Synthesis of a Novel Series of Thieno[3,2-*d*]pyrimidin-4-(3*H*)-ones

Ismail Abdillahi, Gilbert Kirsch*

Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, FR CNRS 2843, 1 Boulevard Arago, 57070 METZ, France
Fax +33(3)87325801; E-mail: kirsch@.univ-metz.fr

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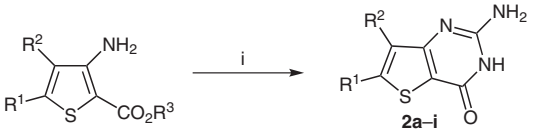
Dedicated to Professor Willi Kantlehner for his contribution to iminium salts chemistry

Abstract: 2-Aminothieno[3,2-*d*]pyrimidin-4-ones were synthesized in one step by condensation of 3-amino(benzo)thiophene carboxylate with chloroformamidine hydrochloride.

Key words: heterocycles, condensation, 3-aminothiophene-2-carboxylate, thieno[3,2-*d*]pyrimidinone, chloroformamidine hydrochloride

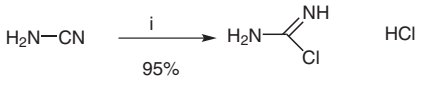
In continuation of our synthetic studies with 3-amino-2-substituted thiophenes,[1] we describe here a new approach to thieno[3,2-*d*]pyrimidin-4(3*H*)-ones. The synthesis was devised to enable the condensed heterocycle structure to be used as a scaffold for preparing new biologically active compounds.

2-Aminothieno[3,2-*d*]pyrimidinones have previously been described in the literature and have been used as a scaffold for preparing a range of biologically active compounds;[2,3,4] the isomeric [3,2-*d*]pyrimidin-4(3*H*)-one derivatives, however, were not previously known. We describe here their preparation from ethyl or methyl 3-aminothiophene-2-carboxylate and chloroformamide hydrochloride as shown in Scheme 1.



Scheme 1 *Reagents and conditions*: (i) chloroformamidine hydrochloride, dimethylsulfone, 140–150 °C, 4 h.

Chloroformamide hydrochloride was prepared in one step from cyanamide and anhydrous hydrogen chloride in excellent yield (Scheme 2).[5] The amino thiophenes esters (**1a**–**g**) were synthesized from β-chloropropenonitrile obtained from β-chloropropenal as described previously (Scheme 3).[6–14]



Scheme 2 *Reagents and conditions*: (i) anhyd HCl, Et_2O, r.t.

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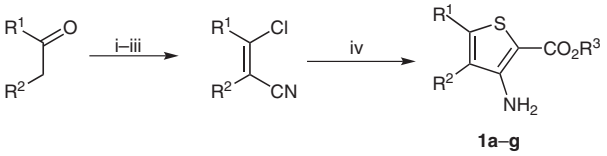
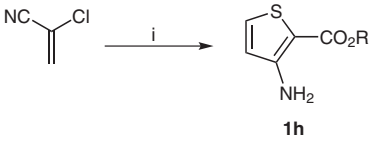


Scheme 3 *Reagents and conditions*: (i) $POCl_3$, DMF, 60 °C, 5 h; (ii) hydroxylamine chloride, EtOH; (iii) Ac_2O; (iv)(a) $Na_2S·9H_2O$, DMF, XCH_2CO_2Et/Me (X = Br, Cl), EtONa/MeONa or (b) $HSCH_2CO_2Et$/Me, K_2CO_3, DMF.

Ethyl 3-aminothiophene-2-carboxylate (**1h**) was prepared from α-chloroacrylonitrile in excellent yield (90%; Scheme 4).[13] In most cases, thiophenes **1** were obtained in good yields (Table 1).



Scheme 4 *Reagents and conditions*: (i) $HSCH_2CO_2Et$, EtOH, EtONa.

Table 1 Formation of Thiophenes **1**

Entry	R^1	R^2	R^3	Product	Overall yield (%)
1	Ph	H	Et	**1a**	74
2	4-MeC_6H_4	H	Et	**1b**	82
3	4-ClC_6H_4	H	Et	**1c**	83
4	4-$MeOC_6H_4$	H	Me	**1d**	72
5	*t*-Bu	H	Et	**1e**	60
6	*c*-Hex		Me	**1f**	40
7	1,2-dihydronaphthalene		Et	**1g**	74
8	H	H	Et	**1h**	90

To extend the scope of our synthesis, we also prepared methyl 3-amino-5-nitrobenzo[*b*]thiophene-2-carboxylate by direct condensation of 2-chloro-3-cyano-5-nitrobenzene with methyl thioglycolate under basic conditions. The synthesis is similar to that described by Beck[15] and involves a nitro group displacement (Scheme 5).

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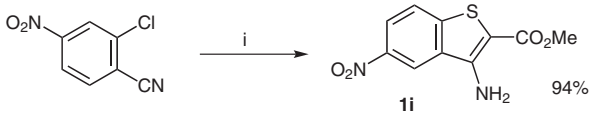
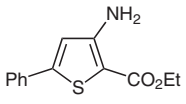
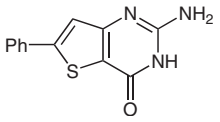
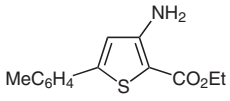
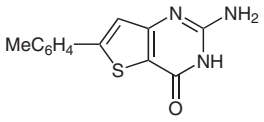
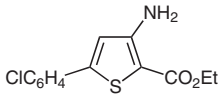
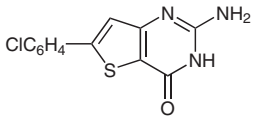
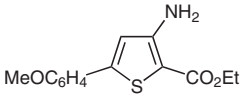
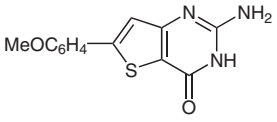
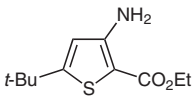
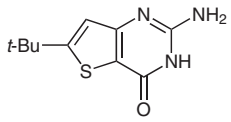
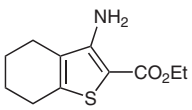
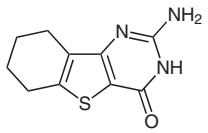
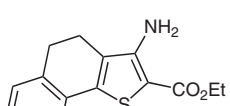
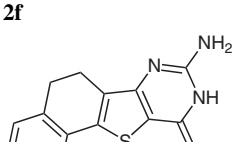
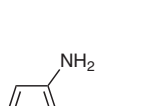
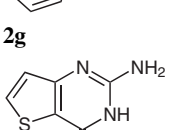
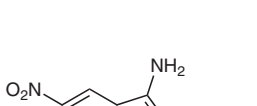
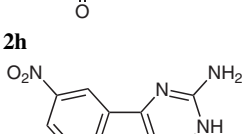


Scheme 5 *Reagents and conditions*: (i) $HSCH_2CO_2Me$, DMF, K_2CO_3.

Table 2 Thieno[3,2-*d*]pyrimidinone Derivatives **2**

Thiophene **1**	Pyrimidinone **2**	Yield (%)
	 **2a**	67
	 **2b**	57
	 **2c**	40
	 **2d**	45
	 **2e**	67
	 **2f**	52
	 **2g**	86
	 **2h**	30
	 **2i**	90

The various 3-aminothiophene (benzothiophene) carboxylates were condensed with chloroformamide hydrochloride by heating the mixture in dimethylsulfone at 140–150 °C for four hours to afford the corresponding pyrimidinone (Scheme 1 and Table 2).

Having prepared the pyrimidinone scaffold, functional transformation will be performed by introducing side chains on the amino group. Transformation of the pyrimidinone into the chloropyrimidines will allow the introduction of nucleophiles via SN_{Ar} reaction, or aryl and aminoaryl side chains by palladium-catalyzed coupling reactions.

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a AC Bruker 250 MHz spectrometer in either $CDCl_3$ or DMSO-d_6. Mass spectra were recorded on a MicroTof-Q 98.

Synthesis of 2-Aminoaryl[3,2-*d*]pyrimidin-4(3*H*)-ones 2a–i; General Procedure

A mixture of the appropriate thiophene and chloroformamidine hydrochloride (1:4) in dimethylsulfone (4 equiv) was heated at 140–150 °C for 4 h. The mixture was cooled to r.t., H_2O (15 mL) was added and ammonium hydroxide was used to neutralize the solution. The precipitate was filtered and washed with H_2O (3 × 100 mL). After drying over P_2O_5 in vacuum, the product was either recrystallized from MeOH or purified by column chromatography.

2-Amino-6-phenylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (2a)

Column chromatography purification ($CHCl_3$–MeOH, 5%).

Yield: 67%; brown solid; mp 318 °C.

^1H NMR (250 MHz, DMSO-d_6): δ = 6.47 (s, 2 H, NH_2), 7.36–7.48 (m, 4 H, 4 × CH), 7.74–7.77 (m, 2 H, 2 × CH), 11.07 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 111.3, 119.8, 125.8 (2 × C), 129.2 (3 × C), 132.9, 149.9, 154.5, 157.9, 160.7.

MS: m/z = 244.05 $[M + H]^+$.

2-Amino-6-(4-methylphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (2b)

Yield: 57%; beige solid; mp 357 °C (MeOH).

^1H NMR (250 MHz, DMSO-d_6): δ = 2.33 (s, 3 H, CH_3), 6.42 (s, 2 H, NH_2), 7.26 (d, ^2J = 7.5 Hz, 2 H, 2 × CH), 7.34 (s, 1 H, CH), 7.64 (d, ^2J = 7.5 Hz, 2 H, 2 × CH), 11 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.8, 110.9, 119.2, 125.7, 129.7, 130.2, 139.0, 150.1, 154.5, 158.0, 160.0.

MS: m/z = 280.05 $[M + Na]^+$.

2-Amino-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (2c)

Yield: 40%; brown solid; mp 321–323 °C (MeOH).

^1H NMR (250 MHz, DMSO-d_6): δ = 6.58 (s, 2 H, NH_2), 7.44 (s, 1 H, CH), 7.50 (d, ^2J = 7.5 Hz, 2 H, 2 × CH), 7.78 (d, ^2J = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 111.7, 120.1, 127.6, 129.2, 131.7, 133.8, 148.6, 154.4, 157.7, 159.5, 178.8.

MS: m/z = 299.99 $[M + Na]^+$.

2-Amino-6-(4-methoxyphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (2d)

Yield: 45%; brown solid; mp 325 °C (MeOH).

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^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.80 (s, 3 H, CH_3), 6.60 (s, 2 H, NH_2), 7.00 (d, ^2J = 7.5 Hz, 2 H, 2 × CH), 7.29 (s, 1 H, CH), 7.68–7.71 (d, ^2J = 7.5 Hz, 2 H, 2 × CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 55.3, 110.5, 114.6, 117.8, 125.4, 127.4, 150.5, 154.0, 157.5, 160.2.

MS: *m*/*z* = 274.064 $[M + Na]^+$.

2-Amino-6-*tert*-butylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (2e)
Yield: 67%; yellow solid; mp 344 °C (MeOH).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.33 (s, 9 H, 3 × CH_3), 6.31 (s, 2 H, NH_2), 6.75 (s, 1 H, CH), 10.91 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 31.5, 34.8, 109.9, 118.6, 154.3, 158.0, 159.9, 164.9.

MS: *m*/*z* = 246.067 $[M + Na]^+$.

2-Amino-6,7,8,9-tetrahydro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (2f)
Yield: 52%; yellow solid; mp 323 °C (MeOH).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.75–1.80 (m, 6 H, 2 × CH_2), 2.70–2.72 (m, 2 H, CH_2), 6.42 (s, 2 H, NH_2), 10.91 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 21.5, 22.8, 23.0, 25.5, 108.8, 130.2, 144.2, 154.3, 157.8, 158.9.

MS: *m*/*z* = 222.07 $[M + H]^+$.

2-Amino-5,6-dihydronaphtho[2′,1′,4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (2g)
Yield: 86%; brown solid; mp 360 °C (MeOH).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.7–2.8 (m, 2 H, CH_2), 2.9–3.0 (m, 2 H, CH_2), 6.59 (s, 2 H, NH_2), 7.2–7.3 (m, 3 H, 3 × CH), 7.38–7.44 (m, 1 H, CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 20.8, 27.6, 110.4, 123.27, 126.3, 127.7, 128.8, 130.0, 131.0, 134.3, 136.0, 142.0, 154.4, 157.9.

MS: *m*/*z* = 292.05 $[M + Na]^+$.

2-Aminothieno[3,2-*d*]pyrimidin-4(3*H*)-one (2h)
Yield: 30%; beige solid; mp >350 °C (MeOH).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.46 (s, 2 H, NH_2), 6.96 (d, ^2J = 5.25 Hz, 1 H, CH), 7.93 (d, ^2J = 5.25 Hz, 1 H, CH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 112.2, 123.4, 134.4, 154.2, 158.2, 159.4.

MS: *m*/*z* = 190 $[M + Na]^+$.

2-Amino-8-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)-one (2i)
Yield: 90%; yellow solid; mp 350 °C (MeOH).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.01 (s, 2 H, NH_2), 8.30 (m, 2 H, 2 × CH), 8.76 (m, 1 H, CH), 11.15 (s, 1 H, NH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 113.0, 118.3, 122.3, 125.2, 133.6, 145.0, 146.5, 155.5, 158.1, 162.7.

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