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A modular approach to 4,5-diaminopyrrolo[2,3-*d*]pyrimidines and 2,4,5-triaminopyrrolo[2,3-*d*]pyrimidines

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Abstract—A short and highly modular approach to various 4,5-diaminopyrrolo[2,3-*d*]pyrimidines and 2,4,5-triaminopyrrolo[2,3-*d*]-pyrimidines was developed starting from 4-chloro-5-halopyrrolo[2,3-*d*]pyrimidines and 5-bromo-2,4-dichloropyrrolo[2,3-*d*]pyrimidine, respectively. Direct amination at the 5-position was achieved without the use of transition metals or other catalysts in 32–86% yield. Ten examples are given.
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There has recently been a resurgence of interest in 4,5-diaminopyrrolo[2,3-*d*]pyrimidines and their derivatives due to their biological properties as antiviral,[1a] anticancer,[1b] antifungal[1c] and CNS[1d,e] agents. To our surprise, this type of pyrrolopyrimidine is not nearly as well represented in the synthetic literature as other derivatives of this common heterocycle.[2] In fact, there are very few reported methods of the preparation of 4,5-diaminopyrrolo[2,3-*d*]pyrimidines with no general and modular approach to these derivatives.[1d,e,3a–d]

As part of our ongoing synthetic work, we were exploring functionalization of pyrrolo[2,3-*d*]pyrimidines, and in particular aminosubstitution at the 5-position. Here we report a novel method of direct synthesis of 4,5-diaminopyrrolo[2,3-*d*]pyrimidines.

Originally, we isolated small amounts of bis adduct **3a** when 5-bromo-4-chloropyrrolo[2,3-*d*]pyrimidine **1a**[4] was heated in 2-propanol with an excess of indoline. Optimization of this transformation led to a direct and modular method of preparation of the title derivatives. Under the optimized conditions, **1a** is heated with an equimolar amount of the corresponding amine in 2-propanol at 90 °C in a sealed tube for 5–16 h. To the resulting crude 4-aminosubstituted product mixture **2a**, another amine is added in excess (3 equiv) and the temperature is raised to 120 °C for another 10–16 h.[5] The desired 4,5-diaminosubstituted pyrrolo[2,3-*d*]pyrimidines **2a**–**g** were isolated by preparative HPLC in 32–86% yield.

The geometry of derivative **3a** was assigned based upon a NOE experiment. Thus, in deuterated acetonitrile at 75 °C we observed two strong correlations as depicted in Figure 1. Molecular modeling using SPARTAN suggested that the phenyl rings of the indolines were anti to one another, and were tilted out of plane. In agreement with this, ^{1}H NMR showed significant line broadening which could be explained by slow rotation. A temperature dependent ^{1}H NMR experiment showed that at 75 °C all peaks were fully resolved.

Table 1 summarizes the experimental data for various amines and 5-halo-4-chloropyrrolo[2,3-*d*]pyrimidines, or 5-bromo-2,4-dichloropyrrolo[2,3-*d*]pyrimidine. 5-Bromo derivative **1a** reacts equally well with both primary and secondary amines as well as with both aromatic and aliphatic amines (entries 1–6; Scheme 1). We observed that 5-chloro analog **1b**[4] had a somewhat similar reactivity to the 5-bromo derivative **1a** but required longer reaction times (entries 7 and 8), and failed to react at the C5 position in reactions with less nucleophilic primary amines. In

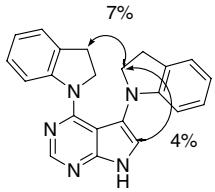

Figure 1. NOE experiment with **3a**.

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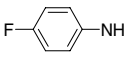
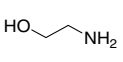
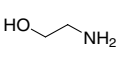
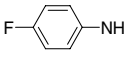
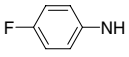
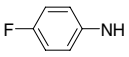
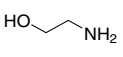
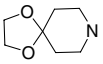
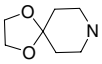
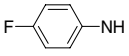
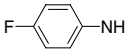
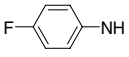
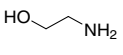
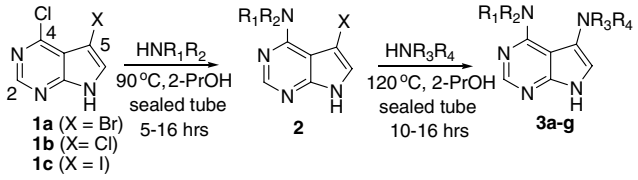
Table 1. Preparation of 4,5-diamino aminopyrrolo[2,3-*d*]pyrimidines and 2,4,5-tris aminopyrrolo[2,3-*d*]pyrimidines

Entry	SM	NR_1R_2	NR_3R_4	Product	Yield (%)
1	**1a**			**3a**	57
2	**1a**			**3b**	64
3	**1a**			**3c**	32
4	**1a**			**3d**	51
5	**1a**			**3e**	42
6	**1a**			**3f**	37
7	**1b**			**3a**	86
8	**1b**			**3g**	61
9	**1c**			**3a**	0
10	**1c**			**3h**	0
11	**4**			**6a**	44
12	**4**			**6b**	34



Scheme 1. Temperature controlled regioselective displacement.

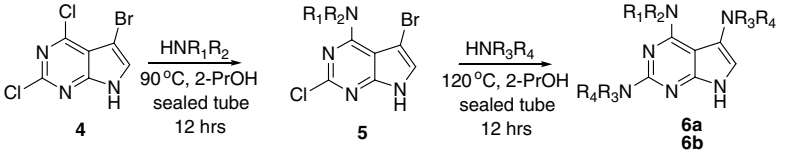
contrast to **1b**, 5-iodo analog **1c**[4] did not afford quantifiable amounts of the desired product under the reaction conditions (entries 9 and 10). These results may be attributed to the low thermal stability of **1c**.[6]

We also found that 5-bromo-2,4-dichloro-pyrrolo[2,3-*d*]-pyrimidine **4** undergoes similar nucleophilic displacements at position 5 (entries 11 and 12; Scheme 2). We observed initial formation of **5** when pyrrolo[2,3-*d*]-pyrimidine **4** (prepared in a similar manner to **1a** starting from commercial 2,4-dichloropyrrolo[2,3-*d*]pyrimidine[4]) was heated in the presence of the corresponding amine. However, further treatment of intermediate **5** with an excess (3 equiv) of either aliphatic or aromatic amines (entries 11 and 12) at 120 °C directly afforded products **6a,b** without any regioselectivity. We found no difference in the relative reactivities of positions 2 and 5 at this, or other temperatures.

All of the ethanolamine derivatives which were prepared, **3c**,**d**,**f**, and **6b**, were oils and had a limited shelf-life when standing at room temperature for several weeks. 4,5-Diaminopyrrolo[2,3-*d*]pyrimidines **3a,b,e,g,h** and 2,4,5-tris aminopyrrolo[2,3-*d*]pyrimidine **6a** were stable in the absence of moisture and acids.

Since nucleophilic attack on pyrrole fused ring systems are not common,[7] and often require mediation by a transition metal,[8a–c] we were surprised by the relative ease of uncatalyzed substitution at the 5-position. Even more surprising was the observation that the reaction of **1a** with 1 equiv of indoline at 150 °C, besides the expected bis adduct **3a**, afforded roughly equal amounts (by LC/MS, 220 nm) of 4-chloro-5-indolinopyrrolo[2,3-*d*]pyrimidiner and 5-bromo-4-indolinopyrrolo[2,3-*d*]pyrimidine. We wondered what might be causing the observed reactivity, and specifically whether molecular strain may facilitate the nucleophilic attack to occur at 5-position of the pyrrolo[2,3-*d*]pyrimidine at elevated temperatures. It is conceivable that the proximity (3.599 Å, 3.623 Å, and 3.687 Å; Cl, Br, I)[9] of the C5 halogens (van der Waals: Cl = 1.80 Å, Br = 1.95 Å, I = 2.15 Å)[10] to the C4 chloro substituent in these molecules causes some molecular strain, altering the electronic composition of the pyrrole ring.[11a,12] Neither measured UV data, nor calculated heats of formation[9] were conclusive in ascertaining the relative degree of molecular strain in the 4-chloro-5-halopyrrolo[2,3-*d*]pyrimidines.

Comparison of ^{13}C NMR chemical shifts of 4-chloro-5-halopyrrolopyrimidines to those of the corresponding unstrained 3-halopyrroles reveals 6–13 ppm *upfield* shift for the 5-carbon of **1a**–**c**. This observation could be explained by greater contribution of sp^3 geometry to hybridization of this carbon in order to accommodate the increasing molecular strain Cl < Br < I in these derivatives (Table 2). This rationale is consistent with our experimental observations, and explains the lower reactivity of the 5-position of **1b** and thermal instability of **1c**. Furthermore, a bulkier substituent than chloro,



Scheme 2. Preparation of 2,4,5-tris aminopyrrolo[2,3-*d*]pyrimidines **6a,b**.

Table 2. Physical properties of 4-chloro-5-halopyrrolopyrimidines

SM	5-Halogen	van der Waals (Å)	UV (nm) (25 °C, AcCN)	C5 ^{13}C shift (ppm)	Lit. 3-halopyrroles C3 ^{13}C shift (ppm)
1b	**Cl**	1.80	218, 268, 301	101.5	107.7[12a]
1a	**Br**	1.95	220, 264, 303	88.7	100.5[12b]
1c	**I**	2.15	222, 267, 307	51.9	65.2[11a]

such as the alkylaminomoieties in **2** and **5**, could also lead to the observed unusual reactivity of the 5-position of pyrrolo[2,3-*d*]pyrimidines.

An alternative possibility for the observed facile reactivity at C-5 is via prior activation of the pyrrole ring. It is possible that protonation first occurs on to C-6, causing activation of the C-5 halo substituent. The nucleophilic displacement could then readily occur, to provide the observed products.

In conclusion, we have demonstrated a direct and versatile approach to the synthesis of 4,5-diaminopyrrolo[2,3-*d*]-pyrimidines. The temperature mediated regioselectivity allows flexibility in the variance of the nature of the amine substituents. It has also been shown that a similar approach can be used for the synthesis of a novel class of pyrrolopyrimidines, the 2,4,5-tris aminopyrrolo[2,3-*d*]-pyrimidines. Direct amination at the 5-position was achieved without the use of transition metals in 32–86% yield.

Acknowledgments

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5. 4,5-Bisindoline derivative **3a**: 5-Bromo-4-chloropyrrolo[2,3-*d*]pyrimidine **1a** (0.232 g, 1 mmol) in 20 mL of 2-propanol and indoline (0.357 g, 3 mmol) were mixed in a sealed tube, and heated at 120 °C for 12 h. Upon full consumption of the starting pyrrolopyrimidine **1a** (monitored by LC/MS), the reaction mixture was cooled down to rt, and diluted with 40 mL of water. The crude product was collected by filtration and further purified by preparative HPLC to yield **3a** (0.201 g, 57%) as a light brown solid. ^{1}H (300 MHz; CD_3CN, 75 °C): δ 3.23 (t, 2H, $J = 8.2$ Hz), 3.34 (t, 2H, $J = 7.8$ Hz), 4.15 (t, 2H, $J = 8.2$ Hz), 4.71 (br t, 2H, $J = 7.7$ Hz), 6.78 (d, 1H, $J = 7.8$ Hz), 6.98 (t, 1H, $J = 7.4$ Hz), 7.28 (t, 1H, $J = 8.0$ Hz), 7.34–7.37 (m, 2H), 7.46–7.53 (m, 2H), 7.69 (s, 1H), 8.00 (d, 1H, $J = 8.0$ Hz), 8.78 (s, 1H); ^{13}C (75 MHz; $CDCl_3$): δ 28.3, 29.6, 54.7, 56.7, 107.6, 116.8, 118.7, 119.4, 123.6, 125.1, 125.6, 126.8, 127.7, 129.8, 133.8, 140.4, 142.2, 150.1, 155.2.4-Indoline-5-ethanolamine derivative **3d**: 5-Bromo-4-chloropyrrolo[2,3-*d*]pyrimidine **1a** (0.232 g, 1 mmol) in 20 mL of 2-propanol and ethanolamine (0.061 g, 1 mmol) were mixed in a sealed tube, and heated at 90 °C for 7 h. Upon full consumption of the starting pyrrolopyrimidine **1a** (monitored by LC/MS) the mixture was cooled down to rt and an excess of indoline (0.357 g, 3 mmol) was added. The reaction was heated at 120 °C for another 18 h. The reaction mixture was cooled down to rt, concentrated, and purified by preparative HPLC to yield **3d** (0.154 g, 51%) as a brown viscous oil. ^{1}H (300 MHz; CD_3OD): δ 3.18 (t, 2H, $J = 7.9$ Hz), 3.62–3.68 (m, 2H), 3.73–3.78 (m, 2H), 3.81 (br m, 2H), 6.44 (d, 1H, $J = 7.4$ Hz), 6.73 (t, 1H, $J = 7.4$ Hz), 6.96 (t, 1H, $J = 7.4$ Hz), 7.18 (d, 1H, $J = 7.3$ Hz), 7.32 (s, 1H), 8.22 (s, 1H); ^{13}C (75 MHz; CD_3OD): δ 31.6, 45.1, 54.1, 61.3, 108.5, 117.8, 119.5, 125.6, 126.7, 129.7, 133.8, 142.2, 150.1, 155.2.
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