Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2191-2194, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00268-6

Transformations of L-Erythrulose: Synthesis of 2-Amino-4-[1'*R* (1',2'-*O*-isopropylidene)-1,2-dihydroxyethyl]-3-furancarbonitrile

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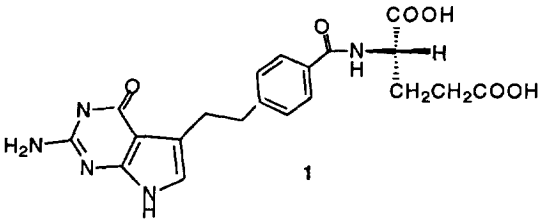
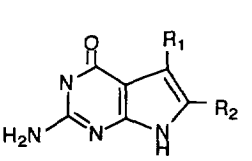
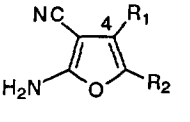
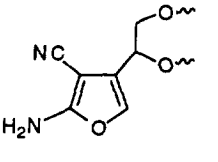
Abstract: The synthesis of 2-amino-4-[1'*R*(1',2'-*O*-isopropylidene)-1,2-dihydroxyethyl]-3-furancarbonitrile **3** in 75% yield from L-erythrulose is described.

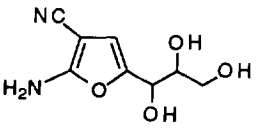
The structural motif pyrrolo[2,3-d]-pyrimidine **A** is present in a number of drugs of current pharmacological interest as folate antimetabolites, such as N-{4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-d]-pyrimidin-5-yl)ethyl]benzoyl}L-glutamic acid **1**.[1] These types of compounds function as potent inhibitors of thymidylate synthase (TS) and thus block de novo DNA biosynthesis.[2] The synthesis of compounds of type **A**, embodied in product **1**, has been recently[1] described using as key step the reaction of 2-amino-3-cyanofurans **B** with guanidine and several related amidines; this methodology is particularly well adapted to the presence of small alkyl groups at C-4. In another approach, products **A** have been prepared from α-hydroxyketones, primary amines and malononitrile *via* the corresponding 2-aminopyrrole-3-carbonitriles.[3]

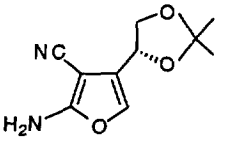












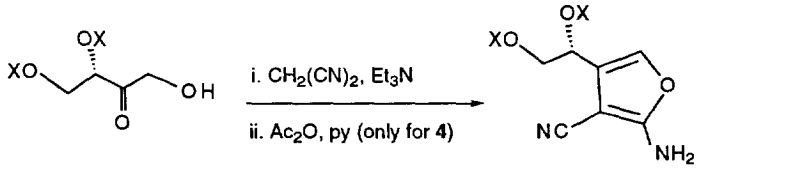
For years we have been interested in the synthesis of "chiral α or β-branched chain furan derivatives."[4] In this context and in view of the particular interest of 2-amino-3-cyanofurans **B** as useful synthetic intermediates

(see above),[5] we embarked on a project directed towards the synthesis of enantiomerically pure C-4 branched chain substituted furans of type **C**. The only related report on this subject has been published by Eger and coworkers.[6] They have described the synthesis of 2-amino-3-(1,2,3-trihydroxypropyl)-3-furancarbonitrile **2** in 25% yield by reacting D-ribose with malononitrile in the presence of zinc chloride. To our knowledge this same protocol, applied to chiral α-hydroxyketones, has not been reported.

In view of these precedents we designed a new approach to the unknown type of compounds **C**. These molecules could be important intermediates for the preparation of chiral analogues of compound **1**. In this paper we report the synthesis of **3** and **5**, as representative members of this type of compounds, in enantiomerically pure form.

The obvious starting material is L-erythrulose **4** (see Scheme). This compound is commercially available and a convenient, chiral C-4 building block for asymmetric synthesis.[7] In spite of the advantages and potential synthetic interest of this product, the chemistry of this material has remained almost unexploited. The present work is a part of our current work on the systematic transformation and manipulation of this chiral building block.[8]

In the standard conditions described by Gewald for the reaction of α-hydroxyketones with malononitrile,[9] L-erythrulose has afforded a complex reaction mixture, difficult to analyze and separate; fortunately, after acetylation of the crude and careful flash chromatography we could isolate compound **5** (Scheme) in a disappointing 12% overall yield from **4**.



4 X= H

6 X= -$C(CH_3)_2$-

5 X= $COCH_3$ (12 % yield from **4**)

3 X= -$C(CH_3)_2$- (75% yield from **6**)

Scheme

From these results it was clear that after the addition of malononitrile to the ketone, the subsequent heterocyclization was not regioselective. In order to solve this problem, we prepared the acetonide **6**[7] (Scheme) and submitted it to the standard experimental conditions. This condensation afforded the desired target **3** in good yield (see Scheme). This product showed analytical and spectroscopic values in full agreement with this structure. In fact, in the IR spectrum we could see the strong and diagnostic band at 2.220 cm^{-1} corresponding to α,β-unsaturated nitriles; in the ^1H NMR spectrum we observed H-5 at 6.76 ppm as a singlet, a broad singlet at 5.15 ppm (2 H, NH_2) and a characteristic ABX system for the three protons: 4.94 ppm (H-1'), 4.21 ppm (H-2A') and 3.86 ppm (H-2B').

In summary, we have described for the first time some C-4 branched chain 2-amino-3-furancarbonitriles in enantiomerically pure form. These compounds offer a rich functionality for further synthetic transformations.

Experimental

General Methods. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent. Optical rotations were determined with a Perkin-Elmer 257 instrument. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

General method for the reaction of malonitrile with L-erythrulose derivatives. The method used here is essentially the same as described by Gewald.[9] To a solution of the ketone **4**, as commercially obtained or **6**[7] in methanol (1.1 M), cooled at 0 °C, triethylamine (1 equiv) and malononitrile (1 equiv) were added. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was submitted to flash chromatography.

2-Amino-4-[(1'*R*)-1,2-diacetoxyethyl]-3-furancarbonitrile 5. This compound was obtained following the **General Method** starting from compound **4**, after flash chromatography eluting with hexane/ethyl acetate 50%, in 12% yield, as a solid: m.p. 58-61°C (dec.); $[\alpha]_D^{25}$ -45.9 (*c* 1.3, $CHCl_3$); IR ν_{max} (KBr) 35500-3.100, 3.430, 2.990, 2.220, 1.750, 1.650, 1.590, 1.450, 1.225, 1.050 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.05 (3 H, s, CH_3), 2.09 (3 H, s, CH_3), 4.25 (1 H, dd, *J* = 6.7 and 10.8 Hz, H-2A'), 4.38 (1 H, dd, *J* = 4.2 and 10.8 Hz, H-2B'), 5.28 (br s, 2 H, NH_2), 5.87 (dd, *J* = 6.7 and 4.2 Hz, H-1'), 6.74 (1 H, s, H-5); ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 170.56 and 169.92 (2xCH_3COO), 163.61 (C-2), 130.56 (C5), 121.73 (C4), 114.32 (CN), 67.83 (C3), 65.54 (C-1'), 64.24 (C-2'), 20.63 (2xCH_3COO). Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11 Found: C, 52.20.; H, 4.77; N, 10.89.

2-Amino-4-[1'*R*(1',2'-*O*-isopropylidene)-1,2-dihydroxyethyl]-3-furancarbonitrile 3. This compound was obtained following the **General Method** starting from compound **6**,[7] after flash chromatography eluting with 20% hexane/ethyl acetate, in 75% yield, as a viscous oil: $[\alpha]_D^{25}$ -8 (*c* 1.06, $CHCl_3$); IR ν_{max} (liq. film) 3.500-3.100, 3.440, 2.990, 2.220, 1.650, 1.590, 1.455, 1.375, 1.225, 1.160, 1.060, 930 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 1.41 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 3.86 (1 H, t, *J* = 8.0 Hz, H-2A'), 4.21 (1 H, dd, *J* = 6.2 and 8.0 Hz, H-2B'), 4.94 (1 H, ddd, *J* = 0.9, 6.2 and 8.0 Hz, H-1'), 5.15 (2 H, br s, NH_2), 6.76 (1H, s, H-5). Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46 . Found: C, 57.41; H, 5.64; N, 13.33.

Acknowledgements. JLM thanks EU (Human Capital and Mobility; Contract no. ERBCHRXCT 92-0027) for generous financial support.

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(*Received in UK* 20 *May* 1996)