

The synthesis of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines

Noha M. Hassanin,^a Tarik E. Ali,^{b,a*} Mohammed A. Assiri,^b Hafez M. Elshaaer,^a and Somaia M. Abdel-Kariem^a

^a Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt

^b Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia

Email: tarik_elsayed1975@yahoo.com, tismail@kku.edu.sa

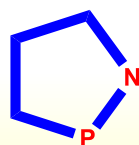
Received 06-28-2020

Accepted 08-26-2020

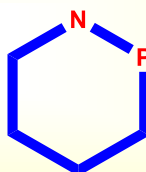
Published online 10-22-2020

Abstract

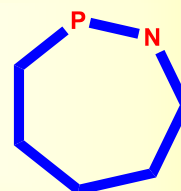
1,2-Azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are prominent phosphorus heterocycles and are of interest due to their potent pharmacological activities. In this review, we provide the available literature data on the synthesis of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines.



1,2-Azaphospholes



1,2-Azaphosphorines



1,2-Azaphosphepines

Keywords: 1,2-azaphospholes, 1,2-azaphosphorines, 1,2-azaphosphepines, phosphorus heterocycles

Table of Contents

1. Introduction
2. Synthetic Methods for Functionalized 1,2-Azaphosphole Derivatives
 - 2.1 Cyclization of ethyl *N*-methyl-3-bromopropylphosphonamidate with NaH
 - 2.2 Cyclization of γ -aminophosphorus compounds with bases
 - 2.3 Reaction of methyleneaminophosphanes with activated alkenes and alkynes
 - 2.4 Cyclization of 2-[2-(*t*-butylimino)cyclohexyl]acetonitrile with PCl_3
 - 2.5 Cyclization of 2-imino-2*H*-chromene-3-carboxamide with chlorodiphenylphosphine and diethyl phosphite
 - 2.6 Cyclization of chromonyl arylidenes and hydrazones with phosphorus tribromide and diethyl phosphite
 - 2.7 Reaction of dialkyl acetylenedicarboxylate with isocyanates and triphenylphosphine
 - 2.8 Dearomatizing anionic cyclization of *N*-alkyl-*N*-benzyl-diarylphosphinamides
 - 2.9 Rearrangement of 4,8-diaza-1-phosphaspiro[2.5]oct-1-ene with GaCl_3
 - 2.10 Thermal ring opening of 2*H*-azaphosphirene complexes
 - 2.11 Photolysis of azidophosphetanes
 - 2.12 Reaction of adduct of phosphalkynes and imidovanadium with acetylenes
 - 2.13 Thermal decomposition of 7-phosphanorbornadiene complex
 - 2.14 Reaction of 1,3,2-diazaphosphole-4,5-dicarbonitriles with alkynes
 - 2.15 Flash vacuum pyrolysis of 5-butyl-3-phenyl-1,2,3,4-triazaphosphole
 - 2.16 Reaction of chlorophosphenium triflate with potassium metal
3. Synthetic Methods for Functionalized 1,2-Azaphosphorine Derivatives
 - 3.1 Cyclization of phosphinamides using various bases
 - 3.2 Cyclization of *N*-[2-ethyl-3-methylhexa-1,3-dien-1-yl]butan-1-imine with RPCl_2
 - 3.3 Cyclization of 2-aminobiphenyl with PCl_3
 - 3.4 Cyclization of naphthylethylamine with thiophosphoryl chloride
 - 3.5 Cyclization of 2-amino-3-ethynylnaphthalenes with triphenoxyphosphine
 - 3.6 Cyclization of 2-(1*H*-indol-3-yl)-*N*-phenethylacetamides with phosphorus oxychloride
 - 3.7 Reaction of a $1\lambda^5,3\lambda^5$ -diphosphete adduct with ethyl isothiocyanate
 - 3.8 Ring expansion of 2,3-dihydro-1,2-azaphospholes by dichlorocarbene
 - 3.9 Reaction of 1,3,2-diazaphosphinines with alkynes
4. Synthetic Methods for Functionalized 1,2-Azaphosphepine Derivatives
 - 4.1 Ring expansion of phospholenes with benzonitrile
 - 4.2 Ring expansion of 1,2-azaphosphinines with dichlorocarbene
5. Conclusions
- Acknowledgements
- References

1. Introduction

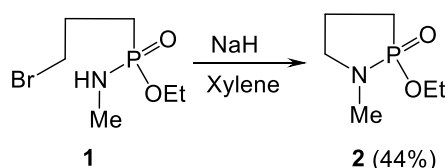
Organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical,¹⁻⁹ agricultural,¹⁰ and chemical agents.¹¹⁻¹⁵ Recently, phosphorus heterocycles^{16,17} have

received considerable interest because of their unique biological activities as antimicrobial¹⁸ and their anticancer effects.^{19–22} Ifosfamide and cyclophosphamide are two important examples of phosphorus heterocycles that were launched on the market more than 30 years ago and are still used in treatment of cancer.^{23,24} Much attention has been directed to the synthesis of phosphorus heterocycles due to their wide-ranging utilities as synthetic intermediates in organic syntheses.^{25–31} Among these phosphorus heterocycles, 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are of interest in several laboratories due to their potent pharmacological activities such as antitumor,³² complexing agents,^{33,34} and inhibitor of mammalian dihydroorotase.³⁵ The present review is focused on the most methodologies for the construction of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines up to the end of 2019 and to supplement the information available in literature. In addition, there is discussion of mechanisms.

2. Synthetic Methods for Functionalized 1,2-Azaphosphole Derivatives

2.1 Cyclization of ethyl *N*-methyl-3-bromopropylphosphonamidate with NaH

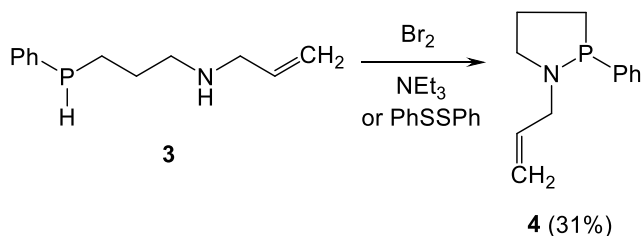
Cyclization of ethyl *N*-methyl-3-bromopropylphosphonamidate (**1**) with sodium hydride in xylene at 120–125 °C gave 2-ethoxy-1-methyl-2-oxido-1,2-azaphospholidine (**2**) (Scheme 1).³⁶



Scheme 1

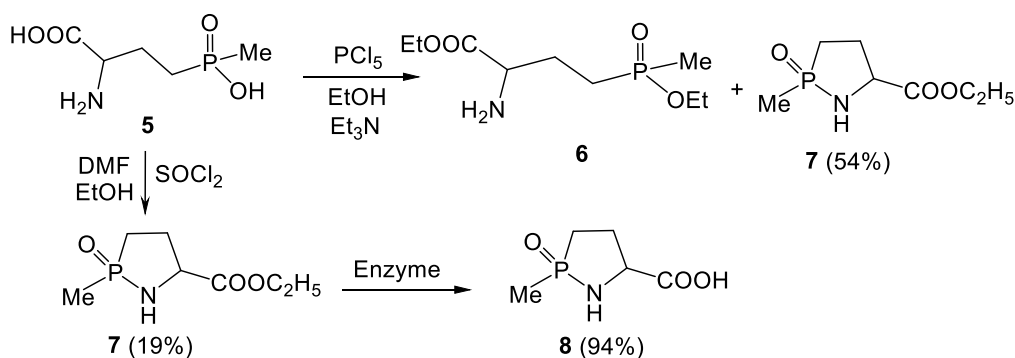
2.2 Cyclization of γ -aminophosphorus compounds with bases

Ring closure of *N*-[3-(phenylphosphanyl)propyl]prop-2-en-1-amine (**3**) by using bromine in the presence of triethylamine or 1,2-diphenyldisulfane at 50–60 °C led to 1-allyl-2-phenyl-1,2-azaphospholidine (**4**) (Scheme 2).³⁶



Scheme 2

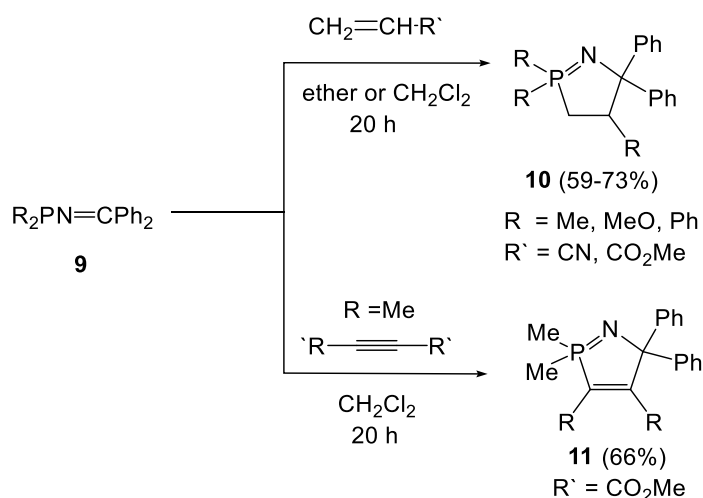
Treatment of 2-amino-4-[hydroxy(methyl)phosphoryl]butanoic acid (**5**) with phosphorus pentachloride in the presence of triethylamine as a catalyst and ethanol at 45–50 °C furnished ethyl 2-amino-4-[ethoxy(methyl)phosphoryl]butanoate (**6**) and ethyl 2-methyl-2-oxido-1,2-azaphospholidine-5-carboxylate (**7**) (Scheme 3). The product **7** was also formed by treatment of acid **5** with thionyl chloride and a catalytic amount of DMF at 100–110 °C, followed by addition of absolute ethanol. Enzyme catalyzed hydrolysis of product **7** to afford the corresponding free acid **8** (Scheme 3).³⁷



Scheme 3

2.3 Reaction of methyleneaminophosphanes with activated alkenes and alkynes

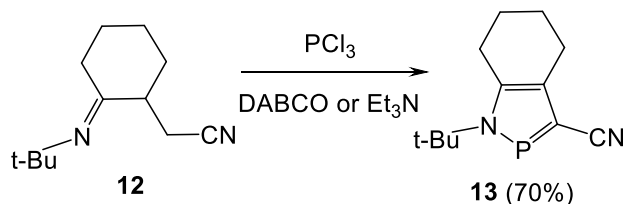
Methyleneaminophosphanes **9** reacted with activated alkenes such as acrylonitrile and methyl acrylate at room temperature to give the corresponding 5,5-diphenyl-4,5-dihydro-3*H*-1,2λ⁵-azaphospholes **10** (Scheme 4), while its reaction with dimethyl acetylenedicarboxylate furnished dimethyl 2,2-dimethyl-5,5-diphenyl-5*H*-1,2λ⁵-azaphosphole-3,4-dicarboxylate (**11**) (Scheme 4).³⁸



Scheme 4

2.4 Cyclization of 2-[2-(*t*-butylimino)cyclohexyl]acetonitrile with PCl₃

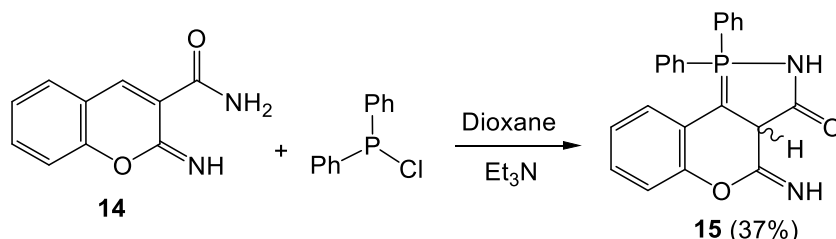
1-*t*-Butyl-4,5,6,7-tetrahydro-1*H*-1,2-benzazaphosphole-3-carbonitrile (**13**) was prepared by condensation of 2-[2-(*t*-butylimino)cyclohexyl]acetonitrile (**12**) with PCl₃ at 50-55 °C in the presence of triethylamine as a base. The yield was improved when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used in place of triethylamine (Scheme 5).³⁹



Scheme 5

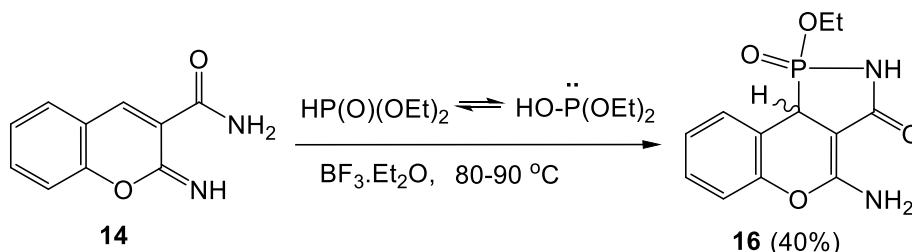
2.5 Cyclization of 2-imino-2*H*-chromene-3-carboxamide with chlorodiphenylphosphine and diethyl phosphite

2-Imino-2*H*-chromene-3-carboxamide (**14**) reacted with chlorodiphenylphosphine in dry dioxane containing a few drops of triethylamine at 90-95 °C to yield 1,1-diphenyl-4-imino-3a,4-dihydro-15-chromeno[4,3-*c*][1,2]azaphosphol-3(2*H*)-one (**15**) (Scheme 6).⁴⁰



Scheme 6

4-Amino-1-ethoxy-1-oxido-1,9*b*-dihydrochromeno[4,3-*c*][1,2]azaphosphole-3(2*H*)-one (**16**) was obtained by treatment of the carboxamide **14** with diethyl phosphite in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a catalyst at 80-90 °C (Scheme 7).⁴¹

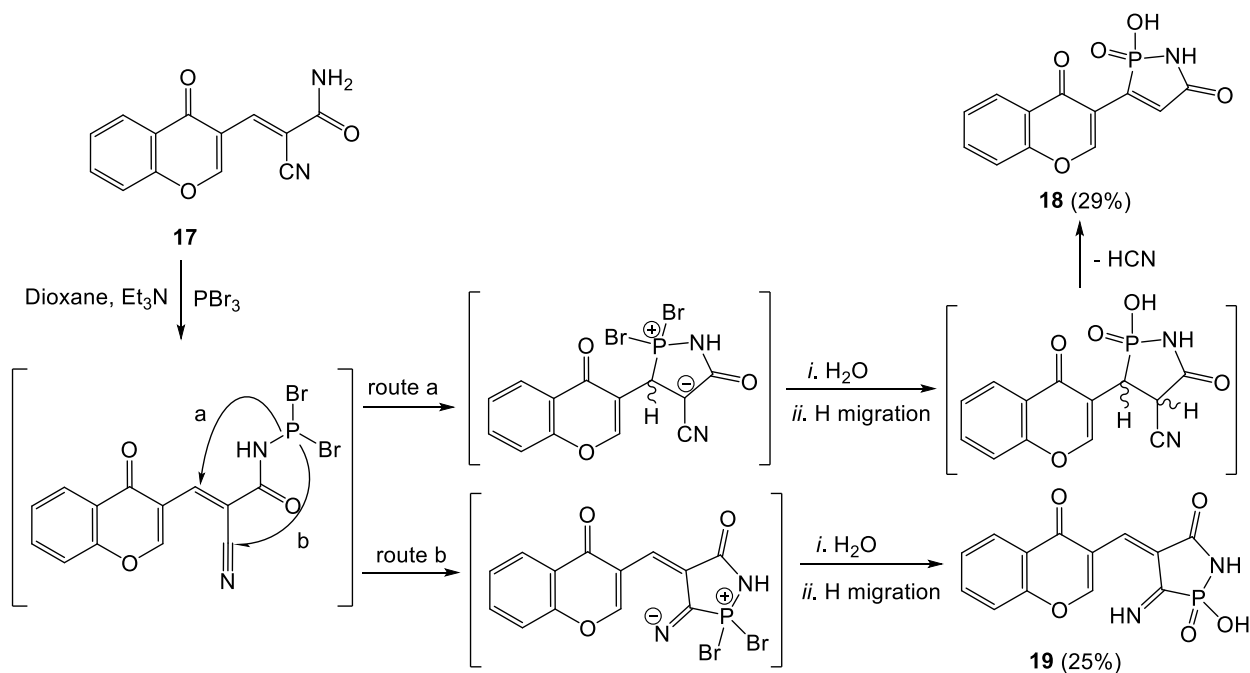


Scheme 7

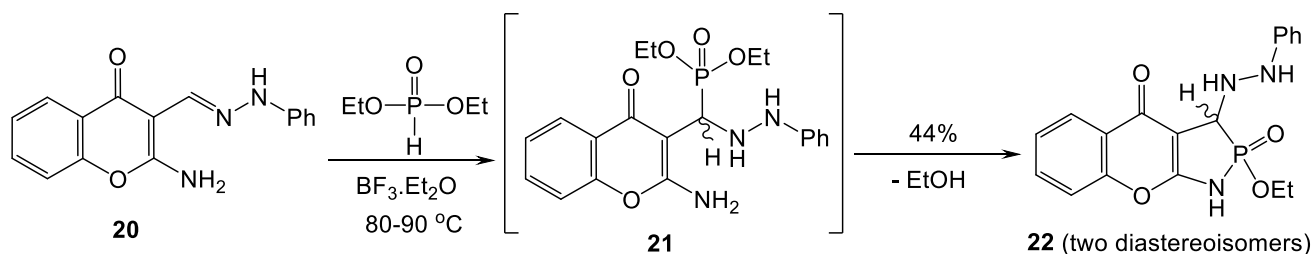
2.6 Cyclization of chromonyl arylidenes and hydrazones with phosphorus tribromide and diethyl phosphite

2-Cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**17**) reacted with phosphorus tribromide in dry dioxane containing a catalytic quantity of triethylamine 90-95 °C to give two isomeric chromonyl-1,2-azaphospholes **18** and **19** (Scheme 8).⁴²

Fusion of the chromonyl phenylhydrazone **20** with diethyl phosphite at 80-90 °C in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as a catalyst under Pudovik reaction conditions resulted in the nonisolable diethyl hydrazinophosphonate **21** (Scheme 9). The latter intermediate underwent spontaneous cyclization by elimination of ethanol to provide the chromeno[3,2-*d*][1,2]azaphosphole **22** as two diastereoisomers (Scheme 9).³²



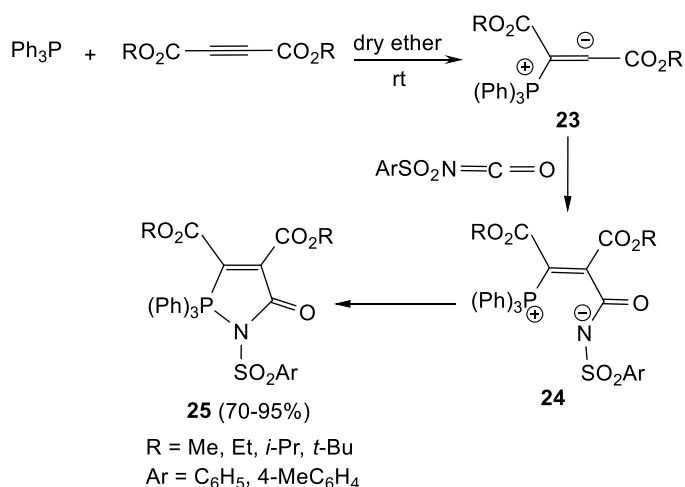
Scheme 8



Scheme 9

2.7 Reaction of dialkyl acetylenedicarboxylate with isocyanates and triphenylphosphine

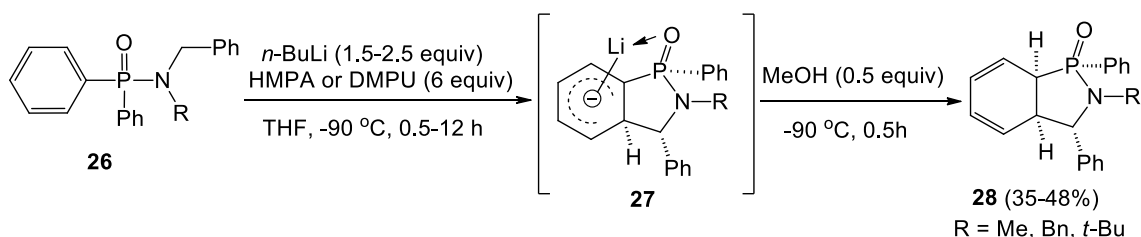
Dialkyl 2,5-dihydro-5-oxo-1,2-azaphosphole-3,4-dicarboxylates (**25**) resulted from a three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylate and arylsulfonyl isocyanates (Scheme 10). The product **25** was a result of the initial addition of triphenylphosphine to the acetylenic diester and subsequent attack of the resulting anion **23** to the carbonyl carbon atom of the arylsulfonyl isocyanate to yield the betaine **24**. The latter betaine underwent spontaneous cyclization to produce the 1,2-azaphosphole **25** (Scheme 10).⁴³



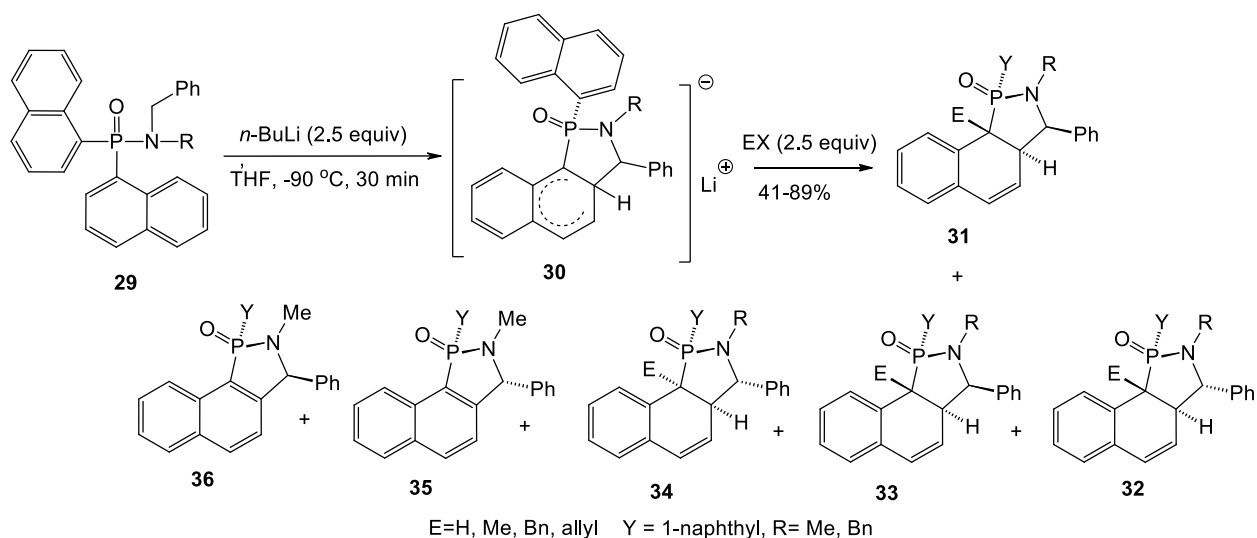
Scheme 10

2.8 Dearomatizing anionic cyclization of *N*-alkyl-*N*-benzyl-diarylphosphinamides

Treatment of *N*-alkyl-*N*-benzyl-diphenylphosphinamides (**26**) at low temperature with *n*-BuLi in THF in the presence of HMPA or DMPU gave the anions **27**. The developed anions **27** underwent anionic cyclization by Michael addition to the *ortho* position of the *P*-phenyl ring, which resulted in tetrahydro-2,1-benzazaphospholes **28** as a dearomatized species trapped with methanol with high regio- and stereo-control (Scheme 11).⁴⁴ Similarly, the cyclization of *N*-alkyl-*N*-benzyl-dinaphthylphosphinamides **29** by using *n*-BuLi in THF and subsequent trapping with a series of alkyl halides afforded a series of tetrahydro-1*H*-naphtho[1,2-*c*]-[1,2]azaphospholes **31-36** (Scheme 12).⁴⁴

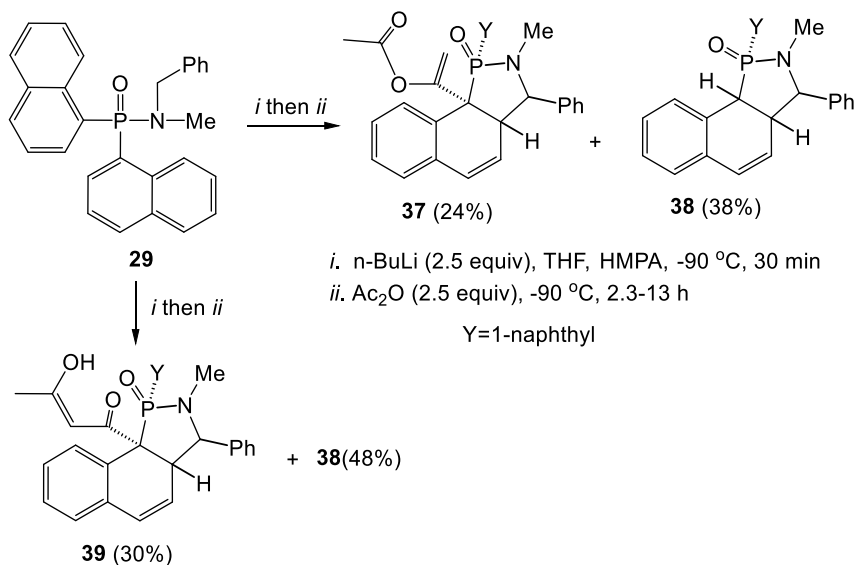


Scheme 11



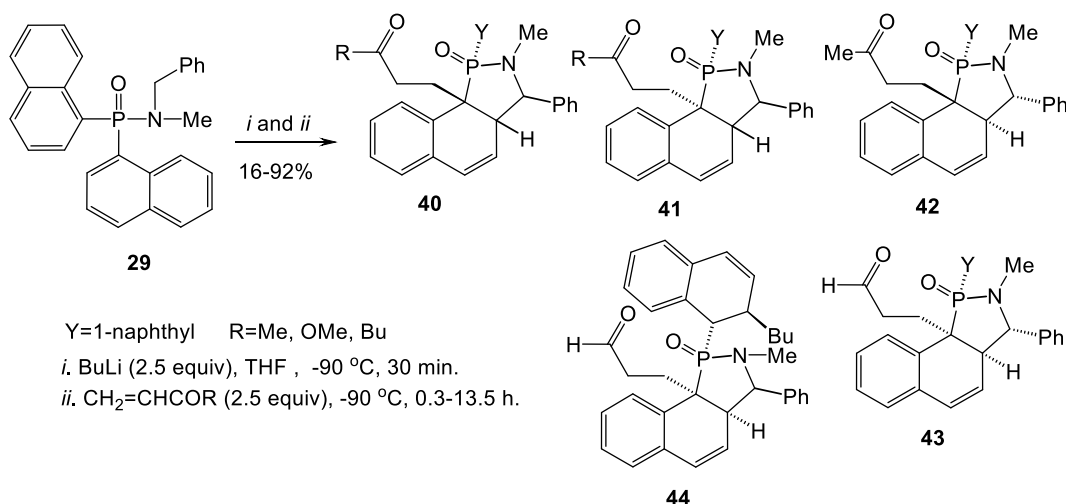
Scheme 12

N-Benzyl-*N*-methyl-dinaphthylphosphinamide (**29**) underwent cyclization by using *n*-BuLi in THF then adding acetic anhydride to isolate the azaphosphole **38** as the major product in the presence or absence of the co-solvent HMPA (Scheme 13). The acylation then deprotonation of the methyl group of the CH₃CO moiety and trapping gave the product of *O*-acetylation **37**, or *C*-acetylation **39** with low yields (Scheme 13).⁴⁵



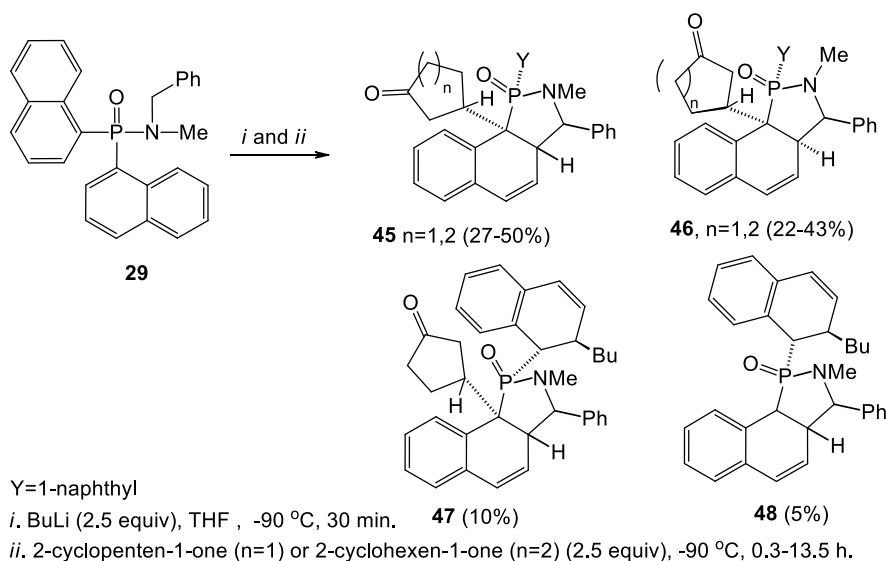
Scheme 13

In the same way, the reaction of compound **29** with *n*-BuLi in THF then acyclic α,β -unsaturated aldehydes and ketones afforded the functionalized tricyclic 1,2-azaphospholes **40–44** (Scheme 14).⁴⁵



Scheme 14

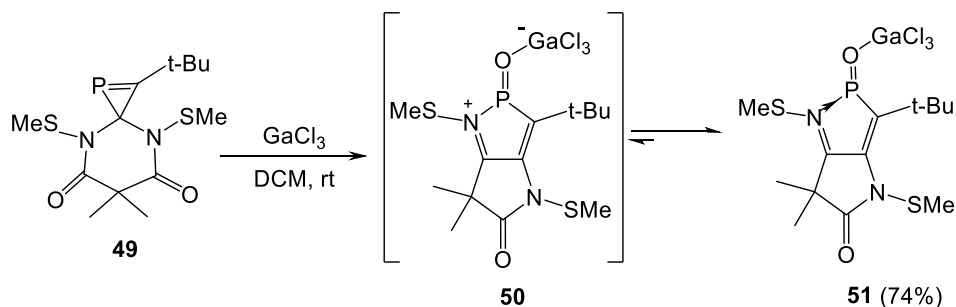
The reaction of starting material **29** with *n*-BuLi in THF followed by addition of 2-cyclopenten-1-one or 2-cyclohexen-1-one took place with good yield and low selectivity to form a mixture of tricyclic 1,2-azaphospholes **45** and **46** with a *cis*-junction in a ratio of 1:1.6 (Scheme 15). Other products (**47** and **48**) were also formed due to the dearomatization of the two naphthalene rings (Scheme 15).⁴⁵



Scheme 15

2.9 Rearrangement of 4,8-diaza-1-phoshaspiro[2.5]oct-1-ene with GaCl₃

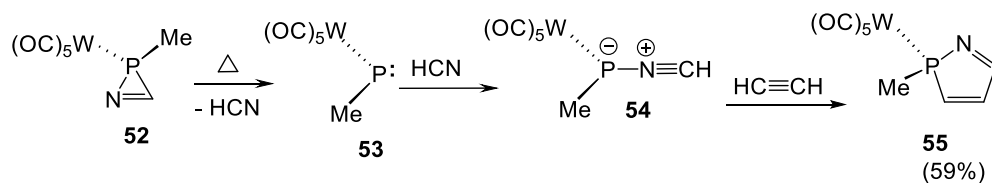
Reaction of 2-*t*-butyl-6,6-dimethyl-4,8-bis(methylthio)-4,8-diaza-1-phoshaspiro[2.5]oct-1-ene-5,7-dione (**49**) with GaCl₃ induced an unexpected rearrangement leading to the formation of the complex **50** which stabilized into 1,2-azaphosphole form **51** (Scheme 16).⁴⁶



Scheme 16

2.10 Thermal ring opening of 2*H*-azaphosphirene complexes

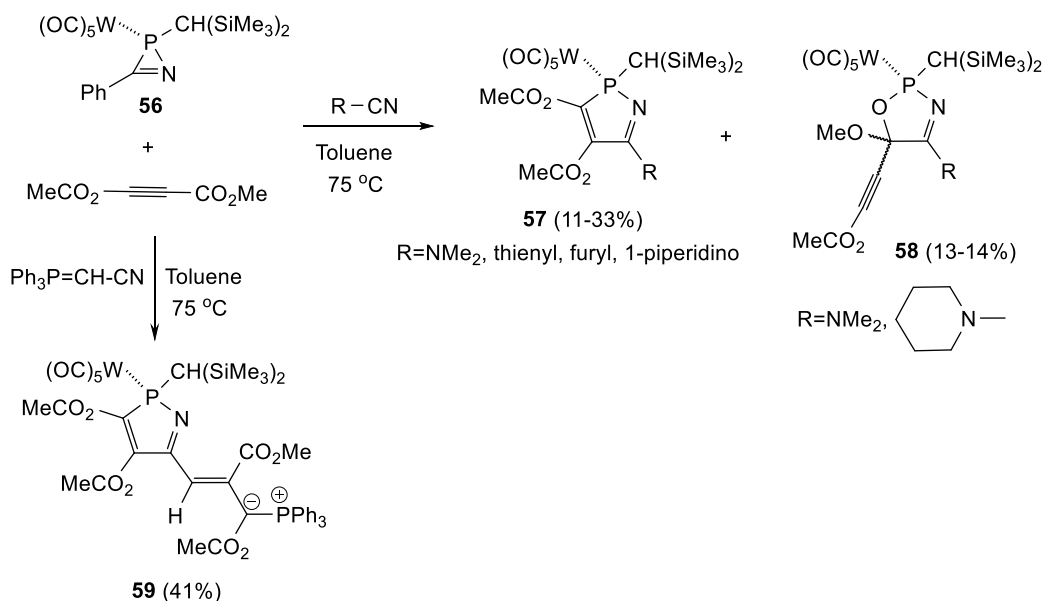
The thermolysis of the (2*H*-azaphosphirene)tungsten carbonyl complex **52** at 60 °C gave the nitrilium phosphanylide complex **54**, which reacted with acetylene to yield the 1,2-azaphosphole complex **55** (Scheme 17).⁴⁷



Scheme 17

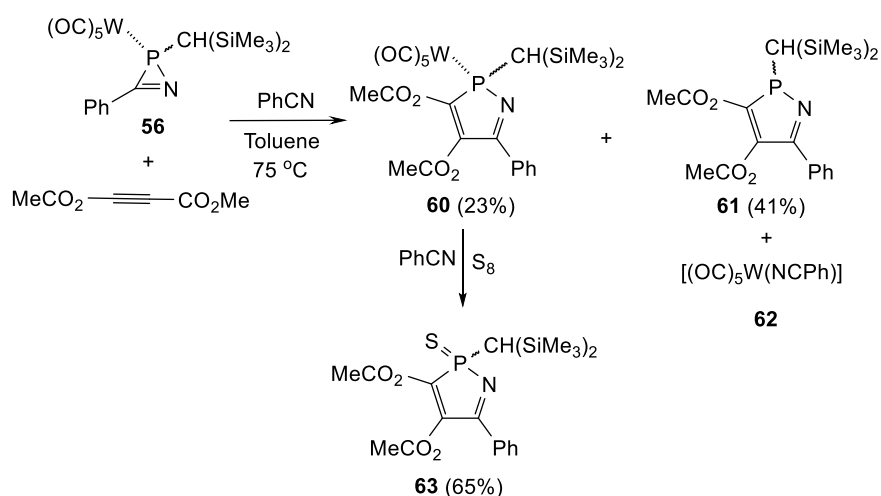
Thermal ring opening of the (2*H*-1,2-azaphosphirene)tungsten complex **56** with dimethyl acetylenedicarboxylate and nitriles yielded the corresponding 1,2-azaphosphole complexes **57** (Scheme 18). When 1-piperidinocarbonitrile or dimethyl cyanamide was used, 1,3,2-oxazaphospholene complexes **58** (*meso* and

racemic in ratio of 1:1) was also obtained beside the desired product **57** (Scheme 18). Furthermore, the reaction of complex **56** with 2-(triphenyl- λ^5 -phosphanyl)acetonitrile led to the formation of 1,2-azaphosphole **59** (Scheme 18).^{33,48-50}



Scheme 18

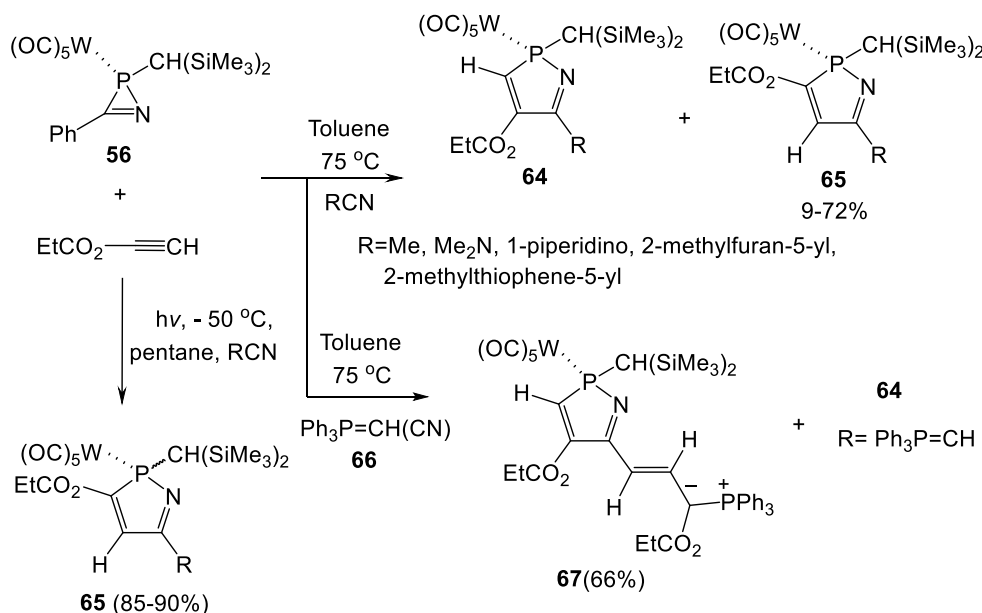
Also, ring opening reaction of 1,2-azaphosphirene complex **56** with dimethyl acetylenedicarboxylate and benzonitrile in toluene furnished a mixture of 2H-1,2-azaphosphole complexes **60** and **61** (Scheme 19). The yield of complex **60** was significantly improved to 90% when the reaction was carried out photochemically in pentane at -50 °C. Heating of complex **60** in benzonitrile with sulfur gave the 2-sulfido-2H-1,2-azaphosphole **63** (Scheme 19).^{33,51-53}



Scheme 19

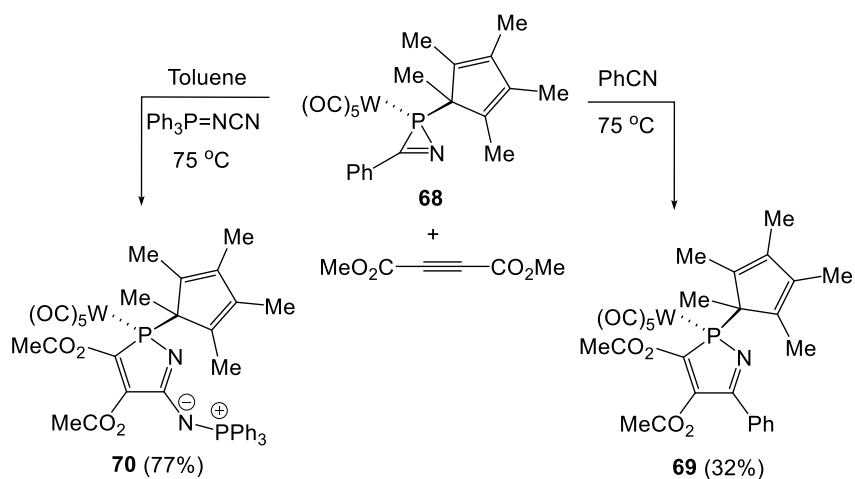
On the other hand, the three component reactions of 2H-azaphosphirene complex **56**, ethyl propiolate and nitriles led to the formation of the regioisomeric 2H-1,2-azaphosphole complexes **64** and **65** (Scheme 20). In case of using $\text{Ph}_3\text{P}=\text{CH}(\text{CN})$ (**66**), a mixture of 1,2-azaphosphole complexes **64** and **67** were formed. Also,

reaction of complex **56** with ethyl propiolate and different nitriles in pentane gave 1,2-azaphospholes **65** in high yield (Scheme 20).^{49,50,52,54}



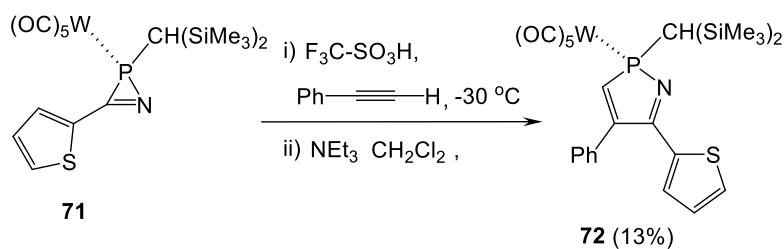
Scheme 20

Similarly, the ring-opening of the 1,2-azaphosphirene complex **68** in benzonitrile in the presence of dimethyl acetylenedicarboxylate as a trapping reagent afforded the 1,2-azaphosphole complex **69**. When the reaction was performed with $Ph_3P=NCN$ in dry toluene, the 1,2-azaphosphole complex **70** was formed in high yield (Scheme 21).^{33,55}



Scheme 21

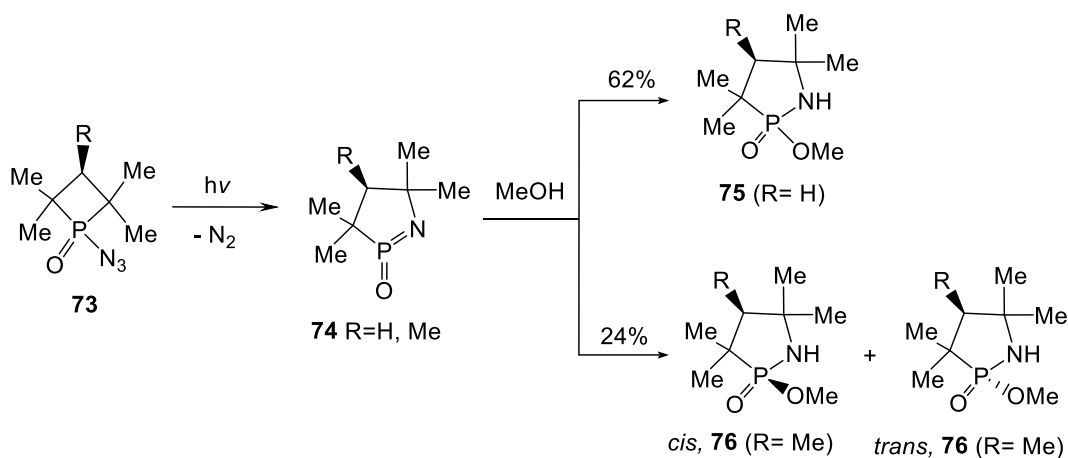
Reaction of the (2*H*-azaphosphirene)tungsten complex **71** with trifluoromethanesulfonic acid, phenylacetylene and triethylamine in CH_2Cl_2 proceeded through P–C bond ring enlargement to afford 2*H*-1,2-azaphosphole complex **72** in low yield (Scheme 22).⁵⁶



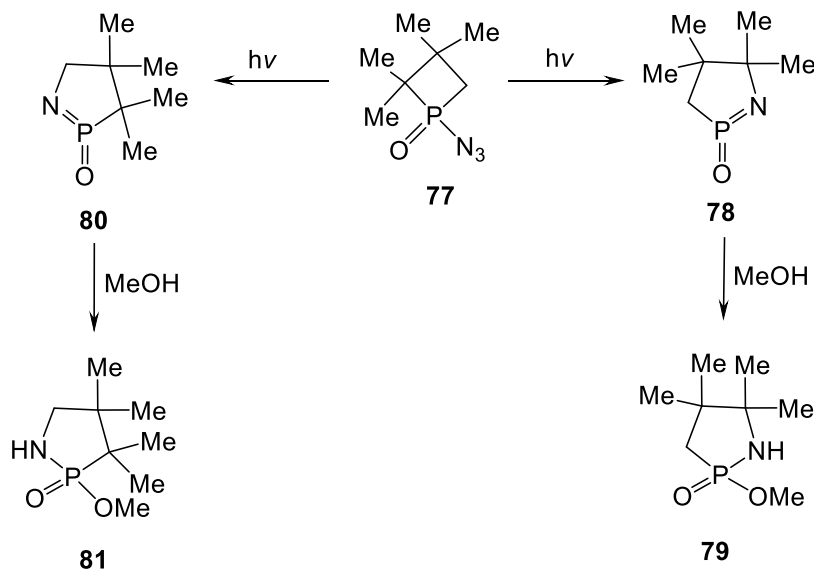
Scheme 22

2.11 Photolysis of azidophosphetanes

Photolysis of 1-azido-2,2,4,4-tetramethylphosphetane 1-oxide **73** ($\text{R}=\text{H}$) afforded the cyclic 1,2-azaphospholidine **75** by elimination of N_2 and addition of methanol (Scheme 23). Likewise, photolysis of azide **73** ($\text{R}=\text{Me}$) gave a mixture of *cis*- and *trans*-1,2-azaphospholidines **76** (Scheme 23).⁵⁷



Scheme 23

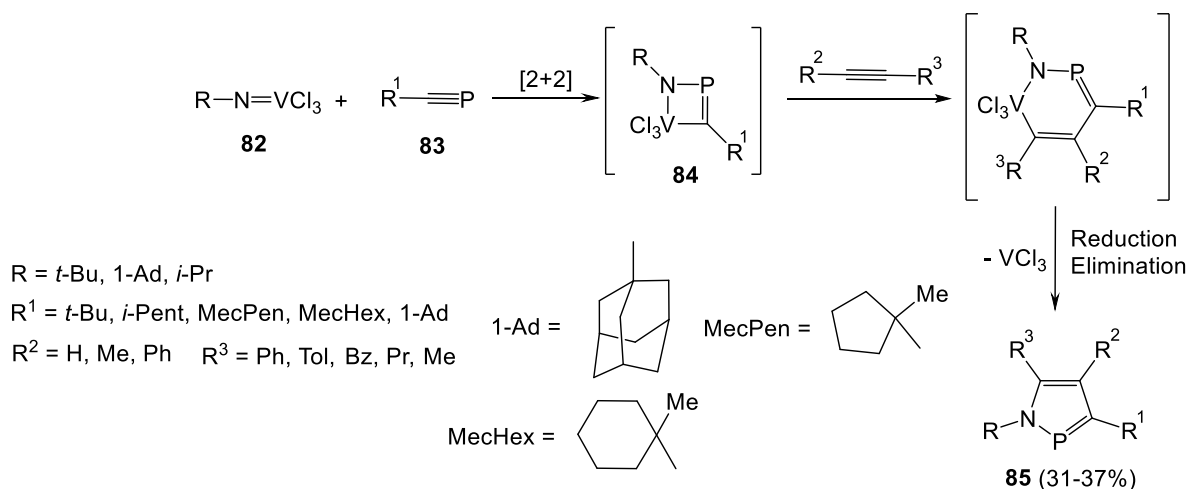


Scheme 24

Unlike **73**, the azide **77** lacks symmetry and has two possible modes of ring expansion. Thus, its photolysis in methanol yielded an approximately equimolar mixture (40% total) of the isomeric 1,2-azaphospholidines **79** and **81** (Scheme 24).⁵⁷

2.12 Reaction of adduct of phosphalkynes and imidovanadium with acetylenes

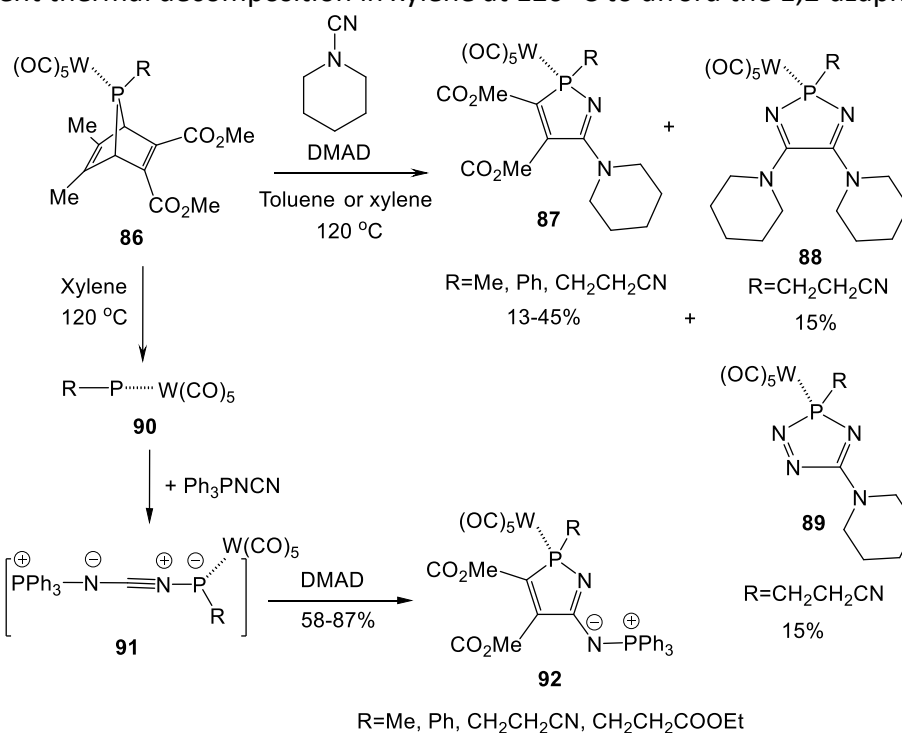
The cycloadduct **84** was generated *in situ* by addition of an equimolar amount of a phosphalkynes **83** to the imidovanadium complexes **82** (Scheme 25). The cycloadduct **84** was treated with an excess of disubstituted acetylenes in toluene at -78 °C to form the tetrasubstituted 1,2-azaphospholes **85** in 31-71% yields (Scheme 25).⁵⁸



Scheme 25

2.13 Thermal decomposition of 7-phosphanorbornadiene complex

In the presence of piperidine-1-carbonitrile and dimethyl acetylenedicarboxylate, 7-phosphanorbornadiene complex **86** underwent thermal decomposition in xylene at 120 °C to afford the 1,2-azaphosphole complex **87**

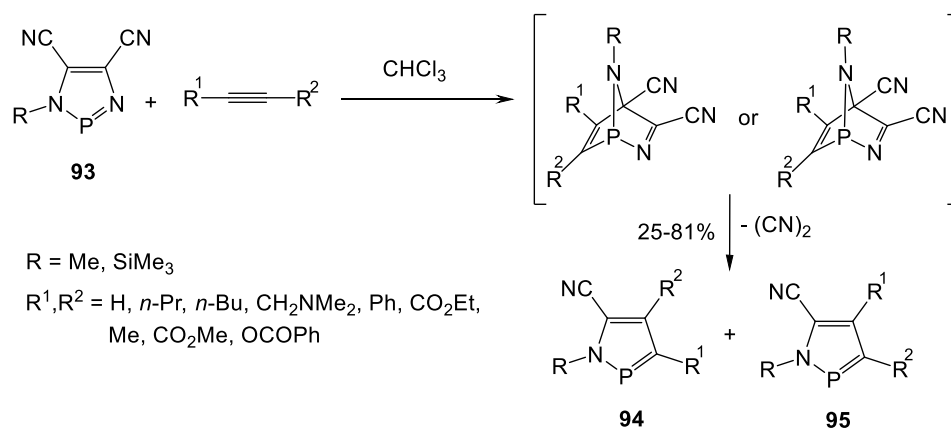


Scheme 26

beside a complicated mixture of the regioisomeric complexes **88** and **89** (Scheme 26). When the reaction was performed in dry toluene, the product 2*H*-1,2-azaphosphole complex **87** only was isolated. When another carbonitrile derivative such as $\text{Ph}_3\text{P}=\text{NCN}$ was used, the thermal decomposition of complex **86** in xylene furnished the 2*H*-1,2-azaphosphole complex **92** through [3+2] cycloaddition reaction of nitrilium phosphane ylide complexes **91** formed with dimethyl acetylenedicarboxylate (Scheme 26).⁵⁹⁻⁶¹

2.14 Reaction of 1,3,2-diazaphosphole-4,5-dicarbonitriles with alkynes

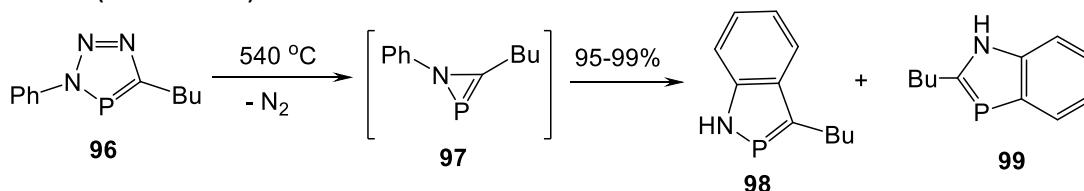
The regioselective cyclization of 1,3,2-diazaphosphole-4,5-dicarbonitriles **93** with symmetrical and non-symmetrical alkynes in chloroform at room temperature yielded the 1,2-azaphosphole-5-carbonitriles **94** (Scheme 27). In some cases of non-symmetrical alkynes, the other isomers **95** were also formed (Scheme 27).⁶²



Scheme 27

2.15 Flash vacuum pyrolysis of 5-butyl-3-phenyl-1,2,3,4-triazaphosphole

Dinitrogen was split off from 5-butyl-3-phenyl-1,2,3,4-triazaphosphole (**96**) on flash vacuum pyrolysis to give the azaphosphirene intermediate **97**. This intermediate underwent 1,5-electrocyclization followed by proton migration to form the annulated 3-butyl-1*H*-[1,2]benzazaphosphole (**98**) and 2-butyl-1*H*-[1,3]benzazaphosphole (**99**) in a ratio of 4:1 (Scheme 28).³⁹

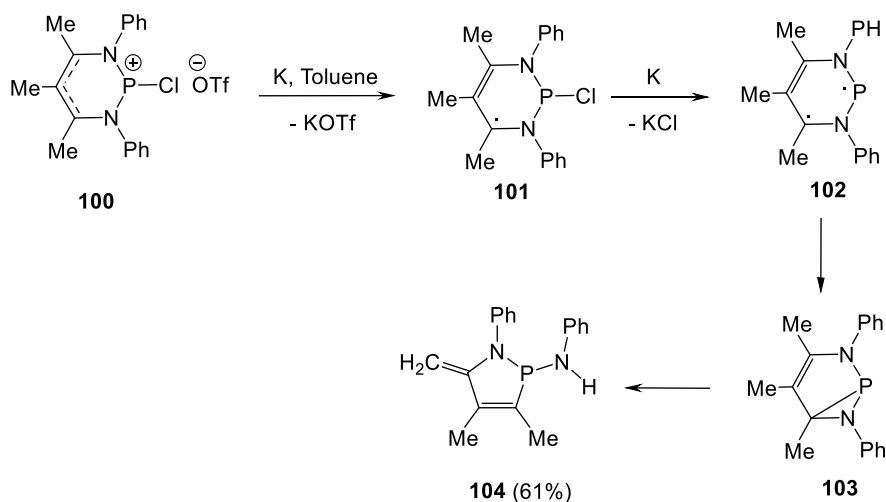


Scheme 28

2.16 Reaction of chlorophosphenium triflate with potassium metal

Treatment of chlorophosphenium triflate **100** with potassium metal in toluene at 25°C resulted in a pale yellow crystalline 1,2-azaphospholidine **104** (Scheme 29). It was assumed that the two-electron reduction of the idealized chlorophosphenium ion **100** proceeded in two steps; addition of the first electron would generate the monoradical **101**. Addition of the second electron would then generate the triplet diradical phosphinidene **102**. The conversion of **102** to **103** took place by an intramolecular P–C bond formation to afford the derivative **103**. Finally, the latter **103** underwent N–C bond cleavage and hydrogen transferred from

β -methyl group to the nascent imido nitrogen center forming the isolated 1,2-azaphospholidine isomer **104** (Scheme 29).⁶³

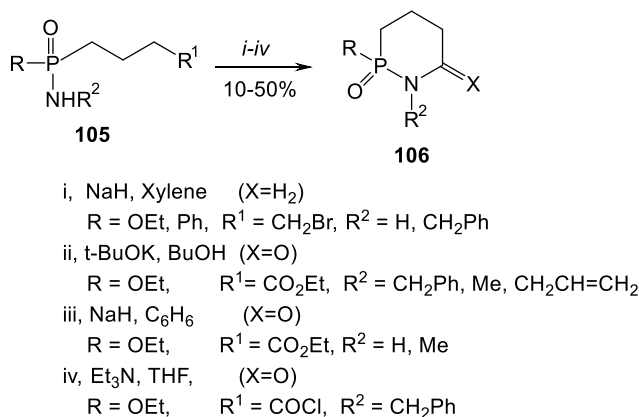


Scheme 29

3. Synthetic Methods for Functionalized 1,2-Azaphosphorine Derivatives

3.1 Cyclization of phosphinamides using various bases

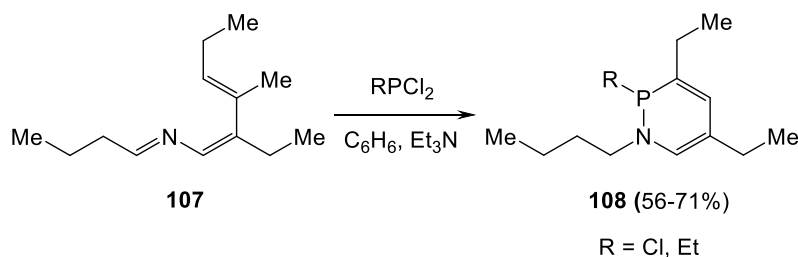
Cyclization of different phosphinamides **105** using various bases at the boiling point of the used solvent furnished 2-oxido-1,2-azaphosphinanes **106** in different yields through removal of ethanol or hydrogen halide (Scheme 30).^{64,65}



Scheme 30

3.2 Cyclization of *N*-[2-ethyl-3-methylhexa-1,3-dien-1-yl]butan-1-imine with R₂PCl₂

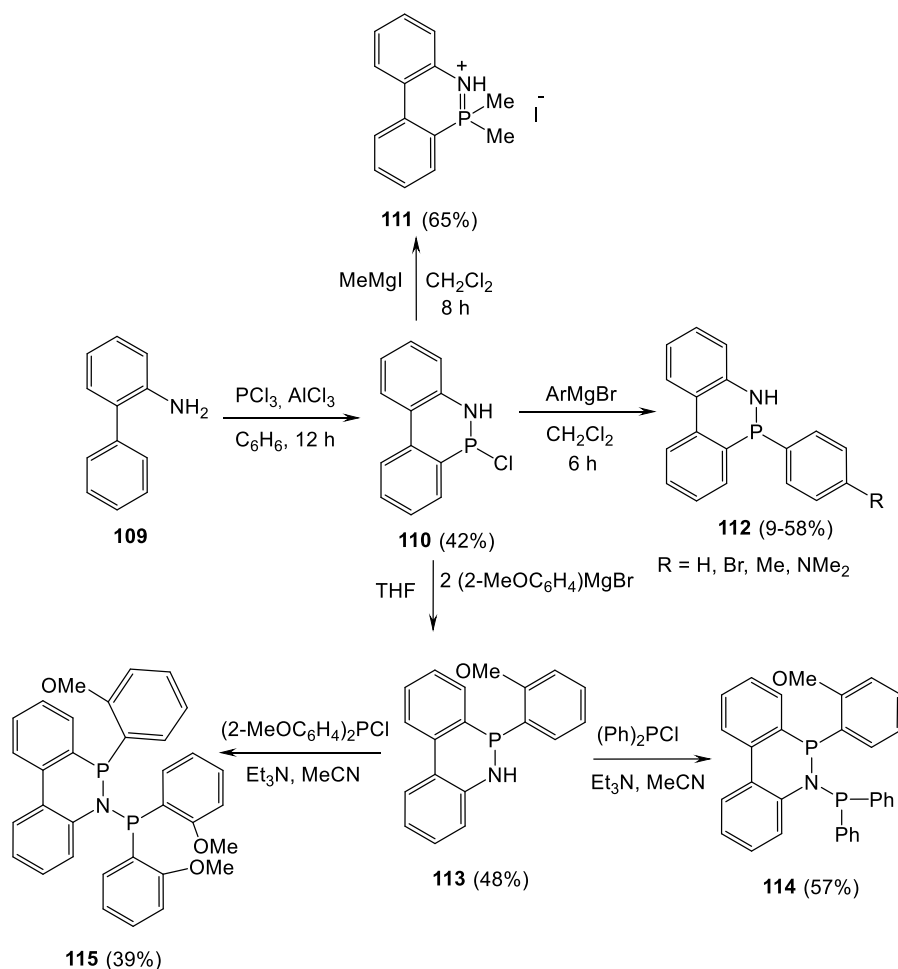
Cyclocondensation of *N*-[2-ethyl-3-methylhexa-1,3-dien-1-yl]butan-1-imine (**107**) with dichlorophosphine derivatives in dry benzene at 50 °C containing Et₃N afforded 1-butyl-3,5-diethyl-1,2-dihydro-1,2-azaphosphorines (**108**) (Scheme 31).⁶⁶



Scheme 31

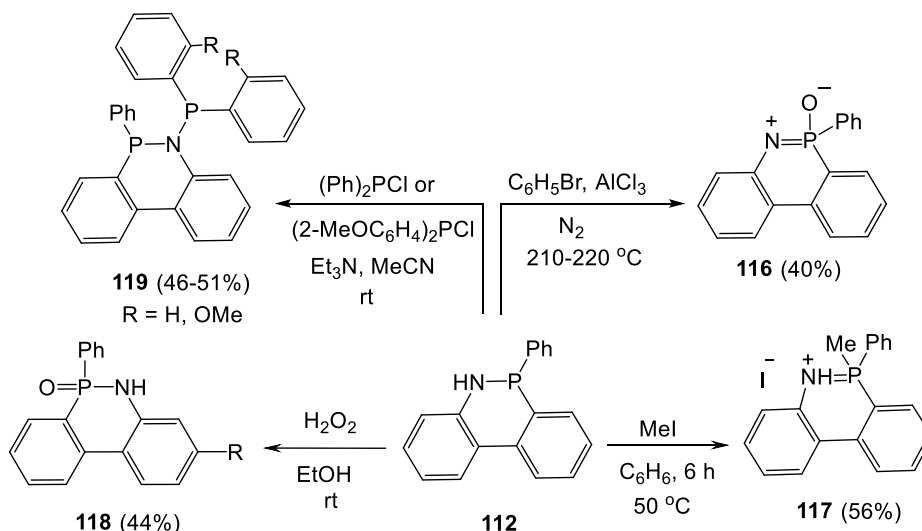
3.3 Cyclization of 2-aminobiphenyl with PCl_3

Reaction of 2-aminobiphenyl (**109**) with phosphorus trichloride in boiling benzene at 65 °C containing a catalytic amount of AlCl_3 afforded 10-chloro-9,10-dihydro-9,10-azaphosphaphenanthrene (**110**). Compound **110** has an active chlorine atom which can be substituted by a wide range of nucleophiles. Thus, treatment of the product **110** with methyl magnesium iodide in CH_2Cl_2 gave 10-methyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-methiodide (**111**) while its reaction with aryl magnesium bromide in dry CH_2Cl_2 at room temperature formed 10-aryl-9,10-dihydro-9,10-azaphosphaphenanthrenes **112** (Scheme 32). Also, reaction of compound **110** with (2-methoxyphenyl) magnesium bromide in THF at 60 °C gave 10-(2-methoxyphenyl)-9,10-dihydro-9,10-azaphosphaphenanthrene (**113**) which was phosphorylated with chlorodiarylphosphine in acetonitrile at room temperature to give 5-(diarylphosphanyl)-6-(2-methoxyphenyl)-5,6-dihydro-dibenzo[*c,e*][1,2]azaphosphinines **114** and **115** (Scheme 32).⁶⁷⁻⁶⁹



Scheme 32

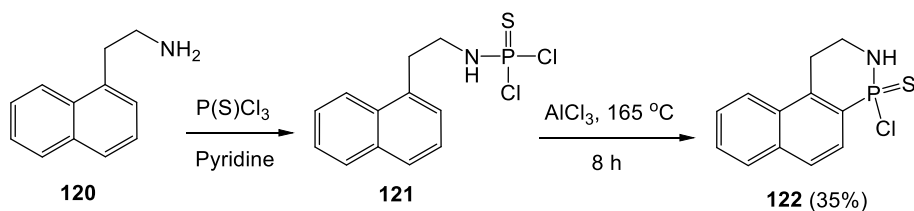
Compound **112** (R = H) acts as a substrate for the preparation of a series of functionalized 1,2-azaphosphaphenanthrenes. Thus, its reaction with bromobenzene in the presence of anhydrous AlCl_3 in current of nitrogen gas furnished 10-phenyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide (**116**) (Scheme 33). Moreover, its reaction with methyl iodide in dry benzene gave 10-phenoxy-9,10-dihydro-9,10-azaphosphaphenanthrene methiodide **117** (Scheme 33). Oxidation of compound **112** by hydrogen peroxide in ethanol at room temperature afforded the corresponding oxide **118**. Furthermore, reaction of compound **112** with chlorodiphenylphosphine or bis(2-methoxyphenyl)chlorophosphine in acetonitrile in the presence of triethylamine gave 5-(diarylphosphanyl)-6-phenyl-5,6-dihydrodibenzo[*c,e*][1,2]azaphosphinines (**119**) (Scheme 33).⁶⁷⁻⁶⁹



Scheme 33

3.4 Cyclization of naphthylethylamine with thiophosphoryl chloride

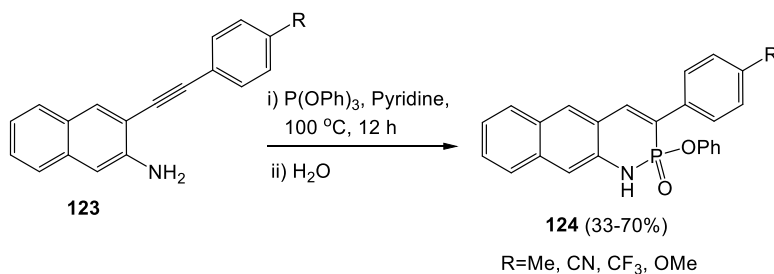
Treatment of naphthylethylamine **120** with thiophosphoryl chloride in dry pyridine at 100 °C gave 2-[(naphthalene-1-yl)ethyl]phosphoramidothioic dichloride (**121**), which with AlCl_3 at 165 °C for 8 h gave 4-chloro-1,2,3,4-tetrahydronaphtho[2,1-*c*][1,2]azaphosphinine 4-sulfide (**122**) (Scheme 34).⁷⁰



Scheme 34

3.5 Cyclization of 2-amino-3-ethynylnaphthalenes with triphenoxyphosphine

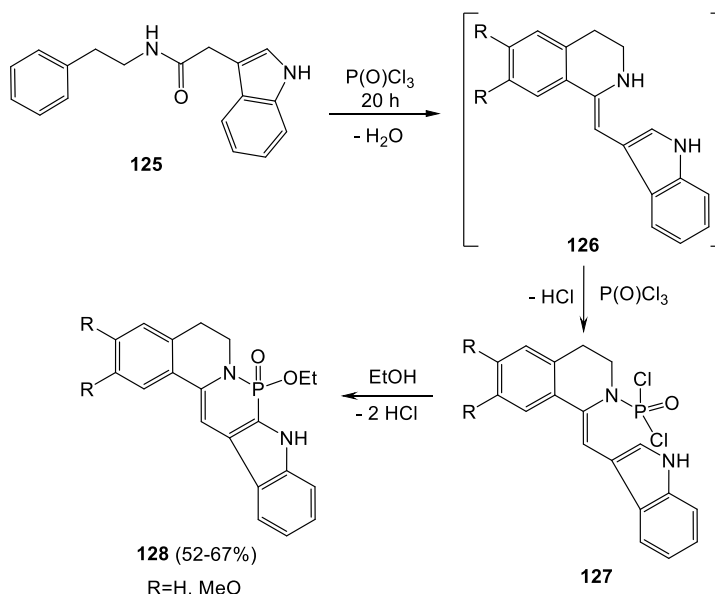
Cyclization of 2-amino-3-ethynylnaphthalenes (**123**) with triphenoxyphosphine in dry pyridine for 12 h furnished naphtho[2,3-*e*][1,2]azaphosphorines (**124**) in moderate yields (Scheme 35).⁷¹



Scheme 35

3.6 Cyclization of 2-(1*H*-indol-3-yl)-*N*-phenethylacetamides with phosphorus oxychloride

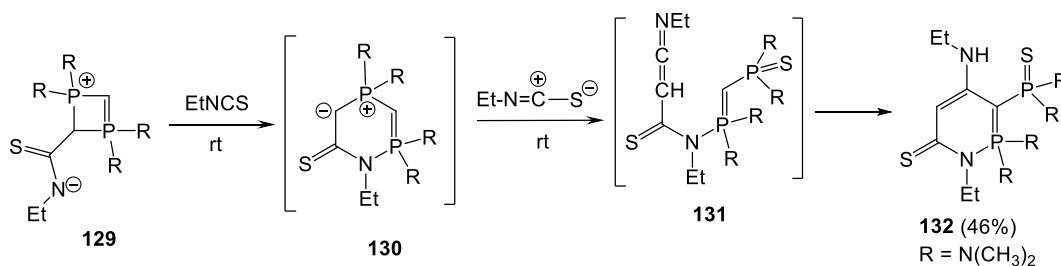
2-(1*H*-indol-3-yl)-*N*-phenethylacetamides (**125**) underwent double condensation using excess of phosphorus oxychloride at 175 °C to form the phosphoramidate derivatives **127** (Scheme 36). Compounds **127** underwent another cyclocondensation reaction through the α -position of the indole nucleus followed by treatment with ethanol at room temperature to yield 8-ethoxy-5,6-dihydro-2,3-disubstituted-9*H*-indolo[2,3-*c*]isoquino[1,2-*f*][1,2]azaphosphorine 8-oxides **128** (Scheme 36).^{72,73}



Scheme 36

3.7 Reaction of a 1 λ^5 ,3 λ^5 -diphosphete adduct with ethyl isothiocyanate

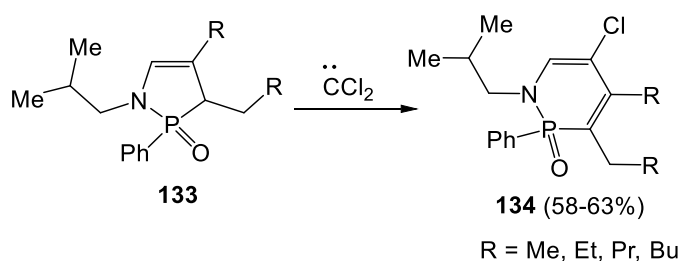
Reaction of 1,2-dihydro-1 λ^5 ,3 λ^5 -diphosphete-2-carbothioamide adduct **129** with ethyl isothiocyanate gave the 1,2,4-azadiphosphinine intermediate **130**, which reacted with a second molecule of ethyl isothiocyanate to give the acyclic ketenimine **131** (Scheme 37). This easily underwent cyclization to afford the isolated 1,2-azaphosphinine **132** (Scheme 37).⁷⁴



Scheme 37

3.8. Ring expansion of 2,3-dihydro-1,2-azaphospholes by dichlorocarbene

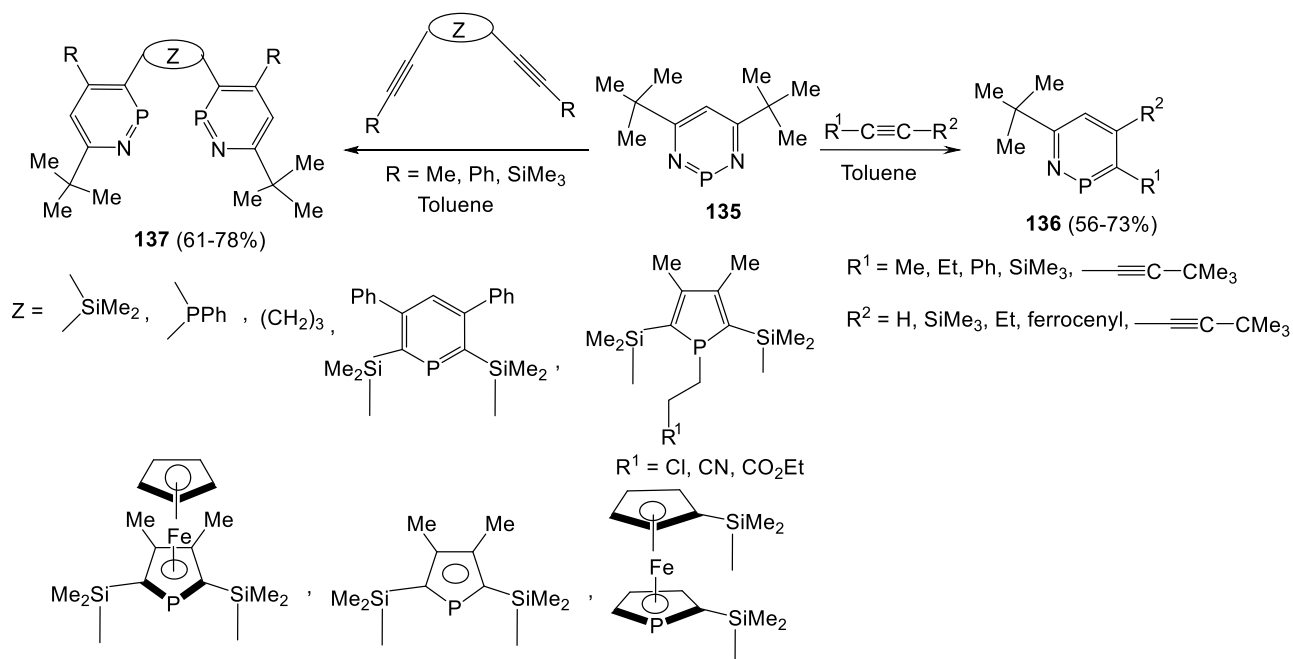
Reaction of 2,3-dihydro-1*H*-1,2-azaphosphole oxides (**133**) with dichlorocarbene at -25 °C gave the corresponding 1,2-azaphosphinine oxides **134** through Ciamician-Dennstedt rearrangement (Scheme 38).⁷⁵



Scheme 38

3.9. Reaction of 1,3,2-diazaphosphinines with alkynes

Reaction of 4,6-di-*t*-butyl-1,3,2-diazaphosphinine (**135**) with different alkynes in toluene 100 °C afforded the corresponding substituted 1,2-azaphosphinines **136** through [4+2] cycloaddition, while its reaction with *bis*-alkynes furnished the 1,2-azaphosphinine-based bidentate ligands **137** (Scheme 39).^{76,77}

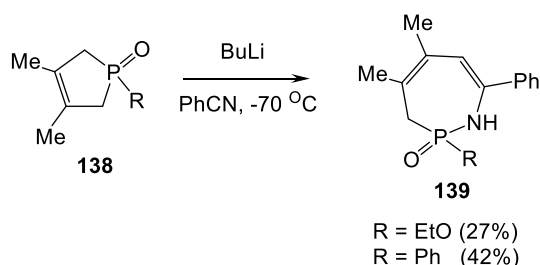


Scheme 39

4. Synthetic Methods for Functionalized 1,2-Azaphosphepine Derivatives

4.1 Ring expansion of phospholenes with benzonitrile

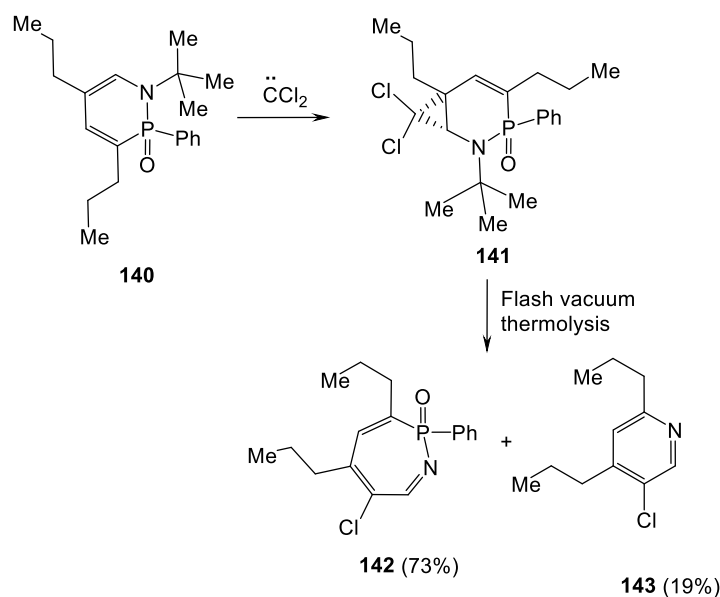
Treatment of 1-oxo-3,4-dimethyl-3-phospholenes (**138**) with *n*-BuLi in benzonitrile at -70 °C followed by hydrolysis formed the corresponding 1,2-azaphosphepine oxides **139** (Scheme 40).⁷⁸



Scheme 40

4.2 Ring expansion of 1,2-azaphosphinines with dichlorocarbene

Reaction of 1-*t*-butyl-2-phenyl-3,5-dipropyl-1*H*-1,2-azaphosphinine (**140**) with dichlorocarbene by regioselective addition to the C₅-C₆ double bond at -25 °C yielded the 3-oxo-2-aza-3-phosphabicycloheptene **141** (Scheme 41). Flash vacuum thermolysis of **141** gave 6-chloro-3,4-dipropyl-2-phenyl-2-oxo-2*H*-1,2-azaphosphepine (**142**) and substituted 3-chloropyridines **143** (Scheme 41).⁷⁹



Scheme 41

5. Conclusions

In conclusion, this survey has presented the synthetic methods for 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines. Most of these synthetic methods require special reaction conditions and specific starting materials that are not available in some laboratories. However, cyclization of amino- and hydrazino compounds with phosphorus reagents or cyclization of aminophosphorus compounds with simple

electrophiles are convenient and easy to perform. We hope that this review may encourage scientists to create new routes towards these ring systems with important biological activity.

Acknowledgements

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through General Research Project under grant number G.R.P./15/41.

References

1. Bansal, R. K. *Topics in Heterocyclic Chemistry: Phosphorus Heterocycles II*, 2010.
<http://doi.org/10.1007/978-3-642-12254-5>
2. Mulzer, J. *Angew. Chem. Int. Ed.* **2001**, 40, 4293.
[http://doi.org/10.1002/1521-3773\(20011119\)40:22<4293::AID-ANIE4293>3.0.CO;2-1](http://doi.org/10.1002/1521-3773(20011119)40:22<4293::AID-ANIE4293>3.0.CO;2-1)
3. Kafarski, P.; Lejczak, B. *Curr. Med. Chem.* **2001**, 1, 301.
<https://doi.org/10.2174/1568011013354543>
4. Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, 97, 1281.
<https://doi.org/10.1021/cr960435y>
5. Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, 63, 193.
<https://doi.org/10.1080/10426509108029443>
6. Mukherjee, S.; Huang, M.-C.; Guerra, F.; Wang, K.; Oldfield, E. J. *Am. Chem. Soc.* **2009**, 131, 8374.
<https://doi.org/10.1021/ja902895p>
7. Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, 104, 6177.
<https://doi.org/10.1021/cr030451c>
8. Turcheniuk, K. V.; Shevchenko, I. V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, 186, 766.
<https://doi.org/10.1080/10426507.2010.507732>
9. Chen, X.-D.; Alidori, S.; Puschmann, F. F.; Santiso-Quinones, G.; Benko, Z.; Li, Z.; Becker, G.; Gruetzmacher, H. F.; Gruetzmacher, H. *Angew. Chem. Int. Ed.* **2014**, 53, 1641.
<https://doi.org/10.1002/anie.201308220>
10. Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Gliphosate: a unique global herbicide*. American Chemical Society: Washington, DC, 1997.
11. Tajti, A.; Keglevich, G. *Organophosphorus Chemistry: Novel Developments* **2018**, 53-65.
<https://doi.org/10.1515/9783110535839>
12. Keglevich, G. *Curr. Org. Chem.* **2019**, 23, 1342.
<https://doi.org/10.2174/1385272823666190726093322>
13. Pudovik, A. N. *Chemistry of organophosphorus compounds*. MIR: Moskow, 1989.
14. Mian, M. R.; Islamoglu, T.; Afrin, U.; Goswami, S.; Cao, R.; Kirlikovali, K. O.; Hall, M. G.; Peterson, G. W.; Farha, O. K. *Chem. Mater.* **2020**, 32, 6998.
<http://doi.org/10.1021/acs.chemmater.0c02373>
15. Bricklebank, N. *Organophosphorus Chem.* **2003**, 33, 289.
<https://doi.org/10.1039/9781847554529-00289>
16. Mathey, F. *Phosphorus-carbon heterocyclic chemistry: the rise of a new domain*. Pergamon: New York, **2001**.

17. Quin, L. D. *The heterocyclic chemistry of phosphorus: systems based on the phosphorus-carbon bond*. Wiley: New York, 1981.
18. Golla, M.; Devineni, S. R.; Syed, R.; Rayalacheru, B. K.; Maram, R.; Chamarthi, N. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 794.
<https://doi.org/10.1080/10426507.2016.1277528>
19. Darrow, J. W.; Drueckenhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976.
<https://doi.org/10.1021/jo00090a014>
20. Abdou, W. M.; Barghash, R. F.; Khidre, R. E. *Monatsh Chem.* **2013**, *144*, 1233.
<https://doi.org/10.1007/s00706-013-0950-6>
21. Yamada, M.; Asai, K.; Yamashita, J.; Suyama, T.; Niimi, T.; Maddali, K.; Fujie, M.; Nakamura, S.; Yamashita, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 2286.
<https://doi.org/10.1080/10426501003598622>
22. Andujar, C. M.; Perez A. I.; Lopez O. F. *Tetrahedron* **2002**, *58*, 2569.
[https://doi.org/10.1016/S0040-4020\(02\)00144-8](https://doi.org/10.1016/S0040-4020(02)00144-8)
23. Gilard, V.; Martino, R.; Malet-Martino, M.; Niemeyer, U.; Pohl, J. *J. Med. Chem.* **1999**, *42*, 2542.
<https://doi.org/10.1021/jm980587g>
24. Smith, B. R.; Eastman, C. M.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 9764.
<https://doi.org/10.1021/jm501105n>
25. Lowe, P.; Feldt, M.; Wuensche, M. A.; Wilm, L. F. B.; Dielmann, F. *J. Am. Chem. Soc.* **2020**, *142*, 9818.
<https://doi.org/10.1021/jacs.0c03494>
26. Ali, T. E.; Halachevea, S. S. *Heteroat. Chem.* **2009**, *20*, 117.
<https://doi.org/10.1002/hc.20520>
27. Latypov, S. K.; Ganushevich, Y. S.; Kondrashova, S. A.; Kharlamov, S. V.; Milyukov, V. A.; Sinyashin, O. G. *Organometallics* **2018**, *37*, 2348.
<https://doi.org/10.1021/acs.organomet.8b00319>
28. Ali, T. E. *Eur. J. Med. Chem.* **2009**, *44*, 4539.
<https://doi.org/10.1016/j.ejmech.2009.06.022>
29. Abdel-Kariem, S. M.; Ali, T. E. *J. Heterocycl. Chem.* **2017**, *54*, 2916.
<https://doi.org/10.1002/jhet.2902>
30. Hansmann, M. M.; Ruiz, D. A.; Liu, L.; Jazzar, R.; Bertrand, G. *Chem. Sci.* **2017**, *8*, 3720.
<https://doi.org/10.1039/C7SC00300E>
31. Sevcik, R.; Prihoda, J.; Necas, M. *Polyhedron* **2017**, *124*, 96.
<https://doi.org/10.1016/j.poly.2016.12.036>
32. Ali, T. E.; Ibrahim, M. A.; El-Edfawy, S. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 819.
<https://doi.org/10.1080/10426507.2017.1287183>
33. Streubel, R.; Wilkens, H.; Rohde, U.; Ostrowski, A.; Jeske, J.; Ruthe, F.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1567.
<https://doi.org/10.1002/ejic.201801135>
34. Sharma, B.; Umadevi, D.; Narahari, S. G. *Phys. Chem. Chem. Phys.* **2012**, *14*, 13922.
<https://doi.org/10.1039/C2CP41834G>
35. Manthey, M. K.; Huang, D. T. C.; Bubbs, W. A.; Christopherson, R. I. *J. Med. Chem.* **1998**, *41*, 4550.
<https://doi.org/10.1021/jm970814z>
36. Collins, D. J.; Hetherington, J. W.; Swan, J. M. *Aust. J. Chem.* **1974**, *27*, 1759.

- <https://doi.org/10.1071/CH9741759>
37. Natchev, I. A. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3699.
<https://doi.org/10.1246/bcsj.61.3699>
38. Schmidpeter, A.; Zeiss, W. *Angew. Chem. Int. Ed.* **1971**, 10, 396.
<https://doi.org/10.1002/anie.197103961>
39. Schmidpeter, A. *Two Adjacent Heteroatoms with at least One Phosphorus, Arsenic, or Antimony. Comprehensive Heterocyclic Chemistry*, **1996**, 709-714.
<https://doi.org/10.1016/B978-008096518-5.00073-3>
40. Ali, T. E.; Assiri, M. A.; El-Shaaer, H. M.; Fouda, A. M.; Hassan, M. M.; Hassanin, N. M. *Heterocycles* **2019**, 98, 681.
<https://doi.org/10.3987/COM-19-14062>
41. Ali, T. E.; Assiri, M. A.; El-Shaaer, H. M.; Hassan, M. M.; Fouda, A. M.; Hassanin, N. M. *Synth. Commun.* **2019**, 49, 2983.
<https://doi.org/10.1080/00397911.2019.1652323>
42. Ali, T. E.; Hassan, M. M. *Res. Chem. Intermed.* **2018**, 44, 173.
<https://doi.org/10.1007/s11164-017-3096-z>
43. Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M. *Mol. Diversity* **2005**, 9, 241.
<https://doi.org/10.1007/s11030-005-3051-6>
44. Ruiz-Gomez, G.; Iglesias, M. J.; Serrano-Ruiz, M.; Lopez-Ortiz, F. J. *Org. Chem.* **2007**, 72, 9704.
<https://doi.org/10.1021/jo701607s>
45. Ruiz-Gomez, G.; Francesch, A.; Cuevas, C.; Serrano-Ruiz, M.; Iglesias, M. J.; Lopez-Ortiz, F. *Tetrahedron* **2012**, 68, 995.
<https://doi.org/10.1016/j.tet.2011.11.094>
46. Liu, L. L.; Stephana, D. W. *Chem. Commun.* **2018**, 54, 1041.
<https://doi.org/10.1039/C7CC09090K>
47. Wang, C.; Mu, W.-H.; Fang, D.-C. *Acta Chim. Sinica* **2006**, 64, 1665.
48. Wilkens, H.; Ruthe, F.; Jones, P. G.; Streubel, R. *Chem. Commun.* **1998**, 1529.
<https://doi.org/10.1039/A802569J>
49. Wilkens, H.; Ostrowski, A.; Jeske, J.; Ruthe, F.; Jones, P. G.; Streubel, R. *Organometallics* **1999**, 18, 5627.
<https://doi.org/10.1021/om990537p>
50. Streubel, R.; Hoffmann, N.; Schiebel, H. M.; Ruthe, F.; Jones, P. G. *Eur. J. Inorg. Chem.* **2002**, 957.
[https://doi.org/10.1002/1099-0682\(200203\)2002:4<957::AID-EJIC957>3.0.CO;2-2](https://doi.org/10.1002/1099-0682(200203)2002:4<957::AID-EJIC957>3.0.CO;2-2)
51. Streubel, R.; Wilkens, H.; Ostrowski, A.; Neumann, C.; Ruthe, F.; Jones, P. G. *Angew. Chem. Int. Ed.* **1997**, 36, 1492.
<https://doi.org/10.1002/anie.199714921>
52. Streubel R.; Wilkens, H.; Jones, P. G. *Chem. Commun.* **1999**, 2127.
<https://doi.org/10.1039/a905752h>
53. Streubel, R.; Wilkens, H.; Ruthe, F.; Jones, P. G. *Tetrahedron* **2000**, 56, 21.
[https://doi.org/10.1016/S0040-4020\(99\)00768-1](https://doi.org/10.1016/S0040-4020(99)00768-1)
54. Streubel, R.; Hoffmann, N.; Ruthe, F.; Jones, P. G. *Polyhedron* **2002**, 21, 119.
[https://doi.org/10.1016/S0277-5387\(01\)00976-7](https://doi.org/10.1016/S0277-5387(01)00976-7)
55. Hoffmann, N.; Wismach, C.; Ernst, L.; Schiebel, H. M.; Jones, P. G.; Streubel, R. *Eur. J. Inorg. Chem.* **2003**, 1815.

- <https://doi.org/10.1002/ejic.200200649>
56. Helten, H.; Frantzius, G.; Schnakenburg, G.; Daniels, J.; Streubel, R. *Eur. J. Inorg. Chem.* **2009**, 2062.
<https://doi.org/10.1002/ejic.200900190>
57. Harger, M. J. P. *J. Chem. Soc. Perkin Trans.1* **1974**, 22, 2604.
<https://doi.org/10.1039/p19740002604>
58. Peters, C.; Tabellion, F.; Schröder, M.; Bergsträber, U.; Preuss, F.; Regitz, M. *Synthesis* **2000**, 417.
<https://doi.org/10.1055/s-2000-6353>
59. Streubel, R.; Schiemann, U.; Jones, P. G.; Huy, N. H. T.; Mathey, F. *Angew. Chem. Int. Ed.* **2000**, 39, 3686.
[https://doi.org/10.1002/1521-3773\(20001016\)39:20<3686::AID-ANIE3686>3.0.CO;2-I](https://doi.org/10.1002/1521-3773(20001016)39:20<3686::AID-ANIE3686>3.0.CO;2-I)
60. Streubel, R.; Schiemann, U.; Huy, N. H. T.; Mathey, F. *Eur. J. Inorg. Chem.* **2001**, 3175.
[https://doi.org/10.1002/1099-0682\(200112\)2001:12<3175::aid-ejic3175>3.0.co;2-c](https://doi.org/10.1002/1099-0682(200112)2001:12<3175::aid-ejic3175>3.0.co;2-c)
61. Streubel, R.; Hoffmann, N.; Frantzius, G.; Wismach, C.; Jones, P. G.; Schiebel, H.; Grunenberg, J.; Vong, H.; Chaigne, P.; Compain, C.; Huy, N. H. T.; Mathey, F. *Organometallics* **2003**, 22, 5427.
<https://doi.org/10.1021/om030547x>
62. Karaghiosoff, K.; Klehr, H.; Schmidpeter, A. *Chem. Ber.* **1986**, 119, 410.
<https://doi.org/10.1002/cber.19861190204>
63. Lu, Z.; Findlater, M.; Cowley, A. H. *Chem. Commun.* **2007**, 27, 2873.
<https://doi.org/10.1039/b704266c>
64. Hewitt, D. G.; Newland, G. L. *Aust. J. Chem.* **1977**, 30, 579.
<https://doi.org/10.1071/ch9770579>
65. Hewitt, D. G.; Teese, M. W. *Aust. J. Chem.* **1984**, 37, 1631.
<https://doi.org/10.1071/ch9841631>
66. Kibardin, A. M.; Mikhailov, V. B.; Levina, E. Ya.; Mikhailov, Yu. B.; Pudovik, A. N. USSR Patent 1410490 A1 19890930, **1989**.
67. Dewar, M. J. S.; Kubba, V. P. *J. Am. Chem. Soc.* **1960**, 82, 5685.
<https://doi.org/10.1021/ja01506a032>
68. Campbell, I. G. M.; Way, J. K. *J. Chem. Soc.* **1960**, 5034.
<https://doi.org/10.1039/jr9600005034>
69. Nifantev, I. E.; Vinogradov, A. A.; Vinogradov, A. A.; Roznyatovsky, V. A.; Grishin, Y. K.; Ivanyuk, A. V.; Sedov, I. V.; Churakov, A. V.; Ivchenko, P. V. *Organometallics* **2018**, 37, 2660.
<https://doi.org/10.1021/acs.organomet.8b00427>
70. Grewal, G. S.; Jindal, R. T.; Bhatia, M. S. *Indian J. Chem.* **1980**, 19B, 404.
71. Takaesu, N. A.; Ohta, E.; Zakharov, L. N.; Johnson, D. W.; Haley, M. M. *Organometallics* **2017**, 36, 2491.
<https://doi.org/10.1021/acs.organomet.7b00281>
72. Morrison, G. C.; Waite, R. O.; Shovel, J. J. *Heterocycl. Chem.* **1966**, 3, 540.
<https://doi.org/10.1002/jhet.5570030435>
73. Shavel, J. J.; Morrison, G. C. US Patent 3452024 A 19690624, 1969.
74. Fluck, E. *Heteroat. Chem.* **1995**, 6, 355.
<https://doi.org/10.1002/hc.520060413>
75. Tan, W. H. L. W.; Foucaud, A. J. *Chem. Res. Synop.* **1991**, 2, 52.
76. Welfele, S.; Mezailles, N.; Maigrot, N.; Ricard, L.; Mathey, F.; Le Floch, P. *New J. Chem.* **2001**, 25, 1264.
<https://doi.org/10.1039/b103779j>
77. Bansal, R. K.; Kumawat, S. K. *Tetrahedron* **2008**, 64, 10945.

<https://doi.org/10.1016/j.tet.2008.09.037>

78. Mathey, F.; Lampin, J. P. *Tetrahedron Lett.* **1972**, 19, 1949.

[https://doi.org/10.1016/S0040-4039\(01\)84759-6](https://doi.org/10.1016/S0040-4039(01)84759-6)

79. Tan, W. W.; Bourdieu, C.; Foucaud, A.; Bedel, C. *Bull. Soc. Chim. Fr.* **1993**, 130, 96.

Authors' Biographies



Tarik E. Ali was born in Cairo, Egypt, in 1975. He is presently full professor of Organic Chemistry, Department of Chemistry, Faculty of Education, Ain Shams University, Cairo, Egypt. Currently, he works at Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia. He graduated with BSc (Physics and Chemistry) from Ain Shams University in 1997. He received his MSc and PhD 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 Higher Education and Scientific Research (Egypt) in organophosphorus laboratory, Institute of Polymers, Bulgarian Academy of Science, Sofia, Bulgaria. His CV was mentioned in *Who's Who in the World* in 2011, 2012, 2013, 2015, 2016, 2018 and 2020. He has published more than 80 scientific papers including 15 review articles, all in international journals. His research interests are in synthesis and chemical reactivity of phosphorus compounds containing bioactive heterocyclic systems.



Noha M. Hassanin was born in 1991 in Kaluobia, Egypt. In 2013, she graduated from Ain Shams University, Faculty of Education, Department of Chemistry. She obtained her MSc Degree in Organophosphorus Chemistry in 2018. She has published about 8 scientific papers in international journals. She is still working on her PhD thesis which includes design and synthesis of biologically active organophosphorus compounds.



Mohammed A. Assiri is presently assistant professor at Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia. He graduated with BSc (Chemistry) from Department of Chemistry, Faculty of Science, King Khalid University, Abha, Saudi Arabia in 2004. Also, he received his MSc and PhD degrees in 2014 and 2016, respectively, in organic and green Chemistry from University of Wyoming, Laramie, WY, USA. His research interests are in activities related to organic chemistry, green chemistry, and chemical engineering.



Hafez M. Elshaaer was born in Cairo, Egypt, in 1959. He is presently full professor of Organic Chemistry, Department of Chemistry, Faculty of Education, Ain Shams University, Cairo, Egypt. He graduated with BSc and MSc from Ain Shams University. He received his PhD degree in Heterocyclic Chemistry from Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Bratislava, Slovakia. He has published 35 scientific papers in international journals. His research interests are in synthesis and chemical reactivity of pyran and chromone systems.



Somaia M. Abdel-Karim was born in 1985 in Cairo, Egypt. She is presently associate professor at Ain Shams

University, Faculty of Education, Department of Chemistry. 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 15 scientific papers in international journals. Her research interests are in synthesis and chemical reactivity of phosphorus compounds containing bioactive heterocyclic systems.

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)