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.elayed1975@yahoo.com (T.E. Ali).

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.

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-triazinyltrimethylphosphinate 3, via Arbuzov reaction through the nonisolable intermediate 2 (Scheme 1) [22].

When 3-chloro-5,6-disubstituted-1,2,4-triazines (1) were treated with diethylcyanomethyl phosphonate (three equivalents) in refluxing dimethylformamidine 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 1H 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
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 image]

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 image]

Phosphorylation of 5,6-bis(4-bromophenyl)-3-hydrazino-1,2,4-triazine (10) via treatment with acetonitrilephosphonium 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[(4-phenylphosphoryl)]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-(triphenylphosphoranylidenene)hydrazino]-1,2,4-triazine (14), which was formed via iminophosphorane mechanism (Scheme 4) [25].

![Scheme 4 image]

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-trimethoxyphosphinyl)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(2H)-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(2H)-one (23) in moderate yields (Scheme 7) [22].

The reaction of 5,6-bis(4-bromophenyl)-3-hydrazino-1,2,4-triazine (10) with acetonitrilephosphonophosphonium chloride, in boiling tetrahydrofuran containing piperidine, furnished 5,6-bis(4-bromophenyl)-3-[3,3,3-triphenyl]-5-methyl-3,4-dihydro-2H-1,2,3-λ5-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]
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).

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-
triazaphosphorine-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-triazaphosphorine-3(2\(H\))thione 34
(Scheme 10) [26].
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-diazaphosphetol[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 dibromotriphenylphosphorane and triethylphosphite, respectively, in toluene containing few drops of triethylamine (Scheme 11) [26].

Similarly, reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (35) with diethylphenylphosphonate and dibromotriphenylphosphorane in dry toluene gave the 1,3,2-diazaphosphetol[3,4-b][1,2,4]triazine derivatives 38 and 39, respectively (Scheme 12) [26].

2.3.2. Five-membered rings

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

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

Treatement of 5,6-bis(4-bromophenyl)-3-hydrazone-1,2,4-triazine (10) with diethyl phoshite and chlorophenyl dichlorophosphate, in tetrahydrofuran containing few drops of piperidine under reflux, led to the direct formation of the 1,2,4,3-triazaphosphol[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-triazaphosphol[4,5-b][1,2,4]triazine (46) was obtained from stirring of compound 10 with dibromo-triphosphorane, in tetrahydrofuran containing piperidine at room temperature for 24 hours (Scheme 15) [25].

4-[(4-Chlorophenyl)phenylidenediamino]-3-mercaptop-6-methyl-1,2,4,5-tetrazine (47) was heated under reflux with diphenylphosphoryl acetoneitrile, 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-thiadiazaphosphazene derivative 50. The reaction pathway proceeded via C-nucleophilic attack by the active methylene of diphenylphosphoronyl acetoneitrile 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-hydradino-1,2,4-triazin-5(4H)-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-tetrazaphosphol[5,1-c][1,2,4]triazinone derivative 54 (Scheme 17) [28].

6-Methyl-2-oxido-2-phenyl-1,2-dihydro-7H-[1,3,4,2]thiazi azaphosphol[5,4-c][1,2,4]triazin-5-one (55) was synthetically obtained by the reaction of 4-amino-3-mercaptop-6-methyl-1,2,4-triazin-5(4H)-one (47) with phenylphosphonic dichloride in tetrahydrofuran containing two equivalent amounts of triethylamine to remove hydrogen chloride (Scheme 18) [28].

2.3.3. Six-membered rings

The interaction between 5,6-bis(4-bromophenyl)-3-hydrazone-1,2,4-triazine (10) and diphenyl[2(4,6-trimethylbenzyloxy)phosphorus oxide under reflux in tetrahydrofuran resulted 7,8-bis(4-bromophenyl)-4,4-diphenyl-3-(2,4,6-trimethylphenyl)-4H-4-λ⁵-1,2,4-triazino[3,2-c]
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 tri(triethylamino)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]. 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-triazino[4H]-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]thiadiazaphosphinines 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

\[ \text{Conditions via reaction of 1,2,4-triazinylldithiocarbamic acid derivative 57 with cyanomethyl phosphonate, diethylphosphoryl phosphate and dibromo-tris(diethylamino)-15-phosphate, respectively (Scheme 21) [26].} \]

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 phosphate, 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].

(Chemical structures and reactions are described and numbered appropriately.)

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].

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(4H)-one (47) with phenacyl triphenylphosphonium bromide in boiling dimethylformamide containing a catalytic amount of piperidine to afford 1,2,4-triazino[4,3-b][1,2,4,5]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]tetrazaphosphinine derivative 77 was obtained by cyclocondensation of 4-amino-3-hydrazino-1,2,4-triazin-5(4H)-one (53) with acetyl triphenyl phosphonium chloride in dimethylformamide containing few drops of piperidine (Scheme 26) [28].

2.7-Dimethyl-2-oxido-1,2,3,4-tetrahydro-8H-[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

(Chemical structures and reactions are described and numbered appropriately.)
References