3-N-ACYL URIDINES: PREPARATION AND PROPERTIES OF A NEW CLASS OF URACIL PROTECTING GROUPS.

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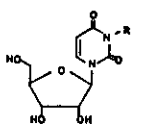
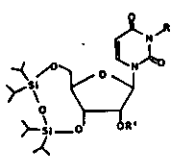
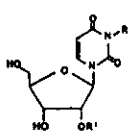
It is customary in oligoribonucleotide chemistry to use acyl groups to protect the exocyclic amino functions of adenine, guanine and cytidine residues. This protection has not been extended to uracil residues, because convenient methods for the preparation of N-3 acylated uridines have not been available. Except for two cases (Reese et.al.[1] and Hata et.al.[2]) the imido function has been left unprotected, and so has been a cause of undersired side reactions, as clearly demonstrated by Reese and his coworkers[3]. We now wish to report the preparation of N-3 acyl uridines as a convenient method of protection of the uracil residue during synthesis. The N-3 acyl uridines were prepared in a "one pot" reaction using trimethylchlorosilane for "transient protection" of the hydroxyls[4], and then introducing the acyl chloride to the reaction mixture. Methanolysis was used to remove the transient hydroxyl protecting groups and the pure N-3-acyl uridines were isolated by separation with reverse phase column chromatography. This procedure was used to prepare five different N-3-acyl uridines in high yields (benzoyl, o-and p-toloyl, p-anisoyl and mesitoyl, compounds (1) - (5)) and these were investigated with regard to their stability to the various reaction conditions likely to be used during oligoribonucleotide syntheses, and to their ease of removal after synthesis. All five derivatives showed excellent properties; the N^3-acyl groups were removed easily using aqueous ammonia in ca. 25, 75, 60 150 and 6000 minutes from the corresponding benzoyl, o-toloyl, p-toloyl, p-anisoyl and mesitoyl derivatives of uridine respectively. These encouraging results have prompted us to demonstrate the applicability of N-3-acyl uridines in solving some of the problems of nucleoside and nucleotide synthesis. A review of the properties of the above N^3-acyl uridines led us to choose the benzoyl derivative as being suitable for our purposes. Firstly the 5'-and 3'- hydroxyl functions were simultaneously protected by formation of compound (6), then methylation produced compound (8) and introduction of a 4-methoxytetrahydropyranyl group (MTHP) produced compound (7). Removal of the disilyl group with the help of fluoride ions yielded (9) and (10) in 86 and 90 % yields respectively. Subsequently the N^3-benzoyl group was removed from (10) to obtain 2'-O-methyluridine in 57% over all yield in five steps. Finally, the compound (9) was employed to synthesize a fully protected mononucleotide block (11) which was subsequently used in oligoribonucleotide synthesis following the phosphotriester approach using the strategy developed by Catlin et.al.[5].



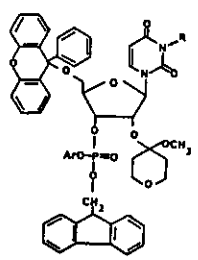
(1) R= Benzoyl
(2) R= p-Toloyl
(3) R= o-Toloyl
(4) R= p-Anisoyl
(5) R= Mesitoyl



(6) R= Benzoyl R'= H
(7) R= Benzoyl R'= MTHP
(8) R= Benzoyl R'= Methyl



(9) R= Benzoyl R'= MTHP
(10) R= Benzoyl R'= Methyl



(11) R= Benzoyl Ar= o-chlorophenyl

References:

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5. J.C. Catlin and F. Cramer; J. Org. Chem. 38, 245 (1973).