Synthesis of 3H-1,3,4-Benzotriazepines from 5-Aryltetrazoles and N-Arylbenzimidoyl Chlorides

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Heating of 5-phenyltetrazole with N-phenylbenzimidoyl chloride in the absence of solvent or in toluene, dioxane, benzonitrile, pyridine or N,N-dimethylformamide results in the formation of 3,4,5-triphenyl-1,2,4-triazole 1. Thermolysis of 1-imidoyl- and 2-imidoyl-5-phenyltetrazoles (obtained from the same reagents under phase-transfer conditions) in dioxane, toluene and benzonitrile leads to 2,5-diphenyl-3H-1,3,4-benzotriazepine 2. In pyridine and N,N-dimethylformamide a mixture of triazole 1 and triazepine 2 in the ratio approximately 1:1.5 is obtained under the same conditions. Heating of imidoyltetrazoles, obtained from 5-aryltetrazoles and N-arylbenzimidoyl chlorides, in m-xylene results in formation of the corresponding 3H-1,3,4-benzotriazepines.

In 1960 the convenient method of synthesis of 3,4,5-trisubstituted 1,2,4-triazoles by reaction of 5-aryltetrazoles with imidoyl chlorides in boiling pyridine was proposed by Huisgen et al.[1] For a long time it was assumed that in the first stage of this reaction 2-imidoyltetrazole is generated, which is converted into imidoylnitrilimine as a result of thermal decomposition and elimination of a nitrogen molecule. The following cyclization of imidoylnitrilimine leads to 1,2,4-triazole.[2,3]

By examination of this process we have found that reaction of 5-aryltetrazoles with N-arylbenzimidoyl chlorides in a dichloromethane–water two-phase system in the presence of tetrabutylammonium bromide results in the formation not only of 2-imidoyltetrazoles but also of isomeric 1-imidoyltetrazoles, and both 1-imidoyl- and 2-imidoyl-tetrazoles as Z,E-isomers. It was also shown, that upon heating of these compounds to 85–120°C in the absence of solvent or in toluene, m-xylene, or dioxane, 3H-1,3,4-benzotriazepines are formed instead of 1,2,4-triazoles.[4]

The present paper is devoted to the further investigation of the reaction of 5-aryltetrazoles with N-arylbenzimidoyl chlorides and, in particular, to study the influence of the reaction media properties and of the electronic structure of substituents in both substrate and reagent on the nature of the end products. It was found out that

upon heating of 5-phenyltetrazole with N-phenylbenzimidoyl chloride to 85–100°C in different solvents or in the absence of solvent, 3,4,5-triphenyl-1,2,4-triazole 1 is formed in high yield. The yield of triazole 1 was in the range 60–80% without solvent or in toluene, dioxane, pyridine or benzonitrile; in N,N-dimethylformamide (DMF) the yield was only 15%. Only DMF is an exception, where formation of triazole 1 is complicated by side reactions, leading to resinous products. Thus, it is obvious that polarity and basicity of solvents do not influence the direction of this reaction.

The situation changes drastically when 1-imidoyl- and 2-imidoyl-tetrazoles [obtained by reaction of 5-phenyltetrazole with N-phenylbenzimidoyl chloride in the dichloromethane (chloroform)–water two-phase system in the presence of tetrabutylammonium bromide] are thermolysed. In toluene, dioxane, benzonitrile, and in the absence of the solvent, 2,5-diphenyl-3H-1,3,4-benzotriazepine 2 is the sole product of the reaction. Upon thermolysis of 1-imidoyl- and 2-imidoyl-tetrazoles in pyridine or DMF both 3,4,5-triphenyl-1,2,4-triazole and 2,5-diphenyl-3H-1,3,4-benzotriazepine are formed in the ratio approximately 1:1.5 (Table 1, Scheme 1).

These results could be satisfactorily interpreted in terms of the reaction mechanism suggested earlier.[4–6] According to references,[4–6] in the first stage of reaction (Scheme 2) 1-imidoyl- and 2-imidoyl-tetrazoles are formed, both of them in the form of Z,E-isomers. Upon heating, 1-imidoyltetrazoles undergo isomerization to 2-imidoyltetrazoles. Further transformations of 2-imid-

Table 1. Influence of the nature of the solvent on the thermolysis products.

| Solvent	Yield (%)	
	Triazole **1**	Triazepine **2**
–	–	33
Toluene	–	65
Dioxane	–	63
Pyridine	21	31
Benzonitrile	–	71
DMF	17	25
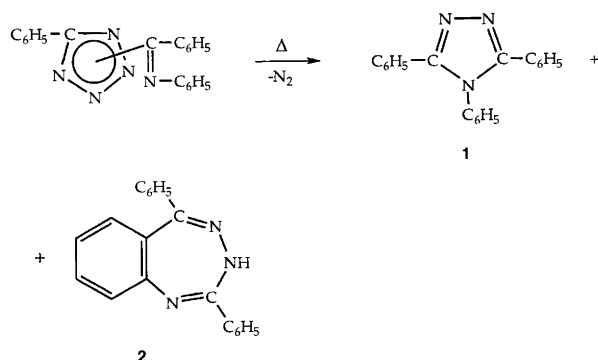
Scheme 1.

oyltetrazoles lead to the reaction products. The structure of the products, formed by thermolysis of these compounds, will obviously depend upon the structure of the isomer (Z or E) that undergoes thermal splitting. The transformation of Z-isomer **3** should lead to the triazepine, and the transformation of E-isomer **4** to triazole. Probable structures of the intermediates, formed under thermolysis of Z- and E-isomers, are shown in Scheme 2.

Thus, it is reasonable to assume that upon heating of 5-phenyltetrazole with N-phenylbenzimidoyl chloride, independent of the properties of the reaction medium, 1-imidoyl- and 2-imidoyl-5-phenyltetrazoles formed are mainly in the form of the E-isomers. The energy barrier for thermolysis of these compounds is obviously lower than the energy barrier for the conversion of the E-isomer into the Z-isomer, which is the reason for the triazole formation during thermolysis.

The situation changes when reaction of 5-phenyltetrazole with N-phenylbenzimidoyl chloride occurs under the phase-transfer conditions. In this case the 1-imidoyl- and 2-imidoyl-5-phenyltetrazoles formed are mainly in the form of Z-isomers. Upon thermolysis of these compounds in toluene, dioxane, benzonitrile or in the absence of the solvent, 2,5-diphenyl-3H-1,3,4-benzotriazepine is formed. In polar solvents that are sufficiently basic (pyridine and DMF), 3,4,5-triphenyl-1,2,4-triazole is formed along with triazepine **2**. The last fact is obviously connected with the ability of basic solvents to shift the equilibrium (1) to the left.

$$E \rightleftharpoons Z \qquad (1)$$
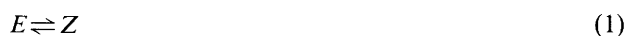
It is necessary to add that the direction of thermolysis of imidoyltetrazoles depends not only upon the conformation of these compounds, but also upon the electronic structure of the substituents in imidoyl moiety. So, upon heating of 5-phenyltetrazole with N-(p-nitrophenyl)benzimidoyl chloride in m-xylene or imidoyltetrazoles (vide supra) one and the same product – 3,5-diphenyl-4-(p-nitrophenyl)-1,2,4-triazole – is formed with the yields 84 and 68%, respectively.

On the other hand, upon thermolysis of imidoyltetrazoles containing electron-donating or weak electron-accepting substituents (obtained by means of the phase-transfer catalysis technique), the corresponding 3H-1,3,4-benzotriazepines are formed in good yield.

Finally it is necessary to point out that thermolysis of (Z)-imidoyltetrazoles provides a convenient method for the synthesis of 3H-1,3,4-benzotriazepines, a little-investigated class of compounds.

Experimental

IR spectra were recorded on a Specord M-80 spectrophotometer using KBr pellets. ^{1}H NMR spectra were measured on Tesla BS-487C spectrometer using solutions in DMSO-d_6 [vs. hexamethyldisiloxane (HMDS) as internal standard].

N-Arylbenzimidoyl chlorides and 5-aryltetrazoles were prepared according to known methods. The physical characteristics and properties of these compounds matched their literature data.[1,7,8]

3,4,5-Triphenyl-1,2,4-triazole. A mixture of 1.46 g of 5-phenyltetrazole and 2.16 g N-phenylbenzimidoyl chloride in 5 ml of toluene was heated for 2.5 h at 90–100°C, the resulting yellow precipitate was removed by filtration and washed with 10 ml of ethanol to give 2.29 g (77%) 3,4,5-triphenyl-1,2,4-triazole, m.p. 299–300°C (from DMF). Literature data:[1] m.p. 297°C. IR (KBr): 3080, 2945, 1680, 1600, 1510, 1475, 1450, 1410, 1360, 1280, 1190, 1080, 1030, 980, 940, 850, 790, 780, 720, 700 cm^{-1}. Anal. $C_{20}H_{15}N_3$: C, H, N.

3,5-Diphenyl-4-(p-nitrophenyl)-1,2,4-triazole. Prepared from 0.86 g of 5-phenyltetrazole and 1.53 g N-(p-nitrophenyl)benzimidoyl chloride in m-xylene, using the above procedure. Yield of 3,5-diphenyl-4-(p-nitrophenyl)-1,2,4-triazole, 1.69 g (84%), m.p. 279°C (from ethanol–DMF 1:2). Literature data:[9] m.p. 280°C. IR (KBr): 3075, 1610, 1600, 1530, 1500, 1480, 1460, 1410, 1365, 1310, 1300, 1180, 1120, 1100, 1080, 1030, 970, 940, 865, 790, 780, 720, 710 cm^{-1}. Anal. $C_{20}H_{14}N_4O_2$: C, H, N.

2,5-Diphenyl-3H-1,3,4-benzotriazepine. A mixture of 0.73 g 5-phenyltetrazole, 0.22 g of NaOH, and 0.1 g of tetrabutylammonium bromide in 20 ml of water was stirred until all the tetrazole dissolved, and to this solution were then added 10 ml dichloromethane and 1.07 g N-phenylbenz-
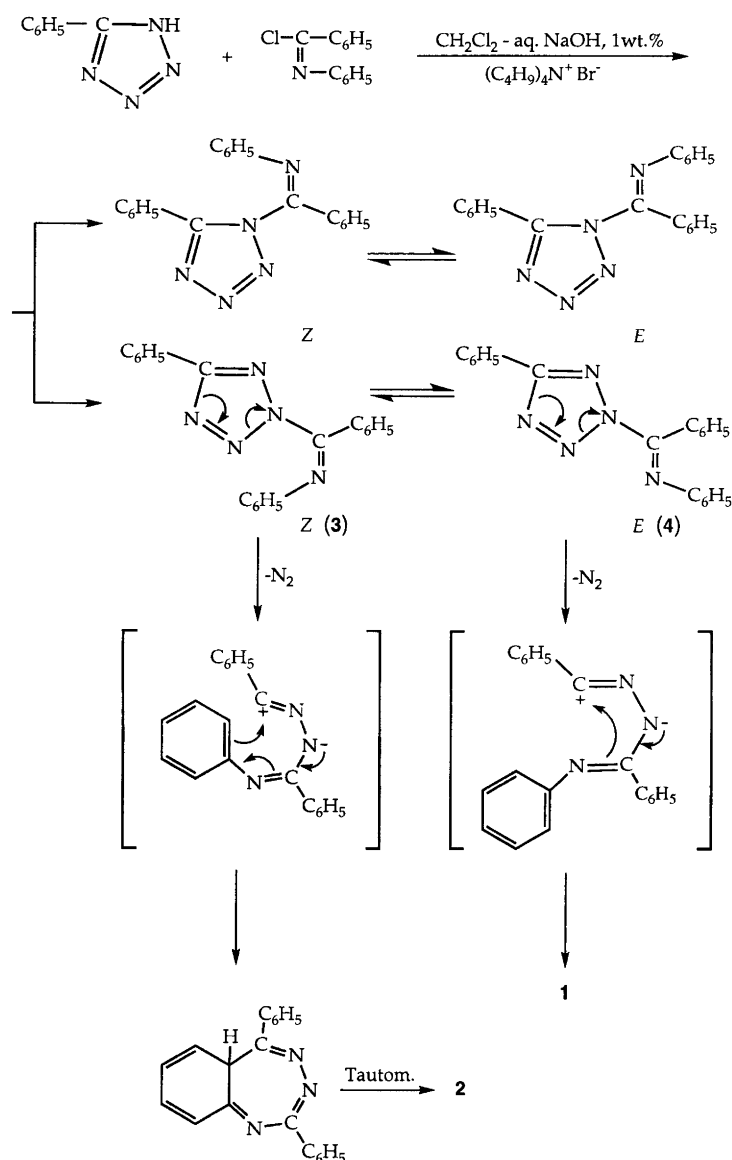
Scheme 2.

imidoyl chloride in 10 ml dichloromethane; the mixture was then stirred for 2 h at 25°C. After phase separation the organic layer was washed consecutively with water (20 ml), aqueous NaOH (1 weight %, 20 ml) and water (20 ml), and dried over anhydrous magnesium sulfate. The solvent was evaporated off under vacuum and to the residue were added 5 ml of toluene and the mixture was heated for 2.5 h at 85–95°C. The solution was cooled and the resulting yellow crystalline precipitate was removed by filtration to give 0.96 g (65%) 2,5-diphenyl-3*H*-1,3,4-benzotriazepine, m.p. 225–226°C (from ethanol–DMF 1:2). IR (KBr): 3350, 1610, 1560, 1500, 1455, 1415, 1330, 1290, 1230, 1180, 1120, 1080, 1040, 980, 930, 785, 775, 765, 755, 695 cm^{-1}. ^{1}H NMR (100 MHz; DMSO-d_6, HMDS): δ 6.95 (m, 2 H, C_6H_4), 7.34 (m, 10 H, 2C_6H_5), 7.81 (m, 2 H, C_6H_4). Found: *M*, 314, calc. for $C_{20}H_{15}N_3$, 297.

Other triazepines were prepared analogously. *m*-Xylene was used as the solvent for thermolysis.

7-Methyl-2,5-diphenyl-3H-1,3,4-benzotriazepine. Yield 62%, m.p. 244–245°C. Anal. $C_{21}H_{17}N_3$: C, H, N. IR v_{NH} (KBr): 3315 cm^{-1}.

7-Chloro-2,5-diphenyl-3H-1,3,4-benzotriazepine. Yield 64%, m.p. 234–236°C. Anal. $C_{20}H_{14}ClN_3$: C, H, N. IR v_{NH} (KBr): 3325 cm^{-1}.

5-Phenyl-2-(p-tolyl)-3H-1,3,4-benzotriazepine. Yield 31%, m.p. 251–252°C. Anal. $C_{21}H_{17}N_3$: C, H, N. IR v_{NH} (KBr): 3340 cm^{-1}.

2-(p-Methoxyphenyl)-5-phenyl-3H-1,3,4-benzotriazepine. Yield 68%, m.p. 240–241°C. Anal. $C_{21}H_{17}N_3O$: C, H, N. IR v_{NH} (KBr): 3335 cm^{-1}.

2-(p-Bromophenyl)-5-phenyl-3H-1,3,4-benzotriazepine. Yield 72%, m.p. 227–228°C. Anal. $C_{21}H_{14}BrN_3$: C, H, N. IR v_{NH} (KBr): 3360 cm^{-1}.

*2 - Phenyl - 5 - (p - tolyl) - 3*H *- 1,3,4-benzotriazepine.* Yield 71%, m.p. 273–274 °C. Anal. $C_{21}H_{17}N_3$: C, H, N. IR ν_{NH} (KBr): 3350 cm^{-1}.

*5 - (p - Bromophenyl) - 2 - phenyl - 3*H *- 1,3,4 - benzotriaz-epine.* Yield 75%, m.p. 249–251 °C. Anal. $C_{21}H_{14}BrN_3$: C, H, N. IR ν_{NH} (KBr): 3350 cm^{-1}.

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