Iodine catalysed synthesis and antibacterial evaluation of thieno-[2,3-*d*]pyrimidine derivatives

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A new route via iodine catalysed heterocyclisation of 2-amino-4,5-dimethylthiophene-3-carboxamide with aromatic aldehydes affording a series of thieno[2,3-*d*]pyrimidine derivatives in a single step have been developed. Some of these compounds exhibited antibacterial activities comparable to Streptomycin as reference drug.

Keywords: thieno[2,3-*d*]pyrimidine, iodine, heterocyclisation, antibacterial evaluation, oxidative catalyst

Thienopyrimidine derivatives as annulated five-membered heteroaromatic ring systems are structurally analogues of biogenic purines with a very wide spectrum of biological activities. A review article covering the literature on thienopyrimidines up to 2004 has been published.[1] Furthermore, new biological activities such as antimicrobial,[2-8] antiviral,[9,10] antidepressant,[11] analgesic and anti-inflammatory[12,13] have been recently reported for these compounds. Various synthetic approaches have been utilised for the synthesis of this class of heterocycles including using $ZnCl_2/Et_3N$ reagent system,[14] microwave irradiation,[15] base-catalysed cyclocondensation of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate with aryl isocyanates,[16] synthesis through tandem [2,3] and [3,3] sigmatropic rearrangement,[17] reaction of aromatic and heterocyclic carboxylic acids using montmorillonite K-10 under solventless conditions[18] and parallel solution-phase combinatorial techniques.[19]

Currently special interest has been devoted to molecular iodine, as a readily available, mild and environmentally friendly Lewis acid and as an oxidising agent for the construction of heterocyclic rings through an oxidative heterocyclisation reaction.[20] Prompted by these findings and due to our interest in the synthesis of fused-pyrimidines of biological importance,[21-25] we now report the synthesis of thieno[2,3-*d*] pyrimidine derivatives through oxidative cyclocondensation of 2-amino-4,5-dimethylthiophene-3-carboxamide **(2)** with various aromatic aldehydes in the presence of molecular iodine. The results of the antibacterial test on the new products are reported.

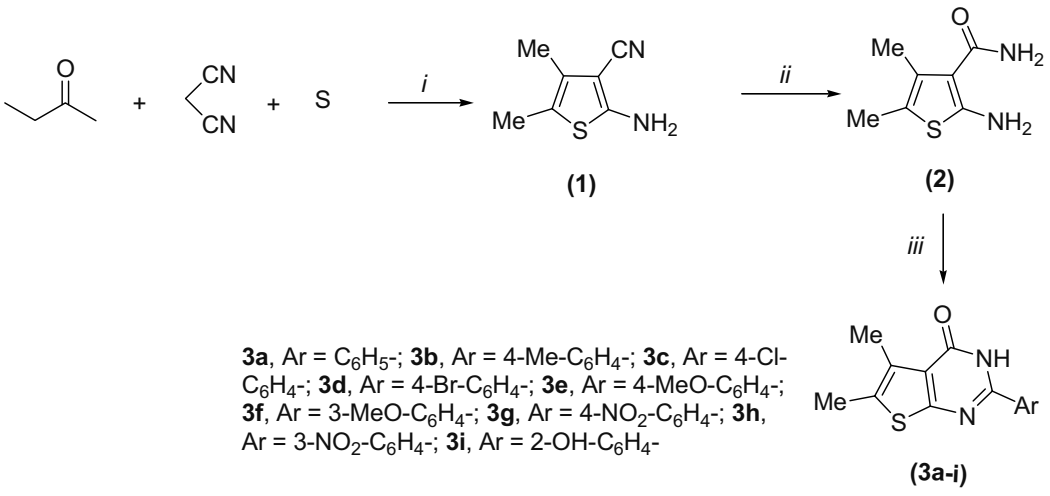
Results and discussion

Chemistry

The starting material 2-amino-4,5-dimethylthiophene-3-carbonitrile **(1)** was prepared according to Gewald procedure.[26] The subsequent hydrolysis of this compound in acidic media afforded the 2-amino-4,5-dimethylthiophene-3-carboxamide **(2)**. This compound was the precursor for the synthesis of various derivatives of thieno[2,3-*d*]pyrimidine **(3a–i)**.

The reaction of compound **(2)** with aromatic aldehydes proceeded in one pot at room temperature within a short period of time after the addition of molecular iodine to furnish the corresponding thieno[2,3-*d*]pyrimidine **(3a–i)** in 70–88% yield. (Table 1)

The structures and purities of these compounds were ascertained from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of compound **(3g)** did not show the signals at δ 6.78 and 7.85 ppm belonging to NH_2 moiety of the precursor but instead showed a singlet signal for NH proton at δ 12.37 ppm which was removed on deuteration. Furthermore, the spectrum showed a doublet–doublet peak at the aromatic region (δ 8.14 and 8.43 ppm, J = 9 Hz) confirming the presence of the aromatic ring system and the



3a, Ar = C_6H_5-; **3b**, Ar = 4-Me-C_6H_4-; **3c**, Ar = 4-Cl-C_6H_4-; **3d**, Ar = 4-Br-C_6H_4-; **3e**, Ar = 4-MeO-C_6H_4-; **3f**, Ar = 3-MeO-C_6H_4-; **3g**, Ar = 4-NO_2-C_6H_4-; **3h**, Ar = 3-NO_2-C_6H_4-; **3i**, Ar = 2-OH-C_6H_4-

i, Et_2NH, EtOH, 60°C; *ii*, *conc.* H_2SO_4; *iii,* ArCHO, I_2, CH_3CN, rt.

Scheme 1

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Table 1 Times, yields and melting points for the synthesised compound (**3a–i**)

Compound	Ar	Time/min	Yield/%[a]	M.p./°C	M.p./°C [Ref.][b]
3a	C_6H_5–	35	80	294	293–297 [27]
3b	4-Me–C_6H_4–	70	78	315–316	314–316 [27]
3c	4-Cl–C_6H_4–	50	75	337–338	338–340 [27]
3d	4-Br–C_6H_4–	45	70	342	342–344 [27]
3e	4-MeO–C_6H_4–	90	88	320–322	323–325 [28]
3f	3-MeO–C_6H_4–	80	78	312	–
3g	4-NO_2–C_6H_4–	20	70	370–372	–
3h	3-NO_2–C_6H_4–	30	72	334	–
3i	2-HO–C_6H_4–	60	74	330–332	–

[a]Isolated yields. [b]Products are characterised from their spectra and microanalytical data comparison with the authentic samples.

occurrence of heterocyclisation. The IR spectrum was also devoid of the stretching vibration bands resembling the NH_2 moiety of the precursor but instead exhibited only one band at 3350 cm^{-1} for the NH moiety. The molecular ion peak of compound **(3g)** was observed at *m/z* 301 (M^+) corresponding to the molecular formula $C_{14}H_{11}N_3O_3S$.

Biological activities

The *in vitro* antibacterial activity of the newly synthesised compounds **(3a–i)** were screened for the antibacterial activity against several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus* PTCC 1074 and *Bacillus subtilis* PTCC 1365); Gram-negative bacteria (*Escherichia coli* HB101 BA 7601C and *Pseudomonas aeruginosa* PTCC 1431) using disc diffusion sensitivity test.[29] Mueller–Hinton agar media were sterilised (15 min at 121 °C) and poured into the plates to a uniform depth of 5 mm and allow to solidify. The microbial suspension (1–2 × 10^8 CFU mL^{-1}) (0.5 McFarland Nephelometery Standards) was streaked over the surface of media using a sterile cotton swab (15 min at 180 °C) to ensure confluent growth of the organisms. The tested compounds were dissolved in dimethylformamide (DMF) and diluted with ethanol to get a solution of 100–500 μg mL^{-1} concentration. The discs measuring 6.25 mm in diameter (Whatman no. 1 filter paper) were impregnated with prepared solution of compounds **(3a–i)** and placed on Muller-Hinton agar media previously inoculated with bacterial suspension. The inhibition zones as a criterion for antimicrobial activity were measured in millimetres at the end of an incubation period of 24 h at 37 °C. The results of these evaluations are given in Table 1. Streptomycin (binds to the 16SrRNA of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit therefore prevents initiation of protein synthesis and leads to death of microbial cell) was chosen as a standard drug at a concentration of 10 μg mL^{-1}. Streptomycin is an antibiotic that inhibits both gram positive and gram negative bacteria, and is therefore a useful broad spectrum antibiotic.

As can be concluded from the data in Table 2, compound **(3f)** has shown the highest sensitivity against *E. coli* and *St. aureus*, and moderately sensitive against *B. Sabtilis*. Compound **(3c)** exhibited the best activity against *E. coli* while compound **(3i)** showed slight to moderate activity against *P. aeruginosa*. All the other compounds were found to exhibit slightly sensitive against the mentioned organisms.

In conclusion, we have described a new route to the synthesis of 2-aryl-5,6-dimethylthieno[2,3-*d*]pyrimidine-4(3H)-ones **(3a–i)** via heterocyclisation of 2-amino-4,5-dimethylthiophene-3-carboxamide **(2)** with various aromatic aldehydes in acetonitrile at room temperature in the presence of molecular iodine as an oxidative catalyst and their antibacterial evaluations.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are not corrected. The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA micro analyser.

Synthesis of 2-amino-4,5-dimethylthiophene-3-carboxamide **(2)**: 2-Amino-4,5-dimethylthiophene-3-carbonitrile (0.25 mol, 3.80 g) was added gradually to 10–15 mL conc. H_2SO_4 and stirred for 2 h at 65–70 °C. Then, the mixture was neutralised in an ice-bath by 25% ammonia. The resulting solid was filtered and recrystallised from water. (Yield = 80%, m.p. 182–183 °C, lit.[30] 184–185 °C).

General procedure for the preparation of thieno[2,3-d]pyrimidine **(3a–i)**: To a solution of 2-amino-4,5-dimethylthiophene-3-carboxamide **(2)** (1 mmol, 0.17 g) and various aromatic aldehydes (1.2 mmol) in acetonitrile (10 mL), molecular iodine (1.3 mmol, 0.33 g) was added. The mixture was stirred at room temperature for 15–30 min. After the reaction was completed (monitored by TLC), 10 mL 5% $Na_2S_2O_3$ solution was added and the resulting precipitate was filtered off. Further purification can be obtained by recrystallisation from ethanol.

Table 2 Antibacterial data of the synthesised compounds (**3a–i**)[a]

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Staphylococcus aureus PTCC 1074	*Bacillus subtilis PTCC 1365*	*Escherichia coli HB 101 BA 7601C*	*Pseudomonas aeruginosa PTCC 1431*
3a	11(–)	10(–)	9(–)	8(–)
3b	8(–)	8(–)	8.5(–)	7(–)
3c	10.5(–)	10(–)	13(+)	9(–)
3d	13(+)	7(–)	11(–)	8(–)
3e	9.5(–)	9.5(–)	10.5(–)	9(–)
3f	16.5(+ +)	12(+)	16(+ +)	10(–)
3g	9(–)	7(–)	9(–)	7(–)
3h	7(–)	7(–)	9(–)	7(–)
3i	11(–)	8.5(–)	10(–)	11(+)
Streptomycin (Standard)	13	9	15	10

[a]Zones of inhibition in millimetre; (+ +) highly sensitive; (+) moderately sensitive; (–) slightly sensitive.

2-(3-Methoxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-4(3H)-one **(3f)**: ^{1}H NMR (DMSO-d_6, ppm) δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 7.13–7.63 (m, 4H, Ar), 12.48 (br s, 1H, NH); IR spectrum (ν, cm^{-1}): 3330 (NH), 1670 (C=O); *m/z* 286 (M^+); Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; S, 11.20. Found: C, 62.82; H, 4.85; N, 9.69; S, 10.98%.

5,6-Dimethyl-2-(4-nitrophenyl)-3,4-dihydrothieno[2,3-d] pyrimidin-4(3H)-one **(3g)**: ^{1}H NMR (DMSO-d_6, ppm) δ 2.33 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 8.14 (d, J = 9 Hz, 2H, Ar), 8.43 (d, J = 9 Hz, 2H, Ar), 12.37 (br s, 1H, NH); IR spectrum (ν, cm^{-1}): 3350 (NH), 1655 (C=O), *m/z* 301 (M^+); Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95; S, 10.64. Found: C, 55.78; H, 3.65; N, 13.89; S, 10.58%.

5,6-Dimethyl-2-(3-nitrophenyl)-3,4-dihydrothieno[2,3-d] pyrimidin-4(3H)-one **(3h)**: ^{1}H NMR (DMSO-d_6, ppm) δ 2.32 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.83–8.26 (m, 4H, Ar), 12.28 (br s, 1H, NH); IR spectrum (ν, cm^{-1}): 3350 (NH), 1650 (C=O); *m/z* 301 (M^+); Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95; S, 10.64. Found: C, 55.75; H, 3.64; N, 13.90; S, 10.55%.

2-(2-Hydroxyphenyl)-5,6-dimethyl-3,4-dihydrothieno[2,3-d] pyrimidin-4(3H)-one **(3i)**: ^{1}H NMR (DMSO-d_6, ppm) δ 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 6.83–7.16 (m, 4H, Ar), 8.75 (br s, 1H, OH), 12.08 (br s, 1H, NH); IR spectrum (ν, cm^{-1}): 3390 (OH), 3330 (NH), 1640 (C=O); *m/z* 272 (M^+); Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.72; H, 4.43; N, 10.24; S, 11.69%.

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