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Synthesis of *N*-(Oxyran-2-ylmethyl)triazoles and -tetrazoles

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Abstract—The alkylation of 5-phenyl-1*H*-tetrazole and 4-nitro-2*H*-1,2,3-triazole with 1-chloro-2,3-epoxypropane and cycloaddition of 1-azido-3-chloropropan-2-ol to acetylenic dipolarophiles gave the corresponding *N*-(3-chloro-2-hydroxypropyl)azoles as intermediate products in the synthesis of *N*-(oxiran-2-ylmethyl)azoles.

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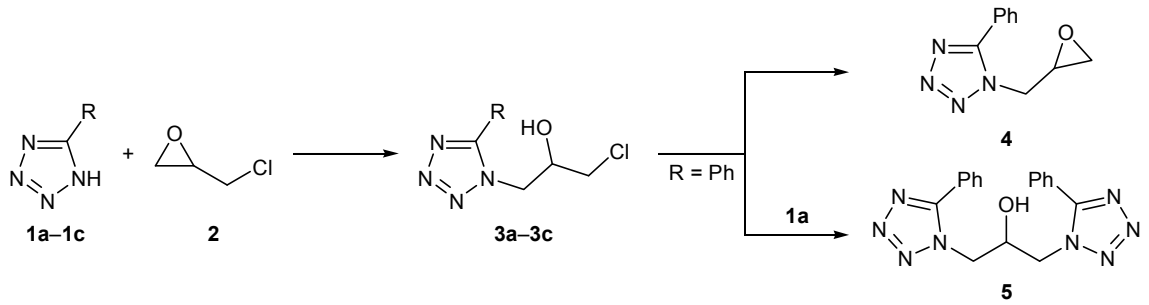
There are fairly scarce published data on the synthesis of azoles with epoxy-containing substituents. This is related primarily to difficulties arising from the high reactivity of epoxy compounds and hence numerous side reactions. In this work we propose several ways of construction of an oxirane ring at an azole cycle with a view to obtaining new mono- and polyfunctional azole-containing monomers which could give rise to new high molecular weight compounds, as well as to interesting and practically important materials based thereon.

The alkylation of 5-phenyltetrazole with 1-chloro-2,3-epoxypropane in acetone in the presence of triethylamine, followed by dehydrochlorination of intermediate chlorohydrin was reported [1] to afford 1-(oxiran-2-ylmethyl)-5-phenyl-1*H*-tetrazole. We tried to reproduce this procedure, but the desired tetrazole **4** was isolated in a poor yield, presumably because of side reaction of intermediate chlorohydrin **3a** with initial 5-phenyl-1*H*-tetrazole (**1a**) to give 1,3-bis(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (**5**) (Scheme 1). The alkylation of **1a** with **2** in acetone–DMF in the presence of potassium hydroxide was also unsuccessful. Probably, under these conditions initially formed chlorohydrin **3a** undergoes dehydrochlorination to azole **4** which then polymerizes by the action of 5-phenyl-1*H*-tetrazole or KOH. No success was achieved in attempted alkylation of tetrazole and such bis-azoles as 5-[2-(tetrazol-5-yl)ethyl]- and 5-[2-(tetrazol-5-yl)butyl]tetrazoles with epichlorohydrin under various conditions (in the presence of triethylamine or NaOH as bases using acetone or DMF as solvent). In all cases, tarry compounds were formed which we failed to identify.

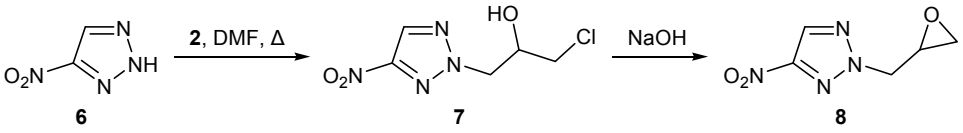
The optimal conditions for the alkylation of NH-azoles with **2** include prolonged (8–12 h) heating of equimolar amounts of the reactants in a polar aprotic solvent in the absence of a catalyst. In this way, we succeeded in synthesizing and identifying not only oxirane-containing tetrazoles **4a** and **4b** (Scheme 1) but also 4-nitro-2-(oxiran-2-ylmethyl)-2*H*-1,2,3-triazole (**8**) (Scheme 2). The latter attracts interest due to particular prospects in using nitro derivatives of 1,2,3-triazoles in various fields of practice [2–5].

Scheme 1.



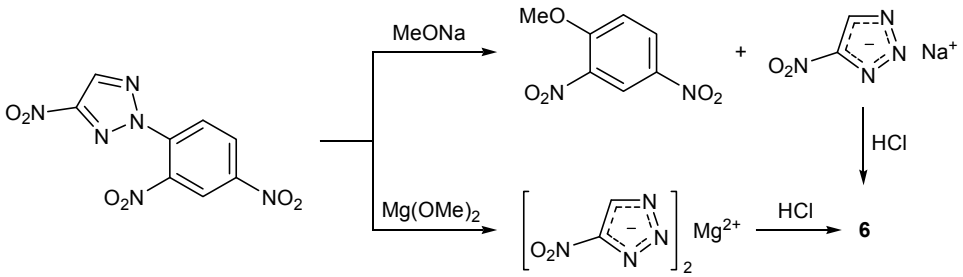
R = Ph (**a**), $MeOC(O)CH_2$ (**b**), $NCCH_2$ (**c**).

Scheme 2.



6 **7** **8**

Scheme 3.



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Initial 4-nitro-2*H*-1,2,3-triazole (**6**) was prepared by modified procedure [6]. The last step of this procedure, alcoholysis of 2-(2,4-dinitrophenyl)-4-nitro-2*H*-1,2,3-triazole implies intermediate isolation of 4-nitro-1,2,3-triazole sodium salt which turned out to be sensitive to temperature, and in some cases it ignited spontaneously on drying on a steam bath. We have found that the isolation of nitrotriazole as magnesium salt **9** (Scheme 3) is more safe. According to the thermogravimetric data, the ignition temperature of **9** is about 280°C, and the salt is isolated as crystal hydrate containing five water molecules. The yield of **9** in this step was 60%, and the overall yield of **6** calculated on the initial phenylhydrazine was 25–30%.

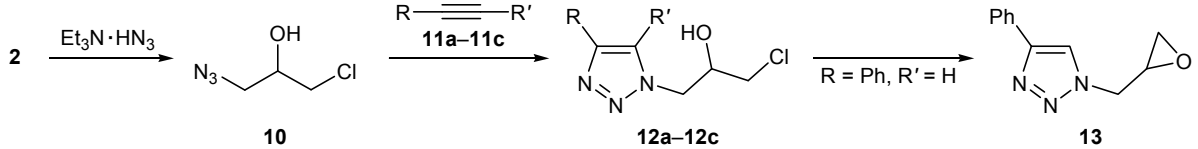
A synthetic route to *N*-glycidyl-substituted 1,2,3-triazoles via cycloaddition of 1-azido-2,3-epoxypropane to acetylenic compounds was considered in [7]. However, high reactivity of oxirane ring promoted various side processes in the direct 1,3-dipolar cycloaddition of 1-azido-2,3-epoxypropane to acetylenic dipolarophiles, which resulted in reduced yield of the target epoxypropyl-1,2,3-triazoles.

We have found that a rational method of synthesis of triazoles **13** involves initial "classical" cycloaddition of 1-azido-3-chloropropan-2-ol (**10**) to acetylenic compounds **11a**–**11c**, followed by dehydrochlorination of the resulting chlorohydrins **12a**–**12c** (Scheme 4). The cycloaddition of azide **10** to unsymmetrical acetylenes could give two regioisomeric triazoles. In the reaction of **10** with phenylacetylene (**11a**) we isolated only one isomer with the phenyl group attached to C^4, as followed from the position of the 5-H signal in the ^{1}H NMR spectrum.

Initial 1-azido-3-chloropropan-2-ol (**10**) was synthesized by reaction of epichlorohydrin (**2**) with triethylammonium azide. It is advisable to perform the reaction in diethyl ether without preliminary isolation of the salt $Et_3N \cdot HN_3$ which is highly hygroscopic and unstable.

The structure of the isolated compounds was confirmed by NMR and IR spectra and elemental analyses. The ^{1}H NMR spectra of **3a**–**3c**, **7**, and **12a**–**12c** contained signals from protons in the chlorohydrin fragment at δ 4.70–4.94, 3.71–3.89, and 4.17–4.55 ppm, while epoxy derivatives **4**, **8**, and **13** displayed signals at δ 2.36–2.95 and 3.55–3.76 ppm due to protons in the oxirane ring and at δ 4.65–4.90 ppm due to "bridging" methylene group. In the IR spectra of **3a**–**3c**, **7**, and **12a**–**12c** we observed absorption bands typical of O–H and C–Cl stretching vibrations in the regions 3198–3364 and 719–783 cm^{-1}, respectively. The oxirane ring in **4**, **8**, and **13** was charac-

Scheme 4.



10 **12a–12c** **13**

R = Ph, R′ = H (**a**); R = R′ = HOC(O) (**b**); R = $HOCPh_2$, R′ = H (**c**).

terized by IR absorption bands at 1249–1261 and 829–875 cm^{-1}, while neither O–H nor C–Cl bands were present in the IR spectra of these compounds.

The isomeric products were identified, and their ratios were determined, on the basis of the ^1H NMR spectra from the positions and intensities of the 5-H signal in nitrotriazole derivatives and *o*-H in 5-phenyltetrazoles. It is known [8, 9] that the signals from the above protons in the spectra of 1-R-4-nitrotriazoles and 1-R-5-phenyltetrazoles are located in a weaker field than those of 2-R-isomers. In the spectra of tetrazoles **3a** and **4** we observed two *o*-H signals at δ 8.09–8.16 and 7.68–7.76 ppm; their intensity ratio indicated predominant formation of the N^1-substituted isomer (~95%). 4-Nitrotriazole derivatives **7** and **8** displayed 5-H signal at δ 8.46 ppm and were identified as N^2-isomers (92%). In addition, small amounts (8%) of 1-substituted 5-nitro-1,2,3-triazoles ($\delta_{4\text{-H}}$ 8.64 ppm) were detected.

EXPERIMENTAL

The IR spectra were recorded on an Infralum FT-801 spectrometer from samples prepared as KBr discs or Nujol mulls. The ^1H NMR spectra were measured on a Varian VXR-500s instrument (500 MHz) from solutions in acetone-d_6 or $CDCl_3$. The elemental analyses were obtained on a Flash EA 1112 Series CHN analyzer. The progress of reactions was monitored by TLC on Silufol plates using ethyl acetate–hexane (2:3) as eluent. Thermogravimetric analysis was performed on a Perkin Elmer SII Diamond TG/DTA instrument (dynamic mode, heating rate 5 deg/min).

1-Chloro-3-(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (3a). A solution of 2 g (0.014 mol) of 5-phenyltetrazole (**1a**) and 1.3 g (0.014 mol) of epichlorohydrin (**2**) in 15 mL of DMF was stirred for 8 h at 80°C, and the solvent was removed under reduced pressure. Yield 1.5 g (45%), mp 84–86°C (from EtOH). IR spectrum, ν, cm^{-1}: 3240 (O–H), 780 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.54 br.s (1H, OH), 3.61 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 7.5 Hz), 3.81 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 2.8 Hz), 4.55 m (1H, CH), 4.77 d.d (1H, CH_2, ^2J = 13.2, ^3J = 5.0 Hz), 4.77 d.d (1H, CH_2, ^2J = 13.2, ^3J = 7.0 Hz), 7.49 m (3H, *m*-H, *p*-H), 7.76 m (2H, *o*-H, N^2-isomer), 8.09 m (2H, *o*-H, N^1-isomer). Found, %: C 50.02; H 4.69; N 23.51. $C_{10}H_{11}ClN_4O$. Calculated, %: C 50.32; H 4.65; N 23.47.

Methyl 2-[1-(3-chloro-2-hydroxypropyl)-1*H*-tetrazol-5-yl]acetate (3b) was synthesized in a similar way. Yield 1.8 g (54%), viscous liquid. IR spectrum, ν, cm^{-1}: 3364 (O–H), 1737 (C=O), 771 (C–Cl). Found, %: C 36.12; H 4.61; N 24.71. $C_7H_{11}ClN_4O_3$. Calculated, %: C 35.83; H 4.73; N 23.88.

2-[1-(3-Chloro-2-hydroxypropyl)-1*H*-tetrazol-5-yl]acetonitrile (3c) was synthesized in a similar way from 0.7 g (6 mmol) of tetrazole **1c** and 0.6 g (6 mmol) of **2** in 10 mL of DMF. Yield 0.6 g (55%), viscous liquid. IR spectrum, ν, cm^{-1}: 3344 (O–H), 2263 (C≡N), 756 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.77 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 7.5 Hz), 3.97 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 2.8 Hz), 4.23 (1H, CH), 4.42 s (2H, CH_2CN), 4.58 d.d (1H, CH_2, ^2J = 13.3, ^3J = 7.8 Hz), 4.78 d.d (1H, CH_2, ^2J = 13.2, ^3J = 5.1 Hz), 7.37 br.s (1H, OH). Found, %: C 36.31; H 4.95; N 32.98. $C_6H_8ClN_5O$. Calculated, %: C 35.74; H 4.00; N 34.74.

1-(Oxiran-2-ylmethyl)-5-phenyl-1*H*-tetrazole (4). A solution of 0.5 g (12.5 mmol) of sodium hydroxide in 5 mL of water was added in portions to a solution of 2 g (8 mmol) of compound **3a** in 15 mL of acetone, and the mixture was stirred for 1 h at 25°C. The precipitate (NaCl) was filtered off, the filtrate was diluted with 10 mL of water and extracted with diethyl ether, and the extract was dried over $CaCl_2$ and evaporated in air. Yield 1.4 g (88%), mp 46–48°C (from EtOAc) [1]. IR spectrum, ν, cm^{-1}: 875, 1250 (oxirane). ^1H NMR spectrum, δ, ppm: 2.26 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 3.4 Hz), 2.46 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 4.1 Hz), 3.55 (1H, 2′-H), 4.31 d.d (1H, CH_2, ^2J = 13.2, ^3J = 3.2 Hz), 4.55 d.d (1H, CH_2, ^2J = 13.2, ^3J = 6.6 Hz), 7.49 m (3H, *m*-H, *p*-H), 7.68 m (2H, *o*-H, N^2 isomer), 8.16 m (2H, *o*-H, N^1-isomer).

1,3-Bis(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (5). A mixture of 5.3 g (36 mmol) of 5-phenyltetrazole, 1.5 g (36 mmol) of sodium hydroxide or 3.6 g (36 mmol) of triethylamine, and 3.3 g (36 mmol) of epichlorohydrin (**2**) in 20 mL of ethanol was stirred for 4 h at 20–25°C. The precipitate was filtered off. Yield 7.4 g (59%), mp 198°C (from EtOH) [1]. IR spectrum: ν 3362 cm^{-1} (O–H). ^1H NMR spectrum, δ, ppm: 3.92 d.d (4H, CH_2, ^2J = 11.8, ^3J = 6.7 Hz), 5.50 t (1H, CH, ^3J = 6.7 Hz), 7.55–7.91 m (10H, H_{arom}), 13.54 s (1H, OH).

4-Nitro-1,2,3-triazole (6). Magnesium salt **9**, 10 g (0.04 mol), was dispersed in 15 mL of water, concentrated aqueous HCl was added to pH 2, and the precipitate was filtered off. Yield 8.5 g (93%), mp 158°C (from EtOAc) [6].

1-Chloro-3-(4-nitro-2*H*-1,2,3-triazol-2-yl)propan-2-ol (7) was synthesized as described above for

3a–**3c** from 2 g (18 mmol) of 6 and 1.7 g (18 mmol) of **2** in 15 mL of DMF. Yield 0.4 g (11%), mp 104–105°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3380 (O–H), 783 (C–Cl). ^1H NMR spectrum, δ, ppm: 4.17 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 7.5 Hz), 4.23 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 2.8 Hz), 4.17 m (1H, CH), 4.84 d.d (1H, CH_2, ^2J = 11.8, ^3J = 7.7 Hz), 5.15 d.d (1H, CH_2, ^2J = 11.8, ^3J = 5.1 Hz), 7.41 br.s (1H, OH), 7.96 s (1H, 5-H). Found, %: C 29.04; H 3.38; N 27.25. $C_5H_7ClN_4O_3$. Calculated, %: C 29.07; H 3.42; N 27.12.

4-Nitro-2-(oxiran-2-ylmethyl)-2*H*-1,2,3-triazole (8) was synthesized as described above for compound **4** from 0.1 g (0.4 mmol) of **7** using 0.024 g (0.6 mmol) of NaOH. Yield 0.06 g (86%), mp 132°C (from EtOAc). IR spectrum, ν, cm^{-1}: 832, 1249 (oxirane). ^1H NMR spectrum, δ, ppm: 2.77 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 3.2 Hz), 2.90 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 4.1 Hz), 3.54 (1H, 2′-H), 4.70 d.d (1H, CH_2, ^2J = 13.2, ^3J = 3.2 Hz), 5.00 d.d (1H, CH_2, ^2J = 13.3, ^3J = 3.2 Hz). Found, %: C 36.24; H 3.97; N 32.15. $C_5H_6N_4O_3$. Calculated, %: C 35.30; H 3.55; N 32.93.

4-Nitro-1,2,3-triazole magnesium salt (9). Magnesium turnings, 2.4 g, were dissolved in 300 mL of methanol on heating, the mixture was heated for 30 min under reflux and cooled to room temperature, and 42 g (0.15 mol) of 4-nitro-2-(2,4-dinitrophenyl)-2*H*-1,2,3-triazole was added. The mixture was heated for 3 h under reflux, 220–225 mL of methanol was distilled off, 400 mL of water was added to the residue under stirring, and the mixture was cooled. The precipitate was filtered off and washed with water. The filtrate was combined with the washings and evaporated on a steam bath, and the residue was recrystallized from propan-2-ol. Yield 34 g (90%).

1-Azido-3-chloropropan-2-ol (10). A dry solution of HN_3 in diethyl ether, prepared from 30 g (0.46 mol) of sodium azide and concentrated HCl, was cooled to 0°C, 23 g (0.23 mol) of triethylamine was added dropwise, 21 g (0.22 mol) of epichlorohydrin (**2**) was then added, and the mixture was stirred for 8 h at 35°C. When the reaction was complete, the mixture was evaporated, and the residue was distilled under reduced pressure. Yield 3.8 g (95%), bp 80–84°C (7 mm). IR spectrum, ν, cm^{-1}: 3258 (O–H), 2108 (N_3), 719 (C–Cl).

1-Chloro-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-ol (12a). A solution of 3.2 g (0.024 mol) of azide **10** and 2 g (0.02 mol) of phenylacetylene (**11a**) in 25 mL of toluene was stirred for 12 h at 85–90°C, and the solvent was removed under reduced pressure. Yield 2.9 g (61%), mp 126–127°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3196 (O–H), 3139 (C–H), 719 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.55 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 7.5 Hz), 3.75 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 2.8 Hz), 4.20 m (1H, CH), 4.64 d.d (1H, CH_2, ^2J = 13.2, ^3J = 7.5 Hz), 4.80 d.d (1H, CH_2, ^2J = 13.2, ^3J = 2.8 Hz), 7.37 br.s (1H, OH), 7.55–7.68 m (5H, H_{arom}), 8.20 s (1H, 5-H). Found, %: C 54.70; H 5.10; N 18.09. $C_{11}H_{12}ClN_3O$. Calculated, %: C 55.59; H 5.09; N 17.68.

1-(3-Chloro-2-hydroxypropyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (12b) was synthesized in a similar way from 2 g (17 mmol) of acetylenedicarboxylic acid (**11b**) and 2.7 g (20 mmol) of azide **10** in 25 mL of ethanol. Yield 3.1 g (73%), mp 105–106°C (decomp., from EtOAc). IR spectrum, ν, cm^{-1}: 3267 (O–H), 768 (C–Cl). Found, %: C 34.13; H 3.72; N 15.06. $C_7H_8ClN_3O_5$. Calculated, %: C 33.68; H 3.23; N 16.83.

1-Chloro-3-{4-[hydroxy(diphenyl)methyl]-1*H*-1,2,3-triazol-1-yl}propan-2-ol (12c) was synthesized in a similar way from 0.5 g (4 mmol) of azide **10** and 0.9 g (4 mmol) of acetylenic alcohol **11c** in 10 mL of toluene. Yield 0.45 g (32%), mp 40–42°C (decomp., from EtOAc). IR spectrum, ν, cm^{-1}: 3291, 3269 (O–H), 3087 (C–H), 757 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.97 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 7.5 Hz), 4.17 m (1H, CH), 4.63 d.d (1H, CH_2, ^2J = 13.3, ^3J = 7.7 Hz), 4.77 d.d (1H, CH_2Cl, ^2J = 11.8, ^3J = 2.8 Hz), 4.83 d.d (1H, CH_2, ^2J = 13.2, ^3J = 2.8 Hz), 6.70 br.s (1H, OH), 6.80 s (1H, 5-H), 7.17–7.44 m (10H, H_{arom}). Found, %: C 63.54; H 5.91; N 11.63. $C_{18}H_{18}ClN_3O_2$. Calculated, %: C 62.88; H 5.28; N 12.22.

1-(Oxiran-2-ylmethyl)-4-phenyl-1*H*-1,2,3-triazole (13) was synthesized as described above for **4** from 0.5 g (2.4 mmol) of **12a** using 0.1 g (2.4 mmol) of NaOH. Yield 0.38 g (96%), mp 80–82°C (from EtOAc). IR spectrum, ν, cm^{-1}: 829, 1261 (oxirane). ^1H NMR spectrum, δ, ppm: 2.26 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 3.4 Hz), 2.46 d.d (1H, 3′-H, ^2J = 6.3, ^3J = 4.1 Hz), 3.75 (1H, 2′-H), 4.33 d.d (1H, CH_2, ^2J = 13.3, ^3J = 3.2 Hz), 4.53 d.d (1H, CH_2, ^2J = 13.3, ^3J = 6.6 Hz), 7.55–7.66 m (5H, H_{arom}), 8.49 s (1H, 5-H). Found, %: C 36.24; H 3.97; N 32.15. $C_5H_6N_4O_3$. Calculated, %: C 35.30; H 3.55; N 32.93.

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