SYNTHESIS OF THIENO[3,2-*d*]PYRIMIDIN-4-ONES AND ALKYLATION THEREOF

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The 3-*R*-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**5a-c**) and 3-*R*-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-ones (**5d-g**) were synthesized using methyl 3-aminothiophene-2-carboxylate and alkyl-, arylisocyanates and isothiocyanates respectively, which in turn converted into its N- и S- alkyl derivates (**8a-e, 9a-g**). 2-Aminothieno[3,2-*d*]pyrimidin-4(3*H*)-one (**14a-c**, **16**) were received as a result the interaction the methyl 3-aminothiophene-2-carboxylate with benzoyl- and pyrimidin-2-yl cyanamides.

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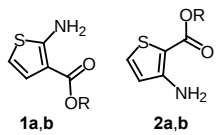
Introduction

The interest for thieno[2,3-*d*]pyrimidines is caused by a wide spectrum of biological activity of these compounds, and half of these reports are revealed in the last decade.[1]

Synthesis of the thieno[2,3-*d*]pyrimidines, which include substituents in position 2, more often realised through the interaction of methyl 2-aminothiophene-3-carboxylates **1** with nitrile compounds[2-4] or cyanamides[5-7] in conditions of acid catalysis. With the isocyanates[8-12] and the isothiocyanates[11,13] in the absence of a catalyst formed compounds with the substituent in position 3. Far less reports about the synthesis of regioisomeric thieno[3,2-*d*]pyrimidines.[7,12] Anyway, 3-aminothiophene-2-carboxylate **2**, that are necessary for it, could be obtained through the condensation esters of mercaptoacetic acid with halogenated propionitriles[14,15] and now are commercially available.

It makes us hope that the synthetic approaches, realized for the 2-aminothiophene-3-carboxylate, could be used in the case of their regioisomers too.



1a,**b** **2a**,**b**

1, **2**: R = Me (**a**), Et (**b**)

Experimental

Instrumentation

Melting points were determined in an open capillary tube and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument in DMSO-d_6 as solvent and TMS as an internal standard. Elemental analyses were performed on a Carlo Erba NA-1500 CHNS Elemental Analyzer. Reaction progress monitored on TLC 0.2 mm silica gel 60 F-254 (Merck) plates using chlorophorme/methanol (20:1) combination as the mobile phase and U.V. light (254 nm) for visualization.

Density functional theory (DFT) calculations were performed using Gaussian 03 program with the B3LYP exchange-correlation functional. The basis (6-311++G*) was used for all atoms. Geometry optimizations were performed with full relaxation of all atoms. Calculations were performed in gas phase without solvent effects. Vibrational frequency calculations were performed to check that the stable structures had no imaginary frequency.

General Procedure for the synthesis of 3-R-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (5a-c) and 3-R-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-ones. (5d-g)

0.01 mole of isocyanate or isothiocyanate was added to solution of 1.57 g (0.01 mol) methyl 3-aminothiophene-2-carboxylate **2a** in anhydrous dioxane. The reaction mixture was heated to 60 °C during 6 h. The solvent was removed in a rotary evaporator, 10 ml of 1M solution MeONa in methanol was added and was heated to 60 °C during 6 h. The solvent was removed in a rotary evaporator, the residue was dissolved in 40 ml of water and treated with hydrochloric acid to weak acid reaction. The formed solid product was filtered and washed with water.

Synthesis of methyl 3-(3-(2-chloroethyl)ureido)thiophene-2-carboxylate. (6)

1.05 g (0.01 mol) 2-chloroethylisocyanate was added to solution of 1.57 g (0.01 mol) methyl 3-aminothiophene-2-carboxylate **2a** in anhydrous dioxane. The reaction mixture was heated to 70 °C during 6 h. The cooled reaction mixture was poured onto water (500 ml). The separated white solid product was filtered, dried and recrystallized from dioxane, (2.26 g, 86%), m.p. 146-148 °C [139-142 °C][12]. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H, OCH_3), 4.06 (t, 2H, *J* = 8.2 Hz, CH_2), 4.47 (t, 2H, *J* = 8.2 Hz, CH_2), 6.32 (s, 1H, NH), 7.11 (d, 1H, *J* = 5.2 Hz, thiophene ring), 7.83 (d, 1H, *J* = 5.2 Hz, thiophene ring), 10.54 (s, 1H, NH). Anal. Calcd. for $C_9H_{11}ClN_2O_3S$: C, 41.15; H, 4.22; N, 10.66. Found: C, 41.08; H, 4.25; N, 10.66.

Synthesis of 6,7-dihydro-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine-9-one. (7)

2.63 g (0.01 mol) compound **6** was dissolved in 10 ml dioxane, was added 5 ml strong ammonia and was boiled the resulting solution within 8 hours. The reaction mass was poured in 100 ml water, treated with hydrochloric acid to weak acid reaction and the separated white solid product was filtered, dried and recrystallized from *i*-PrOH:DMF (1:1), (1.44 g, 74 %), m.p. 182-184 °C. ^{1}H NMR (DMSO-d_6): δ = 4.29 (t, 2H, *J* = 8.3, CH_2), 4.79 (t, 2H, *J* = 8.3, CH_2), 7.09 (d, 1H, *J* = 5.2, H-4 thiophene ring), 7.86 (d, 1H, *J* = 5.2, H-5 thiophene ring). Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.47; H, 3.11; N, 14.42. Found: C, 49.58; H, 3.20; N, 14.52.

General procedure for the synthesis of alkylated 3-R-thieno-[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (8a-e) and 3-R-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidin-4(1*H*)-ones. (9a-g)

0.005 mol compound **5a-g** was dissolved in 5 ml 1M solution MeONa in metanol. The solvent was removed in a rotary evaporator, the residue was dissolved in anhydrous DMF and 0.005 mol alkylhalogenide was added. The reaction mixture was heated to 100 °C during 5 min and after 15 min was poured in 100 ml water. The separated solid product was filtered, dried and recrystallized from *i*-PrOH:DMF (1:1).

General procedure for the synthesis of 2-(pyrimidine-2-ylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-ones. (14a-c)

0.01 mol corresponding *N*-(pyrimidin-2-yl)cyanamide and 0.01 mol strong hydrochloric acid were added to solution of 1.57 g (0.01 mol) methyl 3-aminothiophene-2-carboxylate **2a** in 25 ml *i*-PrOH, was boiled the resulting solution within 3 hours and after cooling to room temperature was poured in 100 ml water. The solution NaOH (0.6 g in 15 ml water) was added. The separated solid product was filtered, dried and recrystallized from *i*-PrOH:DMF (1:1).

Synthesis of *N*-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidine-2-yl)benzamide. (16)

The solution of 0.785 g (0.005 mol) methyl 3-aminothiophene-2-carboxylate **2a** and 0.67 g (0.005 mol) benzoylcyanamide in 20 ml dioxane was heated to 60 °C during 2 h. The separated solid product was filtered, dried and recrystallized from dioxane, (0.80 g, 59%), m.p. 241-242 °C. ^{1}H NMR (DMSO-d_6): δ = 7.21 (d, 1H, *J* = 5.2 Hz, thiophene ring), 7.51 (t, 2H, *J* = 7.5 Hz, ArH), 7.62 (t, 1H, *J* = 7.3 Hz, ArH), 8.03 (d, 1H, *J* = 5.2 Hz, thiophene ring), 8.12 (d, 2H, *J* = 7.9 Hz, ArH), 11.79 (br s, 1H, NH), 12.42 (br s, 1H, NH). Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49. Found: C, 57.57; H, 3.29; N, 15.52.

Spectral data of newly prepared compounds.

3-(4-Chlorophenyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (5a)

Yield: 95 %, m.p. 345-346 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 6.93 (d, 1H, *J* = 5.2, H-4 thiophene ring), 7.29 (d, 2H, *J* = 7.5, ArH), 7.50 (d, 2H, *J* = 7.5, ArH), 8.01 (d, 1H, *J* = 5.2, H-5 thiophene ring), 11.98 (s, 1H, NH). Anal. Calcd. for $C_{12}H_7ClN_2O_2S$: C, 51.71; H, 2.53; N, 10.05. Found: C, 51.68; H, 2.54; N, 10.07.

3-(2,4-Difluorophenyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (5b)

Yield: 82 %, m.p. 344 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 7.05 (d, 1H, *J* = 5.3 Hz, H-4 thiophene ring), 7.15-7.32 (m, 2H, ArH), 7.40-7.49 (m, 1H, ArH), 8.12 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring), 11.88 (s, 1H, NH). Anal. Calcd. for $C_{12}H_6FN_2O_2S$: C, 51.43; H, 2.16; N, 10.00. Found: C, 51.38; H, 2.24; N, 9.93.

3-Isopropylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (5c)

Yield: 62 %, m.p. 235-236 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 1.45 (d, 6H, *J* = 6.8 Hz, $2CH_3$), 5.12 (sept, 1H, CH), 7.24 (d, 3H, *J* = 5.3 Hz, H-4 thiophene ring), 8.05 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring) 12.11 (s, 1H, NH). Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32. Found: C, 51.48; H, 4.84; N, 13.37.

3-Methyl-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-one. (5d)

Yield: 62 %, m.p. 327-328 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.58 (s, 3H, SCH_3), 7.17 (d, 1H, *J* = 5.2 Hz, H-4 thiophene ring), 7.86 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring), 12.04 (s, 1H, NH). Anal. Calcd. for $C_7H_6N_2OS_2$: C, 42.41; H, 3.05; N, 14.13. Found: C, 42.37; H, 3.04; N, 14.06.

3-Phenyl-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-one. (5e)

Yield: 94 %, m.p. 347 °C (destr.). ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 7.19-7.30 (m, 3H, ArH, H-4 thiophene ring), 7.48-7.57 (m, 3H, ArH), 8.08 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring), 11.97 (s, 1H, NH). Anal. Calcd. for $C_{12}H_8N_2OS_2$: C, 55.36; H, 3.10; N, 10.76. Found: C, 55.36; H, 3.18; N, 10.67.

3-(2-Fluorophenyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-one. (5f)

Yield: 70 %, m.p. 295-297 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 7.22 (d, 3H, *J* = 5.2 Hz, H-4 thiophene ring), 7.38-7.49 (m, 3H, ArH), 7.63-7.73 (m, 1H, ArH), 8.00 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring), 11.92 (s, 1H, NH). Anal. Calcd. for $C_{12}H_7FN_2OS_2$: C, 51.78; H, 2.54; N, 10.06. Found: C, 51.84; H, 2.49; N, 9.98.

3-(4-Methoxyphenyl)-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-one. (5g)

Yield: 35 %, m.p. 278-280 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 3.87 (s, 3H, OCH_3), 7.11 (d, 2H, *J* = 7.8 Hz, ArH), 7.25 (d, 1H, *J* = 5.3 Hz, H-4 thiophene ring), 7.29 (d, 2H, *J* = 7.8 Hz, ArH), 8.12 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring), 12.06 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{10}N_2O_2S_2$: C, 53.77; H, 3.47; N, 9.65. Found: C, 53.84; H, 3.42; N, 9.66.

2-(3-(4-Chlorophenyl)-2,4-dioxo-3,4-dihydrothieno[3,2-*d*]pyrimidine-1(2*H*)-yl)acetonitrile. (8a)

Yield: 64 %, m.p. 189 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 5.22 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 7.3 Hz, ArH), 7.44-7.51 (m, 3H, ArH, H-4 thiophene ring), 8.12 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{14}H_8ClN_3O_2S$: C, 52.92; H, 2.54; N, 13.22. Found: C, 52.84; H, 2.43; N, 13.16.

3-(2,4-Difluorophenyl)-1-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (8b)

Yield: 72 %, m.p. 262 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 3.61 (s, 3H, CH_3), 7.04-7.20 (m, 2H, ArH), 7.29 (d, 1H, *J* = 5.3 Hz, H-4 thiophene ring), 7.30-7.45 (m, 1H, ArH), 8.06 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{13}H_8F_2N_2O_2S$: C, 53.06; H, 2.74; N, 9.52. Found: C, 53.17; H, 2.62; N, 9.44.

3-(2,4-Difluorophenyl)-1-(2-oxopropyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (8c)

Yield: 48 %, m.p. 166-168 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.29 (s, 3H, CH_3), 5.02 (s, 2H, CH_2), 7.05-7.19 (m, 2H, ArH), 7.22 (d, 1H, *J* = 5.3 Hz, H-4 thiophene ring), 7.30-7.41 (m, 1H, ArH), 8.05 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{15}H_{10}F_2N_2O_3S$: C, 53.57; H, 3.00; N, 8.33. Found: C, 53.47; H, 2.99; N, 8.26.

3-Isopropyl-1-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. (8d)

Yield: 68 %, m.p. 115-116 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 1.41 (d, 6H, *J* = 6.8 Hz, $2CH_3$), 3.50 (s, 3H, CH_3), 5.17 (sept, 1H, CH), 7.18 (d, 3H, *J* = 5.3 Hz, H-4 thiophene ring), 7.97 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.42; H, 5.34; N, 12.35.

4-((3-Isopropyl-2,4-dioxo-3,4-dihydrothieno[3,2-*d*]pyrimidine-1(2*H*)-yl)methyl)benzonitrile. (8e)

Yield: 77 %, m.p. 204-205 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 1.50 (d, 6H, *J* = 6.8 Hz, $2CH_3$), 5.21 (sept, 1H, CH), 5.32 (s, 2H, CH_2), 7.10 (d, 3H, *J* = 5.3 Hz, H-4 thiophene ring), 7.51 (d, 2H, *J* = 7.4 Hz, ArH), 7.70 (d, 2H, *J* = 7.4 Hz, ArH), 7.90 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91. Found: C, 62.87; H, 4.77; N, 13.01.

3-Methyl-2-(methylthio)thieno[3,2-*d*]pyrimidine-4(3*H*)-one. (9a)

Yield: 64 %, m.p. 196-197 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.62 (s, 3H, SCH_3), 3.54 (s, 3H, NCH_3), 7.21 (d, 1H, *J* = 5.2 Hz, H-4 thiophene ring), 7.99 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring). Anal. Calcd. for $C_8H_8N_2OS_2$: C, 45.26; H, 3.80; N, 13.20. Found: C, 45.30; H, 3.80; N, 13.27.

2-(Methylthio)-3-phenylthieno[3,2-*d*]pyrimidine-4(3*H*)-one. (9b)

Yield: 54 %, m.p. 182-183 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.47 (s, 3H, SCH_3), 7.23-7.34 (m, 3H, ArH, H-4 thiophene ring), 7.52-7.61 (m, 3H, ArH), 7.97 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 56.86; H, 3.63; N, 10.25.

2-(4-Oxo-3-phenyl-3,4-dihydrothieno[3,2-*d*]pyrimidine-2-ylthio)acetonitrile. (9c)

Yield: 52 %, m.p. 194-195 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 4.09 (s, 2H, CH_2), 7.31-7.43 (m, 3H, ArH, H-4 thiophene ring), 7.55-7.63 (m, 3H, ArH), 8.08 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{14}H_9N_3OS_2$: C, 56.17; H, 3.03; N, 14.04. Found: C, 56.11; H, 3.11; N, 13.97.

3-(2-Fluorophenyl)-2-(methylthio)thieno[3,2-*d*]pyrimidine-4(3*H*)-one. (9d)

Yield: 54 %, m.p. 137-139 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.52 (s, 3H, SCH_3), 7.30 (d, 3H, *J* = 5.2 Hz, H-4 thiophene ring), 7.35-7.47 (m, 3H, ArH), 7.57-7.65 (m, 1H, ArH), 8.08 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{13}H_9FN_2OS_2$: C, 53.41; H, 3.10; N, 9.58. Found: C, 53.35; H, 3.15; N, 9.64.

2-(3-(2-Fluorophenyl)-4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidine-2-ylthio)acetonitrile. (9e)

Yield: 20 %, m.p. 117-118 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 4.15 (s, 2H, CH_2), 7.36-7.47 (m, 3H, ArH, H-4 thiophene ring), 7.54 (t, 1H, *J* = 7.8 Hz, ArH), 7.63-7.71 (m, 1H, ArH), 8.11 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{14}H_8FN_3OS_2$: C, 52.98; H, 2.54; N, 13.24. Found: C, 53.06; H, 2.50; N, 13.32.

Methyl 2-(3-(2-fluorophenyl)-4-oxo-3,4-dihydrothieno-[3,2-*d*]-pyrimidin-2-ylthio)acetate. (9f)

Yield: 64 %, m.p. 177-178 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 3.71 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 7.25 (d, 1H, *J* = 5.2 Hz, H-4 thiophene ring), 7.36-7.44 (m, 2H, ArH), 7.48 (t, 1H, *J* = 7.8 Hz, ArH), 7.60-7.68 (m, 1H, ArH), 8.06 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{15}H_{11}FN_2O_3S_2$: C, 51.42; H, 3.16; N, 7.99. Found: C, 51.36; H, 3.09; N, 8.09.

3-(4-Methoxyphenyl)-2-(2-oxopropylthio)thieno[3,2-*d*]pyrimidine-4(3*H*)-one. (9g)

Yield: 66 %, m.p. 161-163 °C. ^{1}H NMR (300 MHz, DMSO-d_6+CCl_4) δ: 2.29 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 7.09 (d, 2H, *J* = 7.8 Hz, ArH), 7.20 (d, 1H, *J* = 5.3 Hz, H-4 thiophene ring), 7.25 (d, 2H, *J* = 7.8 Hz, ArH), 7.99 (d, 1H, *J* = 5.3 Hz, H-5 thiophene ring). Anal. Calcd. for $C_{16}H_{14}N_2O_3S_2$: C, 55.47; H, 4.07; N, 8.09. Found: C, 55.39; H, 4.10; N, 8.13.

2-(Pyrimidin-2-ylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-one. (14a)

Yield: 37 %, m.p. 278-279 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.10-7.15 (m, 2H, H-5 pyrimidine ring, H-4 thiophene ring), 7.92 (d, 1H, *J* = 5.2 Hz, H-5 thiophene ring), 8.71 (d, 2H, *J* = 5.2 Hz, H-4, H-6 pyrimidine ring), 10.98 (br s, 1H, NH), 13.11 (br s, 1H, NH). Anal. Calcd. for $C_{10}H_7N_5OS$: C, 48.97; H, 2.88; N, 28.55. Found: C, 49.07; H, 2.86; N, 28.55.

2-(4,6-Dimethylpyrimidin-2-ylamino)thieno[3,2-*d*]pyrimidine-4(3*H*)-one. (14b)

Yield: 42 %, m.p. 271-272 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.47 (s, 6H, CH_3), 6.81 (s, 1H, H-5 pyrimidine ring), 7.12 (d, 1H, *J* = 5.2 Hz, thiophene ring), 7.85 (d, 1H, *J* = 5.2 Hz, thiophene ring), 10.51 (br s, 1H, NH), 13.39 (br s, 1H, NH). Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06; N, 25.62. Found: C, 52.81; H, 4.10; N, 25.70.

2-(4-Phenylpyrimidin-2-ylamino)thieno[3,2-*d*]pyrimidin-4(3*H*)-one. (14c)

Yield: 88 %, m.p. 256-258 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.20 (d, 1H, *J* = 5.2 Hz, thiophene ring), 7.56-7.62 (m, 3H, ArH), 7.68 (d, 1H, *J* = 5.3 Hz, H-5 pyrimidine ring), 7.20 (d, 1H, *J* = 5.2 Hz, thiophene ring), 8.04 (d, 1H, *J* = 5.2 Hz, thiophene ring), 8.16-8.22 (m, 2H, ArH), 8.74 (d, 1H, *J* = 5.3 Hz, H-6 pyrimidine ring), 11.04 (br s, 1H, NH), 13.35 (br s, 1H, NH). Anal. Calcd. for $C_{16}H_{11}N_5OS$: C, 59.80; H, 3.45; N, 21.79. Found: C, 59.87; H, 3.47; N, 21.87.

Results and Discussion

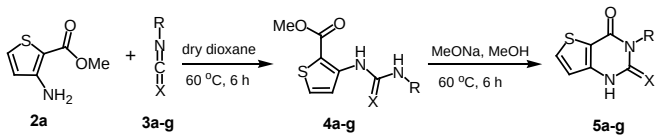
Reaction of isocyanates and isothiocyanates with aminoester **1** as well as their isomers with **2** begins with the formation of the corresponding urea or thiourea, which is the product of nucleophilic attack on the carbon atom of the isocyanate or isothiocyanate groups of the amino nitrogen atom. Further in basic catalysis conditions the interaction resulting urea nitrogen or thiourea with a carbonyl group carbon atom of the ester group and the pyrimidine ring closure of an annelated. Under the conditions of acid catalysis generated thiourea result thieno[1,3]thiazin-4-one.[16,17] Thus the cyclization involves an amino group and the carbonyl carbon of the ester group. However their reactivity apparently depends on the position of the thiophene ring. In fact, pK_a for thiophene-2-carboxylic acid (3.53) is 0,57 lower than for thiophene-3-carboxylic acid (4.10),[18] in other words carboxyl group position 2 has more acid than in position 3. In the same way the protonation of the oxygen atom in thiophene-3-carboxamide is esaier,[19] so it is more basic than in amide group in position 2.

The same result is shown by our quantum-chemical calculations with the GAUSSIAN 03 program.[20] Payment of charges made by the method of Merz-Singh-Kollman,[21] which, in our opinion, the most adequately reflects the reactivity of the atoms in the processes occurring under the charge control. Thus, the data in Table 1 demonstrate that the amino compound **2a** more nucleophilic and electrophilic carbonyl group is more than the compound **1a**.

Table 1. The charge on the amino nitrogen atom and the carbonyl group of compounds **1a**, **2a**, and methyl anthranilate.

Functional group	**1a**	**2a**	methyl anthranilate
$-NH_2$	-0.703	-0.776	-0.776
-C(O)OMe	0.614	0.785	0.601

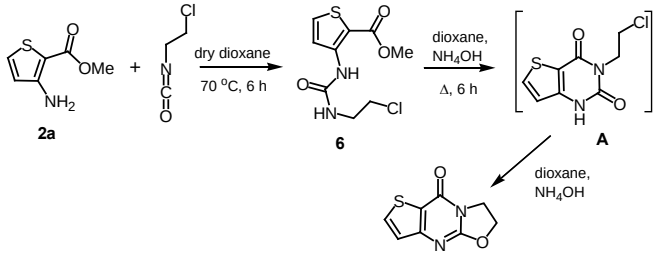
Furthermore, the optimal conformation aminoester **1a** formed in the intramolecular hydrogen bond between the hydrogen atom of the amino group and the carbonyl oxygen stabilizing the initial state. In the methyl 3-aminothiophene-2-carboxylate the formation of such a connection **2a** is difficult as the ester group undergoes steric hindrance by volume of sulfur, which leads to the formation of weak hydrogen bond between the hydrogen atom of the amino group and the bridging nitrogen atom of the ester group, a carbonyl atom and not oxygen, as in the case **1a**. Thus, in aminoester **2a** aminogroup is a more nucleophilic and carbonyl more electrophilic than methyl 2-aminothiophene-3-carboxylate **1a**. The interaction of compound **2a** with isocyanates and isothioscyanates **3a-g** also initially leads to carbamides or thiocarbamides **4a-g**, alkaline treatment of which leads to pyrimidinediones **5a-c** or 2-thioxopyrimidin-4-ones **5d-g** (Scheme 1).



3,**4**,**5**: X = O, R = 4-ClC$_6$H$_4$ (**a**), 2,4-FC$_6$H$_3$ (**b**), *i*-Pr (**c**), X = S, R = Me (**d**), Ph (**e**), 2-FC$_6$H$_4$ (**f**), 4-MeOC$_6$H$_4$ (**g**)

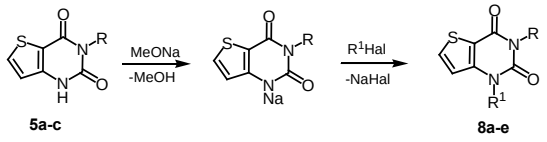
Scheme 1.

Due to interaction of compound **2a** with 2-chloroethylisocyanates methyl 3-(3-(2-chloroethyl)ureido) thiophene-2-carboxylate **6** was received with potential antihypertensive activity.[12] Our attempt to obtain 3-(2-chloroethyl) thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **A** in the conditions similar to the conditions of getting 3-(2-chloroethyl)quinazolin-2,4(1*H*,3*H*)-dione,[22] shows that the reaction proceeds very slowly. In more complicated conditions (two-day boiling ammonia-dioxane solution) leads to the tricyclic compounds 7 (Scheme 2).



Scheme 2.

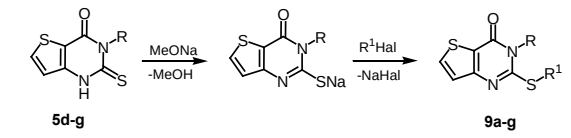
Pyrimidinediones **5a-c**, due to a movable hydrogen atom at position 1, are able to join the reaction of alkylation, just as 3-R-quinazolin-2,4(1*H*,3*H*)-diones[23] and thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones.[24] Treatment of a solution of 1M sodium methoxide in methanol solution was transferred to their corresponding sodium salts. After removal of methanol on a rotary evaporator, the salt was dissolved in dimethylacetamide and treated with a solution of the alkyl halide. The brief heating leads to the forming of alkyl derivatives **8a-e** (Scheme 3).



8: R = 4-ClC$_6$H$_4$, R^1 = CH$_2$CN (**a**), R = 2,4-FC$_6$H$_3$, R^1 = Me (**b**), CH$_2$COCH$_3$ (**c**), R = *i*-Pr, R^1 = Me (**d**), CH$_2$C$_6$H$_4$CN (**e**)

Scheme 3.

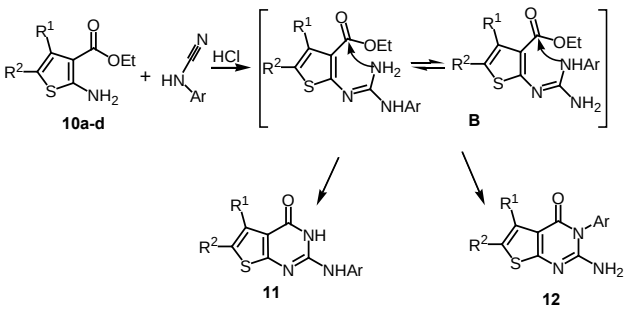
2-Thioxopyrimidin-4-ones **5d-g**, is like the isomeric 2-thioxo-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones[13,25-26] alkylated at the sulfur atom. In this case, the compound **5d-g** are also converted into its sodium salt, which under mild conditions with good yields subjected to alkylation (Scheme 4).



9: R = R^1= Me (**a**); R = Ph, R^1 = Me (**b**), CH$_2$CN (**c**); R = 2-FC$_6$H$_4$, R^1 = Me (**d**), CH$_2$CN (**e**), CH$_2$COOCH$_3$ (**f**); R = 4-MeOC$_6$H$_4$, R^1 = CH$_2$COCH$_3$ (**g**)

Scheme 4.

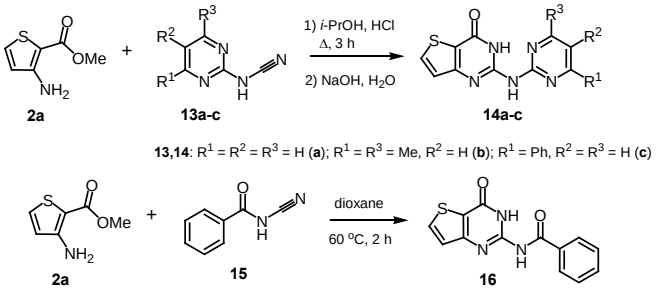
Structural analog of isocyanates and isothiocyanates are cyanamides. Describes the reaction of substituted ethyl 2-aminothiophene-3-carboxylates **10a-d** and a dialkyl- and diarylcyanamides, catalyzed anhydrous HCl (Scheme 5).[6] Dialkyl cyanamides yield 2-dialkylaminothieno [2,3-*d*]-pyrimidin-4(3*H*)-ones under these reaction conditions. However, when *N*-monoarylcyanamides were used two isomeric thienopyrimidin-4-ones **11** and **12** have been obtained as the condensation products of their dry HCl catalyzed reaction with thiophene o-aminoesters **10a-d**. The reaction proceeds via the transient guanidine intermediate **B**, which cyclizes through two alternate pathways to afford the isomeric 2-aminothieno[2,3-*d*]pyrimidin-4 (3*H*)-ones.



R^1 = R^2 = -(CH$_2$)$_4$ (**a**), -(CH$_2$)$_2$-N-(CH$_2$C$_6$H5)CH$_2$- (**b**), R^1 = R^2 = Me (**c**), R^1 = C$_6$H$_5$, R^2 = H (**d**); Ar = C$_6$H$_5$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$.

Scheme 5.

We used the *N*-pyrimidin-2-ylcyanamides **13a-c** and benzoylcyanamide **15**. Previously, we have shown[27-29] that these cyanamides reacted with esters of anthranilic acid to form quinazolin-4(3*H*)-ones similar to compound **11**. Structure of the reaction product of methyl anthranilate with cyanamide **13b** is confirmed RSA.[30] Quantum-chemical calculation results given above indicate that 3-aminothiophene-2-carboxylates **2** largely similar anthranilate than 2-aminothiophene-3-carboxylates **1**. This suggests that the main product cyclization are just compounds **14a-c** and **16** (Scheme 6). Indeed, in the ^{1}H NMR spectrum of compounds **14a-c** singlets observed in the 10.5-11.0 ppm and 13.1-13.5 ppm, which corresponds to sufficiently "sour" magnetically nonequivalent protons of NH groups. In the case of a structure similar to the structure of the compounds **12**, in the spectrum of protons expected signal group NH$_2$. In the ^{1}H NMR spectrum of compound **16** are also present singlets 11.79 and 12.45 ppm



13,**14**: R^1 = R^2 = R^3 = H (**a**); R^1 = R^3 = Me, R^2 = H (**b**); R^1 = Ph, R^2 = R^3 = H (**c**)

Scheme 6.

Conclusion

The interaction of methyl 3-aminothiophene-2-carboxylate with isocyanates, isothiocyanates and the cyanamides leads to 2- and 3-substituted thieno[3,2-*d*]pyrimidine-4(1*H*)-ones (**5a-g**, **14a-c**, **16**). The 3-*R*-thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**5a-c**) and 3-*R*-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-4(1*H*)-ones (**5d-g**) are suitable scaffolds for getting various N- и S-alkyl derivatives. Use of 2-chloroethyl isocyanate allows to obtain tricyclic 6,7-dihydro-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-9-one (7). The interaction of methyl 3-aminothiophene-2-carboxylate with cyanamides is a regioselective process and it leads to *N*-2-substituted 2-aminothieno[3,2-*d*]pyrimidine-4(3*H*)-ones **(14a-c)**.

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