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ORIGINAL PAPER

New route to 2-arylthieno[2,3-d]pyrimidin-4(3H)-ones and isolation of the unoxidized intermediates

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Abstract A new route to the synthesis of 2-arylthieno[2,3-d]pyrimidin-4(3H)-ones has been developed through heterocyclization of 2-amino-4,5-dimethylthiophene-3-carboxamide with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation. The unoxidized intermediates, 2-aryl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones, are isolated when the reactions are carried out either at room temperature or under a nitrogen atmosphere.

Keywords 2-Arylthieno[2,3-d]pyrimidin-4(3H)-ones · 2-Aryl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones · 2-Amino-4,5-dimethylthiophene-3-carboxamide · Aromatic aldehydes · Heterocyclization

Introduction

Thieno[2,3-d]pyrimidines are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant analgesic [1, 2], fungicidal [3, 4], antiviral [5] and antiinflammatory [6, 7, 9, 10] activities. Also, some thieno[2,3-d]pyrimidines show the ability to depress the CNS [8] and are useful as muscle relaxants [9, 10], sedatives [9, 10], diuretics [11, 12], pesticides and herbicides [13, 14].

Various methods have already been proposed for the synthesis of these compounds, and the most general ones involves cyclocondensation of suitably functionalized thiophenes with different electrophiles such as chloroformamidine [15], α-substituted acetonitriles [16], formic acid [17], phosgene [18], ethyl chloroformate [18] and guanidine [19]. To the best of our knowledge, heterocyclization of 2-amino-4,5-dimethylthiophene-3-carboxamide with aromatic aldehydes and isolation of the unoxidized intermediates has not been reported in the literature.

Prompted by these findings, and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities [20–27], as well as in continuation of our works on the synthesis of thieno[2,3-d]pyrimidine derivatives [28–30], we report herein a new route to the synthesis of 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-ones **3a–3d** through the heterocyclization of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation. At room temperature or under a nitrogen atmosphere, the unoxidized intermediates, 2-aryl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **2a–2d**, were isolated.

Results and discussion

Treatment of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** [31] with aromatic aldehydes in refluxing glacial acetic acid gave products identified as 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-ones **3a–3d**. Under these conditions, attempts to isolate the intermediates 2-aryl-5,6-dimethyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **2a–2d** failed when we carefully monitored the reaction, but these intermediates were isolated when the reaction mixture was stirred at room temperature (Scheme 1).

The formation of the products **3a–3d** was assumed to proceed via the air oxidation of the intermediates **2a–2d**,

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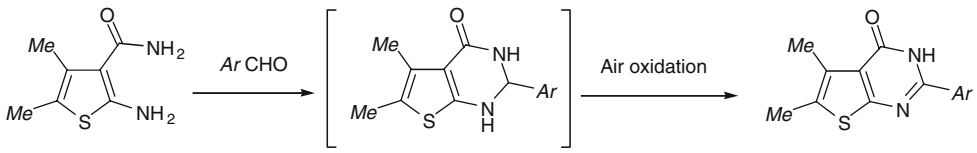
Scheme 1



1 **2a-2d** **3a-3d**

a: *Ar* = 4-*Me*C_6H_4
b: *Ar* = 4-ClC_6H_4
c: *Ar* = 4-BrC_6H_4
d: *Ar* = 4-HOC_6H_4

because when the same reaction mixture was refluxed under a nitrogen atmosphere, the reaction did not proceed to form compounds **3a**–**3d** and the intermediates **2a**–**2d** were isolated. Finally, when these intermediates were heated under reflux in glacial acetic acid, air oxidation occurred and the products **3a**–**3d** were obtained. It is important to mention that if the glacial acetic acid is replaced with another solvent system, such as ethanol containing a few drops of sulfuric acid, similar results are obtained.

The structures of the new products (**2a**–**2d** and **3d**) were established from their spectral and microanalytical data and for known compounds (**3a**–**3c**) by comparison with authentic samples. For example, the IR spectrum of compound **2a** was devoid of the two NH_2 absorption bands at $\upsilon = 3363$, 3305, 3250 and 3152 cm^{-1} of the precursor, but instead showed new absorption bands at $\upsilon = 3412$ and 3291 cm^{-1} for two NH groups. The ^1H NMR spectrum in *DMSO-d*$_6$ showed three singlets at $\delta = 2.15$, 2.30 and 2.36 ppm for methyl groups, a singlet at $\delta = 8.44$ ppm belonging to the CH proton of the pyrimidine ring, two single broad bands at $\delta = 7.42$ and 7.93 ppm for two NH groups, along with two doublets for four aromatic protons at $\delta = 7.22$ and 7.82 ppm. The MS of **2a** showed a molecular ion peak at $m/z = 272$ (M^+) corresponding to the molecular formula $C_{15}H_{16}N_2OS$ (Table 1).

In conclusion, we have described a new route to the synthesis of 2-aryl-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-ones **3a**–**3d** via heterocyclization of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** with aromatic aldehydes in boiling glacial acetic acid followed by air oxidation. The intermediates, 2-aryl-5,6-dimethyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **2a**–**2d**, were isolated when the reactions were carried out either at room temperature or under a nitrogen atmosphere.

Experimental

Melting points were recorded on an Electrothermal (Rochford, UK) type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu (Kyoto, Japan) spectrophotometer as KBr disks. The ^1H NMR (100 MHz) spectra were recorded on a Bruker (Rheinstetten, Germany) AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument. Elemental analysis was performed on a Thermo Finnigan (San Jose, CA, USA) Flash EA microanalyzer, and the results were found to agree satisfactorily with the calculated values (Table 2).

*General procedure for the synthesis of 2-aryl-5, 6-dimethylthieno[2,3-d]pyrimidin-4(3H)-ones **3a–3d***

Method A. 4 mmol of the appropriate aromatic aldehyde was added to a solution of 3 mmol 2-amino-4,5-dimethylthiophene-3-carboxamide **1** in 30 cm^3 boiling glacial

Table 1 Times, yields and melting points for the synthesized compounds **2a**–**2d** and **3a**–**3d**

Entry	Product	Ar	Method A		Method B		mp (°C)	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Found	Reported [30]
1	**2a**	4-MeC_6H_4	50	85	40	87	179–180	–
2	**2b**	4-ClC_6H_4	35	90	30	92	192–193	–
3	**2c**	4-BrC_6H_4	45	87	40	85	189–190	–
4	**2d**	4-HOC_6H_4	30	94	30	92	247–249	–
5	**3a**	4-MeC_6H_4	200	83	170	90	314–316	314–316
6	**3b**	4-ClC_6H_4	120	90	100	92	339–340	338–340
7	**3c**	4-BrC_6H_4	180	85	140	88	341–343	342–344
8	**3d**	4-HOC_6H_4	100	90	70	96	363–365	–

Table 2 Microanalytical data for the new synthesized compounds **2a–2d** and **3d**

Entry	Formula	Calculated				Found			
		C (%)	H (%)	N (%)	S (%)	C (%)	H (%)	N (%)	S (%)
2a	$C_{15}H_{16}N_2OS$	66.15	5.92	10.29	11.77	66.32	6.11	10.07	11.54
2b	$C_{14}H_{13}ClN_2OS$	57.43	4.48	9.57	10.95	57.69	4.27	9.31	11.14
2c	$C_{14}H_{13}BrN_2OS$	49.86	3.89	8.31	9.51	49.57	4.02	8.09	9.68
2d	$C_{14}H_{14}N_2O_2S$	61.29	5.14	10.21	11.69	61.44	5.27	9.94	11.43
3d	$C_{14}H_{12}N_2O_2S$	61.75	4.44	10.29	11.77	61.53	4.63	10.08	11.58

acetic acid. The reaction mixture was heated under reflux for the indicated time. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 93:7), the mixture was cooled to room temperature and subsequently neutralized by 10% NaOH solution. The crude product was collected and recrystallized from *Et*OH/*DMF* to give compounds **3a–3d** in high yields (Table 1).

Method B. A mixture of 1 mmol 2-aryl-5,6-dimethyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **2a–2d** and 20 cm^3 glacial acetic acid was heated under reflux for the indicated time. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 93:7), the mixture was neutralized by 10% NaOH solution. The crude product was collected and recrystallized from *Et*OH/*DMF* to give compounds **3a–3d** in high yields (Table 1).

*5,6-Dimethyl-2-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (**3a**)*
Mp 314–316 °C ([30] 314–316 °C)

*2-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (**3b**)*
Mp 339–340 °C ([30] 338–340 °C)

*2-(4-Bromophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (**3c**)*
Mp 341–343 °C ([30] 342–344 °C)

2-(4-Hydroxyphenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3H)-one (**3d**, $C_{14}H_{12}N_2O_2S$)
Mp 363–365 °C; ^{1}H NMR (100 MHz, *DMSO-d*$_6$): $\delta = 2.33$ (s, CH_3), 2.38 (s, CH_3), 6.75–8.10 (dd, 4H-aromatic ring H), 10.19 (br s, OH), 12.25 (br s, NH); IR (KBr): υ 1658 (CO), 2750–3250 (OH and NH) cm^{-1}; MS: *m*/*z* (%) = 272 [M^+] (17), 255 (31), 225 (15), 168 (18), 153 (48), 138 (22), 120 (33), 104 (38), 82 (56), 63 (41), 43 (100).

*General procedure for the synthesis of 2-aryl-5,6-dimethyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-ones **2a–2d***

Method A. A mixture of 3 mmol 2-amino-4,5-dimethylthiophene-3-carboxamide **1** and 4 mmol of the appropriate aromatic aldehyde in 30 cm^3 glacial acetic acid was stirred at room temperature for the indicated time. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the mixture was neutralized by 10% NaOH solution. The crude product was collected and recrystallized from ethanol to give compounds **2a–2d** in high yields (Table 1).

Method B. A mixture of 2 mmol 2-amino-4,5-dimethylthiophene-3-carboxamide **1** and 3 mmol of the appropriate aromatic aldehyde in 20 cm^3 glacial acetic acid was refluxed under a nitrogen atmosphere for the indicated time. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the mixture was cooled to room temperature and subsequently neutralized by 10% NaOH solution. The crude product was collected and recrystallized from ethanol to give compounds **2a–2d** in high yields (Table 1).

5,6-Dimethyl-2-(4-methylphenyl)-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**2a**, $C_{15}H_{16}N_2OS$)
Mp 179–180 °C; ^{1}H NMR (100 MHz, *DMSO-d*$_6$): $\delta = 2.15$ (s, CH_3), 2.30 (s, CH_3), 2.36 (s, CH_3), 7.22–7.82 (dd, 4H-aromatic ring H), 7.42 (br s, NH), 7.93 (br s, NH), 8.44 (s, 1H, CH-2) ppm; IR (KBr): υ 1645 (CO), 3291, 3412 (two NH) cm^{-1}; MS: *m*/*z* (%) = 272 [M^+] (89), 255 (67), 226 (20), 212 (47), 194 (14), 181 (14), 168 (9), 153 (100), 138 (42), 120 (47), 105 (56), 91 (98), 77 (64), 65 (92), 59 (97), 43 (64).

2-(4-Chlorophenyl)-5,6-dimethyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**2b**, $C_{14}H_{13}ClN_2OS$)
Mp 192–193 °C; ^{1}H NMR (100 MHz, *DMSO-d*$_6$): $\delta = 2.13$ (s, CH_3), 2.33 (s, CH_3), 7.50 (br s, NH), 7.52–8.00 (dd, 4H-aromatic ring H), 7.83 (br s, NH), 8.49 (s, 1H, CH-2) ppm; IR (KBr): υ 1643 (CO), 3327, 3413 (two NH) cm^{-1}; MS: *m*/s (%) = 294 [$M^+ + 2$] (8), 292 [M^+] (23), 277 (9), 275 (26), 248 (4), 246 (11), 234 (5), 232 (14), 214 (7), 212 (20), 188 (7), 153 (45), 139 (46), 138 (49), 115 (33), 113 (11), 111 (32), 89 (60), 59 (90), 43 (100).

2-(4-Bromophenyl)-5,6-dimethyl-2,3-dihydrothieno[2,3-d]pyrimidin-4(1H)-one (**2c**, $C_{14}H_{13}BrN_2OS$)
Mp 189–190 °C; ^{1}H NMR (100 MHz, *DMSO-d*$_6$): $\delta = 2.13$ (s, CH_3), 2.32 (s, CH_3), 7.48 (br s, NH), 7.55−7.95

(5H-aromatic ring H and NH), 8.46 (s, 1H, CH-2) ppm; IR (KBr): υ 1644 (CO), 3324, 3415 (two NH) cm^{-1}; MS: *m/z* (%) = 338 [M^+ + 2] (33), 336 [M^+] (34), 321 (91), 319 (92), 294 (10), 292 (11), 278 (7), 276 (8), 258 (17), 256 (18), 232 (21), 183 (24), 157 (31), 155 (31), 153 (100), 138 (48), 133 (27), 59 (62), 43 (65).

2-(4-Hydroxyphenyl)-5,6-dimethyl-2,3-dihydrothieno [2,3-d]pyrimidin-4(1H)-one (**2d**, $C_{14}H_{14}N_2O_2S$)
Mp 247–249 °C; ^1H NMR (100 MHz, *DMSO-d*$_6$): δ = 2.17 (s, CH_3), 2.30 (s, CH_3), 6.75–7.85 (dd, 4H-aromatic ring H), 7.40 (br s, NH), 8.03 (br s, NH), 8.39 (s, 1H, CH-2), 10.32 (br s, OH) ppm; IR (KBr): υ 1651 (CO), 2800–3300, 3399 (OH and two NH) cm^{-1}; MS: *m/z* (%) = 274 [M^+] (10), 272 (23), 257 (21), 255 (20), 228 (10), 170 (12), 153 (35), 138 (15), 121 (24), 105 (29), 97 (35), 83 (53), 65 (47), 57 (56), 43 (100).

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