Electrochemical Methoxylation of Arylacetates

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Electrochemical methoxylation at the active methylene group of phenylacetates and 1-naphthaleneacetate was conducted successfully at room temperature, in methanol containing potassium iodide as an electron carrier and sodium methoxide as a base and a methoxylating agent. Along with the mono-methoxylated products, dimethoxy, hydroxy, and oxo derivatives as well as the dimers (succinates) were produced as by-products.

Keywords active methylene; electrochemical hydroxylation; electrochemical methoxylation; electron carrier; methoxide anion; 1-naphthaleneacetate; phenylacetate

Only one report has been published so far on the electrochemical halogenation of aliphatic monocarboxylic acids.1) In that case, Fichter and Ruegg obtained β-chloropropionic acid as a major product from propionic acid, albeit in low yield (10 to 14%), together with α-chloropropionic acid in a very small amount.

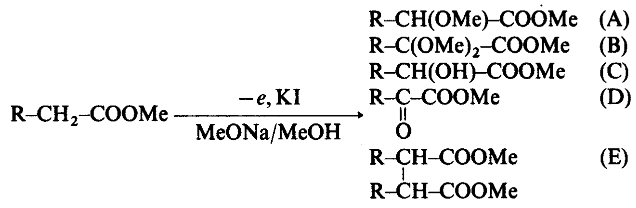
We recently reported2) a methoxylation reaction that takes place at the active methine group of phenyl- or benzylmalonate upon anodic oxidation in methanol containing potassium iodide and sodium methoxide. This reaction apparently involves the formation of iodinated esters as the intermediates.3)

In the present paper, we report methoxylation at the active methylene group of phenylacetates and 1-naphthaleneacetate using potassium iodide as an electron carrier and sodium methoxide as a base and a methoxylating agent. The results are summarized in Table I.

In some cases, as can be seen in Table I, small amounts of the hydroxy derivative, the keto compound, and the dimers (succinates) were produced along with the methoxylated compounds.

It can be considered, as shown in Chart 1, that the electrochemical energy would be used for the oxidation of iodide anion to iodonium cation. The cation thus produced would react with ester anion to give the α-iodo compound, which would liberate iodide anion again by nucleophilic replacement with methoxide anion. Thus, iodide works as a mediator.

TABLE I. Electrochemical Methoxylation



$$\mathrm{R{-}CH_2{-}COOMe} \xrightarrow[\mathrm{MeONa/MeOH}]{-e,\ \mathrm{KI}} \begin{array}{ll} \mathrm{R{-}CH(OMe){-}COOMe} & \mathrm{(A)} \\ \mathrm{R{-}C(OMe)_2{-}COOMe} & \mathrm{(B)} \\ \mathrm{R{-}CH(OH){-}COOMe} & \mathrm{(C)} \\ \mathrm{R{-}\overset{}{\underset{\underset{O}{\|}}{C}}{-}COOMe} & \mathrm{(D)} \\ \mathrm{R{-}CH{-}COOMe} & \mathrm{(E)} \\ \quad| & \\ \mathrm{R{-}CH{-}COOMe} & \end{array}$$

R	Reaction products (% yield)					Recovered (%)
	A	B	C	D	E	
Phenyl	34.2	0	5.9	0	0.1	50.8
4-Chlorophenyl	21.9	12.7	5.0	0	0.9	44.9
4-Chlorophenyl[a]	26.9	47.0	0	17.4	2.8	0
4-Methoxyphenyl	21.5	0	0	0	Trace	74.6
1-Naphthyl	30.9	Trace	0	0	0	60.3

a) Current passed: 4 F/mol of ester.

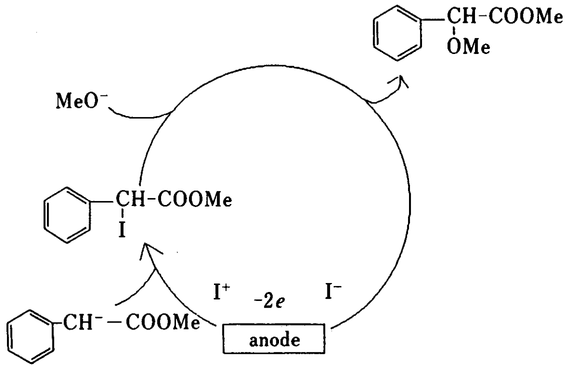


Chart 1

Experimental

Infrared (IR) spectra were taken with a Hitachi model 215 grating spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JEOL JNM-FX 100 spectrometer operating at 99.60 MHz, using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS D-300 spectrometer. Gas-liquid chromatographic (GLC) analyses were performed on a Shimadzu GC-4CM instrument with a flame ionization detector. Thin layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (Art. 5715; Merck). Spots on TLC plates were detected under ultraviolet (UV) light. Low-pressure liquid chromatography (LPLC) was performed with a Chemco Low-Prep pump (81-M-2) and glass column (20 × 1.5 cm) packed with Silica gel SI-25-120 (25–44, Nihon Seimitsu Kagaku Co., Ltd.). Electrolyses were performed by use of a Hokuto Denko HA-105 potentio-galvanostat connected with a Hokuto Denko HF-201 current integrator.

Materials Methyl esters of 4-chlorophenylacetic acid, 4-methoxyphenylacetic acid and 1-naphthaleneacetic acid were prepared from the corresponding acids by reaction with $SOCl_2$ then with MeOH, followed by distillative purification. Methyl 2-(4-chlorophenyl)-2-hydroxyacetate was prepared from the acid by methylation with Me_2SO_4.

Electrolysis Apparatus The electrolysis was performed in an ordinary 300 ml 3-necked glass flask fitted with a thermometer, a cooler on top of which was fixed a $CaCl_2$ tube, and a silicone stopper through which a glass tube that forked into two branches was passed. Two glassy carbon rods (each 6 × 100 mm, Tokai Carbon RA-6) were fixed in those branches of the tube with epoxy-resin, in parallel at a distance of 1 mm as electrodes. The surface area of each electrode beneath the electrolyte solution was 7.8 cm^2. Temperature was adjusted to 22 °C by external cooling with water.

General Procedure of Electrochemical Methoxylation and Product Isolation A solution of each substrate ester (30 mmol) in MeOH (200 ml) containing MeONa (7.0 g) and powdered potassium iodide (5.0 g), was electrolyzed at 450 mA under constant current control until 2 (if not otherwise specified) Faraday/mol (based on substrate ester) of electricity had passed. The reaction mixture after electrolysis was carefully neutralized with anhydrous MeOH–HCl, and the solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (700 ml) and the solution was washed successively with 0.2 M $NaHSO_3$ (70 ml), 2 N Na_2CO_3 (70 ml), and saturated aqueous NaCl (250 ml × 2), dried with anhydrous Na_2SO_4, and evaporated. The product mixture thus obtained was separated by column chromatography on silica gel and purified further by LPLC.

Electrolysis of Methyl Phenylacetate From the silica gel column, the starting ester, dimethyl 2,3-diphenylsuccinate, methyl 2-methoxy-2-phenylacetate, and methyl mandelate were eluted in turn. The latter two compounds were hydrolyzed to the corresponding acids and identified by mixed fusion with commercially available standard samples and comparison of IR spectra.

Dimethyl 2,3-Diphenylsuccinate: Colorless crystals, mp 173—176 °C (lit.[4] mp 176—177 °C). Chemical ionization MS (CIMS) *m/z*: 299 ($M^+ + 1$). High resolution MS (HRMS) *m/z*: 298.1202 [M^+ for $C_{18}H_{18}O_4$] (Calcd for $C_{18}H_{18}O_4$: 298.1203). IR (KBr): 1730 (ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.70 (6H, s, $2 \times COOCH_3$), 4.25 (2H, s, $2 \times CH$), 7.08 (10H, m, aromatic protons).

Electrolysis of Methyl (4-Chlorophenyl)acetate From the silica gel column, the starting ester, dimethyl 2,3-bis(4-chlorophenyl)succinate, methyl (4-chlorophenyl)glyoxylate, methyl 2-(4-chlorophenyl)-2-methoxyacetate, and methyl 2-(4-chlorophenyl)-2,2-dimethoxyacetate were eluted in turn. Since the last two compounds were not readily separable, the mixture was converted to amides by reacting with concentrated NH_4OH in EtOH overnight at room temperature and then separated by column chromatography.

Dimethyl 2,3-Bis(4-chlorophenyl)succinate: Colorless crystals, mp 202—205 °C. IR (CCl_4): 1740 (ester) cm^{-1}. CIMS *m/z*: 367 ($M^+ + 1$ for $C_{18}H_{16}{}^{35}Cl_2O_4$), 369 ($M^+ + 1$ for $C_{18}H_{16}{}^{37}Cl_2O_4$). HRMS *m/z*: 366.0421 [M^+ for $C_{18}H_{16}{}^{35}Cl_2O_4$] (Calcd for $C_{18}H_{16}{}^{35}Cl_2O_4$: 366.0424). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.43 (6H, s, $2 \times COOCH_3$), 4.29 (2H, s, $2 \times CH$), 7.34 (8H, m, aromatic protons).

Methyl (4-Chlorophenyl)glyoxylate: Colorless crystals, mp 60 °C. IR ($CHCl_3$): 1730 (ester), 1685 (ketone) cm^{-1}. CIMS (isobutane) *m/z*: 199 ($M^+ + 1$ for $C_9H_7{}^{35}ClO_3$), 201 ($M^+ + 1$ for $C_9H_7{}^{37}ClO_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.90 (3H, s, $COOCH_3$), 7.48 (2H, d, $J = 10$ Hz, aromatic protons), 8.00 (2H, d, $J = 10$ Hz, aromatic protons). This compound was identified by comparison of the IR spectra and the mixed fusion with the authentic sample synthesized from *p*-chloromandelic acid by $KMnO_4$ oxidation followed by esterification according to the reported procedure.[5]

Methyl 2-(4-Chlorophenyl)-2-methoxyacetate: GC-CIMS (isobutane) *m/z*: 215 ($M^+ + 1$ for $C_9H_{10}{}^{35}ClO_2$), 217 ($M^+ + 1$ for $C_9H_{10}{}^{37}ClO_2$). The corresponding amide (mp 132—134 °C) was identified by mixed fusion and comparing IR spectra with an authentic sample.[6]

Methyl 2,2-Dimethoxy-(4-chlorophenyl)acetate: GC-CIMS (isobutane) *m/z*: 213 ($M^+ - OCH_3$ for $C_{11}H_{14}{}^{35}ClO_4$), 215 ($M^+ - OCH_3$ for $C_{11}H_{14}{}^{37}ClO_4$). This compound was converted to its amide. Colorless crystals, mp 120—122 °C. *Anal.* Calcd for $C_{10}H_{12}ClO_3$: C, 52.25; H, 5.27; N, 6.10. Found: C, 52.20; H, 5.35; N, 6.09. IR (KBr): 1650 and 1640 (amide) cm^{-1}. CIMS *m/z*: 198 ($M^+ - OCH_3$ for $C_{10}H_{12}{}^{35}ClNO_3$), 200 ($M^+ - OCH_3$ for $C_{10}H_{12}{}^{37}ClNO_3$). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.37 (6H, s, $2 \times OCH_3$), 5.64 (1H, s, NH_2), 6.92 (1H, s, NH_2), 7.44 (2H, d, $J = 9$ Hz, aromatic protons), 7.63 (2H, d, $J = 9$ Hz, aromatic protons).

Electrolysis of Methyl 4-Methoxyphenylacetate From the silica gel column, the starting ester, dimethyl 2,3-bis(4-methoxyphenyl)succinate, the starting ester, and 2-methoxy-2-(4-methoxyphenyl)acetate were eluted in turn.

Dimethyl 2,3-Bis(4-methoxyphenyl)succinate: Colorless crystals, mp 185—186 °C (lit.[7] *meso*-isomer 188—189 °C; *dl*-isomer 109—110 °C). IR (KBr): 1730 (ester) cm^{-1}. CIMS *m/z*: 359 ($M^+ + 1$ for $C_{20}H_{22}O_6$). HRMS *m/z*: 358.1419 [M^+ for $C_{20}H_{22}O_6$] (Calcd for $C_{20}H_{22}O_6$: 358.1417). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.71 (6H, s, $2 \times COOCH_3$), 3.80 (6H, s, CH_3O), 5.16 (2H, d, $2 \times CH$), 7.25 (8H, m, aromatic protons).

Methyl 2-Methoxy-2-(4-methoxyphenyl)acetate: Colorless liquid. CIMS (isobutane) *m/z*: 211 ($M^+ + 1$). IR ($CHCl_3$): 1748 (ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.38 (3H, s, OCH_3), 3.71 (3H, s, $COOCH_3$), 3.80 (3H, s, aromatic OCH_3), 4.68 (1H, s, CH), 6.84 (2H, d, $J = 9$ Hz, aromatic protons), 7.32 (2H, d, $J = 9$ Hz, aromatic protons). This compound was converted to its amide by treatment overnight at room temperature with 28% NH_4OH in EtOH. The product was purified by crystallization from MeOH, mp 159—162 °C (lit.[8] mp 161 °C). HRMS *m/z*: 195.0896 [M^+ for $C_{10}H_{13}NO_3$] (Calcd for $C_{10}H_{13}NO_3$: 195.0896).

Electrolysis of Methyl 1-Naphthaleneacetate From the silica gel column, the starting ester, methyl α-methoxy-1-naphthaleneacetate, and methyl α-hydroxy-1-naphthaleneacetate were eluted in turn.

Methyl α-Methoxy-1-naphthaleneacetate: Liquid. IR ($CHCl_3$): 1750 (ester) cm^{-1} Electron impact MS (EIMS) *m/z*: 230 (M^+). ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.66 (3H, s, $COOCH_3$), 3.43 (3H, s, OCH_3), 5.38 (1H, s, CH), 7.27—8.29 (7H, m, aromatic protons).

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