Synthesis of carbamoylamidoximes

V. N. Yarovenko, S. A. Kosarev, I. V. Zavarzin, and M. M. Krayushkin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: yarov@ioc.ac.ru

A convenient procedure was developed for the synthesis of carbamoylamidoximes by the reaction of *N*(*S*)-substituted monothiooxamides with hydroxylamine hydrochloride in pyridine.

Key words: monothiooxamides, amidoximes, hydroxylamine.

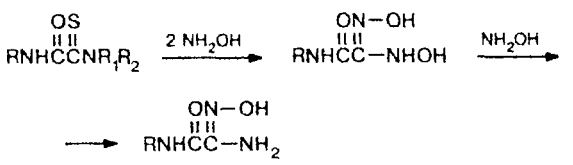
Amidoximes are widely used in the synthesis of complex-forming agents,[1] drugs,[2] and pesticides.[3]

The properties of a wide range of amidoximes have been studied.[4] However, the synthetic potential of the amidoxime fragment directly bonded to the amide group remains unknown primarily because of the absence of a convenient procedure for the preparation of carbamoylamidoximes. At the same time, the latter may be of great interest in the design of complex-forming agents and various amide-containing heterocyclic structures, such as 1,2,4-oxadiazolyl-3-carboxamides, which have been studied as herbicides in recent years.[5]

In this work, we suggest a convenient procedure for the synthesis of carbamoylamidoximes by the reaction of readily available *N*(*S*)-substituted monothiooxamides[6] with hydroxylamine.

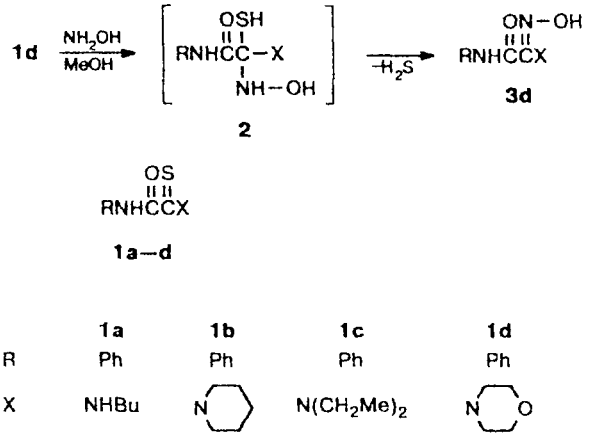
It is known[7] that thioamides react with two molecules of amines or hydrazines to form the corresponding amidines or amidrazones. We suggested that monothiooxamides containing the electron-withdrawing amide group can add two molecules of hydroxylamine. Taking into account that hydroxylamine exhibits reducing properties and can convert *N*-substituted hydroxylamines into amines,[8] it was expected that the use of an excess of hydroxylamine would lead to the formation of the corresponding carbamoylamidoximes (Scheme 1).

Scheme 1



It was found that monothiooxamides **1a—d** reacted with hydroxylamine in methanol even at room temperature (unlike thioamides, which, according to the literature data,[9] react with hydroxylamine only upon prolonged heating). However, when we carried out the reaction at room temperature or upon boiling in methanol, we failed to isolate carbamoylamidoximes, except for only a small amount of *N*-substituted amidoxime **3d**. Apparently, the reaction ceased at the stage of addition of hydroxylamine to the thioamide fragment to form unstable intermediates **2** (Scheme 2).

Scheme 2

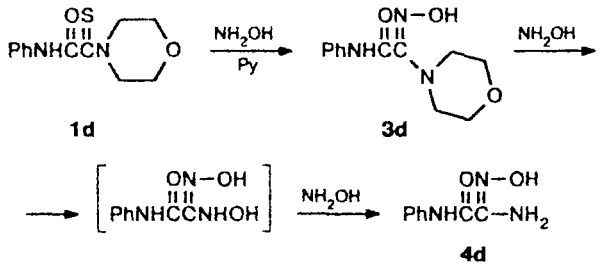


In this connection, we studied the effect of additives that can bind hydrogen sulfide and thus favor the formation of amidoxime. Using compound **1d** as an example, we have established that the reaction in methanol in the presence of triethylamine (or in triethylamine by itself) afforded a mixture of water-soluble compounds, which are apparently products of alkylation of triethylamine with compound **2**. We succeeded in performing the reaction with hydroxylamine in less basic pyridine. After boiling in pyridine for 45 min, the corresponding unsubstituted amidoxime **4d** was formed in 90% yield. The reaction proceeded trough formation of substituted amidoxime **3d**. When the reaction was carried out at room temperature, we succeeded in isolating the latter in 68% yield (Scheme 3).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 10, pp. 2002—2006, October, 1998

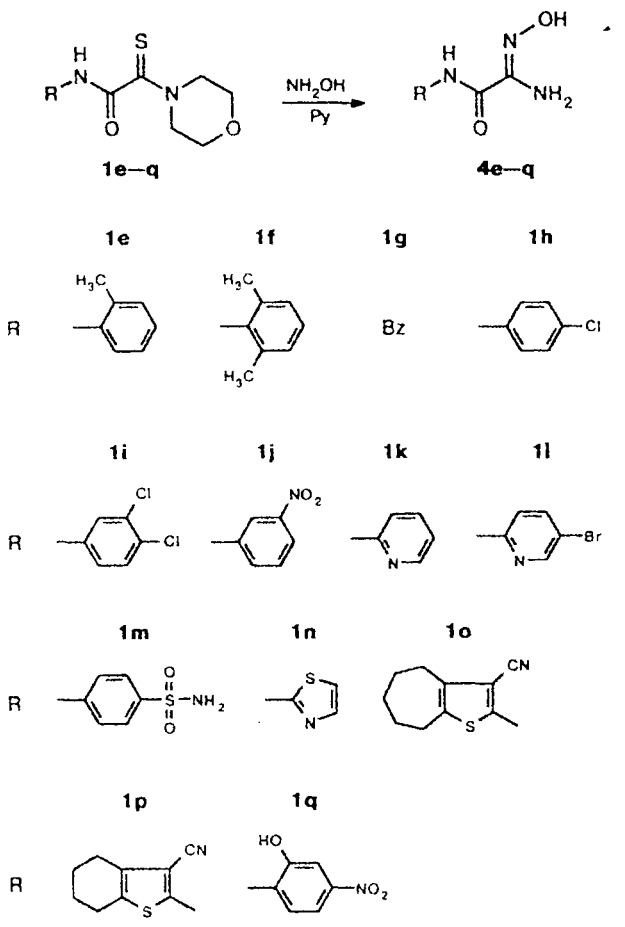
1066-5285/98/4710-1947 $20.00

Scheme 3



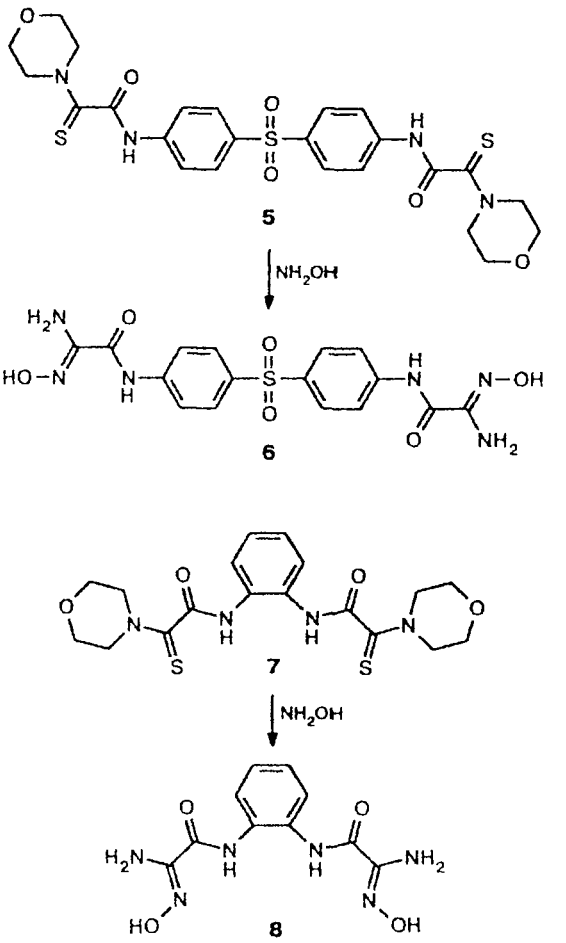
The suggested method is a general procedure, which made it possible to prepare various carbamoylamidoximes **4e—q** in good yields (Scheme 4). It is advantageous to use *N*(*S*)-morpholine derivatives, which can be readily prepared from the corresponding chloroacetamides,[6] as starting monothiooxamides. The synthesis of unsubstituted amidoximes starting from *N*(*S*)-substituted thioamides has not been reported previously.

Scheme 4

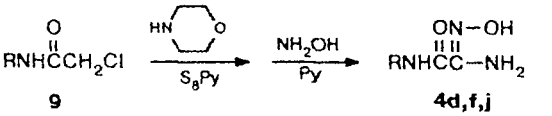


The reactions of hydroxylamine with compounds containing two monothiooxamide functional groups afforded bis-amidoximes (Scheme 5).

Scheme 5



We have also demonstrated that carbamoylamidoximes can be synthesized in rather high yields according to a one-pot procedure by the reaction of the corresponding chloroacetamide with elemental sulfur and amine in pyridine followed by treatment of the reaction mixture with hydroxylamine hydrochloride without isolation of intermediate monothiooxamide that formed.



Therefore, we suggested a convenient procedure for the synthesis of carbamoylamidoximes from available compounds.

Experimental

The IR spectra were obtained on a Specord IR-80 spectrophotometer as KBr pellets. The ^{1}H NMR spectra were recorded on Bruker WM-200 (200 MHz) and Bruker WM-250 (250 MHz) instruments in DMSO-d_6 relative to HMDS. The mass spectra were recorded on a Varian MAT CH-6 instrument with direct introduction of the sample into the ion source; the energy of ionizing electrons was 70 eV; the accelerating voltage was 1.75 kV. The melting points were measured on a Boetius table and were not corrected. All reaction mixtures were analyzed and the purities of the resulting compounds were monitored by TLC on Silufol UV 254 plates using an EtOAc—hexane mixture (1 : 1 by volume) as the eluent.

Reactions of *N(O)*-phenylthiooxamides with hydroxylamine

Preparation of the *N*-substituted amidoxime *N*(1)-phenyl-2-morpholino-2-hydroxyiminoacetamide (3d). A solution of NH_2OH in methanol (5 mL), which was prepared from $NH_2OH \cdot HCl$ (0.2 g, 2.8 mmol) and KOH (0.11 g, 2 mmol) and filtered, was added to a solution of *N*(*S*)-morpholino-*N*(*O*)-phenylthiooxamide **1d** (0.10 g, 0.4 mmol) in methanol (9 mL) and DMF (1 mL). After 12 h (control by TLC), the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was dried over $MgSO_4$. The solvent was removed on a rotary evaporator. The residue was recrystallized from a 1 : 1 ethanol—water mixture. Compound **3d** was isolated in a yield of 0.06 g (68%), m.p. 139—141 °C. Found (%): C, 57.80; H, 6.00; N, 16.90. $C_{12}H_{15}N_3O_2$. Calculated (%): C, 57.83; H, 6.02; N, 16.87. ^{1}H NMR, δ: 3.35 (m, 4 H, $-CH_2-$); 3.65 (m, 4 H, $-CH_2-$); 7.05 (t, 1 H, H arom.); 7.30 (t, 2 H, H arom.); 7.65 (d, 2 H, H arom.); 10.15 (s, 1 H, NH); 10.25 (s, 1 H, OH). MS, *m/z*: 249 $[M]^+$.

Preparation of *N*(2)-unsubstituted amidoximes (general procedure). $NH_2OH \cdot HCl$ (25 mmol) was added to a solution of thiooxamide (5 mmol) in pyridine (5 mL). The reaction mixture was refluxed for 45 min (control by TLC) and cooled to 20 °C. Then water (50 mL) was added. After 12 h, the precipitate that formed was filtered off, washed with water, and

Table 1. Characteristics of compounds **4d—q**, **6**, and **8**

Compound	M	M.p. /°C	Yield (%)	Found / Calculated (%)			Molecular formula
				C	H	N	
4d	179	147—149	90	53.36 53.60	4.90 5.00	23.51 23.50	$C_8H_9N_3O_2$
4e	193	149—151	83	55.75 55.95	5.70 5.69	21.90 21.76	$C_9H_{11}N_3O_2$
4f	207	189—191	75	57.20 57.97	6.10 6.28	20.40 20.28	$C_{10}H_{13}N_3O_2$
4g	193	124—126	80	55.51 55.96	5.50 5.69	21.79 21.76	$C_9H_{11}N_3O_2$
4h[a]	213.6	154—156	87	43.95 44.94	3.55 3.75	20.33 19.67	$C_8H_8ClN_3O_2$
4i[b]	248	139—142	96	38.73 38.74	2.75 2.84	17.30 16.94	$C_8H_7Cl_2N_3O_2$
4j	224	179—181	45	41.95 42.86	3.45 3.57	25.35 25.00	$C_8H_8N_4O_4$
4k	180	171—172	83	46.85 46.67	4.30 4.48	31.00 31.10	$C_7H_8N_4O_2$
4l[c]	259	215—217	94	32.20 32.46	2.68 2.72	21.35 21.63	$C_7H_7BrN_4O_2$
4m	258	223—225	70	37.10 37.21	3.75 3.88	21.50 21.71	$C_8H_{10}N_4O_4S$
4n	186	229—231	59	32.71 32.26	3.30 3.23	29.90 30.10	$C_5H_6N_4O_2S$
4o	278	224—226	76	51.50 51.79	4.97 5.04	21.20 20.14	$C_{12}H_{14}N_4O_2S$
4p	264	219—221	58	50.35 50.00	4.75 4.55	21.05 21.21	$C_{11}H_{12}N_4O_2S$
4q	240	232—233	86	40.15 40.00	3.40 3.33	23.10 23.33	$C_8H_8N_4O_5$
6	420	250—252	77	45.51 45.71	3.93 3.81	20.10 20.00	$C_{16}H_{16}N_6O_6S$
8	280	209—210	30	42.55 42.86	4.40 4.29	30.15 30.00	$C_{10}H_{12}N_6O_4$

[a] Content of Cl (%): found, 16.12; calculated, 16.59. [b] Content of Cl (%): found, 28.19; calculated, 28.58. [c] Content of Br (%): found, 31.10; calculated, 30.85.

Table 2. Spectral characteristics of carbamoylamidoximes **4d—q**, **6**, and **8**

Compound	IR, ν/cm^{-1}				^{1}H NMR, δ				Mass spectrum, *m/z* (I_{rel} (%))
	OH	NH_2	C=O C=N	Other signals	NH (s)	OH (s)	NH_2 (s)	Other signals	
4d	3500	3390 ν_{as} 3320 ν_s 1600 δ	1650	1520, 1440, 1370, 1300, 1240, 1100, 1020, 950, 920	9.50	9.90	5.70	7.10 (t, 1 H, H arom.); 7.30 (t, 2 H, H arom.); 7.70 (d, 2 H, H arom.)	179 $[M]^+$ (60), 162 (52), 144 (10), 132 (12), 119 (11), 104 (8)
4e	3500	3400 ν_{as} 3320 ν_s	1640	1520, 1410, 1360, 1310, 1220, 1090, 1050, 990	9.20	9.90	5.80	2.20 (s, 3 H, CH_3); 7.10—7.30 (m, 3 H, H arom.); 7.65 (d, 1 H, H arom.)	
4f	3500	3400 ν_{as} 3310 ν_s	1640	1510,1400, 1350, 1300, 1210, 1090, 1040, 1000	9.20	9.90	5.65	2.15 (s, 6 H, $(CH_3)_2$); 7.10 (s, 3 H, H arom.)	207 $[M]^+$ (27), 190 (39), 175 (50), 161 (5), 146 (21), 132 (10), 120 (18), 105 (13)
4g	3480	3350 ν_{as} 3310 ν_s	1660	1540, 1430, 1390, 1240, 1100, 1000	8.35	9.80	5.60	4.30 (d, 2 H, $-CH_2-$); 7.30 (m, 5 H, H arom.)	193 $[M]^+$ (2), 176 (58), 159 (3), 148 (5), 132 (27), 106 (54)
4h	3420	3360 1600 δ	1770 1660	1540,1500, 1400, 1100, 980	9.75	10.00	5.70	7.35 (d, 2 H, H arom.); 7.75 (d, 2 H, H arom.)	213 $[M]^+$ (29), 196 (10), 178 (4), 153 (5), 138 (2), 127 (15), 111 (4)
4i	3500	3380 1590 δ	1710 1660	1590, 1530, 1480, 1370, 1300, 1140, 1030, 940	10.00	10.10	5.80	7.55 (d, 1 H, H arom.); 7.75 (d, 1 H, H arom.); 8.10 (s, 1 H, H arom.)	247 $[M]^+$ (23), 232 (10), 212 (4), 187 (10), 161 (18), 145 (5), 124 (13), 109 (8)
4j	3500	3370 ν_{as} 3340 ν_s	1690 1660	1520, 1440, 1350, 1280, 1250, 1100, 970, 920	10.10	10.20	5.80	7.60 (t, 1 H, H arom.); 7.90 (d, 1 H, H arom.); 8.10 (d, 1 H, H arom.); 8.70 (s, 1 H, H arom.)	224 $[M]^+$ (100), 207 (44), 194 (5), 177 (40), 164 (50), 149 (26), 138 (35), 122 (10), 118 (55), 106 (30)
4k	3480	3350	1700 1650	1590, 1520, 1480, 1370, 1300, 1140, 1030, 940	9.25	10.30*	5.90	7.25 (t, 1 H, H arom.); 7.80 (t, 1 H, H arom.); 8.05 (d, 1 H, H arom.); 8.45 (d, 1 H, H arom.)	180 $[M]^+$ (24), 149 (100), 121 (57), 105 (4), 94 (20)
4l	3480	3350	1700 1650	2890, 1570, 1530, 1480, 1380, 1300, 1100, 1020, 980	9.40	10.40	5.90	8.05 (m, 2 H, H arom.); 8.45 (s, 1 H, H arom.);	259/260 $[M]^+$ (20), 229 (100), 199 (54), 183 (4), 172 (20), 156 (39), 145 (17), 129 (2), 119 (16), 106 (2)
4m	3430	3390 ν_{as} 3340 ν_s 1590 δ	1690 1660	1520, 1410, 1400, 1360, 1300, 1160, 1100, 950	9.90	10.05	5.80*	7.20 (s, 2 H, NH_2); 7.75 (d, 2 H, H arom.); 7.90 (d, 2 H, H arom.)	258 $[M]^+$ (90), 241 (62), 224 (9), 211 (10), 199 (20), 182 (38), 161 (30), 147 (29), 134 (11), 119 (20), 107 (20)
4n					10.40	11.30	5.90	7.25 (d, 1 H, —CH—); 7.50 (d, 1 H, —CH—)	186 $[M]^+$ (48), 171 (2), 155 (28), 127 (100), 111 (2), 100 (32)
4o	3480	3350	1700	1560, 1540, 1470, 1360, 1290, 1200, 1100, 980	10.45 2H,NH+OH		5.90	1.60 (m, 4 H, $-CH_2-$) 1.75 (m, 2 H, $-CH_2-$); 2.65 (m, 4 H, $-CH_2-$)	278 $[M]^+$ (22), 261 (9), 236 (2), 219 (25), 203 (2), 192 (10), 176 (15), 164 (20), 150 (10), 138 (15), 122 (9)
4p	3490	3340		2940, 2320, 1550, 1460, 1370, 1330, 1290, 1280, 1250, 1100	10.45 2H,NH+OH		5.95	1.35 (s, 6 H, $-CH_2-$); 2.65 (s, 4 H, $-CH_2-$)	264 $[M]^+$ (11), 248 (3), 237 (4), 220 (8), 205 (7), 176 (10), 160 (2), 149 (11), 128 (2), 115 (2)
4q	3480	3350 1590	1700	1550, 1500, 1430, 1360, 1280, 1200, 1130, 1095, 980	10.40	11.30	5.90*	7.65 (s, 1 H, H arom.); 7.75 (m, 1 H, H arom.); 8.40 (d, 1 H, H arom.); 9.50 (s, 1 H, —OH)	240 $[M]^+$ (20), 223 (10), 208 (30), 195 (4), 179 (12), 164 (6), 154 (12), 124 (10), 107 (10)
6	3480	3330		1590, 1520, 1400, 1370, 1305, 1160, 1105, 970	10.15 4H,NH+OH		5.80 4 H	7.85 (d, 4 H, H arom.); 7.95 (d, 4 H, H arom.);	420 $[M]^+$ (5), 361 (2), 334 (10), 274 (10), 242 (6), 210 (4), 182 (3), 134 (2), 108 (20)
8	3460	3320 ν_{as} 3260 ν_s 1600 δ	1650	2920, 1550, 1520, 1455, 1360, 1100, 970	9.40	10.10	5.70 4 H	7.20 (m, 2 H, H arom.); 7.65 (m, 2 H, H arom.)	280 $[M]^+$ (20), 248 (8), 221 (10), 188 (9), 177 (98), 161 (32), 147 (15), 134 (70), 124 (20), 106 (33)

* Br.s.

dried. The precipitate was recrystallized from a 1 : 1.5 ethanol—water mixture.

The data of elemental analysis, the yields, and the spectral characteristics of compounds **4d—q**, **6**, and **8** are given in Tables 1 and 2.

Preparation of carbamoylamidoximes without isolation of intermediate thiooxamide (general procedure)

A solution containing sulfur (0.20 g, 6 mmol), morpholine (0.90 mL, 0.90 g, 10 mmol), and pyridine (5.00 mL) was stirred for 30 min until a red-orange color appeared. Then the corresponding chloroacetamide (1 mmol) was added with stirring. After 30 min (control by TLC), the solution was filtered off from unconsumed sulfur. The filter was washed with pyridine (2 mL), and $NH_2OH \cdot HCl$ (0.40 g, 6 mmol) was added. The reaction mixture was refluxed for 45 min (control by TLC). Then water (50 mL) was added. After 12 h, the precipitate that formed was filtered off. The filtrate was extracted with EtOAc (3×30 mL). The organic layer was dried over $MgSO_4$ and evaporated on a rotary evaporator. The combined precipitates were recrystallized from a 1 : 1.5 ethanol—water mixture.

***N*(1)-Phenyl-2-amino-2-hydroxyiminoacetamide (4d)** (from *N*-phenyl-2-chloroacetamide **9d**). The yield was 0.09 g (50%), m.p. 146—149 °C. The ^1H NMR and mass spectra coincide with the corresponding characteristics of sample **4d**, which was prepared from monothiooxamide **1d** according to the above-described procedure.

***N*(1)-(3-Nitrophenyl)-2-amino-2-hydroxyiminoacetamide (4i)** (from *N*-(3-nitrophenyl)-2-chloroacetamide **9i**). The yield was 0.11 g (47%), m.p. 179—181 °C. The ^1H NMR and mass spectra coincide with the spectra of sample **4i**, which was prepared from monothiooxamide **1i** according to the above-described procedure.

***N*(1)-(2,6-Dimethyl)phenyl-2-amino-2-hydroxyiminoacetamide (4f)** (from *N*-(2,6-dimethylphenyl)-2-chloroacetamide **9f**). The yield was 0.11 g (53%), m.p. 189—191 °C. The ^1H NMR and mass spectrua coincide with the spectra of sample **4f**, which was prepared from monothiooxamide **1f** according to the above-described procedure.

***N*(1)-[4-(Aminosulfonyl)phenyl]-2-amino-2-hydroxyiminoacetamide (4m)** (from *N*-[4-(aminosulfonyl)phenyl]-2-chloroacetamide **9m**). The yield was 0.18 g (68%), m.p. 223—225 °C. The ^1H NMR and mass spectra coincide with the spectra of sample **4m**, which was prepared from monothiooxamide **1m** according to the above-described procedure.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-33433).

References

1. K. Yamada, Y. Koide, and A. Kagota, *Nippon Kagaku Kaishi*, 1981, **11**, 1773; *Chem. Abstrs.*, 1982, **96**, 168024s.
2. BE Pat. 866163, 1978; *Chem. Abstrs.*, 1979, **90**, 103986p.
3. DE Pat. 3150984, 1983; *Chem. Abstrs.*, 1984, **99**, 122462s.
4. I. A. Poplavskaya and R. G. Kurmangalieva, *Khimiya amidoksimov* [*Chemistry of Amidoximes*], Nauka, Alma-Ata, 1988, 144 pp. (in Russian).
5. DE Pat. 4233195, 1994; *Chem. Abstrs.*, 1994, **120**, 323579m.
6. V. N. Yarovenko, I. V. Zavarzin, A. Yu. Martynkin, and M. M. Krayushkin, *18th International Symposium on the Organic Chemistry of Sulfur. Book of Abstracts*, P-106, Florence, Italy, 1998, 204.
7. K. A. Petrov and L. N. Andreev, *Usp. Khim.*, 1971, **40**, 1020 [*Russ. Chem. Rev.*, 1971, **40** (Engl. Transl.)].
8. *Organic Synthesis*, New York, 1945.
9. L. Stephenson, W. K. Warburton, and M. J. Wilson, *J. Chem. Soc.* (*C*), 1969, 5—6, 861.

Received December 10, 1997;
in revised form June 12, 1998