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

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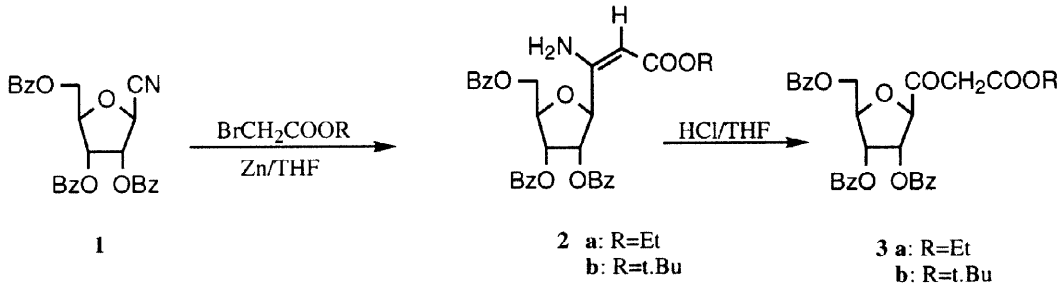
Abstract: A new route to the synthesis of pyrazole and pyrimidine C-nucleosides, involving as the key step a metal catalysed reaction of β-D-ribofuranosyl ketoesters with alkyl cyanoformates, is described. 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl cyanide (**1**) reacts with α-bromoesters, in the presence of zinc dust, to give β-D-ribofuranosyl-enaminoesters **2** which are easily hydrolised to β-ketoesters **3**. The reactions of compounds **3** with alkyl cyanoformates, in the presence of catalytic amounts of [$Cu(acac)_2$], afford C-glycosyl enaminoketosters **4**. These compounds react with benzylhydrazine and acetamidine to give pyrazole and pyrimidine C-nucleosides **5** and **6** respectively.

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] tetronic acid derivatives,[4] pyrazoles, isoxazoles and pyrimidines[5] 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]



1

2 **a**: R=Et
b: R=t.Bu

3 **a**: R=Et
b: R=t.Bu

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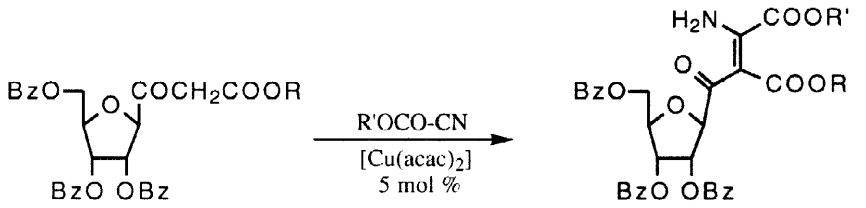
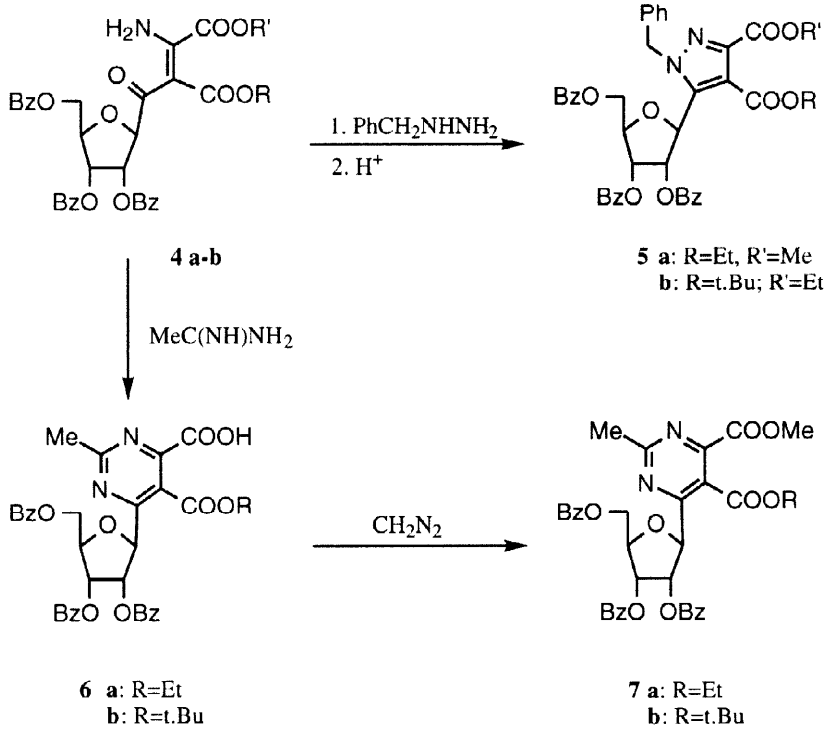
C-Glycosyl ketoester **3** were then reacted with alkyl cyanoformates in the presence of catalytic amounts of metal acetylacetonates. The best yields of C-glycosyl enamino ketoesters **4a-b** were obtained when the reactions were carried out in CH_2Cl_2 at room temperature for 1-5 days in the presence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



3a,b

4 **a**: R=Et; R'=Me
b: R=t.Bu; R'=Et

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 ^{1}H-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]



4 a-b

5 **a**: R=Et, R'=Me
b: R=t.Bu; R'=Et

6 **a**: R=Et
b: R=t.Bu

7 **a**: R=Et
b: R=t.Bu

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 tranformed into the diesters **7** by reaction with diazomethane.

The obtained results demonstrate that C-glycosyl enaminoketoesters **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 pyrazofurine[12] in order to investigate their biological activity.

References and notes

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   Compound **2a** was obtained in 70% yield. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.23 (t, J=7.1 Hz, 3H, Me), 4.10 (q, J=7.1 Hz, 2H, OCH_2) 4.6-4.8 (m, 4H, H-1, H-4 and OCH_2), 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 NH_2).
9. 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 $NaHCO_3$ 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**: ^{1}H-NMR (DMSO-d_6; 200 MHz) δ: 1.12 (t, J= 7.0 Hz, 3H, Me), 3.80 (s, 2H, CH_2), 4.04 (q, J=7.0 Hz, 2H, OCH_2), 4.45-4.65 (m, 2H, OCH_2), 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 ethylpropiolate 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).
10. 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%).

^{1}H-NMR ($CDCl_3$; 200 MHz): two geometric isomers are present in 3:2 ratio. Major isomer, δ: 1.25-1.34 (m, 3H, CH_2-*CH_3*), 1.41 (s, 9H, t.Bu), 4.25-4.39 (m, 2H, *CH_2*-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, benzylhydrazine (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, $CHCl_3$).^{1}H NMR ($CDCl_3$; 200 MHz) δ: 1.44 (t, 3H, J=7.1 Hz, OCH_2*CH_3*), 1.60 (s, 9H, t.Bu), 4.40-4.51 (m, 2H, O*CH_2*CH_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, N*CH_2*Ph), 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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