Reactions of monothiooxamides with *O*-methylhydroxylamine

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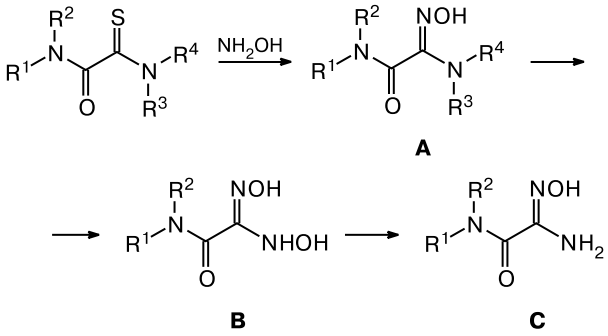
The reactions of monothiooxamides with *O*-methylhydroxylamine were studied. Depending on the substituents in monothiooxamides, the reactions result in the formation of hydroxamic acid derivatives or various *N*-methoxy derivatives of amidoximes.

Key words: monothiooxamides, *O*-methylhydroxylamine, amidoximes, amidines, *N*-methoxyhydroxamic acid.

Monothiooxamides containing amide and thioamide fragments located close to each other are of considerable utility in the synthesis of diverse compounds.[1—4] Previously, we have shown[5] that the reaction of *N*-substituted monothiooxamides with excess hydroxylamine smoothly gives the corresponding amidoximes (Scheme 1).

Scheme 1



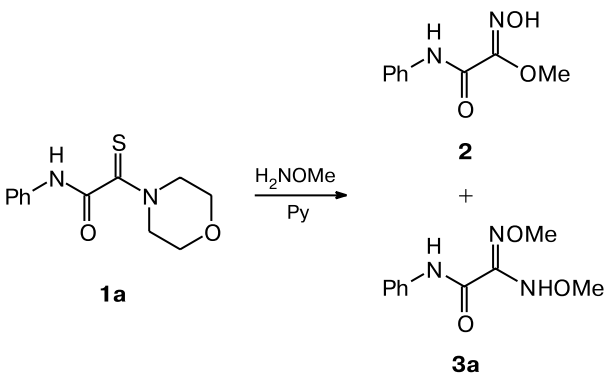
R^1, R^2 = H, Alk, Ar, Het; R^3, R^4 = H, Alk

The reaction involves the intermediate formation of amidoxime **A**, which can be isolated. Apparently, unstable intermediate **B** is formed during the reaction and is rapidly reduced with excess hydroxylamine to amidoxime **C**. The influence of the substituents R^1 and R^2 on the course of the reaction is insignificant; in all cases, amidoximes were obtained in high yields.

N-Methoxy derivatives of amidoximes are known to be of high value for the synthesis of biologically active compounds.[6,7] In this connection, we have attempted to prepare *N*-methoxy derivatives of carbamoylamidoximes by the reaction of monothiooxamides with *O*-methylhydroxylamine.

It was found that in the case of *O*-methylhydroxylamine, the reaction course is not so unambiguous as with hydroxylamine, apparently, due to the lower reducing ability of *O*-methylhydroxylamine compared to hydroxylamine. The effect of substituents in the "amide" moiety of monothiooxamide on the reaction route becomes significant. For example, instead of the expected *N*-methoxy amidoxime derivative of type **C**, *N*-phenyl-2-morpholino-2-thioxoacetamide (**1a**) is converted into a mixture of the methoxy derivative of hydroxamic acid **2** and dimethoxyamidine **3a** (Scheme 2).

Scheme 2



Meanwhile, the *p*-methoxyphenylmorpholide **1b** and 6-chloro-2,4-dimethoxyphenylmorpholide **1c** gave only amidines **3b,c** under the same conditions (Scheme 3).

Only in the case of 2,3-dimethylphenylmorpholide **1d** and benzylmorpholide **1e**, did the reaction give mono-*N*-

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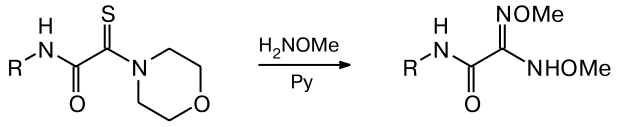
Scheme 3

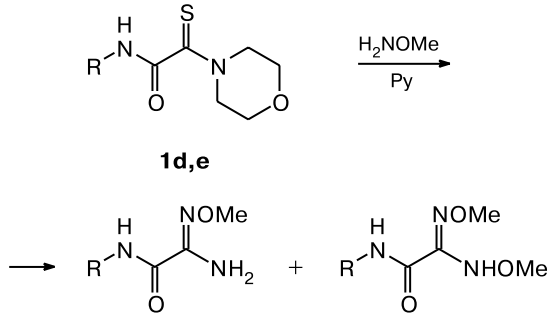


1b,c **3b,c**

R = 4-$MeOC_6H_4$ (**b**), 6-Cl-2,4-$(MeO)_2C_6H_2$ (**c**)

methoxy derivatives of amidoximes **4a,b** mixed with amidine **3d,e** (Scheme 4).

Scheme 4

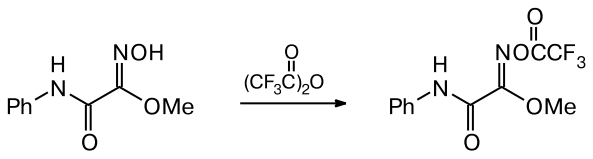


1d,e **4a,b** **3d,e**

R = 2,3-$Me_2C_6H_3$ (**1d**, **3d**, **4a**), $PhCH_2$ (**1e**, **3e**, **4b**)

We modified the hydroxy group of methylhydroxamic acid **2**, which is smoothly acylated with trifluoroacetic anhydride to give the ester **5** (Scheme 5).

Scheme 5



2 **5**

Thus, we showed that the reaction between type **1** thiooxamides and *O*-methylhydroxylamine affords *N*-methoxy-substituted carbamoylamidoximes.

Experimental

^1H NMR spectra were recorded on a Bruker AM-300 instrument in DMSO-d_6. Melting points were measured on a Boetius hot stage and were not corrected. Mass spectra were measured on a Kratos instrument (70 eV) with direct sample injection into the ion source. The starting monothiooxamides were prepared by a known procedure.[5] Commercial *O*-methylhydroxylamine (Aldrich) was used.

Reactions of thiooxamides 1 with *O*-methylhydroxylamine (general procedure). *O*-Methylhydroxylamine (0.42 g, 5 mmol) was added to a solution of morpholide **1** (1 mmol) in 7 mL of pyridine. The mixture was refluxed for 7 h, cooled, and diluted with water. In the case of amides **1a,c,d** the precipitate formed was filtered off, washed with 2% HCl and water, and dried in air. In other cases, the mixture obtained after dilution with water was extracted with AcOEt, the extract was washed with 2% HCl and water and dried with $MgSO_4$, and the solvent was removed. The residue was subjected to column chromatography (silica gel, AcOEt—hexane, 1 : 1) to give mixtures of compounds **2** and **3**; **4** and **3**; or compound **3** alone.

The reaction of thiooxamide **1a** gave compounds **2** and **3a**.

***N*-Phenyl-2-hydroxyimino-2-methoxyacetamide (2).** Yield 15%, m.p. 143—145 °C (EtOH). Found (%): C, 55.63; H, 5.19; N, 14.51. $C_9H_{10}N_2O_3$. Calculated (%): C, 55.69; H, 5.15; N, 14.43. ^1H NMR, δ: 3.10 (s, 3 H, Me); 7.17 (m, 1 H, H arom.); 7.38 (m, 2 H, H arom.); 7.75 (d, 2 H, H arom., J = 7.9 Hz); 10.35 (s, 1 H, OH); 11.00 (br.s, 1 H, NH). MS, *m/z*: 194 $[M]^+$.

***N*-Phenyl-2-methoxyamino-2-(methoxyimino)acetamide (3a).** Yield 30%, m.p. 74—76 °C (EtOH). Found (%): C, 53.96; H, 5.59; N, 18.51. $C_{10}H_{13}N_3O_3$. Calculated (%): C, 53.76; H, 5.82; N, 18.82. ^1H NMR, δ: 3.82, 3.98 (both s, 3 H each, Me); 7.15 (m, 1 H, H arom.); 7.38 (m, 2 H, H arom.); 7.58 (d, 2 H, H arom., J = 7.9 Hz); 8.05 (s, 1 H, NH); 8.37 (br.s, 1 H, NH). MS, *m/z*: 223 $[M]^+$.

The reactions of thiooxamides **1b** and **1c** gave compounds **3b** and **3c**, respectively.

***N*-(4-Methoxyphenyl)-2-methoxyamino-2-(methoxyimino)acetamide (3b).** Yield 47.2%, m.p. 96—98 °C (EtOH). Found (%): C, 52.21; H, 6.09; N, 16.45. $C_{11}H_{15}N_3O_4$. Calculated (%): C, 52.17; H, 5.97; N, 16.59. ^1H NMR, δ: 3.60, 3.70, 3.80 (all s, 3 H each, Me); 6.90, 7.60 (both d, 2 H each, H arom., J = 8.9 Hz); 9.61, 10.28 (both s, 1 H each, NH). MS, *m/z*: 253 $[M]^+$.

***N*-(6-Chloro-2,4-dimethoxyphenyl)-2-methoxyamino-2-(methoxyimino)acetamide (3c).** Yield 44%, m.p. 123—125 °C (EtOH). Found (%): C, 45.39; H, 5.11; N, 13.19. $C_{12}H_{16}ClN_3O_5$. Calculated (%): C, 45.36; H, 5.08; N, 13.22. ^1H NMR, δ: 3.61, 3.80 (both s, 3 H each, Me); 3.92 (s, 6 H, Me); 6.90, 7.90 (both s, 1 H each, H arom.); 9.18, 9.50 (both s, 1 H each, NH). MS, *m/z*: 317 $[M]^+$.

The reaction of thiooxamide **1d** gave compounds **3d** and **4a**.

***N*-(2,3-Dimethylphenyl)-2-methoxyamino-2-(methoxyimino)acetamide (3d).** Yield 12%, m.p. 75—78 °C (EtOH). Found (%): C, 57.39; H, 6.87; N, 16.65. $C_{12}H_{17}N_3O_3$. Calculated (%): C, 57.36; H, 6.82; N, 16.72. ^1H NMR, δ: 2.20, 2.35, 3.80, 4.00 (all s, 3 H each, Me); 7.05 (d, 1 H, H arom., J = 6.9 Hz); 7.15 (t, 1 H, H arom., J = 6.9 Hz); 7.65 (d, 1 H, H arom., J = 6.9 Hz); 8.05 (s, 1 H, NH); 8.30 (br.s, 1 H, NH). MS, *m/z*: 251 $[M]^+$.

***N*-(2,3-Dimethylphenyl)-2-amino-2-(methoxyimino)acetamide (4a).** Yield 27%, m.p. 125—128 °C (EtOH). Found (%): C, 59.80; H, 6.87; N, 18.90. $C_{11}H_{15}N_3O_2$. Calculated (%): C, 59.71; H, 6.83; N, 18.99. ^1H NMR, δ: 2.10, 2.28, 3.85 (all s, 3 H each, Me); 6.02 (s, 2 H, NH_2); 7.05 (m, 2 H, H arom.); 7.30 (d, 1 H, H arom., J = 6.9 Hz); 9.30 (s, 1 H, NH). MS, *m/z*: 221 $[M]^+$.

The reaction of thiooxamide **1e** gave compounds **3e** and **4b**.

***N*-Benzyl-2-methoxyamino-2-(methoxyimino)acetamide (3e).** Yield 42%, m.p. >200 °C (dec.) (EtOH). Found (%): C, 55.72; H, 6.41; N, 17.65. $C_{11}H_{15}N_3O_3$. Calculated (%): C, 55.69; H, 6.37; N, 17.71. ^{1}H NMR, δ: 3.58, 3.75 (both s, 3 H each, Me); 4.35 (m, 2 H, CH_2); 7.30 (m, 5 H, H arom.); 8.80, 9.41 (both s, 1 H each, NH). MS, *m/z*: 206 $[M - OCH_3]^+$.

***N*-Benzyl-2-amino-2-(methoxyimino)acetamide (4b).** Yield 18.5%, m.p. 95—97 °C (EtOH). Found (%): C, 58.26; H, 6.88; N, 20.15. $C_{10}H_{13}N_3O_2$. Calculated (%): C, 57.97; H, 6.28; N, 20.29. ^{1}H NMR, δ: 3.75 (s, 3 H, Me); 4.32 (m, 2 H, CH_2); 5.90 (s, 2 H, NH_2); 7.30 (m, 5 H, H arom.); 8.40 (s, 1 H, NH). MS, *m/z*: 207 $[M]^+$.

Methyl *N*-(trifluoroacetoxy)-2-oxo-2-phenylaminoethaneimidoate (5). A solution of compound **2** (0.039 g, 0.2 mmol) in 5 mL of trifluoroacetic anhydride was kept for 18 h at 20 °C. The reaction mixture was poured into 20 mL of ice water and extracted with AcOEt. The organic layer was washed with water and dried with $MgSO_4$. The residue after removal of the solvent was recrystallized from EtOH to give 0.045 g (77%) of compound **5**, m.p. 193—195 °C (EtOH). Found (%): C, 45.49; H, 3.14; N, 9.69. $C_{11}H_9F_3N_2O_4$. Calculated (%): C, 45.53; H, 3.12; N, 9.65. ^{1}H NMR, δ: 3.40 (s, 3 H, Me); 7.40 (m, 2 H, H arom.); 7.52 (m, 3 H, H arom.). MS, *m/z*: 290 $[M]^+$.

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