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Intramolecular Heterocyclization of *N*-Allyl(phenyl)thiosemicarbazides of Morpholinylacetic Acid

O. A. Nurkenov[a], S. D. Fazylov[a], Zh. B. Satpaeva[a], K. M. Turdybekov[b], D. M. Turdybekov[c], S. A. Talipov[d], and B. T. Ibragimov[d]

[a] *Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, ul. Alikhanova 1, Karaganda, 100008 Kazakhstan*
e-mail: nurkenov_oral@mail.ru

[b] *International Scientific and Production Holding "Phytochemistry," Karaganda, Kazakhstan*

[c] *Multi-Disciplinary Humanitarian Technical University, Karaganda, Kazakhstan*

[d] *Sadykov Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Uzbekistan*

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Abstract—Intramolecular heterocyclization of *N*-allyl(phenyl)thiosemicarbazide of *N*-morpholinylacetic acid in aqueous alkaline medium results in cyclic 5-(morpholinomethyl)-4-allyl(phenyl)-1,2,4-triazole-3-thiones.

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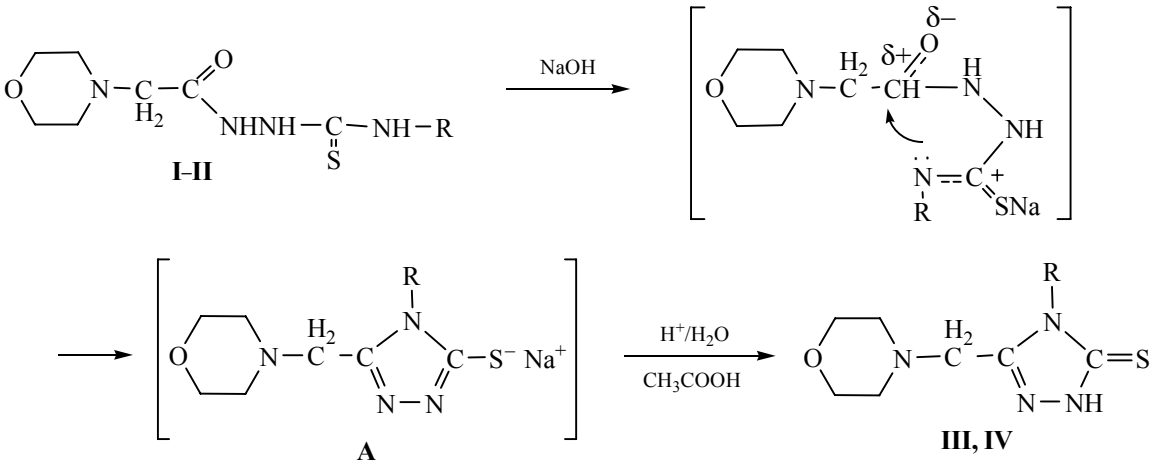
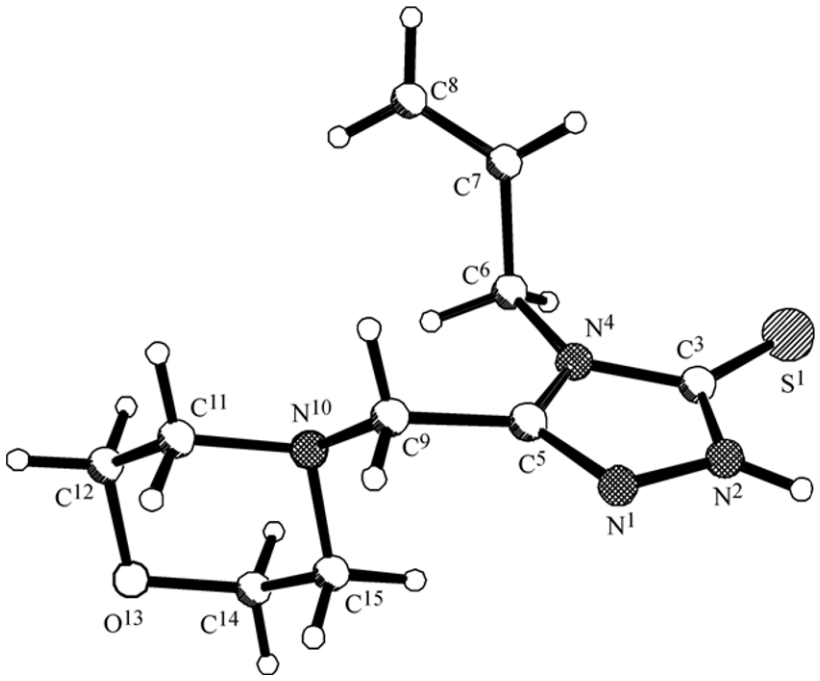
Thiosemicarbazides are widely used in organic chemistry as starting synthon for synthesis of many nitrogen-containing heterocyclic compounds [1]. In view of the antibacterial properties, 1,2,4-triazole-3-thione derivatives are promising, many of them are used in pharmacology [1–3] and agriculture [3–5].

Cyclization of thiosemicarbazide derivatives **I** and **II** was carried out in aqueous alkaline medium by heating the reaction mixture at 80–85°C. In the presence of alkali *N*-allyl(phenyl)thiosemicarbazides of morpholinylacetic acid **I** and **II** were transformed into thiolates, their subsequent acidification resulted in 5-(morpholinomethyl)-4-allyl(phenyl)-1,2,4-triazole-3-thiones **III** and **IV**.

The reaction mechanism was as follows. In the alkaline medium, thiosemicarbazides were almost completely transformed into the thiolates [6], the electronic equilibrium was shifted, favoring the intramole-



R = $CH{=}CHCH_2$ (**I, III**), C_6H_5 (**II, IV**).



General view of the molecule of thione **III**.

cular nucleophilic attack of the nitrogen atom at the electron-deficient carbon atom of the carbonyl group to form stable heterocyclic system.

The synthesized compounds **III** and **IV** were white crystalline substances, soluble in many polar and nonpolar organic solvents. Composition and structure of **III** and **IV** were confirmed by elemental analysis, IR, and ^{1}H NMR spectroscopy.

The IR spectra of the synthesized compounds **III** and **IV** contained the absorption band of NH group in the range of 3300–3100 cm^{-1} and that of C=S group at 1300 cm^{-1}.

In ^{1}H NMR spectrum of 5-(morpholinomethyl)-4-phenyl-1,2,4-triazole-3-thione **IV**, two triplet signals of methylene protons of morpholine moiety were observed at 2.17 and 3.40 ppm. The protons of NCH_2 fragment were registered as narrow singlet at 3.31 ppm. Phenyl ring protons resonated in weak field (7.45–7.54 ppm) resulting in complex multiplet. Thioamide proton of triazole ring appeared as narrow singlet at 13.83 ppm. Ratio of the integral intensities corresponded to the proposed structure of **IV**.

The spatial structure of 5-(morpholinomethyl)-4-allyl-1,2,4-triazole-3-thione **III** was confirmed by X-ray diffraction analysis (see figure).

The bond lengths and angles were close to the ordinary values in similar compounds (Tables 1 and 2) [7].

Morpholine ring in the molecule of **III** took the form of almost ideal *chair* conformation (ΔC_S^{12} 1.2° and $\Delta C_2^{11,12}$ 1.2°) (the intracyclic torsion angles are shown in Table 3). Thiadiazine ring was planar; the atoms N^1, N^2, C^3, N^4, and C^5 were coplanar within ± 0.003 Å. The atoms S^1, C^6, and C^9 were located close to the plane of the ring (the deviations were of 0.026, 0.020, and 0.065 Å, respectively). The atom C^9 was equatorially oriented with respect to the morpholine ring.

In the crystal, the molecules were linked via the hydrogen bonding N^2–H (x, y, z)···S^1 (2 – x, –y, 1 – z) (N···S 3.28 Å, H···S 2.44 Å, ∠NHS 164°), to form dimer pairs.

Thus, intramolecular heterocyclization of *N*-allyl (phenyl)thiosemicarbazides of morpholinylacetic acid **I** and **II** in aqueous alkaline medium gave 5-(morpholinomethyl)-4-allyl(phenyl)-1,2,4-triazole-3- thiones **III** and **IV**.

EXPERIMENTAL

IR spectra were recorded with Nicolet AVATAR-320 spectrometer in KBr pellets. ^{1}H NMR spectra were registered with Bruker DRX500 spectrometer at 500 MHz in DMSO-d_6 solution, relative to internal standard TMS. Melting points were determined with Boetius instrument. TLC analysis was performed on Sorbfil plates, detecting with iodine vapor.

Table 1. Bond lengths in the structure of **III**

Bond	*d*, Å	Bond	*d*, Å
S^1–C^3	1.687(3)	C^7–C^8	1.292(6)
N^1–C^5	1.293(4)	C^9–N^{10}	1.457(4)
N^1–N^2	1.373(3)	N^{10}–C^{11}	1.460(3)
N^2–C^3	1.329(4)	N^{10}–C^{15}	1.461(4)
C^3–N^4	1.373(3)	C^{11}–C^{12}	1.504(5)
N^4–C^5	1.374(3)	C^{12}–O^{13}	1.419(4)
N^4–C^6	1.476(3)	O^{13}–C^{14}	1.416(4)
C^5–C^9	1.493(4)	C^{14}–C^{15}	1.505(4)
C^6–C^7	1.483(5)		

Table 2. Bond angles in the structure of **III**

Angle	ω, deg	Angle	ω, deg
$C^5N^1N^2$	103.8(2)	$N^4C^6C^7$	112.8(2)
$C^3N^2N^1$	113.5(2)	$C^8C^7C^6$	124.5(4)
$N^2C^3N^4$	103.8(2)	$N^{10}C^9C^5$	112.7(2)
$N^2C^3S^1$	128.8(2)	$C^9N^{10}C^{11}$	109.9(2)
$N^4C^3S^1$	127.4(2)	$C^9N^{10}C^{15}$	112.4(2)
$C^3N^4C^5$	107.3(2)	$C^{11}N^{10}C^{15}$	108.7(2)
$C^3N^4C^6$	124.1(2)	$N^{10}C^{11}C^{12}$	109.6(3)
$C^5N^4C^6$	128.6(2)	$O^{13}C^{12}C^{11}$	111.8(3)
$N^1C^5N^4$	111.5(2)	$C^{14}O^{13}C^{12}$	109.9(3)
$N^1C^5C^9$	123.1(2)	$O^{13}C^{14}C^{15}$	112.2(3)
$N^4C^5C^9$	125.3(2)	$N^{10}C^{15}C^{14}$	108.6(3)

X-Ray diffraction analysis of III. Cell parameters and the intensity of 2195 independent reflections were measured with Xcalibur diffractometer (CuK_α, graphite monochromator, θ/2θ-scanning, 2θ ≤ 134°). The crystals were monoclinic; cell parameters: *a* 9.138(1), *b* 8.773(1), *c* 16.176(2)Å, β 104.89(2)°, *V* 1253.3(3) Å^3, *Z* 4 ($C_{10}H_{16}N_4OS$), space group $P2_1/c$, d_{calc} 1.274 g/cm^3. The structure was solved by direct method. Positions of non-hydrogen atoms were refined by the full-matrix least square method in anisotropic approximation. The hydrogen atoms were placed into the geometrically calculated positions and refined in a *rider* model. 1710 reflections with $I \geq 2\sigma(I)$ were used in the calculations. The final divergence factors were: R_1 0.0473 and wR_2 0.1521. The structure was solved and refined using the SHELXS-97 [8] and SHELXL-97 [9] software packages. The coordinates of the atoms of **III** have been deposited to the Cambridge Crystallographic Data Centre (CCDC 886408).

5-(Morpholinomethyl)-4-allyl-1,2,4-triazole-3-thione (III). 2.58 g (0.01 mol) of *N*-allylthiosemicarbazide of morpholinylacetic acid **I** was added to solution of 0.40 g (0.01 mol) of NaOH in 30 mL of distilled water. The reaction mixture was heated at 85°C during 2 h, then cooled and neutralized with hydrochloric acid to pH 6–7. The precipitate was filtered off and recrystallized from 2-propanol. Yield 50%, mp 156–158°C.

For X-ray analysis, the crystals of **III** were obtained by evaporation of a saturated solution in ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 t [4H, $N(CH_2)_2$, *J* 4.25], 3.51 s (2H, NCH_2), 3.55 t [4H, $O(CH_2)_2$, *J* 4.5], 4.69 d (1H, $\underline{CH_2}CH$=), 5.9 m (1H, $CH_2\underline{CH}$=), 5.09–5.21 d.d (1H, CH=$\underline{CH_2}$). Found, %: C 49.98; H 6.71; N 23.31. $C_{10}H_{16}N_4OS$. Calculated, %: C 50.28; H 6.93; N 23.49.

5-(Morpholinomethyl)-4-phenyl-1,2,4-triazole-3-thione (IV) was synthesized similarly from 0.40 g (0.01 mol) of NaOH and 2.94 g (0.01 mol) of *N*-phenylthiosemicarbazide of morpholinylacetic acid **II**. Yield 1.73 g (62.6%), white crystals, mp 186–189°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.17 t [4H, $N(CH_2)_2$, *J* 3.9], 3.31 s (2H, NCH_2), 3.4 t [4H, $O(CH_2)_2$, *J* 4.2], 13.83 br.s (1H, NN$\underline{H}$), 7.45–7.54 m (5H, C_6H_5). Found, %: C 56.50; H 5.84; N 20.27. $C_{13}H_{16}N_4OS$. Calculated, %: C 56.87; H 6.11; N 20.49.

Table 3. Intracyclic torsion angles in the structure of **III**

Angle	τ, deg	Angle	τ, deg
Triazole ring			
$C^5N^1N^2C^3$	0.2(3)	$N^2N^1C^5N^4$	0.3(3)
$N^1N^2C^3N^4$	–0.6(3)	$C^3N^4C^5N^1$	–0.7(3)
$N^2C^3N^4C^5$	0.8(3)		
Triazole ring			
$C^{15}N^{10}C^{11}C^{12}$	–58.9(3)	$C^{12}O^{13}C^{14}C^{15}$	57.7(4)
$N^{10}C^{11}C^{12}O^{13}$	58.1(4)	$C^{11}N^{10}C^{15}C^{14}$	59.1(3)
$C^{11}C^{12}O^{13}C^{14}$	–56.5(4)	$O^{13}C^{14}C^{15}N^{10}$	–59.6(4)

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