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Thieno[2,3-*d*]Pyrimidin-4-Ones. Part 3.* Electrophilic Ipso-Substitution Reactions of Methyl and Methoxycarbonyl Groups

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Authors' contributions

This work was carried out in collaboration between the authors. Authors BZE, KAB, AZK and ISO carried out the synthesis. Author BZE designed the scheme and the protocol for synthetic pathway and wrote the first draft. Authors KMB, NDA, AY and HAA managed the analysis of the study and spectroscopic evaluation. Authors KMS and BZE offered the idea of researches. Author KMS did the collation of the data and editing of the write-up. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Interactions of 5,6-dimethyl- (**1**), 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones (**2**) and 2,3-dimethyl- (**5-7**), 2-methyl-3-methoxycarbonylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones (**14-16**) with nitrating mixture were investigated. For the first time it is shown, that in dependence on the presence of substituent in position 2 and 3 of pyrimidine and thiophene rings reaction goes in various directions; by electrophilic ipso-substitution of methyl groups at C-5 by nitro group, or its oxidation up to carboxyl groups with formation corresponding 5-carboxy derivatives. It is revealed, that at absence of the substituent in position 3 (compound **1**) the electrophilic ipso-substitution of methyl group by nitro group with formation of 5-nitro derivative took

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place. It is found, that at interaction of compounds **2,5-7, 14-16** with nitrating mixture instead of substitution of methyl groups at C-2, goes in an unexpected direction, i.e. there are oxidation of methyl groups or electrophilic ipso-substitution of methoxycarbonyl groups in position 3 by nitro group.

Keywords: thieno[2,3-d]pyrimidin-4-ones; nitrating mixture; electrophilic ipso-substitution; oxidation; methyl groups.

1. INTRODUCTION

Pyrimidin-4-ones [3,4], and compounds, containing pyrimidine ring – thieno- [5,6] and benzopyrimidin-4-ones (quinazolin-4-ones) [7-9] are widely distributed in quickly developing heterocyclic systems. Because condensed pyrimidin-4-ones and their derivatives show plural reaction ability and have various biological and pharmacological activities [10-19].

Electrophilic ipso-substitution reaction is widely used in organic chemistry [20-22]. It allows entering of new functional groups into a molecule, instead of other groups. Reactions are in part investigated on an example of 2-oxo-, -thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones [23].

It was earlier revealed, that bicyclic thieno[2,3-*d*]pyrimidin-4(3H)-ones (such as 2-oxo-, -thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones) at interaction with nitrating mixture (NM) are exposed to electrophilic ipso-substitution of one or two methyl groups with formation 5- or 6-mononitro- and 5,6-dinitro derivatives in good yields [23]. Recently it has been revealed, that tricyclic 2,3-dimethylthieno[2,3-*d*]pyrimidin-4-ones, containing electron-donating methylene chains (**5-7**) under action of NM are exposed to oxidation of methyl groups at C-3 up to carboxylic groups instead of the expected ipso-substitution of methyl groups by nitro group [24].

**Part 1 and 2. See literatures [1] and [2].*

2. MATERIALS AND METHODS

2.1 General Conditions

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 - $CDCl_3$ on Varian 400-MR spectrometer operating accordingly at 400 and 100 MHz. Tetramethylsilane (TMS) was used as internal standard, chemical shifts δ of ^{1}H and ^{13}C were recorded in ppm.

Mass spectra were acquired on a Agilent-6520 Q-TOF LC/MS and VG Autospec-3000 spectrometers. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected.

IR spectra were recorded on Shimadzu FTIR-8400 and IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

The reaction process was monitored by TLC on Sorbfil and Whatman UV-254 precoated aluminum plates using C_6H_6/CH_3OH (3:1 and 5:1) and C_6H_6/CH_3COCH_3 (3:1) solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary.

Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

2.2 Synthesis

2.2.1 Synthesis of 5,6-dimethyl- and 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones (1,2)

2.2.1.1 5,6-Dimethylthieno[2,3-d]pyrimidin-4(3H)-one (1)

To a 6 g (0.03 mol) 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene (**8**) was added 12 mL formamide and a mixture was heated on oil bath at 140-150ºC for 6 h. Reaction mixture was cooled and the residue was filtered, washed with water and dried. The precipitate was recrystallized from ethanol and the desired compound (**1)** was obtained in excellent yield.

Yield: 5.26 g (97%), mp 270ºC, R_f=0.65 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6 – $CDCl_3$) δ: 2.39 (3H, s, 6-CH_3), 2.48 (3H, s, 5-CH_3), 7.81 (1H, s, H-2), 11.95 (1H, s, NH). IR (KBr) cm^{-1}: 1692 (C=O), 1595 (C=N), 1506 (C-N). ESI-MS in m/z (rel. %): 181 ([M+H]$^+$, 3.1), 148 (13.5), 126 (17.7), 99 (16.7), 65 (100). Anal. calcd. for $C_8H_8N_2OS$ (180.15): C, 53.33; H, 4.44; N, 15.55. Found: C, 53.42; H, 4.34; N, 15.66.

2.2.1.2 3,5,6-Trimethylthieno[2,3-d]pyrimidin-4(3H)-one (2)

To a 3 g (0.017 mol) 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one **(1)** dissolved in 20 ml ethanol were added 1.45g (0.026 mol) NaOH and 1.62 mL (3.7 g, 0.026 mol) CH_3I. Reaction mixture was boiled on water bath at 85-90ºC for 7 h and was cooled up to room temperature and distilled water (40 mL) was added. The precipitate was filtered, washed with distilled water and dried. The residue was recrystallized from methanol and the compound **2** was obtained in moderate yield.

Yield: 1.56 g (48.3%), mp 158-160ºC, R_f=0.58 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6 - $CDCl_3$) δ: 2.50 (3H, s, 6-CH_3), 2.52 (3H, s, 5-CH_3), 3.91 (3H, s, N-CH_3), 7.50 (1H, s, H-2). IR (KBr) cm^{-1}: 3040 (NH), 1665 (C=O), 1572 (C=N), 1481 (C-N). ESI-MS in m/z (rel. %): 195 ([M+H]$^+$, 4.0), 154 (70), 126 (100), 99 (60), 65 (86). Anal. calcd. for $C_9H_{10}N_2OS$ (194.07): C, 55.67; H, 5.15; N, 14.43. Found: C, 55.58; H, 5.24; N, 14.52.

2.2.2 Synthesis of 2-oxo- and 2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones (3,4) were carried out according to method described by *Shodiyev et al.* [23] with some changes

2.2.2.1 2-Oxo-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (3)

To a 2 g (10.05 mmol) 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene **(8)** was added 4.2 g (70.2 mmol) urea and a mixture was heated on a sand bath at 220-230ºC for 2 h. The reaction mixture was cooled and was processed with NaOH (5 %), the residue was filtered, acidified with acetic acid (10%). The precipitate washed with distilled water and dried. Yield: 1.8 г (91 %), mp. 350-351ºC (ethanol) (on the literary [23] data mp. 350ºC), R_f=0.4 (C_6H_6/CH_3COCH_3 (3:1)).

2.2.2.2 2-Thioxo-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (4)

To a 2 g (10.05 mmol) 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene **(8)** was added 2.28 g (30 mmol) thiourea and a mixture was heated on a sand bath at 200-210ºC for 2 h. The reaction mixture was cooled and was processed with NaOH (5%), the residue was filtered, acidified with acetic acid (10%). The precipitate washed with distilled water and dried. Yield: 1.6 г (75%), mp. 313-315ºC (ethanol) (on the literary [23] data mp. 313ºC), R_f=0.5 (C_6H_6/CH_3COCH_3 (3:1)).

2.2.3 Synthesis of 2,3-dimethylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones (5-7) were carried out according to method described by *Elmuradov et al.* [1]. *(General procedure)*

To a mixture of 1 mmol 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene (**8**) and 1.5 mmol lactam at cooling (an ice bath) was drop wise added 3.6 mmol $POCl_3$ during 0.5 h. Reaction mixture support 2 h on a boiling water bath, further about 16 h at room temperature, then processed with crushed ice and was added NH_4OH (10%) up to pH 9. The precipitate was filtered, washed with distilled water and dried. The desired compounds (**5-7)** were obtained in good yields.

2.2.3.1 2,3-Dimethylthieno[2,3-d]dihydropyrrolo[1,2-a]pyrimidin-4-one (5)

Yield: 72 %, mp 137-139ºC (hexane), R_f=0.67 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (2H, m, H-7), 2.37 (3H, s, 2-CH_3), 2.47 (3H, s, 3-CH_3), 3.14 (2H, t, *J*=7.6, H-8), 4.16 (2H, t, *J*=7.6, H-6). IR (KBr) cm^{-1} : 1664 (C=O), 1558 (C=N), 1463 (C-N).

2.2.3.2 2,3-Dimethylthieno[2,3-d]tetrahydropyrido[1,2-a]pyrimidin-4-one (6)

Yield: 85%, mp 109-111ºC (heptane), R_f=0.80 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.91 (2H, m, H-8), 1.99 (2H, m, H-7), 2.37 (3H, s, 2-CH_3), 2.47 (3H, s, 3-CH_3), 2.95 (2H, t, *J*=6.7, H-9), 4.02 (2H, t, *J*=6.3, H-6). IR (KBr) cm^{-1}: 1701 (C=O), 1606 (C=N), 1529 (C-N). ESI-MS in m/z (rel. %): 235 ($[M+H]^+$, 3.8), 193 (8.3), 179 (9.1), 166 (69), 154 (17.4), 126 (17.5), 111 (2.3), 82 (20.5), 65 (11.4), 55 (100). Anal. calcd. for $C_{12}H_{14}N_2OS$ (234.21): C, 61.53; H, 5.98; N, 11.96. Found: C, 61.64; H, 6.09; N, 11.83.

2.2.3.3 2,3-Dimethylthieno[2,3-d]tetrahydroazepino[1,2-a]pyrimidin-4-one (7)

Yield: 88.5%, mp 163-164ºC (heptane), R_f=0.82 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.77-1.84 (6H, m, H-7,8,9), 2.37 (3H, s, 2-CH_3), 2.47 (3H, s, 3-CH_3), 3.02 (2H, t, *J*=4.9, H-10), 4.35 (2H, t, *J*=5.2, H-6). IR (KBr) cm^{-1}: 1674 (C=O), 1545 (C=N), 1492 (C-N). ESI-MS in m/z (rel. %): 249 ($[M+H]^+$, 13.7), 207 (21.2), 193 (52.3), 179 (25.7), 166 (100), 154 (69.0), 126 (24.2), 96 (54.5), 69 (42.4), 55 (18.2). Anal. calcd. for $C_{13}H_{16}N_2OS$ (248.32): C, 62.90; H, 6.45; N, 11.29. Found: C, 63.04; H, 6.29; N, 11.39.

2.2.4 Interaction of 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one (1) with nitrating mixture

2.2.4.1 5-Nitro-6-methylthieno[2,3-d]pyrimidin-4(3H)-one (9).

To a 2 g (0.011 mol) compound **1** dissolved in 5.3 mL concentrated H_2SO_4 (ρ=1.820 g/mL) at cooling (an ice bath), were drop wise added nitrating mixture, containing 2.04 mL HNO_3

(ρ=1.360 g/mL) and 3.53 mL H_2SO_4 (ρ=1.820 g/mL) for 1 h. Reaction mixture was mixed at 50ºC for 6 h and after cooling processed with ice. The precipitate was filtered, washed with distilled water up to pH=7 and dried. The desired compound (**9)** was obtained in good yield.

Yield: 1.6 g (69.6%), mp 310ºC (methanol), R_f=0.25 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 2.97 (3H, s, 6-CH_3), 8.06 (1H, s, H-2), 13.41 (1H, s, NH). IR (KBr) cm^{-1}: 3440 (NH), 1691 (C=O), 1596 (C=N), 1505 (NO_2). ESI-MS in m/z (rel. %): 211 ([M]$^+$, 2.8), 193 (47), 174 (18), 165 (100), 138 (65), 110 (45), 83 (40). Anal. calcd. for $C_7H_6N_2O_3S$ (211.17): C, 39.81; H, 2.37; N, 19.90. Found: C, 39.90; H, 2.48; N, 19.81.

2.2.5 Reaction of 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-one (2) with nitrating mixture

2.2.5.1 5-Carboxy-3,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (10).

To a 3.6 g (0.018 mol) compound **2** dissolved in 7.2 mL concentrated H_2SO_4 (ρ=1.820 g/mL) at cooling (an ice bath) were drop wise added nitrating mixture, containing 3.44 mL HNO_3 (ρ=1.360 g/mL) and 4 mL H_2SO_4 (ρ=1.820 g/mL) for 0.5 h. Reaction mixture was mixed at 50ºC for 4 h and after cooling processed with ice. The precipitate was filtered, washed with distilled water up to pH=7 and dried. The desired compound (**10)** was obtained in moderate yield.

Yield: 2.2 g (54 %), mp 245ºC (ethanol), R_f=0.44 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6 - $CDCl_3$) δ: 2.92 (3H, s, 6-CH_3), 3.74 (3H, s, N-CH_3), 7.49 (1H, s, H-2). IR (KBr) cm^{-1}: 3386 (OH), 1706 (O-C=O), 1610 (C=O), 1561 (C=N), 1476 (C-N). ESI-MS in m/z (rel. %): 225 ([M+H]$^+$, 2.0), 179 (5.0), 138 (20.6), 110 (19.6), 95 (34), 83 (51.5), 69 (27), 42 (100). Anal. calcd. for $C_9H_8N_2O_3S$ (224.21): C, 48.21; H, 3.57; N, 12.50. Found: C, 48.31; H, 3.41; N, 12.42.

2.2.6 Interaction of compounds 5-7 with nitrating mixture. Synthesis of 2-methyl-3-carboxythieno[2,3-*d*]pyrimidin-4-ones (11-13). *(General procedure)*

To a cooled (an ice bath) 7.5 mL concentrated H_2SO_4 (ρ=1.820 g/mL) was added 42.73 mmol **5-7** in portions. Then was drop wise added nitrating mixture, containing 14.9 mL HNO_3 (ρ=1.360 g/mL) and 14 mL H_2SO_4 (ρ=1.820 g/mL) for 0.5 h. Reaction mixture was mixed at room temperature for 1 h and was left for 48 h. The mixture processed with ice and the yellow precipitate was filtered, washed with distilled water up to pH=7 and dried. The desired compounds (**11-13)** were recrystallized from ethanol.

2.2.6.1 2-Methyl-3-carboxythieno[2,3-d]dihydropyrrolo[1,2-a]pyrimidin-4-one (11)

Yield: 70%, mp 222-224ºC, R_f=0.45 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (2H, m, H-7), 2.88 (3H, s, 2-CH_3), 3.27 (2H, t, *J*=7.9, H-8), 4.3 (2H, t, *J*=7.5, H-6), 15.36 (1H, s, COOH). IR (KBr) cm^{-1}: 3455 (OH), 1728 (O-C=O), 1682 (C=O), 1562 (C=N), 1481 (C-N).

2.2.6.2 2-Methyl-3-carboxythieno[2,3-d]tetrahydropyrido[1,2-a]pyrimidin-4-one (12)

Yield: 84%, mp 204-205ºC, R_f=0.47 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (2H, m, H-8), 2.08 (2H, m, H-7), 2.90 (3H, s, 2-CH_3), 3.07 (2H, t, *J*=7.0, H-9), 4.14 (2H, t, *J*=6.5, H-6), 15.51 (1H, s, COOH). IR (KBr) cm^{-1}: 3387 (OH), 1698 (O-C=O), 1670 (C=O), 1527

(C=N), 1461 (C-N). ESI-MS in m/z (rel. %): 265 ($[M+H]^+$, 1.5), 247 ($[M-OH]^+$, 80.6), 219 ($[M-COOH]^+$, 64.5), 204 ($[M-COOH(CH_3)]^+$, 3.0), 191 (3.9), 175 (27.1), 138 (24.0), 111 (3.1), 95 (2.3), 82 (100). Anal. calcd. for $C_{12}H_{12}N_2O_3S$ (264.17): C, 54.54; H, 4.54; N, 10.60. Found: C, 54.61; H, 4.63; N, 10.72.

2.2.6.3 2-Methyl-3-carboxythieno[2,3-d]tetrahydroazepino[1,2-a]pyrimidin-4-one (13)

Yield: 80.3%, mp 231-232ºC, R_f=0.45 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.85-1.90 (6H, m, H-7,8,9), 2.91 (3H, s, 2-CH_3), 3.13 (2H, t, *J*=6.0, H-10), 4.48 (2H, t, *J*=5.1, H-6), 15.54 (1H, s, COOH). IR (KBr) cm^{-1}: 3368 (OH), 1704 (O-C=O), 1608 (C=O), 1538 (C=N), 1467 (C-N). ESI-MS in m/z (rel. %): 279 ($[M+H]^+$, 10.0), 261 ($[M-OH]^+$, 100), 149 (2.0). Anal. calcd. for $C_{13}H_{14}N_2O_3S$ (278.24): C, 56.11; H, 5.03; N, 10.07. Found: C, 56.23; H, 5.15; N, 10.18.

2.2.7 Methylation of compounds 11-13. Synthesis of 2-methyl-3-methoxycarbonylthieno[2,3-*d*]pyrimidin-4-ones (14-16) (*General procedure*)

To a 2 mmol compounds **11-13** dissolved in 10 mL absolute methanol was added 2 mL concentrated H_2SO_4 and was boiled at 80-85^{0}C on water bath for 3 h. After cooling of reaction mixture diluted with water (15 mL) and extracted with chloroform (15 mL). The extract dried above anhydrous Na_2SO_4, the solvent was evaporated and the residue was processed by ether. The light yellow precipitate was filtered and desired compounds (**14-16)** were recrystallized from methanol.

2.2.7.1 2-Methyl-3-methoxycarbonylthieno[2,3-d]dihydropyrrolo[1,2-a]pyrimidin-4-one (14)

Yield: 83.4%, mp 142-144ºC, R_f=0.60 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (2H, m, H-7), 2.55 (3H, s, 2-CH_3), 3.16 (2H, t, *J*=7.9, H-8), 3.96 (3H, s, OCH_3), 4.18 (2H, t, *J*=7.5, H-6). IR (KBr) cm^{-1}: 1738 (O-C=O), 1682 (C=O), 1543 (C=N), 1486 (C-N).

2.2.7.2 2-Methyl-3-methoxycarbonylthieno[2,3-d]tetrahydropyrido[1,2-a]pyrimidin-4-one (15)

Yield: 80%, mp 124-126ºC, R_f=0.69 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, m, H-8), 1.99 (2H, m, H-7), 2.54 (3H, s, 2-CH_3), 2.96 (2H, t, *J*=6.8, H-9), 3.97 (3H, s, OCH_3), 4.05 (2H, t, *J*=6.4, H-6). IR (KBr) cm^{-1}: 1727 (O-C=O), 1673 (C=O), 1538 (C=N), 1499 (C-N). ESI-MS in m/z (rel. %): 279 ($[M+H]^+$, 3.8), 247 ($[M-OCH_3]^+$, 100), 219 ($[M-COOCH_3]^+$, 19.2), 206 (1.5), 175 (2.3), 166 (3.1), 138 (2.3), 82 (4.6). Anal. calcd. for $C_{13}H_{14}N_2O_3S$ (278.24): C, 56.11; H, 5.03; N, 10.07. Found: C, 56.01; H, 5.14; N, 9.96.

2.2.7.3 2-Methyl-3-methoxycarbonylthieno[2,3-d]tetrahydroazepino[1,2-a]pyrimidin-4-one (16)

Yield: 85%, mp 104-106ºC, R_f=0.70 (C_6H_6/CH_3OH, 5:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 1.78-1.84 (6H, m, H-7,8,9), 2.53 (3H, s, 2-CH_3), 3.04 (2H, t, H-10), 3.97 (3H, s, OCH_3), 4.37 (2H, t, H-6). IR (KBr) cm^{-1}: 1732 (O-C=O), 1668 (C=O), 1552 (C=N), 1493 (C-N). ESI-MS in m/z (rel. %): 293 ($[M+H]^+$, 1.5), 261 ($[M-OCH_3]^+$, 100), 233 ($[M-COOCH_3]^+$, 2.3), 189 (3.1), 166 (11.5), 96 (20.0), 69 (3.8). Anal. calcd. for $C_{14}H_{16}N_2O_3S$ (292.19): C, 57.53; H, 5.48; N, 9.59. Found: C, 57.64; H, 5.37; N, 9.45.

2.2.8 Interaction of compounds 14-16 with nitrating mixture. Synthesis of 2-methyl-3-nitrothieno[2,3-*d*]pyrimidin-4-ones (17-19) (*General procedure*)

To a cooled (an ice bath) 0.345 ml concentrated H_2SO_4 (ρ=1.835 g/mL) was added 1.5 mmol **14-16**. Then was drop wise added nitrating mixture, containing 0.66 mL HNO_3 (ρ=1.360 g/mL) and 0.585 mL H_2SO_4 (ρ=1.820 g/mL) for 0.5 h. Reaction mixture was mixed at room temperature for 2 h and was left for 48 h. The mixture processed with ice, the yellow precipitate was filtered, washed with distilled water up to pH=7 and dried. The desired 3-nitro products (**17-19)** were recrystallized from ethanol.

2.2.8.1 2-Methyl-3-nitrothieno[2,3-d]dihydropyrrolo[1,2-a]pyrimidin-4-one (17)

Yield: 74%, mp 175-177ºC, R_f=0.51 (C_6H_6/CH_3OH, 5:1, at RT). ^{13}C-NMR ($CDCl_3$) δ: 187.4 (C-4), 186.0 (C-8a), 171.8 (C-9a), 154.4 (C-3), 107.9 (C-2), 96.5 (C-3a), 47.5 (C-6), 33.7 (C-8), 21.6 (C-7), 18.8 (C-10). ^{1}H-NMR ($CDCl_3$) δ: 2.37 (2H, m, H-7), 2.14 (3H, s, 2-CH_3), 3.28 (2H, td, *J*=8.4, *J*=4.0, H-8), 4.21 (2H, t, *J*=7.5, H-6). IR (KBr) cm^{-1}: 1682 (C=O), 1566 (C=N), 1508 (NO_2).

2.2.8.2 2-Methyl-3-nitrothieno[2,3-d]tetrahydropyrido[1,2-a]pyrimidin-4-one (18)

Yield: 63%, mp 162-164ºC, R_f=0.54 (C_6H_6/CH_3OH, 5:1, at RT). IR (KBr) cm^{-1}: 1676 (C=O), 1554 (C=N), 1505 (NO_2).

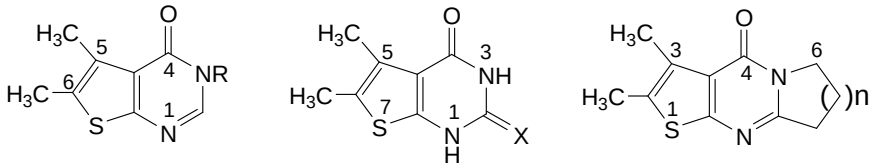
2.2.8.3 2-Methyl-3-nitrothieno[2,3-d]tetrahydroazepino[1,2-a]pyrimidin-4-one (19)

Yield: 65%, mp 117-119ºC, R_f=0.58 (C_6H_6/CH_3OH, 5:1, at RT). ^{13}C-NMR ($CDCl_3$) δ: 186.5 (C-4), 184.8 (C-10a), 172.0 (C-11a), 155.3 (C-3), 106.9 (C-2), 96.2 (C-3a), 42.8 (C-6), 38.2 (C-10), 29.4 (C-7), 26.5 (C-9), 23.9 (C-8), 21.6 (C-12). ^{1}H-NMR ($CDCl_3$) δ: 1.89-1.93 (6H, m, H-7,8,9), 2.15 (3H, s, 2-CH_3), 3.10 (2H, t, *J*=5.6, H-10), 4.36 (2H, t, *J*=4.8, H-6).
IR (KBr) cm^{-1}: 1676 (C=O), 1554 (C=N), 1502 (NO_2), 1441 (C-N).

3. RESULTS AND DISCUSSION

3.1 Chemistry

Reactions of bicyclic (**1,2**) and tricyclic thieno[2,3-*d*]pyrimidin-4-ones (**5-7**) with NM proceed on two independent directions, which represented the certain interest from the point of view of revealing influence of substituents in positions 2 and 3 of pyrimidine and thiophene rings. Therefore in this work we have decided to study interaction of 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one **(1)** - without substituents in positions 2 and 3, 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-one **(2)** - containing methyl group at N-3, 2-oxo- **(3)**, -thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones **(4)** and 2,3-dimethylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones (**5-7**) containing methylene chains with nitrating mixture (NM):

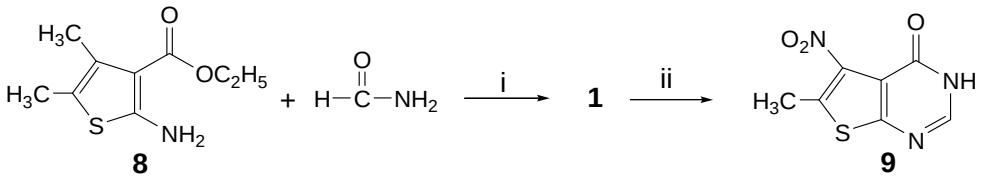


1 R=H; **2** R=CH_3 **3** X=O; **4** X=S **5** n=1; **6** n=2; **7** n=3

Compound **1** was synthesized by condensation of 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene **(8)** with formamide at 110-150ºC. The best condition of cyclization appeared: temperature 140-150^{0}C, duration of reaction 6 h; thus 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one **(1)** was synthesized in excellent yield (97 %) (Scheme 1, i) [25]. It is necessary to emphasize, that yield of compound **1** of the reactions, carried out below 140ºC appeared rather low.

In ^{1}H NMR spectrum of the compound **1** which have been taken off in a mixture of solvents $CDCl_3$-DMSO-d_6, signals of methyl group protons at C-6 are shown as three-proton singlet at 2.48 ppm and methyl group at C-5 has chemical shift at 2.39 ppm (3H, s), the proton at C-2 is observed as one-proton singlet (7.81 ppm), NH group proton also is shown as one-proton singlet in rather weaker field (11.95 ppm).

Reaction of 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one **(1)** with NM was carried out in the ratio of reagents - **1:**NM **-** 1:2 and 1:4, temperature 20ºC and 50ºC, duration of reaction 6, 48, 72, 96, 120, 144, 168 h and have found, that best condition is using of reagents ratio 1:4, temperature 50ºC, duration of reaction 6 h (Scheme 1, ii). In result the reaction product – 5-nitro-6-methylthieno[2,3-*d*]pyrimidin-4(3H)-one **(9)** was obtained in good yield 69.6 % [26]:

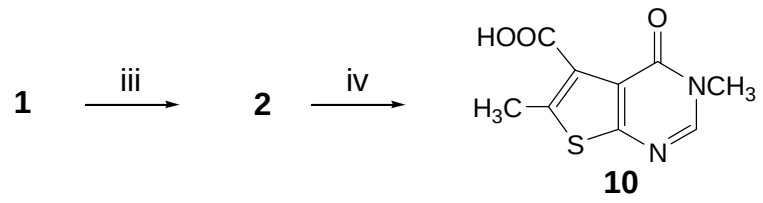


Scheme 1. Reagents and conditions*:* (i) 140-150ºC, 6 h;
(ii) 1: NM – 1:4, 50ºC, 6 h

In a ^{1}H NMR spectrum of the obtained compound **9** ($CDCl_3$-DMSO-d_6) signals of methyl group protons at C-6 are shown as three-proton singlet in rather weaker field (2.97 ppm) in comparison to compound **1**. Thus there is a chemical shift of protons at C-6 and NH group in rather weak field that are connected by influence of entered in position 5 electron-withdrawing nitro group; thus the signal of the second methyl group at C-5 of compound **1** disappears**.** The signal of a proton at C-2 has chemical shift at 8.06 ppm (1H, s), the signal of NH group proton is found at 13.41 ppm (1H, s). In IR-spectrum of this compound the absorption bands of NH group are observed at 3440 cm^{-1}, C=O group - at 1691 cm^{-1}, C=N bond at - 1596 cm^{-1}, C-N bond - at 1463 cm^{-1}, NO_2 group at - 1505 cm^{-1}.

These data show, that at interaction of **1** with NM takes place electrophilic ipso-substitution reaction of methyl group at C-5 by nitro group with formation of 5-nitro-6-methylthieno[2,3-*d*]pyrimidin-4(3H)-one **(9)**. In this aspect compound **1** behaves similarly to 2-oxo-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one [23]. For revealing of substituent influences at N-3

on a reaction directions we study interaction NM and thieno[2,3-d]pyrimidin-4-one (**2**), containing electron-donating methyl group at position 3. For this purpose was synthesized 3,5,6-trimethylthieno[2,3-d]pyrimidin-4(3H)-one **(2)** by alkylation of **1** with methyl iodide (Scheme 2, iii). The obtained compound **2** under action of NM forms 5-carboxy-3,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one **(10)** (Scheme 2, iv)**:**



Scheme 2. Reagents and conditions: (iii) CH_3I, EtOH, KOH, 78ºC; (iv) 2:NM–1:4, 50ºC, 4h

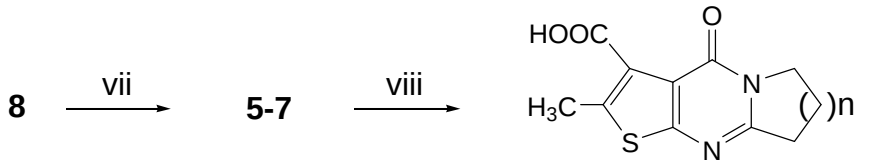
The received results allow drawing a conclusion, that presence of the substituent (methyl group) at N-3 promotes oxidation of CH_3-group at C-5 up to carboxyl group. In absence of it, i.e. in case of unsubstituted 5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one **(1),** as in a case of 2-oxo-, -thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones [23] reaction is accompanied by electrophilic ipso-substitution of 5-CH_3 group by nitro group.

With the purpose of studying influence of oxo (C=O) and thioxo (C=S) group in position 2 on reaction directions we synthesized 2-oxo- **(3)** (Scheme 3, v) and 2-thioxo-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-ones **(4)** by fusion together of 2-amino-3-ethoxycarbonyl-4,5-dimethylthiophene **(8)** with urea or thiourea at heating (200-230^{0}C) for 2h (Scheme 3, vi); thus cyclization products **3,4** were obtained in excellent yields (80-95 %) (on the literary data [23] yields 40-70%):

Scheme 3. Reagents and conditions*:* (v) 8:$(H_2N)_2C=O$ – 1:7, 220-230ºC (vi) 8:$(H_2N)_2C=S$ – 1:3, 200-210ºC

On the literary [23] data the ratio of reagents - **8:**urea (thiourea) was 1:4 (1:1.5). Thus, it was revealed, that increase twice of urea or thiourea amounts promoted essential increase of reaction products **3, 4**.

For expansion of sphere of using this reaction we carried out interaction of 2,3-dimethylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones (**5-7**) with NM. Compounds **5-7** were synthesized by condensation of ester **8** with γ-butyro-, δ-valero- and ε-caprolactams at presence phosphorus oxychloride (Scheme 4, vii). Researches of reactions of compounds **5-7** with NM were shown, as in this case there is a selective oxidation of 3-CH_3 groups up to corresponding carbonic acids - 2-methyl-3-carboxythieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones **(11-13)** in good yields (70-84 %) (Scheme 4, viii):



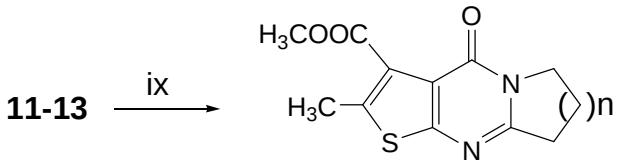
11 n=1; **12** n=2; **13** n=3

Scheme 4. Reagents and conditions*:* (vii) lactam, $POCl_3$, Δ
(viii) 5-7: NM – 1:7.5, rt, 48 h

Attempts to carry out oxidation of second methyl groups at C-2, with increase in duration of reaction, using of tenfold surplus of NM were not successful; thus electrophilic ipso-substitution of 2-CH_3 groups or oxidation up to corresponding carbonic acids didn't occur.

In ^{1}H NMR spectrum of compounds **11-13** ($CDCl_3$) signals of methyl group protons at C-2 are shown as three-proton singlet in the field of 2.88-2.91 ppm, thus there is no signal of methyl group protons of initial compounds **(5-7)** at C-3 (2.37 ppm), one-proton singlet of OH groups (compounds **11-13**) are shown in the field of 15.36-15.54 ppm.

It was theoretically possible to assume, that substitution of hydroxyl group of carbonic acids on methoxyl group can change electronic density at carbon atom at C-2 and promote course of electrophilic ipso-substitution methyl group at C-2. Therefore we synthesized methyl esters by esterification of compounds **11-13** at boiling in absolute methanol at the presence of the concentrated sulfuric acid; 2-methyl-3-methoxycarbonylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones **(14-16)** were obtained in good yields (80-85%) (Scheme 5, ix):



14 n=1; **15** n=2; **16** n=3

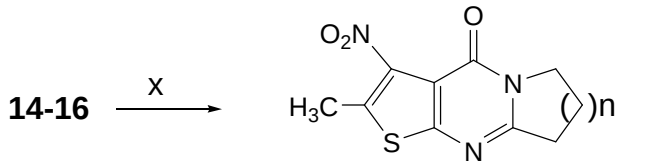
Scheme 5. Reagents and conditions*:* (ix) CH_3OH, H_2SO_4, Δ

In ^{1}H NMR spectrum of compounds **14-16** ($CDCl_3$) signals of methyl group protons are shown in the field of 2.53-2.54 ppm (three-proton singlet), and chemical shifts of methoxyl groups in the field of 3.96-3.97 ppm (as 3H singlet). In the Table 1 are given some characteristics of the synthesized compounds **1-19**.

Table 1. Some characteristics of the synthesized compounds 1-19

Compound	Emperic formula	R_f	Mp, ºC (solvent)	Yield, %
1	$C_8H_8N_2OS$	0.65	270 (ethanol)	97
2	$C_9H_{10}N_2OS$	0.58	158-160 (methanol)	48.3
3	$C_8H_8N_2O_2S$	0.4	350-351 (ethanol)	91
4	$C_8H_8N_2OS_2$	0.5	313-315 (ethanol)	75
5	$C_{11}H_{12}N_2OS$	0.67	137-139 (hexane)	72
6	$C_{12}H_{14}N_2OS$	0.80	109-111 (heptane)	85
7	$C_{13}H_{16}N_2OS$	0.82	163-164 (heptane)	88.5
9	$C_7H_5N_3O_3S$	0.25	310 (methanol)	69.6
10	$C_9H_8N_2O_3S$	0.44	245 (ethanol)	54
11	$C_{11}H_{10}N_2O_3S$	0.45	222-224 (ethanol)	70
12	$C_{12}H_{12}N_2O_3S$	0.47	204-205 (ethanol)	84
13	$C_{13}H_{14}N_2O_3S$	0.45	231-232 (ethanol)	80.3
14	$C_{12}H_{12}N_2O_3S$	0.60	142-144 (methanol)	83.4
15	$C_{13}H_{14}N_2O_3S$	0.69	124-126 (methanol)	80
16	$C_{14}H_{16}N_2O_3S$	0.70	104-106 (methanol)	85
17	$C_{10}H_9N_3O_3S$	0.51	175-177 (ethanol)	74
18	$C_{11}H_{11}N_3O_3S$	0.54	162-164 (ethanol)	63
19	$C_{12}H_{13}N_3O_3S$	0.58	117-119 (ethanol)	65

The esters **14-16** react with NM in the above-described conditions and were obtained 2-methyl-3-nitrothieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones **(17-19)** in good yields (65-74 %) (Scheme 6, x), i.e. thus electrophilic ipso-substitution of 3-methoxycarbonyl groups occurs, but 2-methyl groups don't participate in the reactions:

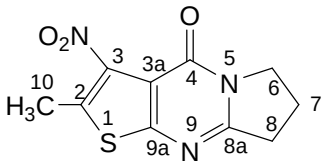


17 n=1; **18** n=2; **19** n=3

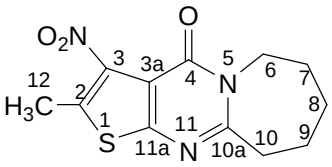
Scheme 6. Reagents and conditions*:* (x) 14-16: NM – 1:9.5, rt, 48h

In a ^{1}H NMR spectrum of compounds **17-19** ($CDCl_3$) signals of methyl group's protons at C-2 are shown as three-proton singlet in the field of 2.14-2.15 ppm; thus, signals of methoxyl groups of initial compounds **(14-16)** at C-3 (3.96-3.97 ppm) disappear.

The ^{13}C NMR spectrum of compounds **17,19** also confirms the resulted structure (see an experimental part):



17



19

Reaction course of thieno[2,3-d]pyrimidin-4-ones in different directions with formation of 3-nitro(carboxy)-2-methyl derivatives (**11-13**, **17-19**) opens wide opportunities for synthesis of new synthones for creation new heterocyclic compounds. Further work in this direction will take place in the future.

4. CONCLUSION

For the first time the interactions of 5,6-dimethyl-, 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-ones (**1,2**) and 2,3-dimethyl- (**5-7**), 2-methyl-3-methoxycarbonylthieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones (**14-16**) with nitrating mixture were investigated.

It is shown, that in the case of thieno[2,3-*d*]pyrimidin-4-ones, without substituents at N-3 electrophilic ipso-substitution of methyl groups at C-5 by nitro group took place. However at interaction of 3,5,6-trimethylthieno[2,3-*d*]pyrimidin-4(3H)-one (**2**) and 2,3-dimethylthieno[2,3-*d*]pyrimidin-4-ones (**5-7)** with NM the oxidation of methyl groups up to carboxyl groups with formation 5-carboxy-6-methylthieno[2,3-*d*]pyrimidin-4(3H)-one (**10**) and 2-methyl-3-carboxythieno[2,3-*d*]dihydropyrrolo-, -tetrahydropyrido-, tetrahydroazepino[1,2-*a*]pyrimidin-4-ones **(11-13)** were observed which are not known for these systems. Such phenomenon (for compounds **5-7**), apparently, is connected by the more electronic density of methyl groups (by the example of compound **5**) at C-3 (q= –0.166 e) in comparison methyl groups at C-2 (q= –0.145 e). Therefore there is a selective oxidation of methyl groups at C-3. It is also confirmed by quantum-chemical calculation methods (Hyper Chem. 7.01, AM1).

Thus it is shown a possibility of electrophilic ipso-substitution reactions of methyl or methoxycarbonyl groups in the series of thieno[2,3-*d*]pyrimidin-4-ones; i.e. under action of nitronic ion (NO_2^+) take only place electrophilic ipso-substitution of one methyl group at C-5 (**1**) and methoxycarbonyl groups at C-3 (**14-16**) or oxidation of methyl groups at C-5 (**2**) and at C-3 (**5-7**). 2-Methyl-3-carboxythieno[2,3-*d*]pyrimidin-4-ones don't react with a nitrating mixture. The advanced synthesis method for 5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3H)-one (**1)** (an excellent yield, 97 %) is developed.

Additionally, starting compounds (**5-7**) were individually evaluated for their antiproliferative activities on mammalian cancer cell models. The tested compounds showed weak affection on human cervix adenocarcinoma cells (HeLa) whereas some of the tested compounds exhibited more consistent inhibition of cell growth on murine myeloma cells (P3X) [10]. New compounds (**11-19**), which are synthesized in this work, are derivatives of starting compounds **5-7**. Further work in this direction will take place in the future.

ACKNOWLEDGMENTS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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