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Transamination of Cyanothioacetamide with Morpholine. Molecular and Crystal Structure of 3-(Morpholin-1-yl)-3-thioxopropanenitrile and 3-(Morpholin-1-yl)-3-thioxopropanethioamide

V. D. Dyachenko[a], A. N. Chernega[b], and S. V. Dyachenko[a]

[a] *Taras Shevchenko Lugansk National University, ul. Oboronnaya 2, Lugansk, 91011 Ukraine*
e-mail: dvd_lug@online.lg.ua

[b] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine*

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Abstract—Transamination of cyanothioacetamide with equimolar amount of morpholine resulted in the formation of 3-(morpholin-1-yl)-3-thioxopropanenitrile, and with twofold excess of morpholine 3-(morpholin-1-yl)-3-thioxopropanethioamide was obtained. By the alkylation of the resulting products 2-[2-(morpholin-1-yl)-2-thioxoethylidene]thiazolidin-4-one, 3-amino-*N*-(4-acetylphenyl)-5-(morpholin-1-yl)-thiophene-2-carboxamide, 3-amino-3-methylthio-1-morpholinoprop-2-ene-1-thione, (2*E*,4*E*)-2-(morpholin-4-yl)thiocarbonyl)-5-phenylpenta-2,4-dienothioamide, and 3-{2'-[2"-(molrpholin-1-yl)-2-thioxoethyl]thiazol-4'-yl}-2*H*-chromen-2-one were synthesized. The 3-(morpholin-1-yl)-3-thioxopropanenitrile and 3-(morpholin-1-yl)-3-thioxopropanethioamide structures were studied by the X-ray diffraction.

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It was shown previously that cyanothioacetamide (**I**) was transaminated with morpholine affording 3-(morpholin-1-yl)-3-thioxopropanenitrile (**II**) and 1-amino-3-(morpholin-1-yl)-1,3-propanedithione (**III**) [1]. Formerly only one example of the thioacetamide transamination with piperidine was known [2], as confirm surveys [3–6].

In this study compounds **II** and **III** were studied by XRD and their alkylation and condensation with cinnamic aldehyde was studied.

The general view of molecules **II** and **III**, and the main bond lengths and bond angles are shown in Figs. 1 and 2, respectively. In both molecules, the conformation of the morpholine substituent $N^1O^1C^{1-4}$ is almost undistorted *chair*: the torsion angles in the ring vary in a narrow range (54.7°–58.7° in the structure **II** and 54.3°–60.3° in the structure **III**), the angular fragments $O^1C^1C^4$ and $N^1C^2C^3$ form dihedral angles with the C^{1-4} plane 128.1° and 129.1° in compound **II** and 126.1° and 130.0° in compound **III**, respectively. The N^1 atom has planar-trigonal configuration of its bonds (the sums of bond angles at the N^1 atom in **II**

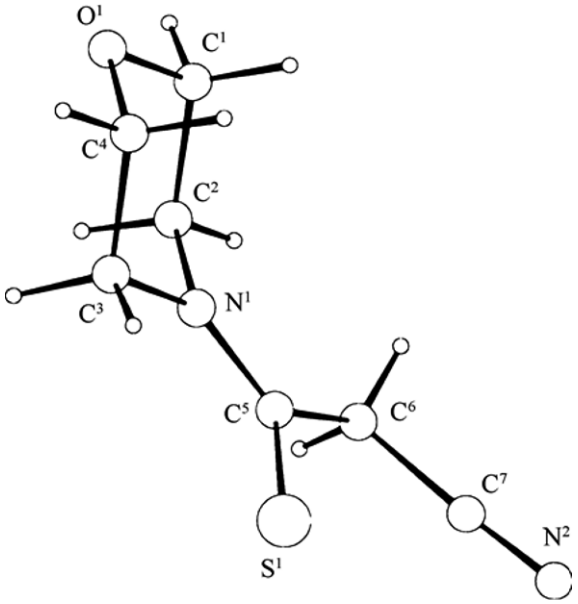


Fig. 1. General view of molecule **II** and numbering of atoms. Selected bond lengths (Å) and bond angles (deg): S^1–C^5 1.663(3), N^1–C^2 1.471(3), N^1–C^3 1.460(3), N^1–C^5 1.324(3), N^2–C^7 1.138(4), C^5–C^6 1.515(4), C^6–C^7 1.456(3), $C^2N^1C^3$ 110.6(2), $C^2N^1C^5$ 125.6(2), $C^3N^1C^5$ 123.7(2), $S^1C^5N^1$ 125.2(2), $S^1C^5C^6$ 120.3(2), $N^1C^5C^6$ 114.5(2), $N^2C^7C^6$ 174.2(3).

and **III** are 359.9(6)° and 360.0(9)°. The system of N^1–C^5(=S^1)–C^6 bonds is almost coplanar with $N^1C^2C^3$ group: the respective dihedral angle is only 7.5° in the molecule **II** and 1.5° in **III**. This conformation is quite favorable for the effective conjugation between the lone electron pair of atom N^1 and the C^5=S^1 π-system. Indeed, the N^1–C^5 bond transmiting this interaction [1.324(3) Å in **II** and 1.330(5) Å in **III]** is significantly shorter than the value of 1.45 Å, typical for an ordinary single N(sp^2)–C(sp^2) bond [7, 8]. Similarly, in the molecule **III** the $n(N^2)$–π(C^7=S^2) interaction results in the shortening of the N^2–C^7 bond to 1.315 (5) Å.

Note that the reaction of cyanothioacetamide **I** with the equimolar amount of morpholine at 20°C in ethanol proceeds along the transamination path [9] to form compound **II**. Use of a twofold excess of morpholine under the same conditions results in the formation of the dithioamide **III**. This may be due to the presence in the reaction mixture of hydrogen sulfide eliminated from the cyanothioacetamide **I** under the action of morpholine. It is known that the addition of hydrogen sulfide to nitriles in basic

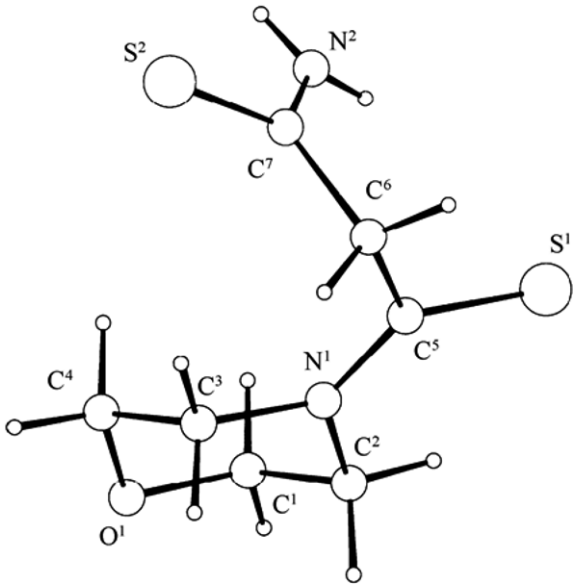
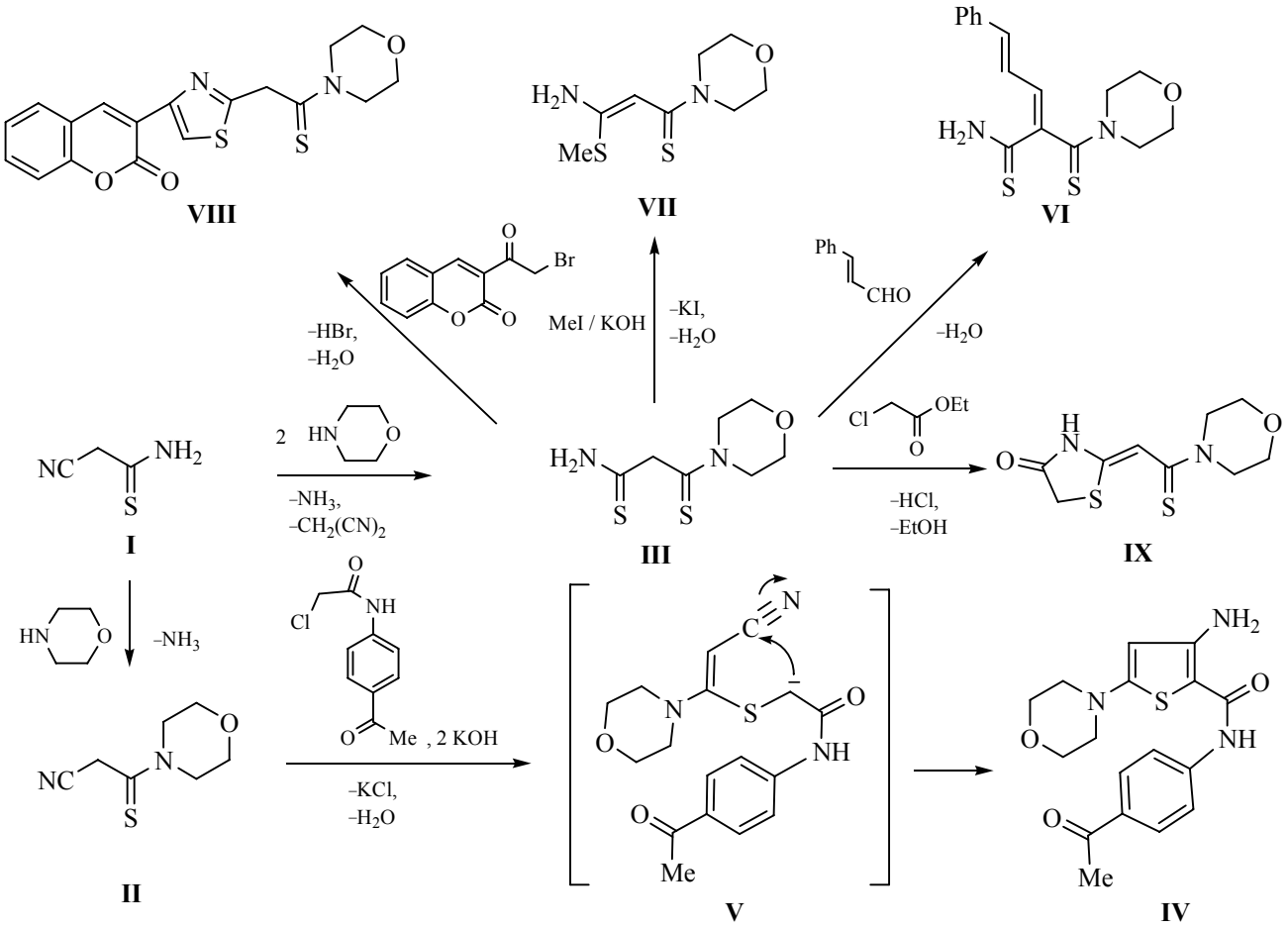


Fig. 2. General view of molecule **III** and numbering of atoms. Selected bond lengths (Å) and bond angles (deg): S^1–C^5 1.683(4), S^2–C^7 1.661(4), N^1–C^2 1.474(5), N^1–C^3 1.473(6), N^1–C^5 1.330(5), N^2–C^7 1.315(5), C^5–C^6 6 1.524 (5), $C^2N^1C^3$ 111.9 (3), $C^2N^1C^5$ 122.4(3), $C^3N^1C^5$ 125.7(3), $S^1C^5N^1$ 124.2(3), $S^1C^5C^6$ 118.2(3), $N^1C^5C^6$ 117.7(3), $S^2C^7N^2$ 122.1(3), $S^2C^7C^6$ 121.4(3), $N^2C^7C^6$ 116.5(3).



Main crystallographic parameters of compounds **II** and **III**, the conditions of the diffraction experiments and the details of structure refinement

Parameter	**II**	**III**
Empirical formula	$C_7H_{10}N_2OS$	$C_7H_{12}N_2OS_2$
M	170.23	204.31
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	*Pc*
a, Å	9.204(2)	5.981(1)
b, Å	7.435(2)	5.604(2)
c, Å	24.518(3)	14.756(3)
β, deg	90.0	99.44(1)
V, Å^3	1677(6)	487.8
Z	8	2
d_{calc}, g cm^{-3}	1.35	1.39
μ, cm^{-1}	29.31	4.82
F(000)	724.2	216.5
Crystal size, mm	0.19×0.34×0.42	0.19×0.22×0.34
Diffraction angle limits θ, deg	65	27
Spheric segment	$0 < h < 10$, $0 < k < 8$, $0 < l < 28$	$0 < h < 7$, $0 < k < 7$, $-18 < l < 18$
Number of reflections:		
measured	1692	1292
independent	1428	1071
in least-squares calc.	1031 [> 3σ(*I*)]	843 [> 3σ(*I*)]
Number of refined parameters	140	117
Number of reflections per parameter	7.4	7.2
Divergence factors:		
R	0.044	0.033
R_w	0.049	0.034
GOOF	1.077	1.164
Weighting factors	2.44, 1.91, 2.34, 0.45, 0.51	0.66, 0.17, 0.52, 0.04, 0.11
Residual electron density Δρ, *e* Å^{-3}	0.30; –0.32	0.19; –0.17

medium is a reversible process [10]. Further addition of hydrogen sulfide to compound **II** just leads to the formation of dithiodiamide **III**.

The alkylation of 3-(morpholin-1-yl)-3-thioxopropanenitrile **II** with α-chloro-4-acetylacetanilide in DMF in the presence of a twofold excess of KOH gave 3-amino-2-(4-acetylphenylcarbamoyl)-5-morpholinothiophene (**IV**). The reaction path involves, apparently, the formation of thioester **V** which is unstable in these conditions and readily undergoes the intramolecular cyclization to form the substituted thiophene **IV**, a promising intermediate for designing drugs with antitumor [11–13] and antidiabetic activity [14, 15].

Compound **III** enters the Knoevenagel condensation with cinnamic aldehyde as a CH component, forming the corresponding alkene **VI**. The alkylation of dithiodiamide **III** with methyl iodide in DMF in the presence of KOH leads to thioether **VII**. The use in this reaction of α-halocarbonyl compounds bromacetylcoumarin or ethyl monochloroacetate as alkylating agents resulted in the synthesis of substituted Hantzsch thiazole **VIII** and thiazolidone **IX**, respectively.

The structures of the obtained compounds **IV, VI–IX** were confirmed by mass spectrometry, IR and ^{1}H NMR spectroscopy (see Experimental). For the ^{1}H NMR spectra the presence is characteristic of the proton signals of morpholine fragment as multiplets at δ 3.11–4.25 ppm, and the characteristic signals of protons of aromatic substituents in the corresponding regions of the δ scale.

EXPERIMENTAL

X-ray diffraction investigation of single crystals of compounds **II** and **III** was carried out at room temperature on an automatic four-circle Enraf-Nonius CAD-4 diffractometer (graphite monochromator, ratio of scanning rates $\omega/2\theta = 1.2$). The extinction in the crystal was accounted for by the method of azimuthal scanning [16]. Both structures were solved by the direct method and refined by the full-matrix least-squares procedure in an anisotropic approximation using a program package CRYSTALS [17]. In both these structures all the hydrogen atoms were revealed from a difference synthesis of electron density. In compound **II** all H atoms were refined isotropically, in the structure **III** only the atoms H^1 and H^2 associated with the N^2 atom were refined, while the remaining H atoms were included in the refinement with fixed positional and thermal parameters. In the refinement

we used the Chebyshev weight scheme [18]. The absolute configuration of **III** was determined by the Flack method [19], the enantipole parameter *p* was refined to the value of 0.01 from 926 reflections with non-averaged Friedel equivalents. The crystallographic data of the studied compounds and conditions of the diffraction experiments are given in the table.

The IR spectra were recorded on an IKS-40 instrument from the samples in mineral oil. The ^{1}H NMR spectra were recorded on a Gemini-200 spectrometer (199.975 MHz) for compounds **II** and **IV** and a Bruker DR-500 (500.13 MHz) instrument for compounds **III, VI–IX**, solvent DMSO-d_6, reference TMS. The mass spectra were recorded on a Kratos MS-890 instrument (70 eV) with direct introduction of substance **III** into the ion source, and Crommas GC/MS-Hewlett-Packard 5890/5972 instrument, column HP-5 MS (70 eV), compounds **VI, VII,** and **IX** were taken as solutions in CH_2Cl_2. Melting points were determined on a Koeffler block. Monitoring of the reaction progress and of the purity of the compounds was performed by TLC (Silufol UV-254, acetone-hexane, 3:5, development in iodine vapor and UV irradiation).

3-(Morpholin-1-yl)-3-thioxopropanenitrile (II). To a stirred suspension of 1.0 g (10 mmol) of cyanothioacetamide **I** in 15 ml of ethanol at 20°C was added 0.87 ml (10 mmol) of morpholine. The mixture was stirred for 30 min and left for a day. The precipitate was then filtered off, washed with ethanol and hexane. Yield 1.3 g (76%), yellow crystals, mp 89°C (EtOH) (published 91–92°C [20], 95°C [21]).

1-Amino-3-(morpholin-1-yl)-1,3-propanedithione (III) was prepared analogously to compound **II** using 1.74 ml (20 mmol) of morpholine. Yield 0.8 g (39%), yellow crystals, mp 143–150°C (decomp.). IR spectrum, ν, cm^{-1}: 3190, 3278, 3356 (NH_2).^{1}H NMR spectrum, δ, ppm: 3.70 m (4H, CH_2NCH_2), 3.91 s (2H, CH_2), 4.42 m (4H, CH_2OCH_2), 8.87 and 9.43 br.s (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 206(6) $[M + 2]^+$, 205 (7) $[M + 1]^+$, 204 (55) $[M]^+$, 171 (8) $[M - SH]^+$, 144 (9), 119 (22), 110 (20), 101 (8), 86 (100) [morpholinyl]$^+$, 60 (39), 54 (18), 42 (23). Found, %: C 40.93, H 6.07, N 13.58. $C_{17}H_{12}N_2OS_2$. Calculated, %: C 41.15, H 5.92, N 13.71.

3-Amino-2-(4-acetylphenylcarbamoyl)-5-(morpholin-4-yl)thiophene (IV). To a stirred solution of 1.7 g (10 mmol) of compound **II** in 15 ml of DMF was added sequentially 5.6 ml (10 mmol) of 10% aqueous solution of KOH and 2.12 g (10 mmol) of 4-acetylchloroacetanilide, the mixture was stirred for 1 h and the same amount of the alkali was added again, the stirring was continued for 2 h and the mixture was left for one day. Then the reaction mixture was diluted with an equal volume of water and the resulting precipitate was filtered off, washed with water, ethanol and hexane. Yield 2.45 g (71%), white powder, mp 199–200°C (BuOH). IR spectrum, ν, cm^{-1}: 3242, 3297, 3425 (NH_2), 1680 (C=O), 1657 [CONH, δ (NH_2)]. ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, Me), 3.17 m (4H, CH_2NCH_2), 3.75 m (4H, CH_2OCH_2), 5.67 s (1H, C^{4}H thiophene), 6.68 br.s (2H, NH_2), 7.80 br.s (4H, C_6H_4), br.s 8.87 (1H, CONH). Found, %: C 58.87, H 5.32, N 12.30. $C_{17}H_{19}N_3O_3S$. Calculated, %: C 59.11, H 5.54, N 12.16.

(2*E*,4*E*)-2-(Morpholin-4-ylthiocarbonyl)-5-phenylpentyl-2,4-dienethioamide (VI). To a stirred suspendsion of 2.4 g (10 mmol) of the CH-acid **III** in 20 ml of ethanol was added 1.26 ml (10 mmol) of cinnamic aldehyde and 3 drops of triethylamine, the mixture was stirred for 2 h and left standing for 48 h. The precipitate formed was filtered off, washed with ethanol and hexane. Yield 2.1 g (66%), colorless crystals, mp 193–195°C (EtOH). IR spectrum, ν, cm^{-1}: 3290, 3433 (NH_2). ^{1}H NMR spectrum, δ, ppm: 3.11–4.09 m (8H, morpholine), 4.91 d (1H, C^{3}H, *J* 9.2 Hz), 5.08 m (1H, C^{4}H), 6.4 d (1H C^{5}H, *J* 9.4 Hz), 7.19 m (2H, Ph, *J* 6.94 Hz), 7.22 m (1H, Ph, *J* 6.94 Hz), 7.31 q (2H, Ph, *J* 7.09 Hz), 10.42 br.s (2H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 319 (100) $[M + 1]^+$. Found, %: C 60.22, H 5.61, N 8.68. $C_{16}H_{18}N_2OS_2$. Calculated, %: C 60.35, H 5.70, N 8.80.

3-Amino-3-methylthio-1-(morpholin-1-yl)prop-2-ene-1-thione (VII). To a stirred suspension of 2.4 g (10 mmol) of dithiodiamide **III** in 15 ml of DMF was added sequentially 5.6 ml (10 mmol) of 10% aqueous solution of KOH and 0.62 ml (10 mmol) of methyl iodide, the mixture was stirred for 5 h and diluted with an equal volume of water. The precipitate was filtered off, washed with water, ethanol, and hexane. Yield 5.1 g (48%), brown powder, mp 102–103°C (EtOH). IR spectrum, n, cm^{-1}: 3178, 3326 (NH_2), 1650 [δ(NH_2)]. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, Me), 3.58 m (4H, CH_2NCH_2), 3.89 m (4H, CH_2OCH_2), 5.31 s (1H, =CH), br.s 9.35 (2H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 219 (100) $[M + 1]^+$. Found, %: C 43.92, H 66.02, N 12.77. $C_8H_{14}N_2OS_2$. Calculated, %: C 44.01, H 66.13, N 12.83.

3-[2'-(2''-(Morpholin-1-yl)-2-thioxoethyl)thiazol-4'-yl]-2*H*-chromen-2-one (VIII). A mixture of 4.2 g

(10 mmol) of compound **III** and 2.67 g (10 mmol) of bromoacetylcoumarine in 15 ml of DMF was stirred for 5 h and then diluted with equal volume of water. The precipitate formed was filtered off, washed with water, ethanol and hexane. Yield 2.68 g (72%), yellow powder, mp 222–224°C (BuOH). IR spectrum, ν, cm^{-1}: 1714 (C=O). ^1H NMR spectrum, δ, ppm: 3.62 m (2H, CH_2N, *J* 4.42 Hz), 3.71 m (2H, NCH_2, *J* 4.42 Hz), 3.99 m (2H, OCH_2, *J* 4.42 Hz), 4.25 m (2H, OCH_2, *J* 4.42 Hz), 4.74 s (2H, CH_2), 7.41 m (1H, H_{arom}, *J* 8.01 Hz), 7.44 d (1H, H_{arom}, *J* 8.01 Hz), 7.63 m (1H, H_{arom}, *J* 8.01 Hz), 7.92 d (1H, H_{arom}, *J* 8.01 Hz), 8.36 s (1H, C^5 H thiazole), 8.73 s (1H, C^5H, coumarine). Found, %: C 57.92, H 4.27, N 7.42. $C_{18}H_{16}N_2O_3S_2$. Calculated, %: C 58.05, H 4.33, N 7.52.

2-[2-(Morpholin-1-yl)-2-thioxoethylidene)thiazolidine-4-one (IX) was prepared analogously to compound **VII** with 1.6 ml (10 mmol) of ethyl chloroacetate as alkylating agent. Yield 1.51 g (62%), yellow crystals, mp 206–208°C (PrOH). IR spectrum, ν, cm^{-1}: 3302 (NH), 1700 (C=O). ^1H NMR spectrum, δ, ppm: 3.48 s (2H, SCH_2), 3.68 m (4H, CH_2NCH_2), 3.92 m (4H, CH_2OCH_2), 6.41 s (1H, CH=), 11.1 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 245 (100) $[M + 1]^+$. Found, %: C 44.13, H 4.81, N 11.32. $C_9H_{12}N_2O_2S_2$. Calculated, %: C 44.24, H 4.95, N 11.47.

REFERENCES

1. Dyachenko, V.D., *Zh. Obshch. Khim*., 2004, vol. 74, no. 4, p. 701.
2. Micheel, F., Krzeminski, Z., Himmelmann, W., and Kuhlkamp, A., *Lieb. Ann*., 1952, vol. 575, nos. 1–3, p. 90.
3. Petrov, K.A. and Andreev, L.N., *Usp. Khim*., 1969, vol. 38, no. 1, p. 41.
4. Petrov, K.A. and Andreev, L.N., *Usp. Khim*., 1971, vol. 40, no. 6, p. 1015.
5. Litvinov, V.P., *Usp. Khim*., 1999, vol. 68, no. 9, p. 817.
6. Jagodzinski, T.S., *Chem. Rev*., 2003, vol. 103, no. 1, p. 197.
7. Burke-Laing, M. and Laing, M., *Acta Cryst., Part B,* 1976, vol. 32, no. 12, p. 3216.
8. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Tailor, R., *J. Chem. Soc., Perkin Trans. 2*, 1987, no. 12, p. S1.
9. Mishchenko, G.L. and Vatsuro, K.V., *Sinteticheskie metody organicheskoi khimii* (Synthetic Methods in Organic Chemistry), Moscow: Khimiya, 1982, p. 297.
10. Zil'berman, E.N., *Reaktsii nitrilov* (Reactions of Nitriles), Moscow: Khimiya, 1972.
11. USA Patent no. 6414013, 2002, *Ref. Zh. Khim*., 2003. 03.04 – 19O.63P.
12. USA Patent no. 7179836, 2007, *Ref. Zh. Khim*., 2007. 07.21 – 19O.83P.
13. USA Patent no. 7423061, 2008, *Ref. Zh. Khim*., 2009. 09.04 – 19O.56P.
14. USA Patent no. 7138529, 2006, *Ref. Zh. Khim*., 2007. 07.21 – 19O.84P.
15. Surikova, T.P., Zakharova, V.D., Mochalov, S.S., and Shabarov, Yu.S., *Khim.-Farm. Zh*., 1989, no. 7, p. 840.
16. North, A.C.T., Phillips, D.C., Scott, F., and Mathews, F.S., *Acta Cryst., Part A*, 1968, vol. 24, no. 2, p. 351.
17. Watkin, D.J., Prout, C.K., Carruthers, J.R., and Betteridge, P.W., *Crystals, no. 10*, Oxford: University of Oxford 1996.
18. Carruthers, J.R. and Watkin, D.J., *Acta Cryst., Part A*, 1979, vol. 35, no. 3, p. 698.
19. Flack, H.D., *Acta Cryst., Part A*, 1983, vol. 39, no. 4, p. 876.
20. Heyde, C., Zug, J., and Hartmann, H., *Eur. J. Org. Chem*., 2000, vol., 19, no. 17, p. 3273.
21. Kosterina, M.F., Morzherin, Yu.Yu., Tkachev, A.V., Rybalova, T.V., Gatilov, Yu.V., and Bakulev, V.A., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2002, no. 4, p. 604.