

SUPPORTING INFORMATION

HIGHLY SELECTIVE HYDROLYSIS OF CHLOROPYRIMIDINES TO PYRIMIDONES IN 12N HYDROCHLORIC ACID

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General Experimental, Analytical, and Spectroscopic Methodologies

Unless otherwise stated, reactions were performed in dry glassware under an atmosphere of argon. Reagents and solvents were purchased from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) was performed using silica gel pre-coated plates (250 μ thickness). Plates were visualized by UV absorbance at 254 nm and developed by spraying with 50% aq. sulfuric acid then heating. Flash chromatography was performed by the method of Still using 230-400 mesh silica gel.¹ NMR spectra were measured in deuterated solvents on 300 MHz or 500 MHz instruments. ¹³C and ¹H chemical shifts are reported in parts per million (ppm) on the δ scale relative to tetramethylsilane (TMS) as internal standard. Isopar H is a mixture of branched hydrocarbons of approximate boiling point range 177°C to 187°.

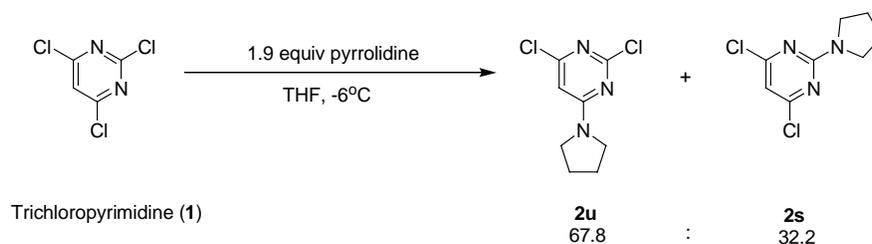
Experimental Section

Typical Experimental Procedure for Selective Destruction of 3s in Presence of 3u by Nucleophilic Reagents (Table 1)

Methanol (2 mL) was added to a 95.15:4.85 mixture of **3u** and **3s** (mw 252.75; 0.256 g, 1.015 mmole) and biphenyl (LC internal standard; 0.0665 g). The mixture was heated to form a homogeneous solution, treated with a solution of sodium methoxide in methanol (0.50 mL of 4.6 M

solution, 2.3 mmoles, 2.27 equiv), and refluxed for 16 h. Analysis by quantitative LC² showed that the amount of **3u** had decreased from 95.15 to 75.97 and that the amount of **3s** had decreased from 4.85 to 0.21, from which it is calculated that $k^s/k^u = 13.95$.

Synthesis of Reference Standards of Monoadducts **2s** and **2u**



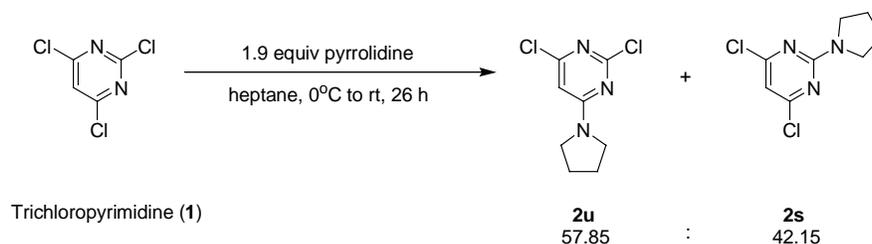
A solution of 2,4,6-trichloropyrimidine (mw 183.42; 20.0 g, 0.1090 moles) in 125 mL THF was cooled to -15°C and treated gradually with a solution of pyrrolidine (mw 71.12; d 0.852; 9.1 mL, 7.75 g, 0.1090 moles, 1.00 equiv) in 22 mL THF at a rate such that the pot temperature remained at $\leq -6^\circ\text{C}$ (1 h). During the add, a thick slurry (triethylamine hydrochloride) developed, and 7 mL THF was added. LC analysis³ indicated 51.5 M% unreacted trichloropyrimidine. More pyrrolidine/THF solution was added until the amount of trichloropyrimidine was 4.6 M% (27 mL of solution of 0.0949 moles pyrrolidine in THF; total pyrrolidine added: 0.204 moles, 1.87 equiv). The mixture was quenched with 100 mL H₂O and warmed to 10°C . The layers were separated and the aqueous layer was extracted with 30 mL EtOAc. The organic layers were washed with 40 mL aq. NaCl. They contained trichloropyrimidine, 2,4-dichloro-6-pyrrolidinylpyrimidine **2u**, 4,6-dichloro-2-pyrrolidinylpyrimidine **2s**, and 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** in a 1.57:66.69:31.67:0.07 mole ratio by LC. The solution was concentrated, seeded, diluted with heptane, and filtered to give a solid consisting of a 93.9:6.1 mixture of **2u** and **2s** by LC (weight: 14 g). The solids were dissolved in 23 mL ethyl acetate at 40°C , 50 mL heptane added, then the solution was cooled to -15°C and filtered to give solids identified as a 99.15:0.85 mixture of **2u** and **2s**. Weight: 9.0 g (mw 218.09; 0.0413 moles, 37.8% yield). This material was recrystallized by the same procedure to give an analytically pure reference

standard of **2u** (containing 0.04 M% **2s**). ^{13}C -NMR (75 MHz, CDCl_3): δ 161.2 (s); 159.4 (s); 159.0 (s); 100.3 (d); 47.2/46.7 (t); 25.3/24.7 (t). ^1H -NMR (300 MHz, CDCl_3): δ 1.96-2.10 (4H, mults); 3.33 (2H, t, $J = 6.6$ Hz); 3.63 (2H, t, $J = 6.6$ Hz); 6.21 (1H, s). MS (CI, CH_4): m/e 218, 220, 222 ($\text{P}^+ + \text{H}$, 100%). *Anal.* Calc'd for $\text{C}_8\text{H}_9\text{N}_3^{35}\text{Cl}$: m/e 217.0173. Found: m/e 217.0172.

The filtrates from all the crystallizations were combined and concentrated to give 15.6 g solids consisting of two components ($R_f = 0.58$ and 0.28) by TLC.⁴ The solids were flash chromatographed on 400 g silica gel (gradient elution, 2% \rightarrow 10% ethyl acetate/cyclohexane). The fractions containing the $R_f = 0.58$ component were combined and concentrated to solids identified as 4,6-dichloro-2-pyrrolidinylpyrimidine **2s** by its spectral characteristics. Weight: 4.93 g (mw 218.09; 0.0226 mole, 20.7% yield). ^{13}C -NMR (75 MHz, CDCl_3): δ 161.2 (2C, s); 159.3 (s); 107.1 (d); 47.1 (2C, t); 25.3 (2C, t). ^1H -NMR (300 MHz, CDCl_3): δ 1.77-2.02 (4H, mults); 3.53-3.60 (4H, mults); 6.51 (1H, s). MS (CI, CH_4): m/e 218, 220, 222 ($\text{P}^+ + \text{H}$, 100%). *Anal.* Calc'd for $\text{C}_8\text{H}_9\text{N}_3^{35}\text{Cl}$: m/e 217.0173. Found: 217.0174.

The fractions containing the $R_f = 0.28$ component were combined and concentrated to a solid identified as 2,4-dichloro-6-pyrrolidinylpyrimidine **2u** in essentially pure form (containing only 0.29 M% **2s**) by LC. Weight: 7.52 g (mw 218.09; 0.0345 mole, 31.6% yield).

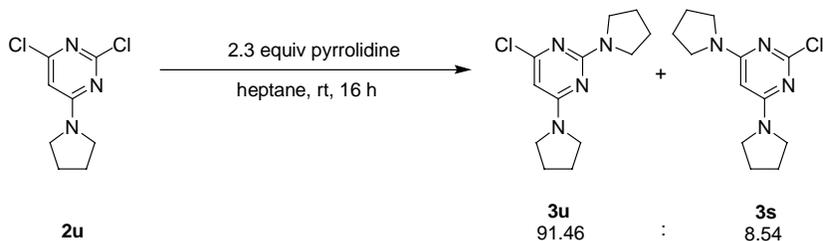
Generation of Monoadducts **2s** and **2u** in Heptane



A solution of 2,4,6-trichloropyrimidine (mw 183.42; d 1.595; 0.126 mL, 201 mg, 1.096 mmole) in 1.7 mL heptane was cooled to -14°C , treated with neat pyrrolidine (mw 71.12; d 0.852; 0.174 mL, 148 mg, 2.08 mmoles, 1.90 equiv) at a rate such that the temperature remained at $\leq 0^\circ\text{C}$ (2 min). The

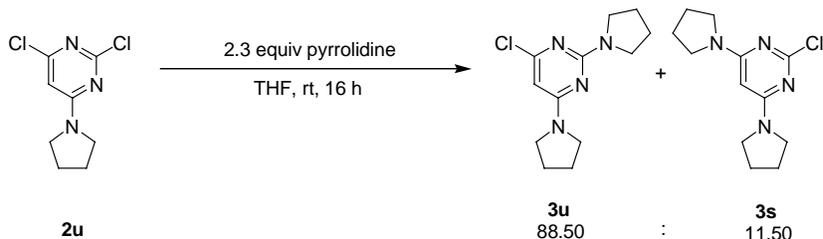
mixture was warmed to 20°C, stirred for 26 h, then CH₂Cl₂ added to give a homogeneous solution which was found to contain trichloropyrimidine, **2u**, and **2s** in a 8.92:52.69:38.39 molar ratio by LC.

Reaction of Monoadduct **2u** with Pyrrolidine in Heptane



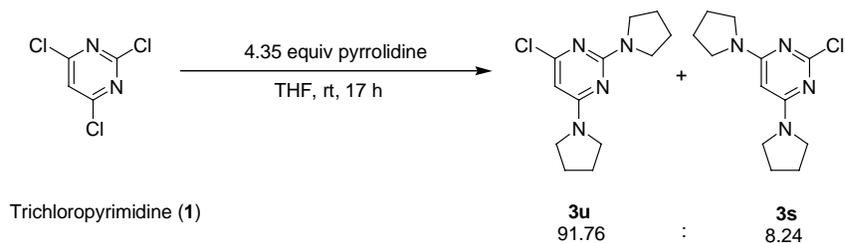
A slurry of 2,4-dichloro-6-pyrrolidinylpyrimidine **2u** (mw 218.09; 0.200 g, 0.917 mmole) in 1.7 mL heptane was treated with neat pyrrolidine (mw 71.12; d 0.852; 0.176 mL, 0.150 g, 2.11 mmole, 2.30 equiv) and stirred at rt. After 16 h, the slurry was diluted with sufficient CH₂Cl₂ to give a homogeneous solution. The solution was found to contain 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** and 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s** in a 91.46:8.54 molar ratio by LC.

Reaction of Monoadduct **2u** with Pyrrolidine in THF



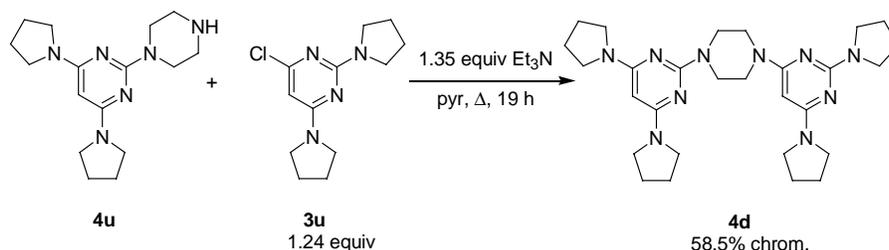
A solution of 2,4-dichloro-6-pyrrolidinylpyrimidine **2u** (mw 218.09; 0.200 g, 0.917 mmole) in 1.7 mL THF was treated with neat pyrrolidine (mw 71.12; d 0.852; 0.176 mL, 0.150 g, 2.11 mmole, 2.30 equiv) and stirred at rt. After 16 h, the thin slurry was diluted with sufficient CH₂Cl₂ to give a homogeneous solution. The solution was found to contain 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** and 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s** in an 88.50:11.50 molar ratio by LC.

Generation of Chloro-bis-pyrrolidinylpyrimidine Isomer Mixture (**3u/3s**) in THF



A solution of 2,4,6-trichloropyrimidine (mw 183.42; d 1.595; 0.126 mL, 201 mg, 1.096 mmole) in 1.7 mL THF was treated with neat pyrrolidine (mw 71.12; d 0.852; 0.398 mL, 339 mg, 4.77 mmoles, 4.35 equiv) and stirred at rt. After 17 h, CH_2Cl_2 was added to give a homogeneous solution which was found to contain 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s** and 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** in an 8.24:91.76 molar ratio by LC.

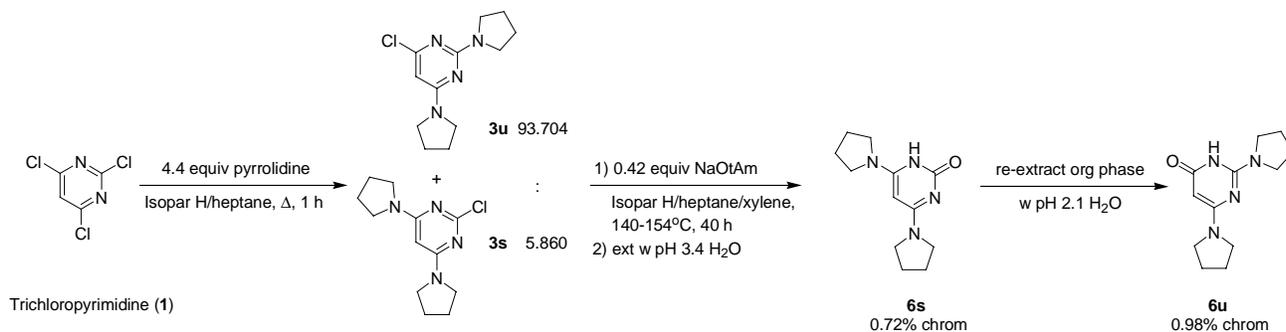
Synthesis of Reference Standard of 2:1 Adduct **4d**



A solution of 6-piperazinyl-2,4-bis-pyrrolidinylpyrimidine **4u** (mw 302.43; 0.806 g, 2.665 mmoles), 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** (252.75; 0.837 g, 3.31 mmoles, 1.24 equiv), and triethylamine (mw 101.19; d 0.726; 0.50 mL, 0.363 g, 3.59 mmoles, 1.35 equiv) in 5 mL pyridine was refluxed for 19 h, then cooled to rt, poured into 50 mL water and 10 mL ethyl acetate. Portions of 5% aq. sodium NaHCO_3 and CH_2Cl_2 were added to get a good phase break. The organic phase contained two components ($R_f = 0.63$ and 0.38) along with pyridine ($R_f = 0.18$) by TLC (eluant: 35% ethyl acetate/cyclohexane). The organic phase (mainly CH_2Cl_2) was extracted twice with pH 4.01 buffer and concentrated to a solid residue, which was flash chromatographed on 60 g silica gel (eluant: 400 mL 10% ethyl acetate/cyclohexane, then 600 mL 50% ethyl acetate/cyclohexane). The fraction containing the $R_f = 0.38$ component was concentrated to a solid identified as 2:1 adduct **4d** by its spectral

characteristics. Weight: 0.808 g (mw 518.71; 1.558 mmole, 58.5% yield). $^{13}\text{C-NMR}$ (75 MHz, CD_2Cl_2): δ 164.3 (2C, s); 162.9 (2C, s); 160.6 (2C, s); 72.6 (2C, d); 46.5 (4C, t); 46.4 (4C, t); 44.5 (4C, t); 26.0 (4C, t); 25.7 (4C, t). $^1\text{H-NMR}$ (300 MHz, CD_2Cl_2): δ 1.86-1.93 (16H, mults); 3.40-3.57 (24H, mults); 4.88 (2H, s). MS (CI, CH_4): m/e 519 ($\text{P}^+ + \text{H}$, 100%).

Synthesis of Reference Standards of Hydroxy-bis-pyrrolidinylpyrimidines **6u** and **6s**



A solution of 2,4,6-trichloropyrimidine (mw 183.42; 50.0 g, 0.273 mole) in 100 mL Isopar H and 350 mL heptane was cooled to -16°C and treated with neat pyrrolidine (mw 71.12; d 0.852; 99.5 mL, 84.77 g, 1.192 mole, 4.37 equiv) at a rate such that the pot temperature remained at $\leq -1^\circ\text{C}$ (13 min). The slurry was refluxed for 1 h, then quenched with 100 mL water, the pH adjusted from 9.2 to 4.9 with conc hydrochloric acid, and the phases separated (all operations done at 80°C). The organic phase was treated with 75 mL water, the pH was adjusted to 5.1 with 3 drops of conc hydrochloric acid, and the phases were separated. The aqueous phases were back-extracted in sequence with 100 mL 90°C heptane. The organic phases were concentrated to 170 mL. The solution was found to contain a 93.704:5.860 (mole ratio, not normalized) mixture of **3u** and **3s** by LC. To this solution was added sodium t-amylate (mw 110.13; 12.6 g, 0.1144 mole, 0.42 equiv), biphenyl (LC internal standard; mw 154.21; 0.1457 g, 0.945 mmole), 40 mL heptane, and 30 mL xylene. The solution was heated at $140\pm 2^\circ\text{C}$ for 17 h, then at $154\pm 1^\circ\text{C}$ for 23 h, then cooled to 100°C . Quantitative LC analysis showed that the level of **3u** dropped from 93.704% to 72.941% while the level of **3s** dropped from 5.860% to 0.046%. From these values it was calculated that $k^s/k^u = 19.35$. The reaction mixture was quenched with 75 mL water, and the phases separated: organic 1A, aqueous 1B. To the organic phase 1A was

added 50 mL water, the pH was adjusted from 11.6 to 3.4 with conc hydrochloric acid at $\geq 75^{\circ}\text{C}$, and the phases were separated: organic 1C, aqueous 1D. The aqueous 1D was extracted with 30 mL heptane, basified to pH 12 with 15% aq. NaOH, extracted with CH_2Cl_2 , and the CH_2Cl_2 layer was concentrated to a foam (weight: 1.36 g) which was slurried in acetone and filtered to give solids (weight: 1.05 g) consisting of one major component ($R_f = 0.40$) and one minor component ($R_f = 0.54$) by TLC (eluant: 90:10:1 CH_2Cl_2 :MeOH: NH_4OH). The solids were flash chromatographed on silica gel (4 cm x 6" column; eluant: 10% MeOH/ CHCl_3). The fractions containing the $R_f = 0.40$ component were combined and concentrated to a residue which was slurried in acetone/ethyl acetate and filtered to give solids identified as 4,6-bis-pyrrolidinyl-2-pyrimidone **6s** by its spectral characteristics. Weight: 0.463 g (mw 234.30; 1.98 mmoles, 0.72% yield). ^{13}C -NMR (75 MHz, CD_2Cl_2): δ 159.2 (2C, s); 158.5 (s); 69.8 (d); 47.3 (4C, t); 25.6 (4C, t). ^{13}C -NMR (125 MHz, 0.92 mL conc HCl/1.0 mL D_2O ; QS to 10.0 mL w H_2O): δ 151.8 (s); 150.2 (s); 69.0 (d); 49.1 (t); 48.0 (t); 25.1 (t); 24.6 (t). ^1H -NMR (300 MHz, CD_2Cl_2): δ 1.91-2.00 (9H, mults); 3.43 (8H, br. s); 4.48 (1H, s). ^1H -NMR (500 MHz, 0.92 mL conc HCl/1.0 mL D_2O ; QS to 10.0 mL w H_2O): δ 1.84 (8H, br s); 3.20 (4H, br s); 3.26 (4H, br s); 4.51 (1H, s); 4.71 (exchangeable protons). MS (CI, CH_4): m/e 235 ($\text{P}^+ + \text{H}$, 100%). *Anal.* Calc'd for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}$: m/e 234.1481. Found: m/e 234.1474.

Organic phase 1C was treated with 50 mL water, the pH was adjusted to 2.1 with conc hydrochloric acid at 75°C , and the phases were separated. The aqueous was extracted with 30 mL heptane at 90°C , basified to pH >12 with 15% aq. NaOH, extracted with CH_2Cl_2 , and concentrated to a solid residue (weight: 2.15 g) which was slurried in CH_2Cl_2 and filtered to give solids (weight: 0.90 g) consisting of one major component ($R_f = 0.54$) by TLC. The solids were flash chromatographed on silica gel (4 cm x 6" column; eluant: 630 mL CH_2Cl_2 /70 mL MeOH/1.75 mL NH_4OH). The fractions containing the $R_f = 0.54$ component were combined and concentrated to a solid residue which was slurried in ethyl acetate and filtered to give solids identified as 2,4-bis-pyrrolidinyl-6-pyrimidone **6s** by its spectral characteristics. Weight: 0.627 g (mw 234.30; 2.68 mmoles, 0.98% yield). ^{13}C -NMR (75 MHz,

CD₂Cl₂): δ 166.3 (s); 162.5 (s); 152.5 (s); 75.7 (d); 47.0 (2C, t); 46.7 (2C, t); 25.8 (2C, t); 25.7 (2C, t). ¹³C-NMR (125 MHz, 0.92 mL conc HCl/1.0 mL D₂O; QS to 10.0 mL w H₂O): δ 168.5 (s); 162.9 (s); 152.8 (s); 49.5 (t); 49.1 (t); 48.3 (t); 47.3 (t); 33.7 (t); 25.0 (t); 24.8 (t); 23.8 (t); 23.7 (t). ¹H-NMR (300 MHz, CD₂Cl₂): δ 1.93 (8H, br s); 3.37 (1H, br s); 3.53 (8H, br s); 4.59 (1H, s). ¹H-NMR (500 MHz, 0.92 mL conc HCl/1.0 mL D₂O; QS to 10.0 mL w H₂O): δ 1.75-1.88 (8H, mults); 3.39 (2H, d, J = 6.4 Hz); 3.55 (8H, br s); 4.75 (exchangeable protons). MS (CI, CH₄): m/e 235 (P⁺ + H, 100%). *Anal.* Calc'd for C₁₂H₁₈N₄O: m/e 234.1481. Found: m/e 234.1491.

Spectra for 2,4,6-tri-pyrrolidinylpyrimidine

¹³C-NMR (75 MHz, CD₂Cl₂): δ 162.2 (2C, s); 160.7 (s); 72.4 (d); 46.5 (2C, t); 46.3 (4C, t); 26.0 (2C, t); 25.7 (4C, t). ¹H-NMR (300 MHz, CD₂Cl₂): δ 1.84-1.94 (12H, mults); 3.36-3.51 (12H, mults); 4.61 (1H, s). MS (EI): m/e 287 (P⁺, 100%).

Effect of Acid Concentration on Rate of Hydrolysis of 3u and 3s. A solution of 0.2049 g 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** in conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 25 mL, 11.14 g, 0.306 mole, 12.22 M) was prepared and the vial sealed (vial #1). A solution of 0.1982 g 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** in 12.3 mL water and 12.7 mL conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 5.660 g, 0.1552 mole, 6.21 M) was prepared and the vial sealed (vial #2). A solution of 0.2027 g 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** in 18.94 mL water and 6.06 mL conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 2.701 g, 0.0741 mole, 2.96 M) was prepared and the vial sealed (vial #3). The three vials were stirred at ambient temperature. After 263 h, each was opened and analyzed by LC. The rate constants for hydrolysis (k^u) were calculated using the

formula $k^u = \frac{-\ln([3u]^f)}{t}$ where t is the reaction time (in hours) and $[3u]^f = \frac{[3u]}{[3u]+[6u]}$.

Table S1. First order rate constants for hydrolysis of 3u

vial	[HCl]	t	[3u]	[6u]	k ^u
1	12.22 M	262.5 h	76.97 ^a	23.03 ^a	9.97 x 10 ⁻⁴ h ⁻¹
2	6.21 M	263 h	88.33	11.67	4.72 x 10 ⁻⁴ h ⁻¹
3	2.96 M	263 h	98.30	1.70	0.65 x 10 ⁻⁴ h ⁻¹

^aNormalized molar ratios determined by quantitative LC

A 39.62:60.12 (molar ratio) mixture of 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** and 4,6-bis-pyrrolidinyl-2-chloropyrimidine **3s** (0.2117 g) in conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 25 mL, 11.14 g, 0.306 mole, 12.22 M) was prepared and the vial sealed (vial #1). A 39.62:60.12 mixture (molar ratio) of 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** and 4,6-bis-pyrrolidinyl-2-chloropyrimidine **3s** (0.1942 g) in 12.3 mL water and 12.7 mL conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 5.660 g, 0.155 mole, 6.21 M) was prepared and the vial sealed (vial #2). A 39.62:60.12 mixture (molar ratio) of 2,4-bis-pyrrolidinyl-6-chloropyrimidine **3u** and 4,6-bis-pyrrolidinyl-2-chloropyrimidine **3s** (0.1958 g) in 18.94 mL water and 6.06 mL conc hydrochloric acid (mw 36.46; 37.5 W%; d 1.1885; 2.701 g, 0.0741 mole, 2.96 M) was prepared and the vial sealed (vial #3). The three vials were stirred at 25°C. Periodically, 1.00 mL aliquots were withdrawn with a volumetric pipet, QS'd to 10.0 mL (volumetric flask) with LC mobile phase, and analyzed for **3s** by LC.⁵ Data are compiled in Table S2. The half-life of **3s** ($t^{1/2}$) was calculated by dividing the number of times the concentration of **3s** dropped by half by the reaction time t (in hours). The rate constant k^s was then calculated from the half-life using the formula $k^s = \frac{-\ln(1/2)}{t^{1/2}}$. Note the excellent fit to a first order kinetic model.

Table S2. First order rate constants for hydrolysis of 3s

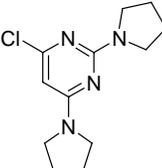
	t	3s (area cts)	number of halvings	$t^{1/2}$	k^s
vial #1	0	438,361.	--	--	--
12.22 M HCl	31 min	192,462.	1.187	0.435 h	1.59 h ⁻¹
	63 min	79,636.	2.461	0.427 h	1.62 h ⁻¹
	90 min	32,106.	3.771	0.398 h	1.74 h ⁻¹
vial #2	0	677,325.	--	--	--
6.21 M HCl	79 min	550,211.	0.300	4.39 h	0.158 h ⁻¹
	243 min	358,855.	0.916	4.42 h	0.157 h ⁻¹
	654 min	110,851.	2.611	4.17 h	0.166 h ⁻¹
vial #3	0	713,275.	--	--	--
2.96 M HCl	312 min	607,641.	0.231	22.49 h	0.0308 h ⁻¹
	3,020 min	139,627.	2.353	21.39 h	0.0324 h ⁻¹

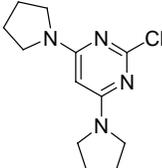
¹³C-NMR Study of Protonation States of 3u and 3s Under Hydrolysis Conditions. Since **3s** ($R_f = 0.20$) is more polar on silica gel TLC (eluant: 10% ethyl acetate/cyclohexane) than **3u** ($R_f = 0.44$), the possibility was considered that **3s** may hydrolyze more rapidly because it is selectively protonated. To investigate this possibility, the two isomers were examined by ¹³C-NMR in 75% CD₃CO₂D, 3N HCl, and 6N HCl (Table S3). Hydrolysis was sufficiently slow in all solvents for clean spectra to be acquired. The signals for C2/C4/C6 of both isomers shifted upfield progressively from 75% CD₃CO₂D

to 3N HCl to 6N HCl, consistent with protonation of an increasing fraction of both species (Table S3). The average upfield shift from 75% CD₃CO₂D to 6N HCl was slightly greater for **3s** (6.6 ppm) than for **3u** (5.2 ppm), however the average upfield shift from CD₂Cl₂ or CDCl₃ to 6N HCl was slightly less for **3s** (10.3 ppm) than for **3u** (10.6 ppm). It is concluded that roughly similar fractions of **3s** and **3u** are protonated at each acid concentration.

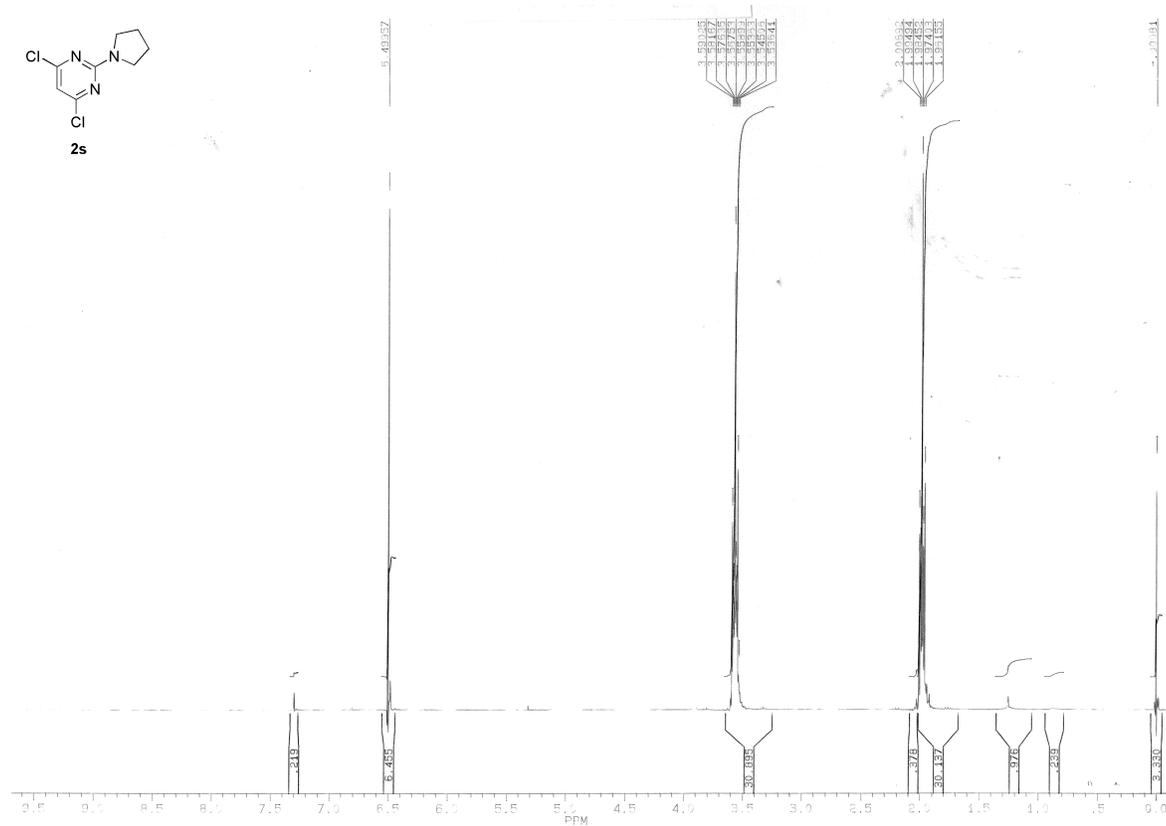
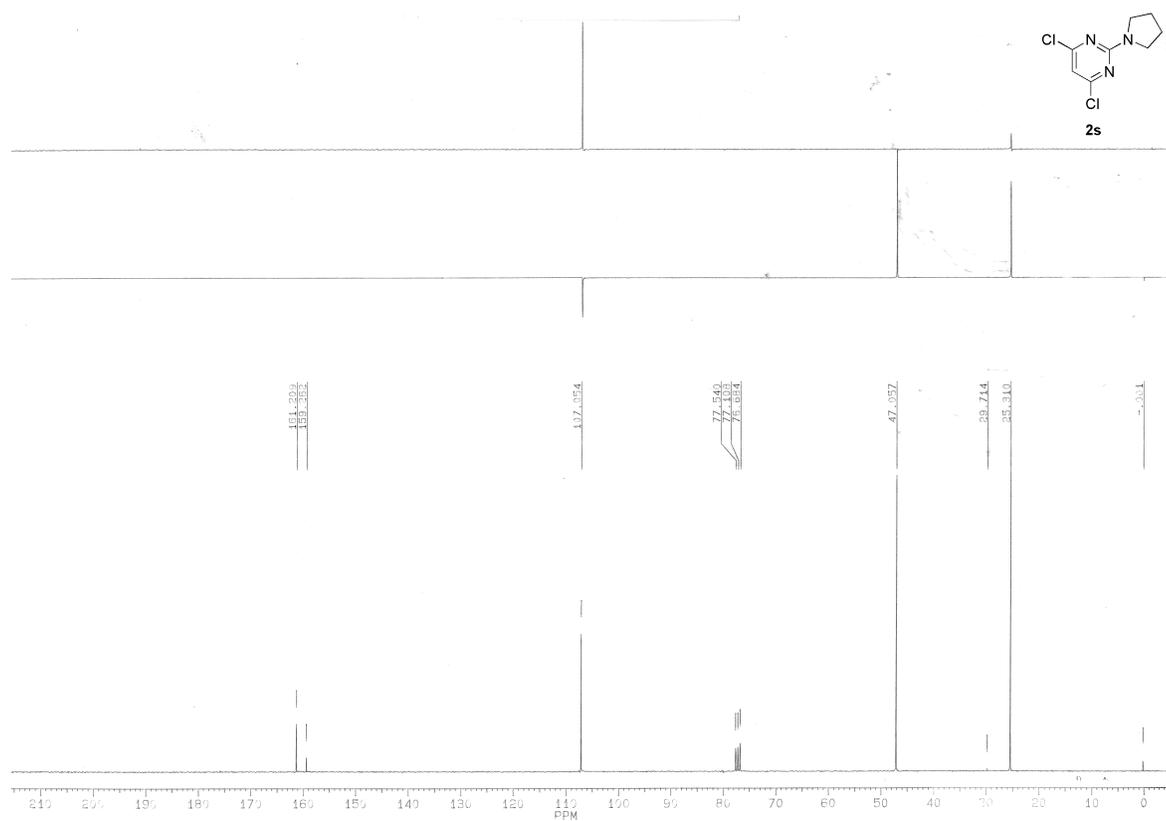
Interestingly, the signals for the pyrrolidine carbons of both isomers remain nearly constant over the range of acid concentration (Table S3). Protonation of one of the pyrrolidine nitrogens is expected to shift the α carbons downfield by ~12 ppm.⁶ Thus, it is concluded that both isomers are protonated exclusively on their pyrimidine nitrogens.

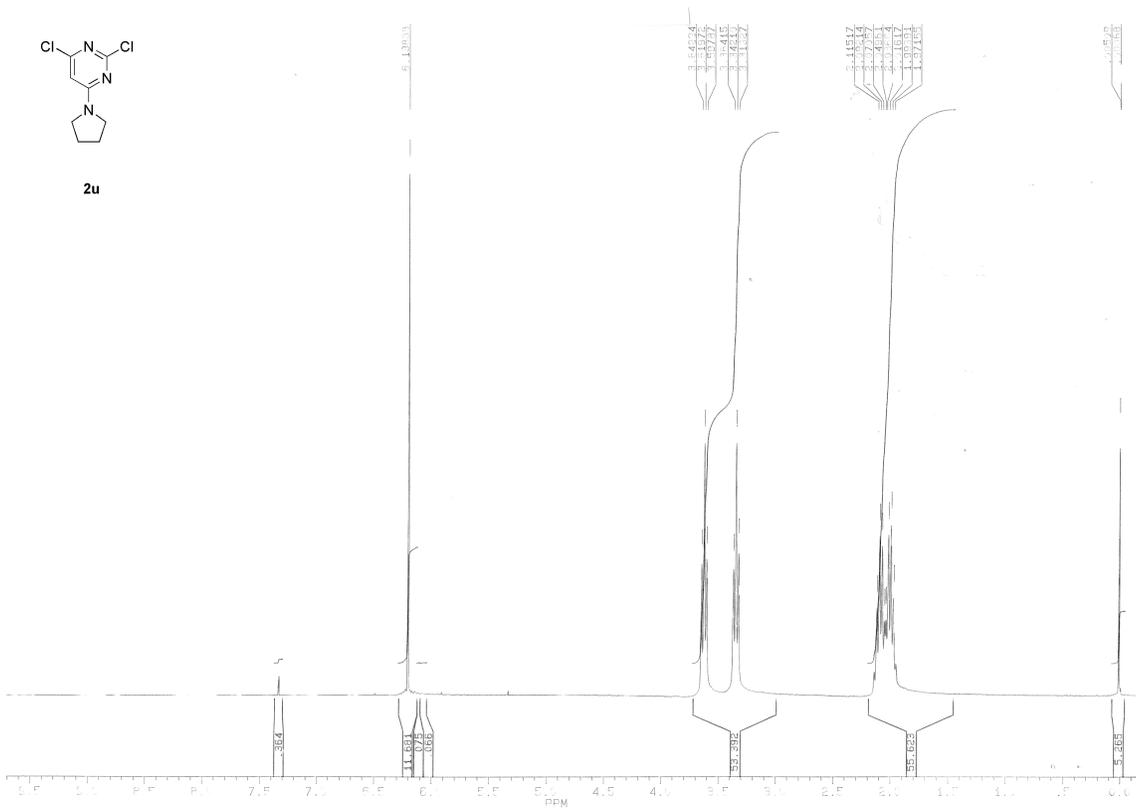
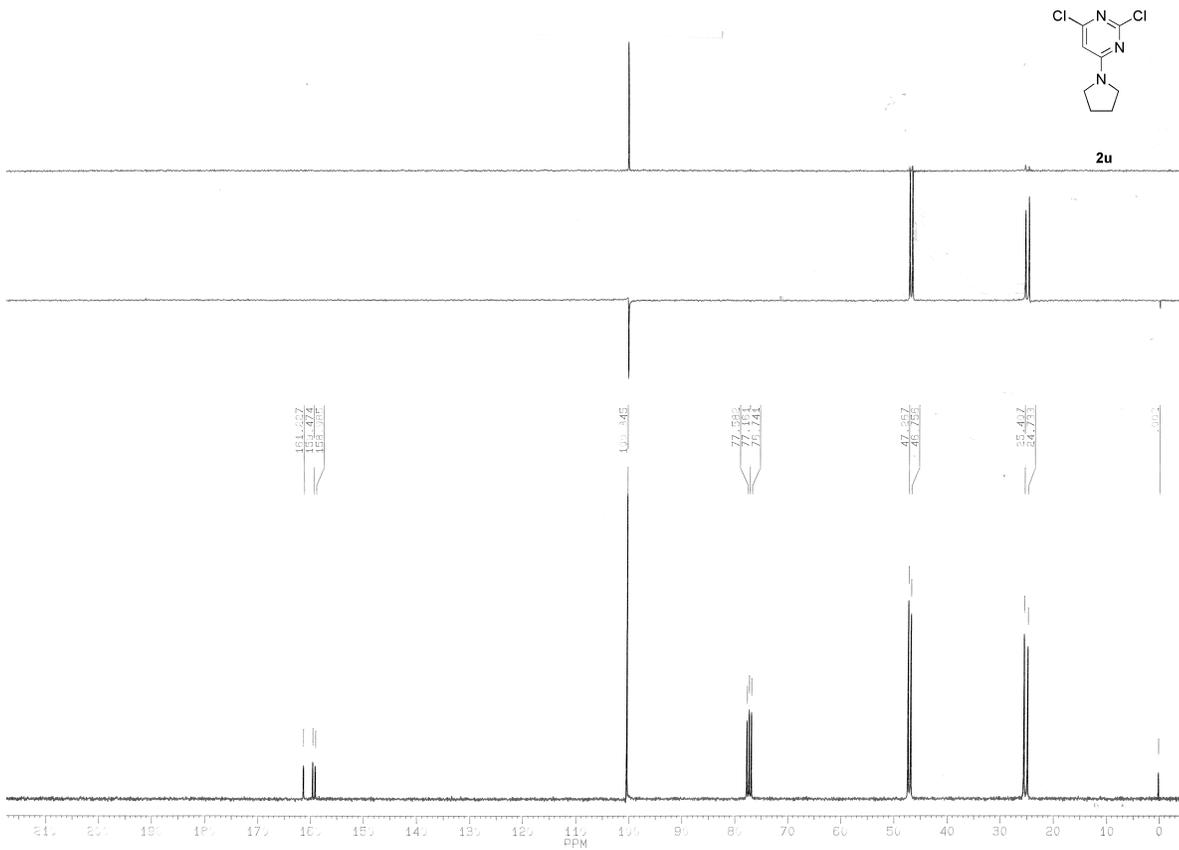
Table S3. ¹³C-NMR spectra for **3u** and **3s** in 0N, 3N, and 6N HCl

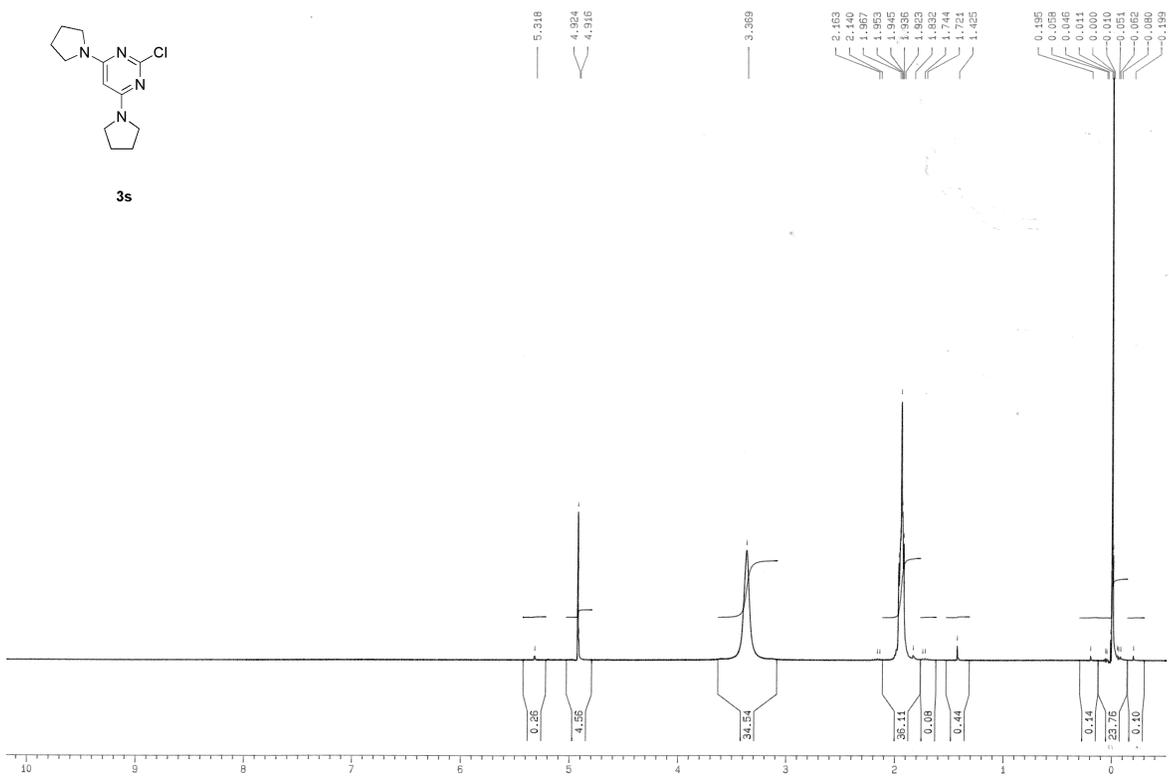
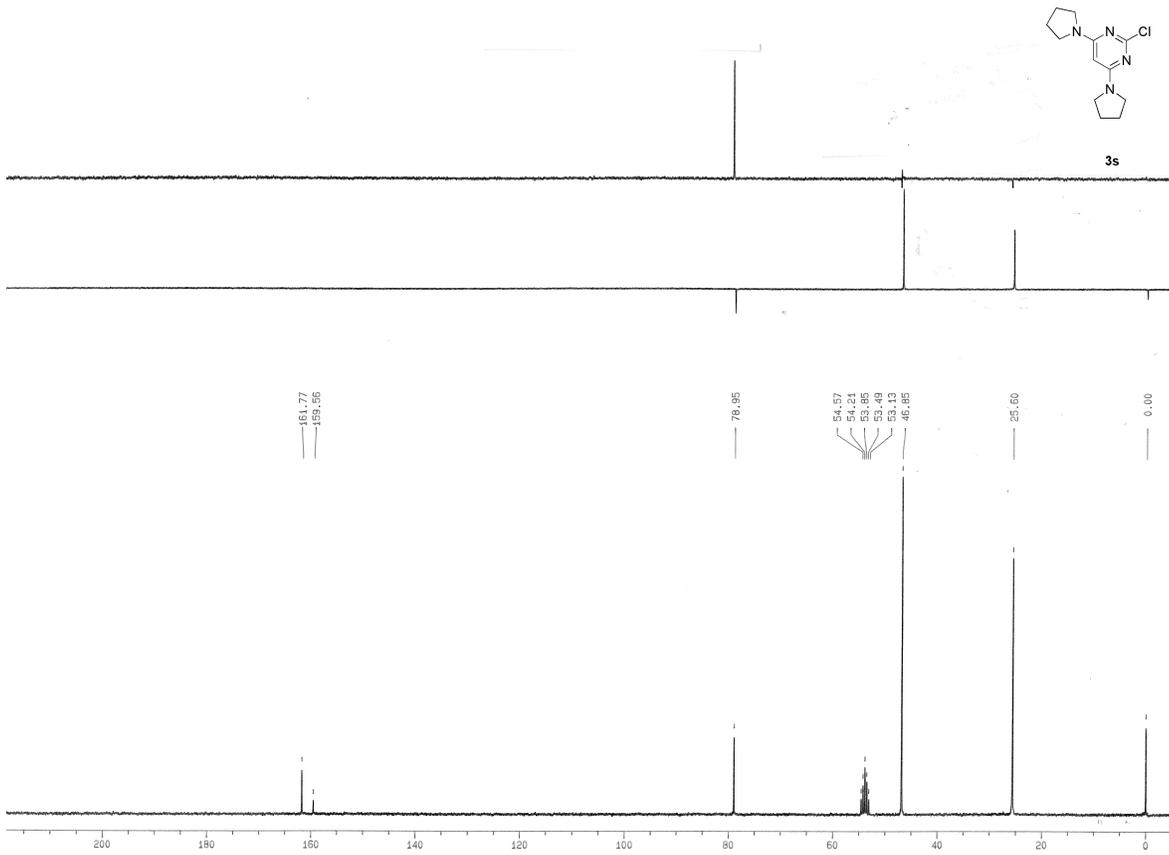
compound	solvent	C2, C4, C6 (ppm δ)	C5 (ppm δ)	pyrrolidine carbons (ppm δ)
 3u	CDCl ₃	158.8 (s); 159.7 (s); 161.3 (s)	90.6 (d)	46.5 (t); 46.2 (t); 25.5 (t)
	1:2:1 (w/w/w)	148.7 (s); 154.2 (s); 160.7 (s)	96.6 (d)	49.3 (br t); 26.7 (br t)
	CD ₃ CO ₂ D:HOAc:			
	H ₂ O			
	1:2:1 (w/w/w)	146.1 (s); 152.0 (s); 159.7 (s)	97.5 (d)	49.6 (br t); 26.8 (br t); 26.0 (br t)
	CD ₃ CO ₂ D:HOAc:			
37% HCl (3.1 N HCl/DCl)				

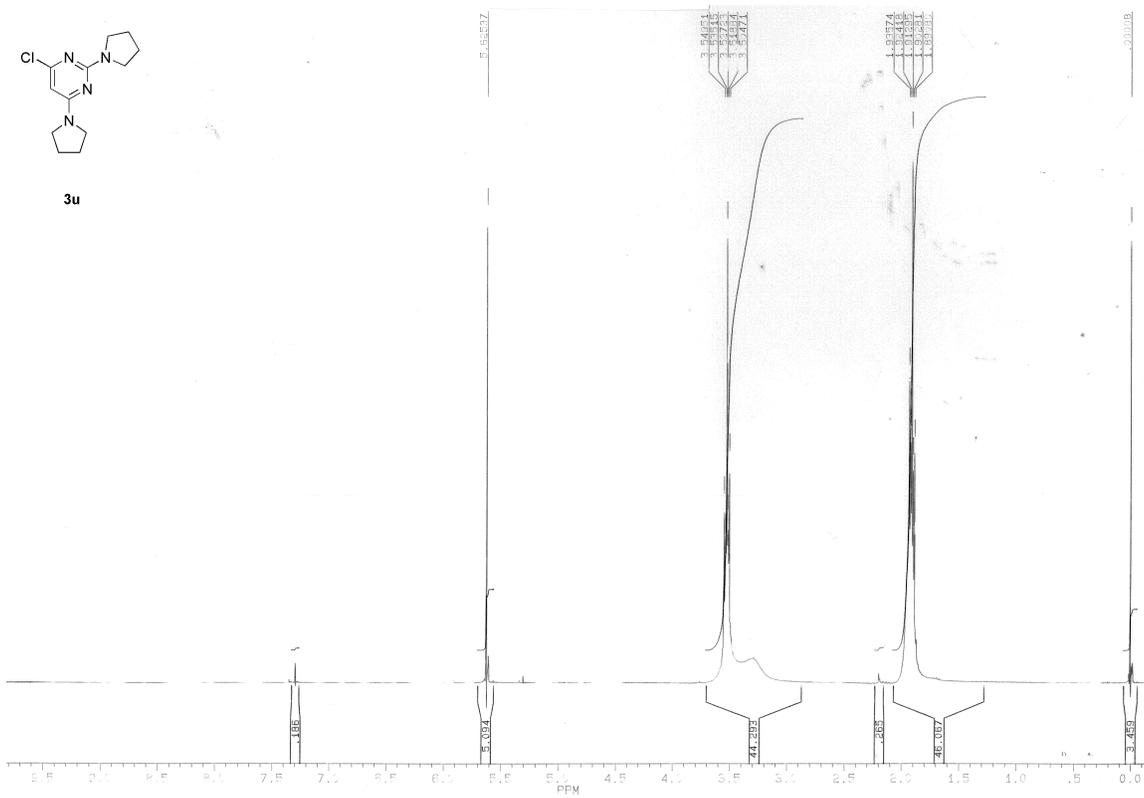
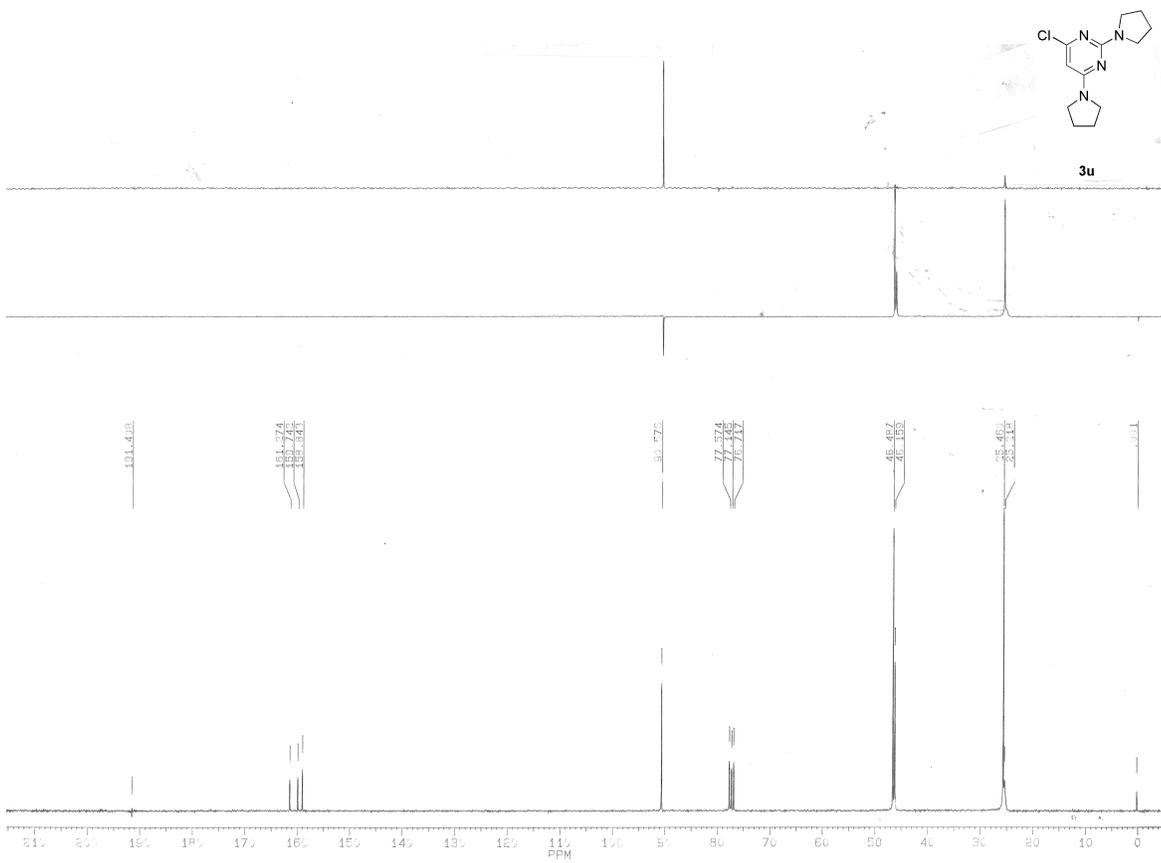
	54:46 (w/w) 37%	143.1 (s); 148.7 (s); 156.1 (s)	94.5 (d)	46.9 (t); 23.6 (br t)
	HCl:D ₂ O (6.4 N HCl/DCl)			
 <p>3s</p>	CD ₂ Cl ₂	159.6 (s); 161.8 (2C, s)	78.9 (d)	46.8 (t); 25.6 (t)
	1:2:1 (w/w/w) CD ₃ CO ₂ D:HOAc:	154.9 (s); 158.6 (2C, s)	78.8 (d)	47.6 (t); 25.2 (t)
	H ₂ O			
	1:2:1 (w/w/w) CD ₃ CO ₂ D:HOAc:	148.2 (s); 154.7 (2C, s)	78.4 (d)	48.7 (t); 25.2 (t)
	37% HCl (3.1 N HCl/DCl)			
	54:46 (w/w) 37%	146.7 (s); 152.7 (2C, s)	76.7 (d)	47.2 (t); 23.6 (t)
	HCl:D ₂ O (6.4 N HCl/DCl)			

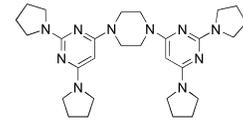
¹³C-NMR and ¹H-NMR Spectra



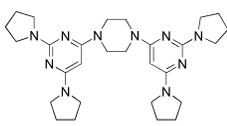
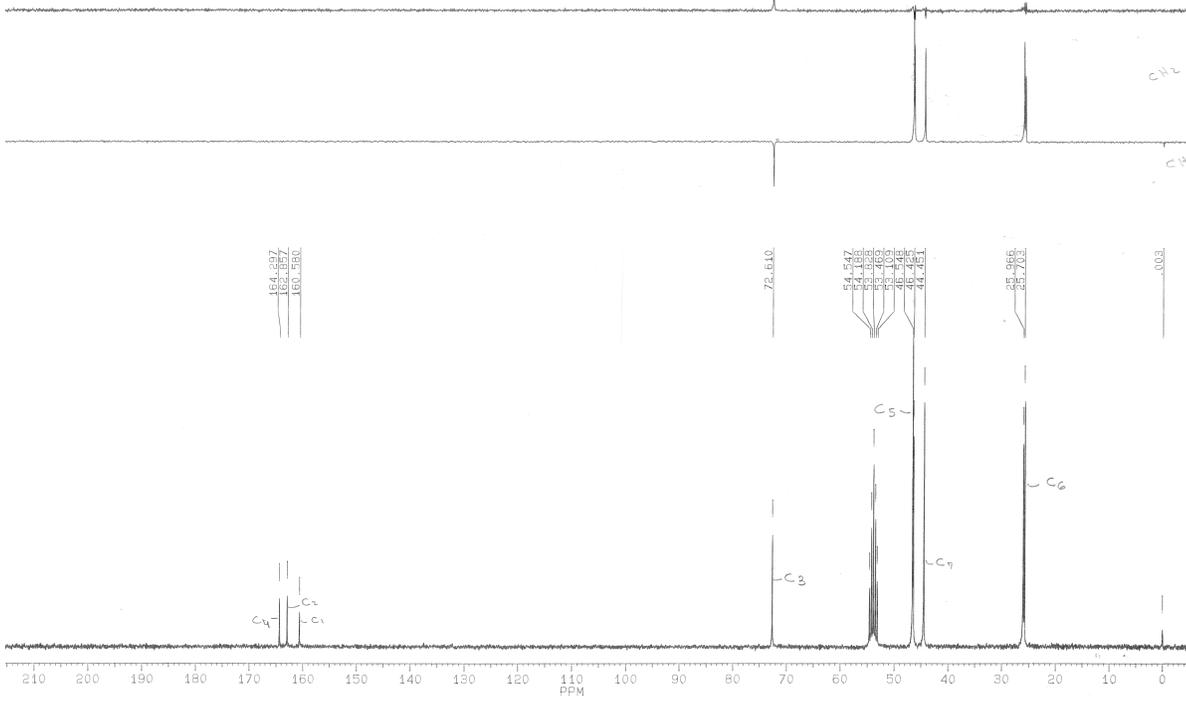




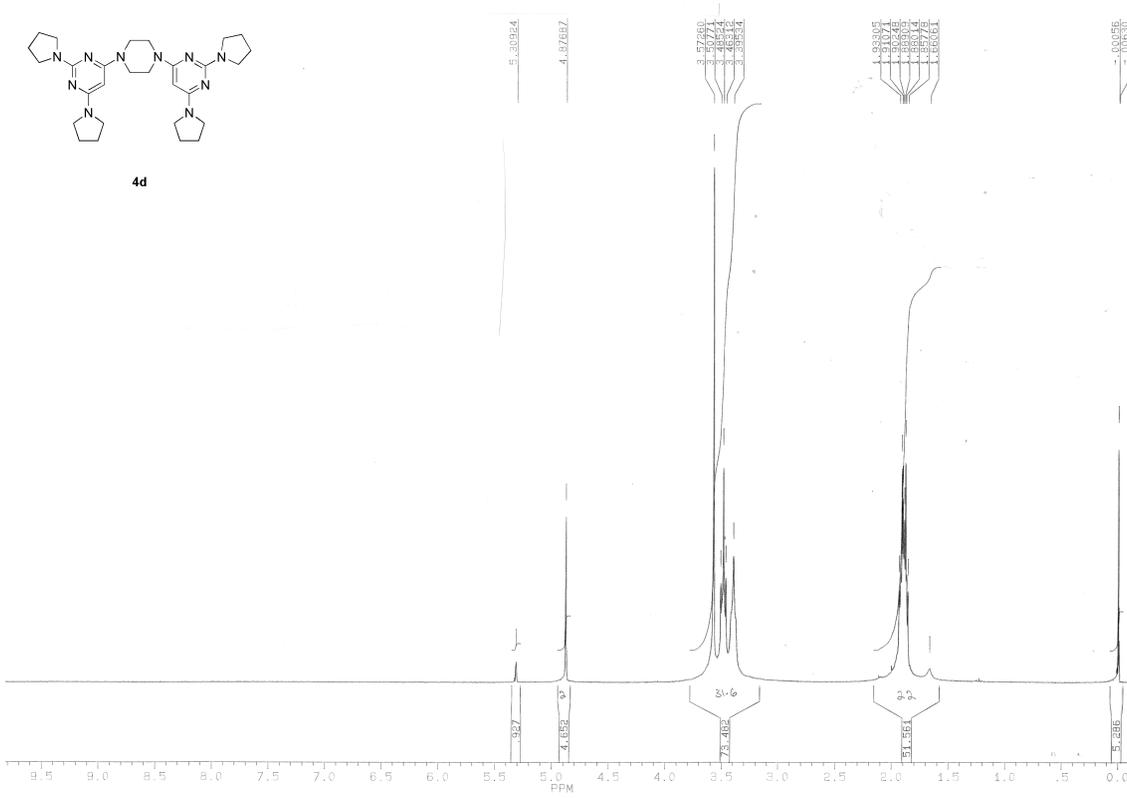


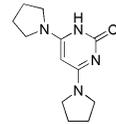


4d

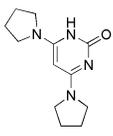
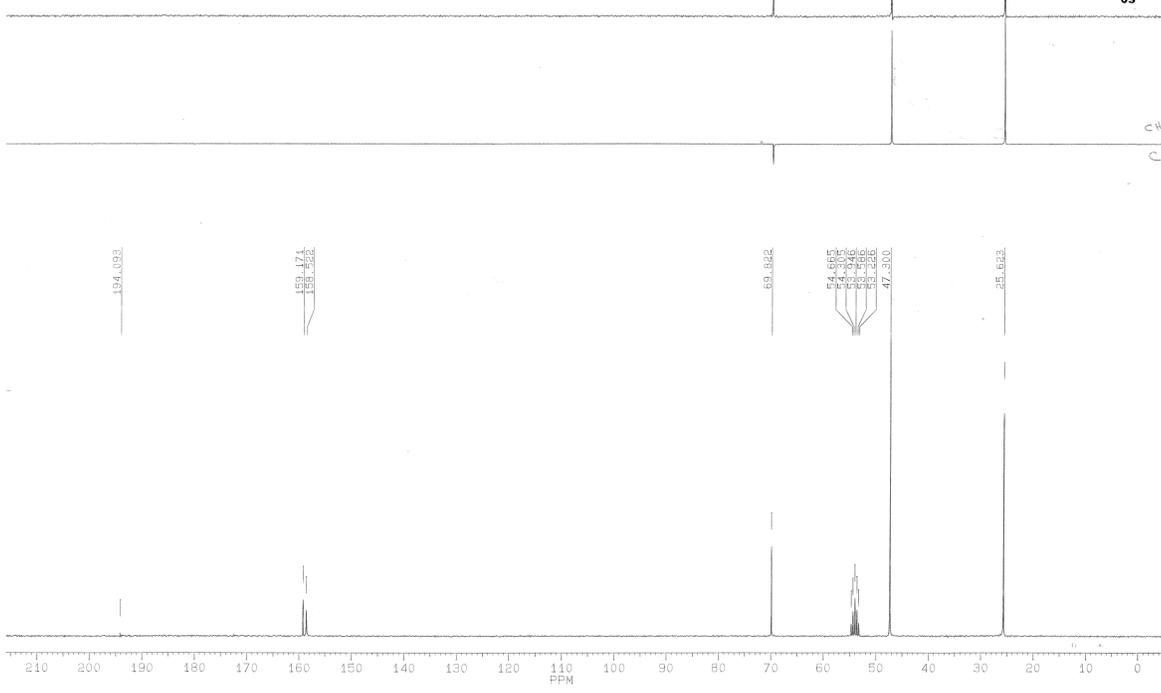


4d

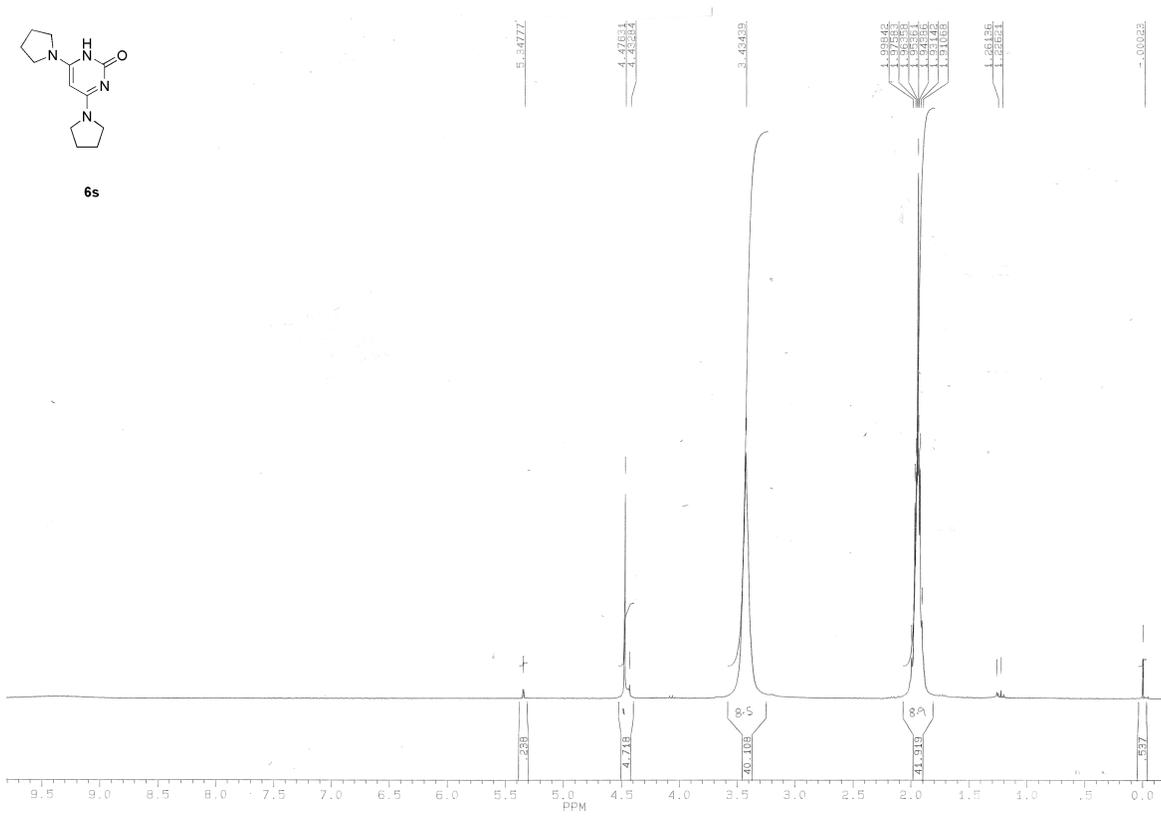


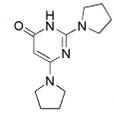


6s

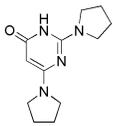
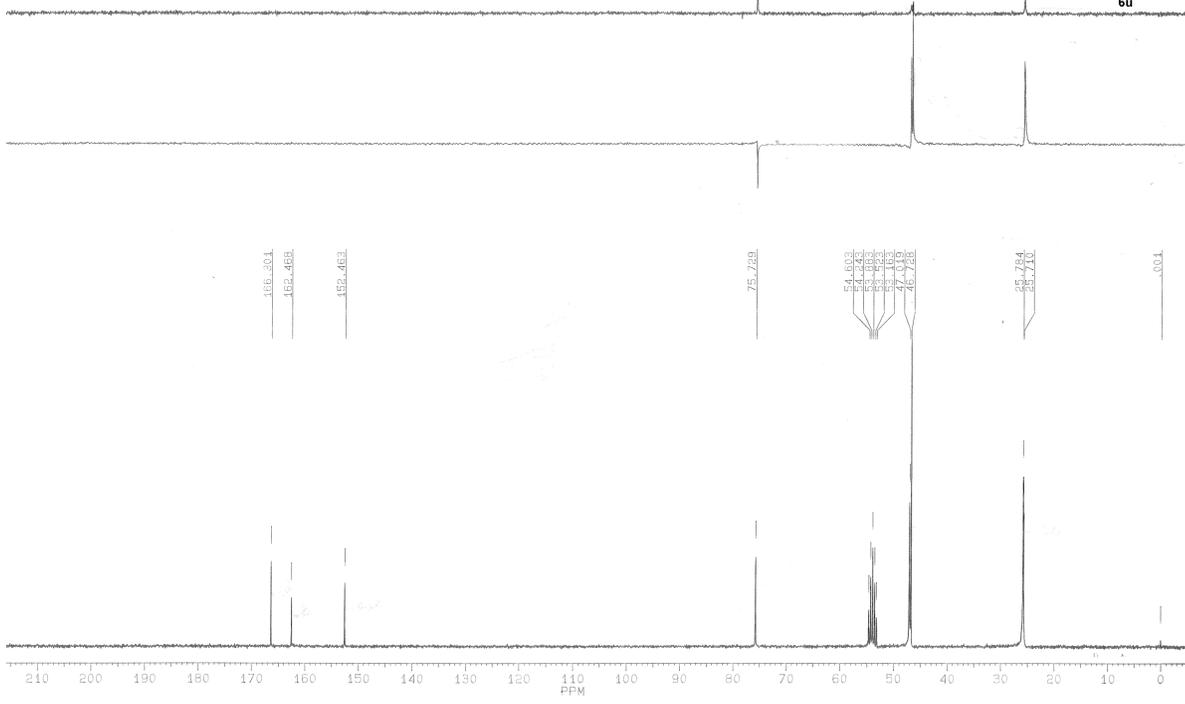


6s

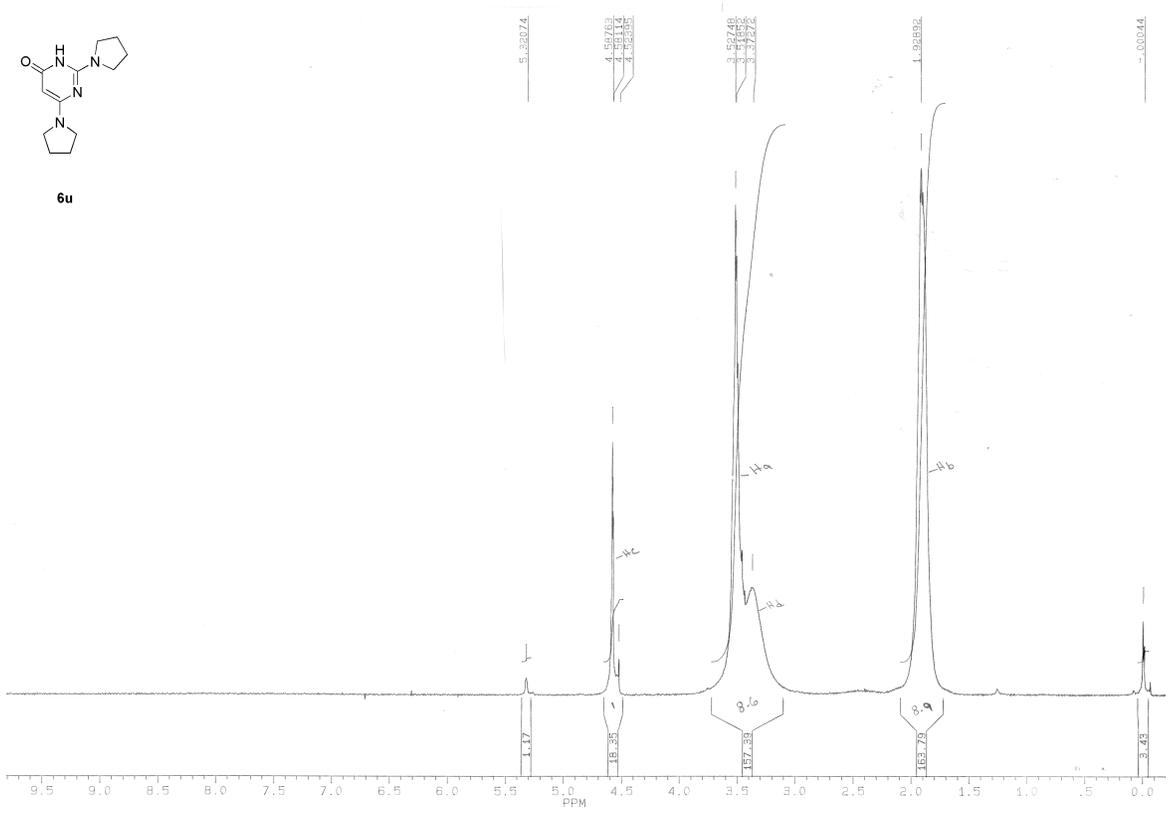




6u



6u



References and Notes

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(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(2) LC assay: column, DuPont Zorbax C8, 25 cm x 4.6 mm; temperature, ambient; flow rate, 2.7 mL/min; detection, 230 nm; mobile phase, 350 mL H₂O/186 mL MeCN/464 mL MeOH. Retention times and response factors (amount/area): 4,6-bis-pyrrolidinyl-2-chloropyrimidine (**3s**), 4.36 min and 6.7272×10^{-8} ; biphenyl, 6.66 min and 2.3298×10^{-7} ; 2,4-bis-pyrrolidinyl-6-chloropyrimidine (**3u**), 10.81 min and 5.4307×10^{-8} .

(3) LC assay: column, DuPont Zorbax C8, 25 cm x 4.6 mm; temperature, ambient; flow rate, 2.9 mL/min; detection, 254 nm; mobile phase, 500 mL methanol/200 mL acetonitrile/300 mL water/0.8 mL triethylamine/0.4 mL acetic acid. Retention times: 2,4,6-trichloropyrimidine, 2.03 min; 2,4-dichloro-6-pyrrolidinylpyrimidine (**2u**), 2.40 min; 2-chloro-4,6-bis-pyrrolidinylpyrimidine (**3s**), 3.18 min.; 4,6-dichloro-2-pyrrolidinylpyrimidine (**2s**), 4.76 min; 6-chloro-2,4-bis-pyrrolidinylpyrimidine (**3u**), 6.52 min; 2,4,6-tripyrrolidinylpyrimidine, 8.94 min.

(4) TLC procedure: plate, silica gel; eluant, 10% ethyl acetate/cyclohexane; visualization, UV (short wavelength); 2,4,6-trichloropyrimidine, $R_f = 0.17$; 2-chloro-4,6-bis-pyrrolidinylpyrimidine (**3s**), $R_f = 0.20$; 2,4-dichloro-6-pyrrolidinylpyrimidine (**2u**), $R_f = 0.28$; 6-chloro-2,4-bis-pyrrolidinylpyrimidine (**3u**), $R_f = 0.44$; 4,6-dichloro-2-pyrrolidinylpyrimidine (**2s**), $R_f = 0.58$; 2,4,6-trichloropyrimidine, $R_f = 0.58$. The reaction mixture is spotted directly. The reaction is judged complete when only **3u/3s** are present.

(5) LC assay: column, DuPont Zorbax C8, 25 cm x 4.6 mm; temperature, ambient; flow rate, 2.9 mL/min; detection, 254 nm; mobile phase, 50%A/20%B/30%C where Reservoir A contains 1L methanol/1 mL triethylamine/0.5 mL acetic acid, Reservoir B contains 1 L acetonitrile, and Reservoir C

contains 1 L water/1 mL triethylamine/0.5 mL acetic acid. Retention times and response factors (amount/area): 4,6-bis-pyrrolidinyl-2-pyrimidone (**6s**), 2.21 min. and 1.3456×10^{-7} ; 4,6-bis-pyrrolidinyl-2-chloropyrimidine (**3s**), 3.36 min. and 2.1855×10^{-8} ; 2,4-bis-pyrrolidinyl-6-pyrimidone (**6u**), 5.57 min. and 5.2339×10^{-8} ; 2,4-bis-pyrrolidinyl-6-chloropyrimidine (**3u**), 7.04 min. and 2.5059×10^{-8} .

(6) based on study of **3u** and **3s** using the Advanced Chemistry Development (ACD) CNMR software package (v. 8.09)