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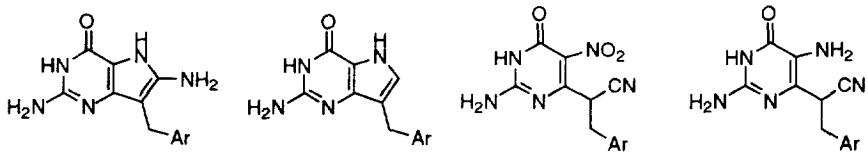
Synthesis of Pyrrolo[3,2-d]pyrimidines (9-Deazaguanines) by Reductive Cyclodeamination Reactions

Arthur J. Elliott,* Pravin L. Kotian, John A. Montgomery and David A. Walsh
BioCryst Pharmaceuticals, Inc., 2190 Parkway Lake Drive, Birmingham, AL 35244

Abstract: An efficient synthesis of 9-deazaguanines by reductive cyclodeamination of 5-nitro-6-cyanomethylpyrimidine derivatives under acidic conditions is described.

Purine nucleoside phosphorylase (PNP) is a salvage enzyme important to the T-cell-mediated part of the immune system and, as such, is an important therapeutic target. The synthesis and PNP inhibitory activity of a series of 7-arylmethyl-2,6-diamino-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-ones (9-deazaguanines) **1** have been disclosed, and the 7-(3-thienyl) derivative **1c** was reported to be under clinical development.[1] The synthesis of **1c** and related compounds was achieved by the reduction of **3c** using sodium dithionite followed by acid catalyzed cyclization of the amino compound **4c**. There is a report in a patent[2] indicating that the reduction of **3** could be done catalytically in one step to give either **1** or the *des*-amino compounds **2**, although no experimental conditions were disclosed. A later report[3] also indicated that, under a variety of conditions, the reduction of **3c** gave mixtures of **1c** and **2c** along with other products which were difficult to separate by column chromatography.



1 **2** **3** **4**

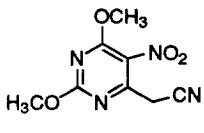
Ar= **a**) Phenyl; **b**) 3-Furanyl; **c**) 3-Thienyl; **d**) 3-Pyridinyl

Our group, using structure-based drug design, has shown that the 6-amino group in **1** is detrimental to PNP binding,[4-6] and the *des*-amino compound, peldesine (**2d**), is in advanced clinical trials for the treatment of T-cell cancers and psoriasis. Therefore, we were interested in a high yield synthesis of the more potent *des*-amino compounds **2** by this reductive deamination reaction. There appears to be precedence for the reaction in the catalytic cyclodeamination of 2-nitrobenzyl cyanides to form indoles.[7-9] Raney Ni catalysis is usually successful at ambient temperatures while Pd catalysts require elevated temperatures. The exact nature of the mechanism for the loss of NH_3 is unclear, although it has been shown[8] that aminoindoles cannot be intermediates since there is no loss of NH_3 from such compounds under the reaction conditions.

The method was also adapted to the synthesis of the pyrrolo[3,2-d]pyrimidine ring system[10] when **5** was reductively cyclized to **6** in 47% yield using 10% Pd/C at 70 °C. Raney Ni gave a somewhat lower yield (27%) when used at room temperature. Herein we report the results of our studies on the reductive cyclization of compounds **3** and the conditions for obtaining compounds **2** in high yields under mild conditions.

Compounds **3a-d**[1] were hydrogenated using 10% Pd/C in EtOH for 2-24 h at room temperature

to give good yields of the uncyclized **4a-d** which, on treatment with 6N HCl, underwent a facile cyclization to the 6-amino compounds **1a-d**.[1] Since a trace of the desired **2a** was detected in the reduction of **3a**, the reaction was attempted at elevated temperature. Reduction of **3a** in EtOH at 40 °C for 24 h followed by acidification with ethereal HCl gave a 19% yield of **2a** along with **1a** but, at 70 °C, only a complex mixture was obtained. It was subsequently found that compounds **3** were unstable in protic solvents at elevated temperature giving, in refluxing EtOH for example, numerous decomposition products and the evolution of NH_3. Since **3a** appeared to be stable in refluxing EtOAc, this solvent was used in a hydrogenation at 70 °C giving again the uncyclized **4a** along with some **1a**. No **2a** could be detected.



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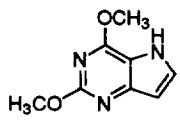

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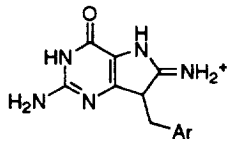

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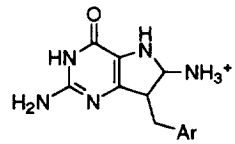

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Surprisingly, when the reduction of **3a** was attempted under acidic conditions rather than adding the acid after the reaction was concluded, the desired product **2a** was obtained in 71% isolated yield and no **1a** could be detected. Similar treatment of **3b** and **3d** gave **2b** (82%) and **2d** (60%) respectively. The reduction of **3c** under these conditions gave only **1c** with no evidence for the formation of any deaminated product **2c**. When Raney Ni was employed as the hydrogenation catalyst for **3c**, the presence of **2c** was detected in the crude reaction mixture but extensive decomposition products prevented it from being obtained in a sufficiently pure state for characterization.

We believe that this cyclodeamination reaction proceeds through the initially formed **4** followed by fast cyclization in acid to the protonated imine **7**. Rapid hydrogenation of **7** gives **8** which can aromatize to **2** by acid catalyzed elimination of NH_3. Since we have observed that the intramolecular cyclization of **4** to **1** is fast, it is unlikely that **4** will exist for a sufficient time to allow partial reduction of the nitrile prior to cyclization to **8**. In the case of **3c**, the Pd catalyst is probably poisoned sufficiently by the sulfur containing thiophene ring so that the reduction of the protonated imine cannot compete with the 1,3-proton shift in **7** to give **1c**.

General procedure: The nitro compound **3** (10 mmol), 10% Pd/C (0.5 g), 6N HCl (3 mL) and MeOH (200 mL) are shaken together under *ca* 50 psig H_2 pressure for 1 h. The catalyst is removed by filtration and the solvent is evaporated *in vacuo*. The residue is dissolved in 10% NaOH (100 mL), the solution is filtered and the filtrate is acidified with acetic acid. The product is collected by filtration, washed with water and dried *in vacuo*.

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