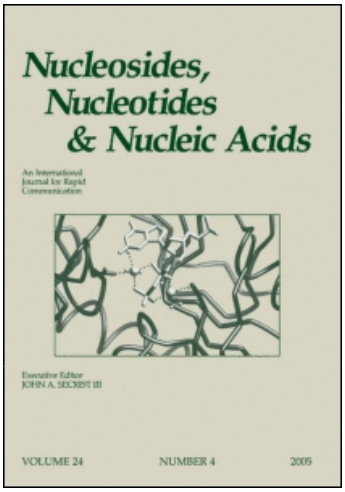

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A Simple and Convenient Method for the Selective N-Acylations of Cytosine Nucleosides

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A SIMPLE AND CONVENIENT METHOD FOR THE SELECTIVE N-ACYLATIONS OF CYTOSINE NUCLEOSIDES

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Abstract: A simple procedure for the selective N-acylation of cytosine nucleosides has been developed by reacting the appropriate nucleoside with acid anhydrides at room temperature employing N,N-dimethylformamide as the solvent.

Of the many 2',3'-dideoxynucleosides tested so far, 2',3'-dideoxycytidine (1) has recently been identified as the most potent in the possible therapy of Acquired Immune Deficiency Syndrome (AIDS)[1]. During the course of a recent synthesis[2] of 1 starting from 2'-deoxycytidine (2), we needed a simple and reliable method for the large-scale preparation of N^4-benzoyl-2'-deoxycytidine (7) through the selective benzoylation of 2. In this communication we disclose our results which meet the above requirements for the selective N-acylations of 1, 2, cytidine (3) and 1-β-D-arabinofuranosylcytosine (4).

Several methods are available in the literature for the selective N-acylations of 2-4. One of the original methods was developed by Khorana and coworkers[3] wherein the nucleosides are peracylated and the O-acyl groups then selectively cleaved to give the N-acyl derivatives. The lengthy nature of this procedure coupled with the moderate yields obtained has prompted many other groups to attempt the direct N-acylations. Direct N-benzoylation of 2 has previously been achieved employing

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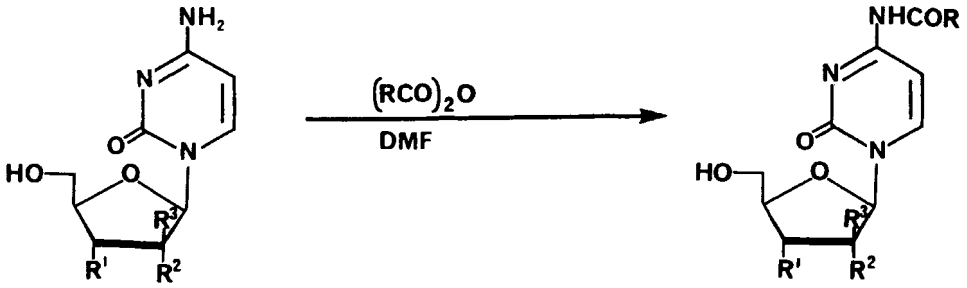

1	R^1=R^2=R^3=H				
2	R^1=OH, R^2=R^3=H				
3	R^1=R^2=OH, R^3=H				
4	R^1=R^3=OH, R^2=H				

Product	R	R^1	R^2	R^3
5	C_6H_5	H	H	H
6	CH_3	H	H	H
7	C_6H_5	OH	H	H
8	CH_3	OH	H	H
9	C_6H_5	OH	OH	H
10	CH_3	OH	OH	H
11	C_6H_5	OH	H	OH
12	CH_3	OH	H	OH

benzoic anhydride[4,5], 2-(chloromethyl)-4-nitrophenyl benzoate[6], 2,4,5-trichlorophenyl benzoate[7], O-ethyl S-benzoyl dithiocarbonate[8], p-nitrophenyl benzoate/1-hydroxybenzotriazole[9] or pentafluorophenyl benzoate[10]. An alternative procedure for the one-flask synthesis of 7 using chlorotrimethylsilane for transient hydroxyl protection has also been reported[11]. Although many of the above methods are elegant in nature, their application for the large-scale preparation of N-acyl derivatives is somewhat hampered by the difficulty in isolation of the products as well as the lack of easy access to some of the acylating agents.

Table: Acylations of Cytosine Nucleosides 1-4 with Benzoic anhydride (A) and Acetic anhydride (B).

Nucleoside	Acylating Agent	Product (yield, %)	m.p. [°C] (Solvent)	Lit. m.p. [°C] or Molecular formula*
1	A	5 (91)**	282-284(dec.) (EtOH)	$C_{16}H_{17}N_3O_4$ (315.3)
	B	6 (95)**	141-142 (EtOAc-EtOH,3:1)	$C_{11}H_{15}N_3O_4$ (253.2)
2	A	7 (91)	220-222(dec.) (EtOH)	205-206[5]
	B	8 (98)	150-175 (EtOH)	154-176[5]
3	A	9 (96)	238-239 ($EtOH-H_2O$,3:1)	238-239[4]
	B	10 (98)	207-209 ($EtOH-H_2O$,1:1)	208-209[4]
4	A	11 (95)	186-189 (EtOH)	188-189[12]
	B	12 (90)**	188-190 (EtOH-EtOAc,3:1)	$C_{11}H_{15}N_3O_6$ (285.2)

* Satisfactory microanalyses obtained: C ± 0.26, H ± 0.21, N ± 0.28

** All the new compounds were also characterized by spectroscopic (IR and ^1H NMR) means.

Our procedure for the selective N-acylations of 1-4 simply consists of stirring the appropriate nucleoside with one equivalent of the acid anhydride in N,N-dimethylformamide at room temperature. After completion of the reaction (~24 h), the solvent was removed under high vacuum and the residue triturated with excess diethyl ether to isolate the products. In all the acylations we attempted so far, we have been able to get quantitative yields (>90%) of the products (See Table). In the case of 2 we also have been able to carry out the benzoylation on a multi-kilogram scale.

In conclusion, the present method is a simple and practical procedure for the selective N-acylations of cytosine nucleosides which we hope will find considerable use in the future.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in (methyl sulfoxide)-d_6 on a Varian EM 390 spectrometer using tetramethylsilane as a reference. Infrared spectra were recorded on a Beckman Model 25 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Tucson, Arizona. Thin-layer chromatography was run on silica gel GF plates (Analtech, Newark, Del.), where the products were visualized by UV light as well as 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with bath temperature below 40°C.

Acylations of Cytosine Nucleosides 1-4; General Procedure: To a suspension of the nucleosides 1-4 (1 equiv.) in N,N-dimethylformamide (~5 mL/mmol of the nucleoside) is added the appropriate acid anhydride (1.1 equiv) and the mixture is stirred at room temperature for 24 h. After removal of the DMF under reduced pressure, the resulting residue is triturated with excess diethyl ether and the crystalline products (5-12) obtained are collected by filtration, washed thoroughly with diethyl ether and air-dried. Analytically pure materials are obtained by recrystallization from appropriate solvents (See Table).

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