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LIPASE-CATALYZED REGIOSELECTIVE ACYLATION OF SUGAR MOIETIES OF NUCLEOSIDES

Atsuhiko UEMURA,* Kenji NOZAKI, Jun-ichi YAMASHITA, and Mitsugi YASUMOTO

Chemical Synthesis Research Laborabory, Taiho Pharmaceutical Co., Ltd.
Kodama-gun, Saitama, 367-02 JAPAN

Abstract: A regioselective acylation of 2'-deoxypyrimidine nucleosides by an acid anhydride in a dry polar aprotic solvent is catalyzed by a lipase from *Pseudomonas fluorescenbce*.

Regioselective acylation of a compound with poly-hydroxyl groups of very similar reactivity is an important but difficult manupulation in organic synthesis.[1-4] Although several reports deal with regioselective acylation of the hydroxyl groups by enzymatic methods,[5-8] none of them concerned with the acylation of nucleosides. We now wish to report a useful method for enzymatic acylation of 2'-deoxypyrimidine nucleosides by the use of an acid anhydride.

Among several enzymes, a lipase from *Pseudomonas fluororescence* (PFL) was found to accelerate acylation of 2'-deoxyuridine (1, X = H) in dimethylacetamide (DMA) at room temperature in the presence of hexanoic anhydride (R = C_5H_{11}) to give 2'-deoxy-5'-O-hexanoyluridine (2, X = H) in a good yield after 1 day. Other lipases such as porcine pancreas (PPL) and *Candida cilindracea* (CCL) were less reactive than PFL under the same reaction conditions. Commercially available carboxylic acids and esters were ineffective under the present reaction conditions. Prolonged reaction period increased the yield of diacylated compound, 3. 2'-Deoxy-3'-O-hexanoyluridine could not be detected on HPLC. The reaction can be carried out in DMSO or DMF and applied to other nucleosides and other acid anhydrides. The results are summarized in Table 1.

As a typical procedure, crude PFL (100 mg) was added to a solution of 1 (X = H) (1 mmol) and hexanoic anhydride (3 mmol) in dry DMA (3 ml) at room temperature, and the mixture was vigorously stirred for 24 h. The reaction was quenched by filtering off the enzyme. The enzyme portion was washed with 25 ml of ethyl acetate. After standard work-up and column chromatography on silica gel (benzene : acetone =5 : 1 v/v) gave 2'-deoxy-5'-O-hexanoyluridine in 70% yield[9] together with 3 in 20% yield.[10]

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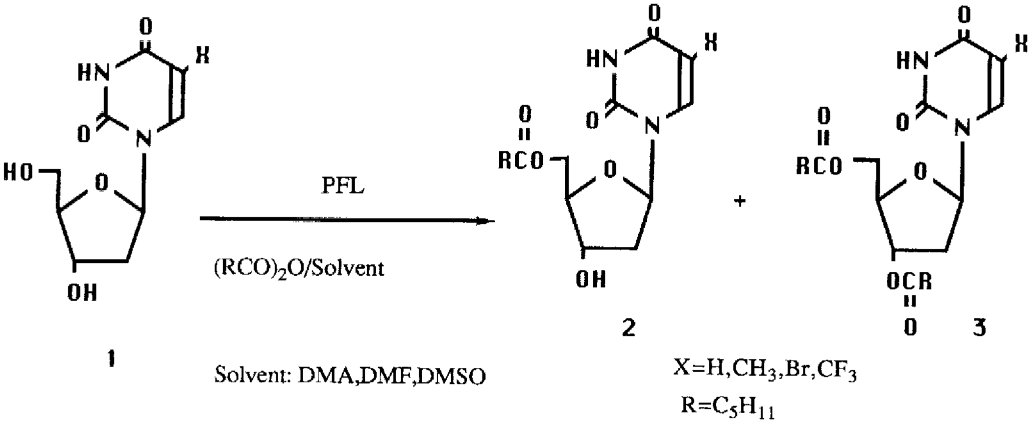

Table 1. Acylation of Various Nucleosides under the Catalysis of PFL.

R	X	Solvent	Conv. (%)	Chem. Yield (%)[a]		
				1	2	3
C_5H_{11}	H	DMA	95	5	73	22
C_5H_{11}	H	DMSO	96	4	75	18
C_5H_{11}	H	DMF	88	12	60	20
C_5H_{11}	CH_3	DMA	94	6	72	12
C_5H_{11}	Br	DMA	83	17	33	50
C_5H_{11}	CF_3	DMA	81	19	31	46
Ph	H	DMA	85	15	58	17

[a] The yields were determined by HPLC (Reverse phase column ODS 1HU from Mitsubishi Chemical Ltd.; Mobil phase, $CH_3CN : H_2O = 7 : 3$ v/v).

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9) ^{1}HNMR ($CDCl_3$) δ 0.92(3H,s), 1.00-1.70(6H,m), 2.00-2.40(4H,m), 3.50-3.65 (3H,m), 5.20(1H,bs), 5.35(1H,bs), 6.12(1H,t), and 11.30(1H,s).

10) ^{1}HNMR ($CDCl_3$) δ 0.90 (6H,s), 1.10-1.90 (12H,m), 2.00-2.70 (6H,m), 4.10-4.40(3H,m), 5.20(1H,m), 5.75(1H,d), 6.30(1H,t), 7.50(1H,d), and 9.20(1H,bs).

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