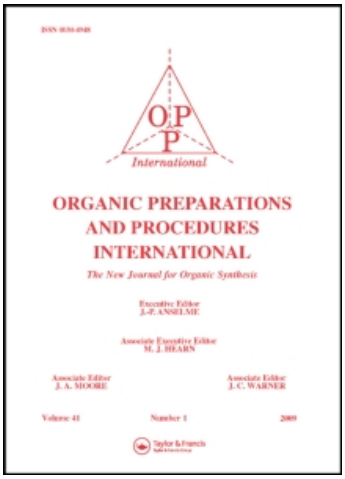


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

Elmar L. Müller[a]; Agnes M. Modro[a]; Tomasz A. Modro[a]
[a] Centre for Heteroatom Chemistry, Department of Chemistry, University of Pretoria, Republic of SOUTH AFRICA

To cite this Article Müller, Elmar L. , Modro, Agnes M. and Modro, Tomasz A.(1999) 'PREPARATION OF β-KETOPHOSPHONATES AND THEIR VINYLOGUES BY OXIDATION OF THE CORRESPONDING ALCOHOLS', Organic Preparations and Procedures International, 31: 2, 216 — 220
To link to this Article: DOI: 10.1080/00304949909355716
URL: http://dx.doi.org/10.1080/00304949909355716

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

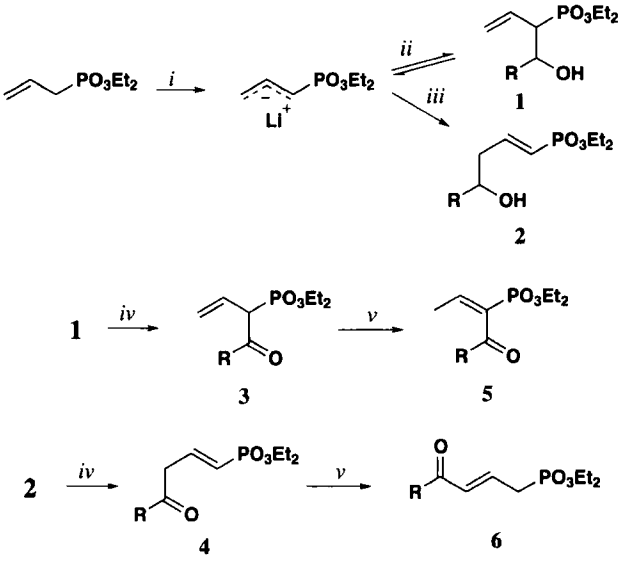
Submitted by (08/19/98)

Elmar L. Müller, Agnes M. Modro and Tomasz A. Modro*

Centre for Heteroatom Chemistry, Department of Chemistry
University of Pretoria, Pretoria 0002, Republic of SOUTH AFRICA

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.

Acknowledgment.- We gratefully acknowledge financial support of this work by the University of Pretoria and the Foundation for Research Development.

REFERENCES

1. a) B. J. Walker, in *Organophosphorus Reagents in Organic Synthesis*; J. I. G. Cadogan, Ed., CH 3, Academic Press, London, 1979; b) W. S. Wadsworth, *Org. React.*, **25**, 73 (1977); c) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989).

2. A. K. Bhattacharya and G. Thyagarajan, *ibid.*, **81**, 415 (1981).

3. E. J. Corey and G. T. Kwiatkowski *J. Am. Chem. Soc.*, **88**, 5654 (1966).

4. T. E. Jacks, H. Nibbe and D. F. Wiemer, *J. Org. Chem.*, **58**, 4584 (1993) and preceeding papers of this series.

5. a) Y. J. Koch and D. Y. Oh, *Tetrahedron Lett.*, **34**, 2147 (1993); b) S. Hong, K. Chang, B. Ku and D. Y. Oh, *ibid.*, **30**, 3307 (1989).

6. R. K. Boeckman, M. A. Walters and H. Koyano *Tetrahedron Lett.*, **30**, 4787 (1989).

7. M. Mikolajczyk and M. Mikina, *J. Org. Chem.*, **59**, 6760 (1994).

8. a) E. L. Müller and T. A. Modro, *Heteroatom Chem.*, **5**, 287 (1994); b) E. L. Müller and T. A. Modro, *Bull. Soc. Chim. Fr.*, **130**, 668 (1993).

9. D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983).

10. J. J. Kiddle and J. H. Babler *ibid.*, **58**, 3572 (1993).

11. J. P. Gerber, T. A. Modro, C. P. Wagener and A. Zwierzak, *Heteroatom Chem.*, **2**, 643 (1991).

12. Phosphonic esters give notoriously low analyses for carbon. Our samples were dried very carefully and submitted for analysis to two different laboratories. For some samples the results were still almost 0.4% too low for C.

13. S. Berger, S. Braun and H.-O. Kalinowski, *NMR-Spektroskopie von Nichtmetallen*, CH 3.3.3.3, Georg Thieme, Stuttgart, 1993.

****

A CONVENIENT REDUCTION OF UNSATURATED BICYCLIC ANHYDRIDES

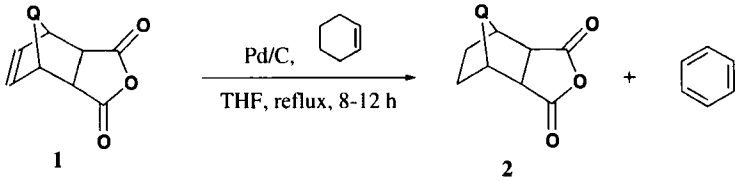
Submitted by Ferenc Csende*[a] and Géza Stájer[b]

[a] *Taxus Pharmaceuticals, H-4440 Tiszavasvári, Vasvári P.u.61, HUNGARY*

[b] *Institute of Pharmaceutical Chemistry, Szent-Györgyi Medical University POB 121, H-6701, Szeged, HUNGARY*

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