Methods for synthesis of $N$-heterocyclyl/heteroaryl-$\alpha$-aminophosphonates and $\alpha$-(azaheterocyclyl)phosphonates

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Abstract
This review describes the most frequently reported synthetic methods for $N$-heterocyclyl-$\alpha$-aminophosphonic acids and their mono- or di-esters bearing a heterocyclic or heteroaryl system at the nitrogen atom, as well as methods for the synthesis of $\alpha$-(azaheterocyclyl)phosphonates. The Pudovik and Kabachnik-Fields reactions are the main pathways for construction of these features besides other miscellaneous methods.

Keywords: $N$-heterocyclyl/heteroaryl-$\alpha$-aminophosphonate, $\alpha$-(azaheterocyclyl)phosphonates, Kabachnik-Fields, Pudovik reactions

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1. Introduction

α-Aminophosphonic acids are considered as mimics of the corresponding α-aminocarboxylic acids. The phosphonic moiety has long been established as a bioisostere of a carboxylic unit. This feature explains the great variety of biological activities displayed by the members of this important class of compound and their applications. These are found ranging from medicine to agriculture, for example, as antibiotics, enzyme inhibitors, anticancer agents and herbicides. The biological properties are mostly associated with the tetrahedral structure of the phosphonyl group acting as a “transition-state” analogue. Because of their ability to mimic the transition states of hydrolysis, phosphonic acid derivatives that contain heterocycles have been shown to be inhibitors of various enzymes, including HIV-protease and human collagenase. At present, the literature concerning the synthesis and application of α-aminophosphonates is very extensive, comprising more than six thousand publications. Hence, several review articles have been developed for the synthesis of α-aminophosphonic acid and their esters and azaheterocyclic phosphonates. The Pudovik and Kabachnik-Fields reactions are the main pathways for construction of α-aminophosphonates. It is perhaps worth mentioning here that both the Pudovik and Kabachnik-Fields reactions are special cases of the Mannich reaction, in which the nucleophilic phosphorus atom takes the place of the enamine or enolate moieties in the Mannich reaction. On the other hand, α-aminophosphonic acids and their esters bearing a heterocyclic or
heteroaryl moiety are considerably fewer considering this number of publications. However, heterocyclic \( \alpha \)-aminophosphonates are becoming a subject of growing interest.

We have recently reviewed the available methods for synthesis of C-heterocyclic \( \alpha \)-aminophosphonates.\textsuperscript{24} In continuation of our work on the preparation of \( \alpha \)-aminophosphonates containing heterocyclic systems,\textsuperscript{25-30} we report in this review article all the available synthetic methods for synthesis of \( N \)-heterocyclyl/heteroaryl-\( \alpha \)-aminophosphonates (Type A) and \( \alpha \)-(azaheterocyclyl)phosphonates (Type B) (Figure 1).

![Figure 1. \( N \)-heterocyclyl/heteroaryl \( \alpha \)-aminophosphonates (Type A) and \( \alpha \)-(azaheterocyclyl) phosphonates (Type B).](image)

### 2. Synthesis of \( N \)-Heterocyclyl/heteroaryl-\( \alpha \)-aminophosphonic Acids and Their Diesters (Type A)

#### 2.1. Pudovik reactions

In the Pudovik reaction dialkyl phosphites are added to imines (Schiff bases). In some reports, these reactions were carried out in straightforward one-pot procedures without any catalyst,\textsuperscript{20} but in most cases it is performed using catalysts such as Lewis acids.\textsuperscript{21}

#### 2.1.1. Five-membered heterocycles with one heteroatom. The \( \alpha \)-(furfurylamino)phosphonic acid diester bearing an anthracene ring (2) was synthesized by addition of diethyl phosphite to the Schiff base 1 in the presence of cadmium iodide as a catalyst in dry benzene according to Scheme 1.\textsuperscript{31}

![Scheme 1](image)
The nucleophilic addition of dimethyl phosphite to imines 3 at 80 °C without solvent and in the presence of metal halides as catalyst gave the corresponding α-aminophosphonates 4. Deprotection of the tert-butyldimethylsilyloxy group with ammonium fluoride at 50 °C in methanol provided 2-deoxyuridine derivatives containing α-aminophosphonate moieties 5 in good yields (Scheme 2).  

![Scheme 2](image)

2.1.2. Five-membered heterocycles with two heteroatoms. Heating a mixture of imines 6 and phosphite diesters at 90-130 °C provided α-(4-antipyryl)amino(substituted)phenylmethylphosphonic acid diesters 7. The reaction of dimethyl phosphite with the imines was complete in 8 hours at 80-90 °C, while the temperatures required for diphenyl phosphite, diethyl phosphite and diisopropyl phosphite were 90 °C, 100-110 °C and 110-130 °C, respectively (Scheme 3).

![Scheme 3](image)

Reaction of N-(6-methoxybenzothiazol-2-yl)-4-fluorophenylimine (8) with dipropyl phosphite in toluene for 15 hours afforded N-(6-methoxybenzothiazol-2-yl)-1-(4-fluorophenyl)-O,O-dipropyl-α-aminophosphonate (9) in 72% yield (Scheme 4).
Scheme 4

Dialkyl \{[(1,3-benzothiazol-2-yl)amino][(benzofuran-2-yl)methyl]phosphonates (11) was synthesized from treatment of \(N\)-[1-benzofuran-2-ylmethylidene]-1,3-benzothiazol-2-amine (10) with dialkyl phosphite at 90 °C (Scheme 5).\(^{36}\)

Scheme 5

2.1.3. Five-membered heterocycles with three heteroatoms. The diethyl [5-(substituted phenyl)-1,3,4-thiadiazol-2-yl]amino)(substituted phenyl)methylphosphonates (13) were designed and prepared by the reaction of \(N\)-(substituted benzylidene)-5-(substituted phenyl)-1,3,4-thiadiazol-2-amins (12) and diethyl phosphite under microwave (MW) irradiation as shown in Scheme 6.\(^{37,38}\)

Scheme 6

The chiral \(N\)-phosphonylimine 14 was initially employed to react with diethyl phosphite in the presence of lithium hexamethyl disilazide (LiHMDS) in THF at 78 °C for 2 hours to isolate the chiral \(\alpha\)-aminophosphonate 15 in good yield although only modest diastereoselectivity was observed (Scheme 7).\(^{39}\)
NPNH

PhPh\(\text{HP(O)(OEt)}_2\)

NPN

H

N

O

P

O

OEt

Ph Ph

14

\(\text{THF, 78 }^\circ\text{C, 2 h} \)

85 \%

15

Scheme 7

2.1.4. Six-membered heterocycles with two heteroatoms. Addition of phosphorous acid to the imine 16 in toluene containing a catalytic amount of BF_3.Et_2O under Pudovik reaction conditions gave \{[(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)amino](phenyl)methyl\}phosphonic acid (17) in good yield (Scheme 7). Addition of diethyl phosphite and \textit{tris}(2-chloroethyl) phosphite to the imine 16 under the same reaction conditions led to the formation of dialkyl \(N\)-quinazolinyl \(\alpha\)-aminophosphonates 18 (Scheme 8).\(^{40}\)

\[
\begin{align*}
\text{Reactions:} & \\
\text{Tolene} & \quad \text{BF}_3\text{Et}_2\text{O} & \quad 85-89\% \\
\text{H-P(O)(OEt)}_2 & \quad \text{P(OCH}_2\text{CH}_2\text{Cl)}_3 & \quad \text{Toluene} \\
& & \quad \text{BF}_3\text{Et}_2\text{O} & \quad 82\% \\
\end{align*}
\]

\[
\begin{align*}
\text{16} & \quad \text{H-P(O)(OH)}_2 & \quad \text{P(OH)}_3 & \quad \text{Toluene} \\
\text{17} & \quad \text{Tolene} & \quad \text{BF}_3\text{Et}_2\text{O} & \quad 82\% \\
\end{align*}
\]

18, \(R=\text{CH}_2\text{CH}_2, \text{ClCH}_2\text{CH}_2\)

Scheme 8

The Schiff bases type 19, that were obtained by the reaction of 3-amino-6-ethyl-2-methylthieno[2,3-\(d\)]pyrimidin-4-one with various substituted benzaldehydes, reacted with different dialkyl phosphite under nitrogen atmosphere to generate the corresponding \(\alpha\)-aminophosphonate derivatives 20 (Scheme 9).\(^{41}\)
2.2. Kabachnik-Fields reactions
The Kabachnik–Fields reaction is a three component reaction, in which a carbonyl compound, an amine, and a di- or tri-alkyl phosphite react in a single-pot, in the presence or absence of catalysts.\textsuperscript{22,23}

2.2.1. Five-membered heterocycles with one heteroatom. A solution of ferric chloride in tetrahydrofuran facilitated the Mannich-type reaction of terephthaldehyde, 3-(2-aminoethyl)-indole (21) and diethyl phosphite to form the corresponding \textit{N}-indolyl-\textit{\alpha}-aminophosphonate 22 in a one-pot, three component reaction (Scheme 10).\textsuperscript{42}
2.2.2. Five-membered heterocycles with two heteroatoms. The reaction of 3-amino-5-methylisoxazole (23), diethyl phosphite with 2- or 4-fluorobenzaldehyde under sonic waves was investigated. It could be seen that the ultrasonic irradiation accelerated the reaction. When there is no ultrasound, the reaction was relatively slow and low yields of product were obtained within 5 hours at 115–120 °C in toluene. Under ultrasonic irradiation, a great improvement in the yield was achieved, to afford N-isoxazolyl-α-aminophosphonates 24 in yields of 78-91% within a short reaction time. The best result was obtained when 3-amino-5-methylisoxazole was reacted with one molar equivalent of dialkyl phosphite and either 2- or 4-fluorobenzaldehyde under ultrasonic irradiation without solvent or catalyst at 78–80 °C for one hour (Scheme 11).\(^4\)

\[\text{Scheme 11}\]

The aminophosphonates 25 were obtained as colorless crystals by mixing 3-amino-5-methyl-1,2-oxazole (23) with 4-chlorobenzaldehyde and trialkyl phosphite in THF solution containing 10% FeCl\(_3\) (Scheme 12).\(^4\)

\[\text{Scheme 12}\]

To a mixture of 4-(N,N-dimethylamino)benzaldehyde, 4-[(thiazol-2-yl)sulfamoyl]aniline (26), and diethyl phosphite, ferric chloride in tetrahydrofuran was added and the reaction was stirred at 60 °C, affording diethyl (4-N,N-dimethylaminophenyl)[4-(thiazol-2-yl)sulfamoylphenylamino]methylphosphonate (27) in 87% yield (Scheme 13).\(^4\)
Scheme 13

The reaction of 2-aminobenzothiazoles (28) with aromatic aldehydes in the presence of dialkyl phosphites afforded the corresponding \(N\)-(benzothiazol-2-yl)-\(\alpha\)-aminophosphonates 29 in good yields under different reaction conditions (Scheme 14).46-48

![Scheme 13]

Scheme 14

Similarly, reaction of 2-aminobenzothiazole (28), diethyl phosphite and triethylorthoformate at 60 °C without catalyst under solvent-free conditions gave the corresponding \(N\)-biphosphonate 30. The reaction did not proceed even after prolonged reaction
time and no desired product was formed. When the reaction was performed in the presence di-\textit{n}-butyl ammonium ionic liquid (DBAIL), it proceeded effectively to produce the desired product 30 in high yield. This result clearly demonstrated that DBAIL is a more efficient catalyst for the synthesis of \(N\)-biphosphonate due to the dibutylamine is an organo catalyst and also this one neutralized with chlorosulfonic acid (Scheme 15).^{49}

\[ \text{DBAIL} = \begin{array}{c}
\text{CH}_3 \\
\text{NH}_2 \\
\text{Cl} \\
\text{SO}_3
\end{array} \]

\[ \text{Neat, } 60^\circ \text{C} \]

\[ 90\% \]

\[ \text{DBAIL} \]

\[ 30 \]

\[ \text{Scheme 15} \]

The dimethyl \(\alpha\)-aminophosphonates 32 and 33 bearing a hydantoin moiety have been synthesized in good yield from 3-amino-5,5-dimethylimidazolidine-2,4-dione (31), formaldehyde and dimethyl phosphite via a Kabachnik–Fields reaction (Scheme 16). Hydrolysis of these diesters with aqueous sodium hydroxide furnished [(4,4-dimethyl-2,5-dioxo-imidazolidin-1-yl)amino]methylphosphonic acid (34) and (5,5-dimethyl-2,4-dioxo-3-[(phosphonomethyl)amino]imidazolidin-1-ylmethyl)phosphonic acid (35), respectively (Scheme 16).^{50}

\[ \text{Scheme 16} \]
2.2.3. **Five-membered heterocycles with three heteroatoms.** A facile and efficient one-step synthesis of \( \alpha \)-aminophosphonate derivatives of 1,3,4-oxadiazole 38 and 1,3,4-thiadiazole 39 was achieved via reaction of 2-amino-5-substituted-1,3,4-oxadiazole 36 and 1,3,4-thiadiazole 37, with diphenyl phosphite and aromatic aldehydes in the presence of acetic acid (Scheme 17).

\[
R = H, Me, Et, i-Pr, CF_3, Ph, \\
Ar = H, Bu, Ph, 4-MeC_6H_4, 4-MeOC_6H_4, \\
\alpha-, m-, p-CIc_6H_4, 4-BrC_6H_4, m-, p-NO_2C_6H_4
\]

**Scheme 17**

2.2.4. **Six-membered heterocycles with one heteroatom.** The reaction of mycoheptin 40 with aromatic aldehydes and hypophosphorous acid led to the formation of \( \alpha \)-aminophosphonic acids 41 (Scheme 18). Similarly, the primary amino group of the pimaricin carbohydrate fragment 42 is added to the carbonyl group of the aromatic aldehydes and hypophosphorous acid to afford the hydrophosphoryl pimaricin derivatives 43 in moderate yields (Scheme 18).

\[
Y = OH, MeO, NO_2, Me_2N, F, Cl, Br
\]

**Scheme 18**
Reaction of 2-aminopyridine or 2-(aminomethyl)pyridine with diethyl phosphite and aromatic aldehydes under different reaction conditions using various catalysts afforded the corresponding $N$-pyridinyl-$\alpha$-aminophosphonates 44 (Scheme 19).47,57-59

\[
\text{Conditions:} \\
i, \text{Nanoparticles ZnO, 100 °C, no solvent} \\
ii, \text{SbCl}_3, \text{Al}_2\text{O}_3, \text{CH}_3\text{CN} \\
iii, \text{TiO}_2, \text{no solvent, 50 °C} \\
iv, \text{Nano Fe}_3\text{O}_4, \text{no solvent, 50 °C}
\]

The synthesis of the corresponding $N$-(3-pyridyl)-$\alpha$-aminophosphonates 45 from ketones, 3-aminopyridine and diethyl phosphite required longer time. However, Matveeva et al.60 found that the heating accelerated only the first step of the process, i.e., the formation of the corresponding imines, whereas the second step of the reaction, i.e. the addition of diethyl phosphite to imines, is better to carry out at room temperature in the presence of [tetra(tert-butyl) phthalocyanine]aluminium chloride ($\text{PcAlCl}$) as a catalyst (Scheme 20).

\[
\text{Conditions:} \\
i, \text{Nanoparticles ZnO, 100 °C, no solvent} \\
ii, \text{SbCl}_3, \text{Al}_2\text{O}_3, \text{CH}_3\text{CN} \\
iii, \text{TiO}_2, \text{no solvent, 50 °C} \\
iv, \text{Nano Fe}_3\text{O}_4, \text{no solvent, 50 °C}
\]

2.2.5. Six-membered heterocycles with two heteroatoms. 4-Chloro-2-phenyl-5-(4-amino-phenylthio)pyridazin-3(2$H$)-one (46) reacted in a three-component reaction with different aldehydes and dialkyl phosphites to provide $N$-pyridazinyl-$\alpha$-aminophosphonates 47 (Scheme 21). Synthesis of 47 was carried out in different solvents under varying conditions using Lewis acid catalysts, ionic liquids, microwave irradiation, and conventional heating. Under optimized conditions, the best result was obtained when the reaction was run for 7 hours in dry toluene at its reflux temperature (Scheme 21).61
Scheme 21

1-Butyl-3-methylimidazolium chloride [BMIM]Cl catalyzed three component reaction of 4-(quinazolin-4-yl)oxy)benzenamine (48) and furfural with dialkyl phosphites under microwave irradiation led to new α-aminophosphonates containing the 4-phenoxyquinazoline moiety 49 (Scheme 22).62

![Scheme 21](image)

Scheme 22

A solution of ferric chloride in tetrahydrofuran facilitated the Kabachnik reaction of terephthaldehyde, guanosine (50) and diethyl phosphite to form the corresponding *N*-purinyl-α-aminophosphonate 51 in a one-pot, three component reaction (Scheme 23).42

![Scheme 22](image)

Scheme 23

![Scheme 23](image)
2.3. Miscellaneous methods

2.3.1. Removal of a BOC group and phosphonylmethylation in acidic medium. Hydrolysis of the tert-butyloxycarbonyl group of the 1,2,4-triazole derivative 52 with formic acid and reaction with the phosphorus reagent in i-Pr₂NEt gave the N-triazolyl-α-aminophosphonate 53 in 52% yield (Scheme 24).

![Scheme 24](image1)

2.3.2. Heteroarylation of acyclic α-aminophosphonates at nitrogen atom. 2-[4-(4,6-Dimethoxypyrimidin-2-yloxy)phenoxy]acetic acid 54 reacted with α-aminophosphonates 55 using dicyclohexylcarbodiimide (DCC) as the dehydration reagent to obtain N-[4-(4,6-dimethoxypyrimidin-2-yloxy)phenoxy]acetyl-α-aminophosphonates 56 in good yields (Scheme 25).

![Scheme 25](image2)

Luo et al.,\textsuperscript{65} reported the first microwave-assisted synthesis of new quinazoline derivates containing α-aminophosphonate. In their method, N′-(substituted-2-cyanophenyl)-N,N-dimethyl-formamidine derivatives 57 and α-aminophosphonates 55 were taken as the raw materials to react in 4:1 v/v isopropanol : acetic acid for 20 min under microwave irradiation (100 °C, 100 psi), and they obtained the N-quinazolinyl-α-aminophosphonates 58 (Scheme 26).
Scheme 26

Alkylation of \( N \)-(4-propargylaminobenzoyl)aminophosphonates 59 with 2-methyl-(6-bromomethyl)-4-quinazolone (60) gave antifolate esters 61. Removal of the alkyl groups from the blocked phosphonate esters 61 was the limiting step of the syntheses of the corresponding aminophosphonic acids 62 by standard silylation procedure (Scheme 27).

Scheme 27

2.3.3. Addition to isothiocyanatomethyl and isocyanatomethyl phosphonates. The microwave-promoted reaction of substituted aminobenzothiazoles 63 with dialkylisothiocyanato-(phenyl)methylphosphonates 64 led to \( N \)-benzothiazolyl-\( \alpha \)-aminophosphonate 65. Under optimized conditions, the products were obtained in dry acetonitrile at 90 °C, and a reaction time of 30 minutes with a power input of 120 W (Scheme 28).
Scheme 28

Addition of isocyanatomethyl phosphonate 64 to 1-ethoxycarbonylmethyl-3-ethyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorine (66) formed the \( N \)-(1,3,2-benzodiazaphosphorinyl)-\( \alpha \)-aminophosphonates 67 (Scheme 29).

Scheme 29

3. Synthesis of \( \alpha \)-(Azaheterocycl)phosphonates (Type B)

3.1. Kabachnik-Fields reactions

3.1.1. Five-membered heterocycles with one heteroatom. The reaction of an aldehyde, pyrrolidine and dialkyl phosphite or trialkyl phosphite in the presence of two equivalents of solid lithium perchlorate at ambient temperatures under solvent-free or microwave conditions resulted in the formation of \( \alpha \)-(pyrrolidinyl)phosphonates 68 in good yields (Scheme 30).
3.1.2. Five-membered heterocycles with two heteroatoms. Condensation of $R$-(-)-phenylglycinol, formaldehyde and dimethyl phosphite in refluxing methanol gave good yields of $\alpha$-(oxazolidinyl)phosphonate 69 in a one-step procedure (Scheme 31).71

Scheme 31

3.1.3. Six-membered heterocycles with one heteroatom. Coupling of aldehydes with 4-alkylpiperidine and dialkyl or trialkyl phosphites under various reaction conditions gave $\alpha$-(piperidinyl)phosphonates 70 (Scheme 32).48,58,69,72,73

Scheme 32

3.1.4. Six-membered heterocycles with two heteroatoms. $N$-alkyl/arylpiperazines were converted into the corresponding dialkyl $\alpha$-(piperizinyl)phosphonomethyl derivatives 71 in a reaction with paraformaldehyde and dialkyl phosphites under microwave irradiation (Scheme 33).69,70

The synthesis of dialkyl [1-(fluorophenyl)piperazin-4-yl]methyl phosphonates 73 was performed by the Kabachnik–Fields reaction of 1-(fluorophenyl)piperazines (72) with formaldehyde and various dialkyl phosphites (Scheme 34).74 These reactions were carried out in water at 80 °C for 16–18 h in vessels closed with screw caps to provide pure $\alpha$-amino-phosphonates 73 in 70–84% yields.
Reaction of morpholine with paraformaldehyde or ferrocenecarbaldehyde and dialkyl phosphites under different reaction conditions afforded the corresponding α-(morpholinyl) phosphonates 74 (Scheme 35). 58,60,69,70

\[
\text{R=Me, Et, CH(CH}_3)_2
\]

$n$-Propyl sulfamic acid onto hydroxyapatite encapsulated superparamagnetic $\gamma$-Fe$_2$O$_3$ nanoparticles [$\gamma$-Fe$_2$O$_3$@HAp-Si-(CH$_2$)$_3$-NHSO$_3$H] as an efficient catalyst was added to a mixture of furan-2-carbaldehyde and morpholine at room temperature followed by addition of dimethyl phosphite to give $\alpha$-(2-furyl)-$\alpha$-(morpholinyl)phosphonate 75 (Scheme 36). 75
3.1.5. Seven-membered heterocycles with two heteroatoms. Installation of the methylphosphonate residues on the endocyclic nitrogen atom of triamine 76 was performed by its reaction with paraformaldehyde and one or two equivalent of tri(t-butyl)phosphite, yielding the monosubstituted 77 or the disubstituted 78 derivative, respectively (Scheme 37).76

Scheme 36

3.2. Heterocyclization of phosphonates
3.2.1. Heterocyclization of α-aminophosphonates. The well-known cyclization of ureas with oxalyl chloride was applied, and this reaction allowed isolation of α-(imidazolyl)phosphonate 80 in excellent overall yields via reaction of 3-phenylureidomethylphosphonate 79 with oxalyl chloride (Scheme 38).77

Scheme 38
[(2{[(Dimethoxyphosphoryl)phenyl[methyl]amino}phenylamino)phenylmethyl]phosphonic acid esters (82) were prepared by reacting the corresponding aldimines 81 and dialkyl phosphite. Cyclocondensation of 82 with phenylphosphonic dichloride in dry toluene in the presence of triethylamine at 40 °C afforded the bis-phosphonates 83 (Scheme 39).78

Scheme 39

3.2.2. Heterocyclization of α-phosphorylated nitrones and imines. The phosphoryl nitrone 84 underwent 1,3-dipolar cycloaddition with maleic anhydride to form the two diastereoisomeric 2-[1-(O,O-diethylphosphoryl)alkene]-3-arylisoxazoline-4,5-dicarboxylates (85) (Scheme 40).79

Scheme 40

Heterocyclization of α-phosphorylated imines 86 with thioglycolic acid in dry solvent can be used for the preparation of α-(thiazolyl)phosphonate 87 (Scheme 41).80
3.3. Miscellaneous methods

3.3.1. Reaction of morpholinium salt with trialkyl phosphite. Vinylogous iminium salts 88 reacted with triethyl phosphite in dry acetonitrile under dry nitrogen to afford α-(morpholinyl) phosphonates 89 in 40% yield (Scheme 42). \(^8\)

\[
\begin{align*}
\text{R}^1=\text{Me, Et} \\
\text{R}=\text{Me, Et, n-Pr}
\end{align*}
\]

Scheme 42

3.3.2. Reaction of thioamides with trialkyl phosphite. The reaction of the trifluorothioacetamide morpholine 90 with triethyl phosphite proceeded without elimination of a fluoride ion to give the α-(morpholinyl)phosphonate 91 (Scheme 43). It should be noted that this reaction required a longer period of heating (19 hours at 150 °C) and excess of triethyl phosphite (nine equivalents). \(^9\)

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{P(OEt)}_3 \\
\text{150 °C, 19 h} & \quad \text{35 %}
\end{align*}
\]

Scheme 43
4. Conclusions

During the last few years the $\alpha$-aminophosphonic acids have attracted considerable attention in the scientific community and a great variety of methodologies have been reported for the synthesis of these compounds. The importance of having new relevant structures has allowed the development of new strategies and synthetic procedures. The authors of this review have collected the most relevant procedures reported on the available synthetic methods for $N$-heterocyclyl/heteroaryl-$\alpha$-aminophosphonates (Type A) and $\alpha$-(azaheterocyclyl)phosphonates (Type B) that will be a fundamental key in the design of new bioactive agents with improved pharmacological properties. The review is arranged according to the methods used and starting with the smallest rings of each method.

5. References

   http://dx.doi.org/10.1021/ja0651005
   http://dx.doi.org/10.1080/10426509108029443
   http://dx.doi.org/10.1021/bi00247a011
   http://dx.doi.org/10.1021/jm00151a005
   http://dx.doi.org/10.1016/0960-894X(94)00474-T
   http://dx.doi.org/10.2174/1568011013354543
   http://dx.doi.org/10.1080/10426509908546274
    http://dx.doi.org/10.1021/ja00393a026
    http://dx.doi.org/10.1016/j.tet.2008.09.083
   http://dx.doi.org/10.2174/138527211795703612
   http://dx.doi.org/10.3998/ark.5550190.0012.617
   http://dx.doi.org/10.2174/157017912801270595
   http://dx.doi.org/10.1016/j.tet.2012.05.008
   http://dx.doi.org/10.1055/s-0033-1338588
   http://dx.doi.org/10.1016/j.tet.2015.01.029
   http://dx.doi.org/10.1021/cr030451c
   http://dx.doi.org/10.1002/ezoc.200300479
   http://dx.doi.org/10.1039/b104967b
   http://dx.doi.org/10.1016/S0040-4039(01)01053-X
   http://dx.doi.org/10.3998/ark.5550190.p009.112
   http://dx.doi.org/10.3998/ark.5550190.0009.209
   http://dx.doi.org/10.1016/j.ejmech.2009.06.022
   http://dx.doi.org/10.1080/10426500802713309
   http://dx.doi.org/10.5155/eurjchem.2.1.25-35.208
   http://dx.doi.org/10.1007/s00706-013-0934-6
http://dx.doi.org/10.1002/hc.21110

http://dx.doi.org/10.1016/j.bmc.2011.11.024

http://dx.doi.org/10.1002/hc.20288

http://dx.doi.org/10.1080/10426509908044977

http://dx.doi.org/10.1080/10426509908053707

http://dx.doi.org/10.1007/s10870-005-5134-8

http://dx.doi.org/10.1080/10426507.2014.965815


http://dx.doi.org/10.1080/00397911003707030

http://dx.doi.org/10.1111/j.1747-0285.2010.01013.x

http://dx.doi.org/10.1007/s11164-015-2088-0

http://dx.doi.org/10.1016/j.ccl.2015.03.026

http://dx.doi.org/10.1016/j.ejmech.2009.07.009

http://dx.doi.org/10.1016/j.jfluchem.2005.08.005

http://dx.doi.org/10.1002/jhet.2541


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