Synthetic methods of cyclic α-aminophosphonic acids and their esters

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Abstract
This review describes the most synthetic methods of cyclic α-aminophosphonic acids and their mono- or di-esters in which at least two atoms of the P–C–N system such as linkage of types C–P, C–N and P–C–N are part of a heterocyclic system.

Keywords: Cyclic α-aminophosphonic acids, Kabachnik-Fields, Pudovik reactions

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1. Introduction

Organophosphorus compounds are important substrates in the study of biochemical processes\textsuperscript{1-4} and compounds of tetracoordinate pentavalent phosphorus are widely used as biologically active compounds. The key role of naturally occurring amino acids in the chemistry of life and as structural units in peptides, proteins, and enzymes has led to intense study on the chemistry and biological activity of synthetic analogues. For a long time the so-called “phosphorus analogues” of the amino acids, in which the carboxylic acid group is replaced by a phosphonic, -P(O)(OH)\textsubscript{2}, or phosphinic acid group, -P(O)(OH)R (in which R may be H, alkyl, or aryl), as well as a phosphonate group, -P(O)(OR)\textsubscript{2} (in which R may be alkyl, or aryl), have attracted particular interest in the preparation of isosteric or bioisosteric analogues of numerous natural products.\textsuperscript{5,8} In this area, α-aminophosphonic acids, as isosteres of α-amino acids (Figure 1) occupy an
important place and reveal diverse and interesting biological and biochemical properties including antibacterial agents,9 enzyme inhibitors,10,11 haptens for catalytic antibodies,12 and anti HIV agents.13

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{C} \quad \text{OH} \\
R & \quad \text{H} \\
\text{H}_2\text{N} & \quad \text{P} \quad \text{OR}^1 \\
R & \quad \text{H} \\
\end{align*}
\]

\(R^1=\text{H, alkyl, aryl}\)

**Figure 1**

Various synthetic methods for \(\alpha\)-aminophosphonic acids and \(\alpha\)-aminophosphonates have been reported14-22 and the most straightforward one is the addition of compounds containing a P–H bond to the C=N bond of imines (the Pudovik reaction) (Scheme 1).23 However, the most useful pathway to the synthesis of \(\alpha\)-aminophosphonates is the Kabachnik-Fields reaction,24-27 which is a one-pot, three-component procedure using carbonyl compound, amine and dialkyl phosphite (Scheme 2). This process was discovered at a time when multicomponent processes were rather “exotic birds”; from a modern point of view this protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis.28

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{R}^2 \\
\text{H} & \quad \text{P} \quad \text{OR}^3 \\
\text{OR}^4 & \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{R} \\
\text{R}^1 & \quad \text{C} \quad \text{OR}^3 \\
\text{R}^2 & \quad \text{OR}^4 \\
\text{OR}^4 & \\
\end{align*}
\]

Scheme 1

Scheme 2

A few reviews have been published to date which are concerned with the synthesis, characterization, stereochemistry and biological activities of acyclic \(\alpha\)-aminophosphonate derivatives,29-31 but none of these focuses solely on the formation of cyclic \(\alpha\)-aminophosphonates. Therefore, this review will focus on the synthesis of cyclic \(\alpha\)-aminophosphonic acids and their mono- or di-esters in which at least two atoms of the P–C–N system are part of a
heterocyclic system. Thus, the heterocyclic systems which contain linkage of types C−P (A), C−N (B) and P−C−N (C) (Figure 2) are considered as cyclic α-aminophosphonate derivatives. The review is built up according to the three previous linkage types and starting with the smallest rings in each type.

2. Type A: Cyclic α-Aminophosphonic Acid Derivatives Bearing an Exocyclic Amino Group (Heterocycles containing the phosphorus as a ring heteroatom)

This type focuses on the synthesis of heterocyclic systems containing the α-aminophosphonate moiety which contains the P−C linkage as a part of the heterocyclic system (the phosphorus as a ring heteroatom).

2.1. The Curtius rearrangement strategy on phosphorus heterocycles

Ring closing metathesis (RCM) strategy was used in synthesis of the seven-membered P-heterocyclic α-aminophosphonate 3. Thus, monoallylation of tert-butyl diallylphosphonoacetate (1) using NaH and allyl bromide in THF at 0 °C followed by RCM utilizing the Grubbs benzylidene catalyst generated 1.2:1 mixtures of diastereomeric P-heterocycles 2 in excellent yield. On application of the Curtius rearrangement strategy to 2, Boc-protected α-aminophosphonate 3 was generated in 48% overall yield as 1.5:1 mixture of separable diastereomers (Scheme 3).32

Subsequent allylation of an approximate of a 1:1 diastereomeric mixture of 2 produced 4 with 3:1 diastereoselectivity. RCM of the major diastereomer gave the [5,5,0]bicyclic tert-butyl-phosphoacetate 5 as the cis-fused diastereomer in excellent yield. This experiment also proved the stereoselectivity (cis = major) in the allylation process of 2. Subjection of 5 to Curtius conditions gave the corresponding α-Boc-bicyclic-α-aminophosphonate 6 in 84% yield (Scheme 4).32
2.2. Addition of dialkyl phosphate to double bond (The Pudovik reaction)

Reaction of 3-(phenylaminomethylene)-2-hydroxy/N-phenylamino-6-methyl-2,3-dihydro-4\(H\)-chromen-4-ones (7) and (8) with diethyl phosphate at 90−100 °C afforded 3-phenylamino-2-ethoxy-6-methyl-2-oxo-2,3,3a,9a-tetrahydro-4\(H\)-1,2-oxa-phosphol[5,4-\(b\)]chromen-4-one (10) and 3-phenylamino-2-ethoxy-6-methyl-2-oxo-1-phenyl-2,3,3a,9a-tetrahydro-4\(H\)-1,2-azaphosphol[5,4-\(b\)]chromen-4-one (11), respectively, as cyclic \(\alpha\)-aminophosphonate derivatives. Formation of the compounds 10 and 11 may be interpreted as resulting from nucleophilic attack.
of the phosphorus atom at the α,β-unsaturated moiety of 7 and 8 (Pudovik reaction) to give the nonisolable intermediate 9. The latter underwent cyclization via elimination of one molecule of ethanol to give the final products 10 and 11, respectively (Scheme 5).33

Scheme 5

2.3. Multicomponent (Kabachnik-Fields reaction)
Aminophosphonylation of 4-benzyloxy-2-butanone (12) was performed with ammonia and diethyl phosphite under mild conditions. The α-aminophosphonic ester 13 was obtained in 65% yield. Its debenzylation afforded diethyl 3-hydroxy-1-amino-1-methylpropylphosphonate 14 as a monohydrate. When a solution of the phosphonate 14 in 1,2-dimethoxyethane was treated with a catalytic amount of sodium hydride, 2-ethoxy-2-oxo-1,2-oxaphospholane 15 was obtained as a crude oil (Scheme 6).34
The synthesis of the phosphorinane analogue 18 was performed by aminophosphonylation of the ketone 16 followed by base catalyzed cyclization. Diethyl 4-hydroxy-1-amino-1-methylbutylphosphonate 17 was directly obtained in 45% yield by aminophosphonylation of 16, followed by treatment with a catalytic amount of sodium hydride in anhydrous 1,2-dimethoxyethane, at 60°C for 5 hours (Scheme 7).\textsuperscript{34}

This section focuses on the synthesis of heterocyclic systems containing the α-aminophosphonate moiety which involves the C-N linkage as a part of the heterocyclic system (the nitrogen as a ring heteroatom).
3.1. Addition of dialkyl/trialkyl phosphite to cyclic imines (Pudovik reaction)

Nucleophilic addition of dialkyl phosphite to cyclic C=N imines is one of the most direct ways to synthesize cyclic α-aminophosphonates of this type. Addition of diisopropyl phosphite to the commercially available 2-methyl-1-pyrroline (19) produced diisopropyl α-aminophosphonate 20 in 84% yield (Scheme 8).

Scheme 8

The pyrrolidinyl phosphonic acid 25 can be formed in 50% overall yield by chlorination of pyrrolidine 21 with t-butyl hypochlorite and subsequent elimination followed by reaction with diphenyl phosphite (Scheme 9).

Scheme 9

The D-labelled pyrroline 27 was formed by an aza-Wittig reaction from azide 26. Addition of diethyl phosphite yielded the pyrrolidinephosphonic acid 28 in 97% yield (Scheme 10).
In a one-pot synthesis of 2-phosphonopyrrolidines 31, the unsaturated 1-azaheterocycles 30 were formed by intramolecular hydroamination of aminoalkynes 29 in the presence of catalytic amounts of Cp₂TiMe₂ at 110 °C (Scheme 11). After addition of diethyl phosphite together with 5 mol % Me₂AlCl, the phosphorylated pyrrolidines 31 were obtained in good overall yields (Scheme 11)\textsuperscript{39}.

Treatment of N-benzylproline (32) with oxalyl chloride followed by decarbonylation led to the formation of the iminium salt 34. 2-Phosphonopyrrolidine 25 was then obtained by addition of diethyl phosphite followed by debenzylation and dealkylation, in 90% overall yield (Scheme 12).\textsuperscript{36}
Addition of diethyl phosphite to α-substituted cyclic imines 36 gave cyclic α-substituted α-aminophosphonates 37. The reaction proceeded in ether or THF as a solvent at room temperature without any catalyst, but boron trifluoride etherate could be used to accelerate the reaction (Scheme 13).  

Addition of diethyl phosphite to perfluoroalkyl substituted cyclic imines 38 does not proceed in the absence of catalyst. Under catalysis, α-perfluoroalkyl substituted cyclic α-aminophosphonates 39 were obtained in higher yields than their non-fluorinated analogues mentioned above. As steric hindrances decreases the reaction rate, the formation of five-membered aminophosphonates 39 (n = 1) proceed faster comparing to those having a six-membered ring (n = 2) and compound 39 bearing a trifluoromethyl group is formed more readily than those having the pentafluoroethyl moiety. In spite of the presence of strong electron withdrawing perfluorinated substituent, α-aminophosphonates 39 (n = 1,2) can be converted into the corresponding α-aminophosphonic acids 40 via the reaction with trimethylbromosilane in
chloroform followed by treatment with aqueous methanol of the intermediate trimethylsilyl ester formed (Scheme 14).40

\[ \text{Rf}=\text{CF}_3, \ n=1,2 \]
\[ \text{Rf}=\text{C}_2\text{F}_5, \ n=1,2 \]

**Scheme 14**

In a similar way, enantioselective hydrophosphonylation of cyclic imines 41 using cyclic phosphites, catalyzed by (S)-YbPB (a yitterbium-binolate complex) provided the 4-thiazolidinyl phosphonates (R)-42 in excellent enantiomeric excess and high chemical yields (Scheme 15).41

Since the chiral auxiliary might be easily removed by hydrolysis of the phosphonic ester, Schlemminger et al.42 carried out the addition of chiral BINOL-phosphite to achiral 3-thiazolines 41 in the presence of BF\(_3\)-OEt\(_2\), obtaining the corresponding thiazolidinyl phosphonates 43 in moderate yield and excellent diastereoselectivity. It is noteworthy that the stereoselectivity of the BINOL-phosphite seemed to be independent of the steric demands of the nearby substituents R (Scheme 16).43
Scheme 15

Scheme 16

3,4-Dihydroisoquinoline (44) added diethyl phosphite to yield the tetrahydroisoquinolyl phosphonate 45 (Scheme 17).44

Scheme 17

Reaction of carbocyclic imines 46 with two equivalent of triethyl phosphite in the presence of one equivalent of TFA in ethanol at 300 °C for 17 h gave the corresponding α-amino-phosphonates 47 and 48 in ratios 89:11 to 99:1, respectively (Scheme 18).45
The synthesis of dialkyl 2-(1,1-dialkyl-5,5-dimethyl-1,3-thiazinan-4-yl)phosphonate (51) and 2,2-dimethyl-3,4-dihydro-2H-1,4-benzothiazine-3-dialkylphosphonate (52) was quite simple, requiring the reflux of a mixture of the cyclic imines 49 or 50, respectively, with dialkyl phosphite in ligroin for 18 hours (Scheme 19).

Quino[2,3-\(b\)][1,5]benzoxazepine \(\alpha\)-aminophosphonates 54 were obtained from the reaction of quino[2,3-\(b\)][1,5]benzoxazepines 53 with triethyl phosphite at room temperature under solvent-free conditions employing a catalyst such as KAl(SO\(_4\))\(_2\), FeCl\(_3\), CaCl\(_2\), NiCl\(_2\) and \(p\)-TSA (Scheme 20).
Oxa-aza mixed macrocycles containing α-aminophosphonate moieties 56 were synthesized by the reaction of diethyl phosphate and the 3,4:9,10-dibenzo-1,12-diaza-5,8-dioxacyclo-pentadecane (55) (Scheme 21).49

3.2. Addition of dialkyl phosphite to nitrones
Addition of dimethyl or diethyl phosphite to the nitrone 57 at 40 °C gave the corresponding N-hydroxyphosphonates 58a,b in quantitative yield. O,N-bis-deprotection of 58a,b by hydrogenolysis over Pd/C in ethanol and aqueous hydrochloric acid afforded the pyrrolidinephosphonates 59a,b as the hydrochlorides in 43% and 61% yield, respectively (Scheme 22).50

Alkylation of pyrroline N-oxides 60 with triethylxonium tetrafluoroborate (Meerwein’s salt) or benzyl iodide followed by reaction with diphenyl phosphite led to the formation of phosphonates 62a,b in 70% and 82% yield, respectively (Scheme 23).51

The treatment of nitrone 63 with sodium diisopropyl phosphite, gave a complex mixture of products, which were isolated as: starting material 63, imine 64 and diisopropyl amino-
phosphonate 65. Compound 65 was also obtained from treatment of 64 with diisopropyl phosphite in the presence of sodium diisopropyl phosphite or DBU in THF (Scheme 24). \(^\text{52}\)

\[ \begin{align*}
57 & \quad \text{Me, N+} \\
58 \quad \text{Me, OH} \quad \text{OR}_2 \quad \text{HPO(OR)2} \\
59a & \quad \text{Me, R}=43\% \\
59b & \quad \text{Et, R}=61\%
\end{align*} \]

Scheme 22

\[ \begin{align*}
60 & \quad \text{Me, N+} \\
61 & \quad \text{Me, OR}_2 \\
a & \quad \text{R}^1=H, \text{R}^2=\text{Et}, \text{X}=\text{BF}_4 \\
b & \quad \text{R}^1=\text{Me}, \text{R}^2=\text{PhCH}_2, \text{X}=\text{I}
\end{align*} \]

Scheme 23

\[ \begin{align*}
63 & \quad \text{Ph, N-Ph} \\
64 & \quad \text{Ph, N-Ph} \\
65 & \quad \text{Ph, N-Ph} \\
63 & \quad \text{32\%} \\
64 & \quad \text{29\%} \\
65 & \quad \text{39\%}
\end{align*} \]

Scheme 24
Ethylation of the nitrone 66 afforded the oxoiminium salt 67, which reacted with diphenyl phosphite to yield the corresponding R-methyl-N-alkoxyphosphonopiperidine 68 in 78% yield. Hydrogenolysis of the N-O bond furnished the phosphonopiperidine 69 in 82% yield (Scheme 25).\(^5^1\)

\[
\begin{align*}
\text{Nitrone} & \quad \xrightarrow{\text{PhCH}_2I (82\%) \text{ or } \text{Et}_3\text{OBF}_4 (78\%)} \quad \text{Oxoiminium salt} \\
\text{Ethylation} & \quad \xrightarrow{\text{HP(O)(OPh)}_2} \quad \text{Phosphonopiperidine} \\
\text{Hydrogenolysis} & \quad \xrightarrow{\text{H}_2, \text{Pd/C}} \quad \text{Phosphonopiperidine} \\
\end{align*}
\]

Scheme 25

3.3. Nucleophilic phosphonylation

The apparently most obvious method to synthesize cyclic α-aminophosphonates, was started from the desired cyclic compound bearing a suitable leaving group such as acetate (AcO), phenylsulfinyl (PhSO), and benzotriazole (Bt) in the α-position to the N atom, which was then substituted by a phosphonate group. Thus, 1-(p-tosyl)-2-acetoxyazetidine (71) was synthesized from easily available compound 70 by anodic acetoxylation at the 2-position. Compound 71 was treated with 1.2 equivalents of trimethyl phosphite to obtain the corresponding 2-phosphonoazetidine (72) (Scheme 26).\(^5^3\)

\[
\begin{align*}
\text{Nitrone} & \quad \xrightarrow{-2e^- \text{ AcOH, AcONa}} \quad \text{Acetoxyazetidine} \\
\text{Anodic acetoxylation} & \quad \xrightarrow{1.2 \text{ eq. P(OMe)}_3} \quad \text{Phosphonoazetidine} \\
\end{align*}
\]

Scheme 26
When 4-acetoxyazetidin-2-one (73) was treated with trialkyl phosphite, phosphonylated azetidinones 74 were formed via an atypical Michaelis-Arbuzov reaction, together with the corresponding alkyl acetate. No reaction occurred with tris(2,2,2-trichloroethyl)phosphite because of its reduced nucleophilicity (Scheme 27).\textsuperscript{54}

![Scheme 27](image)

The phthalimido derivative 75 was evaluated in the reaction with trimethyl phosphite. Campbell and Carruthers stated that the reaction led exclusively to the cis-product 77a (89% yield) (Scheme 28).\textsuperscript{55,56}

![Scheme 28](image)
4-Sulfinylazetidin-2-one (78) was another substrate with an appropriate leaving group for a substitution reaction with a phosphonate group. Treatment of 78 with silylated phosphite in the presence of ZnI2 at room temperature for 6 h gave the 4-phosphonoazetidin-2-one (80) in 77% yield.57 Actually, this reaction was not a real substitution reaction, which was indicated by the stereochemistry of the reaction. Due to the action of the Lewis acid, a reactive iminium salt 79 was formed that reacted \textit{in situ} with the trivalent phosphorus nucleophile (Scheme 29).

\begin{center}
\begin{tikzpicture}
\node[align=center] (1) at (0,0) {\textbf{Scheme 29}};
\node[align=center] (2) at (0,-2) {\textbf{Scheme 30}};\end{tikzpicture}
\end{center}

Subsequent Arbuzov reaction in the presence of the mild Lewis acid ZnCl2 or ZnBr2, converted 81 into the desired oxazolopyrrolidine phosphonate 82 as the only diastereoisomer.
Attempts to obtain 82 directly by replacing benzotriazole with triethyl phosphate in the initial reaction mixture resulted in a mixture of two diastereoisomers.\textsuperscript{58-62} Hydrogenolysis of 82, followed by acidic hydrolysis of the phosphonate moiety with 6 M HCl and subsequent treatment with propylene oxide led to (S)-phosphopyrrolidine 25 (Scheme 30).\textsuperscript{59}

Benzotriazol-1-yl (Bt\textsuperscript{1}) and benzotriazol-2-yl (Bt\textsuperscript{2}) are good leaving groups and give rise to the iminium cations. Thus, treatment of 83 in dry THF with triethyl phosphate in the presence of one equivalent of ZnBr\textsubscript{2} produced phosphapyrrolidinones 84 in moderate to good yields (Scheme 31).\textsuperscript{63}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme31}
\end{center}

**Scheme 31**

An asymmetric synthesis of 5-phosphopyrrolidone 87 was based on a similar principle. Here, the hemiaminal-like C-O bond was cleaved by the action of TiCl\textsubscript{4}. The iminium ion 86 was then trapped by trimethyl phosphate with the formation of 87 in 62% diastereomeric excess (Scheme 32).\textsuperscript{64}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme32}
\end{center}

**Scheme 32**
Decarboxylation–phosphonylation reactions of (4R)-acetoxyproline derivative 88 with Phl(OAc)₂/I₂ under sunlight activation, followed by reaction with trimethyl phosphite in the presence of BF₃·OEt₂, afforded the cyclic α-aminophosphonate 89 and its epimer 90 in 64% and 15% yield, respectively (Scheme 33).

\[
\begin{align*}
\text{88} & \xrightarrow{1) \text{Ph(OAc)₂, I₂, sunlight}} \text{89} + \text{90} \xrightarrow{2) (\text{MeO})_3\text{P}, BF₃·OEt₂} \\
\end{align*}
\]

Scheme 33

\[
\begin{align*}
\text{93} & \xrightarrow{\text{P(OMe)₃, SnCl₄}} \text{94} \xrightarrow{(81\%) - \text{Me₂O}} \text{95} \xrightarrow{1) \text{NaBH}_3\text{CN}, 2) \text{H₂, } 3) \text{6N HCl}} \text{96} \\
\end{align*}
\]

Scheme 34
Maury et al. developed a strategy to synthesize both enantiomers of piperidin-2-yl phosphonic acid. The strategy utilized the oxazolopiperidine derivative 93, which upon treatment with trimethyl phosphite in the presence of SnCl₄ gave the corresponding oxazaphosphorinane derivative 95, which then led to pure (R)-(-)-piperidin-2-ylphosphonic acid (96) in good overall yield after reduction and hydrogenolysis (Scheme 34).

The oxazolopiperidine derivative 97 reacted with a triethyl phosphite in the presence of lithium diethyl phosphite to obtain a mixture of two diastereoisomers 98 (93:7, 68% overall yield), which can be hydrogenated to the corresponding 2-phosphonopiperidine 99 in 86% ee (Scheme 35). 68

![Scheme 35](image)

The phosphonate moiety can easily be introduced onto methoxylated piperidines such as 100 in the presence of a Lewis acid by trapping the iminium ion with triethyl phosphite. 69 This methodology was used to obtain the phosphonopiperidine 102 (Scheme 36).
Scheme 36

3.4. Multicomponent reaction (Kabachnik-Fields reaction)
2-(Diethylphosphono)-2-methylpyrrolidine (104) was obtained in a one-pot reaction by bubbling ammonia into an ethanolic solution of 5-chloropentan-2-one (103) and diethyl phosphite (Kabachnik-Fields reaction) (Scheme 37).70,71

\[
\begin{align*}
\text{H}_2\text{C}-\text{C}=\text{O} & \quad \text{NH}_3 \\
\text{Cl} & \quad \text{HP(O)(OEt)}_2
\end{align*}
\]

\[
\begin{align*}
\text{103} & \quad \text{104} \\
(62\%) & \quad \text{(62\%)}
\end{align*}
\]

Scheme 37

Reaction of alkanedial (105), acetamide, and acetyl chloride with PCl₃ in acetic acid exclusively produced the bisphosphonic acid 106a in 39% yield. When the reaction was performed with pentanedral, the corresponding piperidine 106b was formed (33%) in a 1:1 mixture with the acyclic bis(aminophosphonic acid) 107b (Scheme 38).72
Scheme 38

3.5. Diels-Alder reaction
Davis and co-workers\textsuperscript{73} described [4+2] cycloadditions between azirinylphosphonates 108 with 2,3-dimethylbutadiene (109) or trans-piperylene 111. The diene (100 equivalents) was reacted with the phosphonoazirine for 2-4 days at room temperature. Bicyclic aziridines 110 and 112, respectively were isolated as single stereoisomers by flash chromatography. Catalytic hydrogenation of 110 results in two products. The major products, were identified as quaternary piperidinephosphonates (2S)-(−)-113, which resulted from the expected cleavage of the C-7-N bond in 110. The minor products, obtained in 28\% and 13\% yield, respectively, were identified as pyridines 114. Controlling the conditions for the hydrogenation of 112 led to the reduction of the C-C double bond, affording the phosphonopiperidine 115 (Scheme 39).

Diethyl 3-(diethoxyphosphoryl)-6-alkylpyridazine-1,2(3\textsubscript{H},6\textsubscript{H})-dicarboxylates (118) was obtained in 85\% yield from cycloaddition reaction of 1,3-dienylphosphonates 116 with diethyl azidodcarboxylate (117) in dioxane. Compounds 118 were generally regarded to have a half chair configuration based on the relationship between the vicinal coupling constants and dihedral angles (Scheme 40).\textsuperscript{74}

3-(Dimethylphosphino)piperidine 121 can be synthesized via a Diels-Alder reaction of di-(−)-menthyl azodicarboxylate (120) and 1-trimethylsilyloxybutadiene (119) in the presence of trimethyl phosphite and a Lewis acid, as an inseparable mixture of diastereomers (Scheme 41). However, after hydrogenation of 121, the phosphonopiperidazines 122 and 123 can easily be separated by column chromatography.\textsuperscript{75}
Scheme 39

Scheme 40
3.6. Ring closure of iminophosphonates

Recently, an initial study was made on the reactivity of 1-phosphono-2-aza-1,3-dienes,\(^{76,77}\) which prove to be promising substrates for the synthesis of azaheterocyclic phosphonates. Reaction of the azadienes \(124\) with an excess of diazomethane led to the clean generation of 1-vinyl-2-phosphonoaziridines \(125\) in good yields (Scheme 42).

Reaction of carbanions of \(N\)-phosphonomethyl imines \(126\) with \(\alpha,\beta\)-unsaturated esters \(127\) can lead to three different products: an acyclic adduct \(129\) due to Michael addition, pyrroline \(131\) due to cycloaddition and subsequent elimination of the diethyl phosphate anion, or pyrrolidine \(130\). When sodium hydride was used as a base at room temperature, pyrrolidines \(130\) were
formed exclusively in good yields (77-90%) due to the stereospecificity of the reaction related to the concerted mechanism (Scheme 43).78-80

Scheme 43

The metal-catalyzed cycloaddition reactions of α-iminophosphonate 132 with various dipolarophiles including chiral menthylxylo furanone with (AgOAc) or (LiBr) and a suitable base [DBU, Et3N, BTMG (t-butyltetramethylguanidine)] afforded a wide variety of conformationally constrained cyclic α-aminophosphonate 135 (Scheme 44).81 The imine 136 was alkylated, followed by ring closure via hydrolysis by trifluoroacetic acid to give the 2-phosphonopyrrolidinone 138 (Scheme 45). When hydrochloric acid was used, no cyclization occurred and the corresponding hydrochloride salt of the acyclic amine was recovered from the reaction mixture.82

When unsubstituted acrylic esters83-85 were used in the addition reaction, only ZnCl2 generated carbanions of 139 were reactive. Iminophosphonate 140 was formed in 66% yield with 71% de. The minor diastereomer was easily removed by flash chromatography on silica gel. After hydrolysis, enantiomerically pure (5S)-pyroglutamic acid derivative 141 was isolated. The chiral auxiliary was recovered in 60% yield (Scheme 46).
\[ R^1 = H, \text{Me, Ph, PhCH}_2 \]
\[ R^2 = \text{Me, Et} \]
\[ R^3 = \text{Me, Et} \]

**Scheme 44**

\[ \text{136} \xrightarrow{\text{KHMS}} \text{137} \text{ (72\%)} \]
\[ \text{137} \xrightarrow{\text{CF}_3\text{COOH, CH}_2\text{Cl}_2} \text{ (n=2)} \]
\[ \rightarrow \text{138} \text{ (85\%)} \]
Scheme 46

Treatment of \( N^1-(\text{diethoxyphosphorylmethyl})-N^2-(\text{pentamethylene})\text{benzamide (142)} \) with \( n \)-butyllithium followed by the addition of \( p \)-tolualdehyde led to the formation of diethyl (\( \text{trans} \) and \( \text{cis} \)) \( 2\)-phenyl-5-alkyl/aryl-oxazolin-4-yl)phosphonates 144 in good yields (Scheme 47).86

Scheme 47
Methyl mercaptoacetate was added to a stirred solution of the diethyl trifluoroacetimidoylphosphonate (145) in benzene to give the nonisolable intermediate 146 which was directly cyclized into cyclic α-aminophosphonate 147 (Scheme 48).87

![Scheme 48](image)

3.7. Ring closure of oximinophosphonates
The preparation of the required functionalized β-tosyl oximes 149 was easily accomplished by simple reaction of β-oximes 148 with tosyl chloride in pyridine. Alkyl and phenyl substituted 2H-azirines 150 were prepared from β-ketoximes 149 by treatment with triethylamine at room temperature for 8 hours in dry benzene. Reduction of 150 with sodium borohydride in ethanol gave exclusively cis-aziridines 151 (Scheme 49).88,89

![Scheme 49](image)
Chlorobutryl chloride (152) was allowed to react with trialkyl phosphite. Then the oxime 154 was formed and ring closure was performed after reduction of the oxime with zinc and formic acid to give the cyclic α-aminophosphonates 155 (Scheme 50).\(^\text{90}\)

![Scheme 50]

3.8. Ring closure of acyclic α-aminophosphonates

Treatment of phosphoserine diethyl ester (R)-156 with tosyl chloride afforded the corresponding N-tosylate (R)-157, which, by reaction with mesyl chloride, afforded the O-mesylate derivative (R)-158. Reaction of (R)-158 with NaH in THF gave the aziridine-2-phosphonate (R)-159 (Scheme 51).\(^\text{91}\)

![Scheme 51]
Similarly, Guseinov et al.\textsuperscript{92} reported that acyclic α-aminophosphonate 160 was transformed into phosphonate-containing aziridines 161 by the action of sodium alkoxide (Scheme 52).

\[ \text{Scheme 52} \]

Ring closure through intramolecular nucleophilic substitution was applied in the synthesis of phosphono-β-lactams. The first example consists of an epoxide ring opening by intramolecular attack of a phosphorus-stabilized carbanion (Scheme 53). The epoxide 163 was formed \textit{in situ} by addition of one equiv of LiHMDS (lithium 1,1,1,3,3,3-hexamethyldisilazane) to amide 162. A second equivalent was used to form the lactam 164 in a stereospecific manner: only the trans-β-lactams were formed. Nitrogen deprotection can then be performed using CAN (cerium ammonium nitrite), and the obtained 4-phosphono-β-lactams 165 are potential precursors for the synthesis of carbapenems.\textsuperscript{93-95}

\[ \text{Scheme 53} \]
Chloroamidophosphonates 166 were treated with NaH to involve ring closure to give the cyclic α-aminophosphonates 167 (Scheme 54).96,97

\[
\begin{align*}
&\text{Cl} & &\text{N} & &\text{O} & &\text{R}^1 \\
&\text{Ar} & &\text{P} & &\text{O} & &\text{R}^2 & &\text{NaH} & &\text{THF} & &71-99\% \\
\end{align*}
\]

\[
\begin{align*}
&\text{N} & &\text{Cl} & &\text{O} & &\text{P} & &\text{O} & &\text{Ar} \\
&\text{R}^1 & &\text{P} & &\text{O} & &\text{Ar} & &\text{OR}_2 & &\text{NaH} & &\text{THF} \\
\end{align*}
\]

Ar=Ph, Furyl, Cinnamyl
R^1=Bn, Naphthyl
R^2=Me, Et

Scheme 54

Treatment of the α-aminophosphonate 168 with thionyl chloride in dichloromethane, followed by the addition of NaHCO_3 gave the chloro derivative 169. Reaction of 169 with LiHMDS in THF afforded only the 1,3-trans-azetidine 170, which, on hydrolysis of the phosphonate moiety with TMSBr, followed by purification by ion-exchange chromatography, led to azetidin-2-ylphosphonic acid 171 (Scheme 55).98

\[
\begin{align*}
&\text{OH} & &\text{N} & &\text{P(OEt)}_2 & &\text{Ph} \\
&\text{CH}_2\text{Ph} & &\text{Ph} & &\text{Cl} & &\text{O} & &\text{N} & &\text{P(OEt)}_2 \\
&\text{CH}_2\text{Ph} & &\text{Ph} & &\text{Cl} & &\text{O} & &\text{N} & &\text{P(OEt)}_2 \\
&\text{Ph} & &\text{Ph} & &\text{Cl} & &\text{O} & &\text{N} & &\text{P(OEt)}_2 \\
&\text{CH}_2\text{Ph} & &\text{Ph} & &\text{Cl} & &\text{O} & &\text{N} & &\text{P(OEt)}_2 \\
\end{align*}
\]

\[
\begin{align*}
&1) \text{TMSBr} & &\text{Ph} & &\text{P(OEt)}_2 & &\text{Ph} \\
&2) \text{Dowex} & &\text{Ph} & &\text{P(OEt)}_2 & &\text{Ph} \\
\end{align*}
\]

170

Scheme 55
The cyclization of the $\delta$-chloro-$\alpha$-aminobutanephosphonic acid (172), resulted in the racemic pyrrolidine-2-phosphonic acid 25 which has received some interest as a potential structural mimetic of proline (Scheme 56).\textsuperscript{99}

$$\text{ClP(OH)2NH2}$$

$$\text{O}$$

$$\text{N}$$

$$\text{P(OH)2}$$

Scheme 56

$\alpha$-Aminophosphonates 173 underwent tandem acylation and [4+2] cycloaddition with maleic anhydride under stirring in toluene at ambient temperature for 3 days to isolate epoxyisoindolyl phosphonates 174 in good yields (70-90\%) as colorless solids (Scheme 57).\textsuperscript{100}

Scheme 57

Adding one equivalent of Grubbs second-generation catalyst to the substrates 175 via ring closure methasis (RCM) gave the corresponding 2-phosphonopyrrolines 176 (Scheme 58).\textsuperscript{101}

Scheme 58
When β-allenic α-aminophosphonates 177 were heated in the presence of silver salts to activate the allenic moiety, a mixture of five- and six-membered heterocycles was obtained. The ratio of five-membered to six-membered rings was dependent on steric factors. When R1 and R2 were more sterically demanding groups, the ratio shifted toward the five-membered ring. The largest effect, however, was observed when R3 was changed from H to Me; then, only very small amounts of six-membered rings 181 were formed. When the obtained pyrrolines 182 were submitted to high temperatures (80 °C) under an inert atmosphere, the enamines 183 were formed by tautomerization to the more thermodynamically stable compound (Scheme 59).
Diethyl (6-isobutylamino)bicyclo[3,2,0]hept-2-en-6-yl phosphonate (185) was reacted with HBr and Br₂ to give the hydrobromide salt 186, which underwent ring closure by addition of triethylamine and heating of the mixture in acetonitrile for 14 hours to give diethyl endo-(8-bromo-2-isobutyl-2-azatricycle[3,3,0,0³,6]oct-3-yl)phosphonate (187) (Scheme 60).¹⁰⁴

```
\begin{align*}
\text{185} & \xrightarrow{\text{i}} \text{186} \\
i & 1.05 \text{ equiv. HBr, 1.05 equiv. Br}_2, \text{ extraction with NaHCO}_3 \\
\text{ii} & 1.1 \text{ equiv. Et}_3\text{N, CH}_3\text{CN, Reflux overnight}
\end{align*}
```

Scheme 60

Cyclization of the R-α-amino-δ-alkenylphosphonates 188 was initiated by addition of Hg(OAc)₂ to the double bond followed by cyclization through intramolecular nucleophilic attack by the free amine. Using α-amino-δ-alkenylphosphonates, it was possible to obtain the five- and six-membered rings containing the α-aminophosphonate moiety (Scheme 61).¹⁰⁵-¹⁰⁷ 1,4-Addition of lithiated aminomethylphosphonate 195 to α,β-unsaturated ester 194 proceeded to give the dibenzylaminophosphonate 196 in 94% yield and 98% diastereomeric excess. Reductive deprotection of 196 then led to trans-phosphonopyrrolidone 197 in 66% yield (Scheme 62).¹⁰⁸
Scheme 61

Method A: 1) Hg(OAc)$_2$, acetone, 2) NaBH$_4$, CH$_2$Cl$_2$
Method B: 1) Hg(OAc)$_2$, THF/water, 2) NaHBH$_4$, THF/water

Scheme 62
Cleavage of the sulfinyl group and hydrolysis of the acetal 198 gave the aminocarbonyl derivative, which cyclized to afford the iminophosphonates 199. Catalytic hydrogenation of 199 led to the cyclic α-aminophosphonates 200 (Scheme 63).109

Scheme 63

Addition of three to eight equivalents of amine to the enamide 201 in methanol or toluene afforded the 5-phosphonylated-2-imidazolidinones 202 which could be isolated in moderate yield 17-49% (Scheme 64).110

Scheme 64

Reaction of phosphoserinate (R)-203 with benzaldehyde, followed by reduction with sodium cyanoborohydride in acetic acid, afforded the N-benzyl α-amino-phosphonate (R)-204 in 76% yield. Treatment of (R)-204 with thionyl chloride and subsequent oxidation with sodium periodate in the presence of ruthenium chloride gave the sulfonamide (R)-205 in 70% yield (Scheme 65).111
The $\alpha$-aminophosphonate 206 was submitted to a hydrogenolysis-reductive amination, resulting in the polyhydroxylated piperidinylphosphonate 207 (Scheme 66).\(^{112}\)

Scheme 66

Davis et al.\(^ {109}\) described the stereoselective synthesis of piperidin-2-yl-phosphonates 210a,b. Cleavage of the sulfinyl group and acidic hydrolysis of the ketal in 208a,b gave an amino-carbonyl derivative, which underwent cyclization to afford the iminophosphonates 209a,b. Finally, catalytic hydrogenation of 209a,b led to the cyclic $\alpha$-aminophosphonates $(2R,6S)$-210a and $(2R,6R)$-210b, respectively (Scheme 67).

Ring closing metathesis (RCM) of $\alpha$-aminophosphonates, bearing two terminal alkene chains, was a convenient strategy to synthesize heterocyclic $\alpha$-aminophosphonates. Osipov et al. succeeded in the synthesis of the cyclic aminophosphonates 213.\(^ {113,114}\) Allylation of the nitrogen
atom of α,β-unsaturated α-aminophosphonates 211 gave rise to the 1,7-dienes 212 which can be ring closed to the 3-piperidines 213 using a Ru catalyst (Scheme 68).

\[
\text{Scheme 67}
\]

\[
\text{Scheme 68}
\]
Conversion of $\alpha$-amino-(2-alkynylphenyl)methylphosphonate 214 to 2,3-disubstituted-1,2-dihydroisoquinolin-1-yl phosphonate 215 was performed through 6-endo-cyclization utilizing silver triflate as catalyst (Scheme 69).\(^{115}\)

\[ \text{Scheme 69} \]

### 3.9. Ring closure of acyclic $\beta$-aminophosphonates

The hydrolysis of diethyl ester 216 led in a one-pot procedure to the pure $\beta$-amino-phosphonic acid 217 (yield: 47\%). Cyclization of 217 by boiling in aqueous sodium hydroxide forms within 5 minutes the disodium salt, which gave 86\% of pure aziridine 218 after passage through an ion exchange column (Scheme 70).\(^{116,117}\)

\[ \text{Scheme 70} \]

Treatment of the mesylated $\beta$-aminophosphonate 219 with K$_2$CO$_3$ in DMF resulted in the formation of the $N$-protected aziridines 220 in high yields and purity (>99\%) (Scheme 71).\(^{118}\)

The diastereoisomers of $\beta$-aminophosphonates 221 and 222 were cyclized using NaH, resulting in the diastereoisomers 223 (76\%) and 224 (75\%), respectively, which were subjected
to hydrolysis conditions (TFA-MeOH) or MeMgBr to give the corresponding acids 225 and 226, respectively (Scheme 72).\textsuperscript{73,119-120}

Scheme 71

Scheme 72
3.10. Ring closure of acyclic γ-aminophosphonates

Ring closure of the mesylates 227 in refluxing toluene-water mixture in the presence of K₂CO₃ produced azetidinyl-2-phosphonates (228), which were hydrolyzed into the corresponding azetidinyl-2-phosphonic acids (229) (Scheme 73).¹²¹

\[
\begin{align*}
\text{RHN} & \quad \text{PH(Pr)₂} \\
\text{OMs} & \quad \text{O} \\
\text{K₂CO₃} & \quad \text{toluene} \\
\text{water} & \quad \text{CH₃CN} \\
\text{227} & \quad \text{228}\ (48-66\%) \\
\text{228} & \quad \text{229}\ (63-70\%) \\
\text{R}=\text{allyl, PhCH₂, 2-hydroxyethyl, n-Pr} & \quad \text{R}=\text{PhCH₂, 2-hydroxyethyl}
\end{align*}
\]

Scheme 73

3.11. Ring closure of acyclic δ-aminophosphonates

Treatment of δ-amino-β-ketophosphonates 230 with TFA, followed by reaction with (Boc)₂O, afforded the derivatives 231 in 80–90% yield. Reaction of 231 with NaH and 4-acetamido-benzenesulfonyl azide (4-ABSA) furnished the diazo derivatives 232 in excellent yield (83–91%), which, by treatment with Rh₂(OAc)₄, led to the 3-oxo-pyrrolidine phosphonates 233. Removal of the 3-oxo group in 233 by treatment with NaH, followed by the addition of diethyl chlorophosphonate, and subsequent hydrogenation of 234 provided the cyclic phosphonates 235 in good yield. Finally, cleavage of the Boc-protective group in 235 with TFA afforded the cis-5-substituted pyrrolidine-2-phosphonates 236 in 68–86% yield (Scheme 74).⁸¹,¹²²-¹²³
Scheme 74

3.12. Ring closure of acyclic α-hydroxyphosphonates
Phosphonylated 2-imidazolidinone 239 was prepared from phosphonylated aldehyde 237 and urea 238 (Scheme 75). 124,125
Scheme 75

3.13. Ring closure of isothiocyanatomethylphosphonates

The lithium derivative of diethyl isothiocyanatomethylphosphonate (240) was reacted with aldehyde to afford a mixture of cis- and trans-(2-thioxo)oxazolidine-4-yl)phosphonate (241) which were separated by column chromatography (Scheme 76).\textsuperscript{126,127}

\[
\begin{align*}
\text{(EtO)}_2(O)P &\quad \text{NCS} \\
RCHO &\quad \text{BuLi} \\
\text{240} &\quad \text{241 (60-78\%)} \\
R= &\text{Ph, t-Bu, i-Pr, PhCH=CH, 2-Furyl}
\end{align*}
\]

Scheme 76

Blaszczyk \textit{et al.}\textsuperscript{128} demonstrated that the diastereoselective addition of diethyl isothiocyanatomethylphosphonate (240) to various N-protected imines 242 afforded the cyclic thioxoimidazolidinylphosphonates 245 (Scheme 77).

\[
\begin{align*}
\text{(EtO)}_2(O)P &\quad \text{NCS} \\
\text{(s)-(--)242} &\quad \text{t-BuOK, THF} \\
-75 \degree C, 3h &\quad 52-83\% \\
\text{240} &\quad \text{243} \\
\text{245} &\quad \text{trans : cis = 92.8:98.2}
\end{align*}
\]

Scheme 77
3.14. Miscellaneous

3.14.1. Photocyclization. The antibacterial phosphonoaziridine \textit{247} and a salt of 2H-aziridine \textit{248} were prepared via photocyclization reactions.\textsuperscript{116} Thus, vinylphosphonate \textit{246} was treated with ethyl azidoacetate by irradiation with UV light (Scheme 78).

\[
\begin{array}{c}
\text{N}_3\text{COOEt} \quad \text{hv} \\
\text{N} \quad \text{P(OMe)}_2 \quad \text{COOEt} \\
\text{Me}_3\text{SiCl} \quad \text{NaOH} \\
\text{Et}_3\text{N} \\
\end{array}
\]

\textit{246} \quad \textit{247} \quad \textit{248}

Scheme 78

3.14.2. Reaction of azirine phosphonate with Grignard reagent. Reaction of 2\textit{H}-azirine phosphonate \textit{249} with ethyl magnesium bromide in THF at -78 °C led exclusively to the formation of diethyl \textit{trans}-3-ethyl-3-methylaziridin-2-ylphosphonate \textit{250} (Scheme 79).\textsuperscript{129}

\[
\begin{array}{c}
\text{R}_1\text{MgBr} \quad \text{THF} \\
\text{R}_2\text{N} \quad \text{H} \\
\text{P(OEt)}_2 \\
\end{array}
\]

\textit{249} \quad \textit{250}

R\textsubscript{1}=Me, Ph
R\textsubscript{2}=Et, CH\textsubscript{2}Ph, CH\textsubscript{2}-CH=CH\textsubscript{2}

Scheme 79

3.14.3. Phosphonylation of lactams. Lactam \textit{251} was phosphonylated with triethyl phosphite in the presence of phosphorus oxychloride. The 1,1-diphosphonoazetidine \textit{252} was obtained in only low yields (28%) (Scheme 80).\textsuperscript{130}

\[
\begin{array}{c}
\text{P(OEt)}_2/\text{POCl}_3 \\
\text{NH}_4\text{OH} \\
\end{array}
\]

\textit{251} \quad \textit{252}

Scheme 80
3.14.4. **Hydrolysis of an acetal.** The acetal 254 was hydrolyzed in an acidic medium, and the resulting mixture was treated with several triphenyl phosphite reagents in hydrochloric acid to give diastereomeric mixtures of the N-protected diphenyl pyrrolidinephosphonates 255 (Scheme 81).\(^{131,132}\)

![Scheme 81](image)

3.14.5. **Cycloaddition to phosphorylated nitrile ylide.** Diethyl isocyanomethylphosphonate 256 can be used immediately in a cycloaddition reaction with methacrylonitrile 257 and Cu\(_2\)O as a catalyst, producing the pyrrole 258 in 83% yield (Scheme 82).\(^{133}\)

![Scheme 82](image)

3.14.6. **Cycloaddition to phosphorylated nitrone.** 1,3-Dipolar cycloaddition of nitrone 259 was first examined with terminal alkenes in toluene at 60 °C. *Cis-* and *trans-*diastereomeric isoxazolidines 260 and 261 were obtained in the ratio 90:10 in yields 23-73% (Scheme 83).\(^{134}\)
4. Type C: Cyclic α-Aminophosphonic Acid Derivatives Containing the Phosphorus and Nitrogen as Ring Heteroatoms

4.1. Addition of phosphorus reagents to acyclic imines

4.1.1. Addition of phosphites to acyclic imines (Pudovik reaction). In the reaction of N-(benzylidene)-2-aminoethanol (262) with diethyl/ethylene/bis(β-chloroethyl)chlorophosphite in CHCl₃, 2-(β-chloroethoxy)/ethoxy-2-oxo-3-phenyl-1,4,2-oxazaphosphorines (266) were obtained in good yields as diastereomers A and B (Scheme 84).

Scheme 84

Reaction of 2-(N-benzylidene)aminophenol (267) with diethyl chlorophosphite carried out in the absence of an external HCl acceptor resulted in the formation of two diastereomers of 2-(2′-alkoxy)-2-oxo-3-phenyl-1,4,2-benzoazaphosphorinanes (271) (Scheme 85).

Scheme 85
The Pudovik reaction of hydrazone 272 using diethyl phosphite in boiling THF containing a catalytic amount of sodium hydride produced a cyclic α-aminophosphonate ester 274 as only one isomer (Scheme 86).\textsuperscript{138}
Heterocyclization of bis-thiosemicarbazone 275 with diethyl phosphite at 80 °C in the presence of BF₃·Et₂O at 80 °C for 10 hours, afforded an interesting type of phosphorus heterocycle, namely bis-[3-(4'-biphenyl)-4-[2-ethoxy-6-phenylamino-2-oxo-3,4-dihydro-2H-1,4,5,2-thiadiazaphosphinin-3-yl]-1H-pyrazol-1-yl]phosphine oxide (277) (Scheme 87). The proposed mechanism for formation of 277 may occur via addition of the phosphorus atom of diethyl phosphite to the CH=N exocyclic groups to give the nonisolable intermediate 276, which underwent cyclization by nucleophilic attack of SH groups at the phosphonate to eliminate two molecules of ethanol (Scheme 87).[^139]

![Scheme 87](image)

**Scheme 87**

Addition of diethyl phosphite to the azomethine bond of the hydrazone 278 required heating at 80-100 °C with triethylamine as a catalyst and gave 3-(4-amino-5-ethoxy-3,5-dioxo-1,2,4,3,5-triazadiphosphinan-6-yl)-4H-chromen-4-one (280). Most likely, the addition led to intermediate 279 (not isolated), which underwent intramolecular cyclization via elimination of ethanol affording compound 280 (Scheme 88).[^140]
4.1.2. Addition of isocyanatophosphite to acyclic imines. The phosphorylation pathway for (trichloroethanylidene)-N-methylamine 281 was determined by the nature of the phosphorus reagent. Thus, its reaction with trivalent phosphorus isocyanates as 1,3-dipole gave cyclic C-phosphorylated iminophosphoranes 282 which transformed into α-aminophosphonate 283 as a result of imide-amide rearrangement (Scheme 89).141
Reaction of N-acetyl compound 284 with dimethyl isocyanatophosphite in benzene at 20-60 °C, gave the cycloadduct 285 which underwent imide-amide rearrangement leading to stereoisomeric diazaphospholanes 286 and 287 (Scheme 90).142

Scheme 90

At the same time, dimethyl isocyanatophosphite reacted with imine 288 as a 1,3 dipole giving the diazaphospholanes 290 (Scheme 91).142

Scheme 91

4.2. Multicomponent reactions
4.2.1. Reaction of carbonyl and aminoalcohols with phosphites (Kabachnik-Fields reaction). The Mannich type reaction between 2-aminoethanol and formaldehyde in an aqueous
solution of phosphorous acid did not result in the expected \([((2\text{-}hydroxyethyl)\text{imine})\text{bis(methylphosphonic)} \text{ acid} \ (291)](\text{but in } \([(2\text{-}hydroxy-2\text{-}oxido-1,4,2\text{-}oxazaphosphinan-4\text{-}yl})\text{methyl}]\text{phosphonic acid} \ (292) \text{ as a product of an intramolecular condensation}) \text{ (Scheme 92).}^{143}

\[
\begin{align*}
\text{NH}_2 \quad + \quad \text{O} \quad + \quad \text{HPOOH} \\
\text{OH} \quad \text{P} \quad \text{OH} \quad \text{OH} \\
\text{O} \quad \text{N} \quad \text{P} \quad \text{OH} \quad \text{OH} \\
\text{P} \quad \text{OH} \quad \text{OH} \quad \text{O} \quad \text{H} \\
\text{NH}_2 \\
\end{align*}
\]

Scheme 92

2-Aminophenol was allowed to react with alkyl dichlorophosphinite and various substituted ketones or benzaldehyde in anhydrous tetrahydrofuran containing a small amount of potassium carbonate to give 2-alkoxy-2-oxo-1,4,2-oxazaphosphinane \(294\) in good yield. The reaction was carried out using a one pot procedure (Scheme 93).\(^{144-147}\)

\[
\begin{align*}
\text{NH}_2 \quad + \quad \text{Cl}_{2}\text{POR}_1 \\
\text{OH} \quad \text{Cl} \quad \text{Cl} \\
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{THF/K}_2\text{CO}_3 \quad 62-92\% \\
\end{align*}
\]

Scheme 93
Similarly, when the starting material 2-amino-3-hydroxy-1,4-naphthoquinone (295) reacted with phenyl phosphorodichloridite and ketone or aromatic aldehyde, 2-alkoxy/aryloxy-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]oxazaphosphinane-5,10-dione 2-oxides (296) were obtained in 55-82% yields (Scheme 94).148,149

Scheme 94

The Kabachnik-Fields reaction using 3,4-diamino-6-methyl-1,2,4-triazin-5(4H)-one (297), acetaldehyde and diethyl phosphite in THF in the presence of sodium hydride as a catalyst led to only one isomer of 1,2,4-triazino[4,3-b][1,2,4,5]triazaphosphinine derivative 299 (Scheme 95).138

Scheme 95
The one-pot Kabachnik-Fields reaction of compound 300, acetaldehyde and diethyl phosphite in THF containing sodium hydride as a catalyst produced one isomer of [1,2,4] triazino[3,2-c][1,2,4,5]triazaphosphinine 303, via the nonisolable intermediate 302, which spontaneously was cyclized through $N$-2 of the triazine ring and not the exocyclic $N$-amino, with elimination of a molecule of ethanol (Scheme 96).

![Scheme 96](image)

**Scheme 96**

Diethyl [(3-hydroxypropyl)amino](aryl)methylphosphonate (304) and 1,4,2-oxazaphosphapane derivative 305 were prepared by the Kabachnik-Fields reaction, realizing a three component combination of 3-aminopropanol, $o$-tolualdehyde and diethyl phosphite in toluene (Scheme 97).

![Scheme 97](image)

**Scheme 97**
The eight-membered 3,7-dihydroxy-3,7-dioxoperhydro-1,5,3,7-diazadiphosphocine-1,5-diatic acid (306) was obtained with a one step reaction of glycine, formaldehyde and hypophosphorous acid in acidic aqueous medium (Scheme 98).\(^1\)

![Scheme 98](image)

4.2.2. Reaction of cyclopropanone acetal and 1,2-aminoalcohols with phosphites. Reaction of (2S)-phenylglycinol (307) with cyclopropanone acetal (308) and triethyl phosphate gave the spirophosphonates 309 and 310 in low yield and in diastereoisomeric ratio 89:11 (Scheme 99).\(^2\)

![Scheme 99](image)

4.3. Ring closure of acyclic \(\alpha\)-aminophosphonates

Fluorinated 1-methylaminoalkylphosphonates 311 reacted with \(\text{NH}_3\) to form heterocyclic salts 312, which underwent elimination of ammonia under heating to give the neutral 1,4,2-diazaphospholines 313 (Scheme 100).\(^3\)
Phosphorylated urea 316 was obtained as the result of addition of \( \alpha \)-aminoalkylphosphonates 314 to bis(chloromethyl)isocyanatophosphonate (315). Compound 316 can be cyclized in two ways: a) with elimination of phenol and formation of diazaphospholidine 317, which under the action of phenol was converted into diazaphospholidine 318, and b) in the presence of a base, intramolecular alkylation of oxygen atoms of carbonyl fragment by chloromethyl group took place with the formation of 1,3,4-oxazaphosphol-2-ines 319 (Scheme 101).\(^{154}\)

It was found that diphenyl (\( \alpha \)-methylamino)benzyl phosphonate (320) readily underwent addition to different iso(thio)cyanates in the presence of a catalytic amount of triethylamine, yielding 1,3,4-diazaphospholidines 322a-e. The reaction involved intermediate formation of \( N,N' \)-disubstituted (thio)ureas 321 which underwent fast cyclization by elimination of phenol. The labile exocyclic P-N bond of 322d,e was cleaved upon the action of phenol to give the final product diazaphospholidine 323 (Scheme 102).\(^{155-157}\)

A highly diastereoselective synthetic procedure for the preparation of enantiopure (2S,5S)-4-benzyl-2-alkoxy-2-oxo-5-phenyl-1,4,2-oxazaphosphinanes [(2S, 5S)-1] (326) from (S)-phenylglycinol (307) was achieved by its condensation with benzaldehyde followed by palladium catalyzed hydrogenation to give \( N \)-benzyl-(S)-phenylglycinol (324). The latter compound was condensed with formaldehyde (toluene solvent) and the resulting iminium salt was immediately treated with dialkyl phosphite to afford Mannich products (S)-325. Treatment of carbinol (S)-325 with KH in THF solution afforded cyclized products 326 in good yield (Scheme 103).\(^{158}\) Also, compound 307 was treated with trimethyl phosphite and formaldehyde to give \( N \)-(phosphonomethyl)oxazolidine 327. Treatment of 327 with phenyl magnesium bromide and in the presence of TiCl\(_4\) gave directly the expected 326 (R=Me) but in low yield (Scheme 103).\(^{159}\)
Scheme 101

\[ \text{(PhO)}_2P\text{-CH-NHR}_1\] (320) + RNCX \rightarrow \text{(PhO)}_2P\text{-CH-N-CNHPH}_1\] (321) 28-94\% - PhOH

\[ \text{PhO-P-N\text{-}}\text{N}^\text{+}\text{Me}\] (318) + Cl(CH_2)_2P(O)(OPh) \rightarrow PhOH

\[ \text{ClCH}_2\text{P(O)}\text{-NCO}\] (314) + ClCH_2\text{P(OCO)} \rightarrow \text{ClCH}_2\text{P(OCO)}\] (315)

\[ \text{ClCH}_2\text{P(O)}\text{-NCO}\] (317) \rightarrow \text{Cl(CH}_2)_2\text{P(O)(OPh)}\] (319)

Scheme 102

\[ \text{322a, } R=\text{Ph, } R^1=\text{Me, } X=\text{O}\]
\[ \text{322b, } R=\text{Ph, } R^1=\text{Me, } X=S\]
\[ \text{322c, } R=(\text{EtO})_2(O)P, \ R^1=\text{Me, } X=S\]
\[ \text{322d, } R=(\text{ClCH}_2)(\text{PhO})(O)\] P, \ R^1=\text{Me, } X=\text{O}\]
\[ \text{322e, } R=(\text{ClCH}_2)_2(O)\] P, \ R^1=\text{Me, } X=\text{O}\]
\[ \text{322f, } R=(\text{ClCH}_2)(\text{PhO})(O)\] P, \ R^1=\text{Ph, } X=\text{O}\]
Scheme 103

Compounds 332, 328 and 329 when heated in absolute ethanol containing a catalytic amount of triethylamine afforded 3-[2-(2-chloroethoxy)-2-oxo-4-phenyl-1,4,2-oxazaphosphinan-3-yl]-6-methyl-4-oxo-4H-chromen-4-one (331). Formation of compound 331 is assumed to take place via loss of one HCl molecule from 332, 328 and 329, followed by elimination of both water and aniline in the case of 328 and 329, respectively. Hydrogen bonding between XH and NH groups gives stability to systems 328 and 329, but destruction of this hydrogen bond, after removing a molecule of HCl, may facilitate elimination of water and aniline (Scheme 104).33

5-Chloro-2-nitrobenzoyl chloride (333) was reacted with α-aminophosphonate 334 to afford the nitroamide 335. Catalytic hydrogenation of 335 gave the cyclization precursor 336. Reacting a DMF solution of 336 with NaH followed by warming to 60 °C for a few hours, affording 4-alkyl-7-chloro-2-ethoxy-2,3-dihydro-2-oxido-1H-1,4,2-benzodiazaphosphepin-5 (4H)-ones (337) (Scheme 105).160

4.4. Miscellaneous
4.4.1. Reaction of dialkyl/diphenyl phosphite with hydroxyl alkyl carbamate. 3-Ethyl-2-hydroxy-2-oxo-1,4,2-oxazaphosphorinane (339) was obtained by treating various phosphonic acids diesters with hydroxyl alkyl carbamate mixtures 338. During the first stage of the reaction at 135 °C, transesterification occurred to give urethane phosphonates. In the second stage of the reaction at 170 °C, thermal decomposition of urethane phosphonate led to selective isolation of (339) in low yield (Scheme 106).161-163
Scheme 104

Cl\phantom{\text{COCl}} + \text{R-NH-P(O\text{-Et})_2} \text{Et}_3\text{N} \rightarrow \text{Cl-N-R-P(O\text{-Et})_2} \text{Et}_3\text{N}

Scheme 105

R=Me (68%), Bu (57%), t-Bu (71%)
Scheme 106

5. Conclusions

This review summarizes most synthetic methods giving rise to cyclic α-aminophosphonates. It focuses on the synthesis of cyclic α-aminophosphonic acids and their esters which contain at least two atoms. i.e. C−P, C−N or P−C−N, of the P-C-N system, in the heterocyclic system. The review is built up according to the three linkage types and starting with the smallest rings of each type.

References

   [http://dx.doi.org/10.2174/1568011013354543](http://dx.doi.org/10.2174/1568011013354543)
   PMid:12678760
http://dx.doi.org/10.1080/10426509108029443


http://dx.doi.org/10.1038/272056a0  
Pmid:628432

http://dx.doi.org/10.1021/ja973713z

http://dx.doi.org/10.1021/jm00127a041  
Pmid:2661820

http://dx.doi.org/10.1126/science.8023141  
Pmid:8023141


http://dx.doi.org/10.1021/jo062140i  
Pmid:17253748

http://dx.doi.org/10.1021/jo062609+  
Pmid:17328577

http://dx.doi.org/10.1016/S0040-4039(01)01053-X

http://dx.doi.org/10.1039/b000319k


http://dx.doi.org/10.1021/jo00809a014

http://dx.doi.org/10.1016/S0040-4039(00)99713-2


http://dx.doi.org/10.1021/jo9821426
PMid:16729122

http://dx.doi.org/10.1002/cjoc.200990011

http://dx.doi.org/10.1002/chir.20552
PMid:18381740

http://dx.doi.org/10.1021/jo000219w

http://dx.doi.org/10.1016/S0957-4166(01)00195-1

http://dx.doi.org/10.1248/cpb.49.531

http://dx.doi.org/10.1016/j.tetlet.2005.09.019

http://dx.doi.org/10.1016/S0040-4020(97)00086-0

http://dx.doi.org/10.1021/jo980719d

http://dx.doi.org/10.1016/S0040-4039(01)81876-1

http://dx.doi.org/10.1021/jm00002a007

http://dx.doi.org/10.1039/c3940001793

http://dx.doi.org/10.1016/0223-5234(91)90146-E

http://dx.doi.org/10.1021/ol017289p
PMid:11843615

http://dx.doi.org/10.3987/COM-10-S(E)12

http://dx.doi.org/10.1016/S0040-4039(01)00283-0
   [http://dx.doi.org/10.1016/S0040-4039(99)00422-0](http://dx.doi.org/10.1016/S0040-4039(99)00422-0)

   [http://dx.doi.org/10.1016/S0040-4039(98)02331-4](http://dx.doi.org/10.1016/S0040-4039(98)02331-4)

   [http://dx.doi.org/10.1016/S0040-4039(00)74564-3](http://dx.doi.org/10.1016/S0040-4039(00)74564-3)

   [http://dx.doi.org/10.1139/v82-139](http://dx.doi.org/10.1139/v82-139)

   [http://dx.doi.org/10.1139/v88-054](http://dx.doi.org/10.1139/v88-054)

   [http://dx.doi.org/10.1016/j.tet.2005.08.079](http://dx.doi.org/10.1016/j.tet.2005.08.079)

   [http://dx.doi.org/10.1016/S0960-894X(98)00272-8](http://dx.doi.org/10.1016/S0960-894X(98)00272-8)

   [http://dx.doi.org/10.1080/03086648808079000](http://dx.doi.org/10.1080/03086648808079000)

   [http://dx.doi.org/10.1016/S0040-4020(01)80584-6](http://dx.doi.org/10.1016/S0040-4020(01)80584-6)

   [http://dx.doi.org/10.1002/jlac.1992199201150](http://dx.doi.org/10.1002/jlac.1992199201150)

   [http://dx.doi.org/10.1002/ejoc.200390139](http://dx.doi.org/10.1002/ejoc.200390139)


   [http://dx.doi.org/10.1016/S0040-4039(00)00843-1](http://dx.doi.org/10.1016/S0040-4039(00)00843-1)

   [http://dx.doi.org/10.1016/S0957-4166(03)00089-2](http://dx.doi.org/10.1016/S0957-4166(03)00089-2)


   [http://dx.doi.org/10.1016/j.tetasy.2004.08.034](http://dx.doi.org/10.1016/j.tetasy.2004.08.034)

   [http://dx.doi.org/10.1080/10426509908053719](http://dx.doi.org/10.1080/10426509908053719)

   [http://dx.doi.org/10.3987/R-1984-08-1727](http://dx.doi.org/10.3987/R-1984-08-1727)

  http://dx.doi.org/10.1016/j.clinthera.2004.11.009  
  PMid:15639692

  http://dx.doi.org/10.1016/S0040-4039(03)00005-4

  http://dx.doi.org/10.1021/ja0584119  
  PMid:16802812

  http://dx.doi.org/10.1016/S0040-4039(02)00868-7


  http://dx.doi.org/10.1016/j.tet.2007.10.022

  http://dx.doi.org/10.1002/chem.200600789  
  PMid:17013964

  http://dx.doi.org/10.1080/10426509708043545

  http://dx.doi.org/10.1080/10426500210239

  http://dx.doi.org/10.1002/ejoc.200300654

  http://dx.doi.org/10.1016/S0040-4039(00)79391-9

  http://dx.doi.org/10.1080/10426509408018386

  http://dx.doi.org/10.1021/jo00091a024

  http://dx.doi.org/10.1016/S0040-4039(00)97378-7

  http://dx.doi.org/10.1021/jo040127x  
  PMid:15153008

http://dx.doi.org/10.1016/j.tetasy.2005.02.014

http://dx.doi.org/10.1021/jo0203903
PMid:12353989


http://dx.doi.org/10.1002/1099-0690(200110)2001:20<3891::AID-EJOC3891>3.0.CO;2-R

http://dx.doi.org/10.1021/jo070716d
PMid:17559281


http://dx.doi.org/10.1016/S0040-4020(01)96741-9

http://dx.doi.org/10.1021/jo990060r

http://dx.doi.org/10.1021/ol990855k
PMid:10825956

http://dx.doi.org/10.1021/jo020707z
PMid:12636410

http://dx.doi.org/10.1135/cccc20010507

http://dx.doi.org/10.1021/ol048157+
PMid:15548066

http://dx.doi.org/10.1021/ol049795v
PMid:15070314

http://dx.doi.org/10.1002/jhet.5570190538

http://dx.doi.org/10.1366/0003702824639547


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