UNUSUAL PROTONATION OF OXIME NITROGEN IN ACETOPHENONE O-[3-(5-TETRAZOLYL) PROPYL]OXIME IN SOLID STATE

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Abstract: Two step synthesis of O-[3-(5-tetrazolyl)propyl]oximes from corresponding oximes in the system $Br(CH_2)_3CN$ / K_2CO_3 / 18-crown-6 / toluene with the subsequent treatment with Me_3SiN_3 / Bu_2SnO was carried out. Acetophenone O-[3-(5-tetrazolyl)propyl]oxime formed an internal salt in the solid state. In contrast, the similar proton transfer did not occur in the case of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime.

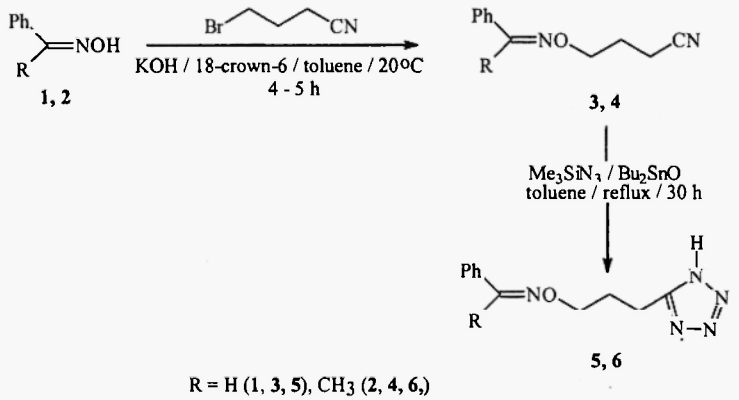
Introduction

Synthesis, reactions and properties of tetrazole derivatives are widely described in numerous reviews [1]. *N*-Unsubstituted tetrazoles can exist as both *1H*- and *2H*-tautomers being in equilibrium in solutions. The amino derivatives of tetrazoles exhibit amino-imino tautomerism caused by acidic properties of *N*-unsubstituted tetrazole ring. The pK_a of tetrazole ring strongly depends on electronic properties of side chain. The electron-withdrawing substituents in tetrazole molecule increase *N-H* acidity. Proton transfer from tetrazole ring to amino group in aminotetrazoles [2] leads to the internal salt formation. Zwitter-ionic structures [3] also have been described.

The aim of the present work is the synthesis and investigation of the O-[3-(5-tetrazolyl)propyl]oximes structure.

Results and Discussions

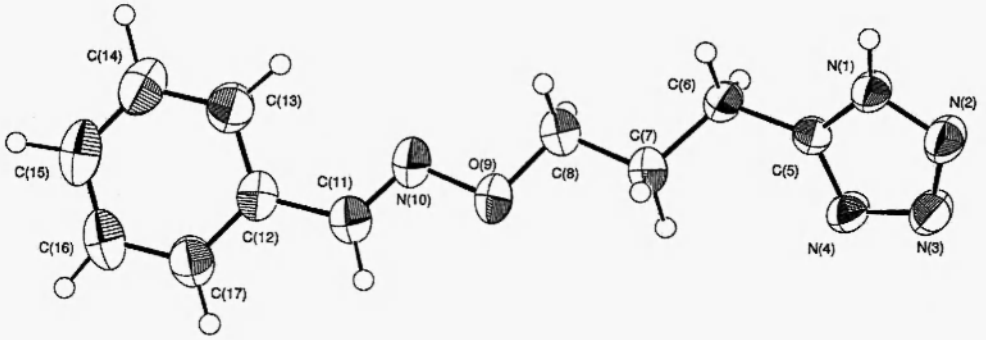
O-[3-(5-tetrazolyl)propyl]oximes were synthesized by two step process (Scheme 1). The phase transfer catalytic alkylation of oximes **1, 2** in the 1-bromo-4-butyronitrile / solid KOH / 18-crown-6 / toluene system [4] led stereoselectively to *E*-isomers of O-[3-cyanopropyl]oximes **3, 4** in yields up to 96 %. In the second step the products **3, 4** interacted with Me_3SiN_3 in the presence of Bu_2SnO in toluene [5] to give *E*-O-[3-(5-tetrazolyl)propyl]oximes **5, 6** in 39-43% yields. The compounds obtained were characterized with mass- and NMR spectroscopic data.



R = H (1, 3, 5), CH_3 (2, 4, 6,)

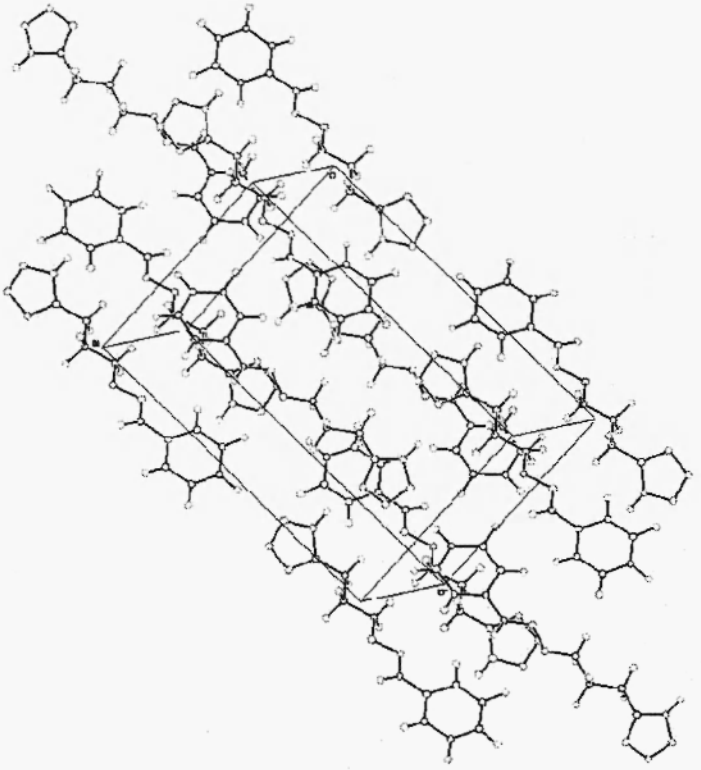
Scheme-1

The Schemes 2-4 illustrate the molecular structures of tetrazoles **5** and **6** obtained by X-ray crystal structure analysis. Crystal data and structure refinement for benzaldehyde and acetophenone O-[3-(5-tetrazolyl)propyl]oximes (**5** and **6**) are given.



Solid-state structure of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**5**).

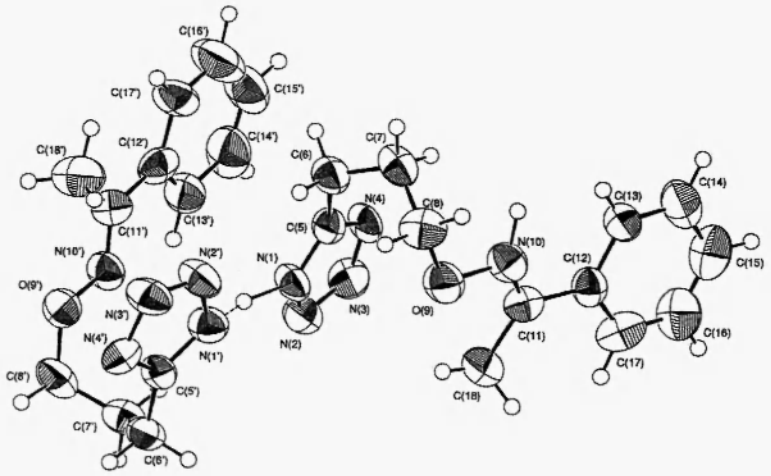
Scheme-2



Crystal packing of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**5**).

Scheme-3

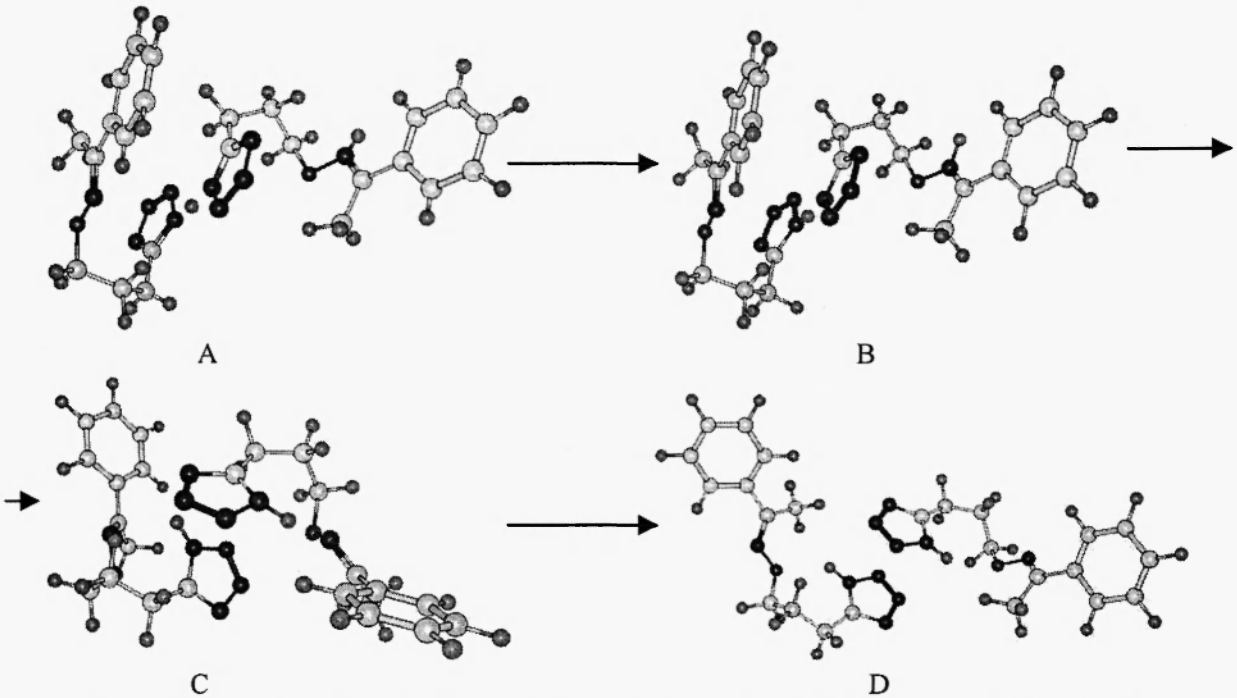
In the case of benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**5**) no charge transfer was observed. Therefore, the usual planar conformation is realized for this compound. The hydrogen bond of N-H···N type was found in the crystal structure. The length of the H-bond is equal 2.824 (2) Å (H···N = 1.97 (3) Å, N-H = 0.86 (3) Å, <N-H···N = 167 (2) Å). By means of these bonds the chains are formed in crystals of tetrazole **5** (Scheme 2 and 3).



Solid-state structure of acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**6**).

Scheme-4

Unusual self-organization was observed for acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**6**) in the solid state (Scheme-4). In the crystal structure of tetrazole **6** two molecules are packed as associates. The proton transfer from N(1) of tetrazole to the N(10) occurred during the crystallization. As the result of this process the quaternization of N(10) took place. The tetrazole ring proton of the second molecule formed a bridge bond connecting N(1) and N(1') atoms. Bridge type proton distances are 1.394 Å from N(1) and 1.402 Å from N(1'). Thus, one of the molecules in the associate accepts the betaine form. In the solid state of oxime **6** the molecules have the "shoe" conformation.



Structures of acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**6**) in the process of optimization using AM1 method.

Scheme-5

The crystallographic and structure refinement data were used as input for the quantum chemical calculations using AM1 method [6] with optimization of all geometric parameters of system (Scheme-5A). The visualization of the optimization process showed that on 10th iteration step there occurred a bridge type hydrogen addition to N(1') atom (Scheme-5B). Further complicated transformations of the system led to the gradual approaching of atoms N(10) and N(1). The hydrogen from N(10) is transferred to N(1) when the distance between N(10) an N(1) is 2.665 Å (Scheme-5C). The further system relaxation led to the equilibrium state shown at the Scheme-5D - formation of two molecules of acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**6**) occurred. These two molecules formed the complex with parallel tetrazole rings (distance between rings is 2.86 Å). The heat of complex formation was -5.419 Kcal/mol. We suppose that above quantum chemical calculations may be considered as a model of the process of oxime ether **6** dissolution and it is confirmed by the ^{1}H and ^{13}C NMR data.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 spectrometer at 200.06 and 50.31 MHz correspondingly at 303K. The chemical shifts are given relative to TMS from solvent ($CDCl_3$) signal (δ_H=7.25). Mass spectra were registered on a GC-MS HP 6890 (70 eV). GC analysis was performed on a Chrom-5 instrument equipped with flame-ionization detector using glass column packed with 5 % OV-101 / Chromosorb W-HP (80 - 100 mesh) (1.2 m x 3 mm).

General procedure for preparation of O-[3-cyanopropyl]oximes 3, 4.

Benzaldehyde O-[3-cyanopropyl]oxime (3). 1-Bromo-4-butyronitrile (1.48 g, 10 mM) was added to the mixture of benzaldehyde oxime (1.35 g, 10mM), solid finely powdered KOH (1.68 g, 30 mM), and 18-crown-6 (264 mg, 1mM) in 10 ml of toluene under vigorous stirring. Reaction was carried out at room temperature during 5 h (MS-GC control). The reaction mixture was filtered; the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using toluene as eluent. The yield of **3** was 1.8 g (96%). MS, m/z (I, %): 188(M^+, 22), 187(28), 157(26), 131(15), 120(25), 105(41), 104(88); 94(18), 89(21), 78(26), 77(100), 65(27), 51(58); ^{1}H NMR, δ ppm: 2.10(m, 2H, CH_2); 2.48(t, 2H, J=7.2 Hz, OCH_2); 4.25(t, 2H, J=6.0 Hz), CH_2CN); 7.36(m, 3H, H-3, H-4, H-5); 7.56(m, 2H, H-2, H-6); 8.07(s, 1H, CH); ^{13}C NMR, δ ppm: 14.1(CH_2); 25.4(OCH_2); 71.4($\underline{C}H_2C$); 119.3; 127.0; 128.7; 131.9; 149.2.

Acetophenone O-[3-cyanopropyl]oxime (**4**) was obtained similarly during 4 hours and used in the next step without purification. MS, m/z (I, %): 202(M^+, 31), 20(28), 171(58), 134(32), 117(30), 118(43), 106(17), 104(73), 94(10), 78(26), 77(100), 51(25).

General procedure for preparation of O-[3-(5-tetrazolyl)propyl]oximes 5, 6.

Benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (5). Trimethylazidosilane (1.5 ml, 11.3 mM) was added to the mixture of **3** (1.06 g, 5.6 mM) and Bu_2SnO (140 mg, 0.56 mM) in dry toluene. Reaction occurred during 30 h under reflux and stirring up to disappearance of **3** (GC control). The product was precipitated by adding the saturated aqueous solution of $NaHCO_3$, filtered, and dried. The yield of **5** was 1g (43%). Oxime **5** was crystallized from ethyl acetate. M.p. 90 - 92° C. ^{1}H NMR, δ ppm: 2.10(m, 2H, CH_2), 2.97(t, 2H, J=8.0 Hz, OCH_2); 4.17 (t, 2H, J=6.4 Hz, CH_2CN); 7.41(m, 3H, H-3, H-4, H-5); 7.61 (m, 2H, H-2, H-6); 8.22(s, 1H, CH); ^{13}C NMR, δ ppm: 19.9(CH_2); 27.0(OCH_2); 72.5(CH_2C); 126.8; 128.8; 129.9; 132.0; 148.8; 156.5. Analysis calculated for $C_{11}H_{13}N_5O$; C, 57.13; H, 5.67; N, 30.28. Found; C, 56.81; H, 5.62; N, 30.01.

Acetophenone O-[3-(5-tetrazolyl)propyl]oxime (6) was synthesized by the similar way in 39% yield. It was crystallized from diethyl ether. M.p. 68 - 70° C. ^{1}H NMR, δ ppm: 2.17(s, 3H, Me); 2.24(m, 2H, CH_2),

3.18(t, 2H, J=7.2 Hz, OCH_2); 4.26 (t, 2H, J=5.6 Hz, CH_2CN); 7.34(m, 3H, H-3, H-4, H-5); 7.56 (m, 2H, H-2, H-6); ^{13}C NMR, δ ppm: 13.0(Me); 20.3(CH_2); 27.4(OCH_2); 72.1($\underline{C}H_2C$); 126.0; 128.6; 129.4; 136.2; 156.3. Analysis calculated for $C_{12}H_{15}N_5O$; C, 58.76; H, 6.16; N, 28.55. Found; C, 58.68; H, 6.15; N, 28.51.

Crystal Structure Determination

The colorless crystals of benzaldehyde and acetophenone O-[3-(5-tetrazolyl)propyl]oximes (**5** and **6**, correspondingly) were grown out from ethyl acetate and ether, respectively, and investigated on a Nonius KappaCCD diffractometer (MoK_α-radiation) at room temperature. The structures were solved by direct method and refined by full matrix least squares. The hydrogen atoms have been localized by difference synthesis. The programs [7] were used for the structure solution and refinement. Crystal data are shown in the Table-1.

Table-1: Crystal data and structure refinement for benzaldehyde O-[3-(5-tetrazolyl)propyl]oxime (**5**) and acetophenone O-[3-(5-tetrazolyl)propyl]oxime (**6**)

	Compound **5**	Compound **6**
Empirical formula	$C_{11}H_{13}N_5O$	$C_{12}H_{15}N_5O$
FW	231.259	245.286
Crystal size (mm)	0.06 x 0.08 x 0.32	0.08 x 0.12 x 0.42
Crystal system	Monoclinic	orthorhombic
Space group	P $2_1/c$	P $ca2_1$
a (Å)	7.7748(3)	13.3695(7)
B (Å)	16.5350(9)	9.5821(5)
c (Å)	9.7161(4)	20.105(1)
β (°)	108.971(3)	90.0(0)
Volume ($Å^3$)	1181.2(1)	2575.6(3)
Z	4	8
Density (calc.), d (g/cm^3)	1.3002	1.265
Absorption coefficient, μ (mm^{-1})	0.09	0.09
No. of independent reflections	2953($2\theta_{max} = 55°$)	1763($2\theta_{max} = 45°$)
No. of reflections with I > 3 σ (I)	1533	1338
No. of refined parameters	145	325
Weighting scheme	$1/w = \sigma^2 + 0.1\ F_o^2$	$1/w = \sigma^2 + 0.1\ F_o^2$
Weighting R index on F^2, wR2	0.094	0.115
Final R factor	0.052	0.059

Crystallographic data have been deposit with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 198244 (**6**) and 198245 (**5**). Copies of these data can be obtained free of charge on application CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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