The Reactions of Heterocyclic Isothiocyanates Bearing an *ortho* Ester Group with *N*-Nucleophiles. The Scope and Some Limitations of the Reaction

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Heterocyclic isothiocyanates bearing an *o*-ester group were converted into thiourea derivatives **2**, **5**, **6**, **7**, and **9** using sterically large primary amines or aminoacids, and to the fused ring systems, *e.g.* 12*H*-pyrido[3',2':4,5]pyrimido[2,1-*b*]benzothiazol-12-one (**3**), and 6,7-dihydro-9*H*-thiazolo[3,2-*a*]thieno[3,2-*d*]-pyrimidin-9-one (**13**), respectively, using bifunctional reagents such as 2-aminothiophenol or cysteamine.

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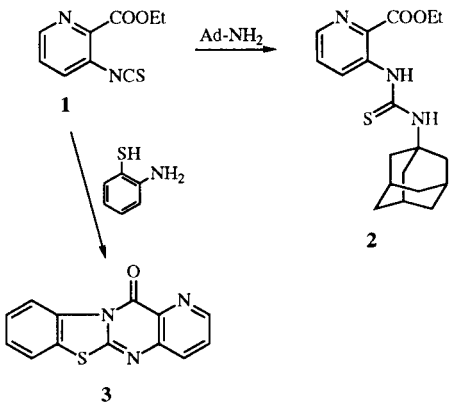
Recently, we have reported on the synthesis and some transformations of heterocyclic isothiocyantes bearing an *ortho* ester group, *e.g.* ethyl 3-isothiocyanatopyridine-2-carboxylate (**1**), ethyl 2-isothiocyanatopyridine-3-carboxylate (**4**), methyl 3-isothiocyanatopyrazine-2-carboxylate, and methyl 3-isothiocyanatothiophene-2-carboxylate [6] (**8**) [1,2,3,4,5].

Several different, mostly fused heterocyclic systems, were formed in these reactions.

In continuation of our research we would like to report on some further transformations and some limitations of these reactions. Ethyl 3-isothiocyanatopyridine-2-carboxylate (**1**) reacted with several primary alkyl or aryl-alkylamines to give 3-substituted pyrido[3,2-*d*]pyrimidine derivatives [1]. Although, with 1-aminoadamantane a thiourea derivative **2** was the only product. The heating of the compound **2** in ethanolic potassium hydroxide or in dry pyridine gave no cyclized product and it seems that the steric hindrance did not allow the cyclization reaction (Scheme 1).

Scheme 1

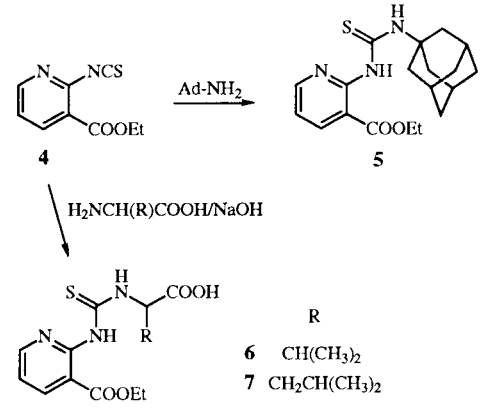


1 **2** **3**

In a condensation reaction between ethyl 3-isothiocyanatopyridine-2-carboxylate (**1**) with 2-aminothiophenol a new tetracyclic system, *e.g.* 12*H*-pyrido[3',2':4,5]-pyrimido[2,1-*b*]benzothiazol-12-one (**3**) was formed in good yield.

Treatment of ethyl 2-isothiocyanatopyridine-3-carboxylate (**4**) with 1-aminoadamantane yielded thiourea derivative **5** and no further cyclization occured under different reaction conditions. The thiourea compounds **6** and **7** were formed in reaction of isothiocyanate **4** with two α-amino acids, *e.g.*, L(+)-valine and L(+)-leucine, and no further cyclization occured under strong reaction conditions. In the reaction with glycine a 3-substituted pyrido[2,3-*d*]-pyrimidine derivative was formed [3]. The optical rotation for compounds **6** and **7** was (+), *i.e.* compounds are dextrorotatory like the starting amino acids, so we can conclude that no racemization occured during these transformations.

Scheme 2

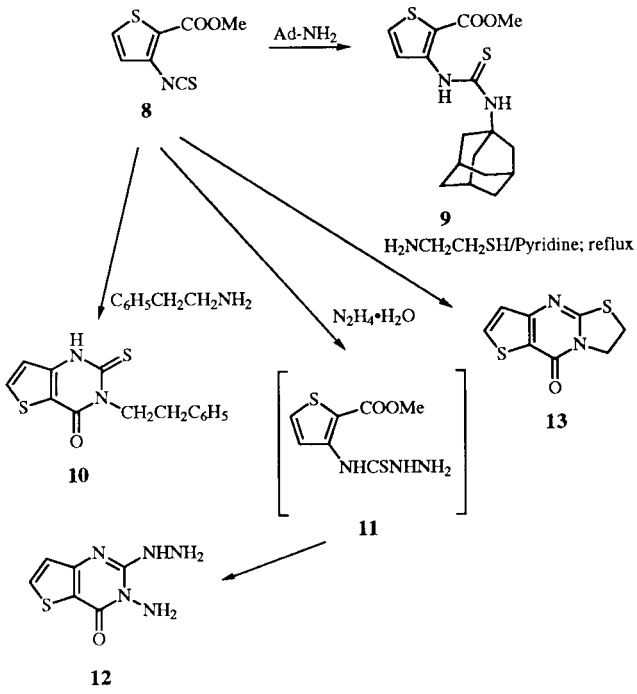


4 **5**

The third isothiocyanate used for the reactions with *N*-nucleophiles was methyl 3-isothiocyanatothiophene-2-carboxylate (**8**) [6]. The reaction of isothiocyanate **8** with 1-aminoadamantane led to the thiourea derivative **9** (Scheme 3). Similar compounds had shown analgesic and antipiretic activity [7].

Treatment of isothiocyanate **8** with phenylethylamine afforded under mild reaction conditions 3-substituted

Scheme 3



thieno[3,2-*d*]pyrimidine derivative **10**. A multiple spin spectrum for the protons of the methylene groups connected to the phenyl ring and the nitrogen atom has been observed. Isothiocyanate **8** underwent reaction with hydrazine hydrate to yield 2-hydrazino-3-aminothieno-[3,2-*d*]pyrimidin-4(3*H*)-one (**12**). Compound **12** could be used as a useful synthon for tricyclic fused systems. After a few seconds noncyclized intermediate 4-(2'-methoxycarbonyl-3-thienyl)thiosemicarbazide (**11**) was isolated. The structure of **11** was determined by mass spectroscopy (M^+231), although we were not able to purify this compound because cyclization took place upon crystallization.

6,7-Dihydro-9*H*-thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-one was synthesized from isothiocyanate **8** in two reaction steps [8]. We present one-step synthesis of 6,7-dihydro-9*H*-thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-one (**13**) from isothiocyanate **8**. Thus, isothiocyanate **8** reacted with 2-aminoethanethiol (cysteamine) in pyridine to yield the tricyclic product **13**. The reaction proceeded in one step only in pyridine, in other solvents (*e.g.* ethanol), 3-(2-hydroxyethyl)thieno[3,2-*d*]pyrimidine derivative was isolated as determined by mass spectrometry.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus CHN-O Rapid analyzer. Electron impact mass spectra were measured at 100 eV on a Varian MAT 311 A mass spectrometer. The nmr spectra were recorded on a Bruker WM-250 spectrometer and Varian VXR 300 spectrometer with TMS as the internal standard. The ir spectra were recorded on a Perkin Elmer model 325 spectrometer and Perkin Elmer FTIR 1600 instrument as potassium bromide pellets. Optical rotations were measured on Perkin-Elmer 240 MC polarimeter.

Ethyl 3-(3-Adamantylthioureido)pyridine-2-carboxylate (**2**).

To a solution of ethyl 3-isothiocyanatopyridine-2-carboxylate **1** (0.12 g, 0.58 mmole) in 5 ml of dry ethanol, 1-aminoadamantane (0.09 g, 0.58 mmole) was added, stirred at room temperature for 2 hours and the precipitated product was filtered off and recrystallized from methanol-*N,N*-dimethylformamide (5:1) to give 0.16 g (77%) of white crystals, mp 204-205°; ir: 3321, 3299, 2920, 2859, 1705, 1565, 1520, 1458, 1440, 1361, 1315 cm^{-1}; ms: (140°) m/z 359 (M^+, 11), 135 (100); ^1H nmr: δ 1.35 (t, J = 7.2 Hz, 3H, CH_3CH_2-), 1.62 (s, 6H, adamantyl CH_2), 2.05 (s, 3H, adamantyl CH), 2.22 (s, 6H, adamantyl CH_2), 4.30 (q, 2H, J = 7.2 Hz, CH_3CH_2-), 7.52 (dd, $J_{5,6}$ = 4.8 Hz, $J_{4,5}$ = 8.2 Hz, 1H, H_5), 8.25 (dd, 1H, $J_{4,6}$ = 1.5 Hz, H_4), 8.37 (dd, 1H, H_6).

Anal. Calcd. for $C_{19}H_{25}N_3O_2S$: C, 63.48; H, 7.01; N, 11.69. Found: C, 63.47; H, 6.98; N, 11.59.

12*H*-Pyrido[3',2':4,5]pyrimido[2,1-*b*]benzothiazol-12-one (**3**).

To a solution of ethyl 3-isothiocyanatopyridine-2-carboxylate **1** (0.2 g, 1 mmole) in 5 ml of dry ethanol, 2-mercaptoaniline (0.125 g, 1 mmole) was added, and the mixture was heating at reflux temperature for 6 hours. The precipitated product was filtered off and recrystallized from methanol to give 0.16 g (66%) of white crystals, mp 247-249°; ir: 1731, 1701, 1590, 1568, 1545, 1460, 1422, 1321, 1300, 761 cm^{-1}; ms: (123°) m/z 253 (M^+, 100); ^1H nmr: δ 7.48-7.68 (m, 2H, aromatic H), 7.87 (dd, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.1 Hz, 1H, H_3), 7.98-8.14 (m, 2H, aromatic H), 8.84 (dd, 1H, $J_{2,3}$ = 5.0 Hz, $J_{2,4}$ = 1.5 Hz, H_2), 8.94 (dd, $J_{2,4}$ = 1.5 Hz, $J_{3,4}$ = 8.0 Hz, 1H, H_4).

Anal. Calcd. for $C_{13}H_7N_3OS$: C, 61.65; H, 2.79; N, 16.59. Found: C, 61.58; H, 2.91; N,16.26.

Ethyl 2-(3-Adamantylthioureido)pyridine-3-carboxylate (**5**).

To a solution of ethyl 2-isothiocyanatopyridine-3-carboxylate **4** (0.23 g, 1.1 mmoles) in 5 ml of dry ethanol, 1-aminoadamantane (0.17 g, 1.1 mmoles) was added, stirred at room temperature for 15 minutes and the precipitated product was filtered off to give 0.3 g (76%) of white crystals, mp 183-185°; ir: 3270, 2920, 2860, 1703, 1605, 1579, 1518, 1459, 1422, 1361, 1282 cm^{-1}; ms: (139°) m/z 359 (M^+, 75), 135 (100); ^1H nmr: δ 1.41 (t, 3H, J = 7.1 Hz, CH_3CH_2-), 1.60-1.82 (m, 6H, adamantyl CH_2), 2.09-2.20 (m, 3H, adamantyl CH), 2.33-2.44 (m, 6H, adamantyl CH_2), 4.41 (q, 2H, J = 7.3 Hz, CH_3CH_2-), 6.97 (dd, $J_{4,5}$ = 7.8 Hz, $J_{5,6}$ = 4.9 Hz, 1H, H_5), 8.29 (dd, 1H, $J_{4,6}$ = 1.9 Hz, $J_{5,6}$ = 5.1 Hz, H_6), 8.37 (dd, 1H $J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 1.9 Hz, H_4), 11.18 (s, 1H, NH), 11.76 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{25}N_3O_2S$: C, 63.48; H, 7.01; N, 11.69. Found: C, 63.61; H, 7.03; N, 11.69.

Ethyl 2-[3-(3-Methyl-1-carboxypropyl)thioureido]pyridine-3-carboxylate (**6**).

To a solution of L-valine (0.59 g, 0.005 mole) in a mixture of dioxane (5 ml), water (5 ml), and 1 *M* sodium hydroxide (5 ml), ethyl 2-isothiocyanatopyridine-3-carboxylate **4** (1.04 g, 0.005 mole) in 3 ml of dioxane was added. The mixture was stirred at 50° for 7 hours and stirring was continued at room temperature for 48 hours. After evaporation of the solvents at reduced pres-

sure, water (10 ml) was added to the residue and acidified with 18% hydrochloric acid to *p*H 3. The precipitated solid was isolated by suction filtration and recrystallized from water-methanol (1:1) to yield 1.3 g (80%) of **6**, mp 138-140°; $[\alpha]_D^{20}$ = +57.9° (c = 0.416, methanol); ir: 3265, 2970, 1722, 1690, 1600, 1543, 1512, 1470, 1430, 1389, 1092, 780; cm^{-1}; ms: (130°) m/z 325 (M^+, 97), 152 (100); ^1H nmr (deuteriochloroform): δ 1.09 and 1.12 (2d, 3H each, J = 6.8 Hz, $(CH_3)_2$-), 1.41 (t, 3H, J = 6.8 Hz, CH_3CH_2), 2.2-2.7 (m, 1H, $(CH_3)_2CHCH$-), 4.37 (q, 2H, J = 6.8 Hz, CH_3CH_2), 5.11 (dd, 1H, J = 7.8 Hz, J = 4.4 Hz, $(CH_3)_2CHCHNH$), 6.95 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 5.3 Hz, H_5), 8.20-8.42 (m, 2H, H_4 and H_6), 10.11 (broad s, 1H, NH), 11.51 (s, 1H, COOH), 12.20 (d, 1H, J = 7.8 Hz, NH).

Anal. Calcd. for $C_{14}H_{19}N_3O_4S$: C, 51.68; H, 5.89; N, 12.91. Found: C, 51.62; H, 5.89; N, 12.91.

Ethyl 2-[3-(3-Methyl-1-carboxybutyl)thioureido]pyridine-3-carboxylate (**7**).

To a solution of L-leucine (0.66 g, 0.005 mole) in a mixture of dioxane (5 ml), water (5 ml), and 1 *M* sodium hydroxide (5 ml) ethyl 2-isothiocyanatopyridine-3-carboxylate (**4**, 1.04 g, 0.005 mole) in 3 ml of dioxane was added. The mixture was stirred at 50° for 15 hours and the stirring was continued at room temperature for 12 hours. After evaporation of the solvents at reduced pressure, water (10 ml) was added to the residue and acidified with 18% hydrochloric acide to *p*H 3 and then acetic acid, ethanol and water in ratio 1:1:1 (5 ml) were added. The precipitated solid was isolated by suction filtration and recrystallized from water-methanol (1:1) to yield 1.5 g (89%) of **7**, mp 60-63°; $[\alpha]_D^{20}$ = +33.4° (c = 0.437, methanol); ir: 3440, 3260, 2962, 1730, 1690, 1605, 1552, 1512, 1290, 1208, 1189, 1090, 780 cm^{-1}; ms: (114°) m/z 339 (M^+, 53), 283 (100); ^1H nmr (deuteriochloroform): δ 1.0 (d, 6H, J = 6.8 Hz, $(CH_3)_2$-), 1.40 (t, 3H, J = 7.3 Hz, CH_3CH_2), 1.7-2.1 (m, 3H, $(CH_3)_2CHCH_2CH$-), 4.39 (q, 2H, J = 7.3 Hz, CH_3CH_2), 5.11 (m, 1H, $(CH_3)_2CHCH_2CH(COOH)NH$), 6.62 (broad s, 1H, NH), 6.97 (dd, 1H, $J_{4,5}$ = 7.3 Hz, $J_{5,6}$ = 5.4 Hz, H_5), 8.20-8.42 (m, 2H, H_4, and H_6), 11.40 (s, 1H, COOH), 11.93 (d, 1H, J = 7.3 Hz, NH).

Anal. Calcd. for $C_{15}H_{21}N_3O_4S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 52.93; H, 6.32; N, 12.31.

Methyl 3-(3-Adamantylthioureido)thiophene-2-carboxylate (**9**).

To a solution of methyl 3-isothiocyanatothiophene-2-carboxylate (**8**, 0.199 g, 1 mmole) in 10 ml of dry methanol, 1-aminoadamantane (0.15 g, 1 mmole) was added, stirred at reflux temperature for 3 hours and the precipitated product was filtered off to give 0.24 g (68%) of white crystals, mp 185-189°; ir: 3301, 3250, 2910, 2859, 1675, 1572, 1522, 1445, 1420, 1359, 1222, 1182, 1089, 860, 780 cm^{-1}; ms: (140°) m/z 350 (M^+, 20), 157 (100); ^1H nmr (deuteriochloroform): δ 1.60-2.29 (m, 15H, adamantyl), 3.9 (s, 3H, CH_3O), 6.37 (broad s, 1H, NH), 7.44 (d, 1H, J = 5.6 Hz, H_4), 8.78 (broad d, 1H, H_5), 10.4 (broad s, 1H, NH).

Anal. Calcd. for $C_{17}H_{22}N_2O_2S_2$: C, 58.26; H, 6.33; N, 7.99. Found: C, 57.94; H, 5.99; N, 8.06.

3-(2-Phenylethyl)-2-thioxo-1,2-dihydrothieno[3,2-*d*]pyrimidin-4(3*H*)-one (**10**).

To a solution of methyl 3-isothiocyanatothiophene-2-carboxylate (**8**, 0.199 g, 1 mmole) in 4 ml of dry methanol, 2-phenylethylamine (0.13 g, 1 mmole) was added, stirred at room temperature for 16 hours and the precipitated product was filtered off and recrystallized from methanol to give 0.24 g (83%) of white crystals, mp 205°; ir: 3210, 1680, 1650, 1557, 1500, 1457, 1439, 1390, 1379, 1340, 1280, 1170, 1115, 770 cm^{-1}; ms: (124°) m/z 288 (M^+, 31), 104 (100); ^1H nmr (DMSO-d_6): δ 3.0 (AA'XX' system, 2H, $C_6H_5CH_2CH_2$-), 4.59 (AA'XX' system, 2H, $C_6H_5CH_2CH_2N$-), 7.05 (d, 1H, J = 5.1 Hz, H_7), 7.20-7.42 (m, 5H, phenyl), 8.17 (d, 1H, J = 5.1 Hz, H_6).

Anal. Calcd. for $C_{14}H_{12}N_2OS_2$: C, 58.31; H, 4.19; N, 9.71. Found: C, 58.56; H, 3.91, N, 9.67.

3-Amino-2-hydrazinothieno[3,2-*d*]pyrimidin-4(3*H*)-one (**12**).

To a solution of methyl 3-isothiocyanathiophene-2-carboxylate (**8**, 0.398 g, 2 mmoles) in 7 ml of dry ethanol, 2.5 ml of 99% hydrazine hydrate was added, stirred at reflux temperature for 7 hours and the precipitated product was filtered off and recrystallized from DMF-water (1:1) to give 0.25 g (64%) of white crystals, mp 220-223°; ir: 3400, 3340, 3200, 1680, 1569, 1542, 1439, 1210, 1010, 885, 779, 665 cm^{-1}; ms: (126°) m/z 197 (M^+, 91), 151 (100); ^1H nmr (DMSO-d_6): δ 4.33 (s, 2H, NH_2), 5.42 (s, 2H, NH_2), 7.1 (d, 1H, J = 5.5 Hz, H_7), 7.99 (d, 1H, J = 5.5 Hz, H_6), 8.15 (s, 1H, NH).

Anal. Calcd. for $C_6H_7N_5OS$: C, 36.54; H, 3.58; N, 35.51. Found: C, 36.57; H, 3.57, N, 35.36.

6,7-Dihydro-9*H*-thiazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-one (**13**).

A solution of methyl 3-isothiocyanathiophene-2-carboxylate (**8**, 0.25 g, 1.3 mmoles) and cysteamine (0.096 g, 1.3 mmoles) in 5 ml of dry pyridine was heated under reflux for 4 hours and left overnight at room temperature. The precipitated product was filtered off and recrystallized from ethanol to give 80 mg of **13**. Additional amount of the product (150 mg) was obtained by evaporating the mother liquor, total yield 87%, mp 192-195° (lit [8] mp 187-189°); ir: 1672, 1550, 1500, 1361, 1230, 1190, 1060, 819, 782, 678, 631 cm^{-1}; ms: (113°) m/z 210 (M^+, 100); ^1H nmr (DMSO-d_6): δ 3.60 (t, 2H, J = 7.3 Hz, NCH_2CH_2S), 4.43 (t, 2H, J = 7.3 Hz, NCH_2CH_2S), 7.22 (d, 1H, J = 5.1 Hz, H_8), 8.12 (d, 1H, J = 5.1 Hz, H_7).

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