Methods for the synthesis of α-heterocyclic/heteroaryl-α-aminophosphonic acids and their esters

Tarik E. Ali* and Somaia M. Abdel-Kariem

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt
E-mail: tarik_elsayed1975@yahoo.com

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.112

Abstract

This review describes a comprehensive account of methods which are commonly applied for the synthesis of *α*-heterocyclic/heteroaryl α-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: α-Aminophosphonates, heterocycles, Kabachnik-Fields, Pudovik reactions

Table of Contents

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.

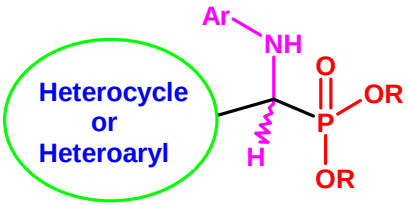
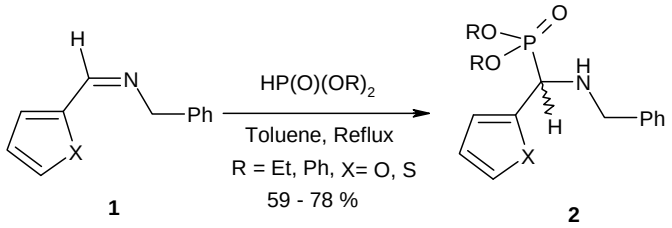


Figure 1. *α*-Heterocyclic/heteroaryl-α-aminophosphonic acids and their esters.

2. Synthesis by Pudovik Reaction

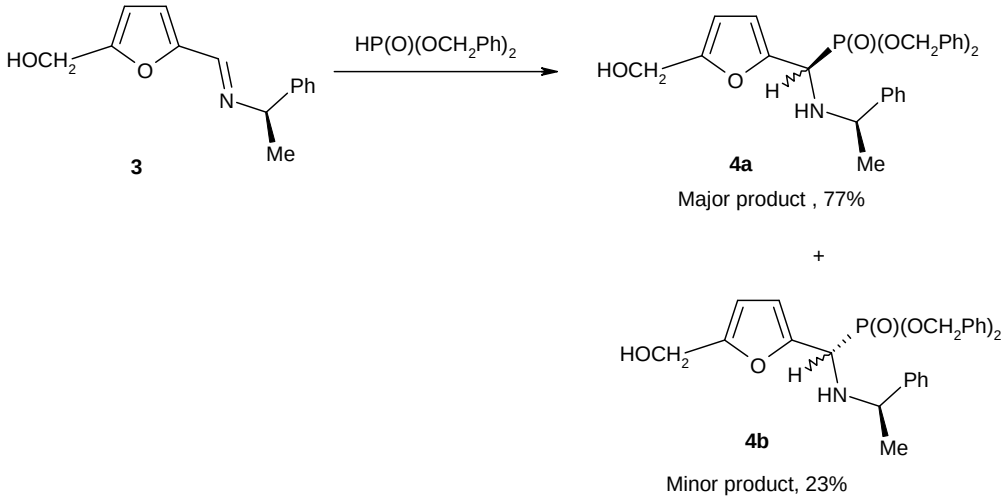
2.1. Five-membered heterocycles with one heteroatom

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]



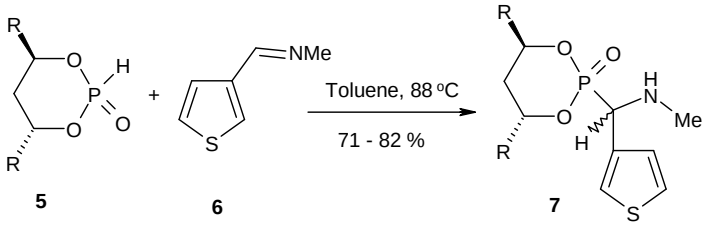
Scheme 1

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



Scheme 2

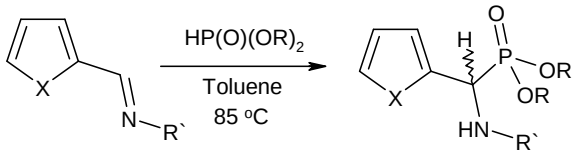
When the cyclic phosphonate **5** was reacted with the Schiff base **6** at 17 °C it afforded the corresponding α-(3-thienyl)-α-aminophosphonate **7**. Reaction of phosphonate **5** (R=COOR) with the imine **6** required ultrasonic conditions to bring the reaction to completion (Scheme 3).[23]



R = a) CH_3, b) $(CH_3)_2$, d) COOR

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]

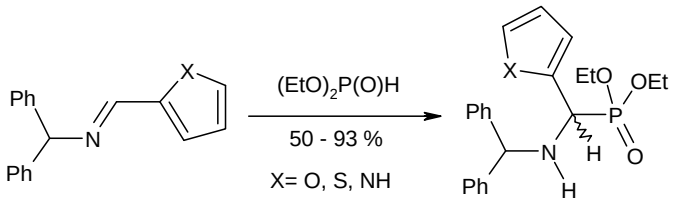


8 **9**

X= O, S R = $C_{10}H_{21}$, Bn R`= *t*-Bu, *i*-Pr

Scheme 4

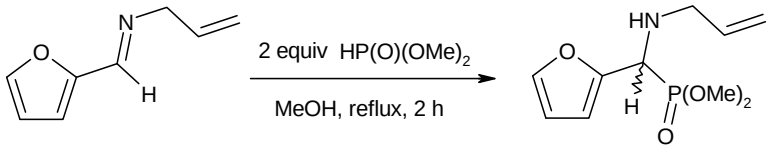
The diethyl phosphonate esters **11** were prepared by heating equimolar mixtures of diethyl phosphite and the corresponding Schiff base **10** in the absence of solvent at temperatures between 90 and 100 ºC (Scheme 5).[25]



10 **11**

Scheme 5

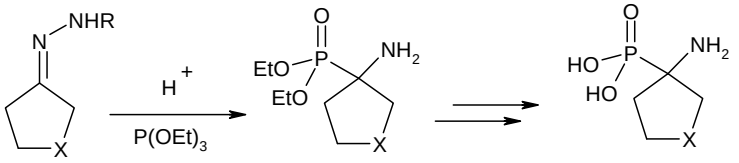
Similarly, addition of two equivalents of dimethyl phosphite to heterocyclic imine **12** in methanol afforded the α-(2-furyl)-α-aminophosphonate **13** (Scheme 6).[26]



12 **13**

Scheme 6

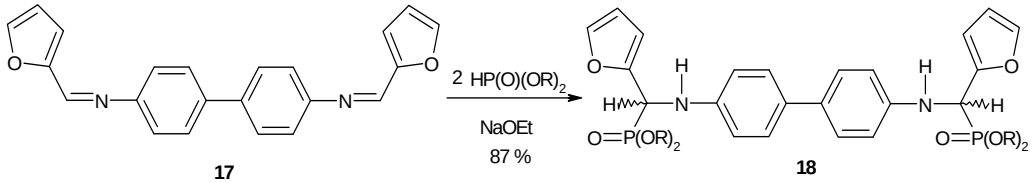
Synthesis of cucurbitine phosphonic analogues **16** was performed through reaction of hydrazone intermediates **14** with triethyl phosphite in acidic media. Subsequent cleavage of N–N bonds gave aminophosphonic acid **16** and not the corresponding α-hydrazinophosphonate (cucurbitine analogue) (Scheme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



14 **15** **16**

Scheme 7

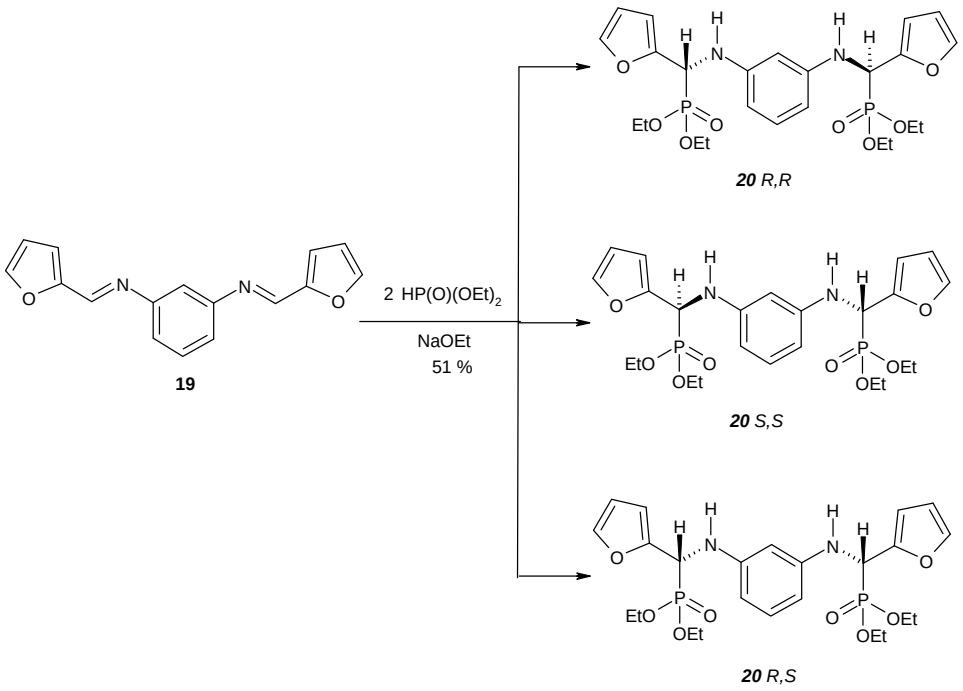
4,4'-Bis[[(dialkoxyphosphonyl)-(2-furyl)methyl]amino]diphenyl (**18**) was prepared by addition of diethyl phosphite to *N*,*N*′-bis(furfurylidene)benzidine (**17**) in sodium ethoxide and stirring at room temperature for 3 hours (Scheme 8).[28]



17 **18**

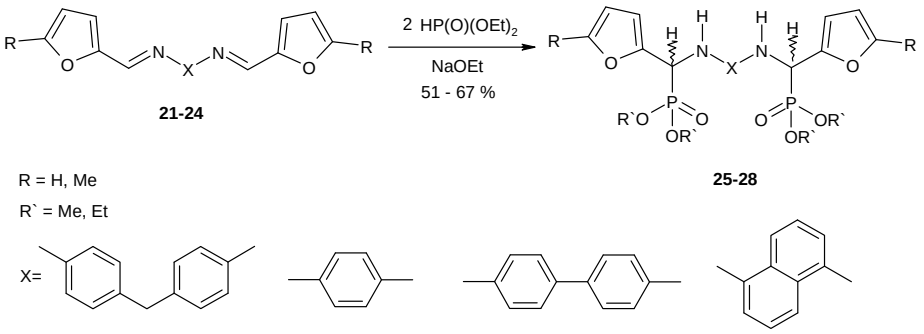
Scheme 8

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]



Scheme 9

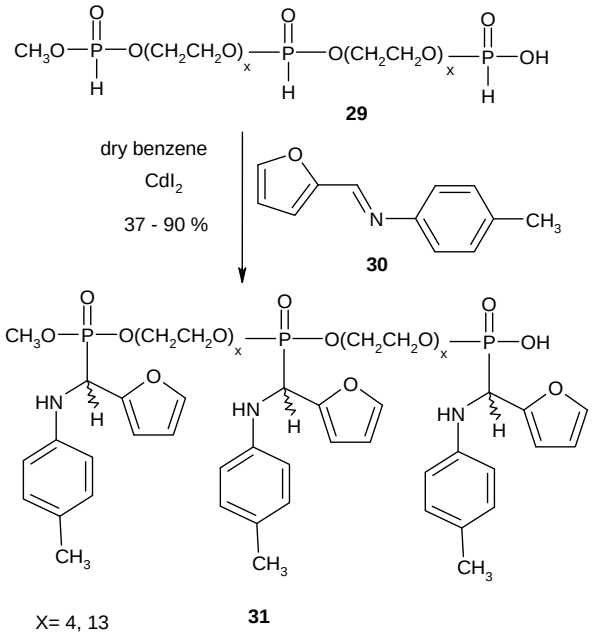
Also, four bis(aminophosphonates) **25**, **26**, **27** and **28** were synthesized through addition of diethyl phosphite to the azomethine bonds of the furan-substituted bis(imines) **21**–**24**. The addition of dialkyl (diaryl) phosphites to bis(imines) should lead to the formation of two diastereomeric 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).[30,31]



Scheme 10

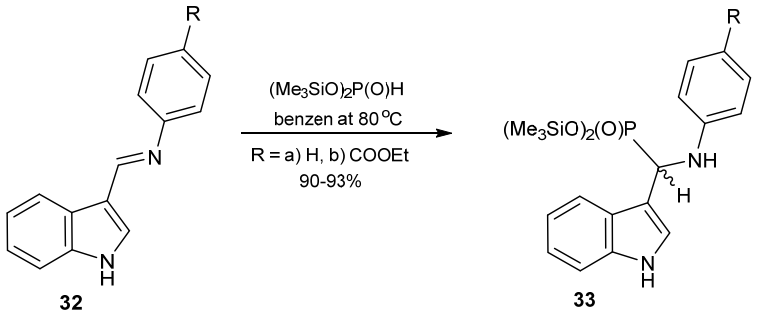
Poly(oxyethylene)aminophosphonates **31** were synthesized through addition of poly (oxyethylene H-phosphonates) **29** to the azomethine bond of *N*-furfurylidene toluidine (**30**), according to Scheme 11. The polymer analogous reaction was carried out in the presence of

catalytic CdI_2, as well as without catalyst. In the presence of CdI_2 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).[32]



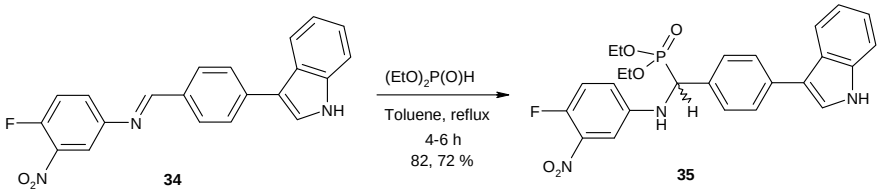
Scheme 11

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).[33]



Scheme 12

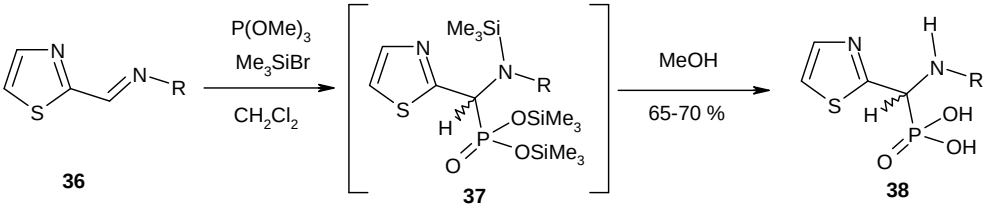
Reaction of the Schiff bases **34** with diethyl hydrogen phosphite *via* Pudovik reaction in refluxing toluene in the absence of catalyst afforded the corresponding α-aminophosphonates **35** (Scheme 13).[34]



Scheme 13

2.2. Five-membered heterocycles with two heteroatoms

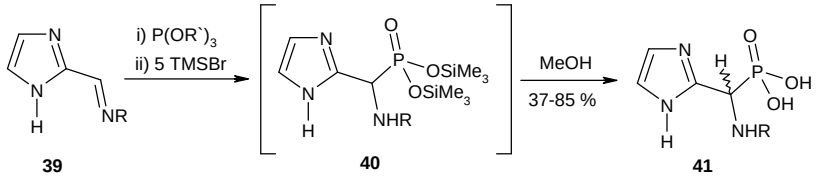
The aldimines **36** were reacted directly with trimethyl phosphite in the presence of bromotrimethylsilane to form the α-(2-thiazolyl)-α-aminophosphonic silylated esters **37**, as intermediates, which were then deprotected giving the α-(2-thiazolyl)-α-aminophosphonic acids **38** (Scheme 14).[35]



R = *n*-Bu, Ph, CH_2Ph

Scheme 14

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 α-(imidazol-2-yl)-α-aminophosphonic acids **41** (Scheme 15).[36,37]

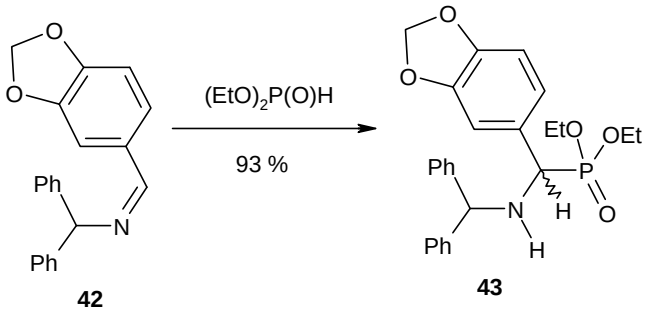


R = butyl, benzyl, 2-pyridyl, 3-pyridyl, 1-imidazolyl, 2-$PyCH_2$, 3-$PyCH_2$, 1-imidazole$(CH_2)_3$

R`= Me, Et

Scheme 15

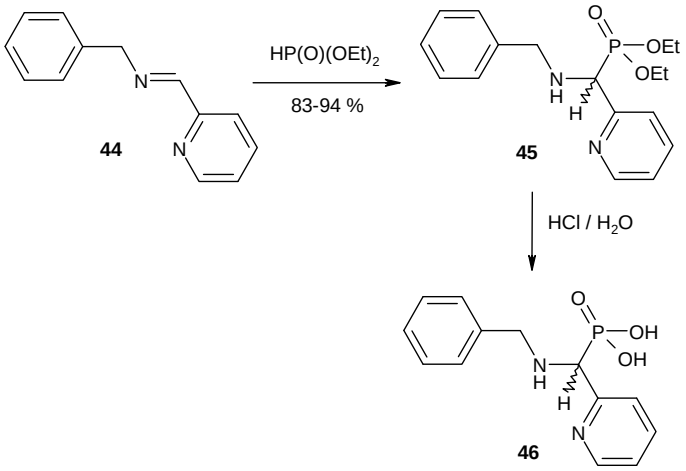
The diethyl 1,3-benzodioxylphosphonate esters **43** were prepared by heating equimolar mixtures of diethyl phosphite and the corresponding Schiff base **42** in the absence of solvent at temperatures between 90 and 100 °C (Scheme 16).[25]



Scheme 16

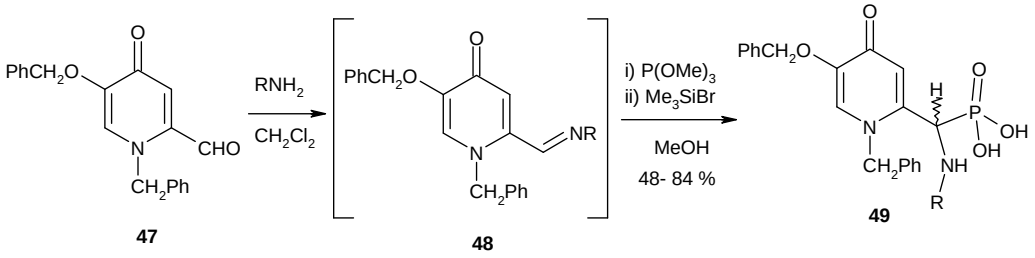
2.3. Six-membered heterocycles with one heteroatom

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).[38]



Scheme 17

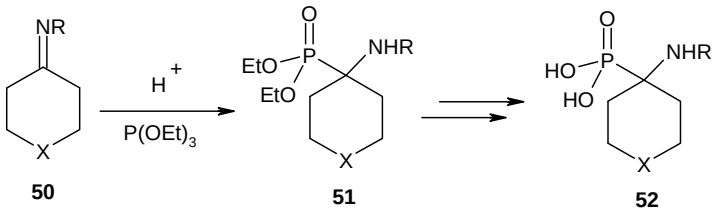
1-(*N*-Benzyl)-2-formyl-5-benzyloxy-pyridone **47** reacted with primary amines to obtain the corresponding imines **48**. The imines then were treated with a mixture of trimethyl phosphite and bromotrimethylsilane, which caused *in situ* formation of tris(trimethylsilyl) phosphite, which instantly reacted 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).[39]



R = Bu, Ph_2CH, $PhCH_2$

Scheme 18

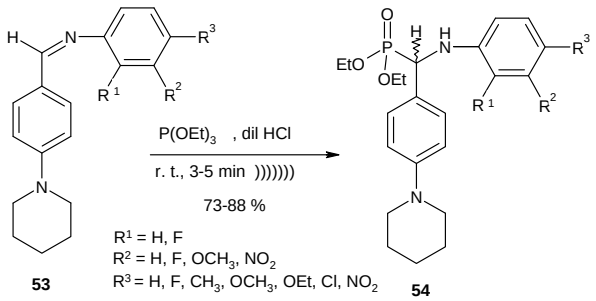
A short and efficient synthesis of new 4-amino(piperidine/tetrahydropyran/ tetrahydrothiopyran)-4-phosphonic acids **52** in good yields was described *via* addition of triethyl phosphite in acidic medium to ketone imines **50** *via* α-aminophosphonates **51** (Scheme 19).[27]



X = O, S, NR`

Scheme 19

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]

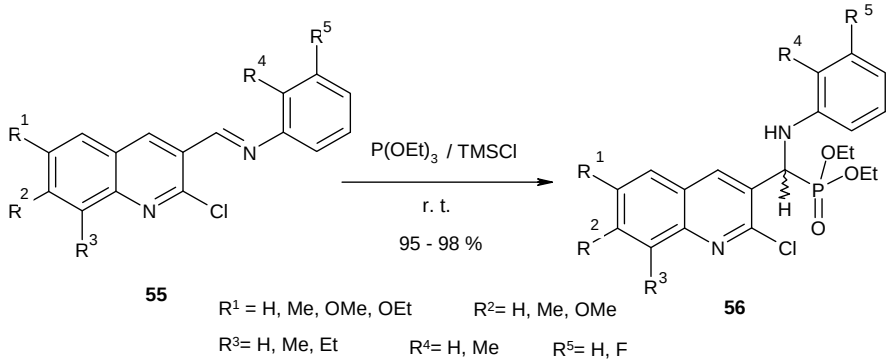


R^1 = H, F
R^2 = H, F, OCH_3, NO_2
R^3 = H, F, CH_3, OCH_3, OEt, Cl, NO_2

Scheme 20

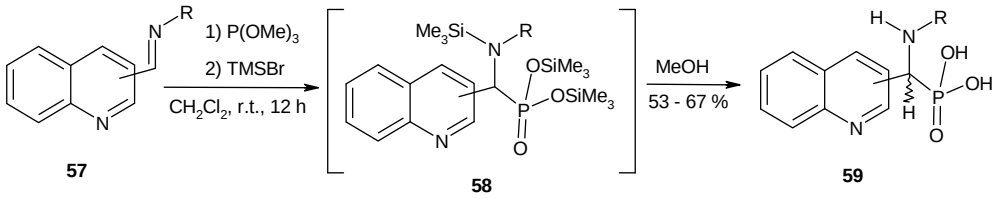
α-(3-Quinolinyl)-α-aminophosphonates **56** were prepared in quantitative yields by reacting imines **55** with triethyl phosphite in the presence of tetramethylsilyl chloride (TMSCl) at room

temperature. The yields of the α-aminophosphonates using this process are in the range of 95–98% (Scheme 21).[41,42]



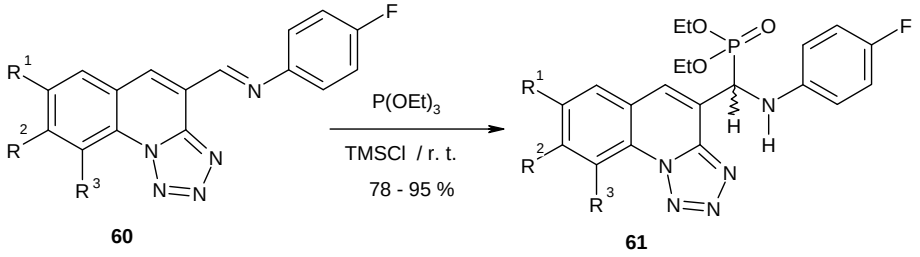
Scheme 21

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 α-(quinolin-2, 3- and 4-yl)-α-(amino)methylphosphonic acids **59** in good yields (Scheme 22).[43]



Scheme 22

The synthesized imines **60** were treated with triethyl phosphite in the presence of TMSCl at room temperature to afford the corresponding diethyl α-(tetrazoloquinolin-3-yl)-α-amino-phosphonate **61** (Scheme 23).[44]



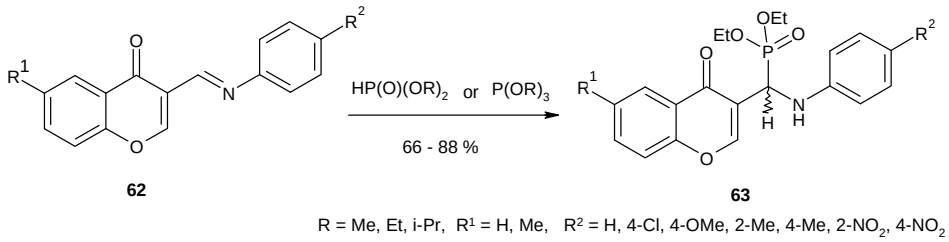
R1 = H, Me, OMe, OEt

R2 = H, Me, OMe

R3 = H, Me, Et, OMe

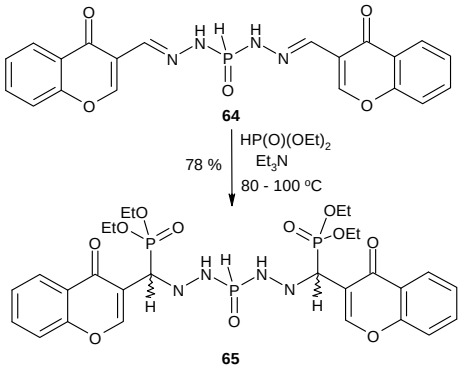
Scheme 23

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).[18,45,46]



Scheme 24

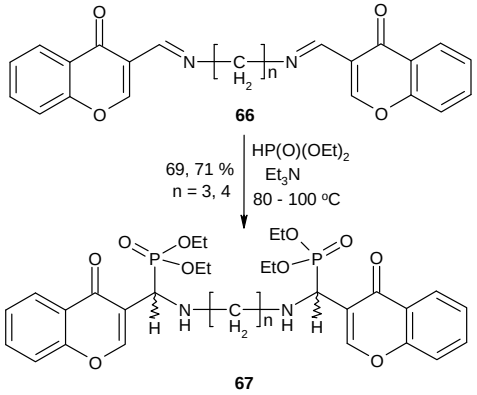
Fusing of the bis-phosphonic hydrazone **64** with diethyl phosphite at 80-100 °C in the presence of catalytic amounts of triethylamine produced N^1,N^5-bis[*N*-methyl(diethoxy-phosphonyl)-1-[(4-oxo-4*H*-chromen-3-yl)]phosphonic dihydrazide (**65**) as the sole product (Scheme 25).[47]



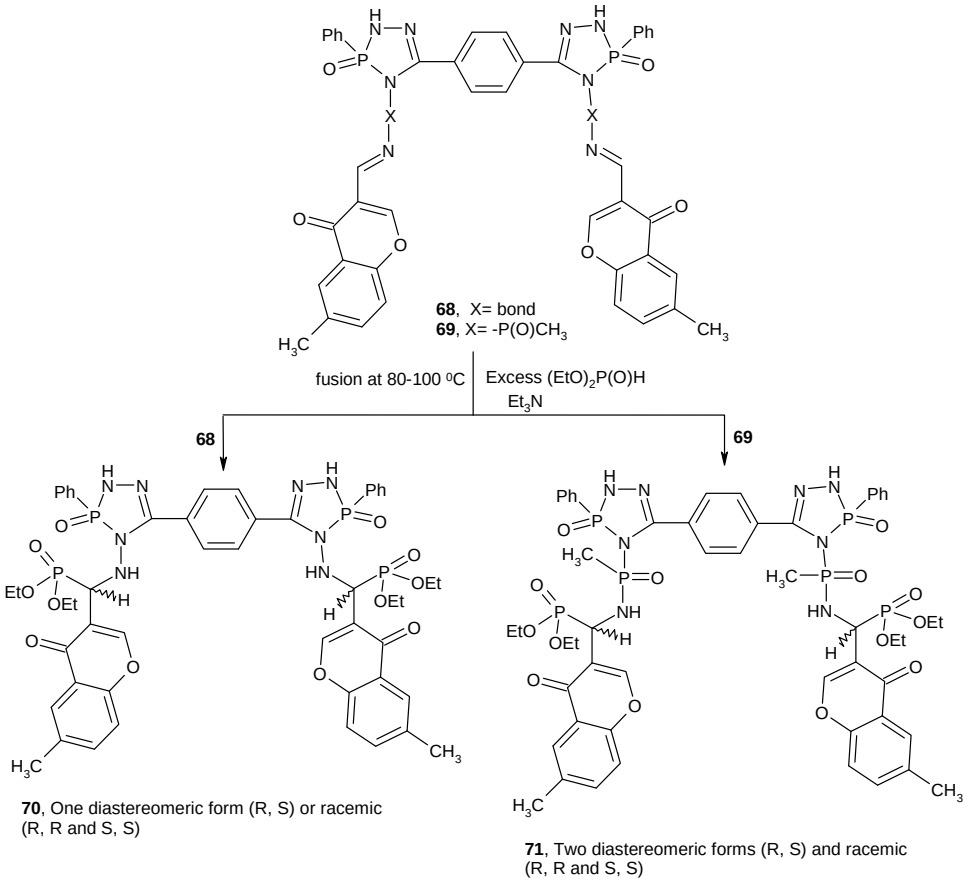
Scheme 25

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-amino-phosphonate) derivatives **67** (Scheme 26).[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'-(1,4-phenylene)bis-[[[(3-oxo-3-phenyl-2,3-dihydro-4*H*-1,2,4,3-triazaphosphol-4-yl)amino](4-oxo-4*H*-chromen-3-yl)methyl]phosphonate] (**70**) and two diastereomeric forms of tetraethyl 5,5'-(1,4-phenylene)bis-[[[(3-oxo-3-phenyl-2,3-dihydro-4*H*-1,2,4,3-triazaphosphol-4-yl)methylphosphoryl]amino](6-methyl-4-oxo-4*H*-chromen-3-yl)methyl] phosphonate] (**71**), respectively (Scheme 27).[17]



Scheme 26



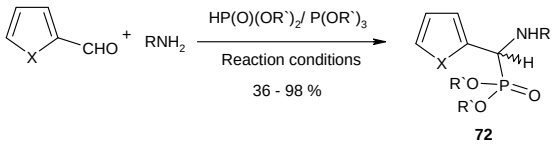
Scheme 27

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 α-heterocyclic-α-aminophosphonates **72** in good to excellent yields under different reaction conditions (Scheme 28) (Table 1).[10,20,48-68]



Scheme 28

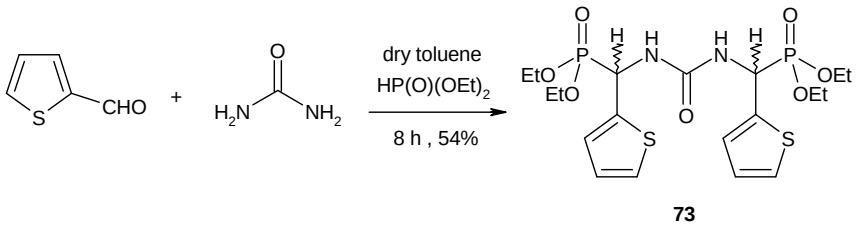
Table 1. Conditions of reactions of furan-, thiophene-, or pyrrole-2-carbaldehyde and different amines with dialkyl or trialkyl phosphites to give the corresponding α-heterocyclic-α-aminophosphonates **72**

Entry No.	X	R in Scheme 28	R'	Reaction conditions	Ref.
1	O, S, NH	Bu, $PhCH_2$	Et, Ph, $PhCH_2$	toluene, reflux	10
2	O	4-$MeOC_6H_4$	Et	NH_4VO_3/RT/stirring	49
3	O, S	Ph	Et	[bnmim][HSO_4]/RT/stirring	50
4	O, S	Ph	Et	1-hexanesulfonic acid sodium salt/ultrasound	51
5	S	Ph	Me	$AlCl_3$/CH_3CN/RT	52
6	O, S	Ph, 4-FC_6H_4	Et	[bmim]BF_4 or [bmim]PF_6	54
7	O	Ph, 4-$MeOC_6H_4$	Et	10 mol %, GaI_3/CH_2Cl_2/RT	55
8	O	$PhCH_2$	Et	$LiClO_4$, 20 mol%, 60 °C, 8 h	56
9	O, S	4-$MeOC_6H_4$	2-$MeOC_6H_4$	$Zn(NTf_2)_2$/10 mol%, CH_2Cl_2, -50 °C	57
10	O, S	[$(Me_3Si)_2NH$]	Et	I_2 (10 mol%), solvent free	58
11	S	$(CH_2)_nCOOH$	Et	MeOH, Et_3N	61
12	O	4-$MeOC_6H_4$	Me	Yttria-zirconia Lewis acid/ aq. CH_3CN/60 °C	48
13	O, S	Ph	Et	[Cu(3,4-tmtppa)] ($MeSO_4$) /(0.16 %mol) /H_2O/80 °C	53
14	O, S, NH	[$(Me_3Si)_2NH$]	Et	$Al(OTf)_3$ (10 mol%)/ solvent free/ 80 °C	59
15	O, NH	Ph, 4-$MeOC_6H_4$	Et, $PhCH_2$	H-β-zeolite, heat, MeCN	60
16	S	$PhCH_2$	Et	toluene, reflux, 3h	20
17	S	Ph	Et	TiO_2 (20 mol%), no solvent, 50 °C	62
18	O	Ph, 3-pyridinyl	Et	Metal oxide, ultrasound	63
19	O	Ph	Me	Homogeneous sulphamic acid (0.7 mol%), neat/RT	64

Table 1. Continued

Entry No.	X	R in Scheme 28	R'	Reaction conditions	Ref.
20	O	4-phenoxyquinazolin-2-yl	Et	[BMIM]Cl/ MW	65
21	O, S	Ph	Me, Et	$Mg(ClO_4)_2$ (5 mol%)	66
22	S	1-(furan-2-yl)methyl	Me	TMG (tetramethyl guanidine), toluene, 50-60 °C, 5-6 h	67
23	O, S	Dibenzo[*d*,*f*][1,3,2] diazaphosphepin-6-yl 6-oxide-	Me, Et	TMG, toluene, 60-70 °C, 4 h	68

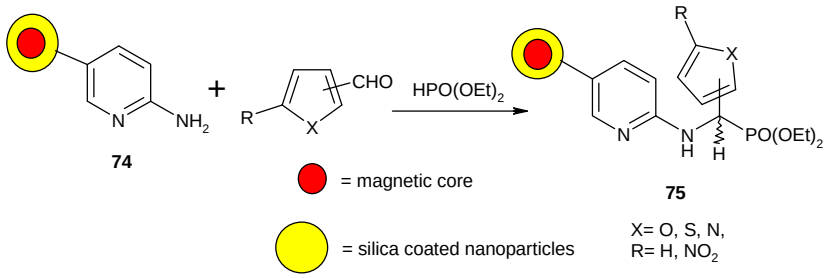
Refluxing thiophene-2-carbaldehyde with a mixture of urea and diethyl phosphite in dry toluene afforded the ureidophosphonate **73** as a major product (Scheme 29).[69]



73

Scheme 29

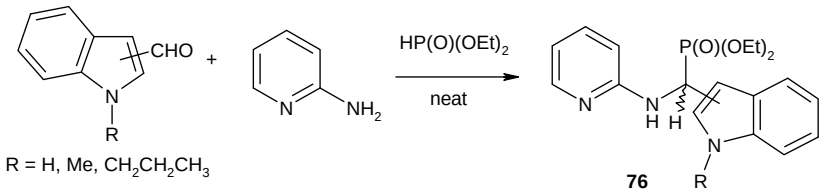
Magnetic iron oxide nanoparticles coated with structurally variable α-heterocyclic-α-aminophosphonates **75** have been obtained by one-pot three-component reaction of 2-amino-pyridine iron oxide nanoparticle **74**, heterocyclic aldehydes and diethyl phosphite (Scheme 30).[70]



74 **75**

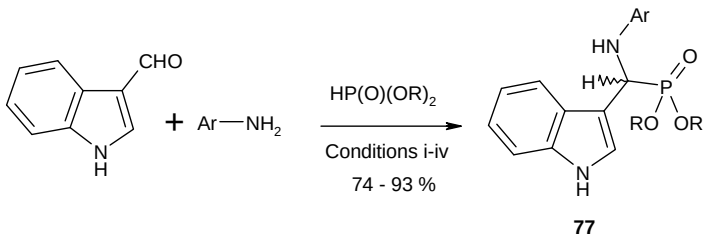
Scheme 30

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]



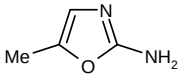
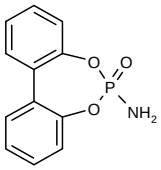
Scheme 31

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]

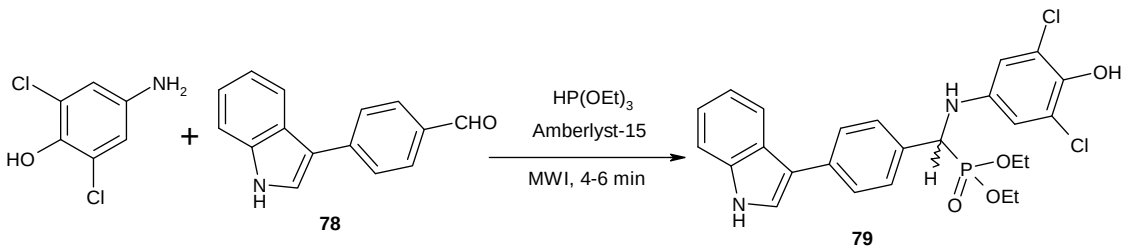


Scheme 32

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

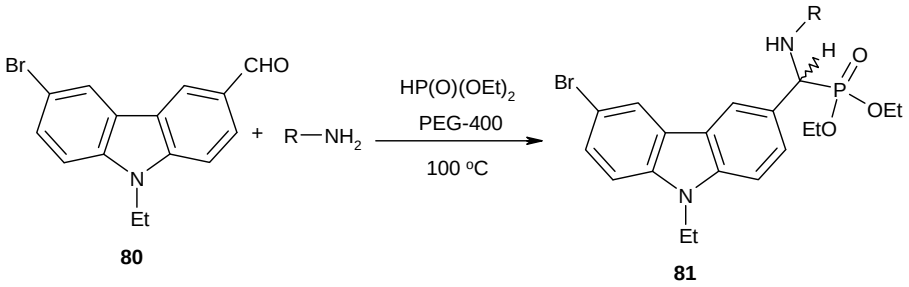
Entry No.	Conditions	Amine	R	Ref.
1	I_2 (10 mol %)/ solvent-free	$(Me_3Si)_2NH$	Et	58
2	$Al(OTf)_3$(10 mol %), solvent-free/ 80 °C	$(Me_3Si)_2NH$	Et	59
3	$Al(OTf)_3$(10 mol %), solvent-free/ 100 °C	$(NH_4)_2CO_3$ or NH_4OAc	Et	73
4	β-zeolite	$PhNH_2$, 4-$MeOC_6H_4NH_2$	Et	60
5	PEG / H_2O / RT		Et	74
6	toluene / TMG / 60 -70 °C / 4h		Me, Et	68

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]



Scheme 33

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 phosphite to the imine by increasing its electrophilicity through hydrogen bonding by its hydroxyl group with the imine nitrogen (Scheme 34).[76]

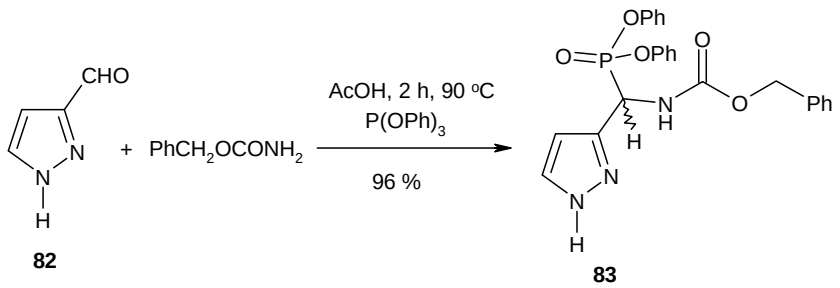


R = Ph, $PhCH_2$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-HOC_6H_4, 4-$NO_2C_6H_4$, 4-$NH_2C_6H_4$, 4-NCC_6H_4, 4-$(Me)_2CHC_6H_4$, 4-Me-4-BrC_6H_3, 4-Cl-3-$CF_3C_6H_3$

Scheme 34

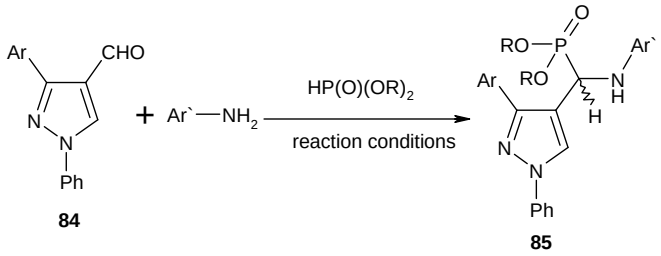
3.2. Five-membered heterocycles with two heteroatoms

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-1*H*-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).[77-80]

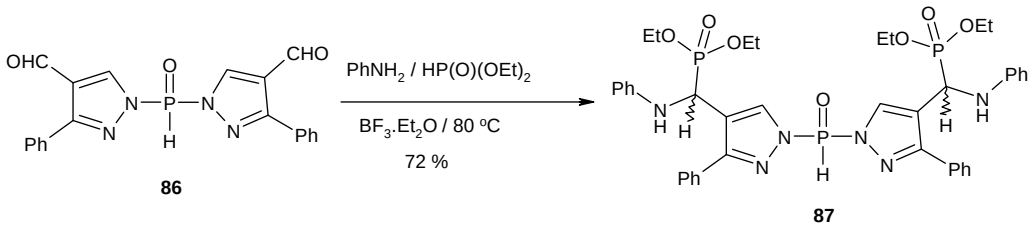


Scheme 36

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

Entry No.	Ar	Ar´	R	Conditions	Ref.
1	Ph	Ph	Et	$BF_3.Et_2O$/70-80 °C	77
2	4-ClC_6H_4	Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-FC_6H_4, 3-Cl-4-FC_6H_3, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$	Et	MW(200W), 80 °C, 3 min	80
3	2-pyridyl	Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$,	Ph	$LiClO_4$, DCM, RT, 24-30 h	79
4	Ph, 4-$MeOC_6H_4$	Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$	Me, Et	Toluene/ 110 °C	78

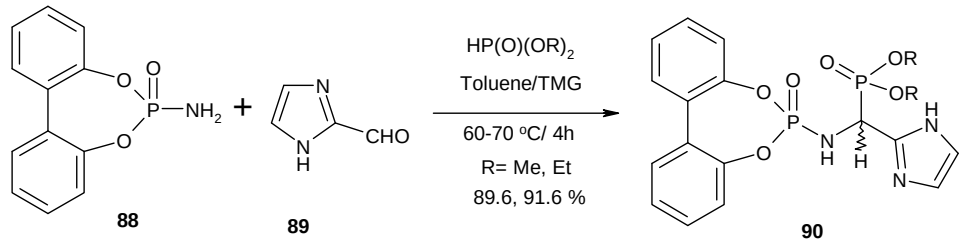
One-pot three-component reaction of bis-(4-formyl-3-phenyl-1*H*-pyrazol-1-yl)phosphine oxide (**86**), aniline and diethyl phosphite in the presence of $BF_3.Et_2O$ at 80 °C under Kabachnik-Fields reaction conditions produced an interesting type of bis(α-aminophosphonate) **87** (Scheme 37).[81]



86 87

Scheme 37

Reaction of 6-amino-6λ^5-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-6λ^5-dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-ylamino)-(1*H*-2-imidazolyl)methylphosphonates (**90**) in good yields (Scheme 38).[68]

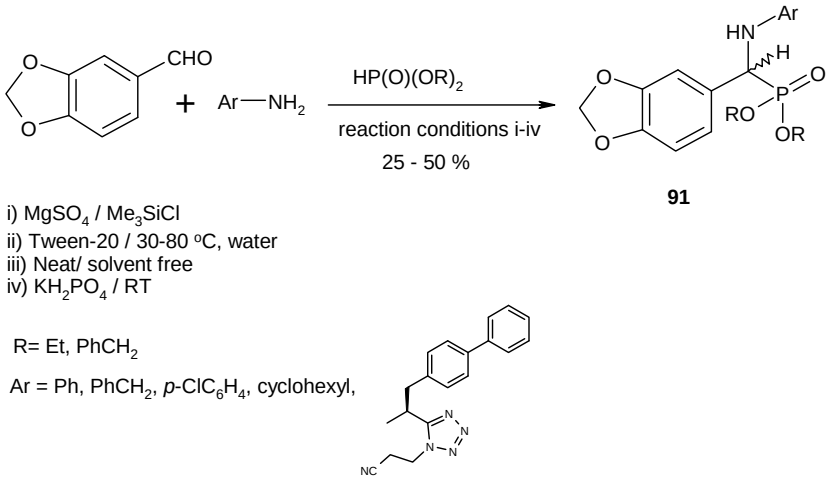


88 89 90

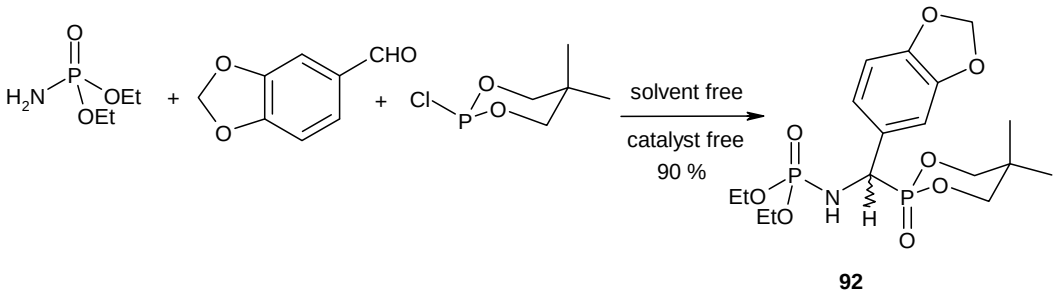
Scheme 38

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-amino-alkylphosphonate 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]

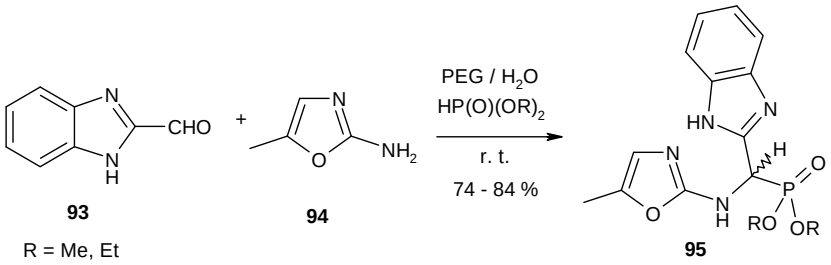


Scheme 39



Scheme 40

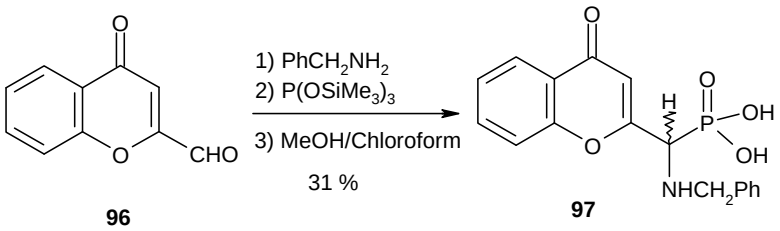
Reaction between 2-formylbenzimidazole (**93**), 2-amino-5-methyloxazole (**94**), and diethyl phosphite by stirring equimolar quantities in a variety of solvents at ambient temperature gave a low yield of the desired α-aminophosphonate **95** in all the experiments. The best result was obtained when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



Scheme 41

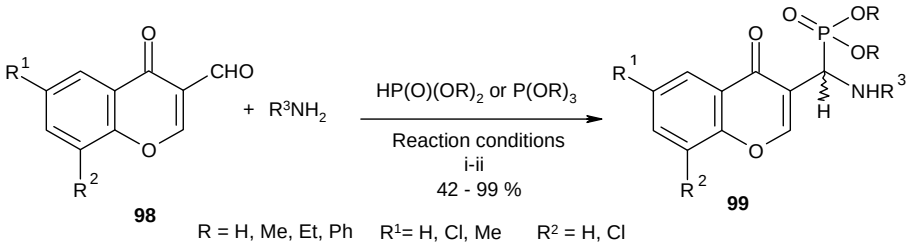
3.3. Six-membered heterocycles with one heteroatom

The action of tris(trimethylsilyl)phosphite on the aldimine formed *in situ* from 2-formyl-chromone (**96**) and benzylamine yielded (*N*-benzylamino)chromon-2-ylmethanephosphonic acid (**97**) (Scheme 42).[87]



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).[46,48]



R = H, Me, Et, Ph R^1= H, Cl, Me R^2 = H, Cl

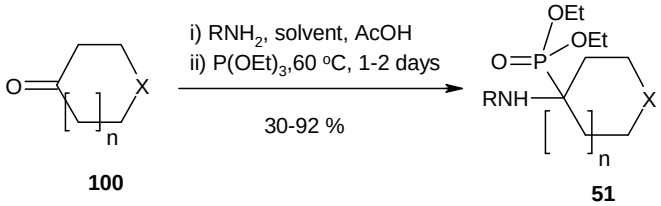
R^3 = Ph, $PhCH_2$, $PhCH_2OCO$, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$

Reaction condition:

i) AcOH or Yttria-Zirconia Lewis acid/ aq. CH_3CN, 60 °C, ii) Catalyst free

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).[88]



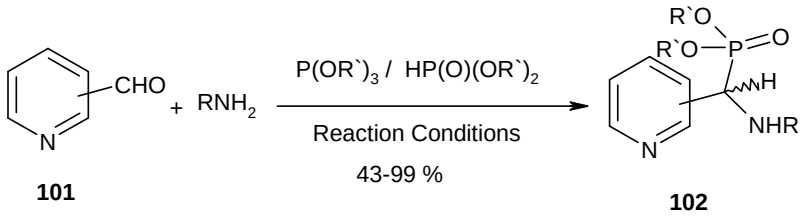
X = NMe, O, S

RNH = $PhCH(CH_3)NH_2$, $PhCH_2NH_2$, $PhCH(CH_2OH)NH_2$

Solvent = EtOH, Toluene, Acetonitrile

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).[10,52,58,59,61,66-68,71,72,84,89-93]



Scheme 45

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**

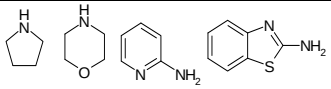
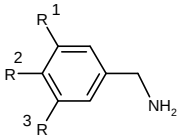
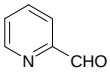
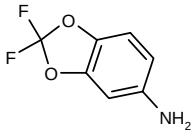
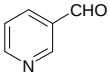
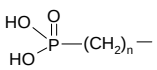
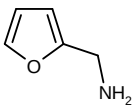
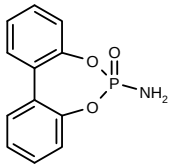
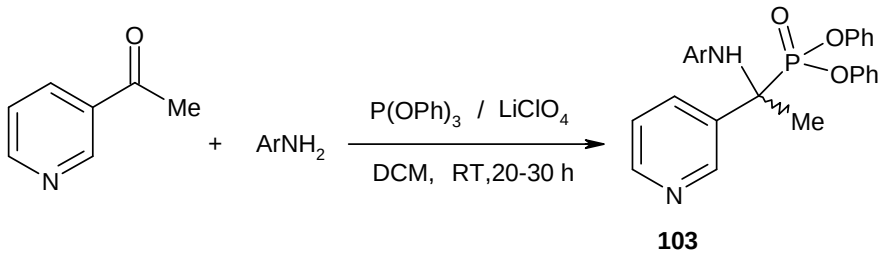
Entry No.	Aldehyde 101	Amine	R´	Conditions	Ref.
1			Me, Et	$MgClO_4$/ neat/ RT/ 2-6 min /or 80 °C / 0.5 – 6 h	66
2		 n=0,1,2 R_1=R_2=R_3=H, OMe	Et	Reflux / 60 °C	92
3			Et	$BF_3.SiO_2$/[bmim][HCl]/ 5-10 min/RT/neat	93
4		Bu, $PhCH_2NH_2$	Et, Ph	toluene	10
5		$PhNH_2$	Et	Nano Fe_2O_3 /neat/ 50 °C	91
6		$PhNH_2$	Et	Solvent free	84
7		 n=1, 2	Et	MeOH/ Et_3N / Me_3Si	61
8		2-, 3-,4-aminopyridine	Et	*t*PcAlCl / molecular sieves	72
9			Me, Et	TMG/ toluene / 50-60 °C, 5- 6 h	67

Table 4. Continued

Entry No.	Aldehyde 101	Amine	R´	Conditions	Ref.
10		$(Me_3Si)_2NH$	Et	$Al(OTf)_3$ (10 mol%) / solvent free /80 °C	59
11		$(Me_3Si)_2NH$	Et	I_2 (10 mol%) / solvent free	58
12		$PhNH_2$	Me	$TiCl_4$ / CH_3CN/ RT	89
13		$PhNH_2$	Me	$AlCl_3$ / CH_3CN/ RT	52
14		2-aminopyridine	Et	Solvent free	71
15			Me, Et	toluene/TMG/ 60 -70 °C	68
16	2-, 3-,4-formylpyridines	$BuNH_2$, $PhNH_2$, Ph_2CHNH_2, $PhCH_2NH_2$	Et	toluene / 110 °C	90

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]



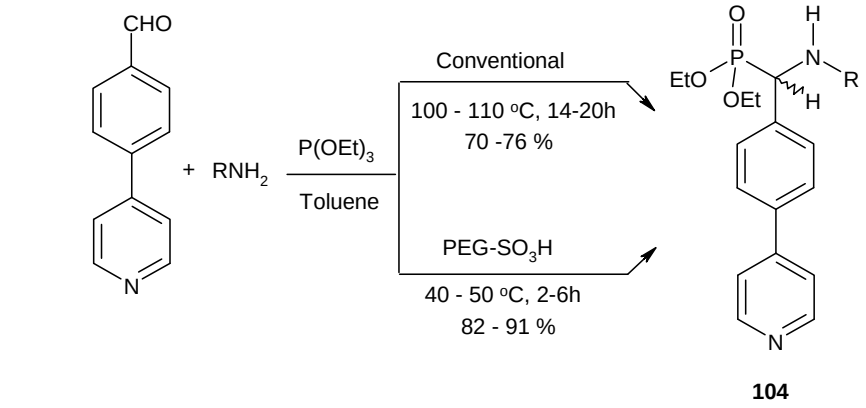
103

Ar= C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-HOC_6H_4, NHC_6H_5

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]

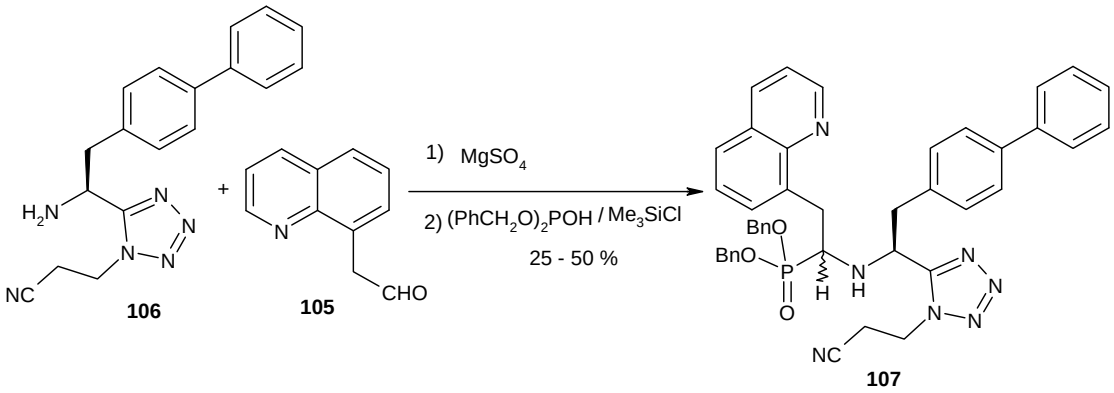
The interesting α-quinonylmethylenyl α-aminophosphonate **107** was prepared in moderate yield through reaction of 8-formylmethylquinoline **105**, 3-[5-[(1*S*)-1-amino-2-(biphenyl-4-yl) ethyl]-1*H*-tetrazol-1-yl]propanenitrile (**106**) and dibenzyl phosphite in the presence of $MgSO_4$ and Me_3SiCl (Scheme 48).[82]



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

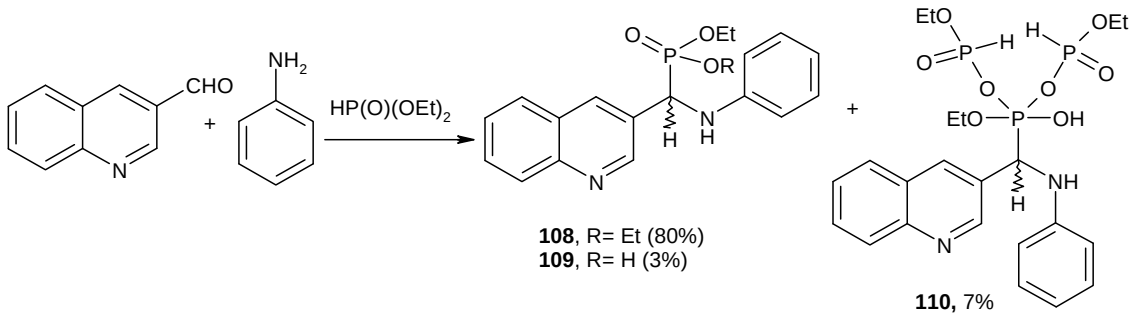
Scheme 47



106 **105** **107**

Scheme 48

One-pot three-component reaction of quinoline-3-carboxaldehyde and aniline with diethyl phosphite under microwave irradiation reaction 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).[96]

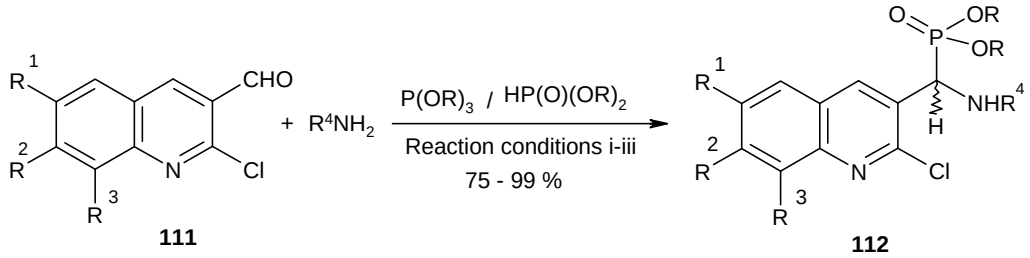


108, R= Et (80%)
109, R= H (3%)

110, 7%

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).[42,48,85]



R = Me, Et , R^1= H, Me, MeO, EtO , R^2 = H, Me, MeO

R^3 = H, Me, Et , R^4 = Ph, $PhCH_2$, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4

Reaction conditions :

i) KH_2PO_4/ r.t.

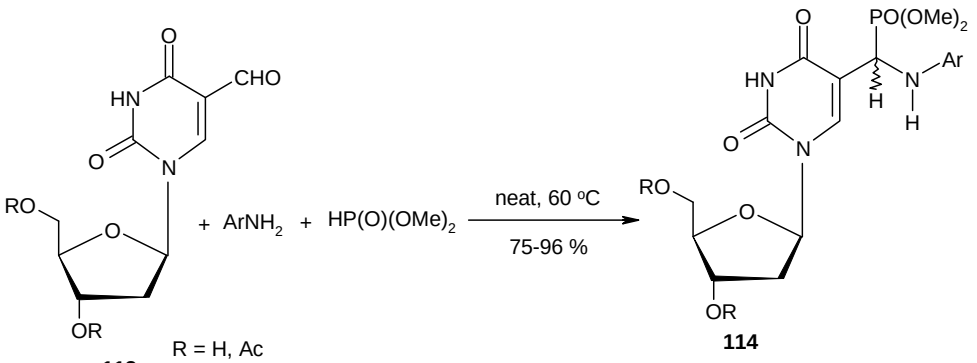
ii) Yttria-Zirconia Lewis acid/ aq. CH_3CN, 60 °C

iii) TMSCl, CH_3CN, reflux

Scheme 50

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).[97,98]

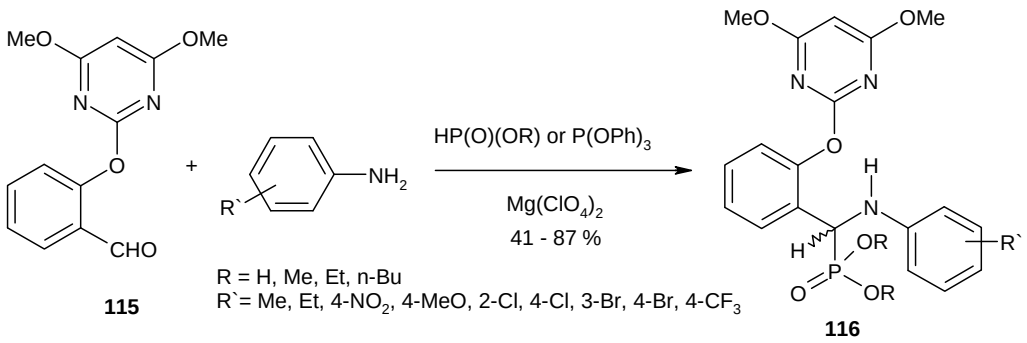


R = H, Ac

Ar= Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, *p*-$OCH_3C_6H_4$

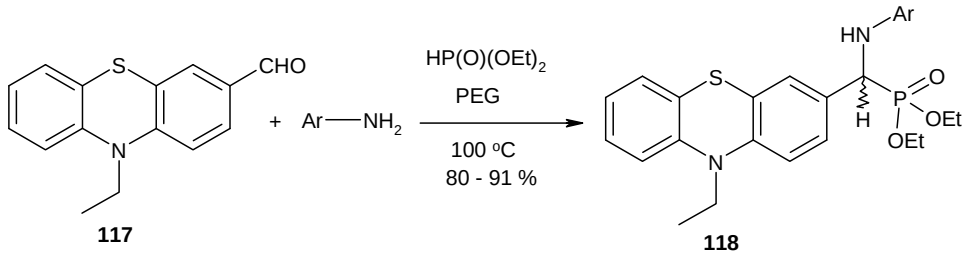
Scheme 51

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).[99]



Scheme 52

The reaction of 10-ethyl-10*H*-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]

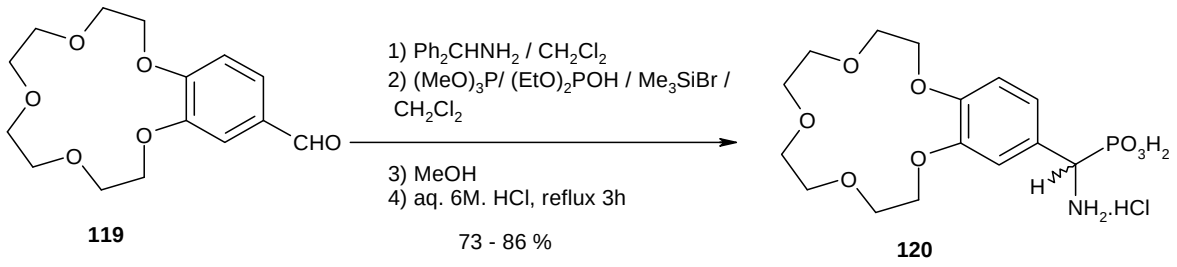


Ar = Ph, $PhCH_2$, C_6H_{11}, 4-$CH_3C_6H_4$, 4-$(OCH_3)C_6H_4$, 4-$(CH_3)_2CHC_6H_4$, 4-Br-3-CH_3-C_6H_3, 4-OH-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4

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 bromotrimethyl-silane as a deprotecting agent of phosphonic esters (Scheme 54).[101]



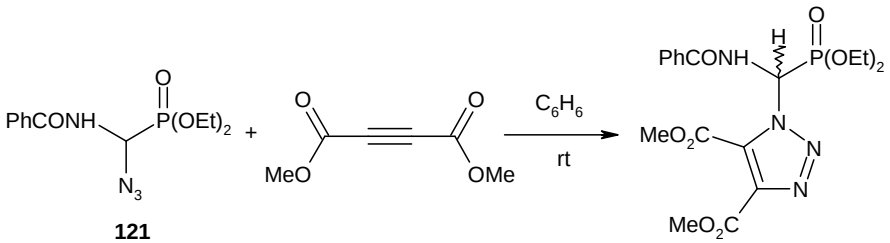
119 **120**

Scheme 54

4. Miscellaneous Methods

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

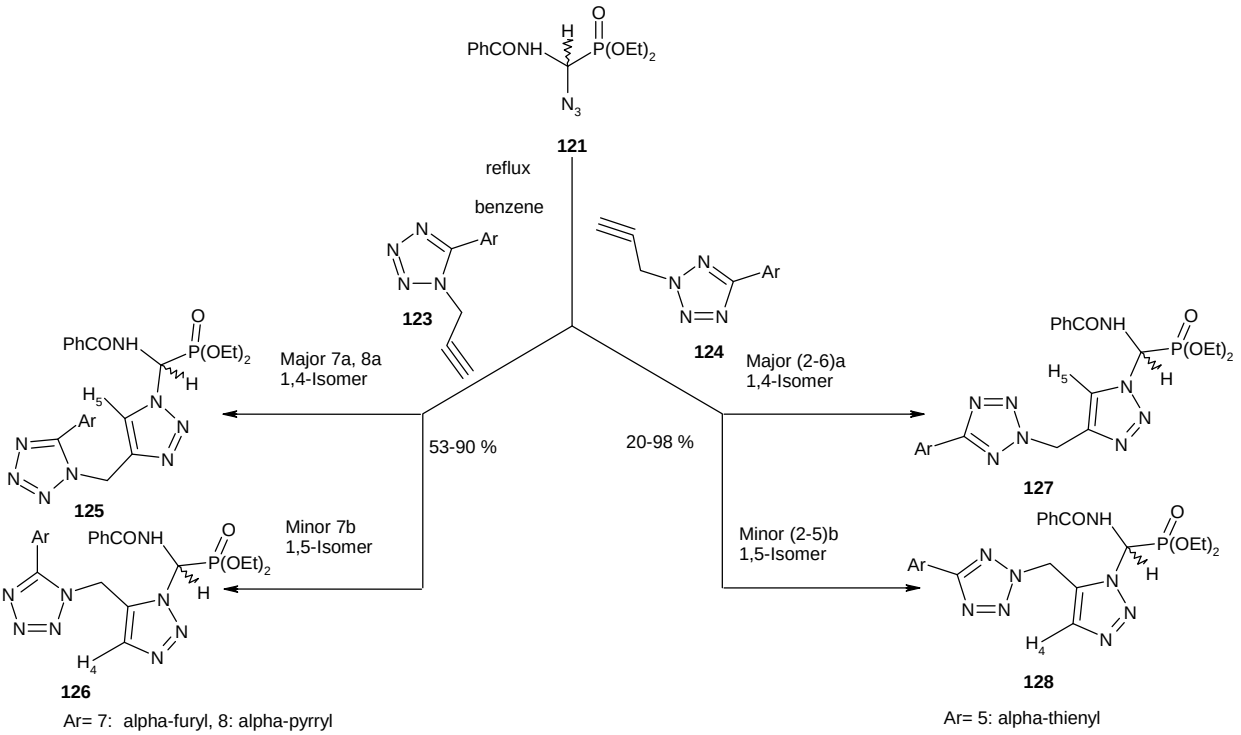
Also, diethyl (2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate (**122**) was prepared by a reaction of diethyl-(2-azido-2-benzoylaminomethyl) phosphonate (**121**) with dimethyl acetylenedicarboxylate in dry benzene at room temperature (Scheme 55).[102]



121 **122**

Scheme 55

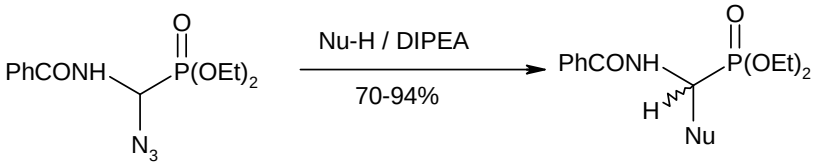
Similarly, some 1-(prop-2-ynyl)-5-aryltetrazoles (**123**) and 2-(prop-2-ynyl)-5-aryltetrazoles (**124**) were submitted to undergo cycloaddition reaction with the azido phosphonate **121** in dry benzene under reflux to give the interesting biheterocyclic α-aminophosphonic acid diesters **125**, **126**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



Scheme 56

4.2. Nucleophilic substitution reactions

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

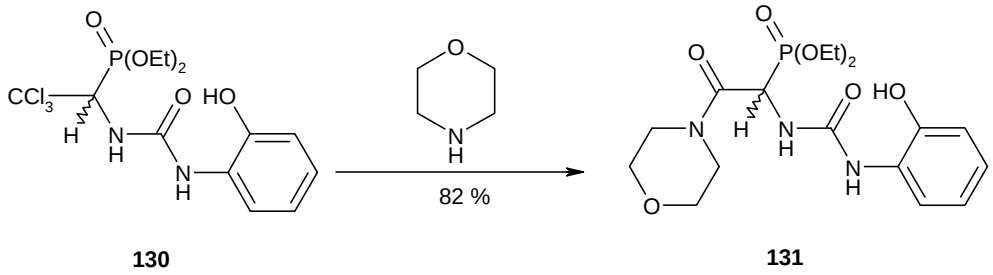


121 **129**

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

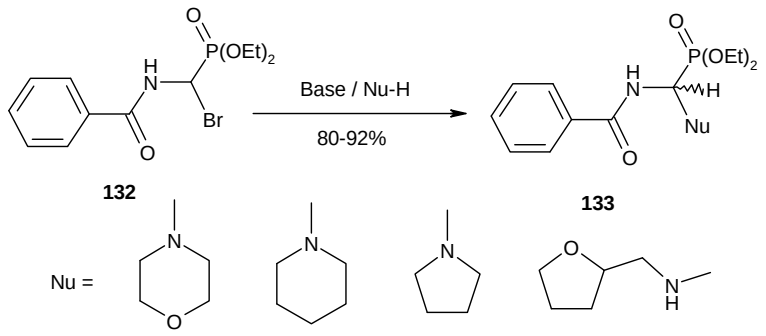
Scheme 57

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]



Scheme 58

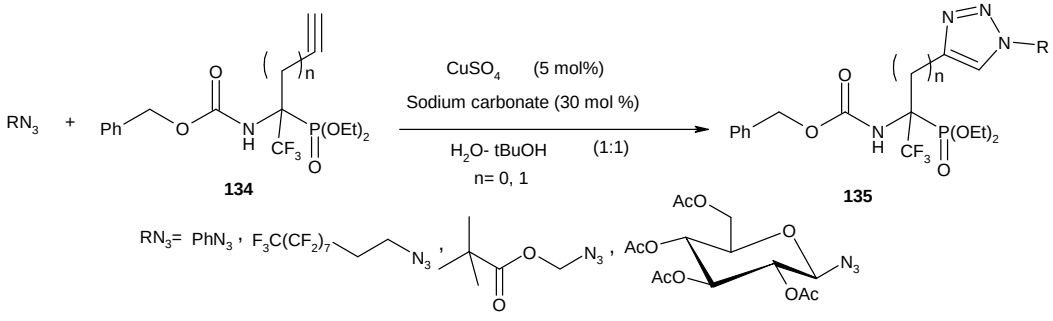
Similarly, the reaction of different amines Nu-H with the α-bromo-α-aminophosphonate derivative **132** resulted in the formation of α-heterocyclic α-aminophosphonates **133** (Scheme 59).[106]



Scheme 59

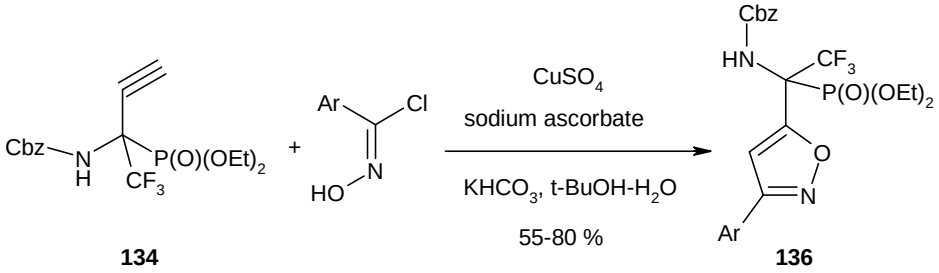
4.3. Cycloadditions of α-alkynylaminophosphonates

The cycloaddition of diethyl [(1-[(benzyloxycarbonyl)amino]-1-(trifluoromethyl)prop/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 α-CF_3-α-(triazol-4-yl)-α-aminophosphonates **135** (Scheme 60).[107]



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]



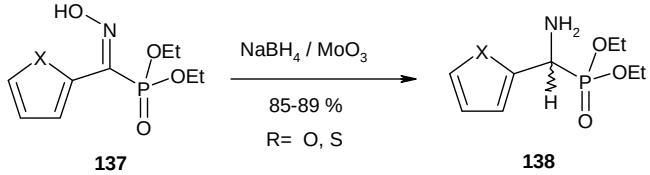
134 **136**

Ar= 4-$CH_3OC_6H_4$, C_6H_5, 4-F-C_6H_4, 4-NO_2-C_6H_4, 4-CF_3-C_6H_4
Cbz = benzyloxycarbonyl

Scheme 61

4.4. Reduction of α-hydroxyimino phosphonate

Simple reduction of the 1-hydroxyiminophosphonate **137** with $NaBH_4$ in the presence of transition metal compounds such as MoO_3 or $NiCl_2.6H_2O$ at ambient temperature in methanol and at normal pressure gave the corresponding diethyl aminoalkyl(aryl)phosphonates **138** in good yields (Scheme 62).[109]

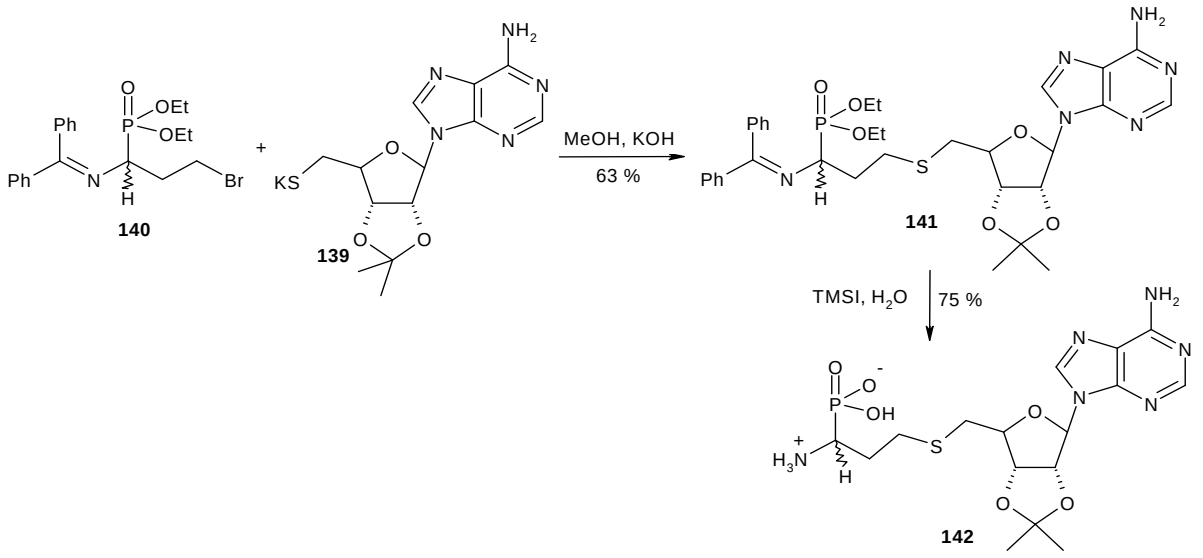


137 **138**

Scheme 62

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

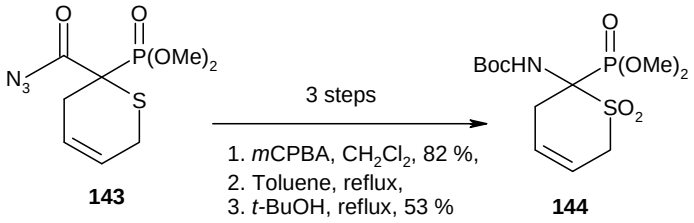
Reaction of the thiolate anion of **139** with diethyl [3-bromo-1-(diphenylmethyleneamino)propyl] phosphonate (**140**) was performed to give the fully protected AdoHcy analogue **141** in 63% yield. Deprotection was achieved via hydrolysis with trimethylsilyl iodide (TMSI) to generate the desired α-aminophosphonic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



Scheme 63

4.6. Curtius rearrangement of α-acylazidophosphonate

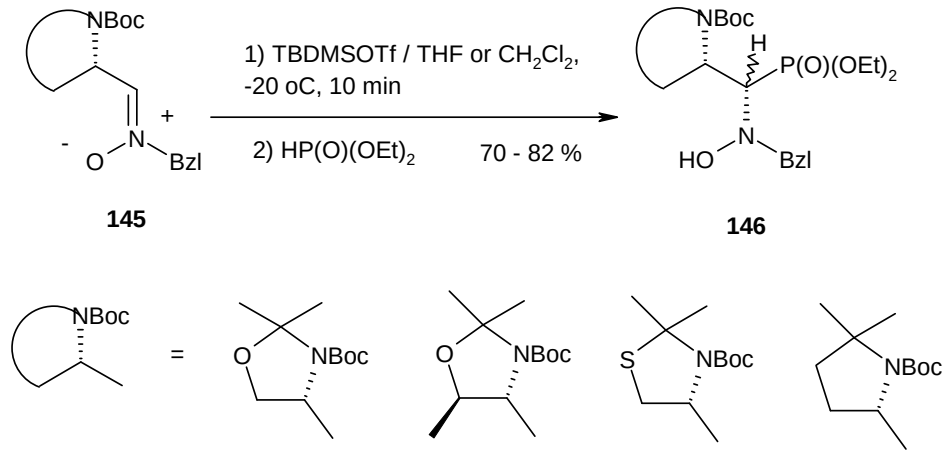
Curtius rearrangement of the *S,S*-dioxide of α-acylazidophosphonate **143** in dichloromethane afforded α-Boc-α-aminophosphonate **144** (Scheme 64).[111]



Scheme 64

4.7. Addition of diethyl phosphite to chiral N-benzyl nitrones

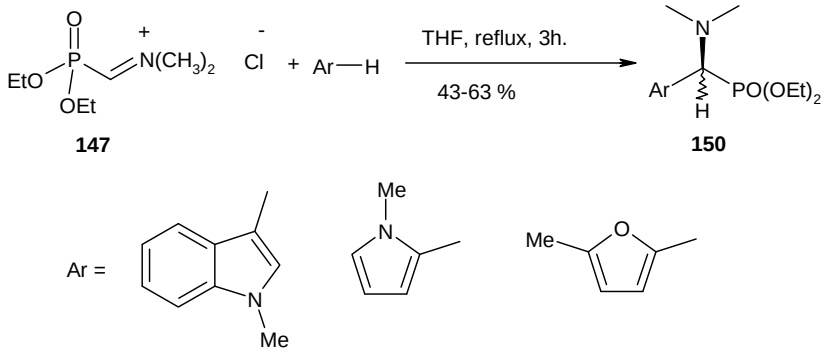
When N,N-diprotected α-aminonitrones **145** were treated with TBDMSOTf and then diethyl phosphite in THF or CH_2Cl_2 at -20 °C, the *syn* α-(hydroxyamino)phosphonates **146** were obtained in good yields after flash chromatography (Scheme 65).[112]



Scheme 65

4.8. From phosphonyliminium salts

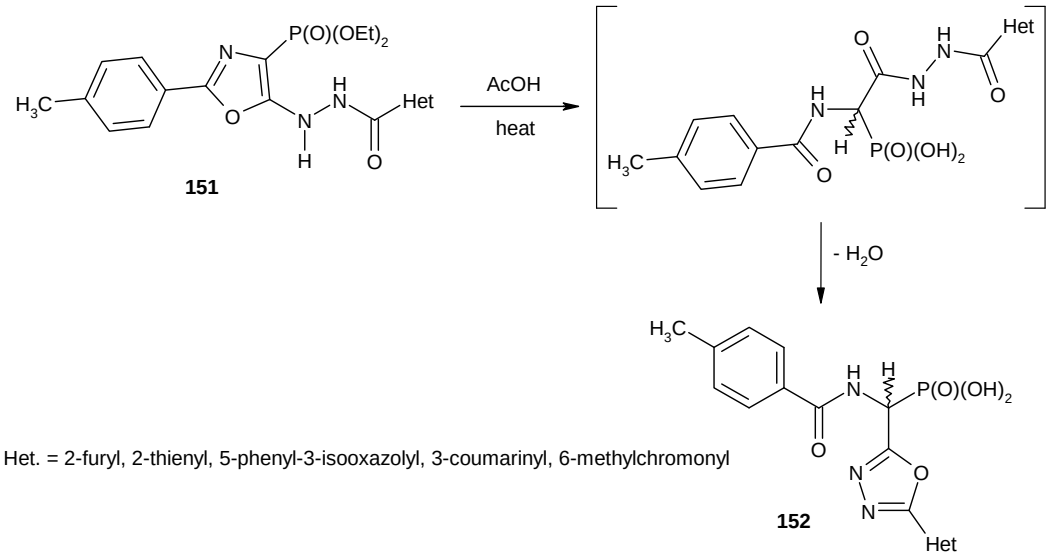
The optimized reaction conditions involved refluxing of the phosphonyliminium salt **147** and some nucleophilic aromatic compounds in THF gave the highest yields of novel α-heteroaryl-α-aminophosphonates **151** (Scheme 66).[113]



Scheme 66

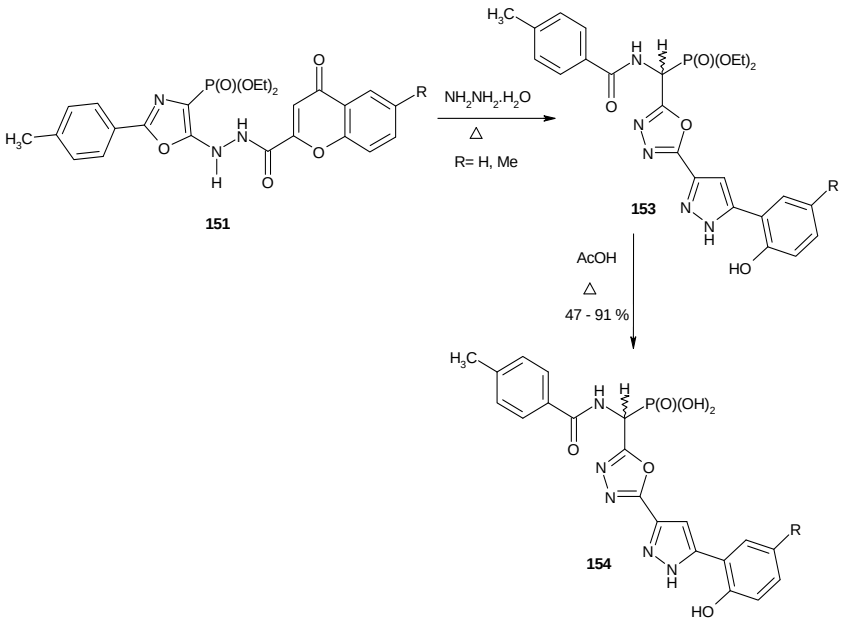
4.9. From oxazolyl phosphonates

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]



Scheme 67

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)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazol-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).[114]



Scheme 68

5. 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 up to the end 2013 on the synthesis of α-heterocyclic/heteroaryl α-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.

6. References

1. Saito, J. B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc*. **2007**, *129*, 1978. http://dx.doi.org/10.1021/ja0651005
2. Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids: Chemistry and biological activity*. John Wiley. Chichester. 2000.
3. Treov, K. D. *Chemistry and application of H–phosphonates*. Elsevier, Amsterdam 2006.
4. Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. http://dx.doi.org/10.1080/10426509108029443
5. Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1991**, *30*, 8165. http://dx.doi.org/10.1021/bi00247a011
6. Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem*. **1986**, *29*, 29. http://dx.doi.org/10.1021/jm00151a005
7. De Lombaert, S.; Blanchard, L.; Tan, T.; Sakane, Y.; Berry, C.; Ghai, R. D. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 145. http://dx.doi.org/10.1016/0960-894X(94)00474-T
8. Kafarski, P.; Lejczak, B. *Current Med. Chem. Anti-Cancer Agents* **2001**, *1*, 301. http://dx.doi.org/10.2174/1568011013354543
9. Emsley, J.; Hall, D. *The Chemistry of Phosphorus*. Harper and Row, London, 1976.
10. Boduszek, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *144*, 433. http://dx.doi.org/10.1080/10426509908546274
11. Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc*. **1981**, *103*, 654. http://dx.doi.org/10.1021/ja00393a026
12. De Risi, C.; Perrone, D.; Dondoni, A.; Pollini, G. P.; Bertolasi, V. *Eur. J. Org. Chem*. **2003**, 1904.
13. (a) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem*. **1994**, *59*, 7930. http://dx.doi.org/10.1021/jo00104a064
    (b) Ordonez, M.; Rojas-Cabera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17.

http://dx.doi.org/10.1016/j.tet.2008.09.083
(c) Kudzin, Z. H.; Kudzin, M. H.; Drabowicz, J.; Stevens, C. V. *Curr. Org. Chem*. **2011**, *15*, 2015.
http://dx.doi.org/10.2174/138527211795703612
(d) Ordonez, M.; Sayago, F. J.; Cativiela, C. *Tetrahedron* **2012**, *68*, 6369.
http://dx.doi.org/10.1016/j.tet.2012.05.008
14. (a) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Saritha, B.; Jayaprakash, S. *Synlett* **2003**, *4*, 505.
http://dx.doi.org/10.1055/s-2003-37508
(b) Agawane, S. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 3499.
http://dx.doi.org/10.1016/j.tetlet.2011.04.112
(c) Ranu, B. C.; Hajra, A. *Green Chem.* **2002**, *4*, 551.
15. (a) Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahedron Lett*. **2001**, *42*, 5561.
http://dx.doi.org/10.1016/S0040-4039(01)01053-X
(b) Dake, S. A.; Raut, D. S.; Kharat, K. R.; Mhaske, R. S.; Deshmukh, S. U.; Pawar, R. P. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 2527;
http://dx.doi.org/10.1016/j.bmcl.2011.02.039
(c) Balint, E.; Takacs, J.; Drahos, L.; Juranovic, A.; Kocevar, M.; Keglevich, G. *Heteroatom. Chem*. **2013**, *24*, 221;
http://dx.doi.org/10.1002/hc.21086
(d) Reddy, M. V. N.; Kumar, B. S.; Balakrishna, A.; Reddy, C. S.; Nayak, S. K.; Reddy, C. D. *Arkivoc* **2007**, *xv*, 246.
http://dx.doi.org/10.3998/ark.5550190.0008.f24
16. Ali, T. E. *Arkivoc* **2014**, (*i*), 21.
17. Ali, T. E.; Halacheva, S. S. *Heteroatom. Chem*. **2009**, *20*, 117.
http://dx.doi.org/10.1002/hc.20520
18. Ali, T. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 88.
http://dx.doi.org/10.1080/10426500802713309
19. Ali, T. E. *Eur. J. Med. Chem*. **2009**, *44*, 4539.
http://dx.doi.org/10.1016/j.ejmech.2009.06.022
20. Bouduszek, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *104*, 63.
http://dx.doi.org/10.1080/10426509508042578
21. Skowronski, R.; Grabowski, G.; Nazarski, R. B.; Lewkowski, J. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *144−146*, 449.
22. Nazarski, R. B.; Lewkowski, J. l. A.; Skowronski, R. *Heteroatom Chem.* **2002**, *13*, 120.
http://dx.doi.org/10.1002/hc.10005
23. Hubert, C.; Garrigues, B.; Munoz, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *152*, 229.
http://dx.doi.org/10.1080/10426509908031632

24. Oussaid, A.; Benyaqad, F.; Oussaid, B.; Pradel, C.; Garriguesa, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1183. http://dx.doi.org/10.1080/10426500307903
25. Hudson, H. R.; Lee, R. J.; Matthews, R. W. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1691. http://dx.doi.org/10.1080/10426500490466274
26. Claeys, D. D.; Moonen, K.; Roman, B. I.; Nemykin, V. N.; Zhdankin, V. V.; Waroquier, M.; Van Speybroeck, V.; Stevens, C. V. *J. Org. Chem.* **2008**, *73*, 7921. http://dx.doi.org/10.1021/jo801138s
27. Louaisil, N.; Rabasso, N.; Fadel, A. *Tetrahedron* **2009**, *65*, 8587. http://dx.doi.org/10.1016/j.tet.2009.07.040
28. Kraicheva, I. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *155*, 127. http://dx.doi.org/10.1080/10426509908044976
29. Kraicheva, I.; Finocchiaro, P.; Failla, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2915. http://dx.doi.org/10.1080/10426500214891
30. Kraicheva, I.; Finocchiaro, P.; Failla, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2345. http://dx.doi.org/10.1080/10426500490485093
31. Kraicheva, I.; Finocchiaro, P.; Failla, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 57. http://dx.doi.org/10.1080/10426500600866903
32. Kraicheva, I.; Bogomilova, A.; Tsacheva, I.; Momekov, G.; Momekova, D.; Troev, K. *Eur. J. Med. Chem.* **2010**, *45*, 6039. http://dx.doi.org/10.1016/j.ejmech.2010.10.002
33. Salkeeva, L. K.; Nurmaganbetova, M. T.; Kurmanaliev, O. S.; Gazizov, T. K. *Russ. J. Org. Chem.* **2002**, *38*, 723. http://dx.doi.org/10.1023/A:1019671324617
34. Krishna, A. B.; Reddy, M. V. N.; Reddy, G. C. S.; Krishna, B. S.; Nayak, S. K.; Reddy, C. S. *Inter. J. Appl. Bio. Pharm. Tech.* **2010**, *I*, 873.
35. Olszewski, T. K.; Boduszek, B.; Sobek, S.; Kozłowski, H. *Tetrahedron* **2006**, *62*, 2183. http://dx.doi.org/10.1016/j.tet.2005.12.016
36. Pyrkosz, M.; Goldeman, W.; Kontecka, E. G. *Inorg. Chim. Acta* **2012**, *380*, 223. http://dx.doi.org/10.1016/j.ica.2011.09.024
37. Boduszek, B.; Olszewski, T. K.; Goldeman, W.; Grzegolec, K.; Blazejewska, P. *Tetrahedron* **2012**, *68*, 1223. http://dx.doi.org/10.1016/j.tet.2011.11.054
38. Menard, L.; Fontaine, L.; Brosse, J. C. *React. Polym.* **1994**, *23*, 201. http://dx.doi.org/10.1016/0923-1137(94)90022-1

39. Boduszek, B.; Korenova, A.; Uher, M.; Vegh, D. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1047. http://dx.doi.org/10.1080/10426500307846
40. Mandhane, P. G.; Joshi, R. S.; Nagargoje, D. R.; Chate, A. V.; Gill, C. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 149. http://dx.doi.org/10.1080/10426507.2010.492363
41. Pokalwar, R. U.; Sadaphal, S. A.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2010**, *3*, 33. http://dx.doi.org/10.1080/17518250903410082
42. Pokalwar, R. U.; Hangarge, R. V.; Madje, B. R.; Ware, M. N.; Shingare, M. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 1461. http://dx.doi.org/10.1080/10426500701681532
43. Michalska, J.; Boduszek, B.; Olszewski, T. K. *Heteroatom Chem.* **2011**, *22*, 617. http://dx.doi.org/10.1002/hc.20704
44. Kategaonkar, A. H.; Sonar, S. S.; Sapkal, S. B.; Gawali, V. U.; Shingate, B. B.; Shingare, M. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 2113. http://dx.doi.org/10.1080/10426500903530867
45. Khidre, M. D.; Abou-Yousef, H. M.; Mahran, M. R. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *140*, 147. http://dx.doi.org/10.1080/10426509808035740
46. Lang, S. Y.; Wang, D. Z.; Cao, L. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009**, *184*, 2560. http://dx.doi.org/10.1080/10426500802529127
47. Ali, T. E. *Arkivoc* **2008**, (*ii*), 71.
48. Ramalingam, S.; Kumar, P. *Catal Lett*. **2008**, *125*, 315. http://dx.doi.org/10.1007/s10562-008-9562-x
49. Sadaphal, S. A.; Kategaonkar, A. H.; Sapkal, S. B.; Shingate, B. B.; Gill, C. H.; Shingare, M. S. *Bull. Cat. Soc. India* **2009**, *8*, 131.
50. Sadaphal, S. A.; Sonar, S. S.; Kategaonkar, A. H.; Shingare, M. S. *Bull. Korean Chem. Soc.* **2009**, *30*, 1054. http://dx.doi.org/10.5012/bkcs.2009.30.5.1054
51. Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *Ultrasonics Sonochem.* **2010**, *17*, 760. http://dx.doi.org/10.1016/j.ultsonch.2010.02.002
52. Manjula, A.; Rao, B. V.; Neelakantan, P. *Synth. Commun.* **2003**, *33*, 2963. http://dx.doi.org/10.1081/SCC-120022468
53. Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F. *J. Organometal. Chem*. **2008**, *693*, 3313. http://dx.doi.org/10.1016/j.jorganchem.2008.07.037
54. Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Green Chem*. **2002**, *4*, 436. http://dx.doi.org/10.1039/b203934f
55. Sun, P.; Hu, Z.; Huang, Z. *Synth. Commun*. **2004**, *34*, 4293.

http://dx.doi.org/10.1081/SCC-200039361
56. El Kaim, L.; Grimaud, L.; Hadrot, S. *Tetrahedron Lett.* **2006**, *47*, 3945. http://dx.doi.org/10.1016/j.tetlet.2006.03.151
57. Ohara, M.; Nakamura, S.; Shibataa, N. *Adv. Synth. Catal.* **2011**, *353*, 3285. http://dx.doi.org/10.1002/adsc.201100482
58. Sobhani, S.; Vafaee, A. *J. Iran. Chem. Soc.* **2010**, *7*, 227.
59. Sobhani, S.; Tashrifi, Z. *Heteroatom Chem*. **2009**, *20*, 109. http://dx.doi.org/10.1002/hc.20517
60. Tillu, V. H.; Dumbre, D. K.; Wakharkar, R. D.; Choudhary, V. R. *Tetrahedron Lett*. **2011**, *52*, 863. http://dx.doi.org/10.1016/j.tetlet.2010.11.105
61. Zhang, X. Y.; Qu, Y. Y.; Fan, X. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 816. http://dx.doi.org/10.1080/10426500902994338
62. Sarvari, M. H. *Tetrahedron* **2008**, *64*, 5459. http://dx.doi.org/10.1016/j.tet.2008.04.016
63. Agawane, S. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 3499. http://dx.doi.org/10.1016/j.tetlet.2011.04.112
64. Sheykhan, M.; Ma'mani, L.; Ebrahimi, A.; Heydari, A. *J. Mol. Catal. A: Chem.***2011**, *335*, 253. http://dx.doi.org/10.1016/j.molcata.2010.12.004
65. Bai, S.; Song, B.; Bhadury, P. S.; Yang, S.; Hu, D.; Xue, W. *Chin. J. Chem.* **2011**, *29*, 109. http://dx.doi.org/10.1002/cjoc.201190035
66. Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263. http://dx.doi.org/10.1021/jo062140i
67. Reddy, M. V. N.; Annar, S.; Krishna, A. B.; Reddy, G. C. S.; Reddy, C. S. *Org. Commun*. **2010**, *3*, 39.
68. Reddy, M. V. N.; Balakrishna, A.; Kumar, M. A.; Reddy, G. C. S.; Sankar, A. U. R.; Reddy, C. S.; Krishna, T. M. *Chem. Pharm. Bull.* **2009***, 57*, 1391. http://dx.doi.org/10.1248/cpb.57.1391
69. Kaboudin, B.; Afsharinezhad, M. B.; Yokomatsu, T. *Arkivoc* **2012**, (*iv*), 44.
70. Siemieniec, J.; Kafarski, P.; Plucinski, P. *Molecules* **2013**, *18*, 8473. http://dx.doi.org/10.3390/molecules18078473
71. Zefirov, N. S.; Matveeva, E. D. *Arkivoc* **2008**, (*i*), 1. http://dx.doi.org/10.3998/ark.5550190.0009.101
72. Matveeva, E. D.; Podrugina, T. A.; Kolesnikova, I. N.; Borisenko, A. A.; Zefirov, N. S. *Russ. Chem. Bull. Int. Ed*. **2009**, *58,* 119.
73. Sobhania, S.; Tashrifia, Z. *Synth. Commun*. **2009**, *39*, 120. http://dx.doi.org/10.1080/00397910802369695

74. Rao, K. U. M.; Jayaprakash, S. H.; Nayak, S. K.; Reddy, C. S. *Catal. Sci. Technol*. **2011**, *1*, 1665.
http://dx.doi.org/10.1039/c1cy00295c
75. Reddy, G. S.; Rao, K. U. M.; Sundar, C. S.; Sudha, S. S.; Haritha, B.; Swapna, S.; Reddy, C. S. *Arabian J. Chem.* **2014**, *7*, 833-838.
http://dx.doi.org/10.1016/j.arabjc.2013.01.004
76. Mungara, A. K.; Park, Y. K.; Lee, K. D. *Chem. Pharm. Bull.* **2012**, *60*, 1531.
77. Ali, T. E. *Heteroatom Chem.* **2013**, *24*, 426.
http://dx.doi.org/10.1002/hc.21110
78. Lang, S. Y.; Yue, F.; Cao, L. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 461.
http://dx.doi.org/10.1080/10426507.2011.625510
79. Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 1462.
http://dx.doi.org/10.1080/10426507.2012.690117
80. Qiu, J.; Liu, G.; Li, J.; Zhao, Y.; Li, H.; Zhang, G. *Chin. J. Org. Chem*. **2011**, *31*, 63.
http://dx.doi.org/10.1080/10426507.2012.690117
81. Abdel-Aziz, S. A.; Ali, T. E.; El-Mahdy, K. M.; Abdel-Karim, S. M. *Eur. J. Chem*. **2011**, *2*, 25.
http://dx.doi.org/10.5155/eurjchem.2.1.25-35.208
82. Lombaert, S. D.; Stamford, L. B.; Blanchard, L.; Tan, J.; Hoyer, D.; Diefenbacher, C. G.; Wei, D.; Wallace, E. M.; Moskal, M. A., Savage, P.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1059.
http://dx.doi.org/10.1016/S0960-894X(97)00159-5
83. Sundar, C. S.; Srinivasulu, D.; Nayak, S. K.; Reddy, C. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 523.
http://dx.doi.org/10.1080/10426507.2011.631641
84. Ranu, B. C.; Hajra, A. *Green Chem.* **2002**, *4*, 551.
http://dx.doi.org/10.1039/b205747f
85. Joshi, R. S.; Mandhane, P. G.; Dabhade, S. K.; Gill, C. H. *Green Chem. Lett. Rev.* **2010**, *3*, 191.
http://dx.doi.org/10.1080/17518251003660147
86. Zhang, J.; Cui, Z.; Wang, F.; Wang, Y.; Miao, Z.; Chen, R. *Green Chem*. **2007**, *9*, 1341.
http://dx.doi.org/10.1039/b710008f
87. Boduszek, B.; Llpfiskt, M.; Kowalska, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *143*, 179.
http://dx.doi.org/10.1080/10426509808045496
88. Rabasso, N.; Louaisil, N.; Fadel, A. *Tetrahedron* **2006**, *62*, 7445.
http://dx.doi.org/10.1016/j.tet.2006.05.016
89. Reddy, Y. T., Reddy, P. N., Kumar, B. S., Rajput, P., Sreenivasulu, N., Rajitha, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 161.

http://dx.doi.org/10.1080/10426500600887461
90. Boduszek, B. *Tetrahedron* **1996**, *52*, 12483. http://dx.doi.org/10.1016/0040-4020(96)00727-2
91. Reddy, B. V. S.; Krishna, A. S.; Ganesh, A. V.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2011**, *52*, 1359. http://dx.doi.org/10.1016/j.tetlet.2011.01.074
92. Huang, K.-B.; Chen, Z.-F.; Liu, Y.-C.; Li, Z.-Q.; Wei, J.-H.; Wang, M.; Xie, X.-L.; Liang, H. *Eur. J. Med. Chem.* **2013**, *64*, 554. http://dx.doi.org/10.1016/j.ejmech.2013.04.024
93. Reddy, M. V.; Dindulkar, S. D.; Jeong, Y. T. *Tetrahedron Lett.* **2011**, *52*, 4764. http://dx.doi.org/10.1016/j.tetlet.2011.07.027
94. Abdel-Megeed, M. F.; Badr, B. E.; Azaam, M. M.; El-Hiti, G. A. *Bioorg. Med. Chem.* **2012**, *20*, 2252. http://dx.doi.org/10.1016/j.bmc.2012.02.015
95. Reddy, C. B.; Kumar, K. S.; Kumar, M. A.; Reddy, M. V. N.; Krishna, B. S.; Naveen, M.; Arunasree, M. K.; Reddy, C. S.; Raju, C. N.; Reddy, C. D. *Eur. J. Med. Chem*. **2012**, *47*, 553. http://dx.doi.org/10.1016/j.ejmech.2011.11.026
96. Juribasic, M.; Stella, L.; Marinic, E.; Vinkovic, M.; Traldi, P.; Tuek-Bozic, L. *Lett. Org. Chem.* **2009**, *6,* 11. http://dx.doi.org/10.2174/157017809787003142
97. Zhang, X. Y.; Qu, Y. Y.; Fan, X. S. *Chin. Chem. Lett.* **2010**, *21*, 1191. http://dx.doi.org/10.1016/j.cclet.2010.04.037
98. Zhang, X.; Qu, Y.; Fan, X.; Bores, C.; Feng, D.; Andrei, G.; Snoeck, R.; Clercq, E. D.; Loiseau, P. M. *Nucleosides, Nucleotides Nucleic Acids,* **2010**, *29*, 616. http://dx.doi.org/10.1080/15257770.2010.496281
99. Tang, W.; Yu, Z. H.; Shi, D. Q. *Heteroatom Chem.* **2010**, *21*, 148. http://dx.doi.org/10.1002/hc.20589
100. Kumar, M. A.; Lee, K. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012**, *187*, 899. http://dx.doi.org/10.1080/10426507.2011.645174
101. Boduszeka, B.; Luboch, E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2527. http://dx.doi.org/10.1080/10426500490485543
102. Achamlale, S.; Mabrouk, H.; Elachqar, A.; El Hallaoui, A.; El Hajji, S.; Alami, A.; Bellan, J.; Mazières, M. R.; Wolf, J. G.; Pierrot, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 357. http://dx.doi.org/10.1080/10426500600919959
103. Achamlale, S.; Elachqar, A.; El Hallaoui, A.; Alami, A.; Elhajji, S.; Roumestant, M. L.; Viallefont, P. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *140*, 103. http://dx.doi.org/10.1080/10426509808035736

104. Boukallaba, K.; Elachqar, A.; El Hallaoui, A.; Alami, A.; El Hajji, S.; Labriti, B.; Martinez, J.; Rolland, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 819. http://dx.doi.org/10.1080/10426500500272046
105. Kockritz, A.; Schnell, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *83*, 125. http://dx.doi.org/10.1080/10426509308034355
106. Boukallaba, K.; Elachqar, A.; El Hallaoui, A.; Alami, A.; El Hajji, S.; Labriti, B.; Atmani, A.; El Bali, B.; Lachkar, M.; Allouchi, H.; Martinez, J.; Rolland, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 1045. http://dx.doi.org/10.1080/10426500601093739
107. Vorobyeva, D. V.; Karimova, N. M.; Vasilyeva, T. P.; Osipov, S. N.; Shchetnikov, G. T.; Odinets, I. L.; Schenthaler, G. R. *J. Fluorine Chem.* **2010**, *131*, 378. http://dx.doi.org/10.1016/j.jfluchem.2009.12.003
108. Vorobyeva, D. V.; Karimova, N. M.; Odinets, I. L.; Roschenthaler, G. V.; Osipov, S. N.; *Org. Biomol. Chem.* **2011**, *9*, 7335. http://dx.doi.org/10.1039/c1ob06040f
109. Demir, A. S.; Tanyeli, C.; Sesenoglu, O.; Demic, S.; Evin, O. O. *Tetrahedron Lett.* **1996**, *37*, 407. http://dx.doi.org/10.1016/0040-4039(95)02171-X
110. Steere, J. A.; Sampson, P. B.; Honek, J. F. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 457. http://dx.doi.org/10.1016/S0960-894X(01)00789-2
111. Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123. http://dx.doi.org/10.1021/jo0262208
112. Risi, C. D.; Perrone, D.; Dondoni, A.; Pollini, G. P.; Bertolasi, V. *Eur. J. Org. Chem.* **2003**, 1904.
113. Risch, N.; Piper, S.; Winter, A.; Risse, A. L. *Eur. J. Org. Chem.* **2005**, 387. http://dx.doi.org/10.1002/ejoc.200400618
114. Golovchenko, A. V.; Solomyannyi, R. N.; Brovarets, V. S. *Russ. J. Gen. Chem.* **2010**, *80*, 723. http://dx.doi.org/10.1134/S1070363210040067

Authors' Biographies

Tarik El-Sayed Ali was born in Cairo, Egypt, in 1975. He is presently assistant professor of Organic Chemistry, Department of Chemistry, Faculty of Education, Ain Shams University, Cairo, Egypt. He graduated with B.Sc. (Physics and Chemistry) from Ain Shams University in 1997. He received his M.Sc. and Ph.D. degrees in 2001 and 2005, respectively, in Heterocyclic Chemistry from Ain Shams University. Awarded a post doctoral scientific grant for supporting young researchers (2007) from the Ministry of High Education and Scientific Research (Egypt) in organophosphorus laboratory, Institute of Polymers, Bulgarian Academy of Science, Sofia, Bulgaria. His CV was included in Who's Who in the World in 2011, 2012, 2013 and 2015. He won the award for the best research article in the field of Heterocyclic Chemistry at the Egyptian universities and research centers in 2011. He has published more than 40 scientific papers including 10 review articles, all in international journals. His research interests are in synthesis and chemical reactivity of phosphorus compounds containing bioactive heterocyclic systems.

Somaia M. Abdel-Karim was born in 1985 in Cairo, Egypt. In 2006 she graduated from Ain Shams University, Faculty of Education, Department of Chemistry. Also, she received her M.Sc. and Ph.D. degrees in 2011 and 2014, respectively, in Organophosphorus Chemistry. She has published about 10 scientific papers, all in international journals. Her research interests are in synthesis and chemical reactivity of phosphorus compounds containing bioactive heterocyclic systems.

