to the described procedure.[5] Then DBCP (0.009 mol) and *n*-propanol or diethylamine (0.023 mol) as a nucleophile were added to the solution containing nickel tetracarbonyl (0.054 mol). The mixture was heated to 70 °C for 3 h with an effective reflux condenser. Reaction products were isolated by the procedure described above.

***n*-Propyl 2-carbomethoxy-2-methylcyclopropane-1-carboxylate (1)**, a mixture of *cis*- and *trans*-isomers, b.p 78 °C (0.2 Torr). ^1H NMR, δ: 0.97 (m, 3 H, $OCH_2CH_2\underline{CH}_3$), 1.2—1.9 (m, 7 H, $OCH_2\underline{CH}_2CH_3$; CH_3; H(2), H(3), H(1)), 2.40 (d.d, 1 H, H(1), $J_{1,2}$ = 6.5 Hz, $J_{1,3}$ = 8.5 Hz), 3.67 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, $COOCH_3$), 4.10 (m, 2 H, $O\underline{CH}_2C_2H_5$).

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N,N-Diethyl-2-carbomethoxy-2-methylcyclopropane-1-carboxamide (2). ***trans*-Isomer**: b.p. 85 °C (1 Torr), n_D^{20} = 1.4655, R_f = 0.10 (silica gel, hexane—ether, 1 : 2). ^{1}H NMR, δ: 1.07 (t, 3 H, $NCH_2\underline{CH}_3$), 1.18 (s, 3 H, CH_3), 1.20 (t, 3 H, $NCH_2\underline{CH}_3$), 1.31 (d.d, 1 H, H (3), $J_{2,3}$ = 4.0 Hz, $J_{1,3}$ = 9.0 Hz), 1.36 (d.d, 1 H, H(2), $J_{1,2}$ = 6.5 Hz, $J_{2,3}$ = 4.0 Hz), 2.27 (d.d, 1 H, H(1), $J_{1,2}$ = 6.5 Hz, $J_{1,3}$ = 9.0 Hz), 3.20—3.50 (4 H, $N(\underline{CH}_2CH_3)_2$), 3.67 (s, 3 H, $COOCH_3$).

***cis*-Isomer**: b.p. 95—96 °C (1 Torr), n_D^{20} = 1.4671, R_f = 0.22 (silica gel, hexane—ether, 1 : 2). ^{1}H NMR, δ: 0.98 (d.d, 1 H, H(2), $J_{2,3}$ = 5.0 Hz, $J_{1,2}$ = 8.5 Hz), 1.00 (t, 3 H, $NCH_2\underline{CH}_3$), 1.15 (t, 3 H, $NCH_2\underline{CH}_3$), 1.68 (d.d, 1 H, H(3), $J_{2,3}$ = 5.0 Hz, $J_{1,3}$ = 6.5 Hz), 1.91 (d.d, 1 H, H(1), $J_{1,3}$ = 6.5 Hz, $J_{1,2}$ = 8.5 Hz), 3.10—3.50 (4 H, $N(\underline{CH}_2CH_3)_2$, 3.53 (s, 3 H, $COOCH_3$).

IR spectra of both isomers of compound **2** contain absorption bands of the amide group (ν(C=O), 1640 and 1710 cm^{-1}).

2-Bromo-1-carbomethoxy-1-methylcyclopropane, *cis*-isomer: b.p. 63—65 °C (7 Torr), n_D^{20} = 1.4782. ^{1}H NMR, δ: 1.21 (d.d, 1 H, H(2), $J_{2,3}$ = 5.0 Hz, $J_{1,2}$ = 8.5 Hz), 1.36 (s, 3 H, CH_3), 1.77 (d.d, 1 H, H(3), $J_{2,3}$ = 5.0 Hz, $J_{1,3}$ = 6.5 Hz), 1.91 (d.d, 1 H, H(1), $J_{1,2}$ = 8.5 Hz, $J_{1,3}$ = 6.5 Hz), 3.65 (s, 3 H, $COOCH_3$).

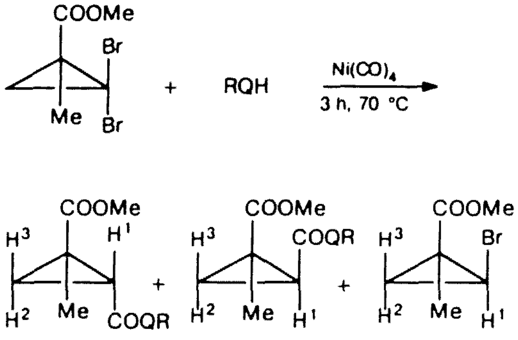
Results and Discussion

Direct and indirect carbonylation of DBCP was studied. Upon indirect reductive carbonylation, nickel tetracarbonyl was preliminarily generated electrochemically under mild conditions in the presence and absence of an organic carrier in an acetonitrile—benzene (3 : 1) mixture by the procedure developed previously.[5] Then the solution obtained was used for carbonylation of DBCP in the presence of excess *n*-propanol or diethylamine. In essence, the process performed is a modification of the known[1,2] method for carbonylation of DBCP and differs in the fact that nickel tetracarbonyl was electrochemically generated in the acetonitrile—benzene system. The synthesis resulted in the formation of a mixture of stereoisomeric derivatives of 2-carbomethoxy-2-methyl-1-cyclopropanecarboxylic acid, observed only at high temperature (Table 1). Upon indirect electrochemical carbonylation of DBCP in the presence of amine, the ratio of *cis*- and *trans*-isomers was 3 : 2. We succeeded in separating them by column chromatography and identified them by ^{1}H NMR spectroscopy.

Table 1. Reductive carbonylation of DBCP in an acetonitrile—benzene (3 : 1) mixture by electrochemically generated $Ni(CO)_4$ (6 eq.)

Organic carrier	Nucleophile (2.5 eq.)	T/°C	Product	Yield of substance (%)
Anthracene	*n*-PrOH	70	1	63
—	*n*-PrOH	70	1	65
—	Et_2NH	70	2	38
—	Et_2NH	25	—	—

Scheme 1



1a, 2a **1b, 2b** **3**

RQ = *n*-PrO (**1**), Et_2N (**2**)

The signals of H(1), H(2), and H(3) protons of the cyclopropane ring of isomers **2a** and **2b** of *N,N*-diethyl-2-carbomethoxy-2-methyl-1-cyclopropanecarboxamide were assigned taking into account the spatial orientation of the ester and amide groups in molecules of substituted cyclopropanes. It is known[6,7] that the synplanar conformation characterized by the bisector position of the C—O fragment developed toward the ring is preferable for monosubstituted cyclopropanes with substituents of the —C(O)R structure (where R = OR, NR_2). In the presence of substituents in *cis*-configurations, the C—O fragment slightly deflects from the bisector orientation to develop toward a less substituted carbon atom. In the both cases, hydrogen *cis*-atoms are exposed to the descreening action of the C—O group,[8] which results in weak-field shifts of their signals in the ^{1}H NMR spectrum. The *cis*-stereoisomer is characterized by the position of the signal of the H(3) proton in a weaker field (1.91 ppm), while the *trans*-stereoisomer is characterized by the downfield shifts of all protons of the ring (1.31, 1.36, and 2.27 ppm). Nevertheless, the value of the downfield shift of the H(3) proton in the *cis*-isomer is maximum, because it is subjected to the deshielding action of two —C(O)R fragments. At this orientation of substituents, the protons of the methyl group of the *trans*-isomer are exposed to the shielding effect of the amide group and, hence, are characterized by the upfield shifts of their signals. The *trans*- and *cis*-configurations were assigned to stereoisomers **a** and **b** on the basis of these considerations. Correctness of the structural assignments was additionally confirmed by comparison of the values of dipole moments (stereoisomer **a**: μ = 3.61±0.04 D, stereoisomer **b**: μ = 3.99±0.04 D).

In another variant, DBCP was carbonylated directly during electrolysis without preliminary generation of $Ni(CO)_4$. Nickel ions were conveyed into a solution by "anodic dissolution" of a nickel electrode directly during electrolysis with a current efficiency of 84 to 90 %. The regime of electrolysis and experimental conditions were selected in such a way that nickel tetracarbonyl formed

Table 2. Electrosynthesis of *N,N*-diethyl-2-carbomethoxy-2-methylcyclopropanecarboxamide (**2**) from 2,2-dibromo-1-carbomethoxy-1-methylcyclopropane

Nucleophile (2.5 eq.)	T/°C	Yield (%)
Et_2NH	8	42
Et_2NH	25	33
Et_2NH	35	28

Note. P_{CO} = 1 atm, Q = 4F/mol; *cis*-**2**/*trans*-**2** ratio 2 : 3.

in quantitative yield in the absence of DBCP and a nucleophile. The results of the electrolysis are presented in Table 2.

It is established that no carbonylation of DBCP occurs in the absence of *n*-propanol under these conditions. The product of stereoselective reduction of dibromide, 2-bromo-1-carbomethoxy-1-methylcyclopropane (**3**) with *cis*-configuration of the bromide and carbomethoxyl substituents, was isolated after the electrolysis. Its ^{1}H NMR spectrum corresponds to that presented in Ref. 9, where the configuration assignment of the corresponding isomers was performed. The established stereodirection of the process is opposite to that established under conditions of direct reduction of DBCP[9] (Ni cathode, MeOH, I = 0.3 A), when the formation of the *trans*-isomer predominated (*cis*/*trans* = 1.0 : 1.4).

The electrolysis in the presence of diethylamine as a nucleophile results in the formation of diethylamide of the corresponding cyclopropanecarboxylic acid and insignificant (<5 %) amounts of monobromocyclopropane. A maximum yield of carbonylation products is observed when 4F/mol DBCP is passed, which formally corresponds to generation of 2 moles of $Ni(CO)_4$ with respect to 1 mole of DBCP. The yield of the products is determined by the temperature regime of the electrolysis. An increase in temperature results in a worsening of parameters of the process. A yield of the products decreases, and a red color of the solution, which is typical of nickel complexes in low degree of oxidation, appears and deepens, which testifies to a deficiency of carbon monoxide. The best result was obtained at 8 °C. In this case, no red color of the solution was observed. It is likely that the concentration of CO necessary for binding Ni ions in low degree of oxidation is not provided at higher temperature due to a lower solubility of CO.

Stereoselectivities of the direct and indirect electrochemical carbonylation differ substantially. As mentioned above, the *cis*-isomer predominates upon indirect carbonylation, while the *trans*-isomer predominates upon direct carbonylation.

In order to explain the results of reductive carbonylation of DBCP by nickel tetracarbonyl, a scheme including the reaction of $Ni(CO)_4$ with a nucleophile and reaction of the complex formed with DBCP was suggested in Ref. 2. Carbonylation at noticeable rates is possible only at high temperatures (higher than 60 °C). Vigorous stirring of a mixture of DBCP, nickel carbonyl, and a nucleophile in DMF or in the acetonitrile—benzene (3 : 1) system for 3 h at 25 °C does not result in reaction between the components of the solution, while upon direct electrochemical carbonylation the best results are achieved at a temperature below 10 °C. This fact as well as the elucidated difference in stereodirection of the electrochemical and chemical carbonylation processes testify that upon direct electrochemical carbonylation the process does not occur *via* the stage of generation of nickel tetracarbonyl. To determine the initial stages of the process, polarograms of the reduction of individual components of an acetonitrile solution against a background of 0.1 M Bu_4NBr were recorded. It turned out that Ni^{II} ions give two reduction waves ($E^1_{1/2}$ = 0.0 V, $E^2_{1/2}$ = −0.67 V), the first of which is a catalytic one and lies in a considerably less cathodic potential range compared to that of DBCP ($E^1_{1/2}$ = −0.87 V). It is likely that upon electrochemical carbonylation Ni^{II} ions are reduced on the electrode to form nickel complexes in the zero degree of oxidation, which are coordinationally unsaturated with CO molecules, and these complexes subsequently react with DBCP or a nucleophile. They are more reactive and, hence, the reductive carbonylation occurs under milder conditions than the chemical carbonylation involving $Ni(CO)_4$.

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