Tetrahedron Letters, Vol. 34, No. 34, pp. 5503-5506, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of [1α,2β,3α]-5-amino-[2,3-bis(benzoyloxymethyl)cyclobutyl] imidazoles : important precursors to new anti-viral purine nucleosides.

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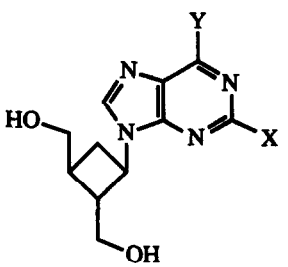
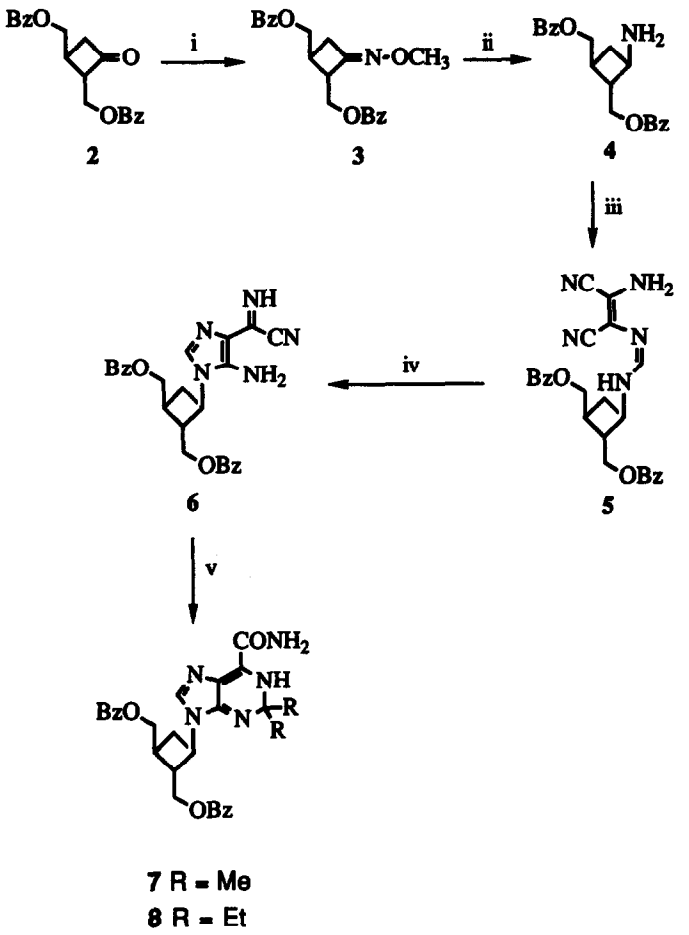
Abstract : Two new carbocyclic imidazoles, **6** and **9** have been synthesised *via* a simple method from the corresponding formamidine **5** ; these intermediates have been shown to be useful for the synthesis of new cyclobutyl nucleoside analogues including the known bis-benzoyl cyclobut-A **11**.

Recently, there has been much interest in the potent anti-viral agents cyclobut-A **1a** and cyclobut-G **1b**, carbocyclic analogues of the natural Oxetanocin[1], and several syntheses have been reported.[2,3] Specific attention has been given to these compounds as they exhibit high activity against HIV infections.[4] However, all of these syntheses rely upon the coupling of a pre-formed purine ring to the carbocyclic moiety and this usually takes place only in moderate yield under forcing conditions. For some time we have been interested in the chemistry of N-substituted (2-amino-1,2-dicyanovinyl) formamidines as useful precursors to purine, imidazole and triazepine heterocycles[5] and we recognised that this approach could be used for a flexible synthesis of various purine derivatives of **1a**. Herein, we report the synthesis of two new imidazole intermediates, **6** and **9** and their use in the formation of new carbocyclic purine nucleosides.



1a; X = H, Y = NH_2
1b; X = NH_2, Y = OH

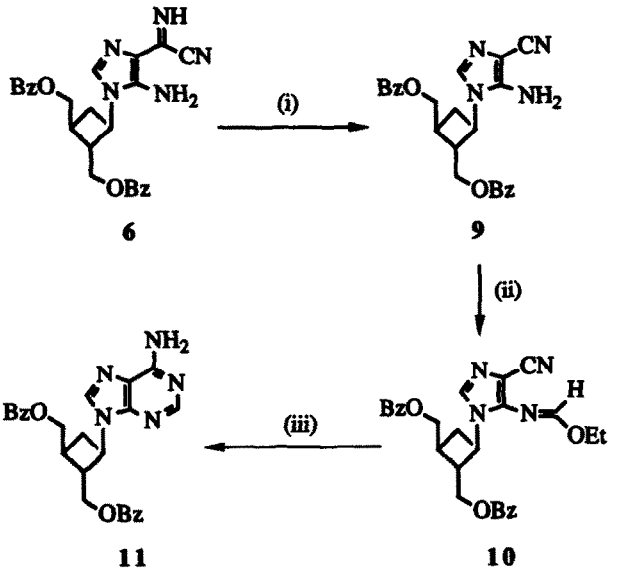
Racemic cyclobutanone **2**[2] was treated with methoxylamine hydrochloride in pyridine to give the methyl oxime **3** as a mixture of geometrical isomers in 91% yield. Reduction of the oxime with sodium



Scheme 1 Reagents and conditions: i, Methoxylamine hydrochloride, pyridine, r.t., 91% ; ii, sodium trifluoroacetoxy borohydride, THF, r.t., 43% ; iii, ethyl (Z)-[2-amino-1,2-dicyanovinyl]formamidine, EtOAc, Cat. $PhNH_3^+Cl^-$, r.t., 80% ; iv, 0.1 equiv. DBU, $CHCl_3$, 0°C, 100% ; v, excess RCOR, r.t., R = Me, 92% ; R = Et, 88%.

trifluoroacetoxy borohydride[6] furnished the amine **4** in 43% yield after chromatography. Reaction of amine **4** with ethyl-(Z)-[2-amino-1,2-dicyanovinyl]formimidate[5c] in the presence of a catalytic amount of anilinium hydrochloride in ethyl acetate gave the amidine **5** as a foam in 80% yield.[7] Cyclisation of **5** with a catalytic amount of DBU in chloroform at 0°C gave the cyanoformimidoyl imidazole **6** in quantitative yield. This

compound is an important intermediate for the synthesis of a variety of purines.[5a-e] For example, **6** reacts with acetone to give the orange dihydropurine **7** in 92% yield and in a similar fashion treatment of **6** with pentan-3-one leads to **8** (88%). Treatment of **6** with an excess of DBU affords the amino-nitrile **9** (58 %). This type of intermediate also represents an important purine precursor as by standard methodology [8] it can be transformed into a plethora of purine analogues. This is exemplified by a simple synthesis of the racemic form of the known bis-benzoyl derivative of cyclobut-A **11** [9] (Scheme 2). Reaction of **9** with triethylorthoformate gave the crude imidate **10**, which was cyclised by treatment with ammonia in anhydrous ethanol to give **11** in 65% overall yield from **9**.



Scheme 2 Reagents and conditions: i, 2 equiv. DBU, $CHCl_3$, r.t., 20h, 58% ; ii, $CH(OEt)_3$, 70-80°C ; iii, NH_3, EtOH, r.t., 65%.

Although the syntheses presented herein were performed with racemic materials, our methodology clearly demonstrates its use for easy access to derivatives of the potent anti-viral agents **1a** and **1b** for purposes of biological testing.

Thanks are due to the SERC for the financial support for this investigation.

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7. All new compounds gave satisfactory spectroscopic data. Representative data for selected compounds; For **5**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 1.86 (m, 1H), 2.39-2.60 (m, 3H), 4.40-4.55 (m, 5H), 6.12 (br.s, 2H), 7.55-7.69 (m, 5H), 7.70-8.00 (m, 2H), 7.98-8.14 (m, 4H), 8.24 (m, 1H). For **6**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 2.29 (m, 1H), 2.57 (m, 1H), 2.77 (m, 1H), 3.22 (m, 1H), 4.40-4.70 (m, 5H), 6.85 (br.s, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 2H), 7.67-7.78 (m, 3H), 7.92 (d, J = 7.5Hz, 2H), 8.09 (d, J = 7.5Hz, 2H), 11.0 (br.s, 1H). For **7**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 1.37 (s, 3H), 1.42 (s, 3H), 2.30-2.60 (m, 3H), 3.21 (m, 1H), 4.38-4.62 (m, 5H), 6.29 (br. s, 1H), 7.48-7.80 (m, 7H), 7.85-8.15 (m, 5H), 8.28 (br. s, 1H) ppm. For **8**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 0.81 (t, J = 7Hz, 3H), 0.88 (t, J = 7Hz, 3H), 1.48-1.76 (m, 4H), 2.40-2.50 (m, 3H), 3.28 (m, 2H), 4.38-4.61 (m, 5H), 5.88 (br.s, 1H), 7.48-8.11 (m, 12H), 8.25 (br.s, 1H). For **9**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 2.18 (m, 1H), 2.55 (m, 1H), 2.74 (m, 1H), 3.20 (m, 1H), 4.40-4.70 (m, 5H), 6.32 (br.s, 2H), 7.60 (m, 4H), 7.74 (m, 3H), 7.95 (d, J = 7.7Hz, 2H), 8.07 (d, J = 7.5 Hz, 2H).

8. See for example: Hurst D. J., "Introduction to the chemistry and biochemistry of pyrimidines, purines and pteridines", Wiley, New York, 1980.

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(Received in UK 24 June 1993; accepted 1 July 1993)