One Pot Synthesis of Variously Substituted γ-Ketophosphonates Using Pentacovalent Oxaphospholenes

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Phosphonate-containing compounds are well known in nature as effective antibacterial and antifungal agents because of the resistance of the P-C bond to hydrolysis.[1] Variously substituted phosphonates have been reported because they exert their biological action as mimics of either carboxylic acids or phosphate esters.[2]

Most of the synthetic methods used for the preparation of phosphonates and mimetics of phosphate esters and carboxylic acids employs Arbuzov reaction,[3] Michaelis-Becker reaction,[4] and Abramov reaction.[5] We had previously reported the carbon analogues of the Ramirez's pentacovalent 1,3,2λ^5-dioxaphospholenes as a new oxaphospholene for the synthesis of biologically active phosphonate-containing aldol compounds.[6] We had efficiently hydrolyzed oxaphospholenes prepared from methyl vinyl ketone (MVK) and trialkylphosphites and synthesized γ-ketophosphonates followed by reductive amination to give γ-aminophosphonates.[7]

In order to extend this methodology for the synthesis of variously substituted phosphonates, we are currently investigating methods for the synthesis of pentacovalent 1,2λ^5-oxaphospholenes. For the last 10 years the synthesis of pentacovalent 1,2λ^5-oxaphospholenes using variously substituted enones and trialkylphosphites proved to be the challenging step in the synthesis of various phosphonates. We now report our new results on the successful synthesis of the 1,2λ^5-oxaphospholenes derived from trialkyl phosphite and several enones.

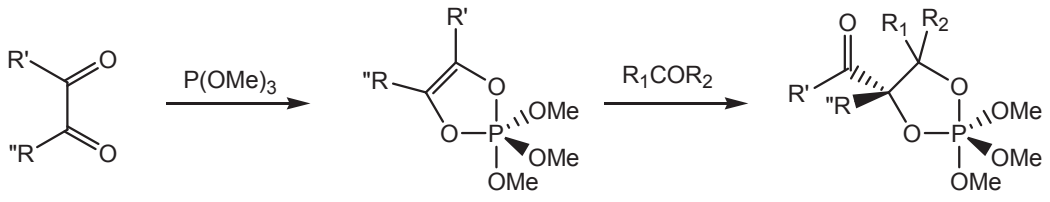
Experimental Section

General. All phosphites were treated with sodium prior to distillation. Synthesis of oxaphospholenes was carried out under a dry argon atmosphere in flame-dried oneor two-necked round-bottom flasks. NMR spectra were obtained on a JOEL Lamda 300 spectrometer and recorded at 300 MHz for ^{1}H (75 MHz for ^{13}C) with $CDCl_3$ as solvent. All ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). High resolution FAB mass spectra were obtained from the Hybrid LC-Quarapole-TOF Tandem Mass. R_f values indicated refer to thin-layer chromatography on Sorbent Technologies 4 × 8 cm, silica gel plates.

General procedure. A mixture of distilled enone (1 eq.) and triethylphosphite (1 eq.) was allowed to stir for 3-4 days at room temperature (except acrylamides: performed at 80 °C). Unreacted triethylphosphite was removed under vacuum at 55 °C (12 mmHg). To the crude oxaphospholene was added excess water (5 eq.) to quench and hydrolyze the reaction. This reaction mixture was allowed to stir for 10 hrs at room temperature. Crude product was extracted with CH_2Cl_2 and purified by column chromatography with 2% MeOH/CH_2Cl_2 to give clear oil as product.

Diethyl 3-oxopentylphosphonate (2). A mixture of distilled ethyl vinyl ketone (2.0 g, 23.81 mmol) and triethylphosphite (3.2 g, 23.81 mmol) was used for the synthesis of **2** (4.2 g, 19.05 mmol, 80%). R_f (5% MeOH/CH_2Cl_2) = 0.48; ^{1}H NMR δ 4.09 (m, 4H), 2.72 (m, 2H), 2.47 (q, J = 7.32 Hz, 2H), 2.02 (m, 2H), 1.32 (t, J = 6.96 Hz, 6H), 1.07 (t, J = 7.32 Hz, 3H); ^{13}C NMR δ 208.7 (d, $J_{C\text{-}P}$ = 14.17 Hz), 61.7 (d, $J_{C\text{-}P}$ = 6.17 Hz), 35.80, 34.99 (d, $J_{C\text{-}P}$ = 3.68 Hz), 19.39 (d, $J_{C\text{-}P}$ = 143.10 Hz), 16.43 (d, $J_{C\text{-}P}$ = 5.55 Hz), 7.82; ^{31}P NMR δ 31.61; IR (cm^{-1}) 3465.5, 2981.4, 2938.0, 2056.7, 1717.3, 1416.5, 1241.9, 1028.8; HRFABMS calcd for $C_9H_{19}O_4P$ $(M+Na)^+$ 245.0919, found 245.0919.

Methyl 3-(diethoxyphosphonyl)propionate (3). Distilled methyl acrylate (2.0 g, 28.5 mmol) and triethylphosphite (4.7 g, 28.50 mmol) were used to make product **3** (4.28 g, 19.09 mmol, 82%). R_f (5% MeOH/CH_2Cl_2) = 0.46; ^{1}H NMR δ 4.11 (m, 4H), 3.71 (s, 3H), 2.61 (m, 2H), 2.08 (m, 2H), 1.33 (t, J = 7.05 Hz, 6H); ^{13}C NMR δ 172.41, 61.73 (d, $J_{C\text{-}P}$ = 6.53 Hz),



1,3,2λ^5-dioxaphospholene

Scheme 1

51.97, 27.34 (d, $J_{C\text{-}P}$ = 3.68 Hz), 21.01 (d, $J_{C\text{-}P}$ = 143.70 Hz), 16.38 (d, $J_{C\text{-}P}$ = 5.85 Hz); ^{31}P NMR δ 29.89; IR (cm^{-1}) 3467.4, 2984.3, 2360.4, 2344.1, 1741.4, 1244.8, 1026.9; HRFABMS calcd for $C_8H_{17}O_5P$ $(M + Na)^+$ 247.0712, found 247.0702.

Dimethyl 3-amino-3-oxopropylphosphonate (4) and **dimethyl 3-(methylamino)-3-oxopropylphosphonate (4a).** A mixture of acrylamide (2.0 g, 28.14 mmol) and trimethyl phosphite (3.49 g, 28.14 mmol) resulted in two products, **4** (0.7 g, 3.86 mmol, 13.7%) and **4a** (3.65 g, 18.70 mmol, 66.5%). **4:** R_f (10% MeOH/CH_2Cl_2) = 0.56; ^{1}H NMR δ 6.97 (bs, 1H), 6.31 (bs, 1H), 3.67 (d, J = 10.80 Hz, 6H), 2.46 (m, 2H), 2.04 (m, 2H); ^{13}C NMR δ 173.36 (d, $J_{C\text{-}P}$ = 15.08 Hz), 52.53 (d, $J_{C\text{-}P}$ = 6.45 Hz), 28.15 (d, $J_{C\text{-}P}$ = 3.68 Hz), 19.75 (d, $J_{C\text{-}P}$ = 142.50 Hz); ^{31}P NMR δ 33.86; IR (cm^{-1}) 3408.6, 2957.3, 2055.8, 1673.9, 1419.4, 1234.2, 1029.8; HRFABMS calcd for $C_5H_{12}NO_4P$ $(M+Na)^+$ 204.0402, found 204.0392; **4a**: R_f (10% MeOH/CH_2Cl_2) = 0.72; ^{1}H NMR δ 6.66 (bs, 1H), 3.68 (d, J = 10.83 Hz, 6H), 2.74 (d, J = 4.05 Hz, 3H), 2.43 (m, 2H), 2.07 (m, 2H); ^{13}C NMR δ 171.52 (d, $J_{C\text{-}P}$ = 16.05 Hz), 52.37 (d, $J_{C\text{-}P}$ = 6.53 Hz), 28.37 (d, $J_{C\text{-}P}$ = 3.68 Hz), 26.18, 19.86 (d, $J_{C\text{-}P}$ = 142.20 Hz); ^{31}P NMR δ 33.95; IR (cm^{-1}) 3435.6, 2956.3, 2056.7, 1659.5, 1564.0, 1235.2, 1034.6; HRFABMS calcd for $C_6H_{14}NO_4P$ $(M+Na)^+$ 218.0559, found 218.0563.

Diethyl 3-amino-3-oxopropylphosphonate (5) and **diethyl 3-(ethylamino)-3-oxopropylphosphonate (5a).** A mixture of acrylamide (0.5 g, 7.03 mmol) and triethyl phosphite (1.21 g, 7.03 mmol) resulted in two products, **5** (0.24 g, 1.15 mmol, 16.3 %) and **5a** (1.16 g, 4.90 mmol, 69.7 %). **5:** R_f (10% MeOH/CH_2Cl_2) = 0.52; ^{1}H NMR δ 6.88 (bs, 1H), 6.13 (bs, 1H), 3.98 (m, 4H), 2.42 (m, 2H), 1.97 (m, 2H), 1.21 (t, J = 7.14 Hz, 6H); ^{13}C NMR 174.06 (d, $J_{C\text{-}P}$ = 16.05 Hz), 61.99 (d, $J_{C\text{-}P}$ = 6.75 Hz), 28.27 (d, $J_{C\text{-}P}$ = 3.75 Hz), 20.89 (d, $J_{C\text{-}P}$ = 142.50 Hz), 16.39 (d, $J_{C\text{-}P}$ = 6.15 Hz); ^{31}P NMR δ 31.26; IR (cm^{-1}) 3466.4, 3195.5, 2957.3, 2924.5, 2853.2, 2039.4, 1679.7, 1419.4, 1061.6, 1023.1; HRFABMS calcd for $C_7H_{16}NO_4P$ $(M+Na)^+$ 232.0715, found 232.0701; **5a**: R_f (10% MeOH/ CH_2Cl_2) = 0.69; ^{1}H NMR δ 5.98 (bs, 1H), 4.10 (m, 4H), 3.29 (m, 2H), 2.46 (m, 2H), 2.09 (m, 2H), 1.32 (t, J = 7.05 Hz, 6H), 1.14 (t, J = 7.23 Hz, 3H); ^{13}C NMR δ 170.77 (d, $J_{C\text{-}P}$ = 14.18 Hz), 61.78 (d, $J_{C\text{-}P}$ = 6.15 Hz), 34.53, 29.28 (d, $J_{C\text{-}P}$ = 3.68 Hz), 21.18 (d, $J_{C\text{-}P}$ = 141.90 Hz), 16.38 (d, $J_{C\text{-}P}$ = 6.15 Hz), 14.71; ^{31}P NMR δ 31.38; IR (cm^{-1}) 3289.9, 3054.7, 2982.4, 2916.8, 1655.6, 1558.2, 1233.3, 1056.8, 1028.8; HRFABMS calcd for $C_9H_{20}NO_4P$ $(M+Na)^+$ 260.1029, found 260.1030.

Dimethyl 3-(benzylamino)-3-oxopropylphosphonate (6). A mixture of *N*-benzylacrylamide (2 g, 12.41 mmol) and trimethyl phosphite (1.53 g, 12.41 mmol) gave **6** (2.73 g, 10.61 mmol, 85.5 %). R_f (5% MeOH/CH_2Cl_2) = 0.32; ^{1}H NMR δ 7.24 (m, 5H), 6.75 (bs, 1H), 4.37 (d, J = 5.49 Hz, 2H), 3.62 (d, J = 10.80 Hz, 6H), 2.48 (m, 2H), 2.04 (m, 2H); ^{13}C NMR δ 170.76 (d, $J_{C\text{-}P}$ = 14.78 Hz), 138.19, 128.57(2), 127.77(2), 127.38, 52.47 (d, $J_{C\text{-}P}$ = 6.83 Hz), 43.68, 28.75 (d, $J_{C\text{-}P}$ = 3.75 Hz), 19.90 (d, $J_{C\text{-}P}$ = 141.90 Hz); ^{31}P NMR δ 33.95; IR (cm^{-1}) 3468.4, 3286.1, 3068.2, 2360.4, 1652.7, 1455.0, 1076.1; HRFABMS calcd for $C_{12}H_{16}NO_4P$ $(M+Na)^+$ 294.0872, found 294.0872.

Diethyl 3-(benzylamino)-3-oxopropylphosphonate (6a). A mixture of *N*-benzylacrylamide (0.5 g, 3.1 mmol) and triethyl phosphite (0.54 g, 3.1 mmol) gave **6a** (0.76 g, 2.8 mmol, 91 %). R_f (10% MeOH/CH_2Cl_2) = 0.37; ^{1}H NMR δ 7.31 (m, 5H), 6.45 (bs, 1H), 4.35 (d, J = 5.7 Hz, 2H), 4.05 (m, 4H), 2.76 (m, 2H), 2.11 (m, 2H), 1.30 (t, J = 7.05 Hz, 6H); ^{13}C NMR δ 170.83 (d, $J_{C\text{-}P}$ = 14.78 Hz), 138.52, 128.65, 127.81, 127.48, 61.80 (d, $J_{C\text{-}P}$ = 6.83 Hz), 43.75, 29.20 (d, $J_{C\text{-}P}$ = 3.75 Hz), 21.13 (d, $J_{C\text{-}P}$ = 141.83 Hz), 16.38 (d, $J_{C\text{-}P}$ = 6.15 Hz); ^{31}P NMR δ 31.11; IR (cm^{-1}) 3464.5, 2982.4, 2927.4, 2359.5, 2056.7, 1652.7, 1557.2, 1455.0, 1232.3, 1053.9, 1027.9; HRFABMS calcd for $C_{14}H_{22}NO_4P$ $(M+Na)^+$ 322.1185, found 322.1191.

Dimethyl 2-cyanoethylphosphonate (7). A mixture of acrylonitrile (2 g, 37.69 mmol) and trimethyl phosphite (4.68 g, 37.69 mmol) gave **7** (5.18 g, 31.76 mmol, 84.3 %). R_f (5% MeOH/CH_2Cl_2) = 0.52; ^{1}H NMR δ. 3.80 (d, J = 7.98 Hz, 6H), 2.65 (m, 2H), 2.12 (m, 2H); ^{13}C NMR δ 118.05 (d, $J_{C\text{-}P}$ = 16.65 Hz), 52.63 (d, $J_{C\text{-}P}$ = 6.83 Hz), 20.85 (d, $J_{C\text{-}P}$ = 144.98 Hz), 11.23 (d, $J_{C\text{-}P}$ = 3.68 Hz); ^{31}P NMR δ 28.56; IR (cm^{-1}) 3456.8, 2961.2, 2856.1, 2249.6, 2056.7, 1644.0, 1457.0, 1312.3, 1241.9, 1035.6; HRFABMS calcd for $C_5H_{10}NO_3P$ $(M+Na)^+$ 186.0297, found 186.0301.

Results and Discussion

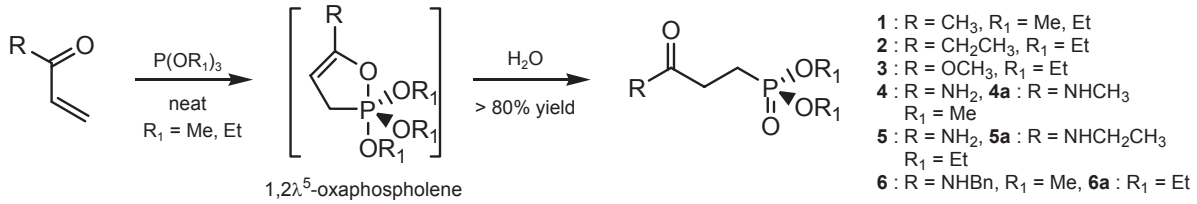
Several attempts have been made for the synthesis of 1,2λ^5-oxaphospholenes to give phosphonate-containing compounds, **1**-**5**. In earlier studies, we reported a new synthetic method for the formation of C-P bond using only MVK as an enone and trialkyl phosphites to synthesize 2,2,2-trialkoxy-2, 2-dihydro-1,2 λ^5-oxaphospholenes to further obtain various aldol compounds.[8] However, this methodology can only produce γ-ketophosphonate derivatives, which has a limitation for synthetic applications. We, therefore, used several different enones and trialkyl phosphites for the synthesis of new 1,2λ^5-oxaphospholenes resulting in novel phosphonate compounds which can be manipulated for various synthesis.

We chose methyl acrylate as well as methyl and ethyl vinyl ketone as an enone to make the corresponding 1,2λ^5-oxaphospholene. As we expected, the corresponding 1,2λ^5-oxaphospholenes from methyl or ethyl vinyl ketone and triethyl phosphite were obtained in good yields at room temperature. A new 1,2λ^5-oxaphospholene was obtained from the reaction of trimethyl or triethyl phosphite with methyl acrylate at room temperature, however, this 1,2λ^5-oxaphospholene was too unstable to purify so we hydrolyzed it with water to get β-methylesterphosphonate **3**, in 82% yield.

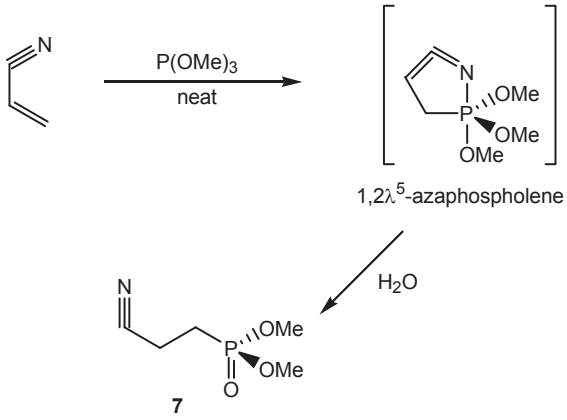
Trialkyl phosphites, trimethyl phosphite and triethyl phosphite, were treated with acrylamide to make the corresponding

Table 1. Ratio of products, **4** and **4a** or **5** and **5a**

Entry	Equiv. of $P(OR)_3$	Reaction temp. (°C)	Products (**4** : **4a** or **5** : **5a**)
1	1.0	20 (RT)	No reaction
2	1.0	20 → 80	1 : 5
3	1.5	20 → 80	1 : 5
4	2.0	20 → 80	1 : 6
5	1.0	80	9 : 1
6	1.5	80	8 : 2



Scheme 2



Scheme 3

1,2λ^5-oxaphospholene at 80 °C which after hydrolysis yielded a mixture of two products, amidophosphonates **4** and **5** and *N*-alkylated amidophosphonates **4a** and **5a**, respectively. These mixtures were separated by column chromatograpy and the ratio was determined to be **4** : **4a** or **5** : **5a** = 1 : 5 (entry 1-4, Table 1). We, therefore, tried to increase the ratio of products, **4** and **5**, by changing the reaction conditions such as amount of phosphite and reaction temperature. When we increased reaction temperature from room temperature to 80 ^{o}C, we obtained **4a** as the major product. However, when we carried out the reaction at 80 ^{o}C, unalkylated products, **4** and **5,** were obtained as the major products, respectively. Varying amount of trialkylphosphites did not affect the ratio of products in our system (see Table 1).

To prevent the production of alkylated amidophosphonate acryl amine was initially protected with benzyl group and the reaction was carried out to obtain only a single β-amidophosphonate, **6**, in 84% yield after hydrolysis.

In conclusion, we have been able to synthesize a new form of 1,2λ^5-oxaphospholenes and hydrolyze it to make variously functionalized phosphonates. Unlike the γ-ketophosphonate prepared from methyl vinyl ketone and triethyl phosphite, these phosphonates can be easily manipulated for the trans formation of functional group to make bioactive compounds.

In addition, we obtained β-cyanophosphonate **7** as the hydrolysis product from our studies shown in Scheme 3. It was not possible to get the corresponding 1,2λ^5-azaphospholenes from trimethylphosphite and acrylonitrile. Currently, we are considering 1,4-addition to obtain this product instead of using our described method.[9] We are also investigating various methods to make more pentacovalent oxaphospholenes for the synthesis of bioactive phosphonate-containing compounds.

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