HETEROCYCLES, Vol. 89, No. 5, 2014, pp. 1125 - 1157. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 20th December, 2013, Accepted, 25th December, 2013, Published online, 10th January, 2014
DOI: 10.3987/REV-13-790

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.

CONTENTS

1. INTRODUCTION

o-Diamines are very active substrates for building of various heterocyclic systems,[1-5] and are largely used in formation of complexes.[6-10] 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.

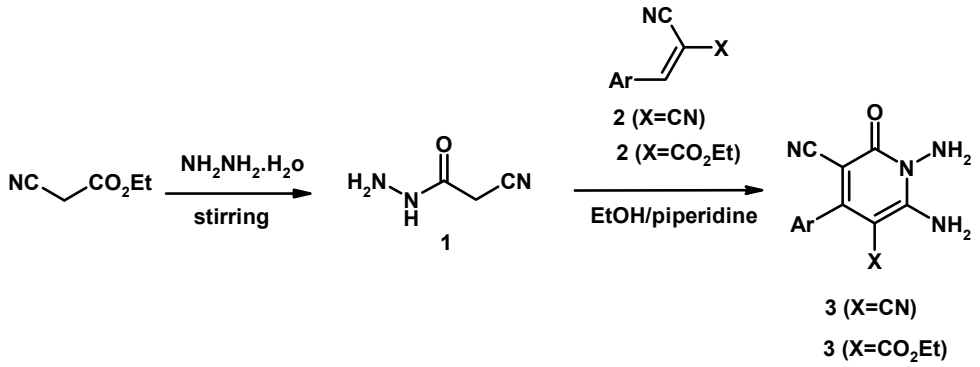
2. Heterocyclization with diaminopyridones

Polyfunctional pyridines are highly reactive reagents that have been used extensively in heterocyclic synthesis,[11-13] and possess biological as well as pharmacological activities.[14-16] [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 arylmethylidinemalononitriles **2** (X=CN) and ethyl 3-cyano-2-(aryl)-prop-2-enoates **2** (X=CO_2Et), 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=CO_2Et), respectively (Scheme 1).[17] This method is a rapid and common for the synthesis of *o*-diaminopyridone derivatives. The proposed mechanism for formation of compounds **3** is depicted in Scheme 2.[17]

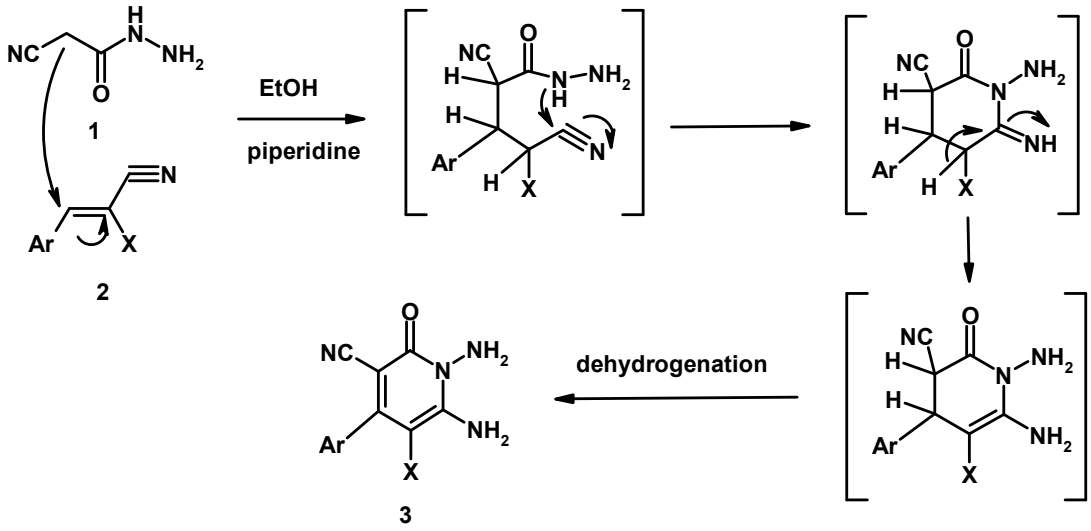
Also, 3-cyano-1,6-diaminopyridone derivatives **5** possessing various alkoxycarbonyl groups were prepared directly from the reaction of 2-cyanoacetohydrazide (**1**) with dialkyl 2,3-dicyanobutenedionates **4** (Scheme 3).[18] The ^{1}H NMR spectrum is a good tool to differentiate between the nucleophilicity of the two amino groups in the diaminopyridone derivatives **3** and **5**. The ^{1}H 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*-NH_2) and (*C*-NH_2) protons, respectively. These results indicate the difference in nucleophilicity between the two amino groups. Thus, the hydrazide β-nitrogen (*N*-NH_2) is more nucleophilic and reacted more rapidly with the electron deficient carbon than the amino group at carbon atom (*C*-NH_2).



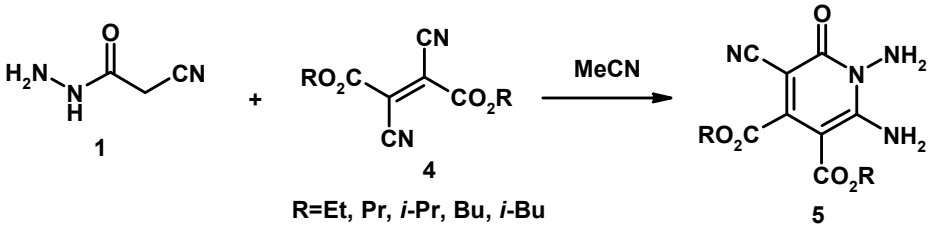
3, X=CN, Ar=4-ClC_6H_4, 4-$O_2NC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 2-furyl, 6-chlorochromon-3-yl, 6-methylchromon-3-yl

3, X= CO_2Et, Ar=4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 2-furyl, 4-$MeOC_6H_4$

Scheme 1



Scheme 2



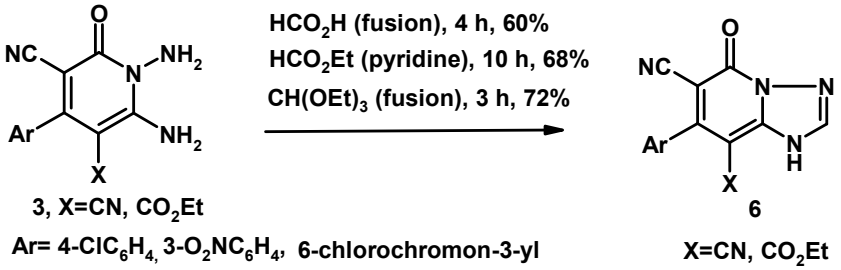
R=Et, Pr, *i*-Pr, Bu, *i*-Bu

Scheme 3

2.2. Synthetic approaches for [1,2,4]triazolo[1,5-a]pyridines

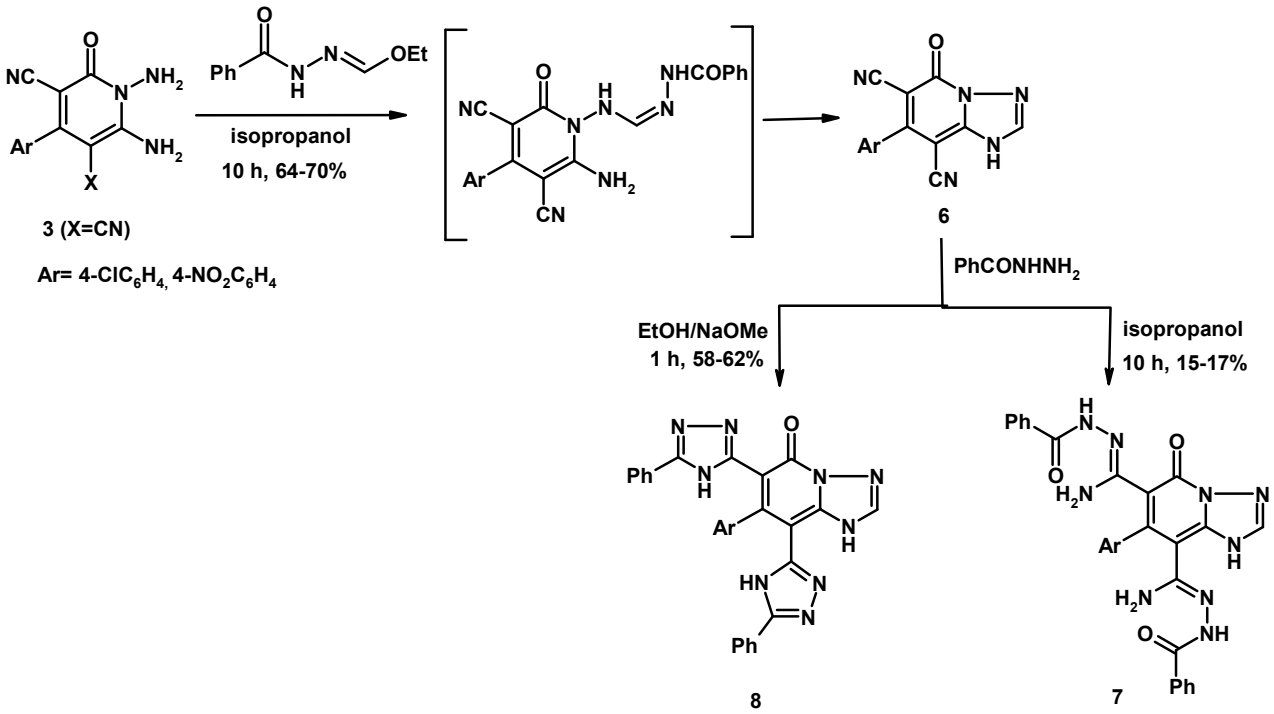
[1,2,4]Triazolo[1,5-*a*]pyridines constitute an important class of heterocyclic systems due to their variable biological activities including antifungal,[19] antimicrobial,[20] antitumor,[21,22] analgesic, anti-inflammatory,[23] and antiviral activity.[24] Different methods are reported for the synthesis of 1,2,4-triazolo[1,5-*a*]-

pyridines,[25-35] the most common one is the condensation of *o*-diaminopyridones **3** or **5** with mono electrophilic reagents. Thus, 7-(aryl)-5-oxo-1*H*-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,[35] ethyl formate,[36] or triethyl orthoformate (Scheme 4).[37]



Scheme 4

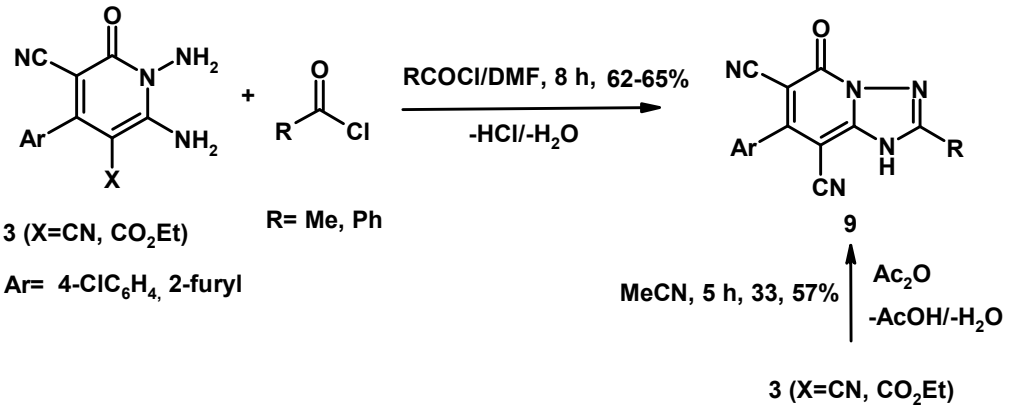
4-Aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile **3** reacted with *N*-ethoxy-methylenebenzohydrazide in isopropanol to give [1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **6** which reacted with benzohydrazide to give triazolopyridones **7** and 7-aryl-6,8-*bis*(5-phenyl-4*H*-1,2,4-triazol-3-yl)-4,5-dihydro-*1H*-[1,2,4]triazolo[1,5-*a*]pyridine-5-ones **8** (Scheme 5).[38]



Scheme 5

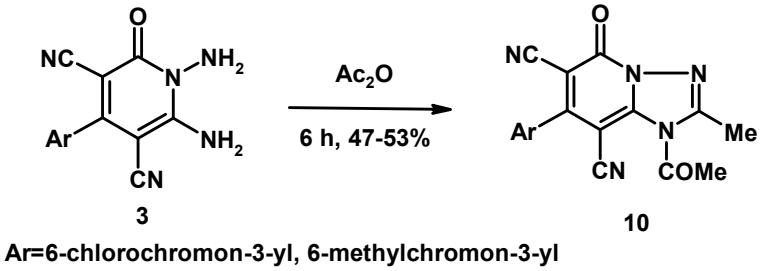
Refluxing diaminopyridone **3** with acetyl chloride and benzoyl chloride in boiling DMF produced

7-(4-chlorophenyl)-5-oxo-1*H*-4,5-dihydro-2-(methyl/phenyl)[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonit riles **9** (Scheme 6).[35] Also, compounds **9** (R=Me) were prepared by the reaction of diaminopyridones **3** with acetic anhydride (Scheme 6).[39]



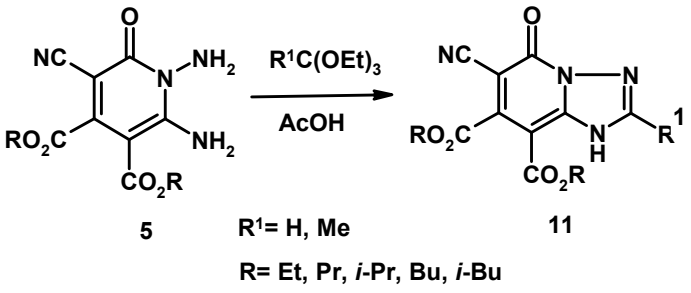
Scheme 6

On the other hand, 1-acetyl-7-(6-chloro/methyl-4-oxo-4*H*-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).[36, 40]



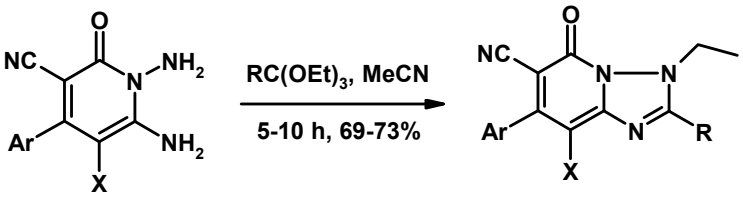
Scheme 7

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).[18]



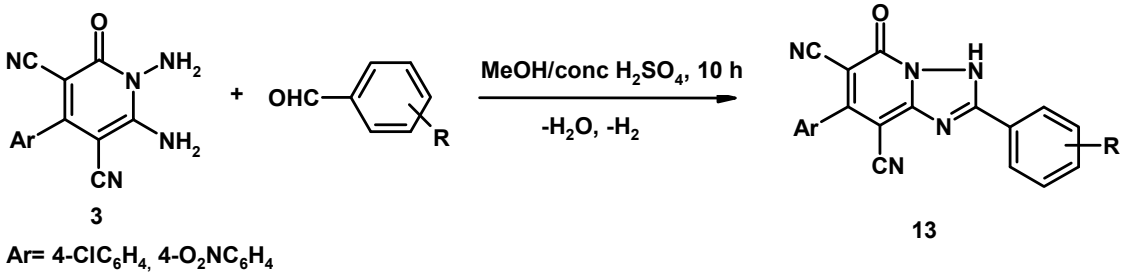
Scheme 8

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]



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-1*H*-[1,2,4]-triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **13** (Scheme 10).[38,39]

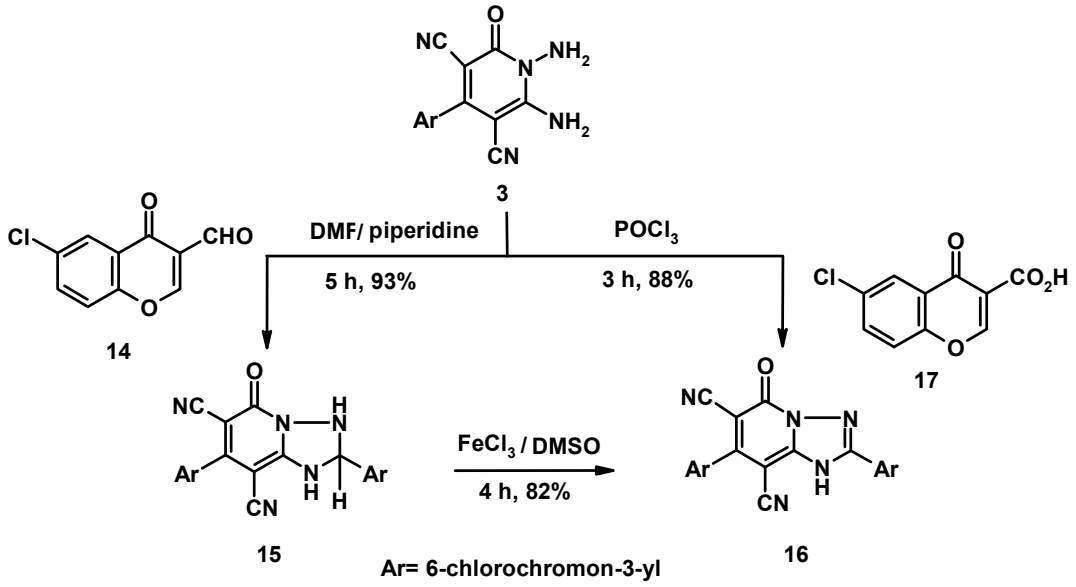


Scheme 10

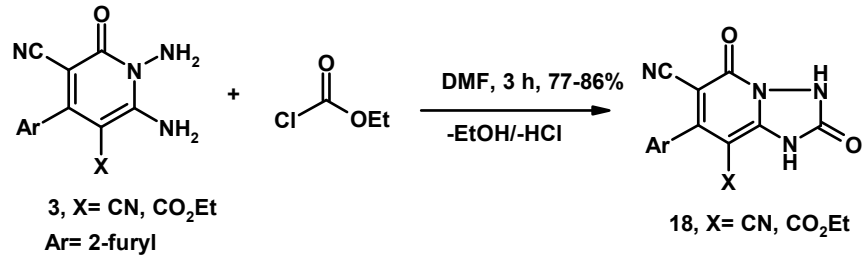
Cyclocondensation of 1,6-diaminopyridone **3** with 6-chloro-3-formylchromone **14** in DMF under reflux containing few drops of piperidine afforded the [1,2,4]triazolo[1,5-*a*]pyridine derivative **15**. Oxidation of the latter compound by ferric chloride in boiling dimethyl sulfoxide (DMSO) yielded 2,7-*bis*(6-chloro-4-oxo-4*H*-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]

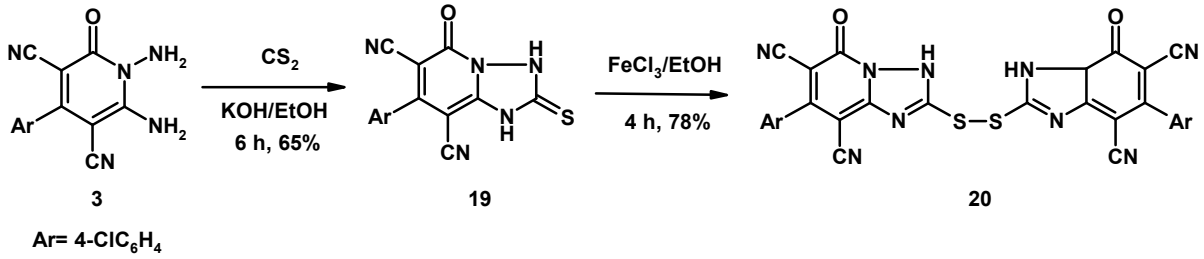
Refluxing 1,6-diaminopyridone **3** with carbon disulfide in ethanolic KOH yielded 2-thioxo[1,2,4]-triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **19**,[41] which oxidized by $FeCl_3$/EtOH to give 7,7-di(4-chlorophenyl)-5,5-dioxo-1,1,5,5-tetrahydro-2,2-dithio-di[1,2,4]triazolo[1,5-*a*]pyridine-6,6,8,8-tetracarbonitrile **20** (Scheme 13).[35]



Scheme 11



Scheme 12

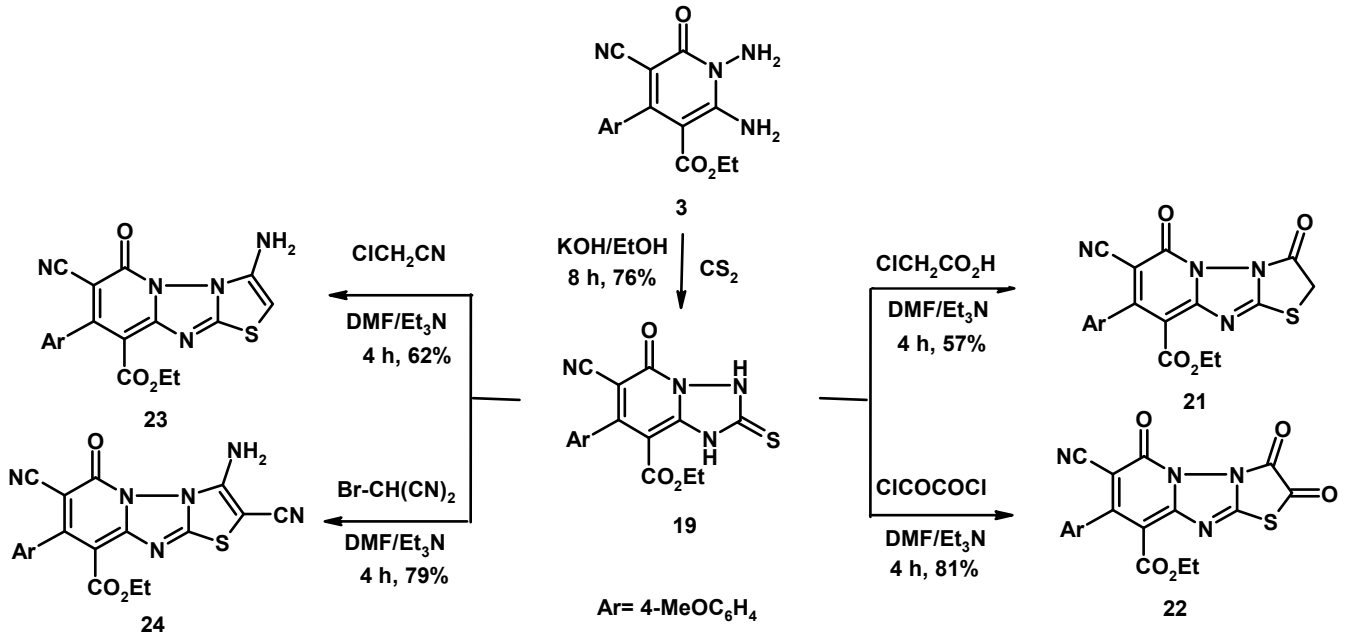


Scheme 13

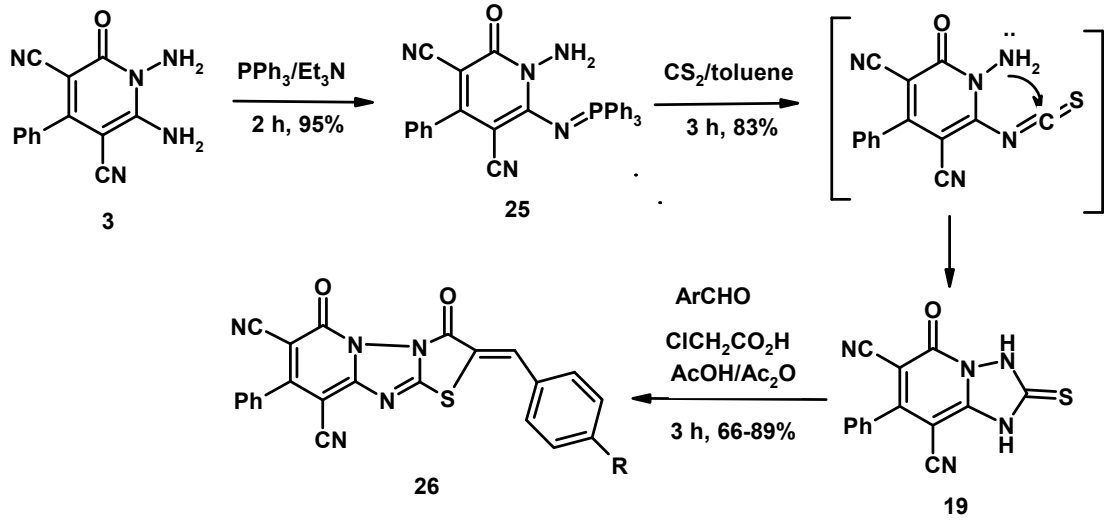
The diaminopyridone derivative **3** reacted with carbon disulfide in ethanolic KOH solution under reflux to yield [1,2,4]triazolo[1,5-*a*]pyridine derivative **19** which reacted with chloroacetic acid, oxalyl chloride, chloroacetonitrile and bromomalonitrile to produce the corresponding thiazolo[3,2:2,3][1,2,4]triazolo-[1,5-*a*]pyridines **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-iminophosph orane **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-*a*]pyridine-7,9-dicarbonitrile **26** (Scheme 15).[43]



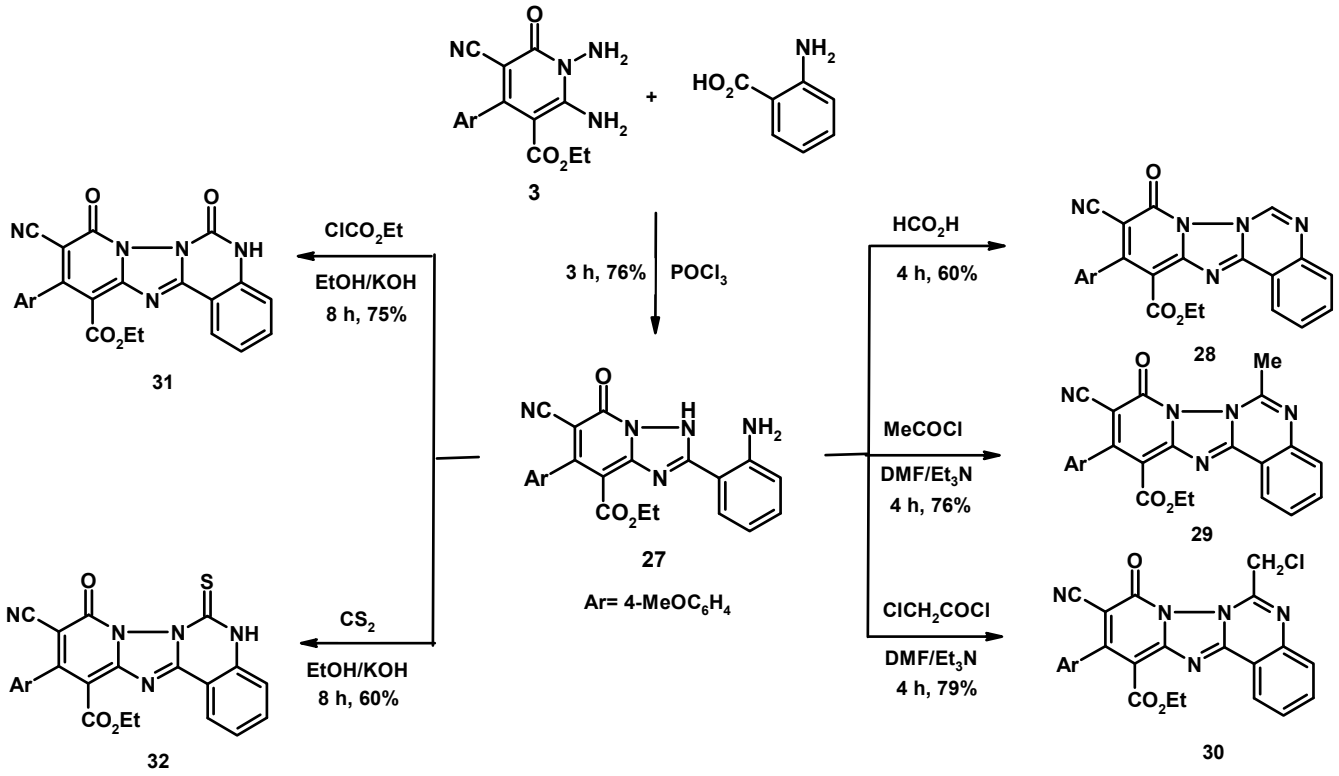
Scheme 14



Scheme 15

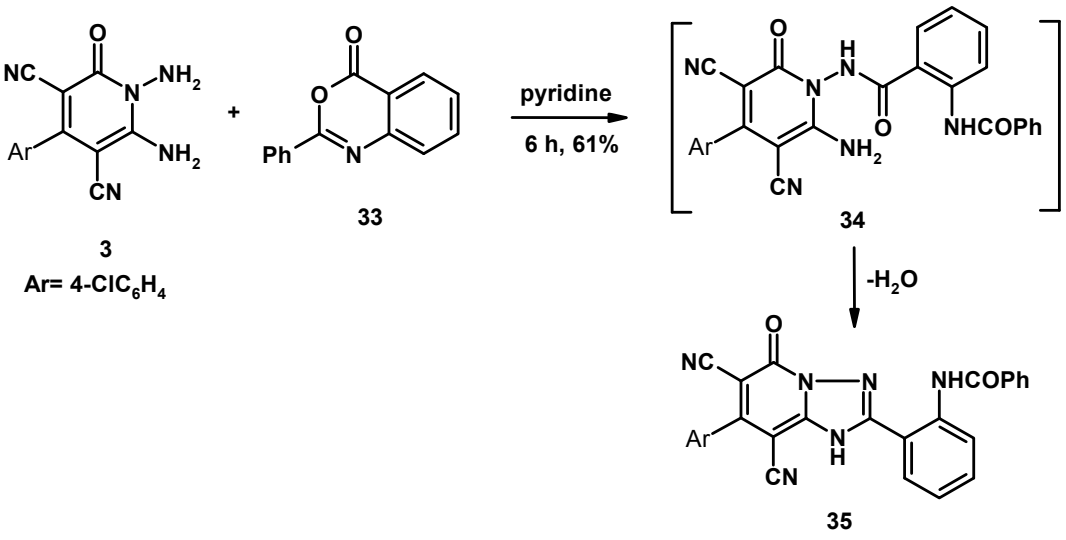
Reaction of diaminopyridone **3** with anthranilic acid in phosphoryl chloride gave ethyl 2-(2-amino-phenyl)-6-cyano-7-(4-methoxyphenyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate **27** which reacted with formic acid, acetyl chloride, chloroacetyl chloride, ethyl chloroformate and

carbondisulfide 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

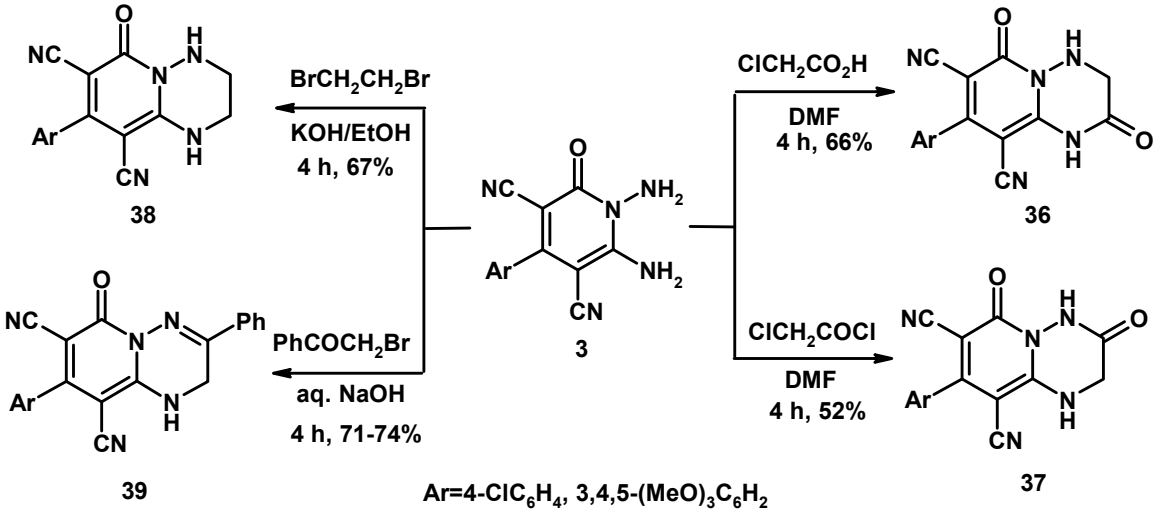
2-(2-Benzoylaminophenyl)-7-(4-chlorophenyl)-5-oxo-1*H*-[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **35** was obtained from the reaction of diaminopyridone **3** and 2-phenyl-4*H*-3,1-benzoxazin-4-one **33**, *via* the non isolable intermediate **34** (Scheme 17).[44]



Scheme 17

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

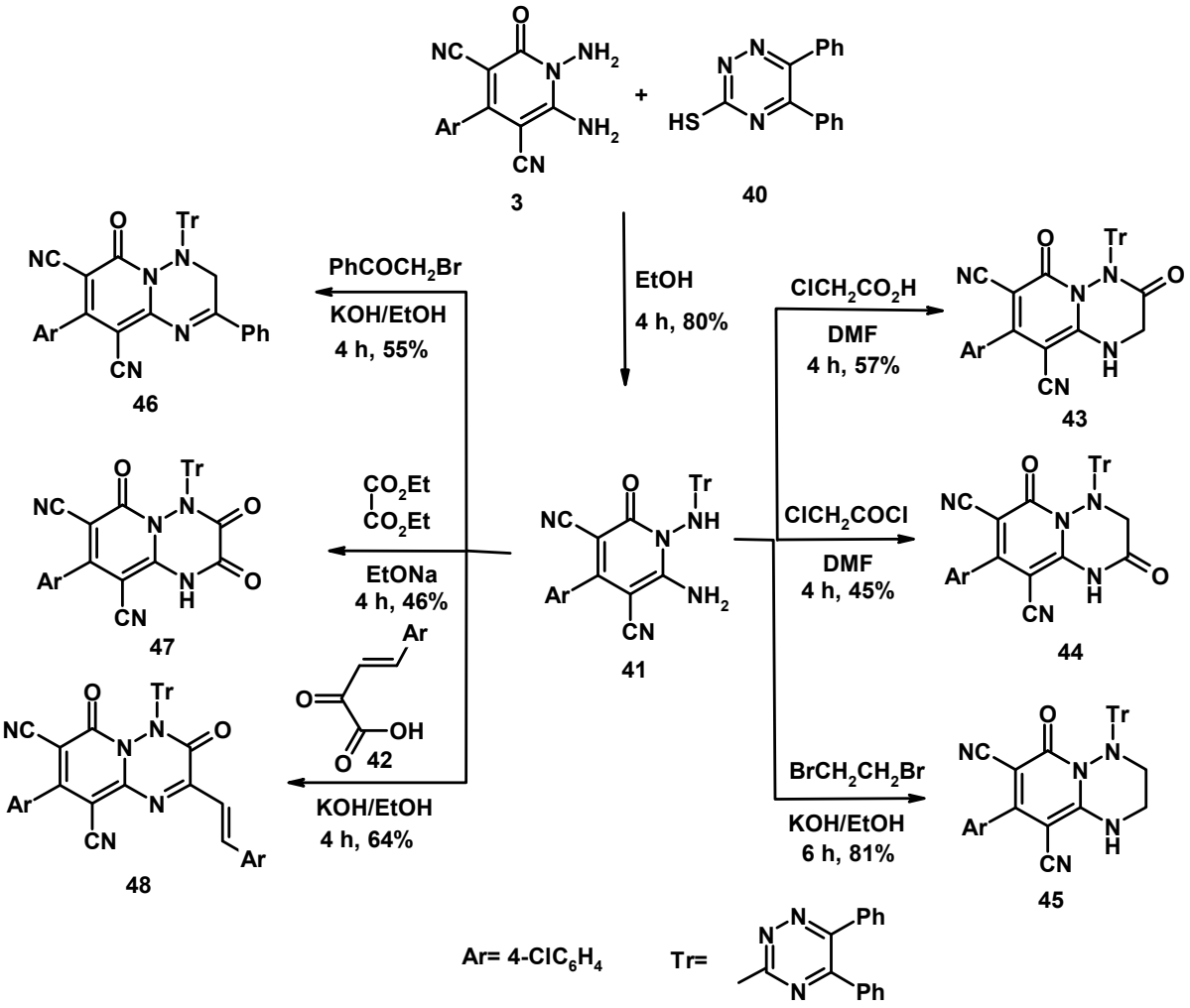
4-Aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **3** were efficiently used for preparation of nitrogen bridgehead pyrido[1,2-*b*][1,2,4]triazines. Thus, the isomeric structures of pyrido[1,2-*b*]-[1,2,4]triazine-7,9-dicarbonitrile derivatives **36** and **37** have been obtained from 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]



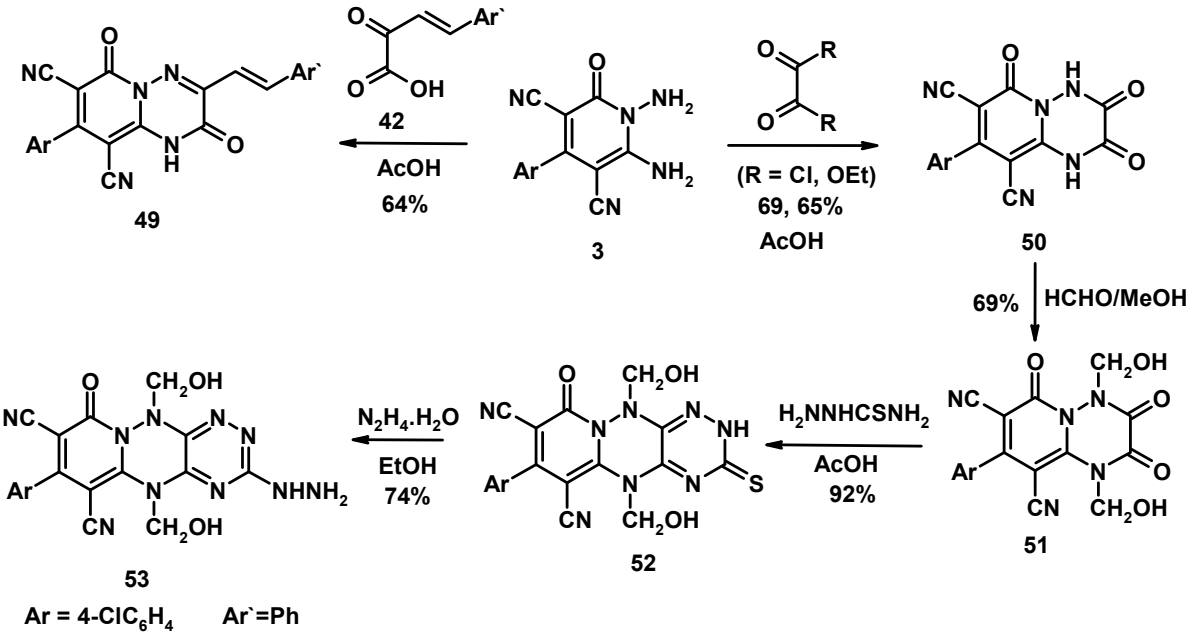
Scheme 18

Condensation of diaminopyridone **3** with 5,6-diphenyl-3-mercapto-1,2,4-triazine **40** gave *N*-(triazinyl-amino)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]

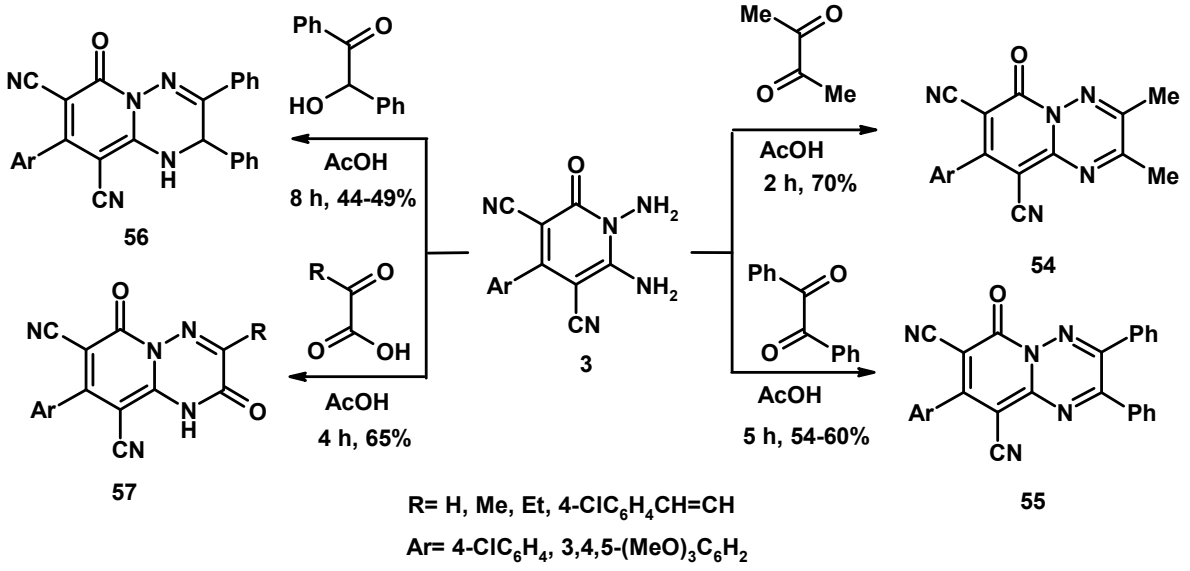


Scheme 19



Scheme 20

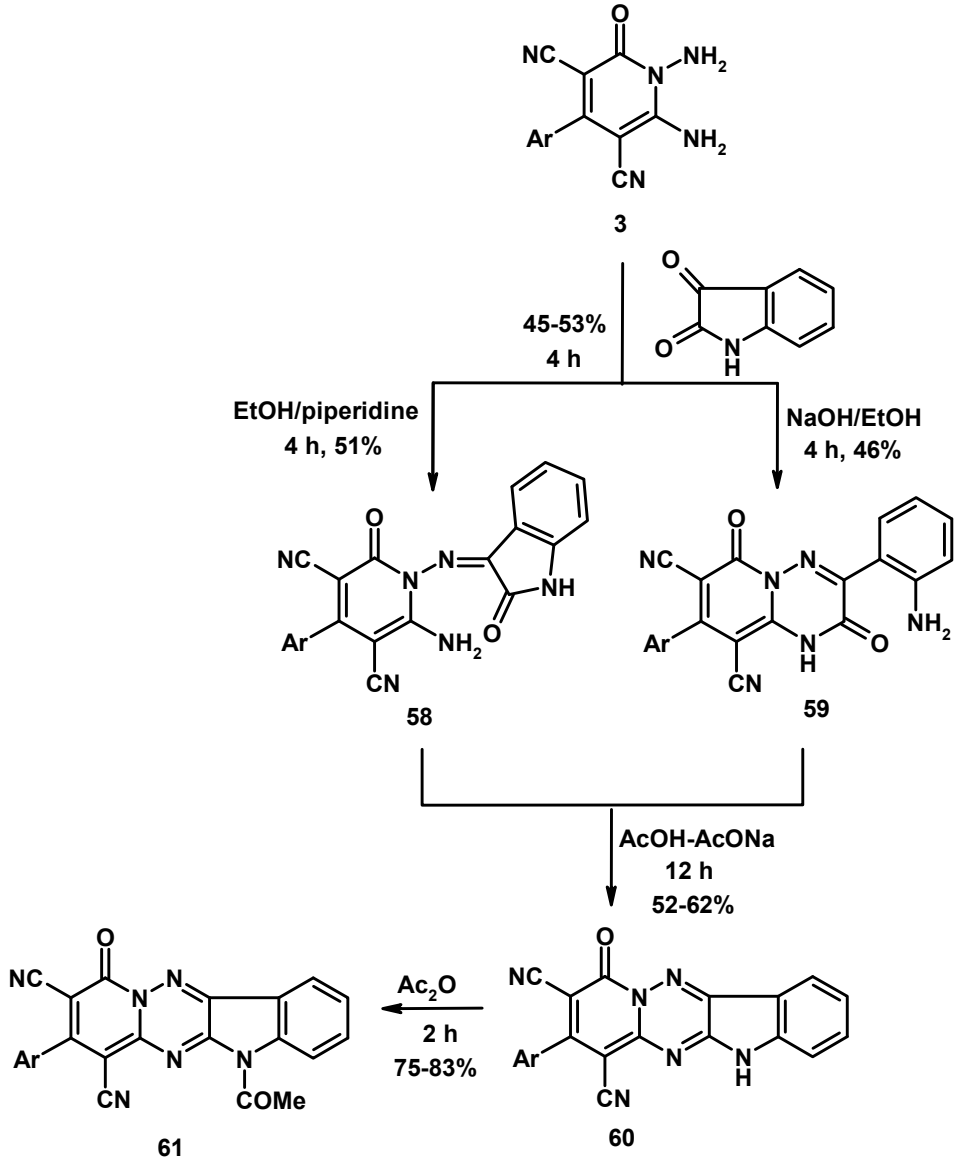
1,2-Dioxygen compounds also used for building of various fused heterocyclic systems. Thus, treatment compound **3** with butane-2,3-dione in glacial acetic acid afforded 2,3-dimethylpyrido[1,2-*b*][1,2,4]-triazine **54**, while the corresponding 2,3-diphenylpyridotriazine derivatives **55** were obtained 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 N^1-amino group (*N*-NH_2) and α-keto functions to form a hydrazone intermediate, which underwent cyclocondensation reaction between the other amino group at C^6 (*C*-NH_2) and the hydroxyl group of the acid functions affording the target pyridotriazine derivatives **57**.



Scheme 21

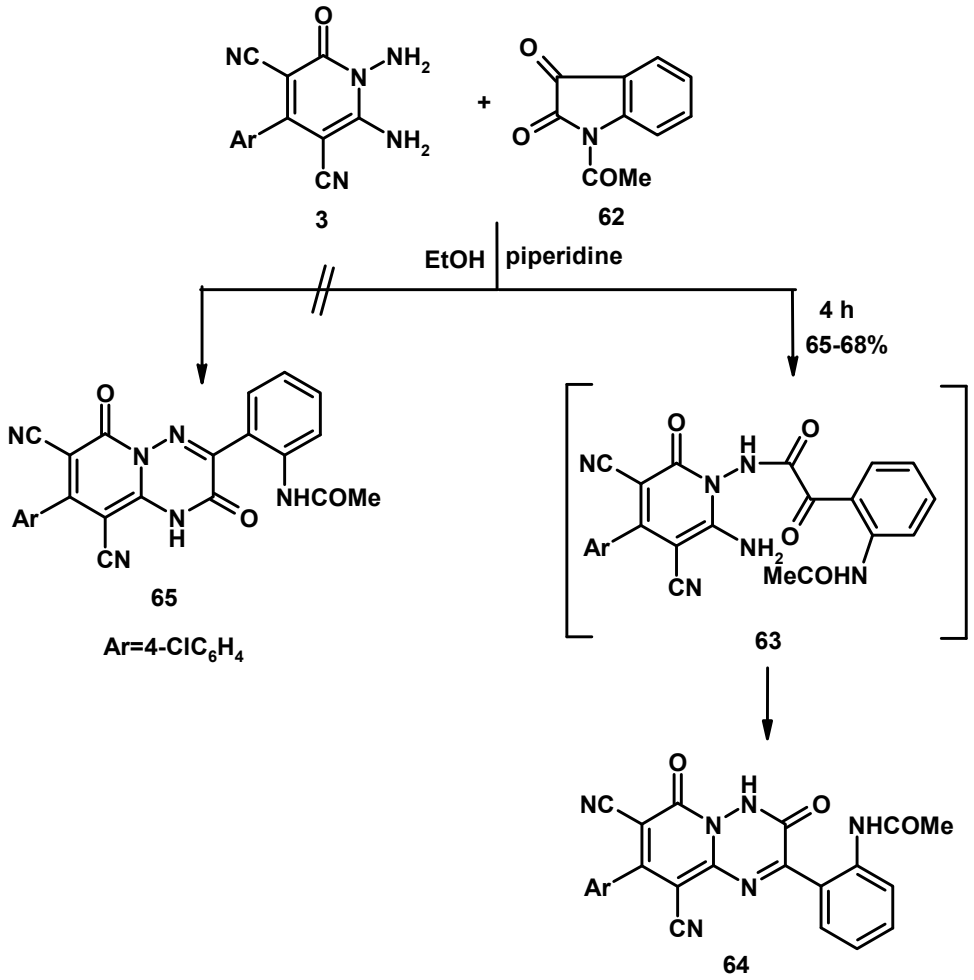
The course of reactions of 1,2,-dioxygen heterocyclic compounds with aromatic heterocyclic *o*-diamines was found to depend on the reaction conditions, type of solvent (dielectric constant), and also the types of substituents (e-donor or e-acceptor) in the diamino compounds. Treatment of compound **3** 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-dihydro-pyridine-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).[45]



Scheme 22

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.[45]

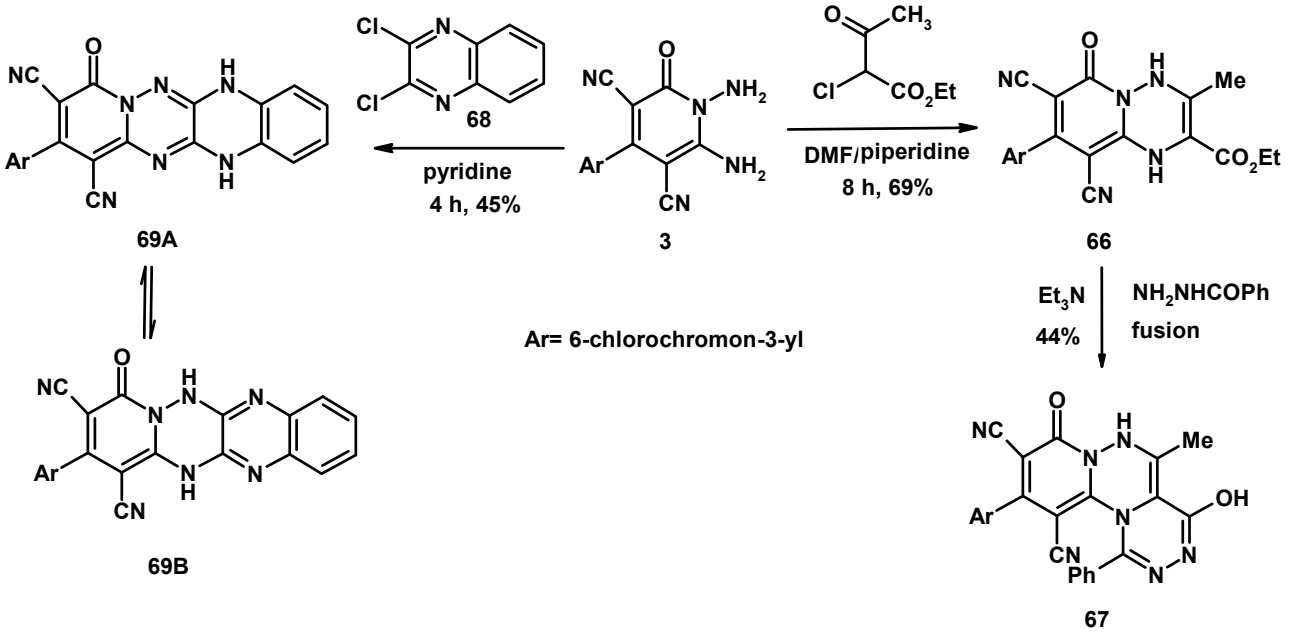


Scheme 23

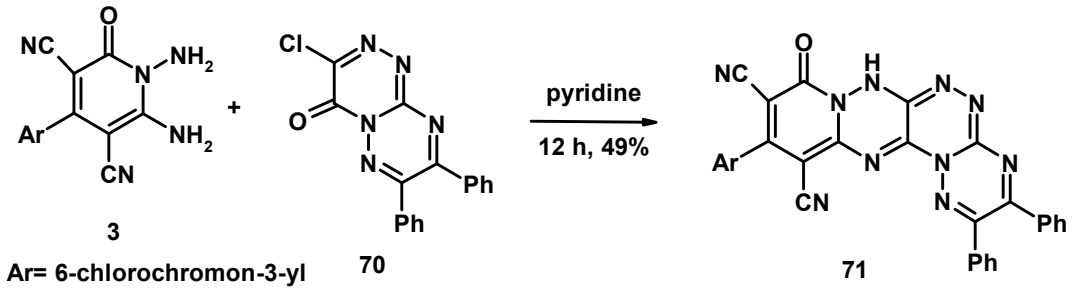
Cyclocondensation of diaminopyridone **3** with ethyl 2-chloro-3-oxobutanoate in DMF under reflux containing a catalytic amount of piperidine produced the pyrido[1,2-*b*][1,2,4]triazine-2-carboxylate derivative **66**, which was transformed to the pyrido[1,2-*b*][1,2,4]triazino[4,5-*d*][1,2,4]triazine derivative **67** upon fusion with benzoic acid hydrazide (Scheme 25).[36] 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).[36]

Also, the reaction of compound **3** with 3-chloro-7,8-diphenyl-4*H*-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).[36]

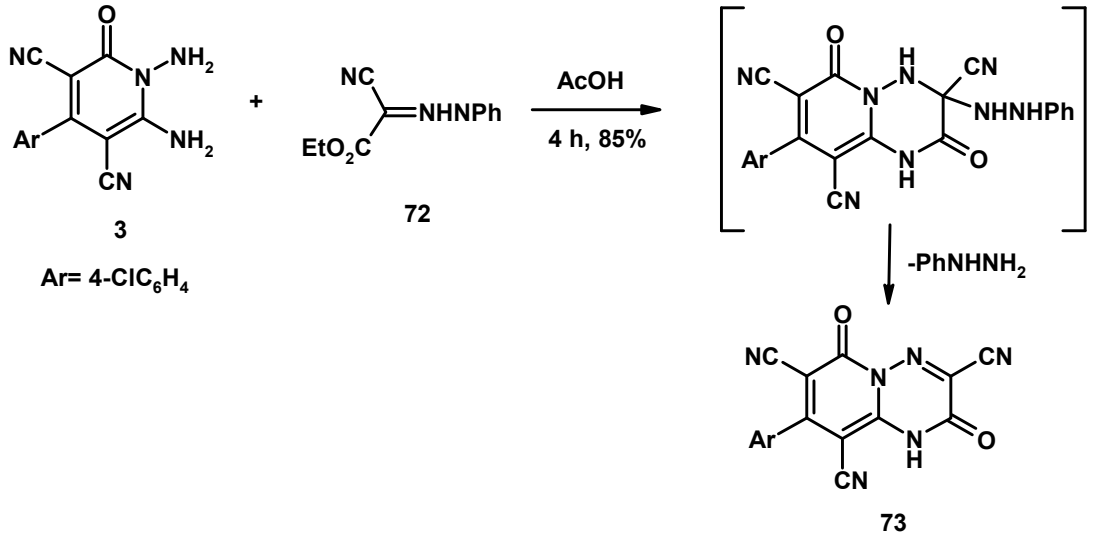
8-(4-Chlorophenyl)-2,6-dioxo-1*H*-pyrido[1,2-*b*][1,2,4]triazine-3,7,9-tricarbonitrile **73** was obtained from the reaction of 1,6-diaminopyridone **3** with ethyl α-cyano-α-phenylazoacetate **72** in acetic acid as shown in Scheme 26.[44]



Scheme 24

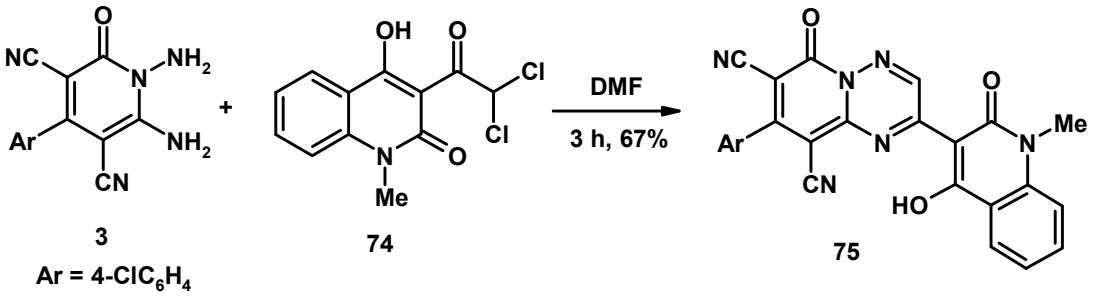


Scheme 25



Scheme 26

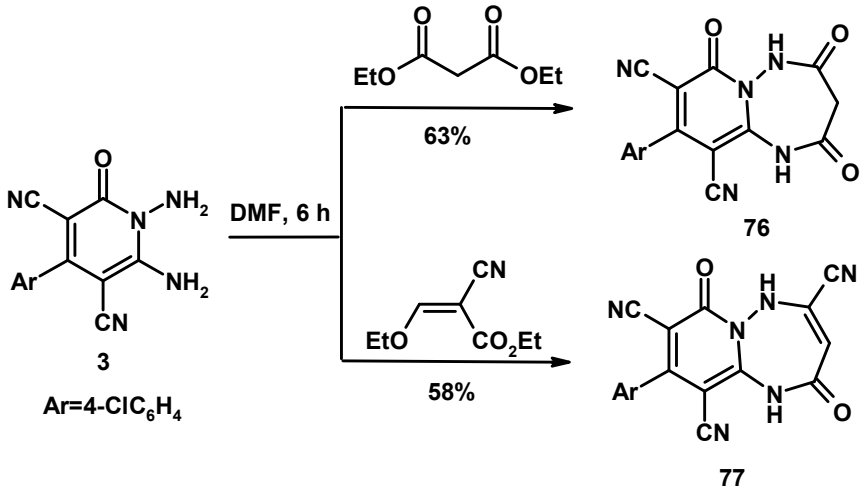
Pyrido[1,2-*b*][1,2,4]triazin-2-yl)quinolin-2(1*H*)-one **75** was obtained from ring closure of diaminopyridone **3** with 3-(2,2-dichloroacetyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one **74** in boiling DMF (Scheme 27).[46]



Scheme 27

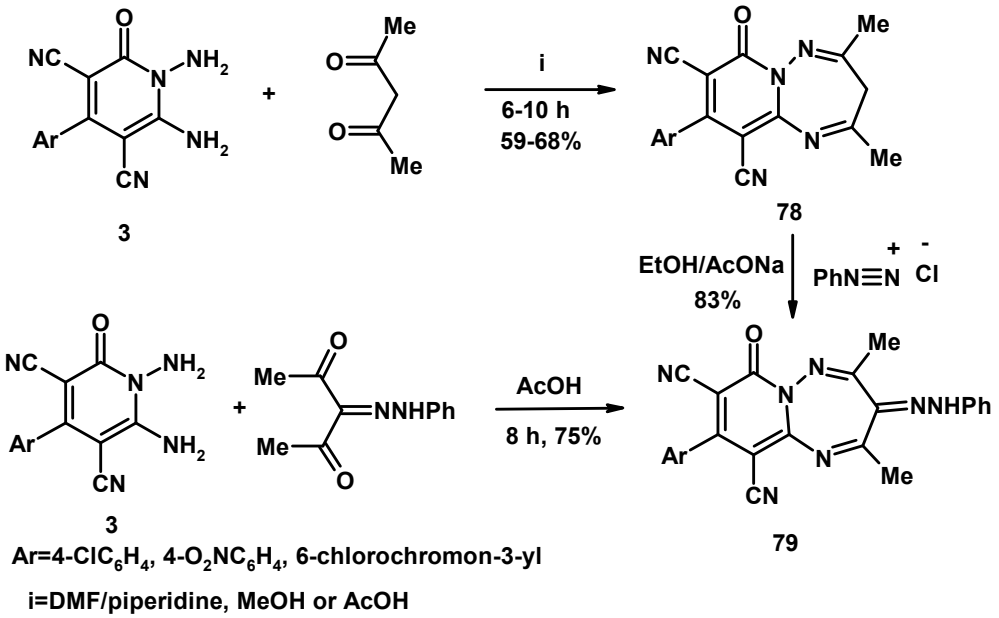
2.4. Synthetic approaches for pyrido[1,2-*b*][1,2,4]triazepines

Reaction of diaminopyridone derivatives with some α,γ-bifunctional electrophiles afforded pyrido[1,2-*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-*b*][1,2,4]triazepine derivatives **76** and **77** were obtained (Scheme 28).[44]



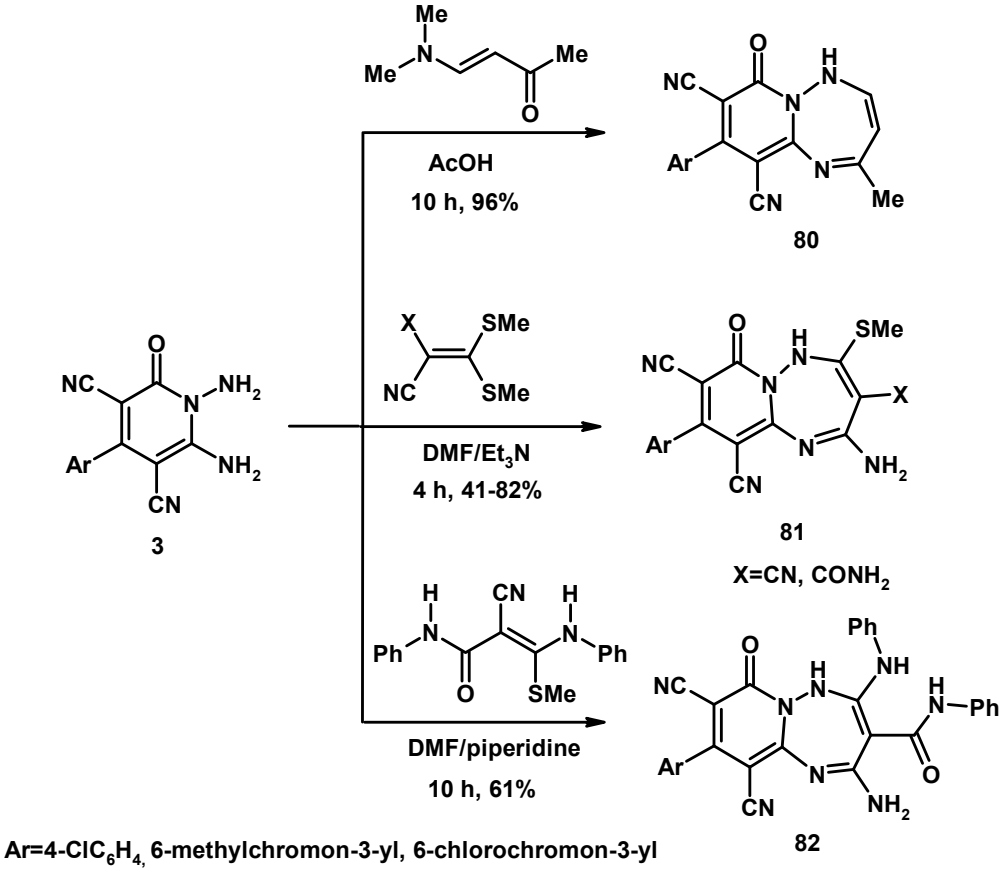
Scheme 28

Treatment of 1,6-diaminopyridones **3** with pentane-2,4-dione afforded 9-aryl-2,4-dimethyl-7-oxo-6,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitriles **78**,[38,44] which reacted with benzene diazonium chloride to give 3-phenylhydrazono-1*H*-pyrido[1,2-*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]



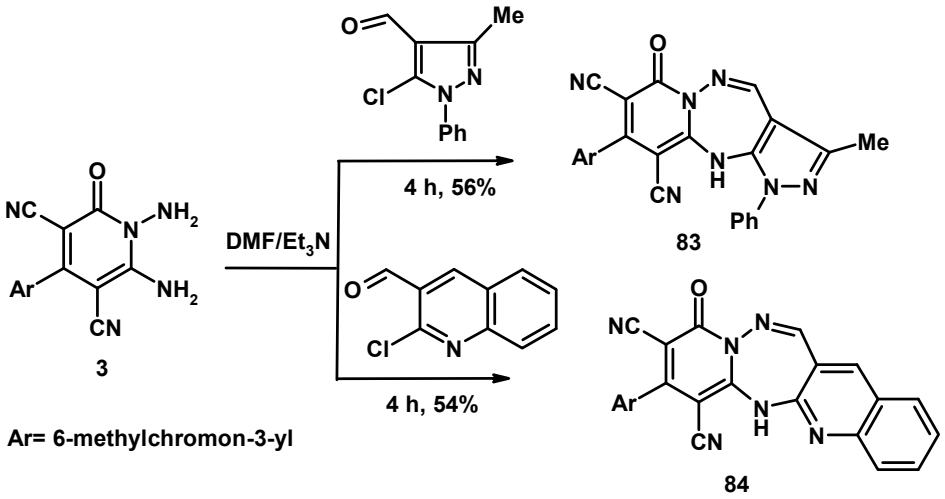
Scheme 29

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]



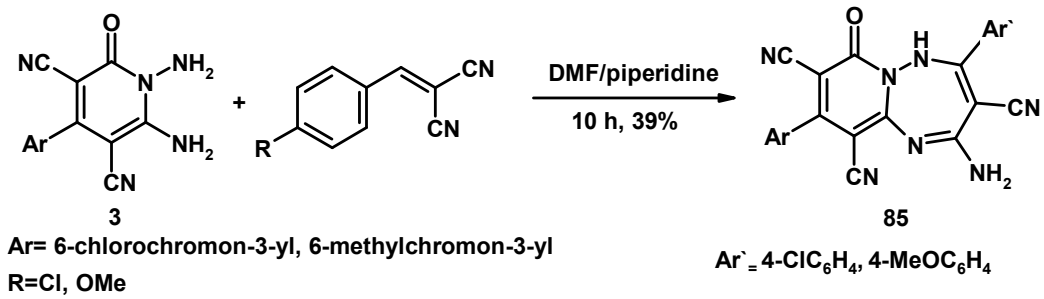
Scheme 30

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).[40]



Scheme 31

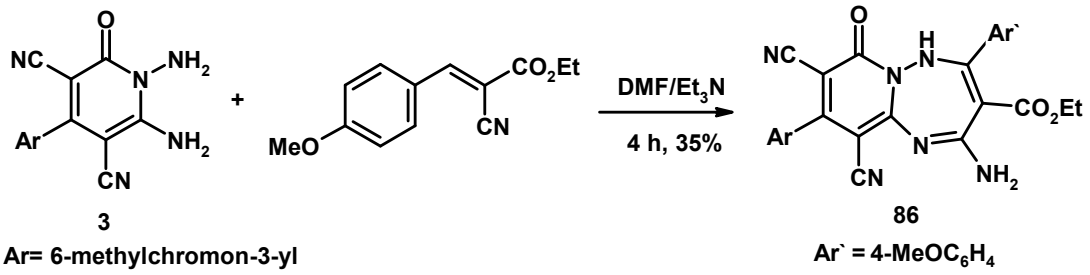
2-Aminopyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile **85** was prepared by reaction of 1,6-diaminopyridone **3** and (4-chlorobenzylidene)malononitrile in boiling DMF and piperidine (Scheme 32).[36,40]



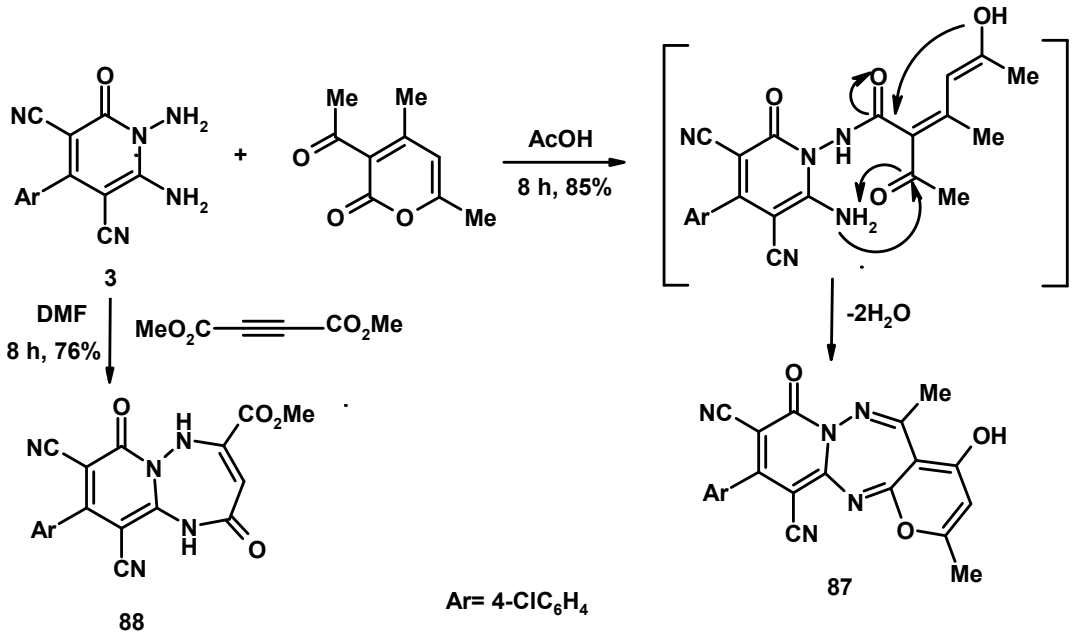
Scheme 32

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-4*H*-chromen-3-yl)-7-oxo-5,7-dihydro-pyrido[1,2-*b*][1,2,4]triazepine-3-carboxylate **86** (Scheme 33).[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).[44]

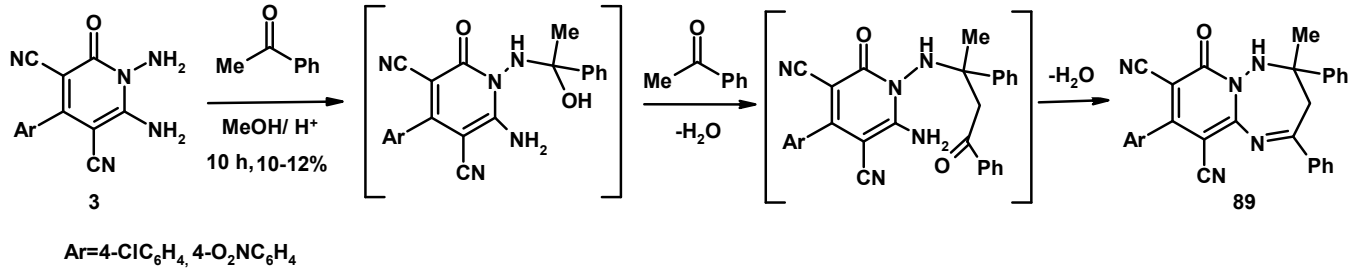


Scheme 33



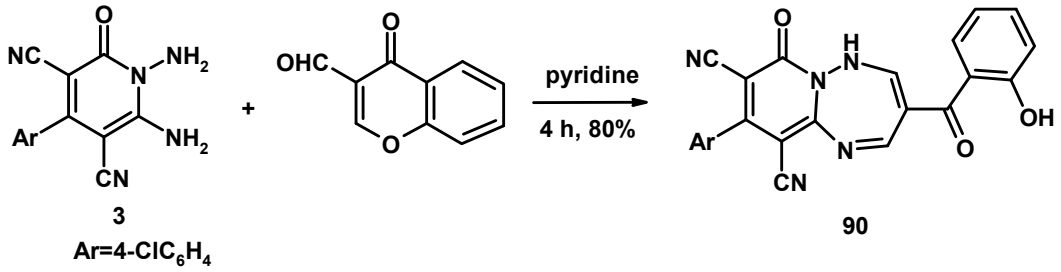
Scheme 34

9-Aryl-4-methyl-2,4-diphenyl-7-oxo-3,4,6,7-tetrahydro-5*H*-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]



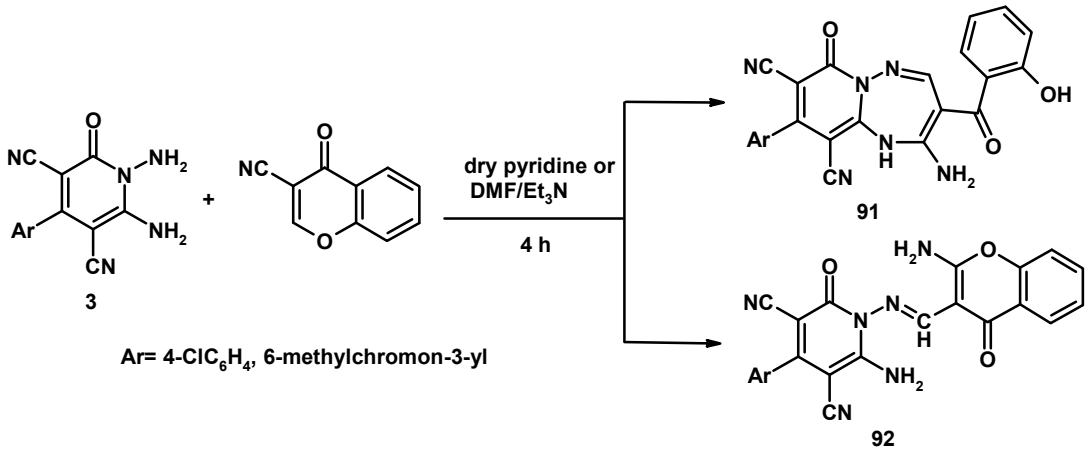
Scheme 35

9-(Aryl)-3-(2-hydroxybenzoyl)-7-oxo-6*H*-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]



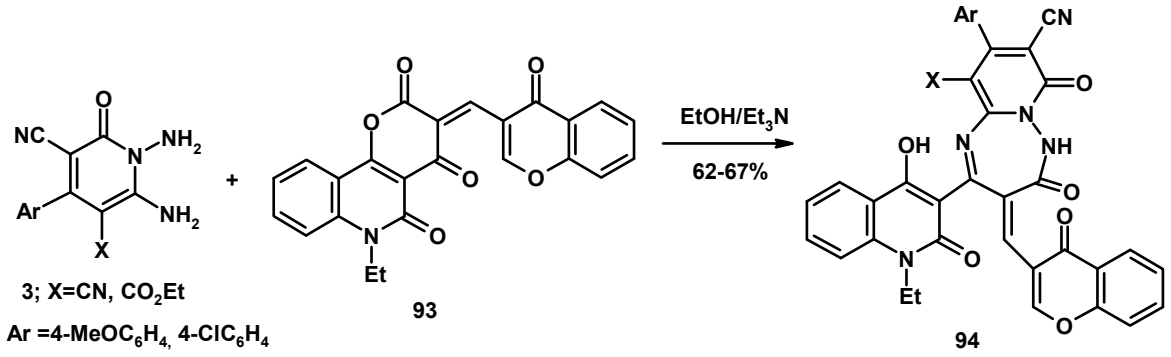
Scheme 36

Treatment of diaminopyridone **3** with chromone-3-carbonitrile in DMF under reflux gave 2-amino-3-(2-hyroxybenzoyl)-7-oxo-9-(aryl)-5*H*-pyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile **91** as described by Abdel-megid,[40,44] while gave the Schiff base **92** as published by Sosnovskikh and Moshkin (Scheme 37).[47]



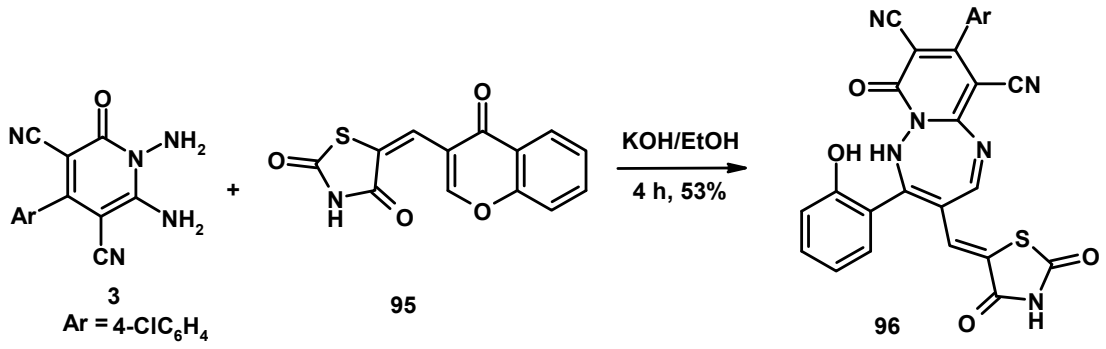
Scheme 37

Reaction of 1,6-diaminopyridone **3** with 6-ethyl-3-[(4-oxo-4*H*-chromen-3-yl)methylidene]pyrano[3,2-*c*]-quinoline-2,4,5-(3*H*,6*H*)-trione **93** afforded the pyrido[1,2-*b*][1,2,4]triazepines **94**, bearing chromone and quinolinone nuclei (Scheme 38). The reactions proceeds initially *via* α-pyrone ring opening by the more nucleophilic amino group (*N*-NH_2) followed by ring closure to produce the desired products.[48]



Scheme 38

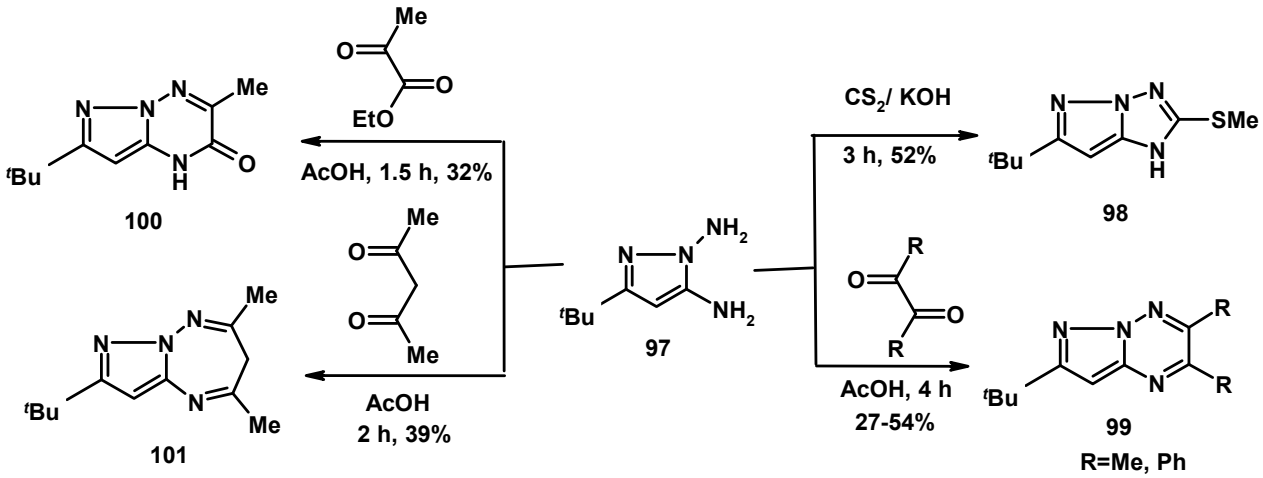
The RORC reactions of chromone derivative **95** with 1,6-diaminopyridone **3** gave pyrido[1,2-*b*][1,2,4]-triazepine derivative **96** (Scheme 39).[49]



Scheme 39

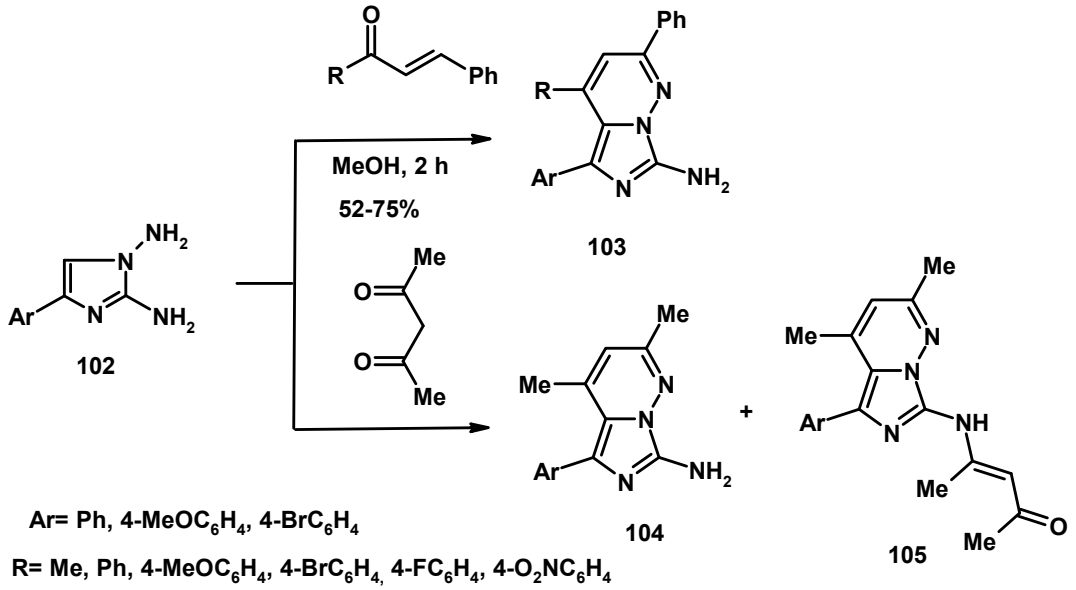
3. Heterocyclization with diaminoimidazoles

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]



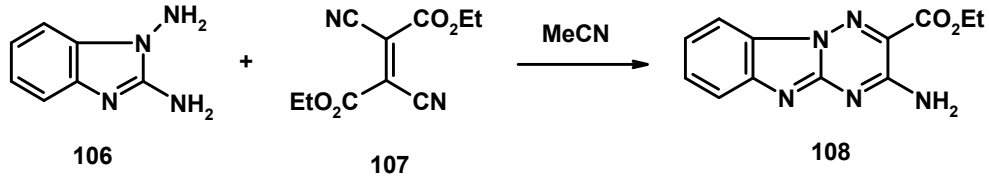
Scheme 40

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[l,5-*b*]pyridazine **104** and 5-(4-bromophenyl)-2,4-dimethyl-7-[(4-oxo-2-pent-2-en-yl)amino]imidazo[l,5-*b*]pyridazines **105** (Scheme 41), compound **104** and **105** were separated by crystallization process.[51]



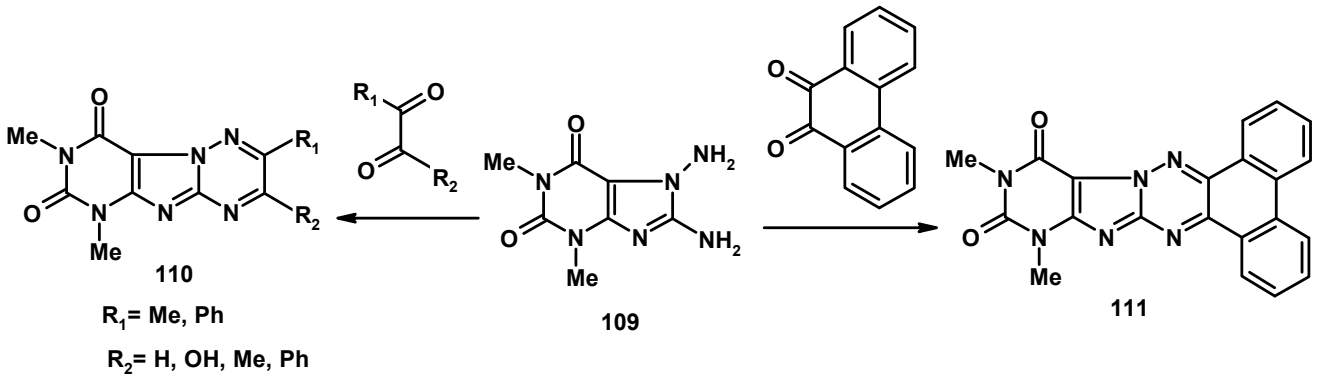
Scheme 41

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]



Scheme 42

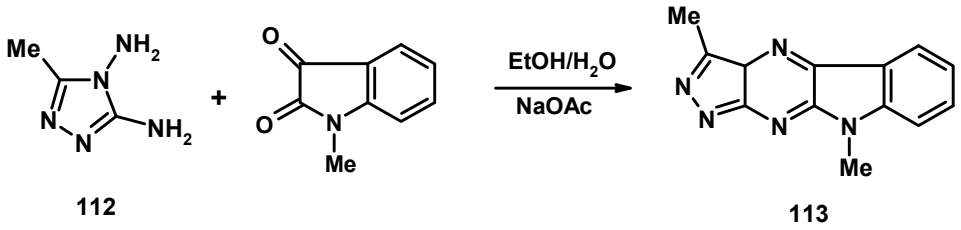
On the other hand, 1,2,4-triazino[2,3-*f*]xanthines **110** and **111** were prepared from the reaction of 5,6-diaminotheophylline **109** with the acyclic and cyclic dicarbonyl compounds, respectively (Scheme 43).[53]



Scheme 43

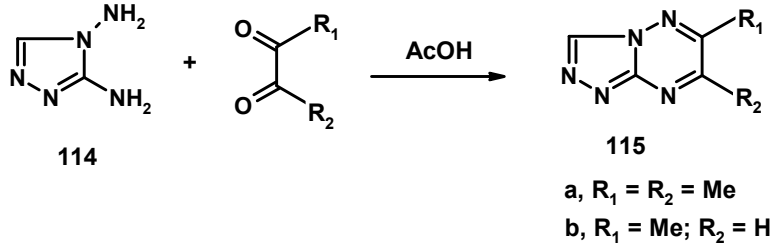
4. Heterocyclization with diaminotriazoles

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]



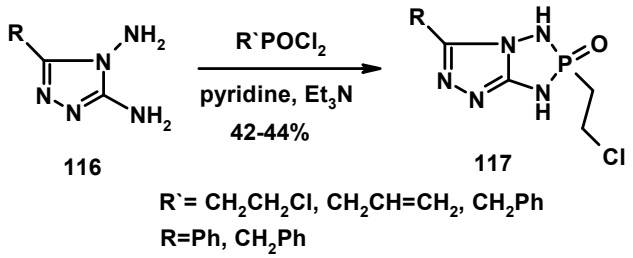
Scheme 44

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]



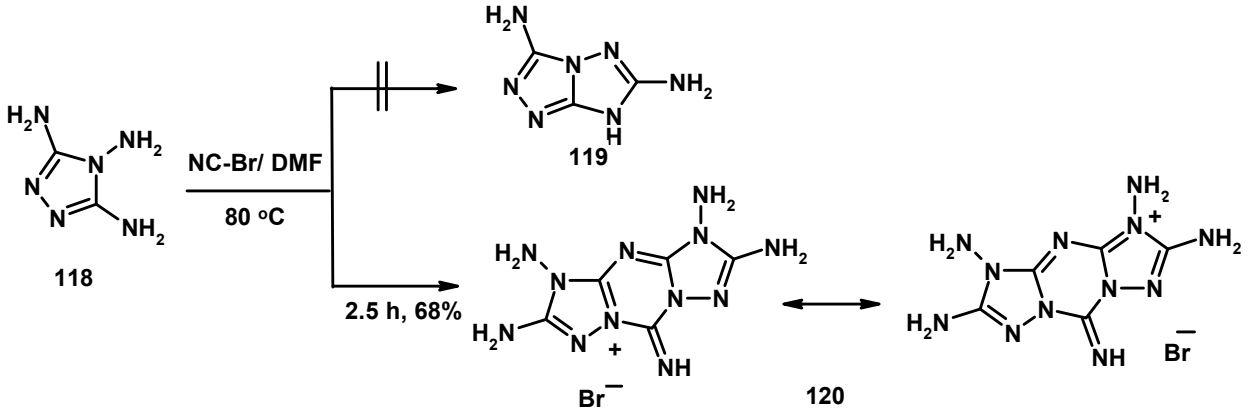
Scheme 45

4-(Phenyl/benzyl)-2-(2-chloroethyl)-1*H*-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]



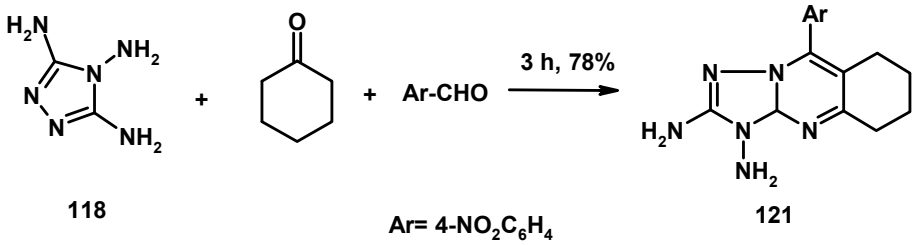
Scheme 46

Reaction of 3,4,5-triamino-4*H*-1,2,4-triazole (guanazine) **118** with cyanogen bromide did not give the hypothical cyclization product, 7*H*-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-3*H*,9*H*-*bis*[1,2,4]triazolo[1,5-*a*:5',1'-*d*][1,3,5]triazinium bromide **120** (Scheme 47).[57]



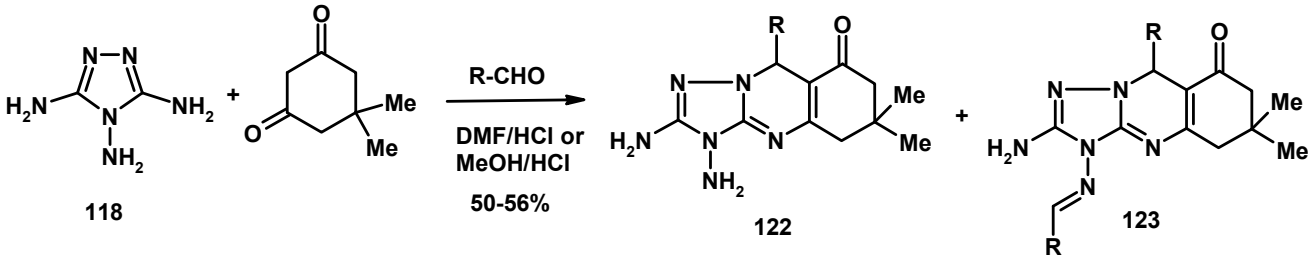
Scheme 47

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]



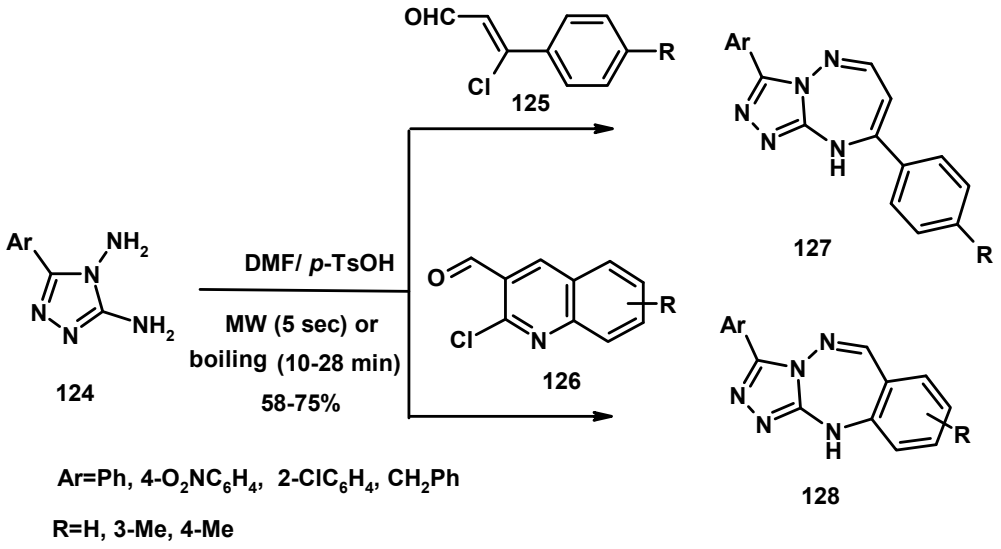
Scheme 48

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_6H_4CHO, compound **123** was isolated as by product in low yield (Scheme 49).[58]



Scheme 49

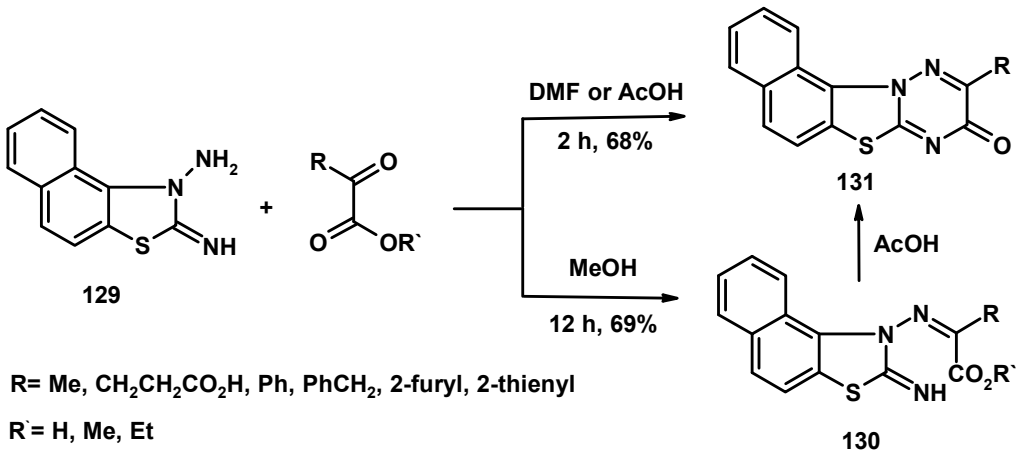
Cyclocondensation of diaminotriazole **124** with β-chlorocinnamaldehyde **125** and 2-chloro-3-formylquinolines **126** in the presence of a catalytic amount of *p*-TsOH produced triazolotriazepines **127** and quinolino[3,2-*f*][1,2.4]triazolo[4,3-*b*][1,2,4]triazepines **128** (Scheme 50).[59,60]



Scheme 50

5. Heterocyclization with diaminothiazoles

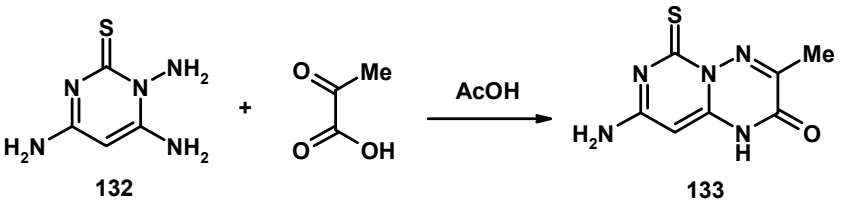
Condensation of 1-amino-2-iminonaphtho[1,2-*d*]thiazole **129** with some *α*-ketocarboxylic acid and their esters in methanol gave the open chain product **130**, however, when the reaction was performed in glacial acetic acid or DMF, cyclic products identified as 10-alkyl/aryl/heteroaryl/aralkyl-9*H*-naphtho[1',2':4,5]-thiazolo[3,2-*b*][1,2,4]triazin-9-ones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



Scheme 51

6. Heterocyclization with diaminopyrimidines

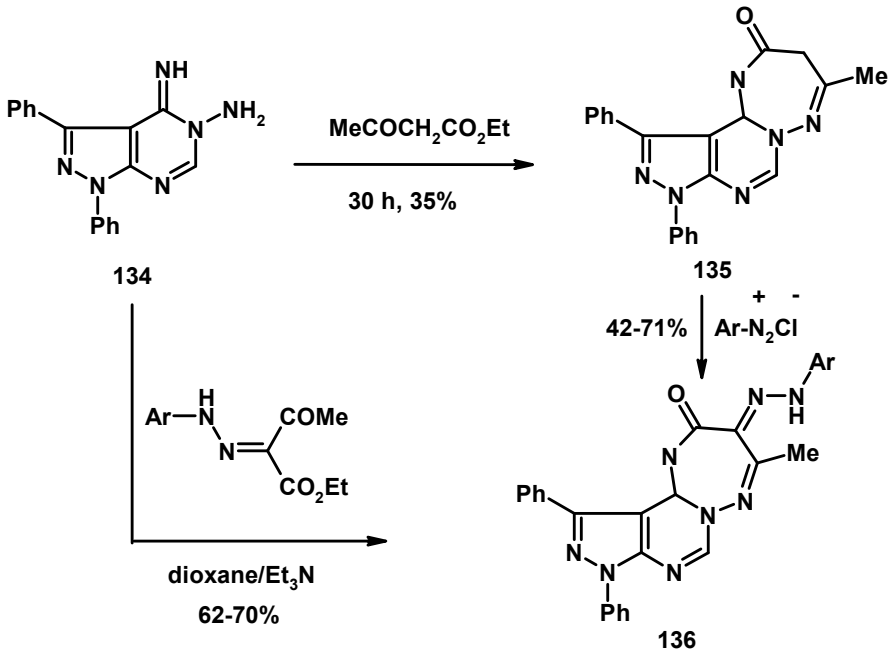
Cyclocondensation of triaminopyrimidinethione **132** with pyruvic acid in glacial acetic acid gave pyrimido[3,4-*b*][1,2,4]triazine derivative **133** (Scheme 52).[62]



132 133

Scheme 52

1,3-Diphenyl-7-methyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*b*][1,2,4]triazepin-5(6*H*)-one **135** was prepared by condensation of 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-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).[63]

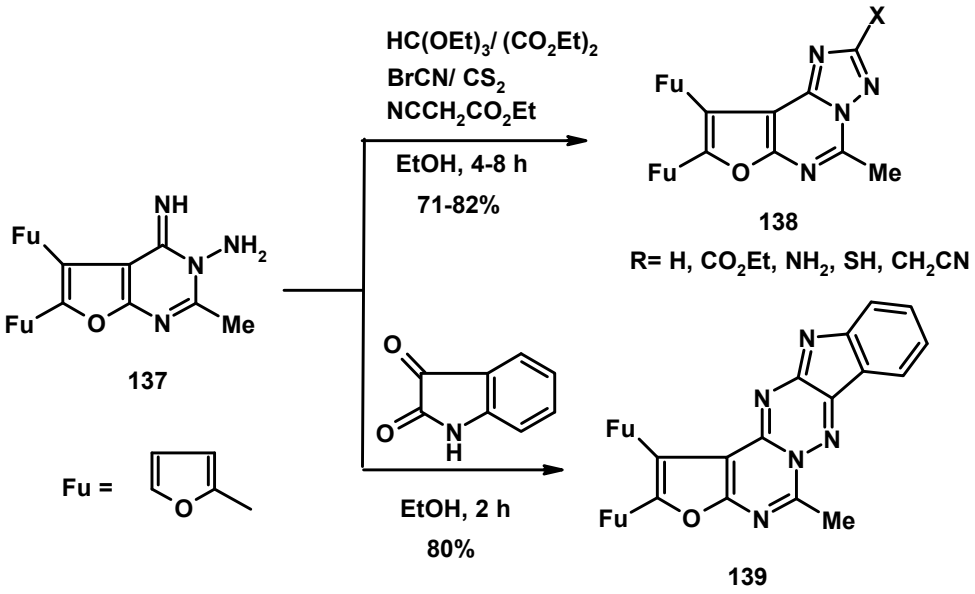


134 135 136

Ar= 3-MeC_6H_4, 3-ClC_6H_4, 3-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$

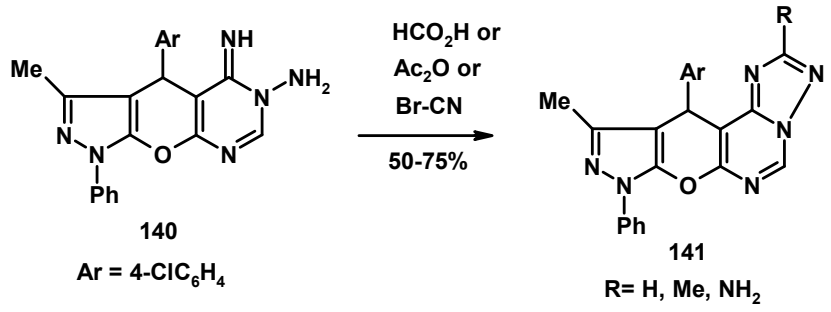
Scheme 53

Furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **138** were prepared by reaction of 5,6-di-(2-furyl)-3*H*,4*H*-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).[64]



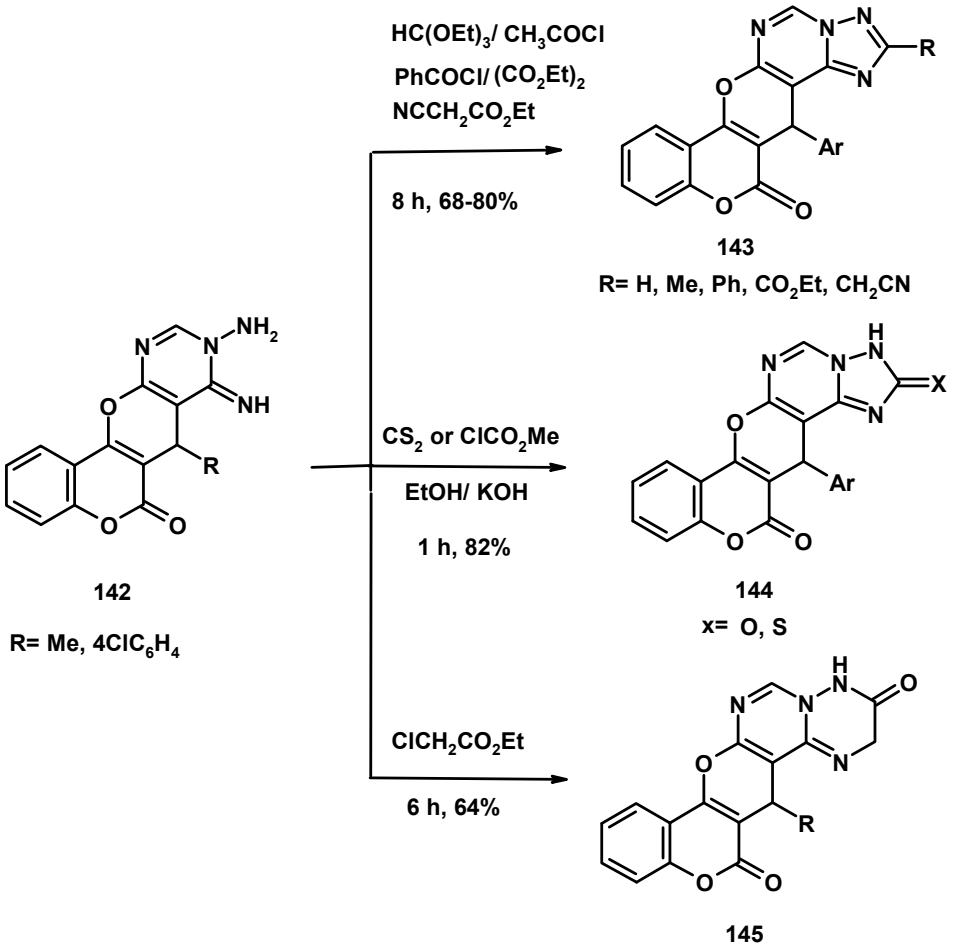
Scheme 54

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]



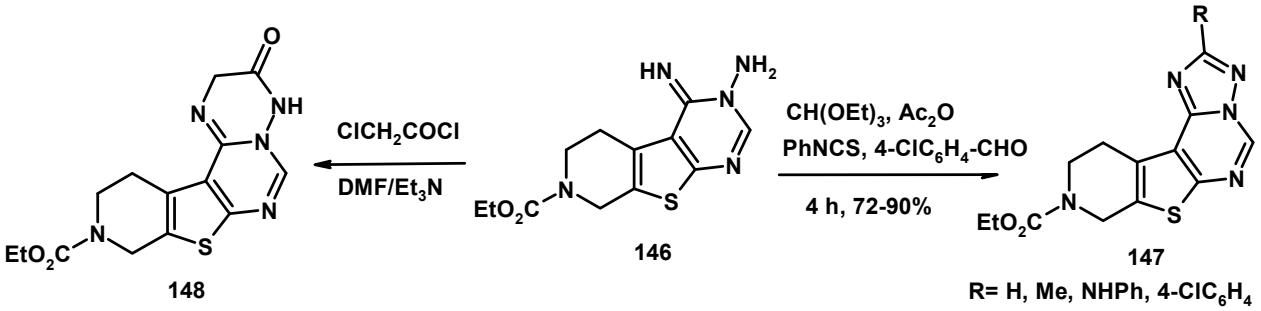
Scheme 55

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-6*H*,7*H*-[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-2*H*,14*H*,15*H*-[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]



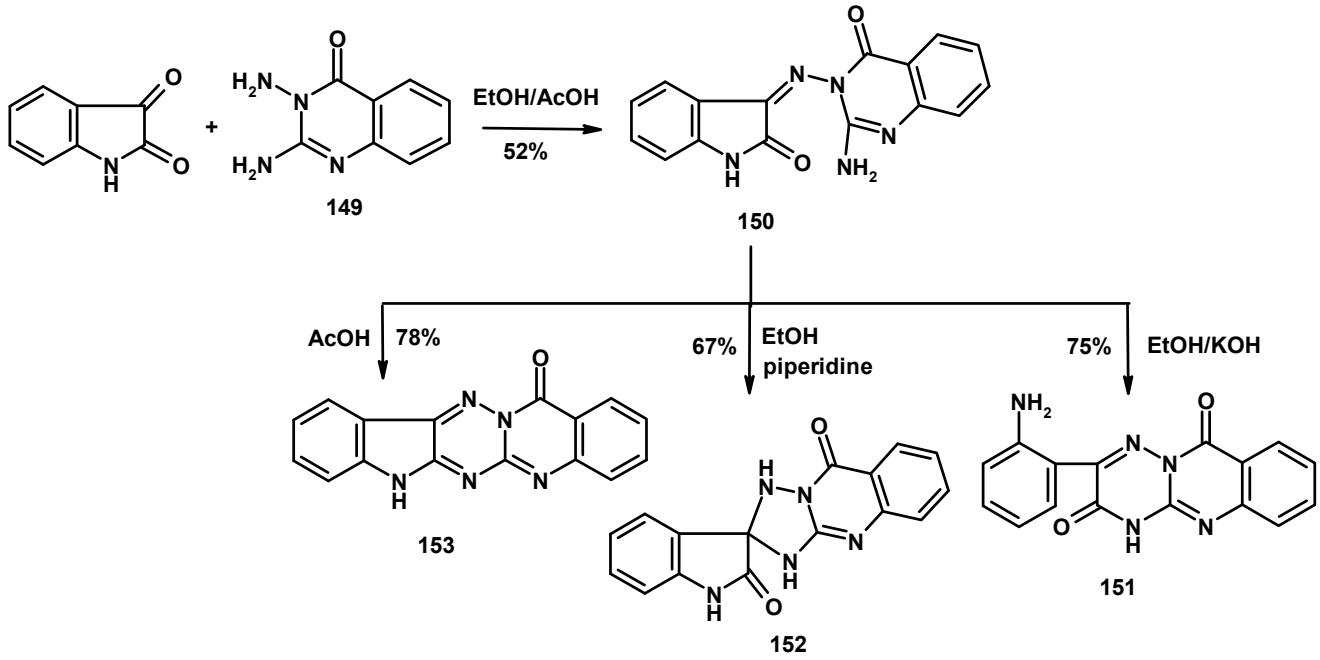
Scheme 56

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(7*H*)-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).[68]



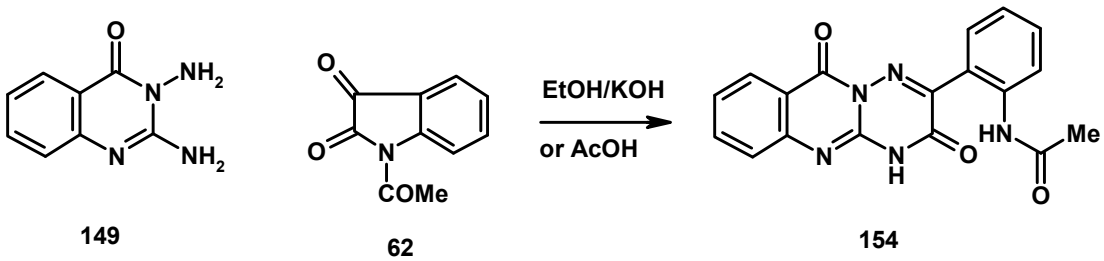
Scheme 57

During an investigation of the reactions of indole-2,3-dione with 2,3-diamino-4(3*H*)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]-2*H*-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[3*H*-indol-3',2'(1*H*)][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).[69]



Scheme 58

On the other hand, treatment of *N*-acetylisatine with 2,3-diamino-4(3*H*)quinazolone **149** led to *N*-2-(triazinoquinazolinone)phenyl acetamide **154** under the same conditions (Scheme 59).[70]

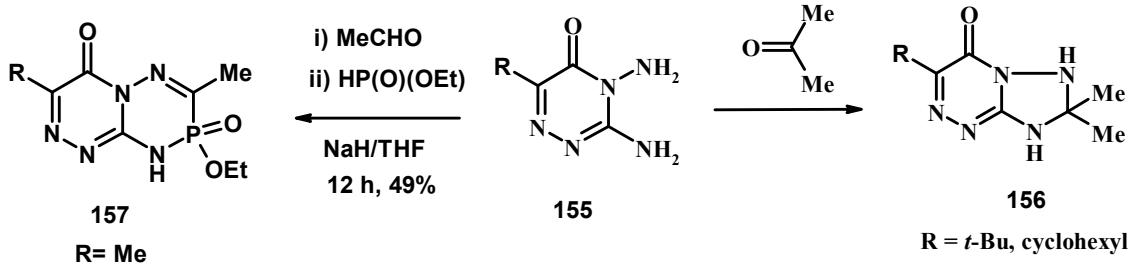


Scheme 59

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 **156**.[71] While, the reaction of compound **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 **157** (Scheme 60).[72]



Scheme 60

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