

C2', 3'- CYCLIC CARBONATES DERIVED FROM URIDINE AND INOSINE

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Abstract

New compounds 5'-O-(4, 4'-dimethoxytrityl)uridine-2', 3'-carbonate and 5'-O-(4, 4'-dimethoxytrityl)inosine-2', 3'-carbonate were obtained in 65 % and 43 % yield, respectively, through the reaction of the corresponding 5'-O-(4, 4'-dimethoxytrityl) nucleosides with 1, 1'-carbonyldiimidazole in dioxane at 20° C.

Resumen

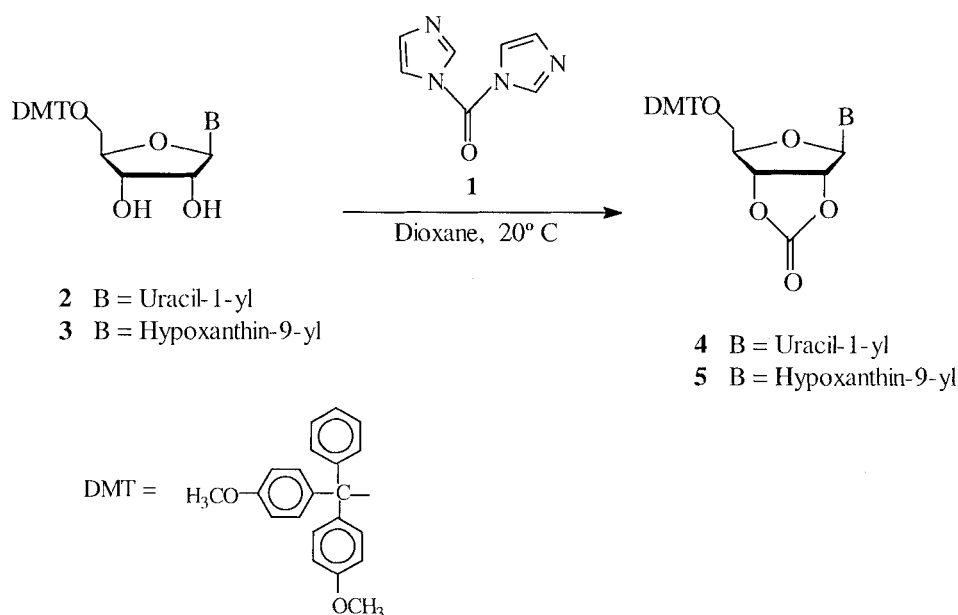
Los nuevos compuestos 5'-O-(4, 4'-dimetoxitritil)uridina-2', 3'-carbonato y 5'-O-(4, 4'-dimetoxitritil)inosina-2', 3'-carbonato fueron obtenidos con 65 % y 43 % de rendimiento, respectivamente, por reacción de los correspondientes 5'-O-(4, 4'-dimetoxitritil)nucleósidos con 1, 1'-carbonildiimidazol en dioxano a 20° C.

Introduction

The need of efficient and novel antiviral molecules has encouraged the synthesis of nucleoside analogues over the last decades [1]. Reactions carried out under mild experimental conditions and displaying regioselectivity are powerful tools in the modification of natural nucleosides, since these polyfunctional compounds are labile in many reaction media and bear several hydroxyl groups having similar reactivity.

On the other hand, alkyl carbonates are widely used as protecting groups for diols and polyols [2]. In addition to their synthetic applications, they are employed in polymer and medicinal chemistry [3]. In this latter field, the lipophilic nature of carbonates can provide prodrugs of pharmacological active compounds, as previously reported for penciclovir [4]. However, carbonates are not extensively applied to nucleoside chemistry because they are generally introduced either through chloroformates [5,6], which are very reactive agents, or enzymatically using oxime carbonates [7]. Moreover, the removal of alkyl carbonates usually requires strong nucleophile reagents or is carried out by taking advantage of the properties of the second alkyl substituent [2].

1, 1-Carbonyldiimidazole (CDI, **1**, Scheme 1) [3] is a convenient reagent alternative to chloroformates, since it is less reactive and harmful than the latter. CDI has been applied as an useful reagent for the regioselective preparation of carbonates of diols and polyols [8,9] and the synthesis of cyclic carbonates of hydroxylated compounds [3]. For the latter purpose, in the field of nucleosides, the preparation of 5'-*O*-trityluridine-2', 3'-carbonate from 5'-*O*-trityluridine with CDI has been reported [10]. In this work we report the preparation of two new 5'-*O*-(4, 4'-dimethoxytrityl)-2', 3'-carbonate nucleosides (**4**, **5**; Scheme 1).



Scheme 1

Experimental

General

4, 4'-Dimethoxytrityl chloride was purchased from Aldrich and 1, 1'-carbonyldiimidazole was obtained from ICN. Solvents were of analytical grade and obtained from commercial sources. Anhydrous dioxane was obtained by reflux over sodium / benzophenone and distilled. 5'-*O*-(4, 4'-Dimethoxytrityl)nucleosides were obtained by reaction of uridine and inosine with 4, 4'-dimethoxytrityl chloride using a standard protocol [11].

Analytical methods

TLC was performed on Silicagel 60 F₂₅₄ plates (Merck) and column chromatography was carried out using silicagel Merck 60. In TLC analyses dichloromethane-methanol 92:8 (v/v) was used as the mobile phase.

Nuclear magnetic resonance spectra were recorded on a Bruker AC-500 spectrometer in CDCl₃. NMR ¹³C chemical shifts assignments bearing an asterisk may be interchanged.

Preparation of 5'-O-(4, 4'-dimethoxytrityl)uridine-2', 3'-carbonate (4) and 5'-O-(4, 4'-dimethoxytrityl)inosine-2', 3'-carbonate (5)

5'-O-(4, 4'-Dimethoxytrityl)uridine (**2**; 0.35 mmoles) or 5'-O-(4, 4'-dimethoxytrityl)inosine (**3**; 0.35 mmoles) were dissolved in 10 ml of anhydrous dioxane under nitrogen. The reaction mixture was kept at 20° C and a solution of 1,1'-carbonyldiimidazole (1.05 mmoles) in 5 ml of dioxane was added dropwise. The system was stirred at 20° C for 4 h until TLC showed disappearance of **2** or **3**. The dioxane was evaporated and the resulting crude was purified by silicagel column chromatography (the elution solvent and the yield are given below), affording new compounds **4** and **5** as white foams, which provided satisfactory spectroscopic data:

Compound **4** (Dichloromethane/methanol 95:5, 65 %)

RMN-¹H: δ (CDCl₃): 3.40 (dd, J₁= 4.6 Hz, J₂= 10.5 Hz, 1H, H 5'_a), 3.50 (dd, J₁= 6.3 Hz, J₂= 10.4 Hz, 1H, H 5'_b), 3.77 (s, 6H, -OCH₃), 4.38-4.41 (m, 1H, H 4'), 5.22 (dd, J₁= 4.0 Hz, J₂= 7.4 Hz, 1H, H 3'), 5.42 (dd, J₁= 1.6 Hz, J₂= 7.4 Hz, 1H, H 2'), 5.65 (d, J= 1.4 Hz, 1 H, H 1'), 5.66 (d, J= 1.4 Hz, 1 H, H 5), 6.79-6.83 (m, 4H, DMT), 7.25-7.30 (m, 7H, DMT), 7.36-7.39 (m, 2H, DMT), 9.42 (s_a, 1H, H 2).

RMN-¹³C: δ (CDCl₃): 55.27 (-OCH₃), 63.20 (C 5'), 67.10 (C 2'), 80.34 (C 3'), 83.11 (C 4'), 86.71 (-OC*Ph₃), 86.88 (C*1'), 103.21 (C 5), 113.29, 127.09, 127.95, 128.08, 130.06, 135.34 (DMT), 142.50 (C 6), 144.31 (DMT), 149.96 (C 2), 153.10 (-O-CO-O-), 158.73 (DMT), 163.01 (C 4).

Compound **5** (Dichloromethane/methanol 92:8, 43 %)

RMN-¹H: δ (CDCl₃): 3.21 (dd, J₁= 6.1 Hz, J₂= 9.8 Hz, 1H, H 5'_a), 3.35 (dd, J₁= 5.9 Hz, J₂= 10.1 Hz, 1H, H 5'_b), 3.71 (s, 6H, -OCH₃), 4.56-4.59 (m, 1H, H 4'), 5.53 (dd, J₁= 3.2 Hz, J₂= 7.5 Hz, 1H, H 3'), 6.00 (dd, J₁= 1.6 Hz, J₂= 7.5 Hz, 1H, H 2'), 6.22 (d, J= 1.6 Hz, 1 H, H 1'), 6.72- 6.75 (m, 4H, DMT), 7.17-7.21 (m, 7H, DMT), 7.29-7.31 (m, 2H, DMT), 7.90 (s, 1H, H 2), 8.11 (s, 1H, H 8).

RMN-¹³C: δ (CDCl₃): 55.27 (-OCH₃), 62.56 (C 5'), 67.11 (C 2'), 80.74 (C 3'), 82.55 (C 4'), 86.03 (-OC*Ph₃), 86.67 (C*1'), 113.32 (DMT), 125.38 (C 5), 127.06, 127.90, 128.21, 130.19, 135.28 (DMT), 139.88 (C 8), 144.17 (DMT*), 146.03 (C 2*), 147.85 (C 4), 153.28 (-O-CO-O-), 158.62 (C 6*), 158.66 (DMT*).

Results and discussion

At first we studied the direct reaction of CDI with uridine and inosine with CDI in anhydrous dioxane. Even using a low excess of CDI (moles CDI/moles nucleoside = 1.1) reactions afforded mixtures of compounds at temperatures ranging from 5° to 70°C. We decided then to use 5'-hydroxyl protected derivatives of uridine and inosine; in our case, the protection was carried out using 4, 4'-dimethoxytrityl chloride. 5'-O-(4, 4'-

Dimethoxytrityl)uridine (**2**) and 5'-O-(4,4'-dimethoxytrityl)inosine (**3**) reacted with CDI in anhydrous dioxane at 20° C, affording clean reactions. The structures of the resulting 2',3'-cyclic carbonates **4** and **5** were confirmed by NMR spectroscopy. Signals at 153.10 ppm in the NMR ¹³C spectrum of **4** and at 153.28 ppm in the spectrum of **5** agreed with the presence of the carbonate function. No signals due to the presence of an imidazole ring were observed. High chemical shifts for H-2' and H-3' in NMR ¹H spectra of **4** and **5** were in agreement with the proposed structures. To our best knowledge, **4** and **5** have not been previously reported in the literature.

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