

A New and Efficient Route to the Synthesis of Pyrazole and Pyrimidine C-Nucleoside Derivatives

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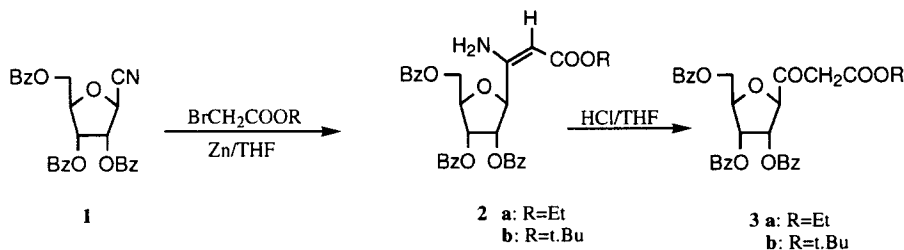
Received 16 February 1998; revised 18 March 1998; accepted 20 March 1998

Abstract: A new route to the synthesis of pyrazole and pyrimidine C-nucleosides, involving as the key step a metal catalysed reaction of β -D-ribofuranosyl ketoesters with alkyl cyanoformates, is described. 2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl cyanide (**1**) reacts with α -bromoesters, in the presence of zinc dust, to give β -D-ribofuranosyl-enaminoesters **2** which are easily hydrolysed to β -ketoesters **3**. The reactions of compounds **3** with alkyl cyanoformates, in the presence of catalytic amounts of $[\text{Cu}(\text{acac})_2]$, afford C-glycosyl enaminoketoesters **4**. These compounds react with benzylhydrazine and acetamidine to give pyrazole and pyrimidine C-nucleosides **5** and **6** respectively.
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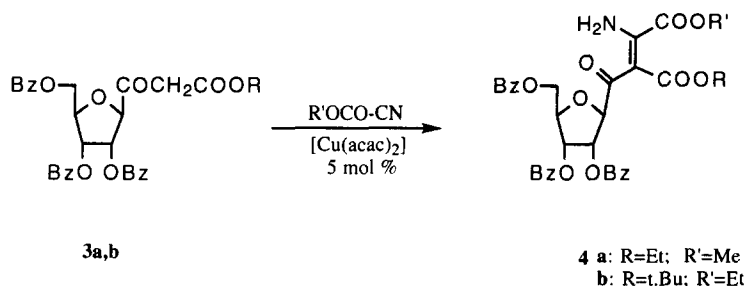
We have reported that nitriles react with β -dicarbonyl derivatives, in the presence of catalytic amounts of metal acetylacetonates or in the presence of stoichiometric amounts of SnCl_4 , to yield β -enaminodicarbonyls derived from the formation of a new C-C bond between the methylene group of dicarbonyls and the cyano group of nitriles.^{1,2} β -Enaminodicarbonyls so obtained are useful intermediates in the synthesis of heterocyclic compounds: pyridines, quinolines,³ tetrone acid derivatives,⁴ pyrazoles, isoxazoles and pyrimidines⁵ have been obtained in mild experimental conditions.

These results prompted us to investigate the metal promoted reactions of protected β -D-ribofuranosyl ketoesters with alkyl cyanoformates in order to obtain C-glycosyl enaminodicarbonyls and to study their utilization as intermediates in the synthesis of C-nucleosides, a class of compounds showing antiviral and antitumoral activities.⁶

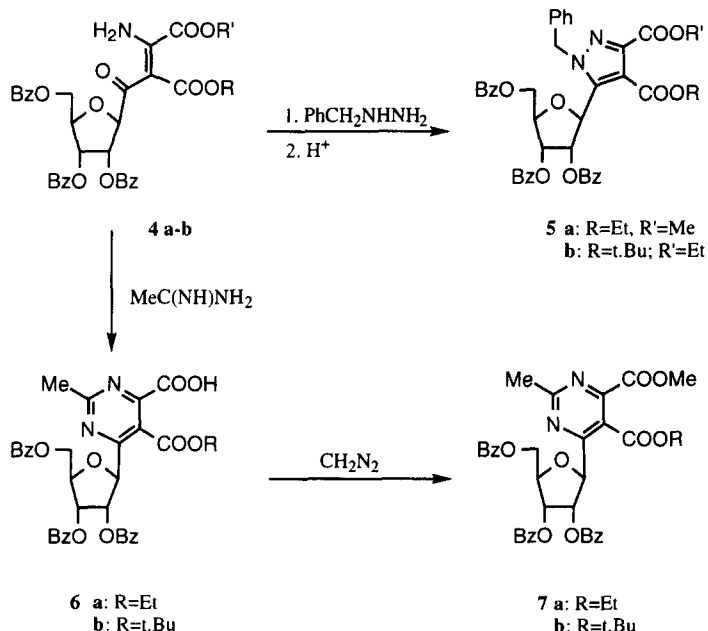
With this aim, 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl cyanide (**1**), prepared from 2,3,5-tri-O-benzoyl- β -D-ribofuranosyl acetate,⁷ was allowed to react with α -bromo esters in the presence of Zn dust in the Blaise reaction conditions.⁸ The obtained C-glycosyl-enaminoketoesters **2** were easily hydrolysed to C-glycosyl ketoesters **3**.⁹



C-Glycosyl ketoester **3** were then reacted with alkyl cyanofornates in the presence of catalytic amounts of metal acetylacetonates. The best yields of C-glycosyl enamino ketoesters **4a-b** were obtained when the reactions were carried out in CH_2Cl_2 at room temperature for 1-5 days in the presence of 5 mol% $[\text{Cu}(\text{acac})_2]$.¹⁰



Compounds **4** were reacted with ambident nucleophiles such as benzylhydrazine and acetamidine. The reaction with benzylhydrazine was carried out in diethyl ether at room temperature for 4-6 h. The ^1H -nmr spectrum of the reaction mixture showed the formation of intermediates which were transformed into the pyrazole C-nucleosides **5** by treatment with a drop of concentrated sulphuric acid.¹¹



In similar reactions compounds **4**, treated with acetamidine at room temperature for 3-5 h, gave the

pyrimidine monocarboxylic acid C-nucleosides **6**, in which the ester group linked to the carbon atom in *alpha* to the nitrogen atom of pyrimidine ring was selectively hydrolysed. For a better characterisation, these compounds were transformed into the diesters **7** by reaction with diazomethane.

The obtained results demonstrate that C-glycosyl enaminketoesters **4** can be useful intermediates in the synthesis of pyrazole and pyrimidine C-nucleosides **5** and **6**, which were obtained in high yields and only as *beta* anomers. We are now studying the possibility of extending these reactions to the synthesis of C-nucleoside derivatives related to pyrazofurine¹² in order to investigate their biological activity.

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Compound **2a** was obtained in 70% yield. ¹H-NMR (CDCl₃, 200 MHz) δ : 1.23 (t, J=7.1 Hz, 3H, Me), 4.10 (q, J=7.1 Hz, 2H, OCH₂), 4.6-4.8 (m, 4H, H-1, H-4 and OCH₂), 4.89 (s, 1H, CH), 5.50-5.70 (m, 2H, H-2 and H-3), 7.3-7.6 (m, 10H, Ph), 7.9-8.2 (m, 7H, Ph and NH₂).
- In a typical reaction, to a solution of compound **2** in THF, 1N HCl was added (*ca.* 1.5 ml of solvent and 0.3 ml of HCl/100 mg of **2**) and the mixture was stirred at room temperature for 4-6 h. Saturated aqueous NaHCO₃ was then added and the mixture was extracted several times with ethyl ether. The combined organic layers were washed with brine, dried and evaporated under reduced pressure without heating. Compounds **3** are very unstable and have to be used immediately after their preparation. Spectroscopic data of **3a**: ¹H-NMR (DMSO-d₆; 200 MHz) δ : 1.12 (t, J= 7.0 Hz, 3H, Me), 3.80 (s, 2H, CH₂), 4.04 (q, J=7.0 Hz, 2H, OCH₂), 4.45-4.65 (m, 2H, OCH₂), 4.65-4.80 (m, 1H, H-4), 4.95 (d, J=4.6 Hz, 1H, H-1), 5.67 (m, 1H, H-2 or H-3), 5.90 (m, 1H, H-2 or H-3), 7.4-7.7 (m, 10 H, Ph), 7.8-8.1 (m, 5H, Ph).
Similar C-glycosyl- β -ketoester has been previously prepared: a) by the reductive hydrolysis of an isoxazole C-nucleoside, obtained in a dipolar cycloaddition reaction from a C-ribofuranosyl nitrileoxide and ethoxyacetylene (Kozikowski A. P.; Goldstein S. *J. Org. Chem.*, **1983**, *48*, 1141); b) by a Michael addition reaction of pyrrolidine on ribofuranosyl ethylpropionate followed by hydrolysis of the obtained enaminoester (Tam S. Y-K.; Klein R. S.; De las Heras F. G.; Fox J. J. *J. Org. Chem.* **1979**, *44*, 4854).
- Synthesis of compound **4b**
To a solution of ketoester **3b** (150 mg, 0.25 mmol) in 0.3 ml of dry dichloromethane, ethyl cyanoformate (0.05 ml, 0.5 mmol) and [Cu(acac)₂] (4 mg, 5% mol) were added. The reaction mixture

was stirred at room temperature for 5 days, diluted with ethyl acetate, filtered on Celite, washed with dilute hydrochloric acid and brine and dried (Na_2SO_4). Compound **4b** was purified by flash chromatography (silica gel, ethyl ether: light petroleum 7:3): white crystalline foam, mp 61-63 °C, 125 mg (yield 70%).

^1H -NMR (CDCl_3 ; 200 MHz): two geometric isomers are present in 3:2 ratio. Major isomer, δ : 1.25-1.34 (m, 3H, $\text{CH}_2\text{-CH}_3$), 1.41 (s, 9H, t.Bu), 4.25-4.39 (m, 2H, $\text{CH}_2\text{-CH}_3$), 4.59-4.76 (m, 3H, CH_2O + H-4), 5.65 (d, $J=1.0$ Hz, 1H, H-1), 5.74 (m, 1H, H-3), 6.05 (m, 1H, H-2), 6.62 (br, 1H, NH), 7.23-7.60 (m, 9H, Ph), 7.82 (d, 2H, $J=7.5$, Ph), 8.01 (d, 4H, $J=7.5$, Ph), 10.65 (s, br, NH); minor isomer shows absorptions at δ : 1.48 (s, 9H, t.Bu), 5.34 (d, 1H, $J=1.5$ Hz, H-1), 5.95 (br, 1H, NH), 8.73 (s, br, 1H, NH).

11. Preparation of compound **5b**

To a solution of triethylamine (0.09 ml, 0.66 mmol) in ethyl ether (2 ml) cooled at 0°C, benzyldiazine (65 mg, 0.33 mmol) was added and the suspension was stirred at 0° C for 15 min. **4b** was then added in one portion (210 mg, 0.3 mmol). The mixture was stirred at 0° C for 15 min and then the temperature was allowed to rise to room temperature. After 5 h the reaction mixture was diluted with ethyl ether and filtered; the resulting solution was washed with 1N hydrochloric acid, brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a residue which was dissolved in 2 ml of ethyl ether and added to a cooled solution of one drop of sulphuric acid in 1 ml of ethyl ether. The mixture was stirred at 0°C for 15 min and then at room temperature for 15 min. The white solid obtained was dissolved in ethyl acetate; the solution was washed with saturated aqueous NaHCO_3 , brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give an oil which was purified by flash chromatography (silica gel, ethyl acetate: light petroleum 1:1): white solid, 175 mg (yield 73%), mp 137-139°C, $[\alpha]_D -40.9$ (c 0.96, CHCl_3). ^1H NMR (CDCl_3 ; 200 MHz) δ : 1.44 (t, 3H, $J=7.1$ Hz, OCH_2CH_3), 1.60 (s, 9H, t.Bu), 4.40-4.51 (m, 2H, OCH_2CH_3), 4.59-4.64 (m, 1H, H-4), 4.74-4.78 (m, 2H, H-5), 5.54 and 5.68 (AB system, 2H, $J=15.0$ Hz, NCH_2Ph), 5.75-5.86 (m, 2H, H-2 and H-3), 5.90 (d, 1H, $J=7.3$ Hz, H-1), 7.08-7.62 (m, 14H, Ph), 7.90-7.96 (m, 4H, Ph), 8.09-8.12 (m, 2H, Ph).

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