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Synthesis of *N*-(Oxiran-2-ylmethyl)-5-phenyltetrazole and Its Reactions with Nitrogen Nucleophiles

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Abstract—The synthesis of *N*-(oxiran-2-ylmethyl)-5-phenyltetrazole was optimized, and its reactions with various nitrogen nucleophiles afforded bicyclic amino alcohols, including those containing an azole ring.

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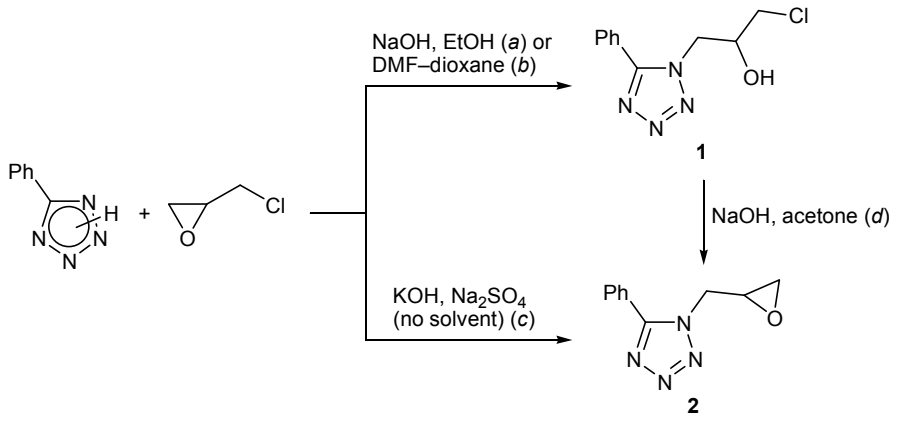
Oxirane compounds are widely used in various branches of industry. High variability of epoxy compounds makes it possible to obtain functional polymers for heat- and chemically resistant compositions, optically transparent lacquer-and-paint materials, and adhesives. However, there are scarce published data on mono- and polyepoxides containing azole (specifically tetrazole) fragments. However, the importance of these compounds is difficult to overestimate since the presence of a reactive oxirane ring linked to a tetrazole fragment makes them promising from the viewpoints of both fundamental and applied chemistry.

In keeping with published data, *N*-(oxiran-2-ylmethyl)-substituted azoles are generally synthesized by alkylation of the corresponding NH-heterocycle with epichlorohydrin in the presence of a base (KOH, NaOH, NEt_3, NaOMe–MeOH) [1–4]. However, application of known procedures to 5-phenyltetrazole involved difficulties mostly related to very poor yield of the target products (Scheme 1).

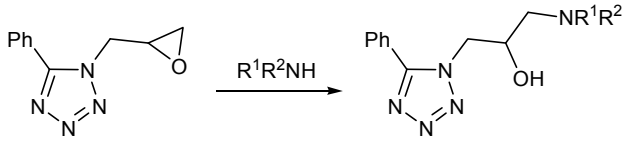
In fact, the alkylation of 5-phenyltetrazole with epichlorohydrin in the presence of NaOH or NEt_3 (Scheme 1, method *a*) was inefficient because of the low yield of **1**. Variation of the alkylation conditions showed that better results can be obtained by prolonged heating the reactants in a polar aprotic solvent (DMF) in the absence of a base [5]. However, a problem arose while attempting to scale up the synthesis; in particular, it was difficult to remove DMF after reaction completion, but even a small amount of DMF hampered crystallization of the product, so that the yield was reduced.

Variation of the solvent showed that the synthesis in dioxane with addition of a small amount of DMF to dissolve the initial 5-phenyltetrazole was more efficient and less laborious (method *b*). Dehydro-

Scheme 1.



Scheme 2.



2 **3–9**

3–**7**, R^1 = H; **3**, R^2 = 1*H*-1,2,4-triazol-3-yl; **4**, R^2 = 1-methyl-1*H*-tetrazol-5-yl; **5**, R^2 = pyridin-2-yl; **6**, R^2 = Ph; **7**, R^2 = $H_2N(CH_2)_2$; **8**, R^1R^2N = morpholin-4-yl; **9**, R^1R^2 = piperidin-1-yl.

chlorination of chlorohydrin **1** thus obtained gave target *N*-(oxiran-2-ylmethyl)tetrazole **2** (*d*). Method *c* ensures introduction of an oxiranylmethyl substituent into tetrazole ring in one step without additional dehydrochlorination of intermediate chlorohydrin. However, the yield of **2** did not exceed 11% in numerous attempts to reproduce this procedure.

The structure of compounds **1** and **2** was confirmed by IR and NMR spectra and elemental analyses. Compound **1** showed in the ^{1}H NMR spectrum signals at δ 4.77, 4.97, 3.61, 3.81, and 4.55 ppm due to nonequivalent protons in the $CH_2CH(OH)CH_2Cl$ fragment. The ^{1}H NMR spectrum of **2** contained signals of the oxirane ring at δ 2.26, 2.46 (CH_2) and 3.55 ppm (CH) and of the bridging methylene group at δ 4.55 and 4.31 ppm. In the IR spectrum of **1** we observed characteristic absorption bands due to stretching vibrations of the O–H (3380 cm^{-1}) and C–Cl bonds (783 cm^{-1}). The oxirane ring in **2** gave rise to IR bands at 1249 and 832 cm^{-1}.

The regioisomers were identified, and their ratio was determined, by the position and intensity of ^{1}H NMR signals of the *ortho*-protons in the 5-phenyl substituent. It is known that the signal of the N^1-substituted isomer is located in a weaker field than the corresponding signal of the N^2-isomer [6, 7]. In the ^{1}H NMR spectrum of **2**, these signals were observed at δ 8.09–8.16 and 7.68–7.76 ppm for the N^1- and N^2-isomers, respectively, with an intensity ratio of 95:5.

The oxirane ring in **2** exhibits a behavior typical of other epoxy compounds. In particular, compound **2** reacted with primary and secondary amines (1*H*-1,2,4-triazole-3-amine, 1-methyl-1*H*-tetrazol-5-amine, pyridin-2-amine, aniline, ethane-1,2-diamine, morpholine, and piperidine) to give the corresponding amino alcohols **3**–**9** (Scheme 2). The reactions were carried out in ethanol at 60–65°C (reaction time 2.5–3 h). Opening of the oxirane ring in these reactions followed the Krasuskii rule, i.e., nucleophilic attack was directed at the least substituted OCH_2 carbon atom.

Because of limited solubility of 1,4-diphenyl-1*H*-1,2,3-triazol-5-amine in ethanol, its reaction with **2** was carried out with addition of DMF to make the reaction mixture homogeneous. We presumed that this reaction would lead to the formation of a bicyclic triazole-containing amino alcohol, as in reactions of **2** with 1*H*-1,2,4-triazole-3-amine and 1-methyl-1*H*-tetrazol-5-amine which are incapable of amine–imine tautomerism [8] and behave as common aromatic amines. However, no expected amino alcohol was isolated. The ^{1}H NMR spectrum of the reaction mixture contained weak multiplet signals assignable to methylene group linked to the tetrazole ring (δ 5.22 and 4.74 ppm) and CH(OH) (δ 3.58 ppm) and CH_2NH groups (δ 2.82, 2.93 ppm); as followed from the signal intensity, the fraction of the corresponding product did not exceed 5%. Variation of the reaction conditions (i.e., increase of temperature and reaction time) did not improve the yield. This result may be accounted for by steric shielding of the nucleophilic amino group in the 1,4-diphenyl-1*H*-1,2,3-triazol-5-amine molecule by bulky phenyl groups.

In the reaction of **2** with ethane-1,2-diamine we isolated monosubstitution product **7** instead of the expected disubstituted compound despite large excess of **2**. The structure of **7** followed from the intensity ratio of signals of the CH_2 and CHOH protons (4:1).

Amino alcohols **3**–**9** are light yellow to rich brown crystalline substances soluble in polar organic solvents and aqueous mineral acids. Compound **2** failed to react with NH-azoles (tetrazole, 5-phenyltetrazole, 4-nitro-1,2,3-triazole, or 1,2,4-triazole) as nitrogen nucleophiles under the given (ethanol, 60°C) or more severe conditions (DMF, 95°C); in all cases, the initial azoles were recovered from the reaction mixtures.

The structure of amino alcohols **3**–**9** was confirmed by NMR and IR spectra and elemental analyses. In the ^{1}H NMR spectra of **3**–**9**, nonequivalent protons of the $CH_2CH(OH)CH_2$ fragment resonated at δ 4.55–4.87, 4.18–4.30, and 3.16–4.37 ppm, respectively, and the OH signal was located at δ 3.38–5.91 ppm. The IR

spectra of **3**–**9** displayed OH stretching band in the region 3160–3184 cm^{-1}, and the spectra of **3**–**6** additionally showed NH stretching band in the region 3320–3360 cm^{-1}.

EXPERIMENTAL

The IR spectra were recorded in KBr or mineral oil on an Infralum FT-801 spectrometer. The ^1H NMR spectra were measured on a Varian VXR-500s instrument at 126 MHz using DMSO-d_6 as solvent. 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 by volume) as eluent.

1-Chloro-3-(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (1). *a*. A 50-mL volumetric flask was charged with 2 g (0.0137 mol) of 5-phenyltetrazole, a solution of 0.55 g (0.0137 mol) of sodium hydroxide in 2 mL of water and 22.3 g (0.24 mol) of epichlorohydrin were added, and the volume of the mixture was adjusted to 50 mL by adding ethanol. The mixture was kept for 6 days at room temperature until pH ~10 was attained, 20 mL of water was added, and the mixture was extracted with ethyl acetate. The combined extracts were dried over $CaCl_2$ and evaporated in air. Compound **1** was isolated in trace amount; mp 84–86°C. IR spectrum, ν, cm^{-1}: 3240 (OH), 780 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.54 br.s (1H, OH), 3.61 d.d (1H, ^2J = 11.8, ^3J = 2.8 Hz) and 3.81 d.d (1H, ^2J = 11.8, ^3J = 7.5 Hz) (CH_2Cl), 4.55 m (1H, CH), 4.77 d.d (1H, ^2J = 13.2, ^3J = 7.0 Hz) and 4.97 d.d (1H, ^2J = 13.2, ^3J = 5.0 Hz) (CH_2), 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.

b. A solution of 2 g (0.014 mol) of 5-phenyltetrazole and 1.3 g (0.014 mol) of epichlorohydrin in a mixture of 5 mL of DMF and 10 mL of dioxane was stirred for 8 h at 80°C. The solvent was removed under reduced pressure. Yield 1.5 g (45%), mp 84–86°C (from EtOH). The product showed no depression of the melting point on mixing with a sample obtained as described in *a*.

1-(Oxiran-2-ylmethyl)-5-phenyltetrazole (2). *c*. Potassium hydroxide, 1.3 g (0.024 mol), and sodium sulfate, 1.5 g (0.0108 mol), were added in portions to a solution of 1 g (0.0068 mol) of 5-phenyltetrazole in 23 g (0.25 mol) of epichlorohydrin maintained at 30°C, and the mixture was stirred for 5 h at 30°C. The precipitate was filtered off, excess epichlorohydrin was distilled off under reduced pressure, and the oily residue was washed with petroleum ether (3×15 mL) and recrystallized. Yield 0.2 g (14%), mp 46–48°C (from EtOAc). IR spectrum, ν, cm^{-1}: 875, 1250 (oxirane). ^1H NMR spectrum, δ, ppm: 2.26 d.d (1H, ^2J = 6.3, ^3J = 4.1 Hz) and 2.46 d.d (1H, ^2J = 6.3, ^3J = 3.4 Hz) (CH_2O), 3.55 m (1H, OCH), 4.31 d.d (1H, ^2J = 13.2, ^3J = 6.6 Hz) and 4.55 d.d (1H, ^2J = 13.2, ^3J = 3.2 Hz) (CH_2), 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). Found, %: C 57.86; H 5.16; N 27.18. $C_{10}H_{10}N_4O$. Calculated, %: C 59.40; H 4.98; N 27.71.

d. A solution of 0.5 g (10 mmol) of sodium hydroxide in 5 mL of water was added in portions to a solution of 2 g (8 mmol) of compound **1** in 15 mL of acetone, and the mixture was stirred for 1 h at 25°C. The precipitate of sodium chloride was filtered off, and the filtrate was diluted with 10 mL of water and extracted with diethyl ether. The extract was dried over $CaCl_2$ and evaporated in air. Yield 1.4 g (88%), mp 46–48°C (from EtOAc). The product showed no depression of the melting point on mixing with a sample obtained as described in *c*.

1-(5-Phenyl-1*H*-tetrazol-1-yl)-3-[(1*H*-1,2,4-triazol-3-yl)amino]propan-2-ol (3). A solution of 0.5 g (0.0025 mol) of **2** and 0.33 g (0.004 mol) of 1*H*-1,2,4-triazol-3-amine in 15 mL of ethanol was stirred for 1.5–6 h at 60–65°C. The solvent was removed under reduced pressure, and the residue was treated with 15 mL of water and extracted with diethyl ether (4×15 mL). The combined extracts were dried over $CaCl_2$ and evaporated, and the residue was recrystallized. Yield 0.2 g (29%), mp 212–215°C (from EtOAc). IR spectrum: ν 3176 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 4.23 m and 4.34 m (1H each, C**H**$_2$NH), 4.28 m (1H, CH), 4.77 d.d (1H, ^2J = 8.2, ^3J = 4.0 Hz) and 4.87 d.d (1H, ^2J = 8.2, ^3J = 2.5 Hz) (CH_2), 5.59 br.s (1H, OH), 7.55 m (3H, *m*-H, *p*-H), 8.07 m (2H, *o*-H), 8.34 s (1H, 4′-H), 8.91 br.s (1H, CH_2N**H**), 10.84 br.s (1H, 1′-H). Found, %: C 50.02; H 4.25; N 38.81. $C_{12}H_{14}N_8O$. Calculated, %: C 50.34; H 4.93; N 39.14.

Compounds **4**–**9** were synthesized in a similar way.

1-[(1-Methyl-1*H*-tetrazol-5-yl)amino]-3-(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (4) was synthesized from 0.5 g (2.5 mmol) of **2** and 0.25 g (2.5 mmol) of 1-methyl-1*H*-tetrazol-5-amine. Yield 0.3 g (41%), mp 205–208°C (from EtOAc). IR spectrum: ν 3173 cm^{-1} (OH). ^1H NMR spectrum, δ, ppm: 3.33 m

(3H, CH_3), 4.75 d.d (1H, ^2J = 8.0, ^3J = 4.0 Hz) and 4.84 d.d (1H, ^2J = 8.0, ^3J = 2.4 Hz) (CH_2), 4.27 m and 4.37 m (1H each, C**H**$_2$NH), 4.49 m (1H, CH), 5.70 br.s (1H, OH), 6.08 s (1H, NH), 7.55 m and 7.88 m (3H, *m*-H, *p*-H), 8.08 m (2H, *o*-H). Found, %: C 48.36; H 4.69; N 41.03. $C_{12}H_{15}N_9O$. Calculated, %: C 47.83; H 5.02; N 41.84.

1-(5-Phenyl-1*H*-tetrazol-1-yl)-3-[(pyridin-2-yl)-amino]propan-2-ol (5) was synthesized from 1 g (5 mmol) of **2** and 0.47 g (5 mmol) of pyridin-2-amine. Yield 0.8 g (54%), mp 68–72°C (from EtOAc). IR spectrum: ν 3165 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 3.47 m and 3.53 m (1H each, C**H**$_2$NH), 4.18 m (1H, CH), 4.55 d.d (1H, ^2J = 8.0, ^3J = 4.0 Hz) and 4.86 d.d (1H, ^2J = 8.0, ^3J = 2.4 Hz) (CH_2), 5.91 br.s (1H, OH), 6.73 br.s (1H, NH), 6.86 m and 7.67 m (2H, 3′-H, 5′-H), 7.52 m (1H, 4′-H), 7.67 m (3H, *m*-H, *p*-H), 8.08 m (2H, *o*-H), 8.08 m (1H, 6′-H). Found, %: C 61.25; H 5.94; N 28.51. $C_{15}H_{16}N_6O$. Calculated, %: C 60.80; H 5.44; N 28.36.

1-Anilino-3-(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (6) was synthesized from 0.5 g (2.4 mmol) of **2** and 0.2 g (2.4 mmol) of aniline. Yield 0.55 g (79%), mp 71–72°C (from EtOAc). IR spectrum: ν 3178 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 3.16 m and 3.24 m (1H each, C**H**$_2$NH), 4.29 m (1H, CH), 4.74 d.d (^2J = 7.8, ^3J = 4.0 Hz) and 4.84 d.d (1H, ^2J = 7.8, ^3J = 1.5 Hz) (CH_2), 5.46 br.s (1H, OH), 5.69 br.s (1H, NH), 6.56 m (1H, *p*′-H), 6.66 m (2H, *o*′-H), 7.54 m (3H, *m*-H, *p*-H), 8.07 m (2H, *o*-H), 8.09 m (2H, *m*′-H). Found, %: C 64.47; H 5.27; N 23.96. $C_{16}H_{17}N_5O$. Calculated, %: C 65.07; H 5.80; N 23.71.

1-[(2-Aminoethyl)amino]-3-(5-phenyl-1*H*-tetrazol-1-yl)propan-2-ol (7) was synthesized from 0.4 g (1.8 mmol) of **2** and 0.048 g (0.9 mmol) of ethane-1,2-diamine. Yield 0.2 g (48%), mp 80–84°C (decomp., from EtOAc). IR spectrum: ν 3169 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.58–2.64 m (4H, CH_2), 3.36–3.42 m (2H, C**H**$_2$NH), 3.38 br.s (4H, OH, NH, NH_2), 4.14 m (1H, CH), 4.66 d.d (1H, ^2J = 8.0, ^3J = 4.0 Hz) and 4.79 d.d (1H, ^2J = 8.0, ^3J = 2.4 Hz) (CH_2). Found, %: C 55.13; H 7.56; N 32.84. $C_{12}H_{18}N_6O$. Calculated, %: C 54.95; H 6.92; N 32.04.

1-(Morpholin-4-yl)-3-(5-phenyl-1*H*-tetrazol-1-yl)-propan-2-ol (8) was synthesized from 0.5 g (2.4 mmol) of **2** and 0.2 g (2.4 mmol) of morpholine in 15 mL of ethanol. Yield 0.1 g (14%), mp 99–101°C (from EtOAc). IR spectrum: ν 3180 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.42 m and 3.55 m (4H each, NCH_2CH_2O), 3.50 m (CH_2N), 4.64 d.d (1H, ^2J = 8.0, ^3J = 4.0 Hz) and 4.77 d.d (1H, ^2J = 8.0, ^3J = 2.4 Hz) (CH_2), 4.24 m (1H, CH), 5.26 br.s (1H, OH), 7.50 m (3H, *m*-H, *p*-H), 8.06 m (2H, *o*-H). Found, %: C 59.39; H 6.24; N 24.35. $C_{14}H_{19}N_5O_2$. Calculated, %: C 58.12; H 6.62; N 24.21.

3-(5-Phenyl-1*H*-tetrazol-1-yl)-1-(piperidin-1-yl)-propan-2-ol (9) was synthesized from 0.5 g (2.4 mmol) of **2** and 0.2 g (2.4 mmol) of piperidine. Yield 0.55 g (84%), mp 64–68°C (from EtOAc). IR spectrum: ν 3186 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 1.52 m (6H, CH_2, piperidine), 2.74 m (4H, CH_2N), 3.41 m (2H, CH_2N), 4.22 m (1H, CH), 4.64 d.d (1H, ^2J = 7.8, ^3J = 4.0 Hz) and 4.77 d.d (1H, ^2J = 7.8, ^3J = 1.5 Hz) (CH_2), 5.15 br.s (1H, OH), 7.54 m (3H, *m*-H, *p*-H), 8.06 m (2H, *o*-H). Found, %: C 61.83; H 4.21; N 24.93. $C_{15}H_{21}N_5O$. Calculated, %: C 62.69; H 3.37; N 24.37.

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REFERENCES

1. Mesropyan, E.G., Galstyan, A.S., and Avetisyan, A.A., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1845.
2. Suzdalev, K.F. and Den'kina, S.V., *Chem. Heterocycl. Compd*., 2011, vol. 47, p. 1085.
3. Kofman, T.P. and Krasnov, K.N., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1651.
4. Vaitkevicienei, V., Grazulevicius, J.V., and Jankauskas, V., *Mol. Cryst. Liq. Cryst*., 2008, vol. 497, p. 241.
5. Golobokova, T.V., Proidakov, A.G., Vereshchagin, L.I., and Kizhnyaev, V.N., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1308.
6. Khan, M.A. and Lynch, B.M., *J. Heterocycl. Chem*., 1970, vol. 7, p. 1237.
7. Vereshchagin, L.I., Kuznetsova, N.I., Kirillova, L.P., Shcherbakov, V.V., Sukhanov, G.T., and Gareev, G.A., *Chem. Heterocycl. Compd*., 1986, vol. 22, p. 745.
8. Schofield, K., Grimmett, M.R., and Keene, B.R.T., *Heteroaromatic Nitrogen Compounds: The Azoles*, Cambridge: Cambridge Univ. Press, 1976.