Oxygen-containing heterocycles from α, α, ω, ω-alkane-tetracarboxylates and electro-generated formaldehyde

Michail N. Elinson*, Sergey K. Feducovich, and Gennady I. Nikishin

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prospect 47, 119991 Moscow B-334, Russia
E-mail: elinson@cacr.ioc.ac.ru

Dedicated to Professor M. G. Voronkov on the occasion of his 80th birthday
(received 09 May 01; accepted 04 Dec 01; published on the web 12 Dec 01)

Abstract
Tetramethyl α,α,ω,ω-alkanetetracarboxylates were transformed into 5- and 6-membered oxygen-containg heterocycles (65–90%) with electro-generated formaldehyde in an undivided cell.

Keywords: Electrooxidation, formaldehyde, hydroxymethylation, electrochemical cyclization, tetrahydrofuran, lactones, 2-oxotetrahydrofuran, 6-oxotetrahydro-2*H*-pyran, cyclopropanes

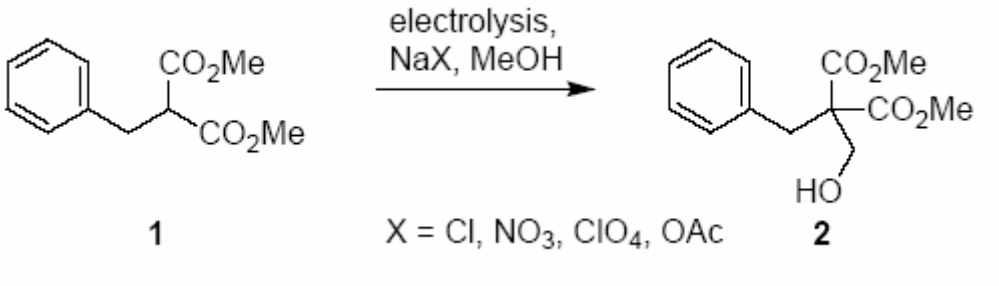
Introduction

Recent advances in electrooxidation have provided organic chemists with a new versatile synthetic device of great promise.[1] Despite the long history of electroorganic chemistry most of the electroorganic reactions that could provide product selectivity have been developed within the last twenty years. Research on various applications has spread gradually to cover many areas of fundamental and industrial organic chemistry. Among them, reactions using mediators and electrochemically generated reagents occupy a special place in electroorganic synthesis.[2] These methods use simple equipment and techniques that may be readily employed in both academic and industrial laboratories. During our studies on electrochemical dehydro-dimerization,[3] trimerization,[4] and cyclotrimerization[5] of dimethyl malonate and electrochemical cyclization of tetramethyl propane-1,1,3,3-tetracarboxylate into cyclopropane-1,1,2,2-tetracarboxylate[6] in methanol in the presence of alkali metal halides as mediators, we found that methanol underwent direct electrochemical oxidation to formaldehyde, if the reaction was carried out with alkali metal chlorides as mediators.

Now we report our results of the synthesis of oxygen-containing heterocycles from tetramethyl alkane-α,α,ω,ω-tetracarboxylates and formaldehyde; the latter was generated in situ by anodic oxidation of methanol.

Results and Discussion

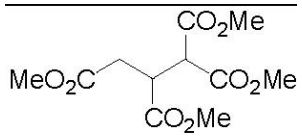
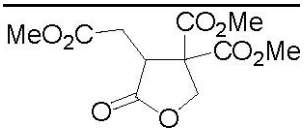
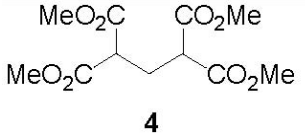
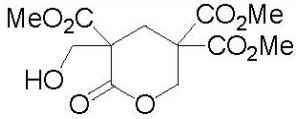
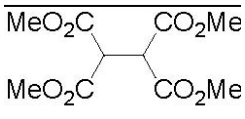
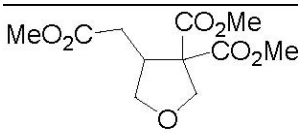
The first step of our research was the investigation of the electrochemical hydroxylation of substituted malonates by in situ generated formaldehyde. The electrochemical oxidation of methanol into formaldehyde was optimized in the case of the reactions of dimethyl benzylmalonate (**1**).



Scheme 1

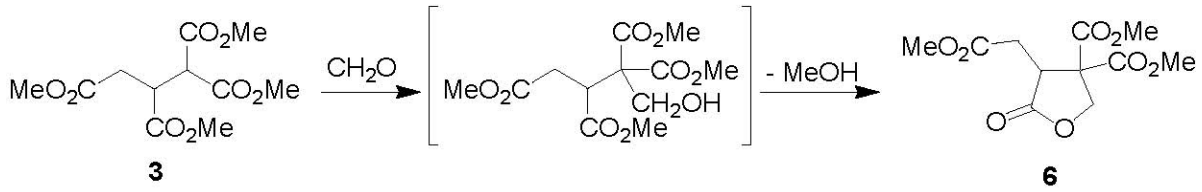
Substrate **1** was electrolyzed and transformed into the hydroxymethylated ester **2** by electrolysis using 6 F/mol of electricity in an undivided cell in the presence of LiCl, $LiNO_3$, $NaClO_4$ or NaOAc furnishing **2** in yields of 78, 82, 86, and 90%, respectively. In all other experiments NaOAc served as the electrolyte. The results are summarized in Table 1.

Table 1. Reaction of α,α,ω,ω−alkanetetracarboxylates with electrochemically generated formaldehyde

Substrate	Electricity [F/mol]	Product	Yield [%][a]
 **3**	6	 **6**	90
 **4**	12	 **7**	65
 **5**	12	 **8**	67

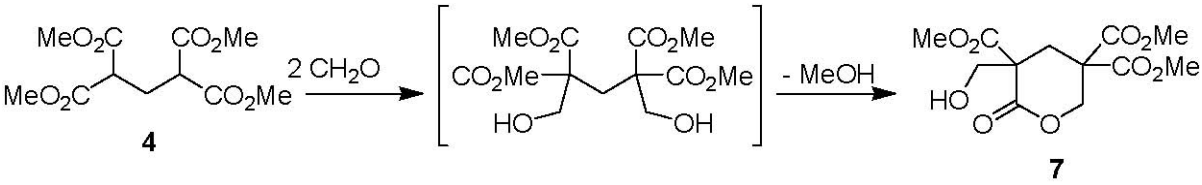
[a] Isolated yields.

In all cases, the first step was hydroxymethylation with electrochemically generated formaldehyde ($CH_3OH - 2e^- - 2H^+ \rightarrow CH_2O$) at the α-carbon of the dimethyl malonate moiety. Where possible, this was followed by lactonization involving an additional remote ester group as shown for the conversion of **3** into **6** (Scheme 2).



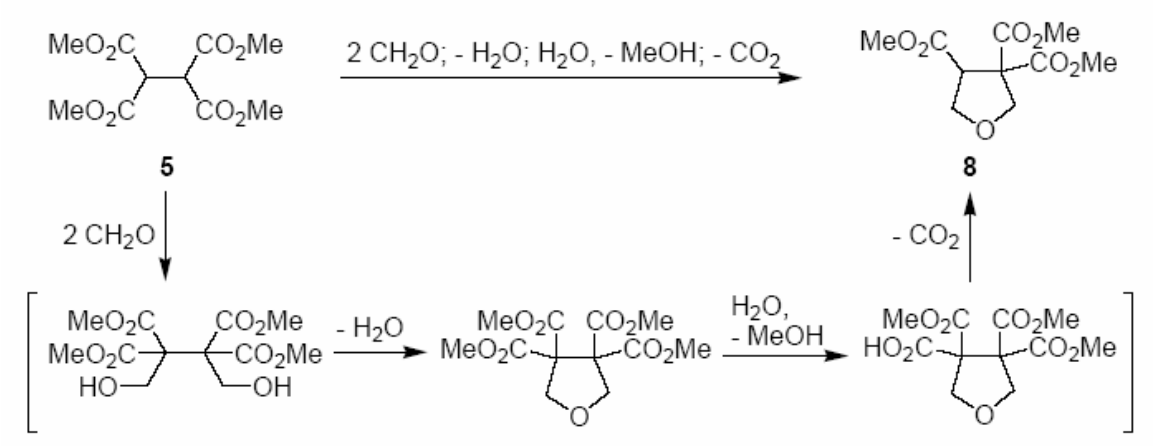
Scheme 2

Ester **4** underwent bis(hydroxymethylation), and involving only one hydroxymethylene group a 6-ring lactone was formed under the electrolysis conditions employed (Scheme 3).



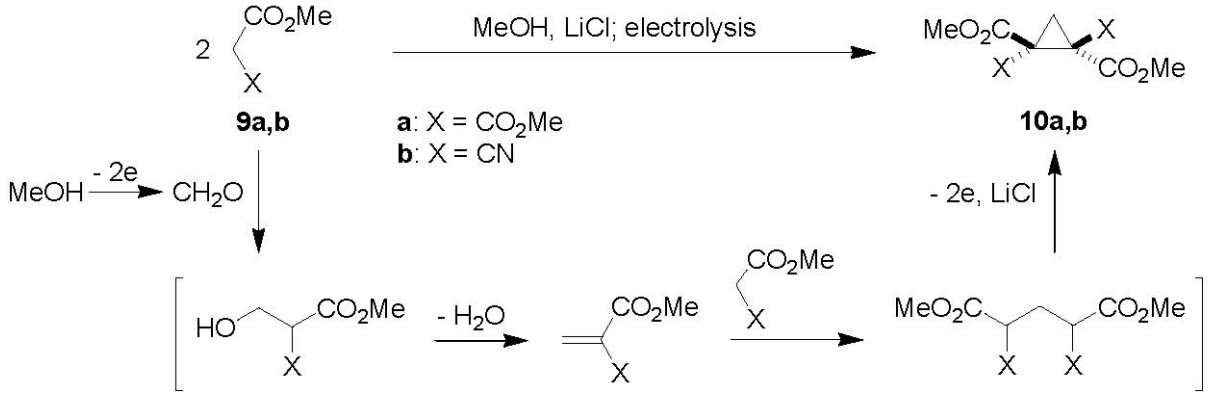
Scheme 3

Ester **5** underwent a more complex transformation during electrolysis in methanol. Formation of product **8** can be envisaged as follows (Scheme 4): Presumably, the initial step is bis(hydroxymethylation). Subsequent elimination of water and cyclization forms the tetrahydrofuran ring rather than a lactone. Hydrolysis of a methoxycarbonyl group followed by decarboxylation generates the final product, trimethyl tetrahydrofurantricarboxylate **8**.



Scheme 4

Electrochemically generated formaldehyde may be employed in more complex reaction sequences including electrochemical reactions. For example, indirect electrochemical processes using alkali metal chlorides as mediators have been accomplished. In this case the potential of the anode is sufficient for the direct oxidation of methanol into formaldehyde as well as the oxidation of the chloride anion. Using this method, the following reactions have been carried out (Scheme 5).



Scheme 5

Electrolysis of dimethyl malonate (**9a**) with methanol in the presence of LiCl afforded tetramethyl cyclopropane-1,1,2,2-tetracarboxylate (**10a**). Similarly, methyl cyanoacetate (**9b**) furnished dimethyl (1*R**,2*S**)-1,2-dicyanocyclopropane-1,2-dicarboxylate (**10b**). The mechanism of these conversions may be envisaged as follows (Scheme 5): The first step involves hydroxymethylation of substrates **9a,b** with electro-generated formaldehyde; subsequent elimination of water forms an activated alkene intermediate which, in turn; undergoes conjugate addition with another molecule **9a** or **9b**. The final step, cyclization and formation of the respective cyclopropanes **10a** and **10b** is the indirect electrochemical process using LiCl as mediator. The mechanism of this last step is similar to that reported for the cyclization of tetramethyl propane-1,1,3,3-carboxylate in the presence of NaBr and NaI as mediators.[7]

Experimental Section

General Procedures. GLC analyses were carried out on a LKhM-80 chromatograph with a flame-ionization detector, 3 m x 3 mm glass columns packed with 5% OV-17 on Inerton (0.16–0.20 mm) or 10% FFAP on Chromaton N-Super (0.13–0.16 mm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometers WM-250 (^{1}H: 250 MHz) and AM-300 (^{1}H: 300 MHz).

Electrolysis of benzyl malonate and alkanetetracarboxylates. General procedure. A solution of ester **1**, **3**, **4** or **5** (8 mmol) and electrolyte LiCl, $LiNO_3$, $NaClO_4$ or NaOAc (4 mmol) in methanol (20 mL) was electrolyzed in an undivided cell equipped with a Pt anode and an Fe

cathode at 20 °C under a constant current density of 200 mA/cm^2 until the quantity of the electricity indicated in Table 1 (6 or 12 F/mol) was passed. The solvent was removed, and the residue was extracted with chloroform; the organic layer was separated, washed with water and dried over Na_2SO_4. The solvent was distilled off, and esters **2**, **6**–**8** were isolated after distillation or crystallization of the crude products.

Dimethyl 2-benzyl-2-(hydroxymethyl)malonate (2). Electrolysis of **1** (1.78 g) in the presence of NaOAc (0.33 g) gave colorless crystals **2** (1.82 mg, 90%); mp 59–60 °C (ether), lit.[9] mp 61 °C. ^{1}H NMR ($CDCl_3$): δ 7.11–7.32 (m, 5H, ArH), 3.88 (d, *J* = 6.5 Hz, 2H, CH_2O), 3.77 (s, 6H, 2 CH_3O), 3.32 (s, 2H, CH_2), 2.31 (t, *J* = 6.5 Hz, 1H, OH).

Dimethyl 4-(methoxycarbonyl)methyl-5-oxotetrahydrofuran-3,3-dicarboxylate (6). Electrolysis of tetramethyl propane-1,1,2,3-tetracarboxylate (**3**) (2.21 g) in the presence of NaOAc gave colorless crystals **6** (1.97 g, 90%); mp 90–91 °C (MeOH). ^{1}H NMR (C_6D_6): δ 4.47 and 3.91 (d and d, *J* = 9.7 Hz, 2H, 2-CH_2), 3.66 (t, *J* = 6.0 Hz, 1H, 4-CH), 3.34 (s, 3H, CH_3O), 3.27 (s , 3H, CH_3O), 3.15 (s, 3H, CH_3O), 2.84 (d, *J* = 6.0 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 174.01, 170.73, 167.52, 68.91, 58.63, 52.92, 51.61, 41.33, 30.51. Anal. Calcd for $C_{11}H_{14}O_8$ (274.22): C, 48.17; H, 5.11. Found: C, 47.91; H, 4.97.

Trimethyl 5-(hydroxymethyl)-6-oxotetrahydro-2*H*-pyran-3,5,5-tricarboxylate (7). Electrolysis of tetramethyl propane-1,1,3,3-tetracarboxylate (**4**) (2.21 g) in the presence of NaOAc gave colorless crystals **7** (1.58 g, 65%); mp 86–87 °C (ether). ^{1}H NMR ($CDCl_3$): δ 4.72 and 4.40 (d and d, *J* = 12.3 Hz, 2H, 2-CH_2), 3.83 and 3.91 (dd and dd, *J* = 10.9, 9.6, 4.9 Hz, 1H and 1H, C*H*$_2$OH), 3.82 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 3.78 (s, H, CH_3O), 3.14 (dd, *J* = 9.6, 4.9 Hz, 1H, OH), 2.79 and 2.64 (d and d, *J* = 15.0 Hz, 2H, 4-CH_2). ^{13}C NMR ($CDCl_3$): δ 170.32, 170.12, 170.01, 168.33, 68.31, 66.62, 53.90, 53.73, 53.41, 54.19, 52.36, 31.20. Anal. Calcd for $C_{12}H_{16}O_9$ (304.25): C, 47.37; H, 5.26. Found: C, 47.11; H, 5.03.

Trimethyl tetrahydrofuran-3,3,4-tricarboxylate (8). Electrolysis of tetramethyl ethane-1,1,2,2-tetracarboxylate (**5**) (2.10 g) in the presence of NaOAc gave a viscous oil **8** (1.32 g, 67%); bp. 158–162 °C (0.1 Torr). ^{1}H NMR (C_6D_6): δ 5.16 d and 4.72 (d and d, *J* = 11.1 Hz, 1H and 1H, 2-CH_2), 4.47 and 3.98 (dd and dd, *J* = 8.8, 9.3, 9.8 Hz, 1H and 1H, 5-CH_2), 3.70 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 3.76 (s, H, CH_3O), 3.35 (dd, *J* = 9.3, 9.8 Hz, 1H, 4-CH). ^{13}C NMR (C_6D_6): δ 168.73, 166.30, 155.04, 66.61, 65.67, 56.88, 54.74, 52.85, 52.02, 42.72. Anal. Calcd for $C_{10}H_{14}O_7$ (246.21): C, 48.78; H, 5.69. Found: C, 48.36; H, 5.35.

Electrolysis of dimethyl malonate and methyl cyanoacetate. General procedure. A solution of ester **9a** or **9b** (20 mmol), LiCl (0.34 g, 8 mmol) in methanol (20 mL) was electrolyzed in an undivided cell equipped with a Pt-anode and an Fe-cathode at 50 °C under a constant current density of 200 mA/cm^2 until 3.5 F/mol of electricity was passed. The solvent was removed, and the residue was extracted with chloroform. The organic layer was separated, washed with water, and dried over Na_2SO_4. The solvent was removed, and products **10a,b** were isolated by flash cromotography (silica gel L 40/100, eluent ether/hexane 1:1).

Tetramethyl cyclopropane-1,1,2,2-tetracarboxylate (10a).[6,8] Electrolysis of dimethyl malonate (**9a**) (2.64 g) in the presence of LiCl gave colorless crystals **10a** (1.40 g, 51%); mp 70–

71°C, lit.[10] mp 71.5–72.0 °C. ^{1}H NMR ($CDCl_3$): δ 3.73 (s, 12H, CH_3O), 2.17 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 166.20, 53.21, 41.13, 23.91.

Dimethyl (1*R,2*S**)-1,2-dicyanocyclopropane-1,2-dicarboxylate (10b).**[8,11] Electrolysis of methyl cyanoacetate (**9b**) (1.98 g) in the presence of LiCl gave colorless crystals **10b** (0.87 g, 42%); mp 131–132 °C, lit.[11] mp 124–127 °C. ^{1}H NMR ($CDCl_3$): δ 3.97 (s, 6H, CH_3O), 2.60 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 162.01, 112.12, 53.80, 28.21, 26.63.

Acknowledgements

The authors gratefully acknowledge the financial support of the Russian Foundation for Basic Research (Leading Scientific Schools) (Project No. 00-15-97328).

References

1. Shono, T. Electroorganic Chemistry as a New Tool in Organic Synthesis *Reactivity and structure: concepts in organic chemistry;* Springer-Verlag: Berlin, 1984; Vol 20
2. *Novel Trends in Electroorganic Synthesis*, Torii, S., Ed.; Springer-Verlag: Berlin, 1998.
3. Elinson, M. N.; Feducovich, S. K.; Nikishin G. I. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1988**, 2534; *Chem. Abstr.* **1989**, *111*, 6702.
4. Elinson, M. N.; Feducovich, S. K.; Nikishin G. I. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1989**, 352; *Chem. Abstr.* **1989**, *111*, 214106.
5. Nikishin G.; Elinson, M. N.; Feducovich, S. K. I. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1986**, 1919. *Chem. Abstr.* **1987**, *107*, 175511.
6. Elinson, M. N.; Feducovich, S. K.; Lindeman, S. V.; Aleksanyan M. S.; Struchkov Yu. T.; Nikishin, G. I. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1989**, 1603; *Chem. Abstr.* **1989**, *111*, 182973.
7. White, D. A. *J. Electrochem. Soc*. **1977**, *124*, 1177.
8. Fedukovich, S. K.; Elinson, M. N.; Nikishin, G. I. *Izv. Akad. Nauk, Ser. Khim.* **1994**, 1835. *Chem. Abstr.* **1995**, *123*, 111565.
9. Kawabata, J.; Nozava, K.; Kawai, K.; Nakajima S. *Liebigs Ann. Chem*. **1990**, 181.
10. Stohmann, F.; Kleber, C. *J. Prakt. Chem*. **1892**, *45*, 476.
11. Huisgen, R.; Mitra, A.; Moran J. R. *Chem. Ber*. **1987**, *120*, 159.