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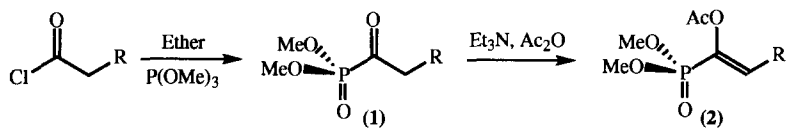
Facile Enolisation of α-Ketophosphonates

Kamyar Afarinkia,* Juan Echenique and Stanley C. Nyburg

Department of Chemistry, King's College, The Strand, London WC2R 2LS, UK.

Abstract: A number of α-ketophosphonate are prepared and shown to be easily enolised. An X-ray crystal structure determination of a β-phenyl-α-ketophosphonate shows the molecule to be present as hydrogen bonded dimers and demonstrates the presence of enol tautomer in solid state. α-ketophosphonate can be converted to the corresponding enolacetate under mild conditions. The enolacetate have the E-configuration exclusively.

α-Ketophosphonates such as **(1)** are fascinating and versatile compounds. The chemical properties of α-ketophosphonates are mainly determined by the phosphorus substituents, but in general are a hybrid between those of secondary amides and ketones.[1] For instance, it is possible to derive hydrazones, imines, and oximes from the carbonyl function;[2] reduce α-ketophosphonates to the corresponding α-hydroxyphosphonates[3] or use them in Wittig reactions.[4] At the same time, they are hydrolysed under extreme pH conditions.[5] Surprisingly, few investigations have been conducted on the chemistry of these compounds and in particular, little is known about their enolisation properties.[6] We recently initiated a programme of research into the chemical properties of α-ketophosphonates and now report on some interesting aspects of their enolisation.



	α-Ketophosphonates		*α-Acetoxyvinylphosphonates*		
R	Yield(%)	δ_P (ppm)	Yield(%)	δ_P (ppm)	J_{PH} (Hz)
H	49	-0.4	7	11.2	11.2**
Me	75	0.0	48	12.7	10.7
Et	23	0.3	55	13.0	10.75
^{i}Pr	80	-0.4	48	13.2	11.6
C_8H_{17}	68	0.0	35	13.0	10.8
4-$MeOC_6H_4$	90 (58)*	17.4	57	14.2	11.8
Ph	75*	16.5	74	13.4	11.8
	100	16.0	67	13.6	10.4

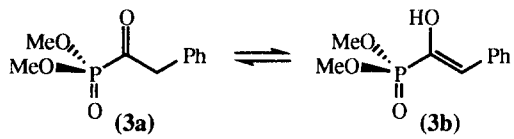
* After single crystalisation from toluene

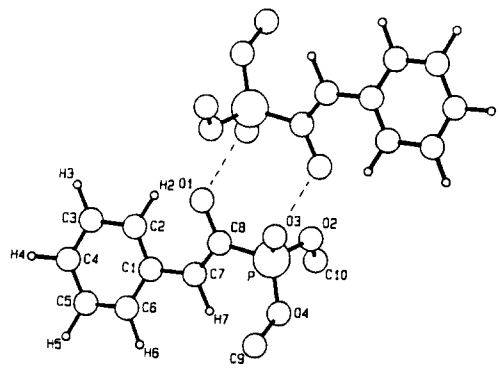
** $J_{PHtrans}$ = 35 Hz

Table 1

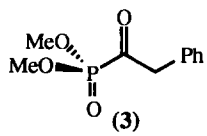
α-Ketophosphonates (**1**) are easily prepared by an Arbuzov type reaction between a phosphite and an acid chloride under relatively mild conditions (Scheme 1).[1] For instance, trimethyl phosphite reacts with acid chlorides at room temperature to afford, after distillation, dimethyl ketophosphonates in modest to excellent yields as mobile liquids.[7] In contrast, reaction of trimethyl phosphite and phenylacetylchloride gives a solid product, the spectroscopic data of which are consistent with the fully enolised tautomer (**3b**) at room temperature (some keto tautomer could be detected at elevated temperatures). For instance, the ^{13}C NMR of DMSO-d_6 solution clearly shows an olefinic CH (confirmed by DEPT) and no methylene carbons. Similarly, ^{31}P NMR *at room temperature* shows one signal at 16.5 ppm and no signals at around 0 ppm, the chemical shift expected for the keto tautomer. A number of other β-aryl-α-ketophosphonates, varying both in the aryl group and in the phosphorus substituents, are also fully enolised in solution and presumably in the solid state. In all these cases, the enol has exclusively the E-configuration as evident from small P-H coupling values of 10-12 Hz.

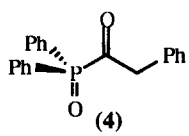
The ease of enolisation of β-aryl-α-ketophosphonates, although surprising is not wholly unprecedented. For example, it has been shown that the composition of the enol tautomer of structurally related phenylpyruvic acid in aqueous DMSO diminishes from 95% in pure DMSO-d_6 to only 5% in pure D_2O.[8] However, even in 40% v/v D_2O in DMSO-d_6 (solubility limit of the compound) no keto tautomer could be observed for compound (**3**) at room temperature. In contrast, phenylpyruvate is half enolised under the same conditions. This ready enolisation can be accounted for in two ways. Firstly, enolisation results in the formation of an extended conjugated π system which results in a thermodynamic gain upon enolisation. Secondly, the enols can be made relatively stable due to strong intramolecular or intermolecular hydrogen bonding. An X-ray crystal structure determination of (**3**) shows the molecule to be present as a hydrogen bonded dimer, the enol OH of one molecule being bridged to the oxygen in the P=O function of another.[9]

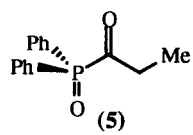


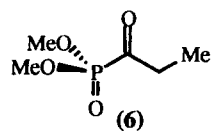


The unexpected ease of enolisation in these systems prompted us to investigate the factors that influence this process. We prepared a number of related α-ketophosphonates and α-ketophosphine oxides and studied their enolisation properties. We found that enolisation is not restricted to β-aryl-α-ketophosphonates although it is most pronounced in that case. For instance, diphenyl(1-oxopropyl)phosphine oxide (**5**) is *partly* enolised in $CDCl_3$ and DMSO-d_6 solutions at room temperature (about 50% at 300 K) whereas for dimethyl 1-oxopropanephosphonate (**6**), the enol form is negligible in $CDCl_3$ (<10% enol at 294 K).









Even though dimethyl 2-phenyl-1-oxoethanephosphonate **(3)** is fully enolised at room temperature, the rate of exchange between tautomers at elevated temperature is slow enough to allow the observation of the keto tautomer by ^{1}H NMR and ^{31}P NMR in DMSO-d_6 (δ_{CH_2} = 4.15 ppm, δ_P = 0.62 ppm). At 373 K, 23% of **(3)** exists as the keto tautomer whereas at 310 K, the composition of the keto tautomer is less than 5%. The same is true for the other two ketophosphonates although the temperature range over which the keto tautomer predominates is different. The variation in the keto-enol equilibrium constants with temperature allows the calculation of the enthalpy change (ΔH°) between the two tautomers for each of the three compounds. Thus the keto-enol compositions of solutions of the compounds in DMSO-d_6 or $CDCl_3$ were determined by ^{31}P NMR at various temperatures and hence equilibrium constants (K) were calculated. A plot of lnK versus 1/RT (where R is the gas constant) gave straight line the slope of which equals ΔH°, enthalpy change on enolisation. The free energy change for enolisation at 298 K in DMSO-d_6 and $CDCl_3$ solutions were also calculated (Table 2). As can be seen, all these α-ketophosphonates are enolisable, although the extent of auto-enolisation depends on the substituents. Notwithstanding experimental errors, it is clear that **(3)**, **(4)** and **(5)** are very prone to auto-enolisation but much less so than **(6)**.

	ΔH° (DMSO-d_6)	ΔG° (DMSO-d_6)	ΔH° ($CDCl_3$)	ΔG° ($CDCl_3$)
(3)	26	8.3	Not determined	Not determined
(4)	24	4.3	89	0.1
(5)	85	2.6	136	1.2
(6)	Not determined	Not determined	-3.2	-5.4

Table 2

Furthermore, in D_2O/DMSO-d_6 solution, the olefinic proton of **(3)** (δ_H = 6.10 ppm) exchanges slowly with deuterium in a temperature dependent manner. The rate of this exchange was measured by ^{1}H-nmr and the data were used to calculate an activation energy of 92 KJ mol^{-1} for the conversion between the two tautomers.

Although not all the dimethyl α-ketophosphonates are auto-enolised, they may nevertheless be easily enolised fully under mild basic conditions (Et_3N, CH_2Cl_2, room temperature) and the enolate can be trapped.[10] All α-ketophosphonates can be converted to the corresponding enolacetate upon treatment with acetic anhydride or to the silylenolether upon treatment with the corresponding silyltriflates. In all cases, the enol derivative is exclusively formed in the (E)-geometry as this places the two bulkiest groups (the alkyl group R and the phosphonyl group) in *trans* positions (Scheme 1).

Under these mild conditions, enolisation is accompanied by slight decomposition of the dimethyl α-ketophosphonate. As might be expected, the major mode of decomposition arises from the action of dimethyl α-ketophosphonate as an acylating agent for the enolised tautomer, the by product being dimethyl phosphite.[11] This decomposition depends very much on the nature of the phosphorus substituent and for example is negligible with diphenyl α-ketophosphine oxide **(5)**. Under more forcing conditions, using organometallic bases, the decomposition is more pronounced and although such metal enolates can be O-derivatised, these are only minor products of the reaction. This could be circumvented by maintaining the metal enolates at low temperature (-100 °C) where the decomposition is again negligible.

In summary, we have demonstrated that the enolisation of α-ketophosphonates is very sensitive to the substituents on the phosphorus and the alkyl side chain but in general, can be achieved under standard conditions. We have also shown that phosphonoenolates derived from α-ketophosphonates can react with electrophiles through oxygen. We are now in the process of exploring the C-alkylation of phosphonoenolates and factors that influence stereoselectivity in that reaction and will report on our results in due course.

ACKNOWLEDGEMENT

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7. All new compounds were fully characterized (ir, nmr, ms) and high resolution mass spectrometry was used to confirm the composition of their molecular ions. NMR data were obtained on a Bruker AM360 MHz NMR. Mass spectra were obtained on a Jeol AX505W mass spectrometer using electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques.
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9. Crystal data: Orthorhombic, *Pbca*, a = 12.53(3) Å, b = 9.495(10) Å, c = 19.09(4) Å. Z = 8 molecules per cell. D_c = 1.33 Mgm^{-3}. Bond C7-C8 is 1.34(3) Å long and hence is a double bond, confirming O1 to be an enol, not keto, oxygen. Pairs of molecules related by centers of symmetry are O1-H....O3 hydrogen bonded with the O...O distance of 2.61(2) Å. Full crystallographic details are deposited in the Cambridge Organic Crystal database.
10. Typical experimental procedure for the preparation of enolacetates: Acetic anhydride (0.93 mL, 9.86 mmol) was added to a stirred solution of dimethyl 1-ketopropanephosphonate (1.368g, 8.24 mmol) and triethylamine (1.29 ml, 9.27 mmol) in dichloromethane (20 mL) mainteined under an atmosphere of dry nitrogen and at 0 °C. After 8 hours, the reaction mixture was washed with icecold water and then dried over $MgSO_4$. Chromatography afforded the desired compound as an oil (0.823 g, 48%); R_f = 0.18 (ether); δ_H (360 MHz, $CDCl_3$) 1.70 (3H, td, J_H = 7.1 Hz, J_P = 3.0 Hz, C<u>H</u>$_3$-C=), 2.24 (3H, s, C<u>H</u>$_3$CO), 3.75 (6H, d, J_P = 11.2 Hz, C<u>H</u>$_3$O), 6.55 (1H, dq, J_H = 7.0 Hz, J_P = 10.7 Hz, C<u>H</u>=); δ_C (90.6 MHz, $CDCl_3$) 12.0 (dq, J_P = 13.1 Hz, <u>C</u>H$_3$-C=), 20.3 (q, <u>C</u>H$_3$CO), 53.1 (dq, J_P = 5.0 Hz, <u>C</u>H$_3$O), 131.0 (dd, J_P = 26.9 Hz, <u>C</u>H=CP), 137.7 (d, J_P = 31.4 Hz, CH=<u>C</u>P), 167.7 (s, <u>C</u>=O); δ_P (146 MHz, $CDCl_3$) 12.7 ppm; HRMS Calcd for $C_7H_{14}PO_5$ (MH^+) 209.0579, found 209.0557.
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