

Communications

Synthesis of 9-Benzyl-6-aminopurines from 5-Amino-1-benzyl-4-cyanoimidazoles

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Received July 16, 2003

Key Words : Aminopurine, Cyanoimidazole, Formimidate, Formamidine, Imidate

Purine, purine nucleosides and their analogues have been extremely useful as anti-cancer agents.¹⁻⁴ Robines, in 1964, reviewed the anti-tumour activity of purine and purine nucleosides from a structure-activity stand-point.⁵ Subsequently, several reviews on this subject have been published.⁶⁻⁹ The chemotherapeutic uses of purines and purine analogues have prompted tremendous efforts towards their synthesis, both in academia and in the pharmaceutical industry.

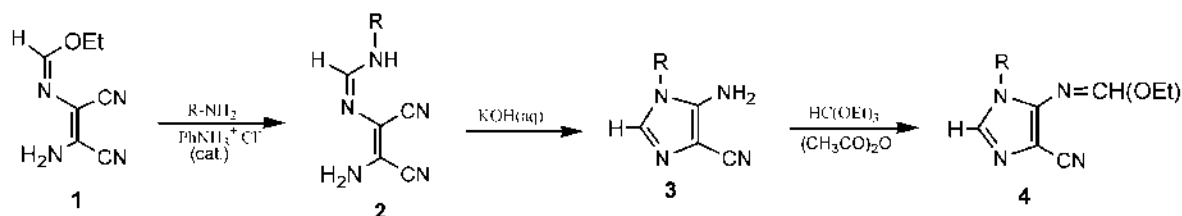
As the purine ring system is a fusion of two aromatic heterocycles, pyrimidine and imidazole, a logical starting point for ring synthesis is an appropriately substituted pyrimidine or imidazole from which the second ring can be constructed by a cyclization process.^{10,11}

5-amino-4-cyanoimidazoles are useful intermediates for purine synthesis.¹² There are few reports of 9-aminopurine derivatives and most of the routes described are from 5-

amino-4-hydrazinopyrimidine precursors, substituted in the 2- and 6-position.¹³⁻¹⁶

We therefore decided to investigate the reactions of 9-benzyl-6-aminopurines **5a-b** were prepared *via* a multistep synthesis from ethyl (*Z*)-N-(2-amino-1,2-dicyanovinyl)-formimidate **1**, by treatment with a benzyl-amine in a 1 : 1 molar ratio in ethanol in the presence of a catalytic amount of aniline hydrochloride to give the corresponding formamidine.^{17,18} (Scheme 1). Cyclisation of the formamidines in the presence of a strong base, aqueous KOH solution, provided the corresponding 5-amino-1-benzyl-4-cyanoimidazoles **3a-b**,^{19,20} which are readily converted to 1-amino-9-benzyl-6-aminopurines **5a-b** by treatment with HC(OEt)₃ and Ac₂O followed by reaction with ammonia.

The initial step involved conversion of the 5-amino-4-cyanoimidazoles **3**^{17,18} to the corresponding ethoxyimidates **4**. These were achieved by a modification of the procedure



a : R=2-ClC₆H₄CH₂-

b : R=3,4-(CH₃O)₂C₆H₃CH₂-

Scheme 1. Reagents and conditions: i. HC(OEt)₃, dioxane, heat; ii. RNH₂, PhNH₃⁺Cl⁻, room temp., 3-4 h; iii. 1 mol dm⁻³ KOH, aq, room temp; iv. HC(OEt)₃, (CH₃CO)₂O, heat.

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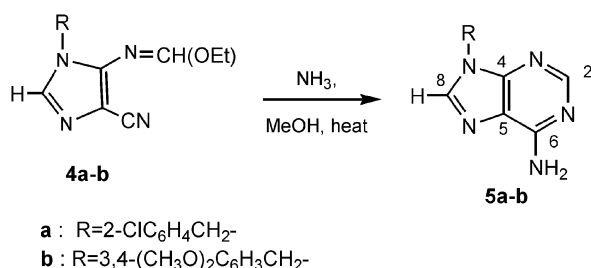
used by Taylor and loeffler²¹ and also by Ried and Laoutidis.²² These were prepared by heating the appropriate cyanoamine with triethyl orthoformate and acetic anhydride on a water-bath at 60-80 °C for several hours.

Once TLC confirmed complete consumption of the starting material, the result in solution were evaporated under vacuum to give a residue that upon treatment with a mixture of dry diethyl ether and hexane (1 : 1), gave the required imidates **4a** and **4b** as a solid in 81-87% respectively yield. The products were recrystallised from a mixture of dry diethyl ether and hexane (1 : 1).

In the infrared spectra the presence of the cyano and C=N stretching vibrations were observed in the range of 2210-2220 and 1630-1650 cm⁻¹ respectively.

The ¹H nmr spectra of the isolated ethoxyimidates **4a-b** showed the presence of the H-2 proton of the imidazole ring in the range of δ 7.26-8.28 ppm. The H-7 proton appeared in the range δ 8.28-8.66 ppm. The CH₂ and CH₃ of the ethoxy group had clear quartet and triplet patterns as expected in the regions of δ 1.32-1.55 and δ 4.31-4.5 ppm respectively. The other bands were in agreement with expected structures. The ¹³C nmr spectra of the imidazoles had the expected number of bands with the C-2 carbon of the imidazole ring in the region of δ 135.4-140.9, the C-7 carbon at δ 159.9-165.5 and the C-4 carbon within the region of δ 98.9-103.0 ppm.

The imidates **4** were converted to the corresponding 9-benzyl-6-aminopurines **5** by treatment with ammonia in the minimum amount of methanol. The reaction were carried out under an argon atmosphere at room temperature. During the first 20 minutes a white precipitate started to form. After 2-3 hours TLC showed no starting material, and filtration of the reaction mixture gave the purines as a powder in 67-83% yield. The purines **5a-b** were fully characterized by micro-analysis and spectroscopic methods.



The elemental analysis and mass spectra of isolated 9-benzyl-6-aminopurines **5a-b** were satisfactory. In the infrared spectra, the NH stretching vibrations were observed as 2-3 bands in the range of 3300-3150 and C=N absorption band in the range 1650-1660 cm⁻¹. The NH₂ protons were observed in the range δ 5.70-5.93 ppm, the proton at position H-2 of the purines system appeared in the regions of δ 8.12-8.26 ppm and the proton at position H-8 were seen as a singlet in the range of δ 8.08-8.22 ppm. The ¹³C NMR spectra of the compounds **5a-b** had the expected number of peaks. The C-8 carbon of the imidazoles ring appeared in the region of 143.5-144.0 ppm. The carbon at positions C-2 and C-6 of the purines system appeared at δ 152.0-152.6 and 158.2-158.4 ppm respectively.

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