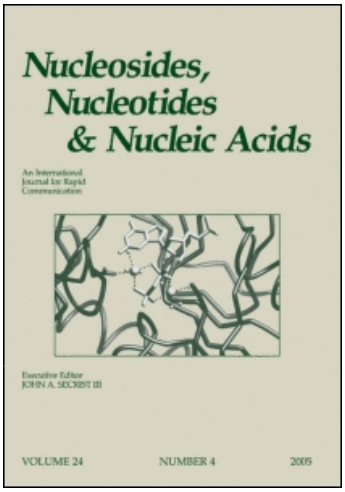

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THE PREPARATION AND UTILITY OF 5-β-D-RIBOFURANOSYL-(2H)-TETRAZOLE AS A KEY SYNTHON FOR C-NUCLEOSIDE CHEMISTRY

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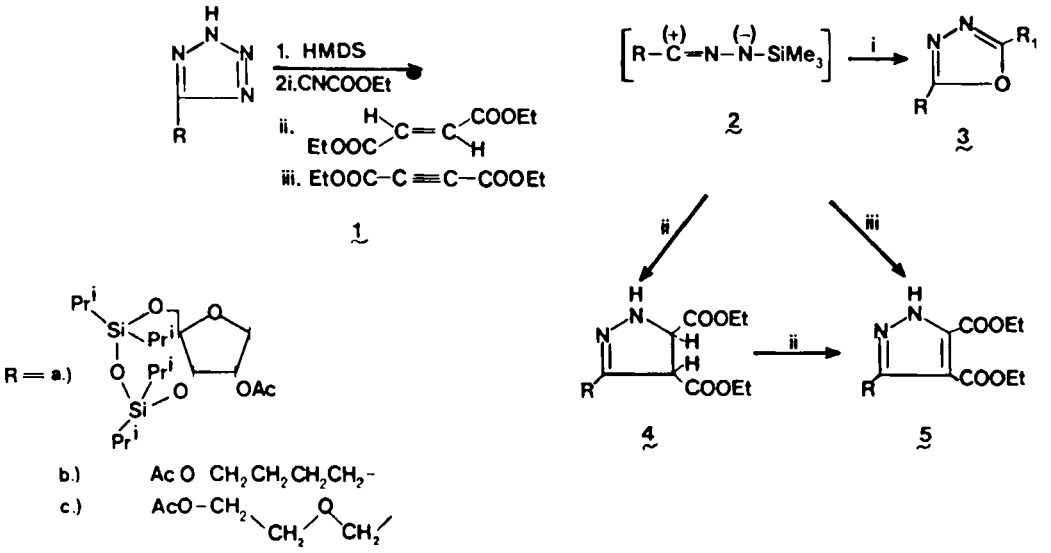
Abstract: A synthesis of 5-β-D-ribofuranosyl-2H-tetrazole (1), 5-β-D-ribofuranosyl-oxadiazoles, diethyl-Δ^2-pyrazoline-4,5-dicarboxylate and diethylpyrazole-4,5-dicarboxylate derivatives is described. Ring transformations of 1 has been investigated in an effort to establish the stability of this synthon for further use in dipolar cycloaddition reactions.

Elaboration of nitrogen heterocycles on a suitable modified carbohydrate moiety was elected to use even though there was an apparent low stereo selectivity achieved by this method. The selection of this approach was made after considering possible options which would overcome or at least diminish the possibility of anomerizations throughout the whole reaction sequence. Since several functionalized 3-ribosyl pyrazoles have been prepared *via* the reaction of sugar diazo alkanes with substituted acetylenes and olefines [1], an alternative route *via* nitrilimines which were generated in situ from 5-[2,3,5-tri-O-benzoyl-β-D-ribofuranosyl]-(2H)-tetrazole (1) to overcome the multistage nature of this synthesis was suggested. In this work we describe the generation of the β-D-ribosylnitrilimine 2 by thermolysis of 1.

A solution of silylated 1 (5 g, 9.5 mmoles) in 20 ml of diethylfumarate was heated at 165° for 20^h. The solvent was then removed to afford an oil which was further chromatographed on silica gel (200 g) with CCl_4, CCl_4-diethyl ether, etc. to afford 1.8 g (29 %) of 4. ^{1}H NMR($CDCl_3$) δ-5.5 (d,1,$H_{1'}$, $J_{1',2'}$= 4 Hz) 3.84-4.12 (m,5,CH_2,H_4);4.26-4.72 (m,4,$H_{4'}$, $H_{5'}$, $H_{5''}$, H_5); C,H,N and 1.4 g (22 %) of 5; ^{1}H NMR, ($CDCl_3$) δ-5.76-6.0 (m,3,$H_{1'}$, $H_{2'}$, $H_{3'}$); C,H,N; 4 was transformed to 5 (61 % in a solution of CCl_4 saturated with Cl_2 which was allowed to stay one day on a



daylight. Identical reaction with dimethylacetylendicarboxylate at 140° for 14h with a similar work up procedure (silica gel, CCL_4-diethylether), followed by chromatography on Sephadeyx LH-20 in CH_2Cl_2 afforded a 64 % yield of 5 ^{1}H NMR ($CDCl_3$) δ-5.88 (d,1,$H_{1'}$, $J_{1',2'}$=4 Hz); 5.94-6.2 (m,2, $H_{2'}$,$H_{3'}$).

The poor yields obtained in these initial investigations discuraged the further use of 1 (R=Tri-O-benzoyl) at this time. However our succes in using 1 in 1,5 dipolar cycloadditions prompted us to initiate investigations designed to optimize the 1,3 dipolar cycloaddition chemistry of D-allono nitrilimines since all the known cycloaddition routes met the demands for stereochemical control at the anomeric center. Thus, several blocking groups were introduced, selection being predicated primarily on their use in future ribose moiety transformations and additionally chemical transformations of 1 were investigated in order to prove or disprove the feasibility of stereocontroled reaction sequences.

The isopropylidation of the deprotected 1 was unsuccessful and 1-(5-O-Benzoyl-2,3,-O-isopropylidene)-β-D-ribofuranosyl) was obtained by an a alternative route from the corresponding carbo nitrile[3] as a white foam (81 %), ^{1}H NMR ($CDCl_3$) δ-4.85 (dd,1,$H_{3'}$); 5.24 (dd,1,$H_{2'}$); 5.48 (d,1,$H_{1'}$, $J_{1',2'}$=4 Hz;) m/e=346 with $\Delta\delta$-of the methyl groups being 15 Hz. Since $\Delta\delta$ was on the limits[4], the debenzoylation and subsequent treatment by t-butyldimethylsilylchloride yielded a stable derivative with acceptable $\Delta\delta$ values. On the other hand 1a was obtained in 75 % yield; ^{1}H NMR ($CDCl_3$) δ-5.34(d,1,$H_{1'}$) in pyridine and Ac_2O, which was further easily

transformed to 2-methyl-2-O-acetyl-3,5-OTPDS- β -D-ribofuranosyl-1,3,4-oxadiazole indicating a ring degradation of a tetrazole into oxadiazole with no anomerization observed as following another convenient criterium[5]. Thorough deprotection of isopropylidene and benzoyl groups with diluted CF_3COOH and NaOMe of 2-methyl - (subbst. β-D-ribofuranosyl-1,3,4-oxadiazole obtained from appropriate 1 and Ac_2O afforded identical products assumed to be in a β configuration with m.p. 105-108°, ^1H NMR(D_2O) -2.5(s,1,CH_3); 3.65 (m,2,$H_{5'}$,$_{5''}$); 4.12 (m,2,$H_{3'}$, $H_{4'}$); 4.4 (dd, 1, $H_{2'}$); 4.92 (d,1, $H_{1'}$, $J_{1',2'}$= 5.5)Hz m/e 216.

Finally, the reaction of 1 with ethylcyanoformate is disclosed. It is well known that even activated carbonitriles are much less reactive dipolarophyles then olefins and alkynes[6] . Silylated 1 was refluxed for 12^h in an excess of ethylcyanoformate (115°). Reagent was removed and the residue furnished after chromatography two products in fair yields; one identified as 1-carboethoxy-- β-D-ribofuranosyl-tetrazole. After deprotection ^1H NMR (D_2O) δ-5.2(d,1,$H_{1'}$, $J_{1',2'}$=5.5 Hz); and the second with an oxadiazole structure 3 respectively. ^1H NMR (D_2O)δ-5.32 (d,1,$H_{1'}$,$J_{1',2'}$= 5.8Hz).The action of cyanoformate as an acylation reagent was established by independent synthesis of 3 from 1 and methylchloroformate.

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9. 5-[2,3,5-Tri-O-Benzoyl-β-D-ribofuranosyl] -(2H)-tetrazole (1)
Sodium azide (780 mg, 12 mmoles) and ammonium chloride (12 mmoles) was added to a solution of 1-cyano-2,3,5-tri-O-benzoyl-β-D-ribofuranose[7] (4.7 g, 10 mmoles) in DMF and stirred at 100° for 8^h. The solid

was collected by filtration, the filtrate evaporated in vacuo and coevaporated several times with CCl_4. The residue was dissolved in 300 ml of EtOAc and washed with 2x30 ml of HCl/H_2O (pH 1), 30 ml of a saturated solution of $NaHCO_3$ and then 30 ml of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4 to yield 4,4 g (86 %) of a solid m.p.71-72°/ ^1H NMR ($CDCl_3$) δ-4.68 (m,3,$H_{4'}$,$H_{5'}$,$H_{5''}$); 5.74(d,1,$H_{1'}$, $J_{1',2'}$=2.3 Hz); 5.96 (m,2,$H_{2'}$,$H_{3'}$); C,H,N; The deprotection was achieved in sodium methoxide in MeOH (reflux) and the crude product crystallized from MeOH; (77 %); m.p.282-286°) C,H,N; m/e 202,B^+ = 113; ^1H NMR (D_2O) δ-3.79(m,2,$H_{5'}$,$_{5''}$); 4.28 (dd,1,$H_{4'}$,$J_{3',4'}$ = 7Hz); 4.43(dd,1,$H_{3'}$, $J_{2',3'}$= 5Hz);4.52 (dd,1,$H_{2'}$, $J_{1',2}$ = 6Hz); 5.17 (d,1,$H_{1'}$). Protection with 1,3.dichloro-1,1,3,3-tetraisopropyldisiloxane was achieved in dry pyridine (R.T., 2^H); 70 % of a foamy product m.p.53-55°, m/e 401 (M^+-iPr).