REACTION OF ETHYL 3-AMINOTHIENO[2,3-B]PYRIDINE-2-CARBOXYLATE: SYNTHESIS OF NEW FUNCTIONALIZED THIENO[2,3-B]PYRIDINE , PYRIDO[3',2':4,5]THIENO[3,2-D][1,3]THIAZINE AND PYRIDO[3',2':4,5]THIENO[3,2-D]PYRIMIDINES

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Abstract : 3-Amino[2,3-b]pyridine-2-carboxylate was reacted with both nucleophilic and electrophilic reagents such as hydrazine hydrate, potassium thiocyanide, acetic anhydride, etc. to obtain new functionalized derivatives of thieno[2,3-b]pyridine, pyrido[3',2':4,5]thieno[3,2-d][1,3] thiazine and pyrido[3',2':4,5]thieno[3,2-d]pyrimidines.

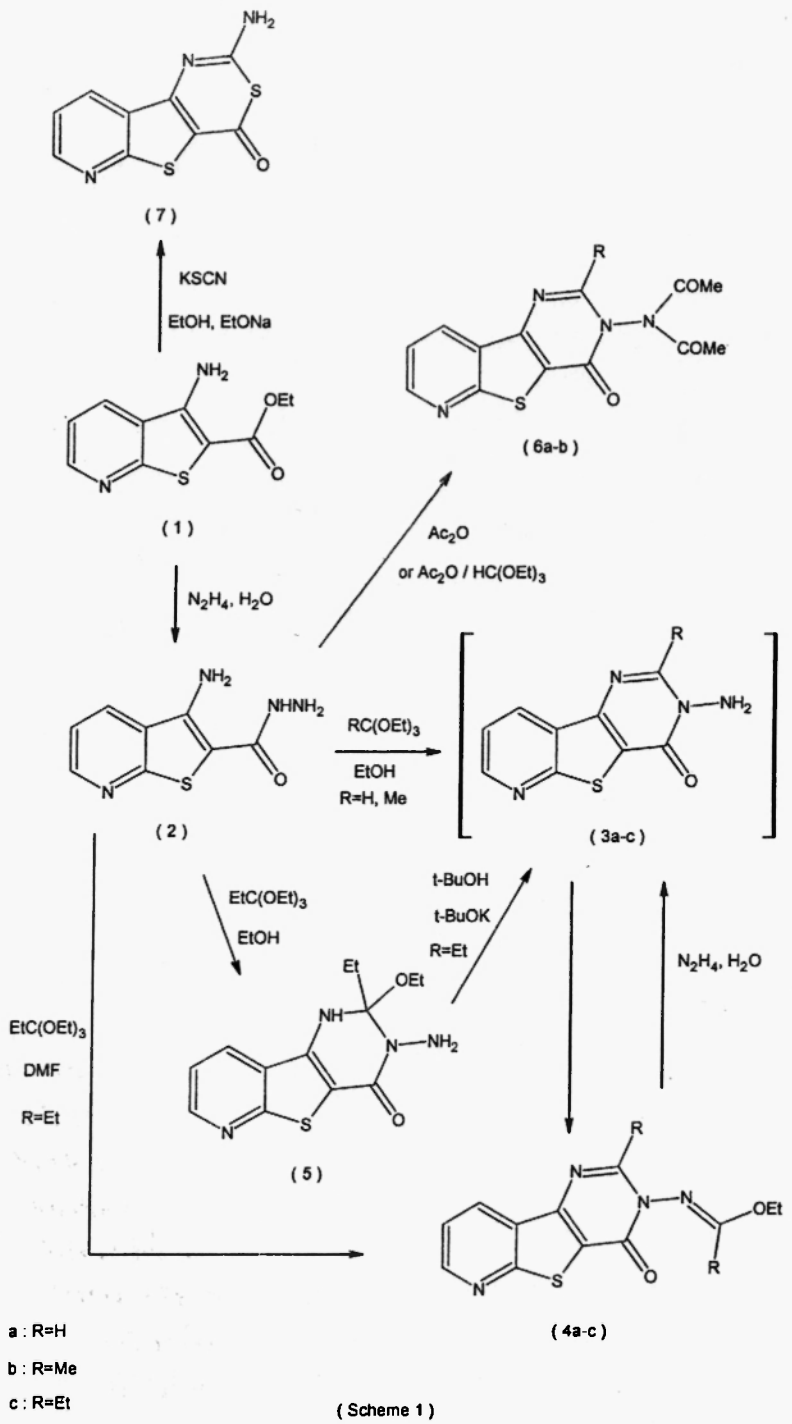
Keywords : Thienopyridines; Pyridothienopyrimidines; Pyridothienothiazine; Thienopyridine-2-carbohydrazide; Orthoesters.

Introduction

Ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate (**1**) is a readily obtainable compound that has been used extensively as intermediate in heterocyclic synthesis (see a recent review on thienopyridines and references cited therein)[1]. In connection with our interest in the synthesis of fused heterocyclic compounds of biological significance[2-8], we report herein a new and simple route for the synthesis of new functionalized derivatives of thieno[2,3-b]pyridine, pyrido[3',2':4,5]thieno[3,2-d][1,3]thiazine and pyrido [3',2':4,5]thieno[3,2-d]pyrimidines that might be of pharmacological importance.

Results and Discussion

Treatment of ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate **1** with hydrazine hydrate gave compound **2** in quantitative yield. ^{1}H NMR and IR spectra of this product clearly indicated the presence of the carbohydrazide moiety in the molecule. When this compound was heated under reflux for 6 hours with triethyl orthoformate or orthoacetate in ethanol, the corresponding tricyclic pyridothienopyrimidines **4a** & **4b** were obtained. Structures of these compounds were established on the basis of spectral analysis of the isolated products. For example, in case of compound **4a** mass spectrum showed a molecular ion peak at m/z 274. The IR spectrum showed the absence of the hydrazino and amino groups that were appeared at 3250& 3120 cm^{-1} in the compound **2** IR spectrum. In addition, the ^{1}H NMR spectrum of compound **4a** showed the presence of the characteristic signals for pyrimidine ring proton at δ 8.70ppm together with the iminoether proton at δ 8.67. The formation of the products **4a & 4b** was assumed to proceed via the seemingly reactive intermediate **3a & 3b** respectively with subsequent condensation with orthoesters to furnish the condensed products **4a & 4b**. Attempts to isolate the reaction intermediates failed when we monitored the reaction under careful observation, but these intermediates were isolated when compounds **4a & 4b** treated with hydrazine hydratre at reflux temperature (Scheme-1).



Scheme-1

Reaction of triethyl orthopropionate with the carbohydrazide derivative **2** gave the rather unexpected product **5** which was successfully converted to the desired compound **3c** on treatmenrt with potassium t-butoxide in t-butanol. This compound underwent smooth condensation with triethyl orthopropionate to

give **4c**, which was then transformed to **3c** on refluxing with hydrazine hydrate. Direct conversion of compound **2** to **4c** was successfully achieved by heating a mixture of the carbohydrazide derivative **2** with triethyl orthopropionate in dimethylformamide.

Treatment of the carbohydrazide derivative **2** with boiling acetic anhydride, gave the acetamido derivative **6b** while heating a mixture of **2**, triethyl orthoformate and acetic anhydride at reflux temperature produced compound **6a**. Structures of **6a** and **6b** were confirmed by the spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **6a** showed one aromatic proton at δ = 8.82 ppm characteristic of a fused pyrimidine ring, as well as methyl protons at δ = 2.42 ppm.

Treatment of ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate **1** with potassium thiocyanate and sodium ethoxide in refluxing ethanol for 4 hours gave 2-amino-4H-pyrido[3',2':4,5]thieno[3,2-d][1,3]thiazine-4-one **7** in high yield. The structure of the product was assigned on the basis of the spectral and microanalytical data. The disappearance of ethyl signal in the spectrum and the shift of the NH_2 group to lower field is a good evidence for the formation of thiazine ring.

In summary, some new functionalized thieno[2,3-b]pyridine, pyrido[3',2':4,5] thieno[3,2-d][1,3]thiazine and pyrido[3',2':4,5]thieno[3,2-d]pyrimidines have been synthesized by a direct synthetic route and their structures were established by their spectral and microanalytical data.

Experimental Section

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

3-Aminothieno[2,3-b]pyridine-2-carbohydrazide (2)

A mixture of ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate[1] **1** (0.001 mol), and hydrazine hydrate (5 ml) was heated under reflux for 2 hrs. After the reaction was complete, the mixture was cooled to room temperature, and then water (50 ml) was added. The precipitate was filtered off and recrystallized from ethanol, yield 90 %; mp 215-217 °C, ^{1}H NMR (d_6-DMSO)δ 4.37 (br.s, 2H, NH_2, exchangeable with D_2O), 7.09 (br.s, 2H, NH_2 exchangeable with D_2O), 7.37 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.37 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.56 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH), 9.0 (br s, 1H, NH, exchangeable with D_2O); IR(KBr disc) υ(cm^{-1}) : 3250 , 3120 ; MS, *m/z*: 208 (M^+). Anal. Calcd for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.90; S, 15.40. Found: C, 46.39; H, 3.62; N, 27.13; S, 15.24.

Ethyl-4-oxopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-3(4H)-ylimidoformate (4a)

A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol), and triethyl orthoformate (0.002 mol) in ethanol(10 ml) was heated under reflux for 6 hrs. The solvent was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give compound **4a** , yield 75 %;

mp 159-160 °C, ^{1}H NMR (d_6-DMSO)δ 1.4 (t, 3H, ^3J = 7Hz, CH_3), 4.4 (q , 2H, ^3J = 7Hz, CH_2), 7.7 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.65 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.67 (s, 1H, CH), 8.7 (s, 1H, CH), 8.86 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; MS, *m/z*: 274 (M^+). Anal. Calcd for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.43; S, 11.69. Found: C, 52.91; H, 3.79; N, 20.18; S, 11.83.

Ethyl-N-(2-methyl-4-oxopyrido[3',2':4,5] thieno[3,2-d]pyrimidin-3(4H)-yl) ethanimidoate (4b)

A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol), and triethyl orthoacetate (0.002 mol) in ethanol(10 ml) was heated under reflux for 6 hrs. The solvent was evaporated in vacuo, the residue was recrystallized from ethanol to give compound **4b** , yield 66 %; mp 168-170 °C, ^{1}H NMR (d_6-DMSO)δ 1.38 (t, 3H, ^3J = 7Hz, CH_3),1.88 (s, 3H, CH_3),2.52 (s, 3H, CH_3), 4.4 (q , 2H, ^3J = 7Hz, CH_2), 7.65 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.59 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.82 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; MS, *m/z*: 302 (M^+). Anal. Calcd for $C_{14}H_{14}N_4O_2S$: C, 55.61; H, 4.67; N, 18.53; S, 10.61. Found: C, 55.32; H, 4.46; N, 18.27; S, 10.77.

Ethyl-N-(2-ethyl-4-oxopyrido[3',2':4,5] thieno[3,2-d]pyrimidin-3(4H)-yl) propanimidoate (4c)

Method A : A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol), and triethyl orthopropionate (0.002 mol) in DMF(10 ml) was heated under reflux for 3 hrs. The solvent was evaporated to dryness under reduced pressure.The residue was recrystallized from ethanol to give compound **4c** , yield 82 %; mp 170-172 °C.

Method B : A mixture of 3-amino-2-ethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one **3c** (1.0 mmol), and triethyl orthopropionate (2.0 mmol) in DMF(10 ml) was heated under reflux for 2 hours. The solvent was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give compound **4c** , yield 73 %; mp 170-172 °C, ^{1}H NMR (d_6-DMSO)δ 1.07 (t, 3H, ^3J = 7Hz, CH_3), 1.18 (t, 3H, ^3J = 7Hz, CH_3), 1.42 (t, 3H, ^3J = 8Hz, CH_3), 2.41 (q , 2H, ^3J = 7Hz, CH_2), 2.62 (q , 2H, ^3J = 7Hz, CH_2), 4.23 (q , 2H, ^3J = 8Hz, CH_2), 7.60 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.55 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.79 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH); MS, *m/z*: 330 (M^+). Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C, 58.16; H, 5.49; N, 16.96; S, 9.71. Found: C, 58.41; H, 5.72; N, 17.06; S, 9.53.

3-Amino-2-ethoxy-2-ethyl-2,3-dihydropyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4(1H)-one (5)

A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol), and triethyl orthopropionate (0.002 mol) in ethanol(10 ml) was heated under reflux for 7 hrs. The solvent was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give compound **5** , yield 45 %; mp 170-173 °C, ^{1}H NMR (d_6-DMSO)δ 1.05 (t, 3H, ^3J = 8Hz, CH_3), 1.32 (t, 3H, ^3J = 7Hz, CH_3), 2.45 (q , 2H, ^3J = 8Hz, CH_2), 4.25 (q , 2H, ^3J = 7Hz, CH_2), 7.40 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 6Hz, CH), 7.52 (br. s, 2H, NH_2, exchangeable with D_2O), 8.50 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.68 (dd, 1H, $^3J_1$ = 6Hz, $^4J_2$ = 2Hz, CH), 9.85 (s, 1H, NH, exchangeable with D_2O) ; IR(KBr disc) υ(cm^{-1}) : 3290 , 3180 ; MS, *m/z*:

292 (M^+). Anal. Calcd for $C_{13}H_{16}N_4O_2S$: C, 53.41; H, 5.52; N, 19.16; S, 10.97. Found: C, 53.24; H, 5.68; N, 19.39; S, 10.83.

General Procedure for the Preparation of 3-Aminopyrido[3',2':4,5] thieno[3,2-d]pyrimidin-4(3H)-one (3a-c)

A mixture of **4a-c** (0.001 mol), and hydrazine hydrate (80% ,7 ml) was heated under reflux for 5 hrs. The reaction mixture was cooled to room temperature and the precipitate was filtered and recrystallized from ethanol to give compounds **3a-c** in 65, 53, and 70% yield respectively.

3-Aminopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (3a)

This compound was obtained as yellow crystal, m.p. 256-258 °C, ^{1}H NMR (d_6-DMSO)δ 5.7 (s, 2H, NH_2), 7.65 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.72 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.79 (s, 1H, CH), 8.85 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; IR(KBr disc) υ(cm^{-1}) : 3210 , 3190 ; MS, *m/z*: 218 (M^+). Anal. Calcd for $C_9H_6N_4OS$: C, 49.53; H, 2.77; N, 25.67; S, 14.69. Found: C, 49.67; H, 2.85; N, 25.44; S, 14.82.

3-Amino-2-methylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (3b)

This compound was obtained as yellow crystal, m.p. 219-220 °C, ^{1}H NMR (d_6-DMSO)δ 2.7 (s, 3H, CH_3), 6.05 (s, 2H, NH_2), 7.62 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 6Hz, CH), 8.57 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.80 (dd, 1H, $^3J_1$ = 6Hz, $^4J_2$ = 2Hz, CH) ; IR(KBr disc) υ(cm^{-1}) : 3230 , 3200 ; MS, *m/z*: 232 (M^+). Anal. Calcd for $C_{10}H_8N_4OS$: C, 51.71; H, 3.47; N, 24.12; S, 13.81. Found: C, 51.45; H, 3.31; N, 24.36; S, 13.63.

3-Amino-2-ethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-one (3c)

This compound was obtained as yellow crystal, m.p. 164-166 °C, ^{1}H NMR ($CDCl_3$)δ 1.48 (t, 3H, ^3J = 8Hz, CH_3), 3.05 (q , 2H, ^3J = 8Hz, CH_2), 5.8 (br, 2H, NH_2), 7.42 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 6Hz, CH), 8.07 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.71 (dd, 1H, $^3J_1$ = 6Hz, $^4J_2$ = 2Hz, CH) ; IR(KBr disc) υ(cm^{-1}) : 3220 , 3190 ; MS, *m/z*: 246 (M^+). Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75; S, 13.02. Found: C, 53.87; H, 4.18; N, 22.92; S, 12.85.

3-Amino-2-ethylpyrido[3',2':4,5] thieno[3,2-d]pyrimidin-4(3H)-one (3c)

Method B : 3-Amino-2-ethoxy-2-ethyl-2,3-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(1H)-one **5** (0.001 mol) was dissolved in t-butanol (10 ml) containing potassium t-butoxide (0.001 mol).The mixture was refluxed for 3 hrs. The solvent was evaporated to dryness under reduced pressure, then water was added and neutralized by 1N HCl.The crude product was collected and recrystallized from ethanol to give compound 3c, yield 43 %; mp 164-166 °C.

N-acetyl-N-(4-oxopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-3(4H)-yl)acetamide (6a)

A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol), triethyl orthoformate (0.004 mol) and acetic anhydride was heated under reflux for 7 hrs. The excess of acetic anhydride was evaporated under reduced pressure. The residue was recrystallized from ethanol to give compound **6a** , yield 53 %; mp 217-218 °C, ^{1}H NMR (d_6-DMSO)δ 2.42 (s, 6H, $2CH_3$), 7.70 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.66 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.82 (s, 1H, CH), 8.90 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; MS, *m/z*: 302 (M^+). Anal. Calcd for $C_{13}H_{10}N_4O_3S$: C, 51.65; H, 3.33; N, 18.53; S, 10.61. Found: C, 51.47; H, 3.54; N, 18.81; S, 10.43.

N-acetyl-N-(2-methyl-4-oxopyrido[3',2':4,5]thieno[3,2-d]pyrimidin-3(4H)-yl)acetamide (6b)

A mixture of 3-aminothieno[2,3-b]pyridine-2-carbohydrazide **2** (0.001 mol) and acetic anhydride was heated under reflux for 3 hrs. The excess of acetic anhydride was evaporated under reduced pressure. The residue was recrystallized from ethanol to give compound **6b** , yield 84 %; mp 150-152 °C, ^{1}H NMR (d_6-DMSO)δ 2.43 (s, 6H, $2CH_3$), 2.56 (s, 3H, CH_3), 7.70 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.65 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.90 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; MS, *m/z*: 316 (M^+). Anal. Calcd for $C_{14}H_{12}N_4O_3S$: C, 53.16; H, 3.82; N, 17.71; S, 10.14. Found: C, 53.34; H, 3.96; N, 17.54; S, 10.01.

2-Amino-4H-pyrido[3',2':4,5]thieno[3,2-d][1,3]thiazin-4-one (7)

A mixture of ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate **1** (0.001 mol), and potassium thiocyanate (0.001 mol) in ethanol(20 ml) containing sodium ethoxide (0.0005 mol) was heated under reflux for 4 hrs. The solvent was evaporated in vacuo, the residue was recrystallized from ethanol to give compound **7** , yield 67 %; mp 190-192 °C, ^{1}H NMR (d_6-DMSO)δ 7.21 (br. s, 2H, NH_2, exchangeable with D_2O), 7.45 (dd, 1H, $^3J_1$ = 8Hz, $^3J_2$ = 5Hz, CH), 8.55 (dd, 1H, $^3J_1$ = 8Hz, $^4J_2$ = 2Hz, CH), 8.68 (dd, 1H, $^3J_1$ = 5Hz, $^4J_2$ = 2Hz, CH) ; IR(KBr disc) υ(cm^{-1}) : 3270 , 3250 ; MS, *m/z*: 235 (M^+). Anal. Calcd for $C_9H_5N_3OS_2$: C, 45.94; H, 2.14; N, 17.86; S, 27.26. Found: C, 46.15; H, 2.03; N, 17.65; S, 27.12.

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