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Highly Selective Hydrolysis of Chloropyrimidines to Pyrimidones in 12 N Hydrochloric Acid

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Abstract:

A chromatography-free process for synthesis of 6-piperazinyl-2,4-bis-pyrrolidinylpyrimidine in isomerically pure form is described. The key step is the purification of a crude 6-chloro-2,4-bis-pyrrolidinylpyrimidine/2-chloro-4,6-bis-pyrrolidinylpyrimidine isomer mixture (generated by reaction of 2,4,6-trichloropyrimidine with pyrrolidine) by a highly selective acid-catalyzed hydrolysis of the 2-chloro isomer to the pyrimidone. The 2-chloro isomer hydrolyzes 350 times faster than the 6-chloro isomer in 6 N HCl and 1750 times faster in 12 N HCl. To put these rate ratios in perspective, the 2-chloro isomer reacts with amines and alkoxides only ~10−17 times faster than does the 6-chloro isomer. A mechanistic investigation using methodological tools developed by Bunnett established that the transition state for hydrolysis of the 6-chloro isomer involves two more molecules of water (each acting as a base) than does the transition state for hydrolysis of the 2-chloro isomer. As the concentration of HCl increases from 3 N to 6 N to 12 N, there are fewer unprotonated water molecules. Thus, the transition state that involves the greater number of unprotonated water molecules (6-chloro-2,4-bis-pyrrolidinylpyrimidine) is expected to be increasingly disfavored with increasing acid concentration, as is observed. The optimized process was run successfully on production scale.

Introduction

2,4,6-Trichloropyrimidine (**1**) is a potentially attractive starting material for synthesis of aminopyrimidines. However, it reacts with alkylamines,[1] arylamines,[2] amide anions,[3] guanidine,[4] and carbamate anions,[5] as well as phenoxide anions,[6] to give mixtures of 2- and 4/6-isomers, resulting in separation problems.

Such a separation problem was encountered in process research directed toward Tirilazad Mesylate (**5**), a drug candidate in development at The Upjohn Company in the early 1990s for treatment of aneurysmal subarachnoid hemorrhage in males. The first step in the first generation process[7] involved the reaction of trichloropyrimidine with pyrrolidine in THF, to generate a 92:8 mixture of 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** and 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s**[8] (Scheme 1). Silica gel chromatography was required to separate the undesired isomer (**3s**).

Sharpless has shown that any impurity that is more reactive than the major component can be removed to any arbitrary level by reacting the mixture to arbitrary conversion but that the impurity must be at least ~20 times more reactive than the major component, or else a significant fraction of the major component will be lost.[9] For example, hypothetically, if a reagent could be found that could react 20 times faster with 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s** than with 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** then, on treatment of the 8:92 mixture with that reagent, 19% yield of **3u** would be lost in driving the level of **3s** down to 0.1%.

Results and Discussion

Nucleophilic Reagents. A **3u**/**3s** isomer mixture was treated with a variety of nitrogen and oxygen nucleophiles, and the relative rates of reaction (k^s/k^u) were measured (Table 1). In all cases the rate ratio was less than 20.

Aqueous Hydrochloric Acid. In contrast with the insufficiently high selectivities obtained with nucleophilic reagents, it was found that, on stirring a **3u**/**3s** mixture in 20° Be (32 wt %; 10.2 M) hydrochloric acid (an inexpensive, commercially available grade), **3s** hydrolyzed 230 times faster than **3u** (Scheme 2)![10] Moreover, the hydrolysis products (pyrimidones **6s** and **6u**) were cleanly separated from **3u** by extraction of the crude hydrolysis mixture in Isopar H[11]/heptane/xylene with pH 2.1 water, as the pyrimidones are stronger bases than the chloropyrimidines. Extraction with pH 3.4 water removed essentially all the 2-pyrim-

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(1) (a) Schneider, R. U.S. Patent 4,025,515, May 24, 1977. (b) Hoegerle, K.; Berrer, D. U.S. Patent 4,082,535, Apr. 4, 1978. (c) Delia, T. J.; Stark, D.; Glenn, S. K. *J. Heterocycl. Chem.* **1995**, *32*, 1177.

(2) (a) Koga, M.; Schneller, S. W. *J. Heterocycl. Chem.* **1992**, *29*, 1741. (b) Schomaker, J. M.; Delia, T. J. *J. Heterocycl. Chem.* **2000**, *37*, 1457.

(3) Delia, T. J.; Meltsner, B. R.; Schomaker, J. M. *J. Heterocycl. Chem.* **1999**, *36*, 1259.

(4) Ladd, D. L. *J. Heterocycl. Chem.* **1982**, *19*, 917.

(5) (a) Zanda, M.; Talaga, P.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 1757. (b) Montebugnoli, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, *58*, 2147. (c) Montebugnoli, D.; Bravo, P.; Brenna, E.; Mioskowski, C.; Panzeri, W.; Viani, F.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2003**, *59*, 7147.

(6) Delia, T. J.; Nagarajan, A. *J. Heterocycl. Chem.* **1998**, *35*, 269.

(7) Jacobsen, E. J.; McCall, J. M.; Ayer, D. E.; Van Doornik, F. J.; Palmer, J. R.; Belonga, K. L.; Braughler, J. M.; Hall, E. D.; Houser, D. J.; Krook, M. A.; Runge, T. A. *J. Med. Chem.* **1990**, *33*, 1145.

(8) The letters **u** and **s** denote the unsymmetrical and symmetrical isomer, respectively.

(9) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(10) A preliminary account of this research has been published: Pearlman, B. *Specialty Chemicals* **1998**, *18*, 94.

(11) Isopar H is a mixture of branched hydrocarbons of approximate boiling point range 177 to 187 °C.

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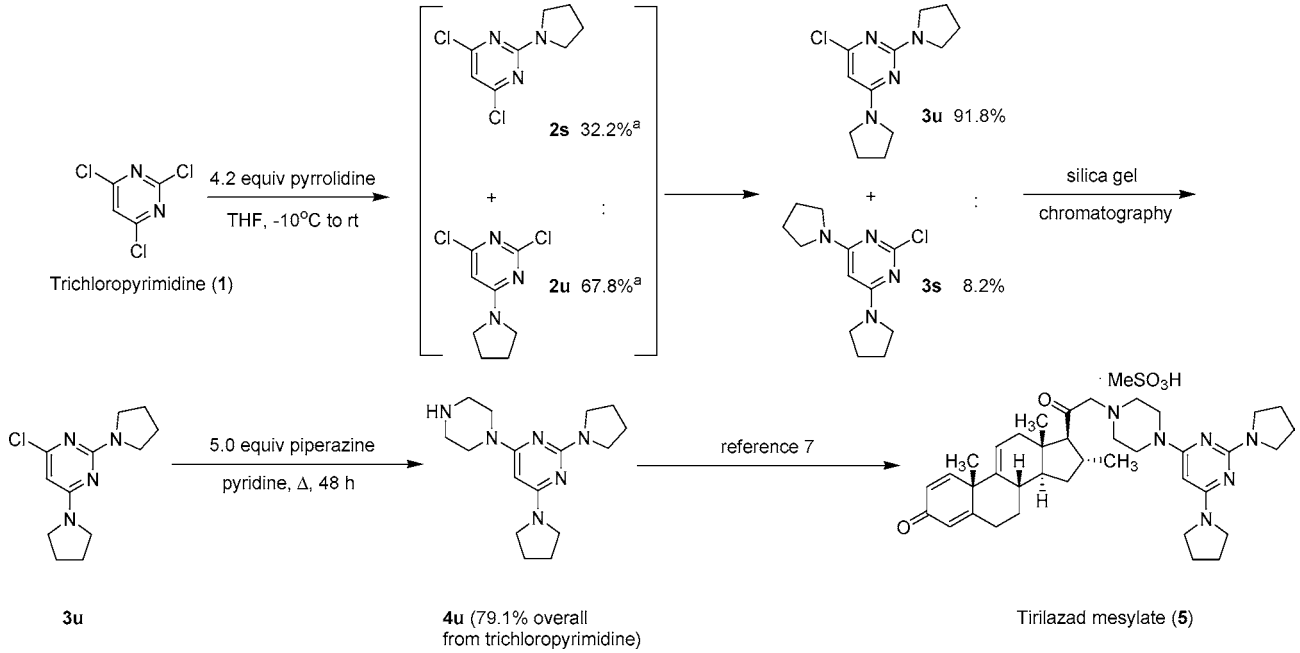
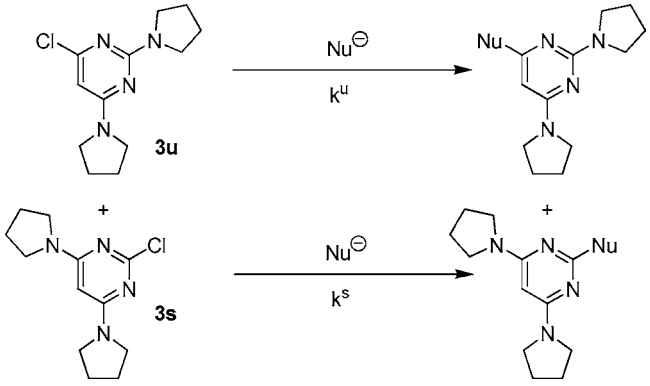
Scheme 1. **First generation process to produce Tirilazad Mesylate**



[a] The two monoadducts **2u** and **2s** are formed in this ratio on treatment of trichloropyrimidine with 1.9 equiv of pyrrolidine (THF, −6 °C). See Supporting Information for details.

Table 1. **Selective destruction of 3s by nucleophilic reagents**



entry	nucleophile	conditions	k^s/k^u
1	piperazine	pyridine, Δ	9.6
2	pyrrolidine	138 °C	17.1
3	benzylamine	190 °C	>14.9
4	$NaOCH_3$	MeOH, Δ	14.0
5	KO*t*Bu	DMSO, 52 °C	13.8

idone **6s** along with only a minor amount of the 6-pyrimidone **6u**, showing that **6s** is slightly more basic than **6u**. The chloropyrimidine **3u** was recovered in isomerically pure form (containing 0.02% **3s**) with a loss of only 2.2% yield of **3u**.

Mechanistic Experiments. Rates of hydrolysis reactions in strong aqueous acid (≥∼3 N) do not, in general, depend linearly on either the proton concentration or the water concentration because, as the proton concentration increases, the protons become increasingly desolvated, thus becoming more "acidic," and the oxygen lone pairs of the water molecules become increasingly hydrogen bonded, thus becoming less "basic." Bunnett has shown that the deviation from linearity gives information about the role of water in the transition state of the rate-determining step.[12] He introduced three variables (ω, ω*, and ϕ) to measure the deviation from linearity, defined by eqs 1−3,

$$\log k + H_o = \omega \log a_{H_2O} + C \quad (1)$$

$$\log k + \log[\mathrm{HCl}] = \omega^* \log a_{H_2O} + C \quad (2)$$

$$\log k + H_o = \phi\,(H_o + \log[\mathrm{HCl}]) + C \quad (3)$$

where H_o is the Hammett acidity function (which measures the effective acidity of the proton as a function of acid concentration) and a_{H_2O} is the activity coefficient of water (which measures the effective basicity/nucleophilicity of water as a function of acid concentration).

To determine the values of the Bunnett coefficients for hydrolysis of the two isomeric chloropyrimidines **3u** and **3s**, the rates of hydrolysis of **3u** and **3s** were measured in 3 N, 6 N, and 12 N hydrochloric acid. Results are tabulated in Table 2.

Values of ω, ω^*, and ϕ were then calculated using eqs 1−3 and the rate data in the first two entries of Table 2. The results are tabulated in Table 3.

Bunnett found that "high" values of ω, ω*, and ϕ (defined as higher than 3.3, −2, and 0.58, respectively) are empirically associated with hydrolysis reactions in which more than one water molecule (one acting as a nucleophile and the rest as bases) are involved in the rate-determining step, that "low" values (i.e., lower than 0, lower than an unspecified value, and lower than 0, respectively) are associated with hydrolysis reactions in which water is not involved in the rate-

(12) (a) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4956. (b) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4968. (c) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4973. (d) Bunnett, J. F. *J. Am. Chem. Soc.* **1961**, *83*, 4978. (e) Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* **1966**, *44*, 1899. (f) Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* **1966**, *44*, 1917.

Scheme 2. **Selective hydrolysis of 3s in 10 N hydrochloric acid**

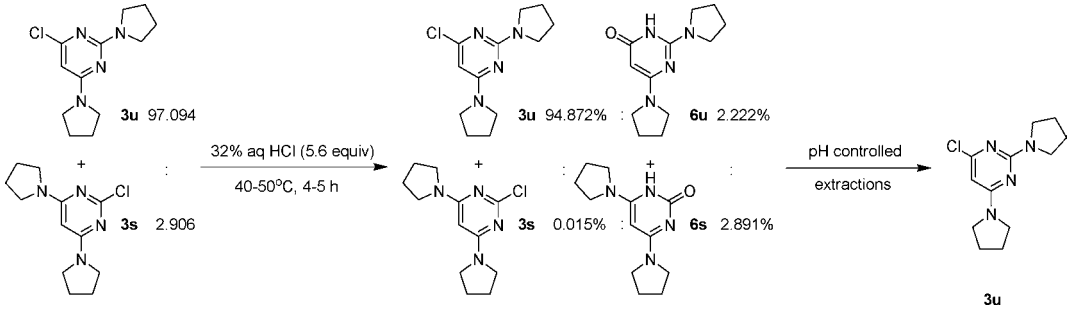
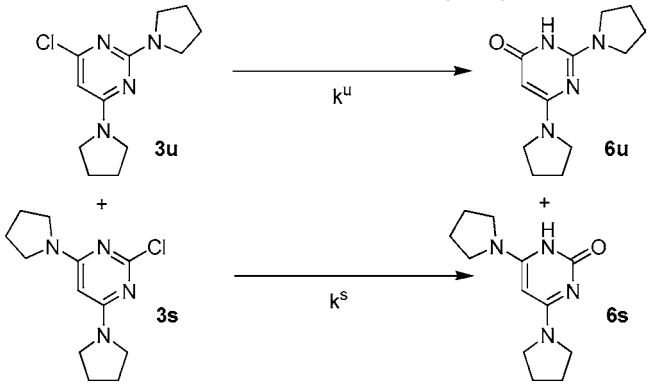


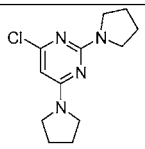
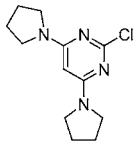
Table 2. **Effect of acid concentration on hydrolysis rate**



entry	[HCl], M (wt %)	k^u, h^{-1}	k^s, h^{-1}	k^s/k^u	H_o[a]	log a_{H_2O}[b]
1	12.22 (37.5)	9.97×10^{-4}	1.74	1750	−4.30	−0.5131
2	6.21 (20.66)	4.72×10^{-4}	0.166	350	−2.19	−0.1752
3	2.96 (10.33)	0.65×10^{-4}	0.0324	500	−1.05	−0.0533

[a] Hammett acidity constant. Values are taken from Table II of ref 13 (H_o' column) rather than from ref 12a because the ref 12a dataset does not include a value for 12.22 M HCl. The values of H_o for 6 N and 3 N HCl given by the two datasets agree very closely. [b] Common logarithm of the activity coefficient of water; values are taken from ref 14.

Table 3. **Values of Bunnett coefficients for hydrolysis of chloropyrimidines**

compound	ω	ω*	ϕ
 **3u**	5.30	-0.09	0.98
 **3s**	3.23	-2.16	0.60
crossover value[a]	3.3	-2	0.58

[a] The values at which the mechanism crosses over from one in which water acts as a nucleophile to one in which it acts as both a base and nucleophile.

determining step, and that values in between are associated with reactions in which one molecule of water is involved as a nucleophile.[12b,f] In the case of the hydrolysis of **3u**, the values of ω, ω*, and ϕ are all "high," indicating that more than one water molecule (one acting as a nucleophile and the rest as bases) are involved in the rate-determining step. In the case of the hydrolysis of **3s**, the values of ω, ω*, and ϕ are on the border between the "high" and "middle" ranges, indicating that the rate-determining step involves one molecule of water acting as a nucleophile and may or may not involve additional molecules of water acting as bases.

Bunnett also pointed out that "an extreme interpretation of ω*-values would be that they represent the number of water molecules of change of hydration between reactants and transition states and that ω represents the same quantity on an adjusted scale."[12c] The values of both ω and ω* for **3u** are about 2 units higher than those for **3s**. Thus, according to this guideline, the transition state for hydrolysis of **3u** involves two more water molecules (each acting as a base) than that for hydrolysis of **3s**.[15]

Activation Parameters. Further insight into the mechanism can be gained by comparing the activation parameters of the two transition states.[16] The difference of the activation free energies for hydrolysis of the two chloropyrimidines ($\Delta G_s^{\ddagger} - \Delta G_u^{\ddagger}$) can be calculated by the Eyring equation (eq 4).

$$\Delta G_s^{\ddagger} - \Delta G_u^{\ddagger} = -RT \ln\left(\frac{k^s}{k^u}\right) \quad (4)$$

$$= -\left(\frac{1.9872 \text{ cal}}{\text{mol K}}\right)(298 \text{ K}) \ln(1750)$$

$$= -4.4 \frac{\text{kcal}}{\text{mol}}$$

The activation entropies and enthalpies were not measured experimentally. However, Bunnett has shown that, on average, the activation entropy ($\Delta S^{\ddagger}$) of a transition state decreases by approximately 4.1 cal/mol K per ω unit.[12c] Thus, a reasonable estimate of the difference of the activation entropies for hydrolysis of the two chloropyrimidines can be calculated from eq 5.

(13) Arnett, E. M.; Mach, G. W. *J. Am. Chem. Soc.* **1966**, *88*, 1177.

(14) values interpolated from table published in: Akerlof, G.; Teare, J. W. *J. Am. Chem. Soc.* **1937**, *59*, 1855.

$$\Delta S_s^{\ddagger} - \Delta S_u^{\ddagger} = \frac{(\omega_s - \omega_u)(-4.1\ \text{cal})}{\text{mol K}} \quad (5)$$

$$= \frac{(3.2 - 5.3)(-4.1\ \text{cal})}{\text{mol K}}$$

$$= \frac{8.6\ \text{cal}}{\text{mol K}}$$

The difference in the activation enthalpies ($\Delta H_s^{\ddagger} - \Delta H_u^{\ddagger}$) can then be calculated from eq 6.

$$\Delta H_s^{\ddagger} - \Delta H_u^{\ddagger} = \Delta G_s^{\ddagger} - \Delta G_u^{\ddagger} + T(\Delta S_s^{\ddagger} - \Delta S_u^{\ddagger}) \quad (6)$$

$$= \left(-4.4\frac{\text{kcal}}{\text{mol}}\right) + (298\ \text{K})\left(\frac{8.6\ \text{cal}}{\text{mol K}}\right)$$

$$= -4.4\frac{\text{kcal}}{\text{mol}} + 2.6\ \frac{\text{kcal}}{\text{mol}}$$

$$= -1.8\frac{\text{kcal}}{\text{mol}}$$

The conclusion that emerges from this analysis is that **3s** hydrolyzes much faster than **3u** because both the activation entropy and activation enthalpy are higher for hydrolysis of **3u** than for hydrolysis of **3s**, by ca. 2.6 and 1.8 kcal/mol, respectively.

Proposed Transition States. To rationalize the conclusion that $\Delta H_u^{\ddagger}$ is greater than $\Delta H_s^{\ddagger}$, we propose that the carbon−oxygen bond in the transition state for hydrolysis of **3u** is stronger (and thus shorter) than that in the transition state for hydrolysis of **3s**, as depicted in Figure 1.

The extremely high selectivity in 12 N HCl can be rationalized in terms of the two proposed transition states. As the concentration of HCl increases from 3 N to 6 N to 12 N, there are fewer "free" (i.e., unprotonated) water molecules. Thus, the transition state that involves the greater number of unprotonated water molecules (**3u**) is expected to be increasingly disfavored with increasing acid concentration, as is observed.

Piperazine Displacement. The crude, isomerically pure chloropyrimidine **3u** was converted into the piperazine derivative **4u** by the procedure outlined in Scheme 3. The yield of **4u** starting from 200 kg trichloropyrimidine was 261 kg (79% yield).[17]

Conclusions

A chromatography-free process for synthesis of isomerically pure 6-piperazinyl-2,4-bis-pyrrolidinylpyrimidine was developed. The key step is the purification of a crude 6-chloro-2,4-bis-pyrrolidinylpyrimidine/2-chloro-4,6-bis-pyrrolidinylpyrimidine (**3u**/**3s**) isomer mixture (generated by treatment of 2,4,6-trichloropyrimidine with pyrrolidine) by a highly selective acid-catalyzed hydrolysis of the 2-chloro isomer to the pyrimidone, which is accomplished simply by stirring the mixture in 12 N HCl at rt. The 2-chloro isomer hydrolyzes completely to the pyrimidone, while the 6-chloro isomer is essentially inert ($k^s/k^u = 1750$). The process was run successfully on production scale.

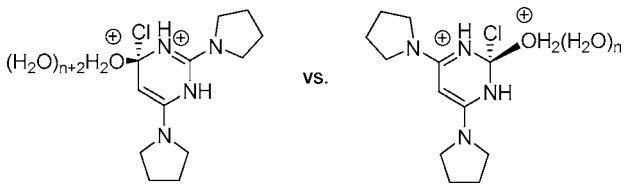


Figure 1. **Proposed transition states for hydrolysis of 3u and 3s, respectively.**

Experimental Section

Generation of Chloro-bis-(pyrrolidinyl)pyrimidine Isomer Mixture (3u/3s). To a 1 L flask was added in sequence sodium carbonate (mw 105.99; 58 g, 0.547 mol, 2.01 equiv), 500 mL heptane, and 2,4,6-trichloropyrimidine (mw 183.42; 50.0 g, 0.273 mol). The slurry was agitated, and 80 mL of water were added. To the mixture was added pyrrolidine (mw 71.12; d 0.852; 55.0 mL, 46.9 g, 0.659 mol, 2.42 equiv) at a rate such that the pot temperature remained below 80 °C. Once the addition was complete, the pot temperature was adjusted to 80 ± 1 °C and the mixture was stirred until the reaction was complete by TLC[18] (12 h). The mixture was quenched with 240 mL of water, the pot temperature was adjusted to ≥70 °C, the phases separated, and the aqueous phase was extracted with 50 mL of 70 °C heptane. The heptane extracts were combined and taken on to the next step. The ratio of **3u** to **3s** was 97.09:2.91 by LC.[19]

Selective Hydrolysis of 3s. The combined heptane extracts from the previous step were cooled to 22 °C. 20° Be Hydrochloric acid (mw 36.46; 32 wt %; 10.2 M; d 1.1593; 150 mL, 55.65 g, 1.526 mol, 5.60 equiv) was added, resulting in a 10−12 °C exotherm. The mixture initially formed two cloudy liquid layers. On stirring, the upper layer became clear and colorless, and the lower layer became hazy yellow-orange. The **3u**/**3s** was exclusively in the lower aqueous layer. The mixture was stirred at 40−50 °C until the level of **3s** was ≤0.07 mol % (4−5 h) by LC.[20] The normalized

(15) Since **3s** is more polar on silica gel TLC than **3u**, the possibility was considered that **3s** may hydrolyze more rapidly than **3u** because a higher percentage of **3s** than **3u** may be protonated. This possibility was investigated by a study of the effect of solvent (75% CD_3CO_2D, 3 N HCl, and 6 N HCl) on the ^{13}C NMR chemical shift of C2/C4/C6 of the two isomers, based on the assumption that the change in chemical shift should be greater for the more basic isomer, because a greater fraction of molecules would be protonated. The signals for C2/C4/C6 of both isomers shifted upfield progressively from 75% CD_3CO_2D to 3 N HCl to 6 N HCl by approximately the same amount, indicating that roughly similar fractions of **3s** and **3u** are protonated at each acid concentration, thus contradicting the premise that a higher percentage of **3s** than **3u** is protonated. See Supporting Information for details.

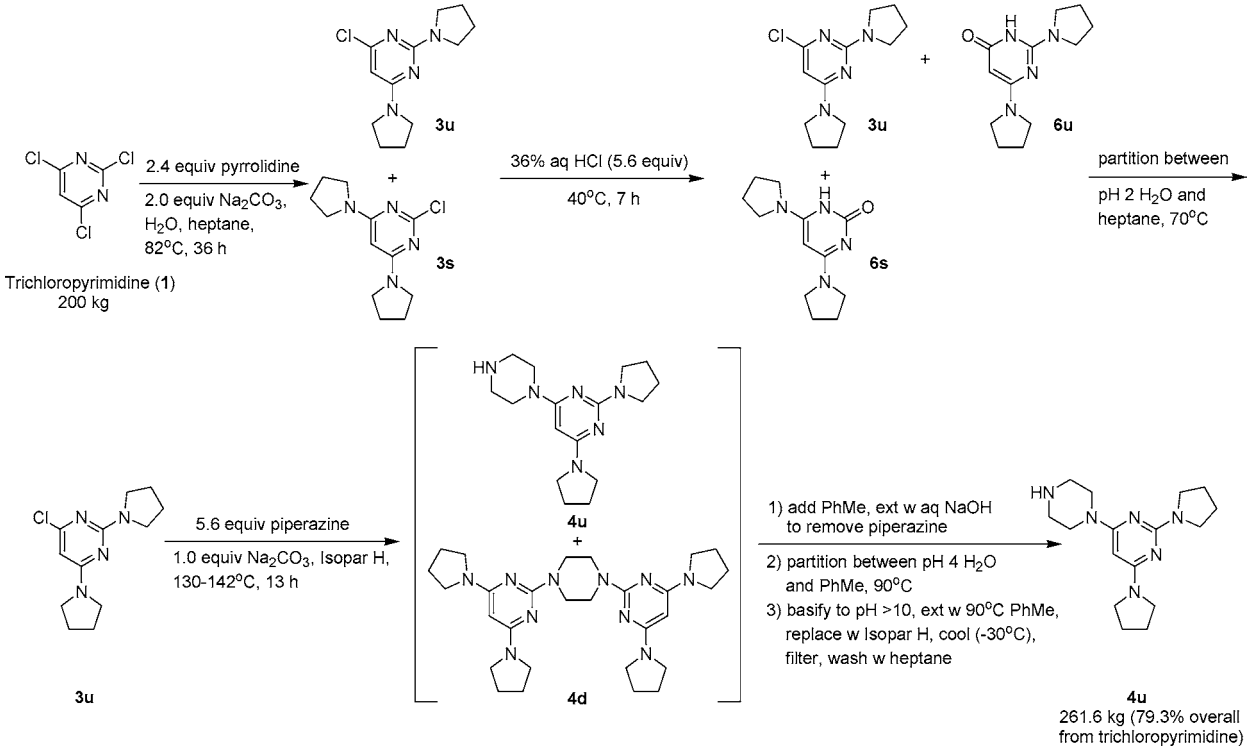
(16) We thank a referee for the suggestion that the high selectivity could be due to a difference in activation entropy, which would be expected to be greater for the transition state requiring the ordering of two extra molecules of water (**3u**).

(17) This process has been patented: Pearlman, B. A.; Padilla, A. G. U.S. Patent 5,225,555, July 6, 1994.

(18) 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.

(19) LC assay: column, DuPont Zorbax C8, 25 cm × 4.6 mm; temperature, ambient; flow rate, 2.9 mL/min; detection, 254 nm; mobile phase, 500 mL of methanol/200 mL of acetonitrile/300 mL of water/0.8 mL of triethylamine/0.4 mL of 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.

Scheme 3. **Optimized process incorporating highly selective acid-catalyzed chloropyrimidine hydrolysis (production run)**



ratio of **3u**:**3s**:**6u**:**6s** was 94.872:0.015:2.222:2.891, from which it was calculated that $k^s/k^u = 227.5$. The mixture was cooled to 14 °C, and 75 mL of 50% aq. sodium hydroxide were added at a rate such that the pot temperature remained ≤50 °C. The slurry was heated to ≥70 °C, and 75 mL of water were added. The pH was adjusted to 1.8 to 2.0 by addition of 3 mL of 50% sodium hydroxide. The pot temperature was kept at ≥65 °C during all the extractions. The homogeneous layers were separated, and the organic layer was extracted sequentially with the following: (1) a solution composed of 50 mL of water and 4 mL of 50% sodium hydroxide; (2) 50 mL of water. Each of the aqueous layers was held separately and back-extracted in sequence with the same 50 mL portion of heptane. The pH 2 extraction removes 95% of the pyrimidones. The pH >10 extraction removes residual pyrimidones missed in the pH 2 extraction. The aqueous layers were discarded. The organic layers were combined and taken on to the next step.

Generation and Isolation of 6-Piperazinyl-2,4-bis-pyrrolidinylpyrimidine (4u). The combined organic layers from the previous step (containing theoretically 0.259 mol of **3u**) were concentrated under a vacuum to a low volume. The vacuum was released, and 90 mL of Isopar H were added. The concentration was continued at a pot temperature of 100 °C at 176 mm vacuum. After releasing the vacuum, anh. sodium carbonate (mw 105.99; 28.8 g, 0.272 mol, 1.05 equiv), anh. piperazine (mw 86.14; 132.0 g, 1.532 mol, 5.93 equiv), and 30 mL of octane (to wash down piperazine that sublimed in condenser) were added. The slurry was heated at 133−135 °C for 21 h, at which time the reaction was judged complete by TLC (eluant: 35% ethyl acetate/cyclohexane; R_f [**4u**] = 0.00; R_f [**4d**] = 0.45; R_f [**3u**] = 0.68) and LC.[21] The normalized ratio of **3u**:**4u**:**4d** by LC was 0.002:97.1:2.897, from which it was calculated that k^{4u}/k^{4d} (the rate constant for formation of **4u** divided by the rate constant for formation of **4d**) = 1.56. The slurry was cooled to 100 °C, and 100 mL of toluene, 250 mL of water, and 15 mL of 50% sodium hydroxide were added. The sodium hydroxide is added to convert sodium bicarbonate to sodium carbonate. Sodium carbonate is more soluble than sodium bicarbonate, thus helping to minimize the volume. The higher basicity of sodium carbonate is also advantageous in extracting trace amounts of pyrimidones. The pot temperature was kept at ≥85 °C during the extractions. The homogeneous phases were separated: organic layer 1A, aqueous layer 1B. The aqueous layer (1B) was extracted with 70 mL of toluene/50 mL of water: organic layer 1C, aqueous layer discarded. To the organic layer 1A was added 250 mL of water and concd hydrochloric acid (mw 36.46; 37.6 wt %; d 1.1885; 47 mL, 21.00 g, 0.576 mol, 2.23 equiv). The pot temperature was adjusted to ≥85 °C, and the pH was adjusted to 3.8−4.0 with concd hydrochloric acid. Toluene (150 mL) was

(20) LC assay: column, DuPont Zorbax C8, 25 cm × 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 1 L of methanol/1 mL of triethylamine/0.5 mL of acetic acid, Reservoir B contains 1 L of acetonitrile, and Reservoir C contains 1 L of water/1 mL of triethylamine/0.5 mL of 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}; 6-chloro-2,4-bis-pyrrolidinylpyrimidine (**3u**), 7.04 min and 2.5059×10^{-8}.

(21) LC assay: column, DuPont Zorbax C8, 25 cm × 4.6 mm; temperature, ambient; flow rate, 4 mL/min; detection, 230 nm; mobile phase, 400 mL of acetonitrile/400 mL of methanol/200 mL of water/1 mL of triethylamine/0.05 mL acetic acid. Retention times and response factors (amount/area): 6-chloro-2,4-bis-pyrrolidinylpyrimidine (**3u**), 2.11 min and 1.8849×10^{-9}; 6-piperazinyl-2,4-bis-pyrrolidinylpyrimidine (**4u**), 6.7 min and 1.3757×10^{-9}; 2:1 adduct (**4d**), 10.8 min and 7.9302×10^{-10}.

added to the thin slurry until all the 2:1 adduct **4d** dissolved. The phases were separated: organic layer 1D, aqueous layer 1E. 1C and 1E were combined, and the pH was adjusted to 3.8−4.0 by the addition of concd hydrochloric acid. The phases were not separated: 1F. To 1D was added 50 mL of water, and the pH was adjusted to 3.8−4.0. The organic layer was discarded, and the aqueous layer was combined with 1F. The phases were separated: organic layer 1G, aqueous layer 1H. 1G was combined with 50 mL of water, and the pH was adjusted to 3.8−4.0 with hydrochloric acid. The organic layer was discarded, and the aqueous layer was combined with 1H: 1I. The combined aqueous layers (1I) were cooled to ∼50 °C, and 50% sodium hydroxide (mw 40.00; d 1.53; 30 mL, 22.95 g, 0.574 mol, 2.22 equiv) was added. The pH of the resulting thick slurry was >10. To the slurry was added 200 mL of toluene and 100 mL of Isopar H. The pot temperature was kept at ≥80 °C during the extractions. The phases were separated, and the organic layer was extracted with water (4 × 100 mL). Each aqueous layer was extracted in sequence with 75 mL of toluene/25 mL of Isopar H. The aqueous layers were discarded, and the organic layers were combined and concentrated under a vacuum. Isopar H (315 mL total) was added intermittently as needed to keep a stirrable slurry. The distillation was continued to a pot temperature of 100 °C at 176 mm of vacuum. The pot volume was ∼425 mL. The slurry was cooled to −15 °C, and the solids were collected. The cake was washed with 300 mL of −15 °C heptane. The cake was dried in an 80 °C vacuum oven to give a bone white solid identified as 6-piperazinyl-2,4-bis-pyrrolidinylpyrimidine (**4u**) in pure form (100.93 wt % relative to a reference standard), containing no impurity above 0.1%, by LC comparison with an authentic standard. Weight: 70.04 g (mw 302.43; 0.232 mol, 85.0% yield overall from 2,4,6-trichloropyrimidine). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 164.4 (s); 162.9 (s); 160.5 (s); 72.6 (d); 51.7 (t); 45.9 (t); 46.5 (2C, t); 46.4 (2C, t); 45.4 (t); 44.8 (t); 25.9 (2C, t); 25.7 (2C, t). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.85−1.95 (8H, mults); 2.84 (4H, t, J = 5.1 Hz); 3.36−3.49 (12H, mults); 4.83 (1H, s). MS (CI, CH_4): *m*/*e* 303 (P^+ + H, 100%).

Synthesis of Reference Standards of 3u and 3s. A solution of 2,4,6-trichloropyrimidine (mw 183.42; 10.0 g, 0.0545 mol) in 50 mL of methanol was cooled to −17 °C and treated dropwise with a solution of pyrrolidine (mw 71.12; d 0.852; 20.0 mL, 17.0 g, 0.240 mol, 4.39 equiv) in 65 mL of methanol at a rate such that the pot temperature remained ≤−8 °C (7 min). The mixture was stirred at rt for 20.5 h. The mixture was found to contain **2u**, **3s**, **2s**, and **3u** in a 1.95:6.06:1.54:90.45 mole ratio by LC analysis.[19] The mixture was quenched with 200 mL of water, diluted with 20 mL of brine, and extracted with ethyl acetate (3 × 100 mL). The organic extracts were back-extracted with the same 100 mL portion of water and then combined and concentrated to an oil which crystallized on seeding to solids consisting of a mixture of three components (R_f = 0.20, 0.28, and 0.44) by TLC.[18] Weight: 13.8 g. A portion of the solids (12.5 g, from 0.0494 mol trichloropyrimidine) was flash chromatographed on 560 g silica gel (gradient elution, 2% → 30% ethyl acetate/cyclohexane). The fractions containing the R_f = 0.44 component were combined, concentrated, diluted with heptane, and filtered to give a solid (mp 79−82 °C) identified as 6-chloro-2,4-bis-pyrrolidinylpyrimidine **3u** by its spectral characteristics. By LC, the material was homogeneous except for 0.10 M% **3s** and 0.52 M% **2s**. Weight: 11.51 g (mw 252.75; 0.0455 mol, 92.2% yield). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3 (s); 159.7 (s); 158.8 (s); 90.6 (d); 46.5 (3C, t); 46.2 (t); 25.5 (4C, t). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89−1.94 (8H, mults); 3.50−3.55 (8H, mults); 5.63 (1H, s). MS (CI, CH_4): *m*/*e* 253/255 (P^+ + H, 100%). Anal. Calcd for $C_{12}H_{17}N_4{}^{35}Cl$: *m*/*e* 252.1142. Found: *m*/*e* 252.1154.

The fractions containing the R_f = 0.20 component were combined and concentrated to a solid (mp 94−96 °C) identified as 2-chloro-4,6-bis-pyrrolidinylpyrimidine **3s** by its spectral characteristics. By LC, the material was 99.92 M% pure. Weight: 0.616 g (mw 252.75; 0.00244 mol, 4.9% yield). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 161.8 (s); 159.6 (s); 78.9 (d); 46.8 (t); 25.6 (t). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.94 (8H, narrow mult); 3.37 (8H, br s); 4.92 (1H, s). Anal. Calcd for $C_{12}H_{17}N_4{}^{35}Cl$: *m*/*e* 252.1142. Found: *m*/*e* 252.1152.

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Supporting Information Available

Experimental procedures; spectroscopic characterization data; ^{13}C and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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