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SYNTHESIS AND CHEMISTRY OF PHOSPHORUS COMPOUNDS SUBSTITUTED BY 1,2,4-TRIAZINE MOIETIES AS MEDICINAL PROBES

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Abstract – Design, synthesis, and chemical behaviors of various phosphorus compounds containing and/ or bearing 1,2,4-triazine moieties are received. Besides, the medicinal, biocidal, and biological activities of these targets were reported. A relation between P-C, P-O, P-N, and P-S bonds was also studied.

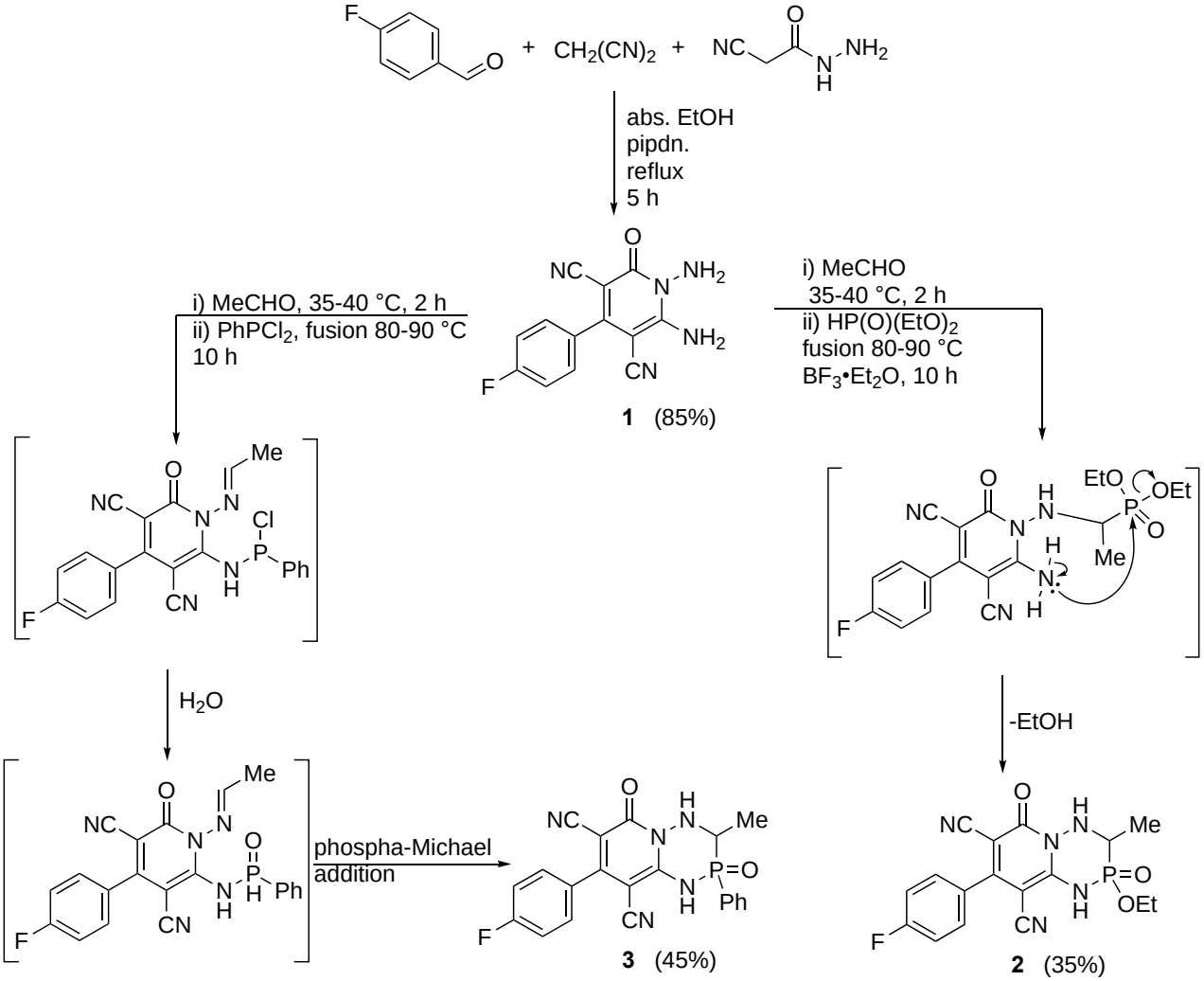
1. INTRODUCTION

Phosphorus atoms or their compounds are required for various metabolic processes in the work of vital cells.[1] Also, phosphorus compounds are critical factors limiting the efficiency of phosphorus effects on crops that will be more economical than relying on chemical fertilization of phosphorus.[2] Presence of P-C, P-O, P-N, and P-S bonds attached to heterocyclic systems often enhances and improves their physical, chemical, and biological properties.[3] Besides, various phosphorus compounds play a vital role in modern life due to their significant medicinal, biological, pharmacological, and agricultural fields, for example, as molluscicidal,[4] herbicidal,[5] anti-HIV,[6] anticancer,[7] antimicrobial,[8] and are used as photochemical probes to inhibit vigitilo disease,[9] as well as antibacterial agents.[10] On the other hand, 1,2,4-triazine nucleus as an essential functional moiety has been used in the development of pharmaceutical and agrochemical properties because of its derivatives bearing multitudinous bioactivities, including anti-inflammatory,[11,12] and antifungal activities.[13] The triazine nucleus was also used to inhibit enzyme effect on some vital properties (cellobiase activity),[14,15] and as antioxidant agents.[16] Recently, phosphorus atoms bonding with nitrogen compounds have gained considerable attention due to their biological effects such as molluscicidal,[17] insecticidal,[18] and herbicidal[19] activities. Different isomers of triazaphospholes have multiple medicinal properties, as antibacterial,[20] anti-breast, anticolonial, and anti-prostate carcinoma cell lines[21] activity. Abdel-Rahman *et al.*[22-26] reported many reviews in the field of phosphorus-1,2,4-triazines, including synthesis, chemistry, and their specific biological properties. Based on these facts, the present

review reports significant attempts to synthesize phosphorus-containing 1,2,4-triazine compounds as well as their physical, chemical, and biological properties.

2. PHOSPHORUS COMPOUNDS CONTAINING-1,2,4-TRIAZINE MOIETY

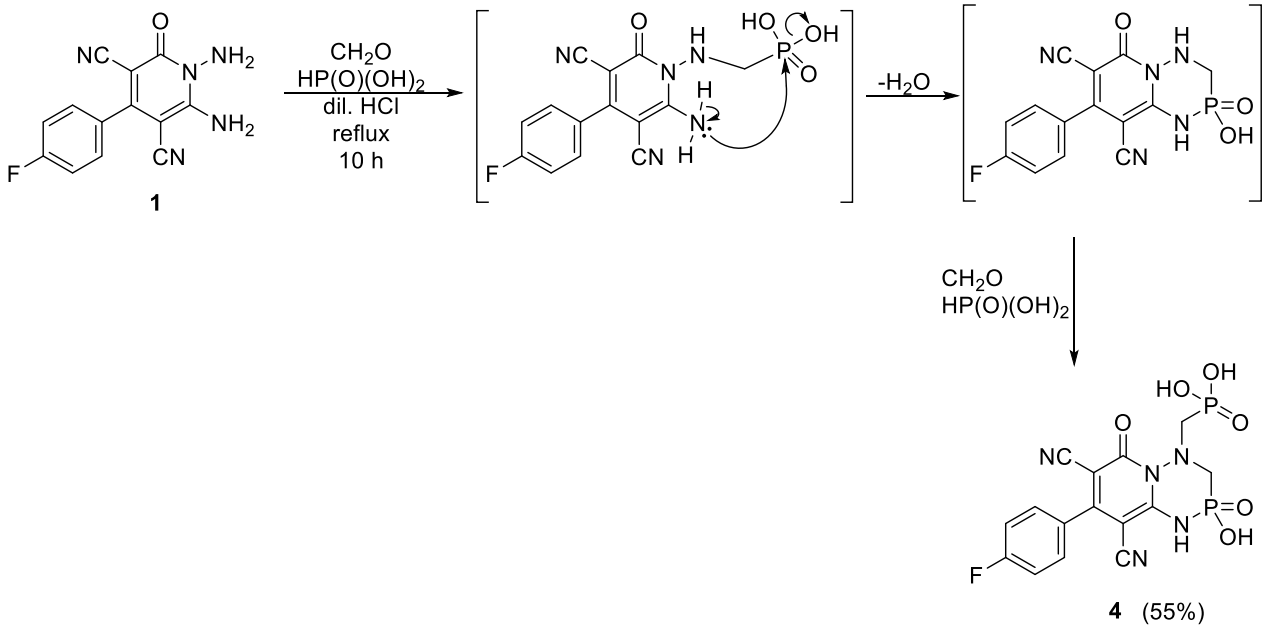
Formation of fluorinated heterocyclic phosphorus-containing 1,2,4-triazine moiety was deduced by Assiri *et al.*[27] Thus, warming of compound **1** with acetaldehyde in the presence of diethyl phosphite and/ or phenyl dichlorophosphine at 35-40 °C followed by fusion for 10 h, produced two isomeric structures **2** and **3** respectively (Scheme 1). The IR spectra of both **2** and **3** showed vibrational bands at 1236 and 1237 cm^{-1} for P=O, while ^{1}H NMR spectra recorded signals at 4.5 and 4.2 ppm for P-CH. ^{31}P NMR spectra also exhibited signals at 22.2 ppm for compound **2**. Mass spectra of **3** recorded *m*/*z* 419.



Scheme 1. Formation of compounds **2** and **3**

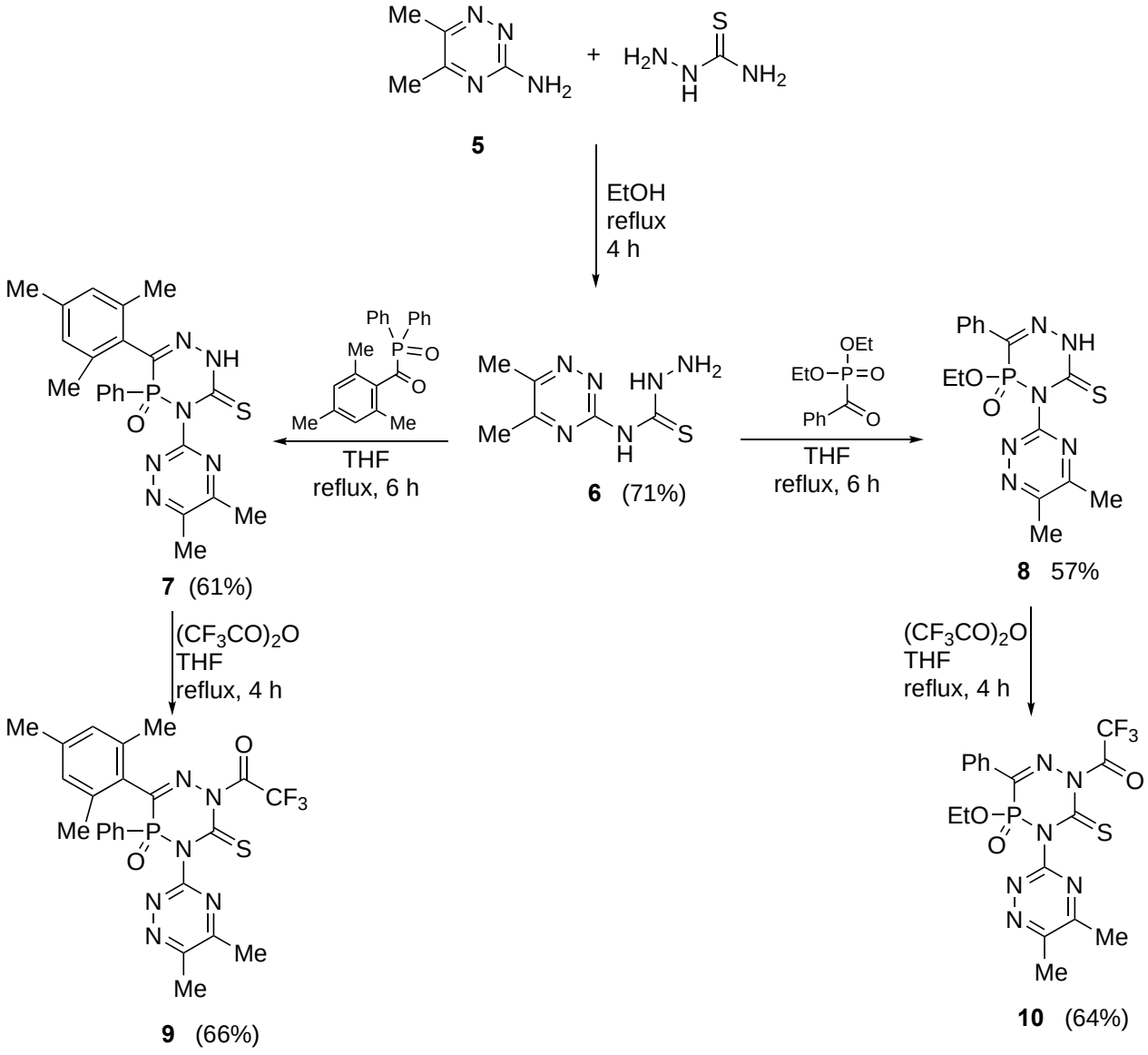
The addition of phosphorous acid to an acidic solution of compound **1** in the presence of formaldehyde led to the formation of ((7,9-dicyano-8-(4-fluorophenyl)-2-hydroxy-2-oxido-6-oxo-1,3,6-

trihydropyrido[1,2-*b*][1,2,4,5]triazaphosphinin-4-yl)methyl)phosphonic acid (**4**) (Scheme 2).[27] Structure of compound **4** was established from the IR spectrum, which recorded a broad vibrational band at 3418 cm^{-1} for OH and NH, 2964 cm^{-1} for CH, and 1230 cm^{-1} for P=O. Also, the ^{1}H NMR spectrum exhibited a signal at 4.54-5.15 ppm for P-CH_2 protons. ^{31}P NMR spectrum showed signals at 11.7 and 19.2 ppm. Mass spectra recorded *m*/*z* 439, which supported that structure.[27]



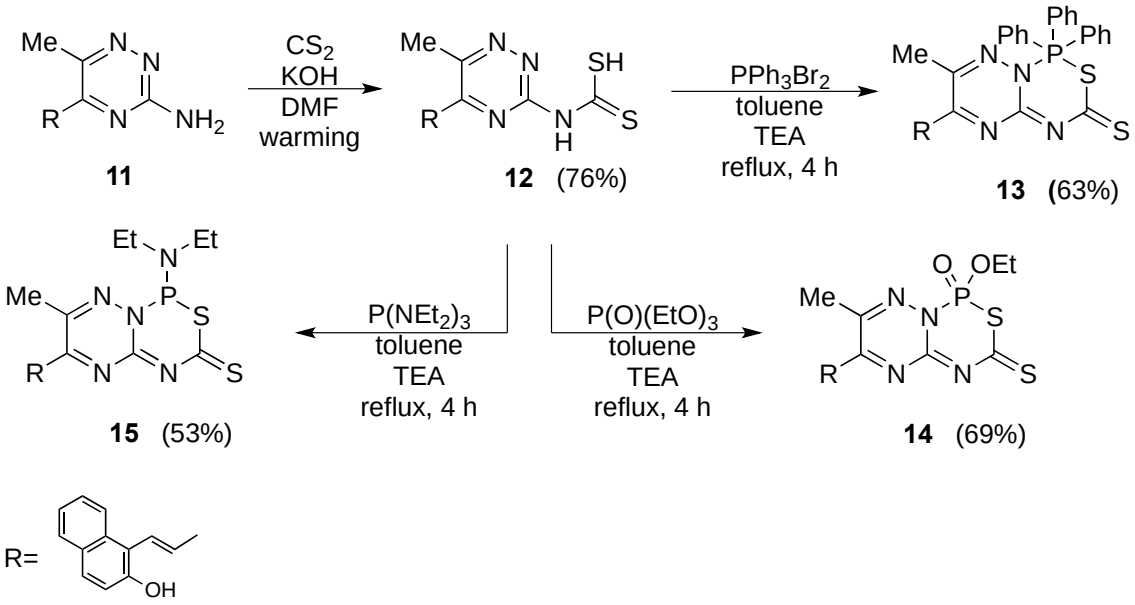
Scheme 2. Formation of compound **4**

Abdel-Rahman[22] obtained some phospha-heterobicyclic systems containing 1,2,4-triazine moiety from heterocyclization of N^4-substituted thiosemicarbazide **6** with diethyl benzoylphosphonate and/ or diphenyl (2,4,6-trimethylbenzoyl)phosphine oxide in dry toluene, to give 4,5,6-trisubstituted-5-phospha-1,2,4-triazin-3(2*H*)-thiones **7** and **8**, respectively. Fluoroacylation of both compounds **7** and **8** by refluxing with 2,2,2-trifluoroacetic anhydride in THF produced the phospha-fluorinated compounds **9** and **10** (Scheme 3).



Scheme 3. Formation of compounds **6**-**10**

Similarly, various phosphorus/sulfur compounds containing heterobicyclic substituted 1,2,4-triazines were synthesized from 3-amino-5-styryl-6-methyl-1,2,4-triazine (**11**).[22] Thus, the treatment of compound **11** with CS_2/KOH in DMF produced the dithiocarbamic acid **12**. Ring closure reactions of compound **12** with phosphorus reagents namely; Ph_3PBr_2, $P(NEt_2)_3$, and $P(O)(OEt)_3$ in boiling toluene/ TEA afforded 1,2,4-triazino[2,3-*c*][1,3,5,2]thiadiazaphosphinine-3-thiones (**13**-**15**), respectively (Scheme 4). All compounds **7**-**15** showed anticancer activity.



Scheme 4. Formation of compounds **12-15**

The SH group of **12**, as a nucleophilic group, attacks the phosphorus atom of $P(NEt_2)_3$ by losing one molecule of $NHEt_2$. It was then followed by a heterocyclization reaction of N^2H of triazine ring with phosphorus atom *via* losing another molecule of $NHEt_2$. The formation of compound **15** is shown in Figure 1.

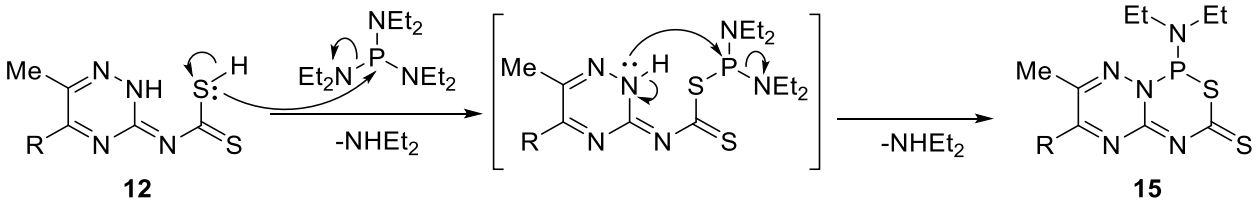
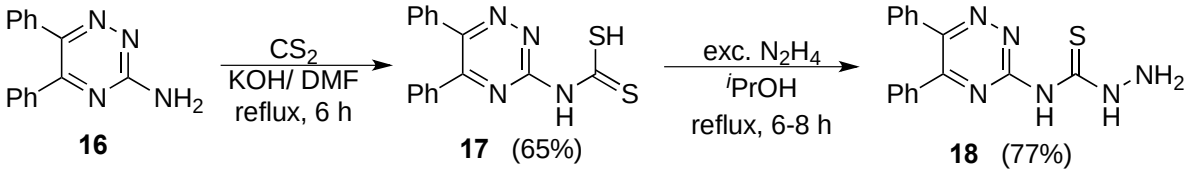
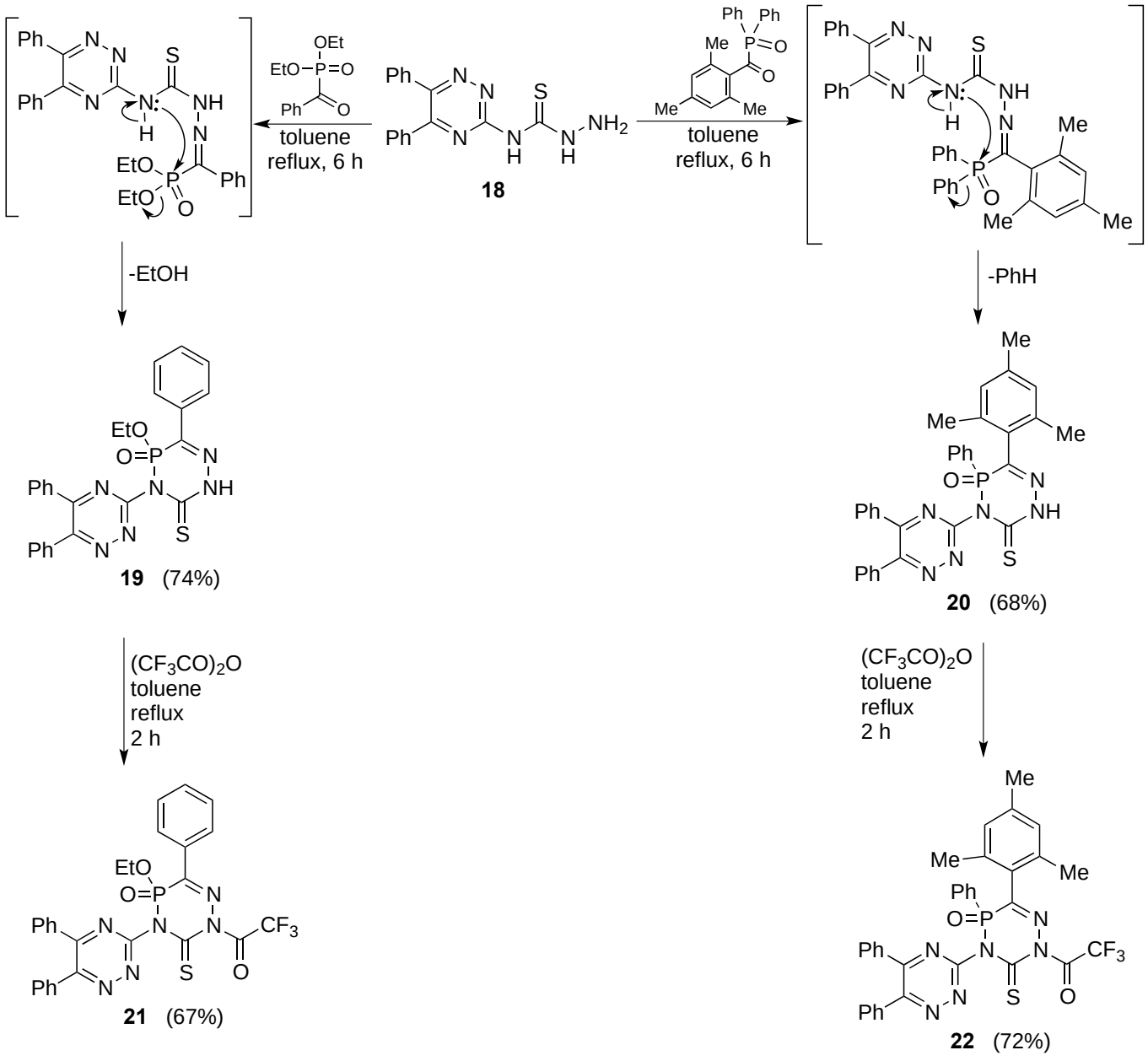


Figure 1. Possible mechanism of formation of compound **15**

The specific synthesis of phosphorus/ fluorinated compounds containing 1,2,4-triazine-thiones deduced[22] from N^4-(5,6-diphenyl-1,2,4-triazin-3-yl)thiosemicarbazide (**18**)[22] (Scheme 5) by full heterocyclization with diethyl benzoylphosphonate and/ or (diphenylphosphoryl)(mesityl)methanone in dry toluene, yielded the 1,2,4,5-triazaphosphinine-3(2*H*)-thione 5-oxides (**19**-**20**). Fluoroacylation of the compounds **19**-**20** by refluxing with 2,2,2-trifluoroacetic anhydride in toluene afforded the 1-(4-(5,6-diphenyl-1,2,4-triazin-3-yl)-5,6-disubsitiuted-5-oxido-3-thioxo-4-hydro-1,2,4,5-triazaphosphinin-2(3*H*)-yl)-2,2,2-trifluoroethan-1-ones (**21**-**22**) (Scheme 6). All the synthesized compounds were evaluated as anticancer agents.



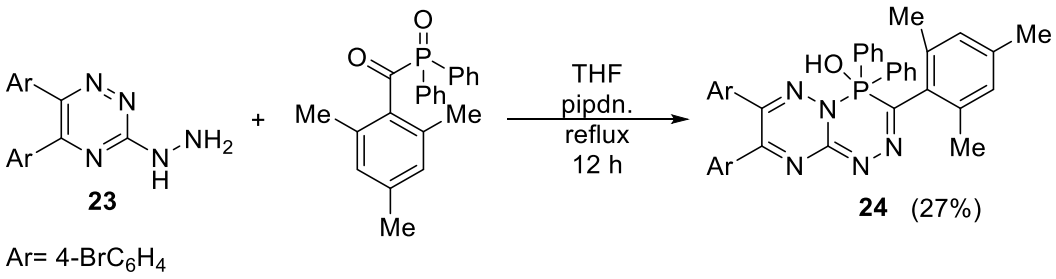
Scheme 5. Formation of compound **18**



Scheme 6. Formation of compounds **19**-**22**

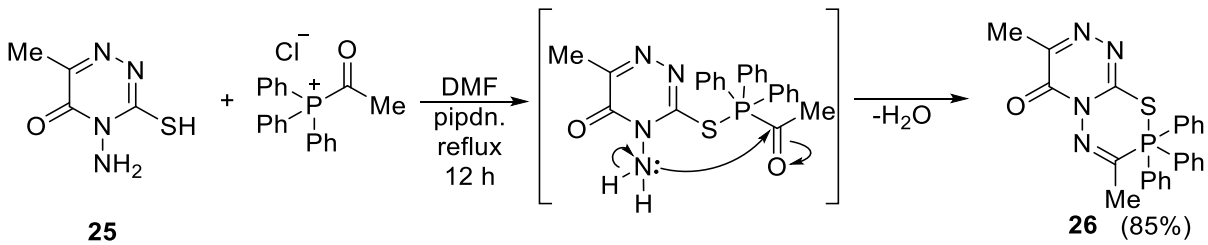
Similarly, cycloaddition reaction of 5,6-diaryl-3-hydrazino-1,2,4-triazine (**23**) with (diphenylphosphoryl)-(mesityl)methanone in THF-piperidine yielded 7,8-bis(4-bromophenyl)-3-mesityl-4,4-diphenyl-4*H*-4λ^5-[1,2,4]triazino[3,2-*c*][1,2,4,5]triazaphosphinin-4-ol (**24**) (Scheme 7). IR spectrum of **24** exhibited a

broadband at 3414 cm^{-1} for the presence of OH. Also, ^{31}P NMR spectrum showed δ at 25.70 ppm. Compound **24** was used as molluscicidal agent against some snails in wastewater.[28]

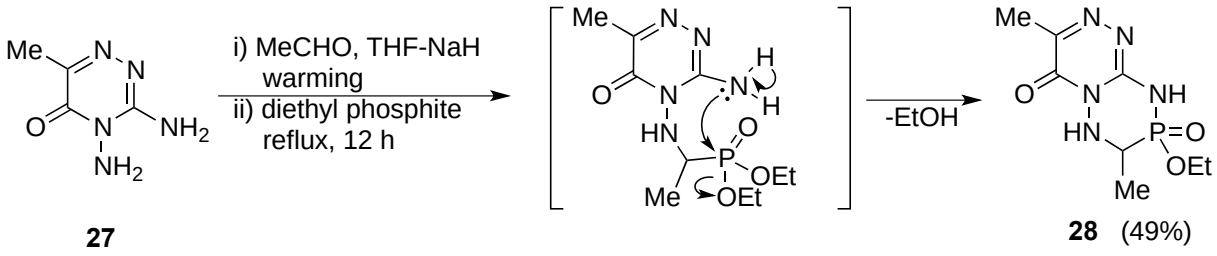


Scheme 7. Formation of compound **24**

4-Amino-3-(mercapto/amino/hydrazine)-6-methyl-1,2,4-triazin-5-ones (**25**,**27**,**29**) were used to obtain fused phospha-heterobicyclic nitrogen systems.[20] The nucleophilic attack by the SH group is more preferred over the NH group towards phosphorus reagents as electrophilic centers. Therefore, treatment of compound **25** with acetyltriphenylphosphonium chloride in refluxing DMF-piperidine for 12 h, afforded 3,7-dimethyl-2,2,2-triphenyl-2*H*,6*H*-2λ^5-[1,2,4]triazino[4,3-*e*][1,4,5,2]thiadiazaphosphinin-6-one (**26**) in excellent yield, while the addition of acetaldehyde and diethyl phosphite to compound **27** in THF-NaH, produced 2-ethoxy-3,7-dimethyl-1,3,4-trihydro-[1,2,4]triazino[4,3-*b*][1,2,4,5]triazaphosphinin-6-one 2-oxide (**28**). Also, 2,7-dimethyl-1,3,4-trihydro-[1,2,4]triazino[4,3-*e*][1,2,4,5,3]tetrazaphosphinin-8-one 2-oxide (**30**) was isolated from refluxing of compound **29** with bis(dimethylamino)methylphosphonate in THF-HCl for 12 h. Moreover, compound **31** was obtained *via* refluxing of compound **29** with acetaldehyde and diethyl phosphite in THF-NaH (Schemes 8-10).[20] ^{31}P NMR of compounds **26**, **28**, **30**, and **31** showed signals at -11.2, 21.5, 27.1, and 22.3 ppm, respectively. All the synthesized compounds exhibited antibacterial activity.

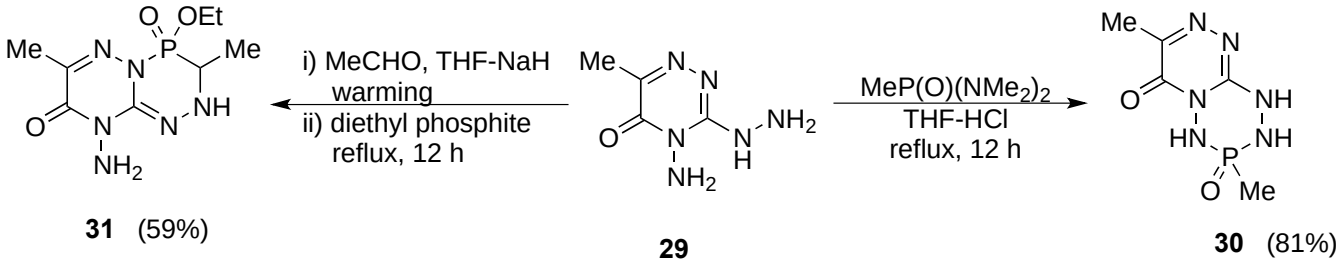


Scheme 8. Formation of compound **26**



27 **28** (49%)

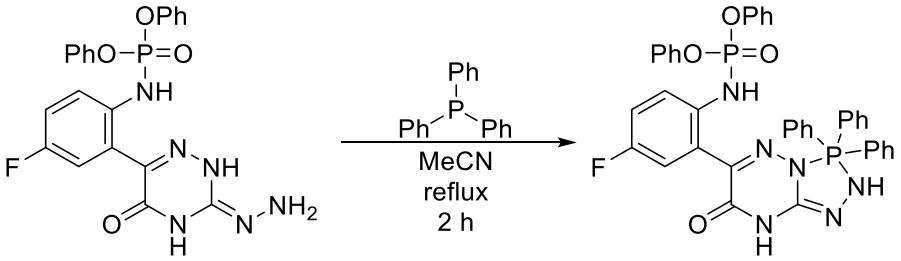
Scheme 9. Formation of compound **28**



31 (59%) **29** **30** (81%)

Scheme 10. Formation of compounds **30**-**31**

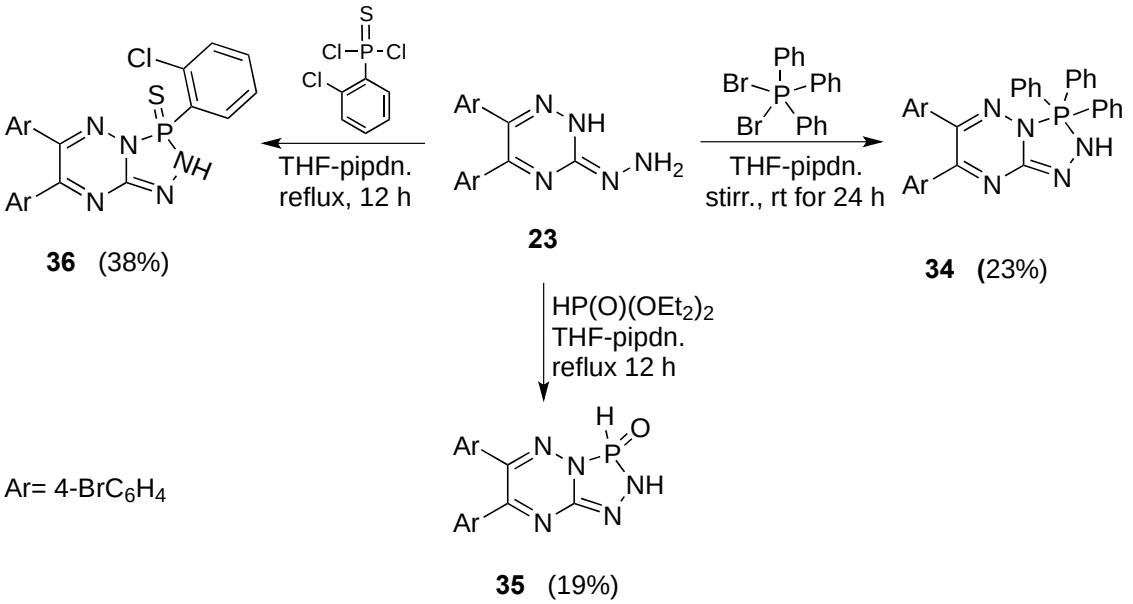
On the other hand, refluxing of 3-hydrazino-6-aryl-1,2,4-triazin-5-one (**32**) with triphenylphosphine in acetonitrile, produced the diphenyl (4-fluoro-2-(7-oxo-3,3,3-triphenyl-2,3,7,8-tetrahydro-3λ^5-[1,2,4,3]-triazaphospholo[4,5-*b*][1,2,4]triazin-6-yl)phenyl)phosphoramidate (**33**) (Scheme 11).[6] Compound **33** showed anti-HIV activity.



32 **33** (81%)

Scheme 11. Formation of compound **33**

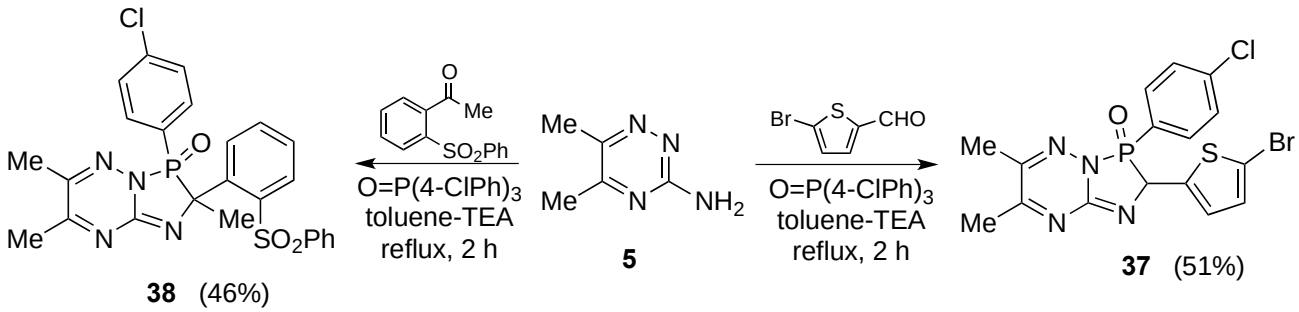
Ali and co-workers[28] obtained 6,7-bis(4-bromophenyl)-[1,2,4,3]triazaphospholo[4,5-*b*][1,2,4]triazines (**34**-**36**) from the interaction between 3-hydrazino-1,2,4-triazine **23** and dibromotriphenyl-λ^5-phosphane, diethyl phosphite, and/ or (2-chlorophenyl)phosphonothioic dichloride in THF-piperidine (Scheme 12).[28] ^{31}P NMR spectrum showed resonated signals at 29.61, 14.52, and 47.72 ppm for compounds **34**-**36**, respectively. Compounds **34**-**36** gave a good molluscicidal activity against *Biomphalaria alexandrina* snails.[28]



36 (38%) **23** **34** (23%) **35** (19%)

Scheme 12. Formation of compounds **34-36**

Abdel-Rahman[22] reported that, cyclocondensation reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (**5**) with 5-bromothiophene-2-carbaldehyde, and/ or 1-(2-(phenylsulfonyl)phenyl)ethan-1-one and tris(4-chlorophenyl)phosphine oxide in toluene-TEA, afforded the 1,4,2-diazaphospholo[1,5-*b*][1,2,4]triazine 3-oxides **37** and **38** (Scheme 13).

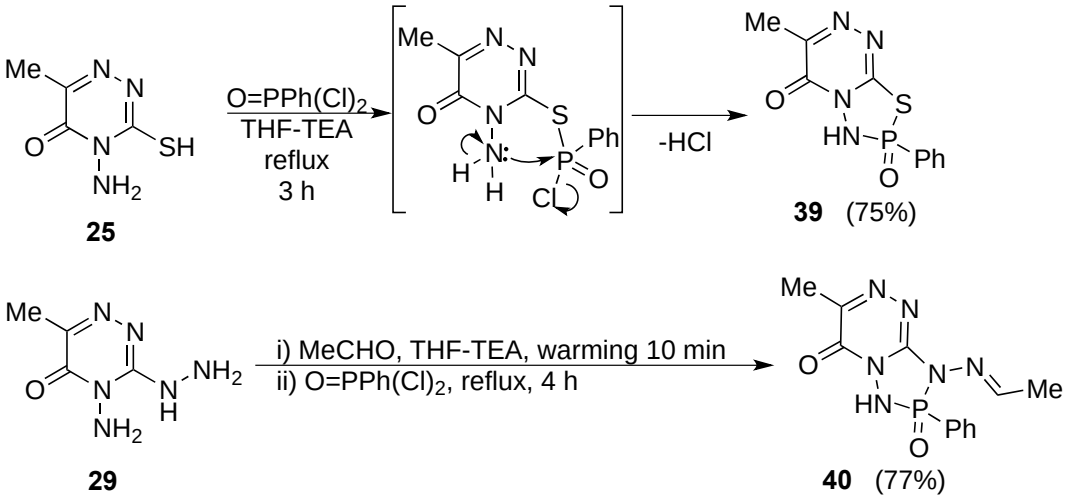


38 (46%) **5** **37** (51%)

Scheme 13. Formation of compounds **37-38**

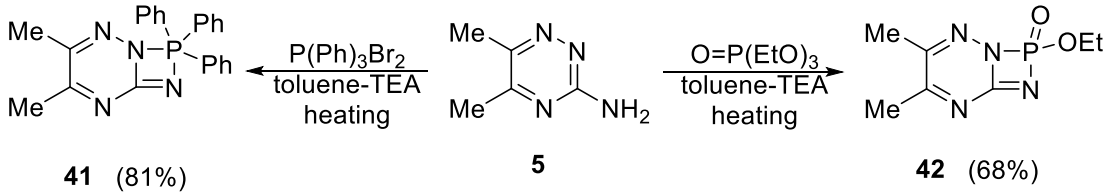
Ali[20] used 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5-one (**25**) and/ or 4-amino-3-hydrazino-6-methyl-1,2,4-triazin-5-one (**29**) to produce the fused phospha-heterobicyclic nitrogen systems. Thus, the reaction of compound **25** with phenylphosphonic dichloride in THF with few drops of triethylamine gave 6-methyl-2-phenyl-1-hydro-[1,3,4,2]thiadiazaphospholo[5,4-*c*][1,2,4]triazin-7-one 2-oxide (**39**). Similarly, the interaction between compound **29** and acetaldehyde/ phenylphosphonic dichloride in THF with few drops of triethylamine led to the direct formation of 3-(ethylideneamino)-6-methyl-2-phenyl-3-hydro-[1,2,4,3]triazaphospholo[5,1-*c*][1,2,4]triazin-7(1*H*)-one 2-oxide (**40**) (Scheme14). IR spectra of both **39** and **40** showed vibrational bands at 1220 and 1284 cm^{-1} for P=O. ^1H NMR spectra also exhibited a

doublet signal at 8.25 ppm with J_{HNP} 3.3 Hz for NH for **39** and **40**. Furthermore, ^{31}P NMR emphasized resonated signals at 55.1 and 26.4 ppm for **39** and **40**. Compounds **39** and **40** showed antibacterial activity.



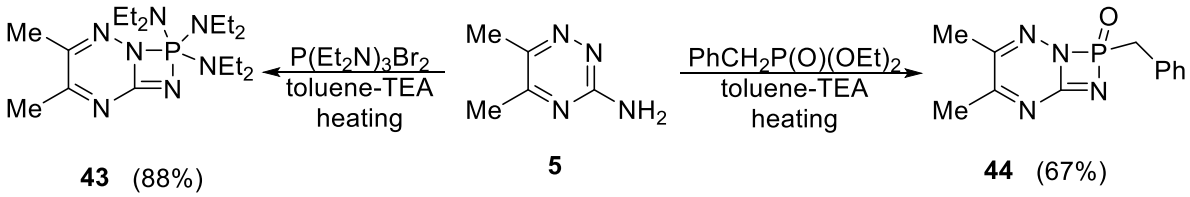
Scheme 14. Formation of compounds **39**-**40**

Various fused phospha-heterobicyclic nitrogen systems such as 1,3,2-diazaphospheto[3,4-*b*][1,2,4]-triazines **41**-**42** were synthesized from treating of 3-amino-5,6-dimethyl-1,2,4-triazine (**5**) with dibromotriphenyl-λ^5-phosphane and/ or triethyl phosphate in dry toluene with drops of triethylamine (Scheme 15).[22]



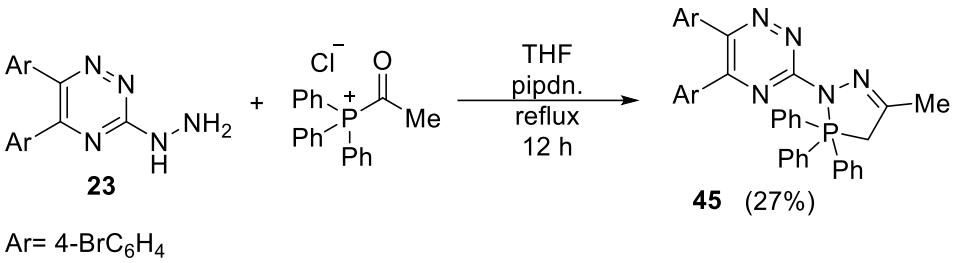
Scheme 15. Formation of compounds **41**-**42**

Similarly, 1,3,2-diazaphospheto[3,4-*b*][1,2,4]triazines **43**-**44** were isolated from the addition of 1,1-dibromo-*N*,*N*,*N*',*N*',*N*'',*N*''-hexaethyl-λ^5-phosphanetriamine and/ or diethyl benzylphosphonate in refluxing toluene-TEA (Scheme 16).[22]



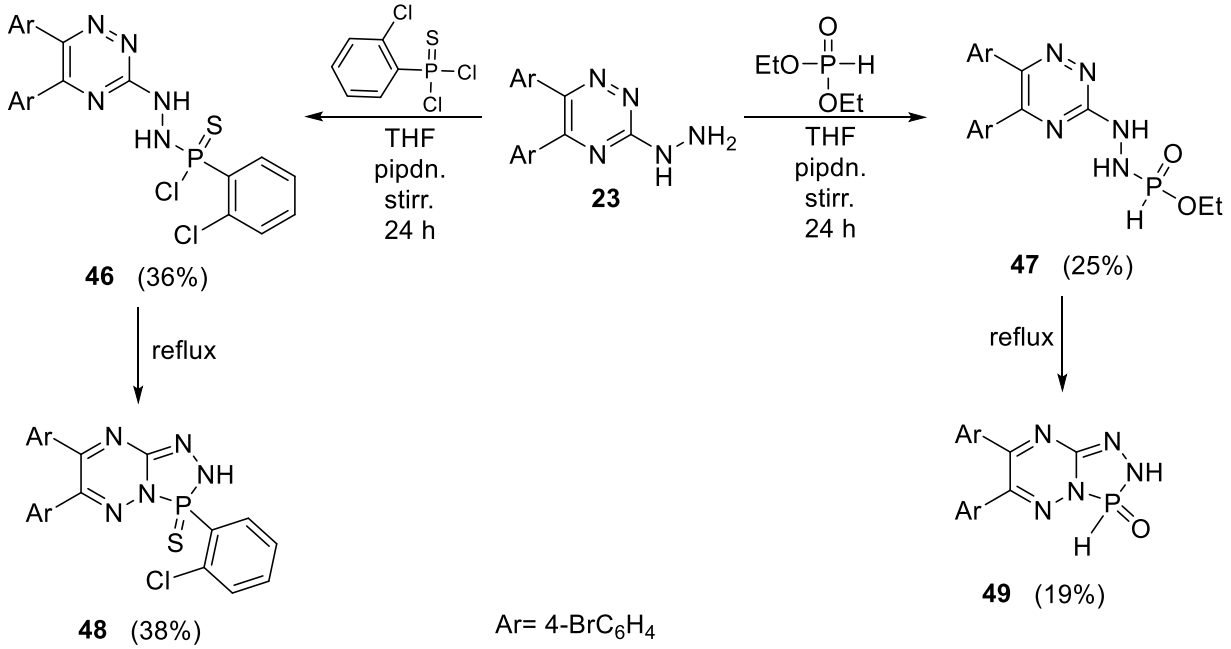
Scheme 16. Formation of compounds **43**-**44**

Besides, the treatment of compound **23** with acetyltriphenylphosphonium chloride in refluxing THF-piperidine for 12 h, afforded the 5,6-bis(4-bromophenyl)-3-(5-methyl-3,3,3-triphenyl-3,4-dihydro-2*H*-1,2,3-λ^5-diazaphosphol-2-yl)-1,2,4-triazine in low yield 27% (**45**) (Scheme 17).[28] ^{31}P NMR spectrum of **45** showed resonated signal at 25.90 ppm.



Scheme 17. Formation of compound **45**

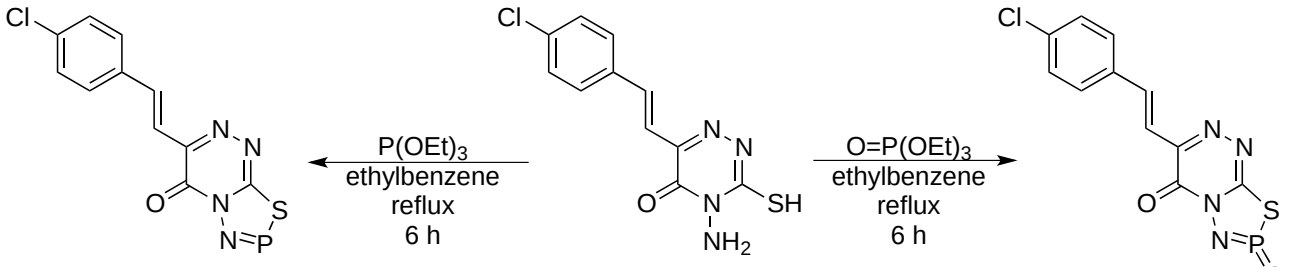
The modification of 1,2,4-triazines by introducing organophosphorus functionalities might be expected to exhibit the potential activities, depending on the position of phosphoryl group of 1,2,4-triazine moiety. Thus, the addition of (2-chlorophenyl)phosphonothioic dichloride and/ or diethyl phosphonate to compound **23** in THF-piperidine by stirring at room temperature, produced the (2-(5,6-bis(4-bromophenyl)-1,2,4-triazin-3-yl)hydrazineyl)(2-chlorophenyl)phosphinothioic chloride (**46**) and/ or ethyl (2-(5,6-bis(4-bromophenyl)-1,2,4-triazin-3-yl)hydrazineyl)phosphinate (**47**), respectively.



Scheme 18. Formation of compounds **46-49**

By continuing the reactions in the same conditions *via* refluxing for 12 h, the 6,7-bis(4-bromophenyl)-2*H*-[1,2,4,3]triazaphospholo[4,5-*b*][1,2,4]triazine 3-oxide (**48**) and 6,7-bis(4-bromophenyl)-3-(2-chlorophenyl)-2*H*-[1,2,4,3]triazaphospholo[4,5-*b*][1,2,4]triazine 3-sulfide (**49**) are formed (Scheme 18).[28] Compounds **47** and **49** showed vibrational band at 1216 and 1218 cm^{-1} for P=O group. ^{31}P NMR spectra of **46**, **47**, **48**, and **49** exhibited signals at 7.28, 53.96, 14.52, and 47.72 ppm, respectively. All compounds **46**-**49** showed molluscicidal activity against *Biomphalaria alexandrina* snails.

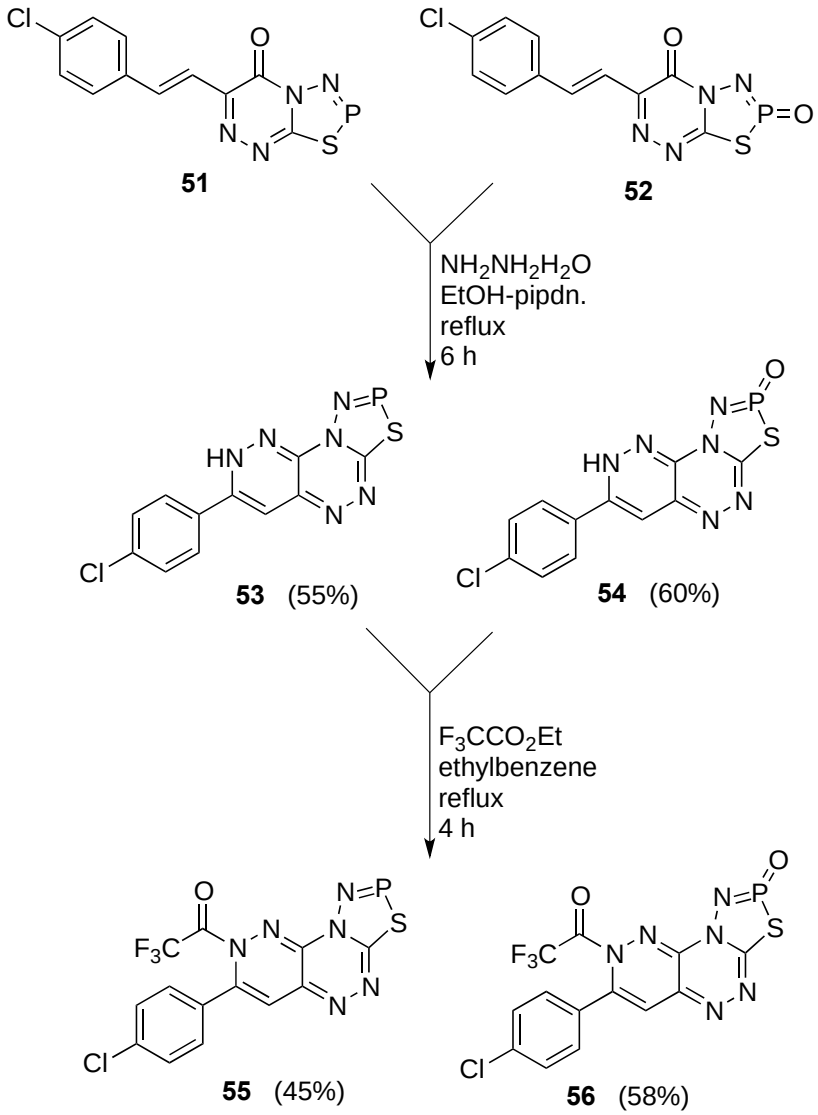
Makki *et al*.[29] synthesized 6-(4-chlorostyryl)-7*H*-[1,3,4,2]thiadiazaphospholo[5,4-*c*][1,2,4]triazin-7-one (**51**) and/ or 6-(4-chlorostyryl)-7*H*-[1,3,4,2]thiadiazaphospholo[5,4-*c*][1,2,4]triazin-7-one 2-oxide (**52**) by refluxing 4-amino-6-(4-chlorostyryl)-3-mercapto-1,2,4-triazin-5(4*H*)-one (**50**) with triethyl phosphite and/ or triethyl phosphate in ethylbenzene for 6 h (Scheme 19). UV spectra of compounds **51** and **52** showed λ_{max} at 310 and 420 nm, higher absorption of **52** referred to the extension of hetero-conjugated system. IR spectra of **51** exhibited vibrational bands at 1200 cm^{-1} for P=N, and that for **52** showed at 1230 cm^{-1} for P=O. ^{31}P NMR spectrum of **52** illustrated a signal at 18.9 ppm. Compounds **51**-**52** showed antibacterial activity against *Escherichia coli* bacteria strains.



51 (65%) **50** **52** (68%)

Scheme 19. Formation of compounds **51**-**52**

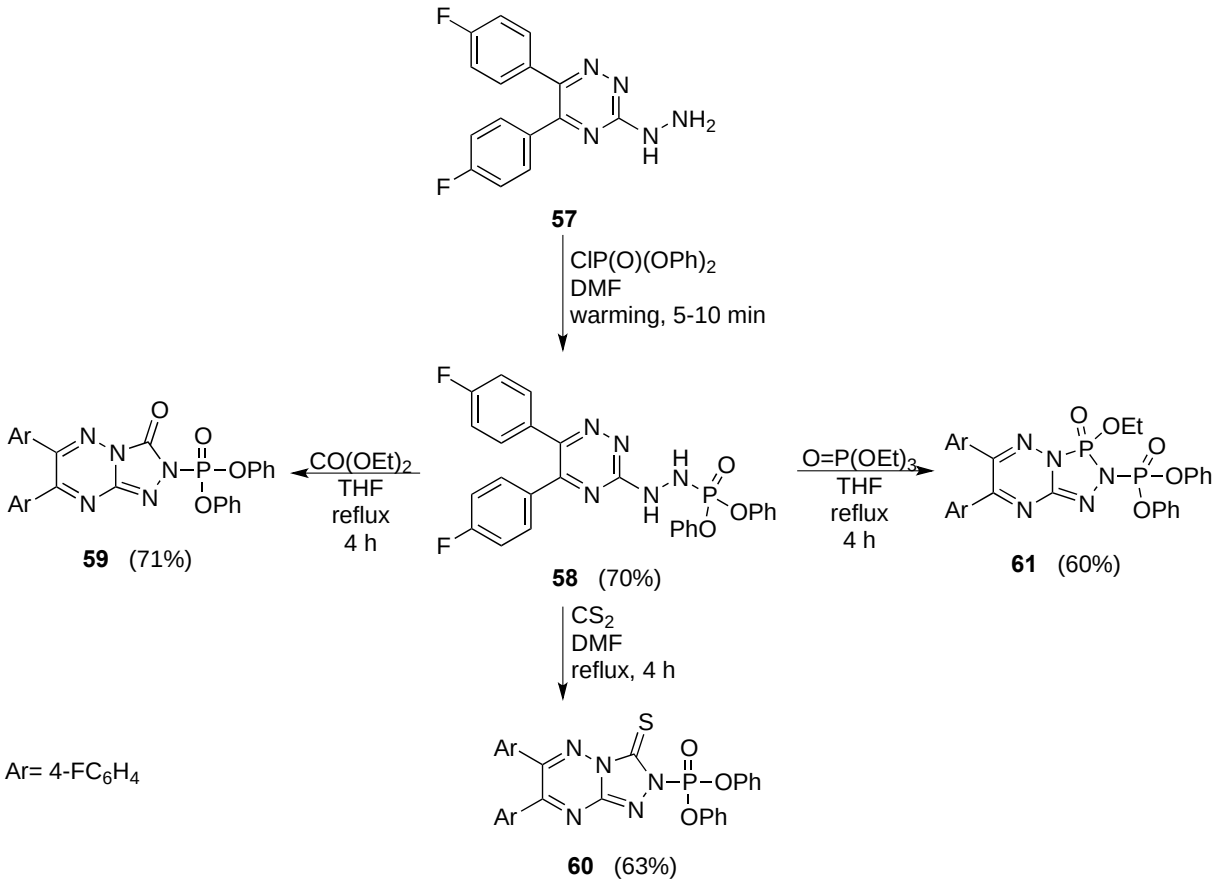
Hydrazinolysis of compounds **51** and/ or **52** by refluxing with hydrazine hydrate in absolute ethanol with few drops of piperidine, afforded the 7-(4-chlorophenyl)-8*H*-pyridazino[3,4-*e*][1,3,4,2]-thiadiazaphospholo[5,4-*c*][1,2,4]triazine (**53**) and 7-(4-chlorophenyl)-8*H*-pyridazino[3,4-*e*]-[1,3,4,2]thiadiazaphospholo[5,4-*c*][1,2,4]triazine 2-oxide (**54**), respectively (Scheme 20). ^{1}H NMR spectra of both compounds **53** and **54** recorded the presence of NH proton at 8.9 ppm with disappearance of ethylenic protons.[29] ^{13}C NMR spectra also showed lack of C=O carbons. Fluoroacylation of compounds **53**-**54** by refluxing with ethyl 2,2,2-trifluoroacetate in ethylbenzene for 4 h, gave the 1-(7-(4-chlorophenyl)-8*H*-pyridazino[3,4-*e*][1,3,4,2]thiadiazaphospholo[5,4-*c*][1,2,4]triazin-8-yl)-2,2,2-trifluoroethan-1-one (**55**) and 1-(7-(4-chlorophenyl)-2-oxido-8*H*-pyridazino[3,4-*e*][1,3,4,2]-thiadiazaphosphoro[5,4-*c*][1,2,4]triazin-8-yl)-2,2,2-trifluoroethan-1-one (**56**) (Scheme 20). IR spectra of **55** and **56** showed new bands at 1700 and 1698 cm^{-1} for C=O of $COCF_3$.[29]



Scheme 20. Formation of compounds **53-56**

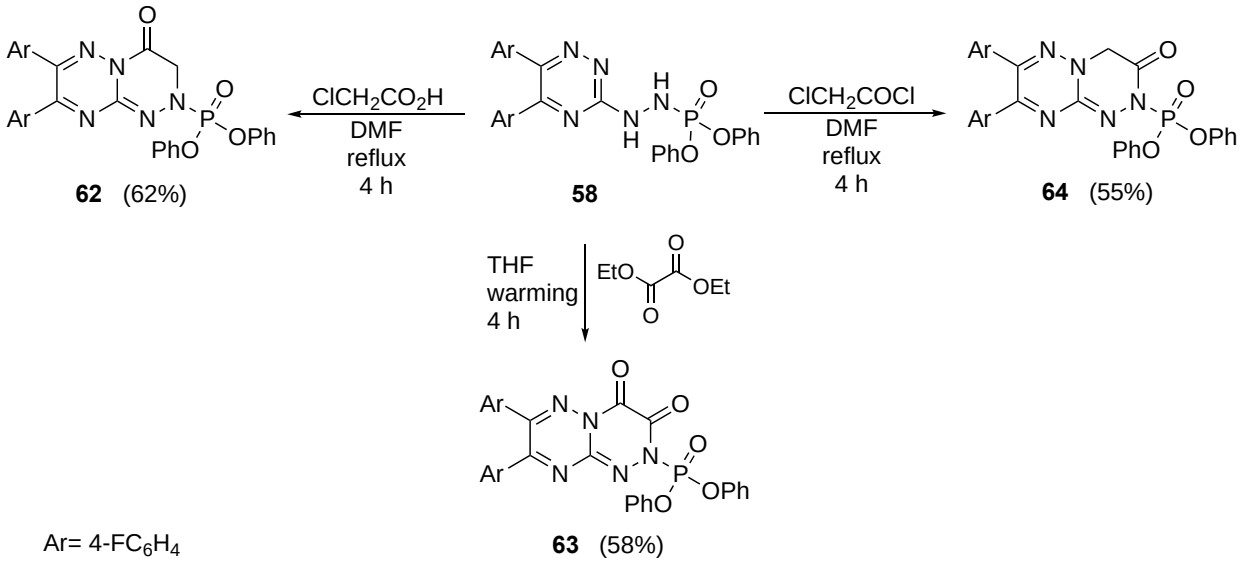
3. PHOSPHORUS COMPOUNDS BEARING 1,2,4-TRIAZINE MOIETY

Various types of fluorinated phosphorus compounds bearing bicyclic nitrogen systems were synthesized by Abdel-Rahman[30] (Schemes 21-23). Thus, warming of 5,6-bis(4-fluorophenyl)-3-hydrazineyl-1,2,4-triazine (**57**) with diphenyl phosphorochloridate in DMF, gave diphenyl (2-(5,6-bis(4-fluorophenyl)-1,2,4-triazin-3-yl)hydrazinyl)phosphonate (**58**). Ring closure reactions of compound **57** by refluxing with diethyl carbonate (THF), CS_2 (DMF), and triethyl phosphate (THF) led to the direct formation of *N*-phosphonate derivates **59-61**, respectively (Scheme 21).[30]



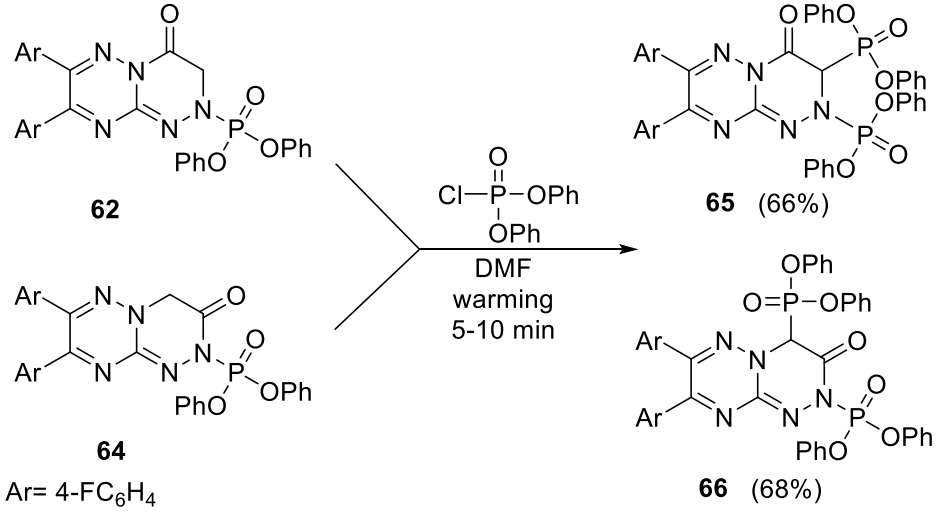
Scheme 21. Formation of compounds **58-61**

Alkylation of compound **58** by refluxing with chloroacetic acid (DMF) and/ or chloroacetyl chloride (DMF), or acylation by warming with diethyl oxalate (THF), produced the diphenyl (7,8-bis(4-fluorophenyl)-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-*b*][1,2,4]triazin-2-yl)phosphonates (**62-64**) (Scheme 22).[30]



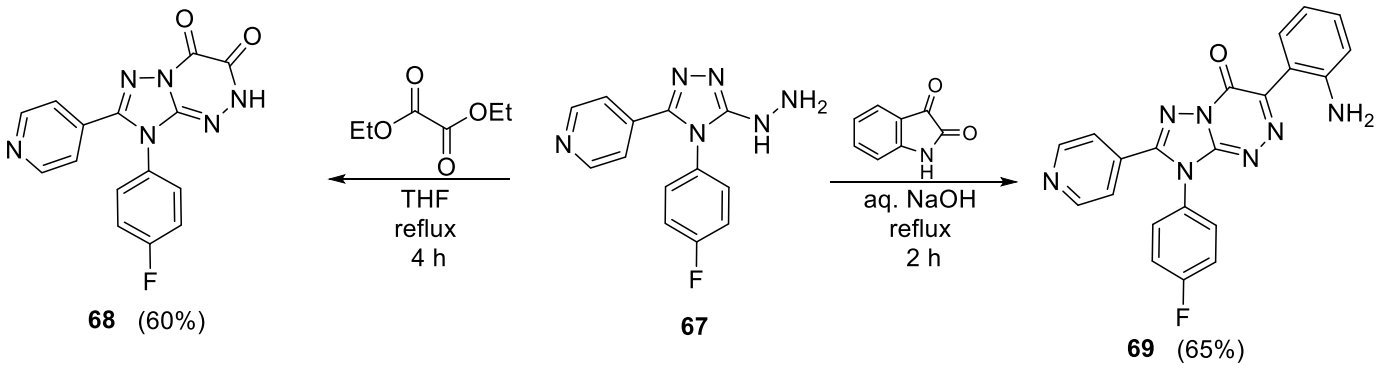
Scheme 22. Formation of compounds **62-64**

Full phosphorylation of compounds **62** and **64** by warming with diphenyl phosphorochloridate in DMF, yielded the tetraphenyl (7,8-bis(4-fluorophenyl)-3/4-oxo-3,4-dihydro-2*H*-[1,2,4]triazino[4,3-*b*][1,2,4]-triazine-2,3-diyl)bis(phosphonates) **65**-**66** (Scheme 23).[30] All the synthesized compounds **58**-**66** were evaluated as CDK2 inhibitors of tumor cells, where the compounds **65**-**66** exhibited highly inhibition effects.[30]



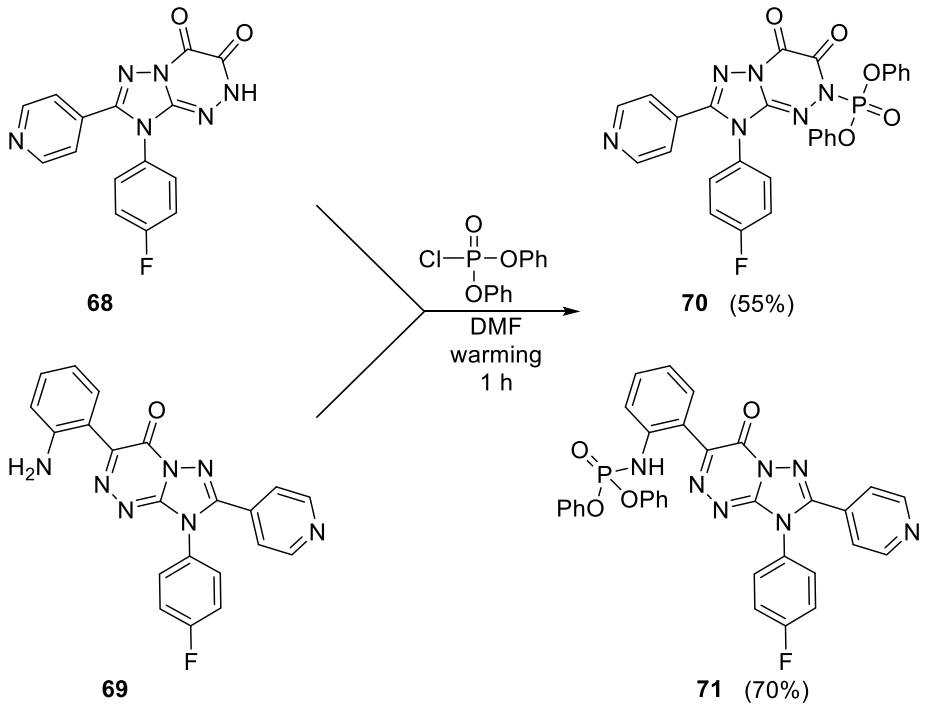
Scheme 23. Formation of compounds **65**-**66**

Abdel-Rahman and co-workers[17] obtained some fused heterobicyclic nitrogen systems bearing phosphato-groups as molluscicidal agents. Thus, reaction of 4-(4-(4-fluorophenyl)-5-hydrazinyl-4*H*-1,2,4-triazol-3-yl)pyridine (**67**) with diethyl oxalate in refluxing THF gave the 8-(4-fluorophenyl)-7-(pyridin-4-yl)-2,8-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-3,4-dione (**68**), while refluxing with isatin in *aq*. NaOH yielded 3-(2-aminophenyl)-8-(4-fluorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-4(8*H*)-one (**69**) (Scheme 24).



Scheme 24. Formation of compounds **68**-**69**

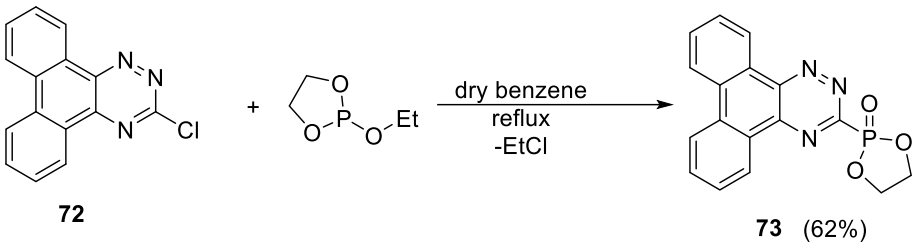
Phosphorylation of both compounds **68** and **69** by warming with diphenyl phosphorochloridate in DMF afforded diphenyl (8-(4-fluorophenyl)-3,4-dioxo-7-(pyridin-4-yl)-3,4-dihydro-[1,2,4]triazolo[5,1-*c*]-[1,2,4]triazin-2(8*H*)-yl)phosphonate (**70**) and diphenyl (2-(8-(4-fluorophenyl)-4-oxo-7-(pyridin-4-yl)-4,8-dihydro-[1,2,4]triazolo[5,1-*c*][1,2,4]triazin-3-yl)phenyl)phosphoramidate (**71**), respectively (Scheme 25).[17]



Scheme 25. Formation of compounds **70-71**

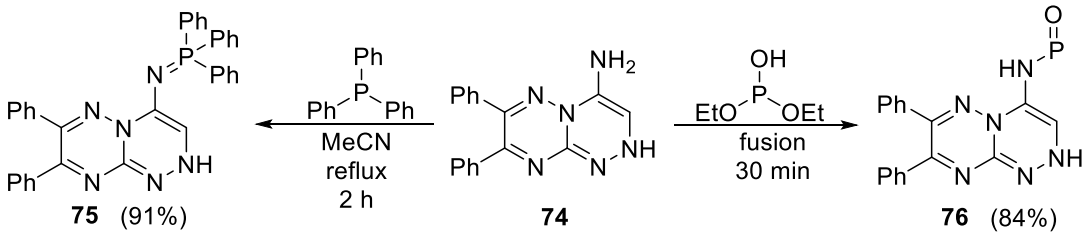
IR spectra of compounds **70-71** recorded *v* at 1190 and 1170 cm^{-1} for the P-O group. ^{31}P NMR spectra also showed a signal at -2 ppm. The synthesized compounds were evaluated as molluscicidal against some snails.[31] Only compound **70** showed high mortality of snails at three concentrations compared to Bayluscide as a standard drug used.

3-Chloro-1,2,4-triazine is considered one of the essential heterocyclic nitrogen systems due to the presence of a chlorine atom, which is easily removed.[32,33] Thus, the reaction of compound **72** with 2-ethoxy-1,3,2-dioxaphospholane by refluxing in dry benzene, yielded the 2-(phenanthro[9,10-*e*][1,2,4]triazin-3-yl)-1,3,2-dioxaphospholane 2-oxide (**73**) (Scheme 26).[33] IR spectrum of compound **73** indicated a vibrational band at 1258 for P=O. Also, the ^1H NMR spectrum exhibited two doublet δ at 3.8 and 4.2 ppm with coupling constant J_{HP} 11.5 Hz for two OCH_2. Moreover, ^{13}C NMR showed two doublet signals at 62.2 and 62.6 ppm with J_{CP} 243 Hz.[33]



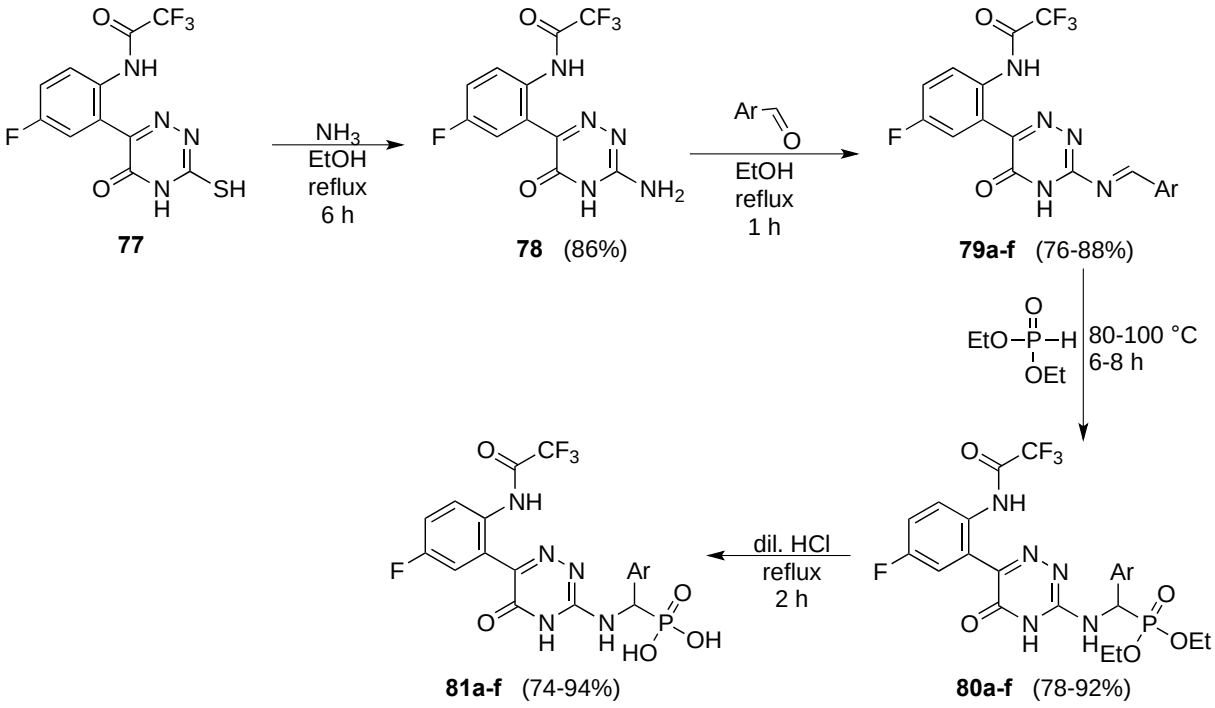
Scheme 26. Formation of compound **73**

Bawazier *et al*.[34] obtained some phosphorus compounds bearing 1,2,4-triazino-1,2,4-triazine derivatives **75** and **76** *via* refluxing with triphenylphosphine in acetonitrile and/ or fusion with diethyl hydrogen phosphite, respectively (Scheme 27). Compound **75** showed a vibrational band at 1210 cm^{-1} for N=P, while compound **76** exhibited at 1229 cm^{-1} for P=O. ^{31}P NMR spectra of **75** and **76** indicated signals at 29.6 and 32.1 ppm, respectively.



Scheme 27. Formation of compounds **75-76**

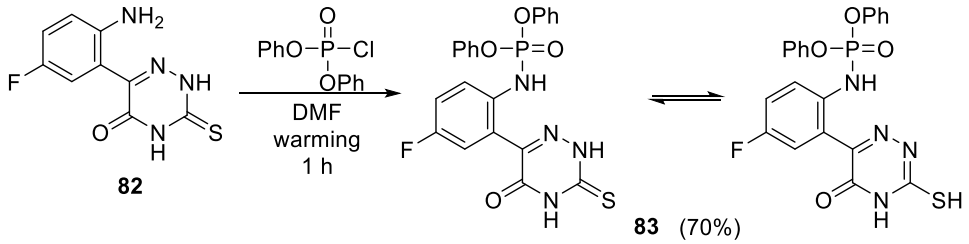
Recently, 3-mercapto/amino/hydrazino-1,2,4-triazin-5-one derivatives have been gathering considerable interest in various applications in chemotherapy and biological area.[35-37] In addition, α-aminophosphonic acid bearing 1,2,4-triazine derivatives have high importance in the pharmacological and biological fields,[38,39] such as HIV inhibitors,[40] protease antagonists,[41] collagenase inhibitors,[42] anticancer,[43] antibacterial,[44] and antiviral,[45] probes. Besides, the introduction of fluorine atoms to heterocyclic nitrogen systems often enhances and improves their biological properties.[46-48] Based upon these observations, Makki *et al*.[16] obtained diethyl (((6-(5-fluoro-2-(2,2,2-trifluoroacetamido)phenyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl)amino)(aryl)methyl)phosphonates **80a-f** and (((6-(5-fluoro-2-(2,2,2-trifluoroacetamido)phenyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl)amino)(aryl)methyl)-phosphonic acids **81a-f** *via* the addition of diethyl phosphate to Schiff bases **79a-f** followed by acidic hydrolysis (Scheme 28). Compound **81f** showed promising high antioxidant activity in comparison with the standard drug used.



Ar; a= 2-$NO_2C_6H_4$, b=3-$NO_2C_6H_4$, c=4-$NO_2C_6H_4$, d=4-BrC_6H_4, e=4-ClC_6H_4, f=4-FC_6H_4

Scheme 28. Formation of compounds **78-81**

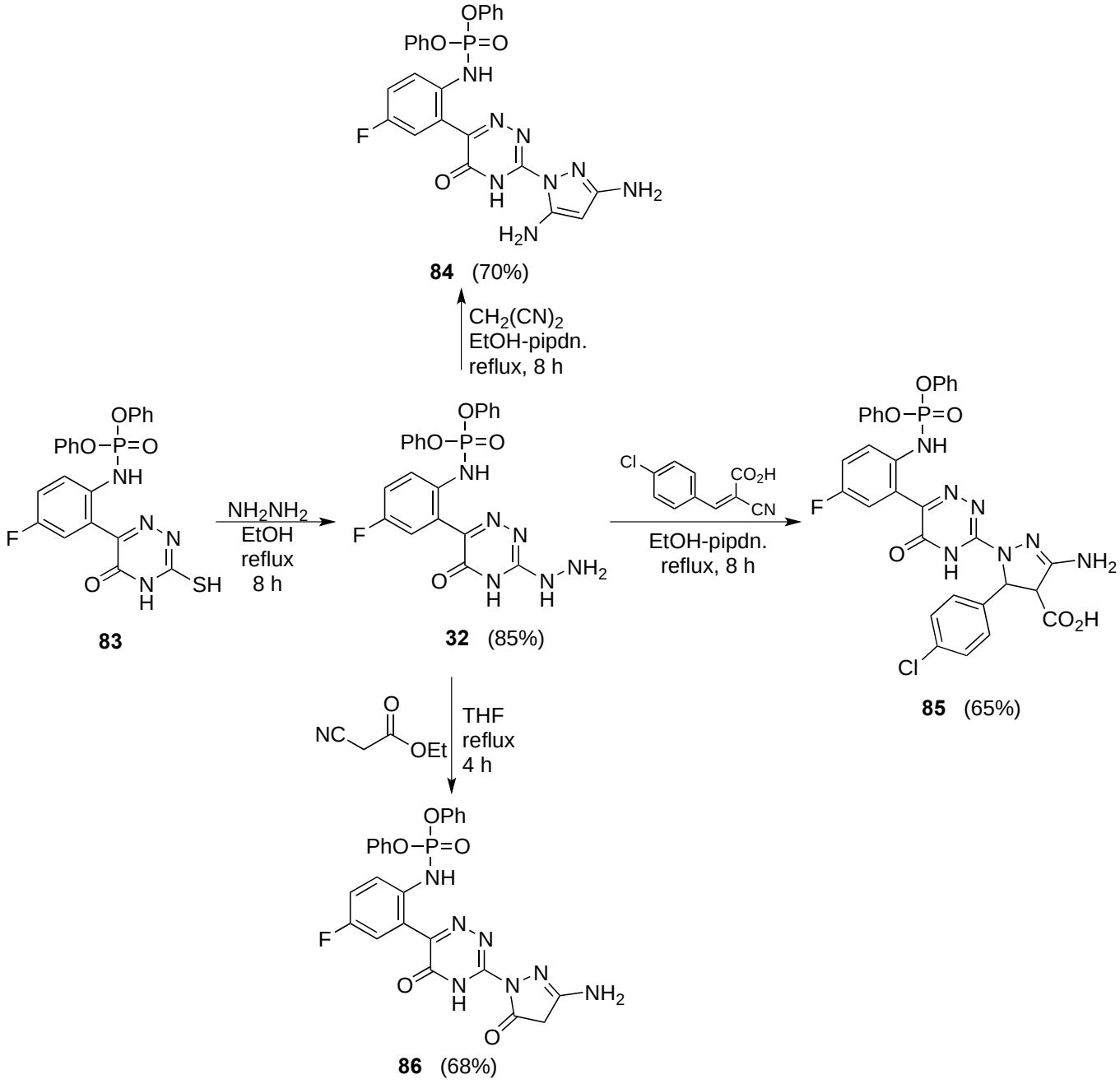
3-Thioxo/amino/hydrazino-1,2,4-triazin-5-ones used as starting nucleophilic agents (as donor electrons), when reacting with phosphorus agents (as acceptor electrons) produced stable derivatives by donation and back donation. Thus, treatment of 6-aryl-3-thioxo-1,2,4-triazin-5-(2*H*,4*H*)one (**82**) with diphenyl-phosphoryl chloride in warming DMF afforded the *N*-phosphato derivative **83** (Scheme 29).[6]



Scheme 29. Formation of compound **83**

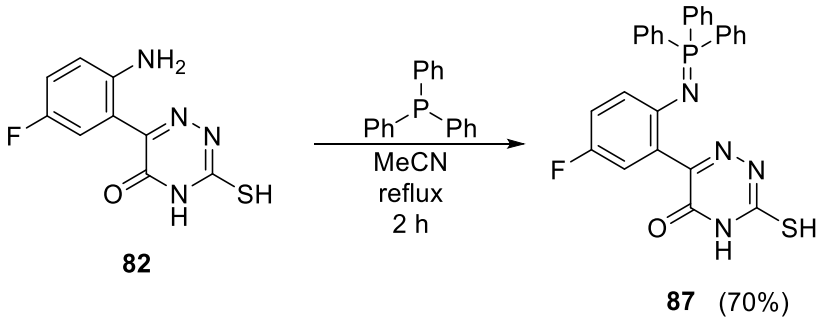
Hydrazinolysis of compound **83** by removal the SH group gave the diphenyl (4-fluoro-2-(3-hydrazineyl-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)phenyl)phosphoramidate (**32**) (Scheme 30).[6] Compound **32** was used as starting material to give fluorine/phosphorus-substituted isolated heterobicyclic nitrogen systems as anti-HIV probes. Therefore, ring closure reactions of **32** with malononitrile (EtOH-piperidine), arylidenecyanoacetic acid (EtOH-piperidine), and/ or ethyl cyanoacetate

(THF), yielded diphenyl (2-(3-(3,5-diamino-1*H*-pyrazol-1-yl)-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)-4-fluorophenyl)phosphoramidate (**84**), 3-amino-5-(4-chlorophenyl)-1-(6-(2-((diphenoxyphosphoryl)amino)-5-fluorophenyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl)-4,5-dihydro-1*H*-pyrazole-4-carboxylic acid (**85**), and/ or diphenyl (2-(3-(3-amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)-4-fluorophenyl)phosphoramidate (**86**), respectively (Scheme 30).[6]



Scheme 30. Formation of compounds **84-86**

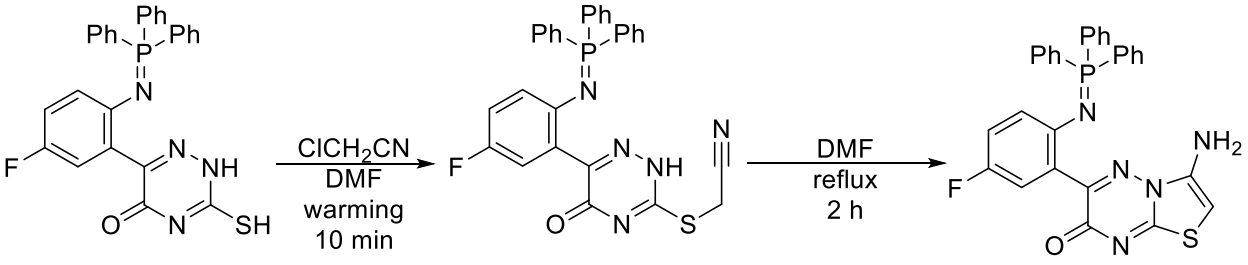
Introduction of phosphine moiety to amino group of compound **82** by refluxing with triphenylphosphine in acetonitrile, gave 6-(5-fluoro-2-((triphenyl-λ^5-phosphanylidene)amino)phenyl)-3-mercapto-1,2,4-triazin-5(4*H*)-one (**87**) (Scheme 31).[49]



82 **87** (70%)

Scheme 31. Formation of compound **87**

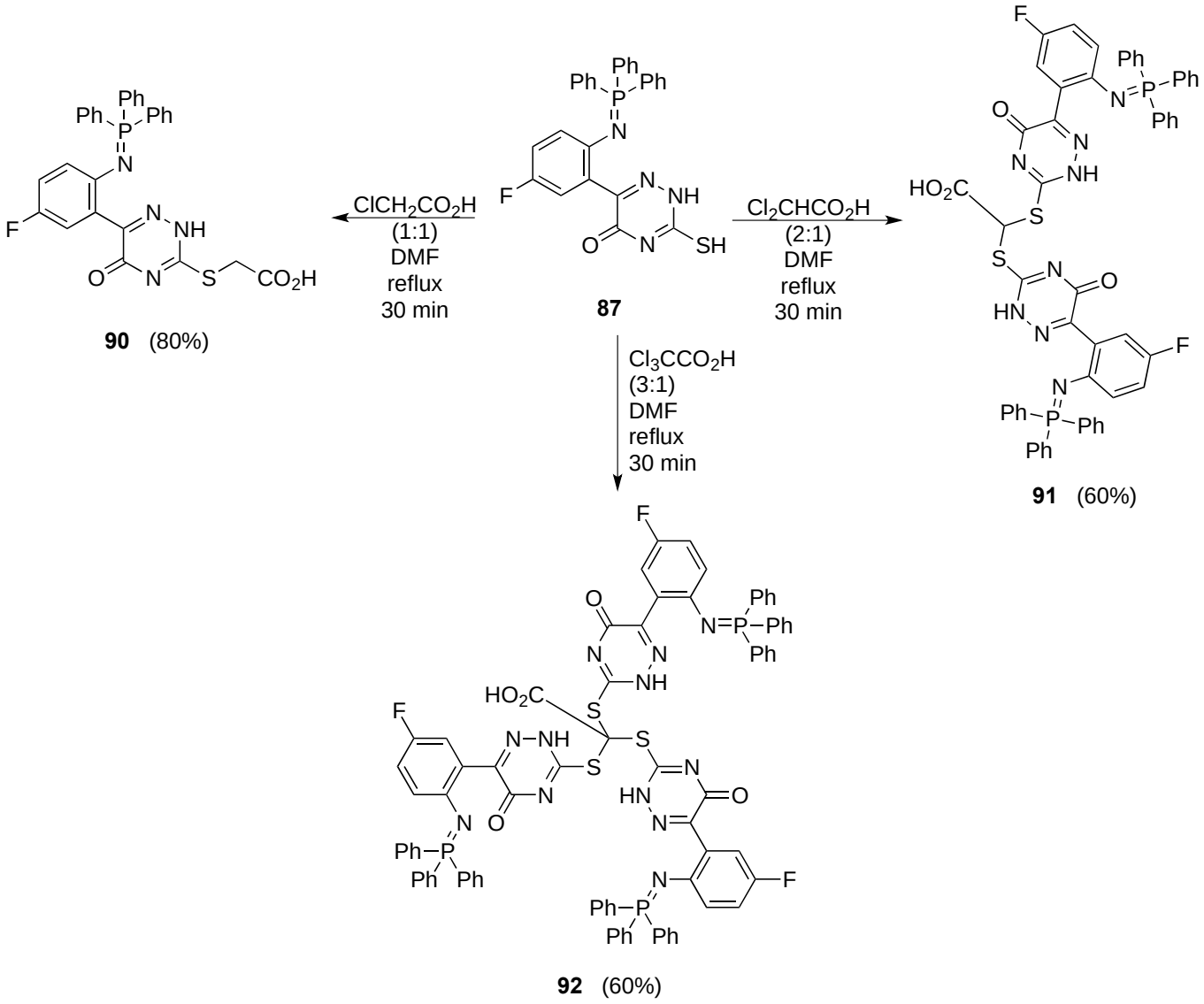
Compound **87** was used as starting material to build a variety of the corresponding S-R and/ or N-R derivatives. Thus, simple alkylation of compound **87** by warming with chloroacetonitrile in DMF at 40 °C for 10 min produced 2-((6-(5-fluoro-2-((triphenyl-λ^5-phosphaneylidene)amino)phenyl)-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio)acetonitrile (**88**), which upon cycloaddition by refluxing in DMF for 2 h, yielded 3-amino-6-(5-fluoro-2-((triphenyl-λ^5-phosphanylidene)amino)phenyl)-7*H*-thiazolo[3,2-*b*][1,2,4]triazin-7-one (**89**) (Scheme 32).[49]



87 **88** (70%) **89** (66%)

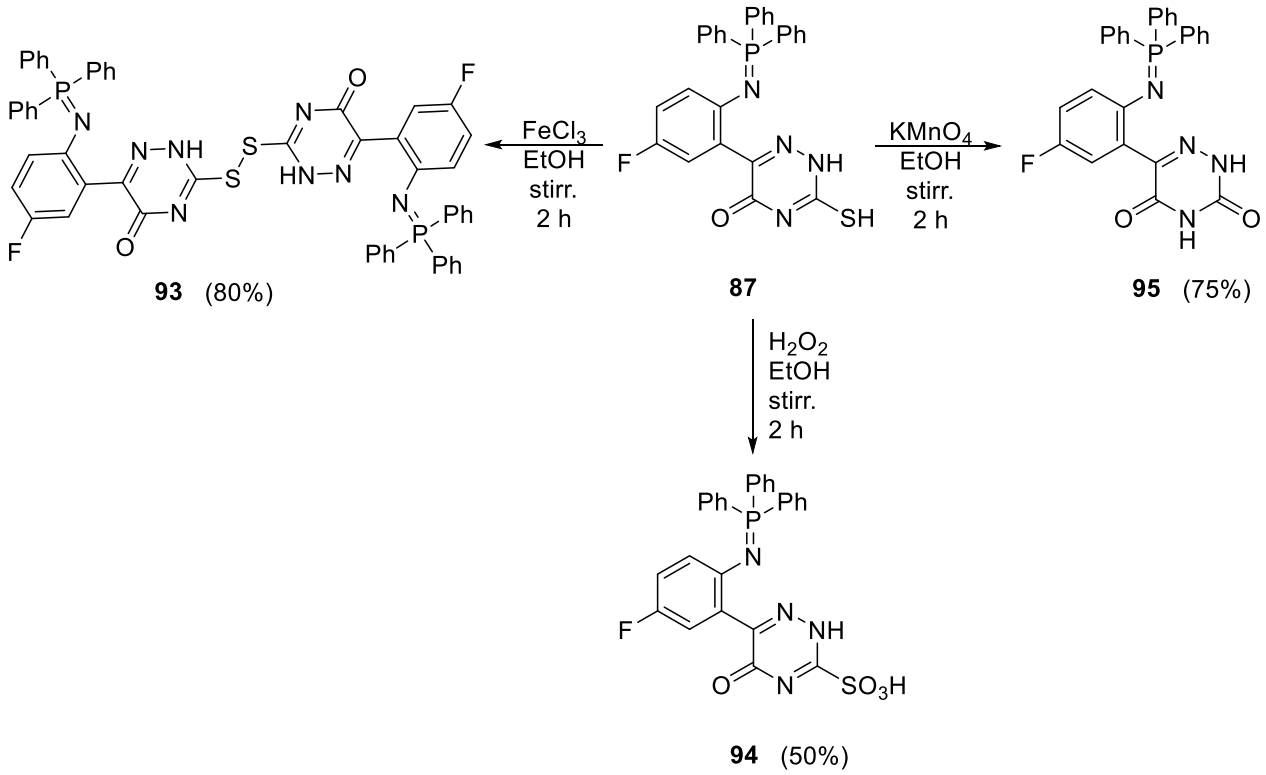
Scheme 32. Formation of compounds **88-89**

Similarly, alkylation of the SH group of compound **87** by refluxing with chloroacetic acid, 1,1-dichloroacetic acid, and/ or 1,1,1-trichloroacetic acid in DMF yielded the *S*-alkyl derivatives **90-92**, respectively (Scheme 33).[49]



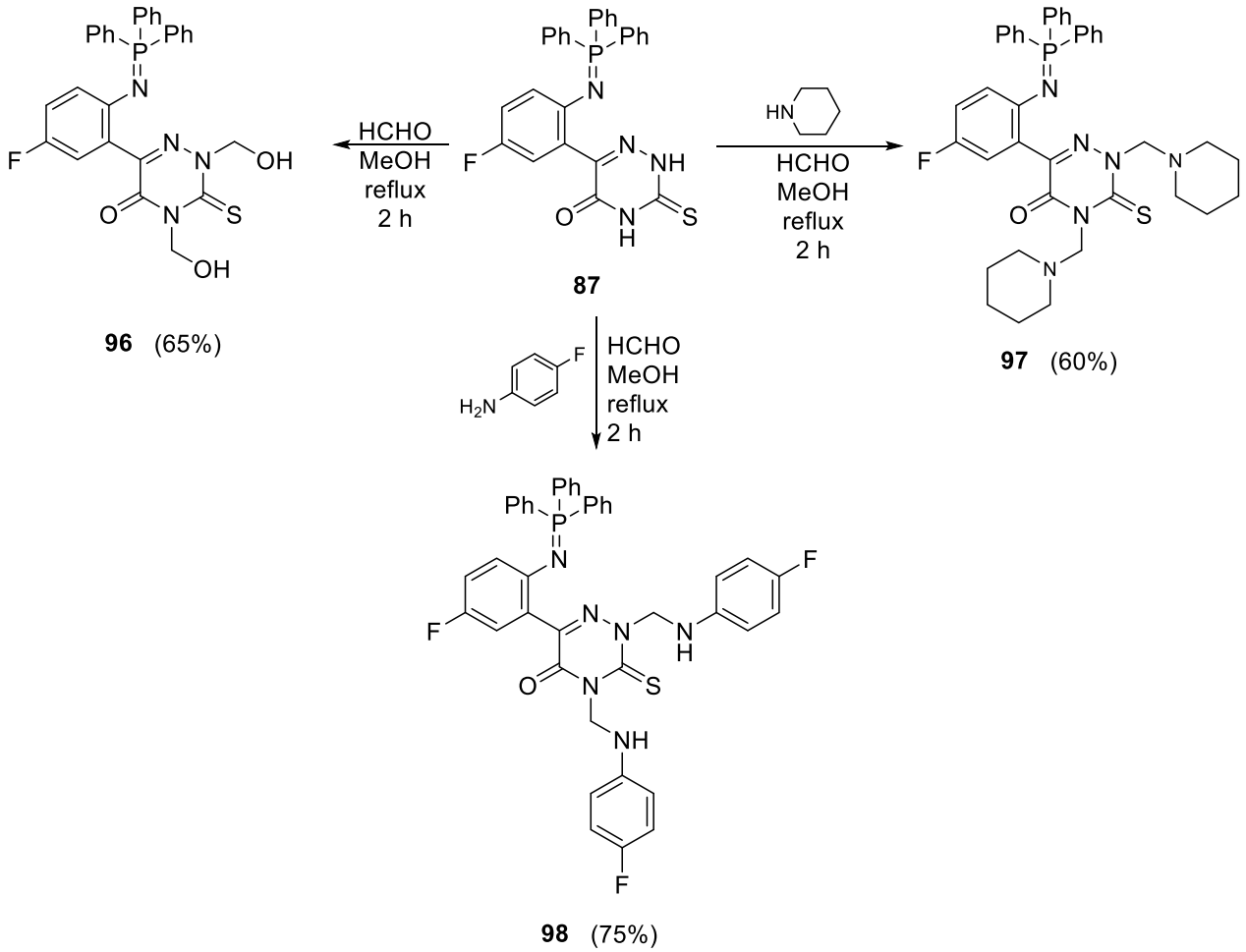
Scheme 33. Formation of compounds **90-92**

Careful oxidation of **87** by stirring with $FeCl_3$ in EtOH, H_2O_2 in EtOH, and/ or alcoholic $KMnO_4$ for 2 h at room temperature, afforded the disulfide **93**, sulfonic acid **94**, and/ or 6-azauracil **95**, respectively (Scheme 34).[49] The synthesized compounds **87**, **92**, **93**, and **95** showed high mortal activity against some snails as molluscicidal agents.[49]



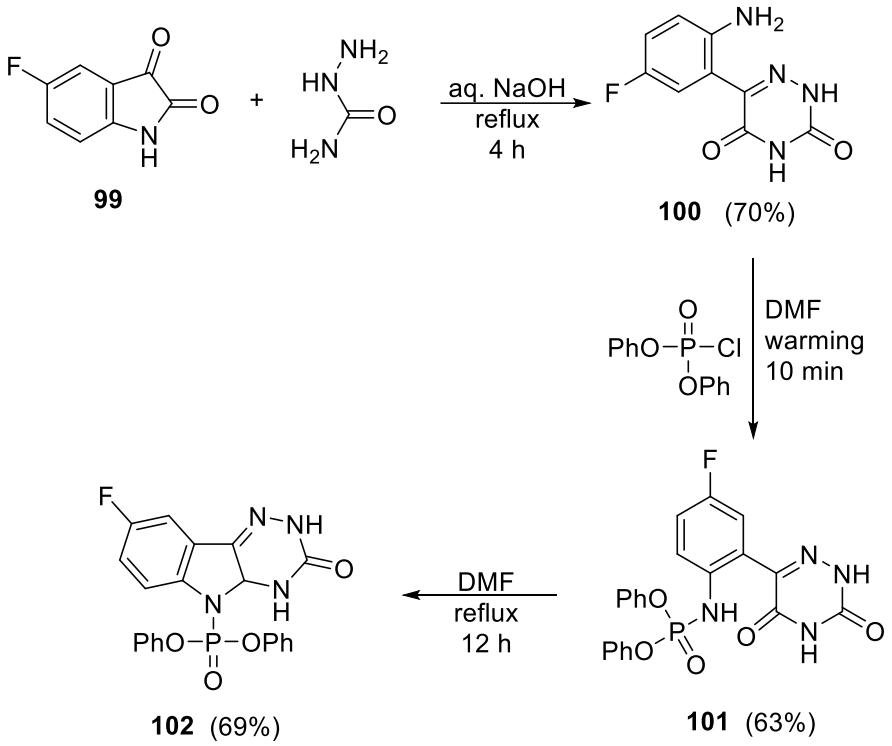
Scheme 34. Formation of compounds **93-95**

On the other hand, specific alkylation of the NH of compound **87** by refluxing with HCHO/MeOH, HCHO/MeOH/piperidine, and/ or HCHO/MeOH/*p*-fluoroaniline, yielded the 2,4-dialkyl-3-thioxo-6aryl-1,2,4-triazin-5-one derivatives **96-98**, respectively (Scheme 35).[49] Compounds **97**,**98** showed moderate mortal activity towards some snails.



Scheme 35. Formation of compounds **96-98**

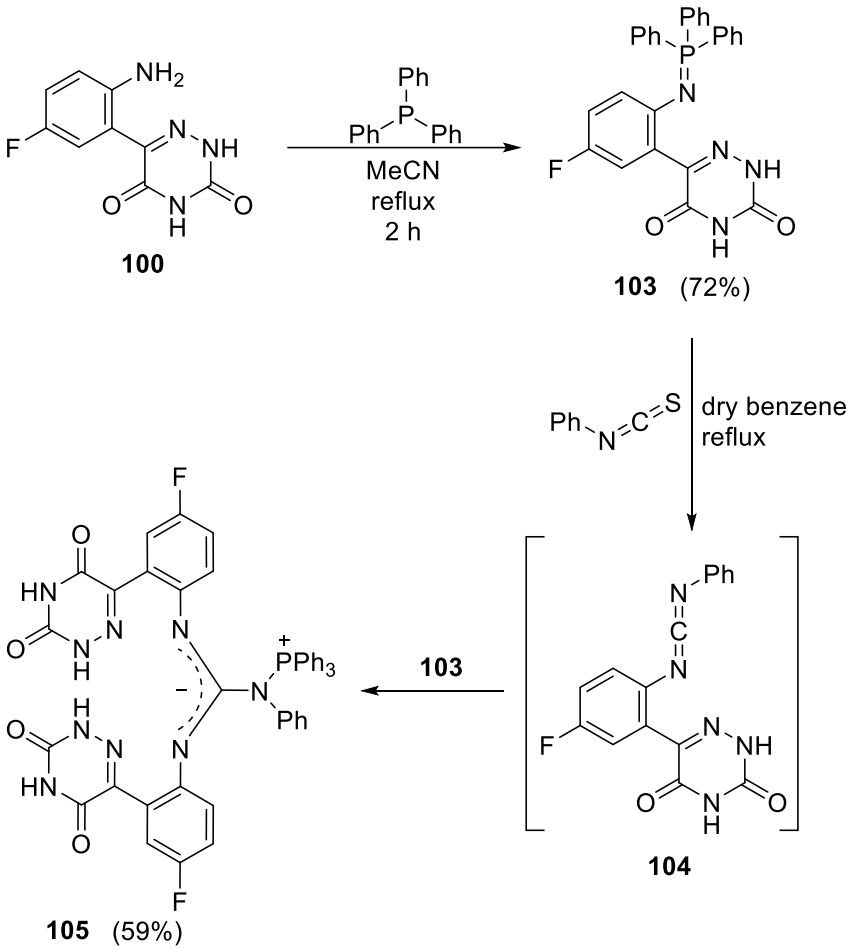
It is interesting that, cyclocondensation of 5-fluoroisatin **99** with semicarbazide in refluxing *aq*. NaOH gave 5-(2`-amino-5`-fluorophenyl)-6-azauracil (**100**). Phosphorylation of compound **100** by warming with diphenyl chlorophosphate in warming DMF produced the *N*-phosphato derivative **101**. Boiling of compound **101** in DMF for 12 h, afforded diphenyl (8-fluoro-3-oxo-2,3,4,4a-tetrahydro-5*H*-[1,2,4]triazino[5,6-*b*]indol-5-yl)phosphonate (**102**) (Scheme 36).[50] Compounds **100**-**102** showed antioxidant activity.



99 **100** (70%) **101** (63%) **102** (69%)

Scheme 36. Formation of compounds **100-102**

According to Molina *et al.*,[51] Abdel-Rahman *et al.*[50] obtained iminophosphoanylides and studied their behavior towards aza-Wittig's type reactions with isothiocyanate leading to mesoionic (Zwitterionic). Thus, treatment of compound **100** with PPh_3 in MeCN, produced the iminophosphine derivative **103**, which upon addition of phenyl isothiocyanate in dry benzene gave the dipole **104**. The second addition of **103** afforded Zwitterion compound **105** (Scheme 37).

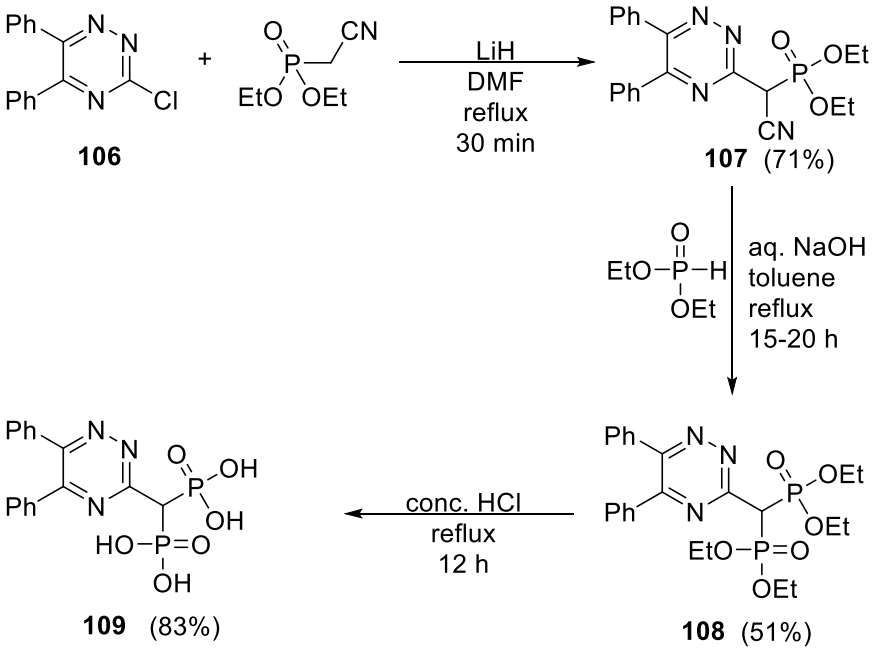


Scheme 37. Formation of compounds **103-105**

The structures of products **103** and **104** were deduced from their spectral data. Therefore, UV absorption spectrum of **103** recorded λ_{max} at 266 nm, while that of **105** exhibited λ_{max} at 315 nm. Higher absorption wavelength of **105** in comparison with **103** confirmed that the 1,3-dipolar electronic system is formed. IR spectrum of **105** showed a characteristic band at 2400 cm^{-1} which is attributed to a 1,3-dipolar group. Also, the IR spectrum of **103** recorded a band at 996 cm^{-1} for the presence of the P=N functional group. In addition, a mass spectral study of **105** revealed the presence of a molecular ion peak at *m*/*z* 805 (0.5%) with a base peak at *m*/*z* 304.[50]

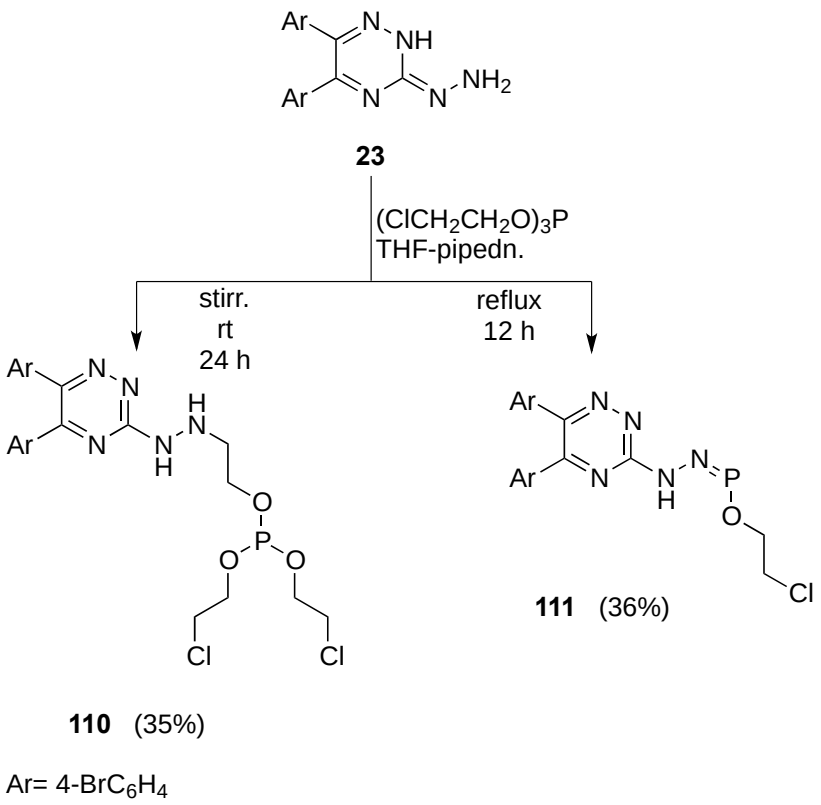
Interestingly, refluxing of 3-chloro-5,6-diphenyl-1,2,4-triazine (**106**) with diethyl (cyanomethyl)-phosphonate in DMF-LiH for 30 min, yielded the diethyl (cyano(5,6-diphenyl-1,2,4-triazin-3-yl)methyl)phosphonate (**107**), which upon refluxing with diethyl phosphonate in toluene and *aq*. NaOH, produced the tetraethyl ((5,6-diphenyl-1,2,4-triazin-3-yl)methylene)bis(phosphonate) (**108**). Acidic hydrolysis of compound **108** by refluxing in conc. HCl for 12 h, afforded ((5,6-diphenyl-1,2,4-triazin-3-yl)methylene)bis(phosphonic

acid) (**109**) (Scheme 38).[52] ^{31}P NMR of the synthesized compounds exhibited signals as **107 (**32.6 ppm), **108** (22.7 and 24.3 ppm for *dd*, J_{pp}= 6Hz), and **109** (22.4 and 24.1 ppm, *ss*).



Scheme 38. Formation of compounds **107-109**

Phosphorus atom found in trivalent phosphine behaves as a powerful nucleophile. Therefore, stirring of 3-hydrazino-5,6-diaryl-1,2,4-triazine (**23**) with tris(2-chloroethoxy)phosphine in THF with drops of piperidine at room temperature for 24 h, afforded 2-(2-(5,6-bis(4-bromophenyl)-1,2,4-triazin-3-yl)hydrazineyl)ethyl bis(2-chloroethyl) phosphite (**110**)[28] which is formed according to Horner-Emmons reactions.[53] Conversely, refluxing of compound **23** with tris(2-chloroethoxy)phosphine in THF with drops of piperidine for 12 h produced the [2-chloroethyl-(5,6-bis(4-bromophenyl)-1,2,4-triazin-3-yl)hydrazino]phosphinite (**111**) (Scheme 39).[28] IR spectrum of compound **111** exhibited vibrational band at 1334 cm^{-1} for N=P. ^{31}P NMR spectra of both **110** and **111** showed signals at 14.45, 19.50 ppm, respectively.



Scheme 39. Formation of compounds **110-111**

4. IMPORTANCE AND APPLICATIONS

Recently, phosphorus compounds containing and bearing 1,2,4-triazine moieties received more interest and expectation of further developing the chemotherapeutic field. Most of these systems revealed a wide range of medicinal and biological properties such as anti-HIV, anticancer, antioxidant, antibacterial, molluscicidal, and anti-inflammatory, insecticide, pesticide, besides potential inhibitors for enzymes.[1-54] Table 1 summarizes the activities of the important compounds.

Table 1. Medicinal and biological activities of the phosphorus compounds containing 1,2,4-triazines

Activity	Compound
Anti-HIV	**32**,**33**
Anticancer	**7, 8, 9, 10, 11, 12, 13, 14, 15, 19, 20, 21, 22**
Antioxidant	**81f, 100, 101, 102**
Antibacterial activity	**26, 28, 30, 31, 39, 40, 51, 52**
Molluscicidal activity	**24, 33, 34, 35, 36, 46, 47, 48, 49, 70, 71, 87, 92, 93, 95, 97, 98**
Potential inhibitors for enzymes	**59, 61, 62, 63, 64, 65, 66**

5. CONCLUSION

This review reports the importance and vital routes to synthesize most phosphorus compounds bonded with 1,2,4-triazine moieties because of their chemical and medicinal properties. It also presents two types of these systems: phosphorus-containing and/ or bearing 1,2,4-triazines with various conditions of the syntheses. We hope it plays a fundamental role in the area of both phosphorus and 1,2,4-triazine fields.

ACKNOWLEDGMENTS

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