Possibility of applying the electrochemical version of the Horner reaction to the synthesis of unsaturated lactones

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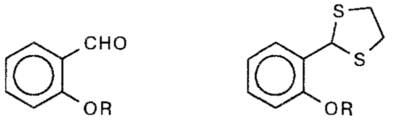
Direct electrochemical reduction of specially synthesized 2-[(diethoxyphosphorylacetoxy]benzaldehyde on a platinum electrode in an aprotic medium is accompanied by ester bond cleavage, and not formation of coumarin via the phosphonate-anion followed by intramolecular Horner cyclization. This could be realized, as a matter of principle, in the presence of an ionol anion (2,6-di-*tert*-butyl-4-methylphenoxide), electrochemically generated *in situ.*

Key words: Wittig-Horner reaction, unsaturated lactones, synthesis, intramolecular cathode cyclization, electrochemically generated base, coumarin, 2,6-di-*tert*-butyl-4-methylphenoxide.

It was reported previously[1] that direct reduction of substituted phosphonates on platinum or glassy carbon electrodes afforded the corresponding carbanions due to C−H bond cleavage. If performed in the presence of carbonyl compounds, this allowed the realization of an electrochemical version of the Wittig-Horner reaction. An interesting extension of this work could be an attempt to carry out intramolecular cathode cyclization of compounds containing separated carbonyl and phosphonate groups. This approach might be useful for the synthesis of unsaturated lactones with different ring size which frequently occur among physiologically active compounds.[2]

To check the possibility of the aforementioned cyclization we tried to perform a cathode synthesis of easily identifiable coumarin. To this end we synthesized 2-[(diethoxyphosphoryl)acetoxy]benzaldehyde (**5**) which should serve as a precursor.



1: **R** = H
5: **R** = $\mathrm{C(O)CH_2\underset{\underset{O}{\|}}{P}(OEt)_2}$

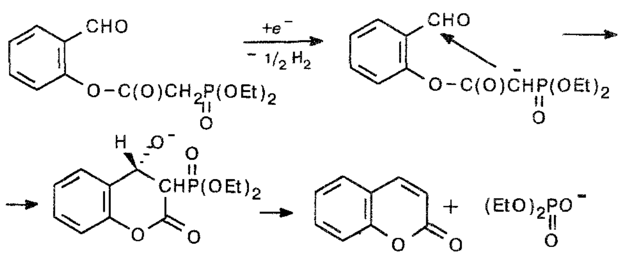
2: **R** = H
3: **R** = $\mathrm{C(O)CH_2Cl}$
4: **R** = $\mathrm{C(O)CH_2\underset{\underset{O}{\|}}{P}(OEt)_2}$

Compound **5** was synthesized as follows: the aldehyde group in salicylaldehyde **1** was protected by reaction with ethanedithiol. The thus prepared compound **2** was acylated with chloroacetyl chloride in pyridine and the corresponding chloroacetate **3** was transformed to phosphonate **4** by reaction with triethyl phosphite. Deprotection of **4** with ceric ammonium nitrate yielded the desired phosphonate **5** in 34% overall yield.

The final stage of the synthesis of coumarin should be the cathode cyclization of **5** according to the following tentative scheme (Scheme 1).

However, it was at the final stage that we encountered difficulties. Galvanostatic electrolysis of **5** on a Pt cathode gave salicylaldehyde **1** as the only product. In our mind, the formation of **1** could be due either to OH^--effected hydrolysis of **5** or to direct cleavage of the ester bond (CO−OAr) on the cathode. An attempt to scavenge electrochemically generated OH^- ions, which could originate from reduction of traces of water, by preliminary electrolysis of the electrolyte in the presence of an anion exchange resin [Amberlyst A-26(Cl^-)] followed by addition of **5** to the electrolysis products did not change the result. Moreover, salicylaldehyde was identified by GLC as a product of potentiostatic ($E_{1/2}$ = −1.8 V) electrolysis of **5** at the first wave potential (Fig.1). It is necessary to say that the value $E_{1/2}$ = −1.5 V for the first reduction wave obtained by voltammetric measurements in dry MeCN on a rotating Pt electrode is close to the corresponding value $E_{1/2}$ = −1.6 V for acetophenone and more positive than the value $E_{1/2}$ = −2.2 V for $(EtO)_2P(O)CH_2COOEt$ despite the fact that the methylene group of the latter is activated by an electron acceptor substituent. It thus may be concluded that the reduction of aryl phosphonacetates on a Pt cathode, unlike previously studied phosphonates,[1,3] effected ester bond CO−OAr cleavage. Nevertheless, we tried to generate the corresponding carbanion using the method of electrochemically generated bases (EGB).[4]

Scheme 1



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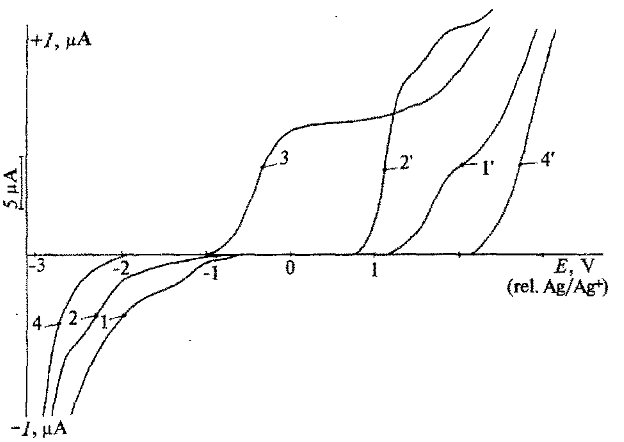
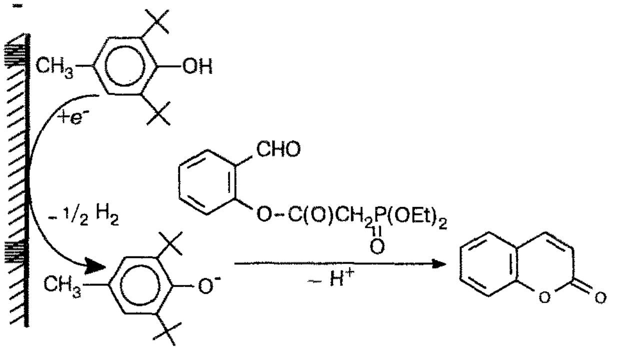


Fig.1. Voltammetric curves in anode and cathode spaces on rotating Pt electrode: *1* — Phosphonate **5** ($C = 1.7$ mmole/l), *2* — 2,6-Di-*tert*-butyl-4-methylphenol ($C = 3.4$ mmole/l), *3* — 2,6-Di-*tert*-butyl-4-methylphenoxide (ionol anion) ($C = 3.4$ mmole/l), *4* — Background current, 0.1 *N* solution of Bu_4NBr in CH_3CN.

The classical example of EGB used in the Wittig reaction[5] is the azobenzene anion radical. However, under the experimental conditions used the reduction of azobenzene is more difficult ($E_{1/2} = -1.8$ V) than that of the phosphonate **5**. It is not surprising therefore that galvanostatic electrolysis of **5** in the presence of azobenzene afforded a complex mixture of products. Coumarin was not detected by TLC. It should be noted that **5** contains, along with active methylene hydrogens, two carbonyl groups which can undergo nucleophilic attack. So we tried to find a «pre-base» which would produce, on cathode reduction, a weakly nucleophilic anion. The ionol anion (2,6-di-*tert*-butyl-4-methylphenoxide) seems to be the anion of choice since it is a strong base and a weak nucleophile.[6]

Our voltammetric experiments showed that ionol gives one reduction wave ($E_{1/2} = -2.4$ V) and two oxidation waves ($E_{1/2} = 1$ and 1.5 V) on a rotating Pt electrode (Fig.1, curve *2*). Electrolysis of ionol at its cathode wave potential afforded an easily oxidizable anion (Fig.1, curve *3*), unstable under the experimental conditions. A freshly prepared solution of the anion in CH_3CN (potentiostatic electrolysis, $C = 0.015$ mole/l) decomposed completely in 3 h without formation of a protonation product (voltamperometry, GLC). The color of the solution turned from greenish to deep-brown. It thus follows that the anion must be used immediately after electrogeneration. In subsequent experiments we added an excess of freshly prepared solution of the ionol anion to a solution of **5**. The resulting mixture was analyzed by means of voltamperometry and GLC. The phosphonate wave disappeared and several unidentified anode and cathode waves arose on the polarization curve. GLC analysis of the reaction mixture after 30 min revealed a small amount of coumarin (*ca.* 10% yield). Simultaneously an unidentified peak with retention time close to coumarin appeared on the chromatogram and its intensity grew with time, especially upon heating.

The presented results allow one to conclude that the ionol anion reacts with aryl phosphonoacetate **5** by different ways and the desired cyclization is a minor process whereas the main reaction leads to nonidentified byproducts:



On the whole, the results revealed the principal possibility of formation of α,β-unsaturated lactones using the EGB method. To achieve satisfactory yields, the study of the appropriate conditions should be continued.

Experimental

Polarization curves were recorded using a rotating Pt disk electrode ($8.3 \cdot 10^{-3}$ cm^2) with frequency of rotation 1620 rpm. A Pt cathode (6 cm^2 area) was used for potentiostatic microelectrolysis. Voltammetric measurements and microelectrolyses were carried out in a divided cell with a glass diaphragm. The working volume of electrolyte was 28 ml. The electrode potential was supported by a P-5827M potentiostat. All electrochemical experiments were carried out using Bu_4NClO_4 and Bu_4NBr in absolute CH_3CN as the supporting electrolytes under Ar. Ag/Ag$^+$ (0.1 N) was taken as the reference electrode. The working concentrations of depolarizer were 0.001—0.01 mole/l for voltammetric measurements and 0.01—0.02 mole/l for microelectrolyses. Acetonitrile was purified by repeated distillation from P_2O_5; the final distillation was without the dessicant. Bu_4NClO_4 and Bu_4NBr were crystallized from ethanol and dried on a rotary evaporator at 90°C.

GLC analyses were carried out on a Gasochrom 1300 chromatograph on a column 2.4 m × 3 mm with SE-30 on Chromaton N-AW, oven temperature 135°C (isothermic mode), injector temperature 190°C. ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer in $CDCl_3$; mass spectra were measured on a CH-6 (Varian MAT, direct insertion probe, EI, 70 eV).

2-(2-Hydroxyphenyl)-1,3-dithiolane (2). Ethanedithiol (7 ml, 0.17 mole) and a catalytic amount of $ZnCl_2$ were placed into a round-bottom flask with a magnetic stirrer. After dissolution of $ZnCl_2$, salicylaldehyde (4.5 ml, 42 mmole) was added. The reaction was monitored by TLC. After disappearance of salicylaldehyde (ca. 30 min) the mixture was neutralized with Et_3N. The excess ethanedithiol was removed under reduced pressure at 60—70°C. Chromatography on a silica gel column (100—160 μ, C_6H_6—AcOEt, 3:1) yielded dithiolane **2** (6.9 g, 86%). ^{1}H NMR ($CDCl_3$, δ):7.4 (d, 1H), 7.22 (t, 1H), 6.9 (q, 2H) (aromatic protons), 5.9 (s, 1H, CH), 3.45 (m, 2H, CH_2), 3.3 (m, 2H, CH_3).

2-(2-Chloroacetoxyphenyl)-1,3-dithiolane (3). Dithiolane **2** (7.45 g, 38 mmole) in 250 ml of CH_2Cl_2 and 7.07 ml of Py were placed in a round-bottom flask under Ar. The mixture was cooled (−20 to −30°C, dry ice—xylene mixture) and chloroacetyl chloride (7.7 ml, 97 mmoles) was added dropwise. After 1 h the reaction mixture was placed in a separating funnel, washed with $NaHCO_3$ solution, then with water, and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (100—160 μ, eluents C_6H_6—hexane, 1:1, and then benzene—ethyl acetate, 3:1) yielding yellow crystals of **3** (9.3 g, 92%). Mass spectrum (*m/z*): 276, 274 $[M]^+$. ^1H NMR ($CDCl_3$, δ): 7.83 (q, 1H), 7.28 (q, 2H), 7.10 (s, 1H) (aromatic protons), 5.8 (s, 1H, CH), 4.35 (s, 2H, CH_2), 3.3 (m, 4H, CH_2CH_2).

2-[2-(Diethoxyphosphoryl)acetoxyphenyl]-1,3-dithiolane (4). The ester **3** (4.0 g, 14.6 mmole) and triethyl phosphite (2.5 ml, 17 mmole) were placed into a two-necked round-bottom flask and heated under reflux at 60—90°C for 1.5 h, then more triethyl phosphite was added portionwise (4×0.5 ml) over 6 h at 120°C. After cooling the reaction mixture, the excess triethyl phosphite was removed under reduced pressure and the residue was chromatographed on a silica gel column (100—160 μ, C_6H_6—ethyl acetate, 1:1) yielding **4** (3.3 g, 60%). Mass spectrum (*m/z*): 376 (M^+). ^1H NMR ($CDCl_3$, δ): 7.8 (q, 1H), 7.22 (q, 2H), 7.03 (q, 1H) (aromatic protons), 5.89 (s, 1H), 4.22 (q, 4H, OCH_2CH_3), 3.32 (m, 2H), 3.45 (m, 2H) (dithiolane fragment), 3.5 (d, $^2J_{^{31}P-^1H}$ = 150 Hz, 2H, CH_2-P(O)), 1.35 (t, 6H, OCH_2CH_3).

2-[(Diethoxyphosphoryl)acetoxy]benzaldehyde (5). Ceric ammonium nitrate (10 g, 18.2 mmole) was added to **4** (2.5 g, 6.6 mmole) in 20 ml of water under intensive heating. The reaction was monitored by TLC (C_6H_6—MeOH, 15:1). After 0.5 h the reaction mixture was placed into a separating funnel, 20 ml of $CHCl_3$ was added, the organic layer was separated, washed with $NaHCO_3$ solution and water, and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (40—100 μ, C_6H_6—MeOH, 15:1) yielding phosphonate **5** (1.47 g, 74%). Mass spectrum (*m/z*): 300 $[M]^+$. ^1H NMR ($CDCl_3$, δ): 10.2 (s, 1H, C(O)H), 7.95 d, 7.85 d, 7.55 d, 7.4 d (4H, aromatic protons), 4.2 (t, 4H, OCH_2CH_3), 3.23 (d, $^2J_{^{31}P-^1H}$ = 63 Hz, 2H, CH2-P(O)), 1.3 (t, 6H, OCH_2CH_3).

Electrochemical reduction of 2-[(diethoxyphosphoryl)acetoxy]benzaldehyde (5). Electrolyses were carried out in a divided cell (t = 15—20°C) in an inert atmosphere. A Pt plate was taken as the cathode (21 cm^2 area) and the anode was from graphite. Five layers of tracing paper were used as a diaphragm. The anolyte was 40 ml of a 0.3 *M* solution of Bu_4NBr and 0.3 M cyclohexene in absolute CH_3CN, and the catholyte was **5** (0.2 g, 0.67 mmol) in 50 ml of 0.3 *M* Bu_4NBr in CH_3CN. The catholyte was stirred with a magnetic stirrer. Electrolyses were carried out under amperostatic conditions, I = 85 mA (J = 4 mA/cm^2). After passage of 1 F/mole of electricity the solvent was removed under reduced pressure without heating. The residue was extracted with ether, washed with water, dried with $MgSO_4$, and chromatographed on silica gel. The yield of salicylaldehyde was 56 mg (~70%).

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New methods of preparation of nitrile oxides and the corresponding disubstituted furoxans by interaction of N_2O_4 with salts of substituted dinitromethanes

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A new method of generation of nitrile oxides through interaction of N_2O_4 with salts of substituted dinitromethanes (**1**) has been worked out. It has been shown by ^1H, ^{13}C, ^{14}N NMR spectroscopy that this reaction proceeds via dinitronitrosomethyl intermediates (one of these has been isolated), and that the reaction is feasible only for substituents capable of conjugation with the nitrile oxide fragment. On the basis of cyclodimerization of the obtained nitrile oxides, preparative methods of synthesis of symmetrically substituted furoxans have been developed.

Key words: denitration, dinitromethanes, dinitronitrosomethanes, nitrile oxides, nitrosation, nitrolic acids, trinitromethanes, furoxans, dinitrogen tetroxide.

The reaction of N_2O_4 with salts of aryldinitromethanes is known to be the method for preparation of aryltrinitromethanes.[1,2] We have shown that this reaction can be directed to the formation of benzonitrile oxides, although formation of aryltrinitromethanes can not be completely prevented. Nitrile oxides **3a—d** have been identified by

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