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Dichlorothiophosphoric Acid and Dichlorothiophosphate Anion as Thionating Agents in the Synthesis of Thioamides

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Abstract—A method for the thionation of carboxylic acid amides with dichlorothiophosphoric acid and dichlorothiophosphate anion, providing thioamides in high yields, was developed. The facility of the thionation and the yields of the final products were shown to depend on the nature of the starting amide. The optimal reaction conditions are reported.

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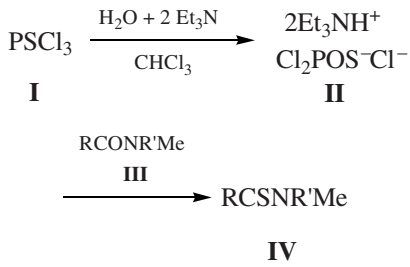
The high synthetic potential of thioamides causes their wide application in organic synthesis, especially for preparing sulfur-containing heterocycles [1–3]. Representatives of this class of compounds are applied in medicine as antitubercular remedies, such as ethionamide and propionamide.

The synthesis of thioamides is well documented. Most commonly, thioamides are prepared by the thionation of the corresponding amides with such reagents as P_2S_5 [4, 5] and Lawesson reagent [6–8]. Reactions of this type are still intensively studied. Recently such new effective thionating reagents as R_3OBF_4/NaHS [9], $(Et_2Al)_2S$ [10] and $(PhCH_2NEt_3)_2MoS_4$ [11] were offered.

The synthesis of several thioamides by the reaction of phosphorus thiochloride with amides has been described in one of the early works of Lawesson [12]. This method has not been further developed, since even upon heating for 5–15 h at 80–150°C in excess $PSCl_3$ the yields of thioamides were no higher than 20–38%.

Earlier in a short communication [13] we described a new synthetic approach to thioamides, involving the dichlorothiophosphate anion (**II**) as a thionating agent. In the present work we studied in detail some variants of application of anion **II** and its conjugate acid **VI** for the synthesis of carboxylic acid thioamides of various nature.

The first variant involves the reaction of a carboxylic acid amide with the dichlorothiophosphate anion formed by controlled hydrolysis of phosphorus thiochloride in the presence of 2/mol of triethylamine (procedure *a*).



R' = Me: R = H (**IVa**), R = Me (**IVb**), R = *t*-Bu (**IVc**); R' = Me: R = Ph (**IVd**), R = *n*-$Me_2NC_6H_4$ (**IVe**), R = *n*-$O_2C_6H_4$ (**IVf**); R' = H: R = Me (**IVg**), R = Ph (**IVh**); R' = Me: R = NMe_2 (**IVi**).

The first stage of the process, hydrolysis of $PSCl_3$, is exothermic. At the second stage, heating of the components at the solvent boiling point is required.

The yields of products **IV** are fairly high, 60–90% (see table). This method was used to synthesize secondary and tertiary thioamides **IVa–IVh** and also tetramethylthiocarbamide **IVi**. Under the reaction conditions, benzamide undergoes dehydration to form of benzonitrile (**V**) as the main product. However, attempted thionation of acetamide and *N*,*N*'-dimethylcarbamide failed, and thionated products were not found.

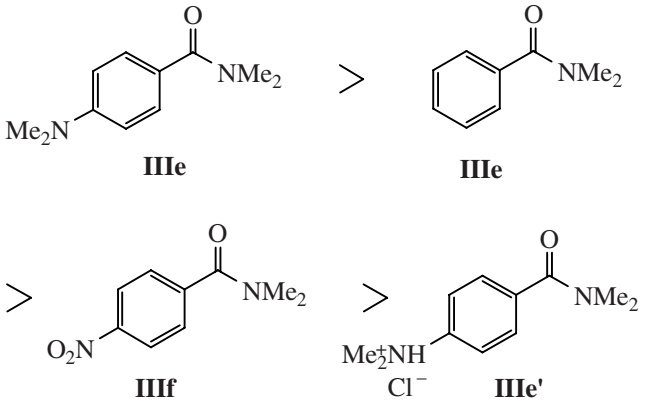
We found that increased electron density on the oxygen atom of the amido group favors thionation.

Thionation times and yields of thioamides by procedures *a–d*

Comp. no.	Procedure *a*		Procedure *b*		Procedure *c*		Procedure *d*	
	time, h	yield, %	time, h	yield, %	time, h	yield, %	time, h	yield, %
IVa	4[a] [13]	91						
IVb	16[a] [13]	93						
IVc	40	60	30	60			7	85
IVd	9	70	8	69	3	70	3	75
IVe	7	86	9[b]	81				
IVf	10	83	9	80				
IVg	36	traces					10	60
IVh	18	75					8	75
IVi	10	89						
V	15	70[c]					7	50[c]

[a] The reaction was carried out at room temperature. [b] In an acid medium, dimethylamide hydrochloride is thionated. [c] The yield of benzonitrile was determined by ^{1}H NMR spectroscopy.

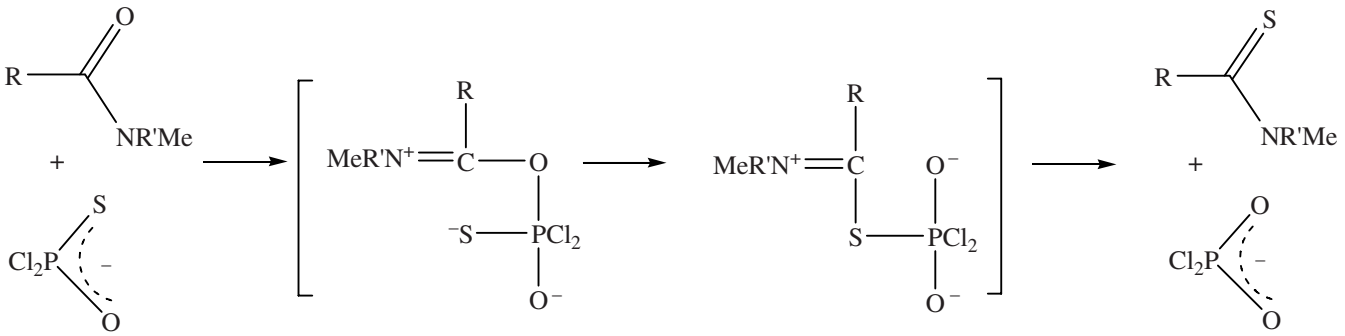
Thus, the reaction rates of *N*,*N*-dimethylbenzamides **IIId–IIIf** decrease in the following order:



Under identical reaction conditions, 69% of *N*,*N*-dimethyl-*p*-(dimethylamino)benzamide (**IIIe**), 53% of *N*,*N*-dimethylbenzamide (**IIId**), and 51% of *N*,*N*-dimethyl-*p*-nitrobenzamide are thionated within 3 h. The slowest reaction (38% within 3 h) takes place with compound **IIIe'** containing a protonated dimethylamino group.

N,*N*-Dimethyltrifluoroacetamide and *N*-methyltrifluoroacetamide, which contain strong electron-acceptor substituents at the carbonyl carbon, fail to enter the thionation reaction. On the other hand, bulky substituents at the carbonyl carbon atom do not prevent reaction, as evidenced by the thionation of *N*,*N*-dimethylpivalamide.

The above findings suggest that the most probable thionation mechanism includes nucleophilic attack by the amide oxygen atom on phosphorus with subsequent migration of the imidoyl group in the O–P–S triad and thioamide elimination (see scheme).



According to this mechanism, an increase in the electrophilicity of the phosphorus atom, for example, in going from anion **II** to its protonated form **VI** should increase reaction rate. Actually, as seen from the table, the use of dichlorothiophosphoric acid **VI** (methods *b* and *c*) allows the reaction time to be shortened considerably. Probably, in procedure *a*, too, the active species is acid **VI** formed in the reaction mixture in a small amount due to the equilibrium established at an elevated temperature:

$$\underset{\mathbf{II}}{Cl_2POS^-} + Et_3NH^+ \rightleftharpoons \underset{\mathbf{VI}}{Cl_2POSH} + Et_3N.$$

According to procedure *b*, dichlorothiophosphoric acid **VI** is generated in the reaction of $PSCl_3$ with equimolar quantities of water and triethylamine. Procedure *c* is based on acidification of anion **II** with dry HCl.

$$PSCl_3 \xrightarrow[-Et_3N\bullet HCl]{H_2O,\ Et_3N} \underset{\mathbf{VI}}{Cl_2POSH} \xleftarrow{HCl} \mathbf{II}.$$

method *b* method *c*

Direct hydrolysis with $PSCl_3$ seems to be the most convenient way to generate acid **VI**. However, in the absence of a base, the reaction with water scarcely proceeds even on prolonged boiling. We found that the reaction of $PSCl_3$ with water is sharply accelerated in the presence of amides which apparently act as nucleophilic catalysts. In this case, hydrolysis proceeds in a few minutes with self-heating of the reaction mixture. This observation formed the basis of procedure *d* in which the reaction is carried out by dissolving the starting amide, $PSCl_3$, and water in dioxane and refluxing the reaction mixture after completion of heat release.

$$\mathbf{I} + H_2O + \mathbf{III} \xrightarrow{\text{dioxane}} \mathbf{VI} + \mathbf{III} \longrightarrow \mathbf{IV}.$$

Procedure *d* allows the reaction time to shortened 3–5 times compared to procedure *a* and provides not only *N*,*N*-dialkylamides, but also *N*-monoalkylthioamides in high yields.

Our discovered thionation reaction involves accessible regents and gives readily soluble by-products, which makes the target compounds much easier to isolate. The facility of isolation of thioamides is an experimental advantage of our described methods over thionation with the Lawesson reagent, which requires chromatographic purification of the target products. Procedure *d* can be used for preparative syntheses of mono- and disubstituted thioamides of carboxylic acids.

EXPERIMENTAL

The ^{31}P and ^{1}H NMR spectra of $CHCl_3$ (^{31}P) and $CDCl_3$ (^{1}H) solutions were recorded on a Varian VXR-300 instrument (121.42 and 299.95 MHz, respectively) against external 85% H_3PO_4 (^{31}P) and internal TMS (^{1}H). The reactions were carried out in moisture-proof conditions under dry air. Dry solvents were prepared by distillation ($CHCl_3$ over P_4O_{10}, dioxane over KOH). The constants of the same compounds obtained by different methods were coincident.

Carboxylic acid thioamides *(general procedures).* *a.* Water, 0.51 g, was added dropwise to a stirred solution of 5 g (0.0295 mol) of $PSCl_3$ and 5.97 g of triethyl-amine in 12 ml of anhydrous chloroform. After a few minutes self-heating of the reaction mixture to boiling occurred. The ^{31}P NMR spectrum of the reaction mix-ture, taken after cooling, contained a signal at 43 ppm corresponding to anion **II**. Carboxylic acid amide, 0.029 mol, was added to the reaction mixture containing **II**. The mixture was heated under reflux until the thionation reaction was complete. The reaction progress was monitored by the ^{31}P NMR spectra in which the signal at 43 ppm, corresponding to anion **II**, gradually disappeared, and a signal at –6 ppm corresponding to the dichlorophosphate anion appeared. After the thionation reaction was complete, the mixture was diluted with 50 ml of water. The product was extracted with 50 ml of chloroform, and the extract was dried over sodium sulfate. The solvent was removed under a vacuum, and the residue was recrystallized from hexane.

b. Water, 0.51 g, was added dropwise to a stirred solution of 5 g of $PSCl_3$ and 2.98 g of triethylamine in 12 ml of anhydrous chloroform. The formation of the thionating agent was monitored, and the thionation reaction was carried out as described in procedure *a*.

c. A solution of anion **II** in anhydrous chloroform was prepared by method *a*. A necessary amount of dry HCl was bubbled through the solution, and then the reaction was carried out as described in procedure *a*.

d. Water, 0.51 g, was added dropwise to a stirred solution of 5 of $PSCl_3$ and 0.0295 mol of carboxylic acid amide in 12 ml of dioxane. The ^{31}P NMR spec-

trum of the reaction mixture, after completion of an exothermic reaction and cooling, contained a signal 43 at ppm, corresponding to dichlorothiphosphoric acid **VI**. The reaction mixture was heated on an oil bath at 100–110°C until the signal at 43 ppm in its ^{31}P NMR spectrum disappeared completely and then treated as described in procedure *a*.

***N*,*N*-Dimethylthiopivalamide (IVc)** was obtained by procedures *a*, *b*, and *d*. Purification was accomplished by chromatography on silica gel, eluent hexane–ethyl acetate (9:1). mp 43°C (40°C [14]). ^{1}H NMR spec-trum, δ, ppm: 1.43 s [9H, $(CH_3)C$], 3.46 s [6H, $(CH_3)_2N$]. Found, %: C 57.80; H 10.24; N 9.61; S 21.42. Calculated, %: C 57.88; H 10.41; N 9.64; S 22.07.

***N*,*N*-Dimethylthiobenzamide (IVd)** was obtained by procedures *a–d*. mp 70°C (69–70 °C [15]). ^{1}H NMR spectrum, δ, ppm: 3.17 s [3H, $(CH_3)_2N$], 3.61 s [3H, $(CH_3)_2N$], 7.33 m (5H aromatic). Found, %: C 68.28; H 6.74; N 8.66; S 18.90. Calculated, %: C 65.41;H 6.71; N 8.48; S 19.40.

***N*,*N*-Dimethyl-*p*-(dimethylamino)thiobenzamide (IVe)** was obtained by procedures *a* and *b*. mp 101°C (103°C [16]). ^{1}H NMR spectrum, δ, ppm : 2.93 s [6H, $(CH_3)_2N$], 3.18 s [3H, $(CH_3)_2N$], 3.51 s [3H, $(CH_3)_2N$], 6.70 d. (2H aromatic, $^3J_{HH}$ 9), 7.25 d (2H aromatic, $^3J_{HH}$ 9). Found, %: C 64.00; H 7.78; N 3.06; S 14.33. Calculated, %: C 63.42; H 7.74; N 13.45; S 15.39.

***N*,*N*-Dimethyl-*p*-nitrothiobenzamide (IVf)** was obtained by procedures *a* and *b*. mp 147°C (145.5–146.5°C [17]). ^{1}H NMR spectrum, δ, ppm: 3.10 s [3H, $(CH_3)_2N$], 3.55 s [3H, $(CH_3)_2N$], 7.39 d (2H arom., $^3J_{HH}$ 9), 8.16 d (2H arom., $^3J_{HH}$ 9). Found, %: C 52.82; H 4.50; N 13.05; S 14.61. Calculated, %: C 51.41; H 4.79; N 13.32; S 15.25.

***N*-Methylthioacetamide (IVg)** was obtained by procedure *d*. Purification was accomplished by chromatography on silica gel, eluent hexane–ethyl acetate (9:1). Mp 58°C (59°C [18]). ^{1}H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 3.12 d (3H, CH_3NH, $^2J_{HH}$ 5), 7.81 s.br (1H, NH). Found, %: C 40.60; H 7.78; N 15.50; S 34.86. Calculated, %: C 40.41; H 7.91; N 15.71; S 35.96.

***N*-Methylthiobenzamide (IVh)** was obtained by procedures *a* and *d*. mp 80°C (80–81° C [19]). ^{1}H NMR spectrum, δ, ppm: 3.25 d (3H, CH_3NH, $^2J_{HH}$ 5), 7.28 t (2H arom., $^3J_{HH}$ 7), 7.37 t (1H arom., $^3J_{HH}$ 7.5), 7.66 d (2H arom., $^3J_{HH}$ 7.5), 7.85 sbr (1H, NH). Found, %: C 63.25; H 5.85; N 9.46; S 21.15. Calculated, %: C 63.54; H 6.00; N 9.26; S 21.20.

Tetramethylthiocarbamide (IVi) was obtained by procedure *a*. mp 78°C (78–79°C [20]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.00 s [12H, $(CH_3)_2N$]. Found, %: C 45.45; H 9.17; N 21.20; S 24.20. Calculated, %: C 45.42; H 9.15; N 21.19; S 24.25.

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