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Research Article

Synthesis, Crystal Structures of S- and N-Benzyl Derivatives Of 5-phenyl-1,3,4-oxadiazol-2-thione

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Abstract: Benzylation reaction is carried out 5-phenyl-1,3,4-oxadiazol-2-thione with benzyl chloride in acetone and HMPA. In the acetone was obtained exclusively S-benzyl derivative and in the case of HMPA - isomeric mixture of S- and N-benzyl derivatives were obtained, individually isolated, characterized, and their structure was proved by spectral methods. By slow evaporation of solvents at room temperature were obtained two polymorphic crystals of 5-phenyl-1,3,4-oxadiazol-2-thione from acetone **1** and ethanol **2**. Crystals of 2-benzylthio-5-phenyl-1,3,4-oxadiazole **3** and 3-benzyl-5-phenyl-1,3,4-oxadiazol-2-thione **4** obtained in similar conditions have structures without the inclusion of solvent molecules.

Keywords: Five-membered heterocycles; 5-phenyl-1,3,4-oxadiazol-2-thione; 2-benzylthio-5-phenyl-1,3,4-oxadiazole; 3-benzyl-5-phenyl-1,3,4-oxadiazol-2-thione; X-ray analysis; Crystal structure

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Introduction

5-Substituted-1,3,4-oxadiazol-2-thiones interesting representatives of one five-membered heterocycles. Numerous compounds of this class show practical interest for researchers having a broad spectrum of biological activity, such as pesticide, antibiotic, anticancer, antihypertensive, antidepressant, analgesic, anti-inflammatory and others [1-4]. The presence in its molecule ambifunctional thioamide NH-C=S and other functional groups gives oxadiazolthiones to exhibit multiple reactivity whereby depending on the reaction conditions and the nature of the reagents can be prepared isomeric (S-, N-) products.

In this paper the task was to continue previously initiated a study on the alkylation reactions oxadiazol-2-thiones [5, 6], namely, to synthesize isomeric S- and N-benzyl derivatives of N-5-phenyl-1,3,4-oxadiazol-2-thione, prove their structure and study crystal structures (Fig. 1).

Materials and Methods

UV spectra were recorded on a spectrometer EPS-3T Hitachi in ethanol. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxcane (HMDSO) was used as internal standard, chemical shift of ^{1}H was recorded in ppm. Melting point were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected.

The reactionary process was monitored by TLC on ALUGRAM Xtra (Germany) precoated aluminum plates using $CHCl_3$/EtOH (24:1) solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary.

The unit cell parameters of the crystals are determined and refined with CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation, graphite monochromator (T=293 K). The three-dimensional set of reflections received at the appropriate diffractometer.

Results

Synthesis

Reaction 5-phenyl-1,3,4-oxadiazol-2-thione with benzyl chloride in acetone. The reaction in equimolar ratios of thione **1**, benzyl chloride and K_2CO_3 was performed by refluxing in dry acetone for 5 hours. Acetone was then removed from the mixture, residue was washed with water, then with alkali solution to remove residues thione and again with water until neutral pH. The resulting product **3** was dried and recrystallized from ethanol.

2-benzylthio-5-phenyl-1,3,4-oxadiazol 3: 95% yield, m.p.97-980^{0}C, R_f=0,71 (chloroform-ethanol, 24: 1), UV spectrum, λmax, 275nm; 1H NMR spectrum ($CDCl_3$), δ, ppm, 4.50 (2H, s, S-CH22), 7.25-8.20 (10H, m, Ar-H).

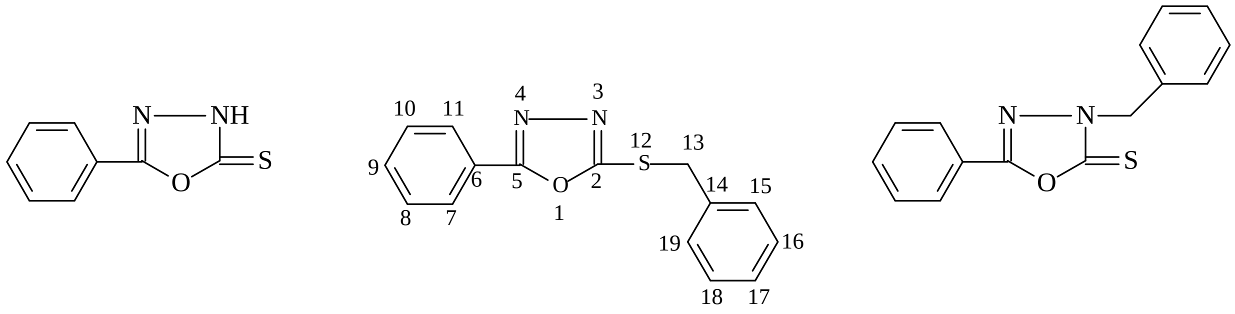
Reacting 5-phenyl-1,3,4-oxadiazol-2-thione with benzyl chloride in hexamethylphosphoric triamide (HMPA).

The reaction was performed by stirring equimolar amounts of thione **1**, benzyl chloride and K_2CO_3 in HMPA at a temperature of water bath (70-80 ^{0}C) for 5 hours. The reaction mixture was poured into ice water, the precipitate was filtered, washed with an alkali solution and several times with cold water. TLC analysis showed two spots, i.e. presence S- and N-benzyl derivatives, which overall yield was 94%. Isolation of individual isomers was carried out on a silica gel column Chemapol 250/400 mm, eluent hexane-chloroform in a ratio of 5:1, 3:1, 1:1.

3-benzyl-5-phenyl-1,3,4-oxadiazol-2-thione 4: yield 3%, m.p.136-137^{0}C, R$_f$=0,88 (chloroform-ethanol, 24:1), UV spectrum, λmax, 302nm; 1H NMR spectrum ($CDCl_3$), δ, ppm, 5.25 (2H, s, N-CH22), 7.24-8.15 (10H, m, Ar-H).

Crystal growth

Single crystals of 5-phenyl-1,3,4-oxadiazol-2-thione were grown from solutions of acetone **1** and ethanol **2** by slow evaporation at room temperature. Crystals of 2-benzylthio-5-phenyl-1,3,4-oxadiazole (S-isomer) **3** and 3-benzyl-5-phenyl-1,3,4-oxadiazol-2-thione (N-isomer) **4** were grown from ethanol and acetone by slow evaporation of the solvent at room temperature.



1,2 **3** **4**

Fig. 1 Schematic formula and numbering of the atoms in the structures **1,2,3** and **4**.

X-ray Structure Determination

The unit cell parameters of the crystals were determined and refined with CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα-radiation, graphite monochromator (T=293 K). The three-dimensional set of reflections received at the appropriate diffractometer. The amendment was introduced to the absorption by Multi-scan [7]. Table 1 shows the main parameters of the X-ray diffraction experiments and refinement calculations of the structures **1,2,3** and **4**.

The structures were solved by direct methods using SHELXS-2014 and refined using SHELXL-2014 programs [8]. All non-hydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters Uiso = nUeq, where n = 1.5 for methyl hydrogens and 1.2 for others and Ueq is the equivalent isotropic thermal parameter of the corresponding C atoms.

Materials X-ray diffraction as a CIF file deposited at the Cambridge center of crystal data (CCDC), from which can be obtained free on request at the following link: www.ccdc.cam.ac.uk/data_request/cif

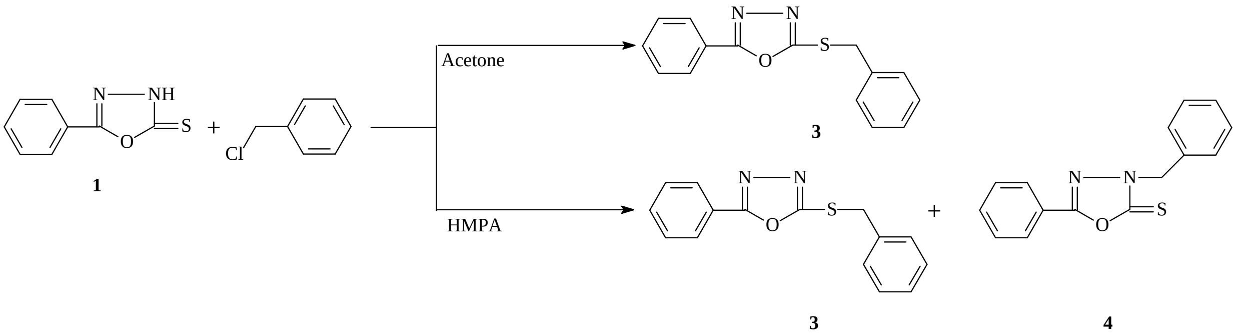
Table 1 Basic crystallographic parameters and characteristics of the X-ray diffraction for structures **1,2,3** and **4**.

Compound	**1**	**2**	**3**	**4**
Molecular formula	$C_8H_6N_2OS$	$C_8H_6N_2OS$	$C_{15}H_{12}N_2OS$	$C_{15}H_{12}N_2OS$
Mr	178.21	178.21	268.33	268.33
Crystal symmetry	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	Pbca	$P2_1/c$	Pbca	$P2_1/n$
Z	8	4	8	4
a, Å	10.017(2)	5.5767(4)	12.6101(6)	11.4540(9)
b, Å	8.6679(17)	19.9882(11)	8.3582(4)	4.6674(3)
c, Å	17.634(4)	7.2282(6)	25.8399(14)	25.078(2)
α, °	90	90	90	90
β, °	90	100.463(7)	90	101.617(8)
γ, °	90	90	90	90
V, $Å^3$	1531.1(5)	792.32(10)	2723.5(2)	1313.21(17)
ρ, g/cm^3	1.546	1.494	1.309	1.357
Crystal dimension (mm)	0.35x0.48x0.55	0.40x0.45x0.55	0.35x0.45x0.50	0.40x0.45x0.50
Range scanned, 2θ °	$4.432 \leq \theta \leq 75.799^{o}$	$6.607 \leq \theta \leq 72.807^{o}$	$5.498 \leq \theta \leq 75.318^{o}$	$3.596 \leq \theta \leq 75.691^{o}$
μ_{exp} (cm^{-1})	3.314	3.202	2.049	2.125
No. reflection collected	1580	1583	2835	2698
No. reflection with $I>2\sigma(I)$	1296	920	1910	1909
R_1 ($I>2\sigma(I)$ and total)	0.0614 (0.0737)	0.0624 (0.1065)	0.0420 (0.0703)	0.0593 (0.0863)
wR_2	0.1740 (0.1985)	0.1507 (0.1842)	0.1269 (0.1597)	0.1565 (0.1735)
GOOF	0.727	0.988	0.975	1.103
Largest diff. peak and hole (e $Å^{-3}$)	0.673 and –0.644	0.404 and –0.251	0.192 and –0.158	0.312 and –0.228
CCDC	1530177	1530178	1530179	1530180

Discustion

The reaction of equimolar ratios of thione, benzyl chloride and K_2CO_3 performed by refluxing in dry acetone. The result obtained and identified with high (95%) yield of the product solely S-2-benzylthio-5-phenyl-1,3,4-oxadiazol **3**. Detection of possible N-benzyl derivative was failed by thin layer chromatography (TLC) or spectroscopic (UV, ^{1}H-NMR) methods, that shows, in these conditions the reaction occurs with the formation of only one isomer.

A small amount (3%) of N-benzyl product was allocated during the reaction in a polar solvent - HMPA. As it is known, increasing polarity aprotic solvent promotes the alkylation of the site with the highest electron density. The reason for this is the ability of these solvents to solvate cations, in the result coordination with ambident anion is weakened. This facilitates the reaction by an atom having the highest electron density, which is the nitrogen atom of ambifunctional system of oxadiazol-2-thiones. Individual S-and N-benzyl derivatives were isolated by column chromatography and they differ in the R_f values of TLC (0,71 and 0,88 for N- and S- isomers respectively). The structures were proven by UV and ^{1}H NMR spectroscopy. Thus in the UV spectrum of S-derivative **3** observes the absorption at 275 nm, in the case of N- benzyl derivative **4** at 302 nm. Also chemical shifts of isomers are clearly different and appear as a singlet for protons of the methylene group in S-CH_2 at 4.50 ppm, and for N-CH_2 at 5.25 ppm The signals of the protons of aromatic rings in the form of a complex signal are in the range 7.24-8.20 ppm.



We have previously found that N-(3-methylthio and N-(3-ethylthio-5-atsetoamido-1,2,4-thiadiazole-2-thione) derivatives of the alkaloid cytisine exhibit clathratogen property including different solvent molecules in their crystal lattices [9-12]. Although the alkaloid cytisine [13] and other derivatives [14, 15] (for example, acyl or benzyl derivatives of cytisine [16, 17]) have not such properties. For this reason, was interesting study of the crystal structures of related oxadiazoles which grown from different solvents.

On this basis, it was of interest to study solvate formation and polymorphism of oxadiazol-2-thiones - related to 1,2,4-thiadiazole-2-thiones. For this purpose were grown visually distinguished two type crystals of 5-phenyl-1,3,4-oxadiazol-2-thione from solutions of acetone **1** and ethanol **2**. Further study of crystals by X-ray diffraction, it was found that they are two different polymorphic modifications of compounds differing packing factor and not containing a solvent molecule (Fig.2).

Further, the crystal structures of two isomeric S- and N-alkyl derivatives of 5-phenyl-1,3,4-oxadiazol-2-thione were studied. Crystals of 2-benzylthio-5-phenyl-1,3,4-oxadiazole (S-isomer) **3** and 3-benzyl-5-phenyl-1,3,4-oxadiazol-2-thione (N-isomer) **4** were grown from ethanol and acetone by slow evaporation of the solvent at room temperature. By determination of the melting point and the unit cell parameters was found that in these solvents grown crystals without the inclusion of solvent molecules (Fig.2.).

Five membered heterocyclic ring in molecular structures **1, 2, 3** and **4** comprise a flat (within ± 0.0015, ± 0.0073, ± 0.0012, and ± 0.0038 Å respectively). The location of phenyl ring relative to the plane of the oxadiazole nucleus charactering with value of torsion angle O1-C5-C6-C7 (12.47, -3.38, -5.76 and 7.01 °for **1, 2, 3** and **4**, respectively). Namely the difference in the values of the torsion angle O1-C5-C6-C7 leads to the formation of different space groups and polymorphs in **1** and **2**.

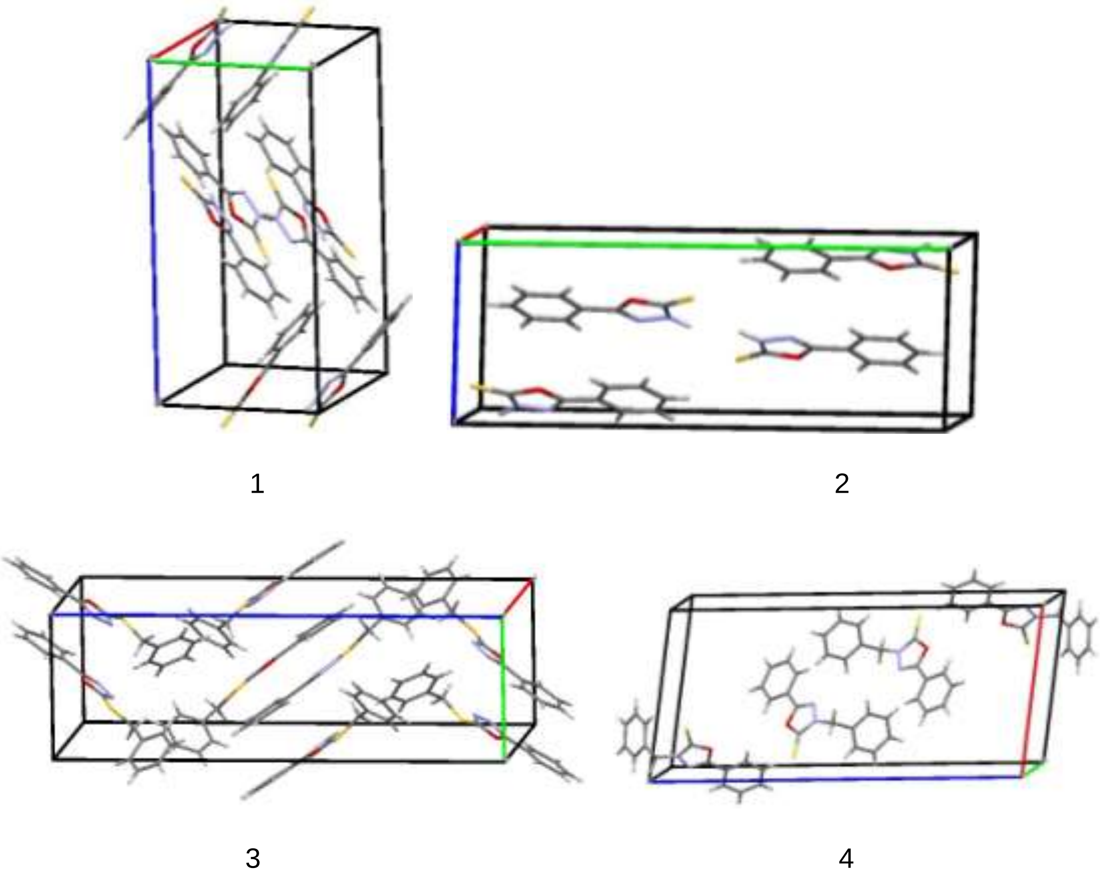


Fig.2 Packing structures **1-4**.

In the structures **1,2,3** and **4** was observed weak π ... π interaction between the five and six membered aromatic rings (atoms O1, C2, N3, N4, C5 and C6, C7, C8, C9, C10, C11) of molecules related by symmetry *1/2-x, -1/2+y, z; x, 3/2-y, -1/2+z; 1/2-x, -1/2+y, z; x,-1+y,z* and with centroid-centroid distance of 3.509 (2), 3.569(3), 3.7270(15), 3.628(2) Å respectively [18].

Thus, were synthesized and proven structures of S- and N-isomers of benzyl-5-phenyl-1,3,4-oxadiazol-2-thione. In the single crystals of isomers **3** and **4** grown from different solvents, unlike crystals of **1** and **2**, is not observed the formation of polymorphs.

In conclusion, it should be noted that the crystals grown from different solvents 5-phenyl-1,3,4-oxadiazole derivatives do not contain solvent molecules and they are not clathrogen.

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