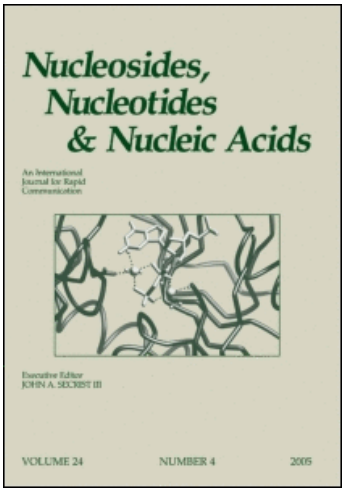

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Novel Intramolecular Introduction of Nucleophiles To 2,2'-Anhydrouridine

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NOVEL INTRAMOLECULAR INTRODUCTION OF NUCLEOPHILES TO 2,2'-ANHYDROURIDINE

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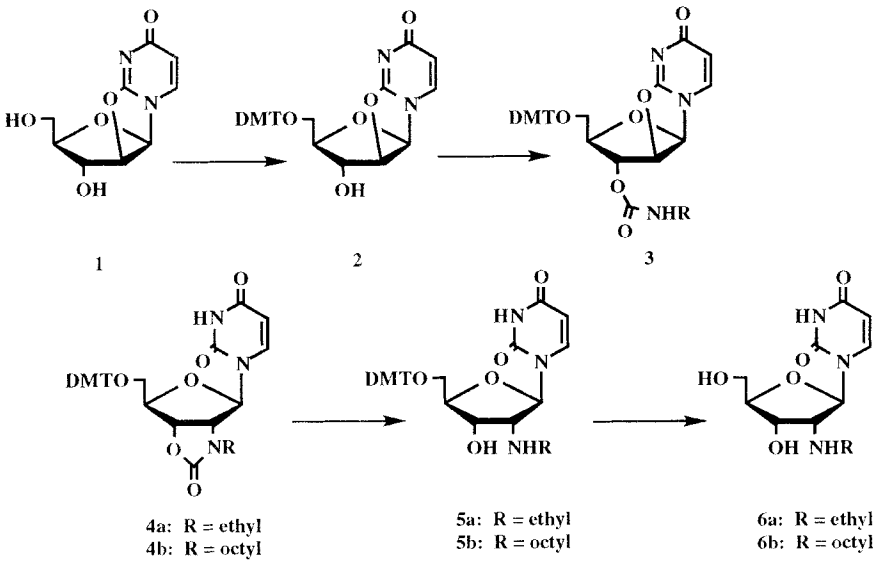
ABSTRACT: 2'-N-alkyluridine nucleosides are synthesized via intramolecular reaction of alkyl isocyanates with 5'-O-protected-2,2'-anhydrouridine.

This work is an extension of our previous investigation on the synthesis of 2'-amino-2'-deoxypyrimidines prepared from treatment of 5'-O-protected-2,2'-anhydrouridine with trichloroacetonitrile.[1] As a result, a viable synthetic alternative to the usual route to 2'-aminopyrimidines via lithium azide[2] was developed.

We have chosen to expand the scope of this versatile approach to synthesize 2'-O-alkyl and 2'-N-alkylpyrimidine nucleosides. We accomplished this by changing the nucleophile from trichloroacetonitrile to metal alkoxides and alkyl isocyanates respectively. For example, a variety of 2'-O-alkyluridines are isolated in good to moderate yields when 5'-protected anhydrouridine **2** is treated with either magnesium or calcium alkoxides in DMF.[3] Similarly, our focus here is on the synthesis of 2'-N-alkyluridines by treatment of **2** with alkyl isocyanates and either sodium hydride or cesium carbonate. In light of the commercial availability of a variety of modified isocyanates, the potential exists to synthesize a large number of 2'-alkylamine nucleosides. Therefore, we have elected to describe the synthesis of 5'-O-dimethoxytrityl-2'-N-ethylaminouridine (**5a**) and 5'-O-dimethoxytrityl-2'-N-octylaminouridine (**5b**) as shown in **Scheme 1**.

Anhydrouridine **1**, synthesized in the usual manner from diphenyl carbonate and sodium bicarbonate in DMF,[4] is dissolved in pyridine and treated with dimethoxytrityl chloride (1.1 eq) and catalytic dimethylaminopyridine. After 16 h at room temperature the reaction was evaporated and partitioned. The 5'-protected anhydrouridine **2** was isolated from silica gel chromatography in moderate yields. Reaction of **2** with ethyl isocyanate in refluxing triethylamine gave only the uncyclized product **3.** (UV λ_{max} 233; MS, M-1=598). However, when the protected anhydrouridine was treated with ethyl isocyanate



Scheme 1

(3.3 eq) and sodium hydride (4 eq) in tetrahydrofuran at reflux the desired cyclized compound **4a** is formed. The concentrated reaction mixture was extracted with dilute sodium bicarbonate to remove excess hydrolyzed reagent and purified by silica gel chromatography to afford the product **4a** in 90% yield. (UV λ_{max} 236, 261; MS, M-1=598).

Deprotection of the cyclized compound is accomplished with refluxing sodium hydroxide in ethanol. Compound **4a** is dissolved in 2:1 ethanol: 6N sodium hydroxide and refluxed for ca. 1 h at which time TLC indicates complete conversion to a more polar product. After partial evaporation the reaction is partitioned between ethyl acetate and saturated ammonium chloride. The desired ethylamine nucleoside **5a** is isolated in 90% yield following silica chromatography. Anal. calcd. for $C_{32}H_{35}N_3O_7$: C, 67.00; H, 6.15; N, 7.33. Found: C, 66.87; H, 6.39; N, 7.20.

Likewise, when **2** is reacted with octyl isocyanate (1.2 eq) and cesium carbonate (1.3 eq) in refluxing tetrahydrofuran **4b** is formed within 4 h. After evaporation the residue is partitioned between ethyl acetate and dilute ammonium chloride then dried to give a foam which can be isolated in 90% yield after silica gel chromatography or used directly in the next step. The product is deprotected as previously described with ethanolic sodium hydroxide. Following extraction and silica gel chromatography compound **5b** is isolated in

83% yield for the two steps. Anal. calcd. for $C_{38}H_{47}N_3O_7$: C, 69.38; H, 7.20; N, 6.39. Found: C, 69.76; H, 7.29; N, 6.43.

Both **5a** and **5b** were detritylated in 80% acetic acid for 1-2 h then concentrated and purified to afford **6a** and **6b**.

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