European Journal of Chemistry 1 (4) (2010) 388-396

European Journal of Chemistry

Journal homepage: www.eurjchem.com

1,2,4-Triazine Chemistry Part II: Synthetic approaches for phosphorus containing 1,2,4-triazine derivatives

Reda Mohammady Abdel-Rahman, Magdy Ahmed Ibrahim and Tarik El-Sayed Ali*

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo, EG-11711, Egypt

**Corresponding author at: Department of Chemistry, Faculty of Education, Ain Shams University, Cairo, EG-11711, Egypt. Tel.: +2.010.3730144; fax: +2022581243.*
E-mail address: tarik_elsayed1975@yahoo.com (T.E. Ali).

REVIEW INFORMATION

Received: 06 June 2010
Received in revised form: 11 August 2010
Accepted: 14 August 2010
Online: 31 December 2010

KEYWORDS

1,2,4-Triazine
Phosphorus
Phosphorylation
Cyclization
Heterocyclization

ABSTRACT

This review represents the methods developed for the synthesis of phosphorus containing 1,2,4-triazine moieties. These methods depends on the phosphorylation of side functional groups of 1,2,4-triazines and cyclization of side functional groups of 1,2,4-triazines with phosphorus reagents to give isolated and fused phosphorus heterocyclic systems.

1. Introduction

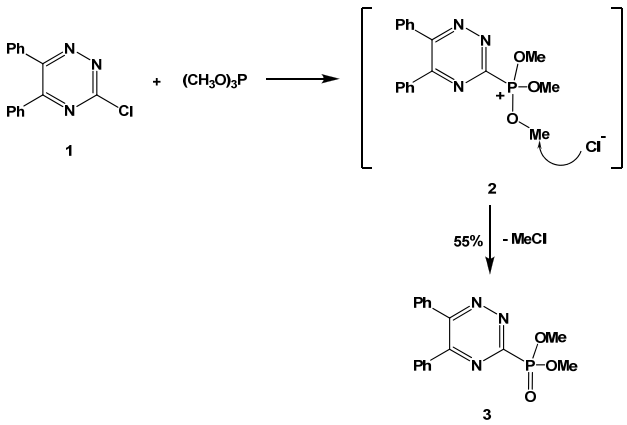
Various substituted 1,2,4-triazine derivatives have a great importance as biological agents in medicinal and agricultural fields [1–6]. Recently, this class of compounds have gained considerable interest because of their herbicidal [7,8], antimicrobial [9-11], anti-HIV [12] and anticancer activities [13,14]. On the other hand, the high biological activity of organophosphorus compounds, such as highly active anti-TMV activity [15], herbicides [16,17], insecticides [18,19], antitumor [20] and war gases, is well known. Our last review [21] has been useful for the chemists engaged in the development of synthesis and chemistry of 1,2,4-triazine systems. The intention of the present review is to cover all the literature methods developed for the synthesis of phosphorus containing 1,2,4-triazine moieties starting from their appearance up to the 2010. Although the literature data for the synthesis of phosphorus containing 1,2,4-triazine moieties are few, the described methods can be divided into three routes: phosphorylation of 1,2,4-triazine at position 3 or its side functional groups at this position and cyclization of side functional groups of 1,2,4-triazines with phosphorus reagents to give isolated and fused phosphorus heterocyclic systems. It is hoped that this review will demonstrate the synthetic potential of the synthesis of phosphorus containing 1,2,4-triazine moieties and generate some new ideas in this area.

2. Synthetic approaches

2.1. Phosphorylation of 1,2,4-triazines

2.1.1. Phosphorylation of 1,2,4-triazine at position 3

Treatment of 3-chloro-5,6-diphenyl-1,2,4-triazine (**1**) with trimethyl phosphite yielded 1,2,4-triazinyldimethylphos phonate **3**, *via* Arbuzov reaction through the nonisolable intermediate **2** (Scheme 1) [22].

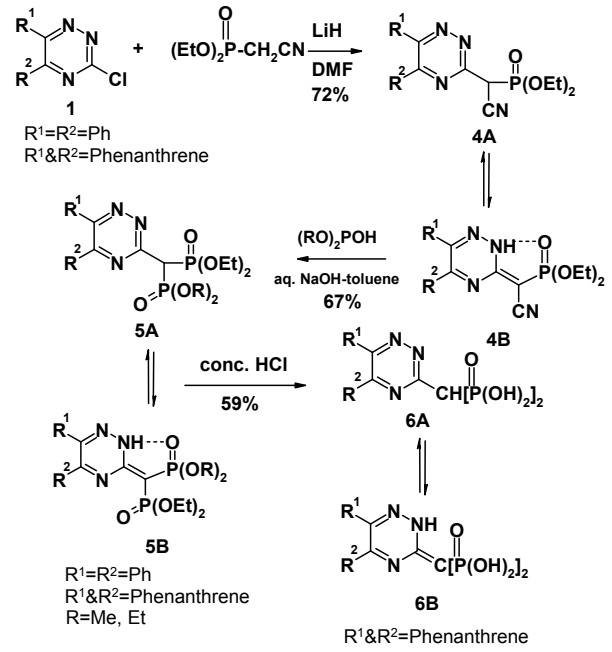


Scheme 1

When 3-chloro-5,6-disubstituted-1,2,4-triazines (**1**) were treated with diethylcyanomethyl phosphonate (three equivalents) in refluxing dimethylformamide containing excess lithium hydride gave the corresponding diethyl 3-cyanomethyl phosphonates (**4**) as the sole reaction product (Scheme 2). Structure **4** was found to be present in two tautomeric isomers **4A** and **4B** as indicated by the NMR spectra. However, the weak signals for the NH in the ^{1}H NMR and IR spectra indicated that **4A** was the predominant tautomer. When phosphonate **4** was treated with one equivalent of dimethyl phosphonate, the reaction was completed by boiling the reactants in toluene containing sodium hydroxide solution for 24 hours, a colourless crystalline material of 1,1-bisphosphonate (**5**) was isolated *via* elimination of hydrogen cyanide as shown in

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.1.4.388-396.154

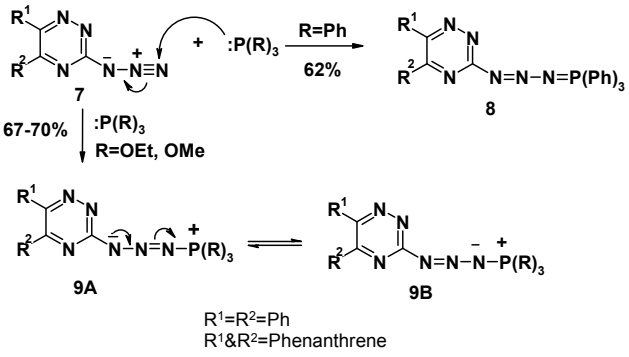
Scheme 2. Hydrolysis of the 1,1-bisphosphonates with concentrated hydrochloric acid gave the corresponding 1,1-bisphosphonic acid (**6**) (Scheme 2) [23].



Scheme 2

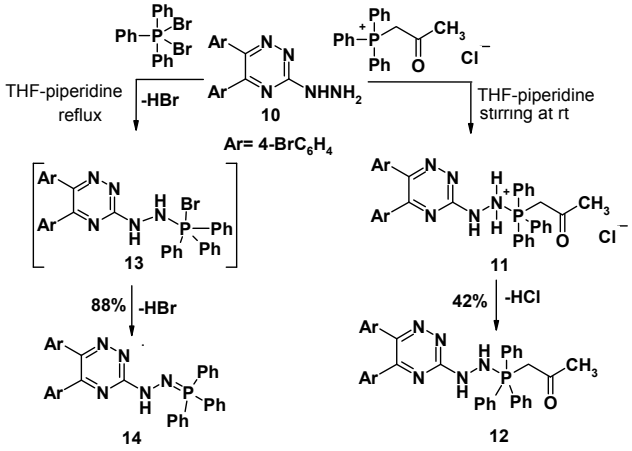
2.1.2. Phosphorylation of side functional groups at position 3 of 1,2,4-triazines

Reaction of 3-azido-5,6-disubstituted-1,2,4-triazines (**7**) with triphenyl phosphine in refluxing dry benzene gave a yellow crystalline product formulated as **8**. Also, the reaction of **7** with trialkyl phosphite under the same condition afforded the phosphazene derivative **9**. The structure of compound **9** may have, one of the two dipolar resonance forms **A** or **B** (Scheme 3) [24].



Scheme 3

Phosphorylation of 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) *via* treatment with acetonyltriphenyl phosphonium chloride, under stirring in tetrahydrofuran and few drops of piperidine for 24 hours at room temperature, achieved 1-[{2-[5,6-*bis*(4-bromophenyl)-1,2,4-triazin-3-yl]hydrazino}(triphenylphosphoranyl)]acetone (**12**) (Scheme 4). Formation of **12** may be due to that phosphorus reagent such as phosphonium salt in which phosphorus atom is more electrophilic than carbon when one of the five groups is a good leaving group. Also, the reaction of **10** with dibromotriphenylphosphorane, in tetrahydrofuran containing piperidine under refluxing conditions, yielded 5,6-*bis*(4-bromophenyl)-3-[2-(triphenylphosphoranylidene)hydrazine]-1,2,4-triazine (**14**), which was formed *via* iminophosphorane mechanism (Scheme 4) [25].



Scheme 4

Ali *et al.* [25] reported that stirring of 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) with *tris*-(2-chloroethoxy) phosphine, in tetrahydrofuran containing piperidine at room temperature, gave the corresponding hydrazidophosphite **15**, while repeating this reaction under reflux resulted iminophosphane derivative **17** *via* the nonisolable intermediate **16** (Scheme 5).

One of the most important of the present investigation was the treatment of 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) with chlorophenyldichlorothiophosphate, diethyl phosphite and diphenyl(2,4,6-trimethylbenzoyl)phosphorus oxide, in tetrahydrofuran containing few drops of piperidine at room temperature to yield phosphonothiohydrazide **18**, phosphonohydrazide **19** and (diphenylphosphoryl){[2-[5,6-*bis*(4-bromophenyl)-1,2,4-triazin-3-yl]hydrazino}(2,4,6-trimethoxyphenyl)methanol (**20**), respectively (Scheme 6) [25].

2.2. Synthesis of isolated phosphorus heterocyclic systems containing 1,2,4-triazines

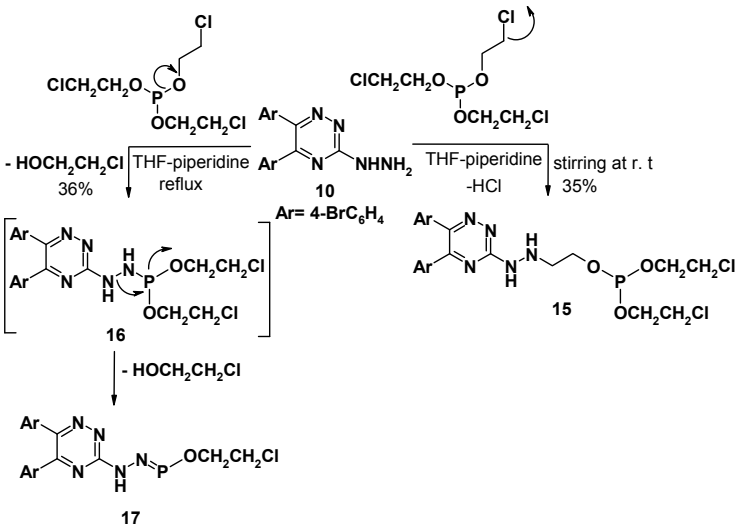
2.2.1. Five-membered rings

Reaction of 5,6-diphenyl-1,2,4-triazin-3(2*H*)-one (**21**) with 2-substituted-1,3,2-dioxaphospholanes (**22**) afforded 2-(1,3,2-dioxaphospholan-2-yl)-5,6-diphenyl-1,2,4-triazin-3(2*H*)-one (**23**) in moderate yields (Scheme 7) [22].

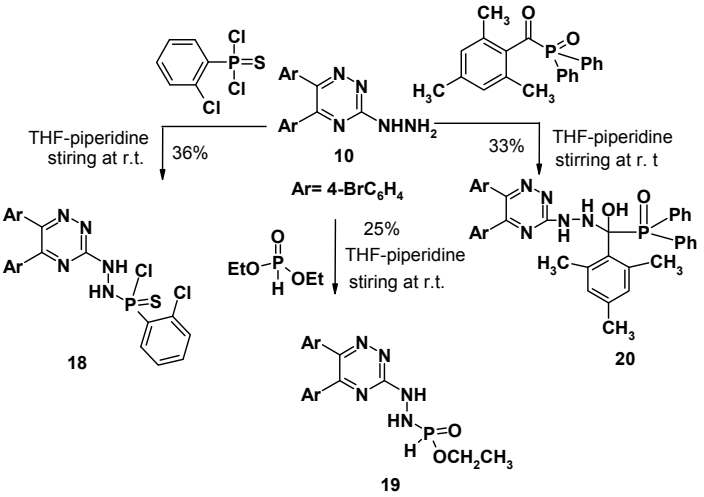
The reaction of 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) with acetonyltriphenylphosphonium chloride, in boiling tetrahydrofuran containing piperidine, furnished 5,6-*bis*(4-bromophenyl)-3-[(3,3,3-triphenyl)-5-methyl-3,4-dihydro-2*H*-1,2,3-λ^5-diazaphosphol-2-yl]-1,2,4-triazine (**25**). Formation of **25** may occur *via* nucleophilic attack of the hydrazine moiety at carbonyl group with loss of one molecule of water to yield the nonisolable intermediate **24**, which underwent losing one molecule of hydrogen chloride (Scheme 8) [25].

2.2.2. Six-membered rings

A facile synthesis of new isolated phosphorus heterocyclic nitrogen system containing 1,2,4-triazine moiety was reported by Abdel-Rahman [26]. Treatment of *N*-(5,6-diphenyl-1,2,4-triazin-3-yl)hydrazinecarbothioamide (**26**) with diethyl benzoylphosphate and/or diphenyl(2,4,6-trimethylbenzoyl)

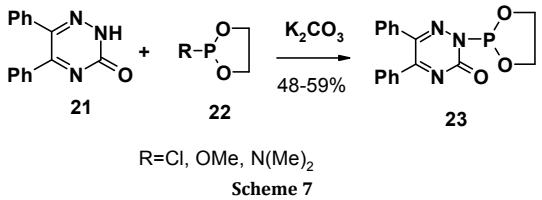


Scheme 5



Scheme 6

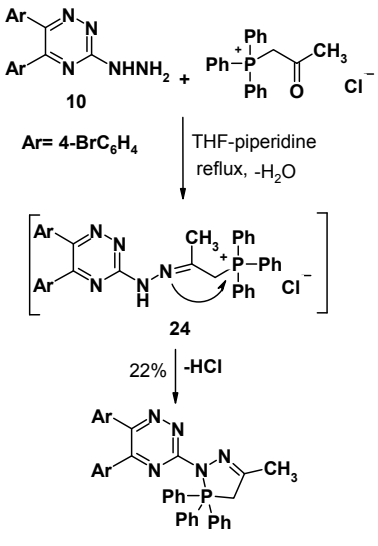
phosphine oxide in boiling toluene afforded 1,2,4,5-triazaphosphorine-3(2*H*)thiones **27** and **28**, respectively (Scheme 9). Refluxing the latter compounds in trifluoroacetic anhydride yielded the 3-trifluoroacetyl-1,2,4,5-triazaphos phorine-3(2*H*)thiones **29** and **30**, respectively (Scheme 9).



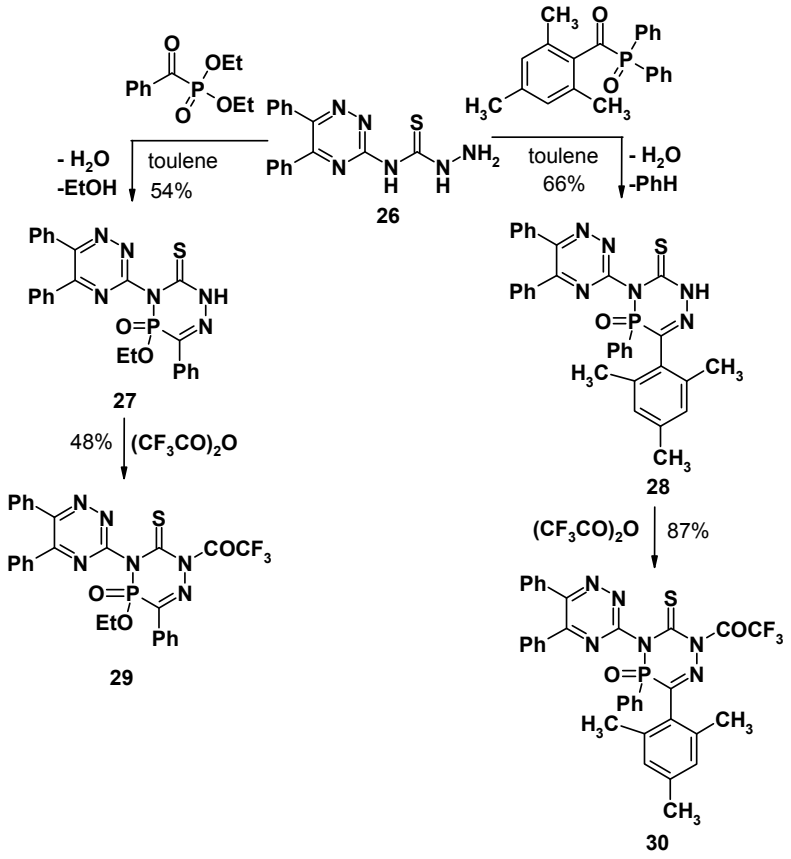
Scheme 7

2.2.3. Seven-membered rings

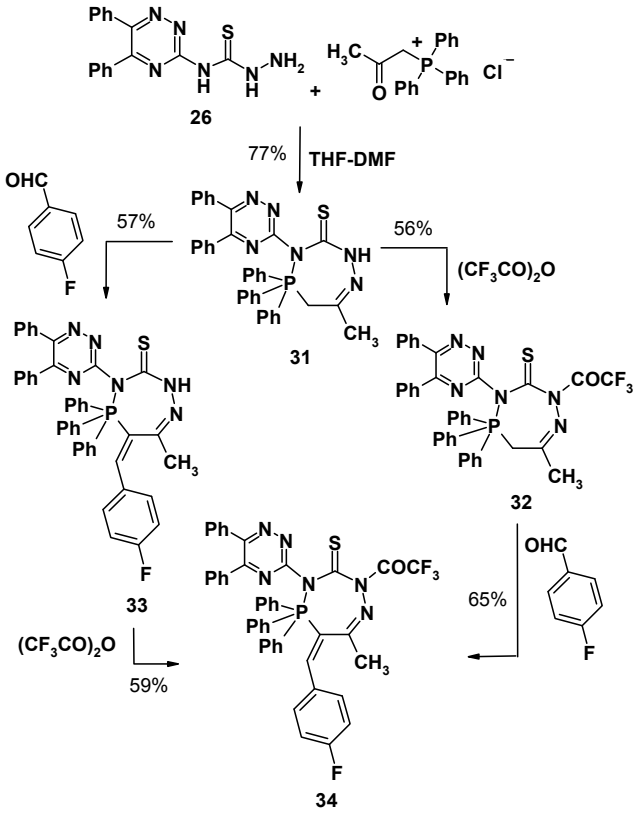
Similarly, cyclocondensation of *N*-(5,6-diphenyl-1,2,4-triazin-3-yl)hydrazinecarbothioamide (**26**) with acetonyl triphenyl-phosphonium chloride in boiling tetrahydrofuran and dimethylformamide led to the direct formation of 1,2,4,5-triazaphosphepine-3-(2*H*)thione **31**. Presence of both NH and CH_2 groups in compound **31** was deduced from acylation and condensation with trifluoroacetic anhydride and trifluoro benzaldehyde, respectively, and vice versa to give the fluorinated-1,2,4,5-triazaphosphepine-3-(2*H*)thione **34** (Scheme 10) [26].



Scheme 8



Scheme 9

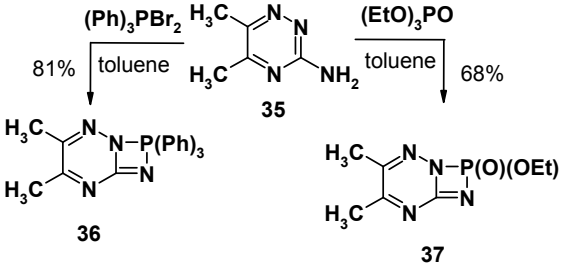


Scheme 10

2.3. Synthesis of fused phosphorus heterocyclic systems containing 1,2,4-triazines

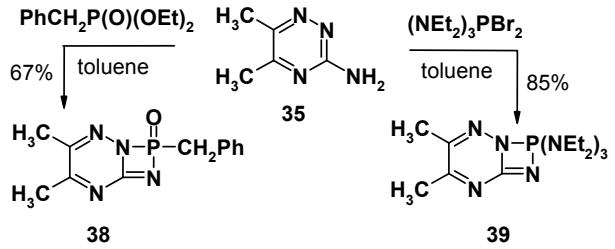
2.3.1. Four-membered rings

A novel class of four-membered ring containing phosphorus such as 1,3,2-diazaphospheto[3,4-*b*][1,2,4] triazines **36** and **37** were synthesized by treating 3-amino-5,6-dimethyl-1,2,4-triazine (**35**) with dibromotriphenylphos phorane and triethyl phosphate, respectively, in toluene containing few drops of triethylamine (Scheme 11) [26].



Scheme 11

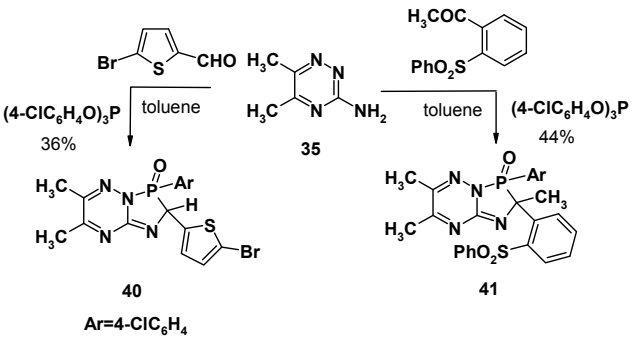
Similarly, reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (**35**) with diethylbenzyl phosphonate and dibromo-*tris*(diethyamino)-λ⁵-phosphane in dry toluene gave the 1,3,2-diazaphospheto[3,4-*b*][1,2,4]triazine derivatives **38** and **39**, respectively (Scheme 12) [26].



Scheme 12

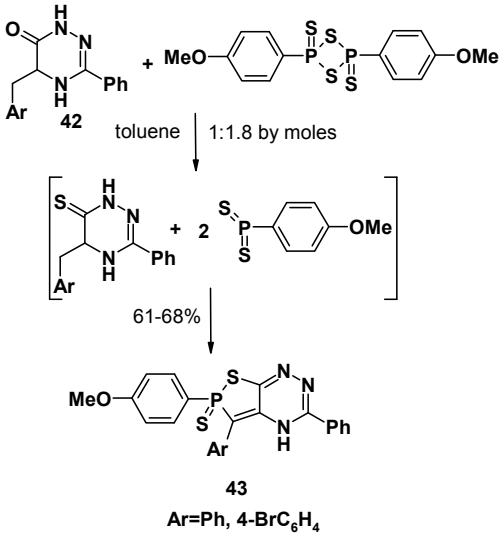
2.3.2. Five-membered rings

On the other hand, condensation of 3-amino-5,6-dimethyl-1,2,4-triazine (**35**) with 5-bromothiophene-2-carboxaldehyde and/or acetophenonesulfonate in the presence of tri(4-chlorophenoxy)phosphine in dry toluene in presence of triethylamine led to the direct formation of the 1,3,5-diazaphospholo[3,2-*b*][1,2,4]triazine systems **40** and **41**, respectively (Scheme 13) [26].



Scheme 13

Ibrahim *et al.* [27] reported the synthesis of novel 1,2-thiaphospholo[4,5-*e*][1,2,4]triazines **43** from treatment of 5-arylmethyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6(*1*H)-one (**42**) with Lawesson's reagent in boiling toluene (Scheme 14).



Scheme 14

Treatment of 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) with diethyl phosphite and chlorophenyldichloro-thiophosphate, in tetrahydrofuran containing few drops of piperidine under reflux, led to the direct formation of the 1,2,4,3-triazaphospholo[4,5-*b*][1,2,4]triazine derivatives **44** and **45**, respectively. Also, 6,7-*bis*(4-bromophenyl)-2,3-dihydro-3,3,3-triphenyl-3-λ⁵-1,2,4,3-triazaphospholino[4,5-*b*] [1,2,4]triazine (**46**) was obtained from stirring of compound **10** with dibromo-triphenylphosphorane, in tetrahydrofuran containing piperidine at room temperature for 24 hours (Scheme 15) [25].

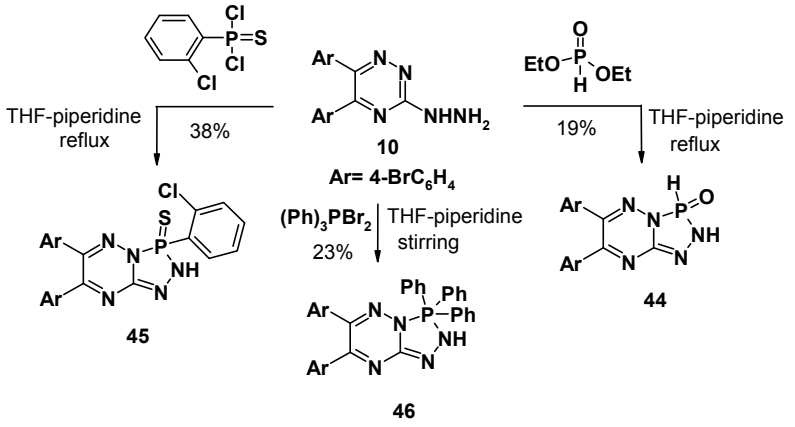
4-{(4-Chlorophenyl)methylidene]amino}-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one (**48**) was heated under reflux with diphenylphosphoryl acetonitrile, for 12 hours in tetrahydrofuran in the presence of sodium hydride as a catalyst, to afford 7-(4-chlorophenyl)-8-(diphenylphosphoryl)-3-methyl-4-oxo-4,8-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (**52**) and not the other expected product 1,3,4-thiadiazaphosphepine derivative **50**. The reaction pathway proceeded *via* C-nucleophilic attack by the active methylene of diphenylphosphoryl acetonitrile on the N–N=CH–Ar moiety to give the intermediate **49**, which underwent cyclization by elimination of one molecule of hydrogen sulfide followed by an air oxidation (route b) (Scheme 16) [28].

On the other hand, 4-amino-3-hydrazino-1,2,4-triazin-5(4*H*)-one (**53**) was used as starting material in one-pot three components reaction with acetaldehyde and phenylphosphonic dichloride, in boiling tetrahydrofuran containing a catalytic amount of triethylamine, to yield 1,2,4,3-triazaphospholo[5,1-*c*][1,2,4]triazinone derivative **54** (Scheme 17) [28].

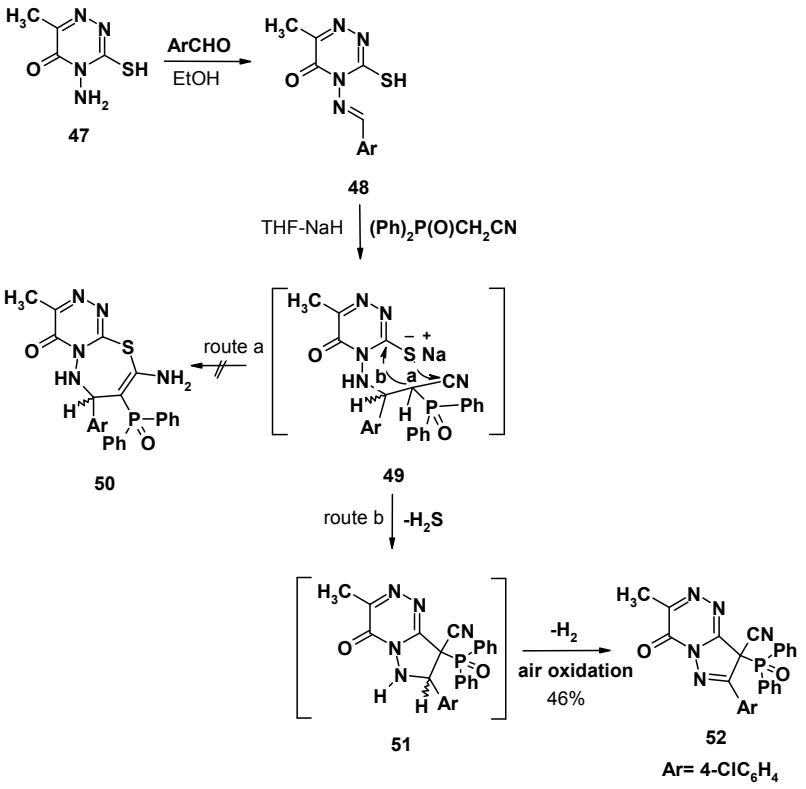
6-Methyl-2-oxido-2-phenyl-1,2-dihydro-7*H*-[1,3,4,2]thiadi azaphospholo[5,4-*c*][1,2,4] triazin-5-one (**55**) was synthe-sized by the reaction of 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one (**47**) with phenylphosphonic dichloride in tetra hydrofuran containing two equivalent amounts of triethyl amine to remove hydrogen chloride (Scheme 18) [28].

2.3.3. Six-membered rings

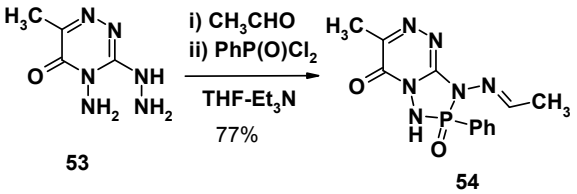
The interaction between 5,6-*bis*(4-bromophenyl)-3-hydrazino-1,2,4-triazine (**10**) and diphenyl(2,4,6-trimethylbenzoyl) phosphorus oxide under reflux in tetrahydrofuran resulted 7,8-*bis*-(4-bromophenyl)-4,4-diphen yl-3-(2,4,6-trimethylphenyl)-4H-4-λ⁵-1,2,4-triazino[3,2-*c*]



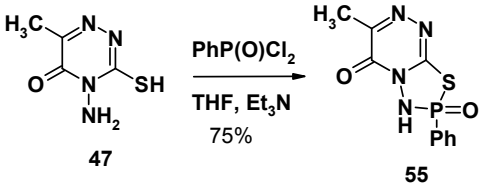
Scheme 15



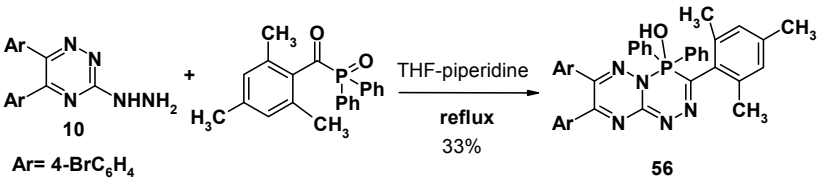
Scheme 16



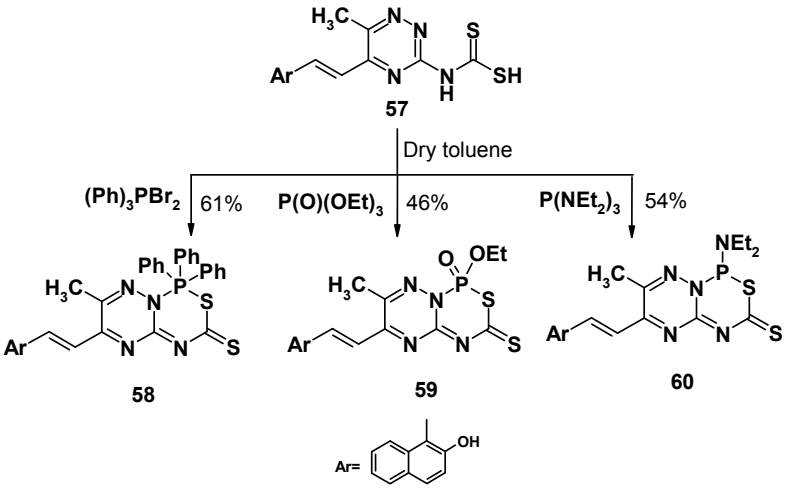
Scheme 17



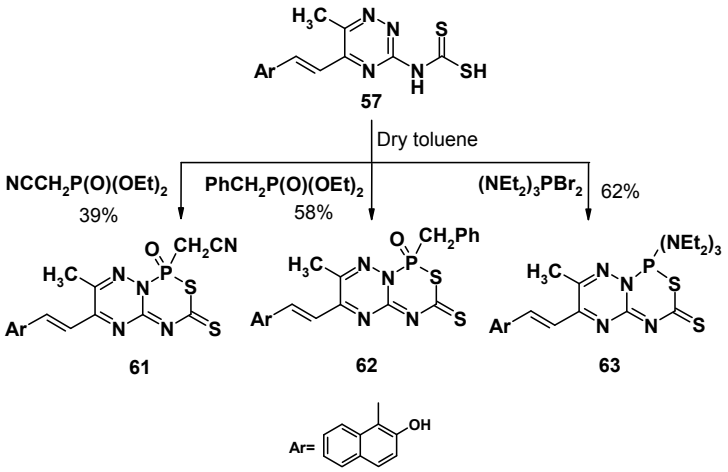
Scheme 18



Scheme 19



Scheme 20



Scheme 21

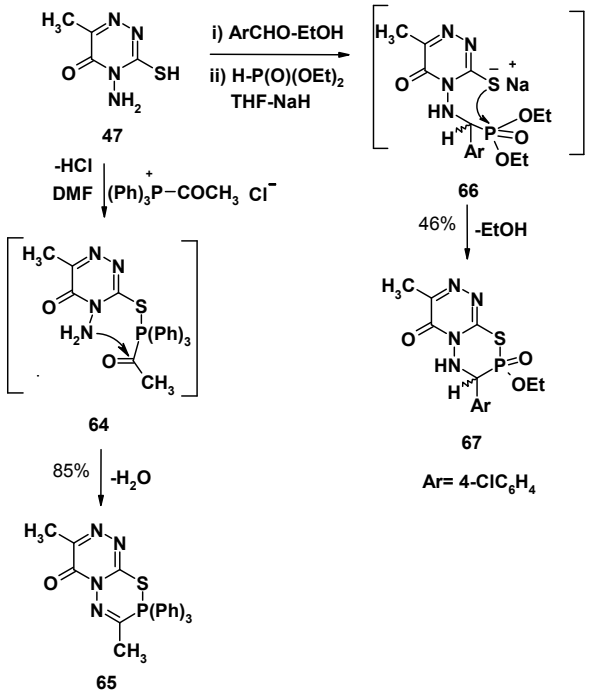
[1,2,4,5]triazaphosphinin-4-ol (**56**) (Scheme 19). Due to the driving force of P=O bond is strong and phenyl groups are bad leaving groups, the nucleophilic attack of hydrazino moiety may be carried out at carbonyl group rather than the P=O group [25].

On the other hand, (6-methyl-5-styryl-1,2,4-triazin-3-yl)dithiocarbamic acid (**57**) can be used as starting material for the building of fused phosphorus containing nitrogen-sulfur heterocyclic systems. Thus, treatment of **57** with some phosphorus reagents such as dibromotriphenylphosphorane, triethyl phosphate and *tris*(diethylamino)phosphine under reflux, in dry toluene containing drops of triethylamine, afforded 1,2,4-triazino[2,3-*c*][1,3,5,2]thiadiazaphosphinines **58-60**, respectively (Scheme 20) [26].

Also, three isomers of 1,2,4-triazino[2,3-c][1,3,5,2]thiadiaza phosphinines **61-63** were obtained under the same reaction conditions via reaction of 1,2,4-triazinyldithiocarbamic acid derivative **57** with cyanomethyl phosphonate, diethylbenzyl phosphate and dibromo-tris(diethyamino)-λ5-phosphane, respectively (Scheme 21) [26]. The behaviour of SH group in compound **57** towards these phosphorus reagents to produce compounds **58-63** is similar to its reaction with various alkylating agents and/or ketonic agents. It is worthy to mention that nucleophilic attack on SH is more preferred than NH group towards the phosphorus reagents [29].

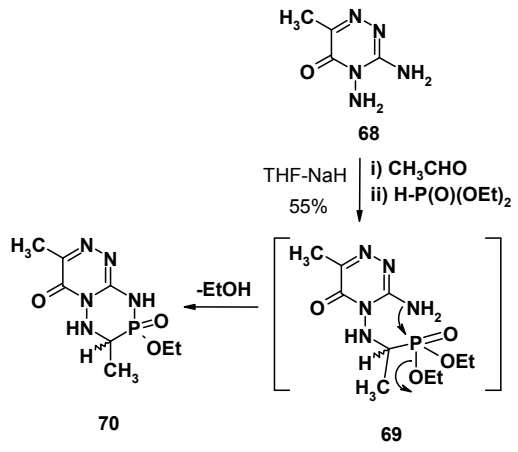
Reaction of 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one (**47**) with acetyltriphenylphosphonium chloride, in boiling dimethylformamide containing a catalytic amount of piperidine, afforded 1,2,4-triazino[4,3-*e*][1,4,5,2]thiadiaza phosphinine **65** (Scheme 22). Formation of the latter compound **65** may occur through the attack of the lone pair electrons of the SH group on phosphorus atom of the

phosphonium salt to remove hydrogen halide which may afford the intermediate **64**, followed by an intramolecular nucleophilic attack of the amino group on carbonyl group with elimination of water to give **65**. Also, condensation of **47** with 4-chlorobenzaldehyde followed by reaction with diethyl phosphite, in boiling tetrahydrofuran containing a catalytic amount of sodium hydride, produced a cyclic α-amino phosphonate ester **67** as only one isomer (Scheme 22) [28].



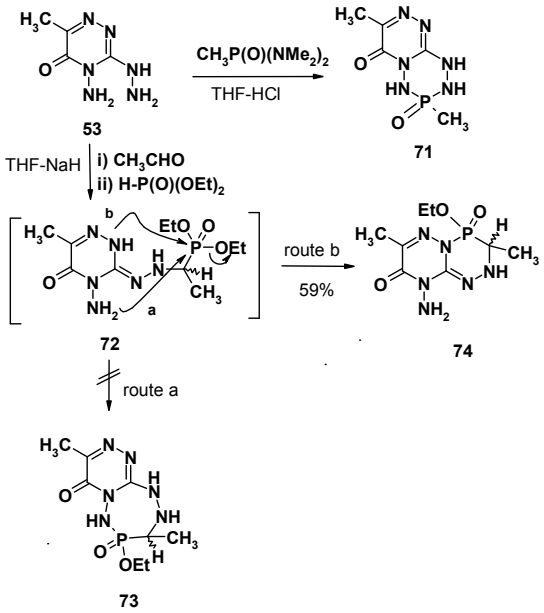
Scheme 22

The Kabachnik–Fields reaction [20] using 3,4-diamino-6-methyl-1,2,4-triazin-5(4H)-one (**68**), acetaldehyde and diethyl phosphite in tetrahydrofuran in the presence of sodium hydride as a catalyst led to only one isomer of 1,2,4-triazino[4,3-*b*][1,2,4,5] triazaphosphinine derivative **70** (Scheme 23) [27].



Scheme 23

2,7-Dimethyl-2-oxido-1,2,3,4-tetrahydro-8*H*-[1,2,4]triazino [4,3-*e*][1,2,4,5,3]tetrazaphosphinin-8-one (**71**) was obtained by cyclocondensation reaction of compound **53** with *bis*(dimethylamino)methylphosphonate, in tetrahydrofuran in the presence of few drops of hydrochloric acid (Scheme 24). Also, the one-pot Kabachnik-Fields reaction of compound **53**, acetaldehyde and diethyl phosphite, in tetrahydrofuran containing sodium hydride as a catalyst, produced one isomer identified as 1,2,4-triazino[3,2-*c*] [1,2,4,5]triazaphosphinine **74**, likely through the nonisolable intermediate **72**, which spontaneously cyclized through N-2 of the triazine ring and not the exocyclic *N*-amino, with elimination of one molecule of ethanol (route b, Scheme 24) [28].

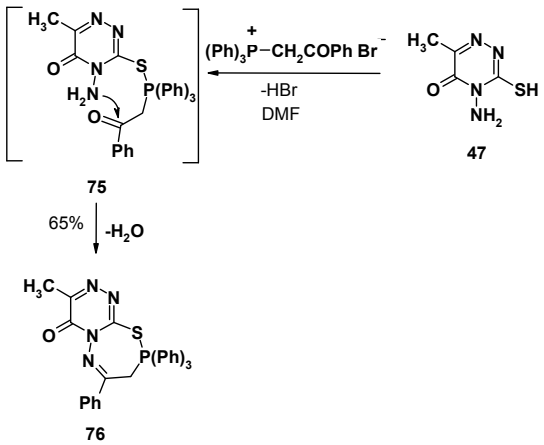


Scheme 24

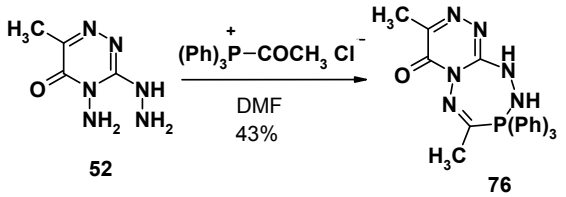
2.3.4. Seven-membered rings

Also, novel seven-membered phosphorus heterocycles was achieved by reaction of 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5(4*H*)-one (**47**) with phenacyl triphenylphosphonium bromide in boiling dimethylformamide containing a catalytic amount of piperidine to afford 1,2,4-triazino[4,3-*f*][1,5,6,2] thiadiazaphosphepine **76** derivative (Scheme 25) [28]. Formation of compound **76** may occur through the attack of the electron pairs of the SH group on phosphorus atom of the phosphonium salt to remove hydrogen halide which may afford the intermediates **75**, followed by an intramolecular nucleophilic attack of the amino group on carbonyl group with elimination of water to **76** [28].

Finally, 1,2,4-triazino [4,3-*e*][1,2,5,6,3]tetrazaphosphepine derivative **77** was obtained by cyclocondensation of 4-amino-3-hydrazino-1,2,4-triazin-5(4*H*)-one (**53**) with acetyl triphenyl phosphonium chloride in dimethylformamide containing few drops of piperidine (Scheme 26) [28].



Scheme 25



Scheme 26

References

[1]. Holla, B. S.; Sarojini, B. K.; Gonsalves, R. *Farmaco* **1998**, *53*, 395-398.
[2]. Holla, B. S.; Sarojini, B. K.; Shridhara, K.; Antong, G. *Farmaco* **1999**, *54*, 149-151.
[3]. Deeb, A.; El-Mariah, F.; Hosny, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5013-5017.
[4]. El-Badawi, M. A.; El-Barbary, A. A.; Loksha, Y. M.; El-Daly, M. *Phosphorus Sulfur Silicon Relat. Elem*. **2002**, *177*, 587-596.
[5]. Ibrahim, M. A. *Heterocycles* **2010**, *81*, 1393-1418.
[6]. Oganisyan, A. S.; Grigoryan, G. O.; Noravyan, A. S.; Dzhagatspanyan, I. A.; Melikyan, G. G. *Pharm. Chem. J.,* **2001**, *35*, 124-126.
[7]. Boehner, B.; Ciba-Geigy, A. G. Eur. Pat. 1986; *Chem. Abstr*. **1986**, *105*, 6522e.
[8]. Timer, M.; Sauvard, S.; Georgescu, C. M. *Biochem. Pharmacol*. **1996**, *15*, 408-410.
[9]. Singh, K.; Barwa, M. S.; Tyagi, P. *Eur. J. Med. Chem.* **2007**, *42*, 394-402.
[10]. Ali, T. E. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 1717-1726.
[11]. Ibrahim, M. A.; El-Mahdy, K. M. *Phosphorus Sulfur Silicon Relat. Elem*. **2009**, *184*, 2945-2958.
[12]. El-Barbary, A. A.; Sakran, A. M.; El-Madani, A. M.; Claus, N. *J. Heterocycl. Chem*. **2005**, *42*, 935-941.
[13]. El-Gendy, Z.; Morsy, J. M.; Allimony, H. A.; Abdel-Monem, W. R.; Abdel-Rahman, R. M. *Pharmazie* **2001**, *56*, 376-384.
[14]. Abdel-Rahman, R. M.; Morsy, J. M.; Hanafy, F.; Amene, H. A. *Pharmazie* **1999**, *54*, 347-355.
[15]. Dai, Q.; Chen, R. *Phosphorus Sulfur Silicon Relat. Elem*. **1997**, *122*, 261-267.
[16]. He, L. N.; Cai, F.; Chen, R. Y., Zhou, J. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *130*, 65-71
[17]. Tang, J. S.; Verkade, J. G.; U S Patent No. 5 260 436 1993; *Chem. Abstr*. **1993**, *120*, 218836v.
[18]. Tiwari, A. K.; Dubey, B. K.; Shukla, I. C. *J. Indian Chem. Soc*. **2003**, *80*, 717-722.
[19]. Shukla, I. C.; Dwived, P. K. *J. Indian Chem. Soc.* **2005**, *82*, 670-675.
[20]. Caruso, F.; Rossi, M.; Tanski, J.; Pettinari, C.; Marchetti, F. *J. Med. Chem.* **2003**, *46*, 1737-1742.
[21]. Ali, T. E.; Abdel-Rahman, R. M.; Makki, M. S. T.; Ibrahim, M. A. *Eur. J. Chem.* **2010**, *1(3)*, 236-245.
[22]. El-Khoshnieh, Y. O. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *139*, 163-172.
[23]. Abdou, W. M.; Ganoub, N. A.; Fahmy, A. F.; Shaddy, A. A. *Monatsch. fur Chem.* **2006,** *137*, 105-116.
[24]. El-Khoshnieh, Y. O.; Ibrahim, Y. A. *Phosphorus Sulfur Silicon Relat. Elem*. **1995**, *101*, 67-73.
[25]. Ali, T. E.; Abdel-Rahman, R. M.; Hanafy, F. I.; El-Edfawy, S. M. *Phosphorus, Sulfur Silicon Relat. Elem*. **2008**, *183*, 2565-2577.
[26]. Abdel-Rahman, R. M. *Trends in Heterocycl. Chem.* **2002**, *8*, 187-194.
[27]. Ibrahim, Y. A.; Kadry, A. M.; Ibrahim, M. R.; Lisgarten, J. N.; Potfer, B. S.; Palmer, R. A. *Tetrahedron* **1999**, *55*, 13457-13462.
[28]. Ali, T. E. *Eur. J. Med. Chem*. **2009**, *44*, 4539-4546.
[29]. Tandura, S. N.; Voronkov, M. G.; Alekseer, N. V. *Top. Curr. Chem*. **1986**, *131*, 99-189.