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REACTIONS OF TRIAZINES AND TETRAZINES WITH DIENOPHILES (REVIEW)

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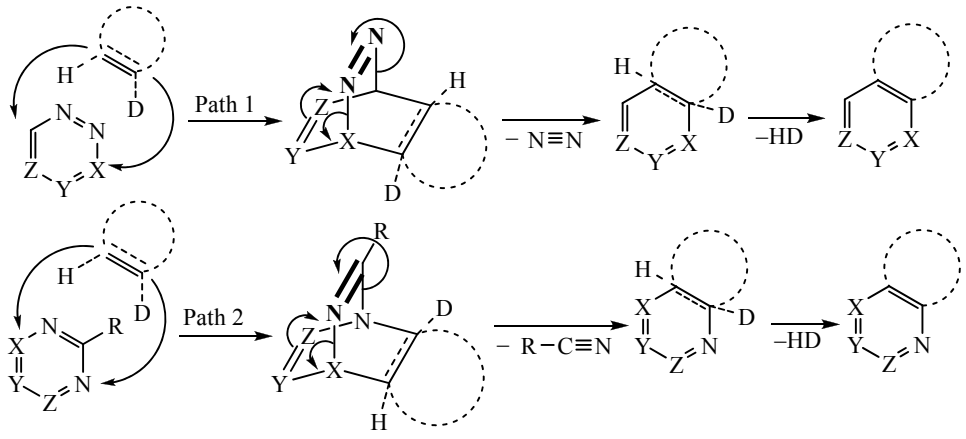
Information on the development of a valuable synthetic methodology based on inverse electron-demand Diels–Alder reaction in the series of π-deficient azadienes (triazines and tetrazines) is summarized and classified. By this method it is possible to obtain mono-, di-, and triazines containing functional substituents both from the initial azine and from the dienophile. Such reactions are often the simplest and even the only possible method for the synthesis of substances with properties suitable for practical applications.

Keywords: azadienes, pyridazines, pyridines, pyrimidines, tetrazines, triazines, Diels–Alder reaction.

Azines can enter into inverse electron-demand Diels–Alder reactions. Here π-deficient triazines and tetrazines are used as dienes, while alkenes or alkynes with electron-donating substituents are used as dienophiles. Cycloaddition initiates a cascade of reactions including elimination of a nitrogen molecule (path 1) or nitrile (path 2) from the cycloadduct, as a result of a retro-Diels–Alder reaction and subsequent aromatization of the intermediate product by one of the possible ways, e.g., by the elimination of an amine



D = NR_2, OR; X, Y, Z = N, CH

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molecule. The final product of such a transformation is pyridazine, pyrimidine, or pyridine. Fundamental papers in this area are listed as references in the paper by Boger [1]. The numerous examples of the reaction published before 1996 can be seen in the reviews [2-4]. Many new interesting examples of the use of the Diels–Alder reaction in the series of triazines and tetrazines have appeared in the last 15 years. The present review is devoted to generalization of these reactions. The reactions are classified according to the type of azadiene.

When applying the Diels–Alder reaction in the series of triazines and tetrazines, it is necessary to resolve problems involving increasing the reactivity and regioselectivity of cycloaddition. It is clear that the energy and structure of the frontier orbitals of both reagents in this case play a crucial role. Unfortunately, the only attempt [1] at a theoretical analysis of the Diels–Alder reaction of all the examined azines is based on semiempirical methods (MNDO and AM1) and does not take account the structure of the frontier orbitals. For this reason, before proceeding to an analysis of specific reactions we used *ab initio* methods (MP2/def2-QZVP//B3LYP/def2-QZVP, *Orca 2.9.0* software [5]) to calculate the charges at the atoms, the highest occupied molecular orbital (HOMO) for aminoethene as model dienophile, and the two lowest unoccupied molecular orbitals (LUMO and LUMO+1) for 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, and tetrazine (Fig. 1). In view of the fact that the LUMO and LUMO+1 are close (or degenerate) in energy, for each of the examined heterocycles two directions of cycloaddition are possible (The C_3 symmetry of 1,3,5-triazine makes these paths identical.) The most important difference between them rests in the subsequent transformation of the cycloadducts. If the regioselectivity of cycloaddition is determined by the LUMO, the cycloadducts must then lose a nitrile molecule as a result of the subsequent retro-Diels–Alder reaction. If, however, the azadiene takes part in the reaction with its LUMO+1 orbital, a nitrogen molecule must be eliminated from the cycloadduct. The significantly higher stability of the nitrogen molecule makes the second path preferred, as shown in the following examples of the reaction. In addition, the charges on the atoms of the heterocycle can have an effect on the preference for one or the other path. For example, the frontier orbital structure of tetrazine predicts possible cycloaddition at the C-3,6 (LUMO+1) or N-1,4 (LUMO) atoms, but the second reaction path is hindered significantly by the increased electron density at the nitrogen atoms.

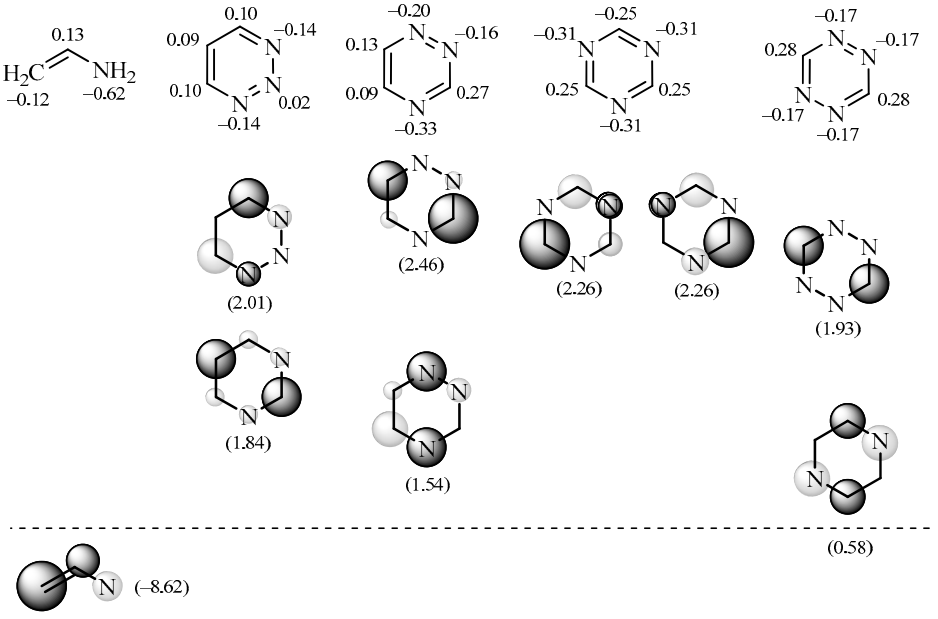
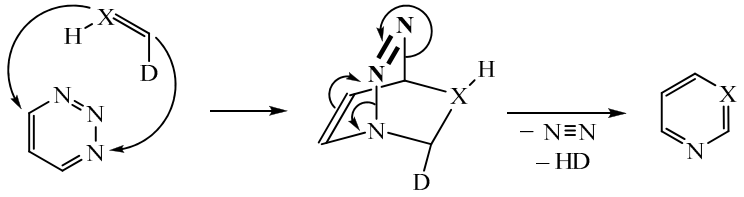


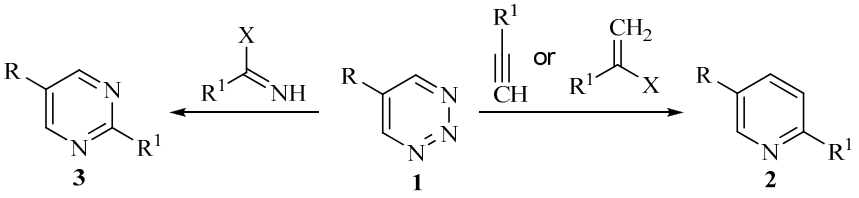
Fig. 1. The charges on the atoms (top row) and the localization of the interacting orbitals (the orbital energies, eV, are given in parentheses) of aminoethene (HOMO), 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, and tetrazine (LUMO and LUMO+1) according to the results of quantum-chemical calculations (MP2/def2-QZVP//B3LYP/def2-QZVP).

1,2,3-TRIAZINES AS DIENES

The Diels–Alder reaction of 1,2,3-triazines with dienophiles takes place at the N-1 and C-4 atoms with the elimination of a nitrogen molecule.



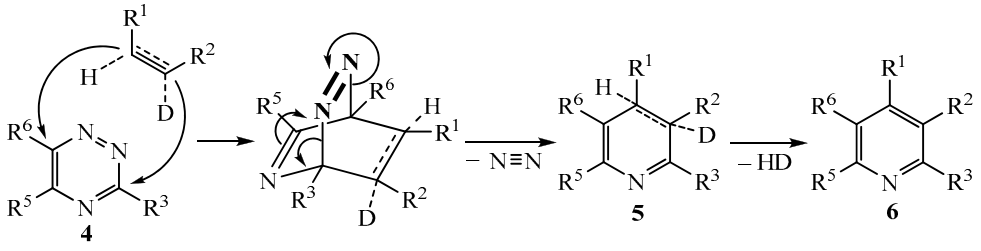
The results from a systematic investigation of the Diels–Alder reaction of 1,2,3-triazines aimed at determining the limits of applicability were presented in [1, 6]. 1,2,3-Triazines **1** react both with typical dienophiles (alkynes and π-electron-rich alkenes) with the formation of substituted pyridines **2** and with heterodienophiles (amidines or imino esters) with the formation of pyrimidines **3**.



R = H, Ph, COOMe, Br; R^1 = Me, Ph, 2-Py; X = NR_2, OR

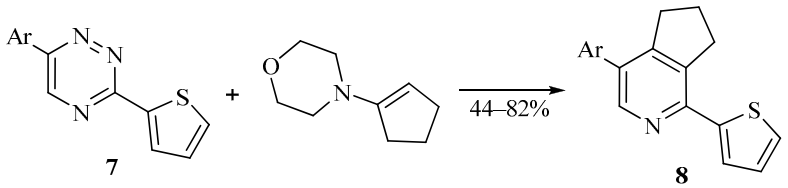
1,2,4-TRIAZINES AS DIENES

The reactions of 1,2,4-triazines **4** with dienophiles are widely used for the preparation of new polysubstituted pyridines **6**. Here cycloaddition at the C-3,6 atoms of triazine is accompanied by elimination of a nitrogen molecule from the cycloadduct and subsequent aromatization of the intermediate dihydropyridine **5**. In this case all substituents from the initial 1,2,4-triazine are retained in the pyridine **6**, and additional substituents from the dienophile are also introduced. Enamines, enols, alkynes, and certain alkenes are used as dienophiles. In view of the fact that 1,2,4-triazines can be obtained by many methods, starting from accessible reagents with widely varied substituents, the Diels–Alder reaction opens a path to a wide range of pyridines, many of which are very difficult or impossible to obtain by other methods.



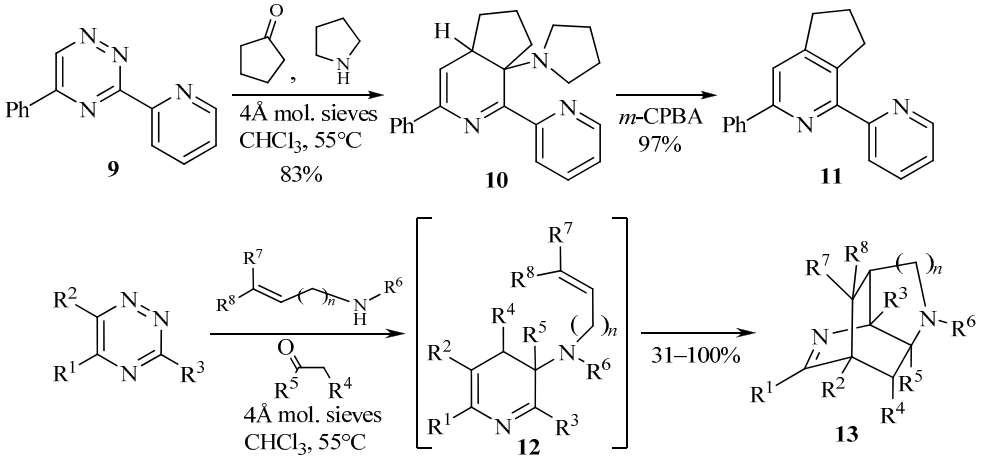
The Diels–Alder reaction of 1,2,4-triazine was studied theoretically in comparison with other heterocyclic dienes by the DFT method. It was predicted that 4-substituted pyridines should be formed preferentially in the reactions of 1,2,4-triazine with asymmetrical dienophiles [7].

It is clear that the Diels–Alder reaction must proceed more readily with electron-rich dienophiles. It is not surprising that enamines are most often used in these reactions. Thus, by the reaction of 6-aryl-3-(thien-2-yl)-1,2,4-triazines **7** with morpholinocyclopentene it was possible to obtain a series of 2-thienylcyclopentenopyridines **8**, which are typical ligands for cyclic metal complexes [8, 9]. Electron-donating (hetero)aromatic substituents reduce the reactivity of the 1,2,4-triazines **7**, making the Diels–Alder reaction possible only at elevated temperatures.



Ar = Ph, 4-MeOC$_6$H$_4$, 2-naphthyl, 2-thienyl

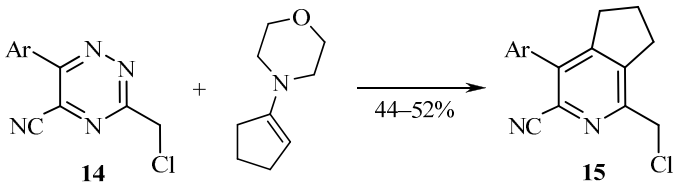
Widespread application of the reaction is restricted by the need to use previously prepared enamines. The enamines can, however, be produced *in situ* by a reaction of secondary amines with aldehydes or ketones, which is facilitated by using molecular sieves (4 Å) to bind the released water. For example, in the presence of molecular sieves the reaction of pyridyltriazine **9** with pyrrolidine and cyclopentanone already takes place at 55°C with the formation of the cyclic adduct **10**. Oxidative aromatization of the latter by the action of *m*-chloroperoxybenzoic acid (*m*-CPBA) gives the substituted bipyridyl **11** [10, 11].



n = 1, 2; R^1, R^2 = H, Ph, Fur; R^4, R^5, R^6, R^7, R^8 = H, various alkyl or cycloalkyl substituents

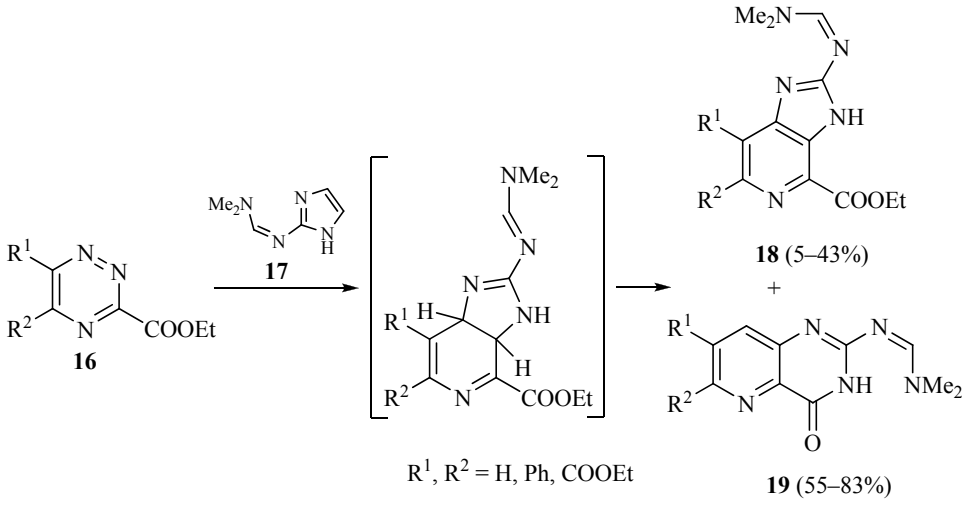
It is interesting that the cycloadduct **12**, containing a vinyl group in the amine substituent, can then enter into an intramolecular Diels–Alder reaction leading to the formation of polycyclic framework products **13**. The use of a cyclic enamine (obtained from cyclopentanone and diallylamine) in this multistep process not only leads to creation of four new C–C bonds, but also makes it possible to regio- and diastereoselectively obtain the tetracyclic product **13** with five new stereogenic centers [12, 13]. Here it is possible to vary the structures of all three reagents: 1,2,4-triazine, ketone, and allylamine.

As expected, the insertion of electron-withdrawing substituents into the 1,2,4-triazine ring increases the reactivity of the azadiene. For example, 6-aryl-3-chloromethyl-5-cyano-1,2,4-triazines **14** react with morpholinocyclopentene significantly more readily than thienyltriazines **7**. As a result, cyclopentenopyridines **15** containing chloromethyl and nitrile groups are formed to open the pathway towards their further functionalization [14].



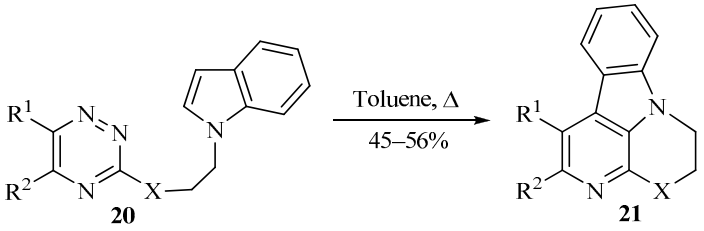
Ar = Ph, tolyl, naphthyl

π-Electron-rich five-membered heterocycles and aminoazoles can be used as dienophiles. However, triazine must be activated by an electron-withdrawing group, such as an ester group. Aromatization of the intermediate cycloadducts (dehydrogenation) takes place with the participation of a second triazine molecule. Thus, the reaction of 1,2,4-triazinecarboxylic esters **16** with 2-(alkylideneamino)imidazoles **17** leads to imidazopyridines **18**. The side products of the reaction are pyrimidopyridines **19**, formed as a result of opening of the imidazole ring and subsequent recyclization involving the ester group [15, 16].



R^1, R^2 = H, Ph, COOEt

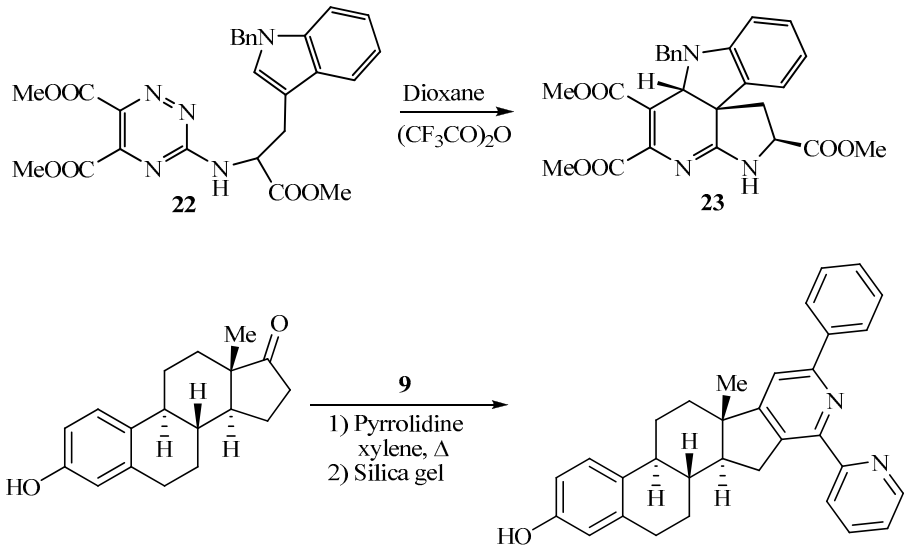
Intramolecular Diels–Alder reactions usually take place more readily than the intermolecular reactions. For instance, heating of the triazine **20**, which contains a dienophilic indole fragment in the side chain, leads to the synthesis of canthine derivatives **21** [17, 18].



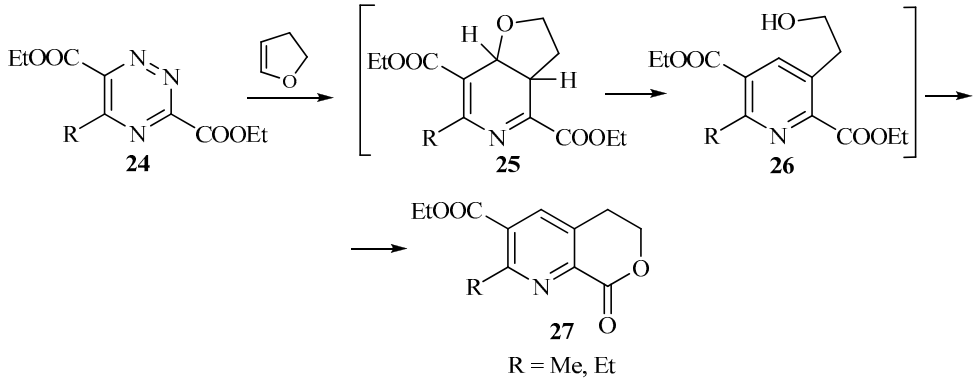
R^1, R^2 = H, Me, Ph, COOMe; X = SO_2, CH_2

The analogous intramolecular Diels–Alder reaction of the triazine **22**, containing a tryptophan fragment, by heating in dioxane in the presence of trifluoroacetic anhydride gives the tricyclic cycloadduct **23**. Aromatization of the adduct **23** is prevented by the comparatively mild reaction conditions [19].

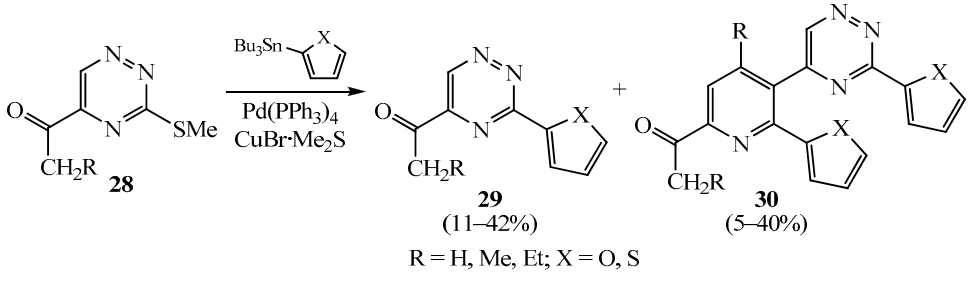
In some cases it is convenient not only to obtain the enamine *in situ* by reaction of the triazine **9** with a ketone, such as estrone, in the presence of pyrrolidine, but also to facilitate the rearomatization of the cycloadducts by the addition of silica gel to the reaction mixture. This leads to a modified estrone with the pyridine ring annelated at the ring D [20].



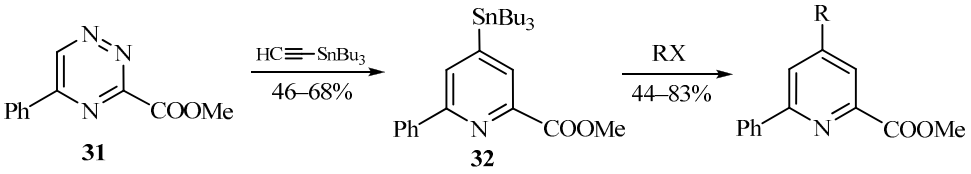
Enols are comparatively rarely used as dienophiles in reactions with 1,2,4-triazines. However, the presence of two ester groups in the 1,2,4-triazine **24** makes it an active azadiene, and permits the reaction with 2,3-dihydrofuran under mild conditions. The cycloadduct **25** formed here undergoes spontaneous aromatization by opening of the tetrahydrofuran ring. This is accompanied by intramolecular transesterification of the pyridinecarboxylate **26**, and the lactone **27** is finally formed with an overall yield of 39-44% [21, 22].



The pyridyltriazine **30** was obtained as an unexpected side product of the Stille reaction of 5-acyl-3-methylthio-1,2,4-triazines **28** with tributylarylstannanes. Its formation clearly results from a secondary Diels–Alder reaction, in which one molecule of the cross-coupling product **29** acts as diene, while the second (in the enolic form) acts as dienophile [23].

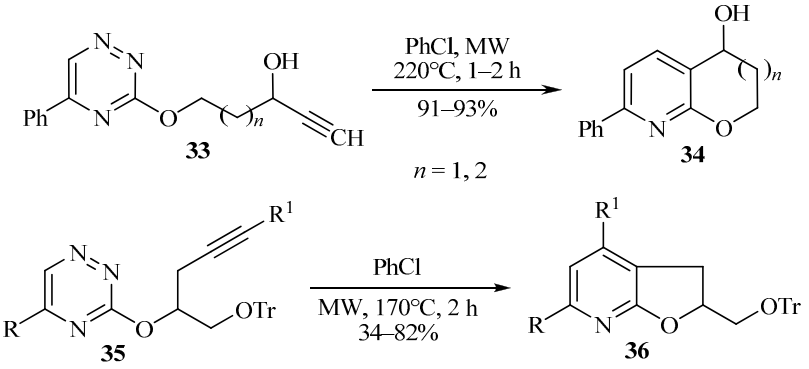


Several examples of 1,2,4-triazine reactions with such low-activity dienophiles as alkynes have been described. It was shown that tributylethynylstannane is a more active dienophile in the considered reactions, compared to, for example, arylacetylenes. Its reaction with the triazine **31** takes place fairly smoothly and regioselectively with the formation of the corresponding 4-(tributylstannyl)pyridine **32**. In the reaction with alkynes, elimination of a nitrogen molecule after cycloaddition clearly leads directly to the aromatic product [24, 25].

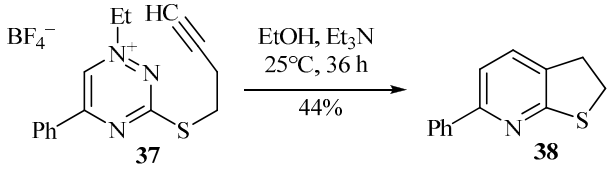


R = Ph, Py, thienyl, PhCO, PyCO, furoyl, thienoyl; X = Cl, Br

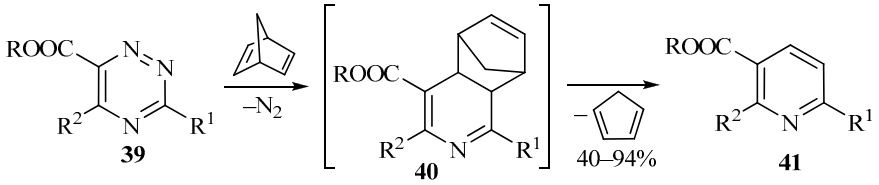
Intramolecular Diels–Alder reactions involving alkynyl side groups have been used quite widely in the synthesis of condensed pyridines. For instance, substituted dihydrofuropyridines (n = 0) and dihydropyranopyridines **34** (n = 1) were obtained from triazines **33**. The reaction time is reduced considerably by activation with microwave irradiation [26]. The analogous reaction of the triazines **35** leads to dihydrofuropyridines **36** [27].



The 1-ethyltriazinium cation **37**, containing a butynylthio group at the position 3, also undergoes an intramolecular Diels–Alder reaction with the formation of the dihydrothienopyridine **38** [28].

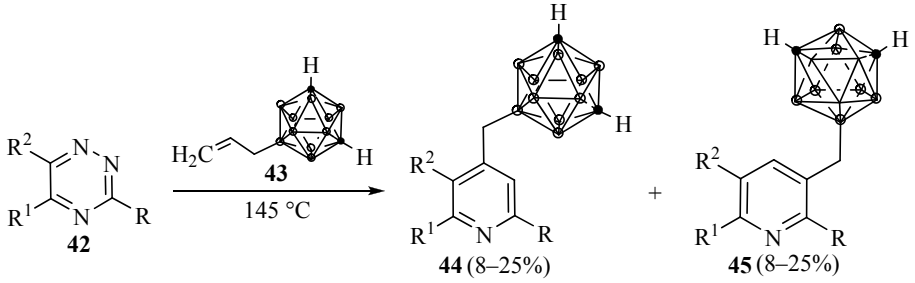


Unactivated alkenes hardly enter into Diels–Alder reactions with 1,2,4-triazines, and heating for many hours at high temperatures is usually required. In spite of this, the reaction of 1,2,4-triazines with 2,5-norbornadiene as dienophile has found widespread application [29]. In particular, heating of 1,2,4-triazine-6-carboxylates **39** with 2,5-norbornadiene leads to the formation of pyridine-3-carboxylates **41**. The intermediate cycloadducts **40** are unstable and its rearomatization takes place under the reaction conditions with the elimination of a cyclopentadiene molecule *via* a retro-Diels–Alder reaction [30, 31]. The advantage of the reaction is that all the substituents from the triazine ring are retained in the final pyridine, while new substituents are not introduced.



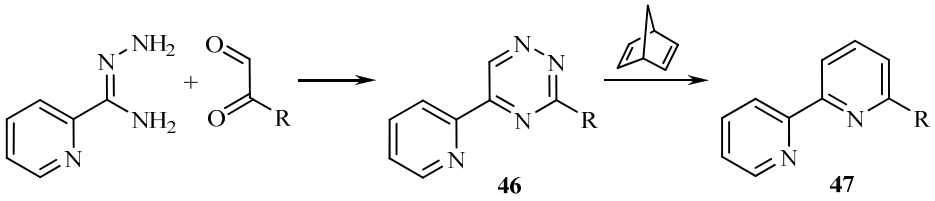
R = Me, Et; R^1 = Ph, Tol, Fur, 4-$O_2NC_6H_4$; R^2 = Me, 4-FC_6H_4

Asymmetrical alkenes react non-regioselectively with 1,2,4-triazines. Thus, prolonged refluxing of the triazines **42** with allyl carborane **43** in xylene leads to a 1:1 mixture of the isomeric pyridines **44** and **45**, containing the *m*-carborane residue in the side chain [32].



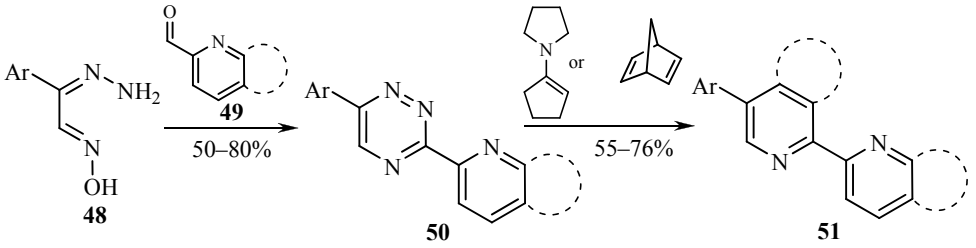
R = Tol, 2-Py; R^1 = H, CN; R^2 = Ph, Tol

Pyridines are often used in coordination chemistry as ligands for transition metals. The use of bi- and terpyridines is particularly widespread. It is not surprising that the transformation of 1,2,4-triazines into pyridines has been used actively in the preparation of new functionalized oligopyridines. It was shown in a large number of elegant examples that the oligopyridyl-1,2,4-triazines **46**, obtained from available building blocks (diketones and amidrazones), react readily with 2,5-norbornadiene to form oligopyridines **47**. This approach based on simple reactions with wide variation of the starting compounds makes it relatively simple, like the LEGO, to "assemble" the most varied oligopyridines [33-38].



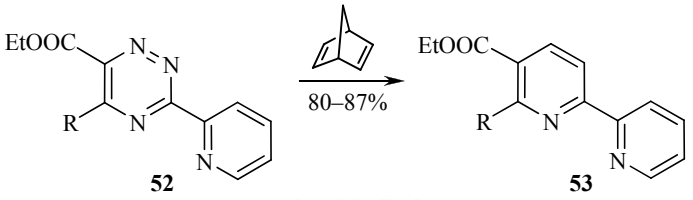
R = 2-pyridyl, bipyridyl, terpyridyl

The numerous examples of using this synthetic approach differ from each other in the choice of method used for synthesis of the initial 1,2,4-triazines, which determines the nature and position of the substituents in the final pyridine ring. The 6-aryl-3-pyridyl(quinolyl)-1,2,4-triazines **50** are prepared from the readily available oximinohydrazones **48** and pyridine(quinoline)carbaldehydes **49**. The further transformation of the 1,2,4-triazines **50** to the 2,2'-bipyridines **51** takes place relatively easily as a result of reaction with morpholinocyclopentene or 2,5-norbornadiene [39-41]. The same reaction with pyridine-2,6-dicarbaldehyde as starting compound leads to substituted 2,2':6',2"-terpyridines [42]. By independent variation of the three reagents it was possible to obtain a wide series of functionalized ligands, the properties of which are controlled by the nature of the substituents.



Ar = Ph, Tol, 4-MeOC$_6$H$_4$, naphthyl, Py, thienyl

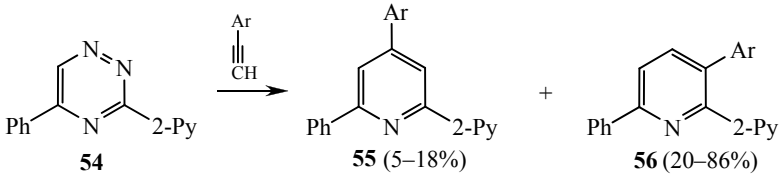
The esters of 2,2'-bipyridine-5-carboxylic acid **53** are formed in the reaction of 3-pyridyl-1,2,4-triazine-6-carboxylate **52** with 2,5-norbornadiene. The electron-withdrawing ester group makes it possible to conduct the reaction under mild conditions (refluxing in ethanol) [43-45].



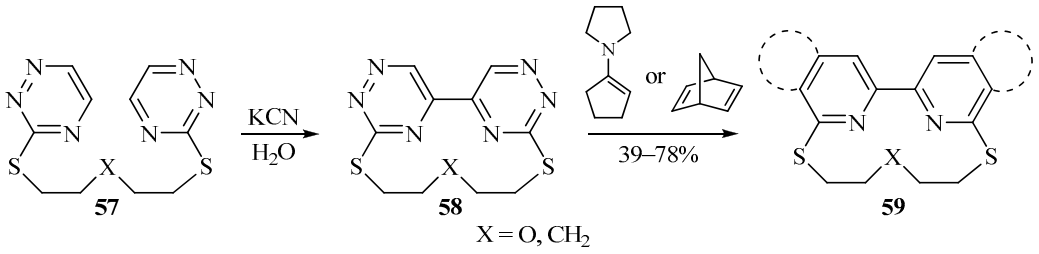
R = Me, Et, Pr

A similar method was used for obtaining the corresponding terpyridines. A one-pot method for the preparation of 5,5"-diethoxycarbonyl-2,2':6',2"-terpyridines by reaction of α-acetoxy-α-chloro-β-ketoesters with pyridine-2,6-bisamidrazone and 2,5-norbornadiene was described. The reaction proceeds through the corresponding bistriazinylpyridine, which is immediately transformed into a terpyridine [46].

6-Phenyl-2,2'-bipyridines are well known as C,N,N ligands for the preparation of luminescent cyclometalated complexes of platinum(II). Phenylbipyridines **55** and **56** with various aromatic substituents in the central pyridine ring were obtained by the Diels–Alder reaction of 6-phenyl-3-(pyridin-2-yl)-1,2,4-triazine (**54**) with arylacetylenes. Arylacetylenes are low-reactive dienophiles in inverse electron demand Diels–Alder reactions, and the reaction therefore requires prolonged refluxing in a high-boiling solvent (1,2-dichloro-benzene). Two regioisomers are formed as a result, and the main product is the more sterically hindered bipyridine **56** (yield 20-86%), whereas the yield of the isomer **55** does not exceed 18%. The authors explain the observed unusual regioselectivity (compared to the synthesis of stannylpyridine **32**) by a π,π interaction in the transition state between the arylacetylene and the outer pyridine ring in the initial triazine **54** [47, 48].

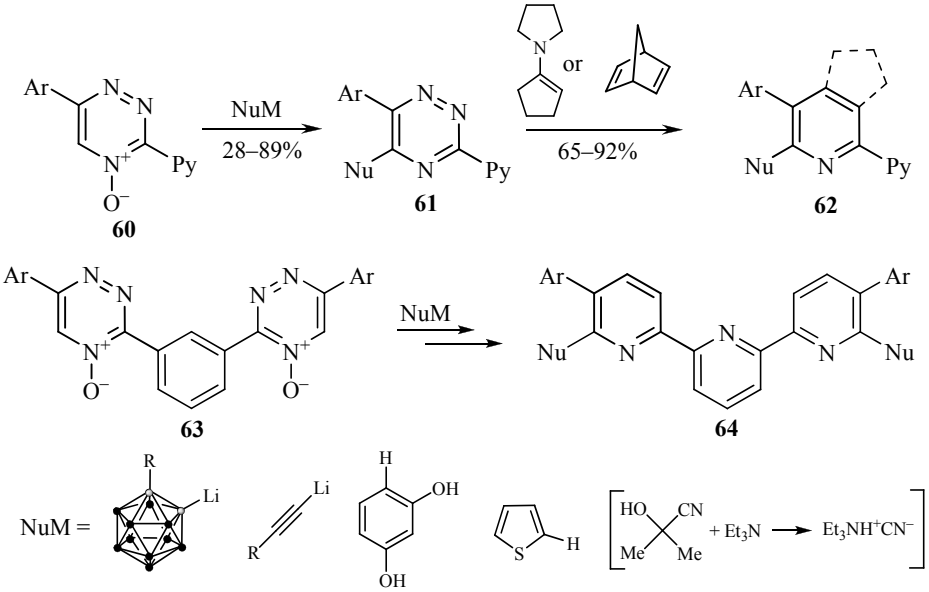


The bitriazines obtained by dimerization of 3-methylthio-1,2,4-triazines by the action of KCN react readily with norbornadiene or morpholinocyclopentene with the formation of the corresponding bipyridines [49, 50]. This method was used in the synthesis of crown thioethers **59** containing a bipyridine fragment. Thus, the cyclization of thiopodands with terminal triazines **57** by the action of KCN leads to thioethers with a bitriazine fragment **58**, which give the corresponding thioethers **59** when heated with 2,5-norbornadiene or pyrrolidinocyclopentene [51-53].



On account of the high electrophilicity, 1,2,4-triazines undergo readily an addition or substitution reactions with nucleophiles, and this is widely used for the synthesis of various functional derivatives of triazine. Reactions of 1,2,4-triazine 4-oxides with C-nucleophiles, which make it possible to insert various substituents directly at the position 5 of the triazine ring, stand out particularly [54]. The combination of the high reactivity of the 1,2,4-triazines in reactions with nucleophiles and their ability of transformation into pyridines as a result of a Diels–Alder reaction makes it possible to obtain new functional derivatives of pyridine [55]. This method proved to be particularly productive in the synthesis of new ligands of the bi- and terpyridines series. The insertion of specific substituents by this method controls specific properties of both the ligands and the metal complexes.

Thus, 3-pyridyl-1,2,4-triazine 4-oxides **60** are easily transformed into cyanide derivatives in reaction with acetone cyanohydrin in the presence of triethylamine with the formation of 5-cyano-3-pyridyl-1,2,4-triazines **61** (Nu = CN). The presence of a nitrile group facilitates the subsequent Diels–Alder reaction of the triazines **61** with 2,5-norbornadiene or morpholinocyclopentene, leading to 6-cyano-2,2'-bipyridines **62** (Nu = CN) [56]. 6,6"-Dicyano-2,2':6',2"-terpyridines were obtained by this method from bistriazinylpyridine *N*,*N*'-dioxide [57-59]. The nitrile group can be converted subsequently into carboxyl, hydroxymethyl, and aminomethyl, and this extends and modifies the chelating moiety of the ligand [58, 59]. Apart from the cyanide anion, various C-nucleophiles have been used in this method: lithiocarboranes [60, 61], lithium acetylides, thiophene, resorcinol [62]. In all cases new ligands (bipyridines **62** or terpyridines **64** with a modified chelating moiety) were obtained.

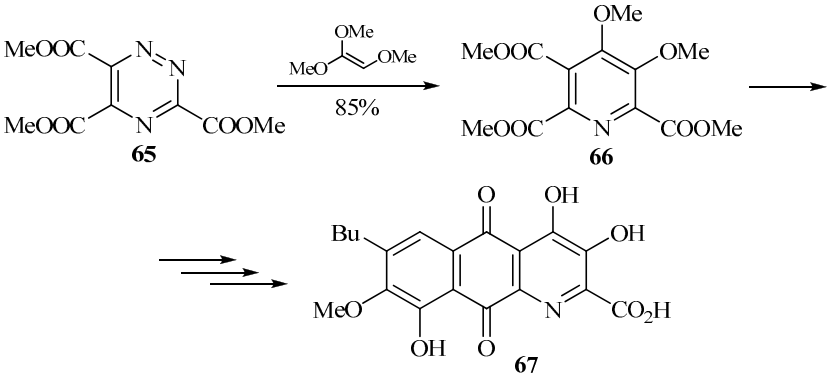


Ar = Ph, Tol, 4-$MeOC_6H_4$, naphthyl, pyridyl, thienyl; Py = 2-pyridyl

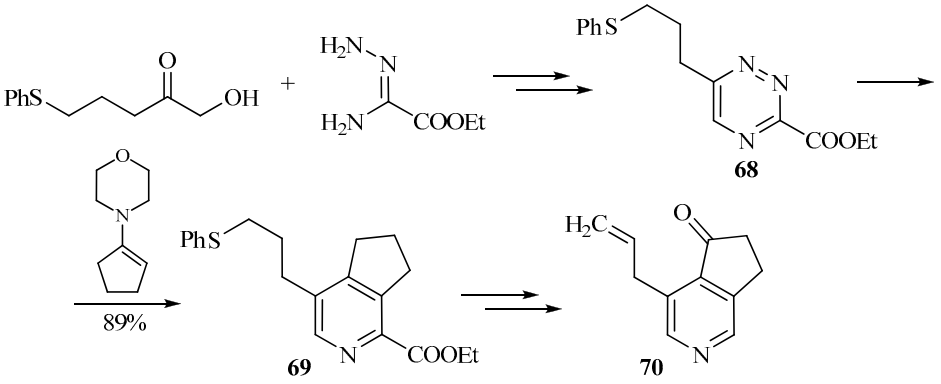
The possibility of simple and extensive modification of oligopyridines enables use of the described method for the preparation of new compounds having useful properties. For example, a method was proposed

for the synthesis of new mesogenic 1,2,4-triazines and their transformation into pyridines or cyanopyridines having liquid-crystal properties [63]. Other examples of preparing liquid-crystalline pyridines and their metal complexes were presented in [64-67].

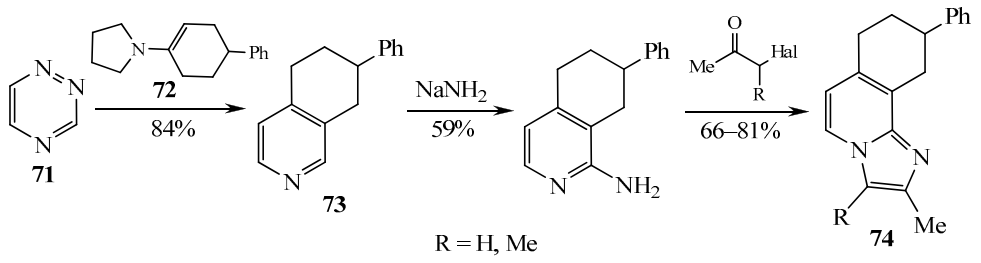
It is worth to examine separately examples of 1,2,4-triazine Diels–Alder reactions in the total synthesis of natural compounds. This method is often the simplest or even the only path to key intermediates. For example, the total synthesis of the natural azaanthraquinone phomazarin **67** was based on the synthesis of the intermediate 3,4-dimethoxypyridine-2,5,6-tricarboxylate (**66**) in the reaction of 1,2,4-triazine-3,5,6-tricarboxylate (**65**) with 1,1,2-trimethoxyethene [68].



An effective synthesis of louisianin series alkaloids, exhibiting antibacterial and antitumor activity, also proved possible due to to the Diels–Alder reaction. For example, the key stage in the synthesis of louisianin C (**70**) is the formation of cyclopentenopyridine **69** when the triazine **68** is heated with morpholinocyclopentene [69, 70].

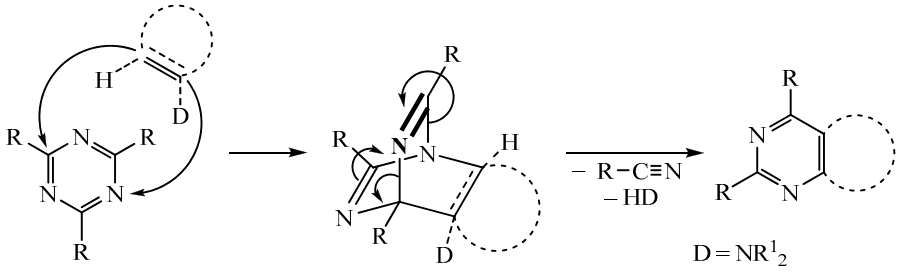


The Diels–Alder reaction of unsubstituted 1,2,4-triazine (**71**) with 1-(4-phenylcyclohex-1-en-1-yl)-pyrrolidine (**72**) leads to 7-phenyl-5,6,7,8-tetrahydroisoquinoline **73**, which is the most important intermediate in the synthesis of tetrahydroimidazo[2,1-*a*]isoquinoline **74** – an inhibitor of the gastric juice secretion [71].

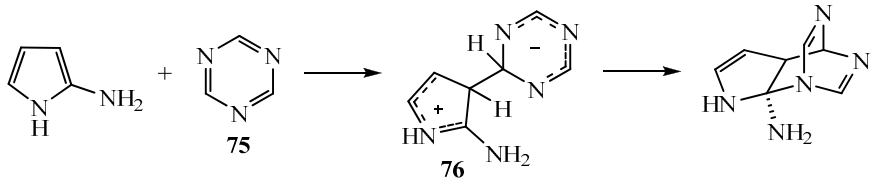


1,3,5-TRIAZINES AS DIENES

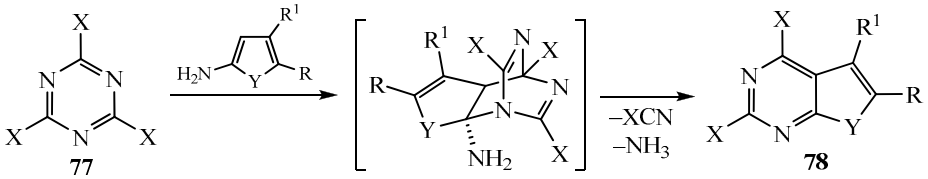
There are no 1,2-conjugated heteroatoms in the 1,3,5-triazine ring, therefore the only possibility for stabilization of the initially formed cycloadduct involves elimination of a nitrile molecule. [4+2] Cycloaddition is only possible at one of the nitrogen atoms and at the carbon atom at the γ-position relative to it. Such addition must obviously be regioselective.



The data from calculation of the frontier orbitals and charges presented at the beginning of this review show that the lowest unoccupied molecular orbital is largely localized at the carbon atom. Such a structure and also the significant difference in the electron density on the nitrogen and carbon atoms promotes nucleophilic addition at this carbon atom, and not a synchronous cycloaddition. The *ab initio* (MP2) quantum-chemical calculations carried out for the Diels–Alder reactions of 1,3,5-triazine (**75**) with 2-aminopyrrole also predict that the cycloadduct is formed by a stepwise mechanism involving nucleophilic addition of the hetarylamine to a carbon atom of the 1,3,5-triazine ring, followed by cyclization of the adduct **76** [72, 73]. This mechanism was confirmed during investigation of the reaction of 2-amino-1-*tert*-butylpyrrole with 2,4,6-tris(trifluoromethyl)-1,3,5-triazine by ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectroscopy [74].

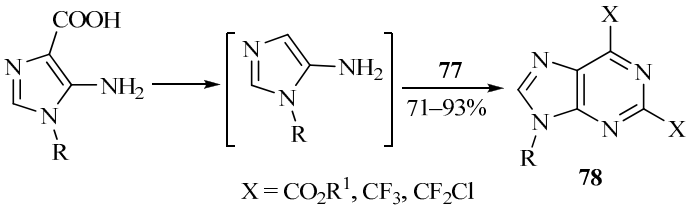


The reaction of 1,3,5-triazines **77** with 2-aminothiophenecarboxylic acid, from which the active dienophile 2-aminothiophene is generated under the reaction conditions, gives thieno[2,3-*d*]pyrimidines **78** (Y = S) [75]. The triazines **77** react similarly with 2-aminopyrrole [76, 77], 2-aminoindole [78], and aminofuran [79, 80], forming the corresponding condensed heterocyclic systems **78** (Y = NR^1, O).

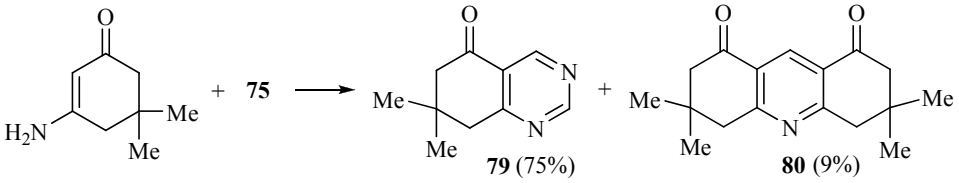


R = H, Me, Ph, CF_3, CN, COOMe, $PO(OEt)_2$; R^1 = H, Me, Ph;
X = COOEt, CF_3, CF_2Cl, H, Ph; Y = NR^1, O, S

In most cases electron-withdrawing groups, such as ester or trifluoromethyl groups, are inserted into the 1,3,5-triazine ring in order to increase the reactivity. Thus, 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**77**) (X = CF_3) reacts with 5-aminoimidazole, generated *in situ* from 5-aminoimidazole-4-carboxylic acid, even at 0°C with the formation of 2,6-bis(trifluoromethyl)purine **78** in high yields [81, 82].

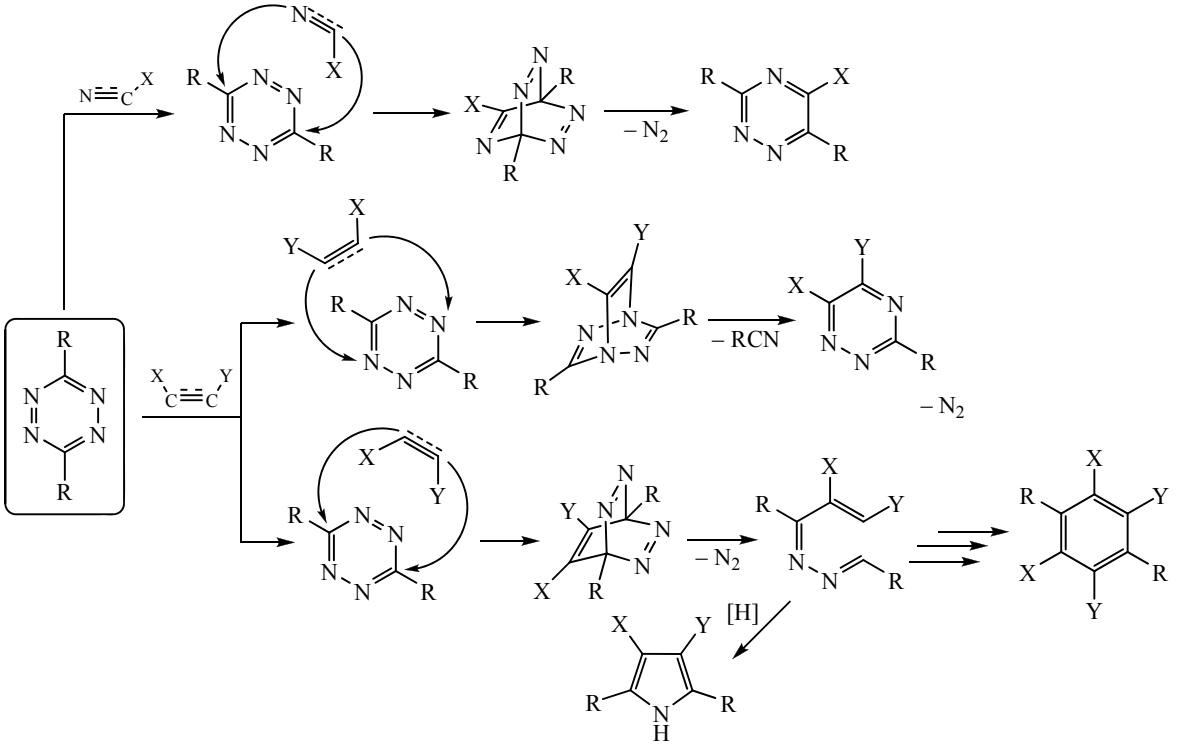


The reaction of unsubstituted 1,3,5-triazine **75** with the enamine obtained from dimedone has been described. Here the triazine **75** can react either with one molecule of the enamine, or with two molecules. In the latter case a double cascade of Diels–Alder and retro-Diels–Alder reactions and aromatization occurs: first with the triazine **75**, and then with the formed bicyclic pyrimidine **79**, leading to the tricyclic pyridine **80** [83].



TETRAZINES AS DIENES

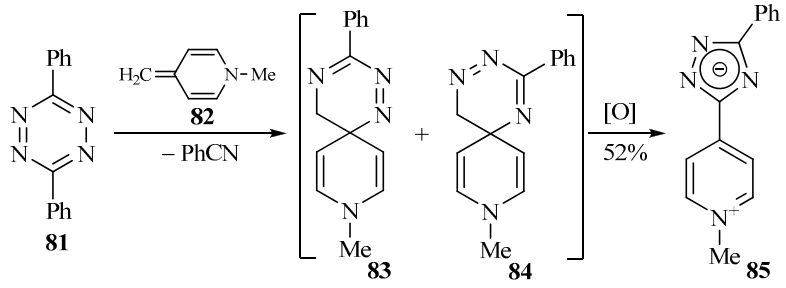
On account of the simultaneous presence of four nitrogen atoms in the ring, tetrazines are even more reactive towards nucleophilic agents than triazines, including inverse electron demand Diels–Alder reactions. Tetrazines are fully capable of competing with triazines in the range of applications of their [4+2] cycloaddition reactions leading to the formation of new heterocyclic systems, in the synthesis of aza ligands, and in the targeted synthesis of natural compounds. Moreover, on account of their exceptional reactivity, tetrazines are finding extensive application in click reactions for the functionalization of various materials.



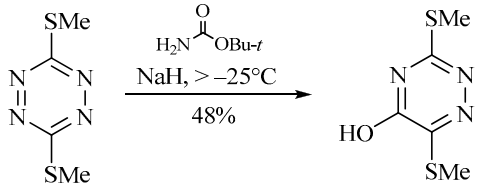
In so far as there are no published data on Diels–Alder reactions of 1,2,3,4-tetrazines and 1,2,3,5-tetrazines, the term tetrazines will henceforth refer to 1,2,4,5-tetrazines (*s*-tetrazines). The principal aspects of the synthetic chemistry of tetrazines up to 2007, including methods for their synthesis and functionalization, and also individual examples of Diels–Alder reactions were examined in a review [84]. The [4+2] cycloaddition of tetrazines is presented above as a method for the construction of new heterocyclic systems.

Tetrazines, like triazines, can enter into the Diels–Alder reaction in several ways. [4+2] Cycloaddition can take place either at the C-3,6 carbon atoms, or at the N-1,4 nitrogen atoms. In the first case a pyridazine ring is formed as a result of C,C-dienophile addition and the subsequent release of a nitrogen molecule. If cycloaddition occurs with participation of a nitrogen heterodienophile, a 1,2,4-triazine ring is formed. The 1,2,4-triazine system is likewise formed during the addition of a C,C-dienophile at the nitrogen atoms of tetrazine with subsequent elimination of a nitrile molecule. Of the above-mentioned pathways the most investigated is the "classic" version of cycloaddition to tetrazines, leading to the formation of pyridazines. The formation of pyridazines in turn makes it possible to use tetrazines in the synthesis of other aromatic systems – pyrroles and benzenes.

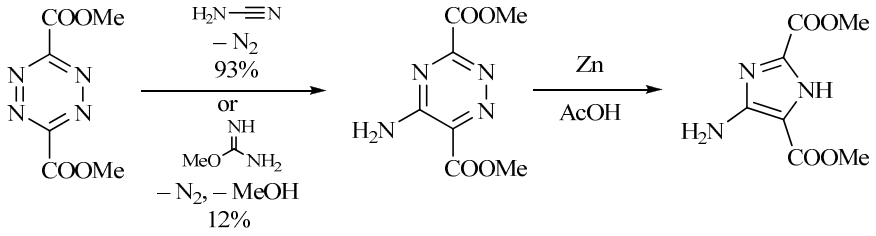
There are single cases of 1,2,4-triazine formation in Diels–Alder reactions. Thus, the addition of 1-methyl-4-methylene-1,4-dihydropyridine (**82**) to diphenyltetrazine **81** leads to the formation of the triazole **85**. The authors suggest that the reaction proceeds through the intermediate spirotriazines **84** and **85**, formed as a result of dienophile cycloaddition at the N-1,4 atoms of the tetrazine and subsequent elimination of a benzonitrile molecule. Such regioselectivity is explained by steric hindrances during the formation of the cycloadduct with participation of the tetrazine carbon atoms [85].



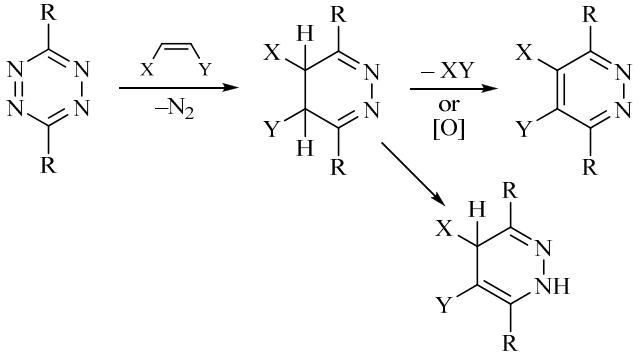
With heterodienophiles it is also possible to transform the tetrazine ring into a 1,2,4-triazine ring. Such dienophiles include carbamates, *O*-alkylisoureas, and cyanamide [86].



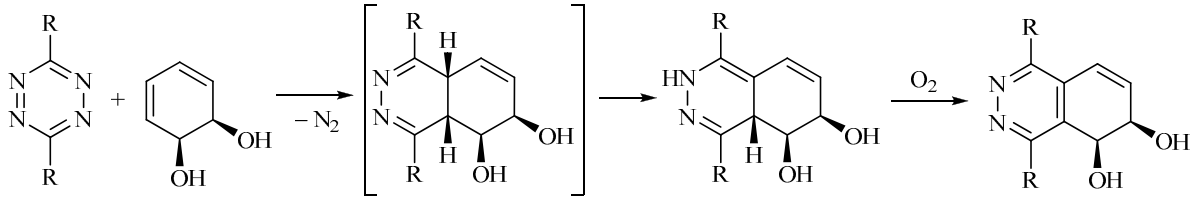
The triazines obtained in this way can serve as precursors in the synthesis of other heterocycles – imidazoles. The latter are formed as a result of reductive ring contraction [87].



The reactions of tetrazines with the formation of pyridazine systems have been most investigated. The formation of an aromatic pyridazine requires the presence of a suitable leaving group in the structure of the olefinic dienophile. Otherwise the reaction stops at the formation of dihydropyridazine, further aromatization of which requires the participation of an oxidizing agent.

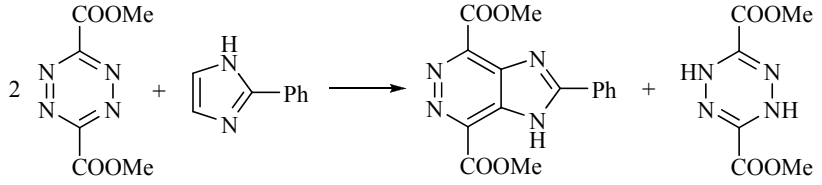


The oxidation path to the aromatization of the product can be illustrated for the case of tetrazine reaction with 5,6-dihydroxycyclohexadiene [88].



R = COOMe

In some cases oxidation of the dihydro adduct can take place spontaneously on account of a second molecule of the starting tetrazine acting as oxidizing agent [89].

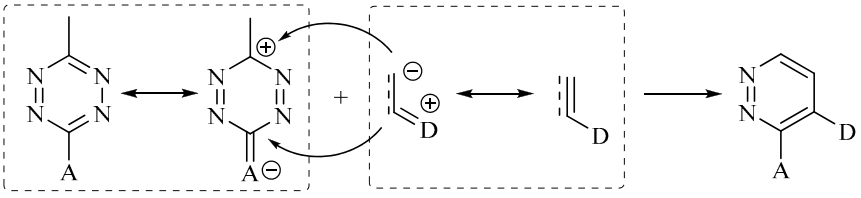


The most active dienophiles providing *auto*-aromatization of the cycloadducts are enamines, followed by enol ethers and vinyl acetates. According to the observations, the rate-determining step in the reactions of tetrazines with olefins is precisely the aromatization stage, and the nature of the leaving group therefore largely determines the rate of the reaction. In order to accelerate the reaction by facilitating the cleavage of the leaving group, protonating agents such as trifluoroacetic acid are added to the reaction mixture [90]. Another widely used method involves reaction activated by microwave radiation, reducing the reaction time from several days to a few hours [91].

Acetylene derivatives are significantly less reactive dienophiles than alkenes. Thus, for example, the reaction rate with ynamines is ten times lower than with enamines. In the case of acetylenes, the limiting step is addition of the dienophile, since the second step (the release of molecular nitrogen) occurs very readily (almost barrier-free), as confirmed both by experimental observations and by quantum-chemical calculations [92-94].

Electron-withdrawing groups in the initial tetrazine lead to a decrease in the LUMO energy of the molecule, facilitating the addition of an electron-rich dienophile [95, 96].

An important aspect of cycloaddition to tetrazines with various substituents at the C-3,6 atoms is the regioselectivity of the reaction. The regioselectivity of cycloaddition is controlled by several factors: localization of the LUMO of the unsubstituted tetrazine molecule, localization of the HOMO of the dienophile, and also steric factors. In the absence of steric hindrances cycloaddition takes place in such a way that the more electron-withdrawing substituent of the tetrazine assumes the *ortho* position of the product in relation to the electron-donating substituent of the dienophile.

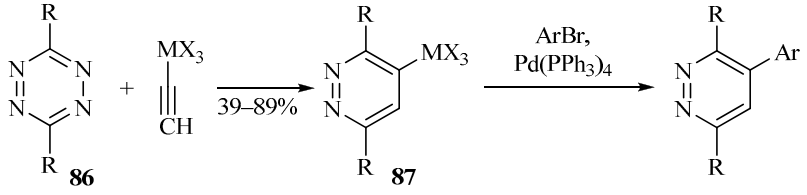


Thus, 6-alkylthio-3-amino-1,2,4,5-tetrazines mostly form the cycloaddition products bearing the electron-donor substituent at the position 4 of the pyridazine ring [97]. Similar results were obtained for the asymmetric 3-alkoxy-6-alkylthio-1,2,4,5-tetrazines [98].

However, when there are bulky substituents in the tetrazine ring, the regioselectivity can change dramatically. Thus, the use of 3-methylsulfinyl-6-methylthio-1,2,4,5-tetrazine as azadiene leads to reverse regioselectivity, evidently due to steric hindrances created by the thionyl group [99]. Similar effect was observed in the reaction of tetrazine with bulky aromatic substituents and a dienophile containing cycloalkyl substituents [100].

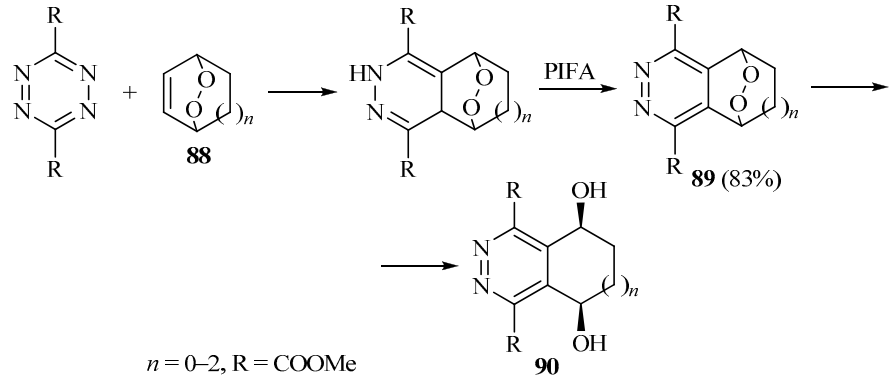
Despite the fact that the range of initial tetrazines is fairly limited, the enormous number of available dienophiles makes it possible to construct various heterocyclic systems based on them. Depending on the type of dienophile, it is possible to obtain an extensive series of substituted pyridazines and dihydropyridazines, condensed systems and spirocycles, bicyclic aza structures, and polyazines.

Thus, reaction of the tetrazines **86** with organoelement derivatives of acetylenes gives pyridazines **87** suitable for further functionalization of the pyridazine ring in cross-coupling reactions catalyzed by palladium complexes [101, 102]. In a similar way, with alkynylboronates as dienophiles it is possible to obtain pyridazylboronates, which are valuable reagents for Suzuki cross-coupling reactions [103].

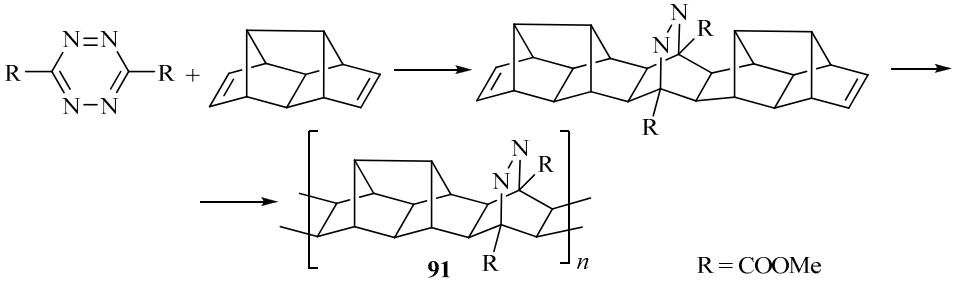


R = Cl, H; MX_3 = $SnBu_3$, $SiMe_3$, $GeMe_3$, $B(OR)_2$

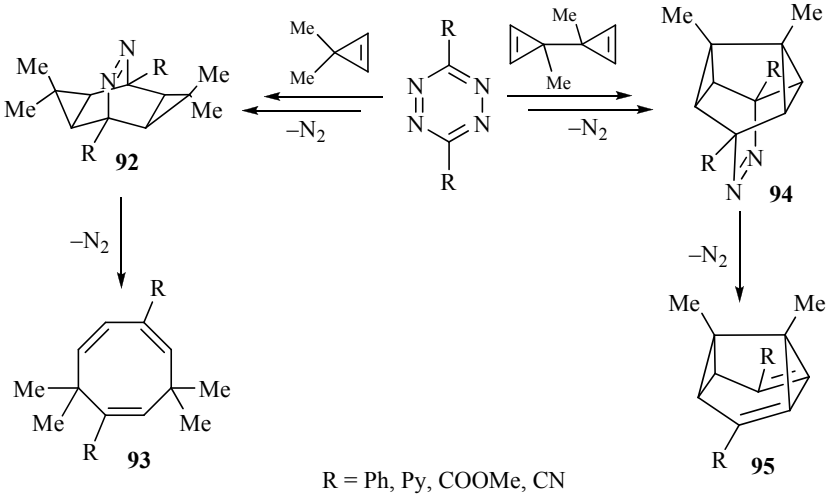
Various condensed systems can be assembled with cyclic dienophiles. Thus, by the reaction of 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine with linear or angular furocoumarins it is possible to obtain pyridazinofurocoumarins – aza analogs of benzo[*j*]angelicin and benzo[*h*]psoralen [104, 105]. The use of benzofuran as dienophile opened up the path to the series of pyridazinopsoralens [106]. The cycloalkene endoperoxides **88** proved to be quite effective dienophiles in the construction of condensed structures based on tetrazine. The products of the such a reaction (pyridazines **89**) can then be transformed into cycloalkane-*cis*-diols **90**, hydroxy ketones, quinones, lactams, and pyrenes [107].



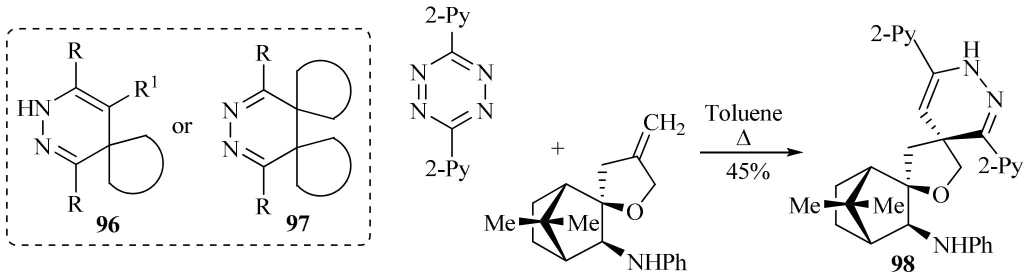
The possibility of repeated cycloaddition of a dienophile to a pyridazine product is used in the synthesis of polycyclic condensed systems based on tetrazines. For example, the polycyclic structures **91**, in which the tetrazine based diazabicyclocyclooctene fragment acts as a rigid linking unit, were obtained as a result of double consecutive addition of bis-alkenes, such as polybornanes and pentacyclic dienes, to tetrazine [108, 109].



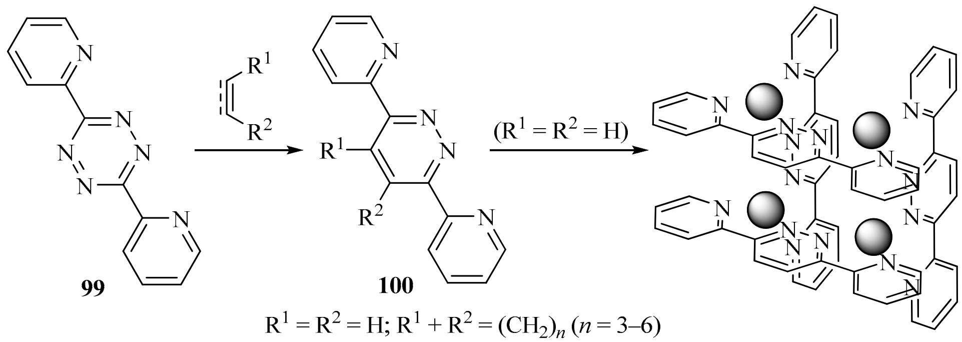
If strained cyclopropenes are used as dienophiles, then diazanorcaradienes **92** [110], homobenzenes, cyclooctatrienes **93** [111], and complex framework structures **94** and **95** [112] are formed.



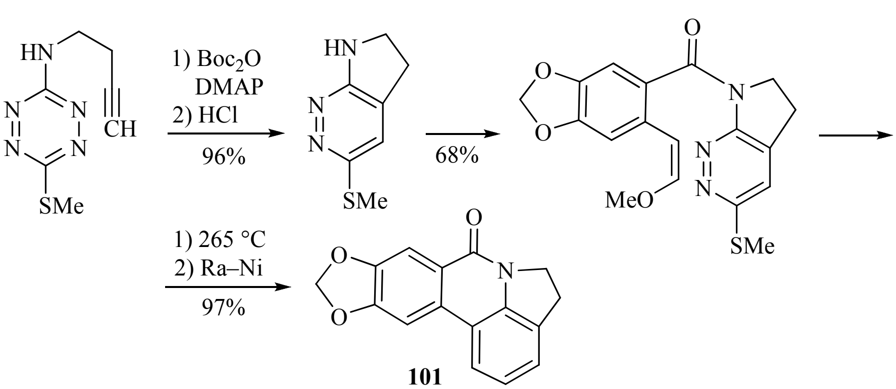
By the Diels–Alder reactions of tetrazines with cyclic olefins containing an exocyclic double bond it is possible to obtain spirocyclic systems with two or three rings (structures **96** and **97**, respectively) [100]. Stereoselective syntheses of asymmetric structures [113], such as the camphor derivatives **98** [114], have also been described.



The synthetic potential of tetrazines in Diels–Alder reactions has been utilized successfully in the design of nitrogen ligands. Thus, 3,6-dipyridyl-1,2,4,5-tetrazine **99** and the pyridazines **100** obtained from it are convenient building blocks for the construction of metal-organic framework (MOF) structures. Cycloaddition reactions give the possibility of additional functionalization of the ligands, making it possible to control the architecture of the created MOFs and to give them additional properties [115]. A family of polytopic pyridazine ligands with various three-dimensional geometries have been synthesized on the basis of a wide range of cyclic dienes and trienes [116]. The 4,4'-bipyridazine and condensed pyridazino[4,5-*d*]pyridazine obtained from unsubstituted tetrazine were used as tetradentate ligands for the design of 3D MOFs [117].

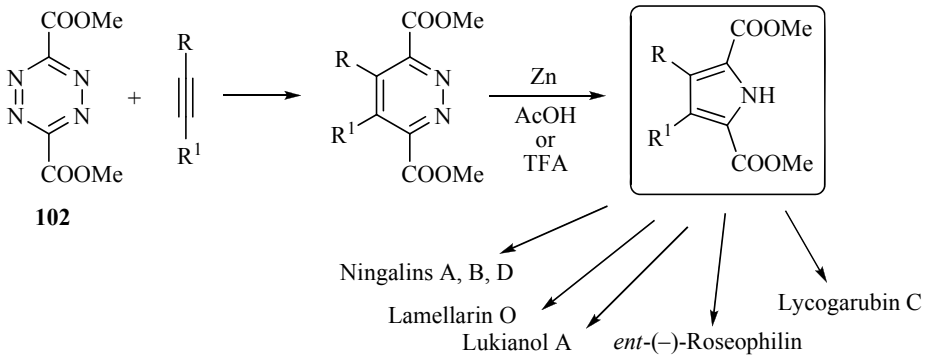


Cycloaddition to tetrazines traditionally remains an effective tool in the targeted synthesis of natural compounds and their analogs. The synthesis of the lycorine alkaloid **101** from plants of the *Amaryllidaceae* family can be cited as an example. The developed synthetic sequence includes two intramolecular cycloaddition reactions [118].

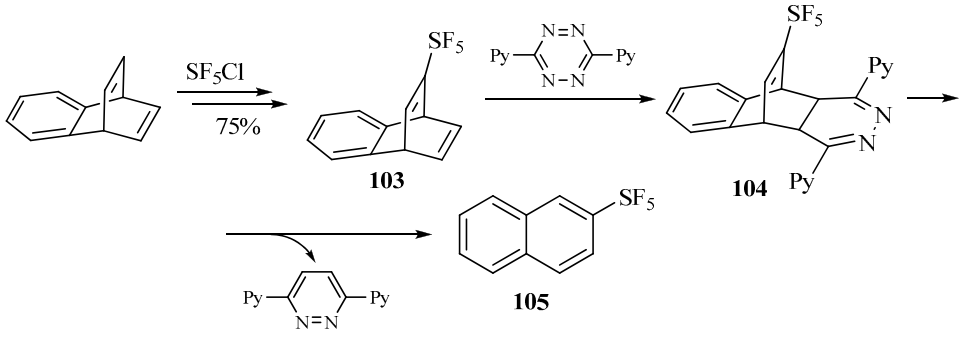


Intramolecular cycloaddition of indole derivatives to tetrazine was used in the synthesis of alkaloids of plants of the *Aspidosperma* family [119]. The Diels–Alder reaction of tetrazines was also used in the synthesis of antibacterial tricyclic diazacarbapenems [120], functionalized C-nucleosides [121], and aza analogs of the alkaloid epibatidine from an Ecuadorian frog skin extract [122].

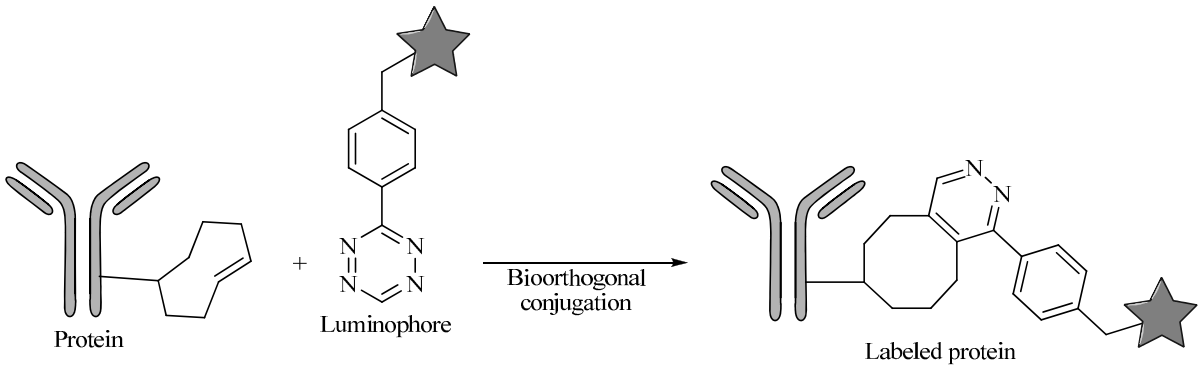
The possibility of converting the pyridazine ring into a pyrrole ring as a result of reductive ring contraction has also been widely used in the synthesis of natural compounds. The cycloaddition of alkenes or acetylenes to 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine **102** forms the basis of the synthesis of such natural products as ningalins A [123], B [124], and D [125], lamellarin O, lukianol A, roseophilin [126], and lycogarubin C [127, 128].



Finally, tetrazine can play an auxiliary role in the synthesis of polycyclic arenes providing elimination of unwanted CH=CH fragment from the intermediate cycloadduct while no part of the tetrazine is incorporated in the final product. A typical example of such use of tetrazine is the synthesis of 2-pentafluorosulfanyl-naphthalene **105**, in the course of which cycloaddition of the readily available pentafluorosulfanylbarrelene **103** to dipyridyltetrazine leads to the dihydro adduct **104**, which undergoes a retro-Diels–Alder reaction and eliminates dipyridylpyridazine [129]. It must be emphasized that compound **105** cannot be obtained by direct insertion of the pentafluorosulfanyl group into the naphthalene ring. A similar method was also used in the synthesis of a benzofuran derivative from 1,4-endoxy-1,4-dihydronaphthalene [130], and also in the functionalization of fullerenes [131, 132].



Tetrazines are finding ever increasing application in click chemistry: for the instant functionalization of biological substrates, polymeric materials, and nanostructures. The high reactivity of tetrazines with respect to dienophiles makes it possible to use them as linking elements for the rapid conjugation of various markers to biological substrates. This method for the functionalization of biomolecules in living systems, which has resulted in a stream of publications in last years, has been named bioorthogonal chemistry. In principle the method involves rapid interaction between the tetrazine, linked to some signal system such as a luminescent or radioactive marker, and a biomolecule functionalized by a suitable dienophile, for which purpose *trans*-cyclooctene is most often used. The high rate of the reaction makes it possible to use this method even with extremely low concentrations of the reagents, which is particularly important for use in living systems [133, 134].



Since aspects of bioorthogonal chemistry belong to a separate field and do not come within the scope of the present review on heterocyclic chemistry, we can only point out that in the last year several reviews have been published on this field, including some reviews covering the progress of tetrazine chemistry in this area [135, 136].

It should also be noted that click reactions of tetrazines have already gone beyond the limits of bioorthogonal chemistry. Thus, the tetrazine method has been used for post-synthesis modification of MOFs [137] and for the functionalization and coupling of polymers under mild conditions without any catalysts [138].

Over the last 15 years, methodology based on the inverse electron demand Diels–Alder reaction of polyazines has developed significantly. Many examples demonstrate the synthetic value of the method, by which it is possible to achieve targeted functionalization of mono- or diazines, to produce new heterocyclic systems, or to employ accessible reagents and simple procedures for performing targeted synthesis of compounds that are extremely difficult to obtain by other methods.

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