FORMATION OF SUBSTITUTED 1,2,4-TRIAZOLES AND 3H-1,3,4-BENZOTRIAZEPINES FROM 5-ARYLTETRAZOLES AND N-ARYLBENZIMIDOYL CHLORIDES* (REVIEW)

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The review discusses the results obtained in the synthesis of substituted 1,2,4-triazoles and 3H-1,3,4-benzotriazepines from 5-aryltetrazoles and N-arylbenzimidoyl chlorides. The further possibilities of obtaining 3H-1,3,4-benzotriazepines, the mechanism of their formation, and the physical and chemical properties have been assessed.

The detailed and numerous investigations of the tetrazole chemistry, carried out in the last decade, have led to original approaches in the synthesis of new nitrogen-containing heterocyclic systems and have significantly improved the methods for the preparation of already known heterocyclic compounds. Different aspects of this problem have been assessed in recent studies of Katritzky [1, 2], in the monograph of Benson [3], as well as in some reviews [4, 5]. It can be assumed that one of the most interesting and promising trends in triazole chemistry is the study of the conversions of these compounds by the action of acyl and imidoyl chlorides. It has been shown in [6, 7] that the acylation of 5-substituted tetrazoles is a simple and effective preparation method (possibly also on the industrial scale) for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles with different structures. On the other hand, in our opinion the reaction of 5-substituted tetrazoles with imidoyl chlorides is of particular interest: depending on the conditions, 3,4,5-trisubstituted 1,2,4-triazoles or the formerly inaccessible 3H-1,3,4-benzotriazepines can be obtained. It can be pointed out that during the past 5-7 years the interest in 1,3,4-benzotriazepines — compounds with a high biological and pharmacological activity — is steadily increasing [8-12]; considerable attention is paid in this series to the 3H-1,3,4-benzotriazepines, which have become available only a few years ago [13-15].

The present review discusses the available literature references on the reaction of 5-substituted tetrazoles with imidoyl chlorides and new experimental data, obtained by the authors of the review. When discussing this problem the main attention is paid to the possible use of this reaction for synthesis, mainly for the preparation of 3H-1,3,4-benzotriazepines, as well as to the mechanism of the conversions of 5-substituted tetrazoles by the action of imidoyl chlorides.

In 1960 Huisgen and coworkers [16] proposed a convenient method for the preparation of 3,4,5-trisubstituted 1,2,4-triazoles, consisting in the reaction of 5-aryltetrazoles with imidoyl chlorides in boiling pyridine. It was considered for a long time that 2-imidoyltetrazole is formed at the first stage of this reaction, which by thermal cleavage and the elimination of a molecule of nitrogen is converted to imidoylnitrilimine. Subsequent cyclization of the imidoylnitrilimine leads to 1,2,4-triazole [17, 18]. However, it has been shown later that in the thermolysis in xylene of the reliably obtained 1- and 2-(N-arylbenzimidoyl)-5-dimethylaminotetrazoles instead of the expected 1,2,4-triazoles, the 3H-1,3,4-benzotriazepines are formed [13, 14]. It was thus evident that the mechanism of the reaction of 5-substituted tetrazoles with imidoyl chlorides, postulated in [16-18], required a thorough revision.

A new important piece of information on the mechanism of this reaction was obtained by the authors of the present review when investigating the reaction of 5-aryltetrazoles with N-arylbenzimidoyl chlorides at the conditions of interphase catalysis in the liquid–liquid system [15]. It was found that isomeric 1- and 2-(N-arylbenzimidoyl)tetrazoles were formed from the 5-aryltetrazoles and N-arylbenzimidoyl chlorides, the thermolysis of which leads to 3H-1,3,4-benzotriazepines. In the further investigation of this reaction the main attention was concentrated on studying the influence of the nature of the reaction medium and of the electron structure of the substituents in the substrate and in the reagent on the character of the products formed.

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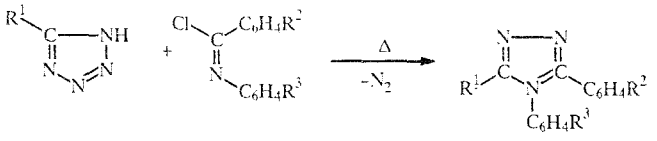
TABLE 1. 1,2,4-Triazoles Ia-i

Compound	mp, °C	Yield, %	Compound	mp, °C	Yield, %
Ia	299...300	77	I	251...252	55
Ib	300...301	73	I	251...253	84
Ic	268...269	90	I	277...278	67
Id	279...280	84	I	268...269	70
Ie	262...263	62			

TABLE 2. Characteristics of 3H-1,3,4-Benzotriazepines IVa-ℓ

Compound	mp, °C	IR spectra, ν, cm^{-1}, NH	Yield, %	Compound	mp, °C	IR spectra, ν, cm^{-1}, NH	Yield, %
IVa	225...226	3350	65	IVg	273...274	3350	71
IVb	243...244	3315	62	IVh	249...250	3350	75
IVc	234...235	3325	64	IVi	245...248	3285	69
IVd	252...253	3340	31	IVk	229...230	3350	48
IVe	238...239	3335	68	IVℓ	237...239	3345	69
IVf	227...228	3360	72				

It was found that heating (to 85-100°C) of 5-phenyltetrazole with N-phenylbenzimidoyl chloride without a solvent or with solvents that differed significantly in their physicochemical properties (toluene, dioxane, pyridine, benzonitrile, and DMFA) gave 3,4,5-triphenyl-1,2,4-triazole with yields of 67, 77, 60, 81, 60, and 14% respectively. In this series the only exception is DMFA, the yield of triazole in which is reduced due to tar formation. Thus, the polarity and the main properties of the solvents do not have a significant influence on the course of this reaction. It must be pointed out that in the preparative connection this method for the preparation of 3,4,5-trisubstituted 1,2,4-triazoles distinguishes itself favorably from the method proposed in [16], since instead of pyridine the considerably less toxic toluene and m-xylene can be used as solvents. The effectiveness of the proposed method was demonstrated on the series of 5-aryl(hetaryl)tetrazoles and N-arylbenzimidoyl chlorides (Table 1). The reaction was carried out in m-xylene at 90-100°C. Benzonitrile was used as the solvent for 5-(pyridin-4-yl)tetrazole because of its poor solubility in m-xylene.



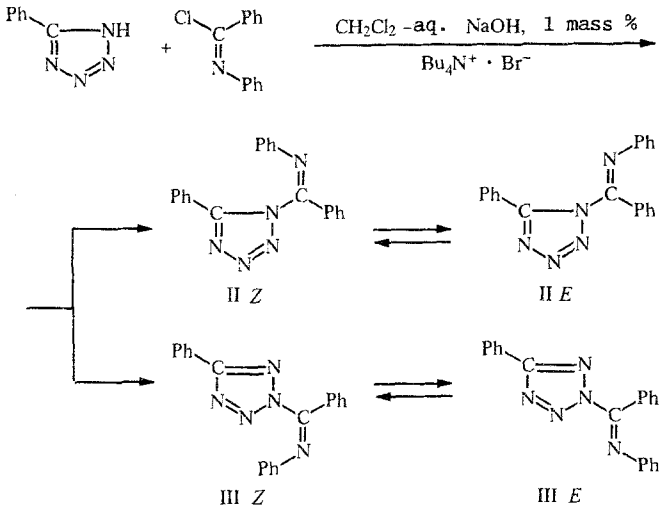
I a-

I a R^1 = Ph, R^2 = R^3 = H; b R^1 = Ph, R^2 = H, R^3 = 4-CH_3; c R^1 = Ph, R^2 = H, R^3 = 4-Cl; d R^1 = Ph, R^2 = =H, R^3 = 4-NO_2; e R^1 = Ph, R^2 = 4-CH_3, R^3 = H; f R^1 = Ph, R^2 = 4-CH_3, R^3 = H; g R^1 = Ph, R^2 = 4-Br, R^3 = H; h R^1 = $C_6H_4NO_2$-4, R^2 = R^3 = H; i R^1 = Py-4, R^2 = R^3 = H

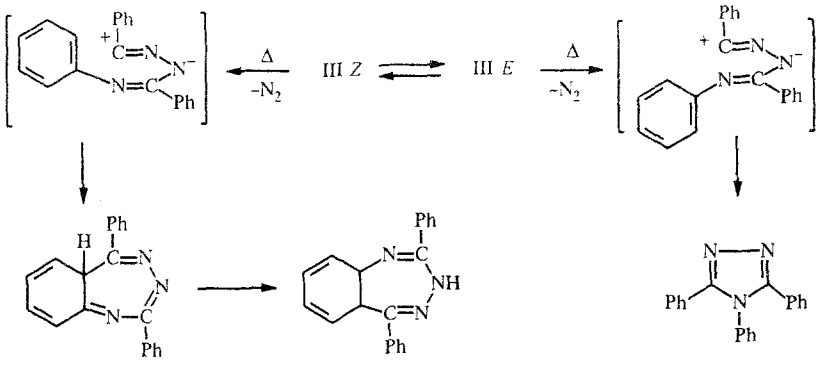
The triazole Ih was also obtained from 5-phenyltetrazole and N-phenyl-4-nitrobenzimidoyl chloride with a yield of 57%.

A completely different picture was obtained in the thermolysis of 1- and 2-imidoyltetrazoles, reliably formed in the reaction of 5-phenyltetrazole with N-phenylbenzimidoyl chloride in a two-phase system consisting of methylene chloride (chloroform) and water in the presence of tetrabutylammonium bromide. When the reaction proceeds without a solvent or in solvents such as toluene, dioxane, and benzonitrile, 2,5-diphenyl-3H-1,3,4-benzotriazepine is formed with a yield of 33, 65, 63, and 77% respectively. The thermolysis of 1 - and 2-imidoyltetrazoles in pyridine or dimethylformamide leads to a mixture of two products: 2,5-diphenyl-3H-1,3,4-benzotriazepine and 3,4,5-triphenyl-1,2,4-triazole with a summary yield of 52 and 42%. Regardless of the nature of the solvent the benzotriazepine–triazole ratio is ~1.5:1.

These results can be interpreted satisfactorily in the following way. According to [15], the reaction of 5-phenyltetrazole with N-phenylbenzimidoyl chloride at the conditions of interphase catalysis gives 1- and 2-(N-phenylbenzimidoyl)-5-phenyltetrazoles, each of which is present in the form of Z- and E-isomers.



According to [13, 15] 1,2,4-triazoles and 3H-1,3,4-benzotriazepines are formed in the thermolysis of 1- as well as of 2-imidoyltetrazoles, whereby the thermolysis of 1-imidoyltetrazoles proceeds through an isomerization stage to 2-imidoyl derivatives. Thermal splitting of 2-imidoyltetrazoles, accompanied by the loss of one molecule of nitrogen, leads to reaction products, the structure of which will depend on which of the isomers (IIIZ or IIIE) is subjected to thermolysis. The conversions of the Z-isomer must lead to 3H-1,3,4-benzotriazepine, of the E-isomer to 1,2,4-triazole. In this instance the mechanism of the thermolysis of IIIZ and IIIE can be presented by the following scheme.



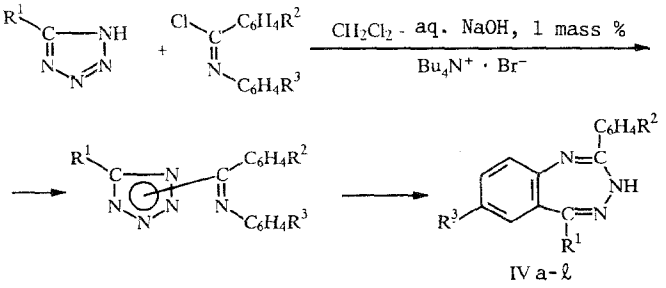
Thus, it is obvious that the 1- and 2-imidoyltetrazoles, formed when 5-phenyltetrazole is heated with N-phenylbenzimidoyl chloride, are present principally in the form of E-isomers, regardless of the properties of the reaction medium. The energy barrier of the thermolysis of these compounds is probably lower than the energy barrier of the Z ⇄ E equilibrium; as a result of this, 3,4,5-triphenyl-1,2,4-triazole is formed in the thermolysis.

A different picture is obtained in the thermolysis of imidoyltetrazoles IIZ, IIE, IIIZ, and IIIE, reliably obtained at the conditions of interphase catalysis. At these conditions the above imidoyltetrazoles are formed in the ratio* (IIZ+IIE):(IIIZ+IIIE) = 1.01; IIZ:IIE = 1.50; IIIZ:IIIE = 0.94.

*Calculated from ^{13}C NMR spectra.

It follows from these data that in the mixture of the isomers the Z-isomers predominate. This explains why 2,5-diphenyl-3H-1,3,4-benzotriazepine is formed in the thermolysis of imidoyltetrazoles, obtained at the conditions of interphase catalysis, regardless of the properties of the reaction mixture. The formation of two products (2,5-diphenyl-3H-1,3,4-benzotriazepine and 3,4,5-triphenyl-1,2,4-triazole) in pyridine and dimethylformamide is evidently due to the fact that these solvents affect the state of the Z ⇄ E equilibrium by shifting it to the side of the E-isomer.

The direction of the thermolysis of imidoyltetrazoles depends not only on the conformation of these compounds but also on the electron structure of the substituents in the imidoyl fragment. Thus, it was found that in the thermolysis of imidoyltetrazoles in xylene, obtained at the conditions of interphase catalysis from 5-phenyltetrazole and N-(4-nitrophenyl)benzimidoyl chloride, not 7-nitro-2,5-diphenyl-3H-1,3,4-benzotriazepine, but 3,5-diphenyl-4-(4-nitrophenyl)-1,2,4-triazole is formed with a yield of 68%. On the other hand in the thermolysis of imidoyltetrazoles in toluene or xylene, containing in the imidoyl fragment electron - donor or weak electron-acceptor substituents, the corresponding 3H-1,3,4-benzotriazepines are formed with good yields (Table 2).

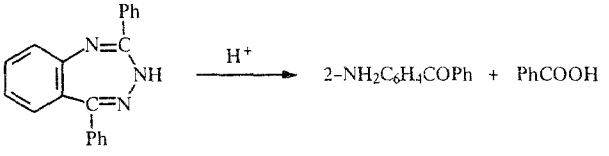


IV a-ℓ

IV a R^1 = Ph, R^2 = R^3 = H; b R^1 = Ph, R^2 = H, R^3 = 4-CH_3; c R^1 = Ph, R^2 = H, R^3 = 4-Cl; d R^1 = Ph, R^2 = 4-CH_3, R^3 = H; e R^1 = Ph, R^2 = 4-OCH_3, R^3 = H; f R^1 = Ph, R^2 = 4-Br, R^3 = H; g R^1 = $C_6H_4CH_3$-4, R^2 = R^3 = H; h R^1 = C_6H_4Br-4, R^2 = R^3 = H; i R^1 = Ph, R^2 = 4-NO_2, R^3 = H; k R^1 = $C_6H_4NO_2$-4, R^2 = = R^3 = H; ℓ R^1 = Py-4, R^2 = R^3 = H

The study of the physicochemical properties of 3H-1,3,4-benzotriazepines has only started. Data are given in [13, 14] on the crystal structure of 7,9-dimethyl-5-dimethylamino-2-phenyl-3H-1,3,4-benzotriazepine. IR spectra and ^1H NMR spectra of the series of 3H-1,3,4-triazepines have been obtained [13, 14]. It has been noticed that the IR spectra of these compounds contain bands in the region 3285-3360 cm^{-1}, which have been identified as stretching vibrations of the $N_{(3)}-H$ bond.

Information on the chemical properties of 3H-1,3,4-benzotriazepines is virtually missing. According to data, obtained by the authors of the review, these compounds are relatively resistant to the action of bases, however they hydrolyze in aqueous solutions of mineral acids. Thus, heating of 2,5-diphenyl-3H-1,3,4-benzotriazepine in 35%; hydrochloric acid for 1.5 h at 90-95°C gives 2-aminobenzophenone and benzoic acid with yields of 95 and 63% respectively.



In conclusion some general comments must be made on the mechanism of the reaction of 5-substituted tetrazoles with imidoyl chlorides and on the possibility of using this reaction as a universal method for the synthesis of 3H-1,3,4-benzotriazepines. Firstly, we cannot answer the question, whether the 1-imidoyltetrazoles are isomerized to the 2-imidoyltetrazoles by preserving the conformation. We are not totally convinced that the thermolysis of 2-imidoyltetrazoles proceeds via the formation of an intermediate imidoyltetrazole, which as the result of a dipolar 1,7-electrocyclization is con-

verted to 3H-1,3,4-benzotriazepine, as this is assumed to happen in the formation of 3H-2-benzazepines and 3H-1,2-benzodiazepines [19-21]. It is possible that the reaction proceeds according to a coordinated mechanism, in one stage. So far there are no unambiguous replies to these questions; their solution requires kinetic investigations.

From the synthesis aspect the reaction of 5-substituted tetrazoles with N-arylbenzimidoyl chlorides can be considered as a sufficiently universal method for the preparation of 3H,1,3,4-benzotriazepines. However, it must be pointed out that the attempts of obtaining 3H-1,3,4-benzotriazepine from 5-methyltetrazole and N-phenylbenzimidoyl chloride, and from 5-phenyltetrazole and N(4-nitrophenyl)benzimidoyl chloride have been unsuccessful.

On the other hand the material presented shows that the reaction of 5-substituted tetrazoles with imidoyl chlorides represents a new promising approach to the synthesis of 1,2,4-triazoles and 3H-1,3,4-benzotriazepines.

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