Tandem *in situ* generation and 1,5-electrocyclization of N-hetaryl nitrilimines. A facile methodology for synthesis of annulated 1,2,4-triazoles and their acyclo *C*-nucleosides

Ahmad Sami Shawali

Department of Chemistry, Faculty of Science, University of Cairo, Egypt
E-mail: as_shawali@mail.com

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Abstract

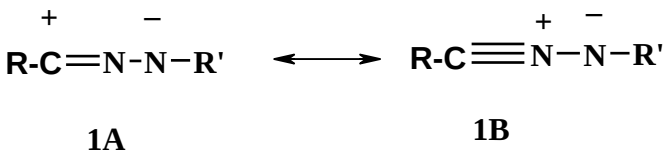
This review summarizes results of literature reports concerning tandem *in situ* generation and 1,5-electrocyclization of N-hetaryl nitrilimines reported by us and other research groups from 1960 to mid 2009. It outlines the utility of such reactions as facile synthetic strategy for synthesis of annulated triazoles and their acyclo *C*-nucleosides.

Keywords: Nitrilimines, 1.5-electrocyclization, heterocycles, acyclo *C*-nucleosides

Contents

1. Introduction

Basically a nitrilimine **1** is a flexible system of three atoms over which four pi-electrons are distributed. Although one can write seven possible resonance structures for such a system, the 1,3-dipolar sextet structure **1A** with its complementary nucleophilic and electrophilic centers will be used throughout this article, although theoretical calculations have indicated that all the octet zwitterionic structure **1B** is the most stable contributor to the resonance hybrid.



1A **1B**

As very authorative reviews[1-10] of the chemistry of the precursors of nitrilimines exist, brief sketches will be given here for the various methods of the generation of nitrilimines as depicted below. The various methods used for generation of nitrilimines include:

1. Thermal[11-13] and photochemical[14-17] extrusion of nitrogen from tetrazoles.

2. Thermal extrusion of carbon dioxide from 1,3,4-oxadiazol-5-ones.[18-20]

3. Thermal extrusion of sulfur dioxide from 1,2,3,4-oxathiadiazol-2-oxide.[21-22]

4. Base induced elimination of hydrogen halide from hydrazonoyl halides.[23-28] The mechanism of this 1,3-elimination reaction has been studied.[26-32] Dehydrohalogenation reaction of the hydrazonyl halides can also be effected by silver nitrate.[28, 33,34]

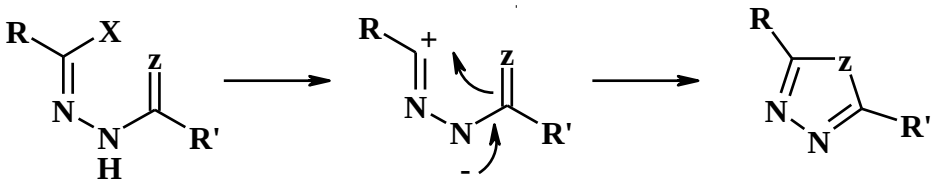
5. Oxidation of aldehyde N-acyl or N-heteroaryl-substituted hydrazones with lead tetra-acetate,[35-38] iron(III) chloride,[39] bromine in acetic acid in the presence of sodium acetate,[36, 40-42] trifluroboron-etherate solution in acetic acid.[43] Also, nitrilimines can be generated electrolytically by anodic oxidation of aldehyde N-susbtituted hydrazones,[37, 44-47] heating them with sulfur,[38] nitrobenzene[39, 48] or stirring with HNO_3 in DMF.[49]

6. Thermolysis of sodium salt of α-nitrohydrazones.[50, 51]

7. Photolysis of sydnones.[52-59]

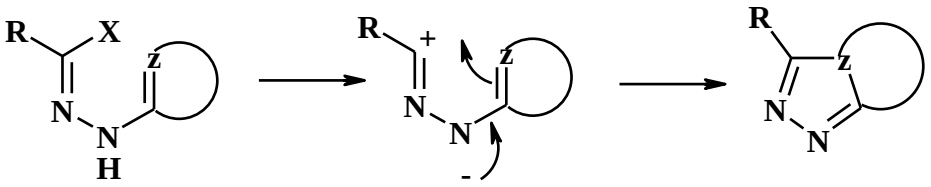
8. Thermal decomposition of 5-aryl-4-arylazoisoxazoles.[60, 61]

Nitrilimines having a double bond at the N-terminus are prone towards the 1,5-electrocyclization as depicted in equation 1. If the double bond is a part of the heterocyclic moiety, such 1,5-electrocyclization will lead to fused ring system as shown in equation 2. Nitrilimines having both α,β- and γ,δ-double bonds are also susceptible to 1,7-electrocyclization of the 8-pi electron system to give the respective triazepine, oxadiazepine or thiadiazepine derivatives according to the nature of Z as shown in equation 3.



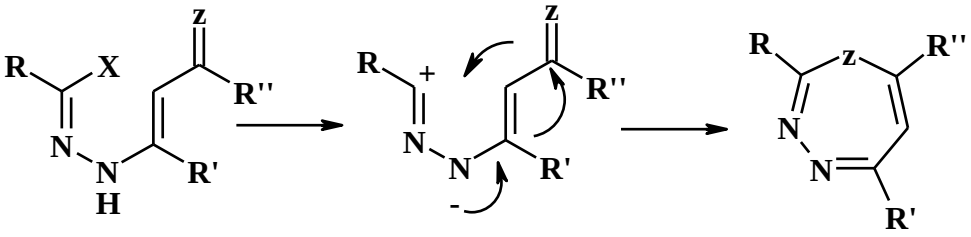
Eq. 1

Z =R''N; O; S



Eq. 2

X = Halogen; Hydrogen



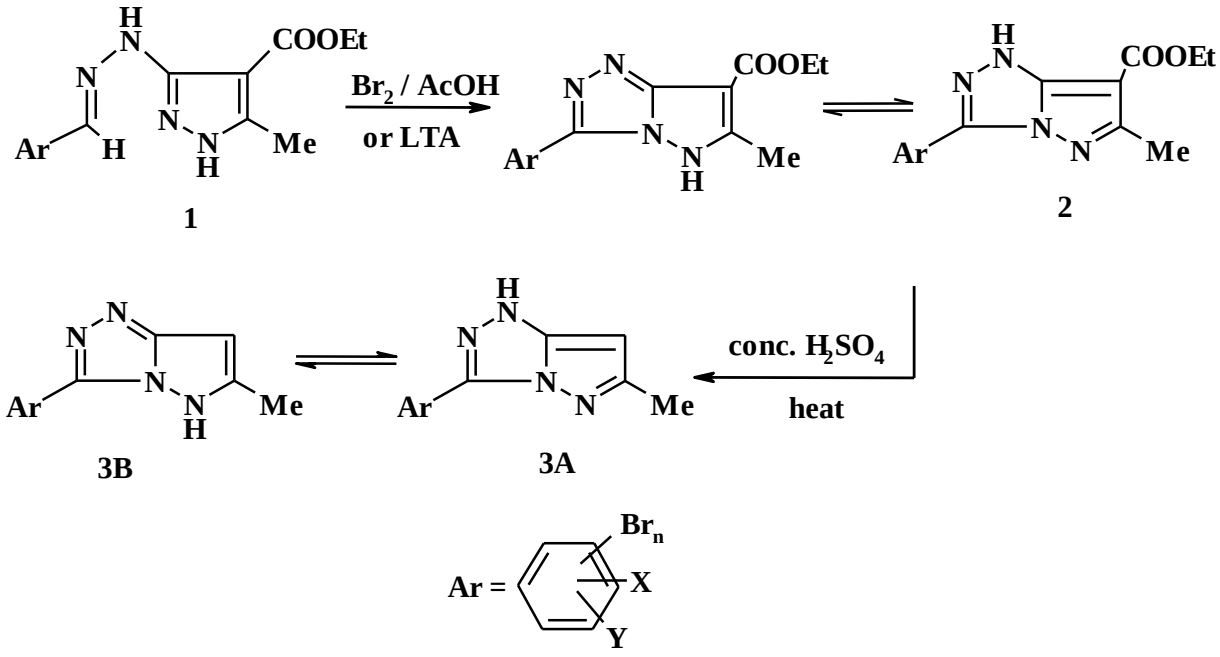
Eq. 3

Z =R'''N; O; S

2. Fused azolo-triazoles

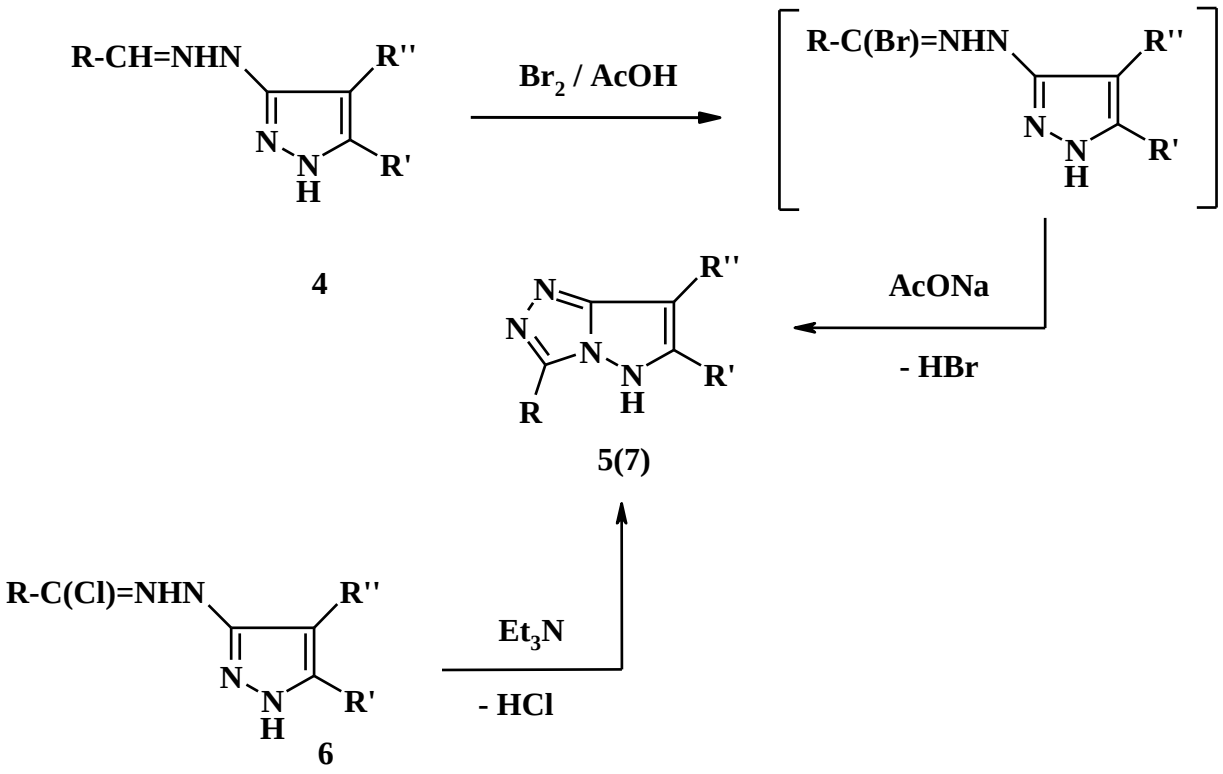
2.1. Pyrazolo[5,1-*c*][1,2,4]triazoles

1*H*-3-Substituted-aryl-6-methyl-7-ethoxycarbonyl-pyrazolo[5,1-*c*][1,2,4]-triazoles **2** were obtained by the action of lead tetraacetate or bromine in acetic acid on 1H-2-methyl-3-ethoxycarbonyl-4-arylidenehydrazinopyrazole **1**.[62, 63] Hydrolysis of **2** and decarboxylation of the resulting carboxylic acids gave the corresponding 1*H*-3-substituted-aryl-pyrazolo-[5,1-*c*][1,2,4]triazoles **3**.[63]



a) X = 2-NO_2, Y = H; **b)** X = 4-NO_2, Y =H; **c)** X = 2-Cl, Y=H; **d)** X = 4-CH_3, Y=H; **e)** X= 2-OCH_3, Y=H; **f)** X=2-OH, Y=H; **g)** X= 4-OH, Y = H; **h)** X = 3-OH, Y=H; **i)** X = 2-OH, Y = 4-OH; **j)** X = 4-OCH_3, Y = H; **k)** X = 2-OCH_3, Y = 4-OCH_3; **l)** X = 4-OH, Y = 3,5-$(t\text{-}C_4H_9)_2$; **m)** X = 2-OCH_3, Y = H, Br_n = 3,5-Br_2; **n)** X = 2-OH, Y = H, Br_n = 3,5-Br_2; **o)** X = 4-OH, Y = H, Br_n = 3,5-Br_2; **p)** X = 3-OH, Y = H, Br_n = 2,4,6-Br_3; **q)** X = 2-OH, Y = 4-OH, Br_n = 3,5-Br_2; **r)** X = 4-OCH_3, Y = H, Br_n = 3-Br, **s)** X = 2-OCH_3, Y = 4-OCH_3, Br_n = 5-Br.

Other pyrazolo[5,1-*c*][1,2,4]triazoles **5(7)** were prepared by either treatment of the hydrazone **4** with bromine in acetic acid in presence of sodium acetate[63] or by treatment of the hydrazonoyl chloride **6** with triethylamine.[64]



4

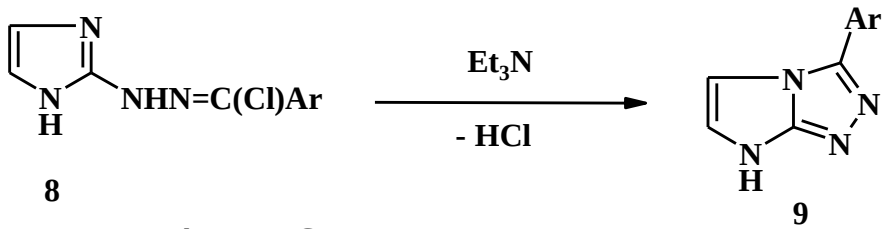
R = OC_2H_5; Me; COMe; NH(*p*-$MeOC_6H_4$)

R'' = H; COOEt

R' = H; Me

2.2. Imidazo[2,1-*c*][1,2,4]triazoles

Imidazo[2,1-*c*][1,2,4]triazoles **9** were prepared by Scott et al[65, 66] *via* heating the hydrazonoyl chloride **8** in aqueous dioxane containing catalytic amount of triethylamine.



8 **9**

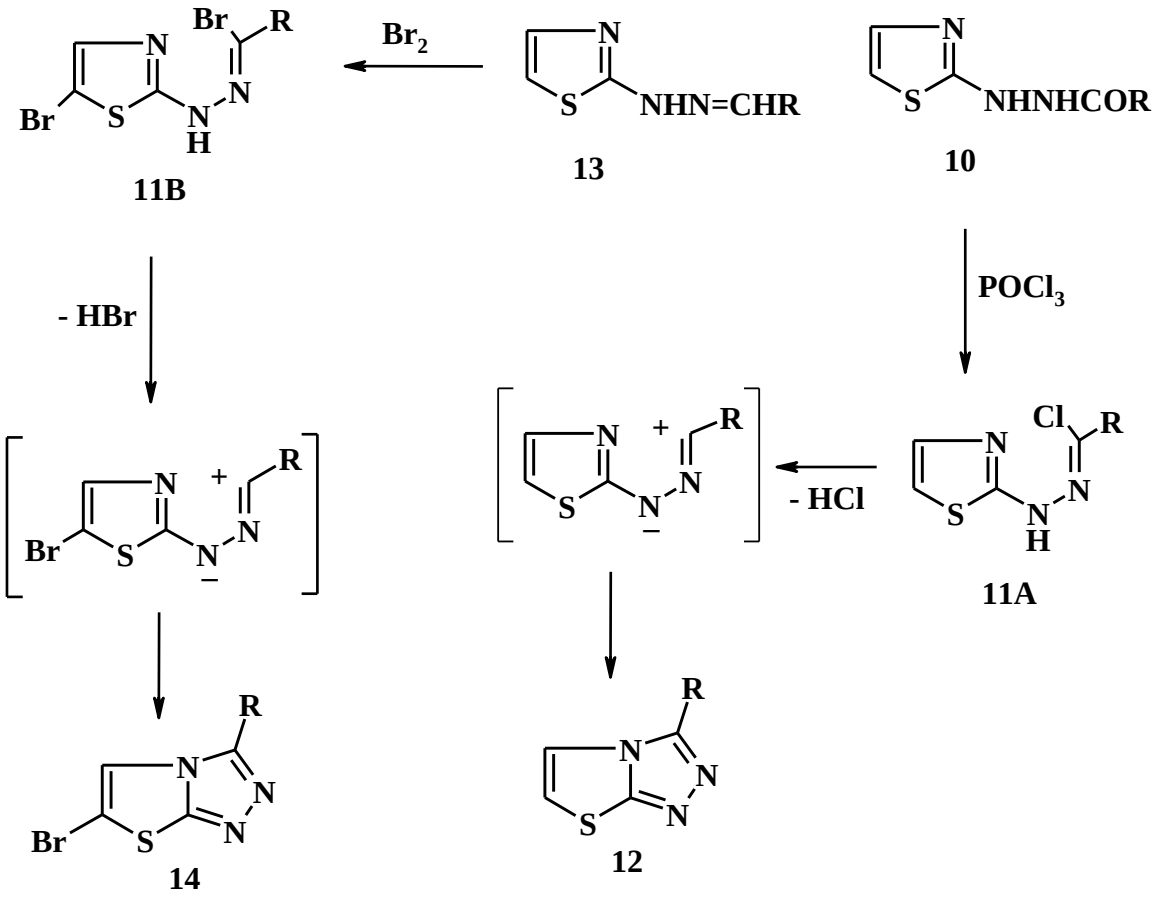
Ar = 4-XC_6H_4

X = H; CH_3; *i*-C_3H_7; Cl; Br; NO_2

2.3. Thiazolo[2,3-*c*][1,2,4]triazoles

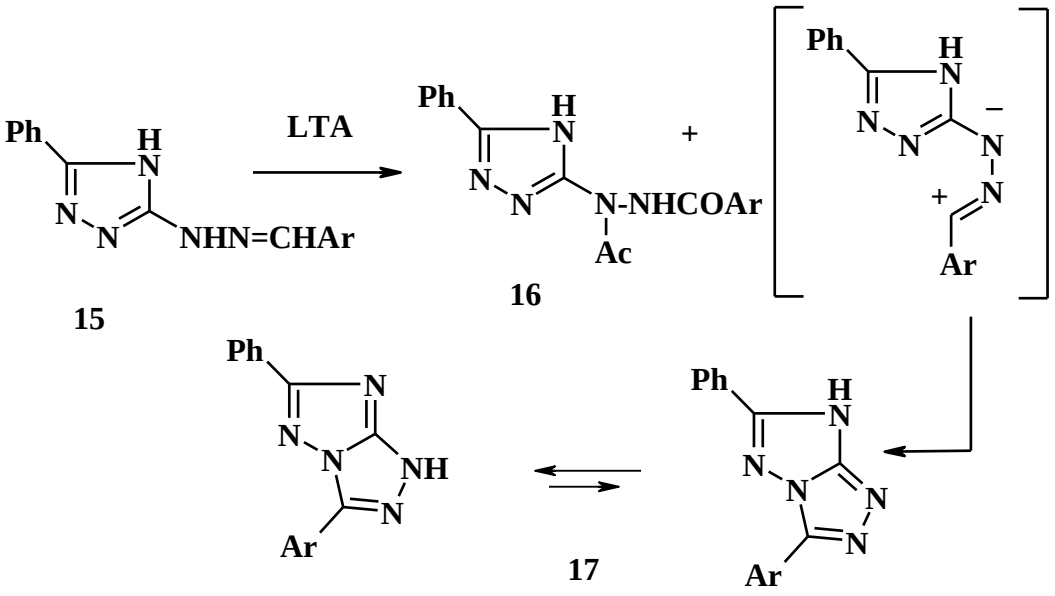
Treatment of the acid hydrazide **10** with $POCl_3$ gives the hydrazonoyl chloride **11A**. The latter was reported to undergo, upon treatment with a base, *in situ* tandem dehyrochloronation and 1,5-electrocyclization of the resulting nitrilimine to yield the corresponding thiazolo[2,3-

c][1,2,4]triazoles **12**.[67-69] Also, bromination of the hydrazone **13** afforded the hydrazonoyl bromide **11B** which underwent *in situ* dehydrobromination to yield the respective thiazolo[2,3-*c*][1,2,4]triazoles **14**.



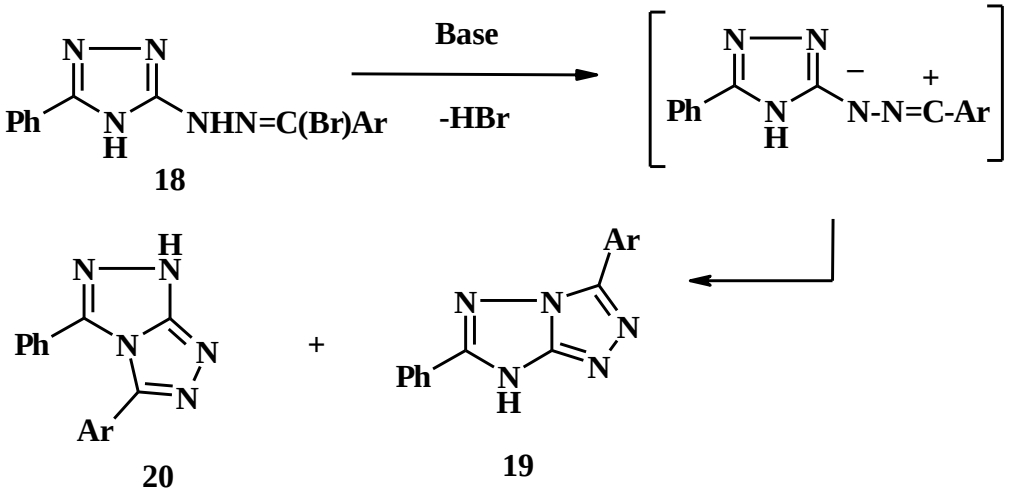
2.4. 1,2,4-Triazolo[5,1-*c*][1,2,4]triazoles

Treatment of aldehyde *N*-(1,2,4-triazol-3-yl)hydrazones **15** with lead tetraacetate gave a mixture of 3-aryl-6-phenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazoles **17** and the N-acetylated hydrazide **16**.[35, 70-71]



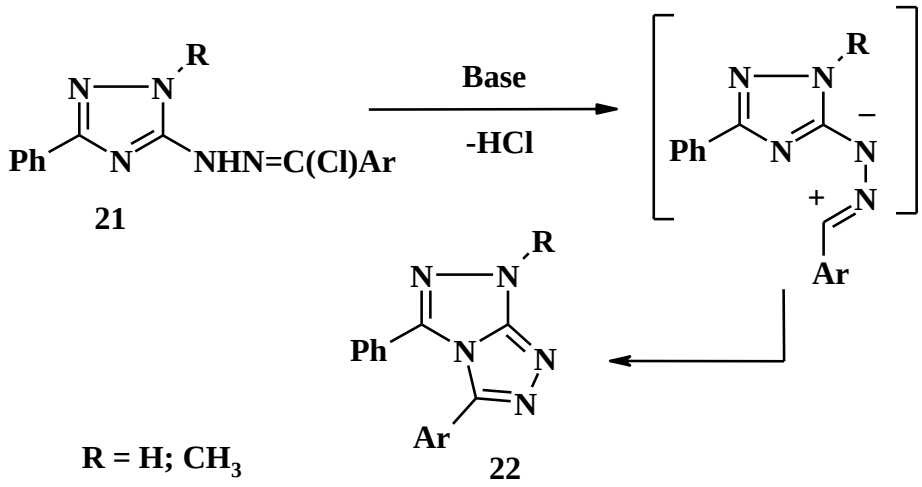
Ar = Ph; *p*-MeOC$_6$H$_4$; *p*-ClC$_6$H$_4$; *P*-NO$_2$C$_6$H$_4$;
m*-NO$_2$C$_6$H$_4$; *p*-MeC$_6$H$_4$; *p*-BrC$_6$H$_4$

Treatment of the hyrazonoyl bromide **18** with bases was reported to give a mixture of 3-aryl-6-phenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazoles **19** and 3-aryl-5-phenyl-1,2,4-triazolo[3,4-*c*][1,2,4] triazoles **20** with the former being predominant products.[72] However, treatment of **18** with sodium acetate in acetic acid yielded mainly **19** as end products.[73]



Ar = Ph; *p*-MeOC$_6$H$_4$; *p*-ClC$_6$H$_4$; *P*-NO$_2$C$_6$H$_4$; *m*-NO$_2$C$_6$H$_4$;
***p*-MeC$_6$H$_4$; *p*-BrC$_6$H$_4$; *p*-(CH$_3$)$_2$CH-C$_6$H$_4$.**

Similiar treatment of **21** with a base forces the cyclization to take place at the less nucleophilic N-4 to give 1,2,4-triazolo[4,3-*c*][1,2,4]triazoles **22**.[74]

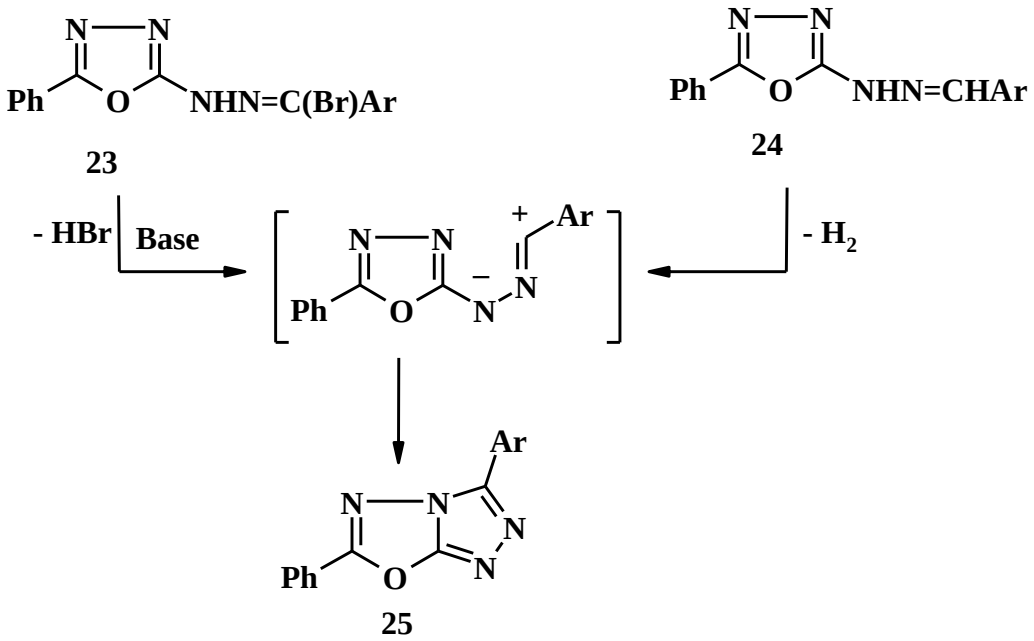


R = H; CH_3

Ar = Ph; *p*-ClC_6H_4; *p*-MeC_6H_4; *p*-$MeOC_6H_4$; *p*-$NO_2C_6H_4$

2.5. 1,2,4-Triazolo[3,4-*b*][1,3,4]oxadiazoles

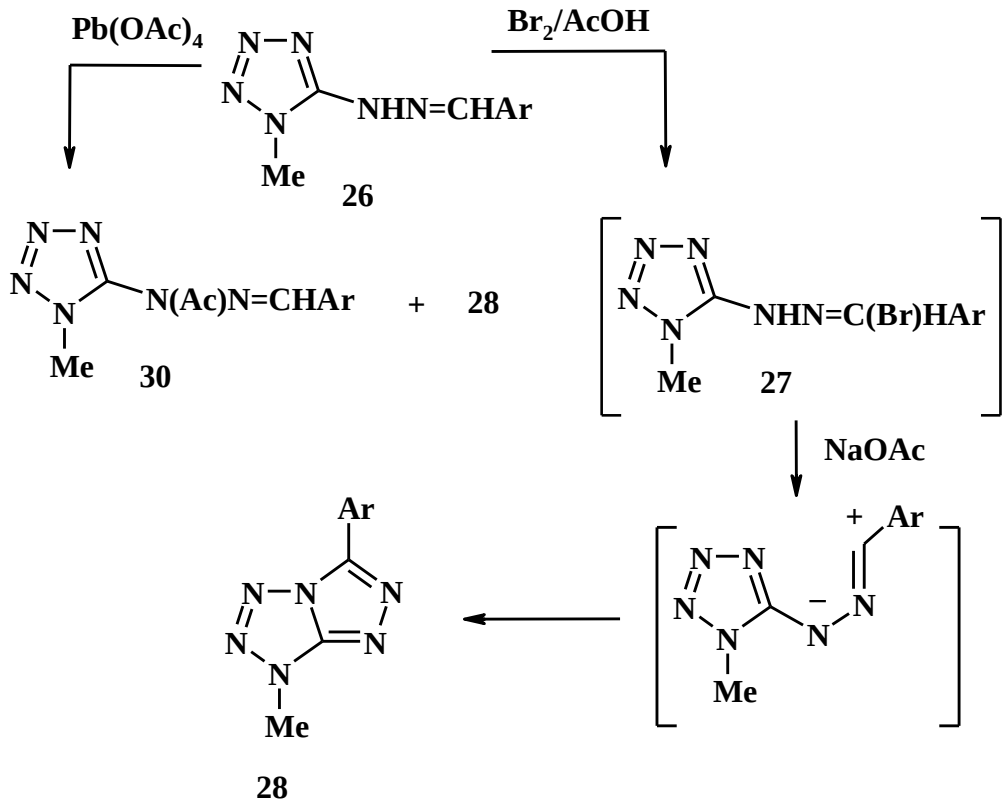
1,2,4-Triazolo[3,4-*b*][1,3,4]oxadiazoles **25** have been prepared by treatment of the hydrazonoyl bromides **23** with triethylamine.[75, 76] The same products were also obtained by oxidative cyclization of the parent hydrazones **24** by heating them in nitrobenzene.[48]



Ar = Ph; *p*-ClC_6H_4; *m*-BrC_6H_4; *p*-BrC_6H_4; *p*-$NO_2C_6H_4$

2.6. 1,2,4-Triazolo[4,3-*d*]tetrazoles

Treatment of N-(tetrazol-5-yl)hydrazones **26** with bromine in acetic acid in the presence of sodium acetate afforded the respective 1,2,4-trizolo[4,3-*d*]tetrazole derivatives **28** *via in situ* 1,5-electrocyclization of the respective nitrilimines generated from dehydrohalogenation of the hydrazonoyl bromide **27**. Attempts to prepare **28** by oxidative cyclization of the hydrazone **26** with lead tetraacetate gave a mixture of **28** and the N-acetyl derivatives **30** of the parent hydrazones.[77-81]



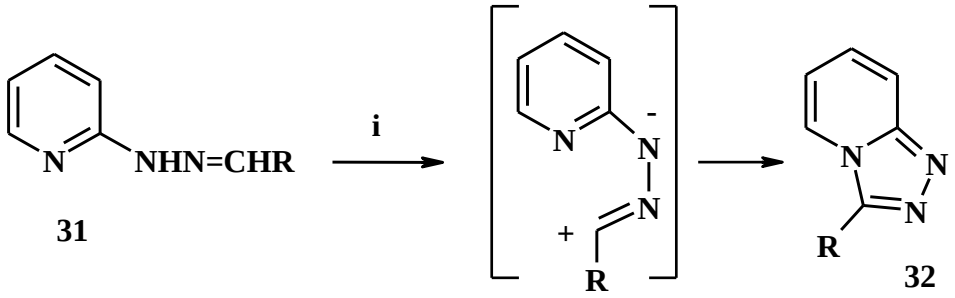
Ar = Ph; *p*-ClC$_6$H$_4$; *p*-BrC$_6$H$_4$; 2-thienyl

3. Fused triazolo-azines

3.1. 1,2,4-Triazolo[4,3-*a*]pyridines

Aldehyde N-(pyrid-2-yl)hydrazones **31** have been cyclized into the respective 1,2,4-triazolo[4,3-*a*]pyridine derivatives **32** upon chemical oxidation with either lead tetraacetate,[35,38,82,83] ferric chloride,[39, 83] iodobenzene-diacetate (IBD),[84] $CuCl_2$[85] or mercuric acetate.[86] Also treatment of **31** with either bromine in acetic acid in presence of sodium acetate,[40, 83] sulfur[38] or with boron trifluride etherate in acetic acid[43] gave the respective **32**. An evidence was presented to indicate that such conversion proceeds *via* the initial formation of nitrilimines as intermediate which then undergo 1,5-electrocyclization to give **32** as end products.[22, 87,88] The latter products were also

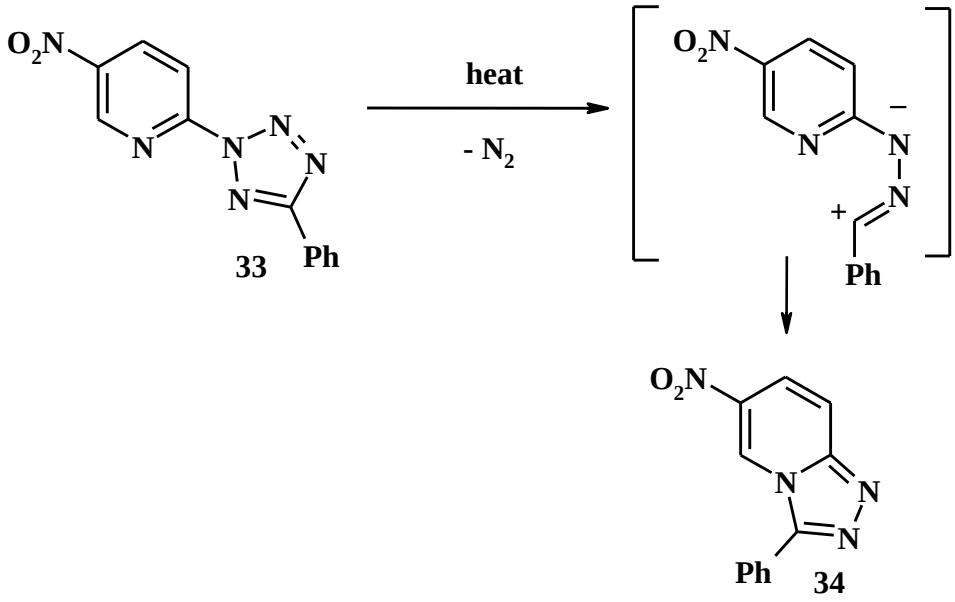
obtained by either anodic oxidation of the parent hydrazones **31** or by refluxing them in nitrobenzene.[39, 44]



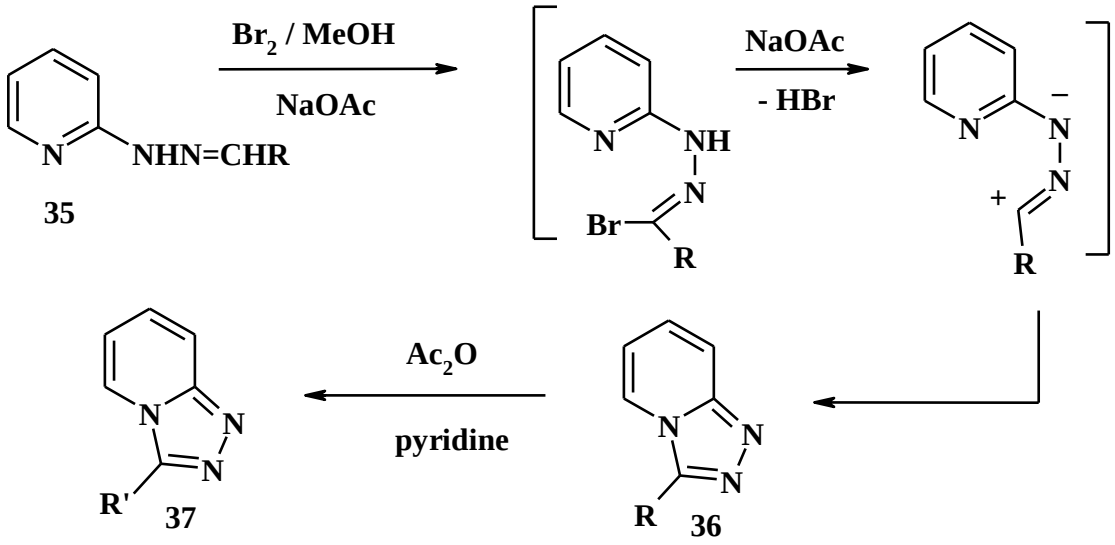
i = $Pb(OAc)_4$; IBD / CH_2Cl_2; $FeCl_3$; Br_2 / AcOH / AcONa; $CuCl_2$ or BF_3-etherate.

R = Ph; 4-MeC_6H_4; 2-$MeOC_6H_4$; 4-$MeOC_6H_4$; 3-$NO_2C_6H_4$; 4-$NO_2C_6H_4$; 4-BrC_6H_4; 4-ClC_6H_4; 2-ClC_6H_4; 2,4-Dichlorophenyl; 3,4-Methylenedioxyphenyl; 2-Carboxyphenyl; 2-Hydroxyphenyl; Furyl.

Nitrilimines generated by thermolysis of 3-(2-pyridyl)tetrazole **33** yielded 1,2,4-trizolo-[4,3-*a*]pyridine **34**.[89]



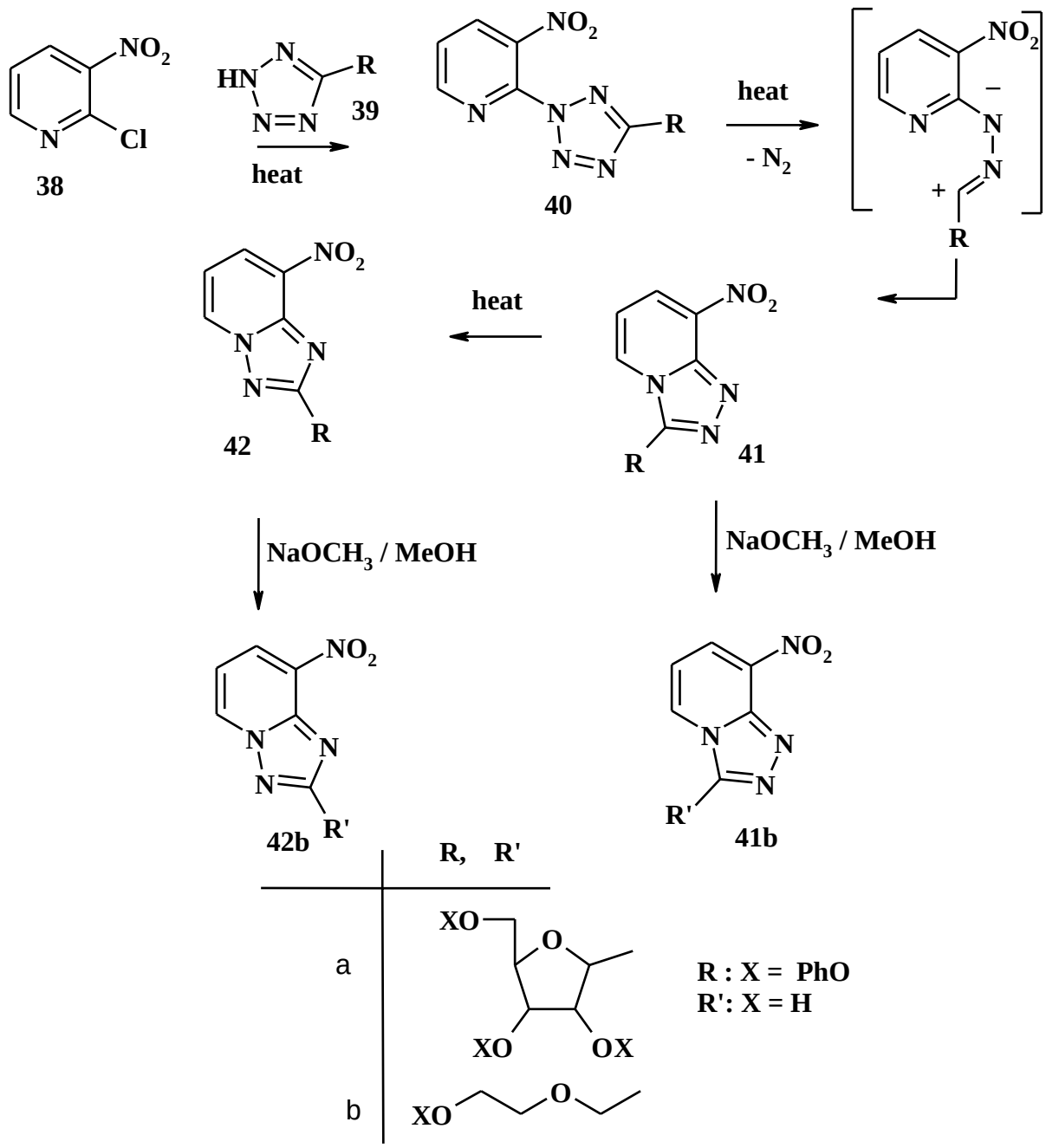
Recently, it was reported that treatment of aldose N-(2-pyridyl)hydrazones **35** with bromine in methanol resulted in the formation of the respective 3-(polyhydroxyalkyl)-1,2,4-triazolo-[4,3-*a*]pyridine derivatives **36**.[90] Acetylation of the latter acyclo *C*-nucleosides afforded the acetylated derivatives 37.[90]



R = $HOCH_2$-$(CHOH)_n$ **R' = $AcOCH_2$-$(CHOAc)_n$** **n = 4, 5**

3.2. [1,2,4]Triazolo[1,5-*a*]pyridines

Reaction of 5-(β-*D*-ribofuranosyl)tetrazols **39** with 2-chloro-3-nitropyridine **38** gave a mixture of 1,2,4-triazolo[4,3-*a*]pyridin-3-yl **41** and 1,2,4-triazolo[1,5-*a*]pyridin-2-yl **42** C-nucleosides. The product **41** is formed *via* in *situ* 1,5-electrocyclization of the initially formed nitrilimines, whereas the product **42** resulted from thermally induced Dimroth like rearrangement of **41**.[91] Treatment of each of **41** and **42** with sodium methoxide in methanol resulted in deprotection of the sugar residue and the formation of C-nucleoside **41b** and **42b** respectively.[91] The acyclic *C*-nucleoside **41** and **42** were also obtained by thermolysis of the respective acyclonucleosides **40**.[91]

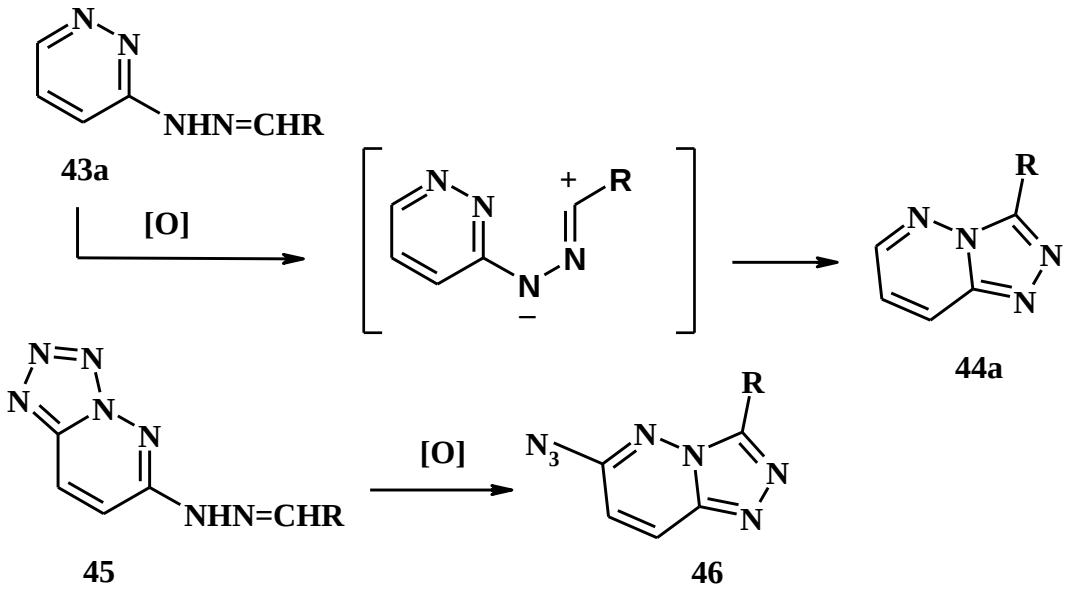


4. Fused triazolo-diazines

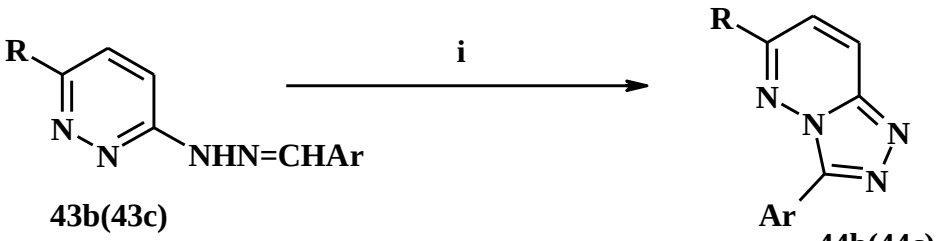
4.1. 1,2,4-Triazolo[4,3-*b*]pyridazines

Aldehyde N-(pyridazin-3-yl) hydrazones **43** yielded the respective 1,2,4-triazolo[4,3-*b*]pyridazines **44** upon treatment with bromine in acetic acid[92-93] or lead tetraacetate (LTA).[92] The latter products were formed *via* in *situ* 1,5-electrocyclization of the corresponding

nitrilimines. It is interesting to find that similar oxidative cyclization of the hydrazones **45** with lead tetraacetate afforded 6-azido-1,2,4-triazolo[4,3-*b*]pyradazines **46**.[94]



When a solution of each of the hydrazones **43b** was refluxed with $CuCl_2$ in dimethylformamide (DMF), the respective 6-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*b*]pyridazines **44b** were produced in 62-70% yields.[95] In addition, it was reported that aldehyde N-(pyridazin-3-yl)hydrazones **43c** have been cyclized upon treating with any of the oxidizing agents including: $Pb(OAc)_4$, Br_2 / Na_2CO_3, $FeCl_3$, NaOCl or Pd / C.[96, 97]



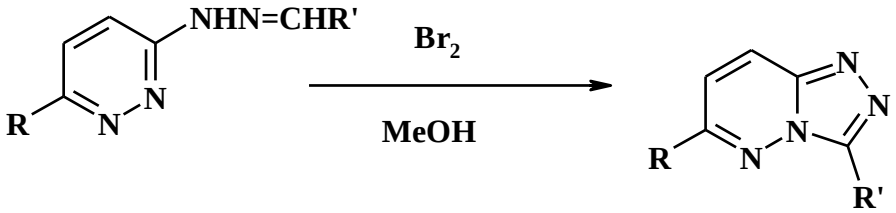
43b(43c) **44b(44c)**

i = $Pb(OAc)_4$; Br_2 / Na_2CO_3 ; $FeCl_3$; NaOCl; $CuCl_2$ / DMF or Pd / C

Ar = 4-ClC_6H_4 ; 3,4-$(MeO)_2C_6H_3$

	R
43b, 44b	Cl
43c, 44c	H

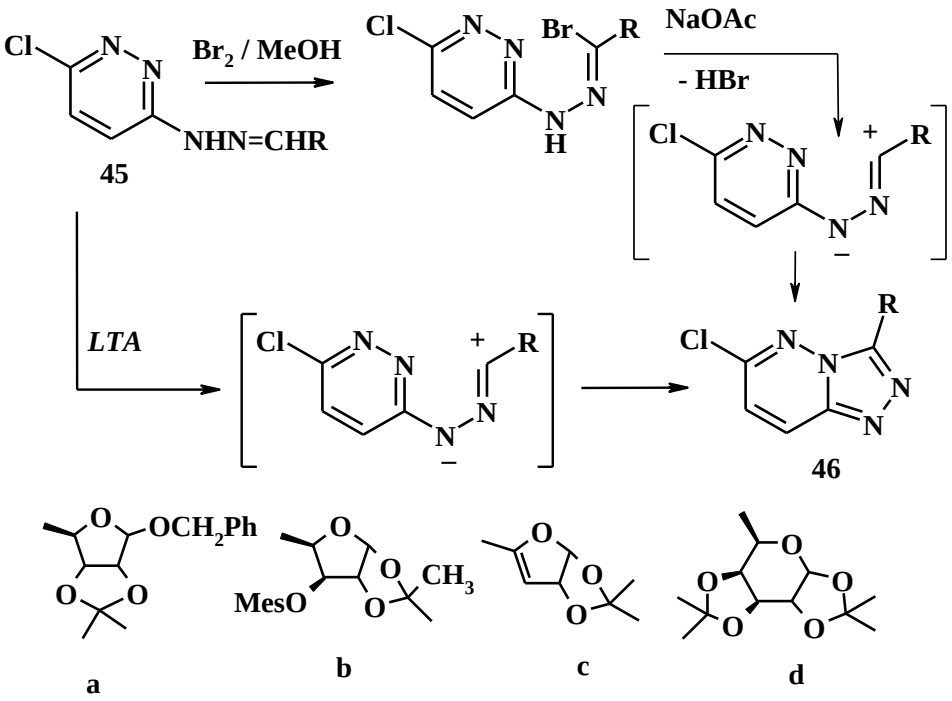
Also, treatment of the hydrazones **43d(43e)** with bromine in methanol afforded the corresponding (2R,3S)-3-(6-chloro-1,2,4-triazolo[4,3-*b*]pyridazine-3-yl)-2,3-diacetoxypropanoic acid methyl ester **44d(e)** and (2R,3S)-3-(6-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine-3-yl)-2,3-diacetoxy-propanoic acid methyl ester **44e**.[98]



43d(43e) **44d(44e)**

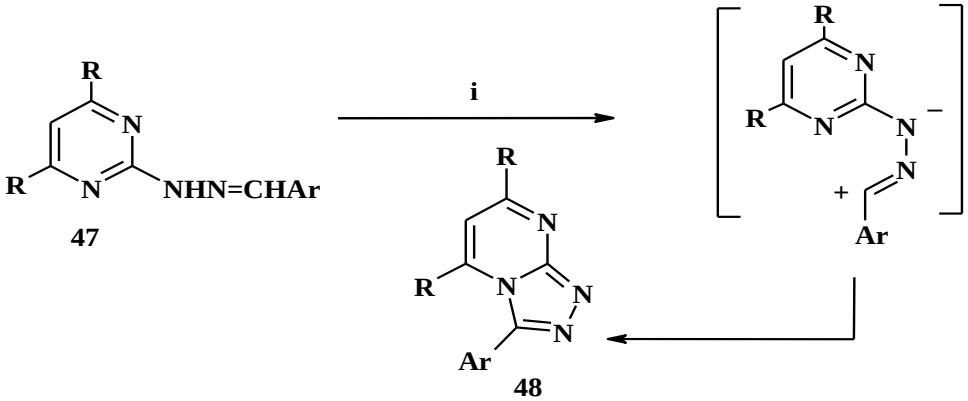
R : d, Cl; e, Ph **R' = $MeOCO(CHOAc)_2$**

Treatment of aldose N-(pyridazin-3-yl)hydrazones of the cyclic sugars **45** with bromine in methanol in the presence of sodium acetate at room temperature yielded the respective 1,2,4-triazolo[4,3-*b*]pyridazines **46**, respectively.[99] Oxidative cyclization of the hydrazone **45** with lead tetraacetate (LTA) in methylene chloride at room temperature afforded also the C-nucleoside **46**.[99]



4.2. 1,2,4-Triazolo[4,3-*a*]pyrimidines

Aldehyde N-(4,6-dimethyl-2-pyrimidinyl)hydrazones **47** gave, upon treatment with lead tetraacetate[100, 101] or with iodobenzene diacetate in dichloromethane[102] the respective 3-aryl-5,7-dimethyl-1,2,4-triazolo[4,3-*a*]pyrimidines **48**. In addition, 3-aryl-[1,2,4]triazolo[4,3-*a*]pyrimidines **48b** were formed by refluxing the parent hydrazones **47b** with $CuCl_2$ in DMF.[85]

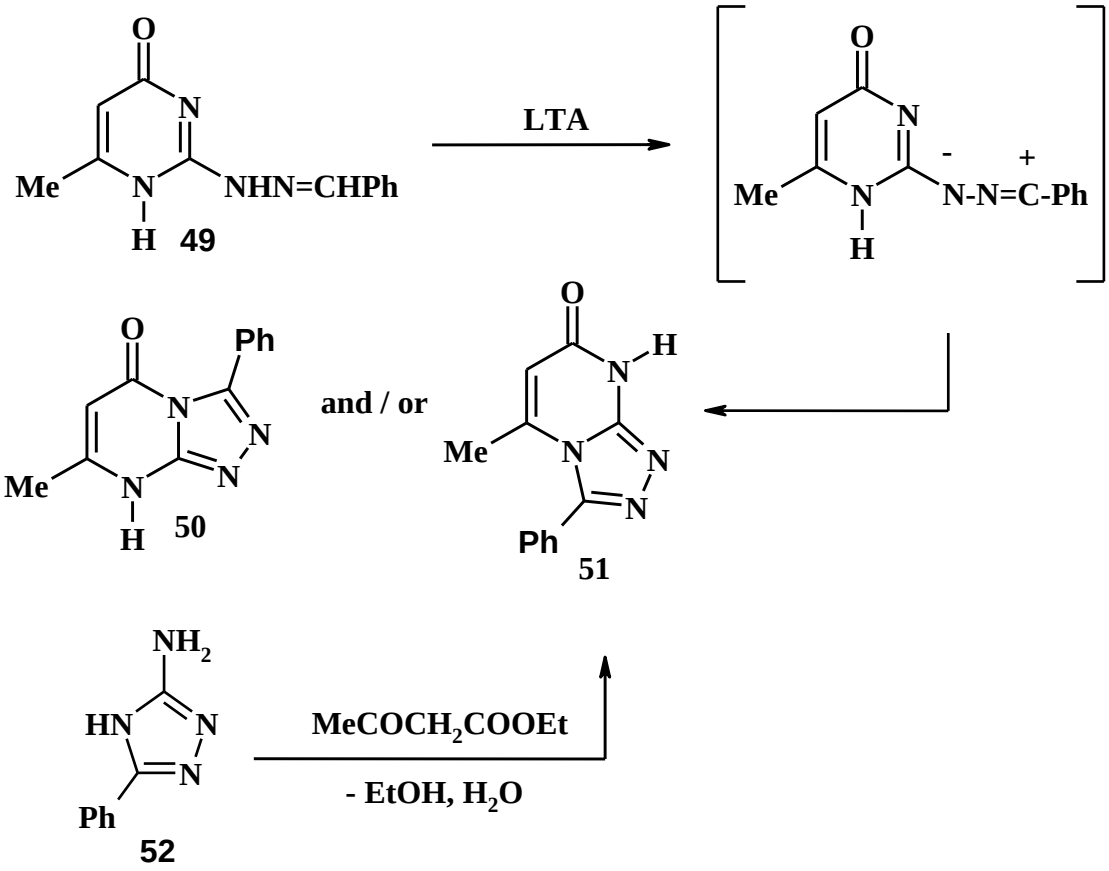


i = $Pb(OAc)_4$; $CuCl_2$ /DMF; or iodobenzene diacetate

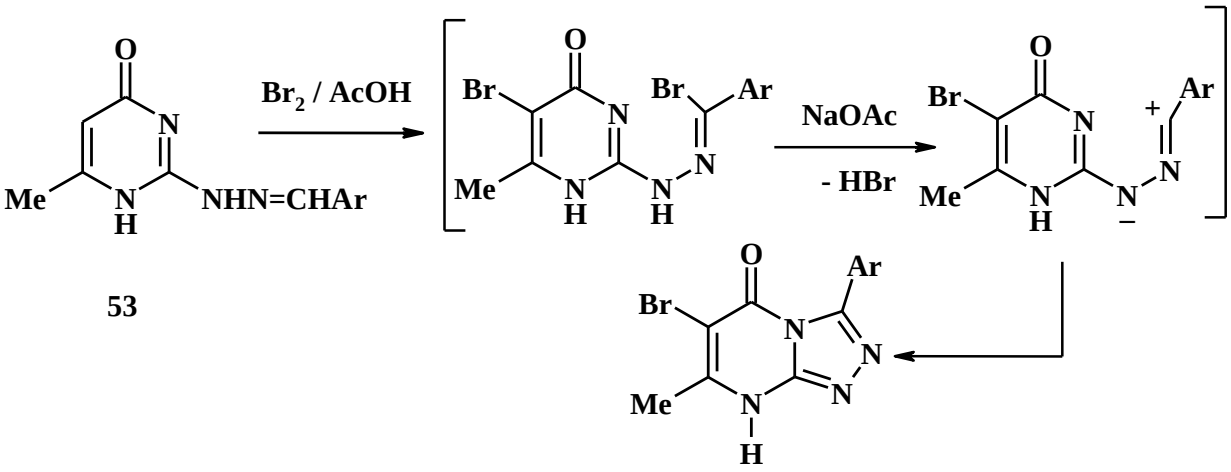
Ar = *p*-ClC_6H_4 ; *m*-ClC_6H_4 ; *p*-MeC_6H_4 ; *p*-$(ON_2)C_6H_4$; *m*-$(ON_2)C_6H_4$; 3,4,-$(MeO)_2C_6H_3$; 3,4,5-$(MeO)_3C_6H_2$; 2-thienyl ; 2-pyridyl ; 3-pyridyl ; 4-pyridyl

47, 48	R
a	CH_3
b	H

Treatment of 2-phenylidenehydrazino-6-methylpyrimidine-4(1H)-one **49** with lead tetraacetate may theoretically afford 3-phenyl-7-methyl-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one **50** and / or 3-phenyl-5-methyl-1,2,4-triazolo[4,3-*a*]pyrimidin-7-one **51**. Practically, however, the reaction furnished one product which was assigned structure **50** by Bower and Doyle[35] and **51** by Allen et al.[103] The latter authors rationalized their conclusion on the basis of obtaining **51** also from the reaction of 3-amino-5-phenyl-1,2,4-triazole **52** with ethyl acetoacetate. Evidently, this rationale is irrelevant since the last reaction may also yield **50**.[103]

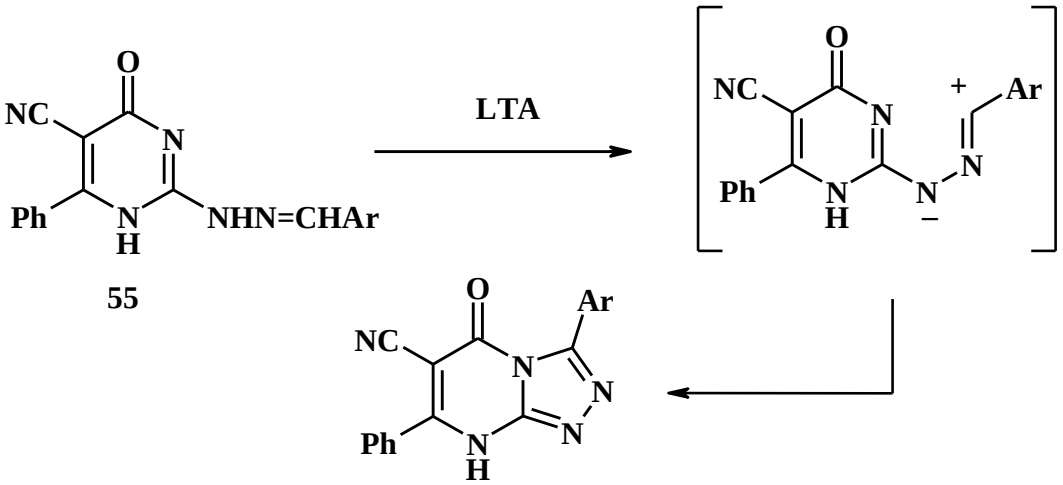


Oxidative cyclization of 2-(arylidenehyrazino)-6-methylpyrimidin-4-one **53** with bromine in acetic acid took place with concomitant bromination of pyrimidine ring to form the respective 1,2,4-triazolo[4,3-*a*]pyrimidin-5-one **54**.[104]



Ar = Ph; *p*-MeOC$_6$H$_4$; *p*-ClC$_6$H$_4$; *m*-N(CH$_3$)$_2$C$_6$H$_4$

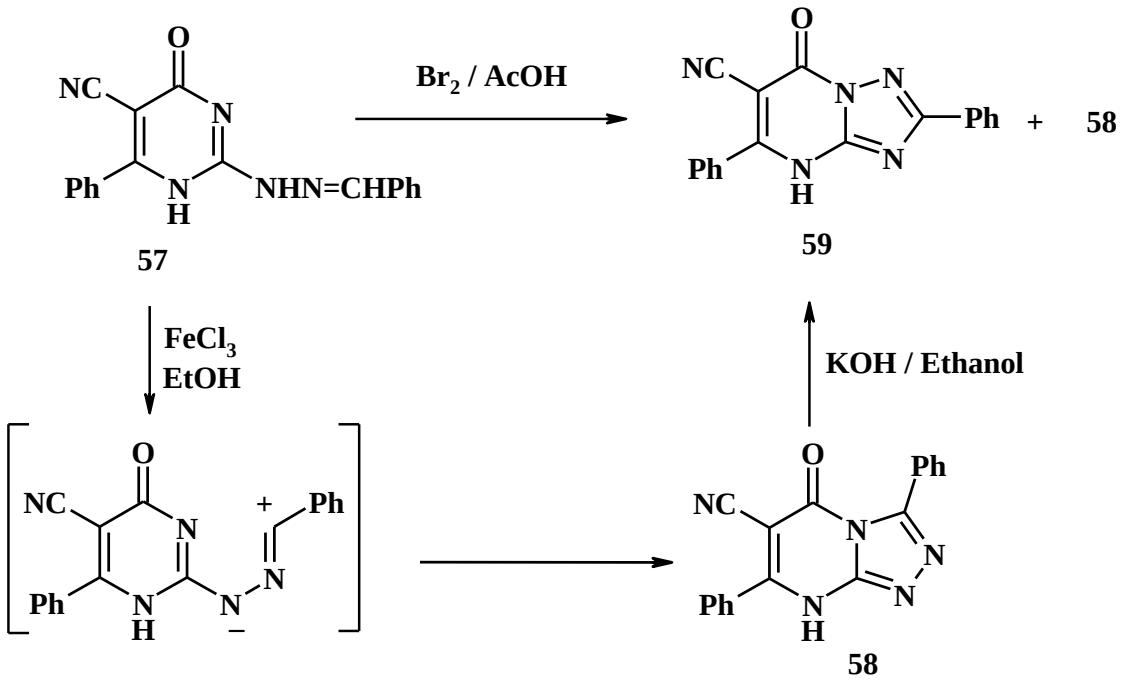
Refluxing the hydrazones **55** with lead tetraacetate in AcOH yielded the corresponding [1,2,4]triazolo[4,3-*a*]pyrimidines **56**.[105]



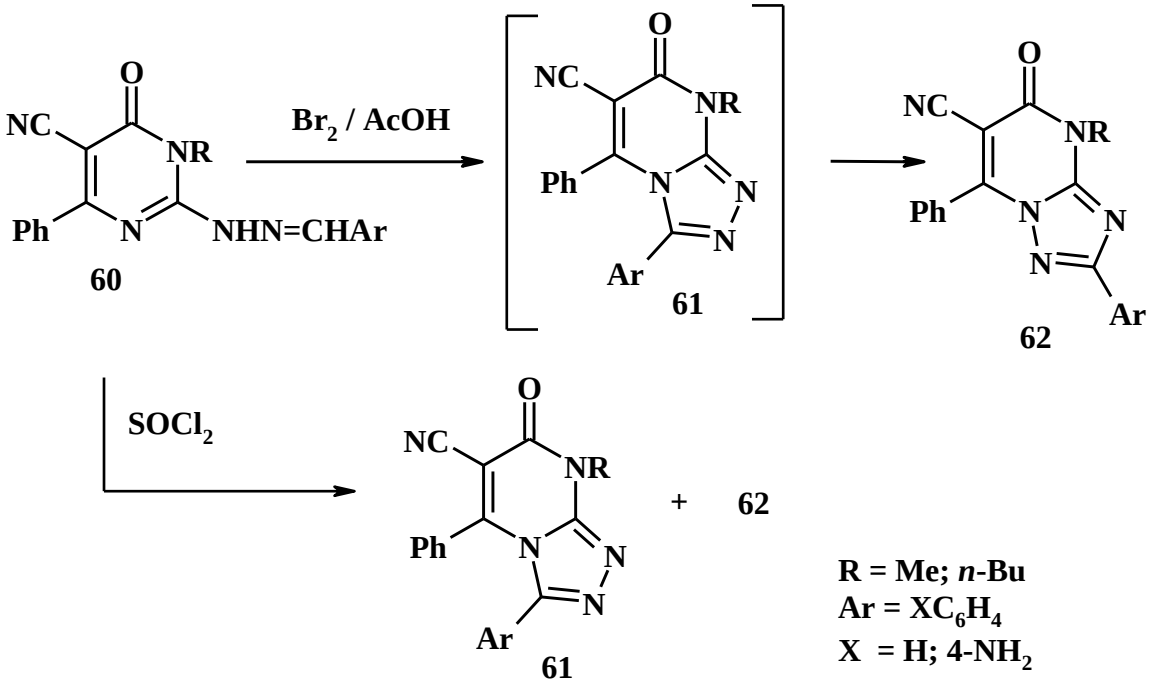
Ar = XC$_6$H$_4$

X = H; 4-NO$_2$; 4-Cl, 2-HO; 4-MeO; 4-Me$_2$N

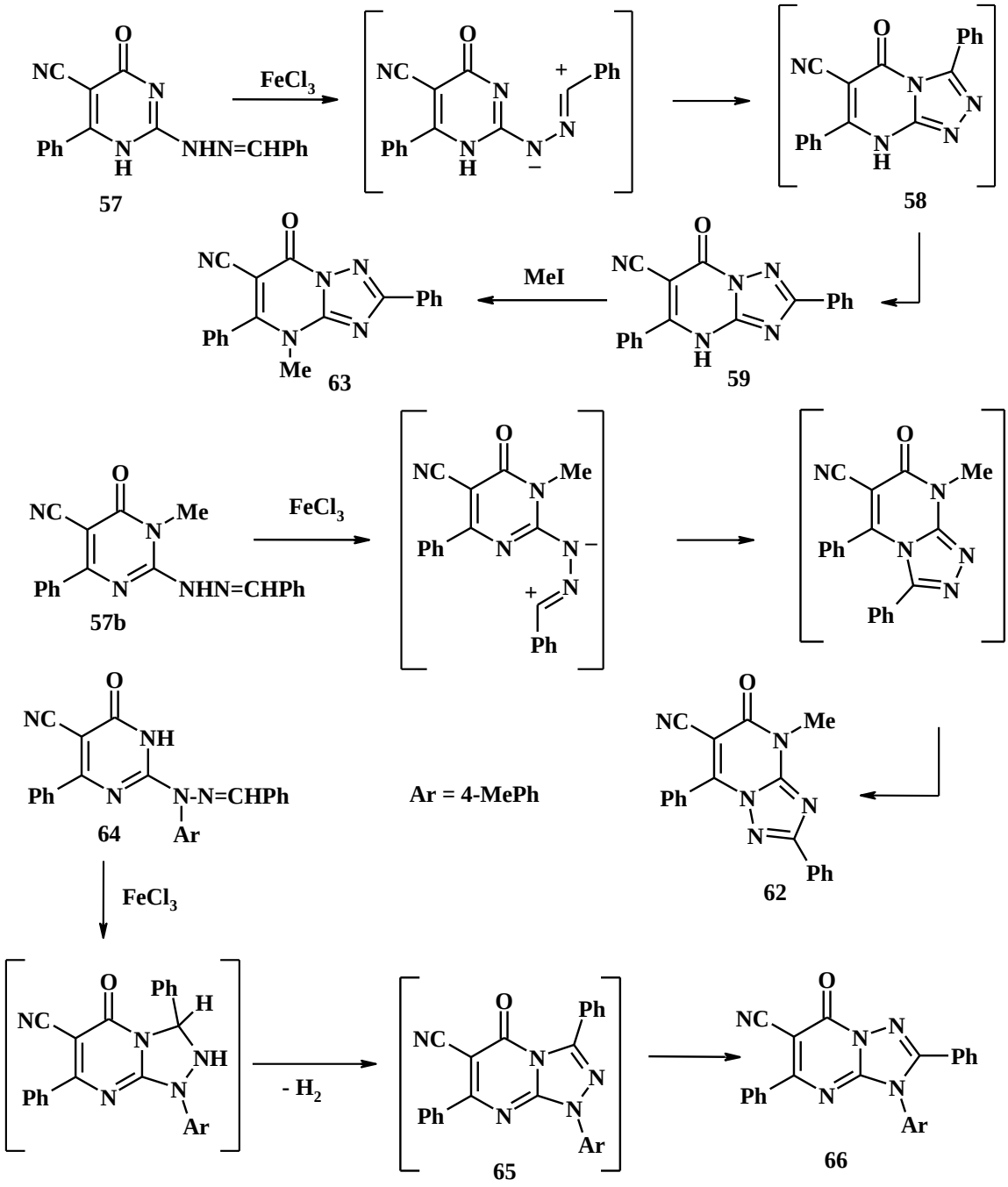
Oxidative cyclization of **57** with $FeCl_3$ gave **58**. When the cyclization of **57** was carried out with Br_2 in acetic acid, it gave **59** as a major product in addition to **58** as minor product. The product **59** resulted from Dimroth rearrangement of the initially formed **58**. The latter was also converted into **59** by heating with KOH in ethanol.[106]



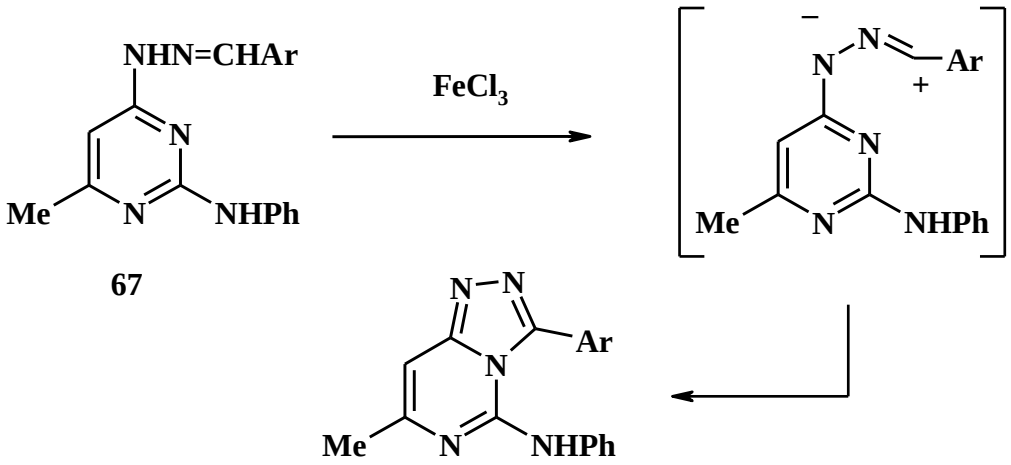
However, similar treatment of the hydrazones **60** with Br_2/AcOH was reported to give the Dimroth rearrangement products **62** directly as end product.[106] On the other hand, the cyclization of **60** with thionyl chloride gave **61** as the major isolated products. Partial Dimroth rearrangement has taken place during this cyclization, where **62** were formed as by products.



Also, oxidative cyclization of the hydrazones **57** with ferric chloride gave **59** as end product *via* Dimroth rearrangement of the initially formed 1,2,4-trazolo[4,3-*a*]pyrimidine derivative **58**. Methylation of **59** with MeI gave the product **63** which was found different from the product **62** which was produced by oxidation of **57b**. Similar oxidation of **64** with $FeCl_3$ afforded **66** *via* Dimroth rearrangement of the initially formed product **65**.[107] In this latter case the reaction seem to proceed *via* intramolecular addition of NH to the C=N double bond, followed by oxidation of the initially formed adduct.



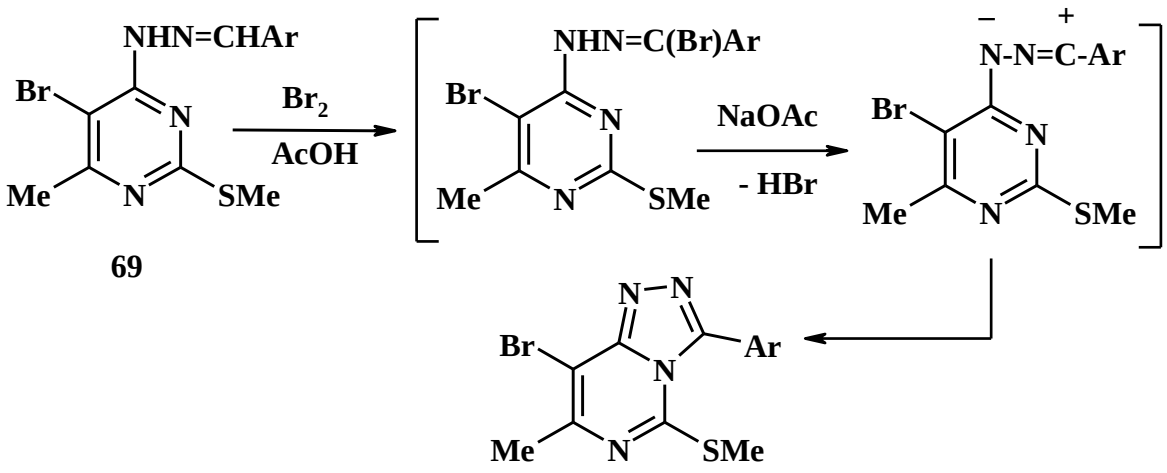
Oxidative cyclization of the hydrazones **67** with $FeCl_3$ in ethanol gave the corresponding **68**.[108]



67 **68**

Ar = 4-XC$_6$H$_4$; X = Cl; MeO

Attempts to cyclize the hydrazones **69** *via* treatment with an excess of Br_2 in AcOH in presence of NaOAc gave the corresponding 8-bromo-1,2,4-triazolo[4,3-*c*]pyrimidines **70**.[108]

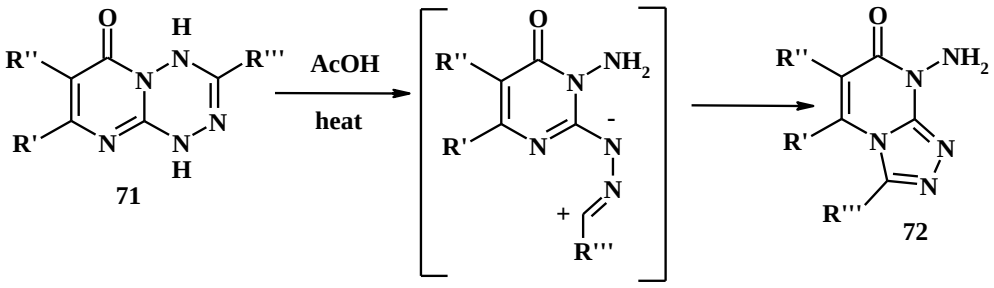


69

70

Ar = 4-XC$_6$H$_4$; X = Cl; NO$_2$

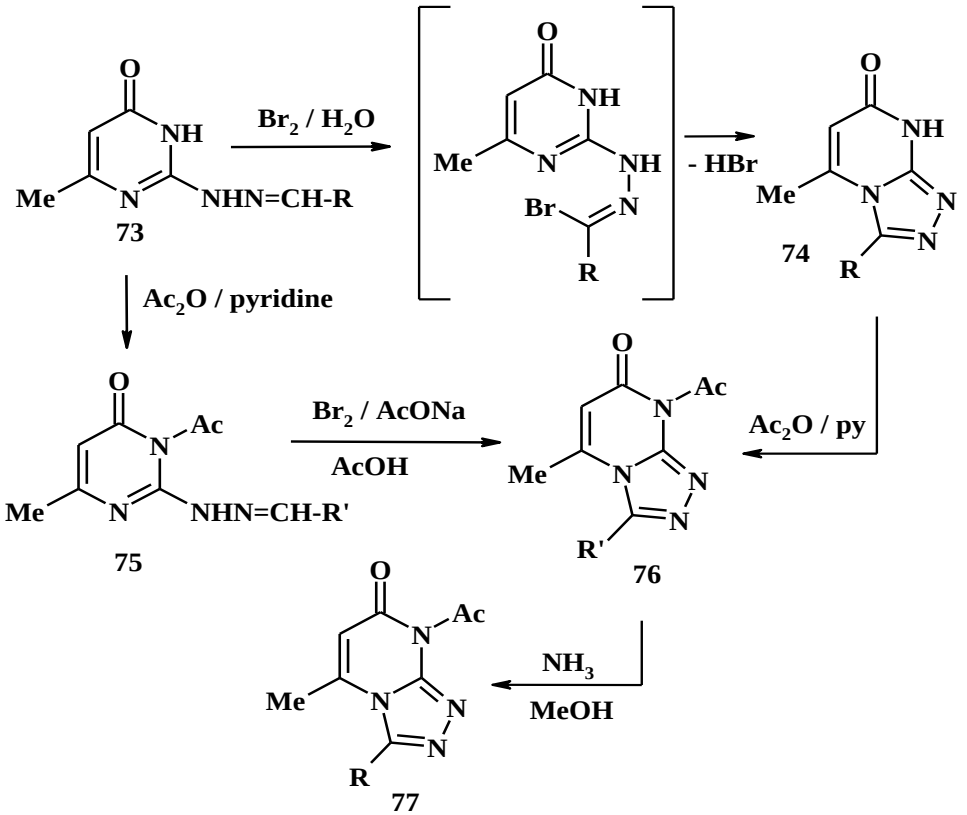
Bitha et al[109] reported that pyrimidino[1,2-b][1,2,4,5]tetrazin-6-ones **71** underwent acid catalyzed ring contraction *via* 1,5-electrocyclization of the generated nitrilimines to give 1,2,4-triazolo[4,3-*a*]pyrimidin-7-ones **72**.



R'= Me; Ph

R'' / R''' = H / Me

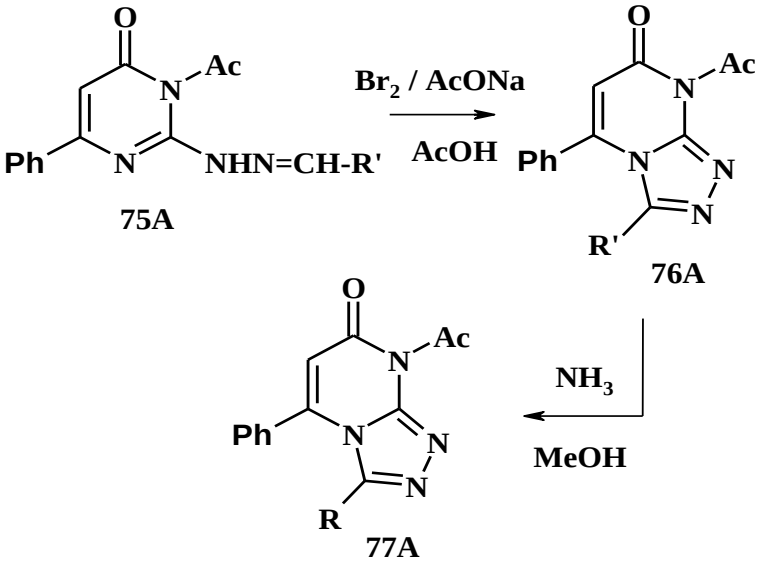
A number of 3-(alditol-1-yl)-5-methyl-7-oxo[1,2,4]triazolo[4,3-*a*]pyrimidines **74** were synthesized by oxidative cyclization of the respective aldose (pyrimidin-2-yl)hydrazones **73** with bromine in water.[110] The other regioisomeric structure was eliminated based on finding that acetylation of **74** afforded the same acetylated acyclo C-nucleoside **76** as those obtained by oxidative cyclization of the hydrazones **75**.[110] Treatment of **76** with methanolic ammonia resulted in deprotection of the sugar residue and the formation of **77**. It was possible to avoid nuclear bromination of **73** and **75** by performing the reaction in the absence of light.



R = $HOCH_2$-$(CHOH)_n$ **R' = $AcOCH_2$-$(CHOAc)_n$**

n = 3, 4

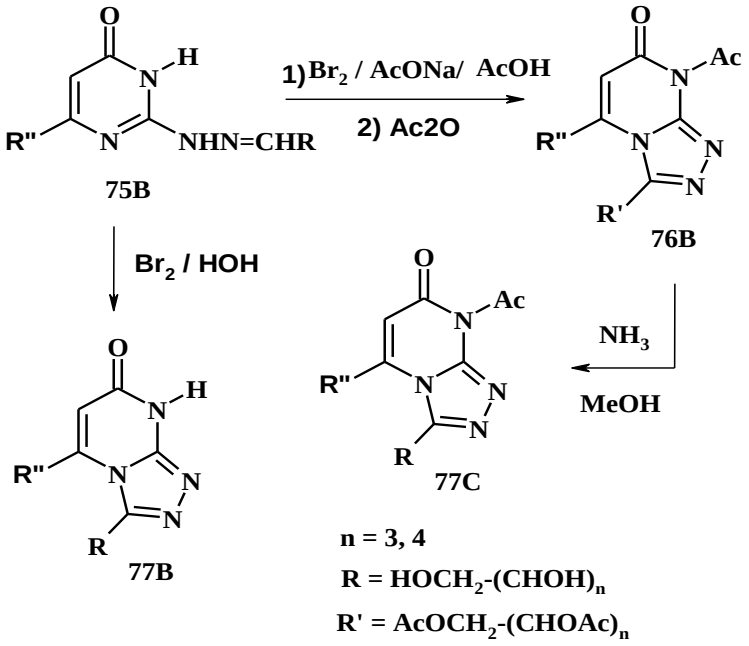
Similarly, it was indicated that poly-O-acetyl-adehydo sugar (3-acetyl)4-oxo-6-phenyl-pyrimidin-2-yl)hydrazones **75A** undergo oxidative cyclization with bromine in acetic acid in the presence of sodium acetate to give the respective 8-acetyl-3-(poly-O-acetyl-alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **76A**.[111] Deacetylation of the latter **76A** with ammonium hydroxide in methanol gave the corresponding 3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **77A**.



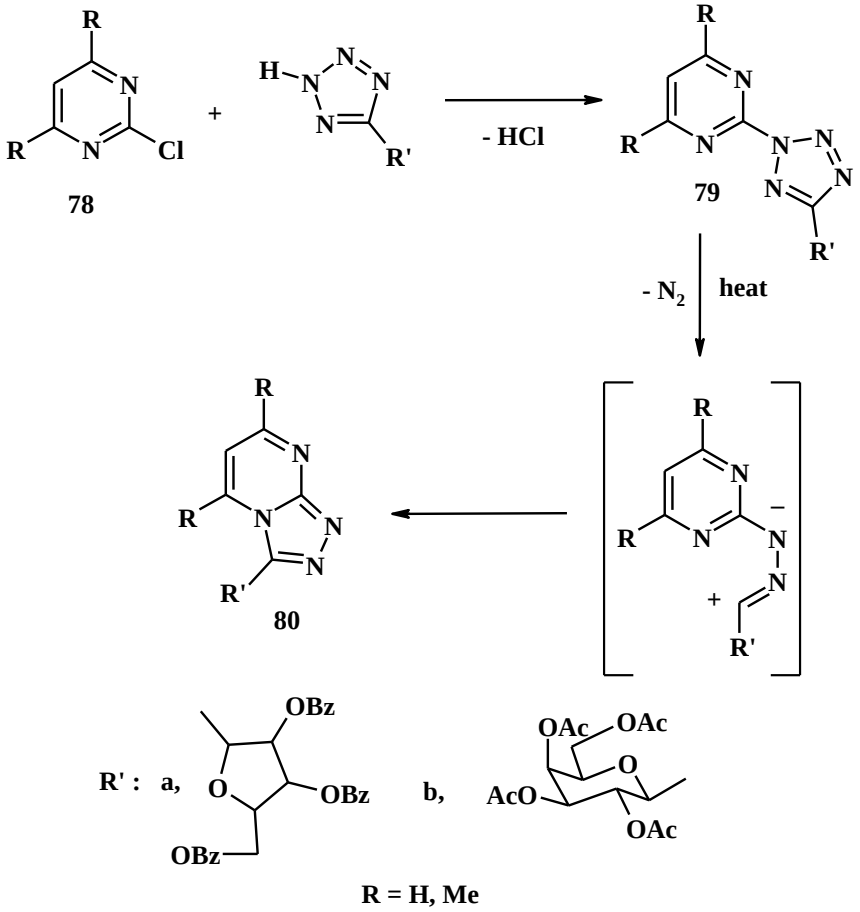
R = $HOCH_2$-$(CHOH)_n$ **R' = $AcOCH_2$-$(CHOAc)_n$**

n = 3, 4

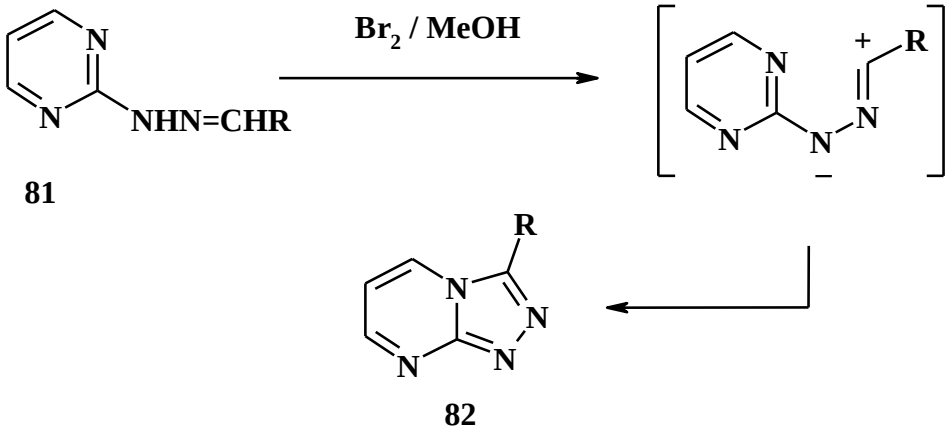
Also, it was indicated that adehydo-sugar 4-oxo-6-phenyl-pyrimidin-2-yl)hydrazones **75B** undergo oxidative cyclization with bromine in water to give the respective 3-(alditol-1-yl)-7-oxo-5-substituted-1,2,4-triazolo[4,3-*a*]pyrimidines **76B**.[112] Similar treatment of **75B** with bromine in acetic acid in the presence of sodium acetate followed by acetic anhydride gave the polyacetyl derivative **76B** whose deacetylation with ammonium hydroxide in methanol gave the corresponding 3-(alditol-1-yl)-7-oxo-5-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidines **77B**.[112]



Thermolysis of tetrazole derivative **79**, prepared from 2-chloro-4,6-disubstituted-pyrimidine **78** and 5-(2,3,5-tri-O-benzoyl-B-D-ribofuranosyl)-tetrazole **5**, afforded the respective 1,2,4-triazolo[4,3-*a*]pyrimidine *C*-nucleoside **80**.[113]



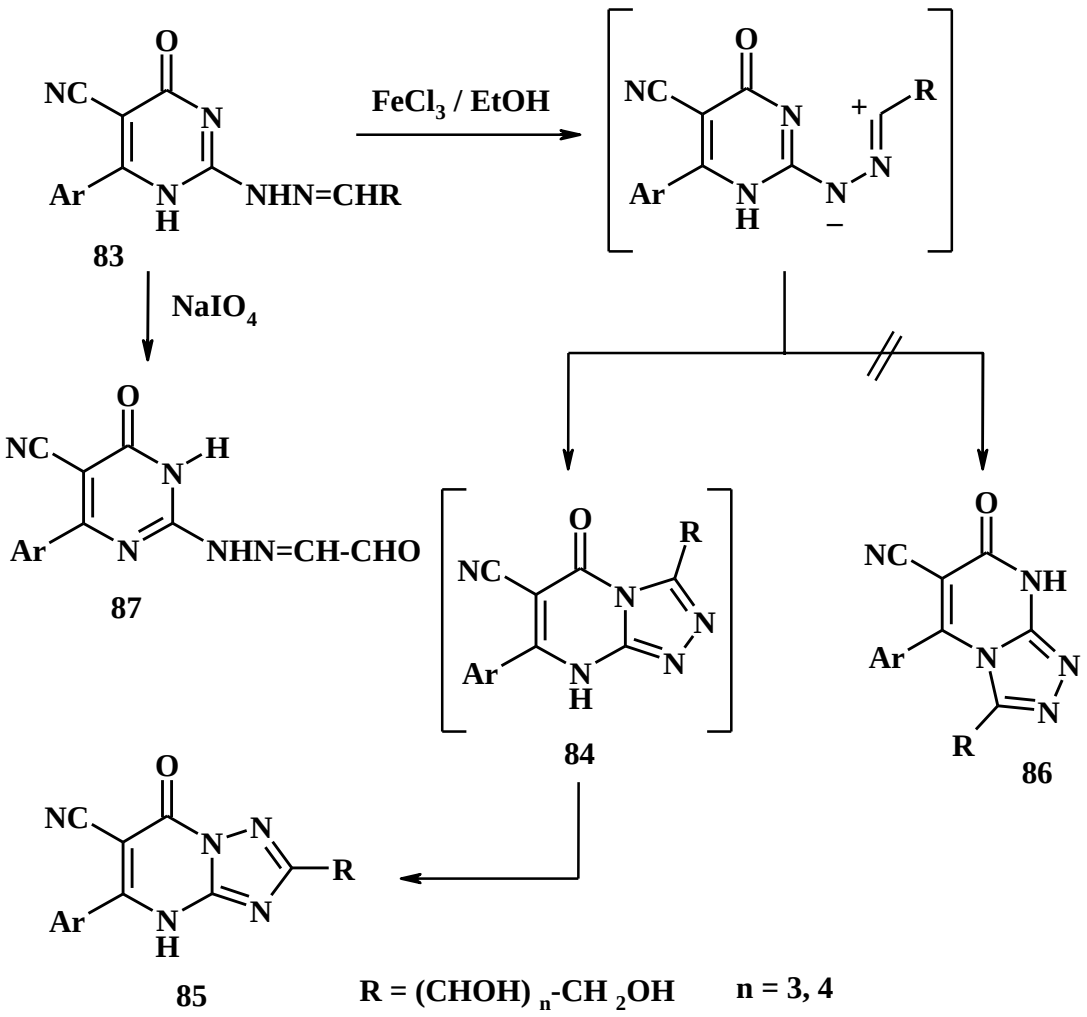
Hydrazones **81**, derived from aldose monosaccharides and 2-hydrazinopyrimidine gave, upon oxidative cyclization with bromine in methanol, the corresponding 3-(alditol-1-yl)-1,2,4-triazolo[4,3-*a*]pyrimidines **82**.[98]



R = HOCH $_2$-(CHOH) $_4$

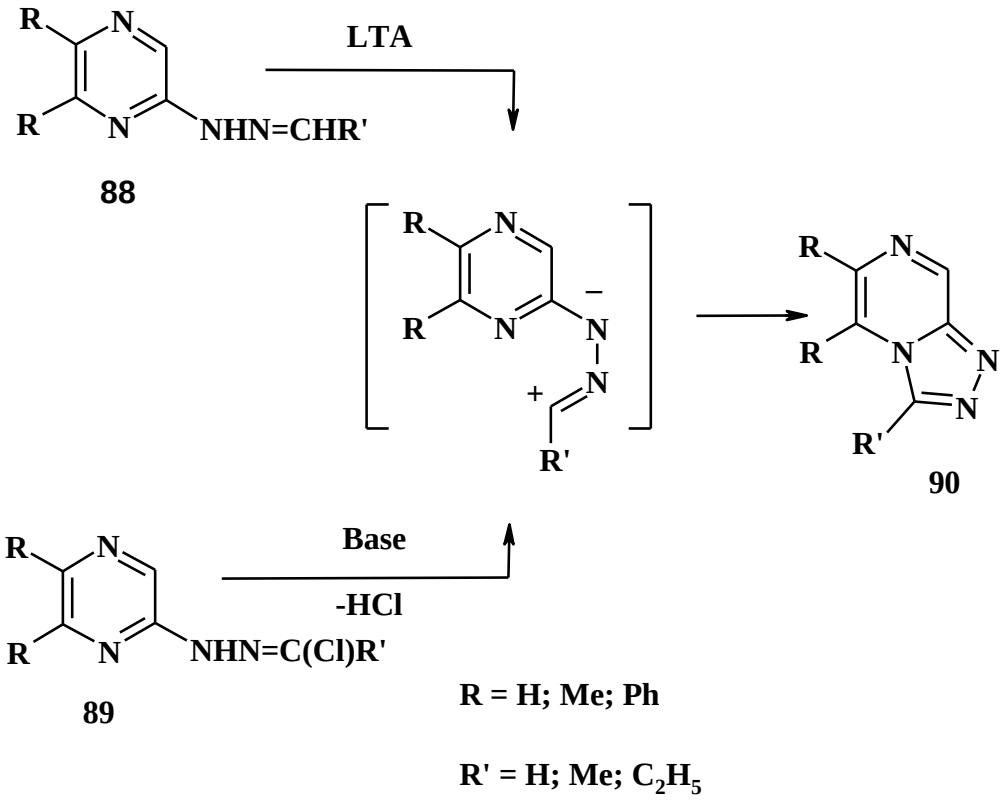
4.3. [1,2,4]Triazolo[1,5-*a*]pyrimidines

Treatment of the aldose hydrazones **83** with ferric chloride in ethanol was reported to give the acyclo C-nucleosides **85** and not the isomeric nucleosides **86**. It seems in this case the initially formed 1,2,4-triazolo[4,3-*a*]pyrimidines **84** underwent *in situ* Dimroth rearrangement to give **85** as end products. Periodate oxidation of **83** afforded the aldehydes **87**.[114, 115]



4.4. 1,2,4-Triazolo[4,3-*a*][1,2,4]pyrazines

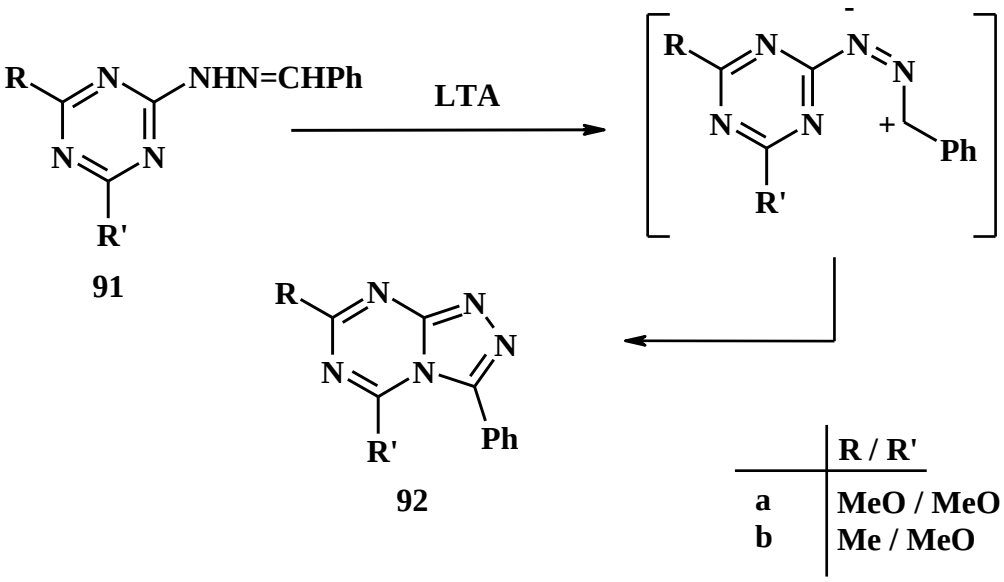
Nitrilimines, generated *in situ* by oxidation of aldehydes N-(pyrazin-2-yl)hydrazones **88** with lead tetra-acetate or dehydrohalogenation of the hydrazonyl chlorides **89**, underwent 1,5-electrocyclization to afford the respective 1,2,4-triazolo[4,3-*a*][1,2-4]pyrazines **90**.[116]



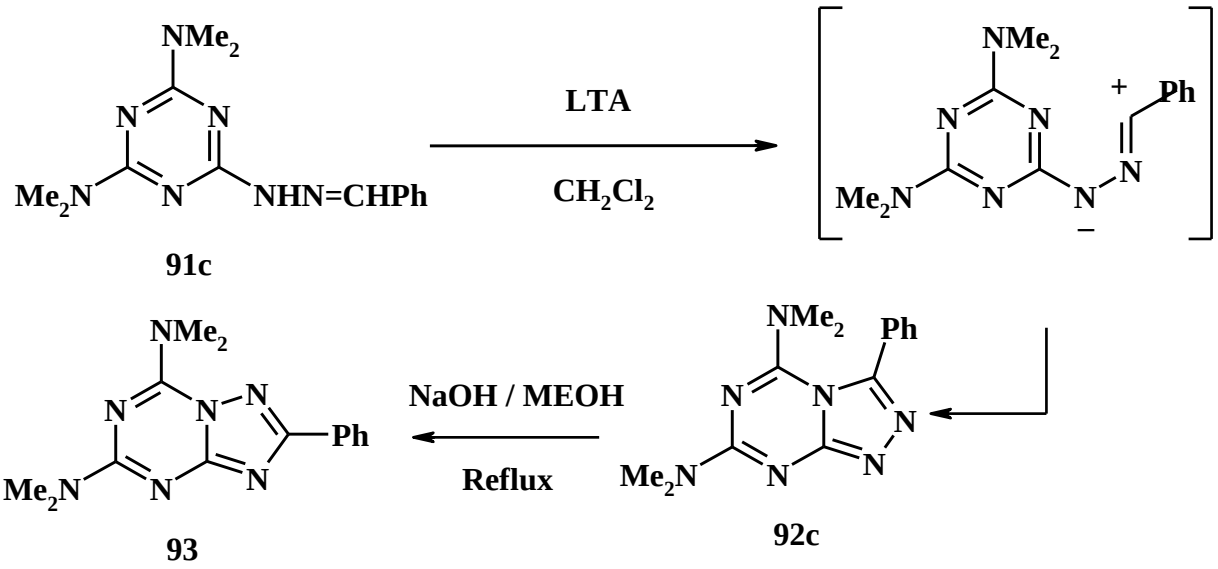
5. Fused triazolo-triazines

5.1. 1,2,4-Triazolo[4,3-*a*][1,3,5]triazines

Nitrilimines derived from oxidative dehydrogenation of aldehyde N-(4,6-disubstituted-1,3,5-triazin-2-yl)hydrazones **91a** with lead tetraacetate gave only **92a** because of the symmetry of **91a**.[100, 117, 118] Also, treatment of aldehyde N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)hydrazones **91b** with lead tetraacetate gave **92b** only as a result of cyclization with the more nucleophilic nitrogen adjacent to the more electron-releasing methoxy group.[118]



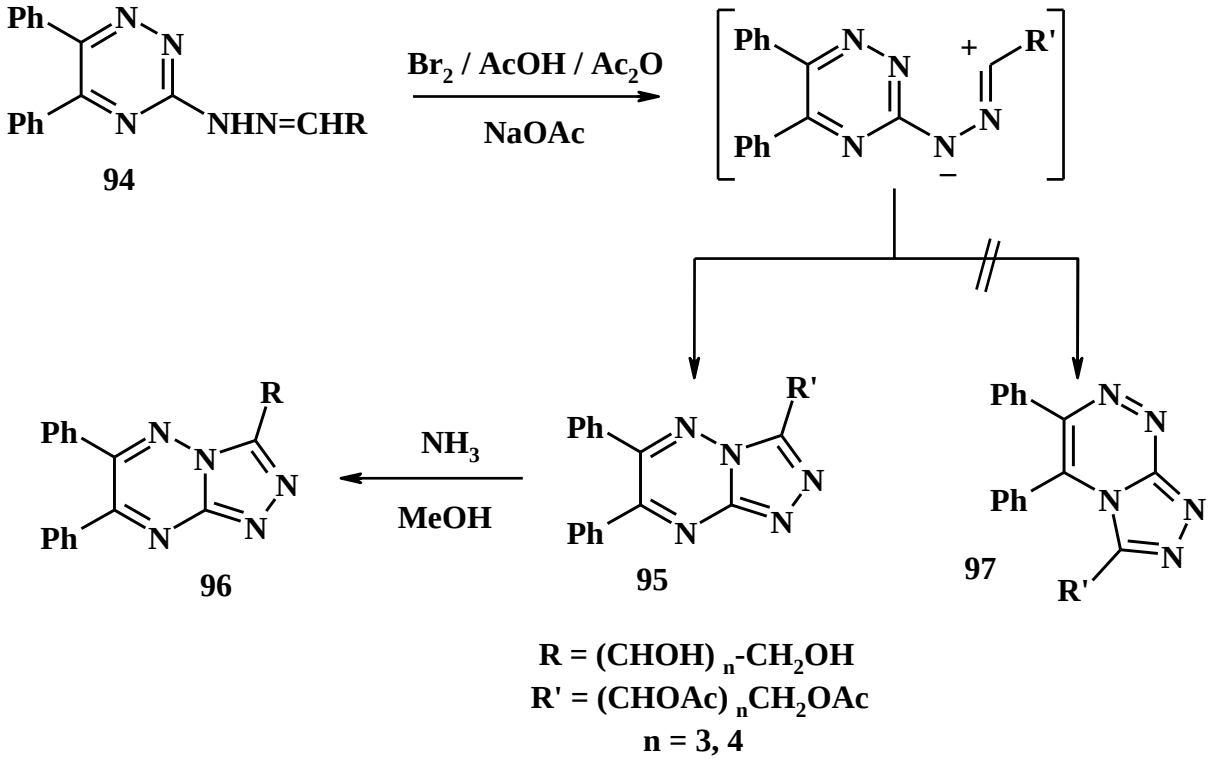
The hydrazone **91c** underwent cyclization upon treatment with lead tetraacetate in CH_2Cl_2 to yield [1,2,4]triazolo[4,3-*a*][1,3,5]triazine **92c**. The latter product underwent Dimroth rearrangement upon heating in MeOH-NaOH to give 1,2,4-triazolo[1,5-*a*][1,3,5]triazine **93** in 95% yield.[119]



5.2. 1,2,4-Triazolo[4,3-*b*][1,2,4]triazines

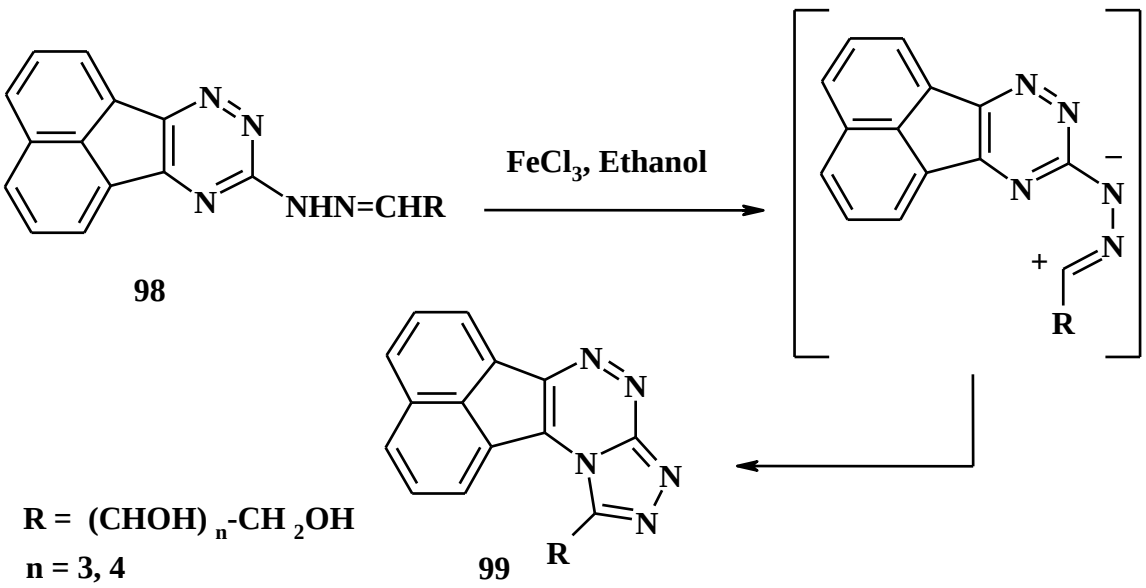
Oxidative cyclization of the hydrazone derivatives of the aldose monosaccharides **94** and concurrent acetylation was reported to occur upon treatment with bromine in acetic acid in the presence of sodium acetate and acetic anhydride and yielded products that were assigned the

structure of 6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine acyclo *C*-nucleosides **95** and not the isomeric structure **97**.[120] Deacetylation of **95** yielded **96**.



5.3. Acenaphtho[1,2-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines

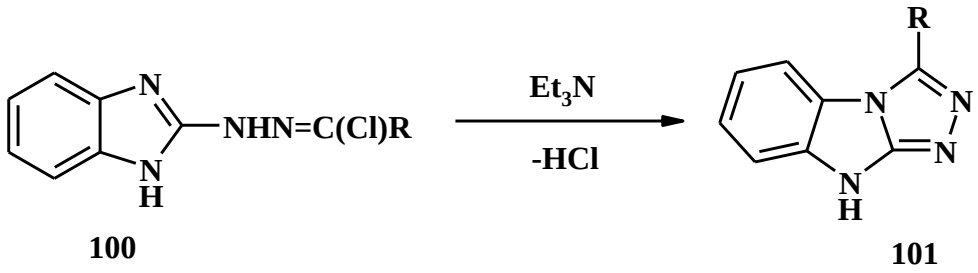
Oxidative cyclization of the hydrazone derivatives of aldose monosaccarides **98** was reported to occur upon treatment with ethanolic ferric chloride and provided 1-(alditol-1-yl)acenaphtho[1,2-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines **99**. The cyclization occurred at N4 rather than N2 of the 1,2,4-triazine ring.[121]



6. Fused triazolo-benzoazoles

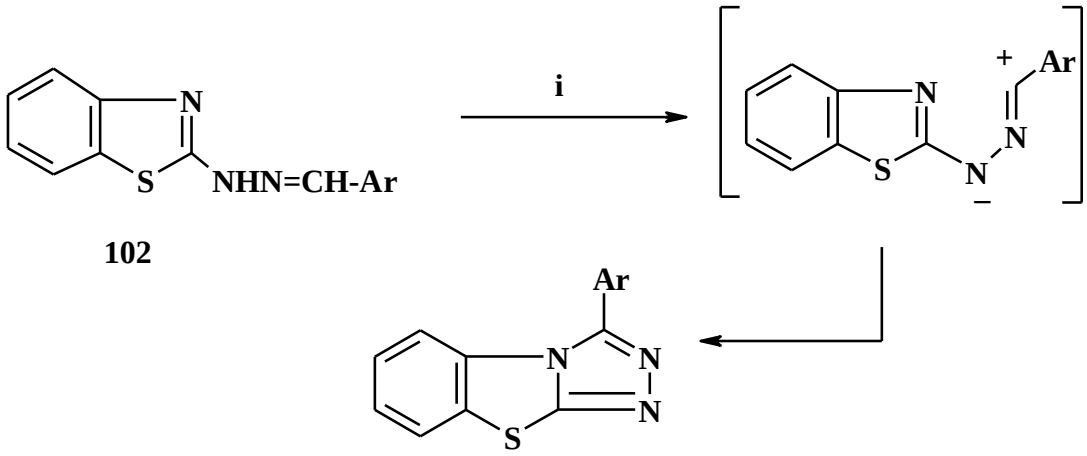
6.1. 1,2,4-Triazolo[4,3-*a*]benozimidazoles

Treatment of the hydrazonoyl chlorides **100** with a base furnished 3-substituted 1H-1,2,4-triazolo[4,3-*a*]benzoimidazoles **101**.[122]



6.2 1,2,4-Triazolo[3,4-*b*]-1,3-benzothiazoles

Bower and Doyle[123] reported that treatment of aldehyde N-(benzothiozole-2yl)hydrazones **102** with lead tetraacetate gave 3-aryl-1,2,4-triazolo[3,4-*b*]-1,3-benzothiazoles **103** *via* tandem generation and electrocyclization of nitrilimines.[83, 124, 125] In addition, the latter conversion has been affected by other reagents such as $FeCl_3$ in ethanol,[126, 127] bromine in acetic acid and bromine in presence of sodium carbonate.[128]

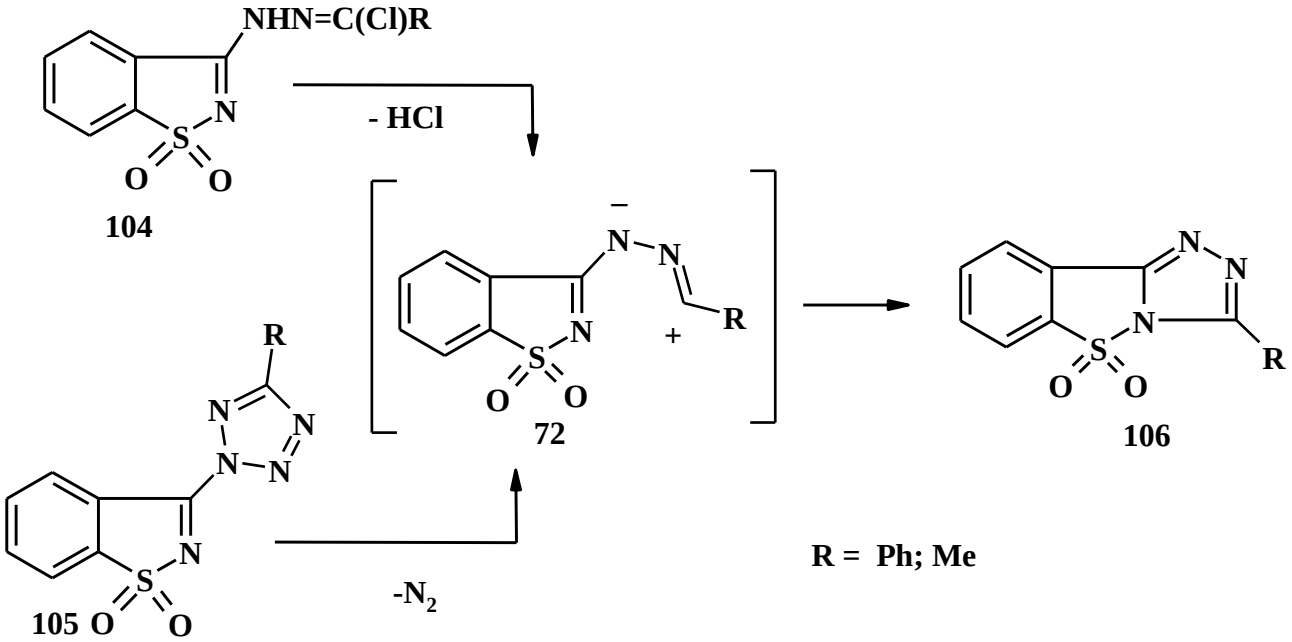


102 **103**

i = a) $Pb(OAc)_4$; b) $FeCl_3$/EtOH; c) Br_2/AcOH; or d) Br_2/Na_2CO_3

Ar = *p*-BrC_6H_4; *p*-$O_2NC_6H_4$

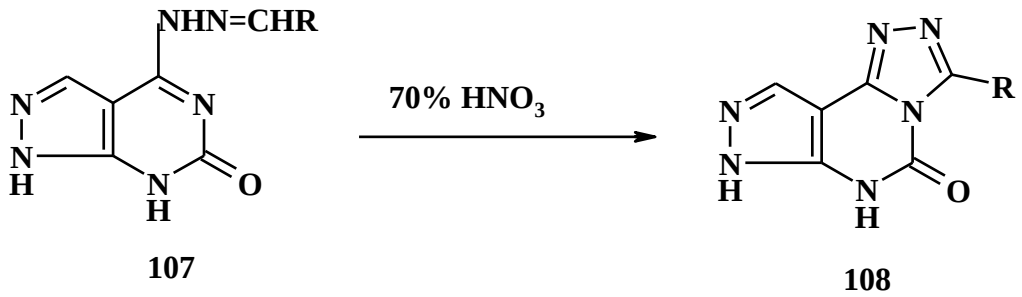
The hydrazonoyl chloride **104**, prepared by the reaction of $POCl_3$ on the hydrazide in DMF, cyclizes *in situ* to give the respective 1,2,4-triazolo[4,3-b]-1,2-benzothiazoles derivative.[129] Also, 3-substituted-1,2,4-triazolo[4,3-*b*][1,2]benzothiazole-5,5-dioxide **106** (R = Me) was obtained upon thermolysis of **105**, prepared by reaction of 3-chloro-1,2-benzothiazole-1,1-dioxide with methyltetrazole in presence of pyridine.[130] Although no mechanistic rationalization was indicated, the formation of the latter products **106** may result *via* tandem generation and electrocyclization of the respective nitrilimine.



7. Fused triazolo-azolo-diazines

7.1. Pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidines

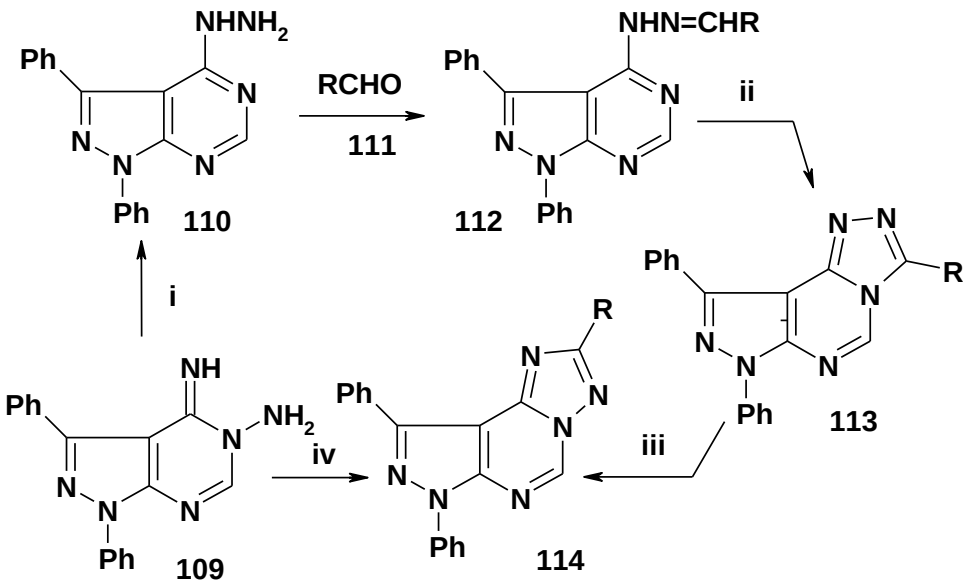
The hydrazones **107** were reported to cyclize upon treatment with 70% nitric acid to afford the corresponding 5-substituted-7*H*-pyrazolo[4,3-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidines **108**.[49]



107 **108**

R = Me; *n*-C_7H_{15}; Ph; *p*-FC_6H_4; *p*-ClC_6H_4; *p*-MeC_6H_4; *p*-$MeOC_6H_4$; *p*-$NO_2C_6H_4$

Recently Shawali et al prepared a series of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines **113** *via* oxidative cyclization of aldehyde *N*-(1,3-diphenylpyrazolo-[3,4-*d*]pyrimidin-4-yl)hydrazones **112**.[134] The required aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones **112** were prepared by condensation of the appropriate aldehydes **111** with 1,3-diphenyl-4-hydrazino-pyrazolo[3,4-*d*]-pyrimidine **110** . The latter was prepared by Dimroth type rearrangement of 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine **109** *via* its treatment with excess hydrazine hydrate at room temperature.[134] Dimroth rearrangement of **113** such a series yielded pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **114**.

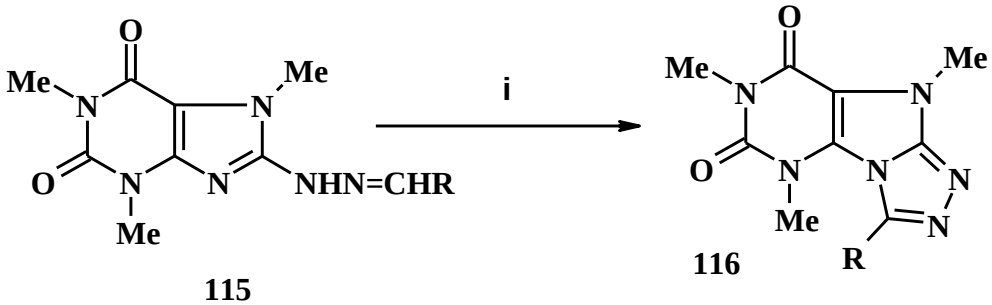


Reagents: i, $H_2NNH_2.H_2O$ / RT; ii, $FeCl_3$ / EtOH / RT;
iii, MeCOONa / heat; iv, RCOCl, $(RCO)_2O$ or RCOOH.

R = a) C_6H_5; b) 4-MeC_6H_4; d) 4-$MeOC_6H_4$; e) 4-$O_2NC_6H_4$;
f) 4-$Me_2NC_6H_4$; g) PhCH=CH-; h) 1-Naphthyl; i) 2-furyl;
j) 2-thienyl; k) CH_3; l) H.

7.2. 1,2,4-Triazolo[4,3-*e*]purine**s**

Stirring the hydrazone **115** with either $CuCl_2$ in warm DMF at 100° or bromine in acetic acid yielded 3-substituted-5,7,9-trimethyl-5,9-dihydro[1,2,4]triazolo[4,3-*e*]purine-6,8-dione **116**.[95, 135]



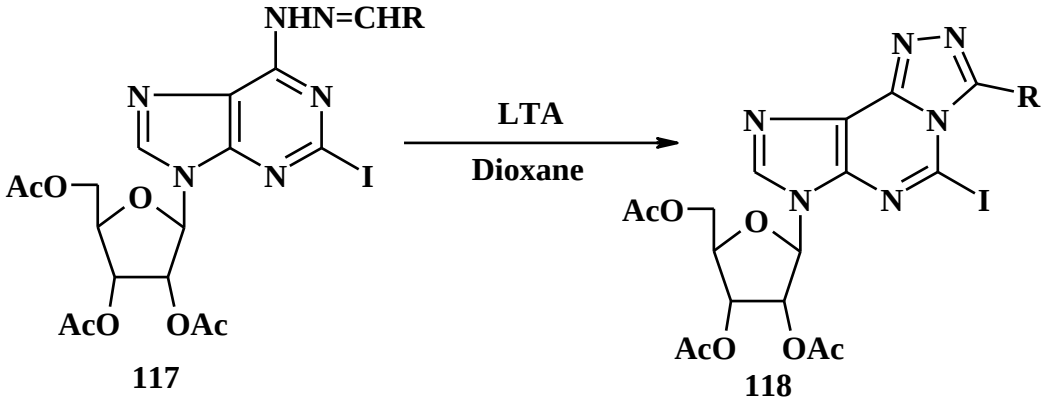
115 **116**

i = $CuCl_2$ / DMF; Br_2 / AcOH

R = Ph; *p*-$MeOC_6H_4$; *p*-BrC_6H_4; *p*-ClC_6H_4;
***P*-$NO_2C_6H_4$; *m*-$NO_2C_6H_4$; *p*-MeC_6H_4;**
2-Thienyl

7.3. 1,2,4-Triazolo[3,4-*i*]purines

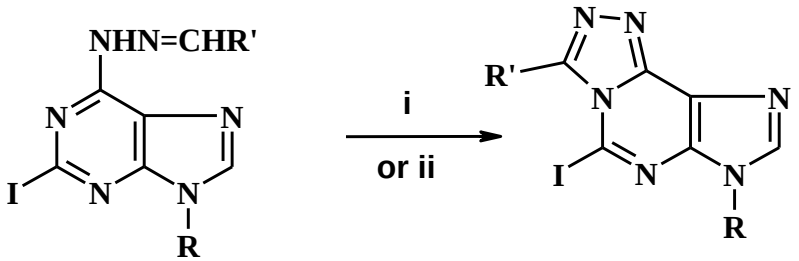
Oxidative cyclization of the hydrazones **117** was accomplished by heating with lead tetraacetate in anhydrous dioxane to afford the corresponding 5-Iodo-7-(2',3',5'-tri-O-acetyl-β-ribofuranosyl)-7*H*-[1,2,4]triazolo[3,4-*i*]purine derivatives **118**.[136] The latter products were also obtained by refluxing **117** with diethyl azodicarboxylate in acetonitrile.[137]



117 **118**

R = H; Ph; *p*-F-C_6H_4; *p*-Cl-C_6H_4; *p*-Br-C_6H_4; *p*-Me-C_6H_4; *p*-MeO-C_6H_4; *p*-O_2N-C_6H_4; 3,4-OCH_2O-C_6H_3

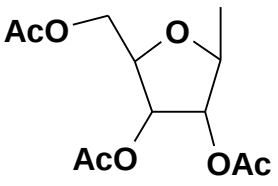
Heating the hydrazones **119** with diethyl azidicarboxylate (DEAD) in acetonitrile at reflux for 5-10 h afforded the respective 5-iodo-7-(2',3',5'-tro-O-acetyl-B-ribofurano-5-yl)-7*H*-[1,2,4]triazolo[3,4-*i*]purines **120**. The latter could also be obtained by heating **119** with lead tetraacetate in anhydrous dioxane.[137]



119 **120**

i = DEAD / MeCN / heat
ii = Pb(OAc)4 / dioxane / heat

R' =

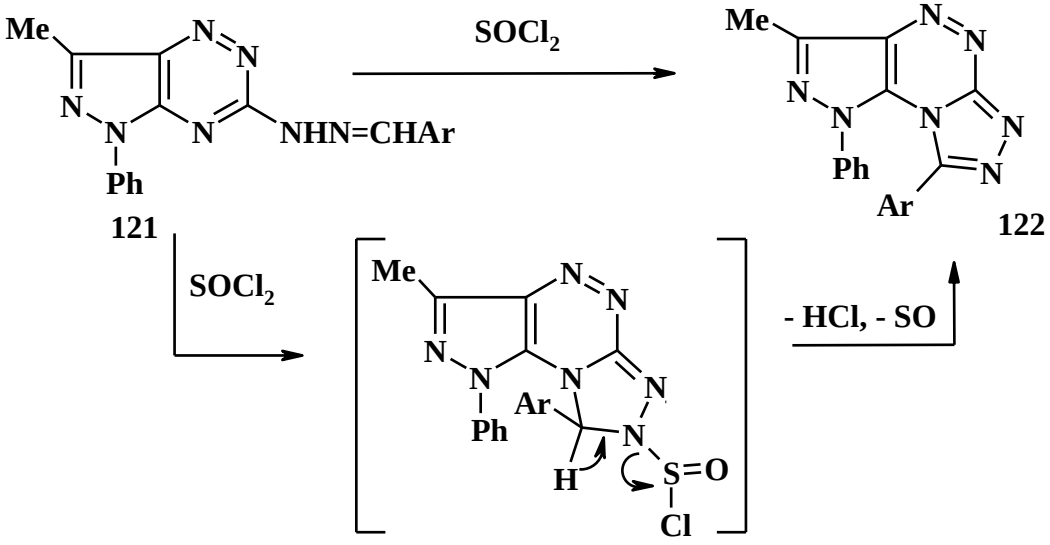


R = H, Me, Ph; XC_6H_4 ;
X = 4-MeO; p-Br; p-Cl ; p-O2N; m-O2N; 4-Me; 4-F

8. Fused triazolo-azolo-triazines

8.1. Pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-c][1,2,4]triazines

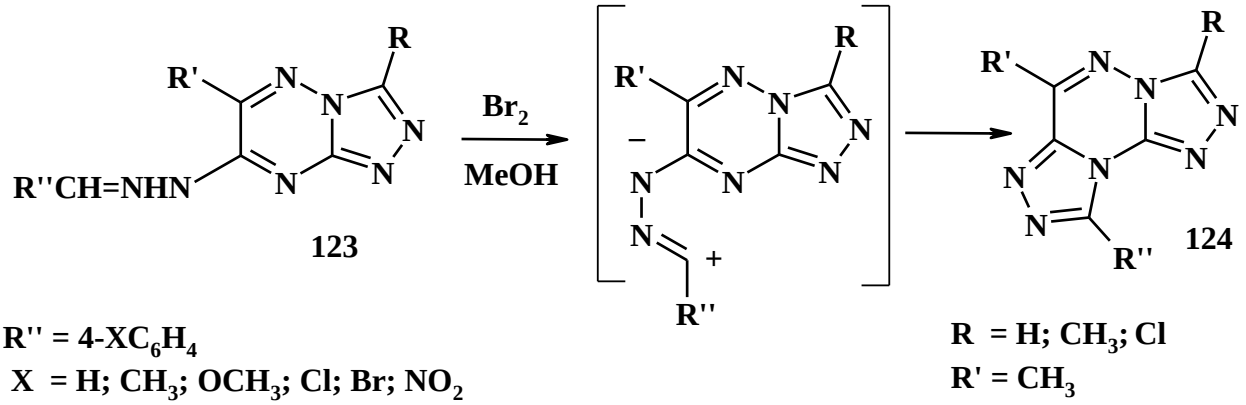
Reaction of aldehyde (7-methyl-5-phenyl-5H-pyrazolo[3,4-*e*][1,2,4]-triazin-3-yl)hydrazones **121** with $SOCl_2$ at reflux afforded the corresponding 1-phenyl-8-aryl-1H-pyrazolo[3,4-*e*][1,2,4]-triazolo[3,4-*c*][1,2,4]triazines **122**.[138]



Ar = XC_6H_4
X = H; 2-Br; 2-HO; 4-MeO; 2-O_2N

8.2. Bis(1,2,4-triazolo)[4,3-*b*:4,3-*d*][1,2,4]triazines

Treatment of aldehyde N-(1,2,4-triazolo[4,3-*b*]triazin-7-yl)hydrazones **123** with bromine in methanol resulted in oxidative cyclization to give the respective *bis*(1,2,4-triazolo)- [4,3-*b*:4.3-*d*][1,2,4]triazines **124**.[139]



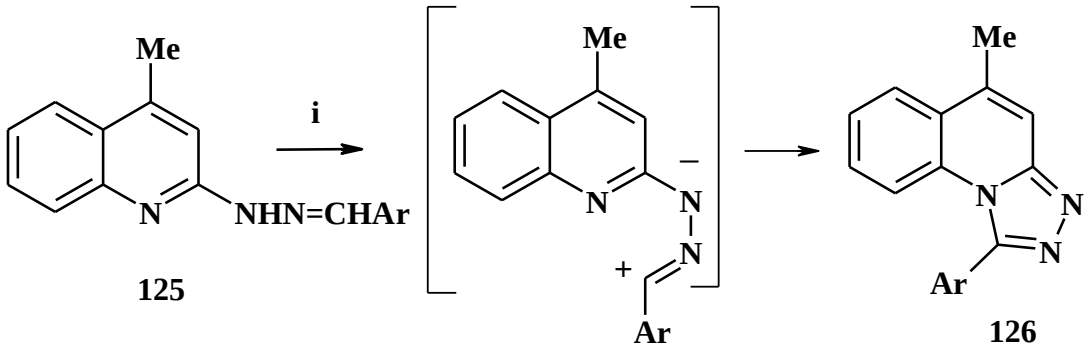
R'' = 4-XC_6H_4
X = H; CH_3; OCH_3; Cl; Br; NO_2

R = H; CH_3; Cl
R' = CH_3

9. Fused triazolo-benzoazines

9.1. 1,2,4-Triazolo[4,3-*a*]quinolines

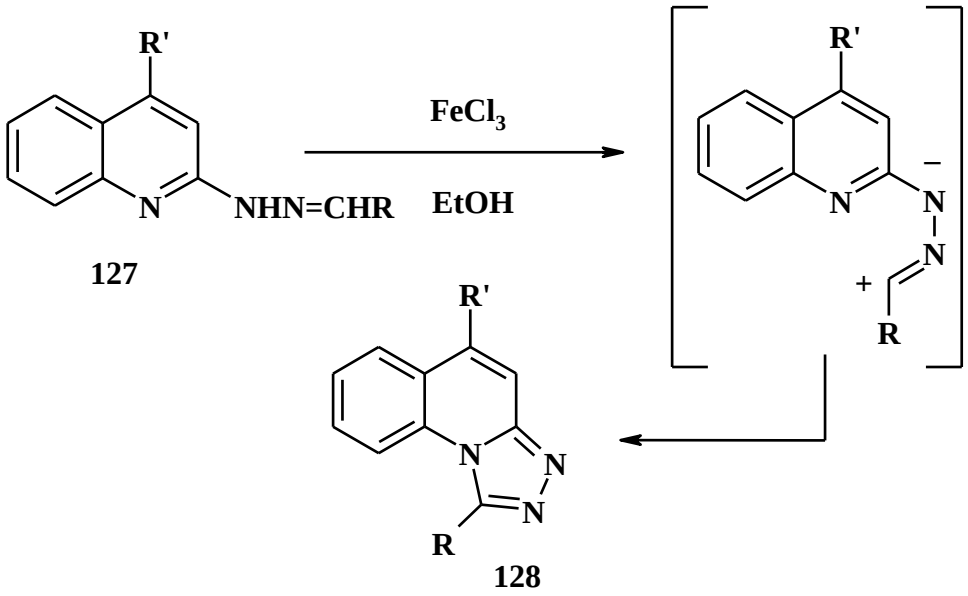
Aldehyde hydrazones **125** underwent oxidative cyclization when treated with lead tetra-acetate in CH_2Cl_2 to give the corresponding 3-aryl-1,2,4-triazolo[4,3-*a*]quinolines **126**. The latter products were also obtained by the reaction of the hydrazones **125** with either Br_2 in $CHCl_3$ in the presence of Na_2CO_3, ethanolic $FeCl_3$, NaOCl in dioxane or refluxing in nitrobenzene.[39, 83, 84]



i = LTA / CH_2Cl_2 ; Br_2 / $CHCl_3$ / Na_2CO_3 ; $FeCl_3$ / EtOH or NaOCl / dioxane

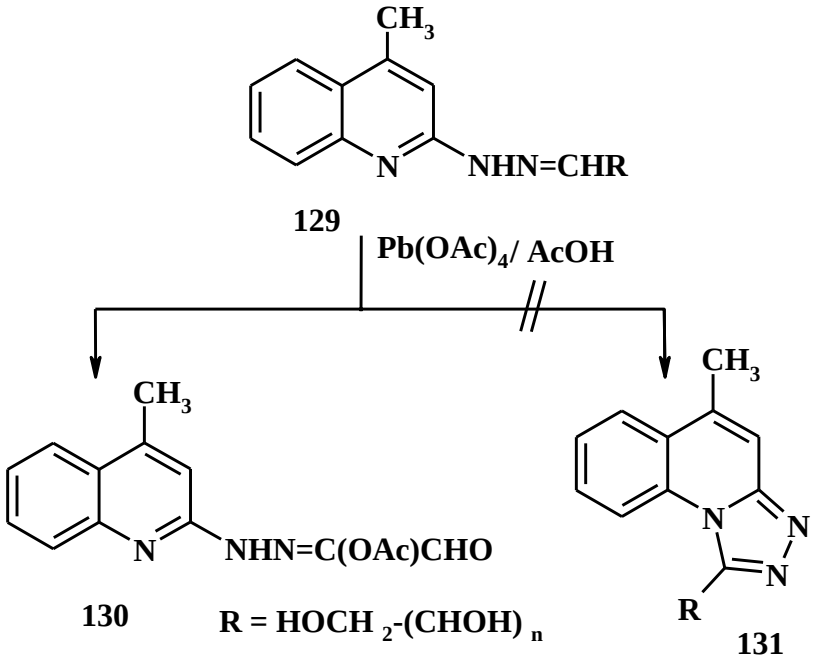
Ar = Ph; *p*-MeC_6H_4; *p*-ClC_6H_4; *p*-$MeOC_6H_4$; 5-NO_2-2-furyl; 2-thienyl

Similarly, the acyclo *C*-nucleosides **128** were produced by oxidation of aldehyde N-(2-quinolinyl)hydrazones **127** with ferric chloride in ethanol.[39, 140]

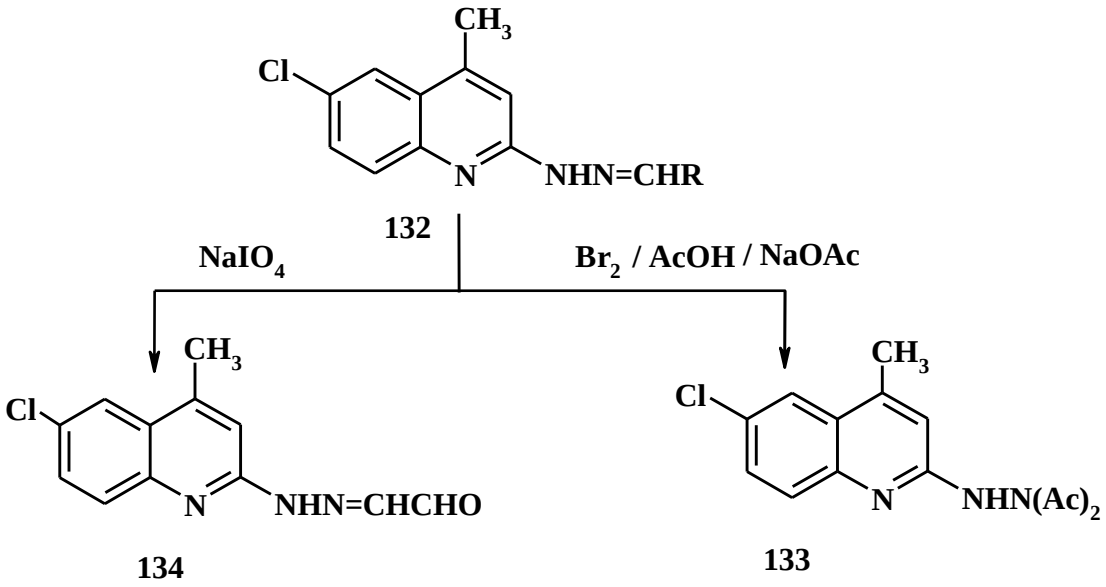


R / R' : a, $(CH_2OH)_4$ -CH_2OH / CH_3; b; Ar / H

Contrary to the foregoing reports, it was indicated that treatment of the aldose hydrazones **129** with lead tetraacetate in acetic acid afforded the hydrazones **130** and not the expected acyclo C-nucleoside **131**.[141]



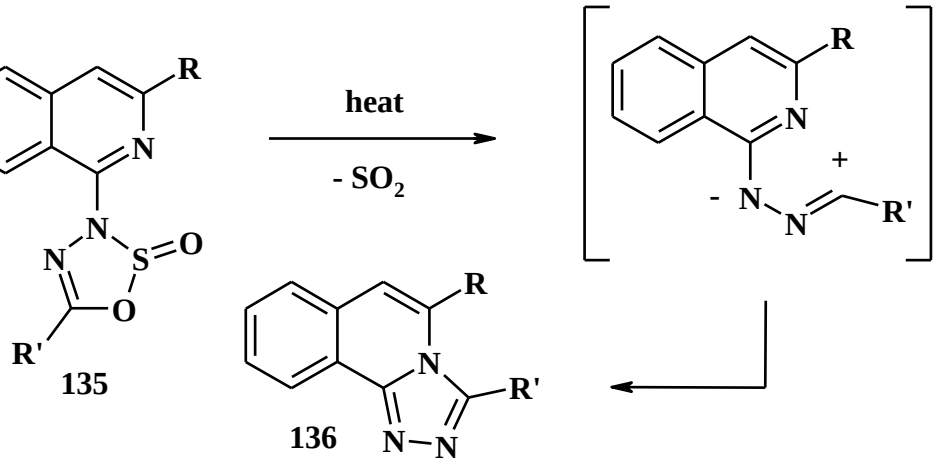
Furthermore, it was indicated that treatment of **132** with ferric chloride in ethanol gave tarry material, while its treatment with sodium periodate or bromine in acetic acid afforded the aldehyde **134** and the *N*,*N*-diacetyl hydrazine derivative **133**, respectively.[141]



R = HOCH $_2$-(CHOH) $_n$
n =3, 4

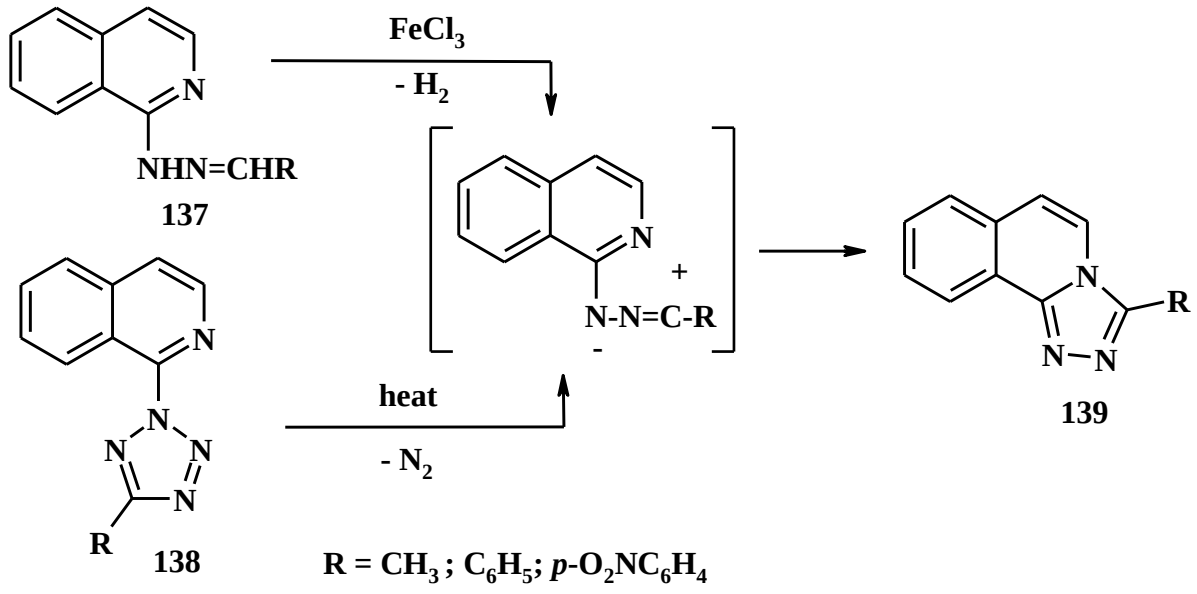
9.2. 1,2,4-Triazolo[4,3-*a*]isoquinolines

Thermolysis of **135** afforded the respective 3-substituted 1,2,4-triazolo[3,4-*a*]isoquinolines **136** *via* cyclization of the initially formed nitrilimines.[22]



R = H; Cl
R' =Me; C_6H_5; *p*-CCC_6H_4; *p*-$O_2NC_6H_4$

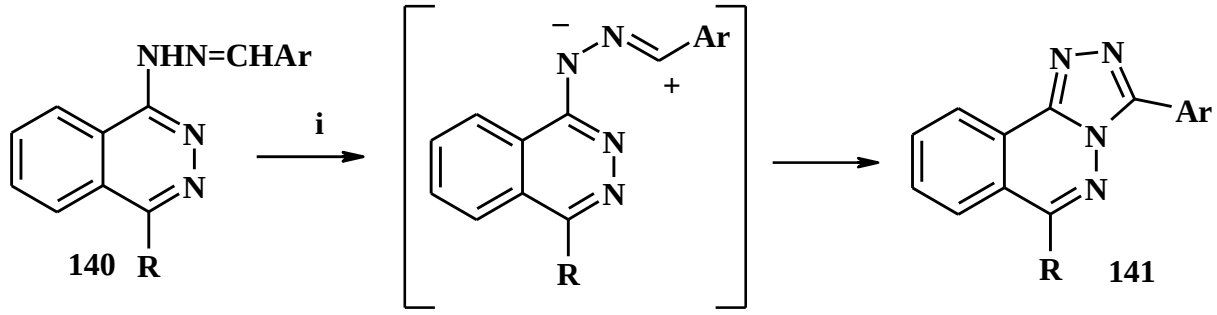
Similarly, nitrilimines, generated by treatment of the hydrazones **137** with ferric chloride[39, 142] or thermolysis of 1-(2-tetrazolyl)isoquinolines **138**[143] afforded the respective 1,2,4-triazolo[3,4-*a*]isoquinolines **139**.



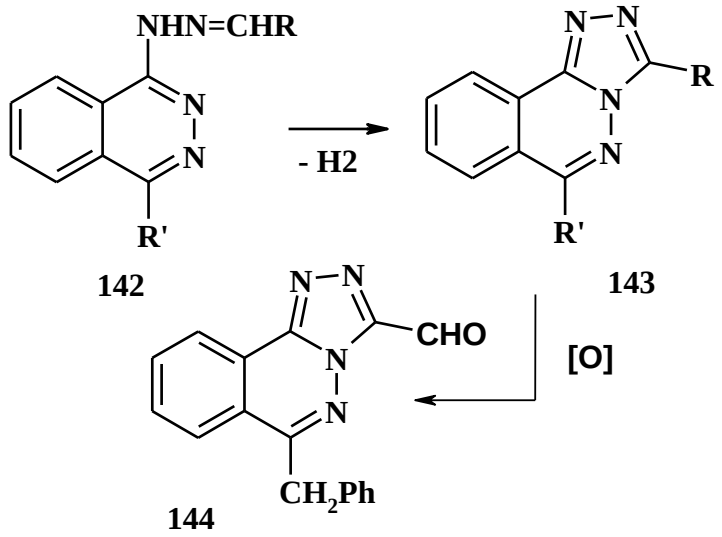
10. Fused triazolo-benzodiazines

10.1. 1,2,4-Triazolo[3,4-*a*]phthalazines

A series of 3-substituted[1,2,4]triazolo[3,4-*a*]phthalazines **141** were obtained by oxidative cyclization of the respective hydrazones **140** by heating with $CuCl_2$ in DMF[95] or heating with Pd / C [144] or treatment with bromine in acetic acid in the presence of sodium acetate.[145, 146]



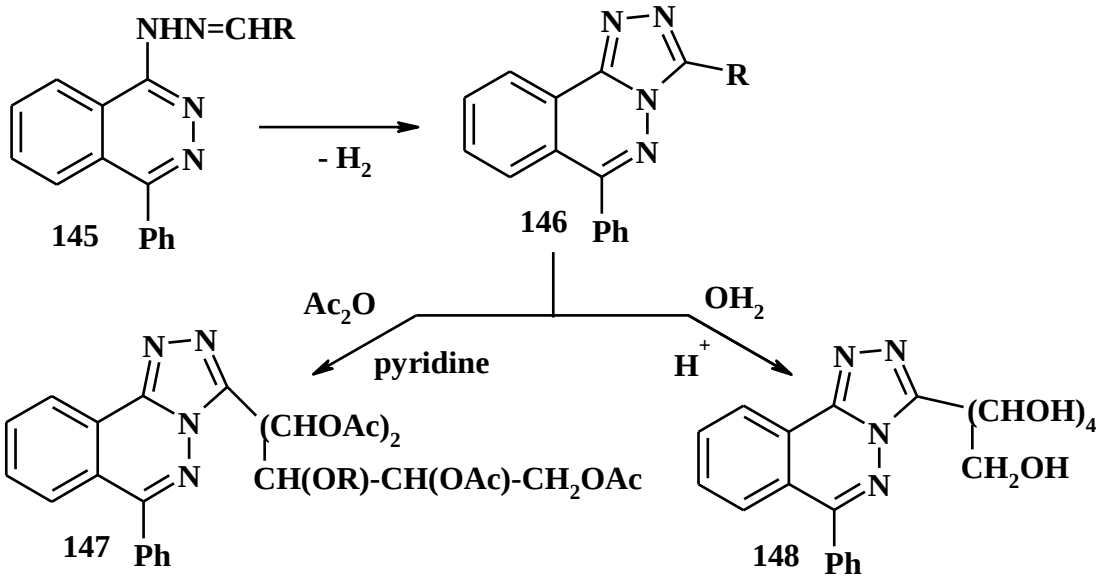
A number of 3-(alditol-1-yl)-1,2,4-triazolo[3,4-*a*]phthalazines **143** were synthesized by thermal dehydrogenation of the respective aldose N-(phthalazin-1-yl)hydrazones **142**. The formation of the latter was also obtained by catalytic dehydrogenation with palladium on charcoal.[147-152] Treatment of the C-acyclonucleosides **143** with sodium metaperiodate in water resulted in the cleavage of the alditol chain and gave the 3-formyl derivative **144**.[153]



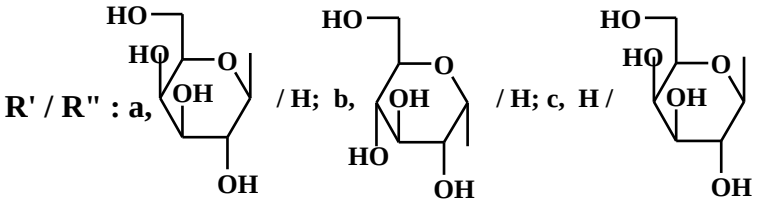
R = (CH2OH) n-CH 2OH; n = 3, 4

R' = Ph, PhCH$_2$

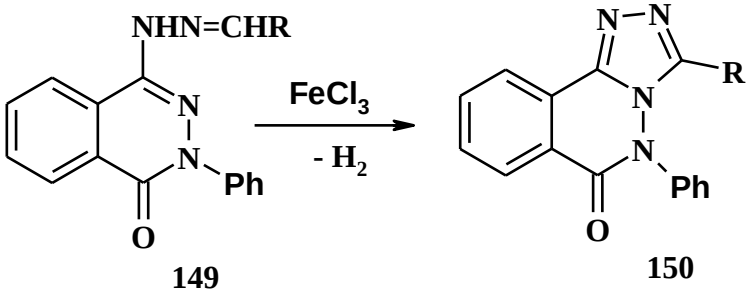
A series of 1,2,4-triazolo[3,4-*a*]pthalazine C-nucleosides **146** were prepared by thermal dehydrogenative cyclization of the respective hydrazones of lactose, maltose and melibiose **145**.[154] Acid hydrolysis of **146** yielded 3-(*D*-gluco-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines **148**. Furthermore, acetylation of **146** with acetic anhydride in pyridine gave the respective octa-O-acetyl derivatives **147**.[154]



R : CHOH-CHOR'-CHOH-CH_2OR"



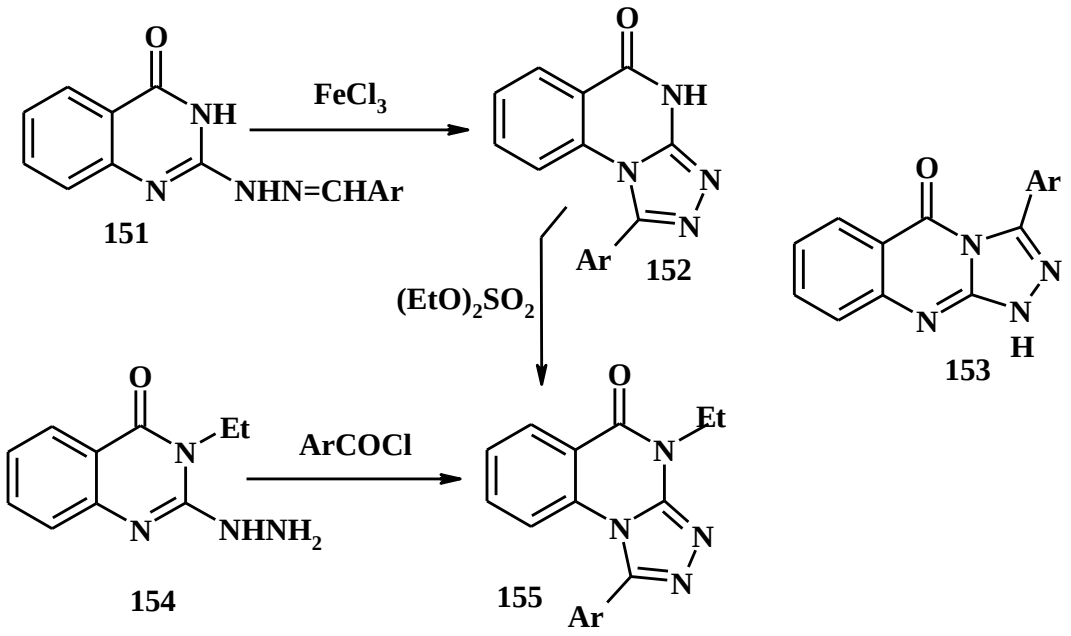
Also, oxidative cyclization of aldose hydrazones **149** by action of ferric chloride in ethanol afforded the corresponding 3-(alditol-1-yl)-1,2,4-triazolophthalazines **150**.[155]



R : -(CHOH)n-CH_2OH n = 3, 4

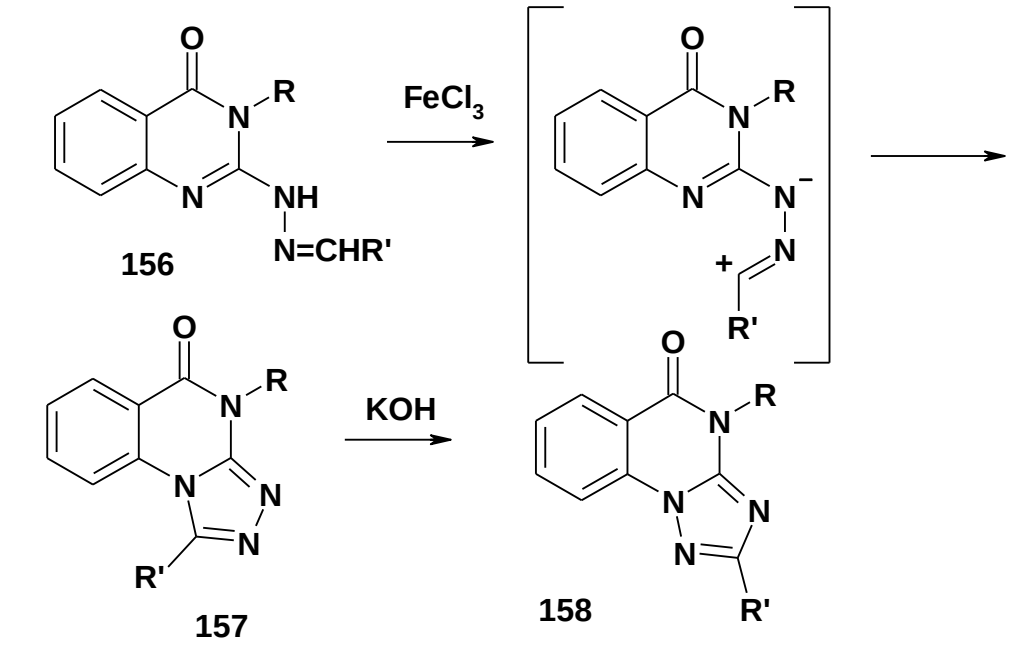
10.2. 1,2,4-Triazolo[4,3-a]quinazolines

Oxidative cyclization of aldehyde N-(2-quinazolinyl)hydrazones **151** with ferric chloride was reported to give the angular 1,2,4-triazolo[4,3-*a*]quinazolines **152** and not the linear triazolo[3,4-*b*]quinazolines **153**.[156] The structure of **152** was confirmed by comparison of its N-ethyl derivatives **155** with an authentic sample prepared by the reaction of **154** with aroyl chloride.[156]

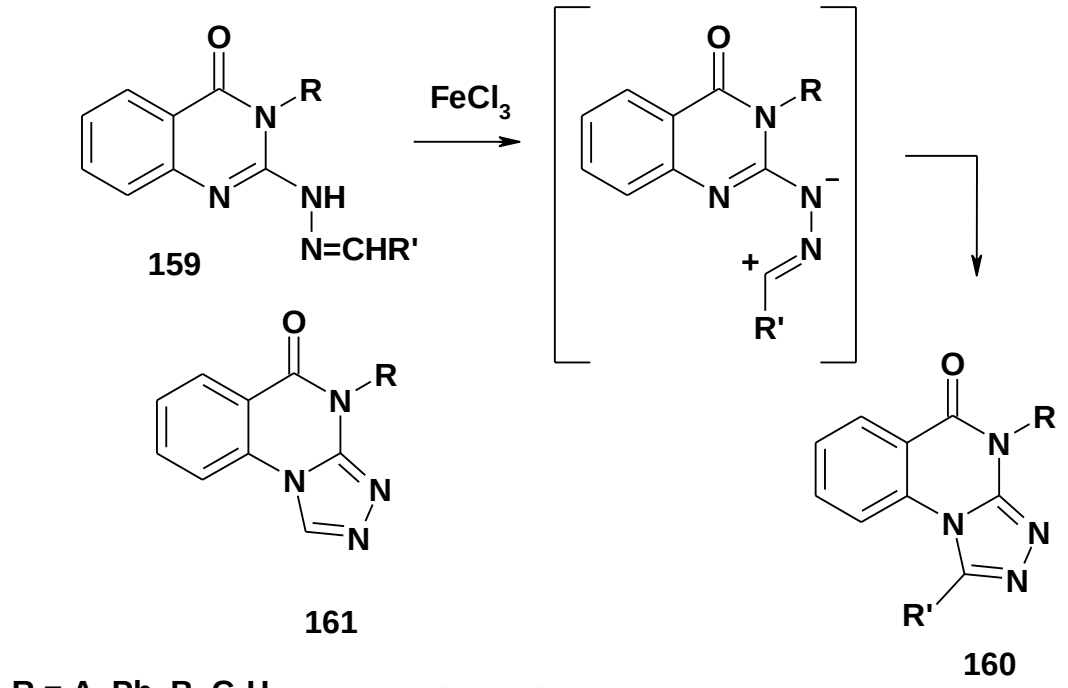


Ar = H; Me; *p*-ClC$_6$H$_4$

Recently two novel series of aldehyde N-(3-phenyl-4-oxoquinazolin-2-yl)hydrazones **156A** and their N-(3-cyclohexyl)- analogs **156B** were prepared by condensation of each of the appropriate 2-hydrazino-3-substituted-quinazolin-4(3H)-one with the aldehydes. Treatment of each of the hydrazones **156** with equivalent amount of iron(III) chloride in ethanol gave the respective 1,4-disubstituted-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one **157**.[157,158] Treatment of each of **157** with potassium hydroxide in refluxing ethanol yielded, in each case, one product that was identified as the respective 2,4-disubstituted-1,2,4-triazolo[1,5-*a*]quinazolin-5(4*H*)-one **158**.[157-159] This isomerization is similar to Dimroth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidine into 1,2,4-triazolo[1,5-*a*]pyrimidine. [159]



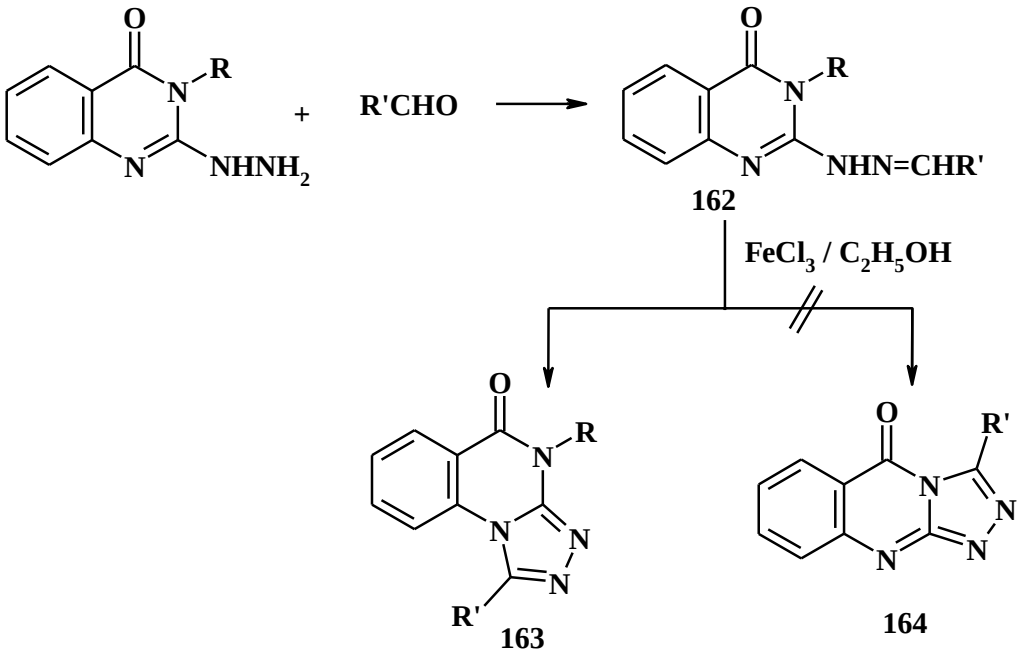
Also, it was recently reported that treatment of each of the aldose N-(3-phenyl-4-oxoquinazolin-2-yl)hydrazones **159A** and aldose N-(3-cyclohexyl-4-oxoquinazolin-2-yl)hydrazones **159B** with equivalent amount of iron(III) chloride in refluxing ethanol was reported to afford the respective 1,4-disubstituted-1,2,4-triazolo[4,3-*a*]quinazolin-5(4H)-ones **160A** and **160B**, respectively.[160] In contrast to the behaviour of **159Aa-c** and **159Ba-c**, when each of the hydrazones **159Ad** and **159Ae** was subjected to oxidative cyclization following the same procedure, both hydrazones were found to give, one and the same product that was identified as 4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4H)-one **161**. Similarly, oxidative cyclization of the hydrazones **159Bd** and **159Be** following the same procedure above gave also one and same compound that was identified 4-cyclohexyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one **161**. The structures of the unexpected products **161A** and **161B** were further evidenced by comparison with authentic samples prepared by refluxing each of 2-hydrazino-3-phenyl-quinazolin-4(3H)-one and its 3-cyclohexyl analog with ethyl orthoformate or formic acid.[160]



R = A, Ph, B, C_6H_{11} **R' = $(CHOH)_nCH_2OH$**

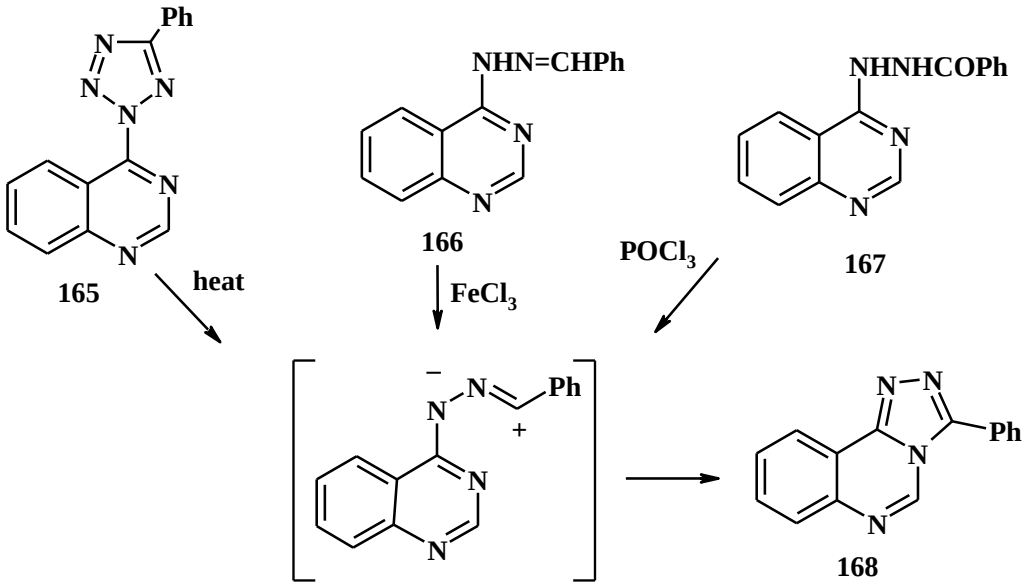
159-160 , R' : a, D-galactose, b, D-Mannose, c, D-arabinose, e, D-xylose, f, D-ribose

Recently, it was reported that aldose hydrazones **162** were prepared by condensation of 3-substituted-2-hydrazinoquinazolin-4(3*H*)-one with equimolar amount of appropriate D-aldose in aqueous ethanolic solution in presence of catalytic amount of acetic acid. Treatment of each of such aldose hydrazones **163** with hot ethanolic ferric chloride resulted in an oxidative cyclization to afford the angularly annelated 1-(alditol-1-yl)-4-substituted-1,2,4-triazolo[4,3-*a*]quinazolin-5(4H)ones **163** rather than to the linearly annulated regioisomers **164**.[161]



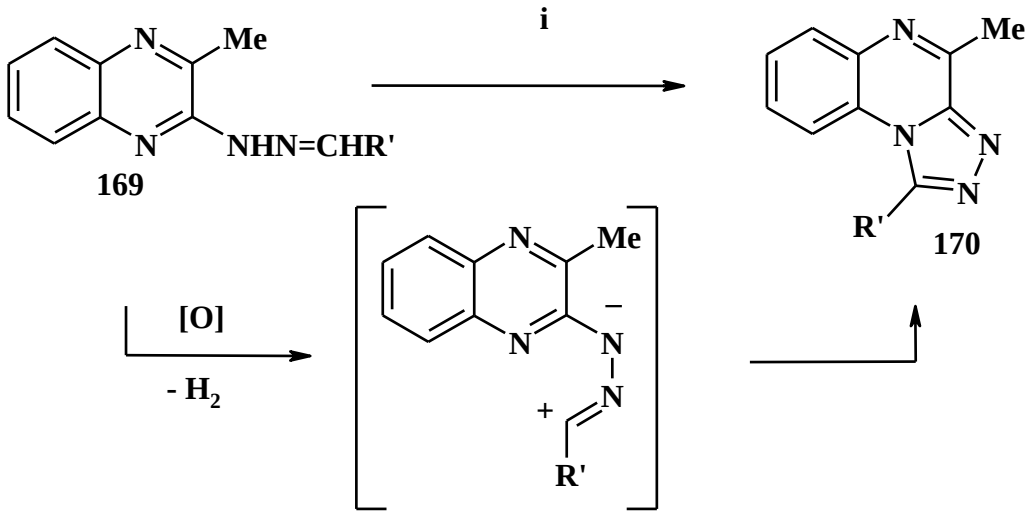
10.3. 1,2,4-Triazolo[4,3-*c*]quinazolines

Nitrilimine generated *in situ* from either aldehyde N-(4-quinazolinyl)hydrazone **166**, *N*-quinazolinyl acid hydrazide **167**[162] or 4-(5-substituted-tetrazol-3-yl)quinazoline **165**,[89] underwent 1,5-electrocyclization to give the corresponding 3-substituted 1,2,4-triazolo[4,3-*c*]quinazoline **168.**



10.4. 1,2,4-Triazolo[4,3-*a*]quinoxalines

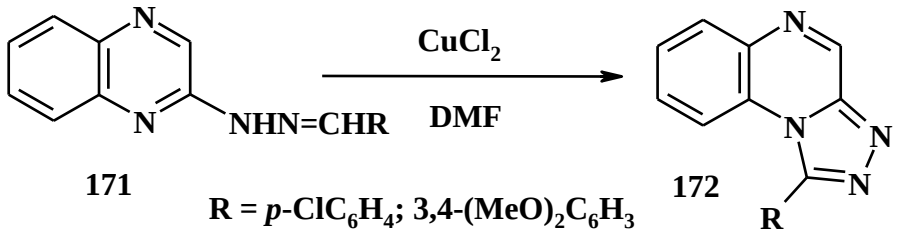
Aldehyde N-(quinoxalin-2-yl)hydrazones **169** were reported to afford, upon heating with ferric chloride, or lead tetra-acetate in CH_2Cl_2 or refluxing in nitrobenzene the corresponding 1,2,4-triazolo[4,3-*a*]quinoxalines **170**.[163-165]



i = $FeCl_3$ / EtOH ; or LTA / CH_2Cl_2

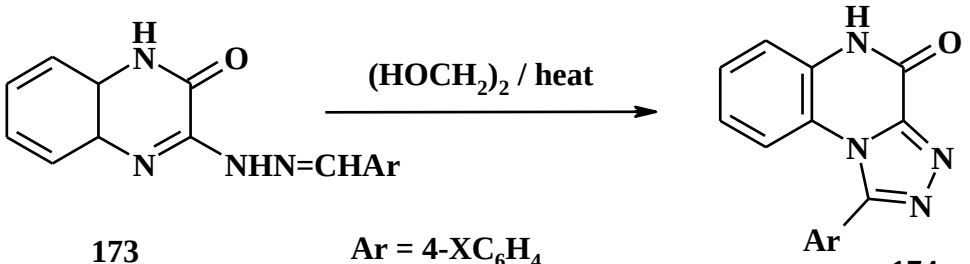
R' = Ph; 4-MeC_6H_4 ; 4-$MeOC_6H_4$; 2-$MeOC_6H_4$; 4-$NO_2C_6H_4$; 4-ClC_6H_4 ; 3-CH_3O-4-HOC_6H_3; 4-FC6H4; 4-Biphenyl; 3HO,4-EtC_6H_3

Aldehyde N-(quinoxalin-2-yl)hydrzones **171** afforded the respective 3-substituted-1,2,4-triazolo[4,3-*a*]quinoxalines **172** in 61-84% yield upon treatment wit $CuCl_2$ in DMF.[95]



R = *p*-ClC_6H_4; 3,4-$(MeO)_2C_6H_3$

In another report it was indicated that heating the hydrazones **173** in ethylene glycol and DMSO for 5-8 h afforded **174**.[166]

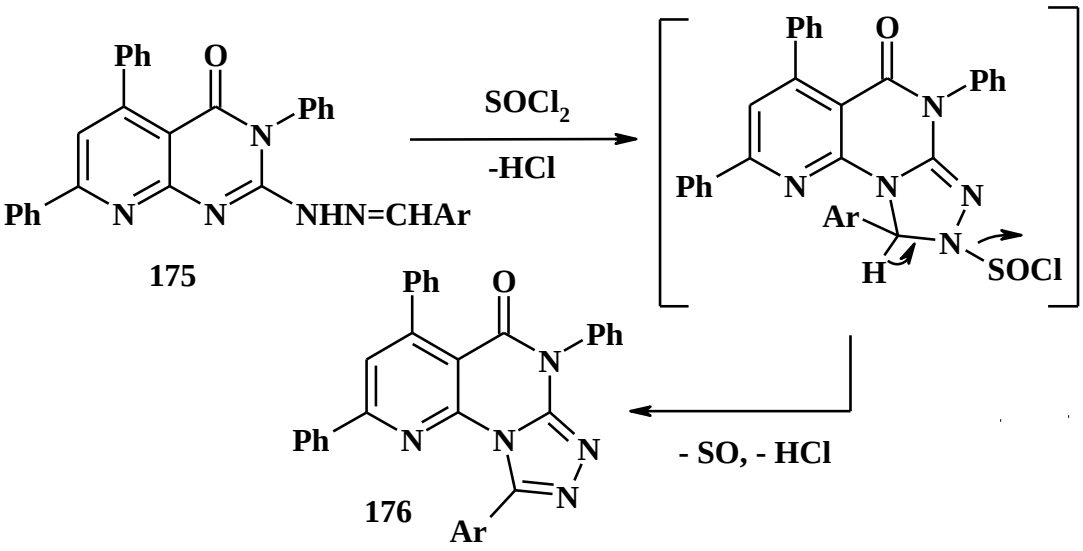


173 **174**

Ar = 4-XC$_6$H$_4$
X = H; Cl; F; MeO

10.5. Pyrido[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines

The hydrazones **175** were reported to cyclize easily on treatment with excess thionyl chloride to give 9-aryl-2,4,6-triphenylpyrido[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(6H)-ones **176**.[167]



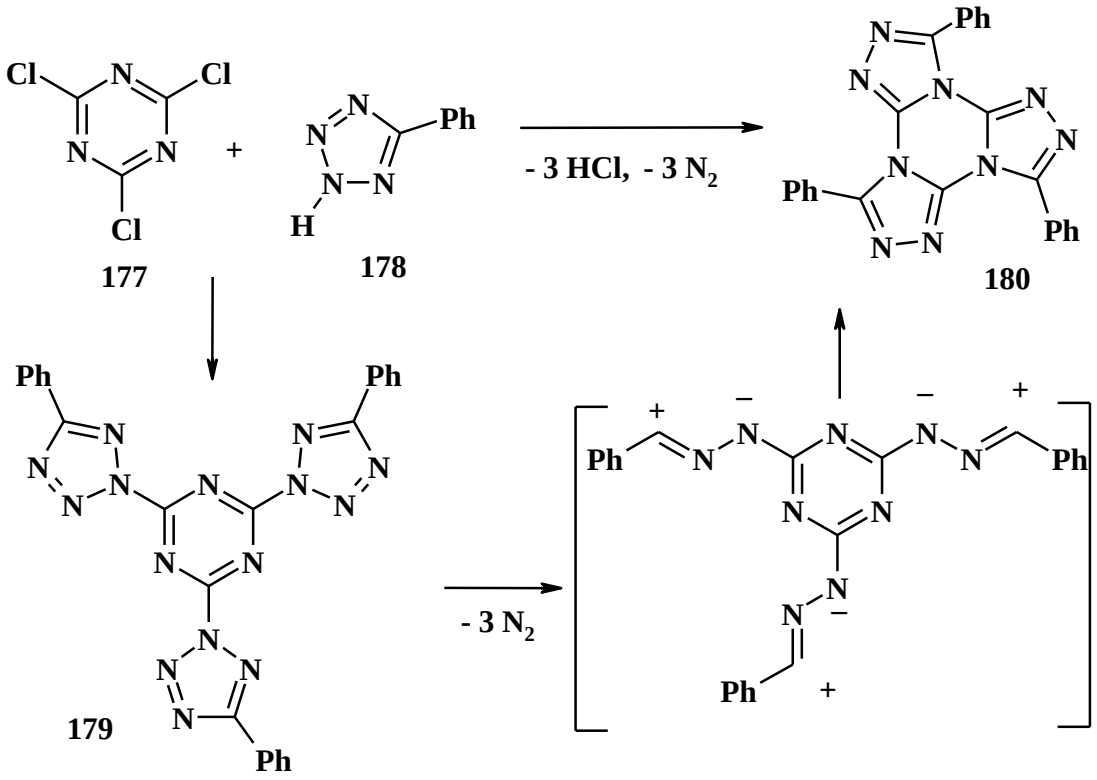
175 **176**

Ar = XC$_6$H$_4$
X = H; 4-Cl; 4-MeO; 4-O$_2$N; 2-HO

11. Fused triazolo-azolo-triazines

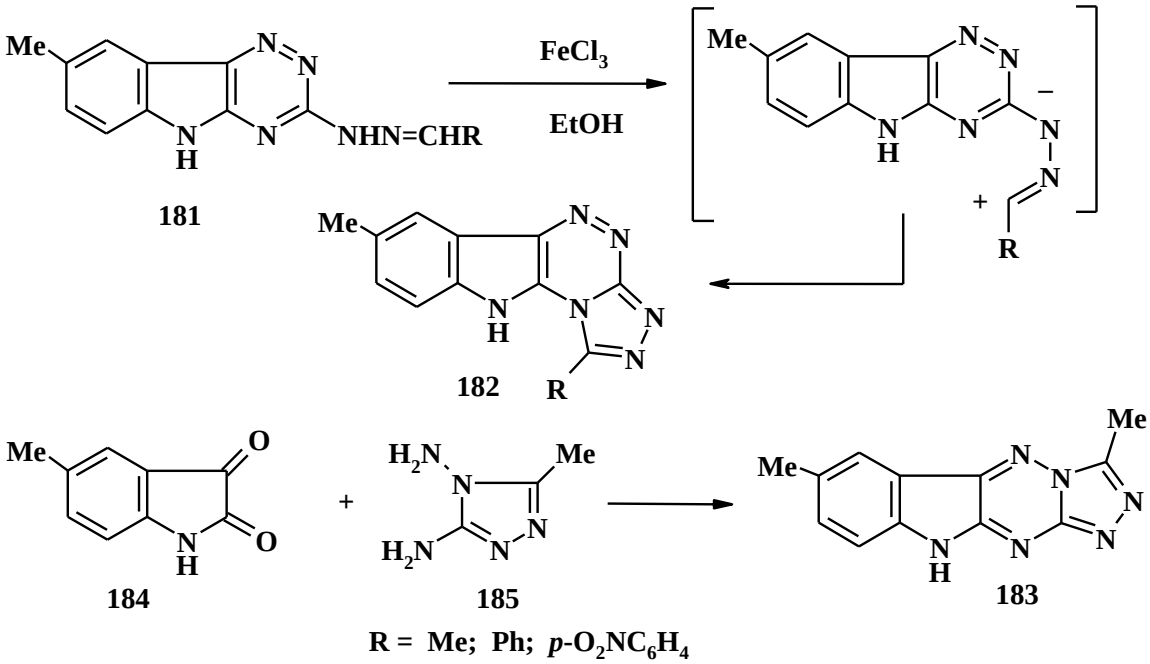
11.1. Tris-[1,2,4-triazolo][4,3-*a*:4,3-*c*:4,3-*e*][1,3,5]triazines

Reactions of 2,4,6-trichloro-1,3,5-triazine **177** with three equivalents of 5-substituted tetrazoles **178** led to the formation of the title heterocyclic system **180**.[89] In this case, the initially formed substitution intermediate **179** underwent nitrogen elimination to give the respective tri-nitrilimine which cyclized *in situ* to give **180** as end product.

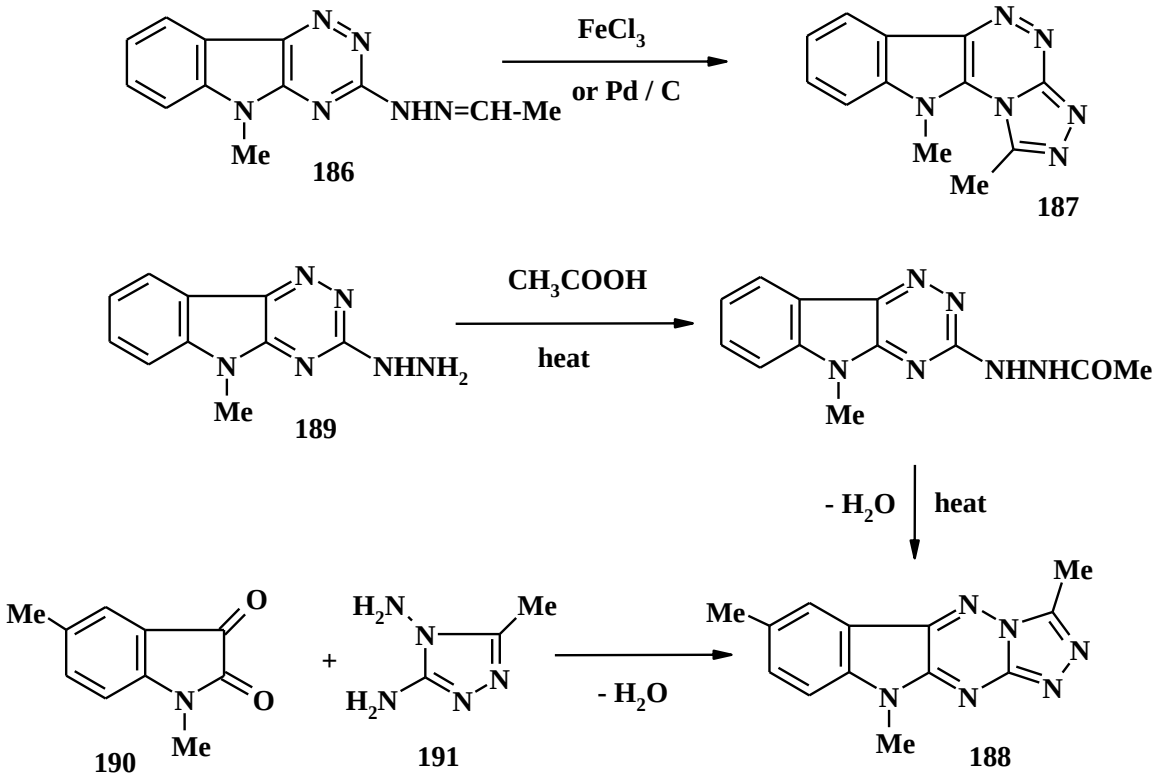


11.2. 1,2,4-Triazolo[4',3' :2,3][1,2,4]-triazino[5,6-b]indoles

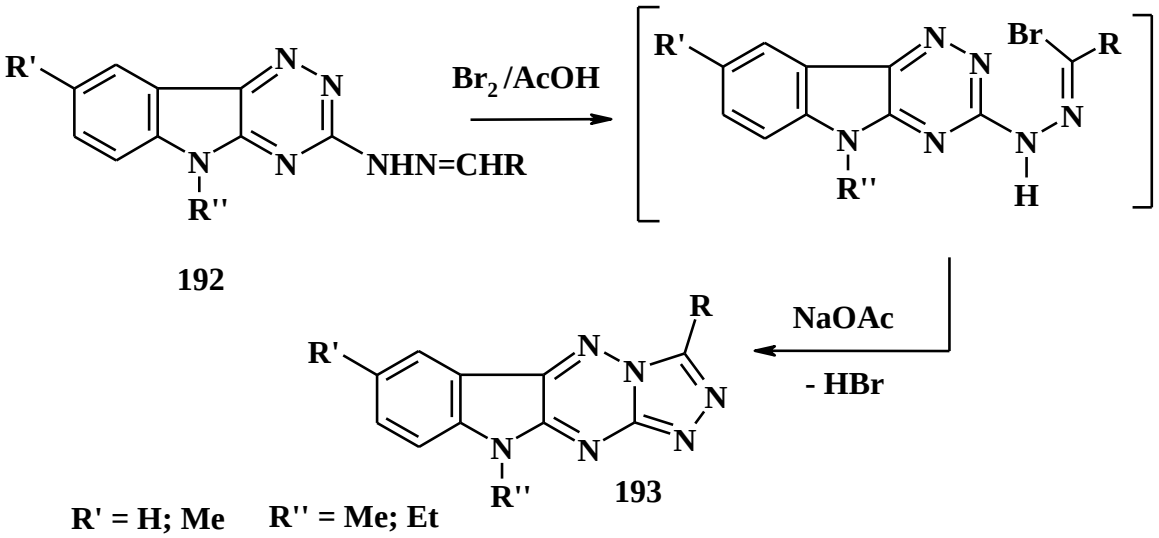
Cyclodehydrogenation of **181** with ethanolic $FeCl_3$ was reported to give **182** and not **183**. Unequivocal synthesis of **183** by condensing diaminotriazole **185** with 5-methylisatin **184**. The isolated product was found different from **182** (R = Me).[168]



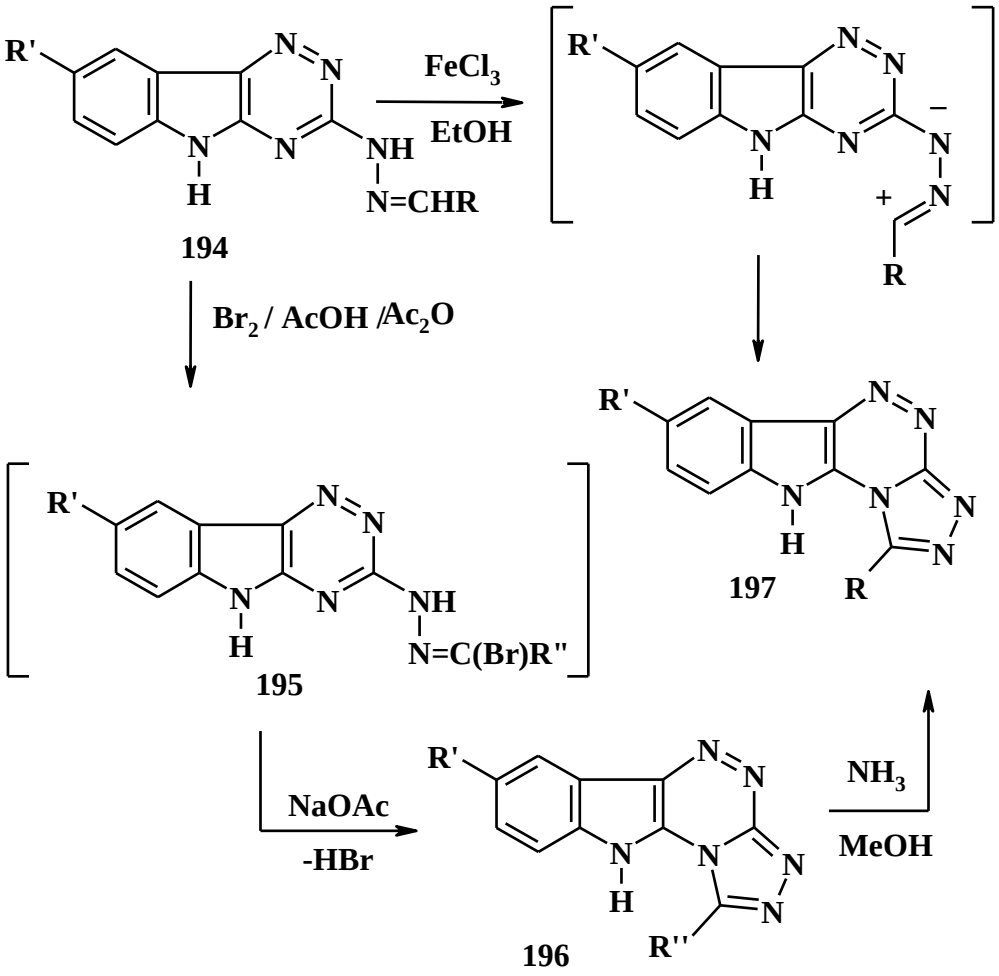
Similarly, oxidative cyclization of **186** with $FeCl_3$ in ethanol or with Pd / on-charcoal was reported to give **187** and not **188**. The distinction between **187** and **188** was based on alternate synthesis of **188** by either the reaction of **189** with acetic acid or the reaction of isatin **190** with diaminotriazole **191**.[169]



However when the hydrazones **192** were treated with bromine in acetic acid in presence of sodium acetate, they yielded 1,2,4-trizolo[3',4':2,3][1,2,4]triazino[5,6-*b*]indoles **193**.[170]



Oxidative cyclization of the aldose hydrazones **194a-d,** derived from 3-hydrazino-5H-1,2,4-triazino[5,6-indole and aldehydes as well as aldose monosaccharides produced the 3-substituted derivatives **197a-c** and the acyclo C-nucleosides **197d**, respectively. Oxidative cyclization of the hydrazones **194d** with with bromine in acetic acid in the presence of sodium acetate and acetic anhydride was reported to afford **196d** with concurrent acetylation of the sugar residue. Treatment of each of the latter with ammonium hydroxide solution in methanol resulted in deprotection of the sugar residue and the formation of C-nucleoside **197d**.[168-170]

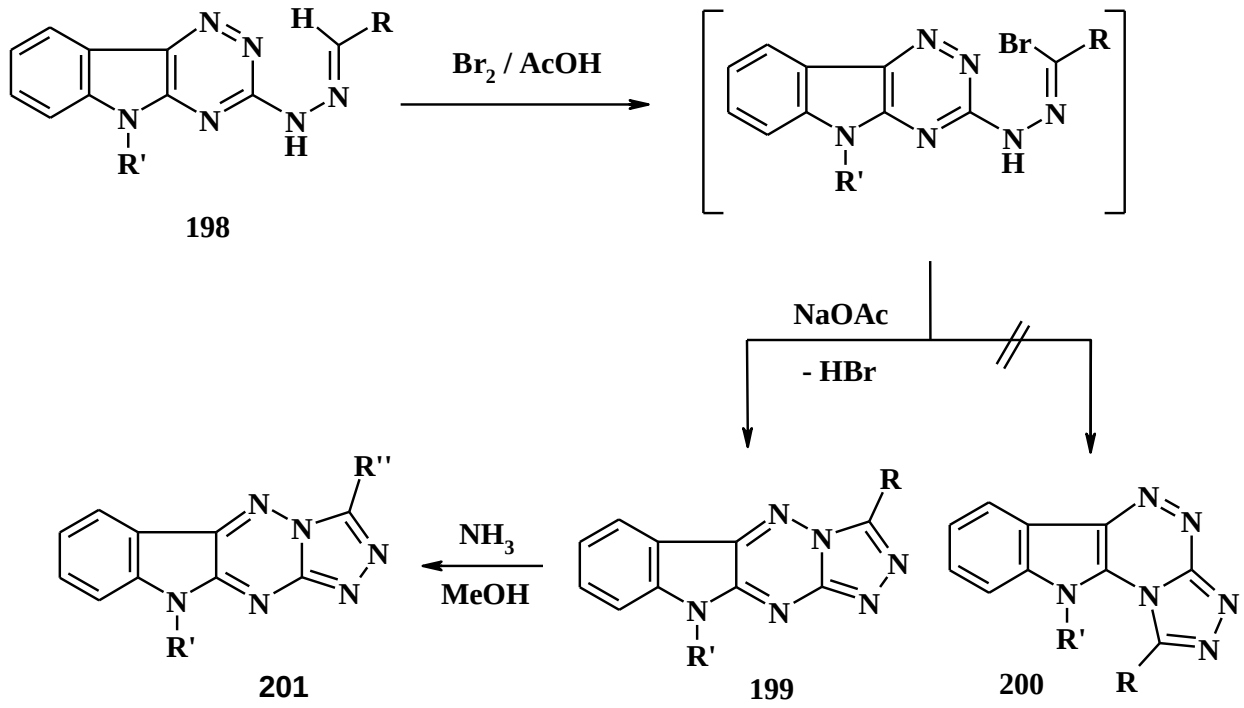


R : a, Me, b, Ph; c, 4-O2NC6H4; d, (CHOH) $_n$-CH $_2$OH

R' = H, Me, Et R'' = (CHOAc) $_n$-CH $_2$OAc

n = 3, 4

Later, it was reported that oxidative cyclization of both poly-O-acetyl derivatives of aldose (5-methyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazones **198A** and aldose (5-ethyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazones **198B** with bromine in acetic acid in the presence of sodium acetate afforded the respective linearly annelated 3-(polyacetoxyalkyl)-10-alkyl-1,2,4-triazolo[4',3':2,3][1,2,4]-triazino-[5,6-*b*]indoles **199A** and **199B**, respectively rather than the their sterically unfavourable angularly annelated isomers **200A** and **200B**.[171-175] Treatment of the latter products **199** with ammonia in methanol resulted in their deacetylation and the formation of the respective acyclo C-nucleosides **201**.[171, 172] The regiospecific outcome of this oxidative cyclization is discussed in terms of electronic and steric factors and the assignment of structures **199A** and **199B** have been based on the basis of chemical as well as spectroscopic evidences.



R' = Me; Et

A, R'' = $HOCH_2$-$(CHOH)_n$

n = 3 : a, D-arabino; b, L-ribo-; d, D-xylo

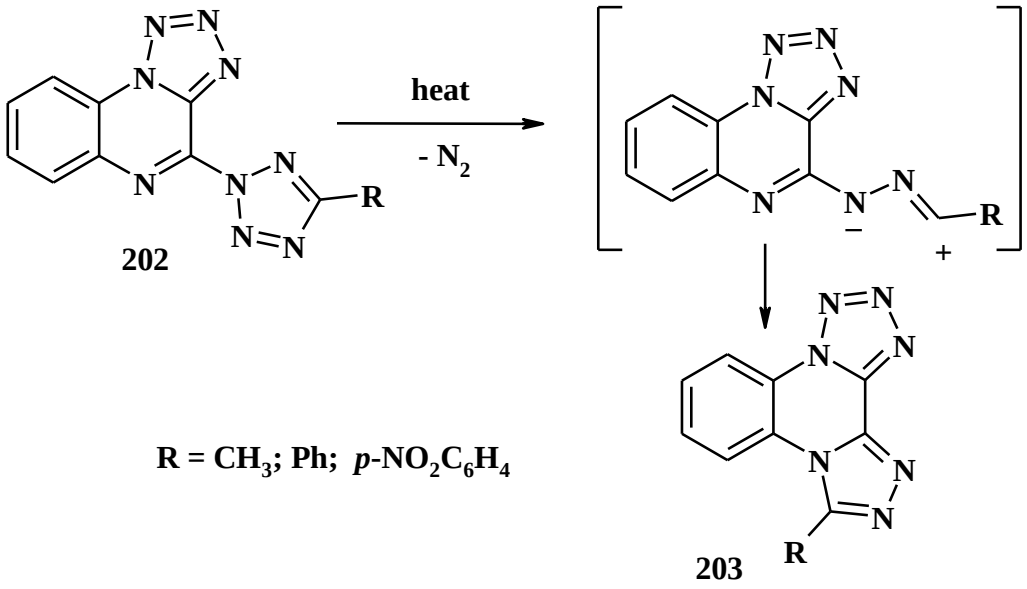
n = 4: e, D-galacto ; f, D-gluco ; g, D-manno

B, R = $AcOCH_2$-$(CHOAc)_n$

12. Fused triazolo-azolo-diazines

12.1. 1,2,4-Triazolo[4,3,-*a*]tetrazolo[5,1-*c*]quinoxalines

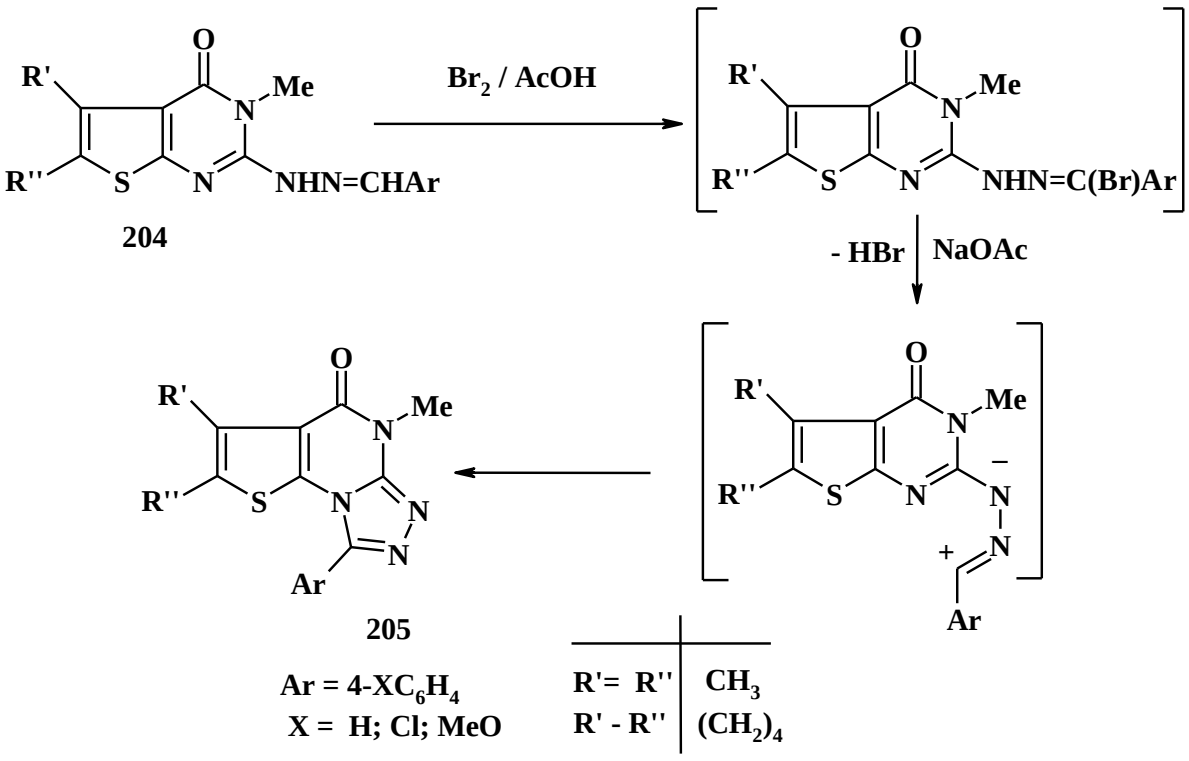
Several derivatives of the title ring system **203** were prepared by thermolysis of **202**, prepared by reaction of 4-chloro-1,2,3,4-tetrazolo[1,5-*a*]quinoxaline with 5-substituted tetrazoles in presence of triethylamine.[176]



13. Fused triazolo-thieno-diazines

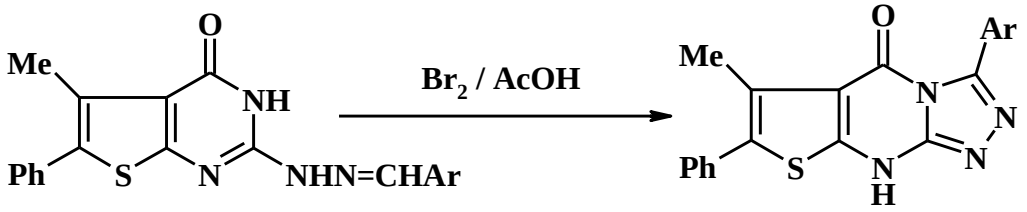
13.1. Thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines

Treatment of the hydrazone **204** with exess Br_2 in AcOH in the presence of NaOAc afforded thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one derivatives **205**.[131]



13.2. Thieno[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidines

3-Aryl-6-methyl-7-phenyl-5*H*,9*H*-thieno[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidine-5-ones **207** were obtained by treatment of the respective hydrazones **206** with Br_2 in AcOH in presence of NaOAc.[132]

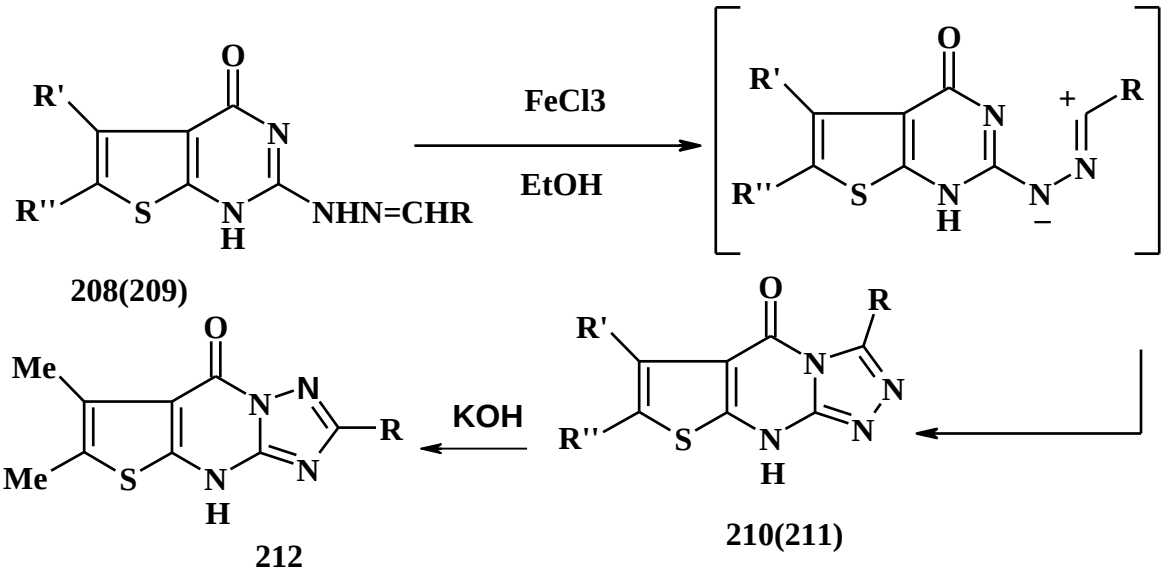


206 **207**

Ar = Ph; *p*-MeC$_6$H$_4$

Reaction of aldehyde hydrazones **208** and **209** with ferric chloride in ethanol gave the triazolopyrimidine acyclo C-nucleosides **210** and **211** respectively.[133]

When **210** (R = R" = Me) was treated with potassium hydroxide in ethanol, it underwent Dimroth type rearrangement to give **212**.



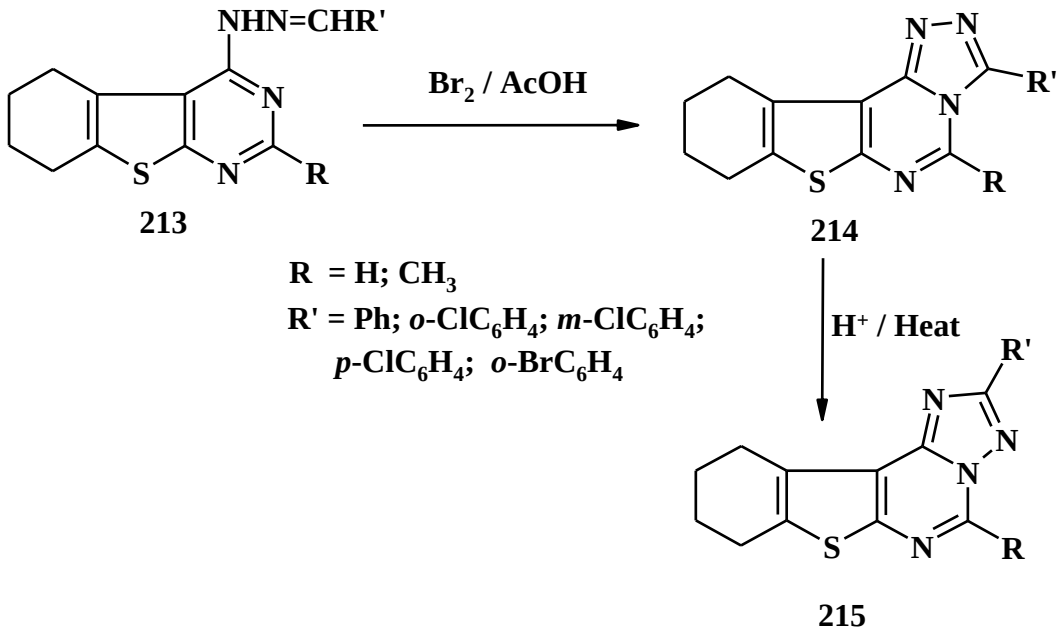
208 (210) R' = R'' = CH$_3$; 209 (211): R', R'' = (CH$_2$)$_4$

R = (CHOH)n-CH$_2$OH n = 3,4

13.3. Cyclohexathieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

Treatment of the hydrazones **213** with Br_2 in AcOH at 45°C was reported to give a mixture of **214** and its rearrangement product **215**. The latter product was the sole isolated product of the

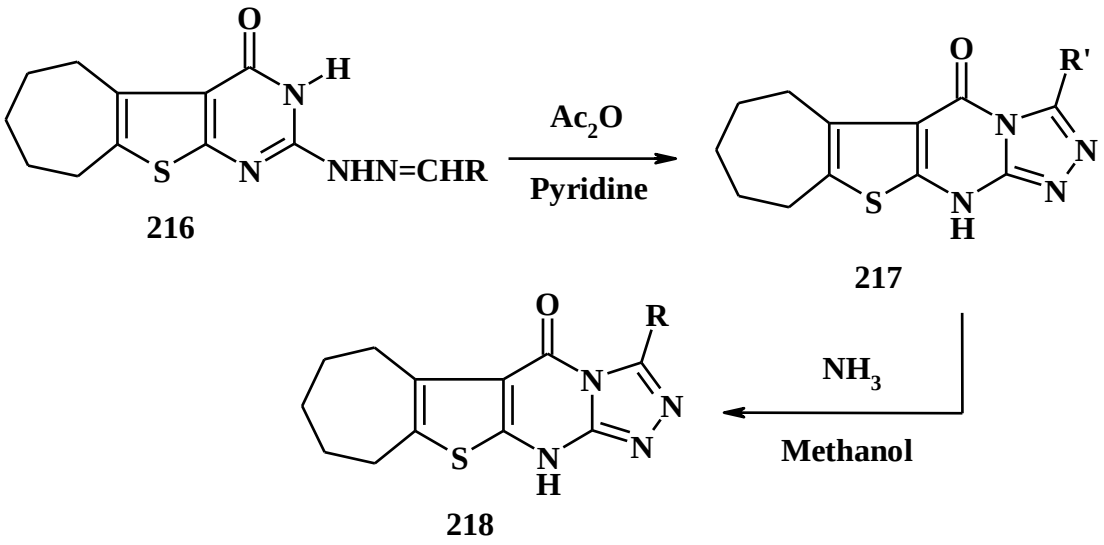
reaction of the hydrazone when reacted with Br_2 in AcOH at reflux temperature. It appears that when acetic acid is used for crystallization at reflux temperature the initial product **214** undergoes Dimroth type rearrangement to the thermodynamically more stable [1,5-*c*] isomer **215**.[177]



213 **214** **215**

13.4. Cycloheptathieno[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidin-5-ones

Recently it was reported that stirring of the sugar hydrazone **216** at room temperature in acetic anhydride–pyridine (1:1) mixture afforded the respective 3-(2',3',4',5'-O-tetraacetyl-glycosyl)-6,7,8,9,10-pentahydrocycloheptathieno[3,2-*e*][1,2,4]triazolo[3,4-*b*]pyrimidin-5-one **217**.[178] Deprotection of the protected acyclo-nucleosides **217** to give 3-glycosyl-6,7,8,9,10-pentahydrocycloheptathieno[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one **218** was achieved by treatment with methanolic ammonia solution (25%) at room temperature for 24 h.[178]



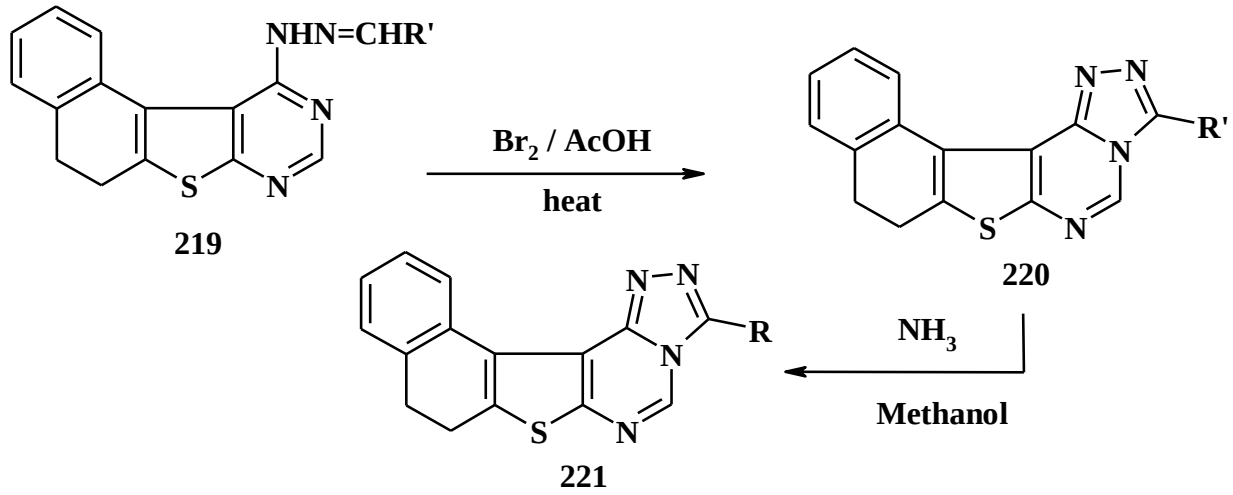
216 **217** **218**

R = (CHOH) $_n$ -CH $_2$OH **R' = (CHOAc) $_n$-CH $_2$OAc**

n = 3,4

13.5. Naphtho[1',2':4,5]thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidines

Oxidative cyclization of the hydrazones **219** using bromine in acetic acid afforded the O-acetylated cyclic C-nucleosides **220**. Deprotection of **220** using ammonium hydroxide solution in methanol gave the target free acyclic C-nucleosides **221**.[179]



219 **220** **221**

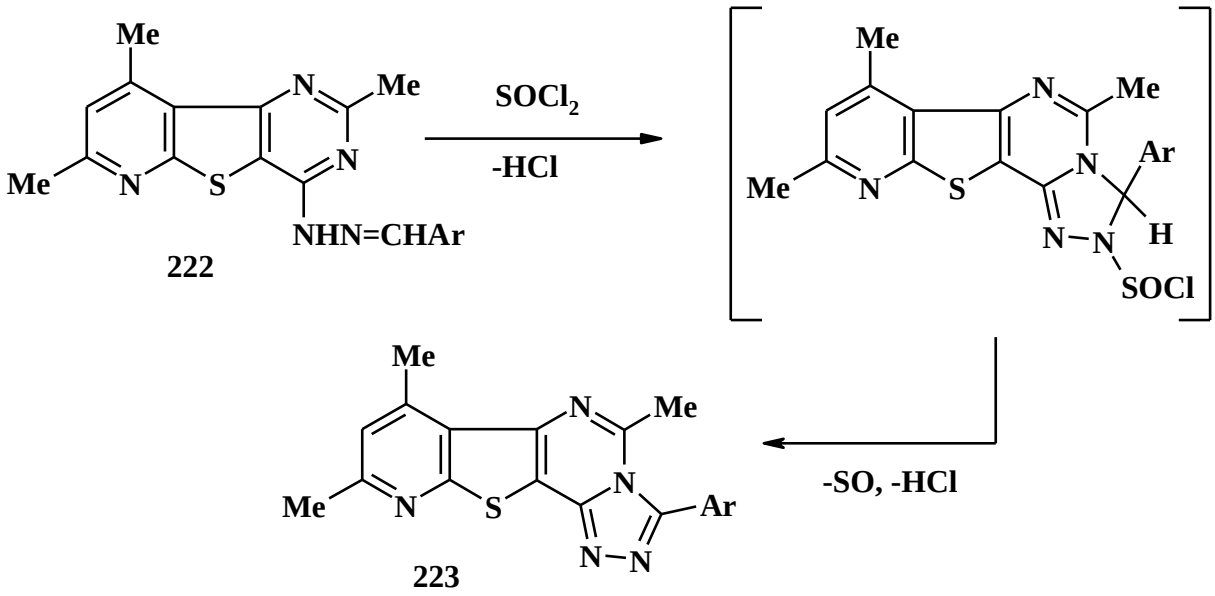
R = (CHOH) $_n$-CH $_2$OH **R' = (CHOAc) $_n$-CH $_2$OAc**

n = 3,4

14. Fused triazolo-thieno-azino-diazines

14.1. Pyrido[3',2':4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines

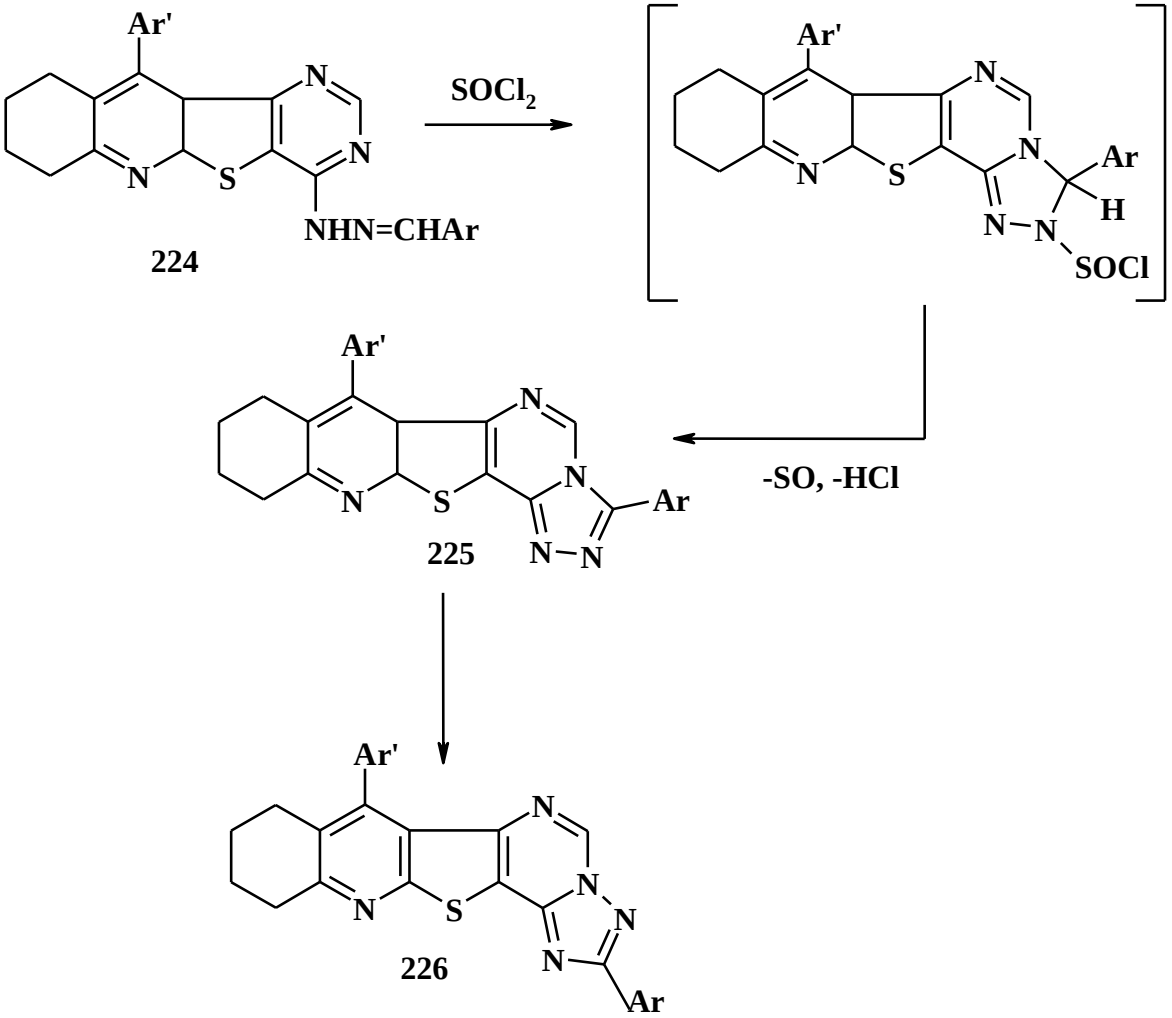
The reaction of **222** with $SOCl_2$ was reported to yield 3-aryl-5,7,9-trimethyl-pyrido[3',2':4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **223**.[180]



Ar = XC_6H_4 X = H; 4-MeO; 4-O_2N

14.2. Quinolino[3',2':4,5]thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

The hydrazones **224** were reported to be easily cyclized upon treatment with $SOCl_2$ to give 2-aryl-7-(*p*-chlorophenyl)-8,9,10,11-tetrahydroquinolino[3',2':4,5]thieno[2,3-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidines **226**. The formation of the latter products seem to result *via* Dimroth rearrangement of the initially formed fused triazoles **225**.[181]



15. Conclusions

The present review has outlined the importance of tandem *in situ* generation and 1,5-electrocyclization of N-hetaryl nitrilimines as a convenient methodology for synthesis of numerous fused 1,2,4-triazoles and some of their acyclo C-nucleosides. It is hoped that it will further stimulate the interest of more chemists to explore the utility of such strategy for synthesis of other heterocycles of industrial and biological potentials.

16. References

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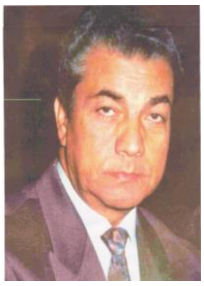
Biographical Sketch



Prof. Ahmad Sami Shawali is presently Emeritus Professor of Physical Organic Chemistry, Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt. He graduated with B.Sc. from the University of Cairo in 1958. He received his M.Sc. and Ph.D. degrees in 1962 and 1966, respectively, from Lowell Technological Institute, presently the University of

Lowell, Massachusetts, USA. He was awarded the degree of Doctor of Science (D.Sc.) from the university of Cairo after recommendation from a British committee from the Royal Chemical Society in 1995. Prof. Shawali has been the recipient of the state award and Egypt State Medal of Science and Arts in 1977. He holds several national and international certificates of merit for his distinguished services. He was appointed Vice-Dean for student affairs in 1989 and he was elected Dean of the Faculty of Science in 1991. He was visiting professor at the university of Texas at El Paso, Texas, USA from 1979 to 1980, University of Kuwait from 1973 to 1977 and King Abdulaziz University, Jeddah, Saudi Arabia from 1982 to 1988. He has published 223 scientific papers including 10 review articles, all in international journals. At present there are more than 1800 citations of his work from 1970 until mid 2006 (i.e about 50 citations / year or 8 citations / paper). He supervised till now 45 M.Sc. and 15 Ph.D. graduate theses. He was invited to present plenary lectures at 29 conferences. His research interests are in the fields of reaction mechanisms, applications of LFERs, chemistry of hydrazonoic acid derivatives, 1,3-dipolar cycloadditions and 1,5-electrocyclizations.