Tetrahedron Letters,Vol.28,No.19,pp 2151-2154,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL AND EFFICIENT SYNTHESIS OF ISOGUANOSINE[1]

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Abstract : Isoguanosine (4b) was synthesized by a one-pot reaction involving a condensation of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (1b) with benzoyl isothiocyanate, treatment of the resulting thiourea derivative with DCC furnished 5-(N^1-benzoylcarbamoyl)amino-imidazole-4-carbonitrile (3b) which was then annulated with ethanolic ammonia to afford isoguanosine in a 68% yield from 1b.

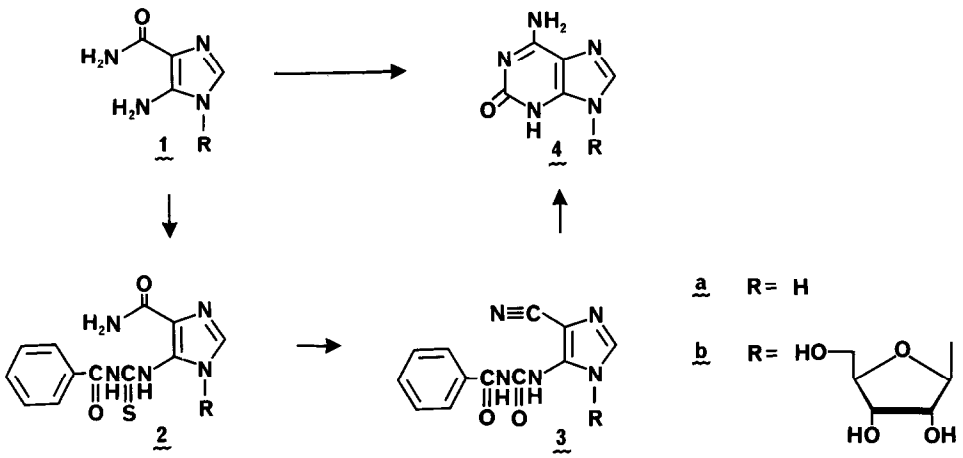
Isoguanosine (crotonoside, 2-hydroxyadenosine), a naturally occurring nucleoside analogs of guanosine, was first isolated from Croton tiglium L.[2] and then from butterfly wings of Prioneris thestylis.[3] This compound has been reported to possess various biological activities such as incorporating into mammalian nucleic acids,[4] stimulating the accumulation of cyclic AMP in the brain,[5] inhibiting IMP : pyrophosphorylase[6] and glutamic acid dehydrogenase.[7] It is unlikely that a full evaluation of the biological activity of isoguanosine will be possible until it become more readily accessible.

A literature survey indicated that the synthesis of isoguanosine was achieved in a low yield, either from a 4,5-dicyanoimidazole[8] or from 2,6-diamino-9-β-(D-ribofuranosyl)purine by a selective deamination with nitric acid.[9] However, the latter process involved the undesirable heavy metal salts such as mercury and lead in the two steps. A photochemical preparation of isoguanosine from adenosine N^1-oxide[10] and from 2-iodoadenosine[11] has also been reported, but these procedures involved several steps and gave a low overall yield.

Recently, a new methodolgy for the preparation of guanosine and 1-methylisoguanosine by N,N'-dicyclohexylcarbodiimide-mediated cyclodesulfurative annulation reaction has been reported.[12-13] Our initial goal was the synthesis of isoguanosine from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide(AICA-ribose) under similar conditions those previously used to prepare 1-methyl-isoguanosine.[12] Although the preparation of isoguanosine from AICA-ribose has been reported by Yamazaki and co-workers,[14-15] we felt that the use of 1,3-dicyclohexylcarbodiimide-mediated cyclodesulfurative methodology will afford a milder and higher yielding alternate synthesis of isoguanosine, consequently, of isoguanosine-type analogs. We now report a new and practical procedure for synthesis of isoguanosine.

For our initial study of the proposed synthetic procedure, we chose to use the

heterocycle instead of the nucleoside. When 5-aminoimidazole-4-carboxamide was reacted benzoyl isothiocyanate, 5-(N^1-benzoylthiocarbamoyl)aminoimidazole-4-carboxamide (2a)[15] was obtained in good yield and then was treated with three equivalents of dicyclohexylcarbodiimide in DMF at room temperature for 24 h. The solvent was removed in vacuo (50°C) and the residues was washed with hot toluene to afford 3a in good yield. The IR spectrum of the product showed a strong absorption at 2221 cm^{-1} which supports the presence of a cyano group in the molecule. Therefore, on the basis of ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis data,[16] we confirmed the structure of 3a as 5-(N^1-benzoylcarbamoyl)aminoimidazole-4-carbonitrile. Compound 3a (0.85 g, 3.33 mmole) was then suspended in a mixture of ethanol (20 ml) and 33% aqueous ammonia (20 ml). The mixture turned out clean solution after 2 h and then gradually became suspended again. After 48 h, the ammonia was removed in vacuo at room temperature and the white solid was collected by filtration to give pure 4a (0.45 g). The solid was recrystallized from DMF and water affording 4a (0.41 g) in 81% yield from 3a. The structural assignment of 4a was based upon the UV, IR, ^{1}H-NMR, ^{13}C-NMR spectral data.[17]



Similarly, a solution of AICA-ribose (1b) (2.82 g, 11 mmole) and benzoyl isothiocyanate in DMF (20 ml) was stirred at room temperature for 3 h (AICA-ribose was totally converted to thioureido derivative 2b). To the resulting solution was added N,N'-dicyclohexylcarbodiimide (DCC) (4.5 g, 22 mmole) and the mixture was continuously to stir at room temperature for 24 h. The solvent was then removed in vacuo (50°) to oil residues. To this residues was added boiling toluene and decanted (50 ml x 4) (to remove excess of DCC and N,N'-dicyclohexylthiourea). The oil residues was then resolved in ethanol (30 ml). To the solution was added 33% aqueous ammonia and subsequently the mixture was stirred at room temperature for 12 h. The white precipitates was started to appear after 2 h. After the reaction was complete, the ammonia was removed in vacuo at room temperature. The white solid was isolated from the mixture by filtration to give 2.4 g of pure 4b (77% yield) from 1b. The solid was recrystallized from a mixture of ethanol and water (v/v, 1:1) to afford 4b (2.1 g, 68%). This synthetic compound was found to be isoguanosine based on a comparision of data for 4b[18] and the reported data.[10-11]

This mild and highly efficient method by means of N,N'-dicyclohexylcarbodiimide-mediated cyclodesulfurative annulation reaction is therefore ideally suited to the formation of isoguanosine-type nucleoside analogs from appropriate o-amino carboxamide precursor. The scope of this methodology is now under investigation.

Acknowledgement : This investigation was supported by a Grant NSC75-0412-B016-64 awarded by the National Science Council of the Republic of China.

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1. Melting points were obtained on a Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer, ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker Model AM-300 spectrometer from National Taiwan University, Taipei, or a Joel FX-100 spectrometer from National Taiwan Normal University, Taipei, using DMSO-d_6 as solvent and as internal standard. UV spectra were recorded on a Shimadzu UV-210A spectrophotometer. AICA hydrochloride and AICA-riboside were purchased from Sigma Chemical Co.. Elemental analysis was carried out in Cheng-Kong University, Tainan.

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16. Compound 3a : IR (KBr) : 3162, 2221, 1709, 1615, 1553, 1468, 1353, 1270, 1210, 700 cm^{-1} ^{1}H-NMR (100 MHz, DMSO-d_6) : δ 13.08 (br s, 1H, D_2O exchangeable), 11.28 (s, 1H, D_2O exchangeable), 10.98 (s, 1H, D_2O exchangeable), 8.00 (d, 1H, C_2-H), 7.5-7.76 (m, 5H, Ar-H).

^{13}C-NMR (100 MHz, DMSO-d_6) : δ 168.4, 150.2, 135.6, 133.1, 131.8, 128.4, 128.2, 113.7. mp > 300°C. Anal. Calcd. For $C_{12}H_9N_5O_2$ (255.2) : C, 56.46; H, 3.55; N, 27.44. Found : C, 56.21; H, 3.52; N, 27.27.

17. Compound 4a : mp > 360°C. UV λ_{max} nm (ε x 10^4) : (0.1N NaOH) 283 (8.0). IR (KBr) : 3051, 2785, 1828, 1698, 1666, 1524, 1450, 1398, 1236, 1179, 1119, 1028, 940, 852, 775 cm^{-1}.

18. Compound 4b : mp 240°C dec. [lit[10] : 237-241°C]. IR (KBr) : 3325, 2945, 1673, 1614, 1526, 1470, 1402, 1317, 1210, 1085, 1055, 866, 802, 774 cm^{-1}. UV λ_{max} nm (ε x 10^4) : (MeOH) 248 (0.8), 292 (1.0), [lit[11] : 248 (0.9), 292 (1.1)]. ^{1}H-NMR (300 MHz, DMSO-d_6) : δ 10.61 (br s, 1H, NH), 7.93 (s, 1H, C_8-H), 7.66 (br s, 2H, NH_2), 5.62 (d, 1H), 5.38 (d, 1H), 5.12 (d, 1H), 4.49 (q,1H), 4.06 (d, 1H), 3.90 (d, 1H), 3.60 (m, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6) : δ 155.72, 152.51, 138.02, 109.72, 87.73, 85.98, 73.09, 70.81, 61.72. FAB mass spectrum, m/e 284 (M+H). Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot \frac{1}{2}H_2O$ (292.2) : C, 41.10; H, 4.83; N, 23.96. Found : C, 41.12; H, 4.85; N, 23.98.

(Received in Japan 24 January 1987)