Intramolecular cyclisation of 2-vinyl- and 2-allylbenzoylphosphonates with trimethyl phosphite via carbene intermediates

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This paper is dedicated to Professor Gurnos Jones to mark the occasion of his 70th birthday

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Abstract

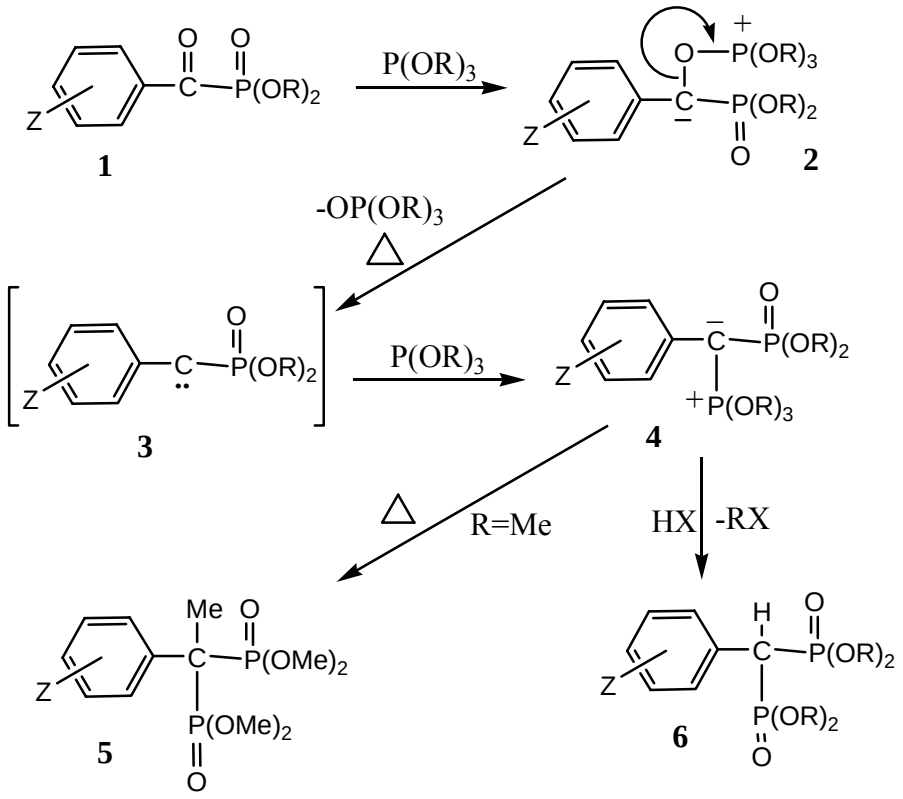
The carbene intermediates 3 (Z = 2-vinyl and 2-allyl, R = Me) have been generated by heating the corresponding 2-substituted dialkyl benzoylphosphonates with trimethyl phosphite and their subsequent reactions investigated. Reactions proceed by both intermolecular trapping of the carbene intermediates by trimethyl phosphite to give novel ylidic phosphonates 4, and by intramolecular carbene insertion to give cyclic systems. For the 2-vinyl-substituted system cyclisation leads to a mixture of the two indenylphosphonate isomers 12 and 13, whereas for the 2-allyl systeminsertion into the π-system occurs to give a cyclopropyl system 21.

Keywords: Intramolecular cyclisations, carbenes, allylbenzoylphosphonates, trimethyl phosphite

Introduction

We have shown that the reactions of trialkyl phosphites with dialkyl benzoylphosphonates 1 lead to the formation of anionic intermediates 2 which in the absence of electrophiles undergo cleavage of the α C-O bond to give the phosphonate-substituted phenylcarbenes 3 (see Scheme 1).[1] Intermolecular trapping of these carbene intermediates by the trialkyl phosphite present in the reaction mixture leads to the formation of novel ylidic phosphonates 4 which can then either rearrange (for R = Me) to give the bisphosphonates 5 or react with proton donors to give the bisphosphonates 6. In aqueous conditions benzylphosphonates may also be formed.[2] However, if

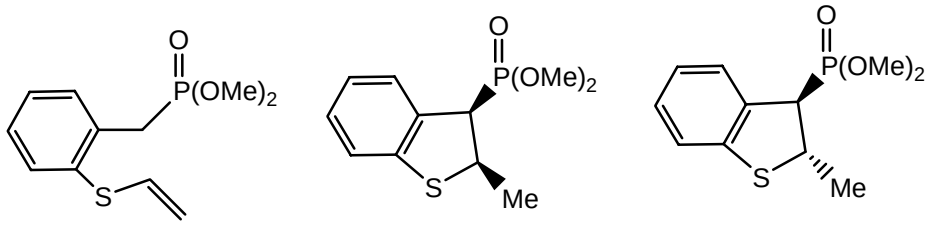
a suitable *ortho*-substituent is present on the phenyl ring, intramolecular trapping of the carbene intermediate 3 may also occur and this can be encouraged by the addition of an inert solvent to the reaction mixture which inhibits the intermolecular trapping mechanism.[1,3-6] This intramolecular reaction between the carbene centre and the *ortho*-substituent can result either in cyclisation or in hydrogen abstraction from the substituent to give a benzylphosphonate.[4]



Scheme 1

Thus, the carbene 3 (Z = 2-EtS, R = Me), from 1 (Z = 2-EtS, R = Me) led not only to the formation of the ylidic phosphonate 4 (Z = 2-EtS, R = Me)but also the benzylphosphonate 7 and the two isomeric 2-methyl-2,3-dihydrobenzo[b]thiophen-3-ylphosphonates 8 and 9.[4] Furthermore, those intramolecular cyclisations observed to date for the phosphonate-substituted carbenes 3 have shown an increased preference for the formation of five-membered rings even when other ring sizes were possible. This has been attributed to the steric rather than the electronic effects of the phosphonate group.[4]

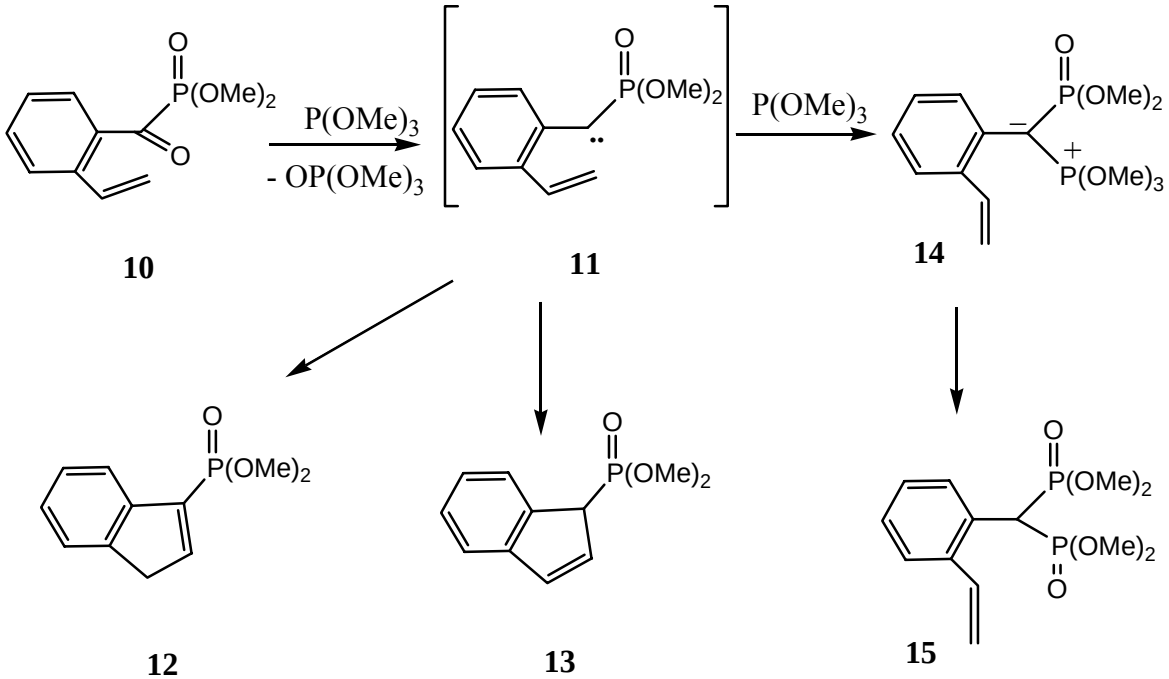
We now report the results of our study of the reactions of the carbenes 3 (X = 2-vinyl and 2-allyl, R = Me) where intramolecular cyclisation can theoretically occur by either insertion into an appropriate C-H bond or by insertion into the π-system of the substituent. In particular, it was of interest to determine whether the mode of cyclisation of these carbenes might be affected by the presence of the adjacent phosphonate group.



7 **8** **9**

Results and Discussion

2-Vinylbenzoic acid was prepared by the addition of isochromanone to molten potassium hydroxide[7] and then converted to the corresponding benzoylphosphonate 10 *via* its acid chloride. Reaction of 10 with trimethyl phosphite led to the formation of the carbene intermediate 11 which then cyclised to give the two indenylphosphonate isomers 12 and 13 in an approximately 2:1 ratio together with some of the ylidic phosphonate 14, subsequently isolated as the bisphosphonate 15 (Scheme 2).

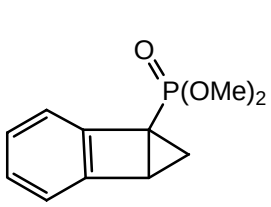


10 **11** **14** **12** **13** **15**

Scheme 2

Since insertion into a terminal C-H bond on the vinyl substituent would give rise to only isomer 13 and no significant rearrangement of 13 to 12 was observed on prolonged heating of the reaction mixture, we must conclude that the formation of 13 occurs predominantly *via* either the

tricyclic phosphonate 16 or the 2*H*-inden-1-ylphosphonate 17. Both these options involve the carbene centre initially interacting with the π-system in the substituent. This is consistent with the conclusions from earlier work on the formation of indene from *ortho*-styrylcarbene where 2*H*-indene was identified as the likely intermediate.[8] It is also interesting to note that the 2-benzoyl-substituted carbene 3 (Z = 2-PhCO, R = Me) cyclises to give the analogous isobenzofuran 18 which in this case does not undergo further rearrangement.[3]



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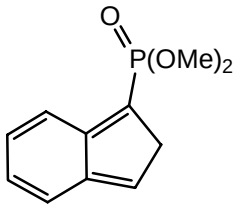

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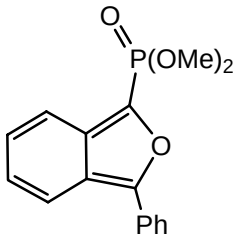

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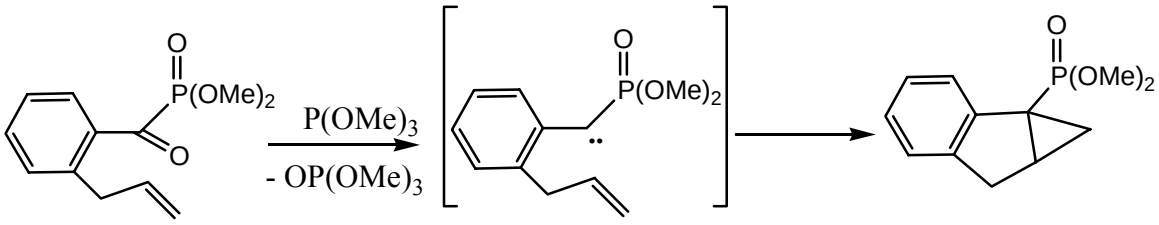
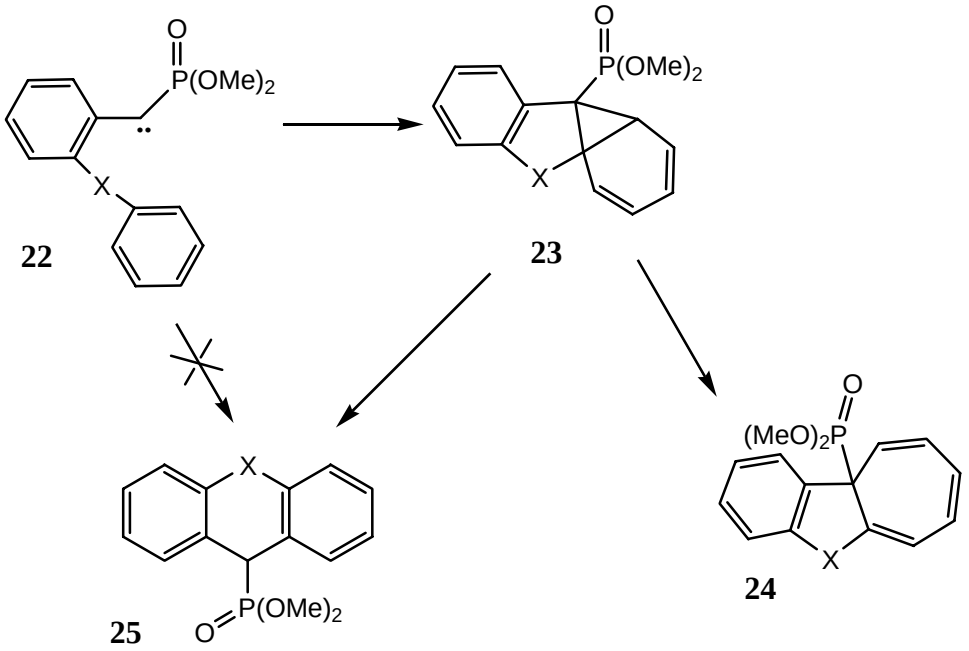
The 2-allyl substituted system 19 was also prepared from the corresponding acid chloride[9] and its reactions with trimethyl phosphite investigated. In this case the reaction of the initially formed carbene 20 proceeded very cleanly to give one main product, the cyclopropyl system 21, in high yield.



19 **20** **21**

This product clearly arises from carbene insertion into the allyl π-system and provides additional support for our earlier proposal that the formation of 10a-dimethoxyphosphinyl-10a*H*-benzo[b]cyclohepta[d]furan 24 (X = O)from the carbene intermediate 22 (X = O)proceeds via the initial formation of the cyclopropyl-containing system 23 (X = O).[5] We were unable to find any evidence for products arising from carbene insertion into one of the C-H bonds on the allyl substituent and this is also consistent with our earlier observation that the formation of the thioxanthenylphosphonate 25 (X = S) from the carbene 22 (X = S) proceeds *via* the π-insertion product 23 (X = S) rather than by insertion into a C-H bond on the phenyl substituent.[5] Further studies are continuing.



Experimental Section

2-Vinylbenzoic acid.[7]

Crushed potassium hydroxide (4.85 g, 0.18 mol) was heated to 185 °C in a stream of dry nitrogen in a round-bottomed flask equipped for distillation. Isochromanone (7 g, 47 mmol) was then added dropwise with stirring to the molten potassium hydroxide and the liberated water distilled from the reaction flask. When all of the isochromanone had been added, the mixture was left to stir at 185 °C for a further 3 h. The reaction mixture was then allowed to cool and the product taken into water (100 mL), washed with ether (100 mL) and the resulting aqueous layer acidified with hydrochloric acid (20%). The resulting aqueous solution was then extracted with ether (2 x 100 mL) and the combined ether extracts then dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to give the product. This material was recrystallised from aqueous ethanol to give the pure 2-vinylbenzoic acid as a white solid (3.35 g, 95%) mp 94 °C (lit.,[7] mp 94 °C).

Dimethyl 2-vinylbenzoylphosphonate (10). A mixture of 2-vinylbenzoic acid (5 g, 34 mmol) and thionyl chloride (11.9 g, 0.1 mol) was stirred overnight under dry nitrogen. All excess thionyl chloride was removed under reduced pressure and trimethyl phosphite (4.6 g, 37 mmol) was then slowly added under dry nitrogen. When ^{31}P NMR spectroscopy showed the reaction was complete, the mixture was distilled *in vacuo* to give 10 (5 g, 58%) as a pale yellow oil; bp 94 °C at 0.01 mmHg, MS 240 [M]. ^{31}P NMR ($CDCl_3$) δ 0.3; ^{1}H NMR ($CDCl_3$) δ 3.91 (d, J_{PH} = 11 Hz, 6H), 5.39 (dd, J = 1 Hz and 11 Hz, 1H), 5.68 (dd, J = 1 Hz and 17 Hz, 1H), 7.23 (dd, J 11 Hz and 17 Hz, 1H), 7.43 (td, J = 1.5 and 8 Hz, 1H), 7.53-7.63 (m, 2H), 8.36 (d, J 8 Hz, 1H); ^{13}C NMR($CDCl_3$) δ 54.2 (d, J_{PC} = 7 Hz), 117.6, 127.5, 127.8 (d, J_{PC} = 4 Hz), 131.8 (d, J_{PC} = 1 Hz),

133.5, 133.6 (d, J_{PC} = 63 Hz), 135.1, 139.2 (d, J_{PC} = 9 Hz), 201.0 (d, J_{PC} = 173 Hz). The benzoylphosphonate 10 was analysed as its 2,4-dinitrophenyl hydrazone derivative, mp 138 °C. Anal. Calcd for $C_{17}H_{17}N_4O_7P$: C, 48.57; H, 4.05; N, 13.3. Found: C, 48.42; H, 4.04; N, 13.64.

The reaction of dimethyl 2-vinylbenzoylphosphonate with trimethyl phosphite

Trimethyl phosphite (1 g, 8 mmol) was added to the benzoylphosphonate 10 (1.0 g, 4.2 mmol) and the mixture heated at 100 °C for 30 min under dry nitrogen. Analysis of the reaction mixture by NMR spectroscopy indicated the formation of several carbene-derived products these being the indenylphosphonates 12 and 13 (in the ratio 2:1), the ylidic phosphonate 4 (Z = 2-vinyl, R = Me) and its decomposition product 6 (Z = 2-vinyl, R = Me). Some phosphonate phosphate formation[1] was also observed due to the ingress of moisture. The reaction mixture was then heated for a further 12 h at 100 °C to monitor any change in the product ratio. After this time ^{31}P NMR spectroscopy showed the ylidic phosphonate 4 (Z = 2-vinyl, R = Me) had been converted entirely to its decomposition product 6 (Z = 2-vinyl, R = Me) but that the ratio of the indenylphosphonate isomers had been little affected, the ratio of 6 (Z = 2-vinyl, R = Me):12:13 being 5:4:2. Volatile components in the reaction mixture were removed by heating under reduced pressure (80 °C at 0.01 mmHg) and the carbene-derived components isolated by reverse phase HPLC on a Dynamax C-18 column (aqueous methanol 60%).

Tetramethyl 1-(2-vinylphenyl)methane-1,1-diphosphonate (6). (Z = 2-vinyl, R = Me) This material, the decomposition product of the initially formed ylidic phosphonate 4 (Z = 2-vinyl, R = Me), was obtained as a colourless oil. HRMS calcd for $C_{13}H_{20}O_6P_2$ 334.0735 [M], found 334.0735. ^{31}P NMR ($CDCl_3$) δ 21.4; ^{1}H NMR ($CDCl_3$) δ 3.63 (d, J_{PH} = 11 Hz, 6H), 3.77 (d, J_{PH} = 11 Hz, 6H), 4.23 (t, J_{PH} = 26 Hz, 1H), 5.42 (dd, J = 1.5 Hz and 11 Hz, 1H), 5.61 (dd, J = 1.5 Hz and 17 Hz, 1H), 6.96 (dd, J = 11 Hz and 17 Hz, 1H), 7.29-7.38 (m, 2H), 7.43 (m, 1H), 7.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 39.9 (t, J_{PC} = 134 Hz), 53.6 (m, J = 3 Hz), 54.1 (m, J = 3 Hz), 118.7 (br s), 126.7 (t, J_{PC} = 7 Hz), 127.5 (t, J_{PC} = 2 Hz), 127.8 (t, J_{PC} = 2.5 Hz), 128.1 (t, J_{PC} = 2.5 Hz), 130.3 (t, J_{PC} = 5 Hz), 134.6, 138.5 (t, J_{PC} = 8 Hz).

Dimethyl 1-indenylphosphonate (13). This material, containing a trace of the isomeric dimethyl 3-indenylphosphonate, was isolated as a colourless liquid. HRMS calcd for $C_{11}H_{13}O_3P$ 224.0602 [M], found 224.0602. ^{31}P NMR ($CDCl_3$) δ 27.1; ^{1}H NMR ($CDCl_3$) δ 3.45 (d, J_{PH} = 11 Hz, 3H), 3.63 (d, J_{PH} = 11 Hz, 3H), 4.11 (dm, J_{PH} = 34 Hz, 1H), 6.50 (m, 1H), 6.97 (m, 1H), 7.10 (dm, J = 7.5 Hz, 1H), 7.18 (m, 1H), 7.37 (m, 1H), 7.69 (dm, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 49.3 (d, J_{PC} = 135 Hz), 53.3 (d, J_{PC} = 7 Hz), 53.6 (d, J_{PC} = 7 Hz), 121.5, 124.8 (d, J_{PC} = 2 Hz), 125.5 (d, J_{PC} = 3 Hz), 127.6 (d, J_{PC} = 2 Hz), 130.2 (d, J_{PC} = 8 Hz), 134.5 (d, J_{PC} = 11 Hz), 138.6 (d, J_{PC} = 5 Hz), 144.7 (d, J_{PC} = 5 Hz).

Dimethyl 3-indenylphosphonate (12). This material, containing a trace of the isomeric dimethyl 1-indenylphosphonate, was isolated as a colourless liquid. HRMS calcd for $C_{11}H_{13}O_3P$ 224.0602 [M], found 224.0602. ^{31}P NMR ($CDCl_3$) δ 17.0; ^{1}H NMR ($CDCl_3$) δ 3.52 (m, 2H), 3.73 (d, J_{PH} = 11 Hz, 6H), 7.20 (m, 1H), 7.28 (tm, J = 7.5 Hz, 1H), 7.34 (dt, J_{PH} = 10 Hz, J = 2 Hz, 1H), 7.44 (dm, J = 7.5 Hz, 1H), 7.59 (dm, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.1 (d, J_{PC}

= 18 Hz), 52.6 (d, J_{PC} = 6 Hz), 121.8, 123.9, 125.8, 126.8, 132.7 (d, J_{PC} = 194 Hz), 141.6 (d, J_{PC} = 16 Hz), 143.4 (d, J_{PC} = 14 Hz), 149.7 (d, J_{PC} = 12 Hz).

Dimethyl 2-allylbenzoylphosphonate (19). Trimethyl phosphite (1.36 g, 11 mmol) was added to 2-allylbenzoyl chloride[9] (1.8 g, 10 mmol) and the mixture allowed to stand at room temperature taking care to exclude moisture from the reaction mixture. When ^{31}P NMR spectroscopy showed the reaction was complete the volatile components were removed *in vacuo* to give 19 in essentially quantitative yield in a good state of purity. Attempts to obtain an analytically pure sample by distillation were unsuccessful. ^{31}P NMR ($CDCl_3$) δ 0.7; $_1$H NMR ($CDCl_3$) δ 3.91 (d, J_{PH} = 11 Hz, 6H), 5.39 (dd, J = 1 Hz and 11 Hz, 1H), 5.68 (dd, J = 1 Hz and 17 Hz, 1H), 7.23 (dd, J = 11 Hz and 17 Hz, 1H), 7.43 (td, J = 1.5 Hz and 8 Hz, 1H), 7.53-7.63 (m, 2H), 8.36 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 37.6, 54.0 (d, J_{PC} = 7 Hz), 115.8, 126.3, 131.4 (d, J_{PC} = 4 Hz), 132.3 (d, J_{PC} = 1 Hz),133.4, 134.3 (d, J_{PC} = 63 Hz), 136.5, 141.3 (d, J_{PC} = 10 Hz), 200.7 (d, J_{PC} = 172 Hz).

The benzoylphosphonate 19 was analysed as its 2,4-dinitrophenyl hydrazone derivative, mp 137 ^{o}C Anal. Calcd for $C_{18}H_{19}N_4O_7P$: C, 49.78; H, 4.41; N, 12.90. Found: C, 49.77; H, 4.68; N, 12.82.

The reaction of dimethyl 2-allylbenzoylphosphonate with trimethyl phosphite. Trimethyl phosphite (1 g, 8 mmol) was added to the benzoylphosphonate 19 (1.0 g, 4 mmol) and the mixture heated at 100 ^{o}C for 3 h under dry nitrogen. Volatile components in the reaction mixture were removed by heating under reduced pressure (80 ^{o}C at 0.01 mmHg) and the mixture analysed by ^{31}P NMR spectroscopy which showed the formation of one main component, 21 (90%). The formation of a second carbene-derived product 6 (Z = 2-allyl, R = Me) (10%), the decomposition product of the ylidic phosphonate 4 (Z = 2-allyl, R = Me), was confirmed by NMR spectroscopy [^{31}P NMR ($CDCl_3$) δ 22.9; ^{1}H NMR ($CDCl_3$) δ 4.15 (1H, t, J_{PH} 26 Hz)].

A sample of the major product 21 was isolated by reverse phase h.p.l.c. on a Dynamax C-18 column (aqueous methanol 70%) as a colourless oil. HRMS calcd for $C_{12}H_{15}O_3P$ 238.0759 [M], found 238.0759. ^{31}P NMR ($CDCl_3$) δ 29.6; ^{1}H NMR ($CDCl_3$) δ 0.59 (ddd, J = 4.4 Hz and 6.4 Hz, J_{PH} = 6.4 Hz, 1H), 1.77 (ddd, J = 8.5 Hz and 4.4 Hz, J_{PH} = 14 Hz, 1H), 2.40 (ddddd, J = 8.5 Hz, 6.8 Hz, 4.9 Hz and 1 Hz, J_{PH} = 11.5 Hz, 1H), 3.03 (br dd, J = 17 Hz, J_{PH} = 5.6 Hz, 1H), 3.29 (dd, J = 17 Hz and 6.8 Hz, 1H), 3.69 (d, J_{PH} = 11 Hz, 3H), 3.87 (d, J_{PH} = 11 Hz, 3H), 7.13-7.18 (m, 3H), 7.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.3 (d, J_{PC} = 3 Hz), 26.9 (d, J_{PC} = 203 Hz), 34.2, 52.7 (d, J_{PC} = 6 Hz), 52.9 (d, J_{PC} = 6 Hz), 124.0 (br s), 125.7 (br s), 126.5 (br s), 126.6 (br s), 141.9, 142.0 (d, J_{PC} = 4 Hz),

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