Chemistry of Heterocyclic Compounds, Vol. 33, No. 7, 1997

N-3-OXOALKYLAMIDES AND -THIOAMIDE IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. PART 1. SYNTHESIS OF 1,1-DIETHOXY-3-ISOTHIOCYANATOBUTANE AND REACTIONS BASED ON IT

A. S. Fisyuk, L. V. Berdovich, D. V. Temnikov, and L. N. Knyaz'kova

The reaction of 3-isothiocyanatobutanal with ethanol in the presence of ethyl orthoformate produced 1,1-diethoxy-3-isothiocyanatobutane. The latter was used to devise methods of preparing 3-methylaminobutanal diethylacetal, N-(4-diethoxybutyl-2)thioamides, N-(4-oxybutyl-2)-thioamides, and 6-methyl-3-phenyl-5,6-dihydropyridine-2(1H)-thione.

1,3-Isothiocyanatocarbonyl compounds, obtainable by many methods [1, 2, 3], are widely used in organic synthesis for preparing 1,3-amino ketones [4], 1,3-isothiocyanato alcohols [5], 1,3-amino alcohols [6], derivatives of 1,3-oxazine [7, 8], 1,3-thiazine [9, 10, 11], pyrimidine [12, 13], and pyridine [14]. However, their synthetic possibilities have not been fully studied. It is well known that reactions of 1,3-isothiocyanatocarbonyl compounds with cryptobases (Grignard reagents [15], lithium aluminum hydride [6], sodium borohydride [7], cyanide anion [8]) cannot be carried out at the isothiocyanato group – they take place either at the carbonyl group or at both functional groups simultaneously. At the same time, conversion of the isothiocyanato group to a thiocarbamoyl group in 1,3-isothiocyanatocarbonyl compounds is of interest, since it results in the formation of difficult-to-prepare N-3-oxoalkylthioamides, used in the synthesis of 5,6-dihydropyridine-2(1H) thiones [16].

By reacting 3-isothiocyanatobutanal (I) with ethanol in the presence of ethyl orthoformate we obtained the previously unknown 3-isothiocyanatobutanal diethyl acetal (II) in a 76% yield. The reactions of compound II with Grignard reagents take place at the isothiocyanato group and result in the formation of N-(4-diethoxybutyl-2)thioamides III, IV, which on hydrolysis in an acetonitrile – water mixture (pH 4-5) are converted to N-4-oxobutylthioamides V, VI, which are oily substances. Hydrolysis of acetal IV with a saturated aqueous solution of oxalic acid results in the formation of a crystalline substance which, after treatment with sodium bicarbonate solution, forms compound VI, a hydrogen-bonded molecular complex of N-4-oxobutylthiophenylacetamide and oxalic acid VII.

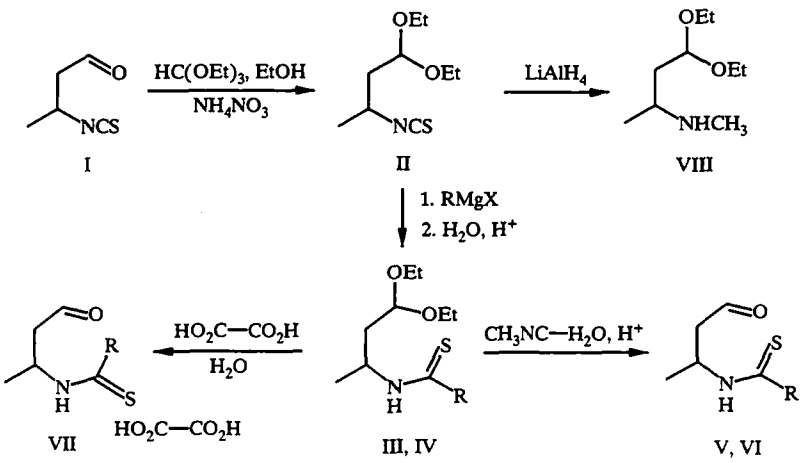
Acetals of 3-aminoaldehydes, used in the synthesis of heterocyclic compounds [17], are not easy to prepare [18]. We have shown that 1,1-diethoxyalkyl-3-isothiocyanates are convenient starting compounds for preparing acetals of 1,3-methylaminoaldehydes. The reaction of compound II with lithium aluminum hydride in ether results in the formation of methyl(1,1-diethoxybutyl-2)amine (VIII) in a 65% yield.

The IR spectra of compounds II-IV, VII (Table 1) in the region 1155-1035 cm^{-1} contain signals of the acetal fragment. Signals of the stretching vibrations of the N–H bond of compounds III, IV, VII and the "thioamide II" band for compounds III, IV are observed in the regions 3360-3300 cm^{-1} and 1515-1520 cm^{-1}, respectively. In addition, the spectrum of compounds II shows the band of the NCS group (2110 cm^{-1}), and the spectrum of compound IV shows signals of the aromatic ring (1650 cm^{-1}).

The IR spectra of compounds V, VI (Table 1) in the regions 2800-2810, 2715-2720, and 1720-1710 cm^{-1} show bands characteristic of vibration of the C–H and C=O bands of the aldehyde group, and the "thioamide II" band is present in the region 1500-1520 cm^{-1}. In the spectra of compounds V, VI recorded in a thin layer, there is a broad band with its center at

Omsk State University, Omsk 644077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 921-927, July, 1997. Original article submitted April 7, 1997.

0009-3122/97/3307-0805$18.00

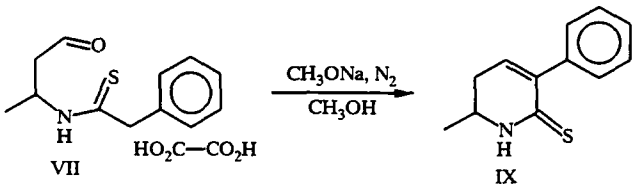


III, V R = CH_3; IV, VI, VII R = CH_2Ph

3250-3230 cm^{-1}, characteristic of the vibrations of an N−H associated bond. Dissolution of compounds V, VI in chloroform causes a band to appear in the spectra in the region 3350-3360 cm^{-1} that is free from association of the N−H bond of thioamide. In the IR spectrum of compound VII (Vaseline oil) in the region 3230-3050 cm^{-1}, a band system is present that is characteristic of vibrations of the associated bonds N−H and O−H of the thioamide and carboxyl groups, and at 1720 cm^{-1} there is a broad band of overlapping absorption signals of the C=O groups of carbonyl and carboxyl. The vibrational bands of the atoms of the aromatic ring and thioamide fragment are observed at 1630 and 1520, 1500 cm^{-1}.

Isothiocyanatoacetal II is characterized by low stability to electron impact. Its mass spectrum does not contain a molecular ion peak, but does contain peaks, characteristic of acetals, of the ions $\Phi_1[M^+ - C_2H_5O^\cdot]$, $\Phi_2[\Phi_1 - C_2H_4]^+$, $\Phi_3[(EtO)_2CH]^+$, $\Phi_4[\Phi_3 - C_2H_4]^+$, $\Phi_5[\Phi_4 - C_2H_4]^+$, as well as the peaks of $\Phi_6[CH_3CHNCS]^+$ and $\Phi_7[HNCSH]^+$, characteristic of isothiocyanates [9, 19].

A study of the cyclization of N-3-oxoalkylthioamides V-VII under action of bases showed that compounds VI, VII reacting with sodium methoxide in a nitrogen atmosphere at room temperature form 6-methyl-3-phenyl-5,6-dihydropyridine-2(1H)-thione (IX). Compound V under these conditions is converted into a mixture that is difficult to separate.



The IR spectrum of compound IX at 3350 shows the absorption band of the N−H bond, vibration signals of the aromatic ring at 1620, and the "thioamide II" band (1490 cm^{-1}).

The ^1H NMR spectra of compounds II-IX are completely consistent with their structure (Table 2). The most characteristic are the signals of the protons of the aldehyde groups (compounds IV-VI, d. d, 9.70-9.47 ppm), the proton of $C\underline{H}(OEt)_2$ (compounds II-IV, VIII; d. d, 4.61-4.51 ppm), phenyl group protons (compounds IV, VI, VII, m, 7.37-7.10 ppm), two magnetically nonequivalent protons of the methylene group of the N-4-diethoxybutyl and N-4-oxobutyl fragments (compounds II-V, VIII, and V-VII, m, 1.86-1.69; m, 1.80-1.48 and m, 2.82-2.66; m, 2.65-2.60 ppm), and methine proton (compounds II-VIII, m, 2.58-5.10 ppm). The four protons ($C\underline{H}(OEt)_2$, CH_2, $C\underline{H}Me$) of compounds II-IV, VIII, and (CHO, CH_2, $C\underline{H}Me$) of compounds V-VII form a spin system of type ABXM. The SSCC values for these protons are given to a first-order approximation in Table 2. The value of the SSCC for 5-H and 6-H (J^3 = 12.0 and 5.8 Hz) of compound IX indicates an axial orientation of the proton at $C_{(6)}$, i.e., an equatorial position of the methyl group $C_{(6)}-CH_3$.

TABLE 1. Properties of the Synthesized Compounds

Compound	Empirical formula	Found, %			Calculated, %			mp, °C, bp, °C (Torr)	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N	C	H	N			
II	$C_9H_{17}NO_2S$	52,98	8,55	—	53,17	8,43	6,89	121...122 (15)	2110, 1155, 1070, 1050	76
III	$C_{10}H_{21}NO_2S$	54,66	9,73	6,40	54,76	9,65	6,39	117...119 (0,09)	3340, 1515, 1150, 1125, 1105, 1070, 1055	44
IV	$C_{16}H_{25}NO_2S$	64,91	8,76	—	65,05	8,53	4,74	*	3300, 1650, 1520, 1130, 1060, 1035	69
V	$C_6H_{11}NOS$	49,66	7,51	—	49,63	7,63	9,65	70...75 (0,1)	3360, 3230, 2810, 2715, 1720, 1500	49
VI	$C_{12}H_{15}NOS$	66,13	6,97	—	65,12	6,83	6,33	*	3250, 2800, 2725, 1710, 1660, 1520*[2]	87
VII	$C_{14}H_{17}NO_5S$	54,32	5,70	—	54,01	5,50	4,50	158...160	3225, 3150, 3050, 1630, 1720, 1520, 1500*[3]	87
VIII	$C_9H_{21}NO_2$	61,32	11,90	8,07	61,68	12,08	7,99	77...78 (20)	3330, 1155, 1130, 1090, 1055	65
IX	$C_{12}H_{13}NS$	71,01	6,61	6,80	70,90	6,45	6,89	153...154*[4]	3350, 1620, 1490	73

*Silica gel in the system, 1:1 chloroform–ethyl acetate.

*[2]Thin layer.

*[3]In Vaseline oil.

*[4]From CCl_4.

TABLE 2. ESR Spectra of Synthesized Compounds II-IX

Compound	OEt		CH(—O—)$_2$; CHO; =CH (J^3)	CHH'		CH—Me (J^3)	CH_3	$NCOCH_2$; $NCOCH_3$ NCH_3	Ph	NH
	CH_2	CH_3		HCH' (J^3)	HCH' (J^3)					
II	3,55	1,10 (7,0; 7,0) 1,11 (7,0; 7,0)	4,53 (4,4; 7,1)	1,82 (4,4; 8,9)	1,71 (7,1; 4,8)	3,80 (4,8; 8,9; 6,6)	1,27	—	—	—
III	3,54	1,16 (7,0; 7,0) 1,12 (7,1; 7,1)	4,61 (5,6; 5,6)	1,86 (5,6; 5,6)	1,80 (5,6; 5,6)	4,59 (5,6; 5,6; 6,7)	1,21	2,42	—	8,10
IV	3,43	0,99 (7,1; 7,1) 1,10 (7,1; 7,1)	4,51 (6,0; 5,8)	1,78 (6,0; 5,8)	1,72 (5,8; 5,8)	5,10 (5,8; 5,8; 6,8)	1,14	4,01	7,25	8,04
V	—	—	9,70 (1,6; 1,6)	2,82 (1,6; 6,3)	2,65 (1,6; 6,3)	4,87 (6,3; 6,3; 6,7)	1,26	2,41	—	7,76
VI	—	—	9,65 (1,5; 1,5)	2,72 (1,5; 6,5)	2,60 (1,5; 6,5)	4,80 (6,5; 6,5; 6,5)	1,14	3,97	7,24	—
VII*	—	—	9,47 (1,6; 1,6)	2,66 (1,6; 6,3)	2,62 (1,6; 6,3)	4,73 (6,3; 6,3; 6,6)	1,16	3,80	7,19	—
VIII	3,49	0,99 (7,1; 7,1) 1,10 (7,1; 7,1)	4,52 (5,1; 6,7)	1,69 (6,7; 6,7)	1,48 (5,1; 5,7)	2,58 (5,7; 6,7; 6,3)	0,97	2,29	—	1,66
IX	—	—	6,48 (3,3; 6,0)	2,46 (6,0; 5,8)	2,23 (3,3; 12,0)	3,75 (5,8; 12,0; 6,5)	1,31	—	7,27	8,04

*Solvent, DMSO-D_6.

We have thus shown a new approach to the synthesis of 5,6-dihydropyridine-2(1H)-thiones and acetals of 3-aminoaldehydes. The possibility of transformation of the isothiocyanato group of acetals of 1,3-isothiocyanatoaldehydes into other functional groups with subsequent regeneration of the carbonyl function opens up new possibilities for the preparation of N-3-oxoalkyl-substituted bifunctional compounds, making them promising compounds for building heterocycles.

EXPERIMENTAL

The ESR spectra were recorded on the instruments Bruker-AC 200 P and Tesla BS-587 (80 MHz) in $CDCl_3$. The internal standard was TMS. The IR spectra were recorded on a Specord IR-75 spectrometer in $CHCl_3$ solutions. The mass spectra of compound II were obtained on a Finnigan MAT-112 instrument. The course of the reaction and purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates, with development using iodine vapor and UV light.

3-Isothiocyanatobutanal (I) was obtained by the method of [1].

1,1-Diethoxy-3-isothiocyanatobutane (II). To a solution of 0.38 g (4.7 mmole) of ammonium nitrate in 3.5 ml of absolute ethanol is added 9.43 g (73.0 mmole) of 3-isothiocyanatobutanal in 11.84 g (79.9 mmole) of triethyl orthoformate. The reaction mass is stirred for 24 h at room temperature with protection from atmospheric moisture. The reaction mixture is then washed with a 5% solution of sodium hydrocarbonate (3 × 10 ml). The organic layer is dried with anhydrous $MgSO_4$, the solvent is evaporated, and the residue is vacuum-distilled in a stream of nitrogen. There is obtained 11.25 g (76%) of 1,1-diethoxy-3-isocyanatobutane, n_D^{20} 1.5067. Mass spectrum, m/z (I, %): $[M - C_2H_5O^{\cdot}]^+$ 158 (17.4), $[M - C_2H_5O^{\cdot} - C_2H_4]^+$ 130 (14.3), 103 (42.8) $[(EtO)_2CH)]^+$, 86 (100) $[CH_3CHNCS]^+$, 75 (48.4) $[(EtO)_2CH) - C_2H_4]^+$, 71 (16.3), 70 (17.0), 69 (23.6), 60 (13.5) $[HNCSH]^+$, 47 (66.6) $[(EtO)_2CH) - 2C_2H_4]^+$.

N-(4,4-Diethoxybutyl-2)thioamides (III, IV). To 15 mmole of alkylmagnesium halide in 13 ml of absolute ether is slowly added dropwise with stirring and in a nitrogen atmosphere at room temperature 15 mmole of 1,1-diethoxy-3-isothiocyanatobutane II in 5 ml of absolute ether. The reaction mixture is then heated on a water bath for 30 min, cooled, and the ether is separated. The thick, oily substance is washed with 5 ml of ether, then 10 ml of ether and 15 ml of a 10% sodium hydrocarbonate solution are added with cooling. The ether layer is separated, and the aqueous layer is extracted with ether (4 × 10 ml). The combined ether extract is washed with saturated NaCl solution and dried with anhydrous $MgSO_4$. After the solvent is removed, compound III is purified by vacuum distillation. The ether extract of compound IV is purified by flash chromatography on alumina and used without additional purification to obtain compound VII. In order to obtain an analytically pure sample of V, the substance is purified by column chromatography on silica gel (1:1 chloroform–ethyl acetate eluent).

N-(4-Oxobutyl-2)thioamides (V, VI). N-(4,4-Diethoxybutyl-2)thioamides III (2.25 g, 10.3 mmole) or IV (0.78 g, 2.6 mmole) are dissolved in 20 ml of an acetonitrile–water mixture (1:1 in the case of III; 1:0.6 in the case of IV). The mixture is acidified with conc. HCl to pH 4-5 and left standing for 10-12 h. The solution is then neutralized with dry sodium hydrocarbonate and extracted with ether (3 × 15 ml). The combined ether extract is dried with anhydrous $MgSO_4$. After the solvent is removed, compound V is purified by vacuum distillation. Compound VI is purified by column chromatography on silica gel (with chloroform as eluent).

Complex of N-(4-oxobutyl)phenylthioacetamide and Oxalic Acid (VII). A mixture of 0.19 g (0.65 mmole) of N-(4,4-diethoxybutyl-2)phenylthioacetamide IV and 1 ml of saturated oxalic acid solution is stirred for 2 h at room temperature. The precipitated white crystals are filtered off, washed with a small amount of water, then ether, and dried in a vacuum. Compound VII is obtained in an amount of 0.176 g (87%).

Diethyl Acetal of N-methyl-3-aminobutanal (VIII). To a suspension of 2.51 g (66.2 mmole) of lithium aluminum hydride in 50 ml of absolute ether is added dropwise with stirring and boiling a solution of 6.64 g (32.7 mmole) of diethyl acetal of 3-isothiocyanatobutanal II in 30 ml of absolute ether. The reaction mixture is stirred while kept boiling for 5.5 h, then washed with 5 ml of water, 10 ml of a 15% KOH solution, and once again with 10 ml of water. The organic layer is separated, and the combined wash waters are extracted with chloroform (3 × 15 ml). The combined organic extract is dried with anhydrous $MgSO_4$, the solvent is evaporated off, and the residue is distilled in a vacuum. Compound VIII, n_D^{20} 1.4350, is obtained in an amount of 3.72 g (65%).

6-Methyl-3-phenyl-5,6-dihydropyridine-2(1H)-thione (IX). To a solution of sodium methoxide, prepared from 50 mg of sodium and 1 ml of absolute methanol, is added a solution of 44 mg (0.014 mmole) of compound VII in 0.5 ml of absolute methanol. The reaction mixture is stirred in a nitrogen atmosphere for 5 h. The solvent is then evaporated off, and the residue is recrystallized from CCl_4. Compound IX is obtained in an amount of 21 mg (73%).

This work was financially supported by the Russian Fund for Basic Research (project code 97-03-33119a).

REFERENCES

1. A. V. Peretokin, A. D. Shutalev, V. V. Mergenova, A. M. Chupin, L. A. Ignatova, Yu. F. Malina, and B. V. Unkovskii, Zh. Org. Khim., **51**, 1004 (1985).
2. J. Bernat, L. Kniezo, D. Petercakova, J. Imrich, and P. Kutschy, Z. Chem., **28**, 141 (1988).
3. J. Burkhardt, Chem. Ber., **103**, 1589 (1970).
4. L. A. Ignatova, Yu. E. Kazantsev, and B. V. Unkovskii, Zh. Org. Khim., **5**, 1792 (1969).
5. USSR Inventor's Certificate 1,165,678; A. V. Peretokin, T. D. Sokolova, A. S. Fisyuk, Yu. F. Malina, and B. V. Unkovskii, Byull. Izobret., No. 25, (1985).
6. USSR Inventor's Certificate 64,393; I. P. Boiko, Yu. F. Malina, A. V. Peretokin, B. V. Unkovskii, and A. B. Khasirdzhev, Byull. Izobret., No. 3 (1979).
7. USSR Inventor's Certificate 423,796; A. B. Khasirdzhev, N. F. Korolenok, and B. V. Unkovskii, Byull. Izobret., No. 4 (1974).
8. USSR Inventor's Certificate 1,168,558; A. V. Peretokin and B. V. Unkovskii, Byull. Izobret., No. 27 (1985).
9. A. S. Fisyuk, A. S. Moskovkin, I. V. Miroshnichenko, M. Ya. Botnikov, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., No. 7, 985 (1992).
10. A. S. Fisyuk, A. V. Peretokin, E. A. Ryzhova, and I. P. Boiko, Khim. Geterotsikl. Soedin., No. 6, 850 (1996).
11. J. E. Jansen and R. A. Mathes, J. Am. Chem. Soc., **77**, 5431 (1955).
12. B. V. Unkovskii, L. A. Ignatova, M. M. Donskaya, and M. G. Zaitseva, Organic Synthesis Problems: Collection of Zh. O. Kh. (1965), p. 202.
13. R. Neidlein and H.-G. Hege, Chemiker Ztg., **98**, 513 (1974).
14. G. Zigeuner, W.-B. Lintschinger, A. Fuchsgruber, and K. Kollmann, Monatsch. Chem., **107**, 155 (1976).
15. B. V. Unkovskii, L. N. Knyaz'kova, and T. D. Sokolova, Third Regional Conference of the Republics of Central Asia and Kazakhstan on Chemical Reagents: Abstracts of papers. Vol. 1, Pt. 1, Tashkent (1990), p. 22.
16. A. S. Fissyuk, M. A. Vorontsova, and D. V. Temnikov, Tetrah. Lett., **37**, 5203 (1996).
17. L. A. Ignatova, A. D. Shutalev, B. V. Unkovskii, N. G. Sinilova, and A. P. Duplishcheva, Khim.-Farm. Zh., No. 12, 1447 (1985).
18. A. Wohl, Ber., **34**, 1914 (1901).
19. G. Budzikevich, C. Djerassi, and D. Williams, Interpretation of Mass Spectra of Organic Compounds [Russian translation], Mir, Moscow (1966), pp. 70, 145.