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SHORT COMMUNICATIONS

Formation of 2-(2-Cyclohexenyl)-5-R-tetrazoles in Acid-Catalyzed Alkylation of 5-Substituted Tetrazoles with 1,3-Cyclohexadiene

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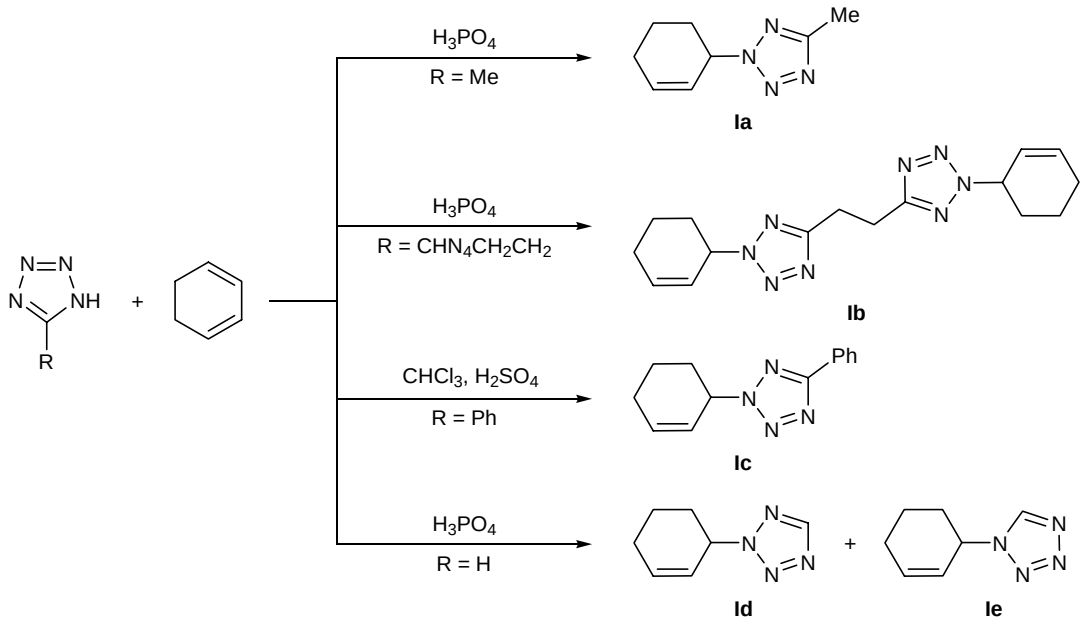
Various methods for introduction of substituent to nitrogen atoms of a tetrazole ring are known. Among these, a specific place is occupied by procedures based on alkylation of tetrazoles with alcohols and olefins in mineral acids (see [1, 2] and references therein). Such reactions possess a wide synthetic potential, and they underlie selective methods of synthesis of 1,3- and 1,4-substituted tetrazolium salts [1], as well as of 2-mono- and 2,5-disubstituted tetrazoles [2–4]. It is also important that this approach can also be extended to other heterocycles [2]. The desired selectivity in the alkylation is achieved by variation of the acidity of the medium. Here, the nature of the alkylating agent is also essential.

While extending studies in this field, we examined the behavior of 1,3-cyclohexadiene with respect to a series of 5-substituted tetrazoles in acid media and proposed a procedure for the preparation of previously unknown 2-(2-cyclohexenyl)-5-R-tetrazoles [5] which attract interest as potential biologically active compounds. An efficient medium for the alkylation process was 87% phosphoric acid. Other acids, such as sulfuric or perchloric, cannot be used, for they promote oligo- and polymerization of the alkylating agent. The alkylation of 5-methyltetrazole and its dinuclear analog in 87% phosphoric acid occurs in 40–50 min at room temperature, and the corresponding 2,5-disubstituted tetrazoles **Ia** and **Ib** are formed in high yield (70–88%)

Scheme 1.



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and with high selectivity. 5-Phenyltetrazole is poorly soluble in phosphoric acid; therefore, its reaction with 1,3-cyclohexadiene under analogous conditions is very slow and is accompanied by side transformations of the diene. We succeeded in successfully effecting the alkylation of 5-phenyltetrazole in the two-phase system chloroform–sulfuric acid. As a result, 2-(2-cyclohexenyl)-5-phenyltetrazole (**Ic**) was selectively formed.

The alkylation of unsubstituted tetrazole in phosphoric acid gives a mixture of 2- and 1-(2-cyclohexenyl)tetrazoles **Id** and **Ie** in an overall yield of 75% (isomer ratio ~2:1). Pure isomer **Id** can be isolated from the product mixture by distillation. The absence of selectivity in the reaction of unsubstituted tetrazole with 1,3-cyclohexadiene may be explained by incomplete protonation of the substrate [6], as well as by isomerization of initially formed 2-substituted tetrazole **Id** into 1-substituted compound **Ie**. Analogous isomerizations were reported for 2-*tert*-butyltetrazole [7] and 2-(1-adamantyl)tetrazole [8]. By special experiment we showed that pure tetrazole **Id** in 87% phosphoric acid is slowly converted into isomer **Ie**. After 4 days at room temperature, the isomer ratio **Id**:**Ie** is ~1:2.3.

Thus the described reactions represent the first successful examples of selective alkylation of tetrazoles with dienes. The alkylation of 5-phenyltetrazole with 2,3-dimethylbutadiene in the presence of *p*-toluenesulfonic acid at 140°C (reaction time 24–45 h) led to formation of an inseparable mixture of two isomers and addition products at the double bonds [9]. By contrast, the procedure proposed by us for acid-catalyzed synthesis of tetrazole derivatives and tetrazolium salts [1, 4] is characterized by mild conditions and high yield and purity of the target products.

Tetrazoles **Ia**–**Id** were identified as 2-substituted isomers on the basis of the ^{1}H and ^{13}C NMR spectra, which were in agreement with published data for structurally related 2-mono- and 2,5-disubstituted tetrazoles [4, 6, 7]. The ratio of isomeric *N*-(2-cyclohexenyl)-tetrazoles was estimated from the intensities of the 5-H signals which are located at δ 8.90 and 9.36 ppm in the ^{1}H NMR spectrum recorded in CD_3SOCD_3. The 5-H signal of the 1-isomer appears in a weaker field than that from the 2-isomer [6, 7]. The NMR spectra were recorded on a Tesla-567A spectrometer (100 MHz) using HMDS as internal reference.

Alkylation of 5-substituted tetrazoles with 1,3-cyclohexadienes in phosphoric acid. 1,3-Cyclohexadiene, 10.5 ml (0.11 mol), was added dropwise over a period of 10 min to a solution of 0.1 mol of 5-substituted tetrazole (R = H, Me) (or 0.05 mol for R = CH_2CH_2X, where X = 5-tetrazolyl) in 70 ml of 87% phosphoric acid under stirring at room temperature. The mixture was stirred for 30–40 min, poured into water, and extracted with chloroform or diethyl ether (4×25 ml). The extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was distilled under reduced pressure (compounds **Ia** and **Id**) or recrystallized from aqueous ethanol (**Ib**).

2-(2-Cyclohexenyl)-5-methyltetrazole (Ia). Yield 88%, bp 86°C (2 mm), n_D^{20} = 1.5062. ^{1}H NMR spectrum (CD_3SOCD_3), δ, ppm: 2.42 s (3H, Me), 5.90–6.20 m (1H, =CH–), 5.60–5.92 m (1H, CH=), 5.30–5.60 m (1H, CH), 1.35–2.22 m [6H, $(CH_2)_3$]. ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 162.7 (C^5), 59.8 (N–C), 133.2 (–C=), 124.1 (=C–), 29.9 (CH_2), 25.2 (CH_2), 20.1 (CH_2), 11.3 (Me). Found, %: C 58.28; H 6.99; N 34.25. $C_8H_{12}N_4$. Calculated, %: C 58.51; H 7.37; N 34.12.

1,2-Bis[(2-cyclohexenyl)tetrazol-5-yl]ethane (Ib). Yield 70%, mp 91–93°C. ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 5.90–6.25 m (1H, =CH–), 5.52–5.95 m (1H, –CH=), 5.20–5.40 m (1H, CH), 1.35–2.31 m [6H, $(CH_2)_3$], 3.30 s (2H, CH_2). ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 162.6 (C^5), 59.8 (N–C), 131.3 (–C=), 122.4 (=C–), 30.6 (CH_2), 25.5 (CH_2), 21.0 (CH_2), 26.0 (CH_2). Found, %: C 58.68; H 6.56; N 33.55. $C_{16}H_{22}N_8$. Calculated, %: C 58.89; H 6.79; N 33.33.

2-(2-Cyclohexenyl)tetrazole (Id). Yield 49%, bp 69°C (1.5 mm). n_D^{20} = 1.5094. ^{1}H NMR spectrum (CD_3COCD_3), δ, ppm: 8.69 s (1H, 5-H), 5.95–6.22 m (1H,=CH–), 5.70–5.95 m (1H, –CH=), 5.40–5.70 m (1H, CH), 1.6–2.3 m [6H, $(CH_2)_3$]. ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 152.9 (C^5), 60.0 (N–C), 133.5 (–C=), 123.9 (=C–), 29.9 (CH_2), 25.2 (CH_2), 20.0 (CH_2). Found, %: C 55.73; H 6.89; N 37.50. $C_7H_{10}N_4$. Calculated, %: C 55.98; H 6.71; N 37.31.

Alkylation of 5-phenyltetrazole with 1,3-cyclohexadiene in the two-phase system chloroform–sulfuric acid. 5-Phenyltetrazole, 2 g (14 mmol), and 1,3-cyclohexadiene, 1.4 ml (15 mmol), were added in succession under vigorous stirring to a mixture of 25 ml of chloroform and 5–6 drops of concentrated sulfuric acid, and the mixture was heated for about 20 h on a water bath. The mixture was diluted with water and neutralized with an aqueous solution of sodium hydroxide to slightly alkaline reaction. The organic phase was separated, and the aqueous phase was extracted with chloroform (4×25 ml). The combined extracts were dried over anhydrous magnesium

sulfate, filtered, and evaporated to obtain 2.5 g (11 mmol, 80%) of 2-(2-cyclohexenyl)-5-phenyltetrazole (**Ic**) as a colorless oily liquid, n_D^{20} 1.5766. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 8.10–8.20 m (2H, H_{arom}), 7.53–7.62 m (3H, H_{arom}), 6.05–6.30 m (1H, =CH–), 5.83–6.05 m (1H, –CH=), 5.45–5.70 m (1H, CH), 1.60–2.40 m [6H, $(CH_2)_3$]. ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 162.6 (C^5); 60.3 (N–C); 133.5 (–C=); 124.2 (=C–); 30.1 (CH_2); 25.3 (CH_2); 20.3 (CH_2); 128.5, 130.6, 129.3, 127.3 (C_{arom}). Found, %: C 68.88; H 6.65; N 24.39. $C_{13}H_{14}N_4$. Calculated, %: C 69.00; H 6.24; N 24.76.

Isomerization of 2-(2-cyclohexenyl)tetrazole (Id). A solution of 1 g (0.67 mmol) of tetrazole (**Id**) in 2 ml of 87% phosphoric acid was kept for 4 days at room temperature. The solution was poured into water and extracted with chloroform (3×5 ml). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to obtain 0.7 g (70%) of a mixture of 1- and 2-(2-cyclohexenyl)tetrazoles.

REFERENCES

1. Voitekhovich, S.V., Gaponik, P.N., and Ivashkevich, O.A., *Usp. Khim*., 2002, vol. 71, p. 819.
2. Ostrovskii, V.A. and Koren, A.O., *Heterocycles*, 2000, vol. 53, p. 1421.
3. Koldobskii, G.I. and Kharbash, R.V., *Russ. J. Org. Chem*., 2003, vol. 39, p. 453.
4. Voitekhovich, S.V., Gaponik, P.N., Pytleva, D.S., Lyakhov, A.S., and Ivashkevich, O.A., *Pol. J. Chem*., 2002, vol. 76, p. 1371.
5. Katritzky, A.R., Maimait, R., Xu, Y.-J., and Gyoung, Y.S., *J. Org. Chem*., 2002, vol. 67, p. 8230.
6. Koren', A.O. and Gaponik, P.N., *Khim. Geterotsikl. Soedin*., 1990, p. 1643.
7. Gaponik, P.N. and Voitekhovich, S.V., *Russ. J. Org. Chem*., 1998, vol. 34, p. 746.
8. Saraev, V.V. and Golod, E.L., *Russ. J. Org. Chem*., 1997, vol. 33, p. 571.
9. Katritzky, A.R., Qi, M., and Wells, A.P., *Khim. Geterotsikl. Soedin*., 1996, p. 1520.