Pergamon

Tetrahedron Vol. 51, No. 14, pp. 4083-4088, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00125-5

Photo-Oxidation of 2-Furyl-Alkyl-Phosphonates: Synthesis of New Cyclopentenone Derivatives

Franco D'Onofrio*, Giovanni Piancatelli, and Massimo Nicolai

Centro CNR di Studio per la Chimica delle Sostanze Organiche Naturali, Dipartimento di Chimica,
Università "La Sapienza", P.le Aldo Moro 5, 00185 Roma, Italy

Abstract: The furan ring in the title compounds was opened with singlet oxygen in methanol. New phosphonate cyclopentenone derivatives were synthesized.

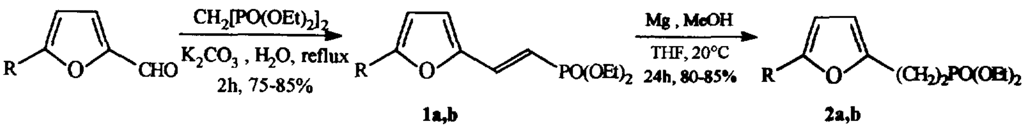
Furans have proven to be useful precursors to a wide variety of building blocks and intermediates in organic synthesis.[1]

In their chemistry, the ring opening plays a fundamental role. Particularly, the preparation of 1,4-dicarbonyl derivatives from furans has attracted a great attention, in order to develop strategies for the synthesis of naturally occurring cyclopentenones.[2]

In addition to their well-known utility in organic synthesis, the phosphonate groups are sometimes of interest from a biological point of view due their isostericity with the phosphate group.[3]

Our continuous interest in the chemistry of both furans and cyclopentenones prompted us to achieve those conditions for the ring opening of furan derivatives that are compatible with the presence of a phosphonate group in the molecular structure, particularly in view of their stepwise conversion to carbocyclic compounds.

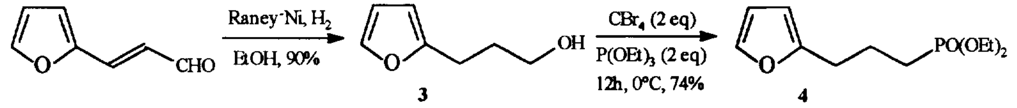
Starting materials **2a,b** were obtained in good yields by a two step procedure involving first the condensation of tetraethylmethylene diphosphonate (TEMPD) with the suitable aldehyde to give **1a,b** and then the reduction of the double bond by the action of magnesium in presence of methanol as hydrogen donor. This procedure, previously reported for the reduction of the double bond in carbonyl-conjugated vinylfurans was found to give the best results.[4]



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

a : R=H **b** : R=CH_3

Compound **4** was synthesised from the alcohol **3**, obtained in near quantitative yield by Raney-Ni catalysed hydrogenation of the commercially available β-2-furyl-acrolein, in a one step procedure: treatment of **3** with double molar ratio of both CBr_4 and $P(OEt)_3$ gave directly **4** without isolation of the intermediate bromide in good yield.



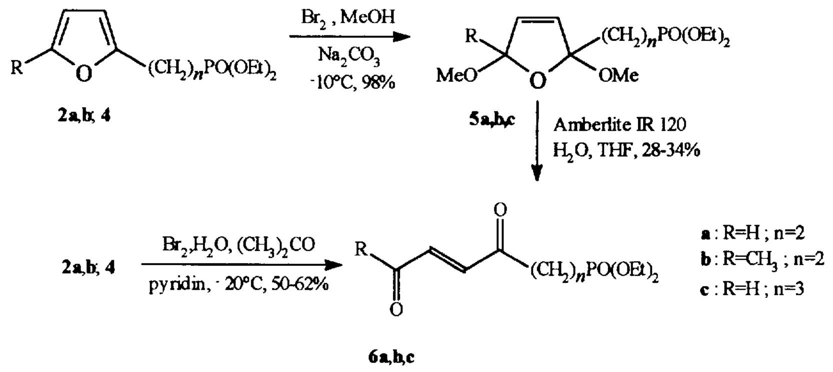
The most general methods for the furan ring opening to γ-dicarbonyl compounds are:[5]

a) hydrolytic opening in acidic medium to give saturated 1,4-diketones:

b) reaction with bromine in methanol and subsequent acidic hydrolysis of the intermediate 2,5-dimethoxy-2,5-dihydro-furan derivatives to give 2,3-unsaturated-1,4-diketones:

c) oxidation (PCC, MCPBA, singlet oxygen) to give 2,3-unsaturated-1,4-diketones.

The hydrolytic opening method failed with our substrates. The prolonged reaction times and the elevated acidity of the medium required for the ring opening, caused low yields of the desired 1,4-dicarbonyl compounds due the extensive decomposition of both substrates and products.



Equally ineffective was the bromo-methoxylation method. Although the 2,5-dimethoxy-2,5-dihydrofuran derivatives **5a-c** were obtained in near quantitative yields by treatment of **2a,b** and **4** with bromine in methanol, the acid catalysed hydrolytic deprotection of the carbonyl functions required too drastic conditions: the best yield (28-34%) were obtained by using Amberlite IR-120 ion exchange resin. Better results were obtained by a scarcely used modification of this method:[6] treatment of substrates with bromine in H_2O gave directly **6a,b,c** in moderate yields (50-60%). Nevertheless the problem of the furan ring opening in our substrates was successfully resolved by the singlet oxygen oxidation method.

The photo-oxidation of **2a,b**, **4** and **1b** carried out in a 1% methanol solution of substrates, at 0°C, with bubbling oxygen and in the presence of Rose Bengal as photosensitizer under irradiation with a 200W tungsten lamp) followed by reaction with dimethyl sulphide, gave the corresponding 2,3-unsaturated-1,4-dicarbonyl compounds **6a-d** that required no further purification and were directly converted in nearly quantitative yields to **7a-c** by reduction of the double bond with NaI in acetone in the presence of dilute HCl.[7] Data are summarized in Table 1.

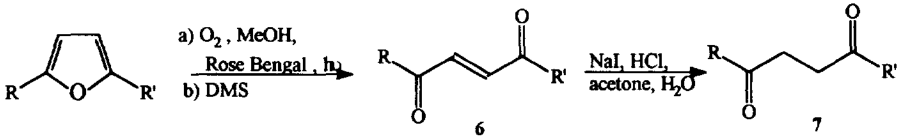


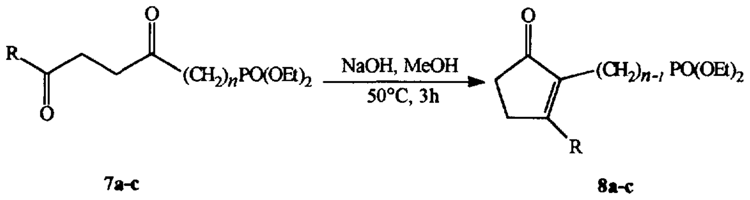
Table 1. Synthesis of 1,4-dicarbonyl compounds 7a-c

Substrate	R	R'	6	7	Yield (%)
2a	H	$-(CH_2)_2-PO(OEt)_2$	**6a**	**7a**	92
2b	CH_3	$-(CH_2)_2-PO(OEt)_2$	**6b**	**7b**	96
4	H	$-(CH_2)_3-PO(OEt)_2$	**6c**	**7c**	94
1b	CH_3	$-CH=CH-PO(OEt)_2$	**6d**	**7b**	76*

* Double quantity of NaI and HCl

It is to be noted that the photo-oxidation method works well also on the unsaturated substrate **1b**. In this case, by using double quantity of both NaI and HCl, it was possible to reduce both the double bonds. This procedure represents an alternative route to **7b**; on the other hand, due the worst overall yield, for the obtainment of **7a** it is preferable to use the procedure involving the prior reduction of the double bond conjugated with the phosphonate group in the compound **1a**.

All the 1,4-dicarbonyl compounds **7a-c** were cyclised in the usual conditions to the cyclopentenones **8a-c** in excellent yields. In the case of **7b** ($R=CH_3$) the isomeric cyclopentenone **8c** was obtained only in traces.



8a : R=H, n=2 ; yield 76%
8b : $R=CH_3$, n=2 ; yield 92%
8c : R=H, n=3 ; yield 76%

In conclusion we found that in alkyl-phosphonate furan derivatives, the opening of the furan ring is possible without affecting the phosphonate group and the application to the synthesis of substituted cyclopentenones is demonstrated. Compounds **8a-c** were never described before in the literature and studies devoted to their utilisation in the synthesis of natural products are currently in progress.

Experimental.

Synthesis of 1a,b; general procedure.

A solution of the suitable furaldehyde (20 mmol), tetraethylmethylenediphosphonate (20 mmol), K_2CO_3 (40 mmol) in 6.6 ml of H_2O was refluxed for 2 h. Then the cold mixture was poured into water and extracted with CH_2Cl_2. Neutral extracts were dried over Na_2SO_4 and the solvent evaporated under reduced pressure to yield a crude product that was chromatographed on silica gel using diethyl ether as eluent.

Diethyl 2-(2-furyl)-vinyl-phosphonate, 1a : ^{1}H-NMR ($CDCl_3$) δ: 1.32 (t, 6H, J=7Hz), 4.09 (dq. 4H, J_1=7Hz, J_2=7Hz), 6.08 (dd. 1H, J_1=17Hz, J_2=2Hz), 6.43 (dd, 1H, J_1=3Hz, J_2=2Hz), 6.53 (d, 1H, J=3Hz), 7.23 (dd, 1H, J_1=22Hz, J_2=17Hz), 7.44 (d, 1H, J=2Hz). MS (m/z): M^+=230.

Diethyl 2-(5-methyl-2-furyl)-vinyl-phosphonate, 1b : ^{1}H-NMR ($CDCl_3$) δ: 1.31 (t, 6H, J=7Hz), 2.30 (s, 1H), 4.07 (dq. 4H, J_1=7Hz, J_2=7Hz), 5.96 (dd, 1H, J_1=17Hz, J_2=17Hz), 6.41 (d, 1H, J=3Hz), 7.15 (dd, 1H, J_1=22Hz, J_2=17Hz). MS (m/z): M^+=244.

Synthesis of 2a,b; general pocedure.

To a solution of **1a,b** (4 mmol) in anydrous 9:1 MeOH/THF (50 ml), Mg (16 mmol) was added. The mixture was stirred at room temperature under nitrogen for 24 h. Then was poured in dilute HCl and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed on SiO_2 (eluent ethyl acetate) to give pure **2a,b**.

Diethyl 2-(2-furyl)-ethan-phosphonate, 2a : ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 6H, J=7Hz), 1.96-2.16 (m, 2H), 2.80-2.98 (m, 2H), 4.07 (dq. 4H, J_1=7Hz, J_2=7Hz), 6.10 (d, 1H, J=3Hz), 6.25 (dd, 1H, J_1=3Hz, J_2=2Hz), 7.44 (d, 1H, J=2Hz). MS (m/z): M^+=232.

Diethyl 2-(5-methyl-2-furyl)-ethan-phosphonate, 2b : ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 6H, J=7Hz), 1.90-2.13 (m, 2H), 2.17 (s, 3H), 2.65-2.85 (m, 2H), 4.03 (dq, 4H, J_1=7Hz, J_2=7Hz), 5.78 (m, 1H), 5.82 (d, 1H, J=2Hz). MS (m/z): M^+=246.

Synthesis of diethy 3-(2-furyl)-propan-1-phosphonate, 4.

3-(2-furyl)-propan-1-ol (1.5 g, 11.9 mmol), 4.2 ml of triethyl phosphite (23.8 mmol) and 7.9 g of CBr_4 (23.8 mmol) were mixed at 0°C. The reaction mixture was stirred at room temperature for 12 h then diluted with Et_2O, washed with brine and the organic extract dried over Na_2SO_4. The solvent was distilled under reduced pressure and the crude product chromatographed on SiO_2 (eluent Et_2O to give 2.17 g of pure **4** (yield 74%). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (t, 6H, J=7Hz), 1.99 (dt. 2H, J_1=7Hz, J_2=7 Hz), 2.73 (t, 2H, J=7Hz), 3.90-4.17 (m, 6H), 5.99 (d, 1H, J=3Hz), 6.25 (dd, 1H, J_1=3Hz, J_2=2Hz), 7.28 (d, 1H, J=2Hz). MS (m/z): M^+=246.

Preparation of 7a-c; general procedure.

A 1% *w/v* solution of substrates (0.5 mmol) in MeOH containing a catalytic amount of Rose Bengal (5 mg) was irradiated, at 0°C, with a 200-W tungsten lamp for 2h under a slow stream of oxygen. An equimolar amount of dimethyl sulphide was then added and the reaction mixture was allowed to warm to room temperature. A few minutes later, the solvent was removed under reduced pressure to give the crude α,β–unsaturated-1,4-dicarbonyl compounds **6a-d** that were diluted with 10ml of acetone. 1Mmol of NaI and 0.08 ml of concentrated HCl were added to this solution (double quantity for the obtainment of **7b** starting from **6d**). After 10 min (1h starting from **6d**), the mixture was diluted with Et_2O and washed with a solution of $Na_2S_2O_3$ (0.1 N). The organic layer was washed with brine and concentrated under reduced pressure. Chomatography on SiO_2 (eluent ethyl acetate) gave pure products **7a-c**.

Diethyl 3-oxo-5-formyl-pent-4-en-1-yl-phosphonate, 6a : ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 6H, J=7Hz), 1.70-2.20 (m, 4H), 4.07 (dq, 4H, J_1=7Hz, J_2=7Hz), 5.97 (m, 2H), 10.92 (s, 1H). IR ($CHCl_3$): 1692, 1634 cm^{-1}. MS (m/z): M^+=248.

Diethyl 3,6-dioxo-hept-4-en-1-yl-phosphonate, 6b : ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 6H, J=7Hz), 1.85-2.10 (m, 2H), 2.31 (s, 3H), 2.82-2.97 (m, 2H), 4.03 (dq, 4H, J_1=7Hz, J_2=7Hz), 6.78 (s, 2H). IR ($CHCl_3$): 1695, 1630 cm^{-1}. MS (m/z): M^+=262.

Diethyl 4-oxo-6-formyl-hex-5-en-1-yl-phosphonate, 6c : ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 6H, J=7Hz), 1.60-2.10 (m, 4H), 3.90-4.20 (m, 6H), 6.78 (s, 2H), 10.90 (s, 1H). IR ($CHCl_3$) : 1690, 1635 cm^{-1}. MS (m/z): M^+=262.

Diethyl 3,6-dioxo-hept-1,4-dien-1-yl-phosphonate, 6d. : ^{1}H-NMR ($CDCl_3$) δ : 1.28 (t, 6H, J=7Hz), 2.58 (s, 3H), 4.08 (dq, 4H, J_1=7Hz, J_2=7Hz), 5.70-7.10 (m, 4H). IR ($CHCl_3$): 1680, 1615 cm^{-1}. MS (m/z): M^+=260.

Diethyl 3-oxo-5-formyl-pentan-1-phosphonate, 7a : ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 6H, J=7Hz), 1.50-1.65 (m, 2H), 1.90-2.10 (m, 2H), 2.67-2.85 (m, 4H), 4.06 (dq, 4H, J_1=7Hz, J_2=7Hz), 9.77 (s, 1H). IR ($CHCl_3$): 1715 cm^{-1}. MS (m/z): M^+=250.

Diethyl 3,6-dioxo-heptan-1-phosphonate, 7b : ^{1}H-NMR ($CDCl_3$) δ: 1.21 (t, 6H, J=7Hz), 1.80-2.02 (m, 2H), 2.08 (s, 3H), 2.50-2.75 (m, 6H), 3.98 (dq, 4H, J_1=7Hz, J_2=7Hz). IR ($CHCl_3$): 1710 cm^{-1}. MS (m/z): M^+=264.

Diethyl 4-oxo-6-formyl-hexan-1-phosphonate, 7c : ^{1}H-NMR ($CDCl_3$) δ: 1.31 (t, 6H, J=7Hz), 1.80-2.02 (m, 2H), 2.61 (t, 2H, J=7Hz), 2.68-2.78 (m, 4H), 3.95-4.16 (m, 6H), 9.78 (s, 1H). IR ($CHCl_3$): 1712 cm^{-1}. MS (m/z): M^+=264.

Synthesis of cyclopentenones 8a-c; general procedure.

A solution of **7a-c** (1.45 mmol) in 43 ml of MeOH and 6 ml of NaOH (0.1 *M*) was stirred at room temperature for 24h. Then the mixture was poured in water, extracted with ethyl acetate and washed with brine.Neutral extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Chomatography on SiO_2 (eluent ethyl acetate) gave pure products **8a-c**.

Diethyl 2-cyclopent-1-enonyl-methan-phosphonate, 8a : ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, 6H, J=7Hz), 2.37-2.42 (m, 2H), 2.55-2.70 (m, 2H), 2.73 (dd, 2H, J_1=21Hz, J_2=1Hz), 4.07 (dq, 4H, J_1=7Hz, J_2=7Hz), 7.70 (m, 1H). IR ($CHCl_3$): 1702, 1638 cm^{-1}. MS (m/z): M^+=232.

Diethyl 2-cyclopent-3-metyl-1-enonyl-methan-phosphonate, 8b : ^{1}H-NMR ($CDCl_3$) δ: 1.20 (t, 6H, J=7Hz), 2.08 (d, 3H, J=4Hz), 2.28-2.38 (m, 2H), 2.42-2.58 (m, 2H), 2.71 (d, 2H, J=21Hz), 4.10 (dq, 4H, J_1=7Hz, J_2=7Hz). IR ($CHCl_3$): 1702, 1640 cm^{-1}. MS (m/z): M^+=246.

Diethyl 2-(2-cyclopent-1-enonyl)-ethan-phosphonate, 8c : ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 6H, J=7Hz), 2.35-2.42 (m, 2H), 2.50-2.62 (m, 4H), 3.92-4.20 (m, 6H), 7.46 (s, 1H). IR ($CHCl_3$): 1697, 1625 cm^{-1}. MS (m/z): M^+=246.

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(*Received in UK* 30 *November* 1994; *revised* 6 *February* 1995; *accepted* 9 *February* 1995)