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CONDENSED 1,2,3-TRIAZOLES (REVIEW)*

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Methods for the synthesis of condensed 1,2,3-triazoles, including mesoionic compounds, in the literature up to 2007 inclusively are presented. They are classified according to the method by which the molecular skeleton is formed. Mesoionic condensed compounds of the 1,2,3-triazole series are examined separately.

Keywords: azides, diazo compounds, 1,2,3-triazoles, condensed heterocycles, mesoionic compounds, rearrangements, cyclization, cycloaddition.

Compounds of the 1,2,3-triazole series have various chemical, biological, and technical characteristics [1-7]. In medicinal chemistry greatest attention has been paid to the synthesis of 1,2,3-triazoles condensed with other heterocycles and investigation of their biological activity. Even in 1935 research was started on the possibility of using 1,2,3-triazolo[4,5-*d*]pyrimidines (8-azapurines) as chemotherapeutic agents for the treatment of various diseases and particularly malignant tumors. The search for new biologically active compounds in the series of condensed 1,2,3-triazoles is continuing to the present day. Thus, for example, substances acting against the hepatitis C virus [8] and compounds inhibiting benzodiazepine and adenosine receptors [9, 10] were found.

In addition, thanks to the ability of 1,2,3-triazoles to undergo reversible ring opening reactions, to stabilize the carbanionic centers, and to decompose with the formation of acetylenes and aminocarbenes, these compounds are of particular interest as synthons for the production of new heterocyclic systems.

At the present time the literature contains several reviews on 1,2,3-triazoles as a whole [1-7], but there are no reviews on condensed 1,2,3-triazoles. A large number of separate articles and information contained in certain reviews are perhaps all that there is. At the same time such information would be useful to scientists working in the field. From this there arose the need to summarize and classify the fragmentary material on condensed 1,2,3-triazoles. This review is devoted to methods for the synthesis of condensed heterocycles containing a 1,2,3-triazole fragment and covers the literature up to and including 2007. In the review these methods are classified according to the method by which the molecular skeleton is formed. In addition, methods for the production of mesoionic condensed triazole-containing heterocycles are examined separately, and examples of the use of the obtained compounds in various regions of science and technology are also presented. Methods for the synthesis of benzo- and naphtho-1,2,3-triazoles are not included since information on compounds of this series is well represented in the earlier reviews [1, 2]. Methods described in the literature for the synthesis of condensed 1,2,3-triazoles can be divided into four groups: Annulation of the triazole ring to other heterocycles; annulation of a new heterocycle to the 1,2,3-triazole molecule; simultaneous formation of a 1,2,3-triazole ring and another heterocycle; modification of condensed triazoles.

* Dedicated to Academician Boris Aleksandrovich Trofimov on his seventieth jubilee.

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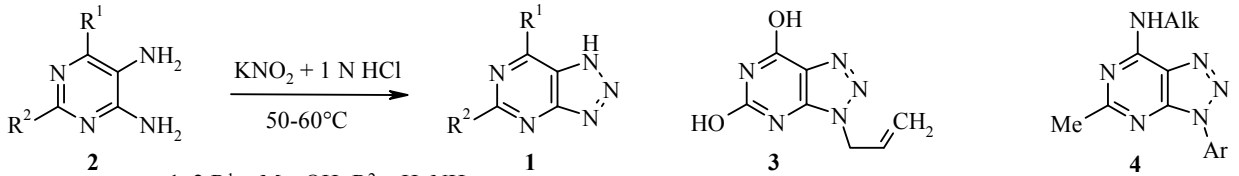
1. ANNULATION OF A 1,2,3-TRIAZOLE RING TO HETEROCYCLES

The annulation of the 1,2,3-triazole ring to heterocycles can be realized by the standard methods for the construction of a 1,2,3-triazole ring, i.e., by cyclization of diazo compounds and diazonium salts with the participation of the imino and amino groups respectively, by oxidative cyclization of aminohetarylhydrazones, and by heterocyclization of nitro compounds or azides and rearrangement.

1.1. Cyclization of Diazo Compounds and Diazonium Salts Involving the Imino and Amino Groups

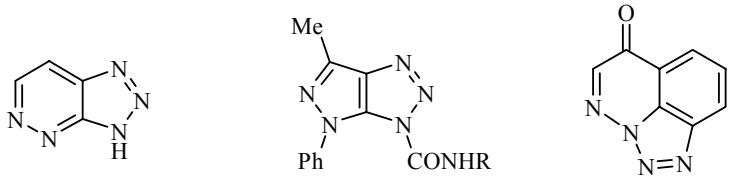
1.1.1. Diazotization of *o*-Diamines. A convenient method for the production of triazolo[4,5-*d*]pyrimidines **1** is the diazotization of the corresponding 4,5-diaminopyrimidines **2** [5]. The reaction takes place through an intermediate *o*-aminodiazonium salt with the formation of triazolo[4,5-*d*]pyrimidines having various substituents at positions 5 and 7 [11-13].



2 **1** **3** **4**

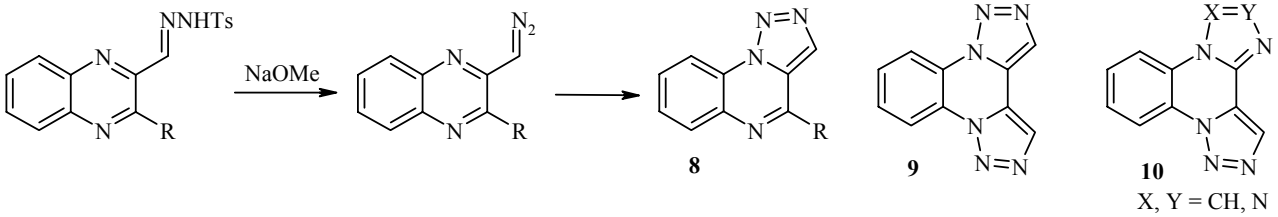
1, **2** R^1 = Me, OH; R^2 = H, NH_2

1-Alkyl- and 1-aryltriazolopyrimidines **3** [14] and **4** [15] were obtained similarly by the diazotization of 6-amino-substituted pyrimidines. This method was also used for the synthesis of triazolo[4,5-*c*]pyridazine (**5**) [16], pyrazolo[4,5-*d*]triazoles **6** [17], and tricyclic 6H-ν-triazolo[4,5,1-*ij*]cinnolin-6-one (**7**) [5].



5 **6** **7**

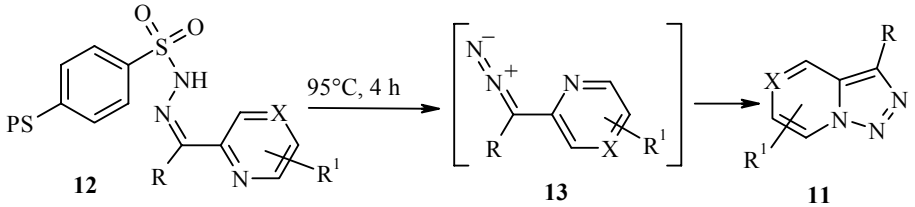
1.1.2. Thermal and Basic Decomposition of Arylsulfonylhydrazones. The thermal or basic decomposition of tosylhetarylhydrazones (the Bamford-Stevens reaction) leads to the generation of diazoimines, which undergo cyclization with participation of the nitrogen atom of the heterocycle and the diazo group and the formation of condensed 1,2,3-triazoles. 4-Substituted 1,2,3-triazolo[1,5-*a*]quinoxalines **8** [18, 19] and various tetracyclic systems **9** and **10** [20] have been synthesized in this way.



8 **9** **10**

X, Y = CH, N

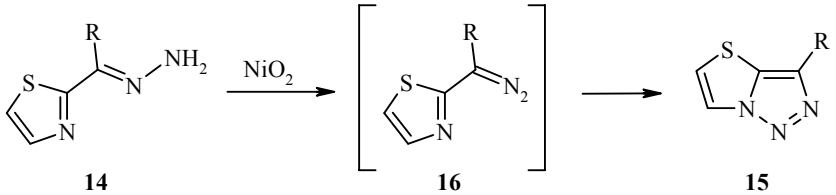
A solid-phase version of the Bamford–Stevens reaction was used for the production of the condensed triazole-containing heterocycles **11** [21]. In our opinion, the intermediate diazo compound **13** is generated and undergoes intramolecular cyclization to the triazole **11** when the polystyrenesulfonylhydrazone **12** is heated in morpholine for 4 h. 3-Methylthiazolo[3,2-*e*][1,2,3]triazole was obtained similarly [21].



12 **13** **11**

12 PS = polystyrene; **11–13** X = CH, N; R = H, Me; R^1 = H, Et

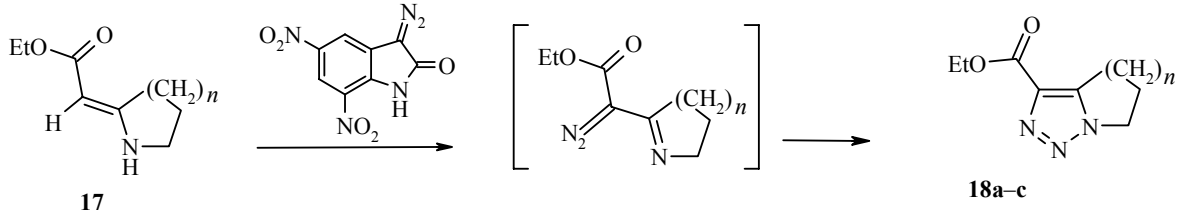
Oxidation of the hydrazone **14** leads to the formation of a 1,2,3-triazolo[5,1-*b*]thiazole ring **15** probably through the formation and cyclization of the intermediate compound **16** [22].



14 **16** **15**

14–16 R = H, Me, Ph

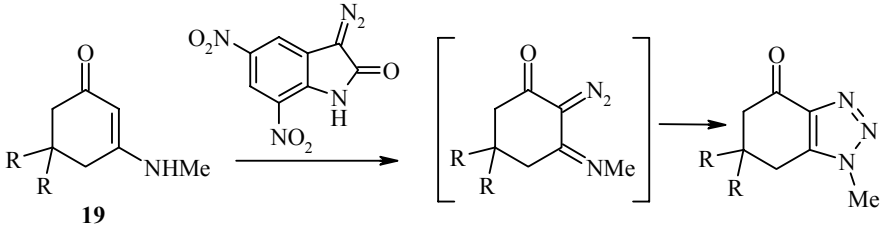
1.1.3. Synthesis of Condensed Triazoles by a Diazo Transfer Reaction. Heterocyclic diazoimines and their cyclic isomers 1,2,3-triazoles can also be synthesized by diazo transfer on compounds containing active methylene groups. Thus, dihydro-4H-pyrrolo[1,2-*c*][1,2,3]triazole (**18a**), tetrahydro[1,2,3]triazolo-[1,5-*a*]pyridine (**18b**), and tetrahydro[1,2,3]triazolo[1,5-*a*]azepine (**18c**) were obtained by diazo transfer in cyclic enamino esters **17** after boiling in toluene [23]. 3-Diazo-5,7-dinitro-1,3-dihydro-2H-indol-2-one was used as diazo transfer agent.



17 **18a–c**

17 n = 1–3; **18 a** n = 1, **b** n = 2, **c** n = 3

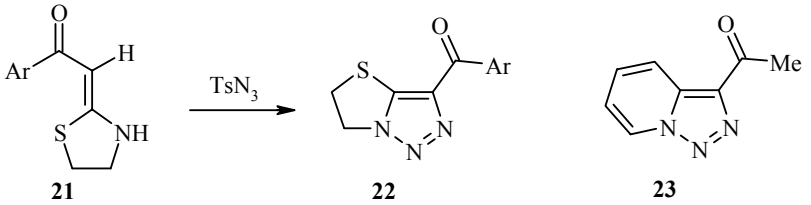
Diazo transfer on the enamines **19** takes place similarly with the formation of benzotriazolone **20**.



19 **20**

19, **20** R = H, Me

Cyclic S,N-acetals **21** react with tosyl azide in boiling dioxane with the formation of dihydrothiazolotriazoles **22** [24]. 1,2,3-Triazolo[1,5-*a*]pyridines **23** were obtained similarly by diazo transfer on pyridine-2-ylacetone [2].

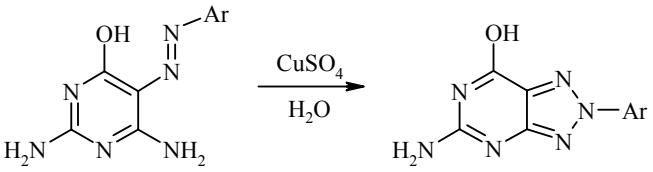


21 **22** **23**

21, **22** Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

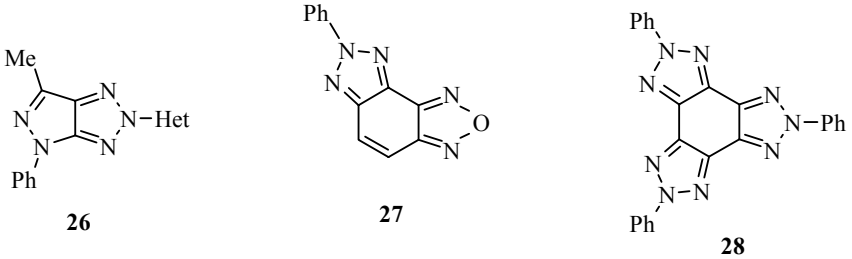
1.2. Oxidation of *o*-Aminoazo Compounds

The oxidation of arylazo heterocycles having an amino group in the *ortho* position is a convenient method for the production of condensed 2H-1,2,3-triazoles. 5-Amino-2-aryl-7-hydroxytriazolo[4,5-*d*]pyrimidines **24** were synthesized on the basis of this method by the cyclization of 2,4-diamino-5-arylazo-6-hydroxypyrimidine **25** [5].



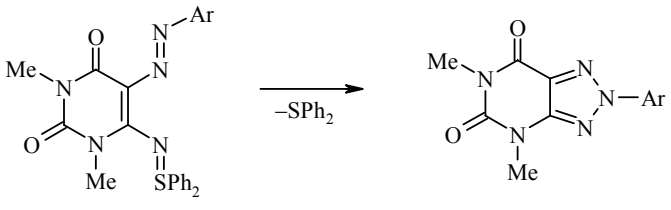
25 **24**

The pyrazolotriazoles **26** [25] and oxadiazolobenzotriazoles **27** [26] are formed similarly from the corresponding arylazopyrazoles and benzooxadiazoles. If there are several azo groups in the initial molecule polycyclic systems such as benzotristriazole **28** are formed [27].



26 **27** **28**

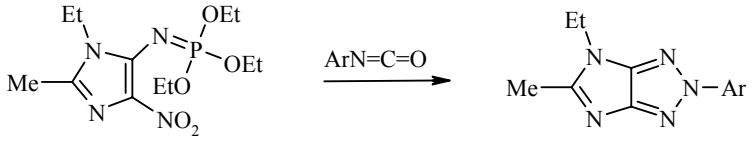
The cyclization of azosulfiminohetarylhydrazones **29** in toluene leads to the formation of 1,2,3-triazolouracil **30** [28, 29].



29 **30**

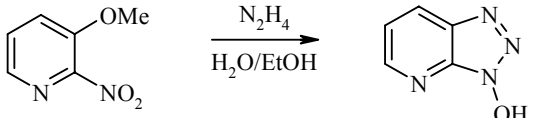
1.3. Cyclization of *o*-Substituted Nitro Compounds in the Synthesis of Triazole-Containing Heterocyclic Systems

Nitro compounds are widely used in the synthesis of nitrogen-containing heterocycles. Thus, a series of 2-arylimidazo[4,5-*d*][1,2,3]triazoles **31** were synthesized with yields of up to 60% by the reaction of triethyl N-(4-nitroimidazol-5-yl)phosphorimidate **32** with aryl isothiocyanates in acetonitrile at 60°C [30].



32 **31**

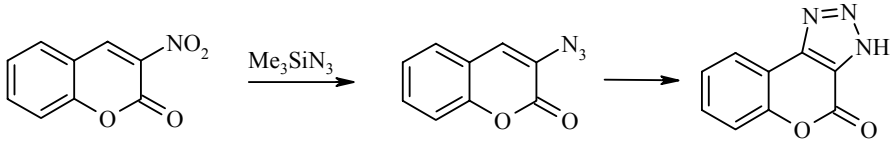
The [1,2,3]triazolo[4,5-*b*]pyridin-3-ol **34**, which is widely used as a catalyst in the synthesis of peptides, is formed when methoxynitropyridine **33** is boiled in hydrazine [31].



33 **34**

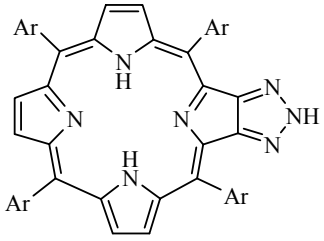
1.4. Cyclization Reactions of Azides

Under the influence of trimethylsilyl azide 3-nitrocoumarin **35** forms chromeno[3,4-*d*][1,2,3]triazol-4(3H)-one **36** as a result probably of 1,5-dipolar electrocyclization of the intermediate 3-azidocoumarin **37** [32].



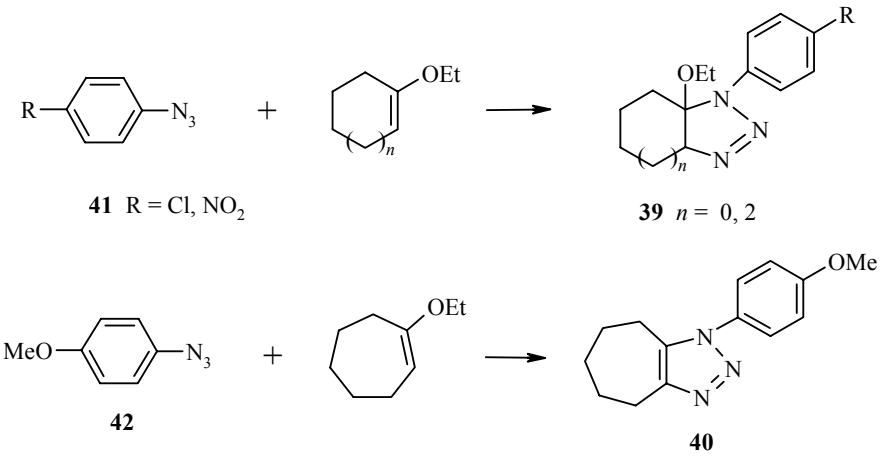
35 **37** **36**

An analogous reaction was used for the production of porphyrinotriazoles **38** from nitroporphyrins [33].



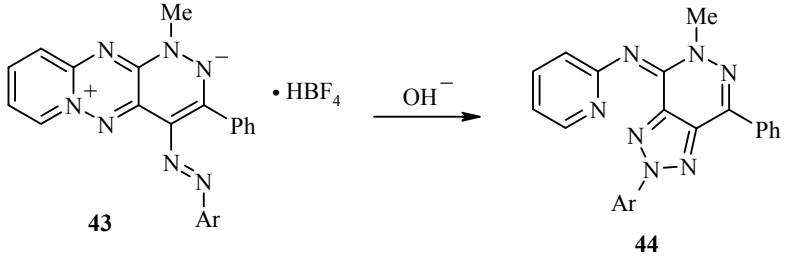
38

The cycloaddition of azides to cycloalkenes is a general method for the synthesis of cycloalkyl-condensed 1,2,3-triazoles of types **39** and **40**. It is interesting to note that nonaromatic compounds **39** are formed in the reaction of aryl azides **41** having electron-accepting substituents while the aromatic compound **40** is formed in the reaction of the azide **42** containing a methoxy group [34].



1.5. Rearrangements

Treatment of the arylazopyridazo[1,2,4]triazine tetrafluoroborate **43** with strong bases leads to the formation of the corresponding base, which undergoes a Bolton–Katritzky rearrangement to [1,2,3]triazolo-[4,5-*d*]pyridazine **44** [35].

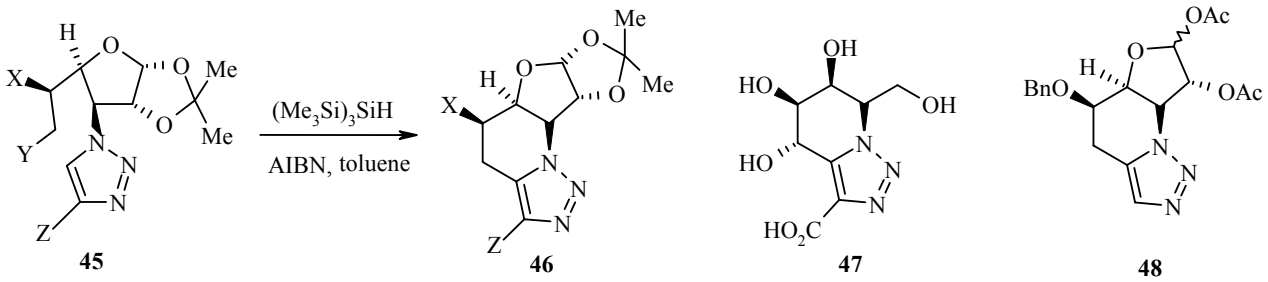


2. ANNULATION OF A HETEROCYCLE TO THE 1,2,3-TRIAZOLE FRAGMENT

An alternative method for the production of condensed systems containing a 1,2,3-triazole fragment is annulation of the heterocycle to the triazole as a result of intramolecular and intermolecular cyclization of the substituents at positions 1, 4, and 5 of the ring.

2.1. Intramolecular Cyclizations

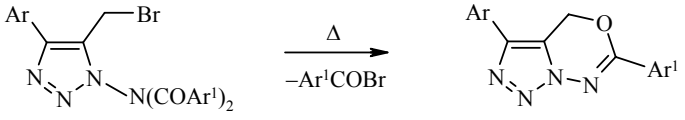
2.1.1. Intramolecular Cyclization of Halo Derivatives of Triazole. Intramolecular free-radical cyclization was first used in the synthesis of triazole-containing condensed systems in [36]. The condensation of halo derivatives of triazolyltetrahydrofuranose **45** in the presence of tris(trimethylsilyl)silane and AIBN (2,2′-azobisisobutyronitrile) takes place at position 5 of the triazole ring with the formation of the tricyclic compound **46** [37]. Later the same authors used the derivatives **46** in the synthesis of compounds **47** and **48**, which are precursors of glycosidase inhibitors.



45 **46** **47** **48**

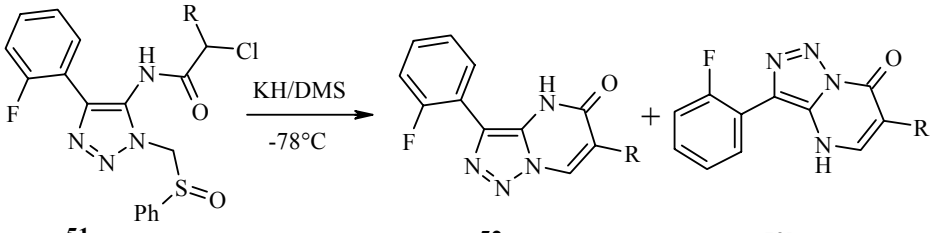
45, **46** X = OH, OAc; Z = H, $SiMe_3$; **45** Y = Br, I

The halo derivatives of 1-diaroylaminotriazole **49**, which release an aroyl fragment and form triazolo[1,5-*a*][1,3,4]oxadiazine **50** when heated, were used as initial reagents for the synthesis of oxygen-containing bisheterocycles [38].



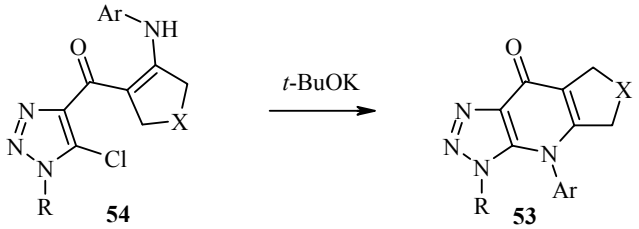
49 **50**

In [39] it was shown that intramolecular alkylation of the active methylene group with elimination of the phenylsulfonyl group occurs during the action of a base on the triazole **51**. The reaction is accompanied by a Dimroth rearrangement, and as a result two isomeric triazoles **52a** and **52b** are therefore formed in a ratio of 10:1.



51 **52a** **52b**

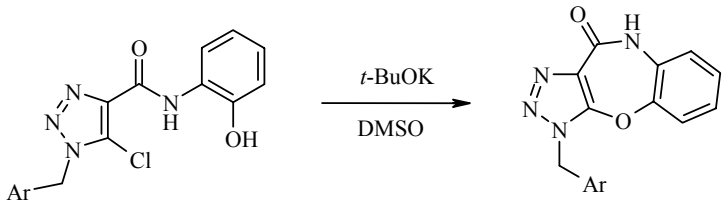
The triazoles **53**, condensed with a pyridine ring at positions 4 and 5 (X = O, NR), were obtained by treating the respective enamines **54** with potassium *tert*-butoxide [40].



54 **53**

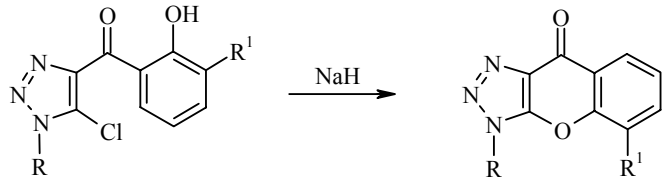
X = O, NR

5-Chorotriazoles **55**, containing a phenyl fragment at position 4, also undergo cyclization under the influence of potassium *tert*-butoxide. 1,2,3-Triazolo[4,5-*b*][1,5]benzoxazepin-10(9H)-ones **56** are formed as a result [41].



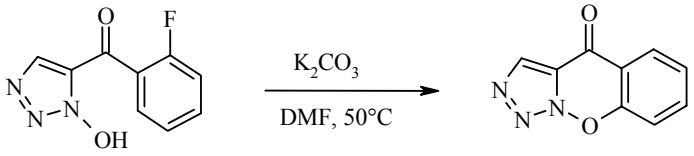
55 **56**

In the presence of a strong base 4-aroyl-5-chlorotriazoles **57** undergo cyclization to triazolobenzopyran derivatives **58** with almost quantitative yields [42].



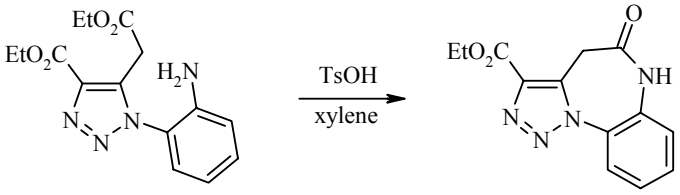
57 **58**

The condensed heterocycles azaxanthones **59** are of interest as analogs of natural substances. They are produced by the intramolecular substitution of fluorine in 4-(2-fluorobenzoyl)-1-hydroxy-1,2,3-triazole **60** under mild conditions and with yields of 80-90% [43].



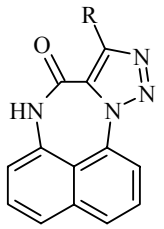
60 **59**

2.1.2. Cyclocondensation of Carbonyl and Cyano Groups with an Amino Function. When the 5-substituted triazoloaniline **61** is boiled in xylene the *o*-amino group reacts with the ethoxycarbonyl function with the formation of the triazolodiazepine **62** [44].



61 **62**

Cyclocondensation of carbonyl and amino groups is widely used in the synthesis of various 1,2,3-triazoles **63** [45], **64** [46], **65** [47], and **66** [48], condensed with a diazepine ring, and also with pyrimidine **67** [49] and **68** [50] and pyrrole **69** [51] rings.



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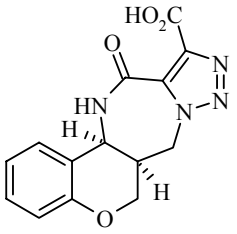

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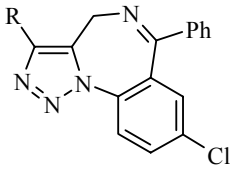

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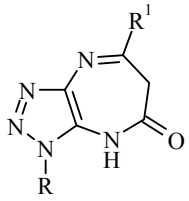
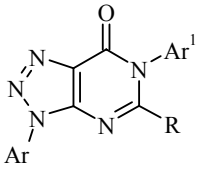
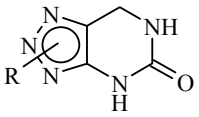


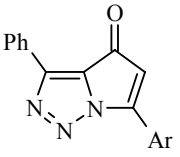
66 R^1 = Alk, OH



67

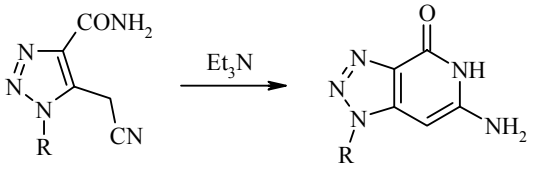


68 R = Alk



69

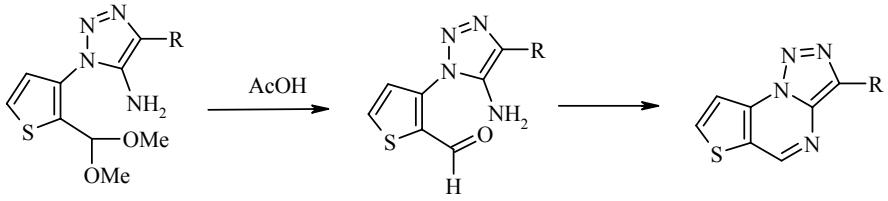
The synthesis of 6-amino-1,2,3-triazolo[4,5-*c*]pyridin-4(5H)-ones **70** (8-aza-3-deazaguanines) was based on intramolecular cyclization of the cyano and amide groups of 4-triazolecarboxamides **71** by the action of bases [52, 53].



71 **70** R = H, Rib **72**

1,2,3-Triazolo[1,5-*a*]pyrazine **72** was obtained similarly as a result of the cyclization of cyano and anilide groups [54]. Triazolopyrazine **72** is a suitable subject for the production of new compounds of this series since it has three modifiable groups – cyano, amino, and ester.

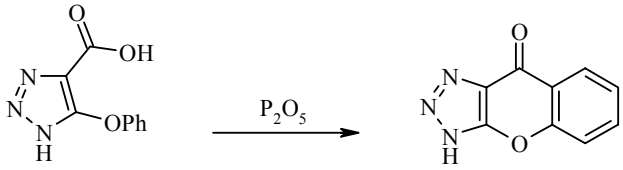
Treatment of the dimethyl acetal **73** with 50% acetic acid leads to the generation of the triazolylthiophene **74**, the aldehyde group of which undergoes cyclocondensation with the amino group leading to the formation of the tricyclic system **75** [55].



73 **74** **75**

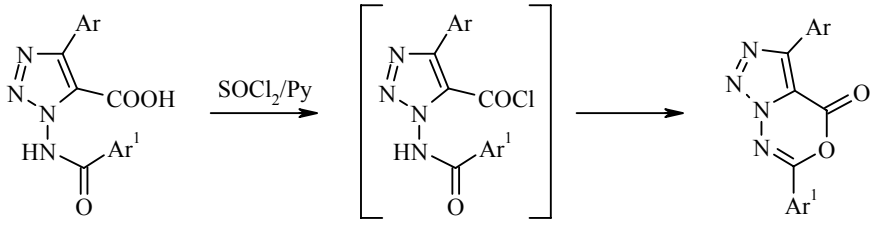
73–75 R = Ph, CO_2H

2.1.3. Cyclization of 1,2,3-Triazolecarboxylic Acids. Treatment of 5-phenoxy-1,2,3-triazole-4-carboxylic acid **76** with polyphosphoric acid or phosphorus oxide leads to interaction of the carboxyl group with the phenoxy group, dehydration, and the formation of triazolochromone **77** [56, 57].



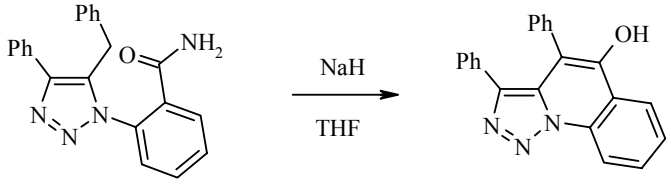
76 **77**

Intramolecular acylation at the oxygen atom of the carbamoyl group takes place during the cyclization of 5-triazolecarboxylic acid **78** to [1,2,3]triazolo[1,5-*a*][1,3,4]oxadiazin-4-one **79** [58].



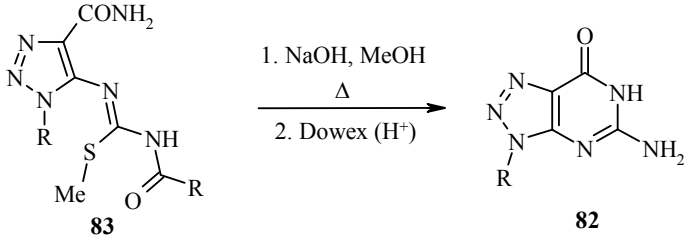
78 **79**

2.1.4. Other Intramolecular Cyclizations. Intramolecular interaction between the carboxamide and benzyl groups of the amide **80** occurs during treatment with sodium hydride in boiling THF and is accompanied by the elimination of a molecule of ammonia, leading to the formation of triazolo[1,5-*a*]quinoline **81** [59].



80 **81**

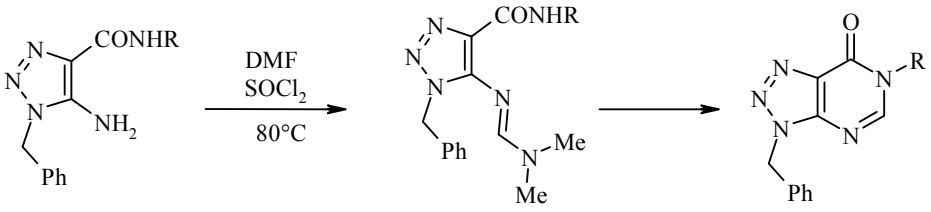
3-Substituted 5-aminotriazolo[4,5-*d*]pyrimidines **82** were synthesized by boiling methyl 1,2,3-triazol-5-ylimidothiocarbamates **83** in a water–alcohol solution of alkali followed by neutralization on Dowex resin [60].



83 **82**

82, **83** R = $-(CH_2)_mPO(OEt)_2$, $-CH_2O(CH_2)_mPO(OEt)_2$

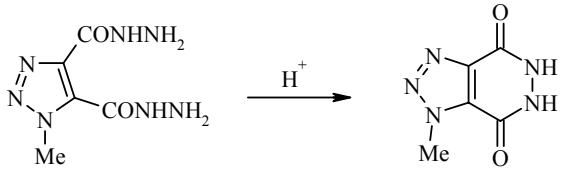
If the amide of 5-aminotriazolecarboxylic acid **84** is used in the Vilsmeier reaction the intermediate amidine **85** undergoes cyclization to 6-substituted triazolopyrimidine **86** [61].



84 **85** **86**

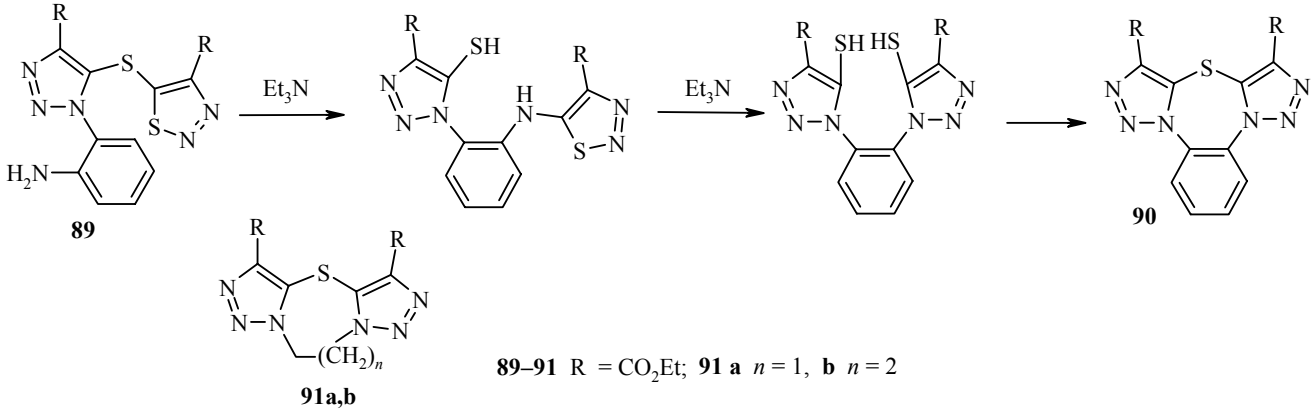
84–86 R = H, Me, Ph, Bn

When triazoledicarbohydrazide **87** was heated in 10% hydrochloric acid the triazolopyridazinedione **88** was obtained [62, 63].



87 **88**

The action of triethylamine on 5-[1-(2-aminophenyl)-1,2,3-triazol-5-ylsulfanyl]-1,2,3-thiadiazole **89** leads to intramolecular nucleophilic substitution of the thiol group, accompanied by rearrangement of the thiadiazole ring to a triazole ring and the release of hydrogen sulfide with the formation of di[1,2,3]triazolo-[1,5-*a*:5',1'-*d*][3,1,5]benzothiadiazepine **90** [64].



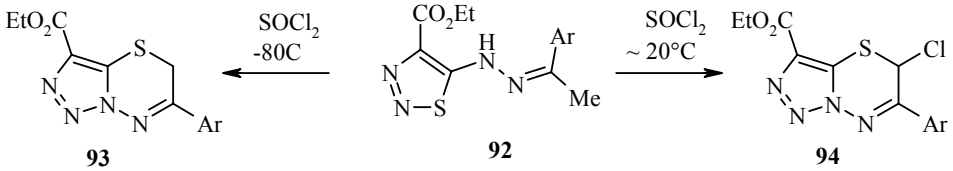
89 **90**

91a,b

89–91 R = CO_2Et; **91 a** $n = 1$, **b** $n = 2$

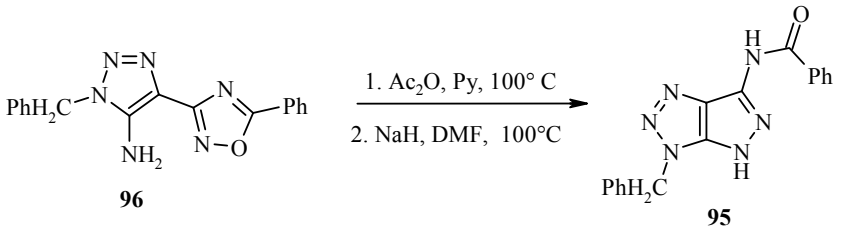
Bis[1,2,3]triazolo[1,5-*f*:5',1'-*b*][1,3,6]thiadiazepine **91a** and [1,5-*g*:5',1'-*b*][1,3,7]thiadiazocine **91b** were obtained similarly [65].

The transformation of the hydrazone **92** into 5H-[1,2,3]triazolo[1,5-*b*][1,3,4]thiadiazine **93** probably also involves a thiadiazole–triazole rearrangement [66] and provides a unique method for the synthesis of triazoles condensed with a thiadiazine ring. It is interesting to note that realization of the reaction at room temperature leads to the formation of 5-chloro[1,2,3]triazolo[1,5-*b*][1,3,4]thiadiazine **94**.



93 **92** **94**

Treatment of the amine **96** with acetic anhydride followed by reaction with sodium hydride in DMF leads to the formation of 6-aminopyrazolo[3,4-*d*][1,2,3]triazole **95** [67]. The reaction probably includes a Bolton–Katritzky rearrangement in the product from acylation of the initial amine.

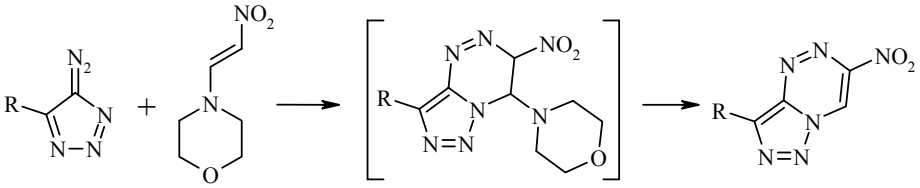


96 **95**

2.2. Intermolecular Cyclizations

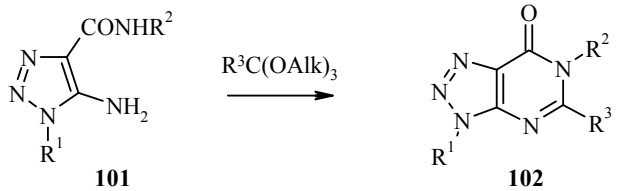
In this section examples of the formation of heterocycles as a result of the reactions of substituents at positions 4 and 5 of triazole, the NH of the triazole ring, and the corresponding reagent are examined.

2.2.1. Cycloaddition of 5-Diazo-1,2,3-triazoles. 5-Diazo-1,2,3-triazoles **97** undergo regiospecific cycloaddition to 1-morpholinyl-2-nitroethylene **98** with elimination of the morpholine from the intermediate **99** and the formation of the triazolotriazine **100** [2].



97 **98** **99** **100**

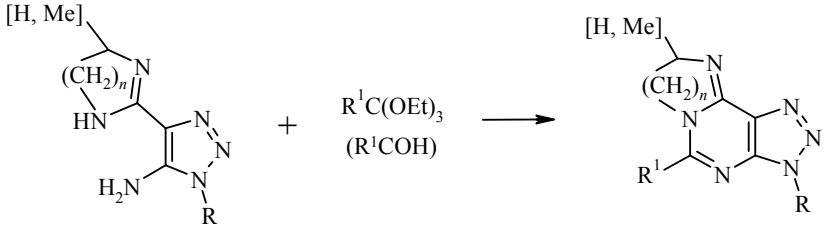
2.2.2. Cyclization of Two Nucleophilic Groups under the Influence of an Electrophilic Reagent. The reaction of 5-amino-1,2,3-triazole-4-carboxamides **101** with orthoesters or formamide provides a convenient method for the synthesis of 1,2,3-triazolo[4,5-*d*]pyrimidines **102** with various substituents at positions 1, 4, and 6 of the heterocyclic system [2, 61, 68].



101 **102**

101, **102** R^1 = H, Alk, Ar, R^2 = H, Alk, Ar, R^3 = H, Alk

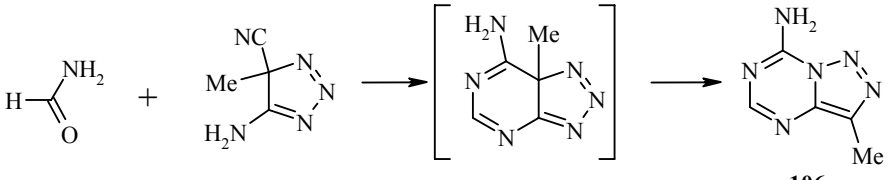
In the reaction of the aminotriazoles **103** with orthoesters or aldehydes the amino group and the NH group of the imidazoline are "stitched", and 6,7-heteroannulated 1,2,3-triazolo[4,5-*d*]pyrimidines **104** are formed [69].



103 **104**

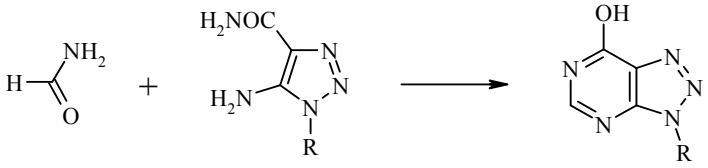
103, **104** n = 1–3, R = Bn, Ar

5-Amino-4-cyano-4-methyl-1,2,3-triazole **105** reacts with formamide at room temperature and forms substituted 1,2,3-triazolo[1,5-*a*]-1,3,5-triazine **106** through the intermediate compound **107**, which undergoes rearrangement to the final reaction product [2].



105 **107** **106**

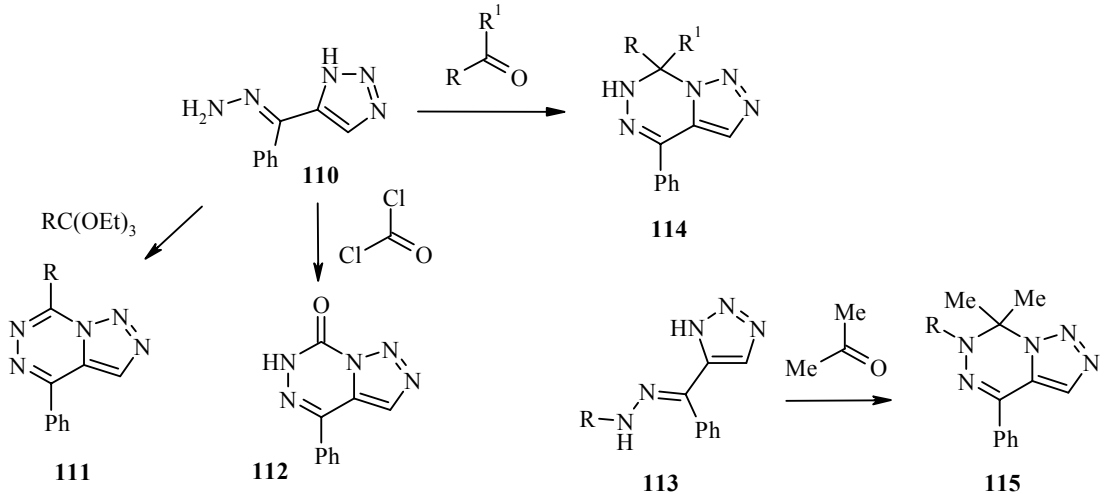
During the treatment of 1-substituted 5-amino-4-carbamoyl-1,2,3-triazoles **108** with formamide 3-alkyl-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidines **109** are formed [10].



108 **109**

108, **109** R = Bz, $PhCH_2CH_2$, $2\text{-}ClC_6H_4CH_2$

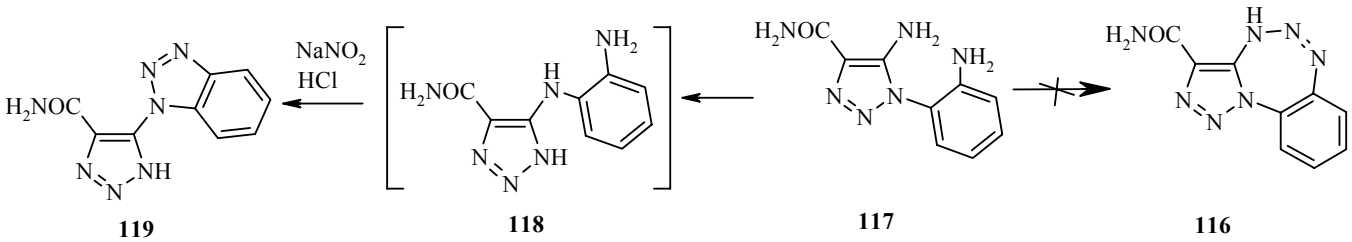
An interesting example of the synthesis of triazolotriazines with a nodal nitrogen atom was described in [70]. The terminal amino group and the cyclic nitrogen atom in the triazole **110** react with orthoesters to form the triazines **111**. Reaction with phosgene leads similarly to 1,2,3-triazolo[1,5-*d*][1,2,4]triazin-7-one **112**. The initial compound **110** and also its substituted derivatives **113** react with ketones with the formation of the corresponding 1,2,3-triazolo[1,5-*d*][1,2,4]triazines **114** and **115**.



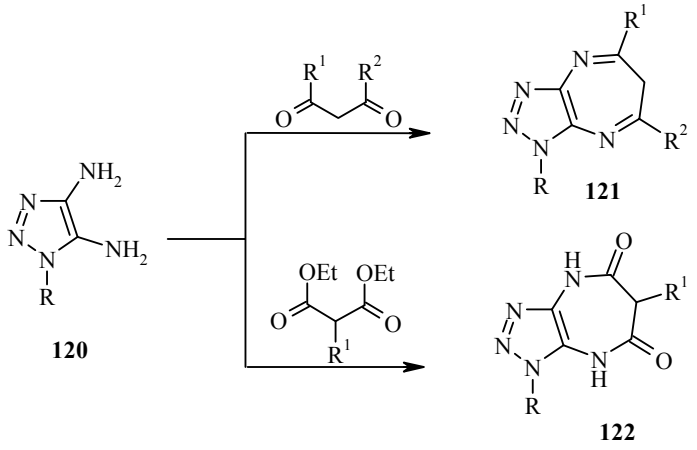
110 **114**

111 **112** **113** **115**

When very different conditions were used for the diazotization of the diamine **117**, instead of the expected cyclization of the diazo compound and the formation of 1,2,3-triazolo[1,5-*e*][1,2,3,5]benzotetraazepine a Dimroth rearrangement of compound **117** led to the triazole **118**. Reaction of the latter with sodium nitrite led to 4-(benzotriazol-1-yl)-1,2,3-triazole **119** [71].

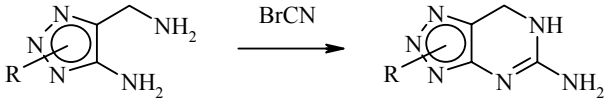


Triazoles condensed with a seven-membered heterocycle are formed during the reaction of 4,5-diamino-1,2,3-triazoles with 1,3-dicarbonyl compounds. Thus, 1,2,3-triazolo[4,5-*b*][1,4]diazepines **121** and **122** were obtained in the reaction of diaminotriazole **120** with acetylacetone, dibenzoylmethane, and benzoylacetone boiled in ethanol with a catalytic amount of hydrochloric acid. It should be noted that the diazepine **121** (R^1 = Me, R^2 = Ph) is formed exclusively in the reaction of the triazole **120** with benzoylacetone, while 1,2,3-triazolo-[4,5-*b*][1,4]diazepine-5,7-diones **122** are formed with moderate yields in reaction with malonic ester and its derivatives [48].



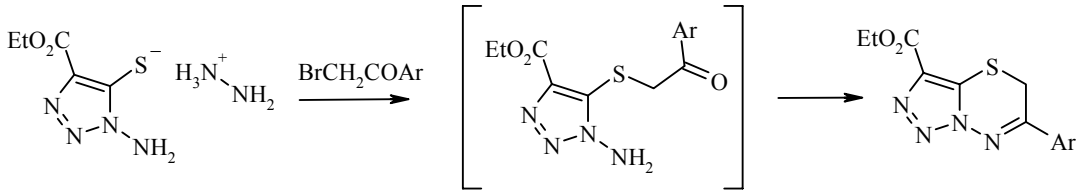
120 R = Ph, Bn; **121** R^1, R^2 = Me, Ph; **122** R^1 = H, Me, Ph

N-Alkyl-2-amino-1,6-dihydro-8-azapurines **123** were obtained during treatment of the diaminotriazole **124** with cyanogen bromide in methanol [50].



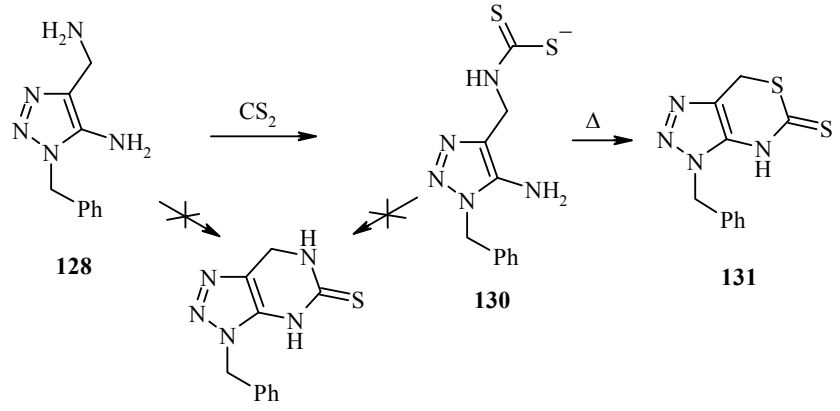
123, **124** R = 1-Me, 2-Me, 3-Bn

The reaction of 1-amino-5-mercaptotriazole **125** with α-bromoacetophenones [72], which have two electrophilic centers, leads to the formation of the intermediate sulfide **126**, which undergoes cyclization to the triazolothiadiazine **127** under the reaction conditions.



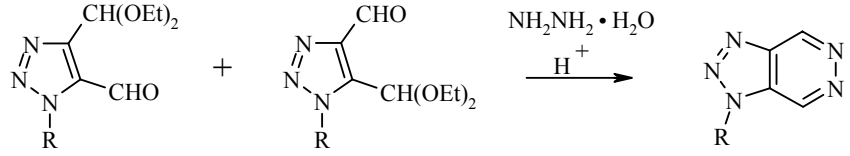
125 **126** **127**

Heating of the diaminotriazole **128** with carbon disulfide in pyridine did not lead to the formation of the expected 8-azapurine **129** [73]. The product of this reaction was the dithiocarbamate **130**, which underwent cyclization under the reaction conditions to the sulfur-containing condensed heterocycle 1,2,3-triazolo-[4,5-*d*][1,3]thiazine **131** [74]. The structure of the latter was confirmed by X-ray crystallographic analysis.



128 **129** **130** **131**

2.2.3. Condensation of Two Electrophilic Groups by the Action of Nucleophilic Reagents. Derivatives of triazolopyridazine **132** are formed during the treatment of a mixture of acetals **133** and **134** with hydrazine hydrate [14]. It is interesting that both components of the mixture react with the formation of one and the same compound.



133 **134** **132**

132–134 R = Ph, Bn, Ar

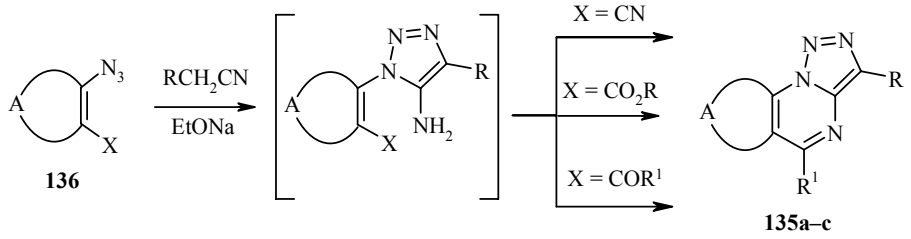
The synthesis and properties of the substituted 1,2,3-triazolo[4,5-*d*]pyridazines were described in detail in the review [75] and will not be discussed here.

3. REACTIONS LEADING TO THE SIMULTANEOUS FORMATION OF A 1,2,3-TRIAZOLE RING AND ANOTHER HETEROCYCLE

This group of syntheses of condensed triazoles includes the reactions of vicinal cyano and carbonyl azides with derivatives of acetonitrile and ethyl acetate and also the intramolecular cycloaddition of azides.

3.1. Reactions of Vicinal Cyano and Carbonyl Azides with Derivatives of Acetonitrile and Ethyl Acetate

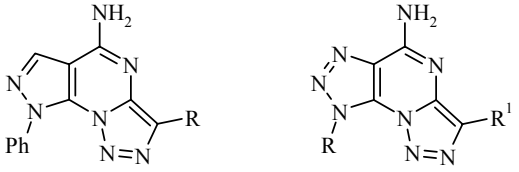
The synthesis of 5-amino-1,2,3-triazolo[1,5-*a*]pyrimidines **135a** was based on the reaction of vicinal cyano azides **136** (X = CN), derivatives of aromatic hydrocarbons, thiophenes, pyrazoles, or 1,2,3-triazoles with derivatives of acetonitrile in the presence of bases [76]. Pyrimidotriazoles of the **135b** and **135c** types are formed in the reaction of the carbonyl derivatives **136** (X = CO_2R, COR).



136 **135a–c**

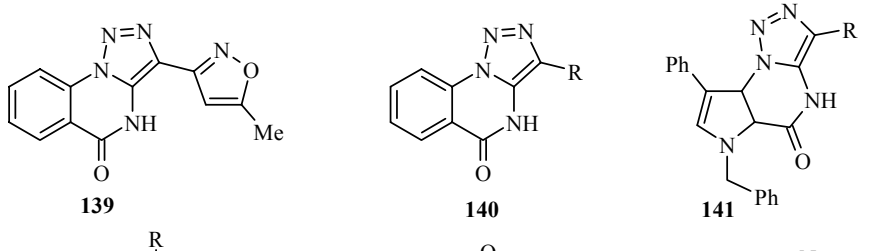
135 a–c R = H, Alk, Ar; **a** $R^1 = NH_2$, **b** R^1 = OH, **c** R^1 = H, Alk, Ar

The triazolopyrimidines **137** and **138** condensed with pyrazole and triazole rings were obtained similarly by the reactions of the corresponding cyano azides with derivatives of acetonitrile and cyanoacetic acid [77, 78].

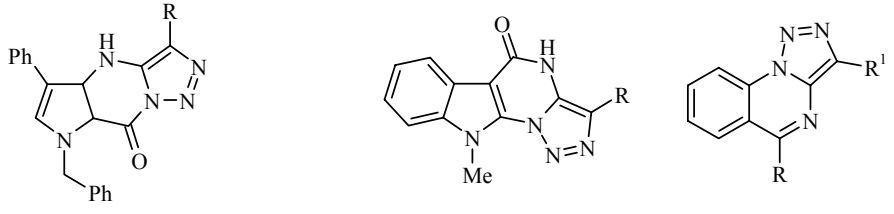


137 **138**

Triazoles condensed with a pyrimidine ring are formed in the reaction of vicinal azido carboxylic acids **136** or their esters (X = COOR, where R = H, Alk) with derivatives of acetonitrile. 1,2,3-Triazolo[1,5-*a*]quinazo-lines **139** [79] and **140** [80, 81] and also triazoles **141-143**, condensed with pyrrolopyrimidine [82, 83] and indolopyrimidine rings [84], were synthesized in this way. Triazolo[1,5-*a*]quinazolines of type **144** are formed during the reaction of 2-azidoacetophenones **136** (X = COR, where R = Alk) with arylacetonitriles in aprotic solvents [85].



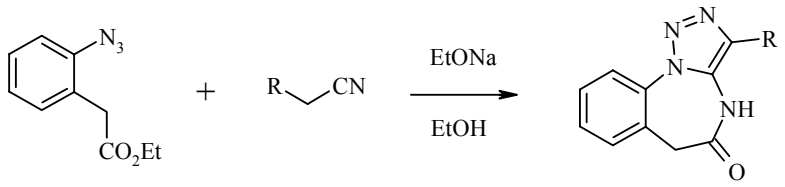
139 **140** **141**



142 **143** **144**

140 R = Ph, CO_2Et, $CONH_2$, CONHMe; **141–143** R = $CONH_2$, CN, CO_2Et, Ph;
144 R = COPh, CN, CO_2Et, Ar, 1-naphthyl, SO_2Ph, 2-pyridyl; R^1 = Me, NH_2

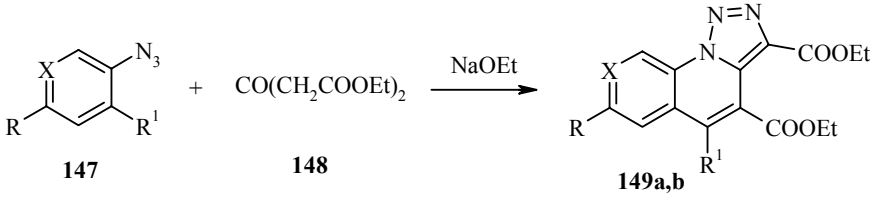
If ethyl 2-azidophenylacetate **145** is used in this reaction 1,2,3-triazolo[1,5-*a*]-1,3-benzodiazepine **146** is formed [86].



145 **146**

146 R = Ph, $CONH_2$, CONHMe, CO_2Et

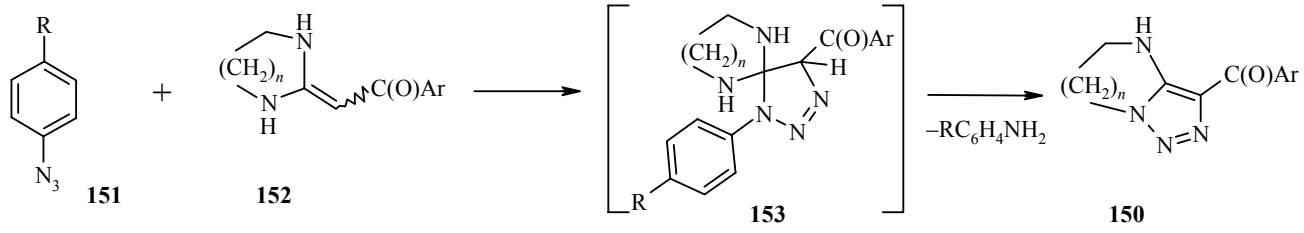
In the reactions of the azides **147** with diethyl 1,3-acetonedicarboxylate **148** the 1,2,3-triazolo-[1,5-*a*]quinolines **149a** (X = CH) or 1,2,3-triazolonaphthiridines **149b** (X = N) are formed [44].



147 **148** **149a,b**

147, 149a,b R = H, Cl; **147** X = CH, N; R^1 = CN, COMe, CHO, COPh, CO_2Me;
149 a X = CH, **b** X = N; R^1 = NH_2, Me, H, Ph, OH

Cyclic enaminals also enter readily into reaction with azides. Thus, for example, condensed triazoles **150** were obtained as a result of the reaction of the aryl azide **151** with the cyclic aminals of acylketenes **152** at room temperature in dioxane [87]. Even under the reaction conditions the initially formed adduct **153** undergoes a Dimroth rearrangement and deamination.

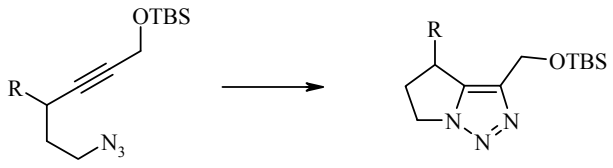


151 **152** **153** **150**

151, **153** R = H, MeO, Cl, NO_2; **150, 152, 153** Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4ClC_6H_4,
n = 1, 2

3.2. Intramolecular Cycloaddition of Azides at Multiple Bonds

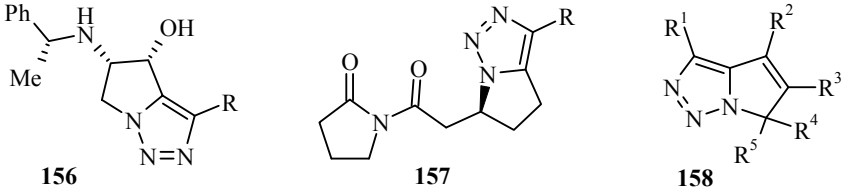
In the intramolecular cycloaddition of azides to a double bond or triple bond a triazole ring and another ring are formed at the same time. The size of the latter depends on the length of the carbon chain linking these groups. Thus, mono- and disubstituted 5,6-dihydro-4H-pyrrolo[1,2-*c*][1,2,3]triazoles **155** – analogs of an antitumor dihydropyrrolizidine alkaloid – were synthesized by boiling the azide **154** in toluene [88].



154 **155**

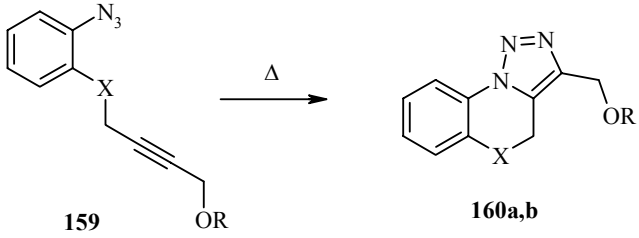
154, 155 TBS – *tert*-butyldimethylsilyl, R = H, OH

5-Amino-substituted 4-hydroxy-5,6-dihydro-4H-pyrrolo[1,2-*c*][1,2,3]triazoles **156** [89], 6-substituted dihydropyrrolotriazoles **157** [90], and pyrrolotriazoles **158** [91] were obtained by analogous intramolecular cycloaddition reactions when the respective azides were boiled in benzene or toluene.



156 **157** **158**

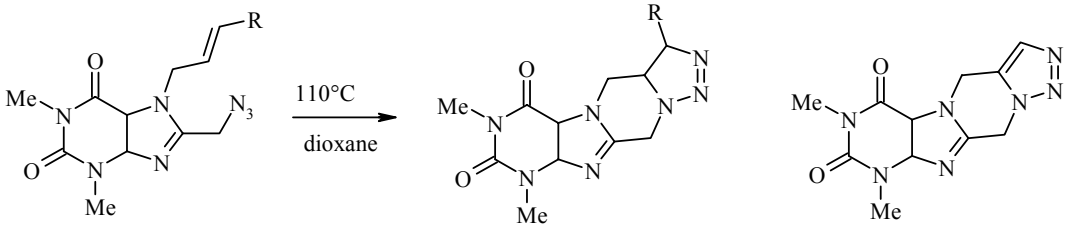
The azide and ethynyl functions in compound **159** are separated by four carbon atoms. During cyclization to the tricycles **160** an oxazine or thiazine ring is formed in addition to triazole [92].



159 **160a,b**

159, **160** R = H, Me; **159** X = O, S; **160 a** X = O, **b** X = S

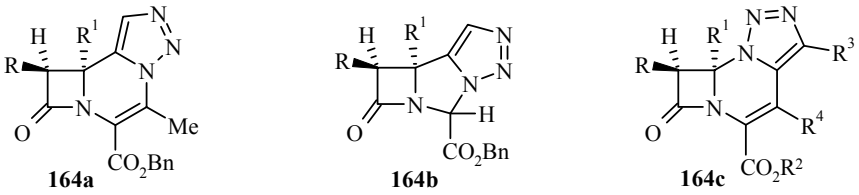
Triazolo[1,5-*a*]pyrazines **161** and **162** condensed with the theophylline system [93] were produced by cyclization of the corresponding azides of type **163**.



163 **161** **162**

161, **163** R = H, Me, Ph

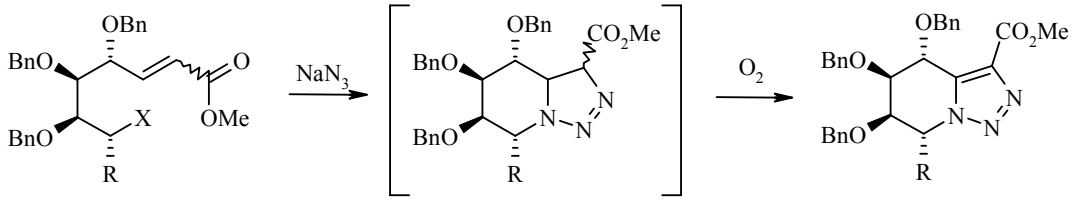
Various representatives of β-lactam antibiotics **164** were synthesized by intramolecular cyclization of an azide group and a triple bond [7, 94].



164a **164b** **164c**

164 a–c R, R^1 = Alk, **c** R^2, R^3 = H, R^4 = Me; R^2 = *t*-Bu, R^3 = Alk, R^4 = H

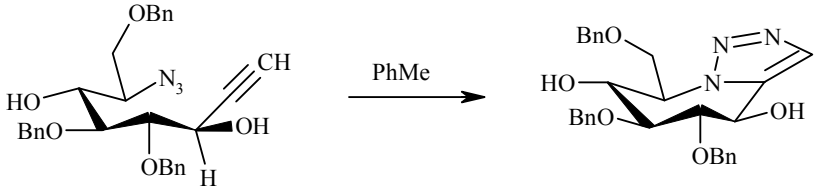
In connection with the fact that various imino sugars are important inhibitors of glycosidases and glycosyltransferases [95] a method was recently developed for the synthesis of new bicyclic triazoles **165** starting from transformed natural sugars [96]. When treated with sodium azide in DMF the tosylates and mesylates of D-arabinose and L-fucose **166**, produced in several stages, undergo cyclization *in situ* to the triazoline intermediate **167**. Aromatization by the action of atmospheric oxygen leads to the formation of the triazole **165** [96].



166 **167** **165**

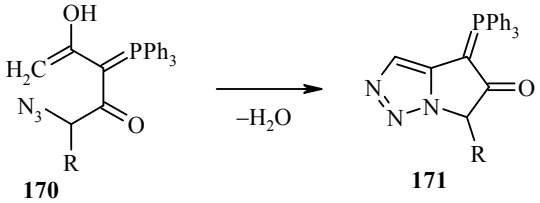
166 X = OTs, OMs; **165–167** R = H, Me

The cyclization of compound **168**, the terminal and acetylene groups of which are separated by a chain of five carbon atoms, leads to the formation of the azepines **169** [97].



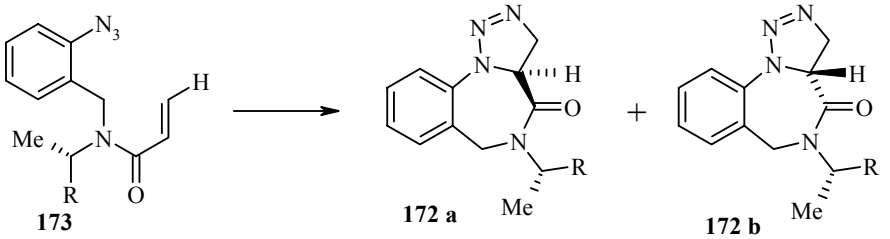
168 **169**

In the review [2] there are examples of the intramolecular cycloaddition of the azide group to the enolic double bond in compound **170** with the formation of the triazole **171**.



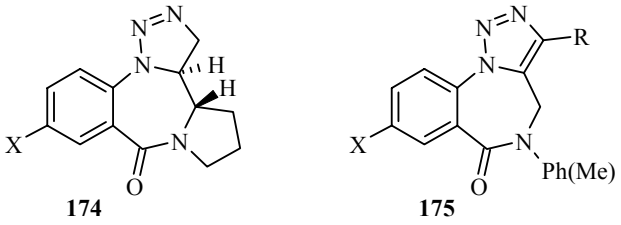
170 **171**

The first example of a stereoselective synthesis in the series of diazepine triazole-containing condensed heterocycles was the production of [3,3-*a*]dihydro-1,2,3-triazolo[1,5-*a*]-1,4-benzodiazepin-4-ones **172a** and **172b** in a ratio of 3:2 from the unstable alkenoylaryl azides **173**, which undergo cyclization even at room temperature [98].

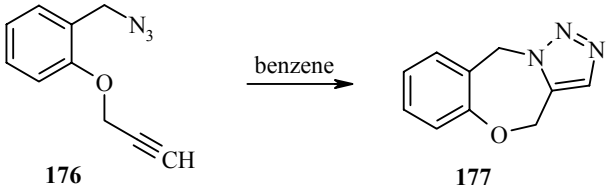


172, **173** R = Ph, CO_2CH_2Ph

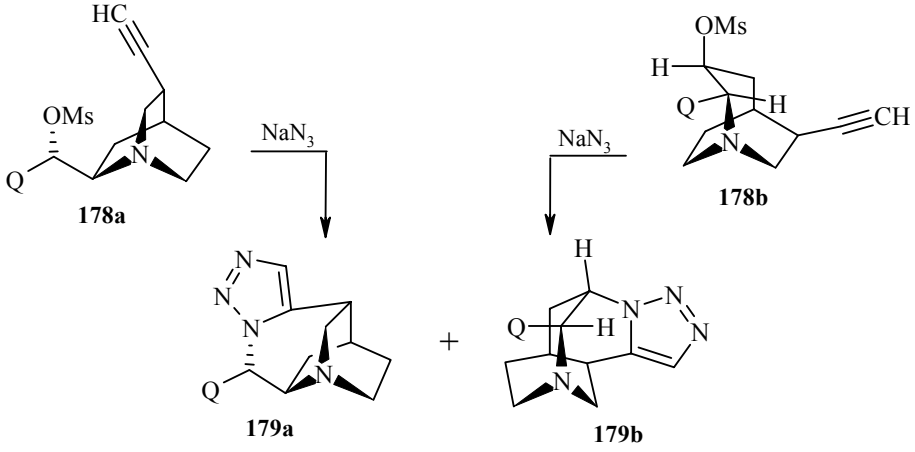
[1,2,3]Triazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepine **174** [99] and [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine **175** [100-102] are formed similarly from the corresponding azidoalkene and azidoacetylene.



When boiled in benzene 1-azidomethyl-2-(propyn-2-yloxy)benzene **176** undergoes intramolecular cyclization with the formation of the benzoxazepine **177** [103].



The condensed triazoles **179** were obtained by the intramolecular 1,3-dipolar cycloaddition of the azides of quinine alkaloids **178**, generated *in situ* in trifluoroethanol from the O-mesyl derivatives and sodium azide [104].

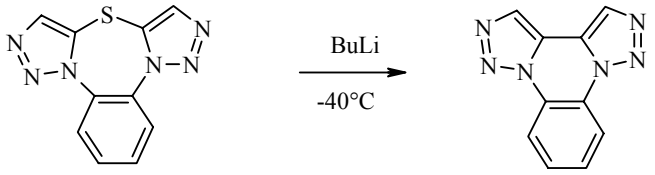


178, **179** Q = 4-quinolyl

4. MODIFICATION OF CONDENSED TRIAZOLE-CONTAINING HETEROCYCLES

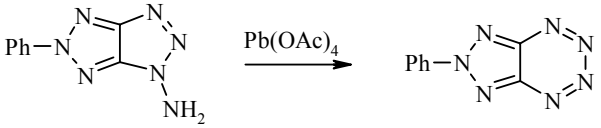
Examples of the use of condensed triazole-containing heterocycles as synthons for the production of other polycondensed triazole-containing systems have been described in the literature.

Thus, another heterocycle bis[1,2,3]triazoloquinoxaline **181** is formed during the treatment of bis[1,2,3]triazolo[1,5-*a*:5',1'-*d*][3,1,5]benzothiadiazepine **180** with butyllithium in THF at -40°C [105].



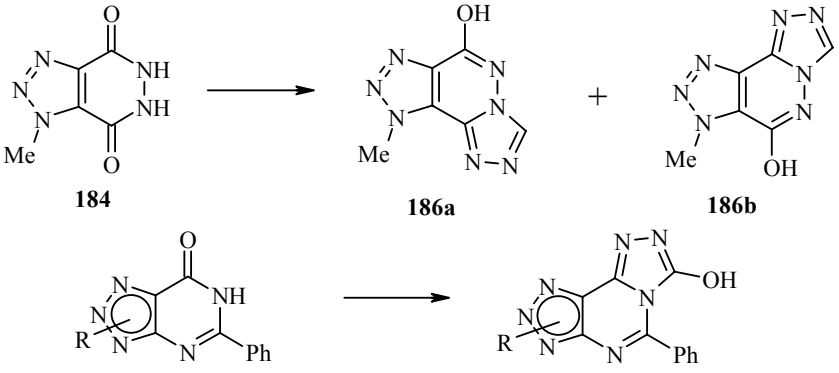
180 **181**

During the oxidation of 1-amino-5-phenyl[1,2,3]triazolo[4,5-*d*]-1,2,3-triazole **182** with lead tetraacetate in methylene chloride at 0°C ring enlargement occurs, and triazolo-1,2,3,4-tetrazine **183** is formed [106].



182 **183**

Tricyclic ν-triazolo-*s*-triazolopyridazines **186** [62, 63] and triazolopyrimidines **187** [107] were synthesized from triazolopyridazinedione **184** and triazolopyrimidinones **185** in several stages. The synthesis includes replacement of the oxygen atoms by chlorine, nucleophilic substitution of the halogen by an ethylhydrazinocarboxylate fragment, and subsequent condensation of the cyclic nitrogen atom with the ester group.



184 **186a** **186b**

185 **187**

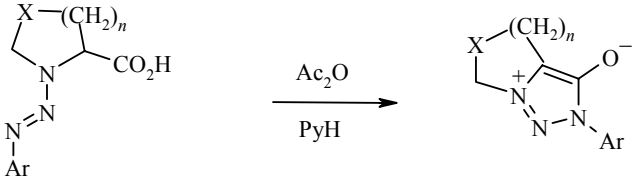
185, **187** R = 1-Me, 2-Me, 3-Me, 3-Bn

We note that this method has extremely wide possibilities since the introduction of various substituents into the condensed triazole-containing heterocycle makes it possible to use many of the already mentioned methods for the annulation of an additional ring and the production thereby of new triazole-containing polycondensed systems.

5. MESOIONIC CONDENSED COMPOUNDS CONTAINING A 1,2,3-TRIAZOLE FRAGMENT

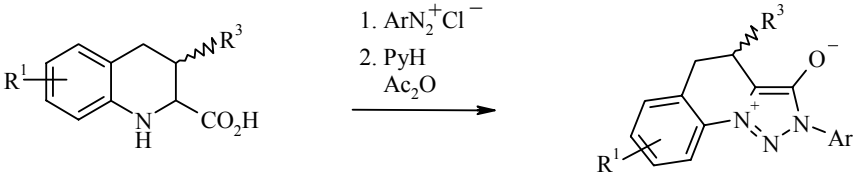
Among the whole variety of condensed heterocycles containing a 1,2,3-triazole fragment it is possible to single out the mesoionic heterocycles into a separate group [108]. Apart from the fact that they are suitable synthons in the synthesis of other compounds [109-114] condensed mesoionic triazoles are of independent interest since a large number of products of practical significance have been found among compounds of this series [115, 116]. It is known [117] that certain triazole-containing mesoionic heterocycles have anti-inflammatory and immunosuppressant properties.

The synthesis of condensed mesoionic 1,2,3-triazoles can be realized either by the construction of the triazole ring using substituents in the other ring or by cyclization of the substituents of the triazole ring. The first group of syntheses includes: the heterocyclization of triazenes **188** to pyrrolo- and thiazolotriazoles **189**, in which intramolecular acylation of the triazene group occurs with subsequent aromatization of the triazole ring [116, 117]; the reactions of benzoquinolines **190** and benzoquinazolines **191** with diazonium salts, generated *in situ*, with the formation of 4,5-dihydro[1,2,3]triazolo[1,5-*a*]quinolinium-3-olates **192** and 5-oxo[1,2,3]triazolo-[1,5-*a*]quinazolin-3-olates **193** [118]; the cyclization of heteroaromatic nitro compounds of the **194-196** type by the action of trialkyl phosphite to the condensed triazoles **197** and **198** [119, 120].

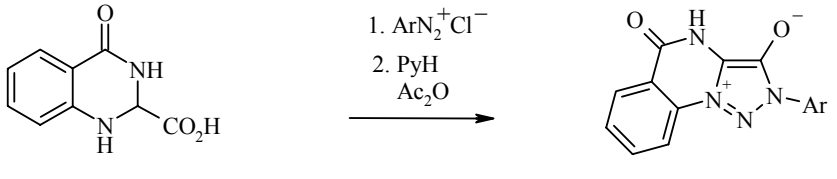


188 **189**

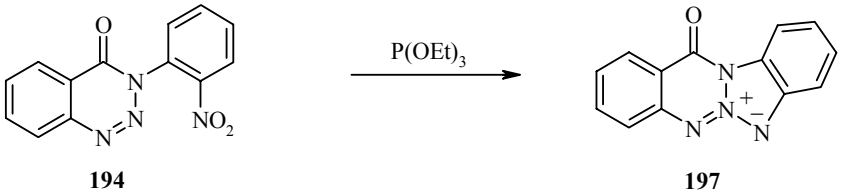
188, **189** X = CH_2, S; n = 1, 2



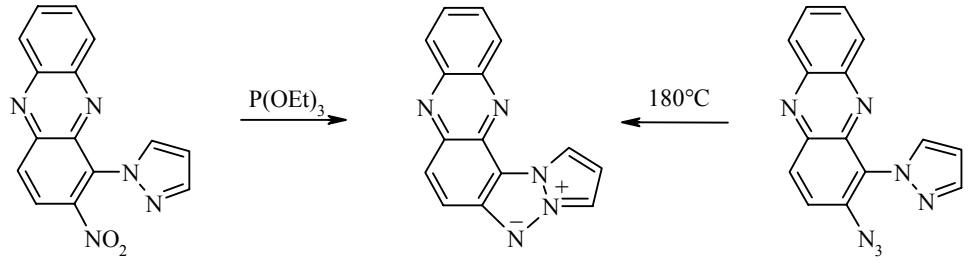
190 **192**



191 **193**



194 **197**

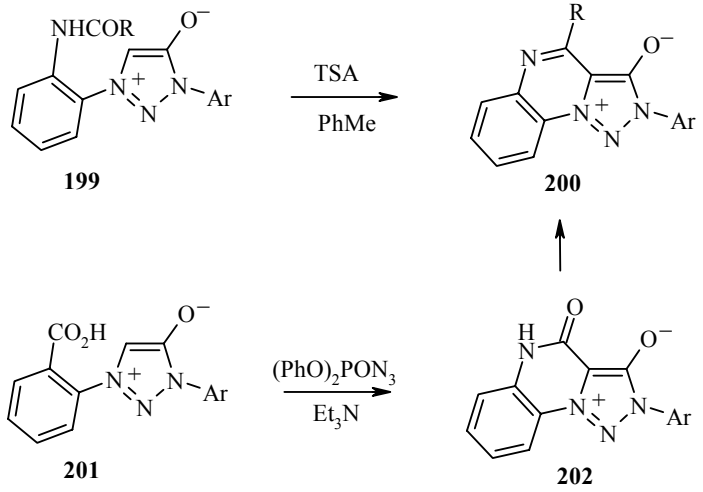


195 **198** **196**

A highly reactive nitrene is probably generated in the reactions of the nitro compounds **194** and **195** under the influence of the trialkyl phosphite and with photochemical decomposition of the azides. This then participates in the formation of the N–N bond of the 1,2,3-triazole ring by attacking the unshared electron pair of the nitrogen atom.

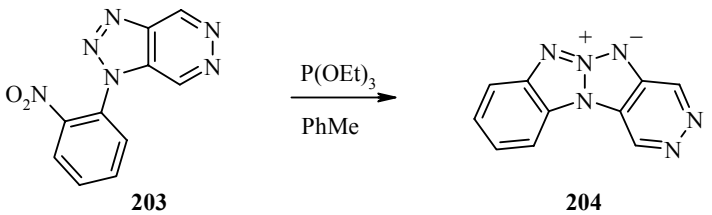
The second group of methods for the synthesis of mesoionic condensed triazoles includes reactions with electrophilic attack on the triazole ring and also intramolecular cyclization of substituents in zwitterionic 1,2,3-triazoles.

5-Substituted [1,2,3]triazolo[1,5-*a*]quinoxaline-3-olates **200** are formed when the triazolates **199** are boiled with *p*-toluenesulfonic acid in toluene [118]. The reaction of the acid **201** with diphenylphosphoryl azide in anhydrous toluene leads to the formation of the cyclic amide **202**, which can be transformed into the triazolates **200** either with a Grignard reagent or through a chloroimine.



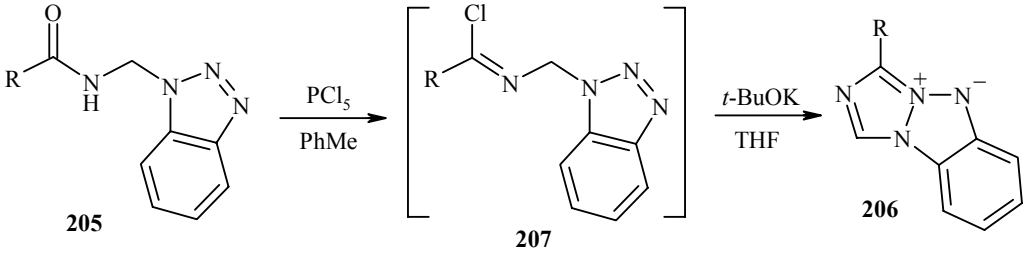
199 **200** **201** **202**

An example of reductive cyclization of the nitroaryltriazole **203** to benzo-1,2,3-triazolo[1',2':1',2']-1,2,3-triazolo[4,5-*d*]pyridazin-6-yl **204** with triethoxyphosphine in toluene at 120°C was given in [121].



203 **204**

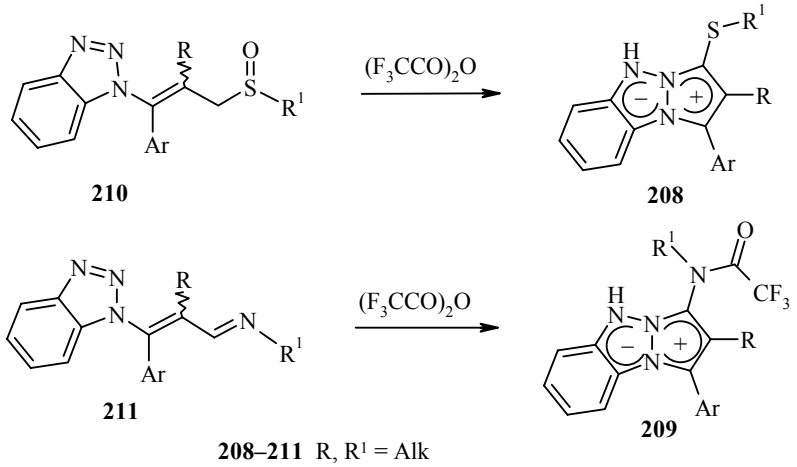
α-Benzotriazolylamides **205** are suitable synthons for the production of 3-aryl-1,2,4-triazolo-[1,2-*a*]benzotriazoles **206** [122]. Treatment of compounds **205** with phosphorus pentachloride leads to the formation of N-(benzotriazol-1-ylmethyl)arylimidoyl chloride **207**, which undergoes cyclization during subsequent treatment with potassium *tert*-butoxide with the formation of the mesoionic product **206**.



205 **207** **206**

205–207 R = Ar, Het

Recently [123, 124], 2,3-benzo[1,3-*a*,6*a*]triazapentalenes **208** and **209** were synthesized from the sulfoxides of 1-substituted benzotriazoles **210** and azomethines **211**, which undergo cyclization under the influence of trifluoroacetic anhydride.

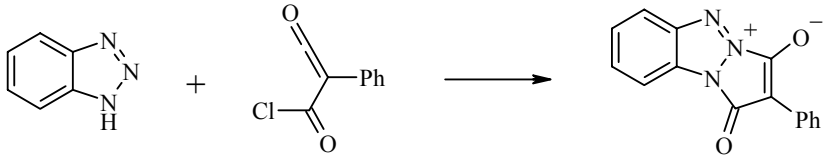


210 **208**

211 **209**

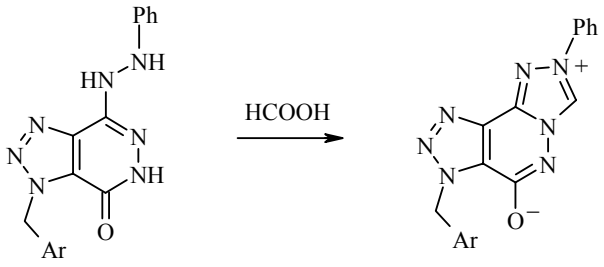
208–211 R, R[1] = Alk

In addition, benzotriazole **212** reacts with chlorocarbonylphenylketene **213** to form 1-oxopyrazolo-[1,2-*a*][1,2,3]benzotriazolium-3-olate **214** [2, 125].



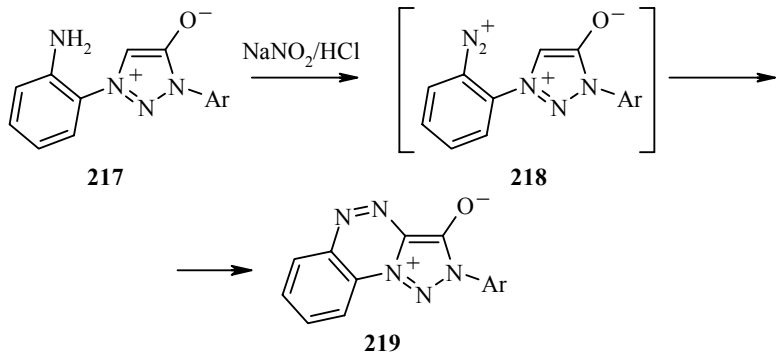
212 **213** **214**

When heated with formic acid the triazole **215** forms the mesoionic tricyclic compound **216** with a yield of 87% [109]. Compounds **216** are interesting in that the formation of the mesoionic structure did not affect the 1,2,3-triazole ring as such.



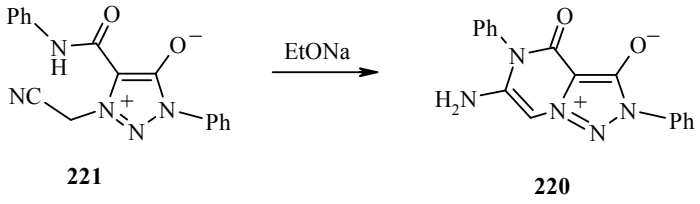
215 **216**

Diazotization of the aniline **217** leads to rapid cyclization of the intermediate diazo compound **218** and the formation of the [1,2,3]triazolo[5,1-*c*]benzotriazinium system **219** [118].



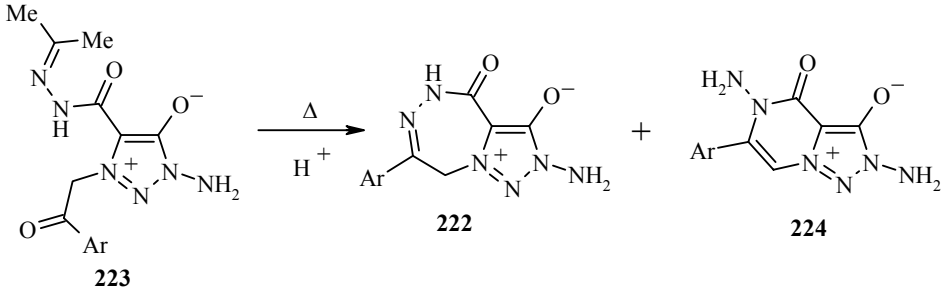
217 **218** **219**

As already mentioned, the intramolecular interaction of the cyano and amino groups under basic conditions provides a convenient approach to the synthesis of heterocycles. In [126] it was proposed to use the method for the production of condensed mesoionic triazole-containing heterocycles **220** starting from alkylated triazoles **221**.



221 **220**

With the appropriate choice of substituents, capable of entering together in the reaction, at positions 3 and 4 of the triazole ring it is possible to synthesize other heterocyclic systems. Thus, for example, we synthesized the first representatives of the series of mesoionic [1,2,3]triazolo[5,1-*d*][1,2,5]triazepines **222** by acid hydrolysis of the triazoles **223** containing phenacyl and hydrazide fragments [127]. Here [1,2,3]triazolo[1,5-*a*]pyrazinium-3-olate **224** was isolated as a side product.



223 **222** **224**

The methods for the synthesis of triazole-containing heterocyclic systems described in the review are extremely diverse. Annulation of the triazole ring to various heterocycles by the diazotization of *o*-diamines, oxidation of hetarylhydrazones, or diazo transfer to CH-active cyclic compounds is a simple, accessible, and convenient path to triazole-containing systems. Intramolecular cycloaddition of azides at multiple bonds has now also been used. The possibilities of this method are limited by the difficulty of obtaining suitable azides, but various important heterocyclic systems have been produced by this method. The most original method for the production of condensed triazoles with a bridging nitrogen atom is the reaction of derivatives of cyanoacetic acid with vicinal cyano- and carbonylazides. The most widely used method for the production of triazole-containing heterocyclic systems is annulation of the heterocycle to the 1,2,3-triazole fragment as a result of intramolecular cyclization of the reactive groups and also condensation of disubstituted triazoles with bifunctional compounds.

Apart from the ability of triazoles to undergo reversible ring opening an interesting feature of these compounds is the formation of mesoionic structures. It was found that certain triazole-containing mesoionic heterocycles have anti-inflammatory and immunodepressant properties and herbicidal activity. Triazapentalenes are convenient synthons for the production of new difficultly obtainable derivatives of 1-(*o*-aminophenyl)-4-alkyl(aryl)-5-arylpyrazoles and also explosives.

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