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SYNTHESIS AND CHEMISTRY OF 4-AMINO-1,2,4-TRIAZIN-5-ONES

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Abstract– This review summarizes research results concerning the synthesis and chemical reactivity of 4-amino-1,2,4-triazin-5-ones and their related compounds.

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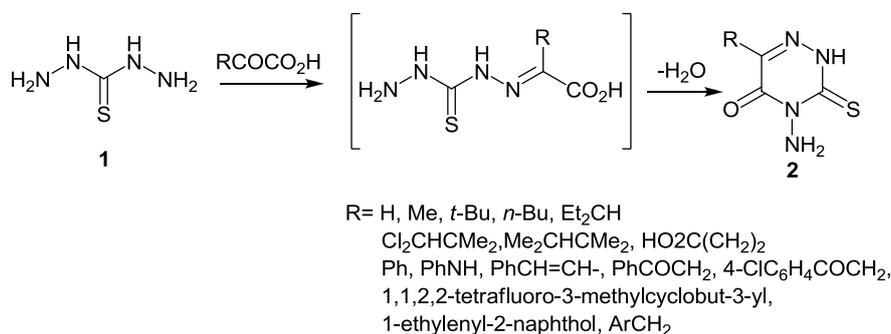
1. INTRODUCTION

Various substituted 1,2,4-triazin-5-one derivatives have a great importance as biological agents in medicinal and agricultural fields.¹⁻⁷ Recently, significant activities have been directed toward this class of compounds, in particular, 4-amino-1,2,4-triazin-5-one derivatives which have considerable interest because of their herbicidal,^{8,9} antimicrobial,¹⁰⁻¹² anti-HIV,¹³ and anticancer activities.^{14,15} In view of the above observations, the intention of the present review is to cover research results concerning the synthesis and reactions of 4-amino-1,2,4-triazin-5-one derivatives which have not been reviewed hitherto.

2. SYNTHETIC APPROACHES FOR 4-AMINO-1,2,4-TRIAZIN-5-ONES

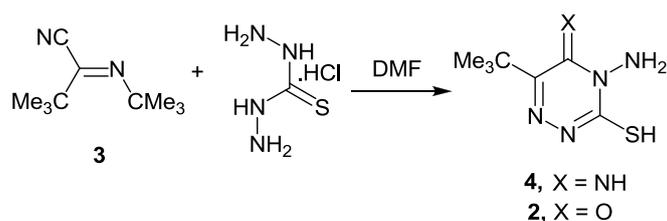
2.1. Synthesis from thiocarbohydrazide

4-Amino-3-thioxo-6-substituted-1,2,4-triazine derivatives **2** are commonly prepared by condensation of thiocarbohydrazide **1** with α -ketocarboxylic acids (Scheme 1).¹⁶⁻²⁸



Scheme 1

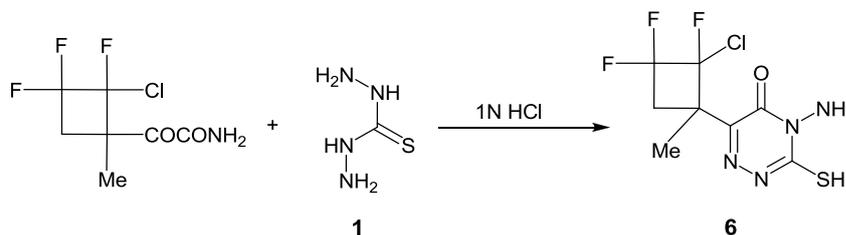
Reaction of thiocarbohydrazide hydrochloride with 2-(*tert*-butylimino)-3,3-dimethylbutanenitrile **3** in DMF produced 5-imino-4,5-dihydro-1,2,4-triazine **4** which was hydrolyzed in ethanol containing hydrochloric acid to give 3-mercapto-4-amino-6-*tert*-butyl-1,2,4-triazin-5-one **2** (Scheme 2).²⁹



Scheme 2

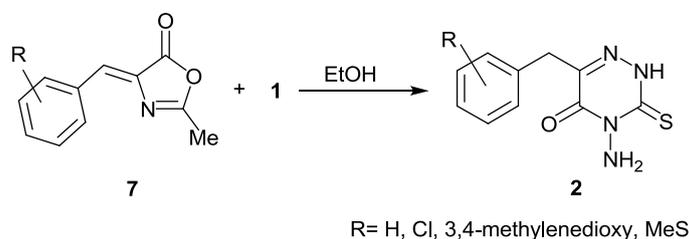
Condensation of **1** with 2-(1-methyl-2-chloro-2,3,3-trifluoro-cyclobut-1-yl)-2-oxoacetamide **5** in 1N HCl

yielded 4-amino-6-(1-methyl-2-chloro-2,3,3-trifluoro-cyclobut-1-yl)-1,2,4-triazin-5(4*H*)-one **6** (Scheme 3).³⁰



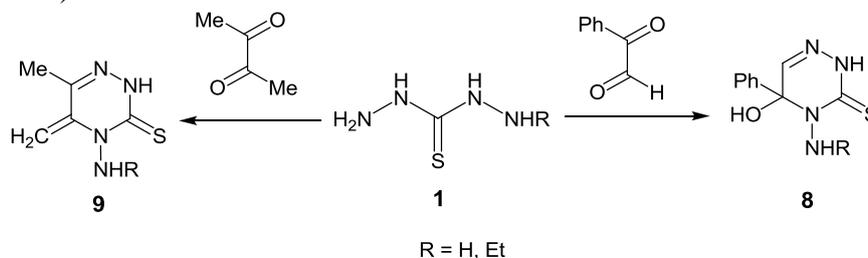
Scheme 3

Also, direct condensation of **1** with oxazolone **7** gave 4-amino-3-thioxo-1,2,4-triazine derivative **2** (Scheme 4).⁹



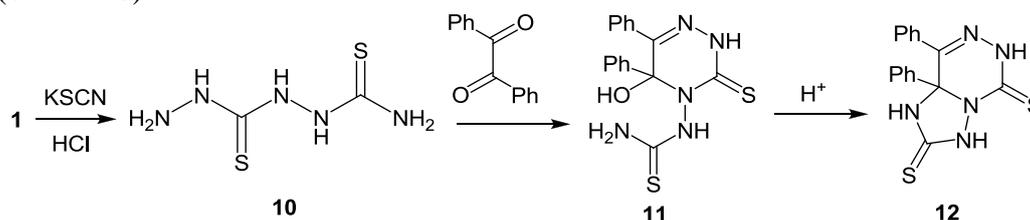
Scheme 4

Cyclocondensation of **1** with phenylglyoxal and diacetyl yielded 4-aminotriazinethiones **8** and **9**, respectively (Scheme 5).³¹



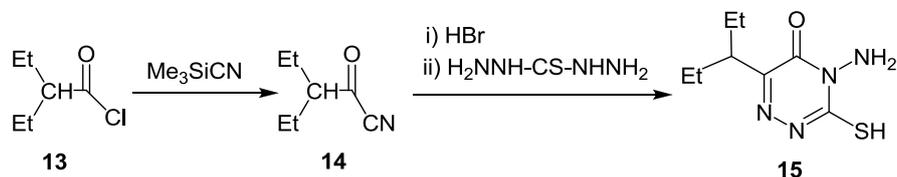
Scheme 5

Condensation of benzil with 1-(carbothioamide)thiocarbohydrazide **10**, obtained from **1** and potassium isothiocyanate, afforded 5-hydroxy-5,6-diphenyl-1,2,4-triazin-3(2*H*)-thione **11** which on dehydration in acid medium gave 1,9-dihydro-8,9-diphenyl-1,2,4-triazolo[2,3-*d*][1,2,4]triazine-3,6-dithione **12** (Scheme 6).³²⁻³⁴



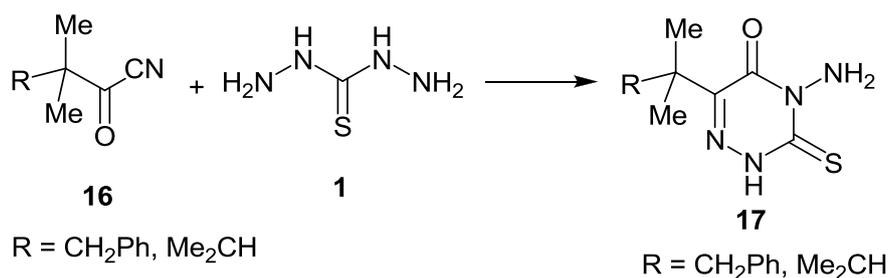
Scheme 6

Treatment of 2-ethylbutanoyl chloride **13** with Me_3SiCN afforded 3-ethyl-2-oxo-pentanenitrile **14** which on hydrolysis with HBr followed by addition of thiocarbohydrazide **1** afforded 4-amino-3-mercapto-6-(3-pentyl)-1,2,4-triazin-5(4*H*)-one **15** (Scheme 7).³⁵



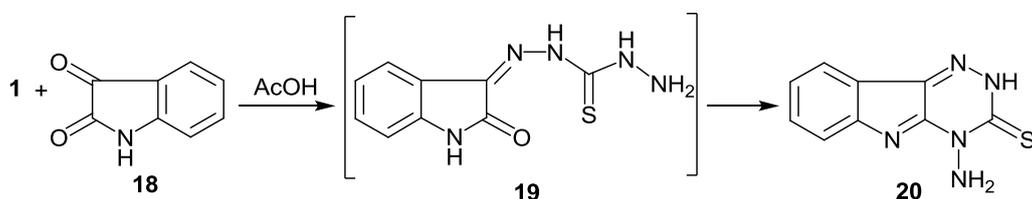
Scheme 7

Similarly, Kranz *et al.*^{36,37} obtained 4-amino-1,2,4-triazin-5(4*H*)ones **17** by converting $\text{RCMe}_2\text{CO}_2\text{H}$ into the corresponding acid chloride, then treating with Me_3SiCN to give acyl cyanides, 3,3-dimethyl-2-oxo-4-phenylbutanenitrile derivatives **16**, followed by cyclocondensation with thiocarbohydrazide **1** (Scheme 8). Condensation of **17** with Me_2CHCHO afforded the corresponding hydrazones which are a better herbicides, with greater selectivity, than 6-(2-fluoro-1,1-dimethylethyl)-4-(2-methyl-propylidene)amino-3-methylthio-1,2,4-triazin-5(4*H*)-one.



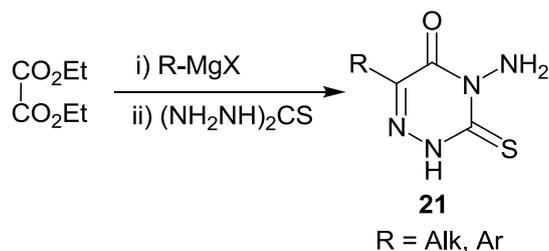
Scheme 8

Thiocarbohydrazide **1** reacted with isatin **18** in glacial acetic acid to give 4-amino-2,4-dihydro-3*H*-[1,2,4]triazino[5,6-*b*]indole-3-thione **20** via the intermediate isatin α -thiocarbohydrazone **19** (Scheme 9).³⁸



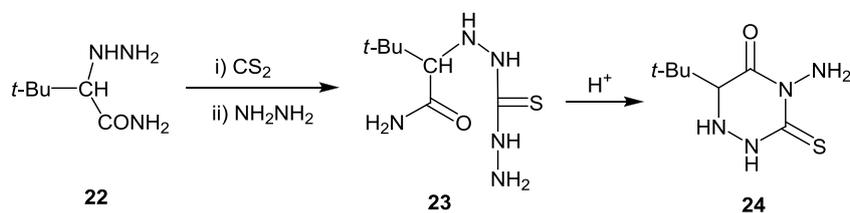
Scheme 9

On the other hand, 6-alkyl(aryl)-4-amino-3-thioxo-1,2,4-triazin-5(2*H*,4*H*)-ones **21** were prepared by reaction of diethyl oxalate with Grignard reagents followed by treatment with **1** in refluxing EtOH containing HCl (Scheme 10).³⁹



Scheme 10

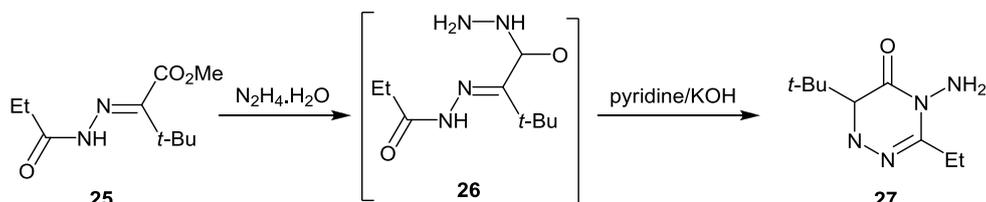
Treatment of α -bromoacetamide with hydrazine hydrate gave α -hydrazinoacetamide **22**, which on refluxing with CS_2 followed by addition of hydrazine hydrate yielded thiocarbohydrazide derivative **23**. Cyclization of the latter compound in acid medium gave the thione derivative **24** (Scheme 11).⁴⁰



Scheme 11

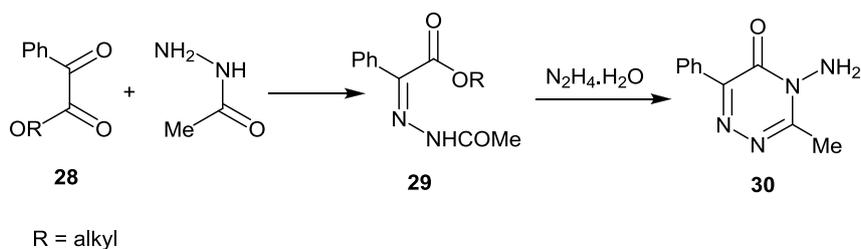
2.2. Synthesis from acid hydrazides

Reaction of methyl 2-[2(2,2-dimethylpropanoyl)hydrazono]butanoate **25** with hydrazine hydrate in pyridine containing KOH gave 4-amino-1,2,4-triazin-5-one **27** via the hydrazide **26** (Scheme 12).⁴¹



Scheme 12

Metamitron **30** was prepared by condensation of phenylglyoxate **28** with acetohydrazide to give *N*-acetyl ester **29** followed by cyclocondensation with hydrazine hydrate in pyridine (Scheme 13).⁴²

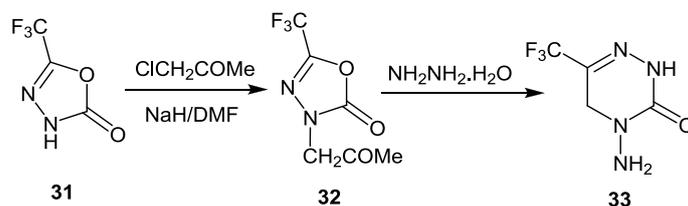


Scheme 13

2.3. Synthesis from oxadiazole

Reaction of chloroacetone with trifluoromethyl-1,3,4-oxadiazol-2(3*H*)-one **31** in NaH/DMF gave the

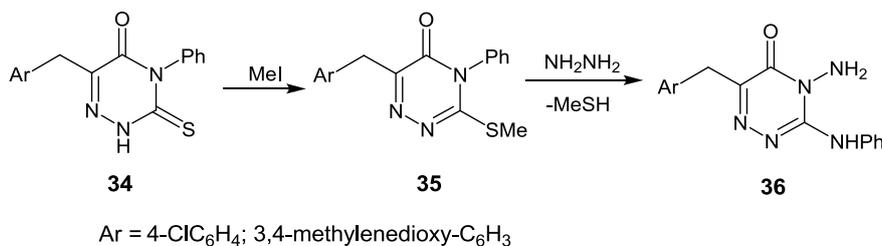
acetone derivative **32** which on treatment with hydrazine hydrate produced 2,3,4,5-tetrahydro-3-oxo-4-amino-6-(trifluoromethyl)-1,2,4-triazine **33** as insecticide (Scheme 14).⁴³



Scheme 14

2.4. Synthesis from *N*⁴-phenyl-1,2,4-triazine

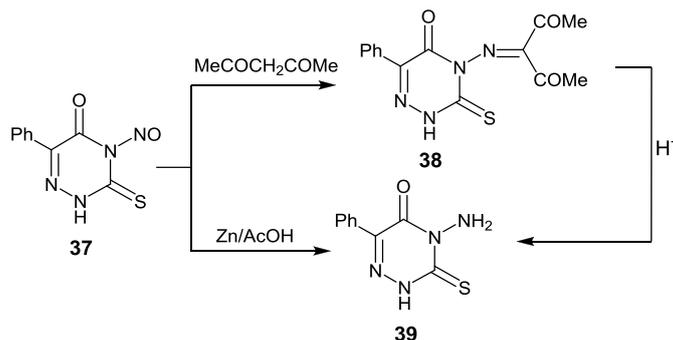
Methylation of 6-arylmethyl-4-phenyl-3-thioxo-1,2,4-triazin-5-ones **34** afforded the corresponding 3-methylthio derivatives **35** which on hydrazinolysis gave 4-amino-3-anilino-4,5-dihydro-1,2,4-triazin-5-ones **36**. Formation of **36** occurred *via* intramolecular nucleophilic attack of hydrazine with loss of MeSH (Scheme 15).⁴⁴



Scheme 15

2.5. Synthesis from *N*⁴-nitroso-1,2,4-triazine

Direct nitrosation of 6-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazine-5(4*H*)-one with sodium nitrite in hydrochloric acid medium at 0 °C gave 4-nitroso-6-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazine-5(4*H*)-one **37**.⁴⁵ Reaction of compound **37** with acetylacetone (like the Ehrlich-Sachs reaction of aromatic compound) in weakly alkaline medium resulted in formation of 4-(diacetylmethyleneamino)-6-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazine-5(4*H*)-one **38**.⁴⁶ Hydrolysis of **38** in acid medium gave 4-amino-6-phenyl-3-thioxo-2,3-dihydro-1,2,4-triazine-5(4*H*)-one **39**. Compound **39** was also obtained directly from reduction of **37** with zinc powder in acetic acid (Scheme 16).⁴⁷



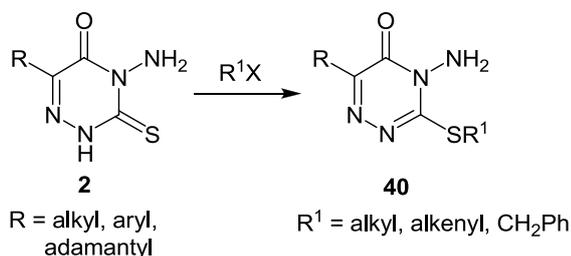
Scheme 16

3. REACTIONS OF 4-AMINO-1,2,4-TRIAZIN-5-ONES

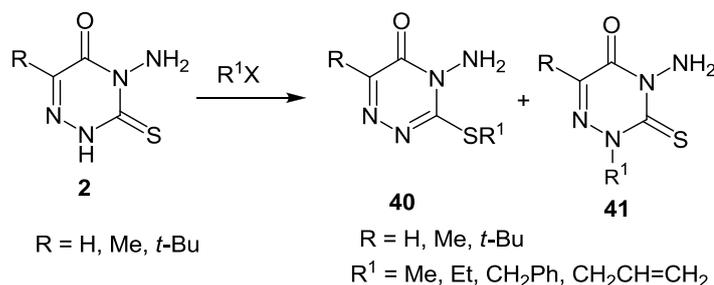
The chemical reactivity of 4-amino-1,2,4-triazin-5-one derivatives toward a variety of reagents are summarized below.

3.1. Alkylation

Alkylation of 4-amino-3-mercapto-1,2,4-triazin-5(4*H*)-ones **2** with a various alkylating agents produced the corresponding 3-alkylthio analog **40** as herbicides (Scheme 17).⁴⁸⁻⁵¹ While alkylation of **2** in aqueous sodium hydroxide solution gave a mixture of 3-alkylthio derivatives **40** and *N*²-alkyl derivatives **41** (Scheme 18).^{52,53}

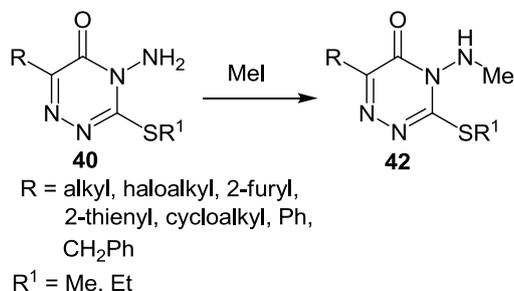


Scheme 17



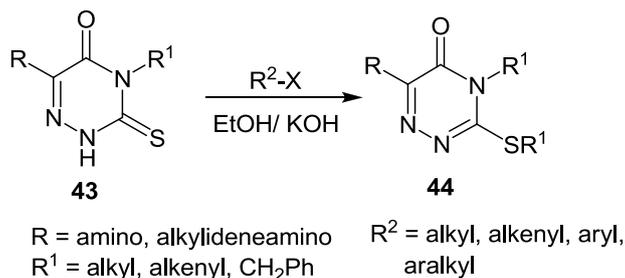
Scheme 18

Herbicidal and insecticidal *N*⁴-methylamino-3-alkylthio-6-substituted-1,2,4-triazin-5(4*H*)-ones **42** were obtained *via* methylation of the corresponding 4-amino-3-alkylthiotriazine **40** using Bu₄N⁺Br⁻ as a phase transfer catalysis (Scheme 19).⁵⁴



Scheme 19

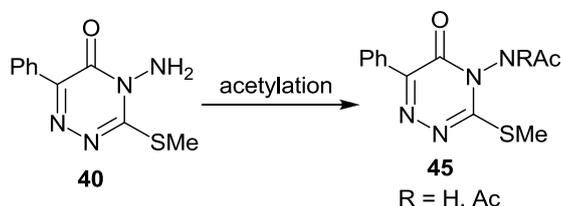
On the other hand, alkylation of 4-amino/alkylideneamino-3-thioxo-1,2,4-triazine-5-ones **43** in ethanolic KOH gave the corresponding alkylthio analog **44** as herbicides (Scheme 20).⁵⁵



Scheme 20

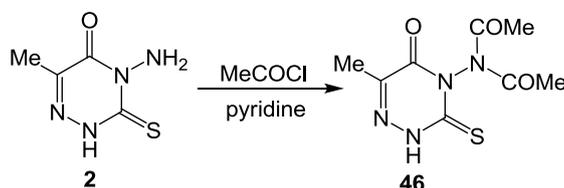
3.2. Acetylation

Acetylation of 4-amino-3-methylthio-6-phenyl-1,2,4-triazin-5-one **40** afforded the acetylated derivative **45** (Scheme 21).⁵⁶



Scheme 21

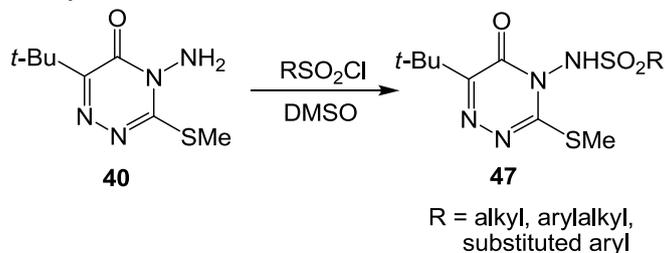
The diacetylamino derivative **46** was obtained when 4-amino-1,2,4-triazin-5-one **2** was treated with an excess of acetyl chloride in pyridine (Scheme 22).¹⁷



Scheme 22

3.3. Sulfonation

6-*t*-Butyl-3-methylthio-4-sulfimido-1,2,4-triazin-5-ones **47** were obtained as herbicides from treatment of *N*⁴-aminotriazine **40** with sulfonyl chloride derivatives in DMSO at -8 °C (Scheme 23).⁵⁷

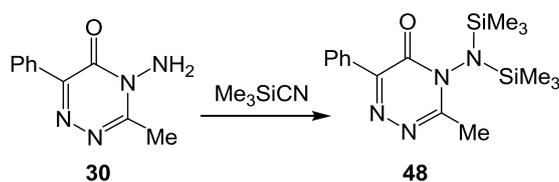


Scheme 23

3.4. Silylation

Bis(trimethylsilyl)amino-1,2,4-triazin-5-one **48** was obtained when metamitron **30** was refluxed with

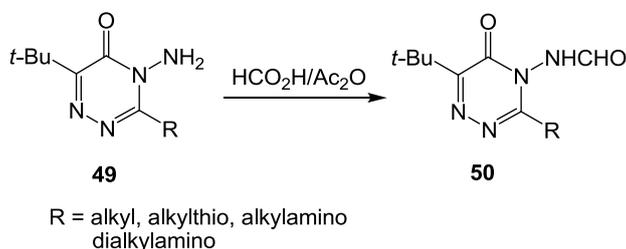
Me_3SiCN at 175 °C. Compound **48** more effective preemergence herbicides than currently used herbicides (Scheme 24).⁵⁸



Scheme 24

3.5. Formylation

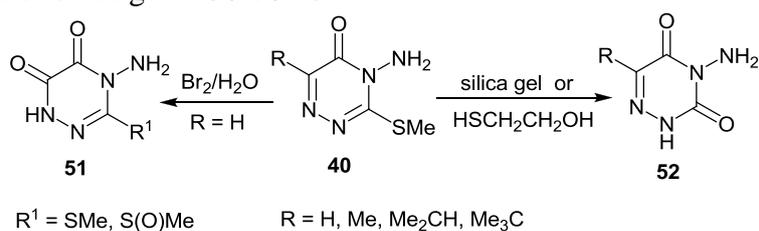
4-Formylamino-6-*t*-butyl-1,2,4-triazin-5-ones **50** were obtained as herbicides *via* treatment of the corresponding N^4 -aminotriazine **49** with a mixture of $\text{HCO}_2\text{H}/\text{Ac}_2\text{O}$ in dry ether as reported by Roy *et al.* (Scheme 25).⁵⁹



Scheme 25

3.6. Oxidation

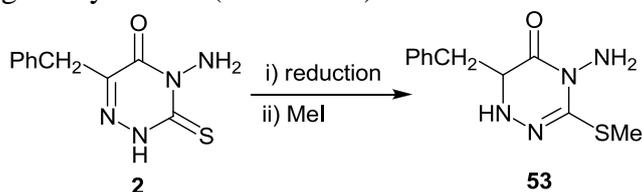
Oxidation of 4-amino-3-methylthio-1,2,4-triazin-5-one **40** (R = H) with bromine in water yielded 4-amino-1,2,4-triazine-5,6-dione derivative **51** (Scheme 26).⁵³ While the corresponding isomer, 4-aminotriazine-3,5-dione **52** was obtained by heating **40** in the presence of 2-mercaptoethanol⁶⁰ or from oxidation on the surface of silica gel at 50-70 °C.⁶¹



Scheme 26

3.7. Reduction

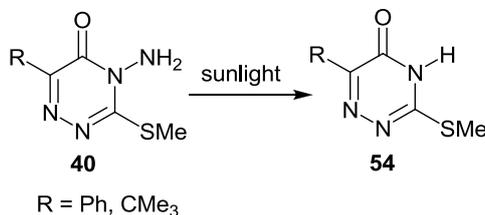
3-Methylthio-4-methylamino-1,6-dihydro-1,2,4-triazin-5-one **53** was obtained by the reduction of **2** and successive methylation using methyl iodide (Scheme 27).⁶²



Scheme 27

3.8. Photolysis

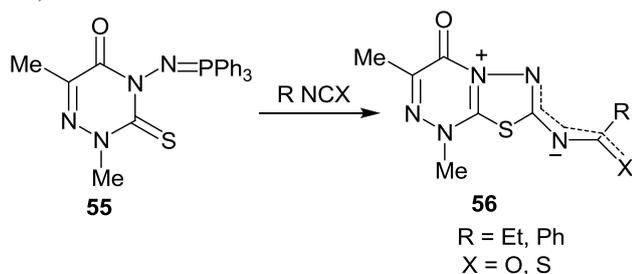
Photo-induced deamination reactions of 4-amino-3-methylthio-1,2,4-triazinones **40** by sunlight gave the deaminated product **54** (Scheme 28).^{63,64}



Scheme 28

3.9. Aza Wittig Reaction

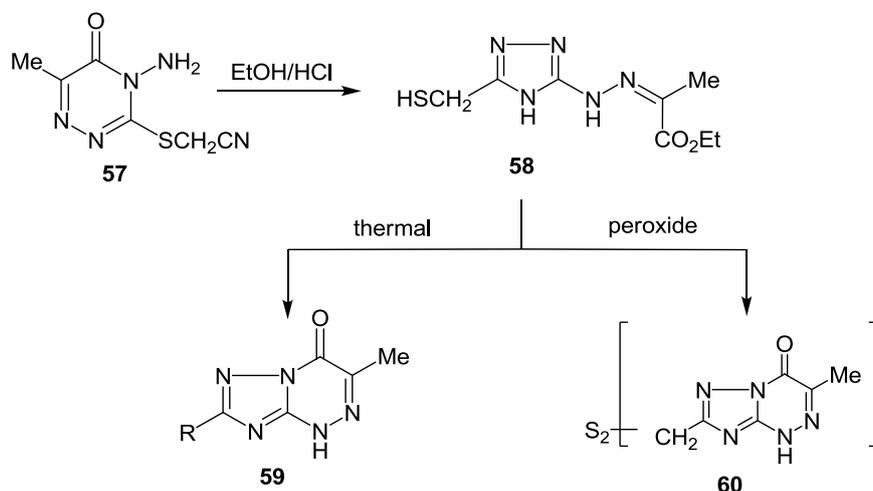
Aza Wittig-type reaction of iminophosphorane **55**, obtained from **2** and triphenylphosphine, with several types of iso(thio)cyanate leads to 1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazines **56** which displayed mesoionic or zwitter ionic character (Scheme 29).⁶⁵



Scheme 29

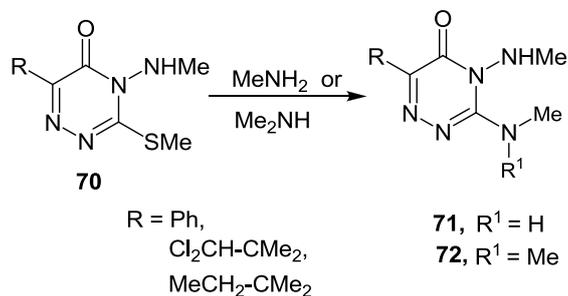
3.10. Rearrangement

Rearrangement of 4-amino-3-[(cyanomethyl)thio]-6-methyl-1,2,4-triazin-5(4*H*)-one **57** in ethanol containing HCl gave ethyl 2-[(5-mercaptomethyl-1,2,4-triazol-3-yl)hydrazone]propionate **58**. Thermal cyclization of **58** gave **59**, while oxidation with peroxid in dioxane afforded the disulphide **60** (Scheme 30).⁶⁶



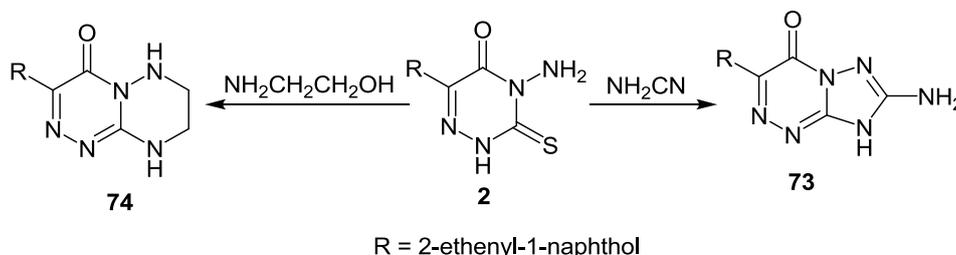
Scheme 30

Amination of **70** using methylamine and dimethylamine in isopropyl alcohol containing AcOH and small amount of toluene sulphonic acid gave **71** and **72**, respectively (Scheme 33).^{48,74,75}



Scheme 33

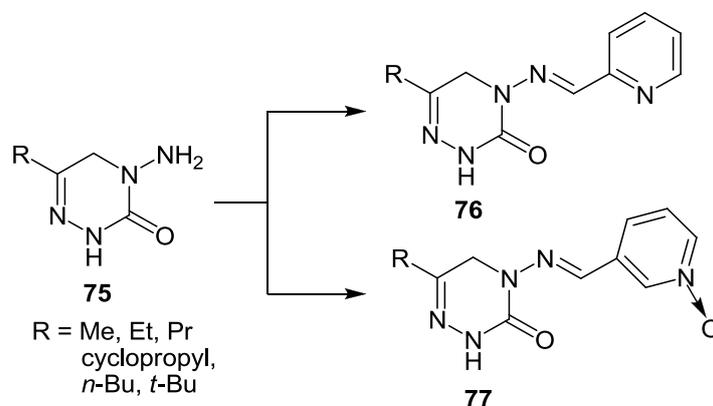
Fusion of compound **2** with cyanamide and ethanolamine afforded [1,2,4]triazolino[5,1-*c*][1,2,4]triazin-4-one **73** and [1,2,4]triazino[4,3-*b*][1,2,4]triazin-4-one **74**, respectively (Scheme 34).¹⁵



Scheme 34

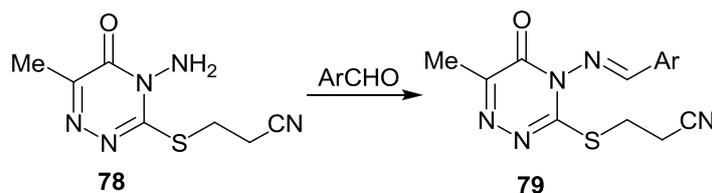
3.12. Condensation reactions

Condensation of 2,3,4,5-tetrahydro-4-amino-3-oxo-1,2,4-triazine **75** with pyridine-2-carboxaldehyde and pyridine-3-carboxyaldehyde-*N*-oxide in ethanol gave the corresponding hydrazones **76** and **77**, respectively (Scheme 35).^{76,77}



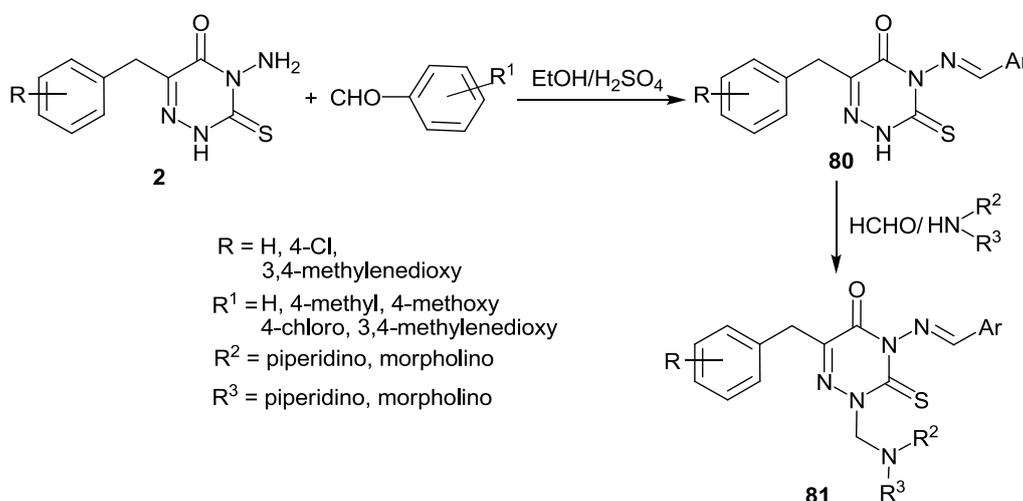
Scheme 35

Condensation of 3-cyanoethylthiotriazinone **78** with aromatic aldehydes yielded the corresponding hydrazone **79** (Scheme 36).⁷⁸



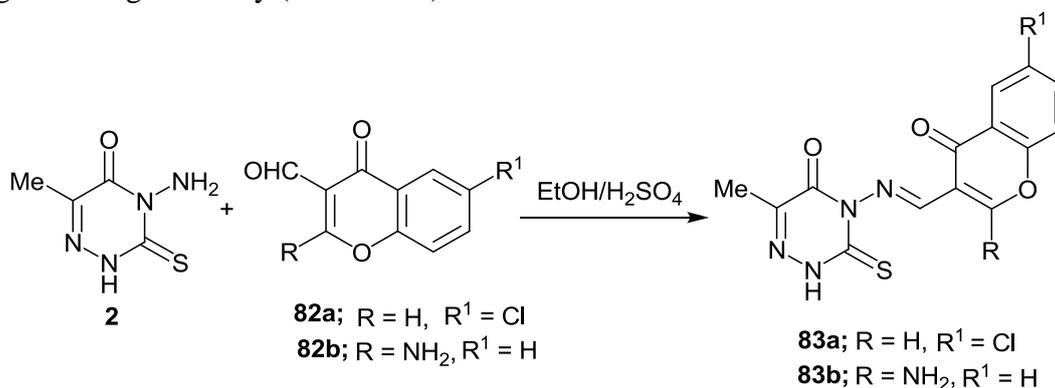
Scheme 36

Condensation of 6-arylmethyl-4-aminotriazinones **2** with aromatic aldehydes in EtOH containing H₂SO₄ gave the corresponding hydrazones **80** which on treatment with Mannich bases afforded 2-aminomethyl-4-(arylidene)amino-1,2,4-triazin-5(4*H*)-ones **81** of high antifungal activity (Scheme 37).²⁶



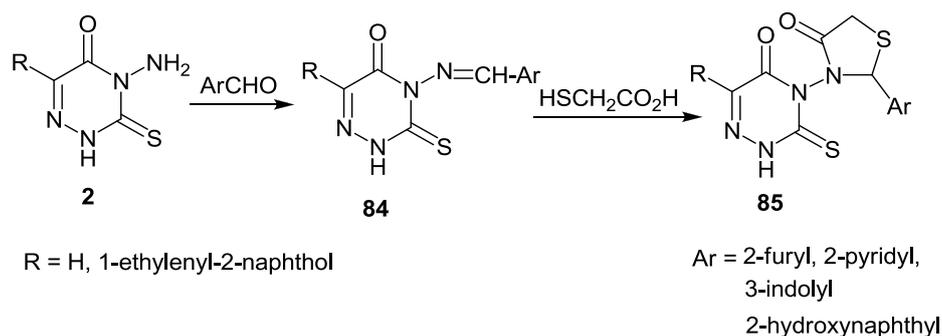
Scheme 37

Also, condensation of **2** with 3-formylchromone **82a** and its 2-amino analog **82b** afforded the hydrazones **83a,b** of high antifungal activity (Scheme 38).^{79,80}



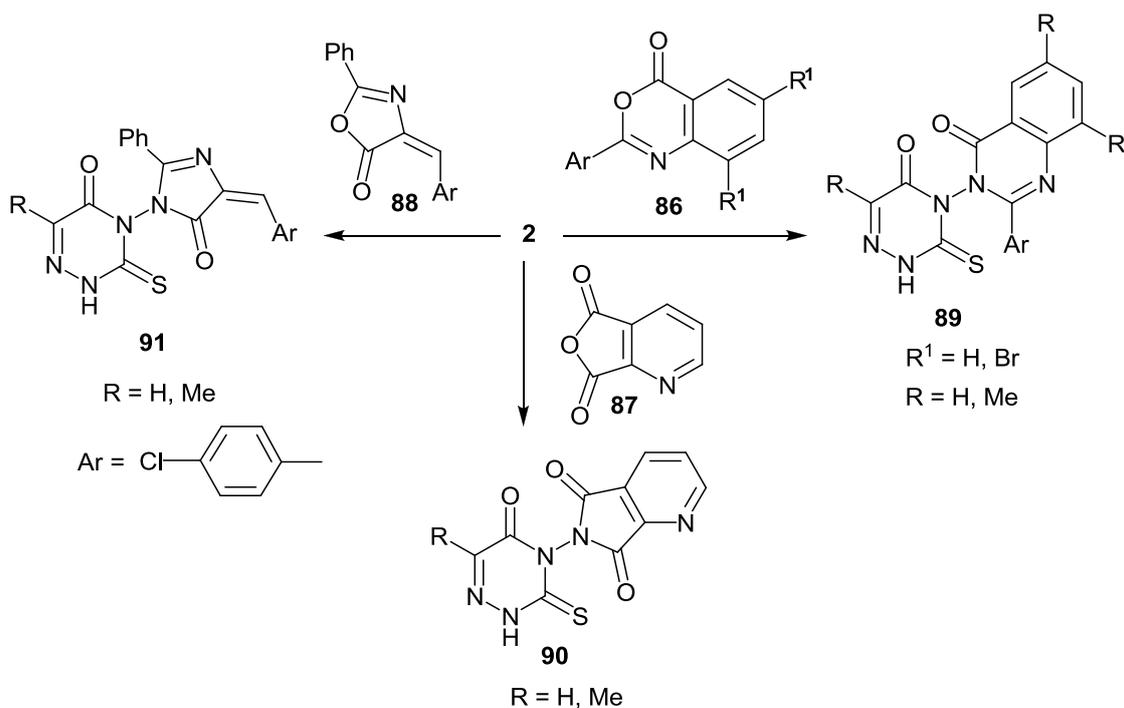
Scheme 38

Condensation of **2** with aromatic aldehydes produced the hydrazone **84** which upon cycloaddition with mercaptoacetic acid yielded 3-thiazolidinyl-1,2,4-triazine derivative **85** as anticancer agents (Scheme 39).²⁷



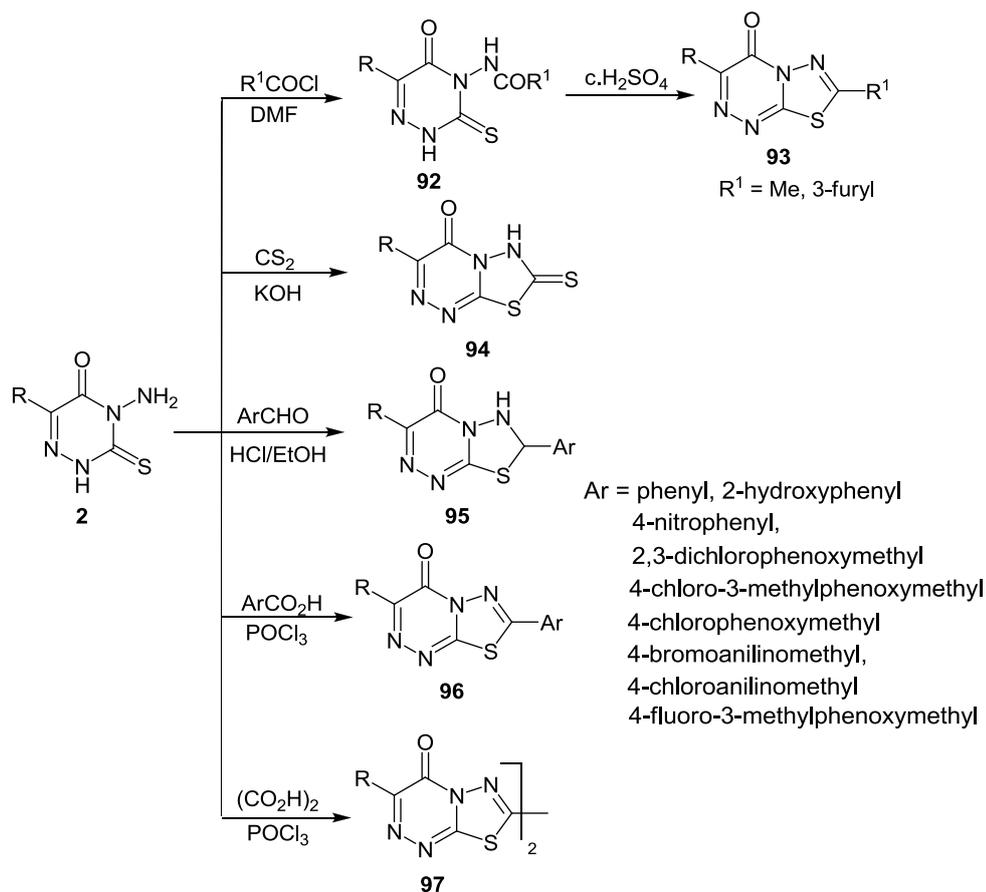
Scheme 39

Condensation of **2** with cyclic oxygen compounds such as 3,1-benzoxazin-4-one **86**, pyridine-2,3-dicarboxylic anhydride **87**, and oxazolinone **88** in dry pyridine furnished 1,2,4-triazine derivatives connected with quinazolinone **89**, pyridine-2,3-dicarboximide **90** and imidazolinone **91** moieties (Scheme 40).^{27,81}



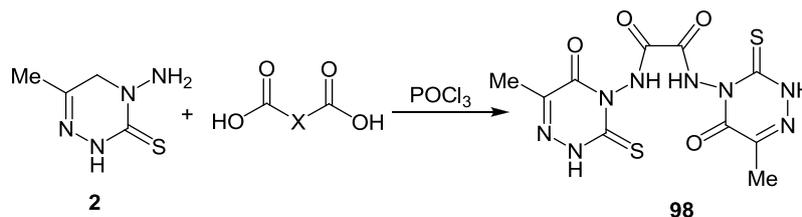
Scheme 40

Acylation and aroylation of **2** using acid chlorides in DMF yielded *N*⁴-acyl/aroylamino-3-mercapto-6-substituted-1,2,4-triazin-5-one **92** which upon cyclization using conc. H₂SO₄ gave 3-substituted-7-methyl/furyl-3-yl-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazol-4-one **93**.⁸¹ Also, a facile route to synthesis some fused 1,2,4-triazino[3,4-*b*]thiadiazolone **94-96** was achieved from the condensation of **2** with CS₂, aromatic aldehydes and aromatic carboxylic acid, respectively.^{7,82-86} On the other hand, condensation of **2** with oxalic acid in POCl₃ gave *bis*[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazol-4-one **97** of high anti-tumor activity (Scheme 41).⁸²



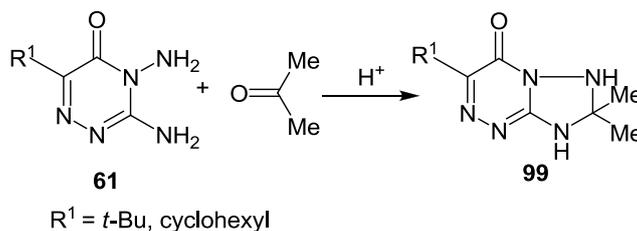
Scheme 41

Some novel *N,N*-bis(1,2,4-triazin-4-yl)dicarboxylic acid amides **98** were obtained by heating **2** with different carboxylic acids (oxalic, malonic, fumaric, maleic, succinic, phthalic) in POCl₃ (Scheme 42).⁸¹



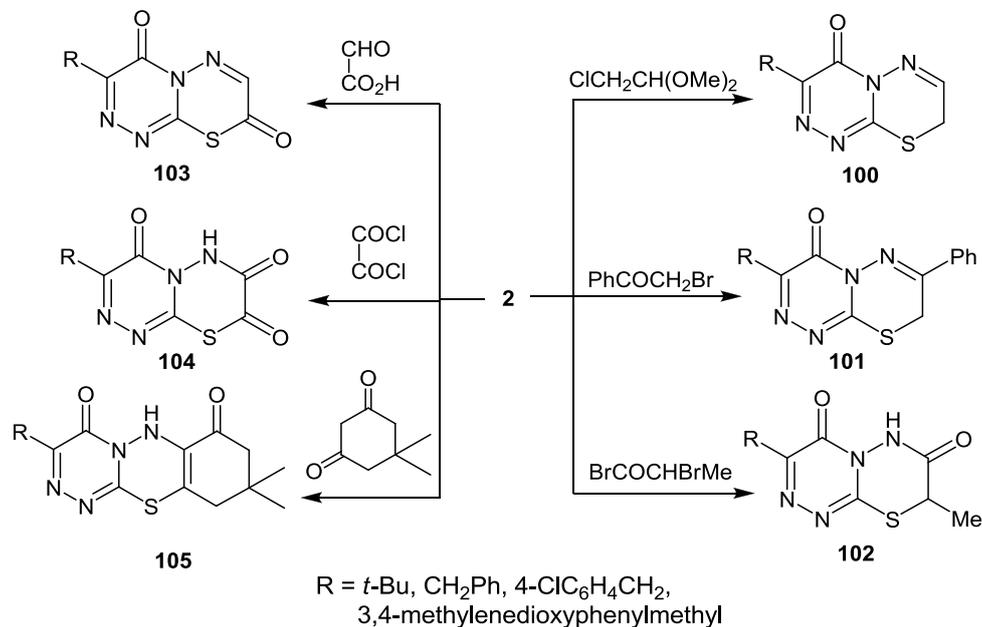
Scheme 42

Condensation of 3,4-diamino-1,2,4-triazin-5(1H)-ones **61** with acetone in the presence of weak organic acid gave 1,2,3,7-tetrahydro[1,2,4]triazolo[3,2-*c*][1,2,4]triazin-7-ones **99** (Scheme 43).⁸⁷



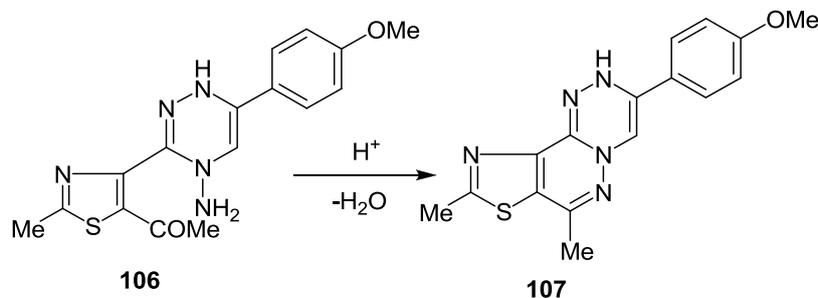
Scheme 43

On the other hand, some [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazinone derivatives **100-105** were prepared from the reaction of compound **2** with chloroacetaldehyde-dimethylacetal, phenacyl bromide, 2-bromopropionylbromide, glyoxalic acid, oxalyl chloride, and dimedone, respectively (Scheme 44).^{82,88}



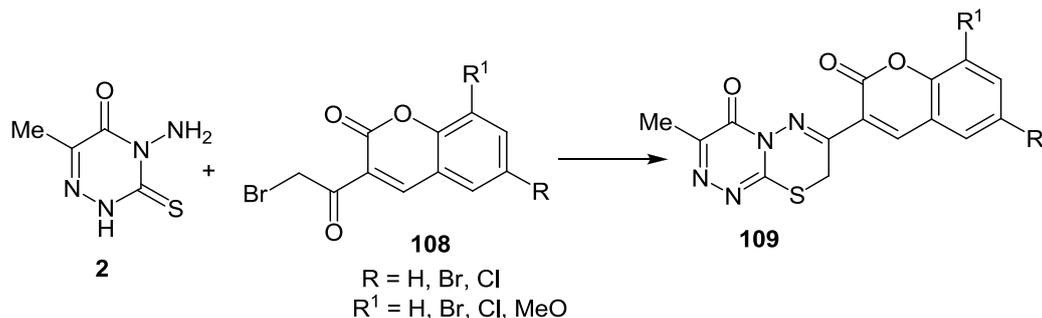
Scheme 44

Thiazolo[4,5-*d*]pyridazino[2,3-*c*]-2*H*-triazine **107** was yielded from heating 5-acetylthiazole **106** in acid medium (Scheme 45).⁸⁹



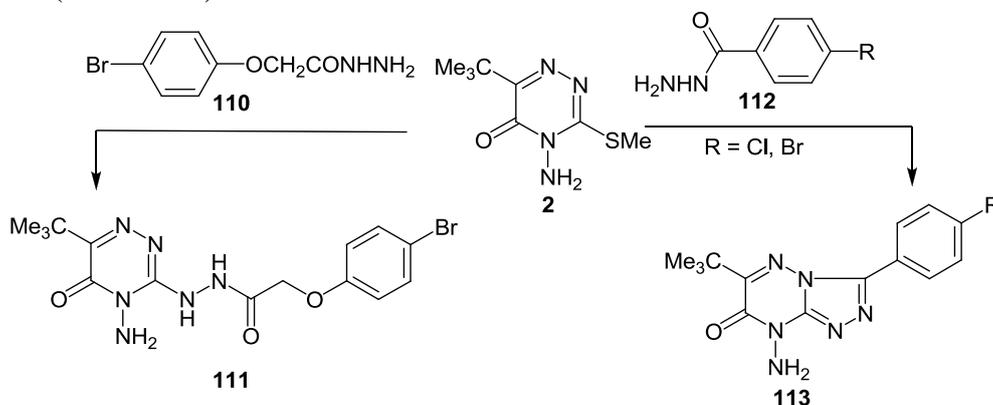
Scheme 45

7-(2-Oxo-2*H*-1-benzopyran-3-yl)-3-methyl-4*H*,8*H*-[1,2,4]triazino[3,4-*b*][1,3,4]thiadiazin-4-ones **109** were prepared from condensation of **2** with 3-(ω -bromoacetyl)coumarins **108** (Scheme 46).⁹⁰



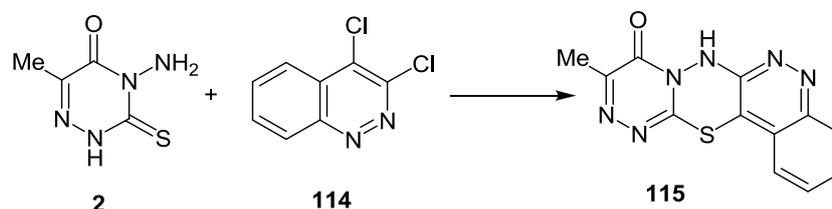
Scheme 46

Fusion of **2** with 2-(4-bromophenoxy)acetic acid hydrazide **110** gave N^1 -[4-amino-6-(*tert*-butyl)-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl]- N^2 -[2-(4-bromophenoxy)acetyl]hydrazine **111**. While, fusion with hydrazide **112** gave 8-amino-6-(*tert*-butyl)-3-(4-substituted)-7,8-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]-triazin-7-one **113** (Scheme 47).⁹¹



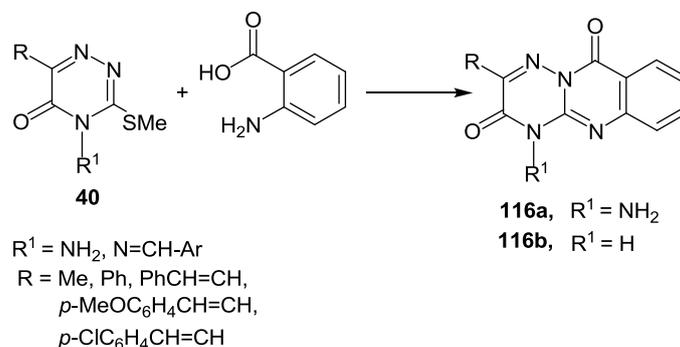
Scheme 47

1,2,4-Triazino[3,4:2,3][1,2,4]thiadiazino[5,6-*c*]cinnolin-9-one **115** was prepared by cyclocondensation of the **2** with 3,4-dichlorocinnoline **114** (Scheme 48).⁹²



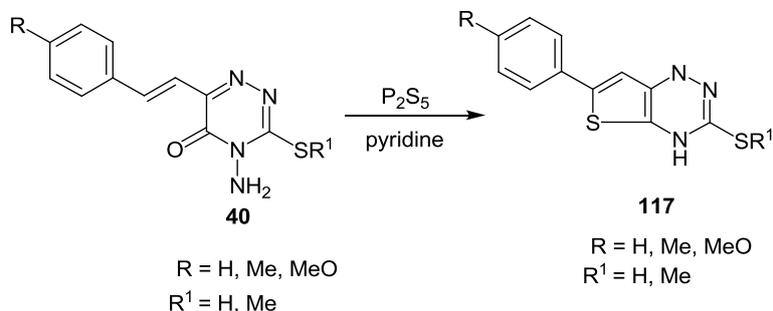
Scheme 48

Cyclocondensation of 4-amino-3-methylthiotriazine **40** with anthranilic acid yielded 1,2,4-triazino[3,2-*b*]quinazolines **116a** ($R^1 = \text{NH}_2$). Heating N -benzylidene derivative of **40** ($R^1 = \text{NCH-Ar}$) with anthranilic acid afforded the deaminated product **116** ($R^1 = \text{H}$) with extrusion of PhCN as reported by Badwy *et al.* (Scheme 49).⁹³



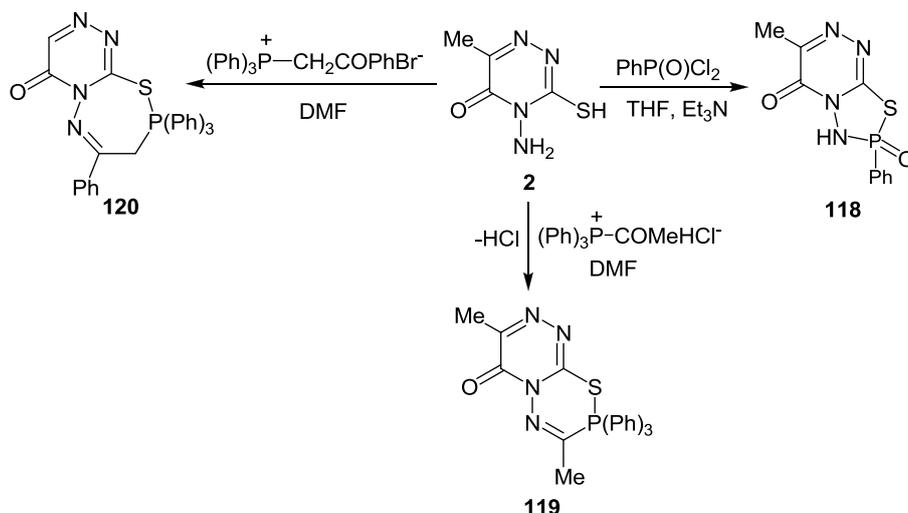
Scheme 49

Also, thieno[2,3-*e*][1,2,4]triazines **117** were prepared by the action of phosphorus pentasulphide on 4-amino-6-styryl-triazin-5-ones **40** with concomitant deamination of the *N*⁴-amino group as published by Eid and coworkers (Scheme 50).⁹⁴



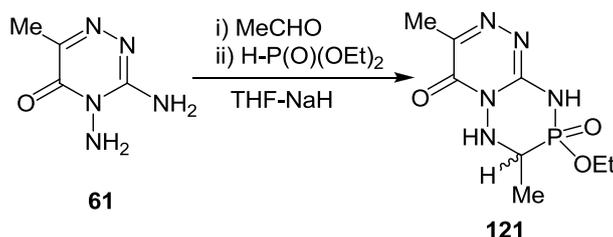
Scheme 50

Condensation of **2** with phenylphosphonic dichloride, acetyltriphenylphosphonium chloride and phenacyltriphenylphosphonium bromide afforded 6-methyl-2-oxido-2-phenyl-1,2-dihydro-7*H*-[1,3,4,2]-thiadiazaphospholo[5,4-*c*][1,2,4]triazin-5-one **118**, [1,2,4]triazino[4,3-*e*][1,4,5,2]thiadiazaphosphinine **119** and [1,2,4]triazino[4,3-*f*][1,5,6,2]thiadiazaphosphepine **120**, respectively (Scheme 51).⁹⁵



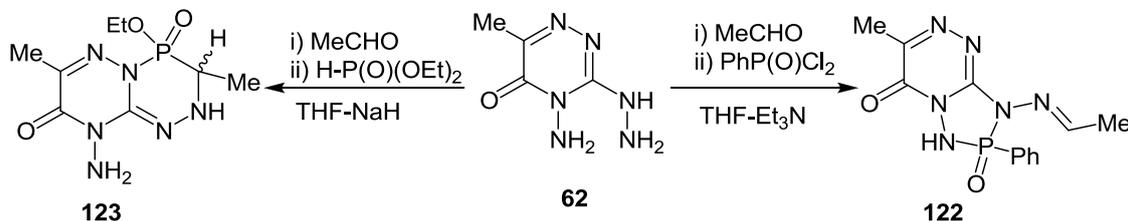
Scheme 51

Kabachnik-Fields reaction⁹⁶ using 3,4-diamino-6-methyl-1,2,4-triazin-5(4*H*)-one **61**, acetaldehyde and diethyl phosphonate gave [1,2,4]triazino[4,3-*b*][1,2,4,5]triazaphosphinine derivative **121** (Scheme 52).⁹⁵



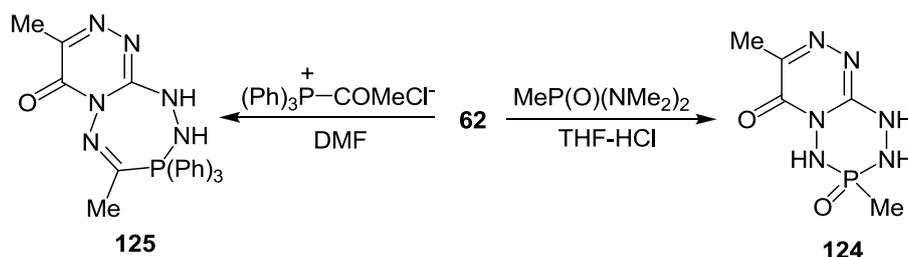
Scheme 52

On the other hand, condensation of **62** with acetaldehyde/phenylphosphonic dichloride and acetaldehyde/diethyl phosphonate afforded [1,2,4,3]triazaphospholo[5,1-*c*][1,2,4]triazine **122** and [1,2,4]-triazino[3,2-*c*][1,2,4,5]triazaphosphinine **123**, respectively (Scheme 53).⁹⁵



Scheme 53

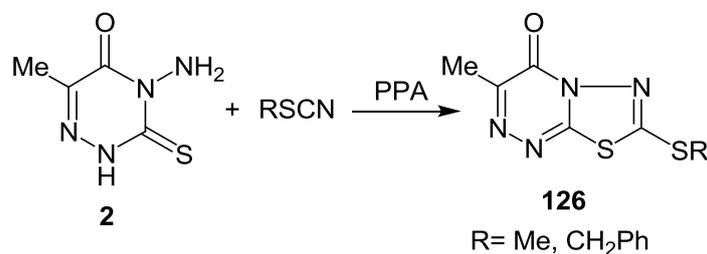
Novel six and seven-membered phosphorus heterocycles, namely 2,7-dimethyl-2-oxido-1,2,3,4-tetrahydro-8*H*-[1,2,4]triazino[4,3-*e*][1,2,4,5,3]tetrazaphosphinin-8-one **124** and 4,8-dimethyl-3,3,3-triphenyl-2,3-dihydro[1,2,4]triazino[4,3-*e*][1,2,5,6,3]tetrazaphosphepin-7(1*H*)-one **125** were obtained by cyclocondensation of **62** with bis(dimethylamino)methylphosphonate and acetyltriphenylphosphonium chloride, respectively (Scheme 54).⁹⁵



Scheme 54

3.13. Cycloaddition reactions

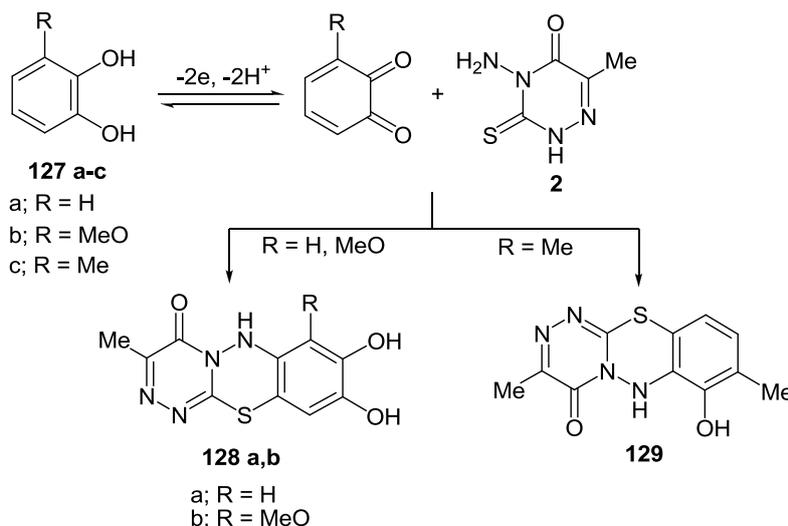
2-Alkylthio-6-substituted-5-oxo-5*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazines **126** were obtained by cycloaddition of **2** to RSCN catalyzed by polyphosphoric acid (Scheme 55).⁹⁷



Scheme 55

3.14. Electrochemical reactions

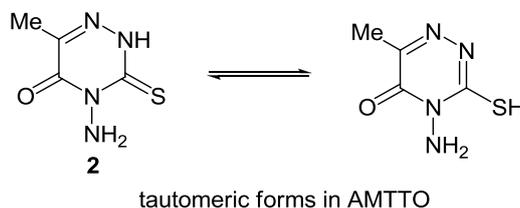
Electrochemical oxidation of catechols **127a-c** in the presence of 4-amino-6-methyl-1,2,4-triazine-3-thione **2** as a nucleophile afforded [1,2,4]triazino[3,4-*b*][1,3,4]thiadiazines **128a,b** and **129** (Scheme 56).⁹⁸



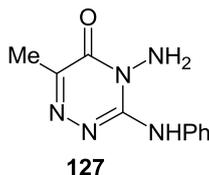
Scheme 56

3.15. Formation of complexes

Reaction of 4-amino-6-methyl-5-oxo-1,2,4-triazine-3-thione (AMTTO, **2**) with palladium(II) chloride in THF produced palladium complex [(AMTTO)PdCl₂]₃.4.5THF in excellent yield. Treating **2** with palladium(II) chloride in methanol and palladium(II) bromide in THF gave the complexes [(AMTTO)PdCl₂].MeOH and [(AMTTO)PdBr₂]₂.3.5THF, respectively.⁹⁹



4-Amino-1,2,4-triazin-5-ones are biochemically highly active substances and their use as herbicides has been suggested, for example 4-amino-6-*t*-butyl-3-methylthio-1,2,4-triazin-5-one (Metribuzin, **40**) and 4-amino-3-methyl-6-phenyl-1,2,4-triazin-5-one (Goltix, **30**).¹⁰⁰ This type of compounds can also be used for the determination of metal ions because of their ability to form complex compounds,¹⁰¹ but no transition metal complex of these ligands has been isolated in the solid state. On the other hand, cobalt(II) and nickel(II) complexes of 4-amino-6-methyl-5-oxo-3-phenylamino-1,2,4-triazine (ATAZ, **127**) afforded MX₂(ATAZ)₂.2H₂O complexes (M = Co or Ni; X = Cl, Br, I or NCS).^{17,102,103}



A few (1:1) and (1:2) metal complexes of cobalt(II), nickel(II), copper(II) and zinc(II) have been isolated with the ligand derived from the condensation of 4-amino-3-mercapto-6-methyl-5-oxo-1,2,4-triazine **2** with 2-acetylpyridine,¹⁰ (Figures 1 and 2). Due to insolubility in water and most of the common organic solvents and infusibility at higher temperatures, all the complexes are thought to be polymeric in nature.

A square-planar geometry was suggested for copper(II) and octahedral for cobalt(II), nickel(II) and zinc(II) complexes. The metal complexes have higher antimicrobial effect than the free ligand.

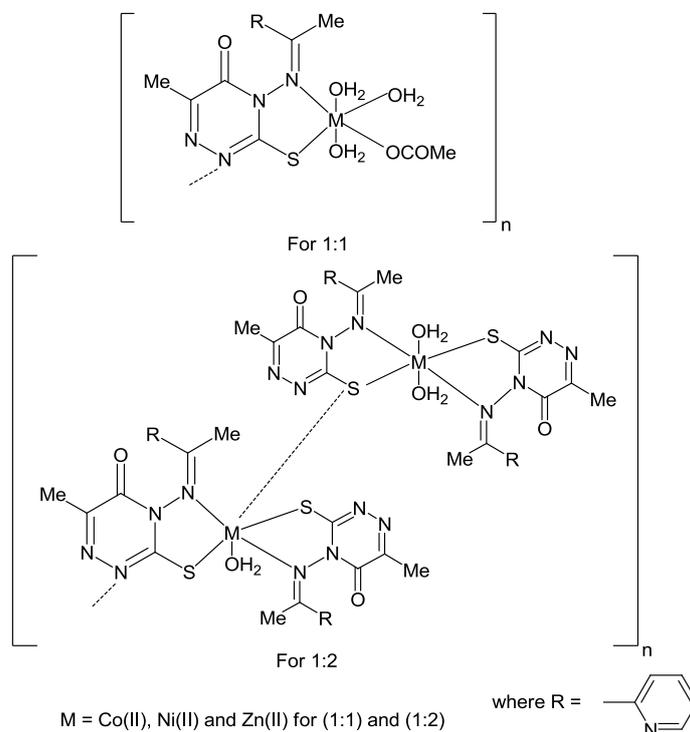


Figure 1

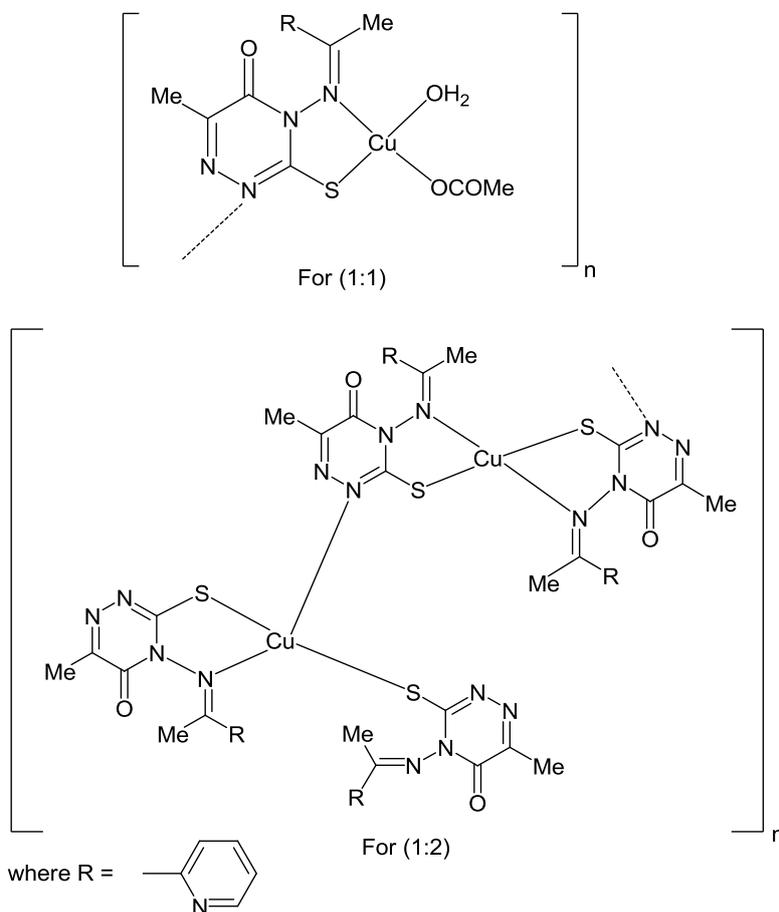


Figure 2

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