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

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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.

Keywords: 1,2-azaphospholes, 1,2-azaphosphorines, 1,2-azaphosphepines, phosphorus heterocycles
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 heterocycles16,17 have
received considerable interest because of their unique biological activities as antimicrobial\textsuperscript{18} and their anticancer effects.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{32} complexing agents,\textsuperscript{33,34} and inhibitor of mammalian dihydroorotase.\textsuperscript{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).\textsuperscript{36}

![Scheme 1](image)

2.2 Cyclization of $\gamma$-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-diphenylisulfane at 50-60 °C led to 1-allyl-2-phenyl-1,2-azaphospholidine (4) (Scheme 2).\textsuperscript{36}

![Scheme 2](image)

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).\textsuperscript{37}
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-3H-1,2λ5-azaphospholes 10 (Scheme 4), while its reaction with dimethyl acetylenedicarboxylate furnished dimethyl 2,2-dimethyl-5,5-diphenyl-5H-1,2λ5-azaphosphole-3,4 dicarboxylate (11) (Scheme 4).  

Scheme 4

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

1-t-Butyl-4,5,6,7-tetrahydro-1H-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).  

Scheme 5
2.5 Cyclization of 2-imino-2\textit{H}-chromene-3-carboxamide with chlorodiphenylphosphine and diethyl phosphate

2-Imino-2\textit{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-\textit{c}][1,2] azaphosphol-3(2\textit{H})-one (15) (Scheme 6). \(^{40}\)

![Scheme 6](image)

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

![Scheme 7](image)

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

2-Cyano-3-(4-oxo-4\textit{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 phosphate at 80-90 °C in the presence of BF\textsubscript{3}Et\textsubscript{2}O as a catalyst under Pudovik reaction conditions resulted in the nonisolable diethyl hydrazino-phosphonate 21 (Scheme 9). The latter intermediate underwent spontaneous cyclization by elimination of ethanol to provide the chromeno[3,2-\textit{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).
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). 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).

Scheme 10

\[
\begin{align*}
\text{Ph}_3\text{P} + \text{RO}_2\text{C}=\text{CO}_2\text{R} & \quad \xrightarrow{\text{dry ether, rt}} \quad \text{RO}_2\text{C} \quad \xrightarrow{\Phi} \quad \text{CO}_2\text{R} \\
\text{ArSO}_2\text{N}=\text{C}=\text{O} & \quad \text{24} \\
\text{RO}_2\text{C} \quad \xrightarrow{\text{(Ph)}_3\text{P}} \quad \text{CO}_2\text{R} & \quad \text{SO}_2\text{Ar} \\
\text{25 (70-95\%)} & \\
\text{R} = \text{Me, Et, i-Pr, t-Bu} \quad \text{Ar} = \text{C}_6\text{H}_5, 4\text{-MeC}_6\text{H}_4
\end{align*}
\]

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 CH$_3$CO 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).$^{45}$
2.9 Rearrangement of 4,8-diaza-1-phosphaspiro[2.5]oct-1-ene with GaCl₃
Reaction of 2-t-butyl-6,6-dimethyl-4,8-bis(methylthio)-4,8-diaza-1-phosphaspiro[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).\(^\text{46}\)

\[
\text{Scheme 15}
\]

2.10 Thermal ring opening of 2H-azaphosphirene complexes
The thermolysis of the (2H-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).\(^\text{47}\)

\[
\text{Scheme 16}
\]

\[
\text{Scheme 17}
\]

Thermal ring opening of the (2H-1,2-azaphosphirene)tungsten complex 56 with dimethyl acetylene-dicarboxylate 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-\(\lambda^5\)-phosphanyl)acetonitrile led to the formation of 1,2-azaphosphole 59 (Scheme 18).33,48-50

![Scheme 18 diagram]

Also, ring opening reaction of 1,2-azaphosphirene complex 56 with dimethyl acetylenedicarboxylate and benzonitrile in toluene furnished a mixture of 2\(H\)-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-2\(H\)-1,2-azaphosphole 63 (Scheme 19).33,51-53

![Scheme 19 diagram]

On the other hand, the three component reactions of 2\(H\)-azaphosphirene complex 56, ethyl propiolate and nitriles led to the formation of the regioisomeric 2\(H\)-1,2-azaphosphole complexes 64 and 65 (Scheme 20). In case of using Ph\(_3\)P=CH(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).\textsuperscript{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$_3$P=NCN in dry toluene, the 1,2-azaphosphole complex 70 was formed in high yield (Scheme 21).\textsuperscript{33,55}

Scheme 21

Reaction of the (2$H$-azaphosphirene)tungsten complex 71 with trifluoromethanesulfonic acid, phenylacetylene and triethylamine in CH$_2$Cl$_2$ proceeded through P–C bond ring enlargement to afford 2$H$-1,2-azaphosphole complex 72 in low yield (Scheme 22).\textsuperscript{56}
2.11 Photolysis of azidophosphetanes

Photolysis of 1-azido-2,2,4,4-tetramethylphosphetane 1-oxide 73 (R=H) afforded the cyclic 1,2-aza-phospholidine 75 by elimination of N$_2$ and addition of methanol (Scheme 23). Likewise, photolysis of azide 73 (R = Me) gave a mixture of cis- and trans-1,2-azaphospholidines 76 (Scheme 23).
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).\textsuperscript{57}

### 2.12 Reaction of adduct of phosphaalkynes and imidovanadium with acetylenes

The cycloadduct 84 was generated in situ by addition of an equimolar amount of a phosphaalkynes 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).\textsuperscript{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 2H-1,2-azaphosphate complex 87 only was isolated. When another carbonitrile derivative such as Ph₃P=NCN was used, the thermal decomposition of complex 86 in xylene furnished the 2H-1,2-azaphosphate complex 92 through [3+2] cycloaddition reaction of nitrilium phosphane ylide complexes 91 formed with dimethyl acetylenedicarboxylate (Scheme 26).

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).

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-1H-[1,2]benzazaphosphole (98) and 2-butyl-1H-[1,3]benzazaphosphole (99) in a ratio of 4:1 (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 RPCl2
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-aza-phosphorines (108) (Scheme 31). 66
3.3 Cyclization of 2-aminobiphenyl with PCl₃

Reaction of 2-aminobiphenyl (109) with phosphorus trichloride in boiling benzene at 65 °C containing a catalytic amount of AlCl₃ afforded 10-chloro-9,10-dihydro-9,10-azaphenapthenanthrene (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 CH₂Cl₂ gave 10-methyl-9,10-dihydro-9,10-azaphenapthenanthrene 10-methiodide (111) while its reaction with aryl magnesium bromide in dry CH₂Cl₂ at room temperature formed 10-aryl-9,10-dihydro-9,10-azaphenapthenanthrenes 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-azaphenapthenanthrene (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).
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 \(\text{AlCl}_3\) 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](image_url)

### 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 \(\text{AlCl}_3\) 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](image_url)

### 3.5 Cyclization of 2-amino-3-ethynynaphthalenes with triphenoxyphosphine
Cyclization of 2-amino-3-ethynynaphthalenes (123) with triphenoxyphosphine in dry pyridine for 12 h furnished naphtho\([2,3-e\])[1,2]azaphosphorines (124) in moderate yields (Scheme 35).\(^{71}\)
3.6 Cyclization of 2-{1H-indol-3-yl}-N-phenethylacetamides with phosphorus oxychloride

2-{1H-indol-3-yl}-N-phenethylacetamides (125) underwent double condensation using excess of phosphorus oxychloride at 175 °C to form the phosphoramide 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-9H-indolo[2,3-c]isoquino[1,2-f][1,2]azaphosphorine 8-oxides 128 (Scheme 36).

Scheme 36

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

Reaction of 1,2-dihydro-1λ^5,3λ^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).
3.8. Ring expansion of 2,3-dihydro-1,2-azaphospholes by dichlorocarbene

Reaction of 2,3-dihydro-1H-1,2-azaphosphole oxides (133) with dichlorocarbene at -25 °C gave the corresponding 1,2-azaphosphinine oxides 134 through Ciamician-Dennsted rearrangement (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).
4. Synthetic Methods for Functionalized 1,2-Azaphosphine 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-azaphosphine oxides 139 (Scheme 40). 78

![Scheme 40](image)

4.2 Ring expansion of 1,2-azaphosphinines with dichlorocarbene
Reaction of 1-t-butyl-2-phenyl-3,5-dipropyl-1H-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-2H-1,2-azaphosphine (142) and substituted 3-chloropyridines 143 (Scheme 41). 79

![Scheme 41](image)

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.

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