Reaction of 3-aminopyrrole with chloropyrimidines to give pyrroloaminopyrimidines

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Abstract

Reaction of 3-aminopyrrole with chloropyrimidines occured only at the 3-amino group. The activating group(s) (Cl, NO_2 or CF_3), their relative positions (C4/C6, C2, or C5), and the effect of added base (DIPEA) or acetic acid on the course of the reaction, was studied. When chloro groups were present on both C4/C6 and C2, the only or major product was from the displacement of the C4/C6 chloro group. Only in the reaction of 2,4,6-trichloropyrimidine was substitution at C2 competitive with reaction at C6. Both chloro groups of 2,4-dichloro-3-nitropyrimidine were displaced to give a novel compound with three-linked heterocyclic rings. Reactions of less reactive chloropyrimidines appeared to be favored by acid catalysis.

Keywords: Aminopyrroles, chloropyrimidines, pyrrolylaminopyrimidines, S_NAr, acid catalysis

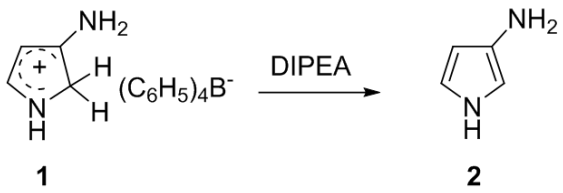
Introduction

Pyrimidines play an important role in the drug discovery process.[1] This is likely a reflection of the similarity between the pyrimidine ring and the bases found in nucleosides and nucleotides.[2] It has been noted that the reaction of halogenopyrimidines with amines is the most used and important reaction in pyrimidine chemistry.[3] Much of recent aminolysis work has been driven by the search for biologically active aminopyrimidine derivatives given that aminopyrimidines derivatives are part of marketed drugs[4,5] and figure in recent[6-8] studies of possible biological activity. Bioactivity has also been associated with 3-aminopyrrole derivatives.[9] We have reported that the reaction of 1-substituted-2-aminopyrroles with 2,4,5,6-tetrachlorpyrimidine gave pyrrolopyrimidine derivatives via S_NAr reactions at either C3,C5 or the amino group depending on the size of the 1-substituent.[10] Recently 3-aminopyrrole has become available as its tetraphenylborate salt.[11] The reaction of 3-aminopyrrole with commercially available chloropyrimidines has been studied and here, in the absence of steric effects, only pyrroloaminopyrimidines have been obtained—compounds with two linked heterocyclic rings

both known to possess bioactivity. In one case, three linked rings were obtained from the reaction of two chloro groups.

Results and Discussion

Reactions of 3-aminopyrrole (**2**) with eight commercially available chloropyrimidines were studied. The 3-aminopyrrole (**2**) was formed in situ form its tetraphenylborate salt **1** and DIPEA.

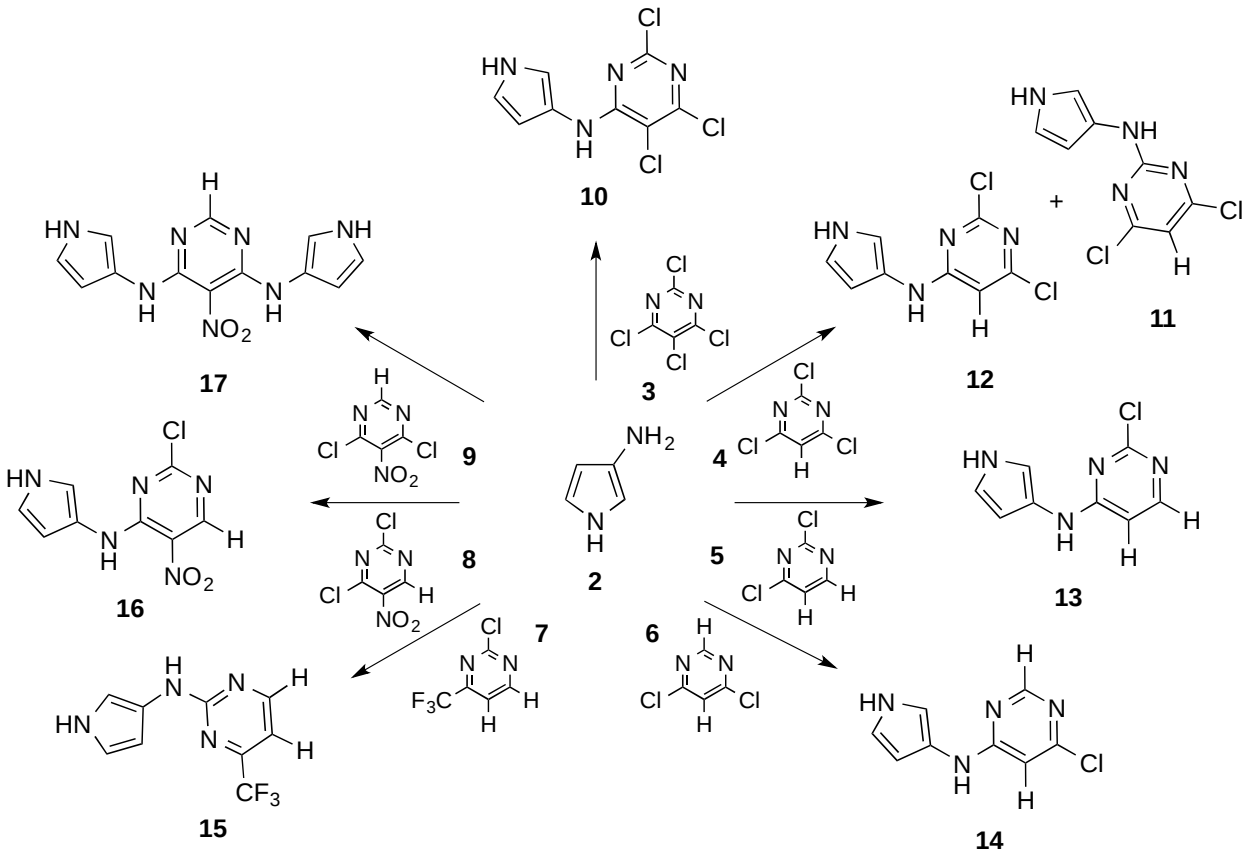


Scheme 1. In situ generation of 3-aminopyrrole.

Studies were carried out under acidic conditions with added acetic acid (method II) and basic conditions with added DIPEA (method I), in order to determine what role, if any, acid catalysis played. Results are summarized in Scheme 2 and Table 1. Yields were determined by the isolation of the product(s), and by quantitative NMR analysis of the reaction mixtures. The large variation in yields, observed in certain reactions by the two analytical methods, reflected the instability of some of the pyrroloaminopyrimidine products obtained. Stability of the pyrroloaminopyrimidines **10**-**17** appeared to depend on how electron-withdrawing the pyrimidines attached to amino group were.[12] Structures were supported by H^1 and C^{13} NMR and HRMS. No evidence for tautomerism of pyrroloaminopyrimidines **10**-**17** was detected.[13,14] Reaction was observed with all of the chloropyrimidines, although the results with 2-chloropyrimidine were problematic and not reported in Table 1 and Scheme 2. Previous work indicated that 2-chloropyrimidine was not very reactive.[15] In this study unstable products were obtained with 2-chloropyrimidine. Decomposition was also observed when this reaction was carried out in an NMR tube. These results would seem to indicate that it was likely the parent pyrrolaminopyrimidine was formed, but it was unstable.

Autocatalysis by acid, of the aminolysis of chloropyrimidines, is well known. [8,16] Acid catalysis, as measured (Table 1) by a significant change in yield (taken in this study as >10% increase in yield), was observed with some, but not all of the chloropyrimidines (discussed below). With the exception of 2,4,6-trichloropyrimidine (**4**), only one substitution product was obtained in each case. Here substitution occurred at both C4/C6 (major product **12**) and C2 (minor product **11**). The structure of **11** was confirmed by single crystal X-ray crystallography.

Both chloro groups of 2,4-dichloro-3-nitropyrimidine (**9**) were displaced to give **17**, a novel compound with three-linked heterocyclic rings.



Scheme 2. Reactions of chloropyrimidines with 3-aminopyrrole.

Results summarized in Scheme 2 and Table 1 allowed us to examine the effect of the number (0-3) of electron-withdrawing activating groups on the reaction of chloropyrimidines towards S_NAr with 3-aminopyrrole (**2**), the nature of the activating group(s) (Cl, NO_2 or CF_3), their relative positions (C4/C6, C2, or C5), and the effect of added base (DIPEA) or acetic acid on the course of the reaction. No steric effect was observed in the reactions with 3-aminopyrrole, and the only products observed were reactions of the 3-amino group. In contrast the reaction of 2,4,5,6-tetrachloropyrimidine (**3**) with 1-alkyl-2-aminopyrroles, was found to depend on the 1-alkyl substituent: with the 1-methyl derivative reactions occurred at the 2-amino and C5 positions; whereas, with the 1-tert-butyl derivative, only reaction at C3 was observed.[10] As noted above, 2-chloropyrmidine reacted with 3-aminopyrrole (**2**) to give unstable products. Reactions of 2-chloropyrimidine with aliphatic amines and anilines have been reported.[15] This suggested that 3-aminopyrrole was at least as nucleophilic as aniline. Only the reaction with 2,4-dichloro-3-nitropyrimidine (**9**) gave the disubstituted product **17**. In comparison polychlorinated pyrimidines have been reported to react with 1-3 equivalents of aliphatic amines.[3]

Table 1. Reaction of 3-aminopyrrole salt (**1**) with pyrimidines (**3-9**) under optimized conditions

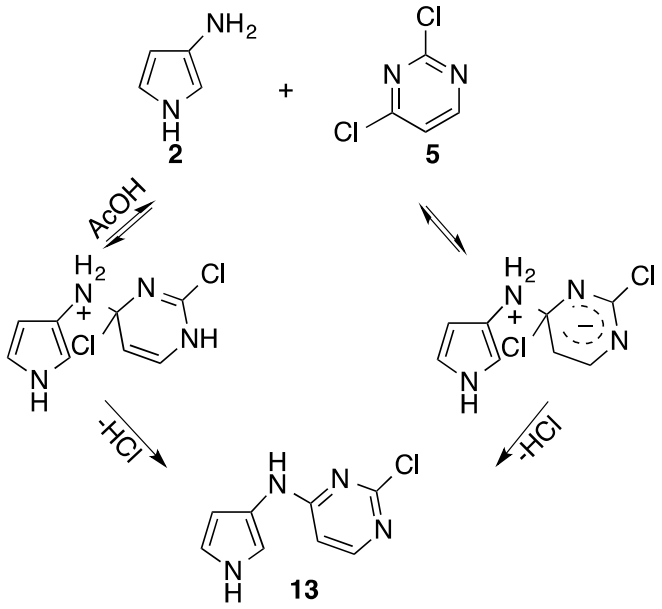
Entry	R_1	R_2	R_3	R_4	Pyrimidine (equiv.)	Method (I[a] or II[b])	Temp. (^oC)	Time (h)	Product: (Yield)[c]
1	Cl	Cl	Cl	Cl	**3** (1.5)	I	Reflux	2.5	**10:** 89%
2	Cl	Cl	H	Cl	**4** (1.5)	I	Reflux	2.5	**11:** 19%[d] (12%) **12:** 62%[d] (50%)
3	Cl	Cl	H	Cl	**4** (1.5)	II	20	18	**11:** 15%[d] (~3%) **12**: 70%[d] (52%)
4	Cl	Cl	H	H	**5** (1.5)	I	Reflux	2	**13:** 46%[d] (15%)
5	Cl	Cl	H	H	**5** (1.5)	II	20	18	**13:** 73%[d] (40%)
6	H	Cl	H	Cl	**6** (2.5)	I	Reflux	5	**14:** 61%[d] (41%)
7	H	Cl	H	Cl	**6** (1.5)	II	20	22	**14:** 80%[d] (52%)
8	Cl	CF_3	H	H	**7** (1.5)	I	Reflux	17	**15:** 46%[d] (17%)
9	Cl	CF_3	H	H	**7** (1.5)	II	20	18	**15:** 58%[d] (22%)
10	Cl	Cl	NO_2	H	**8** (1.0)	I	20	0.75	**16:** 71%[d] (54%)
11	H	Cl	NO_2	Cl	**9** (1.0)	I	20	1	**17:** 64%

[a] Method I: DIPEA (3 equiv.)/4Å Molecular sieves. [b] Method II: MeOH/glacial AcOH (1 equiv.). [c] Isolated yield of pure compound. [d] ^{1}H NMR integrated yield.

Previously it has been reported that nucleophilic attack on chloropyrimidines occurs as follows: C4/C6>C2>>C5.[3] Similar results were obtained in this study. In those pyrimidines (**3-5** and **8**) where chloro groups were present on both C4/C6 and C2, the only or major product was from the displacement of the C4/C6 chloro group. Only in the reaction of 2,4,6-trichloropyrimidine (**4**) with **2** was substitution at C2 competitive with reaction at C6 to give **11** as a minor product. As expected a 5-nitro group was a better activating group than a chloro group. This can be seen be comparing the reactions 4,6-dichloro-5-nitropyrimidine (**9**) with that of 2,4,5,6-tetrachloropyrimidine (**3**). Only the former reacted with two equivalents of 3-aminopyrrole (**2**). The CF_3 group activated the chloro group on C2 (chloropyrimidine **7**) and **15** was obtained.

S_NAr reactions of chloropyrimidines with amines can occur under non-acidic conditions or be acid catalyzed (autocatalytic) as shown in Scheme 3 using 2,6-dichloropyrimidine (**5**) as a model compound. Cycloaddition of 3-aminopyrrole (**2**) with 1,3,5-triazine has been found to be acid catalyzed.[17] This was attributed to a lowering of the LUMO-HOMO interaction that made

cycloadditon easier.[18] S_NAr reactions of 2,4,6-trihalo-1,3,5-triazines have also been found to be acid catalyzed.[17] In this study it was found that acid catalysis was important with chloropyrimidines (**5-7**); derivatives that only have one activating group present on the pyrimidine ring plus the leaving group. Acid catalysis was not a factor when two (**4**, **8** and **9**) or three (**3**) activating groups were present on the pyrimidine ring. These are the chloropyrimidines that, based on the number of electron-withdrawing attached to the ring, would be expected to be the most reactive towards nucleophilic attack, and also the least basic. Under acid catalyzed conditions the reaction is between 3-aminopyrrole (**2**) and conjugate acid of the chloropyrimidine. Their respective stoichiometric concentrations are inversely related to acidity. As a result only the more basic (less reactive) chloropyrimidines are sufficiently protonated in acetic acid to react with **2**. If too strong an acid is used (or higher concentration), the stoichiometric concentration of 3-aminopyrrole (**2**) was too low for reaction to take place.



Scheme 3. Pathways for pyrroloaminopyrimidine formation.

In general it can be seen that the S_NAr reactions of very reactive chloropyrimidines with 3-aminopyrrole (amine) would be favored by basic conditions (higher stoichiometric concentration of amine); whereas, reactions of less reactive chloropyrimidines would be favored by acid catalysis (higher stoichiometric concentration of the more electrophilic chloropyrmidine conjugate acid).

X-ray structure of **11** was determined at the Penn State small molecule crystallographic facility established using funds from an NSF Chemistry Research Instrumentation and Facilities grant CHE-0131112 . Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1055668. Copies of the data can be obtained, free of charge, on

application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). See also supporting information.

Experimental Section

General. All reactions were performed under an atmosphere of either argon or nitrogen gas. Reactions were monitored by TLC analysis and visualization was accomplished with a 254 nm UV light. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$, acetone-d_6 or DMSO-d_6. Chemical shifts were reported in parts per million with the residual solvent peak or TMS used as an internal standard. ^{1}H NMR spectra were recorded at 400 MHz and are tabulated as follows: chemical shift, multiplicity (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad), number of protons, and coupling constants. ^{13}C NMR were recorded at 100 MHz using a proton-decoupled pulse sequence with a d_1 of 5 sec, and are tabulated by observed peak. All of the chloro-pyrimidines (**3-9**) used in this study were commercially available. The 1*H*-pyrrol-3(2*H*)-iminium tetraphenylborate (**1**) salt was synthesized according to a newly published procedure and further purified by recrystallization as reported below.[11]

Further purification of the 1*H*-pyrrol-3(2*H*)-iminium tetraphenylborate salt (1). A grey suspension of tin (2.382 g, 20.07 mmol) and 3-nitropyrrole (450.0 mg, 4.014 mmol) in AcOH (25 mL) was stirred at room temperature for 2.5 h. The thick reaction mixture was diluted with distilled water (3.0 mL) and the resulting thin suspension was pressure-filtered through a plug of celite (~1", pre-flushed with water) into a stirred solution of $NaBPh_4$ (5.49 g, 16.1 mmol) in distilled water (25 mL). The celite plug was flushed with distilled water until no longer yellow in color. The resulting yellow precipitate was isolated by vacuum filtration, washed with distilled water (50 mL) and dried in vacuo over P_2O_5. The dry yellow solids were suspended in DCM (50 mL) to which MeOH (7 mL) was then added with stirring. The cloudy green/brown mixture was vacuum-filtered and the filtrate was slowly diluted with hexane (250 mL) with stirring. After 15 min, the green suspension was vacuum-filtered. The isolated solids were washed with hexane (50 mL) and dried *in vacuo* over P_2O_5 to afford **1** as a light green solid (1.40 g, 87%).

Pyrimidine reactions under anhydrous/basic conditions (Method I)

2,5,6-Trichloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (10). To a suspension of **1** (100 mg, 0.249 mmol) and powdered 4Å molecular sieves (500 mg) was added DIPEA (130 µL, 0.747 mmol, 3 equiv.). The resulting mixture was stirred at room temperature for 5 min and then **3** (81.4 mg, 0.374 mmol, 1.5 equiv.) was added. The reaction mixture was heated to reflux over 10 min and at reflux for 2.5 h. After cooling to room temperature, the dark green reaction mixture was concentrated under reduced pressure (60-65 ^{o}C) and the dark green solids were added to the top of a preconditioned column for flash column chromatography (SiO_2; 1:1 hexane/EtOAc). The light green product fractions were concentrated under reduced pressure (60 ^{o}C), transferred to a pre-weighed vial with DCM (1.0 mL), re-concentrated by a stream of Ar (g) and dried in vacuo over P_2O_5 to afford **10** as a dark green solid (58.1 mg, 89%): R_f 0.56 (1:1 hexane/EtOAc);

Mp 165.5-167.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.38-7.37 (m, 1H), 7.35 (br s, 1H), 6.73 (td, 1H, *J* 2.8, 2.4 Hz), 6.23 (td, 1H, *J* 2.8, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.4, 155.4, 121.8, 116.9, 110.1, 109.8, 102.3; HRMS (TOF ES$^+$): *m/z* calcd for $C_8H_6Cl_3N_4$ 262.9658, found 262.9636.

4,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-2-amine (11) and 2,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (12). According to method I, **1** (200 mg, 0.498 mmol), 4Å molecular sieves (500 mg), DIPEA (260 µL, 1.49 mmol, 3 equiv.) and **4** (86.0 µL, 0.747 mmol, 1.5 equiv.) in DCM (5.0 mL) were reacted at reflux for 2.5 h. The crude reaction mixture was concentrated under reduced pressure (40 °C) in the presence of SiO_2 (500 mg) and chromatographed (SiO_2; 2:1 -> 1:1 hexane/EtOAc gradient). Products **11** and **12** were isolated and recrystallized from a boiling 2:1 hexane/EtOAc solution which was slowly cooled to 0 °C for 1 h. The resulting solids were isolated by vacuum filtration, washed with hexanes (5 mL) and dried in vacuo over P_2O_5 to afford **11** as dark yellow/green crystals (14.2 mg, 12%): R_f 0.68 (1:1 hexane/EtOAc); Mp >260 °C; ^{1}H NMR (400 MHz, acetone-d_6, ~2:1 mixture of rotamers) δ 9.91 (br s, 1.5H), 9.12 (br s, 0.5H), 7.27 (td, 1H, *J* 2.8, 2.4 Hz), 6.78 (s, 1H), 6.71 (td, 1H, *J* 2.8, 1.6 Hz), 6.26 (ddd, 1H, *J* 2.8, 2.4, 1.6 Hz); ^{13}C NMR (100 MHz, acetone-d_6, major rotamer) δ 161.8, 161.0, 159.2, 123.3, 116.3, 108.3, 108.1, 101.4; HRMS (TOF ES$^+$) *m/z* calcd for $C_8H_7N_4Cl_2$ 229.0048, found 229.0044. Product **12** was isolated as a grey solid (56.9 mg, 50%): R_f 0.48 (1:1 hexane/EtOAc); Mp >260 °C; ^{1}H NMR (400 MHz, acetone-d_6, ~1:1 mixture of rotamers) δ 10.26 (br s, 0.5H), 9.99 (br s, 0.5H), 9.28 (br s, 0.5H), 8.66 (br s, 0.5H), 7.34 (br s, 0.5H), 6.91 (br s, 0.5H), 6.85 (br s, 0.5H), 6.72 (br s, 0.5H), 6.66 (br s, 0.5H), 6.54 (br s, 0.5H), 6.13 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6, mixture of rotamers) δ 165.6, 161.2, 160.2, 160.0, 159.5, 157.6, 122.9, 120.8, 118.3, 118.2, 116.5, 116.3, 113.1, 112.9, 109.1, 109.0, 104.8, 103.4, 101.3, 99.7; HRMS (TOF ES$^+$): *m/z* calcd for $C_8H_7Cl_2N_4$ 229.0048, found 229.0039.

2-Chloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (13). According to method I, **1** (200 mg, 0.498 mmol), 4Å molecular sieves (500 mg), DIPEA (260 µL, 1.49 mmol, 3 equiv.) and **5** (111 mg, 0.747 mmol, 1.5 equiv.) in DCM (5.0 mL) were reacted at reflux for 2 h. The crude reaction mixture was concentrated under reduced pressure (40 °C) in the presence of SiO_2 (500 mg) and chromatographed (SiO_2; 1:1 hexane/EtOAc). The isolated product was recrystallized from a boiling 2:1 hexane/DCM solution which was slowly cooled to 0 °C for 1 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (10 mL) and dried in vacuo over P_2O_5 to afford **13** as a pale yellow solid (14.9 mg, 15%): R_f 0.12 (1:1 hexane/EtOAc); Mp 132.6-133.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ~1.5:1 mixture of rotamers) δ 10.85 (br s, 0.4H), 10.60 (br s, 0.6H), 9.85 (br s, 0.6H), 9.36 (br s, 0.4H), 7.96 (br s, 1H), 7.13 (br s, 0.6H), 6.74 (br s, 0.4H), 6.66 (br s, 1H), 6.57 (br d, 1H, *J* 4.4Hz), 6.06 (br s, 0.6H), 5.99 (br s, 0.4H); ^{1}H NMR (400 MHz, acetone-d_6, ~1.5:1 mixture of rotamers) δ 10.14 (br s, 0.4H), 9.90 (br s, 0.6H), 9.02 (br s, 0.6H), 8.28 (br s, 0.4H), 7.98 (br s, 1H), 7.38 (br s, 0.6H), 6.72 (br s, 1.4H), 6.60 (d, 1H, *J* 5.6 Hz), 6.11 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) δ 161.3, 161.2, 159.3, 156.5, 124.0, 122.3, 118.9, 117.5, 117.3, 112.9, 109.4, 109.2, 107.0, 105.3, 102.9, 102.1; HRMS (TOF ES$^+$) *m/z* calcd for $C_8H_8ClN_4$ 195.0437, found 195.0432.

6-Chloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (14). According to method I, **1** (100 mg, 0.249 mmol), 4Å molecular sieves (500 mg), DIPEA (130 µL, 0.747 mmol, 3 equiv.) and **6** (92.8 mg, 0.623 mmol, 2.5 equiv.) in DCM (2.0 mL) were reacted at reflux for 5 h. The crude reaction mixture was concentrated under reduced pressure (55 ^{o}C) and chromatographed (SiO_2; 1:1 hexane/EtOAc). The isolated product was triturated with DCM (1.5 mL) to remove a black impurity and dried in vacuo over P_2O_5 to afford **14** as a grey solid (20.0 mg, 41%): R_f 0.30 (1:1 hexane/EtOAc); Mp 179.2-182.3 ^{o}C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6, ~1.5:1 mixture of rotamers) δ 10.84 (br s, 0.4H), 10.57 (br s, 0.6H), 9.63 (br s, 0.6H), 9.25 (br s, 0.40), 8.35 (br s, 1H), 7.14 (br s, 0.6H), 6.90-6.35 (br m, 2.4H), 6.03 (br s, 1H); ^{1}H NMR (400 MHz, acetone-d_6, ~2.3:1 mixture of rotamers) δ 10.05 (br s, 1H), 8.77 (br s, 0.3H), 8.32 (br s, 1.7H), 7.33 (br s, 0.3H), 6.78 (br s, 1.7H), 6.62 (br s, 1H), 6.11 (q, 1H, *J* 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) 164.2, 160.6, 159.3, 157.2, 123.5, 121.5, 118.4, 116.6, 112.6, 108.8, 104.9, 101.6, 100.9 ; HRMS (TOF ES$^+$) *m/z* calcd for $C_8H_8ClN_4$ 195.0437, found 195.0429.

***N*-(1*H*-pyrrol-3-yl)-4-(trifluoromethyl)pyrimidin-2-amine (15).** According to method I, **1** (200 mg, 0.498 mmol), 4Å molecular sieves (500 mg), DIPEA (260 µL, 1.49 mmol, 3 equiv.) and **7** (90.2 µL, 0.747 mmol, 1.5 equiv.) in DCM (12.0 mL) were reacted at reflux for 17 h. The crude reaction mixture was concentrated under reduced pressure (40 ^{o}C) in the presence of SiO_2 (500 mg) and chromatographed (SiO_2; 4:1 DCM/EtOAc). The isolated product was impure by TLC and was chromatographed a second time under identical conditions. The isolated yellow oil was recrystallized from a boiling 2:1 hexane/DCM solution which was slowly cooled to 0 ^{o}C for 1 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (10 mL) and dried in vacuo over P_2O_5 to afford **15** as a yellow/green crystalline solid (19.2 mg, 17%): R_f 0.57 (4:1 DCM/EtOAc); Mp 130.5-131.5 ^{o}C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.81 (br s, 1H), 8.99 (br s, 1H), 8.62 (br s, 1H), 7.34 (br s, 1H), 6.98 (d, 1H, *J* 4.8 Hz), 6.70 (td, 1H, *J* 2.0, 2.8 Hz), 6.28 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6, mixture of rotamers) δ 161.0, 160.3 (2C), 155.6, 124.1 (2C), 124.0, 116.1, 115.9, 107.7, 105.2, 101.0; HRMS (TOF ES$^+$) *m/z* calcd for $C_9H_8F_3N_4$ 229.0701, found 229.0688.

2-Chloro-5-nitro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (16). According to method I, **1** (150 mg, 0.373 mmol), 4Å molecular sieves (50 mg), DIPEA (195 µL, 1.12 mmol, 3 equiv.) and **8** (72.4 mg, 0.373 mmol) in DCM (4.0 mL) were reacted at room temperature for 45 min. The crude reaction mixture was concentrated under reduced pressure (45 ^{o}C) in the presence of SiO_2 (500 mg) and chromatographed (SiO_2; 2:1 hexane/EtOAc). The isolated red solids were recrystallized from a boiling 1:1 hexane/EtOAc solution which was slowly cooled to 0 ^{o}C for 1.5 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (15 mL) and dried in vacuo over P_2O_5 to afford **16** as a red/brown crystalline solid (48.3 mg, 54%): R_f 0.34 (2:1 hexane/EtOAc); Mp >260 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 10.35 (br s, 1H), 9.07 (s, 1H), 7.27 (dd, 1H, *J* 2.0, 2.4 Hz), 6.73 (dd, 1H, *J* 2.4, 2.8 Hz), 6.43 (td, 1H, *J* 2.8, 1.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 157.2, 151.0, 127.1, 120.7, 116.5, 110.8, 102.9; HRMS (TOF ES$^+$) *m/z* calcd for $C_8H_7ClN_5O_2$ 240.0288, found 240.0273.

5-Nitro-*N*^{4},*N*^{6}-di(1*H*-pyrrol-3-yl)pyrimidine-4,6-diamine (17). According to method I, **1** (100 mg, 0.249 mmol), 4Å molecular sieves (500 mg), DIPEA (130 μL, 0.747 mmol, 3 equiv.) and **9** (48.3 mg, 0.249 mmol) in DCM (2.0 mL) were reacted at room temperature for 1 h. The dark red crude reaction mixture was concentrated under reduced pressure (45 ^{o}C) and chromatographed (SiO_2; 1:1 -> 2:1 EtOAc/hexane gradient) to afford **17** as a dark red solid (22.8 mg, 64%): R_f 0.22 (1:1 hexane/EtOAc); Mp >260 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (br s, 2H), 10.83 (br s, 2H), 8.23 (s, 1H), 7.37 (dd, 2H, *J* 2.4, 4.0 Hz), 6.70 (dd, 2H, *J* 2.4, 2.8 Hz), 6.35 (dd, 2H, *J* 2.8, 4.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.1, 153.7, 122.1, 117.1, 112.1, 111.7, 103.4; HRMS (TOF ES$^+$) *m/z* calcd for $C_{12}H_{12}N_7O_2$ 286.1052, found 286.1036.

Pyrimidine reactions under acidic conditions (Method II)

4,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-2-amine (11) and **2,6-Dichloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (12).** To a pale green suspension of **1** (100 mg, 0.249 mmol) in a 3:1 DCM/MeOH (2.0 mL) mixture was added **4** (43.0 μL, 0.374 mmol, 1.5 equiv.) followed by glacial AcOH (14.3 μL, 0.249 mmol). The reaction mixture was stirred at room temperature for 18 h and then Et_3N (173.5 μL, 1.25 mmol, 5 equiv.) was added to basify the mixture and break up any tetraphenylborate salts formed during the reaction. This mixture was stirred at room temperature for 6 h and was then concentrated under reduced pressure (40 ^{o}C) in the presence of cellulose (500 mg). The resulting dry dark brown solids were added to the top of a preconditioned column for flash column chromatography (SiO_2; 2:1 hexane/EtOAc). Two products were isolated (**11** and **12**) and these product fractions were concentrated under reduced pressure (40 ^{o}C). Product **11** was isolated as a dark green/black oil which was dissolved in a boiling 2:1 hexane/DCM (12 mL) solution, filtered through a tightly packed plug of cotton, concentrated by boiling to 5 mL and slowly cooled to -14 ^{o}C for 15 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **11** as a pale orange solid (3.4 mg, 6% yield, ~50% pure by ^{1}H NMR). Product **12** was isolated as a green solid and was recrystallized from a boiling 2:1 hexane/DCM solution which was slowly cooled to 0 ^{o}C for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with hexane (10 mL) and dried in vacuo over P_2O_5 to afford **12** as a grey solid (29.7 mg, 52%). The spectral properties of **11** and **12** were identical to those reported above.

2-Chloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (13). According to method II, **1** (100 mg, 0.249 mmol), **5** (55.6 mg, 0.374 mmol, 1.5 equiv.) and glacial AcOH (14.3 μL, 0.249 mmol) were combined in a 3:1 DCM/MeOH (2.0 mL) mixture at room temperature for 18 h. The dark green mixture was reacted with Et_3N (173.5 μL, 1.25 mmol, 5 equiv.) at room temperature for 5 h. The crude mixture was concentrated under reduced pressure (40 ^{o}C) in the presence of cellulose (500 mg) and chromatographed (SiO_2; 1:1 hexane/EtOAc). The isolated green oil was dissolved in DCM (10 mL) and filtered through a tightly packed plug of cotton. The filtrate was brought to a boil, concentrated to 5 mL, diluted with hexane (10 mL) and slowly cooled to 0 ^{o}C for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **13** as a light green solid (19.4 mg, 40%). The spectral properties of **13** were identical to those reported above.

6-Chloro-*N*-(1*H*-pyrrol-3-yl)pyrimidin-4-amine (14). According to method II, **1** (100 mg, 0.249 mmol), **6** (55.6 mg, 0.374 mmol, 1.5 equiv.) and glacial AcOH (14.3 μL, 0.249 mmol) were combined in a 3:1 DCM/MeOH (2.0 mL) mixture at room temperature for 22 h. The dark blue/green mixture was reacted with Et_3N (173.5 μL, 1.25 mmol, 5 equiv.) at room temperature for 3.5 h. The crude mixture was concentrated under reduced pressure (40 ^oC) in the presence of cellulose (500 mg) and chromatographed (SiO_2; 1:1 hexane/EtOAc). The isolated product was recrystallized from a boiling 2:1 DCM/hexane mixture which was slowly cooled to 0 ^oC for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with hexane (10 mL) and dried in vacuo over P_2O_5 to afford **14** as a grey solid (25.2 mg, 52%). The spectral properties of **14** were identical to those reported above.

***N*-(1*H*-pyrrol-3-yl)-4-(trifluoromethyl)pyrimidin-2-amine (15).** According to method II, **1** (100 mg, 0.249 mmol), **7** (45.1 μL, 0.374 mmol, 1.5 equiv.) and glacial AcOH (14.3 μL, 0.249 mmol) were combined in a 3:1 DCM/MeOH (2.0 mL) mixture at room temperature for 18 h. The dark green mixture was reacted with Et_3N (173.5 μL, 1.25 mmol, 5 equiv.) at room temperature for 7 h. The crude mixture was concentrated under reduced pressure (40 ^oC) in the presence of cellulose (500 mg) and chromatographed (SiO_2; DCM -> 10:1 DCM/EtOAc gradient). The resulting yellow/green oil was recrystallized from a boiling 7:1 hexane/DCM mixture which was slowly cooled to -14 ^oC for 15 h. The resulting precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **15** as a pale yellow/green solid (12.6 mg, 22%). The spectral properties of **15** were identical to those reported above.

Procedure for ^{1}H NMR integrated yields. *Method I:* To a suspension of **1** (25.0 mg, 0.0620 mmol) and powdered 4Å molecular sieves in DCM (1.0 mL) was added DIPEA (32.5 μL, 0.186 mmol) in one portion at room temperature. After 5 min, the pyrimidine (equiv. specified in Table 1) was added and the reaction mixture was stirred at room temperature or at reflux for the time period specified in Table 1. *Method II:* A mixture of **1** (25.0 mg, 0.0620 mmol), pyrimidine (0.0953 mmol, 1.5 equiv.) and glacial AcOH (3.6 μL, 0.0620 mmol) in a 3:1 DCM/MeOH (1.0 mL) solution was stirred at room temperature for the time period specified in Table 1. At this time, Et_3N (43.4 μL, 0.313 mmol, 5 equiv.) was added and the resulting mixture was stirred at room temperature for ~5 h. The reaction mixture (from either *Method I* or *II*) was concentrated by a stream of Ar or N_2 gas and dried *in vacuo* over P_2O_5. To the dry black solids was added 4-chlorobenzaldehyde (8.7 mg, 0.0620 mmol). This mixture was dissolved in either acetone-d_6 (1.0-2.0 mL) or DMSO-d_6 (1.0 mL) and filtered through a tightly packed plug of cotton (*Method I*, to remove 4 Å molecular sieves) into an NMR tube. A ^{1}H NMR (400 MHz, d_1 4.0 s, NS 64) was taken of the reaction mixture and the product peaks (**11:** δ 6.26 (acetone-d_6, 1H); **12:** δ 6.13 (acetone-d_6, 1H); **13:** δ 6.11 (acetone-d_6, 1H); **14:** δ 6.11 (acetone-d_6, 1H); **15:** δ 6.70 (acetone-d_6, 1H); **16**: δ 6.43 (DMSO-d_6, 1H)) were integrated against the aldehyde resonance (δ 10.02 in acetone-d_6, δ 10.00 in DMSO-d_6). For reaction mixtures in which a product –NH resonance overlapped with the aldehyde peak, 1 drop of D_2O was added to the mixture prior to integration.

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