

SYNTHESIS OF SOME 5-ARYL(HETARYL)TETRAZOLES BY ULTRASONICATION

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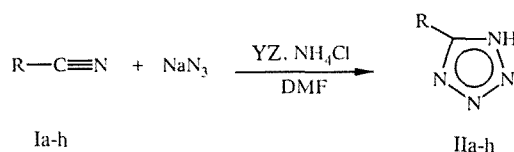
The influence of ultrasound on the 1,3-dipolar cycloaddition of azides to organic nitriles to form of 1H-5-aryl(hetaryl)tetrazoles was studied. It was shown that ultrasound decreases the reaction time, and increases the yield of the desired compounds.

The chemical literature at present shows a growing number of publications on the favorable influence of ultrasound upon different reactions, including cycloaddition. Thus, for example, in [1, 2] success is reported in significantly stimulating the process and in attaining high yields upon sonochemical exposure in reactions of this type.

The most universal method for the synthesis of 1H-5-substituted tetrazoles is based on the addition of hydrazoic acid to organic nitriles [3] and takes place through a 1,3-dipolar cycloaddition mechanism [4, 5], with a time requirement of many hours of heating of the reaction mixture, especially if the nitrile molecule contains an electron-donor substituent [6].

In this connection, it was of interest to study the influence of ultrasound on the reaction of azides with aromatic and heterocyclic nitriles.

The reaction was conducted by the method of [3] in DMF at a temperature of 100-105°C by treatment with ultrasound at a frequency of 22 KHz:



I and IIa) R = phenyl; b) R = 4-methoxyphenyl; c) R = 3,4-dimethoxyphenyl; d) R = nitrophenyl; e) R = chlorophenyl; f) R = 4-bromophenyl; g) R = 4-pyridyl, h) R = 3-pyridyl.

As shown in Table 1, the application of ultrasound accelerates the reaction by comparison with the usual conditions. The yields of compounds IIb, IIe, and IIg increased by 10-25%. However, compounds IIa, IIc, IId, IIg, and IIh were obtained with yields lower or equal to those from the usual conditions. This is connected with the rapid decomposition of the ammonium azide formed *in situ* [7] and the escape of the gaseous decomposition products from the reaction mixture. Consequently, when a 20% excess of sodium azide instead of 10% was used, the yields of tetrazole increased: IIa from 50% to 79%, and IIg, from 69% to 78%.

It is known that the use of alkylammonium azides (di- or trialkyl) [4] in reactions with nitriles in DMF is more favorable for the formation of 5-substituted tetrazoles, and in fact, compounds IIa and IIh were obtained with higher yields using them.

The yield of 1H-5-phenyltetrazole (IIa) by ultrasonication and using dimethylammonium azide previously isolated as in [4] was practically unchanged, while the duration of the reaction decreased from 7 h to 20 min.

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TABLE 1. Synthesis of 1H-5-Substituted Tetrazoles Under the Usual Conditions and by Ultrasonication

Compound	Ultrasound 100-105°C		Normal conditions [2], 100-130°C	
	Reaction time, h	Yield, %	Reaction time, h	Yield, %
IIa	0,7	57	7,0	75
	0,7	79*		
	0,3	79* ²	7,0	82 [4]
	0,6	82* ³		
IIb	4,0	76	24,0	68
IIc	4,0	68	24,0	78
IId	0,3	83	7,0	86
IIe	0,5	77	9,0	57
II f	0,75	93	7,0	69
II g	0,5	69	7,0	72
	0,5	78*		
II h	0,6	61	7,0	75
	0,6	65*		
	0,5	66* ⁴	2,0	47

*Using excess of sodium azide (nitrile:NaN₃:NH₄Cl = 1:1.2:1); for the remaining experiments, the ratio was 1:1.1:1.

²Using previously prepared dimethylammonium azide.

³Dimethylammonium azide prepared *in situ*.

⁴Using triethylamine hydrochloride in dry DMF instead of NH₄Cl.

The yield of compound IIa using dimethylammonium azide prepared *in situ*, and ultrasonication was 82%. The reaction time was 10 min under these circumstances, while in [4] the preparation of dimethylammonium azide already required 4 h, and the formation of 1H-5-phenyltetrazole required 7 h.

To obtain tetrazole IIh, triethylamine hydrochloride in dry DMF was used instead of ammonium chloride, both under the usual conditions, and under ultrasonication. The yield under the usual conditions was 47%, while under ultrasonication conditions it was 66%, and the reaction time was decreased four-fold.

Thus, these results indicate that ultrasound accelerates both the cycloaddition of azides (ammonium azide, dimethylammonium azide, triethylammonium azide) to aromatic nitriles and the formation of aminoazides.

The synthesized compounds IIa-h were identical with those obtained by other routes.

EXPERIMENTAL

The ultrasound disperser used was a YZDN-A with a frequency of 22 kHz. The reaction progress and the purity of the 1H-5-substituted tetrazoles was monitored by TLC on Silufol plates in the system butyl acetate – acetate – acetic acid – water = 8:2:2:1.

Elemental analysis data for the synthesized compounds for C, H, and N corresponded with the calculated values.

1H-5-Substituted Tetrazoles. A solution of 0.1 mole of starting nitrile, 0.11 mole of sodium azide, and 0.1 mole of ammonium chloride in 50 ml of DMF was prepared at room temperature. Ultrasound irradiation was then begun with the irradiating dispersion tube of the YZDN-A deeply immersed in the reaction mixture, resulting in an increase in the temperature of the reaction mixture. The irradiation power level was regulated so that the temperature of the reaction mixture was 100-105°C. Irradiation was continued until the disappearance of the nitrile by TLC. The reaction mixture was cooled, the DMF was removed under vacuum, the residue was dissolved in water, and acidified to pH 2 with hydrochloric acid. The resulting precipitate was filtered off, washed with water, dried, and crystallized from water or from 20% propanol-2 to give yields of 52-94%.

Compounds IIa and IIh were prepared analogously, using triethyl- or dimethylammonium chloride or dimethylammonium azide prepared according to [4] instead of ammonium chloride.

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