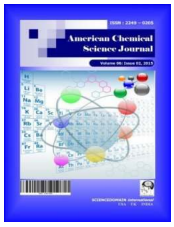

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Thieno[2,3-*d*]Pyrimidine-4-Ones. Part 5.# Hydrogen Chloride Promoted Synthesis of 2-Substituted Thieno[2,3-*d*]Pyrimidine-4-Ones and their Structural Investigations

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Authors' contributions

This work was carried out in collaboration between the all authors. Authors DKA and BBZ carried out the synthesis and analytical works. Authors BZE and BAU designed the scheme and the protocol for synthetic pathway, wrote the first draft and managed the analysis of the study and spectroscopic evaluation. Author BZE offered idea of researches and did the collation of the data and editing of the write-up. All authors read and approved the final manuscript.

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ABSTRACT

Synthesis of some novel 2-substituted thieno[2,3-*d*]pyrimidine-4-ones have been studied. It was found that in this case the 2-amino-4,5-dimethylthiophene carboxamide (**1**) can serve effective synthone for the synthesis 2-aryl-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-4-ones (**3-13**). Interaction of amide **1** with substituted aromatic aldehydes in the presence of concentrated hydrochloric acid leads to the formation of compounds **3-13**. It was impossible to isolate intermediates (**2**), substances with asymmetric carbon atom in position 2. It was revealed that intermediates **2** by oxidation on air easily turn into 2-arylthieno[2,3-*d*]pyrimidine-4-ones. The structure of synthesized compounds was confirmed by IR- and ^{1}H NMR-spectroscopy.

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#Part 1-4. See literatures [5-8]

Keywords: Thieno[2,3-d]pyrimidine-4-ones; aromatic aldehydes; electrophilic addition; oxidation; 2-arylthieno[2,3-d]pyrimidine-4-ones.

1. INTRODUCTION

Bi- and tricyclic thieno[2,3-*d*]pyrimidine-4-ones are widely distributed among the N- and S-containing heterocyclic compounds. At the same time, they are very interesting objects from theoretical and practical points of view. These heterocycles have plural reactionary ability [1] and there are among of them many perspective pharmacological active substances [2,3], including cancer [4].

Given the chemical and pharmacological characteristics of thieno[2,3-*d*]pyrimidine-4-ones, during the last years been systematically studied synthesis, modification and searching for biologically active compounds in a series of polycyclic thieno[2,3-*d*]pyrimidine-4-ones [5-8]. The obtained results show that the thieno[2,3-*d*]pyrimidine-4-ones, in which the molecule has different functional (alkyl, carbonyl, and activated methylene) groups, C=N bond, and fragments react with electrophilic and nucleophilic substitution or joining an ipso-substitution of the alkyl and alkoxy groups by nitro group. Such synthetic investigations yielded a number of new compounds, among which are found substances with high cytotoxic activity [9].

Continuing our previous studies [5-10], in this work we have studied the interaction of 2-amino-4,5-dimethylthiophenecarboxamide with substituted aromatic aldehydes and got the 2-arylthieno[2,3-*d*]pyrimidine-4-ones. The synthesized 2-aryl derivatives may serve as starting compounds for the preparation of new derivatives, substituted at the C=O groups and the C=N bonds of thieno[2,3-*d*]pyrimidine-4-ones.

2. MATERIALS AND METHODS

2.1 General Conditions

^{1}HNMR spectra was recorded in TFA-*d* and TFA-*d*+AcOH-d_4, on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxcane (HMDSO) was used as internal standard, chemical shift δ of ^{1}H was recorded in ppm.

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 Whatman UV-254 precoated aluminum plates using C_6H_6/CH_3COCH_3 (2:1) 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 2-aryl-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-ones (3-13). (General procedure)

To a mixture of 1.45 mmol 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 1.45 mmol aromatic aldehyde in ethanol (20 ml) was added 0.1 ml concentrated HCl. Reactionary mixture was boiled for 4 h and formed precipitate was filtered, washed with ethanol and recrystallized from hexane. The desired compounds (**3-13)** were obtained in good yields.

2.2.1.1 2-Phenyl-5,6-dimethyl-3,4-dihydrothieno [2,3-d]pyrimidin-4-one (3)

Reaction carried out according to the general procedure. From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.154 g (0.145 ml, 1.45 mmol) benzaldehyde compound **3** was obtained in moderate yield.

Yield: 0.185 g (52%), mp 292-294°C (mp 294°C, [11]), R_f=0.45 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.11 (3H, s, 6-CH_3), 2.14 (3H, s, 5-CH_3), 7.34 (2H, t, J=7.8, H_{Ar}-3',5'), 7.49 (1H, t, J=7.5, H_{Ar}-4'), 7.61 (2H, d, J=8.0, H_{Ar}-2',6'). IR (KBr) cm^{-1}: 3436 (NH), 2920 (CH_3), 1658 (C=O), 1539 (C=N), 1487 (C-N).

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

From 0.2 g (1.45 mmol) amide (**1**) and 0.18 g (0.15 ml, 1.45 mmol) *o*-hydroxybenzaldehyde compound **4** was obtained in good yield.

Yield: 0.12 g (62%), mp 329-331°C, R_f=0.56 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.09 (3H, s, 6-CH_3), 2.13 (3H, s, 5-CH_3), 6.83

(1H, d, J=8.3, H_{Ar}-5'), 6.87 (1H, t, J=7.9, H_{Ar}-6'), 7.31 (1H, td, J=1.2, J=8.5, H_{Ar}-4'), 7.63 (1H, dd, J=1.3, J=8.3, H_{Ar}-3'). IR (KBr) cm^{-1}: 3346 (OH), 2966 (CH_3), 1649 (C=O), 1513 (C=N), 1474 (C-N).

2.2.1.3 2-(4-Hydroxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (5)

From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.18 g (1.45 mmol) 4-hydroxybenzaldehyde analouguesly above mentioned method the compound **5** was obtained.

Yield: 0.17 g (53%), mp 338-340°C, R_f=0.69 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.09 (3H, s, 6-CH_3), 2.12 (3H, s, 5-CH_3), 6.83 (2H, d, J=8.7, H_{Ar}-3',5'), 7.6 (2H, d, J=8.9, H_{Ar}-2',6'). IR (KBr) cm^{-1}: 3081 (OH), 2960 (CH_3), 1655 (C=O), 1523 (C=N), 1491 (C-N).

2.2.1.4 2-(4-Methoxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (6)

Reaction carried out according to the general procedure. From 0.2 g (1.45 mmol) amide (**1**) and 0.197 g (0.176 ml, 1.45 mmol) 4-methoxybenzaldehyde product **6** was obtained in good yield.

Yield: 0.24 g (58%), mp 321-322°C, (mp 320-322°C, [11]), R_f=0.72 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.09 (3H, s, 6-CH_3), 2.12 (3H, s, 5-CH_3), 3.58 (3H, s, OCH_3), 6.84 (2H, d, J=8.9, H_{Ar}-3',5'), 7.63 (2H, d, J=9.4, H_{Ar}-2',6'). IR (KBr) cm^{-1}: 3170 (NH), 2963 (CH_3), 1669 (C=O), 1527 (C=N), 1463 (C-N).

2.2.1.5 2-(4-Dimethylaminophenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (7)

From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.216 g (1.45 mmol) 4-dimethylaminobenzaldehyde analouguesly above mentioned method the compound **7** was obtained in good yield.

Yield: 0.252 g (58%), mp 232-234°C, R_f=0.63 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.13 (3H, s, 6-CH_3), 2.15 (3H, s, 5-CH_3), 3.11 (3H, s, $N(CH_3)_2$), 7.64 (2H, d, J=9.0, H_{Ar}-3',5'), 7.94 (2H, d, J=9.0, H_{Ar}-2',6'). IR (KBr) cm^{-1}: 3299 (NH), 2910 (CH_3), 1649 (C=O), 1521 (C=N), 1490 (C-N).

2.2.1.6 2-(4-Nitrophenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (8)

From 0.2 g (1.45 mmol) amide (**1**) and 0.22 g (1.45 mmol) 4-nitrobenzaldehyde analouguesly above mentioned method the compound **8** was obtained in good yield.

Yield: 0.27 g (61%), mp 372-374°C, (mp 370-372°C, [11]), R_f=0.58 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.13 (3H, s, 6-CH_3), 2.16 (3H, s, 5-CH_3), 7.89 (2H, d, J=8.8, H_{Ar}-2',6'), 8.17 (2H, d, J=8.8, H_{Ar}-3',5'). IR (KBr) cm^{-1}: 2917 (CH_3), 1660 (C=O), 1556 (C=N), 1520 (NO_2), 1454 (C-N).

2.2.1.7 2-(3-Bromophenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (9)

Reaction carried out according to the general procedure. From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.17 ml (1.45 mmol) 3-bromobenzaldehyde the compound **9** was obtained in good yield.

Yield: 0.25 g (66%), mp 298-300°C, R_f=0.8 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.11 (3H, s, 6-CH_3), 2.14 (3H, s, 5-CH_3), 7.18 (1H, t, J=8.0, H_{Ar}-5'), 7.55 (1H, dd, J=1.2, J=8.0, H_{Ar}-4'), 7.6 (1H, dd, J=1.8, J=8.0, H_{Ar}-6'), 7.7 (1H, s, H_{Ar}-2'). IR (KBr) cm^{-1}: 2912 (CH_3), 1662 (C=O), 1543 (C=N), 1505 (C-N).

2.2.1.8 2-(2-Hydroxy-5-bromophenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (10)

From 0.2 g (1.45 mmol) amide (**1**) and 0.3 g (1.45 mmol) 2-hydroxy-5-bromobenzaldehyde analouguesly above mentioned method the compound **10** was obtained in good yield.

Yield: 0.25 g (50%), mp 305-307°C, R_f=0.52 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.1 (3H, s, 6-CH_3), 2.13 (3H, s, 5-CH_3), 6.72 (1H, d, J=8.9, H_{Ar}-3'), 7.37 (1H, dd, J=2.3, J=8.9, H_{Ar}-4'), 7.74 (1H, d, J=2.3, H_{Ar}-6'). IR (KBr) cm^{-1}: 3119 (OH), 2913 (CH_3), 1674 (C=O), 1538 (C=N), 1472 (C-N).

2.2.1.9 2-(3-Hydroxy-4-methoxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (11)

Reaction carried out according to the general procedure. From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.22 g

(1.45 mmol) 3-hydroxy-4-methoxybenzaldehyde the compound **11** was obtained in good yield.

Yield: 0.26 g (59%), mp 294-295°C, R_f=0.83 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*+AcOH-d_4) δ: 2.09 (3H, s, 6-CH_3), 2.12 (3H, s, 5-CH_3), 3.65 (3H, s, OCH_3), 6.82 (1H, d, J=8.7, H_{Ar}-5'), 7.23 (1H, d, J=2.4, H_{Ar}-2'), 7.31 (1H, dd, J=2.5, J=8.7, H_{Ar}-6'). IR (KBr) cm^{-1}: 3165 (OH), 2918 (CH_3), 1657 (C=O), 1552 (C=N), 1493 (C-N).

2.2.1.10 2-(3,4-Dimethoxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (12)

From 0.2 g (1.45 mmol) amide (**1**) and 0.24 g (1.45 mmol) 3,4-dimethoxybenzaldehyde analouguesly above mentioned method the compound **12** was obtained in good yield.

Yield: 0.3 g (63%), mp 276-278°C, R_f=0.87 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*+AcOH-d_4) δ: 2.1 (3H, s, 6-CH_3), 2.13 (3H, s, 5-CH_3), 3.65 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 6.85 (1H, d, J=8.6, H_{Ar}-5'), 7.27 (1H, d, J=2.4, H_{Ar}-2'), 7.41 (1H, dd, J=2.4, J=8.6, H_{Ar}-6'). IR (KBr) cm^{-1}: 3446 (NH), 2923 (CH_3), 1678 (C=O), 1521 (C=N), 1496 (C-N).

2.2.1.11 2-Styryl-5,6-dimethyl-3,4-dihydrothieno[2,3-d]pyrimidine-4-one (13)

Reaction carried out according to the general procedure. From 0.2 g (1.45 mmol) 2-amino-4,5-dimethylthiophene carboxamide (**1**) and 0.191 g (0.182 ml, 1.45 mmol) cinnamaldehyde the compound **13** was obtained in good yield.

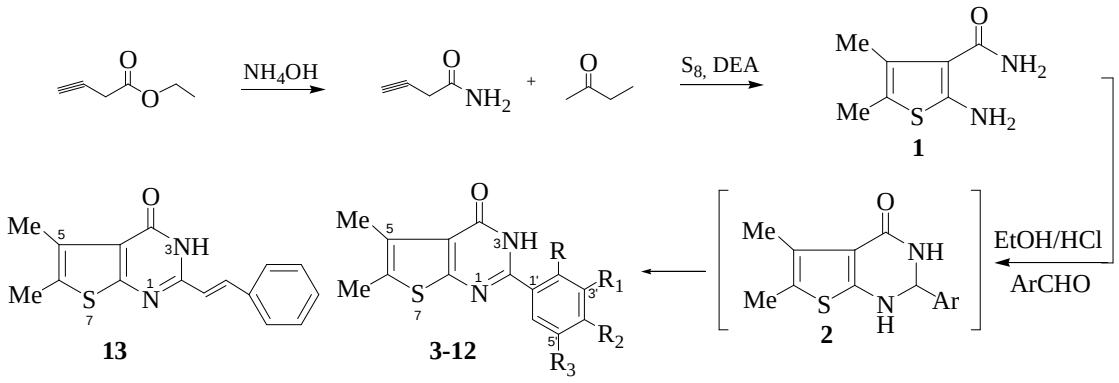
Yield: 0.25 g (62%), mp 269-271°C, R_f=0.72 (C_6H_6/CH_3COCH_3 (2:1), at RT). ^{1}H-NMR (TFA-*d*) δ: 2.08 (3H, s, 6-CH_3), 2.11 (3H, s, 5-CH_3), 6.63 (1H, d, J=16.2, =C*H*-2), 7.07 (2H, t, J=7.6, H_{Ar}-3',5'), 7.15 (1H, t, J=7.5, H_{Ar}-4'), 7.28 (2H, d, J=7.3, H_{Ar}-2',6'), 7.84 (1H, d, J=16.2, =C*H*-Ph). IR (KBr) cm^{-1}: 3160 (NH), 2919 (CH_3), 1661 (C=O), 1545 (C=N), 1446 (C-N).

3. RESULTS AND DISCUSSION

3.1 Chemistry

Interaction of 2-amino-4,5-dimethyl thiophene carboxamide (**1**) with aromatic aldehydes proceeds with the formation of the new pyrimidine ring; i.e are formed bicyclic thienopyrimidinones, containing various substituted aromatic radicals in the position 2 of the pyrimidine ring.

Cyclization of an equimolar ratio of 2-amino-4,5-dimethyl thiophene carboxamide and aldehyde conducted by refluxing in the presence of concentrated HCl in ethanol. It should be emphasized that in this case are formed exclusively 2-aryl-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-4-ones (**3-13**) in good yields (52-66%), i.e formation of intermediates - 2-aryl-5,6-dimethyl-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-4-ones (**2**), compounds with an asymmetric carbon atom at C-2 is not detected:



Compounds **3, 6, 8** early have been synthesized from amide (**1**) and aldehydes by iodine catalyzed cyclization method and studied their antibacterial activity [11]. Amide **1** was obtained from 2-amino-4,5-dimethylthiophene-3-carbonitrile, which was prepared according to Gewald procedure [12]. We synthesized compound **1** by interaction of ethylmethylketone and an amide of the cyanoacetic acid in the presence sulphur and diethyl amine.

Table 1. Yields and R, R_1, R_2, R_3 in compounds 3-13

3	Starting compounds		R	R_1	R_2	R_3	Product	Empiric formula	Yield, %
	Amide	Aldehyde							
1	**1**	Benzaldehyde	H	H	H	H	**3**	$C_{14}H_{12}N_2OS$	52
2	**1**	2-Hydroxy-benzaldehyde	OH	H	H	H	**4**	$C_{14}H_{13}N_2O_2S$	62
3	**1**	4-Hydroxy-benzaldehyde	H	H	OH	H	**5**	$C_{14}H_{12}N_2O_2S$	53
4	**1**	4-Methoxy-benzaldehyde	H	H	OMe	H	**6**	$C_{15}H_{14}N_2O_2S$	58
5	**1**	4-Dimethylamino-benzaldehyde	H	H	NMe_2	H	**7**	$C_{16}H_{18}N_3OS$	58
6	**1**	4-Nitrobenzaldehyde	H	H	NO_2	H	**8**	$C_{14}H_{11}N_3O_3S$	61
7	**1**	3-Bromo benzaldehyde	H	Br	H	H	**9**	$C_{14}H_{11}N_2O_2BrS$	66
8	**1**	2-Hydroxy-5-bromobenzaldehyde	OH	H	H	Br	**10**	$C_{14}H_{11}N_2O_2Br$	50
9	**1**	3-Hydroxy-4-methoxybenzaldehyde	H	OH	OMe	H	**11**	$C_{15}H_{14}N_2O_3S$	59
10	**1**	3,4-Dimethoxy-benzaldehyde	H	OMe	OMe	H	**12**	$C_{16}H_{16}N_2O_3S$	63
11	**1**	3-Phenylprop-2-enal	-				**13**	$C_{16}H_{14}N_2O_2S$	62

In ^{1}H NMR spectrum of the compounds **3-13** which have been taken off in TFA-*d* or in a mixture of solvents TFA-*d*+AcOH-d_4, signals of methyl groups protons at C-6 are shown as three-proton singlet at 2.08-2.13 ppm and methyl groups at C-5 has chemical shift (CS) at 2.11-2.16 ppm (3H, s), the aromatic protons H_{Ar} are observed at 6.63-8.17 ppm in rather weaker fields. In IR-spectrum of compounds **3-13** the absorption bands of OH group are observed in the range of 3081-3436 cm^{-1}, NH group - 3160-3446 cm^{-1}, C=O group -1649-1691 cm^{-1}, C=N bond - 1513-1556 cm^{-1}, C-N bond - 1446-1505 cm^{-1}, NO_2 group – 1520 cm^{-1}.

These data show, that at interaction of **1** with aromatic aldehydes leads only to the formation of 2-aryl-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-4-ones (**3-13**).

Reactions of compound **1** and aldehydes with formation of 2-aryl-5,6-dimethyl-3,4-dihydrothieno[2,3-*d*]pyrimidine-4-ones opens wide opportunities for synthesis of new synthones 2-aryl derivatives for creation of novel heterocyclic compounds. Further work in this direction will take place in the future.

4. CONCLUSION

It was revealed that interaction of 2-amino-4,5-dimethylthiophenecarboxamide (**1**) with substituted aromatic aldehydes in catalyst free conditions leads to the formation of novel bicyclic 2-substituted thieno[2,3-*d*]pyrimidine-4-ones. It was impossible to synthesis compounds with asymmetric carbon atom in position 2 of pyrimidine ring and it was found that intermediates **2** easily turn into **3-13**. These compounds may be used as perspective synthons for creation of polysubstituted thieno[2,3-*d*]pyrimidine-4-ones. Some analogues of the thieno[2,3-*d*]pyrimidine-4-ones were individually evaluated for their antiproliferative activities on mammalian cancer cell models [9]. The synthesized compounds in this paper are analogues of biologically active thieno[2,3-*d*]pyrimidine-4-ones. Research in this area continues.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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