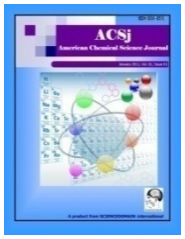

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Thieno [2, 3-d] Pyrimidine-4-Ones. Part 4.* Directions of Reactions of the 2-Oxo-, -Thioxo-5, 6-Dimethyl-3, 4-Dihydrothieno [2, 3-d] Pyrimidine-4-Ones with Electrophilic Reagents

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Authors' contributions

This work was carried out in collaboration between all authors. Author ISO carried out the synthesis. Author BZE designed the scheme and the protocol for synthetic pathway and wrote the first draft. Authors KMS and BZE offered 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.

Original Research Article

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ABSTRACT

Interaction of 5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (1), -thione(2) with alkylation agents (methyl-, ethyl-, n-propyl-, n-butyl iodides, allylbromide, benzyl chloride) in different conditions (in the presence of catalyst and/or without catalyst) were investigated. It was shown that methyl group in position 5 under action of nitrating mixture (NM) takes place aromatic ipso-substitution reaction or its oxidation up to corresponding carboxylic acid. Directions of reactions depend on nature of substituent in position N-3. It is revealed, that at absence of the substituent in position 3 (compounds 1, 2, 11) the electrophilic ipso-substitution of methyl group by nitro group with formation of 5-nitroderivatives took place. It is found, that at interaction of compounds 3, 19 with NM instead of substitution of methyl groups at C-5 go in an expected direction, i.e. there are oxidation of methyl groups.

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Keywords: *Thieno [2, 3-d] pyrimidine-4-ones; alkylation; nitrating mixture; electrophilic ipso-substitution; oxidation.*

1. INTRODUCTION

Previously, we have shown that the direction of the methylation reaction of 2- thioxo-5, 6 -dimethyl-3, 4-dihydrothieno [2, 3-*d*] pyrimidine-4-one [4,5] depends on the nature of the alkylating agent and solvent, reaction temperature and other factors. In difference of that the alkylation of 2-oxo-5, 6-dimethyl-3,4-dihydrothieno [2, 3-*d*] pyrimidine-4-one (1), irrespective of the above mentioned factors goes mainly at N-3 nitrogen atom [5]. This class of compounds is practical interest because pyrimidine-4-ones, their fused analogues with thiophene [6-11], benzene rings [12-19] and their derivatives show antimicrobial [20-25], bactericidal [26,27], cytotoxic [28,29] and anticholinesterase [30,31] activities.

**Parts 1-3. See literatures [1-3].*

2. MATERIALS AND METHODS

2.1 General Conditions

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

Mass spectra were acquired on a Kratos MS-30 (UK) spectrometer. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected.

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

The reactionary process was monitored by TLC on SilufolUV-254 precoated aluminum plates using C_6H_6/CH_3OH (3:1 and 5:1) or $CHCl_3/CH_3OH$ (9:1 and 15:1) solvent systems 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 2-oxo-5, 6-dimethyl-, 2-thioxo-5, 6-dimethyl- and 2-oxo-3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-*d*] pyrimidine-4-ones (1-3)

2.2.1.1 Synthesis of 2-oxo- and 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d]pyrimidine-4-ones (1, 2)

Synthesis of 2-oxo- and 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-ones (1, 2) were carried out according to the method described by Shodiyev M. [5]

2.2.1.2 2-Oxo-3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (3)

To a solution of 0.2 g (5 mmol) of sodium hydride in 20 ml absolute DMF were added 1 g (5 mmol) of 2-oxo-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one and 0.34 ml (5.5 mmol) methyl iodide. Reaction mixture was heated at 60–65ºC for 8 h, and was diluted with water, and the formed precipitate was filtered off, washed with water and dried.

Yield: 0.6 g (57 %), mp 263-265^{0}C, R_f=0.55 (C_6H_6/CH_3OH, 3:1, at RT).

2.2.1.3 Synthesis of 2-oxo-1, 3, 5, 6-tetramethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (4) in the interphase catalysis (IPC) conditions

In a two-necked flask equipped with a mechanical stirrer, a reflux condenser were placed the 40 ml of benzene, 2 g (10 mmol) of 2-oxo-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one, 2 g (50 mmol) of sodium hydroxide, 1.28 g (4 mmol) of tetrabutylammonium bromide (TBAB), 1.36 ml (22 mmol, ρ=2,28 g/ml) of methyl iodide and 40 ml of water. The reaction mixture was stirred and heated on a water bath at 45-55ºC for 6 h. The mixture was transferred to a separating funnel, the aqueous layer was separated, and the benzene layer was washed with water, dried over Na_2SO_4. The solvent was distilled off and the residue was recrystallized from hexane.

Yield: 1.43 g (63 %), mp 118-120^{0}C, R_f=0.7 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.25 (3H, s, 6-CH_3), 2.33 (3H, s, 5-CH_3), 3.33 (3H, s, N(1)-CH_3), 3.43 (3H, s, N(3)-CH_3). IR (KBr) cm^{-1}: 1694 (C=O), 1659 (C=N), 1482 (C-N). ESI-MS in m/z (rel. %): 224 ([M]$^+$; 93), 182([M-42]$^+$; 24), 181 (21), 171 (27), 165 (30), 145 (30), 126 (22), 85 (33), 57 (100).

2.2.1.4 Synthesis of 2-oxo-1, 3-diethyl-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (5) in the presence of TBAB

Reaction carried out analogously to synthesis of compound 4; from of 40 ml benzene, 2 g (10 mmol) of 2-oxo-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one, 2 g (50 mmol) of sodium hydroxide, 1.28 g (4 mmol) of TBAB, 1.7 ml (22 mmol, ρ=1,41 g/ml) of ethyl bromide and 40 ml of water was obtained compound 5 in moderate yield.

Yield: 1.3 g (51 %), mp 110-112^{0}C (hexane), R_f=0.73 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, N(1)-$CH_2C\underline{H}_3$), 1.24 (3H, t, N(3)-$CH_2C\underline{H}_3$), 2.29 (3H, s, 6-CH_3), 2.30 (3H, s, 5-CH_3), 3.89 (4H, q, N(1)-CH_2, N(3)-CH_2). IR (KBr) cm^{-1}: 1692 (C=O), 1654 (C=N), 1573 (C-N).

2.2.1.5 Synthesis of 2-oxo-1, 3-dibenzyl-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (6)in the interphase catalysis (IPC) condition

By above-mentioned method from 40 ml of benzene, 2 g (10 mmol) of 2-oxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one, 2 g (50 mmol) of sodium hydroxide, 1.28 g (4 mmol) of TBAB, 2.7 ml (22 mmol, ρ=1.026 g/ml) of benzyl chloride and 40 ml of water was synthesized substance 6 in good yield.

Yield: 2.86 g (75 %), mp 202-204^{0}C (ethanol), R_f=0.75 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s, 6-CH_3), 2.30 (3H, s, 5-CH_3), 5.04 (2H, s, N(1)-CH_2), 5.17 (2H, s, N(3)-CH_2), 7.2-7.4 (10H, m, 2(C_6H_5)). IR (KBr) cm^{-1}: 1692 (C=O), 1654 (C=N), 1573 (C-N). ESI-MS in m/z (rel. %): 376 ([M]$^+$; 100), 333 (36), 285 (59), 196 (14), 152 (26), 133 (12), 91 (11).

2.2.1.6 2-Methylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (11)

To a solution of 1 g (4.7 mmol) of 2-thioxo- 5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one in 40 mL of ethanol was added 0.32 ml (5,17 mmol) of methyl iodide, and the solution was refluxed for 4 h. The reaction mixture was work-up with water and the formed precipitate was filtered, washed with water and dried.

Yield: 0.64 g (61 %), mp 273-275^{0}C (ethanol), R_f=0.73 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s, 6-CH_3), 2.31 (3H, s, 5-CH_3), 2.49 (3H, s, S-CH_3), 12.54 (1H, s, NH). IR (KBr) cm^{-1}: 1690 (C=O), 1650 (C=N), 1570 (C-N). ESI-MS in m/z (rel. %): 226 ([M]$^+$; 17), 183 (44), 167 (31), 147 (67), 87 (27), 59 (100).

2.2.1.7 2-Ethylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (12)

Reaction carried out analogously to synthesis of compound 11; from 2.12 g (10 mmol) of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one, 40 ml of ethanol 1.2 g(11 mmol, 0.83 ml, ρ=1.45 g/ml) of ethyl bromide the product 12 was obtained in good yield.

Yield: 1.38 g (58 %), mp 222-224^{0}C (ethanol), R_f=0.71 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, S-$CH_2C\underline{H}_3$), 2.31 (3H, s, 6-CH_3), 2.34 (3H, s, 5-CH_3), 3.12 (2H, q, S-CH_2), 12.5 (1H, s, NH). IR (KBr) cm^{-1}: 1697 (C=O), 1642 (C=N), 1481 (C-N). ESI-MS in m/z (rel. %): 240 ([M]$^+$; 100), 197 (32), 181 (38), 143 (18), 87 (67).

2.2.1.8 2-Propylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (13)

By above-mentioned method from 1.06 g (5 mmol) of 2-thioxo-5, 6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one, 40 mL of ethanol, 0.935 g (5.5 mmol, 0.53 ml, ρ=1.75 g/ml) propyl iodide was synthesized compound 13.

Yield: 0.77 g (61 %), mp 178-180^{0}C (ethanol), R_f=0.70 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 0.98 (3H, t, $(CH_2)_2C\underline{H}_3$), 1.67 (2H, m, S-CH_2-$C\underline{H}_2$), 2.31 (3H, s, 6-CH_3), 2.33 (3H, s, 5-CH_3), 3.12 (2H, t, S-CH_2), 12.5 (1H, s, NH). ESI-MS in m/z (rel. %): 254 ([M]$^+$; 100), 211 (30), 195 (38), 101 (75), 100 (48).

2.2.1.9 2-Butylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (14)

Reaction carried out analogously to synthesis of compound 11; from 1.06 g (5 mmol) of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one, 40 ml of ethanol, 1.01 g (5.5 mmol, 0.626 ml, ρ=1.616 g/ml) n-butyl iodide was obtained reaction product 14 in moderate yield.

Yield: 0.6 g (45 %), mp 190-191^{0}C (ethanol), R_f=0.65 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (CD_3OD) δ:0.96 (3H, t, $(CH_2)_3C\underline{H}_3$), 1.47 (2H, m, S-$(CH_2)_2$-$C\underline{H}_2$), 1.71 (2H, m, S-CH_2-$C\underline{H}_2$), 2.35 (3H, s, 6-CH_3), 2.39 (3H, s, 5-CH_3), 3.2 (2H, t, S-CH_2), 12.45 (1H, s, NH).IR (KBr) cm^{-1}: 1692 (C=O), 1595 (C=N), 1506 (C-N).

2.2.1.10 2-Allylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (15)

By above-mentioned method from 1.06 g (5 mmol) of 2-thioxo-5, 6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one, 40 ml of ethanol, 0.665 g (5.5 mmol, 0.47 ml, ρ=1.398 g/ml) of allylbromide was synthesized compound 15 in moderate yield.

Yield: 0.69 g (55 %), mp 158-160^{0}C (ethanol), R_f=0.67 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.31 (3H, s, 6-CH_3), 2.34 (3H, s, 5-CH_3), 3.83 (2H, d, S-CH_2), 5.14 (1H, d, =CHH), 5.33 (1H, d, =CHH), 5.93 (1H, m, CH=), 12.55 (1H, s, NH). ESI-MS in m/z (rel. %): 252 ([M]$^+$; 100), 209 (55), 208 (35), 199 (32), 193 (31), 155 (37), 99 (48).

2.2.1.11 2-Benzylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (16)

Reaction carried out analogously to synthesis of compound 11; from 1.06 g (5 mmol) of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one, 40 ml of ethanol, 0.69 g (5.5 mmol, 0.63 ml, ρ=1.026 g/ml) of benzyl chloride, was obtained substance 16 in good yield.

Yield: 0.93 g (62 %), mp 243-245^{0}C (ethanol), R_f=0.60 (C_6H_6/CH_3OH, 3:1, at RT).^{1}H-NMR (CD_3OD) δ: 2.36 (3H, s, 6-CH_3), 2.40 (3H, s, 5-CH_3), 4.45 (2H, s, S-CH_2), 7.23-7.42 (5H, m, C_6H_5), 12.5 (1H, s, NH). IR (KBr) cm^{-1}: 1650 (C=O), 1551 (C=N), 1493 (C-N).

2.2.1.12 Synthesis of 2-benzylthio-3-benzyl-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (17) in the interphase catalysis (IPC) conditions

In a two-necked flask equipped with a mechanical stirrer, a reflux condenser were placed 40 ml of benzene, 2.12 g (10 mmol) of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d]pyrimidine-4-one, 2 g (50 mmol) of sodium hydroxide, 1.28 g (4 mmol) of TBAB, 2.71 ml (22 mmol, ρ=1.026 g/ml) of benzyl chloride and 40 ml of water. The reaction mixture was stirred and heated on a water bath at 45-55ºC for 6 h. The reaction mixture was transferred to a separating funnel, the aqueous layer was separated, and the benzene was distilled off. The residue was recrystallized from hexane.

Yield: 1.84 g (45 %), mp 110-111^{0}C, R_f=0.8 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.29 (3H, s, 6-CH_3), 2.38 (3H, s, 5-CH_3), 4.35 (2H, s, N(3)-CH_2), 5.24 (2H, s, S-CH_2), 7.16-7.30 (10H, m, 2(C_6H_5)). IR (KBr) cm^{-1}: 1674 (C=O), 1509 (C=N), 1453 (C-N).

2.2.1.13 Interaction of 2-methylthio-5, 6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one (11) with NM. Synthesis of 2-methylthio-5-nitro-6-methyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (18)

To a solution of 1.13 g (5 mmol) 2-methylthio-5,6-dimethyl-3, 4-dihydrothieno [2, 3-d]pyrimidine-4-one (11) dissolved in 5 mL of sulfuric acid was added the nitrating mixture consisting of 0.2 ml (5 mmol) fuming nitric acid and 2 ml (40 mmol) of conc. sulfuric acid. Reaction mixture was left for 12 h (20-25ºC) and work-up with water, and the formed precipitate filtered off, washed with water and dried and reaction product (18) was obtained in moderate yield.

Yield: 0.7 g (55 %), mp 310-312^{0}C (ethanol), R_f=0.35 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.40 (3H, s, 6-CH_3), 2.52 (3H, s, S-CH_3), 12.5 (1H, s, NH).

2.2.1.14 Interaction of 2-oxo-5, 6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one (1) with NM. Synthesis of 2-oxo-5-nitro-6-methyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (19)

To a solution of 6.0 g (30 mmol) 2-oxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (1) dissolved in 10 ml of sulfuric acid at intensive stirring was added drop wise 3.78 g

(60 mmol) of fuming nitric acid dissolved in 5 ml sulfuric acid. Reaction mixture was left for 12 h (20-25ºC) and work-up with water, and the formed precipitate filtered off, washed with water and dried and reaction product (19) was obtained in moderate yield.

Yield: 3.6 g (46 %), mp 328-330^{0}C(ethanol), R_f=0.73 ($CHCl_3/CH_3OH$, 15:1, at RT). ^{1}H-NMR (CF_3COOD) δ: 2.33 (3H, s, 6-CH_3), 10.5 (1H, s, N(1)H), 11.35 (1H, s, N(3)H). ESI-MS in m/z (rel. %): 227 ([M]$^+$; 100), 199 (30), 184 (54), 181 (10), 138 (90).

2.2.1.15 Reaction of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (2) with NM. Synthesis of 2-thioxo-5,6-dinitro-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one (20)

1.0 g (5 mmol) of 2-Thioxo-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (2) was dissolved in 5 ml of sulfuric acid and was added the nitrating mixture consisting of 0.4 ml (10 mmol) of fuming nitric acid and 2 ml (40 mmol) of sulfuric acid. The reaction mixture was left for 12 h (20-25ºC), work-up with water, and the precipitate was filtered, washed with water and dried.

Yield: 0.75 g (60 %), mp 350ºC (ethanol), R_f=0.37 ($CHCl_3/CH_3OH$, 9:1, at RT). ESI-MS in m/z (rel. %): 274 ([M]$^+$; 100), 231 (40), 228 (90), 215 (10), 185 (70).

2.2.1.16 Synthesis of 2-methylthio-3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (21).

2.2.1.16.1 Methylation of 2-methylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (11) with methyl iodide

To a solution of 1.13 g (5 mmol) of 2-methylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one in 40 ml of ethanol was added 0.78 g (5.5 mmol, 0.35 ml, ρ=2,28 g/ml) of methyl iodide was heated for 4 h and the reaction mixture work-up with water. The precipitate was filtered, washed with water, dried and compound 21 was obtained in good yield.

Yield: 0.8 g (67 %), mp 128-130^{0}C (aq. ethanol), R_f=0.8 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s, 6-CH_3), 2.36 (3H, s, 5-CH_3), 2.58 (3H, s, N(3)-CH_3), 3.46 (3H, s, S-CH_3).

2.2.1.16.2 Methylation of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (2) with dimethyl sulfate

2.12 g (10 mmol) of 2-thioxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (2) dissolved in 50 ml (5%) of sodium hydroxide was added 3.78 g (30 mmol, 2.84 ml, ρ=1, 33 g/ml) dimethyl sulfate and was stirred at room temperature for 3 h. The formed precipitate was filtered, washed with water and dried. Recrystallization from aqueous ethanol gave compound 21 in high yield.

Yield: 2.0 g (84 %), mp 128-130ºC, R_f=0.8 (C_6H_6/CH_3OH, 3:1, at RT).

2.2.1.17 Interaction of 2-methylthio-3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-onewith NM. Synthesis of 2-methylthio-3, 6-dimethyl-5-carboxy-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (22)

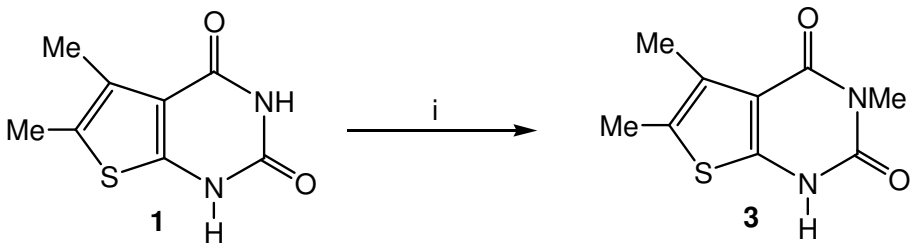
To a solution of 1.2 g (5 mmol) of 2-methylthio-3, 5, 6-trimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one in 5 ml of sulfuric acid and was added the nitrating mixture consisting of 0.2 ml (5 mmol) of fuming nitric acid and 2 ml (40 mmol) of conc. sulfuric acid. The reaction mixture was stirred for 10 h (20-25^{0}C) and diluted with water, and the precipitate was filtered, washed with water and dried. The product 22 was obtained in good yield.

Yield: 0.8 g (59 %), mp 165-167ºC (ethanol), R_f=0.45 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR ($CDCl_3$) δ: 2.64 (3H, s, 6-CH_3), 2.81 (3H, s, N(3)-CH_3), 3.61 (3H, s,S-CH_3), 10.76 (1H, s, COOH).

3. RESULTS AND DISCUSSION

3.1 Chemistry

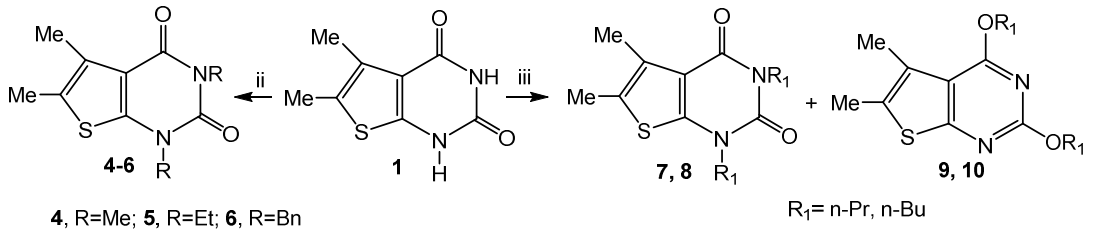
Alkylation of 2-oxo-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (1), methyl iodide proceeds mainly in a "soft" reaction center- N-3 atom to give the 2-oxo-3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (3) (Scheme 1, Table 1) [4]:



Scheme 1. Reagents and conditions: (i) 1, MeX (X=I, OTs), reflux

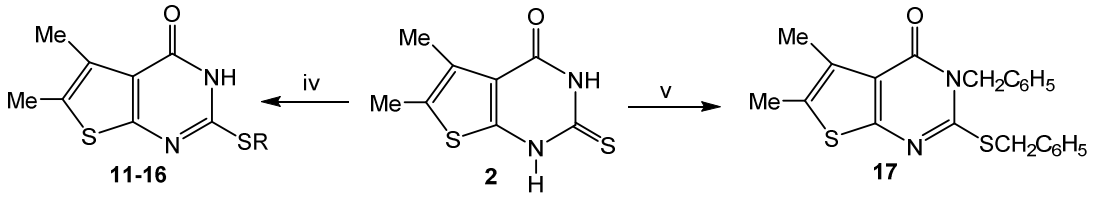
We studied the alkylation of 1 with ethyl-, n-propyl-, n-butyl iodides, ethyl bromide, benzyl chloride in the absence of a phase transfer catalyst and in the presence of tetrabutylammonium bromide (TBAB). It turned out that the reaction in the absence of catalysts doesn't take place. In the case of the alkylation of 1 with methyl iodide, ethyl bromide, and benzyl chloride in presence of TBAB at a ratio of 1: alkylating agent: TBAB - 1:2.2:0.4 were obtained the 1, 3-dialkylation products4-6 (Scheme 2):

In the case of higher alkyl halides (n-propyl-,-butyl iodides) direction of the reaction varies, i.e. were formed with 1, 3-di-n-propyl (-butyl)-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-ones (7,8) and 1-n-propyl (-butyl)-4-n-propyl (-butyl)-oxy-5,6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-ones (9,10) (Scheme 2).



Scheme 2. Reagents and conditions: (ii) 1: RX: TBAB=1:2.2:0.4, 45-55ºC, 6 h (iii) 1: R_1I: TBAB=1:2.2:0.4, 45-55ºC, 6 h

Unlike compound 1 alkylation of 2-thioxo-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (2) with methyl-, n-propyl-, n-butyl iodides, ethyl-, allyl bromides, benzylchloride (BC) goes in a direction of formation of the 2-alkyl (allyl-, benzyl) thio-5,6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-ones (11-16) ingoodyields (Scheme 3, Table 1):



Scheme 3. Reagents and conditions: (iv) 2: RX=1:1.1, EtOH, reflux, 4 h (v) 2: BnCl=1:2.2, 45-55ºC, 6 h

Using the ratio 2: BC- 1:2.2 in the presence of TBAB to give 2-benzylthio-3-benzyl-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (17) (Scheme 3).

We have recently shown that the methyl group in position 5 of 2, 3-polymethylene-5,6-dimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-ones under action of a nitrating mixture is oxidized to form 2, 3-polymethylene-5-carboxy-6-methyl-3,4-dihydrothieno [2, 3-d]pyrimidine-4-ones [3]. Same phenomenon is observed in the case of 3, 5, 6-trimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (3). In difference that, the methyl group of 2-oxo-, -thioxo-5,6-dimethyl-3, 4-dihydrothieno [2,3-d] pyrimidine-4-onesor a methoxyl group of 2,3-polymethylene-5-methoxycarbonyl-6-methyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-ones in the same conditions electrophilic aromatic ipso-substitution by nitro group take place [3].

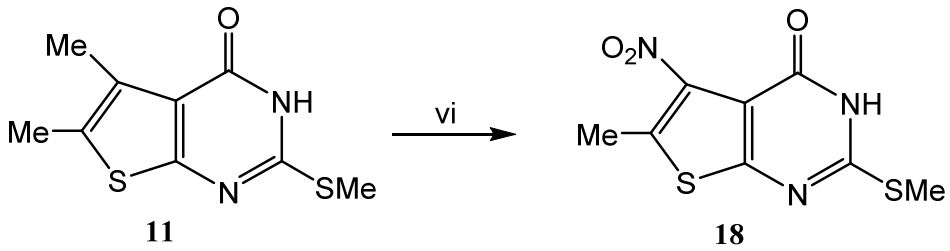
These data show that the direction of the reaction of 5, 6-dimethyl-(5-methoxycarbonyl-6-methyl) 2H, 3H (2H, 3-CH_3, 2,3-disubstituted)-thieno [2, 3-d] pyrimidine-4-ones are very different in depending on the nature of the substituents at positions 2,3 and 5. Thieno [2, 3-d] pyrimidine-4-ones having a hydrogen atom at the N-3 nitrogen atom are subjected to an electrophilic ipso-substitution of the methyl group at C-5 by nitro group. The presence of methyl groups (for example, in the case of 3,5,6-trimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-ones) or 2,3-polymethylene chain of 5,6-dimethyl-2,3-polymethylene-3,4-dihydrothieno [2, 3-d] pyrimidine-4-ones take place the oxidation of 5-CH_3- groups up to corresponding carboxylic acid. If the methyl groups at C-5 of 5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-ones converted into a carboxyl group, and the methoxycarbonyl groups at the

same C-5 atom undergo electrophilic ipso-substitution to give 5-nitro-6-methyl-2, 3-polymethylene-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-ones.

Table 1. Some characteristics of the synthesized compounds 1-6, 11-22

Compound	Empiric formula	R_f	Mp, ºC	Yield, %
1	$C_8H_8N_2O_2S$	0.40	350	85
2	$C_8H_8N_2OS_2$	0.50	313-315	64
3	$C_9H_{10}N_2O_2S$	0.55	263-265	57
4	$C_{10}H_{12}N_2O_2S$	0.70	118-120	63
5	$C_{12}H_{16}N_2O_2S$	0.73	110-112	51
6	$C_{22}H_{20}N_2O_2S$	0.75	202-204	75
11	$C_9H_{10}N_2OS_2$	0.73	273-275	61
12	$C_{10}H_{12}N_2OS_2$	0.71	222-224	58
13	$C_{11}H_{14}N_2OS_2$	0.70	178-180	61
14	$C_{12}H_{16}N_2OS_2$	0.65	190-191	45
15	$C_{11}H_{12}N_2OS_2$	0.67	158-160	55
16	$C_{15}H_{14}N_2OS_2$	0.60	243-245	62
17	$C_{22}H_{20}N_2OS_2$	0.80	110-111	45
18	$C_8H_7N_3O_3S_2$	0.35	310-312	55
19	$C_7H_5N_3O_4S$	0.73	328-330	46
20	$C_6H_2N_4O_5S_2$	0.37	350	60
21	$C_{10}H_{12}N_2OS_2$	0.80	128-130	67 84
22	$C_{10}H_{10}N_2O_3S_2$	0.45	165-167	59

In order to expand the scope of aromatic electrophilic ipso-substitution of the methyl group at C-5 by nitro group, which was first time discovered by us, we studied interaction of 2-methylthio-5, 6-dimethyl-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (11) with NM (Scheme 4, Table 1):

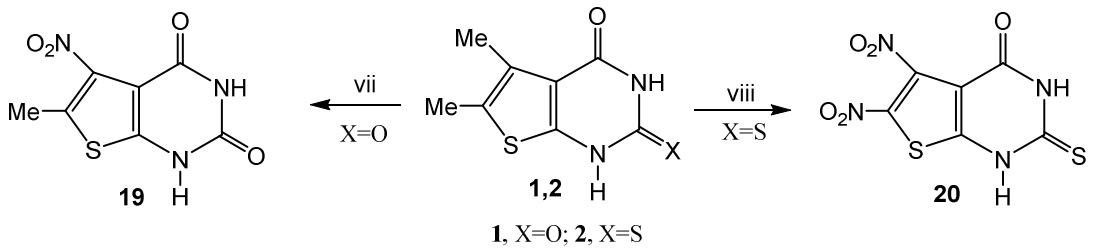


11 18

Scheme 4. Reagents and conditions: (vi) 11: NM=1:1, 20-25ºC, 12 h

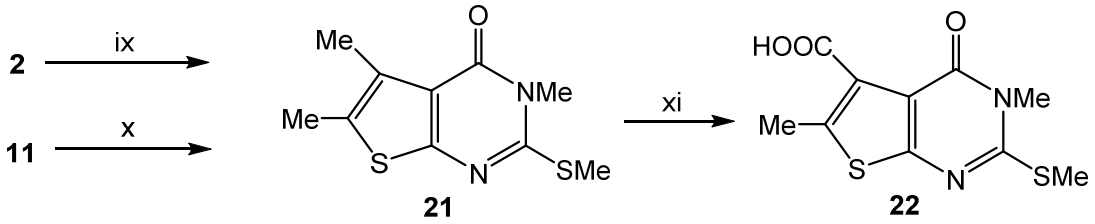
It was found that compound 11 is reacted with a nitrating mixture and forms 2-methylthio-6-methyl-5-nitro-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-one (18) in good yield, i.e. in this case electrophilic-ipso substitution of methyl group by nitro group takes place, which was observed in the case of 2H, 2-CH_3, 2-oxo-, -thioxo-3H-3, 4-dihydrothieno [2, 3-d] pyrimidine-4-ones.

Interactions of compounds 1 and 2 with NM were carried out and 5-mono- (19) and 5, 6-dinitro-derivatives (20) have been synthesized (Scheme 5, Table 1):



Scheme 5. Reagents and conditions: (vii) 1: NM=1:2, 20-25ºC, 12 h (viii) 2: NM=1:2, 20-25ºC, 12 h

In the case of the presence of methyl group at the N-3 nitrogen atom of compound 11, i.e. in the case of 2-methylthio-3,5,6-trimethyl-3,4-dihydrothieno [2, 3-d] pyrimidine-4-one (21) under the action of oxidation of NM occurs oxidation of methyl group at the C-5 up to carboxyl group with formation of 2-methylthio-3,6-trimethyl-5-carboxy-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (22) (Scheme 6, Table 1):



Scheme 6. Reagents and conditions: (ix) 2: Me_2SO_4=1:3, 20-25ºC, 3 h (x) 11: MeI=1:1.1, EtOH, 45-55ºC, 4 h (xi) 21: NM=1:1, 20-25ºC, 10 h

Such direction of the reaction was observed at interaction of 3,5,6-trimethyl-3,4-dihydrothieno [2,3-d]pyrimidine-4-one, 2,3-dimethyl-3,4-dihydrothieno [2,3-d]-dihydropyrrolo-, tetrahydropyrido-, -tetrahydroazepino [1, 2-a] pyrimidine-4-ones with NM [3].

Research on studying of the direction of the electrophilic aromatic ipso-substitution or oxidation of methyl (methoxycarbonyl) groups of the thiophene ring is important for theoretical organic chemistry and for a creation of biologically active compounds, so far as formed substances are perspective synthons for building of new heterocyclic compounds.

4. CONCLUSION

It was expand the use of our recently identified electrophilic aromatic ipso-substitution or oxidation of methyl group at C-5 of thiophenes, fused with pyrimidine ring, without substituents or consisting different substituents at positions 2 and/or 3.

It was confirmed that 5,6-dimethyl-thienopyrimidinones having substituents at the N-3 are subjected to oxidation of the methyl group at C-5, while their derivatives with NH-group in position 3 take place an aromatic electrophilic ipso-substitution of 5-CH_3 group by nitro group. Substituents at C-2 or their nature do not affect to the reaction course. To aromatic electrophilic ipso-substitution or oxidation tugged exceptionally methyl group in position 5;

wherein methyl group at C- 6 is not participated, and it is explained by different electronegativity of carbon atoms at C-5 or C-6.

Some annulated tricyclic thieno [2, 3-d] pyrimidinones 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) [28]. Further work in this direction will take place in the future.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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