STRUCTURES SYNTHESIS, AND PROPERTIES OF 1,2,3-THIADIAZOLES (REVIEW)

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Methods of synthesis and the physical, chemical, and biological properties of 1,2,3-thiadiazoles are systematized.

1,2,3-Thiadiazoles were first described by Pechman at the end of the last century [1], and a little later by Wolf [2]. The reports of these authors were for a long time the only ones in this area. At the beginning of the 1960's, with the appearance of modern methods of analysis of organic compounds and new approaches to the construction of heterocyclic systems utilizing pericyclic reactions, the chemistry of 1,2,3-thiadiazoles received a powerful stimulus to its development. A large number of new 1,2,3-thiadiazoles were synthesized containing a wide variety of substituents. It was observed that these compounds, in contrast to 1,3,4- and 1,2,5-thiadiazoles, being crypto-diazo compounds, readily rearrange, and are converted by thermal and light energy into organic compounds of diverse structure [3-6]. In the last decade, compounds have been obtained which display high biological activity. Such a compound, produced on the industrial scale, is thidazuron, 1-phenyl-3-(1,2,3-thiadiazol-5-yl)urea, a defoliant for fine fibered cotton. Much work is currently in hand on the synthesis of analogs of this compound with a view to finding more active pesticides.

1,2,3-Thiadiazole and its derivatives therefore comprise a class of compounds with interesting properties, and the chemistry of this heterocycle is a rapidly extending, growing and independent branch of the chemistry of heterocyclic compounds. There are, however, no reviews in the literature devoted solely to 1,2,3-thiadiazoles. In reviews describing the properties of thiadiazoles in general, information on 1,2,3-thiadiazoles is either obsolescent [6], or is highly condensed and far from complete [3-5].

The present review surveys and systematizes information on the synthesis and properties of 1,2,3-thiadiazoles which has for the most part appeared over the last 10-15 years. Of the earlier publications, only those which have fundamental significance for the chemistry of 1,2,3-thiadiazoles are included.

1. NOMENCLATURE, STRUCTURE, AND PHYSICOCHEMICAL PROPERTIES

In IUPAC nomenclature, the numbering of the atoms in the 1,2,3-thiadiazole ring is as follows:

Stiefvater [7] has examined the microwave spectrum of 1,2,3-thiadiazole, and determined the angles and bond lengths in the gaseous state. X-ray diffraction studies of the structures of a number of 1,2,3-thiadiazoles have been carried out [8-12], including some with zwitterionic structure [9-12]. It was shown that the heteroatoms and carbon atoms lie in one plane, and the C–S and N–S bond lengths are 0.169 nm, typical of heterocycles with $3p\pi$–$2p\pi$ conjugation.

Chemical shifts in the ^{13}C NMR spectra of 1,2,3-thiadiazole and its derivatives have been reported [13-16] (Table 1). Comparison of these values with those for carbon in

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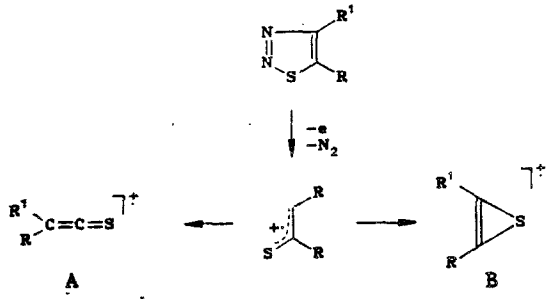
TABLE 1. Structural and Spectral Characteristics of 1,2,3-Thiadiazole

Bond lengths (cf. [7])	Valence angles, deg (cf. [7])	^{13}C NMR (cf. [15])		PMR (cf. [18])	
		$C_{(4)}$	$C_{(5)}$	C^4—H	C^5—H
a 0,16971 *b* 0,12897 *c* 0,13662 *d* 0,13686 *e* 0,16888	α 92,91 β 111,21 γ 113,95 δ 114,15 σ 107,79	147,3	135,8	8,8	8,8

imidazole, 1,2,3-triazole, thiophene, furan, and thiazole shows them to be shifted to lower field by 10-20 ppm [17]. The chemical shifts of the protons in thiadiazole are also shifted to lower field as compared with the signals for the protons in other five-membered aromatic heterocycles [11, 18]. These observations show that 1,2,3-thiadiazoles are π-deficient.

Mass spectral studies have shown that fragmentation takes place exclusively with the loss of a molecule of nitrogen. Depending on the substitutents, either a thioketal A or a cation-radical B is formed [19-21].



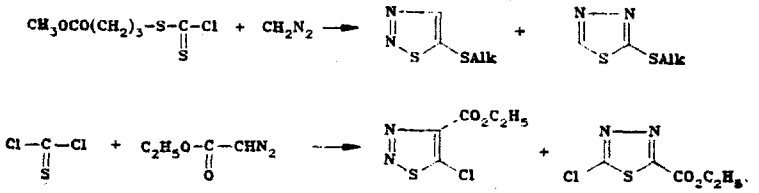
The photoelectronic [22], magnetic circular dichroism (MCD) [23], and NQR spectra on ^{14}N nuclei [24] have been studied. Quantum chemical calculations of the UV, NQR, and MCD spectra have been carried out for thiadiazoles, and it has been found that the ab initio method gives good values for the ionization constants and splitting constants in the NQR spectra, and the PPP method for transitions in the electronic and MCD spectra [22-24].

2. SYNTHESIS OF 1,2,3-THIADIAZOLES

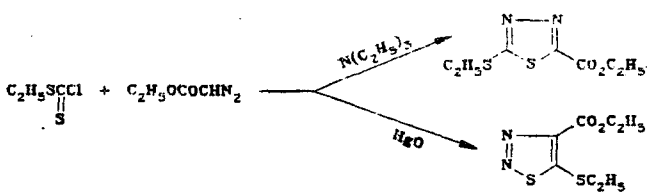
Methods of synthesis of 1,2,3-thiadiazoles may be arbitrarily divided into four groups: 1) Cycloaddition of diazoalkanes to compounds containing the C=S bond; 2) Heterocyclization of 2-diazothiones; 3) Reaction of hydrazones with thionyl chloride; and 4) Other methods.

2.1. Cycloaddition of Diazoalkanes to Compounds with C=S Bonds

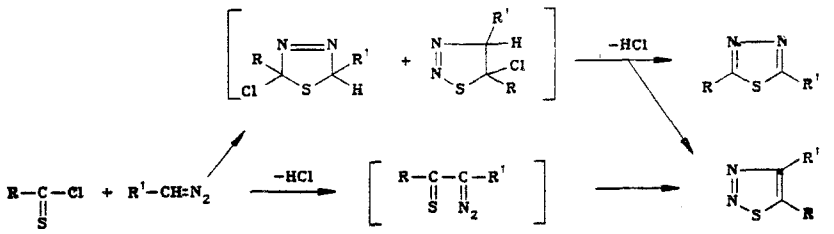
Reaction of diazoalkanes with chlorodithioformates, carbon disulfide, and thiophosgene gives mixtures of 1,2,3- and 1,3,4-thiadiazoles [25-28].



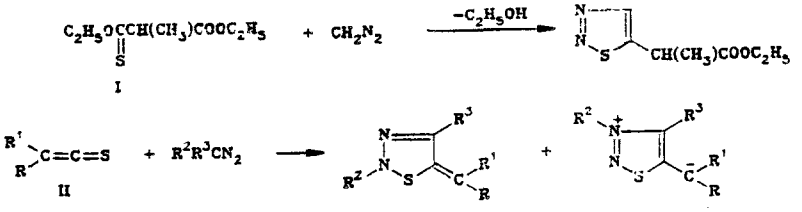
It is interesting that ethyl chlorodithioformate gives preferentially the 1,3,4-thiadiazole on reaction with ethyl diazoacetate in the presence of triethylamine, and the 1,2,3-thiadiazole in reactions with its mercury salt [25].



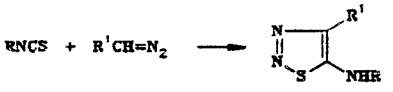
It appears that the 1,2,3- and 1,3,4-thiadiazoles are formed by different mechanisms: 1,3,4-thiadiazoles by cycloaddition of the diazo compound followed by elimination of hydrogen chloride, and 1,2,3-thiadiazoles principally by acylation of the diazo compound followed by cyclization of the resulting diazothione.



In contrast to the examples given above, the thioester (I) and thioketenes (II) react with diazoalkanes to give exclusively 1,2,3-thiadiazoles [29, 30].



Isothiocyanates react with diazoalkanes to give 5-amino-1,2,3-thiadiazoles. This reaction was first described by Pechman [1] with phenyl isothiocyanate and diazomethane, and has been subsequently extended to a variety of isothiocyanates and diazoalkanes [31-48].



Kinetic studies have shown that the reactivities of isothiocyanates and diazoalkanes decrease in the following sequence [48]:

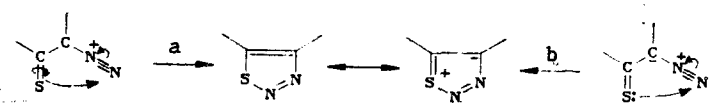
$$R^1 = PhCO > C_2H_5O_2C > p\text{-}NO_2Ph > m,o,p-ClPh > CH_2=CH-;$$
$$R = H > CH_2=CH- > C_2H_5O_2C- > PhCO.$$

In addition to the formation of thiadiazoles, decomposition of the diazo compounds occurs followed by reaction of the resulting carbenes with the starting materials and products. The yields obtained in these syntheses are therefore low, being with few exceptions in the range 30-70%. Introduction of electron-acceptor substitutents into the isothiocyanate increases the yields of thiadiazoles. If the changes in yield are equated with the rate of the main reaction, this observation is in accordance with excitation theory calculations [49-51].

This method enables 5-amino-1,2,3-thiadiazoles with a variety of substituents in the 4-position to be obtained, but in view of the great explosive hazards attending the use of diazo compounds, its synthetic potential and practical value are limited.

2.2. Heterocyclization of 2-Diazothiones

Cyclization of α-diazothioketones or α-diazothioamides affords exclusively 1,2,3-thiadiazoles. This system contains six π-electrons, and its conversion into the thiadiazole encounters a low energy barrier whether by electrocyclization (a) [52], or like the cyclization of azidoazomethine to tetrazole [53] without rotation around the C=S bond (b).



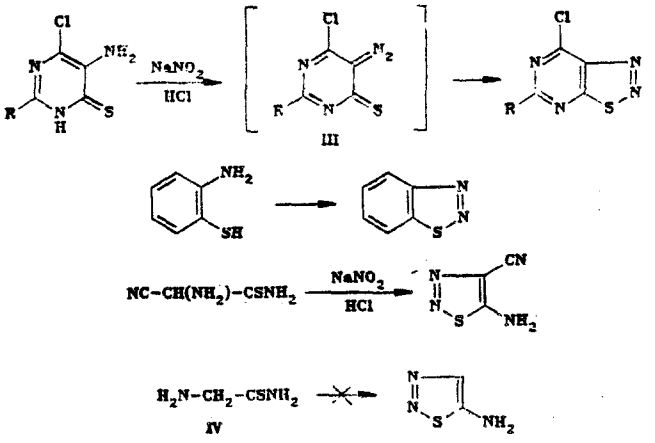
a and b

This method was used to synthesize condensed benzo[d], pyrimido[4,5-d]- [54], and amino- [55-57] and carbonyl-substituted [58, 59] 1,2,3-thiadiazoles.

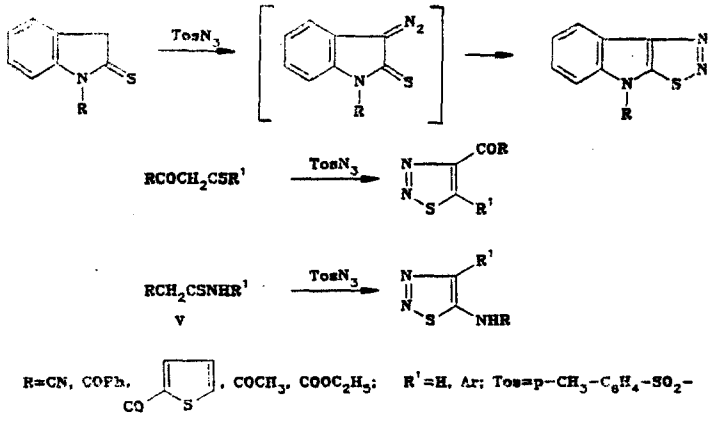
Diazothiones, which are compounds of low stability, cyclize to 1,2,3-thiadiazoles under the conditions of their preparation. The existence of these compounds has been shown by the isolation of the complex of 2-diazobenzenethione with iron nonacarbonyl, obtained by reacting benzo[d]-1,2,3-thiadiazole with $Fe_3(CO)_9$ [60].

Diazothiones may be generated by introducing the diazo group into compounds containing the carbon–sulfur double bond, constructing a C=S group in a diazo compound, or by the simultaneous introduction into organic compounds of diazo and thione groups.

2.2.1. Introduction of the Diazo Group into Thiones. Diazotization of aliphatic, aromatic, or heterocyclic 2-aminothiones gives 1,2,3-thiadiazoles, apparently via the intermediate diazothiones (III) [54, 58, 59]. The formation of 1,2,3-thiadiazoles by this method requires the presence of substituents in the thione molecule which stabilize the diazo compound. For example, Shafran et al. [58] were unable to obtain 5-amino-1,2,3-thiadiazoles by diazotizing 2-aminothioacetamide (IV).

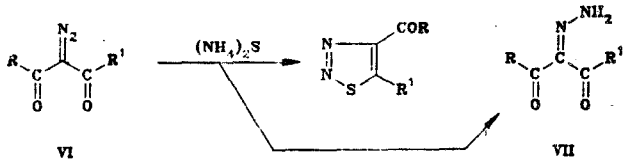


When thioketones containing acidic methylene protons are reacted with tosyl azide, the diazo function is also introduced into the molecule [61-63]. The resulting diazothiones rapidly cyclize to 1,2,3-thiadiazoles. With the thioamides (V), 5-amino-1,2,3-thiadiazoles are obtained [61, 62, 64, 65].

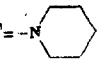


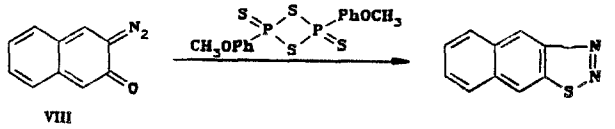
2.2.2. Introduction of the C=S Bond into Diazo Compounds. The introduction of the C=S bond into diazo compounds is severely restricted by the lability of the diazo compounds. The conversion of ketonic and amide groups with sulfurizing agents has been described [59, 66-68], together with the reaction of α-diazonitriles with hydrogen sulfide [55-57, 69] and the cleavage of thioesters [70].

Reaction of the acyldiazoalkanes (VI) with ammonium sulfide affords 4-carbonyl derivatives of 1,2,3-thiadiazole [59, 66].



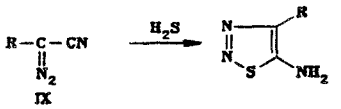
VI VII

It has been reported [59] that in the case of  instead of thiadiazoles, the hydrazone (VII), a reduction product of the diazo compound, is formed. Other types of sulfurizing agent have been used. For example, reaction of the diazoketones (VIII) with P_4S_{10} or Lawesson's reagent gives naphtho[2,3-d]-1,2,3-thiadiazole [67, 68].



VIII

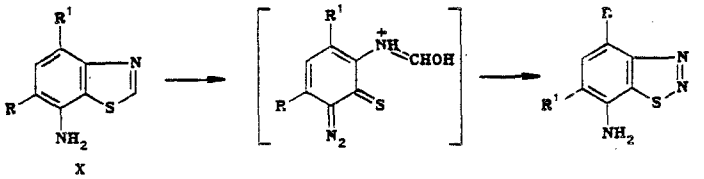
It is reasonable to assume that α-diazothioamides are intermediates in the reaction of diazoacetonitriles (IX) with hydrogen sulfide, leading finally to the formation of 5-amino-1,2,3-thiadiazoles. It is interesting that this reaction was described for different compounds independently and almost simultaneously by Konstantinova [55], Shafran [56], and Nakai [57].



IX

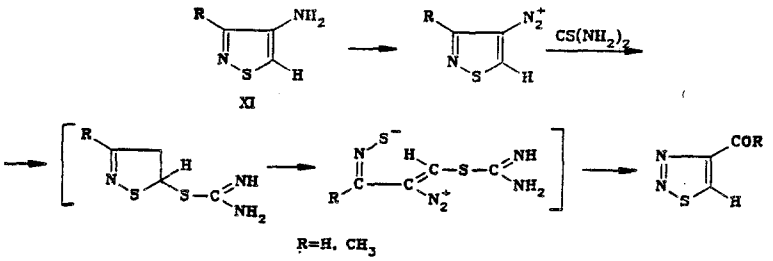
R=H, Alk., Ar. $COOC_2H_5$, COPh, $CONH_2$, $CONHCH_3$

When the aminobenzo[d]thiazoles (X) are diazotized, the thiazole ring is opened. As in the preceding reactions, it is likely that a diazothione is formed as an intermediate, this then cyclizing to the thiadiazole.



X

Diazotization of 4-aminobenzothiazoles (XI) followed by treatment with thiourea affords 4-carbonyl derivatives of 1,2,3-thiadiazole. This reaction probably proceeds via the following mechanism [71, 72]:

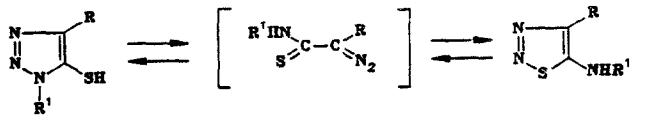


XI

R=H, CH_3

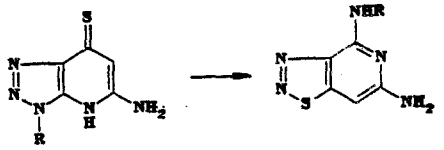
2.2.3. Simultaneous Introduction of Diazo and Thione Groups into Organic Compounds. This method includes opening of the 1,2,3-thiadiazole and -triazole rings, and the reaction of chloral tosylhydrazone with sodium sulfide.

On heating with acids, 5-mercapto-1,2,3-triazoles (XII) rearrange to 5-amino-1,2,3-thiadiazoles [31, 65, 73-80] (see also section 3.2)



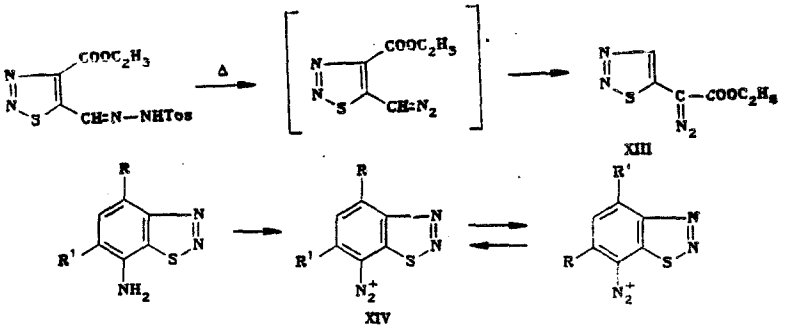
XII R=H, Alk, Ar, COOAlk, COPh; R'=H, Alk; Ar

It has been found that 1-aryltriazoles rearrange more easily than the 1-alkyl compounds, and that 1-benzyl-5-mercapto-1,2,3-triazole does not rearrange at all. In neutral solvents, or on fusion, 1,2,3-triazolo-[4,5-b]pyridine-4-thiones rearrange to 1,2,3-thiadiazolo[4,5-c]pyridines [75-77]. Replacement of the hydrogen in the 1-position of the triazole ring by the ribose residue results in considerable acceleration of recyclization.



R=H, β-D-ribofuranosyl

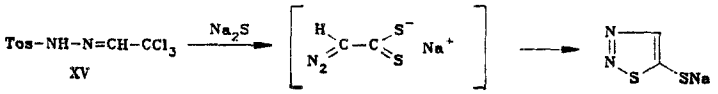
The introduction into the 5-position of 1,2,3-thiadiazole of a diazo-methyl group results in its conversion into the isomeric thiadiazole (XIII) [81]. A similar reaction has been described for condensed thiadiazoles (XIV) [82].



XIII

XIV

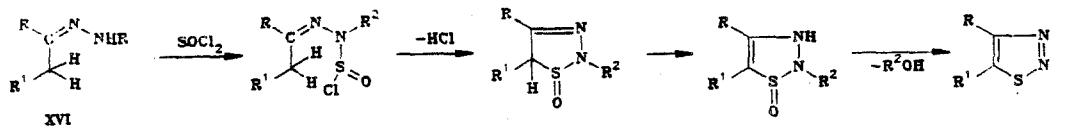
The reaction of the chloral hydrazone (XV) with sodium sulfide also apparently gives the diazothione, which cyclizes to 5-mercapto-1,2,3-thiadiazole [83].



XV

2.3. Reaction of Hydrazones with Thionyl Chloride

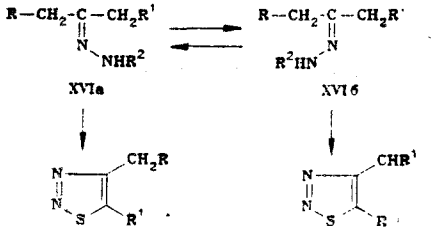
The most widely used method for the preparation of 1,2,3-thiadiazoles is by reacting hydrazones (XVI) with thionyl chloride [59, 84-105]. The yields in these syntheses are 30-80%. The following reaction mechanism is based on the isolation of intermediates and on kinetic studies [105].



XVI

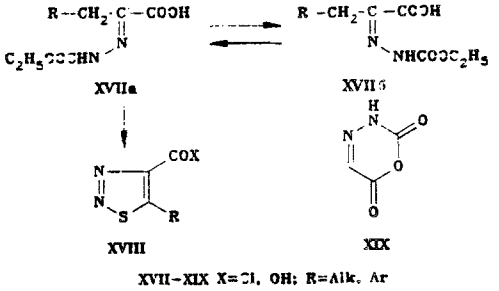
R=H, Alk, CH_2Ph, Ar, OAr; R'=H, Cl, Alk, Ph, COOH; —R—R'—=—$(CH{=}CH)_n$—
—N(R)—CON(R)—CO—; R^2=$COOC_2H_5$, $CONH_2$, Tos

It has been shown that the reaction of the aryl derivatives (XVI) with thionyl chloride is regioselective [88], whereas alkyl derivatives give a mixture of isomeric thiadiazoles [13].



It has been shown to be possible to use S_2Cl_2 or SCl_2 in this reaction in place of thionyl chloride [92, 103, 104], but the yields of thiadiazoles are substantially reduced.

The synthesis of thiadiazoles from hydrazones and thionyl chloride cannot be used when amino, mercapto, hydroxy, or other groups capable of reacting with thionyl chloride are present. It has been found [59] that the hydrazone (XVII), which contains a carboxyl group, gives in addition to the thiadiazole (XVIII), the oxadiazine (XIX), which is an intramolecular cyclization product.

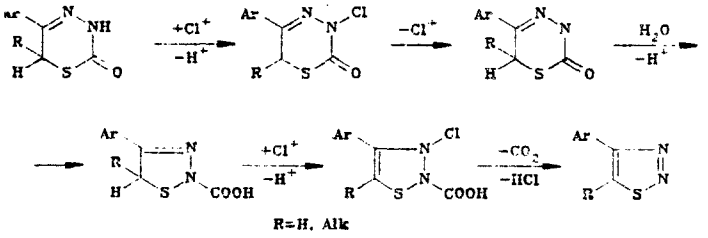


XVII–XIX X=Cl, OH; R=Alk, Ar

Since it has been shown [14, 85] that the Z-isomer is involved in cyclization, this method would be expected to be capable of extension to compounds containing reactive groups, but which are E-isomers.

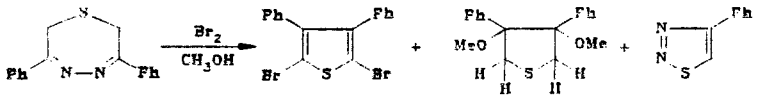
2.4. Other Methods

The transformation of 1,3,4-thiadiazin-2-ones in the presence of tert-butyl hypochlorite gives 1,2,3-thiadiazoles in yields of 35-85%. The authors have suggested the following mechanism [106]:

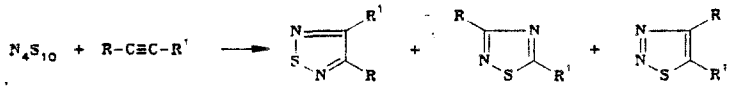


R=H, Alk

2,7-Dihydro-3,6-diphenyl-1,4,5-thiadiazepine on treatment with bromine is converted into a mixture of thiophens and 4-phenyl-1,2,3-thiadiazole [107]. It is interesting that treatment with chlorine gives the thiadiazole only.



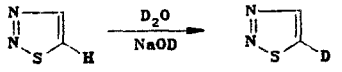
Reaction of N_4S_{10} with acetylene derivatives gives a mixture of thiadiazoles containing 9% of the 1,2,3-thiadiazole (XX) [108].



The information considered in this section leads to the conclusion that the best methods for the synthesis of 1,2,3-thiadiazoles are the reaction of hydrazones with thionyl chloride and the heterocyclization of diazothioketones and diazothioamides.

3. CHEMICAL PROPERTIES

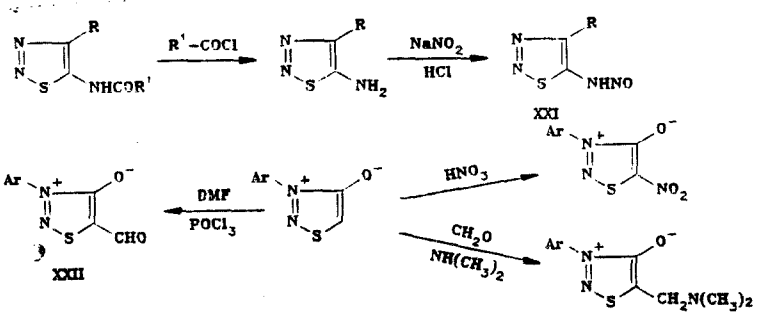
1,2,3-Thiadiazole undergoes reactions characteristic of other five-membered heterocycles. For example, boiling 1,2,3-thiadiazole with D_2O in the presence of NaOD results in replacement of the hydrogen in the 5-position of the ring by deuterium [109], the hydrogen in the 4-position remaining unchanged.



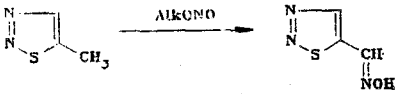
Similarly, alkoxy and methylthio groups, together with halogen atoms in the 5-position are readily replaced by C-, S-, and N-nucleophiles [87, 96, 110-114]. The possibility of nucleophilic substitution in the 4-position has not been studied.

Bromination of alkylated 1,2,3-thiadiazoles with N-bromosuccinimide results in replacement of a hydrogen in the side chain. In the case of monoalkyl derivatives, the ring hydrogen is not replaced [85, 115].

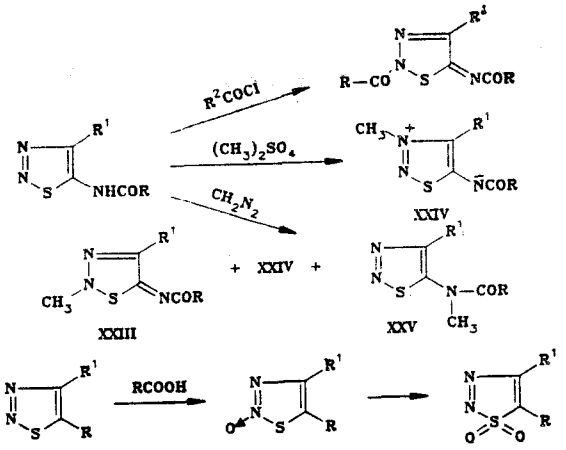
As NMR spectroscopy shows (see section 1), the 1,2,3-thiadiazole ring is π-deficient. This largely determines its chemical behavior. Acylation of 5-amino-1,2,3-thiadiazoles requires severe conditions, and the reaction with nitrous acid affords N-nitrosoamines (XXI) rather than the diazonium salts [31, 116]. In addition, 1,2,3-thiadiazoles are not known to undergo electrophilic replacement of ring hydrogen. An exception is the zwitterionic 3-phenyl-1,2,3-thiadiazol-4-olate (XXII). As a result of the influence of the ionized hydroxy group, the hydrogen in the 5-position of the ring becomes labile. This compound reacts with nitric acid, and undergoes Mannich aminomethylation and Vilsmeier formylation [116].



In consequence of the electron-acceptor properties of the ring, 5-methyl-1,2,3-thiadiazole functions as a CH-acid, and reacts readily with alkyl nitrites to give 5-hydroxyiminomethyl-1,2,3-thiadiazole [117].



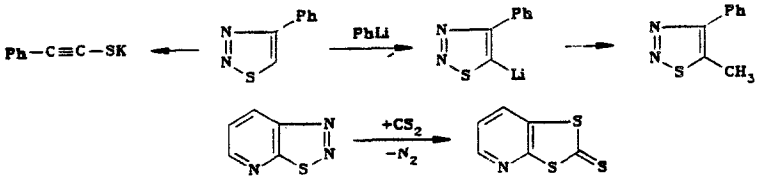
The alkylation [11, 31, 113, 114, 116, 118], acylation [11, 31, 114, 116, 118, 119] and oxidation by peracids [14, 120] of 1,2,3-thiadiazoles have been reported. There has been a report [31] of the alkylation of 5-acylamino-1,2,3-thiadiazoles by trimethyloxonium tetrafluoroborate in the 2-position of the ring. However, the proof given of the structure of the product (XXIII) is unreliable. It was later shown that alkylation with dimethyl sulfate gives the 1-methyl derivative (XXIV) [11], and diazomethane affords a mixture of thiadiazoles (XXIII-XXV) [11, 116].



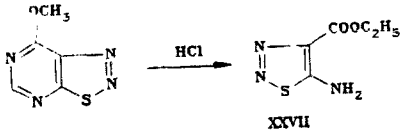
1,2,3-Thiadiazones are unique in their ease of decomposition by bases, transformations into other heterocycles, and their photo- and thermochemical decomposition.

3.1. Reactions With Bases and Acids

Treatment of 4-phenyl-1,2,3-thiadiazole with phenyllithium gives the thiadiazolyllithium (XXVI). Replacement of phenyllithium by potassium tert-butoxide or KOH, however, gives the potassium salt of mercaptoacetylene [121, 122]. Treatment with carbon disulfide with heating or in the presence of bases results in the conversion of 1,2,3-thiadiazoles into 1,3-dithiolanes [122, 123].



The 1,2,3-thiadiazole ring is more stable to acids than to bases. For example, on boiling 1,2,3-thiadiazolo[4,5-d]pyrimidines with aqueous hydrochloric acid, opening of the pyrimidine ring occurs [124]. The resulting 5-amino-1,2,3-thiadiazone (XXVII) is not converted into 5-mercapto-1,2,3-triazole on treatment with acids [31], although this conversion does take place on treatment with bases.



3.2. Photo- (and Thermo-)chemical Reactions

The photolysis of 1,2,3-thiadiazoles has been reported in several communications [125-132], in which it was shown that the photochemical decomposition of 1,2,3-thiadiazoles gives thiofulvenes (XXIX), thioanthrenes (XXX), thiophens (XXXI), and 1,2,5-trithiepins (XXXII) (Fig. 1).

The irradiation of thiadiazoles condensed with polyene rings gives rise to by-products. The effect of ring size on the course of the reaction has been examined, and it was found that as the ring size increased there was a tendency for sulfur to be eliminated and for dimerization to occur [128]. The formation of such a "rich" mixture of products in the photochemical degradation of thiadiazoles is explained by secondary reactions between the biradical (XXVIII), the thiirene (XXXV), and the thioketene (XXXIII) [128-135]. The formation of thiirenes in the photolysis of thiadiazole and its derivatives has been demonstrated by IR spectroscopy [136, 137]. These findings were confirmed in [109], which may be regarded as a model of chemical experimental methodology. These workers not only confirmed the formation of the thioketene (XXXIII) and ethynyl mercaptan (XXXIV) when thiadiazole was irradiated with ultraviolet light in an argon matrix, but they also showed in experiments with ^{13}C and ^{2}H tagged thiadiazoles that both the biradical (XXVIII) and the thiirene (XXXV) lay on the reaction coordinate. It was shown conclusively that (XXXIII) and (XXXIV) are formed by two routes (a and b, Fig. 1). The thioketene (XXXIII) is formed

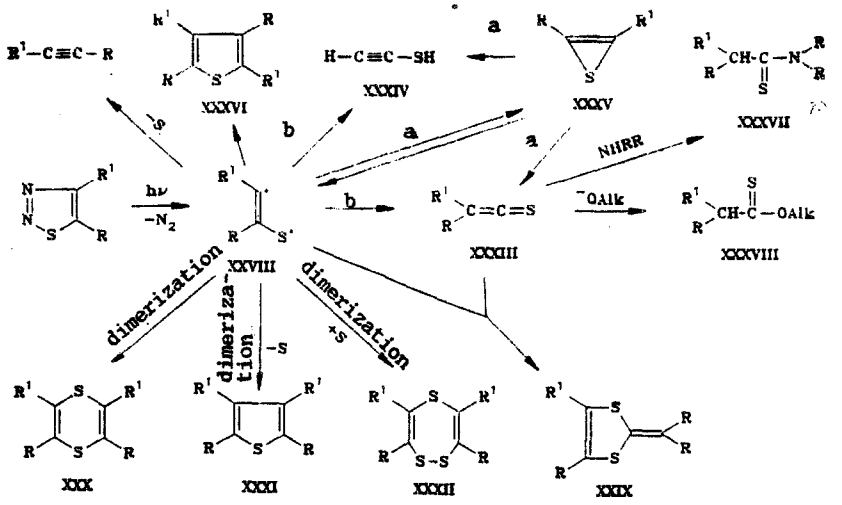


Fig. 1. Photochemical and thermal decomposition of 1,2,3-thiadiazoles.

preferentially by route b, and ethynyl mercaptan (XXXIV) by route a.

Photolysis of thiadiazoles in the presence of acetylenes results in 1,3-dipolar cycloaddition, with the formation of thiophenes (XXXVI) [109, 138, 139].

Thiadiazole 2-N-oxide, on irradiation with visible light, isomerizes to the 3-N-oxide, but on irradiation with UV it decomposes [14, 131, 140, 141].

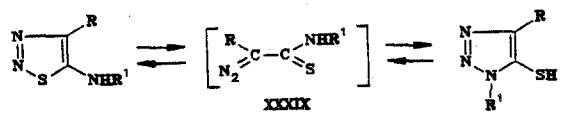
Thermolysis of 1,2,3-thiadiazoles leads to the formation of the thioketenes (XXXIII). Their formation has been established by flash thermolysis [142, 143], chemically [128], and by photoelectronic spectroscopy [144].

The thioketenes formed by photolysis or thermolysis of thiadiazoles are converted in the presence of amines into the thioamides (XXXVII), and in the presence of alcohols, into thioesters (XXXVIII) [121, 131, 135].

There is, unfortunately, no information in the literature on the photo- or thermochemical degradation of thiadiazoles containing amino, mercapto, or hydroxy groups in the 4- or 5-positions of the ring. Such studies would be of practical value, since such compounds are intermediates in the synthesis of thiadiazoles with useful properties. The only publication in this area is a study of the stability of 5-chloro-, 5-amino-, and 5-acetamido-1,2,3-thiadiazoles to mechanical treatment [145], in which it was shown that unlike the 5-acetamido-compounds, 5-chloro- and 5-amino-1,2,3-thiadiazoles decompose explosively at high pressures.

3.3. Transformation into Other Heterocycles.

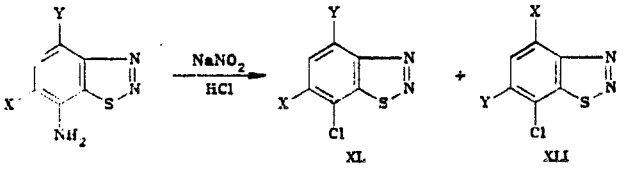
On treatment with bases, 5-amino-1,2,3-thiadiazoles rearrange to 5-mercapto-1,2,3-triazoles [31, 119, 146-148]. This reaction is reversible. Either by treatment with acids [65] or on heating in high-boiling solvents, 5-mercapto-1,2,3-triazoles are converted into 5-amino-1,2,3-thiadiazoles (see also Section 2.2). Electron-acceptor substituents accelerate both the forward and reverse reactions. Kinetic studies of the conversion of 5-amino-1,2,3-thiadiazoles into 5-mercapto-1,2,3-triazoles show that there is a good correlation between the rate constant and the Hammet constant [149]. It has been shown that 5-glycosylamino-, 5-ureido-, and 5-acetamido-1,2,3-thiadiazoles are not converted into triazoles [18, 31]. On the other hand, 1-glycosylated 1,2,3-triazolo[4,5-b]pyridine-4-thiones rearrange considerably faster than the unsubstituted compounds [73]. These findings lead to the conclusion that of the two isomeric rings, the more stable is the ring with a bulky substituent in the side chain. The intermediate in this reaction is the diazothione (XXXIX), which, depending on the substituents and the reaction medium, cyclizes to the thiadiazole or the triazole.



XXXIX

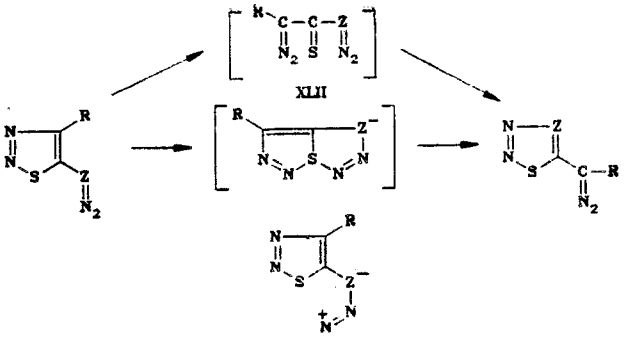
R^1=H, CH_3, Ar; R=H, CH_3, $COOC_2H_5$, COPh

The ease of fission of the N–S bond is one of the main reasons for the conversion of 1,2,3-thiadiazoles into other heterocycles. For example, diazotization of substituted 7-aminobenzo[d]-1,2,3-thiadiazoles followed by reduction with hypophosphorous acid or replacement by chlorine by the Sandmeyer reaction gives, generally speaking, both the normal product (XL) and the rearranged product (XLI) [82]. Bulky substituents in the 6-position favor the rearrangement. It remains unclear, however, whether rearrangement is possible in the unsubstituted compounds.



XL XLI

The introduction into the 5-position of the 1,2,3-thiadiazole ring of a diazomethyl group or an azido group also results in recyclization to the isomeric thiadiazole and thiatriazole respectively [81, 150].

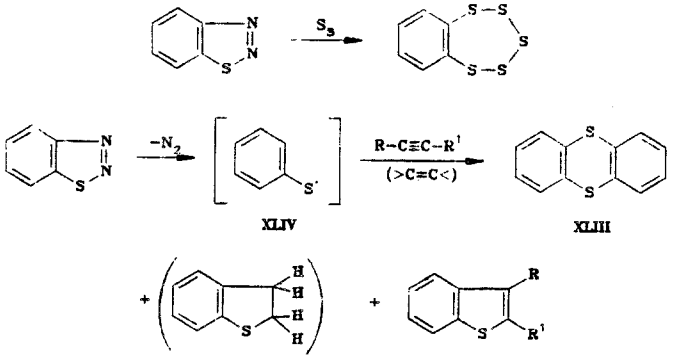


XLII

Z=CH. N

In principle, the reaction could follow three routes, either stepwise via the intermediate diazothione (XLII) or thiadiazolo[1,5-d]thiadi(or tri)azoles, or as a concerted reaction. This rearrangement takes place only when an electron-acceptor substituent is present in the 4-position of the ring.

Benzo[d]-1,2,3-thiadiazole reacts with sulfur to give benzopentathiepin [151], which on treatment with alkenes or alkynes in the presence of organic peroxides, which are radical sources, are converted into benzo[d]thiophens [152]. The isolation of the dithianthrene (XLIII) as a by-product indicates that the biradical (XLIV) is involved in the reaction.



XLIV XLIII

4. PRACTICAL APPLICATIONS

1,2,3-Thiadiazoles show a wide spectrum of physiological and biological activity. They display pesticidal [153-184], antiinflammatory [182], hypotensive [183], antibacterial [184-191], antiallergic [192-194], antitumor [195], and antihelmintic [196] activity. Compounds of this type inhibit enzymes such as monoamine oxidase [182, 197], phenylethanolamine

N-methyltransferase [198], and adenosine kinase [199]. The inhibition of β-adrenoreceptors by 1,2,3-thiadiazole derivatives [200], and the use of these compounds for the removal of stones from the bladder [201] have been described.

The greatest attention has been paid to the pesticidal properties of 5-ureido-, 5-thioureido-, 5-alkoxycarbonylamino-, and 5-acylamino-1,2,3-thiadiazoles. These compounds include herbicides [95, 102, 104, 118, 153-163], growth regulants [95, 154, 164], fungicides [155, 165, 166-173], and defoliants [96, 97, 157, 158, 175-180].

At the present time, 1-phenyl-3-(1,2,3-thiadiazol-5-yl)urea (dropp, defolite, thidiazuron) is used in the field as a defoliant for fine-fibered cotton [202, 203]. The effects of thidiazuron on fish and rats have been studied [204-208], and it was shown that the compound decomposed in the bodies of the animals, the products being excreted in the urine [208]. The great advantage of thidiazuron over other defoliants is its low toxicity and rapid breakdown to harmless compounds in the soil and under the influence of microorganisms [209, 210]. Its defoliant activity is due to the inhibition of photosynthesis [211]. Thidiazuron has been found to possess high cytokinin activity [211-215]. There has been shown to be a relationship between its defoliant effects and the liberation of ethylene by the leaves of the treated cotton [216]. The effects of thidiazuron are enhanced by a variety of organic and inorganic compounds [217-233].

CONCLUSION

This review shows the scientific and practical importance of the study of the properties of 1,2,3-thiadiazoles. The ease of rupture of the C—N and N—S bonds is the reason for the high reactivity of the ring in photo- (and thermo-)chemical breakdown and transformations into other heterocycles. In turn, the ease of breakdown of the 1,2,3-thiadiazole ring to compounds of lowmolecular weight favors the use of its derivatives as pesticides of low toxicity.

In spite of the considerable advances made during the last decade, little attention has been paid to nucleophilic and electrophilic substitution of the ring hydrogen atoms, the limits to the extension of the recyclization reaction are unclear, the photo- (and thermo-)chemical breakdown of compounds containing labile groups has not been examined, and all the methods used for the preparation of 1,2,3-thiadiazoles have considerable technological deficiencies.

Without question, solution of these problems will result in the coming decades in the discovery of novel chemical reactions of 1,2,3-thiadiazole, and its derivatives, in consequence of the lability of the ring to chemical, thermal, and light energy, and will find new applications in the fields of technology and biology.

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