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Heterocyclic azides: advances in their chemistry

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This is the first systematic review on the synthesis and reactions of heterocyclic azides with acetylene and acetonitrile derivatives, alkenes, enamines and dicarbonyl compounds. Examples are given for the application of these reactions to the synthesis of mono-, bi- and tricyclic compounds and ensembles of various heterocycles, *e.g.*, azines and azoles (including 1,2,3-triazole derivatives and nonaromatic 1,2,3-triazolines), amidines and diazo compounds. Methods for the synthesis of supramolecular structures, coordination compounds, ligands, bioconjugates and biologically active compounds based on reactions with heterocyclic azides are considered. The review describes the use of these transformations in biological chemistry to study processes in living systems, as well as in materials chemistry for the production of luminophores and sensors for metals. Original studies published mainly over the past 15 years are discussed.
The bibliography includes 222 references.

Contents

1. Introduction

Azides are widely used in modern organic synthesis for the preparation of amines, heterocyclic compounds with small, medium or macrocycles, natural compounds and their analogues and also for the design of new high energy materials. These compounds are highly reactive and are involved in reactions with nucleophiles and electrophiles, radical reactions and cycloaddition reactions with derivatives containing double or triple bonds.[1,2] The copper-catalyzed azide – alkyne cycloaddition (CuAAC, referred also to as the click reaction), independently discovered by

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Meldal and Sharpless, and the related cycloaddition reactions catalyzed by ruthenium and miscellaneous metals resulted in the development of a powerful methodology for the synthesis of 1,4- and 1,5-disubstituted triazoles [3–8] and, as a consequence, in the disclosure of new compounds with practically useful properties.[9–27] Advances in the chemistry of azides are presented in the reviews [2, 3, 15, 19, 24] and the fundamental monograph by Bräse and Banert.[1] However, these publications address mainly the reactions of aromatic azides. Reviews focused on the properties and transformations of heterocyclic azides are lacking in the literature. Meanwhile, the recent years have witnessed a significant increase in the number of papers dealing with the synthesis and the chemical and biological properties of azides of the heterocyclic series.[2, 9, 16, 23, 26–47] New methods for the synthesis of these compounds were developed, kinetic studies of their decomposition were performed, and theoretical studies of their structures and reactivity were conducted.[33–47] Heterocyclic azides are successfully used in organic synthesis to prepare various heterocycles, diazo compounds, amidines, bioconjugates and other practically useful organic compounds.[23, 28] Some heterocyclic azides exhibit antiviral properties and other types of biological activity and were employed to prepare new luminophores and sensors for metal ions.[23, 28, 43]

This review is concerned with the chemistry of heterocyclic azides. This is the first review, in which methods for the synthesis of heterocyclic azides are analyzed and brought together. The reactions of these compounds with acetylene and acetonitrile derivatives, alkenes, enamines and active methylene dicarbonyl compounds are considered. Tetrazoles are demonstrated to be a potential source of azides in the cycloaddition to alkynes and acetonitrile derivatives. The review considers reactions of heterocyclic azides, which were applied to synthesize mono-, bi- and tricyclic compounds, amidines and diazo compounds, as well as different heterocyclic ensembles (of azines and azoles, in particular 1,2,3-triazole derivatives and nonaromatic 1,2,3-triazolines). These reactions were used to prepare supramolecular structures, ligands, metal complexes, bioconjugates and biologically active compounds. The review summarizes applications of heterocyclic azides in the biological chemistry to study processes in living systems and in the materials chemistry for the development of luminophores and sensors for metals.

2. Methods for the synthesis of heterocyclic azides

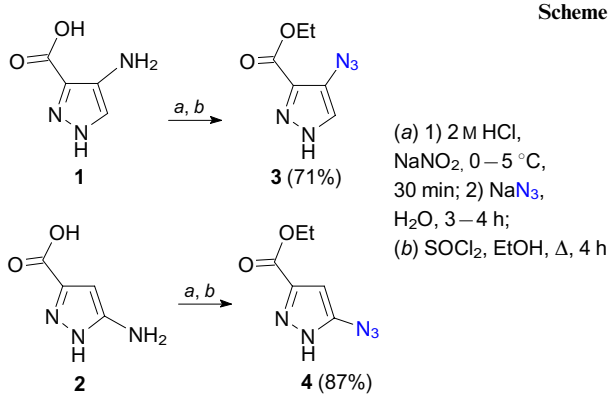
The methods considered in this Section are classified according to the nature of the reagent, which is used to introduce the azide group into heterocyclic compounds.

2.1. Reactions of diazonium salts with sodium azide

The reaction of diazonium salts with sodium azide is a conventional preparatively convenient method for the synthesis of aromatic azides. The similar reactions of heterocyclic diazo compounds afford heterocyclic azides.[1] In these examples of the synthesis of heterocyclic azides, the authors, with rare exceptions, did not isolate heterocyclic diazo compounds but used them *in situ* for the reaction with sodium azide. For example, Vatsadze and co-workers [48] performed the diazotization of aminopyrazoles **1** and **2** followed by the treatment with an aqueous solution of NaN_3 and synthesized 4-azido- (**3**) and 5-azido-1*H*-pyrazole-3-carbocyclic acids (**4**) in two steps (Scheme 1).[48]

It is worth noting that Fabbrizzi *et al.*[49] applied a similar approach nine years earlier. The diazotization of diamine **5**

Scheme 1



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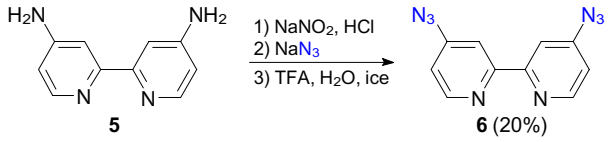
Translation: T.N.Safonova

Scheme 2

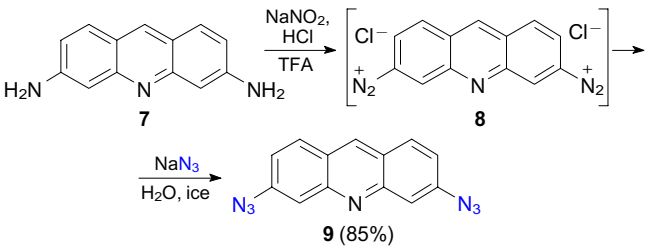


TFA is trifluoroacetic acid

in the presence of sodium azide afforded diazide **6** in low yield (Scheme 2).

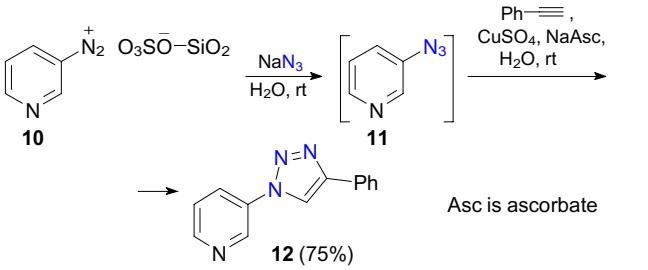
In order to synthesize a hybrid molecule of acridine with two triazole rings, Sparapani *et al.*[50] investigated the diazotization of 2,8-diaminoacridine **7**. It was demonstrated that intermediate diazo compound **8** can be used *in situ* for the reaction with sodium azide giving 2,8-diazidoacridine **9** in good yield (Scheme 3).

Scheme 3



Zarei *et al.*[51] demonstrated that 3-aryldiazonium silica sulfate **10** can be employed in the reaction with sodium azide to prepare 3-azidopyridine **11** (Scheme 4). The authors noted the thermal stability of the starting diazonium salts and a high reaction rate. Azide **11** generated in this way was used *in situ* for the synthesis of pyridyltriazole **12**.

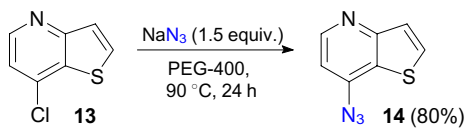
Scheme 4



2.2. Replacement of a halogen atom and a nitro group by the reaction with sodium azide

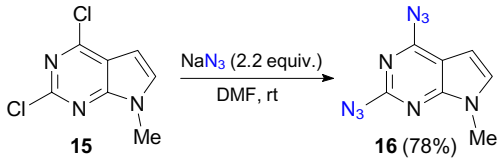
The replacement of a halogen atom or a nitro group by the azide group is widely used in the synthesis of azido-containing heterocycles. In some cases, the reaction requires the activation. Thus, Rodrigues *et al.*[52] found that low-molecular-weight polyethylene glycol (PEG-400) catalyzes the replacement of the halogen atom in 7-chlorothieno[3,2-*b*]-pyridine **13** in the reaction with sodium azide giving azide **14** in high yield (Scheme 5).

Scheme 5



By contrast, the nucleophilic substitution of chlorine atoms in 2,4-dichloro-7-methylpyrrolo[2,3-*d*]pyrimidine (**15**) by azide groups in the reaction with sodium azide in DMF occurs at room temperature and affords diazide **16** (Scheme 6).[53] It was noted that this product is light-unstable.

Scheme 6



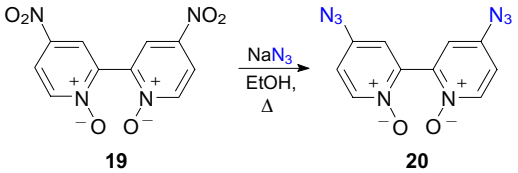
rt is room temperature

The reaction of commercially available imidazolium chloride **17** with sodium azide afforded azide **18** containing the imidazolium ring (Scheme 7).[54] Azide **18**, synthesized *in situ*, can be utilized to transfer the diazo group to active methylene carbonyl compounds and acetonitrile derivatives (see Section 3.4). It is worth noting that azide **18** has an advantage over sulfonyl azides, because the reaction with this compound affords water-soluble by-products, which can easily be separated from the target compounds.

Scheme 7

It was demonstrated that the nitro group can also be replaced by the azide group. For example, dinitro compound **19** can easily be transformed into diazide **20** under reflux in ethanol in the presence of sodium azide (Scheme 8).[49]

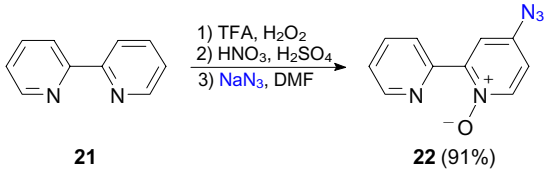
Scheme 8



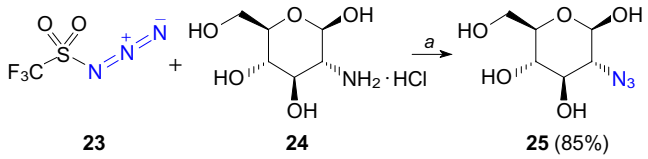
Baron *et al.*[55] developed a method for the selective oxidation of one pyridine ring of molecule **21** followed by the nitration and the replacement of the nitro group by the azide group under the treatment with sodium azide. This process gave 4-azidodipyridine *N*-oxide **22** (Scheme 9).

Aromatic azides are commonly synthesized through the diazo transfer to the amino group using highly electrophilic

Scheme 9



Scheme 10



23 **24** **25** (85%)

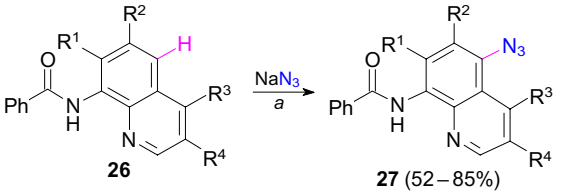
(*a*) $CuSO_4 \cdot 5H_2O$, K_2CO_3 or Et_3N, MeOH

azides.[1,38] This promising method is still little used in the synthesis of heteroaromatic azides. The reaction of trifluorosulfonyl azide (**23**) with aminoglucose **24** made it possible to prepare 2-azidoglucose **25** (Scheme 10).[56]

2.3. Direct azidation of heterocycles with sodium azide

Zhu and co-workers[57] developed an efficient method for the regioselective synthesis of 5-azido-8-aminoquinolines **27** based on the copper diacetate-catalyzed insertion of the azide group into the C–H bond of 8-aminoquinolines **26** in the presence of $K_2S_2O_8$ (Scheme 11). The authors demonstrated that the acylamide group plays an important role in the regioselective CH-activation of quinolines.

Scheme 11



26 **27** (52–85%)

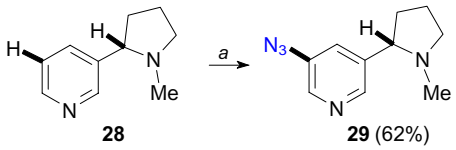
(*a*) $Cu(OAc)_2$ (0.25 equiv.), $K_2S_2O_8$ (2.0 equiv.), TBAB (1.0 equiv.), DBU (1.0 equiv.), 40 °C; TBAB is tetra-*n*-butylammonium bromide, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; R^1 = Me, H; R^2 = Me, OMe, CH_2OMe; R^3 = H, Me; R^4 = H, Me, Ph

2.4. Borylation – azidation of heterocycles

Srinivasan *et al.*[58] proposed a one-pot method for the generation of 5-azidopyridine and 3-azidoquinoline derivatives involving the iridium-catalyzed C–H-borylation and the azidation catalyzed by copper trifluoromethanesulfonate (triflate, TfO). The generated azides were utilized in the *in situ* click reaction accompanied by the formation of 1-hetaryl-1,2,3-triazoles.[58]

Thus, using (–)-nicotine (**28**) as the starting reagent, Srinivasan *et al.*[58] accomplished the regioselective synthesis of 3-azidonicotine **29** (Scheme 12). This method of synthesis of azidonicotine is of interest for medicinal chemistry and agriculture since nicotine and its derivatives are powerful ligands, which modulate nicotinic acetylcholine receptors, and also due to a considerable synthetic potential of azides.

Scheme 12

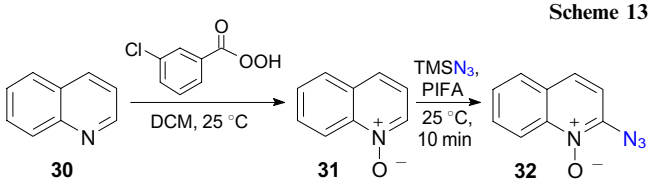


28 **29** (62%)

(*a*) 1) $[Ir(cod)OMe]_2$ (0.25 mol.%), B_2Pin_2, dtbpy (0.5 mol.%), THF, 80 °C,14 h; 2) NaN_3, $Cu(OTf)_2$ (1.0 mol.%), EtOH, air, 40 °C, 8 h; cod is 1,5-cyclooctadiene, B_2Pin_2 is bis(pinacolato)diboron, dtbpy is 2,6-di-*tert*-butylpyridine

Li *et al.*[59] performed the one-pot two-step synthesis, involving the oxidation of quinoline **30** with 3-chloroperoxybenzoic acid and the oxidative C(2)–H azidation of *N*-oxide **31** with trimethylsilyl azide ($TMSN_3$) in the presence of [bis(trifluoroacetoxy)iodo]benzene (PIFA). This synthesis afforded 2-azidoquinoline *N*-oxide **32** in good yield (Scheme 13).

Scheme 13

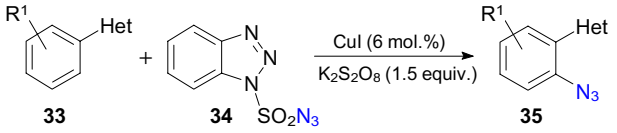


30 **31** **32**

DCM is dichloromethane

The copper salt-catalyzed *ortho*-azidation of the aromatic ring of compound **33** with benzotriazolylsulfonyl azide **34** was used to synthesize a series of azides **35** containing different heterocycles (Scheme 14).[60] It was demonstrated that the heterocycle plays an important role in directing the reaction towards the *ortho* position, which made it possible to develop a regioselective method for the synthesis of compounds **35**.

Scheme 14



33 **34** **35**

R^1 = H, 2-OBn, 2-Me, 2-Cl, 4-Me, 4-OMe, 4-CN, 4-CHO, 4-CO_2Me;

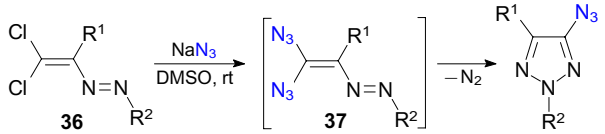
Het =  (R^2 = H, 4-Me, 5-Me, 5-Cl) (52–92%),

 (R^1 = H, 72%),  (R^1 = H, 78%),  (R^1 = H, 42%)

2.5. Azidation of 4,4-dichloro-1,2-diazadienes

Nenajdenko and co-workers[47] developed an original approach to the synthesis of 4-azido-2,5-disubstituted 1,2,3-triazoles based on the reaction of 4,4-dichloro-1,2-

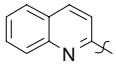
Scheme 15



36 **37** **38** (32–95%)

R^1, R^2 = Ar, Het

Examples of products **38**

R^2 = Ph: R^1 = Ph (90%), 2-$O_2NC_6H_4$ (92%), 4-$Me_2NC_6H_4$ (67%), 4-$F_3CC_6H_4$ (89%), 2-$MeOC_6H_4$ (87%),  (89%),  (92%),  (88%),  (60%),  (32%);

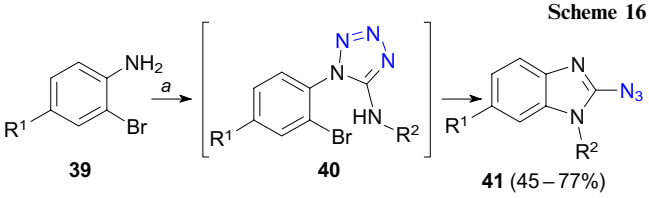
R^2 = 4-MeC_6H_4: R^1 = 4-$O_2NC_6H_4$ (87%), 3,4,5-$(MeO)_3C_6H_2$ (89%)

diazabuta-1,3-dienes **36** with sodium azide (Scheme 15). The authors demonstrated that the reaction afforded unstable intermediate 1,1-diazidoethenes **37**, which underwent the elimination of a nitrogen molecule and 1,5-cyclization to give final products **38**. This method was employed to prepare a large number of 4-azido-1,2,3-triazoles **38** containing various aryl and heteroaryl substituents at the 2 and 5 positions of the ring. Examples of these compounds are given in Scheme 15.

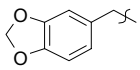
2.6. Multicomponent synthesis of 2-azidobenzimidazoles

Ramana and Punniyamurthy [61] described the three-component synthesis of 2-azidobenzimidazoles with varying substituents in the benzene and imidazole rings. This method involves the tandem addition, substitution, electrocyclization, N-arylation and tautomerization. 2-Bromoaniline derivatives **39**, sodium isothiocyanate and azide serve as the starting compounds. All reactions occur under mild conditions through the formation of unstable intermediates **40** to form target products **41** in moderate yields (Scheme 16).

Scheme 16



a — 1) R^2NCS, DMF, rt; 2) NaN_3 (3 equiv.), Et_3N (3 equiv.), $Cu(OAc)_2 \cdot H_2O$ (50 mol.%), rt; R^1 = H, Me, Cl; R^2 = Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, 2,4-$Me_2C_6H_3$, Bu^n, cyclo-C_6H_{11},



3. Catalytic and thermal cycloaddition reactions of heterocyclic azides

3.1. Reactions with alkynes

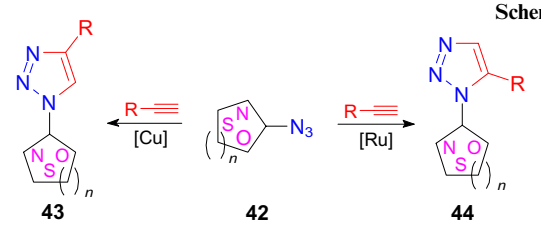
Two decades after the discovery of the CuAAC reaction by Meldal and Sharpless, this reaction remains an efficient approach to the synthesis of 1,2,3-triazole derivatives.[62–64] In recent years, the main trends in the development of this approach were related to the synthesis and utilization of new ligands and the directed synthesis of biologically active compounds, including bioconjugates and hybrids of triazoles with various heterocyclic compounds. In this Section, the data are classified according to the type of reaction products.

3.1.1. Synthesis of bicyclic ensembles of 1,2,3-triazole with miscellaneous heterocycles

Reactions of heteroaromatic azides **42** with acetylenes in the presence of copper or ruthenium salts are commonly used to synthesize bicyclic compounds containing miscellaneous heterocycles along with 1,2,3-triazole (Scheme 17).

In most cases, 1,2,3-triazoles were synthesized from heteroaromatic azides in the presence of different copper-based catalysts. Like in the reactions with aromatic azides, the reactions of heteroaromatic azides **42** with acetylenes in the presence of copper compounds give 1,4-disubstituted triazoles **43**, while ruthenium catalysts promote the formation of 1,5-disubstituted triazoles **44** (see Scheme 17). This reaction was performed with numerous heterocyclic azides

Scheme 17

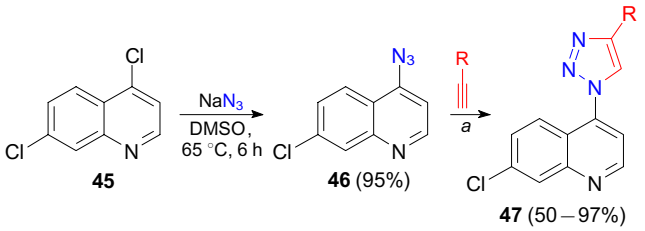


containing purine,[65] thiophene,[66–68] pyrazole,[69] tetrazole,[70] oxadiazole,[71] pyridine,[72–77] pyrazine,[78] 1,2,3-triazine,[79] pyrimidine,[80] indole,[81–83] pyrrole,[83] pyrrolopyridine,[83] thienopyrrole,[83] benzothiophene,[84] benzisoxazole,[85] benzothiadiazole,[86] benzofuran,[87] quinoline,[88–91] cinnoline [92] and thienopyridine moieties.[93,94]

The reactions of heteroaromatic azides with acetylenes can be catalyzed not only by monovalent copper salts [47,95,96] but also by monovalent ruthenium salts.[47,97] Meanwhile, a combination of divalent copper sulfate and sodium ascorbate is most commonly used in the synthesis of bicyclic triazoles.[30,55,96,98–102] Sodium ascorbate reduces divalent copper to monovalent copper, which *in situ* catalyzes the reaction of azide with acetylene.

Rosado-Solano *et al.*[99] synthesized hybrids of 1,2,3-triazole and 7-chloroquinoline by the reaction of dichloroquinoline **45** with sodium azide giving azide **46** followed by the reaction of the latter with phenylacetylene. The synthesized hybrid compounds **47** exhibited high insecticidal and antifeedant † activities (Scheme 18).

Scheme 18



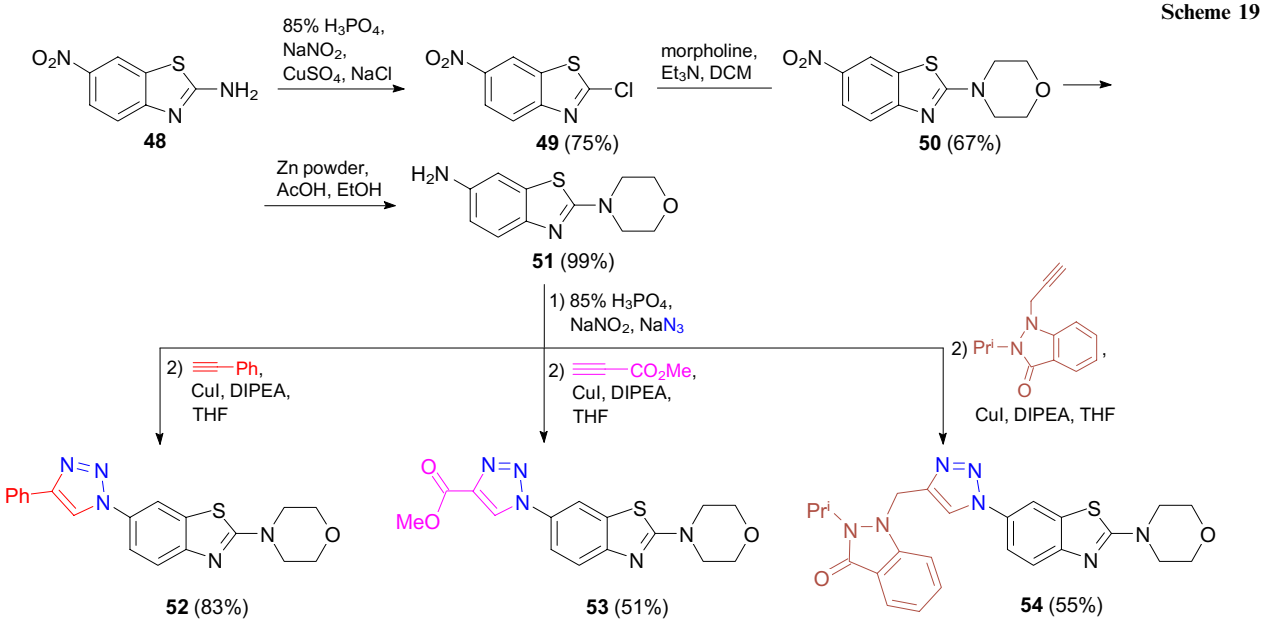
(*a*) $CuSO_4 \cdot 5H_2O$–NaAsc (1 : 2), MeOH–H_2O–THF (6 : 1 : 4), rt, 12 h;
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, CH_2OH, CMe_2OH

Avila *et al.*[103] accomplished the three-step synthesis from 2-aminobenzothiazole **48** through the formation of intermediates **49** and **50** to prepare 6-nitrobenzothiazole **51** and used this compound as a versatile building block (Scheme 19). The authors synthesized triazolylbenzothiazoles **52**–**54** by the reaction of compound **51** with different acetylene derivatives in phosphoric acid in the presence of sodium nitrite and azide and in the presence of copper iodide with addition of *N*,*N*-diisopropylethylamine (DIPEA). Compound **54** exhibited neuroprotective properties in human neuroblastoma cells.[103]

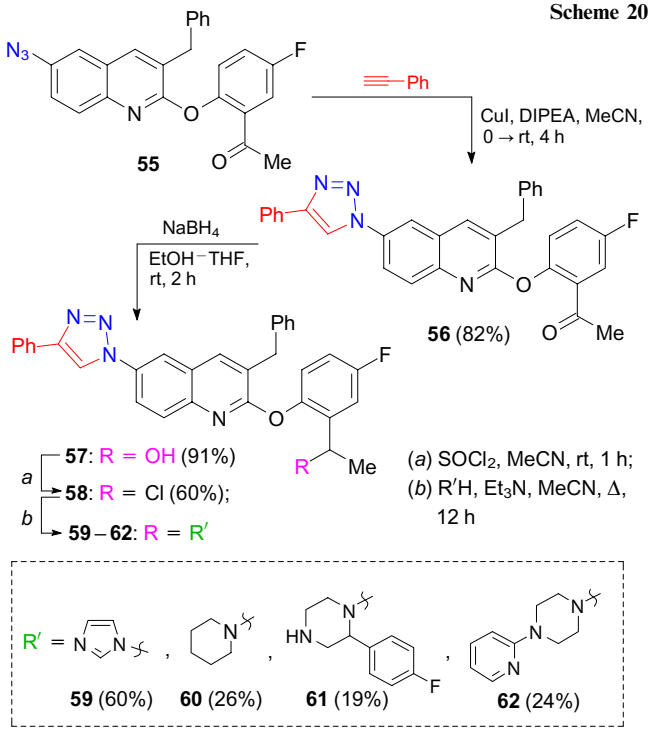
Chattopadhyaya and co-workers [104] synthesized 1,2,3-triazolylquinolines **56**–**62** by the copper(I) iodide-catalyzed reaction of phenylacetylene with azide **55** (Scheme 20). Some of these compounds were found to exhibit tuberculostatic activity. It was demonstrated that derivative **59**

† Antifeedants are compounds protecting plants and materials from consumption by animals.

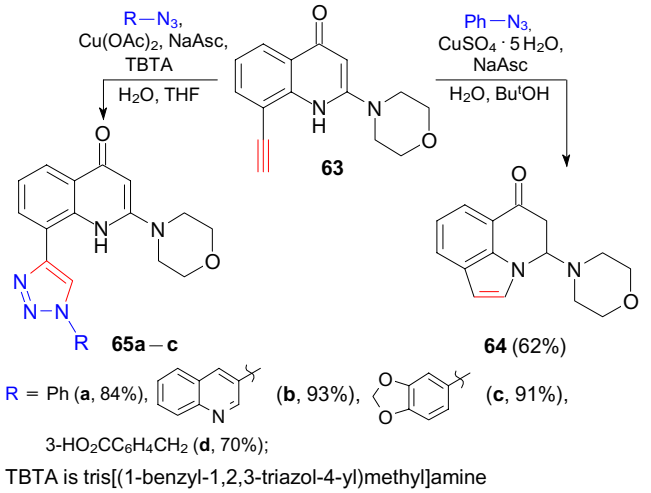
Scheme 19



Scheme 20



Scheme 21



inhibits the growth of mycobacterium tuberculosis H37Rv up to 98% at a fixed concentration of 6.25 μg mL^{-1}.[104]

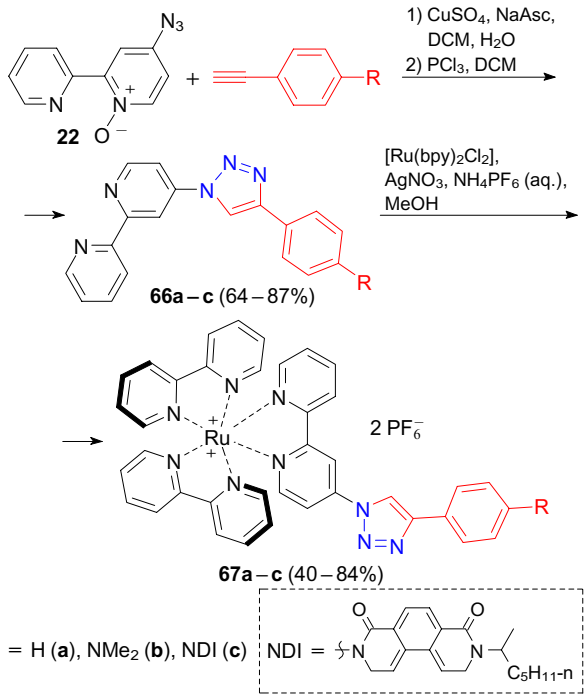
Pirali *et al.*[96] demonstrated that the replacement of the catalyst can lead to a change in the pathway of the reaction of azides with acetylenes. Thus, the use of copper sulfate as the catalyst facilitates the intramolecular cyclization involving the acetylene moiety and the NH group of quinoline **63** to form tricyclic compound **64** (Scheme 21). On contrast, the reaction of the same starting compounds in the presence of divalent copper acetate affords heterocyclic ensembles **65a–d** containing the dihydroquinolone and triazole rings as the click reaction products.[96] Using combinatorial chemistry methods, Pirali *et al.*[96] synthesized a small library of this scaffold with different substituents at the 1 position of the triazole ring. For this purpose, the reaction was performed with azides containing electron-withdrawing or electron-donating substituents, hydrogen bond donors and acceptors and ionized functions. Compounds **65a–d** were tested for the ability to inhibit the signalling pathway of phosphoinositide 3-kinase (PI3K). Derivative **65d** bearing the 3-carboxybenzyl group at the 1 position of the triazole ring showed the highest inhibitory activity.[96]

Pokhodylo *et al.*[105] synthesized the bicyclic ensemble of nonaromatic 1-phenylpyrrolidine-2,5-dione and 1,2,3-triazole in high yield. The reaction of 3-azido-1-phenylpyrrolidine-2,5-dione with phenylacetylene was performed in the presence of the CuI–Et$_3$N system as the catalyst.

3.1.2. Synthesis of tricyclic ensembles based on 1,2,3-triazole

The reaction of azido-substituted dipyridines or bis(azidocarbazoles) with acetylenes gives linearly fused tricyclic compounds.[55] Thus, Baron *et al.*[55] found that 4-azidodipyridine *N*-oxide **22** (see Scheme 9) smoothly reacts with arylacetylenes in the presence of catalytic amounts of copper sulfate and sodium ascorbate in the two-phase dichloromethan–H$_2$O system (Scheme 22). The reduction

Scheme 22



of the oxide function of intermediate dipyridine-substituted 1,2,3-triazoles affords compounds **66a**–**c**, which react with $[Ru(bpy)_2Cl_2]$ (bpy is 2,2′-dipyridine) to form ruthenium complexes **67a**–**c**. These complexes were isolated as the corresponding hexafluorophosphates and were characterized by electrochemical and spectroscopic methods.[55]

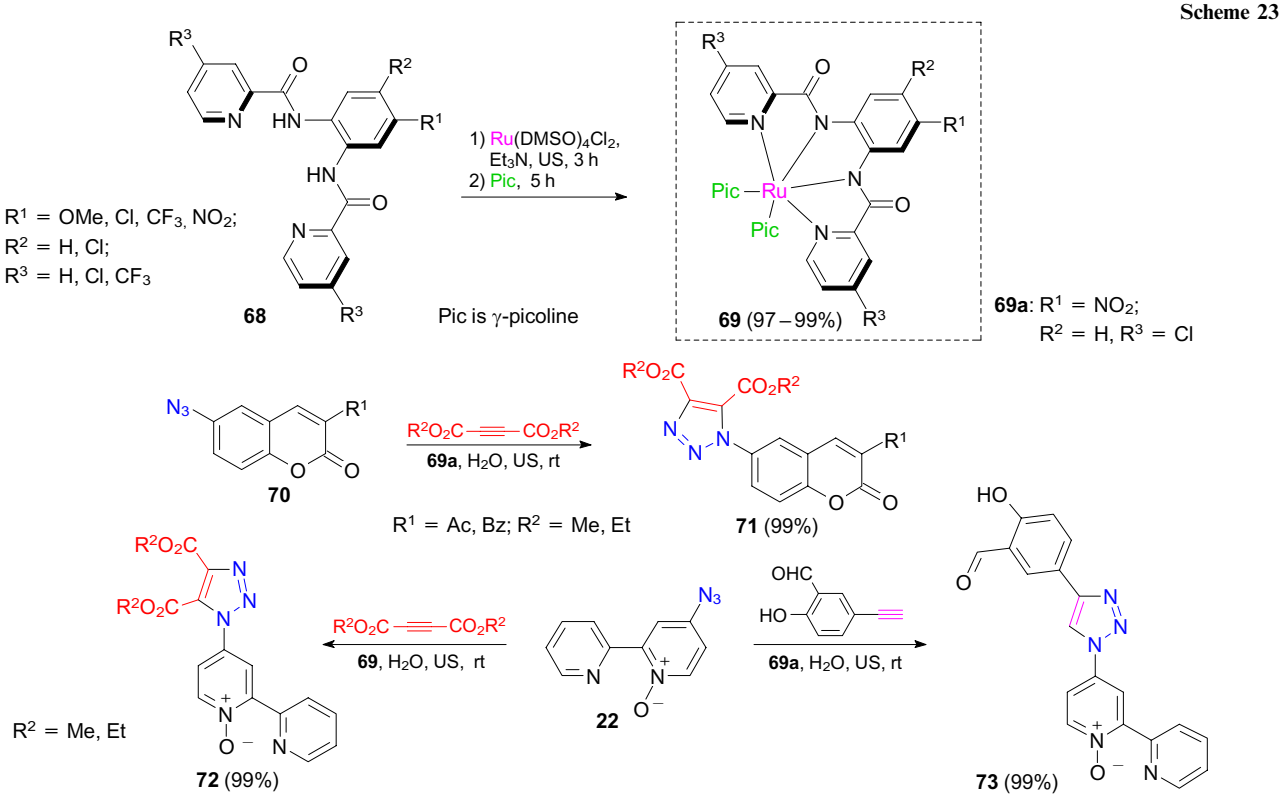
The reactions of compounds **68** with ruthenium salts produced a series of Ru^{II} complexes **69**.[106] It was found that the structure of these complexes affects their ability to catalyze the cycloaddition reactions of 4-azidopyridine *N*-oxide (**22**) with acetylenedicarboxylic esters in water under ultrasonic (US) activation (Scheme 23). Complex **69a** ($R^1 = NO_2$, $R^2 = H$, $R^3 = Cl$) was found to be an efficient heterogeneous catalyst for the regioselective synthesis of tricyclic 1,4,5-trisubstituted 1,2,3-triazoles. It was demonstrated that this catalytic system is applicable to the preparation of tricyclic (**71**, **72**) and tetracyclic (**73**) heteroaromatic ensembles based on azides **70** and **22**.[106]

Elliott and co-workers[107] utilized 4-azido-2,2′-bipyridine (**74**) to synthesize 1,2,3-triazoles containing two (**66a**) and three (**75**) pyridine rings or the ferrocenyl moiety (**76**). The cycloaddition of azide **74** to the corresponding alkynes was performed in the presence of the copper sulfate—sodium ascorbate catalytic system (Scheme 24).

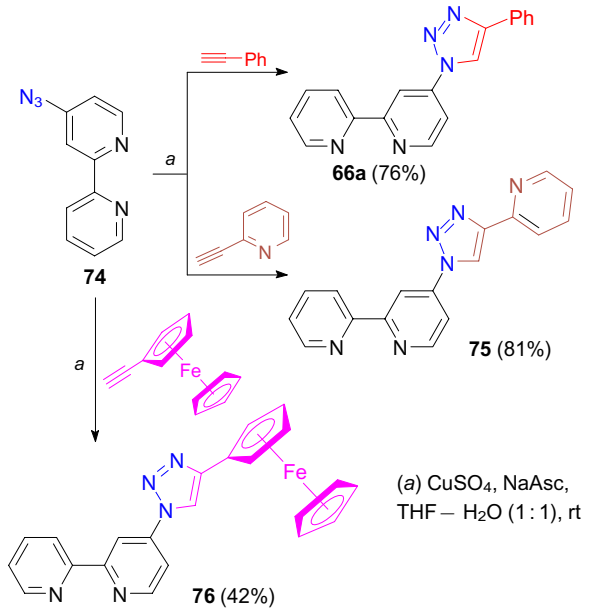
The reaction of 3,6-diazido-1-propylcarbazole (**77**) with alkylacetylenes in the presence of the complex $[Cu(MeCN)_4]PF_6$, TBTA and DIPEA in dichloromethane gave another type of linearly fused tricyclic compounds **78a**,**b** containing two triazole rings and a carbazole moiety (Scheme 25).[108] The use of copper perchlorate hydrate in the presence of NaI and DBU made it possible to perform the one-pot synthesis of iodo derivatives **79a**,**b**.[108] It was demonstrated that the alkylation of compounds **78** and **79** with trimethyloxonium tetrafluoroborate occurs at the 3 position of the triazole ring to form bis(triazolium) tetrafluoroborates **80a**,**b** and **81a**,**b**, respectively.

Mullaney *et al.*[108] studied in detail the properties of acyclic halogen- and hydrogen-bonding bis-triazolium carbazole receptors **80** and **81** by NMR titration experiments in an NMR cell, analyzing the changes in the signals in the ^1H NMR spectra. Significant downfield shifts of the triazolium and carbazole protons observed upon the addition of appropriate ammonium salts are indicative of the binding of the anion within the receptor cavity. It was found that the binding energy of halide ions with iodine-substituted receptors **81** is much higher than the hydrogen-bonding energy

Scheme 23



Scheme 24



for its analogues **80**. Taking into account the ability of acyclic receptors **80** to **81** to bind anions, the authors [108] synthesized the previously unknown rotaxane **83** based on triazolium salt **81c** and isophthalamide **82** (Scheme 26). The NMR titration experiments in a mixture of aqueous solvents demonstrated that this rotaxane has a strong binding affinity for bromide.

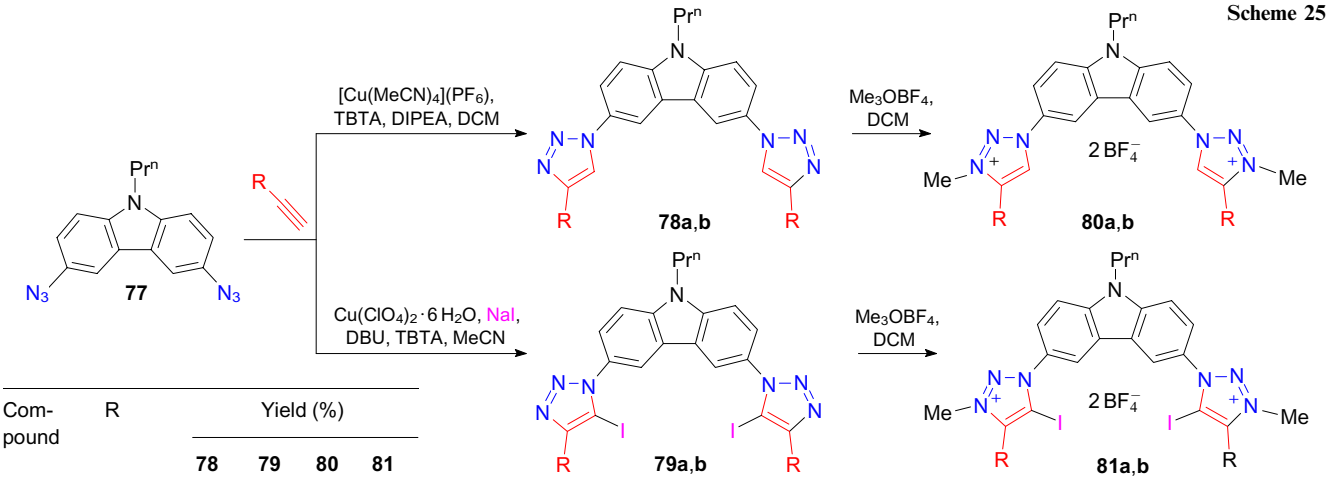
3.1.3. Polycyclic ensembles of 1,2,3-triazoles

This Section considers the reactions of heterocyclic azides with acetylene derivatives giving compounds containing more than three rings. Among these products there are macrocycles, metal complexes and linearly fused triazole-containing heterocyclic compounds composed of moieties that are connected by different linkers.[49, 50, 53, 109–117]

Bucevicius *et al.*[53] performed the reaction of 2,4-diazidopyrimidine (**84**) with arylacetylenes using the CuI–DIPEA–AcOH system as the catalyst and synthesized 2,4-bis(aryl-1,2,3-triazol-1-yl)pyrrolo[2,3-*d*]pyrimidines **85** and **86** (Scheme 27). The authors reported that polycyclic triazoles **85** exhibit properties of D–π–A–π–D chromophores (D is a donor, A is an acceptor). The introduction of small polar substituents made it possible to tune the frontier molecular orbital energies and increase the energy gap between these orbitals to 0.9 eV, whereas the introduction of bulky substituents led to a decrease in the energy gap to 0.4 eV. It was demonstrated [53] that these compounds exhibit the pronounced intramolecular charge transfer (ICT) from excited states of the derivatives with electron-donating groups. The optimization of ICT resulted in an increase in the fluorescence quantum yield of derivatives **85** to 73%.

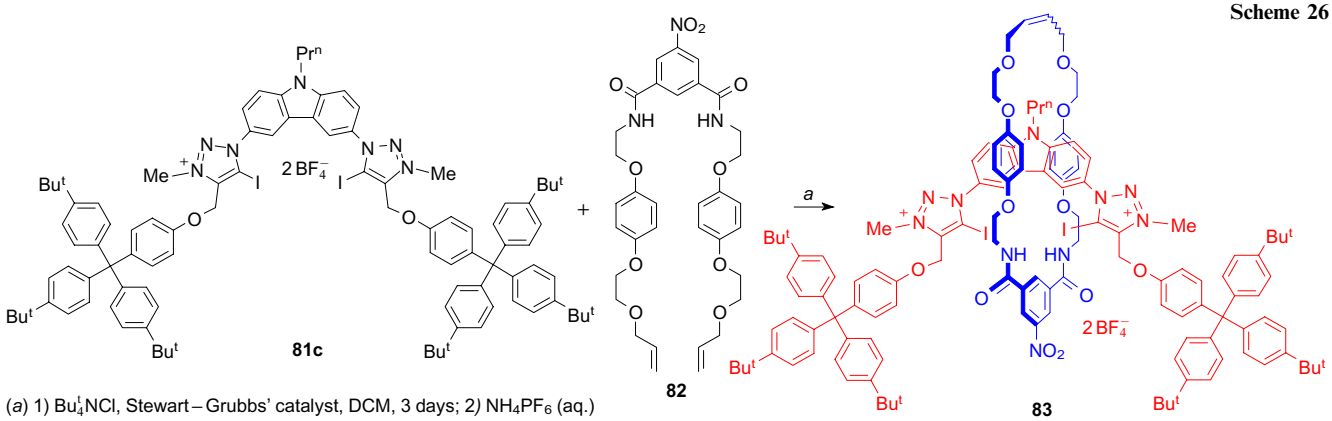
With the aim of synthesizing compounds capable of complexation, König and co-workers [110] modified 3,5-

Scheme 25



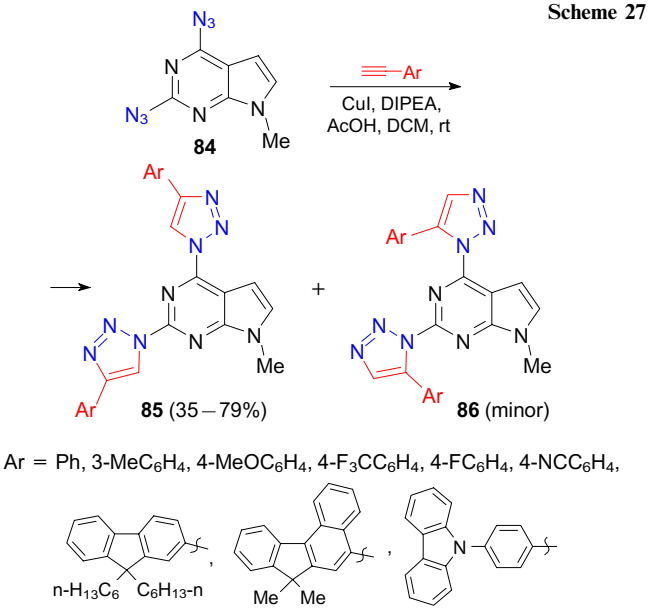
Compound	R	Yield (%)			
		78	**79**	**80**	**81**
a	n-C_8H_{17}	70	23	38	33
b	4-Bu^tC_6H_4	71	74	56	55

Scheme 26



(*a*) 1) Bu$^t_4$NCl, Stewart–Grubbs' catalyst, DCM, 3 days; 2) NH_4PF_6 (aq.)

Scheme 27



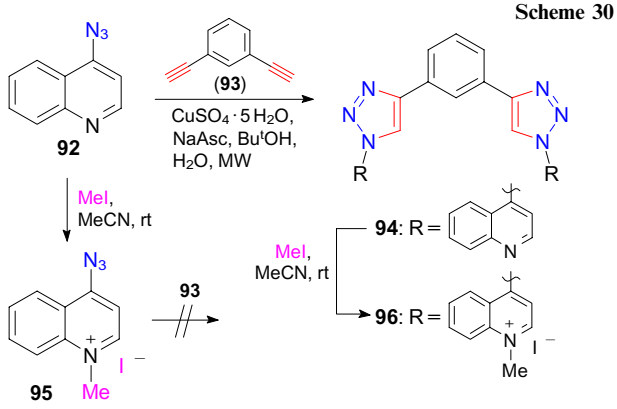
Ar = Ph, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-FC$_6$H$_4$, 4-NCC$_6$H$_4$,

dichlorotriazine **87** to prepare azide **88**, which was subjected to the click reaction with phenylacetylene (Scheme 28). However, the authors did not report the complexation properties of compounds **88** and **89**.

Neidle and co-workers [50] used the structural modeling for the design of a series of acridines linearly fused to two triazole rings and capable of selectively interacting with human telomeric quadruplex DNAs. The click reaction of 2,8-diazidoacridine (**9**) with arylacetylenes **90** gave compounds **91** (Scheme 29). The proposed selectivity concept was validated against two promoter quadruplexes from the c-kit gene with known molecular structures and also against duplex DNA using fluorescence spectroscopy. It was found that two lead compounds [n = 2: R = NEt$_2$, N(CH$_2$)$_4$] reduce the thermal stability of the c-kit quadruplexes and duplex DNA structures. Besides, these compounds have selective inhibitory effects on the proliferation of cancer cell lines. One compound, **91** (n = 2, R = N(CH$_2$)$_4$), was found to inhibit the activity of the enzyme telomerase, which is selectively expressed in tumor cells.

It is worth noting that the development of this approach by Mendes *et al.*[109] led to the design of polycyclic compounds, which contain two quinoline moieties connected *via* the bis(triazolyl)phenylene linker. The microwave (MW)-assisted Cu^{I}-catalyzed cycloaddition of 4-azidoquinoline (**92**) to 1,3-diethynylbenzene (**93**) afforded polycyclic compound **94** (Scheme 30) submitted for biological evaluation.

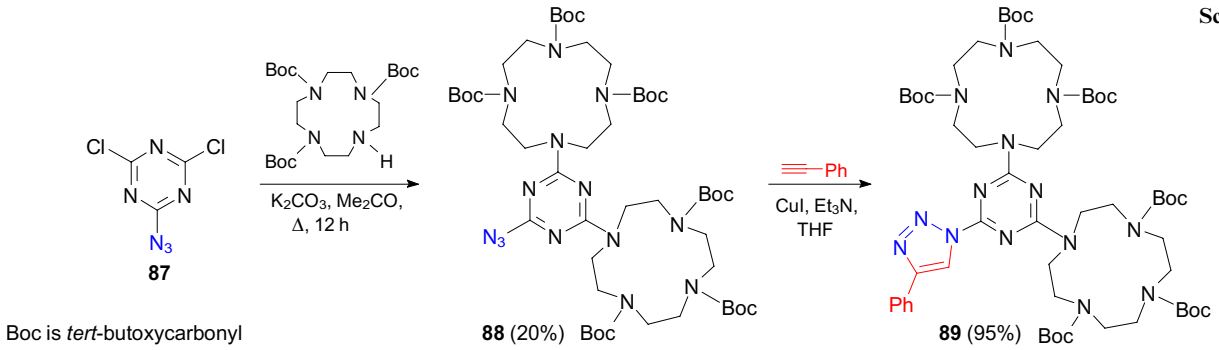
Scheme 30



The quaternization of the nitrogen atom of quinoline **92** with methyl iodide easily produces 4-azido-*N*-methylquinolinium **95**. However, attempts to perform the reaction of this salt with dialkyne **93** failed. Therefore, product **96** was synthesized by the direct methylation of base **94**.[109] Salt **96** showed high activity against a number of cancer cell lines, including cancer stem cells. The eradication of cancer stem cells provides an efficient route to new effective anticancer drugs.[98]

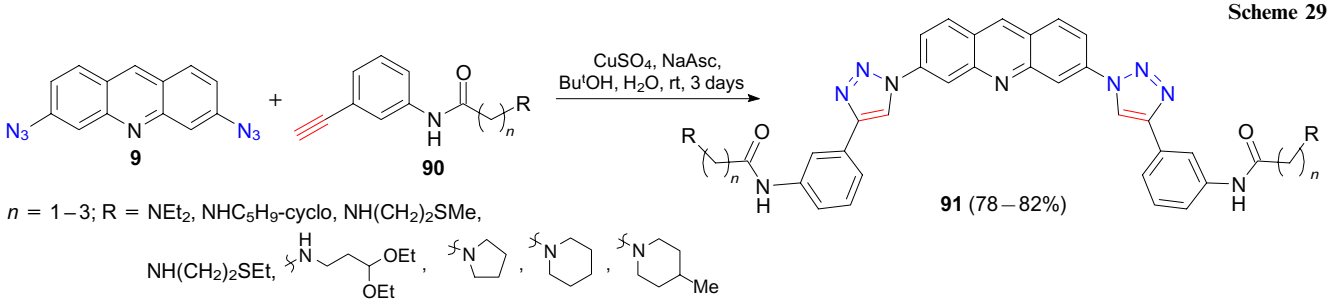
Dobscha *et al.*[111] used carbazole (**97**) to prepare azides **98a**–**c** and bifunctional building blocks **99a**–**c**. The latter were utilized to synthesize AAA-type C(3)-symmetric tricarbazole macrocycles (**100a**–**c**) with different alkyl chains

Scheme 28



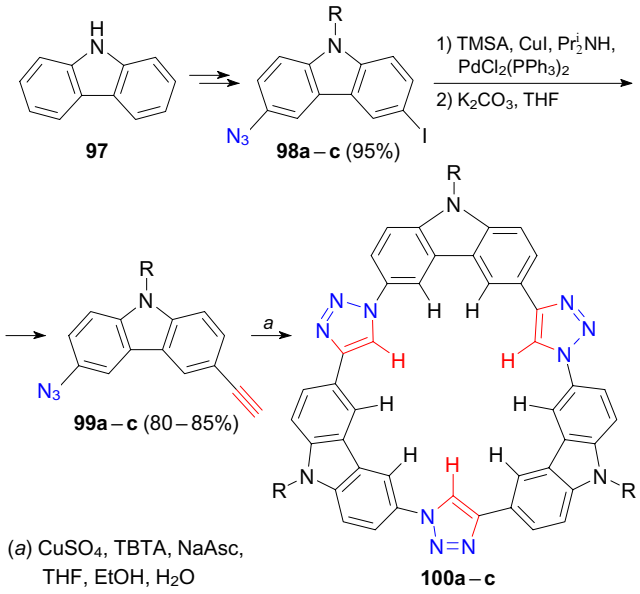
Boc is *tert*-butoxycarbonyl

Scheme 29



n = 1–3; R = NEt$_2$, NHC$_5$H$_9$-cyclo, NH(CH$_2$)$_2$SMe,

Scheme 31



Compound **100**	R	Yield of macrocyclization (%)	Overall yield (%)
a	n-C_6H_{13}	70	40
b	n-$C_{10}H_{21}$	65	35
c	n-$C_{18}H_{37}$	68	35

containing three carbazole rings and three triazole rings (Scheme 31). For example, macrocycle **100c** with a long alkyl substituent was prepared in seven steps in an overall yield of 35% with respect to the starting carbazole **97**. Intermediate carbazole **99c** containing the azide and alkyne groups in the 3 and 6 positions, respectively, was generated in the reaction of iodine derivative **98c** with trimethylsilylacetylene (TMSA) in the presence of the CuI–$PdCl_2(PPh_3)_2$ catalytic system.[111] In the final step, compound **99c** underwent trimerization to give final product **100c** in moderate yield.

In order to establish the general features of the transformation of carbazoles **101** and **102** into macrocycles, Dobscha *et al.*[111] developed a stepwise method for the synthesis of compounds **100** (Scheme 32). The concept of the stepwise synthesis of the tricarbazole macrocycle scaffold is based on the progressive growth of the oligomer chain. Examining possible synthetic pathways based on different preparations of building blocks led the authors to the stepwise protection—deproection scheme, enabling the control of the chain growth of macrocyclic precursors. This approach made it possible to prepare tris(triazole-carbazoles) **100** in yields from 70 to 80% in the macrocyclization step (the overall yield was 5–25%).

In the cited study,[111] the authors presented the first evidence that the reaction sequence controls the hierarchical assembly of non-biological macrocycles; in the case under consideration, on graphite surfaces. Scanning tunneling microscopy showed that the first steps of the process affect the next levels of supramolecular ordering.

3.2. Reactions with alkenes

Reactions of heterocyclic azides with alkenes are less common in the literature compared to the reactions with acetylenes. These reactions afford nonaromatic 1,2,3-triazolines as primary products, which are less stable than 1,2,3-triazoles and can undergo different transformations.[118] The stabilization of such compounds is most often accomplished using transformations into aromatic 1,2,3-triazoles. The metal-catalyzed reactions of azides with acetylenes are currently most commonly applied to synthesize 1,2,3-triazoles, while the data on the reactions of azides, including heterocyclic azides, with alkenes are scarce. Only the reactions with activated alkenes, such as sterically hindered or electron-rich (including enols and enamines), were described in the literature. The reactions of enamines with heterocyclic azides are considered in Section 3.3.

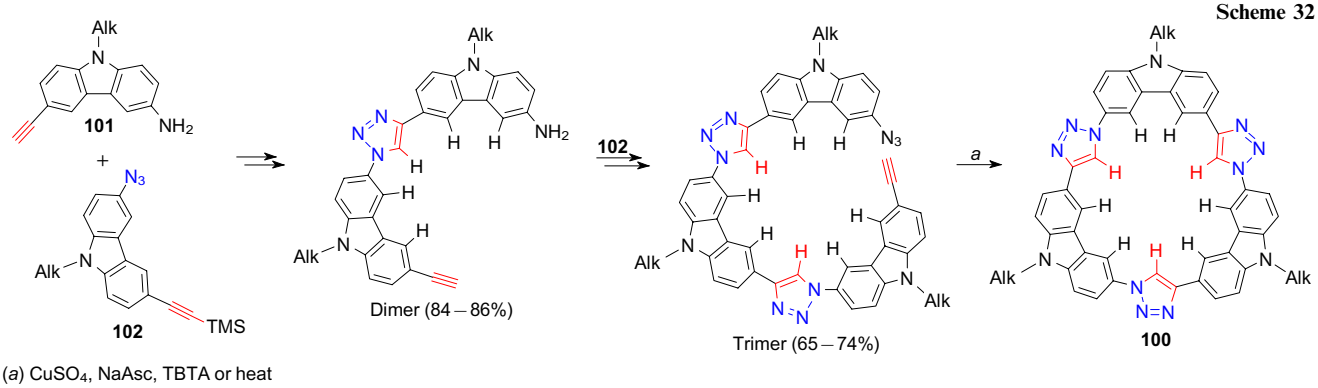
3.2.1. Synthesis of 1,2,3-triazoles by organocatalytic reactions

Yuan *et al.*[119] studied the organocatalytic reaction of allyl ketones (*e.g.*, allyl phenyl ketone) with aliphatic and aromatic azides, in particular with 2-azidopyridine, in the presence of heterocyclic carbenes. The authors demonstrated that this reaction of 1,4-dimethyl-1,2,4-triazolium tetrafluoroborate (**103a**) with bases in acetonitrile at 80 °C afforded 1,2,3-triazoles **104** in the highest yields (Scheme 33).

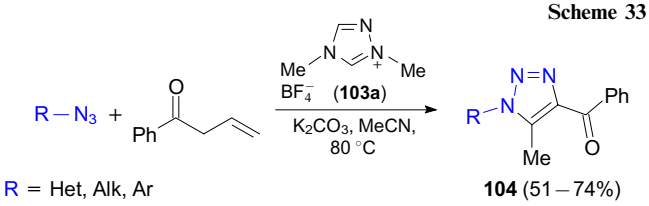
The reaction mechanism shown in Scheme 34 provides an explanation for the formation of the final product. Initially, the adduct **A** is formed through hydrogen bonding between the starting ketone and catalyst **103a**.[119] Then the intermediate **A** reacts with azide RN_3 to form intermediate azide **B**, and the catalyst returns to the catalytic cycle. The intermediate **B** undergoes a 1,3-sigmatropic hydrogen shift and is transformed into the intermediate **C**. The 1,5-electrocyclization of the latter affords the intermediate **D**. The final step involves the aerobic oxidation of the intermediate **D** giving product **104**.

In continuation of their work, Li *et al.*[120] performed experimental and theoretical studies of the reaction of

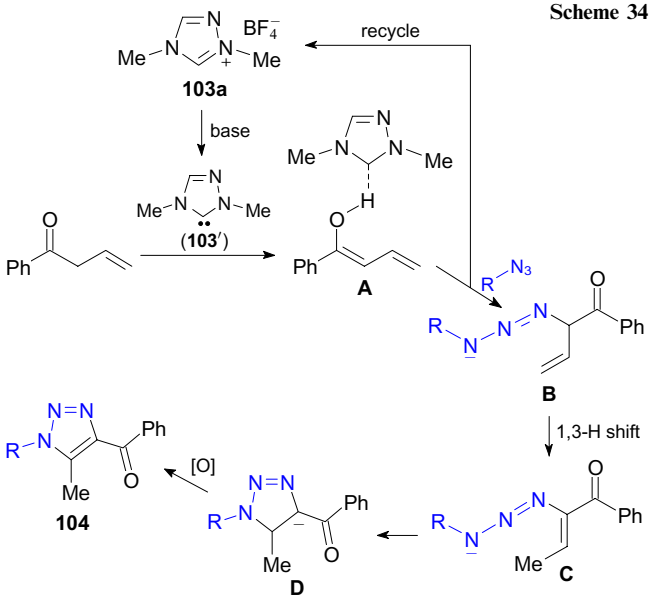
Scheme 32



Scheme 33

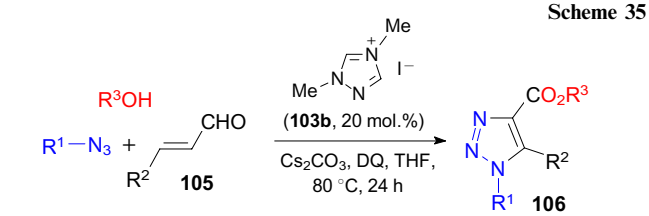


Scheme 34

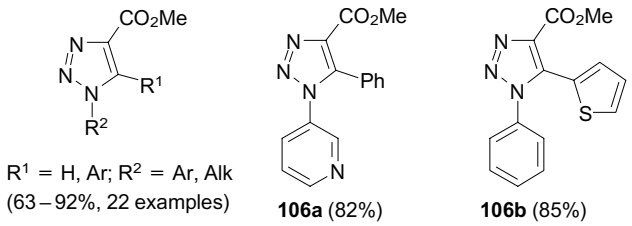


acrolein and its derivatives (**105**) with aliphatic, aromatic and heteroaromatic azides in the presence of 1,4-dimethyl-1,2,4-triazolium iodide (**103b**) and significantly extended the field of application of this process (Scheme 35).

Scheme 35

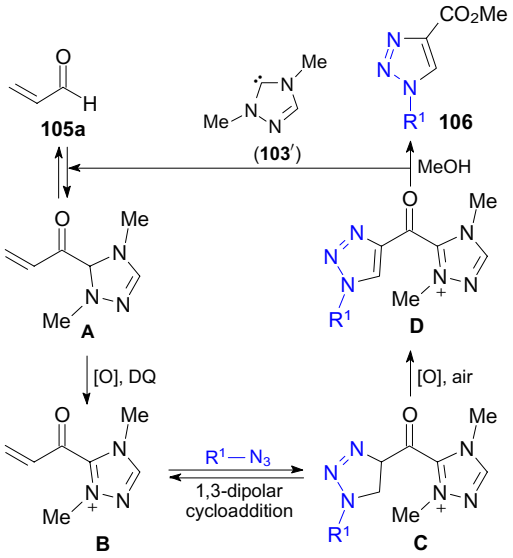


Examples of products **106**



It was demonstrated [120] that, in the absence of a catalyst, the reaction does not afford triazoles **106**. The monitoring of the reaction by mass spectrometry showed a molecular ion with a mass corresponding to the ion **D** (Scheme 36). Based on these data, the authors proposed the mechanism, involving the oxidation of the intermediate **A** to form ketone **B**, the reaction of the ketone with azide, the

Scheme 36

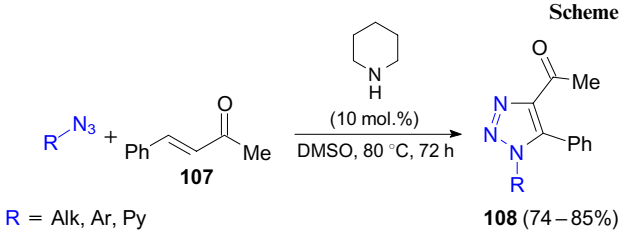


subsequent oxidation of the resulting triazoline **C** giving triazole **D**, the elimination of the catalyst, its reintroduction into the reaction cycle and the formation of final product **106**.

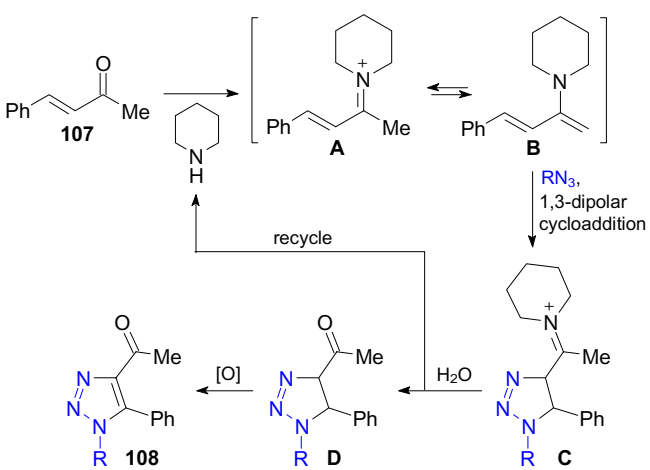
Li *et al.*[121] demonstrated the use of the iminium catalysis in the 1,3-dipolar cycloaddition of azides to α,β-unsaturated ketones **107** (Scheme 37). These reactions can be performed using different dialkylamines as the catalyst, which made it possible to synthesize 1-substituted 1,2,3-triazoles **108** in high yields with high regioselectivity.[121] Aliphatic, aromatic and heterocyclic azides can be subjected to this reaction.

The mechanism of this reaction involves the initial reaction of α,β-unsaturated ketone **107** with the catalyst (piperidine) to form the iminium intermediate **A** existing in

Scheme 37



Scheme 38

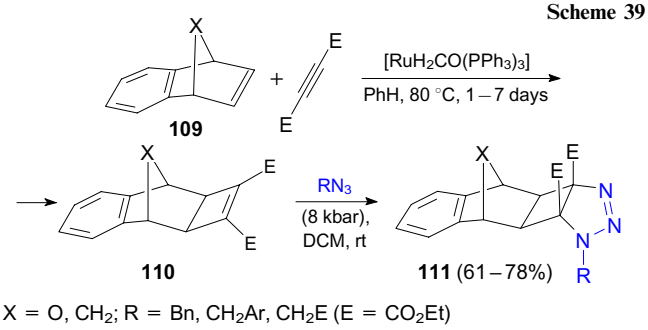


equilibrium with dienamine **B**.[121] The latter undergoes the 1,3-dipolar cycloaddition with azide, generating the intermediate **C**, which is converted into the intermediate **D** through the elimination of piperidine. The subsequent aerobic oxidation of the intermediate **D** affords final product **108** (Scheme 38).

3.2.2. Reactions of sterically hindered alkenes

Margetić *et al.*[122] described the reaction of alkenes **109** with acetylenedicarboxylic acid ester giving norbornene derivatives **110** and investigated the reaction of these products with aromatic and heteroaromatic azides. It was shown that this reaction performed at room temperature under high pressure requires a shorter time and affords triazolines **111** in good yields (Scheme 39). It is worth noting that the reactions of heterocyclic azides produce the corresponding triazolines in higher yields compared to the reactions with aromatic derivatives. Polycyclic triazolines **112** were synthesized in a similar way.

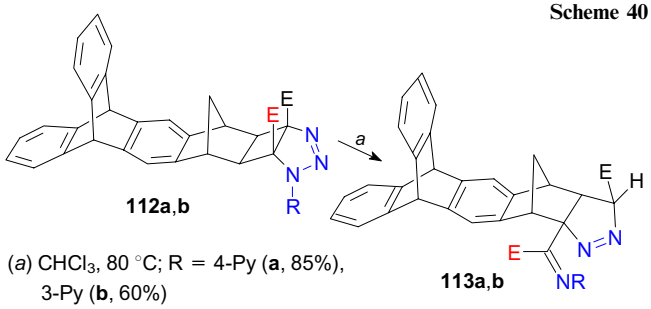
Scheme 39



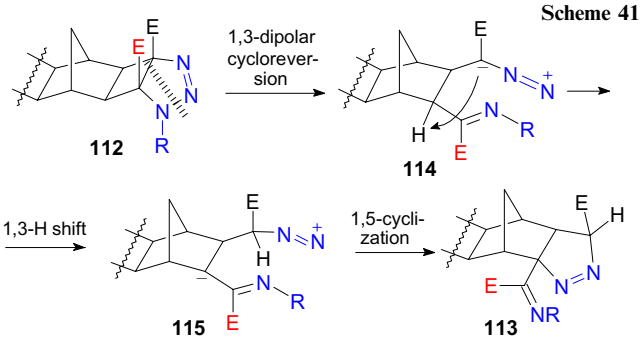
The prolonged heating of polycyclic compounds **112a**,**b** in chloroform at 80 °C leads to the simultaneous transformation of the triazoline ring and the cyclobutene moiety selectively producing triazolines **113** containing an imino group in the side chain (Scheme 40).

According to the mechanism proposed by Margetić *et al.*,[122] the reaction starts with the intramolecular 1,3-dipolar cycloreversion of compound **112**, resulting in the cleavage of the triazole and four-membered aliphatic rings to form diazoimine **114** (Scheme 41). The next step involves the 1,3-migration of a hydrogen atom giving zwitterion **115**. According to the density functional theory (DFT), this

Scheme 40



Scheme 41

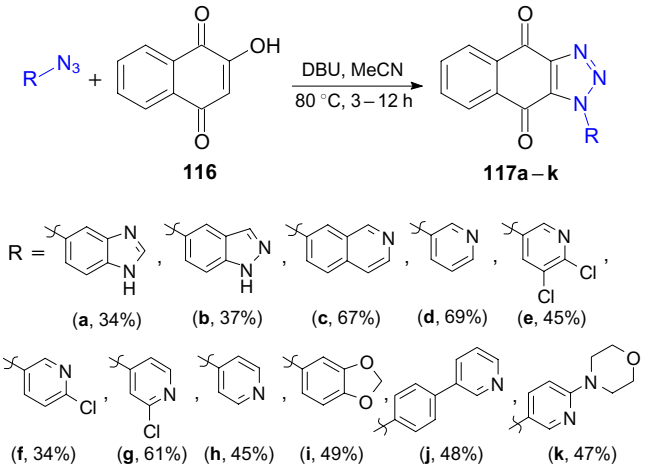


zwitterion is 26.2 kcal mol^{-1} more stable than diazoimine **114**. The intramolecular 1,5-electrocyclization of zwitterion **115** affords the final product **113**.

3.2.3. Reactions of 2-hydroxynaphthalenes

In order to synthesize dihydroorotate dehydrogenase inhibitors, Pan *et al.*[123] performed the reactions of aromatic and heterocyclic azides with hydroxynaphthoquinone (**116**) and prepared a series of naphtho[2,3-*d*][1,2,3]triazole-4,9-diones (Scheme 42). It was demonstrated that the synthesized compounds **117a**–**f** exhibit the desired biological activity at micromolar concentrations.[123]

Scheme 42



Almost simultaneously and independently of Pan *et al.*,[123] Zuo *et al.*[124] performed the reaction of naphthoquinone **116** with another set of heterocyclic azides under the same conditions (see Scheme 42). Compounds **117g**–**k** described in the study [124] were found to show an inhibitory effect on indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase.[124]

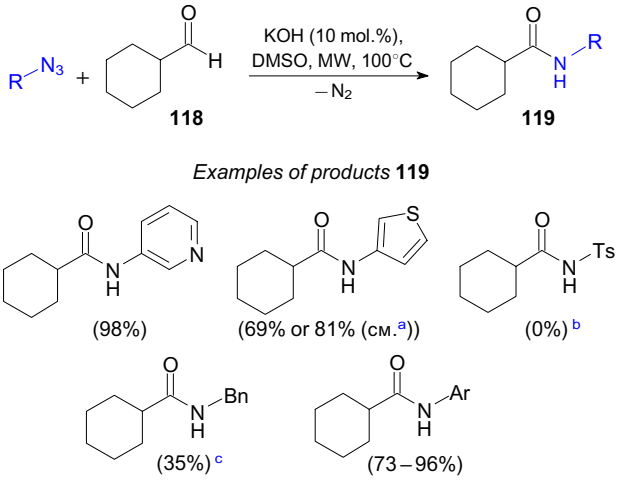
Houk and co-workers [125] performed kinetic studies of the reactions of aromatic azides and 4-azidopyridine with norbornene and showed that the activation energy of the reaction of 4-azido-2,3,5,6-tetrafluoropyridine (20.6 kcal mol^{-1}) is lower than that for pentafluorophenyl azide (21.8 kcal mol^{-1}). The authors also demonstrated that in this reaction, the dominant molecular orbital interaction is that between the lowest molecular unoccupied orbital (LUMO) of azide and the highest occupied molecular orbital (HOMO) of norbornene. Therefore, the reaction of azides with sterically hindered alkenes can be

assigned to inverse electron demand cycloaddition reactions.

3.2.4. Reactions of acetaldehyde derivatives. Synthesis of amides

Xie *et al.*[126] found that aldehydes containing the active methylene or methine group react with aromatic or heteroaromatic azides and benzyl azide derivatives to form amides. The authors optimized the reaction conditions and demonstrated that the reactions in DMSO in the presence of KOH or Cs_2CO_3 with, *e.g.*, cyclohexanecarbaldehyde (**118**) can be used to prepare various amides **119** in high yields (Scheme 43).

Scheme 43

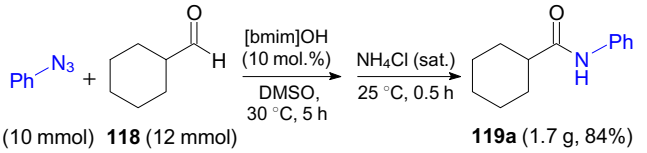


Conditions: [a] 30 °C, 6–24 h, quenched by 0.5 M aq. AcOH; [b] 80–160 °C, 2–10 h; [c] 120 °C, 1 h; Ts is *p*-toluenesulfonyl (tosyl)

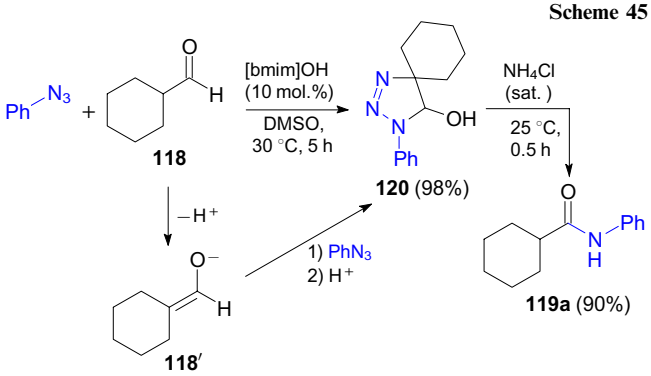
More recently, Gu *et al.*[127] studied this reaction in the presence of the ionic liquid 1-n-butyl-3-methylimidazolium (bmim) chloride. The authors developed a one-pot method and demonstrated its application to the preparation of amide **119a** on a gram scale (Scheme 44).

The formation of 1,2,3-triazolines as intermediates in this reaction was confirmed by additional experiments.[127] Thus, triazoline **120** was isolated in 98% yield and identified

Scheme 44



Scheme 45



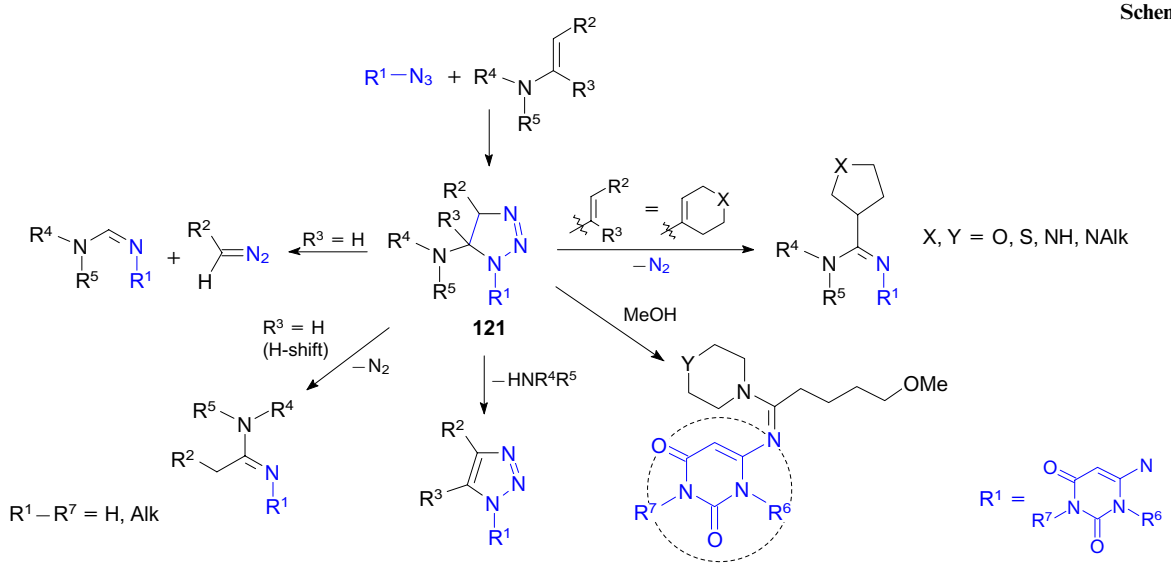
in the reaction of phenyl azide with cyclohexanecarbaldehyde (**118**) (Scheme 45). The treatment of triazoline **120** with a saturated ammonium chloride solution gave a cyclohexanecarboxylic acid anilide **119a**. Based on these data, Gu *et al.*[127] proposed the reaction mechanism, involving the generation of enolate anion **118′**, which reacts with azides to form triazoline **120**. The elimination of a nitrogen molecule completes the formation of anilide **119a**.

3.3. Reactions with enamines

3.3.1. Reaction pathways of azides with enamines in relation to azides of the heterocyclic series

This Section is devoted to the reactions of heterocyclic azides with enamines with an emphasis on the application of these reactions in organic synthesis for the preparation of amidines, diazo compounds, 1,2,3-triazoles and 1,2,3-triazolines, in particular mono- and bicyclic compounds, and ensembles of 1,2,3-triazoles with miscellaneous heterocycles. In general terms, the possible reaction pathways of heterocyclic azides with enamines are presented in

Scheme 46



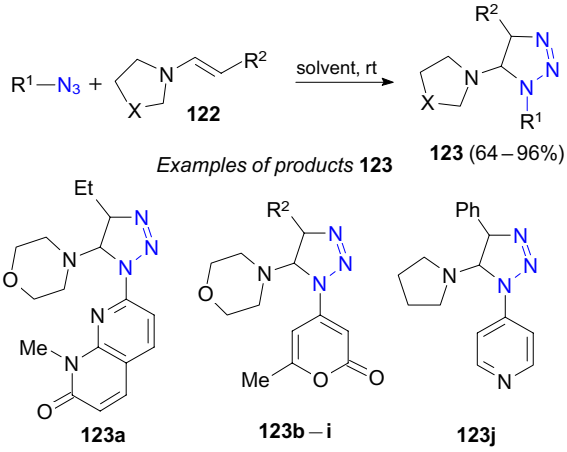
Scheme 46. As seen in this scheme, this reaction initially affords triazolines **121**. A number of triazolines were isolated in the individual state and characterized by spectroscopic methods. However, most of these compounds are unstable and are transformed into more stable organic compounds. In this Section, the data on the reactions of heterocyclic azides available in the literature are classified according to the type of the products shown in Scheme 46.

3.3.2. Formation of stable 1,2,3-triazolines

The reaction of azides with enamines initially affords 1,2,3-triazolines.[28] In a number of the reactions of enamines **122** with heterocyclic azides, researchers obtained 1,2,3-triazolines **123** stable under ambient conditions (Scheme 47).[28, 128] Known triazolines **123** are limited to ensembles containing the pyridopyridone (**123a**), pyran (**123b–i**) or pyridine (**123j**) rings in the 1 position and also alkyl and aryl substituents in the 4 position of the triazoline ring. Hence, it can be suggested that the presence of electron-deficient heterocyclic substituents in the 1 position of triazolines **123** enhances the stability of nonaromatic triazolines.

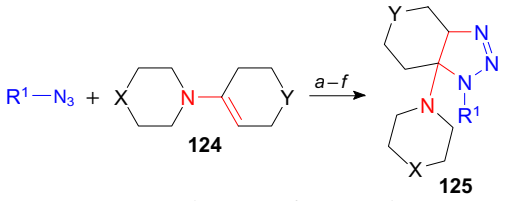
The reaction of azides with endocyclic enamines **124**, in which the aliphatic ring contains the endocyclic C=C bond, affords fused 1,2,3-triazolines. It appeared that triazolines **125a–y** do not undergo aromatization and they were isolated as the final reaction products (Scheme 48).[129–133] Julino *et al.*[132] found that all reactions, which were examined in their study, gave only *cis*-annulation products **125l–o**. In the synthesis of 1,2,3-triazoline

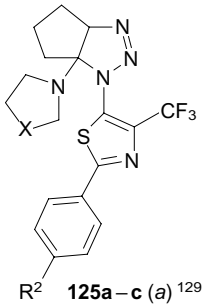
Scheme 47



R^2 = Ph (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**), 4-ClC_6H_4 (**e**), 4-FC_6H_4 (**f**), 4-BrC_6H_4 (**g**), 2,4-$Cl_2C_6H_3$ (**h**), CH_2SMe (**i**)

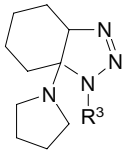
Scheme 48



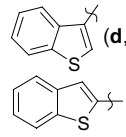


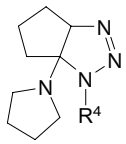
125a–c (*a*) [129]

X = CH_2: R^2 = H (**a**, 84%),
R^2 = Me (**b**,15%);
R^2 = Me, X = OCH_2 (**c**, 56%)

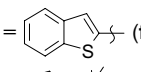
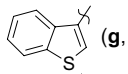
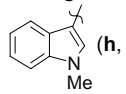


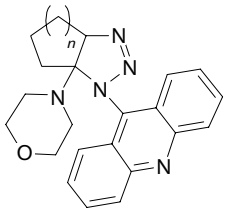
125d,e (*b*) [130]

R^3 =  (**d**, 99%),
 (**e**, 99%)



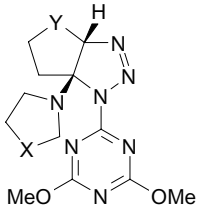
125f–h (*b*) [130, 131]

R^4 =  (**f**, 99%),
 (**g**, 99%),
 (**h**, 92%)



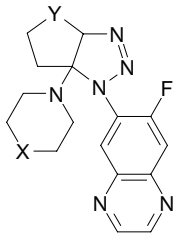
125i–k (*c*) [132]

n = 1 (**i**, 79%),
2 (**j**, 71%),
3 (**k**, 65%)



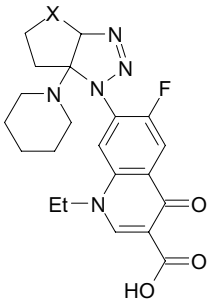
125l–o (*d*) [133]

Y = OCH_2:
X = CH_2 (**l**, 76%),
$(CH_2)_2$ (**m**, 72%),
OCH_2 (**n**, 63%);
X = OCH_2,
Y = CH_2 (**o**, 84%)



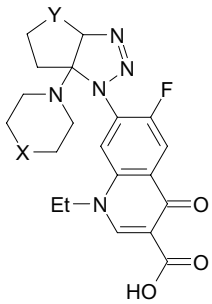
125p–t (*e*) [28]

X = CH_2: Y = CH_2 (**p**, 76%),
$(CH_2)_2$ (**q**, 57%);
X = O: Y = CH_2 (**r**, 63%),
$(CH_2)_2$ (**s**, 25%), $(CH_2)_3$ (**t**, 40%)



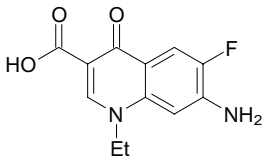
125u,v (*f*) [28]

X = CH_2 (**u**, 65%),
$(CH_2)_2$ (**v**, 67%)



125w–y (*f*) [28]

X = O, Y = $(CH_2)_3$ (**w**, 64%);
X = NMe: Y = $(CH_2)_2$ (**x**, 98%),
CH_2 (**y**, 68%)



126 (10%)

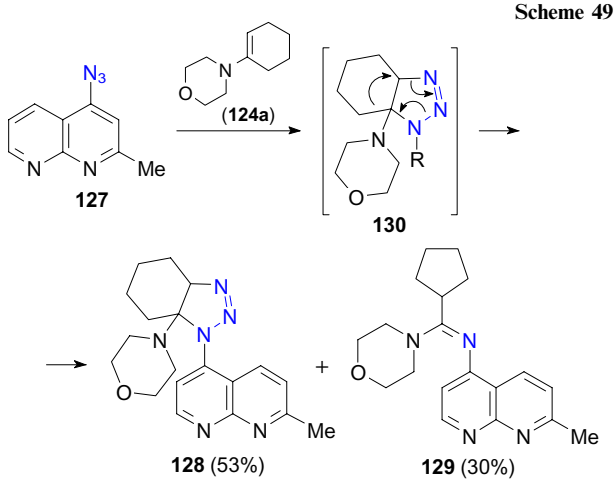
(*a*) Et_2O, −78 °C;
(*b*) PhH, rt; (*c*) DCM, rt, dark, N_2;
(*d*) MeOH, rt; (*e*) Pr^iOH, or Et_2O, or 1,4-dioxane; (*f*) 1,4-dioxane, rt

125y, the authors also identified amine **126** as the minor product generated through the reduction of the azido group (see Scheme 48).[28]

3.3.3. Synthesis of amidines. Elimination of a nitrogen molecule from triazoline and contraction of an annulated ring

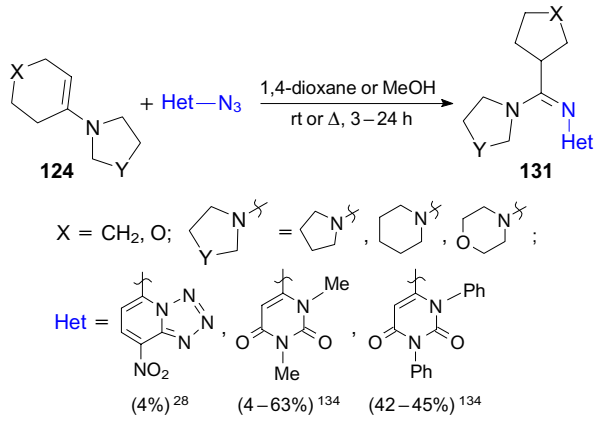
The reaction of highly electrophilic azide **127** with endocyclic enamine, cyclohexen-1-ylmorpholine (**124a**), also afforded triazoline **128** (Scheme 49).[134] However, amidine **129** was detected as an alternative product,[28] generated through the contraction of the 1,2,3-triazoline-annulated alicyclic moiety and the elimination of a nitrogen molecule from intermediate triazoline **130**.

Scheme 49



The reactions of other highly electrophilic azides with endocyclic enamines **124** occur only through this pathway of transformation of triazolines **130** and give amidines **131** in low yields (Scheme 50).[28, 135]

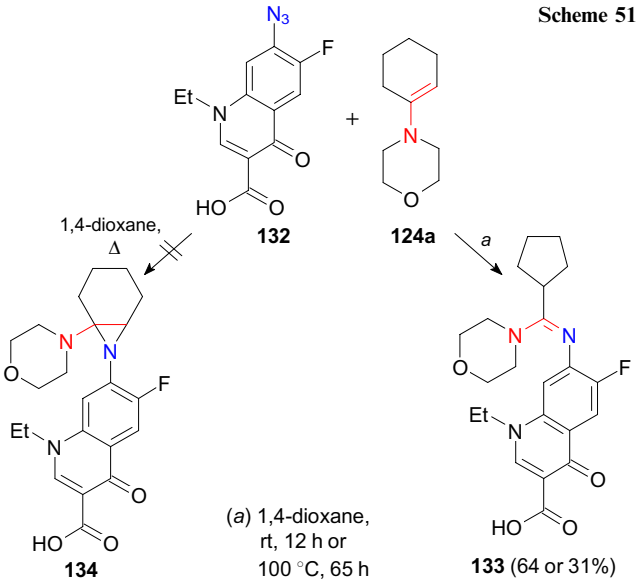
Scheme 50



The reaction of azide **132** with enamine **124a** afforded amidine **133** (Scheme 51), whereas the expected aziridine **134** was not detected in the reaction mixture.[28]

Another highly electrophilic azide, 5-azido-1-methyl-4-nitro-1*H*-imidazole (**135**), behaves in a similar way in the reaction with endocyclic enamines **124**.[133, 136] The mechanism of formation of amidines **136** proposed in the studies [133, 136] involves the *in situ* generation of enamine **124**

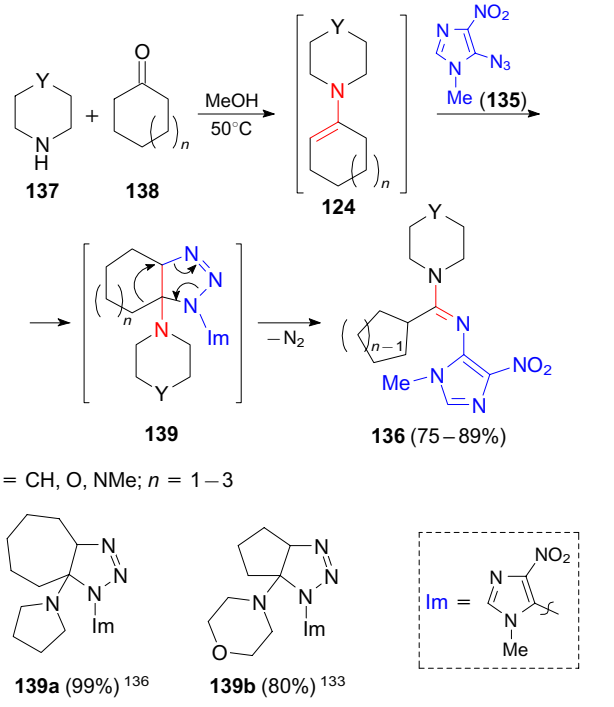
Scheme 51



from appropriate amines **137** and cyclic ketones **138** followed by their reaction with azide **135** and also the formation and contraction of the alicyclic moiety of triazoline **139** (Scheme 52). It should be emphasized that compounds **136** were synthesized using a one-pot three-component method. Triazolines **139a**,**b** proved to be quite stable, which made it possible to isolate them from the reaction mixture in the individual state and partially characterized. The stability of compound **139a** is apparently attributed to the presence of the pyrrolidine moiety. The stability of cyclopentanone derivative **139b** is apparently due to the high reaction barrier, resulting in the formation of the strained four-membered ring.

It is worth noting that under short-term reflux in ethanol or methanol, triazoline **139b** is transformed into

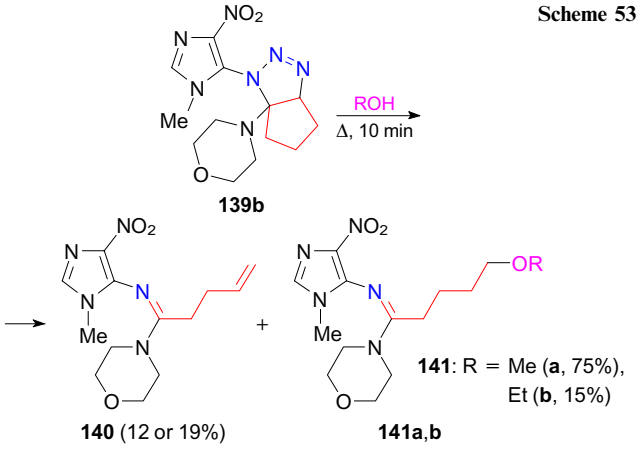
Scheme 52



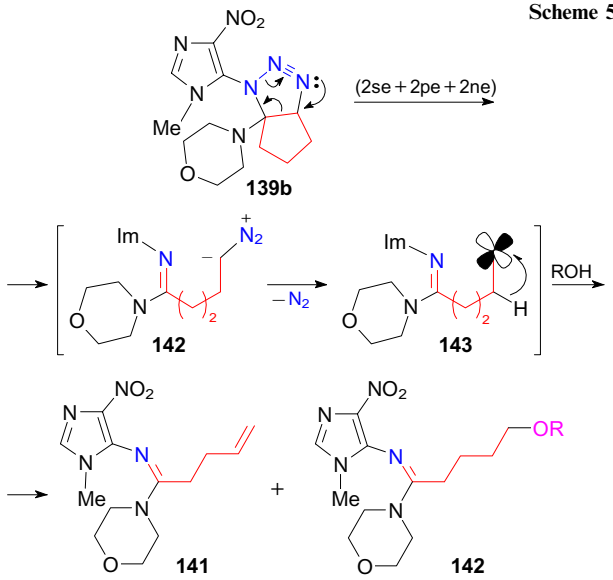
amidines **140** and **141** containing the alkene and alkoxy groups (Scheme 53).[137]

The mechanism of formation of amidines **140** and **141** proposed in the study [137] involves the simultaneous opening of the triazoline and pentane rings of molecule **139b** giving intermediate diazo compound **142** (Scheme 54). This diazo compound is transformed into carbene **143** through the elimination of a nitrogen molecule. The carbene is stabilized through the transformation into stable alkene **141** and ethers **142**. Apparently, this reaction pathway is attributed to a higher hindrance of triazoline-annulated cyclopentane compared with six-membered (and larger) rings and the fact that the reaction mechanism involving the contraction of the alicyclic moiety presents a significant barrier.

Scheme 53

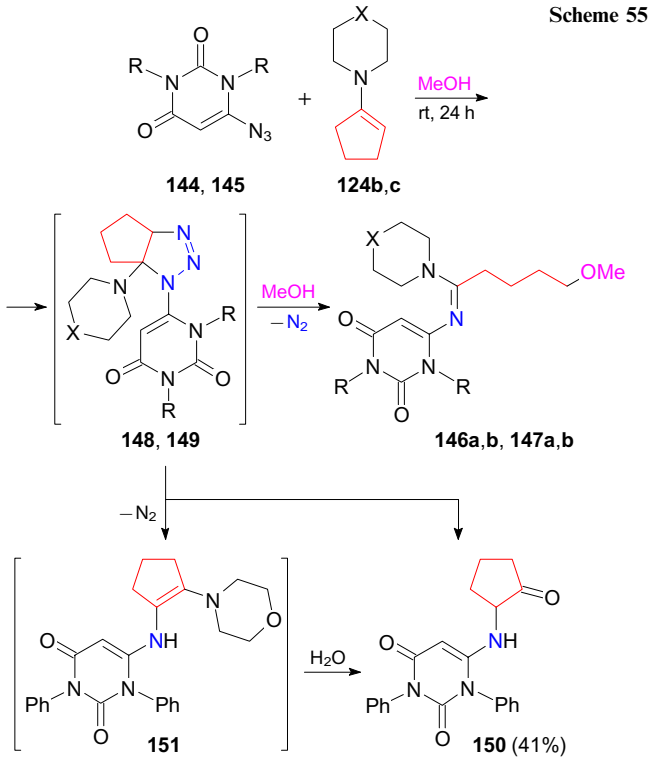


Scheme 54



It is worth noting that azides **144** and **145** react with enamines **124b**,**c** at room temperature to form amidines **146** and **147** containing the methoxybutyl moiety (Scheme 55).[137] Presumably, the reaction proceeds through the formation of intermediate 1,2,3-triazolines **148** and **149**. Interestingly, in one case, the reaction affords, along with amidine **147b** (50% yield), aminocyclopentanone **150** in a comparable amount (41% yield). It was suggested [137] that compound **150** is formed through the hydrolysis of intermediate diaminocyclopentene **151**.

Scheme 55

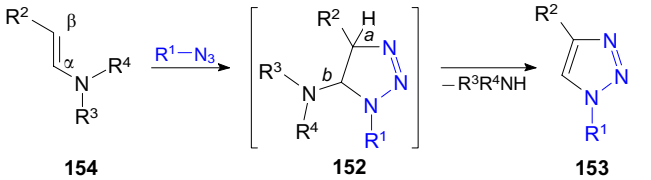


R = Me (**144**, **146**), Ph (**145**, **147**); X = CH_2 (**124b**; **146a**, 75%; **147a**, 76%), O (**124c**; **146b**, 77%; **147b**, 50%)

3.3.4. Synthesis of 1,2,3-triazoles. Elimination of secondary amine from triazoline

The most commonly used procedure for transformations of unstable 1,2,3-triazolines **152** is based on their aromatization giving 1,2,3-triazoles **153** accompanied by the elimination of amine and the *a* and *b* bond cleavage (Scheme 56).[28, 138–140] In these reactions, the electronic effect of the substituent R^1 was not revealed. Meanwhile, either an electron-deficient heterocycle or a carbonyl function should be present in the β position of enamine **154**.

Scheme 56

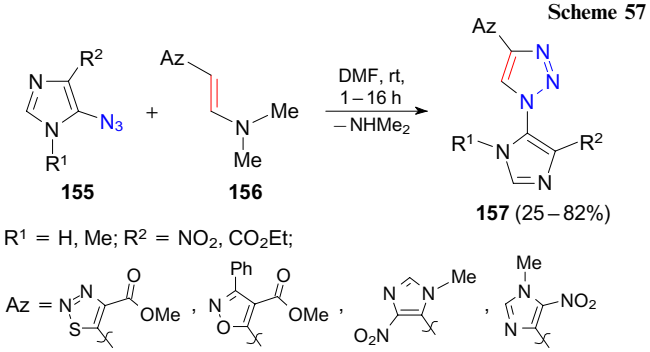


R^3 = H: R^4 = Alk, Ar, Bn, All; R^3, R^4 = Alk, Bn, Ar, Het, RSO_2, $(RO)_2P(O)$, RC(O),

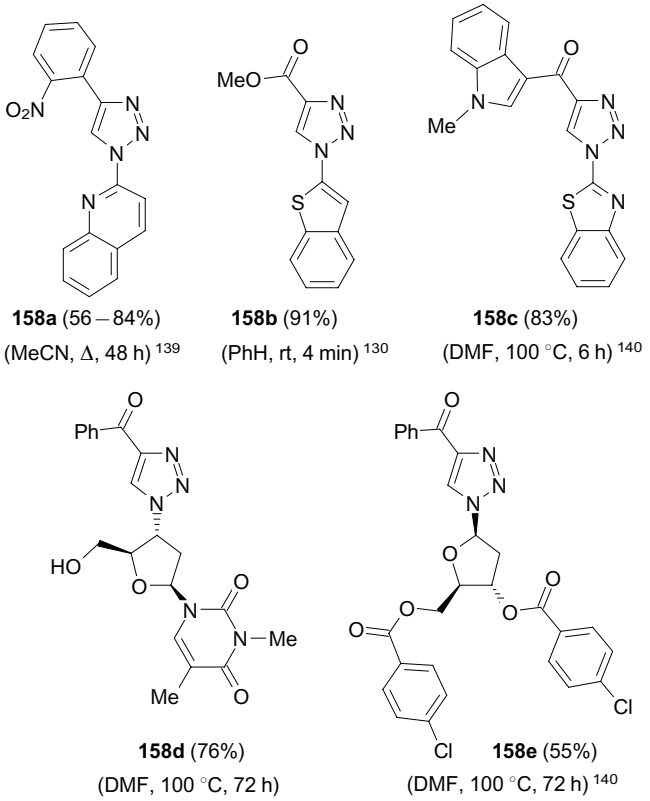
Thus, the reaction of azidoimidazoles **155** with azolylenamines **156** in DMF at room temperature afforded tricyclic ensembles **157** containing the imidazole, triazole or other azole (Az) rings (Scheme 57).[138]

Similarly, the reactions of azidoquinoline, azidobenzothiophene, azidobenzothiazole and azidotetrahydrofurans afforded linearly fused heterocyclic compounds **158a**–**e** containing moieties of the starting azides in the 1 position of the triazole ring.[130, 139, 140]

Scheme 57



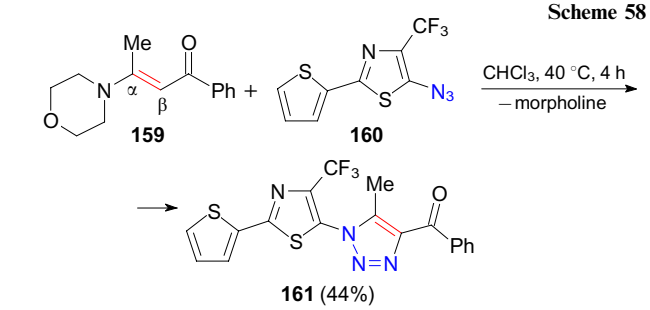
Structures 158



It is worth noting that we found the only example, in which the substituent at the α position of enaminone **159** does not cause changes in the type of the reaction product. The reaction of this compound with azide **160** in chloroform produces 1,2,3-triazole **161** in moderate yield (Scheme 58).[129]

The above transformations give 1,2,3-triazoles (mainly unsubstituted at the 5 position of the ring); therefore, they have common features with CuAAC reactions (see Section 3.1). Meanwhile, the click reactions afford exclusively 1,2,3-triazoles with the free 5 (copper-catalyzed reactions) or 4 (ruthenium-catalyzed reactions) positions. Hence, the reactions of α-substituted enamines similar to those presented in Scheme 58 hold promise for increasing chemical diversity of 1,2,3-triazoles.[129]

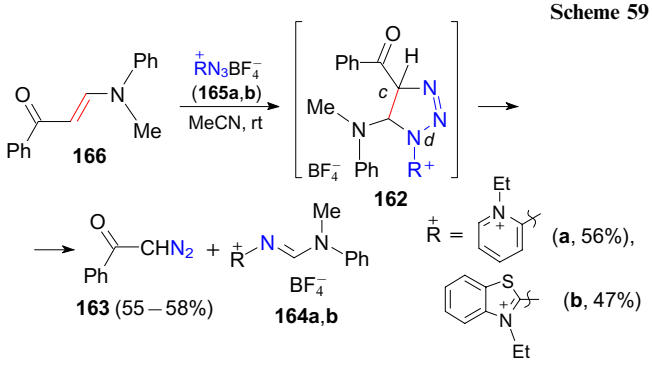
Scheme 58



3.3.5. Synthesis of diazo compounds and formamidines through cycloreversion of the triazoline ring

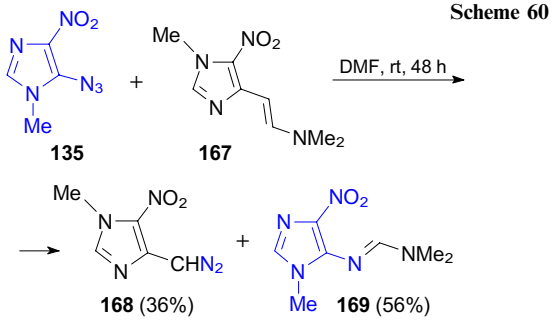
Another direction of the transformation of 1,2,3-triazolines **162** involves the *c* and *d* bond cleavage giving diazo compound **163** and amidines **164a**,**b** (Scheme 59). The reaction of azinium tetrafluoroborates **165a**,**b** with enaminone **166** is an example of reactions proceeding exclusively through this pathway.[141]

Scheme 59

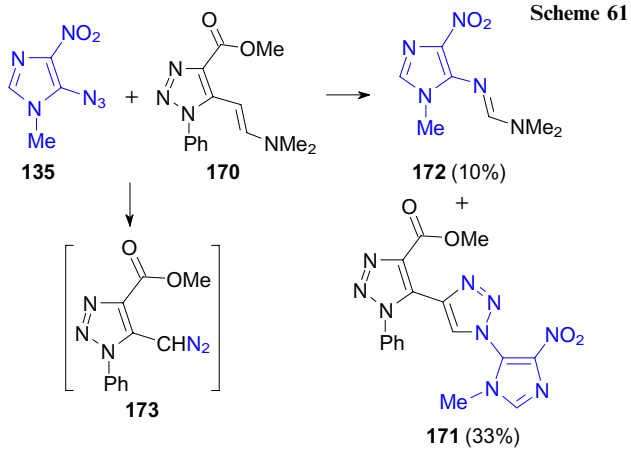


The similar reaction of azidoimidazole **135** with enamine **167** in DMF at room temperature affords imidazolyldiazomethane **168** and amidine **169** (Scheme 60).[138]

Scheme 60



Scheme 61



In the cited study,[138] the authors performed the reaction of azide **135** with enamine **170** and obtained 1,2,3-triazole **171** along with amidine **172**, which indicates that the reaction proceeds through two pathways. In this case, the formation of diazo compound **173** was not observed (Scheme 61).

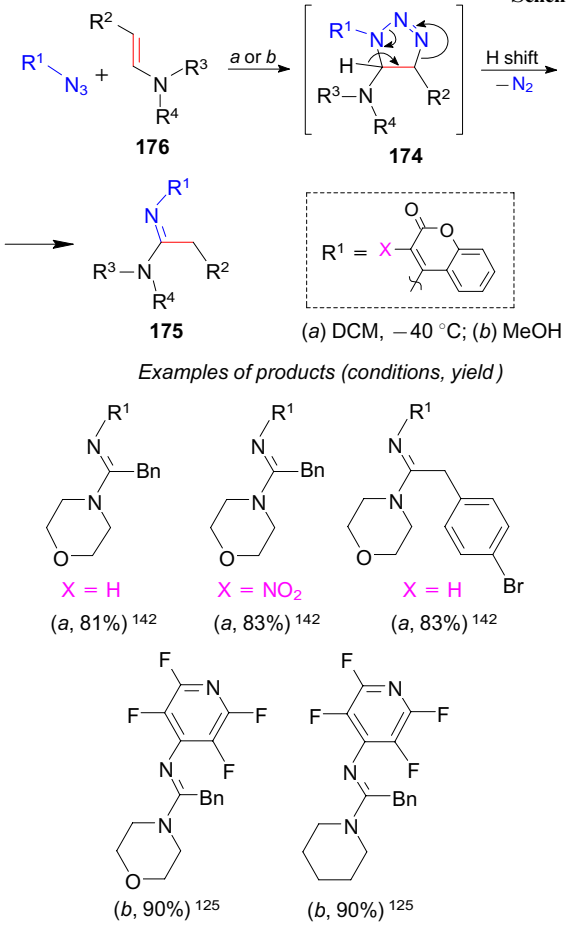
3.3.6. Active methylene amidines. Tandem elimination of a nitrogen molecule/sigmatropic hydrogen shift

The radically different pathway of the ring transformation involves the elimination of a nitrogen molecule from 1,2,3-triazolines **174** accompanied by the sigmatropic hydrogen shift to form amidines **175** (Scheme 62). This direction of the 1,2,3-triazoline ring opening is apparently due to the electron-withdrawing properties[28, 125, 142] of the substituent R^1 in azides rather than due to the type of the substituent R^2 in enamines **176**. These reactions were described for enamines with R^2 = Ar,[125, 142] Pr^i,[28] Bn[28, 142] and Et.[28, 142]

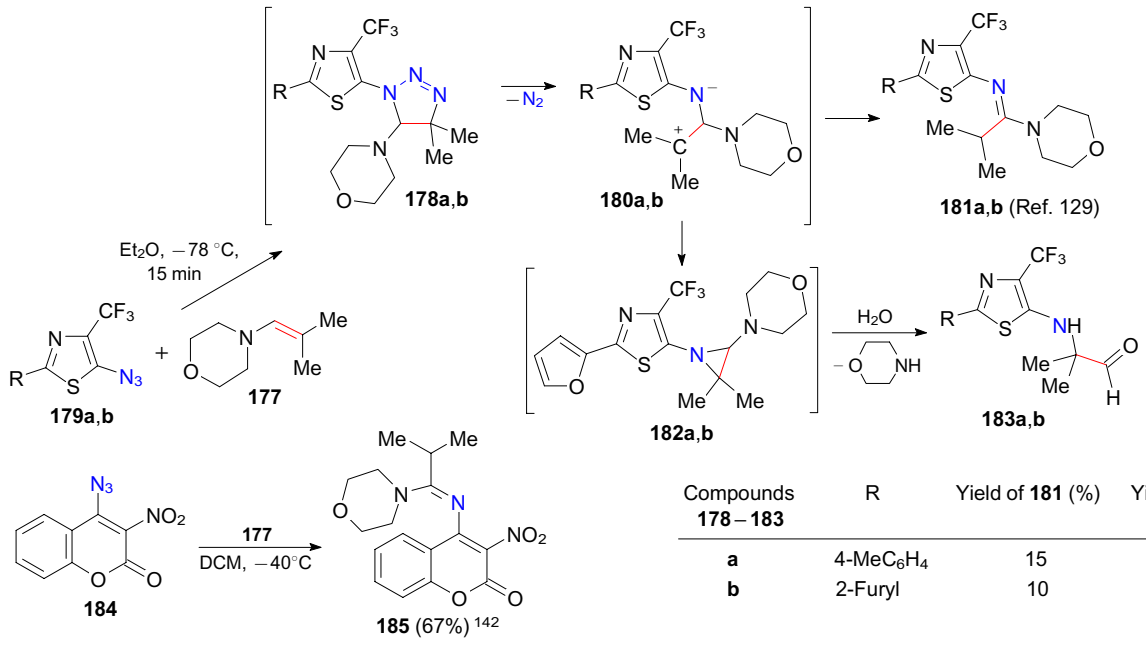
As demonstrated in relation to 4-(2-methylprop-1-en-1-yl)morpholine (**177**), the β-substitution at the double bond of enamines does not hinder the elimination of a nitrogen molecule from intermediate triazolines **178a**,**b**, which are presumably generated in the reactions with electrophilic azides **179a**,**b** (Scheme 63).[129, 142] Burger *et al.*[129] suggested that the reaction initially affords 1,3-dipoles **180a**,**b**,which can be stabilized through both the 1,2-*H*-shift giving amidines **181a**,**b** and 1,3-dipolar cyclization to form 2-(morpholino)aziridines **182a**,**b** followed by the hydrolysis giving 5-aminothiazoles **183a**,**b**. It is worth mentioning that the reaction of 4-azido-3-nitrochromone **184** with enamine **177** affords exclusively amidine **185**.

Notably, a similar tandem elimination of a nitrogen molecule and sigmatropic shift (see Scheme 63) was observed in the reactions described in the following Sections: in Section 3.2.4 devoted to the synthesis of amides from aldehydes and in Section 3.3.3, which considers the methods for the synthesis of amidines with simultaneous contraction of the triazoline-annulated carbocycle. Actually, all these reactions involve the elimination of the N_2 molecule from the initially formed triazoline followed by the 1,2-shift of either a hydrogen atom (see Sections 3.2.4 and 3.3.6) or the alkyl group (see Section 3.3.3). Therefore, the trend in the generation of the 1,2,3-triazoline intermediate is of a general character and brings together the reactions of heterocyclic azides with different substrates.

Scheme 62



Scheme 63



Compounds **178**–**183**	R	Yield of **181** (%)	Yield of **183** (%)
a	4-MeC$_6$H$_4$	15	65
b	2-Furyl	10	68

3.4. Reactions of heterocyclic azides with active methylene carbonyl compounds and nitriles

3.4.1. Reactions with 1,3-dicarbonyl compounds

The reaction of aromatic azides with 1,3-dicarbonyl compounds (Dimroth reaction), along with CuAAC reactions, is an efficient method for the synthesis of 1-aryl-1,2,3-triazoles.[143, 144] The reactions of heteroaromatic azides with carbonyl compounds, in particular 1,3-dicarbonyl compounds, are less represented in the literature compared with aryl azides. Meanwhile, a greater diversity of heterocyclic azides compared with aromatic azides resulted in a wider range of triazole ensembles with miscellaneous heterocycles. It should be taken into account that heteroaromatic azides are also able to transfer the diazo group[28] and can be used to synthesize aliphatic diazo compounds.

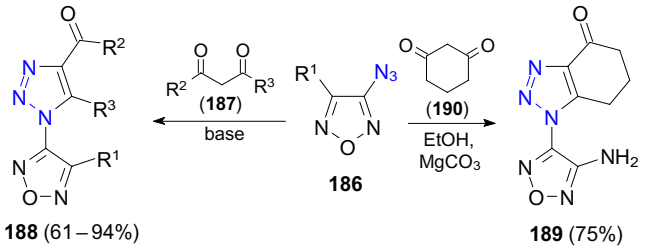
This Section summarizes the literature data on the reactions of heterocyclic azides with mono- and dicarbonyl compounds. The data are classified according to the type of the heterocycle bound to the azide group.

3.4.1.1. Five-membered heterocyclic azides

3.4.1.1.1. Azido-1,2,5-oxadiazoles

Batog *et al.*[145] studied the 1,3-dipolar cycloaddition of 4-azido-1,2,5-oxadiazoles (azidofurazans) **186** to 1,3-dicarbonyl compounds. The authors used the following starting compounds: azidofurazans containing amino, methoxy, methyl and phenyl groups and 1,3-diketones **187** with different substituents R^2 and R^3 (Scheme 64). The reactions involving azide **186a** ($R^1 = NH_2$) were studied in most detail. The conditions of the synthesis were optimized by varying the solvents (EtOH, MeOH, H_2O, aqueous ethanol) and activating bases (Et_3N, MeONa, Na_2CO_3, K_2CO_3, $MgCO_3$). It was demonstrated that these transformations (with rare exceptions) afforded triazolylfurazans **188** and **189** as the major products, which are formed in good yields through the cycloaddition of azides **186** to 1,3-dicarbonyl compounds.

Scheme 64

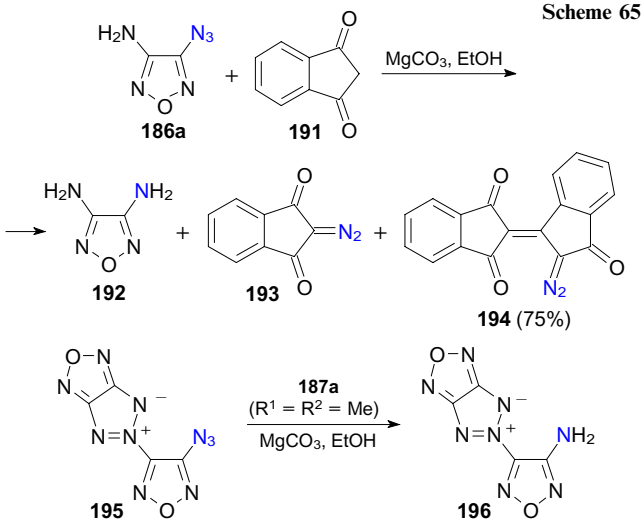


R^1 = NH_2, OMe, Me, Ph; R^2, R^3 = Alk, Ph, OAlk, CH_2OMe

Triazolylfurazans **188** and **189** were successfully synthesized in the presence of different bases, such as triethylamine, alkali metal carbonates and $MgCO_3$ (see Scheme 64). It was demonstrated that water can be used as the solvent in the reactions of azide **186a** with 1,3-dicarbonyl compounds. This reaction with cyclohexane-1,3-dione (**190**) gives product **189** containing, apart from the oxadiazole ring, the cyclohexanone-1,2,3-triazole moiety.[143, 145]

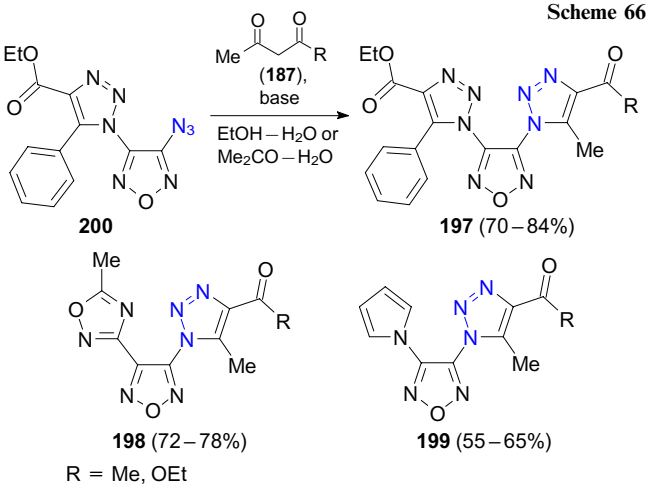
Only in two cases, the reaction of azidofurazans with 1,3-diketones did not yield 1,2,3-triazoles. In one case, the reaction of azide **186a** with 1,3-dioxoindan (**191**) occurred through the diazo transfer to form diaminofurazan **192** and diazo compounds **193** and **194** (Scheme 65). Diazo compound **194** was formed through the dimerization of diketone **193** followed by the reaction of the intermediate dimer with azide **186a**. In the second case, the reaction of azidofurazan **195** with acetylacetone (**187a**) gave 4-aminofurazan **196**. Batog *et al.*[145] did not detect the corresponding diazo compound because of the low stability of such derivatives under the reaction conditions.

Scheme 65



Later, this research group[146] published the data on the synthesis of ensembles of three heterocycles (**197**–**199**) by the reaction of azidofurazans with 1,3-diketones (Scheme 66). The transformations were performed in ethanol, aqueous ethanol or aqueous acetone in the presence of Et_3N or K_2CO_3 and a small molar excess of diketone. For example, tricyclic ensemble **197** was synthesized from bicyclic azide **200** and diketones **187**.

Scheme 66

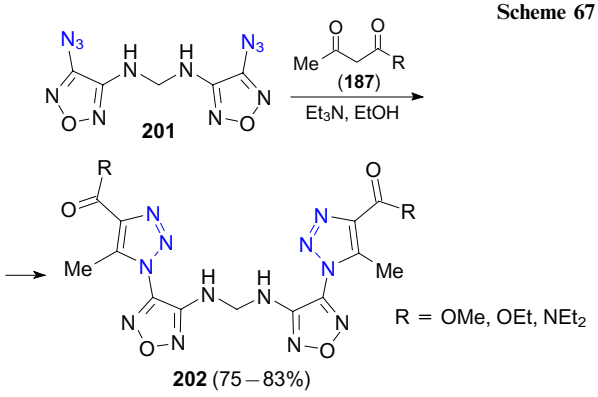


R = Me, OEt

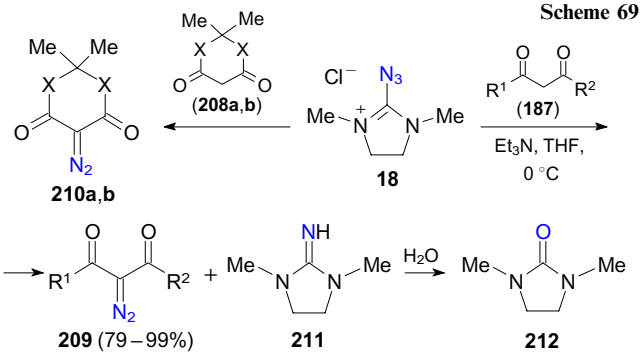
Among the synthesized triazolylfurazans, there are compounds exhibiting various biological activities.[147] In particular, these derivatives activate soluble guanylate cyclase and display anticancer activity.

In order to extend the range of biologically active triazolylfurazan derivatives, Batog *et al.*[147] synthesized compounds **202**, in which two triazolylfurazan moieties are linked by the diaminomethylene bridge, by the reaction of azide **201** with diketones **187** in the presence of triethylamine as the base (Scheme 67).

Scheme 67



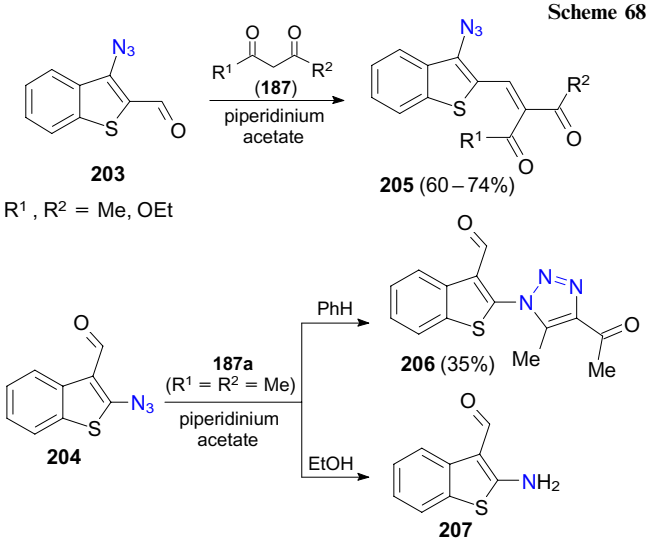
Scheme 69



3.4.1.1.2. Thienylazides

Degl'Innocenti *et al.*[148] synthesized two isomeric azides, 3-azido-2-formyl- (**203**) and 2-azido-3-formylbenzo[*b*]thiophenes (**204**), and compared their reactions with 1,3-dicarbonyl compounds **187**. It was found that the reactions of azide **203** with diethyl malonate, ethyl acetoacetate and acetylacetone in ethanol or benzene in the presence of piperidinium acetate afford condensation products **205** in moderate yields (Scheme 68). Azide **204** reacts with acetylacetone (**187a**) in the presence of piperidinium acetate differently from azide **203**. In benzene, the reaction involves the cycloaddition giving bicyclic compound **206**, whereas the reaction in ethanol occurs through the diazo transfer to form amine **207** (*cf.* Scheme 65). In both cases, the corresponding diazo compound was not detected in the reaction mixture.

Scheme 68



3.4.1.1.3. 5-Azidoimidazoles

Kitamura *et al.*[54] found that 2-azido-1,3-dimethylimidazolinium chloride **18** efficiently transfer the diazo group to 1,3-dicarbonyl compounds (Scheme 69).

With the aim of examining the field of application and limitations of this method, Kitamura *et al.*[54] studied the diazo transfer to different 1,3-dicarbonyl compounds **187** and **208**. Diketones and compounds containing simultaneously the ketone and alkoxycarbonyl groups easily react with azidoimidazole **18** to give the corresponding diazo compounds **209** in high yields. Diazo transfer reagent **18** was utilized to synthesize cyclic diazocarbonyl compounds **210**.[54]

The diazo transfer reactions of active methylene compounds **187** and **208** afford mixtures of diazo compounds **209** and **210** and azide conversion products, such as imidazolidine-2-imine **211** and imidazolidin-2-one **212**. In the case of the most commonly used tosyl azide, the reaction gives, apart from diazo compounds, tosylamide, which is often difficult to separate from the diazo compound. In this reaction, reagent **18**, unlike tosyl azide, is transformed into water-soluble imine **211**, which can easily be separated from the target diazo compound by washing the reaction mixture with water.

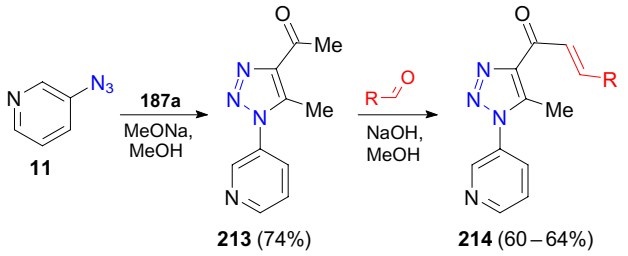
3.4.1.2. Six-membered heterocyclic azides

3.4.1.2.1. Azido derivatives of pyridine and quinoline

The reactions of azidoazines with 1,3-dicarbonyl compounds afford 1,2,3-triazoles containing azinium rings in the 1 position as the major products.

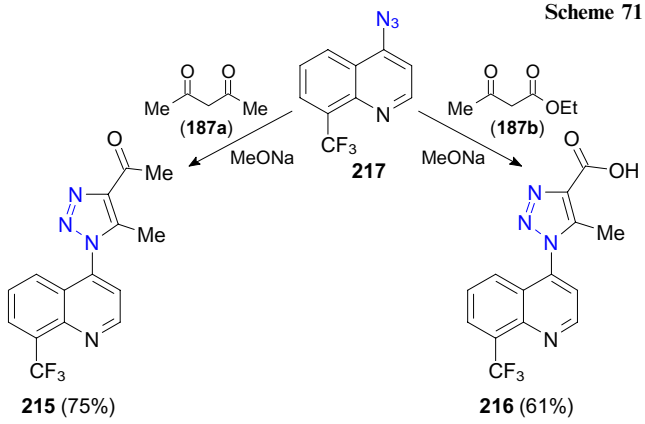
Thus, Kaushik *et al.*[149] synthesized 4-acetyl-5-methyl-1-(3-pyridyl)-1*H*-1,2,3-triazole (**213**) in moderate yield by the reaction of 3-azidopyridine (**11**) with acetylacetone (**187a**) in the presence of sodium methoxide (Scheme 70). Triazole **213** was used as the substrate to prepare chalcone analogues **214**. It is worth noting that in this case, the Claisen–Schmidt condensation with aldehydes occurs selectively. Thus, the reaction involves only the acetyl group of compound **213**.

Scheme 70



Holla *et al.*[150] synthesized triazoles **215** and **216** in moderate yields from 4-azido-8-trifluoromethylquinoline (**217**) and acetylacetone (**187a**) or ethyl acetoacetate (**187b**), respectively (Scheme 71). The synthesis of triazole **216** was accompanied by the hydrolysis of the ethoxycar-

Scheme 71



bonyl group to the carboxyl one. The synthesized compounds were utilized in the synthesis of drugs with high antibacterial activity.

Kumari *et al.*[151] used acetylacetone (**187a**), 4-azido-7-chloroquinoline (**218**), aromatic aldehydes **219**, isatin (**220**) and proline (**221**) as the reagents and performed the one-pot five-component synthesis of compounds **222** containing the carbonyl-bridged spiroxindole and 1,2,3-triazole moieties (Scheme 72). Additional experiments demonstrated that synthesized triazoles **223** and **224** and spiro compound **225** are intermediates in the synthesis of spiropyrans **222**. Presumably, the reaction proceeds through intermediate **226**.[151]

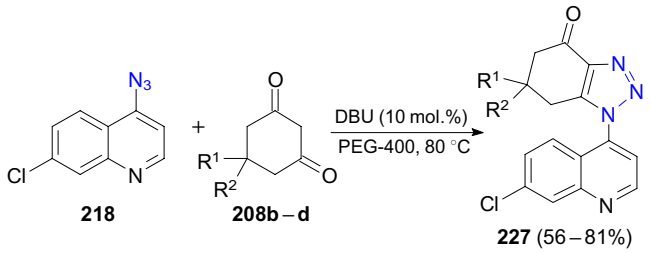
Singh *et al.*[152] studied the reaction of 4-azido-7-chloroquinoline (**218**) with cyclic 1,3-dicarbonyl compounds **208b**–**d** giving bicyclic ensembles **227** bearing the cyclohexanonetriazoles and 7-chloroquinoline moieties (Scheme 73).

Dyadyuchenko *et al.*[153] demonstrated that the treatment of pyridotetrazoles **228** with acetylacetone or ethyl acetoacetate in the presence of Et_3N gives rise to the triazole ring, like in the case of azides (Scheme 74). The reaction produced 1-pyridinyltriazoles **229** in moderate yields. Apparently, under the conditions of the synthesis, the equilibrium tetrazole ring opening occurs to give the azide form, which is involved in the reaction.

3.4.1.2.2. Azidopyridazines

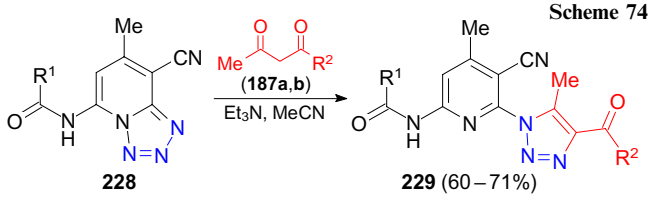
In 2014, Brooke *et al.*[153] published the synthesis of analogues of compound **230a**, a known inhibitor of the important glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3). In order to establish the structure–inhibitory activity relationship for the glycolytic enzyme, a series of differently substituted acetyltriazoles **230**–**232** were synthesized by the reactions of heterocyclic azides with acetylacetone **187a** (Scheme 75). It was demonstrated that the variation of the substituent in the triazole or pyridazine moiety does not cause a significant change in the inhibitory activity of the compound. Meanwhile, the introduction of small substituents on the phenyl ring leads to a slight increase in the activity.

Scheme 73



208: R^1 = R^2 = Me (**b**), H (**c**); R^1 = Me, R^2 = H (**d**)

Scheme 74

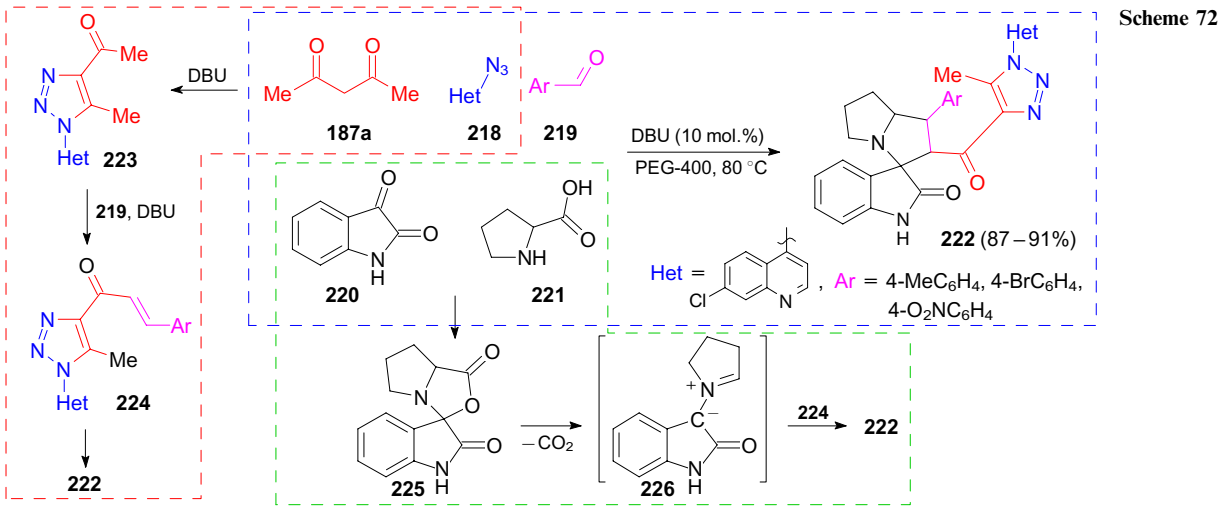


R^1 = 2,6-$F_2C_6H_3$, cyclo-C_3H_5, cyclo-C_6H_{11}; R^2 = Me, OEt

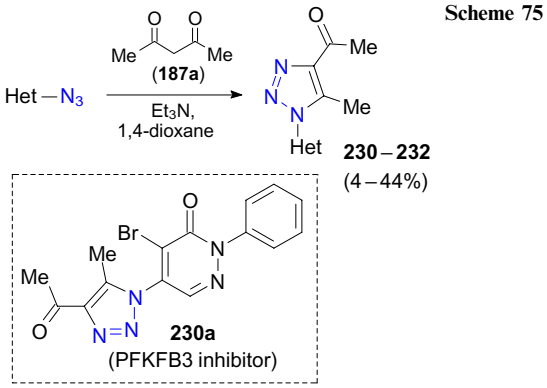
3.4.1.2.3. Azidopyrimidines

Raauf *et al.*[155] reported the three-step synthesis of derivatives of the bacteriostatic antibiotic trimethoprim (**233**) containing the triazole ring. In the first step, trimethoprim (**233**) was transformed into aminoimidazopyrimidine **234** by the reaction with bromoacetic acid (Scheme 76). Then the diazotization of amine **234** followed by the treatment with sodium azide gave heterocyclic azide **235**. In the third step, the reaction of azide **235** with acetylacetone and ethyl acetoacetate in the presence of sodium ethoxide afforded triazoles **236a**,**b** in 59 and 81% yields, respectively. These

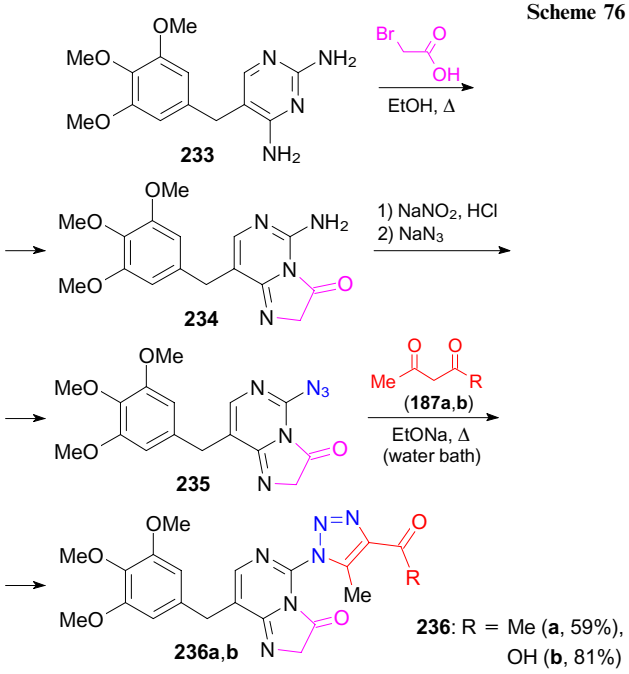
Scheme 72



Scheme 75



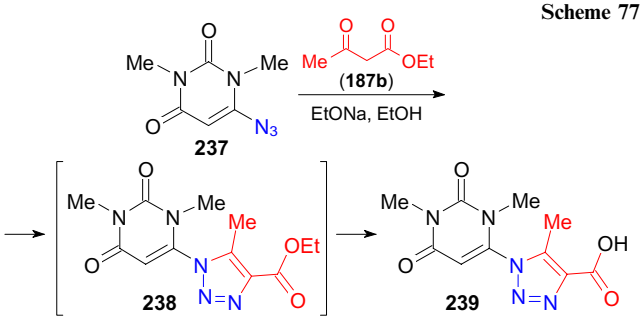
Scheme 76



products exhibited antibacterial activity at the level of trimethoprim (**233**).

El-Etrawy and Abdel-Rahman[156] performed the reaction of 6-azido-1,3-dimethyluracil (**237**) with ethyl acetoacetate (**187b**) under reflux in ethanol in the presence of sodium ethoxide (Scheme 77). It was found that the triazole ring formation is accompanied by the hydrolysis of the ester group of intermediate ester **238** giving acid **239**. It is worth noting that Holla *et al.*[150] also observed the hydrolysis of

Scheme 77

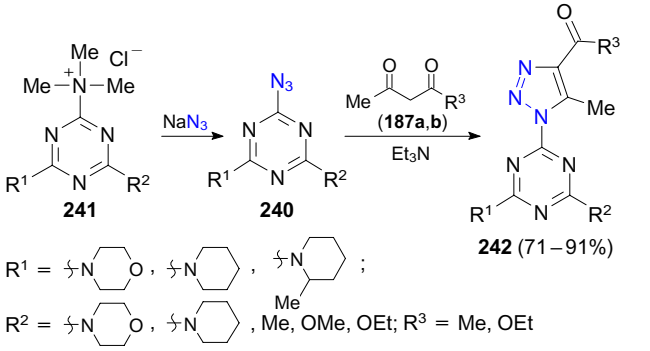


the ester group in the reaction with sodium ethoxide or methoxide.

3.4.1.2.4. Azidotriazines

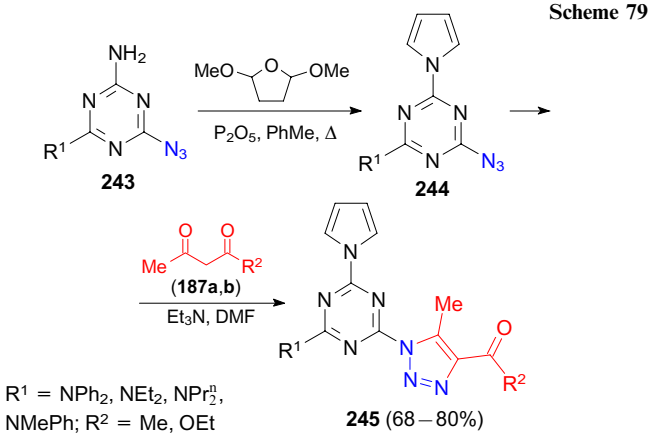
Mikhailychenko *et al.*[157] and Chesnyuk *et al.*[158] published the results of research on the reactions of azido derivatives of *sym*-triazines with dicarbonyl compounds. In the study,[157] a new procedure was developed for the synthesis of azidotriazines **240**, involving the reaction of trimethylammonium salts **241** with sodium azide (Scheme 78). The cyclization of azides **240** with acetylacetone and ethyl acetoacetate gave 1-triazinyl-1,2,3-triazoles **242** in high yields.

Scheme 78

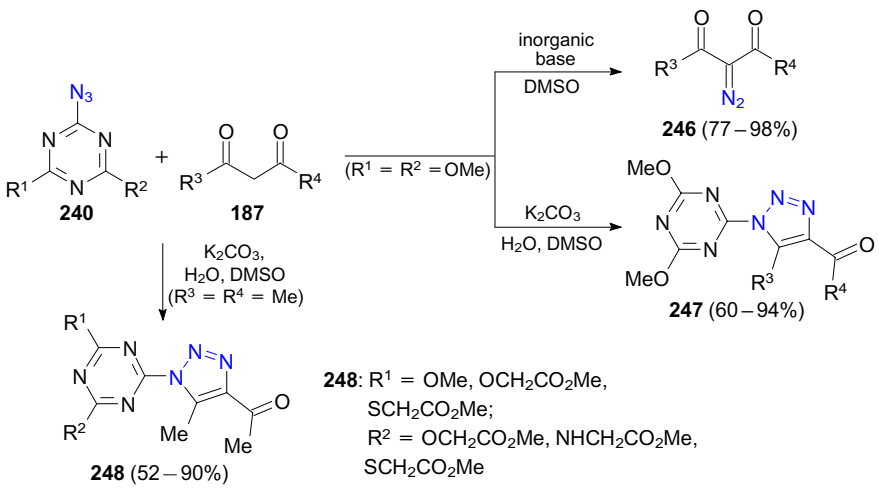


In the study,[158] the authors synthesized pyrrole-containing azides **244** by the Clauson–Kaas reaction of aminoazides **243** with 2,5-dimethoxytetrahydrofuran (Scheme 79). The reaction of azides **244** with acetylacetone and ethyl acetoacetate in DMF in the presence of Et_3N produced tricyclic ensembles **245** containing the pyrrole, triazine and triazole rings.

Scheme 79



Scheme 80



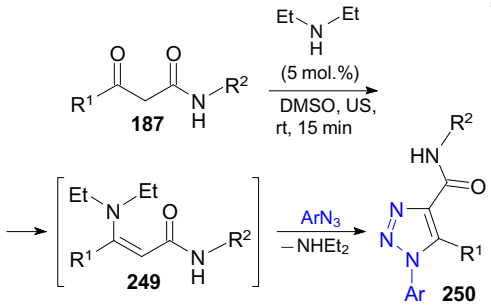
The research on the reaction of azidotriazines with 1,3-dicarbonyl compounds was further developed by Ma and co-workers.[159] The authors demonstrated that 2-azido-4,6-dimethoxy-1,3,5-triazine (**240a**, $R^1 = R^2 = OMe$) is a safe and efficient diazo transfer reagent and developed a procedure for the synthesis of diazodiketones **246** from azide **240a** and different 1,3-dicarbonyl compounds **187** (Scheme 80). The optimal reaction conditions include the use of highly polar DMSO as the solvent and $NaHCO_3$ as the base.[159]

In continuation of their work, this research group[160] found the conditions, under which the reaction of azido derivatives of 4,6-disubstituted *sym*-triazines with active methylene compounds affords triazoles **247** as the major products (see Scheme 80). The authors suggested that the nature of the solvent plays a key role in this process. As opposed to aprotic solvents (*e.g.*, DMSO), in which the diazo transfer reaction is the major process,[159] the regiospecific [3 + 2]-cycloaddition occurs in water to give trisubstituted 1,2,3-triazoles **247**. The optimal reaction conditions are as follows: a mixture of H_2O and DMSO (1 : 1) in the presence of K_2CO_3 at room temperature. This method was used to synthesize triazoles **247** in high yields by the reaction of azide **240a** with a series of 1,3-dicarbonyl compounds **187**. High regioselectivity was observed in all reactions, in which unsymmetrical dicarbonyl compounds **187** were utilized.[159, 160] Apart from azide **240a**, the reaction with acetylacetone was performed using a series of other azido-1,3,5-triazines **240** (see Scheme 80). These reactions produced triazinotriazoles **248** in yields from 50 to 92%, which confirmed a wide field of application of this method. Yan *et al.*[160] proposed the reaction mechanism, which accounts for the solvent effect on the reaction pathway and which was confirmed by DFT calculations.

3.4.1.3. Reactions of heterocyclic azides with 1,3-dicarbonyl compounds in the presence of secondary amines. Enamine organocatalysis

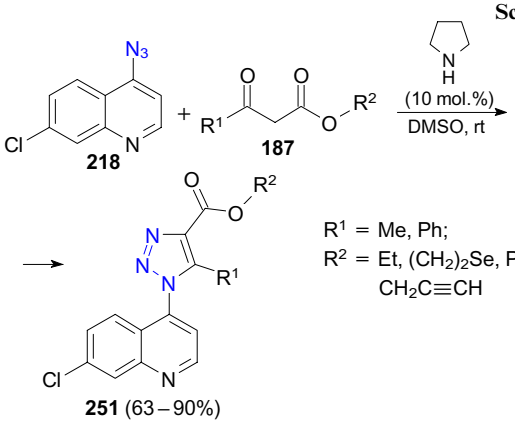
The synthetic methodology of organocatalysis is an alternative to the metal salt catalysis. This methodology was applied to the synthesis of 1,2,3-triazole derivatives by the reaction of carbonyl compounds with aromatic azides in the presence of secondary amines. The mechanism of this transformation involves the generation of enamines **249** from dicarbonyl compounds **187** and amines followed by their rapid cyclization under the treatment with azides to form 1,2,3-triazoles **250** (Scheme 81).[24, 28, 161, 162]

Scheme 81



Thus, Saraiva *et al.*[163] described the synthesis of bifunctional compounds **251** containing triazolylcarboxylate and 7-chloroquinoline moieties based on the pyrrolidine-catalyzed cycloaddition of azide **218** to 1,3-dicarbonyl compounds **187** (Scheme 82). Compounds **251** exhibited antioxidant activity.

Scheme 82

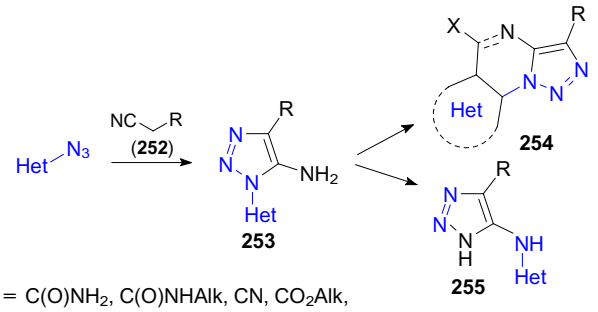


Sokolnikova *et al.*[164] reported the advantages of the use of diethanolamine over diethylamine and demonstrated these advantages in relation to the synthesis of bicyclic 1,2,3-triazole ensembles containing the 1,2,4-triazole and 1,2,3-triazine rings in high yields.

3.4.2. Reactions with acetonitrile derivatives

The reaction of heterocyclic azides with acetonitriles **252** under basic conditions generally gives 5-aminotriazoles **253**

Scheme 83



R = C(O)NH$_2$, C(O)NHAlk, CN, CO$_2$Alk, Ar, Het, C(O)Ar, C(O)Het, SO$_2$Ar, C(S)NAlk$_2$, *etc.*

(Scheme 83). In the presence of an appropriate substituent in the *ortho* position with respect to the azide group, further reactions of **253** can occur to form fused polycyclic systems **254**. In some cases, the Dimroth rearrangement takes place giving isomeric triazole **255**. This reaction is generally regioselective and has a predictable outcome. In most studies, this reaction was considered as a method for the synthesis of polyheterocyclic compounds with valuable promising properties for application in medicine, engineering and agriculture.[165–170]

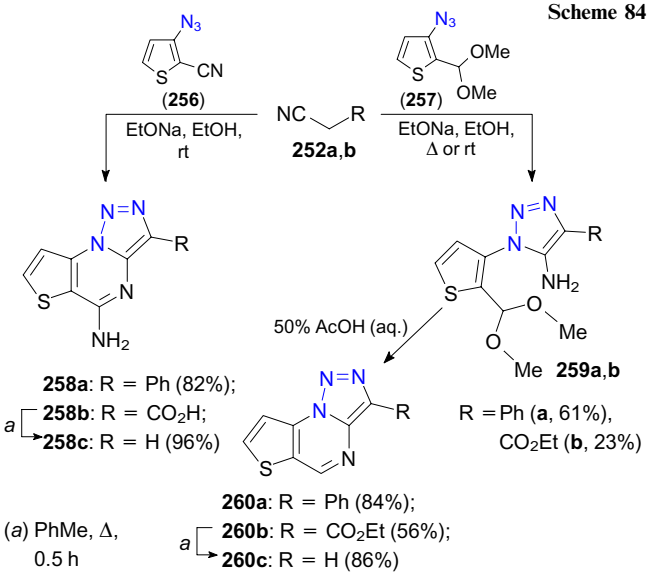
3.4.2.1. Five-membered heterocyclic azides

3.4.2.1.1. Azidothiophenes

This Section summarizes the studies, in which the cycloaddition of azidothiophenes to acetonitriles was used to synthesize polycyclic systems containing the pyrimidine ring, because a substituent suitable for cyclization was present almost in all cases in the *ortho* position with respect to the azide group. In most cases, these polycyclic compounds were successfully synthesized.

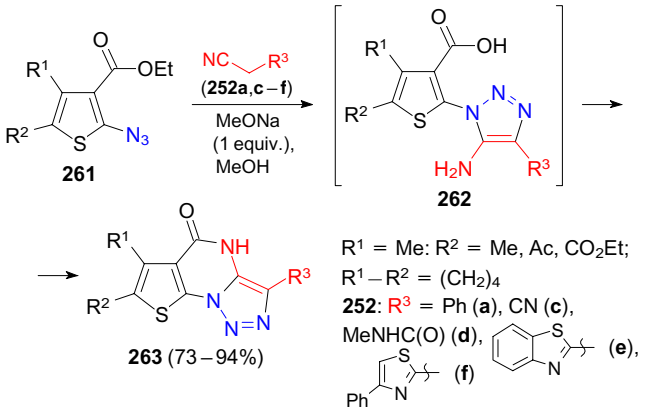
For instance, Westerland[171] studied the reaction of acetonitrile derivatives **252a**,**b** [R = Ph (**a**), CO$_2$Et (**b**)] with 3-azidothiophenes **256** and **257** bearing the cyano or protected aldehyde group, respectively, at the 2 position (Scheme 84). The reactions of 3-azido-2-cyanothiophene (**256**) with a fourfold excess of sodium ethoxide afforded triazolopyrimidines **258a**,**b** through the sequential formation of the triazole and pyrimidine rings. The reaction of 3-azido-2-(dimethoxymethyl)thiophene (**257**) with acetonitriles **252a**,**b** in ethanol in the presence of sodium ethoxide gave aminotriazoles **259**, which underwent cyclization to [1,5-*a*]pyrimidines **260** in 50% acetic acid. The transformation using ethyl cyanoacetate (**252b**) is complicated by the saponification of the ester group and the resulting carboxylic acid is readily decarboxylated, which accounts for the low yield of 5-amino-1,2,3-triazole **259b**. The decarboxylation of triazolopyrimidine **260b** under reflux in toluene for 0.5 h produces unsubstituted heterocycle **260c**.

Scheme 84



Pokhodylo *et al.*[172–175] published a series of papers on the reactions of 2-azido- and 3-azidothiophenes with acetonitriles. The presence of the alkoxycarbonyl group in the *ortho* position with respect to the azide group allows the preparation of polycyclic systems in high yields. The cycloaddition of acetonitriles **252a**,**c**–**f** to 2-azidothiophenes **261** in the presence of sodium methoxide apparently occurs through the formation of intermediate aminotriazoles **262** (were not isolated) within 1–2 min; the process is accompanied by heat release. The reaction affords thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **263** (Scheme 85).[175]

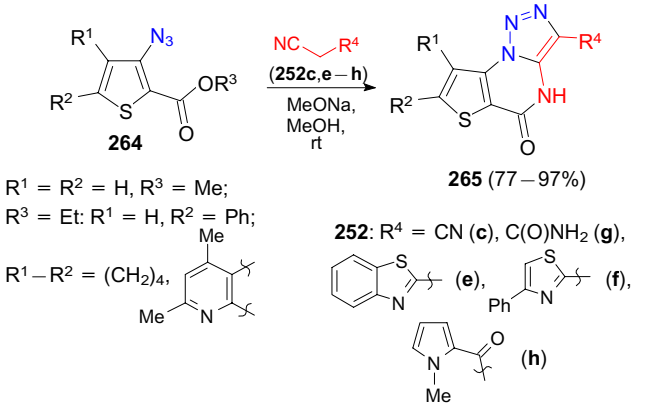
Scheme 85



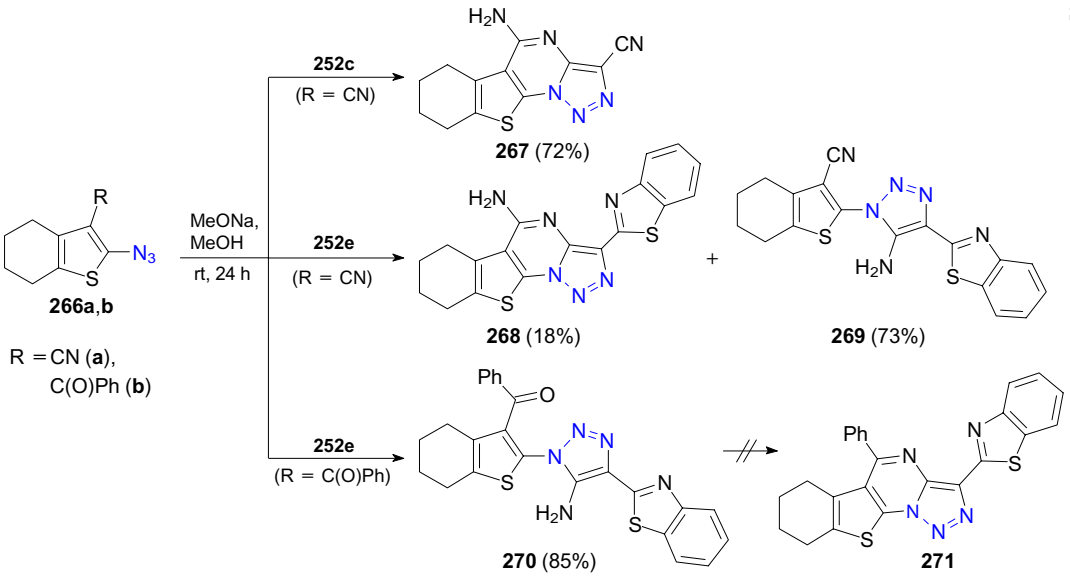
The reaction of 3-azidothiophenes **264** with active methylene nitriles **252c**,**e**–**h** in the presence of sodium methoxide at room temperature produced thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **265** isomeric to tricyclic compounds **263** (Scheme 86).[174]

In the study,[172] the authors described the reactions, which give either aminopyrimidines **267** and **268** or triazoles

Scheme 86



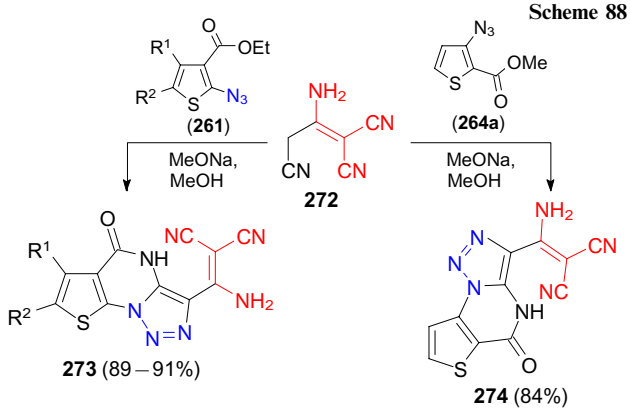
Scheme 87



269 and **270** depending on the substituent in the 3 position of the thiophene ring of compound **266** and acetonitrile derivative **252**. It was demonstrated that **270** is not transformed into pyrimidine **271** through the cyclization involving the benzoyl and amino groups (Scheme 87).

In continuation of research, these authors [173] studied the reactions of azidothiophenes **261** and **264a** with malononitrile dimer **272**. It appeared that these reactions produce pyrimidones **273** and **274** fused to both the thiophene and triazole rings (Scheme 88). The structures of the reaction products were investigated in detail by NMR spectroscopy.

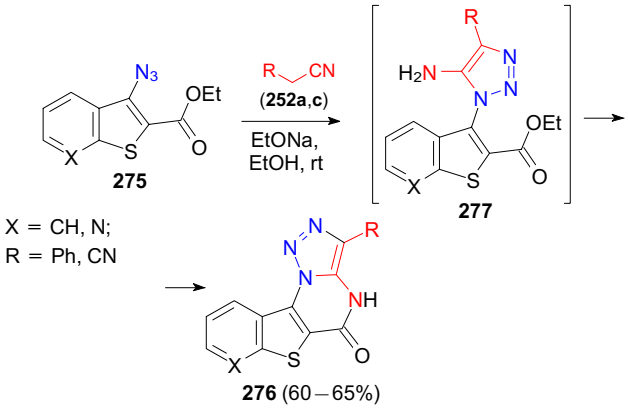
Scheme 88



The researcher group [166] from the University of Palermo prepared tetracyclic systems **276** by the reactions of nitriles **252a**,**c** with azides **275** (Scheme 89) and then modified these systems at the pyrimidine nitrogen atom. This allowed the authors to synthesize a series of compounds and evaluate them for anticancer activity, the substituents being selected using the Virtual Lock and Key approach.[176] Several derivatives exhibited high antiproliferative activity.[166] As in most of the above examples, the reactions of azidothiophene with acetonitriles directly afford triazolopyrimidines **276**; only in one case, intermediate aminotriazole **277** (X = N, R = CN) was isolated in 35% yield.

Campos *et al.*[177] failed to prepare tetracyclic compounds **279** from arylacetonitriles **252i** (R = Ar) and 3-azido-substituted pyrazinothiophene **278** by means of procedures

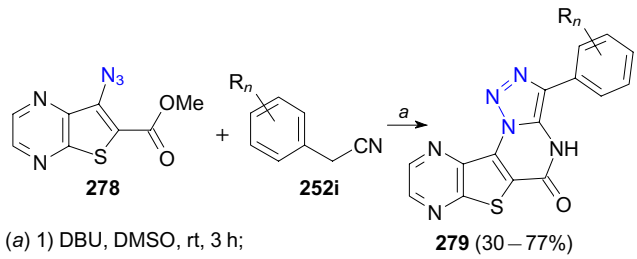
Scheme 89



described in the literature [166, 173] and developed a new method based on the use of DMSO in the presence of DBU (Scheme 90). The authors suggested that this reaction proceeds through the formation of intermediate 5-amino-1,2,3-triazoles, which undergo cyclization into pyrazino[2′,3′:4,5]thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **279** upon treatment with an aqueous solution of ammonium chloride.

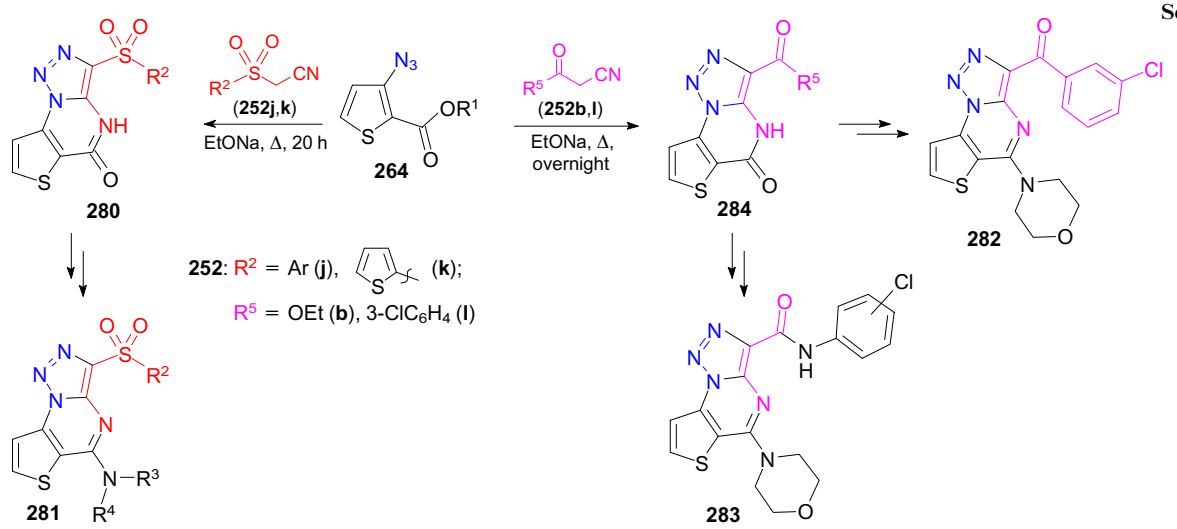
In the past decade, it was found that triazolothienopyrimidines display valuable biological properties. Thus, they act as serotonin 5-HT$_6$ receptor antagonists,[168] inhibitors of kidney urea transporter UT-B [167] and inhibitors of human

Scheme 90



(*a*) 1) DBU, DMSO, rt, 3 h;
2) NH_4Cl (aq.);
R_n = 4-Me, 4-Br, 3,4-Cl_2, 4-OH, 4-OMe, 3,4,5-$(OMe)_3$, 2,3-benzo

Scheme 91

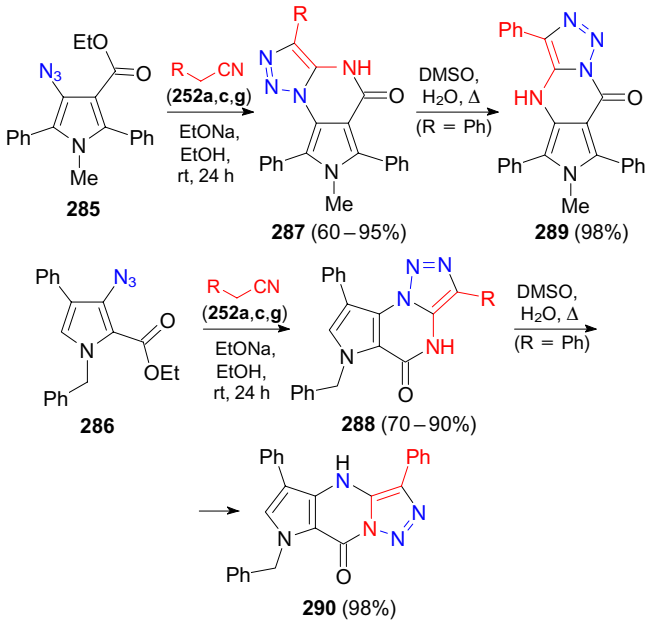


immunodeficiency virus type 1 (HIV-1) replication.[165] Ivachtchenko *et al.*[168] performed the reaction of sulfonylacetonitriles **252j**,**k** with 3-azidothiophenes **264** under reflux in a basic medium and obtained key intermediates **280** in 80–90% yield. The latter compounds were utilized to synthesize a library of compounds with the general structure **281** (Scheme 91). Kim *et al.*[165] reported the synthesis of triazolothienopyrimidines **281**–**283**. In these reactions, intermediate cycloaddition products **280** and **284** are generated under the same conditions (under reflux in ethanol with sodium ethoxide). Anderson *et al.*[167] synthesized building blocks **280** by this reaction at room temperature. (see Scheme 91).

3.4.2.1.2. Azido derivatives of pyrroles, indoles, pyrazoles, isoxazoles and imidazoles

In order to synthesize potential DNA intercalators with anticancer activity, Lauria *et al.*[169, 178–180] conducted systematic studies on the reactions of acetonitrile derivatives with various azidoazoles containing an ester group in the *ortho* position with respect to the azide group. In most cases, the reactions produce polycyclic systems similar to those described above for thiophenes (see Scheme 89). The authors demonstrated[179] that the reaction of azidopyrroles **285** and **286** with acetonitriles **252a**,**c**,**g** [R = Ph (**a**), CN (**c**), $C(O)NH_2$ (**g**)] gave pyrrolo[1,2,3]triazolo[1,5-*a*]pyrimidines **287** and **288** and examined the possibility of Dimroth rearrangements occurring in these compounds (Scheme 92). After unsuccessful attempts to perform this rearrangement in an 20% aqueous solution of KOH or on heating in ethanol, the following appropriate conditions were found: heating of the reagents under reflux in DMSO in the presence of trace water. Under these conditions, triazolopyrimidines **287** and **288** with R = Ph are quantitatively rearranged into isomeric pyrrolo[1,2,3]triazolo[1,5-*a*]pyrimidines **289** and **290** (see Scheme 92). Attempts to perform this rearrangement with other derivatives **287** and **288** failed apparently because of their poor solubility in DMSO.

Scheme 92

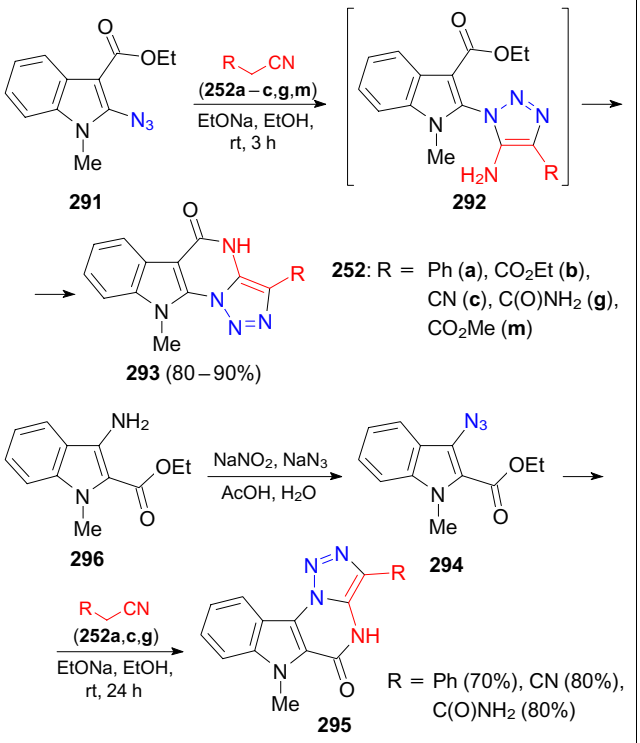


2-Azidoindoles **291** react with acetonitriles **252a**–**c**,**g**,**m** under conditions similar to those used for the reactions of pyrroloazides, but they undergo faster cyclization through the formation of intermediates **292** to pyrimidines **293** (Scheme 93).[178] However, attempts to prepare isomeric triazolopyrimidines **295** from 3-azidoindoles **294** and cyanoacetic esters **252b**,**m** [R = CO_2Et (**b**), CO_2Me (**m**)] failed. Thus, after 48 h only 3-aminoindole **296**, which was the starting compound for the synthesis of azide **294**, was detected in the reaction mixture.[169]

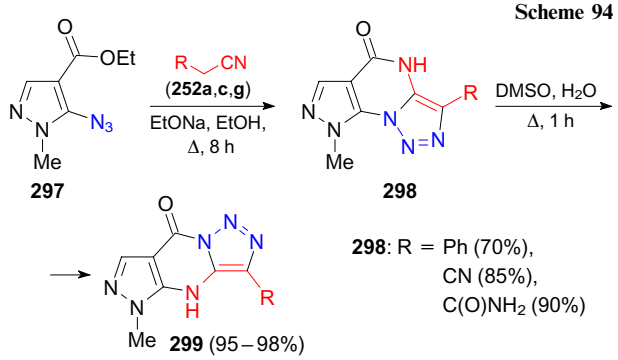
In continuation of their research, Lauria *et al.*[180] studied the reaction of 1-methyl-5-azidopyrazole-4-carboxylate **297** with acetonitriles **252a**,**c**,**g** (Scheme 94). In this case, the cycloaddition did not occur at room temperature. Thus, after 24 h the reaction mixture contained mainly the starting compounds, whereas the heating in ethanol under reflux made it possible to prepare triazolopyrimidines **298** within 8 h. Like pyrrole derivatives, compounds **298** undergo the Dimroth rearrangement to isomeric tricyclic compounds **299** under reflux in aqueous DMSO (see Scheme 94). Later, Hassan *et al.*[181] described the synthesis of compound **298** (R = $C(O)NH_2$) at room temperature in 94% yield.

Since the pyrazole ring of compound **300** contains an aldehyde group, the reaction of active methylene compounds **252** occurs primarily with this group. For instance, Chen *et al.*[182] synthesized acrylonitrile-containing compound **301a** in 95% yield by the reaction of aldehyde **300** with malononitrile (**252c**) at room temperature in ethanol in

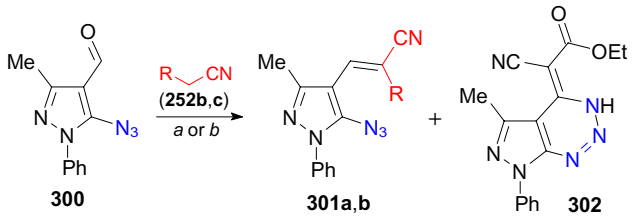
Scheme 93



Scheme 94

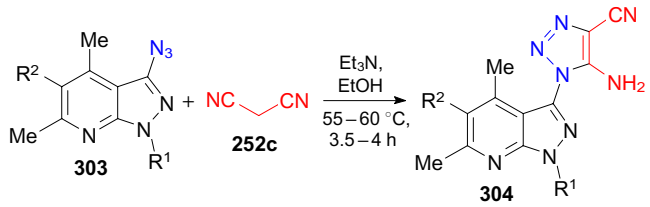


Scheme 95

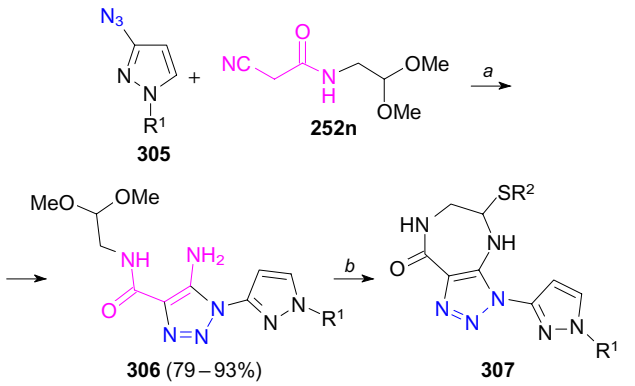


(*a*) EtOH, PyH, stirring (for R = CN (**301a**));
(*b*) MeONa, DCM, Δ (for R = CO_2Et (**301b**))

Scheme 96



R^1 = R^2 = H (66%); R^1 = Me: R^2 = H (80%), Cl (74%)



(*a*) 1) Bu^tOK, MeOH, rt, stirring 1 h; 2) Δ, 0.5 h;
(*b*) 1) HCO_2H, rt, 10–12 h; 2) R^2SH, HCO_2H, rt, 8 h

the presence of a small amount of pyridine (Scheme 95). The reaction of azidoaldehyde **300** with cyanoacetic ester (**252b**) required refluxing in ethanol in the presence of sodium methoxide. In this case, the reaction produced 5-azidopyrazole **301b** (55% yield) and pyrazolo[3,4-*d*][1,2,3]triazine **302** (20% yield).[182]

Along with the domino reactions, there are examples of the synthesis of aminotriazoles from compounds, which do not contain the ethoxycarbonyl or cyano group in the *ortho* position with respect to the azide group. Thus, Dmitrieva *et al.*[183] performed the reaction of azides **303** with malononitrile (**252c**) to prepare ensembles of pyrazolo[3,4-*b*]pyridine and triazole **304** in the presence of triethylamine as the base (Scheme 96). Syrota *et al.*[184] utilized the stronger base, potassium *tert*-butoxide, for the cycloaddition of N-substituted cyanoacetamide **252n** to 3-azidopyrazole **305** to prepare triazole **306**. The latter compound was used as one of intermediates in the synthesis of fused diazepines **307**.

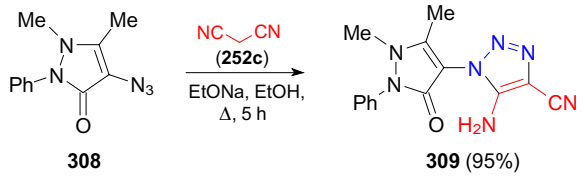
Within the framework of the program on the synthesis of new 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazolone derivatives and evaluation of their anticancer properties and radiosensitivity, Aly and El-Gazzar[185] synthesized aminotriazole **309** in high yield by the reaction of azide **308** with malononitrile **252c** (Scheme 97). However, this bicyclic ensemble did not exhibit significant biological activity.

The reaction of 3-azido-5-methylisoxazole (**310**) with acetonitrile **252i** (R = 4-$MeOC_6H_4$) affords aminotriazole **311**, containing the isoxazole ring in the 1 position, in low yield (Scheme 98).[186] It is worth noting that compound **311** and its analogues, containing mainly aryl substituents in the 1 and 4 positions of the triazole ring, were patented in 2009 as nicotinic acetylcholine receptor modulators.[186]

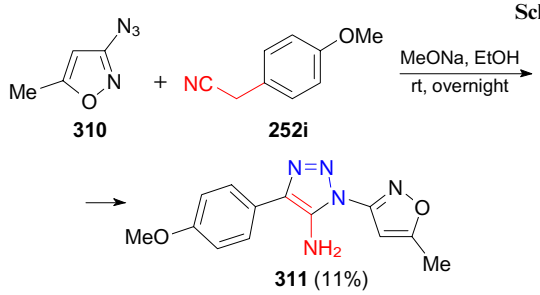
Nenajdenko and co-workers[187] synthesized ensembles composed of the triazole and isoxazole moieties by the reactions of 5-aryl-3-azidoisoxazoles **312** with malononitrile (**252c**) and 2-cyanoacetic ester (**252b**) (Scheme 99) and reported that the NMR spectra of these products show double sets of signals. The authors attributed this to the presence of two tautomeric forms (**313** and **314**).

Despite the fact that thioamides, like cyanoacetamides, react with aromatic azides to form 5-arylamino-1,2,3-triazole-4-carbothioamides,[188] the reactions of these compounds with heterocyclic azides can have different outcomes. For example, amidines **316** were synthesized

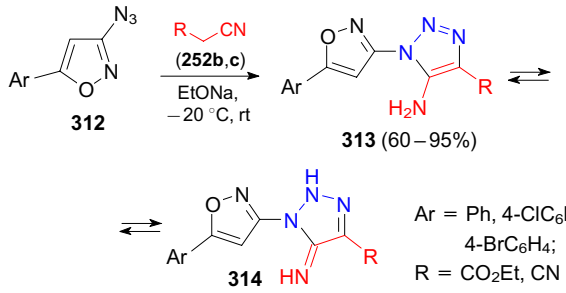
Scheme 97



Scheme 98

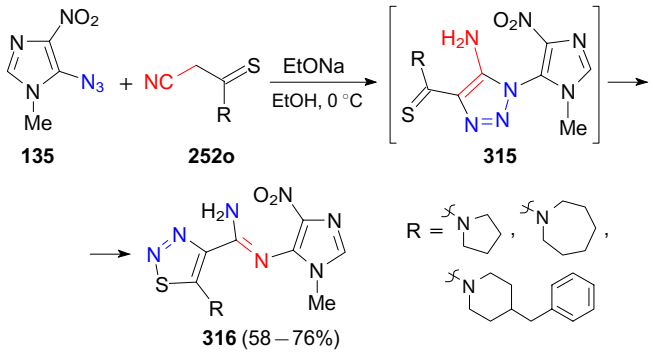


Scheme 99



from 5-azidoimidazole **135** and cyanothioacetamides **252o** through a rearrangement of intermediate triazoles **315** (Scheme 100).[188] Apparently, the heterocyclic substituent in the 1 position plays a key role in the 1,2,3-triazole ring opening. Attempts to perform this rearrangement with 5-amino-1-aryltriazole-4-thiocarboxyate failed.[188]

Scheme 100

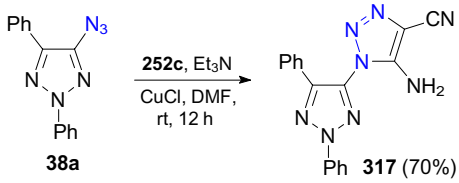


3.4.2.1.3. Azido derivatives of triazoles, oxadiazoles and thiadiazoles

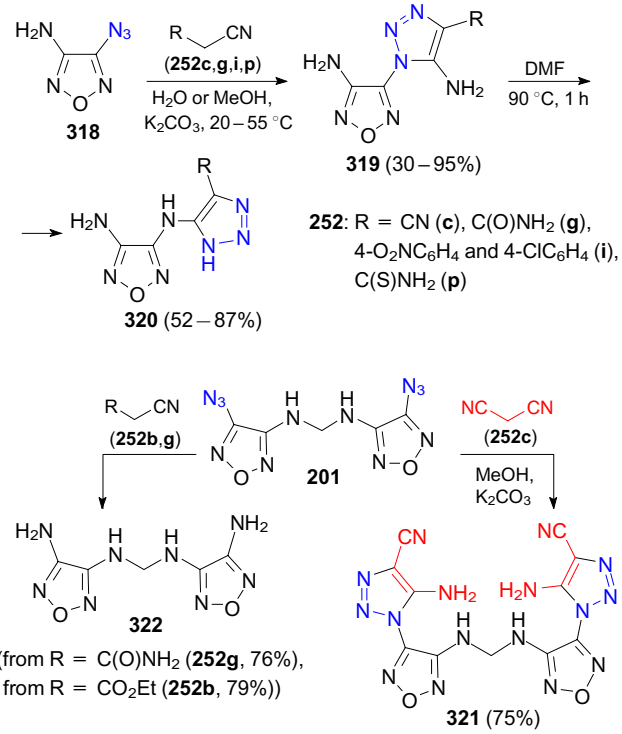
The reaction of 4-azidotriazole **38a** ($R^1 = R^2 = Ph$) with malononitrile (**252c**) afforded product **317** consisting of two triazole rings with different substituents (Scheme 101).[47]

It was demonstrated that 4-amino-3-azido-1,2,5-oxadiazoles **318** react with acetonitriles **252c**,**g**,**i**,**p** in the presence of potassium carbonate to form (1*H*-1,2,3-triazol-1-yl)furazans **319**;[189] in some cases, the reaction occurs in water

Scheme 101



Scheme 102



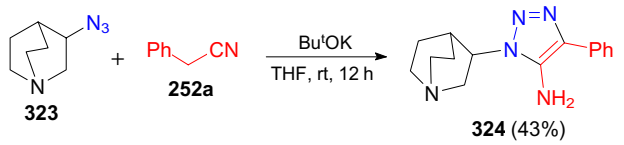
(Scheme 102). Compounds **319** undergo the Dimroth rearrangement into diaminofurazans **320** over 1 h on heating in DMF, except for 1,2,3-triazole derivatives containing the thioamide group in the 4 position. Attempts to subject the latter compounds to a rearrangement failed. The results obtained in the study[189] were used by another research group[190] to synthesize high energy materials based on triazolylfurazan **319** (R = CN). In continuation of their works, Batog *et al.*[147] synthesized diamine **321** in good yield through the double cycloaddition of malononitrile (**252c**) at the azido groups of compound **201**. The reactions of this diazide with 2-cyanoacetamide and cyanoacetic ester gave only diamine **322** (see Scheme 102) in 76 and 79% yield, respectively.

3.4.2.2. Six-membered heterocyclic azides

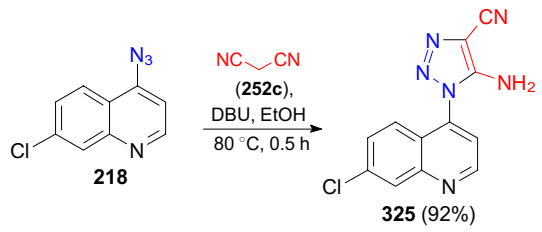
There are a few studies on the reactions of acetonitriles with azides containing six-membered heterocycles. The transformation pathways and the structures of the reaction products are generally similar to the above examples for azido derivatives of five-membered heterocycles. The reaction of 3-azidoquinuclidinol (**323**) with phenylacetonitrile (**252a**) giving aminotriazole **324** (Scheme 103) is presented in the patent.[191] The authors evaluated compound **324** for biological activity against nicotinic receptors.

The reaction of azide **218** with malononitrile (**252c**) afforded triazole **325** (Scheme 104). The structure and the spectroscopic, electronic, photophysical and thermody-

Scheme 103



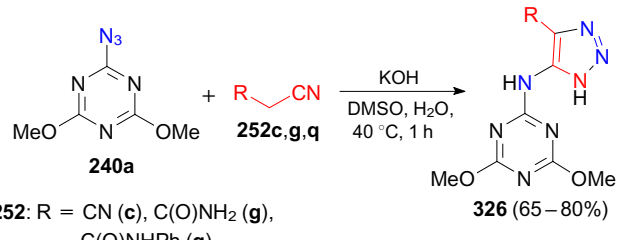
Scheme 104



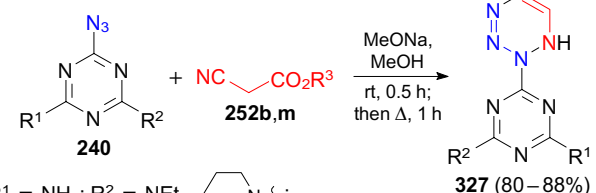
namic properties of this product were studied by both experimental and computational methods.[192]

Acetonitrile derivatives were used along with dicarbonyl compounds (Section 3.4.1) within the framework of studies of methods for the synthesis of azido-1,3,5-triazines and their interactions with active methylene reagents.[193, 194] The reaction of azido-1,3,5-triazine **240a** with malononitrile (**252c**) and cyanoacetamides **252g,q** afforded Dimroth rearrangement products **326** (Scheme 105).[160] Meanwhile, Chesnyuk *et al.*[193] synthesized related compounds under similar reaction conditions and assigned the structures of exotic tetrazines **327** to these compounds. It should be mentioned that the ^{1}H NMR spectra of compounds **327** showed signals of impurities (apparently, tautomers), they were not sufficiently well assigned and the X-ray diffraction data were not reported in the studies.[160, 194] Nevertheless, it can be stated that the products of the both reactions presented in Scheme 105 have similar NMR spectra. Thus, the proton signals at δ 15.05–15.10 and a broadened signal at δ 8.5–9.8, which are observed in the spectra of compounds **326** and **327**, belong, most likely, to two NH groups. Based on these data, we believe that both research groups[160, 193] synthesized compounds **326** containing the triazolylamino-1,3,5-triazine skeleton.

Scheme 105



252: R = CN (**c**), C(O)NH$_2$ (**g**), C(O)NHPh (**q**)

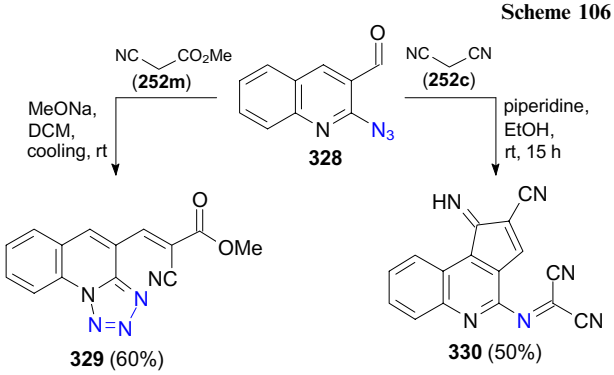


R^1 = NH$_2$: R^2 = NEt$_2$,  ;

R^2 = NMe$_2$: R^1 = NMe$_2$, PhNMe; **252**: R^3 = Et (**b**), Me (**m**)

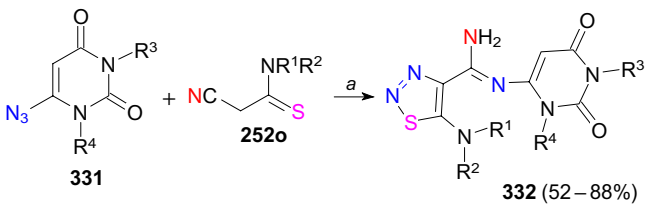
2-Azidoquinoline-3-carboxaldehyde **328**, like pyrazole **300**, reacts with cyanoacetic ester (**252m**) and malononitrile (**252c**) involving mainly the aldehyde group (Scheme 106).[194] In the former case, the reaction affords acrylate **329**; in the latter case, tricyclic compound **330** is produced. The mechanism of the formation of the latter compound involves two competitive processes: the reaction with the participation of an aldehyde group and malononitrile giving the cyclopentene moiety and the insertion of nitrene, which is generated from the tetrazole ring, into the C–H bond of malononitrile (**252c**) to form the imidoyl dicyanide moiety of compound **330**.

Scheme 106

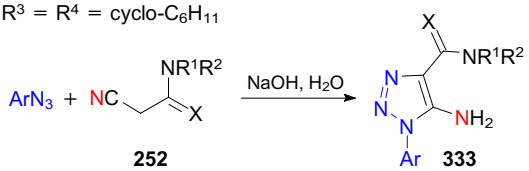


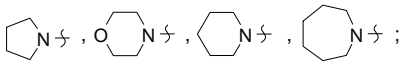
2-Cyano(thio)acetamides **252** [R = C(X)NR^{1}R^2; X = O, S] show a specific behaviour in the reactions with heterocyclic azides **331**. Thus, Bakulev and co-workers[195] prepared a series of 1,2,3-thiadiazole-4-carbamidines **332** by this reaction, whereas the reactions of cyanothioacetamides and cyanoacetamides with aromatic azides produced 4-amino-1-aryltriazoles **333** (Scheme 107).[196]

Scheme 107



(*a*) NaOH, H$_2$O; R^4 = Me: R^3 = Me, 4-MeOC$_6$H$_4$; R^3 = R^4 = cyclo-C$_6$H$_{11}$



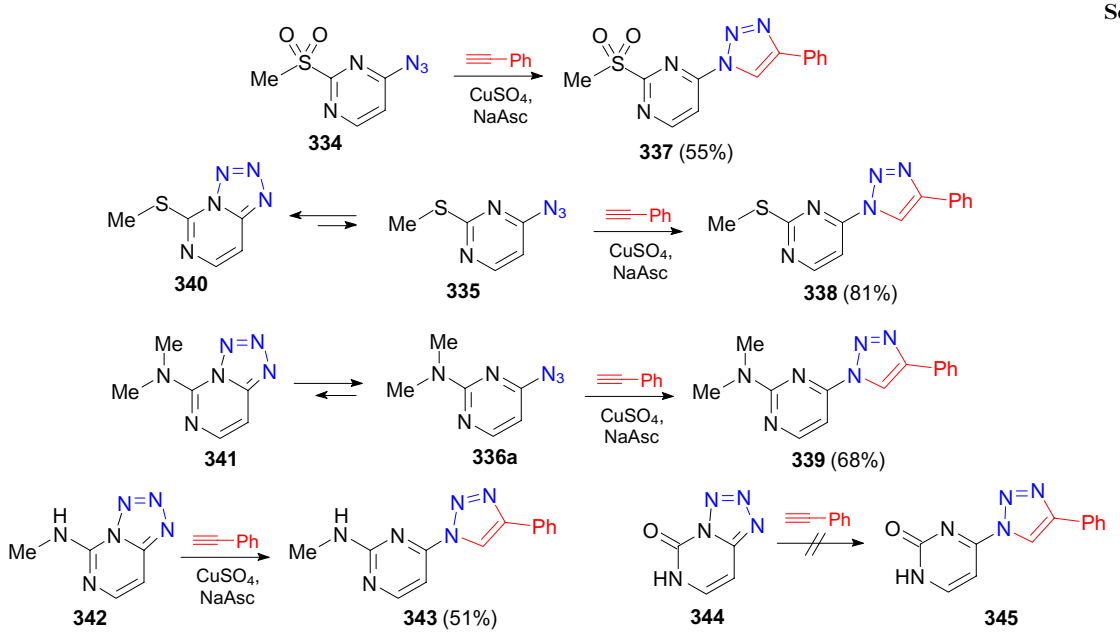
NR^{1}R^2 = NH$_2$, NHPh,  ;

Ar = 2-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$; X = S, O

4. Tetrazoles as a source of heterocyclic azides in organic synthesis

The azide–tetrazole tautomeric equilibrium is considered as one of the key properties of hetaryl azides.[197] This phenom-

Scheme 108



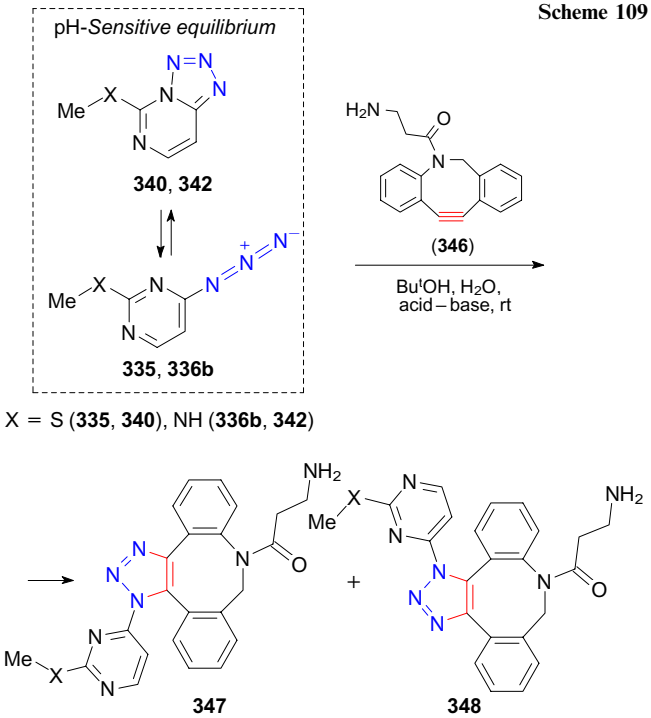
enon was studied in detail by experimental and theoretical methods.[198–200] It was demonstrated that the position of equilibrium depends on the substituents, the solvent and the temperature. For example, Thomann *et al.*[98] studied the effect of the substituents on the isomer ratio of 2-substituted 4-azidopyrimidines **334**–**336** and the possibilities of using tetrazolopyrimidines in the synthesis of 1-pyrimidyl-1,2,3-triazoles **337**–**339** (Scheme 108). For this purpose, the structures of the synthesized compounds were thoroughly analyzed by NMR and IR spectroscopy and X-ray crystallography. Based on these data, it was demonstrated that the isomer ratio can be controlled by varying the substituents on the ring. It was shown that the tetrazole form can act as a disguise for the azido group (compounds **340**–**342**) masking its high reactivity in metal-catalyzed reactions with acetylene derivatives. It is worth noting that tetrazoles containing substituents that stabilize the cyclic form exhibited much lower reactivity in these processes (see the transformation **342** → **343**) or did not react with acetylenes (triazole **345** was not generated from tetrazole **344**).[98] Meanwhile, tetrazoles **340** and **341**, existing in equilibrium with azides **335** and **336a**, are easily transformed into 1,2,3-triazoles **338** and **339**. The authors noted that the rate of the CuAAC reaction of tetrazoles is affected by the following three factors: the ratio of the tetrazole and azide forms and the electronic and steric effects of the substituents[98] (see Scheme 108).

Using the acid sensitivity of tetrazole derivatives **340** and **342**, Thomann *et al.*[98] developed a pH-dependent method for the selective azide–alkyne cycloaddition based on tetrazoles. The reaction involving cyclic alkyne **346** in aqueous media affords a mixture of isomeric triazoles **347** and **348** (Scheme 109).

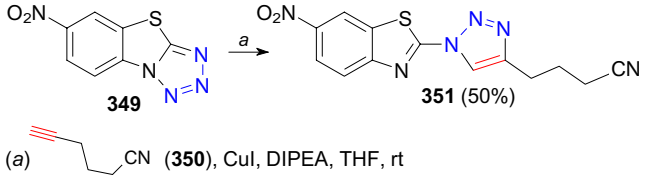
Avila *et al.*[103] demonstrated that tetrazole **349** reacts with 6-cyanopentyne (**350**) to form compound **351** bearing the benzothiazole and triazole rings in low yield (Scheme 110). A similar product containing the benzothiazole and pyridine rings was described in the studies.[201, 202]

Gevorgyan and co-workers[203] found the optimal conditions for the reaction of pyridotriazoles **352** with terminal acetylenes (Scheme 111). Copper triflate served as the catalyst and toluene as the solvent. Under the optimal conditions, pyrido-, quinolino- and qunoxalinotriazoles **353** were synthesized in high to moderate yields.[203]

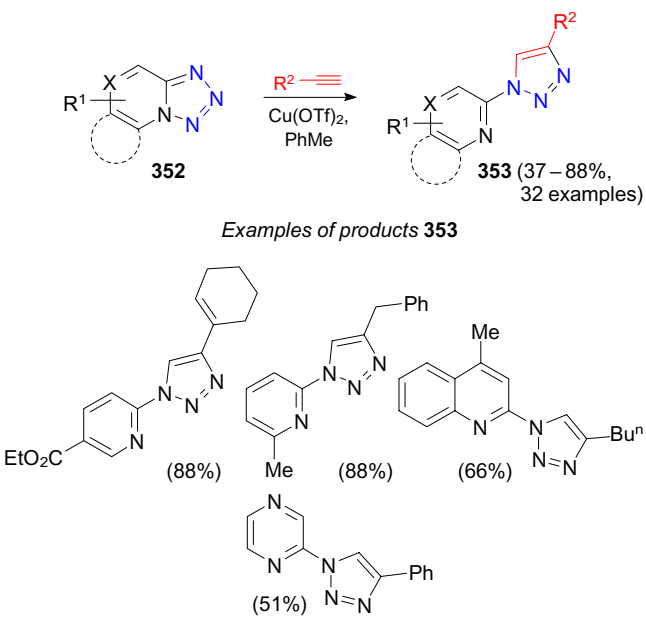
Scheme 109



Scheme 110



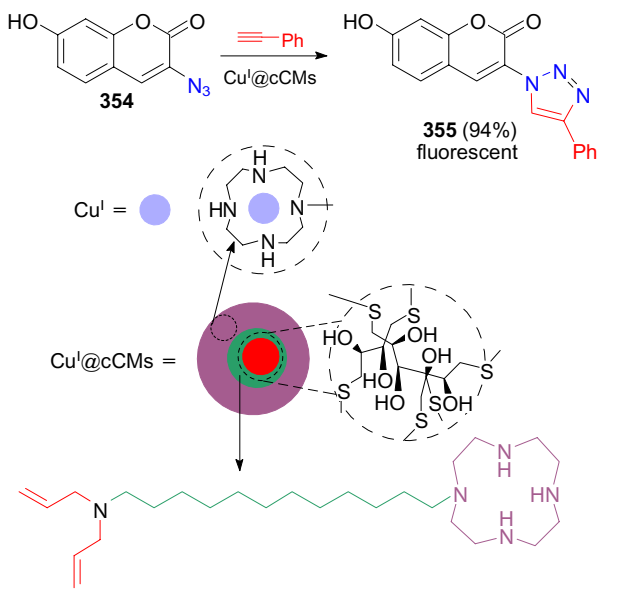
Scheme 111



5. Use of reactions of heterocyclic azides in biological chemistry

In recent years, CuAAC-based bioorthogonal reactions were often used in biological chemistry [204] to study biological processes in cells of living organisms. However, examples of the application of heterocyclic azides in bioorthogonal reactions are scarce. Xiang *et al.*[205] reported the synthesis of Cu^{I}-chelated cyclen micelles and the successful use of these micelles as a nanocatalyst for the reactions of azides with acetylenes both in water and living cells. 3-Azido-7-hydroxycoumarin **354** (Scheme 112) reacts with phenylacetylene and propargyl bromide giving hetaryltriazoles **355** in high yields.[205] The potential of the intracellular catalysis of click reactions involving azide **354** and phenylacetylene (see Scheme 112) by copper(I)-chelated cross-linked cyclen micelles (Cu^{I}@cCMs) was examined in experiments with living cells by confocal microscopy. The experimental results demonstrated that Cu^{I}@cCMs is not only an efficient catalyst for transformations in solutions but also an ideal catalyst for the intracellular click reaction due to activation of the azide–alkyne cycloaddition.

Scheme 112



6. Heterocyclic azides in the synthesis of bioconjugates

High antiviral and anticancer activity of modified nucleosides and their use as drugs (*e.g.*, the commonly known drugs ribavirin, zidovudine, *etc.*) have attracted attention of many research teams to these compounds. This Section describes the reactions of heterocyclic azides, in particular of glycosyl azides, with acetylene derivatives and active methylene carbonyl compounds and acetonitriles giving biologically active bioconjugates.

6.1. Reactions of azidonucleosides with acetylene derivatives

The reactions of heteroaromatic azides with cyclooctyne or azocine easily occur in the absence of metal catalysts to give 1,2,3-triazole-containing purine and pyrimidine nucleotides and nucleosides.[30, 70, 83, 202, 206–212] The steric hindrance in the cycloalkyne molecule is a driving force for these processes.

In the studies,[208, 211] an efficient method was developed for the synthesis of highly functionalized triazole derivatives based on the reactions of azidoadenine nucleosides and nucleotides **356a–c** with cycloalkynes **346**, **357** and **358** (Scheme 113). It is worth noting that these transformations occur in the absence of a catalyst or microwave irradiation both in aqueous solutions and cell culture media at ambient temperature and give products **359–361**.

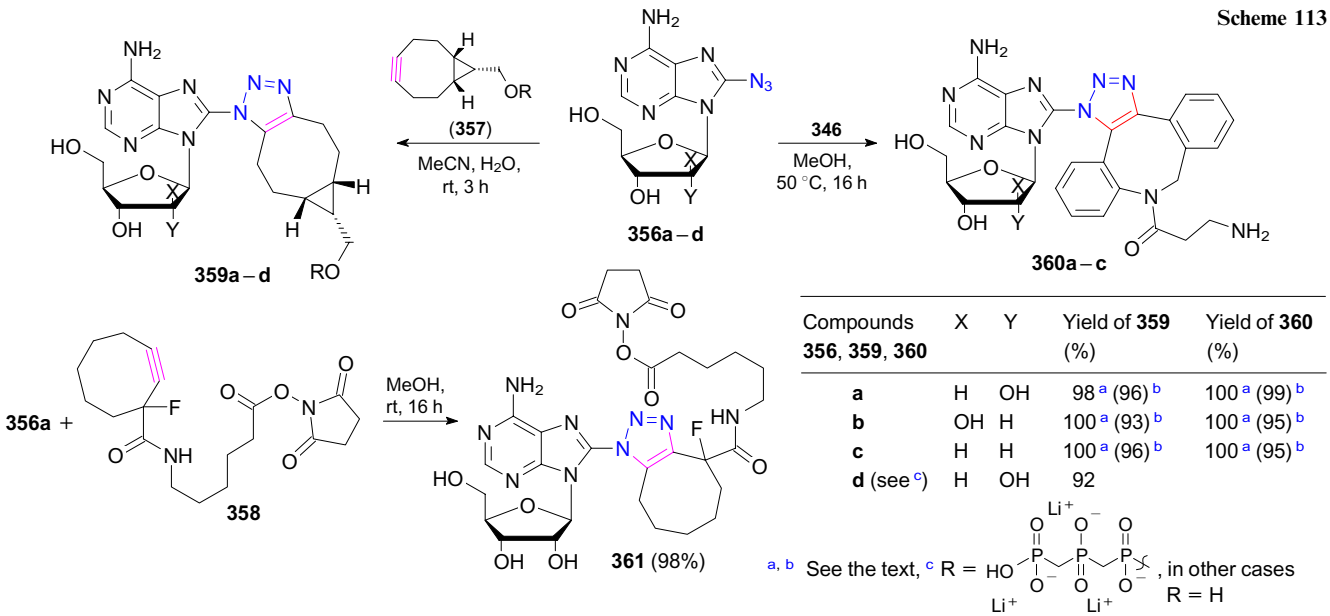
A similar reaction was described for 5-azidouracils **362a,b** (Scheme 114).[211] This reaction afforded cycloadducts **363–365**, the yields of which were determined by NMR spectroscopy (marked with the superscript [a]) and after the purification by reversed-phase high-performance liquid chromatography (RP HPLC) (see [b]).

It was found that the position of the azide group in the adenine molecule has no effect on its reactivity, whereas 5-azidouridine derivatives are much more reactive compared with 2-azido- and 8-azidoadenosines. Zayas *et al.*[211] demonstrated that triazole-containing adenosines and uridines have fluorescence properties sufficient for their use for direct visualization of human breast adenocarcinoma (MCF-7 cell line) in living cells.

The reaction of azide **366** with acetylenes afforded a series of 2-triazolyl-5′-*O*-[*N*-(salicyl)sulfamoyl]adenosines **367** (Scheme 115). The biochemical and biological evaluation of these compounds as inhibitors of adenylating enzymes, which catalyze the arylation of adenine at the OH group of phosphate and are involved in siderophore biosynthesis by *Mycobacterium tuberculosis*.[207] It was found that most of 4-substituted triazoles **367** exhibit activity at the subnanomolar level.

2-Arylethynyl derivatives of carbaadenosine were shown to be selective A3 adenosine receptor (A3AR) agonists.[206] To enhance the stability of these compounds, Gupte *et al.*[207] synthesized their analogues by replacing the ethynyl group with the 1,2,3-triazole moiety (Scheme 116). The reactions of azides **368** with substituted acetylenes afforded triazolyladenines **369** containing different substituents at the N(6) and C(2) atoms. The authors characterized the *in vivo* binding of these compounds to adenosine receptors in the

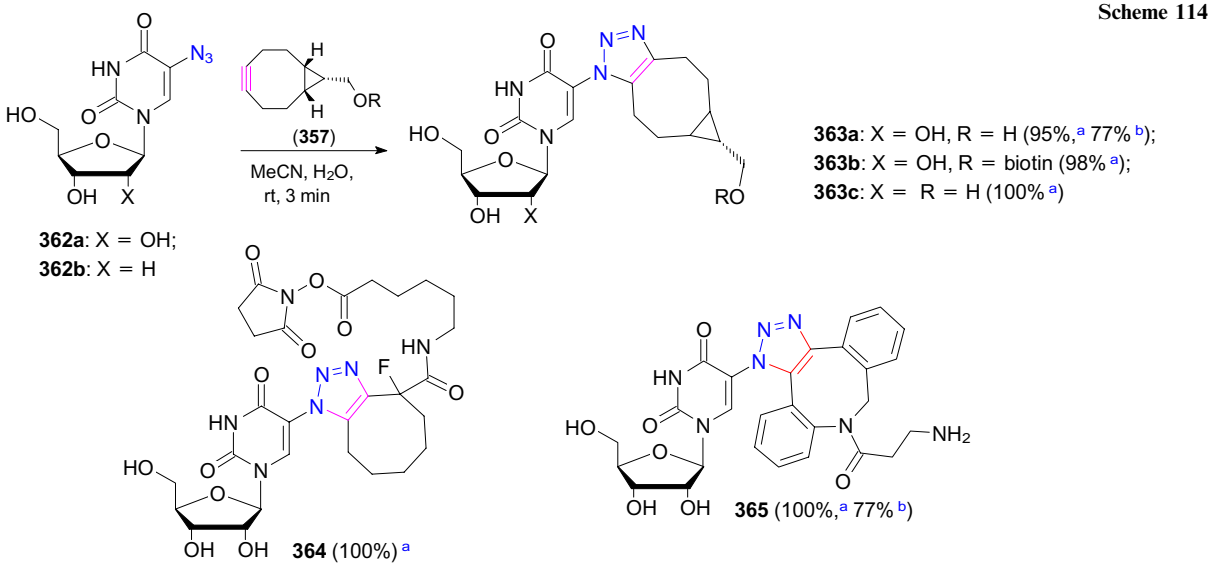
Scheme 113



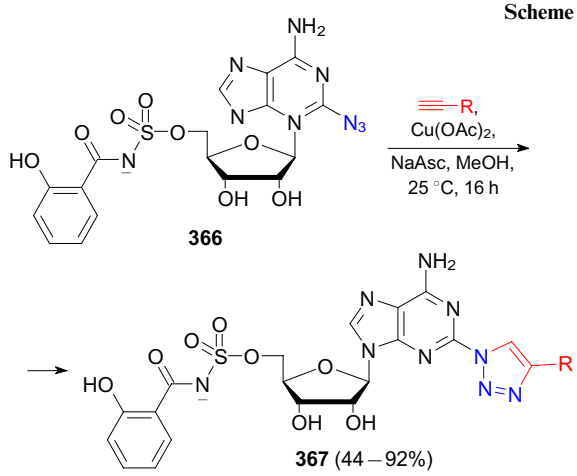
Compounds 356, 359, 360	X	Y	Yield of 359 (%)	Yield of 360 (%)
a	H	OH	98 [a] (96) [b]	100 [a] (99) [b]
b	OH	H	100 [a] (93) [b]	100 [a] (95) [b]
c	H	H	100 [a] (96) [b]	100 [a] (95) [b]
d (see [c])	H	OH	92	

[a, b] See the text, [c] R = , in other cases R = H

Scheme 114



Scheme 115



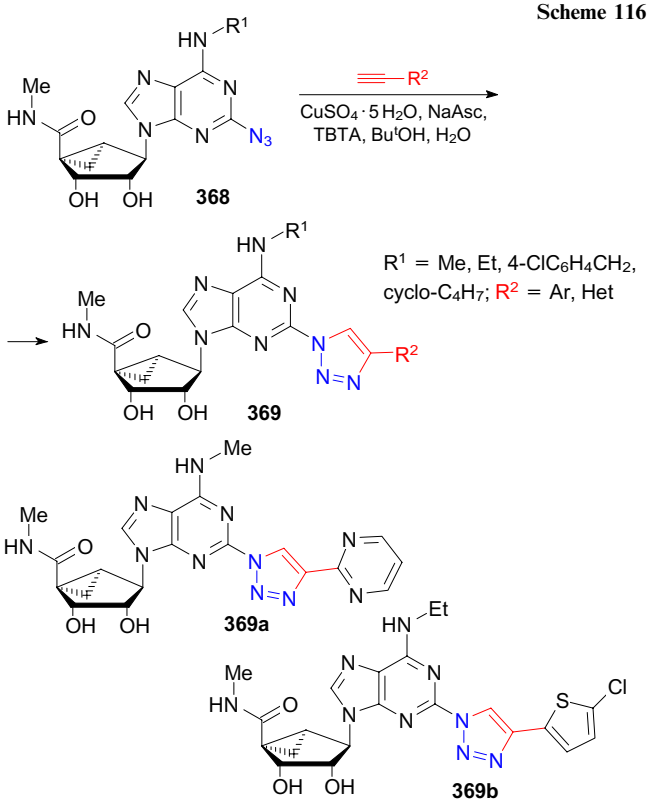
R = Pr^n, Bu^n, Bu^t, Ph, cyclo-C_3H_5, 2-HOC_6H_4, 2-Py, 4-Py, *etc.*

concentration range of 0.3 – 12 nmol L^{-1} to assess their efficiency as agents against chronic neuropathic pain. The introduction of the 2-pyrimidyl group into molecule **369a** leads to an increase in the *in vivo* duration of action of the drug. Compound **369b** containing the 5-chloro-2-thienyl moiety retained 85% efficiency of analgesia for 1 h. It was found that the introduction of bulkier groups at the N(6) atom increases the duration of action of the synthesized derivatives [206] (see Scheme 116).

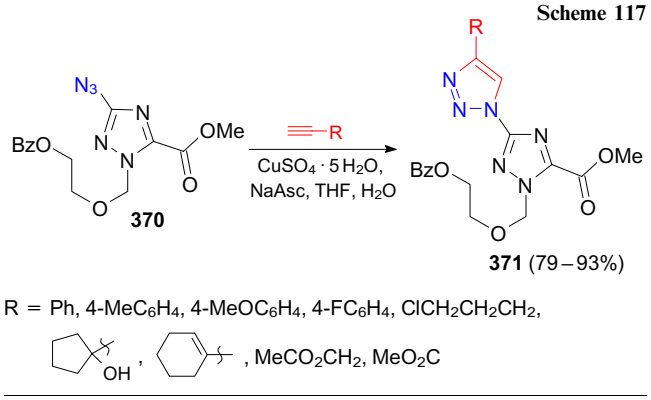
Lakshman *et al.*[210] demonstrated that 2,6-diazidopurines undergo the double CuAAc reaction to form 2,6-bis(triazolyl) derivatives of purine. It was also found that the 1,2,3-triazole ring is a good leaving group and it can be replaced by thiol moieties.[83, 202, 209, 213] Some adenosine derivatives containing the triazole ring were found to exhibit anticancer activity.[83, 202, 209, 213]

The CuAAC reaction of azide **370** with alkyl- and arylacetylenes in the presence of copper sulfate and sodium ascorbate was used to synthesize bis(triazolyl)acyclic

Scheme 116



Scheme 117



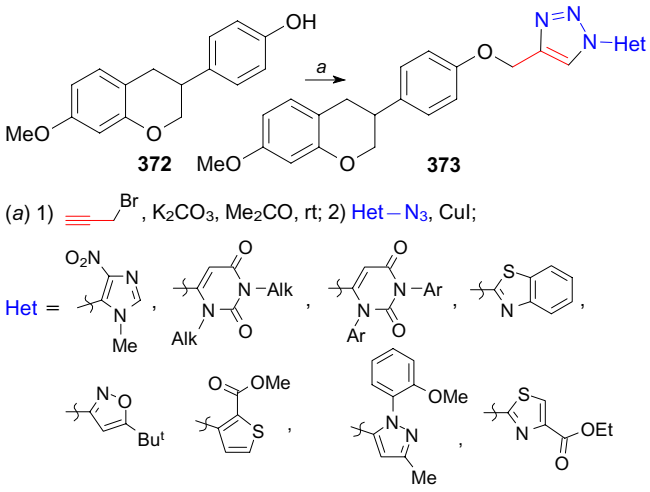
nucleoside analogues **371** (Scheme 117).[70] These acyclonucleosides show inhibition of the tobacco mosaic virus growth. The authors suggested that the bis(triazolyl) ensemble is an important structural unit responsible for antiviral activity of compounds **371**.

6.2. Natural compound conjugates

In order to synthesize new biologically active compounds, we performed the reaction of methylequol (**372**) with propargyl bromide and heterocyclic azides in the presence of K_2CO_3 and CuI[214] and developed a facile one-pot method for the synthesis of hybrid molecules **373** containing equol moieties and different heterocycles, such as 1-methyl-4-nitroimidazole, pyrimidinedione, benzotriazole, thiophene, triazole, isoxazole and pyrazole (Scheme 118).

Hybrid molecules of coumarin, triazole and the above heterocycles were synthesized using a similar approach.[215]

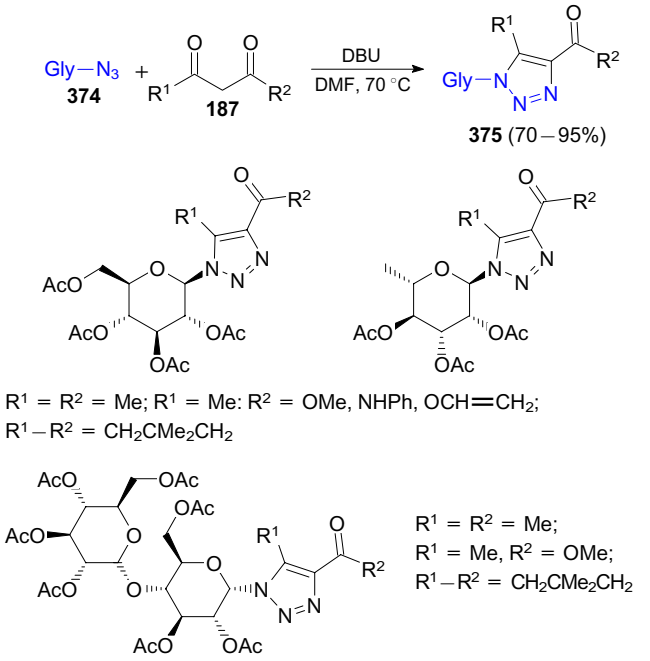
Scheme 118



6.3. Reactions of glycosyl azides with active methylene carbonyl compounds

Kundu *et al.*[216] synthesized a large series of 1,4,5-trisubstituted glycosyl-1,2,3-triazoles **375** in good yields by the cycloaddition of glycosyl azides **374** to 1,3-dicarbonyl compounds **187** (Scheme 119).

Scheme 119



6.4. Reactions of glycosyl azides with acetonitrile derivatives

The key step in the construction of a heterocyclic moiety in the synthesis of nucleoside analogues involves the cycloaddition of azido glycosides to acetonitriles or other appropriate compounds. Although this reaction was described in 1972,[217] the procedure for the synthesis of 5-amino-4-carbamoyl-1-ribo(arabino)furanosyl-1,2,3-triazole in DMF in the presence of aqueous KOH on cooling to 0 °C continues to be used without changes or with insignificant

modifications.[170, 218–221] The reaction occurs regiospecifically; however, in an alkaline medium the carbohydrate moiety is often partially or fully deprotected, which leads to a significant decrease in the yield of the target products. Another specific feature of this reaction is the furanose ring anomerization, which was mentioned not by all authors. This transformation depends on both the nature of the carbohydrate moiety and the reaction conditions, thereby suggesting the stepwise mechanism of the formation of the 1,2,3-triazole ring.

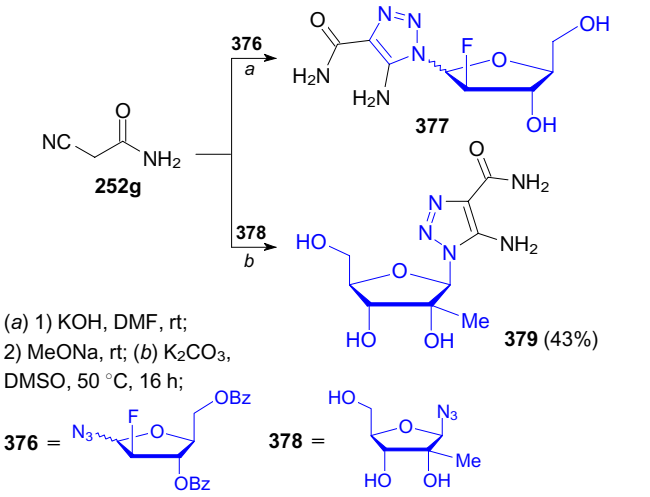
The cycloaddition of 2-cyanoacetamide (**252g**) to 2-deoxy-2-fluoro-L-arabinofuranosyl azide **376** was described by Ölgen and Chu[218] (Scheme 120). The authors stated that α-azide **376** gives α-L-arabinofuranosyl-1,2,3-triazole **377** in 76% yield; β-azide produces the corresponding β-isomer in 51% yield. 2-C-methyl-β-D-ribofuranosyl azide **378** was synthesized from unprotected 1,2,3-triazole **379** using a similar procedure.[219]

Firestine *et al.*[220] studied the reaction of azide **380** with *tert*-butyl cyanoacetate in order to prepare 1,2,3-triazole-4-carboxylate **381**. It was demonstrated that the synthesis of the target product requires the use of sodium 2-cyanoacetate **252** (Scheme 121).

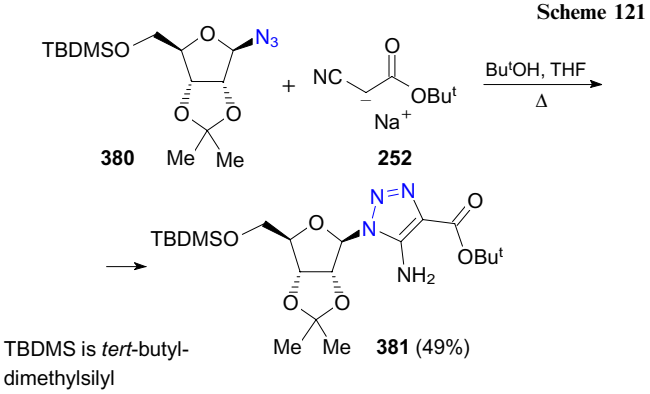
Yang *et al.*[221] studied the cycloaddition of glycosyl azide **382** to cyanoacetamide (**252g**) and 3-bromopropiolate (**383**) (Scheme 122) (see also Section 3.1 devoted to reactions of heterocyclic azides with acetylenes). The reaction afforded triazoles **384** and **385**. 8-Azaadenosines **386a–g** were synthesized from amide **384** through the cyclization followed by the modification of the amide group into the amidine moiety. Compound **386g** exhibited high activity against hepatitis B virus.

Salemeh *et al.*[222] demonstrated that 3-azido-1-methylthio-β-D-galactopyranoside (**387**) also reacts with cyanoacetamide (**252g**) to form 1-glycosyl-1,2,3-triazole **388** (Scheme 123).

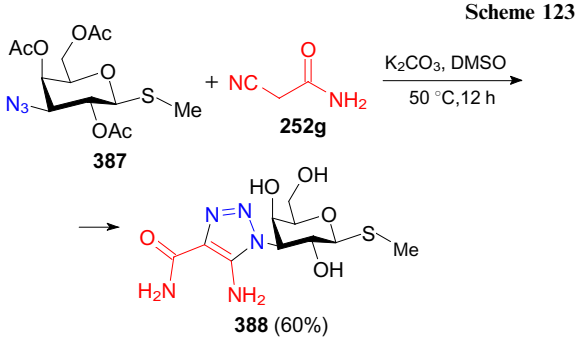
Scheme 120



Scheme 121



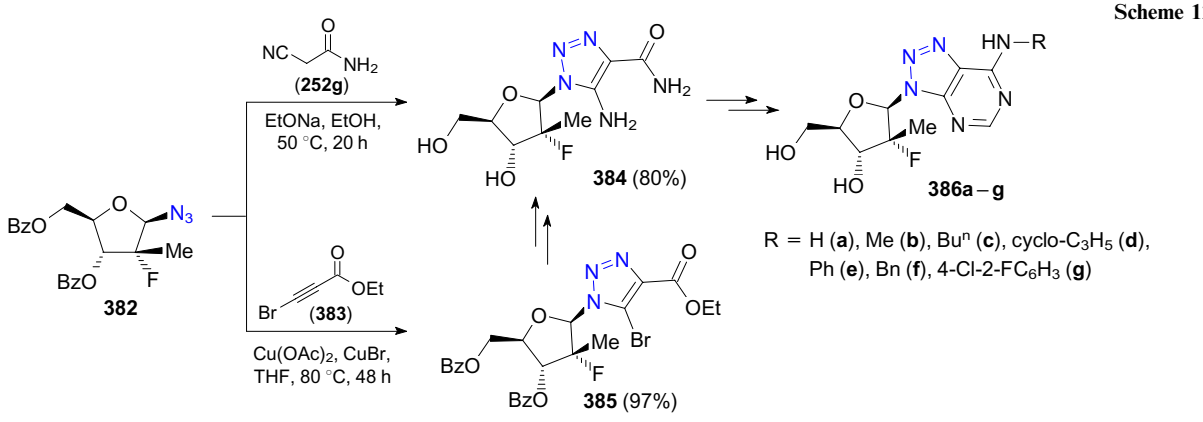
Scheme 123



7. Conclusion

Heterocyclic azides exhibit diverse biological activity and have a spectrum of action different from that of aromatic analogues. An example is the antiviral drug zidovudine (3′-azido-3′-deoxythymidine) used in the treatment of human immunodeficiency virus (HIV) infection. Heteroaromatic azides react with cyclic alkenes at a higher rate compared with aromatic azides and give the target products in higher yields. It was found that the chemical reactions involving heterocyclic azides and enamines are characterized by a greater diversity compared with the similar trans-

Scheme 122



formations in the aromatic series. These reactions afford diazo compounds, *N*-hetarylamidines and 1,2,3-triazolines fused to nonaromatic carbocycles, which are inaccessible by the reactions with aromatic azides. Besides, the reactions of heteroaromatic azides with 1,3-dicarbonyl compounds and 2-cyanothioacetamides produce another type of compounds, such as 1,2,3-thiadiazole and 1,2,3-triazoline derivatives and different ensembles consisting of three heterocycles.

It was found that heteroaromatic azides undergo reactions which are not typical of their aromatic analogues, such as the diazo transfer to active methylene compounds, the tandem elimination of a nitrogen molecule/sigmatropic rearrangements in the transformations of 1,2,3-triazolines, the carbocycle contraction in bicyclic 1,2,3-triazolines and the azide–tetrazole ring–chain tautomerization.

This review is devoted to heterocyclic azides taking into account the differences in the properties of heterocyclic and aromatic azides, rich chemistry of heterocyclic azides, including reactions with alkenes, enamines, 1,3-dicarbonyl compounds and acetonitrile derivatives, which are extensively used in organic synthesis, medicinal and biological chemistry, and a large number of publications on this issue. This is the first systematic review on the methods of synthesis and reactions of heterocyclic azides with derivatives of acetylene and acetonitrile, alkenes, enamines and active methylene dicarbonyl compounds. It was demonstrated that heterocyclic azides can be utilized in biological chemistry to study the reactions in living systems, as well as in organic synthesis to prepare mono-, bi- and tricyclic compounds and ensembles of different heterocycles, luminophores and sensors for metals.

While analyzing the data during preparation of the review, we realized that, despite advances in the chemistry of heterocyclic compounds, the data on the kinetic studies of heterocyclic azides in reactions with compounds containing multiple bonds are scarce, the bioorthogonal reactions of these compounds are poorly known and the results of theoretical calculations are almost lacking. We believe that the further progress in this field will be related to the kinetic and theoretical studies, the development of new bioorthogonal reactions and the synthesis of new biologically active compounds based on heterocyclic azides.

This review was written with the financial support of the Russian Science Foundation (Project No. 18-13-00161P).

8. List of abbreviations and designations

A3AR — A3 adenosine receptor,
Asc — ascorbate,
Boc — *tert*-butoxycarbonyl,
bmim — 1-*n*-butyl-3-methylimidazolium,
bpy — 2,2′-dipyridine,
B_2Pin_2 — bis(pinacolato)diboron,
cod — 1,5-cyclooctadiene,
CuAAC — copper-catalyzed azide–alkyne cycloaddition,
CuI@cCMs — copper(I)-chelated cross-linked cyclen micelles,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCM — dichloromethane,
DFT — density functional theory,
DIPEA — *N*,*N*-diisopropylethylamine,
dtbpy — 2,6-di-*tert*-butylpyridine,
DQ — 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone,
HIV-1 — human immunodeficiency virus type 1,
HOMO — highest occupied molecular orbital,
ICT — intramolecular charge transfer,
LUMO — lowest unoccupied molecular orbital.
MW — microwave irradiation,
PEG-400 — low-molecular-weight polyethylene glycol,
Pic — 4-picoline,
PIFA — [bis(trifluoroacetoxy)iodo]benzene,
PFKFB3 — 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3,
Py — pyridyl,
RP HPLC — reversed-phase high-performance liquid chromatography,
rt — room temperature,
TBAB — tetra-*n*-butylammonium bromide,
TBDMS — *tert*-butyldimethylsilyl,
TBTA — tris[(1-benzyl-1,2,3-triazol-4-yl)methyl]amine,
TFA — trifluoroacetic acid,
TfO — trifluoromethanesulfonate (triflate),
TMSA — trimethylsilylacetylene,
$TMSN_3$ — trimethylsilyl azide,
Ts — *p*-toluenesulfonyl (tosyl),
US — ultrasound.

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