An Efficient Synthesis of 4-Chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one and Its 7-Substituted Analogues

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Abstract: An efficient synthesis of 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one was achieved in four steps starting from dimethyl malonate in 23% overall yield. This synthesis was demonstrated on 100 g scale to obtain 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one in 98.5% purity. Similarly, 7-[(2,4-dimethoxyphenyl)methyl]-4-chloro[2,3-*d*]pyrimidin-6-one and 7-(α-methylbenzyl)-4-chloro[2,3-*d*]pyrimidin-6-one were synthesized by the reaction of methyl 2-(4,6-dichloropyrimidin-5-yl)acetate with an appropriately substituted benzylamine.

Key words: formamidine acetate, α-methylbenzylamine dimethyl malonate, methyl bromoacetate

Azaheterocycles constitute a very important class of compounds. In particular, pyrimidine derivatives include a number of natural and pharmaceutical products (Figure 1).[1–5] A subcategory of azaheterocycles are pyrrolino[2,3-*d*]pyrimidin-6-one derivatives, which are notable pharmacaphores in a number of diverse therapeutic areas.[6,7]

Recently, we required a robust synthetic route towards 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one (**12a**). A survey of literature revealed that the synthesis of **12a** could be accomplished in six steps starting from ethyl cyanoacetate (Scheme 1).[6–9] Although compound **12a** was obtained following literature procedures in low yield (8%), we were interested in developing a streamlined and environment-friendly synthesis of **12a**, which avoids the use of pyridinium bromide perbromide, nickel, and zinc. Herein, we report a streamlined four-step synthesis of 4-

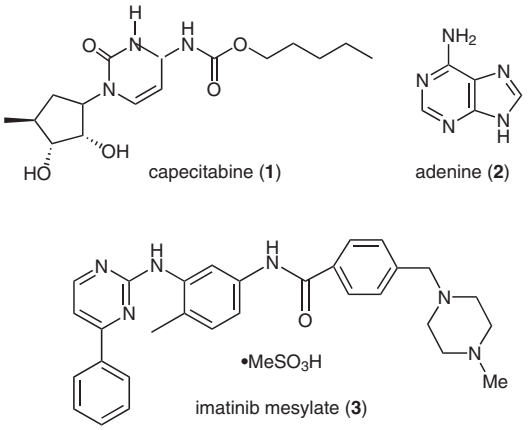
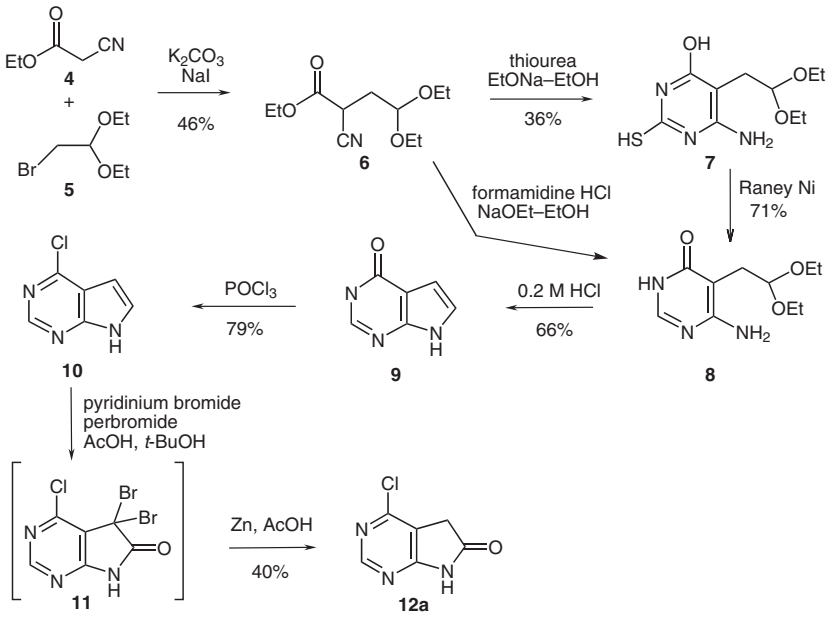


Figure 1 Representative compounds containing a pyrimidine substructure



Scheme 1 Literature synthesis of **12a**

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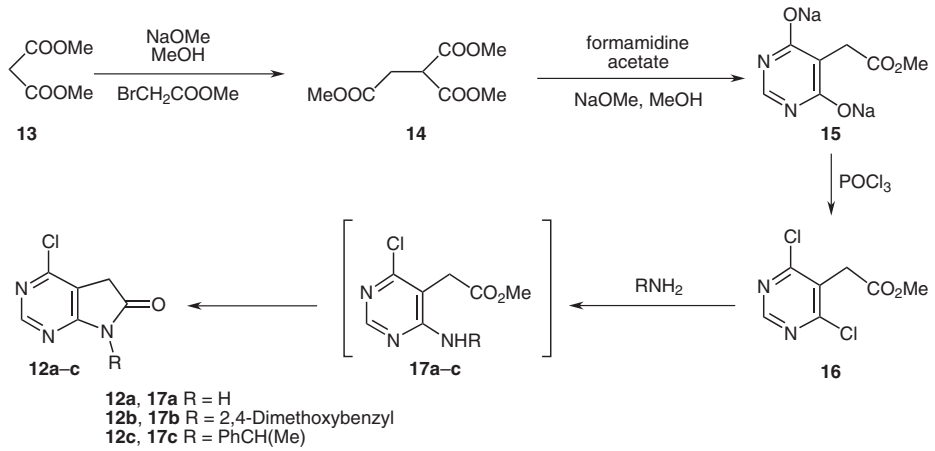

Scheme 2 Synthesis of compounds **12a–c**

chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one (**12a**) and its 7-substituted derivatives **12b**,**c** starting from dimethyl malonate (Scheme 2).

The synthesis of **14** was achieved successfully in 61% yield by alkylation of dimethyl malonate with methyl bromoacetate in methanol using sodium methoxide.[10] Pyrimidine ring construction was completed by the reaction of **14** with formamidine acetate in methanol using sodium methoxide.[8] Pyrimidine disodium salt **15** was isolated and dried prior to its use in the synthesis of **16**. Chlorination of **15** using $POCl_3$ followed by workup provided **16** in good yield (77%) and HPLC purity (97.7%).

The synthesis of **12a** from **16** was investigated in various solvents with different reaction parameters using aqueous 2 M ammonia and the data obtained from this study are listed in Table 1. The reaction progress was determined by LC-MS. Based upon the LC-MS data, formation of intermediate **17a** and product **12a** was observed along with three other impurities **18**–**20** as shown in Figure 2.

The data in Table 1 (entry 5) indicate that propan-2-ol as a reaction solvent provided best outcome with respect to the formation of **12a**. LC-MS data indicated that the reaction was not clean as the above mentioned impurities **18**–**20** were present. The formation of impurities **18**, **19**, and **20** may be due to the reaction of i) excess ammonia with intermediate **17a** and product **12a** and ii) transesterification of **17a** with propan-2-ol because of reaction concentration. Therefore, the impact of ammonia strength, reaction concentration, temperature, and time on the formation of **12a** in propan-2-ol were studied (Table 2). The data (entries 1 and 2) in Table 2 indicate that the reaction with 3.7 equivalents of 1.0 M ammonia provided best conversion to **12a**. Based upon this data, the reaction was scaled to 100 grams using propan-2-ol at 90 °C. The in-process data obtained from the scale-up batches are listed in Table 3.

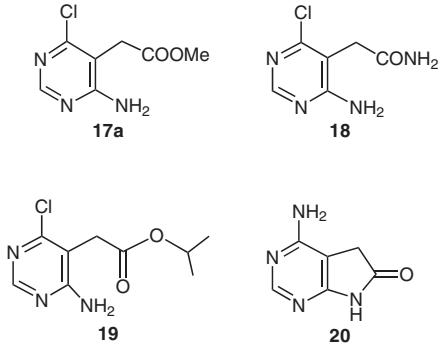

Figure 2 Structures of intermediate and impurities present in the synthesis of **12a**

Table 1 Solvent Screening in the Synthesis of **12a**

Entry	NH_3 (M)/equiv	Sealed-tube reaction conditions			HPLC analysis of reaction mixture (area%)				
		Solvent	Temp (°C)	Time (h)	**17a**	**18**	**19**	**20**	**12a**
1	2.0/5.0	H_2O	60	6	7	31	0	0	0
2	2.0/5.0	MeCN	60	6	33	40	0	0	8
3	2.0/5.0	MeOH	60	6	54	31	0	3	8
4	2.0/5.0	EtOH	60	6	26	16	0	15	35
5	2.0/5.0	*i*-PrOH	60	12	6	8	8	9	63
6	2.0/5.0	*i*-PrOH	100	24	6	4	20	12	60
7	2.0/5.0	*n*-BuOH	95	12	0	47	0	1	34

Table 2 Data from the Investigation of NH_3 concentration, Time, and Temperature Study for the Synthesis of **12a**

Entry	NH_3 in *i*-PrOH			Temp	Time	HPLC analysis of the reaction (area%)				
	Concn (M)	Equiv	Volume	(°C)	(h)	**12a**	**17a**	**18**	**19**	**20**
1	1.0	3.7	15	90	16	70.8	11.0	1.9	4.9	4.6
2	1.0	3.7	15	105	16	68.5	12.5	0.8	3.4	5.6
3	1.3	3.5	9	95	24	65.6	17.0	0.9	3.4	6.7
4	1.3	4.0	7	105	24	63.8	7.4	2.2	5.6	4.9
5	1.4	4.6	8	100	4	64.2	8.1	4.7	10.6	5.7
6	1.5	4.4	7	95	16	59.7	5.6	5.1	8.3	8.0
7	1.5	4.0	6	105	5	62.8	5.5	6.6	5.6	7.0
8	1.8	4.4	6	100	6	59.5	3.0	10.2	7.2	9.0
9	2.0	4.4	5	90	8	63.6	6.0	3.1	7.9	9.5
10	2.0	4.4	5	90	16	58.6	7.1	4.6	11.0	10.9
11	2.0	5.3	6	95	8	62.8	8.2	5.9	9.2	9.8

Table 3 In-Process Data of **12a** from the Scale-Up Reactions in an Autoclave at 90 °C in Propan-2-ol

Entry	**16**	HPLC analysis of reaction (area%)				
	(g)	**12a**	**17a**	**18**	**19**	**20**
1	100	68.0	8.3	6.8	8.4	5.5
2	100	66.4	6.4	5.3	8.3	4.9
3	100	72.1	7.2	10.8	5.1	1.9
4	100	70.1	6.3	5.2	5.9	4.5

As the reaction mixture contained predominantly the desired product **12a** along with other impurities, a workup strategy was designed to reject the impurities and to obtain pure product. This workup strategy involved: a) removal of inorganic salts by filtration, b) concentration of reaction mixture, c) dissolution of residue in ethyl acetate followed by activated charcoal treatment to remove majority of **20**, d) aqueous wash of ethyl acetate layer and concentration to obtain crude product, and e) crystallization of crude product from dichloromethane and *n*-heptane to obtain **12a**. Following this purification strategy, **12a** was obtained in 60% yield with excellent purity (98.5%).

Synthesis of **12b** was accomplished by treating **16** with 2,4-dimethoxylbenzylamine and Hünig's base in DMF followed by cyclization of intermediate **17b**. The reaction workup followed by crystallization from toluene provided **12b** of desired quality. This synthetic sequence was successfully used to manufacture 140 kilograms of **12b** with 99.5% purity. Similarly, synthesis of **12c** was completed by the reaction of **16** with α-methylbenzylamine. Synthesis of **12a** via debenzylation of **12b** or **12c** using Pd/C under various conditions or organic sulfonic acids (such as methanesulfonic acid, *p*-toluenesulfonic acid, triflic acid) was unsuccessful.[11]

In summary, a four-step synthesis of 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one and its 7-substituted derivatives was developed starting from dimethyl malonate. This practical synthetic sequence was successfully scaled up in preparing multi kilogram quantities of **12b**. The efficient synthesis of 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one was demonstrated on a scale of 100 grams in 23% overall yield with 98.5% purity. Further, this developed sequence for the synthesis of 4-chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one is not only streamlined but also has a diminished environmental impact as it avoids the use of metals (nickel and zinc) and pyridinium bromide perbromide.

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. Mass spectra were recorded on a Finnigan Trace MS 2000 spectrometer. IR spectra were recorded on an FTS-185 IR spectrometer as KBr pellets with absorption in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are expressed in ppm downfield relative to TMS (0 ppm) and coupling constants (*J*) are given in Hz. Standard abbreviations are used to describe the signal patterns. HRMS were obtained using a Waters GCT Premier TOF mass spectrometer with EI source. All of the solvents and materials used were reagent grade and purified as required. Compound **14** was prepared following the literature procedure.[10]

Disodium 5-(2-Methoxy-2-oxoethyl)pyrimidine-4,6-bis(olate) (15)

Formamidine acetate (489 g, 4.70 mol) was added in one portion to a solution of NaOMe (576 g, 10.66 mol) in MeOH (3.5 L) at 0–3 °C under N_2. Triethyl ethane-1,1,2-tricarboxylate (**14**; 729 g, 3.03 mol) was added dropwise over 10 min by maintaining a reaction temperature below 10 °C. The reaction mixture was stirred at 25 °C for 16 h. The slurry was filtered and washed with EtOH (500 mL) and heptane (500 mL). The product obtained was dried at 35 °C under vacuum; yield: 650 g (80%); mp 259–279 °C.

IR (KBr): 1709 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 3.41 (s, 2 H), 3.69 (s, 3 H), 7.90 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 178.3, 172.0, 150.2, 98.7, 54.9, 31.3.

HRMS: *m*/*z* calcd for $C_7H_6N_2Na_2O_4$: 228.0123; found: 228.0146.

Methyl 2-(4,6-Dichloropyrimidin-5-yl)acetate (16)
A suspension of the disodium salt **15** (502 g, 1.80 mol) was added to $POCl_3$ (2.5 L, 10.00 equiv, 2.53 mol) over 1 h with stirring by keeping the temperature below 50 °C. The resulting mixture was stirred at 50 °C for 0.5 h, and then the suspension was heated to 80 °C slowly over 1 h. The homogenous solution obtained was stirred at 80 °C for 1 h. The temperature of the reaction was then raised to 100 °C and maintained for 2 h. HPLC analysis indicated consumption of starting material. The reaction mixture was cooled to 60 °C and $POCl_3$ was removed under vacuum. The concentrated reaction mixture was added dropwise to ice water (12 L). The pH was adjusted to 7–8 with aq 10 M NaOH. The slurry was stirred for 20 min at 20 °C and filtered. The wet cake was dissolved in MTBE (2 L), filtered, and the MTBE layer was washed with H_2O (500 mL). The MTBE layer was separated and refluxed with activated charcoal (20 g) for 1 h. The mixture was cooled to r.t. and filtered. The filtrate was concentrated to 200 mL under vacuum and heptane (200 mL) was added to the residue. The slurry obtained was stirred for 30 min and filtered. The product obtained was washed with *n*-heptane (100 mL) and dried under vacuum; yield: 373 g (77%); off-white solid; HPLC purity: 97.7%; mp 65–67 °C.

IR (KBr): 1734 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 3.75 (s, 3 H), 3.98 (s, 2 H), 8.70 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 168.1, 162.4, 156.6, 126.7, 52.7, 35.6.

HRMS: *m*/*z* calcd for $C_7H_6Cl_2N_2O_2$: 219.9806; found: 219.9890.

4-Chloro-2-pyrrolino[2,3-*d*]pyrimidin-6-one (12a)
To a 5 L autoclave was added **16** (100 g, 452.45 mmol, 1.00 equiv) and ammonia/*i*-PrOH (2.6 M, 600 mL, 1.56 mol, 3.5 equiv). The mixture was further diluted with *i*-PrOH (960 mL, final ammonia strength was 1 M) at 20 °C and the flask was filled with N_2. The contents were heated to 90–93 °C and stirred for 16 h. The reaction was sampled after 16 h and analyzed by HPLC. The data indicated that the starting material was consumed and the product area was about 70%. The autoclave was cooled to r.t. and the reaction mixture was concentrated to obtain a brown solid (103.5 g). The solid was dissolved in EtOAc (1.4 L). Activated charcoal (10 g; 0.1 wt) was added, and the mixture was refluxed for 1 h. After filtration, the charcoal was discarded and the organic layer was washed with brine (3 × 140 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford 70.6 g of a yellow solid. Four batches were prepared on a 100 g scale in an autoclave and combined to obtain 284 g of crude **12a**. This crude product (284 g) was refluxed in CH_2Cl_2 (1.4 L) for 5 h and then *n*-heptane (280 mL) was added dropwise. The mixture was stirred for 1 h and cooled to r.t. slowly. The slurry obtained was filtered and washed with *n*-heptane (50 mL). The product obtained was dried under vacuum; yield: 183 g (60%); pale yellow solid; HPLC purity: 98.5%; mp 188–190 °C.

IR (KBr): 1680 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 3.62 (s, 2 H), 8.51 (s, 1 H), 11.68 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 174.9, 166.8, 157.8, 151.6, 117.3, 34.1.

HRMS: *m*/*z* calcd for $C_6H_4ClN_3O$: 169.0043; found: 169.0034.

Isolation of Methyl 2-(4-Amino-6-chloropyrimidin-5-yl)acetate (17a) and Isopropyl 2-(4-Amino-6-chloropyrimidin-5-yl)acetate (19)
The mother liquor from the above reaction was concentrated to afford about 90 g of a yellow solid. This sample was enriched with **17a**, **18**, **19**, and **20**. Compound **17a** was isolated by column chromatography using EtOAc and petroleum ether (bp 60–80 °C) (80:20). Compound **20** was isolated using preparative HPLC. Compounds **18** and **20** were not isolated.[12]

17a
White solid; mp 129–131 °C.

IR (KBr): 3302, 3223 (NH_2), 1724 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.69 (s, 2 H), 3.73 (s, 3 H), 5.74 (br s, 2 H), 8.26 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 170.2, 163.4, 159.7, 156.6, 108.1, 52.7, 33.7.

HRMS: *m*/*z* calcd for $C_7H_8ClN_3O_2$: 201.0305; found: 201.0303.

19
White solid; mp 131–134 °C.

IR (KBr): 3319, 3202 (NH_2), 1728 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 6.2 Hz, 6 H), 3.66 (s, 2 H), 5.03 (m, 1 H), 5.60 (br s, 2 H), 8.3 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 169.3, 163.5, 159.7, 156.5, 108.5, 69.7, 34.3, 21.6.

HRMS: *m*/*z* calcd for $C_9H_{12}ClN_3O_2$: 229.0618; found: 229.0626.

7-[(2,4-Dimethoxyphenyl)methyl]-4-chloro[2,3-*d*]pyrimidin-6-one (12b)
To a 3-necked flask equipped with a mechanical stirrer, thermocouple, and N_2 inlet was added **16** (56 g, 253.4 mmol) and DMF (392 mL, 7 vol). The reaction mixture was degassed by purging with N_2. DIPEA (40.9 g, 316.7 mmol) was added to the reaction mixture under N_2. 2,4-Dimethoxybenzylamine (48.7 g, 291.3 mmol) was charged into the flask at 20–35 °C. The reaction contents were warmed to 50–60 °C and stirred at this temperature for 4 h. The reaction completion was checked by HPLC analysis. The reaction contents were cooled to 40–45 °C. H_2O (360 mL) was added dropwise into the flask by maintaining a temperature of 40–45 °C. The reaction mixture was stirred at 40–45 °C for 6 h and analyzed by HPLC. The reaction pH was adjusted to 6.5–7.5 with aq 0.3 M HCl (123.2 g). H_2O (364 mL) was charged dropwise to the flask by maintaining a temperature of 35–45 °C. The contents were stirred at 35–45 °C for 2 h. The reaction slurry was cooled to 5–10 °C and stirred for 2 h. The slurry was filtered and the cake was washed with DMF–H_2O (28 mL:84 mL, 1:3). The wet cake was transferred to a 3 neck flask equipped with a mechanical stirrer, thermocouple, and reflux condenser. Toluene (190 mL) was added and the contents were heated to 75–85 °C. The contents were stirred at 75–85 °C for 75 min. The contents were cooled to 2–7 °C and stirred for 2 h. The slurry was filtered and the cake was washed with cold toluene (48 mL). The product was dried under vacuum at 50–60 °C for 10–12 h; yield: 81 g (88%); yellow solid; HPLC purity: 99.9%, mp 170–173 °C.

IR (KB): 1680 cm^{-1} (C=O).

^{1}HNMR (DMSO-d_6): δ = 3.71 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 2 H), 4.73 (s, 2 H), 6.37 (dd, *J* = 2.6, 8.3 Hz, 1 H), 6.55 (d, *J* = 2.2 Hz, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H), 8.58 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 173.5, 166.1, 160.4, 58.0, 157.9, 151.5, 128.3, 116.8, 115.6, 104.9, 98.8, 56.0, 55.7, 38.2, 33.5.

HRMS: *m*/*z* calcd for $C_{15}H_{14}ClN_3O_3$: 319.0724; found: 319.0738.

7-(α-Methylbenzyl)-4-chloro[2,3-*d*]pyrimidin-6-one (12c)
Synthesis of **12c** on a 10 g scale was accomplished in a similar manner following the procedure described for **12b** from **16** and α-methylbenzylamine; yield: 9.67 g (78%); brown solid; HPLC purity: 99.9%; mp 82–85 °C.

IR (KBr): 1680 cm^{-1} (C=O).

^1H NMR (DMSO-d_6): δ = 1.84 (d, *J* = 7.0 Hz, 3 H), 3.78 (d, *J* = 4.8 Hz, 2 H), 5.60 (m, 1 H), 7.30 (m, 5 H), 8.58 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 173.3, 166.0, 157.5, 151.7, 140.3, 128.8, 127.8, 127.1, 116.8, 50.5, 33.6, 17.2.

HRMS: *m*/*z* calcd for $C_{14}H_{12}ClN_3O$: 273.0669; found: 273.0676.

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(12) The structures of compounds **18** and **20** shown in Figure 2 are postulated based upon the mass data.

