HETEROCYCLES, Vol. 85, No. 9, 2012, pp. 2073 - 2109. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 23rd March, 2012, Accepted, 15th June, 2012, Published online, 25th June, 2012
DOI: 10.3987/REV-12-739

SYNTHETIC METHODS FOR PHOSPHORUS COMPOUNDS CONTAINING PYRAZOLE RINGS

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

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

Abstract – The present review considers all the literature data on methods developed for the synthesis of phosphorus compounds containing pyrazole rings starting from their appearance up to the 2011. The described methods for the synthesis of phosphorus compounds containing pyrazole rings can be divided into three routes: a) direct phosphorylation of pyrazole rings, b) ring closure of acyclic phosphorus compounds with different reagents into phosphono-pyrazoles and c) cyclization of side functional groups to give isolated and fused phosphorus heterocyclic systems containing pyrazole rings.

CONTENTS

1. INTRODUCTION

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials.[1] Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. Pyrazole and its derivatives, a class of well known nitrogen containing heterocyclic compounds, occupy an important position in medicinal and pesticide chemistry with having a wide range of bioactivities such as antimicrobial,[2] anticancer,[3] anti-inflammatory,[4] anti-depressant,[5] anti-convulsant,[6] anti-hyperglycemic,[7] antipyretic,[8] antibacterial,[9] antifungal activities,[10] CNS regulants[11] and selective enzyme inhibitory activities.[12] It has been found that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases.[13] It has been shown *in vivo* that some of the pyrazole derivatives have appreciable antihypertensive activity.[14] These compounds also exhibited properties such as cannabinoid hCB1 and hCB2 receptor, inhibitors of p38 Kinase and CB1 receptor antagonists.[15,16]

On the other hand, it is known that phosphorus substituents regulate important biological functions such as pesticides, antichloine esterase, antiviral, antimicrobial activity, and war gases,[17-20] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting for the preparation of biologically active compounds.

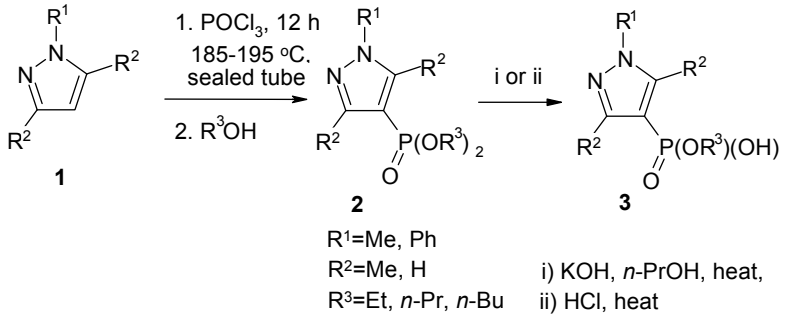
Pyrazole derivatives containing a phosphorus atom have been showed good biological activities, for example, pyraclofos and flupyrazofos which have been developed as good insecticides.[21-23] For many years, the synthesis of phosphorus derivatives of pyrazoles has been a subject of interest in several laboratories. The present survey considers all the literature data on methods developed for the synthesis of phosphorus compounds containing pyrazole moieties starting from their appearance up to the 2011. The described methods for the synthesis of phosphorus compounds containing pyrazole rings can be divided into three routes: a) direct phosphorylation of pyrazole rings, b) ring closure of acyclic phosphorus compounds with electrophilic and nucleophilic reagents into phosphonopyrazoles and c) cyclization of side functional groups to give isolated and fused phosphorus heterocyclic systems containing pyrazole rings. It is hoped that this survey will demonstrate the synthetic potential of the synthesis of phosphorus containing pyrazole moieties and generate some new ideas in this area.

2. SYNTHETIC APPROACHES

2.1. DIRECT PHOSPHORYLATION OF PYRAZOLE RINGS.

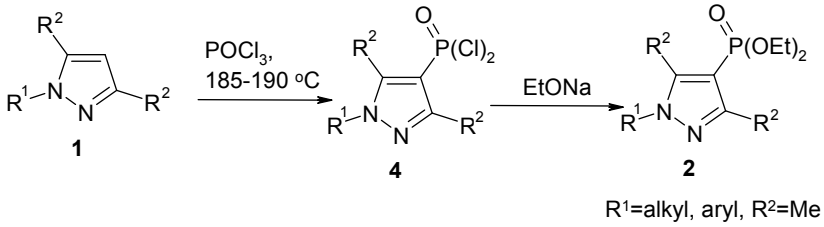
2.1.1. *C*-Phosphorylation of pyrazole rings

It is known that pyrazoles with unsubstituted 4-positions and lacking electron-withdrawing groups in the ring can facilitate the reaction in this position. This property was used in the synthesis of a series of phosphonylated pyrazoles.[24,25] Thus, heating of alkyl substituted pyrazoles **1** and $POCl_3$ in an ampule for 12 h, followed by treatment with absolute alcohol afforded dialkyl 1,3,5-trialkylpyrazol-4-yl-phosphonates **2** in 31-44% yield (Scheme 1). The dibutyl 1-phenylpyrazol-4-yl-phosphonate **2** (R^3= *n*-Bu) could be converted into the monobutyl ester **3** by heating with KOH in propanol, followed by acidification. Hydrolysis of the dialkyl esters **2** with acids gave syrupy phosphonic acids that could not be purified.



Scheme 1

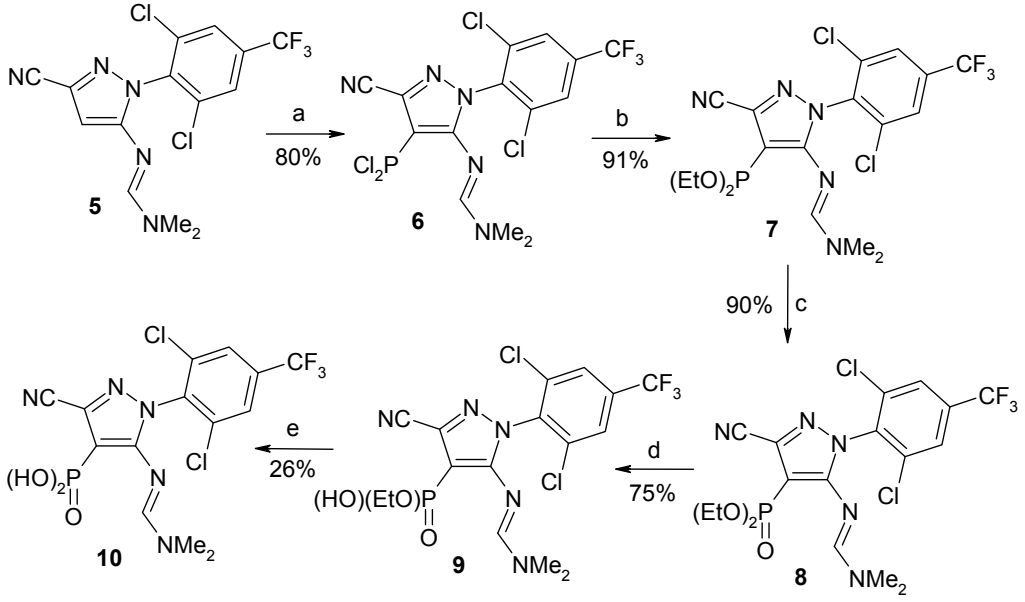
Applying of a similar type of substitution reaction on the pyrazole **1** *via* its treatment with phosphoryl chloride afforded the dichloride derivative **4** which underwent esterification with sodium ethoxide to give the corresponding ester **2** (Scheme 2).[25]



Scheme 2

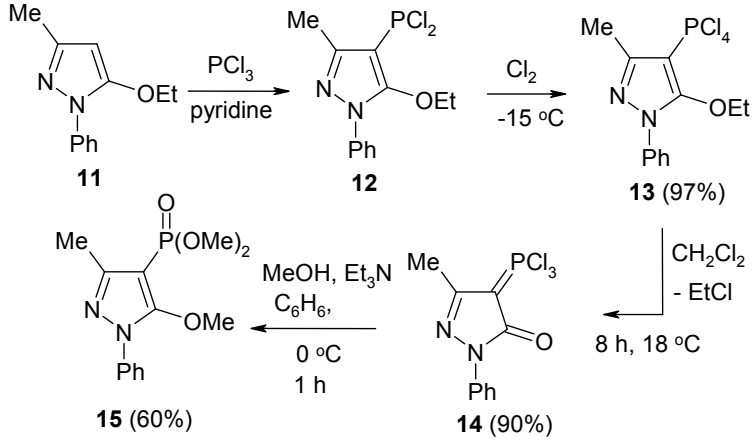
The synthesis of diethyl 3-cyanopyrazol-4-ylphosphonate **8** and the corresponding phosphonic acid **10** was achieved (Scheme 3).[26,27] The synthetic route depends on phosphonylation of the pyrazole derivative **5** with phosphorus trichloride, followed by esterification to give the diester **7**. The latter diester underwent an oxidation with hydrogen peroxide to prepare the corresponding phosphonate **8**. Conversion of the phosphonate **8** to the phosphonic acid **10** occurred in two steps, *via* the monoalkyl ester **9** (Scheme 3). The envisaged end products were used for pest control and preparation of veterinary drugs, since they are useful for the control of arthropods and helminthes.

Treatment of 5-ethoxy-3-methyl-1-phenylpyrazole (**11**) with phosphorus trichloride in pyridine provided 5-ethoxy-3-methyl-1-phenylpyrazol-4-yl-dichlorophosphine (**12**). Chlorination of **12** with chlorine afforded the phosphorane **13**. This phosphorane **13** underwent elimination of ethyl chloride to yield the phosphorus ylide **14** under strictly controlled conditions. The latter compound reacted with methanol to yield the dimethylpyrazol-4-yl-phosphonate **15** (Scheme 4).[28]



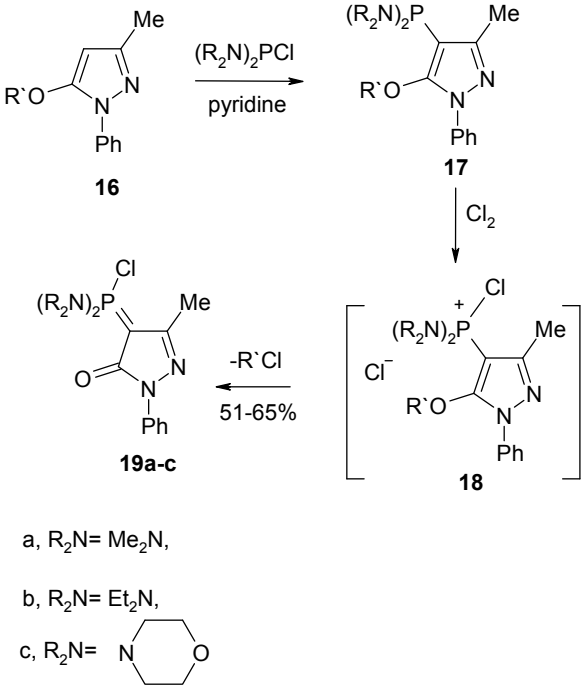
(a) 1. PCl_3, pyridine, -30 °C, (15 min.); 15 °C (2 h); 2. Et_3N, 1 h; (b) Et_3N, EtOH, Et_2O, 0 °C (20 min.); 20 °C (14 h); (c) H_2O_2 in EtOH at -30 °C, 47 in EtOH at -50 °C (15 min.): heating to 20 °C and workup; (d) LiN_3, DMF, 1 h 95-100 °C; (e) TMSI, MeCN, 24 h, 20 °C.

Scheme 3



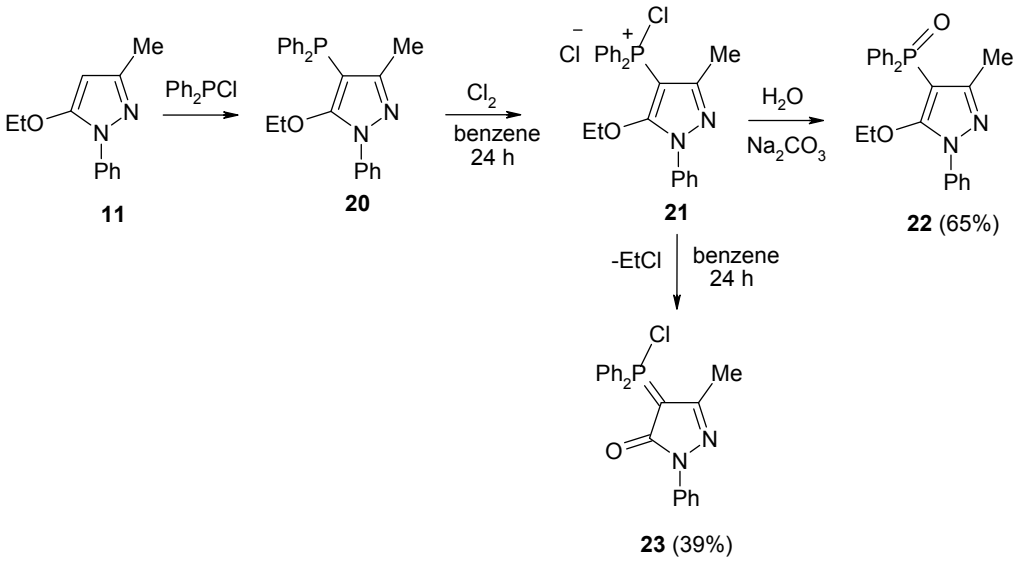
Scheme 4

Reaction of 5-alkoxy-3-methyl-1-phenyl-1*H*-pyrazole (**16**) with dialkylaminophosphinyl chloride in pyridine afforded 4-dialkylaminophosphinyl pyrazoles **17**. Further, it was found that the chlorination of **17** with chlorine led to stable chloro phosphorus ylides **19a-c** rather than to the expected chlorophosphonium chloride **18** (Scheme 5).[29]



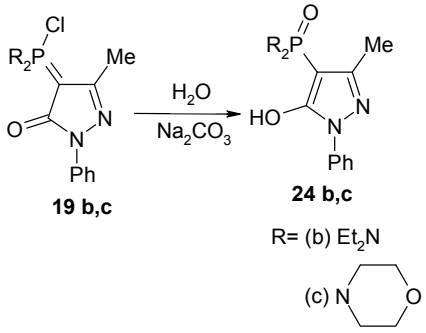
Scheme 5

Similarly, the pyrazole **11** reacted with chloro(diphenyl)phosphine to give the phosphine **20**. Contrary to the behavior of compounds **17**, the phosphine **20** was chlorinated to provide a rather stable chlorophosphonium salt **21** that could not be isolated in a pure state, although its structure was supported by ^{31}P NMR spectral data as well as by hydrolyzing it to diphenyl (3-methyl-1-phenyl-5-ethoxypyrazol-4-yl) phosphine oxide (**22**). When the chlorophosphonium salt **21** was maintained at 20 ^{o}C in benzene for 24 h, it decomposed to give 4-[chloro(diphenyl)-λ^{5}-phosphanylidene]-3-methyl-1-phenyl-5*H*-pyrazol-5-one (**23**) and ethyl chloride (Scheme 6).[29]



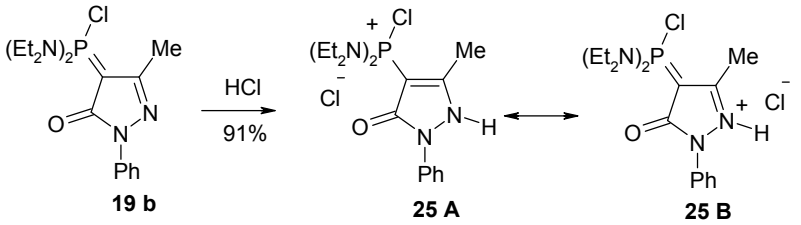
Scheme 6

The chloro phosphorus ylides **19b,c** were readily hydrolyzed by atmospheric moisture or by reaction with aqueous sodium carbonate to give the corresponding phosphonates **24** (Scheme 7).[29]



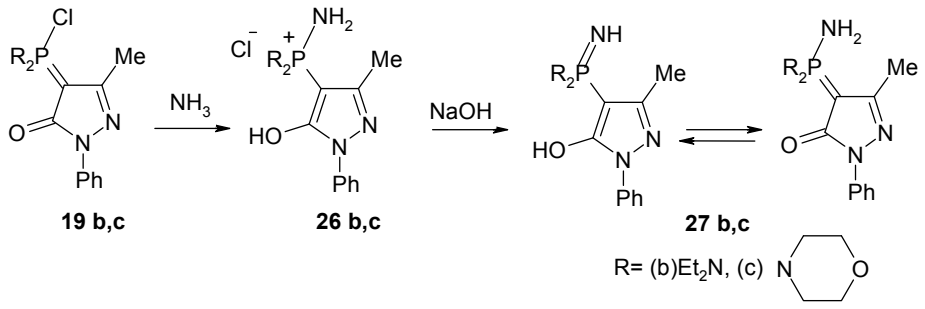
Scheme 7

Also, the chloro phosphorus ylide **19b** reacted with hydrogen chloride to furnish tetraethyldiamino (3-methyl-5-oxo-1-phenyl-2,5-dihydropyrazol-4-yl)chlorophosphonium chloride (**25A,B**) as air-stable compounds (Scheme 8).[29]



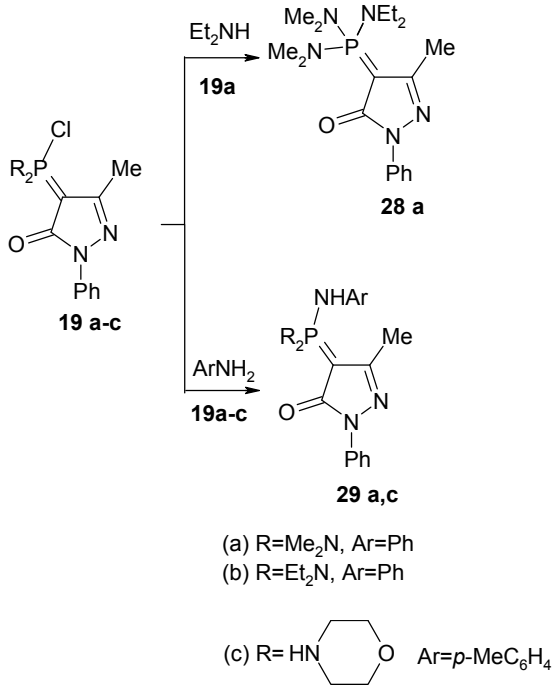
Scheme 8

Under the action of gaseous ammonia, the chlorine atoms in the chloro phosphorus ylides **19b**,**c** were readily displaced by amino groups to produce the iminophosphonates **27b**,**c** (Scheme 9).[29]



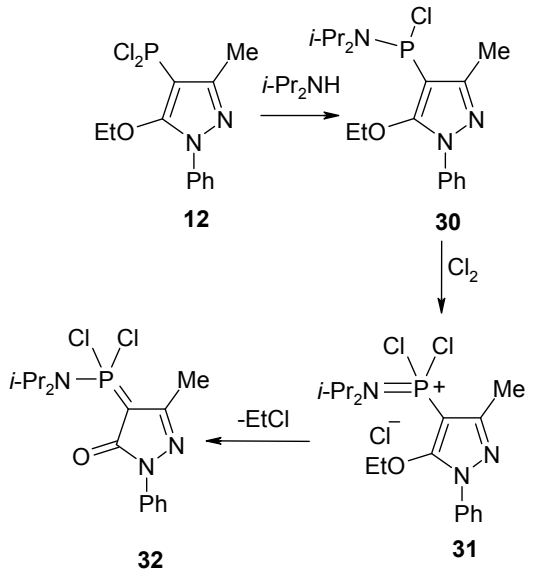
Scheme 9

The ease of substitution of the chlorine atom in chloro phosphorus ylides **19a-c** by a dialkylamino or an arylamino group was mainly governed by steric effects of substituents at the phosphorus atom. For example, in the case of dimethylamino groups bonded to the phosphorus atom, the reaction with diethylamine and aniline was carried out for 24 h to reach completion (Scheme 10).[29]



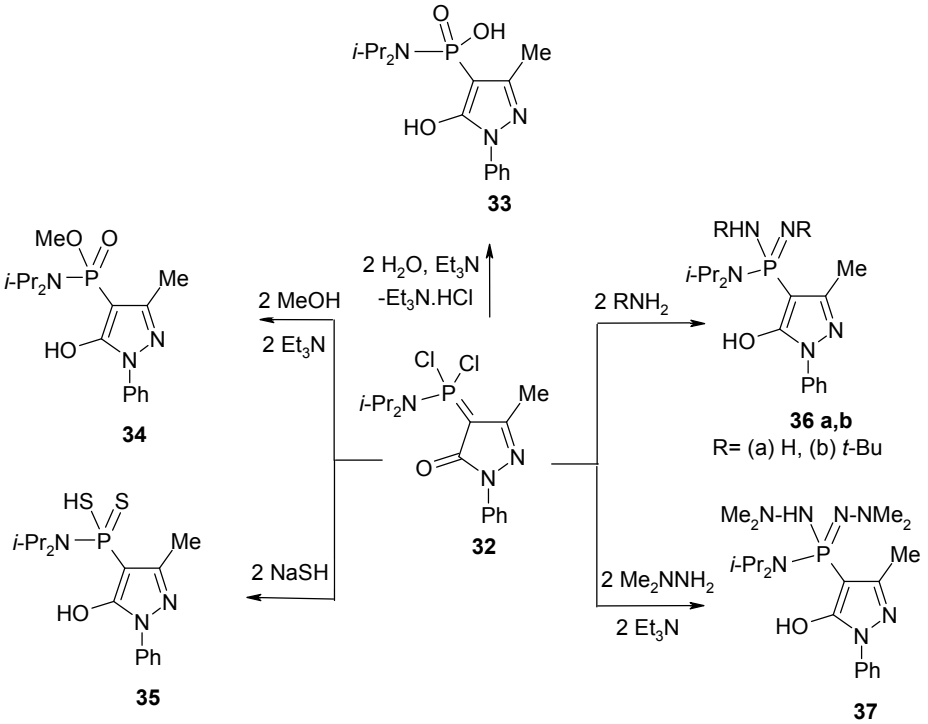
Scheme 10

Treatment of the phosphine derivative **12** with diisopropylamine gave 4-[chloro(diisopropylamino) phosphino]pyrazole (**30**). Chlorination of **30** led to the stable dichlorophosphonium chloride **31**, which underwent transformation into the 4-[dichloro(diisopropylamino)-λ^5-phosphanylidene]-3-methyl-1-phenyl-5*H*-pyrazol-5-one (**32**), as a result of dealkylation through loss of ethyl chloride (Scheme 11).[30]



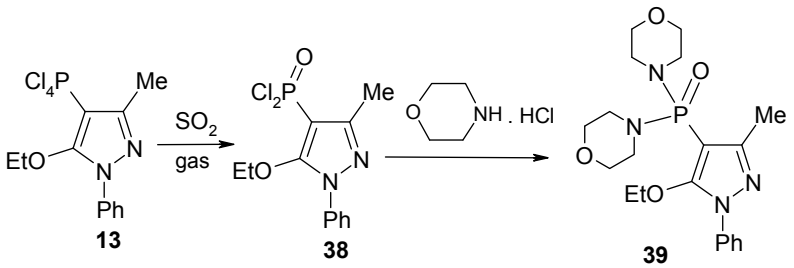
Scheme 11

Further, the chlorine atoms in the dichloro phosphorus ylide **32** at the electrophilic phosphorus atom could readily be substituted by various groups through interaction with O-, N-, and S-nucleophiles, giving the corresponding compounds **33-37** (Scheme 12).[30]



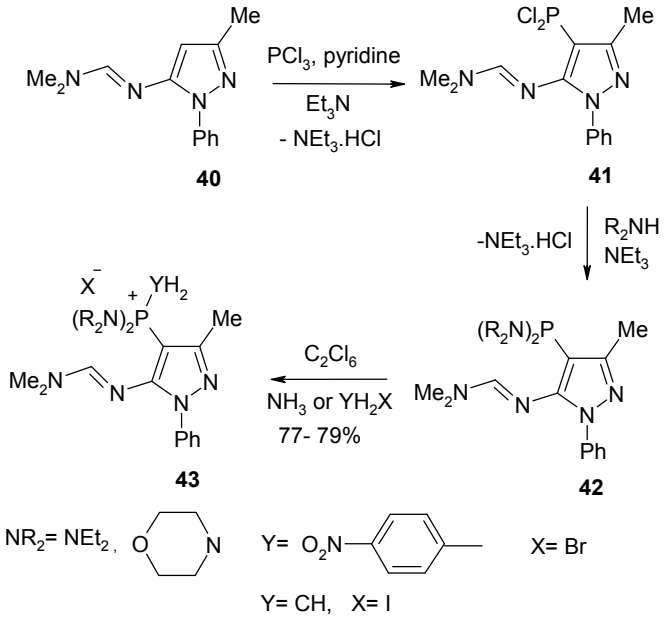
Scheme 12

The sulfur dioxide gas was bubbled through the reaction mixture of compound **13** to give 5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl-phosphonic dichloride (**38**), which was transformed into 4-[5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(4-morpholinyl)phosphoryl]morpholine (**39**), by its reaction with morpholine hydrochloride in the presence of aprotic solvent (Scheme 13).[30]



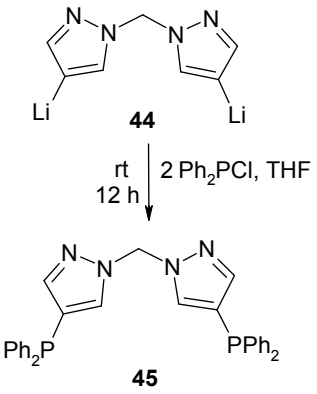
Scheme 13

It was found that dichlorophosphino moiety was successfully introduced into the 4-position of the pyrazole ring using N^1,N^1-dimethyl-N^2-5-pyrazolylformamidine **40** as the model system. Thus, reaction of compound **40** with phosphorus trichloride in the presence of pyridine and triethylamine gave 4-[5-(3-methyl-1,3-diazobut-1-enyl)-3-methyl-1-phenyl]pyrazolyl-dichlorophosphine (**41**). The latter compound was treated with secondary amine to give *bis*(dialkylamino)phosphines **42** which were transformed into the corresponding phosphonium salts **43** by the action of methyl iodide and/or 4-nitrobenzyl bromide (Scheme 14).[31]



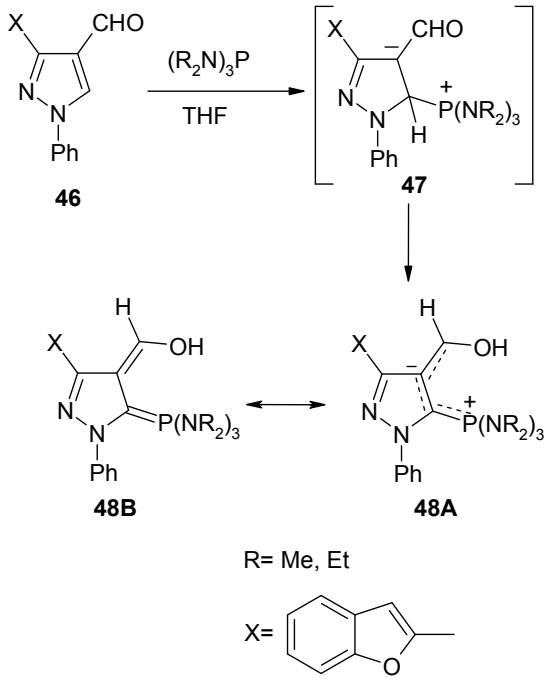
Scheme 14

Treatment of the 4-lithiated *bis*-pyrazole **44** with chlorodiphenylphosphine in THF gave *bis*-(4-{diphenylphosphinyl}-1*H*-pyrazole)methane (**45**). This compound was used as a ligand with some metals as Hg, Sn….etc (Scheme 15).[32]



Scheme 15

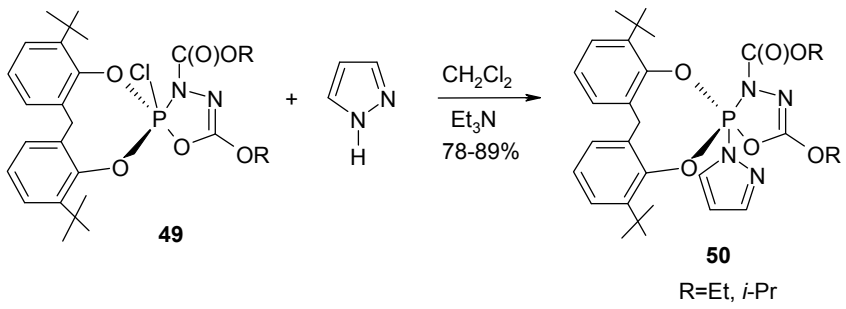
The reactions of *tris*(dimethylamino)phosphine with the aldehyde **46** proceeded smoothly in THF to afford *tris*-aminophosphonium dipolar ion structure **48A,B**. Nucleophilic attack of the phosphines at *C*-5 of the α,β-unsaturated system in the aldehyde **46** afforded the *C*-phosphonium betaine **47**, which followed by further hydrogen migration to give the more stable ylide enol structure **48A,B** (Scheme 16).[33]



Scheme 16

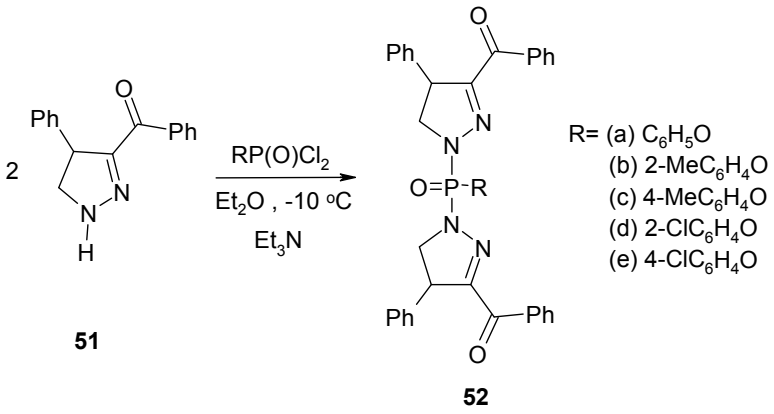
2.1.2. *N*-Phosphorylation of pyrazole rings

Reaction of compound **49** with pyrazole in dichloromethane in the presence of triethylamine as a base afforded 5-alkoxy-2,2-methylenediphenol-2-(1*H*-pyrazol-1-yl)-1,3,4,2-λ^5-oxadiazaphosphole-3(2*H*)-carboxylic ester **50** (Scheme 17).[34]



Scheme 17

Condensation of two molecules of 3-benzoyl-4-phenyl-2-pyrazoline (**51**) with various alkyl/aryl phosphorodichloridate in diethyl ether in the presence of triethylamine resulted in the formation of alkyl/aryl *bis*(3-benzoyl-4,5-dihydro-4-phenyl-1*H*-pyrazol-1-yl)phosphinates **52a-e** (Scheme 18).[35]

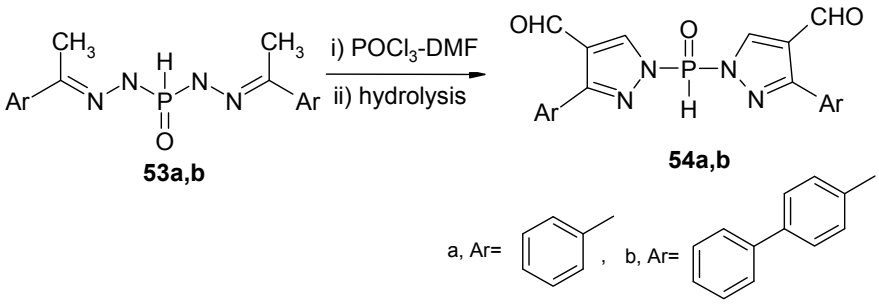


Scheme 18

2.2. RING CLOSURE OF ACYCLIC PHOSPHORUS COMPOUNDS WITH ELECTROPHILIC AND NUCLEOPHILIC REAGENTS INTO PHOSPHONOPYRAZOLES

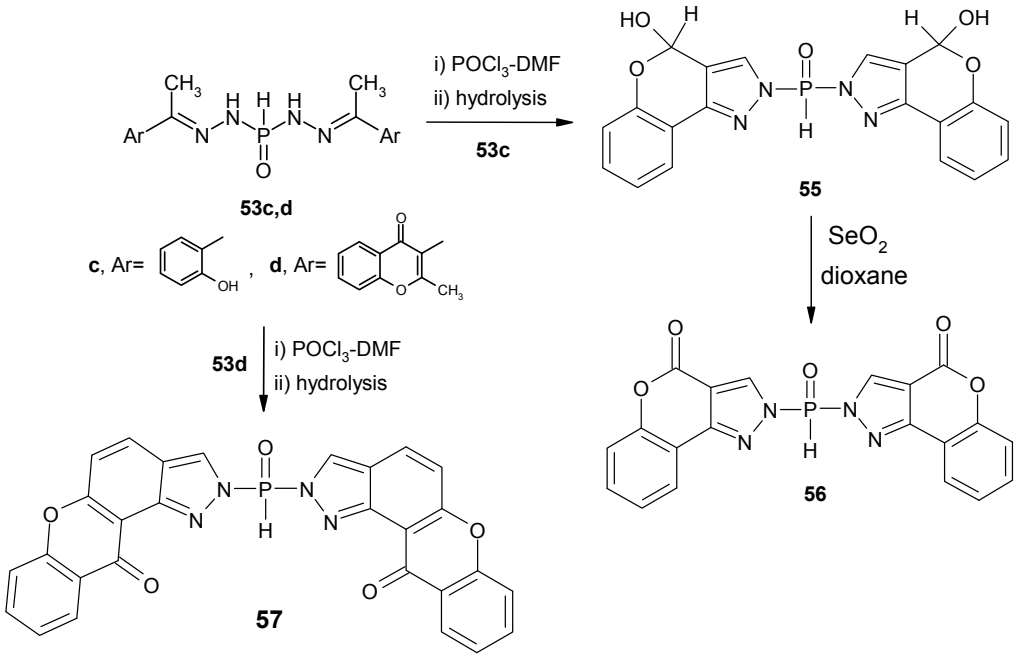
2.2.1. Cyclization of phosphonic dihydrazones

A convenient procedure for the synthesis of 4-formylpyrazole derivatives is based on the Vilsmeier-Haack reactions with methyl ketone aryl hydrazones. Thus, application of Vilsmeier-Haack reaction on phosphonic dihydrazones **53a,b** afforded *bis*-{4-formyl-3-aryl-1*H*-pyrazol-1-yl}phosphine oxides (**54a,b**) (Scheme 19).[36]



Scheme 19

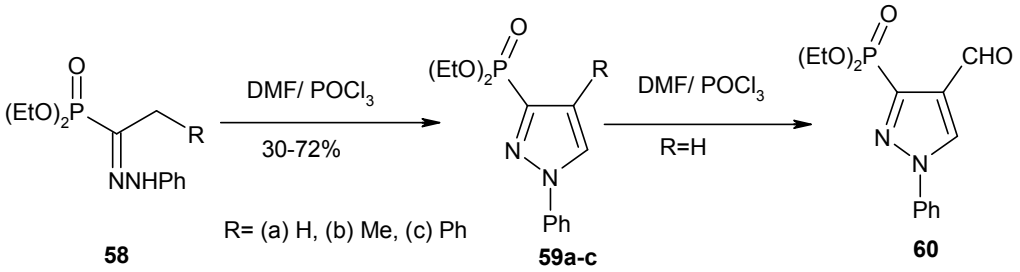
Similarly, application of the Vilsmeier-Haack reaction on phosphonic dihydrazones **53c,d** which contain active functional groups in *ortho* positions that led to new fused pyrazole systems. Thus, when phosphonic dihydrazone **53c** was treated with Vilsmeier reagent afforded a red crystalline product namely, *bis*-{4-hydroxy-2,4-dihydrochromeno[4,3-*c*]pyrazol-2-yl}phosphine oxide (**55**). The oxidation reaction of **55** with selenium dioxide in dry dioxane yielded *bis*-{chromeno[4,3-*c*]pyrazol-4-oxo-2-yl}phosphine oxide (**56**) (Scheme 20).[36] Consequently, the effect of Vilsmeier reagent on the phosphonic dihydrazone **53d** afforded *bis*-{chromeno[2,3-*g*]indazol-11-oxo-2-yl}phosphine oxide (**57**) in moderate yield (Scheme 20). This transformation involved monoformylation at each methyl group of **53d**, followed by two steps of cyclization process.[36]



Scheme 20

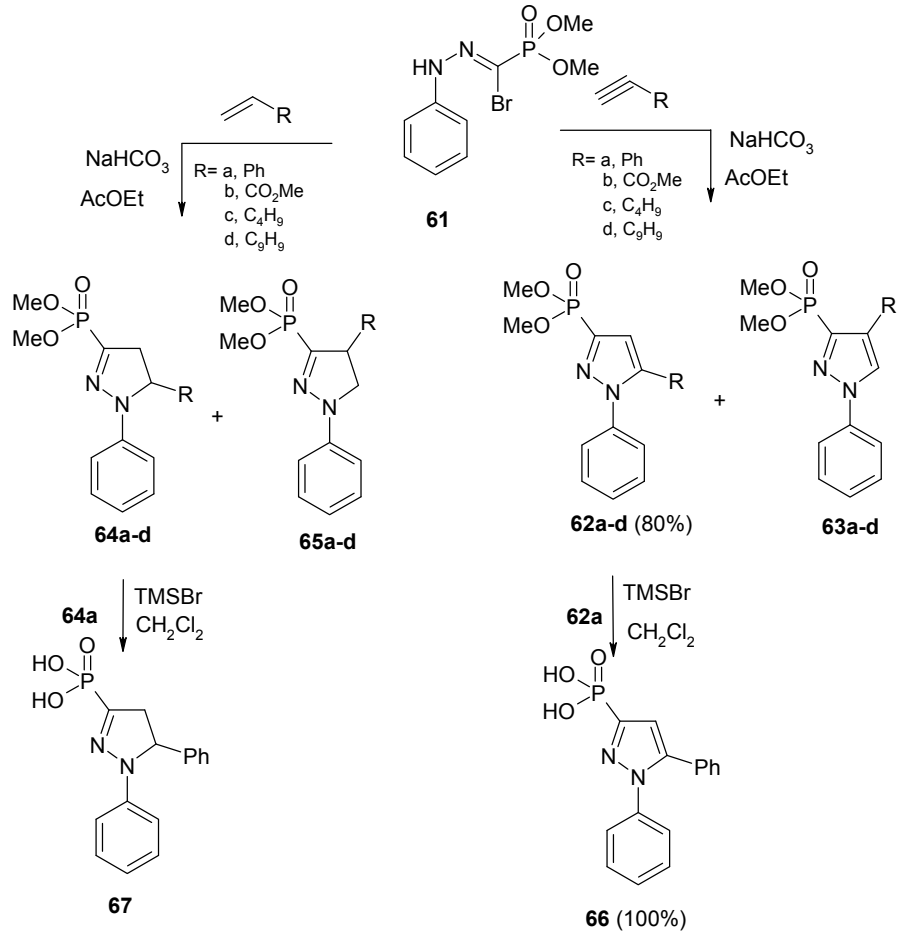
2.2.2. Cyclization of α-hydrazonomethylphosphonate

The reaction of phosphonyl hydrazones **58** with the Vilsmeier reagent (DMF/$POCl_3$) in equimolar ratio afforded 1-phenyl-3-diethoxyphosphonyl pyrazoles **59**. Compound **59a** underwent formylation *via* its reaction with another mole of the Vilsmeier reagent to give the corresponding aldehyde **60** (Scheme 21).[37]



Scheme 21

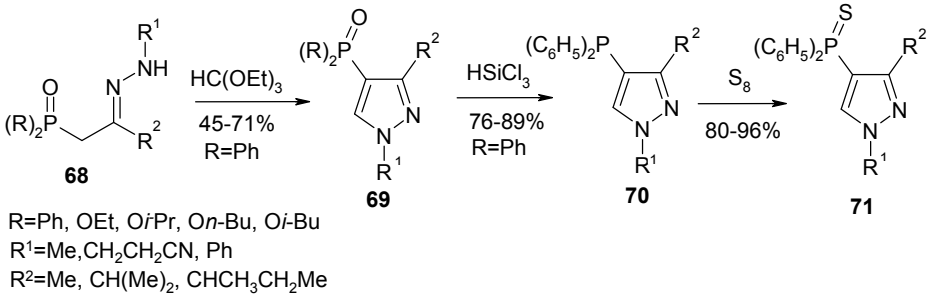
Dimethyl[bromo(phenylhydrazono)methyl]phosphonate (**61**) underwent cycloaddition reaction with different alkynes to give a mixture of 3-pyrazolylphosphonates **62a-d** and **63a-d**, while its reaction with alkenes afforded a mixture of 3-pyrazolinylphosphonates **64a-d** and **65a-d**. Also, their phosphonic acids, 1,5-diphenyl-1*H*-pyrazole-3-phosphonic acid (**66**) and 1,5-diphenyl-4,5-dihydro-1*H*-pyrazole-3-phosphonic acid (**67**) were obtained in quantitative yield *via* hydrolysis of the diesters **62a** and **64a**, respectively, with a 10 fold excess of trimethylsilyl bromide in methylene chloride (Scheme 22).[38]



Scheme 22

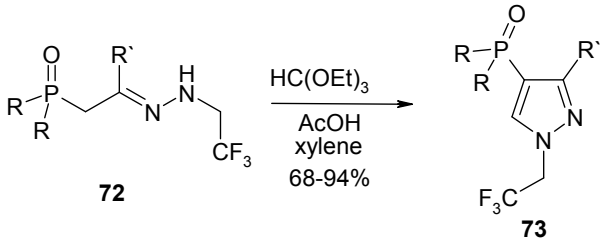
2.2.3. Cyclization of β-hydrazonomethylphosphonate

Cyclization of β-hydrazonophosphonate **68** with triethyl orthoformate yielded 4-phosphopyrazoles **69**. Furthermore, reaction of **69** with $HSiCl_3$ led to pyrazoles **70**, which underwent sulfuration by sulfur to afford **71** (Scheme 23).[39]



Scheme 23

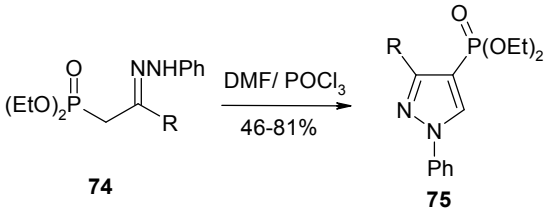
Similarly, cyclization of some *N*-(2,2,2-trifluoroethyl)-β-phosphonate hydrazones **72** into the corresponding 4-phosphonopyrazoles **73** was achieved *via* their reaction with triethyl orthoformate in xylene containing few drops of glacial acetic acid (Scheme 24).[40]



R = Ph, -$OCH_2C(Me)_2CH_2O$-, -$OCH_2C(Me)(C_3H_7)CH_2O$-
R` = $CH(Me)_2$, $CH(C_6H_{11})_2$, $CH(i\text{-}C_3H_7)$, Ph

Scheme 24

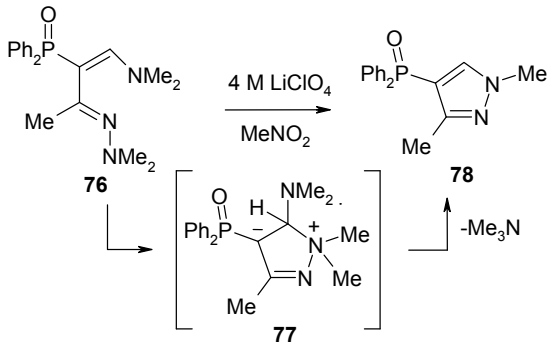
1-Phenyl-4-diethoxyphosphonylpyrazoles **75** were obtained by reaction of phosphonyl ethylene hydrazones **74** with Vilsmeier reagent (Scheme 25).[37]



R= H, Me, Ph

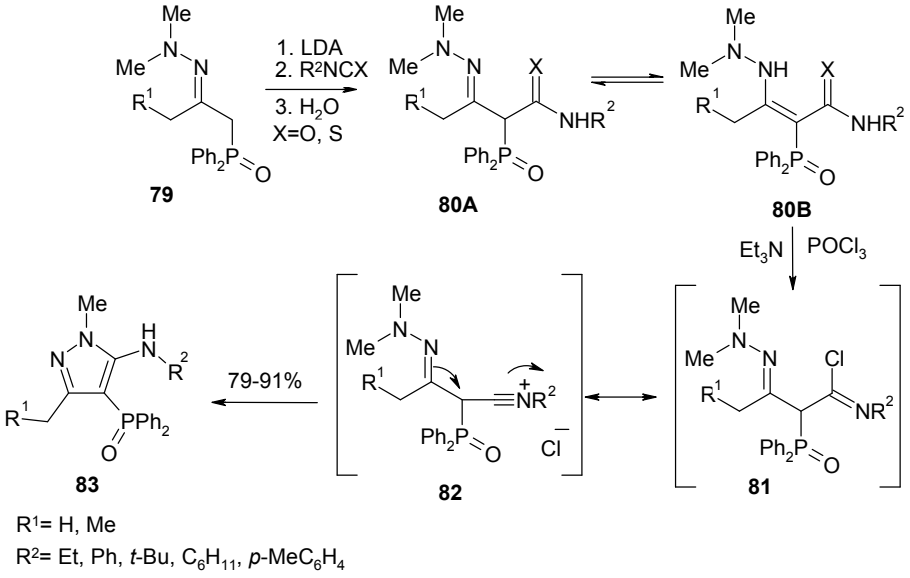
Scheme 25

Palacios *et al.*,[41] explored the behavior of substrate **76** in the presence of $LiClO_4$ as a catalyst. Addition of $LiClO_4$ to [3-(dimethylhydrazono)-2-(diphenylphosphinoyl)but-1-enyl]dimethylamine (**76**) in the presence or even in the absence of dienophile and using nitromethane as a solvent led to the formation of 4-(diphenylphosphinoyl)-1,3-dimethyl-1*H*-pyrazole (**78**). The formation of this pyrazole **78** could be explained by intramolecular cyclization involving nucleophilic attack of the dimethylamino group at *N*-1 to the carbon–carbon double bond to give pyrazolidine **77** which underwent loss of trimethylamine to afford the 4-phosphorylated pyrazole **78** (Scheme 26).



Scheme 26

Treatment of β-hydrazono phosphine oxides **79** with lithium diisopropylamide (LDA) in THF followed by addition of isocyanates or isothiocyanates and aqueous work-up giving the functionalized phosphine oxides **80A,B**. Compounds **80A,B** were reacted with phosphoryl chloride in the presence of triethylamine led to the formation of diphenyl (5-aminopyrazol-4-yl)phosphine oxides (**83**) (Scheme 27).[42]

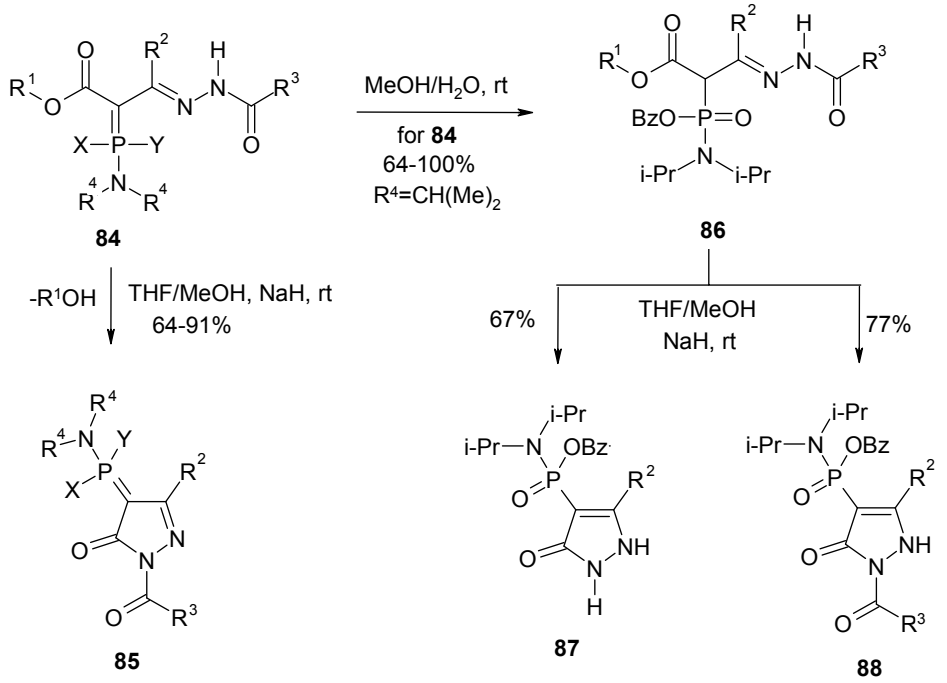


Scheme 27

The phosphoranylidene hydrazones **84** could be easily converted into the corresponding 5-oxo-4-phoshoranylidene-4,5-dihydro-1*H*-pyrazoles **85** by treatment with a catalytic or a stoichiometric amount of sodium hydride in a mixture of tetrahydrofuran/methanol (1:1) at room temperature. Compounds **86** could also be obtained by hydrolytic cleavage of **84** (R^4 =*i*-Pr), by magnetically stirring in methanol/water (95:5) at room temperature (Scheme 28). The hydrazone derivatives **86** have proven once again their synthetic utility as they were converted in good yields into (3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)phosphonamidates **87** and **88** by treatment with a catalytic amount of sodium hydride in tetrahydrofuran/methanol (1:1). The formation of 2-unsubstituted 3-oxo-pyrazole **87** took place by base-promoted hydrolytic cleavage of the aminocarbonyl group linked to the nitrogen atom at the 2-position of the pyrazole ring (Scheme 28).[43]

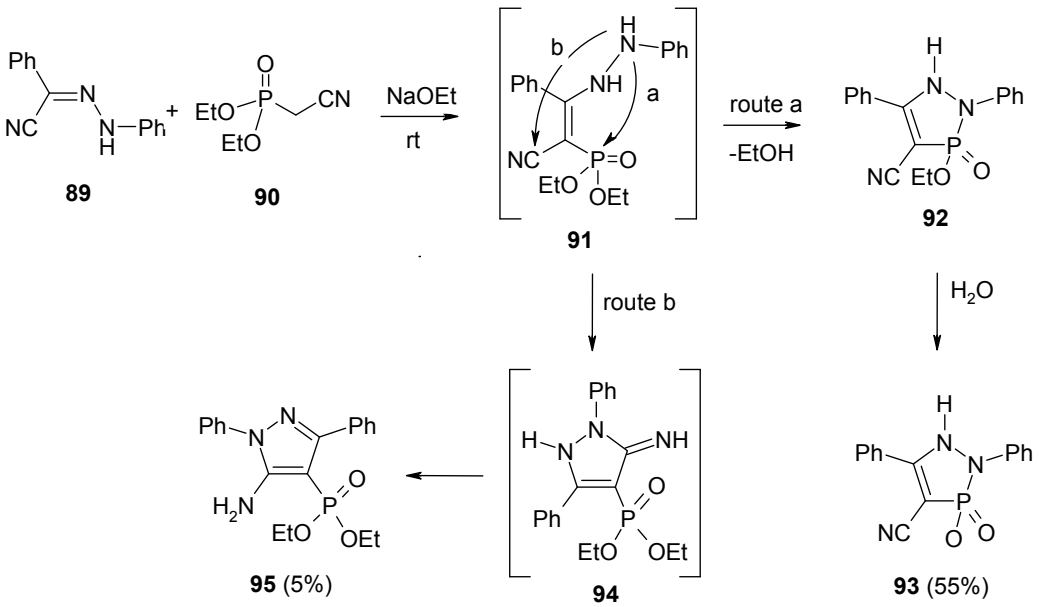
2.2.4. Cyclization of α-cyanomethylphosphonate

Treatment of phenyl hydrazone **89** with diethylphosphonoacetonitrile (**90**) in sodium ethoxide at room temperature with stirring afforded two different products namely, 4-cyano-2,5-diphenyl-1,2,3-diazaphosphole (**93**) (route a) and diethyl 5-amino-1,3-diphenylpyrazol-4-ylphosphonate (**95**) (route b) (Scheme 29).[44]



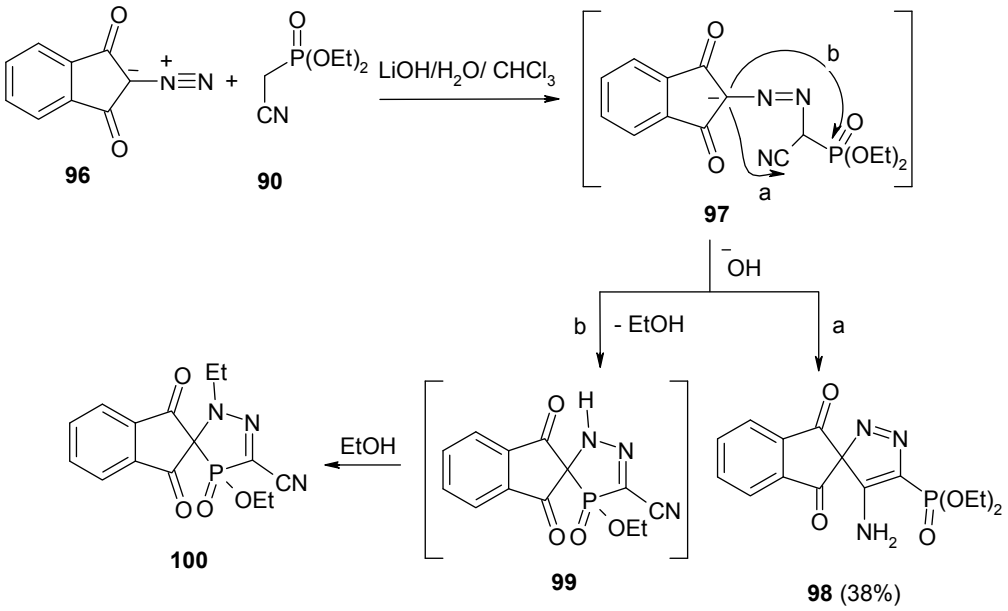
R^1= Me, Et, R^2= Me, Et, X= OMe, OBn, $N(R^4)_2$, Y= OBn, $N(R^4)_2$, R^4= Me, *i*-Pr

Scheme 28



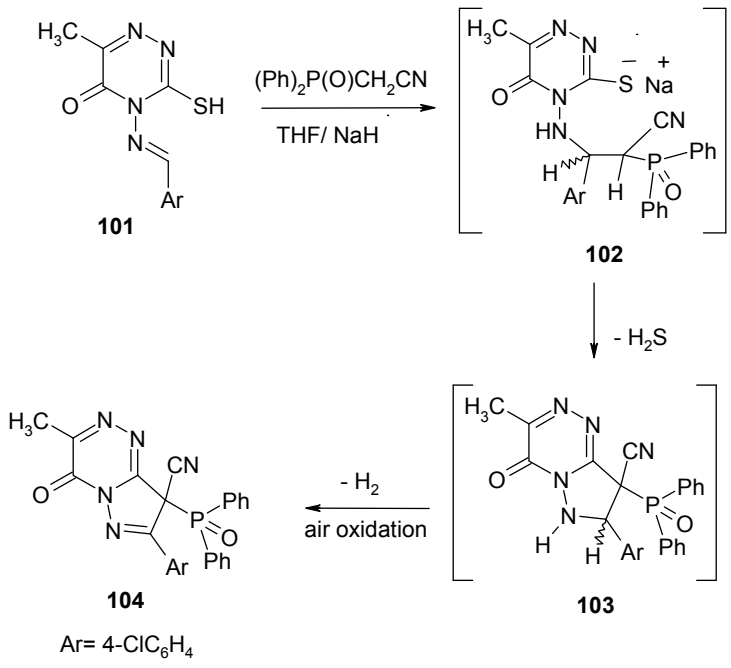
Scheme 29

2-Diazo-1,3-indandione (**96**) was treated with a little excess of molar amount of diethyl cyanomethyl-phosphonate (**90**) in a mixture of $LiOH/H_2O/CHCl_3$ at room temperature then heated for 30 h at the reflux temperature to give diethyl (4`-amino-1,3-dioxo-1,3-dihydrospiro[indene-2,3`-pyrazol]-5`-yl) phosphonate (**98**) and 4-ethoxy-1-ethyl-1,3-dioxo-1,2,3,4-tetrahydrospiro[1,2,4]diazaphosphole-5,2`-indene]-3-carbonitrile-4-oxide (**100**) (Scheme 30).[45]



Scheme 30

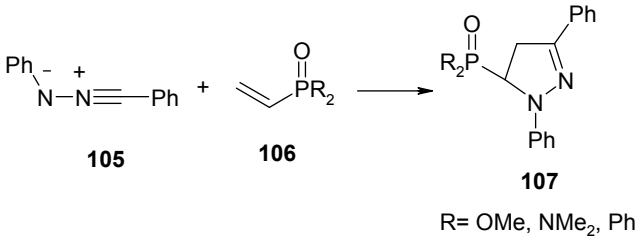
Meanwhile, the Schiff base **101** was heated under reflux with diphenylphosphoryl acetonitrile for 12 h in THF in the presence of sodium hydride as a catalyst to afford 7-(4-chlorophenyl)-8-(diphenylphosphoryl)-3-methyl-4-oxo-4,8-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (**104**) (Scheme 31). This reaction pathway proceeds *via C*-nucleophilic attack by the reactive methylene of diphenylphosphoryl acetonitrile on the N–N=CH–Ar moiety to give the intermediate **102** which underwent cyclization by elimination of one molecule of H_2S followed by an air oxidation process (Scheme 31).[46]



Scheme 31

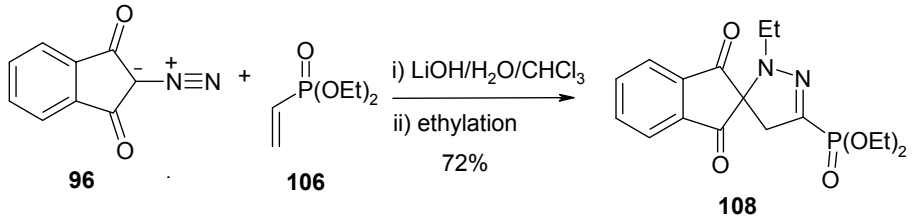
2.2.5. Cyclization of α,β-unsaturated phosphonate

An alternative route to dihydropyrazole phosphorus compounds **107** was provided in the addition of the nitrile imine **105** to vinylphosphorus compounds **106** (Scheme 32).[47]



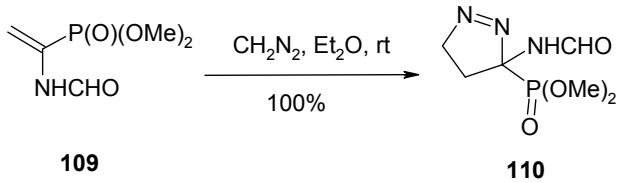
Scheme 32

Reaction of 2-diazo-1,3-inandione (**96)** with diethyl vinylphosphonate (**106**) was proceeded in the presence of ($LiOH/H_2O/CHCl_3$) to produce diethyl (1`-ethyl-1,3-dioxo-1,2`,3,4`-tetrahydrospiro-[indene-2,5`-pyrazol]-3`-yl)phosphonate (**108**) (Scheme 33). Compound **108** showed high antibacterial activity towards *B. tumefaciens*, *S. aureus*, *K. pneumoniae*, *A. niger*, *A. flavus* and *P. crysogenous*.[45]



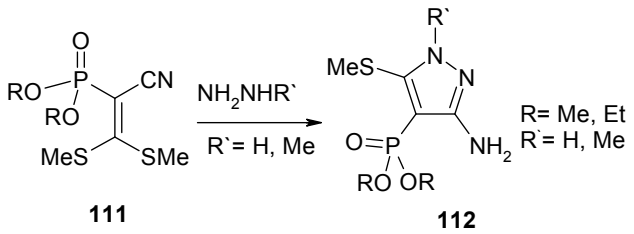
Scheme 33

Also, it was found that the cycloaddition of diazomethane onto dimethyl 1-(formylamino)-ethylenephosphonate (**109**) smoothly proceeds in ether at room temperature to furnish dimethyl 3-(formylamino)-4,5-dihydro-3H-pyrazol-3-phosphonate (**110**) in a quantitative yield (Scheme 34).[48]



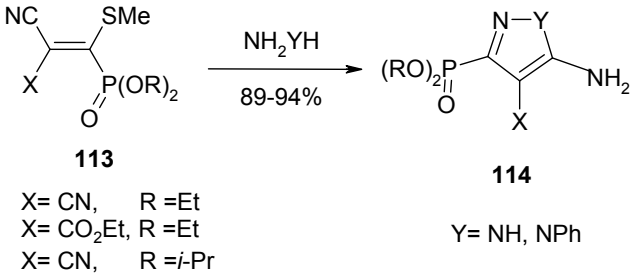
Scheme 34

Dialkyl (1-cyano-2,2-bismethylsulfanylvinyl)phosphonates (**111**) reacted with hydrazines to yield the 4-pyrazolylphosphonates **112** (Scheme 35).[49]



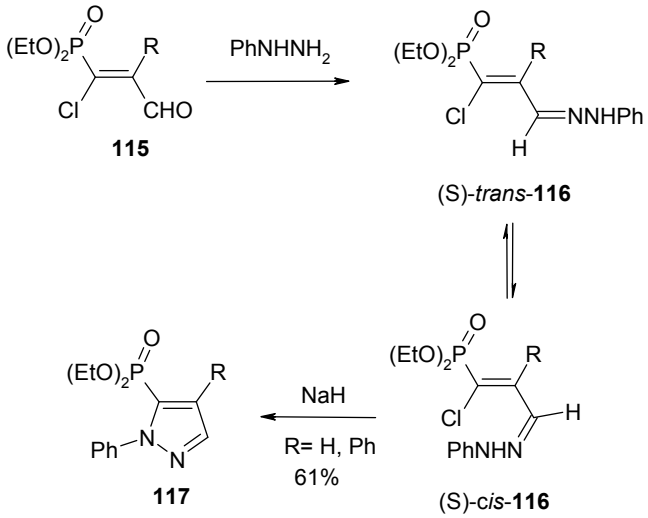
Scheme 35

Similarly, cyclization reaction of dialkyl (2-cyano-2-substituted-1-methylsulfanylvinyl)phosphonates **113** with some hydrazines to construct the phosphonylpyrazoles **114** were achieved under carefully controlled reaction temperature (Scheme 36).[50]



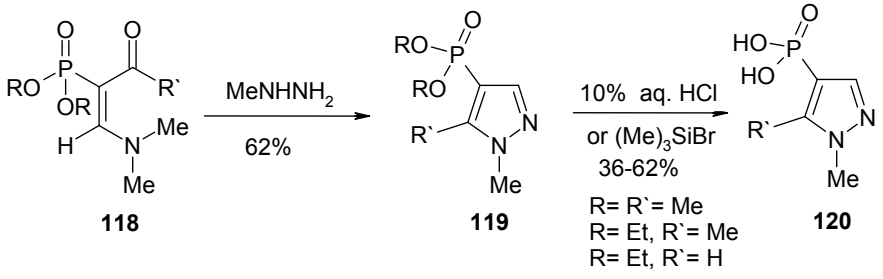
Scheme 36

1-Phenyl-5-diethoxyphosphonyl pyrazoles **117** were readily prepared by the action of phenylhydrazine on **115** in the presence of sodium metal (Scheme 37).[37]



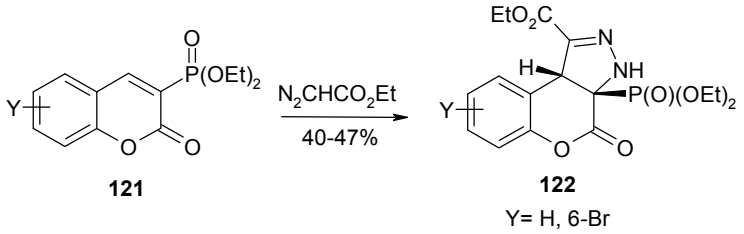
Scheme 37

Also, the phosphonic enamines **118** were reacted with methylhydrazine to provide (1-methyl-1*H*-pyrazol-4-yl)phosphonates **119**. The hydrolysis of the phosphonates **119** could be affected either with HCl or bromotrimethylsilane to give the corresponding (1-methyl-1*H*-pyrazol-4-yl)phosphonic acids **120** (Scheme 38).[51]



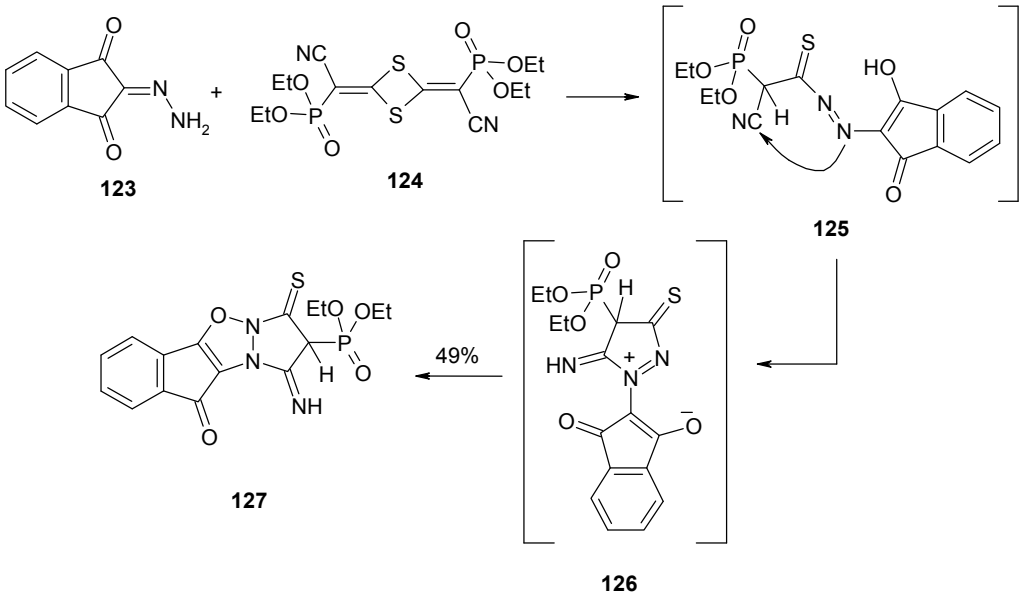
Scheme 38

The reaction of 3-phosphonocoumarins **121** with an excess of ethyl diazoacetate in benzene or chloroform at room temperature for 60 days afforded ethyl 3a-(diethoxyphosphoryl)-4-oxo-3,3a,4,9b-tetrahydrochromeno[3,4-*c*]pyrazole-1-carboxylates (**122**) in moderate yields (Scheme 39).[52]



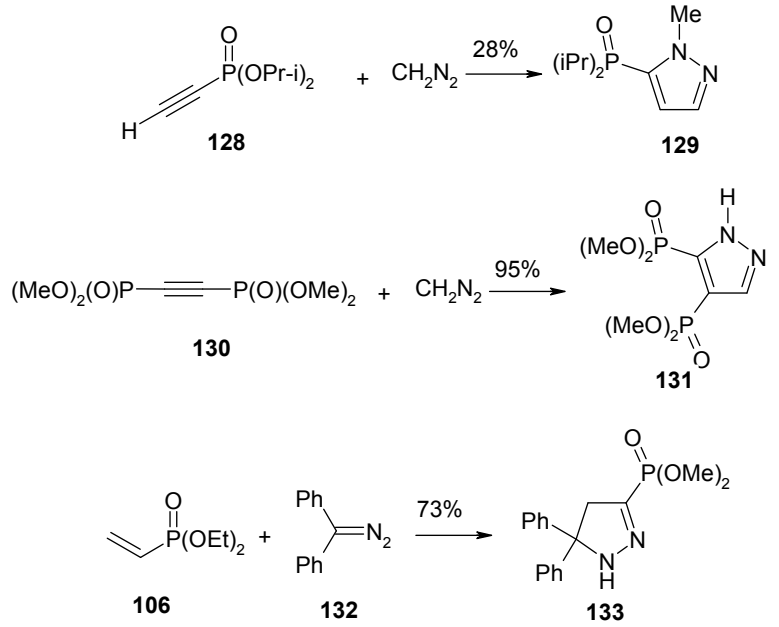
Scheme 39

On treating 1,3-indandion-2-hydrazone (**123**) with 1,3-dithietane **124**, gave the unexpected diethyl 2-imino-3*H*-4-thioxo(11,12-dihydroindan-10-one)[12,11-*a*](5,13,1-oxadiazole)[13,1-*b*](1,13-pyrazole-3-yl)phosphonate (**127**). The formation of the product **127** could be rationalized by the generally accepted mechanism of the initial formation of the reactive intermediate **125** to give the oxadiazole **127** *via* the dipolar intermediate **126** (Scheme 40).[53]



Scheme 40

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles with alkenes was used in the synthesis of heterocyclic phosphorus derivatives in two different ways: the first in which the phosphorus substituent is present in the alkene (or alkyne) and the second in which it was attached to the 1,3-dipole. Diisopropyl ethynyl phosphonate (**128**) upon reaction with diazomethane was converted into the pyrazolyl phosphonate **129** in 28% yield.[54] The ethynyldiphosphonate **130** was converted into the diphosphonyl pyrazole **131** in 95% yield in a similar reaction with diazomethane.[55] Also, at low temperatures diphenyldiazomethane (**132**) was added to diethyl vinylphosphonate (**106**) to yield dihydropyrazolyl-phosphonate **133** in 73% yield (Scheme 41).[56]



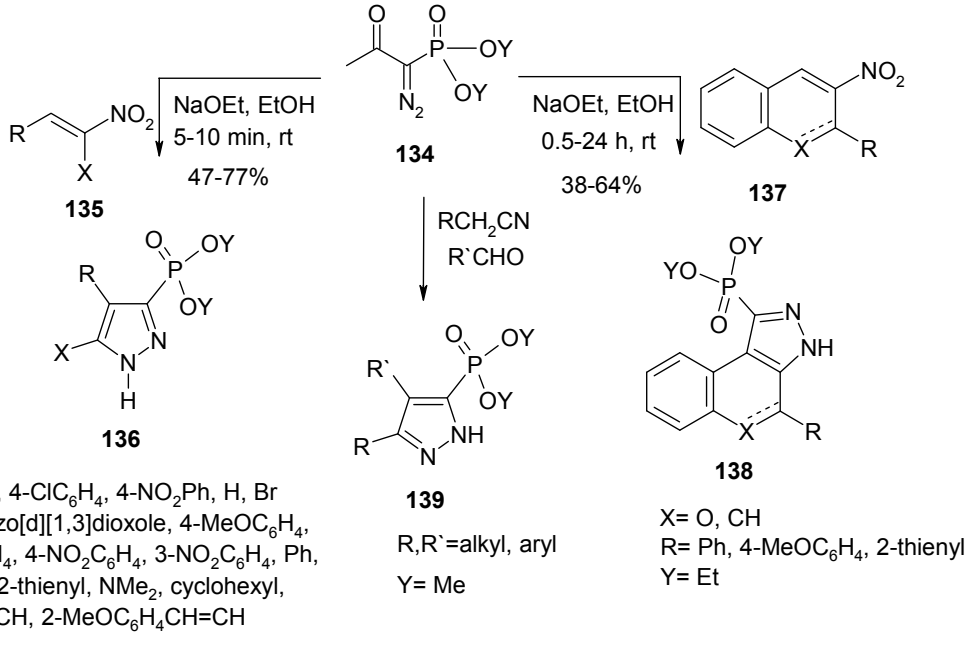
Scheme 41

2.2.6. Cyclization of α-diazomethylphosphonate

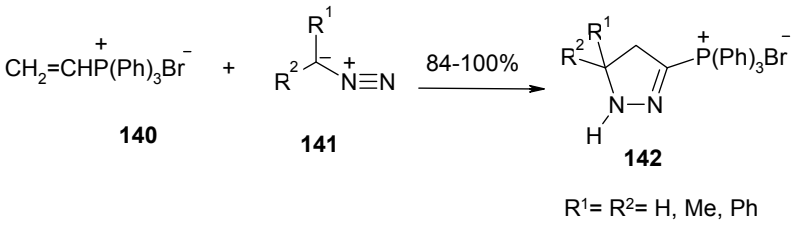
1,3-Dipolar cycloaddition of the anion of diethyl 1-diazo-methylphosphonate, generated *in situ* from diethyl 1-diazo-2-oxopropylphosphonate (**134**) (Bestmann-Ohira reagent), with conjugated nitroalkenes **135** provided regioisomerically pure phosphonylpyrazoles **136** in moderate to good yields. These pyrazoles were formed in one-pot *via* spontaneous elimination of the nitro group. However, nitropyrazoles could be synthesized by the same strategy using α-bromonitroalkenes. The methodology worked for the synthesis of phosphonylpyrazoles **138** fused to other carbo- and heterocycles as well (Scheme 42).[57,58] Similarly, recently a new multicomponent reaction allowed to give the regioselctive synthesis of phosphonopyrazoles **139** by combination an aldehyde, cyano acid derivative and diethyl 1-diazo-2-oxopropylphosphonate (**134**) (Scheme 42).[59]

2.2.7. Cyclization of triphenylphosphonium halide salts

5-Alkyl/aryl substituted 2-pyrazolin-3-yltriphenylphosphonium salts **142** were prepared from vinyl triphenylphosphonium bromide (**140**) and substituted diazomethanes **141** in high yields (Scheme 43).[60,61]

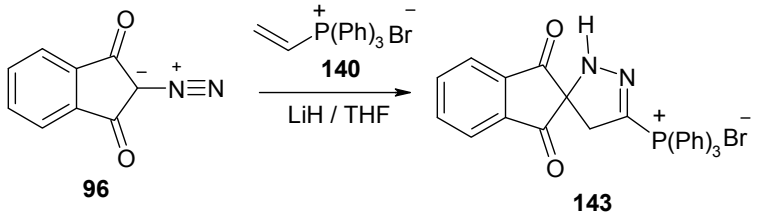


Scheme 42



Scheme 43

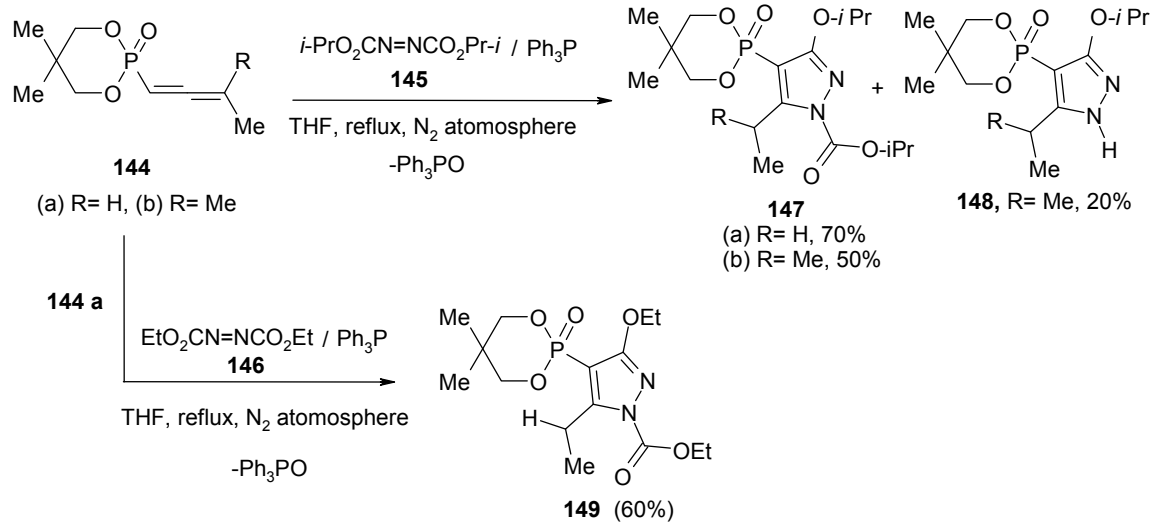
1,3-Dipolar cycloaddition reaction between 2-diazo-1,3-indandione (**96**) and vinyl triphenyl phosphonium bromide (**140**) in basic medium, led to the corresponding phosphonium salt **143** (Scheme 44).[62]



Scheme 44

2.2.8. Cyclization of allenyl phosphonate

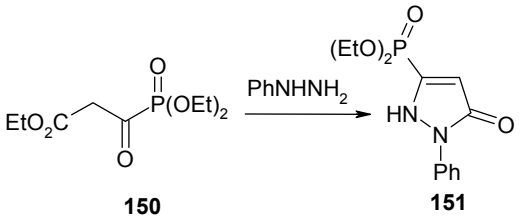
Recently, the phosphorane-promoted addition of dialkyl azodicarboxylates ROCN=NCO$_2$R [R= Et (DEAD) or *i*-Pr (DIAD)] was elegantly utilized to generate new pyrazole derivatives. Thus, reaction of allenes **144** with dialkyl azodicarboxylates **145** and **146** was performed in the presence of triphenylphosphine to afford the 4-phosphonopyrazoles **147-149** (Scheme 45).[63]



Scheme 45

2.2.9. Cyclization of 1,3-dicarbonylphosphonate

1,3-Dicarbonylphosphonate **150** was condensed with phenylhydrazine to give the pyrazoline phosphonate **151** in low yield (Scheme 46).[64]

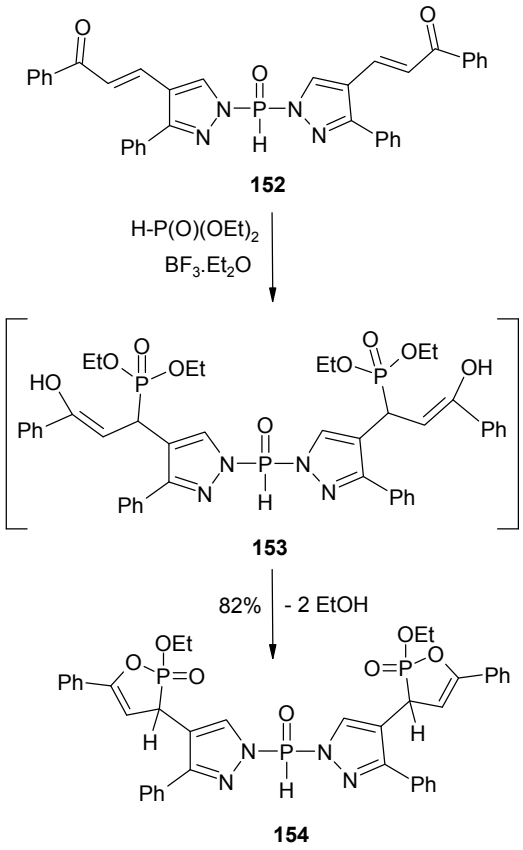


Scheme 46

2.3. SYNTHESIS OF ISOLATED AND FUSED PHOSPHORUS HETEROCYCLIC SYSTEMS CONTAINING PYRAZOLES RINGS

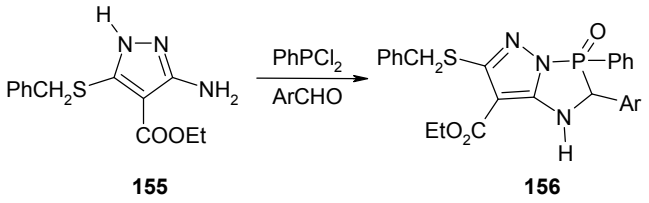
2.3.1. Five-membered rings

It was found that the one-pot reaction of *bis*-chalcone **152** with diethyl phosphite in the presence of $BF_3.Et_2O$ at 80 ^oC for 8 h, afforded *bis*-{[2-ethoxy-2-oxo-5-phenyl-2,3-dihydro-1,2-oxaphosphol-3-yl]-3-phenyl-1*H*-pyrazol-1-yl}phosphine oxide (**154**) (Scheme 46). The proposed mechanism involved an initial Michael type addition of phosphorus atom of diethyl phosphite to the activated double bond in compound **152** followed by cyclization via elimination of ethanol molecules to give **154** (Scheme 47).[36]



Scheme 47

The cyclization reaction of 3-amino-5-benzylthio-4-ethoxycarbonylpyrazole (**155**) with phenylphosphonus dichloride and aromatic aldehydes gave 2-aryl-6-benzylthio-7-ethoxycarbonyl-3-phenyl-2,3-dihydro-1*H*-pyrazolo[5,1-*e*][1,4,2]diazaphosphole-3-oxides **156** (Scheme 48).[65]

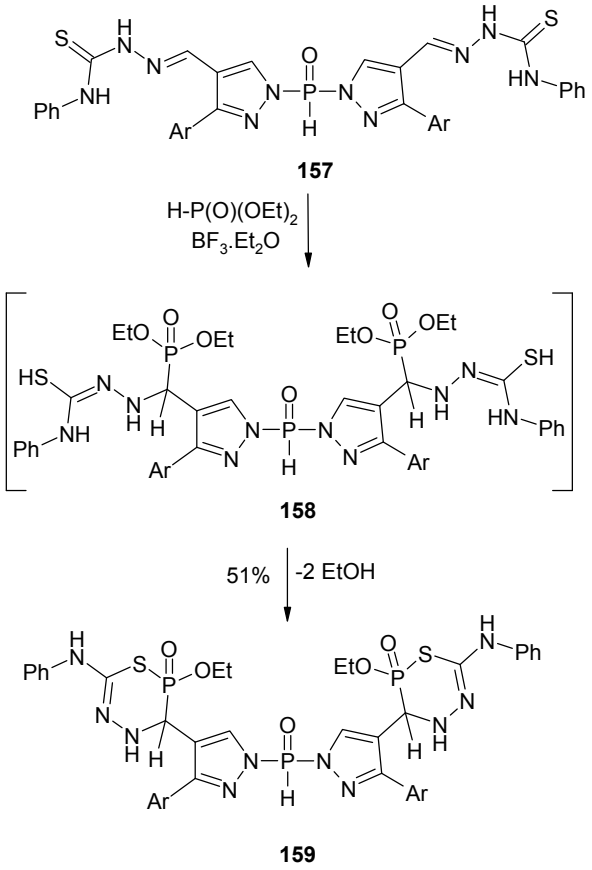


Ar=Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

Scheme 48

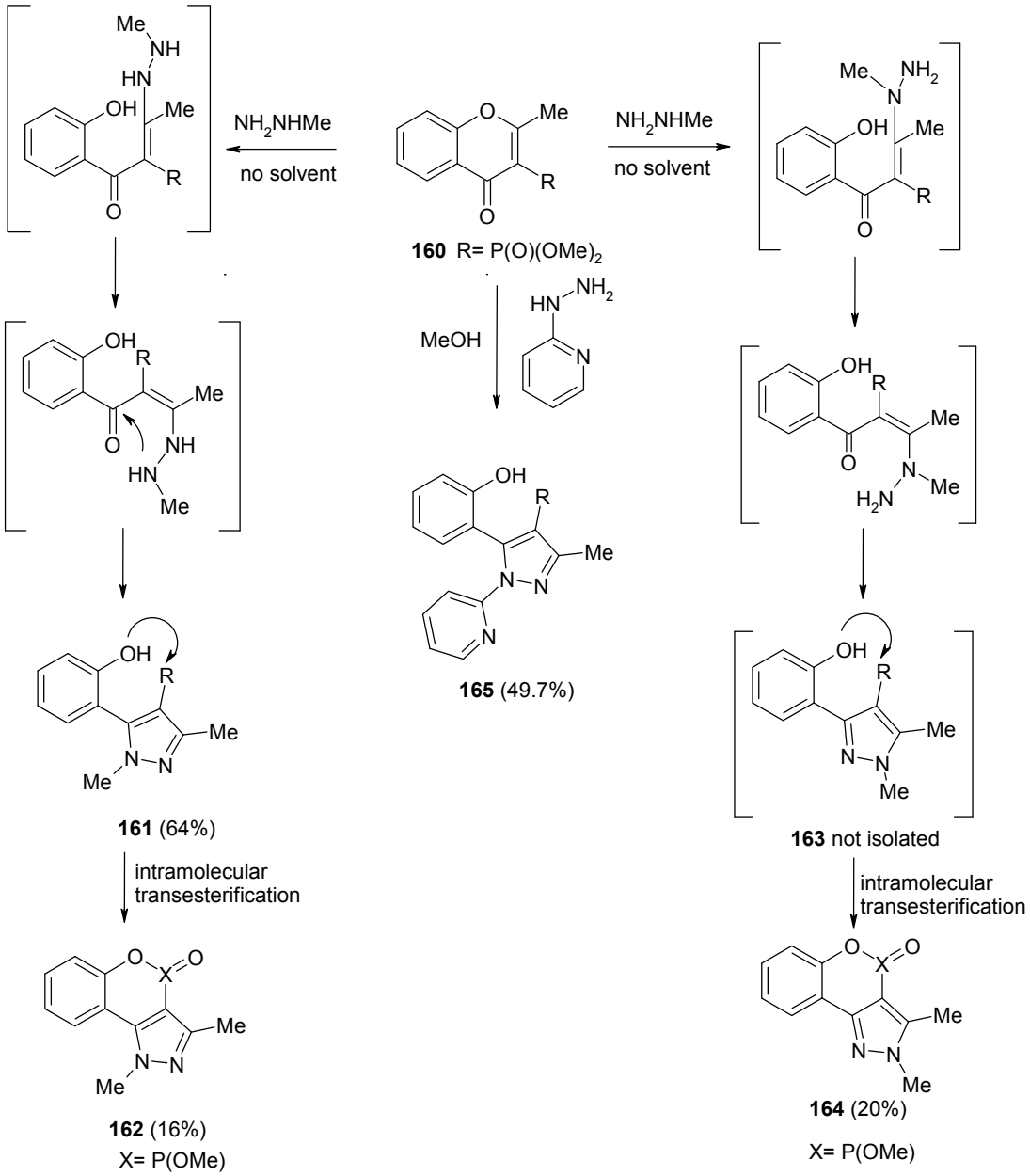
2.3.2. Six-membered rings

Abdel-Ghaffar *et al.*[36] have reported that heterocyclization of *bis*-thiosemicarbazone **157** with diethyl phosphite at 80 °C in the presence of $BF_3.Et_2O$ for 10 h, afforded an interesting type of phosphorus heterocycle, namely *bis*-{3-(4`-biphenyl)-4-[2-ethoxy-6-phenylamino-2-oxo-3,4-dihydro-2*H*-1,4,5,2-thiadiazaphosphinin-3-yl]-1*H*-pyrazol-1-yl}phosphine oxide (**159**) (Ar= 4`-biphenyl) (Scheme 49). The formation of **159** may be occurred *via* addition of phosphorus atom of diethyl phosphite to $CH=N_{exocyclic}$ groups to give the nonisolable intermediate **158**, which underwent cyclization by nucleophilic attack of SH groups at phosphonate groups to eliminate two molecules of ethanol (Scheme 49).[36]



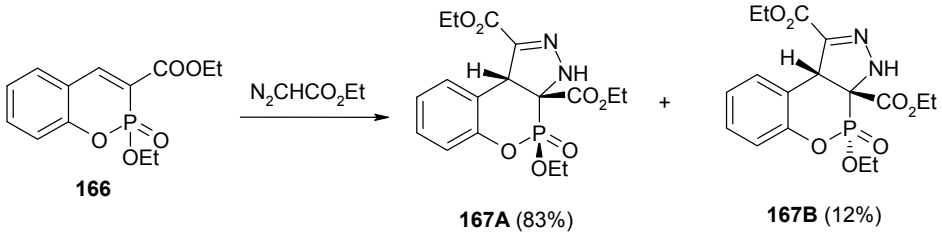
Scheme 49

Reaction of dimethyl-4-oxo-4*H*-chromen-3-ylphosphonate (**160**) with an equimolar amount of methyl-hydrazine, performed on a larger scale without any solvent, gave three isolated products. The major product, 5-(2-hydroxyphenyl)-1,3-dimethyl-4-phosphonyl-substituted pyrazole **161** was isolated from the reaction mixture by addition of acetone, while the two other products were separated chromatographically from the remaining mixture. The second reaction product **162** was originated from an analogous cyclization of **161** in the lowest yield. Unexpectedly, no isomeric 3-(2-hydroxyphenyl)-1,5-dimethyl-4-phosphonyl-substituted pyrazole **163** was obtained. Instead, compound **164** was isolated in 20% yield. Probably **163**, formed in the first step of the reaction, was unstable under the chromatographic conditions and underwent intramolecular cyclization giving rise to **164** (Scheme 50). The reaction proceeded according to the general mechanism described for the reaction of chromone with nitrogen nucleophiles, including hydrazines. Attack of a nitrogen nucleophile at *C*-2 of the chromone led to the opening of the γ-pyrone ring. Similarly, reaction of **160** with 2-hydrazinopyridine in methanolic solution afforded 5-(2-hydroxybenzoyl)-3-methyl-1-(2-pyridinyl)-1*H*-pyrazol-4-phosphonic acid dimethyl ester (**165**). Compounds **161** and **165** reacted with Pt(II), Cu(II) and Pd(II) salts forming metal complexes which showed low cytotoxic activity against human acute leukemia HL-60 and NALM-6 and melanoma WM-115 cell lines. The cytotoxic effect of its palladium and platinum complexes are rather low (Scheme 50).[66-69]



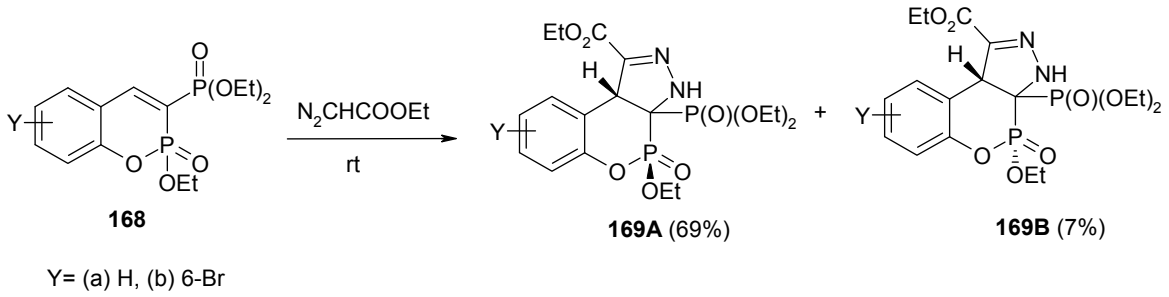
Scheme 50

Two diastereoisomeric 1,3a-diethoxycarbonyl-4-ethoxy-4-oxo-3,9b-dihydro-4,5-benzoxaphosphorino-[3,4-*c*]pyrazoles (**167A**,**B**) were isolated from reaction of 3-ethoxycarbonyl-1,2-benzoxaphosphorine (**166**) with ethyl diazoacetate. Compounds **167A,B** are epimers towards phosphorus atom of the oxaphosphole ring (Scheme 51).[52]



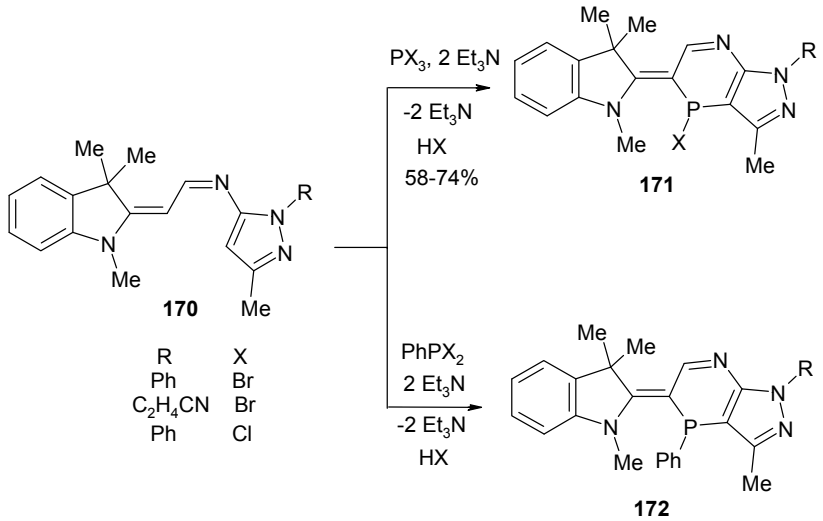
Scheme 51

Also, the 1,3-dipolar cycloaddition of ethyl diazoacetate to 1,2-benzoxaphosphorin-3-phosphonates **168a,b** proceeded with the formation of two epimeric methylenebisphosphonates **169A** and **B** (Scheme 52).[52]



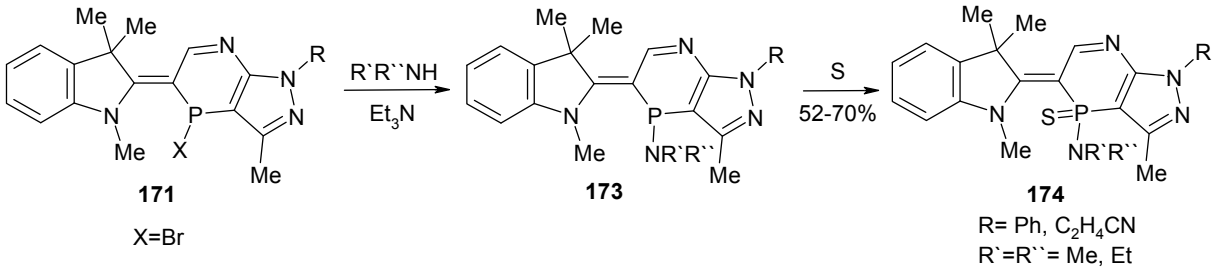
Scheme 52

The *C*-phosphorylation of 1,3,3-trimethyl-2-(3-methyl-1-(cyanoethyl/phenyl)-5-pyrazolylimino-ethylidene)indolines **170** with phosphorus trihalide and dibromo(phenyl)phosphine proceeded simultaneously at the two nucleophilic carbon centers to result in the pyrazoloazaphosphinines **171** and **172**, respectively. The cyclization was most effective when conducted in dichloromethane in the presence of triethylamine as the base (Scheme 53).[70]



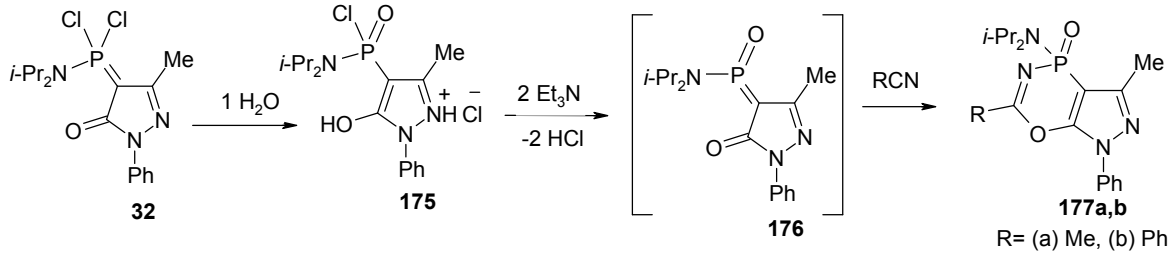
Scheme 53

The cyclic bromophosphines **171** easily reacted with secondary amines and anilines to give unstable aminophosphines **173** identified by NMR spectra. The latter compound was transformed to stable 3-methyl-4-morpholino-1-substituted-5-(1,3,3-trimethyl-2,3-dihydro-1*H*-2-indolylidene)-4,5-dihydro-1*H*-4λ^5-pyrazolo[3,4-*b*][1,4]azaphosphinine-4-thione **174** *via* reaction with sulfur element (Scheme 54).[70]



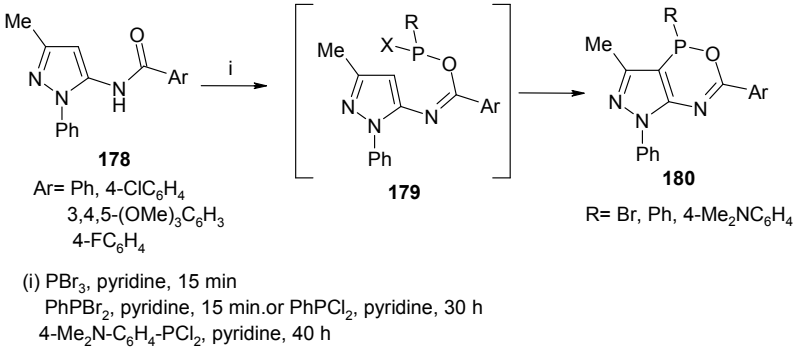
Scheme 54

5-Hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl-*N*,*N*-diisopropyl phosphonamidic chloride hydrochloride (**175**) was obtained *via* partial hydrolysis of the dichloride **32**. The reaction of **175** with triethylamine led to the abstraction of hydrogen chloride in the presence of aceto- or benzonitrile to afford a new type of phosphorus containing heterocyclic system namely, 1-(diisopropylamino)-3,8-dimethyl-5-phenyl-1,5-dihydro-1λ^5-pyrazolo[4,3-e][1,3,4]oxazaphosphorin-1-one (**177**) suggesting the formation of diisopropylaminophosphorus ylide **176** as an intermediate (Scheme 55).[30]

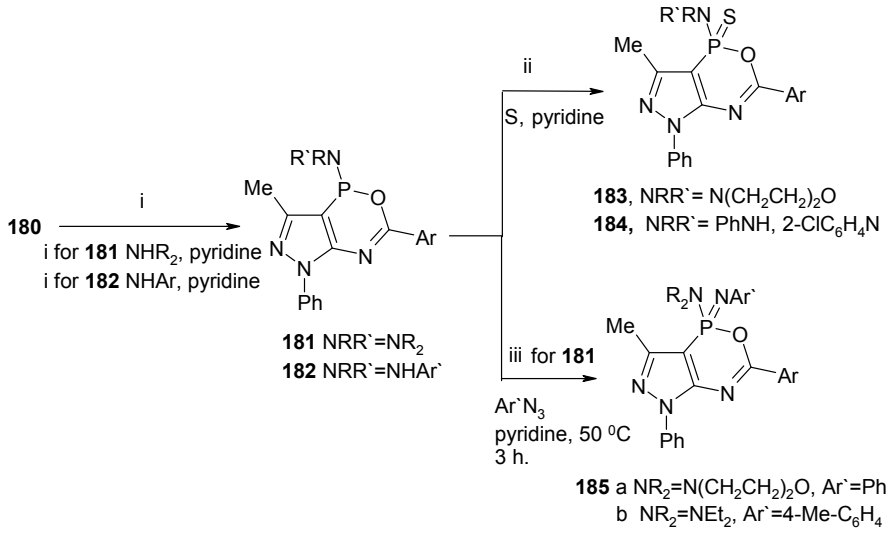


Scheme 55

Reaction of 1-aryl-5-arylcarboxamidopyrazoles **178** with phosphorus trihalide gave pyrazolo[4,3-*c*]-[1,5,2]oxazaphosphinines **180**, which were formed through the acyclic *O*-phosphorylated intermediate **179** (Scheme 56). Upon treatment with secondary aliphatic amines or anilines, cyclic bromoanhydrides **180** underwent halogen substitution yielding amides **181** and **182** respectively, which could be oxidized with elemental sulfur to give air-stable cyclic thioamides **183** and **184**. Also, the amides **181** reacted with some arylazides to give the iminoamides **185** (Scheme 57).[71]

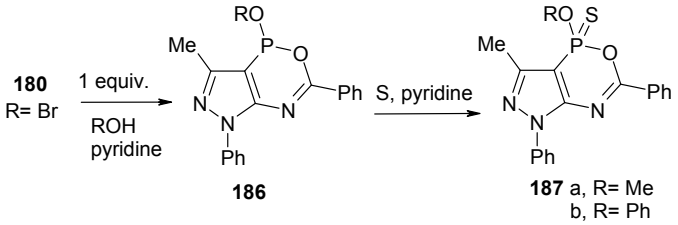


Scheme 56



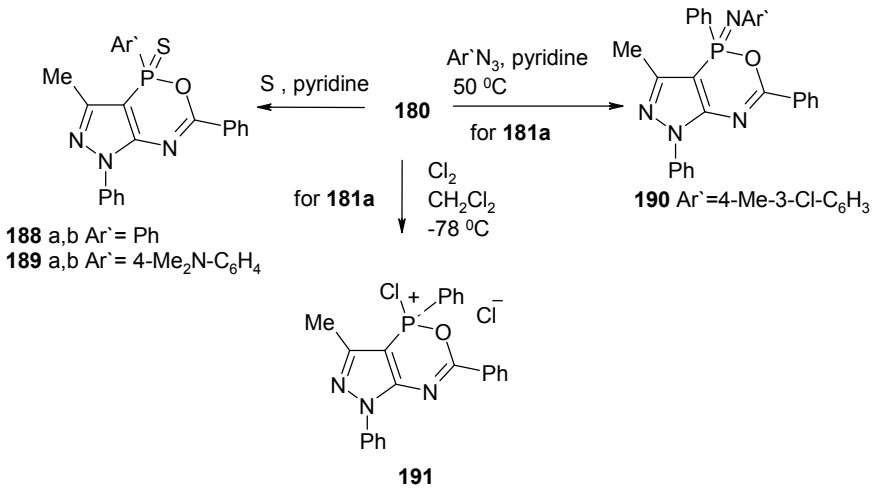
Scheme 57

Also, bromoanhydrides **180** (R=Br) reacted with equivalent amount of alcohol or phenol giving the corresponding cyclic esters **186**, which were oxidized with elemental sulfur to give the thioesters **187** (Scheme 58).[71]



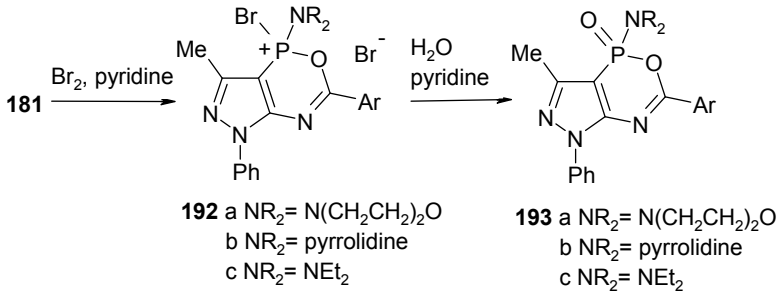
Scheme 58

Cyclic phosphines **180** (R=Ph) could also be transformed into air-stable derivatives of phosphorus (v). Thus, they were oxidized into thioxides **188** and **189** by elemental sulfur and iminated with arylazides to cyclic phosphaza compounds **190**. Also, cyclic phosphine **180** reacted with chlorine giving the chlorophosphonium chloride **191** (Scheme 59).[71]



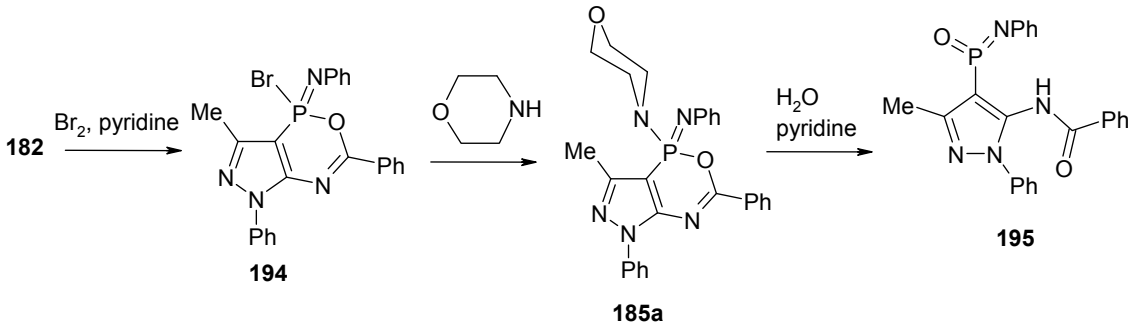
Scheme 59

Bromination of amides **181** gave the bromophosphonium bromides **192** which were hydrolyzed with water in the presence of a base giving cyclic phosphorus (v) amides **193** (Scheme 60).[71]



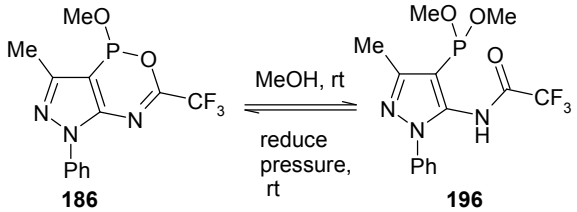
Scheme 60

Also, bromination of anilides **182** led to bromophosphaza compound **194**, which was reacted with morpholine affording the iminoamide **185a**. The latter compound underwent hydrolysis in aqueous pyridine to yield the 5-carboxamidopyrazole **195** (Scheme 61).[71]



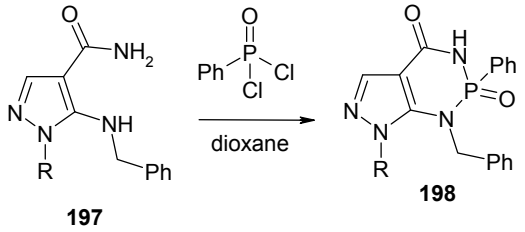
Scheme 61

It should be noted that reaction of opening cyclic esters with an excess of alcohol was reversible. It was found during an attempt to isolate acyclic ester **196** that it was stable in methanol solution in the absence of water and oxygen, however under evaporating methanol in vacuo cyclic ester **186** was obtained (Scheme 62).[71]



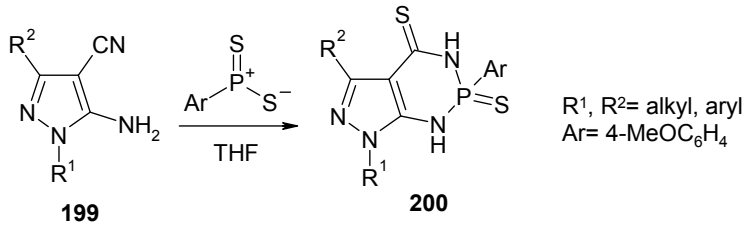
Scheme 62

When 1-substituted 5-benzylamino-4-pyrazolecarboxamides **197** were reacted with phenylphosphonic dichloride in dioxane, 7-alkyl-1-benzyl-2-phenyl-2-oxido-1,2,3,7-tetrahydro-4*H*-pyrazolo[3,4-*d*][1,3,2]-diazaphosphinin-4-one **198** was produced (Scheme 63).[72]



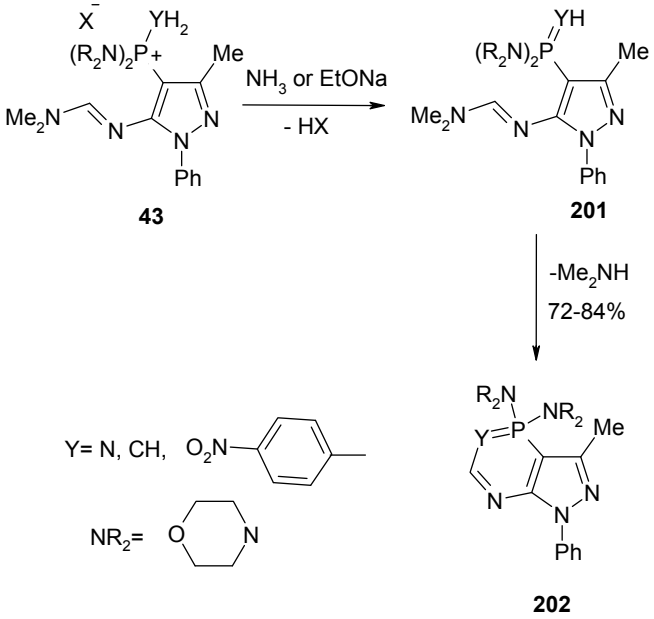
Scheme 63

The pyrazolodiazaphosphinethione **200** was also achieved in high yield from treatment of aminocyanopyrazole **199** with Lawesson's reagent in THF (Scheme 64).[73]



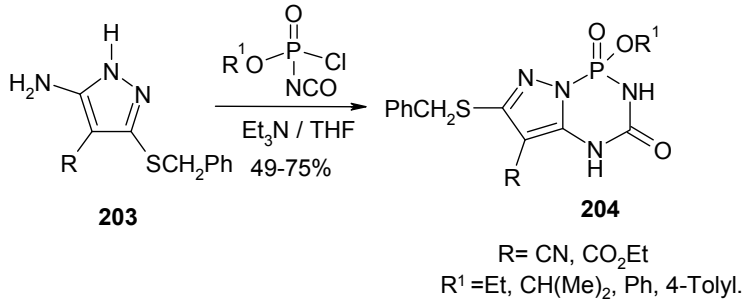
Scheme 64

The phosphonium salts **43** reacted with ammonia or sodium ethoxide to give the corresponding phosphorus ylides **201**, which underwent intramolecular nucleophilic substitution *in situ* to form pyrazolo[5,4-*b*]azaphosphinines **202** (Scheme 65).[31,74]



Scheme 65

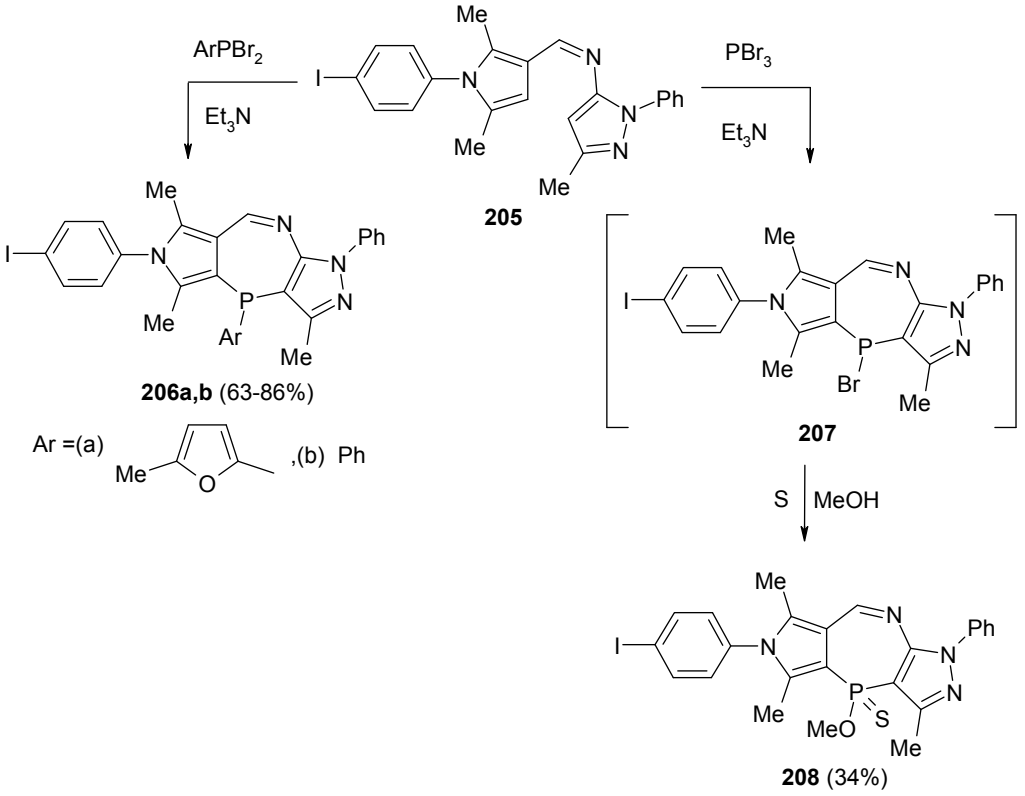
6-Benzylthio-5-alkyl-1-alkoxy/aryloxy-1-oxido-1,2-dihydropyrazolo[1,5-*c*][1,3,5,2]triazaphosphinin-3-(4*H*)-ones **204** were synthesized by reaction of 3-benzylthio-5-aminopyrazoles **203** with alkyl phosphorochloroiso-cyanates in THF in the presence of Et_3N (Scheme 66).[75,76]



Scheme 66

2.3.3. Seven and higher-membered rings

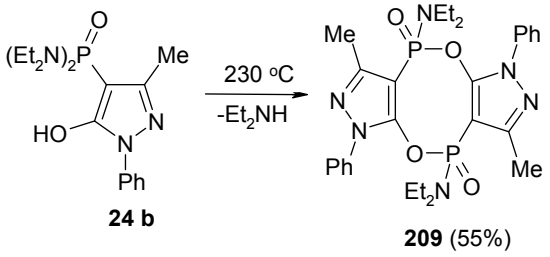
Treatment of *N*-[1-(1-*p*-iodophenyl-2,5-dimethyl-3-pyrrolyl)methylidene]-*N*-(3-methyl-1-phenyl-1*H*-5-pyrazolyl)amine **205** with dibromoarylphosphines provided 6-(*p*-iodophenyl)-3,5,7-trimethyl-4-(substituted)-1-phenyl-4,6-dihydro-1*H*-pyrazolo[3,4-*b*]pyrrolo[3,4-*e*][1,4]azaphosphepine (**206a,b**). Further, reaction of **205** with phosphorus tribromide in pyridine in the presence of sulfur element and methanol afforded 6-(*p*-iodophenyl)-4-methoxy-3,5,7-trimethyl-1-phenyl-4,6-dihydro-1*H*-4Δ^5-pyrazolo-[3,4-*b*]pyrrolo[3,4-*e*]azaphosphepine-4-thione (**208**), through the formation of azaphosphepine **207** as intermediate (Scheme 67).[77]



Scheme 67

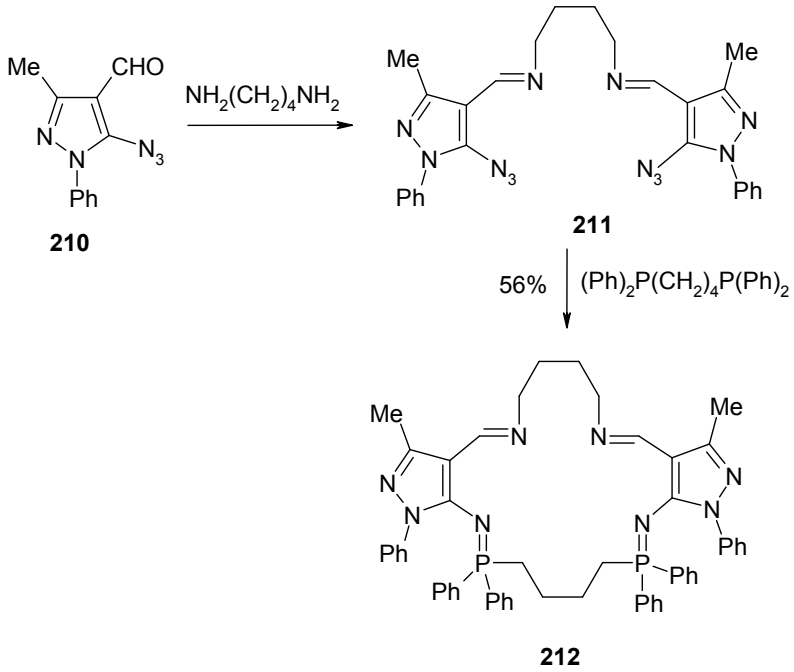
5-Hydroxy-3-methyl-1-phenylpyrazolyl-4-phosphonic tetraethyldiamide (**24b**) was found to display unusual chemical behavior. Thus, on heating it to 230 ^{o}C under vacuum, one molecule of diethylamine was eliminated to give 3,8-dimethyl-1,6-diphenyl-4,9-dioxo-4,9-*bis*-(diethylamino)-4,5,9,10-

tetrahydro[1,5,2,6]dioxadiphosphocino[3,4-*d*:7,8-*d*]dipyrazole (**209**) (Scheme 68).[29]



Scheme 68

The condensation of 5-azido-4-formyl-3-methyl-1-phenyl-1*H*-pyrazole (**210**) with 1,4-diaminobutane in ethanol at room temperature provided the *bis*(azide) **211** in moderate yield, which was treated with 1,4-*bis*(diphenylphosphino)butane affording the 20-membered macrocyclic *bis*(iminophosphorane) **212** as a crystalline solid (Scheme 69).[78]



Scheme 69

CONCLUSION

Phosphorus compounds containing pyrazole rings prove to be of interest for a variety of socially relevant fields: the medicinal and pharmaceutical field, the agrochemical and biochemical field, the field of metal complexation, and so forth. Because of these well-known biological properties of compounds containing pyrazole rings have attracted and are still attracting the attention of many research groups. Their efforts resulted in a vast diversity of synthetic pathways and a better understanding of the reactivities of this class of compounds. During the preparation of this review, we have been trying to sort the different synthetic pathways into general subdivisions based on the used reagents type and cyclization reactions. Some examples of biologically active compounds have already been presented in this review, and from our

point of view, more research in this exciting field will result in even more active examples upon further biotesting.

REFERENCES

1. (a) C. A. Zificsak and D. J. Hlasta, *Tetrahedron,* 2004, **60**, 8991; (b) T. Haino, M. Tanaka, K. Ikeda, K. Kubo, A. Mori, and Y. Fukazawa, *Tetrahedron Lett.,* 2004, **45**, 2277.
2. M. Boyne, C. Stratton, F. Johnson, and P. Tonge, *ACS Chem. Biol*., 2006, **1**, 43.
3. I. V. Magedov, M. Manpadi, S. Van Slambrouck, W. F. A. Steelant, E. Rozhkova, N. M. Przhevalskii, S. Rogelj, and M. Kornienko, *J. Med. Chem.,* 2007, **50**, 5183.
4. G. C. Rovnyak, R. C. Millonig, J. Schwartz, and V. Shu, *J. Med. Chem.,* 1982, **25**, 1482.
5. (a) E. Palaska, M. Aytemir, IT. Uzbay, and D. Erol, *Eur. J. Med. Chem*., 2001, **36**, 539; (b) P. Y. Rajendra, R. A. Lakshmana, L. Prasoona, K. Murali, and K. P. Ravi, *Bioorg. Med. Chem. Lett*., 2005, **15**, 5030.
6. (a) Z. Ozdemir, B. Kandilici, B. Gumusel, U. Calis, and A. Bilgin, *Eur. J. Med. Chem*., 2007, **42**, 373; (b) O. Ruhogluo, Z. Ozdemir, U. Calis, B. Gumusel, and A. Bilgin, *Arzneimittel Forschung*, 2005, **55**, 431.
7. K. L. Hees, J. J. Fitzgerald, K. E. Steiner, J. F. Mattes, B. Mihan, T. Tosi, D. Mondoro, and M. L. McCaleb, *J. Med. Chem.,* 1996, **39***,* 3920.
8. A. Sener, R. Kasımogullari, M. K. Sener, I. Bildirici, and Y. Akcamur, *J. Heterocycl. Chem.*, 2002, **39**, 869.
9. X. H. Liu, P. Cui, B. A. Song, P. S. Bhadury, H. L. Zhu, and S. F. Wang, *Bioorg. Med. Chem.,* 2008, **16**, 4075.
10. E. Akbas and I. Berber, *Eur. J. Med. Chem*., 2005, **40**, 401.
11. P. Schmidt, K. Eichenberger, and M. Wilhelm, *Angew. Chem.,* l96l, **73**, 15.
12. G. A. Wachter, R. W. Hartmann, T. Sergejew, G. L. Grun, and D. Ledergerber, *J. Med. Chem.,* 1996, **39**, 834.
13. M. E. Camacho, J. Leon, A. Entrena, J. Velasco, M. D. Cfrrion, G. Escamaes, A. Vivo, D. Acuna-Castroviego, M. A. Gallo, and A. Espinosa, *J. Med. Chem.*, 2004, **47**, 5641.
14. S. Demirayak, A. S. Karaburum, and R. Beis, *Eur. J. Med. Chem.*, 2004, **39**, 1089.
15. R. Silvestri, M. G. Cascio, G. L. Regina, F. Piscitelli, A. Lavecchia, A. Brizzi, S. Pasquini, M. Botta, E. Novellino, V. D. Marzo, and F. Corelli, *J. Med. Chem.*, 2008, **51**, 1560.
16. M. J. Graneto, R. G. Kurumbail, M. L. Vazquez, H. S. Shieh, J. L. Pawlitz, J. M. Williams, W. C. Stallings, L. Geng, A. S. Naraian, F. J. Koszyk, M. A. Stealey, S. D. Xu, R. M. Weier, G. J. Hanson, R. J. Mourey, R. P. Compton, S. J. Mnich, J. D. Anderson, J. B. Monahan, and R. Devraj, *J. Med.*

Chem., 2007, **50**, 5712.

17. F. Palacios, C. Alonso, and J. M. De Los Santos, *Chem. Rev.*, 2005, **105**, 899.
18. R. Engel, Handbook of Organophosphorus Chemistry; M. Dekker: New York, 1992.
19. P. Kafarski and B. Lejezak, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 1991, **63**, 193.
20. A. D. Y. Toy and E. N. Walsh, Phosphorus Chemistry in Everyday Living; American Chemical Society: Washington DC, 1987; p. 333.
21. Y. Kono, Y. Sato, and Y. Okada, *Pestic. Biochem. Physiol.,* 1983, **20**, 225.
22. J. H. Kim, K. G. Kang, C. K. Park, K. Kim, B. H. Kang, S. K. Lee, and J. K. Roh, *Pestic. Sci.*, 1998, **54**, 237.
23. M. K. Chung, J. C. Kim, and S. S. Han, *Food, Chem. Toxicol.*, 2002*,* **40***,* 723.
24. A. Michaelis and R. Pasternack, *Ber. Dtsch. Chem. Ges.,* 1899, **32**, 2398.
25. I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.,* 1961, **31**, 129 (*Chem. Abstr.,* 1961, **55**, 22292).
26. U. Doeller, M. Maier, A. Kuhlmann, D. Jans, A. M. Pinchuk, A. P. Marchenko, and G. N. Koydan, PCT Int. Appl. WO2005082917, 2005 (*Chem. Abstr.,* 2005, **143**, 261878).
27. A. P. Marchenko, G. N. Koidan, A. N. Kostyuk, A. A. Tolmachev, E. G. Kapustin, and A. M. Pinchuk, *J. Org. Chem.,* 2006, **71**, 8633.
28. A. A. Tolmachev, A. I. Sviridon, and A. N. Kostyuk, *Zh. Obshch. Khim.,* 1993, **63**, 1904.
29. A. A. Tolmachev, A. I. Konovets, A. N. Kostyuk, A. N. Chernega, and A. M. Pinchuk, *Heteroatom Chem.*, 1998, **9**, 41.
30. A. I. Konovets, A. N. Kostyuk, A. M. Pinchuk, A. A. Tolmachev, A. Fischer, P. G. Jones, and R. Schmutzler, *Heteroatom Chem.*, 2003, **14**, 452.
31. G. V. Oshovsky, A. M. Pinchuk, and A. A. Tolmachev, *Mendeleev Commun.,* 1999, **4**, 129.
32. C. Pettinari and R. Pettinari, *Coordination Chem. Rev.*, 2005, **249**, 663.
33. W. M. Abdou, R. F. Barghash, and M. S. Bekheit, *Monatsh. Chem.,* 2011, **142**, 649.
34. K. V. P. P. Kumar, N. S. Kumar, and K. C. K. Swamy, *New J. Chem.*, 2006, **30**, 717.
35. K. V. Raghu, C. Devendranath Reddy, and K. S. Rao, *Heteroatom Chem.*, 1997, **8**, 55.
36. S. A. Abdel-Ghaffar, T. E. Ali, K. M. El-Mahdy, and S. M. Abdel-Kariem, *Eur. J. Chem.*, 2011, **2**, 25.
37. H. Chen, D. Qian, G. Xu, Y. Liu, X. Chen, X. Shi, R. Cao, and L. Liu, *Synth. Commun.*, 1999, **29**, 4025.
38. P. Conti, A. Pinto, L. Tamborini, V. Rizzob, and C. De Micheli, *Tetrahedron*, 2007, **63**, 5554.
39. A. B. Akacha, N. Ayed, B. Baccar, and C. Charrier, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 1988, **40**, 63.
40. Z. Hassen, A. B. Akacha, and B. Hajjem, *Phosphorus, Sulfur, Silicon Relat. Elem.,* 2003, **178**, 2349.
41. F. Palacios, D. Aparicio, Y. Lopez, J. M. Santos, and J. M. Ezpeleta, *Tetrahedron*, 2006, **62**, 1095.

42. F. Palacios, D. Aparicio, and J. M. Santos, *Tetrahedron*, 1996, **52**, 4123.
43. O. A. Attanasi, G. Baccolini, C. Boga, L. D. Crescentini, G. Giorgi, F. Mantellini, and S. Nicolini, *Eur. J. Org. Chem.,* 2008, 5965.
44. N. R. Mohamed, M. M. T. El-Saidi, H. M. Hassaneen, and A. W. Erian, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 2004, **179**, 521.
45. W. M. Abdou, M. D. Khidre, and R. E. Khidre, *Eur. J. Med. Chem.*, 2009, **44**, 526.
46. T. E. Ali, *Eur. J. Med. Chem.*, 2009, **44**, 4539.
47. I. G. Kolokol'tseva, V. N. Chistoketov, B. I. Ionin, and A. A. Petrov, *Zh. Obshch. Khim.*, 1968*,* **38**, 1248 (*Chem. Abstr.*, 1968*,* **69**, 96834).
48. N. S. Goulioukina, N. N. Makukin, and I. P. Beletskaya, *Tetrahedron,* 2011, **67**, 9535.
49. H. G. Krug, R. Neidlein, R. Boese, and W. Kramer, *Heterocycles,* 1995, **41**, 721.
50. R. Lu and H. Yang, *Tetrahedron Lett.*, 1997, **38**, 5201.
51. R. G. Franz, *AAPS Pharmsci,* 2001, **3**, 1.
52. N. I. Petkova, R. D. Nikolova, A. G. Bojilova, N. A. Rodios, and J. Kopf, *Tetrahedron,* 2009, **65**, 1639.
53. W. M. Abdou and N. A. F. Ganoub, *Heteroatom Chem.*, 2000, **11**, 196.
54. B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 1963, 3351.
55. D. Seyferth and J. D. H. Paetsch, *J. Org. Chem.*, 1969*,* **34**, 1483.
56. A. N. Pudovik, R. D. Gareev, and L. I. Kuznetsova, *Zh. Obshch. Khim.*, 1969*,* **39**, 1536 (*Chem. Abstr*., 1969*,* **71**, 113049).
57. R. Muruganantham, S. M. Mobin, and I. N. N. Namboothiri, *Org. Lett.*, 2007, **9**, 1125.
58. R. Muruganantham and I. N. N. Namboothiri, *J. Org. Chem.,* 2010, **75**, 2197.
59. A. R. Martin, K. Mohanan, L. Toupet, J. J. Vasseur, and M. Smietana, *Eur. J. Org. Chem*., 2011, 3184.
60. E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, 1971, **36**, 4033.
61. E. E. Schweizer and C. S. Labaw, *J. Org. Chem.*, 1973, **38**, 3069.
62. W. M. Abdou, M. D. Khidre, and R. E. Khidre, *J. Heterocycl. Chem.,* 2008, **45**, 1571.
63. M. Chakravarty, N. N. B. Kumar, K. V. Sajna, and K. C. K. Swamy, *Eur. J. Org. Chem.,* 2008, 4500.
64. M. H. Maguire, R. K. Ralph, and G. Shaw, *J. Chem. Soc*., 1958, 2299.
65. R. Lu, H. Liu, G. Yang, and H. Yang, *Gaod Xuexiao Huaxue Xuebao,* 1996, **17**, 1240 (*Chem. Abstr*., 1996, **125**, 247941).
66. E. Budzisz, M. Malecka, and B. Nawrot, *Tetrahedron*, 2004, **60**, 1749.
67. E. Budzisz, M. Miernicka, I. P. Lorenz, P. Mayer, U. Krajewska, and M. Rozalski, *Polyhedron,*

2009, **28**, 637.

68. M. Małecka, W. Massa, K. Harms, and E. Budzisz, *J. Mol. Struct.*, 2005, **737**, 259.
69. E. Budzisz, U. Krajewska, M. Rozalski, A. Szulawska, M. Czyz, and B. Nawrot, *Eur. J. Pharm.*, 2004, **502**, 59.
70. A. A. Tolmachev, S. I. Dovgopoly, A. N. Kostyuk, E. T. S. Kozlov, A. O. Pushechnikov, and W. Holzer, *Heteroatom Chem.*, 1999, **10**, 391.
71. D. M. Volochenyuk, A. O. Pushenikov, D. G. Krotko, G. N. Koydan, A. P. Marchenko, A. N. Cherenga, A. M. Pinchuk, and A. A. Tolmachev, *Synthesis*, 2003, 906.
72. R. Chen and J. Wang, *Chinese Chem. Lett.*, 1990, **1**, 59.
73. F. Allouche, F. Chabehoub, M. Salem, and G. Kirsch, *Synth. Commun.*, 2011, **41**, 1500.
74. A. M. Pinchuk, A. S. Merkulov, G. V. Oshovsky, and A. A. Tolmachas, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 1999, **713**, 144.
75. H. Yang and R. Lu, *Synth. Commun.*, 1994, **24**, 59.
76. R. Lu, H. Yang, and L. Wang, *Gaod Xuexiao Huaxue Xuebao*, 1996, **17**, 236 (*Chem. Abstr.*, 1996, **124**, 289673).
77. A. A. Tolmachev, A. O. Pushechnikov, D. G. Krotko, S. P. Ivonin, and A. N. Kostyuk, *Chem. Heterocycl. Compd.*, 1998, **34**, 1098.
78. P. Molina, M. Alajarin, A. Arques, P. Sanchez-Andrada, A. Vidal, and M. V. Vinader, *J. Organomet. Chem.*, 1997, **529**, 121.

Tarik El-Sayed Ali was born in Cairo, Egypt, in 1975. He is presently associate 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. He has published more than 23 scientific papers including 5 review articles, all in international journals. His research interests are in synthesis and chemical reactivity of phosphorus compounds contain 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 obtained MS degree in Organophosphorus Chemistry in 2011. Her PhD thesis includes design and synthesis of biologically active organophosphorus compounds.