

ELECTROCHEMICAL OXIDATION OF 2,2'-DIFURYLMETHANE AND ITS AROMATIC AND HETEROCYCLIC ANALOGUES IN METHANOL

J.ŠROGL, M.JANDA, I.STIBOR and Z.SALAJKA

Department of Organic Chemistry,

Prague Institute of Chemical Technology, 166 28 Prague 6

Received May 19th, 1976

Electrochemical methoxylation of 2,2'-difurylmethane (*I*), 2-(2-thienylmethyl)furan (*II*), 2-benzylfuran (*III*) and 2,2'-dithienylmethane (*IV*) is described. Compound *I* afforded the tetramethoxy derivative in the sense of the Clauson-Kaas reaction, *II* and *III* gave products with methoxylated furan ring and *IV* was oxidized only on the methylene bridge. Reactions of compounds *I-III* afforded excellent preparative yields. A substantial effect of oxygen on the outcome of the electrochemical experiments was found.

The investigation of anodic behaviour of five-membered heterocycles containing one hetero atom bears an interesting problem: is it possible to oxidize selectively one aromatic or heteroaromatic system in a molecule, containing another such system? Moreover, the study of this problem is motivated by the effort to synthesize analogues of γ -acetylacrylates which are known to exhibit a wide spectrum of biological activity. One of the syntheses of γ -acetylacrylates starts from 2-methylfuran, and its first step is the electrochemical methoxylation of this compound¹. For this reason we have chosen for the study of anodic methoxylation the substituted 2-methylfurans *I-III*. 2,2'-Dithienylmethane (*IV*) was studied for comparison with the compound *I*.

EXPERIMENTAL

Materials and Methods

The starting compounds, 2,2'-difurylmethane² (*I*), 2-(2-thienylmethyl)furan³ (*II*), 2-benzylfuran⁴⁻⁶ (*III*), and 2,2'-dithienylmethane⁷ (*IV*), were prepared according to procedures described in the literature. Neither the melting points nor the boiling points are corrected. The ¹H-NMR spectra were taken in deuteriochloroform on Tesla BS 477 (60 MHz) and Varian XL 100 (100 MHz) instruments. The shifts are given in ppm and are related to tetramethylsilane as internal standard. Mass spectra were measured on Gas Chromatograph - Mass Spectrometer LKB 9000. Infrared spectra were taken on a Perkin-Elmer 325 instrument, using carbon disulphide for the region 400-1200 cm⁻¹ and tetrachloromethane for the region 1200-4000 cm⁻¹. Gas-liquid analyses were performed on a Chrom-31 chromatograph, equipped with a flame-ionisation detector, using nitrogen as carrier gas. Thin-layer chromatography was carried out on Silufol (Kavalier, Sázava) plates, column chromatography on a "Silpearl" silica gel of the same prove-

nience. Spots were detected either by a UV-indicator or by spraying with a 10% solution of cerium oxide in 10% sulphuric acid and subsequent heating to 90°C.

Electrochemical oxidations were carried out in all-glass electrolyzers of the two types: Type 1: This electrolyzer contained 250 ml of electrolyte, and was equipped with a carbon anode (a rod; diameter 25 mm, height 300 mm) and with a cylindrical nickel cathode. The reaction mixture was stirred with nitrogen which was introduced through a sintered glass at the bottom of the electrolyzer. Type 2: This electrolyzer had a cylindrical anode made of a platinum sheet (45 cm²) and a concentric cylindrical cathode, made of a twisted nickel sheet.

The reaction mixture was stirred using a magnetic stirring bar. In experiments, carried out at constant potential of the working electrode, a potentiostat (VPZ Běchovice) and a commercial saturated calomel electrode (s.c.e.) Radelkis were used. One end of the salt bridge was a capillary, placed 1–2 mm from the working electrode, the other end was inserted into the cell with the reference electrode. The electrolytes used are specified in the descriptions of the electrolysis experiments.

Bis(2,5-dimethoxy-2,5-dihydrofuryl)methane (V)

A solution of 2,2'-difurylmethane (20 g; 0.135 mol) and ammonium bromide (4 g) in methanol (250 ml) was electrolysed at –30°C in an electrolyser of the type 1 at a constant current of 4A till the total amount of electricity of 4 F/mol was achieved. The solution was neutralized (pH 8) with a methanolic sodium methoxide solution. The methanol was evaporated *in vacuo* and ether (250 ml) was added to the residue. The obtained suspension was dried over magnesium sulphate, the ether was evaporated and the residue distilled, yielding 26 g (70%) of a liquid, b.p. 112°C/0.3 Torr. Crystallisation from n-heptane afforded 5 g of the isomer melting at 92°C. For C₁₃H₂₀O₆ (272.3) calculated: 57.30% C, 7.35% H, 45.50% OCH₃; found: 57.46% C, 7.20% H, 45.40% OCH₃. ¹H-NMR spectrum: 2.43 (s, 2 H, CH₂); 3.09 (s, 6 H, OCH₃); 3.50 (s, 6 H, OCH₃); 5.34 (s, 2 H, H-5); 5.91, 5.97, 6.08, 6.14 (AB syst. 4 H, H-3, H-4). IR-spectrum (cm⁻¹): 612, 672, 851, 802, 820, 844, 935, 982, 1013, 1050, 1100, 1140, 1175, 1190, 1220, 1320, 1340, 1370, 1418, 1438, 1445, 1465, 1630, 2820, 2870, 2900, 2930, 2950, 2980.

2-(2-Thienylmethyl)-2,5-dimethoxy-2,5-dihydrofuran (VI)

a) A mixture of the compound II (2 g; 0.012 mol) and ammonium bromide (2 g) was electrolysed in methanol (70 ml) at –50°C (electrolyser of the type 2) at a constant current of 1A till the total amount of electricity of 6 F/mol was achieved. The pH of the mixture was then adjusted to 8 by addition of methanolic sodium methoxide and the methanol was evaporated *in vacuo*. After addition of ether (150 ml) and drying over magnesium sulphate, the solution was taken down and the residue distilled, affording 1.2 g of a crude fraction, boiling at 80–90°C/0.3 Torr. Column chromatography (dichloromethane) afforded 0.5 g (20%) of chromatographically pure VI ($R_F = 0.55$, dichloromethane, b.p. 80°C/0.5 Torr. For C₁₁H₁₄O₃S (226.3) calculated: 56.20% C, 6.20% H, 14.90% S; found: 55.74% C, 6.16% H, 15.20% S. ¹H-NMR spectrum: *cis* VI: 3.16 (s, 3 H, OCH₃); 3.47 (s, 3 H, OCH₃); 3.34 (s, 2 H, CH₂); 5.77 (s, 1 H, H-5); 5.90 (m, 2 H, H-3, H-4); 6.90 (m, 2 H, H-3', H-4'); 7.15 (m, 1 H, H-5'); *trans* VI: 3.25 (s, 3 H, OCH₃); 3.34 (s, 2 H, CH₂); 3.92 (s, 3 H, OCH₃); 5.39 (s, 1 H, H-5); 5.90 (m, 2 H, H-3, H-4); 6.90 (m, 2 H, H-3', H-4'); 7.15 (m, 1 H, H-5'). IR spectrum (cm⁻¹): 627, 690, 749, 800, 820, 851, 867, 962, 977, 1014, 1040, 1096, 1114, 1154, 1192, 1222, 1330, 1340, 1375, 1435, 1460, 2835, 2930, 2995, 3070.

b) A mixture of the compound II (6 g; 0.037 mol) and sodium perchlorate (6 g) in methanol (250 ml) was electrolysed at –20°C (electrolyser of the type 1) at a constant current (200 mA). The potential between the working and auxiliary electrode was 3.5 V, the total amount of electri-

city 4 F/mol. The methanol was evaporated and the residue shaken between water and ether. The ethereal layer was washed with a saturated sodium hydrogen carbonate solution and dried over anhydrous sodium sulphate. Distillation afforded 3 g (40%) of *VI* which was identical with the product of the preceding preparation.

c) A mixture of *II* (2 g; 0.012 mol), sodium perchlorate (2 g) and methanol (70 ml) was electrolysed in an electrolyser of the type 2 at -30°C under dry nitrogen at the working electrode potential of 1.6 V relative to S.C.E. A methanolic solution of sodium perchlorate was used as the salt bridge. The same electrolyte was placed in a separate 30 ml cell connected with the porous tip of S.C.E. The resistance of the whole connection was lower than 10^5 Ohm. After the total amount of electricity of 4 F/mol had been achieved (the current being about 80 mA), the mixture was worked up as described under *a*). Column chromatography afforded 0.5 g of the starting *II* and 1.2 g (64%) of the chromatographically pure *VI*.

2-Benzyl-2,5-dimethoxy-2,5-dihydrofuran (*VII*)

Compound *III* (8 g; 0.05 mol) and ammonium bromide (4 g) in methanol (100 ml) were electrolysed on a platinum anode at -50°C under dry nitrogen. The total amount of electricity was 8 F/mol and the constant electrolysis current was 1A. The work-up procedure was analogous to that described for the compound *V*. Column chromatography of the crude product afforded 4.5 g of *VII*, b.p. $90^{\circ}\text{C}/0.3$ Torr ($R_F = 0.52$, dichloromethane). For $\text{C}_{13}\text{H}_{16}\text{O}_3$ (220.3) calculated: 72.00% C, 7.25% H, 25.20% OCH_3 ; found: 72.00% C, 7.13% H, 25.04% OCH_3 . $^1\text{H-NMR}$ spectrum: 3.09 (s, 3 H, OCH_3); 3.22 (s, 2 H, CH_2); 3.48 (s, 3 H, OCH_3); 5.15 (s, 1 H, H-5); 5.83 (s, 2 H, H-3, H-4); 7.24 (m, 5 H, H-arom.). IR-spectrum (cm^{-1}): 840, 865, 904, 963, 976, 1015, 1065, 1095, 1112, 1157, 1188, 1236, 1300, 1341, 1367, 1436, 1451, 1462, 1493, 2830, 2930, 2955, 3035, 3060, 3085.

An identical experiment in the atmosphere of pure oxygen afforded after distillation of the crude product 9.9 g (89%) of the chromatographically pure *VII*.

Electrochemical Methoxylation of 2,2'-Dithienylmethane (*IV*)

The compound *IV* (9 g; 0.05 mol) was electrolysed in methanol (230 ml) with conc. sulphuric acid (1 ml) on a carbon anode under dry nitrogen at -20°C till the total amount of electricity of 8 F/mol was achieved. The work-up procedure was the same as described for the preparation of *V*. Column chromatography of the crude product (gradient elution with a mixture of n-heptane, benzene and methanol) afforded the following compounds: 2 g of the starting compound *IV*; 2 g (25%) of 1,1-bis(2-thienyl)dimethyl ether (*VIII*), $R_F = 0.46$ (benzen). For $\text{C}_{10}\text{H}_{10}\text{OS}_2$ (210.3) calculated: 57.5% C, 4.85% H, 14.85% OCH_3 ; found: 57.38% C, 4.96% H, 15.54% OCH_3 . $^1\text{H-NMR}$ spectrum: 3.80 (s, 3 H, OCH_3); 5.50 (s, 1 H, CH); 6.95 (m, 4 H, H-3, H-4); 7.25 (m, 2 H, H-5). IR-spectrum (cm^{-1}): 695, 838, 856, 953, 1035, 1082, 1115, 1227, 1287, 1356, 1414, 1436, 1461, 1513, 1530, 2820, 2900, 2910, 2940, 2990, 3175, 3105. Mass spectrum (m/e , %): 78 (100), 32 (28), 51 (24), 52 (24), 50 (20), 39 (15), 179 (10), 111 (6), 210 (3). The third fraction consisted of 2,2'-dithienyl ketone (*IX*) (1 g; 13%); $R_F = 0.15$ (benzene) m.p. 87°C ; ref.⁸ reports $88-89^{\circ}\text{C}$. $^1\text{H-NMR}$ spectrum: 7.21 (q, 2 H, H-4, $J_{3,4} = 5$ Hz, $J_{4,5} = 3$ Hz), 7.70 (d, 2 H, H-3), $J_{3,4} = 5$ Hz; 7.92 (d, 2 H, H-5, $J_{4,5} = 3$ Hz). IR-spectrum (cm^{-1}): 829, 861, 1043, 1076, 1112, 1220, 1263, 1283, 1348, 1357, 1413, 1512, 1623, 3075, 3105. Mass spectrum (m/e , %): 116 (100), 194 (58), 39 (45), 83 (18), 166 (10), 45 (8), 117 (8), 118 (5).

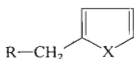
RESULTS AND DISCUSSION

The methoxylation of 2,2'-difurylmethane was carried out under conditions which proved to be successful in the cases of other substituted furan derivatives. When ammonium bromide was used as electrolyte, bis(2,5-dimethoxy-2,5-dihydrofuryl)-methane (*V*) was isolated in 70% yield. The $^1\text{H-NMR}$ spectra showed that this product was a mixture of stereoisomers.

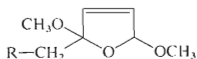
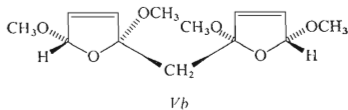
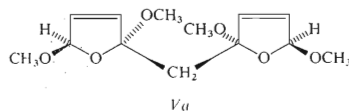
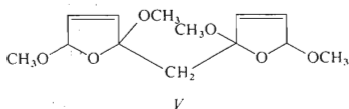
We were able to isolate from this mixture one crystalline isomer which could have the structure *Va* or *Vb*. Since the predominant products are usually derivatives with the *trans*-relation of the methoxy groups, we assume that the crystalline product has the configuration *Va*. Further experiments with the starting compound *I* were aimed at the preservation of one furan nucleus in the electrochemical reaction. Therefore, we varied within a wide range the concentration, temperature and the total amount of electricity. However, in all cases we obtained only a mixture of the starting compound *I* and the tetramethoxy derivative *V*. On the basis of this result we can conclude that the reaction intermediate is by an order of magnitude less stable than the starting compound *I* and the reaction proceeds preferentially to the stage of the tetramethoxy derivative *V*.

In the methoxylation of 2-(2-thienylmethyl)furan the electrochemical oxidation potentials of the two heterocyclic rings differ only slightly. In the literature we can find 1.7 V for furan⁹ and 1.9 V for thiophene¹⁰ (related to s.c.e.). We carried out first experiments in methanolic solutions of ammonium bromide. Whereas the methoxylation of furan derivatives gives excellent results in this medium¹¹, thiophene derivatives afford products, which arise by an attack of the heterocyclic nucleus by bromine, generated from the electrolyte¹². Under these conditions a mixture of products was obtained containing, according to gas-liquid chromatography, 66% of 2-(2-thienylmethyl)-2,5-dimethoxy-2,5-dihydrofuran (*VI*). This product was isolated by column chromatography in 20% yield. The crude reaction mixture showed a positive test for bromine and the presence of brominated compounds is therefore highly probable. According to gas-liquid chromatography (120 cm, XE-60, Chromaton 0.20–0.25 mm) the mixture contains about 16% of such compounds. In order to suppress the formation of brominated compounds, we carried out the reaction using sodium perchlorate as an auxiliary electrolyte. Under conditions of a constant current a mixture of at least four products was formed. However, using the controlled potential of the working electrode (1.6 V, s.c.e.) we found conditions leading only to the desired product which was isolated in 64% yield. The reaction was further developed to the preparative scale. When a carbon anode was used and the potential between the working and auxiliary electrode was 3.5 V formation of other products was suppressed and the compound *VI* was isolated in 40% yield. The lower yield in this case was due to formation of polymeric products. Both gas-liquid chromatography and $^1\text{H-NMR}$ spectra showed that the ratio

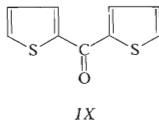
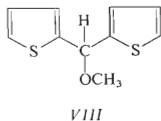
of stereoisomers in the product *VI* is 7 : 3 (probably *trans* : *cis*). It was found that when the reaction mixture after electrolysis in methanolic sodium perchlorate was treated with strong bases (sodium methoxide) during the work-up procedure, resinous material was formed and the product composition completely changed.



- I*, X = O, R = 2-furyl
II, X = O, R = 2-thienyl
III, X = O, R = phenyl
IV, X = S, R = 2-thienyl



- VI*, R = 2-thienyl 64%
VII, R = phenyl 89%



Alkoxylation of 2-benzylfuran in ammonium bromide solution was not accompanied with brominated compounds and when the electrolysis was performed under dry nitrogen, 2-benzyl-2,5-dimethoxy-2,5-dihydrofuran (*VII*) was isolated

in 40% yield. When the mixture was saturated with oxygen during the electrochemical reaction the yield more than doubled (89%) and the polymeric compounds did not form at all. Both the modifications of the reaction were carried out many times and it was proved that the above observation was completely reproducible. We can suggest two tentative explanations of this fact. It is known from the literature¹³ that in an electrochemical reaction the oxygen can interact with primarily formed radical-cations. On the other hand, it is possible that the oxygen interacts with the electrode surface because the introduction of oxygen causes a 50–100% current increase (under identical conditions). As shown by ¹H-NMR spectra, the product VII represents a single, practically pure isomer, probably *trans*.

The methoxylation of IV was carried out in methanolic sulphuric acid. Five components, including the starting compound, were found in the crude reaction product and the reaction itself was accompanied with an extensive formation of polymeric substances. Their formation can be explained by the instability of products, arising by cleavage of the thiophene ring. Two compounds, representing more than 80% of the product mixture, were isolated by chromatography. They were identified as 1,1-bis(2-thienyl)dimethyl ether (VIII) (25%) and 2,2'-dithienyl ketone (IX).

Analysis of samples, taken during the electrolysis, showed that all the products are formed from the beginning of the reaction. In further experiments, carried out at a constant potential of the working electrode, the formation of polymeric products was suppressed when the electrolysis was performed in an oxygen atmosphere. It was hitherto not possible to effect a preferential formation of any of the products. The same results were obtained also in the attempts to oxidize electrochemically the compound IV in methanol–dichloromethane (1 : 1) using tetraethylammonium perchlorate as an auxiliary electrolyte.

We can thus conclude that a preparative method for the selective oxidation of a heterocyclic system in the presence of another heterocyclic or aromatic system was developed. This reaction hitherto fails in the case of a selective oxidation of two identical systems. From the point of view of further synthesis of analogues of γ -acetylacrylates, the first step – electrochemical oxidation – is preparatively feasible.

REFERENCES

1. Šrogl J.: This Journal 29, 1380 (1964).
2. Braun W. M., Sawatzky H.: Can. J. Chem. 34, 1147 (1956).
3. Golfarb Ya. L., Danyushevskii Ya. L.: Izv. Akad. Nauk SSSR, Ser. Khim. 1963, 540.
4. Mndzhoyan A. L.: Sintezy Geterocyklicheskich Soedin. 1, 22 (1956).
5. Mndzhoyan A. L.: Sintezy Geterocyklicheskich Soedin. 1, 11 (1956).
6. Mndzhoyan A. L.: Sintezy Geterocyklicheskich Soedin. 2, 17 (1956).
7. Goldfarb Ya. L., Danyushevskii Ya. L.: Izv. Akad. Nauk SSSR, Ser. Khim. 1956, 1361.
8. Hartough H. D.: *Thiophene and Its Derivatives*, p. 349. Interscience, New York 1952.
9. Ebersson L., Nyberg K.: J. Amer. Chem. Soc. 88, 1686 (1966).

10. Loveland J. W., Dimeler G. R.: *Anal. Chem.* **33**, 1196 (1961).
11. Elming N. in the book: *Advances in Organic Chemistry*, (R. A. Raphael, E. C. Taylor, H. Wynberg, Eds), Vol. 2, p. 67. Interscience, New York 1960.
12. Němec M., Šrogl J., Janda M.: *This Journal* **37**, 3122 (1972).
13. Blaedel W. J., Hass R. G.: *Anal. Chem.* **42**, 918 (1970).

Translated by M. Tichý.