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Communications

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

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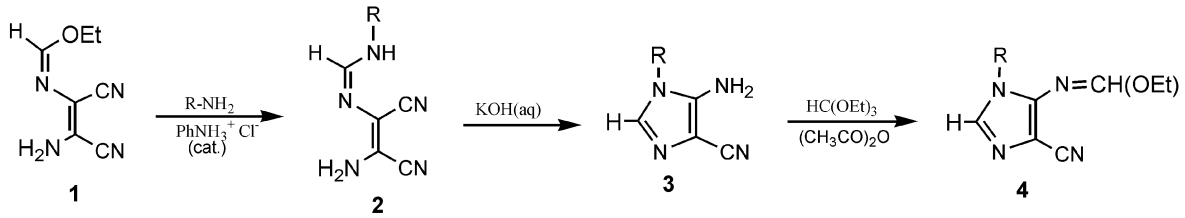
Purine, purine nucleosides and their analogues have been extremely useful as anti-cancer agents.[1-4] Robines, in 1964, reviewed the anti-tumour activity of purine and purine nucleosides from a structure-activity stand-point.[5] Subsequently, several reviews on this subject have been published.[6-9] 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 heterocyclces, 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 Ac_2O 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-$ClC_6H_4CH_2$-
b : R=3,4-$(CH_3O)_2C_6H_3CH_2$-

Scheme 1. Reagents and conditions; i, $HC(OEt)_3$, dioxane, heat; ii, RNH_2, $PhNH_3^+Cl^-$, room temp., 3-4 h; iii, 1mol dm^{-3} KOH, aq. room temp; iv, $HC(OEt)_3$, $(CH_3CO)_2O$, heat.

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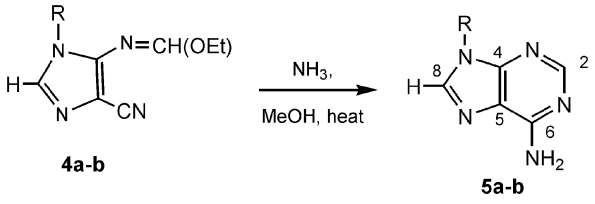
used by Taylor and loeffler[21] and also by Ried and Laoutidis.[22] These were prepared by heating the appropriate cyanoamine with triethyl orthoformate and acetic anhydride on a water-bath at 60-80 °C for several hours.

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 CH_2 and CH_3 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 ^{13}C 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 staring 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.



4a-b **5a-b**

a : R=2-$ClC_6H_4CH_2$-
b : R=3,4-$(CH_3O)_2C_6H_3CH_2$-

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 NH_2 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 ^{13}C 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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