HETEROCYCLIZATION WITH SOME HETEROCYCLIC DIAMINES: SYNTHETIC APPROACHES FOR NITROGEN BRIDGEHEAD HETEROCYCLIC SYSTEMS

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Abstract – This review represents the methods developed for the synthesis of a variety of nitrogen bridgehead heterocyclic systems such as [1,2,4]triazolo[1,5-a]pyridines, pyrido[1,2-b][1,2,4]triazines, pyrido[1,2-b][1,2,4]triazepines, pyrazolo[1,5-b][1,2,4]triazole, pyrazolo[1,5-b][1,2,4]triazine, pyrazolo[1,5-b][1,2,4]triazepine, [1,2,4]triazolo[3,4-b][1,2,4]triazine, [1,2,4]triazolo[4,3-b][1,2,4]triazepines, pyrimido[3,4-b][1,2,4]triazine from the heterocyclization of some heterocyclic diamines with a variety of electrophilic reagents.

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1. INTRODUCTION

o-Diamines are very active substrates for building of various heterocyclic systems, and are largely used in formation of complexes. In symmetrical diamines, the product will be the same irrespective of which amine participates first in the reaction. In the case of unsymmetrical diamines, the substituents influence the initial participation of a particular amino group in the reaction, resulting in chemoselective products. The electron withdrawing/donating nature of substituents in diamine influences the nucleophilicity of the amino groups. The present review article concise on the utilities of heterocyclic diamines in heterocyclic synthesis via reactions with a large numbers of electrophilic reagents.

2. Heterocyclization with diaminopyridones

Polyfunctional pyridines are highly reactive reagents that have been used extensively in heterocyclic synthesis, and possess biological as well as pharmacological activities. [1,2,4]Triazolo[1,5-a]pyridines, pyrido[1,2-b][1,2,4]triazines and pyrido[1,2-b][1,2,4]triazepines are also interesting compounds due to their pronounced biological importance. o-Diaminopyridone derivatives are widely used in the synthesis of a variety of nitrogen bridgehead triazolo[1,5-a]pyridines, pyrido[1,2-b][1,2,4]triazines and pyrido[1,2-b][1,2,4]triazepines via heterocyclization of o-diaminopyridones with some mono electrophilic reagents, α,β-bifunctional and α,γ-bifunctional electrophiles, respectively.

2.1. Synthesis of o-diaminopyridones

Refluxing alcoholic solution of 2-cyanoacetohydrazide (1) with arylmethyldinemalononitriles 2 (X=CN) and ethyl 3-cyano-2-(aryl)-prop-2-enoates 2 (X=CO2Et), in the presence of a few drops of piperidine as a catalyst, produced 4-(aryl)-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles 3 (X=CN) and ethyl 1,2-diamino-5-cyano-4-(aryl)-6-oxo-1,6-dihydropyridine-3-carboxylates 3 (X=CO2Et), respectively (Scheme 1). This method is a rapid and common for the synthesis of o-diaminopyridine derivatives. The proposed mechanism for formation of compounds 3 is depicted in Scheme 2. Also, 3-cyano-1,6-diaminopyridine derivatives 5 possessing various alkoxycarbonyl groups were prepared directly from the reaction of 2-cyanoacetohydrazide (1) with dialkyl 2,3-dicyanobutenedionates 4 (Scheme 3). The 1H NMR spectrum is a good tool to differentiate between the nucleophilicity of the two amino groups in the diaminopyridine derivatives 3 and 5. The 1H NMR spectra usually showed two exchangeable signals in the range δ 4.61-5.70 ppm and 8.30-10.78 ppm characteristic for the (N-NH2) and (C-NH2) protons, respectively. These results indicate the difference in nucleophilicity between the two amino groups. Thus, the hydrazide β-nitrogen (N-NH2) is more nucleophilic and reacted more rapidly with the electron deficient carbon than the amino group at carbon atom (C-NH2).
2.2. Synthetic approaches for [1,2,4]triazolo[1,5-a]pyridines

[1,2,4]Triazolo[1,5-a]pyridines constitute an important class of heterocyclic systems due to their variable biological activities including antifungal,\textsuperscript{19} antimicrobial,\textsuperscript{20} antitumor,\textsuperscript{21,22} analgesic, anti-inflammatory,\textsuperscript{23} and antiviral activity.\textsuperscript{24} Different methods are reported for the synthesis of 1,2,4-triazolo[1,5-a]-
pyridines, the most common one is the condensation of $o$-diaminopyridones 3 or 5 with mono electrophilic reagents. Thus, 7-(aryl)-5-oxo-1H-4,5-dihydro[1,2,4]triazolo[1,5-a]pyridine derivatives 6 were prepared by heterocyclization of 4-aryl-1,6-diaminopyridones 3 with formic acid, ethyl formate, or triethyl orthoformate (Scheme 4).

![Scheme 4](image)

4-Aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile 3 reacted with $N$-ethoxy-methylenebenzohydrazide in isopropanol to give [1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile 6 which reacted with benzohydrazide to give triazolopyridones 7 and 7-aryl-6,8-bis(5-phenyl-4H-1,2,4-triazol-3-yl)-4,5-dihydro-1H-[1,2,4]triazolo[1,5-a]pyridine-5-ones 8 (Scheme 5).

![Scheme 5](image)

Refluxing diaminopyridone 3 with acetyl chloride and benzoyl chloride in boiling DMF produced...
7-(4-chlorophenyl)-5-oxo-1H-4,5-dihydro-2-(methyl/phenyl)[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles 9 (Scheme 6). Also, compounds 9 (R=Me) were prepared by the reaction of diaminopyridones 3 with acetic anhydride (Scheme 6).

On the other hand, 1-acetyl-7-(6-chloro/methyl-4-oxo-4H-chromon-3-yl)-2-methyl-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles 10 were prepared by heterocyclization of diaminopyridone derivatives 3 with acetic anhydride (Scheme 7).

2-Substituted[1,2,4]triazolo[1,5-a]pyridine derivatives 11 was prepared in high yield by cyclocondensation of 3-cyano-1,6-diaminopyridone derivatives 5 with carboxylic acid orthoesters such as triethyl orthoformate or triethyl orthoacetate (Scheme 8).
Diaminopyridones 3 reacted with triethyl orthoformate and triethyl orthoacetate as cyclizing and alkylating agent in acetonitrile to give the unexpected 3-ethyl[1,2,4]triazolo[1,5-a]pyridine derivatives 12 (Scheme 9).39

\[ \text{Ar}= 2\text{-furyl} \]
\[ \text{R}= \text{H, Me} \]

Scheme 9

1,6-diaminopyridones 3 reacted with aromatic aldehydes in refluxing methanol in the presence of catalytic amount of sulfuric acid to give 7-aryl-2-(4-fluorophenyl)-5-oxo-1,5-dihydro-1H-[1,2,4]-triazolo[1,5-a]pyridine-6,8-dicarbonitrile 13 (Scheme 10).38,39

\[ \text{Ar}= 4\text{-ClC}_6\text{H}_4, 4\text{-O}_2\text{NCC}_6\text{H}_4 \]

Scheme 10

Cyclocondensation of 1,6-diaminopyridone 3 with 6-chloro-3-formylchromone 14 in DMF under reflux containing few drops of piperidine afforded the [1,2,4]triazolo[1,5-a]pyridine derivative 15. Oxidation of the latter compound by ferric chloride in boiling dimethyl sulfoxide (DMSO) yielded 2,7-bis(6-chloro-4-oxo-4H-chromen-3-yl)-5-oxo-1,5-dihydro-1,2,4-triazolo[1,5-a]pyridine-6,8-dicarbonitrile 16.36 Compound 16 was also obtained by refluxing compound 3 with 6-chlorochromone-3-carboxylic acid 17 in phosphoryl chloride (Scheme 11).40

7-(2-Furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-a]pyridine derivatives 18 were prepared by the reaction of diaminopyridones 3 with ethyl chloroformate in boiling DMF (Scheme 12).39

Refluxing 1,6-diaminopyridone 3 with carbon disulfide in ethanolic KOH yielded 2-thioxo[1,2,4]-triazolo[1,5-a]pyridine-6,8-dicarbonitrile 19,41 which oxidized by FeCl₃/EtOH to give 7,7-di(4-chlorophenyl)-5,5-dioxo-1,1,5,5-tetrahydro-2,2-dithio-di[1,2,4]triazolo[1,5-a]pyridine-6,6,8,8-tetracarbonitrile 20 (Scheme 13).35
Scheme 11

The diaminopyridone derivative 3 reacted with carbon disulfide in ethanol KOH solution under reflux to yield [1,2,4]triazolo[1,5-a]pyridine derivative 19 which reacted with chloroacetic acid, oxalyl chloride, chloroacetonitrile and bromomalonitrile to produce the corresponding thiazolo[3,2:2,3][1,2,4]triazolo-[1,5-a]pyridines 31-34, respectively (Scheme 14).42

Also, reaction of 1,6-diaminopyridone 3 with triphenylphosphine gave 1-amino-6-(triphenylphosphoranylideneamino)-2-oxo-4-phenyl-1,2-dihydro-pyridine-3,5-dicarbonitrile-iminophosphorane 25 which reacted with carbon disulfide in dry toluene to give compound 19. The latter compound
reacted with aromatic aldehydes, chloroacetic acid and fused sodium acetate in acetic acid/acetic anhydride to give 2-(4-substitutedbenzylidene)-3,6-dioxo-8-phenyl-3,6-dihydro-2H-thiazolo[3,2:2,3]-[1,2,4]triazolo[1,5-α]pyridine-7,9-dicarbonitrile 26 (Scheme 15). 43

![Scheme 14](image1)

**Scheme 14**

Reaction of diaminopyridone 3 with anthranilic acid in phosphoryl chloride gave ethyl 2-(2-amino-phenyl)-6-cyano-7-(4-methoxyphenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-α]pyridine-8-carboxylate 27 which reacted with formic acid, acetyl chloride, chloroacetyl chloride, ethyl chloroformate and

![Scheme 15](image2)

**Scheme 15**
carbon disulfide to give the corresponding pyrido[1,2:2,3][1,2,4]triazolo[1,5-c]quinazoline derivatives 28-32, respectively (Scheme 16).42

Scheme 16

2-(2-Benzoylaminophenyl)-7-(4-chlorophenyl)-5-oxo-1H-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile 35 was obtained from the reaction of diaminopyridone 3 and 2-phenyl-4H-3,1-benzoazin-4-one 33, via the non isolable intermediate 34 (Scheme 17).44

Scheme 17
2.3. Synthetic approaches for pyrido[1,2-b][1,2,4]triazines

4-Aryl-1,6-diamino-1,2-dihydropyridine-3,5-dicarbonitriles 3 were efficiently used for preparation of nitrogen bridgehead pyrido[1,2-b][1,2,4]triazines. Thus, the isomeric structures of pyrido[1,2-b]-[1,2,4]triazine-7,9-dicarbonitrile derivatives 36 and 37 have been obtained from condensation of diaminopyridones 3 with chloroacetic acid and chloroacetyl chloride in refluxing DMF. Also, heterocyclization of diaminopyridones 3 with dibromoethane and phenacyl bromide in basic media gave pyrido[1,2-b][1,2,4]triazine-7,9-dicarbonitriles 38 and 39, respectively (Scheme 18).45

Scheme 18

Condensation of diaminopyridone 3 with 5,6-diphenyl-3-mercapto-1,2,4-triazine 40 gave N-(triazinylamino)pyridine derivative 41. Heterocyclization of compound 41 with chloroacetic acid, chloroacetyl chloride, 1,2-dibromoethane, phenacyl bromide, diethyl oxalate, and α,β-unsaturated oxoacid 42 led to the direct formation of the pyrido[1,2-b][1,2,4]triazine derivatives 43-48, respectively (Scheme 19).35

On the other hand, cyclocondensation of compound 3 with α,β-unsaturated keto-acid 42 in refluxing glacial acetic acid yielded 8-aryl-2,6-dioxo-3-substituted-1,2,5,6-tetrahydropyrido[1,2-b][1,2,4]triazine-7,9-dicarbonitriles 49, while its treatment with diethyl oxalate in dry dioxane and/or with oxalyl chloride in warming DMF afforded the 2,3,6-trioxo analogue 50 (Scheme 20). Hydroxymethylation of compound 50 using methanol-formaldehyde produced the 1,4-dihydroxymethylpyridotriazine derivative 51 which upon full heterocyclization by refluxing with thiosemicarbazide in glacial acetic acid led to the direct formation of 7-oxo-2-thioxo-2,3,5,6,7,11-hexahydropyrido[1′,2′:2,3][1,2,4]triazino[5,6-e]triazine-8,10-dicarbonitrile 52. Careful hydrazinolysis of compound 52 afforded the corresponding 3-hydrazino-1,2,4-triazine derivative 53 (Scheme 20).45
Scheme 19

Scheme 20
1,2-Dioxygen compounds also used for building of various fused heterocyclic systems. Thus, treatment compound 3 with butane-2,3-dione in glacial acetic acid afforded 2,3-dimethylpyrido[1,2-b][1,2,4]-triazine 54, while the corresponding 2,3-diphenylpyridotriazine derivatives 55 were obtained from refluxing 3 with benzil in glacial acetic acid. The dihydro analogous 56 were obtained from refluxing compounds 3 with benzoin under the same reaction conditions. Oxidation of compounds 56 in methanolic ferric chloride produced compounds 55 (Scheme 21).45 Also, some new 8-aryl-2,6-dioxo-1,2-dihydropyrido[1,2-b][1,2,4]triazine-7,9-dicarbonitriles 57 have been synthesized from cyclocondensation of compounds 3 with α-oxocarboxylic acids namely; glyoxalic, pyruvic, α-oxobutyric and 4-chlorostyrylglyoxalic in refluxing glacial acetic acid (Scheme 21).45 It must be noted that this reaction occurred preferentially firstly between the N1-amino group (N-NH₂) and α-keto functions to form a hydrazone intermediate, which underwent cyclocondensation reaction between the other amino group at C₆ (C-NH₂) and the hydroxyl group of the acid functions affording the target pyridotriazine derivatives 57.

Scheme 21

The course of reactions of 1,2,-dioxygen heterocyclic compounds with aromatic heterocyclic α-diamines was found to depend on the reaction conditions, type of solvent (dielectric constant), and also the types of substituents (e-donor or e-acceptor) in the diamino compounds. Treatment of compound 3 with indole-2,3-dione in absolute ethanol containing a few drops of piperidine yielded the Schiff base condensate, 6-amino-4-aryl-2-oxo-1-[2-oxo-1,2-dihydro-3-indolo-3-ylidine)amino]-1,2-dihydropyridine-3,5-dicarbonitrile 58. When that reaction was carried out in boiling alcoholic sodium hydroxide solution, it gave 3-(2-aminophenyl)pyridotriazine derivative 59. Refluxing both 58 and 59 in glacial
acetic acid/fused sodium acetate gave the full condensation product, indolotriazinopyridine 60, which on further acetylation by heating in acetic anhydride yielded the N-acetyl derivative 61 (Scheme 22).  

\[
\begin{align*}
\text{AcOH-AcONa} & \quad 12 \text{ h} \\
& \quad 52-62\% \\
\text{AcOH-AcONa} & \quad 12 \text{ h} \\
& \quad 52-62\% \\
\end{align*}
\]

Reaction of diaminopyridone 3 with N-acetylisatine 62 in absolute ethanol containing a few drops of piperidine produced 8-aryl-2-(2-acetanilido)-3,6-dioxo-3,6-dihydro-4\(H\)-pyrido[1,2-\(b\)][1,2-4]triazine-7,9-dicarbonitrile 64, via the non isolable intermediate 63 and not to the isomeric product 65 as illustrated in Scheme 23.
Cyclocondensation of diaminopyridone 3 with ethyl 2-chloro-3-oxobutanoate in DMF under reflux containing a catalytic amount of piperidine produced the pyrido[1,2-b][1,2,4]triazine-2-carboxylate derivative 66, which was transformed to the pyrido[1,2-b][1,2,4]triazino[4,5-d][1,2,4]triazine derivative 67 upon fusion with benzoic acid hydrazide (Scheme 25). On the other hand, the interaction of 3 with 2,3-dichloroquinoxaline 68 under reflux led to the formation of the corresponding quinoxalino[2,3-e]-pyrido[1,2-b][1,2,4]triazine 69. Compound 69 exists in two tautomeric forms 69A and 69B due to amino-imino tautomerism (Scheme 24).

Also, the reaction of compound 3 with 3-chloro-7,8-diphenyl-4H-1,2,4-triazino[4,3-b][1,2,4]triazine 70 in pyridine under reflux led to the formation of the corresponding pyrido[1,2-b][1,2,4]triazino-[3′,2′:3,4]triazino[5,6-e][1,2,4]triazine 71, respectively (Scheme 25).

8-(4-Chlorophenyl)-2,6-dioxo-1H-pyrido[1,2-b][1,2,4]triazine-3,7,9-tricarbonitrile 73 was obtained from the reaction of 1,6-diaminopyridone 3 with ethyl α-cyano-α-phenylazoacetate 72 in acetic acid as shown in Scheme 26.
Scheme 24

Scheme 25

Scheme 26
Pyrido[1,2-\textit{b}][1,2,4]triazin-2-yl)quinolin-2(1\textit{H})-one 75 was obtained from ring closure of diaminopyridone 3 with 3-(2,2-dichloroacetyl)-4-hydroxy-1-methylquinolin-2(1\textit{H})-one 74 in boiling DMF (Scheme 27).\(^{46}\)

![Scheme 27](image)

2.4. Synthetic approaches for pyrido[1,2-\textit{b}][1,2,4]triazepines

Reaction of diaminopyridone derivatives with some \(\alpha,\gamma\)-bifunctional electrophiles afforded pyrido[1,2-\textit{b}][1,2,4]triazepines. When 1,6-diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile 3 was allowed to react with diethyl malonate and ethyl ethoxymethylenecyano acetate in boiling DMF, 9-(4-chlorophenyl)-pyrido[1,2-\textit{b}][1,2,4]triazepine derivatives 76 and 77 were obtained (Scheme 28).\(^{44}\)

![Scheme 28](image)

Treatment of 1,6-diaminopyridones 3 with pentane-2,4-dione afforded 9-aryl-2,4-dimethyl-7-oxo-6,7-dihydropyrido[1,2-\textit{b}][1,2,4]triazepine-8,10-dicarbonitriles 78,\(^{38,44}\) which reacted with benzene diazonium chloride to give 3-phenylhydrazono-1\textit{H}-pyrido[1,2-\textit{b}][1,2,4]triazepine-8,10-dicarbonitrile 78. Compound 79 was also prepared from treating diaminopyridone 3 with 3-phenylazo-2,4-pentanedione (Scheme 29).\(^{44}\)
Pyrido[1,2-b][1,2,4]triazepines 80-82 were prepared by the reaction of 1,6-diaminopyridone 3 with 4-(dimethylamino)but-3-en-2-one, 2-cyano-3,3-bis-(methylthio)acrylonitrile and 2-cyano-3-(methylsulfanyl)-N-phenyl-3-(phenylamino)prop-2-enamide, respectively (Scheme 30).36,40
Condensation of diaminopyridone 3 with 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde and 2-chloro-3-formylquinoline in DMF containing few drops in triethylamine afforded the heteroannulated pyrido[1,2-b][1,2,4]triazepines namely pyrazolo[3,4-e]pyrido[1,2-b][1,2,4]triazepine 83 and quinolino[2,3-e]pyrido[1,2-b][1,2,4]triazepine 84, respectively (Scheme 31).\(^\text{40}\)

![Scheme 31](image)

2-Aminopyrido[1,2-b][1,2,4]triazepine-3,8,10-tricarbonitrile 85 was prepared by reaction of 1,6-diaminopyridone 3 and (4-chlorobenzylidene)malononitrile in boiling DMF and piperidine (Scheme 32).\(^\text{36,40}\)

![Scheme 32](image)

Condensation of diaminopyridone 3 with ethyl 2-cyano-3-(4-methoxyphenyl)prop-2-enoate under the same reaction conditions in boiling DMF containing two drops of triethylamine yielded ethyl 2-amino-8,10-dicyano-4-(4-methoxyphenyl)-9-(6-methyl-4-oxo-4H-chromen-3-yl)-7-oxo-5,7-dihydro-

pyrido[1,2-b][1,2,4]triazepine-3-carboxylate 86 (Scheme 33).\(^\text{40}\)

Treatment of 1,6-diaminopyridone 3 with dehydroacetic acid and dimethyl acetylene-dicarboxylate afforded pyrano[2,3-e]pyrido[1,2-b][1,2,4]triazepine 87 and methyl pyrido[1,2-b][1,2,4]triazepine-4-carboxylate 88, respectively (Scheme 34).\(^\text{44}\)
9-Aryl-4-methyl-2,4-diphenyl-7-oxo-3,4,6,7-tetrahydro-5H-pyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile 89 was prepared by the reaction of 1,6-diaminopyridone 3 with acetophenone in methanol in the presence of catalytic amount of sulfuric acid (Scheme 35).38

9-(Aryl)-3-(2-hydroxybenzoyl)-7-oxo-6H-pyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile 90 was prepared by the reaction of diaminopyridone 3 and chromone-3-carbaldehyde in dry pyridine (Scheme 36).44
Treatment of diaminopyridone 3 with chromone-3-carbonitrile in DMF under reflux gave 2-amino-3-(2-hydroxybenzoyl)-7-oxo-9-(aryl)-5\textit{H}-pyrido[1,2-\textit{b}][1,2,4]triazepine-8,10-dicarbonitrile 91 as described by Abdel-megid,\textsuperscript{40,44} while gave the Schiff base 92 as published by Sosnovskikh and Moshkin (Scheme 37).\textsuperscript{47}

Reaction of 1,6-diaminopyridone 3 with 6-ethyl-3-[(4-oxo-4\textit{H}-chromen-3-yl)methylidene]pyrano[3,2-\textit{c}]-quinoline-2,4,5-(3\textit{H},6\textit{H})-trione 93 afforded the pyrido[1,2-\textit{b}][1,2,4]triazepines 94, bearing chromone and quinolinone nuclei (Scheme 38). The reactions proceeds initially via \(\alpha\)-pyrone ring opening by the more nucleophilic amino group (\(N\text{-NH}_2\)) followed by ring closure to produce the desired products.\textsuperscript{48}
The RORC reactions of chromone derivative 95 with 1,6-diaminopyridone 3 gave pyrido[1,2-b][1,2,4]-triazepine derivative 96 (Scheme 39).49

![Scheme 39](image)

3. Heterocyclization with diaminoimidazoles

Condensation of 1,5-diamino-3-tert-butylpyrazole 97 with carbon disulfide, α, β-dicarbonyl compounds (diacetyl, benzil), ethyl pyruvate and acetylacetone gave the corresponding pyrazolo[1,5-b][1,2,4]triazole 98, pyrazolo[1,5-b][1,2,4]triazine 99 and 110 and pyrazolo[1,5-b][1,2,4]triazepine 101 ring systems, respectively (Scheme 40).50

![Scheme 40](image)

Cyclization of 1,2-diamino-4-arylimidazoles 102 with 1,3-disubstituted propenones produced imidazo[1,5-b]pyridazines 103. While reaction of 1,2-diamino-4-arylimidazoles 102 with acetylacetone gave a mixture of 7-amino-5-(4-bromophenyl)-2,4-dimethylimidazo[1,5-b]pyridazine 104 and 5-(4-bromophenyl)-2,4-dimethyl-7-[(4-oxo-2-pent-2-en-yl)amino]imidazo[1,5-b]pyridazines 105 (Scheme 41), compound 104 and 105 were separated by crystallization process.51
Ethyl 3-amino[1,2,4]triazino[2,3-a]benzimidazole-2-carboxylate 108 was obtained selectively by the reaction of 1,2-diaminobenzimidazole 106 with diethyl (E)-2,3-dicyanobutenedioate 107 in boiling acetonitrile (Scheme 42).52

On the other hand, 1,2,4-triazino[2,3-f]xanthines 110 and 111 were prepared from the reaction of 5,6-diaminooxanthine 109 with the acyclic and cyclic dicarbonyl compounds, respectively (Scheme 43).53
4. Heterocyclization with diaminotriazoles

Cyclocondensation of 3,4-diamino-5-methyl-1,2,4-triazole hydrochloride 112 with 1-methylisatine gave 3,10-dimethyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indole 113 (Scheme 44). 54

```
112
\[ \text{Me} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ + \]
\[ \text{EtOH/H}_2\text{O} \quad \text{NaOAc} \]
\[ \rightarrow \]
\[ \text{Me} \quad \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ \text{113} \]
```

Scheme 44

3,4-Diamino-1,2,4-triazole hydrobromide 114 reacted with α-dicarbonyl compounds in acetic acid to afford the corresponding [1,2,4]triazolo[3,4-b][1,2,4]triazine derivative 115 (Scheme 45). 55

```
114
\[ \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ + \]
\[ \text{AcOH} \]
\[ \rightarrow \]
\[ \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ \text{R}_1 \quad \text{R}_2 \]
\[ \text{115} \]
\[ a, \text{R}_1 = \text{R}_2 = \text{Me} \]
\[ b, \text{R}_1 = \text{Me}; \text{R}_2 = \text{H} \]
```

Scheme 45

4-(Phenyl/benzyl)-2-(2-chloroethyl)-1H-1,3,3a,5,6-pentaza-2-phosphapentalen-2-oxide 117 was prepared by the reaction of 5-phenyl/benzyl-1,2-diamino-1,3,4-triazole 116 with 2-chloroethylphosphonyl dichloride in pyridine containing triethylamine (Scheme 46). 56

```
116
\[ \text{N} \quad \text{N} \quad \text{NH}_2 \]
\[ + \]
\[ \text{R'}\text{POCl}_2, \text{pyridine, Et}_3\text{N} \]
\[ \rightarrow \]
\[ \text{R}\text{POCl} \quad \text{Cl} \]
\[ \text{117} \]
\[ \text{R} = \text{CH}_2\text{CH}_2\text{Cl, CH}_2\text{CH} = \text{CH}_2, \text{CH}_2\text{Ph} \]
\[ \text{R'} = \text{Ph, CH}_2\text{Ph} \]
\[ \text{42-44\%} \]
\[ \text{Scheme 46} \]
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Reaction of 3,4,5-triamino-4H-1,2,4-triazole (guanazine) 118 with cyanogen bromide did not give the hypothetical cyclization product, 7H-1,2,4-triazolo[4,3-b][1,2,4]triazole 119 but afforded an unexpected product identified as 2,3,5,6-tetraamino-9-imino-3H,9H-bis[1,2,4]triazolo[1,5-a:5',1'-d][1,3,5]triazinium bromide 120 (Scheme 47). 57
Heterocyclization of 3,4,5-triamino[1,2,4]triazole 118 with 4-nitrobenzaldehyde and cyclohexanone afforded 2,3-diamino-9-(4-nitrophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[5,1-b]quinazoline 121 (Scheme 48).\(^{58}\)

In a similar manner, tetrahydro[1,2,4]triazolo[5,1-b]quinazolin-8-ones 122 were prepared from the reaction of 3,4,5-triamino[1,2,4]triazole 118 with aldehydes and dimedone. In case of 4-BrC\(_6\)H\(_4\)CHO, compound 123 was isolated as by product in low yield (Scheme 49).\(^{58}\)

Cyclocondensation of diaminotriazole 124 with β-chlorocinnamaldehyde 125 and 2-chloro-3-formylquinolines 126 in the presence of a catalytic amount of \(p\)-TsOH produced triazolotriazepines 127 and quinolino[3,2-\(f\)][1,2,4]triazolo[4,3-\(b\)][1,2,4]triazepines 128 (Scheme 50).\(^{59,60}\)
5. Heterocyclization with diaminothiazoles

Condensation of 1-amino-2-iminonaphtho[1,2-\(d\)]thiazole 129 with some \(\alpha\)-ketocarboxylic acid and their esters in methanol gave the open chain product 130, however, when the reaction was performed in glacial acetic acid or DMF, cyclic products identified as 10-alkyl/aryl/heteroaryl/aralkyl-9\(H\)-naphtho[1'2':4,5]-thiazolo[3,2-\(b\)][1,2,4]triazin-9-ones 131 were obtained (Scheme 51).61

6. Heterocyclization with diaminopyrimidines

Cyclocondensation of triaminopyrimidinethione 132 with pyruvic acid in glacial acetic acid gave pyrimido[3,4-\(b\)][1,2,4]triazine derivative 133 (Scheme 52).62
1,3-Diphenyl-7-methyl-1H-pyrazolo[3’,4’:4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one **135** was prepared by condensation of 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1H-pyrazolo[3,4-d]pyrimidine **134** with ethyl acetoacetate. Reaction of compound **135** with diazotized aromatic amines produced the arylazo derivatives **136**. The latter compounds were also obtained from the reaction of compound **134** with ethyl 2-arylhydrazono-3-oxobutanoate (Scheme 53).

Furo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines **138** were prepared by reaction of 5,6-di-(2-furyl)-3H,4H-4-imino-2-methylfuro[2,3-d]pyrimidin-3-amine **137** with triethyl orthoformate, diethyloxalate, ethyl cyanoacetate, cyanogen bromide and carbon disulfide, respectively. Also, condensation of compound **137** with isatine gave the condensation products 12,13-di-(2-furyl)-9-methylfuro[2’,3’:5,6]-pyrimido[3,4-b][2,3-e]indolo[1,2,4]triazine **139** (Scheme 54).
Cyclocondensation of compound 140 with an excess formic acid, acetyl chloride and cyanogen bromide gave the corresponding 8,10-diphenyl-11-(4-chlorophenyl)-pyrazolo[4′,3′:5,6]pyrano[3,2-e][1,2,4]-triazolo[1,5-c]pyrimidine derivatives 141 (Scheme 55).65

The polyfused [1,2,4]triazolo[1,5-c]pyrimidines 143 were prepared by reaction of 9-amino-7-(4-chlorophenyl)-8,9-dihydro-8-imino-6H,7H-[1]benzopyrano[3,4:5,6]pyrano[2,3-d]pyrimidin-6-ones 142 with triethyl orthoformate, acetyl chloride, benzoyl chloride, diethyl oxalate and ethyl cyanoacetate. Also, treating 142 with carbon disulfide and methyl chloroformate in alcoholic potassium hydroxide solution gave [1,2,4]triazolo[1,5-c]pyrimidines 144. Also, reaction of 142 with ethyl chloroacetate afforded the 15-(methyl/4-chlorophenyl)-3,4-dihydro-2H,14H,15H-[1]benzopyrano[3′,4′:5,6]pyrano[2,3-d]pyrimido-[1,6-b][1,2,4]triazine-3,14-dione 145 via elimination of EtOH and HCl (Scheme 56).66,67
Condensation of ethyl 3-amino-4-imino-3,4,5,6,7,8-hexahydropyrido[4,3:4,5]thieno[2,3-d]pyrimidine-7-carboxylate 146 with triethyl orthoformate, acetic anhydride and phenylisothiocyanate gave the corresponding ethyl pyrido[4,3:4,5]thieno[2,3-d]-1,2,4-triazolo[3,2-f]pyrimidine-8(7H)-carboxylate 147. Also, condensation of 146 with chloroacetyl chloride in DMF/TEA gave 4-oxo-2,3,4,8,10,11-hexahydropyrido[4,3:4,5]thieno[2,3-d]-1,2,4-triazolo[3,2-f]pyrimidine-9-carboxylate 148 (Scheme 57).
During an investigation of the reactions of indole-2,3-dione with 2,3-diamino-4(3H)quinazolinone 149 in various solvents, a mixture of products were obtained. This reaction when carried out in ethanol containing catalytic amounts of acetic acid yielded several products obtained via 3-[2-amino-4-quinazolinone)imino]-2H-indol-2-one 150. Boiling of the latter compound in ethanolic KOH gave 1,2,4-triazino[3,2-b]quinazoline-2,6-dione 151, while in ethanol containing a few drops of piperidine it yielded spiro[3H-indol-3',2'(1H)][1,2,4]triazolo[5,1-b]quinazoline-2,9-dione 152. Also, boiling 150 in glacial acetic acid afforded indolo[2',3':5,6][1,2,4]triazino[3,2-b]quinazolin-14-one 153 (Scheme 58).

On the other hand, treatment of N-acetylisatine with 2,3-diamino-4(3H)quinazolone 149 led to N-2-(triazinoquinazolinone)phenyl acetamide 154 under the same conditions (Scheme 59).

7. Heterocyclization with diaminotriazine
Condensation of 3,4-diamino-4,5-dihydro-1,2,4-triazin-5-ones 155 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 \textbf{156}\textsuperscript{71} While, the reaction of compound \textbf{155} with acetaldehyde and diethyl phosphite in THF in the presence of sodium hydride as a catalyst gave [1,2,4]triazino[4,3-b][1,2,4,5]triazaphosphinine derivative \textbf{157} (Scheme 60).\textsuperscript{72}

\begin{center}
\includegraphics[width=\textwidth]{scheme60.png}
\end{center}

\textbf{Scheme 60}

\textbf{REFERENCES}

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