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Synthesis of Pyridinecarbothionylaminopyridines and Conversion of Thioamide to Amide

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Pyridinecarbothionylaminopyridines as structural isomers were obtained by the reactions of 2,3-and 2-4-lutidine with aminopyridines and sulfur. Reaction of 2,6-lutidine with active methyl group anilines in the presence of sulfur gave the desired thioamides **5**. Reaction of synthesized thioamides **5** with sulfur and SiO_2 or SeO_2 gave the corresponding amide **6**. We now report conversion of thioamide to amide by using oxidizing inorganic reagent.

Key Words: Aminopyridines, Lutidines, Thioamides, Amides, Oxidizing inorganic reagent.

INTRODUCTION

Thioamides are highly reactive compounds and because of the diversity of their chemical properties, found wide application in technology, in agriculture, in medicine and not least in synthetic practice. The amide moiety is an important constituent of many biologically significant compounds and an understanding of the formation, properties and reaction of amides is future development in such areas as polypeptide and protein chemistry[1].

Compounds having an active methyl group with *para* (or *meta*)-substituted anilines in presence of sulfur according to the modified Willgerodt-Kindler reaction easily afforded to corresponding thioamides and benzothiazoles[2-7]. The latter was also formed by the oxidative cyclization of the former with potassium ferricyanate in an alkaline solution according to the modified Jacobson method[8-11].

In order to search for novel chemotherapeutical agents, we tried reactions of lutidine (s) with active methyl group and anilines or aminopyridines in the presence of sulfur. All the executed reactions gave the desired thioamides but failed to obtain benzothiazoles. In order to obtain a great quantity of benzothiazoles, we needed novel reaction conditions. When a mixture of synthesized thioamide with sulfur and SiO_2 was heated at 180 ºC, but amide not benzothiazole was obtained.

Therefore, we now report synthesis of pyridinecarbothionylaminopyridines as a structural isomer and conversion of thioamide to amide by using oxidizing inorganic reagent.

EXPERIMENTAL

The typical experimental procedure for *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene (**5a**) is as follows: A mixture of 2,6-lutidine (1.07g, 10 mmol) and 3-methylaniline (1.07 g, 10 mmol) with sulfur powder (0.4 g 12.5 mmol) was refluxed at 150 ºC for 5 h, H_2S gas was vigorously evolved. The unchanged 2,6-lutidine and 3-methylaniline were completely removed by vaccum distillation in an oil bath. The residue was refluxed with hot 3 N NaOH solution (50 mL × 3) and chloroform 100 mL. The combined extracts were carefully acidified with dil. HCl. The combined chloroform was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with *n*-hexane and ethyl acetate (50:1, v/v), to provide the *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene (**5a**) as a yellow crystalline solid (1.09 g, 45 %). mp 142-143ºC; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (s, 1H, NH), 2.42 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.08 - 8.62 (m, 7H, ph); Mass m/z (rel. intensity, %) 242 ([M]$^+$, 100), 227, 209 (84.7), 119, 92.

The typical experimental procedure for conversion of thioamide **5** to amide **6** is as follows: A mixture of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene **5a** and SiO_2 was heated at 170 ºC for 10 h. After cooling, chloroform (100 mL) was added. The reaction mixture was filtered to remove SiO_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was

purified by flash column chromatography on silica gel eluted with *n*-hexane and ethyl acetate (80:1, v/v), to provide *N*-(6'-methyl-2'-pyridinecarbonyl)-3-methylaminobe nzene **6a** (0.45 g, 20 %) and 5-methyl-2-(6'-methylpyridyl)be nzothiazole **7a** (0.31 g, 13 %) as a cyclic compound. **6a**; m.p. 90-93 ºC, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.94 - 8.12 (m, 7H, ph); Mass m/z (rel. intensity, %) 241 (100), 121, 92, 77, 65.

The typical experimental procedure for *N*-(6'-methyl-2'-pyridinecarbonyl)-3-methylaminobenzene **6a** is as follows: A mixture of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene **5a** and SeO_2 was heated at 140 ºC for 3 h. After cooling, chloroform (100 mL) was added. The reaction mixture was filtered to remove SeO_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with *n*-hexane and ethyl acetate (80:1, v/v), to provide *N*-(6'-methyl-2'-pyridinecarbonyl)-3-methylaminobenzene **6a**.

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-methylaminobenzene (5a):** Yield: 49 % R_f: 0.66 (TLC eluent; *n*-Hexane Ethyl acetate = 6 : 1, v/v) m.p.: 142-143 ºC; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 1H, NH), 2.42 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.08 - 8.62 (m, 7H, ph); Mass m/z (rel. Int, %) 242 (100), 227 (33.8), 209 (84.7), 119 (15.3), 92 (34.0), 65 (37.9) IR (KBr, ν_{max}, cm^{-1}): 1350 (C=S)

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-methylaminobenzene (5b):** Yield: 45 % R_f: 0.65 (TLC eluent; *n*-Hexane: Ethyl acetate = 6:1, v/v) m.p.: 144-145 ºC; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 1H, NH), 2.42 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.08 -8.62 (m, 7H, ph); Mass m/z (rel. Int, %) 242 (100), 227 (33.8), 209 (84.7), 119 (15.3), 92 (34.0), 65 (37.9).

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-methoxyaminobenzene (5c):** Yield: 53 % R_f: 0.63 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 140-142 ºC; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 1H, NH), 2.64 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.26- 8.59 (m, 7H, ph); Mass m/z (rel. Int, %) 258 (100), 243 (6.0), 225 (64.0), 119 (16.0), 92 (38.0), 77 (18.0), 65 (20.0).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-methoxyaminobenzene (5d):** Yield: 62 % R_f: 0.63 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 144-145 ºC; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 1H, NH), 2.63 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.00 - 8.63 (m, 7H, ph); Mass m/z (rel. Int, %) 258 (73.5), 243 (9.3), 225 (100), 140 (24.2), 119 (14.7), 92 (48.5), 77 (8.1), 65 (19.2).

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-ethoxyaminobenzene (5e):** Yield: 47 % R_f: 0.62 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 141-143 ºC; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.02 - 4.12 (q, 2H, CH_2), 6.94 - 8.63 (m, 7H, ph); Mass m/z (rel. Int, %) 272 (56.0), 239 (100), 207 (25.5), 154 (37.6), 136 (42.5), 119 (24.1), 92 (92.5), 65 (53.3).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-ethoxyaminobenzene (5f):** Yield: 57 % R_f: 0.62 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 147-148 ºC; ^{1}H NMR ($CDCl_3$) δ 1.40-1.47 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.02 - 4.13 (q, 2H, CH_2), 6.94 - 8.62 (m, 7H, ph); Mass m/z (rel. Int, %) 272 (64.9), 239 (100), 211 (19.8), 154 (20.2), 136 (32.7), 119 (13.8), 92 (48.1), 65 (28.6).

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-bromoaminobenzene (5g):** Yield: 45 % R_f: 0.68 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p. : 138-140 ºC; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 1H, NH), 2.64 (s, 3H, CH_3), 7.26 - 8.60 (m, 7H, ph); Mass m/z (rel. Int, %) 307 (100), 273 (50.6), 227 (17.1), 119 (23.8), 92 (55.9), 65 (31.9) IR (KBr, ν_{max}, cm^{-1}): 1360 (C=S).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-bromoaminobenzene (5h):** Yield: 38 % R_f: 0.68 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 141-143 ºC; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 1H, NH), 2.64 (s, 3H, CH_3), 7.26 - 8.60 (m, 7H, ph); Mass m/z (rel. Int, %) 307 (100), 275 (49.6), 227 (14.6), 119 (16.1), 92 (42.4), 65 (24.2).

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-chloroaminobenzene (5i):** Yield: 39 % R_f: 0.66 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 144-145 ºC; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 1H, NH), 2.86 (s, 3H, CH_3), 7.45 - 8.48 (m, 7H, ph); Mass m/z (rel. Int, %) 261 (100), 229 (60.1), 119 (15.2), 92 (43.6), 65 (25.6).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-chloroaminobenzene (5j):** Yield: 42 % R_f: 0.66 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 148-149 ºC; Mass m/z (rel. Int, %) 261 (100), 229 (86.8), 119 (23.3), 92 (55.0), 65 (30.6).

***N*-(6-Methyl-2-pyridinecarbonyl)-3-methylaminobenzene (6a):** Yield: 20 % R_f: 0.46 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 90-93 ºC; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 6.94 -8.12 (m, 7H, ph); Mass m/z (rel. Int, %) 226 (74.1), 197 (16.7), 93 (100), 77 (13.9), 65 (30.6), 52 (7.4) IR (KBr, ν_{max}, cm^{-1}): 1670 (C=O).

5-Methyl-2-(6-methylpyridyl)benzothiazole (7a): Yield: 13 % R_f: 0.40 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 148-150 ºC; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.21 - 8.13 (m, 7H, ph); Mass m/z (rel. Int, %) 241 (100), 121 (29.6), 92 (6.5), 77 (15.7), 65 (13.0), 51 (6.5).

***N*-(6-Methyl-2-pyridinecarbonyl)-3-bromoaminobenzene (6b):** Yield: 87 % R_f: 0.48 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 92-93 ºC; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 1H, NH), 2.62 (s, 3H, CH_3), 7.25 - 8.10 (m, 7H, ph); Mass m/z (rel. Int, %) 292 (36.7), 263 (4.0), 120 (8.7), 93 (100), 65 (36.7), 52 (5.3) IR (KBr, ν_{max}, cm^{-1}): 1683 (C=O).

5-Bromo-2-(6-methylpyridyl)benzothiazole (7b): Yield: 12 % R_f: 0.42 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 145-147 ºC; ^{1}H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3), 7.21- 8.13 (m, 7H, ph); Mass m/z (rel. Int, %) 305 (100), 225 (12.4), 133 (17.1), 107 (37.1), 63 (62.9).

***N*-(6-Methyl-2-pyridinecarbonyl)-3-methoxylaminobenzene (6c):** Yield: 25 % R_f: 0.43 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 96-98 ºC; $_1$H NMR ($CDCl_3$) δ 2.64 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.25 - 8.12 (m, 7H, ph); Mass m/z (rel. Int, %) 242 (56.0), 213 (16.0), 93 (100), 65 (25.3), 52 (8.0).

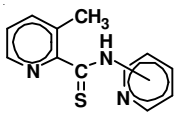
***N*-(6-Methyl-2-pyridinecarbonyl)-3-ethoxylaminobenzene (6d):** Yield: 28 % R_f: 0.45 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 95-97 ºC; ^{1}H NMR ($CDCl_3$) δ 1.14-1.44 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.98 - 4.08 (q, 2H, CH_2), 6.88 - 8.11 (m, 7H, ph); Mass m/z (rel. Int, %) 256 (89.8), 227 (20.4), 120 (39.8), 92 (100), 65 (40.7), 52 (1.2).

***N*-(6-Methyl-2-pyridinecarbonyl)-3-chloroaminobenzene (6e):** Yield: 30 % R_f: 0.49 (TLC eluent; *n*-Hexane: Ethyl acetate = 6 : 1, v/v) m.p.: 97- 98 ºC; ^{1}H NMR ($CDCl_3$) δ

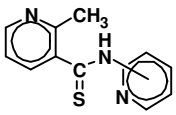
2.16 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.25 - 8.11 (m, 7H, ph); Mass m/z (rel. Int, %) 246 (64.8), 217 (10.1), 120 (15.7), 93 (100), 65 (34.2), 51 (4.6).

RESULTS AND DISCUSSION

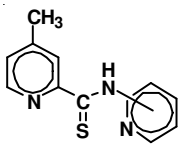
The results for reaction of 2,3-lutidine and aminopyridine(2-aminopyridine, 3-amionpyridine and 4-aminopyridine) with sulfur are as follows. The reaction of 2,3-lutidine and 2-aminopyridine with sulfur was formed *N*-(3-methyl-2-pyridinecarbothionyl)-2-aminopyridine **1a** and *N*-(2-methyl-3-pyridinepyridinecarbothionyl)-2-aminopyridine **2a**. And in case of 3-aminopyridine, products are *N*-(3-methyl-2-pyridinecarbothionyl)-3-aminopyridine **1b** and *N*-(2-methyl-3-pyridinepyridinecarbothionyl)-3-aminopyridine **2b**. Products of the last one are *N*-(3-methyl-2-pyridinecarbothionyl)-4-aminopyridine **1c** and *N*-(2-methyl-3-pyridinepyridinecarbothionyl)-4-aminopyridine **2c**. The reaction of 2,4-lutidine on behalf of 2,3-lutidine with 2-aminopyridine and sulfur was obtained N-(4-methyl-2-pyridinecarbothionyl)-2-aminopyridine **3a** and *N*-(2-methyl-4-pyridinepyridinecarb-othionyl)-2-aminopyridine **4a**. And in case of 3-aminopyridine, products are *N*-(4-methyl-2-pyridinecarbothionyl)-3-aminopyridine **3b** and *N*-(2-methyl-4-pyridinepyridinecar-bothionyl)-3-aminopyridine **4b**. Likewise products of the last one are *N*-(4-methyl-2-pyridinecarbothionyl)-4-aminopyridine **3c** and *N*-(2-methyl-4-pyridinepyridinecarbothionyl)-4-aminopyridine **4c**.



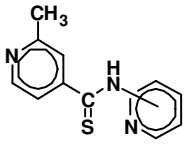
1a : *ortho*-
b : *meta*-
c : *para*-



2a : *ortho*-
b : *meta*-
c : *para*-

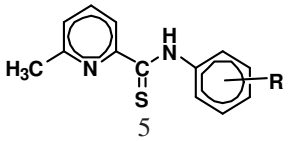


3a : *ortho*-
b : *meta*-
c : *para*-



4a : *ortho*-
b : *meta*-
c : *para*-

In general, various synthetic of amide have been known, we report synthesis of amide from thioamide by using SiO_2 or SeO_2 for the first time.

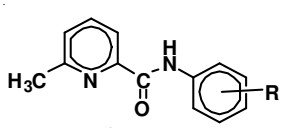


5

R: **5a** = *m*-CH_3 **5d** = *p*-OCH_3 **5h** = *p*-Br
5b = *p*-CH_3 **5e** = *m*-OC_2H_5 **5i** = *m*-Cl
5c = *m*-OCH_3 **5f** = *p*-OC_2H_5 **5j** = *p*-Cl
5c = *m*-Br

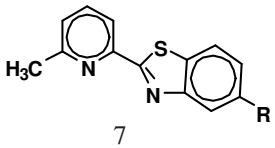
Frist of all, *N*-(6'-methyl-2'-pyridinecarbothionyl)-3 (or 4)-substituted aminobenzenes (**5a-J**) as starting materials were synthesized respectively by treatment of 2,6-lutidine and the corresponding anilines with sulfur powder.

Reactions of synthesized thioamides **5** in the presence of SiO_2 (0.4 g) gave corresponding amides **6** and benzothiazoles **7** as minor products. The reaction mixture was heated at 170 ºC for 10 h.



6

R = *m*-CH_3 (**6a**); *m*-Br (**6b**)
m-OMe (**6c**); *m*-OC_2H_5 (**6d**)
m-Cl (**6e**)



7

R: = CH_3 (**7a**)
= Br (**7b**)

In case of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-bromoaminobenzene (0.39 g, 45%) 5 g, *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-bromoaminobenzene (2.54 g, 87 %) **6b** and 5-bromo-2-(6'-methylpyridyl)benzothiazole (0.36 g, 12 %) **7b** were obtained in excellent yield. In case of conversion of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-substituted aminobenzenes (**5c**, **5e** and **5i**), only *N*-(6'-methyl-2'-pyridinecarbonyl)-3-substituted aminobenzenes (**6c**, **6d** and **6e**) were obtained. In addition, we selected SeO_2 on behalf of SiO_2 to convert from thioamide to amide. Reaction of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene **5a** in the presence of SeO_2 gave only *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methylaminobenzene **6a** (2.03 g, 90 %) in excellent yield. And also reaction of *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-substituted aminobenzene (**5a**, **5e**, **5g** and **5i**) in the presence of SeO_2 gave only *N*-(6'-methyl-2'-pyridinecarbonyl)-3-substituted aminobenzene (**6b**, **6c**, **6d** and **6e**) in excellent yield.

In conclusion, the reactivity of SeO_2 about conversion of thioamide **5** to amide **6** is higher than that of SiO_2. Further investigations will be necessary to clarify the mechanism about conversion of thioamide to amide. Details on these will be reported in the near future.

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