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Dedicated to the Corresponding Member of the Russian Academy of Sciences B. V. Gidaspov on occasion of his 70th anniversary

2-Substituted and 2,5-Disubstituted Tetrazoles

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Abstract—The review summarizes the novel data on preparation methods and chemical characteristics of 2-substituted and 2,5-disubstituted tetrazoles. The most urgent problems in the chemistry of these compounds are analyzed.

I. INTRODUCTION

Outstanding advances of the pharmaceutical chemistry in the last decades are to a large extent due to creation of new medicines whose structure contains a tetrazole ring.

Within this series were found highly efficient antibiotics [1–3], drugs with antiulcer [4, 5] and tuberculocidal [6] activity, compounds that may be used in treatment of diabetes [7], cutaneous fungi [8, 9], cerebral ischemia [10], and other diseases [11–15].

Especially important among the drugs of this series are Losartan and its analogs [16–22]. Losartan is the first representative of nonpeptide blockaders for angiotensine **II**. The extensive use of Losartan in medical practice resulted in crucial positive changes in treatment of cardiovascular diseases.

Preparation of a number of new drugs, first of all, of Losartan and its analogs, and also application of tetrazoles for other uses [23–25] would be impossible without thorough investigation of synthetic methods and physicochemical properties of 2-substituted and 2,5-disubstituted tetrazoles.

However see a small review [26] published about thirty years ago and already out-of-date nowhere in later surveys [27–33] on tetrazole chemistry the title compounds were treated in sufficient detail.

The present article is aimed to fill in the gap between the growing interest in 2-substituted tetrazoles and the lack of summing-up material on the chemistry of these compounds.

The review treats preparation methods and chemical characteristics of 2-substituted and 2,5-disubstituted tetrazoles; therewith the most attention is paid to reports published within the last 10–15 years.

II. PREPARATION METHODS FOR 2-SUBSTITUTED AND 2,5-DISUBSTITUTED TETRAZOLES

II.1. *2-Substituted Tetrazoles*

2-Substituted tetrazoles can be synthesized by several methods: by elimination of substituent in position 5 in 2,5-disubstituted tetrazoles, by oxidation of tetrazole with sodium perborate or by alkylation (arylation) of tetrazole. No direct synthetic methods are known for these compounds.

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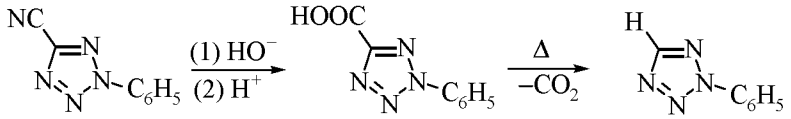
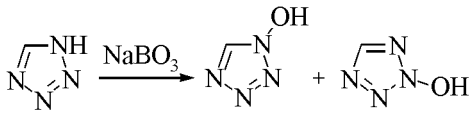
For instance, in an early investigation of tetrazoles it was demonstrated that 2-phenyl-5-cyanotetrazole was cleanly hydrolyzed into 2-phenyltetrazole-5-carboxylic acid whose thermal decarboxylation furnished 2-phenyltetrazole.

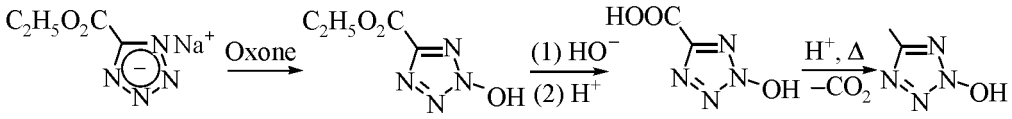


Unfortunately, this method was not further developed and was virtually forgotten. However, elimination of a methyl group in 2-aryl-5-methyltetrazoles by oxidation or substitution of a chlorine atom in 2-aryl-5-chlorotetrazoles effected by such reductant as Li in a mixture *t*-BuOH-THF may turn out quite feasible for preparation of 2-substituted tetrazoles, especially when the other procedures are inefficient.

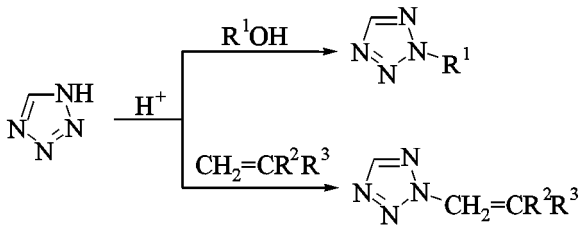


Recently a simple method was described of hydroxy group introduction into the tetrazole ring [35]. It was found that tetrazole oxidation with sodium perborate in the presence of pivalic acid afforded a mixture of 1- and 2-hydroxytetrazoles in 1 : 1.9 ratio.

Somewhat later 2-hydroxytetrazole was shown to arise at oxidation of ethyl tetrazole-5-carboxylate sodium salt with OXONE [36]. The method is exceedingly selective: the 1- and 2-hydroxytetrazoles form in the ratio ~1 : 70.

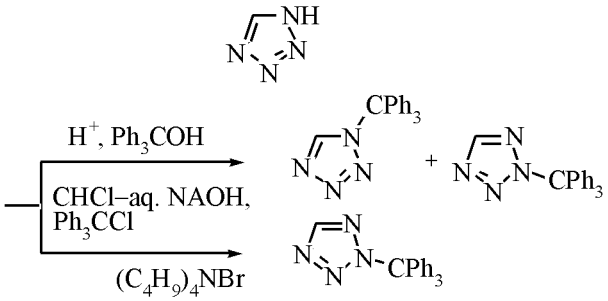


Tetrazole alkylation is among the common methods of 2-substituted tetrazoles preparation. However low selectivity of alkylation obviously reduces the validity of this reaction as universal preparation method for 2-substituted tetrazoles. The data on these reactions were collected up to 1998 in [37]. Below we present the results published within last 3–4 years and also analyze some earlier publications that we consider as important but which have not been mentioned in this review. It was commonly believed quite recently that the ratio of isomeric 1- and 2-alkyltetrazoles arising at alkylation of tetrazole did not depend on the alkylating agent or on the properties of the reaction medium. This concept was rejected when at alkylation of tetrazole with *t*-BuOH, 2-PrOH, and cyclohexanol in 96% sulfuric acid only 2-substituted tetrazoles were obtained [38]. Similarly occurred tetrazole alkylation with propylene and isobutylene [39, 40].



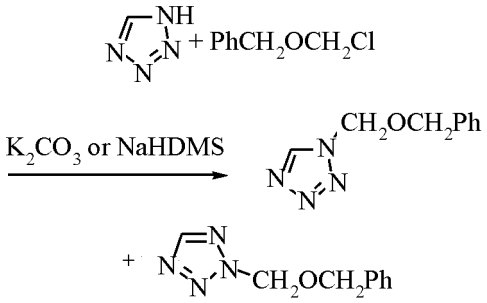
R^1 = *i*-Pr, *t*-Bu, cyclohexyl; R^2 = H; R^3 = Me; R^2 = R^3 = Me.

Very important results were obtained in the study on tetrazole alkylation with triphenylcarbinol in concn. H_2SO_4 [41] and with triphenylchloromethane under conditions of a phase-transfer catalysis [42]. In the first instance formed a mixture of 1- and 2-trityltetrazoles in 1 : 6 ratio, and in the second case a pure 2- substituted isomer was obtained.

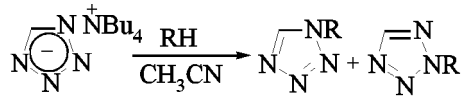


These data are of fundamental importance. It was previously shown at tetrazole alkylation with methyl iodide and dimethyl sulfate under conditions of phase-transfer catalysis that both in uncatalyzed and catalyzed processes formed a mixture of isomeric 1- and 2-methyltetrazoles in ~4 : 6 ratio [43]. The comparison of these results with the data on tetrazole alkylation with triphenylchloromethane reveals that a significant change in regioselectivity of tetrazole alkylation may be expected in reactions occurring along S_N1 mechanism.

Finally, it should be noted that the selectivity of the reaction is somewhat affected by the character of the base. For instance, at tetrazole alkylation with benzyl chloromethyl ether in the presence of sodium or potassium hydroxide the corresponding 1- and 2-alkyltetrazoles arise in ~1 : 1 ratio [44, 45]. In the reaction carried out in the presence of sodium hexametyldisilazide (NaHMDS) the isomer ratio shifted to 1-isomer and equals to ~1.4 : 1 [46].

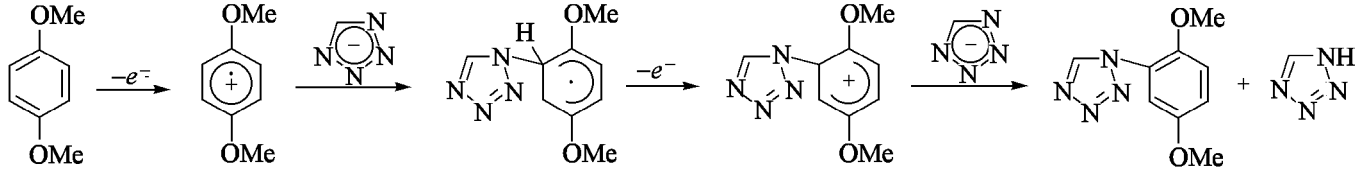


Fundamentally important results were obtained in the study of electrochemical alkylation of tetrazole with 1,4-dimethoxybenzene and 1,3,5-trimethoxybenzene [47]: the corresponding 1- and 2-aryltetrazoles formed in 2 : 3 ratio.



RH = 1,4-$(MeO)_2C_6H_4$, 1,3,5-$(MeO)_3C_6H_3$.

The reaction is presumed to proceed through an intermediately formed cation-radical along $S_{RN}1$ mechanism. It can be regarded as a promising procedure of tetrazoles arylation (on the following scheme a mechanism of N^1-isomer formation is given as for example).



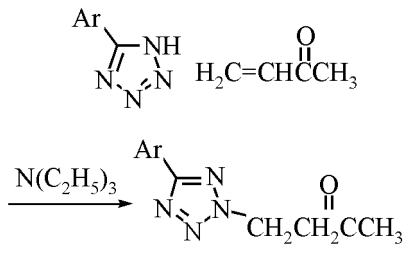
II.2. *2,5-Disubstituted Tetrazoles*

Although the 2,5-disubstituted tetrazoles attract exclusive interest the preparation methods for these compounds are not sufficiently developed. Within last decades not a single new approach was theoretically advanced for building up a tetrazole ring with substituents in positions 2 and 5 of the heteroring. The traditional, well known methods of 2,5-disubstituted tetrazoles preparation from aldehydes arylhydrazones and aryl azides, from aldehydes tosylhydrazones and aryldiazonium salts, from 1,2,3-triazoles, by alkylation (arylation) of 5-substituted tetrazoles, and also some other methods are considered in detail in reviews [26–29, 37].

As seen, the number of methods for 2,5-disubstituted tetrazoles preparation is small. The principal procedure disregarding the difficulty in separation of arising 1,5- and 2,5-disubstituted tetrazoles is alkylation (arylation) of 5-substituted tetrazoles. The other procedures by various reasons are now used only in special cases.

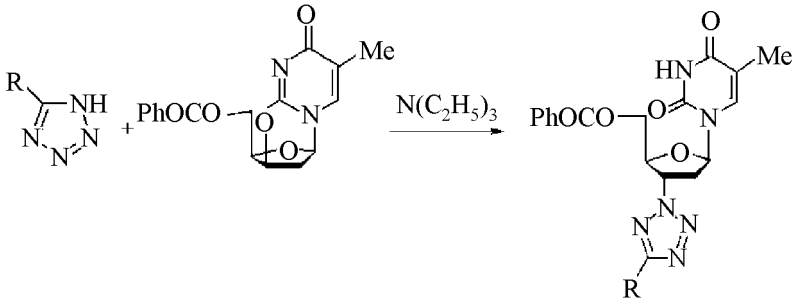
The alkylation of 5-substituted tetrazoles with alkyl halides, esters of sulfuric and arenesulfonic acids, and also with unsaturated compounds in the presence of bases affords isomeric 1,5- and 2,5-disubstituted tetrazoles. The regioselectivity of the process is low [20, 37, 48–50].

The regioselectivity is not affected by performing the reaction under conditions of phase-transfer



catalysis: the ratio of isomeric tetrazoles remains virtually similar [43]. Only some cases are known of these reactions occurring with high selectivity. For instance, alkylation of 5-aryltetrazoles triethylammonium salts with methyl vinyl ketone aforded only 4-(5-aryltetrazol-2-yl)-2-butanones [51].

A similar pattern of the process is observed when 5-substituted tetrazoles triethylammonium salts react with 5'-*O*-benzoyl-2,3'-anhydrothymidine [52].



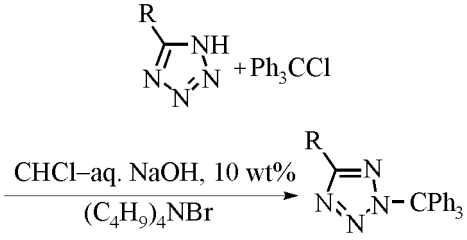
R = Me, Ph, Bn.

Here the high selectivity of alkylation is due first of all to the specific structure of 5-substituted tetrazoles triethylammonium salts where the N^1 atom of the heteroring is blocked by the bulky triethylammonium cation and also to sterical factors in 5'-*O*-benzoyl-2,3'-anhydrothymidine.

These examples serve as an important confirmation of the assumption that the alkylation selectivity of 5-substituted tetrazoles can significantly depend on the spatial structure of reagents, and these factors should be taken into consideration. However this approach is not general because this concept cannot provide understanding of some known facts of high selectivity observed at alkylation of 5-substituted tetrazoles.

At the end of nineteen seventies and the beginning of nineteen eighties when started the extensive application of tetraszoles in the synthesis of versatile pharmaceuticals a problem arose of developing protective methods for the N–H bond in these compounds. The comparison of efficiency of numerous protective groups used in the organic synthesis [53] suggests that protection of the N–H bond in tetrazoles would be best provided by triphenylmethyl (trityl) group. Its protection characteristics are due mostly to sterical factors.

It was demonstrated that in alkylation of 5-substituted tetrazoles with triphenylchloromethane [18, 42, 54–57], triphenylchloromethane on a polymeric support [58], and also with 4,4'-dioxytriphenylchloromethane [59] regardless of the structure of the substituent in position 5 of the hetroring formed exclusively 2-trityltetrazoles. The reaction is carried out in anhydrous tetrahydrofuran [18, 19, 55] or in a two-phase system dichloromethane (chloroform)–aqueous NaOH in the presence of tetrabutylammonium [59].

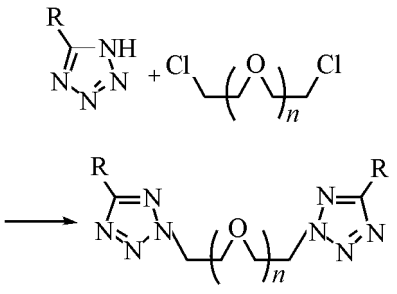


R = Alk, Ar, Het.

It should be stressed that in the preparative respect the phase-transfer catalysis is obviously more attractive for here can be avoided such disadvantages of the noncatalytic procedures as the use of anhydrous solvents and carrying out the reactions under inert gas atmosphere.

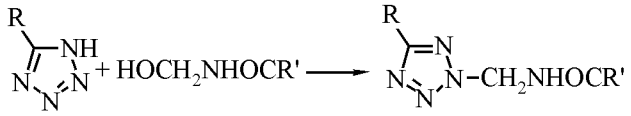
It is presumable that tritylation of 5-substituted tetrazoles follows S_N1 mechanism. In this case the limiting stage consists in triphenylchloromethane ionization providing triphenylmethyl cation characterized by high thermodynamic stability. At the same time the more stable is the carbocation the higher is its selectivity toward one of the two competing nucleophilic centers [60]. It is probably just the reason of the high alkylation selectivity of 5-substituted tetrazoles with triphenylchloromethane.

Basing on certain reasons to this type reactions should be assigned also the reactions of 5-substituted tetrazoles with chloroethyl ethers [61]:



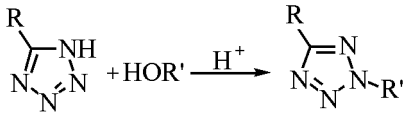
R = Ar; *n* = 1–3.

and with aliphatic and aromatic carboxylic acids *N*-hydroxymethylamides [62, 63] that also occur with high selectivity.



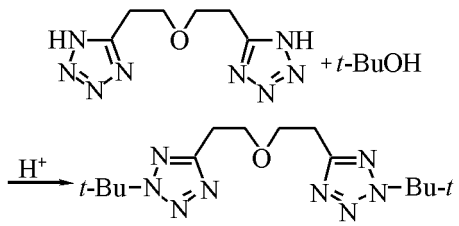
R = NO_2, Ar: R' = Me, $CH{=}CH_2$, Ar.

Highly efficient is also preparation of 2,5-disubstituted tetrazoles by alkylation of 5-substituted tetrazoles with alcohols or unsaturated compounds in the presence of concn. H_2SO_4 or $HClO_4$ [37–41, 64].

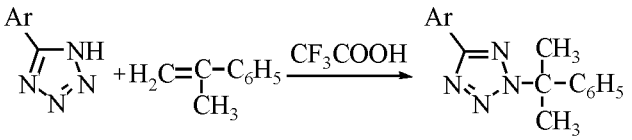


R = Alk, Ar; R' = *i*-Pr, *t*-Bu, Ph_3C.

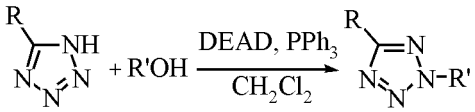
The method is of sufficiently general character and can be used for preparation both of mono- and ditetrazoles [65, 66].



Besides the 2,5-disubstituted tetrazoles formed in very high yield in reaction of 5-aryltetrazoles with α-methylstyrene in the presence of trifluoroacetic acid [67].

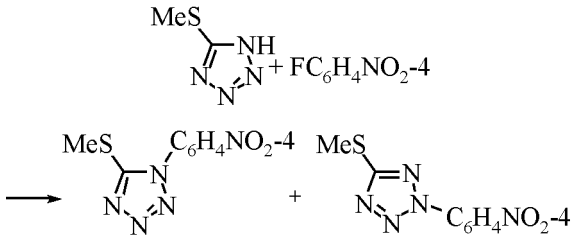


Finally the attention should be drawn to yet another, although preparatively difficult, method of 2,5-disubstituted tetrazoles synthesis, namely, to Mitsunobu alkylation [68]. The procedure consists in treating of 5-substituted tetrazoles with alcohols in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine under inert gas atmosphere [69]. 2,5-Disubstituted tetrazoles under these conditions form in 59–74% yield, but the reaction cannot occur with sterically hindered alcohols.

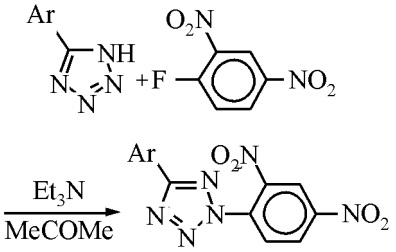


R = Alk, Ph, PhNH; R' = Alk.

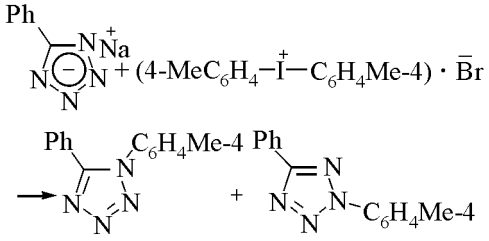
Arylation of 5-substituted tetrazoles for preparation of 2-aryl derivatives did not gain acceptance up till now. However it is due mostly to low nucleophilicity of tetrazolides, and in some cases to the spatial shielding by the substituents in the position 5 of the heteroring. Our data show that numerous attempts to arylate 5-phenyltetrazole with 4-nitrofluorobenzene both under homogeneous conditions and under conditions of phase-transfer catalysis failed. At the same time the heating of 5-methylsulfanyltetrazole with 4-nitrofluorobenzene in DMF in the presence of sodium hydroxide gave rise to 5-(methylsulfanyl-1-(4-nitrophenyl)- and 5-(methylsulfanyl-2-(4-nitrophenyl)-tetrazoles in 1 : 3 ratio in an overall yield 50% [70].



Under very mild conditions and in practically quantitative yield 5-aryltetrazoles are arylated with 2,4-dinitrofluorobenzene [71].



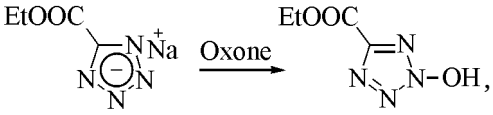
Separate place in this reaction series belongs to reactions of 5-phenyltetrazole arylation with diaryliodonium salts. It was shown that a reaction between 5-phenyltetrazole sodium salt with bis(4-methylphenyl)iodonium bromide in *t*-BuOH furnished the corresponding isomeric 1- and 2-aryltetrazoles in ~1 : 1 ratio and overall yield about 30% [72].



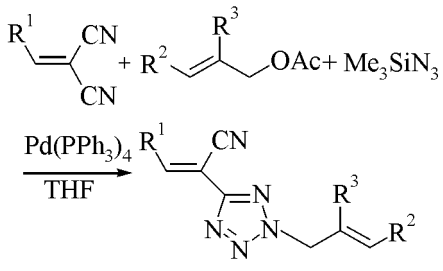
At the same time the arylation of 5-phenyltetrazole ammonium salt with bis(4-methoxyphenyl)iodonium bromide in methanol afforded only 2-(4-methoxyphenyl)-5-phenyltetrazole [73].

Finally, the last process that should be mentioned is the electrochemical alkylation of 5-phenyltetrazole with 1,4-dimethoxybenzene. Under these conditions unlike the case of unsubstituted analog (Section II.1) was obtained only 2-(2,5-dimethoxyphenyl)-5-phenyltetrazole in 44% yield [47].

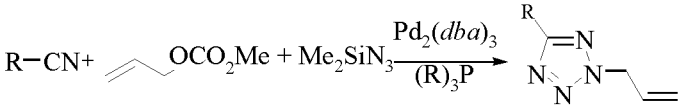
Among the preparation methods for 2,5-disubstituted tetrazoles a lot less known than the above cited should be mentioned the OXONE oxidation of ethyl tetrazole-5-carboxylate sodium salt [36]:



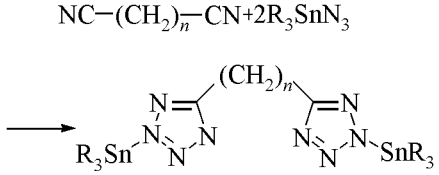
the treating of a mixture of alkyl- or arylmethylenemalononitriles and allyl acetate with trimethylsilyl azide in the presence of a palladium catalyst [74]:



a version of the above method consisting in reaction of various nitriles with allyl methyl carbonate and trimethylsilyl azide [75],



and also nitrile reaction with trialkyltin azides [76–79]:



R = Me, Et, *i*-Pr, *t*-Bu; *n* = 1–6.

III. CHEMICAL PROPERTIES OF 2-SUBSTITUTED AND 2,5-DISUBSTITUTED TETRAZOLES

To 2-substitueted and 2,5-disubstituted tetrazoles belongs somewhat separate place in the tetrazole series with respect to their chemical properties. This is due to specific features in the electronic structure [80–82], dipole moments [40, 83], enthalpies of formation [40, 84] and some other physicochemical characteristics [85] of these compounds as compared to their isomers 1-substituted and 1,5-disubstituted tetrazoles. The most significant difference is observed in reactions with electrophilic reagents, acids, in thermal transformations and some other processes.

We consider below the chemical properties of 2-substituted and 2,5-disubstituted tetrazoles. We discuss in succession the electrophilic and nucleophilic substitution at the carbon atom in the heteroring and in the side chain, the reactions of these compounds with acids, treatment with oxidants, thermal transformations of 2,5-disubstituted tetrazoles, and some other reactions.

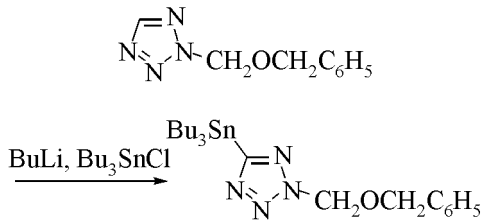
III.1. *Electrophilic Substitution*

Electrophilic substitution at the carbon atom of the heterocycle is among the best studied reactions in tetrazole chemistry

It is remarkable that 1-substituted tetrazoles relatively readily undergo mercuration with mercury salts [27, 86], iodination with iodine in the system $KMnO_4$–H_2SO_4 [87], enter into aminomethylation reaction [88].

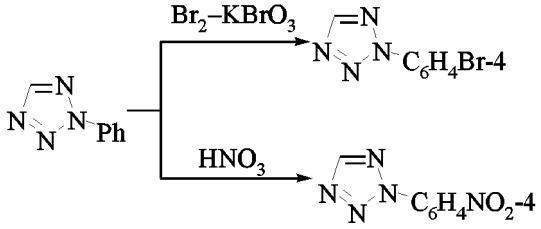
At the same time these reactions are regarded as unusual for 2-substituted tetrazoles although these assumptions do not agree with the data on electronic structure of these compounds [81]. In this connection a single as yet example should be mentioned of electrophilic substitution at the carbon atom of the heterocycle in 2-substituted tetrazole. It was

demonstrated that successive treatment of 2-benzyloxymethyltetrazole with butyllithium and tributyltin chloride afforded in 67% yield the corresponding 2,5-disubstituted tetrazole [45].



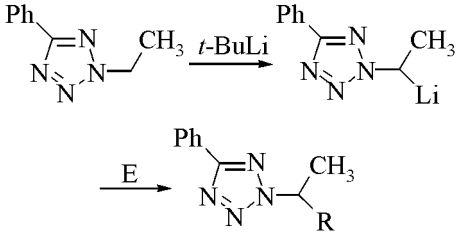
The information on electrophilic substitution in the side chain of 2-substituted tetrazoles is also very scanty.

It is known that treating 2-phenyltetrazole with a mixture of bromine and potassium bromate or with nitric acid provided respectively 2-(4-bromophenyl)- and 2-(4-nitrophenyl)tetrazoles [26, 89].

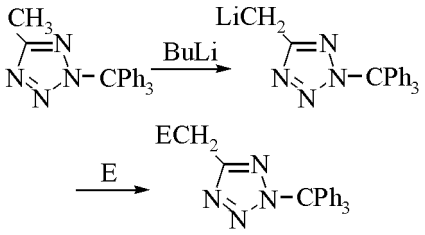


The electrophilic substitution was studied in more detail in the series of 2,5-disubstituted tetrazoles. On examples from the series of 2-alkyl-5-phenyl- and 5-methyl-2-trityltetrazoles was carried out successive treatment with *tert*-*p*-butyllithium or butyllithium in THF at −78°C and then with benzaldehyde or some other electrophile to obtain the corresponding adducts in high yield [57, 90].

It is of fundamental importance that this reaction can be performed with quite different electrophilic reagents, from alkyl halides aliphatic and aromatic aldehydes and ketones to trimethylchlorosilane and bromine.

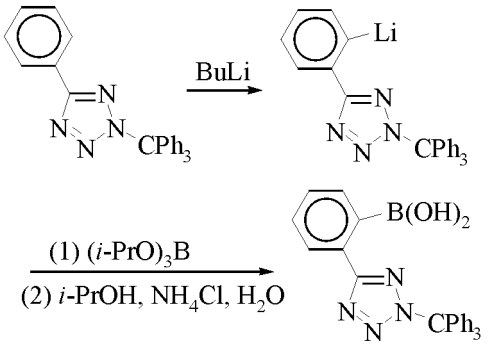


E = HCHO, EtCHO, PhCHO, Me_3SiCl.

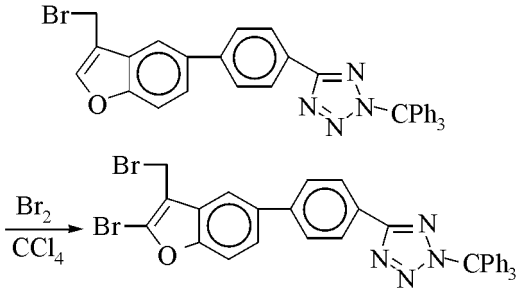


E = Br_2, PhCHO, PhCH2Br, Me3SiCl.

As one more example of electrophilic substitution in the series of 2-disubstituted tetrazoles may be cited the formation of 5-(2-boranophenyl)-2-trityltetrazole from 2-trityl-5-phenyltetrazole and triisopropyl borate shown below [54, 55].



Finally, several instances of 5-aryl-2-trityltetrazoles bromination with bromine in CCl_4 was described [18].

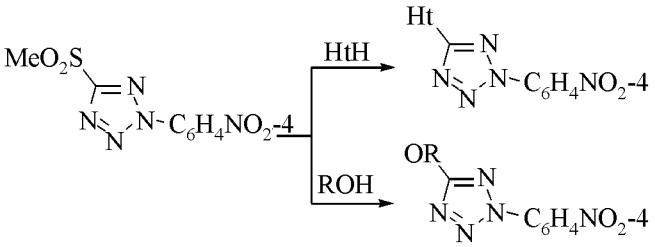


III.2. *Nucleophilic Substitution*

The nucleopphilic substitution at the carbon atom of the heteroring in 2,5-disubstituted tetrazoles was not systematically studied lately.

The investigation of 5-bromo-1-methyl- and 5-bromo-2-methyltetrazoles reactivity toward nucleophiles of different character showed that the bromine replacement by hydroxide ion occurred with greater difficulty in the 2-methyl derivative than in 1-methyl one [91]. Similar behavior of these substrates was

observed in the study of their reaction kinetics with piperidine [92]. These results are well consistent with

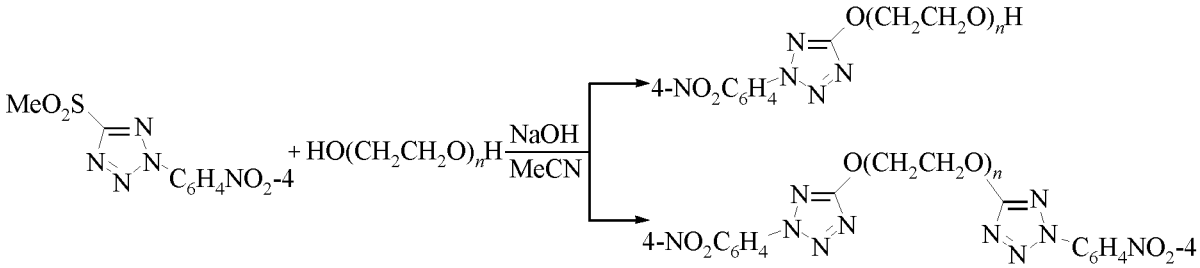


Ht piperidine-1-yl, benzimidazole-1-yl; R = Me, Et, *i*-Pr, Bu.

The data recently obtained in the study of chemical properties of isomeric 1- and 2-aryl-5-methylsulfonyltetrazoles [93–97]. It was shown by a number of examples that reaction of 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole with N- and O-nucleophiles afforded in good yield the corresponding 2,5-disubstituted tetrazoles [96, 97].

The conditions of these reactions depend primarily on the nucleophile character. The methylsulfonyl group is cleanly replaced with piperidine at heating without a solvent. With such nucleophiles as benzimidazole and alcohols the desired products are obtained by performing reaction in acetonitrile or in the respective alcohol in the presence of sodium hydroxide.

It should be added to the above stated that 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole in the presence of NaOH cleanly reacted with such nucleophiles as ethylene glycol, di- and triethylene glycols, and depending on the reagents ratio products of mono- or disubstitution were obtained [97].

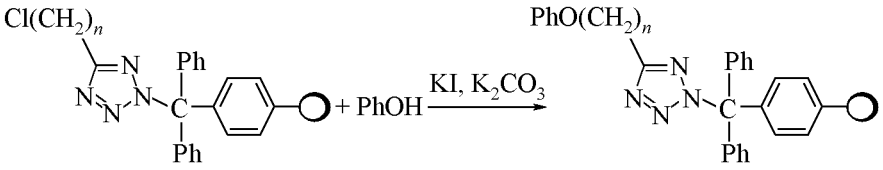


n = 1–3.

And, finally, in nucleophilic substitution at the carbon atom of the hetrocycle the 2.5-disubstituted tetrazoles are a lot less reactive than their isomers, 1,5-disubstituted derivatives. The difference is obviously caused by dissimilar electronic structure of these compounds [81, 82].

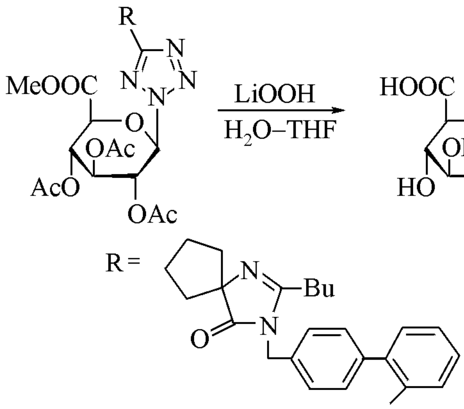
Nucleophilic substitutions in the side chain of 2,5-disubstituted tetrazoles may be illustrated by several most characteristic examples.

A chlorine atom in 2-phenyl-5-chloromethyltetrazole under mild conditions is replaced by iodine (Finkelstein reaction) and then the iodine is substituted by treating with aniline or piperidine to afford the corresponding 5-amino-2-phenyltetrazoles [26]. The chlorine in 5-(α-chloroalkyl)tetrazoles tritylated with triphenylchloromethane on polymeric support is as cleanly substituted by such nucleophiles as phenols, thiophenol, phthalimide, and 5-phenyltetrazole [58].

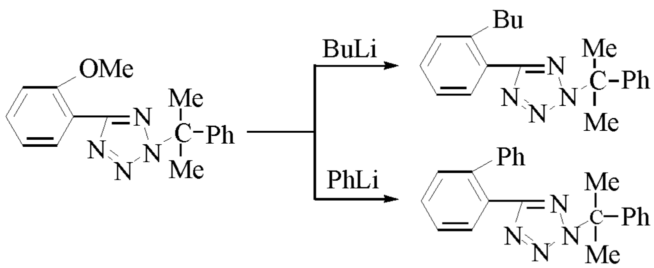


n = 3–6.

Another example of nucleophilic substitution in a side chain of 2,5-disubstituted tetrazoles is deprotection of carboxy and hydroxy groups by treating with lithium hydroperoxide in aqueous THF. The reaction occurs quantitatively under mild conditions and the other important feature is that the reaction leaves intact the other functional groups [20].

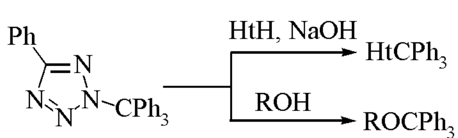


In aromatic nucleophilic substitution the methoxy group is a difficultly leaving group. However the presence in the aromatic substrate of a tetrazole ring in an *ortho*-position to the methoxy group notably increases its reactivity with respect to nucleophilic reagents. For instance, the treatment of 2-cumyl-5-(2-methoxyphenyl)- or 2-cumyl-5-(2,3-dimethoxyphenyl)tetrazoles with butyllithium or phenyllithium at room temperature in a mixture of ether with hexane gave rise to the corresponding 2,5-disubstituted tetrazoles [67].

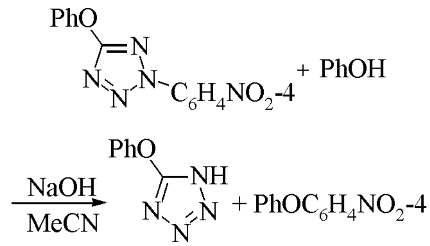


It should be noted in conclusion that the reactivity of 2,5- disubstituted tetrazoles towards nucleophilic reagents is to a large extent determined by the character of the substituent in the *2* position of the heteroring It was demonstrated that the tetrazole ring in 5-aryl-2-benzoyltetrazoles easily underwent substitution by N- and O-nucleophiles of various structure, and therefore these compounds were used as efficient acylating agents [98].

In a similar process heterocyclic substrates containing an N–H bond and alcohols undergo tritylation in eaction with 2-trityl-5-phenyltetrazole [42].



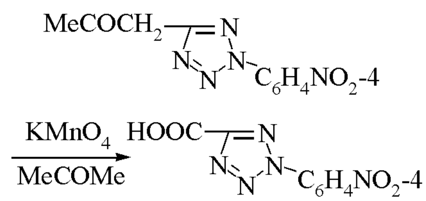
Another example of such transformations consists in nucleophilic substitution of the tetrazole ring in 2-(4-nitrophenyl)-5-phenoxytetrazole at treatment with a phenoxide ion in acetonitrile in the presence of sodium hydoxide [96].

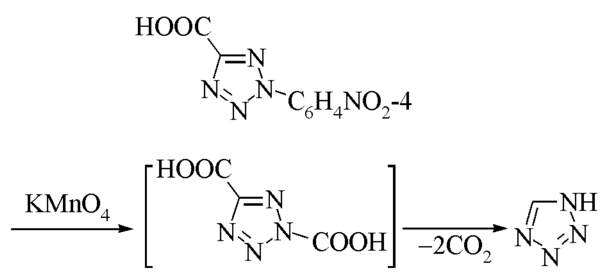


III.3. *Reactions with oxidants*

The tetrazole ring of 2,5-disubstituted tetrazole is stable against oxidation.

Some reactions of these compounds with such oxidants as potassium permanganate and lead tetraacetate described in early publications [26] are considered below.



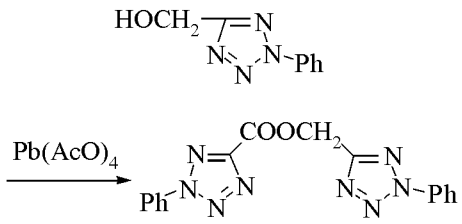


It is presumed that at the treatment of [2-(4-aminophenyl)tetrazole-5-yl]carboxylic acid with potassium permanganate the phenyl substituent suffers an oxidative degradation to yield a dicarboxylic acid whose decarboxylation results in tetrazole. However this way of tetrazole formation is dubious for the exclusively high resistance to oxidation of the phenyl ring is well known.

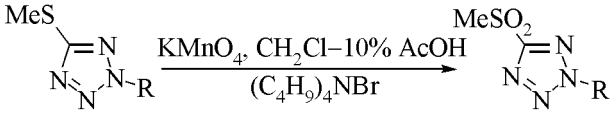
Therefore it is obvious that the reaction mechanism should be refined for the information thus obtained may be crucial for understanding of numerous

specific features in the chemical behavior of 2,5-disubstituted tetrazoles.

The characteristic behavior of 2,5-disubstituted tetrazoles in oxidation reactions can be revealed also by an example of 5- hydroxymethyl-2-phenyltetrazole. Thus, this oxidation with lead tetraacetate cannot be stopped at the stage of aldehyde formation, and the process results in an ester.

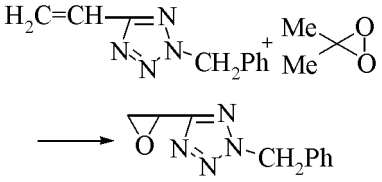


Much later the potassium permanganate was successfully used for oxidation of 5-methylthiotetrazoles under conditions of the phase-transfer catalysis to furnish the corresponding sulfones [70].

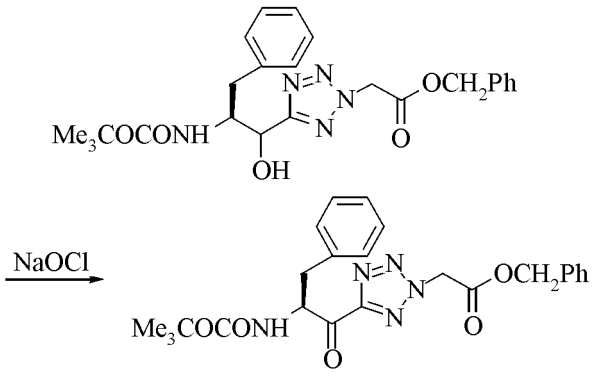


R = 4-$NO_2C_6H_4CH_2$, 4-$NO_2C_6H_4$.

A highly efficient epoxidizing oxidant generated *in situ*, dimethyldioxirane, in reaction with 2-benzyl-5-vinyltetrazole provided the corresponding epoxide [99].

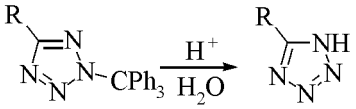


The oxidation of biologically active tetrazole-containing substrates of sophisticated structure in a system tetramethylpiperidine N-oxide – sodium hypochloride – potassium bromide provides a possibility to convert secondary alcohols into the corresponding ketones. An important feature of this process is that the other functional groups remain intact [50].



III.4. *Reactions with Acids*

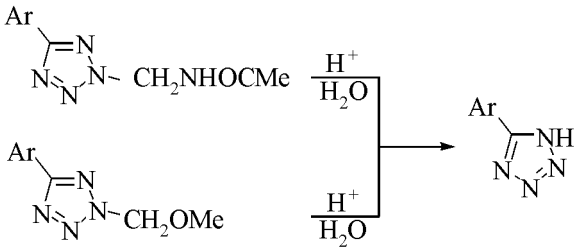
The stability of 2,5-disubstituted tetrazoles against acids depends on the character of the substituent in the *2* position of the heterocycle. Thus 5-aryl-2-methyltetrazoles dissolved in 20–45% sulfuric acid at 20°C remain unchanged for several days [100, 101]. However at the presence in the tetrazole ring in the *2* position such substituents as dimethylphenylmethyl [67], triphenylmethyl [42, 55-57, 102], and 4,4'-dimethoxytriphenylmethyl [59] groups the stability of the compounds toward acids changes drastically. Actually, at the treatment of 5-alkyl(aryl)-2-trityltetrazoles with trifluoroacetic [55, 58], hydrochloric [42, 57, 102], or sulfuric [55] acid occurred their hydrolysis under mild conditions.



R = Alk, Ar.

According to our data under similar conditions takes place hydrolysis of 5-aryl-2-acetylaminomethyl- and 5-aryl-2-methoxymethyltetrazoles.

An exception from this series of tetrazoles is 2-hydroxytetrazole-5-carboxylic acid that at heating with hydrochloric acid undergoes decarboxylation into 2-hydroxytetrazole [36].



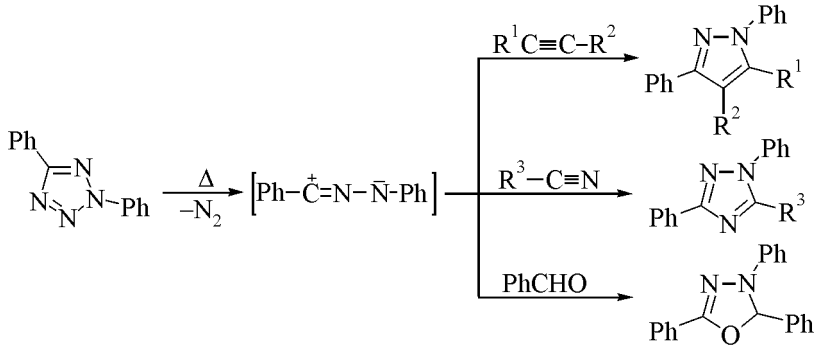
III.5. *Thermal Transformations of 2,5-Disubstituted Tetrazoles*

The investigation of thermal transformations occurring with nitrogen-containing heterocycles is among the most promising and extensively developing lines of research in the chemistry of heterocyclic

compounds [32, 103–110]. Already for over forty years, starting with the pioneering studies of Huisgen, the tetrazoles have been the most interesting subjects of this research. Just the data obtained in the study on thermolysis of 2,5-disubstituted tetrazoles [111, 112] underlie the general fundamental concept of formation of 1,3-dipoles and their participation in the reactions of 1,3-dipolar cycloaddition, 1,5- and 1,7-electrocyclization [113].*

The thermolysis of 2,5-disubstituted tetrazoles is a general preparative procedure for synthesis of versatile heterocyclic compounds: pyrazoles, 1,2,4-triazsoles, 1,3,4-oxadiazoles, and other heterocyclic substrates [26, 103–105, 113].

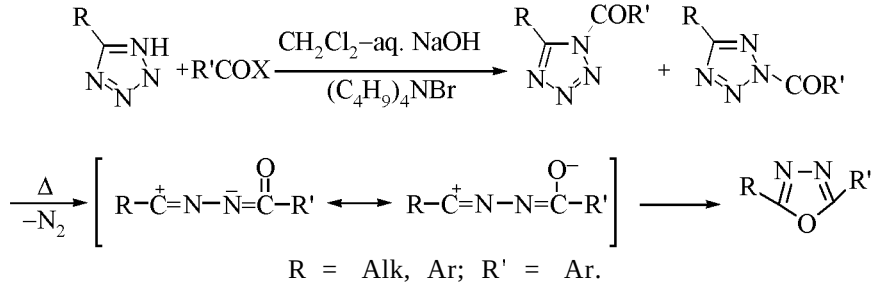
The studies of thermolysis of 2,5-disubstituted tetrazoles in the recent decades were centered primarily on the mechanistic problems of the thermal transformations of *N*-acyl- and *N*-imidoyltetrazoles



and on the synthetic prospects of the reaction [103, 104, 110].

It was shown experimentally that the previously assumed formation of *N*-acyltetrazoles in reaction of 5-substituted tetrazoles with acylating agents in the presence of bases [111, 112] actually occurred. The *N*-acyltetrazoles were obtained, isolated, and identified at acylation of 5-substituted tetrazoles under conditions of the phase-transfer catalysis [98, 116–118].

In a later study the formation of *N*-acyltetrazoles in acylation of 5-substituted tetrazoles in a gas phase was confirmed by mass spectrometry [119]. It was also found that acylation of 5- substituted tetrazoles under conditions of the phase-transfer catalysis resulted in a mixture of isomeric 1- and 2-acyltetrazoles with 2-isomer prevailing. The thermolysis of this mixture in toluene or *m*-xylene disregarding isomer ratio gave rise to 1,3,4-oxadiazoles in 90–98% yield.



R = Alk, Ar; R' = Ar.

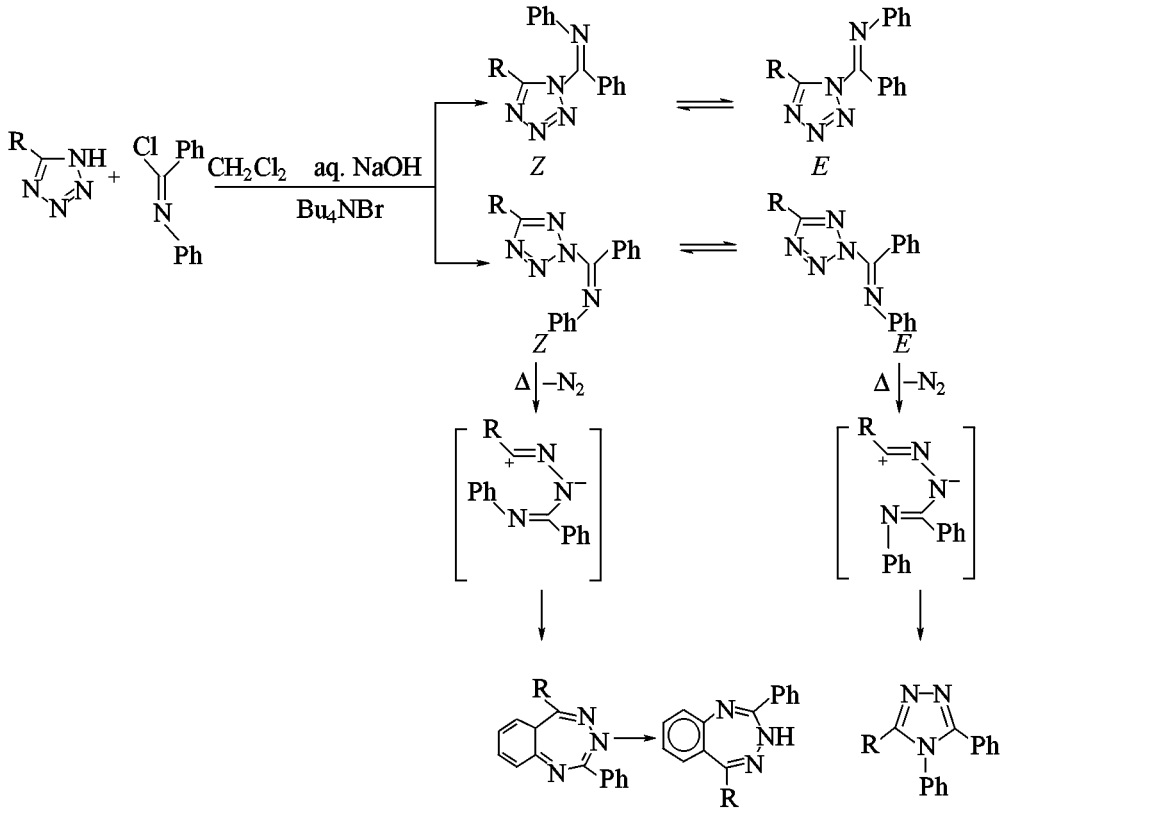
The consideration of the large body of experimental data obtained in the recent years suggests that the thermolysis of the *N*-acyltetrazoles may be regarded as one of the most simple and efficient methods of synthesis of 1,3,4-oxadiazoles of various structures [104, 120–125].

In the recent years alongside the studies on the thermal transformations of N-acyltetrazoles fundamental investigations were carried out concerning the

* Taking into consideration the outstanding contribution of Professor R. Huisgen into development of the 1,3-dipole concept and the great importance of the 1,3-cycloaddition reaction for the chemistry of heterocyclic compounds the reaction was later named "Huisgen reaction" [114, 115].

thermolysis mechanism of *N*-imidoyltetrazoles and application of this reaction to the synthesis of hard-to-obtain 3*H*-1,3,4-benzotriazepines.

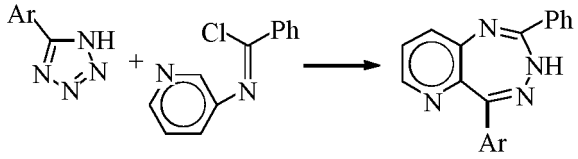
In 1960 Huisgen et al demonstrated that the heating of 5-substituted tetrazoles with imidoyl chlorides in pyridine gave rise to 1,2,4-triazoles in good yield



[126]. It was presumed that in the first stage of the reaction arose *N*-imidoyltetrazoles which further transformed into 1,2,4-triazoles.

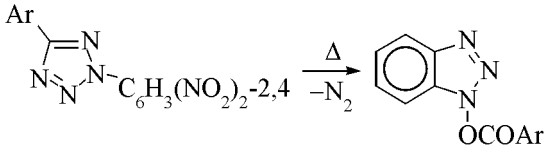
However it was found later that the heating to 100–110°C of *N*-imidoyltetrazoles prepared by treating 5-substituted tetrazoles with imidoyl chlorides in pyridine at the cold [127] or by phase-transfer catalysis with the same reagents [103, 128–131] afforded instead of the expected 1,2,4-triazoles the previously unknown 3*H*-1,3,4-benzotriazepines in a high yield. These results may be rationalized as follows. Under conditions of the phase-transfer catalysis the reaction of 5-substituted tetrazoles with imidoyl chlorides furnished 1- and 2-imidoyltetrazoles as a mixture of *Z*- and *E*-conformers At heating of the mixture the 1-imidoyltetrazoles isomerized into 2-imidoyl derivatives that further suffer transformations along two paths. The thermolysis of *Z*-conformers resulted in 3*H*-1,3,4-benzotriazepines, *E*-conformers furnished 1,2,4-triazoles. The ratio of the thermolysis products depends both on the conformers ratio and on the difference in the rate constants of reactions of these compounds.

The comparison of various procedures for preparation of 1,3,4-benzotriazepines suggests that the thermolysis of *N*-imidoyltetrazoles is one of the most available ways of building up the benzotriazepine system, and our data show that it is suitable also for the synthesis of 3*H*-pyrido[6,7-*b*]-1,3,4-triazepines.

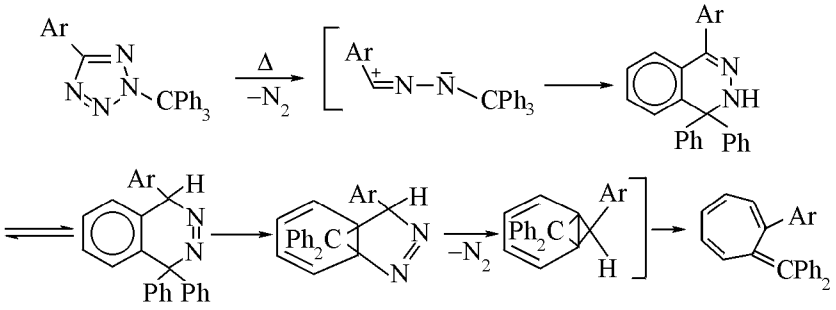


In continuation of discussion on the problems of the thermal transformation of 2,5-disubstituted tetrazoles it should be noted that the reactivity of 1,3-dipoles arising at thermolysis of these substrates notably depends on the character of the substituent in

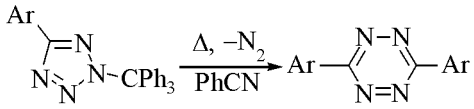
the *2* position of the heteroring and on the properties of the reaction medium. These trends are obviously seen by the example of 5-aryl-2-(2,4-dinitrophenyl)-tetrazoles [71] and some other compounds from this series.



The thermal transformation of 5-aryl-2-tritiltetrazoles takes an unusual route. At heating of the compounds in dodecene to 180°C arise 1-aryl-8,8-diphenylheptafulvenes:



whereas at replacing benzonitrile for dodecane the reaction furnished 3,6-disubstituted 1,2,4,5-tetrazines [42].



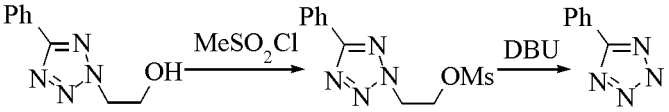
Finally the last fact that should be mentioned is the thermolysis of 2-alkenyl-5-R-tetrazoles to give the corresponding pyrazoles [132, 133].

III.6. *Other Reactions*

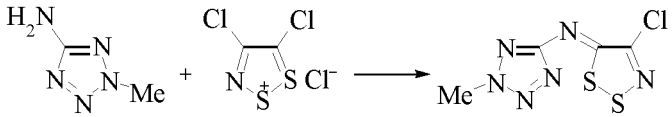
Further we discuss the reactions of 2-substituted and 2,5- disubstituted tetrazoles that were not collected into separate sections due to their small number.

Among these reactions are transformations of 2-phenyltetrazole-5-carboxylic acid typical for ordinary carboxylic acids and also reduction of a nitro group in 2-(4-nitrophenyl)tetrazole and some other processes [26].

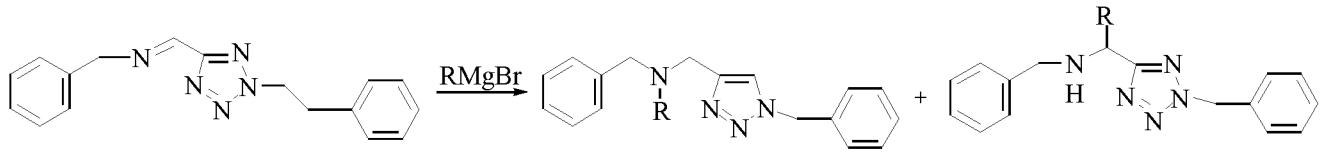
Among reactions of 2,5-disubstituted tetrazoles that were studied lately the dehydration of hydroxyalkyltetrazoles into the corresponding alkenyl derivatives should be mentioned [132]:



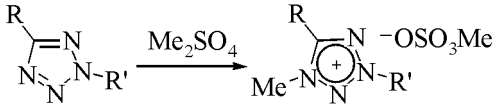
then the reaction of 5-amino-2-methyltetrazole with 4,5-dichloro-1,2,3-dithiazolium chloride [134]:



and also Grignard reagents addition to 2-benzyltetrazole imine [135].



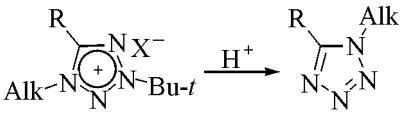
2-Substituted and 2,5-disubstituted tetrazoles similarly to isomeric 1-substituted and 1,5-disubstituted derivatives undergo quaternization when treated with such alkylating agents as dimethyl sulfate and triethyloxonium tetrafluoroborate. Therewith the



R = H, Alk, Ar; R' = Alk.

corresponding 2,4,5-trisubstituted tetrasolium salts are obtained [66, 136, 137].

Note that successful occurrence of these reaction depends to a great extent on the structure of the substituent in the 2 position of the heterocycle. It was shown that 2-trityl-5-phenyltetrazole did not undergo quaternization when heated with dimethyl sulfate to 100°C for several hours [42] whereas the less sterically loaded substrates, 2-(*tert*-butyl)-5-R-tetrazoles, cleanly react with dimethyl sulfate at 60°C [137]. It should be noted that tetrazolium salts containing in 2 position of the heterocycle a *tert*-butyl group at treating with concn. HCl are converted into the corresponding 1,5-disubstituted tetrazoles [137].



2-Substituted and 2,5-disubstituted tetrazoles form complexes with metals. These compounds are significantly less studied than the complexes of 1,5-disubstituted tetrazoles. It was noted that the 2-substituted tetrazoles are less prone to complexing than their 1-substituted isomers [138]. The complexes of 5-vinyl-2-methyltetrazole with Cu(II), Ni(II), Co(II) and Pd(II) chlorides were investigated. It was shown that the metal ion coordination occurred at the nitrogen in position 4 of the heteroring [139, 140]. Recently complexes were described of 2-methyl-5-(2-pyridyl)- and 2-*tert*-butyl-5-(2-pyridyl)tetrazoles with Pd(II) chloride and Ru(II) bipyridine chloride [141].

IV. CONCLUSION

Main trend in the present development of tetrazole chemistry is the search for entirely new routes to building up of the tetrazole ring and application of the tetrazole-containing substrates to medical practice.

The reason of it lies in the fact that the traditional methods of tetrazoles preparation are to a large extent exhausted. It is true first of all with respect to 2-substituted and 2,5-disubstituted derivatives. It is obvious that the lack of new efficient synthetic procedures for 2-substituted and 2,5- disubstituted tetrazoles is the most urgent problem hampering further studies of physicochemical characteristics and application fields of these compounds. Therewith certain positive trends in this respect are seen consisting in attempts to use new synthetic approaches and reagents in preparation of 2,5-disubstituted tetrazoles.

It concerns primarily the successful use of metal complexes as catalysts for the synthesis of 2,5-disubstituted tetrazoles carried out within the last 2–3 years, and also the studies on 5- tetrazoles alkylation with alcohols and unsaturated compounds in the presence of acid catalysts.

Among the studies treating new aspects of tetrazole chemistry should be mentioned the research on thermal transformation of *N*-imidoyl- and 2-tritiltetrazoles opening unexpected possibilities of application of 2,5-disubstituted tetrazoles to organic synthesis.

Finally, the analysis of the trends in development of tetrazole chemistry suggests that in the next decade much more attention will attract the study of 2,5-disubstituted tetrazoles than it has happened before, and it is also presumable that the practical applications of these compounds also will be extended not only in the medicine

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REFERENCES

1. Yakovlev, V.P. and Kaplar-Vuchevats M., *Antibiotiki i khimioterapiya*, 1994, no. 39, p. 56.
2. Navashin, S.M., *Antibiotiki i khimioterapiya* (1,2-Antibiotics and Chemotheraphy), 1995, no. 40, p. 11.
3. Mimura, H., Gato, K., Kitamura, S., Kitagava, T., and Kohda, S., *Chem. Pharm. Bull.*, 2002, no. 50, p. 766.
4. Uchida, M., Komatsu, M., Morita, S., Kanbe, T., Yamasaki, K., and Nakagawa, K., *Chem. Pharm. Bull.*, 1989, no. 37, p. 958.
5. Ueda, I., Ishii, K., Sinozaki, K., Seiki, M., and Hatanaka, M., *Chem. Pharm. Bull.*, 1991, no. 39, p. 1430
6. Waisser, K. and Kunes, J., Hrabálek, A., Machacek, M., and Odlerova, Z., *Coll. Czech. Chem. Commun.*, 1996, no. 61, p. 791.
7. Momose, Y., Maekawa, T., Odaka, H., Ikeda, H., and Sohda, T., *Chem. Pharm. Bull.*, 2002, no. 50, p. 100.
8. Ichikawa, T., Kitazaki, T., Matsushita, Y., Hosono, H., Yamada, M., Mizuno, M., and Itoh, K., *Chem. Pharm. Bull.*, 2000, no. 48, p. 1947.
9. Ichikawa, T., Yamada, M., Yamaguchi, M., Kitazaki, T., Matsushita, Y., Higashikawa, K., and Itoh, K., *Chem. Pharm. Bull.*, 2001, no. 49, p. 1110.
10. O'Neill, M.J., Bond, A., Ornstein, P.L., Ward, M.A., Hicks, C.A., Hoo, K., Bleakman, D., and Lodge, D., *Neuropharmacology*, 1998, no. 37, p. 1211.
11. Armour, D. R., Chung, K.M.L., Congreve, M.,

Evans, B., Guntrip, S., Hubbard, T., Kay, C., Middlemiss, D., Mordaunt, J.E., Pegg, N.A., Vinader, M.V., Ward, P., and Watson, S.P., *Bioorg. Med. Chem. Letters*, 1996, no. 6, p. 1015.
12. Brüner-Osborne, H., Egebjerg, J., Nielsen, E.Ø., Madsen, U., and Krogsgaard-Larsen, P., *J. Med. Chem.*, 2000, no. 43, p. 2609.
13. Ilies, M., Banciu, M.D., Ilies, M.A., Scozzafava, A., Caproiu, M.T., and Supuran, C.T., *J. Med. Chem.*, 2002, no. 45, p. 504.
14. Hallinan, E.A., Tsymbalov, S., Dorn, C.R., Pitzele, B.S., Hansen, D.W., Moore, W.M., Jerome, G.M., Connor, J.R., Branson, L.F., Wi-domski, D.L., Zhang, Y., Currie, M.G., and Manning, P.T., *J. Med. Chem.*, 2002, no. 45, p. 1686.
15. Liljebris, C., Larsen, S.D., Ogg, D., Palazuk, B.J., and Bleasdale, J.E., *J. Med. Chem.*, 2002, no. 45, p. 1785.
16. Noda, K., Saad, Y., Kinoshita, A., Boyle, T.P., Graham, R.M., Husain, A., and Karnik, S.S., *J. Biol. Chem.*, 1995, no. 270, p. 2284.
17. Wexler, R.R., Greenlee, W.J., Irvin, J.D., Goldberg, M.R., Prendergast, K., Smith, R.D., and Timmermans, P.B.M.W.M., *J. Med. Chem.*, 1996, no. 39, p. 625.
18. Sung-eun, Yoo, Seung-Heui, Lee, Soo-Kyung, Kim, and Sung-Hou, Lee, *Bioorg. Med. Chem.*, 1997, no. 5, no. 445.
19. Fedyuk, D.V., Maletina, I.I., and Yagupol'skii, L.M., *Ukr. Khim. Zh.*, 1997, no. 63, no. 47.
20. Byard, S.J. and Herbert, J.M., *Tetrahedron*, 1999, no. 55, p. 5931.
21. Matsoukas, J. and Weisemann, R., *J. Med. Chem*, 1999, no. 42, p. 1714.
22. Mavromoustakos, T., Kolocouris, A., Zervou, M., Roumelioti, P., Le Bourdonnec, B., Meulon, E., Yous, S., Goossens, J.-F., Houssin, R., and Henichart, J.-P., *J. Med. Chem.*, 2000, no. 43, p. 2685.
23. Zubin, E.M., Romanova, E.A., and Oretskaya, T.S., *Usp. Khim.*, 2002, no. 71, p. 273.
24. Ye, X.R., Xin, X.Q., and Xin, F.B., *J. Appl. Electrochem*, 1997, no. 27, p. 659.
25. Ishiyama, M., Miyazono, Y., Sasamoto, K., Ohkura, Y., and Ueno, K., *Talanta*, 1997, no. 44, p. 1299.
26. Lippmann, E. and Könnecke, A., *Z. Chem.*, 1976, no. 16, p. 90.
27. Koldobskii, G.I., Ostrovskii, V.A., and Poplavskii, V.S., *Khim. Geterotsikl. Soed.*, 1981, p. 1299.
28. Koldobskii, G.I. and Ostrovskii, V.A., *Usp. Khim.*, 1994, no. 63, p. 847.
29. Wittenberger, S.J., *Org. Prep. Proced.*, 1994, no. 26, no. 499.
30. Butler, R.N., *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.R., Rees, C.W., and Scriven, E.F.V., Eds., Oxford: Pergamon, 1996, no. 4, p. 621.
31. Ostrovskii, V.A. and Koldobskii, G.I., *Ros. Khim. Zh.*, 1997, no. 41, p. 84.
32. Moderhack, D., *J. Prakt. Chem.*, 1998, no. 340, p. 687.
33. Zubarev, V.Yu. and Ostrovskii, V.A., *Khim. Geterotsikl. Soed.*, 2000, p. 867.
34. Bladin, J.A., *Ber.*, 1885, no. 18, p. 2907.
35. Begtrup, M. and Vedsø, P., *J. Chem. Soc., Perkin Trans. I*, 1995, p. 243.
36. Giles, R.G., Lewis, N.J., Oxley, P.W., and Quick, J.K., *Tetrahedron Lett*, 1999, no. 40, p. 6093.
37. Ostrovskii, V.A. and Koren, A.O., *Heterocycles*, 2000, no. 53, p. 1421.
38. Koren', A.O. and Gaponik, P.N., *Khim. Geterotsikl. Soed.*, 1990, p. 1643.
39. Koren', A.O. and Gaponik, P.N., *Khim. Geterotsikl. Soed.*, 1991, p. 1280.
40. Gaponik, P.N., *Cand. Sci. (Chem.) Dissertation*, St. Petersburg, p. 2000.
41. Grigor'ev, Yu.V., Gaponik, P.N., and Koldobskii, G.I., *Zh. Org. Khim.*, 2001, no. 37, p. 1740.
42. Myznikov, L.V., Artamonova, T.V, Bel'skii, V.K., Stash, A.I., Skvortsov, N.K., and Koldobskii, G.I., *Zh. Org. Khim.*, 2002, no. 38, p. 1413.
43. Osipova, T.F., Ostrovskii, V.A., Koldobskii, G.I., and Erusalimskii, G.B., *Zh. Org. Khim.*, 1984, no. 20, p. 398.
44. Yokoyama, M., Hirano, S., Matsushita, M., Hachiya, T., Kobayashi, N., Kubo, M., Togo, H., and Seki, H., *J. Chem. Soc., Perkin Trans. I*, 1995, p. 1747.
45. Bookser, B.C., *Tetrahedron Lett.*, 2000, no. 41, p. 2805.
46. Satoh, Y. and Moliterni, J.,, *Synlett.*, 1998, p. 528.
47. Hu, K., Niyazybetov, M.E., and Evans, D.H., *Tetrahedron Lett.*, 1995, no. 39, p. 7027.
48. Bang-Andersen, B., Lenz, S.M., Skjærbæk, N., Søby, K.K., Hansen, H.O., Ebert, B., Bøgesø, K.P., Krogsgaard-Larsen, P., *J. Med. Chem.*, 1997, no. 40, p. 2831.
49. Bethel, P.A., Hill, M.S., Mahon, M.F., and Molloy, K.C., *J. Chem. Soc., Perkin Trans. I*, 1999, p. 3507.
50. May, B.C.H. and Abell, A.D., *Tetrahedron Lett.*, 2001, no. 42, p. 5641.
51. Poplavskii, V.S., Titova, I.E., Ostrovskii, V.A., and Koldobskii, G.I., *Zh. Org. Khim.*, 1989, no. 25, p. 2182.
52. Ostrovskii, V.A., Studentsov, E.P., Poplavskii, V.S., Ivanova, N.V., Gurskaya, G.V., Zavodnik, V.E.,

Jasko, M.V., Semizarov, D.G., and Krayevsky, A.A., *Nucleos. Nucleot.*, 1995, no. 14, p. 1289.
53. Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, New York: J.Wiley & Sons, Inc., 1999.
54. Duncia, J.V., Pierce, M.E., and Santella, J.B. III,, *J. Org. Chem.*, 1991, no. 56, p. 2395.
55. Larsen, R.D., King, A.O., Chen, C.Y., Corley, E.G., Foster, B.S., Roberts, F.E., Yang, C., Lieberman, D.R., Reamer, R.A., Tscha-en, D.M., Verhoeven, T.R., Reider, P.J., Lo, Y.S., Rossano, L.T., Brookes, A.S., Meloni, D.J., Moore, J.R., and Arnett, J.F., *J. Org. Chem.*, 1994, no. 59, p. 6391.
56. Lo, Y.S., Rossano, L.T., Meloni, D.J., Moore, J.R., Lee, Y.-C., and Amett, J.F., *J. Heterocyclic Chem.*, 1995, no. 32, p. 355.
57. Huff, B.E., LeTourneau, M.E., Stazak, M.A., and Ward, J.A., *Tetrahedron Lett.*, 1996, no. 37, p. 3655.
58. Matthews, D.P., Geen, J.E., and Shuker, A.J., *J. Comb. Chem.*, 2000, no. 2, p. 19.
59. Artamonova, T.V., Nordlander, E., and Koldobskii, G.I., *Zh. Org. Khim.*, 2000, no. 36, p. 767.
60. Bethell, D. and Gold, V., *Carbonium Ions. An Introduction*, London: Interscience, 1964. Translated under the title *Karbonievye Iony*, Moscow: Mir, 1970.
61. Chupakhin, O.N., Fedorova, O.V., and Rusinov, G.L., *1st Int Conf. on Chemistry and Biological Activity of Heterocycles and Alkaloids*, Moscow, 9–12 October, 2001, no. 1, p. 176.
62. Koldobskii, G.I., Soldatenko, D.S., Gerasimova, E.S., Khokhryakova, N.R., Shcherbinin, M.B., Lebedev, V.P., and Ostrovskii, V.A., *Zh. Org. Khim.*, 1997, no. 33, p. 1854.
63. Rusinov, G.L., Ishmetova, R.I., and Chupakhin, O.N., *Zh. Org. Khim.*, 1997, no. 33, p. 583.
64. Koren', A.O. and Gaponik, P.N., *Khim. Geterotsikl. Soed.*, 1991, p. 1280.
65. Voitekhovich, S.V. and Gaponik, P.N., *Vestsi NAN Belarusi, Ser. Khim.*, 2000, p. 68.
66. Voitekhovich, S.V., Gaponik, P.N., Pytleva, D.S., Lyakhov, A.S., and Ivashkevich, O.A., *Pol. J. Chem.*, 2002, no. 76, p. 1371.
67. Norman, D.P.G., Bunnell, A.E., Stabler, S.R., and Flippin, L., *J. Org. Chem.*, 1999, no. 64, p. 9301.
68. Mitsunobu, O., *Synthesis*, 1981, p. 1.
69. Purchase, C.F. and White, A.D., *Synth. Commun*, 1996, no. 26, p. 2687.
70. Alam, L.V., Kharbash, R.V., and Koldobskii, G.I., *Zh. Org. Khim.*, 2000, no. 36, p. 950.
71. Könecke, A., Lepom, P., and Lippmann, E., *Z. Chem.*, 1978, no. 18, p. 214.
72. Akiyama, T., Imasaki, Y., and Kawanisi, M., *Chem. Lett.*, 1974, p. 229.
73. Zubarev, V.Yu., Putis, S.M., and Ostrovskii, V.A., *Khim. Geterotsikl. Soed.*, 2001, no. 400.
74. Gyoung, Y.S., Shim, J.-G., and Yamamoto, Y., *Tetrahedron Lett.*, 2000, no. 41, no. 4193.
75. Kamijo, S., Jin, T., and Yamamoto, Y., *J. Org. Chem.*, 2002, no. 67, p. 7413.
76. Goodger, A., Hill, M., Mahon, M.F., McGinley, J., and Molloy, K.C., *J. Chem. Soc. Dalton Trans.*, 1996, p. 847.
77. Hill, M., Mahon, M.F., and Molloy, K.C., *J. Chem. Soc., Dalton Trans.*, 1996, p. 1857.
78. Bhandari, S., Mahon, M.F., and Molloy, K.C., *J. Chem. Soc., Dalton Trans.*, 1999, p. 1951.
79. Bethel, P.A., Hill, M.S., Mahon, M.F., and Molloy, K.C., *J. Chem. Soc., Perkin Trans. I*, 1999, p. 3507.
80. Ostrovskii, V.A., Panina, N.S., Koldobskii, G.I., Gidaspov, B.V., and Shirobokov, I.Yu., *Zh. Org. Khim.*, 1979, no. 15, p. 844.
81. Gaponik, P.N., Ivashkevich, O.A., Bubel', O.N., Degtyarin, M.M., and Naumenko, V.N., *TEKh.*, 1989, no. 25, p. 33.
82. Ivashkevich, O.A., Gaponic, P.N., Koren, A.O., Bubel, O.N., and Fronchek, E.V., *Int. J. Quant. Chem.*, 1992, no. 43, p. 813.
83. Ostrovskii, V.A., Serebryakova, N.M., Koldobskii, G.I., and Odokienko, S.S., *Zh. Org. Khim.*, 1984, no. 20, p. 2464.
84. Kozyro, A.A., Simirskii, V.V., Krasulin, A.P., Sevruk, V.M., Kabo, G.Ya., Frenkel', M.L., Gaponik, P.N., Grigor'ev, Yu.V., *ZhFKh.*, 1990, no. 64, p. 656.
85. Markgraf, J.H. and Sadighi, J.P., *Heterocycles*, 1995, no. 40, p. 583.
86. Gaponik, P.N. and Grigor'ev, Yu.V., *Metallorg. Khim.*, 1988, no. 1, p. 846.
87. Gaponik, P.N., Grigor'ev, Yu.V., and Koren', A.O., *Khim. Geterotsikl. Soed.*, 1988, p. 1699.
88. Karavai, V.P. and Gaponik, P.N., *Khim. Geterotsikl. Soed.*, 1991, p. 66.
89. Lippmann, E. and Könnecke, A., *Z. Chem.*, 1975, no. 15, p. 226.
90. Moody, C.J., Rees, C.W., and Young, R.G., *J. Chem. Soc., Perkin Trans. I*, 1991, p. 323.
91. Hattory, K., Lieber, E., and Horwitz, J.P., *J. Am. Chem. Soc.*, 1956, no. 78, no. 411.
92. Barlin, G.B., *J. Chem. Soc. B*, 1967, p. 641.
93. Gol'tsberg, M.A. and Koldobskii, G.I., *Zh. Org. Khim.*, 1996, no. 32, p. 1238.
94. Gol'tsberg, M.A. and Koldobskii, G.I., *Khim. Geterotsikl. Soed.*, 1996, p. 1515.
95. Koreneva, A.P. and Koldobskii, G.I., *Zh. Org.*

Khim., 1999, no. 35, p. 1542.
96. Kharbash, R.V., Alam, L.V., Koreneva, A.P., and Koldobskii, G.I., *Khim. Geterotsikl. Soed.*, 2001, p. 1646.
97. Kharbash, R.V., Gol'tsberg, M.A., Artamonova, T.V., Nordlander, E., and Koldobskii, G.I., *Zh. Org. Khim.*, 2002, no. 38, p. 1409.
98. Myznikov, Yu.E., Koldobskii, G.I., Vasil'eva, I.N., and Ostrovskii, V.A., *Zh. Org. Khim.*, 1988, no. 24, p. 1550.
99. Yoo, E.S., Kim, R.H., and Jeong, N. Korean, *J. Med. Chem.*, 1991, no. 1, p. 65; *Chem. Abstr.*, 1992, no. 117, no. 48442g.
100. Moskvin, A.V., Ostrovskii, V.A., and Koldobskii, G.I., *Zh. Org. Khim.*, 1978, no. 14, p. 1792.
101. Moskvin, A.V., Ostrovskii, V.A., Shirobokov, I.Yu., Koldobskii, G.I., and Gidaspov, B.V., *Zh. Org. Khim.*, 1978, no. 14, p. 2440.
102. Bhupathy, M., Bergan, J.J., McNamara, J.M., Volante, R.P., and Reider, P.J., *Tetrahedron Lett.*, 1995, no. 36, p. 9445.
103. Ivanova, S.E., Koldobskii, G.I., and Ostrovskii, V.A., *Khim. Geterotsikl. Soed.*, 1993, p. 907.
104. Koldobskii, G.I. and Ivanova, S.E., *Zh. Obshch. Khim.*, 1994, no. 64, p. 1698.
105. Koldobskii, G.I. and Ivanova, S.E., *Zh. Org. Khim.*, 1995, no. 31, p. 1601.
106. Broggini, G., Molteni, G., and Zecchi, G., *Heterocycles.*, 1998, no. 47, p. 541.
107. Rodemacher, P., *Adv. Heterocyclic Chem.*, 1999, no. 72, p. 361.
108. Groundwater, P.W. and Nyerges, M., *Adv. Heterocyclic Chem.*, 1999, no. 73, p. 97.
109. Hajos, G., Reide, Z., and Kollenz, G., *Eur. J. Org. Chem.*, 2001, p. 3405.
110. Morgenstern, O., *Pharmazie*, 2000, no. 55, p. 871.
111. Huisgen, R., Sauer, J., and Sturm, J., *Angew. Chem.*, 1958, no. 70, p. 272.
112. Huisgen, R., Seidel, M., Sauer, J., McFarland, J.W., and Wallbillich, G., *J. Org. Chem.*, 1959, no. 24, p. 892.
113. Huisgen, R., *The Adventure Playground of Mechanisms and Novel Reactions*, Washington: Am. Chem. Soc., DC., 1994.
114. Demko, Z.P. and Sharpless, K.B., *Angew. Chem. Int. Ed.*, 2002, no. 41, p. 2113.
115. Rostovtsev, V.V., Green, L.G., Fokin, V.V., and Sharpless, K.B., *Angew. Chem. Int. Ed.*, 2002, no. 41, p. 2596.
116. Osipova, T.F., Koldobskii, G.I., and Ostrovskii, V.A., *Zh. Org. Khim.*, 1984, no. 20, p. 1119.
117. Osipova, T.F., Koldobskii, G.I., and Ostrovskii, V.A., *Zh. Org. Khim.*, 1984, no. 20, p. 2468.
118. Myznikov, Yu.E., Koldobskii, G. I., Ostrovskii, V.A., and Poplavskii, V.S., *Zh. Obshch. Khim.*, 1992, no. 62, p. 1367.
119. Seldes, A.M., D'Accorso, N., Souto, M.F., Alho, M.M., and Arabehety, C.G., *J. Mass. Spectrom.*, 2001, no. 36, p. 1069.
120. Fascio, M.L. and D'Accorso, N.B., *J. Heterocyclic. Chem.*, 1995, no. 32, p. 815.
121. Kraft, A., *Lieb. Ann. Recueil.*, 1997, p. 1463.
122. Gadaginamath, G.S., Shyadlingeri, A.S., and Kavali, R.R., *Indian J. Chem.*, 1999, no. 38B, p. 188.
123. Detert, H. and Schollmeier, D., *Synthesis.*, 1999, p. 999.
124. Sauer, J., Pabst, G.R., Holland, U., Hyun-Sook, Kim, and Loebbecke, S., *Eur. J. Org. Chem.*, 2001, p. 697.
125. Chien, Y.-Y., Wong, K.-T., Chou, P.-T., and Cheng, Y.-M., *J. Chem. Soc. Chem. Commun.*, 2002, p. 2874.
126. Huisgen, R., Sauer, J., and Seidel, M., *Chem. Ber.*, 1960, no. 93, p. 2885.
127. Boyd, G.V., Cobb, J., Lindley, P.F., Mitchel, J.C., and Nicolaou, G.A., *J. Chem. Soc., Chem. Commun.*, 1987, p. 99.
128. Koldobskii, G.I., Nikonova, I.V., Zhivich, A.B., Ostrovskii, V.A., *Zh. Obshch. Khim.*, 1992, no. 62, p. 194.
129. Koldobskii, G., Ivanova, S., Nikonova, I., and Ostrovskii, V., *Acta Chem. Scand.*, 1994, no. 48, p. 596.
130. Artamonova, T.V. and Koldobskii, G.I., *Zh. Org. Khim.*, 1997, no. 33, p. 1850.
131. Artamonova, T.V., Alam, L.V., and Koldobskii, G.I., *Zh. Org. Khim.*, 2000, no. 36, p. 1749.
132. Moody, C.J., Rees, C.W., and Young, R.G., *J. Chem. Soc., Perkin Trans. I*, 1991, p. 329.
133. Voitekhovich, S.V., Gaponik, P.N., Klyaus, B.G., and Ivashkevich, O.A., *Khim. Geterotsikl. Soed.*, 2002, p. 1607.
134. Rees, C.W., Sivadasan, S., White, A.J.P., and Williams, D.J., *J. Chem. Soc., Perkin Trans. I*, 2002, p. 1535.
135. Yoo, S. and Gong, Y., *Heterocycles*, 1997, no. 45, p. 1251.
136. Könnecke, A. and Lippmann, E., *Z. Chem.*, 1977, no. 17, p. 261.
137. Koren, A.O., Gaponik, P.N., Ivashkevich, O.A., and Kovaleva, T.V., *Mendeleev Commun.*, 1995, p. 10.

138. Lavrenova, L.G., Bogatikov, A.N., Sheludyanova, L.A., Ikorskii, V.N., Larionov, S.V., and Gaponik, P.N., *Zh. Neorg. Khim.*, 1991, no. 36, p. 1220.
139. Aliev, Z.G., Goncharov, T.K., Grachev, V.P., Kurmaz, S.V., and Roshchupkin, V.P., *Koordinats. Khim.*, 1991, no. 17, p. 1101.
140. Starikov, A.G., Dzhardimalieva, G.I., Uflyand, I.E., Goncharov, T.K., and Pomogailo, A.D., *Izv. Akad. Nauk, Ser. Khim.*, 1993, p. 76.
141. Downard, A.J., Steel, P.J., and Steenwijk, J., *Aust. J. Chem.*, 1995, no. 48, p. 1625.