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An unexpected cyclization discovered during the synthesis of 8-substituted purines from a 4,5-diaminopyrimidine

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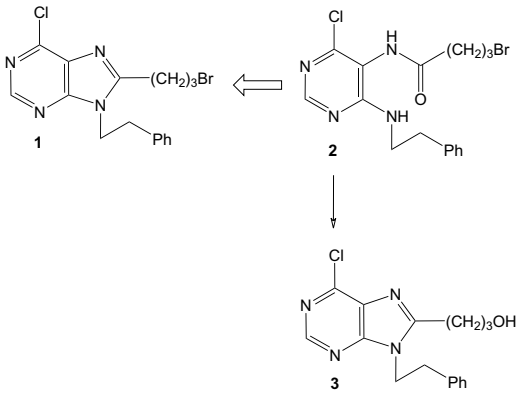
Abstract

Attempted conversion of 4-chloro-5-(*N*-4-bromobutanoyl)amino-6-phenethylaminopyrimidine (**2**) to 6-chloro-8-[1-(3-bromo)propyl]-9-phenethylpurine (**1**) under standard cyclization conditions did not give the targeted product. Instead, an unexpected cyclization occurred to give 6-chloro-5-[1-(3-hydroxy)propyl]-9-phenethylpurine (**3**), which can be viewed as a hydrolysis product of the resulting halide. The cyclization reaction was optimized and compound **3** was prepared in excellent yield. A mechanism involving transient generation of a spiro-tetrahydrofuran is also proposed.

Inhibitors of fructose 1,6-bisphosphatase (FBPase) represent a new class of potential drug candidates for the treatment of type 2 diabetes.[1] Despite efforts dating back over two decades, no suitable drug candidates were identified until recently when our structure-guided drug design approach successfully predicted that critical AMP-binding interactions could be achieved by a phosphonate group linked to the 8-position of the purine base via a 3-atom linker.[2] In early work to test this concept, we attempted to prepare 8-(γ-bromoalkyl)-purines with the expectation that the desired phosphonate analogs could be synthesized via an Arbuzov reaction. Since intramolecular cyclization of 5-(*N*-acyl)amino-6-aminopyrimidines is often used to prepare various 8-substituted purines,[3] we chose an analogous approach to prepare our required adenine analogs (Scheme 1). Surprisingly, attempted cyclization of 5-(*N*-4-bromobutanoyl)aminopyrimidine **2** under standard conditions did not give the desired 8-[(3-bromo)propyl]purine **1**, but rather gave the corresponding 8-[(3-hydroxy)propyl]purine **3** (Scheme 1). Herein, we describe the optimization of this cyclization reaction and propose a potential reaction mechanism.



Scheme 1.

Pyrimidine **2** was readily prepared in two steps. Substitution of 5-amino-4,6-dichloropyrimidine with phenethylamine (Et_3N, *n*-BuOH, 100 °C, 12 h, 95%) gave 5-amino-6-chloro-4-phenethylaminopyrimidine, which was subsequently acylated with 4-bromobutanoyl chloride (pyridine, CH_2Cl_2, 25 °C, 16 h, 93%) to give **2**. Acyl pyrimidines have been cyclized to purines under basic reaction conditions such as liquid ammonia in methanol[4] and aqueous sodium hydroxide[5] but these types of reaction conditions were deemed not suitable for compound **2** due

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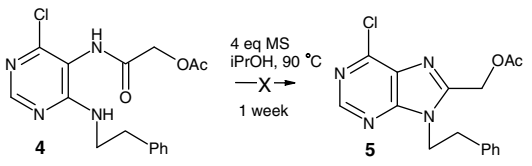
to the presence of a reactive primary bromide group. Reaction conditions such as aqueous sulfuric acid,[6] polyphosphoric acid,[7] phosphorus oxychloride,[8] and *p*-toluenesulfonic acid[9] have also been reported for the conversion of acyl pyrimidines to purines. Thus, compound **2** was subjected to these acidic reaction conditions, but no desired product was detected; only decomposition of the starting material **2** was observed. Acyl 1,2-phenylenediamines are often converted into benzimidazoles under various intramolecular cyclization reaction conditions, and these reactions were also explored for conversion of pyrimidine **2** to purine **1**. However, treatment of **2** with either phosphorus oxychloride in DMF[10] or neat phosphorus oxychloride in the presence of lutidine did not give desired product **1**. Subsequent treatment of **2** with lutidine hydrogen chloride in *N*,*N*-dimethylacetamide (DMAc) at 140 °C[11] surprisingly gave a new purine derivative, which was identified as compound **3** (Table 1, entry 1). Addition of 4 Å molecular sieves resulted in doubling of the yield (entries 2 and 3). To study the dehydration effect of molecular sieves, magnesium sulfate was used in place of molecular sieves; this change resulted in a lower yield of **3** (35%; entry 4). It was subsequently discovered that a similar yield was obtained in the absence of magnesium sulfate (entry 5). These results suggest that the function of the molecular sieves is not simply to promote dehydration, but may also involve scavenging of HBr.[12] Further optimization of this reaction with regard to solvent and temperature resulted in excellent conversion of **2** to **3** (Table 1, entries 6–8).[13]

Table 1
Formation of purine **3** via the cyclization of pyrimidine **2**

Entry	Additives	Conditions[a]	Yield (%)
1	Lutidine–HCl (1.2 equiv)	DMAc, 140 °C, 24 h	20[b]
2	Lutidine–HCl (1.2 equiv)	DMAc, 140 °C, 24 h[c]	43[b]
3	Lutidine–HCl (1.2 equiv)	DMAc, 140 °C, 24 h[d]	50
4	$MgSO_4$ (10 equiv)	*n*-BuOH, 120 °C, 15 h	35
5	None	*n*-BuOH, 120 °C, 15 h	30[b]
6	MS (10 equiv)	*n*-BuOH, 120 °C, 15 h	66
7	MS (4 equiv)	*n*-BuOH, 120 °C, 16 h	76
8	MS (4 equiv)	*i*-PrOH, 90 °C, 92 h	92

[a] The reaction was conducted under nitrogen atmosphere.
[b] Some unreacted **2** was recovered.
[c] Five equiv (based on weight) of 4 Å molecular sieves (MS) was added.
[d] Ten equiv of MS was added.

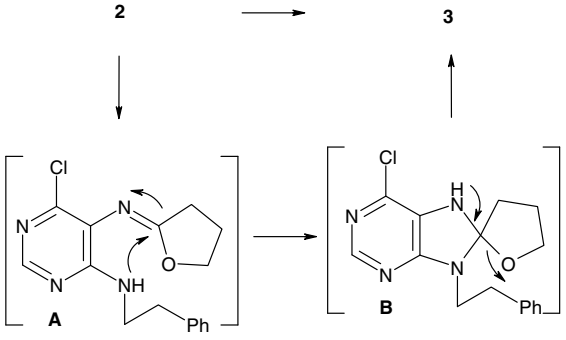
Plausible reaction pathways can be envisioned to explain the conversion of **2** to **3**. Cyclization of **2** to the corresponding purine followed by the hydrolysis of the ω-bromide to the ω-hydroxyl is one viable route. However, cyclization followed by hydrolysis seems to be unlikely given the current anhydrous reaction conditions.



(1)

Another observation seems to rule out direct purine ring formation when 4-chloro-5-(*N*-acetoxyacetyl)amino-6-phenethylaminopyrimidine (**4**) was subjected to the current reaction conditions, and even after one week no cyclization was observed; only starting material was recovered (Eq. 1).

An alternative mechanism is proposed (Scheme 2), in which intramolecular displacement of the bromide by the amide oxygen gives intermediate **A**; this is followed by intramolecular addition of the neighboring amino group to the cyclic imidate, affording spiro-tetrahydrofuran **B**, which spontaneously ring-opens to give compound **3**.



Scheme 2.

Our result of Eq. 1 is consistent with this proposed mechanism since compound **4** cannot undergo the cyclic imidate formation as compound **2**. Other existing reports also provide support to this proposed mechanism. For example, Fishwick and co-workers reported the conversion of bromoalkylacyl amines to cyclic imidates (similar to **A**)[14] and these cyclic imidates can undergo cyclization reactions.[15] Upon treatment of **2** with silver tetrafluoroborate under Fishwick's conditions ($AgBF_4$, TEA, acetone), **3** was indeed isolated (15% yield, not optimized) along with two other products. Analysis by ^1H NMR and mass spectroscopy indicated that the two new products were the *Z*- and *E*-isomer of **A**,[16] providing strong support for the proposed pathway.

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13. *General procedure*: A solution of **2** (1.02 g, 2.56 mmol) in anhydrous 2-propanol (50 mL) was treated with powder 4 Å molecular sieves (4.5 g), and the resulting mixture was heated to reflux under nitrogen for 92 h. The cooled reaction mixture was filtered through a Celite pad (washed with EtOAc, 3 × 20 mL), and the filtrate was evaporated to give a yellow solid that was purified by flash chromatography (SiO_2, 3 × 17 cm, 60% EtOAc–hexane) to give **3** as a white solid. Mp 96–97 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.68 (1H, s), 7.25–7.05 (5H, m), 5.58 (2H, t, $J = 7.2$ Hz), 4.48 (1H, t, $J = 7.2$ Hz, D_2O exchangeable), 3.48–3.33 (2H, m), 3.11 (2H, t, $J = 7.2$ Hz), 2.72 (2H, t, $J = 7.2$ Hz), 1.86 (2H, p, $J = 7.2$ Hz); UV (MeOH) λ_{max} 270 (1.43×10^{-3}); HRMS calcd for $C_{16}H_{17}N_4OCl$: 316.7900, found, 316.7900. Anal. Calcd for $C_{16}H_{17}N_4OCl$: C, 60.66; H, 5.41; N, 17.69. Found: C, 60.38; H, 5.17; N, 17.69.
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16. Products were isolated via preparative TLC (SiO_2, 50% EtOAc–hexane). **A** (*Z*-isomer, 12% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.18 (1H, s), 7.34–7.19 (5H, m), 5.21 (1H, br peak), 4.37 (2H, m), 3.72 (2H, m), 2.91 (2H, t, $J = 7$ Hz), 2.76 (2H, t, $J = 8$ Hz), 2.21 (2H, m); MS: 317.3 and 319.3 (M+1). **A** (*E*-isomer, 2% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.30 (1H, s), 7.36–7.19 (5H, m), 6.25 (1H, br peak), 4.47 (2H, t, $J = 7$ Hz), 3.78–3.63 (4H, m), 2.89 (2H, t, $J = 7$ Hz), 2.48 (2H, m), 2.01 (2H, m); MS: 317.3 and 319.3 (M+1).