# Synthetic Applications of Dialkyl <br> (Chloromethyl)phosphonates and $\mathbf{N}, \mathbf{N}, \mathbf{N}^{〔}, \mathbf{N}^{\text {}}$-Tetraalkyl(chloromethyl)phosphonic Diamides 

Rachel Waschbüsch, John Carran, Angela Marinetti, Philippe Savignac

## To cite this version:

Rachel Waschbüsch, John Carran, Angela Marinetti, Philippe Savignac. Synthetic Applications of Dialkyl (Chloromethyl)phosphonates and N,N,N‘, ${ }^{6}$-Tetraalkyl(chloromethyl)phosphonic Diamides.
Chemical Reviews, 1997, 97 (8), pp.3401-3424. 10.1021/cr9700078 . hal-03166518

HAL Id: hal-03166518

## https://hal.science/hal-03166518

Submitted on 11 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Synthetic Applications of Dialkyl (Chloromethyl)phosphonates and N,N,N‘, $\mathbf{N}^{\bullet}$-Tetraalkyl(chloromethyl)phosphonic Diamides 

Rachel Waschbüsch, John Carran, Angela Marinetti and Philippe Savignac*

Hétéroatomes et Coordination, URA CNRS 1499, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France.
Tel: [+33] 01693345 79; Fax: [+33] 01693339 90; e-mail: dcph@poly.polytechnique.fr

## Contents

I. Introduction
II. Synthesis of Diethyl Chloromethylphosphonate
III. Diethyl 1-Lithiochloromethylphosphonate : Preparation and Uses

1. Preparation and Stability
2. Reaction with Chlorotrimethylsilane
A. Peterson Reaction
B. Deuteriation
C. Alkylation
3. Reaction with Carbon Tetrachloride / bromide and Further Transformations
A. Reaction with Carbon Tetrachloride
B. Reaction with Carbon Tetrabromide
4. Reaction with Carbonyl Compounds
5. Reaction with Imines
6. Reaction with Carbon Dioxide and Further Transformation
7. Reaction with Esters
8. Reaction with Diethyl Carbonate
9. Reaction with Phosphoryl Chlorides
IV. Diethyl Chloromethylphosphonate : Chlorine Substitution
10. Amino Derivatives
11. Sulfur-containing Derivatives
12. Phosphorus Derivatives
13. Malonate Derivatives
14. Friedel-Crafts Reactions
15. Aromatic Derivatives
16. Radical Reaction
V. Other Chloromethylphosphonic Acid Derivatives
17. 2-Chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane
18. 2-Chloromethyl-2-oxo-4,5-o-phenyl-1,3,2-dioxaphospholane
19. Ylid Chemistry of Diphenyl Chloromethylphosphonate
20. 2-Chloromethyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholane
21. 3-t-Butyl-2-chloromethyl-6,6-dimethyl-2-oxo-1,3,2-oxazaphosphorinane
22. Bis(dimethylamino) Chloromethylphosphonamide
23. 2-Chloromethyl-1,3-dimethyl-2-oxo-1,3,2-diazaphospholane
24. N,N'-Dimethyl-N,N'-(1,2-cyclohexyl) Chloromethylphosphonamide

VI. Conclusion<br>VII. Acknowledgements<br>VIII. References and Notes

## I. Introduction

A number of reviews dealing with phosphonate chemistry have appeared over the years. ${ }^{1}$ Most concern the use of phosphonate stabilized carbanions as olefination reagents in Horner-Wadsworth-Emmons (H.W.E.) reactions. A few deal with specific classes of compounds such as difluoromethyl or vinylphosphonates. This review will emphasize the peculiar properties of $\alpha$-chloro-substituted phosphonates.

Horner-Wadsworth-Emmons reactions were not commonly observed from the chloromethylphosphonate carbanion since the chlorine atom is not a strong enough withdrawing group to induce the cleavage of the P-C bond (see reactions with carbonyl compounds, section III 4). Indeed, most of the chemistry of chloromethylphosphonate $\mathbf{1}$ deals with the cleavage of the carbon-chlorine bond by either a halogen-metal exchange reaction or action of nucleophiles. On the other hand, introduction of functional groups on the carbon bearing both the phosphorus group and chlorine make the P-C bond more labile and Horner-Wadsworth-Emmons reactions can thus occur. In this way, chloromethylphosphonate $\mathbf{1}$ can be used as a reagent for the preparation of a number of functionalized organic substrates such as alkenes or alkynes. To date, the finding of new methods based on these reactions is still of growing interest.

Both the preparation of $\alpha$-substituted phosphonates from chloroalkyl derivatives and their applications to the synthesis of non phosphorylated organic compounds will be highlighted here. We will cover the literature from 1950 to the present date. At first, we shall give a detailed account of the properties of diethyl chloromethylphosphonate $\mathbf{1}$, as the parent compound. Literature reports on the higher analogues will be discussed in the final part of this review.

## II. Synthesis of Diethyl Chloromethylphosphonate

Diethyl chloromethylphosphonate $\mathbf{1}$ is a stable, easy to handle liquid (b.p. $109-110^{\circ} \mathrm{C} /$ $\left.10 \mathrm{mmHg} ; \mathrm{NMR}^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+16.0 \mathrm{ppm}, \mathrm{d}^{20} 1.1992, \mathrm{n}_{\mathrm{D}}{ }^{20} 1.4415\right)$. It is a commercially available (Aldrich, Fluka), but expensive compound. Nevertheless, it is conveniently prepared, on laboratory scale, by ethanolysis of chloromethylphosphonyl dichloride 2 (b.p. 77-78 ${ }^{\circ} \mathrm{C}$ / $\left.10 \mathrm{mmHg} ; \mathrm{NMR}{ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+38.0 \mathrm{ppm}, \mathrm{d}^{20} 1.6361, \mathrm{n}^{20} 1.4978\right)$ which is itself commercially available (Aldrich, Fluka). The Kinnear-Perren reaction between phosphorus trichloride and dichloromethane in the presence of $\mathrm{AlCl}_{3}$ is currently used on laboratory scale for the synthesis of 2 in $85 \%$ yield. ${ }^{2}$ On industrial scale, 2 is synthesised via the hydroxymethylphosphonic acid (obtained by heating phosphorous acid and paraformaldehyde at $100{ }^{\circ} \mathrm{C}$ ). ${ }^{4 \mathrm{a}}$ The so formed 1-hydroxymethylphosphonic acid is converted into 2 under drastic conditions with phosgene $\left(\mathrm{COCl}_{2}\right)$ at $150^{\circ} \mathrm{C}$ in the presence of $\mathrm{Ph}_{3} \mathrm{P}$ as catalyst; yields are almost quantitative. ${ }^{3}$ Thionyl chloride $\left(\mathrm{SOCl}_{2}\right)$ at $55-65{ }^{\circ} \mathrm{C}$ in the presence of pyridine has also been introduced as chlorinating agent but the yield of 2 is lower ( $57 \%)^{4 \mathrm{a}-\mathrm{b}}$ An alternative two step method whereby the phosphorus acid is substituted with phosphorus trichloride can also be used. The mixture of phosphorus trichloride and anhydrous paraformaldehyde is heated at $250^{\circ} \mathrm{C}$ for 10 h in an autoclave to give $\mathbf{2}$ with a maximum yield of $60-65 \%$ (Scheme 1). ${ }^{5}$ Treatment of phosphorus trichloride with excess paraformaldehyde yields 2 and other products such as the bis(chloromethyl) chloromethylphosphonate. 5 d Standard alcoholysis of $\mathbf{2}$ with ethanol in anhydrous conditions yields diethyl chloromethylphosphonate 1.





## Scheme 1.

Diester homologues of $\mathbf{1}$ are obtained from chloromethylphosphonyl dichloride $\mathbf{2}$ by alcoholysis in THF or $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The quenching alcohol can be simply added pure and the resulting hydrogen chloride removed with a stream of dry air or under vacuum, however the addition of a tertiary amine remains the most widely used method. The direct addition of sodium alcoholates is also a useful synthetic method (Scheme 2 and Table 1). Formation of organosilicon esters from $\mathbf{2}$ is not usual, it occurs via the reaction of trialkylsilanol acetates and $\mathbf{2}$ with continuous removal of the acetyl chloride formed by distillation. ${ }^{6}$


Scheme 2.

Table 1. Reactions of 2 with alcohols

| $\mathrm{R}^{1} \mathrm{OH}$ | Yield (\%) | Ref. |
| :---: | :---: | :---: |
| methanol | 66 or 90 | 7 or 8, 9 |
| ethanol | 72-95 | 5c, 7, 8, 10-14 |
| 1-chloro-2-ethanol | 66 or 72 | 5 f or 15 |
| 2-ethylsulfanyl-ethanol | 32 | 16 |
| 2-2'-(5'-vinylpyridyl)-ethanol |  | 17 |
| 1,1,1-trichloro-2-ethanol | 59 or 90 | 5 f or 11 |
| 1,1,1-trifluoro-2-ethanol | 92 | 11 |
| 2-morpholino-ethanol | 76 | 18 |
| $n$-propanol | 82 | 19 |
| isopropanol | 74-79 or 85 | $8,14,20$ or 11 |
| butanol | 55-94 | 8,20,21 |
| isopentanol | 79 | 20 |
| 4-hydroxy-2,2,6,6-tetramethyl- | 97 | 22 |
| piperidinoxide |  |  |
| n-pentanol, hexanol, nonanol, |  | 19 |
| decanol, 6-methylheptanol |  |  |
| 2-ethyl-hexanol | 94-99 | 19, 9 |
| octanol | 51 | 23 |
| ethanediol | 63 | 24 |
| 1,2-propanediol | 81 | 24 |
| 1,3-propanediol | 47 or 94 | 25 |


| 2,2-dimethyl-1,3-propanediol | 42 or 93 | 26 or $27,11,28$ |
| :--- | :---: | :---: |
| pentaerythritol | 77 | 29 |
| 1,4-butanediol | 42 | 30 |
| vinyl alcohol | 35 | 31 |
| allyl alcohol | 60 or 78 or 92 | 20,32 or 13 or 11 |
| 3-hydroxy-1-propyne | 73 | 33 |
| phenol | $77-96$ | $9,34,7,35,5 f$ |
| 4-chlorophenol | 80 | $36,5 f$ |
| 2-chlorophenol | 87 | 37 |
| 4-methylphenol (cresol) | $74-77$ | $7,9,38$ |
| 4-tertiobutylphenol | 90 | 37 |
| pyrocatechol |  | 39 |

Compound $\mathbf{1}$ is also prepared by selective and successive chemical or electrochemical reduction of two chlorine atoms of the readily available diethyl trichloromethylphosphonate. The chemical procedure involves the double exchange of chlorine with $n$-butyllithium in the presence of chlorotrimethylsilane as protecting group (Scheme 3). After treatment, $\mathbf{1}$ is obtained in almost quantitative yield. ${ }^{40}$ The electrochemical reduction of diethyl trichloromethylphosphonate was successfully applied to the synthesis of diethyl chloromethylphosphonate $\mathbf{1}$ on preparative scale. ${ }^{41}$ It was formed with a small amount of diethyl dichloromethylphosphonate (less than $10 \%$ ), and was obtained in pure form and good yield ( $80 \%$ ) after distillation. This electrochemical method can compete with chemical reduction and is currently of increasing use. ${ }^{42,43}$


## Scheme 3.

## III. Diethyl 1-Lithiochloromethylphosphonate : Preparation and Uses

Several phosphonate derivatives owe their use to the ease of formation of a carbanion in $\alpha$ to phosphorus. Similarly, by abstraction of a proton of the methylene group with a lithiated base, $\mathbf{1}$ forms the 1 -lithiochloromethylphosphonate $\mathbf{3}$ which has wide applications. It has been shown, by application of known carbanionic reactions to $\mathbf{3}$ (Scheme 4), that it is a good nucleophile useful in providing several functionalised phosphonates with or without a chlorine atom on the $\alpha$-carbon.



Scheme 4.

## 1. Preparation and Stability

In THF at low temperature, $n$-butyllithium, $s$-butyllithium and lithium diisopropylamide (LDA) cleanly abstract a proton from the methylene group of $\mathbf{1}$ to give a quantitative yield of 1-lithiochloromethylphosphonate $\mathbf{3}$ (Scheme 5). Compound $\mathbf{1}$ is not very sensitive to the structure of these lithiated reagents and no significant effect on the nature of the reaction products has been observed. By contrast $t$-butyllithium gives in part $\mathrm{H} / \mathrm{Li}$ and Cl / Li exchanges resulting in a mixture of $\mathbf{3}(90 \%)$ and diethyl 1-lithiomethylphosphonate ( 10 $\%$ ). Generated under these conditions, $\mathbf{3}$ is stable exclusively at low temperature. An $\alpha$ elimination is probably accomplished thermally producing chlorocarbene or diethyl phosphonocarbene in which the leaving group would be the diethyl phosphite or the chloride anion respectively. Complete reaction of $\mathbf{3}$ is often handicapped by its instability but this disadvantage can be overcome on generation of $\mathbf{3}$ from $\mathbf{1}$ and two equivalents of LDA. The first equivalent of LDA deprotonates the methylene group to give $\mathbf{3}$, while the second equivalent participates in the stabilisation of the carbanionic species by steric interaction between the phosphoryl group and the hindered amide. Under these conditions $\mathbf{3}$ can be kept at $0{ }^{\circ} \mathrm{C}$ (NMR ${ }^{31} \mathrm{P}$ (THF) $\delta=+45.3 \mathrm{ppm}$ ) for 30 min without apparent degradation. ${ }^{44}$ The effect of hindered amides on the thermal stability of $\alpha$-phosphorylated carbanions has also been observed with other lithiochloromethyl- and lithioalkylphosphonate carbanions.


## Scheme 5.

## 2. Reaction with Chlorotrimethylsilane

At low temperature, 3 reacts readily and quantitatively with TMSCl to give the monosilylated compound only. When the reaction between $\mathbf{1}$ and TMSCl was accomplished at low temperature in the presence of two equivalents of lithiated reagent ( $n-\mathrm{BuLi}$ or LDA), the 1-lithiochloro(trimethylsilyl)methylphosphonate 4 was obtained directly (Scheme 6). ${ }^{40}$ The trimethylsilyl group has been shown to be useful as a directing group (Peterson reaction) as well as a protecting group for further reactions.


## Scheme 6.

## A. Peterson Reaction

When 1-lithiochloro(trimethylsilyl)methylphosphonate 4 reacted with carbonyl compounds, an unambiguous preference of a Peterson over a Horner-Wadsworth-Emmons reaction was observed. In this case the trimethylsilyl group acts as a directing group. Thus, vinylphosphonates 5 are formed from $\mathbf{4}$ and aldehydes or ketones by elimination of trimethylsilanolate. Usually mixtures of the E and Z isomers are obtained (Scheme 7). ${ }^{45}$ This method of converting carbonyl to vinyl groups is an efficient approach for preparing both isomers of vinylphosphonates 5. The alternative approach to 5, the Horner-WadsworthEmmons reaction using 1-lithiochloromethylenebisphosphonates 50 (see section III 9), affords selectively the Z isomer. ${ }^{46}$


## Scheme 7.

When the carbonyl compound is an aromatic or heteroaromatic aldehyde, 1-alkynylphosphonates 6 are obtained in high yield ( $87-96 \%$ ) from 1-chlorovinylphosphonates (E+Z) $\mathbf{5}$ in a one pot process by treatment at low temperature with LiHMDS or LDA and subsequent elimination (syn and anti) of LiCl (Scheme 8). ${ }^{47}$ Compounds 6 are difficult to obtain by other methods. ${ }^{48}$


## Scheme 8.

The Peterson reaction also provides a route to phosphorylated sulfines by reaction of 4 with $\mathrm{SO}_{2}$. Compound $\mathbf{7}$ is rather unstable and was converted into a [4+2] cycloadduct $\mathbf{8}$ by Diels-Alder reaction with 2,3-dimethylbutadiene (Scheme 9).49


## Scheme 9

## B. Deuteriation

Conditions have been devised to produce 1,1-dideuteriated diethyl chloromethylphosphonate 9. These involve the deuteriation and desilylation under basic conditions of the thermally stable 1 -lithiochloro(trimethylsilyl)methylphosphonate 4 . Trapping this carbanion at low temperature with $\mathrm{D}_{2} \mathrm{O}$ generates LiOD in the reaction medium which promotes the elimination of the protecting trimethylsilyl group by nucleophilic attack on the silicon atom. This process provides access to 1,1-dideuteriated chloromethylphosphonate 9 in nearly quantitative yield and with high incorporation of deuterium ( $\mathrm{D} \%>95$ ). ${ }^{50}$ Trapping of the carbanion 4 with formic acid followed by removal of the trimethylsilyl group with LiOD / $\mathrm{D}_{2} \mathrm{O}$ provides access to monodeuteriated diethyl chloromethylphosphonate $\mathbf{1 0}$ (Scheme 10). ${ }^{40}$


Scheme 10.

## C. Alkylation

Formation of diethyl chloroalkylphosphonates $\mathbf{1 2}$ by direct alkylation of the lithiated reagent $\mathbf{3}$ with alkyl halides is not recommended. The acid-base equilibrium between $\mathbf{3}$ and $\mathbf{1 2}$ induces competing side formation of dialkylated products which renders this route not applicable on a preparative scale. By contrast the 1-lithiochloro(trimethylsilyl)methylphosphonate $\mathbf{4}$ in THF at low temperature is particularly well suited to the alkylation reaction. The trimethylsilyl group acts as a protecting group and desilylation of the adducts can be easily conducted under basic conditions with $\mathrm{LiOH} / \mathrm{H}_{2} \mathrm{O}$ in THF or with LiOEt or NaOEt in ethanol to give pure diethyl chloroalkylphosphonates $\mathbf{1 2}$ in high yield (Scheme 11). ${ }^{40}$



## Scheme 11.

Prior to elimination of the trimethylsilyl group the intermediates $\mathbf{1 1}$ can undergo at low temperature a halogen-metal exchange reaction to give the 1 -lithio(trimethylsilyl)alkylphosphonates. These react with dibromoethane at a temperature lower than $-80^{\circ} \mathrm{C}$ to produce pure diethyl bromo(trimethylsilyl)alkylphosphonates $\mathbf{1 3}$ by a new halogen-metal exchange reaction. The trimethylsilyl group is eliminated under the same conditions as for chlorinated compounds $\mathbf{1 1}$ to give pure diethyl bromoalkylphosphonates $\mathbf{1 4}$ in good yield (Scheme 12). ${ }^{40}$



## Scheme 12.

## 3. Reaction with Carbon Tetrachloride / bromide and Further Transformations

## A. Reaction with Carbon Tetrachloride

The lithiated reagent $\mathbf{3}$ abstracts a chlorine atom from carbon tetrachloride to produce, in a clean reaction, the transient diethyl 1,1-dichloromethylphosphonate $\mathbf{1 5}$ which is sufficiently acidic to undergo a hydrogen-lithium exchange with trichloromethyllithium generated in the reaction medium. The thus obtained 1-lithiodichloromethylphosphonate $\mathbf{1 6}$ is a carbenoid species capable of undergoing ambiphilic reactions depending on the temperature. At low temperature $\left(-100^{\circ} \mathrm{C}\right)$ where the carbon-lithium bond has mainly covalent character, $\mathbf{1 6}$ behaves as an ordinary nucleophile and reacts with various electrophiles to give
the expected products of alkylation (17) or olefination (18, Scheme 13). At higher temperature $\left(-70{ }^{\circ} \mathrm{C}\right)$, due to metal-assisted ionization, $\mathbf{1 6}$ behaves as an electrophile and as such it can react, for example, with lithium salts $(\mathrm{LiBr})$ added to the reaction medium to give 1 lithiobromochloro 22 and 1-lithiodibromomethylphosphonate 23. At higher temperatures, 16 undergoes $\alpha$-elimination and is converted to a carbene.
Thus as nucleophile 16 reacts at low temperature with alkyliodides and activated alkyl bromide to give in high yields diethyl 1,1-dichloroalkylphosphonates $\mathbf{1 7 , 5 1}$ it also reacts smoothly with aldehydes and ketones to give gem-dichloroolefins $\mathbf{1 8}$ through a Horner-Wadsworth-Emmons reaction (Scheme 13). ${ }^{52}$ A large variety of carbonyl compounds can participate in the reaction, such as aliphatic and aromatic aldehydes, cyclic ketones, sterically hindered ketones, enolizable ketones, conjugated ketones, etc. Examples of this are shown in Table 2.


## Scheme 13.

Table 2. Gem-dichloroolefins from H-W-E reactions of 16
Dichloroolefin 18 Yield (\%) Ref
(

$62^{*}$ 52


| $\mathrm{R}=\mathrm{H}$ | 77 | 52 |
| :--- | :--- | :--- |
| $\mathrm{R}=\mathrm{Me}$ | 78 | 52 |



7152


8452


70 52


88 52


90


80*
52


70 52



78 53


80 53

$\mathrm{R}=\mathrm{H}$
$82^{*}$
$\mathrm{R}=\mathrm{Me} \quad 90$53


7953


$\mathrm{R}=\mathrm{C}_{6} \mathrm{H}_{5}$
80
53
$R=M e$
65


10


7053
(



73
53


84
$84^{*} \quad 53$


5855

Purified on alumina, not distilled

The chlorination reaction described in Scheme 13 has been applied to the large scale synthesis of diethyl dichloromethylphosphonate 15 (the use of lithium salts, LiCl and LiBr , increases stability of the lithium intermediate $\mathbf{1 6}$ and increases yields of $\mathbf{1 5}$ up to $60-90 \%$ ). ${ }^{56}$, 57 On preparative scale chlorination of carbanion $\mathbf{3}$ can also be effected with diethyl trichloromethylphosphonate to give $\mathbf{1 5}$ in an efficient reaction and respectable yield (80$86 \%) .{ }^{56}$ However, a recently reported procedure offers a safer, more efficient route to $\mathbf{1 5}$ via the Grignard reagent obtained from diethyl trichloromethylphosphonate and magnesium isopropylchloride. ${ }^{58,59}$ In addition to their use in gem-dichloroolefins formation, $\mathbf{1 5}$ and $\mathbf{1 7}$ have further synthetic applications. Conversion to dichlorophosphines 19 followed by vacuum gas-solid HCl elimination (VGSR) provides a route to non-stabilized phosphaalkynes 20 which have been illustrated by the synthesis of series of derivatives. ${ }^{60}$ Compound $\mathbf{1 5}$ on reaction with diaromatic ketones is also an efficient precursor of symmetrical or unsymmetrical diarylacetylenes through the Fritsch-Buttenberg-Wiechell rearrangement (Scheme 14). ${ }^{61}$




18

Scheme 14.

|  |  |  |
| :---: | :---: | :---: |
| $\begin{gathered} 2 n \text {-BuLi } \\ -78 \text { to } 0^{\circ} \mathrm{C} \end{gathered}$ |  |  |
| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | Yield (\%) |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 95 |
| $p-\mathrm{MeC}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 93 |
| $p-\mathrm{MeOC}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 88 |
| $p-\mathrm{FC}_{6} \mathrm{H}_{4}$ | $p-\mathrm{FC}_{6} \mathrm{H}$ | 89 |
| $p-\mathrm{MeOC}_{6} \mathrm{H}_{4}$ | $p$-MeO | $\mathrm{H}_{4} 86$ |

## B. Reaction with Carbon Tetrabromide

The lithium reagent $\mathbf{3}$ abstracts one bromine atom in tetrabromomethane to produce the transient diethyl 1-bromo-1-chloromethylphosphonate 21 which in turn is deprotonated by the tribromomethyllithium generated in the reaction medium to give the 1-lithio-1-bromo-1-chloromethylphosphonate $\mathbf{2 2}$. In the presence of lithium bromide in large excess, 22 formally undergoes a chlorine-bromine exchange to produce the 1 -lithio-1,1-dibromomethylphosphonate 23. This lithium reagent is an excellent precursor to gem-dibromoolefins $\mathbf{2 4}$ via the Horner-Wadsworth-Emmons reaction (Scheme 15, Table 3). ${ }^{62} \mathrm{gem}$-Dibromoolefins are used as source of alkynes (Fritsch-Buttenberg-Wiechell reaction). ${ }^{63}$ On acidic hydrolysis, 23 gives the diethyl dibromomethylphosphonate $\mathbf{2 5}$ in 80-90 \% yield.

## Scheme 15.




 25

Table 3. Gem-dibromoolefins from H-W-E reactions
Dibromoolefin $24 \quad$ Yield (\%) Ref.

|  |  |  | 64 |
| :---: | :---: | :---: | :---: |
| R | $\mathrm{R}=\mathrm{H}$ |  | 64 |
|  | $\mathrm{R}=\mathrm{Me}$ | 53 | 62 |
|  |  | 70 | 62 |
|  | $\mathrm{R}=\mathrm{H}$ | 45 | 62 |
|  | $\mathrm{R}=\mathrm{Me}$ | 61 | 62 |
|  |  | 67 | 62 |
|  | $\mathrm{R}=\left(\mathrm{CH}_{2}\right)_{5} \mathrm{OPv}$ |  | 63 d |
|  | $\mathrm{R}=\mathrm{C}_{8} \mathrm{H}_{17}$ |  | 63c, d |
|  | $\mathrm{R}=\mathrm{C}_{6} \mathrm{H}_{5}$ | 50 | 62 |




| $\mathrm{R}=\left(\mathrm{CH}_{2}\right)_{3} \mathrm{OBz}$ | 63 d |
| :--- | :--- |
| $\mathrm{R}=\mathrm{C}_{8} \mathrm{H}_{17}$ | 63 c |
| $\mathrm{R}=\mathrm{C}_{6} \mathrm{H}_{13}$ | 63 c |
| $\mathrm{R}=\mathrm{C}_{6} \mathrm{H}_{5}$ | 40 |



63 c



50
62


61
62

## 4. Reaction with Carbonyl Compounds

A solution of $\mathbf{3}$ in THF at low temperature reacts with carbonyl compounds to give an intermediate chlorohydrin 26, stable under the reaction conditions. On heating, elimination of lithium chloride occurs to form the epoxyphosphorus derivatives 27 without side reactions (Darzens procedure). Formation of the chloroalkene via a Horner-Wadsworth-Emmons type rearrangement is never observed. The reaction is well suited to either aliphatic and aromatic aldehydes or ketones. Even sterically hindered or readily enolizable ketones react generally in good yield (Scheme 16, Table 4). ${ }^{65}$ Several other metallic derivatives of diethyl chloromethylphosphonate $\mathbf{1}$, including sodium or potassium, have been reported to provide access to epoxyphosphonates, however they are not particularly effective for this method and the reaction remains synthetically limited. ${ }^{66} \mathrm{~A}$ useful supplement to the Darzens condensation, applicable to aliphatic aldehydes, has been used to convert $\mathbf{1}$ into phosphonomycin. ${ }^{67}$


Scheme 16.
27
Table 4. 1,2-Epoxyalkylphosphonates 2765

| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | Yield (\%) |
| :---: | :---: | :---: |
| Me | Me | 80 |
| Et | Et | 89 |
| $i$-Pr | $i$-Pr | 88 |
| Me | Et | 85 |
| Me | $i-\mathrm{Pr}$ | 86 |
| Me | $t-\mathrm{Bu}$ | 75 |
| Me | $i-\mathrm{Bu}$ | 81 |
| Me | $-\mathrm{CH}=\mathrm{CH}_{2}$ | 36 |
| Me | $-\mathrm{C}(\mathrm{Me})=\mathrm{CH}_{2}$ | 75 |
| Me | $-\mathrm{CH}(\mathrm{OMe})_{2}$ | 76 |
| Me | $c y c l o-\mathrm{Pr}$ | 90 |
| Me | $\mathrm{C} 6 \mathrm{H}_{5}$ | 51 |
| H | Me | 65 |
| H | $i-\mathrm{Pr}$ | 66 |
| H | $i-\mathrm{Bu}$ | 56 |

This method of converting carbonyl compounds to epoxyphosphonates 27 has been extended to a large variety of acyclic and cyclic ketones, which lead to 2,2-disubstituted derivatives. Epoxyphosphonates 27 are well suited starting materials for the preparation of 1,1-disubstituted 1-formylmethylphosphonates $\mathbf{2 8} .{ }^{68}$ Lewis acids, especially $\mathrm{BF}_{3} \cdot \mathrm{Et}_{2} \mathrm{O}$, are effective catalysts in the rearrangement of epoxyphosphonates 27 into 1,1-disubstituted 1 -formylmethylphosphonates $\mathbf{2 8}$. The $[1,2]$ transfer of the phosphorus moiety is conducted in dichloromethane with high selectivity and in good yield (Scheme 17, Table 5)..$^{69}$


Scheme 17.
Table 5. 1-Formylphosphonates $28{ }^{69}$

| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | Yield (\%) |
| :---: | :---: | :---: |
| Me | Me | 76 |
| Me | Et | 78 |
| $i$-Pr | Me | 75 |
| Me | $n$-Pr | 75 |
| $c y c l o-\mathrm{Pr}$ | Me | 72 |
| $t$-Bu | Me | 62 |
| Me | $n$-Pent | 68 |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | Me | $6868 \mathrm{a}, 69$ |
| Et | Et | 78 |


| $n-\mathrm{Pr}$ | $n-\mathrm{Pr}$ | 75 |
| :---: | :---: | :---: |
| $i-\operatorname{Pr}$ | $i-\operatorname{Pr}$ | 76 |
| $i$-Bu | $i$-Bu | 76 |
|  |  | 25 |
|  |  | 61 |
|  |  | 71 |
|  |  | 60 |

Side reactions do not usually occur except with cyclic ketones which undergo a competing proton migration and consequently give a mixture of 1,1 -disubstituted formylphosphonates 28 and 1-hydroxyallylphosphonates 29 (Scheme 18). ${ }^{69}$


## Scheme 18.

A further application of the reaction between $\mathbf{3}$ and carbonyl compounds is the synthesis of $\beta$-ketophosphonates $\mathbf{3 2}$ when the intermediate chlorohydrin $\mathbf{3 0}$ issued from $\mathbf{3}$ and an aldehyde ( $\mathrm{R}=$ aliphatic, aromatic or heteroaromatic) is treated at low temperature with excess LDA ( 2.2 equiv.). Under these conditions 30 undergoes deprotonation and subsequent elimination of lithium chloride to provide selectively the lithio phosphonoenolate $\mathbf{3 1}$ in its stable chelate form. Under acidic conditions 31 gives the synthetically useful $\beta$ ketophosphonates 32. The overall result is that diethyl 1-lithio-1-chloromethylphosphonate $\mathbf{3}$ allows the direct phosphonomethylation of a large variety of alkyl and aryl aldehydes under advantageous experimental conditions and in good overall yield (Scheme 19, Table 6). 70



Scheme 19.
32

Table 6. 2-Oxoalkylphosphonates 3270

| R | Yield (\%) |
| :---: | :---: |
| $i-\operatorname{Pr}$ | 89 |
| $i$-Bu | 90 |
| $n-\mathrm{Bu}$ | 92 |
| $n$-Hept | 88 |
| $\mathrm{Me}-\mathrm{CH}=\mathrm{CH}$ | $85^{\text {a }}$ |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | $41^{\text {c }}$ |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | 68 |
| 4-Cl- $\mathrm{C}_{6} \mathrm{H}_{4}$ | $40^{\text {c }}$ |
| 4-MeO-C6 $\mathrm{H}_{4}$ | 70 |
|  | 65 |
| 4-(Me) $2^{\text {N }}$ - $\mathrm{C}_{6} \mathrm{H}_{4}$ | $76^{\text {b }}$ |
| 2-thienyl | 72 |
| a Polymerises on distillation <br> b Product partially polymerised <br> c Base used $=n$-BuLi |  |

## 5. Reaction with Imines

Reaction of $\mathbf{3}$ with aryl imines leads to the lithiated intermediate $\mathbf{3 3}$ which on elimination of LiCl cyclise to give the aziridines $\mathbf{3 4}$ in moderate to good yield. Elimination of the chlorine atom is preferred with respect to Horner-Wadsworth-Emmons reaction, presumably due to entropic considerations. Significant stereochemical control of the reaction is observed, the syn isomer of the aziridine 34 is mainly formed and represents 80 to $100 \%$ of the final product (Scheme 20, Table 7)..$^{71}$



Scheme 20.
Table 7.1,2-Aziridinealkylphosphonates 3471

| $\mathrm{Ar}^{1}$ | $\mathrm{Ar}^{2}$ | Yield (\%) |
| :---: | :---: | :---: |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 85 |
| $3-\mathrm{Cl}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 30 |
| 4-Cl-C6 $\mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 95 |
| 3- $\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 67 |
| 4- $\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 51 |
| $3-\mathrm{Me}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 70 |
|  | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 94 |
| 4-MeO-C6 $\mathrm{H}_{4}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 53 |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | $4-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 80 |

## 6. Reaction with Carbon Dioxide and Further Transformation

Chlorocarboxymethylphosphonate 35 was first obtained as a crystalline compound from the reaction of $\mathbf{3}$ with carbon dioxide. In order to prevent any acid-base equilibrum on the formation of $\mathbf{3 5}$ it is important to quench a THF solution of $\mathbf{3}$ with dry ice in large excess in diethyl ether followed by treatment under acidic conditions. The dilithiated reagent $\mathbf{3 6}$ is a useful precursor for the conversion of carbonyl compounds into $\alpha$-chloroacrylic acids $\mathbf{3 7}$ via a Horner-Wadsworth-Emmons type reaction (Scheme 21). ${ }^{72}$ There is a stereochemical preference for production of the Z isomer with aromatic and heteroaromatic aldehydes whereas both Z and E isomers are produced with aliphatic aldehydes and ketones (Table 8).



Scheme 21.
Table 8. $\alpha$-Chloroacrylic acids 3772

| $\mathrm{R}^{1}$ | $\mathrm{R}^{2}$ | Isomer | Yield (\%) |
| :---: | :---: | :---: | :---: |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | H | Z | 67 |
| 2-MeO-C6 $\mathrm{H}_{4}$ | H | Z | 83 |
| $4-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | H | Z | 83 |
| 4-(Me) $2^{\text {N }}$ - $\mathrm{C}_{6} \mathrm{H}_{4}$ | H | Z | 86 |
| $4-\mathrm{Cl}-\mathrm{C}_{6} \mathrm{H}_{4}$ | H | Z | 86 |
|  | H | Z | 91 |
| 3-pyridyl | H | Z | 41 |
| 2-thiophenyl | H | E+Z | 85 |
| $\mathrm{C}_{6} \mathrm{H}_{5}-\mathrm{CH}=\mathrm{CH}-$ | H | E+Z | 96 |


| $\mathrm{C}_{6} \mathrm{H}_{5}$ | Me | $\mathrm{E}+\mathrm{Z}$ | 65 |
| :---: | :---: | :---: | :---: |
| $\mathrm{Me}\left(\mathrm{CH}_{2}\right)_{3}$ | H | $\mathrm{E}+\mathrm{Z}$ | 88 |
| $(\mathrm{Me})_{2} \mathrm{CH}$ | H | $\mathrm{E}+\mathrm{Z}$ | 91 |
| $(\mathrm{Me})_{2} \mathrm{CH}-\mathrm{CH}_{2}$ | H | $\mathrm{E}+\mathrm{Z}$ | 85 |
| Et | Me | $\mathrm{E}+\mathrm{Z}$ | 80 |
| $(\mathrm{Me})_{2} \mathrm{CH}$ | Me | $\mathrm{E}+\mathrm{Z}$ | 45 |
| $(\mathrm{Me})_{2} \mathrm{C}=\mathrm{CH}\left(\mathrm{CH}_{2}\right)_{2}$ | Me | $\mathrm{E}+\mathrm{Z}$ | 84 |

In addition to its use in the formation of $\alpha$-chloroacrylic acids, $\mathbf{3 5}$ is a valuable synthetic intermediate for several other purposes, for example, direct conversion of $\mathbf{3 5}$ into the carboxylic acid chloride $\mathbf{3 8}$ is achieved in quantitative yield by treatment with sulfuryl or thionyl chloride in dichloromethane at room temperature (Scheme 22). ${ }^{73,74}$ However, sulfuryl chloride is much less selective than thionyl choride for the conversion of the carboxylic acid into its acid chloride, and it can also chlorinate the carbon in $\alpha$ to the phosphorus atom. ${ }^{75}$ The crude carboxylic acid chloride $\mathbf{3 8}$ is used for further transformations, because it decomposes on distillation.


## Scheme 22.

Diethyl chloroketylphosphonate 39 is the product formed when the carboxylic acid chloride 38 is treated with triethylamine or pyridine in ether at $-40^{\circ} \mathrm{C}$ (Scheme 23). ${ }^{76} \mathrm{At}$ room temperature the ketene solution gradually darkens indicating its instability. However, $\mathbf{3 9}$ has been trapped in situ and converted to series of cycloadducts such as cyclobutanone $\mathbf{4 0}$ or $\beta$ lactam 41.


## Scheme 23.






Thioesters $\mathbf{4 2}$ were obtained by reaction of $\mathbf{3 8}$ with thiols in dichloromethane at room temperature in the presence of triethylamine (Scheme 24). In this way the thioates $\mathbf{4 2}$ were isolated in $95 \%$ crude yield ( $32 \%$ after column chromatography). ${ }^{77}$ These derivatives are valuable synthetic intermediates, sufficiently pure for subsequent use without purification.


## Scheme 24.

An almost quantitative yield of $\mathbf{4 3}$ results from reaction of $\mathbf{3 8}$ with sodium azide in biphasic medium ( $\mathrm{Et}_{2} \mathrm{O} / \mathrm{H}_{2} \mathrm{O}$ ). This offers the advantages of mild conditions and thus provides a convenient preparation of acylazide $\mathbf{4 3}$ in $89 \%$ yield. On heating in refluxing benzene, $\mathbf{4 3}$ undergoes a Curtius rearrangement into isocyanate $\mathbf{4 4}$ in $88 \%$ yield (Scheme 25). ${ }^{74}$ An early reported preparation of 44 used a Michaelis-Arbuzov reaction between triethylphosphite and dichloromethyl isocyanate, but the yield of pure diethyl 1chloromethylisocyanate $\mathbf{4 4}$ did not exceed 10-15 \%.78



## 7. Reaction with Esters

The lithium reagent $\mathbf{3}$ in the presence of one equivalent of LDA selectively attacks the carbonyl group of carboxylic esters and analogues to produce the lithio chloroenolates $\mathbf{4 5}$. In most cases, chelates $\mathbf{4 5}$ which are highly stabilised do not undergo Horner-WadsworthEmmons reactions with carbonyl compounds. Acidic hydrolysis of these enolates gives the 1-chloro-2-oxoalkylphosphonates 46 a-h which are isolated in high yields (Scheme 26 and Table 9). ${ }^{79,80}$ This reaction can easily be used to provide a large scale conversion of various carboxylic esters into 1-chloro-2 oxoalkylphosphonates 46 a-d.

These compounds ( $\mathbf{4 6} \mathbf{~ a - d}$ ) can also be obtained from the lithiated derivative of diethyl trichloromethylphosphonate in reaction with acid chlorides. This occurs via a halogen-metal exchange reaction at $-125^{\circ} \mathrm{C}$ in a THF / diethyl ether mixture in moderate to good yield. ${ }^{81}$ This route is analogous to that reported for the synthesis of triethyl 1chloromethylphosphonocarboxylate 49 (Scheme 29).



Scheme 26.

Table 9. 1-Chloro-2-oxoalkylphosphonates 46

| $\mathbf{4 6}$ | R | $\mathrm{Yield}(\%)$ | Ref. |
| :---: | :---: | :---: | :---: |
| $\mathbf{a}$ | Me | 82 | 79 |
| $\mathbf{b}$ | Et | 81 | 79 |
| $\mathbf{c}$ | $\left(\mathrm{CH}_{2}\right)_{4} \mathrm{Me}$ | 75 | 79 |
| $\mathbf{d}$ | $\mathrm{C}_{6} \mathrm{H}_{5}$ | 72 | 79 |
| e | $\mathrm{CO}_{2} \mathrm{Et}$ | 76 | 79,80 |
| $\mathbf{f}$ | $\mathrm{CO}_{2}-i-\mathrm{Pr}$ | 40 | 79,80 |
| $\mathbf{g}$ | $\mathrm{CH}_{(\mathrm{OEt})_{2}}$ | 81 | 79 |
| $\mathbf{h}$ | H | 85 | 79,82 |

Reaction of $\mathbf{3}$ with ethyl or isopropyl oxalate provides a convenient preparation of $\alpha$ chlorinated phosphonopyruvates $\mathbf{4 6} \mathbf{e}$, $\mathbf{f}$. The reaction proceeds in the presence of LDA via the formation of a transient lithio enolate $45\left(\mathrm{R}=\mathrm{CO}_{2} \mathrm{Et}, \mathrm{R}=\mathrm{CO}_{2} i-\mathrm{Pr}\right)$ and without any byproducts (Scheme 26). ${ }^{79,82}$ After acidic hydrolysis the 1 -chloro phosphonopyruvates 46 e, $\mathbf{f}$ are isolated in moderate to good yield (Table 9). With the same process the reaction between $\mathbf{3}$ and ethyloxalatemonoamide gives 1-chloro phosphonopyruvamide ( $38 \%$ ). ${ }^{80}$

In a similar manner, reaction of $\mathbf{3}$ with ethyl diethoxyacetate affords 1-chloro-3,3-diethoxy-2-oxopropylphosphonate $\mathbf{4 6} \mathbf{g}$ in $81 \%$ yield after acidic hydrolysis of the corresponding lithio chelate (Scheme 26). The product is obtained in the keto form only. ${ }^{79}$

Reaction of $\mathbf{3}$ at low temperature with ethyl formate, or DMF, produces in high yield the synthetically useful 1-chloro-2-oxoethylphosphonate $\mathbf{4 6} \mathbf{h}$ (Scheme 26), an excellent precursor to imino or enaminophosphonates. This water soluble compound exists in keto-enol tautomeric forms (Scheme 27). ${ }^{79,80}$ By a similar procedure the carbanion derived from chloroalkylphosphonates 12 (Scheme 11) reacts with ethyl formate, the most practical formylating agent, to give 1 -formylchloroalkylphosphonates. ${ }^{79}$


Scheme 27.

An alternative procedure for the preparation of the 1-chloro-2-oxoethylphosphonate $\mathbf{4 6} \mathbf{h}$ is the mild selective chlorination of the readily accessible diethyl 2-oxoethylphosphonate with gaseous chlorine in $\mathrm{CCl}_{4}$ in $79 \%$ yield. ${ }^{83}$ This procedure was also used for the preparation of a series of 1-alkyl-1-chloro-1-formylmethylphosphonates. ${ }^{84} \mathrm{~A}$ more recent approach consists in the chlorination of phosphorylated enol ethers in $\mathrm{CCl}_{4}$ at room temperature, followed by hydrolysis of the phosphorylated $\alpha, \beta$-dichloroethers. The resulting hemiacetal decomposes to form $\mathbf{4 6}$ h. ${ }^{85}$

## 8. Reaction with Diethyl Carbonate

Reaction of $\mathbf{3}$ with diethyl carbonate affords the lithio chelated phosphonoenolate 47b by elimination of EtOH from the unstable intermediate 47a. When the reaction of carbanion 3 is performed in the presence of one equivalent of LDA the yield of phosphonoenolate 47b is quantitative, while a maximum yield of $50 \%$ is achieved when no additional LDA is used. Generated in situ, 47b has been used as a source of triethyl $\alpha$-chlorophosphonocarboxylate 49 prepared in $87 \%$ yield or as a precursor to $\alpha$-chloroacrylic ethyl esters 48 in a Horner-Wadsworth-Emmons type reaction with carbonyl compounds. These $\alpha, \beta$-unsaturated esters usually have Z geometry when prepared from aromatic aldehydes or a mixture of Z and E geometries when prepared from aliphatic aldehydes (Scheme 28 and Table 10). ${ }^{86}$


Scheme 28.

Table 10. $\alpha$-Chloroacrylic esters $48{ }^{86}$

| R | $\mathrm{Z} / \mathrm{E}$ ratio | Yield (\%) |
| :---: | :---: | :---: |
| $i-\mathrm{Pr}$ | $60 / 40$ | 33 |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | $100 / 0$ | 75 |
| 2-Cl-C ${ }_{6} \mathrm{H}_{4}$ | $100 / 0$ | 81 |
| 4-Me-C $\mathrm{C}_{4}$ | $100 / 0$ | 44 |
| 4-F- $\mathrm{C}_{6} \mathrm{H}_{4}$ | $100 / 0$ | 62 |
| 2-thiophenyl | $100 / 0$ | 88 |

Of significant synthetic importance is the application of the halogen-metal exchange reaction to the generation of lithiodichloromethylphosphonate from $n$-butyllithium and diethyl trichloromethylphosphonate at $-90^{\circ} \mathrm{C}$ in a mixture of THF / diethyl ether. Trapping with ethylchloroformate provides a convenient and advantageous route to 49 in $80 \%$ yield (Scheme 29). 87 An alternative procedure for the preparation of 49 via a carbanionic pathway is the reaction of ethyl trichloroacetate in THF at room temperature with the sodium carbanion of triethyl phosphonocarboxylate. Despite mild experimental conditions the yield of 49 remains modest ( $52 \%$ ). ${ }^{88}$


## Scheme 29.

The other available synthetic procedures for the preparation of triethyl $\alpha$ chlorophosphonocarboxylate 49 are multi-step procedures. A nearly quantitative yield of triethyl 1,1-dichlorophosphonocarboxylate was obtained from triethylphosphonocarboxylate and sodium hypochlorite at pH 7.1 by moderating the reaction temperature. The subsequent selective reduction of the dichlorophosphonocarboxylate to the corresponding monochloro ester 49 was efficiently accomplished with sodium sulfite (Scheme 30). ${ }^{89}$


49
Scheme 30.

## 9. Reaction with Phosphoryl Chlorides

Condensation of $\mathbf{3}$ with phosphoryl chlorides, in the presence of LDA, results in the lithiochloromethylenebisphosphonate $\mathbf{5 0 . 4 6}$ The intermediate $\mathbf{5 0}$ acts as a phosphonomethylenation reagent in reaction with carbonyl compounds providing an efficient route to vinylphosphonates $\mathbf{5 3}$ of controlled geometry via a Horner-Wadsworth-Emmons reaction (Scheme 31, Table 11). ${ }^{90,91}$ This olefination reaction using $\mathbf{5 0}$ has been found to be the method of choice for preparing Z vinylphosphonates.
The intermediate bisphosphonate $\mathbf{5 0}$ can be a symmetrical or unsymmetrical reagent obtained by condensation of $\mathbf{3}$ with a variety of phosphoryl chlorides including acyclic or cyclic chlorophosphates, chlorophosphoramides, chlorodiphenylphosphine oxide ${ }^{92}$, chlorothiophosphates, etc. In the case of unsymmetrical bisphosphonates, condensation of $\mathbf{5 0}$ with carbonyl compounds is accompanied by the elimination of the more electrophilic phosphorus moiety.


Scheme 31.

Table 11. 1-Chloro-1-vinylphosphonates 53


The chemistry of $\mathbf{5 0}$ also provides novel routes to chloromethylenebisphosphonates $\mathbf{5 1}$ and 52 after either acidic hydrolysis ( HCl 6 M ) (except where $\mathrm{Y}=\mathrm{NMe}_{2}$ ) or reaction with an alkyl halide, respectively. This chemistry is well suited to the preparation of bisphosphonates bearing various substituents on carbon $\left(\mathrm{R}^{3}\right)$ and phosphorus ( Y ) atoms. $90,93,94 \mathrm{a}$ When considering this reaction, it should be noted that formation of methylenebisphosphonates is work-up dependent. On treatment in acidic medium $(\mathrm{HCl} 6 \mathrm{M}) \mathbf{5 1}$ is obtained in moderate to good yield (Table 12). On treatment in basic medium only formation of diethyl chloromethylphosphonate $\mathbf{1}$ and diethylphosphate is observed resulting from total cleavage of a P-C bond by attack of the LiOH on one of the phosphoryl groups. ${ }^{90}$

Table 12.1-Chloromethylenebisphosphonates 5190
Y Yield (\%)
$\mathrm{EtO} \quad 81$

$(\mathrm{Me})_{2} \mathrm{~N}$
53
$\mathrm{C}_{6} \mathrm{H}_{5} \quad 69$

The chloromethylenebisphosphonates $\mathbf{5 1}$ can also be obtained by monodehalogenation of the corresponding dichloromethylenebisphosphonates which are readily prepared by the direct chlorination ${ }^{94}$ of tetraalkyl methylenebisphosphonates with sodium hypochlorite (as in Scheme 30). Positive chlorine abstraction has been observed during the reaction between potassium fluoride and tetraisopropyl dichloromethylenebisphosphonate in the presence of 18-crown-6 ether. This reaction requires seven days for completion and is followed by work-up and chromatography ( $55 \%$ ). ${ }^{95} \mathrm{~A}$ more effective reaction involving chlorine abstraction occurs between tetraethyl dichloromethylenebisphosphonate and $n-\mathrm{BuLi}$ at $-80{ }^{\circ} \mathrm{C}$ followed by hydrolysis with a saturated $\mathrm{NaHCO}_{3}$ solution to yield the monochloromethylphosphonate derivative $\mathbf{5 1}$ in $79 \%$ yield (Scheme 32). ${ }^{96}$



## Scheme 32.

The same result can be achieved by reduction with NaSH at approximately $0{ }^{\circ} \mathrm{C}$, although reductions are particularly sensitive to the nature of the phosphonate esters. Yields are also closely dependent on the reaction temperature used, for example lower temperatures are required for ethyl esters $\left(0^{\circ} \mathrm{C}, 91 \%\right.$ yield; $25^{\circ} \mathrm{C}, 49 \%$ yield) than for isopropyl $\left(0^{\circ} \mathrm{C}, 84 \%\right.$ yield; $25^{\circ} \mathrm{C}, 94 \%$ yield)..$^{97}$ This dehalogenation reaction was also performed using $\mathrm{Na}_{2} \mathrm{SO}_{3}$ as the reducing agent. ${ }^{94 \mathrm{c}, \mathrm{d}} \mathrm{A}$ recently introduced procedure is the selective electrochemical reduction of one chlorine atom of tetraethyl dichloromethylenebisphosphonate which has been accomplished in $70 \%$ yield using a buffered medium. ${ }^{98}$

## IV. Diethyl Chloromethylphosphonate : Chlorine Substitution

Nucleophilic substitution of the chlorine atom in $\mathbf{1}$ with other groups (amines, thiols, phenols, thiophenols) produces several useful derivatives. It is particularly important to note that nucleophilic substitution of the chlorine atom (route a) competes with the direct attack of the nucleophile on the carbon atom of the ester groups resulting in the cleavage of a $\mathrm{C}-\mathrm{O}$ bond (route b) (Scheme 33). However, the undesirable alkylation reaction (route b) can be avoided by using phosphonate esters bearing electron withdrawing groups $\left(\mathrm{R}=\mathrm{CCl}_{3}\right.$ or $\left.\mathrm{CF}_{3}\right) .{ }^{102}$ The attack of the nucleophilic reagent on the ester carbon atom is thus slowed down. Alkylation can also be avoided by using phosphonamides instead of phosphonate esters. ${ }^{99}$


Scheme 33.

## 1. Amino Derivatives

It has been increasingly recognized that a number of aminophosphonic acids structurally related to natural aminocarboxylic acids are able to inhibit or perturb a given metabolic reaction. So it is common to find the introduction of a phosphonic acid group in place of the normal carboxylic acid group.This analogy has induced a lot of work devoted to the nucleophilic amination of $\mathbf{1}$, the aminating agents being $\mathrm{NH}_{4} \mathrm{OH},{ }^{100} \mathrm{R}^{1} \mathrm{R}^{2} \mathrm{NH}^{101}$ or $\mathrm{NaN}_{3} .{ }^{102}$ The first method for the preparation of diethyl aminomethylphosphonate involved the amination of $\mathbf{1}$ with a $25 \%$ aqueous solution of $\mathrm{NH}_{3}$ in a sealed tube at $150{ }^{\circ} \mathrm{C} . .^{100}$ It has been demonstrated that the replacement of Cl by $\mathrm{NH}_{2}$ is more rapid in $\mathrm{H}_{2} \mathrm{O}$ than in absolute ethanol. The only product obtained was 54 ( $45 \%$ yield); 54 treated with aqueous solution of HCl at $120-140{ }^{\circ} \mathrm{C}$ for 3 h gives 55 in $94 \%$ yield (Scheme 34 ). ${ }^{100}$ Other methods for the preparation of $\mathbf{5 5}$ involve the interaction of chloromethylphosphonic acid with $\mathrm{NH}_{4} \mathrm{OH}(25 \mathrm{~h}$ at $100{ }^{\circ} \mathrm{C}$ ), 100 an aqueous solution of methylamine ( 7 h at $150^{\circ} \mathrm{C}$ and 25 bar ), ${ }^{101 \mathrm{a}}$ aniline in excess ( 20 h at $160-170^{\circ} \mathrm{C}$ ), ${ }^{101 \mathrm{~b}}$ hydrazine hydrate ${ }^{101 \mathrm{c}}$ or polymethylenediamines $(20 \mathrm{~h}$ at reflux in water). ${ }^{101 \mathrm{~d}}$ By the reaction of tertiary amines with $\mathbf{1}\left(120-130^{\circ} \mathrm{C}\right.$ for 12 h in a sealed tube) a series of diethoxyphosphinylmethyl trialkylammonium salts were obtained in low yield (15-19 \%). ${ }^{101 e}$


## Scheme 34.

An almost quantitative yield of azidophosphonate results from reaction of bis(trifluoroethyl) chloromethylphosphonate $\mathbf{5 6}$ with sodium azide in DMSO at $90{ }^{\circ} \mathrm{C}$. This reaction offers the advantages of mild conditions and higher yields than those obtained from other dialkylesters issued from 2. Chloromethylphosphonates bearing less attracting groups than the trifluoromethyl lead to increasing $\mathrm{C}-\mathrm{O}$ bond cleavage instead of $\mathrm{C}-\mathrm{Cl}$ cleavage. Reduction of the intermediate azido phosphonate with $\mathrm{H}_{2}$ over $\mathrm{Pd} / \mathrm{C}$ followed by acidic hydrolysis delivers the aminomethylphosphonic acid 59 in $66 \%$ overall yield (Scheme 35). ${ }^{102}$ The process has been applied to the synthesis of 1,1-dideuteriomethylphosphonic acid $\mathbf{6 0}$ ( $55 \%$ overall yield from dideuteriated 56, (\%D)>95). ${ }^{102}$ Azidophosphonamides have been
also prepared from reaction of chloromethylphosphonamide with sodium azide in DMF at $140^{\circ} \mathrm{C} .{ }^{103}$




58

## Scheme 35.

An unsuccessful attempt to prepare the triazole derivatives of $\mathbf{1}$ was by reaction of diethyl chloromethylphosphonate $\mathbf{1}$ with potassium-1H-1,2,4-triazole in DMSO as solvent. Rather 1-ethyl-1H-1,2,4-triazole was isolated in this experiment. ${ }^{104}$

A novel rearrangement involving an intramolecular substitution of the chlorine atom by an aromatic amine has recently been described. When the unsymmetrical phosphonic diamide 61 is treated with alkoxide, loss of a proton from the anilino-group leads to the synthesis of $\mathbf{6 3}$ via a highly reactive three membered ring intermediate 62 (Scheme 36). ${ }^{105 a}$ This reaction has been extended to chlorophosphonamidates in which the N -phenyl group has been replaced by N -alkyl. In this case the reaction can give two products: by P-N cleavage of the three membered ring to give an $\alpha$-aminophosphonate, or by P-C cleavage to give a phosphoramidate. ${ }^{105 b-c}$



## Scheme 36.

## 2. Sulfur-containing Derivatives

Nucleophilic displacements of chlorine in $\mathbf{1}$ by sulfur containing reagents has been well developed. This reaction is of synthetic importance because it gives access to synthetically useful $\alpha$-phosphoryl sulfide derivatives 64. However, full utilization of this reaction is often handicapped by the formation of alkyl sulfide through the dealkylation process. ${ }^{106}$ Reaction of $\mathbf{1}$ with sodium alkyl or aryl mercaptides in boiling ether produces the $\alpha$-phosphoryl sulfides 64 in low to reasonable yield ( $15-58 \%$ ) (Scheme 37). ${ }^{107}$ Recently the reaction has been extended to sodium mercaptoethanol which reacts with $\mathbf{1}$ in boiling THF to give the substitution product in only $40 \%$ yield. ${ }^{108}$ Sodium sulfide $\left(\mathrm{Na}_{2} \mathrm{~S}\right)$ on reaction with compound 1 undergoes a double substitution to provide the corresponding sulfide in low yield (6\%). ${ }^{107}$


Scheme 37

A variation of this reaction with sulfur containing reagents is exemplified by the reaction of $\mathbf{1}$ with dimethyl sulfide. This gives a sulfonium salt which via its ylid is converted into an epoxyphosphonate by reaction with acetaldehyde and thence to phosphonomycin. ${ }^{67}$

phosphonomycin
The reaction between $\mathbf{1}$ and thiourea was also reported. It was found that thiourea in excess at $125-130^{\circ} \mathrm{C}$ without solvent effects both a substitution reaction of the chlorine and a dealkylation reaction of the phosphonate 1 leading to the formation of the salt $\mathbf{6 5}$ as the main product ( $20 \%$, Scheme 38). ${ }^{109}$


## Scheme 38.



## 3. Phosphorus Derivatives

The methylenebisphosphonate 66 is obtained from 1 and sodium diethylphosphite (Scheme 39). Apart from diphosphonate 66, a large quantity of solid products is formed as the result of dealkylation of phosphonate esters $\mathbf{1}$ by sodium dialkyl phosphite, thus the yield of $\mathbf{6 6}$ $(47 \%)^{110}$ is significantly lower than that obtained by other methods.


## Scheme 39.

Reaction of $\mathbf{1}$ with triethylphosphite under drastic conditions ( $190{ }^{\circ} \mathrm{C}$ for 8 h ) affords 66 in $27 \%$ yield, according to a Michaelis-Arbuzov process. ${ }^{111}$ Under analogous conditions, tetraethylpentamethylene-1,5-diphosphonite reacts with 1 to afford the pentamethylene-1,5bis(diethoxyphosphonylmethyl)phosphinates 67 in high yield ( $88 \%$, Scheme 40). ${ }^{112}$ The Michaelis-Arbuzov reaction between $\mathbf{1}$ and the tris(trimethylsilyl)phosphite is also described. ${ }^{113}$



67
Scheme 40.

## 4. Malonate Derivatives

By a similar procedure, compounds containing an activated methylene group react in their anionic form with $\mathbf{1}$ to give substituted derivatives, e.g. sodiomalonate reacts with $\mathbf{1}$ leading to a mixture of ethyl phosphonomalonate 69 and ethyl malonate resulting from a dealkylation of 68. After acidic hydrolysis and decarboxylation, 69 is converted into $\beta$ phosphonopropionic acid 70 (Scheme 41). ${ }^{101 \mathrm{~b}}$


Scheme 41.
5. Friedel-Crafts Reactions

Reaction of 2 with four equivalents of aniline in acetonitrile gives $70 \%$ yield of chloromethylphosphonodianilide 71. Attemps to cyclize $\mathbf{7 1}$ by treatment with $\mathrm{AlCl}_{3}$ at 160 $170{ }^{\circ} \mathrm{C}$ give unidentified polymeric materials probably because of the presence of the secondary nitrogen atom. By contrast, the corresponding N,N'-dimethylphosphonodianilide 72, prepared either by bismethylation of $\mathbf{7 1}$ or by reaction of $\mathbf{2}$ with N -methylaniline, undergoes an intramolecular Friedel-Crafts cyclisation on heating with $\mathrm{AlCl}_{3}$ at $160-170{ }^{\circ} \mathrm{C}$ to give 73 in $63 \%$ yield (Scheme 42). Extension of the cyclization reaction to monoamide derivatives by treatment of 2 with two equivalents of N -methylaniline and $\mathrm{AlCl}_{3}$ was unsuccessful and the starting material recovered. It seems that the propensity for cyclisation is reserved for phosphonodiamides bearing tertiary nitrogen atoms. ${ }^{114}$



## Scheme 42.

## 6. Aromatic Derivatives

A variety of compounds 74 containing a phosphonomethyl group bonded to an aryl group have been prepared in one step from $\mathbf{1}$ and aryl bromides when combined in THF at first with $t$-butyllithium at $-78{ }^{\circ} \mathrm{C}$ and then with cuprous iodide at $0^{\circ} \mathrm{C}$ (Scheme 43). The carboncarbon coupling takes place slowly at room temperature. A series of compounds can be obtained in 56-69 \% overall yield using this process. ${ }^{115}$


Scheme 43.
Table 13. 1-Arylmethylphosphonates 74115

Ar-Br





## 7. Radical Reaction

This new approach to the synthesis of $\gamma$-functionalized phosphonates 76 and $77\left(R^{1}\right.$ or $\mathrm{R}^{2}=$ alkyl, ethoxy, butoxy, acetoxy, acetyl, and cyanide groups) is based on the addition reaction of $\alpha$-phosphorylmethyl radicals to terminal alkenes and alkynes. ${ }^{116}$ The radical species are formed in benzene or toluene from 1-halogenophosphonates, using tin or silicon hydrides as radical sources (Scheme 44). The reaction has been applied to both electron-rich and electron-deficient alkenes and alkynes. Under these conditions the direct generation of the diethoxyphosphonylmethyl radical 75 from diethyl chloromethylphosphonate $\mathbf{1}$ allows moderate yields of functionalized phosphonates 76 and 77 (10-62 \%). The only by-product is diethyl methylphosphonate, which is formed via recombination of the intermediate radical with an hydrogen atom. Thus, this methodology is an alternative to the Michaelis-Abuzov and Michaelis-Becker methods for the synthesis of phosphonates, which suffer from a lack of generality.


## Scheme 44

## V. Other Chloromethylphosphonic Acid Derivatives

Several chloromethylphosphonic acid derivatives, other than 1, have been utilized as synthetic intermediates. The literature concerning their preparation and properties also reports their utility in organic synthesis. The structure of these chloromethylphosphonic acid derivatives plays an important role in determining the outcome of their reactions. The presence
on the phosphorus atom of suitable alkoxy or aminoalkoxy groups promotes specific transformations and allows better stereochemical control of the reactions.

## 1. 2-Chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane

2-Chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane 78 is a stable, easy to handle solid ( $\mathrm{mp} \mathrm{116-118}{ }^{\circ} \mathrm{C}$; NMR ${ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+11.4 \mathrm{ppm}$ ). An early reported preparation of $\mathbf{7 8}$ includes condensation of $\mathbf{2}$ with 2,2-dimethylpropane-1,3-diol in dioxane in the presence of pyridine with a modest yield ( $42 \%$ ). ${ }^{26}$ On laboratory scale, a recently reported synthesis offers an easy and efficient route to $\mathbf{7 8}$ ( $93 \%$ yield) from the same starting materials. The reaction takes place in dichloromethane without base using a vacuum procedure. ${ }^{27}$ The product is soluble in THF, benzene, acetone, ethanol, and water (Scheme 45).


## Scheme 45.

Generation of the lithio derivative of $\mathbf{7 8}$ is accomplished with LDA at low temperature. The carbanion 79 is very unstable and has to be kept at low temperature, however it is stabilized when generated from two equivalents of LDA. This method of generating 79 was found to be preferable to the use of $n-\mathrm{BuLi}$, as $\mathbf{7 9}$ is formed in high yield with LDA with only a trace of by-products. ${ }^{44}$ Metallation of $\mathbf{7 8}$ in the presence of TMSCl gives $\mathbf{8 0}$ as the equatorial conformer ( $\mathrm{NMR}{ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+42.6 \mathrm{ppm}$ ) which is stable at $0{ }^{\circ} \mathrm{C}$ (Scheme 46). Other silyl chlorides, $\mathrm{TESCl}, \mathrm{TIPSCl}$, and TBDMSCl , condense to give their respective organosilylated derivatives. ${ }^{53} \mathbf{7 8}$ has been used on reaction with ethylchloroformate in the presence of two equivalents of LDA for the preparation of $\mathbf{8 1}$ which, on reaction with aldehydes, undergoes a typical Horner-Wadsworth-Emmons reaction. ${ }^{118}$ The selectivity observed is never high and the thus obtained $\alpha$-chlorinated acrylic esters $\mathbf{4 8}$ show a $\mathrm{Z} / \mathrm{E}$ ratio of 25 / 75 (Scheme 47).


Scheme 46.



Scheme 47.
Other applications of $\mathbf{7 8}$ include condensation with diphenylchlorophosphine and $\alpha, \beta$-unsaturated aldehydes $\mathbf{8 2}$ to give 1,3-butadienylphosphine $\mathbf{8 4}$ (Scheme 48). ${ }^{119}$ The newly formed double bond shows a Z / E ratio of 70 / 30 .


Scheme 48.
84

## 2.4,5-o-Phenyl-2-chloromethyl-2-oxo-1,3,2-dioxaphospholane

4,5-o-Phenyl-2-chloromethyl-2-oxo-1,3,2-dioxaphospholane $\mathbf{8 5}$ is obtained via two methods. In the more recent approach 2 reacts with pyrocatechol at $140-160{ }^{\circ} \mathrm{C}$ for 1.5 h to give 85 with a good yield ( $90 \%$ ) (b.p. $158-160{ }^{\circ} \mathrm{C} / 3 \mathrm{mmHg}, \mathrm{mp} 63-64{ }^{\circ} \mathrm{C}$; NMR $\left.{ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+19.1 \mathrm{ppm}\right) .{ }^{120}$ This method gives better results than that described earlier from 2-chloro-4,5-benzo-1,3,2-dioxaphosphole 86 and paraformaldehyde at high temperature $\left(200{ }^{\circ} \mathrm{C}\right)$ for 3 h for which the yield did not exceed $50 \%$ (Scheme 49). ${ }^{5 \mathrm{a}}$




Scheme 49.

Compound $\mathbf{8 5}$ can be used in the synthesis of alkyl and aryl (o-oxyphenoxymethyl) phosphinic acids 89. Attack at the phosphorus atom of $\mathbf{8 5}$ by a Grignard reagent leads to ring opening. ${ }^{121}$ The magnesium atom appears to be bonded to the phosphoryl group rather than the phenolic oxygen and thus the intermediate magnesium ion does not undergo intramolecular chloride displacement. After neutralisation with HCl , it gives the o-phenyl esters 87, which upon reflux in toluene in the presence of triethylamine cyclise to give the phosphorines 88 (Scheme 50). The cyclic esters $\mathbf{8 8}$ are very easily hydrolysed to the phosphinic acids 89. Cleavage of the phosphorine ring is observed on contact with atmospheric moisture. Compounds $\mathbf{8 9}$ are able to eliminate water on reflux in xylene, thereby quantitatively reverting to the cyclic esters $\mathbf{8 8}$.


## Scheme 50.

A similar reaction using various alkoxides in absolute alcohol instead of the Grignard reagents is equally described. ${ }^{120}$ This leads to the ring opened compound 90 which recyclises, when heated under reflux in an inert solvent, to give mixtures of the dioxaphosphorin-2-oxides 91 and phosphonates 92 in ratio depending on the amount of residual alcohol in the reaction mixture (Scheme 51).


Scheme 51


91

## 3. Ylid Chemistry of Diphenyl Chloromethylphosphonate

Diphenyl chloromethylphosphonate has been utilized as an ylid precursor (bis-ochlorophenyl chloromethylphosphonate is also described). The triphenyl(diphenylphosphonomethylene)phosphorane $\mathbf{9 5}$ is obtained on a large scale by quaternarization of triphenylphosphine with diphenyl chloromethylphosphonate 93 at $175^{\circ} \mathrm{C}$ for 4 h followed by treatment with an aqueous solution of sodium hydroxide. The desired ylid 95 was recrystallized from ethyl acetate ( $\mathrm{mp} 149-150^{\circ} \mathrm{C}$ ) in an overall yield of $77 \%$. It proved to be very stable towards storage at room temperature but reacted smoothly with a variety of aromatic and aliphatic aldehydes at $100-110^{\circ} \mathrm{C}$ in DMSO to produce only the trans isomers of the appropriate diphenyl vinylphosphonates 96 (Scheme 52). ${ }^{122}$ The use of stabilized ylids such as $\mathbf{9 5}$ offers the advantage of not requiring strongly basic reagents for carbanion formation.


## Scheme 52.

|  |  |
| :--- | :---: |
| R | Yield (\%) |
| 2-naphthyl | 66 |
| 4-chlorobenzyl | 84 |
| 4-nitrobenzyl | 92 |
| valeryl | 95 |

95
RCHO
toluene, $110^{\circ} \mathrm{C}$

## 4. 2-Chloromethyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholane

A mixture of diastereomeric ( $2 \mathrm{~S}, 4 \mathrm{~S}, 5 \mathrm{R}$ ) and ( $2 \mathrm{R}, 4 \mathrm{~S}, 5 \mathrm{R}$ ) 2-chloromethyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholanes 97a and 97b is obtained in $60 \%$ yield from the reaction of (-)-ephedrine with $\mathbf{2}$ in THF in the presence of triethylamine at room temperature. The 3 / 1 mixture of the two diastereomers is separated by silica gel column chromatography to afford enantiomerically pure samples of $\mathbf{9 7 a}\left(\mathrm{mp} 85{ }^{\circ} \mathrm{C}\right.$; NMR ${ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+35.84$ ppm ) and 97b $\left(\mathrm{mp} 80^{\circ} \mathrm{C} ; \mathrm{NMR}^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+34.47 \mathrm{ppm}\right)$ respectively (Scheme 53). ${ }^{123}$






## Scheme 53.

Deprotonation of each diastereomer with $n$-BuLi in THF at low temperature followed by alkylation at the same temperature results in formation of the corresponding $\alpha$-substituted oxazaphospholanes 98a and 98b in moderate yield ( 40 to $65 \%$ ). Reaction of each isomer with
potassium phthalimide in toluene at $50^{\circ} \mathrm{C}$ under sonication conditions gives the corresponding N-phthalimido oxazaphospholanes which are converted into (R) and (S) aminoalkylphosphonic acids 99a and 99b after acidic hydrolysis followed by treatment with ethanolic hydrazine (Scheme 54). ${ }^{123}$


## Scheme 54.

## 5. 3-t-Butyl-2-chloromethyl-6, 6-dimethyl-2-oxo-1,3,2-oxazaphosphorinane

The readily available N - $t$-butyl-3, 3-dimethyl-1,3-amino alcohol is coupled with $\mathbf{2}$ in dichloromethane in the presence of triethylamine to afford racemic 2-chloromethyl-1,3,2oxazaphosphorinane $\mathbf{1 0 0}$ in $72 \%$ yield. Displacement of the chloride is accomplished by treatment with an allylic potassium alkoxide in the presence of a stoichiometric amount of 18-crown-6 ether to give the corresponding racemic 1,3,2-oxazaphosphorinane 101. Deprotonation of $\mathbf{1 0 1}$ at $-70^{\circ} \mathrm{C}$ with $n$-BuLi in THF generated the phosphorus-stabilized anion which underwent a [2,3]-Wittig rearrangement to afford the 2-(1'-hydroxybut-3'-enyl)-1,3,2-
oxazaphosphorinanes 102 in good yield (Scheme 55). ${ }^{124}$ In the rearrangement, a single product is observed when $R^{1}=R^{2}=H$ or $R^{1}=M e, R^{2}=H$; a mixture of two diastereomeric products is observed when $\mathrm{R}^{1}=\mathrm{H}$ and $\mathrm{R}^{2}=\mathrm{Me}$.

The same reaction sequence has been performed starting from optically pure 4 -(N-t-butylamino)-2-butanol. The corresponding rearrangement products were obtained in enantiomerically pure form.



Scheme 55.

## 6. Bis(dimethylamino) chloromethylphosphonamide

$\operatorname{Bis}($ dimethylamino) chloromethylphosphonamide $\mathbf{1 0 3}$ is a highly hygroscopic white crystalline solid (bp 117-118 ${ }^{\circ} \mathrm{C} / 4 \mathrm{mmHg}$; mp $48.5-49.5^{\circ} \mathrm{C}$; NMR ${ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+30.4$ $\mathrm{ppm})$. The compound is prepared by the reaction of $\mathbf{2}$ with excess dimethylamine in THF. The
reaction proceeds in nearly quantitative crude yield. The lithium reagent $\mathbf{1 0 4}$ prepared at low temperature from $\mathbf{1 0 3}$ and $n$-butyllithium, reacts with aldehydes to give an intermediate chlorohydrin 105. In the presence of a second equivalent of metalating agent, $\mathbf{1 0 5}$ undergoes dehydrochlorination to produce, after hydrolysis, the synthetically useful 2oxoalkylphosphonamides 107 in high yield (Scheme 56). ${ }^{70,125}$


Scheme 56.

## 7. 2-Chloromethyl-1,3-dimethyl-2-oxo-1,3,2-diazaphospholane

2-Chloromethyl-1,3-dimethyl-2-oxo-1,3,2-diazaphospholane $\mathbf{1 0 8}$ is a stable but moisture sensitive solid (mp $75-77{ }^{\circ} \mathrm{C}$, $\left.\mathrm{NMR}{ }^{31} \mathrm{P}\left(\mathrm{CDCl}_{3}\right) \delta=+29.8 \mathrm{ppm}\right) .{ }^{117}$ The compound is prepared in THF by reaction of chloromethylphosphonyl dichloride 2 with $\mathrm{N}, \mathrm{N}^{\prime}-$ dimethylethylenediamine in the presence of triethylamine. The reaction proceeds in nearly quantitative crude yield. When reacted simultaneously with 2 equivalents of LDA and a chloroformate, 108 yields the lithium enolate $\mathbf{1 0 9}$. On reaction with an aldehyde, the $\alpha$ chlorinated acrylic esters 48 are formed. The cyclic diazaphospholane moiety appears to exert a major influence on the stereoselectivity of the reaction and 48 show predominantly E stereochemistry (Scheme 57 and Table 14). ${ }^{118}$ By contrast, 48 are obtained from the triethyl $\alpha$-chlorophosphonocarboxylate $\mathbf{4 9}$ as either isomeric mixtures or pure Z isomers (Scheme 28 and Table 10).


Scheme 57.



E
(Major)

Table 14. $\alpha$-Chlorinated acrylic esters $48{ }^{118}$

| R | Yield (\%) | $\mathrm{Z} / \mathrm{E}$ |
| :---: | :---: | :---: |
| $n-\mathrm{Pr}$ | 94 | $2 / 98$ |
| $i-\mathrm{Bu}$ | 99 | $3 / 97$ |
| $\mathrm{Et}_{2} \mathrm{CH}$ | 99 | $3 / 97$ |
| $n-\mathrm{C}_{6} \mathrm{H}_{12}$ | 96 | $2 / 98$ |
| cyclo- $\mathrm{C}_{6} \mathrm{H}_{12}$ | 98 | $2 / 98$ |
| $n-\mathrm{C}_{9} \mathrm{H}_{19}$ | 99 | $2 / 98$ |
| $\mathrm{C}_{6} \mathrm{H}_{5}$ | 99 | $9 / 91$ |

## 8. $\mathbf{N}, \mathbf{N}^{\prime}$-Dimethyl-N,N'-(1,2-cyclohexyl) Chloromethylphosphonamide

Compound 110 is synthesised in benzene from the reaction between chloromethylphosphonyl dichloride $\mathbf{2}$ and 1,2-bis(N-methylamino)cyclohexane in the presence of triethylamine. When the ( $\mathrm{R}, \mathrm{R}$ )-1,2-bis(N-methylamino)cyclohexane (a readily available $\mathrm{C}_{2}$ symmetrical template) is used, the resulting phosphonamide $\mathbf{1 1 0}$ is obtained. In the presence of a base such as $n$-BuLi or LDA in THF at $-100^{\circ} \mathrm{C}, \mathbf{1 1 0}$ can be alkylated at the prochiral $\alpha$ position to give essentially a single diastereoisomer of the alkylated phosphonamides $\mathbf{1 1 1}$ in
high yields and excellent optical purity (Scheme 58 and Table 15). ${ }^{126}$ Attack takes place from the "pro R" side of the planar anion, through a Li-coordinated intermediate. Furthermore these phosphonamides can easily be hydrolysed under mild conditions to give optically pure (R)- $\alpha$ chloroalkylphosphonic acids again in excellent yields. The opposite enantiomer (S) of the phosphonic acids $\mathbf{1 1 2}$ can be obtained starting from the phosphonamide $\mathbf{1 1 0}$ prepared from the (S,S)-diamine.


## Scheme 58.

Table 15. Optically active 1-chloroalkylphosphonic acids $\mathbf{1 1 2}{ }^{126}$

| $(\mathrm{R}, \mathrm{R})$ Series RX | Ratio (R : S) of $\mathbf{1 1 1}$ | Yield of $\mathbf{1 1 2}(\%)$ |
| :---: | :---: | :---: |
| MeI | $90: 10$ | $95(\mathrm{R})$ |
| EtI | $>99: 1$ | 98 |
| $n-\mathrm{PrI}$ | $>99: 1$ | 97 |
| $\mathrm{CH}_{2}=\mathrm{CHCH}_{2} \mathrm{Br}$ | $>99: 1$ | quant |
| $\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{CH}_{2} \mathrm{Br}$ | $91: 9$ | quant |

(S, S) series RX
$\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{CH}_{2} \mathrm{Br}$
7 : 93
98 (S)

EtI
$>1: 99$
97
$\alpha$-Aminoalkylphosphonic acids 115, which are probably the most important analogues of $\alpha$-amino acids in biological systems, ${ }^{127}$ can be synthesised in enantiomerically pure or enriched form via a similar methodology by using the chloromethylphosphonamide $\mathbf{1 1 0}$ and sodium azide as precursor of the amino group (Scheme 59 and Table 16). 103



Scheme 59.
Table 16. Optically active 1-aminoalkylphosphonic acids 115103

| $(\mathrm{R}, \mathrm{R})$ Series RX | Ratio (R : S) of $\mathbf{1 1 4}$ | Yield of $\mathbf{1 1 5}(\%)$ |
| :---: | :---: | :---: |
| MeI | $90: 10$ | $82(\mathrm{R})$ |
| EtI | $>95: 5$ | 84 |
| $n$-PrI | $>99: 1$ | 86 |
| $\mathrm{CH}_{2}=\mathrm{CHCH}_{2} \mathrm{Br}$ | $>99: 1$ | 88 |
| $\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{CH}_{2} \mathrm{Br}$ | $>99: 1$ | 87 |

(S, S) series RX
MeI 8:92 84 (S)

An alternative approach for the asymmetric synthesis of $\alpha$-aminoalkylphosphonic acids from 110 is based on the stereoselective addition of the corresponding lithiated carbanion to imines. The thus obtained aziridines 116 are then ring opened by hydrogenolytic cleavage to give the $\alpha$-aminoalkylphosphonamides 117 which are in turn hydrolysed to the corresponding phosphonic acids, isolated as the dimethyl phosphonate 118 (Scheme 60). ${ }^{128}$


$$
\begin{aligned}
\mathrm{R}^{1}= & p \text {-tolylsulfonyl } \\
& p \text {-methoxyphenyl } \\
& \text { phenyl }
\end{aligned}
$$



117

## Scheme 60.

The chloromethylphosphonamide 110 is also used as chiral starting material for the synthesis of the enantiomerically pure cyclopropylphosphonamides $\mathbf{1 1 9}$. The stereocontrolled conjugate addition of anion derived from 110 to $\alpha, \beta$-unsaturated esters leads to the corresponding 1-chloro-3-carboxypropyl phosphonate adduct which undergoes intramolecular expulsion of the chlorine atom to give the corresponding cyclopropanes 119 (Scheme 61). Further transformations of $\mathbf{1 1 9}$ allowed the synthesis of 2-aminocyclopropylphosphonic acid 120 in optically pure form. ${ }^{129}$


Scheme 61
120

## VI. Conclusion

This review demonstrates the versatility of chloromethylphosphonyl compounds as starting materials for preparing a vast array of useful functionalized phosphonates and nonphosphorylated organic materials. These can be realised either by the use of 1lithiochloromethylphosphonate or by nucleophilic substitution of the chlorine atom. The rich and various chemistry of chloromethylphosphonic acid derivatives, esters and amides, covers a large area from the formation of synthetically useful derivatives to the preparation of phosphorus compounds possessing biological activity. In addition, many of the methods described in this aricle can be accomplished with complete stereochemical control thanks to the suitable choice of substituents of the phosphorus atom. We hope that this review will help the exploration of this valuable area of phosphorus chemistry.

## VII. Acknowledgements

In collecting the literature, the authors have benefited greatly from collaboration with Mrs Françoise Girard who is gratefully acknowledged. We are also grateful to the Centre National de la Recherche Scientifique for financial support to R. W. and J. C.

## VIII. References

(1) (a) Johnson, A.W. Ylid Chemistry; Academic Press: New York, 1966. (b) Boutagy, J.; Thomas, R. Chem. Rev. 1974, 74, 87. (c) Wadsworth, W. Org. React.. 1977, 25, 73. (d)

Walker, B.J. in Organophosphorus Reagents in Organic Synthesis; Cadogan, J.I.G., ed.; Academic Press: London, 1979; Chapter 3, p 155. (e) Battacharya, A.K.; Thyagarajan, G. Chem. Rev. 1981, 81, 415. (f) Burton, D.J.; Yang, Z-Y. Tetrahedron 1992, 48, 189. (g) Minami, T.;Motoyoshiya, J. Synthesis 1992, 333. (h) Johnson, A.W.; Kaska, W.C.; Ostoja Starzewski, K.A.; Dixon, D.A. Ylides and Imines of Phosphorus; John Wiley and sons: New York, 1993. (i) Burton, D.J.; Yang, Z-Y.; Qiu, W. Chem. Rev. 1996, 96, 1641.
(2) Kinnear, A. M.; Perren, E. A. J. Chem. Soc. 1952, 3, 3437.
(3) Kleiner, H.-J. Hoechst AG, Personal Communication.
(4) (a) Bannard, R.A.B.; Gilpin, J.R., Vavasour, G.R.; McKay, A.F. Can. J. Chem. 1953, 31, 976. (b) Sasse, K., in Houben-Weyl, OrganischePhosphor-Verbindungen 1, Georg Thieme Verlag., 1963, p. 388.
(5) (a) Kabachnik, M. I.; Schepeleva, E. S. Dokl. Akad. Nauk SSSR 1950, 75, 219; Chem. Abstr. 1951, 6569. (b) Crofts, P. C.; Kosolapoff, G. M. J. Am. Chem. Soc. 1953, 75, 5738. (c) Kabachnik, M. I.; Medved, T. Ya. Izv. Akad. Nauk SSSR Ser. Khim. 1950,

635; Chem. Abstr. 1951, 8444. (d) Kabachnik, M. I.; Schepeleva, E. S., Izv. Akad. Nauk SSSR Ser. Khim. 1951, 185; Chem. Abstr. 1951, 10191. (e) Korshak, V. V.; Gribova, I. A.; Andreeva M. A. Izv. Akad. Nauk SSSR Ser. Khim. 1957, 631; Engl. Transl. 641. (f) McConnell, R. L.; McCall, M. A.; Coover, H. W. Jr. J. Org. Chem. 1957, 22, 462.
(6) Orlov, N. F.; Mileshkevich, V. P.; Vainburg, V. M. J. Gen. Chem. USSR (Engl. Transl.) 1966, 36, 1089; Zh.Obshch.Khim. 1966, 36, 1075.
(7) Tsvetkov, E. N.; Malevannaya, R. A.; Kabachnik, M. I. J. Gen. Chem. USSR (Engl. Transl.) 1969, 39, 1490 ; Zh. Obshch. Khim. 1969, 39, 1520.
(8) Petrov, K. A.; Maklyaev, F. L.; Bliznyuk, N. K., J. Gen. Chem. USSR (Engl. Transl.) 1960, 30, 1604; Zh. Obshch. Khim. 1960, 30, 1602.
(9) Toy, A. D. F.; Rattenbury, K. H. (Victor Chemical Works) Patent 1958, U. S. 2,863,903 ; Chem. Abstr. 1959, 9151h.
(10) Schwarzenbach, G.; Zurc, J. Monatsh. Chem. 1950, 81, 202.
(11) Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. Phosphorus, Sulfur, and Silicon 1995, 103, 91.
(12) Cann, P. F.; Howells, D.; Warren, S. J. Chem. Soc., Perkin Trans. II 1972, 304.
(13) Toy, A. D. F.; Rattenbury K. H. (Victor Chemical Works) Patent 1955, U. S. 2,714,100 ; Chem. Abstr. 1955, 14380c.
(14) Savignac, P.; Lavielle G. Bull. Soc. Chim. Fr. 1974, 1506.
(15) Korshak, V. V.; Gribova, I. A.; Shitikov, V. K. Izv. Akad. Nauk SSSR Ser. Khim. 1958, 210; Engl. Transl. 196
(16) Kabachnik, M. I.; Godovikov, N. N.; Godyna E. I. J. Gen. Chem. USSR (Engl. Transl.) 1963, 33, 1305; Zh. Obshch. Khim. 1963, 33, 1335
(17) Druzin, M. I.; Rubtsova, I. K.; Zhuravleva, M. A.; Shner, S. M.; Val'kova, A. K.; Britsina, T. A. Patent 1973 USSR 323,008; Zh. Khim. 1973, 21, N117P.
(18) Maksudov, N. Kh.; Makhamatkhanov, M. M.; Aripov, A. Seitkasymov Zh. Uzb. Khim. Zh. 1978, 70; Chem. Abstr. 1978, 89, 24451m.
(19) Toy, A. D. F.; Rattenbury, K. H. (Victor Chemical Works) Patent 1958, U. S. 2,836,504; Chem. Abstr. 1958, 12895b; Patent 1957, Brit. 783,018; Chem. Abstr. 1958, 52, 2888a.
(20) Shepeleva, E. S.; Sanin, P. I. Dokl. Akad. Nauk SSSR 1956, 109, 555; Chem.. Abstr. 1957, 51, 4934i.
(21) Kabachnik, M. I.; Medved', T. Ya.; Polikarpov, Yu. M.; Yudina, K. S. Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.) 1967, 568; Izv. Akad. Nauk SSSR Ser. Khim. 1967, 591.
(22) Sosnpvsky, G.; Konieczny, M. Z. Naturforsch., Teil B 1973, 28, 488; Chem. Abstr. 1974, 81, 3735b.
(23) Petrov, K. A.; Parshina, V. A.; Petrova, G. M., J. Gen. Chem. USSR (Engl. Transl.) 1969, 39, 1216; Zh. Obshch. Khim. 1969, 39, 1247.
(24) Petrov, K. A.; Baksova, R. A.; Khorkhoyanu, L. V. J. Gen. Chem. USSR (Engl. Transl.) 1965, 35, 731; Zh. Obshch. Khim. 1965, 35, 732.
(25) Stowell, M. H. B.; Ueland, J. M.; McClard, R. W., Tetrahedron Lett. 1990, 31, 3261
(26) McConnell, R. L.; Coover, H. W. Jr. J. Org. Chem. 1959, 24, 630.
(27) Teulade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Liétge, S.; Collignon, N. J. Organomet. Chem. 1986, 304, 283.
(28) Teulade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Collignon, N. J. Organomet. Chem. 1986, 312, 283.
(29) Maier, L. Synth. React. Inorg. Met.-Org. Chem. 1976, 6, 133-155; Chem. Abstr. 1976, 85, 21557g.
(30) Soborovskii, L. Z.; Baina, N. F., J. Gen. Chem. USSR (Engl. Transl.) 1959, 29, 1115; Zh. Obshch. Khim. 1959, 29, 1144.
(31) Gefter, E.L.; Kabachnik, M.I. Dokl. Akad. Nauk SSSR 1957, 194; Chem. Abstr. 1958, 52, 295a.
(32) Cade, J. A. J. Chem. Soc. 1959, 2266.
(33) Cherbuliez, E.; Gowhari, M.; Rabinowitz, J. Helv. Chim. Acta 1964, 47, 2098.
(34) Vaghefi, M. M.; Bernacki, R. J.; Hennen, W. J.; Robins, R. K. J. Med. Chem. 1987, 30, 391.
(35) Guillemin, J. C.; Le Guennec, M.; Denis, J. M. J. Chem. Soc., Chem. Commun. 1989, 988.
(36) Toy, A. D. F.; Rattenbury, K. H. (Victor Chemical Works) Patent 1953, U. S. 2,922,810; Chem. Abstr. 1960, 54, 9848c.
(37) McCall, M. A.; McConnell, R. L. Patent 1959, U. S. 2,900,405 ; Chem. Abstr. 1960, 54, 416b.
(38) Toy, A. D. F.; Rattenbury, K. H. (Victor Chemical Works) Patent 1960, U. S. 2,960,552; Chem. Abstr. 1961, 12358i.
(39) Tsvetkov, E. N.; Degtyarev, A. N.; Bovin, A. N. J. Gen. Chem. USSR (Engl. Transl.) 1986, 56, 2249; Zh. Obshch. Khim. 1986, 56, 2542.
(40) Teulade, M.-P.; Savignac, P. J. Organomet. Chem. 1988, 338, 295.
(41) Tue, Bi B.; Devaud, M.,Tetrahedron Lett. 1987, 28, 3799.
(42) Jubault, P.; Feasson, C.; Collignon, N. Tetrahedron Lett. 1995, 36, 7073.
(43) Le Menn, J.-C.; Tallec, A.; Sarrazin, J.,J. Chem. Educ. 1991, 68, 513.
(44) Teulade, M.-P.; Savignac, P.; About-Jaudet, E.; Collignon, N. Phosphorus and Sulfur 1988, 40, 105.
(45) Waschbüsch, R.; Carran, J.; Savignac, P. Tetrahedron, 1996, 52, 14199.
(46) Aboujaoude, E.E.; Liétjé, S.; Collignon, N.; Teulade, M-P.; Savignac, P. Tetrahedron Lett. 1985, 26, 4435.
(47) Dizière, R.; Savignac, P. Tetrahedron Lett. 1996, 37, 1783.
(48) Anisimov, K. N.; Nesmeyanov, A. N. Izv. Akad. Nauk SSSR, Otds. Khim. Nauk 1955, 1006; Chem. Abstr. 1956, 50, 11267h.; Ionin, B. I.; Petrov, A. A. Zh. Obshch. Khim. 1962, 32, 2387; Chem. Abstr. 1963, 58, 9115b.; Ionin, B. I.; Lebedev, V. B.; Petrov, A. A. Dokl. Akad. Nauk SSSR 1963, 152, 1354; Chem. Abstr. 1964, 60, 1560d.; Pudovik, A. N.; Aladzheva, I. M. Zh. Obshch. Khim. 1963, 33, 707; Chem. Abstr. 1963, 59, 2851f.; Sturtz, G.; Charrier, C. C. R. Acad. Sci. 1965, 261, 1019.; Sturtz G. Bull. Soc. Chim. Fr. 1967, 1345.; Chattha, M. S.; Aguiar, A. M. J. Org. Chem. 1971, 36, 2719.; Shen, Y.; Lin, Y.; Xin, Y. Tetrahedron Lett. 1985, 26, 5137.; Hägele, G.; Goudetsidis, S.; Wilke, E.; Seega, J.; Blum, H.; Murray, M. Phosphorus, Sulfur, and Silicon 1990, 48, 131.; Shen, Y.; Qi, M. J. Chem. Soc. Perkin Trans. I 1993, 2153.; (f) Midura, W. H.; Mikolajczyk, M. Tetrahedron Lett. 1995, 36, 2871.
(49) Porskamp, P.A.T.W.; Lammerink, B.H.M.; Zwanenburg, B. J. Org. Chem.. 1984, 49, 263.
(50) Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. J. Chem. Soc., Perkin Trans. I 1994, 821.
(51) (a) Coutrot, P.; Laurenço, C.; Normant, J. F.; Perriot, P.; Savignac, P.; Villiéras, J. Synthesis 1977, 615. (b) Compounds 17 can also be obtained in good yields by an electrochemical synthesis. see (42)
(52) Savignac, P.; Petrova, J.; Dreux, M.; Coutrot, P. Synthesis 1975, 535.
(53) Laurenço, C.; Waschbüsch, R.; Carran, J.; Marinetti, A.; Savignac, P. unpublished work.
(54) Expert, J.; Gelas-Mialhe, Y.; Vessière, R. J. Heterocyclic Chem. 1985, 22, 1285.
(55) Pflieger, D.; Muckensturm, B. Tetrahedron 1989, 45, 2031.
(56) Savignac, P.; Dreux, M.; Coutrot, P. Tetrahedron Lett. 1975, 9, 609.
(57) Savignac, P.; Petrova, J.; Dreux, M.; Coutrot, P. J. Organomet. Chem. 1975, 91, C45.
(58) Marinetti, A.; Savignac, P. Org. Synth. 1997, 74, 108.
(59) Carran, J.; Waschbüsch, R.; Marinetti, A.; Savignac, P. Synthesis, 1996, 1494.
(60) (a) Guillemin, J. C.; Le Guennec, M.; Denis, J-M. J. Chem. Soc., Chem. Commun. 1989, 988. (b) Cabioch, J-L.; Pellerin, B.; Denis, J-M. Phosphorus, Sulfur and Silicon, 1989, 44; 27. (c) Guillemin, J.C.; Janati, T.; Guenot, P.; Savignac, P.; Denis, J-M Angew. Chem. Int. Ed. Engl. 1991, 30, 196.
(61) Mouriès, V.; Waschbüsch, R.; Carran, J.; Savignac, P. Synthesis (submitted).
(62) Savignac, P.; Coutrot, P. Synthesis 1976, 197.
(63) (a) Köbrich, G. Angew. Chem. Int. Ed. Engl. 1965, 4, 49. (b) Harada, T., Hara, D., Hattori, K; Oku, A. Tetrahedron Lett. 1988, 29, 3821. (c) Kunishima, M., Hioki, K.; Ohara, T.; Tani, S. J. Chem. Soc., Chem. Commun. 1992, 219. (d) Sato, H.; Isono, N.; Miyoshi, I.; Mori, M. Tetrahedron, 1996, 52, 8143.
(64) Xu, L.; Lin, G.; Tao, F.; Brinker, U.H. Acta Chem. Scand. 1992, 46, 650.
(65) Coutrot, P.; Savignac, P. Synthesis 1978, 34.
(66) (a) Martynov, V. F.; Timofeev, V. E. Zh. Obshch. Khim. 1964, 34, 3890. Chem. Abstr. 1965, 62, 19457. (b) Martynov, V. F.; Timofeev, V. E. Zh. Obshch. Khim. 1962, 32, 3449. Chem. Abstr.1963, 58, 9121. (c) Churi, R. H.; Griffin, C. E. J. Amer. Chem. Soc. 1966, 88, 1824. (d) Redmore, D. Chem. Rev. 1971, 71, 315.
(67) Christensen, B. G.; Firestone, R. A. German Offen. 1924135, 1969; Chem. Abstr. 1970, 72, 43870.
(68) (a) Churi, R. H.; Griffin, C. E. J. Amer. Chem. Soc. 1966, 88, 1824. (b) Sprecher, M.; Kost, D. Tetrahedron Lett., 1969, 703. (c) Griffin, C. E.; Kundu, S. K. J. Org. Chem.. 1969, 34, 1532. (d) Griffin, C. E.; Ranieri, R. L., Phosphorus 1976, 6, 161. (e) Arbuzov, B. A.; Polezhaeva, N. A.; Vinogradova, V. S. Izv. Akad. Nauk. SSSR, Ser. Khim. 1967, 1146. Chem. Abstr. 1968, 68, 13092. (f) Razumov, A. I.; Liorber, B. G.; Moskva, V. V., Sokolov, M. P. Russian Chemical Reviews 1973, 42, 538. (g) Redmore, D. Chem. Rev. 1971, 71, 315.
(69) Teulade, M-P.; Savignac, P. Synth.Comm.un. 1987, 17, 125.
(70) Savignac, P.; Coutrot, P. Synthesis 1978, 682.
(71) Coutrot, P.; Elgadi, A.; Grison, C. Heterocycles 1989, 28, 1179.
(72) Savignac, P.; Snoussi, M.; Coutrot, P. Synth. Commun. 1978, 8, 19.
(73) Coutrot, P.; Ghribi, A. Synthesis 1986, 661.
(74) Coutrot, P.; Grison, C.; Charbonnier-Gerardin, C. Tetrahedron 1992, 48, 9841.
(75) (a) Bodnarchuk, N.D.; Malovik, V.V.; Derkach, G.I. Zh. Obshch. Khim. 1969, 39, 1707. (b) Bodnarchuk, N.D.; Malovik, V.V.; Derkach, G.I. Zh. Obshch. Khim. 1970,

40, 1210. (c) Bodnarchuk, N.D.; Malovik, V.V.; Derkach, ;G.I. Kirsanov, A.V. Zh. Obshch. Khim. 1971, 41, 1464.
(76) Motoyoshiya, J.; Hirata, K. Chem.Lett. 1988, 211.
(77) Coutrot, P.; Charbonnier, C.; Grison, C. Synthesis 1991, 23.
(78) Shokol, V.A.; Kozhushko, B.N.; Doroshenko, V.V.; Kirsanov, A.V. Zh. Obshch. Khim. 1973, 43, 12.
(79) Teulade, M-P.; Savignac, P.; Aboujaoude, E.E.; Collignon, N. J. Organomet. Chem. 1985, 287, 145.
(80) Feistauer, H.; Neidlein, R. Helv. Chim. Acta 1995, 78, 1806.
(81) Villiéras, J.; Perriot, P.; Normant, J.F. Synthesis 1978, 29.
(82) Ioffe, S.T.; Vatsuro, K.V.; Petrovskii, P.V.; Kabachnik, M.I. Izv. Akad. Nauk. SSSR, Ser. Khim. 1971, 731.
(83) Ismailov, V.M.; Moskva, V.V.; Zykova, T.V. Zh. Obshch. Khim. 1983, 53, 2793.
(84) Ismailov, V.M.; Moskva, V.V.; Guseinov, F.I.; Zykova, T.V.; Sadykov, I.S. Zh. Obshch. Khim. 1986, 56, 2005.
(85) Guseinov, F.I.; Moskva, V.V.; Ismailov, V.M. Zh. Obshch. Khim. 1993, 63, 93.
(86) Tay, M. K.; About-Jaudet, E.; Collignon, N.; Teulade, M-P.; Savignac, P. Synth.Commun. 1988, 18, 1349.
(87) Villiéras, J.; Perriot, P.; Normant, J.F. Synthesis 1978, 31.
(88) Grell, W.; Machleidt, H. Justus Liebigs Ann. Chem. 1966, 693, 134.
(89) Mc Kenna, C.; Khawli, L.A. J. Org. Chem. 1986, 51, 5467.
(90) Teulade, M-P.; Savignac, P.; Aboujaoude, E.E.; Lietge, S.; Collignon, N. J. Organomet. Chem. 1986, 304, 283.
(91) (a) Lowen, G.T.; Almond, M.R. J. Org. Chem. 1994, 59, 4548. (b) Cabioch, J.L.; Denis, J-M. J. Organomet. Chem. 1989, 377, 227.
(92) Savignac, P.; Teulade, M-P.; Aboujaoude, E.E.; Collignon, N. Synth. Commun. 1987, 17, 1559.
(93) (a) Hutchinson, D.W.; Semple, G. J. Organomet. Chem. 1985, 291, 145. (b) Hutchinson, D.W.; Semple, G. J. Organomet. Chem. 1986, 309, C7.
(94) (a) Quimby, O.T.; Curry, J.D.; Nicholson, D.A.; Prentice, J.B.; Roy, C.H. J. Organomet. Chem. 1968, 13, 199. (b) Quimby, O.T., Prentice, J.B. U.S. Patent 3,772, 412, 1973. (c) Mc Kenna, C.; Khawli, L.A.; Ahmad, W-Y.; Pham, P.; Bongartz, J-P. Phosphorus and Sulfur 1988, 37, 1. (d) Vepsäläinen, J.; Nupponen, H.; Pohjala, E.; Ahlgren, M.; Vainiotalo, P. J. Chem. Soc. Perkin Trans 2 1992, 835.
(95) Hutchinson, D.W.; Semple, G. Phosphorus and Sulfur 1984, 21, 1.
(96) Seyferth, D.; Marmor, R.S. J. Organomet. Chem. 1973, 59, 237.
(97) Nicholson, D.A.; Vaughn, H. J. Org. Chem. 1971, 36, 1835.
(98) Devaud, M.; Azzouzif, F.; Bi, B.T. J.Chem. Res. 1991, 1052.
(99) Kirby, A.J.; Warren, S.G. The Organic Chemistry of Phosphorus; Elsevier Publishing Company: Amsterdam, 1967.
(100) (a) Kabachnik, M.I.; Medved, T.J. Izv. Akad. Nauk. SSSR, 1950, 635. Chem. Abstr. 1951, 45, 8444. (b) Kabachnik, M.I.; Medved, T.J. Izv. Akad. Nauk. SSSR, 1951, 95. Chem. Abstr. 1952, 46, 421. (c) Kabachnik, M.I.; Medved, T.J.Sbornik Statei Obshchei Khim. Akad Nauk SSSR 1952, 2, 12. Chem. Abstr. 1954, 48, 564.
(101) (a) Maier, L. Phosphorus and Sulfur 1991, 62, 29. (b) Kreutzkamp, N.; Mengel, W. Arch. Pharm. 1962, 295, 773. (c) Tsirul'nikova, N.V.; Temkina, V.Y.; Sushitskaya, T.M.; Rykov, S.V. Zh. Obshch. Khim. 1981, 51 1028. (d) Cameron, D.G.; Hudson, H.R.; Ojo, I.A.O.; Pianka, M. Phosphorus and Sulfur 1988, 40, 183. (e) Divinskaya, L.P.; Limanov, V.E..; Skvortsova, E.K.; Putyatina, G.M.; Starkov, A.V.; Grinshtein, N.I.; Nifant'ev, E.E. Zh. Obshch. Khim. 1966, 361244.
(102) Berté-Verrando, S.; Nief, F.; Patois, C.; Savignac, P. Phosphorus, Sulfur and Silicon 1995, 103, 91.
(103) Hanessian, S.; Bennani, Y.L. Tetrahedron Lett. 1990, 31, 6465.
(104) Maier, L.; Kunz, W. Phosphorus and Sulfur 1987, 30, 201.
(105) (a) Petrov, K.A.; Chauzov, V.A.; Erokhina, T.S.; Pastukhova, I.V. Zh. Obshch. Khim. 1977, 47, 2501. (b) Harger, M.J.P. J. Chem. Soc. Perkin Trans 1 1983, 2127.
(c) Harger M.J.P.; Williams, A. J. Chem. Soc. Perkin Trans 1 1989, 563.
(106) (a) Savignac, P.; Lavielle, G. Bull. Soc. Chim. Fr. 1978, 1506. (b) Savignac, P.; Coutrot, P. Synthesis 1974, 818.
(107) (a) Arbuzov, B.A.; Bogonotseva, N.P. Zh. Obshch. Khim. 1956, 26, 2419. (b) Arbuzov, B.A.; Bogonotseva, N.P. Zh. Obshch. Khim. 1957, 27, 2360. (c) Wegener, W.; Courault, K. Z. Chem. 1980, 20, 337.
(108) Villemin, D.; Thibault-Starzyk, F. Synth. Commun. 1993, 23, 1053.
(109) Mizrakh, L.I.; Yakovlev, V.G.; Yukhno, E.M.; Mamonov, V.I.; Svergun, V.I. Zh. Obshch. Khim.. 1971, 41, 2654.
(110) (a) Petrov, K.A.; Maklyaev, F.L.; Bliznyuk, N.K. Zh. Obshch. Khim. 1960, 30, 1602. (b) Richard, J.J.; Burke, K.E.; O'Laughlin, J.W.; Banks, C.V. J. Am. Chem. Soc. 1961, 83, 1722.
(111) Ginzburg, V.A.; Iakuovich, A.I. Zh. Obshch. Khim. 1958, 28, 728.
(112) Maier, L. Helv. Chim. Acta 1970, 53, 1940.
(113) Vaghefi, M.M.; Bernacki, R.J.; Hennen, W.J.; Robins, R.K. J. Med. Chem. 1987, 30, 1391.
(114) Collins, D.J.; Drygala, P.F.; Swan, J.M. Aust. J. Chem. 1944, 37, 1009.
(115) Poindexter, M.; Katz, T.J. Tetrahedron Lett. 1988, 29, 1513.
(116) Balczewski, P.; Mikolajczyk, M. Synthesis 1995, 392.
(117) Ulrich, H.; Tucker, B.; Sayigh, A. A. R. J. Org.Chem. 1967, 32, 1360.
(118) Patois, C.; Savignac, P. Synlett 1991, 517.
(119) Teulade, M-P.; Savignac, P. Tetrahedron Lett. 1989, 30, 6327.
(120) Tsvetkov, E.N.; Degtiarev, A.N.; Bovin, A.N. Zh. Obshch. Khim. 1986, 56, 2542.
(a) Bovin, A.N.; Tsvetkov, E.N. Izv. Akad. Nauk. SSSR, 1989, 4, 943. (b) Bovin, A.N.; Tsvetkov, E.N. Zh. Obshch. Khim. 1991, 61, 1732. (c) Bovin, A.N.; Chekhlov, A.N.; Tsvetkov, E.N. Izv. Akad. Nauk. SSSR, 1992, 9, 2174.
(122) (a) Jones, G.H.; Hamamura, E.K.; Moffatt, J.G. Tetrahedron Lett. 1968, 5731. (b) Böhringer, M.P.; Graff, D.; Caruthers, M.H. Tetrahedron Lett. 1993, 34, 2723.
(123) Jacquier, R.; Lhassani, M.; Petrus, C.; Petrus, F. Phosphorus, Sulfur and Silicon 1993, 81, 83 .
(124) (a) Denmark, S.E.; Miller, P.C. Tetrahedron Lett. 1995, 36, 6631. (b) Denmark, S.E.; Dorow, R.L. J. Org. Chem. 1990, 55, 5926.
(125) Lavielle, G.; Carpentier, M. Savignac, P. Tetrahedron Lett. 1973, 173.
(126) (a) Hanessian, S.;Bennani, Y. L.;Delorme, D. Tetrahedron Lett. 1990, 31, 6461. (b) Benanni, Y.L.; Hanessian, S. Tetrahedron, 1996, 52, 13837.
(127) (a) Dhawan, B.;Redmore, D. Phosphorus and Sulfur 1987, 32, 119. (b) Neuzil, E.; Cassaigne, A. Exp. Ann Biochim. Med. 1980, 34, 165. (c) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. J. Med. Chem. 1986, 29, 29. (d) Giannousis, P. P.;Bartlett, P. A. J.Med. Chem. 1987, 30, 1603. (e) Logusch, E.W.; Walker, D.M.; Mc Donald, J.F.; Leo, G.C.; Franz, J.E. J. Org. Chem. 1988, 53, 4069. (f) Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M. J. Med. Chem. 1989, 32, 1652. (g) Kupczyk-Subotkowska, L.; Mastalertz, P. Int. J. Peptide Protein Res. 1983, 21, 485. (h) Hassall, C.H. in Antibiotics, Hahn, F.E. ed., Springer Verlag: Berlin, 1983, VI, page 1. (i) Jacobsen, N.E.; Bartlett, P.A.; J. Am. Chem. Soc. 1981, 103, 654. (j) Bartlett, P.A.; Kezer, W.B. J. Am. Chem. Soc 1984, 106, 4282 (k) Hassall, C.H.; Atherton, F.R.; Hall, M.J.; Lambert, R.W.; Llyod, W.J.; Ringrose, P.S. Peptides, Proc. Eur. Pept. Sym., 17th, 1982, Blaha, K.; Malon, P.G. ed., Walter de Gruyer Co.: Berlin, New York. (1) Bartlett, P.A.; Marlowe, C.K. Biochemistry 1983, 22, 4618. (m) Kase, K.; Yamamoto, M; Kogushi, T.; Okashi, R.; Kasai, M.; Shirahata, K.; Kawamoto, I.; Shuto, K.; Karasawa, A. US Patent 4,522,812; Chem. Abstr. 1983, 98, 107793. (n) Horigushi, M.; Kandatsu, M. Nature, 1959, 184, 901. (o) Park, B.K.; Hirota, A.; Sakai, H. Agr. Biol. Chem. 1977, 41, 161.
(128) Hanessian, S.; Bennani, Y.L.; Hervé, Y. Synlett, 1993, 35.
(129) Hanessian, S.; Cantin, L-D.; Roy, S.; Andreotti, D.; Gomtsyan, A. Tetrahedron Lett. 1997, 38, 1103.

