Russian Chemical Reviews **74** (4) 339 – 379 (2005) © 2005 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2005v074n04ABEH000893

1,2,3-Triazole and its derivatives. Development of methods for the formation of the triazole ring

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Abstract. Data on the synthetic routes to substituted 1,2,3-triazoles, including those containing functional groups, based on cyclisation of various nitrogen compounds published during the last 15 years are described. Examples of using new triazole derivatives in agrochemistry, medicine and engineering are given. The bibliography includes 583 references.

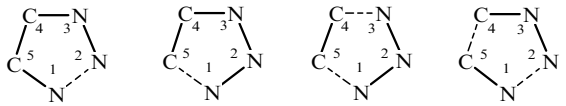
I. Introduction

The 1,2,3-triazole (*v*-triazole) heterocyclic system has been known for more than one hundred years. The synthesis of the first representatives of these compounds was reported in the late 19th century by Pechmann;[1] during the subsequent decades, several routes to various substituted triazoles, including polyfunctional ones, have been developed. The results of synthetic studies have been reported in a number of publications, the most recent of which are reviews;[2–19] the structures, properties and chemical transformations of 1,2,3-triazole and its derivatives are considered in some sections of monographs.[14, 20, 21] In the last two decades, the chemistry of 1,2,3-triazoles has gained a new impetus to the development due to the discovery of diverse biological activities of many triazole derivatives. The number of patents dealing with the use of these derivatives as drugs and agrochemicals has grown. This has attracted the attention of researchers to the development of new and perfection of the known methods for the synthesis of triazole derivatives.

The triazole ring itself is relatively stable, which allows one to carry out various chemical modifications of substituents and functional groups. These modifications are usually carried out by standard synthetic methods, which are fully reflected in the monographs cited above. However, on treatment with strong bases or highly nucleophilic reagents (as well as on thermolysis and photolysis), the triazole ring can open to give reactive intermediates, which undergo diverse chemical transformations to yield new carbo- and heterocyclic structures.[22] These problems are considered in a large number of publications from the last decade, for example, the works.[23–37]

This review covers the data dealing with the formation of the 1,2,3-triazole ring published mainly from 1986 to 2002.

The methods of formation of a heterocyclic system are usually considered in terms of the closure of particular bonds in pre-arranged structural blocks. Within the framework of this approach, the information on triazole synthesis can be classified into four sections dealing with the methods of formation of particular bonds of the triazole ring, namely, the N(1) – N(2), C(5) – N(1) [or C(4) – N(3)], C(5) – N(1) and C(4) – N(3) bonds; and the C(4) – C(5) and N(1) – N(2) bonds.



In some cases, researchers propose original methods for the synthesis of triazole systems. However, by considering the stepwise mechanisms of relevant reactions, one can often assign them formally to one of the above groups.

II. Methods of formation of the N(1) – N(2) bond

1. Condensation of amines with α-diazocarbonyl compounds

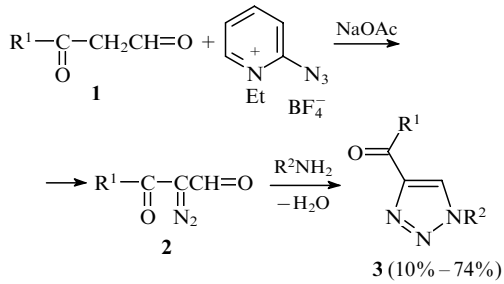
A possible way of formation of a triazole ring is the reaction of amines with α-diazodicarbonyl compounds, which proceeds through intermediate α-diazoimines. Since α-diazoimines are highly reactive, they readily cyclise into isomeric 1*H*-1,2,3-triazoles even during their synthesis. The diazo derivatives of 1,3-dicarbonyl or other compounds with an active methylene group can act as triazole precursors.[38]

The simplest derivative of α-diazo-β-oxoaldehydes, namely, the diazo derivative of malonodialdehyde, condenses with aniline hydrochloride to give 1-phenyltriazole-4-carbaldehyde in a high yield.[39] However, other α-diazo-β-oxoaldehydes have long been poorly accessible. It has been found recently[40] that 2-azido-1-ethylpyridinium tertrafluoroborate transfers the diazo group onto various β-oxoaldehydes **1** in the presence of bases with retention of the aldehyde function. These reactions underlay a general method for the synthesis of α-diazo-β-oxoaldehydes **2**, which were used to prepare 1-substituted 4-acyltriazoles **3**.[41–45] The diazomethyl ketone $R^1C(O)CH=N_2$ impurity formed at the diazotisation stage did not influence the subsequent synthesis of acyltriazoles. Ammonia, aliphatic and aromatic amines, hydroxylamine and semicarbazide were involved in the condensation with α-diazo-β-

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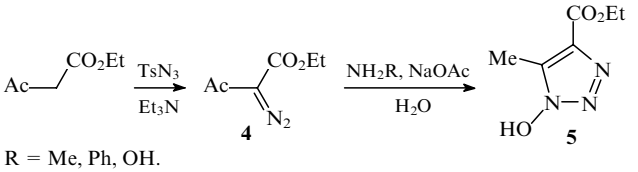
Received 23 December 2003
Uspekhi Khimii **73** (4) 369 – 410 (2005); translated by Z P Bobkova

oxoaldehydes.[41] An advantage of this method is the formation of only one regioisomer, because condensation is directed at the more electrophilic formyl group rather than the acyl group. With hydroxylamine or semicarbazide, triazole oximes or semicarbazones **3** are formed in some cases



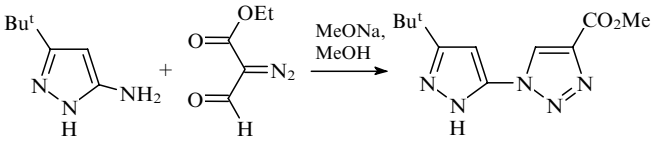
R^1 = Me, EtO, 2,4-$Cl_2C_6H_3$, 2,4-$Br_2C_6H_3$; R^2 = H, Pr^i, Bu^i, Ph, 1-naphthyl (Naph), 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 2,4-$Br_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, HO, EtO, NH_2CONH.

When diazo β-oxoesters **4** react with hydroxylamine [46] or with aniline and methylamine,[47] the ester group is retained in the triazole **5** molecule.

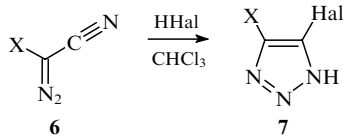


R = Me, Ph, OH.

This method has also been used to prepare hetaryltriazoles, for example, methyl 1-(5-pyrazolyl)triazole-4-carboxylate.[48]



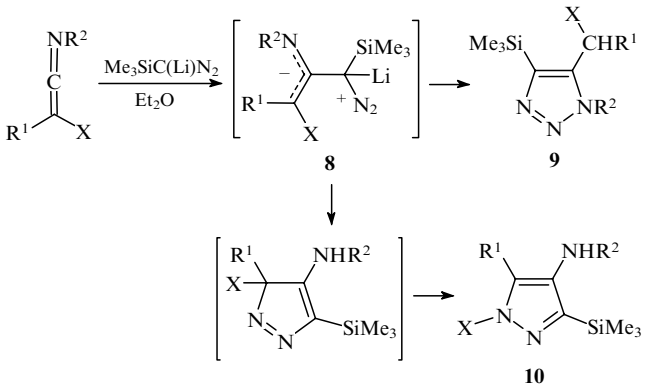
Carbonyl derivatives of α-diazoacetonitrile **6** [X = RC(O)] readily cyclise under the action of hydrogen halides to give 4-acyl-5-halotriazoles **7**,[49] the yields of which (45% – 94%) depend on the nature of the halogen and the substituent. This method was used to prepare 5-chlorotriazole derivatives with amide, urethane,[50] and phosphoryl groups.[51]



X = RC(O): Hal = Cl, Br, I; R = EtO, NH_2, MeNH, Ph;
X = $(RO)_2P(O)$: Hal = Cl; R = Me (62%), Et (86%).

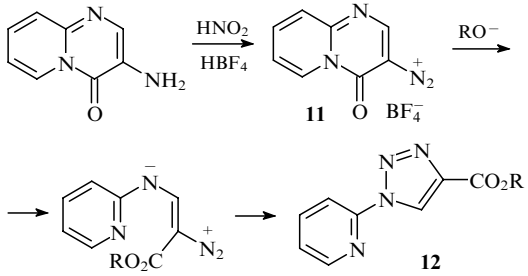
Detailed study of the reaction has shown that the scope of its application is limited to diazo compounds that have only α-carbonyl or α-phosphoryl groups.[52] The reaction mechanism formally includes two steps, in particular, the addition of hydrogen halide to α-carbonyldiazonitrile to give intermediate α-diazohaloimine, which then undergoes a heteroelectrocyclic process yielding 5-halotriazole. In essence, cyclisation of α-carbonyldiazonitriles can be considered as a series of tandem pseudopericyclic processes.[52]

Triazoles can be obtained from α-aminodiazo compounds if the molecule does not contain any other nucleophilic centres. For example, the cyclisation route of diazo(lithio)trimethylsilylmethane **8** depends on the nature of the substituent X: for X = Alk or Ar, the reaction gives 4-trimethylsilyltriazoles **9**, while in the presence of electron-withdrawing substituents, 3-trimethylsilylpyrazoles **10** are formed most often.[53, 54]



R^1 = Me, Ph; R^2 = Et, Ph; X = Alk, Ar, Ac, EtO_2C, NC, $PhSO_2$, $(EtO)_2PO$.

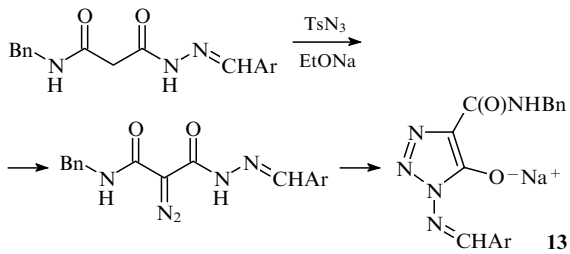
Recyclisation of 4-oxopyrido[*a*]pyrimidinyldiazonium **11** in the presence of alcoholates resulting in alkyl 1-(2-pyridyl)triazole-4-carboxylates **12** can be assigned to the same type of reaction.[55]



R = Me, Et, Pr^n, Bu^n, n-C_5H_{11}.

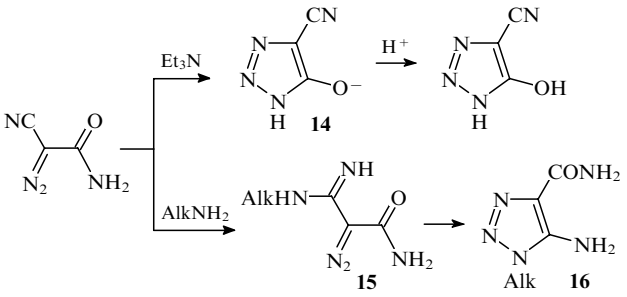
Similarly, 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones are converted into the corresponding 1-(pyridazin-2-yl)triazole-4-carboxylates.[56] Diazotisation of 7β-aminocephalosporin sulfones also gives a 1,2,3-triazole derivative. The opening of the β-lactam ring and the attack by the diazonium cation on the nitrogen atom are the key steps in this process.[57]

Cyclisation of diazo compounds of this type containing amide, amidine or imidate groups is a convenient method for the preparation of polyfunctional derivatives of triazole. An example is the synthesis of 4-substituted 1-(arylideneamino)triazol-5-olates **13**.[58]

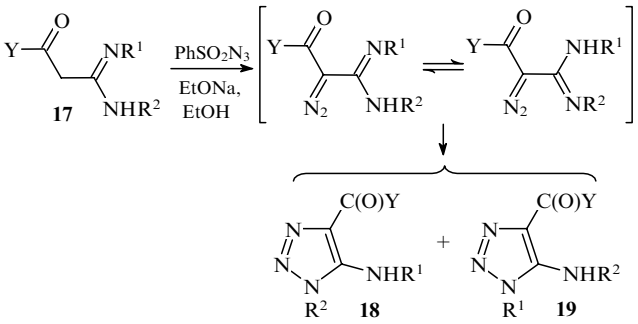


Ar = 4-FC_6H_4, 4-$MeOC_6H_4$.

If the molecule of the diazo compound contains a cyano group, apart from the above-listed groups, base-induced cyclisation occurs through attack by the terminal nitrogen atom of the diazo group on the nucleophilic nitrogen atom of the amide to give 4-cyanotriazol-5-olates **14**. When primary amines are used, amine addition to the cyano group takes place giving rise to α-diazo-*N*-alkylamidine **15**, whose cyclisation involves the amidine nitrogen atom and results in 1-alkyl-5-amino-4-carbamoyltriazoles **16**.[59]



Cyclisation of amidine **17** containing different substituents at nitrogen atoms affords either one of isomers **18**, **19** or their mixture, depending on the nature of the radicals R^1 and R^2 (see Ref. 60).



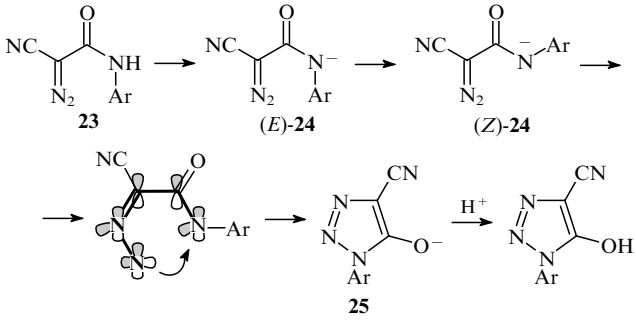
R^1 = H, Me; R^2 = Me, Bn, 2-Py, 4-MeC_6H_4, 4-BrC_6H_4;
Y = NH_2, MeNH, EtO.

For example, in the case of R^1 = H, R^2 = Bn, and Y = NH_2 regioisomer **18** is formed in 74% yield, while with R^2 = 2-pyridyl, the reaction route changes, triazole **19** becoming the predominant product (yield 83%). In the case of R^1 = Me, R^2 = Bn, Y = NHMe, the reaction mixture contains both isomers (yield 56%).[60]

Triazoles **20a** and **21a** have been prepared through the α-diazo derivative of cyanoacetic acid *N*-benzylidenehydrazide[61] using the transformation sequence shown in Scheme 1 (pathway *a*).

Similar 2-(*N*-methylcarbamoyl)- (**22b**) and 2-ethoxycarbonyl derivatives (**22c**) react with tosyl azide and sodium ethoxide immediately to give sodium salts of hydroxytriazoles **21** (pathway *b*) rather than intermediate diazo compounds.[61] The use of diazo transfer to these hydrazides is impossible due to a side reaction involving the hydrazide group. However, arylmethylidene-protected acetohydrazides react with tosyl azide (pathway *c*) to be smoothly converted into the sodium salts of 1-(arylmethylideneamino)hydroxytriazoles **20b**,**c**.[62] It has been noted that in the case of carbamoyl derivatives, no isomeric triazoles resulting from cyclisation at the nitrogen atom of the amide group are formed. Acidification of aqueous solutions of sodium salts yields 5-hydroxytriazoles, which occur in equilibrium with the open forms of diazo compounds.[63–65] After removal of the benzylidene protection and upon acidification, 1-aminotriazolates **21a–c** also mainly exist as the open form of diazo compounds.[59]

The mechanism of heterocyclisation of 2-cyanoacetamides into 5-hydroxytriazoles has been studied in detail.[66,67] It was shown that 2-diazo-2-cyanoacetamides undergo partial cyclisation on refluxing in ethanol in which the equilibrium between the cyclic and open forms is rapidly established, whereas in the case of diazomalonodiamide, the equilibrium is established very slowly. In polar solvents, the equilibrium shifts towards cyclic forms. The position of the equilibrium depends only slightly on the electronic and steric properties of the substituent at the carboxamide nitrogen atom, although electron-withdrawing substituents have been noted to destabilise to some extent the cyclic structure.[67] On the basis of experimental values of the activation energy of the cyclisation, the ρ reaction parameters and the kinetic isotope effects, together with the results of theoretical calculations, it has been concluded that the cyclisation mechanisms of *N*-aryl and *N*-alkyl derivatives of diazocyanoacetamides are different. In the former case, the reaction starts with proton elimination from the amide nitrogen atom of *N*-aryl derivatives **23** to give imidolate anion **24**, which then isomerises and cyclises into triazolate anion **25** by an electrocyclic mechanism. The process ends in the protonation of the triazolate anion to give 5-hydroxytriazole.[67] These transformations have been considered in a review.[68]

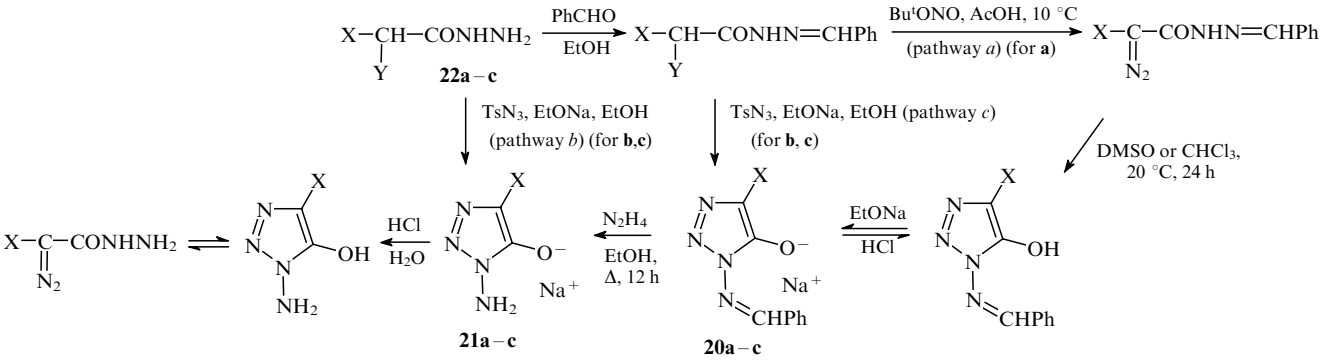


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$EtO_2CC_6H_4$.

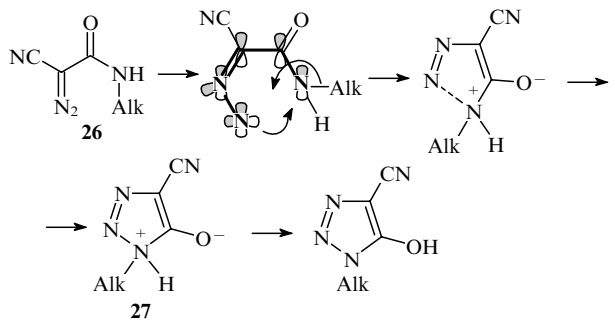
Apparently, cyclisation of *N*-sulfonyldiazomalonamides [$ArSO_2NHCOC(=N_2)CONHSO_2Ar$] to 1-sulfonyltriazoles occurs in a similar way.[69]

Meanwhile, in the case of *N*-alkyl derivatives **26**, which have a lower NH-acidity, the substituents rotate around the C–N bond to give cyclic zwitterionic structure **27** (monorotatory mechanism).[67]

Scheme 1

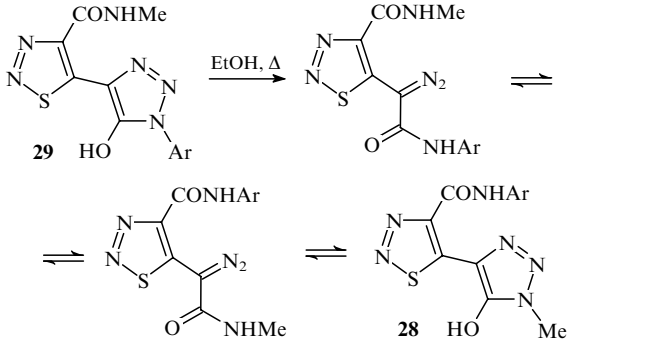


X = CN, Y = NH_2 (**a**); Y = H: X = MeNHCO (**b**), CO_2Et (**c**).

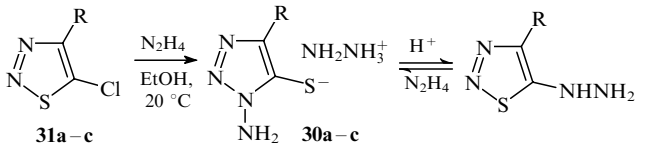


Alk = H, Me, n-C_6H_{13}, Bn.

Proceeding from the ability of triazolates to undergo easy cleavage of the heterocycle to be converted into linear diazo compounds, researchers[64, 69] have developed a method for the synthesis of 4-substituted 1-alkyl-5-hydroxytriazoles **28** from more readily available 1-aryl derivatives **29**.[65, 70] The rearrangement proceeds on refluxing the starting triazolate in ethanol and includes the following steps: triazole ring opening, isomerisation of diazoacetamide and triazole ring closure.

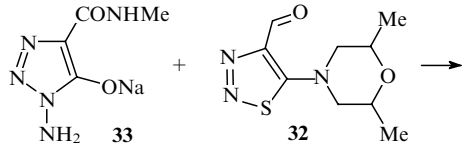


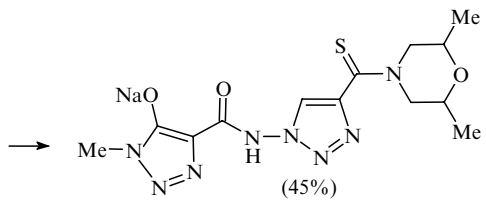
The ability of 5-amino-1,2,3-thiadiazoles to isomerise into 5-mercaptotriazoles has been used in the synthesis of 1-amino-4-R-5-thiolates **30** from the corresponding 5-chlorothiadiazoles **31** on treatment with excess hydrazine.[71–73] In the case of the ethoxycarbonyl derivative **31c**, the reaction proceeds at room temperature, whereas for derivatives **31a**,**b**, replacement of the chlorine atoms in thiadiazole requires heating. When the resulting thiolate **30** is treated with an acid, triazole ring transformation takes place to give hydrazinothiadiazole.[71]



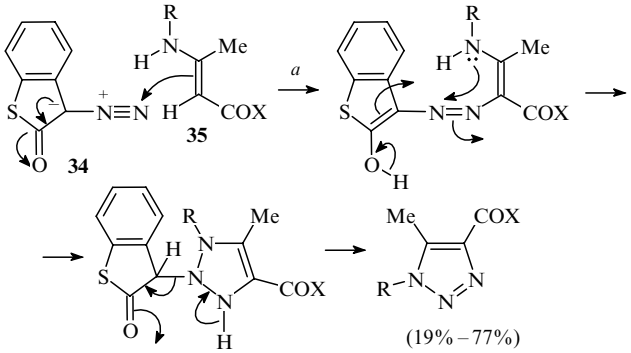
R = H (**a**), Ph (**b**), CO_2Et (**c**).

On treatment of 5-morpholino-1,2,3-thiadiazole-4-carbaldehyde with primary amines, the imine readily undergoes the Conforth rearrangement, being converted into 1-R-4-morpholinothiocarbonyl-1,2,3-triazole.[74] The tandem Conforth rearrangement was carried out in the reaction of thiadiazole-4-carbaldehyde **32** with 1-amino-4-carbamoyltriazol-5-olate **33**.[75]





Recently, a new method for triazole synthesis has been reported in which the heterocycle is formed *via* diazo transfer.[76] Using the reaction of 3-diazobenzo[*b*]thiophen-2-one (**34**) with N-substituted enaminocarbonyl compounds **35** as an example, a process mechanism has been proposed.

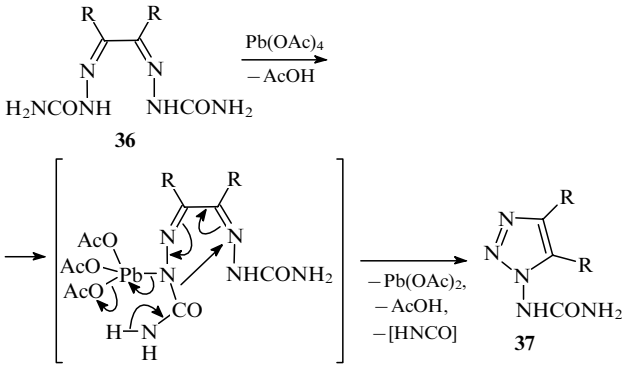


R = Me, Bu^t; X = Me, EtO; *a* is PhH or PhMe, Δ.

This reaction has been carried out for not only various enaminones,[76] but also for 3-diazo derivatives of 5-nitrooxyindole, 1-methyl-5-nitro-oxyindole and 5,7-dinitro-oxyindole as substrates.[76, 77]

2. Cyclisation of nitrogen derivatives of 1,2-dicarbonyl compounds

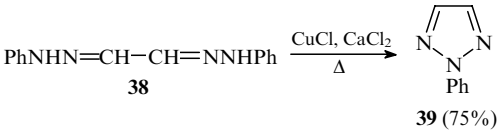
This pathway to 1,2,3-triazoles was first proposed by Pechmann[78] and later developed by many researchers. It was shown that heating bishydrazones or bissemicarbazones of α-dicarbonyl compounds in the presence of oxidants such as MnO_2, HgO, $Hg(OAc)_2$, $FeCl_3$, NiO_2, CuCl, $CuSO_4$, and $Pb(OAc)_4$ gives rise to substituted triazoles. The process includes the complexation stage and subsequent cyclisation in which a metal compound in a reduced state is eliminated. The transformations of α-diketone bissemicarbazones **36** into 1-ureidotriazoles **37** on treatment with lead tetraacetate has been studied:[79]



R = H, Me, Ph, 4-MeC_6H_4, 4-BrC_6H_4.

The product yields in this cyclisation are usually relatively low. Despite a number of modifications, this method has not received wide use.[2] Nevertheless, substituted 2*H*-triazoles can be synthesised in this way.[14, 15] Thus the oxidation of glyoxal phenylosazone **38** yields bis(phenylazo)ethylene, which is then converted into 2-phenyltriazole **39** on treatment with $FeCl_3$, CuCl or $CuSO_4$, but the yields do not exceed 50%. The optimal conditions for this

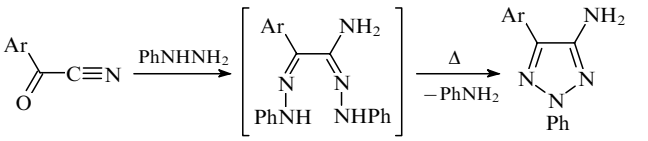
reaction were chosen, namely, heating of a mixture of osazone, CuCl and anhydrous $CaCl_2$ with continuous evaporation of the product *in vacuo*; the yield of 2-phenyltriazole **39** was thus increased to 75%.[80]



38 **39** (75%)

An example of the preparation of bis(triazol-2-yl)-substituted arylenes using α-diketones and arylenebis(hydrazines) has been reported.[81] Proceeding from D-arabinose osazone, 2-(3-nitrophenyl)-4-(β-D-erythrofuranosyl)triazole has been synthesised.[82] The potential of using osazones of low-molecular-weight carbohydrates for the preparation of heterocyclic compounds, including 1,2,3-triazole derivatives, is described in a review.[83]

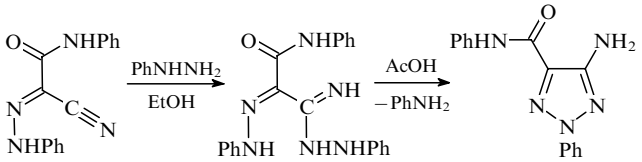
Heating of aroyl cyanides with phenylhydrazine (ratio 1 : 2) results in 4-amino-5-aryl-2-phenyltriazoles **40**.[84] The researchers assume that the reaction proceeds through the formation of intermediate α-amino-α′-arylglyoxal bis(phenylhydrazones) **41**, which cyclise with the loss of an aniline molecule.



41 **40** (52% – 72%)

Ar = Ph, 3-MeC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$.

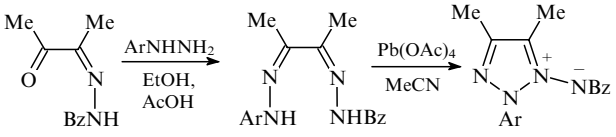
The intermediate product of phenylhydrazine addition at the C≡N bond (compound **42**) has been isolated in a similar transformation of 2-oxocyanoacetanilide phenylhydrazone **43**.[85]



43 **42**

The oxidative cyclisation of analogous arylhydrazones of 2-oxocyanoacetamidines has resulted in the synthesis of a series of 4-amino-2-aryl-5-cyanotriazoles,[86] and the reaction of acyl cyanides with methylhydrazine gave 4-amino-5-aryl-2-methyltriazoles.[87]

In the case of dimethylglyoxal bishydrazones with *N*-aryl and *N′*-benzoyl groups (compound **44**), oxidation with lead tetraacetate results in rather stable triazole derivatives of the ylide type **45**.[28] These compounds are additionally stabilised due to negative charge delocalisation involving the carbonyl group.



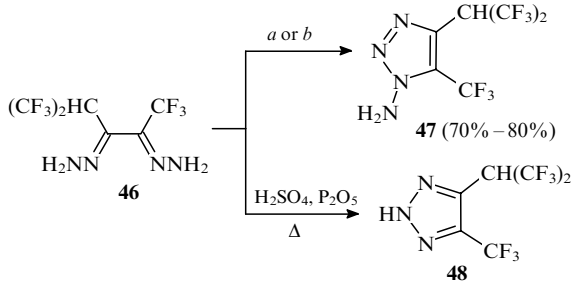
44 **45**

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$.

Note that cyclisation of N-unsubstituted phenylglyoxal bishydrazone furnishes 1-amino-4-phenyltriazole.[14]

The oxidation of asymmetric dimethylglyoxal aroylhydrazones yielding isomeric *N*-(4,5-dimethyltriazol-1-yl)arylcarboximido acids has been considered.[88] The oxidative cyclisation of bis(acetylhydrazones) of 1,2-dicarbonyl compounds results in the formation of 1-(*N*-acetyl)- and *N,N*-bis(acetylamino)triazoles.[89]

It is noteworthy that cyclisation of the bishydrazone of polyfluorinated diketone **46** induced by bromine or sulfuryl chloride at room temperature gives only 1-amino-4-hexafluoroisopropyl-5-trifluoromethyltriazole **47**.[90, 91]

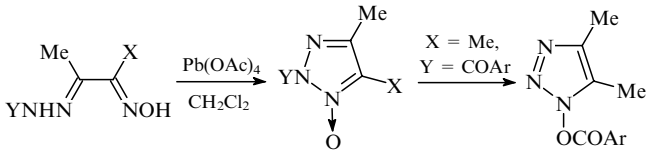


46 **47** (70% – 80%) **48**

(*a*) Br_2, CH_2Cl_2; (*b*) SO_2Cl_2, $CaCl_2$.

Cyclisation giving triazole with a more electron-withdrawing group at the 5-position also takes place during the oxidation of (5-hydroperfluoropentyl)glyoxal bishydrazone on treatment with SeO_2.[92] Under more rigorous conditions, compound **46** was converted into a deamination product, namely, 4,5-disubstituted 2*H*-triazole **48**.[93] The formation of only one regioisomer of 1-phenylsulfonyltetrahydrobenzotriazole is observed in the reaction of methyl derivatives of cyclohexane-1,2-diones with phenylsulfonylhydrazine.[94]

The oxidative cyclisation of α-arylhydrazono ketone anils affords 1,2-diaryltriazolium derivatives,[95] while that of α-hydroxyimino ketones results in the corresponding triazole *N*-oxides.[96] This method was used to prepare a series of 5-acyltriazole *N*-oxides **49**.[97]

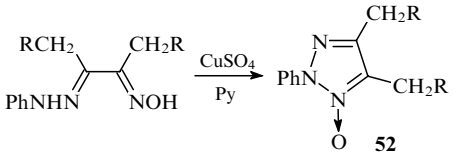


49, **50** **51**

Y = Ar: X = COMe, COPh (**49**); X = Me, Y = ArCO (**50**);
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$.

When *N*-aroylhydrazones of α-hydroxyimino ketones are used in this reaction, migration of the aroyl group to the oxygen atom takes place in the intermediate *N*-oxides **50** to give triazoles **51**.[98]

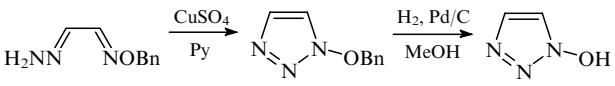
The oxidative cyclisation of (*N*-phenylhydrazono)oximes of ethyl acetoacetate on treatment with MnO_2 affords different isomers of 4(5)-methyl-2-phenyl-5(4)-ethoxycarbonyltriazole *N*-oxide depending on the position of the oximino and hydrazono groups in the initial compound.[99] This method has been used to prepare symmetric 4,5-disubstituted 2-phenyltriazole 1-oxides **52**. Cyclisation induced by other oxidants, *i.e.*, *N*-iodosuccinimide or copper sulfate, shows a higher efficiency of the latter compound (the yield exceeds 90% almost in all cases).[100]



52

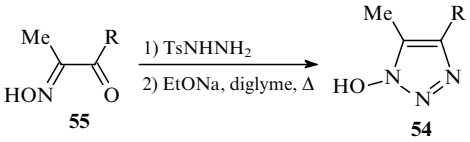
R = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-Naph, cyclo-C_6H_{11} (Cy).

The same reagent was used to prepare 1-(benzyloxy)triazole **53** from *O*-benzyloxime glyoxal monohydrazone.[101] The possibility of debenzylation of triazole **53** to give unsubstituted 1-hydroxytriazole was demonstrated.



53

It is worth noting that 1-hydroxy-1*H*-triazoles and their O-derivatives have attracted the attention of researchers as new condensing reagents in the peptide synthesis, which are able to suppress racemisation and other side reactions. To study the properties of compounds of this class, a series of new 1-hydroxytriazole derivatives have been prepared [46, 102] by different synthetic routes. Alkyl- and aryl-substituted 1-hydroxytriazoles **54** were synthesised by treatment of 1,2-diketone *N*-tosylhydrazone oxime **55** with sodium ethoxide with subsequent short-term refluxing in diglyme.[46]

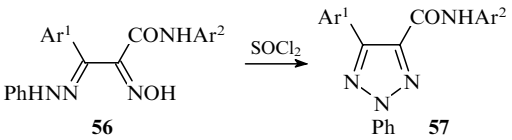


55 **54**

R = Me, Ph, 4-MeOC$_6$H$_4$.

This method proved to be inapplicable for the synthesis of 1-hydroxy-1*H*-triazole with an ester group (R = CO_2Me); this compound was prepared by cyclisation of the oxime of ethyl diazoacetoacetate.[46]

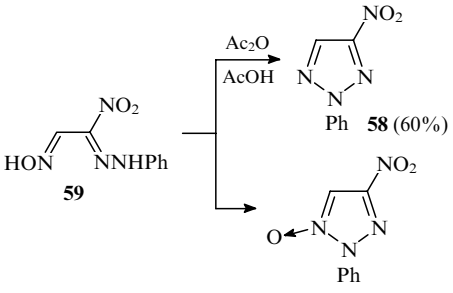
The cyclisation of phenylhydrazone oximes **56** induced by dehydrating agents (Ac_2O, $SOCl_2$) affords 2-phenyltriazoles **57** with an unsubstituted 1-position.[103]



56 **57**

Ar^1 = Ph, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; Ar^2 = Ph, 4-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$.

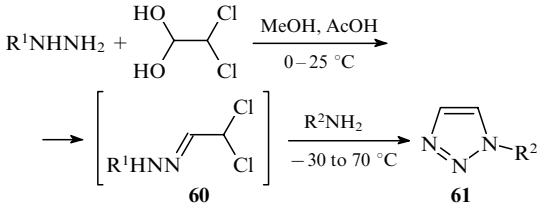
Similarly, aroylglyoxal 1,2-bis(phenylhydrazones) [ArCOC(=NNHPh)CH(=NNHPh), where Ar = Ph, 2-furyl] are converted into 4-aroyl-2-phenyltriazoles.[104] This route was used to synthesise 4-nitro-2-phenyltriazole **58** from 2-nitro-2-phenylhydrazonoacetoxime **59**.[105] It is noteworthy [106] that in the oxidative cyclisation {K_3[Fe(CN)$_6$], KOH, dioxane}, this oxime results in triazole with an *N*-oxide group at the 1-position.



59 **58** (60%)

However, 2-nitro-2-phenylhydrazonoacetamidoxime forms 4-amino-5-nitro-2-phenyltriazole only on heating with urea.[105] On coupling of 2-nitroacetaldehyde oxime with 1,2,4-triazole-3-diazonium salts followed by the cyclisation of the corresponding hydrazonoacetaldehyde oximes, 4-nitro-2-(1,2,4-triazol-3-yl)-1,2,3-triazoles were prepared.[107, 108]

Several approaches have been proposed to obtain unsubstituted triazole. Harada *et al.*[109] carried out cyclisation of glyoxal monoxime monohydrazone on treatment with acetic anhydride, and the resulting 2-acetyltriazole was subjected to alcoholysis. Unsubstituted triazole is formed in the reaction of tosylhydrazine with a mixture of ammonia and glyoxal on heating in aqueous methanol [110] or on bubbling ammonia into water or into an organic solvent.[111] A two-step method based on the reaction of dichloroacetaldehyde with sulfonylhydrazines with the subsequent cyclisation of the resulting hydrazone **60** under the action of ammonia has been developed.[112] A drawback of this approach is related to the use of toxic dichloroacetaldehyde and its proneness to polymerisation. The procedure modified by other researchers [113] does not imply the isolation of the intermediate hydrazone and provides triazole **61** (R^2 = H) in 55% yield. By introducing aliphatic, aromatic or heteroaromatic amines into this reaction instead of ammonia, a series of 1-substituted triazoles **61** have been obtained. The solvents used were water, alcohols, acetonitrile, dioxane, DMSO, or DMF.[113, 114]



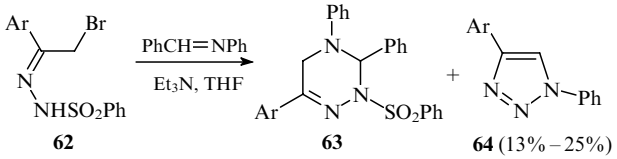
60 **61**

R^1 = R^{3}CO, R^{3}SO$_2$: R^3 = Me, Et, Pr^n, Pr^i, Bu^n, Ph, XC$_6$H$_4$ (X = Alk, AlkO, Cl, Br, NO$_2$); R^2 = H, Alk, Ar, Het.

This method was utilised to prepare 1,1′-bitriazole.[115] 1-Aminotriazole served as the amino component; it was prepared by treatment of arylsulfonylhydrazone of dichloroacetaldehyde with hydrazine hydrate in the presence of Et_3N (PrOH, 40 °C, yield 65%) [116, 117] or by cyclisation of glyoxal bishydrazone in aqueous hydrogen peroxide in the presence of catalytic amounts of transition metal oxides.[118]

Similarly, reactions of methyl- and benzylamine with 1,1-dichloroacetone tosylhydrazone afford 1-methyl(or benzyl)-4-methyltriazoles in high yields, while the reactions with chloral tosylhydrazone give the corresponding 5-amino-substituted triazoles.[119] The reaction of ω,ω-dichloroacetophenone with tosylhydrazine resulted in 1-tosylamino-4-phenyltriazole (yield 20%).[119]

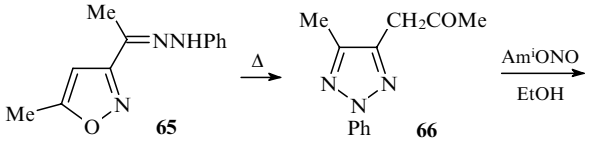
By the reactions of hydrazones of substituted ω-bromoacetophenones **62** with benzylideneaniline in the presence of Et_3N, mixtures of aryl-substituted tetrahydrotriazines **63** and 4-aryl-1-phenyltriazoles **64** have been obtained.[120]



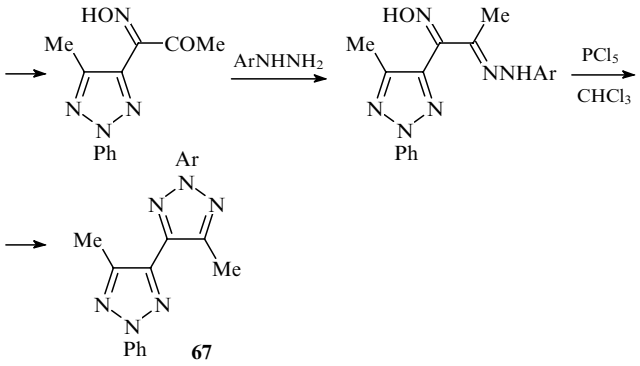
62 **63** **64** (13%–25%)

Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$.

The thermally induced ring transformation in phenylhydrazones of 3-acetylisoxazoles **65** to give 4-acetonyl-2-phenyltriazoles **66** can be assigned to the same Section. The subsequent nitrosation, transition of oximino derivatives into arylhydrazones and treatment of these products with PCl_5 yield 2,2′-diaryl-4,4′-bistriazoles **67**.[121] Substituted phenylhydrazones of acetylisoxazoles undergo the same transformations.

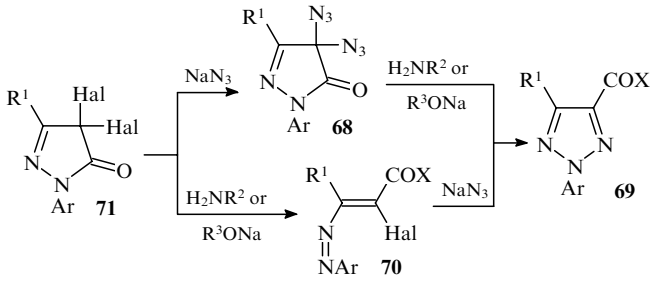


65 **66**



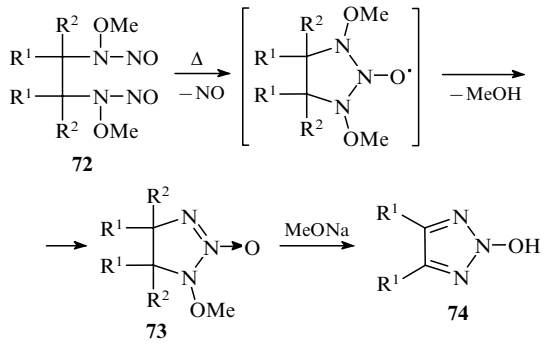
Ar = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$; Am^i is isoamyl.

1-Aryl-4,4-diazidopyrazolin-5-ones **68** open the pyrazoline ring at room temperature in the presence of alkali to give the intermediate hydrazodiazide, which cyclises into 2-aryltriazole-4-carboxylic acids with nitrogen extrusion.[122] Subsequently, other researchers have shown that if amines or alkoxides are introduced into the reaction instead of alkali, the reaction gives the corresponding derivatives of acid **69**.[123] The same products can be prepared by the reaction of NaN_3 with arylazovinyl halide **70**, which is formed upon ring opening in dihalopyrazolinone **71** on treatment with bases.



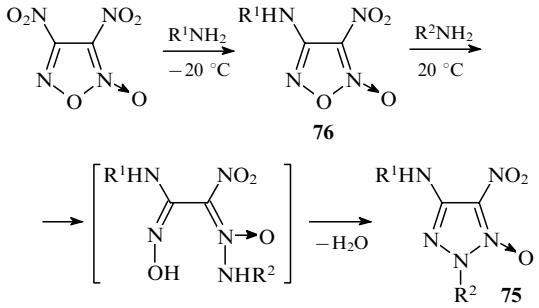
R^1 = Me, Ph; Ar = Ph, 4-$O_2NC_6H_4$; X = NH_2, EtNH, EtO; R^2, R^3 = Alk.

The formation of the triazole ring on heating 1,2-bis(*N*-methoxy-*N*-nitrosoamino)ethane **72** (R^1 = R^2 = H) has been described.[124] On treatment with sodium methoxide, *N*-oxide **73** is converted into 2-hydroxytriazole **74**.[124]



If 1,2-dialkyl-substituted 1,2-bis(*N*-alkoxy-*N*-nitrosoamino)-ethanes **72** (R^1 = Alk, R^2 = H) are introduced in this reaction, 4,5-dialkyl-2-hydroxytriazoles **74** (R^1 = Alk) are produced. In the case of tetrasubstituted *N*-alkoxy derivatives **72** (R^1 = R^2 = Alk), the reaction stops after the formation of 1-alkoxy-4,5-dihydrotriazole 2-oxide **73**.[125]

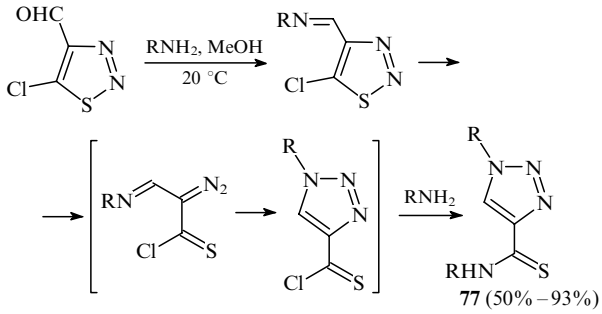
Proceeding from readily available 3,4-dinitrofuroxan, a new method for the synthesis of 4-amino-substituted 5-nitro-2*R*-triazole 1-oxides **75** *via* *N*-alkylamino derivatives **76** has been developed.[126–128]



R^1 = H, Me, Et, $HO(CH_2)_2$, $NC(CH_2)_2$; R^2 = Me, Et, CH_2 = $CHCH_2$.

These transformations occur similarly to the recyclisation of benzofuroxans into 1,2,3-triazole oxides under the action of acylanilide anions.[129, 130]

5-Chloro-1,2,3-thiadiazole-4-carbaldehyde reacts with a number of amines to give 1-substituted triazole-4-thiocarboxamides **77**. The mechanism proposed for ring transformation includes the formation of imino derivatives, thiadiazole ring opening at the N–S bond, and triazole ring closure.[131]

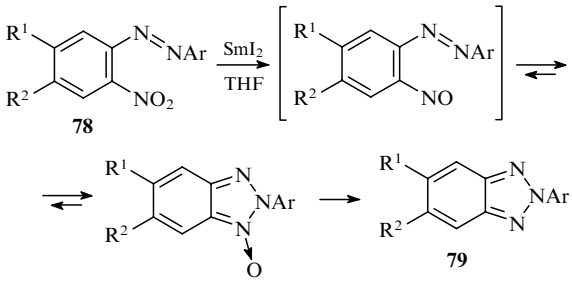


R = Me, Et, Bn, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, NH_2, $O(CH_2CH_2)_2N$.

The mechanism of recyclisation of 3-benzoyl-5-phenyl-1,2,4-oxadiazole arylhydrazones into 2-aryl-4-benzoylamino-5-phenyltriazoles depends on the nature of substituents in arylhydrazone.[132, 133]

3. Cyclisation of *ortho*-disubstituted nitrogen derivatives of aromatic compounds

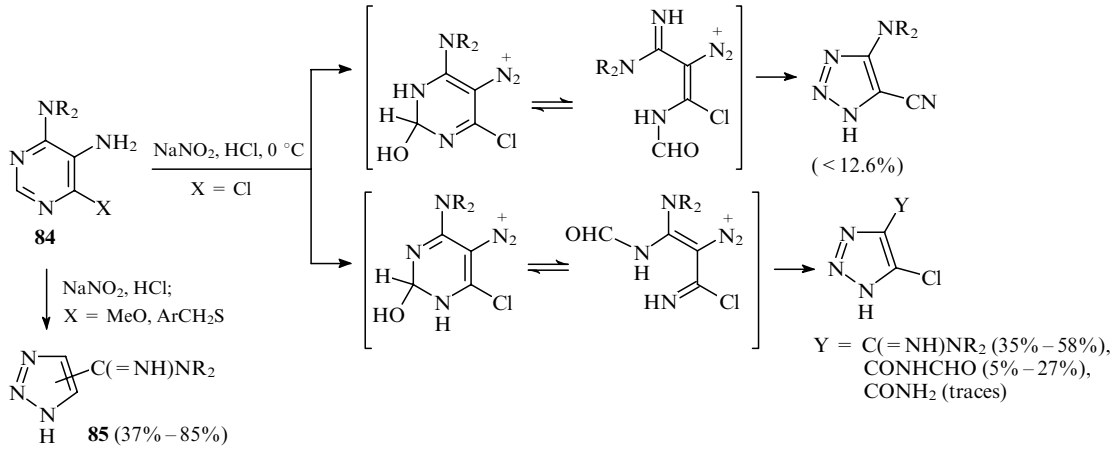
The presence of two nitrogen-containing functional groups in the *ortho*-position of the benzene ring allows the use of these compounds for construction of the benzotriazole system. Depending on the nature of the groups and the reagents used, the intramolecular cyclisation can yield different substituted benzotriazoles, in particular, *N*-oxides and *N*-hydroxy derivatives.[14] Data on the reductive cyclisation of *o*-nitrophenylazobenzenes **78** into 2-arylbenzotriazoles **79** on treatment with SmI_2 have been published recently.[134] The putative reaction mechanism includes the reduction of the nitro group to the nitroso group, intramolecular cyclisation to give 2-arylbenzotriazole 1-oxide and its subsequent deoxygenation.



R^1, R^2 = H, Cl; Ar = 2-HO-5-MeC_6H_3, 2-HO-3,5-$Bu^t_2C_6H_2$.

The electrochemical reduction of 2-hydroxy-5-methyl-2′-nitroazobenzene during the preparation of 2-(2*H*-benzotriazol-2-

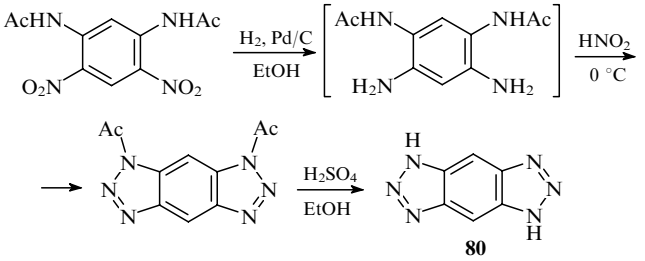
Scheme 2



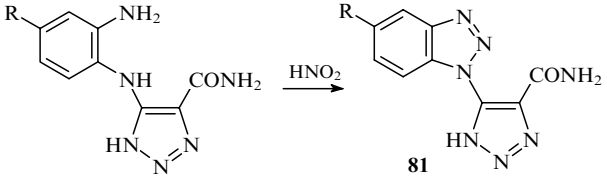
R – R = Me_2, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$; Ar = Ph, 3,4-$Cl_2C_6H_3$.

yl)-4-methylphenol (known as the light stabiliser Benazol-P) proceeds in a similar way.[135]

The synthesis of 1*H*,5*H*-benzo[1,2-*d*:4,5-*d*′]bistriazole **80**, which is converted into 1,5- and 1,7-diamino derivatives upon amination, has been accomplished using diazotisation of the diacetyl derivative of tetraaminobenzene.[136]

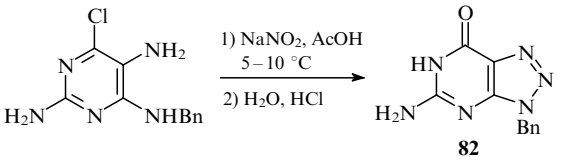


This method underlies the synthesis of a series of 1-(4-carboxamidotriazol-5-yl)benzotriazoles **81** [137]

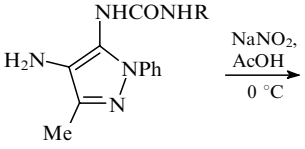


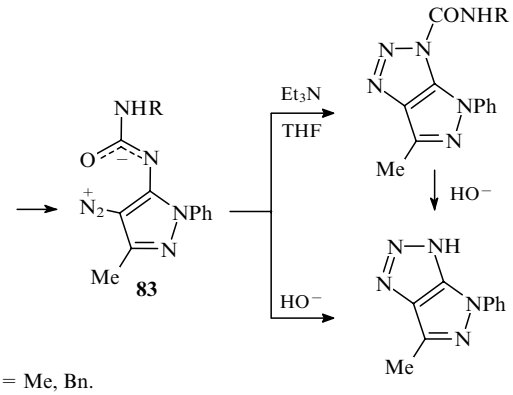
R = H, Me, MeO, F, Cl, CF_3.

and the regioselective synthesis of 9-substituted 8-azaguanines **82**.[138, 139]



4-Diazopyrazoles **83**, which are prepared by diazotisation of *N*-alkyl-*N*′-(4-aminopyrazol-5-yl)ureas proved to be convenient synthons for the construction of various heterocyclic systems, for example, pyrazolo[4,5-*d*]triazole.[140]

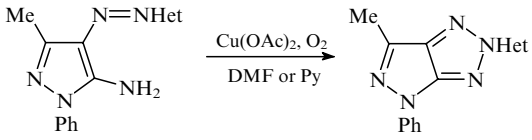




R = Me, Bn.

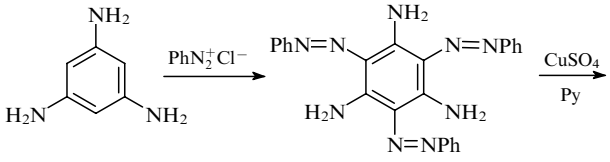
Diazotisation of 4-dialkylamino-5-aminopyrimidines **84** in an acidic aqueous medium results in opening of the pyrimidine ring followed by attack by the diazo group on a nitrogen atom. This affords triazoles of different structures, depending on the substituent at the 6-position of pyrimidine.[141] For example, in the presence of 6-MeO or 6-$ArCH_2S$ groups in the pyrimidine ring, only 4(5)-carboxamidinotriazoles **85** are formed, whereas in the case of the 6-Cl substituent, cyano- and carboxamidotriazoles have also been isolated as minor products (Scheme 2).

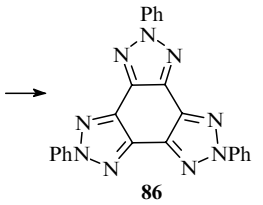
The anodic oxidation of 2-arylazo-3-aminocrotononitrile to 2-aryl-4-cyanotriazole [142] and oxidative cyclisation of pyrazole azo compounds containing an amino group can be assigned to the same type of triazole ring construction.[143]



Het = 2-Py, thiazol-2-yl, pyrazol-5-yl.

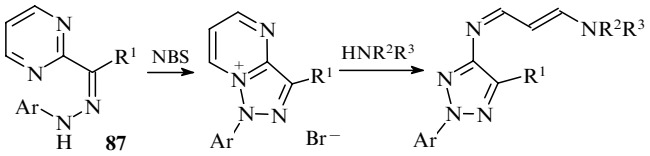
A similar method has been used to synthesise derivatives of benzotriazole and more complex fused systems,[144, 145] including those containing several triazole rings, for example, heterocyclic compound **86**.[146]





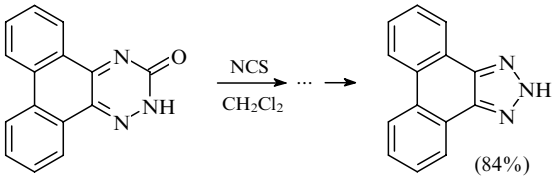
86

A review [147] has been devoted to the closure of the triazole ring in 2-acylazine hydrazones. The triazoloazinium cations thus formed tend to undergo cleavage of the six-membered ring on treatment with nucleophilic agents. For pyrimidine **87**, this sequence can be represented as follows:



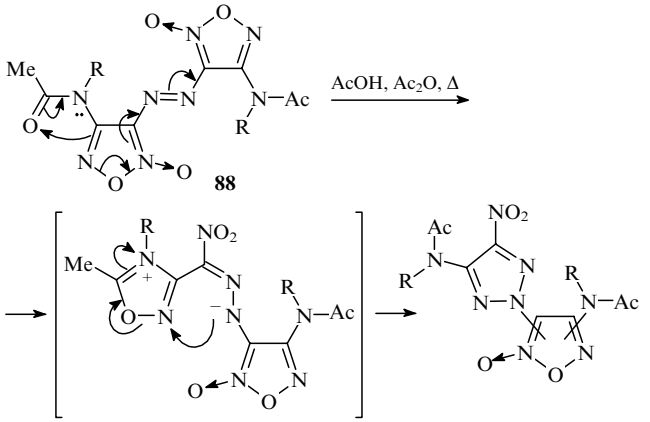
NBS is *N*-bromosuccinimide.

The transformation of annelated 1,2,4-triazin-3-one into the corresponding 1,2,3-triazole induced by *N*-chlorosuccinimide (NCS) has been described;[148] by analogy with the ring transformations known previously,[149] this process includes N-chlorination, azine ring opening and triazole ring closure followed by the removal of chlorine.



(84%)

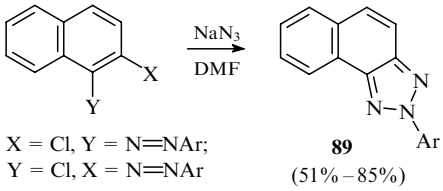
A thermal rearrangement of 4,4′-diacetamido-3,3′-azodifuroxans **88** has been detected.[150] The presence of acetamide groups in the starting azodifuroxan was shown to be a necessary condition for this process. According to the reaction mechanism proposed by the researchers, two successive rearrangements take place. The first one is the transformation of one furoxan ring into a 1,2,4-oxadiazole ring with O(1)–N(5) bond cleavage and formation of the nitromethylene fragment, while the second ring transformation gives rise to a new bond of the triazole ring. Isomerisation of the furoxan fragment is possible at the final stage, resulting in the formation of two isomeric products.



R = H, Me.

4-Acetylamino-3-arylazofuroxans undergo the same cascade rearrangement in an alkaline medium to give 2-aryl-4-acetylamino-5-nitro-2*H*-triazoles (Ar = 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 2,4-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$),[151] while 4-acetyl(or benzoyl)-3-methylfuroxan phenylhydrazones are transformed on heating into 5-acetyl-4-methyl(or phenyl)-2-phenyl-2*H*-triazole 1-oxide oximes.[152]

The reaction of *vic*-chlorinated 1- or 2-arylazonaphthalenes with sodium azide can also be ascribed to this type of reaction. In both cases, 2-aryl-2*H*-naphtho[1,2-*c*]triazoles **89** are formed.[153]

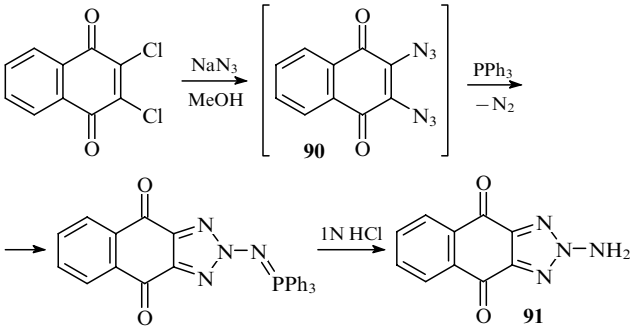


X = Cl, Y = N=NAr;
Y = Cl, X = N=NAr

89 (51%–85%)

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

Triphenylphosphine-induced cyclisation of 2,3-diazido-1,4-naphthoquinone **90** prepared *in situ* has been reported.[154,155] The reaction proceeds smoothly, the yield of 2-aminobenzotriazole **91** being nearly quantitative.

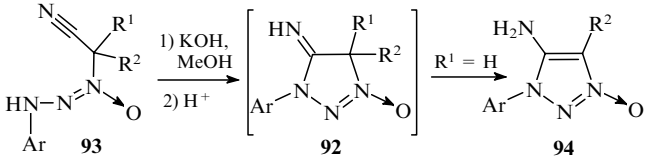


Although the reaction mechanism has not been studied in detail, it is assumed that PPh_3 adds to the terminal nitrogen of the azide group according to the Staudinger reaction type, while the second nitrogen atom of the same group attacks the neighbouring azide group. This is accompanied by elimination of a nitrogen molecule, which is really observed in experiments. Thus, this reaction is similar to thermal and photochemical intramolecular cyclisations of aryl azides which involve neighbouring unsaturated substituents.[154]

III. Methods of formation of the C(5)–N(1) or C(4)–N(3) bond

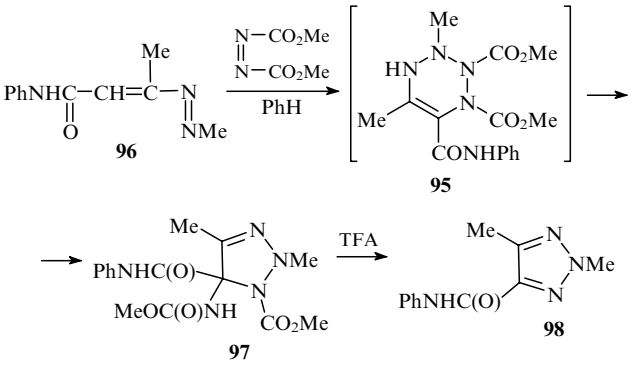
This group of reactions includes examples of intramolecular cyclisation of cyano-containing triazenes.

Recently, a new approach to the synthesis of iminodihydrotriazole 1-oxides **92**, namely, KOH-induced cyclisation of cyano-containing aromatic and heterocyclic triazene 1-oxides **93**, has been proposed.[156,157] A possible sequence of transformations includes base-induced formation of an anionic centre on N(3) of the triazene oxide fragment and nucleophilic attack by this centre on the electron-deficient carbon atom of the nitrile group. In the case of 3-(het)aryltriazene 1-oxides containing an active hydrogen atom in the α-position to the cyano and triazene oxide groups, the iminodihydrotriazole 1-oxides **92** (R^1 = H) formed are isomerised into the *N*-oxides of aminotriazoles **94**.



Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 1,2,4-triazol-3-yl; R^1 = R^2 = Me; R^1–R^2 = $(CH_2)_5$.

Formally, the rearrangement of unstable 1,2,3,4-tetrahydro-1,2,3,4-tetrazine **95**, which is formed upon the reaction of azoalkene **96** with dimethyl azodicarboxylate and is converted into 1,5-dihydro-2*H*-triazole **97** already during the reaction, can also be classified as the method in question for 1,2,3-triazole ring formation. The product **97** eliminates methyl carbamate on treatment with trifluoroacetic acid (TFA) to give 2,4,5-trisubstituted 2*H*-triazole **98** in 80% yield.[158]

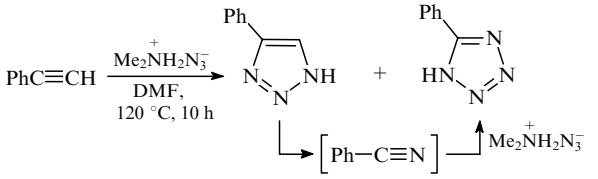


IV. Methods of formation of two C—N bonds

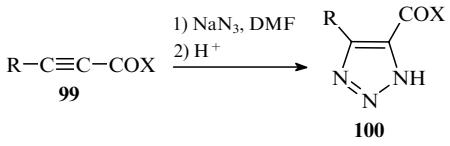
This group of reactions is used most often to prepare the triazole system and can be exemplified by the largest number of cases. This approach is based on 1,3-dipolar cycloaddition of organic azides to unsaturated compounds.

1. Reactions of azides with substituted acetylenes

The published examples of reactions of azides with alkynes, resulting in triazole derivatives, are rather numerous. It is expedient to start this Section by considering reactions of inorganic azides, which were the first to be used in this method for triazole synthesis. Unsubstituted 1,2,3-triazole was first prepared in a relatively low yield by the addition of HN_3 to acetylene at 100 °C in a sealed tube under an elevated pressure;[159] subsequently, conditions were chosen to bring the product yield up to 86%.[160] Recently, it has been shown[161] that phenylacetylene reacts with dimethylammonium azide to give a mixture of 4-phenyltriazole and 5-phenyltetrazole.



The presence of an amide or an acyl group in phenylacetylene **99** (R = Ph) allows the reaction with sodium azide to be carried out with heating in DMF; the reaction gives 5-amido- or 5-acyltriazoles **100** (R = Ph), respectively, in high yields.[162–165]

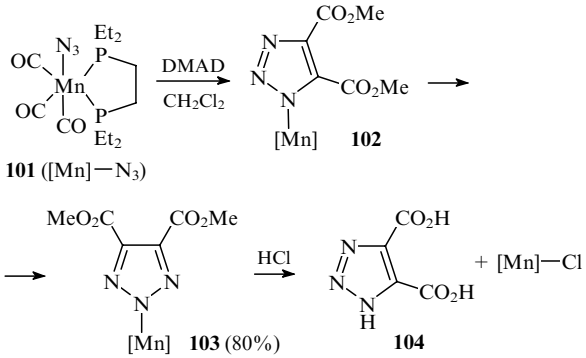


R = Ph: X = NH_2, CH_2COAr; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$;
R = CH_2NAlk_2, X = NH_2.

In the case of 3-(*N,N*-dialkylaminomethyl)propiolamides **99** (R = CH_2NAlk_2, X = NH_2), carboxamidotriazoles **100** (R = CH_2NAlk_2) are also formed. This was used for the design of complex biologically active compounds containing a triazole ring with secondary aminomethyl substituents.[166, 167]

Triazole derivatives have also been synthesised under the same conditions by the reaction of NaN_3 with acetylenic aldehydes,[168] 1-alkylthio-2-chloroacetylenes[169] and esters of long-chain oxoacetylenic fatty acids.[170] The use of hydrogen azide or metal azides in the cycloaddition results in 1,2,3-triazoles unsubstituted at the ring nitrogen atom. However, conduction of these reactions, especially on a preparative scale, is associated with a risk of explosion. The safety aspects for the work with sodium azide on an industrial scale, in particular, in the production of 1,2,3-triazoles, have been discussed in a brief review.[171] The use of trimethylsilyl azide as the reagent reduces the risk and allows one to synthesise 1-trimethylsilyltriazoles, from which the silyl group can subsequently be removed.[172]

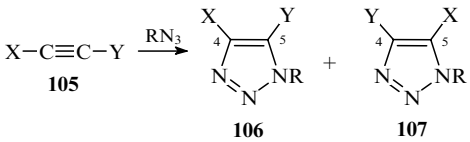
The azide group bound in the complex with Mn(I) **101** proved to undergo cycloaddition to dimethyl acetylenedicarboxylate (DMAD) at room temperature. This yields (under kinetic control) 1-triazolate complex **102**, which is converted into thermodynamically more stable 2-triazolate complex **103**.[173] Treatment of this product with HCl results in triazole-4,5-dicarboxylic acid **104**.



The phenylpalladium(II) azide complex shows a similar behaviour in the reaction with DMAD.[174] A series of 2-allyltriazoles have been obtained in a three-component condensation of allyl methyl carbonate, trimethylsilyl azide and a substituted acetylene catalysed by a Pd(0) complex. Presumably, a π-allylpalladium azide complex is formed first; then it undergoes 1,3-dipolar cycloaddition at the triple bond to give 1-(η^3-allylpalladium)triazoles; these rearrange to 2-(η^3-allylpalladium)triazoles, which are converted into 2-substituted triazoles, formed in moderate yields, through reductive elimination of Pd(0).[175]

The cycloaddition to a triple bond proceeds more easily with organic azides than with inorganic ones, especially when the alkyne molecule contains substituents.[2] This reaction underlies the development of synthetic routes to numerous N-substituted 1,2,3-triazoles. For instance, substituted 1-trityltriazoles have been prepared by the reaction of acetylene with sterically hindered trityl azides carried out by heating in various organic solvents under a pressure of up to 20 kg cm^{-2}.[176]

The cycloaddition of aryl azides and benzyl azides to substituted acetylenes containing electron-withdrawing groups proceeds most easily.[18] In the case of symmetric alkynes **105** (X = Y), one product is formed, while the reactions with asymmetric alkynes **105** (X ≠ Y) may yield both regioisomers **106** and **107**.[177]

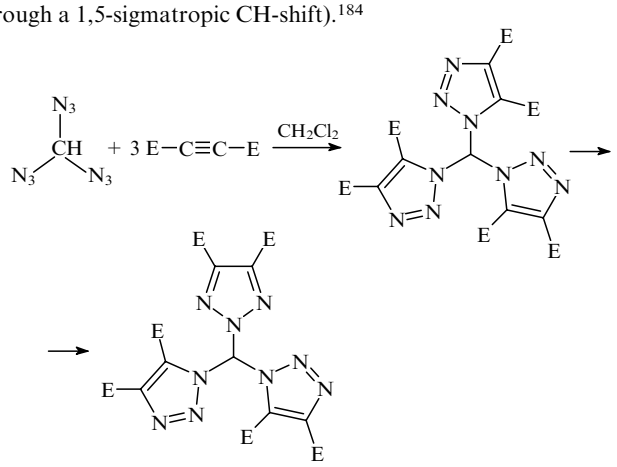


R = Ph, Bn: X = H, CO_2Me; Y = Ph, CO_2Me, CO_2Et;
R = 4-C_5F_4N: X = H, Y = Ph; R = $Ph(CH_2)_n$: X = H,
Y = CONHBn; *n* = 1, 3.

The formation of both regioisomers has also been noted for the reactions of pentafluorophenyl azide and 4-azidotetrafluoropyridine with phenylacetylene[178] and benzyl azide and 3-phenylpropyl azide with acetylenic amides **105** (X = H, Y = CONHBn).[179] In the last-mentioned case, the 1,4-regioiso-

mers **107** were formed in substantially predominant amounts, which was attributed to lower steric strain in these compounds compared to the 1,5-isomers **106**.

Dimethyl acetylenedicarboxylate is often used as the starting alkyne, and then the chemical modification of both ester groups is carried out for the preparation of various 4,5-bifunctional 1-aryltriazoles.[180–183] Diazido- and triazidomethanes readily react with DMAD to afford bis- and tris(triazol-1-yl)methanes; however, in the latter compound, one triazole ring isomerises (apparently, through a 1,5-sigmatropic CH-shift).[184]



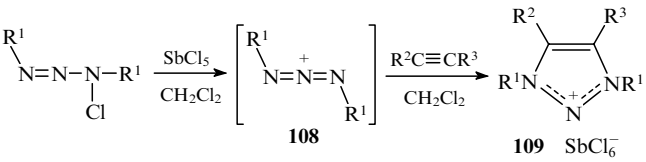
E = CO_2Me.

Acetylene dicarboxylic acid diamide is much less reactive than DMAD and requires more rigorous conditions to be involved in reactions with organic azides.[18, 179, 185]

The hydroxymethyl and chloromethyl acetylene derivatives **105** (X = Y = CH_2OH, CH_2Cl) have been made to react with aryl azides containing various substituents in the ring (Cl, Br, MeO, NO_2).[180, 186] The functional groups were utilised for further modifications of the triazoles.

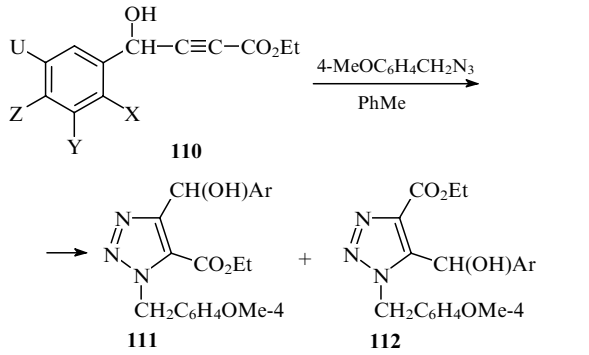
The influence of the electronic nature of the substituents in the acetylene molecule on the regiochemistry of the cycloaddition of aromatic azides can be illustrated in relation to the use of phenoxyacetylene and methylpropiolate as dipolarophiles; this results in 1-aryl-substituted 5-phenoxytriazoles[187] and 4-methoxycarbonyltriazoles.[188, 189]

The nitrogen heteroallene cations **108** (1,3-diaza-2-azoniaallene salts) can also enter into cycloaddition with substituted acetylenes, giving rise to 1,2,3-triazolium salts **109**.[190, 191]



R^1 = 4-MeC_6H_4, 4-ClC_6H_4, 2,4,6-$Cl_3C_6H_2$; R^2 = R^3 = H, Me, Et, Bu^n, Bu^t, $HOCH_2$, $ClCH_2$, Ph, CO_2Me.

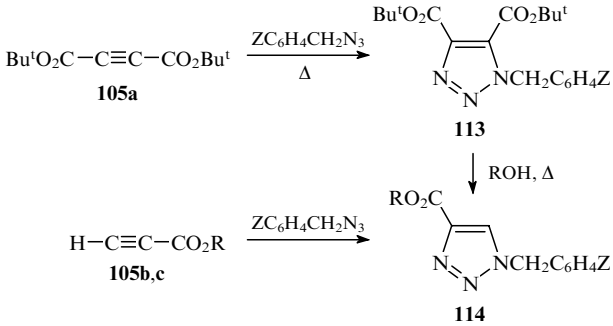
A large series of 4,5-disubstituted and 4(5)-monosubstituted 1-benzyltriazoles have been prepared on the basis of substituted benzyl azides $RC_6H_4CH_2N_3$, where R = H, 2-Me, 3-Me, 4-Me, 3-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-NO_2, 3-NO_2, and 4-NO_2, which were made to react with DMAD, phenylacetylene and ethyl propiolate.[177] It was shown that the reaction of benzyl azides with unsubstituted ethyl propiolate, unlike the reaction with phenylacetylene, is strictly regioselective, giving rise to 1-benzyl-4-ethoxycarbonyltriazoles. However, when a terminal group is introduced into the ethyl propiolate, both regioisomers are formed. Thus the cyclocondensation of ethyl 4-aryl-4-hydroxybut-2-ynoates **110** with 4-methoxybenzyl azide gives, most often, mixtures of ethyl 1-(4-methoxybenzyl)triazole-4(5)-carboxylates **111** and **112** in ~1 : 1 ratio. Only in two cases was the ratio different (3 : 1 for X = NO_2, Y = U = H, Z = NHAc and 1 : 1.5 for X = $NHCOOCH_2Ph$, Y = U = H, Z = CF_3).[192]



X = NO_2, $NHCO_2CH_2Ph$; Y = H, Me, MeO; Z = H, Me, CF_3, MeO, Pr^iO, NHAc, $NHCO_2Bu^t$; U = H, Me, MeO, Pr^iO, $MeOCH_2O$.

The cyclisation of substituted 2-fluorobenzyl azides with acetylenic acid derivatives **105** (X = H, Y = CO_2H, $CONH_2$; X = Y = CO_2Me; X = Y = $CONH_2$) has been carried out on heating in toluene, dioxane or DMSO.[193, 194]

The influence of solvents on the course of 1,3-dipolar cycloaddition of di-*tert*-butylacetylenedicarboxylate **105a** to substituted benzyl azides and the concomitant transformations of ester groups in the triazole ring has been studied.[195]



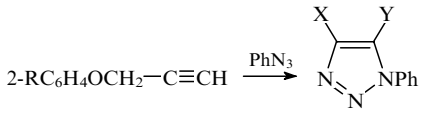
Z = H, 2-Me, 3-Me, 4-Me, 3-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2; R = Me (**b**), Et (**c**).

It was found that the reaction proceeds much more slowly in boiling benzene or THF than in methanol or ethanol and results in the expected 4,5-bis-*tert*-butyl esters **113** (yields 73% – 94%). However, long-term refluxing of functionally substituted benzyl azides (Z ≠ H, Me) in alcohols results in trans-esterification with partial decarboxylation. This affords 4-alkoxycarbonyltriazoles **114**, whose formation has been confirmed by alternative synthesis from alkynes **105b**,**c** (yields 88% – 95%).

Protected acetylenedicarboxaldehydes can be involved in reactions with azides. During the reactions, the acetal protection is removed. For example, bis[(4,5-diformyltriazol-1-yl)methyl]-benzene acetal has been obtained from bis(azidomethyl)benzene and acetylenedicarboxaldehyde bis(diethyl acetal).[196]

Using the same azide, bis(triazolylmethyl)benzene has been prepared with dibenzoylacetylene as the dipolarophile.[197]

4,5-Diaroyloxymethyl-1-phenyltriazoles are produced from phenyl azide and symmetric bis(aroyloxymethyl) derivatives of acetylene **105** (X = Y = CH_2OCOAr).[198] In the case of monosubstituted acetylenes **105** (X = H; Y = CH_2OCOAr, CH_2OAr, CH_2OH), the reaction gives mixtures of 4- and 5-substituted 1-aryltriazole isomers, for example, compounds **115** and **116** (see the studies[199–201]) with predominance of the former compound.

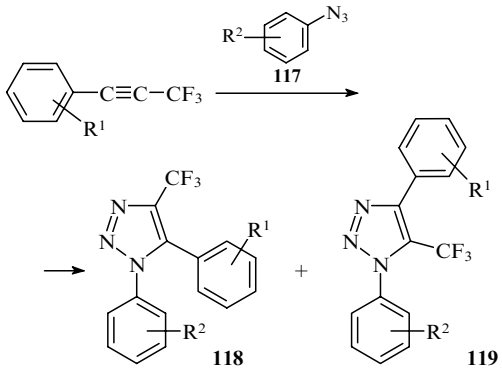


115: X = $CH_2OC_6H_4R$-2, Y = H;
116: X = H, Y = $CH_2OC_6H_4R$-2

R = H, Me, F, Cl, Br, I, NO_2.

Propargylthio derivatives also react with organic azides. 1-Pyrazolyl-2-propargylthiobenzoimidazole was converted into the corresponding triazolylmethylthiobenzoimidazole derivative.[202] The synthesis of 1-[(triazol-1-yl)methyl]-1,5-benzodiazepine by the reaction of 1-propargyl-4-phenyl-1,5-benzodiazepin-2-one with benzyl azide has been reported.[203]

The cycloaddition reaction of substituted trifluoromethylphenylacetylenes with aryl azides **117** showed a high regioselectivity; as expected,[204] the 4-CF_3 regioisomer **118** predominated in all cases. This was confirmed by quantum-chemical calculations for the frontier orbitals of the reacting species.[205, 206]



R^1	R^2	The ratio **118** : **119**
2-Cl	H	93 : 7
4-Cl	H	82 : 18
4-NO_2	H	72 : 28
4-MeO	H	80 : 20
4-NH_2	H	88 : 12
4-NO_2	2,6-Cl_2	71 : 29
4-MeO	2,6-Cl_2	79 : 21
4-Cl	4-NO_2	80 : 20

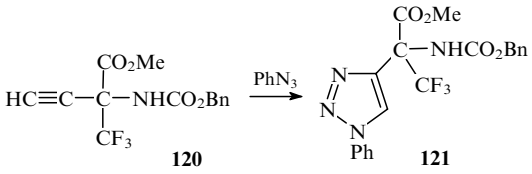
The calculations showed that on introduction of an electron-withdrawing CF_3 group, the reaction obeys orbital control and the transition state leading to regioisomer **118** becomes preferred. It is noteworthy that the theory of frontier orbitals is not always able to predict quantitatively the isomer ratio. For this purpose, it is proposed to calculate the local electron density indices in terms of electron density functional theory, which are sensitive to changes in the chemical potential upon the introduction of substituents.[207]

Although the nature of the substituents in both phenyl groups has little influence on the cycloaddition regioselectivity, it does influence the reaction rate (the presence of electron-withdrawing NO_2 group in the azide molecule retards the process).[204]

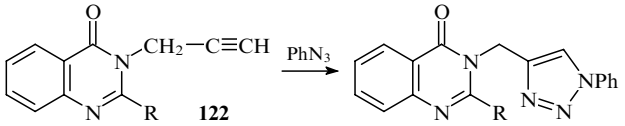
The reaction of pentafluorophenylacetylene with aryl azides affords only the 1,4-regioisomer, which corresponds to the electron density distribution in the reacting molecules;[208] the reaction of conjugated trifluoromethyldiacetylenes with phenyl azide involves only one triple bond, which carries the CF_3 group, and also results in one 1,4-isomer.[208]

The similar effect of an electron-withdrawing substituent (CO_2Alk) at the triple bond of the alkyne on the regioselectivity of cycloaddition with phenyl azide is also observed for methyl 3-phenylpropiolate and methylbut-2-ynoate, which were converted into 4- and 5-methoxycarbonyl-substituted triazoles in 66 : 34 and 70 : 30 ratios, respectively.[209] A similar result has been obtained in reactions of a chiral azide, 1-[(*R*)-3-azido-3-cyclohexylpropanoyl]pyrrolidin-2-ol, with methyl propiolate and ethyl but-2-ynoate [210] and a number of aryl azides with methyl 4-oxo(or hydroxy)but-2-ynoates.[211, 212] However, in the case of 1-phenylseleno-2-(*p*-tolylsulfonyl)acetylene, triazole with the tosyl group at the 5-position is formed predominantly.[213]

The bulky Me_3Si group in the acetylene molecule is favourable for the formation of 1-(het)aryl-4-trimethylsilyltriazoles in the reaction of trimethylsilylacetylene **105** (X = H, Y = $SiMe_3$) with aryl azides and azido derivatives of seleno(thio)phene.[214, 215] These examples were used to establish the logarithmic dependence of the reaction rate on the pressure and to select the optimal conditions for the preparation of 1,4-disubstituted triazoles (20 °C, ~1 GPa).[216] The presence of the bulky tertiary substituent in the propargylamine **120** molecule is also favourable for the formation of only 4-substituted 1-phenyltriazole **121** in a high yield.[217]



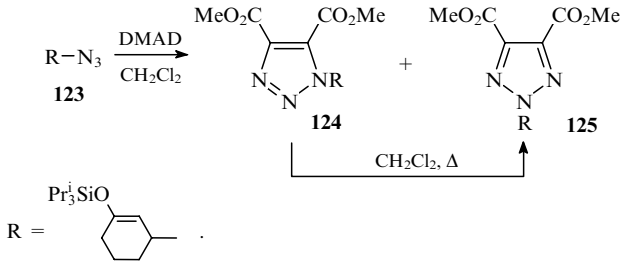
Steric factors may be responsible for the predominant formation of 4-substituted 1-phenyltriazoles upon the reaction of phenyl azide with *tert*-butyl 2-(*tert*-butyloxycarbonylamino)-4-oxohex-5-ynoate [218, 219] and trimethylstannylacetylene.[220] A similar result has been obtained in the reaction of phenyl azide with 3-propargylquinazolones **122**.[221]



R = H, Me, Ph.

Thus, 1,3-dipolar cycloaddition of aliphatic and aromatic azides to terminal alkynes under kinetic control conditions results in the corresponding 1,4-disubstituted triazoles.

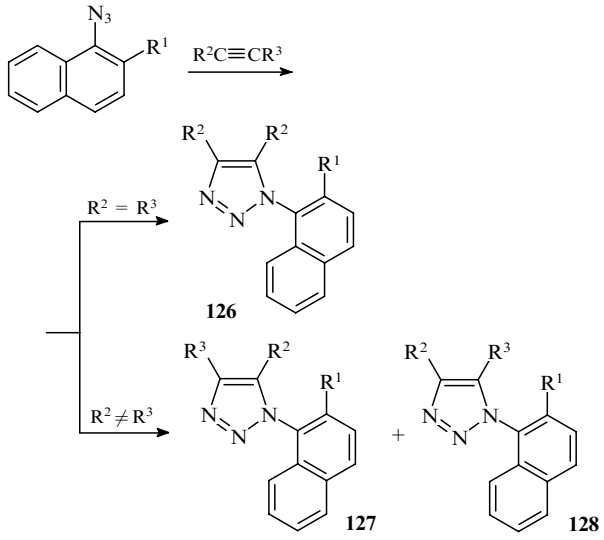
The formation of an unusual isomer was detected in the reaction with a symmetrical alkyne. Monitoring of the reaction of the triisopropylsilyl ether of the enol of 3-azido cyclohexanone **123** with DMAD in boiling CH_2Cl_2 has shown that 1-cyclohexenol triazole derivative **124** is formed initially; after 17 h, the presence of substantial amounts of the 2-isomer **125** can be detected (the yields are 27% and 45%, respectively); after 72 h, only triazole **125** remains in the reaction mixture.[222]



This fact suggests that 1-substituted triazole **124** is ionised under the given conditions followed by recombination of ions into thermodynamically more stable 2-isomer **125**. The suggestion is based on new theoretical and experimental data on triazole [223, 224] and benzotriazole [225, 226] tautomerism.

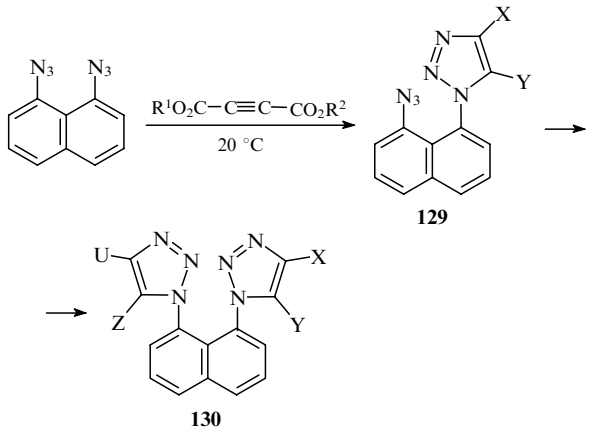
Cycloaddition of 1-naphthyl azides to symmetrical disubstituted alkynes also proceeds under relatively mild conditions to give 4,5-disubstituted 1-naphthyltriazole **126**,[182] whereas the reaction with asymmetric alkynes yields predominantly 4-substituted 1-naphthyltriazole **127**.[24, 227] Thus in the reaction of 1-naphthyl azide with ethyl propiolate, the yield of the 4-ethoxycarbonyl

derivative **127** ($R^1 = R^2 = H$, $R^3 = CO_2Et$) amounts to 71%, and the yield of 5-regioisomer **128** ($R^1 = R^2 = H$, $R^3 = CO_2Et$) is only 18%.[227]



R^1 = H, Me: $R^2 = R^3 = CO_2Et$; R^2 = H, $R^3 = CO_2Et$; R^2 = Me, $R^3 = CO_2Me$.

In the presence of two azido groups located in the *peri*-positions, the reaction with diethyl acetylenedicarboxylate proceeds in several stages: first, two isomeric monotriazolylnaphthalenes **129** are formed, the 4-ethoxycarbonyl derivative (Y = H, X = CO_2Et) being the predominant isomer; on long-term keeping of the reaction mixture, a mixture of 1,8-ditriazolylnaphthalenes **130** is formed.[227]



X	Y	Z	U	Yield of **130** (%) [a]
CO_2Et	H	H	CO_2Et	52
CO_2Et	H	CO_2Et	H	24
H	CO_2Et	CO_2Et	H	2

[a] For $R^1 = R^2 = Et$.

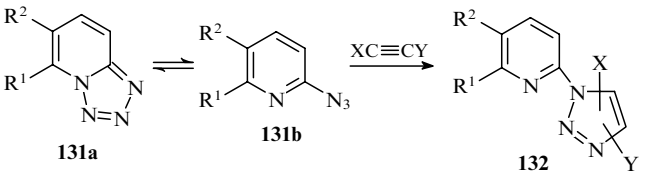
Various dialkyl acetylenedicarboxylates ($R^1 \neq R^2$) have been employed in the cyclocondensation with 1,8-diazidonaphthalene. The subsequent chemical transformations of the azide and ester groups gave rise to diverse functional derivatives **130**.[227–229]

Recently, it has been found that Cu(I)-catalysed cycloaddition of azides to terminal acetylenes is regiospecific and gives 1,4-disubstituted triazoles.[230–236] The use of encapsulation techniques in the reaction of phenyl azide with phenylacetylene made it possible not only to increase appreciably the reaction rate but also to obtain the only isomer, 1,4-diphenyltriazole.[237]

A new, in principle, method for regiocontrol of the dipolar cycloaddition, based on the chemical recognition principle, has been proposed.[238] The method implies selective spatial fixation of the reacting molecules of a dipolar compound and a dipolarophile. A crown ether fragment (in the azide molecule) and a terminal ammonium group (in the substituted acetylene molecule) are used as the structural blocks than ensure the chemical recognition. Due to the formation of a bound complex between these blocks, the cycloaddition becomes pseudo-intramolecular, which facilitates the reaction and markedly increases the regioselectivity (only 3% of the second regioisomer) compared to the model reaction carried out without complex formation (in this case, up to 43% of the second isomer is formed).[238]

Heterocyclic azides have also been used in reactions with acetylene derivatives, for example, 6-azido-2,3-diphenylindole,[239] tetrathiafulvalene azido derivatives,[240] fluoroquinolonecarboxylic acid azido derivatives[241] and azidobenzo[*b*]thiophenes.[214, 242] 9-Azidoacridine reacts with alkynes to give regioisomers of 9-(4,5-disubstituted 1*H*-1,2,3-triazol-1-yl)acridines; only in the case of trimethylsilylacetylene, does the reaction proceed regioselectively.[243] The attempts to introduce acetylene and its homologues into the reaction with 5- and 6-azido-2-methylbenzothiazoles did not lead to the desired outcome, whereas the use of more reactive organomagnesium derivatives RC≡CMgBr (R = Me, Ph) (Iotsich complexes) made it possible to obtain the corresponding 1,5-disubstituted triazoles.[244]

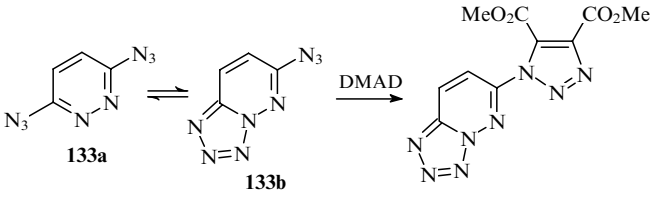
For azido derivatives of azines, the influence of additional factors on the cycloaddition reaction has been noted. On the one hand, the electron-withdrawing properties of the heterocycle favour polarisation of the azide fragment. On the other hand, in the case of α-isomers, there exists a tautomeric equilibrium between the azidoazine and the cyclic form, tetrazoloazine, the stability of which is determined by the nature and the positions of substituents in the azine ring. The influence of these factors accounts for the different reactivities of substituted 2-azidopyridines **131** upon reaction with DMAD. Previously, it has been shown[245] that 2-azido-6-chloropyridine **131** (R^1 = Cl, R^2 = H) forms the corresponding 1-pyridyltriazole **132** (R^1 = Cl, R^2 = H) in boiling chloroform, whereas unsubstituted 2-azidopyridine and its 5-derivatives (R^1 = H; R^2 = H, Br, NO_2) react with DMAD only on strong heating in the absence of a solvent. The reaction of 2-azidopyridine with methyl propiolate (X = H, Y = CO_2Me) and diphenylacetylene (X = Y = Ph) proceeds in a similar way.[246] The 6-CF_3 derivative reacts with phenylacetylene to give a mixture of 4- and 5-regioisomers in ~1 : 1 ratio.[247]



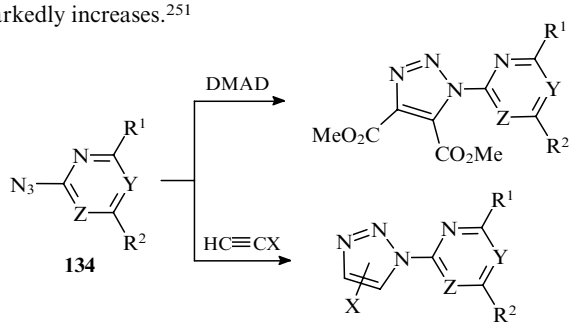
R^1 = H, Cl, CF_3; R^2 = H, Br, NO_2; X = Y = CO_2Me; X = Y = Ph; X = H: Y = CO_2Me, Ph.

According to a publication,[248] 4- and 6-substituted (by Cl, Br, CF_3) 2-azidopyridines form 1-pyridyl-4-methoxycarbonyltriazoles in high yields on refluxing with methyl propiolate in $CHCl_3$. 4-Azidotetrafluoropyridine reacts with diphenylacetylene on heating in CCl_4; however, the yield of the cycloadduct is very low under these conditions.[249]

The reaction of azido derivatives of pyrimidine and pyrazine with DMAD and methyl propiolate takes place under milder conditions than the reaction with azidopyridines due to the stronger electron-withdrawing properties of the heterocycle.[246, 250] 3,6-Diazidopyridazine **133a** reacts with transformation of only one azido group even under drastic conditions, because the second azido group exists predominantly in the cyclic tetrazole form (tautomer **133b**).[250]



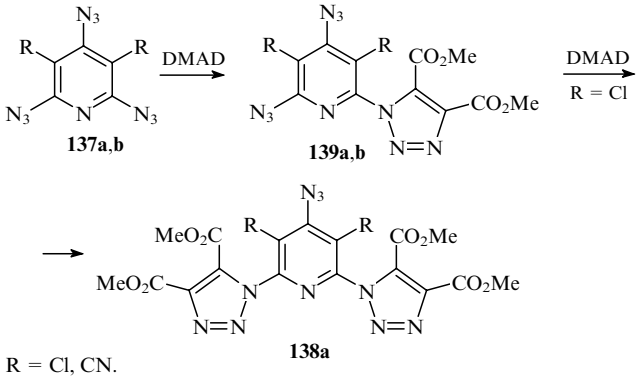
2- and 4-Azidopyrimidines **134**, containing a phenyl and/or *o*-hydroxyphenyl group in the heterocycle react with DMAD, phenylacetylene and propargyl alcohol to give substituted 1-pyrimidyltriazoles in 70%–90% yields. It was found that conducting the reaction at 140 °C in the presence of excess alkyne is optimal, whereas on heating in solvents, the reaction time markedly increases.[251]



Y = CH, Z = N; Y = N, Z = CH; R^1, R^2 = H, Ph, 2-HOC_6H_4; X = Ph, CH_2OH.

On the basis of cycloaddition of 6-azidouracils to DMAD and phenylacetylene, a method for the synthesis of new potentially biologically active triazolyluracils has been developed.[252] This reaction readily proceeds on refluxing in toluene and the product yields are high. Recently, it has been shown that a broad range of mono- and bis(triazolyl)pyrimidines can be synthesised on the basis of diazidopyrimidines and acetylenic dipolarophiles. The presence of an active azido group in the pyrimidine ring of the monosubstituted derivatives permits the nucleophilic substitution of this group by various functional groups. Moreover, azidation of triazolylpyrimidines demonstrated nucleofugicity of the 1*H*-1,2,3-triazolyl fragment,[253] whose mobility is governed by the nature of substituents in the pyrimidine and triazole rings (Scheme 3). The researchers cited found an unusual reaction of bis(triazolyl)pyrimidine **135** with acetylacetone, which can be formally considered as replacement of two carbon fragments of DMAD by the corresponding fragments of 'dehydrated' acetylacetone ('Ac–C≡C–Me') to give compound **136** (see Section IV.3).

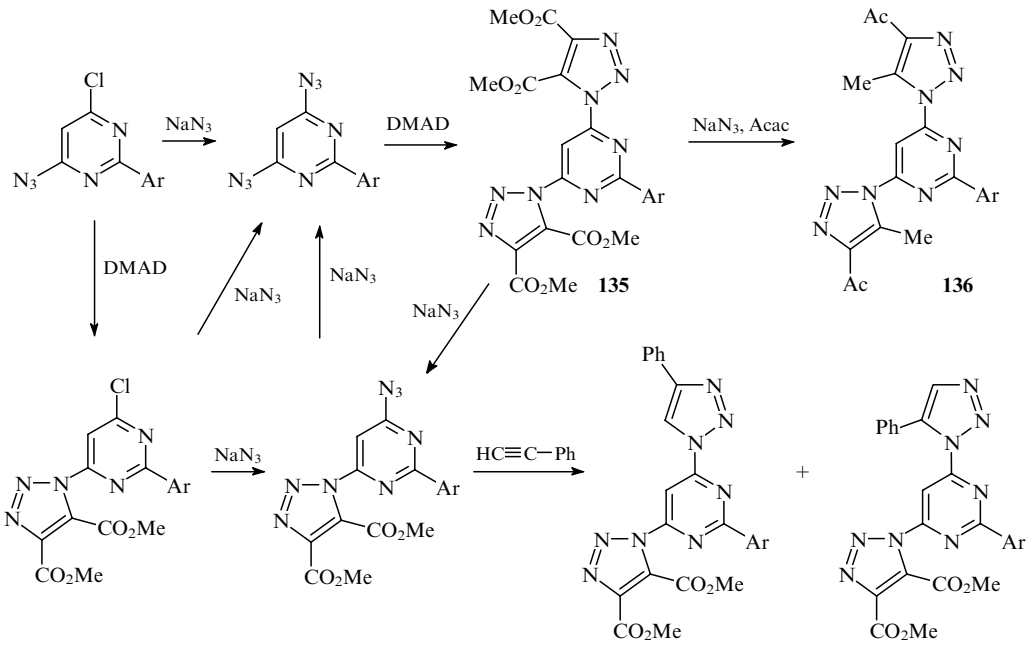
When the pyridine ring contains three azide groups at the 2-, 4- and 6-positions, the route and level of the cycloaddition depend to a large extent on the nature of the dipolarophile. Using triazidopyridine **137** as an example, it was found that two DMAD molecules easily add to 2- and 6-azido groups yielding bis(triazolyl)pyridine **138a** in a high yield.[254–256]



R = Cl, CN.

On the basis of quantum-chemical calculations (PM3), it has been shown that the electron densities on the frontier orbitals are different for the α- and γ-azide groups in molecule **137a**. For example, the HOMO has a high orbital density on the α-azide group and a low density on the γ-analogue, which results in reactions with electron-deficient dipolarophiles (for example, DMAD) at the azide group in the 2-position. Conversely, the higher orbital density on the γ-azide group in the LUMO of molecule **137a** is favourable for reactions with electron-enriched dipolarophiles (for example, with norbornene) to give aziridine. It also follows from the calculations that the presence of the triazolyl group in molecule **139a** does not change the situation significantly, and therefore, the reaction with DMAD further involves the second α-azido group.[255] A similar reaction of a more electron-deficient dicyano-substituted pyridine **137b** with DMAD stops after the formation of the monoadduct 2,4-diazido-6-triazolyl-3,5-dicyanopyridine **139b** (yield 34%).[257] The thermal reaction of

Scheme 3

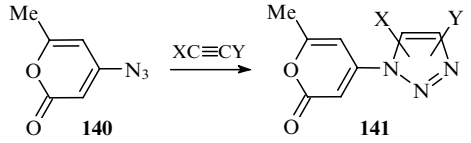


Acac is acetylacetone.

4-azido-2,6-bis-(2-pyridyl)pyridine with DMAD gives the 2*H*-azirine derivative rather than triazole.[258]

7-R-8-Azidoquinolines (R = H, Me) readily react with DMAD and dehydrobenzene to give esters of 1-(8-quinolyl)triazole-4,5-dicarboxylic acids and benzotriazole, respectively, in high yields.[259]

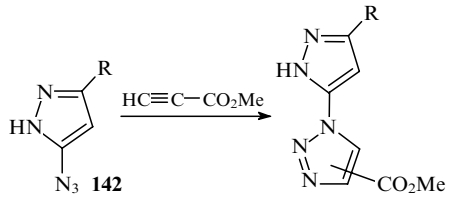
On heating with symmetric alkynes (X = Y), 4-azido-6-methyl-2*H*-pyran-2-one **140** gives disubstituted triazolylpyrones **141** in high yields.[260] In the case of phenylacetylene (X = H, Y = Ph), the reaction products contain both regioisomers, 5-phenyl-substituted triazole **141** (Y = 5-Ph) somewhat predominating over the 4-regioisomer **141** (Y = 4-Ph), whereas ethoxyacetylene (X = H, Y = OEt) furnishes only 5-ethoxytriazole **141** (Y = 5-OEt).[260]



X = Y = Ph; X = Y = CH_2OH; X = H, Y = Ph; X = H, Y = OEt.

A series of 4-(triazol-1-yl)-2*H*-benzopyran-2-ones have been prepared by cyclocondensation of 7-diethylamino-4-azidobenzopyranone with mono- and disubstituted acetylenes (H, Ph, CH_2Cl and CH_2OH as substituents).[261]

Examples of the synthesis of azolyltriazoles have been reported. 5-Azidopyrazoles **142** were used for the synthesis of pyrazolyltriazoles. It was found that the reaction with methyl propiolate takes place on refluxing the reactants in acetonitrile or toluene; 4-regioisomers predominated in the reaction products.[48,262] The cyclocondensation with DMAD occurs in the usual way; dipolarophiles such as phenylacetylene, ethyl phenylpropiolate and ethyltrimethylsilyl propiolate proved insufficiently reactive and did not enter into this reaction.[262]



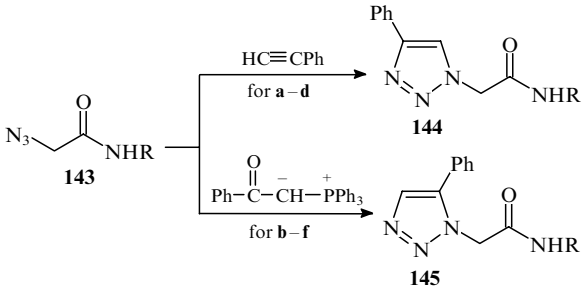
R = Ph (45%); H, Bu^t (79%–86%).

2-Azidoimidazole has not been involved into the reaction with methyl propiolate even in boiling toluene,[262] whereas 5-azido-2-aryl-4-trifluoromethylthiazoles (Ar = 2-thienyl, 2-furyl, 4-MeC_6H_4) form mixtures of the corresponding substituted (triazol-1-yl)thiazoles.[263,264]

The synthesis of some (triazol-1-yl)oxazolines[265] and furazans[266,267] have been described. In relation to the reaction of 3-azido-4-aminofurazan with ethoxycarbonylacetylenes, it was shown that the use of an ionic liquid as the reaction medium shortens the time of synthesis several-fold.[268]

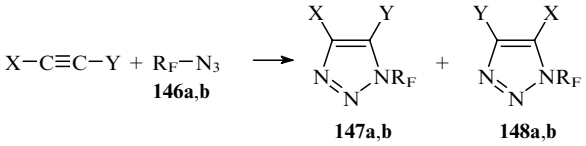
Despite the fact that examples of the use of various alkynes and azides in 1,3-dipolar cycloadditions are quite diverse and have been considered previously in many publications, the range of reagents used to prepare new triazole derivatives has been markedly extended in recent years. For example, dehydrobenzenes and 2,3-dehydronaphthalene generated in the reaction mixture *in situ* have been used in this reaction as dipolarophiles. This resulted in the synthesis of a series of substituted 1-naphthylbenzotriazoles and 1-(2-methyl-1-naphthyl)naphtho[2,3-*c*]triazole.[259]

Various alkyl azides[269–272] and amidoalkyl azides **143**[273] have been made to react with asymmetric acetylene derivatives. This was found to give predominantly 1,4-disubstituted triazoles **144**. An exception is acetophenone triphenylphosphorus ylide (formally, the latent form of phenylacetylene), which reacts with amidoalkyl azides **143** to give the corresponding 5-phenyl isomers **145** in high yields.[273]



R = Ph (**a**), 2-MeC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 2-ClC_6H_4 (**d**), 4-ClC_6H_4 (**e**), Bn (**f**).

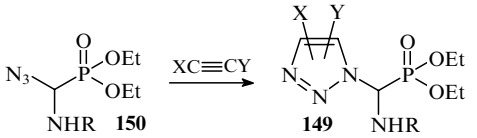
The earlier attempts to involve fluorinated alkyl azides into cycloaddition with diphenylacetylene have failed.[274] However, recently, reactions of 2*H*-perfluoropropyl azide **146a** and methyl 3-azidoperfluoropropionate with various acetylene derivatives have been carried out.[275] The reaction with monosubstituted acetylenes is carried out in an autoclave with heating to 90–130 °C, while that with disubstituted acetylenes is carried out at 170 °C. The regioselectivity of cycloaddition (ratio of **147**:**148** isomers) depends on the type of substituents in the reactants.



X = Bu^n, Ph, CO_2Me, $SiMe_3$; Y = H, Ph, CO_2Me; R_F = CF_3CHFCF_2 (**a**), $MeO_2C(CF_2)_2$ (**b**).

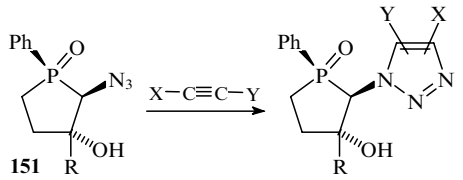
X	Y	Yields (%)	
		147a	**148a**
Ph	H	32	62
Bu^n	H	37	58
CO_2Me	H	70	18
$SiMe_3$	H	50	–
CO_2Me	CO_2Me	96	–
Ph	Ph	88	–
$SiMe_3$	Ph	35	5

Derivatives of α-azido-α-amino acids have also been used as substrates in reactions with dipolarophiles.[276,277] Esters of α-amino-α-(triazol-1-yl)phosphonic acid **149** are readily formed upon condensation of diethyl α-azido-α-aminophosphonic acid **150** with alkynes.[278,279] In the case of monosubstituted acetylenes (X = H; Y = Bu, CH_2Cl, CH_2Br), the 1,4-disubstituted triazole to 1,5-isomer ratio in the reaction products varies from 2:1 to 5:1; in other cases, the 5-regioisomer is detected in only minor amounts.



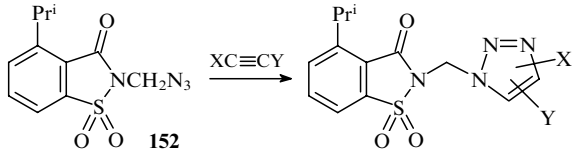
R = PhCO, $CO_2CH_2CCl_3$; X = H, Ph, CO_2Me; Y = Bu^n, CH_2Cl, CH_2Br, PrCH(OH), Ph, CO_2Me, CO_2Et.

Several publications are devoted to cycloaddition to alkynes of other phosphorus-containing azides: ω-azidoalkyltriphenylphosphonium bromides[280] and azidomethylphosphonates.[281–284] From 2-azido-3-hydroxy-1-phenylphospholane 1-oxides **151**, a number of optically active triazole derivatives have been prepared.[285–290]



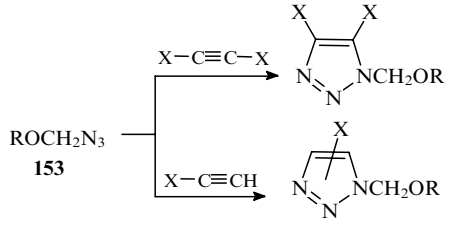
R = H, Alk; X, Y = H, Alk, CO_2Alk.

The influence of spatial factors on the regioselectivity of the cycloaddition to asymmetrical alkynes has been studied in relation to the reaction of the azidomethyl derivative of sulfone **152**.[291] The regioselectivity was found to be controlled by the steric effects of the substituents X and Y. As the substituent bulk increases in the series H < Ph < Bu^t < Me_3Si, the ratio of the regioisomers in the reaction products varies in parallel, except for the Me_3Si group. The steric effect of the last-mentioned group acts in the same direction as the electronic effect, whose role is to stabilise the induced positive charge on the acetylene β-carbon atom in the transition state. Both effects promote the formation of 4-trimethylsilyl isomers as the only products in high yields. An increase in the pressure to 10 kbar increases substantially the reaction rate.[291]



X = H: Y = CO_2Me, $SiMe_3$, SO_2Ph; X = Ph, Y = CO_2Et;
X = Bu^t, Y = SO_2Ph; X = $SiMe_3$: Y = CO_2Me, SO_2Ph, SO_2NMe_2.

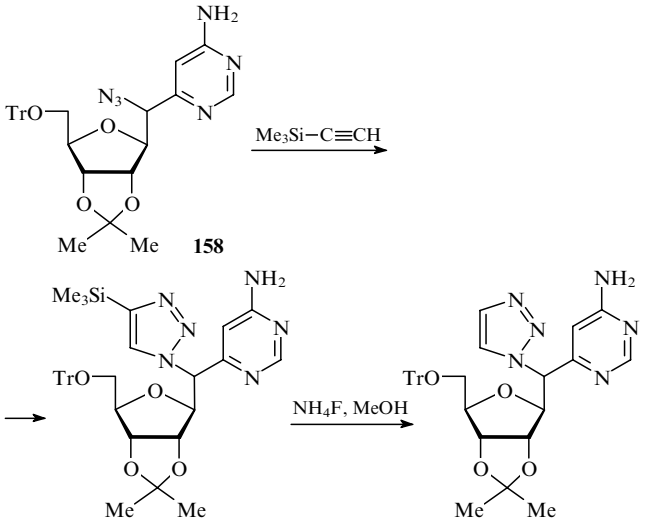
The 1,3-dipolar cycloaddition of the substituted alkoxymethyl azides **153** to symmetrical and asymmetrical alkynes has been used to prepare an extensive series of 1-alkoxymethyltriazole derivatives.[292] The yields of the isolated compounds varied from 11% to 95%; the low yields can be attributed to the low thermal stability of the starting alkyl azides.



R = $HO(CH_2)_2$, $MeO_2C(CH_2)_2$, $BnO(CH_2)_2$, $(BnOCH_2)_2CH$, $BnO(BnOCH_2)CHCH_2$; X = CO_2Me, Ph, 4-ClC_6H_4, 2-Py.

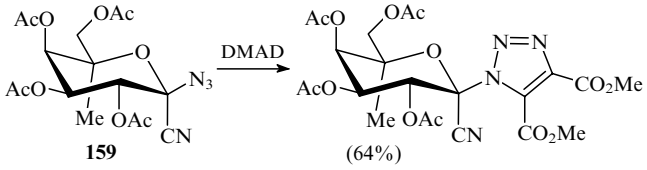
Interesting results have been obtained[293] by refluxing 2-(4-pyridyl)ethyl azide **154** with substituted acetylenes in toluene. In the case of phenylacetylene, a mixture of 4- and 5-phenyl-2-(4-pyridyl)ethyltriazole **155** was synthesised (regioisomer ratio 1 : 2, quantitative yield). If the reaction is carried out with diphenylacetylene, 4,5-diphenyltriazole **156a** is formed in a relatively low yield. In the case of dibenzoylacetylene, in addition to 4,5-dibenzoyl derivative **156b**, the rearrangement product **157b** was obtained (yield 8%, **156b** : **157b** = 4 : 1). The compounds **155**, **156a**, which are quaternised at the pyridine nitrogen atom, undergo the retro-Michael rearrangement to give 1-unsubstituted triazoles (Scheme 4).[293]

The synthesis of a number of β-lactams containing a triazolyl group from the corresponding azides has been described.[294] New-type homo-C-nucleosides have been obtained by the 1,3-dipolar cycloaddition of trimethylsilylacetylene to the azide groups of 4-amino-6-(ribofuranosyl)azidomethylpyrimidine **158** epimers.[295, 296]

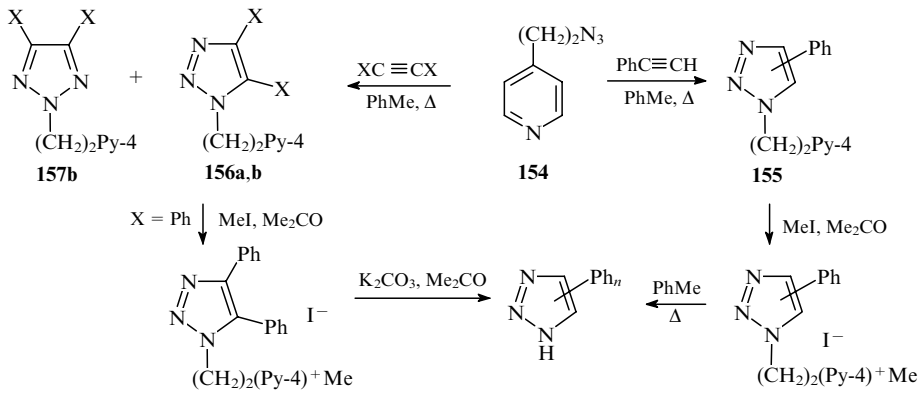


Tr is triphenylmethyl (trityl).

Quite a few examples of using this strategy for the preparation of glycosylated triazoles from azido derivatives are documented. Thus on refluxing in toluene with DMAD, acetylated 1-azidoglycopyranosyl cyanide **159** gives the cycloaddition product in a good yield.[297–299]



Scheme 4



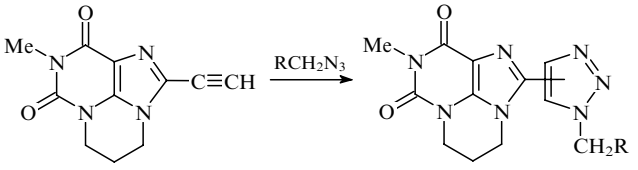
X = Ph (**a**), COPh (**b**); *n* = 1, 2.

Under the same conditions, DMAD reacts with 3-azido-3-deoxy-α-D-glucofuranose derivatives [298, 300] and with 6-azido-6-deoxycyclodextrins.[301, 302] The reactions of acetylated cellobiosyl, lactosyl, maltosyl and melibiosyl azides with various esters of acetylenedicarboxylic acid affords the corresponding 1-glycobiosyltriazoles, which were used in the synthesis of oligosaccharides and anthracycline antibiotics.[303]

The reactions of 5-azido-5-deoxy-α-D-xylofuranose derivatives, methyl 5-azido-5-deoxy-β-D-ribofuranoside and other azido sugars with various acetylene derivatives were carried out to prepare nucleoside analogues containing triazole as the nitrogenous base.[19, 231, 232, 304–315] The other compounds used as substrates in the reaction with alkynes include 3′-azido-2′,3′-dideoxythymidine and 3′-azido-2′,3′-dideoxyuridine,[185, 316] 3′-azido-3′-deoxythymidine and 5′-azido-5′-deoxythymidine,[317, 318] as well as azido derivatives of acyclonucleosides [319] and the carbocyclic analogue of furanose.[320]

The cycloaddition using a soluble polymer (based on polyethylene glycol succinate) with one of the reactants attached to it, either azide (for example, 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose) or acetylene (for example, propargyl alcohol), has been proposed.[306] Except for the reaction of polymer-supported azide with diphenylacetylene, both versions of this process give products in quantitative yields. The product is removed from the polymer support by treatment of the methanol solution with excess ammonia followed by ether precipitation of the polymer.

The reaction of organic azides with alkynes allows the use of broad ranges of both reactants. For example, various acetylene derivatives containing heterocyclic fragments were used as dipolarophiles. Pyrimido[1,2,3-*cd*]purine-8,10-dione **160** as the acetylene derivative and a number of organic azides were made to react to give 2-(4- and 5-triazolyl) derivatives (~1 : 1) of heterocyclic system **161**.[321]



160 **161** (37% – 64%)

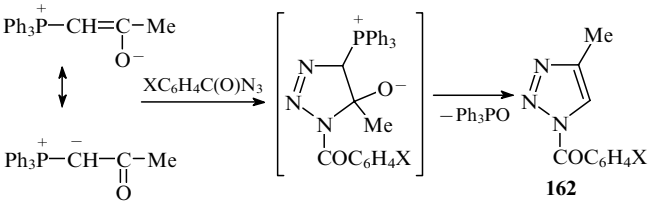
R = $HOCH_2$, $HOCH_2CH(OH)$, $HOCH_2(CHOH)_2CH(OH)$, CO_2Me, Ph.

The reaction of 9-propargylguanidine with $AcOCH_2.CH_2OCH_2N_3$ affords the 1,4- and 1,5-regioisomers in a 7 : 3 ratio (overall yield 71%).[322] The use of a $ZnCl_2$-doped natural phosphate as the catalyst allows one to shorten the reaction time by an order of magnitude without changing the yield and the isomer composition.

The dipolar 1,3-cycloaddition has been used successfully to synthesise triazole derivatives of various classes of large molecules and some polymers, in particular, crown ethers,[323, 324] rotaxanes,[325–327] pseudorotaxanes,[328] dendrimers [329] and polystyrenes.[236]

N-substituted histidine analogues have been obtained by the reaction of azides with *C*-propargylglycine, while reactions with terminal alkynes containing peptide residues gave peptidotriazoles.[230] This strategy has found application as a tool for studying proteins, for example, the protein shell of the plant mosaic virus [330] and a number of enzymes.[331] The reaction between N-protected propargylamine and the azide obtained from D-leucine is a route to cyclic peptides with triazole fragments capable of self-organisation and formation of peptide nanotubes.[234]

Numerous examples of the use of phosphorus-containing alkynes in reactions with azides have been described. 4,5-Disubstituted triazoles have been prepared on the basis of symmetric disubstituted acetylenes with diphenyl and thiophosphinoyl groups.[332, 333] Phosphorus ylides containing an α-oxo group in the chain (Wittig reagents, see above) behave similarly to electron-enriched acetylenes; they react with organic azides to give the corresponding triazoles.[2, 8, 273] This method has been used to obtain two benzoyltriazole isomers based on acetone triphenylphosphorus ylide (acetylmethyltriphenylphosphorane).[334] In a similar reaction with *o*- and *m*-phthalimidobenzoyl azides, 4-methyltriazoles **162** are formed in high yields. Presumably, the azide adds to the enol form of the ylide and this is followed by elimination of a triphenylphosphine oxide molecule.

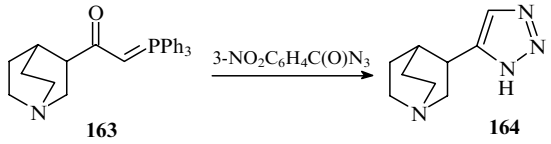


162

X = 2- and 3-phthalimido.

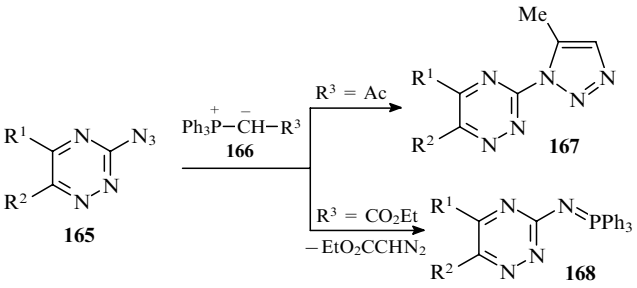
It was shown that the preparation of 1-aryl-5-substituted triazoles from aryl azides and phosphonium ylides is sharply accelerated when the reactions are initiated by microwave irradiation of the reactant mixture supported on SiO_2.[335]

The reaction of the 3-quinuclidine analogue of the Wittig reagent **163** with 3-nitrobenzoyl azide has yielded a product that was debenzoylated during chromatography on Al_2O_3, being converted into N-unsubstituted (3-quinuclidinyl)triazole **164**.[336]



163 **164**

The use of glycosyl azides as substrates in the cycloaddition of 2-oxoalkylidenetriphenylphosphoranes has been reported.[337] Azido derivatives of 5,6-diphenyl-*as*-triazine **165** and its phenanthrene analogue react with acetylmethylenetriphenylphosphorane **166** (R^3 = Ac) being converted into 1-azinyl-5-methyltriazoles **167** in high yields.[338] However, the replacement of the acetyl substituent in the phosphorane by the ethoxycarbonyl group results in the formation of only iminophosphoranes **168**. In the latter case, ethyl diazoacetate is also formed in 70% yield.[338]

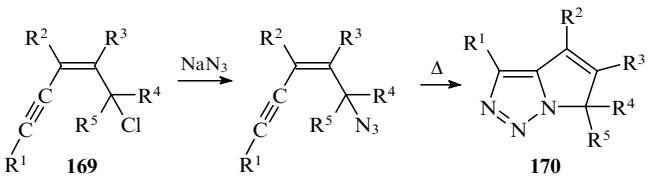


165 **166** **167** **168**

R^1 = R^2 = Ph, R^1 – R^2 = *o*,*o*′-biphenylene, R^3 = Ac, CO_2Et.

5-Substituted 1-[1-(diethoxyphosphonyl)alkyl]triazoles are formed in good yields in the reaction of diethyl 1-azidoalkylphosphonates with 2-oxoalkylidenetriphenylphosphoranes.[339] Acetyl- and benzoylphosphoranes were transformed into 4β-(triazol-1-yl)podophyllotoxin derivatives to study their cytotoxic properties.[340]

Worth mentioning are numerous examples of the combination of two functions, an azide group and a triple bond linked by an at least three-carbon bridge in one molecule. The cyclisation of the azide obtained from enyne **169** allows the synthesis of annelated triazole systems, for example, pyrrolotriazole **170**.[341]

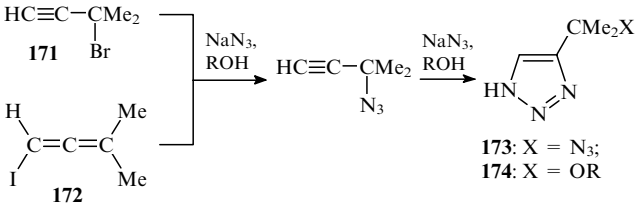


169 **170**

R^1, R^2, R^3, R^4, R^5 = H, Me; R^2-R^3 = $(CH_2)_4$.

A similar result has been attained in the case of a saturated chain of three carbon atoms.[210]

If the azide group and the triple bond are separated in the molecule by only a methylene group, the presence of nucleophilic agents is needed for cyclisation. Thus treatment of bromobutyne **171** or iodoallene **172** with sodium azide in alcohol at room temperature affords a mixture of 4-(1-azido-1-methylethyl)-1*H*-triazole **173** and 4-(1-alkoxy-1-methylethyl)-1*H*-triazole **174**.[342]

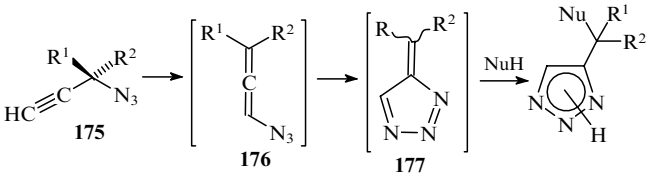


171 **172**

173: X = N_3;
174: X = OR

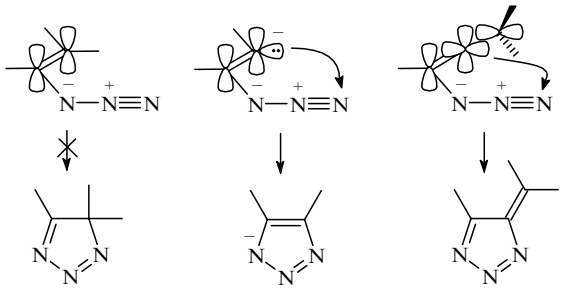
R = Me, Et.

The mechanism of the reaction that includes the rearrangement of propargyl azide **175** to short-lived allenyl azide **176**, which rapidly forms triazafulvene **177**, has been studied.[342] The last-mentioned product adds a nucleophilic molecule at the exocyclic double bond, being converted into the final product.



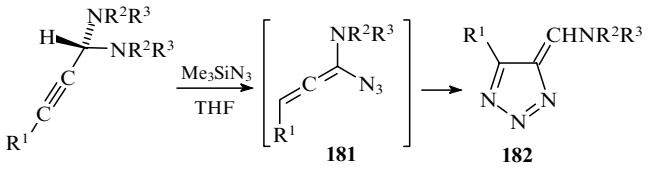
175 **176** **177**

This route was supported by an experiment with optically active 3-azido-3-methylbut-1-yne **175** (R^1 = H, R^2 = Me), where complete product racemisation was observed. These transformations cannot be accomplished in an aporotic solvent such as chloroform. It was shown that in the absence of nucleophiles, propargyl azides polymerise as a result of intermolecular 1,3-dipolar cycloaddition. The ring closure in vinyl azides takes place only for α-azidoenamines;[343] simple vinyl azides are not converted into triazoles [344] due to the low nucleophilicity of the C(5) atoms and, in some cases, also an unfavourable geometry. The probability of cyclisation becomes higher for not only the vinyl azide carbanion but also for the allenyl azide anion owing to the presence of a p orbital at the central carbon atom of the allene system.[342, 345]



The transformation of various propargyl derivatives, first into propargyl azides **178** and then into triazoles is carried out with isolation of intermediate compounds, which makes this method of synthesis safe and convenient. However, it was shown that, depending on the structure of the starting compounds and on the conditions, the reaction may give isomeric allenes and triazafulvenes, which react with nucleophiles to give isomeric N-unsubstituted triazoles,[346] for example, **179** and **180** (Scheme 5). This approach has been used to synthesise various biologically active compounds containing a triazole ring with secondary aminomethyl substituents.[166, 347–349]

Azidoaminoallenes **181**, which are formed as intermediate products in the reaction of phenylpropiolaldehyde aminals with trimethylsilyl azide, undergo intramolecular cyclisation to give 4-alkylidene-4*H*-triazoles **182**.[350]



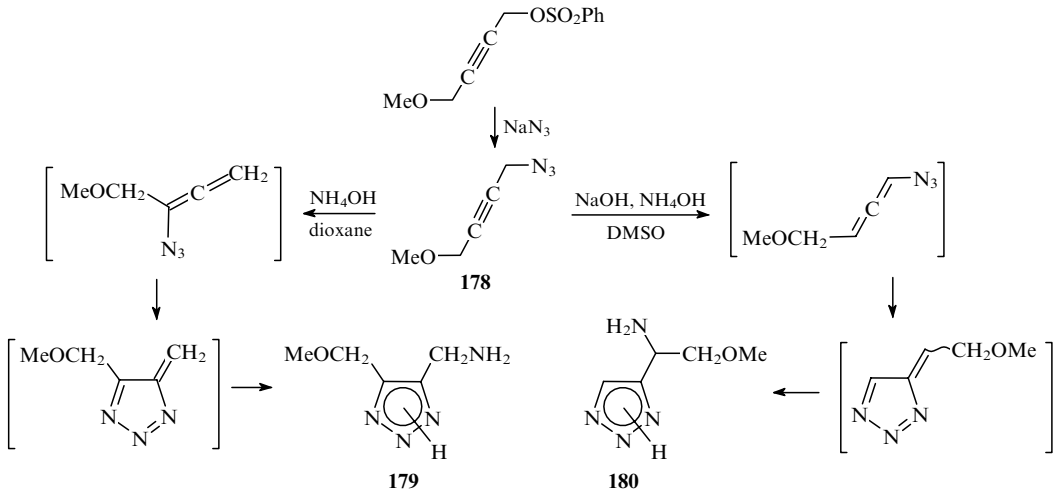
181 **182**

R^1 = $EtOCH_2$, Me_2NCH_2, Ph; R^2-R^3 = Me_2, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2NMe(CH_2)_2$.

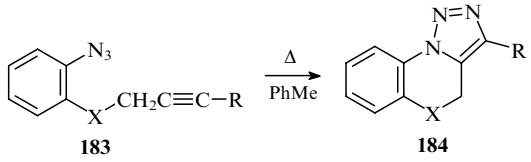
Subsequently, several modifications of this method as applied to various allene systems, including those containing heterocyclic rings, have been developed.[351]

The intramolecular cyclisation of *ortho*-propargyloxy(or thio)-substituted phenyl azides **183**, which takes place on heating in toluene, affords annelated triazoles **184**.[352]

Scheme 5



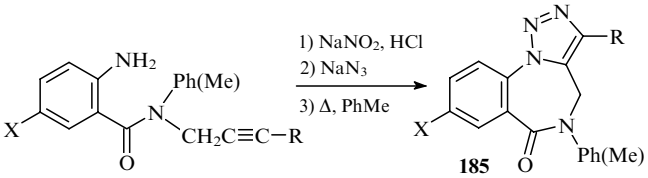
178 **179** **180**



183 **184**

X = O, S; R = H, $HOCH_2$, $MeOCH_2$, Ph.

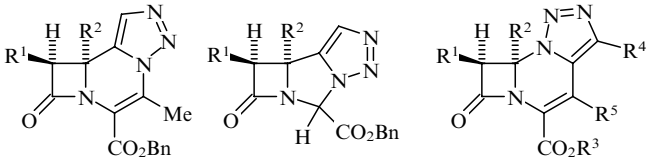
The same approach was used to prepare a series of triazolo[1,5-*a*]benzodiazepinones **185**.[353,354] The key stages of the preparation of triazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-one derivatives on a polymer support have been optimised.[355]



185

X = H, Cl, F, NO_2, NH_2; R = H, Me, Ph.

Other examples of intramolecular cyclisation involving an azide group and a triple bond present in various structures have been reported in original studies [356–358] and in a review.[359] Thus numerous annelated triazoles with a β-lactam fragment (for example, compounds **186**–**188**) have been obtained from azide derivatives of β-lactam antibiotics; these products can be used for subsequent structural modifications and as antibacterial agents.[359]



186 **187** **188a**,**b**

R^1, R^2 = Alk; R^3, R^4 = H, R^5 = Me (**188a**); R^3 = Bu^t, R^4 = Alk, R^5 = H (**188b**).

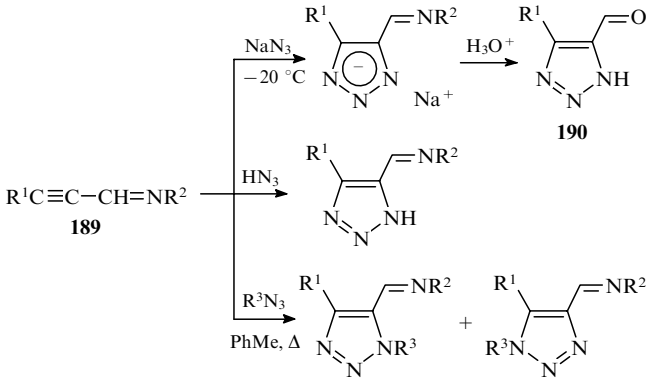
The azide molecule entering into intramolecular 1,3-cycloaddition to give triazole can contain not only a triple bond but also a double bond, either C=C or C=N. Examples of such reactions are documented.[360–365]

Of particular interest as the initial components for the synthesis of the triazole ring are acetylene aldehydes and aldimines (1-aza-1,3-enynes).[366] Both inorganic (HN_3, NaN_3) and organic (R^3N_3) azides were found to add to acetylene aldimines **189** at the triple bond to give substituted triazoles containing a formyl or iminomethyl group at the 5-position.[367–373] The structure of the product depends on the nature of the azide.

Sodium azide adds to the triple bond of azaenynes in DMF even at −20 °C to give salts that are hydrolysed to formyltriazoles **190**. If the azaenyne contains a trimethylsilyl group (**189**, R^1 = Me_3Si), this reaction is accompanied by desilylation to yield 5-formyltriazole **190** (R^1 = H), whereas the germanium analogue (**189**, R^1 = Et_3Ge) retains the substituent. Hydrazoic acid adds chemospecifically to the aldimine triple bond. The reaction of acetylenic aldimimes with organic azides occurs under much more drastic conditions and goes to completion only after long-term heating of the reactants in toluene. The addition is also chemospesific and involves the triple bond, the process regioselectivity increasing with an increase in the bulk of the substituent at the triple bond (from Ph to Bu^t, Me_3Si, and Et_3Ge) and on passing from alkyl azides to aryl azides (Scheme 6).

Acetylenic silyl ketones react with various azides in boiling toluene as effective dipolarophiles to give mixtures of isomeric triazoles in which the 1,4-regioisomer markedly predominates.[271]

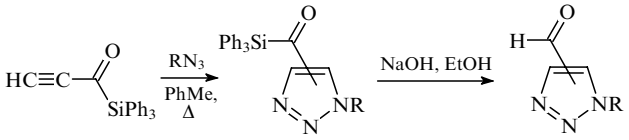
Scheme 6



189 **190**

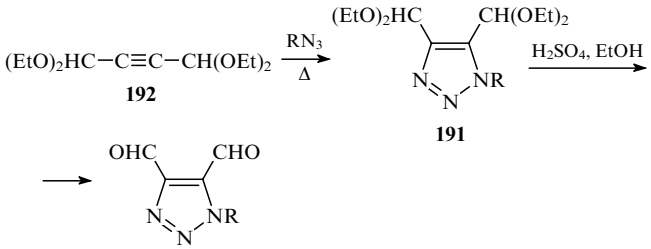
R^1 = Alk, Ar, $SiMe_3$, $GeEt_3$; R^2 = Alk;
R^3 = Bn, EtO_2C, Ph, $MeOC_6H_4$, $O_2NC_6H_4$.

Desilylation of the resulting triazolylacylsilanes induced by alkali furnishes the corresponding triazolecarboxaldehydes.



R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, $PhSCH_2$, $Me_3SiCO(CH_2)_2$, Ad (1-adamantyl), benzo[*b*]thiophen-3-yl.

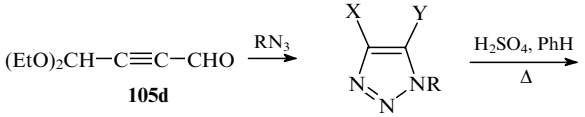
Dialdehydes of the triazole series can easily be obtained from diacetals **191**. These are formed on long-term heating of acetylenedicarbaldehyde bis(diethyl acetal) **192** with phenyl and alkyl azides in a sealed tube.[374]



192 **191**

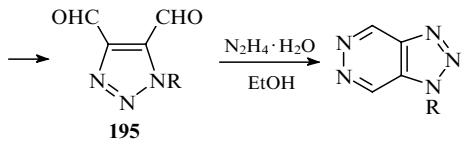
R = n-C_6H_{13}, n-$C_{10}H_{21}$, Br, Ph.

However, in the case of more labile 2-azidonitrobenzene, the reaction with alkyne is usually carried out at a lower temperature to prevent the azide from decomposition and, hence, the reactivity of diacetal **192** is insufficient. The removal of the acetal protection from one aldehyde group allows one to transform (benzene, 55 °C) alkyne **105d** and 2-azidonitrobenzene into a mixture of two monosubstituted triazole-4,5-dicarboxaldehyde diethyl acetals **193** and **194** (R = 2-$O_2NC_6H_4$) in which isomer **193** predominates.[375] Similar mixtures were obtained from other azides under the same conditions. Acid hydrolysis of the mixtures (with azeotropic distillation of water with benzene) gives rise to 1-substituted dialdehydes **195**, which react with hydrazine hydrate yielding triazolo[4,5-*d*]pyridazines. These products can also be obtained directly from mixtures of compounds **193** and **194**.



105d

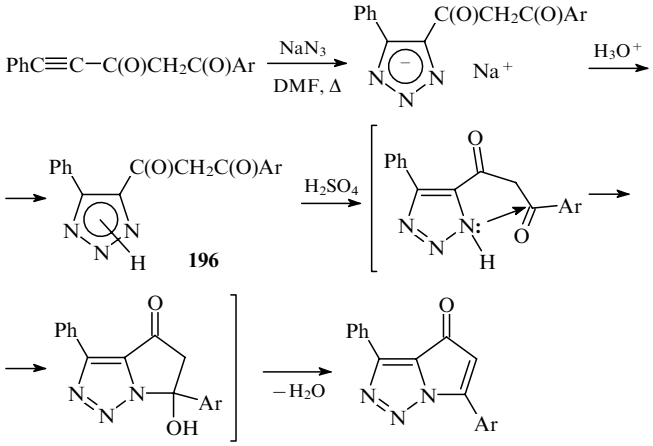
193: X = $(EtO)_2CH$, Y = CHO;
194: X = CHO, Y = $(EtO)_2CH$



195

R = Bn, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$.

The addition of the azide anion to acetylene β-diketones carried out under drastic conditions (heating in DMF) is also chemospecific, involving the triple bond.[165] The yield of the resulting triazole diketones **196** reaches 60% – 70%. As triazole dialdehydes, these polyfunctional compounds can be used in the synthesis of annelated heterocyclic systems. For example, on heating in sulfuric acid, compound **196** undergoes dehydration to give an annelated pyrrolone ring.

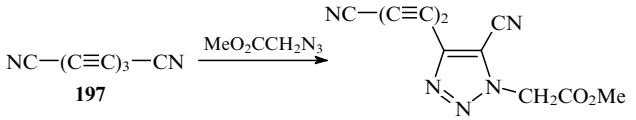


196

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$.

The condensation of 1-aroyl-2-phenylacetylenes (Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$) with aryl azides (Ar = 2-ClC_6H_4, 4-ClC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$) takes place in boiling toluene to give mixtures of 4,5-regioisomers in which 1-aryl-4-aroyl-5-phenyltriazole predominates.[376, 377] Only *o*-nitrophenyl azide does not enter into this reaction.[377]

It was shown that the addition of benzyl azide to diacetylene compounds in which triple bonds are separated by alkyl or aryl groups affords ditriazolyl derivatives as the only products. If the triple bonds are separated by a carbonyl group, NaN_3 adds to only one triple bond; benzyl azide taken in an equivalent amount forms the monoadduct, while a twofold amount results in the formation of mono- and diadduct isomers (Ref. 378).† However, terminal dicyanopolyynes (for example, compounds **197**) with conjugated triple bonds react regioselectively with methyl azidoacetate to give the product of cycloaddition only to the terminal triple bond.[379]



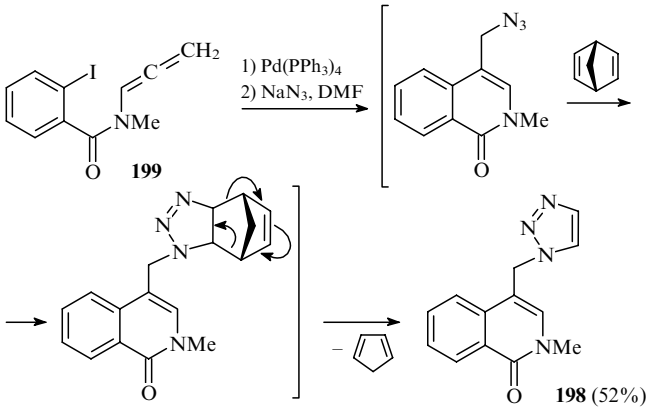
197

2. Reactions of azides with alkenes

Compounds with double C=C bonds can also undergo 1,3-dipolar cycloaddition with azides, the reaction being highly regioselective.[264] This strategy is a key route to 4,5-dihydro-1*H*-1,2,3-triazoles (or Δ^2-1,2,3-triazolines) including those labelled by ^{13}C and ^{15}N isotopes.[380] The preparation and chemical transformations of these heterocycles are the subjects of numerous papers and several reviews (for example Refs 4, 25, 381). The systems containing a triazoline fragment are usually unstable and can decompose under ambient conditions being converted into aziridines (with elimination of a nitrogen molecule), diazo compounds, imines or enamines, or undergo intramolecular rearrangements.[381] For this reason, the formation of triazolines often cannot be detected during cyclocondensation. The stability of the triazoline ring can be increased by introducing stabilising substituents or by synthesising fused systems or conformationally stable complex structures.

When phenyl azide reacts with the simplest allene, propa-1,2-diene, the resulting methylenetriazolines are aromatised to 4- and 5-methyltriazoles formed in very low yields.[345]

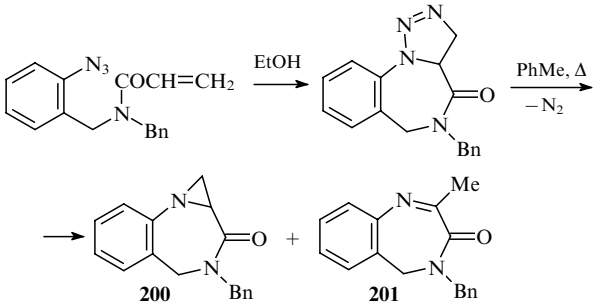
Cascade synthesis of 1-substituted triazoles **198** starting from aryl iodide **199** containing an allene fragment has been performed. The process includes the following reaction sequence: palladium complex-catalysed cyclisation of allene into the iodomethyl derivative, reaction with sodium azide, cyclocondensation of the resulting organylmethyl azide with norbornadiene to an unstable triazoline and the retro-diene decomposition of the last-mentioned product.[272]



199 **198** (52%)

Examples of using other aryl iodides [272] and alkoxymethyl azides and their S-analogues [292] in a similar reaction with norbornadiene are also known.

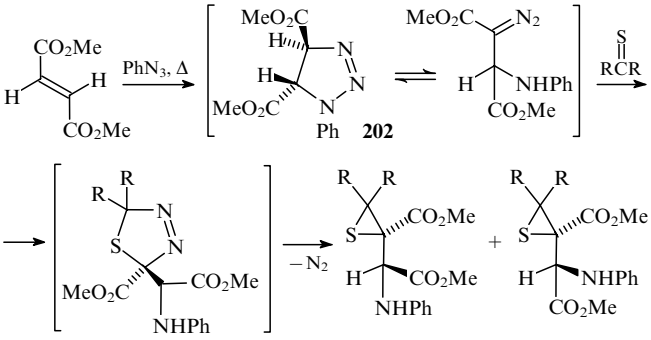
The reaction of methyl azide with acrylic and crotonic acid derivatives is not stereospecific, resulting in triazolines which occur in equilibrium with their open forms, *i.e.*, aminodiazo compounds. In some cases, this reaction is complicated by the reactions of the latter compounds with the starting alkenes.[382] The presence of an electron-releasing substituent at the N(1) atom of the triazoline ring stabilises the molecule, while that at C(4) or C(5) has a destabilising effect.[4] The formation of unstable triazolines with electron-withdrawing substituents and easy opening of the triazoline ring is used to obtain new interesting structures, for example, compounds **200** and **201**.[383, 384]



200 **201**

Heating of thiobenzophenone or 9*H*-fluorene-9-thione with dimethyl fumarate and excess phenyl azide gave a mixture of diastereoisomeric thiiranes.[385] The researchers believe that this transformation involves triazoline derivative **202** as a reactive intermediate.

† The reactions of diacetylenes and their derivatives with sodium azide and organic azides are also considered in the review by I A Maretina, B A Trofimov *Adv. Heterocycl. Chem.* **82** 158 (2002).



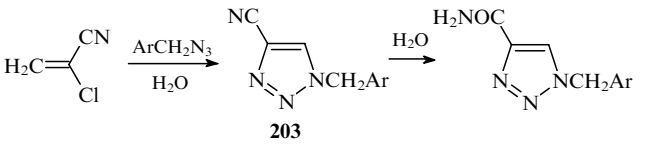
R = Ph, R – R = *o*,*o*′-biphenylene.

The regioselectivity of the cycloaddition of aromatic azides to 5-substituted furan-2-ones was studied.[386] In those cases where thermally stable triazolines are formed, they can be dehydrogenated by treatment with oxidants such as $KMnO_4$,[387, 388] NiO_2,[382] Br_2 [389] and O_2 [390] to be converted into the corresponding triazoles. The presence in the same molecule of an azido group and a double bond bridged by several carbon atoms is favourable for intramolecular cyclisation.[389, 391]

The presence of a good leaving group, for example, Hal (Cl, Br), RO (R = H, Alk, Ar, Ac), RSO_n (n = 0, 1, 2), Alk_2N, NO_2 or CN at the olefin double bond is favourable for regiospecific cycloaddition to azide. When the carbon atom next to the double bond bears a hydrogen atom (*i.e.*, in the presence of a H – C = C – X fragment, which is a latent alkyne), the formation of triazoline during the reaction is often followed by spontaneous ejection of this group with aromatisation of the triazole ring.

Below we consider reactions with azides classified according to the nature of the leaving group in the alkene.

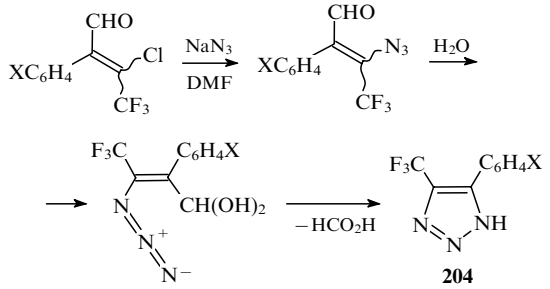
The reaction of substituted benzyl azides with 2-chloroacrylonitrile, which is accompanied by HCl elimination, leads to 1-benzyltriazole-4-carbonitriles.[392, 393] The discovery of high biological activity and the possibility of practical use of 1-(2,6-difluorobenzyl)triazole-4-carboxamides [194] brought about the task of optimisation of the synthesis of their precursor, 4-cyano derivative **203** (Ar = 2,6-$F_2C_6H_3$), whose yield was increased to 98% by conducting the reaction in a two-phase system.[392] This procedure was extended to the synthesis of other 1-benzyl-4-cyanotriazoles **203** and 1-(het)aryl-4-cyanotriazoles.



203

Ar = Ph, 4-NCC_6H_4, 2,6-$F_2C_6H_3$.

The reaction of sodium azide with 2-aryl-4,4,4-trifluoro-3-chlorobut-2-enal yields 5-aryl-4-trifluoromethyltriazoles **204**.[394] The reaction mechanism proposed includes substitution of the azido group for the chlorine atom followed by attack by the terminal nitrogen of the azido group on the double bond of the aldehyde hydrate with elimination of formic acid.

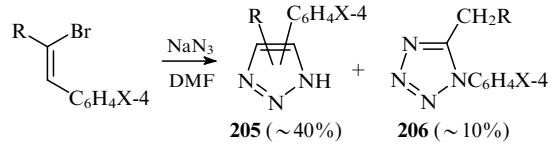


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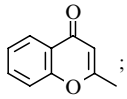
X = H, 4-Br, 3-CF_3, 4-CF_3.

When the substrate contains two chloroacrolein groups connected by a *p*-phenylene bridge, the reaction gives 1,4-bis(4-trifluoromethyltriazol-5-yl)benzene.[394]

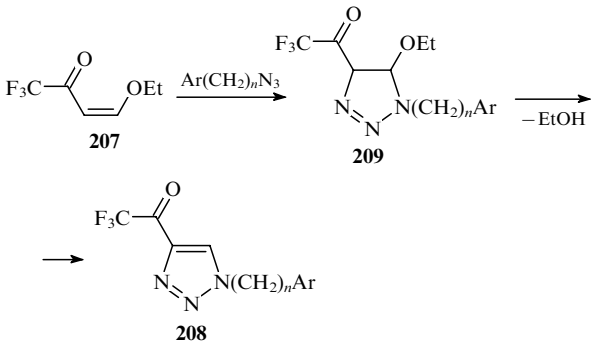
The reaction of (*Z*)-2-α-bromostyrylchromones with NaN_3 in boiling DMF gives, in addition to the expected 4(5)-aryl-5(4)-(2-chromonyl)triazoles **205**, minor amounts of tetrazole derivatives **206**.[395] The latter products result from the reaction of the ketene imines, formed as side products, with NaN_3.



205 (~40%) **206** (~10%)

R =  ; X = H, Cl.

1,3-Dipolar cycloaddition of aryl (or benzyl) azides to activated alkene **207** proceeds on moderate heating without solvents to give the corresponding 4-trifluoroacetyltriazoles **208** in high yields.[396] The presence of an active vicinal hydrogen atom in the intermediate triazoline **209** promotes elimination of the EtOH molecule.

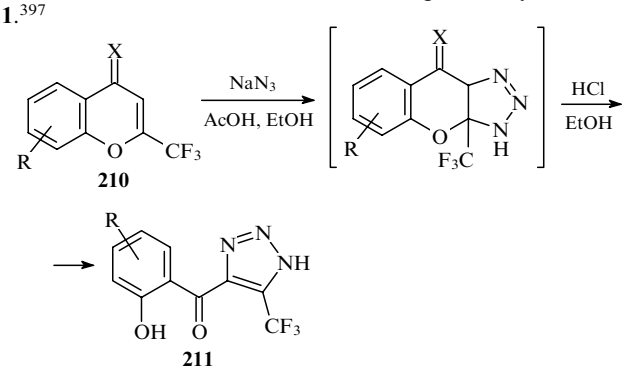


207 **209** **208**

n = 0: Ar = 2-MeC_6H_4, 4-ClC_6H_4; *n* = 0, 1: Ar = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$.

Elimination of the EtOH molecule to give a triazole derivative was also observed on heating a mixture of azidothymidine and vinyl ethyl ether.[185]

5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran proved to be inert with respect to benzyl azide even on strong heating.[396] However, when heated with NaN_3 in AcOH, 2-trifluoromethylchromones substituted at the benzene ring and similar imines **210** give cycloadducts that are cleaved in an acid medium to give 4-aroyltriazoles **211**.[397]



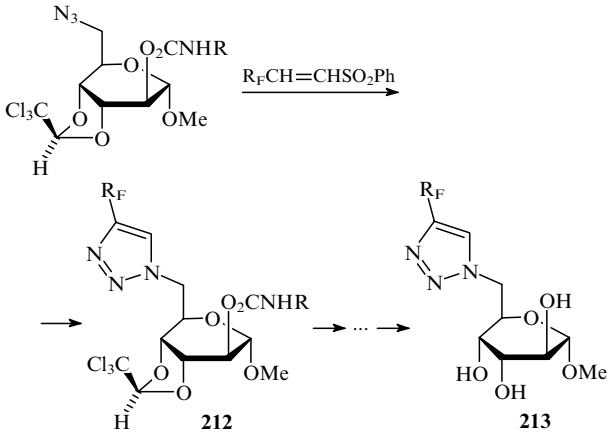
210 **211**

X = O, NH; R = Me, Cl, NO_2.

1-Pyridyltriazoles have been prepared in low yields by heating mixtures of vinyl acetate with various Cl- and CF_3-substituted isomeric azidopyridines.[248]

Reactions with a sulfur-containing leaving group are known. The parent triazole can be obtained in a yield of up to 55% on

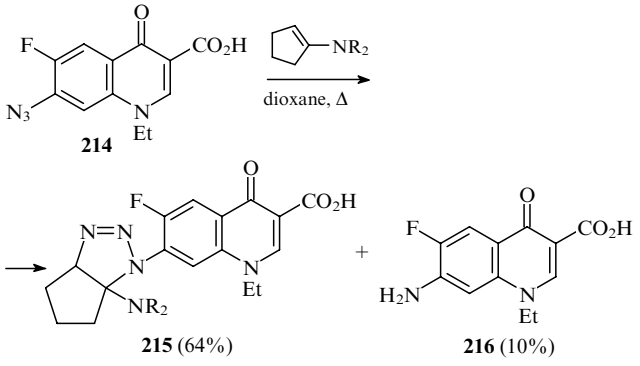
heating an alkali metal azide or Me_3SiN_3 with vinyl sulfoxide or vinyl sulfone ($RSO_nCH=CH_2$; n = 1, 2) in toluene.[398] A similar approach has been used to prepare 5-(4-hydroxyphenyl) derivatives of triazole-4-carboxamides [399, 400] and 4-perfluoroalkyltriazoles, containing residues of D-galactose and D-altrose derivatives (compounds **212**, **213**).[401]



R = Cy; R_F = n-C_4F_9, n-C_6F_{13}.

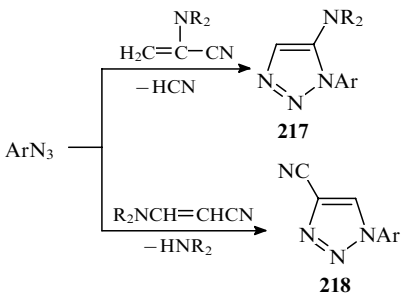
It was shown that a similar reaction can be carried out between 5-azidoxylofuranose and vinyl phenyl sulfoxide. The use of 1-(5-deoxy-α-D-xylofuranosyl)triazole azide grafted on a polymer (polyethylene glycol monomethyl ether) makes it possible to increase the yield from 68% to 94%.[306]

Examples of using various enamines with azides are encountered rather often in the literature. The 7-azido derivative of 6-fluoroquinolone-3-carboxylic acid **214** reacts with alkenes (norbornene, dicyclopentadiene and some enamines) to afford thermally unstable triazolyl adducts; only in the case of 1-morpholinocyclopentene, was the triazoline derivative **215** isolated together with side product 7-aminofluoroquinolone **216**.[241]



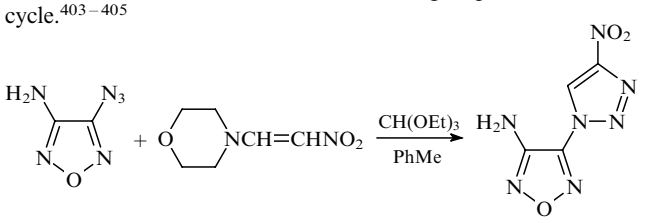
R–R = $(CH_2)_2O(CH_2)_2$.

Aryl azides readily react with α- and β-aminoacrylonitriles, but give different cycloaddition products. In the former case, spontaneous ejection of HCN from the intermediate triazoline takes place to give 1-aryl-5-aminotriazole **217**, and in the latter case, the corresponding amine is evolved and 1-aryl-4-cyanotriazole **218** is formed.[402] Fragments of secondary cyclic amines (pyrrolidine, piperidine and morpholine) were used as substituents in aminoacrylonitriles. In all cases, the yields of triazoles were 75%–95%. Despite the captodative character of α-aminoacrylonitriles, their dipolarophilic properties in the cycloaddition are comparable with those of β-aminoacrylonitriles, which is inconsistent with their possible participation in the cyclisation of biradical intermediate species and confirms the one-step concerted Huisgen mechanism.[402]



Ar = Ph, MeC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$;
R–R = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$.

When the nitroethylene molecule contains a morpholine residue, cycloaddition to the azide is accompanied by morpholine elimination with retention of the nitro group in the heterocycle.[403–405]



To prevent decomposition of the starting azide under the action of the evolved morpholine, the reaction is carried out in the presence of triethyl orthoformate.

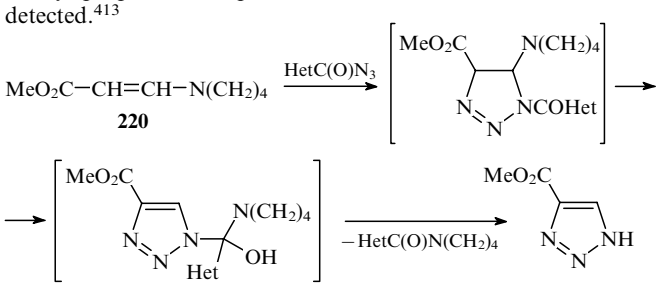
In the reaction of 3-dimethylaminocrotonic acid, its esters or amides with mono-, di- or trinitrophenyl azides, the dimethylamine molecule is eliminated during cyclisation to give the corresponding 1-[$(O_2N)_nC_6H_{5-n}$]-triazole-4-carboxylic acid derivatives (n = 1–3).[406]

The reactions of thiazole azides **219a–c** with enamines have been studied.[264] The reaction of 2-morpholinoprop-1-enyl phenyl ketone with 2-(2-thienyl)-5-azidothiazole **219a** occurs under very mild conditions with evolution of morpholine to yield 5-(triazol-1-yl)thiazole. Using derivatives **219b**,**c** as examples, it was shown that in the absence of a hydrogen atom at the enamine double bond, the triazoline ring easily loses a nitrogen molecule yielding a mixture of 5-aminothiazole derivatives. The reaction of methyl acrylate with azide **219c** affords 5-aziridinothiazole (Scheme 7).

Acyl azides react with alkenes in a similar way, although in some cases, the products of the Curtius rearrangement are formed in parallel.[356]

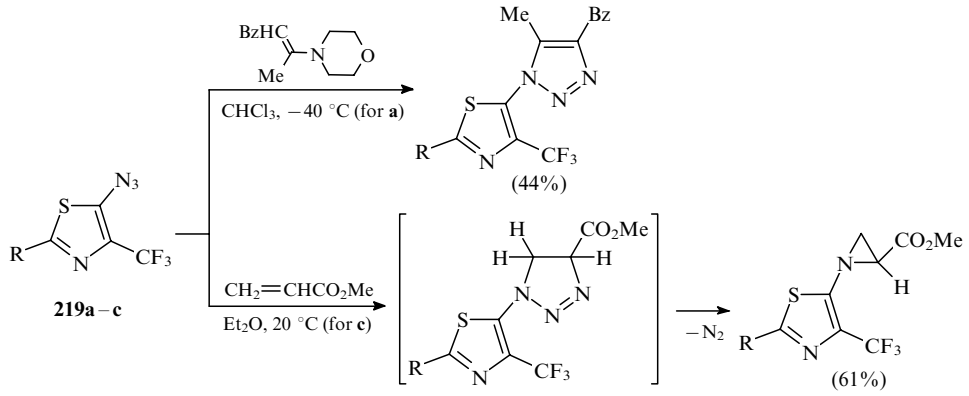
In some cases, a compound with the enamine fragment is used in the cyclisation as the dipolarophile.[407–409] 1,4-Disubstituted triazoles are formed as the result of ejection of the amine molecule from the triazoline that has already formed.[410, 411] Study of the kinetics of the reaction of aryl azides with methyl 3-pyrrolidinoacrylate **220** has shown that cycloaddition is a concerted asynchronous process controlled by the LUMO of the azide and the HOMO of the dipolarophile.[412]

An unusual rearrangement was found for the products of cycloaddition of heterocyclic acyl azides to aminoacrylate **220**, whereas in the reaction of the latter with methyl crotonate or methyl propiolate, no products of such a transformation were detected.[413]



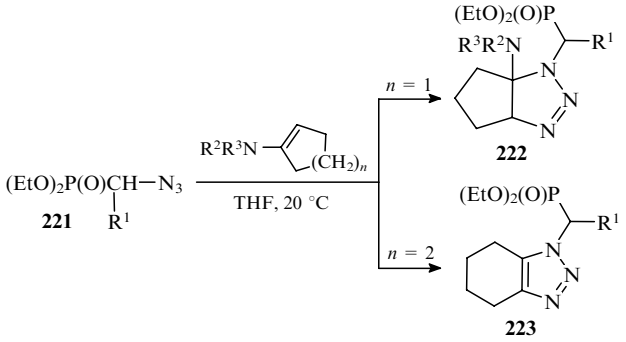
Het = 2-furyl, 2-thienyl, selenophen-2-yl, thieno[3,2-*b*]thiophen-2-yl.

Scheme 7



R = 2-thienyl (**a**), 2-furyl (**b**), 4-MeC$_6$H$_4$ (**c**).

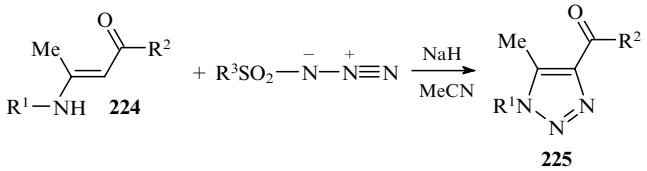
A number of publications have been devoted to the cycloaddition of azidoalkylphosphonates **221** to enamines.[282,283,414] It was shown that, depending on the enamine structure, the reaction can either stop after the formation of 1-phosphorylmethyl-5-amino-Δ^2-triazolines **222** or afford bicyclic 1-phosphorylmethyltriazole **223** *via* elimination of the amine molecule.[414]



R^1 = H, Me, Ph; R^2–R^3 = $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$.

Upon reaction with enamines — amino derivatives of unsaturated acid esters R^{1}R^{2}NCH=CHCO$_2$Alk — substrates **221** are converted into 4-alkoxycarbonyl-1-phosphoryl-methyltriazoles.[414]

β-Amino-α,β-unsaturated carbonyl compounds **224** have been proposed for the synthesis of 4-acyltriazoles and alkyl triazole-4-carboxylates.[415]

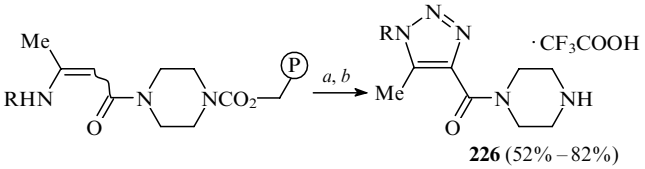


R^1 = Bu^n, n-$C_{10}H_{21}$, Bn, Ph, *p*-Tol; R^2 = Me, EtO; R^3 = Me, *p*-Tol.

R^1	Bu^n	n-$C_{10}H_{21}$	Bn	Ph	*p*-Tol	Bu^n	Bn
R^2	Me	Me	Me	Me	Me	EtO	EtO
Yield of **225** (%) (R^3 = Me)	79	87	97	20	37	83	72
Yield of **225** (%) (R^3 = *p*-Tol)	40	30	50	40	10	2	23

It was shown that reactions of **224** with tosyl (mesyl) azide are accompanied by the 'diazo transfer', *i.e.*, elimination of sulfonylamine and an attack by the diazo group on the enamine nitrogen. The reaction affords only one regioisomer of triazole **225**, whose yield depends on the reactant structure. It is noteworthy that the product yields are higher with mesyl azide.[415]

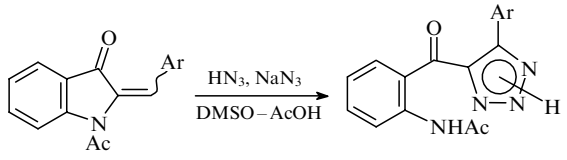
This strategy is also applicable for the solid-state synthesis of 4-carbamoyltriazoles **226**.[416]



(*a*) TsN$_3$, Pr$^i_2$NEt, DMF; (*b*) TFA, CH_2Cl_2, 20 °C;
(P) is the polymer support;
R = CH_2CO_2Bn, $CH_2C_6H_4OMe$-4, $(CH_2)_2C_6H_4NO_2$-4.

It has been shown[417] that methyl 3-pyrrolidino-3-formylcrotonate dimethyl acetal is much more reactive in cycloaddition to 4-nitrophenyl azide than the cyclic analogue, namely, enaminofuranone.

The reaction of arylidene derivatives of *N*-acetylindoxyl **227** with hydrazoic acid proceeds as the nucleophilic addittion of the N_3^- anion to the C=C double bond accompanied by cleavage of the C–N bond followed by closure of the triazole ring.[418–420] The reaction takes place on heating substrate **227** with sodium azide in a DMSO–acetic acid mixture to give 4-(2-acetylaminobenzoyl)-5-aryltriazoles **228.**



R = Ph, 4-Pr^{i}C$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-Py.

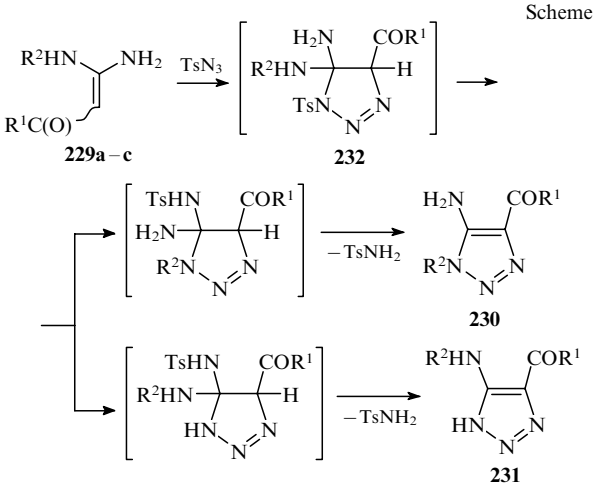
However, benzylideneacetophenone and 1,2-dibenzoylethylene, which do not differ much in structure from enamide **227**, do not form triazole or triazoline derivatives when reacted with 2-(4-pyridyl)ethyl azide, the corresponding enaminoketones being formed instead.[293]

Acyl ketene aminals can also act as active dipolarophiles in dipolar cycloaddition.[421] By reactions of acylketene aminals **229** with tosyl azide, a series of 5-amino-4-acetyl-1,2,3-triazoles **230** and **231** substituted at the endo-N(1)- or exocyclic nitrogen have been synthesised (Scheme 8).[422]

The reaction takes place in THF at room temperature (only substrates **229b** require refluxing). The researchers believe that the reaction is accompanied by the Dimroth rearrangement of cycloadduct **232** formed intially with subsequent elimination of the $TsNH_2$ molecule. In the case of aminals **229b**,**c**, the reaction is regioselective to give 5-R^{2}NH-4-acyltriazoles **231**; in other cases, isomer mixtures were obtained.[422]

The reactions of similar morpholine or piperidine enaminals containing various electron-withdrawing groups with *p*-nitrophenyl azide resulted in the preparation of only 1-aryltriazoles

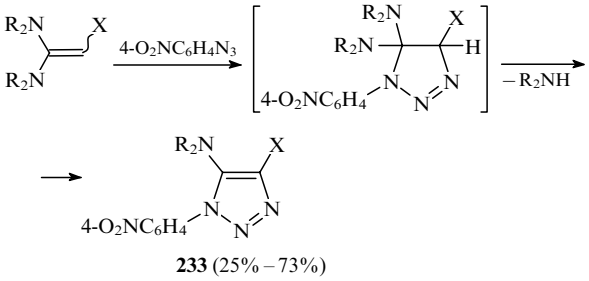
Scheme 8



R^1 = Me, Ph; R^2 = Ph (**a**), PhCO (**b**), 4,6-dimethylpyrimidin-2-yl (**c**).

Aminal	R^1	Yield (%)	
		230	**231**
229a	Me	73	13
	Ph	53	33
229b	Me	–	70
229c	Me	–	94

with the functional substituent at the 4-position of the heterocycle (compounds **233**).[423]



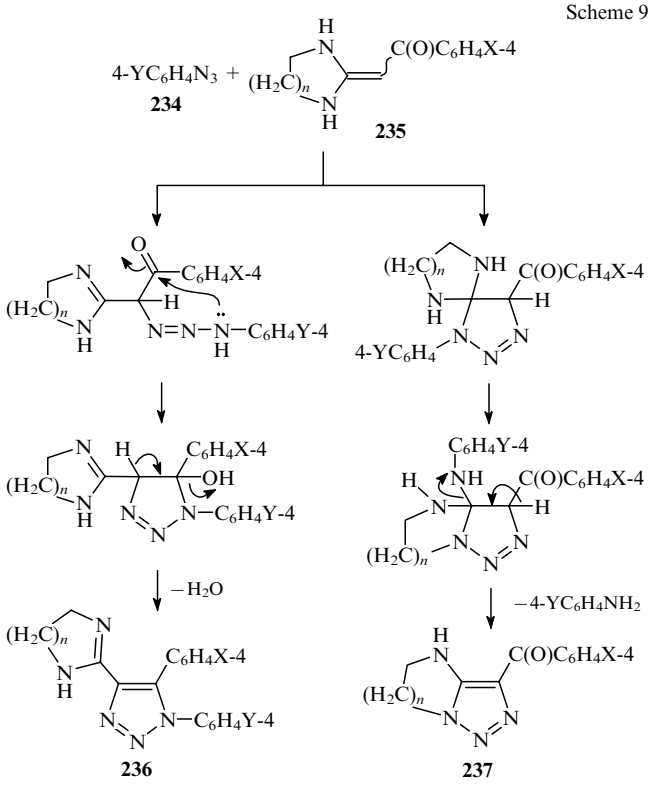
233 (25% – 73%)

X = COMe, COPh, CO_2Me, CO_2Et, CO_2Bn, Ts, NO_2;
R – R = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$.

In the general case, the reaction of aryl azides with cyclic acyl ketene aminals can follow two pathways to give triazoles of two structural types: annelated and/or fully substituted,[424,425] the product ratio being dependent on the nature of substituents in the reactants. These dependences were studied qualitatively for the reaction of *para*-substituted phenyl azides **234** with aminals **235**, containing a *para*-substituted benzoyl fragment at the double bond. The reaction rate decreases with a decrease in the electron-withdrawing properties of the *para*-substituent Y in aryl azide in the series: NO_2 > Cl > H > OMe and in the electron-releasing properties of the substituent X in the enaminal in the series OMe > Me > H > Cl (Scheme 9).[424]

All the enaminals studied react with 4-nitrophenyl azide very easily to give only fully substituted triazoles with two aryl groups **236** (yields 87% – 97%) even at room temperature in dioxane. With other azides, the reaction is much slower; refluxing of reactants in dioxane gives product mixtures. In addition to triazoles **236** (yields 8% – 71%), compounds **237** are formed, which include a fused triazole system with a bridgehead nitrogen atom (yields 6% – 31%). On the basis of the results obtained, the researchers cited proposed a sequence of transformations (see Scheme 9) and concluded that enaminals of this structure react with aryl azides both as nucleophiles and as 1,3-dipolarophiles. In the former case, the terminal nitrogen atom of the azide group

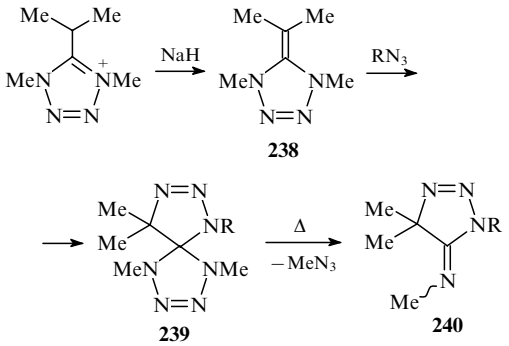
Scheme 9



X = H, Me, MeO, Cl; Y = H, MeO, Cl, NO_2; n = 1, 2.

attacks the β-carbon atom of enaminal to give an adduct whose subsequent cyclisation and dehydration afford 1,4,5-trisubstituted triazole **236**. In the alternative process, enaminals react as usual dipolarophiles. The resulting adducts undergo the Dimroth rearrangement followed by deamination to give fused triazoles **237**.[424] The reaction with aminals of benzoyl-substituted heterocyclic ketenes was also carried out using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranozyl azide,[426,427] while protected ribozyl azide was used in the reaction with aryl ketene aminals.[428]

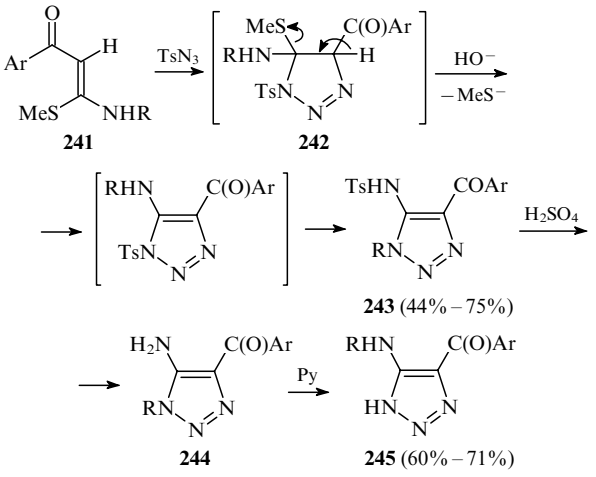
Isopropylidenedihydrotetrazoles **238**, which contain an enaminal fragment, also react with alkyl azides to give spiro compounds **239**. These products undergo [3 + 2]-cyclo-reversion during thermolysis to eject methyl azide. The final products **240** exist as mixtures of iminodihydrotriazole geometric isomers in which the *E*-isomer predominates.[429]



R = Me, CD_3, CH_2Bu^t.

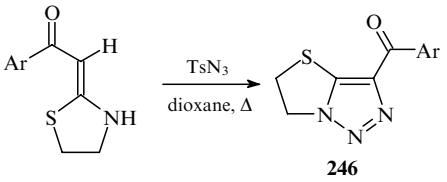
The aroyl derivatives of *S,S*- and *S,N*-acetals of polarised ketenes are also able to react with azides: on heating in DMSO with NaN_3, the former are converted into 4-aroyl-5-methylthiotriazoles, while the latter give only 5-aroyltetrazoles under the same conditions.[430] In addition, the aroyl derivatives of ketene *S,N*-acetals of ketenes **241** do not react with tosyl azide in boiling dioxane,[431] but they react in ethanol in the presence of alkali even

at room temperature. In this case, intermediate triazolines **242** eliminate MeSH and undergo the Dimroth rearrangement, resulting in 1-aryl-4-aroyl-5-tosylaminotriazoles **243**. On treatment with sulfuric acid, the products give off the tosyl group, while the 5-aminotriazoles **244** thus produced undergo one more Dimroth rearrangement on refluxing in pyridine, being converted into substituted 5-anilinotriazoles **245**.[431]



R = Me, Et, Pr^n, Pr^i, Bu^n, Cy, Bn, $(EtO)_2CHCH_2$, Ph;
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4.

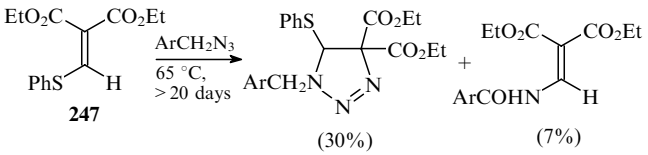
The reaction of tosyl azide with aroyl derivatives of cyclic ketene *S,N*-acetals carried out under the same conditions (NaOH, EtOH) is accompanied by resinification, but this reaction performed by refluxing in dioxane gives annelated triazoles **246** in good yields.[431]



Ar = Ph (69%), 4-ClC_6H_4 (60%), 4-$MeOC_6H_4$ (65%).

If cyclic ketene *N,X*-acetals (X = Me_2C, MeN, O, S) react with azides that possess enhanced electrophilicity, this yields unstable triazoline adducts, which immediately eliminate N_2. Simultaneously, the triazoline ring is cleaved giving rise to other nitrogen-containing heterocycles.[432]

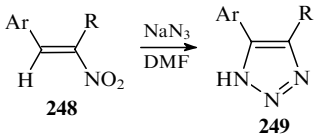
In the case of two geminal acceptor groups at the double bond (*e.g.*, alkene **247**), the reaction with organic azide proceeds with difficulty and gives, in addition to dihydrotriazole, a side acyclic enamine product, which is apparently formed upon rearrangement rather than upon triazoline decomposition.[433]



Ar = 4-$MeOC_6H_4$.

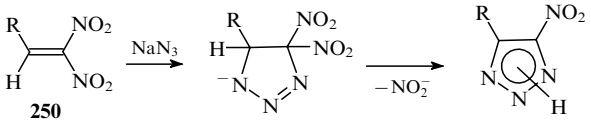
Alkenes that contain an electron-withdrawing nitro group at the double bond readily react with azides. Furan- and indole-based α,β-unsaturated ketones containing an α-nitro group have been used to prepare 4-hetaryl-5-acyltriazoles.[434] The reaction of α-nitroalkenes ($R^1CH=CR^2NO_2$) with methyl and phenyl azides was found [435, 436] to give only 1-Me(Ph)-4-R^2-4-NO_2-5-R^1-triazolines, which are converted into 1-Me(Ph)-4-R^2-5-R^1-triazoles after elimination of HNO_2. The reactions of β-nitrostyrene and nitropropene homologues with the same azides give not only isomeric 1- and 3-substituted triazoles containing no nitro group but also 1-substituted 4-nitrotriazole.[437] Apparently, this product results from oxidative cyclisation of the intermediate diazo compound $PhCHNHR^1C(NO_2)=N_2$, which is the open form of the corresponding triazoline.[437]

Recently, it has been shown that the double bond in β-nitrostyrenes **248** can be involved in dipolar cycloaddition with elimination of a nitro group. This gave triazoles **249** in high yields.[438]



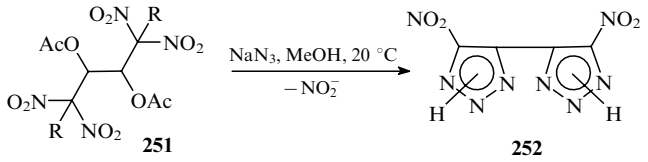
R is cyclohex-1-enyl; Ar = Ph, 4-$MeOC_6H_4$.

Of particular interest as the initial components for the synthesis of nitrotriazoles are *gem*-dinitroethylenes **250**, which are prepared either from alkyl dinitroacetate and the products of its transformation or starting from 1,1,1-trinitroalkanes.[439–441]



R = H, Me, Bu^n, 4-MeC_6H_4, Me_2N.

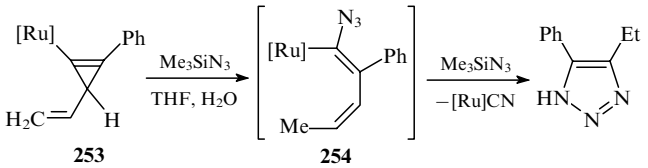
The reaction of tetranitrobutane-2,3-diol diacetates **251** with NaN_3 smoothly produces dinitro-substituted bis-triazole **252**, probably through the intermediate tetranitrobutadiene.[440]

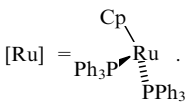


R = H (67%), Br (34%).

Unlike the diacetate, the monoacetate of tetranitrobutanediol forms only one triazole ring under these conditions, which is confirmed by the subsequent oxidation of the product to 5-nitrotriazole-4-carboxylic acid.[440]

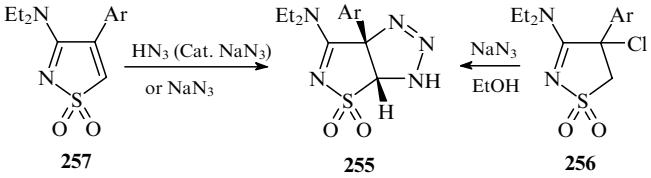
The reaction of vinylcyclopropenylruthenium complex **253** with excess Me_3SiN_3 follows an unusual route, resulting in 4-ethyl-5-phenyltriazole.[442] Presumably, the addition of Me_3Si to an exocyclic double bond is accompanied by cyclopropenyl ring opening. The presence of traces of water in the solvent promotes elimination of the silyl group from the intermediate and the formation of complex **254**. The repeated attack by Me_3SiN_3 on the double bond of the intermediate results in the [3+2]-cycloaddition product, which is converted into a triazole ring after elimination of the cyanoruthenium fragment.[442, 443]





Cyclocondensation has been carried out for 3-aminoisothiazole 1,1-dioxide.[444] The reaction of these cyclic sulfones containing an amidine fragment yields a mixture of several products depending on the conditions. The highest yield (70%) of the bicyclic adduct, namely, dihydrogenated isothiazolo[4,5-*d*]tri-

azole **255,** was attained by using isothiazoline **256** or isothiazole **257** as the starting compounds.



257 **255** **256**

Ar = 4-MeOC$_6$H$_4$.

Cations of nitrogen-containing heteroallenes (1,3-diaza-2-azoniaallene salts) can be introduced in cycloadditions as the 1,3-dipolar component; they react stereoselectively, for example, with glycals.[445]

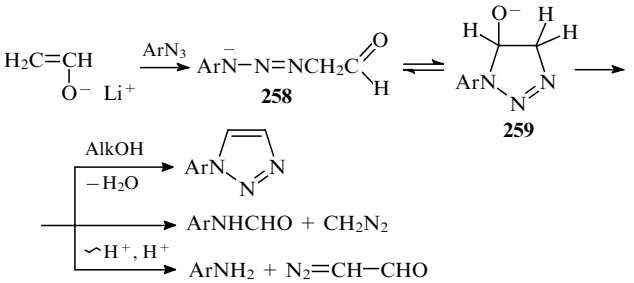
3. Reactions of azides with CH-active compounds

Depending on the reaction mechanism and the nature of the activating groups [most often, C(O)R or C≡N], the key stages of these reactions can formally be considered as either ionic (the nucleophilic addition of a carbanion to the azide group) or azide cycloaddition to the olefin intermediate (enol or enolate) or to the C=C=NH fragment.

Back in 1902, Dimroth[446] performed the reaction of phenyl azide with ethyl acetoactate in ethanol in the presence of EtONa and obtained 1-phenyl-5-methyltriazole-4-carboxylic acid. Subsequently, Huisgen *et al.*[447] successfully used ethyl formylacetate in this reaction and obtained 1-phenyltriazole-4-carboxylic acid.[403] Later, other organic azides and various dicarbonyl compounds containing CH-active groups (acetylacetone, ethyl malonate, acetoacetate and cyanoactate, *etc.*) have been used to prepare substituted triazoles. Other examples of such reactions are documented in reviews.[2,3,8] The reaction of azides with cyanomethylenecarbonyl compounds has some specific features. Apart from aminotriazoles, products of reduction of the azido group were found in the reaction mixture; in several cases, these were the major components.

Previously, Olsen showed[448] that methyl (or benzyl) azide is capable of reactions with ketones in Bu^{t}OH in the presence of Bu^{t}OK to give 1-methyl(benzyl)-5-alkyl-5-hydroxytriazolines, which are readily dehydrated to the corresponding 5-alkyltriazoles. Later, acetaldehyde enolate was involved in cyclocondensation with some acetaldehyde arylazides to give 1-aryltriazoles in high yield (Scheme 10).[449]

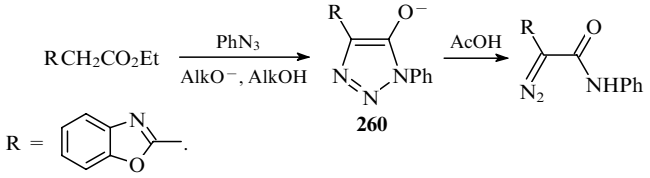
Scheme 10



Ar = C$_6$H$_4$R: R = H, 2-Me, 4-Me, 3-OMe, 4-OMe, 2-SMe, 2-SEt.

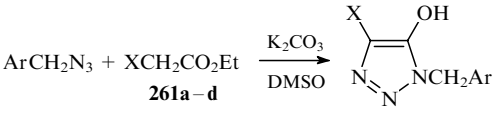
Only phenyl azides with electron-releasing substituents in the aromatic ring can be used in this reaction. This increases the stability of the triazoline ring and, hence, the equilibrium shifts from triazene ketone **258** towards hydroxytriazoline **259**, which is dehydrated on treatment with MeONa or Bu^{t}OK. The reaction is complicated by side reactant destruction processes.

The reactions of organic azides with arylacetic esters can be exemplified by the reaction of phenyl azide with ethyl benzoxazolyl-2-acetate. This affords 1-phenyltriazol-5-olate **260**; attempts to isolate the product as a neutral compound resulted in triazole ring opening.[450]



260

The reaction of diethyl malonate **261a** with benzyl azides in DMSO[451] gives the corresponding 1-benzyl-5-hydroxy-4-ethoxycarbonyltriazoles. However, with ethyl phenylacetate **261b**, the yield of triazole was relatively low (8%), and esters **261c**,**d** did not react at all.

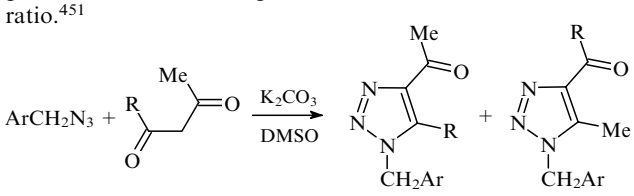


Ar = Ph, 4-MeOC$_6$H$_4$, 3,5-Cl$_2$C$_6$H$_3$; X = CO$_2$Et (**a**), Ph (**b**), F (**c**), NO$_2$ (**d**).

Diethyl malonate reacts with aryl azides in EtOH in a similar way;[187] 4-nitrophenyl and tosyl azide react with alkyl malonates in HMPT to give 2-diazomalonates.[452]

Ethyl alkylidenemalonates react with NaN$_3$ in DMSO to give triazoles *via* intermediate 4,5-dihydrotriazoles and with benzyl azide to give 1-benzyl-4,5-dihydrotriazole. On treatment with Bu^{t}OK in DMSO, the latter products undergo either aromatisation to triazoles, or deethoxycarbonylation without aromatisation, or lose nitrogen, being converted into ethyl (benzylamino)methylidenemalonates.[453]

The reaction of azides with 1,3-diketones allows the synthesis of triazole ketones. For example, benzyl azides react with acetylacetone to afford 1-substituted 4-acetyl-5-methyltriazoles in high yields (at R = Me **262**≡**263**); the reaction with benzoylacetone gives mixtures of two regioisomers, **262** and **263**, in a ~1 : 1.5 ratio.[451]

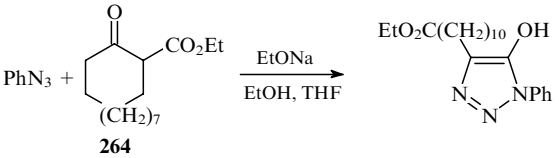


262 **263**

Ar = Ph, 3,5-Cl$_2$C$_6$H$_3$; R = Me, Ph.

Analogous reactions between 4-nitrophenyl azide and various 1,3-diketones and alkyl acetoacetates in HMPT resulted in the synthesis of carbonyl compounds with a triazole ring.[452,454] Ethyl 1-aryl-5-methyltriazole-4-carboxylates, formed upon reactions of the aryl azides RC$_6$H$_4$N$_3$ (R = H, 2-Me, 3-Me, 4-Me, 2-MeO, 4-MeO, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br) with ethyl acetoacetate in the presence of EtONa, were subjected to alkaline hydrolysis giving rise to a series of the corresponding acids in 43%–80% yields.[455]

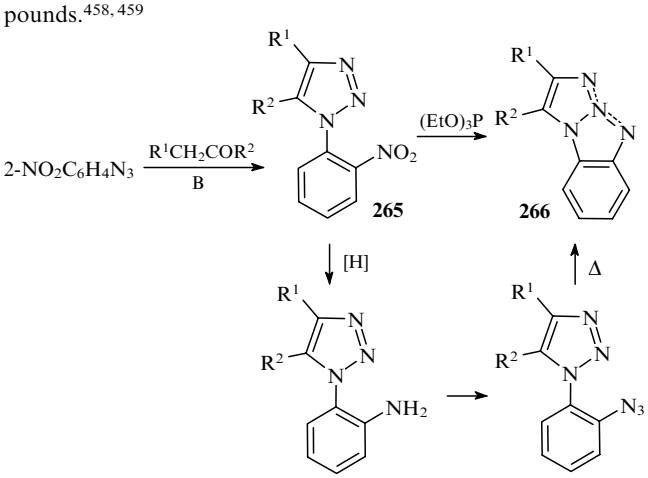
Phenyl azide reacts with methyl γ-methoxyacetoacetate in the presence of Et$_3$N in boiling MeOH (the yield of methyl 5-methoxy-1-phenyltriazole-4-carboxylate is ⩽24%[201]) and reacts with macrocyclic oxo ester **264** yielding 5-hydroxytriazole due to opening of the macrocycle.[456]



264

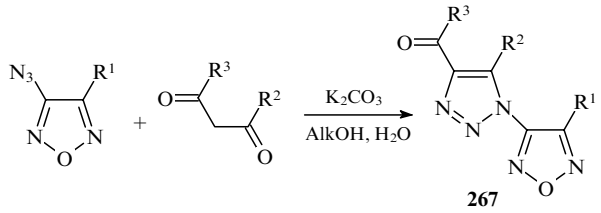
The reaction of 2-nitrophenyl azide with ethyl benzoylacetate affords the 1-nitrophenyl derivative of triazole **265**, which was used to prepare the triazolo[1,2-*a*]benzotriazole system **266**.[457]

A similar protocol was also realised for other carbonyl compounds.[458, 459]



R^1 = COPh, R^2 = OEt; R^2 = Me: R^1 = COMe, CO_2Et, Ph.

The reaction of azides with CH-activated compounds has found wide use in the synthesis of polynuclear heterocyclic structures. The reactions of substituted azidofurazans with β-dicarbonyl compounds furnished a series of (triazol-1-yl)furazans **267** in high yields.[460, 461]



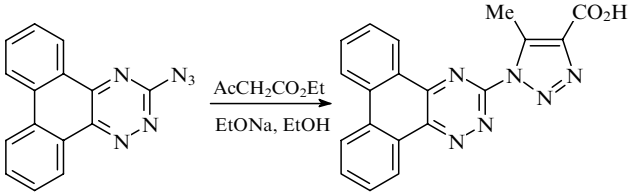
R^1 = Me, Ph, MeO, NH_2; R^2 = Me, Et, Pr^n, $MeOCH_2$, $ClCH_2$, Ph; R^3 = Me, Ph, MeO, EtO.

The predominant formation of one regioisomer is in line with the data on the reaction of 2-azidothiazoles with 1,3-dicarbonyl compounds.[462]

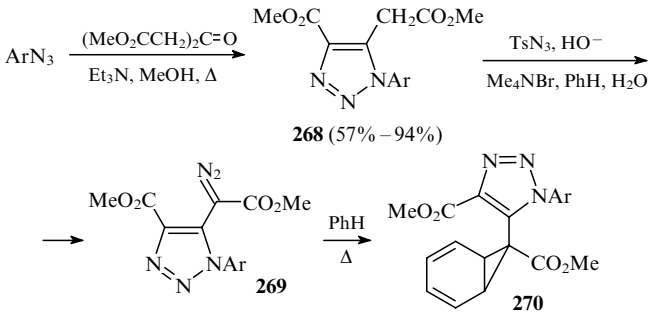
By condensing various CF_3-substituted 2- and 4-azidopyridines with $RC(O)CH_2CO_2Et$ (R = Me, Ph, 4-Py), a broad range of 1-pyridyl-5-methyl(or aryl)triazole-4-carboxylates have been prepared.[247]

Starting from 4-azidoquinolines, ethyl *p*-nitrobenzoylacetate and other CH_2-active compounds, a series of 1-(4-quinolyl)triazoles have been synthesised.[463, 464] 1-(Acridin-9-yl)-4-methoxycarbonyl-5-R-triazoles [R = Me, Et, Pr, $(CH_2)_4Cl$, CH_2CO_2Me, Ph] have been prepared from 9-azidoacridines. The regiospecificity of the base-catalysed reaction may be indicative of an ionic mechanism of the successive steps.[36]

Refluxing 3-azidophenanthro[9,10-*e*][1,2,4]triazine and ethyl acetoacetate produces, in a high yield, 1-hetaryl-5-methyltriazole-4-carboxylic acid, which is readily decarboxylated on heating above the melting point.[338]

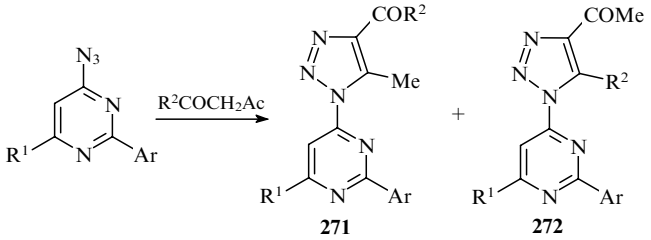


The reaction of aryl azides with dimethyl acetonedicarboxylate carried out by refluxing the reactants in MeOH in the presence of Et_3N gave disubstituted triazoles **268**. Repeated treatment of these esters with tosyl azide under phase transfer catalysis conditions resulted in diazo derivatives at the methylene group, triazoles **269**, which were converted into triazolylnorcaradienes **270** (in the *endo*-hetaryl, *exo*-methoxycarbonyl configuration) on heating in benzene.[465]



Ar = Ph, $4\text{-}ClC_6H_4$, $4\text{-}BrC_6H_4$, $4\text{-}NO_2C_6H_4$, $4\text{-}MeCOC_6H_4$, $2,4\text{-}Cl_2C_6H_3$.

It has been shown[466] that the reaction of 2- and 4-azidopyrimidines with β-dicarbonyl compounds (acylacetones) in EtOH or dioxane in the presence of Et_3N gives 1-pyrimidinyl-4-acyl-1,2,3-triazoles in good yields. In the case of acetylacetone, the reaction of 2-aryl-4-azidopyrimidines gives rise to 4-acetyl-5-methyltriazoles (at R^2 = Me, **271** ≡ **272**), whereas in the case of benzoylacetone, mixtures containing equal amounts of regioisomers **271** and **272** are formed. The reaction rate depends on the nature of the substituent in the 2-aryl groups of pyrimidine. On the one hand, electron-releasing substituents retard the process; on the other hand, the most pronounced accelerating effect was noted for *o*-hydroxyphenyl derivatives, which form a strong intramolecular hydrogen bond between the hydroxyl group and the neighbouring pyrimidine nitrogen.[466]



R^1 = H, Ph; Ar = Ph, $4\text{-}BrC_6H_4$, $2\text{-}HOC_6H_4$, $2\text{-}MeOC_6H_4$, $4\text{-}MeOC_6H_4$; R^2 = Me, Ph.

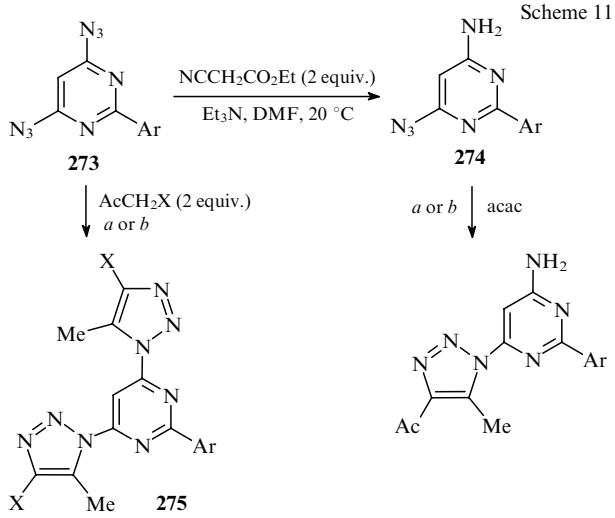
The reactions of (het)aryl azides with alkyl cyanoacetates give in some cases (het)arylamines as side products (the formal reduction of the azido group to the amino group). One factor directing the reaction along this pathway is the enhanced CH-acidity of the dipolarophile. When interpreting the experimental results, researchers consider two possible reaction pathways. Azide cycloaddition to the double bond of the enol form of the dipolarophile gives 5-hydroxytriazoline, while its open form, unstable triazene of type **258** (see Scheme 10), spontaneously decomposes to amine and diazo ketone (or diazo ester).[38, 467, 468]

When two azide groups are present at the 4- and 6-positions of the pyrimidine ring (compound **273**), the reaction with cyanoacetate does not lead to triazoles but stops after the formation of 4-azido-6-aminopyrimidine **274** (Scheme 11).[469]

When other β-dicarbonyl compounds are used (acetylacetone, ethyl acetoacetate and ethyl benzoylacetate), diazidopyrimidine **273** is converted into bis(triazolyl)pyrimidines, although completion of the reaction requires long-term refluxing. Only in one case, when 1 equivalent of acetylacetone is made to react with diazidopyrimidine **273**, 4-amino- and 4-azido-6-(triazol-1-yl)pyrimidines were detected in minor amounts apart from bis(triazolyl)pyrimidine **275**.[469]

However, in the reaction of diazido-1,3,5-triazines **276** with compounds having a reactive CH_2 group, both azide substituents

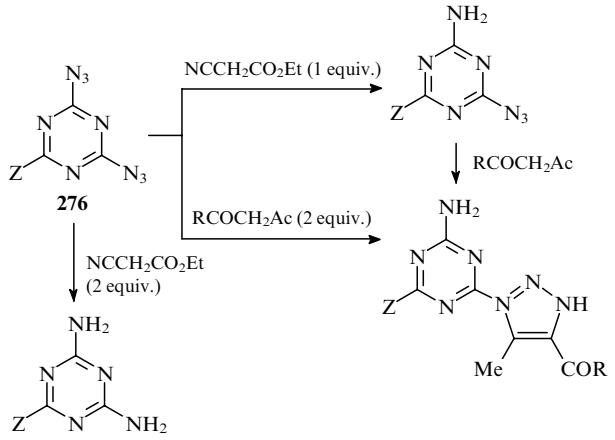
Scheme 11



Ar = 4-MeOC$_6$H$_4$; X = CO_2Et, Ac;

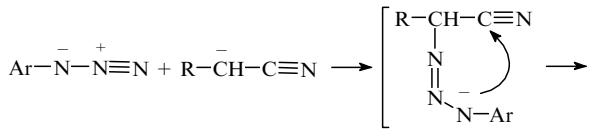
(*a*) Et_3N, DMF, 20 °C; (*b*) Et_3N, EtOH, Δ.

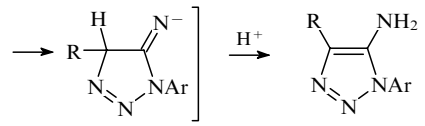
can be transformed into amino groups due to the better acceptor properties of the heterocycle.[468]



Z = MeO, EtO, NH_2; R = Me, EtO.

For azides with fragments having lower electron-withdrawing ability than pyrimidine and 1,3,5-triazine rings, 'diazo transfer' processes in the triazene and its decomposition (see Scheme 10) do not play a crucial role, the reaction being directed along the usual route to give 5-aminotriazoles. The reaction of phenyl azide with CH_2-active compounds containing a cyano group was first performed by Dimroth.[470] The reaction does not follow a concerted mechanism; it starts with attack of the electrophilic terminal nitrogen atom of the azide on the anion derived from the cyanomethylene component, resulting in the formation of the intermediate triazene, in which the anionic nitrogen atom attacks the electrophilic carbon atom of the cyano group in the same molecule. 'Quenching' (protonation) of the anion and isomerisation of the imine produce the final product, namely, aminotriazole.[3]



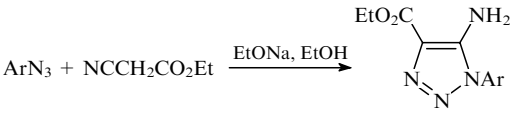


R = Ph, CO_2Alk, $CONH_2$, CN.

This route is important from the synthetic standpoint;[4] however, its use is restricted due to the lability of both the starting compounds and the reaction products under the given conditions. For example, it is known that 1-substituted 5-aminotriazoles readily undergo the Dimroth rearrangement; therefore, to prevent this transformation, the reaction is usually carried out at a lower temperature. In some cases, the optimal condition is to perform the process at room temperature in the presence of Bu^tOK in Bu^nOH or anhydrous K_2CO_3 in DMSO.[451]

The substituents of choice in the RCH_2CN molecule are Ph, CO_2Alk, $CONH_2$ and CN. Aryl and vinyl azides readily react with these cyano derivatives (examples are documented [3, 6, 34, 471]), while HN_3 and acyl azides do not react. Benzyl and alkyl azides give ambiguous results. For example, in the above-mentioned reaction of benzyl azide with ethyl cyanoacetate (EtONa, EtOH, 20 °C), the yield of ethyl 1-benzyl-5-aminotriazole-4-carboxylate did not exceed 5%.[472] The yield was increased by increasing the reaction time (30%)[473] or by conducting it under an elevated pressure of 5 kbar (53%). The attempt to replace the solvent by DMSO was unsuccessful.[451] On refluxing phenylethyl azide in ethanol in the presence of EtONa, the yield of 5-aminotriazole was low.[474]

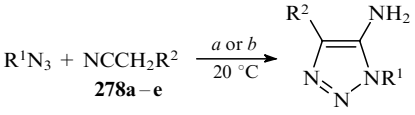
Various substituted phenyl azides were used for the synthesis of *N*-aryl-5-aminotriazoles .[475]



Ar = 3-ClC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 3-F$_3$CSC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2,5-Cl$_2$C$_6$H$_3$, 3,4-Cl$_2$C$_6$H$_3$, 2,4,6-Cl$_2$C$_6$H$_2$, 2-Cl-3-F-4-F$_3$CC$_6$H$_2$.

Similar products have been obtained from hetaryl azides, for example, 4-azidopyridine and its *N*-oxide,[26] 6-azido-2,3-diphenylindole,[239] 5-azido-2-trifluoromethylpyrimidine.[475] Most often, the reaction is carried out at 0–20 °C to prevent the Dimroth rearrangement.

Other acetonitriles have also been used in reactions with azides. For example, 1,4-disubstituted 5-aminotriazoles **277** were prepared by the reaction of 4-nitrophenyl and 4-pyridyl azides with nitriles **278a–c** (condition *a*)[26, 76] and benzyl azide with nitriles **278d,e** (condition *b*).[476, 477]

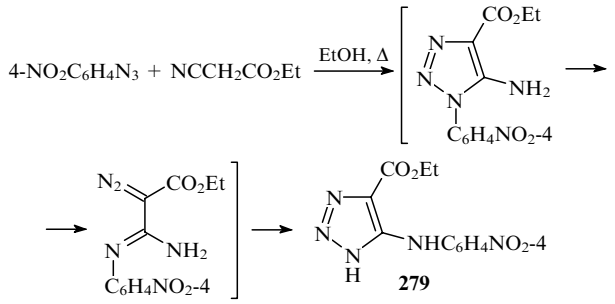


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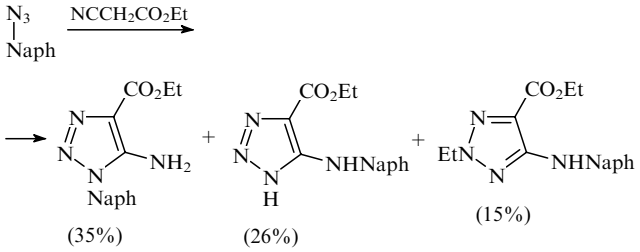
R^1 = Bn, 4-O$_2$NC$_6$H$_4$, 4-Py, 4-Py-*N*-oxide; R^2 = CO_2Me (**a**), Ph (**b**), 4-ClC$_6$H$_4$ (**c**), 4-MeOC$_6$H$_4$ (**d**), 4-MeC$_6$H$_4$ (**e**);
(*a*) MeONa, MeOH; (*b*) Bu^tOK, THF.

1-(Acridin-9-yl)-5-amino-4-aryltriazoles (Ar = Ph, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Py) and analogous 4-carbamoyltriazoles have been synthesised on the basis of 9-azidoacridines and cyano derivatives.[36]

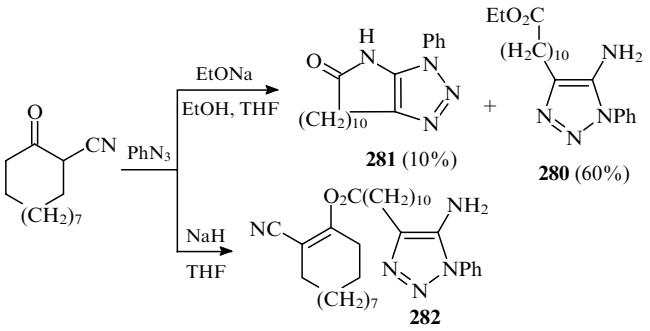
Refluxing a mixture of 4-nitrophenyl azide and ethyl cyanoacetate in EtOH yielded the Dimroth rearrangement product, 5-arylamino derivative **279**.[26]



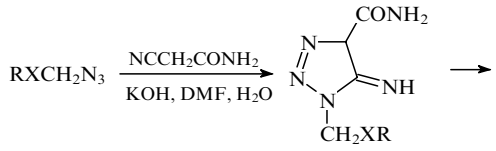
An analogous compound has been isolated, together with the product of its alkylation, in pronounced amounts in addition to the expected 5-amino-4-ethoxycarbonyltriazole, upon the reaction of 1-naphthyl azide with ethyl cyanoacetate.[478]

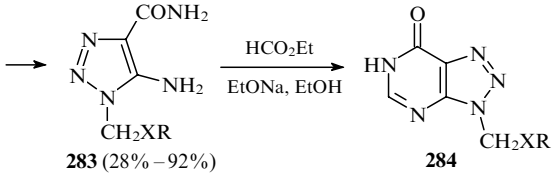


The chemoselectivity of the reaction of phenyl azide with the cyanoketone group incorporated in a macrocyclic system depends on the type of the base.[456] In the presence of EtONa, the macrocycle in the intermediate adduct is cleaved to give 5-aminotriazole **280** and the product of its intramolecular N-acylation **281** as an impurity. When NaH is used, acylation is intermolecular, giving rise to the product of O-acylation of the enol form of the starting cyanoketone **282**.[456]



The reaction of azides with cyanoacetamide proceeds smoothly giving the corresponding 5-amino-4-carboxamidotriazoles in high yields. Depending on the nature of the azide, the reaction is carried out in EtOH in the presence of EtONa at various temperatures (0–5 °C,[479] 20 °C[474] or 70 °C[138]), in DMF in the presence of KOH (0 °C)[292] or in DMSO in the presence of K_2CO_3 (35–40 °C).[451] The resulting 5-amino-4-carbamoyltriazoles are of interest as biologically active compounds[480,481] and the starting compounds for the synthesis of fused heterocyclic systems.[8,482] The preparation of these derivatives (**283**) by the reaction of substituted methyl azides with cyanoacetamide and their further transformation into 8-azapurines **284**, which are acyclic analogues of nucleosides, have been reported.[292,483]

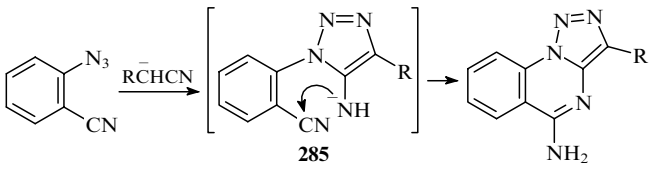




R = $BnO(CH_2)_2$, $(BnOCH_2)_2CH$, $BnO(BnOCH_2)CHCH_2$; X = O, S.

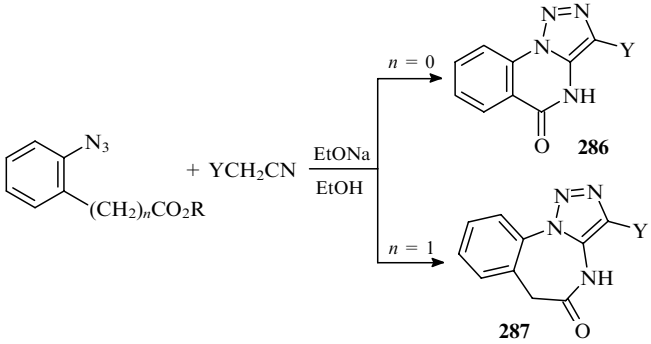
5-Amino-4-carbamoyltriazole 1-β-ribozide has been prepared in a similar way; it can be used to prepare 9-β-ribozides of 8-azahypoxanthines.[484,485] 2,9-Disubstituted 8-azapurin-6-ones were synthesised without isolation of intermediate triazoles.[486]

Of special interest from the synthetic standpoint is the reaction of the cyano carbanions RCH^-CN with *ortho*-substituted aryl azides (substituents CN, NO_2, CO_2H). Previously, it was found that aminotriazole **285** formed *in situ* is involved in the formation of the new ring:[487–489] the amide anionic centre attacks the electrophilic centre of the *ortho*-substituent.



R = Ph, CO_2Et, $CONH_2$, CN.

When aryl azide (or benzyl azide) contains a carbonyl group, the cyclisation ends with the formation of substituted 4*H*-triazolo[1,5-*a*]quinazolinones **286** and their seven-membered analogues **287**, respectively.[490–492]

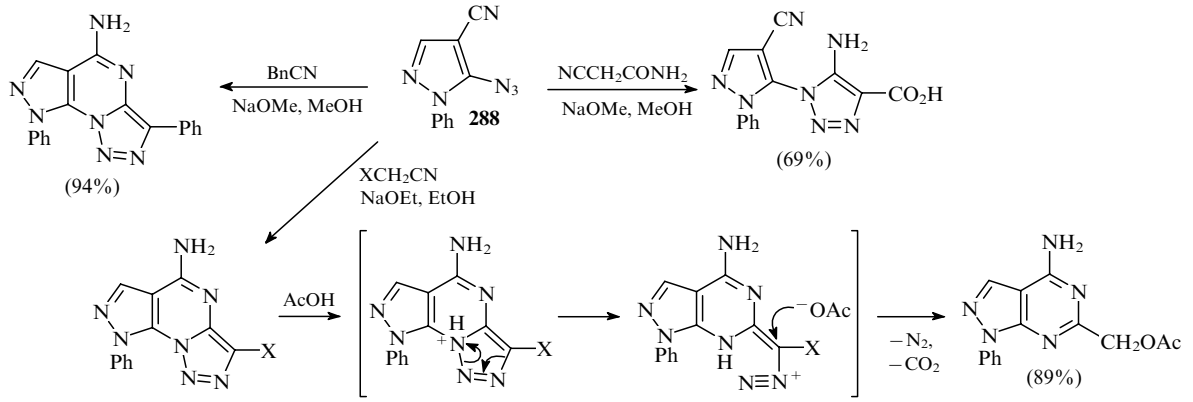


R = H, Et; Y = Ph, $CONH_2$, CONHMe, CO_2Et.

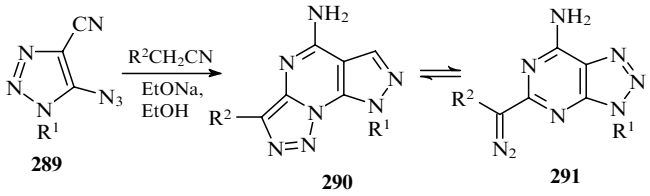
Azidocyano derivatives of five-membered nitrogen heterocycles react in this way with the anions derived from substituted acetamides, the subsequent transformations of the compounds formed being dependent on the nature of the heterocycle and the acetamide. For example, 5-azido-4-cyanopyrazole **288** is converted into different products when reacted with phenylacetonitrile, cyanoacetamide and cyanoacetic acid and its esters.[493] Interestingly, the mechanism of the last-mentioned transformation includes opening of the triazole ring at the N–N bond, ejection of the nitrogen molecule and decarboxylation (Scheme 12).

In the reaction of 5-azido-4-cyanotriazoles **289** with substituted acetonitriles, it is possible to detect both tautomers of the product, namely, cyclic **290** and open **291** tautomers, whose ratio depends on the polarity of the medium and the nature of the substituent.[494,495]

Scheme 12

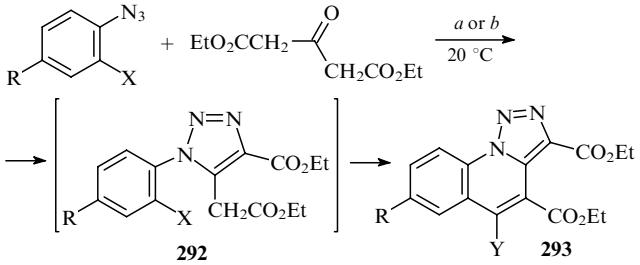


X = CO_2H, CO_2Et.



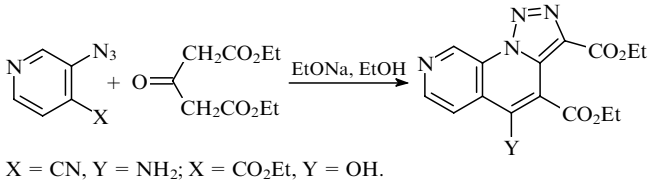
R^1 = Bn, 4-ClC_6H_4; R^2 = Ph, CN, CO_2Et.

Subsequently, the scope of this reaction was extended. The reactions of various *ortho*-substituted aryl azides with the diethyl acetonedicarboxylate carbanion generated under the action of bases or an ion exchange resin in the OH-form have been studied.[489] The reactions take place in ethanol at room temperature. The side fragment in the intermediate 1-aryltriazole **292** interacts immediately with the *ortho*-substituent. The closure of the additional ring affords tricyclic system **293**.



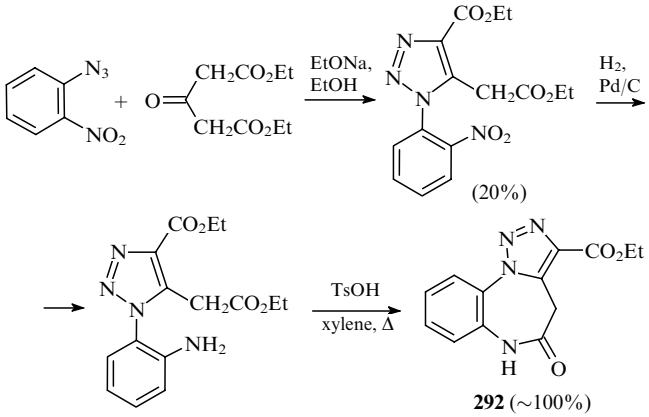
R = H, Cl; X = CHO, COMe, COPh, CN, CO_2Me; Y = H, Me, Ph, NH_2, OH; (*a*) EtONa, EtOH; (*b*) Amberlite IRA-400 (OH), EtOH.

The amino or hydroxy derivative of 1,2,3-triazolo[1,5-*a*][1,7]naphthyridine is formed in a similar way from azidopyridine containing a CN or a CO_2Et group, respectively, when made to react with diethyl acetonedicarboxylate.[489]

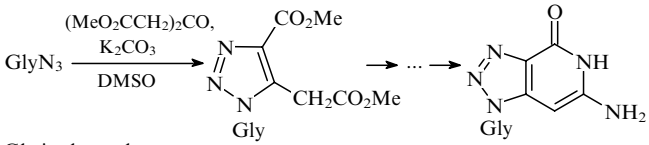


X = CN, Y = NH_2; X = CO_2Et, Y = OH.

Only in the case of 2-nitrophenyl azide, was 1-(2-nitrophenyl)-triazole isolated; it was reduced to the corresponding *o*-aminophenyl derivative, which was refluxed in xylene containing some *p*-toluenesulfonic acid to give 1,2,3-triazolo[1,5-*a*]benzo[1,5]diazepin-6-one **292** in a quantitative yield[489]

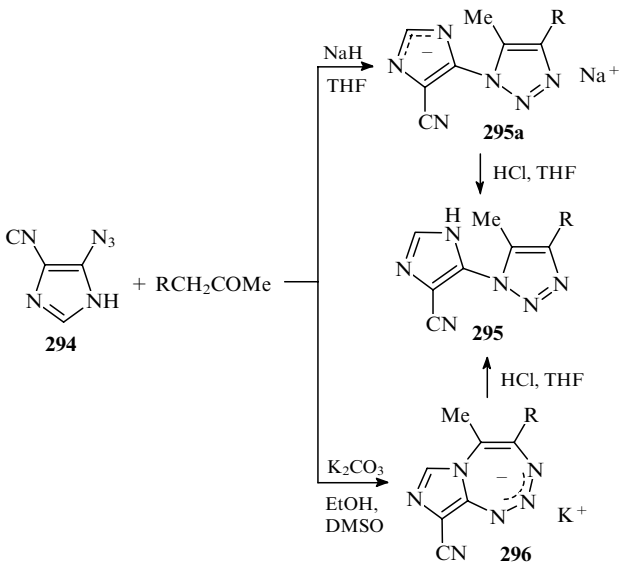


Similar transformations have been employed in the synthesis of 8-aza-3-deazaguanine nucleosides; the reaction between protected glycosyl azides and dimethyl acetonedicarboxylate was carried out in DMSO in the presence of K_2CO_3.[496]



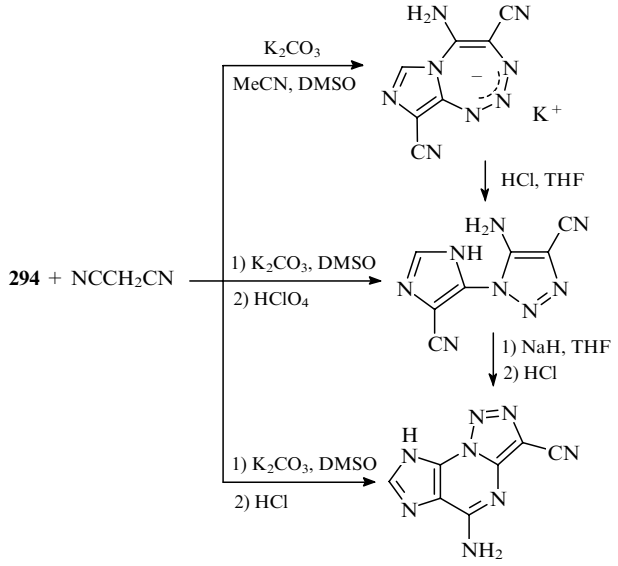
Gly is glycosyl.

The behaviour of 5-azido-4-cyanoimidazole **294** in the reaction with compounds containing an active CH_2-group differs from that presented above for the benzene and pyridine analogues. It was shown that, depending on the conditions of reactions with β-dicarbonyl compounds, either imidazolate (**295a**) or tetrazepinate salts (**296**) can be isolated; on treatment with HCl in tetrahydrofuran, these products are converted into the corresponding imidazolyltriazole **295** in high yields.[497]



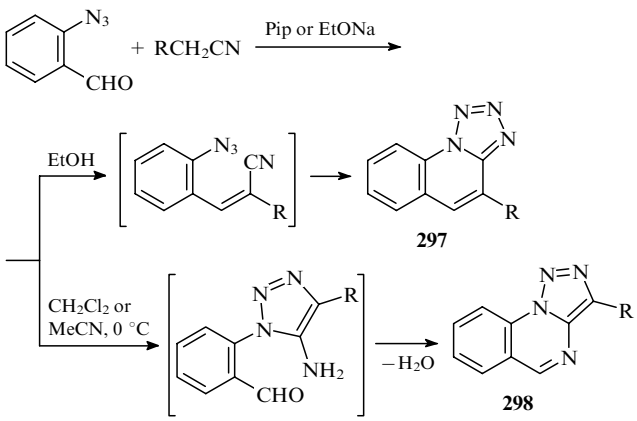
R = COMe, COPh, CO_2Me.

The outcome of the reaction of the same azide with malononitrile depends on the conditions of product isolation. It has been assumed [497] that imidazo[5,1-*d*][1,2,3,5]tetrazepinate salts play a key role in these transformations.



When the phenyl azide molecule contains an *o*-CHO group, the reaction pathway is determined by the conditions, in particular, by the solvent used. The reaction of 2-azidobenzaldehyde with substituted acetonitriles in EtOH in the presence of piperidine or EtONa results in tetrazolo[1,5-*a*]quinolines **297** (first, the Knoevenagel condensation takes place at the aldehyde group and only after that, does the 1,3-cycloaddition of the azide group to the C≡N bond of the intermediate nitrile occur). However, the same reaction in an aprotic solvent at 0 °C yields triazolo[1,5-*a*]quinazolines **298**.[498] With the protected aldehyde function (as the oxime or *N*-methylnitrone), this reaction produces only triazolo[1,5-*a*]quinazolines **298**, irrespective of the conditions.[498]

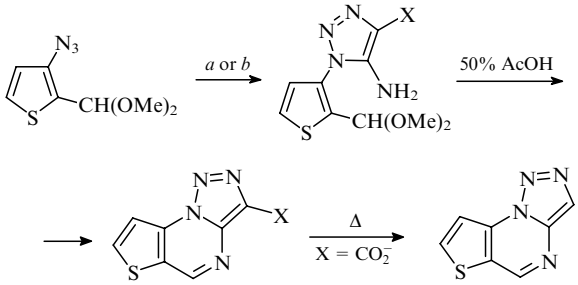
The attempts to induce a regioselective attack by cyano carbanions on the carbonyl group in 2-azidoacetophenone failed, 5-methyltriazolo[1,5-*a*]quinazolines being isolated as the only products.[489]



R = Ph, 3,4-$(MeO)_2C_6H_3$, 2-Py, COPh, CO_2Et, CN, $PhSO_2$;
Pip is piperidine.

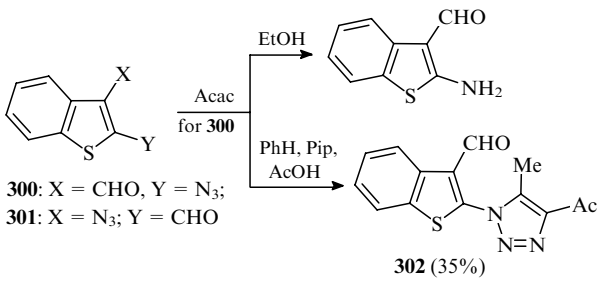
The behaviour of mono- and dimethyl-6-azido-5-formyluracils towards ethyl cyanoacetate and malononitrile in ethanol is similar to that of 2-azidobenzaldehyde: in the presence of piperidine, only the corresponding tetrazolo[1′,5′:1,6]pyrido[2,3-*d*]pyrimidines are formed.[499]

The reaction of 3-azidothiophene-2-carboxaldehyde with substituted acetonitriles was carried out using the acetal protection of the aldehyde group in order to prevent the aldol-crotonic condensation. The protection was removed after the formation of aminotriazole; the condensation of the free aldehyde group with the amino group gave a pyrimidine ring in the tricyclic system **299**.[488]

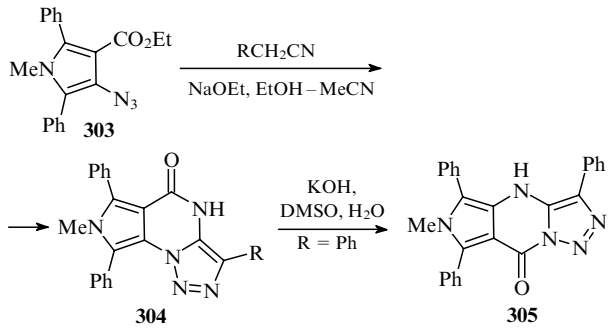


(*a*) $PhCH_2CN$, MeONa, MeOH, Δ;
(*b*) EtO_2CCH_2CN, EtONa, EtOH, Δ.

The behaviour of two isomeric azido derivatives of benzo[*b*]-thiophenealdehydes **300** and **301** towards 1,3-dicarbonyl compounds has been studied.[500] It was shown that only the 2-azido isomer **300**, does form triazole **302** (benzene, piperidine acetate as the catalyst) when made to react with acetylacetone, while in EtOH, reductive deazotisation takes place. The 3-azido isomer reacts with diethyl malonate, ethyl acetoacetate and acetylacetone to give 2-alkylidene derivatives of 3-azidobenzothiophene.[500]



If the (het)aryl azide molecule contains an ester group, instead of the aldehyde group, an amide fragment is formed in the resulting ring. This was shown using azidopyrrole **303** as an example. It was noted that the reaction products did not undergo the Dimroth rearrangement under classical conditions; only upon refluxing in the DMSO – water system, did phenyl derivative **304** rearrange to heterocycle **305** in a quantitative yield.[501, 502]



R = Ph, CN, $CONH_2$.

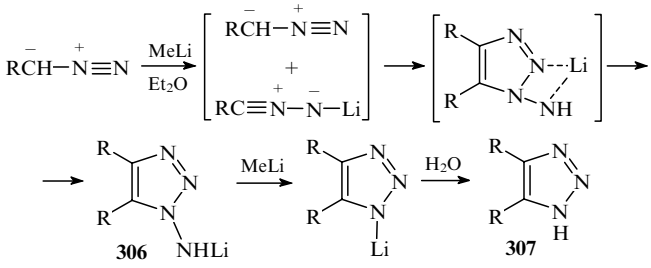
To conclude the Section devoted to the methods of synthesis of triazoles from azides, it is pertinent to list once again the most advanced modifications of the experimental conditions used to carry out dipolar cycloaddition. Apart from the dependence on the nature of reactants, solvents and temperature, the rate and completeness of the reaction were found to depend markedly on the pressure in the reaction system.[214, 216, 242, 291, 473]

The use of ionic liquids as the reaction media allows one to sharply reduce the reaction time.[268] Cascade synthesis of 1-substituted triazoles from allene derivatives of aryl iodides, NaN_3 and norbornene has been carried out.[272] The reactions of organic azides with acetylene amides, azidomethylphosphonates with low-activated acetylenes and enamines and aryl azides with methylenephosphoranes have been successfully carried out in the absence of solvents on exposure to microwave radiation.[179, 233, 283, 335]

New methods the regiocontrol of dipolar cycloaddition include encapsulation conditions for the reactants[237] or the 'chemical recognition' principle (for example, the presence of the crown-ether fragment in the azide molecule and the terminal ammonium group in the substituted acetylene).[238] A series of substituted triazoles with a high degree of purity have been prepared by solid-state synthesis using polymer-supported 3-aminocrotonamides and tosyl azide,[416] 2-azidocarboxylic acids,[503, 504] 5-azido-4-hydroxyvaleric acid.[505] However, in this version, it is impossible to use low-reactivity compounds and it is inconvenient to monitor the reaction. It has been proposed to avoid these difficulties by using soluble polymers with grafted dipolarophiles.[306, 506] As a polymer of this type, monomethyl ether of polyethylene glycol with a molecular mass of 5000 (MeO-PEG 5000) was proposed. This polymer is soluble in many organic solvents, which allows one to monitor the cycloaddition using spectral methods. The removal of the target products from the polymer is accomplished under mild conditions by treatment with $NaBH_4$ in ethanol. Using this procedure, several carbohydrate triazole derivatives have been prepared.[306, 506] Another variant implies attachment of the azide function to a polymer and carrying out cyclocondensation with DMAD or terminal acetylenes containing Ph, CO_2Me, CH_2Cl, CH_2Br, CH_2OH or CH_2CH_2OH group. The reaction mixture is then treated with formic acid to isolate the regioisomers, namely, 4- and 5-substituted triazoles.[507] The solid-state combinatorial synthesis of substituted carboxamidotriazoles by successive treatment of supported 3-oxobutyramide with triethyl orthoformate and tosyl azide has been described.[508]

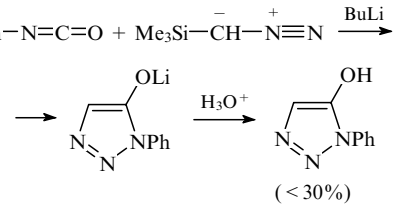
V. Methods of formation of the C(4) – C(5) and N(1) – N(2) bonds

This line of research is not very popular in triazole synthesis. This is mainly limited to the condensation of diazo derivatives with compounds containing activated C = N bonds. It was found in the mid-20th century that metallated derivatives of diazoethane and phenyldiazomethane form 4,5-dimethyl- or 4,5-diphenyltriazoles, respectively.[509, 510] Some suggestions have been made concerning the reaction mechanism and the structures of intermediates but they have long remained unproved. In a recent publication,[511] the reaction of trimethylsilyldiazomethane with butyllithium was studied, the structure of the dimerisation product formed was determined and theoretical calculations were performed that made it possible to correct the existing views on the structure of the reacting species and the dimerisation mechanism. The general scheme includes the reaction between two dipolar diazomethane molecules, the formation of the lithium derivative of *N*-aminotriazole **306** and cleavage of the exocyclic N – N bond. Treatment of the reaction mixture with water results in disubstituted triazoles **307**.[511]



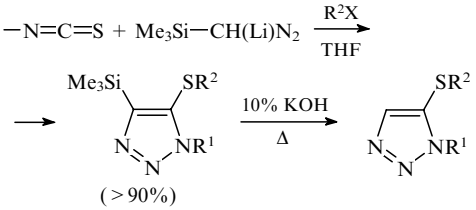
R = Me, Ph, Me_3Si.

Phenyl isocyanate reacts with trimethylsilyldiazomethane in the presence of butyllithium to give 5-hydroxy-1-phenyltriazole.[512]



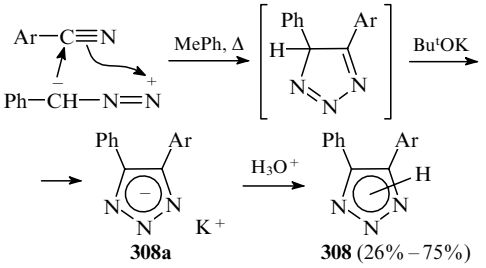
C-Metallated diazoalkanes are also capable of this type of cyclocondensation. Indeed, the α-diazomethylzirconium complex reacts with phenyl and naphthyl isocyanates to give triazole derivatives.[513]

Isothiocyanates easily react with the lithium salt of trimethylsilyldiazomethane but the reaction pathway depends on the solvent used: 2-amino-1,3,4-thiadiazoles are formed in Et_2O; only conducting the reaction in THF, does allow one to prepare 1-substituted 5-alkylthio-4-trimethylsilyltriazoles.[514] The Me_3Si group is readily removed by refluxing of the reaction products with 10% KOH.



R^1 = Me, Bu^n, Bn, Ph, $CH_2 = CHCH_2$; R^2X = MeI, BnBr.

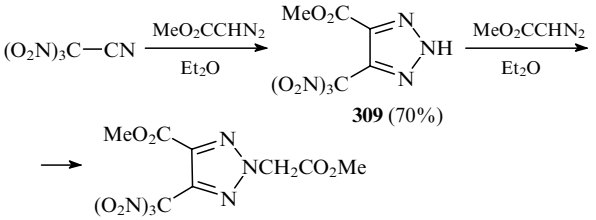
4,5-Diaryltriazoles **308** are formed in the reaction of phenyldiazomethane with substituted benzonitriles in the presence of Bu^{t}OK according to the dipolar cycloaddition pattern to an activated C≡N bond.[515] The function of a base is to eliminate a proton in the cycloadduct to give anion **308a**, the treatment of which with an aqueous solution of an acid gives the corresponding triazole.



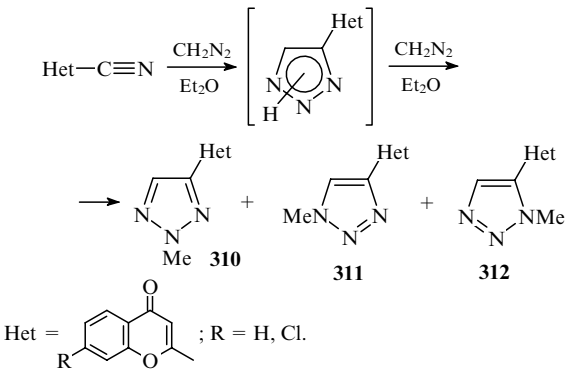
Ar = Ph, 4-MeC$_6$H$_4$, 2-BrC$_6$H$_4$, 4-ClC$_6$H$_4$.

It is noteworthy that azines of aromatic aldehydes (Bu^{t}OK, DMSO, 20 °C) enter into a similar reaction to give symmetric 4,5-diaryltriazoles (Ar = Ph, 3-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$), but the product yield does not exceed 40%.[515]

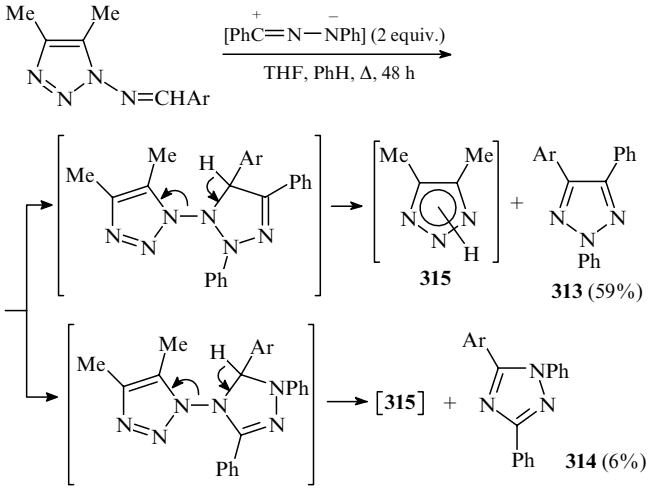
Other cyano derivatives in which the C≡N bond is activated can also react with diazo compounds. For example, cyanotrinitromethane reacts with methyl diazoacetate in ether at room temperature to give 5-methoxy-4-trinitromethyl-2*H*-triazole **309**, which undergoes N-alkylation on long-term storage in the reaction mixture.[516, 517]



2-Cyanochromone and its 7-chloro derivative reacts with excess diazomethane to give a set of three *N*-methylated triazoles **310**–**312** in which the 2-methyl derivatives **310** predominate.[518] Presumably, prototropic triazole is first formed and then it undergoes N-methylation. The reaction of diazomethane with nitrophthalonitriles proceeds in a similar way, but involving only one cyano group.[519]



In order to obtain N– N′ bonded triazole rings, attempts have been made to involve *N*-arylideneaminotriazoles and diphenylnitrile imine in cycloaddition.[520] However, the C=N bond in *N*-arylideneaminotriazoles proved to be inactive and only in the case of Ar = 4-NO$_2$C$_6$H$_4$, did the reaction give triaryltriazole isomers in satisfactory yields. Diphenylnitrile imine was generated *in situ* by treatment of *N*-phenylbenzoylhydrazonoyl chloride with triethylamine in an aprotic solvent (THF–benzene), and the suspension obtained in this way was kept at the boiling point of the solvent mixture. Presumably, the reaction proceeds *via* isomeric cycloadducts, each of them decomposing with cleavage of the exocyclic N–N bond to give 1,2,3-triazole derivatives **313** and 1,2,4-triazole derivatives **314**, respectively.[520] The intermediate 4,5-dimethyltriazole **315** adds a second nitrile imine molecule (at the 1- or 2-position).



Ar = 4-O$_2$NC$_6$H$_4$.

VI. Conclusion

The methods of synthesis of substituted 1,2,3-triazoles described in the review were used in the last decade to prepare a great diversity of compounds, the properties of which proved to be rather attractive for practical purposes, in particular, for the development of drugs and plant protection and growth control agents.

For example, it has been proposed to use polyunsaturated conjugated systems containing terminal 5-hydroxytriazole groups as dyes for photographic materials,[512] and bis(triazol-2-yl)-substituted arylenes with different bridging fragments, in organic electroluminescence devices.[81] (2*H*-Benzotriazol-2-yl)-4-methylphenol is known as the Benazol-P light stabiliser.[135] Fluorescing bleaching agents can be prepared on the basis of triazole derivatives.[521] In view of the substantial energy content of nitrogen derivatives, it has been proposed to use nitrotriazoles as components of explosive mixtures,[107, 108, 522] and 1,1′-bitriazole,[115] 1*H*-triazole and its 1-amino derivatives can be used as nitrogen generators for the automobile safety bags.[523–526]

1-Benzyl-4,5-dibenzoyl- and -4,5-dialkoxycarbonyltriazoles inhibit the corosion of some metals in acid media;[527–530] 4-alkyl(hydroxy, nitroso, mercapto)-triazoles can also be used to protect aluminium and its alloys.[531]

In recent years, 1-hydroxy-1*H*-triazoles and their *O*-derivatives have attracted the attention of researchers engaged in the search for new coupling reagents for peptide synthesis to suppress racemisation.[46, 102] For instance, ethyl 1-hydroxytriazole-4-carboxylate can be used in combination with diisopropylcarbodiimide in solid-state peptide synthesis [46, 532, 533] and in combination with peptide hydrazides for the assembly of peptide segments.[534, 535]

Data on the biological action of triazole derivatives and the possible use of these compounds in agrochemistry, veterinary and medicine have been reported in a number of publications and patents. Particular aspects of the activity are considered in special reviews.[14, 536–539] 1-Aryl-5-phenoxytriazoles have been proposed as herbicides,[187] while a number of 2-[2-alkyl- and cycloalkyl(2*H*-triazol-4-yl)]acrylonitriles have been proposed as insecticides, nematocides and acaricides.[540] Some (het)aryltriazoles have shown high insecticide and pesticide activities,[96, 247, 248, 541–543] and halogen and haloalkyl derivatives of 1-(diarylmethyl)triazoles have exhibited insecticide properties.[544]

Triazolyl analogues of natural antibiotics have shown excellent antibacterial action.[545, 546] Antibacterial properties have also been found for triazolyl derivatives of esters of β-enamino acids,[547] 7β-(triazolyl-4-formamido)cephalosporins,[548–550] 4-aryl-1-[5-methyl-1-(4-chlorophenyl)triazole-4-carbonyl]thiosemicarbazides and their heterocyclic derivatives.[551] Antiinflammatory activities have been found for carboxamidotriazoles,[400] while sterically hindered 5-(4-hydroxyphenyl) derivatives of triazole-4-carboxylic acids and amides have proved active in the therapy of arthritis.[399] For 5-amino-4-carbamoyltriazoles,[481] dimethyl triazole-4,5-dicarboxylate with *N*-arylacetamide substituents[552] and some bistriazoles,[553] various types of antimicrobial activities have been found. 1-Benzyl-5-aminotriazoles constitute a new class of antiproliferative agents for the therapy of psoriasis and coccidiosis.[554–557]

1-Aryltriazole-4,5-dimethanol derivatives[180] and 1-(1-phenyltriazol-5-yl)alkyl-4(1*H*)-quinolones[558] possess a cytotoxic action, while 5-amino-1-{[3,5-dichloro-4-(chlorobenzoyl)phenyl]-methyl}-4-carboxamidotriazole exhibited anti-HIV action, along with cytotoxic properties.[559–561] Clinical investigations of the last-mentioned compound have demonstrated that it is well tolerated in the case of oral administration, decreases a tumour, and stabilises the patient's condition.[537] Some 5-amino-4-carboxamidotriazoles inhibit metastases,[562–564] and one of the 4β-(1-triazolyl)podophyllotoxins has demonstrated even stronger cytotoxic properties *in vivo* than the anticancer drug etoposide used in clinical practice.[340] Some triazole *N*-nucleosides also possess antitumour and antiviral properties.[426, 565] 17-(Triazol-1-yl)steroids induce a decrease in testosterone and dihydrotestosterone levels and can be used for the therapy of benign hypertrophy and prostatic cancer.[566–568]

Some substituted 1-(4-quinolyl)triazoles are analgesics, being superior to indometacin as regards this type of activity.[463, 464] For the series of fused diazepine systems, it has been shown that the neuroleptic properties are due to the presence of the 1,2,3-triazole fragment in the structure.[569] 1-Aryl-5-pyridyltriazoles have formed a new structural group of anticonvulsants, which are comparable in action with known clinical drugs and, in addition, possess a very low neurotoxicity.[570, 571] Fluorinated 1-arylalkyltriazoles also exhibit an antispasmodic action,[193] 4(5)-carboxamide and -alkylcarbamoyl derivatives have been recommended for the therapy of neuropathic diseases, in particular, epilepsy,[572–575] while triarylmethyltriazoles have been proposed for treatment of central nervous system diseases.[176]

A series of substituted 5-dimethylaminomethyltriazoles with (thio)morpholino groups in the heterocycle or in the side chain are antagonists of neurokinin receptors and exhibit the properties of opioid analgesics.[576] Preparations of this type have been proposed for the curing and prevention of inflammations, headaches and neuralgias.[166, 347–349] Some 4-piperidyl-substituted triazoles[270] and substituted triazolo[1,5-*a*]quinazolines[577] are active with respect to muscarin receptors and are of particular interest as drugs against Alzheimer's disease. Tricyclic benzoazepine compounds containing a carbamoyltriazole fragment can be used as antiallergic drugs.[192, 578, 579] Substituted amidinotriazoles showed an antihypertensive effect, while having low toxicity.[141] 5-(2-Nitroanilino)triazoles and 1-(4-carbamidotriazol-5-yl)benzotriazoles possess a vasodilatory action caused by activation of potassium channels.[137, 480]

Some 1-(β-D-ribofuranosyl)-5-alkylcarbamoyltriazole derivatives[337, 580, 581] and carbocyclic analogues of ribavirin containing a 4-carbamoyltriazole fragment[315] showed high anti-HIV and antihepatitis activities.

Many publications are devoted to the interaction of functional derivatives of 1,2,3-triazole with various bioreceptors and enzymes but these studies are beyond the scope of this review. We would only like to note that triazole compounds are attractive components in biochemical and medical investigations, as they are formed in high yields in aqueous or aqueous-organic media from organic azides and terminal alkynes *via* Cu(I)-catalysed cycloaddition and are readily bound to biological targets through hydrogen bonds and dipole interactions, while still remaining chemically inert linkers.[582, 583]

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[b] — *Chem. Heterocycl. Compd. (Engl. Transl.)*
[c] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[d] — *Russ. Chem. Bull., Int. Ed. (Engl. Transl.)*
[e] — *Chem.-Pharm. J. (Engl. Transl.)*
[f] — *Russ. J. Appl. Chem. (Engl. Transl.)*