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A Short, Facile Synthesis of 2-Amino-1,5-dihydro-4H-pyrrolo[3,2-*d*]-pyrimidin-4-one (9-Deazaguanine)

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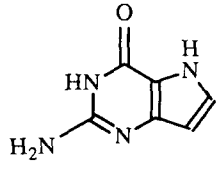
Abstract: 9-Deazaguanine has been synthesized in four steps in an overall isolated yield of 18% from ethyl (ethoxymethylene)cyanoacetate and diethyl aminomalonate.

We became interested in the synthesis of 2-amino-1,5-dihydro-4H-pyrrolo[3,2-*d*]pyrimidin-4-one (9-deazaguanine, **1**) for use as a possible intermediate in the large-scale preparation of peldesine **2**,[1] a potent inhibitor of purine nucleoside phosphorylase (PNP, EC 2.4.2.1) currently in Phase III clinical trials.



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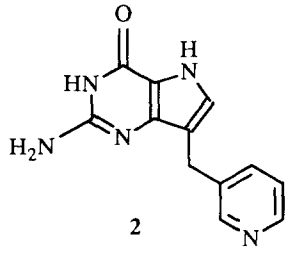

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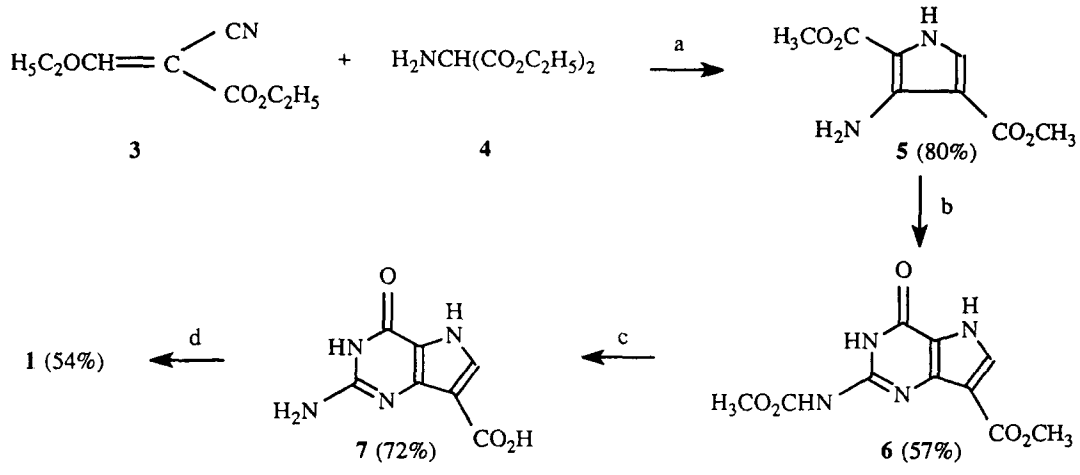
There have been three previously reported syntheses of **1**. The method of Imai[2] requires 10 steps and proceeds in an overall yield of less than 1%; the procedure reported by Kline[3] was difficult to reproduce in our hands; the recent synthesis described by Taylor[4] (who also could not reproduce Kline's method) requires seven steps from a commercially available starting material, and requires a chromatographic separation of isomers of a protected intermediate. We describe herein our discovery of a novel, economical four-step synthesis of **1** from readily available starting materials.

An approach based on a modification of the Knorr pyrrole synthesis using the commercially available masked aldehyde, ethyl (ethoxymethylene)cyanoacetate **3**, and diethyl aminomalonate **4** reacted at reflux with sodium methoxide in methanol for three hours gave an 80% yield of **5** as pale-yellow prisms (mp 172 - 174 °C, toluene). Enamine formation of **3** with **4**, ring formation, ester hydrolysis, decarboxylation, and ester transfer from ethyl to methyl all occur in one pot.

In order to convert the amino substituent in **5** to a guanidino substituent for cyclization to give the pyrrolo[3,2-*d*]pyrimidin-4-one ring system, **5** was reacted with the readily available 1,3-bis(methoxycarbonyl)-S-methylisothiourea[5] in acetic acid at 100 °C overnight. Under the reaction conditions, the protected guanidino intermediate cyclized to give **6** (white powder, mp > 300 °C) directly in 57% yield. This reaction sequence is reminiscent of a method published by Kim[6] to convert unreactive amines to guanidino derivatives. Hydrolysis of **6** with 10% sodium methoxide in methanol gave a 72% yield of **7** isolated as the hydrochloride (pale-brown solid, mp > 300 °C). Acid **7** was decarboxylated in polyphosphoric acid (PPA) at 180 °C for 2 h. Target **1** was



Reagents: a) 1. sodium methoxide, reflux, 3 h; 2. H_2O, AcOH; b) 1,3-bis(methoxycarbonyl)-S-methylisothiourea, AcOH, 100 °C, 14 h; c) 1. 10% sodium methoxide, 70 °C, 14 h; 2. AcOH; 3. 6 N HCl; d) 1. PPA, 180 °C, 2 h; 2. NH_4OH; 3. HCl.

obtained as tan needles (hydrochloride, mp > 300 °C) in 54% yield; the ^{1}H-NMR, mass spectrum, IR, UV and TLC (silica gel; 15% methanol in chloroform) were identical to an authentic sample of **1**[3].

In summary, a facile, four-step synthesis (overall isolated yield = 18%) of 9-deazaguanine **1** from economical and commercially available starting materials has been developed. Future reports will describe the conversions of intermediate **7** and target **1** to potent inhibitors of purine nucleoside phosphorylase.

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