ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 12, pp. 1834–1837. © Pleiades Publishing, Inc., 2006.
Original Russian Text © M.V. Zatsepina, A. Hrabalek, T.V. Artamonova, G.I. Koldobski, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 12, pp. 1844–1847.

Tetrazoles: L.* Microwave-Activated Alkylation of 5-Aryltetrazoles and 1-Substituted Tetrazole-5-thiones with 1,3-Dibromo-2,2-bis(bromomethyl)propane

M. V. Zatsepina[a], A. Hrabalek[b], T. V. Artamonova[a], and G. I. Koldobskii[a]

[a] *St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia*
e-mail: koldobsk@tu.spb.ru

[b] *Faculty of Pharmacy, Charles University in Prague, Heyrovskeho 1203, Hradec Kralove, 50005 Czech Republic*
e-mail: hrabalek@faf.cuni.cz

Received May 16, 2006

Abstract—Alkylation of 5-aryltetrazoles and 1-substituted tetrazole-5-thiones with 1,3-dibromo-2,2-bis-(bromomethyl)propane in dimethylformamide in the presence of sodium hydroxide leads to the formation of tetrakis(5-aryltetrazol-2-ylmethyl)methanes and tetrakis(1-R-tetrazol-5-ylsulfanylmethyl)methanes, respectively. Microwave activation considerably shortens the reaction time and increases the yield.

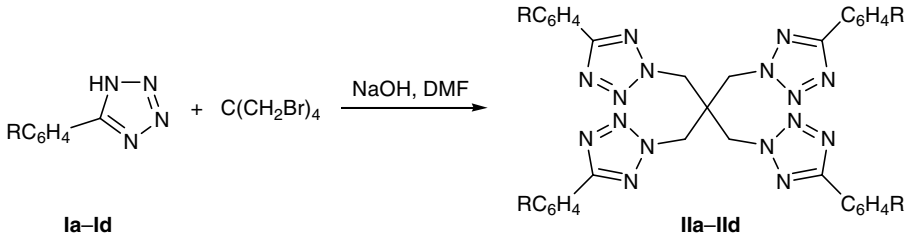
DOI: 10.1134/S1070428006120128

We previously showed that alkylation of 1-aryl-4,5-dihydro-1*H*-tetrazol-5-ones and 1-phenyl-4,5-dihydro-1*H*-tetrazole-5-thione with tetrakis(2-chloroacetoxymethyl)methane provides a simple and effective procedure for the preparation of tetrazole-containing substrates which can be used in divergent syntheses of dendrimers [1]. In the present work we examined the alkylation of a series of 5-aryltetrazoles and 1-substituted 4,5-dihydro-1*H*-tetrazole-5-thiones with 1,3-dibromo-2,2-bis(bromomethyl)propane under conditions of conventional heating and microwave activation. It is known that the use of microwave activation in organic synthesis makes it possible to considerably increase the reaction rate and yield and in some cases to improve the selectivity [2–5].

While studying alkylation of 5-substituted tetrazoles with alkyl halides, one should keep in mind that in most cases these reactions give rise to mixtures of isomeric 1,5- and 2,5-disubstituted tetrazoles which are often difficult to separate [6, 7]. However, contrary to the expectations, the reaction of 5-aryltetrazoles **Ia–Id** with 1,3-dibromo-2,2-bis(bromomethyl)propane in dimethylformamide in the presence of sodium hydroxide gave only the corresponding 2,5-disubstituted derivatives **IIa–IId** in 80–87% yield (Scheme 1).

The product structure was determined on the basis of detailed analysis of their ^{13}C NMR spectra. According to published data for numerous 1,5- and 2,5-disubstituted tetrazole derivatives, the positions of the C^5 signal in their ^{13}C NMR spectra differ considerably: it is located at about δ_C 150 and 160 ppm, respectively [8]. Therefore, isomeric 1,5- and 2,5-disubstituted tetrazoles can be distinguished with a high reliability. In the ^{13}C NMR spectra of all compounds **IIa–IId**, the

Scheme 1.

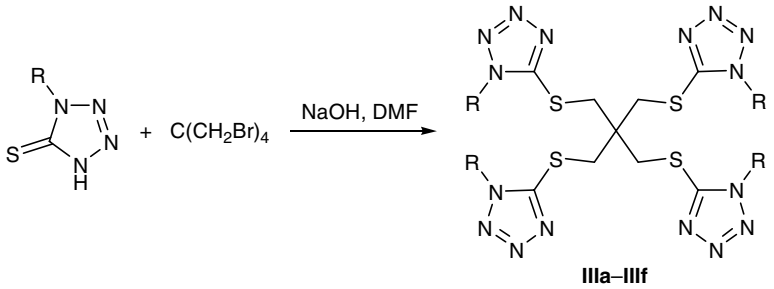


Ia–Id **IIa–IId**

R = H (**a**), 4-F (**b**), 4-Br (**c**), 4-O_2N (**d**).

* For communication XLIX, see [1].

Scheme 2.



III, R = Me (**a**), cyclohexyl (**b**), Ph (**c**), 4-BrC_6H_4 (**d**), 2,4,6-$Me_3C_6H_2$ (**e**), 1-naphthyl (**f**).

C^5 atom of the heteroring resonated in the region δ_C 162.7–167.2 ppm, indicating that these compounds are 2,5-disubstituted isomers. Presumably, the observed regioselectivity is determined by specific steric structure of the alkylating agent.

It should be emphasized that the alkylation of 5-aryltetrazoles with 1,3-dibromo-2,2-bis(bromomethyl)propane occurs at a fairly high temperature (120–130°C) and requires a long time (20–27 h). Such relatively severe conditions considerably restrict the synthetic potential of the proposed procedure for the preparation of polytetrazoles. These obstacles may be circumvented by carrying out the process under conditions of microwave activation. The microwave-assisted alkylation of 5-aryltetrazoles with 1,3-dibromo-2,2-bis(bromomethyl)propane required much shorter time, the yield of the target products slightly increased, while the selectivity of the process did not change (see table).

Analogous results were obtained in the alkylation of 1-substituted tetrazole-5-thiones with the same reagent. The reaction occurred at 110°C in 4–10 h, and the corresponding sulfanyl-substituted tetrazoles **IIIa**–**IIIe** were formed in 60–94% yield (Scheme 2). An exception was tetrazole **IIIf** whose yield was as low as 43%; presumably, the reason is steric effect of the substituent at N^1 (R = 1-naphthyl) in the heteroring. When the reaction was performed under microwave irradiation, the rate of the process and the yield of the alkylation products increased. For example, in the alkylation of 1-phenyl-4,5-dihydro-1*H*-tetrazole-5-thione [9] the reaction time shortened from 5 to 1 h, and the yield increased from 66 to 91%. Regardless of the reaction conditions and substrate structure, the alkylation of 1-substituted tetrazole-5-thiones was characterized by high regioselectivity: in all cases, only the corresponding sulfanyl derivatives were formed. Our results are consistent with published data on the alkylation of 1-alkyl(aryl)tetrazole-5-thiones with various haloalkanes and sulfuric acid esters [10, 11].

Thus we have shown that alkylation of 5-aryltetrazoles and 1-substituted tetrazole-5-thiones with haloalkanes under conditions of microwave activation is a promising method for the preparation of tetrazole-containing compounds with a complex structure.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400s spectrometer from samples prepared as KBr pellets. The ^1H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ (compound **IIa**) or DMSO-d_6 (**IIb**–**IId**, **IIIa**–**IIIf**) on a Bruker AC-400 spectrometer. The elemental compositions were determined on a LECO 932 CHNS(O) analyzer. A Milestone P/N 44072 microwave furnace was used to perform microwave-assisted reactions.

Alkylation of 5-aryltetrazoles **Ia**–**Id** with 1,3-dibromo-2,2-bis(bromomethyl)propane under conditions of conventional heating and microwave activation

Compound no.	Thermal reaction			Microwave activation		
	temperature, °C	time, h	yield, %	temperature, °C	time, h	yield, %
IIa	120	20	87	120	2	93
IIb	130	20	85	130	10	89
IIc	130	24	87	130	5	90
IId	130	27	80	130	17	82

Tetrakis(5-phenyl-2*H*-tetrazol-2-ylmethyl)-methane (IIa). *a*. A mixture of 1.80 mmol of 1,3-dibromo-2,2-bis(bromomethyl)propane, 9 mmol of 5-phenyltetrazole, 9 mmol of NaOH, and 15 ml of DMF was stirred for 20 h at 120°C. The solvent was removed under reduced pressure, 50 ml of a 5% aqueous solution of sodium hydroxide was added to the residue, and the precipitate was filtered off, washed with 50 ml of water, and dried in air. Yield 87%, mp 157–159°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 691, 731, 788, 881, 923, 1004, 1024, 1039, 1073, 1199, 1283, 1356, 1451, 1467, 1530, 2972, 3013, 3035, 3071. ^1H NMR spectrum, δ, ppm: 8.15–7.40 m (20H, H_{arom}), 5.30 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 165.8, 130.8, 128.9, 127.0, 126.4, 53.8, 43.9. Found, %: C 60.82; H 4.58; N 34.55. $C_{33}H_{28}N_{16}$. Calculated, %: C 61.10; H 4.35; N 34.55.

b. A mixture of 1.80 mmol of 1,3-dibromo-2,2-bis-(bromomethyl)propane, 9 mmol of 5-phenyltetrazole, 9 mmol of NaOH, and 15 ml of DMF was stirred for 20 h at 120°C under microwave irradiation (65 W). The mixture was then treated as described above in *a* to isolate 93% of compound **IIa** with mp 157–159°C (from acetonitrile).

Tetrazoles **IIb**–**IId** were synthesized in a similar way.

Tetrakis[5-(4-fluorophenyl)-2*H*-tetrazol-2-ylmethyl]methane (IIb). Reaction time 20 h (130°C). Yield 85%, mp 197–198°C (from EtOAc–EtOH, 1:2). IR spectrum, ν, cm^{-1}: 524, 617, 682, 759, 844, 1033, 1095, 1157, 1238, 1357, 1427, 1469, 1542, 1612, 2927, 2962, 3008, 3066, 3089. ^1H NMR spectrum, δ, ppm: 7.94–7.26 m (16H, H_{arom}), 5.52 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 167.2, 132.6, 127.0, 120.3, 119.7, 57.9, 47.4. Found, %: C 49.63; H 3.20; N 31.45. $C_{33}H_{24}N_{16}$. Calculated, %: C 55.00; H 3.36; N 31.10.

Tetrakis[5-(4-bromophenyl)-2*H*-tetrazol-2-ylmethyl]methane (IIc). Reaction time 24 h (130°C). Yield 87%, mp 214–215°C (from DMF–acetonitrile, 1:3). IR spectrum, ν, cm^{-1}: 507, 681, 753, 834, 1013, 1001, 1013, 1036, 1071, 1135, 1190, 1271, 1354, 1415, 1456, 1606, 2961, 2999. ^1H NMR spectrum, δ, ppm: 7.94–7.63 m (16H, H_{arom}), 5.54 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 163.2, 132.0, 128.1, 125.5, 123.9, 53.9, 43.7. Found, %: C 41.33; H 2.21; N 23.51. $C_{33}H_{24}N_{16}$. Calculated, %: C 41.10; H 2.51; N 23.24.

Tetrakis[5-(4-nitrophenyl)-2*H*-tetrazol-2-ylmethyl]methane (IId). Reaction time 27 h (130°C). Yield 80%, mp 230–232°C (from DMF). IR spectrum, ν, cm^{-1}: 690, 734, 854, 865, 1013, 1036, 1109, 1288, 1313, 1346, 1428, 1465, 1522, 1606, 3018, 3043, 3099, 3013. ^1H NMR spectrum, δ, ppm: 8.30–8.05 m (16H, H_{arom}), 5.65 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 162.7, 148.6, 132.3, 127.7, 124.5, 54.5, 43.7. Found, %: C 48.06; H 2.68; N 33.76. $C_{33}H_{24}N_{20}O_8$. Calculated, %: C 47.83; H 2.92; N 33.80.

Tetrakis(1-methyl-1*H*-tetrazol-5-ylsulfanylmethyl)methane (IIIa). A mixture of 1.80 mmol of 1,3-dibromo-2,2-bis(bromomethyl)propane, 9 mmol of 1-methyl-4,5-dihydro-1*H*-tetrazole-5-thione, 9 mmol of NaOH, and 15 ml of DMF was stirred for 6 h at 110°C. The solvent was removed under reduced pressure, 50 ml of a 5% aqueous solution of sodium hydroxide was added to the residue, and the precipitate was filtered off, washed with 50 ml of water, and dried in air. Yield 73%, mp 236–237°C (from DMF). IR spectrum, ν, cm^{-1}: 701, 830, 848, 1029, 1078, 1172, 1227, 1278, 1391, 1410, 1467, 1654, 1676, 2934, 2954, 2981. ^1H NMR spectrum, δ, ppm: 3.92 s (12H, CH_3), 3.74 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 153.5, 44.7, 39.03, 34.0. Found, %: C 30.19; H 4.08; N 41.79; S 23.65 $C_{13}H_{20}N_{16}S_4$. Calculated, %: C 29.53; H 3.81; N 42.39; S 24.26.

Tetrazoles **IIIb** and **IIId**–**IIIf** were synthesized in a similar way.

Tetrakis(1-cyclohexyl-1*H*-tetrazol-5-ylsulfanylmethyl)methane (IIIb). Reaction time 4 h (110°C). Yield 94%, mp 175–176°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 753, 818, 850, 895, 1003, 1084, 1152, 1192, 1204, 1275, 1374, 1391, 1410, 1430, 1453, 1467, 2858, 2935. ^1H NMR spectrum, δ, ppm: 4.35–4.20 m (4H, C_6H_{11}), 3.80 s (8H, CH_2), 2.00–1.15 m (40H, C_6H_{11}). ^{13}C NMR spectrum, δ, ppm: 152.2, 57.7, 44.7, 31.8, 24.6. Found, %: C 50.05; H 6.47; N 28.44; S 15.82. $C_{33}H_{52}N_{16}S_4$. Calculated, %: C 49.47; H 6.54; N 27.97; S 16.01.

Tetrakis(1-phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)methane (IIIc). A mixture of 1.80 mmol of 1,3-dibromo-2,2-bis(bromomethyl)propane, 9 mmol of 1-phenyl-4,5-dihydro-1*H*-tetrazole-5-thione, 9 mmol of NaOH, and 15 ml of DMF was stirred for 1 h at 110°C under microwave activation (60 W). The solvent was removed under reduced pressure, 50 ml of a 5% aqueous solution of sodium hydroxide was added to the residue, and the precipitate was filtered off, washed with 50 ml of water, and dried in air. Yield 91%, mp 158°C (from propan-2-ol).

Tetrakis[1-(4-bromophenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]methane (IIId). Reaction time 4 h

(110°C). Yield 60%, mp 190–191°C (from DMF–ethanol, 5:1). IR spectrum, ν, cm^{-1}: 551, 827, 1007, 1072, 1244, 1273, 1289, 1386, 1427, 1492, 1654, 2980, 3059, 3093. ^1H NMR spectrum, δ, ppm: 7.90–7.50 m (16H, H_{arom}), 3.80 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 154.2, 133.2, 132.2, 127.1, 124.3, 44.8. Found, %: C 36.53; H 2.25; N 20.59. $C_{33}H_{24}Br_4N_{16}S_4$. Calculated, %: C 36.26; H 2.20; N 20.51.

Tetrakis[1-(2,4,6-trimethylphenyl)-1*H*-tetrazol-5-ylsulfanylmethyl]methane (IIIe). Reaction time 10 h (110°C). Yield 84%, mp 238–239°C (from DMF). IR spectrum, ν, cm^{-1}: 584, 620, 730, 854, 973, 1013, 1032, 1093, 1165, 1240, 1282, 1395, 1438, 1488, 1608, 2862, 2922, 2953, 2980, 3028. ^1H NMR spectrum, δ, ppm: 7.15 s (8H, H_{arom}), 3.85 s (8H, CH_2), 2.35 (12H, CH_3), 1.75 (24H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 155.5, 141.7, 135.4, 129.8, 128.0, 44.6, 20.93, 16.81. Found, %: C 57.60; H 6.07; N 24.18; S 13.78. $C_{45}H_{52}N_{16}S_4$. Calculated, %: C 57.18; H 5.54; N 23.71; S 13.57.

Tetrakis[1-(1-naphthyl)-1*H*-tetrazol-5-ylsulfanylmethyl]methane (IIIf). Reaction time 5 h (110°C). Yield 43%, mp 209–211°C (from DMF–ethanol, 7:1). IR spectrum, ν cm^{-1}: 577, 665, 774, 800, 855, 960, 971, 1052, 1085, 1124, 1242, 1262, 1349, 1395, 1408, 1426, 1465, 1509, 1598, 1668, 2931, 2972, 3019, 3065. ^1H NMR spectrum, δ, ppm: 8.30–7.15 m (28H, H_{arom}), 3.80 s (8H, CH_2). ^{13}C NMR spectrum, δ_C, ppm: 156.2, 133.9, 132.2, 128.8, 128.7, 128.5, 128.1, 127.4, 126.0, 125.7, 121.5, 44.6, 38.7. Found, %: C 60.66; H 4.03; N 23.09; S 12.73. $C_{49}H_{36}N_{16}S_4$. Calculated, %: C 60.23; H 3.71; N 22.93; S 13.12.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 06-03-32286a).

REFERENCES

1. Zatsepina, M.V., Artamonova, T.V., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 1056.
2. Xu, Y. and Guo, Q.-X., *Heterocycles*, 2004, vol. 63, p. 903.
3. Hayes, B.L., *Aldrichim. Acta*, 2004, vol. 37, p. 66.
4. Romanova, N.N., Gravis, A.G., and Zyk, N.V., *Usp. Khim.*, 2005, vol. 74, p. 1059.
5. Kuznetsov, O.V., Raev, V.A., Kuranov, G.L., Arapov, O.V., and Kostikov, R.R., *Russ. J. Org. Chem.*, 2005, vol. 41, p. 1719.
6. Ostrovskii, V.A. and Koren, A.O., *Heterocycles*, 2000, vol. 53, p. 1421.
7. Koldobskii, G.I., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 469.
8. Butler, R.N., *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.R., Rees, C.W., and Scriven, E.F.V., Eds., Oxford: Pergamon, 1996, vol. 4, p. 621.
9. Artamonova, T.V., Zatsepina, M.V., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2004, vol. 40, 1318.
10. Gol'tsberg, M.A. and Koldobskii, G.I., *Russ. J. Org. Chem.*, 1996, vol. 32, 1194.
11. Koldobskii, G.I., Hrabalek, A., and Esikov, K.A., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 447.