J. Chem. Sci., Vol. 120, No. 1, January 2008, pp. 131–136.

Facile one-pot synthesis of functionalized organophosphonate esters via ketone insertion into bulky arylphosphites

RAMASWAMY MURUGAVEL* and SUBRAMANIAM KUPPUSWAMY

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400 076
e-mail: rmv@chem.iitb.ac.in

Abstract. The reaction of phosphorus trichloride with 2,6-di*iso*propyl phenol in the presence of LiCl under reflux conditions for 24 h produces a mixture of $(ArO)PCl_2$ and $(ArO)_2PCl$ (Ar = 2,6-iPr$_2$C$_6$H$_3$). The hydrolysis of the aryloxy compounds in acetone/H_2O results in the formation of two novel phosphonate ester derivatives $[(ArO)P(O)(OH)(CMe_2OH)]$ (**1**) and $[(ArO)_2P(O)(CMe_2OH)]$ (**2**), respectively in a moderate yield. The title compounds have presumably formed via acetone insertion to the P–H bonds of $(ArO)P(O)(H)(OH)$ and $(ArO)_2P(O)(H)$, respectively, in the presence of HCl produced during the hydrolysis. Compounds **1** and **2** have been characterized by elemental analysis, and ESI-mass, Infrared and NMR spectroscopic techniques. Further, solid state structures of **1** and **2** have been established by single crystals X-ray diffraction studies.

Keywords. One-pot synthesis; acetone insertion; new phosphonate esters; X-ray structure.

1. Introduction

Phosphonates have been recognized for a long time as important intermediates in synthetic organic chemistry.[1,2] On the other hand, phosphonic acids[3,4] and phosphate esters[5–10] are important classes of compounds in inorganic chemistry, being widely used for synthesizing large molecular clusters and zeolite building blocks. Although several synthetic methods are available to prepare phosphonate esters through Arbuzov reaction, very few examples have been reported for their synthesis via phosphite insertion into electropositive centers under highly acidic conditions.[11] Modified Mannich type procedure has been applied to synthesize newer phosphonates, starting from phosphorus acid, amine and formaldehyde according to (1). This reaction however proceeds efficiently only under highly acidic conditions. A further limitation of this reaction is that only formaldehyde can be used as the carbonyl source at low pH.[12] This methodology was later extended to the synthesis of aminoethylene phosphonic acid and N-benzyl-α-aminophosphonic acids.[13–15]

$$R_2NH + HCHO + HP(O)(OH)_2 \xrightarrow{HCl} R_2NCH_2P(O)(OH)_2 + H_2O. \quad (1)$$

Acidic nature of the P–H protons is not only useful for the phosphonate ester preparation, but has also found several applications such as reducing reagent,[15] synthesis of biologically relevant compounds,[16] and selective diastereomer formation.[17] A further problem that arises due to the application of a strongly acidic medium is the ester hydrolysis, leading to the loss or decomposition of desired products. Hence the preparation of phosphonates esters is best carried out under mild conditions. We have overcome this problem by starting from aryloxy P(III) chlorides and performing the synthesis of phosphonic acid as well as the subsequent carbonyl compound insertion in one-pot, exploiting the HCl by-product formed in the P–Cl hydrolysis step. In this communication, we report the details of this investigation.

2. Experimental

3.1 *Apparatus*

All reactions were carried out under anaerobic conditions unless specified otherwise. The ^{1}H (Me_4Si internal standard) and ^{31}P (85% H_3PO_4 external standard) NMR spectra were recorded on a Varian AS 300 spectrometer. Infrared spectra were obtained on a Perkin Elmer Spectrum One FT–IR spectrometer. Microanalyses were performed on a Thermo Finnigan (FLASH EA 1112) or a Carlo Eraba 1106 microanalyzer. ESI-Mass spectra were obtained on a

*For correspondence

Waters Q-TOF micro-YA-105 spectrometry. Commercial grade solvents were purified by employing conventional procedures and were distilled prior to their use. Commercially available starting materials such as PCl_3 (s.d. Fine-Chem.), LiCl (Lancaster) and 2,6-diisopropyl phenol (Lancaster) were used as procured.

2.2 *Synthesis of $(ArO)PCl_2$ and $(ArO)_2PCl$*

Phosphorus trichloride (10 mL, 115 mmol), 2,6-di*iso*propyl phenol (5 mL, 43 mmol) and LiCl (125 mg) were heated under reflux for 24 h. The reaction mixture was allowed to cool to room temperature and filtered. The unreacted phosphorus trichloride was removed under reduced pressure. The resultant liquid was distilled under vacuum at 125°C/0·5 torr. The distillate is $(ArO)PCl_2$ while the liquid that did not distil under this pressure is predominately the disubstituted product $(ArO)_2PCl$.

2.3 *Synthesis of [(ArO)P(O)(OH)(CMe$_2$OH)] (1)*

$(ArO)PCl_2$ was treated with aqueous acetone at room temperature. Resultant mixture was filtered out and filtrate was kept at room temperature for the crystallization. Colourless needle shape single crystals of **1** were isolated after 2 days. m.p: 182–183°C. Yield: 1·4 g (12%). Anal. Calcd. for $C_{15}H_{25}PO_4$ (Mr = 300·33): C, 59·99; H, 8·39. Found; C, 59·02; H, 8·23. IR (KBr, cm^{-1}): 3423 (*br*), 3116 (*w*), 2975 (*s*), 2930 (*w*), 2870 (*w*), 2329 (*br*), 1634 (*br*), 1467 (*m*), 1445 (*m*), 1383 (*w*), 1333 (*w*), 1240 (*s*), 1159 (*vs*), 1097 (*m*), 1046 (*w*), 970 (*vs*), 937 (*vs*), 852 (*m*), 800 (*m*), 752 (*m*). ^{1}H NMR (pyridine-d_5, 300 MHz) δ: 7·13–7·22 (*m*, 3H, Ar–H), 4·40–4·49 (septet, 2H, $CH(CH_3)_2$; $^3J_{HH}$ = 6·9 Hz), 2·00 (*s*, 3H, CH_3), 1·95 (*s*, 3H, CH_3), 1·29–1·31 (*d*, 12H, $CH(CH_3)_2$, $^3J_{HH}$ = 6·9 Hz). ^{31}P NMR (pyridine-d_5, 121 MHz) δ: 22·6 ppm. ESI Mass spectrum (acetone): *m*/*z* 1201 $(4M + 1)^+$, 901 $(3M + 1)^+$, 601 $(2M + 1)^+$, 301 $(M + 1)^+$.

2.4 *Synthesis of [(ArO)$_2$P(O)(CMe$_2$OH)] (2)*

The distillation residue containing $(ArO)_2PCl$ was dissolved in H_2O/acetone and allowed to crystallize in aerobic atmosphere at room temperature. After 3 days well formed colorless rectangular crystals of 2 were obtained from the reaction mixture. M.p: 172–174°C. Yield: 2.4 g (25%). Anal. Calcd. for $C_{27}H_{41}PO_4$ (Mr = 460·59): C, 70·41; H, 8·97. Found; C, 69·5; H, 9·55. IR (KBr, cm^{-1}): 3310 (*s*), 3062 (*w*), 2954 (*s*), 2867 (*m*), 1466 (*m*), 1439 (*m*), 1378 (*w*), 1333 (*w*), 1248 (*s*), 1188 (*m*), 1165 (*s*), 1092 (*m*), 1108 (*w*), 1045 (*w*), 975 (*w*), 931 (*vs*), 883 (*w*), 798 (*w*), 772 (*m*), 763 (*m*). ^{1}H NMR (pyridine-d_5, 300 MHz) δ: 7·20 (*s*, 6H, Ar–H), 5·53 (*br*, 1H, OH), 3·86–3·95 (septet, 4H, $CH(CH_3)_2$; $^3J_{HH}$ = 6·6 Hz), 2·01 (*s*, 3H, CH_3), 1·95 (*s*, 3H, CH_3), 1·25–1·28 (*d*, 12H, $CH(CH_3)_2$, $^3J_{HH}$ = 6·6 Hz), 1·12–1·14 (*d*, 12H, $CH(CH_3)_2$, $^3J_{HH}$ = 6·6 Hz). ^{31}P NMR (pyridine-d_5, 121 MHz) δ: 15·4 ppm. ESI Mass spectrum (pyridine): *m*/*z* 461 $(M + 1)^+$.

2.5 *Single crystal X-ray diffraction studies*

Intensity data for **1** and **2** were collected on a Bruker AXS and Oxford XCalibur CCD diffractometers, respectively. All calculations were carried out using the programs in WinGX module.[18] The structure solution was achieved by direct methods using SIR-92.[19] The final refinement of the structure was carried out using full least-squares methods on F^2 using SHELXL-97.[20] Selected crystal data are given table 1. The details of crystal structure determination can either be

Table 1. Crystal data for **1** and **2**.

Compound	**1**	**2**
Identification code	mur119	rm118a
Empirical formula	$C_{15}H_{25}O_4P$	$C_{27}H_{41}O_4P$
Fw	300·32	460·57
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0·71073	0·71073
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$	P-1
a (Å)	10·5157(17)	9·1694(13)
b (Å)	5·7611(9)	11·1482(10)
c (Å)	13·306(2)	14·1469(9)
α (°)	90	90·253(6)
β (°)	95·445(2)	104·059(7)
γ (°)	90	99·521(9)
V (Å^3)	802·5(2)	1382·0(2)
Z	2	2
D (calcd.) (mg/m^3)	1·243	1·107
Abs coeff. (mm^{-1})	0·181	0·127
F(000)	324	500
Cryst size (mm^3)	0·15 × 0·05 × 0·05	0·36 × 0·32 × 0·30
θ range (°)	1·54 to 24·15	1·49 to 25·00
Data/restraints/params	1429/1/189	4870/0/317
Goodness-of-fit on F^2	1·111	1·007
R_1 [$I > 2\sigma(I)$]	0·0254	0·0597
R_2 [$I > 2\sigma(I)$]	0·0632	0·1137

obtained from CCDC (deposition numbers 671174 and 671175) or directly from the authors.

3. Results and discussion

3.1 *Synthesis and characterization*

The reaction of 2,6-diisopropyl phenol with PCl_3 in the presence of LiCl under reflux conditions for 24 h produces $(ArO)PCl_2$ and $(ArO)_2PCl$. The reaction mixture was distilled under vacuum to obtain pure $(ArO)PCl_2$. Hydrolysis of $(ArO)PCl_2$ in the presence of aqueous acetone leads to the formation of the bulky aryloxy group substituted phosphonate ester derivative $[(ArO)P(O)(OH)(CMe_2OH)]$ (**1**). Similarly, the hydrolysis of $(ArO)_2PCl$ under similar conditions leads to the isolation of phosphonate diester $[(ArO)_2P(O)(CMe_2OH)]$ (**2**) in moderate yield.

The single crystals of **1** and **2**, obtained directly from the reaction mixture, have been found to be analytically pure. The compounds have been further characterized by IR, ESI-mass and NMR spectroscopic techniques. Elemental analysis values in each case supported the chemical formulation for these compounds. Infrared spectrum of **1**, shows a broad vibration at 2329 cm^{-1} corresponding to the presence of PO–H group. The strong bands observed at around 1159 and 3423 cm^{-1} are readily assignable to P=O and CO-H vibrations, respectively. In solution, compound **1** shows a single resonance in the ^{31}P NMR spectroscopy at δ 22·6 ppm. The observed ^1H NMR spectral pattern and the ratio of integrated intensities further lend evidence to the structure of **1**. The multiplets appearing in the range δ 7·13–7·22 ppm correspond to the aryl protons. As expected, the methine protons (C–H of the isopropyl group) appear as a septet centered at δ 4·45 ppm ($^3J_{HH}$ = 6·6 Hz). The methyl protons (CH_3 of the isopropyl group) are observed as a doublet at δ 1·30 ppm. Two singlets of similar intensity appearing at δ 1·95 and 2·00 ppm are assigned to the two methyl groups of the CMe_2 moiety attached to phosphorus.

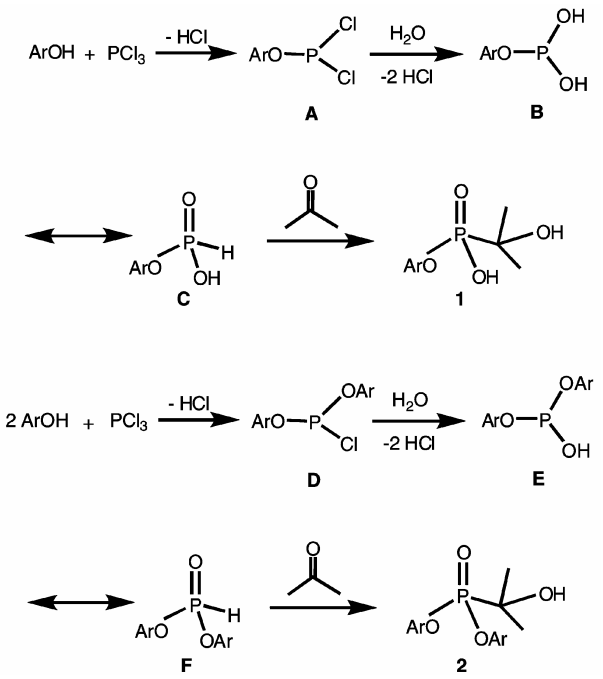
Unlike **1**, compound **2** does not show any absorption at around 2300 cm^{-1} in the infrared spectrum indicating the absence of P–OH group in the molecule. The ^1H NMR spectrum is consistent with the presence of two aryloxides and one CMe_2OH group on the central phosphorus atom. The ^{31}P NMR spectrum shows a single resonance at δ 15·4 ppm, which is slightly downfield shifted compared to **1** due to presence of an additional aryloxide on phosphorus.

3.2 *Mechanism*

Since the Mannich type reactions on P-H centers occur only in acidic medium, it is easy to explain the formation of **1** and **2** in the present case by invoking the mechanism shown in scheme 1. Although the original intention was to convert the phosphorus halides to the corresponding acids $(ArO)P(OH)_2$ and $(ArO)_2P(OH)$ by hydrolysis, the use of water/acetone as the reaction medium led to interesting results. Thus, the acids **B** or **E** formed during the hydrolysis (scheme 1) undergo facile tautomerization to produce the phosphonic acid esters **C** or **F** with reactive P–H bonds (the nucleophile), which are now ready to attack the electrophilic carbonyl group of the acetone used in the reaction medium. Thus the insertion of P–H bond in **C** or **F** into the C=O bond leads to the isolation of stable phosphonate mono and diesters **1** and **2** respectively. The HCl liberated during the hydrolysis of P–Cl bond, which has not left the system by dissolution in the residual water, catalyses the last step shown in scheme 1. The yield of the reactions in the present case is probably proportional to the amount of HCl available in the system during the final step.

3.3 *Molecular structure of 1*

A single crystal X-ray diffraction measurement of **1** indicates that the compound crystallises in mono-



Scheme 1. Plausible pathway for the formation of **1** and **2**.

clinic crystal system. The final refined molecular structure is shown in figure 1 along with selected structural parameters. The central phosphorus atom in **1** is surrounded by four different ligands thus rendering the molecule chiral (at least in the solid state, space group $P2_1$) because of the presence of distinct P=O and P–O(H) moieties (P1–O3 1·468(2) and P1–O2 1·554(2) Å). The P–O(Ar) is the longest P–O bond in the molecule (1·580 Å). Due to the presence of bulky CMe_2OH and OAr substituents, the tetrahedral angles around phosphorus varies in the range 100·5(1)–115·3(1)°.

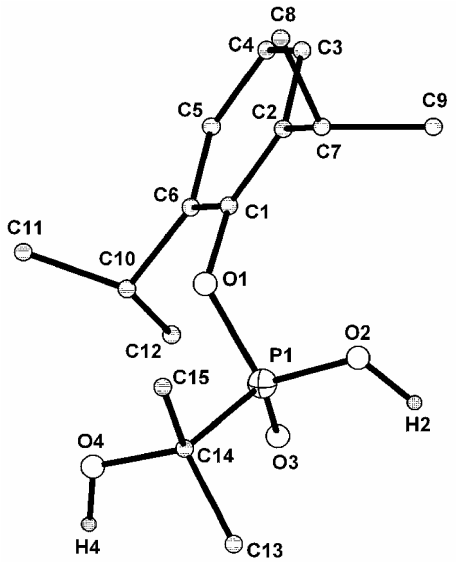


Figure 1. Molecular structure of **1**. Selected bond distances [Å]: P(1)–O(1) 1·580(2), P(1)–O(2) 1·554(2), P(1)–O(3) 1·468(2), P(1)–C(14) 1·825(3), C(1)–O(1) 1·424(3), C(14)–O(4) 1·443(3); bond angles [°]: O(1)–P(1)–O(2) 105·1(1), O(1)–P(1)–O(3), 115·3(1), O(1)–P(1)–C(14) 100·5(1), O(3)–P(1)–O(2) 114·3(1), O(2)–P(1)–C(14) 106·6(1), O(3)–P(1)–C(14) 113·7(1).

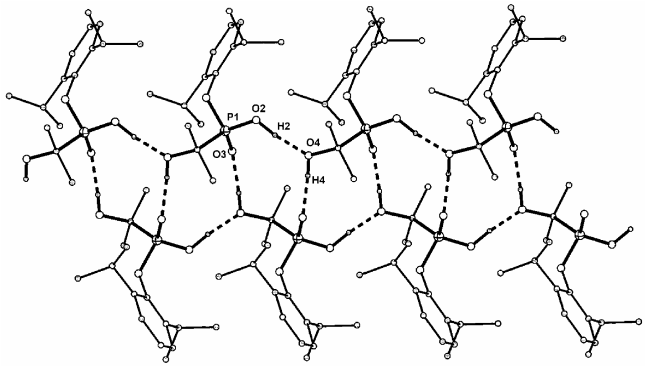


Figure 2. *Corrugated sheet*-type supramolecular assembly in **1**.

In solid state, due to the presence of P–O(H), C–O(H), and P=O moieties, an intricate supramolecular hydrogen bond network is built. Two unique hydrogen bonds found in the lattice (O2–H2…O4 and O4–H4…O3) results in the formation of an extended corrugated sheet type of structure as shown in figure 2. (Hydrogen bond parameters: O2···O4 = 2·589(3) Å, H2···O4 = 1·63(4) Å, O2–H2 = 0·99(4) Å, O2–H2···O4 = 163(4)°; O3···O4 = 2·636(3) Å, H4···O3 = 1·76(4) Å, O4–H4 = 0·88(4) Å, O4–H4···O3 = 169(4)°). The *corrugated sheet*-type supramolecular assembly with alternating ten membered [HOCPOHOCPO] rings found in **1** is rare among structurally characterized phosphonic acid derivatives.[21–26] For comparison, hydrogen bond assembly of 2,6-diisopropyl phenyl phosphate monoester reveals a polymeric chain,[27] whereas phosphate diesters[28] or cyclic phosphates[29] force a hydrogen bonded dimeric structure with a eight membered ring.

3.4 *Molecular structure of 2*

A single crystal X-ray diffraction measurement of **2** indicates that the compound, unlike **1**, crystallizes in the centrosymmetric space group $P\bar{1}$ and adopts a dimer motif in the lattice about the inversion centre (figure 3). The appearance of the dimer is highly reminiscent of the characteristic pattern seen for carboxylic and organophosphorus acids, with the C–

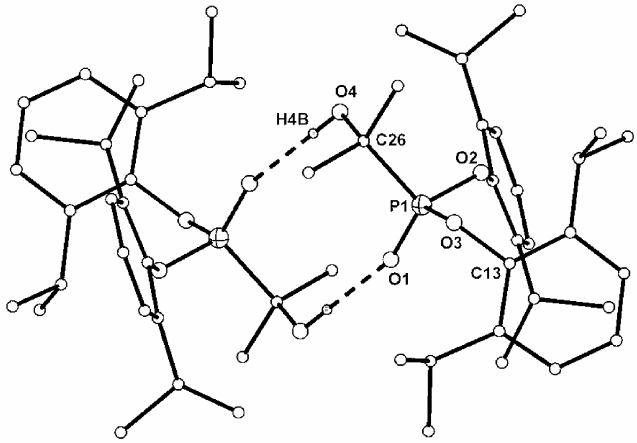


Figure 3. Ten-membered macrocycle formation via O–H···O intermolecular hydrogen bonding interaction in **2**. Selected bond distances [Å]: P(1)–O(1) 1·460(2), P(1)–O(2) 1·594(2), P(1)–O(3) 1·594(2), P(1)–C(26) 1·826(4), C(1)–O(2) 1·427(4), C(26)–O(4) 1·427(4); bond angles [°]: O(1)–P(1)–O(3) 116·1(1), O(1)–P(1)–O(2) 112·9(1), O(1)–P(1)–C(26) 113·7(2), O(3)–P(1)–O(2) 102·9(1), O(2)–P(1)–C(26) 109·9(2), O(3)–P(1)–C(26) 100·1(1).

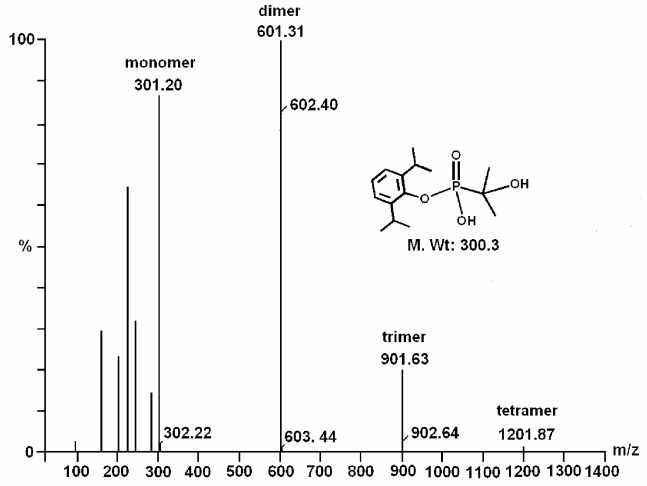


Figure 4. ESI-Mass spectrum of **1**.

OH group of each molecule in **2** pointing towards to the P=O group of the other crystallographically equivalent molecule, with the exception that the OH group is not situated directly on phosphorus but on the neighbouring carbon (Hydrogen bond parameters: O4–H4B = 0·76(4) Å, H4B···O1 = 1·97(4) Å, O4···O1 = 2·712(4) Å O4–H4B···O1 = 169(4)°).[30] The central phosphorus adopts a distorted tetrahedral geometry (100·1(1)–116·1(1)°) as in **1** with the average phosphorus angle being 109·3°. There are two types of P–O bond distances (P–O(C) and P═O), with the former being appreciably longer (1·594(2) Å) than the latter (1·460(2) Å).

3.5 *Aggregation in solution*

The aggregation of main group compounds containing multiple hydroxyl groups has been of great interest for some time.[22] The case of silanols associating in solution and in the solid-state has been investigated in detail.[31] In view of the strikingly different solid state aggregation (H-bonding pattern) of **1** and **2**, ESI-mass spectral studies were carried out in solution in order to see any such association behaviour is prevalent also in solution. As it has been shown in figure 4, the molecular ion for **1** appears at *m/z* 301. In addition to this additional peak at *m/z* 601 and 901 are also observed with appreciable intensity, which correspond to the dimeric and trimeric forms of **1** (in fact the base peak corresponds to the dimer). The weak peak observed at *m/z* 1201 corresponds to the tetrameric form of **1**, suggesting that inspite of presence of two bulky substituents on phosphorus, compound **1** does undergo facile aggregation in solution. The picture however changes drastically for **2**, where the molecular ion is observed at *m/z* 461 and no other signals corresponding to the formation of any aggregates with higher mass number. This is however explainable because of the introduction of an additional aryloxide on phosphorus as well as the removal of acidic P–O(H) proton, compared to **1**.

4. Conclusion

In conclusion, we have demonstrated in this preliminary communication a facile, one-pot synthesis for the preparation of functional phosphonate esters by a simple acetone insertion reaction under mild acidic conditions. Hydrolysis of P–Cl bond in the presence of electron deficient acetone carbonyl centre leads to the *in situ* formation of the products. This methodology could open up new possibilities in making newer phosphonates. Further, compounds **1** and **2** could be used as ligands in rapidly expanding main group and transition metal phosph(on)ate chemistry. We are currently exploring these possibilities.

Acknowledgements

This work was supported by the Department of Science and Technology (DST) in the form of a Swarnajayanti Fellowship. We thank the DST funded National Single Crystal Diffraction Facility at Indian Institute of Technology (IIT) Bombay for the diffraction data and SAIF, IIT Bombay for the spectral data.

References

1. Muthiah C, Praveen Kumar K, Aruna Mani C and Kumara Swamy K C 2000 *J. Org. Chem.* **65** 3733 and references therin
2. Kumara Swamy K C and Sathis Kumar N 2006 *Acc. Chem. Res.* **39** 324
3. Walawalkar M G, Roesky H W and Murugavel R 1999 *Acc. Chem. Res.* **32** 117
4. Murugavel R and Shanmugan S 2007 *Chem. Commun.* 1257
5. Murugavel R, Walawalkar M G, Dan M, Roesky H W and Rao C N R 2004 *Acc. Chem. Res.* **37** 763
6. Murugavel R, Kuppuswamy S, Boomishankar R and Steiner A 2006 *Angew. Chem. Int. Ed.* **45** 5536
7. Murugavel R and Kuppuswamy S 2006 *Angew. Chem. Int. Ed.* **45** 7022

8. Pothiraja R, Sathiyendiran M, Butcher R J and Murugavel R 2005 *Inorg. Chem.* **44** 6314
9. Murugavel R, Sathiyendiran M, Pothiraja R and Butcher R J 2003 *Chem. Commun.* 2546
10. Murugavel R, Sathiyendiran M and Walawalkar M G 2001 *Inorg. Chem.* **40** 427
11. Horak J and Ettel V 1961 *Collection of Czechoslovak Chem. Commun.* **26** 2401
12. Redmore D 1976 *Top. Phosphorus Chem.* **8** 515
13. Moedritzer K and Irani R R 1966 *J. Org. Chem.* **31** 1603
14. Redmore D 1978 *J. Org. Chem.* **43** 996
15. Redmore D 1978 *J. Org. Chem.* **43** 992
16. Drag M, Grzywa R and Oleksyszyn J 2007 *Bioorg. Med. Chem. Lett.* **17** 1516
17. Plazuk D, Zakrzewski J and Rybarczyk-Pirek A 2006 *J. Organomet. Chem.* **691** 3098
18. Farrugia L J WinGX Version 1.64.05 1999 *J. Appl. Crystallogr.* **32** 837
19. Altomare A, Cascarano G, Giacovazzo C and Gualardi A 1993 *J. Appl. Crystallogr.* **26** 343
20. Sheldrick G M SHELXL-97 Program for structure refinement 1997 University of Göttingen: Germany
21. Chandrasekhar V, Sasikumar P, Boomishankar R and Anantharaman G 2006 *Inorg. Chem.* **45** 3344
22. Mehring M, Schurmann M and Ludwig R 2003 *Chem. Eur. J.* **9** 837
23. Weakley T J R 1976 *Acta Crystallogr.* **B32** 2889
24. Aragoni M C, Arca M, Blake A J, Lippolis V, Schröder M and Wilson C 2002 *Acta Crystallogr.* **C58** 260
25. Merz K and Knűfer A 2002 *Acta Crystallogr.* **C58** 187
26. Yi X Y, Li Y Z and Zheng L M 2002 *Acta Crystallogr.* **E58** 820
27. Onada A, Okamura T, Yamamoto H and Ueyama N 2001 *Acta Crystallogr.* **E57** 1022
28. Murugavel R unpublished results (structure of di-*tert* butylphosphate)
29. Kumara Swamy K C, Kumaraswamy S and Kommana P 2001 *J. Am. Chem. Soc.* **123** 12642
30. Etter M C 1984 *Acc. Chem. Res.* **23** 120
31. Chandrasekhar V, Boomishankar R and Nagendran S 2004 *Chem. Rev.* **104** 5847