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New Promising Methods of Synthesis of Pyridinecarbothioamides

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Abstract—New methods of synthesis of pyridinecarbothioamides from the corresponding cyanopyridines with the use of phosphorus pentasulfide as a thiontion agent were developed. The first method was based on the reaction of cyanopyridine with phosphorus pentasulfide in alcoholic ammonium solution followed by hydrolysis. The method provided the corresponding thioamides in 60–90% yield. The second procedure included the reaction of phosphorus pentasulfide with 4-cyanopyridine in aqueous ammonia solution, which led to the formation of pyridine-4-carbothioamides in quantitative yield.

Keywords: thioamides, pyridinecarbothioamide, cyanopyridine, phosphorus pentasulfide

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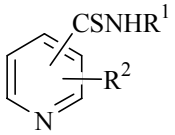
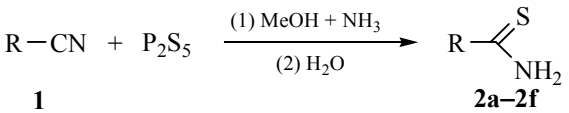
Development of thioamide synthesis procedures is of significant practical interest. These compounds find wide technical, agricalturalapplications and are used in the synthesis of heterocyclic compounds [1]. Among the biologically active thioamides the pyridinecarbothioamides exhibit a wide range of biologic action [2–5].



R^1 = H, Et, $(CH_2)_2NMe_2$, $-(CH_2)_2$-2-Py; R^2 = Pr, SH, S-$(CH_2)_2NMe_2$.

Two methods of synthesis of carbothioamides described in reviews [6–8] are the most widely known. The first one involved thionation of amides with phosphorus pentasulfide or Lawesson's reagent; the second one is the reaction of nitriles with hydrogen sulfide. Besides that few methods of nitriles conversion to thioamides with the help of such thionation reagents as thioacetamide [9], alkali metals or ammonium hydrosulfides [10, 11], $(P_4S_{10}O)^{2-}Na_2^{2+}$ [12], *O*,*O*-dialkyldithiophosphoric acids [13–16], a mixture of aluminum oxide with ammonium *O*,*O*-diethyldithiophosphate under microwave irradiation [17] have been described.

We developed a promising preparative method of synthesis of pyridinecarbothioamides **2a–2f** in 60–92% yield that included the reaction of aromatic nitriles **1a–1f** with phosphorus pentasulfide in alcoholic solution of ammonia at 30–40°C followed by hydrolysis with water (method *a*).



1 **2a–2f**

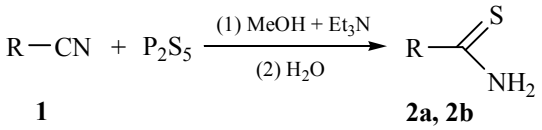
R = 4-Py (**2a**), 2-Py (**2b**), 2-Cl-3-Py (**2c**), 4-Cl-2-Py (**2d**), 6-Cl-2-Py (**2e**), (5-Cl-3-Py)CH_2 (**2f**).

The reaction of phosphorus pentasulfide with the nitrile solution was found to be exothermic; the reaction mixture solidified after the process was finished. The subsequent treatment of the crystalline mixture with water caused its complete dissolution with an intensive heating and gas evolution; after that the target pyridinethiocarbamide precipitated as crystalline species from the solution. Most probably *O*,*O*-dimethyldithiophosphoric acid ammonium salt in this case was the thionation agent [18, 19].

Further we discovered that triethylamine can be used in the reaction instead of ammonia (method *b*). The reaction proceeded under similar conditions and led to the formation of the target pyridinecarbothioamides **2a–2f** in 60–92% yield.

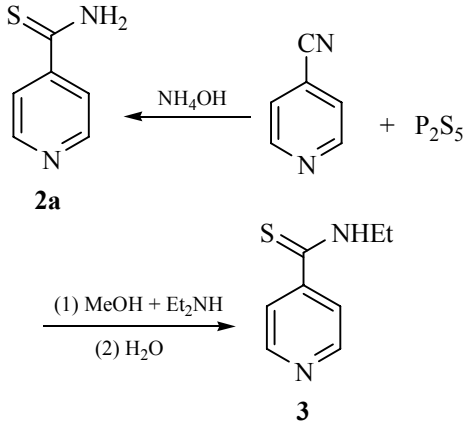
^{1}H and ^{13}C NMR spectroscopy data (DMSO-d_6) for thioamides **2a–2f**, and **3**

Comp. no.	δ_H, ppm (J, Hz)	δ_C, ppm
2a	7.68 m, 8.61 m, 9.74 s, 10.10 s	121.1, 146.7, 150.0, 198.0
2b	7.55 m, 7.94 m, 8.47 m, 8.56 m, 9.89 s, 10.03 s	124.6, 126.5, 137.5, 147.7, 151.7, 195.0
2c	7.42 m, 7.77 d.d (J 7.2, 1.4), 8.35 m, 9.83 s, 10.20 s	123.5, 137.7, 139.0, 144.0, 149.0, 198.4
2d	7.74 d.d (J 5.7, 2.4), 8.47 d (J 1.8), 8.57 d (J 5.4), 9.95 s, 10.32 s	124.3, 126.1, 143.8, 149.3, 153.5, 193.2
2e	7.71 d (J 7.2), 8.01 t (J 7.9), 8.40 d (J 7.9), 9.76 s, 10.20 s	125.0, 128.3, 140.0, 146.9, 163.6, 194.1
2f	7.74 d (J 8.4), 7.78 d (J 8.4), 8.31 s, 3.83 s, 9.47 s, 9.57 s	46.6, 123.7, 132.7, 140.0, 148.6, 150.0, 204.0
3	7.56 m, 8.56 m, 1.21 t (J 7.8), 3.67 m, 10.53 s	12.9, 41.6, 121.6, 148.4, 150.1, 194.9



1 **2a, 2b**

By an example of 4-cyanopyridine we showed that *N*-substituted thioamides can be prepared similarly using in this case diethylamine instead of triethylamine. The reaction led to the formation of *N*-ethylpyridin-4-carbothioamide **3** in 54% yield.



The reaction of 4-cyanopyridine with phosphorus pentasulfide can proceed in aqueous solution of ammonium without methanol. In this case the reaction afforded pyridine-4-carbothioamide **2a** in 98% yield.

The structure of all prepared compounds was confirmed by NMR spectroscopy data (see table).

The elaborated procedure simplified preparation of pyridinecarbothioamides and may be applied to the synthesis of various compounds of this class. The target pyridinecarbothioamides crystallized easily from the reaction mixture and almost did not contain any admixtures that significantly facilitated the process of their isolation and purification. Carrying out the reaction with aqueous ammonia did not require the use of organic solvents. The thionation reagent in all the reactions was most probably ammonium dithiophosphate.

EXPERIMENTAL

We used 2- and 4-pyridinecarbonitriles, 2-chloro-3-pyridinecarbonitrile, 6-chloro-3-pyridinecarbonitrile, and 2-chloro-4-pyridinecarbonitrile purchased from Aldrich.

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AM-360 spectrometer at 360.13, 90.58, and 145.78 MHz respectively. Tetramethylsilane was used as an internal reference for ^{1}H and ^{13}C NMR spectra; for ^{31}P NMR spectra 85% phosphoric acid was used as an external reference. The reaction progress was monitored by the means of TLC on Kieselgel 60 F_{254} (Merck) plates eluting with a mixture methylene chloride–methanol, 9 : 1.

Pyridine-4-carbothioamide (2a). *a*. Ground phosphorus pentasulfide (115 g, 0.5 mol) was added to a solution of 4-cyanopyridine (52 g, 0.5 mol) in 250 mL of 20% ammonium in methanol under vigorous stirring maintaining the reaction mixture temperature below 35–40°C. The reaction mixture was kept at room temperature for 12 h, and then 150 mL of water was added that caused dissolution of the solid and intensive exothermic gas liberation. After cooling of the reaction mixture to room temperature the precipitate was filtered off, washed with water, and dried. Yield 92% (64 g), R_f = 0.39, mp = 209°C (mp = 209–210°C [20]).

Found, %: C 52.05; H 4.29; N 20.32; S 23.34. $C_6H_6N_2S$. Calculated, %: C 52.15; H 4.38; N 20.27; S 23.20.

b. Phosphorus pentasulfide (6 g, 0.028 mol) was added to a solution of 4-cyanopyridine (3 g, 0.028 mol) and triethylamine (8 g, 0.079 mol) in 30 mL of methanol under vigorous stirring at 30–40°C. The reaction mixture was kept for 12 h at room temperature then 50 mL of water was added. The formed precipitate was filtered off and dried. Yield 58% (2.3 g).

c. Ground phosphorus pentasulfide (7 g, 0.031 mol) was added to a solution of 4-cyanopyridine (3.2 g, 0.03 mol) in 40 mL of 23% aqueous ammonia at stirring. Warming of the reaction mixture up to 70–75°C was observed. After cooling the precipitate was filtered off, washed with water, and dried. Yield 91% (3.8 g).

d. Phosphorus pentasulfide (4.8 g, 0.022 mol) was added to 25 mL of 23% aqueous ammonia. The reaction mixture warmed up to 60°C. Then 4-cyanopyridine (2.2 g, 0.02 mol) was added to the obtained solution, and then the reaction mixture was stirred at 40–50°C for 0.5 h. After cooling the precipitate was filtered off, washed with water, and dried. Yield 98% (2.7 g).

Pyridine-2-carbothioamide (2b) was prepared similarly according to method *a*. After the reaction ended, 150 mL of water was added and the mixture was heated up to 70–75°C by water bath till the gas evolution stopped. After cooling the precipitate was filtered off, washed with water, and dried. Yield 89% (61.8 g), R_f 0.45, mp 137°C (136–137°C [21]). Found, %: C 52.09; H 4.31; N 20.30; S 23.30. $C_6H_6N_2S$. Calculated, %: C 52.15; H 4.38; N 20.27; S 23.20.

2-Chloro-3-carbothioamide (2c) was prepared similarly according to method *a*. Yield 78%, R_f 0.55, mp 165°C (decomp.).

6-Chloropyridine-2-carbothioamide (2d) was prepared similarly according to method *a*. Yield 94%, mp 176°C (decomp.). Found, %: C 41.69; H 2.96; Cl 20.56; N 16.19; S 18.60. $C_6H_5ClN_2S$. Calculated, %: C 41.74; H 2.92; Cl 20.54; N 16.23; S 18.57.

4-Chloropyridine-2-carbothioamide (2e) was prepared similarly according to method *a*. After the end of reaction 150 mL of water was added and the mixture was heated at 70–75°C with the help of a water bath till the gas evolution stopped. After cooling the precipitate was filtered off, washed with water, and dried. Yield 60%, mp 180°C (decomp.). Found, %: C 41.82; H 3.05; Cl 20.29; N 16.22; S 18.62. $C_6H_5ClN_2S$. Calculated, %: C 41.74; H 2.92; Cl 20.54; N 16.23; S 18.57.

2-(Chloropyrid-2-yl)thioacetamide (2f) was prepared similarly according to method *a*. After the end of reaction 150 mL of water was added and the mixture was heated at 70–75°C with the help of a water bath till the gas evolution stopped. After cooling the precipitate was filtered off, washed with water, and dried. Yield 60%, mp 170°C (decomp.). Found, %: C 45.15; H 3.70; Cl 18.90, N 15.11; S 17.14. $C_7H_7ClN_2S$. Calculated, %: C 45.04; H 3.78; Cl 18.99; N 15.01; S 17.18.

***N*-Ethylpyridine-4-carbothioamide (3).** Phosphorus pentasulfide (36 g, 0.16 mol) was added to a solution of 4-cyanopyridine (16 g, 0.15 mol) and diethyamine (30 g) in 100 mL of methanol at stirring at 35–40°C. The reaction mixture was kept at room temperature for 12 h. Then 100 mL of water was added, and the reaction mixture was heated at 60–70°C by the water bath. After cooling the precipitate was filtered off, washed with water, and dried. Yield 54% (13.7 g), R_f 0.55, mp 102°C. Found, %: C 57.83; H 5.99; N 16.79; S 19.39. $C_8H_{10}N_2S$. Calculated, %: C 57.80; H 6.06; N 16.85; S 19.29.

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