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# Tetrazoles: LV. Perparation of 2-Anilino-5-aryl(hetaryl)-1,3,4-oxadiazoles from 5-Substituted Tetrazoles under Microwave Activation

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**Abstract**—In reaction of 5-aryl(hetaryl)tetrazoles with phenyl isocyanate under the conditions of microwave activation the corresponding 2-anilino-5-aryl(hetaryl)-1,3,4-oxadiazoles formed in high yields. The application of the microwave activation fourfold reduced the reaction time.

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2,5-Disubstituted-1,3,4-oxadiazoles are extensively used in the sybthesis of versatile pharmaceuticals [2–4].

A special place in this series belongs to 2-arylamino-5-aryl-1,3,4-oxadiazoles that can be prepared by several procedures where the main method is the cyclization of 1,4-disubstituted thiosemicarbazides in the presence of reagents like tosyl chloride in pyridine [5] or dicyclohexylcarbodiimide [6]. The disadvantage of this method consists in the multistage synthesis of the initial 1,4-disubstituted thiosemicarbazides.

At the same time 2-arylamino-5-aryl-1,3,4-oxadiazoles can be obtained in a good yield in the reaction of 5-phenyltetrazole with aromatic isocyanates [7]. Huisgen et al. suggested the mechanism of this reaction that was proved in [8–11] (see the scheme).

The investigation of the transformation mechanism under heating of acyltetrazoles and also 2,5-disubstituted tetrazoles [12] is an important stage in the development of concepts on the structure and reactivity of 1,3-dipoles and on the involvement of these intermediates into reactions of 1,5-electrocyclization and 1,3-dipolar cycloaddition.

Therefore the new wide opportunities were demonstrated of tetrazoles application to the synthesis of heterocyclic substrates whose preparation by another way was experimentally complicated.

In extension of research on the preparation methods and chemical properties of tetrazoles and on the application of these compounds to organic synthesis we investigated the reaction of 5-aryl(hetaryl)tetrazoles with phenyl isocyanate under the conditions of microwave activation (MWA).

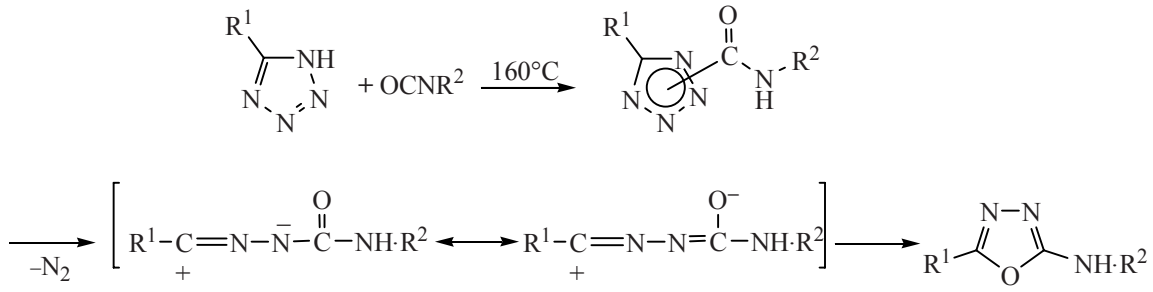
Based on the data obtained in the study of the chemical properties of tetrazoles under MWA conditions [1, 13, 14] it was presumable that the rate of the reaction of 5-substituted tetrazoles with the phenyl isocyanate would significantly grow under the microwave irradiation. Actually, the reaction of 5-aryl(hetaryl)tetrazoles with the phenyl isocyanate under MWA conditions provided in a good yield the corresponding 2-anilino-5-aryl(hetaryl)-1,3,4-oxadiazoles, and compared to nonactivated process the reaction time was 4 times shorter (see the table).

The course of the reaction between the 5-substituted tetrazoles and the phenyl isocyanate is considerably affected by the nature of the used solvent. Thus in the series of solvents under study (DMF, DMSO, nitrobenzene) the latter proved to be the most efficient.

Finally, one more important trend calls for attention established in the study of the reactions between the 5-substituted tetrazoles and the phenyl isocyanate. For instance, at heating of 5-(4-pyridyl)tetrazole with the phenyl isocyanate in nitrobenzene at 150°C for 8 h no reaction occurred. Under the same conditions and at the

* For Communication LIV, see [1].

**Scheme.**



microwave irradiation the corresponding 1,3,4-oxadiazole formed in 2 h in 96% yield.

Similar trends were formerly found in the study of reactions of isomeric 5-pyridyltetrazoles with phenyl isothiacyanate under MWA conditions [14].

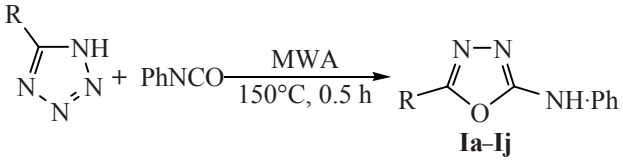
These results are well consistent with to-day concepts on the effect of the microwave irradiation on the course of the chemical reactions [15].

According to common standpoint the microwave radiation significantly affects the course of reactions with high activation energies.

Yields (%) of 2-anilino-5-aryl(hetaryl)-1,3,4-oxadiazoles **Ia–Ij** obtained under heating (2 h, 150°C) and MWA (0.5 h, 150°C)

| Compound no. | Heating | MWA |
|---|---|---|
| **Ia** | 86 | 81 |
| **Ib** | 71 | 84 |
| **Ic** | 85 | 82 |
| **Id** | 97 | 81 |
| **Ie** | 85 | 73 |
| **If** | 84 | 92 |
| **Ig** | 86 | 73 |
| **Ih** | 96 | 90 |
| **Ii** | –[a] | 96[b] |
| **Ij** | 55 | 94 |

Reaction time: [a] 8 h, [b] 2 h.



**Ia–Ij**

R = 4-$Me_2NC_6H_4$ (**a**), 4-$MeOC_6H_4$ (**b**), 4-$MeC_6H_4$ (**c**), Ph (**d**), 4-$ClC_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**), 2-pyridyl (**g**), 3-pyridyl (**h**), 4-pyridyl (**i**), 2-furyl (**j**).

Although the data on the activation parameters of the thermal transformation of N-acyl derivatives of 5-substituted tetrazole are now lacking, from the findings obtained in the study of the thermolysis mechanism of 2,5-disubstituted tetrazoles [16, 17] it is possible to presume that these reactions proceed with a high activation energy. Evidently this circumstance is among the principal reasons of the strong influence of the microwave irradiation on the reactions of the 5-substituted tetrazoles with the phenyl isocyanate.

## EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Shimadzu FTIR-8400s from pellets with KBr. $^1$H NMR spectra were registered on a spectrometer Bruker WM-400 in DMSO-$d_6$. Reactions under MWA conditions were carried out in a reactor Milestone P/N 44072. Elemental analyses were performed on an analyzer LECO CHNS(O)-932. The purity and homogeneity of compounds obtained were checked by TLC on Silufol plates, eluent acetone–hexane, 1 : 2.

Reactions of 5-aryl(hetaryl)tetrazoles with the phenyl isocyanate were carried out by identical procedure both at heating and under MWA conditions.

**2-Anilino-5-(4-dimethylaminophenyl)-1,3,4-oxadiazole (Ia)**. A mixture of 0.5 g (2.6 mmol) of 5-(4-dimethylaminophenyl)tetrazole and 0.35 g (2.9 mmol) of phenyl isocyanate in 5 ml of nitrobenzene was stirred for 0.5 h in a microwave reactor at 150°C (70 W). The reaction mixture was cooled to 20°C, diluted with 20 ml of hexane, the separated precipitate was filtered off, washed with hexane (2×20 ml), and dried in air. Yield 81%, mp 256–257°C (from acetonitrile) [5]. $^1$H NMR spectrum, δ, ppm: 3.00 s (6H, $NCH_3$), 6.81 d ($2H_{arom}$), 6.97 t ($1H_{arom}$), 7.34 t ($2H_{arom}$), 7.56 d ($2H_{arom}$), 7.69 d ($2H_{arom}$), 10.47 s (1H, NH).

Oxadiazoles **Ib–Ij** were obtained similarly.

**2-Anilino-5-(4-methoxyphenyl)-1,3,4-oxadiazole (Ib)**. Yield 84%, mp 203°C (from ethanol) [9]. $^1$H NMR spectrum, δ, ppm: 3.82 s (3H, $OCH_3$), 6.99 t (1$H_{arom}$), 7.11 d (2$H_{arom}$), 7.34 t (2$H_{arom}$), 7.60 d (2$H_{arom}$), 7.83 d (2$H_{arom}$), 10.58 s (1H, NH).

**2-Anilino-5-(4-methylphenyl)-1,3,4-oxadiazole (Ic)**. Yield 82%, mp 226–227°C (from acetonitrile). IR spectrum, ν, cm$^{-1}$: 3284, 3134, 3064, 2925, 2853, 2786, 1711, 1620, 1615, 1606, 1594, 1577, 1556, 1547, 1519, 1449, 1313, 1300, 1230, 1190, 1122, 1090, 1047, 1019, 957, 901, 859, 821, 789, 753, 726, 691, 569, 504. $^1$H NMR spectrum, δ, ppm: 2.37 s (3H, $CH_3$), 7.00 t (1$H_{arom}$), 7.36 m (4$H_{arom}$), 7.59 d 2$H_{arom}$), 7.79 d (2$H_{arom}$), 10.62 s (1H, NH). Found, %: C 71.39; H 4.91; N 16.21. $C_{15}H_{13}N_3O$. Calculated, %: C 71.71; H 5.18; N 16.73.

**2-Anilino-5-phenyl-1,3,4-oxadiazole (Id)**. Yield 81%, mp 218°C (from ethanol) [7]. $^1$H NMR spectrum, δ, ppm: 7.00 t (1$H_{arom}$), 7.34 t (2$H_{arom}$), 7.61 m (5$H_{arom}$), 7.89 d (2$H_{arom}$), 10.67 s (1H, NH).

**2-Anilino-5-(4-chlorophenyl)-1,3,4-oxadiazole (Ie)**. Yield 73%, mp 258–260°C (from ethanol) [9]. $^1$H NMR spectrum, δ, ppm: 7.02 t (1$H_{arom.}$), 7.35 t (2$H_{arom}$), 7.58–7.65 m (4$H_{arom}$), 7.88 d (2$H_{arom}$), 10.70 s (1H, NH).

**2-Anilino-5-(4-nitrophenyl)-1,3,4-oxadiazole (If)**. Yield 92%, mp 269–270°C (from acetic acid) [18]. $^1$H NMR spectrum, δ, ppm: 7.03 t (1$H_{arom}$), 7.37 t (2$H_{arom}$), 7.61 d (2$H_{arom}$), 8.11 d (2$H_{arom}$), 8.39 d (2$H_{arom}$), 10.83 s (1H, NH).

**2-Anilino-5-(2-pyridyl)-1,3,4-oxadiazole (Ig)**. Yield 73%, mp 230–231°C (from toluene). IR spectrum, ν, cm$^{-1}$: 3311, 3177, 3035, 2991,2935, 2873, 1664, 1585, 1561, 1546, 1502, 1456, 1437, 1384, 1312, 1251, 1233, 1150, 1094, 1060, 1033, 985, 893, 864, 791, 755, 741, 724, 625, 500. $^1$H NMR spectrum, δ, ppm: 7.02 t (1$H_{arom.}$), 7.37 t (2$H_{arom}$), 7.60 m (3$H_{arom}$), 8.00 m (2$H_{arom}$), 8.71 d (1$H_{arom}$), 10.83 s (1H, NH). Found, %: C 65.45; H 4.17; N 23.34. $C_{13}H_{10}N_4O$. Calculated, %: C 65.54; H 4.20; N 23.53.

**2-Anilino-5-(3-pyridyl)-1,3,4-oxadiazole (Ih)**. Yield 90%, mp 237–238°C (from ethanol) [6]. $^1$H NMR spectrum, δ, ppm: 7.02 t (1$H_{arom}$), 7.36 t (2$H_{arom}$), 7.62 d (3$H_{arom}$), 8.24 d (1$H_{arom}$), 8.73 d (1$H_{arom}$), 9.05 s (1$H_{arom}$), 10.83 C (1H, NH).

**2-Anilino-5-(4-pyridyl)-1,3,4-oxadiazole (Ii)**. Reaction time 2 h. Yield 96%, mp 216–218°C (from ethanol) [6]. $^1$H NMR spectrum, δ, ppm: 7.02 t (1$H_{arom.}$), 7.36 t (2$H_{arom}$), 7.60 d (2$H_{arom}$), 7.80 d (2$H_{arom}$), 8.78 d (2$H_{arom}$), 10.85 s (1H, NH).

**2-Anilino-5-(2-furyl)-1,3,4-oxadiazole (Ij)**. Yield 94%, mp 204–205°C (from toluene). IR spectrum, ν, cm$^{-1}$: 3334, 3178, 3127, 3057, 2940, 2877, 1939, 1855, 1667, 1620, 1509, 1448, 1441, 1408, 1370, 1309, 1295, 1237, 1226, 1159, 1087, 1054, 1030, 1018, 1008, 988, 960, 901, 886, 881, 863, 841, 825, 797, 769, 749, 740, 720, 688, 627, 590, 501, 447. $^1$H NMR spectrum, δ, ppm: 6.75 s (1$H_{arom}$), 7.01 t (1$H_{arom}$), 7.12 d (1$H_{arom}$), 7.35 t (2$H_{arom}$), 7.56 d (2$H_{arom}$), 7.97 s (1$H_{arom}$), 10.71 s (1H, NH). Found, %: C 63.27; H 4.24; N 18.56. $C_{12}H_9N_3O_2$. Calculated, %: C 63.44; H 3.96; N 18.50.

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