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METHODS FOR THE SYNTHESIS OF MONO- AND POLYNUCLEAR NH-TETRAZOLES.* (REVIEW)

V. Yu. Zubarev and V. A. Ostrovskii

Data on methods for the synthesis of monocyclic and polynuclear NH-unsubstituted tetrazoles are reviewed.

Keywords: amidrazones, nitriles, new reagents, solvents, NH-tetrazoles, diazotization, structure modification, application region, cyclization, cycloaddition.

The chemistry of heterocyclic compounds developed at the highest rate toward the end of the twentieth century. Among the numerous series of heterocycles special attention must be paid to tetrazoles, which have been the subjects of intensive research and applied investigations. The methods of synthesis and also the chemical and physical properties of the compounds were reviewed in [1-13], but the volume of the cited material does not always make it possible to single out the most important trends. In our opinion, special attention is deserved by N-unsubstituted tetrazoles, which include highly effective medicinal products that have been produced industrially (e.g., losartan). In addition, they are key substrates in electrophilic reactions, leading to N-substituted tetrazoles with various structures and also to tetrazolium salts. The (N-unsubstituted tetrazole → N-substituted tetrazole) scheme is fundamentally important for the preparative chemistry of tetrazoles. Flexible wide-ranging production systems have been created on the same principle [11, 14].

According to the authors of the review [13], the same may apply to an even greater degree to polynuclear NH-tetrazoles. However, information on these unique subjects of heterocyclic chemistry is extremely sparse and has not been specially analyzed.

The aim of the present review was to classify modern methods for the production of both monocyclic and polynuclear N-unsubstituted tetrazoles.

GENERAL METHODS FOR THE SYNTHESIS OF NH-UNSUBSTITUTED TETRAZOLES

The formal scheme for the production of NH-tetrazoles can be represented in the way showed in the Scheme 1.

We will discuss traditional and modern approaches to the production of NH-tetrazoles in the light of the flow chart.

* Dedicated to Prof. H. Elguero on the occasion of his 65th birthday.

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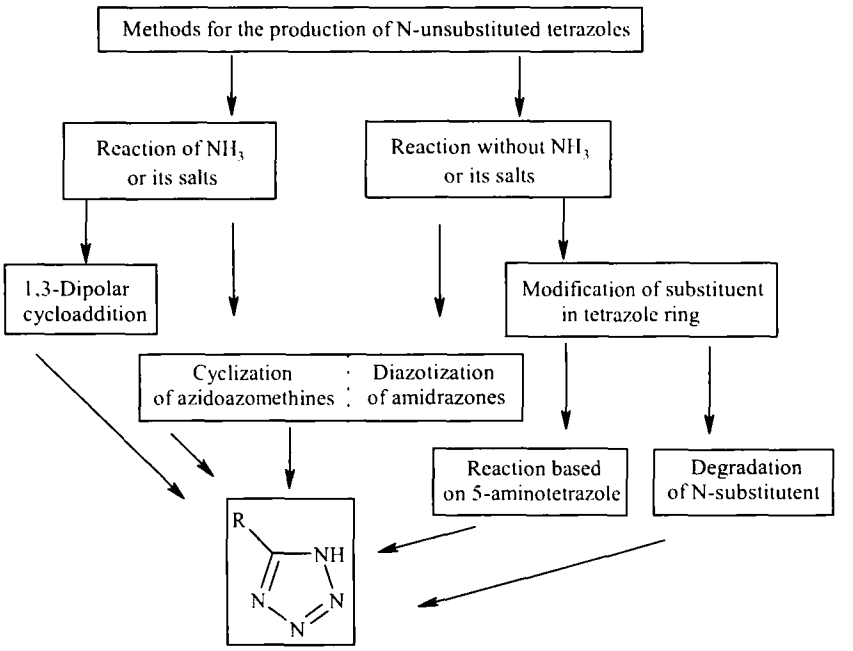
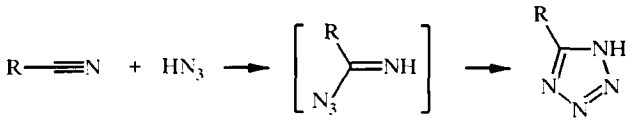
Scheme 1



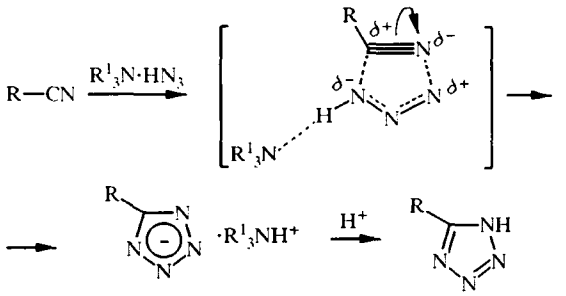
Flow chart of possible methods for the synthesis of N-unsubstituted tetrazoles

The Formation of the 5-Tetrazolyl Ring with Hydrazoic Acid and its Derivatives

The early papers described the production of 5-substituted tetrazoles by the reaction of hydrazoic acid with nitriles [15]. According to these authors, the process takes place through the formation of an intermediate azidoazomethine:



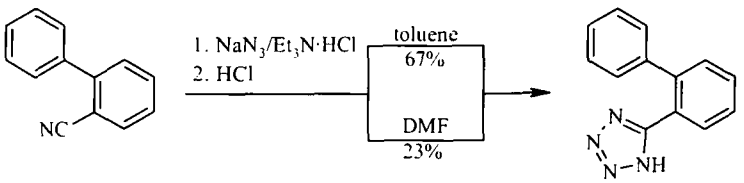
This method has not found practical application on account of the high toxicity and explosive nature of hydrazoic acid. (At the present time the ammonium salt is mainly used as azidizing agent.) The reaction is usually conducted in a high-boiling aprotic dipolar solvent (DMF, DMAA) at 100-120°C. By studying the kinetics of the reaction of alkylammonium azides with nitriles in protic and aprotic polar solvents at 80-120°C it was possible to conclude that the process takes place by a mechanism of 1,3-dipolar cycloaddition [16].



A similar mechanism was the subject of a theoretical analysis by the semi-empirical and non-empirical methods of quantum chemistry [17]. The rate of cycloaddition increases with increase in the electron-withdrawing characteristics of the substituent R in the nitrile and the electron-donating characteristics of the substituents R^1 in the ammonium salts of hydrazoic acid. In connection with the fact that tetraalkylammonium azides do not react under these conditions a hypothesis according to which the attacking particle is an H-bonded complex of the ammonium salt with hydrazoic acid was put forward. The mechanism of 1,3-cycloaddition is characterized by low values of the entropy of activation, and the process is as a rule conducted at a high temperature and with prolonged holding. The authors of [16] do not rule out the possibility that the process takes place through the formation of intermediate azidoazomethines in cases where the nitrile group in the structure of the initial substrate is bonded directly to a strong electron-withdrawing substituent (trifluoroacetonitrile, oxalonitrile, etc.). The rate of such processes can be increased substantially by the action of high pressure [18-20] and ultrasound [21].

The effect of the solvent nature on the reaction mechanism of nitriles with alkylammonium azides is a subject of debate.

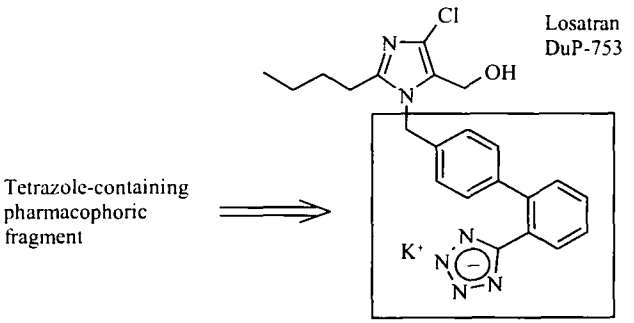
The authors of one of the publications [22] propose to conduct the reaction of triethylammonium azide with nitriles in nonpolar aromatic solvents (toluene, benzene, etc.). In this case the triethylammonium salt of tetrazole that forms separates from the solution, and this leads to a displacement of the equilibrium toward the target compound. The precipitated salt can be isolated by extraction from the organic phase with water, after which tetrazole derivative is precipitated from the solution by acidification. The unreacted nitrile remains in the organic phase and can be reused, which is extremely useful both in laboratory practise and under industrial conditions. The conversion of the sterically hindered nitriles to the corresponding tetrazoles in toluene takes place more completely than in the case where DMF is used [22]. This effect is explained by the fact that in DMF solvation of triethylammonium azide by the solvent dipoles occurs, leading to a decrease in the activity of the azidizing agent. If nonpolar aromatic solvents are used, the polar triethylammonium azide is blocked to a lesser degree.



In some cases an increase in the yield of the respective 5-substituted tetrazoles is brought about by the use of different types of azidizing agent (azides of alkali metals, trialkylstannyl and trialkylsilyl azides, aluminum triazide). In these papers there are no reliable data on the mechanisms of the reactions.

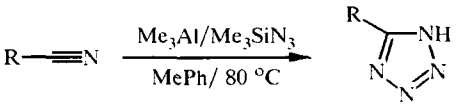
The importance of the development of new effective methods for the synthesis of 5-substituted tetrazoles is explained by the need to satisfy the demands of the pharmaceutical market for 5-tetrazolyl-containing non-peptide antagonists of angiotensin II receptor [23-30].

The molecular structure of these modern drugs contains a common 5-[2-(4-R-phenyl)]phenyl-5-tetrazolyl fragment. A typical representative of this series is the compound patented by DuPont:

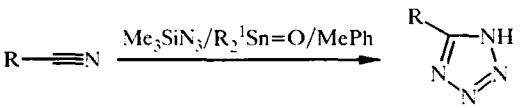


The synthesis of losartan and its analogs involves the formation of the tetrazole ring from sterically hindered substrates and cannot be realized satisfactorily by classical methods. A large number of papers on the chemistry of 5R-tetrazoles in recent years have been directed toward the solution of this very problem. New and improved versions of the familiar methods for the production of 5R-tetrazoles have been proposed.

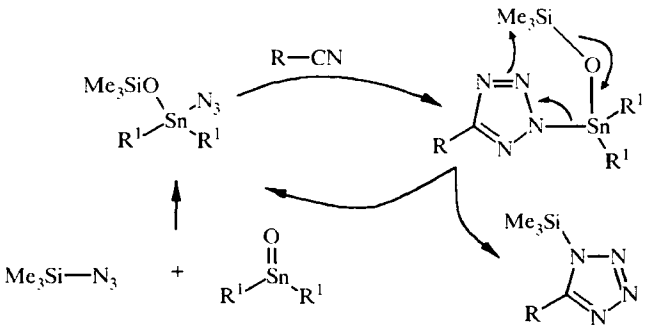
Thus, on the basis of well-known papers on the use of aluminum triazide, produced *in situ* from aluminum chloride and sodium azide [31-33], as azidizing agent an equimolar mixture of trimethylaluminum and trimethylsilyl azide was used for the transformation of aliphatic and aromatic nitriles into tetrazoles [34]. In this case trimethylaluminum acts as Lewis acid and facilitates the addition of azide, further activating the sterically hindered nitrile.



Another effective azidizing agent is trialkylstannyl azide, produced *in situ* from caustic and toxic trialkylstannyl chloride [35]. An alternative version of the synthesis of N-unsubstituted tetrazoles was proposed in order to remove the risk associated with the toxic substances.

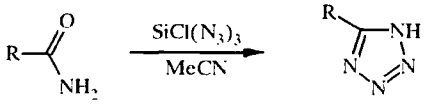


It has been reported that trimethylsilyl azide reacts with nitriles in the presence of dialkylstannyl oxide, giving good yields of the respective tetrazoles [36, 37]. The authors of the cited papers propose an original cyclic mechanism for the process, in which trimethylsilyloxydialkylstannyl azide acts as azidizing agent.

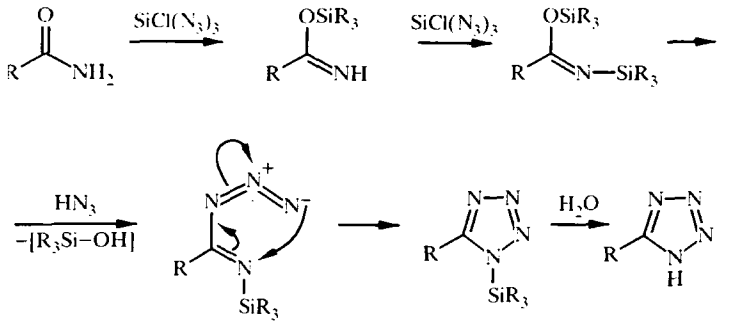


In the opinion of the authors [38] the yield of tetrazoles in the reaction of nitrile with ammonium azide is increased by the addition of surfactants. Methods for the production of 5-substituted tetrazoles from nitriles with Lewis acids have been patented [39, 40]. It has also been reported that during the production of 5-methyltetrazole from acetonitrile by azidation with the sodium azide–aluminum trichloride system it is possible to increase the yields of the desired compound substantially by the addition of 0.6-0.8% of water to the reaction medium [41].

Recently it was shown that the primary amides of carboxylic acids may provide a fundamentally new reagent for the synthesis of 5-substituted tetrazoles [42]. In this case triazidochlorosilane, previously used for the transformation of aldehydes into nitriles or acid azides [43, 44] and also for the production of 1,5-disubstituted tetrazoles from ketones [45], is used as azidizing agent. This azidizing agent is produced *in situ* from tetrachlorosilane and three equivalents of sodium azide.

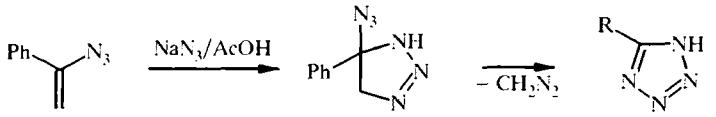


In the opinion of the authors of [42] the mechanism of the reaction can be represented in the following way:

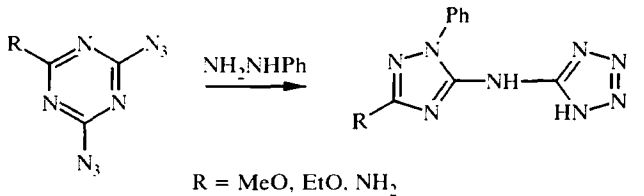


$SiR_3 = (Cl_n(N_3)_{3-n}Si)-$

We will examine some examples of the production of 5-substituted tetrazoles by the transformation of the structure of the azide derivatives of other heterocyclic compounds. The intermediate 5-azido-5-phenyl-1,2,3-triazoline, obtained from α-styryl azide, is transformed (with the elimination of diazomethane) into 5-phenyltetrazole [46].

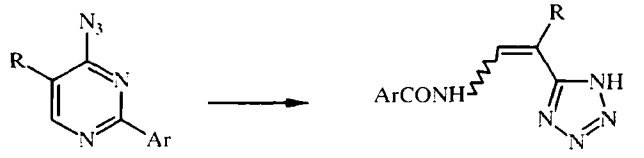


Opening of the azine ring, containing azide substituents, can lead to NH-tetrazoles with original structure. Thus, the reaction of diazides of *sym*-triazines with hydrazine or phenylhydrazine leads to 5-triazolylaminotetrazoles [47]:



R = MeO, EtO, NH_2

Derivatives of 4-azidopyrimidine can also be transformed into 5-substituted tetrazoles [48]:

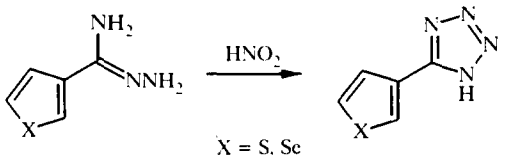


R = CO_2Et, NO_2

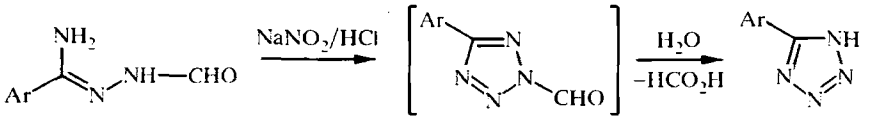
The unusual case of the formation of 5-phenyltetrazole from phenylacetylene and dimethylammonium azide through the intermediate benzonitrile, formed as a result of the thermolysis of 4-phenyl-1,2,3-triazole, has been described [49].

Production of 5R-Tetrazoles by Diazotization of the Amidrazones of Carboxylic Acids

An alternative method for the production of 5-substituted tetrazoles is diazotization of amidrazones. This method for the production of 5-substituted tetrazoles has been known for a fairly long time [50, 51], and its advantage is the relative safety of the process, since the initial reagents do not contain an azide group. For example, the action of nitrous acid on the amidrazones of thiophenecarboxylic and selenophenecarboxylic acids gives the corresponding tetrazoles with high yields [52]:



In the general case a wide range of N-unsubstituted tetrazoles can be obtained during the diazotization of the amidrazones of carboxylic acids. Unfortunately a series of side products are formed together with the desired tetrazoles when this method is used. Another restricting factor is the inadequacy of the methods used for the synthesis of the initial amidrazones [53]. Of the later publications it is necessary to mention the paper [54], in which an effective method for the synthesis of 5-aryltetrazoles by the nitrosation of N-formylamidrazones is described.

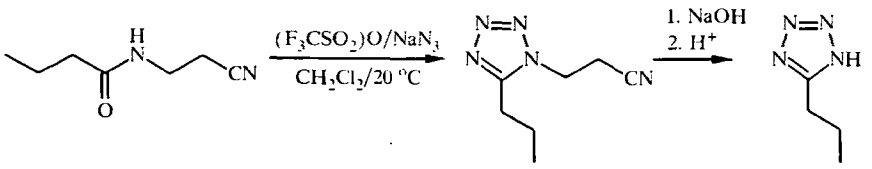


Methods for the production of 5-substituted tetrazoles that are essentially special versions of the above-mentioned diazotization of amidrazones have been patented. Thus, the reaction of formylhydrazine with arylimidates at 0°C leads to high yields of the corresponding 5-aryltetrazoles [55]. A two-stage method for the production of 5-substituted tetrazoles was described; at the first stage the sterically hindered nitriles react with hydrazine in toluene at room temperature, after which the intermediate amidrazone is treated with isoamyl nitrite in the presence of acetic acid at 0°C [56].

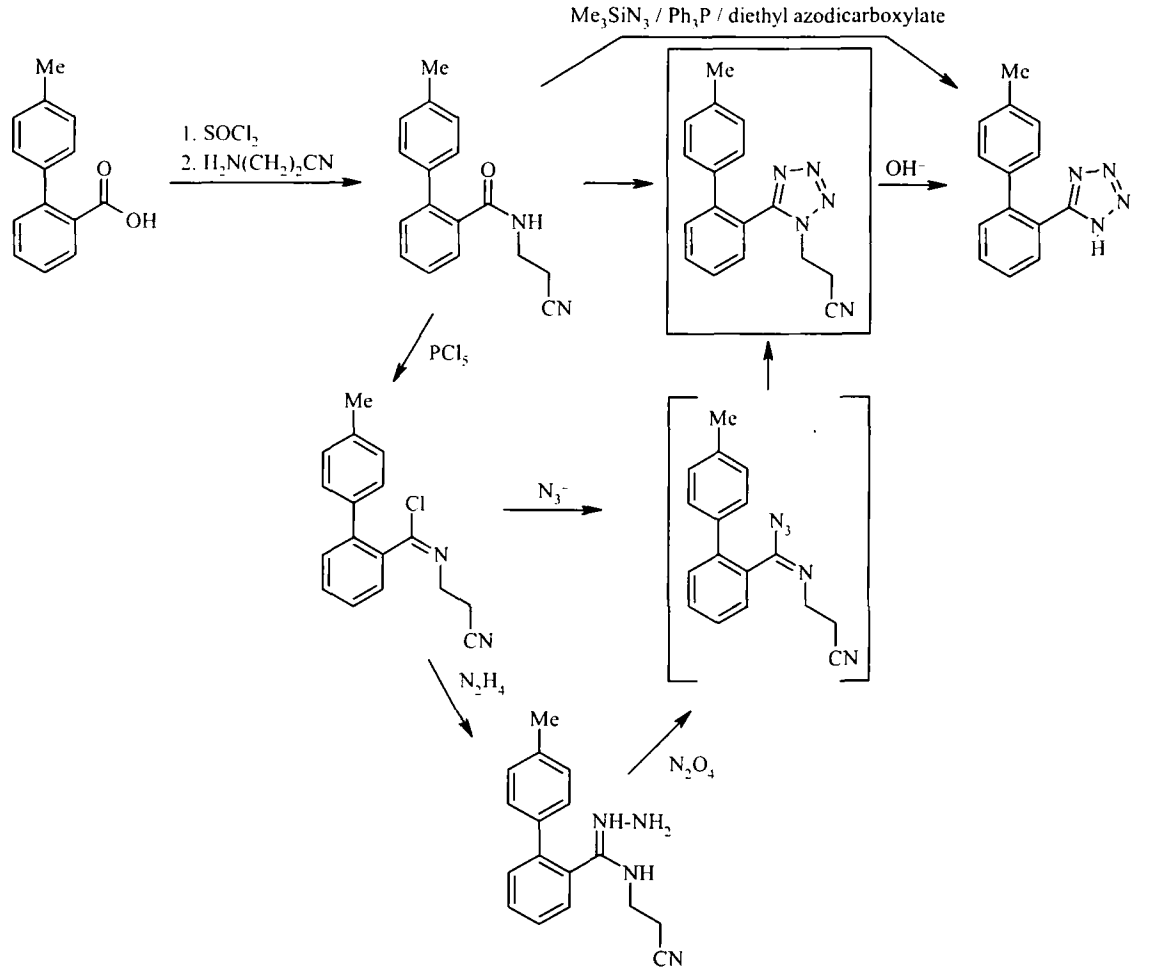
Production of 5R-Tetrazoles by Modification of the Structure of Tetrazole-containing Compounds

Degradation of the substituent in the ring has long been used for the production of tetrazoles. The use of this method is often preferable to the alternative versions. Thus, methods based on the oxidative degradation of alkyl substituents at the carbon atom of the tetrazole ring are used for the production of high-purity unsubstituted tetrazole, required for the synthesis of oligonucleotides. These methods depend on the high stability of tetrazole to the action of oxidizing agents.

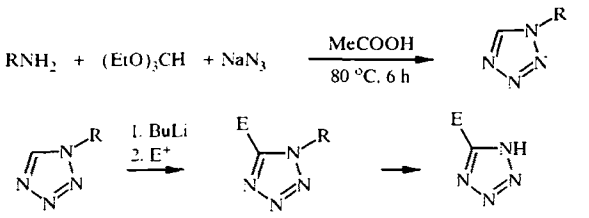
Removal of the "protecting groups" at position 1 of the ring has become a widely used procedure in the chemistry of tetrazoles. Acid or alkaline hydrolysis is used for this purpose. For example, if the N-monocyanoethyl derivative of amides is used as initial substrate, the $N_{(1)}$ -cyanoethyl derivative of tetrazole formed in the course of the reaction can be easily hydrolyzed with the formation of the corresponding N-unsubstituted 5R-tetrazole [57].



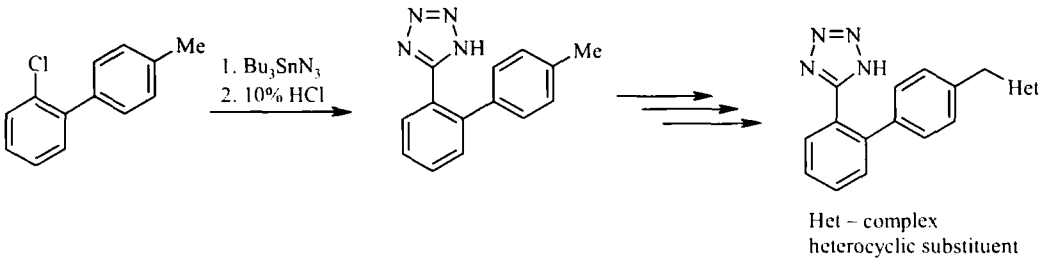
A single-step method has also been proposed for the production of 5-substituted tetrazoles by transformations of the cyanoethyl derivative of amide [58]. The scheme below shows the advantage of this method compared with the alternatives:



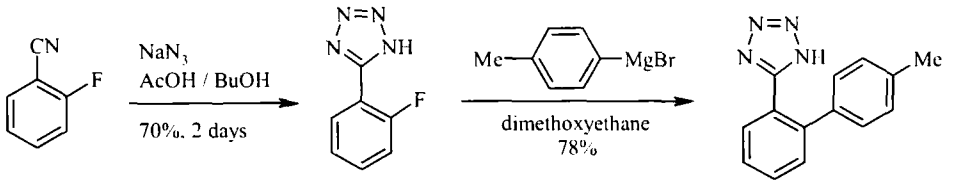
An original method for the synthesis of N-unsubstituted tetrazoles from the 1-substituted derivatives is known [59]. The authors examined three versions of the elimination of the $N_{(1)}$ substituent at the last stage of the synthesis (reduction with hydrogen and acid or oxidative degradation). The initial 1-substituted tetrazole substrates were obtained from the corresponding amines in a single stage.



Complex functional groups can of course be introduced at position 5 of the tetrazole ring, using various modifications of the structure of an existing substituent. For example, the highly toxic trialkylstannyl azide was earlier used for the production of various analogs of the above-mentioned losartan:



An alternative scheme used *o*-fluorobenzonitrile, the modification of which does not involve significant steric hindrances [60].



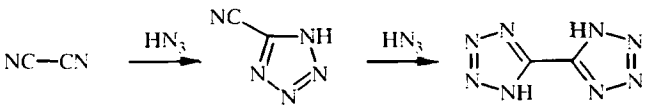
Various compounds have been obtained by the modification of the exocyclic amino group in 5-aminotetrazole [61]. (Some of them cannot be realized by other methods.) Of greatest interest is the diazotization of the amino group in 5-aminotetrazole with the formation of tetrazolyldiazonium salts, which are distinguished by high reactivity [62]. By coupling 5-tetrazolyldiazonium with nucleophiles it is possible to obtain a wide range of compounds having practically important properties. However, in view of the high risk, operations with the diazonium salt of tetrazole require the observance of special safety procedures and can only be used on the laboratory scale.

Although at first sight all the methods for the production of 5R-tetrazoles described above fit into long known formal schemes, the range of initial substrates, reagents, solvents, and catalysts used for the synthesis of 5-monosubstituted tetrazoles has expanded substantially in recent years. The further development of synthetic methods for the production of tetrazoles will make it possible to produce previously inaccessible compounds and will also help toward a solution of the practical problems in the industrial production of tetrazoles.

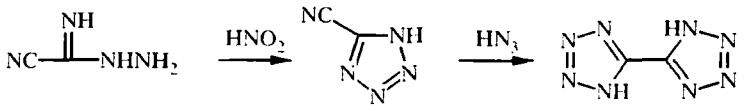
METHODS FOR THE SYNTHESIS OF POLYNUCLEAR COMPOUNDS CONTAINING TERMINAL NH-TETRAZOLYL GROUPS

The presence of several tetrazole rings in a molecular structure leads to the appearance of qualitatively new characteristics. Some polytetrazolyl compounds have been proposed or have even found use as complex-forming agents (products for analytical chemistry), components of cinephotomaterials, in medicine, and as components of energy-containing and gas-generating compositions.

5,5'-Bitetrazole has attracted attention primarily as an energy-containing compound with a high nitrogen content (88%). It was first synthesized by Oliveri-Mandala [63] and Lifschitz [64] from dicyanogen and hydrazoic acid, and the intermediate product in this case was 5-cyanotetrazole [65].



Later a safer method was described for the synthesis of 5,5'-bitetrazole from 5-cyanotetrazole, which was obtained from cyanoguanidine [66].

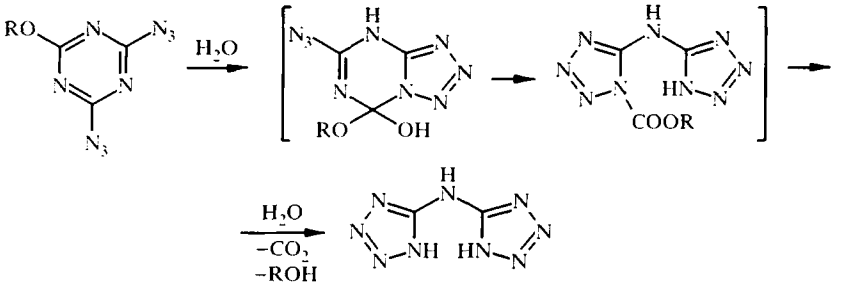


5,5'-Bitetrazole was synthesized with a small yield from 5-cyanotetrazole through the amidrazone of 5-tetrazolecarboxylic acid [67].

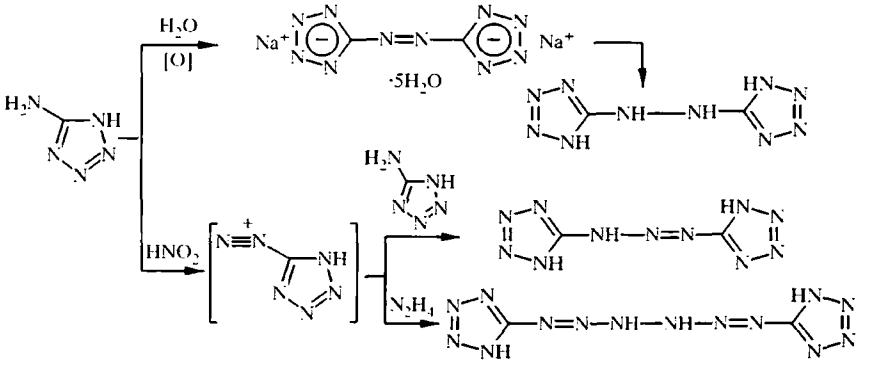
The method for the production of 5,5'-bitetrazole according to Friederich [68], based on the formation of dicyanogen *in situ* from sodium cyanide followed by the reaction of dicyanogen with hydrazoic acid, is well-known. A safer method for the production of 5,5'-bitetrazole by the diazotization of bisamidrazone of oxalic acid has also been mentioned [66]. However, in spite of its obvious appeal the method has not yet been widely used on account of the formation of a large number of side products. Probably, Friederich's method remains to this day the most suitable of the described methods for the synthesis of 5,5'-bitetrazole.

5,5'-Bitetrazole is an interesting model for physicochemical investigations, and its properties have therefore been studied in a fair amount of detail; the molecular structure in the crystalline state was established [69], the acid–base [70] and complexing characteristics [71] were studied, and the thermodynamic characteristics were investigated [72]; the spectra of its disodium salt in water were studied by the ^{13}C and ^{15}N NMR methods [73].

Di(5-tetrazolyl)amine. When 6-alkoxy-2,4-diazido-1,3,5-triazines are heated in water, the carbon atom of the ring and the alkoxy group attached to it are eliminated. This leads to di(5-tetrazolyl)amine [74], which was obtained earlier by different methods [75, 76]:



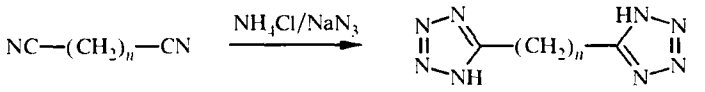
Bi-5-tetrazolyls Obtained from 5-Aminotetrazole. Oxidation of the exocyclic amino group of 5-aminotetrazole by potassium permanganate in an alkaline medium gave disodium salt of azotetrazole, which could also be isolated in the form of pentahydrate [2]. It was reported that this compound can be reduced to 1,2-di(5-tetrazolyl)hydrazine [77]. The lead derivative of tetrazole has been used as the ignition mass in electric primers [78].



The diazotization of 5-aminotetrazole leads to the formation of tetrazolyldiazonium salts, which are distinguished by their high lability and reactivity. The coupling of 5-tetrazolyldiazonium with 5-aminotetrazole leads to 1,3-di(5-tetrazolyl)triazene [79, 80], while coupling with hydrazine leads to bis(diazo-5-tetrazolyl)hydrazine [78], which contains 87.5% of nitrogen in its structure. The last compound is characterized by extremely high sensitivity to impact, friction, and heat.

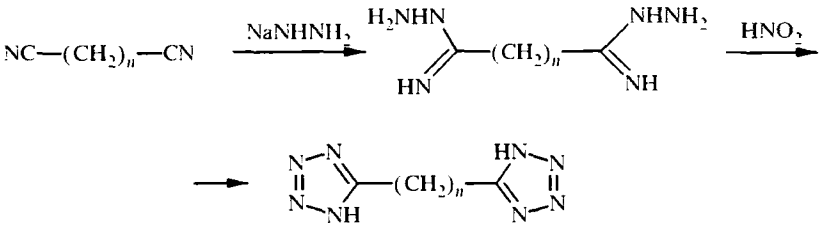
α,ω-Di(5-tetrazolyl)alkanes. The methods for the production of α,ω-di(5-tetrazolyl)alkanes are largely the same as in the case of 5,5'-bitetrazole. As a rule they all come down to two versions: reaction of dinitriles of dibasic carboxylic acids with azides or diazotization of bisamidrazones of these acids.

One of the first methods for the production of di-5-tetrazolylalkyl derivatives involves the prolonged heating of the respective dinitrile and sodium azide in a mixture with acetic acid and isopropyl alcohol at high temperature in a sealed tube [81]. We note that in the classical paper [15] the α,ω-di(5-tetrazolyl)alkanes were synthesized together with the monocyclic compounds. The method was based on the reaction of the respective dinitrile with ammonium azide in DMF.



One representative of α,ω-di(5-tetrazolyl)alkanes – 1,4-di(5-tetrazolyl)butane – was obtained with a small yield by the reaction of adipodinitrile with sodium azide in THF in the presence of aluminum chloride [82].

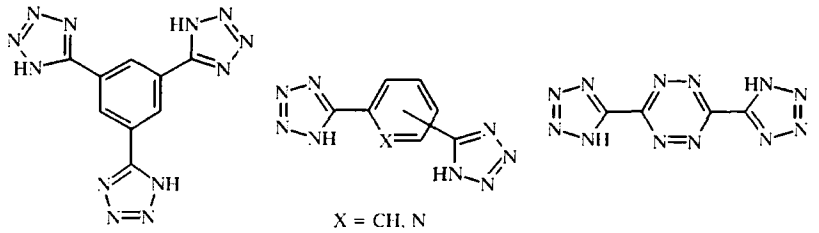
We note that in view of the universality and other advantages of the method described in [15] its modifications are even now irreplaceable in the synthesis of 5-substituted tetrazoles. As far as the production of bitetrazoles by the diazotization of bisamidrazones is concerned, only one publication on this subject is known [83], where the corresponding di-5-tetrazolyl derivatives with the number of methylene units n = 4, 6, and 8 are described.



It has been reported [83] that 3,5-diaminopyrazole was obtained by introducing of bisamidrazone with n = 1 in the reaction, but when n = 2 a difficultly identified mixture of substances was formed.

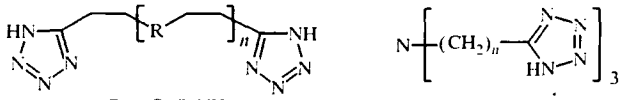
Compounds of the investigated series were proposed as plasticizers for solid rocket fuels [84], antiveiling agents in photographic processes [85, 86], and stabilizers in the thermal decomposition of chlorine-containing thermoplastic molded compositions [87, 88]. In spite of the obvious practical significance of these compounds there is no information on their acid–base characteristics. According to our data, α,ω-di(5-tetrazolyl)alkanes with between one and five methylene groups are dibasic NH acids of medium strength. The first thermodynamic dissociation constants for the given series lie in the range between 3.42 ± 0.01 [pK_a^1 for di(5-tetrazolyl)methane] and 5.30 ± 0.02 [pK_a^1 for 1,5-di(5-tetrazolyl)pentane]. The corresponding second dissociation constants lie in the range between 5.30 ± 0.02 and 6.10 ± 0.03 respectively [89].

NH-Tetrazolyls as Substituents in Arenes and Heteroarenes. Polynuclear tetrazoles used as substrates for the production of polycyclic 1,3,4-oxadiazoles were prepared from the di- and trinitriles of the respective benzoic acids [90-92]. Similarly, the obtained di-5-tetrazolyl derivatives of pyridine found use in medicine as immunodepressants [93, 94]. From amidrazone of 5-tetrazolecarboxylic acid, mentioned earlier as a substrate in the synthesis of 5,5'-bitetrazole, 3,6-di(5-tetrazolyl)-1,2,4,5-tetrazine was obtained [95].



X = CH, N

Aminoalkyltetrazoles. A systematic study of physicochemical properties of di- and tri-5-tetrazolyl-containing compounds is described in a series of papers forming part a series on aminoalkyltetrazoles [96-102] and also in a series of associated papers [103, 104], which examined the synthesis and the acid–base and complexing characteristics of compounds containing terminal NH-tetrazolyl fragments linked by bridging groups (aliphatic chains containing heteroatoms). Such compounds can be assigned to the class of podands in which 5-tetrazolyl fragments serve as terminal donor groups.

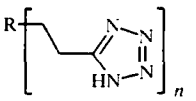


R = O, S, NH
n = 1–4

n = 1, 2

It was shown that they exhibit the characteristics of monobasic NH acids of medium strength and form stable 1:1 complexes with the ions of transition metals. Here, in comparison with standard complexones such polybasic tetrazole ligands form complexes characterized by larger values of the stability constants. On account of these characteristics some of the investigated tetrazoles were proposed for use in analytical chemistry [105-108].

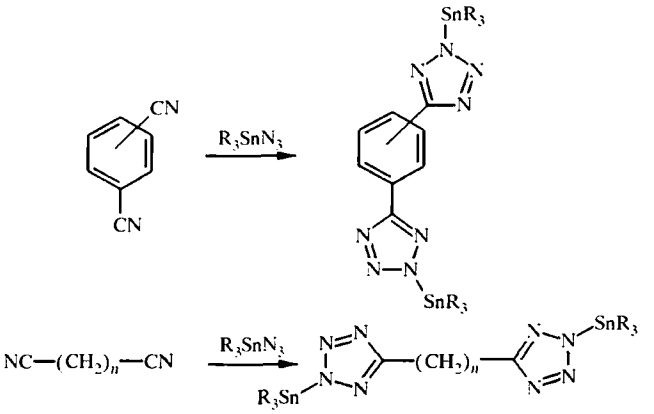
This line has now received motivation for development. Various 2-(5-tetrazolyl)ethyl derivatives have been synthesized, and their physicochemical and chemical characteristics have been studied [89, 109-111].

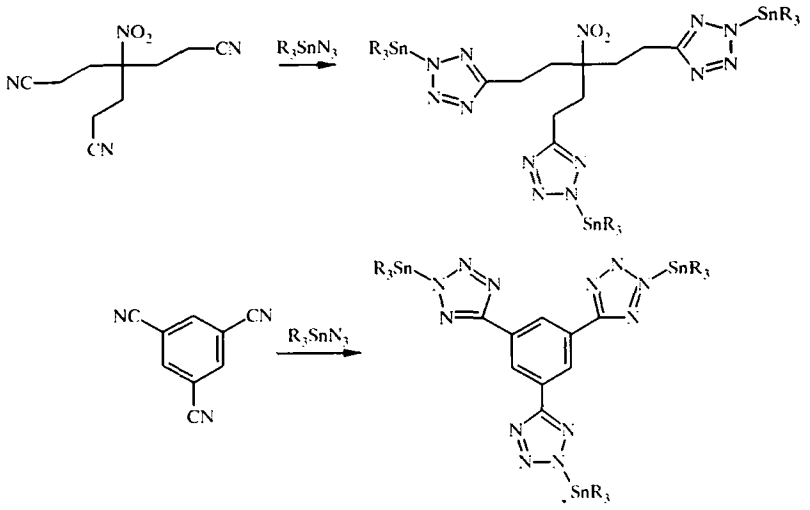


R – derivatives of CH-, OH-, and NH-acids, n = 1–4

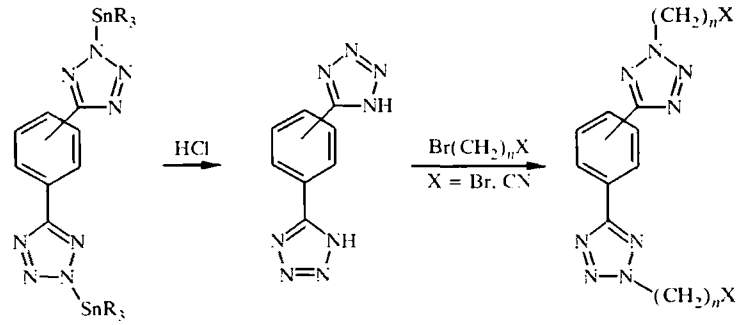
Polyfunctional Tetrazoles from Nitriles and Trialkylstannyl Azides

A detailed investigation of the structure of polyfunctional 2-trialkylstannyl-substituted tetrazoles showed that such compounds form a complex supermolecular crystal structure, having hexameric and pentameric macrocyclic fragments [112-114]. Polynuclear 2,5-disubstituted tetrazoles were obtained by the reaction of the respective nitriles with trialkylstannyl azides (R = Me, Et, *i*-Pr, *t*-Bu).



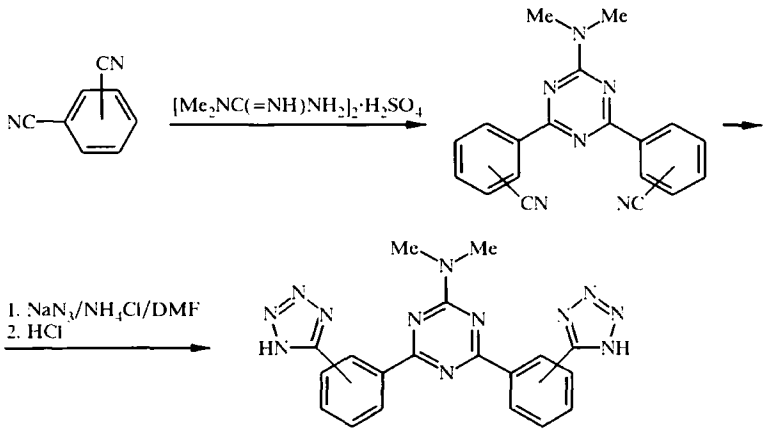


Referring to their unpublished data, the authors report that such 2-trialkylstannyl-substituted bis- and tristetrazoles under the conditions of acid catalyst give the corresponding 5-tetrazolyls, for which the reaction with bromoalkanes was studied [112].



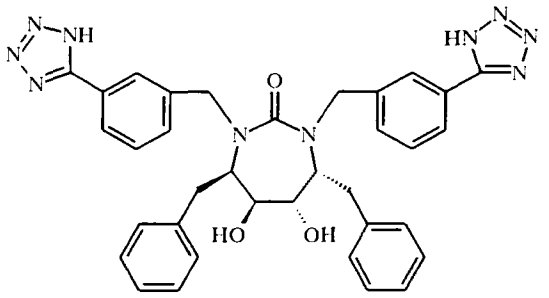
Unfortunately, data on the alkylation of polynuclear 5-tetrazolyl substrates are extremely limited, which is due to the difficulties of isolation and identification of the individual isomers, the number of which exceeds two.

The brief communication [115] describes the production of a series of 2-dimethylamino-4,6-bis[(5-tetrazolyl)phenyl]-1,3,5-triazines with the 5-tetrazolyl rings in various arrangements in the phenylene fragments.



It has been noted that 15 h is sufficient for the complete conversion of benzonitriles containing nitrile groups at the *meta* or *para* positions into the corresponding bitetrazoles, but in the case of the *ortho* isomer the product from cycloaddition at only one nitrile group is isolated. To complete the cycloaddition process with the inclusion of the second nitrile requires a further 48 h.

Dibasic 5-tetrazolyl derivatives are effective agents for the treatment of diabetes [116] and oncological diseases [117]. The corresponding derivatives of cyclic ureas have been proposed as nonpeptide inhibitors of HIV protease [118].



The examined publications make it possible to conclude that polynuclear heterocyclic systems represent complex subjects for investigation. Each of the tetrazole rings is capable of taking part in various types of equilibria and of reacting with electrophiles. Investigation of the heterocyclic compounds requires a detailed study of the structure, acid–base characteristics, and reactivity of the compounds both in the gas phase and in the condensed phase. An intra- and intermolecular hydrogen bond may appear in such polyfunctional systems. Modification of the structure of N-unsubstituted tetrazoles may lead to compounds having unusual structures. One promising direction of investigation is of course the synthesis of macrocyclic tetrazole-containing compounds such as the tetrazolophanes obtained by Ried [119-122] and Butler [123-125] or the tetrazole-containing analogs of 12-crown-4 polyether recently synthesized by ourselves [111].

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