Russian Journal of Organic Chemistry, Vol. 38, No. 9, 2002, pp. 1231–1243. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 9, 2002, pp. 1289–1300.

REVIEW

Dedicated to Full Member of the Russian Academy of Sciences V.A. Tartakovskii on the 70th Anniversary of His Birth

5-Amino-3-nitro-1,2,4-triazole and Its Derivatives

T. P. Kofman

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 198013 Russia
fax: (812) 112 7791

Received May 25, 2002

Abstract—The review summarizes published data on the structure, tautomeric properties, direct and indirect methods of preparation, chemical properties, and reactivity of 5-amino-3-nitro-1,2,4-triazole which is one of the most important synthons of the symmetric triazole series.

I. INTRODUCTION

The chemistry of 1,2,4-triazole and its nitro and azido derivatives, as well as of the other nitrogen-containing heterocycles based thereon, has received successful development in the last few decades, in many respects due to studies performed by Russian chemists. Fruitful works in this field under the guidance of V.A. Tartakovskii [1] at the Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, and of research teams at the St. Petersburg State Institute of Technology and Ural State Technical University should be noted. 5-Amino-3-nitro-1,2,4-triazole (ANTA) occupies a specific place among nitro compounds of the 1,2,4-triazole series. Direct practical applications of 5-amino-3-nitro-1,2,4-triazole

1070-4280/02/3809-1231 $27.00 © 2002 MAIK "Nauka / Interperiodica"

[2–4] gave an impetus to both development of acceptable procedures for its preparation [3] and extensive studies of its structure and physical, chemical, and energy properties [5–11]. However, the most important is that 5-amino-3-nitro-1,2,4-triazole is a polydent synthon which, unlike the other members of the nitrotriazole series, possesses an exocyclic amino group neighboring to the pyrrole-like ring nitrogen atom in addition to endocyclic nucleophilic centers. At present, the synthetic potential of 5-amino-3-nitro-1,2,4-triazole is far from being exhausted.

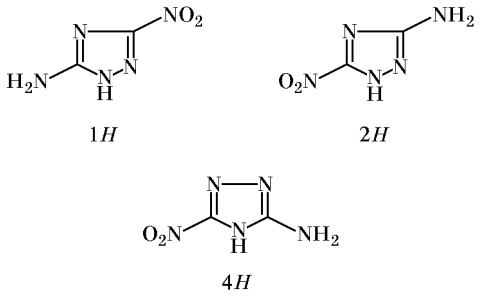
Like other 5-substituted 3-nitro-1,2,4-triazoles, 5-amino-3-nitro-1,2,4-triazole is capable of undergoing N-substitution (addition) reactions. Alkylation of 5-amino-3-nitro-1,2,4-triazole can involve both the endocyclic nitrogen atom and the amino group to give isomeric products. Disubstituted derivatives can also be obtained. Reactions of ANTA with difunctional electrophilic reagents could occur at its one or another nucleophilic center to give functionally substituted and isomeric derivatives; also, both reaction centers in the substrate and in the reagent may be involved. In such cases either independent transformations or ring fusion to give polycyclic systems are possible. Furthermore, quite promising are various transformations of functional groups in the exocyclic moiety of *N*-alkyl(or aryl)-5-amino-3-nitro-1,2,4-triazole derivatives. These reactions may occur either independently or with participation of the 5-amino group. Finally, both 5-amino-3-nitro-1,2,4-triazole and its N-substituted derivatives could give rise to transformations of the exocyclic amino group, e.g., diazotization, oxidation, or nitration.

To what extent these or other purposeful transformations of ANTA and its derivatives are possible will become clear after analysis of the material accumulated while developing methods for preparation of these compounds and studying their reactivity and some properties.

II. STRUCTURE AND TAUTOMERISM OF 5-AMINO-3-NITRO-1,2,4-TRIAZOLE

The structure and tautomerism of ANTA were studied by quantum-chemical methods [6–8], X-ray diffraction [9, 10], IR spectroscopy [8], and ^{1}H, ^{13}C, and ^{15}N spectroscopy [11]. Specific attention was given to tautomeric properties of ANTA [5, 7–11] which, like all 5-substituted 3-nitro-1,2,4-triazoles, can exists as three tautomeric forms (1*H*, 2*H*, and 4*H*) shown in Scheme 1. A question as to which tautomer prevails is fairly important. This follows even from nomenclature discrepancies, for 5-amino-3-nitro-1,2,4-triazole itself is referred to as 1*H* and 2*H* tautomers in the literature [8]. Although ANTA is capable of eliminating a proton from the ring nitrogen atom (pK_a 7.05) and its amino group can be protonated, in none of publications the possibility for formation of the corresponding inner salt was discussed. This is confirmed by spectral data.

Scheme 1.



We formerly believed that the 1*H* tautomer prevails on the basis of the following experimental data. First, the hydrogen atom in the series of 5-substituted 3-nitro-1,2,4-triazoles is usually located on the distal heteroatom with respect to the nitro group (in keeping with the dipole moments [12]); second, the hydrogen atom in 5-amino-1,2,4-triazole is located on the nitrogen atom neighboring to the amino group (according to the X-ray diffraction data [13]). Recent studies of the structure of 5-amino-3-nitro-1,2,4-triazole have confirmed the validity of our concepts. Though quantum-chemical calculations, depending on the procedure used, give contradictory results concerning the structure of particular molecular fragments, in most cases the calculated energy parameters and dipole moments indicate that just 5-amino-3-nitro-1,2,4-triazole is the most stable [7, 8] both in the gas phase and in polar solvents ($\varepsilon > 4.8$ [8]).

The structures of 5-amino-3-nitro-1,2,4-triazole, its hydrate, and hydrazinium salt [9, 10] were studied by X-ray diffraction. It was found that the geometric parameters of the ring in 5-amino-3-nitro-1,2,4-triazole and its hydrate and anion are similar to those of the other triazoles: the heteroring is almost planar (within 0.002–0.006 Å). In all cases, strong intramolecular hydrogen bonds N–H···N–H are formed, and the substituents slightly deviate from the ring plane. The bond lengths and bond angles in the anion are similar to those found for 5-amino-3-nitro-1,2,4-triazole and its hydrate, but the substituents deviate from the ring plane to a greater extent. According to the X-ray diffraction data, 5-amino-3-nitro-1,2,4-triazole is a polymorphic compound: it exists as α- [9]

and β-modifications [10]. The α-form is formed by crystallization from a chloroform–ethanol mixture, and the β-form, from 1-butanol. It is important that in both structures the hydrogen atom is attached to the nitrogen atom adjacent to the carbon atom which is linked to the amino group, i.e., both structures correspond to the 1*H* tautomer.

The α-form gives rise to monoclinic crystals (*C*2/*c* symmetry, $Z = 8$) in which the molecules are tightly linked through intermolecular hydrogen bonds, thus forming twisted bands; contiguous chains are linked through N–H···O intermolecular hydrogen bonds [9]. Crystals of the β-form of 5-amino-3-nitro-1,2,4-triazole have a $P2_1/n$ symmetry ($Z = 4$); the molecules in crystal form extended planar and broad bands [10]. The nitro group in the α-form deviates from the ring plane by 10.5°, and the amino group, by 5.4°. All hydrogen atoms in 5-amino-3-nitro-1,2,4-triazole hydrate (monoclinic crysals) are involved in intermolecular hydrogen bonds. The substituents deviate from the heteroring plane to a lesser extent: the nitro group deviates by 4.3°, and the amino group, by 2.1°. Hydrazinium 5-amino-3-nitro-1,2,4-triazolate has orthorhombic crystals in which the molecules form a 3D network of intermolecular hydrogen bonds. The bond lengths and bond angles in the anion are analogous to those in neutral 5-amino-3-nitro-1,2,4-triazole molecule and its hydrate, but the substituents deviate from the heteroring plane to a greater extent: 7.6° for the nitro group and 13.8° [9] for the amino group.

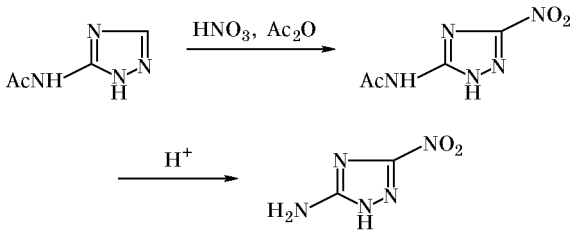
Thus both X-ray diffraction data and results of quantum-chemical calculations indicate that 5-amino-3-nitro-1,2,4-triazole exists as 1*H* tautomer [7, 8].

III. METHODS OF SYNTHESIS OF 5-AMINO-3-NITRO-1,2,4-TRIAZOLE

All presently known methods of preparation of 5-amino-3-nitro-1,2,4-triazole and many its derivatives are based on transformations of various compounds of the triazole series. The latter are prepared most frequently from accessible 5-amino-1,2,4-triazole and 3,5-diamino-1,2,4-triazole (guanazole). 5-Amino-3-nitro-1,2,4-triazole itself can be obtained using conventional procedures for direct introduction of a nitro group into azole ring, such as nitration and diazotization or oxidation of the corresponding aminotriazoles. In addition, an indirect procedure includes partial reduction of one nitro group in 3,5-dinitro-1,2,4-triazole (DNT).

III.1. Nitration of 5-acetamido-1,2,4-triazole. According to this procedure, 5-amino-3-nitro-1,2,4-triazole was synthesized for the first time in 1979 by M.S. Pevzner [14]. The synthetic scheme consists of three steps, the key of which is nitration of 5-acetamido-1,2,4-triazole. The latter was obtained in turn by acetylation of 5-amino-1,2,4-triazole. The nitration was carried out using a mixture of equal volumes of concentrated nitric acid and acetic anhydride at 0 to 3°C. Hydrolysis of 5-acetamido-3-nitro-1,2,4-triazole gave target 5-amino-3-nitro-1,2,4-triazole (Scheme 2).

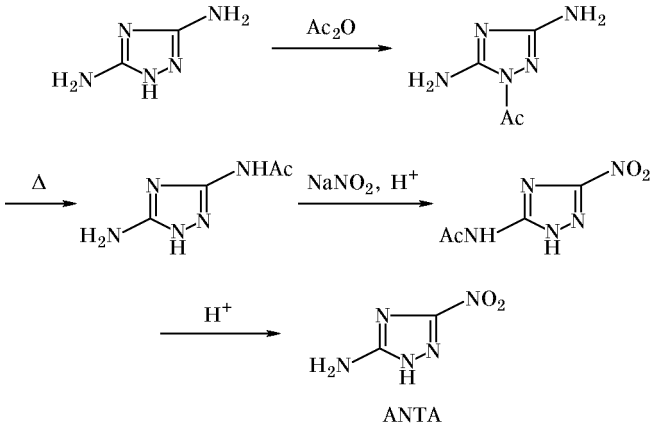
Scheme 2.



Disadvantages of this procedure are a number of steps, hazardous nitration with acetyl nitrate, and the necessity of strictly following the required conditions to avoid side processes. In addition, the hydrolysis stage (heating in boiling hydrochloric acid) takes a long time, and the yield of the target product is as low as ~22% (calculated on the 5-acetamido-1,2,4-triazole taken). The above reaction is an example of direct introduction of a nitro group into triazole ring, which undoubtedly involves initial *N*-nitration at the ring nitrogen atom with subsequent intramolecular migration of the nitro group from position *1* to *5*, typical of triazoles [15].

III.2. Diazotization of 3-acetamido-5-amino-1,2,4-triazole. The procedure is related to that described above. Both these utilize 5-acetamido-3-

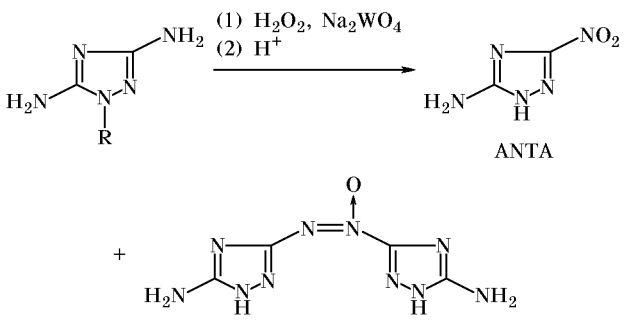
Scheme 3.



nitro-1,2,4-triazole as intermediate, which is then subjected to hydrolysis. The difference is the method of synthesis of 5-acetamido-3-nitro-1,2,4-triazole (Scheme 3). One amino group in guanazole was protected via acylation at the ring nitrogen atom and subsequent thermal rearrangement. Diazotization of the acetamino derivative [16] gave 49% of 5-acetamido-3-nitro-1,2,4-triazole, and the overall yield of 5-amino-3-nitro-1,2,4-triazole (on the initial guanazole) in the four-step synthesis was about 30%. Apart from the long stage of hydrolysis of 5-acetamido-3-nitro-1,2,4-triazole in boiling hydrochloric acid (see above), the procedure is hazardous. The diazotization stage gives a highly sensitive intermediate diazo compound which is insoluble in the reaction medium. Therefore, there is a risk of its accumulation and explosion.

III.3. Oxidation of guanazole and *N*-acylguanazole. In 1982, a procedure was proposed (and then improved) for preparation of ANTA in one or two steps from guanazole [17, 18] or *N*-acylguanazole [17] by oxidation with 30% hydrogen peroxide in the presence of sodium tungstate (yield 60%). In the oxidation of guanazole, azoxy-3,3′-bis(5-amino-1,2,4-triazole) was formed together with 5-amino-3-nitro-1,2,4-triazole [18] (Scheme 4).

Scheme 4.

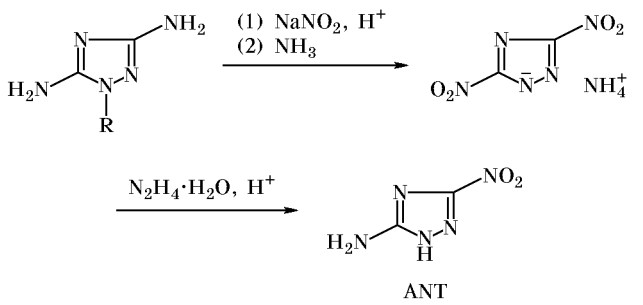


The formation of intermediate N-acylated 5-amino-3-nitro-1,2,4-triazole in the oxidation of *N*-acylguanazole was detected by ^{1}H NMR spectroscopy (in the crude product isolated by extraction). We failed to isolate this intermediate because of its fast hydrolysis to give 5-amino-3-nitro-1,2,4-triazole and acetic acid.

The procedure requires the use of sodium tungstate and a large excess of hydrogen peroxide. On the other hand, taking into account that the target product is isolated from the reaction mixture by extraction, the waste solution containing the catalyst and excess oxidant may be utilized by recycling after reinforcement with more concentrated hydrogen peroxide to a required concentration.

III.4. Reduction of 3,5-dinitro-1,2,4-triazole. In the last decade a procedure has been developed for preparation of 5-amino-3-nitro-1,2,4-triazole by reduction of 3,5-dinitro-1,2,4-triazole ammonium salt with hydrazine [2]. At present, this procedure is regarded as the best one, and, judging by published data, just it has found large-scale application [2, 3]. The method includes three stages: diazotization of guanazole to 3,5-dinitro-1,2,4-triazole, its transformation into ammonium salt, and reduction of one nitro group in the latter with hydrazine hydrate (Scheme 5).

Scheme 5.



The key stage, namely the transformation of 3,5-dinitro-1,2,4-triazole ammonium salt into hydrazinium salt, is carried out by mixing with hydrazine hydrate and subsequent heating to 60–80°C. Free 5-amino-3-nitro-1,2,4-triazole can be isolated from the resulting hydrazinium salt by acidification to pH 2–4.

Some problems in the stages preceding the key one are concerned not with the synthesis of guanazole and its diazotization but isolation of intermediate product, 3,5-dinitro-1,2,4-triazole salt, from the reaction mixture after diazotization. It seems reasonable to extract 3,5-dinitro-1,2,4-triazole with a solution of a tertiary amine (e.g., trilaurylamine) in toluene or chlorinated hydrocarbon with subsequent treatment of the extract with gaseous ammonia [19].

IV. REACTIONS OF 5-AMINO-3-NITRO-1,2,4-TRIAZOLE

Derivatives of 5-amino-3-nitro-1,2,4-triazole can be obtained by reactions occurring at the heteroatom and exocyclic amino group. Here, we can speak about its polydent reactivity. 5-Amino-3-nitro-1,2,4-triazole is capable of reacting with various electrophilic reagents with participation of one or both reaction centers and transformation of the free amino group.

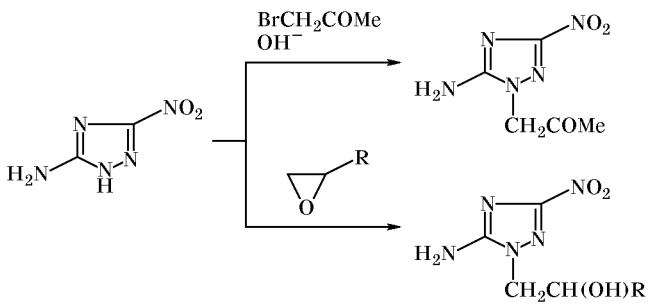
IV.1. Reactions at the ring nitrogen atom. The reactivity of NH acids of the triazole series in substitution and addition processes is determined by their

nucleophilicity and basicity. The basicity of anions derived from 5-substituted nitrotriazoles, 5-amino-3-nitro-1,2,4-triazole among them, with respect to hydrogen and carbon was studied while determining pK_a values and equilibrium constants for reversible hydroxymethylation [20]. Their nucleophilic reactivity in the addition to methyl vinyl ketone was examined in [21]. Satisfactory correlations were obtained for pK_a versus σ_R^0 and σ_I and for $\log k$ versus pK_a. Also, linear relations were observed between $\log k$ and σ_I^0 and basicity parameters with respect to hydrogen and carbon. These data suggest that the reactivity of 5-amino-3-nitro-1,2,4-triazole should be typical of the series of substituted 3-nitrotriazoles. Therefore, ANTA should be fairly reactive toward various electrophilic reagents and the reaction conditions should be consistent with the pK_a values. In this respect, the most closely related analog of 5-amino-3-nitro-1,2,4-triazole among the series of 5-substituted 3-nitro-1,2,4-triazoles is 3-nitro-1,2,4-triazole (pK_a 5.95 [20]). Various reactions of the latter were studied in sufficient detail. Nevertheless, known reactions of 5-amino-3-nitro-1,2,4-triazole are few in number. The reasons are (1) that this compound was difficultly accessible in the early stages of development of the chemistry of 5-substituted 3-nitro-1,2,4-triazoles and (2) that ANTA derivatives can be synthesized by indirect methods starting from numerous compounds of the 3,5-dinitro-1,2,4-triazole series.

Direct substitution at the ring nitrogen atom includes alkylation of 5-amino-3-nitro-1,2,4-triazole with epoxy derivatives and bromoacetone [22], addition to methyl vinyl ketone [23], and some arylation and hetarylation reactions [3, 24–27] which were aimed mainly at obtaining high-energy compounds.

The alkylation with epoxy derivatives is very important for estimation of the nucleophilicity of the endo- and exocyclic reaction centers, for high reactivity of epoxy compounds toward various amines is

Scheme 6.

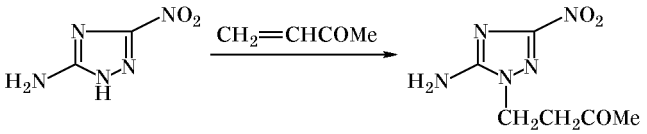


R = H, Me, CH_2Cl.

well known [28]. As shown in [22], 5-amino-3-nitro-1,2,4-triazole, like other triazoles with a similar acidity [29], reacts in the presence of bases or in aqueous ethanol containing no base. As a result, N^1-substituted compounds are formed exclusively in a high yield. The amino group remains intact. Opening of a substituted oxirane ring follows the Krasuskii rule and yields secondary alcohols. Likewise, the alkylation of ANTA sodium salt with bromoacetophenone occurs at the ring nitrogen atom (Scheme 6). The structure of the products was confirmed by their chemical transformations and by independent syntheses. 5-Amino-3-nitro-1-(2-oxopropyl)-1,2,4-triazole was examined by ^{13}C, ^{15}N, and ^{14}N NMR spectroscopy. The spectral data also confirmed the site of substitution in the ANTA molecule, namely the N^1 atom [30].

5-Amino-3-nitro-1,2,4-triazole reacts with methyl vinyl ketone [23] in a way similar to the other 5-substituted 3-nitro-1,2,4-triazoles [31], i.e., addition product at the ring nitrogen atom is formed but only when the synthesis is carried out in the absence of a catalyst (Scheme 7).

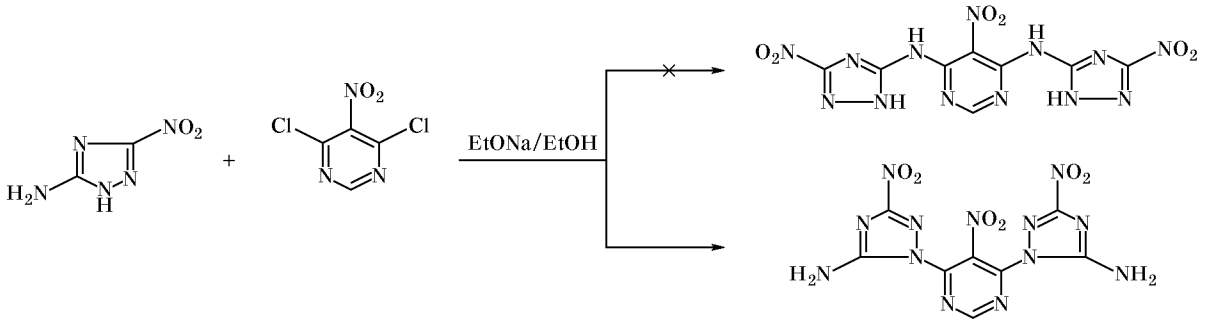
Scheme 7.



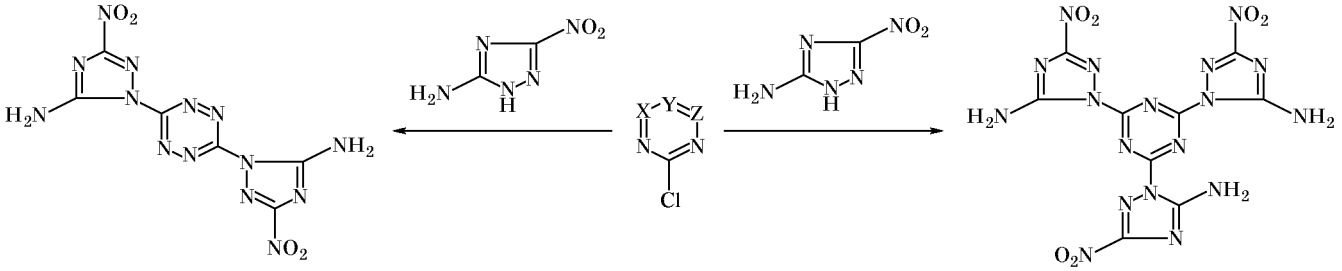
The structure of the resulting ketone was proved by its transformation into the corresponding hydrazone [23] which was identical to the product obtained by reduction of 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole with hydrazine [32]. More profound transformations leading to fusion of the substituent to the ring with participation of the amino group occur in the presence of a base or on treatment of 5-amino-3-nitro-1-(3-oxobutyl)-1,2,4-triazole with alkali [23].

Picrylation of 5-amino-3-nitro-1,2,4-triazole was briefly noted in [24]; various substrates were used to obtain its heteryl derivatives, e.g., halogen derivatives of pyrimidine [3, 25, 26], 1,3,5-triazine, and 1,2,5,6-tetrazine [3], as well as compounds of the 3,5-dinitro-1,2,4-triazole series [27]. Formerly, the site of substitution in 5-amino-3-nitro-1,2,4-triazole was far from being clear. The arylation of ANTA with picryl fluoride gave a product of substitution at the amino group [24]. The product of its reaction with 4,6-dichloro-5-nitropyrimidine in ethanol in the presence of sodium ethoxide was initially assigned the structure of 5-nitro-4,6-bis(3-nitro-1,2,4-triazol-5-yl-

Scheme 8.



Scheme 9.

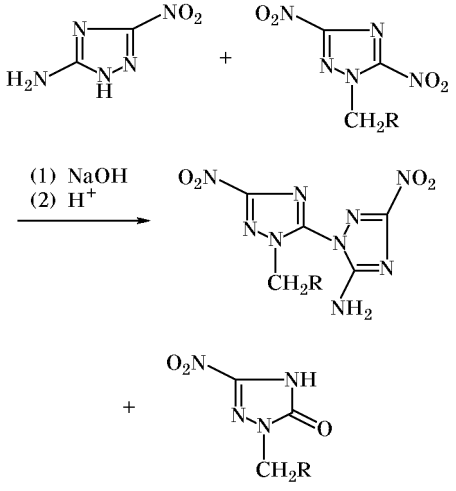


X = Z = N, Y = CCl; X = Z = CCl, Y = N.

amino)pyrimidine [25] which implies replacement at the amino group, unusual for alkylation of 3-substituted 5-amino-1,2,4-triazoles in the presence of bases. These compounds react at the amino group only in the absence of alkali, and numerous examples of such reactions are known [33–35]. The subsequent studies have shown that 5-amino-3-nitro-1,2,4-triazole is not an exception in the series of 5-substituted 3-nitro-1,2,4-triazoles: the reaction involves not the exocyclic amino group but the ring nitrogen atom, and the product is 4,6-bis(5-amino-3-nitro-1,2,4-triazol-1-yl)-5-nitropyrimidine [3, 26] (Scheme 8). Its structure was proved by the ^{13}C and ^{15}N NMR spectra. Analogous triazine and tetrazine derivatives were synthesized by Lee *et al.* [3] (Scheme 9).

3,5-Dinitro-1,2,4-triazole derivatives were used as electrophilic reagents toward 5-amino-3-nitro-1,2,4-triazole anion [27]. These reactions were nonselective with respect to the substrate but selective with respect to the reagent. The resulting N–C-bitriazoles were N^1-derivatives of 5-amino-3-nitro-1,2,4-triazole with free amino group which can be oxidized. Side processes included either independent replacement of the 5-amino group in 3,5-dinitro-1,2,4-triazole derivatives by hydroxide ion with formation of the corresponding triazolones or elimination of a labile N^1-substituent according to the retro-Michael pattern in the case of 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole (Scheme 10).

Scheme 10.

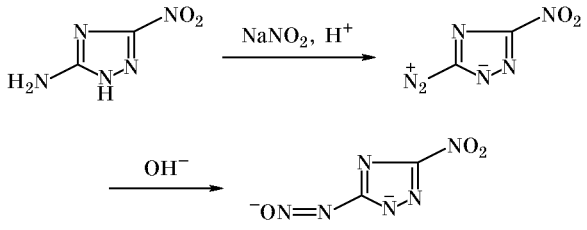


R = H, CH_2COMe.

IV.2. Reactions at the exocyclic amino group. Apart from picrylation [24] (see above), the amino group in 5-amino-3-nitro-1,2,4-triazole can be subjected to diazotization, oxidation with various

oxidants, and protonation. Diazotization of 5-amino-3-nitro-1,2,4-triazole under standard conditions gives the corresponding diazo compound with zwitterionic structure. In alkaline medium the inner salt is converted into dianion [36] (Scheme 11).

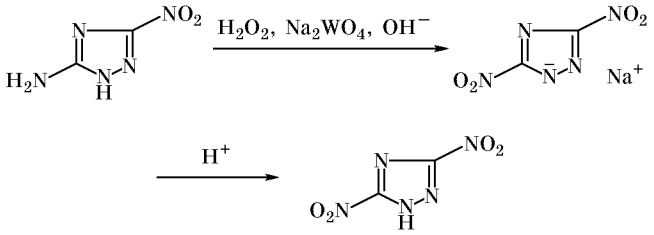
Scheme 11.



Under appropriate conditions the diazonium salt may be brought into azo coupling or converted into a 5-substituted 3-nitro-1,2,4-triazole which is difficult or even impossible to obtain by other methods.

Oxidation of the amino group in 5-amino-3-nitro-1,2,4-triazole was also reported. Its very slow oxidation to 3,5-dinitro-1,2,4-triazole occurs even during the synthesis of 5-amino-3-nitro-1,2,4-triazole from guanazole by treatment with H_2O_2–Na_2WO_4 [18] (Scheme 12). A considerable difference in the rates of the oxidation steps indicates very low reactivity of the amino group in 5-amino-3-nitro-1,2,4-triazole. Almost complete conversion was attained only on prolonged oxidation (about 7 days). The oxidation of 5-amino-3-nitro-1,2,4-triazole can be accelerated to a considerable extent by adding an alkali, i.e., by converting it into the anionic form. Then the basicity of the amino group strongly increases due to delocalization of the negative charge over the heteroring. It should be emphasized that N-substituted 5-amino-3-nitro-1,2,4-triazoles having no labile proton (which cannot be converted into anionic form) are not oxidized with the above system.

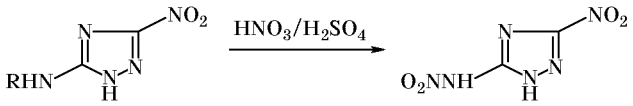
Scheme 12.



This reaction may be important only as an example of oxidation of the amino group in 5-amino-3-nitro-1,2,4-triazole to nitro group and as a method for indirect estimation of its reactivity. From the practical viewpoint, such a procedure for synthesizing 3,5-dinitro-1,2,4-triazole is unreasonable. However, the possibility for oxidation of weakly basic 5-amino-3-nitro-1,2,4-triazole via conversion into the anionic form to enhance the reactivity of amino group should be taken into account while considering reactions of other heterocyclic NH acids whose oxidation in the H-form is hindered.

Treatment of 5-acetamido-3-nitro-1,2,4-triazole with a mixture of sulfuric and nitric acids leads to formation of the corresponding *N*-nitroacetamide. Acid hydrolysis of the latter gives 3-nitro-5-nitroamino-1,2,4-triazole [16] (Scheme 13). According to our data, preliminary protection of the amino group is unnecessary.

Scheme 13.

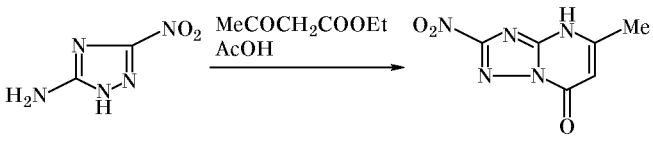


R = H, Ac.

The product is a dibasic NH acid which is characterized by pK_{a1} –0.06 (at the nitroamino group) and pK_{a2} 7.33 (at the endocyclic nitrogen atom). This is a fairly rare case when the acidity of an organic acid is comparable with that of mineral acids.

IV.3. Transformations involving substitution at the ring nitrogen atom with participation of the amino group. The molecule of 5-amino-3-nitro-1,2,4-triazole possesses two reaction centers: the endocyclic nitrogen atom and the amino group located in the position appropriate for intramolecular cyclizations. Therefore, in the general case reactions of ANTA with the corresponding difunctional electrophilic reagents could lead to formation of polycyclic systems with a nitro group in the azole moiety. An example is a classical version of synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidines [37] by heating 5-amino-3-nitro-1,2,4-triazole with ethyl acetoacetate in boiling acetic acid. As a result, 5-methyl-2-nitro-7-oxo-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine was obtained [38] (Scheme 14).

Scheme 14.



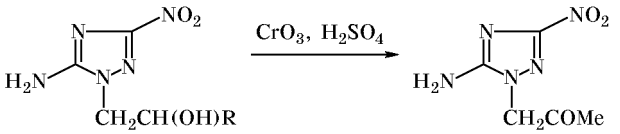
Its analogs, 6-nitro-substituted 1,2,4-triazolo-[1,5-*a*]pyrimidines, are known as antimicrobial and antiviral agents [39]. At present, the only route to 2-nitro analogs of such compounds is condensation of difunctional substrates with 5-amino-3-nitro-1,2,4-triazoles, for direct introduction of a nitro group into position *2* of 1,2,4-triazolo[1,5-*a*]pyrimidine by nitration or diazotization of the corresponding derivatives is practically unfeasible.

V. TRANSFORMATIONS OF 5-AMINO-3-NITRO-1,2,4-TRIAZOLE DERIVATIVES

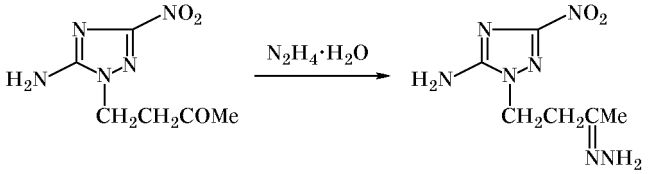
This section describes selective transformations of functional group in the N^1-substituent of 5-amino-3-nitro-1,2,4-triazole without involving the other ring substituents, reactions of the amino group without participation of functional group in the N^1-substituent, and transformations involving both these.

V.1. Reactions of functional group in the *N*-alkyl substituent. The following reactions of this type were reported: oxidation of 5-amino-1-(2-hydroxypropyl)-3-nitro-1,2,4-triazole to the corresponding ketone with Jones' reagent [22] (Scheme 15), reaction of 5-amino-3-nitro-1-(3-oxobutyl)-1,2,4-triazole with hydrazine to obtain the corresponding hydrazone [23] (Scheme 16), and esterification of 5-amino-1-(2-carboxyethyl)-3-nitro-1,2,4-triazole with methanol in the presence of oleum [40] (Scheme 17).

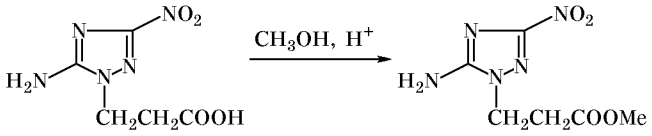
Scheme 15.



Scheme 16.

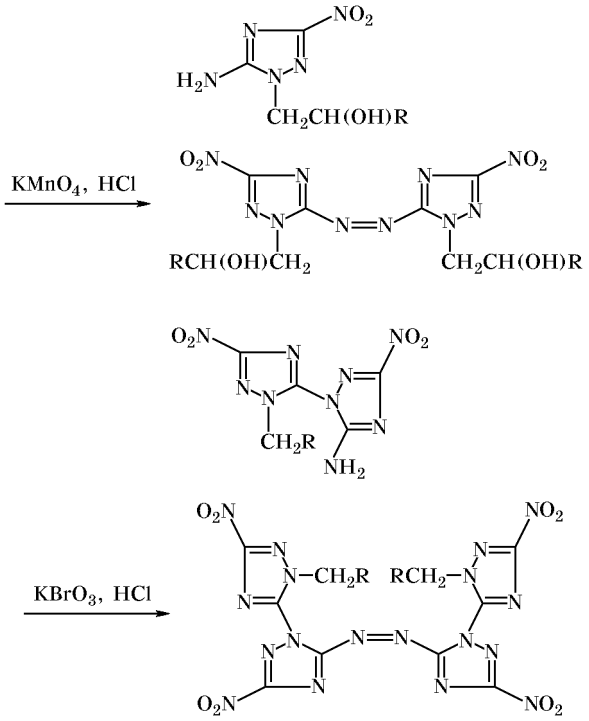


Scheme 17.



V.2. Transformations of the amino group. These include oxidation of the amino group. Unlike ANTA, 5-amino-3-nitro-1,2,4-triazoles having a substituent on the nitrogen are not oxidized with such oxidants as hydrogen peroxide and sodium tungstate [18]. The use for the same purpose of potassium permanganate in alkaline medium was also unsuccessful. On the other hand, 5-amino-3-nitro-1,2,4-triazoles are fairly readily oxidized with potassium permanganate or potassium bromate in hydrochloric acid (i.e., with Cl_2 and ClBr *in statu nascendi*). As a result, the corresponding azo derivatives are obtained in high yield. The procedure is applicable for both *N*-alkyl- [22] and *N*-hetaryl-substituted 5-amino-3-nitro-1,2,4-triazoles [27] (Scheme 18).

Scheme 18.



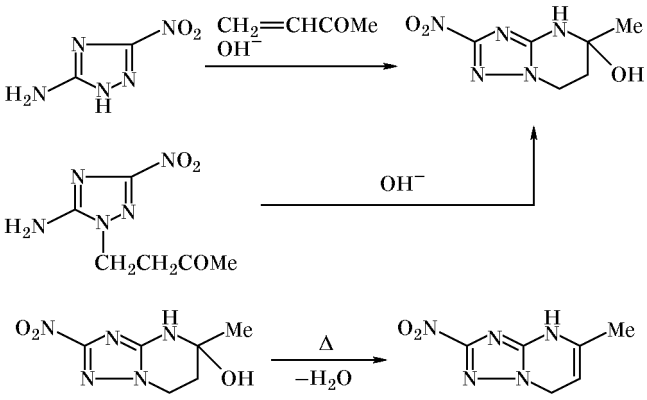
R = H, CH_2COCH_3.

Selective oxidation of the amino group in the first case should be noted: The side-chain functional group remains intact [22].

V.3. Reactions involving the amino group and functional group in the *N*-alkyl substituent. An example of such transformations is the addition of methyl vinyl ketone to 5-amino-3-nitro-1,2,4-triazole in alkaline medium to afford 5-hydroxy-5-methyl-2-nitro-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]-pyrimidine [23]. The same product was obtained in an attempt to effect dealkylation of 5-amino-3-nitro-1-(3-oxobutyl)-1,2,4-triazole by treatment with a base

(according to the retro-Michael reaction pattern) [23]. Instead of the expected heterolytic cleavage of the N^1-C bond with elimination of methyl vinyl ketone, intramolecular ring closure occurred to give bicyclic product with fused triazole ring (Scheme 19). In this case, the azine version could be expected through the reaction of the side-chain carbonyl group at the amino group with elimination of water. However, the above fused system was formed as a result of proton transfer. The product lost water molecule to give 5-methyl-2-nitro-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine on heating at 100–120°C [23].

Scheme 19.

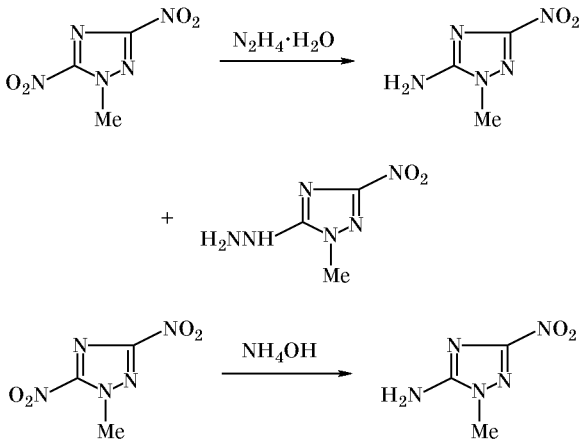


VI. SYNTHESES OF 5-AMINO-3-NITRO-1,2,4-TRIAZOLE DERIVATIVES VIA TRANSFORMATIONS OF VARIOUS COMPOUNDS OF THE 1,2,4-TRIAZOLE SERIES

Known reactions of this type can be divided into four groups. These are reduction or replacement of the nitro group in 3,5-dinitro-1,2,4-triazole derivatives, reduction of the azido group in N-substituted 5-azido-3-nitro-1,2,4-triazoles, oxidation of *N*-alkylguanazoles, and direct nitration of RNH-1,2,4-triazoles.

VI.1. Transformations of 3,5-dinitrotriazole derivatives. In fact, the first representative of the 5-amino-3-nitro-1,2,4-triazole series was not the parent compound itself but its 1-methyl derivative. The latter was synthesized as early as 1970 while studying nucleophilic replacement of the nitro group in position *5* of 1-methyl-3,5-dinitro-1,2,4-triazole by ammonia [41] and hydrazine [42]. In the latter case, substitution of the nitro group was the main reaction pathway, and reduction of 5-hydrazino-1-methyl-3-nitro-1,2,4-triazole gave 5-amino-1-methyl-3-nitro-1,2,4-triazole in high yield (Scheme 20). Later on, the procedure for nitro group reduction with hydrazine was extended to oxoalkyl derivatives of 3,5-dinitro-1,2,4-triazole [32]. In such a way, a large number of compounds of the 5-amino-3-nitro-1,2,4-triazole series were synthesized by reduction of other N-functionally substituted 3,5-dinitro-1,2,4-triazoles [40].

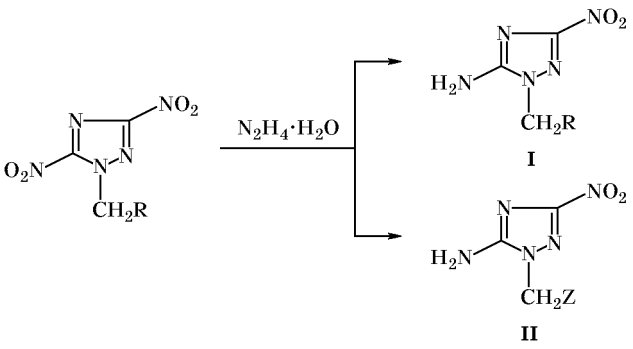
Scheme 20.



It should be emphasized that in all cases (with no exceptions) only the 5-nitro group in the 3,5-dinitro-1,2,4-triazole ring was reduced and that almost all products thus obtained had the structure of N^1-substituted 5-amino-3-nitro-1,2,4-triazoles. Nevertheless, while performing the reduction with hydrazine, it should be kept in mind that, depending on the functional group present in the *N*-alkyl group of 3,5-dinitro-1,2,4-triazole, either the 5-nitro group or both the nitro group and the side-chain functional group may be involved. Furthermore, the two groups can be transformed independently or ring fusion can occur.

Selective reduction of the nitro group was reported for *N*-alkyl-, *N*-alkenyl-, *N*-hydroxyalkyl-, *N*-acetamidoalkyl-, *N*-carboxyalkyl-, and *N*-nitroxyalkyl-3,5-dinitro-1,2,4-triazoles [**I**: R = H, $CH{=}CH_2$, CH(OH)Me, NHCOMe, $CH_2NHCOMe$, COOH, CH_2COOH, $CH(ONO_2)Me$]. Independent transforma-

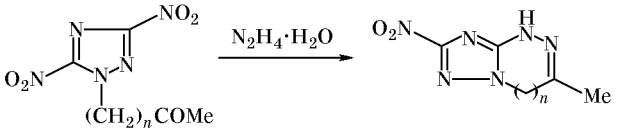
Scheme 21.



tions of the two functionalities were reported for triazol-1-ylalkylcarboxylic acid esters and 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole. The former are converted into the corresponding hydrazides, and the latter gives hydrazone provided that the amount of the reducing agent is sufficiently large (Scheme 21; **II**: R = CH_2COMe, COOMe, CH_2COOMe, Z = $CH_2C(=NNH_2)Me$, $CONHNH_2$, $CH_2CONHNH_2$).

In the reaction of 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole with an equimolar or nearly equimolar amount of hydrazine and in the reduction of 3,5-dinitro-1-(2-oxopropyl)-1,2,4-triazole, regardless of the amount of reducing agent, the only products were the corresponding fused triazoles (Scheme 22).

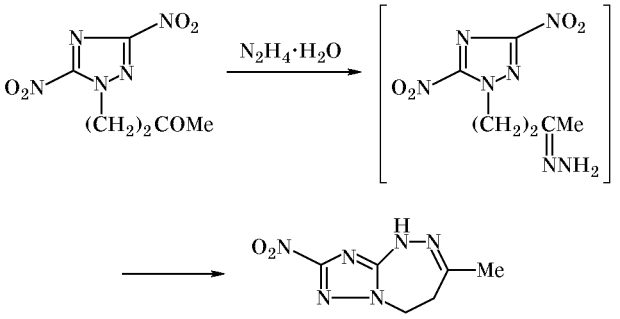
Scheme 22.



n = 1, 2.

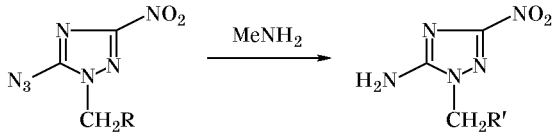
These data indicate that the reaction initially occurs at the carbonyl group of 3,5-dinitro-1-(3-oxobutyl)-1,2,4-triazole to give the corresponding hydrazone; the latter undergoes either further reduction or intramolecular nucleophilic substitution of the nitro group, leading to ring closure (Scheme 23).

Scheme 23.



VI.2. Reduction of the azido group in 5-azido-3-nitro-1,2,4-triazole derivatives. Transformations of compounds belonging to the 5-azido-3-nitro-1,2,4-triazole series were reported in only one publication [43]. First, such compounds are few in number and, second, there are no reasons to use them as starting material for the synthesis of 5-amino-3-nitro-1,2,4-triazole derivatives. Nevertheless, the number of reported examples is sufficient to demonstrate the general character of this approach. It should be noted that the underlying reaction is nontrivial: treatment of N-substituted 5-azido-3-nitro-1,2,4-triazoles with strongly basic aliphatic amines results in reduction of the 5-azido group instead of the expected replacement, which is typical of nitrotriazole derivatives having a labile substituent at C^5. Most probably, the reaction follows the addition–elimination pattern with predominant attack by nucleophilic reagent on the terminal nitrogen atom of the azido group rather than on the carbon atom attached thereto. It is most reasonable to carry out the process by treatment of 5-azido-3-nitro-1,2,4-triazole derivatives with 25% aqueous methylamine at 40–50°C (Scheme 24).

Scheme 24.

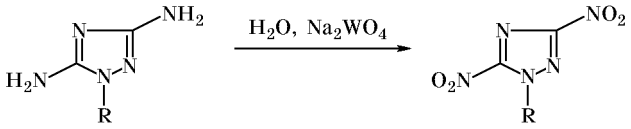


R = R′ = H, COOH; R = COOMe, R′ = CONHMe.

Here, as in the preceding case, the reduction with methylamine could give rise to the respective transformations of functional group in the N^1-substituent provided that it is sensitive to the reagent (e.g., an ester moiety).

VI.3. Oxidation of N-substituted guanazoles. The oxidation of one amino group in guanazole with sodium tungstate is applicable to N-substituted guanazoles, including those having a functional group in the *N*-alkyl chain. The reaction occurs exclusively at the distal amino group, the side-chain functionality remaining unchanged. The products, N-substituted 5-amino-3-nitro-1,2,4-triazoles are formed in 60–80% yield [18] (Scheme 25).

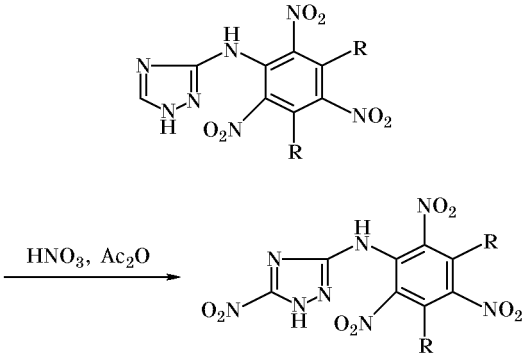
Scheme 25.



R = Me, CH_2COOH, $CH_2CH(OH)Me$.

VI.4. Nitration of 3-arylamino-1,2,4-triazoles. Direct introduction of a nitro group into triazole ring by nitration with acetyl nitrate was reported for the first time by Pevzner *et al.* [14] who synthesized 5-amino-3-nitro-1,2,4-triazole from 3-acetamido-1,2,4-triazole. Later on, the procedure was extended to 3-arylamino-1,2,4-triazoles [33, 34] (Scheme 26).

Scheme 26.



R = H [33], Cl [34].

Li *et al.* [33] described an unusual version of picrylation of 3-amino-1,2,4-triazole: the latter was treated with *N*-methyl-*N*,2,4,6-tetranitroaniline, and the compound thus obtained was subjected to nitration with mixtures of concentrated nitric acid with acetic anhydride or acetic acid. According to the authors, two isomeric products were formed: 1-nitro-3-(*N*-nitropicrylamino)-1,2,4-triazole and 5-nitro-3-(*N*-nitropicrylamino)-1,2,4-triazole. Undoubtedly, the first of these is precursor of the second.

VII. CONCLUSION

All methods for preparation of 5-amino-3-nitro-1,2,4-triazole derivatives are based on transformations of the parent compound and those belonging to the same series. These transformations occur with retention of the triazole ring or involve the amino group or functional group in the N^1-substituent. The latter reactions may be selective or they may proceed with participation of the ring substituents. Other compounds of the triazole series, specifically derivatives of guanazole, 5-azido-3-nitro-1,2,4-triazole, or 3,5-dinitro-1,2,4-triazole can also be used as starting material.

5-Amino-3-nitro-1,2,4-triazole can react with various electrophilic reagents, both mono- and difunctional ones, following the N-substitution (addition) pattern. The alkylation and arylation in alkaline medium occur exclusively at the N^1 atom. Reactions with appropriate difunctional reagents can lead to intramolecular ring closure with formation of fused systems. Polycyclic systems can also be obtained via transformation of the N^1-substituent, as a result of which a functional group capable of reacting with the amino group appears. Although the amino group in 5-amino-3-nitro-1,2,4-triazole and especially in its N-substituted derivatives is relatively low reactive, it can be brought into reactions with nitrating, nitrosating, and oxidizing agents.

The data on chemical transformations of 5-amino-3-nitro-1,2,4-triazole, discussed in the present review, open the way to diverse modification of its structure and synthesis of new practically important compounds of this series.

REFERENCES

1. Pevzner, M.S., Kulibabina, T.N., Ioffe, S.L., Maslina, I.A., Gidaspov, B.V., and Tartakovskii, V.A., *Khim. Geterotsikl. Soedin.*, 1979, no. 4, pp. 550–554; Myasnikov, V.A., Vyazikov, V.A., Yudin, I.L., Shitov, O.P., and Tartakovskii, V.A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, no. 5, p. 1239; Vyazikov, V.A., Shitov, O.P., and Tartakovskii, V.A., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 7, pp. 1038–1044.
2. Lee, K. and Storm, C.B., *Report 1990 LA 11907-MS Order N DE 900180 47*; *Energy Res. Abstr.*, 1990, Abstr. 15 (22), no. 49 392; *Chem. Abstr.*, 1991, vol. 115, no. 235 797 x; Simpson, R.L., Pagoria, P.F., Mitchell, A.R., and Coon, C.L., *Propellants, Explos., Pyrotech.*, 1994, vol. 19, no. 4, pp. 174–179; *Chem. Abstr.*, 1994, vol. 121, no. 208 549 k; Lee, K. and Storm, C.B., US Patent no. 767 603, 1994; *Chem. Abstr.*, 1994, vol. 121, no. 112 821 s.
3. Lee, K.Y., Storm, C.B., Hiskey, M.A., and Coburn, M.D., *J. Energ. Mater.*, 1991, vol. 9, no. 5, pp. 415–428; *Chem. Abstr.*, 1992, vol. 116, no. 217 504.
4. Williams, G.K., Polopoli, S.F., and Brill, T.B., *Combust. Flame*, 1994, vol. 98, no. 3, pp. 197–204; *Chem. Abstr.*, 1994, vol. 121, no. 160 343 j; Langlet, A. and Oestmark, H., WO Patent no. 9 402 434, 1994; *Chem. Abstr.*, 1994, vol. 120, no. 302 722 n; Volk, F. and Bathelt, H., *Int. Symp. Energ. Mater. Technol.*, 1995, pp. 82–89; *Chem. Abstr.*, 1998, vol. 128, no. 117 001 d; Volk, F. and Bathelt, H., *Theory Pract. Energ. Mater. (Proc. Int. Autumn Seminar on Propellants, Explosives, and Pyrotechnics)*, 1997, pp. 341–349; *Chem. Abstr.*, 1998, vol. 128, no. 142 753 h.
5. Licht, H.H., Braun, S., Schaefer, M., Wanders, B., and Ritter, H., Abstracts of Papers, *29th Int. Annual Conf. of ICT*, 1998, 47.1–47.15; *Chem. Abstr.*, 1998, vol. 129, no. 163 575 n.
6. Delpeyroux, D., Charrue, P., and Simonetti, Ph., *High Temp.–High Pressures*, 1998, vol. 30, no. 5, pp. 625–628; *Chem. Abstr.*, 1999, vol. 130, no. 15 532 b.
7. De Paz, J.L.G. and Giller, J., *Propellants, Explos., Pyrotech.*, 1993, vol. 18, no. 1, pp. 33–40; *Chem.*

Abstr., 1993, vol. 118, no. 237 100 a; De Paz, J.L.G. and Giller, J., *Propellants, Explos., Pyrotech.*, 1994, vol. 19, no. 1, pp. 32–41; *Chem. Abstr.*, 1994, vol. 120, no. 248 723 y.

8. Sorescu, D.C., Bennet, C.M., and Thompson, D.L., *J. Phys. Chem., Part A*, 1998, vol. 102, no. 50. pp. 10 348–10 357.
9. Garcia, E. and Lee, K.Y., *Acta Crystallogr., Sec. C: Cryst. Struct. Commun.*, 1992, vol. 48, no. 9, pp. 1682–1683; Sromer, D.T. and Storm, C.B., *Acta Crystallogr., Sec. C: Cryst. Struct. Commun.*, 1991, vol. 47, no. 11, pp. 2476–2478; Garcia, E., Lee, K.Y., and Storm, C.B., *Acta Crystallogr., Sec. C: Cryst. Struct. Commun.*, 1992, vol. 48, no. 9, pp. 1683–1685.
10. Lee, K.-Y., Gilardi, R., Hiskey, M.A., and Stine, J.R., *Mater. Res. Soc. Symp. Proc.*, 1998, pp. 418–443.
11. Licht, H.H., Ritter, H., Bircher, H.R., and Bigier, P., *Magn. Reson. Chem.*, 1998, vol. 36, no. 5, pp. 343–350; *Chem. Abstr.*, 1998, vol. 129, no. 148 711 k.
12. Pevzner, M.S., Fedorova, E.Ya., Shokhor, I.N., and Bagal, L.I., *Khim. Geterotsikl. Soedin.*, 1971, no. 2, pp. 275–278.
13. Makarskii, V.V., Starova, G.A., Frank-Kamenetskaya, O.V., Lopyrev, V.A., and Voronkov, M.G., *Khim. Geterotsikl. Soedin.*, 1977, no. 8, pp. 1138–1139; Starova, G.A., Frank-Kamenetskaya, O.V., Makarskii, V.V, and Lopyrev, V.A., *Kristallografiya*, 1978, vol. 23, no. 4, p. 849.
14. Pevzner, M.S., Kulibabina, T.N., Povarova, N.A., and Kilina, L.V., *Khim. Geterotsikl. Soedin.*, 1979, no. 8, pp. 1132–1135.
15. Habraken, C.L. and Cohen-Fernandez, P., *J. Chem. Soc., Chem. Commun.*, 1972, no. 2, pp. 37–38.
16. Pevzner, M.S., Gladkova, N.V., and Kravchenko, T.A., *Russ. J. Org. Chem.*, 1996, vol. 32, no. 8, pp. 1186–1189.
17. Namestnikov, V.I., Kofman, T.P., and Pevzner, M.S., USSR Inventor's Certificate no. 979 342, 1982; *Byull. Izobret.*, 1982, no. 45.
18. Kofman, T.P. and Paketina, E.A., *Russ. J. Org. Chem.*, 1997, vol. 33, no. 8, pp. 1125–1132.
19. Lee, K.Y., Ott, D.G., and Stinecipher, M.M., *Ind. Eng. Chem. Proc. Res. Dev.*, 1981, vol. 20, no. 2, pp. 358–360.
20. Serov, Yu.V., Pevzner, M.S., Kofman, T.P., and Tselinskii, I.V., *Zh. Org. Khim.*, 1990, vol. 26, no. 4, pp. 903–907.
21. Serov, Yu.V., Pevzner, M.S., Kofman, T.P., and Tselinskii, I.V., *Zh. Org. Khim.*, 1990, vol. 26, no. 6, pp. 1356–1359.
22. Kofman, T.P. and Paketina, E.A., *Russ. J. Org. Chem.*, 1995, vol. 31, no. 7, pp. 987–991.
23. Kofman, T.P. and Paketina, E.A., *Zh. Org. Khim.*, 1994, vol. 30, no. 5, pp. 774–776.
24. Ou, Y., Chen, B., Li Jiarong, Dong, S., Li Jianjun, and Jia, H., *Heterocycles*, 1994, vol. 38, no. 7, pp. 1651–1664.
25. Laval, F., Wartenberg, C., and Morignat, M.L., EP no. 320 370, 1989; *Chem. Abstr.*, 1989, vol. 111, no. 194 786 q.
26. Wartenberg, C., Charrue, P., and Laval, F., *Propellants, Explos., Pyrotech.*, 1995, vol. 20, no. 1, pp. 23–26; *Chem. Abstr.*, 1995, vol. 122, no. 243 506 m.
27. Kofman, T.P., Kartseva, G.Yu., Namestnikov, V.I., and Paketina, E.A., *Russ. J. Org. Chem.*, 1998, vol. 34, no. 7, pp. 1032–1038; Kofman, T.P., *Russ. J. Org. Chem.*, 2001, vol. 37, no. 8, pp. 1158–1168.
28. Malinovskii, M.S., *Okisi olefinov i ikh proizvodnye* (Olefin Oxides and Their Derivatives), Moscow: Goskhimizdat, 1961, pp. 248–299.
29. Kofman, T.P., Vasil'eva, I.V., and Pevzner, M.S., *Khim. Geterotsikl. Soedin.*, 1976, no. 9, pp. 1281–1285; *Khim. Geterotsikl. Soedin.*, 1977, no. 10, pp. 1407–1410.
30. Semenov, V.V., Ugrak, V.I., Shevelev, S.A., Kanishchev, M.I., Baryshnikov, A.T., and Fainzil'berg, A.A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, no. 8, pp. 1827–1837.
31. Kofman, T.P., Uspenskaya, T.L., Medvedeva, N.A., and Pevzner, M.S., *Khim. Geterotsikl. Soedin.*, 1976, no. 7, pp. 991–994.
32. Kofman, T.P., Kirpenko, Z.V., and Pevzner, M.S., *Khim. Geterotsikl. Soedin.*, 1982, no. 8, pp. 1113–1117.
33. Li, J., Chen, B., and Ou, Y., *17th Proc. Int. Pyrotechn. Seminar*, 1991, vol. 1, pp. 196–199; *Chem. Abstr.*, 1992, vol. 116, no. 177 199 m.
34. Wang, L., Chen, B., and Ou, Y., *Hecheng Huaxue*, 1993, vol. 1, no. 3, pp. 252–254; *Chem. Abstr.*, 1994, vol. 121, no. 57 402.
35. Coburn, M.D. and Jackson, T.B., *J. Heterocycl. Chem.*, 1968, vol. 5, no. 2, pp. 199–203; Wilshire, J.F.K., *Aust. J. Chem.*, 1966, vol. 19, no. 10, pp. 1935–1945.
36. Stepanov, S.D., Pevzner, M.S., Serov, Yu.V., and Temchenko, T.P., *Zh. Org. Khim.*, 1989, vol. 25, no. 9, pp. 2013–2019.
37. Fisher, G., *Z. Chem.*, 1990, vol. 30, no. 9, pp. 309–315.

38. Kofman, T.P., Uvarova, T.A., Kartseva, G.Yu., and Uspenskaya, T.L., *Russ. J. Org. Chem.,* 1997, vol. 33, no. 12, pp. 1784–1793.

39. Rusinov, V.L., Petrov, A.Yu., Pilicheva, T.L., Chupakhin, O.N., Kovalev, G.V., and Komina, E.P., *Khim.-Farm. Zh.,* 1986, vol. 20, no. 2, pp. 178–182; *ibid.,* no. 8, pp. 947–952; Rusinov, V.L., Myasnikov, A.V., Pilicheva, T.L., Chupakhin, O.N., Kiprianova, E.A., and Garagulya, A.D., *Khim.-Farm. Zh.,* 1990, vol. 24, no. 1, pp. 39–40.

40. Kofman, T.P. and Kirpenko, Z.V., *Zh. Org. Khim.,* 1994, vol. 30, no. 5, pp. 765–769.

41. Bagal, L.I., Pevzner, M.S., Egorov, A.P., and Samarenko, V.Ya., *Khim. Geterotsikl. Soedin.,* 1970, no. 2, pp. 269–274.

42. Bagal, L.I., Pevzner, M.S., Egorov, A.P., and Samarenko, V.Ya., *Khim. Geterotsikl. Soedin.,* 1970, no. 7, pp. 997–1000.

43. Kofman, T.P., Pakhomov, K.E., and Pevzner, M.S., *Khim. Geterotsikl. Soedin.,* 1982, no. 6, pp. 848–849.