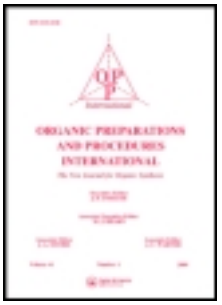

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PREPARATION OF β-KETOPHOSPHONATES AND THEIR VINYLOGUES BY OXIDATION OF THE CORRESPONDING ALCOHOLS

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PREPARATION OF β-KETOPHOSPHONATES AND THEIR VINYLOGUES BY OXIDATION OF THE CORRESPONDING ALCOHOLS

Submitted by (08/19/98)

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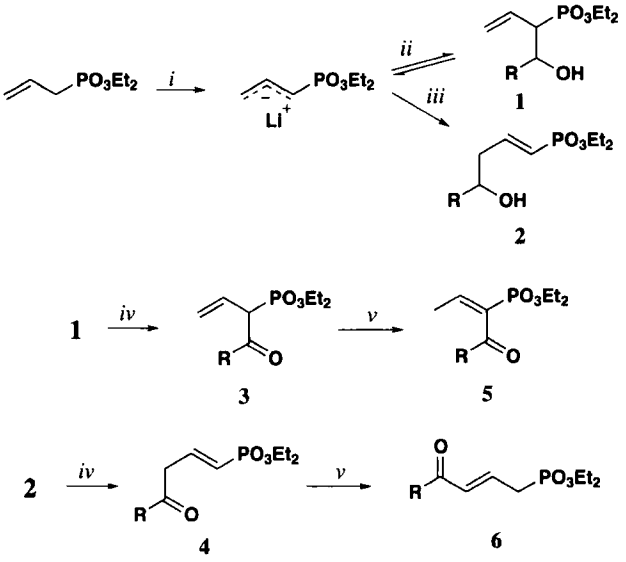
Application of β-ketophosphonates as substrates in the Wadsworth-Emmons olefination is well documented,[1] but the synthetic routes to those substrates are limited. The application of the Arbusov reaction[2] and the acylation of alkylphosphonate anions[3] suffer from specific restrictions. More recent developments are derived from the work of Wiemer,[4] Oh,[5] and Boeckman,[6] while Mikolajczyk and co-workers demonstrated synthetic potential of the vinylogues of the β-ketophosphonate substrates.[7] Our recent work on phosphonic systems, has shown that lithiated diethyl prop-2-enylphosphonate adds easily to aldehydes yielding, depending upon the reaction conditions, α-vinyl-β-hydroxyalkylphosphonates ('kinetic' products, **1**), or δ-(hydroxyvinyl)phosphonates ('thermodynamic' products, **2**).[8] We report now that the oxidation of adducts **1** and **2** leads directly to the corresponding ketophosphonate systems **3** and **4**.

The presence of the olefinic bond in the substrates limited the application of the conventional oxidizing reagents. It was found, however, that the Dess-Martin periodinane reagent, recommended for selective oxidation of primary and secondary alcohols,[9] gave excellent results with the ketones being formed almost quantitatively and in a state of high purity. Although the primary oxidation products **3** and **4** are stable enough for structure determination and for metallation reactions, they



i) BuLi, THF, -78° *ii*) RCHO, THF, -78°, aq. NH_4Cl, -78° *iii*) RCHO, THF, -78°, then r.t., aq. NH_4Cl, r.t.
iv) Dess-Martin reagent, CH_2Cl_2, r.t. *v*) Neat, r.t. several days or CH_2Cl_2, 1 mol % TsOH

undergo slow spontaneous change upon storage. The transformation could be accelerated and brought to completion upon addition of small quantities of acid and it involved acid-catalyzed prototropic isomerization leading to α,β-unsaturated ketones **5** and **6**, the latter product representing the vinylogue of a simple β-ketophosphonate. Similar, but base- catalyzed isomerization of alkenylphosphonates driven by the formation of a fully conjugated triene system was reported previously,[10] and confirms earlier observations of a weak effect of the PO_3Et_2 group on an adjacent olefinic bond.[11] The structures of the oxidation products **3-6** were determined by spectroscopic methods and by the elemental analyses.[12] All compounds showed the characteristic band for the carbonyl group in their IR spectra, as well as the absence of the OH group. The ^1H NMR spectra of products **3** revealed a very distinctive doublet of doublets pattern due to the ABX system of the single α-H atom. A similar, two-hydrogen signal of the α-CH_2 group (dd) was observed for products **6**. The isomerization **3** → **5** could be also easily demonstrated by the change of the ^1H NMR signals of the olefinic hydrogens which appeared in the spectra of **5** as a doublet of quartets (one H). As demonstrated before,[8] hydroxyphosphonates **2** are formed exclusively as stereoisomers (E). The configuration was retained in the oxidation reaction (formation of **4**), as well as in the prototropic isomerization to **6**, as demonstrated by a 'large' (*ca* 17 Hz) vicinal coupling constant of the *trans*-olefinic protons in **4** and **6**.

The configuration at the vinylic bond in **5** was determined from the value of the $^3J_{CP}$ coupling constant for the γ-CH_3 signal in the ^{13}C NMR spectra. A 'large' (*ca* 20 Hz) value indicated a *trans*-orientation of the C and P atoms;[13] hence the (E) configuration for all products **5**. Since the isomerization **3** → **5** and **4** → **6** was accompanied by the change from the allylic to the vinylic (or *vice-versa*) phosphonic skeleton, it could be also monitored by the ^{31}P NMR spectroscopy. The average ^{31}P chemical shift values for the allylic phosphonates (**3** and **6**) were $\delta_P = 22.4 \pm 2.6$ ppm, while for the vinylic phosphonates (**4** and **5**) the average value was $\delta_P = 15.5 \pm 1.2$ ppm. Finally, the structures of all products, deduced from their ^{31}P and ^1H NMR spectra, was confirmed unambigously by recording the proton-coupled, as well as proton-decoupled, ^{13}C NMR spectra of all compounds. Both types of ^{13}C NMR spectra were in excellent agreement with the assigned structures. Further transformations of ketophosphonates **3-6** are being currently investigated in our laboratory.

EXPERIMENTAL SECTION

NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 300 spectrometer and the ^{31}P chemical shifts are given relative to 85% H_3PO_4. IR spectra were recorded from CCl_4 solutions on a Bomem Michelson 100 spectrophotometer. Periodinane reagent was prepared from 2-iodobenzoic acid as described in the literature.[9]

Oxidation of diethyl hydroxyalkylphosphonates 1 and 2. General Procedure.- A solution of the phosphonate (typically 1.0 mmol) in CH_2Cl_2 (15 mL) was added at room temperature to a solution of periodinane (0.561 g, 1.3 mmol) in CH_2Cl_2 (10 mL) with stirring. After one hour, aqueous $Na_2S_2O_3$ (5%) and $NaHCO_3$ (5%) was added. The mixture was stirred and the CH_2Cl_2 layer was separated, washed thoroughly with water and dried ($MgSO_4$). The solvent was evaporated under reducted

Table 1. Ketophosphonates **3-6**

Cmpd	R	Yield (%) mp. (%C)	^{31}P	NMR ($CDCl_3$) $^{1}H^{a}$	MS[b] (m/z,%)	IR (CO) (cm^{-1})	Analyses (Found) C	H
3a	C_6H_5	98 oil	19.3	4.80 (1H, dd, 24.0, 9.1)	282 (4, M^+), 177 (100, $M^+ - C_6H_5$)	1685	59.57 (59.30)	6.78 (6.82)
3b	*p*-$NO_2C_6H_4$	97 89-90	20.1	4.85 (1H, dd, 23.8, 9.5)	327 (8, M^+), 177 (100, $M^+ - O_2NC_6H_4CO$)	1698	51.38 (51.25)	5.54 (5.60)
3c	$C_6H_5CH_2$	99 oil	20.5	4.71 (1H, dd, 24.5, 9.3)	296 (12, M^+), 177 (100, $M^+ - C_6H_5CH_2CO$)	1715	60.80 (60.77)	7.14 (7.25)
3d	C_6H_5CH=CH	92 oil	21.2	4.75 (1H, dd, 24.1, 10.0)	308 (2, M^+), 177 (100, $M^+ - C_6H_5CHCHCO$)	1680	62.33 (61.99)	6.87 (7.02)
3e	C_2H_5	99 oil	21.6	4.69 (1H, dd, 23.8, 9.5)	234 (15, M^+), 177 (100, $M^+ - C_2H_5CO$)	1720	51.28 (51.40)	8.18 (8.25)
3f	C_5H_{11}	98 oil	22.2	4.68 (1H, dd, 23.5, 9.6)	276 (21, M^+), 177 (100, $M^+ - C_5H_{11}CO$)	1718	56.51 (56.15)	9.12 (9.30)
3g	cycl-C_6H_{11}	89 oil	24.8	4.70 (1H, dd, 24.0, 9.8)	288 (7, M^+), 177 (100, $M^+ - C_6H_{11}CO$)	1724	58.32 (57.98)	8.74 (8.60)
4a	C_6H_5	86 oil	17.3	5.79 (1H, dd, 19.7, 17.3)	282 (6, M^+), 105 (100, $C_6H_5CO^+$)	1672	59.57 (59.20)	6.78 (6.90)
4b	*p*-$NO_2C_6H_4$	78 74-76	16.8	5.81 (1H, dd, 19.9, 17.0)	327 (2, M^+), 150 (100, $O_2NC_6H_4CO^+$)	1686	51.38 (51.20)	5.54 (5.60)
5a	C_6H_5	82 oil	13.5	no α-CH; 6.93 (1H, dq, 24.1, 7.2, β-CH)	281 (87, $M^+ - 1$), 77, (100, $C_6H_5^+$)	1664	59.57 (59.42)	6.78 (6.51)
5b	*p*-$NO_2C_6H_4$	80 93-94	14.4	no α-CH; 6.98 (1H, dq, 23.5, 7.0, β-CH)	327 (78, M^+), 122 (100, $O_2NC_6H_4^+$)	1673	51.38 (51.15)	5.54 (5.80)
5c	$C_6H_5CH_2$	84 oil	15.2	no α-CH; 6.88 (1H, dq, 22.9, 7.1, β-CH)	296 (72, M^+), 91 (100, $C_7H_7^+$)	1662	60.80 (61.02)	7.14 (7.30)
5d	C_6H_5CH=CH	82 oil	14.8	no α-CH; 6.91 (1H, dq, 24.0, 6.9, β-CH)	308 (42, M^+), 131 (100, $C_6H_5CHCHCO^+$)	1669	62.23 (62.05)	6.87 (6.90)
5e	C_2H_5	88 oil	15.8	no α-CH; 6.99 (1H, dq, 22.8, 6.6, β-CH)	234 (22, M^+), 177 (100, $M^+ - C_2H_5CO$)	1662	51.28 (51.15)	8.18 (8.09)
5f	C_5H_{11}	74 oil	15.6	no α-CH; 6.89 (1H, dq, 21.9, 6.6, β-CH)	276 (62, M^+), 177 (100, $M^+ - C_5H_{11}CO$)	1675	56.51 (56.83)	9.12 (9.51)
5g	cycl-C_6H_{11}	89 oil	15.9	no α-CH; 6.87 (1H, dq, 22.0, 7.1, β-CH)	288 (66, M^+), 177 (100, $M^+ - C_6H_{11}CO$)	1678	58.32 (57.95)	8.74 (8.45)
6a	C_6H_5	84 oil	25.3	2.88 (2H, dd, 23.6, 7.4)	282 (18, M^+), 177 (100, $M^+ - C_6H_5CO$)	1680	59.57 (59.18)	6.78 (6.90)
6b	*p*-$NO_2C_6H_4$	88 70-72	26.8	2.96 (2H, dd, 24.1, 7.2)	327 (10, M^+), 177 (100, $M^+ - O_2NC_6H_4CO$)	1683	51.38 (51.18)	5.54 (5.68)

a) For the sake of brevity, only the signal of the hydrogen(s) at the α-carbon ith respect to the P atom is given. The signal was critical for the confirmation of the structures of the products. For **5** (no α-CH), the signal for the β-CH proton is given. b) Recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV. Only the M^+ and the base peak are given.

pressure. The products, as demonstrated by the ^{31}P NMR spectroscopy (single signals) and by the TLC, were pure enough to be characterized without further purification.

Isomerization of the primary products 3 and 4 to the conjugated products 5 and 6. General Procedure.- Ketone **3** or **4** was dissolved in CH_2Cl_2, *p*-toluenesulfonic acid (*ca* 0.01 mol equiv) was added and the solution was kept at room temperature until ^{31}P NMR spectroscopy demonstrated full conversion to **5** or **6** (2-3 days). The solution was washed with dilute aqueous Na_2CO_3 (5%) and water and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The products were pure enough to be characterized without further purification. Selected data on the prepared ketophosphonates **3-6** are given in Table 1.

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A CONVENIENT REDUCTION OF UNSATURATED BICYCLIC ANHYDRIDES

Submitted by Ferenc Csende*[a] and Géza Stájer[b]

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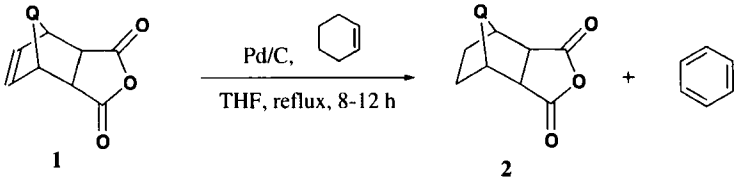
Bicyclic anhydrides **2a-2d** and those related amides, which can be obtained from saturation of Diels-Alder adducts, are valuable intermediates for the synthesis of pharmacologically important componunds.[1-3] Catalytic hydrogenation is a widely used method for the saturation of alkenes. The procedure is carried out under hydrogen atmosphere as the reducing agent in the presence of some catalyst *e.g.* Pd/C, PtO_2, Raney-Ni[4-6] , or with rare-earth alloy containing adsorbed hydrogen.[7] We reinvestigated these method due to flammable property of the hydrogen and catalyst (*e. g.* Raney-Ni) and searched for simpler and safer conditions for the reduction. This paper reports a simple and convenient modification of a method described earlier by Raphael *et al.* [8]

This method employs cyclohexene as hydrogen transfer agent, instead of higlhly flammable hydrogen gas, in the presence of Pd/C catalyst at room temperature in dry THF solvent. We had to modify the reduction temperature from 20-25° to reflux temperature. In this way, **2a-2d** were obtained in good to excellent yield (89-98%). In the course of reduction cyclohexene was converted to benzene nearly quantitatively and only small amount of cyclohexene takes part in a disproportion process as side reaction resulting in cyclohexane.[9]



1 2

a) Q = CH_2, *endo* b) Q = CH_2, *exo* c) Q = O, *endo* d) Q = CH_2-CH_2, *endo*

EXPERIMENTAL SECTION

Melting points were determined using an Electrothermal block and are uncorrected. Infrared spectra were recorded for KBr discs with a Perkin-Elmer 177 instrument. ^{1}H- and ^{13}C-NMR spectra were