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

Reda Mohammady Abdel-Rahmana, Mohammed Saleh Tawfik Makkiab, Tarik El-Sayed All, and Magdy Ahmed Ibrahimb

*Corresponding author: Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, 11711, Cairo, Egypt. Tel.: +200103730144; fax: +2022581243. E-mail address: tarik_elayed1975@yahoo.com (T.E. Ali).

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 processes 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 (HCO2H or AcOH) or neutral [HC(OEt)3 or MeC(OEt)3] media. On the other hand, when R was an electron donating group and the reagent was acidic (HCO2H 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).

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 Cs2 in KOH yielded 6,7-diphenyl-3-mercapto-8-methyl-7H-triazolo[4,3-b][1,2,4]triazine (10) (Scheme 3) [16].
Effect of electron donating or attracting substituents in the orientation of cyclization reactions was clearly appeared freely. Thus, reaction of 8-substituted-5H-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-triazine[5,6-b]indole (15) and not the angular isomer 16. The unequivocal synthesis of the latter was accomplished by reaction of 5-isopropylsulfinic-3-thiosemicarbazone (17) with 1,2-dibromoethane (Scheme 4) [18].

Alkylation of 6-aryl-1-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].

Treatment of 24 with ammonium thiocyanate in EtOH/HCl produced 25, which was reacted with CsOH 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].

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-5H-thiazolo[2,3-c][1,2,4]triazin-3(2H)-one (29) and not the isomeric structure 30 (Scheme 8) [22].

Alkylation of 1,2,4-triazinethione 21 (R=Me) using bromomalononitrile and ethyl bromocyanocacetate 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].
Selective transformation of 3-prop-3-ythithio-1,2,4-triazin-5(2H)-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].

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].

Also, hydrazinolysis of 39 using N-acetylhydrazine yielded the 1H-4,5-diphenyl-5H-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.

A simple nucleophilic displacement of S-atom in 4-amino-3-mercaptop-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-substitutedaminotriazino-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].

On the other hand, the reactivity of compound 42 towards both nuclophilic and electrophilic reagents in different medium have been reported [28] where the nucleophilicity increase in order $>$ 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$_2$SO$_4$ afforded 1,2,4-triazino[3,4-b][1,3,4]thiadiazine-4,8-dione (49) (Scheme 14) [26].

Cyclocondensation of aminotriazine (50) with $\alpha$-bromoketones (R$^1$=H, Ph, R$^4$=p-PhC$_6$H$_4$) in DMF or isopropanol gave imidazo[1,2-b][1,2,4]triazine derivatives (52) (Scheme 15) [27].
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]triazine (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 (158), while a simple nucleophilic attack of primary amine on the 5-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-7H-triazolo[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 CS2 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 acetonitrile in acetic acid, while refluxing 5 with benzoin in the presence of AcO/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 5H-1,2,4-triazino[5,6-b]indole-3-thione (77) which reacted with chloroacetic acid and ArCHO in presence of Ac2O-AcONa to afford 2-aryldiene-3-oxo-triazolo[3,2-b][1,2,4]triazino[5,6-b]indoles (78) and not (79) (Scheme 23).
The isomeric structure 79 was obtained from refluxing 76 with chloroacetic acid in Ac₂O-AcONa to give 3-[2-(4-thiazolidinone)diazol]indol-2-one (80) which condensed with ArCHO in AcOH/NaOAc to yield the arylidene (81). Heterocyclization of 81 via treatment with concentrated H₂SO₄ gave 2-arylidene-3-oxothiazolo[2,3-][1,2,4]triazino[5,6-b]indole (79) (Scheme 23) [35]. The greater reactivity of the α,β-unsaturated keto acid (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].

Treatment of 3-hydrazino-1,2,4-triazotriazine (82) with aroyl isothiocyanate in dioxane yielded 4-aryltiosemicarbazido 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(2H)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).
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].

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


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

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

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

A facile route to synthesis of isolated and/or fused heterocyclic systems containing phosphorus atom and 1,2,4-triazine moiety were obtained by Ali et al. [43]. Thus, treatment of 5 (Ar=4-BrC₆H₄) with acetonil 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][triphenylphosphoranyi]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-2H,2,3,5-5-diazophosphol-2-yl]-1,2,4-triazine (106) (Scheme 31).
One of the most important of the orientation cyclization reactions of 3-hydrazone-1,2,4-triazine \( S \) 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 phosphonohydrazidotriodo 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].

\[
\begin{align*}
\text{Scheme 32}
\end{align*}
\]

5. Chemoselective Orientation of Cyclization:

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

\[
\begin{align*}
\text{Scheme 33}
\end{align*}
\]

As extension of this study, reaction of 111 with bifunctional compounds in which, one of the functionalized carbon was sp³ and the other were sp³, sp² or sp, indicated that initially the sulfur atom of the 1,2,4-triazinethione attacked sp³ carbon followed by ring closure at N⁰ of the 1,2,4-triazinethione. When both the \( \alpha \) and \( \beta \)-carbons of the \( \alpha, \beta \)-bifunctional reactant were sp³, the thiazolo[3,2-b][1,2,4]triazine (112) was produced, while if \( \alpha \)-carbon is sp³ and the \( \beta \)-carbon was either sp³ or sp, the thiazolo[2,3-c][1,2,4]triazine (114) was produced (Scheme 34) [41].

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-(8H)-ones (116) in overall good yields 78-84% and not 1,2,4-triazolo[3,4-c][1,2,4]triazin-5-(7H)-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.

\[
\begin{align*}
\text{Scheme 35}
\end{align*}
\]

Cyclization of 3-azido-1,2,4-trazines (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.

\[
\begin{align*}
\text{Scheme 36}
\end{align*}
\]
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 10H-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).

Methylation of 21 in ethanolic NaOH solution afforded a mixture of 126A and 126B, which on hydrazinolysis produced hydrazines 127 and 128, respectively. Cydocondensation of 127 and 128 via condensation with benzaldehyde followed by treatment with FeCl₃ furnished 129 and 124, respectively (Scheme 39) [45].

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. Cydocondensation of 127 and 128 via condensation with benzaldehyde followed by treatment with FeCl₃ furnished 129 and 124, respectively (Scheme 39) [45].

Whether 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-2H-[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 nonisolable 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=O by losing one molecule of furan as depicted in Scheme 41 [51].

Scheme 39

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 40

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-oxophenacyanitriile [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).
It is interesting that, the behavior of 5 towards tetracyanoethylene [141] and tetracyanoethylene [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-dicarboximide [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 NH₂ 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 with N-2 of triazine moiety on the nitrile group, while treatment of 141 with sodium hydride as a catalyst produced only one isomer of 1,2,4-triazino[3,2-c][1,2,4,5]triazaphosphinine derivative [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].

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.

References

[52]. Volovensko, Y. M.; Resnyanskaya; E. V. Mendeleev Commun. 2002, 12, 119-120.