Synthesis of some new 2-arylthieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives

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Some new derivatives of 2-arylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones have been prepared through a condensation reaction of 2-amino-4,5-dimethylthiophene-3-carboxamide with aroyl halides in boiling pyridine followed by cyclisation with 10% NaOH.

Keywords: 2-amino-4,5-dimethylthiophene-3-carboxamide, aroyl halides, condensation, cyclisation, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones

Thieno[2,3-*d*]pyrimidines are a class of fused heterocycles some of which have interesting biological activities. These compounds are reported to possess significant analgesic,[1,2] antiviral,[3] fungicidal[4] and antiinflammatory[5,6,9] activities. Furthermore, a number of these compounds were found to exhibit CNS depressing[7] and DHFR inhibitory activities[8] and are useful as muscle relaxants,[9] sedatives,[9] diuretics,[10] pesticides and herbicides.[11]

Various methods for the synthesis of these compounds have been reported in the literature that mainly involve cyclocondensation of suitably functionalised thiophenes with different electrophiles such as chloroformamidine,[8] α-substituted acetonitriles,[12] formic acid,[13] phosgen,[14] ethyl chloroformate,[14] guanidine[15] and nitriles.[16] To the best of our knowledge, reaction of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** with aroyl halides and isolation of intermediates has not been reported in the literature.

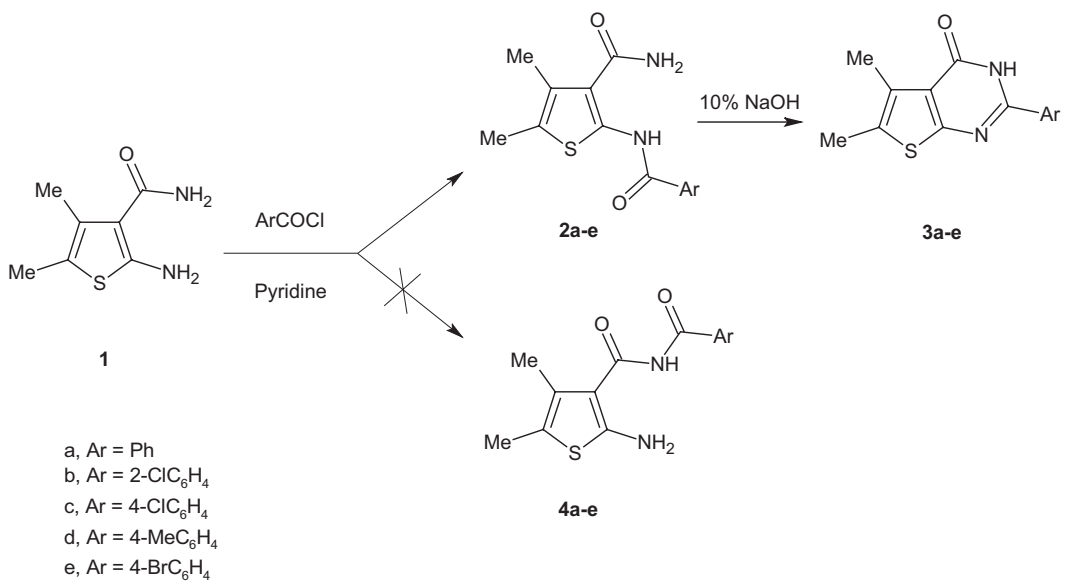
Prompted by these findings and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities,[17-22] and in continuation of our work on the synthesis of new thieno[2,3-*d*]pyrimidine derivatives,[23,24] we report here a convenient synthesis of some new 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a–e** that might be of pharmacological importance.

Results and discussion

When 2-amino-4,5-dimethylthiophene-3-carboxamide **1**[25] was allowed to interact with aroyl halides in refluxing pyridine, condensation reaction occurred giving the 2-substitutedbenzamido-4,5-dimethylthiophene-3-carboxamides **2a–e** as the result of a nucleophilic attack of the amino group in 2-position of thiophene at the carbonyl group of aroyl halides. Since the IR spectra have not shown the imido group for compounds **4a–e** at around 1700 cm^{-1} and the fact that the amino group is more reactive than the amido group as nucleophile, we believe that the compounds **4a–e** have not been formed (Scheme 1).

When compounds **2a–e** were heated under reflux for 7 hours with 10% NaOH, cyclisation reaction occurred and the cyclic products **3a–e** were obtained. The structural assignment of all compounds **2–3** was based upon spectral and microanalytical data (see Experimental). For example, the ^1H NMR spectrum of **3a** was devoid of the NH_2 and NH signals of the precursor **2a** at δ 7.50 and 12.73 ppm respectively, but instead showed a broad 1H signal at δ 12.96 ppm for NH proton as well as the characteristic signals for aromatic protons at δ 7.2–8.4 ppm. The IR spectrum did not show the stretching vibration bands at 3416, 3323, and 3203 cm^{-1} for NH and NH_2 absorptions of the precursor, but instead showed a new absorption band at 3097 cm^{-1} for NH group. The MS of **3a** showed a molecular ion peak at *m/z* 256 (M^+) corresponding to the molecular formula $C_{14}H_{12}N_2OS$.

In conclusion, condensation of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** with aroyl halides in refluxing pyridine gave the corresponding 2-substitutedbenzamido-4,5-dimethylthiophene-3-carboxamides **2a–e** that subsequently were cyclised with 10% NaOH under reflux to give the cyclic products **3a–e**.



Scheme 1

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Experimental

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were determined on a Shimadzu GCMS 17A instrument. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser.

General procedure for the synthesis of 2-substitutedbenzamido-4,5-dimethylthiophene-3-carboxamides **(2a–e)**

To a solution of 2-amino-4,5-dimethylthiophene-3-carboxamide **1** (3 mmol) in boiling pyridine (30 ml), the appropriate aroyl halid (3 mmol) was added. The reaction mixture was heated under reflux for 8 hours. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 93:7), the solvent was evaporated in vacuo. The residue was recrystallised from ethanol/water to give compounds **2a–e**.

2-Benzamido-4,5-dimethylthiophene-3-carboxamide **(2a)**: White crystals (0.66 g, 80%), m.p. 216–218°C. FT IR (KBr, υ_{max}/cm^{-1}): 3416, 3323, and 3203 (NH and NH_2), 1651 (two C=O stretching and NH_2 bending). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.23 (s, 6H, 2Me), 7.50 (br s, 2H, NH_2), 7.6-8.0 (m, 5H, phenyl), 12.73 (s, 1H, NH). MS: *m/z* 274 (M^+, 40), 257 (48), 155 (43), 105 (100), 77 (98), 44 (52), 28 (96). Found: C, 61.07; H, 5.31; N, 10.03; S, 11.56. Calc. for $C_{14}H_{14}N_2O_2S$ (274): C, 61.29; H, 5.14; N, 10.21; S, 11.69%.

2-(2-Chlorobenzamido)-4,5-dimethylthiophene-3-carboxamide **(2b)**: Brown crystals (0.63 g, 68%), m.p. 221–223°C. FT IR (KBr, υ_{max}/cm^{-1}): 3427, 3309, and 3205 (NH and NH_2), 1657 (two C=O stretching and NH_2 bending). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.31 (s, 6H, 2Me), 7.4–7.9 (m, 6H, aromatic ring H and NH_2), 12.68 (s, 1H, NH). MS: *m/z* 310 (M^+ + 2, 12), 308 (M^+, 36), 293 (17), 291 (51), 155 (52), 141 (33), 139 (100), 113 (30), 111 (90), 44 (38), 28 (86). Found: C, 54.24; H, 4.09; N, 9.28; S, 10.55. Calc. for $C_{14}H_{13}ClN_2O_2S$ (308.78): C, 54.46; H, 4.24; N, 9.07; S, 10.38%.

2-(4-Chlorobenzamido)-4,5-dimethylthiophene-3-carboxamide **(2c)**: Brown crystals (0.65 g, 70%), m.p. 235–238°C. FT IR (KBr, υ_{max}/cm^{-1}): 3476, 3316, and 3171 (NH and NH_2), 1640 (two C=O stretching and NH_2 bending). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.27 (s, 6H, 2Me), 7.52 (br s, 2H, NH_2), 7.6–7.95 (dd, 4H, aromatic ring H), 12.70 (s, 1H, NH). MS: *m/z* 310 (M^+ + 2, 11), 308 (M^+, 32), 294 (16), 292 (47), 155 (61), 141 (33), 139 (100), 113 (25), 111 (73), 44 (51), 28 (74). Found: C, 54.63; H, 4.43; N, 8.89; S, 10.49. Calc. for $C_{14}H_{13}ClN_2O_2S$ (308.78): C, 54.46; H, 4.24; N, 9.07; S, 10.38%.

4,5-Dimethyl-2-(4-methylbenzamido)thiophene-3-carboxamide **(2d)**: Brown crystals (0.63 g, 73%), m.p. 233–235°C. FT IR (KBr, υ_{max}/cm^{-1}): 3459, 3305, and 3180 (NH and NH_2), 1637 (two C=O stretching and NH_2 bending). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.35 (s, 6H, 2Me), 2.46 (s, 3H, Me), 7.3–7.9 (m, 6H, aromatic ring H and NH_2),12.75 (s, 1H, NH). MS: *m/z* 288 (M^+, 38), 271 (41), 155 (36), 119 (94), 91 (100), 44 (61), 28 (78). Found: C, 62.31; H, 5.36; N, 9.92; S, 11.25. Calc. for $C_{15}H_{16}N_2O_2S$ (288): C, 62.48; H, 5.59; N, 9.71; S, 11.12%.

2-(4-Bromobenzamido)-4,5-dimethylthiophene-3-carboxamide **(2e)**: Brown crystals (0.82 g, 78%), m.p. 244–246°C. FT IR (KBr, υ_{max}/cm^{-1}): 3479, 3316, and 3179 (NH and NH_2), 1641 (two C=O stretching and NH_2 bending). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.25 (s, 6H, 2Me), 7.48 (br s, 2H, NH_2), 7.6–7.90 (dd, 4H, aromatic ring H), 12.72 (s, 1H, NH). MS: *m/z* 354 (M^+ + 2, 41), 352 (M^+, 42), 338 (58), 336 (59), 185 (98), 183 (100), 157 (53), 155 (78), 44 (38), 28 (72). Found: C, 47.46; H, 3.89; N, 8.11; S, 8.91. Calc. for $C_{14}H_{13}BrN_2O_2S$ (353): C, 47.60; H, 3.71; N, 7.93; S, 9.08%.

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

A mixture of 2-substitutedbenzamido-4,5-dimethylthiophene-3-carboxamides **2a–e** (1 mmol) in 10% NaOH solution (20 ml) was heated under reflux for 7 hours. After the completion of the reaction (monitored by TLC, $CHCl_3$:MeOH, 93:7), the mixture was cooled to room temperature. The precipitate was collected and recrystallised from ethanol to give compounds **3a–e**.

5,6-Dimethyl-2-phenylthieno[2,3-d]pyrimidin-4(3*H*)*-one* **(3a)**: White crystals (0.22 g, 86%), m.p. 293–295°C(Lit[25] 290°C). FT IR (KBr, υ_{max}/cm^{-1}): 3097 (NH), 1660 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.26 (s, 3H, Me), 2.39 (s, 3H, Me), 7.2–8.4 (m, 5H, phenyl), 12.96 (broad, 1H, NH). MS: *m/z* 256 (M^+, 84), 241 (100), 154 (23), 138 (47), 101 (41), 58 (33), 44 (54), 28 (85). Found: C, 65.42; H, 4.53; N, 11.09; S, 12.36. Calc. for $C_{14}H_{12}N_2OS$ (256): C, 65.60; H, 4.72; N, 10.93; S, 12.51%.

2-(2-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3*H*)*-one* **(3b)**: White crystals (0.22 g, 76%), m.p. 300–303°C. FT IR (KBr, υ_{max}/cm^{-1}): 3065 (NH), 1665 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.37 (s, 3H, Me), 2.42 (s, 3H, Me), 7.4–7.7 (m, 4H, aromatic ring H), 12.62 (br s, 1H, NH). MS: *m/z* 292 (M^+ + 2, 26), 290 (M^+, 76), 277 (17), 275 (50), 153 (19), 138 (37), 102 (50), 59 (41), 44 (24), 28 (100). Found: C, 57.97; H, 3.62; N, 9.44; S, 11.21. Calc. for $C_{14}H_{11}ClN_2OS$ (290.77): C, 57.83; H, 3.81; N, 9.63; S, 11.03%.

2-(4-Chlorophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3*H*)*-one* **(3c)**: White crystals (0.25 g, 84%), m.p. 338–340°C. FT IR (KBr, υ_{max}/cm^{-1}): 3060 (NH), 1661 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.34 (s, 3H, Me), 2.40 (s, 3H, Me), 7.2–8.1 (dd, 4H, aromatic ring H), 12.75 (broad, 1H, NH). MS: *m/z* 292 (M^+ + 2, 34), 290 (M^+, 100), 277 (27), 275 (79), 154 (31), 138 (42), 101 (48), 58 (46), 44 (37), 28 (89). Found: C, 58.05; H, 3.95; N, 9.49; S, 11.16. Calc. for $C_{14}H_{11}ClN_2OS$ (290.77): C, 57.83; H, 3.81; N, 9.63; S, 11.03%.

5,6-Dimethyl-2-(4-methylphenyl)thieno[2,3-d]pyrimidin-4(3*H*)*-one* **(3d)**: White crystals (0.22 g, 82%), m.p. 314–316°C. FT IR (KBr, υ_{max}/cm^{-1}): 3060 (NH), 1655 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.33 (s, 6H, 2Me), 2.38 (s, 3H, Me), 7.2-8.15 (dd, 4H, aromatic ring H), 12.40 (br s, 1H, NH). MS: *m/z* 270 (M^+, 64), 255 (100), 154 (31), 138 (55), 102 (57), 91 (96), 57 (37), 44 (41), 28 (73).Found: C, 66.47; H, 5.39; N, 10.58; S, 11.74. Calc. for $C_{15}H_{14}N_2OS$ (270): C, 66.64; H, 5.22; N, 10.36; S, 11.86%.

2-(4-Bromophenyl)-5,6-dimethylthieno[2,3-d]pyrimidin-4(3*H*)*-one* **(3e)**: White crystals (0.26 g, 78%), m.p. 342–344°C. FT IR (KBr, υ_{max}/cm^{-1}): 3063 (NH), 1656 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, TMS): δ 2.40 (s, 6H, 2Me), 7.6–8.2 (dd, 4H, aromatic ring H), 12.55 (br s, 1H, NH). MS: *m/z* 336 (M^+ + 2, 75), 334 (M^+, 76), 321 (98), 319 (100), 153 (21), 138 (35), 102 (49), 59 (51), 44 (38), 28 (72). Found: C, 50.03; H, 3.19; N, 8.17; S, 9.76. Calc. for $C_{14}H_{11}BrN_2OS$ (335): C, 50.16; H, 3.31; N, 8.36; S, 9.57%.

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