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Dichlorophosphate Anion in the Synthesis of Thioamides

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Abstract—Phosphorus thiochloride reaction with dimethylformamide and dimethylacetamide leading to corresponding thioamides is studied. The thionylating agent is dichlorothiophosphate anion generated in the reaction course.

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Thioamides exhibit high synthetic potential providing their wide use in organic synthesis, especially for preparation of sulfur-containing heterocycles [1, 2]. Some compounds of this class are used in medicine. A known example is antituberculous remedies such as ethionamide and propionamide. In this connection there is a great number of publications in the field of the synthesis of thioamides. A preferred metod of preparation of thioamides is thionylation of the corresponding amides. Many publications deal with the use for this purpose of such traditional agents as P_2S_5 [3, 4] and the Lawesson reagent [5, 6, 7]. Wide investigation of such type reactions continues, and new thionylating agents such as R₃OBF₄/NaSH [8], $(Et_2Al)_2S$ [9], $(PhCH_2NEt_3)_2MoS_4$ [10], etc. were offered recently.

A possibility of preparation of dimethylthoformamide and some other thioamides by the reaction of phosphorus thiochloride with corresponding amides has been studied [11]. This method has not been developed further because even at heating of an amide for 5–15 h at $80-150^{\circ}$ C in PSCl₃ excess the yield of corresponding thioamide was low. For example dimethylthioformamide was obtained in 38% yield.

While studying complex formation of phosphorus chlorides with a series of nucleophilic agents we found that $PSCl_3$ reacts with dimethylformamide in chloroform even at room temperature. We studied this reaction at various reagent ratio in chloroform solution. Conversion of $PSCl_3$ was monitored by ³¹P NMR spectroscopy. It was found that at equimolar reagent ratio only a half of phosphorus thiochloride takes part in the reaction while all DMF is consumed. At 1:2 $PSCl_2:DMF$ ratio all the starting substances are consumed. Detailed investigation of the reaction permitted us to offer the following scheme for this transformation.



Most probably, in the reaction of $PSCl_3$ with DMF the dichlorothiophosphate anion **II** is generated, which then reacts with the second DMF molecule to give thioamide **IV** and dichlorophosphate anion **III**.

Subsequent reaction of the thioamide with chloroimmonium salt III leads to the salt V stable under the reaction conditions. Treating the reaction mixture with water causes hydrolysis of this salt leading to the



Dynamics of alteration of the integral intensities of signals in the ³¹P NMR spectra of $PSCl_3-CH_3CONMe_2$ reaction mixture. (1) -5.9 ppm, Cl_2POO^- ; (2) 43.9 ppm, Cl_2POS^- ; (3) 32.9 ppm, $PSCl_3$.

equimolar mixture of thioamide and amide. Hence, in the reaction with phosphorus thiochloride only a half of staring amide can be converted to thioamide. The highest dimethylthioformamide yield was 42% on the starting DMF.

The salt V was isolated pure when the reaction mixture was worked up under the anhydrous conditions. The salt is an extremely hygroscopic crystalline substance which we characterized spectroscopically and by elemental analysis. Structure of the salt V was confirmed by an independent synthesis from chloro-immonium salt III and dimethylthioformamide.

$$\mathbf{I} \xrightarrow{\mathrm{POCl}_3} \mathbf{III} \xrightarrow{\mathbf{IV}} \mathbf{V}.$$

Physical constants of compounds obtained by both the methods coinside. Thus, it is evident that in the reaction of PSCl₃ with DMF the thionylating agent is not phosphorus thiochloride but the dichlorothiophosphate anion **II** generated from it. We failed to register this anion in the reaction mixture because of its fast reaction with DMF. Analogous reaction with dimethylacetamide proceeds much slower. According to ³¹P NMR data, the first step of the reaction is accumulation of the Cl₂POS⁻ anion which then transforms completely to dichlorophosphate anion. Thus the offered scheme is confirmed by this observation. The ³¹P NMR data reflecting the reaction progress are shown in the figure.

$$2MeCONMe_{2} \xrightarrow{PSCl_{3}} Me_{2}^{+} CMe^{-}S^{-}CMe^{-}NMe_{2}$$

$$Cl_{2}POO^{-} Cl^{-}$$

$$VI \qquad VII$$

$$\xrightarrow{H_{2}O} MeCSNMe_{2} + VI.$$

$$VIII$$

To confirm unambiguously the role of dichlorothiophosphate anion as a thionylating agent we carried out its synthesis and the subsequent reaction with amide. Dichlorothiophosphate anion was generated by us by the controlled hydrolysis of $PSCl_3$ in the presence of triethylamine.

$$\begin{array}{ccc} \operatorname{PSCl}_3 + \operatorname{H}_2\operatorname{O} \xrightarrow{2\operatorname{Et}_3\operatorname{N}} & \begin{array}{c} 2\operatorname{Et}_3\operatorname{NH}^+ & \stackrel{\mathbf{I}}{\longrightarrow} \operatorname{IV}.\\ \operatorname{Cl}_2\operatorname{POS}^- & \operatorname{Cl}^- & \stackrel{\mathbf{I}}{\longrightarrow} \operatorname{IV}. \end{array}\\ & \mathbf{IX} \end{array}$$

The mixture of dichlorothiophosphate and triethylammonium chloride **IX** formed was directly used for thionylation. Reaction of **IX** with DMF and dimethylacetamide in chloroform at room temperature proceeds practically quantitatively and leads to corresponding thioamides. In this case the reagent ratio is equimolar, and the yields of thioamide exceed 90%. Hence, contrary to the reaction with PSCl₃ it is possible to achieve complete conversion of amide to thioamide.

Note that the method offered is based on the available reagents. It permits to achieve the yields close to quantitative, and is promising for wide synthetic use.

EXPERIMENTAL

 31 P and 1 H NMR spectra of CHCl₃ (31 P) and CDCl₃ (1 H) solutions were taken on a Varian VXR-300 spectrometer, operating frequences 121.42 and 299.95 MHz respectively. Chemical shifts were measured against external 85% phosphoric acid (31 P) and internal TMS (1 H). Reactions were carried out in anhydrous conditions under the flow of dry argon. The component content in the reaction mixture was evaluated from the integral intensities of corresponding signals in 31 P NMR spectra.

The dimethylthioformamide **IV** and dimethylthioacetamide **VIII** constants obtained in the course of this work agree with the published data [12, 13].

Dimethylthioformamide (IV). *a*. PSCl₃, 5 g, and anhydrous DMF, 4.2 g, were dissolved in 30 ml of anhydrous chloroform and kept at 20°C with stirring until the signal of PSCl₃ (32.9 ppm) in ³¹P NMR spectrum of reaction mixture disappeared completely. The process has completed in 5 days. The mixture obtained was diluted with 50 ml of water, dimethylthioformamide was extracted with 30 ml of chloroform, the extract was dried over sodium sulfate, and solvent was removed in a vacuum. Dimethylthioformamide containing 5% of DMF was obtained. After vacuum distillation pure dimethylthioformamide was obtained, bp 96–97°C (12 mm Hg), yield 42%.

b. To a solution of 5 g of phosphorus thiochloride and 2.9 g of triethylamine in dry chloroform 0.5 g of water was added dropwise with stirring at 20°C. The mixture obtained was left for 16 h at room temperature to complete transformation of PSCl₃ into dichlorothiophosphate anion. The ³¹P NMR spectrum δ_{p} , -43 ppm. The obtained solution of anion **X** in chloroform was treated with 2.1 g of DMF at 20°C with the protection of reaction mixture from air moisture. Resulting mixture was stirred for 4 h until the disappearance of a signal related to dichlorothiophosphate anion from the ³¹P NMR spectrum. The reaction mixture was diluted with 50 ml of water and dimethylthioformamide was extracted with 30 ml of chloroform. The extract obtained was dried over sodium sulfate, solvent was removed at reduced pressure, an the product was distilled in a vacuum. Yield 91%.

2,6-Dimethyl-4-thia-2,6-diaza-2,5-hexadiene dichlorophosphate chloride (**V**). *a*. PSCl₃, 5 g, and 4.2 g of anhydrous DMF were dissolved in 30 ml of anhydrous chloroform and kept at 20°C to complete disappearance of PSCl₃ signal (34.9 ppm) from ³¹P NMR spectrum. The reaction has completed in 5 days. Solvent was removed in a vacuum, the crystalline residue was washed with diethyl ether and dried under an oil pump vacuun. Yield of the salt **V** 6.0 g (97%). ³¹P NMR spectrum, $\delta_{\rm P}$, -5.0 ppm. ¹H NMR spectrum, δ , ppm: 3.29 s [6H, (CH₃)₂N], 8.26 s (1H, CH). Found, %: C 22.11; H 4.12; Cl 33.70; N 8.67; P 10.41; S 9.97. C₆H₁₄Cl₃N₂O₂PS. Calculated, %: C 22.83; H 4.47; Cl 33.70; N 8.87; P 9.81; S 10.16.

b. A solution of 2.1 g of phosphorus oxychloride and 1 g of DMF in 15 ml of anhydrous chloroform was kept at 20°C for 16 h to complete conversion of POCl₃ to dichlorophosphate anion, ³¹P NMR spectrum, $\delta_{\rm p}$, -6.1 ppm. The solution obtained was treated with 1.2 g of dimethylthioformamide. After 1 h formation of salt V was registered. The salt was isolated as described in the procedure *a*. Yield of the salt V 4.1 g (96%). The constants of the compounds obtained by both the methods are identical.

Hydrolysis of compound (V). Water, 30 ml, was added dropwise with stirring and cooling with ice water to 5 g of the dry salt **V**. Dimethylthioformamide formed was extracted with chloroform, the extract obtained was dried over sodium sulfate, solvent was removed in a vacuum, and the residue was distilled in a vacuum. Yield of dimethylthioformamide 42%.

Dimethylthioacetamide (VIII). *a*. Dimethylthioacetamide VIII was obtained analogously to dimethylthioformamide from PSCl₃ and dimethylacetamide according to the procedure *a*. Reaction duration 45 days, bp $105-106^{\circ}$ C (12 mm), yield 41%.

b. Dimethylthioacetamide **VIII** was obtained analogously to dimethylthioformamide according to the procedure *b* from triethylammoniun dichlorothiophosphate **IV**. Reaction completed in 16 h, yield 93%.

2,3,5,6-Tetramethyl-4-thia-2,6-diaza-2,5-hexadiene dichlorophosphate chloride (VII) was prepared analogously to the product V. ¹H NMR spectrum, δ , ppm: 2.54 s (3H, CH₃); 3.24 s [6H, (CH₃)₂N]. ³¹P NMR spectrum, $\delta_{\rm P}$, ppm: -4.9 s. Hydrolysis of salt VII gave dimethylthioacetamide in 43% yield.

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