Tetrahedron Letters,Vol.25,No.44,pp 5061-5062,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

5-FLUOROURACIL DERIVATIVES. VII.[1] TERT-AMINE PROMOTED N-GLYCOSIDATION OF PYRIMIDINES

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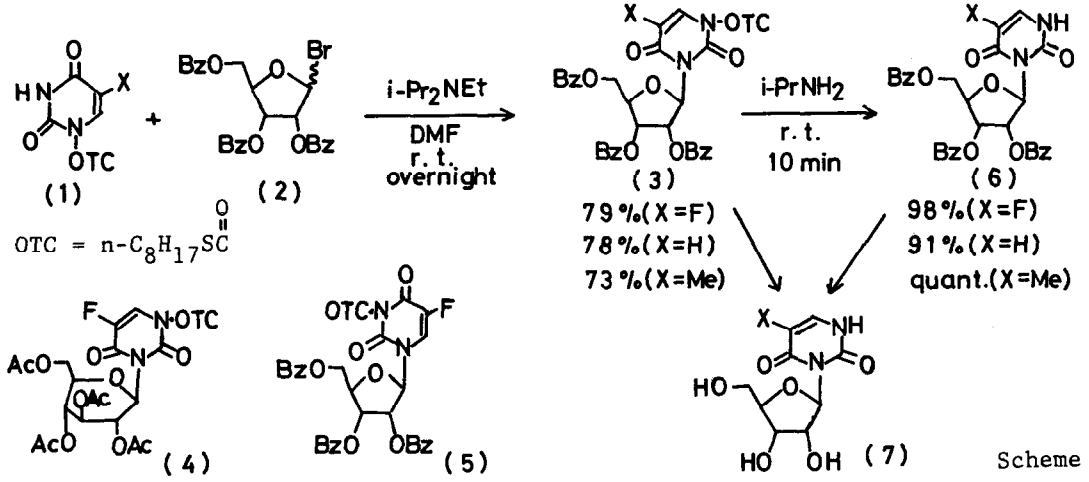
Abstract: Acylglycosyl halides react smoothly with N_1- and N_3-(octylthio)-carbonylpyrimidines in the presence of tert-amine to give the corresponding nucleosides in good yields.

There are known a variety of nucleosides which have biological activities such as antitumor and antiviral. Glycosidation which involves the reaction of nitrogen heterocycles with sugar derivatives is a principal method for the synthesis of N-glycosides. Several methods for this type of the reaction are conventionally employed, 1) the method using heavy metal salts,[2] 2) the fusion method,[3] 3) Hilbert-Johnson's,[4] and 4) Vorbrüggen's.[5] There have been recently reported new methods using DCC[6] and onium salts[7] of azaaromatics as condensing agents and a phase transfer catalyst.[8] Our recent report showed a convenient synthetic procedure of N_1- or N_3-alkyl-5-fluorouracil (5-FU).[1] This process involves the reaction of 5-FU protected with the (octylthio)carbonyl (OTC) group with alkyl halides in the presence of a tert-amine. This procedure has now been found to be applicable to nucleoside synthesis. To our knowledge, glycosylation of nitrogen heterocycles promoted by a tert-amine has not been reported until now. We describe here preliminary results of the reaction of glycosyl halides with (octylthio)carbonylpyrimidines in the presence of ethyldiisopropylamine (EDA).[9]

Our attention was first directed to the synthesis of N_3-glycosylpyrimidines, positional isomers of natural nucleosides because of biological and structural interests of them.[10] For this purpose N_1-protected pyrimidines were prepared in good yields by the reaction of the parent pyrimidines with S-octyl chlorothioformate as reported previously.[1] 1-(Octylthio)carbonyl-5-fluorouracil (1, X=F) was allowed to react with acetylglucosyl bromide (1.1 equiv) in the presence of EDA (1.1 equiv) at room temperature overnight and 3-β-D-glucopyranosyl-5-FU (4) was obtained in 75% yield accompanied with no α-anomer. N_3-ribosylpyrimidine derivatives (3) were similarly obtained in good yields (Scheme I).[11] Holý reported that an N_3-ribofuranosylthymine derivative was not obtained by the Hilbert-Johnson-type reaction,[10] while the present method gave smoothly the fully protected thymidine (3, X=Me) in 73% yield. Use of 3-(octylthio)-carbonyl-5-FU furnished the corresponding nucleoside (5) in 74% yield by the



Scheme I

reaction with ribofuranosyl bromide (2). Thus, pyrimidine nucleosides protected by the OTC and acyl groups were successfully synthesized. Glycosyl bromides were better substrates than the corresponding chlorides, and EDA was more effective as a promoter than triethylamine.

Deprotection of the OTC group was achieved very efficiently by treatment with isopropylamine without liberation of the acyl group on the sugar moieties (Scheme I) while ammonia in methanol and sodium methoxide brought about removal of both protecting groups in nearly quantitative yield.

We have here demonstrated that tert-amines, particularly EDA are an effective promoter of N-glycosidation of pyrimidines. This reaction does not need toxic heavy metal salts and application of heat. These facts and utilization of the OTC group may enable the present procedure to provide a practical alternative to the method for the synthesis of various pyrimidine nucleosides which possess sugar residues at the desired position without contamination of positional isomers. Furthermore, azoles such as benzimidazole could be converted to the nucleosides similarly by the present method.[12]

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11. Ribofuranosyl bromide (2) was prepared by the reaction of 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribose (1.3 equiv based on pyrimidine) with hydrogen bromide in acetic acid and used continuously without purification.
12. Benzimidazole also smoothly reacted with peracetylglucosyl bromide in the presence of EDA to afford the corresponding nucleoside in high yield.

(Received in Japan 9 July 1984)