ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 5, pp. 728–730. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © L.V. Myznikov, Yu.A. Efimova, T.V. Artamonova, G.I. Koldobskii, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 5, pp. 723–725.

Tetrazoles: LVI. Synthesis of 5-Substituted Tetrazoles under Microwave Activation in the Presence of Heterogeneous Catalyst (Zinc Oxide)

L. V. Myznikov, Yu. A. Efimova, T. V. Artamonova, and G. I. Koldobskii†

St. Petersburg State Technological Institute, St. Petersburg, 190013 Russia
e-mail: postleo@mail.ru

Received July 7, 2010

Abstract—Reactions of aromatic and heteroaromatic nitriles with sodium azide in the presence of zinc oxide under the conditions of microwave activation provide 5-aryl(hetaryl)tetrazoles in high yields.

DOI: 10.1134/S1070428011050125

The significant interest in tetrazole chemistry in the last decades has been due to the wide application of these compounds in versatile fields. They found application in pharmaceutics as lipophilic spacers and substitutes of carboxylic acids, as components of explosives, as ligands in the coordination chemistry, and also as precursors in the preparation of diverse heterocyclic compounds [2–5].

The search for new and refinement of the known methods of the synthesis of 5-substituted tetrazoles is one of the most important problems of the chemistry of these compounds. As a rule the 5-substituted tetrazoles are obtained by the reaction of azides with nitriles in the presence of catalysts. The formerly described methods possess some disadvantages like the application of strong Lewis acids, expensive and toxic metals, the formation of explosive derivatives of hydrazoic acid. Besides these reactions proceed under fairly severe conditions and require long heating. Sufficiently simple and safe method was developed in [6]. The tetrazoles were obtained in water medium in the presence of zinc salts. The drawbacks of this method were the low reaction rate and the necessity to heat the reaction mixture at 170°C in a pressure reactor in the case of nitriles of low reactivity.

Recently a great attention is attracted by the search for and application of safe heterogeneous catalysts which may be used in the synthesis many times thus reducing the amount of toxic wastes.

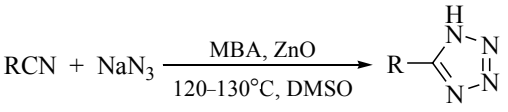
Zinc oxide is known to be used as catalyst of the Friedel–Krafts reaction [7], in Beckmann rearrangement [8], sulfonation [9], and in the synthesis of cyclic urea derivatives from diamines [10]. The zinc oxide was reported to be used in the composition of catalysts for alcohols dehydration [11]. Kantam et al. [12] showed that nanocrystalline ZnO was an efficient heterogeneous catalyst of [1+3]-cycloaddition of sodium azide to nitriles leading to the formation of 5-substituted tetrazoles. However the preparation of tetrazoles in the presence of zinc oxide required a prolonged heating. The presumed mechanism of this reaction was discussed in [13, 14].

We studied the reactions of nitriles of diverse structures with sodium azide in the presence of heterogeneous catalyst, commercial ZnO, under the conditions of microwave activation (MWA). We selected as investigation objects aliphatic, aromatic, and heteroaromatic nitriles in order to determine the limits of the application of ZnO in [1+3]-cycloaddition under the MWA conditions. The solvent is known to affect significantly the course of such reactions. It proved that reactions carried out in DMF both at the thermal heating and in MWA conditions required

*For Communication LV, see [1].

† Deceased.

for the completion no less than 24 h. We showed that in a microwave reactor at 120–130°C in the presence of ZnO in DMSO 5-aryltetrazoles with electron-acceptor substituents in the phenyl ring **Ib–If** and 5-hetaryltetrazoles **Ig–Ii** formed in high yields. The comparison of data obtained in the reaction at the thermal heating and at MWA shows that MWA makes it possible to obtain tetrazoles in higher yields than in the unactivated process within the same time (see the table). The low yield of 5-phenyltetrazoles may be ascribed to the volatility of benzonitrile. We failed to isolate the target products in attempts to carry out the synthesis of 5-substituted tetrazoles along this procedure from aliphatic nitriles. The phthalodinitrile gave exclusively the product of monoaddition **Ic** whereas at the catalysis with zinc salts *o*-di(tetrazol-5-yl)benzene was obtained [6, 13, 14].



Ia–Ii

R = $MeOC_6H_4$ (**a**), Ph (**b**), 2-CNC_6H_4 (**c**), 3-BrC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-ClC_6H_4 (**f**), 2-pyridyl (**g**), 3-pyridyl (**h**), 4-pyridyl (**i**).

The catalyst can be easily regenerated and repeatedly used without notable reduction in the activity.

Thus the method of preparation of 5-substituted tetrazoles in the presence of zinc oxide can be considerably improved if the reaction is carried out in DMSO medium under the conditions of microwave activation. This method may be regarded as one of the most safe procedures for preparation of tetrazoles.

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. Reactions under MWA conditions were carried out in a reactor Milestone P/N 44072. The purity and homogeneity of compounds obtained was checked by TLC on Sorbfil plates, eluent ethyl acetate–tetrachloromethane, 2 : 3.

The reactions of nitriles with sodium azide were performed by the same procedure both at the thermal heating and under MWA conditions.

5-(4-Methoxyphenyl)tetrazole (Ia). To a solution of 0.67 g (5 mmol) of 4-methoxybenzonitrile in 6 ml of DMSO was added 0.49 g (7.5 mmol) of sodium azide and 0.4 g (5 mmol) of zinc oxide, and the reaction mixture was stirred in the microwave reactor at 130°C (70 W) for 12 h. Then zinc oxide was filtered off, the filtrate was evaporated in a vacuum, the product obtained was dissolved in 10 ml of cold water. The mixture was treated with concn. HCl till pH 2, the separated precipitate was filtered off, washed with water, and dried in air. Yield 0.34 g (39%), mp 226–228°C (ethyl acetate) [15]. IR spectrum, ν, cm^{-1}: 3438, 3143, 3075, 3015, 2985, 2923, 2842, 2726, 2557, 2482, 1616, 1585, 1501, 1468, 1443, 1407, 1300, 1182, 1163, 1120, 1056, 1034, 1020, 992, 834, 807, 800, 752, 698, 636, 612, 522. ^{1}H NMR spectrum, δ, ppm (DMSO-d_6): 3.82 s (3H, CH_3), 7.14 d ($2H_{apom.}$), 7.95 d ($2H_{arom}$).

Yield of 5-substituted tetrazoles **Ia–Ii** in DMCO (130°C) under the conditions of thermal heating and MWA

Compound no.	Time, h	Yield, %	
		thermal heating	MWA
Ia	12	16	39
Ib[a]	4	16	37
Ic	0.25	67	74
Id	1	20	73
Ie[a]	4	44	62
If	4	26	66
Ig	2	41	90
Ih	2	53	64
Ii	1	54	73

[a] 120°C.

Tetrazoles **Ib–Ii** were similarly obtained, tetrazoles **Ib, Ie** were prepared at heating to 120°C.

5-Phenyltetrazole (Ib), mp 215°C (ethyl acetate) [16]. IR spectrum, ν, cm^{-1}: 3432, 3129, 3078, 3055, 2980, 2917, 2849, 2794, 2702, 2608, 2544, 2481, 2458, 1609, 1564, 1486, 1467, 1409, 1288, 1257, 1164, 1101, 1085, 1057, 1036, 1016, 994, 959, 926, 791, 784, 725, 704, 689. ^{1}H NMR spectrum, δ, ppm (acetone-d_6): 7.36 m ($3H_{arom}$), 8.15 m ($2H_{arom}$).

5-(2-Cyanophenyl)tetrazole (Ic), mp 223–224°C (ethanol) [17]. IR spectrum, ν, cm^{-1}: 3746, 3422, 3131, 3079, 3060, 3014, 2993, 2979, 2957, 2917, 2876, 2834, 2751, 2721, 2689, 2674, 2644, 2618, 2545, 2503, 2467, 2229, 1857, 1722, 1625, 1608, 1581, 1569, 1492, 1481, 1454, 1407, 1384, 1279, 1242, 1200, 1167, 1098, 1066, 1042, 1013, 1000, 970, 864, 783, 757, 745, 723, 707, 666, 555, 518, 501. ^{1}H NMR spectrum, δ, ppm (DMSO-d_6):

7.77 t ($1H_{arom}$), 7.92 t ($1H_{arom}$), 8.07 t ($2H_{arom}$).

5-(3-Bromophenyl)tetrazole (Id), mp 150°C (aqueous ethanol) [15]. IR spectrum, ν, cm^{-1}: 3430, 3123, 3060, 2963, 2917, 2852, 2753, 2619, 1633, 1574, 1469, 1444, 1402, 1251, 1241, 1156, 1092, 1073, 1011, 1003, 995, 888, 790, 746, 738, 675, 653. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 7.55 t ($1H_{arom}$), 7.78 d ($1H_{arom}$), 8.03 d ($1H_{arom}$), 8.17 s ($1H_{arom}$).

5-(4-Bromophenyl)tetrazole (Ie), mp 260–261°C (acetic acid) [15]. IR spectrum, ν, cm^{-1}: 3426, 3120, 3090, 3064, 2999, 2972, 2902, 2846, 2730, 2640, 2483, 1605, 1561, 1527, 1482, 1455, 1432, 1405, 1299, 1278, 1254, 1193, 1158, 1121, 1076, 1068, 1054, 994, 829, 743, 725, 708, 692, 503, 452. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 7.80 d ($2H_{arom}$), 7.96 d ($2H_{arom}$).

5-(4-Chlorophenyl)tetrazole (If), mp 246–248°C (acetic acid) [15]. IR spectrum, ν, cm^{-1}: 3434, 3093, 3067, 3001, 2975, 2907, 2852, 2728, 2634, 2480, 1610, 1489, 1435, 1399, 1277, 1257, 1161, 1095, 1054, 1017, 990, 882, 831, 746, 588, 542, 507, 466. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 7.76 d ($2H_{arom}$), 8.03 d ($2H_{arom}$).

5-(2-Pyridyl)tetrazole (Ig), mp 212–213°C (water) [18]. IR spectrum, ν, cm^{-1}: 3429, 3091, 3065, 3031, 3003, 2979, 2962, 2906, 2852, 2834, 2795, 2761, 2684, 2661, 2620, 1640, 1603, 1557, 1484, 1450, 1401, 1378, 1285, 1246, 1223, 1167, 1159, 1104, 1091, 1068, 1025, 998, 950, 795, 743, 726, 704, 630, 504, 470. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 7.61 t ($1H_{arom}$), 8.07 t ($1H_{arom}$), 8.21 d ($1H_{arom}$), 8.77 s ($1H_{arom}$).

5-(3-Pyridyl)tetrazole (Ih), mp 235°C (water) [19]. IR spectrum, ν, cm^{-1}: 3438, 3111, 3082, 3052, 2923, 2508, 2362, 2129, 1995, 1644, 1578, 1575, 1494, 1479, 1460, 1401, 1336, 1304, 1264, 1112, 1080, 1033, 920, 832, 749, 707, 685, 614, 464. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 7.62 m ($1H_{arom}$), 8.37 d ($1H_{arom}$), 8.74 d ($1H_{arom}$), 9.18 s ($1H_{arom}$).

5-(4-Pyridyl)tetrazole (Ii) [18]. IR spectrum, ν, cm^{-1}: 3418, 3270, 3168, 3099, 3072, 3058, 3037, 2527, 1631, 1529, 1441, 1389, 1354, 1292, 1251, 1238, 1201, 1187, 1145, 1122, 1095, 1042, 991, 869, 848, 751, 714, 527, 460. ^1H NMR spectrum, δ, ppm (DMSO-d_6): 8.01 d ($2H_{arom}$), 8.80 d ($2H_{arom}$).

ACKNOWLEDGMENTS

The study was carried out under the financial support of the Russian Foundation of Basic Research (grant no. 08-03-00342a).

REFERENCES

1. Efimova, Yu.A., Karabanovich, G.G., Artamonova, T.V., and Koldobskii, G.I., *Zh. Org. Khim.,* 2009, vol. 45, p. 1249.
2. Koldobskii, G.I. and Ivanova, S.E., *Zh. Obshch. Khim*., 1994, vol. 64, p. 1698.
3. Singh, H., Chala, A.S., Kapoor, V.K., Paul, D., and Malhotra, R.K. *Prog. Med. Chem.,* 1980, vol. 17, p. 151.
4. Koldobskii, G.I. and Ivanova, S.E., *Zh. Org. Khim.,* 1995, vol. 31, p. 1601.
5. Artamonova, T.V. and Koldobskii, G.I., *Zh. Org. Khim.,* 1998, vol. 34, p. 1091.
6. Demko, Z.P. and Sharpless, K.B., *J. Org. Chem.,* 2001, vol. 66, p. 7945.
7. Sarvari, M.H. and Sharghi, H., *J. Org. Chem.,* 2004, vol. 69, p. 695.
8. Sharghi, H. and Sarvari, M. H., *Synthesis,* 2002, p. 1057.
9. Metwally, M.A. and Abdel-Wahab, B.F., *Org. Commun.,* 2009, vol. 2, p. 84.
10. Kim, Y.J. and Varma, R.S., *Tetrahedron Lett.,* 2004, vol. 45, p. 7205.
11. Vaidya, S.H., Bhandari, V.M., and Chauudharic, R.V., *Appl. Catal. A.,* 2003, vol. 242, p. 321.
12. Kantam, M.L.,Kumar, K.B.S., and Sridhar, C., *Adv. Synth. Catal.,* 2005, vol. 347, p. 1212.
13. Himo, F.,Demko, Z.P.,Noodleman, L., and Sharpless, K.B., *J. Am. Chem. Soc.,* 2002, vol. 124, p. 12210.
14. Himo, F., Demko, Z.P., Noodleman, L., and Sharpless, K.B., *J. Am. Chem. Soc.,* 2003, vol. 125, p. 9983.
15. Lieber, E. and Ramachandran, J., *Can. J. Chem.,* 1959, vol. 37, p. 101.
16. Herbst, R.M. and Wilson, K.R., *J. Org. Chem.,* 1957, vol. 22, p. 1142.
17. Finnegan, W.G.,Henry, R.A., and Lofquist, R., *J. Am. Chem. Soc.,* 1958, vol. 80, p. 3908.
18. Kaczmarek, J.,Smagowski, H., and Grzonka, Z., *J. Chem. Soc., Perkin, Trans. 2,* 1979, p. 1670.
19. McManus, J.M. and Herbst, R.M., *J. Org. Chem.,* 1959, vol. 24, p. 1464.