LIST OF PUBLICATIONS

1. An Easy Access to Trisubstituted Vinyl Chlorides and Improved Synthesis of Chloro/ Bromostilbenes

2. Chlorophosphonates: Inexpensive Precursors for Stereodefined Chloro-Substituted Olefins and Unsymmetrical Disubstituted Acetylenes

3. Direct Synthesis of $\alpha$-Substituted Phosphonates


5. Synthesis and Structures of New Oxidation/ Cycloaddition Products of Cyclodiphosph(III)azanes

6. Formation of phosphonates and pyrophosphates in the reactions of chlorophosphate esters with strong organic bases
   K. V. P. P. Kumar, K. Praveen Kumar, M. Vijjulatha and K. C.

7. Characterization of second stage Mitsunobu-type intermediates
   K. Praveen Kumar, N. B. Kumar, K. C. Kumara Swamy (*to be submitted*)

*Work not reported in this thesis:*
8 The Reaction of Chlorophosphates with Strong Bases: Synthesis and Characterization of the Phosphonate Salts
M. Vijjulatha, K. Praveen Kumar, K. C. Kumara Swamy and J. J. Vittal,

9 Oxidative Addition Reactions of Cyclodiphosph(III)azanes
K. C. Kumara Swamy, P. Kommana, M. Vijjulatha and **K. Praveen Kumar**,

**PAPERS PRESENTED IN SYMPOSIA**

1. New Halogeno- and Pseudohalogeno-Phosphites and Phosphoranes
S. Kumaraswamy, C. Muthiah, **K. Praveen Kumar** and K. C. Kumara Swamy, *Frontiers in Inorganic Chemistry*, IISc, Bangalore, July, 8-10, **1998**.


3 Synthesis, Structure and Reactivity of Products Other than the Morrison-Brunn-Huisgen Intermediate in a Mitsunobu type reaction.
K. V. P. Pavan Kumar, N Satish Kumar, **K. Praveen Kumar** and K. C. Kumara Swamy, *6th National Symposium in Chemistry* (CRSI), IIT Kanpur, INDIA, Feb 6-8, **2004**.

**Synopsis**
This thesis is divided into two parts: Part-A and Part B. Part A embodies the synthesis of various phosphonates and their utility in organic synthesis. The purpose of this part of the study is (i) to develop a simple methodology for the synthesis of a variety of organophosphonates by using the readily prepared (and cheap) key precursor (OCH₂CMe₂CHRO)PCl, (ii) to develop a simple and convenient method for the synthesis of di-substituted chloro/bromo olefins and chloro-dienes by the Horner-Wadsworth-Emmons (HWE) reaction using phosphonates and (iii) to investigate the formation of phosphonates and pyrophosphates in the reaction of chlorophosphate esters with strong organic bases.

Part B involves (i) a study of the reaction of dialkyl azodicarboxylates with different cyclodiphosphosph(III)azanes in an effort to isolate and characterize compounds analogous to the intermediates proposed in the Mitsunobu reaction and (ii) investigations on the oxidative addition reactions of cyclodiphosphazanes followed by structural characterization of the resulting products.

The compounds reported herein are characterized by IR and NMR (¹H, ¹³C, ³¹P) techniques, elemental analyses (representative examples) and X-ray structure determination (where feasible). References corresponding to each part are compiled after the respective experimental sections. In the appendix, selected atomic coordinates for compounds studied by X-ray crystallography are given as reference material.

PART-A

Chapter 1 reviews the literature on different methods for the synthesis of phosphonates and their utility in organic synthesis. Selected results from Chapter 2 (Results and Discussion) are described below:

(1) Phosphite Precursors

The precursors 1a-c and 2-7 used in the present study are prepared by standard procedures available in the literature.
(2) Synthesis of Phosphonates

(a) Synthesis of chloro- and bromophosphonates via $\alpha$-hydroxyphosphonates

The $\alpha$-chlorophosphonates $10a-e$ have been prepared by treating the $\alpha$-hydroxyphosphonates $8a-e$ (prepared by the Pudovik reaction of $2$ with aldehydes) with thionyl chloride; the $\alpha$-bromophosphonates $11a-c$ have been prepared by treating the $\alpha$-hydroxyphosphonates $8a-b$ and $8f$ with thionyl bromide in dichloromethane at room temperature (Scheme 1).

In contrast to the above, the reaction of $9a-b$ with thionyl chloride leads to the formation of the $\gamma$-chlorinated vinylphosphonates $12a-b$. A possible pathway for the formation of $12a-b$ is discussed. The structure of $12a$ is also unambiguously proved by the X-ray crystallography. Compound $12a$ rearranges to the phosphonate $14$ ($\sim 95\%$ purity) upon treatment with $K_2CO_3$/ xylene. This result has implications as regards the utility of $12a$ in the HWE reaction (see below).
(b) Direct synthesis of chloro and α-trimethylsilyloxyphosphonates phosphonates

The compounds (OCH$_2$CMe$_2$CH$_2$O)PX [X = Cl (1a), OSiMe$_3$ (3)] when reacted with various aromatic aldehydes afforded the α-chlorophosphonates (10a-g) in moderate yields (Scheme 3); in the reaction with 9-anthraldehyde, we also isolated the rather unusual bisphosphonate 15 (X-ray) in yields of ~35%. Interestingly, in the reaction of 1a with cinnamaldehyde or furfuraldehyde, we again isolated γ-chlorophosphonate 12a or the ring-chlorinated product 13, respectively. The α-trimethylsilyloxyphosphonates 16a-h were also readily obtained by treating 3 with various aldehydes (Scheme 3). Possible pathways for the formation of these α-chloro/α-trimethylsilyloxyphosphonates as well as 15 are discussed.
(c) α-Phosphate esters of phosphonates, α-azidophosphonates and α-aminophosphonates

Treatment α-tosyl phosphonates \((\text{OCH}_2\text{C(CH}_3\text{)}_2\text{CH}_2\text{O})\text{P(O)}\text{CH(OTs)Ar)}\) (17a-d) (obtained from α-hydroxyphosphonates) with sodium azide did not lead to reproducible yields of α-azidophosphonates. Although the reaction of \((\text{OCH}_2\text{CMe}_2\text{CH}_2\text{O})\text{P(O)N}_3\) (5) with 2-bromo-benzyl alcohol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), afforded the azide 2-Br-C\(_6\)H\(_4\)CH\(_2\)N\(_3\) (18), attempts to convert the hydroxyphosphonate 8a-c to α-azidophosphonates using 5 or (PhO\(_2\))\(_2\)P(O)N\(_3\) resulted in the phosphate esters (of the phosphonate) 19 (using 8b) or 20a-c (Scheme 4) possibly because of the hydrolysis of the reacting azides. The structure of 20c was also established by single crystal X-ray diffraction studies.

![Scheme 4](image)

\[\delta(P) -8.7(d), 7.4 (d), ^3J(PP) = 30.0 \text{ Hz}\]

However, we did succeed in preparing the α-azidophosphonates 21a-c by reacting the bromophosphonates 11a-c with sodium azide in 47-59% yield (Scheme 5). Our approach offers a convenient alternative to those available in the literature for other azidophosphonates.

![Scheme 5](image)

\[\delta(P) 10.2\]

\[\delta(P) 10.6\]

\[\delta(P) 10.6\]
In view of the wide-ranging biological activity of the α-aminophosphonates and α-aminophosphonic acids, compounds 22a-f were prepared by treating the P(III) precursors 1b-c with urethane followed by an appropriate aldehyde in yields of 30-40%. Compounds 22a and 22d were obtained pure and 22b-c/22e-f in a state of purity ~95%, because of the difficulty in separating them from the α-hydroxyphosphonates (formed via hydrolysis of 1b-c). All these compounds are isolated as isomeric (probably diastereomeric) mixtures that can be distinguished by 31P NMR. This route provides scope for preparing a wide variety of aminophosphonates.

(3) Synthetic Utility of Phosphonates

Synthesis of disubstituted vinyl chlorides and chloro substituted dienes

A comparative study of the efficiency of different bases and solvents in the reaction of α-chloro/bromophosphonates with aldehydes for the Horner-Wadsworth-Emmons (HWE) reaction revealed that the system K$_2$CO$_3$/xylene/reflux gives the best yields of substituted olefins and hence this method was used for the HWE reaction (Scheme 6). Thus we prepared compounds 23a-g, 25a-d by reacting 10a-b, 10d or 11a-b with various aldehydes in the presence of K$_2$CO$_3$ in xylene at 140°C. The E/Z ratio is based on the δ(1H) value for C$_6$H$_4$-OCH$_3$ or C$_6$H$_4$-CH$_3$ protons and the well-separated δ(13C) values for the ipso-carbon. We also extended this method for synthesis of chloro substituted dienes.26a-f (Scheme 7). The identity of 26a has been confirmed by X-ray crystallography.
(4) Formation of phosphonates and pyrophosphates in the reactions of chlorophosphate esters with strong organic bases

The reaction of 6a-b and 7 with DBU in toluene (or THF for 7) resulted in the phosphonate salts 27-29 (rather than the expected phosphoramidate salts with a P-N bond) are the major products. Compounds 27-28 could be isolated as pure solids. In the case of 29, two isomeric products ($\delta$(P) 29.4, 30.0; probably diastereomeric) are formed along with a product that showed a $\delta$(P) of 5.4.
Although DBN is also a dinitrogen base similar to DBU, we did not observe a phosphonate salt in reactions using DBN. The only product that could be isolated in a pure state was the pyrophosphate 30 [δ(P) –31.1]. Even in the reaction using 6b, the analogous pyrophosphate 31 is a major product. In the reaction of 6a with N-methyl imidazole, the pyrophosphate (30%) along with two other peaks is observed in the $^{31}$P NMR. In the analogous reaction of 7 with DBN or N-methyl imidazole, a peak at δ(P) -12.4, ascribable to the pyrophosphate 30, was a major product. A possible rationale for these results is discussed.

Chapter 3 describes the experimental details pertaining to part A.

PART-B

Chapter 4 contains a review of literature on the general features of the Mitsunobu reaction and oxidative addition reactions of cyclodiphosphosph(III)azanes. The results obtained are discussed in Chapter 5.

In connection with the isolation of Mitsunobu intermediates, we reacted cyclodiphosphazanes 2, 3 or 6 with diethyl azodicarboxylate (DEAD)/ diisopropyl azodicarboxylate (DIAD). Rather than the intermediate of type 1 (proposed in the Mitsunobu reaction), we obtained the tautomeric forms 8-11 respectively (Scheme 8); the analogous compound [(CO$_2$-i-Pr)HNN(CO$_2$-i-Pr)](t-BuN)P(µ-N-t-Bu)$_2$POCH$_2$CMe$_2$CH$_2$O[P(µ-N-t-Bu)$_2$PN-t-Bu](N(CO$_2$-i-Pr)-NH(CO$_2$-i-Pr)) (12) was obtained from its P(III) precursor (7). By contrast, the oxo-products 13 or 14 were obtained by starting with their P(III) precursors (4, 5). X-ray structures of 8 and 10-13 confirm these assertions.
When compound 8 is treated with one mole equivalent of 2,2,2-trifluoroethanol, the P(III)-Cl end reacts and the proton from the liberated HCl adds to the nitrogen at P=N-t-butyl end to afford 15 (eq. 1; X-ray). The cation in this compound can be considered to be a protonated form of the betaine (CF$_3$CH$_2$O)P(µ-N-t-Bu)$_2$P$^+$ (NH-t-Bu){N-(CO$_2$-i-Pr)-N¯(CO$_2$-i-Pr)}. This kind of species is one of the intermediates proposed in the Mitsunobu reaction.

We extended this reaction of 8 with the phenols 2,6-Cl$_2$C$_6$H$_3$OH, 2,6-Me$_2$C$_6$H$_3$OH, 2-Me-6-t-BuC$_6$H$_3$OH and 2,6-(t-Bu)$_2$C$_6$H$_3$OH to yield 16-19. An X-
ray structural analysis 16 clearly reveals an additional 2,6-dichlorophenol moiety in the crystal structure. There is a significant change in $^{31}$P NMR chemical shifts when compound 9 is treated with various phenols as well as 2,2,2-trifluoroethanol (but not isopropanol), but attempted crystallization gave back 9 suggesting that the interaction is weak.

Addition of benzoic acid to 9, prepared in situ, produced compound 20 (X-ray); analogous compounds 21–24 also could be obtained similarly. These structures are essentially the type of second stage intermediate proposed in the Mitsunobu reaction. Interestingly, we could effect esterification using the in situ formed analogous compound $(t$-$\text{BuNH})P(\mu\text{-N}-t\text{-Bu})_2P^+[(\text{HN}-t\text{-Bu})\{\text{N-(CO}_2\text{Et)}\text{-N(H)(CO}_2\text{Et)}\}] (\text{II})$; $\delta(P)$ 3.8 and 82.9 with ethanol leading to ethyl 4-nitrobenzoate, 4-NO$_2$C$_6$H$_4$CO$_2$Et (25) (Scheme 9).
Oxidative addition of tetrachloro-1,2-benzoquinone to 9 and 10 leads to the novel compounds 26 and 27, respectively, containing both tetra- and pentacoordinate phosphorus centres. The reaction of 3 with two mole equivalents of o-chloranil gives the bis-cycloaddition product [(Cl₄C₆-1,2-O₂)(t-BuNH)PN-t-Bu]₂ (28) cleanly.

Chapter 6 gives the experimental details pertaining to Chapter 5.