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SYNTHETIC METHODS OF 1,3,2-DIAZAPHOSPHININE SYSTEMS

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Abstract – The present review considers all the literature data on methods developed for the synthesis of 1,3,2-diazaphosphinine systems starting from their appearance up to end 2018. The described main methods depended on the cyclization of 1,3-diamines, 1,2-aminoamide (β -aminoamide) and 1,2-aminonitrile (β -aminonitrile) compounds with phosphorus halides and sulfides.

1. INTRODUCTION

The synthesis of 1,3,2-diazaphosphinine derivatives has been reported¹ in 1963 and during the ensuing years their chemical, spectral, and biological properties have been intensively studied.²⁻⁶ Compounds bearing 1,3,2-diazaphosphinine moiety are known to exhibit antimicrobial,⁷ antiviral,⁸ and antitumor activities.^{9,10} Despite the numerous examples of 1,3,2-diazaphosphinines in the literature, there are relatively a few methods for their synthesis. Indeed, the vast majority of the methods are essentially a reaction between a phosphorus reagent and 1,3-diaminopropane derivatives. There are variations on this general theme. For example, one or both nitrogen atoms may be secondary amines, one or both nitrogen atoms may be aromatic, one can be an amide or nitrile nitrogen, and one or both nitrogen atoms can be part of an aromatic heterocyclic ring. Reactions can be performed with a variety of phosphorylating agents, including phosphoryl halide, phosphorus pentasulfide and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent). The only other significant method for the synthesis of 1,3,2-diazaphosphinine is alkylation of the nitrogen of a *bis*-phosphonamide. The present survey includes all the literature data on methods developed for the synthesis of 1,3,2-diazaphosphinine derivatives starting from their appearance up to end 2018. The described methods for the synthesis of 1,3,2-diazaphosphinine derivatives can be divided into four routes: a) cyclization of 1,3-diamine

compounds *via* phosphorus halides and sulfides, b) cyclization of 1,2-aminoamide (β -aminoamide) compounds *via* phosphorus halides and sulfides, c) cyclization of 1,2-aminonitrile (β -aminonitrile) compounds *via* phosphorus halides and sulfides, d) miscellaneous methods. It is hoped that this survey will demonstrate the synthetic potential of the synthesis of 1,3,2-diazaphosphinine and generate some new ideas in this area.

2. SYNTHETIC APPROACH

2.1. CYCLIZATION OF 1,3-DIAMINE COMPOUNDS *VIA* PHOSPHORUS HALIDES AND SULFIDES

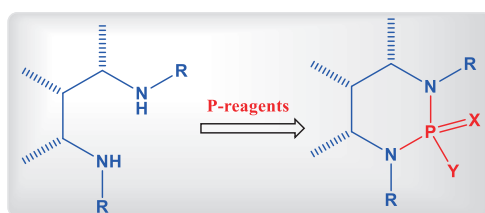
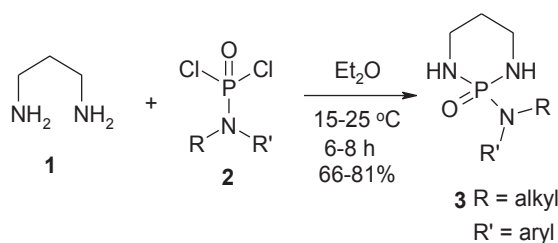


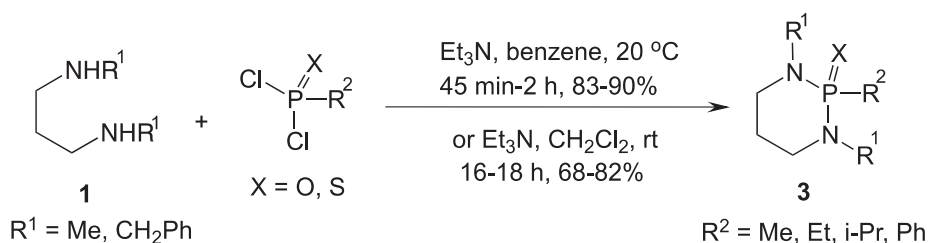
Figure 1

Treatment of 1,3-diaminopropane (**1**) with phosphoramidic dichloride **2** in dry ether led to the formation of 1,3,2-diazaphosphorine 2-oxide **3** in good yields (Scheme 1).^{9,10}



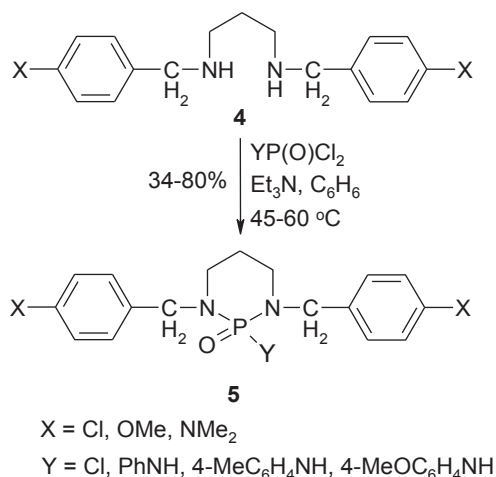
Scheme 1

Similarly, the reaction of 1,3-diaminopropane derivatives **1** with phosphoryl dichloride derivatives in benzene or methylene chloride in the presence of triethylamine gave the 1,3,2-diazaphosphinines **3** (Scheme 2).¹¹⁻¹⁵



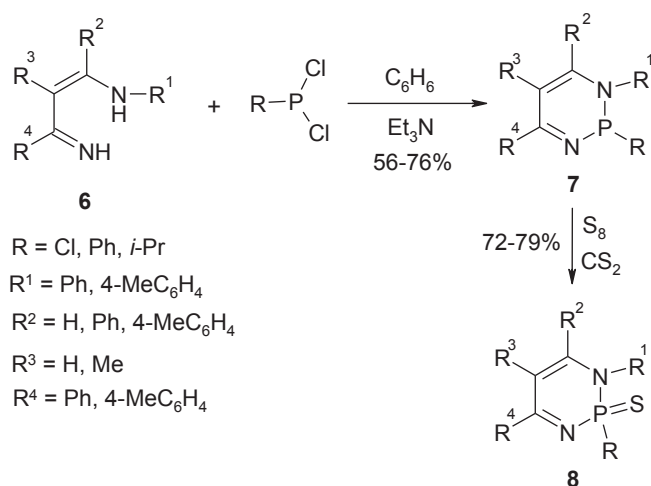
Scheme 2

1,3-Bis(aralkyl)-1,3,2-diazaphosphorine 2-oxide derivatives **5** were prepared from the reaction of *N,N*-bis(*p*-substituted benzyl)-1,3-diaminopropane **4** and POCl₃ and its derivatives YP(O)Cl₂ in dry benzene (Scheme 3).^{9,10}



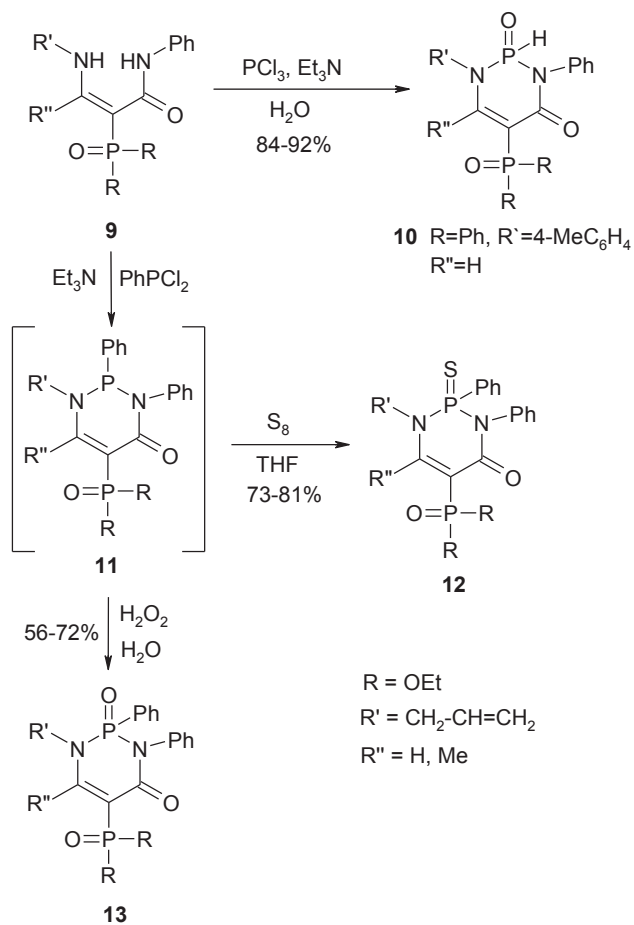
Scheme 3

On the other hand, the reaction of 4-amino-1-azabutadienes **6** with different phosphorus halides gave 1,3,2-diazaphosphorine derivatives **7** in good yields. Treatment of the latter products with elemental sulfur in carbon disulfide yielded the corresponding sulfide analogues **8** (Scheme 4).¹⁶⁻¹⁸



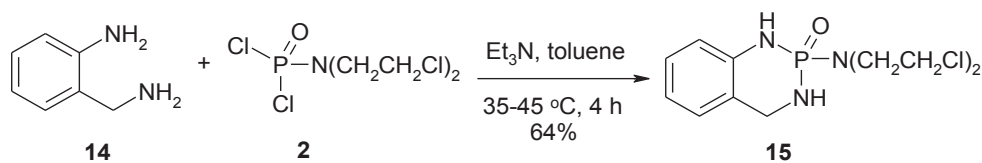
Scheme 4

Cyclocondensation reaction of substituted β -enaminoamides **9** with phosphorus trichloride gave the 2-oxo-1,3,2-diazaphosphinin-4-one **10**. Similarly, cyclocondensation of compound **9** with dichlorophenylphosphine, followed by sulfuration with sulfur or oxidation with hydrogen peroxide afforded the 2-thio and 2-oxo derivatives **12** and **13**, respectively (Scheme 5).¹⁹



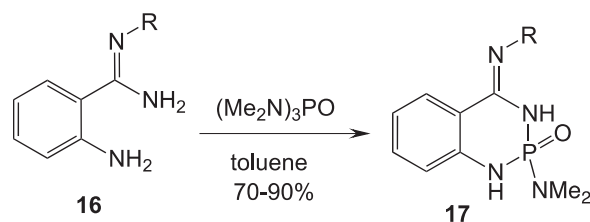
Scheme 5

Also, cyclocondensation reaction of 2-(aminomethyl)aniline (**14**) with *N,N*-bis(2-chloroethyl)amino-phosphoramidic dichloride (**2**) in toluene containing triethylamine as a catalyst afforded *N,N*-bis(2-chloroethyl)-2-oxido-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphinin-2-amine (**15**) (Scheme 6).^{20,21}



Scheme 6

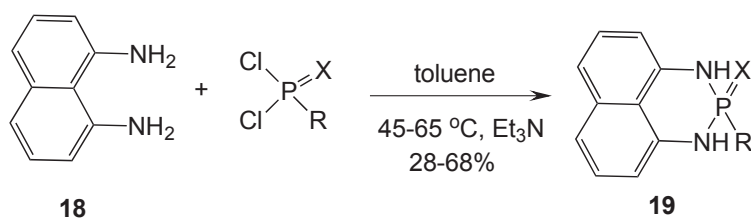
1,3,2-Diazaphosphorine 2-oxide derivatives **17** were prepared in 70-90% yields by refluxing of amidines **16** and hexamethylphosphoric triamide in toluene for 48 h (Scheme 7).²²



R = Et, Pr, *i*-Pr, *i*-Am, CH₂Ph, *o*-Tolyl, 2-aminobenzimidazolyl,
2-aminotriazolyl, 2-(3-amino-5-methylpyrazolyl)

Scheme 7

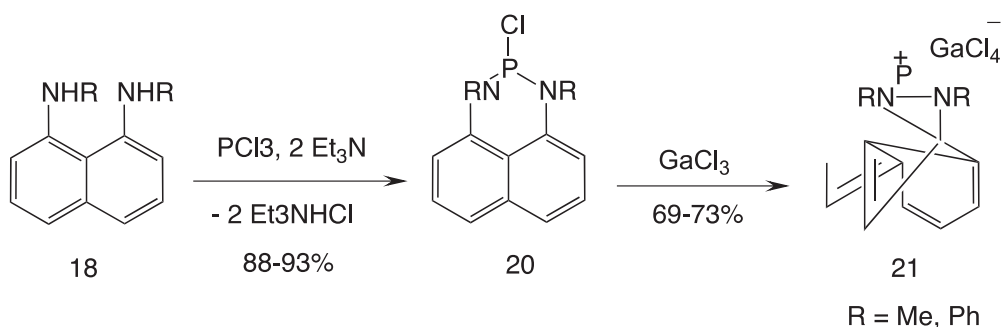
When 1,8-diaminonaphthalene (**18**) was reacted with various dichlorophosphinyl derivatives in equimolar quantities, the naphtho[1,8-*de*][1,3,2]diazaphosphorine derivatives **19** were obtained (Scheme 8).^{21,23}



R = NHCOR', CCl₃, N(CH₂CH₂Cl)₂, OCH₂CH₂Cl, 4-MeC₆H₄,
X = O, S

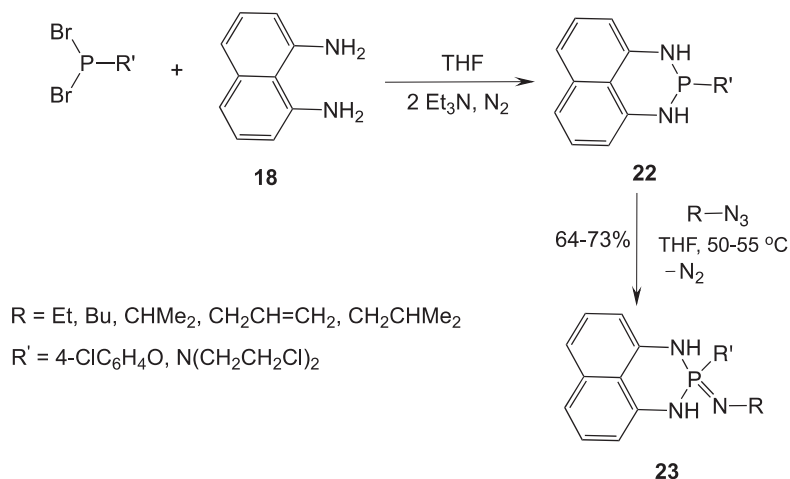
Scheme 8

The heterocyclic chlorophosphines **20** were obtained from base-induced condensation of a secondary 1,8-diaminonaphthalene (**18**) with phosphorus trichloride. The latter products were converted into cyclic phosphonium cations **21** by promotion halide abstraction *via* treatment with GaCl₃ reagent (Scheme 9).²⁴



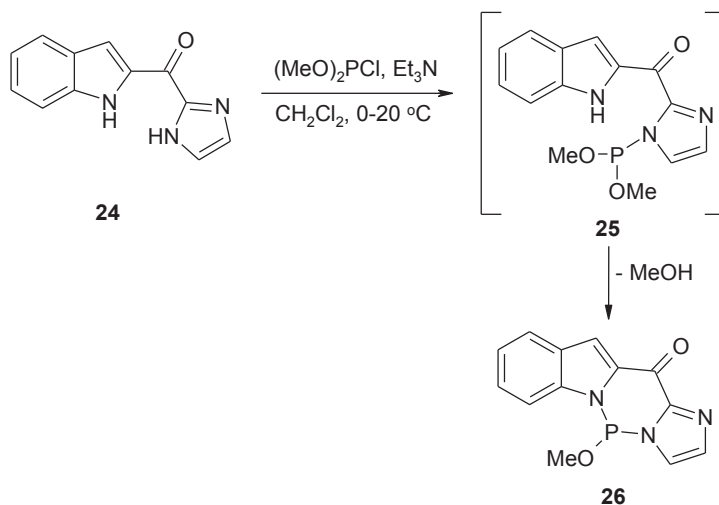
Scheme 9

Some dibromophosphites were reacted with 1,8-diaminonaphthalene (**18**) in the presence of two moles of triethylamine in dry THF under N₂ atmosphere to afford the corresponding diazaphosphinines **22**. They were further reacted with different alkyl azides in THF at 50-55 °C under N₂ atmosphere to isolate the corresponding iminophosphoranes **23** in 64-73% yields (Scheme 10).²⁵



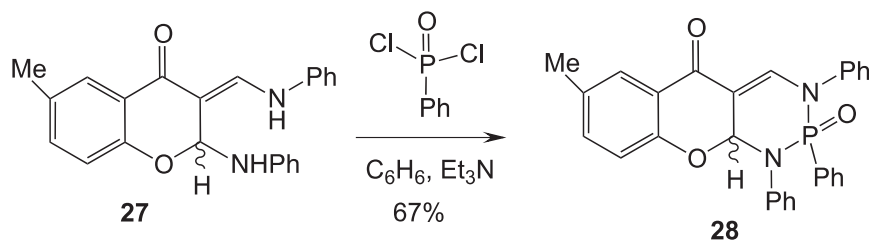
Scheme 10

Reaction of 1*H*-imidazol-2-yl(1*H*-indol-2-yl)methanone (**24**) with dimethyl chlorophosphate in the presence of triethylamine in dichloromethane furnished 5-methoxy-7,8-dihydro-10*H*-imidazo[1,2-*c*]-indolo[2,1-*f*][1,3,2]diazaphosphinin-10-one (**26**) (Scheme 11).²⁶

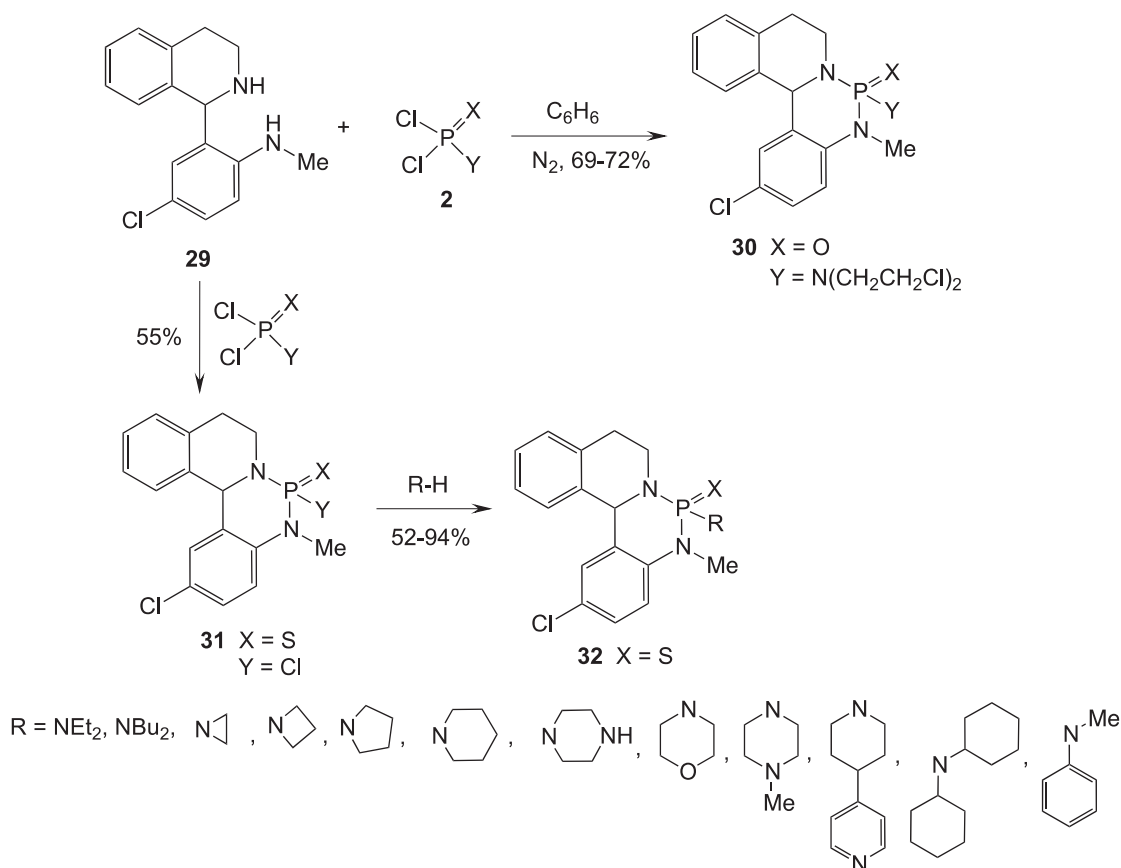


Scheme 11

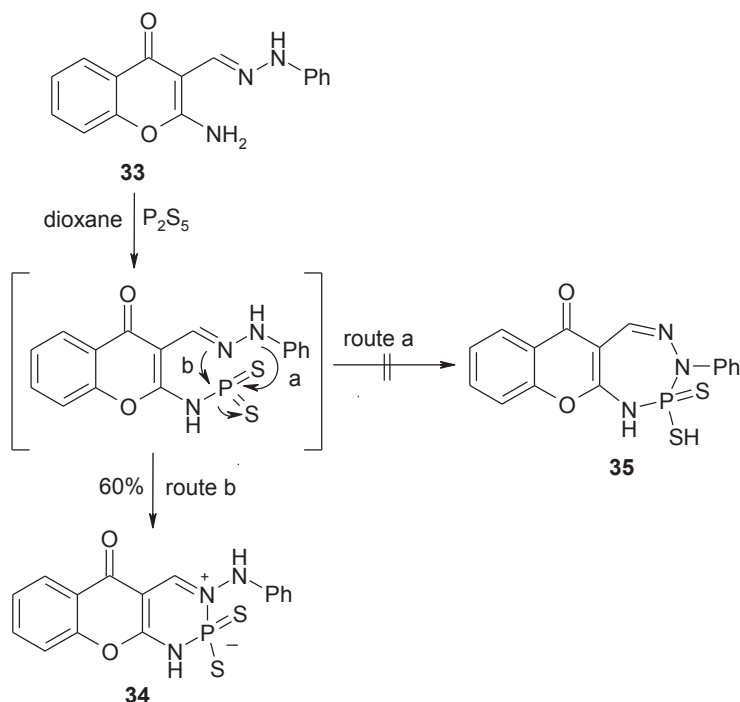
Ali²⁷ reported that cyclization of 3-(phenylaminomethylene)-2-*N*-phenylamino-6-methyl-2,3-dihydro-4*H*-chromen-4-one (**27**) with phenylphosphonic dichloride was performed in dry benzene containing a few drops of triethylamine under reflux to produce 7-methyl-2-oxo-1,2,3-triphenyl-10*a*-tetrahydro-5*H*-chromeno[2,3-*d*][1,3,2]diazaphosphinin-5-one (**28**) in good yield (Scheme 12).

**Scheme 12**

The isoquino[2,1-*c*][1,3,2]benzodiazaphosphorine 2-oxide (**30**) was synthesized in 69% yield by the condensation of 1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**29**) with *N,N*-bis(2-chloroethyl)-aminophosphoramidic dichloride (**2**) in dry benzene using the evolution of hydrogen chloride gas as the means of ensuring the completion of the reaction. The cyclic intermediate **31** that obtained from the reaction of compound **29** with thiophosphoryl chloride, was condensed with various secondary amines in dry benzene to give isoquino[2,1-*c*][1,3,2]benzodiazaphosphorine 2-sulfides **32** (Scheme 13).²⁸

**Scheme 13**

The reaction of (2-aminochromenyl)phenylhydrazone **33** with phosphorus pentasulfide in dry dioxane, could not generate the phosphorus heterocycles **35**, but produced the system chromono[2,3-*d*][1,3,2]-diazaphosphinine 2-sulfide **34** in 60% yield as shown in Scheme 14.²⁹



Scheme 14

2.2. CYCLIZATION OF 1,2-AMINOAMIDE (β -AMINOAMIDE) COMPOUNDS VIA PHOSPHORUS HALIDES AND SULFIDES

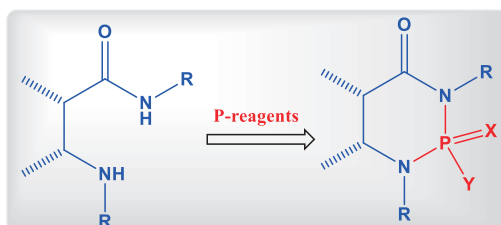
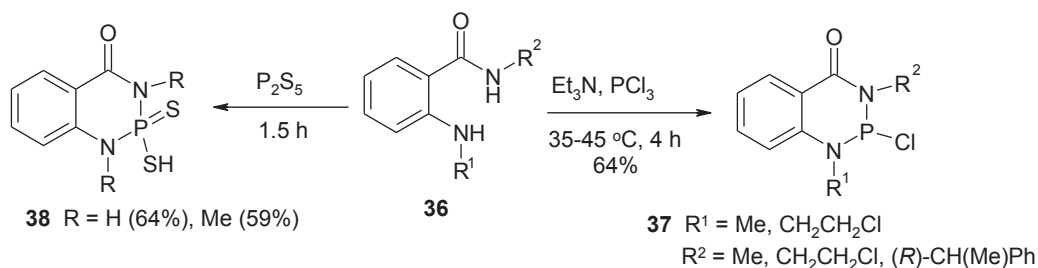


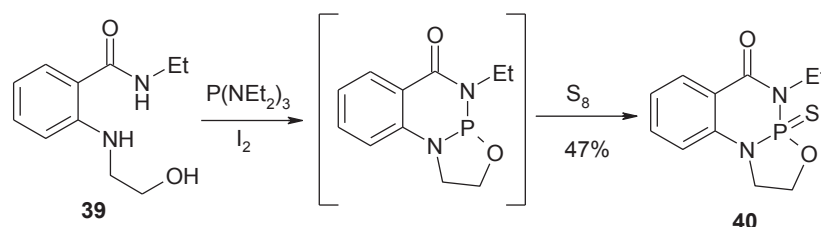
Figure 2

Treatment of 2-aminobenzamide derivatives **36** with phosphoryl trichloride in the presence of triethylamine afforded the 2-chloro-1,3,2-diazaphosphinine derivatives **37**, while its treatment with phosphorus pentasulfide gave 1,3,2-diazaphosphinine 2-sulfide derivatives **38** (Scheme 15).³⁰⁻³³



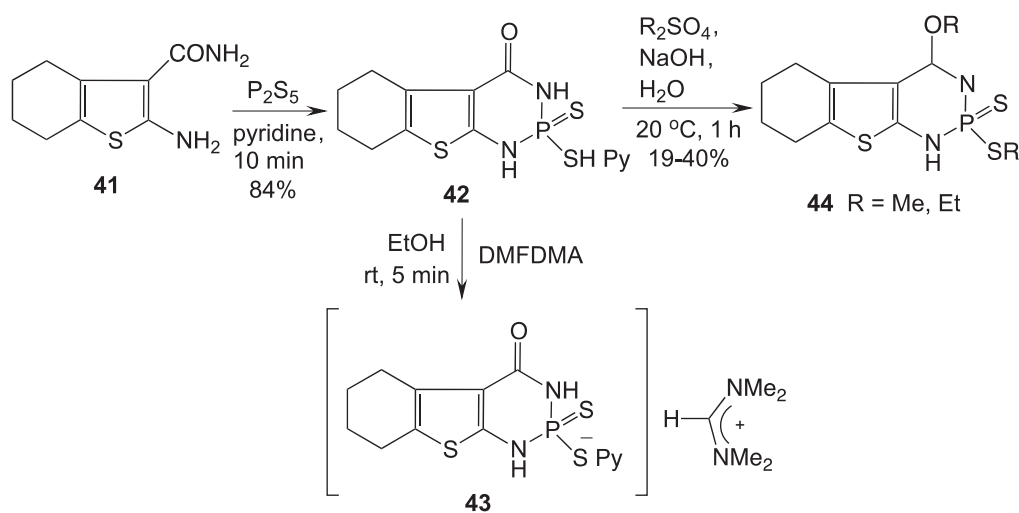
Scheme 15

Reaction of 2-[*N*-(2'-hydroxy)ethyl]amino-*N*-ethylbenzamide (**39**) with *tris*(diethylamino)phosphine in the presence of iodine as catalyst, followed by addition of sulfur *in situ* produced 1,3,2-oxazaphospholidino[3,2-*a*][1,3,2]benzodiazaphosphorine sulfide **40** in 47% yield (Scheme 16).³⁴



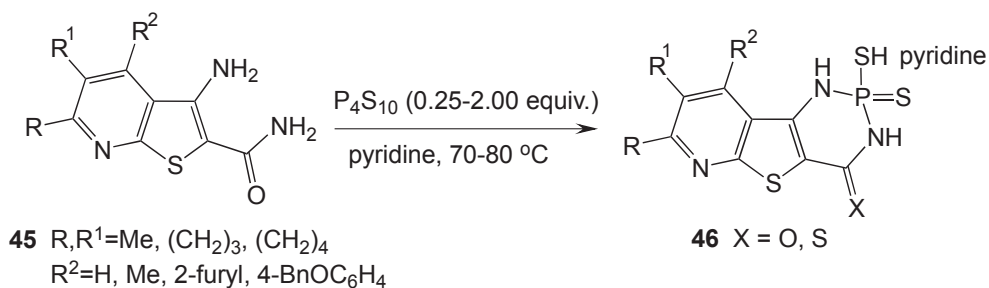
Scheme 16

The reaction of 2-amino-3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**41**) with phosphorus pentasulfide in dry pyridine afforded pyridinium 4-oxo-2-sulfanyl-4,5,6,7-tetrahydrobenzo[*b*]thiopheno[2,3-*d*]-[1,3,2]diazaphosphinane 2-sulfide (**42**) in 84% yield. The latter solid was treated with dimethylformamide dimethyl acetal (DMFDMA) to give the stable tetramethylformamidinium salt **43**, while its alkylation upon the action of dialkyl sulfate in an alkaline medium gave tri- and dialkyl derivatives **44** (Scheme 17).³⁵



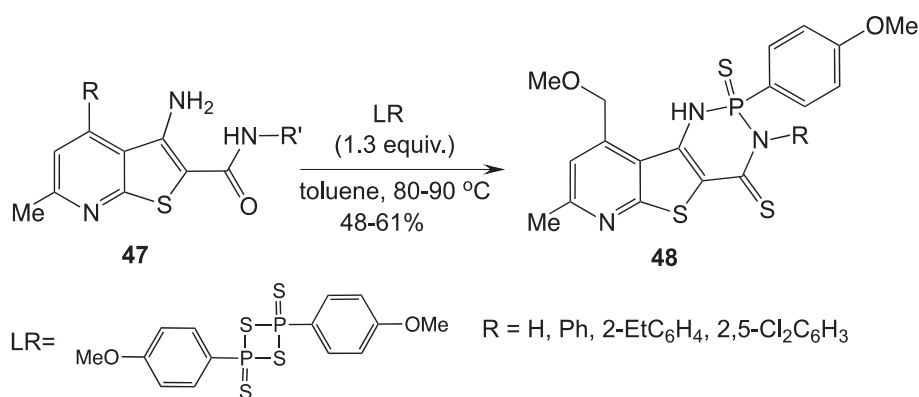
Scheme 17

Thiophosphorylation reaction of 3-aminothienopyridine-2-carboxamides **45** using 0.25 equivalent of P_4S_{10} in refluxing absolute pyridine, gave tetrahydropyrido[3',2':4,5]thieno[2,3-*d*][1,3,2]-diazaphosphorines **46**. Using excess of P_4S_{10} led to a mixture of compound **46** ($X=O$) and the thionated derivatives ($X=S$) in variable yields (Scheme 18).³⁶



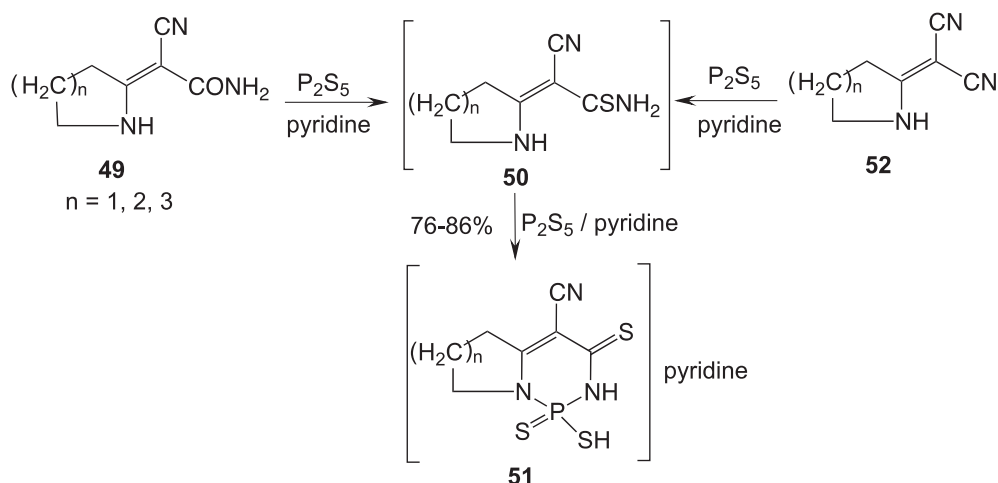
Scheme 18

The reaction of thieno[2,3-*b*]pyridinaminoamides **47** with Lawesson's reagent (LR) in a 1.0:1.3 molar ratio in dry toluene gave the diazaphosphinine-thione derivatives **48** in 48-61% yields (Scheme 19).³⁷



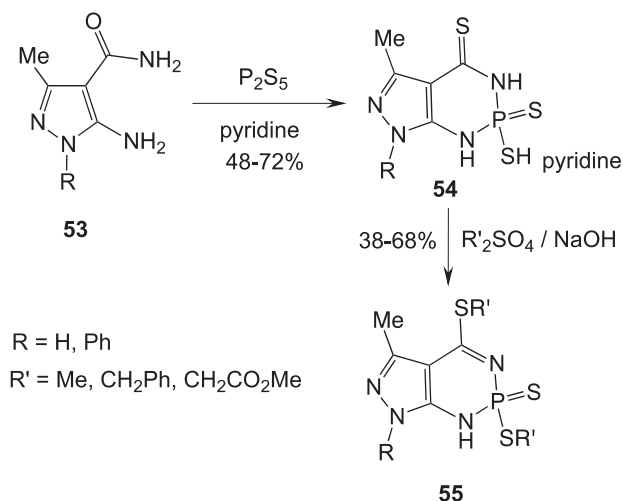
Scheme 19

Treatment of 2-(β-cyano-β-carbamoyl)polymethylene derivatives **49** with phosphorus pentasulfide in the presence of pyridine led to the formation of pyridinium 1,6-polymethylene-5-cyano-2-mercapto-2,4-disulfido-1,3,2λ⁵-diazaphosphinane 2-sulfides (**51**) in 76-86% yields. The diazaphosphinanes **51** were also formed *via* the interaction between enaminodinitriles **52** and phosphorus pentasulfide in pyridine (Scheme 20).^{38,39}



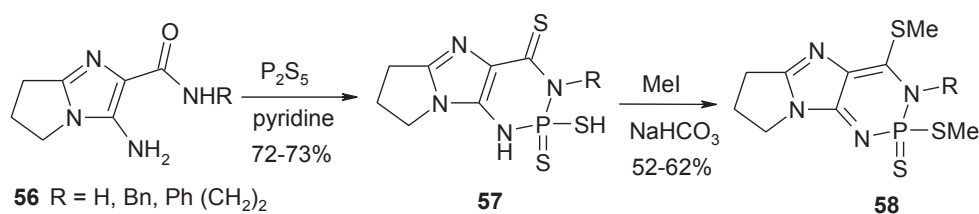
Scheme 20

Reaction of 3-methyl-4-carbamoyl-5-aminopyrazole derivatives **53** with P_2S_5 in pyridine produced the pyridinium 1,3,2-diazaphosphorine 2-sulfides **54**. Diazaphosphorines **54** in the form of sodium salts readily enter the S-alkylation to form the corresponding 2,4-dialkyl derivatives **55** (Scheme 21).⁸



Scheme 21

The interaction of *N*-alkyl(aryl)-3-amino-5*H*,6*H*,7*H*-pyrrolo[1,2-*a*]imidazole-2-carboxamides (**56**) with phosphorus pentasulfide in 1:2 molar ratio in pyridine, afforded 3-alkyl-2-mercapto-1,2,3,6,7,8-hexahydro-4*H*-pyrrolo[2',1':2,3]imidazo[4,5-*d*][1,3,2]diazaphosphinine-4-thione 2-sulfides (**57**) in 72-73% yields. The latter products were converted by the action of methyl iodide into the corresponding dimethyl derivatives **58** in 52-62% yields (Scheme 22).⁴⁰



Scheme 22

2.3. CYCLIZATION OF 1,2-AMINONITRILE (β-AMINONITRILE) COMPOUNDS VIA PHOSPHORUS HALIDES AND SULFIDES

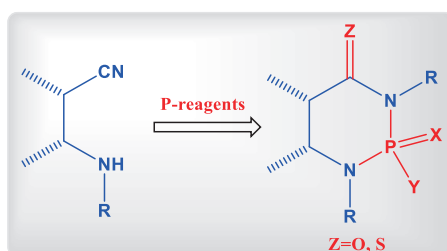
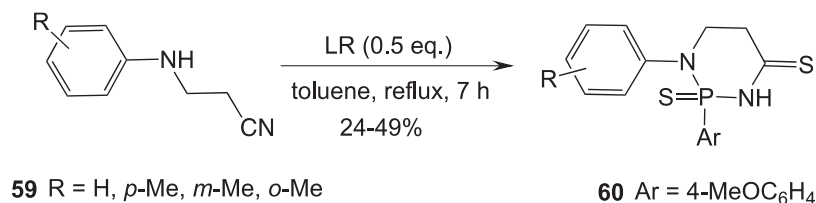


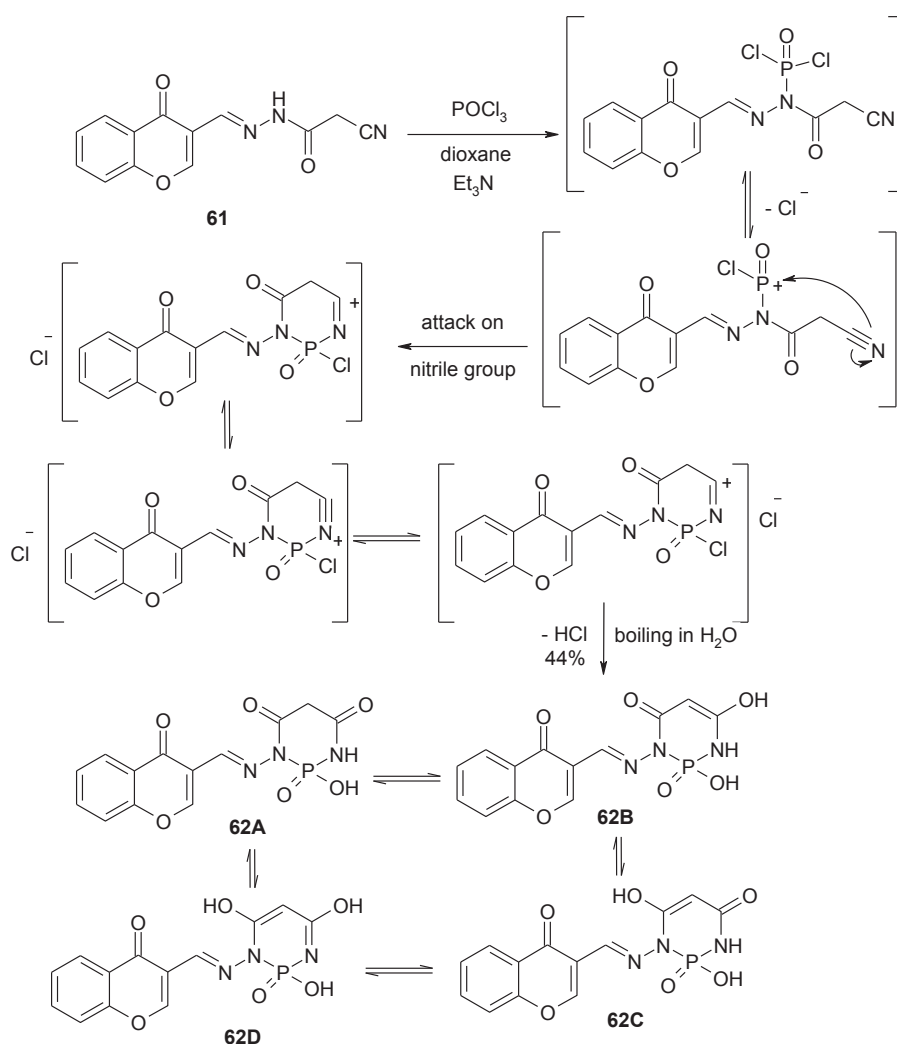
Figure 3

The reaction of *N*-aryl- β -aminopropionitriles **59** with Lawesson's reagent (LR) in a molar ratio of 2:1 in refluxing toluene for 7 h readily afforded the 2-sulfido-1,3,2-diazaphosphorine-4-thione **60** in 24-49% yields (Scheme 23).⁴¹



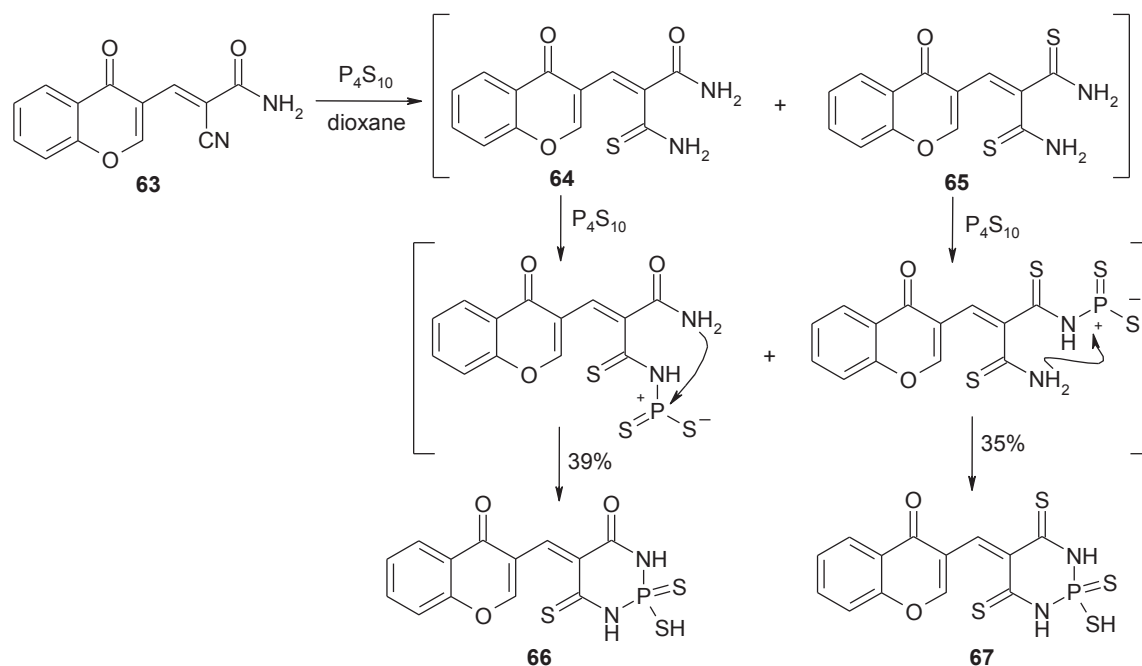
Scheme 23

When phosphoryl chloride was added to a solution of 2-cyano[(4-oxo-4*H*-chromen-3-yl)-methylidene]acetohydrazide (**61**) in dry dioxane containing two equivalent of triethylamine, the 1,3,2-diazaphosphinylchromone **62** was obtained in 44% yield. The spectral data suggested that the product **62** can exist in four tautomeric forms **A–D**, as a result of keto-enol and amino-imino tautomerism (Scheme 24).⁴²



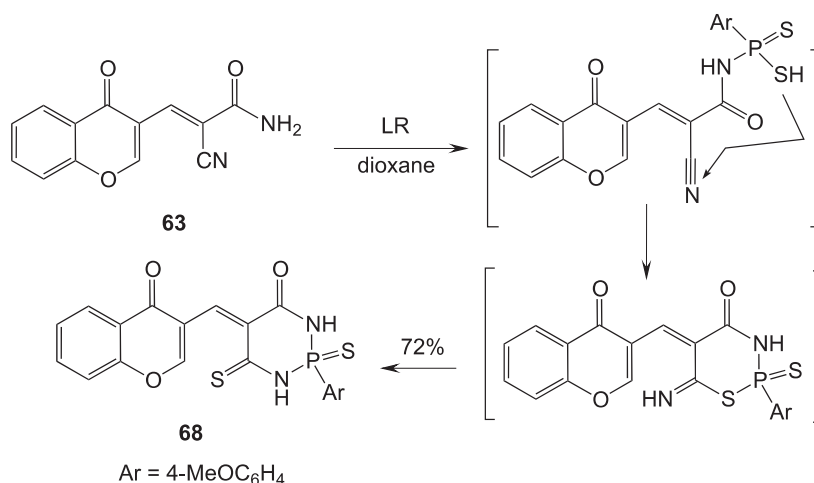
Scheme 24

2-Cyano-3-(4-oxo-4*H*-chromon-3-yl)prop-2-enamide (**63**) was allowed to react with phosphorus pentasulfide in boiling dioxane to give a mixture of two products that could be separated. The first product with a yield of 39% was identified as 5-[(4-oxo-4*H*-chromen-3-yl)methylidene]-2-sulfanyl-2-sulfido-6-thioxo-1,3,2-diazaphosphinan-4-one (**66**), while the second product was identified as 5-[(4-oxo-4*H*-chromen-3-yl)methylidene]-4,6-dithioxo-2-sulfanyl-2-sulfido-1,3,2-diazaphosphinane (**67**) in 35% yield (Scheme 25).⁴³



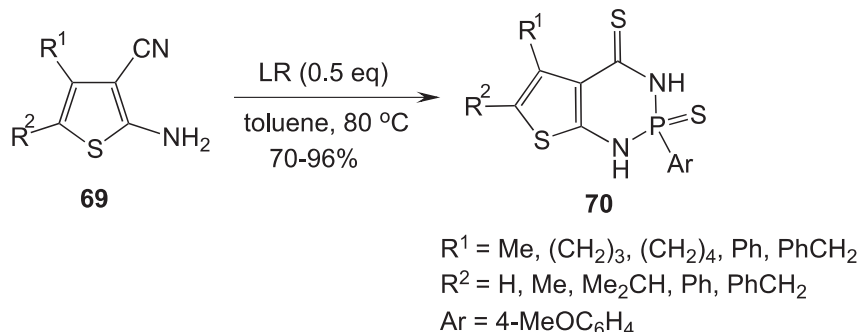
Scheme 25

The (chromonyl)cianoacetamide **63** reacted with Lawesson's reagent (LR) in dry dioxane, giving rise to a sole product which was identified as 2-(4-methoxyphenyl)-5-[(4-oxo-4*H*-chromen-3-yl)methylidene]-2-sulfido-6-thioxo-1,3,2-diazaphosphinan-4-one (**68**) in 72% yield (Scheme 26).⁴³



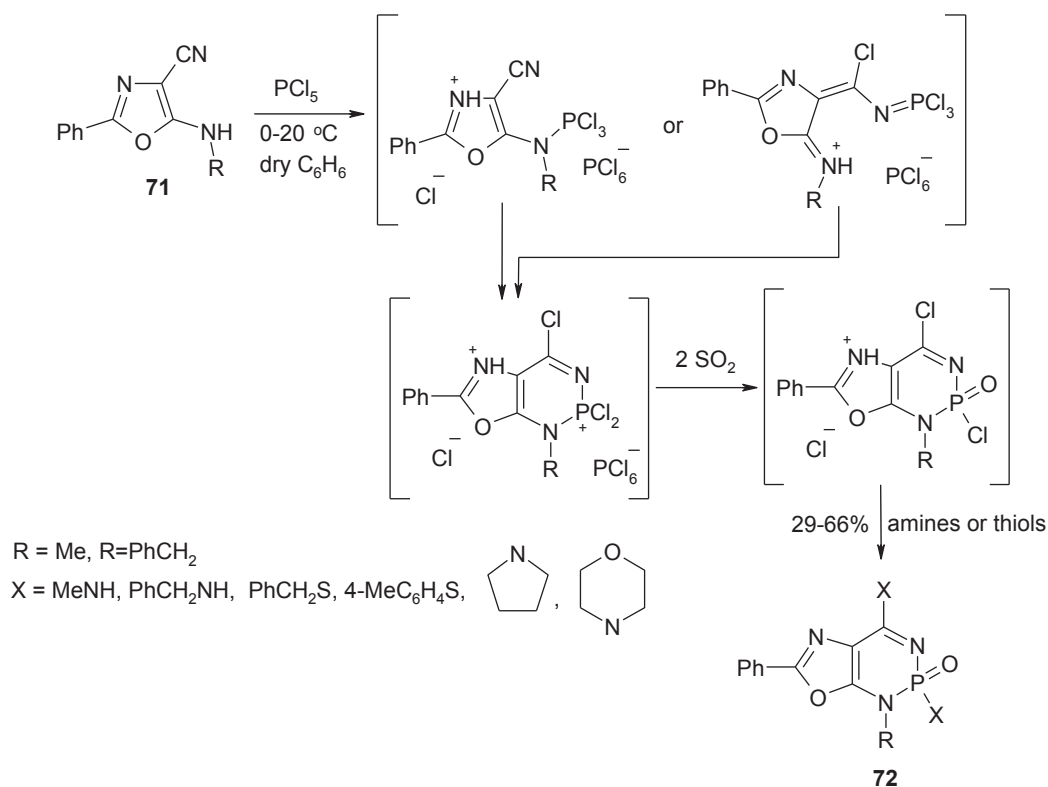
Scheme 26

Reaction of 2-amino-3-cyanothiophenes (**69**) with a stoichiometric amount of Lawesson's reagent (LR) in toluene at 80 °C, for 24–48 h, led to the formation of 6-thioxothieno[2,3-*d*][1,3,2]diazaphosphorine 2-sulfides (**70**) in 70–96% yield (Scheme 27).⁴⁴



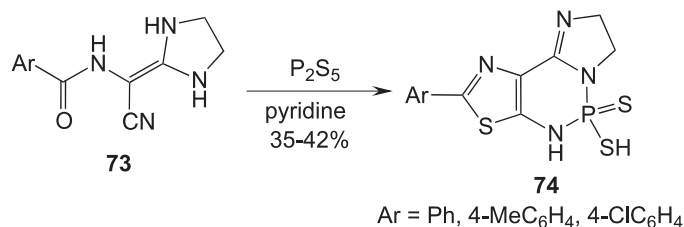
Scheme 27

Condensation of 5-alkylamino-2-phenyl-1,3-oxazole-4-carbonitriles (**71**) with excess of phosphorus pentachloride at 5–20 °C in benzene gave phosphorylation products which could not be isolated in the pure state, and they were reacted further with sulfur dioxide and then with excess different amines or thiols to yield 1,2-dihydro[1,3]oxazolo[5,4-*d*][1,3,2]diazaphosphinine derivatives **72** with different yields (Scheme 28).⁴⁵



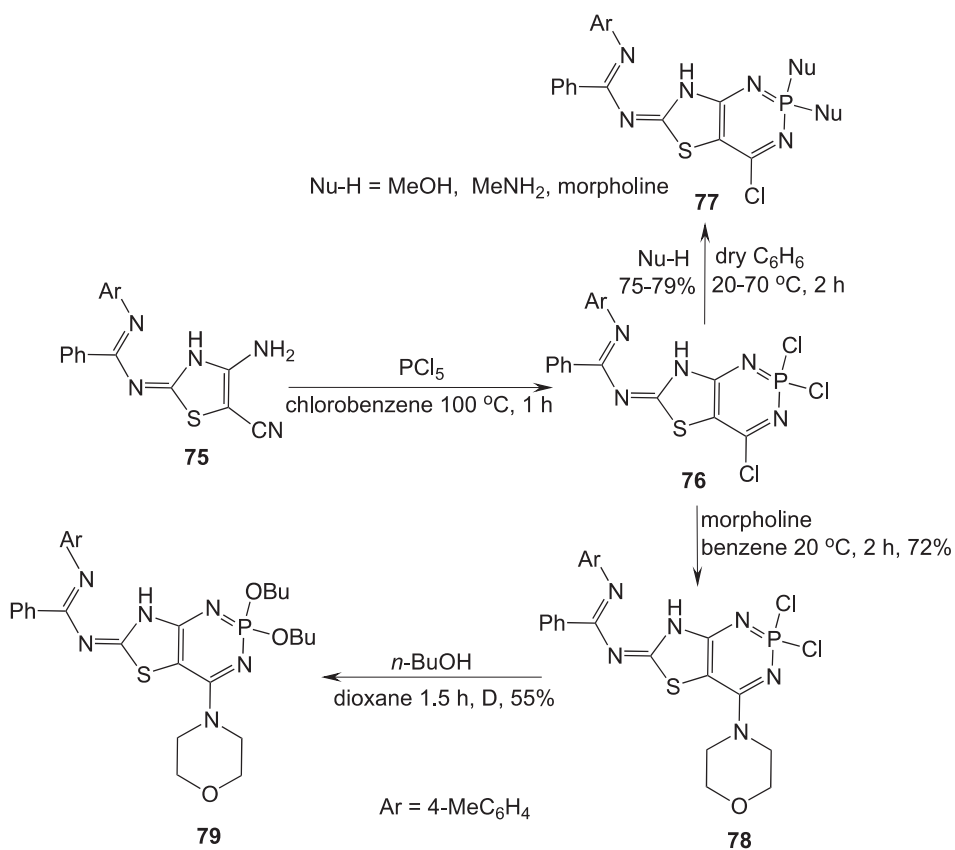
Scheme 28

Treatment of the imidazolyl nitrile **73** with two equivalent P_2S_5 in pyridine, the 4,5,7,8-tetrahydroimidazo[1,2-*c*][1,3]thiazolo[4,5-*e*][1,3,2]diazaphosphinines **74** were obtained in 35-42% yields (Scheme 29).⁴⁶



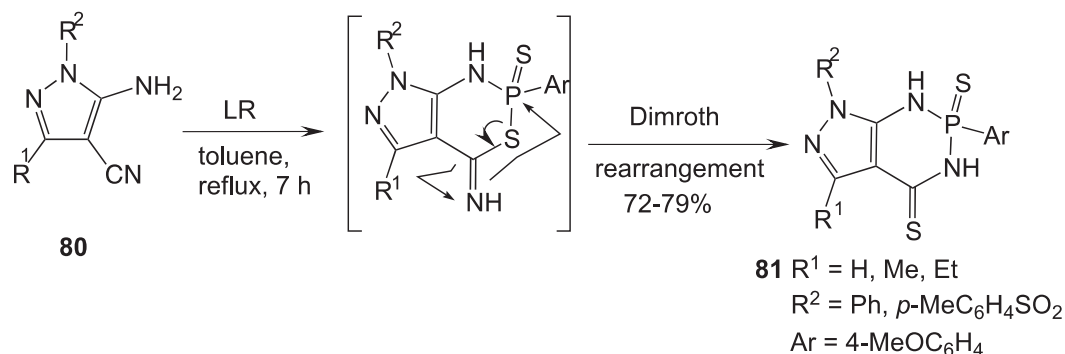
Scheme 29

An interesting heterocyclization occurred when 4-amino-3-benzyl-5-cyano-2,3-dihydro-(*N*-phenylbenzimidoyl)iminothiazole (**75**) was treated with phosphorus pentachloride. The reaction proceeded quite regioselectively with the participation of the amino and cyano groups. The anellation products **76**, containing three reactive chlorine atoms, reacted differently with amines and alcohols depending on the nature of the nucleophile and the temperature. These peculiarities of the compounds **76** were exploited with respect to the synthesis of thiazolo[4,5-*d*][1,3,2]diazaphosphorine derivatives **77-79** bearing various substituents at positions 2 and 4 (Scheme 30).⁴⁷



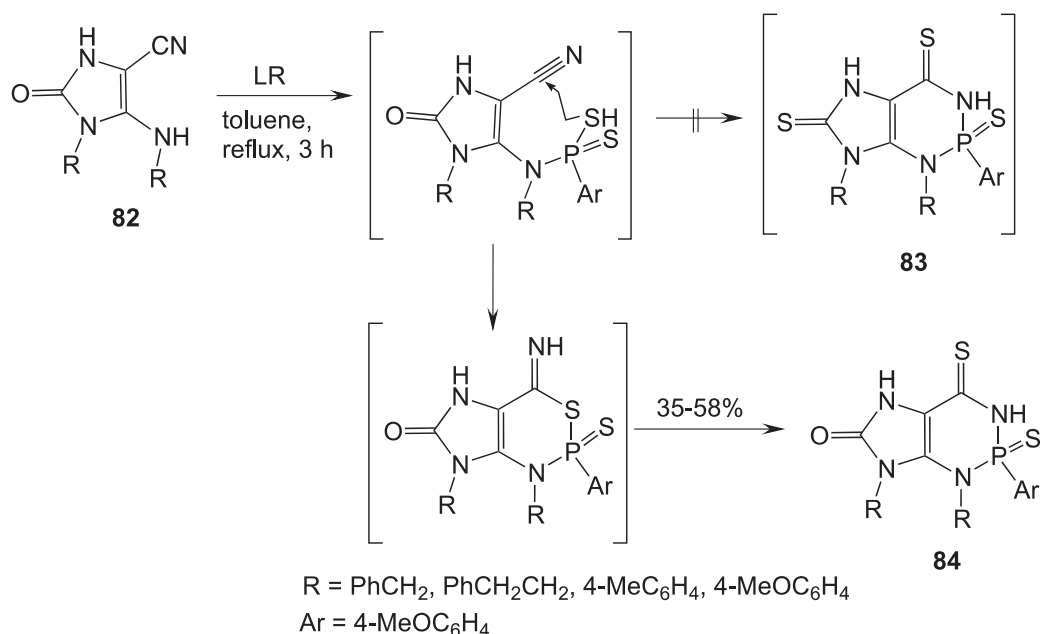
Scheme 30

The cyclization reaction between Lawesson's reagent (LR) and aminocyanopyrazoles **80** in boiling toluene gave the corresponding pyrazolo[3,4-*d*][1,3,2]diazaphosphinine-4-thiones **81** in 72-79% yield (Scheme 31).⁴⁸



Scheme 31

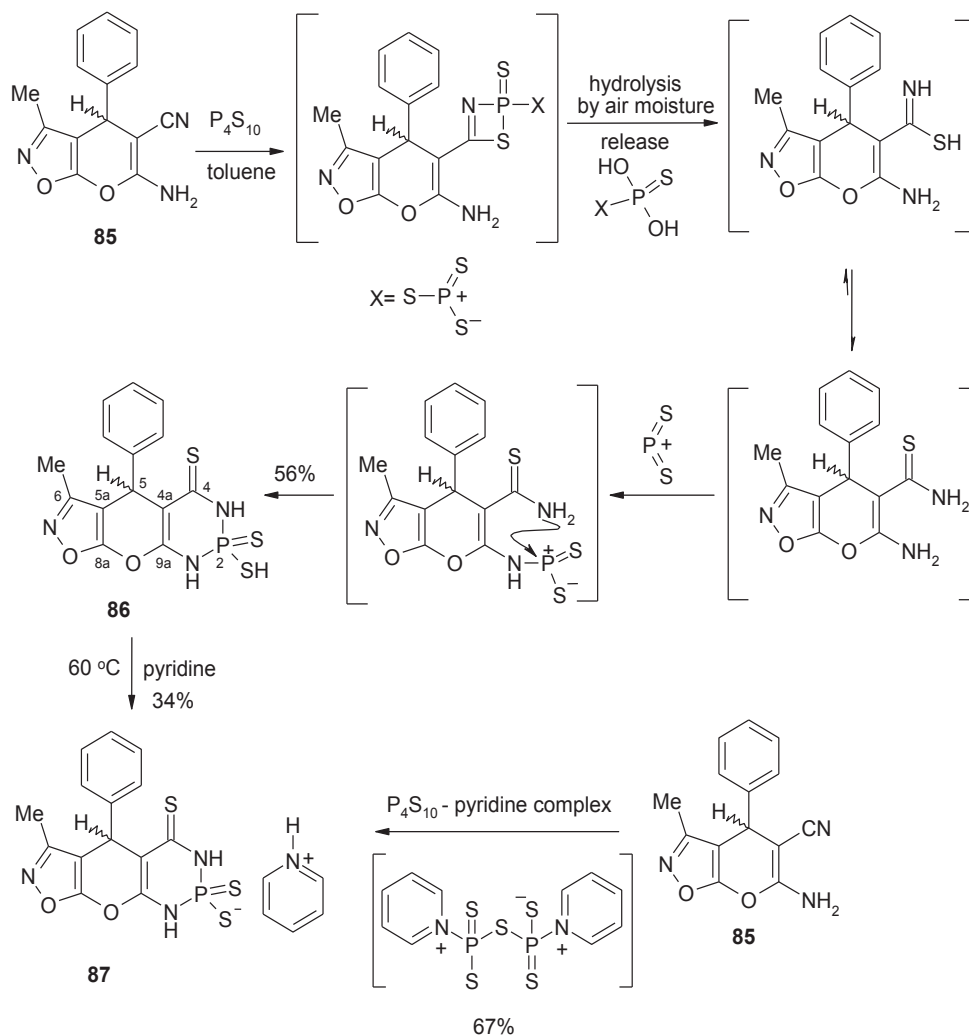
The reaction of the substituted imidazol-2-ones **82** with Lawesson's reagent in toluene for 3 h yielded imidazodiazaphosphinines **84** in 35-58% yield rather than their thio derivatives **83** that needed 10 h to be detected only as 4% yield (Scheme 32).⁴⁹



Scheme 32

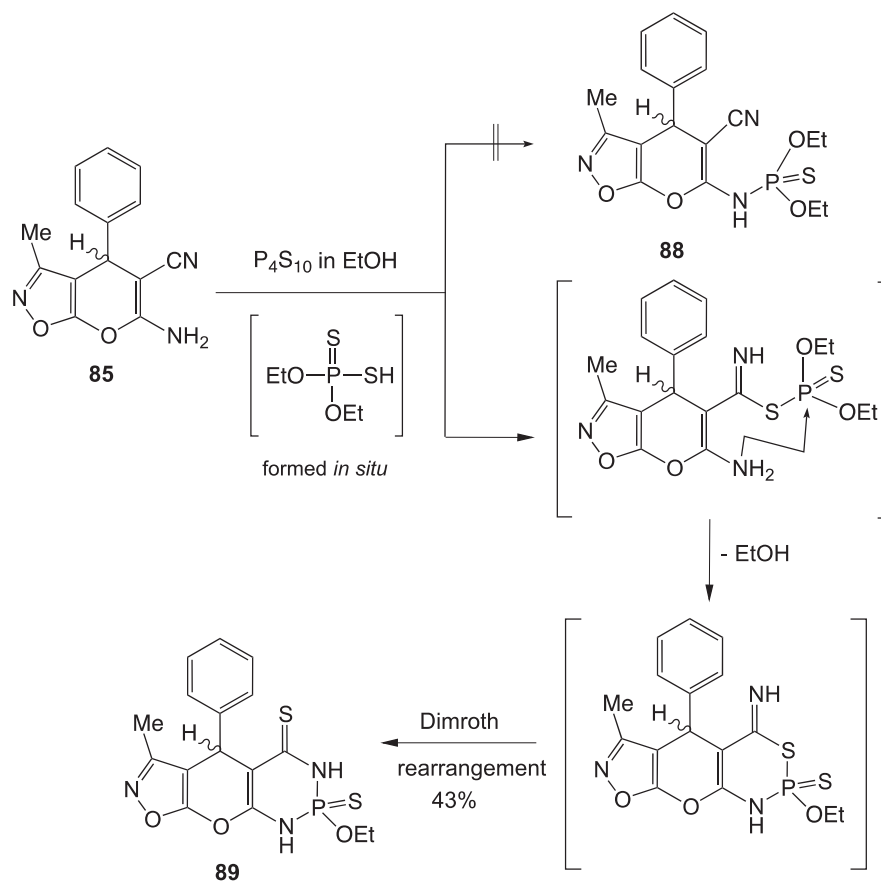
When 6-amino-3-methyl-4-phenyl-4*H*-pyrano[3,2-*d*][1,2]oxazole-5-carbonitrile (**85**) was treated with molar equivalents of tetraphosphorus decasulfide in dry toluene, the 6-methyl-5-phenyl-2-sulfanyl-2-sulfido-1,2,3,5-tetrahydro-4*H*-[1,2]oxazolo[4',5':5,6]pyrano[2,3-*d*][1,3,2]diazaphosphinine-4-thione (**86**) was obtained in 56% yield (Scheme 33). When compound **85** was allowed to react with P₄S₁₀-pyridine

complex in dry pyridine at 80 °C, the pyridinium sulfide salt **87** was separated with 67% yield (Scheme 34). The isolated product **87** was also obtained *via* warming of compound **86** in pyridine at 60 °C (Scheme 33).⁵⁰



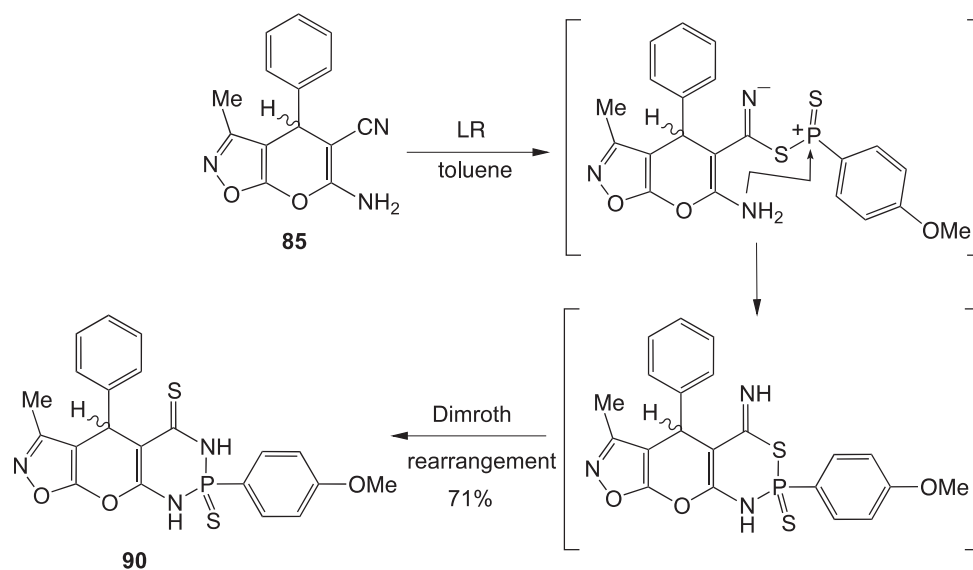
Scheme 33

Reaction of α -aminocarbonitrile **85** with *O,O*-diethyldithiophosphoric acid (formed *in situ* from reaction tetraphosphorus decasulfide with absolute ethanol) furnished the corresponding diazaphosphinane **89** and not the expected **88**. The formation of the diazaphosphinane ring can be explained on the basis of an initial nucleophilic addition of thiol group at the nitrile group, followed by the attack of amino group at phosphorus atom, which in turn rearranged to the desired fused triheterocyclic system *via* a Dimroth rearrangement (Scheme 34).⁵⁰



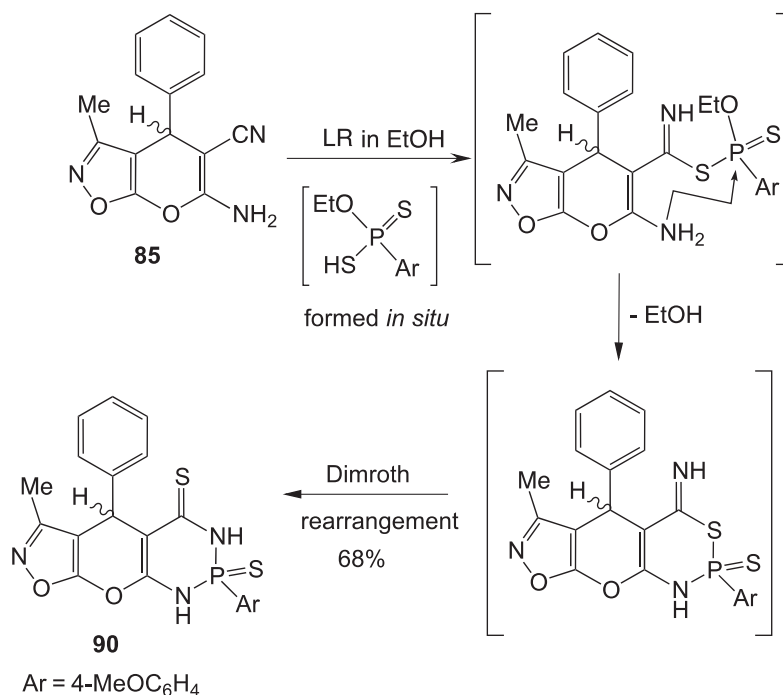
Scheme 34

Similarly, refluxing of 1,2-aminocarbonitrile **85** with Lawesson's reagent (LR) in dry toluene led to the formation 2-(4-methoxyphenyl)-6-methyl-5-phenyl-2-sulfido-1,2,3,5-tetrahydro-4H-[1,2]oxazolo[4',5':5,6]-pyrano[2,3-d][1,3,2]diazaphosphinine-4-thione (**90**) (Scheme 35).⁵⁰



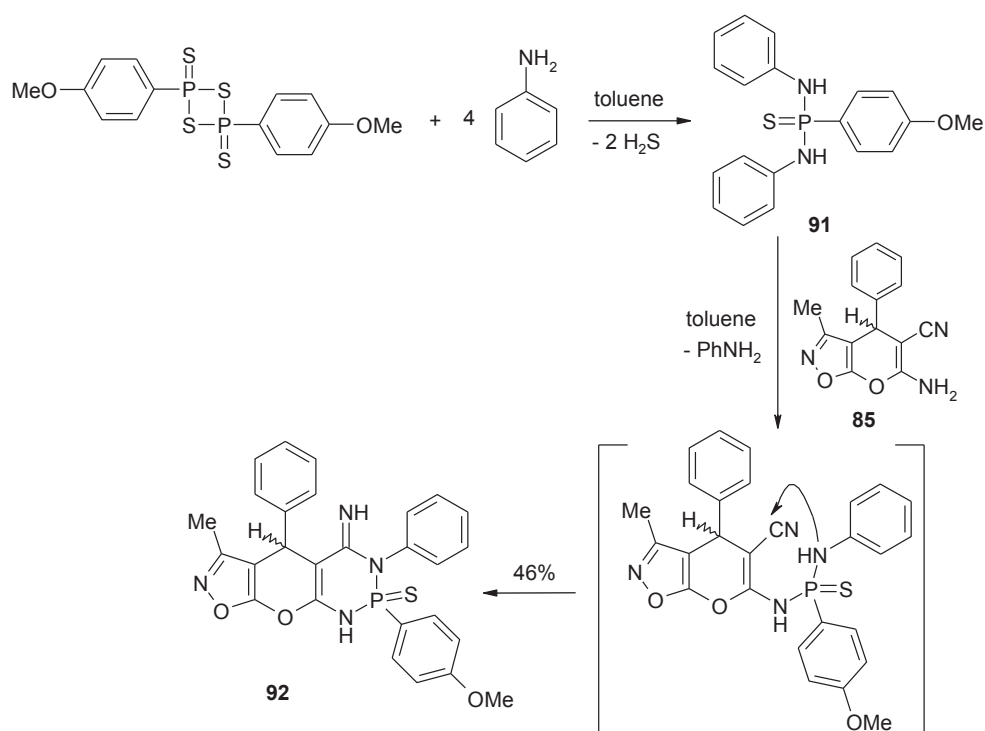
Scheme 35

Heating of the α -aminocarbonitrile **85** with Lawesson's reagent (LR) in absolute ethanol, gave the pyrano[2,3-*d*][1,3,2]diazaphosphinine-4-thione **90** (Scheme 36).⁵⁰



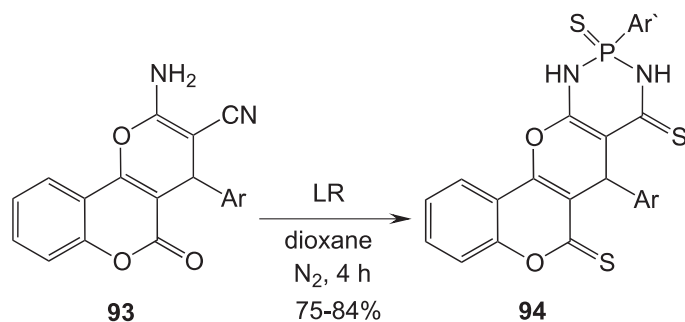
Scheme 36

On the other hand, addition of pyrano[3,2-*d*][1,2]oxazole-5-carbonitrile **85** to *P*-(4-methoxyphenyl)-*N,N'*-diphenylphosphonothioic diamide (**91**), which was prepared from reaction of LR with four folds of distilled aniline in dry toluene gave the isolated product **92** (46% yield) in a pure form (Scheme 37).⁵⁰



Scheme 37

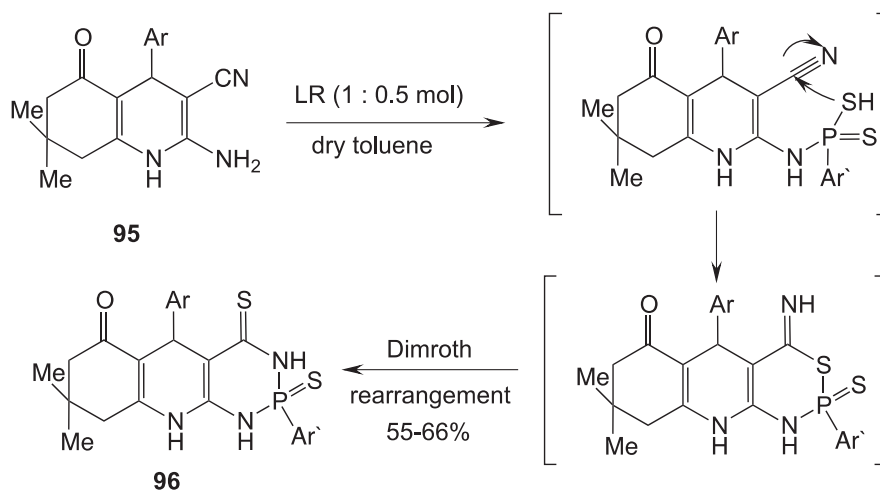
Likewise, the reaction of 1,2-aminocarbonitriles **93** with Lawesson's reagent (LR) in dry dioxane afforded two diastereoisomers of 1,3,2-diazaphosphinane derivatives **94** with high yields. The first step was attributed to the thionation of coumarinic carbonyl while the second step corresponded to rearrangement of the diazaphosphinane moiety (Scheme 38).⁵¹



Ar = Ph, *p*-ClC₆H₄, *p*-MeC₆H₄, *p*-MeOC₆H₄, *p*-tBuOC₆H₄, 3,4-(MeO)₂C₆H₄, 2-pyridinyl
 Ar' = 4-MeOC₆H₄

Scheme 38

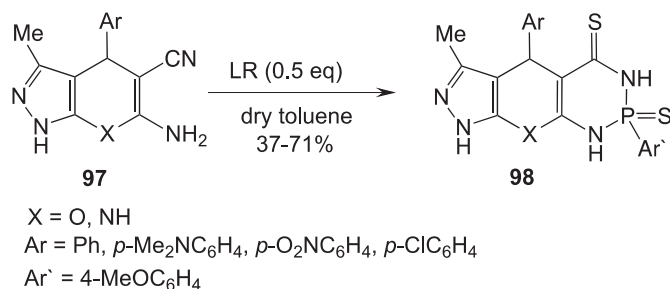
Mohamed *et al.*⁵² reported that the reaction of hexahydroquinolines **95** with Lawesson's reagent (LR) in dry toluene under reflux gave the thiazaphosphinine intermediate, which underwent Dimroth rearrangement producing 1,3,2-diazaphosphinino[4,5-*b*]quinolin-6-one derivatives **96** in 55-66% yields (Scheme 39).



Ar = Ph, 4-O₂NC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄
 Ar' = 4-MeOC₆H₄

Scheme 39

Refluxing of each pyrazolopyridines (X=NH) and pyranopyrazoles (X=O) derivatives **97** with Lawesson's reagent in dry toluene afforded pyrazolo[4',3':5,6]pyrido/pyrano[2,3-*d*][1,3,2]diazaphosphorine-4-thiones **98** in 37-71% yields (Scheme 40).⁵²

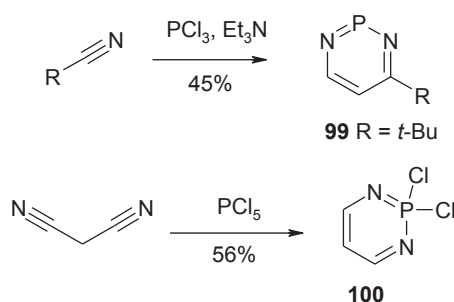


Scheme 40

2.4. MISCELLANEOUS METHODS

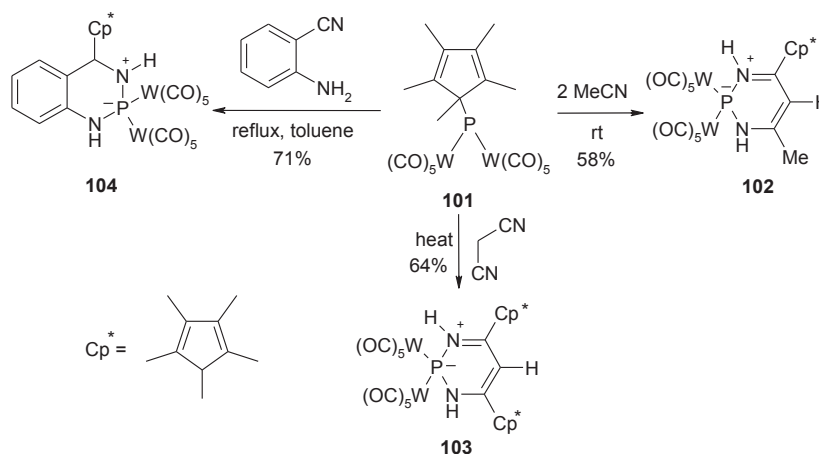
2.4.1. CYCLIZATION OF ALKYL/ARYL CYANIDE AND DINITRILE COMPOUNDS WITH PHOSPHORUS HALIDES AND PHOSPHINIDENE COMPLEX

Treatment of alkyl cyanide with phosphorus trichloride in the presence of triethylamine afforded 1,3,2-diazaphosphinine derivative **99**, while treatment of malononitrile with phosphorus pentachloride produced 2,2-dichloro-1,3,2λ⁵-diazaphosphinine **100** (Scheme 41).⁵³



Scheme 41

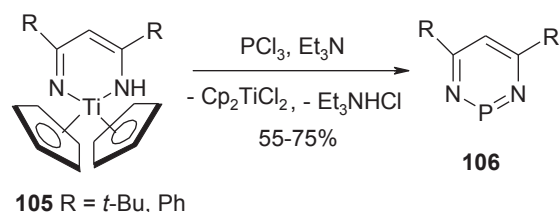
Insertion reaction of nitriles such as acetonitrile, malononitrile and 2-aminobenzonitrile into the unstrained P–C bond of the phosphinidene complex **101** gave 1,2-dihydro-1,3,2-diazaphosphinine derivatives **102-104**, respectively with different yields (Scheme 42).^{54,55}



Scheme 42

2.4.2. TREATMENT OF 1,3,2-DIAZATITANACYCLOHEXA-3,6-DIENES WITH PHOSPHORUS TRICHLORIDE

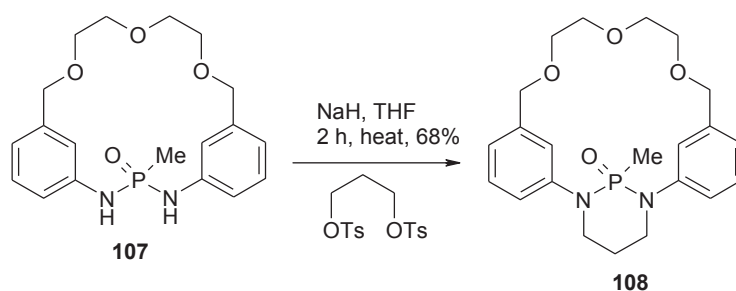
1,3,2-Diazaphosphinine derivatives **106** was obtained in good yields from the reaction of the corresponding 1,3,2-diazatitanacyclohexa-3,6-dienes (**105**) with PCl_3 in the presence of triethylamine (Scheme 43).^{56,57}



Scheme 43

2.4.3. CYCLIZATION OF PHOSPHONAMIDE VIA 1,3-BIS(TOLYLSULFONYLOXY)-PROPANE

Alkylation of phosphonamide derivative **107** with propane-1,3-diyl *bis*(tolylsulfonate) in the presence of sodium hydride in tetrahydrofuran gave the diazaphosphinine derivative **108** (Scheme 44).⁵⁸



Scheme 44

3. CONCLUSION

During the last few years the 1,3,2-diazaphosphinines 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 2018 on the available synthetic methods for 1,3,2-diazaphosphinines that will be a fundamental key in the design of new bioactive agents with improved pharmacological properties. The review was arranged according to the used methods. The most described methods depended on the cyclization of 1,3-diamine, 1,2-aminoamide, 1,2-aminonitrile *via* phosphorus halides and sulfides.

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