Methods for the synthesis of $\alpha$-heterocyclic/heteroaryl-$\alpha$-aminophosphonic acids and their esters

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Abstract
This review describes a comprehensive account of methods which are commonly applied for the synthesis of $\alpha$-heterocyclic/heteroaryl $\alpha$-aminophosphonic acids and their esters. In the following order, protocols based on the methodologies listed below are discussed: (a) Pudovik reaction; (b) Kabachnik-Fields reaction and (c) Miscellaneous Methods.

Keywords: $\alpha$-Aminophosphonates, heterocycles, Kabachnik-Fields, Pudovik reactions

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1. Introduction

α-Aminophosphonic acids are considered mimics of the corresponding α-aminocarboxylic acid.\(^1\) The phosphonic moiety has long been established as a bioisostere of a carboxylic unit. These features explain the large range of biological activities displayed by the members of this important class of compounds and the applications.\(^2\)\(^-\)\(^5\) They have been found in areas ranging from medicine to agriculture, for example, as antibiotics,\(^6\) enzyme inhibitors,\(^7\) anticancer agents\(^8\) and herbicides.\(^9\),\(^10\) These biological properties mostly are associated with the tetrahedral structure of the phosphonyl group acting as a “transition-state” analogue.\(^11\) Because of their ability to mimic transition states of hydrolysis, phosphonic acid derivatives having heterocycles at the α-positions have been shown to be inhibitors of various enzymes, including HIV-protease and human collagenase.\(^12\)

At present, the literature concerning the synthesis and application of α-aminophosphonates is very extensive, comprising more than six thousand publications. Hence, several approaches\(^13\) have been developed for the synthesis of α-aminophosphonates. Two main pathways are: (i) the Pudovik reaction, where dialkyl phosphites are added to imines, and (ii) the Kabachnik-Fields three component reaction, in which a carbonyl, an amine and a di- or tri-alkyl phosphite react in a single-pot. In some reports, these reactions were carried out as straightforward one-pot procedures without any catalyst,\(^14\) but in most cases they were performed using catalysts.\(^15\) On the other hand, α-aminophosphonic acids and their esters bearing a heterocyclic moiety at the α-position are becoming the subject of growing interest. To our knowledge, there are several methods for the synthesis of α-heterocyclic/heteroaryl α-aminophosphonates (Figure 1). In connection with our work on the preparation of α-aminophosphonates containing heterocyclic systems,\(^16\)\(^-\)\(^19\) we report in this review article all the available synthetic methods of α-heterocyclic/heteroaryl α-aminophosphonates which were published until 2013.

![Figure 1. α-Heterocyclic/heteroaryl-α-aminophosphonic acids and their esters.](image_url)
2. Synthesis by Pudovik Reaction

2.1. Five-membered heterocycles with one heteroatom
The Schiff bases 1 were subjected to react in situ with diethyl phosphite in toluene at 110 °C to give the corresponding α-aminophosphonate esters 2. When diphenyl phosphite was used in the reaction with imines 1, the addition reaction took place even at room temperature, giving the diphenyl esters in high yields (Scheme 1).²⁰

![Scheme 1](image)

Stereoselective synthesis of (5-hydroxymethylfuran-2-yl)-N-(α-methylbenzylamino)phosphonates 4a,b was performed by the addition of dibenzyl phosphite to the N-(furylmethylene)-(R)-α-methylbenzylamine (3), resulting in diastereoisomeric esters (Scheme 2).²¹,²²

![Scheme 2](image)

When the cyclic phosphonate 5 was reacted with the Schiff base 6 at 17 °C it afforded the corresponding α-(3-thienyl)-α-aminophosphonate 7. Reaction of phosphonate 5 (R=COOR) with the imine 6 required ultrasonic conditions to bring the reaction to completion (Scheme 3).²³
Scheme 3

Reaction of the Schiff bases 8 with dialkyl phosphites in toluene at 85 °C provided the corresponding α-aminophosphonates 9 (Scheme 4).24

Scheme 4

The diethyl phosphonate esters 11 were prepared by heating equimolar mixtures of diethyl phosphite and the corresponding Schiff base 10 in the absence of solvent at temperatures between 90 and 100 °C (Scheme 5).25

Scheme 5

Similarly, addition of two equivalents of dimethyl phosphite to heterocyclic imine 12 in methanol afforded the α-(2-furyl)-α-aminophosphonate 13 (Scheme 6).26
Scheme 6

Synthesis of cucurbitine phosphonic analogues 16 was performed through reaction of hydrazone intermediates 14 with triethyl phosphite in acidic media. Subsequent cleavage of N–N bonds gave aminophosphonic acid 16 and not the corresponding α-hydrazinophosphonate (cucurbitine analogue) (Scheme 7).27

Scheme 7

4,4'-Bis[[(dialkoxyphosphonyl)-(2-furyl)methyl]amino]diphenyl (18) was prepared by addition of diethyl phosphite to N,N'-bis(furfurylidene)benzidine (17) in sodium ethoxide and stirring at room temperature for 3 hours (Scheme 8).28

Scheme 8

Similarly, addition of diethyl phosphite to the azomethine bonds of the bis-Schiff base 19 was carried out, affording 1,3-bis[N-[(diethoxyphosphonyl)-(2-furyl)methyl]amino]benzene (20). In this case NMR studies revealed that the reaction product is a mixture of the two possible diastereomeric forms: R,S (meso) and the enantiomeric pair R,R and S,S (Scheme 9).29
Also, four bis(aminophosphonates) 25, 26, 27 and 28 were synthesized through addition of diethyl phosphite to the azomethine bonds of the furan-substituted bis(imines) 21–24. The addition of dialkyl (diaryl) phosphites to bis(imines) should lead to the formation of two diastereomeric forms, meso and racemic diastereomers. Thus, this synthesis in most cases occurs with high stereoselectivity, yielding as major product only one of the diastereomers, as previously obtained in similar reactions (Scheme 10).

Poly(oxyethylene)aminophosphonates 31 were synthesized through addition of poly(oxyethylene H-phosphonates) 29 to the azomethine bond of N-furfurylidene toluidine (30), according to Scheme 11. The polymer analogous reaction was carried out in the presence of

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**Scheme 9**

**Scheme 10**
catalytic CdI₂, as well as without catalyst. In the presence of CdI₂ the addition of P-H groups to the azomethine 30 proceeded with higher reaction rate compared to the non-catalyzed reaction and the poly (α-aminophosphonates) 31 were obtained in good yields in 3 hours. In the absence of catalyst the reaction time was longer, up to 15 hours (Scheme 11).  

\[
\begin{align*}
\text{Scheme 11} \\
\text{Reaction of Schiff bases 32 with bis(trimethylsilyl)hydrogen phosphite in boiling benzene gave α-(3-indolyl)-α-aminophosphonates 33 in yields 90-93% (Scheme 12).}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 12} \\
\text{Reaction of the Schiff bases 34 with diethyl hydrogen phosphite via Pudovik reaction in refluxing toluene in the absence of catalyst afforded the corresponding α-aminophosphonates 35 (Scheme 13).}
\end{align*}
\]
2.2. Five-membered heterocycles with two heteroatoms

The aldimines 36 were reacted directly with trimethyl phosphite in the presence of bromotrimethylsilane to form the $\alpha$-(2-thiazolyl)-$\alpha$-aminophosphonic silylated esters 37, as intermediates, which were then deprotected giving the $\alpha$-(2-thiazolyl)-$\alpha$-aminophosphonic acids 38 (Scheme 14).35

Similarly, the reaction of imines 39 with tris(trimethylsilyl) phosphite (generated in situ from triethyl or trimethyl phosphite and bromotrimethylsilane) to give the silylated intermediates 40 which were then treated with methanol, producing the desired desilyated $\alpha$-(imidazol-2-yl)-$\alpha$-aminophosphonic acids 41 (Scheme 15).36,37

The diethyl 1,3-benzodioxylphosphonate esters 43 were prepared by heating equimolar mixtures of diethyl phosphite and the corresponding Schiff base 42 in the absence of solvent at temperatures between 90 and 100 °C (Scheme 16).25
2.3. Six-membered heterocycles with one heteroatom

Addition of diethyl phosphite to the Schiff base 44 at room temperature without a solvent in the presence of catalytic amounts of sodium ethoxide afforded diethyl [(N-benzylamino)(2-pyridinyl)methyl]phosphonate (45) which underwent acidic hydrolysis to give the corresponding α-aminophosphonic acid 46 (Scheme 17).\(^\text{38}\)

Scheme 17

1-(N-Benzyl)-2-formyl-5-benzyloxy-pyridone 47 reacted with primary amines to obtain the corresponding imines 48. The imines then were treated with a mixture of trimethyl phosphite and bromotrimethylsilane, which caused in situ formation of tris(trimethylsilyl) phosphite, which instantly reacted with the imines, giving silylated phosphonate intermediates. Treatment of the intermediates with methanol caused removal of the silylated groups and the formation of the final α-(pyridinyl)-α-aminophosphonic acids 49 (Scheme 18).\(^\text{39}\)
A short and efficient synthesis of new 4-amino(piperidine/tetrahydropyran/tetrahydrotiopyran)-4-phosphonic acids 52 in good yields was described via addition of triethyl phosphite in acidic medium to ketone imines 50 via α-aminophosphonates 51 (Scheme 19).27

Some piperidine-incorporated α-aminophosphonates 54 were prepared in excellent yields by reacting imines 53 with triethyl phosphite in the presence of dilute HCl under ultrasound irradiation (Scheme 20).40

α-(3-Quinolinyl)-α-aminophosphonates 56 were prepared in quantitative yields by reacting imines 55 with triethyl phosphite in the presence of tetramethylsilyl chloride (TMSCl) at room temperature.
temperature. The yields of the \( \alpha \)-aminophosphonates using this process are in the range of 95–98% (Scheme 21).\(^{41,42} \)

![Scheme 21](image)

**Scheme 21**

Nucleophilic addition of the silylated phosphorus ester to imines 57 proceeded easily at room temperature for 12 hours. The formed silylated phosphonic intermediates 58 were treated with methanol as a desilylating agent to produce the desired \( \alpha \)-(quinolin-2, 3- and 4-yl)-\( \alpha \)-(amino)methylphosphonic acids 59 in good yields (Scheme 22).\(^{43} \)

![Scheme 22](image)

**Scheme 22**

The synthesized imines 60 were treated with triethyl phosphite in the presence of TMSCl at room temperature to afford the corresponding diethyl \( \alpha \)-(tetrazoloquinolin-3-yl)-\( \alpha \)-amino-phosphonate 61 (Scheme 23).\(^{44} \)

![Scheme 23](image)

**Scheme 23**
The Schiff bases 62 reacted with dialkyl phosphite or trialkyl phosphite in presence or absence of solvent to give α-(chromon-3-yl)-α-aminophosphonates 63 (Scheme 24).\textsuperscript{18,45,46}

$$\text{O}$$
$$\text{O}$$
$$\text{N}$$
$$\text{R}$$
$$\text{R}$$
$$\text{O}$$
$$\text{O}$$
$$\text{N}$$
$$\text{H}$$
$$\text{P}$$
$$\text{O}$$
$$\text{OEt}$$
$$\text{EtO}$$
$$\text{EtO}$$
$$\text{R}$$
$$\text{R}$$
$$\text{H}$$
$$\text{HP(O)(OR)2 P(OR)3}$$

66 - 88 %

R = Me, Et, i-Pr, R\textsuperscript{1} = H, Me, R\textsuperscript{2} = H, 4-Cl, 4-OMe, 2-Me, 4-Me, 2-NO\textsubscript{2}, 4-NO\textsubscript{2}

Scheme 24

Fusing of the bis-phosphonic hydrazone 64 with diethyl phosphite at 80-100 °C in the presence of catalytic amounts of triethylamine produced N\textsuperscript{1},N\textsuperscript{5}-bis[N-methyl(diethoxyphosphonyl)-1-[(4-oxo-4H-chromen-3-yl)]phosphonic dihydrazide (65) as the sole product (Scheme 25).\textsuperscript{47}

$$\text{O}$$
$$\text{O}$$
$$\text{N}$$
$$\text{N}$$
$$\text{H}$$
$$\text{P}$$
$$\text{N}$$
$$\text{H}$$
$$\text{O}$$
$$\text{H}$$
$$\text{N}$$
$$\text{O}$$
$$\text{O}$$
$$\text{O}$$
$$\text{O}$$
$$\text{P}$$
$$\text{P}$$
$$\text{O}$$
$$\text{O}$$
$$\text{OEt}$$
$$\text{EtO}$$
$$\text{EtO}$$

80 - 100 °C

78 %

64

65

Scheme 25

Similarly, the addition of diethyl phosphite to compounds 66 was carried out in dry benzene containing few drops of triethylamine as catalyst to yield the corresponding bis-(α-aminophosphonate) derivatives 67 (Scheme 26).\textsuperscript{47}

Also, addition of diethyl phosphite to azomethine bonds of interesting compounds 68 and 69 on fusion at 80–100 °C in the presence of a catalytic amount of triethylamine yielded one diastereomeric form of tetraethyl 5,5\textsuperscript{-}(1,4-phenylene)bis-[[[3-oxo-3-phenyl-2,3-dihydro-4H-1,2,4,3-triazaphosphol-4-yl)amino](4-oxo-4H-chromen-3-yl)methyl]phosphonate] (70) and two diastereomeric forms of tetraethyl 5,5\textsuperscript{-}(1,4-phenylene)bis-[[[3-oxo-3-phenyl-2,3-dihydro-4H-1,2,4,3-triazaphosphol-4-yl)methylphosphoryl]amino](6-methyl-4-oxo-4H-chromen-3-yl)methyl] phosphonate] (71), respectively (Scheme 27).\textsuperscript{17}
Scheme 26

Scheme 27

3. Synthesis by Kabachnik-Fields Reaction

3.1. Five-membered heterocycles with one heteroatom

Three component one-pot reaction of heterocyclic aldehydes such as furan-2-carbaldehyde,
thiophene-2-carbaldehyde and pyrrole-2-carbaldehyde with different amines such as butylamine, cyclohexylamine, aniline, benzylamine, 4-chloroaniline, 4-methoxyaniline, 4-fluoroaniline, 4-methoxyaniline, HMDS (1,1,1,3,3,3-hexamethyldisilazane), aminoalkylphosphonic acid and heteroaryl amines with dialkyl or trialkyl phosphites gave the corresponding \( \alpha \)-heterocyclic-\( \alpha \)-aminophosphonates 72 in good to excellent yields under different reaction conditions (Scheme 28) (Table 1). 10,20,48-68

\[
\begin{align*}
\text{X} & \quad \text{R in Scheme 28} & \quad \text{R'} & \quad \text{Reaction conditions} & \quad \text{Ref.} \\
1 & \text{O, S, NH} & \text{Bu, PhCH}_2 & \text{Et, Ph, PhCH}_2 & \text{toluene, reflux} & 10 \\
2 & \text{O} & \text{4-MeO}_2\text{C}_6\text{H}_4 & \text{Et} & \text{NH}_4\text{VO}_3/\text{RT}/\text{stirring} & 49 \\
3 & \text{O, S} & \text{Ph} & \text{Et} & \text{[bnim][HSO}_4]/\text{RT}/\text{stirring} & 50 \\
4 & \text{O, S} & \text{Ph} & \text{Et} & \text{1-hexanesulfonic acid sodium salt/ultrasound} & 51 \\
5 & \text{S} & \text{Ph} & \text{Me} & \text{AlCl}_3/\text{CH}_3\text{CN}/\text{RT} & 52 \\
6 & \text{O, S} & \text{Ph, 4-FC}_6\text{H}_4 & \text{Et} & \text{[bnim][BF}_4 \text{ or [bnim][PF}_6 & 54 \\
7 & \text{O} & \text{Ph, 4-MeO}_2\text{C}_6\text{H}_4 & \text{Et} & \text{10 mol %, Ga}_{3}\text{/CH}_2\text{Cl}_2/\text{RT} & 55 \\
8 & \text{O} & \text{PhCH}_2 & \text{Et} & \text{LiClO}_4, 20 \text{ mol%}, 60 ^\circ \text{C}, 8 \text{ h} & 56 \\
9 & \text{O, S} & \text{4-MeO}_2\text{C}_6\text{H}_4 & \text{2-MeO}_2\text{C}_6\text{H}_4 & \text{Zn(NTf}_2)_2/10 \text{ mol%}, \text{CH}_2\text{Cl}_2, -50 ^\circ \text{C} & 57 \\
10 & \text{O, S} & \text{[Me}_3\text{Si}]_2\text{NH} & \text{Et} & \text{I}_2 (10 \text{ mol%}), \text{solvent free} & 58 \\
11 & \text{S} & \text{(CH}_3\text{)}_3\text{COOH} & \text{Et} & \text{MeOH, Et}_3\text{N} & 61 \\
12 & \text{O} & \text{4-MeO}_2\text{C}_6\text{H}_4 & \text{Me} & \text{Yttria-zirconia Lewis acid/ aq. CH}_3\text{CN/60 \text{ °C}} & 48 \\
13 & \text{O, S} & \text{Ph} & \text{Et} & \text{[Cu(3,4-tmtppa)] (MeSO}_4 \text{)} /(0.16 \text{ %mol) /H}_2\text{O/80 \text{ °C}} & 53 \\
14 & \text{O, S, NH} & \text{[Me}_3\text{Si}]_2\text{NH} & \text{Et} & \text{Al(OTf)}_3 (10 \text{ mol%)/ solvent free/ 80 \text{ °C}} & 59 \\
15 & \text{O, NH} & \text{Ph, 4-MeO}_2\text{C}_6\text{H}_4 & \text{Et, PhCH}_2 & \text{H-β-zeolite, heat, MeCN} & 60 \\
16 & \text{S} & \text{PhCH}_2 & \text{Et} & \text{toluene, reflux, 3h} & 20 \\
17 & \text{S} & \text{Ph} & \text{Et} & \text{TiO}_2 (20 \text{ mol%), no solvent, 50 \text{ °C}} & 62 \\
18 & \text{O} & \text{Ph, 3-pyridinyl} & \text{Et} & \text{Metal oxide, ultrasonic} & 63 \\
19 & \text{O} & \text{Ph} & \text{Me} & \text{Homogeneous sulphamic acid (0.7 mol%), neat/RT} & 64
\end{align*}
\]
Table 1. Continued

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>X</th>
<th>R in Scheme 28</th>
<th>R'</th>
<th>Reaction conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>O</td>
<td>4-phenoxyquinazolin-2-yl</td>
<td>Et</td>
<td>[BMIM]Cl/ MW</td>
<td>65</td>
</tr>
<tr>
<td>21</td>
<td>O, S</td>
<td>Ph</td>
<td>Me, Et</td>
<td>Mg(ClO₄)₂ (5 mol%)</td>
<td>66</td>
</tr>
<tr>
<td>22</td>
<td>S</td>
<td>1-(furan-2-yl)methyl</td>
<td>Me</td>
<td>TMG (tetramethyl guanidine), toluene, 50-60 °C, 5-6 h</td>
<td>67</td>
</tr>
<tr>
<td>23</td>
<td>O, S</td>
<td>Dibenzo[d,f][1,3,2]diazaphosphepin-6-yl 6-oxide-</td>
<td>Me, Et</td>
<td>TMG, toluene, 60-70 °C, 4 h</td>
<td>68</td>
</tr>
</tbody>
</table>

Refluxing thiophene-2-carbaldehyde with a mixture of urea and diethyl phosphite in dry toluene afforded the ureidophosphonate 73 as a major product (Scheme 29).^69_

![Scheme 29](image)

Scheme 29

Magnetic iron oxide nanoparticles coated with structurally variable α-heterocyclic-α-aminophosphonates 75 have been obtained by one-pot three-component reaction of 2-aminopyridine iron oxide nanoparticle 74, heterocyclic aldehydes and diethyl phosphite (Scheme 30).^70_

![Scheme 30](image)

Scheme 30

α-(Indol-2-yl or 3-yl)-α-aminopyridinylphosphonates 76 were obtained from the corresponding indole aldehydes, 2-aminopyridine and diethyl phosphite without any solvent (Scheme 31).^71,72_
Diethyl α-(indol-3-yl)-α-aminophosphonates 77 were synthesized through the reaction of 3-formylindole, diethyl phosphite and heterocyclic amines and/or ammonium carbonate or ammonium acetate under various reaction conditions (Scheme 32) (Table 2). 58-60,68,73,74

**Table 2. Conditions reaction of 3-formylindole, diethyl phosphite and amines to give diethyl indolyl-α-aminophosphonates 77**

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Conditions</th>
<th>Amine</th>
<th>R</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (10 mol %)/ solvent-free</td>
<td>(Me₃Si)₂NH</td>
<td>Et</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>Al(OTf)₃ (10 mol %), solvent-free/ 80 °C</td>
<td>(Me₃Si)₂NH</td>
<td>Et</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>Al(OTf)₃ (10 mol %), solvent-free/ 100 °C</td>
<td>(NH₄)₂CO₃ or NH₄OAc</td>
<td>Et</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>β-zeolite</td>
<td>PhNH₂, 4-MeOC₆H₄NH₂</td>
<td>Et</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>PEG / H₂O / RT</td>
<td></td>
<td>Et</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>toluene / TMG / 60 -70 °C / 4h</td>
<td>Me, Et</td>
<td></td>
<td>68</td>
</tr>
</tbody>
</table>

α-(Indol-3-yl)-α-aminophosphonate 79 was synthesized by the reaction of an aromatic amine, 3-(4-formylphenyl)indole (78) and diethyl phosphite under MW conditions in the presence of Amberlyst-15 (Scheme 33). 75
Various substituted anilines carrying either electron donating or electron withdrawing substituents, and also benzylamine, reacted with 9-ethyl-6-bromo-3-formylcarbazole (80) and diethyl phosphite in PEG-mediated reactions to give the desired α-(carbazol-3-yl)-α-amino-phosphonates 81 in good yields. In this reaction PEG-400 not only acts as the solvent but also accelerates the imine formation and the nucleophilic addition of phosphate to the imine by increasing its electrophilicity through hydrogen bonding by its hydroxyl group with the imine nitrogen (Scheme 34).76

$$\text{Scheme 33}$$

$$\text{Scheme 34}$$

3.2. Five-membered heterocycles with two heteroatoms
In a one-pot synthesis, 3-formylpyrazole (82) reacted with benzyl carbamate and triphenyl phosphite in acetic acid to give α-(pyrazol-3-yl)-α-aminophosphonate 83 in moderate yield (Scheme 35).20
Scheme 35

1-Phenyl-3-aryl/heteroaryl-1H-pyrazol-4-carboxaldehyde (84) are reported to react with arylamines and dialkyl/diphenyl phosphites under Kabachnik-Fields reaction conditions in the presence or absence of catalysts to give the corresponding α-(pyrazol-4-yl)-α-amino-phosphonates 85 (Scheme 36) (Table 3).

Scheme 36

Table 3. Conditions of reactions of 1-phenyl-3-aryl/heteroaryl-1H-pyrazol-4-carboxaldehyde (84) with arylamines and dialkyl/diphenyl phosphites to give pyrazolyl-α-aminophosphonates 85

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Ar</th>
<th>Ar′</th>
<th>R</th>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>Et</td>
<td>BF₃·Et₂O/70-80 °C</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-MeC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-IC₆H₄, 4-FC₆H₄, 3-Cl-4-FC₆H₃, 3,4-Me₂C₆H₃, 4-ClC₆H₄</td>
<td>Et</td>
<td>MW(200W), 80 °C, 3 min</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>2-pyridyl</td>
<td>4-HOOC₆H₄, 4-MeOC₆H₄, 4-MeNC₆H₅</td>
<td>Ph</td>
<td>LiClO₄, DCM, RT, 24-30 h</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>Ph, 4-MeOC₆H₄</td>
<td>Ph, 4-MeC₆H₄, 2-MeC₆H₄, 4-MeOC₆H₄</td>
<td>Me, Et</td>
<td>Toluene/ 110 °C</td>
<td>78</td>
</tr>
</tbody>
</table>
One-pot three-component reaction of bis-(4-formyl-3-phenyl-1H-pyrazol-1-yl)phosphine oxide (86), aniline and diethyl phosphite in the presence of BF₃·Et₂O at 80 °C under Kabachnik-Fields reaction conditions produced an interesting type of bis(α-aminophosphonate) 87 (Scheme 37).¹¹

![Scheme 37](image)

Reaction of 6-amino-6λ⁵-dibenzo[d,f][1,3,2]dioxaphosphepin-6-oxide (88) with 2-formyl-imidazole (89) and dialkyl phosphites in dry toluene in the presence of tetramethylguanidine (TMG) as a catalyst at 60–70 °C for 4 hours afforded dimethyl/diethyl(6-oxo-6λ⁵-dibenzo[d,f][1,3,2]dioxaphosphepin-6-ylamino)-(1H-2-imidazoly)methylphosphonates (90) in good yields (Scheme 38).⁶⁸

![Scheme 38](image)

Substituted α-(benzodioxol-5-yl)-α-aminophosphonates 91 could be prepared under various mild conditions by reaction of veratraldehyde, and dialkyl phosphites (Scheme 39).⁸²-⁸⁵

Three-component Mannich type reactions starting from aldehydes or ketones, amines and phosphites have proved to be a facile method for the preparation of various α-aminalkylphosphonate compounds. A rapid method for the synthesis of N-phosphoramino-α-aminophosphonate 92 involved reacting veratraldehyde with diethyl phosphoramidate and a cyclic trivalent chlorophosphite at 50–60 °C neat, without solvent or catalyst, for an appropriate time (Scheme 40).⁸⁶
Scheme 39

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{CHO} \\
\text{ArNH}_2
\end{array} \quad \begin{array}{c}
\text{HP(O)(OR)}_2
\end{array} \\
\overset{\text{reaction conditions i-iv}}{\text{(25 - 50 %)}} \quad \begin{array}{c}
\text{91}
\end{array}
\end{align*}
\]

\(i) \ \text{MgSO}_4 / \text{Me}_3\text{SiCl} \)
\(ii) \ \text{Twee-20} / 30-80^\circ\text{C}, \text{water} \)
\(iii) \ \text{Neat/ solvent free} \)
\(iv) \ \text{KH}_2\text{PO}_4 / \text{RT} \)

\(R = \text{Et, PhCH}_2 \)
\(\text{Ar} = \text{Ph, PhCH}_2, \ p-\text{ClC}_6\text{H}_4, \ \text{cyclohexyl} \)

Scheme 40

Reaction between 2-formylbenzimidazole (93), 2-amino-5-methyloxazole (94), and diethyl phosphite by stirring equimolar quantities in a variety of solvents at ambient temperature gave a low yield of the desired \(\alpha\)-aminophosphonate 95 in all the experiments. The best result was obtained when the reaction was carried out using PEG in water (Scheme 41).^{74}

Scheme 41

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{CHO} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{Cl}
\end{array} \quad \begin{array}{c}
\text{O}
\end{array} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{EtO}
\end{array} \\
\overset{\text{solvent free}}{\text{(90 %)}} \quad \begin{array}{c}
\text{92}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{CHO} \\
\text{NH}_2
\end{array} \quad \begin{array}{c}
\text{PEG / H}_2\text{O}
\end{array} \quad \begin{array}{c}
\text{Ar}
\end{array} \\
\overset{\text{r. t.}}{\text{(74 - 84 %)}} \quad \begin{array}{c}
\text{95}
\end{array}
\end{align*}
\]

\(R = \text{Me, Et} \)
\(\text{Ar} = \text{Ph, PhCH}_2, \ p-\text{ClC}_6\text{H}_4, \ \text{cyclohexyl} \)
3.3. Six-membered heterocycles with one heteroatom

The action of tris(trimethylsilyl)phosphite on the aldimine formed \textit{in situ} from 2-formylchromone (96) and benzylamine yielded (N-benzylamino)chromon-2-ylmethanephosphonic acid (97) (Scheme 42).\textsuperscript{87}

\begin{equation}
\text{PhCH}_2\text{NH}_2 \xrightarrow{1) \text{PhCH}_2\text{NH}_2} \text{P(\text{OSiMe}_3)_3} \xrightarrow{2) \text{MeOH}/\text{Chloroform}} \text{NHCH}_2\text{Ph}
\end{equation}

\textbf{Scheme 42}

3-Formylchromones (98) reacted easily with amines and dialkyl phosphites or trialkyl phosphites under different reaction conditions to form the α-(chromon-3-yl)-α-amino-phosphonates 99 in moderate to high yields (Scheme 43).\textsuperscript{46,48}

\begin{equation}
\text{R}^1= \text{H, Me, Et, Ph} \quad \text{R}^1= \text{H, Cl, Me} \quad \text{R}^2 = \text{H, Cl} \quad \text{R}^3 = \text{Ph, PhCH}_2\text{OCO, 4-MeC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 2-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4
\end{equation}

Reaction conditions:

\begin{align*}
i) & \text{AcOH or Yttria-Zirconia Lewis acid/ aq. CH}_3\text{CN, 60 °C, ii) Catalyst free} \\
\text{42 - 99 %} & \\
\end{align*}

\textbf{Scheme 43}

The one pot three component reactions of heterocyclic ketones 100, amine and triethyl phosphite in ethanol or toluene/acetonitrile at 60 °C afforded α-aminophosphonates 51 in low to good yields (Scheme 44).\textsuperscript{88}

\begin{equation}
\text{RNH}_2, \text{solvent, AcOH} \xrightarrow{1) \text{RNH}_2, \text{solvent, AcOH}} \text{P(OEt)}_3, 60{\circ} \text{C, 1-2 days} \xrightarrow{2) \text{P(OEt)}_3, 60{\circ} \text{C, 1-2 days}} \text{NHCH}_2\text{Ph}
\end{equation}

\textbf{Scheme 44}
2-, 3-, And 4-formylpyridines 101 reacted with different alkyl and aromatic amines and trialkyl phosphite or dialkyl phosphite under different reaction conditions to give the corresponding α-(pyridyl)-α-aminophosphonates 102 in good to excellent yields (Scheme 45) (Table 4).

\[
\begin{align*}
\text{Reaction Conditions} & \quad 43-99 \% \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 45}
\end{align*}
\]

**Table 4.** Reaction conditions of 2-, 3- and 4-formylpyridines 101 and amines with tri- or di-alkyl phosphite to give the corresponding pyridyl α-aminophosphonates 102

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Aldehyde 101</th>
<th>Amine</th>
<th>R'</th>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Me, Et</td>
<td>MgClO4/ neat/ RT/ 2-6 min /or 80 °C / 0.5 – 6 h</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>Et</td>
<td>Reflux / 60 °C</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>Et</td>
<td>BF3·SiO2/[bmim][HCl]/ 5-10 min/RT/neat</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Bu, PhCH2NH2</td>
<td>Et, Ph</td>
<td>toluene</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PhNH2</td>
<td>Et</td>
<td>Nano Fe2O3/ neat/ 50 °C</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PhNH2</td>
<td>Et</td>
<td>Solvent free</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>Et</td>
<td>MeOH/ Et3N / Me3Si</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>2-, 3-,4-aminopyridine</td>
<td>Et</td>
<td>rPcAlCl / molecular sieves</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Me, Et</td>
<td>TMG/ toluene / 50-60 °C, 5- 6 h</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Continued

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Aldehyde 101</th>
<th>Amine</th>
<th>R’</th>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>(Me₃Si)₂NH</td>
<td>Et</td>
<td></td>
<td>Al(OTf)₃ (10 mol%) / solvent free /80 °C</td>
<td>59</td>
</tr>
<tr>
<td>11</td>
<td>(Me₃Si)₂NH</td>
<td>Et</td>
<td>I₂ (10 mol%) / solvent free</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PhNH₂</td>
<td>Me</td>
<td></td>
<td>TiCl₄ / CH₃CN / RT</td>
<td>89</td>
</tr>
<tr>
<td>13</td>
<td>PhNH₂</td>
<td>Me</td>
<td></td>
<td>AlCl₃ / CH₃CN / RT</td>
<td>52</td>
</tr>
<tr>
<td>14</td>
<td>2-aminopyridine</td>
<td>Et</td>
<td></td>
<td>Solvent free</td>
<td>71</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>Me, Et</td>
<td></td>
<td>toluene/TMG / 60 - 70 °C</td>
<td>68</td>
</tr>
<tr>
<td>16</td>
<td>2-, 3-, 4- formylpyridines</td>
<td>BuNH₂, PhNH₂, Ph₂CHNH₂, PhCH₂NH₂</td>
<td>Et</td>
<td>toluene / 110 °C</td>
<td>90</td>
</tr>
</tbody>
</table>

Reactions of various arylamines, 3-acetylpyridine and triphenyl phosphite in the presence of lithium perchlorate were carried out to give α-(pyridine-3-yl)-α-aminophosphonates 103 in high yields (Scheme 46).\(^{94}\)

![Scheme 46](image)

Scheme 46

The three-component reaction of 4-(pyridin-4-yl)benzaldehyde and triethyl phosphite with various aryl/heteroaryl substituted primary amines led to the formation of diethyl (aryl/heteroaryl aminopyridine-4-yl)phenyl)methyl phosphonates 104 (Scheme 47).\(^{95}\)

The interesting α-quinonimethylenyl α-aminophosphonate 107 was prepared in moderate yield through reaction of 8-formylmethylquinoline 105, 3-[5-[(1S)-1-amino-2-(biphenyl-4-yl) ethyl]-1H-tetrazol-1-yl]propanenitrile (106) and dibenzyl phosphite in the presence of MgSO₄ and Me₃SiCl (Scheme 48).\(^{82}\)
CH$_2$O $+$ RNH$_2$ $\xrightarrow{P(OEt)$_3$, Toluene}$ 104

R= 4-pyridyl, 1-(pyridin-3-yl)methyl, 1,3-thiazol-2-yl, 1,3-benzothiazol-2-yl, 5-nitro-1,3-benzothiazol-2-yl

Scheme 47

One-pot three-component reaction of quinoline-3-carboxaldehyde and aniline with diethyl phosphite under microwave irradiation proceeded in the formation of diethyl [α-anilino-(3-quinolylmethyl)]phosphonate 108 in a relatively good yield of about 80%. Unexpectedly, the corresponding monoester 109 (3%) and a very interesting phosphorus compound that proved to be bis(hydrophosphonate) phosphate monoester derivative 110 (7%) were isolated as by-products (Scheme 49).*6

Scheme 48

Scheme 49
A mixture of a 2-chloro-3-formylquinoline derivative 111, an amine and dialkyl phosphite and/or trialkyl phosphite was added to the solvent used under the reaction conditions shown to afford the corresponding α-(quinolin-3-yl)-α-aminophosphonates 112 in good to excellent yields (Scheme 50).

\[
\begin{align*}
\text{R} &= \text{Me, Et, } R^1 = H, \text{Me, MeO, EtO, } R^2 = H, \text{Me, MeO, } \\
R^3 &= \text{H, Me, Et, } R^4 = \text{Ph, PhCH}_2, \text{3-MeC}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4, \text{4-FC}_6\text{H}_4
\end{align*}
\]

Reaction conditions:

i) KH$_2$PO$_4$/ r.t.

ii) Yttria-Zirconia Lewis acid/ aq. CH$_3$CN, 60 °C

iii) TMSCl, CH$_3$CN, reflux

3.4. Six-membered heterocycles with two or more heteroatoms

Hybrid compounds of α-aminophosphonate 114 with pyrimidine nucleosides were synthesized in good to excellent yields starting from 5-formyl-2-deoxyuridine (113), aniline and dimethyl phosphite in one pot (Scheme 51).

\[
\begin{align*}
\text{R} &= \text{H, Ac, } R^1 = \text{H, Ac, } R^2 = \text{Ph, p-FC}_6\text{H}_4, \text{p-BrC}_6\text{H}_4, \text{p-ClC}_6\text{H}_4, \text{p-CH}_2\text{C}_6\text{H}_4, \text{p-OCH}_2\text{C}_6\text{H}_4
\end{align*}
\]

Scheme 51

The target α-aminophosphonates 116 were synthesized via the Mannich-type reactions of aldehyde 115, aromatic amines, and dialkyl phosphites or triphenyl phosphite in the presence of Mg(ClO$_4$)$_2$ in moderate to good yields. It was found that Mg(ClO$_4$)$_2$ can reduce the reaction time and improve the yields of products greatly (Scheme 52).
Scheme 52

The reaction of 10-ethyl-10H-phenothiazine-3-carbaldehyde 117, anilines, and diethyl phosphite in PEG-400 was complete in 24 hour at room temperature; the corresponding α-aminophosphonates 118 was obtained in low yield (30%). However, the yield was dramatically increased by increasing the temperature to 100 °C. Under optimized conditions, the reaction proceeded well at 100 °C and the desired α-aminophosphonate 118 (Ar=Ph) was obtained in 91% yield. PEG-400 was found to be more effective in the synthesis of 118 (Ar=Ph) in terms of reaction time (6 h) and yields (91%) (Scheme 53).100

Scheme 53

3.5. Macrocycles

α-Aminophosphonic acid derivatives of benzo-15-crown-5-ether 120 can be easily obtained from the 4-formylbenzo-15-crown-5 (119), primary amines, and trimethyl phosphite or diethyl phosphite. The aminophosphonic acid 120 was obtained as a free base by using bromotrimethylsilane as a deprotecting agent of phosphonic esters (Scheme 54).101
4. Miscellaneous Methods

4.1. From diethyl α-azido-α-(benzoylaminomethyl)phosphonate

Also, diethyl (2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate (122) was prepared by a reaction of diethyl-(2-azido-2-benzoylaminomethyl) phosphonate (121) with dimethyl acetylenedicarboxylate in dry benzene at room temperature (Scheme 55).102

Similarly, some 1-(prop-2-ynyl)-5-aryltetrazoles (123) and 2-(prop-2-ynyl)-5-aryltetrazoles (124) were submitted to undergo cycloaddition reaction with the azido phosphonate 121 in dry benzene under reflux to give the interesting biheterocyclic α-aminophosphonic acid diesters 125, 126 and 127, 128, respectively (Scheme 56).103
4.2. Nucleophilic substitution reactions

The reactions of different heterocyclic nucleophiles (benzimidazole, imidazole, pyrazole, 3,5-dimethylpyrazole and 1,2,4-triazole) with diethyl $\alpha$-azido-$\alpha$-aminomethylphosphonate (121) were conducted at room temperature in acetone in the presence of DIPEA (diisopropyl-ethylamine) resulting in the corresponding $\alpha$-heterocyclic $\alpha$-aminophosphonates 129 (Scheme 57).\(^ {104}\)

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

121

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

124

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

125

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

126

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

127

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

128

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

129

\[
\begin{align*}
\text{PhCONH} & \quad \text{P(OEt)}_2 \\
& \quad \text{N}_3 \\
\end{align*}
\]

131

Nu-H= Benzimidazole, Imidazole, Pyrazole, 3,5-Dimethylpyrazole, 1,2,4-Triazole

Scheme 57

Nucleophilic substitution of trichloromethyl moiety in ureidophosphonate 130 with morpholine gave diethyl \{1-[3-(2-hydroxyphenyl)ureido]-2-morpholino-2-oxoethyl\}phosphonate (131) in 82 % yield (Scheme 58).\(^ {105}\)
Similarly, the reaction of different amines \( \text{Nu-H} \) with the \( \alpha \)-bromo-\( \alpha \)-aminophosphonate derivative 132 resulted in the formation of \( \alpha \)-heterocyclic \( \alpha \)-aminophosphonates 133 (Scheme 59).

4.3. Cycloadditions of \( \alpha \)-alkynylaminophosphonates

The cycloaddition of diethyl \([1-[(\text{benzyloxy} carbonyl)\text{amino}]-1-(\text{trifluoromethyl})\text{prop}}\text{but-2-yn-1-yl]phosphonate (134) to organic azides proceeded only at 80 °C in the presence of a solvent mixture to afford the corresponding \( \alpha \)-CF\(_3\)-\( \alpha \)-(triazol-4-yl)-\( \alpha \)-aminophosphonates 135 (Scheme 60).
Also, the ethynyl-substituted aminophosphonate 134 demonstrated comparable reactivity towards different nitrile oxides under similar reaction conditions, yielding the corresponding isoxazole-containing α-trifluoromethyl α-aminophosphonates 136 in good yield (Scheme 61).\(^{108}\)

Scheme 61

4.4. Reduction of α-hydroxyiminophosphonate

Simple reduction of the 1-hydroxyiminophosphonate 137 with NaBH\(_4\) in the presence of transition metal compounds such as MoO\(_3\) or NiCl\(_2\).6H\(_2\)O at ambient temperature in methanol and at normal pressure gave the corresponding diethyl aminoalkyl(aryl)phosphonates 138 in good yields (Scheme 62).\(^{109}\)

Scheme 62

4.5. Hydrolysis of S-adenosyl-L-homocysteine derivative

Reaction of the thiolate anion of 139 with diethyl [3-bromo-1-(diphenylmethyleneamino)propyl] phosphonate (140) was performed to give the fully protected AdoHcy analogue 141 in 63% yield. Deprotection was achieved via hydrolysis with trimethylsilyl iodide (TMSI) to generate the desired α-aminophosphonic acid nucleoside 142 in 75% yield (Scheme 63).\(^{110}\)
Scheme 63

4.6. Curtius rearrangement of $\alpha$-acylazidophosphonate
Curtius rearrangement of the S,S-dioxide of $\alpha$-acylazidophosphonate 143 in dichloromethane afforded $\alpha$-Boc-$\alpha$-aminophosphonate 144 (Scheme 64).\textsuperscript{111}

Scheme 64

4.7. Addition of diethyl phosphite to chiral N-benzyl nitrones
When N,N-diprotected $\alpha$-aminonitrone 145 were treated with TBDMSOTf and then diethyl phosphite in THF or CH$_2$Cl$_2$ at -20 °C, the syn $\alpha$-(hydroxyamino)phosphonates 146 were obtained in good yields after flash chromatography (Scheme 65).\textsuperscript{112}
4.8. From phosphonyliminium salts

The optimized reaction conditions involved refluxing of the phosphonyliminium salt 147 and some nucleophilic aromatic compounds in THF gave the highest yields of novel α-heteroaryl-α-aminophosphonates 151 (Scheme 66).113

4.9. From oxazolyl phosphonates

Heating diethyl 5-(2-acylhydrazino)-2-[(4-methylphenyl)-1,3-oxazol-4-yl]phosphonates 151 in acetic acid led to the formation of the phosphonic acid derivatives 152 through ring opening and recyclization of the oxazole derivative and ester hydrolysis (Scheme 67).114
Finally, reaction of the oxazolyl phosphonates 151 (Het=6-methylchromone) with hydrazine hydrate in ethanol for 2 hours afforded diethyl [5-[5-(2-hydroxyphenyl/2-hydroxy-5-methylphenyl)-1H-pyrazol-3-yl]-1,3,4-oxidiazol-2-yl][(4-methylbenzoyl)amino]methylphosphonates 153 in good yields, which were boiled in acetic acid to afford the corresponding phosphonic acid derivatives 154 (Scheme 68).

Scheme 67

Scheme 68
5. 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 up to the end 2013 on the synthesis of \(\alpha\)-heterocyclic/heteroaryl \(\alpha\)-aminophosphonic acids and their esters that will be a fundamental key in the design of new bioactive agents with improved pharmacological properties. The review is built up according to the used methods and starting with the smallest rings of each method.

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