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Dedicated to Professor V.A.Ostrovskii on occasion of his sixtieth birthday

Tetrazoles: LI.* Synthesis of 5-Substituted Tetrazoles under Microwave Activation

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Abstract—Reaction of nitriles with sodium azide in the presence of $ZnCl_2$ under microwave activation (MWA) leads to the formation of 5-tetrazoles in high yields; therewith the process is 2-3 times shorter than the inactivated reaction.

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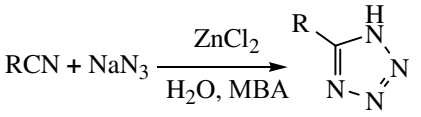
One of the most important goals of 5-substituted tetrazoles chemistry is the search for new methods of their preparation and the improvement of the known procedures. This aim is first of all due to the application of tetrazoles in the synthesis of pharmaceuticals widely used in the treatment of cardiovascular diseases [2–4].

Till the middle of the previous century there were no preferred methods among the numerous procedures applied to the preparation of 5-substituted tetrazoles. The situation changed in 1958 after Finnegan et al. publication [5] on the synthesis in high yield of 5 substituted tetrazoles at heating nitriles of diverse structure with sodium azide in DMF in the presence of ammonium chloride. Afterwards the Finnegan method obtained universal recognition and was widely applied to the preparation of versatile 5-substituted tetrazoles.

A considerable advancement in this direction was done by Sharpless et al [6] who found that nitriles cleanly reacted with sodium azide in water in the presence of Lewis acids, $ZnCl_2$ or $ZnBr_2$. Under these conditions the 5-substituted tetrazoles formed in high yield, and the reaction in water was practically secure.

In this study we evaluated the opportunity of 5-substituted tetrazoles preparation in water under conditions of microwave irradiation. It was formerly shown that microwave activation in the synthesis of 5-substituted tetrazoles in solvents like dimethoxyethane, dioxane, or DMF considerably reduced the reaction time not decreasing the yield of the final products [7–10]. The synthesis of 5-substituted **X** tetrazoles in water in the presence of $ZnBr_2$ was also described, but the reaction conditions were not mentioned [11, 12].

We found that nitriles of diverse structures reacted with NaN_3 in water in the presence of $ZnCl_2$ under the microwave irradiation to give in good yields 5-substituted



Ia – If

I, R = $PhCH_2$ (**a**), 4-$MeOC_6H_4$ (**b**), Ph (**c**), 4-BrC_6H_4 (**d**), 4-$NO_2C_6H_4$ (**e**), 2-pyridyl (**f**).

Reaction conditions and yields of 5-substituted tetrazoles **Ia–Ig**

Tetrazole	Microwave activation		Yield, %
	Temperature, °C	Time, h	
Ia	95	6	78
Ib	92	12	63
Ic	95	8	64
Id	92	10	60
Ie	95	8	86
Ig	95	2	68
Ig	95	14	67

* For communication L, see [1].

tetrazoles (see the table). The essential fact is that the reaction duration under microwave irradiation is 2-3 times less than in the inactivated process.

Under similar conditions reacted aromatic dinitriles, for instance, *o*-phthalodinitrile, and the corresponding ditetrazole **Ig** formed in 67% yield (see the table).

The above should be supplemented with the information that in some cases (tetrazoles **Ia** and **Id**) the reaction was performed in a mixture H_2O–1-BuOH, 40:1, in order to increase the solubility of initial nitriles.

In continuation of the study on the methods of tetrazole preparation we evaluated the opportunity of MWA application to the synthesis of the 5-substituted tetrazoles in the presence of ZnO. Recently this type catalyst was used in an inactivated process by an example of nanocrystalline ZnO [16].

Our attempt to use as catalyst a commercially available ZnO in reaction of 2-cyanopyridine with NaN_3 in DMF at the microwave irradiation was successful, and 5-(2-pyridyl)tetrazole was obtained in 65% yield.

Thus the application of MWA in the synthesis of 5-substituted tetrazoles permits successful application of widely spread commercial ZnO instead of difficultly available nanocrystalline substance.

In-depth analysis of the available experimental data on application of the microwave activation in tetrazole chemistry [17], including the findings of this study, permits to make an important conclusion that the preparation of 5-substituted tetrazoles under the conditions of the microwave irradiation is one of the most promising procedures for the synthesis of these compounds.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker WM-400 from solutions in DMSO-d_6. Reactions under microwave irradiation were performed in a reactor P/N 44072. Commercial ZnO used corresponded to State Russian Standard GOST 10262-73. The purity and homogeneity of compounds obtained was checked by TLC on Silufol plates, eluent ethyl acetate–CCl_4, 2:3.

5-Benzyltetrazole (**Ia**). In 30 ml of water a mixture of 10 mmol of benzyl cyanide, 11 mmol of NaN_3, and 10 mmol of $ZnCl_2$ was stirred for 6 h at 95°C under conditions of microwave activation. The reaction solution was cooled to 18°C, concn. HCl was added to pH 1, and the reaction mixture was stirred for 1 h. The separated precipitate was filtered off, washed with water, and dried in air. Yield 78%, mp 124°C (from water) [5]. ^{1}H NMR spectrum, δ, ppm: 4.20 s (2H CH_2), 7.27–7.34 μ (5H_{arom}).

Tetrazoles **Ib–Ig** were obtained in the same way.

5-(4-Methoxyphenyl)tetrazole (**Ib**), mp 228°C (from 2-propanol) [13]. ^{1}H NMR spectrum, δ, ppm: 3.84 s (3H, OCH_3), 7.15 d (2H_{arom}), 7.97 (2H_{arom}).

5-Phenyltetrazole (**Ic**), mp 215°C (from a mixture ethanol–water, 1:2) [5]. ^{1}H NMR spectrum, δ, ppm: 7.61–8.04 (5H_{arom}).

5-(4-Bromophenyl)tetrazole (**Id**), mp 268–269°C (from 2-propanol) [13]. ^{1}H NMR spectrum, δ, ppm: 7.78–7.91 m (4H_{arom}).

5-(4-Nitrophenyl)tetrazole (**Ie**), mp 219°C (from ethanol) [14]. ^{1}H NMR spectrum, δ, ppm: 8.27 d (2H_{arom}), 8.42 d (2H_{arom}).

5-(2-Pyridyl)tetrazole (**If**), *a*. mp 220–222°C (from ethyl acetate) [15]. ^{1}H NMR spectrum, δ, ppm: 7.59–8.76 m (4H_{arom}).

b. In 40 ml of DMF a mixture of 10 mmol of 2-cyanopyridine, 12 mmol of NaN_3, and 10 mmol of ZnO was stirred for 6 h at 120°C under conditions of microwave activation. DMF was removed under a reduced pressure, the residue was treated with H_2O (30 ml), ZnO was filtered off, the filtrate was acidified with concn. HCl to pH 6, the separated precipitate was filtered off and dried in air. Yield 65%, mp 220–222°C (from ethyl acetate).

1,2-Bis(5-tetrazolyl)benzene (**Ig**), mp 224–225°C (from 2-propanol) [6]. ^{1}H NMR spectrum, δ, ppm: 7.79–8.08 m (4H_{arom}).

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