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SYNTHESIS AND PROPERTIES OF ETHYL ESTERS OF 4-DIALKYLAMINO-2-METHYLTHIOTHIENO[2,3-*d*]-PYRIMIDINE-6-CARBOXYLIC ACIDS

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The reaction of 4-dialkylamino-6-chloro-2-methylthiopyrimidine-5-carbaldehydes with ethyl mercaptoacetate in the presence of triethylamine gives the corresponding ethyl esters of thieno[2,3-d]-pyrimidine-6-carboxylic acids. These esters were subjected to alkaline hydrolysis, hydrazinolysis, and lithium aluminum hydride reduction to give the corresponding acids, hydrazides, and (thieno[2,3-d]-pyrimidin-6-yl)methanols.

Keywords: pyrimidines, thieno[2,3-*d*]pyrimidines, reduction, cyclocondensation.

We have recently synthesized the ethyl esters of several 4-alkylamino- and 4-arylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids bearing a primary amino group at $C_{(5)}$ in the heterocyclic system and studied the reactions of these compounds with electrophilic and nucleophilic reagents. These studies led to the development of simple and efficient methods for the synthesis of a number of new *ortho*- and *peri*-condensed heterocyclic systems containing the thieno[2,3-*d*]pyrimidine fragment [1-4]. A study of the properties of the ethyl esters of several 5-amino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids also showed that the ester group in the *ortho* position relative to the primary amino group is quite inert toward various nucleophiles. Such inactivity of the ester group may be a result of the electronic effect of the neighboring amino group and intramolecular hydrogen bonding between the ester and amino groups in the 5-aminothieno[2,3-*d*]-pyrimidine-6-carboxylates [5]. In order to obtain more information on the reactivity of thieno[2,3-*d*]pyrimidine-6-carboxylic acid esters, we synthesized ethyl esters of thieno[2,3-*d*]pyrimidine-6-carboxylic acids with an amino group at $C_{(5)}$ of the heterocyclic system and studied the reactions of these compounds with nucleophilic reagents. We should note that thieno[2,3-*d*]pyrimidines and compounds containing the thienopyrimidine fragment [6-15] as well as their pyridine analogs [16, 17] display useful pharmacological properties. Thus, the 6-substituted thieno[2,3-*d*]pyrimidines obtained in the present work may be used as intermediates for the synthesis of biologically active compounds including synthesis of both classic and lipophilic antifolates. Another reason for this study was the paucity of information in the literature on the synthesis and properties of esters of thieno[2,3-*d*]pyrimidine-6-carboxylic acids [18, 19].

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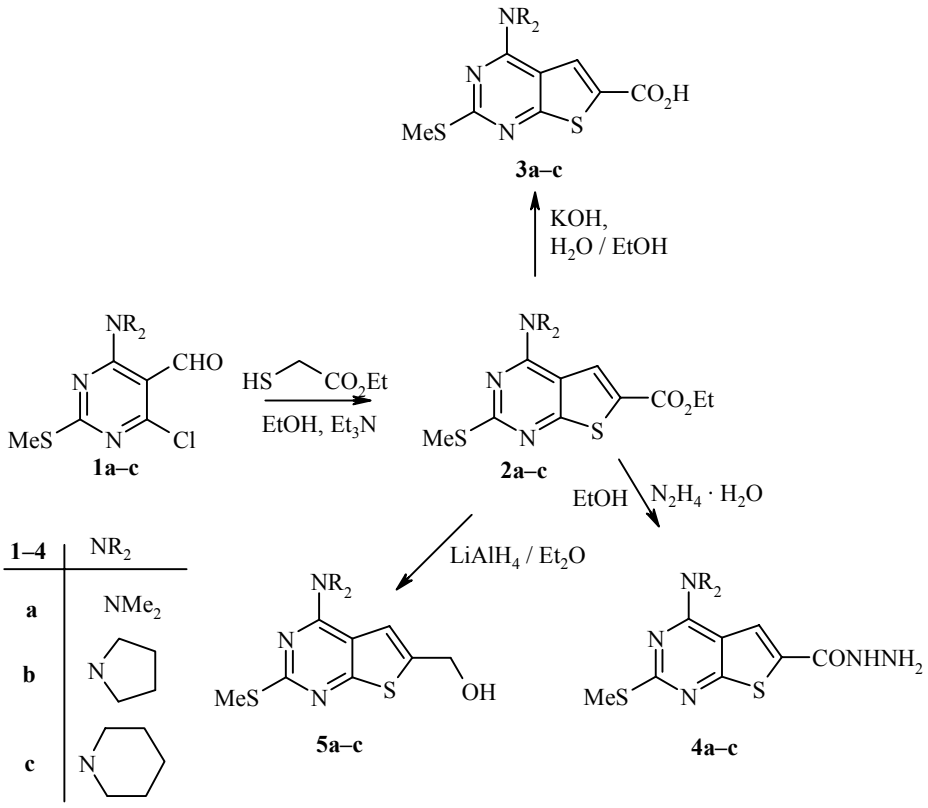

Ethyl esters of 4-dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids **2a-c** were synthesized by heating the corresponding 6-chloro-4-dialkylamino-2-methylthiopyrimidine-5-carbaldehydes **1a-c** with ethyl mercaptoacetate at reflux in the presence of triethylamine. The hydrolysis of esters **2a-c** to give the corresponding acids **3a-c** was carried out at room temperature using a solution of potassium hydroxide in aqueous ethanol. To our surprise, the ester group in **2a-c** proved rather inert relative to nitrogen nucleophiles. The corresponding amides could not be obtained by the reaction of **2a-c** with diethylamine, aniline, or 4-methoxyaniline even upon heating in a large excess of amine without solvent. We should also note that the replacement of the methylthio group by the corresponding amines, which we noted previously in a study of the ethyl esters of 5-amino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids [21], does not proceed. Hydrazides **4a-c** were obtained in 64-93% yield only upon prolonged heating of esters **2a-c** at reflux with excess hydrazine hydrate. The reduction of esters **2a-c** with lithium aluminum hydride proceeds at room temperature and leads to the corresponding (thieno[2,3-*d*]pyrimidin-6-yl)methanols **5a-c**.

The structures of products **2-5** were indicated by IR and ^{1}H NMR spectroscopy and elemental analysis. Thus, for example, the ^{1}H NMR spectra of esters **2a-c** show the ethyl ester signals at 1.39-1.41 ppm for the CH_3 group and 4.32-4.39 ppm for the OCH_2 group, while the singlet for the proton at $C_{(5)}$ of the thienopyrimidine system is found at 7.98-8.09 ppm. For comparison, the signal of the aldehyde group of **1a-c** in the ^{1}H NMR spectra is found at 10.17-10.27 ppm [20]. The IR spectra of **2a-c** show the ester carbonyl band at 1687-1702 cm^{-1}. The ^{1}H NMR spectra of (thieno[2,3-*d*]pyrimidin-6-yl)methanols **5a-c** show singlets for the methylene and hydroxy groups at 4.75-5.14 and 2.66-2.95 ppm, respectively, while the signal for the proton at $C_{(5)}$ is shifted upfield relative to esters **2a-c** due to the electron-donor effect of the hydroxymethyl group and is observed at 7.00-7.66 ppm.

EXPERIMENTAL

The IR spectra were taken in vaseline oil on a Perkin-Elmer Spectrum BX II FT-IR spectrometer. The ^{1}H NMR spectra were taken on a Tesla 587A spectrometer at 80 MHz using TMS as the internal standard. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Alufol silica gel 60 F_{254} plates.

Ethyl Esters of 4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids (2a-c). Triethylamine (0.61 g, 6 mmol) was added dropwise to a mixture of the corresponding aldehyde **1a-c** (3 mmol) and ethyl mercaptoacetate (0.4 g, 3.3 mmol) in ethanol (10 ml). The reaction mixture was heated at reflux until the starting carbaldehydes disappeared according to thin-layer chromatography (5-9 h). After cooling to room temperature, the precipitate was filtered off and recrystallized to give **2a-c**.

Ester 2a was obtained in 67% yield; mp 150-151°C (2-propanol). The reaction time was 9 h. IR spectrum, ν, cm^{-1}: 1687 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, (*J*, Hz): 1.39 (3H, t, *J* = 7, CH_3); 2.55 (3H, s, SCH_3); 3.39 (6H, s, $2NCH_3$); 4.33 (2H, q, *J* = 7, OCH_2); 8.06 (1H, s, 5-H). Found, %: C 48.33; H 5.19; N 14.40. $C_{12}H_{15}N_3O_2S_2$. Calculated, %: C 48.46; H 5.08; N 14.13.

Ester 2b was obtained in 90% yield; mp 160.5-161.0°C (2-propanol). The reaction time was 7 h. IR spectrum, ν, cm^{-1}: 1700 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, (*J*, Hz): 1.41 (3H, t, *J* = 6, CH_3); 1.90-2.18 (4H, m, $2CH_2$); 2.59 (3H, s, SCH_3); 3.65-3.96 (4H, m, $2NCH_2$); 4.39 (2H, q, *J* = 6, OCH_2); 8.09 (1H, s, 5-H). Found, %: C 52.26; H 5.54; N 13.34. $C_{14}H_{17}N_3O_2S_2$. Calculated, %: C 51.99; H 5.30; N 12.99.

Ester 2c was obtained in 78% yield; mp 101.5-102.0°C (2-propanol). The reaction time was 5 h. IR spectrum, ν, cm^{-1}: 1701 (CO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, (*J*, Hz): 1.39 (3H, t, *J* = 6, CH_3); 1.55-1.85 (6H, m, $3CH_2$); 2.55 (3H, s, SCH_3); 3.60-3.97 (4H, m, $2NCH_2$); 4.36 (2H, q, *J* = 6, OCH_2); 7.98 (1H, s, 5-H). Found, %: C 53.70; H 5.69; N 12.46. $C_{15}H_{19}N_3O_2S_2$. Calculated, %: C 53.39; H 5.68; N 12.45.

4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acids (3a-c). The corresponding ester **2a-c** (0.06 mol) was added in portions to a solution of KOH (0.1 g, 1.8 mmol) in ethanol (5 ml) and water (2.5 ml). The reaction mixture was stirred at room temperature until the starting esters disappeared as indicated by thin-layer chromatography (4-28 h), then concentrated to one-third original volume, and brought to pH 2 by adding 10% hydrochloric acid. The precipitate was filtered off, washed with water, and recrystallized to give **3a-c**.

Acid 3a was obtained in 93% yield; mp >245°C (dec.) (methanol). The reaction time was 10 h. IR spectrum, ν, cm^{-1}: 1684 (CO), 3110 (OH). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm: 2.86 (3H, s, SCH_3); 3.75 (3H, s, NCH_3); 3.84 (3H, s, NCH_3); 8.57 (1H, s, 5-H). Found, %: C 44.79; H 4.30; N 15.82. $C_{10}H_{11}N_3O_2S_2$. Calculated, %: C 44.59; H 4.12; N 15.60.

Acid 3b was obtained in 83% yield; mp >250°C (dec.) (dioxane). The reaction time was 28 h. IR spectrum, ν, cm^{-1}: 1675 (CO), 3394 (OH). ^{1}H NMR spectrum (CF_3CO_2D), δ, ppm: 2.05-2.58 (4H, m, $2CH_2$); 2.82 (3H, s, SCH_3); 3.98-4.25 (4H, m, $2NCH_2$); 8.49 (1H, s, 5-H). Found, %: C 48.84; H 4.74; N 14.19. $C_{12}H_{13}N_3O_2S_2$. Calculated, %: C 48.80; H 4.44; N 14.23.

Acid 3c was obtained in 72% yield; mp >265°C (dec.) (2-propanol). The reaction time was 4 h. IR spectrum, ν, cm^{-1}: 1668 (CO), 3392 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.45-1.90 (6H, m, $3CH_2$); 2.51 (3H, s, SCH_3); 3.62-4.05 (4H, m, $2NCH_2$); 8.01 (1H, s, 5-H). Found, %: C 50.53; H 4.86; N 13.73. $C_{13}H_{15}N_3O_2S_2$. Calculated, %: C 50.47; H 4.89; N 13.58.

Hydrazides of 4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acids (4a-c). A mixture of the corresponding ester **2a-c** (0.9 mmol) and hydrazine hydrate (0.9 g, 17.8 mmol) in ethanol (5 ml) was heated at reflux with stirring until the starting esters disappeared as indicated by thin-layer chromatography (9-21 h). After cooling to room temperature, the precipitate was filtered off, washed with water, and recrystallized to give **4a-c**.

Hydrazide 4a was obtained in 64% yield; mp 273.5-275.0°C (DMF). The reaction time was 9 h. IR spectrum, ν, cm^{-1}: 1601 (CO), 3259, 3322 (NH, NH_2), ^1H NMR spectrum (CF_3CO_2D), δ, ppm: 2.44 (3H, s, SCH_3); 3.33 (3H, s, NCH_3); 3.41 (3H, s, NCH_3); 8.13 (1H, s, 5-H). Found, %: C 42.73; H 4.46; N 24.63. $C_{10}H_{13}N_5OS_2$. Calculated, %: C 42.39; H 4.62; N 24.71.

Hydrazide 4b was obtained in 93% yield; mp >300°C (dec.) (DMF). The reaction time was 18 h. IR spectrum, ν, cm^{-1}: 1665 (CO), 3359 (NH, NH_2). ^1H NMR spectrum (CF_3CO_2D), δ, ppm: 1.77-2.10 (4H, m, $2CH_2$); 2.38 (3H, s, SCH_3); 3.55-3.92 (4H, m, $2NCH_2$); 8.04 (1H, s, 5-H). Found, %: C 46.79; H 5.15; N 22.76. $C_{12}H_{15}N_5OS_2$. Calculated, %: C 46.58; H 4.89; N 22.63.

Hydrazide 4b was obtained in 89% yield; mp 208-210°C (2-propanol). The reaction time was 21 h. IR spectrum, ν, cm^{-1}: 1660 (CO), 3297, 3329 (NH, NH_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.55-1.75 (6H, m, $3CH_2$); 2.5 (3H, s, SCH_3); 3.7-3.92 (4H, m, $2NCH_2$); 4.04 (2H, br. s, NH2); 7.88 (1H, s, NH); 8.46 (1H, s, 5-H). Found, %: C 48.57; H 5.42; N 21.41. $C_{13}H_{17}N_5O_2$. Calculated, %: C 48.28; H 5.30; N 21.65.

(4-Dialkylamino-2-methylthiothieno[2,3-*d*]pyrimidin-6-yl)methanols (5a-c). The corresponding ester **2a-c** (1 mmol) was added in portions to a stirred mixture of $LiAlH_4$ (0.03 g, 0.79 mmol) in anhydrous diethyl ether (15 ml). The reaction mixture was stirred at room temperature until the starting esters disappeared as indicated by thin-layer chromatography (3-6 h). Then, water was added dropwise and the organic layer was separated. The aqueous layer was extracted with three 30-ml chloroform portions. The organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized to give **5a-c**.

Pyrimidinylmethanol 5a was obtained in 60% yield; mp 190-191°C (2-propanol). The reaction time was 3 h. IR spectrum, ν, cm^{-1}: 3306 (OH). ^1H NMR spectrum (CF_3CO_2D), δ, ppm: 2.80 (3H, s, SCH_3); 3.69 (6H, s, $2NCH_3$); 5.14 (2H, s, CH_2); 7.66 (1H, s, 5-H). Found, %: C 47.37; H 5.10; N 16.60. $C_{10}H_{13}N_3OS_2$. Calculated, %: C 47.04; H 5.13; N 16.46.

Pyrimidinylmethanol 5b was obtained in 83% yield; mp 175-177°C (benzene). The reaction time was 6 h. IR spectrum, ν, cm^{-1}: 3186 (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.84-2.15 (4H, m, $2CH_2$); 2.57 (3H, s, SCH_3); 2.95 (1H, br. s, OH); 3.6-3.88 (4H, m, $2NCH_2$); 4.75 (2H, s, CH_2); 7.0 (1H, s, 5-H). Found, %: C 51.29; H 5.11; N 14.79. $C_{12}H_{15}N_3OS_2$. Calculated, %: C 51.22; H 5.37; N 14.93.

Pyrimidinylmethanol 5c was obtained in 67% yield; mp 94-96°C (5:1 hexane–2-propanol). The reaction time was 2 h. IR spectrum, ν, cm^{-1}: 3291 (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.60-1.85 (6H, m, $3CH_2$); 2.56 (3H, s, SCH_3); 2.66 (1H, br. s, OH); 3.65-3.90 (4H, m, $2NCH_2$); 4.82 (2H, s, CH_2); 7.04 (1H, s, 5-H). Found, %: C 52.95; H 5.50; N 14.55. $C_{13}H_{17}N_3OS_2$. Calculated, %: C 52.85; H 5.80; N 14.22.

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