Desulfurizing agent for thioamides

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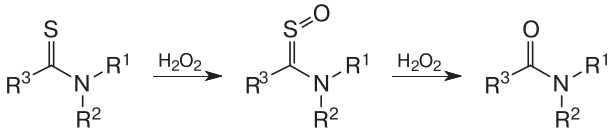
Thioamides treated with thionyl chloride in an ionic liquid were successfully converted into amides.

Key words: thioamides, ionic liquids, thionyl chloride, amides.

Thioamides are widely used in the synthesis of various compounds, including different heterocyclic structures.[1,2] Desulfurization of available thioamides is one of the convenient approaches to the preparation of amides, which are also known to be of considerable interest in organic and bioorganic chemistry.

The transformation of a thioamide group into the amide can formally be considered as a process of oxidative desulfurization, which begins with the attack on the sulfur atom of the thiocarbonyl group by an electrophilic or radical species. It is believed, for example, that in the oxidation of thioamides with hydrogen peroxide, the formation of the amide is preceded by the stage of the formation of the sulfinyl group[3] (Scheme 1).

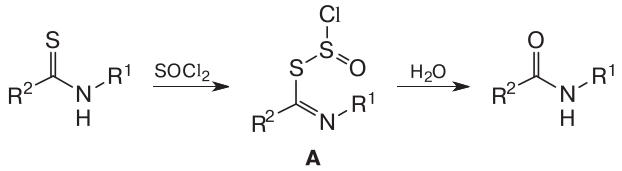
Scheme 1



Expanding the scope of reactions allowing the activation of an available thiocarbonyl group under the action of an electrophilic agent in order to convert a thioamide fragment into the amide one seems to be an attractive problem.

We assumed that thionyl chloride in an ionic liquid may be a convenient activating and, as a consequence, desulfurizing reagent. There are literature data on the reaction of thioamides with thionyl chloride in different solvents, which leads to the mixtures of amides with other products[4] or, in some cases, is inefficient.[5] In our opinion, the reaction of the thiocarbonyl group with thionyl chloride can lead to an unstable compound **A**, the hydrolysis of which results in the formation of the carbonyl group, provided that the reaction atmosphere is not inert (Scheme 2). Apparently, the process should be accelerated by electrophilic catalysts. However, we were unable to find information on the reactions of thionyl chloride in ionic liquids, which prompted us to study the reaction of this agent with thioamides.

Scheme 2



A

Earlier,[6] we have developed a convenient method for the synthesis of monothiooxamides, which consists in the reaction of α-chloroacetamides with pre-prepared solutions of elemental sulfur in amines, and showed the possibility to synthesize various compounds on their basis, including arenes and pyridines **1a—d**.[7] The desulfurization reaction was studied based on these products.

We have shown for the first time that the conversion of monothiooxamides **1a—d** to oxalic acid amides **2a—d** can be successfully accomplished within 2—3 min at room temperature by treatment with thionyl chloride in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (Scheme 3).

Note that the reaction of monothiooxamides with thionyl chloride without using an ionic liquid or in the presence of Lewis acids ($AlCl_3$, $SnCl_4$) both in solvents (CH_2Cl_2, $ClCH_2CH_2Cl$) and without them does not give oxalic acid amides, rather it leads to the formation of multicomponent mixtures.

We have demonstrated the general nature of this approach (Scheme 4) and extended it to the desulfuriza-

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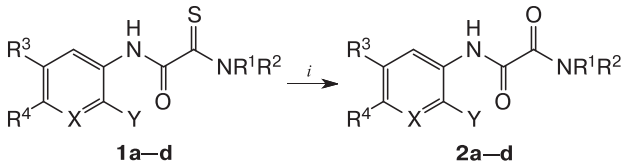
Scheme 3



1a—d **2a—d**

1, **2**	X	Y	NR^1R^2	R^3	R^4
a	CH	NO_2	Morpholin-4-yl	H	H
b	CH	NO_2	NHPh	H	Cl
c	CH	NO_2	NHPh	H	H
d	N	H	Morpholin-4-yl	NO_2	H

Reagents and conditions: *i*. $SOCl_2$, 1-butyl-3-methylimidazolium hexafluorophosphate, 2—3 min, room temperature.

tion of readily available thioamides **4a,b** (see Ref. 8) and **7** (see Ref. 9), as well as thiooxamides **10a,b** (see Ref. 10).

The method allows one to "remove" sulfur from the dithioester group of thiooxamides **13a—c** under mild conditions (see Ref. 8) to form acid thioesters **14a—c** (Scheme 5).

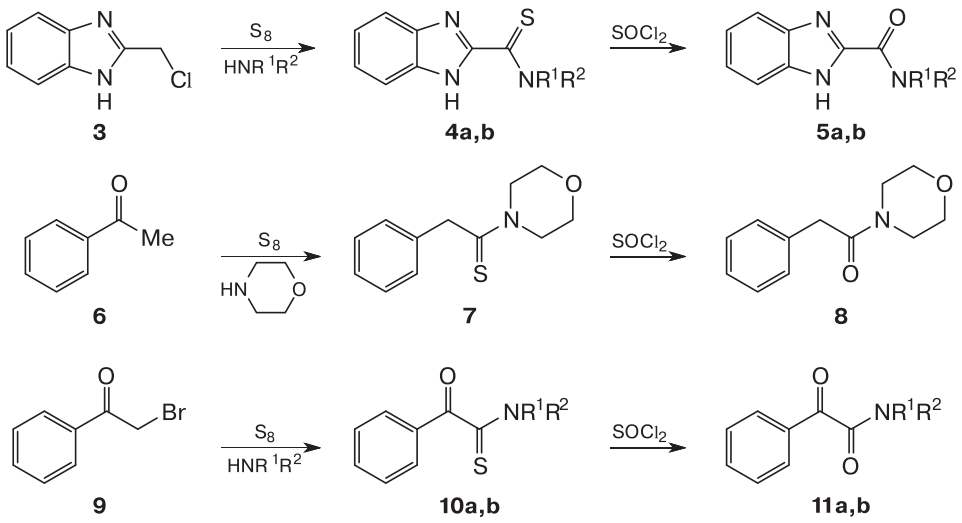
Table 1. Yields of amides **2a—d**, **5a,b**, **8**, **11a,b**, and **14a—c** obtained by the reactions of the corresponding thioamides with thionyl chloride in an ionic liquid

Compound	Yield (%)	Compound	Yield (%)
2a	70	**8**	75
2b	73	**11a**	65
2c	74	**11b**	69
2d	70	**14a**	74
5a	68	**14b**	67
5b	57	**14c**	70

The yields of amides obtained by the reactions of thioamides with thionyl chloride in the ionic liquid are summarized in Table 1.

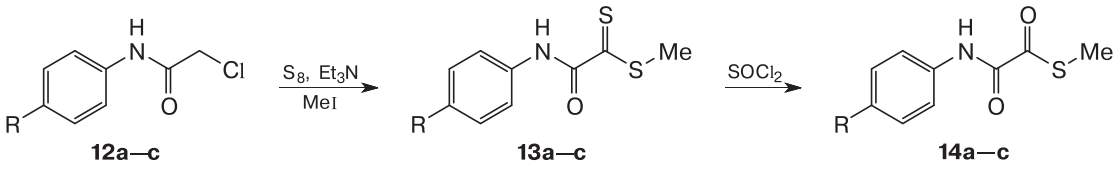
It can be suggested that the new desulfurizing agent will be of interest in organic synthesis in the cases when thioamide derivatives are more readily available than amides, provided that the latter are the target compounds.

Scheme 4



4, **5**, **10**, **11**: NR^1R^2 = morpholin-4-yl (**a**), NHPh (**b**)

Scheme 5



R = H (**a**), Cl (**b**), Br (**c**)

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer in DMSO-d_6. Mass spectra were recorded on a Varian MAT CH-6 instrument (70 eV) with direct sample injection into the radiation source, control voltage 1.75 kV. Melting points were measured on a Boetius heating stage and were not corrected. TLC on Merck Silica gel 60 F254 plates was used to analyze all reaction mixtures and control the purity of the isolated products.

Synthesis of oxoacetamides (general procedure). Thioamide (0.1 mmol) was dissolved in a minimal amount of an ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate), followed by the addition of thionyl chloride (0.15 mmol). After 2—4 min, the mixture was extracted with benzene or diethyl ether (3×5 mL), the organic layer was washed with water, the solvent was evaporated *in vacuo*. The product was purified on a chromatographic plate (eluent petroleum ether—ethyl acetate, 3 : 1).

2-Morpholin-4-yl-*N*-(2-nitrophenyl)-2-oxoacetamide (2a). White crystals, the yield was 70%, m.p. 147—149 °C. ^{1}H NMR, δ: 3.60 (d, 2 H, CH_2, J = 4.6 Hz); 3.80 (d, 4 H, 2 CH_2, J = 4.4 Hz); 3.90 (s, 2 H, CH_2); 7.45 (s, 1 H, Ar); 7.85 (s, 2 H, Ar); 8.05 (s, 1 H, Ar); 11.25 (s, 1 H, NH). MS, *m/z*: 279 $[M]^+$. Found (%): C, 51.74; H, 4.52; N, 15.21. $C_{12}H_{13}N_3O_5$. Calculated (%): C, 51.61; H, 4.69; N, 15.05.

***N*-(4-Chlorophenyl-2-nitro)-*N′*-phenylethanediamide (2b).** White crystals, the yield was 73%, m.p. 163—165 °C. ^{1}H NMR, δ: 7.40 (s, 1 H, Ar); 7.60 (s, 3 H, Ar); 7.90 (s, 2 H, Ar); 8.20 (s, 1 H, Ar); 8.35 (s, 1 H, Ar); 10.90 (s, 1 H, NH); 11.60 (s, 1 H, NH). MS, *m/z*: 319 $[M]^+$. Found (%): C, 52.74; H, 3.10; N, 13.27. $C_{14}H_{10}ClN_3O_4$. Calculated (%): C, 52.60; H, 3.15; N, 13.14.

***N*-(2-Nitrophenyl)-*N′*-phenylethanediamide (2c).** White crystals, the yield was 74%, m.p. 287—289 °C. ^{1}H NMR, δ: 7.20 (s, 1 H, Ar); 7.45 (s, 3 H, Ar); 7.85 (s, 3 H, Ar); 8.15 (s, 1 H, Ar); 8.20 (s, 1 H, Ar); 10.80 (s, 1 H, NH); 11.75 (s, 1 H, NH). MS, *m/z*: 285 $[M]^+$. Found (%): C, 58.81; H, 3.94; N, 14.62. $C_{14}H_{11}N_3O_4$. Calculated (%): C, 58.95; H, 3.89; N, 14.73.

2-Morpholin-4-yl-*N*-(5-nitropyridin-3-yl)-2-oxoacetamide (2d). White crystals, the yield was 70%, m.p. 188—190 °C. ^{1}H NMR, δ: 3.80 (s, 6 H, 3 CH_2); 4.20 (s, 2 H, CH_2); 8.00 (s, 1 H, H_{Py}); 8.35 (s, 1 H, H_{Py}); 8.55 (s, 1 H, H_{Py}); 11.80 (s, 1 H, NH). MS, *m/z*: 280 $[M]^+$. Found (%): C, 47.03; H, 4.37; N, 19.82. $C_{11}H_{12}N_4O_5$. Calculated (%): C, 47.15; H, 4.32; N, 19.99.

2-Morpholinocarbonyl-1*H*-benzimidazole (5a). White crystals, the yield was 68%, m.p. 181—183 °C (*cf.* Ref. 11: m.p. 181—182 °C). ^{1}H NMR, δ: 3.90 (s, 2 H, CH_2); 4.10 (s, 2 H, CH_2); 4.25 (s, 4 H, 2 CH_2); 7.40 (s, 2 H, Ar); 7.80 (s, 2 H, Ar); 10.90 (s, 1 H, NH). MS, *m/z*: 231 $[M]^+$.

***N*-Phenyl-1*H*-benzimidazole-2-carboxamide (5b).** White crystals, the yield was 57%, m.p. 234—235 °C (*cf.* Ref. 12: m.p. 235—236 °C). ^{1}H NMR, δ: 7.35 (s, 2 H, Ar); 7.45 (s, 1 H, Ar); 7.60 (s, 1 H, Ar); 7.80 (s, 2 H, Ar); 8.20 (s, 2 H, Ar, NH); 8.50 (s, 2 H, Ar); 10.35 (s, 1 H, NH). MS, *m/z*: 237 $[M]^+$.

4-(Phenylacetyl)morpholine (8). White crystals, the yield was 75%, m.p. 73—74 °C (*cf.* Ref. 13: m.p. 73—76 °C). ^{1}H NMR, δ: 2.30 (s, 2 H, CH_2); 3.90 (s, 2 H, CH_2); 4.10 (s, 2 H, CH_2); 4.30 (s, 4 H, 2 CH_2); 7.40 (s, 2 H, Ar); 7.80 (s, 2 H, Ar); 7.90 (s, 1 H, Ar).

1-Morpholino-2-phenylethane-1,2-dione (11a). White crystals, the yield was 65%, m.p. 59—60 °C (*cf.* Ref. 14: m.p. 58—60 °C). ^{1}H NMR, δ: 3.90 (s, 4 H, 2 CH_2); 4.30 (s, 4 H, 2 CH_2); 8.20 (s, 2 H, Ar); 8.40 (s, 2 H, Ar); 8.65 (s, 1 H, Ar). MS, *m/z*: 219 $[M]^+$.

2-Oxo-*N*,2-diphenylacetamide (11b). White crystals, the yield was 69%, m.p. 62—63 °C (*cf.* Ref. 15: m.p. 62—63 °C). ^{1}H NMR, δ: 7.35 (s, 2 H, Ar); 7.60 (s, 2 H, Ar); 7.75 (s, 1 H, Ar); 7.90 (s, 1 H, Ar); 8.30 (s, 2 H, Ar); 8.45 (s, 2 H, Ar); 10.45 (s, 1 H, NH). MS, *m/z*: 225 $[M]^+$.

***S*-Methyl 2-oxo-2-(phenylamino)ethanethioate (14a).** White crystals, the yield was 74%, m.p. 241—243 °C. ^{1}H NMR, δ: 2.35 (s, 3 H, Me); 7.60 (s, 1 H, Ar); 7.85 (s, 2 H, Ar); 8.00 (s, 1 H, Ar); 8.15 (s, 1 H, Ar); 10.70 (s, 1 H, NH). MS, *m/z*: 195 $[M]^+$. Found (%): C, 55.44; H, 4.80; N, 7.10. $C_9H_9NO_2S$. Calculated (%): C, 55.37; H, 4.65; N, 7.17.

***S*-Methyl 2-[(4-chlorophenyl)amino]-2-oxoethanethioate (14b).** White crystals, the yield was 67%, m.p. 168—170 °C. ^{1}H NMR, δ: 2.30 (s, 3 H, Me); 7.65 (s, 1 H, Ar); 7.80 (s, 2 H, Ar); 8.15 (s, 1 H, Ar); 10.60 (s, 1 H, NH). MS, *m/z*: 230 $[M]^+$. Found (%): C, 47.15; H, 3.42; Cl, 15.58; N, 6.15; S, 13.79. $C_9H_8ClNO_2S$. Calculated (%): C, 47.06; H, 3.51; Cl, 15.44; N, 6.10; S, 13.96.

***S*-Methyl 2-[(4-bromophenyl)amino]-2-oxoethanethioate (14c).** White crystals, the yield was 70%, m.p. 184—186 °C. ^{1}H NMR, δ: 2.33 (s, 3 H, Me); 7.70 (s, 1 H, Ar); 7.80 (s, 2 H, Ar); 8.20 (s, 1 H, Ar); 10.85 (s, 1 H, NH). MS, *m/z*: 274 $[M]^+$. Found (%): C, 39.36; H, 2.98; Br, 29.02; N, 5.03; S, 11.84. $C_9H_8BrNO_2S$. Calculated (%): C, 39.43; H, 2.94; Br, 29.15; N, 5.11; S, 11.70.

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