

Methods for synthesis of *N*-heterocyclyl/heteroaryl- α -aminophosphonates and α -(azaheterocyclyl)phosphonates

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Abstract

This review describes the most frequently reported synthetic methods for *N*-heterocyclyl- α -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 α -(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- α -aminophosphonate, α -(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.¹ The phosphonic moiety has long been established as a bioisostere of a carboxylic unit. This feature explains the great variety of biological activities²⁻⁵ 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,⁶ enzyme inhibitors,⁷ anticancer agents⁸ and herbicides.⁹ The biological properties are mostly associated with the tetrahedral structure of the phosphonyl group acting as a “transition-state” analogue.¹⁰ 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.¹¹ 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 esters¹²⁻¹⁸ and azaheterocyclic phosphonates.¹⁹ The Pudovik^{20,21} and Kabachnik-Fields^{22,23} 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 α -aminophosphonates are becoming a subject of growing interest.

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

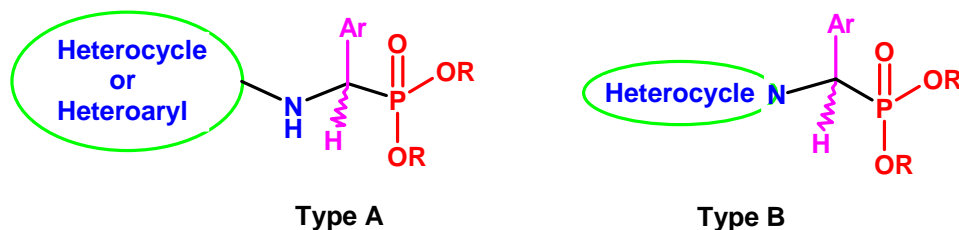


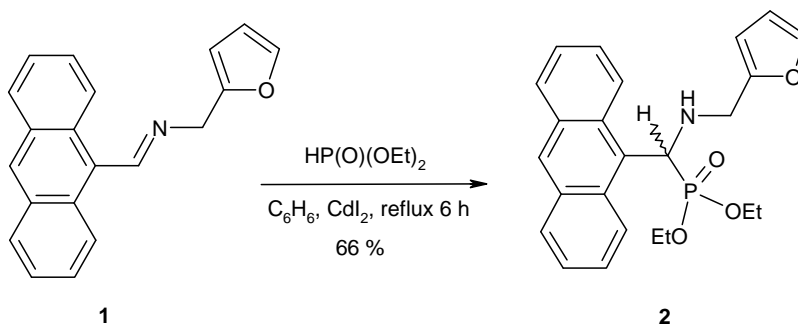
Figure 1. *N*-heterocyclyl/heteroaryl α -aminophosphonates (Type A) and α -(azaheterocyclyl) phosphonates (Type B).

2. Synthesis of *N*-Heterocyclyl/heteroaryl- α -aminophosphonic Acids and Their Diesters (Type A)

2.1. Pudovik reactions

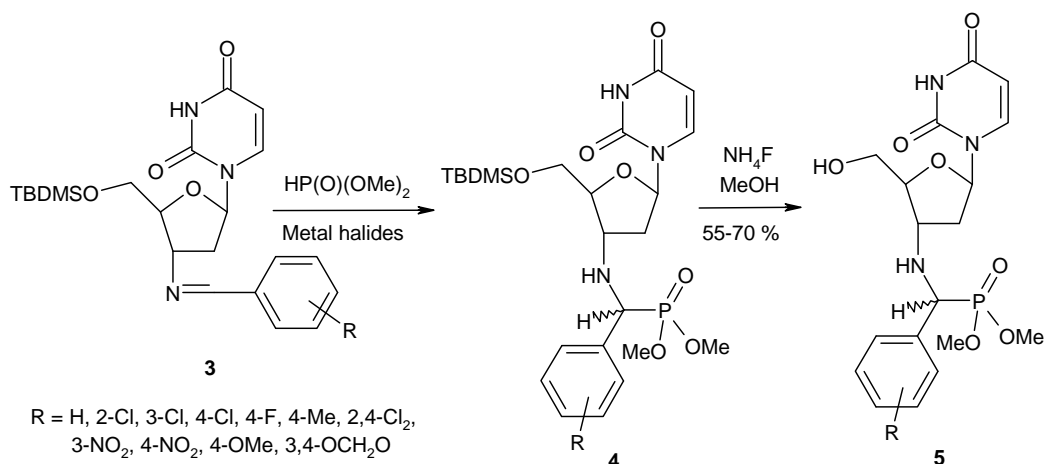
In the Pudovik reaction dialkyl phosphites are added to imines (Schiff bases). In some reports, these reactions were carried out in straightforward one-pot procedures without any catalyst,²⁰ but in most cases it is performed using catalysts such as Lewis acids.²¹

2.1.1. Five-membered heterocycles with one heteroatom. The α -(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 1.³¹



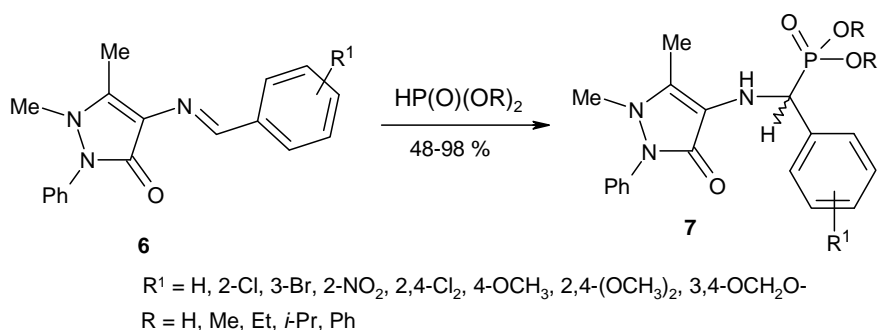
Scheme 1

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).³²



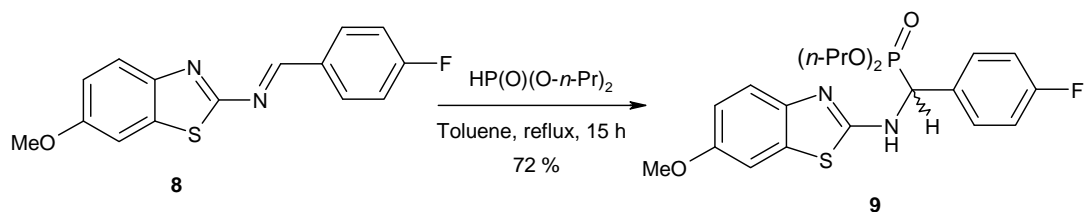
Scheme 2

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-antipyril)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).^{33,34}



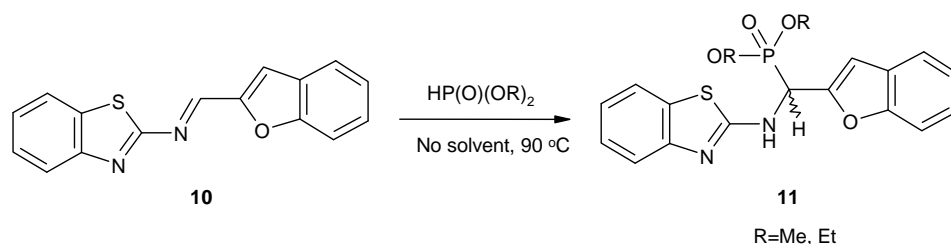
Scheme 3

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).³⁵



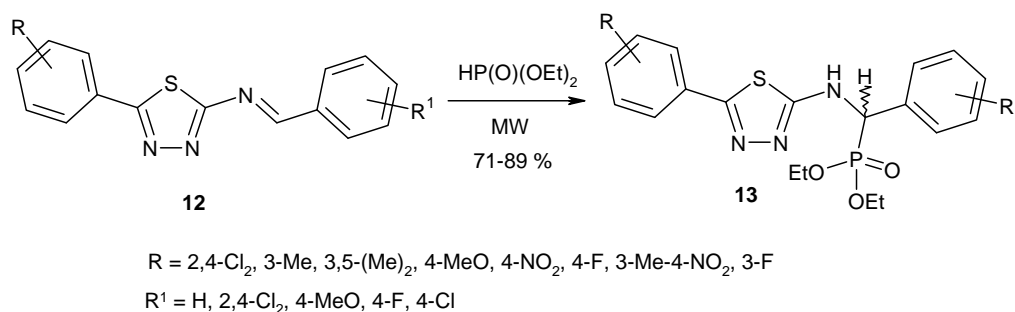
Scheme 4

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



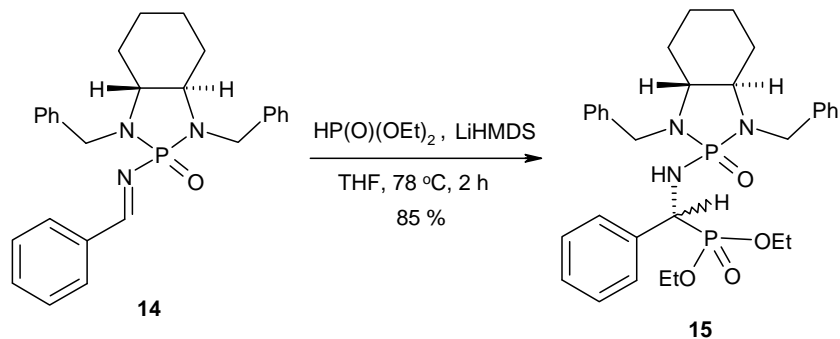
Scheme 5

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-amines (**12**) and diethyl phosphite under microwave (MW) irradiation as shown in Scheme 6.^{37,38}



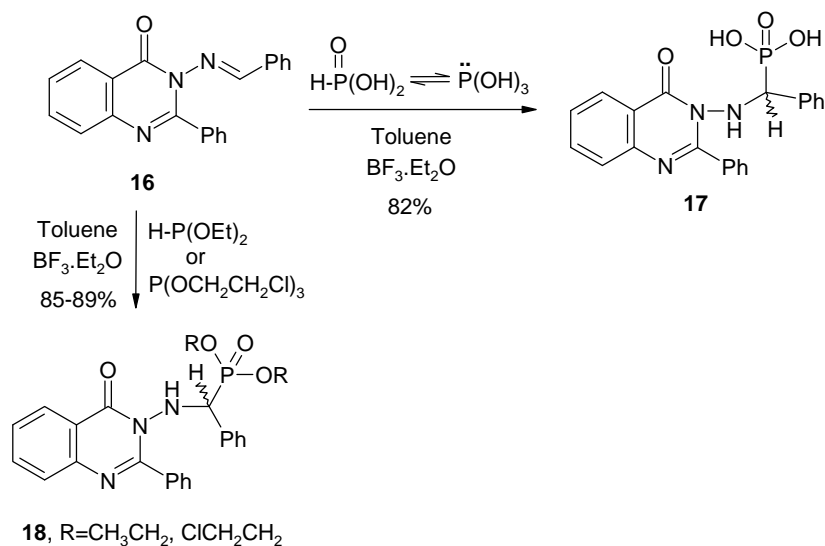
Scheme 6

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 α -aminophosphonate **15** in good yield although only modest diastereoselectivity was observed (Scheme 7).³⁹



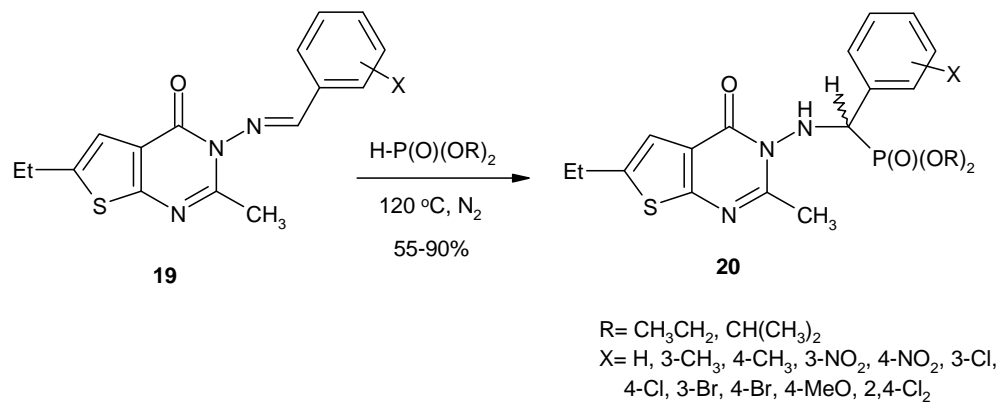
Scheme 7

2.1.4. Six-membered heterocycles with two heteroatoms. Addition of phosphorous acid to the imine **16** in toluene containing a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ under Pudovik reaction conditions gave $\{[(4\text{-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)amino}](\text{phenyl)methyl}\}$ phosphonic acid (**17**) in good yield (Scheme 7). Addition of diethyl phosphite and *tris*(2-chloroethyl) phosphite to the imine **16** under the same reaction conditions led to the formation of dialkyl *N*-quinazolinyl α -aminophosphonates **18** (Scheme 8).⁴⁰



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 α -aminophosphonate derivatives **20** (Scheme 9).⁴¹

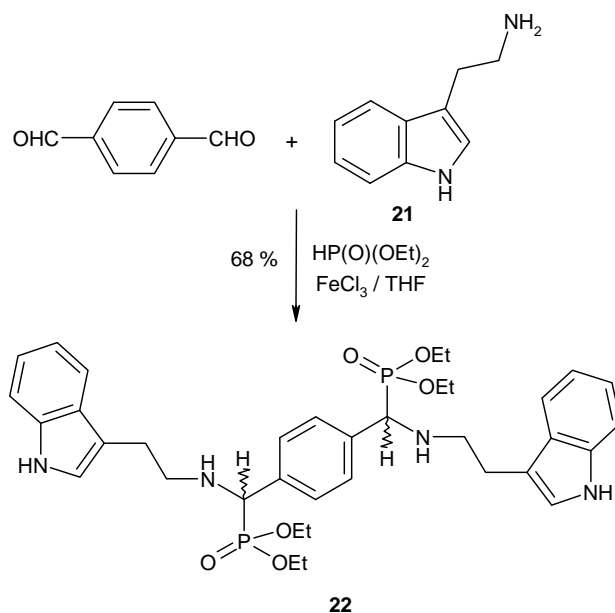


Scheme 9

2.2. Kabachnik-Fields reactions

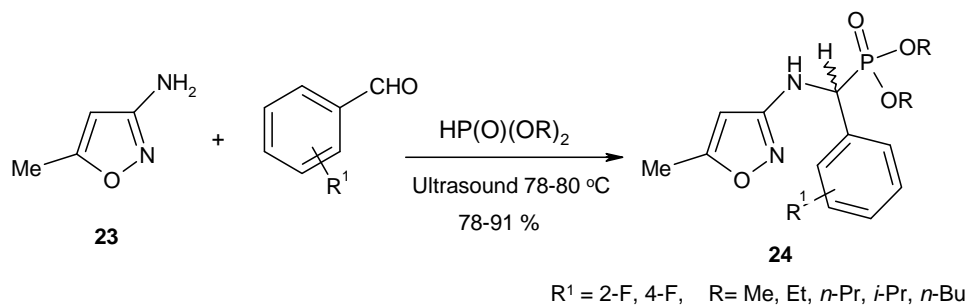
The Kabachnik–Fields reaction is a three component reaction, in which a carbonyl compound, an amine, and a di- or tri-alkyl phosphite react in a single-pot, in the presence or absence of catalysts.^{22,23}

2.2.1. Five-membered heterocycles with one heteroatom. A solution of ferric chloride in tetrahydrofuran facilitated the Mannich-type reaction of terephthalaldehyde, 3-(2-aminoethyl)-indole (**21**) and diethyl phosphite to form the corresponding *N*-indolyl- α -aminophosphonate **22** in a one-pot, three component reaction (Scheme 10).⁴²



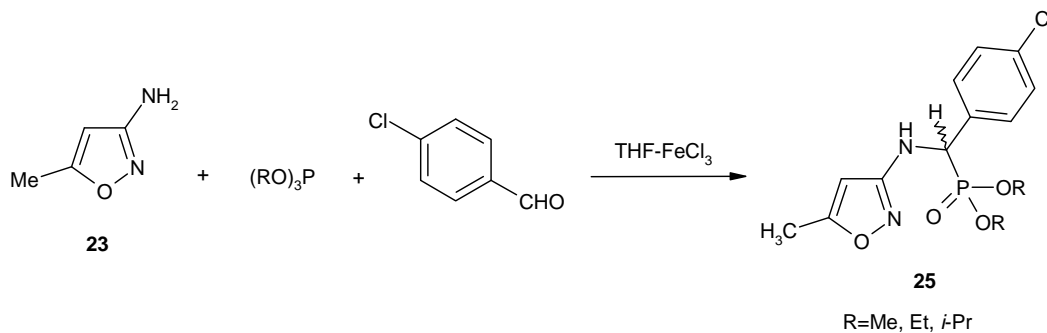
Scheme 10

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).⁴³



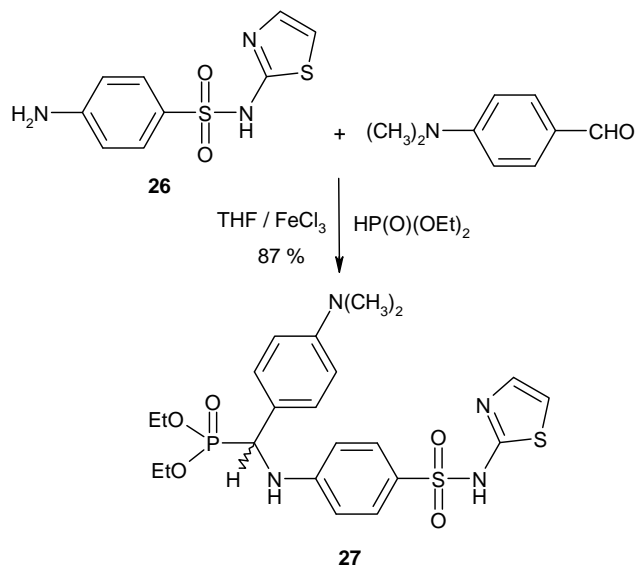
Scheme 11

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% FeCl₃ (Scheme 12).⁴⁴



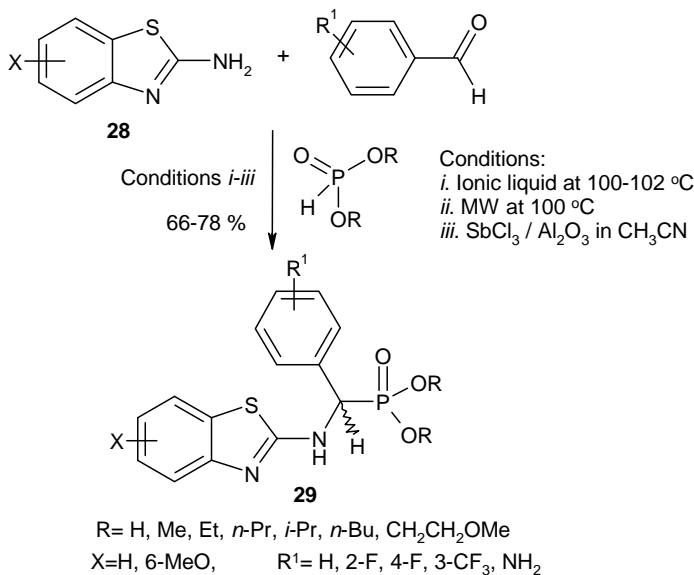
Scheme 12

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).⁴⁵



Scheme 13

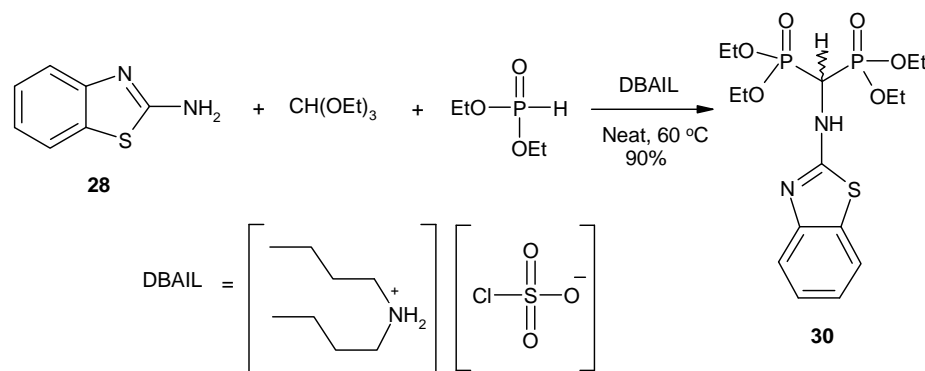
The reaction of 2-aminobenzothiazoles (**28**) with aromatic aldehydes in the presence of dialkyl phosphites afforded the corresponding *N*-(benzothiazol-2-yl)- α -aminophosphonates **29** in good yields under different reaction conditions (Scheme 14).⁴⁶⁻⁴⁸



Scheme 14

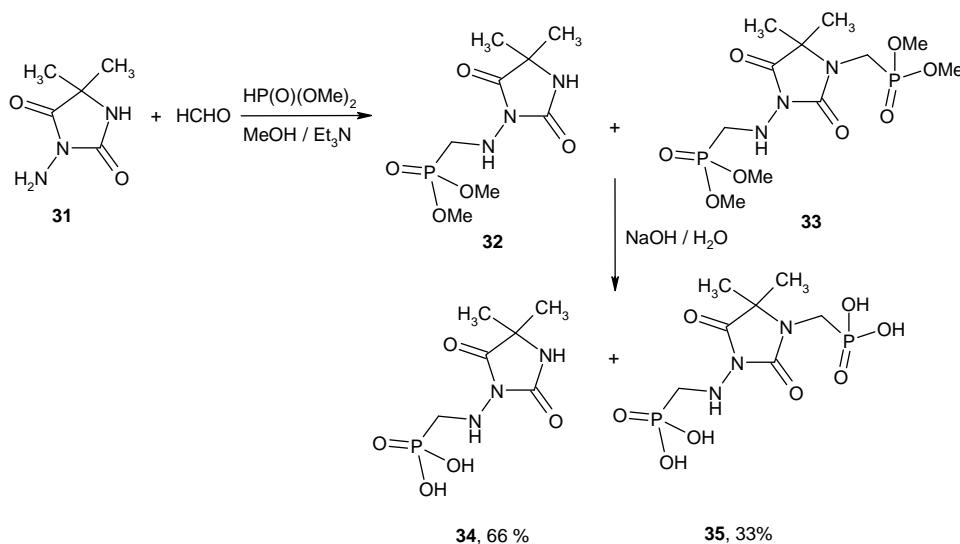
Similarly, reaction of 2-aminobenzothiazole (**28**), diethyl phosphite and triethylorthoformate at 60 °C without catalyst under solvent-free conditions gave the corresponding *N*-biphosphonate **30**. The reaction did not proceed even after prolonged reaction

time and no desired product was formed. When the reaction was performed in the presence di-*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



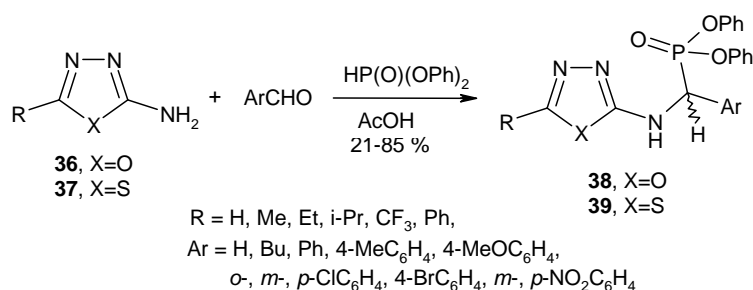
Scheme 15

The dimethyl α -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-dioxoimidazolidin-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



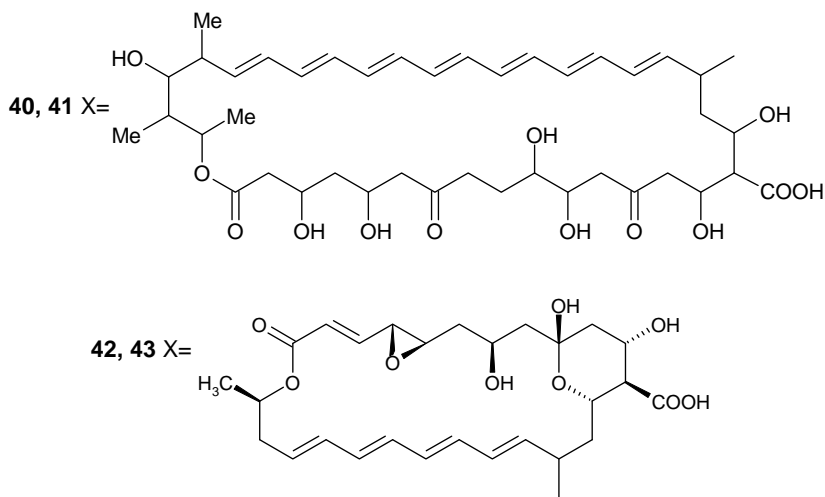
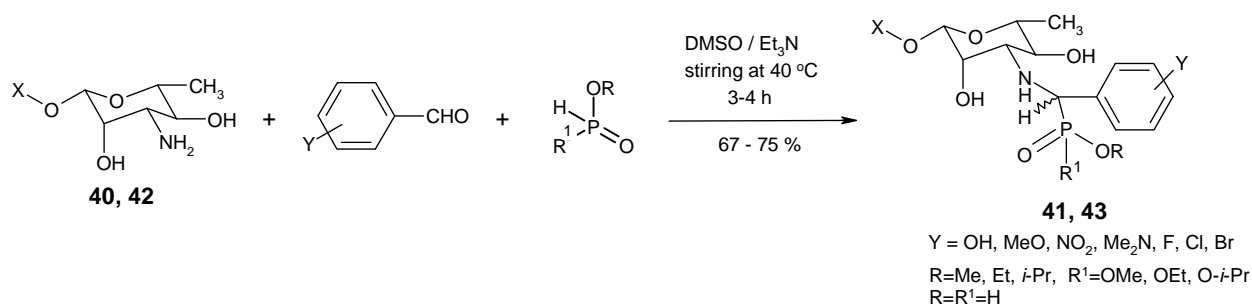
Scheme 16

2.2.3. Five-membered heterocycles with three heteroatoms. A facile and efficient one-step synthesis of α -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).⁵¹⁻⁵⁴



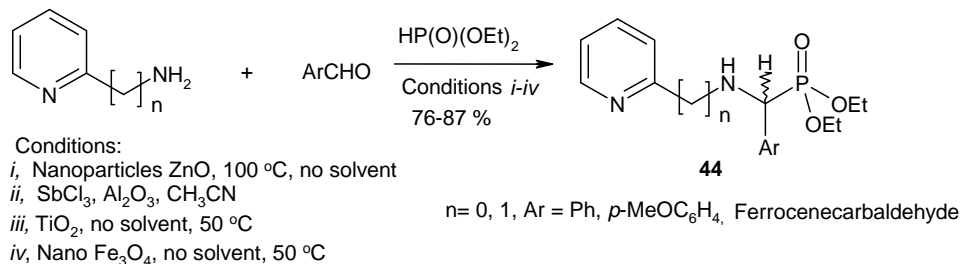
Scheme 17

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 α -aminophosphonic acids **41** (Scheme 18).⁵⁵ 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).⁵⁶



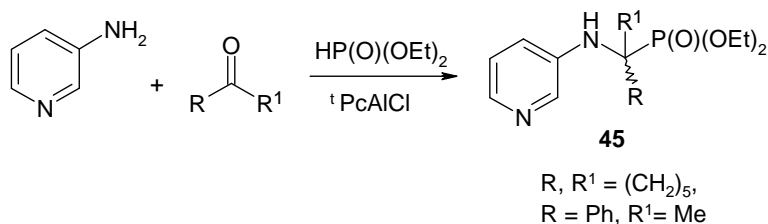
Scheme 18

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- α -aminophosphonates **44** (Scheme 19).^{47,57-59}



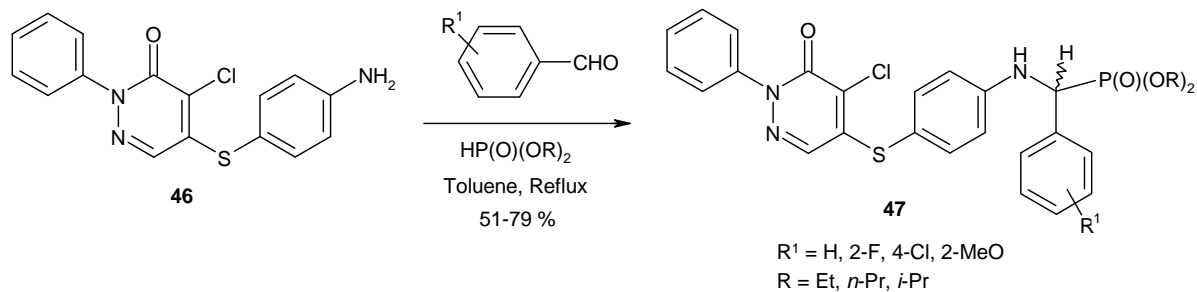
Scheme 19

The synthesis of the corresponding *N*-(3-pyridyl)- α -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 (^tPcAlCl) as a catalyst (Scheme 20).



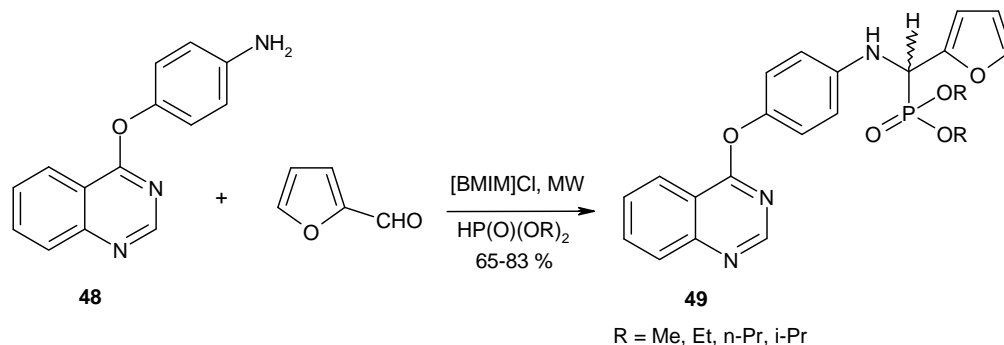
Scheme 20

2.2.5. Six-membered heterocycles with two heteroatoms. 4-Chloro-2-phenyl-5-(4-aminophenylthio)pyridazin-3(2*H*)-one (**46**) reacted in a three-component reaction with different aldehydes and dialkyl phosphites to provide *N*-pyridazinyl- α -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



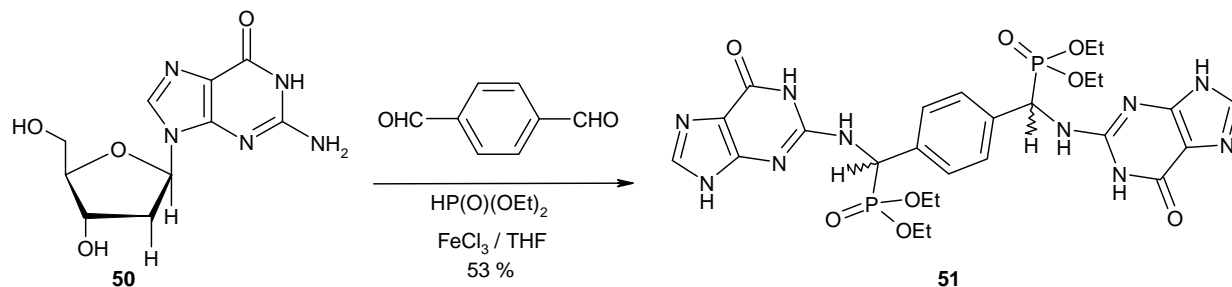
Scheme 21

1-Butyl-3-methylimidazolium chloride [BMIM]Cl catalyzed three component reaction of 4-(quinazolin-4-yloxy)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 22

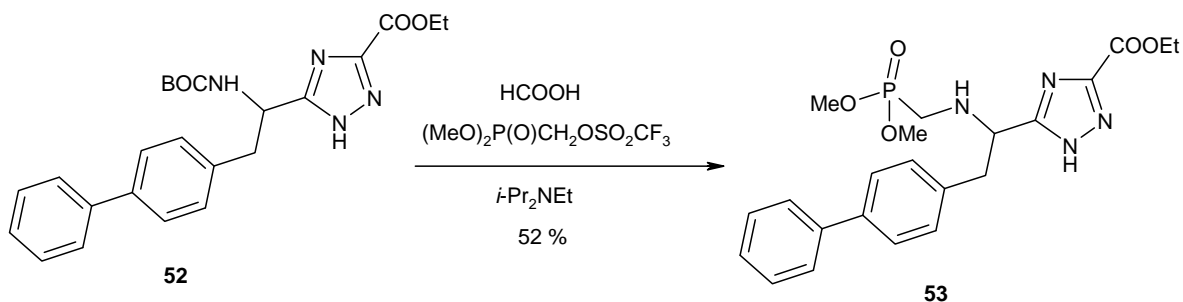
A solution of ferric chloride in tetrahydrofuran facilitated the Kabachnik reaction of terephthalaldehyde, guanosine (**50**) and diethyl phosphite to form the corresponding *N*-purinyl- α -aminophosphonate **51** in a one-pot, three component reaction (Scheme 23).⁴²



Scheme 23

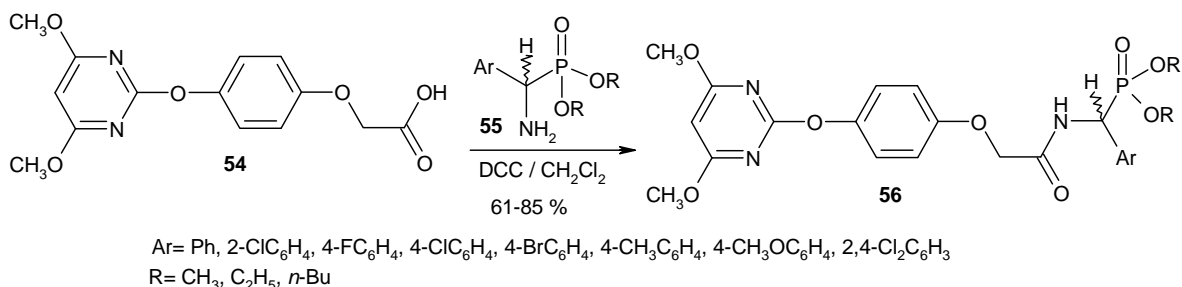
2.3. Miscellaneous methods

2.3.1. Removal of a BOC group and phosphonylmethylation in acidic medium. Hydrolysis of the *tert*-butoxycarbonyl 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).⁶³



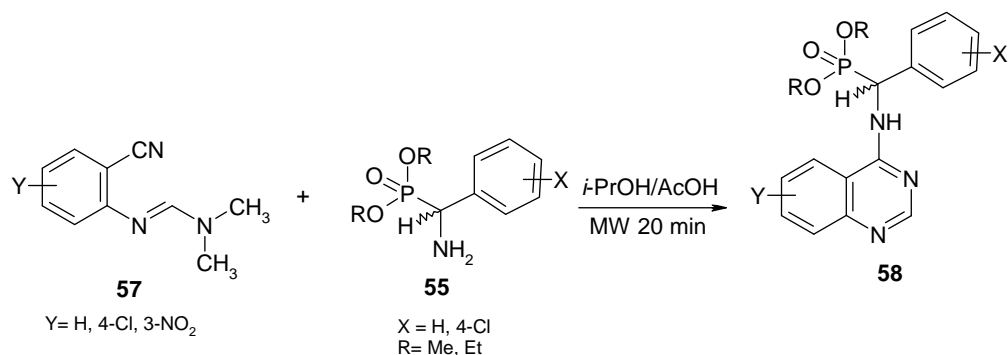
Scheme 24

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).⁶⁴



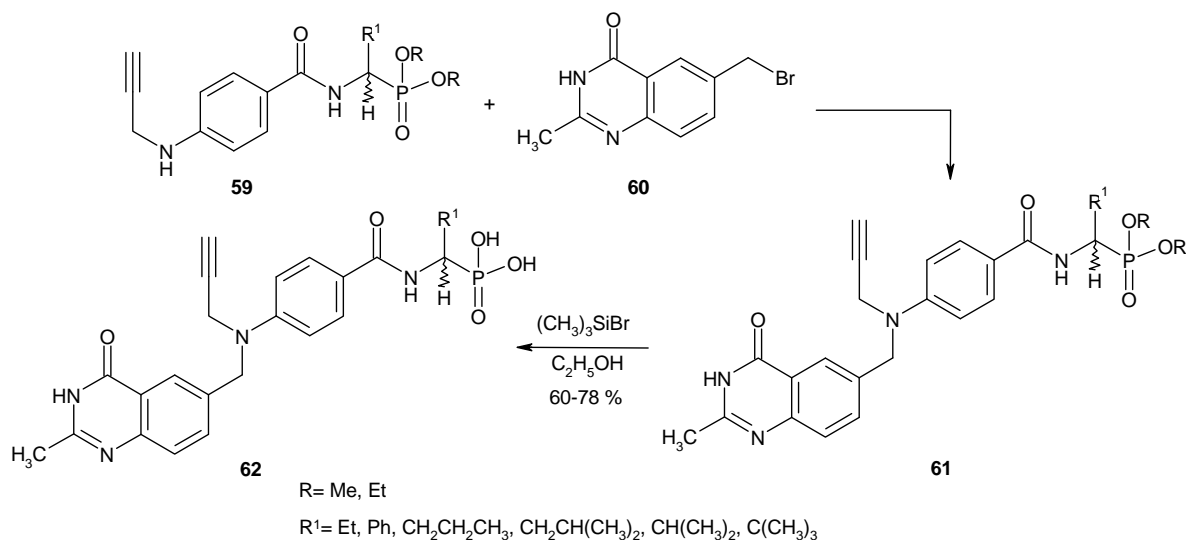
Scheme 25

Luo *et al.*⁶⁵ reported the first microwave-assisted synthesis of new quinazoline derivatives containing α -aminophosphonate. In their method, *N'*-(substituted-2-cyanophenyl)-*N,N*-dimethylformamide 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).



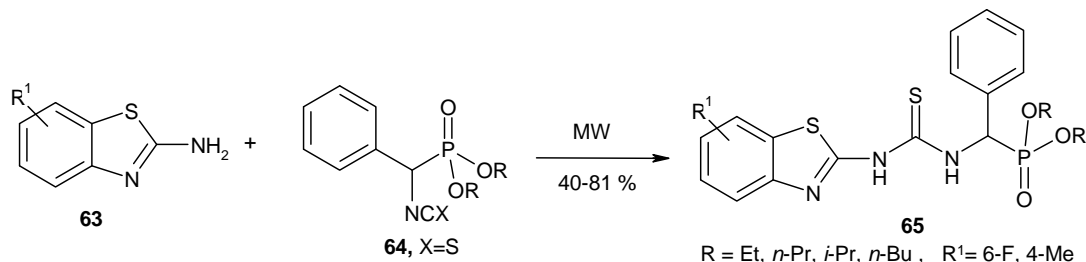
Scheme 26

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).⁶⁶



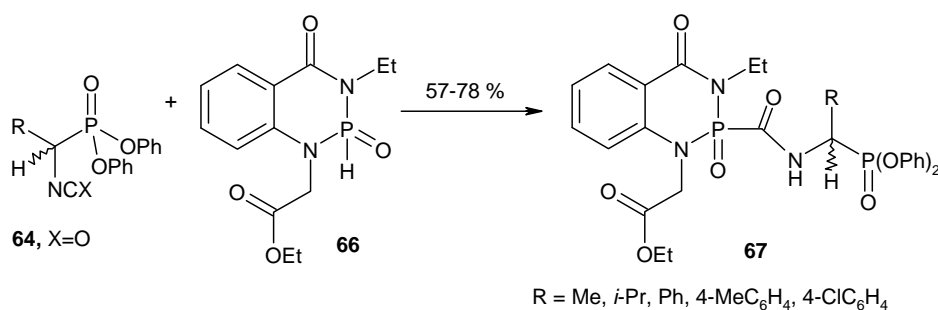
Scheme 27

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- α -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).⁶⁷



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)- α -aminophosphonates **67** (Scheme 29).⁶⁸

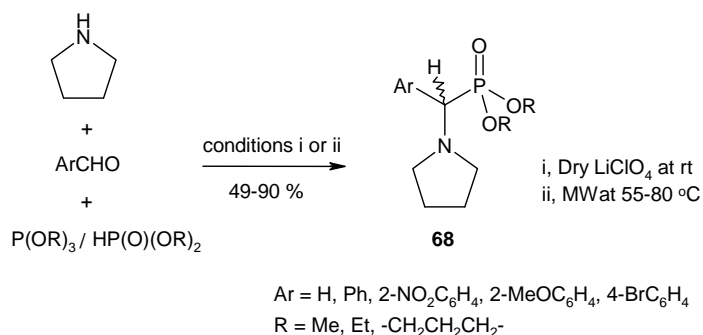


Scheme 29

3. Synthesis of α -(Azaheterocycl)phosphonates (Type B)

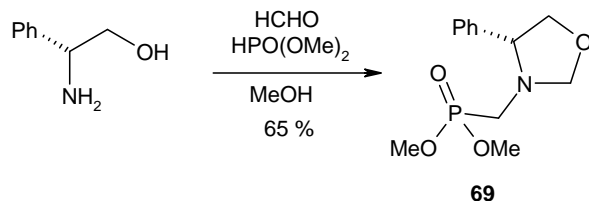
3.1. Kabachnik-Fields reactions

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 α -(pyrrolidinyl)phosphonates **68** in good yields (Scheme 30).^{69,70}



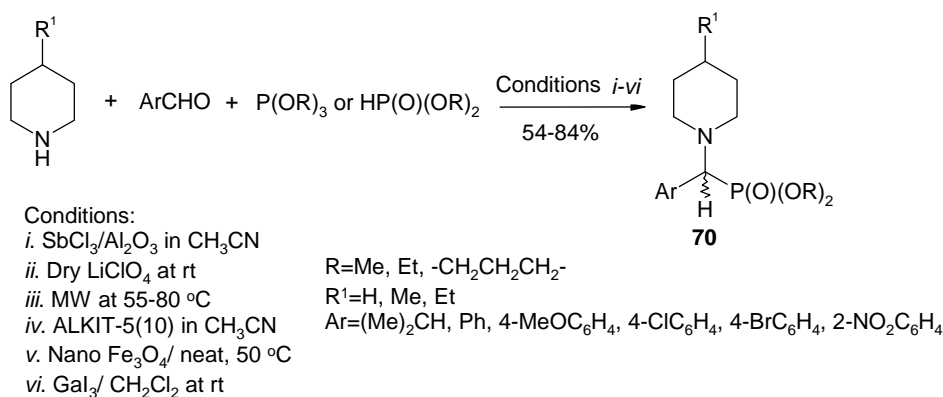
Scheme 30

3.1.2. Five-membered heterocycles with two heteroatoms. Condensation of *R*-(-)-phenylglycinol, formaldehyde and dimethyl phosphite in refluxing methanol gave good yields of α -(oxazolidinyl)phosphonate **69** in a one-step procedure (Scheme 31).⁷¹



Scheme 31

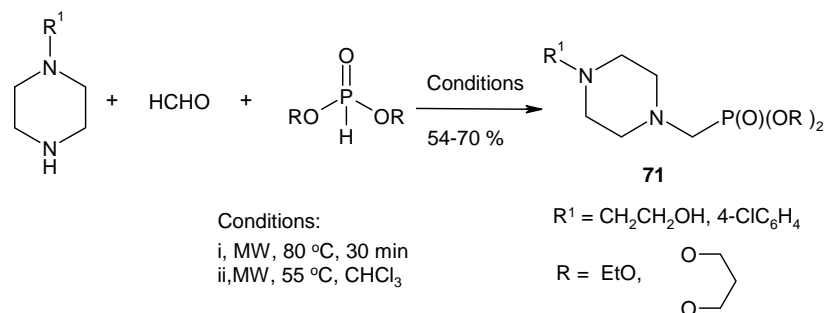
3.1.3. Six-membered heterocycles with one heteroatom. Coupling of aldehydes with 4-alkylpiperidine and dialkyl or trialkyl phosphites under various reaction conditions gave α -(piperidinyl)phosphonates **70** (Scheme 32).^{48,58,69,72,73}



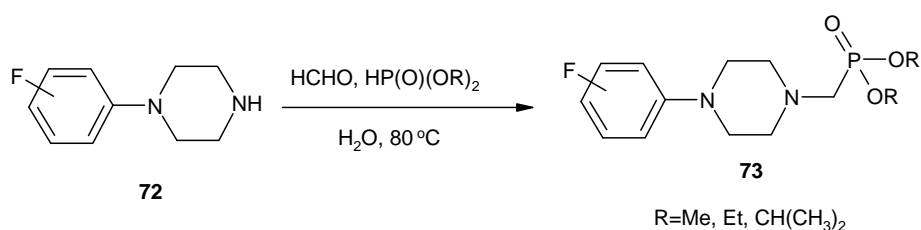
Scheme 32

3.1.4. Six-membered heterocycles with two heteroatoms. *N*-alkyl/arylpiperazines were converted into the corresponding dialkyl α -(piperiziny)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 α -amino-phosphonates **73** in 70–84% yields.

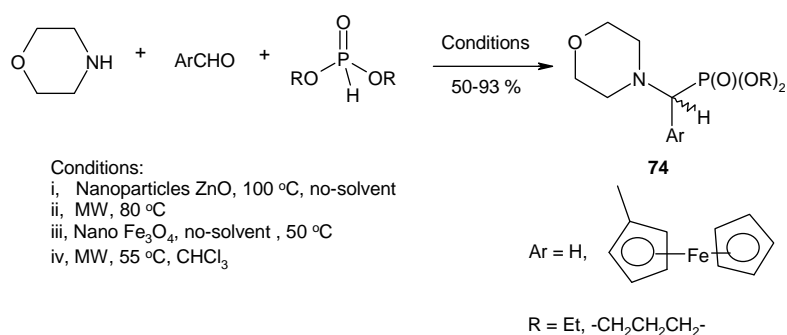


Scheme 33



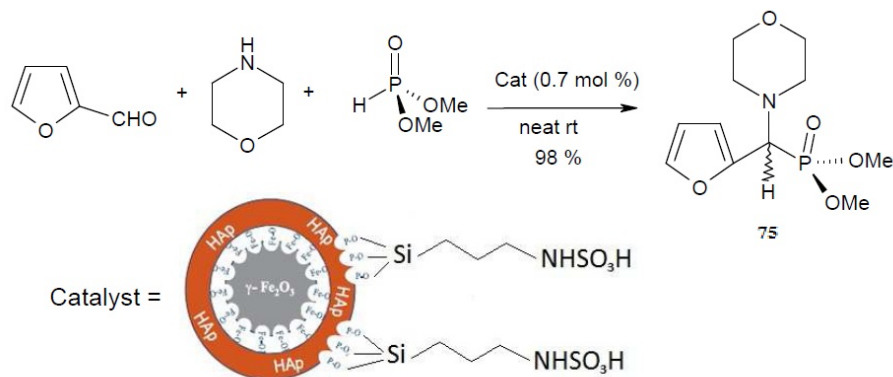
Scheme 34

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}



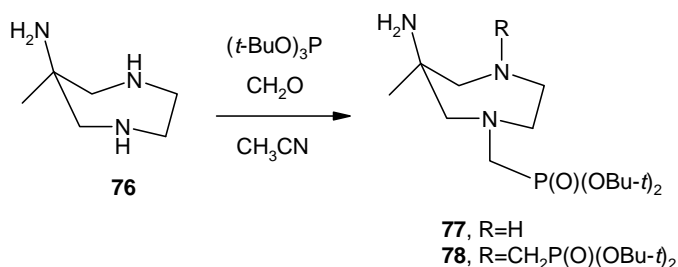
Scheme 35

n-Propyl sulfamic acid onto hydroxyapatite encapsulated superparamagnetic γ -Fe₂O₃ nanoparticles [γ -Fe₂O₃@HAp-Si-(CH₂)₃-NHSO₃H] 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 α -(2-furyl)- α -(morpholinyl)phosphonate **75** (Scheme 36).⁷⁵



Scheme 36

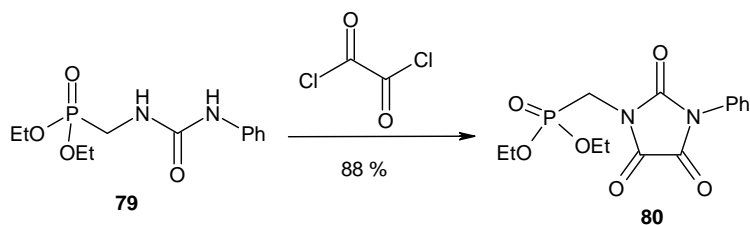
3.1.5. Seven-membered heterocycles with two heteroatoms. Installation of the methylphosphonate residues on the endocyclic nitrogen atom of triamine **76** was performed by its reaction with paraformaldehyde and one or two equivalent of tri(*t*-butyl)phosphite, yielding the monosubstituted **77** or the disubstituted **78** derivative, respectively (Scheme 37).⁷⁶



Scheme 37

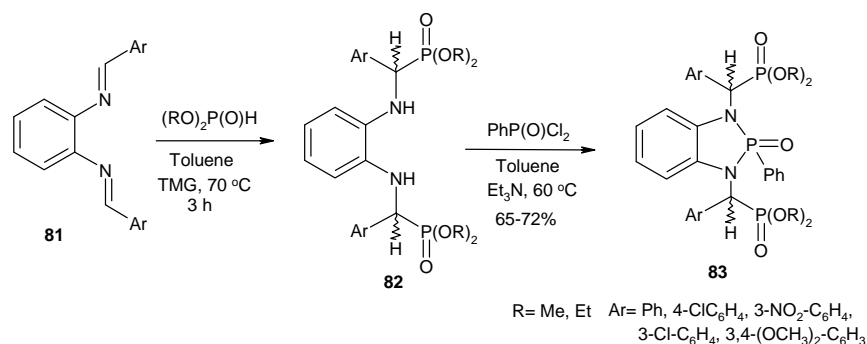
3.2. Heterocyclization of phosphonates

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



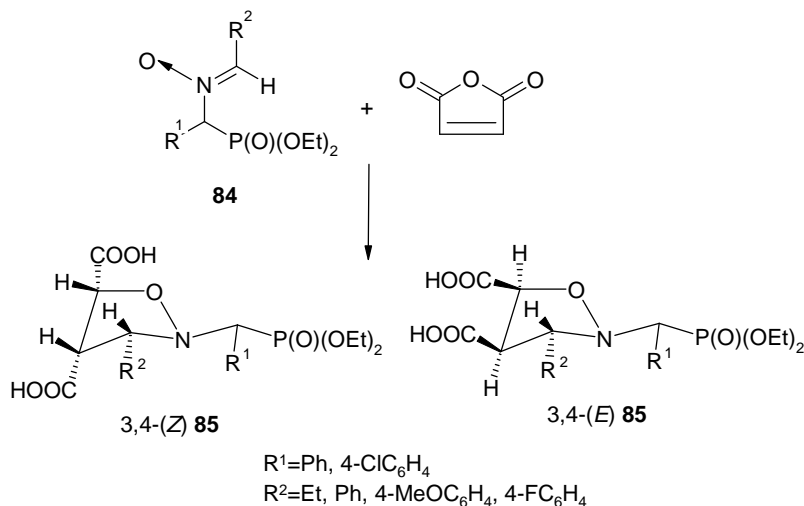
Scheme 38

[(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



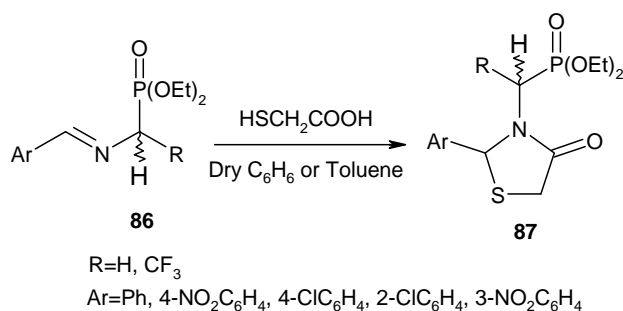
Scheme 39

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

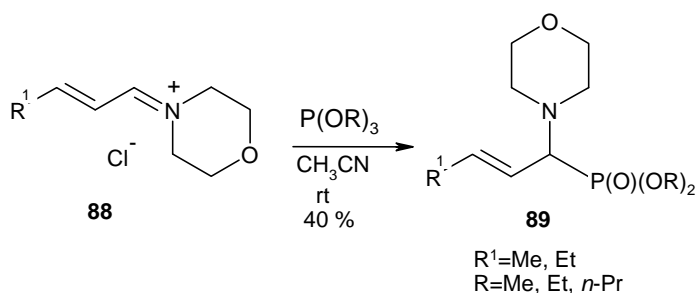
Heterocyclization of α -phosphorylated imines **86** with thioglycolic acid in dry solvent can be used for the preparation of α -(thiazolyl)phosphonate **87** (Scheme 41).⁸⁰



Scheme 41

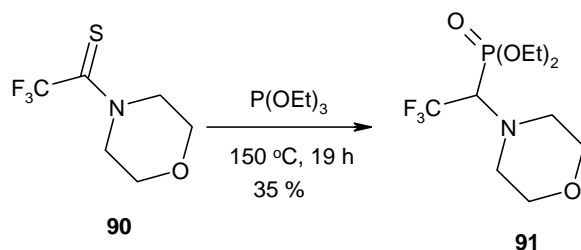
3.3. Miscellaneous methods

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).⁸¹



Scheme 42

3.3.2. Reaction of thioamides with trialkyl phosphite. The reaction of the trifluorothioacetamidomorpholine **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).⁸²



Scheme 43

4. Conclusions

During the last few years the α -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- α -aminophosphonates (Type A) and α -(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.

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