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Tetrazoles: XLIX.* Alkylation of Tetrazoles with Tetrakis(chloroacetoxymethyl)methane

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Abstract—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 in boiling acetonitrile in the presence of potassium bromide and triethylamine gives tetrakis[2-(4-aryl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)acetoxymethyl]-methanes and tetrakis[2-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)acetoxymethyl]methane, respectively. The alkylation process is considerably accelerated under microwave irradiation.

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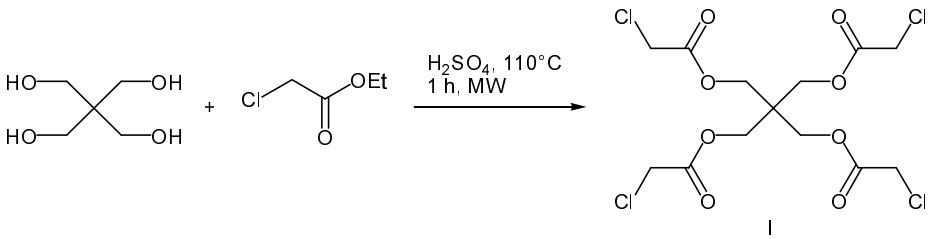
While studying possible synthetic routes to dendrimers containing a tetrazole ring as structural fragment, we developed procedures for the preparation of a number of tetrazole derivatives which can be used as a framework in the divergent synthesis of dendrimers [2]. In continuation of these studies, we found that heterocyclic systems including more than two tetrazole rings can be obtained by alkylation of 1-aryltetrazoles with tetrakis(2-chloroacetoxymethyl)methane (**I**). Compound **I** was synthesized by heating a mixture of 2,2-bis(hydroxymethyl)propan-1,3-diol with ethyl chloroacetate for 6 h at 130°C. Under the conditions of microwave activation (MW), tetraester **I** can be obtained in 98% yield at a lower temperature (110°C) and in a shorter time (1 h) (Scheme 1).

As initial tetrazole derivatives we used 1-aryl-4,5-dihydro-1*H*-tetrazol-5-ones **IIa** and **IIb** and 1-phenyl-4,5-dihydro-1*H*-tetrazole-5-thione (**IV**). These substrates were selected for the following reasons. As shown previously [3, 4], the alkylation of 1-aryltetrazol-5-ones and 1-aryltetrazole-5-thiones occurs with high regioselectivity: in the first case, 1-aryl-4-alkyl-4,5-dihydro-1*H*-tetrazol-5-ones are formed, and in the second, 1-aryl-5-alkylsulfanyl-1*H*-tetrazoles. We expected that analogous relations should be held in the alkylation of the same substrates with tetrakis-(2-chloroacetoxymethyl)methane (**I**).

In fact, the reactions of tetrazol-5-ones **IIa** and **IIb** with tetrakis(2-chloroacetoxymethyl)methane in boiling acetonitrile in the presence of potassium bromide and triethylamine in 4 h gave substituted tetrazoles **IIIa** and **IIIb** in 62 and 63% yield, respectively (Scheme 2). The alkylation of 1-phenyl-4,5-dihydro-1*H*-tetrazole-5-thione (**IV**) with compound **I** under similar conditions (reaction time 1 h) resulted in the formation of 85% of tetrakis[2-(1-phenyltetrazol-5-ylsulfanyl)acetoxymethyl]methane (**V**) (Scheme 3). When the alkylation of **IV** was performed in a two-phase liquid–liquid system in the presence of tetrabutylammonium bromide as phase-transfer catalyst,

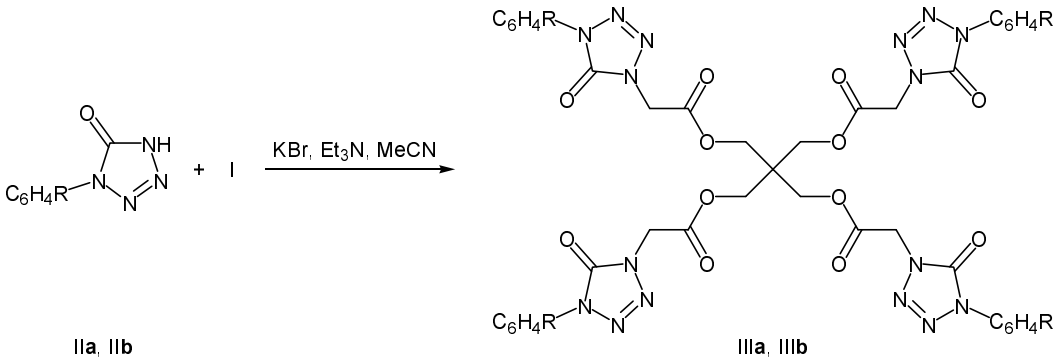
Scheme 1.



I

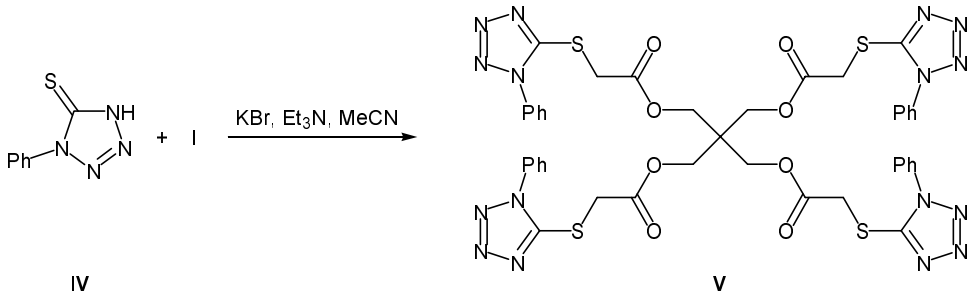
* For communication XLVIII, see [1].

Scheme 2.



R = H (**a**), 4-O_2N (**b**).

Scheme 3.



tetrazole derivative **V** was formed in 88% yield at room temperature (20°C), but the reaction time was considerably longer (4–5 h). The best results were obtained by carrying out the alkylation of tetrazoles **IIa**, **IIb**, and **IV** under microwave irradiation (see table). Under these conditions, the reaction time was shorter and the yield of the alkylation products increased, while the selectivity remained unchanged. However, the obtained results did not allow us to draw an ultimate conclusion, for microwave activation is known to change the direction of alkylation of some ambident heteroanions [5, 6]. Nevertheless, the alkylation of tetrazoles with tetraester **I** provides a synthetic route to tetrazole-containing precursors of dendrimers.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400s spectrometer from samples prepared as KBr pellets. The NMR spectra were measured on a Bruker AC-200 instrument in DMSO-d_6 or $CDCl_3$ (**IIIb**). Microwave-assisted reactions were performed using a Milestone P/N 44072 microwave furnace.

Tetrakis(2-chloroacetoxymethyl)methane (I). *a*. A mixture of 7.35 mmol of 2,2-bis(hydroxymethyl)-propane-1,3-diol, 33.1 mmol of ethyl chloroacetate, and 0.04 mmol of 94% sulfuric acid was stirred for 6 h at 130°C. The mixture was then cooled to 40°C and washed with 50 ml of petroleum ether, and the solid residue was dried in air. Yield 2.66 g (82%), mp 94–95°C (from ethanol) [7]. IR spectrum, ν, cm^{-1}: 793, 946, 1003, 1014, 1165, 1191, 1278, 1301, 1316, 1383, 1412, 1474, 1753, 2911, 2958, 2970, 3009, 3019. ^1H NMR spectrum, δ, ppm: 4.09 s (8H, CH_2), 4.28 s (8H, CH_2). Found, %: C 35.48; H 3.54. $C_{13}H_{16}Cl_4O_8$. Calculated, %: C 35.31; H 3.62.

b. A mixture of 7.35 mmol of 2,2-bis(hydroxymethyl)propane-1,3-diol, 33.1 mmol of ethyl chloroacetate, and 0.04 mmol of 94% sulfuric acid was stirred for 1 h at 110°C in a heat-resistant reactor placed in a microwave furnace (50 W). The mixture was cooled

Alkylation of tetrazoles **IIa**, **IIb**, and **IV** with tetraester **I** under conditions of conventional heating and microwave activation (MW)

Initial tetrazole	Product	Conventional heating (82°C)		MW activation (75°C)	
		time, h	yield, %	time, h	yield, %
IIa	**IIIa**	4	62	3	85
IIb	**IIIb**	4	63	2	80
IV	**V**	1	85	0.3	92

to 40°C and washed with 50 ml of petroleum ether, and the solid residue was dried in air. Yield 3.18 g (98%), mp 94–95°C (from ethanol).

Tetrakis[2-(4-phenyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)acetoxymethyl]methane (IIIa). *a*. A mixture of 3.09 mmol of 1-phenyl-4,5-dihydro-1*H*-tetrazol-5-one (**IIa**), 0.68 mmol of tetraester **I**, 3.5 mmol of potassium bromide, and 3.5 mmol of triethylamine in 10 ml of acetonitrile was stirred for 4 h at 82°C. The mixture was cooled to 18°C, 100 ml of 1% aqueous sodium hydroxide was added, and the precipitate was filtered off, washed with water (2×20 ml), and dried in air. Yield 0.4 g (62%), mp 209–211°C (from DMF–ethanol, 7:3). IR spectrum, ν, cm^{-1}: 690, 733, 757, 837, 992, 1071, 1100, 1130, 1155, 1198, 1316, 1369, 1400, 1414, 1463, 1502, 1597, 1631, 1726, 1735, 1770, 2959, 2997. ^1H NMR spectrum, δ, ppm: 4.29 s (8H, CH_2), 5.13 s (8H, CH_2), 7.44–7.85 m (20H, H_{arom}). Found, %: C 52.30; H 3.90; N 23.72. $C_{41}H_{36}N_{16}O_{12}$. Calculated, %: C 52.12; H 3.81; N 23.73.

b. A mixture of 3.09 mmol of 1-phenyl-4,5-dihydro-1*H*-tetrazol-5-one (**IIa**), 0.68 mmol of tetraester **I**, 3.5 mmol of potassium bromide, and 3.5 mmol of triethylamine in 10 ml of acetonitrile was stirred in a heat-resistant reactor for 3 h at 75°C under microwave irradiation (40 W). The mixture was cooled to 18°C, 100 ml of 1% aqueous sodium hydroxide was added, and the precipitate was filtered off, washed with water (2×20 ml), and dried in air. Yield 0.54 g (85%), mp 209–211°C (from DMF–ethanol, 7:3).

Compounds **IIIb** and **V** were synthesized in a similar way.

Tetrakis[2-(4-nitrophenyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)acetoxymethyl]methane (IIIb). mp 115–116°C (from ethyl acetate–ethanol, 9:1). IR spectrum, ν, cm^{-1}: 685, 736, 749, 834, 856, 990, 1089, 1127, 1208, 1343, 1396, 1416, 1502, 1524, 1597, 1741, 2956, 2994, 3091, 3122. ^1H NMR spectrum, δ, ppm: 4.27 s (8H, CH_2), 4.90 s (8H, CH_2), 8.20 d (8H, H_{arom}), 8.37 d (8H, H_{arom}). Found, %: C 43.78; H 3.02; N 24.99. $C_{41}H_{32}N_{20}O_{20}$. Calculated, %: C 43.77; H 2.85; N 24.91.

Tetrakis[2-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-acetoxymethyl]methane (V). The product was purified by column chromatography on silica gel using ethyl acetate–carbon tetrachloride (1:1) as eluent, mp 52–53°C. IR spectrum, ν, cm^{-1}: 694, 761, 894, 1014, 1057, 1074, 1150, 1245, 1278, 1298, 1391, 1462, 1500, 1595, 1743, 2933, 2987, 3064. ^1H NMR spectrum, δ, ppm: 4.11 s (8H, CH_2), 4.31 s (8H, CH_2), 7.64 s (20H, H_{arom}). Found, %: C 48.92; H 3.50; N 22.35. $C_{41}H_{36}N_{16}O_8S_4$. Calculated, %: C 48.81; H 3.57; N 22.22.

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REFERENCES

1. Nikulin, V.V., Artamonova, T.V., and Koldobskii, G.I., *Russ. J. Org. Chem*., 2005, vol. 41, p. 444.
2. Artamonova, T.V., Zatsepina, M.V., and Koldobskii, G.I., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1318.
3. Poplavskaya, Yu.V., Alam, L.V., and Koldobskii, G.I., *Russ. J. Org. Chem*., 2000, vol. 36, p. 1793.
4. Gol'tsberg, M.A. and Koldobskii, G.I., *Russ. J. Org. Chem*., 1996, vol. 32, p. 1194.
5. Xu, Y. and Guo, Q.-X., *Heterocycles*, 2004, vol. 63, p. 903.
6. Kuznetsov, D.V., Raev, V.A., Kuranov, G.L., Arapov, O.V., and Kostikov, R.R., *Russ. J. Org. Chem*., 2005, vol. 41, p. 1719.
7. McCasland, G.E. and Smith, D.A., *J. Am. Chem. Soc*., 1952, vol. 74, p. 564.