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1,2,4-Triazine Chemistry Part I: Orientation of cyclization reactions of functionalized 1,2,4-triazine derivatives

Reda Mohammady Abdel-Rahman[a], Mohammed Saleh Tawfik Makki[a], Tarik El-Sayed Ali[b,*] and Magdy Ahmed Ibrahim[b]

[a] *Department of Chemistry, Faculty of Science, King Abdel-Aziz University, Jeddah, 21589, Saudi Arabia*
[b] *Department of Chemistry, Faculty of Education, Ain shams University, Roxy, 11711, Cairo, Egypt*

**Corresponding author at: Department of Chemistry, Faculty of Education, Ain shams University, Roxy, 11711, Cairo, Egypt. Tel.: +200103730144; fax: +2022581243. E-mail address: tarik_elsayed1975@yahoo.com (T.E. Ali).*

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ABSTRACT

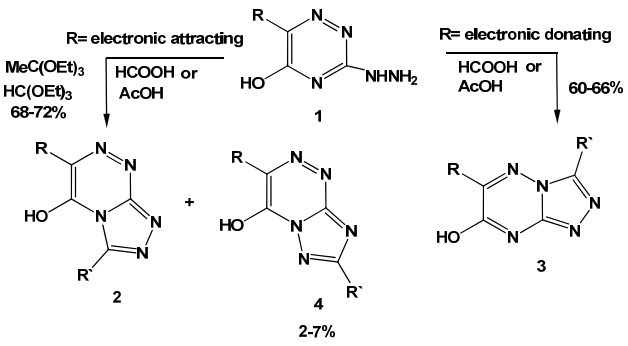
Orientation of heterocyclization reactions of functionalized 1,2,4-triazines were studied by effect of substituents in 1,2,4-triazine moieties, type of the solvent used in the reaction and the temperature effect. Also, it was found that cyclization process depended mainly on the chemoselective and regioselectivity states of the parent substrate as well as preferring cite of ring closure.

1. Introduction

1,2,4-Triazines play a vital role in many biological processes and as synthetic drugs. Furthermore, many heterocyclic systems bearing 1,2,4-triazines are found to exhibit remarkable pharmacological effects [1-5]. In search for new anti-HIV and anticancer agents, some additional heterocyclic moieties were incorporated in the 1,2,4-triazine nucleus *via* the interaction between functionalized 1,2,4-triazines with various nucleophilic and electrophilic reagents in different media [6-12]. In the present review article, we study the factors which affect on the orientation of cyclization reactions of functionalized 1,2,4-triazine derivatives.

2. Effect of substituents

Substituents in functionalized 1,2,4-triazines have an effect on the orientation of cyclization reactions according to the nature of substituents. These effects at position 6 of 3-hydrazino-5-hydroxy-1,2,4-triazine (**1**) on the orientation of cyclization to form 1,2,4-triazolo[1,2,4]triazines, was examined by Daunis *et al.* [13]. Thus, when R was an electron attracting group, 1,2,4-triazolo[3,4-*c*][1,2,4]triazines (**2**) were formed in the presence of acidic (HCO_2H or AcOH) or neutral [$HC(OEt)_3$ or $MeC(EtO)_3$] media. On the other hand, when R was an electron donating group and the reagent was acidic (HCO_2H or AcOH), 1,2,4-triazolo[4,3-*b*][1,2,4]triazine derivatives (**3**) were formed. Compound **4** was obtained as *by*-product with **2** and the amount of **4** increased with long reaction time (Scheme 1).



Scheme 1

Reaction of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (**5**) with unsymmetrical 1,3-dicarbonyl compounds, **6**, should be expected to give the isomeric pyrazole derivatives **7** and/or **8** [14]. However, the only isomer **7** was isolated in good yield due to the direction of enolization of 1,3-diketone being towards aryl group (Scheme 2) [15].

Also, refluxing 3-hydrazino-4,5-dihydro-4,5,6-triphenyl-1,2,4-triazine (**9**) with CS_2 in KOH yielded 6,7-diphenyl-3-mercapto-8-methyl-7*H*-triazolo[4,3-*b*][1,2,4]triazine (**10**) (Scheme 3) [16].

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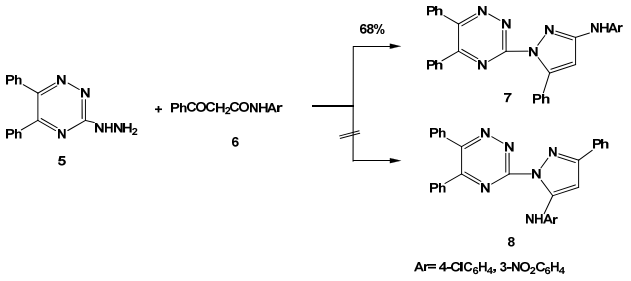
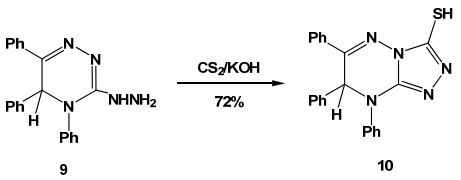
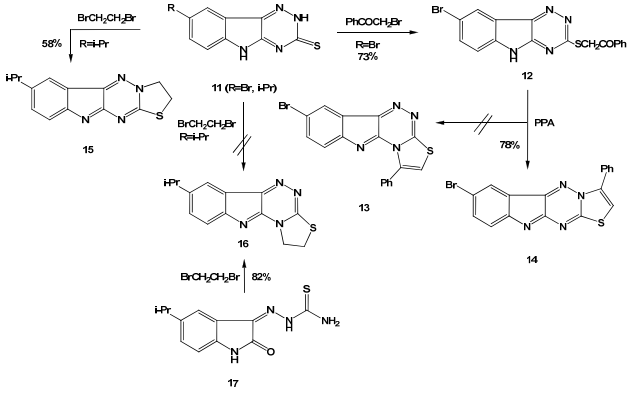


Scheme 2



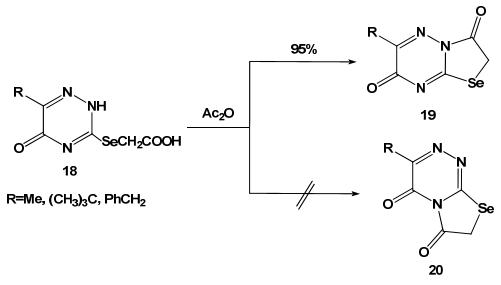
Scheme 3

Effect of electron donating or attracting substituents in the orientation of cyclization reactions was clearly appeared freely. Thus, reaction of 8-substituted-5*H*-2,3-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione (**11**) (R=Br) with phenacyl bromide gave **12**. Cyclization of **12** with polyphosphoric acid yielded 7-bromo-3-phenyl-thiazolo[3',2':2,3][1,2,4]triazino [5,6-*b*] indole (**14**) and not the isomer **13** (Scheme 4) [17]. Also, reaction of **11** (R=i-Pr) with 1,2-dibromoethane gave the cyclized product, 7-isopropyl-2,3-dihydrothiazolo[3',2':2,3] [1,2,4] triazino[5,6-*b*]indole (**15**) and not the angular isomer **16**. The unequivocal synthesis of the latter was accomplished by reaction of 5-isopropylisatin-3-thiosemicarbazone (**17**) with 1,2-dibromoethane (Scheme 4) [18].



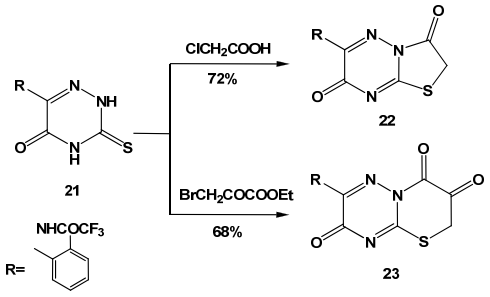
Scheme 4

Boiling 3-(carboxymethylseleno)-6-substituted-2,6-dihyd ro-1,2,4-triazin-5-one (**18**) *via* in Ac_2O produced 6-substituted-7*H*-selenazolo[3,2-*b*][1,2,4]triazine-(2H,3H)-3,7-diones (**19**) which was formed *via* cyclization through N-2 and not N-4 of triazine moiety (Scheme 5) [19].



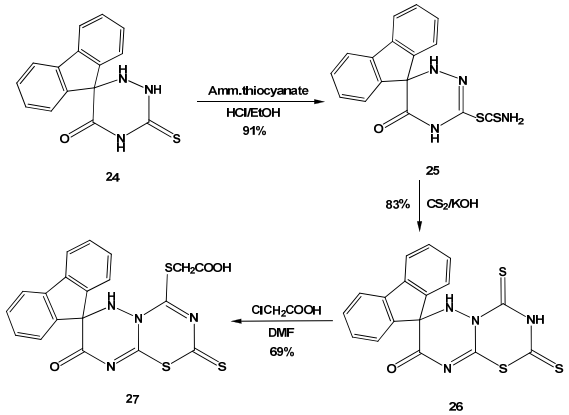
Scheme 5

Alkylation of 6-aryl-3-thioxo-1,2,4-triazin-5-one (**21**) depends on the type of functional group in position 6 of 1,2,4-triazine moiety. Thus, alkylation of **21** with chloroacetic acid or ethyl bromopyruvate took place at the sulfur atom followed by cyclization on N-2 and not N-4 of 1,2,4-triazine moiety to yield the linear products **22** and **23**, respectively (Scheme 6) [20].



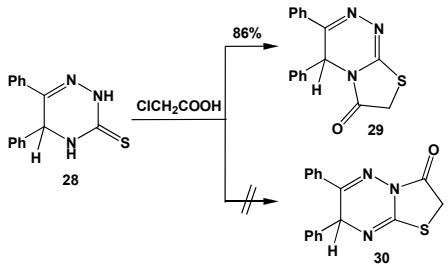
Scheme 6

Treatment of **24** with ammonium thiocyanate in EtOH/HCl produced **25**, which was reacted with CS_2/KOH to furnish the triazinothiadiazine derivative **26** through cyclization occurred at N-2 and not N-4 of 1,2,4-triazine moiety. Alkylation of **26** using chloroacetic acid afforded 4-carboxymethylmercapto-6,7-dihydro-2-thioxo-7-spiro-(9-fluorene)-1,3,5-thiadiazino[3,2-*b*] [1,2,4]triazin-8-one (**27**) (Scheme 7) [21].



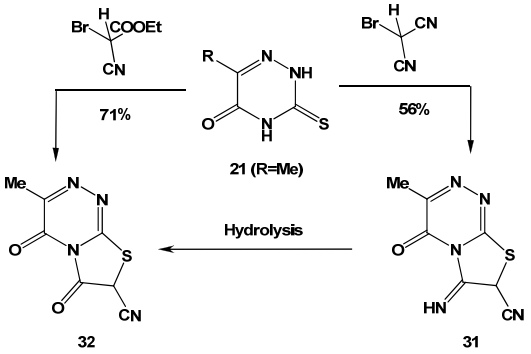
Scheme 7

Cyclization of 5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione (**28**) with chloro-acetic acid led to the formation of 5,6-diphenyl-5*H*-thiazolo[2,3-*c*][1,2,4]triazin-3(2*H*)-one (**29**) and not the isomeric structure **30** (Scheme 8) [22].



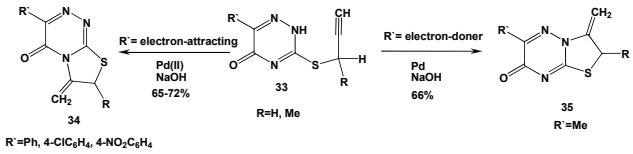
Scheme 8

Alkylation of 1,2,4-triazinethione **21** (R=Me) using bromomalononitrile and ethyl bromocyanoacetate led to the formation of **31** and **32**, respectively, which were formed through cyclization on N-4 and not N-2 of 1,2,4-triazine moiety. Hydrolysis of compound **31** afforded **32** (Scheme 9) [23].



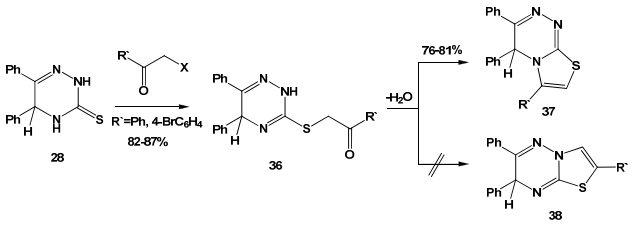
Scheme 9

Selective transformation of 3-prop-3-ynlthio-1,2,4-triazin-5(2*H*)-ones (**33**) to thiazolo [2,3-*c*][1,2,4]triazin-4-ones (**34**) and thiazolo[3,2-*d*][1,2,4]triazin-7-ones (**35**) was performed under conditions of Pd(II) salt or NaOH catalysis. Formation of **34** and **35** depends on the nature of group at position 6 of the triazine moiety (Scheme 10) [24].



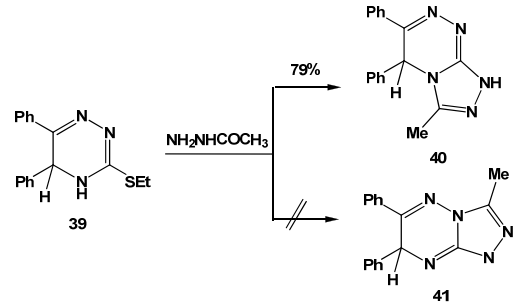
Scheme 10

Alkylation of 5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazin-3-thione (**28**) gave the corresponding *S*-alkyl derivative **36** which upon cyclization afforded **37** and not the isomeric structure **38** (Scheme 11) [25].



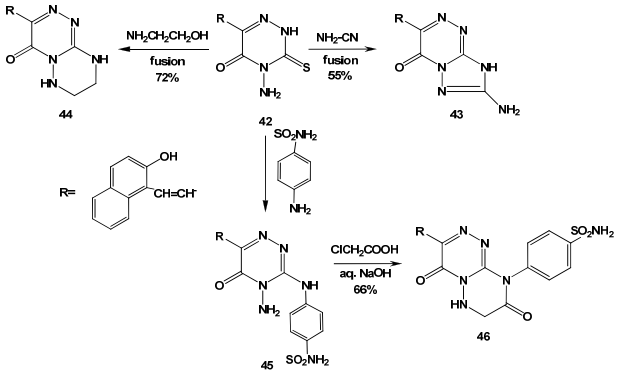
Scheme 11

Also, hydrazinolysis of **39** using *N*-acetylhydrazine yielded the 1*H*-4,5-diphenyl-5*H*-6-methyl-1,2,4-triazolo[3,4-*c*][1,2,4] triazine (**40**) and not (**41**) (Scheme 12) [25]. The reaction proceeded through nucleophilic displacement of ethylthio group, followed by cyclization at N-4 and not N-2 atom.



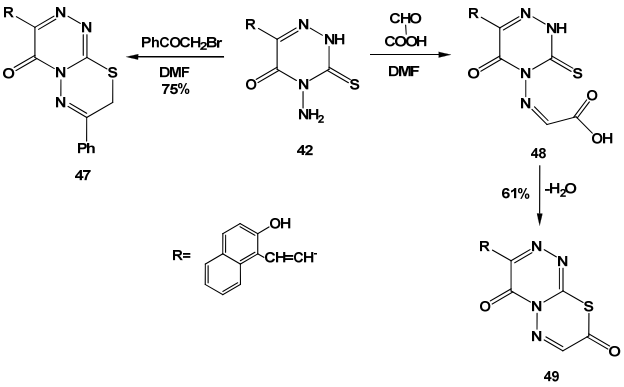
Scheme 12

A simple nucleophilic displacement of *S*-atom in 4-amino-3-mercapto-1,2,4-triazin-5-one (**42**) was carried out *via* its refluxing with cyanamide and ethanolamine to give 1,2,4-triazino[5,1-*c*][1,2,4]triazin-4-one (**43**) and 1,2,4-triazino[4,3-*d*][1,2,4]triazin-4-one (**44**), respectively. Also, refluxing **42** with sulfanilamide gave 3-substitutedamino-1,2,4-triazine-5-one (**45**) which upon ring closure reaction by refluxing with chloroacetic acid in aqueous NaOH solution afforded 1,2,4-triazino[4,3-*b*][1,2,4]triazine (**46**) (Scheme 13) [26].



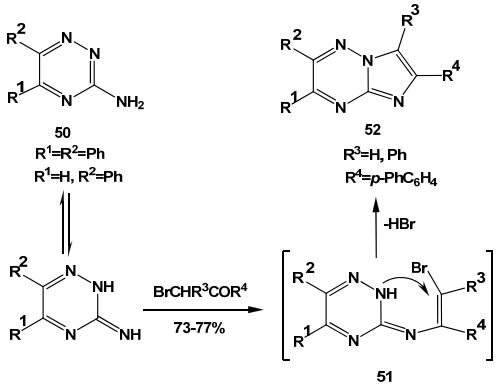
Scheme 13

On the other hand, the reactivity of compound **42** towards both nucleophilic and electrophilic reagents in different medium have been reported [28] where the nucleophilicity increase in order S> O> N. Thus, treatment of **42** with phenacyl bromide in refluxing DMF yielded 1,2,4-triazino[3,4-*b*][1,3,4]thiadiazin-4-one (**47**) while its boiling with glyoxylic acid in DMF followed by careful dehydration with concentrated H_2SO_4 afforded 1,2,4-triazino[3,4-*b*][1,3,4]thiadiazine-4,8-dione (**49**) (Scheme 14) [26].



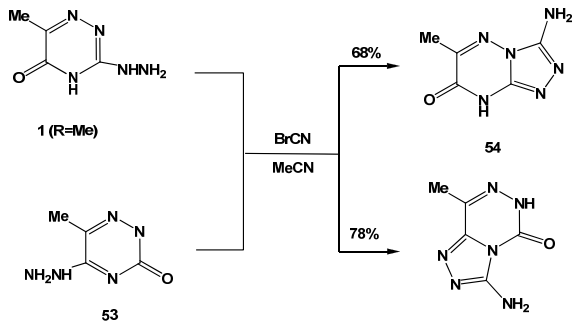
Scheme 14

Cyclocondensation of aminotriazine (**50**) with α-bromoketones (R^3=H, Ph, R^4=*p*-PhC_6H_4) in DMF or isopropanol gave imidazo[1,2-*b*][1,2,4]triazine derivatives (**52**) (Scheme 15) [27].



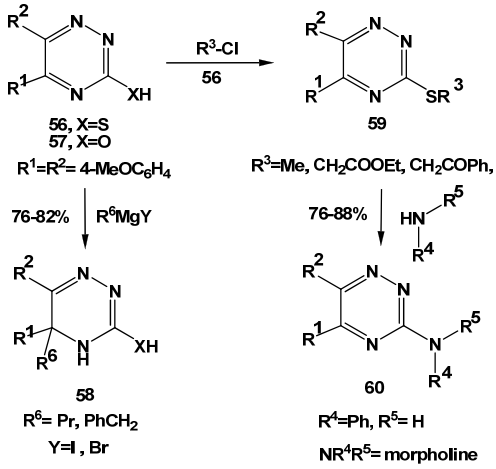
Scheme 15

Tadashi and Eikah [28] reported the ring closure reaction of 3-hydrazino-1,2,4-triazin-5-one (**1**) and 5-hydrazino-1,2,4-triazin-3-one (**53**) with cyanogen bromide in acetonitrile afforded the bridge head nitrogen systems triazolo[4,3-*b*][1,2,4]triazinone (**54**) and triazolo[4,3-*d*][1,2,4] triazine (**55**), respectively (Scheme 16).



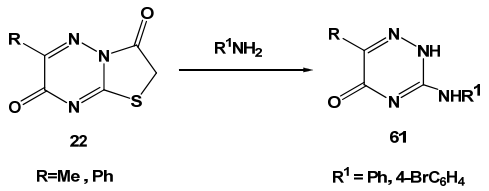
Scheme 16

Effect of substituents on the reactivity of the functional groups and electronic activity of heterocyclic systems was studied by Mansour *et al.* [29]. Thus, compounds **56** and **57** under the action of Grignard reagents yielded the 4,5-dihydro derivatives (**58**), while a simple nucleophilic attack of primary amine on the *S*-alkyl derivatives (**59**) yielded 3-substituted amino-5,6-diaryl-1,2,4-triazines **(60)** (Scheme 17).



Scheme 17

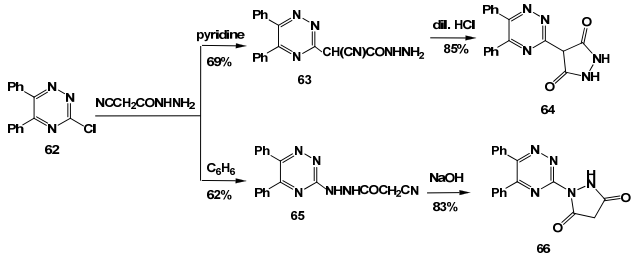
3-Substitutedamino-1,2,4-triazinones (**61**) were obtained in 60-67% yield from the nucleophilic attack of primary amines on 6-substituted-2,3-dihydro-7*H*-thiazolo[3,2-*b*][1,2,4] triazine-3,7-diones (**22**) (Scheme 18) [30].



Scheme 18

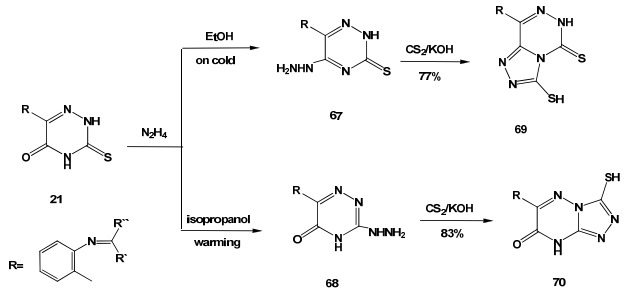
3. Role of solvent

The type of solvent plays an strong role on the type of heterocyclization reactions. Thus, Abdel-Rahman *et al.* [31], reported the relatively easier replacement of the chlorine atom at 3-position of 3-chloro-5,6-diphenyl-1,2,4-triazine nucleus by cyanoacetic acid hydrazide in pyridine or dry benzene followed by cyclization to produce compounds **63-66** (Scheme 19).



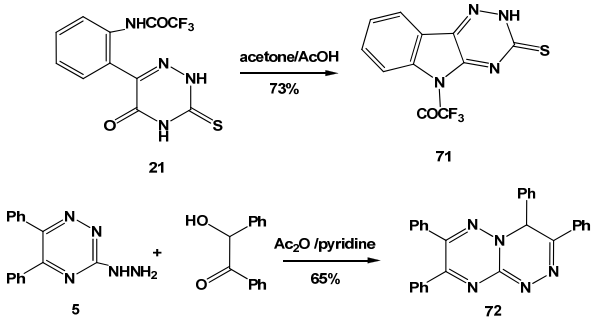
Scheme 19

Treatment of 3-thioxo-1,2,4-triazin-5-ones (**21**) with hydrazine hydrate was studied in different solvents [32]. Thus, when the reaction carried out on cold ethanol, 5-hyrazino derivatives (**67**) was obtained, while on warming isopropanol produced 3-hydrazino derivative (**68**). Refluxing **67** and **68** with CS_2 in KOH solution afforded the isomeric structures **69** and/or **70**, respectively (Scheme 20).



Scheme 20

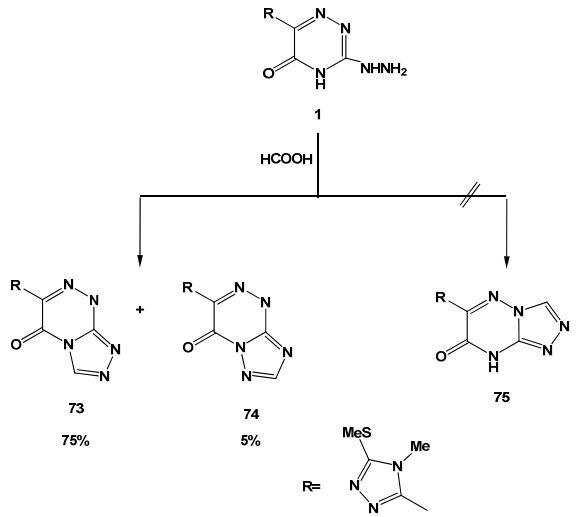
5-Trifluoroacetyl-3-thioxo-1,2,4-triazino[5,6-*b*]indole (**71**) [20] was obtained from boiling compound **21** with acetone in acetic acid, while refluxing **5** with benzoin in the presence of Ac_2O/pyridine yielded 1,2,4-triazino[4,3-*b*][1,2,4]triazine (**72**) (Scheme 21) [32].



Scheme 21

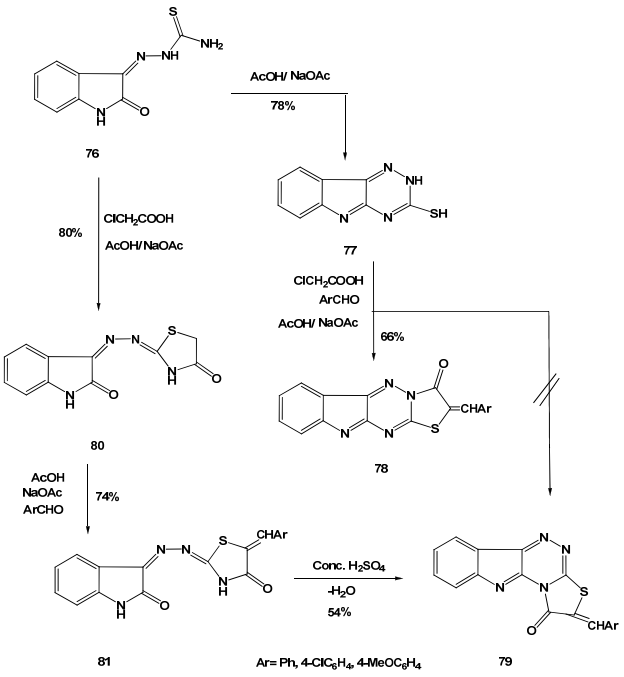
Cyclization of 3-hydrazino-6-(4-methyl-3-methylthio-1,2,4-triazol-5-yl)-1,2,4-triazin-5-one (**1**) in the presence of HCOOH led to the formation of a mixture **73** and **74** and not the corresponding isomer **75** (Scheme 22) [33].

Abdel-Rahman *et al.* [34], reported the role of medium in the orientation of cyclization reactions. Thus, reaction of isatin-3-thiosemicarbazone (**76**) with glacial acetic acid in the presence of freshly fused sodium acetate yielded 5*H*-1,2,4-triazino[5,6-*b*]indole-3-thione (**77**) which reacted with chloroacetic acid and ArCHO in presence of Ac_2O-AcONa to afford 2-arylidene-3-oxo-triazolo[3,2-*b*][1,2,4]triazino[5,6-*b*]indoles (**78**) and not (**79**) (Scheme 23).



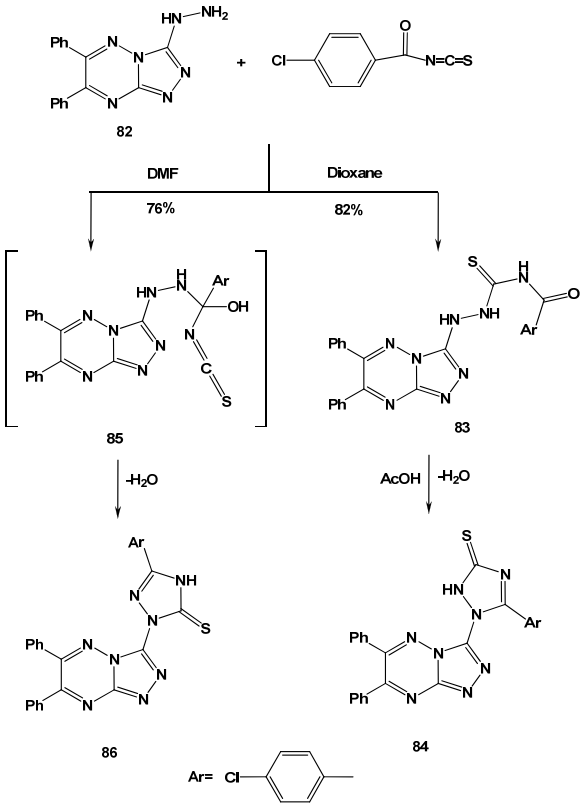
Scheme 22

The isomeric structure **79** was obtained from refluxing **76** with chloroacetic acid in Ac_2O-AcONa to give 3-[2-(4-thiazolidinone)diazo]indol-2-one (**80**) which condensed with ArCHO in AcOH/NaOAc to yield the arylidene (**81**). Heterocyclization of **81** *via* treatment with concentrated H_2SO_4 gave 2-arylidene-3-oxothiazolo[2,3-*c*][1,2,4]triazino[5,6-*b*] indole (**79**) (Scheme 23) [35].



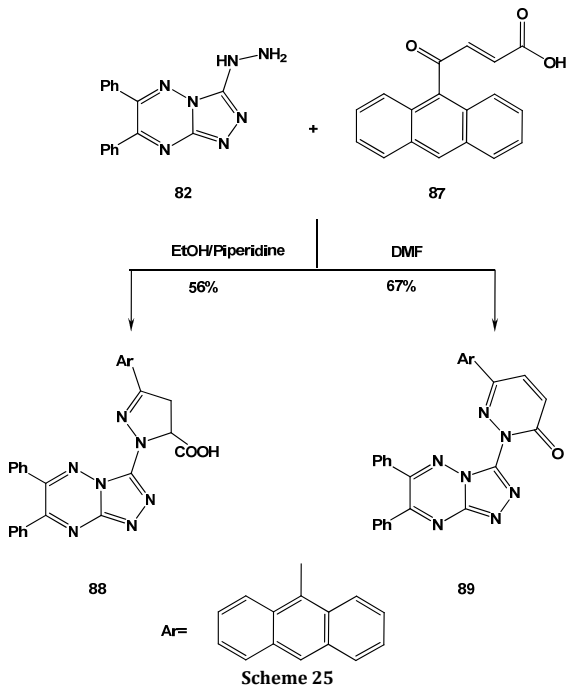
Scheme 23

Treatment of 3-hydrazino-1,2,4-triazolotriazine (**82**) with aroyl isothiocyanate in dioxane yielded 4-aroylthiosemi carbazido derivative (**83**) which on refluxing in glacial acetic acid produced 1-(6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4] triazin-3-yl)-5-(4-chlorophenyl)-1,2,4-triazole-3(2*H*)thione (**84**) [36]. When the reaction was carried out in polar solvent as DMF, the isomeric structure **86** was directly produced *via* intermediate 85 (Scheme 24).



Scheme 24

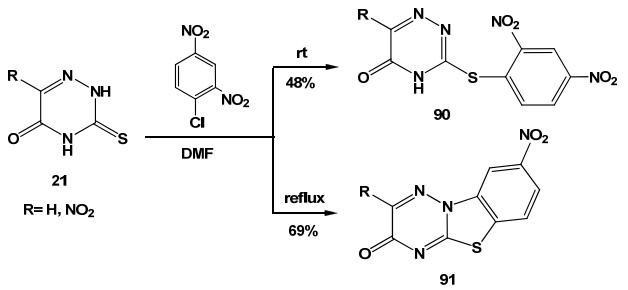
The greater reactivity of the α,β-unsaturated keto acid (**87**) towards the nucleophilic 3-hydrazinotriazolotriazine derivative (**82**) was depended on the solvent [37]. Refluxing compounds **82** and **87** in ethanol containing few drops of piperidine yielded 1-(6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazin-3-yl)-3-(anthracen-10-yl)-5-carboxy-4,5-dihydropyrazoline (**88**) while when the reaction was carried out in boiling DMF produced 1-(6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazin-3-yl)-3-(anthracen-10-yl) pyridazin-6-one (**89**) (Scheme 25) [38].



Scheme 25

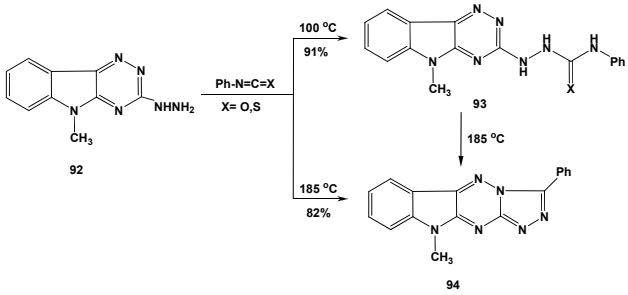
4. Temperature effect

The effect of temperature on the orientation of cyclization reactions was observed in many reactions of functionalized 1,2,4-triazines. Reaction of **21** with 2,4-dinitro-chlorobenzene at room temperature in DMF afforded 3-[(2,4-dinitrophenyl)thio[4,5-dihydro-6-phenyl-1,2,4-triazin-5(4H)-ones (**90**) while when the reaction took place in refluxing DMF gave 1,2,4-triazino[3,2-*b*]benzothiazolones (**91**) was obtained (Scheme 26) [39].



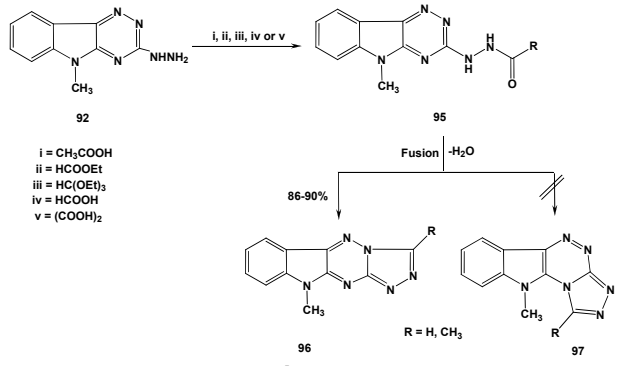
Scheme 26

Reaction of 3-hydrazino-5-methyl-1,2,4-triazino[5,6-*b*]indole (**92**) with phenyliso (isothio)cyanate at 100 °C afforded phenyl(thio)semicarbazide **93**. Heating the later compounds above their melting points gave only one product namely, 1,2,4-triazolo [4`,3`:2,3][1,2,4]triazino[5,6-*b*]indole (**94**). Compound **94** was also obtained directly when the reaction of **92** with phenyliso(isothio)cyanate took place at 185 °C (Scheme 27) [40].



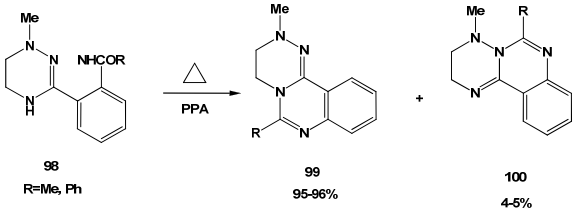
Scheme 27

3-Hydrazinoindolotriazine derivative (**92**) underwent sterically controlled regiospecific heterocyclization with a variety of one carbon cyclizing agents to give the sterically more favored linearly annulated 10-methyl-1,2,4-triazolo[4`,3`:2,3][1,2,4]triazino[5,6-*b*]indoles (**96**) by fusion of the hydrazide derivatives (**95**) above their melting point. The angular isomer **97** was not isolated (Scheme 28) [40].



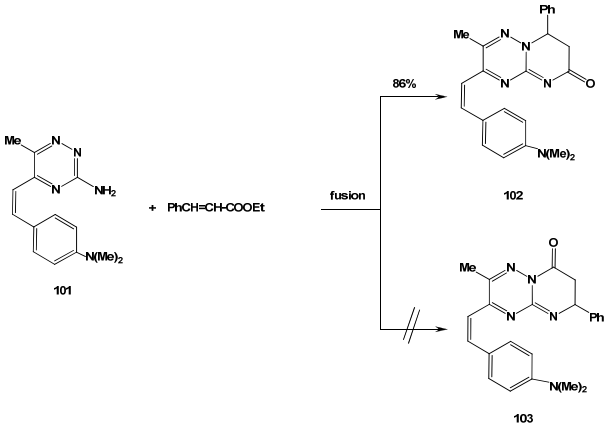
Scheme 28

Cyclization of **98** using polyphosphoric acid yielded 1,2,4-triazinoquinazolines (**99**) with a small amount of **100** as by-product (Scheme 29) [41].



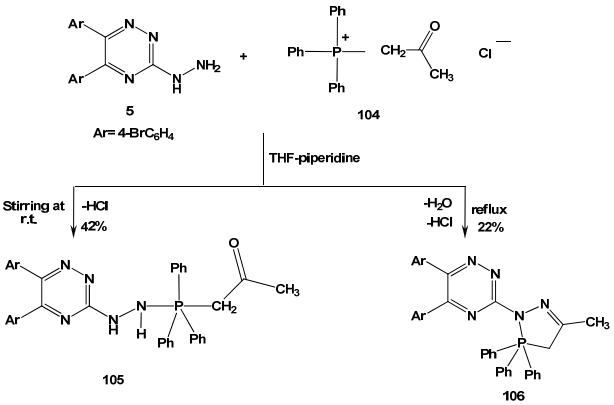
Scheme 29

Interestingly, Abdel-Rahman *et al.* [42], found that 3-amino-1,2,4-triazine derivative (**101**) on fusion with ethyl cinnamate led to the direct formation of 3,4-dihydro-4-phenyl-7-methyl-8-(4-dimethyl-aminostyryl)-pyrimido[3,2-*d*]triazin-2-one (**102**) and not the isomeric product **103** which due to high temperature led to a facile eliminate EtOH followed by addition of N-2 on CH=CH and not vice versa (Scheme 30).



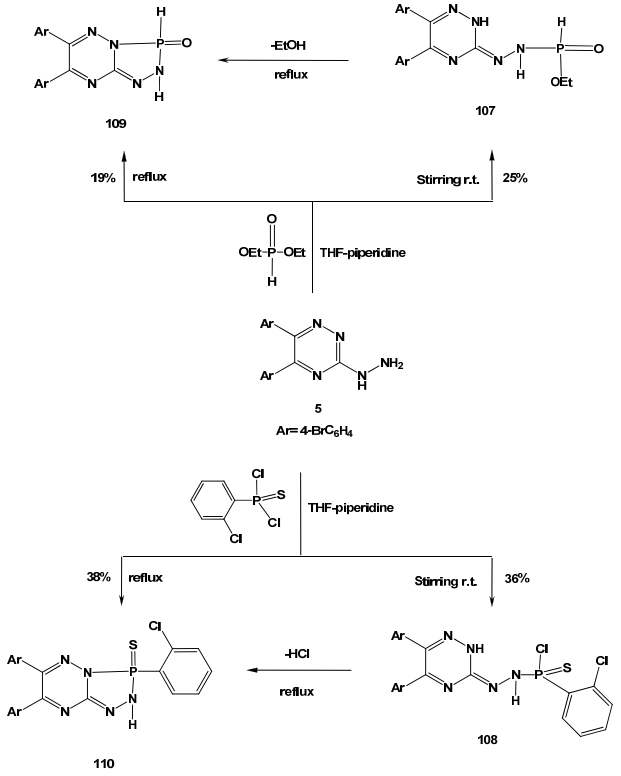
Scheme 30

A facile route to synthesis of isolated and/or fused heterobicyclic systems containing phosphorus atom and 1,2,4-triazine moiety were obtained by Ali *et al.* [43]. Thus, treatment of **5** (Ar=4-BrC_6H_4) with acetonyl triphenylphosphonium chloride (**104**) under stirring in THF and few drops of piperidine for 24 hours at room temperature achieved 1-{2-[5,6-*bis*(4-bromophenyl)-1,2,4-triazine-3-yl]hydrazino](triphenylphosphoranyl)}acetone (**105**), while repeat this reaction under reflux led to the formation of 5,6-*bis*(4-bromophenyl)-3-[(3,3,3-triphenyl]-5-methyl-3,4-dihydro-2*H*-1,2,3-λ^5-diazophosphol-2-yl]-1,2,4-triazine (**106**) (Scheme 31).



Scheme 31

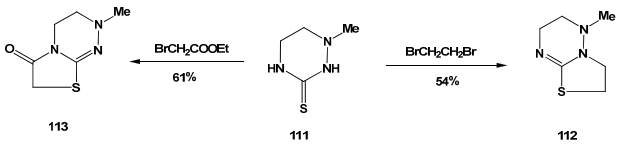
One of the most important of the orientation cyclization reactions of 3-hydrazino-1,2,4-triazine **5** was produced by its treatment with diethyl phosphite and 2-chlorophenyl-dichlorothiophosphate in THF containing few drops of piperidine at room temperature yielded the phosphonohydrazide (**107**) and phosphonohydrazidothioic acid (**108**), respectively. The same reactions under refluxing led to the direct formation of the 1,2,4,3-triazaphospholo [4,5-*b*][1,2,4]triazine derivatives (**109**) and (**110**), respectively, which also were obtained by refluxing of **107** and **108** in THF containing few drops of piperidine (Scheme 32) [43].



Scheme 32

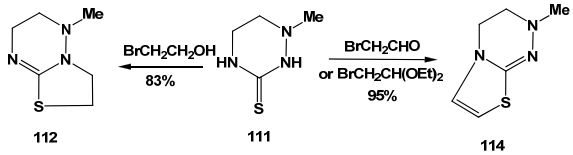
5. Chemoselective Orientation of Cyclization:

Trepamier *et al.* [44] reported that allowing 1,4,5,6-tetrahydro-1-methyl-1,2,4-triazin-3 (2*H*)-thione (**111**) to react with 1,2-dibromoethane and ethyl bromoacetate yielded 2,3,6,7-tetrahydro-5-methyl-5*H*-thiazolo[3,2-*b*][1,2,4]triazine (**112**) and 3,4-dihydro-2-methyl-2H-thiazolo[2,3-c][1,2,4]tri azin-6-(7*H*) one (**113**), respectively (Scheme 33) [41].



Scheme 33

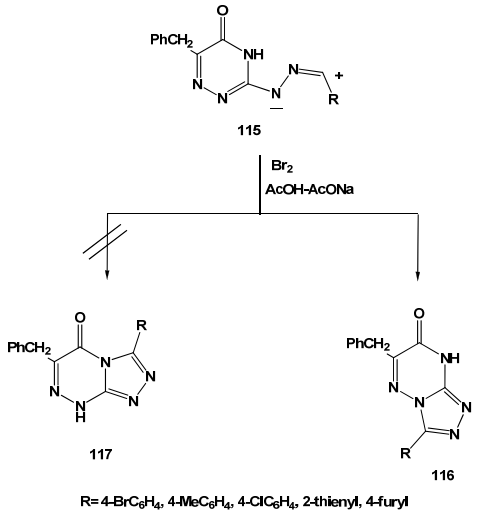
As extension of this study, reaction of **111** with bifunctional compounds in which, one of the functionalized carbon was sp^3 and the other were sp^3, sp^2 or sp, indicated that initially the sulfur atom of the 1,2,4-triazinethione attacked sp^3 carbon followed by ring closure at N^2 of the 1,2,4-triazinethione. When both the α and β-carbons of the α,β-bifunctional reactant were sp^3, the thiazolo[3,2-*b*][1,2,4]triazine (**112**) was produced, while if α-carbon is sp^3 and the β-carbon was either sp^2 or sp, the thiazolo[2,3-*c*][1,2,4]triazine (**114**) was produced (Scheme 34) [41].



Scheme 34

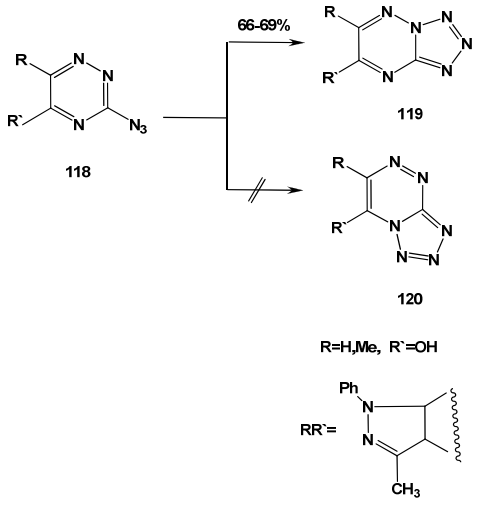
6. Regioselectivity of electrocyclization:

Regioselectivity in 1,5-electrocyclization of *N*-[1,2,4-triazin-3-yl]nitrilimines (**115**) was studied by Shawali *et al.* [45]. Thus, 1,5-electrocyclization of such nitrilimines (**115**) provided 1,2,4-triazolo[4,3-*b*][1,2,4]triazin-7-(8*H*)-ones (**116**) in overall good yields 78-84% and not 1,2,4-triazolo[3,4-*c*][1,2,4]triazin-5-(7*H*)-ones (**117**) (Scheme 35). This indicated that in 1,2,4-triazin-5(4H)-ones the presence of N-1 atom increases the basicity of N-2 in relation to N-4 which is situated between two electron-deficient carbon atoms, and thus the N-2 is more nucleophilic than N-4.



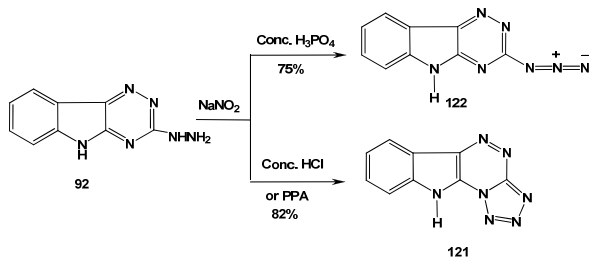
Scheme 35

Cyclization of 3-azido-1,2,4-triazines (**118**) in boiling ethanol afforded linear product, tetrazolo[4,5-*b*][1,2,4]triazines (**119**), and not the angular isomer **120** (Scheme 36) [46,47]. The reaction proceeds through ring closure towards the N-2 atom rather than N-4 atom.



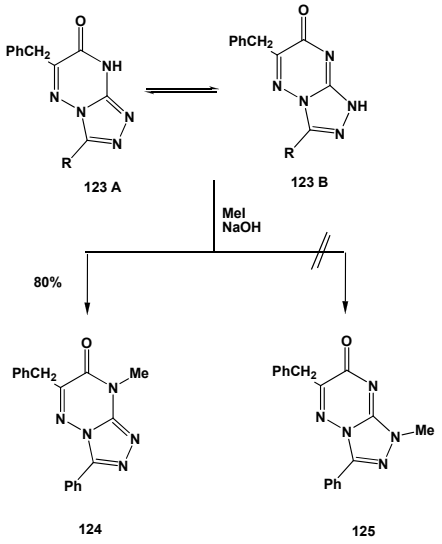
Scheme 36

Joshi *et al.* [48] reported that reaction of 3-hydrazino-1,2,4-triazino[5,6-*b*]indole (**92**) with nitrous acid (prepared from sodium nitrite/polyphosphoric acid or HCl) gave 10*H*-tetrazolo[5`,1`:3,4][1,2,4]triazino [5,6-*b*]indole (**121**), but when compound **92** reacted with nitrous acid (prepared from sodium nitrite/phosphoric acid) yielded the azide **122** (Scheme 37).



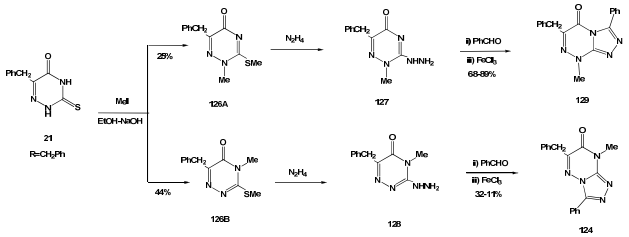
Scheme 37

Treatment of compound **123** with methyl iodide in ethanolic NaOH solution yielded product **124** and not **125**. The predominance of the form **124** is compatible with Clar`s rule which is used to interpret the relative stability of the fused heterocyclic isomers [49,50]. The form **124** having one Clar`s circle more than the other form **125** is expected to be more stable as it has higher degree of aromatic stability (Scheme 38).



Scheme 38

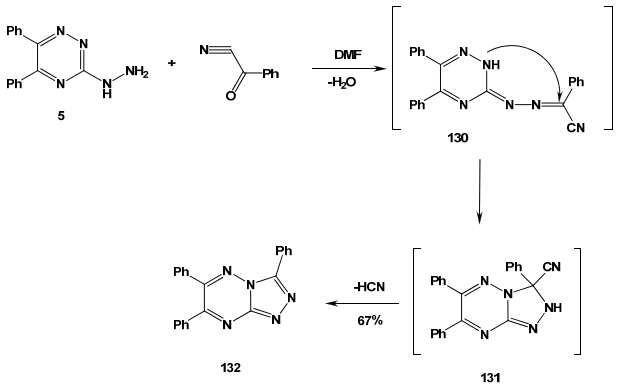
Methylation of **21** in ethanolic NaOH solution afforded a mixture of **126A** and **126B**, which on hydrazinolysis produced hydrazines **127** and **128**, respectively. Cyclocondensation of **127** and **128** *via* condensation with benzaldehyde followed by treatment with $FeCl_3$ furnished **129** and **124**, respectively (Scheme 39) [45].



Scheme 39

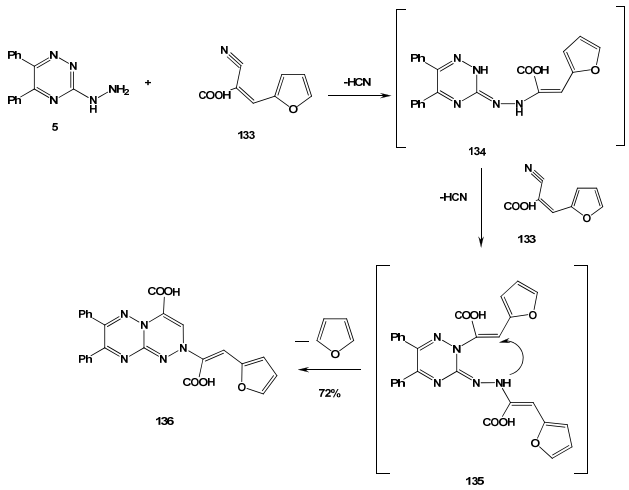
7. Preferring cite of ring closure

Some recent articles [51,52] reported the high reactivity of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (**5**) as a nucleophilic electron donor towards different types of electron acceptors activated carbonitriles in boiling DMF as a strongly polar aprotic solvent. Thus, refluxing **5** with 2-oxophenyacetonitrile [52] in DMF yielded 3,6,7-triphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (**132**) *via* nucleophilic attack of compound **5** to 2-oxophenyl-acetonitrile with losing one molecule of water followed by ring closure reaction by losing one molecule of HCN (Scheme 40).



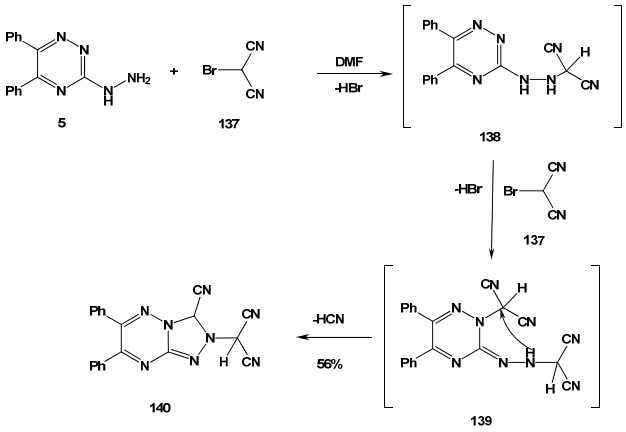
Scheme 40

Treatment of compound **5** with 2-cyano-3-(furan-2-yl)prop-2-enoic acid (**133**) in boiling DMF yielded 2-[1-carboxy-2-(furan-2-yl)ethenyl]-7,8-diphenyl-2*H*-[1,2,4]triazino [4,3-*b*] [1,2,4]triazine-4-carboxylic acid (**136**). Compound **136** was formed *via* nucleophilic attack of **5** towards **133** to give the nonisoable intermediate **134** which underwent another nucleophilic attack of N-2 of 1,2,4-triazine moiety to give the intermediate **135** followed by addition-elimination reaction through attack of NH of hydrazone (**135**) at C=C by losing one molecule of furan as depicted in Scheme 41 [51].



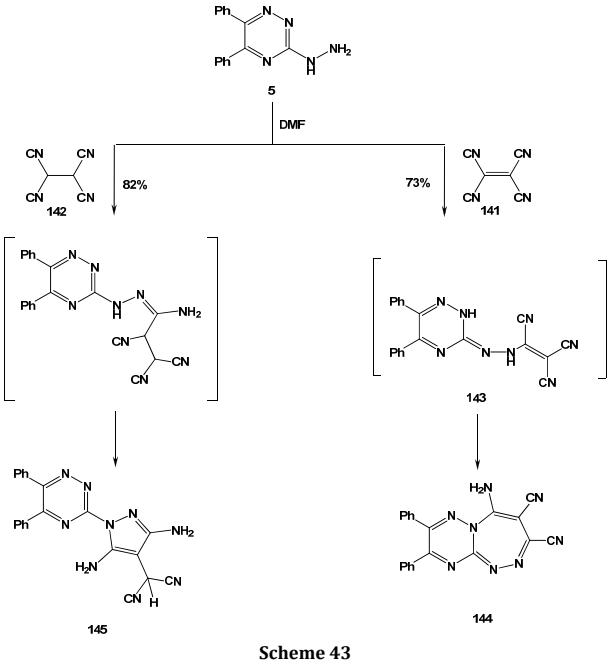
Scheme 41

Similarly [51], refluxing compound **5** with α–bromomalononitrile (**137**) in boiling DMF afforded 2-dicyanomethyl-3-cyano-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (**140**) *via* nucleophilic attack of **5** towards two molecules of **137** with losing two molecules of HBr followed by one molecule of HCN (Scheme 42).



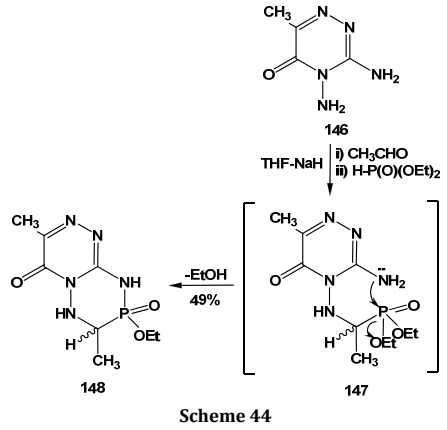
Scheme 42

It is interesting that, the behavior of **5** towards tetracyanoethylene (**141**) and tetracyanoethane (**142**) is different in the route of attack and ring closure reactions. Thus, boiling compound **5** with **141** in DMF furnished 3-amino-8,9-diphenyl[1,2,4]triazino[3,2-*c*] [1,2,4]triazepine-4,5-dicarbo nitrile (**144**), while treatment of **5** with **142** under the same conditions [53] yielded 1-(5,5-diphenyl-1,2,4-triazin-3-yl)-3,5-diamino-4-dicyanomethyl-pyrazoline (**145**). Formation of **144** was occurred *via* nucleophilic attack of NH_2 of the hydrazine group on **141** to remove HCN , followed by heterocyclization *via* addition of N-2 of triazine moiety on the nitrile group, while formation of **145** was occurred through addition of hydrazine group on two geminal nitrile groups of **142** (Scheme 43) [51].



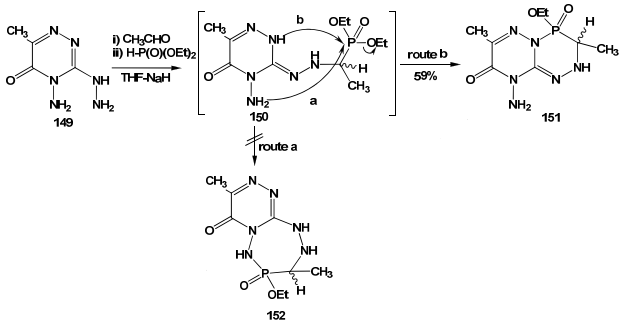
Scheme 43

The Kabachnik-Fields reaction using 3,4-diamino-6-methyl-1,2,4-triazin-5(4*H*)-one (**146**), acetaldehyde and diethyl phosphite in THF 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 **148**. The reaction occurred by condensation of NH_2 at position 4 that is more basic than NH_2 at position 3, with acetaldehyde followed by addition of diethyl phosphite then cyclization by removing one molecule of ethanol (Scheme 44) [2].



Scheme 44

Also, the one-pot Kabachnik-Fields reaction of compound **149**, acetaldehyde and diethyl phosphite in THF containing sodium hydride as a catalyst produced one isomer of 1,2,4-triazino[3,2-*c*][1,2,4,5]triazaphosphinine (**151**), likely through the nonisolable intermediate **150**, which spontaneously cyclized through *N–2* of the triazine ring and not the exocyclic *N*-amino group, with elimination of one molecule of ethanol (route b, Scheme 45) [2].



Scheme 45

Conclusion

In this review, we have focused on the factors which affect most on the orientation of heterocyclization reactions of functionalized 1,2,4-triazines. From the results described in this review, these effects are: effect of substituents in 1,2,4-triazine moieties, type of the solvent used in the reaction, the temperature effect, chemoselective cyclization, regioselectivity of electrocyclization and preferring cite of ring closure.

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