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α-Alkyl(aryl)sulfenyl substituted β-ketophosphonates: synthesis, properties and reactivity

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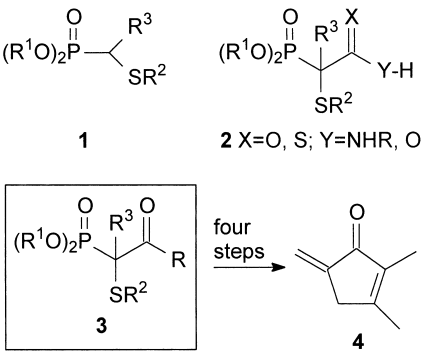
This paper is dedicated to Professor Reinhard Schmutzler on the occasion of his 70th birthday

Abstract—A new synthesis of the title compounds via acylation of α-lithio-α-phosphorylalkyl sulfides is described. Two additional approaches to these compounds, although less efficient, involve: (a) sulfenylation of O-silylated dialkyl β-ketophosphonates and (b) the Arbuzov reaction of triethyl phosphite with α-chloro-α-methylthiomethyl phenyl ketone. The keto–enol tautomerism of the title compounds and reactivity of the anions derived from them with electrophilic reagents were investigated. The P(O)-olefination products obtained from electron rich aromatic aldehydes were found to undergo the acid-catalyzed desulfenylation reaction affording α,β-unsaturated ketones.

1. Introduction

α-Phosphoryl sulfides **1** are an important class of heteroatom compounds useful in organic synthesis, medicine and technics.[1] Therefore, for the past two decades their synthesis, chemistry and applications have been intensively investigated in our laboratory.[2] Especially attractive was the Horner–Wittig reaction of **1** since vinyl sulfides produced in this reaction could be transformed into carbonyl compounds.[3] Thus, starting from the properly substituted α-phosphoryl sulfides **1**, we were able to elaborate the synthesis of aromatic ketones,[4] α-alkylsulfenyl ketones[5] and 1,4-diketones.[6] The latter were applied by us in the synthesis of cyclopentenone natural products like dihydrojasmone and methylenomycin B.[2] Moreover, nucleophilic (1,2 vs 1,4-addition)[7] and radical approaches[8] to the synthesis of highly functionalized phosphonates starting from **1** were also devised in our laboratory.

In addition to the above applications of **1**, their reactions with bifunctional reagents of the X=C=Y type (CO_2, RNCO, RNCS) allowed the synthesis of α-phosphoryl acetic acids **2** (X=Y=O),[9] acetamides **2** (X=O, Y=NHR)[10] and thioacetamides **2** (X=S, Y=NHR)[10] (Scheme 1) from which 1,2-dicarbonyl compounds, unsaturated γ- and δ-lactones as well as α-thioethene-thioamides were obtained. An alternative approach to **2** involved sulfenylation of α-phosphoryl acetic acid and α-phosphoryl propionic acid with Me_2S_2,[9] PhSCl[11] and ClSCN.[11]



1 **2** X=O, S; Y=NHR, O

3 **4**

Scheme 1.

A closely related class of α-sulfenylated β-ketophosphonates **3** was first synthesized by Lee and Oh[12] via sulfenylation of the α-phosphoryl enamine anions followed by hydrolysis of the resulting products. According to this method, the sulfenylation reaction was carried out using Ph_2S_2, PhSCl and $MeSO_2SMe$ as sulfenylation reagents. Dimethyl disulfide turned out to be unreactive towards the enamine anions. The above authors also reported that acylation of the α-phosphonate carbanions derived from **1** was an unsatisfactory approach to **3**. However, according to our experience acylation of the lithium salts of α-phosphoryl sulfides **1** with carboxylic acid esters can be successfully carried out to give **3** in moderate to high yields, thus becoming an alternative approach to these

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compounds. They were later applied by us as precursors of the corresponding α-phosphonate radicals in the synthesis of highly functionalized phosphonates[7] and in the first radical approach[13] to methylenomycin B **4**—a cyclopentanoid antibiotic. A recent paper by Olivato and his co-workers[14] on the synthesis of some aromatic β-ketophosphonates **3** prepared by the reaction of diethyl methylthio-1-lithiomethylphosphonate with substituted benzoyl chlorides prompted us to disclose herein full details of our synthetic approaches to **3** as well as investigation of the keto–enol tautomerism in this interesting class of compounds. We report also the behaviour of the ambident anion derived from **3** towards electrophilic reagents (alkyl halides, acyl halides and carbonyl compounds).

2. Results and discussion

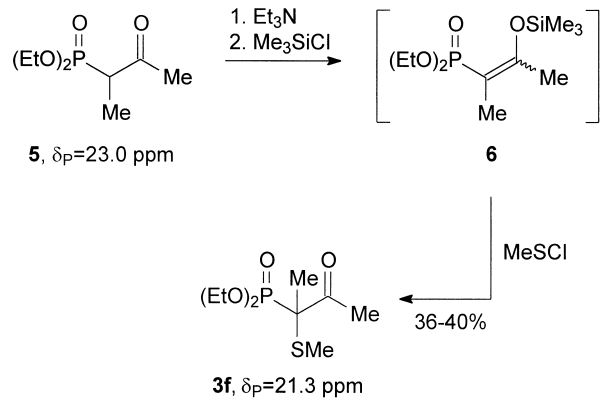
2.1. Synthesis

Searching for a convenient protocol for preparing the desired sulfenylated β-ketophosphonates **3**, three methods were selected and tested: (A)-acylation of **1**-Li with carboxylic acids esters, (B)-sulfenylation of O-silylated diethyl 2-oxoalkylphosphonates **6** and (C)-simultaneous introduction of the keto and sulfenyl groups via the Arbuzov reaction of triethyl phosphite with α-chloro-α-methylthiomethyl phenyl ketone **7**.

In the first place, method A was checked using differently substituted α-phosphoryl sulfides **1**. Generation of the lithium derivatives from **1** with *n*-butylithium in dry THF occurred smoothly at −78 °C under an argon atmosphere. The reversible acylation of the resulting lithium derivatives **1**-Li was carried out with ethyl acetate, ethyl propionate, and methyl benzoate. Due to a greater acidity of the product **3** as compared with the substrate **1**, the reaction required two fold excess of **1**-Li to convert **3** into **3**-Li (Scheme 2).

As a consequence, the purification step required separation of **3** from the starting material **1** by high vacuum distillation or silica gel chromatography. In this way, the acylation products **3a**-**e** were obtained in 44–78% yields, The regenerated sulfides **1** could be reused in further reactions. The stability of diethyl phosphonates **3b**-**e** was remarkable. For instance, **3b** was for the first time synthesized in our laboratory in 1978 and after 25 years its purity was still above 90%. The methyl ester analogues were much less stable.

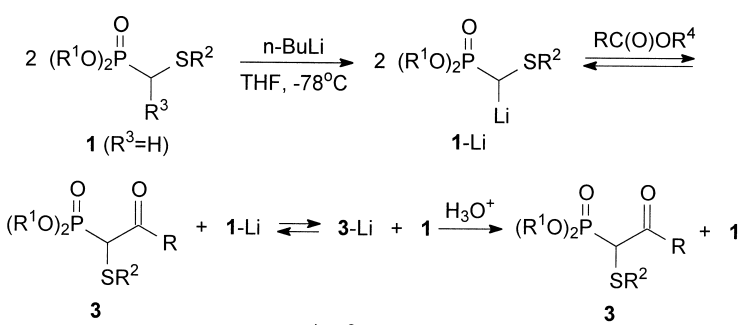
Next, the second possible synthesis of **3** in the reaction of O-silylated β-ketophosphonates with sulfenyl chlorides was examined. Thus, diethyl 1-methyl-2-oxopropylphosphonate **5** was treated with trimethylsilyl chloride in the presence of triethylamine and the O-silylated derivative **6** formed was reacted, without isolation, with methylsulfenyl chloride. The corresponding sulfenylated product **3f** was obtained in 36–40% yields. (Scheme 3).



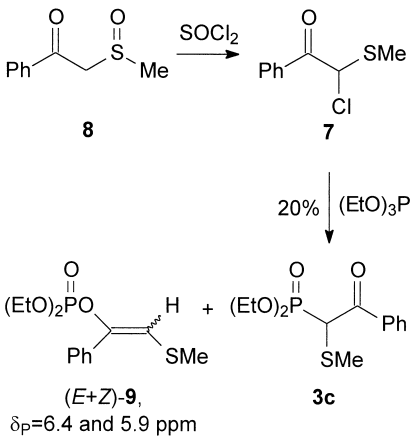
Scheme 3.

Due to lower yields of **3f** and some inconveniences connected with the synthesis and storage of methylsulfenyl chloride this synthetic approach to **3** was not further developed.

Finally, although we were aware that the reaction of trialkyl phosphites with α-halogenoketones affords mainly, if not exclusively, enol phosphates (Perkov reaction),[15] we attempted to find experimental conditions for the formation of a β-ketophosphonate (Arbuzov reaction) in the reaction between triethyl phosphite and a reactive 1-chloro-1-methylthiomethyl phenyl ketone **7**. The latter was quantitatively obtained in the Pummerer reaction of the β-ketosulfoxide **8** with thionyl chloride (Scheme 4).



Scheme 2.



Scheme 4.

Unfortunately, only in one case (see Table 1), when $(EtO)_3P$ was added to hot **7** at 140 °C without any solvent, the Arbuzov reaction product **3c** was obtained in 20% yield together with the Perkov reaction product **9** which was a mixture of the geometrical *E* and *Z* isomers in a ca. 2:1 ratio as revealed by the ^{31}P NMR spectra. A further structural assignment was based on the ^{1}H NMR spectra in which vinyl protons in the *E* and *Z* isomers of **9** appeared as two doublets at δ_H=6.05 ppm ($^3J_{H-P(cis)}$=2.2 Hz) and δ_H=6.24 ppm ($^3J_{H-P(trans)}$=3.2 Hz).

Table 1. Ratio of the Perkow (**9**) and Arbuzov (**3c**) reaction products under different experimental conditions

Entry	Procedure	**9** (*E*:*Z*)/**3c**[a]
1	$(EtO)_3P$ is added to **7** at 140 °C without solvent	75 (1.8:1)/25
2	**7** is added to $(EtO)_3P$ at 140 °C without solvent	100 (2.1:1)/0
3	**7** in benzene (1:1) is added to hot $(EtO)_3P$ in benzene (1:1)	100/0
4	**7** in hot benzene (1:1) is added to $(EtO)_3P$ in benzene (1:1) at 25 °C	100 (1.8:1)/0

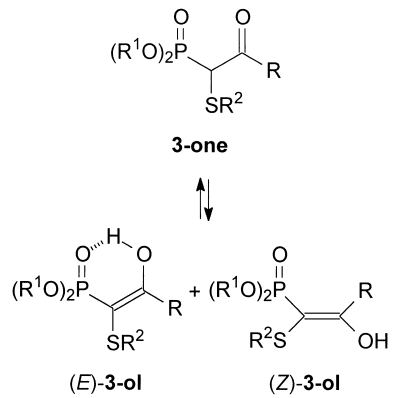
[a] Based on ^{31}P NMR spectra.

Summing up, the most convenient method for the synthesis of the β-ketophosphonates **3** involves the acylation reaction of the lithio derivatives of α-phosphoryl sulfides **1** with carboxylic acid esters, due to easy access to both substrates in large quantities and satisfactory yields of the desired products.

2.2. Keto–enol tautomerism

The ^{31}P NMR spectra of all the isolated products **3a-e** revealed two well separated signals which were ascribed to the keto-form, **3**-one, and the enol-form, **3**-ol, being in equilibrium as shown in Scheme 5. In a few cases additional signals of equal intensity due to the *E* and *Z* geometrical isomers of the enol-form of **3** were observed. The results of these measurements are collected in Table 2.

A further spectral analysis confirmed unequivocally the presence and structures of the tautomeric forms of **3**. Thus, the ^{1}H NMR spectra showed characteristic signals due to PCH and P–C=C–CH_3 protons as well as different signals due to MeS and OH groups. Similarly, in the ^{13}C NMR



Scheme 5.

Table 2. ^{31}P NMR chemical shifts and ratio of tautomeric forms of **3** in deuterated solvents

Phosphonate **3**	Solvent	Keto-form, **3**-one δ_P (%)	Enol-form, **3**-ol δ_P (%)
3b	DMSO-d_6	18.9 (92)	26.4 (8)
	$CDCl_3$	18.3 (92)	24.4 (8)
	Benzene-d_6	18.2 (66)	26.6 (33)
3c	DMSO-d_6	19.9 (83.5)	21.6 (16.5)
	$CDCl_3$	19.5 (83.5)	20.7 (16.5)
	Benzene-d_6	19.6 (77)	20.7 (23)
3e	DMSO-d_6	19.3 (96)	26.7 (4)
	Methanol-d_4	20.3 (95)	27.1, 26.5 (5)[a]
	$CDCl_3$	18.3 (92)	26.4, 25.1 (8)[a]
	Acetone-d_6	18.9 (89)	27.2 (11)
	Benzene-d_6	18.5 (81)	26.9 (19)

[a] Two signals correspond to *E* and *Z* forms of enol.

spectra typical signals for the P–CH and C=C carbons were observed. Accordingly, characteristic C=O and C=C frequencies in the IR spectra for both forms **3**-one and **3**-ol were visible. Moreover, in solvents of extreme polarity an increase in the intensity of absorption bands was observed for C=O in acetonitrile and for C=C in carbon tetrachloride.

The results mentioned above indicated that polar solvents favoured keto-forms having bigger dipole moments while nonpolar ones like CCl_4 favoured enol-forms, which were stabilized by intramolecular hydrogen bonds (Scheme 5). To further confirm this observation and to measure the **3**-one/**3**-ol ratios in various nondeuterated solvents, a series of ^{31}P NMR measurements was carried out (see Table 3).

An inspection of Table 3 revealed that in all the phosphonates **3** the keto-form prevailed (>70%). In protic solvents (MeOH) which are able to form hydrogen bonds with the carbonyl group the amount of the keto-form, **3**-one, increased even to 90%. The opposite bias was observed for the PhS containing **3d** for which the enol-form, **3**-ol, predominated, especially in low polar solvents (85% of **3**-ol in C_6H_6). The increase of the solvent polarity caused a decrease of the amount of the enol-form up to 64% in $CHCl_3$. Again in MeOH, due to stronger C=O···HOMe hydrogen bonds, the amount of the enol form of **3d** further decreased to 46.5% favouring the keto-form while the neat **3d** revealed high contents of the enol-form (83%) due to

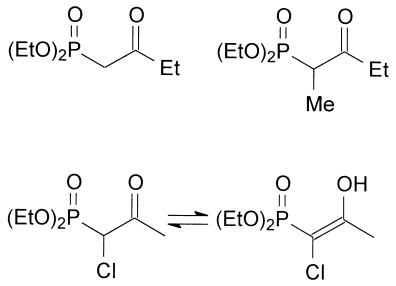
Table 3. Solvent effect on keto–enol equilibria

Phosphonate **3**	Solvent[a]									
	C_6H_6 δ_P [ppm] (%)		$CH_3C(O)CH_3$ δ_P [ppm] (%)		$CHCl_3$ δ_P [ppm] (%)		MeOH δ_P [ppm] (%)		Neat δ_P [ppm] (%)	
	Enol	Ketone	Enol	Ketone	Enol	Ketone	Enol	Ketone	Enol	Ketone
3a	28.0 (26.5)	19.4 (73.5)	27.55 (17.0)	19.25 (83.0)	28.20 (16.0)	20.0 (84.0)	27.23 (6.0)	20.86 (94.0)	28.0 (15.5)	20.2 (84.5)
3b	25.5 (29.5)	17.1 (70.5)	25.0 (19.7)	16.8 (80.3)	25.7 (13.5)	17.6 (86.5)	25.0 (9.4)	18.4 (90.6)	25.3 (22.0)	17.4 (78.0)
3c	20.9 (16.0)	18.3 (84.0)	19.8 (14.0)	17.9 (86.0)	20.7 (13.5)	18.7 (86.5)	22.9 (19.5)	21.1 (79.5)	21.5 (22.0)	19.8 (78.0)
3d	23.9 (85.0)	16.2 (15.0)	22.9 (72.0)	18.2 (28.0)	23.2 (64.0)	16.0 (36.0)	22.8 (46.5)	16.4 (53.5)	23.1 (83.0)	16.0 (17.0)

[a] The spectra were recorded at 25 °C and c=2 mol/L.

inter- and intramolecular hydrogen bonds of the P═O···H–O type.

The existence of **3** in tautomeric forms demonstrates a strong effect of the RS group on the acidity of the PCH hydrogen. In this context, it is interesting to point out that the ^{31}P NMR spectra of the β-ketophosphonates without sulfenyl substituents shown in Scheme 6 did not reveal even traces of enol forms. They are present, however, in α-chloro substituted β-ketophosphonates as reported by Savignac.[16]



Scheme 6.

2.3. Reactions with electrophilic reagents

Deprotonation of α-sulfenyl-β-ketophosphonate **3** leads to the formation of the corresponding enolate anion which should exhibit ambident reactivity. Moreover, the carbanionic center of the enolate anion derived from **3** should be well stabilized by the presence of three electron withdrawing groups: phosphoryl, carbonyl and sulfenyl. Therefore, its lower reactivity could be expected. For these reasons we decided to examine briefly the reactions of **3** with electrophilic reagents under basic conditions (Fig. 1).

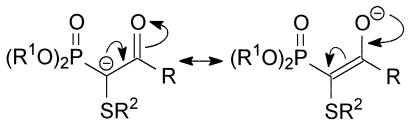
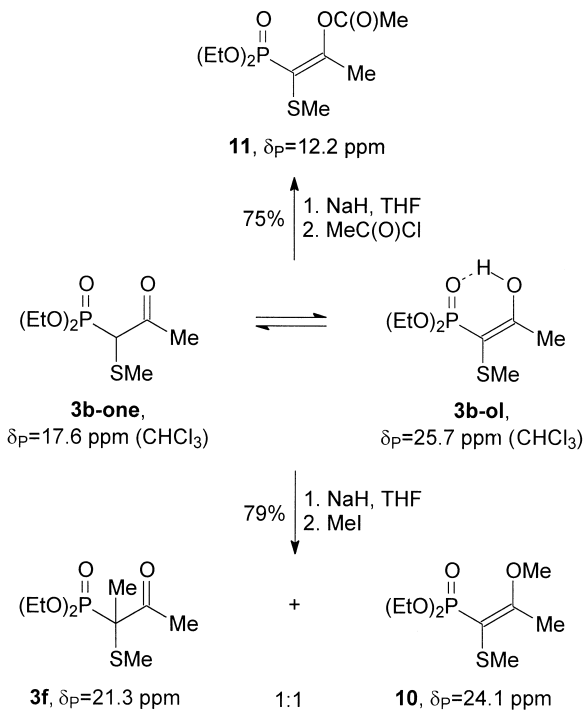


Figure 1.

As expected, the reaction of methyl iodide with the anion generated from **3b** with sodium hydride gave ca. 1:1.2 mixture of the C-methylated product **3f** and the O-methylated derivative **10** which were easily separated by column chromatography. Acetylation of the ambident anion of **3b** with acetyl chloride occurred exclusively at oxygen to give the corresponding *O*-acetyl vinylphosphonate **11** (Scheme 7).

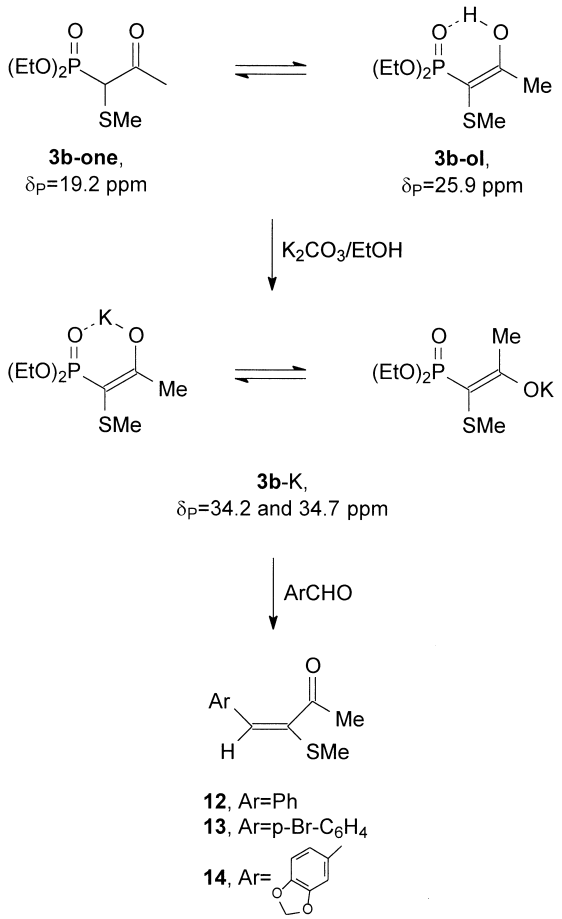


Scheme 7.

Just as other phosphonates,[17] the phosphonates **3** should react with carbonyl compounds in terms of the Horner–Wittig reaction to give the corresponding olefination products. Taking into account a relatively high acidity of the α-methine hydrogen, we used for the Horner–Wittig reaction with aromatic aldehydes weak bases for deprotonation as the first reaction step. However, in the presence of sodium bicarbonate in ethanol the reaction of **3b** with benzaldehyde did not occur within 18 h at room temperature. On the other hand, solid potassium carbonate in the same solvent was much more effective although the reaction was found to be sluggish.[†] Thus, when all three reaction components (K_2CO_3, PhCHO, **3b**) were used in equimolar

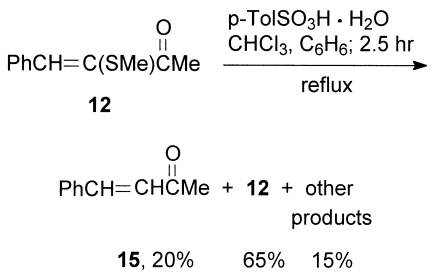
[†] Two signals observed in the ^{31}P NMR spectra of the potassium salt of **3b** were tentatively ascribed to *E* and *Z* geometrical forms of this salt.

amounts, the yield of the olefinic product **12** was only 16% after 7 h at room temperature (^{31}P NMR assay). It was increased to 50% after 72 h. When molar ratio of the reagents was 1.5:1:1, the product **12** was formed in 35% yield after 18 h at room temperature. Two hours at reflux in ethanol leads to **12** in 64% yield. Finally, it was found that the formation of **12** was almost complete after 72 h at 1.5:1.6:1 molar ratio of the reagents. It was found that the reaction afforded only one geometrical isomer of **12**. Its geometry was assigned as *Z* by using the additive increments method,[18] that is, comparison of the calculated chemical shifts of the β-proton for *E*-**12** (δ_H=7.21 ppm) and *Z*-**12** (δ_H=7.62 ppm) with the experimental value δ_H=7.61 ppm. The reaction of **3b** with *p*-bromobenzaldehyde in the presence of potassium carbonate used in equimolar ratio gave after 72 h at room temperature the corresponding enone **13** in 60% yield. However, in the Horner–Wittig reaction of **3b** with piperonal, carried out under the optimum reaction conditions determined for benzaldehyde (1.5:1.6:1 molar ratio of K_2CO_3, piperonal, **3b**, 72 h, rt), the corresponding enone **14** was formed in 17% yield only. A much lower reactivity of piperonal in this reaction as compared with benzaldehyde is undoubtedly connected with a lesser electrophilicity of the aldehyde carbon atom due to resonance effect involving the oxygen lone electron pairs of the dioxymethylene moiety (Scheme 8).



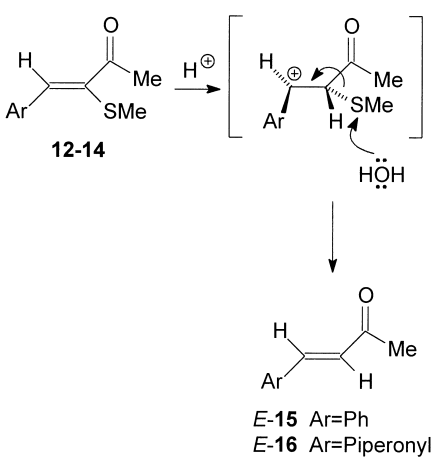
Scheme 8.

The resonance effect of the lone electron pairs of two oxygen atoms of the piperonyl moiety was also responsible for a greater sensitivity of the enone **14** than **12** towards acids. During routine work up involving quenching the reaction mixture with a saturated aqueous solution of ammonium chloride followed by extraction with chloroform (acidic conditions) and final purification by column chromatography on silica gel, the crude enone **14** was completely converted into the sulfur free α,β-unsaturated ketone **16**. Under these conditions the enone **13** was completely stable while only small amounts of benzylideneacetone **15** as the desulfenylation product from **12** were observed. The acid-catalyzed desulfenylation of the enone **12** was independently confirmed by the reaction of the isolated **12** with *p*-toluenesulfonic acid monohydrate carried out under reflux for 2.5 h in a mixture of chloroform and benzene (Scheme 9). It was found that benzylideneacetone **15** was formed in 20% yield in addition to 65% of the unreacted substrate **12** and 15% of unidentified higher boiling products.



Scheme 9.

The observed differences in acid sensitivity of the enones **12**, **13** and **14** may be easily rationalized by assuming the following mechanistic pathway for their desulfenylation process (Scheme 10). The first step is the addition of a proton to the carbon–carbon double bond according to anti-Markovnikov rule to form the intermediate benzyl carbocation. Then, nucleophilic attack of water on sulfur causes desulfenylation and the formation of a sulfur-free enone. Since the piperonyl moiety better stabilizes the benzyl carbocationic intermediate than the unsubstituted phenyl group the desulfenylation reaction occurs in this case much faster.



Scheme 10.

Although it was found that aliphatic aldehydes (formaldehyde, acetaldehyde) react with **3b** in the presence of K_2CO_3 much faster than aromatic ones (75–100% of the conversion of **3b** after 18 h at 25 °C as indicated by ^{31}P NMR), the instability of the olefination products formed precluded their isolation as pure compounds. Thus, our results provide additional evidence that α-sulfenylated enones are not stable and their synthesis and transformations demand care.[19] New conditions for the Horner–Wittig reaction of **3** with carbonyl compounds are under current studies.

3. Experimental

3.1. General

The ^1H NMR (60, 200 and 300 MHz), ^{13}C NMR (15.1, 50.3 and 75.4 MHz) and ^{31}P NMR (24.3, 81 and 121.5 MHz) spectra were recorded using R12B Perkin–Elmer, Jeol JNM-FX 60, Bruker AC-200, Bruker MSL-300 spectrometers. Chemical shifts in ^1H NMR spectra are reported relative to TMS. ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external standard. Mass spectra were obtained using a LKB 2091 and a Finnigan Mat 95 spectrometers. Column chromatography was carried out using a Merck silica gel (60, 70–230 and 230–400 mesh) using a gradient of indicated solvents which were distilled before use. Deuterated solvents for NMR-measurements were of commercial grade. All other commercial solvents were purified according to standard procedures and finally distilled before use. Melting and boiling points were uncorrected. HMDSO denotes hexamethyldisiloxane.

3.2. General procedure for synthesis of dialkyl 1-alkyk(aryl)sulfenyl 2-oxoalkylphosphonates (3)

To a stirred solution of dialkyl 1-alkyl(aryl)sulfenylmethylphosphonate **1** (0.07 mol) in dry tetrahydrofuran (70 mL), a solution *n*-butyllithium (0.07 mol+10% excess) in diethyl ether was added dropwise at −78 °C under argon atmosphere. After 45 min. a solution of the corresponding carboxylic ester (ethyl acetate, ethyl propionate or methyl benzoate; 0.035 mol) in tetrahydrofuran (35 mL) was added at this temperature. The resulting solution was stirred for 1 h, then temperature was raised to 0–5 °C and the solution was acidified with 10% aqueous hydrochloric acid. The solvent was evaporated and the residue was extracted with chloroform (100 mL). The chloroform solution was washed with 10% aqueous sodium hydroxide (3×50 mL) to remove the starting material. The basic aqueous solution containing mainly the product **3** in the form of sodium enolate was washed with chloroform (40 mL) then acidified with 10% aqueous solution of HCl and again extracted with chloroform (3×50 mL). The combined chloroform solutions (150 mL) were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was further purified by distillation or by column chromatography over silica gel using benzene/acetone in a gradient as the eluent.

3.2.1. Dimethyl 1-methylthio-2-oxopropylphosphonate (3a). Yellow oil, bp 47–48 °C/0.05 mm Hg, n_D^{24}=1.4795; yield 72% (crude); [Found: C, 34.30; H, 6.22; P, 14.87. $C_6H_{13}O_4PS$ requires C, 33.96; H, 6.17; P, 14.59]; ν_{max} (CCl_4) 2980, 2950, 2910, 2840, 1710, 1580 cm^{-1}; δ_H (CCl_4) 2.08 (3H, s, =C–CH_3, enol), 2.15 (3H, s, (O)C–CH_3, ketone); 2.30 (3H, s, SCH_3, ketone+enol); 3.67 (7H, d, *J*=12.0 Hz, CH_3OP, P(O)CH); 3.75 and 3.78 (3H, 2×d, *J*=10.6 Hz, CH_3O–P); δ_C ($CDCl_3$) 13.5 (d, *J*=4.5 Hz, SCH_3, ketone), 17.5, 24.6 (two brs, =CCH_3, SCH_3, enol), 25.9 (s, C(O)*C*H_3), 50.1 (d, *J*=138.7 Hz, P–C, ketone), 51.8, 52.4 (d, *J*=9 Hz, $POCH_3$, ketone), 197.3 (s, C=O).

3.2.2. Diethyl 1-methylthio-2-oxopropylphosphonate (3b). Yellow oil, bp 54–56 °C/0.05 mm Hg, n_D^{24}=1.4697; yield 78% (crude); [Found C, 39.96; H, 7.13; P, 12.92; S, 13.53. $C_8H_{17}O_4PS$ requires C, 39.99; H, 7.13; P, 12.89; S, 13.34]; ν_{max} (CCl_4) 1580, 1710 cm^{-1}; δ_H (C_6D_6) 1.01 (6H, t, *J*=7.1 Hz, $POCH_2CH_3$), 1.04 (6H, t, *J*=7.1 Hz, $POCH_2$-CH_3, enol), 1.87 (3H, d, *J*=1.0 Hz, SCH_3, ketone), 1.90 (3H, d, *J*=1.0 Hz, SCH_3, enol), 2.19 (3H, s, (O)CCH_3, ketone), 2.20 (3H, d, *J*=1.4 Hz, =C–CH_3, enol), 3.50 (1H, d, *J*=19.4 Hz, PCH, ketone), 3.71–4.03 (4H, m, $POCH_2CH_3$, enol), 3.98 (4H, 2×dq, *J*=7.1, 10.4 Hz, $POCH_2CH_3$, ketone), 12.93 (1H, brs, OH, enol); δ_C ($CDCl_3$) 15.31 (d, *J*=6.3 Hz, SCH_3, ketone), 15.56 (distd.d, SCH_3+$POCH_2$-CH_3, enol), 15.57 (d, *J*=5.4 Hz, $POCH_2CH_3$, ketone), 19.09, 18.82 (2×s, CH_3–C=C, *E*/*Z*of enol form); 27.23 (s, $C(O)CH_3$, ketone), 57.27 (d, *J*=138.0 Hz, P–C, ketone), 61.95 (d, *J*=4.8 Hz, $POCH_2CH_3$, enol), 63.03 (d, *J*=5.3 Hz, $POCH_2CH_3$, ketone); no visible signal from the enol C=C (8% of the enolic form only based on ^{31}P NMR); 198.99 (s, C=O); *m*/*z* (EI) 240 (M^+ (31)); 198 (100); 183 (31); 170 (27), 169 (43), 155 (38), 142 (42), 141 (20), 127 (45), 124 (24), 123 (21), 86 (60), 81 (23), 65 (32), 61 (36), 45 (35), 43 (82), 25 (41), 27 (37%).

3.2.3. Diethyl 1-methylthio-2-oxo-2-phenylethylphosphonate (3c). White crystals, mp 57 °C, yield 67% (crude); [Found: C, 51.70; H, 6.43; P, 10.22; S, 10.78. $C_{13}H_{19}O_4PS$ requires C, 51.64; H, 6.33; P,10.24; S, 10.60]; ν_{max} (film) 3440, 3050, 2970, 2905, 1670, 1570, 1585 cm^{-1}; δ_H ($CDCl_3$) 1.30 (6H, dt, *J*=7.1 0.6 Hz, $POCH_2CH_3$, ketone+enol), 2.25 (3H, ds, *J*=1.0 Hz, SCH_3, ketone); 3.57, 3.69, (3H, 2×s, SCH_3, enol-*E*/*Z*=1:1), 4.15–4.34 (4H, m, $POCH_2CH_3$, ketone+enol), 4.54 (1H, d, *J*=18.2 Hz, P–CH, ketone); 6.55 (1H, vbrs, OH, enol), 7.42–8.03 (5H, m, C_6H_5, ketone+enol); δ_C ($CDCl_3$) (major ketone form), 14.42 (s, $POCH_2CH_3$), 15.90 (d, *J*=5.7 Hz, SCH_3), 44.75 (d, *J*=117.7 Hz, P–C), 63.23 (m, $POCH_2$-CH_3), 128.42, 128.22, 133.26 (3xs, CH in C_6H_5); 134.81 (d, *J*=5.2 Hz, C in C_6H_5), 190.96 (s, C=O); *m*/*z* (EI) 105 (100), 77 (26%).

3.2.4. Diethyl 1-phenylthio-2-oxopropylphosphonate (3d). Yellow oil, n_D^{24}=1.5310; yield 48–50%; [Found: C, 52.17; H, 6.60; P, 10.16; S, 11.17. $C_{13}H_{19}O_4PS$ requires C, 51.64; H, 6.33; P, 10.24; S, 10.60]; ν_{max} (CCl_4) 1589, 1710 cm^{-1}; δ_H (CCl_4) 1.12 (6H, t, *J*=7.2 Hz, $POCH_2CH_3$, enol), 1.30 (6H, t, *J*=7.2 Hz, $POCH_2CH_3$, ketone), 2.20, 2.21 (3H, d, *J*=1.3 Hz, P–C=C–CH_3, enol), 2.26 (3H, s, $C(O)CH_3$), 3.45–4.31 (5H, m, PCH+$POCH_2CH_3$, ketone+enol), 6.70–7.50 (5H, m, C_6H_5), 14.20 (1H, vbrs, OH, enol); δ_C (C_6D_6/HMDSO) (major enol form) 13.98 (d, *J*=5.9 Hz, $POCH_2CH_3$), 17.93 (d, *J*=5.4 Hz, P–C=C–CH_3), 60.74

(d, J=5.8 Hz, POCH_2CH_3), 123.45, 126.95 (m, C_6H_5), 132.34 (d, J=115.2 Hz, P–C=), 182.57 (s, P–C=C); m/z (EI) 148 (95), 147 (27), 123 (44), 121 (100), 109 (21), 91 (25), 77 (29), 65 (23), 45 (26), 43 (59), 29 (41), 27 (24%); HRMS (EI): M^+ found 302.0741. $C_{13}H_{19}O_4PS$ requires 302.0754.

3.2.5. Diethyl 1-methylthio-2-oxobutylphosphonate (3e). Yellow oil, bp 105 °C/0.1 mm Hg (Kugelrohr), n_D^{24}=1.4725; yield 44%, [Found: C, 42.45; H, 7.44. $C_9H_{19}O_4PS$ requires C, 42.51; H, 7.53]; δ_H ($CDCl_3$) 1.09 (3H, t, J=7.2 Hz, C(O)CH_2CH_3, ketone), 1.18 (3H, dt, J=7.5, 0.4 Hz, =CCH_2CH_3, enol), 1.33 (6H, 2×dt, J=7.1, 1.6 Hz, POCH$_2$-CH_3, ketone), 2.15 (3H, d, J=1.0 Hz, SCH_3, enol), 2.20 (3H, d, J=1.0 Hz, SCH_3, ketone), 2.63–2.87 (2H, m, C–CH_2CH_3. enol+ketone), 3.62 (1H, d, J=19.4 Hz, PCH, ketone), 4.09–4.28 (4H, m, $POCH_2CH_3$, ketone+enol), 12.03 (1H, m, OH, enol); δ_C ($CDCl_3$) 6.94 (s, (O)CCH_2CH_3, ketone), 10.60 (s, =CCH_2CH_3, enol), 14.72 (d, J=5.8 Hz, POCH$_2$$CH_3$, ketone) 16.14 (s, POCH$_2$$CH_3$, enol), 19.1 (s, SCH_3, enol), 25.18(d, J=10.9 Hz, =CCH_2, enol), 32.95 (s, (O)CCH_2, ketone), 50.77 (d, J=137.9 Hz, PCH, ketone), 61.42 (d, J=4.7 Hz, POCH_2CH_3, enol), 62.39 (d, J=4.1 Hz, POCH_2CH_3, ketone), 201.33 (s, C=O); no visible signal from C=C.

3.2.6. Acetylation of diethyl 1-methylthio-2-oxopropylphosphonate (3b). To a stirred solution of **3b** (0.01 mol, 2.40 g) in dry THF (15 mL), sodium hydride (0.022 mol, 50% dispersion in oil, oil removed by washing with n-pentane) was added at room temperature under argon atmosphere. After stirring for 1.5 h, a solution of acetyl chloride (0.01 mol, 0.785 g) in THF (15 mL) was added dropwise and stirring was continued for further 1 h. The THF was evaporated and the residue was partitioned between chloroform and water. The chloroform solution was dried over $MgSO_4$, evaporated and the residue (79% yield) was distilled to give pure **11** as a yellow oil; bp 62–63 °C/0.05 mm Hg; n_D^{25}=1.4775.

[Found: C, 42.45; H, 6.83; P, 11.37; S, 11.45. $C_{10}H_{19}O_5PS$ requires C, 42.54; H, 6.78; P, 10.97; S, 11.35]; ν_{max} (film) 1760 (C=O); 1600 (C=C) cm^{-1}; δ_H (CCl_4) 1.30 (6H, t, J=7 Hz, CH_3CH_2OP), 2.10 (3H, s, C=C–CH_3), 2.23 (3H, s, OC(O)CH_3); 2.25 (3H, s, SCH_3), 3.95 (4H, m, CH_3CH_2-OP); δ_P (CCl_4) 12.2; m/z (EI) 282 M^+ (0.5), 240 (72), 225 (29), 169 (39), 155 (40), 86 (100), 43 (75%).

3.3. Methylation of diethyl 1-methylthio-2-oxopropylphosphonate (3b)

To a stirred solution of **3b** (2.4 g, 0.01 mol) in dry tetrahydrofuran (15 mL), sodium hydride (0.022 mol, 50% dispersion in oil) was added in portions at room temperature under argon atmosphere. The resulting solution was stirred for 2 h and then a solution of methyl iodide (0.01 mol, 1.42 g+25% excess) in THF (10 mL) was added dropwise. After 1 h, the solvent was evaporated and the crude product was partitioned between chloroform (70 mL) and water (50 mL). The chloroform solution was washed with water (40 mL) and dried over anhydrous $MgSO_4$ then filtered and evaporated to give the crude material in 79% yield (**3f**:**10**=1:1) which was further purified using column chromatography over silica gel. For separation of the C-methylated derivative **3f**, benzene/carbon tetrachloride in a 1:1 ratio was used. For separation of the O-methylated derivative **10**, benzene/acetone in a 2:1 ratio or CCl_4/benzene in a 1:1 ratio were employed.

3.3.1. Diethyl 1-methyl-1-methylthio-2-oxopropylphosphonate (3f). Yellow oil, n_D^{20}=1.4728; [Found: C, 42.51; H, 7.58; P, 12.45; S, 12.33. $C_9H_{19}O_4PS$ requires C, 42.51; H, 7.53; P, 12.18; S, 12.61]; ν_{max} (film) 1700 (C=O), 1250 (P=O) cm^{-1}; δ_H (CCl_4) 1.30 (6H, t, J=6.7 Hz, POCH$_2$-CH_3), 1.46 (3H, d, J=14.7 Hz, PCCH_3), 2.02 (3H, s, C(O)CH_3); 2.3 (3H, s, SCH_3); 4.1 (4H, m, POCH_2CH_3); δ_C ($CDCl_3$) 10.71 (d, J=5.86 Hz, P–C–CH_3), 14.49 (d, J=5.85 Hz, POCH$_2$$CH_3$), 16.11 (d, J=3.9 Hz, P–C–S–CH_3), 24.11 (s, C(O)CH_3); 61.46 (d, J=3.9 Hz, POCH_2-CH_3), 199.3 (brs, C=O); δ_P (CCl_4) 21.3; m/z (EI) M^+ (3), 212 (100), 208 (19), 197 (87), 183 (15), 169 (37), 155 (55), 73 (28), 59 (49), 43 (47), 29 (26%).

3.3.2. Diethyl 2-methoxy-1-methylthio-2-propenylphosphonate (10). White crystals, mp 70–71 °C (benzene/acetone=1:2). [Found: C, 42.33, H, 7.58; P, 11.89; S, 12.73. $C_9H_{19}O_4PS$ requires C, 42.51, H, 7.53; P, 12.18; S, 12.61]; ν_{max} (film) 1565 (C=C) cm^{-1}; δ_H ($CDCl_3$) 1.3 (6H, t, J=7.2, POCH$_2$CH_3), 2.12 (3H, s, C=C–CH_3), 3.00 (6H, s, SCH_3,OCH_3), 3.98 (4H, m, POCH_2CH_3); δ_P (CCl_4) 24.1; m/z (EI) 254 M^+ (37), 239 (45), 193 (25), 183 (76), 165 (40), 155 (55), 141 (22), 103 (27), 101 (17), 87 (23), 81 (21), 73 (22), 65 (32), 61 (50), 59 (20), 47 (25), 45 (23), 43 (100), 29 (61), 28 (18), 27 (42%).

3.4. Diethyl 1-methyl-1-methylthio-2-oxopropylphosphonate (3f) from sulfenylation of diethyl 1-methyl-2-oxopropylphosphonate (5) with methylsulfenyl chloride

To a stirred solution of **5** (2.08 g, 0.01 mol) in dry diethyl ether (15 mL), triethyl amine (1.06 g, 0.01 mol+5% excess) was added dropwise at 0 °C followed by trimethylsilyl chloride (1.19 g, 0.01 mol+10% excess). After 1 h, freshly distilled (at −40 °C) methylsulfenyl chloride was added dropwise to the resulting O-silylated phosphonate **6** and the mixture was stirred for additional 0.5 h. Then it was allowed to warm to room temperature. After 1 h, the precipitated triethyl ammonium chloride was partitioned between water (40 mL) and chloroform (60 mL). The chloroform solution was washed with water (40 mL) and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified using column chromatography over silica gel with a gradient of benzene/acetone as eluent to give the title compound **3f**; 36–40% yield, yellow oil; n_D^{20}=1.4735; δ_P (CCl_4)=21.3 ppm.

3.4.1. 1-Chloro-1-methylthiomethyl phenyl ketone (7). To a stirred solution of the sulfoxide **15** (1.78 g, 9.78 mmol) in DCM, thionyl chloride (9.7 mmol, 1.16 g, 0.7 mL) was added at −10 °C and the resulting mixture was stirred for 15 min at this temperature. Then, the cooling bath was removed and the mixture was stirred at room temperature for additional 1 h to give, after evaporation of the solvent, the crude product as the yellow liquid (1.514 g, 77%) which was used for further transformations without purification

(purity 97%); δ_H (CCl_4) 2.12 (3H, s SCH_3); 6.33 (1H, s, CH–Cl); 7.15–8.10 (5H, m, C_6H_5).

3.5. General procedure for reaction of diethyl 1-methylthio-2-oxopropylphosphonate (3b) with aldehydes

To a stirred solution of **3b** (120 mg, 0.5 mmol) and K_2CO_3 in EtOH (4 mL) a solution of the relevant aldehyde in ethanol (2 mL) was added at room temperature under argon atmosphere. The resulting mixture was stirred for 72 h. Then, saturated aqueous ammonium chloride was added, the solvent evaporated and the residue extracted with chloroform (3×10 mL). The combined chloroform solutions were washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude product which was further purified by column chromatography over silica gel using petroleum ether/acetone in a gradient as the eluent.

3.5.1. 3-Methylthio 4-phenyl-but-3-en-2-one (12). Yellow oil, 69% yield (based on the converted **3b** as 100%); ν_{max} (film) 2956, 2929, 1724, 1506, 1450, 1315, 812, 756 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3H, s, SCH_3); 2.55 (3H, s, $-C(O)CH_3$); 7.35–7.43 (3H, m, H_{arom}-7, 7′, 9); 7.61 (1H, s, H–C=); 7.79 (2H, m, H_{arom}-8, 8′); δ_C ($CDCl_3$) 17.29 (C-5); 27.49 (C-1); 128.22 (C-7, 7′); 128.98 (C-9); 130.54 (C-8, 8′); 134.63 (C-3); 137.82 (C-6); 140.69 (C-4); 200.36 (C-2). *m/z* (CI) MH^+ 193. HRMS (CI): MH^+, found 193.0687. $C_{11}H_{13}SO$ requires 193.0682.

3.5.2. 4-(4-Bromophenyl)-3-methylthiobut-3-en-2-one (13). Yellow oil, 67% yield (based on the converted **3b** as 100%). ν_{max} (film) 2962, 1716, 1603, 1446, 1261, 762 cm^{-1}; δ_H ($CDCl_3$) 2.23 (3H, s, SCH_3); 2.54 (3H, s, $C(O)CH_3$); 7.50 (1H, s, H–C=); 7.54 (2H, d, J=8.68 Hz, H_{arom}); 7.67(2H, d, J=8.50 Hz, H_{arom}). δ_C ($CDCl_3$) 17.26 (C-5); 27.51 (C-1); 123.74 (C-9); 131.57 (C-7, 7′); 132.14 (C-8, 8′); 133.51 (C-3-); 138.51 (C-6); 138.99 (C-4); 197.84 (C-2); *m/z* (CI) MH^+ 271. HRMS (CI): MH^+, found: 270.9792. $C_{11}H_{12}OBrS$ requires 270.9791.

3.5.3. 4-(3,4-Methylenedioxyphenyl)but-3-en-2-one (14). Yellow oil, 59% yield (based on the converted **3b** as 100%); ν_{max} (film) 3018, 2962, 1732, 1689, 1603, 1504, 1259, 1217, 754 cm^{-1}; δ_H ($CDCl_3$) 2.35 (3H, s, $-C(O)CH_3$); 6.01 (2H, s, $O-CH_2-O$); 6.54 (1H, d, J=16.1 Hz; $=CH(C(O)CH_3)$); 6.81 (1H, d, J=7.56 Hz; H_{arom}-9); 7.02 (1H, d, J=7.67 Hz; H_{arom}-10); 7.04 (1H, s, H_{arom}-6); 7.42 (1H, d, J=16.1 Hz; $=CH$–Ph); δ_C ($CDCl_3$) 27.56 (C-1); 101.67 (C-11); 106.53 (C-6); 108.66 (C-9); 124.88 (C-10); 125.31 (C-3); 128.83 (C-5); 143.26 (C-4); 148.45 (C-8); 149.88 (C-7); 206.70 (C-2). *m/z* (CI) MH^+ 191. HRMS (CI) MH^+, found: 191.0708. $C_{11}H_{11}O_3$ requires 191.0708.

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