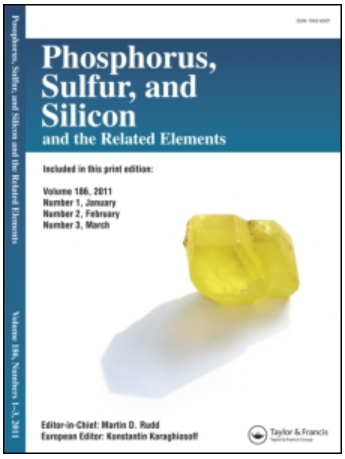

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THE REACTION OF ACETYLACETONE WITH DIALKYLPHOSPHITES: Synthesis of Dialkyl 1-methyl-3-oxo-1-butenyl-phosphonates

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Acetylacetone and its related compounds were transformed into the dialkyl 1-methyl-1-trimethylsiloxyl-3-oxo-butylphosphonates, which after treatment with trifluoroacetic acid were converted into the dialkyl 1-methyl-3-oxo-1-butenylphosphonates.

INTRODUCTION

The dialkyl 3-oxo-1-alkenyl-phosphonates were useful starting materials for synthesis of heterocyclic compounds.[1] But they are not accessible by the general Arbusov reaction. Hirao reported a palladium-catalyzed method for the synthesis of the vinylphosphonates, however, it only provided the non-functional ones.[2] The reaction of acetylacetone with dialkylphosphites under strong basic condition yielded the lactones.[3,4] In this paper, the reaction of acetylacetone and its related compounds with dialkylphosphites at neutral or acidic conditions was investigated.

RESULTS AND DISCUSSION

When equal moles of acetylacetone and of dialkylphosphites were mixed and heated at 70°C for several days, only a 4–9% yield of dialkyl 1-methyl-3-oxo-1-butenyl-phosphonates **4a–c** was isolated. Adding 0.1 eq. trifluoroacetic acid to the mixture shortened the reaction time to 48 hr but the yields were not improved much (Table I, Scheme 1), most of the starting materials had not reacted.

Since this approach gave only low yields, it was thought desirable to use the enol form[5] of acetylacetone, **3a–f**. This was achieved in two ways (Scheme 1). In Method A, the acetylacetone was treated with chlorotrimethylsilane and triethylamine to give the silyl enol ether,[6] **2a**, which was caused to react with one eq. of each dialkylphosphite to produce the dialkyl-1-methyl-1-trimethylsiloxy-3-oxo-butylphosphonates **3a–c** in 63–66% yield, respectively. In Method B, the dialkyl trimethylsilylphosphites were heated with acetylacetone, and **3b** and **3c** were isolated in 56, 51%. However, when the silyl enol ether **2a** was mixed with dialkylphosphite at 20°C there was no addition product formed as indicated by

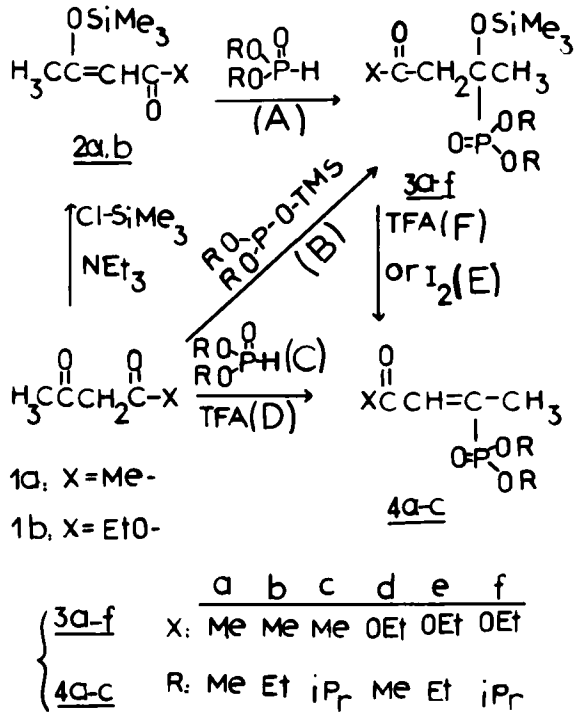
TABLE I

Spectral data of compounds **3a–f** and **4a–c**

Compound bp °C/mmHg	Elemental analyses[a] C%	H%	^{31}P NMR (ppm)	IR (cm^{-1})	Yield[b] %
3a 100/0.24	42.16 (42.55	8.08 8.16)	25.25	1708 1720 sh	64A
3b 130/3.0	46.71 (46.45	9.22 8.78)	23.13	1708 1720 sh	66^{A} 56^{B}
3c 112/1.0	49.08 (49.68	9.27 9.23)	21.41	1708 1720 sh	63^{A} 51^{B}
3d 115–117/0.46	42.49 (42.31	7.86 7.69)	26.95	1737	46^{A}
3e 114–116/0.46	45.52 (45.88	8.69 8.53)	24.85	1736	64^{A}
3f 110–112/0.44	48.67 (48.91	8.84 8.96)	21.50	1739	69^{A}
4a 110/4.0	44.12 (43.75	6.79 6.77)	21.01	1700 1720 sh 1612	4.0^{C} 6.3^{D} 64^{F}
4b 111/3.0	49.02 (49.09	7.90 7.73)	18.22	1694 1720 sh 1610	9.1^{C}; 6.8^{D} 48^{E}; 55^{F}
4c —	52.85 (53.25	8.52 8.47)	15.54	1698 1612	4.6^{C}; 10^{D} 72^{E}; 74^{F}

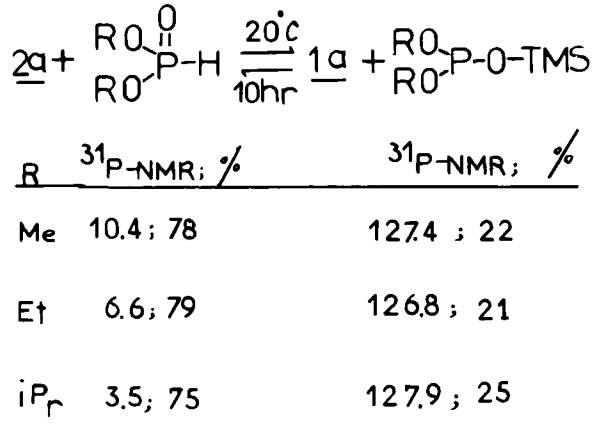
[a] The calculated values are given in parenthesis.
[b] The yields for the corresponding methods are given.

^{31}P-NMR spectra. But the ^{31}P-NMR showed in addition to the signal of the dialkylphosphite a new peak at about 127 ppm, which was assigned to the corresponding dialkyl trimethylsilylphosphite by comparison with an authentic sample. When acetylacetone was mixed with the trimethylsilylphosphite at 20°C, there was no addition product formed either. The ^{31}P-NMR spectra indicated the appearance of dialkylphosphite. These phenomena show that the equilibrium can be reached from both ends as shown in Scheme 2. For three different systems, the equilibrium to the left with dialkylphosphite is favored with a factor of 3–4/1 at 20°C. This means that in the presence of a trimethylsilyl group acceptor such as acetylacetone, the trimethylsilylphosphite will be desilylated under relative mild condition. This is a common phenomenon for compounds containing phosphorus and silicon.[7] When the temperature was raised to 75–100°C the addition of the phosphorus compounds to the carbonyl group took place.[8] Method A not only gave better yields than Method B, but also the silyl enol ether of acetylacetone was more convenient to handle than the trimethylsilylphosphites, which had a bad smell. The silyl enol ether of ethyl acetoacetate, **2b**, was also caused to react with



SCHEME 1 The transformation of acetylacetone and related compounds into dialkyl 1-methyl-3-oxo-1-butenylphosphonates.

the dialkyl phosphites to give the corresponding compounds **3d–f** in 46, 64, 69% yields by Method A. All compounds, **3a–f**, contain a chiral center. Hence the two methylene hydrogens are magnetically nonequivalent in the ^{1}H-NMR spectra with chemical shifts at 2.3–2.4 ppm and 2.6–2.8 ppm respectively. And each of the methylene hydrogens appeared as a doublet of doublet caused by coupling with the phosphorus atom and the other methylene hydrogen atom. It is



SCHEME 2 The equilibrated mixtures from both ends of the reaction: **2a** with dialkylphosphite or of acetylacetone, **1a**, with dialkyl trimethylsilyl phosphite.

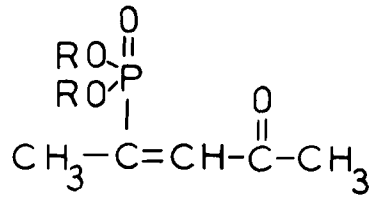
interesting that this chiral center even affected the two alkoxy groups on the phosphorus atom. For example the two methoxy groups in compound **3a** showed two overlapped doublets with the center at 3.67 ppm. Similarly, in each of the compounds **3b–f** the two alkoxy groups were magnetically nonequivalent as shown by the ^{1}H-NMR spectra.

The next step is to remove the trimethylsilanol from the compounds **3a–f**. It can not be achieved by simply warming up. In Method E, about 15% molar eq. of iodine was introduced to induce the formation of the double bond at 75°C in methanol and carbon tetrachloride as mixed solvents. In Method F, trifluoroacetic acid was used as the reagent and solvent for this conversion at 50°C. Both Method E and F were effective for the synthesis of **4a–c** with isolated yields of about 50–70%. But the same treatment of **3e–f** gave complicated mixtures as shown by the ^{1}H-NMR spectra and the expected products were not obtainable. The mechanism of Method E and F is not clear yet. However, since in both cases the medium contained acidic protons, it would seem that the silyl ether was hydrolyzed to the corresponding alcohol, which then was dehydrated to the conjugated ene compounds **4a–c**, (catalyzed by the acid or iodine).

In Table I are listed the ^{31}P-NMR data for the compounds **3a–c**. It is seen that the signal is shifted upfield when going from methyl to ethyl to isopropyl-ester. For the analogues **3d–f, 3f** had the absorption at the highest field. In compounds **4a–c**, the same trend is observed. This is due to the higher steric hindrance of the isopropyl group as compared to ethyl and methyl groups. Also, when the **4a–c** were compared with their corresponding precursors **3a–c**, the introduction of a double bond caused the ^{31}P-NMR signal to shift to the higher field. This is obviously due to the diamagnetic effect of the double bond. The IR showed the presence of a ketone group (near 1700 cm^{-1}) and a double bond (1610 cm^{-1}) in the compounds **4a–c**, (Table I). The ^{13}C-NMR data in Table II clearly show that

TABLE II

^{13}C NMR[a] shifts and the ^{13}C–^{31}P coupling constants[b] of **4a–c**



Compd.	C1	C2	C3	C4	C5	C of R	
4a	14.3	139.4	137.1	197.9	31.7	52.6	
	(7.4)	(170.6)	(8.8)	(25.0)	(3.0)	(5.9)	
4b	14.5	140.5	136.3	197.4	31.5	61.9	16.2
	(6.5)	(169.9)	(9.1)	(23.5)	(2.8)	(5.7)	(5.8)
4c	14.4	141.7	135.6	196.3	31.3	70.0	23.8
	(6.1)	(170.2)	(9.2)	(24.2)	(1.9)	(5.5)	(7.1)

[a] The C-13 NMR shifts were in ppm, TMS as internal references.
[b] Coupling constants in parenthesis given in hertz.

in the compounds **4a–c** there is a carbon carbon double bond in which one end is bonded to the phosphorus atom and is split by phosphorus with a coupling constant of about 170 Hz. Also, the carbonyl carbons are split by the phosphorus atom with a coupling constant of about 24 Hz. The ^{1}H-NMR indicates a methyl group near 2.1 ppm as a doublet with a coupling constant of J_{PCCH} 15.4 Hz, and a vinyl hydrogen at 6.8 ppm as a doublet with a coupling constant of about J_{PCCH} 25 Hz for all three compounds **4a–c**. These spectroscopic data prove the structures of the compounds **4a–c**. And the vinyl hydrogen is cis- to the phosphoryl group, since for a trans- vinyl one would see a coupling constant of about 50 Hz.[9]

In conclusion, the intermediates dialkyl 1-methyl-1-trimethylsiloxy-3-oxo-butyl-phosphonates are good precursors for the preparation of dialkyl 1-methyl-3-oxo-1-butenyl-phosphonates. The reactions of these compounds are under further investigation.

EXPERIMENTAL

Methods. ^{1}H-NMR spectra were taken on a Cameca-RMN 250 MHz spectrometer and chemical shifts are expressed in ppm relative to an internal $SiMe_4$ standard in CCl_4 unless otherwise indicated. ^{13}C-NMR spectra were taken on a FT-80 NMR spectrometer and chemical shifts are expressed in ppm relative to an internal $SiMe_4$ standard in $CDCl_3$ unless otherwise indicated. ^{31}P-NMR spectra were taken on a FT-80 NMR spectrometer and chemical shifts are expressed in ppm relative to an external H_3PO_4(85%) standard, positive value for down field shift. IR spectra were measured as film on a NaCl cell on a Shimadzu 430 spectrometer. Mass spectra were taken on an AEI-50 spectrometer. Boiling points are uncorrected. Elemental analyses were performed by the Analytical Laboratory, Institute of Chemistry, Academia Sinica, Beijing, China.

Synthesis of ethyl 3-trimethylsiloxy-2-ene-butylate, **2b**. To the solution of ethyl acetoacetate (26 g, 0.20 mole) and trimethylchlorosilane (25 g, 0.23 mole) in 200 ml dried benzene was added triethylamine (25.0 g, 0.25 mole). According to a known procedure[6] it gave compound **2b**, 32 g (0.16 mole, 80%), b.p. 57.5–58.5°C/0.40 mmHg. ^{1}H NMR: δ at 0.27 ppm (9H, s), 1.26 ppm (3H, m), 2.25 ppm (3H, s), 4.06 ppm (2H, m), 5.08 ppm (1H, s).

Synthesis of dimethyl 1-methyl-1-trimethylsiloxy-3-oxo-butylphosphonate, **3a**. The mixture of 4-trimethylsiloxy-3-pentenyl-2-one[6] (3.5 g, 0.020 mole), **2a**, and dimethylphosphite (2.2 g, 0.020 mole) was heated at 75°C with stirring for 10 hr and then 100°C for 24 hr. Distillation of the reaction mixture gave compound **3a**, 3.6 g (0.013 mole, 64%). ^{1}H NMR: δ at 0.11 ppm (9H, s), 1.47 ppm (3H, d, J = 16.2 Hz), 2.07 ppm (3H, s), 2.34 ppm (1H, dd), 2.81 ppm (1H, dd), 3.67 ppm (6H, m).

Synthesis of diethyl 1-methyl-1-trimethylsiloxy-3-oxo-butylphosphonate, **3b**. Method (A): The mixture of 4-trimethylsiloxy-3-pentyl-2-one (17.2 g, 0.10 mole), **2a**, and diethylphosphite (14.0 g, 0.10 mole) was heated at 100°C with stirring for 24 hr. Distillation gave compound **3b**, 20.5 g (0.066 mole, 66%). Method (B):[8] The mixture of acetylacetone (3.0 g, 0.030 mole) and diethyl trimethylsilylphosphite (6.0 g, 0.029 mole) was heated to 100°C with stirring. After 11 hr, it was distilled on an oil bath to give compound **3b**, 5.0 g (0.016 mole, 56%). ^{1}H NMR: δ at 0.15 ppm (9H, s), 1.30 ppm (6H, m), 1.51 ppm (3H, d, J = 15.9 Hz), 2.12 ppm (3H, s), 2.37 ppm (1H, dd), 2.84 ppm (1H, dd), 4.03 ppm (4H, m).

Synthesis of di-isopropyl 1-methyl-1-trimethylsiloxy-3-oxobutylphosphonate, **3c**. According to method (A), 4-trimethylsiloxy-3-pentenyl-2-one, **2a**, (17.2 g, 0.10 mole) and di-isopropylphosphite (17.0 g, 0.10 mole) gave compound **3c**, 21.2 g (0.063 mole, 63%). According to method (B), acetylacetone (2.5 g, 0.025 mole) and di-isopropyl trimethylsilylphosphite (6.0 g, 0.025 mole) are compound **3c**, 4.3 g (0.013 mole, 51%). ^{1}H NMR: δ at 0.15 ppm (9H, s), 1.30 ppm (12H, m), 1.52 ppm (3H, d, J = 16.2 Hz), 2.11 ppm (3H, s), 2.32 ppm (1H, dd), 2.84 ppm (1H, dd), 4.61 ppm (2H, m).

Synthesis of dimethyl 1-methyl-1-trimethylsiloxy-2-(ethyloxycarbonyl)-ethylphosphonate, **3d**. Compound **2b**, (10.0 g, 0.0495 mole) and dimethylphosphite (7.0 g, 0.063 mole) were mixed and heated to

100°C with stirring. After 14 hr, the mixture was distilled to give compound **3d**, 7.10 g (0.0228 mole, 46%). ^{1}H NMR: δ at 0.10 ppm (9H, s), 1.20 ppm (3H, m), 1.53 ppm (3H, d, J = 16.3 Hz), 2.33 ppm (1H, dd), 2.62 ppm (1H, dd), 3.65 ppm (6H, m), 3.98 ppm (2H, m).

Synthesis of diethyl 1-methyl-1-trimethylsiloxy-2-(ethyloxycarbonyl)-ethylphosphonate, **3e**. As above, 2b (10.0 g, 0.0495 mole) and diethylphosphite (7.0 g, 0.0507 mole) gave **3e**, 10.8 g (0.0318 mole, 64%). ^{1} NMR: δ at 0.14 ppm (9H, s), 1.33 ppm (9H, m), 1.60 ppm (3H, d, J = 16.4 Hz), 2.40 ppm (1H, dd), 2.68 ppm (1H, dd), 4.04 ppm (6H, m).

Synthesis of di-isopropyl 1-methyl-1-trimethylsiloxy-2-(ethyloxycarbonyl)-ethylphosphonate, **3f**. As above, **2b**, (10.0 g, 0.0495 mole) and di-isopropylphosphite (8.5 g, 0.0512 mole) gave **3f**, 12.5 g (0.034 mole, 69%). ^{1}H NMR: δ at 0.14 ppm (9H, s), 1.29 ppm (15H, m), 1.58 ppm (3H, d, J = 15.8 Hz), 2.35 ppm (1H, dd), 2.66 ppm (1H, dd), 4.03 ppm (2H, m), 4.60 ppm (2H, m).

Synthesis of dimethyl 1-methyl-3-oxo-1-butenylphosphonate, **4a**. Method (C): Acetylacetone (6.5 g, 0.065 mole) and dimethylphosphite (10.0 g, 0.01 mole) were mixed and heated to 70°C with stirring. After 24 hr, the mixture was distilled on an oil bath to give compound **4a**, 0.5 g (0.0026 mole, 4.0%). Method (D): Acetylacetone (10.0 g, 0.10 mole) and dimethylphosphite (11.0 g, 0.10 mole) were mixed, then 1 ml trifluoroacetic acid and 1 ml trifluoroacetic anhydride added and the mixture heated to 50°C with stirring. After 4 days, the mixture was distilled to give compounds **4a**, 1.2 g (0.0063 mole, 6.3%). ^{1}H NMR: δ at 2.08 ppm (3H, d, J = 15.4 Hz), 2.28 ppm (3H, s), 3.66 ppm (6H, m), 6.83 ppm (1H, d, J = 25.5 Hz). EIMS: m/z = 192 (M^+).

Syntheses of diethyl 1-methyl-3-oxo-1-butenylphosphonate, **4b**. Method (C): acetylacetone (10.0 g, 0.10 mole) and diethylphosphite (14.0 g, 0.10 mole) were mixed and heated to 75°C with stirring. After 7 days, it was distilled to give compound **4b**, 2.0 g (0.0091 mole, 9.1%). Method (D): acetylacetone (10.0 g, 0.10 mole) and diethylphosphite (14.0 g, 0.10 mole) gave compound **4b**, 1.5 g (0.0068 mole, 6.8%). Method (E): To a solution of compound **3b** (4.40 g, 0.0142 mole) in 2 ml methanol and 5 ml carbon tetrachloride, iodine (0.52 g, 0.002 mole) was added. Then it was heated to 75°C with stirring overnight. The low boiling substances were removed with a rotary evaporator. To the residue 200 ml ethyl acetate was added. Then the solution was washed with 1 N HCl, 5% $NaHCO_3$ and 40% NaCl, and dried with anhydrous magnesium sulfate. After evaporation, it gave compound **4b**, 1.52 g (0.0085 mole, 48%). The purity of the compound was confirmed by the ^{1}H-NMR spectrum. ^{1}H NMR: δ at 1.34 ppm (6H, m), 2.13 ppm (3H, d, J = 15.4 Hz), 2.28 ppm (3H, s), 4.05 ppm (4H, m), 6.85 ppm (^{1}H, d, J = 25.4 Hz). EIMS: m/z = 220 (M^+).

Syntheses of di-isopropyl 1-methyl-3-oxo-1-butenylphosphonate, **4c**. Method (D): acetylacetone (10.0 g, 0.10 mole) and diisopropylphosphite (17.0 g, 0.10 mole) were mixed with 1 ml trifluoroacetic acid to give compound **4c**, 2.5 g (0.010 mole, 10%). The purity of the compound was confirmed by the HPLC. Method (E): compound **3c** (4.02 g, 0.0119 mole) and iodine, (0.50 g, 0.002 mole), 2 ml methanol and 5 ml carbon tetrachloride gave compound **4c** 2.12 g (0.0085 mole, 72%). Method (F): The mixture of compound **3c** (3.45 g, 0.010 mole) and 2 ml trifluoroacetic acid was heated to 50°C with stirring overnight. The low boiling substances were removed with a rotary evaporator. The residue was treated with 200 ml ethyl acetate, washed with 5% $NaHCO_3$, 40% NaCl, dried with anhydrous magnesium sulfate, filtered, and evaporated to give compound **4c**, 1.92 g (0.0077 mole, 77.4%). The purity of the compound was confirmed by the HPLC. ^{1}H NMR: δ at 1.30 ppm (12H, m), 2.08 ppm (3H, d, J = 15.4 Hz), 2.25 ppm (3H, s), 4.56 ppm (2H, m), 6.83 ppm (1H, d, J = 25.3 Hz). EIMS: m/z = 248 (M^+).

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