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The reaction of 2,4,6-trichloropyrimidine **1** with a variety of 4-substituted anilines **2** has been investigated. Monosubstitution occurs readily for all anilines except those containing strongly electron-withdrawing groups. The yields of the isomeric products **3** and **4** parallel the Hammett constants of the ring substituents. The main product when ethanol was used as the solvent was the 4-substituted-2,6-dichloropyrimidine **3**. Spectral and X-ray data confirmed this assignment. However, a solvent dependence on the **3**:**4** ratio was demonstrated. In some cases, excess aniline under forcing conditions led to 2,4-disubstituted products.

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2,4,6-Trichloropyrimidine **1** is a valuable precursor to substituted pyrimidines with potential biological properties. As a commercially available compound that readily undergoes nucleophilic displacement of the chlorine atoms, a wide range of substituents can be introduced into the pyrimidine ring through this precursor. Over nearly a century of exploration nitrogen nucleophiles such as ammonia [1], methylamine [2], dimethylamine [3], benzylamine [4], pyrrolidine [5], and ethanolamines [6] have been employed in this way. Very recently we extended the scope of nitrogen nucleophiles by examining the reaction of **1** with sodium amide to ascertain the utility of an anionic nitrogen nucleophile [7].

One type of nitrogen nucleophile that has received very little attention is the aromatic amine, exemplified by aniline. Only a few reports have appeared that describe this reaction. For example, 2,3-dimethylaniline reacts with **1** to give a monosubstituted product in 75% yield [8]. Compounds with commercial applications have been prepared from **1** with a limited number of anilines [9,10] and *N*-alkylanilines [11]. Yet there continues to be interest in such derivatives, particularly anilinouracils, based on biological rationale [12-14]. As a consequence of this paucity of literature we embarked on a systematic study of **1** with a range of 4-substituted aniline derivatives. In particular, we were interested to learn if more than one chlorine could be replaced, as well as the relative ease of displacing a chloro group with electronically diverse anilines.

In order to investigate the reactivity of **1** with aromatic amines we chose a variety of 4-substituted anilines **2** that possess substituents ranging from strongly electron-donating to strongly electron-withdrawing.

Based on our previous experiences with other nucleophiles as well as one of the literature citations [8], the initial procedure involved stirring **1** with one equivalent of the aniline **2** in ethanol for periods up to 72 hours. Sodium carbonate was employed to neutralize the liberated hydrogen chloride. The 4-monosubstituted compounds **3a-3k** were obtained in good to moderate yields as the major isomer. Analysis by hplc of these reaction mixtures was

used initially to follow the progress of the reaction. The identity of these products is based initially on ^{13}C nmr and confirmed in several examples by X-ray crystallographic data (*vide infra*).

Mixtures of 4- and 2-substituted products have been obtained in previous studies involving neutral nitrogen nucleophiles in which the ratio of the two isomers is very nearly statistical, namely 2:1-3:1 [1-4,6]. Although we observed some of the 2-substituted isomer in the ^1H nmr spectrum of the crude reaction mixture when ethanol was used as the solvent and the reaction was conducted at room temperature, the ratio of **3** to **4** was *ca.* 10:1. This chemical behavior has been observed in the reaction of **1** with phenolate ions [15].

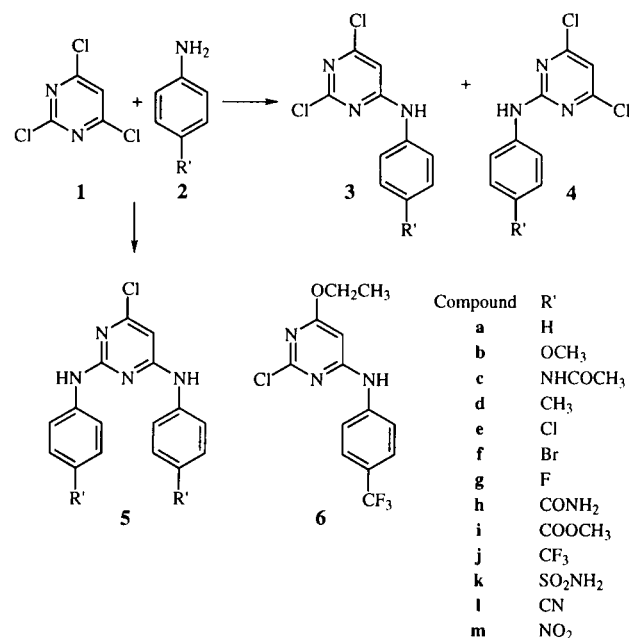


Figure 1.

When the reactions were conducted under reflux conditions using a slight excess of aniline, higher yields were obtained. We occasionally observed solvolysis at elevated temperatures and longer reaction times in nucleophilic

solvents. Similar reactions run in dioxane at room temperature led to a ratio of approximately 2:1 for **3** and **4**. At reflux temperatures in dioxane this ratio is about 1:1. Both products could be isolated by column chromatography and were characterized by ^{13}C nmr, with the spectrum of **3** indicating four unique carbon atoms in the pyrimidine ring in accordance with an unsymmetrical structure, while the symmetrical 2-substituted derivative **4** showed only three unique carbon atoms in the pyrimidine ring. Table 1 summarizes these experiments and the results obtained.

Table 1

Results for Reaction of 2,4,6-Trichloropyrimidine with 4-Substituted Anilines to Yield Monosubstituted Derivatives

Aniline	Product	Time	Temp. [a]	Eq. Aniline	Yield
2a	3a	72 hr	rt	1.0	74%
2a	3a	18 hr	reflux	1.1	78%
2a	3a	72 hr	rt		
		2 hr	reflux	2.0	91%
2b	3b	72 hr	rt	1.0	87%
2b	3b	18 hr	reflux	1.1	93%
2b	3b	72 hr	rt		
		1.5 hr	reflux	2.0	99%
2c	3c	48 hr	rt	1.0	88%
2c	3c	18 hr	reflux	1.1	93%
2d	3d	19 hr	rt	1.0	73% [b]
2d	3d	18 hr	reflux	1.1	90%
2e	3e	96 hr	rt	1.0	70%
2e	3e	18 hr	reflux	1.1	71%
2e	3e	96 hr	rt		
		1 hr	reflux	2.0	84%
2f	3f	27 hr	rt	1.0	62% [b]
2f	3f	18 hr	reflux	1.1	84%
2g	3g	23 hr	rt	1.0	57% [b]
2g	3g	18 hr	reflux	1.1	83%
2h	3h	21 hr	rt	1.0	63%
2h	3h	18 hr	reflux	1.1	86%
2i	3i	66 hr	rt	1.0	45% [b]
2i	3i	18 hr	reflux	1.1	70%
2j	3j	48 hr	155 °C	1.1	18% [c]
2k	3k	18 hr	rt	1.0	34%
2k	3k	18 hr	reflux	1.1	47%
2k	3k	18 hr	rt	2.0	62%
2l	no reaction	>48 hr	up to 200 °C	1.1	no reaction
2m	no reaction	>48 hr	up to 200 °C	1.1	no reaction

[a] Reactions run in ethanol; [b] Recrystallized from ethanol; [c] Purified by column chromatography.

X-ray crystallographic analysis of **3a**, **3b**, and **3e** confirmed that the arylamino substituent is in the 4-position [16]. ORTEP diagrams of **3a** (Figure 2), **3b** (Figure 3), and **3e** (Figure 4) as well as selected bond distances and bond angles for **3a** (Table 2), **3b** (Table 3), and **3e** (Table 4) provide details for this assignment.

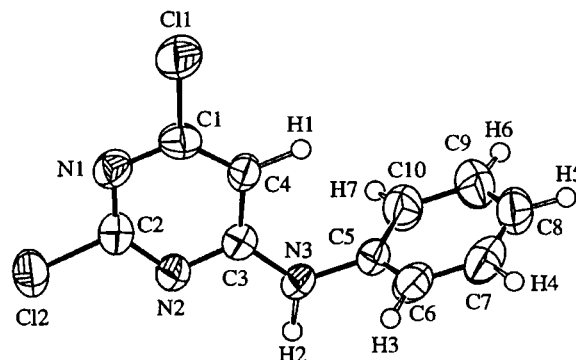
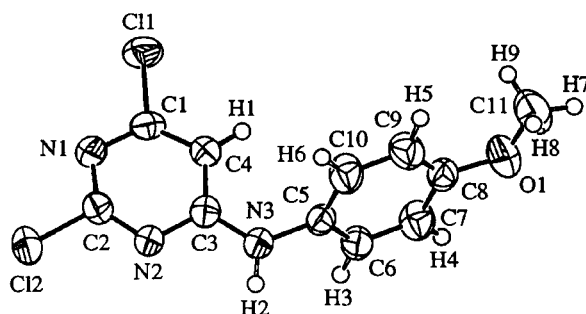
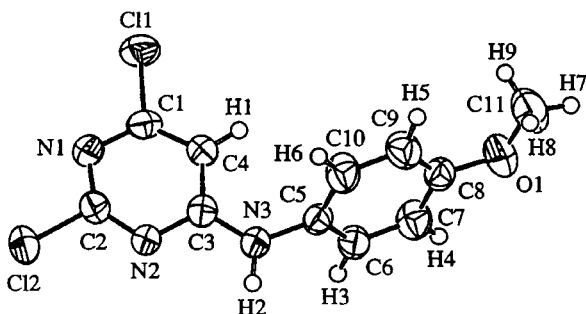
Figure 2. ORTEP Drawing of **3a**.Figure 3. ORTEP Drawing of **3b**.Figure 4. ORTEP Drawing of **3e**.

Table 2

Selected Bond Distances and Bond Angles for **3a**

Intramolecular Bond Distances			Intramolecular Bond Angles			
Atom	Atom	Distance [a]	Atom	Atom	Atom	Angles [b]
N(3)	C(3)	1.329(5)	C(3)	N(3)	H(2)	120.86
N(3)	H(2)	1.062	C(3)	N(3)	C(5)	122.8(4)
N(3)	C(5)	1.451(5)	C(5)	N(3)	H(2)	115.76
N(2)	C(3)	1.359(5)	N(2)	C(3)	N(3)	116.1(5)
C(3)	C(4)	1.411(6)	N(3)	C(3)	C(4)	123.8(5)

[a] Distances are in Angstroms. Estimated standard deviations in the least significant figure are given in parentheses. [b] Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Table 3
Selected Bond Distances and Bond Angles for **3b**

Intramolecular Bond Distances			Intramolecular Bond Angles			
Atom	Atom	Distance [a]	Atom	Atom	Atom	Angles [b]
N(3)	C(3)	1.343(3)	C(3)	N(3)	H(2)	119(2)
N(3)	H(2)	0.89	C(3)	N(3)	C(5)	123.5(2)
N(3)	C(5)	1.434(3)	C(5)	N(3)	H(2)	116(2)
N(2)	C(3)	1.361(3)	N(2)	C(3)	N(3)	116.5(2)
C(3)	C(4)	1.407(3)	N(3)	C(3)	C(4)	123.1(2)

[a] Distances are in Angstroms. Estimated standard deviations in the least significant figure are given in parentheses. [b] Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Table 4
Selected Bond Distances and Bond Angles for **3e**

Intramolecular Bond Distances			Intramolecular Bond Angles			
Atom	Atom	Distance [a]	Atom	Atom	Atom	Angles [b]
N(3)	C(3)	1.361(3)	C(3)	N(3)	H(2)	113(2)
N(3)	H(2)	0.86	C(3)	N(3)	C(5)	130.4(2)
N(3)	C(5)	1.415(3)	C(5)	N(3)	H(2)	116(2)
N(2)	C(3)	1.346(3)	N(2)	C(3)	N(3)	119(2)
C(3)	C(4)	1.409(3)	N(3)	C(3)	C(4)	120.1(2)

[a] Distances are in Angstroms. Estimated standard deviations in the least significant figure are given in parentheses. [b] Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

The solvent-dependent difference in the isomer ratio of **3** to **4** prompted us to investigate several solvents using **2b** as the nucleophile. The reactions were run at room temperature until tlc indicated completion. The results are shown in Table 5.

Table 5
Reaction of 2,4,6-Trichloropyrimidine with
4-Methoxyaniline as a Function of Solvent

Solvent	% Yield	3:4 Isomer Ratio
Ethanol	97%	11.6
Acetone	92%	7.6
Acetonitrile	94%	5.2
Ethyl Acetate	86%	2.4
Dioxane	90%	1.7
Chloroform	95%	0.8

A dependence of the **3**:**4** isomer ratio on the solvent identity was clearly indicated, and appears to roughly correspond to the polarity of the solvent.

As expected, yields were quite high for those anilines that are electronically neutral or contain an electron-donating group (**3a-3d**). Anilines containing moderate electron-withdrawing groups (**3e-3i**) provided slightly lower yields (Table 1). However, treatment of **1** with anilines **2l** and **2m**, containing cyano and nitro groups respectively, failed completely to provide any of the corresponding monosubstituted products, **3l** and **3m**, even at temperatures up to 200 °C in a Parr apparatus.

When the reactions were run in refluxing ethanol for 18 hours with 1.1 equivalents of **2** relative to **1** the yields closely parallel the Hammett para-sigma constants (Figure 5) [17]. Some solvolysis of the chlorines of **1** accompanied a poor reaction with **2j** to give compound **6**. In an effort to employ higher temperatures without using a nucleophilic solvent we carried out the reaction of **1** with **2l** in dioxane, dimethyl sulfoxide, dimethylformamide, sulfolane, and 2-methoxyethanol at elevated temperatures. None of the desired product was observed.

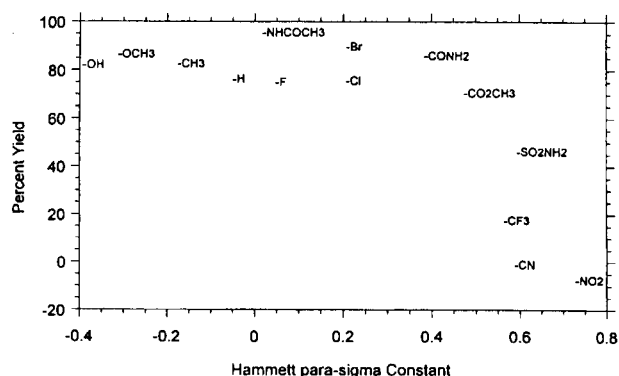


Figure 5. A Plot of the Hammett *para*-Sigma Constant versus the % Yield for the Reaction of 2,4,6-Trichloropyrimidine with a Series of 4-Substituted Anilines.

In an effort to increase the nucleophilicity of the less reactive anilines, anionic anilides were prepared. Thus, the anilide of **2j** was prepared using dry tetrahydrofuran and potassium hydride and treated with **1**. After workup a small yield of **3j** was obtained which could not be satisfactorily purified. Much of the recovered material was intractable. Similar results were obtained when using **2l**.

It has been demonstrated that all but strongly electron-withdrawing anilines can effectively be used to form 4-anilino-2,6-dichloropyrimidines. Some success in forming a 2,4-disubstituted product was achieved with anilines containing electron-donating, neutral, or weakly electron-withdrawing groups to form **5a**, **5d**, and **5f**. For example, treatment of **1** with **2a** in aqueous hydrogen chloride at reflux for 3 days produced **5a** in 26% yield. The poor

yield was due mainly to the hydrolysis of the chlorine groups under the harsh conditions. An improved procedure was realized by refluxing **1** with **2a** in dioxane for several days, affording a separable mixture of **3a**, the desired **5a** in 56% yield, and 2,4,6-tris(phenylamino)-pyrimidine. The 2,4-disubstitution pattern in **5a** was assigned by ^{13}C nmr, which showed non-equivalent carbon signals for the two aniline substituents.

Compounds such as 6-anilinouracils that exhibited potential as inhibitors of DNA Polymerase III and Herpes Simplex Virus Type 1 [12,13] prompted us to examine the potential for biological activity of this series of aniline derivatives. Antitumor screening by the National Cancer Institute using a broad collection of tumor cell lines failed to demonstrate even modest anticancer activity. This observation was true also in the screening protocol at Wayne State University. Antimalarial screening, conducted by the Walter Reed Army Institute of Research, showed mild antimalarial activity for **3b** and **3k**, but not enough to warrant further testing.

EXPERIMENTAL

General Conditions.

Melting points were measured in open capillary tubes using a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Proton and carbon magnetic resonance spectra were recorded using a GE QE-300 (300 MHz for ^1H nmr, 75 MHz for ^{13}C nmr) spectrometer using dimethyl- d_6 -sulfoxide or deuteriochloroform containing tetramethylsilane as an internal standard. Analyses by hplc were performed using a Spectra Physics HPLC equipped with a SP8800 ternary pump and a LKB Bromme 2151 variable wavelength detector, set at 240 nm, and a 4.6 mm x 25 mm Zorbax SB-Phenyl column. The eluant was methanol/water of varying compositions, with a flow rate of 1.0 ml/min and a sample injection size of 20 μl . Reactions were also monitored by thin layer chromatography, using Eastman Kodak silica gel chromatography sheets containing fluorescent indicator and various combinations of hexane/ethyl acetate or chloroform/methanol as eluants. Mass spectral data were obtained using a Hewlett Packard 5995A MS instrument by means of direct insertion probe (DIP) method. Elemental analyses were performed by Galbraith Laboratories of Knoxville, Tennessee. X-ray diffraction data were obtained using a Rigaku AFC6S diffractometer with graphite monochromated Mo-K α radiation and a 12 KW rotating anode generator. Chemicals and reagents were purchased from either Fisher Scientific or Aldrich Chemical Company and were used without further purification, with the exception of tetrahydrofuran, which was dried by distillation over K metal and benzophenone.

2,4-Dichloro-6-(phenylamino)pyrimidine (**3a**).

A 50 ml flask was charged with 1.0 g (5.5 mmoles) of 2,4,6-trichloropyrimidine **1**, 0.51 g (5.5 mmoles) of aniline **2a**, 0.64 g (6.0 mmoles) of sodium carbonate, and 25 ml of absolute ethanol. The thin white slurry was allowed to stir at room temperature for 72 hours. The reaction progress was followed by

thin layer chromatography with 8:2 hexane/ethyl acetate as eluant. After completion of the reaction, an equal volume of water was added with cooling. The resulting white precipitate was filtered, washed with water, and dried in a vacuum overnight to yield 0.97 g (74%) of a white powder. The yield of crude product was increased to 91% when 2.0 equivalents of the aniline were used and the reaction refluxed for 2 hours. The crude product was recrystallized twice from hot ethanol to obtain analytically pure **3a**, mp 134-136 $^{\circ}\text{C}$; ^1H nmr (dimethyl- d_6 sulfoxide): δ 6.7 (s, 1H, aromatic), 7.1 (t, 1H, aromatic), 7.3 (t, 2H, aromatic), 7.5 (d, 2H, aromatic), 10.2 (s, 1H, NH); ^{13}C nmr (dimethyl- d_6 sulfoxide): δ 105.3, 122.0, 125.2, 129.9, 138.8, 159.1, 159.6, 163.1; ms: m/z 240.9 (M+1, 43), 239.9 (M $^+$, 80), 238.9 (M-1, 58), 237.9 (M-2, 100).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{N}_3\text{Cl}_2$: C, 50.03; H, 2.94; N, 17.50. Found: C, 49.95; H, 3.05; N, 17.42.

The following products were prepared in a manner similar to that used for **3a**.

2,4-Dichloro-6-(4-methoxyphenylamino)pyrimidine (**3b**).

Reaction of **1** with **2b** yielded 1.3 g (87%) of a light gray solid. The yield was increased to 99% when 2.0 equivalents of *p*-methoxyaniline were used and the reaction refluxed for 1.5 hours. Crude **3b** was recrystallized three times from ethanol to yield analytically pure **3b**, mp 160-162 $^{\circ}\text{C}$; ^1H nmr (deuteriochloroform): δ 3.7 (s, 3H, CH_3), 6.6 (s, 1H, aromatic), 6.9 (d, 2H, aromatic), 7.2 (d, 2H, aromatic), 7.7 (br s, 1H, -NH); ^{13}C nmr (dimethyl- d_6 sulfoxide): δ 56.2, 105.3, 115.2, 124.2, 131.5, 157.2, 158.7, 159.7, 163.4; ms: m/z 271 (M+1, 74), 270 (M $^+$, 28), 269 (M-1, 100), 254 (M-15, 63).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{Cl}_2\text{O}$: C, 48.91; H, 3.36; N, 15.56. Found: C, 49.04; H, 3.41; N, 15.65.

2,4-Dichloro-6-(4-acetamidophenylamino)pyrimidine (**3c**).

Reaction of **1** with **2c** yielded 1.4 g (88%) of a light gray solid which was purified by column chromatography using a 3:1 ethyl acetate/hexane mixture as the eluant; mp 236-238 $^{\circ}\text{C}$; ^1H nmr (dimethyl- d_6 sulfoxide): δ 2.0 (s, 3H, CH_3), 6.6 (s, 1H, aromatic), 7.4 (br, 2H, aromatic), 7.5 (d, 2H, aromatic), 9.9 (s, 1H, NH), 10.1 (s, 1H, -NH); ^{13}C nmr (dimethyl- d_6 sulfoxide): δ 24.7, 105.3, 120.5, 122.8, 133.7, 136.9, 159.0, 159.7, 163.1, 168.9; ms: m/z 298 (M+1, 48), 297 (M $^+$, 12), 296 (M-1, 71), 254 (M-43, 100).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{Cl}_2\text{O}$: C, 48.51; H, 3.39; N, 18.86. Found: C, 48.57; H, 3.46; N, 18.83.

2,4-Dichloro-6-(4-methylphenylamino)pyrimidine (**3d**).

Reaction of **1** with **2d** provided 1.0 g (73%) of product as white crystals, mp 158-161 $^{\circ}\text{C}$. The yield was increased to 90% using 1.1 equivalents of **2d** with reflux; ^1H nmr (dimethyl- d_6 sulfoxide): δ 2.3 (s, 3H, methyl), 6.7 (s, 1H, aromatic), 7.2 (d, 2H, aromatic), 7.4 (d, 2H, aromatic), 10.1 (s, 1H, -NH); ^{13}C nmr (dimethyl- d_6 sulfoxide): δ 20.4, 104.4, 121.4, 129.4, 133.7, 135.2, 158.1, 158.8, 162.3; ms: m/z 255 (M+1, 57), 254 (M $^+$, 70), 253 (M-1, 87), 252 (M-2, 100), 218 (M-36, 24).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{N}_3\text{Cl}_2$: C, 51.99; H, 3.57; N, 16.54. Found: C, 51.75; H, 3.63; N, 16.48.

2,4-Dichloro-6-(4-chlorophenylamino)pyrimidine (**3e**).

Reaction of **1** with **2e** provided a 70% crude yield and 1.1 g (65%) of a white, crystalline solid after recrystallization from

ethanol. The yield was increased to 84% by using 2.0 equivalents **2e** under reflux; mp 168–170 °C; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.8 (s, 1H, aromatic), 7.4 (d, 2H, aromatic), 7.6 (d, 2H, aromatic), 10.3 (s, 1H, -NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 96.6, 104.1, 122.4, 128.9, 137.0, 158.2, 158.7, 161.9; ms: m/z 276 (M+2, 43), 275 (M+1, 79), 274 (M⁺, 100), 238 (M-36, 25).

Anal. Calcd. for C₁₀H₆N₃Cl₃: C, 43.75; H, 2.20; N, 15.31. Found: C, 43.65; H, 2.20; N, 15.09.

2,4-Dichloro-6-(4-bromophenylamino)pyrimidine (**3f**).

Reaction of **1** with **2f** provided 1.1 g (62%) after recrystallization from hexane/ethyl acetate, mp 195–197 °C. The yield was increased to 84% crude yield when 1.1 equivalents of **2f** were used and the reaction refluxed for 18 hours; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.8 (s, 1H, aromatic), 7.5 (m, 4H, aromatic), 10.3 (s, 1H, NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 104.1, 115.8, 122.5, 131.8, 137.4, 158.2, 158.6, 161.8; ms: m/z 321 (M+2, 46), 320 (M+1, 51), 319 (M⁺, 100), 318 (M-1, 94), 317 (M-2, 57) 316 (M-3, 58).

Anal. Calcd. for C₁₀H₆N₃BrCl₂: C, 37.65; H, 1.90; N, 13.17. Found: C, 37.71; H, 1.93; N, 13.04.

2,4-Dichloro-6-(4-fluorophenylamino)pyrimidine (**3g**).

Reaction of **1** with **2g** provided 0.8 g (57%) of a white powder after recrystallization with difficulty from hexane/ethyl acetate, mp 144–146 °C. The crude yield was increased to 84% when 1.1 equivalents of **2g** were used and the reaction refluxed for 18 hours; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.7 (s, 1H, aromatic), 7.2 (t, 2H, aromatic), 7.6 (br t, 2H, aromatic), 10.3 (s, 1H, -NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 104.3, 115.5, 115.8, 122.5, 135.1, 157.5, 158.8, 162.2; ms: m/z 259 (M+1, 67), 258 (M⁺, 66), 257 (M-1, 91) 256 (M-2, 100), 222 (M-36, 27).

Anal. Calcd. for C₁₀H₆N₃Cl₂F: C, 46.54; H, 2.34; N, 16.28. Found: C, 46.36; H, 2.31; N, 16.14.

2,4-Dichloro-6-(4-amidophenylamino)pyrimidine (**3h**).

Reaction of **1** with **2h** provided 0.97 g (63%) of a white powder dec 254–256 °C. The yield was increased to 86% when 1.1 equivalents of **2h** were used and the reaction refluxed for 18 hours; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.8 (s, 1H, aromatic), 7.3 (s, 1H, -NH), 7.6 (d, 2H, aromatic), 7.9 (d, 2H, aromatic); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 104.5, 119.7, 128.0, 129.3, 141.1, 158.2, 158.7, 161.9, 167.3; mass/charge 284 (M+1, 68), 283 (M⁺, 54), 282 (M-1, 100), 281 (M-2, 57), 268 (M-15, 53), 266 (M-17, 85), 240 (M-43, 11), 238 (M-45, 14).

Anal. Calcd. for C₁₁H₈N₄OCl₂: C, 46.66; H, 2.85; N, 19.79. Found: C, 46.64; H, 3.02; N, 19.25.

2,4-Dichloro-6-(4-methylformatophenylamino)pyrimidine (**3i**).

Reaction of **1** with **2i** provided 0.7 g (41%) of **3i** after recrystallization from hot hexane/ethyl acetate, mp 244–246 °C; ¹H nmr (dimethyl-d₆ sulfoxide): δ 3.9 (s, 3H, methyl), 6.9 (s, 1H, aromatic), 7.8 (d, 2H, aromatic), 8.0 (d, 2H, aromatic); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 51.9, 104.9, 119.5, 124.2, 130.3, 142.6, 158.4, 158.6, 161.7, 165.7; ms: m/z 299 (M+1, 74), 298 (M⁺, 64), 297 (M-1, 97), 296 (M-2, 80), 266 (M-32, 100).

Anal. Calcd. for C₁₂H₉N₃Cl₂O₂: C, 48.34; H, 3.04; N, 14.10. Found: C, 48.34; H, 3.16; N, 13.79.

2,4-Dichloro-6-(4-sulfonamidophenylamino)pyrimidine (**3j**).

Reaction of **1** with **2j** yielded 0.6 g (34%) of a pink solid. The yield was increased to 62% when 2.0 equivalents of **2j** were

used and the reaction refluxed for several hours. The resulting product was a white solid; mp 238–240 °C; ¹H nmr (dimethyl-d₆ sulfoxide): δ 3.8 (H₂O), 6.9 (s, 1H, aromatic), 7.4 (d, 2H, -NH₂), 7.8 (m, 4H, aromatic), 11.2 (s, 1H, -NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 104.7, 120.2, 126.9, 138.9, 141.2, 158.5, 158.7, 161.9; ms: m/z 320 (M+1, 64), 319 (M⁺, 100), 318 (M-1, 88), 317 (M-2, 99), 256 (M-63, 22), 238 (M-81, 39) 203 (M-116, 31).

Anal. Calcd. for C₁₀H₈N₄Cl₂O₂S: C, 37.64; H, 2.52; N, 17.56. Found: C, 37.96; H, 2.74; N, 17.04.

4-Chloro-2,6-bis(phenylamino)pyrimidine (**5a**).

A 100 ml flask was charged with 1.0 g (5.5 mmoles) of **1**, 1.0 g (2.1 equivalents, 11.2 mmoles) of **2a**, 1.0 g (2.1 equivalents, 11.2 mmoles) of 37% by weight HCl, and 25 ml of water. The reaction was heated to 100 °C for 3 days. The resulting thin white slurry was neutralized with NaOH to pH 7.0, and the gummy solid was filtered, washed with water, and allowed to air dry. The light yellow solid was then dissolved in boiling ethanol, and the insoluble material filtered off. A small amount of silica gel was added to the ethanol solution, the solvent evaporated, and the residue purified by column chromatography using a hexane/ethyl acetate gradient. The first fraction (418 mg, 26%) was the desired **5a**, crude mp 96–104 °C; recrystallized from ethanol, mp 107–109 °C; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.2 (s, 1H, aromatic), 6.9 (t, 1H, aromatic), 7.1 (t, 1H, aromatic), 7.28 (t, 2H, aromatic), 7.34 (t, 2H, aromatic), 7.7 (2 overlapping d, 4H, aromatic), 9.6 (2 overlapping s, 2H, -NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 95.8, 119.9, 120.9, 122.0, 123.0, 129.2, 129.4, 139.4, 140.0, 158.0, 159.4, 161.8; ms: m/z 296 (M⁺, 100), 295 (M-1, 90).

Anal. Calcd. for C₁₆H₁₃N₄Cl: C, 64.76; H, 4.42; N, 18.88. Found: C, 64.59; H, 4.46; N, 18.82.

6-Chloro-2,4-bis(phenylamino)pyrimidine (**5a**) Using Dioxane as Solvent.

A 100 ml flask was charged with 2.0 g (11.0 mmoles) of **1**, 2.1 g (22.6 mmoles, 2.1 equivalents) of **2a**, 2.3 g (22.6 mmoles, 2.1 equivalents) of sodium carbonate, and 25 ml of dioxane. The reaction was heated to reflux for four days, after which the dioxane was removed by rotary evaporation and water added to the residue. The aqueous mixture was extracted with portions of methylene chloride, the organics dried and evaporated to yield an orange, gummy material. This material was absorbed onto 1 g of silica gel and chromatographed using a hexane/ethyl acetate gradient. The third fraction (1.8 g, 56%) was a light yellow, crystalline material, mp 99–104 °C; a portion recrystallized from ethanol to yield a white crystalline solid, mp 107–109 °C, **5a**; ¹H nmr (dimethyl-d₆ sulfoxide): δ 6.2 (s, 1H, aromatic), 6.9 (t, 1H, aromatic), 7.1 (t, 1H, aromatic), 7.28 (t, 2H, aromatic), 7.34 (t, 2H, aromatic), 7.7 (2 overlapping d, 4H, aromatic), 9.6 (2 overlapping s, 2H, -NH); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 95.8, 119.9, 120.9, 122.0, 123.0, 129.2, 129.4, 139.4, 140.0, 158.0, 159.4, 161.8; ms: m/z 296 (M⁺, 100), 295 (M-1, 94).

Anal. Calcd. for C₁₆H₁₃N₄Cl: C, 64.76; H, 4.42; N, 18.88. Found: C, 64.81; H, 4.39; N, 18.88.

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- [16] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre with the supplementary publication numbers given below. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). A brief summary of the crystallographic data is also provided here for each compound. For **3e**: *Crystal data* for $C_{10}H_6N_3Cl_3$, $M = 274.54$. Color, habit: colorless, block. Monoclinic, space group $P2_1/n$, $a = 8.454(2)$, $b = 11.488(2)$, $c = 12.166(2)$ Å, $\beta = 108.41(2)^\circ$, $V = 1121.0(4)$ Å³, $Z = 4$, $D_c = 1.627$ g/cm³, $\mu(\text{Mo-K}\alpha) = 7.93$ cm⁻¹. Crystal dimensions: $0.25 \times 0.15 \times 0.30$ mm. The crystal was mounted on a glass fiber. Data were measured to $50^\circ 2\theta$ at 296 K on a Rigaku AFC6S diffractometer using ω - 2θ scans with graphite-monochromated Mo-K α radiation. A total of 2219 reflections were collected of which 2071 were unique ($R_{\text{int}} = 0.021$). The structure was solved by direct methods (MITHRIL, DIRDIF) and was refined on F^2 to give $R = 0.058$ ($R_w = 0.063$) for 1956 independent reflections and 163 parameters. All non-hydrogen atoms were refined anisotropically and all hydrogen atoms were positionally refined with fixed isotropic B values. Atomic coordinates and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number (139223). For **3b**: *Crystal data* for $C_{11}H_9N_3Cl_2O$, $M = 270.12$. Color, habit: colorless, block. Monoclinic, space group $P2_1/c$, $a = 7.512(2)$, $b = 13.208(2)$, $c = 12.462(2)$ Å, $\beta = 102.91(2)^\circ$, $V = 1205.3(4)$ Å³, $Z = 4$, $D_c = 1.488$ g/cm³, $\mu(\text{Mo-K}\alpha) = 5.24$ cm⁻¹. Crystal dimensions: $0.25 \times 0.15 \times 0.30$ mm. The crystal was mounted on a glass fiber. Data were measured to $50^\circ 2\theta$ at 296 K on a Rigaku AFC6S diffractometer using ω - 2θ scans with graphite-monochromated Mo-K α radiation. A total of 2391 reflections were collected of which 2213 were unique ($R_{\text{int}} = 0.023$). The structure was solved by direct methods (MITHRIL, DIRDIF) and was refined on F^2 to give $R = 0.070$ ($R_w = 0.071$) for 2104 independent reflections and 181 parameters. All non-hydrogen atoms were refined anisotropically and all hydrogen atoms were positionally refined with fixed isotropic B values. Atomic coordinates and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number (139225). For **3a**: *Crystal data* for $C_{10}H_7N_3Cl_2$, $M = 240.09$. Color, habit: clear, block. Monoclinic, space group $P2_1/n$, $a = 11.115(3)$, $b = 7.898(4)$, $c = 12.931(2)$ Å, $\beta = 106.16(2)^\circ$, $V = 1090.3(6)$ Å³, $Z = 4$, $D_c = 1.462$ g/cm³, $\mu(\text{Mo-K}\alpha) = 5.64$ cm⁻¹. Crystal dimensions: $0.15 \times 0.10 \times 0.30$ mm. The crystal was mounted on a glass fiber. Data were measured to $50^\circ 2\theta$ at 296 K on a Rigaku AFC6S diffractometer using ω - 2θ scans with graphite-monochromated Mo-K α radiation. A total of 2185 reflections were collected of which 2074 were unique ($R_{\text{int}} = 0.045$). The structure was solved by direct methods (MITHRIL, DIRDIF) and was refined on F^2 to give $R = 0.037$ ($R_w = 0.032$) for 764 independent reflections and 136 parameters. All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included in fixed positions. Atomic coordinates and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number (139224).
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