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Conversion of Thioamide to Benzothiazole with Oxidizing Agents

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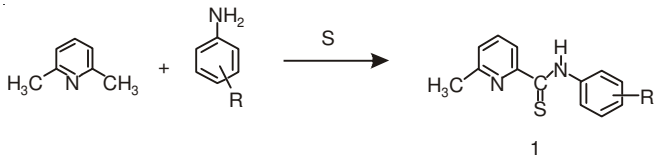
In order to search for novel chemotherapeutical agents, we tried reactions of lutidine(s) with active methyl group and anilines in the presence of sulfur and we report synthesis of amide from thioamide by using SeO_2, ZrO_2 or $KMnO_4$. Benzothiazoles was formed by the oxidative cyclization of thioamides with oxidizing agent (SeO_2, ZrO_2 and $KMnO_4$) in an alkaline solution. We know reactivity of SeO_2 as an oxidizing agent is higher than that of ZrO_2 and $KMnO_4$.

Keywords: Thioamide, Benzothiazole, Oxidizing agent, Oxidaive cyclization.

INTRODUCTION

Thioamides and amides are very reactive compounds and have, 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, property and reaction of amides is future development in such areas as polypeptide and protein chemistry[1]. Benzothiazoles are bicyclic ring system. A number of 2-amino-benzothiazoles have been studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments[2,3]. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole ring found to be possessing pharmacological activities such as antiviral[4], antibacterial[5], antimicrobial[6] and fungicidal activities[7]. They are also useful as antiallergic[8], antidiabetic[9], antitumor[10], antiinflammatory[11], anthelmintic[12] and anti-HIV agents. Compounds having an active methyl group with *para* (or *meta*)-substituted anilines in the presence of sulfur according to the modify Willgerodt-Kindler reaction easily afforded to corresponding thioamides **1** and benzothiazoles **2**[13-18]. The latter **2** was also formed by the oxidative cyclization of the former **1** with potassium ferricyanate in an alkaline solution according to the modified Jacobson method[19,20]. In order to search for novel chemotherapeutical agents, we tried reactions of 2,6-lutidine with active methyl group and anilines in the presence of sulfur. All the executed reactions gave the desired thioamides **1** (**Scheme-I**) but failed to obtain benzothiazoles **2**. In order to obtain a great quantity of benzothiazoles, we needed novel reaction conditions. When a mixture of synthesized thioamide **1** with SeO_2 was heated at 180 °C, but amide **3** not benzothiazole **2** was obtained. In case of ZrO_2 in Na_2CO_3 solution, only benzothiazole **2** was formed. And also we now report reactions of synthesized thioamides with SeO_2, ZrO_2 and $KMnO_4$.



1

R : 1a = m –CH_3 : 49 % R : 1b = p – CH_3 : 45 % R : 1c = m – OCH_3 : 53 %
1d = p – OCH_3 : 62 % 1e = m – OCH_2H_5 : 47 % 1f = p – OC_2H_5 : 57 %
1g = m – Cl : 39 % 1h = p – cl : 42 % 1i = m – Br : 41 %
1j = p – Br : 38 %

Scheme-I: Isolated yields of thioamides

EXPERIMENTAL

The typical experimental procedure for *N*-(6'-methyl-2'-pyridinecarbothionyl)-3-methyl-aminobenzene (**1a**) is as follows: A mixture of 2,6-lutidine (1.07 g, 10 mmol) and 3-methylaniline (1.07 g, 10 mmol) with sulfur powder (0.4 g, 12.5 mmol) was refluxed at 150 °C 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 3N 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 (**1a**) as a yellow crystalline solid (1.09 g, 45 %).

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-methylaminobenzene (1a):** Yield 49 %; m.p. 142-143 °C; R_f 0.66 (TLC eluent; *n*-Hexane: Ethyl acetate = 6: 1, v/v); IR (KBr, ν_{max}, cm^{-1}) 1350 (C=S); ^{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), 65 (37.9).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-methylamino benzene (1b):** Yield 45 %; m.p. 144-145 °C; R_f 0.65 (TLC eluent; *n*-Hexane: Ethyl acetate = 6: 1, v/v; ^{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), 65 (37.9).

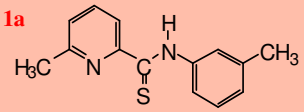
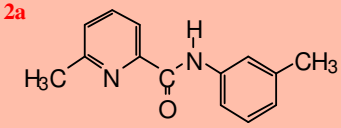
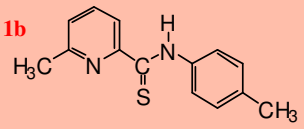
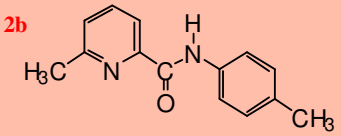
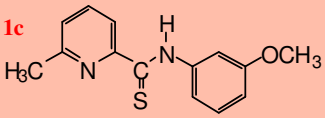
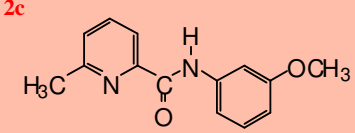
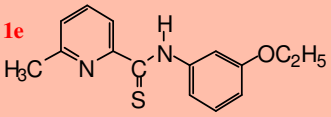
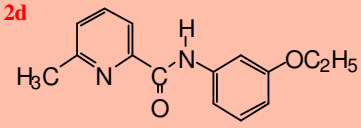
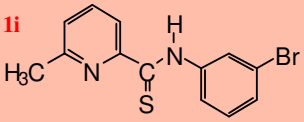
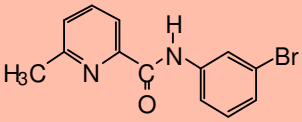
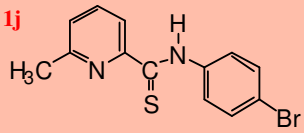
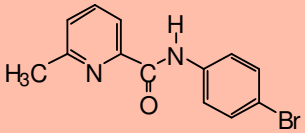
***N*-(6-Methyl-2-pyridinecarbothionyl)-3-methoxy-aminobenzene (1c):** Yield 53 %; m.p. 140-142 °C; R_f 0.63 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 1H, NH), 2.64 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.26-8.59 (m, 7H, ph); Mass: *m/z* (rel. Int, %): 258 (100), 243 (6), 225 (64), 119 (16), 92 (38), 77 (18), 65 (20).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-methoxy-aminobenzene (1d):** Yield 62 %; m.p. 144-145 °C; R_f 0.63 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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-ethoxy-aminobenzene (1e):** Yield 47 %; m.p. 141-143 °C; R_f 0.62 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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 (15.3), 92 (37.6), 136 (42.5), 119 (24.1), 92 (92.5), 65 (53.3).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-ethoxy-aminobenzene (1f):** Yield 57 %; m.p. 147-148 °C; R_f 0.62 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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 (25.5), 154 (20.2), 136 (32.7), 119 (13.8), 92 (48.1), 65 (28.6).

TABLE-1
SYNTHESIZED AMIDES FROM THIOAMIDES

Thioamide	Amide	Oxidizing agent	Yield* (%)
1a 	**2a** 	SeO_2	96
		ZrO_2	68
		$KMnO_4$	15
1b 	**2b** 	SeO_2	89
		ZrO_2	56
		$KMnO_4$	21
1c 	**2c** 	SeO_2	95
		ZrO_2	62
		KMnO4	3
1e 	**2d** 	SeO_2	98
		ZrO_2	73
		$KMnO_4$	12
1i 	**2e** 	SeO_2	97
		ZrO_2	67
		$KMnO_4$	10
1j 	**2f** 	SeO_2	87
		ZrO_2	59
		$KMnO_4$	16

*Isolated yield

***N*-(6-Methyl-2-pyridinecarbothionyl)-3-chloroaminobenzene (1g):** Yield 39 %; m.p. 144-145 °C; R_f 0.66 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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 (1h):** Yield 42 %; m.p. 148-149 °C; R_f 0.66 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); Mass: *m/z* (rel. Int, %): 261 (100), 229 (86.8), 119 (23.3), 92 (55), 65 (30.6).

***N*-(6-Methyl-2- pyridinecarbothionyl)-3-bromoaminobenzene (1i):** Yield 45 %; m.p. 138-140 °C; R_f 0.68 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); IR (KBr, ν_{max}, cm^{-1}) 1350 (C=S); ^{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).

***N*-(6-Methyl-2-pyridinecarbothionyl)-4-bromoaminobenzene (1j):** Yield 38 %; m.p. 141-143 °C; R_f 0.68 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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).

Typical experimental procedure for conversion of thioamide 1 to amide: A mixture of 6-methyl-pyridine-2-carbothioic acid *m*-tolylamide **1a** and SeO_2 was heated at 140 for 10 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 ethylacetate (80:1, v/v), to provide 6-methyl-pyridine-2-carboxylic acid *m*-tolylamide.

6-Methyl-pyridine-2-carboxylic acid *m*-tolylamide (2a): (0.45 g, 20 %) m.p. 90-93 °C; ^{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, 93 (100), 77, 65.

6-Methyl-pyridine-2-carboxylic acid *p*-tolylamide (2b): Yield 89 %; m.p. 97-98 °C; R_f 0.46 (TLC eluent; *n*-hexane: ethyl acetate = 6:1, v/v); ^{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).

6-Methyl-pyridine-2-carboxylic acid (3-methoxyphenyl)-amide (2c): Yield 95 %; m.p. 96-98 °C; R_f 0.43 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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), 213 (16), 93 (100), 65 (25.3), 52 (8).

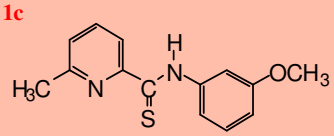
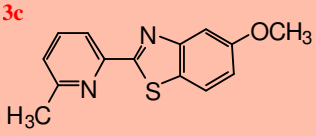
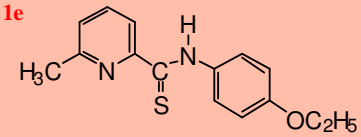
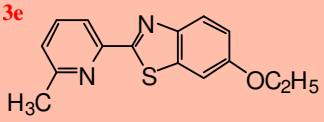
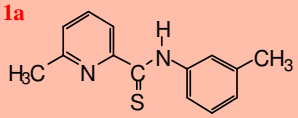
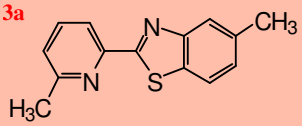
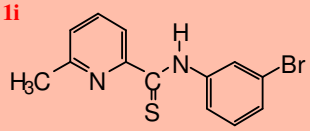
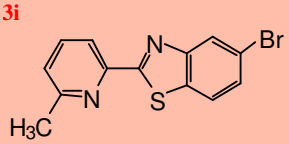
6-Methyl-pyridine-2-carboxylic acid (3-ethoxyphenyl)amide (2d): Yield 98 %; m.p. 95-97 °C; R_f 0.45 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{1}H NMR ($CDCl_3$): δ 1.41-1.44 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.98-4.08 (q, H, CH_2) 6.88-8.11 (m, 7H, ph); Mass: *m/z* (rel. Int, %): 256 (89.8), 227 (20.4), 120 (39.8), 92 (100), 65 (40.7), 52 (1.2).

6-Methyl-pyridine-2-carboxylic acid (3-bromophenyl)amide (2e): Yield 97 %; m.p. 92-93 °C; R_f 0.48 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, H, NH), 2.62 (s, 3H, CH_3), 7.25-8.10 (m, 7H, ph); Mass: *m/z* (rel. Int, %): 292 (36.7), 263 (4), 120 (8.7), 93 (100), 65 (36.7), 52 (5.3); IR (KBr, ν_{max}, cm^{-1}): 1683 (C=O).

6-Methyl-pyridine-2-carboxylic acid (4-bromophenyl)amide (2f): Yield 87 %; m.p. 92-93 °C; R_f 0.48 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, H, NH), 2.62 (s, 3H, CH_3), 7.25-8.10 (m, 7H, ph); Mass: *m/z* (rel. Int, %): 292 (36.7), 263 (4), 120 (8.7), 93 (100), 65 (36.7), 52 (5.3); IR (KBr, ν_{max}, cm^{-1}): 1683 (C=O).

General procedure for the synthesis of 5-methoxy-2-(6-methylpyridyl)benzothiazole (3c): A mixture of *N*-(6-methyl-2-pyridinecarbothionyl)-3-methoxy-aminobenzene

TABLE-2
BENZOTHIAZOLE FORMATION FROM THIOAMIDE WITH ZrO_2 IN Na_2CO_3 SOLUTION

Thioamide	Oxidizing agent	Benzothiazole	Yield* (%)
1c 	ZrO_2	**3c** 	62
1e 	ZrO_2	**3e** 	65
1a 	ZrO_2	**3a** 	51
1i 	ZrO_2	**3i** 	46

*Isolated yield

(**1c**) (0.5 g, 1.9×10^{-3} mol) and zirconium(IV) oxide (0.5 g, 3.8×10^{-3} mol) in 3N-Na_2CO_3 solution was refluxed for 3 h. After the reaction was completed, the reaction mixture was diluted with chloroform 100 mL and neutralized with aqueous diluted HCl. It was extracted with chloroform (three times), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chlomatography on silica gel eluted with *n*-hexane and ethyl acetate (5:1, v/v), to provide 5-methoxy-2-(6-methylpyridyl)benzothiazole 3c as yellow crystalline solid (0.16 g, 62 %); m.p. 145 °C; R_f 0.41 (TLC eluent; *n*-hexane:ethyl acetate = 3:1, v/v); ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.03-8.15 (m, 6H, ph); Mass: *m/z* (rel. Int, %): 256 (100), 241 (38.4), 213 (35.8), 123 (3.8), 95 (8.2), 69 (2.6).

5-Methoxy-2-(6-methylpyridyl)benzothiazole (3a): Yield 13 %; m.p. 148-150 °C; R_f 0.40 (TLC eluent; *n*-hexane: ethyl acetate = 6:1, v/v); ^{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), 51 (6.5).

5-Bromo-2-(6-methylpyridyl)benzothiazole (3i): Yield 12 %; m.p. 145-147 °C; R_f 0.42 (TLC eluent; *n*-hexane:ethyl acetate = 6:1, v/v); ^{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).

6-Ethoxy-2-(6-methylpyridyl)benzothiazole (3e): Yield 35 %; m.p. 150 °C; R_f 0.35 (TLC eluent; *n*-hexane:ethyl acetate = 3:1, v/v); ^{1}H NMR ($CDCl_3$): 1.40-1.47 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.02-4.13 (q, 2H, CH_2), 6.94-8.96 (m, 6H, ph); Mass: *m/z* (rel. Int, %): 270 (84.9), 242 (100), 213 (21.7), 124 (4.2), 92 (16.1), 65 (8.8).

RESULTS AND DISCUSSION

In order to search for novel chemotherapeutical agents, we tried reactions of lutidine(s) with active methyl group and anilines in the presence of sulfur. All the executed reactions gave the desired thioamides **1** (Table-1). In general, various synthetic methods of amide have been known, we report synthesis of amide from thioamide by using SeO_2, ZrO_2 or $KMnO_4$ (Table-2). Reaction of synthesized thioamides **1** in the presence of SeO_2, ZrO_2 or $KMnO_4$ (0.4 g) gave corresponding amides **2**. The reaction mixture was heated at 140 °C for 3 h. Synthesis of amides from thioamides with SeO_2 was executed in high yield (87-98 %). Reactivity of SeO_2 as an oxidizing agent is higher than that of ZrO_2 (56-73 %) and $KMnO_4$ (3-21 %). Benzothiazoles (**3a-d**) was formed by the oxidative cyclization of thioamides with ZrO_2 in an alkaline solution (Table-2). The reaction mixture was refluxed Na_2CO_3 in solution for 3 h. The residue was purified by flash column chromatography or silica gel eluted with hexane and ethyl acetate to provide benzothiazoles. In conclusion the reactions of 2,6-lutidine and amines in the presence of sulfur according to the modified willgerodt-kindler reaction easily afforded to corresponding thioamides in good yields.

Conversion of thioamides to amides with SeO_2 was executed in high yields. We know reactivity of SeO_2 as an oxidizing agent is higher than that of ZrO_2 and $KMnO_4$. Benzothiazoles was formed by the oxidative cyclization of thioamides with ZrO_2 in Na_2CO_3 solution. Further investigations will be necessary to clarify the mechanism about conversion of thioamide to amide and oxidative cyclization of thioamide.

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