CHEMISTRY LETTERS, pp. 1793-1796, 1981. 

# STUDIES ON NUCLEOSIDES AND NUCLEOTIDES.[1] SYNTHESIS OF 1-[5-(E)-ENOFURANOSYL]URACIL DERIVATIVES VIA ACI-NITROESTERS

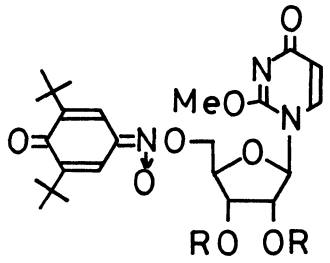
Junji KIMURA, Tatsuhiko SHIMIZU, and Oyo MITSUNOBU
College of Science and Engineering, Aoyama Gakuin University
Chitosedai, Setagaya-ku, Tokyo 157

When the aci-nitroester obtained from $N^3$-methyl- or $O^2$-methyluridine was allowed to react with acetylmethylenetriphenylphosphorane, 1-[(E)-5,6,8-trideoxy-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-3-methyl- or $O^2$-methyl-uracil (12 or 14) was selectively obtained.

In connection with creation of pharmaceuticals, it is important to exploit a new methodology for functionalization and transformation of a hydroxyl group of nucleosides. Recently, nucleoside 5'-aldehydes prepared by Pfitzner-Moffatt oxidation of 2',3'-O-protected nucleosides have been utilized as starting materials for the synthesis of nucleoside antibiotics.[2]

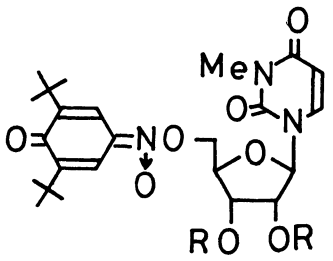
We have reported the preparation of unsaturated carboxylic esters via aci-nitroesters from simple alcohols.[3] In this paper, we wish to report the synthesis of 1-[5-(E)-enofuranosyl]uracil derivatives.

When 2',3'-O-isopropylideneuridine was allowed to react with 2,6-di-t-butyl-4-nitrophenol (1), diethyl azodicarboxylate (2), and triphenylphosphine (3), intramolecular dehydration occurred giving 2',3'-O-isopropylidene-$O^2$,5'-cyclouridine.[4] In order to prevent the undesirable cyclouridine formation, the uracil moiety was protected by methyl group. $O^2$-Methyl- or $N^3$-methyl-2',3'-O-isopropylideneuridine reacted smoothly with 1, 2, and 3 at room temperature overnight to give the corresponding aci-nitroester (4 or 5) in 67% or 70% yield, respectively. Similarly, $O^2$-methyluridine was allowed to react with 1 in the presence of 3 molar amounts of 2 and 3 to afford the corresponding aci-nitroester (6) in 64% yield.[5] When $N^3$-methyluridine was used, aci-nitroester (7) was isolated in 39% yield, undesirable N-hydrazinouridine derivative (8) being obtained in 41% yield. It is noteworthy that, in



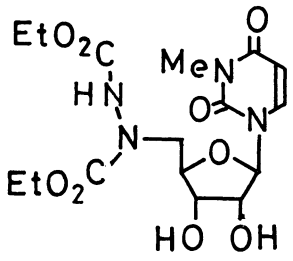
4 R= 

6 R= H



5 R= 

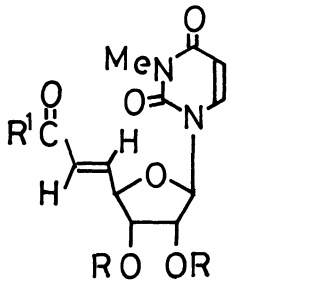
7 R= H

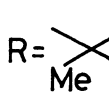


8

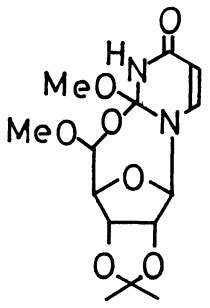
both cases, the product derived from the reaction at 2' and/or 3'-hydroxyl group could not be obtained.

Next, we investigated the reaction of aci-nitroester with a stabilized phosphorane. When aci-nitroester 5 was refluxed with 2 molar amounts of ethoxymethylenetriphenylphosphorane (9) in benzene for 6 h, 1-[(E)-5,6-dideoxy-7-ethoxy-2,3-O-isopropylidene-β-D-ribo-hept-5-eno-1,4-furanosid-7-ulosyl]-3-methyluracil (10) was obtained in 70% yield.[6] Examination by $^1$H-NMR spectroscopy showed that 10 was the pure E-isomer, $C_5$,H and $C_6$,H appearing as sharp doublets of doublets at 7.05 and 6.01 ppm with $J_{5',6'}$=16.8 Hz, $J_{4',5'}$= 5.5 Hz, and $J_{4',6'}$= 1.5 Hz. Similarly, aci-nitroester 7 was refluxed with acetylmethylenetriphenylphosphorane (11) in benzene for 2 h to give 1-[(E)-5,6,8-trideoxy-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-3-methyluracil (12) in 50% yield.[7]

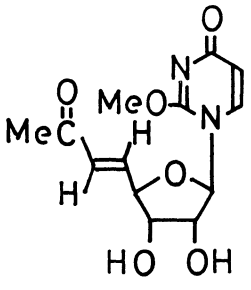


10 R=  R$^1$=EtO

12 R= H R$^1$=Me



13



14

It is generally known that aci-nitroesters are unstable and partly decompose into the corresponding carbonyl compounds and oximes by heat or light.[8] This is also the case for the aci-nitroesters derived from uridine derivatives. Thus, a solution of 4 in methanol was refluxed for 10 h to give cyclonucleoside (13; 67% yield)[9] which would be formed by intramolecular conjugate addition of initially formed $O^2$-methyluridine 5'-aldehyde hemiacetal. When aci-nitroesters were isolated by preparative layer chromatography (PLC), a small amount of oxime was invariably obtained. The formation of the oxime suggests that the aci-nitroesters are to considerable extent decomposed during work-up involving PLC.

We therefore examined the preparation of enofuranosyluracils by one-pot reaction without isolation of the aci-nitroesters. $N^3$-Methyl-2',3'-O-isopropylideneuridine was allowed to react with 1, 2, and 3 in THF at room temperature overnight and 9 was added. The resulting solution was successively refluxed for 6 h giving 10 in 82% yield. Similarly, the reaction of 6 or 7 with 1, 2, and 3 and successively with 11, 1-[(E)-5,6,8-trideoxy-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-$O^2$-methyluracil (14) or 12 was obtained in 73% or 43% yield, respectively.

As described above, the conversion of uridine into aci-nitroesters and subsequent reaction with stabilized phosphoranes provides a useful procedure for the preparation of 1-[5-(E)-enofuranosyl]uracil derivatives. Overall yield was increased by one-pot reaction. Of particular significance is the selective functionalization of 5'-carbon atom of uridines without protection of 2'- and 3'-hydroxyl groups.

General Procedure. Synthesis of 14 (One-pot reaction). To a solution of $O^2$-methyluridine (200 mg, 0.78 mmol), 1 (195 mg, 0.78 mmol), and 3 (613 mg, 2.34 mmol) in THF (3 ml) was added 2 (407 mg, 2.34 mmol) in THF (2 ml) at room temperature for 1 h. The reaction mixture was stirred overnight and 11 (496 mg, 1.56 mmol) in benzene (10 ml) was added. The resulting solution was refluxed for 2 h and evaporated under reduced pressure. The product was separated by PLC (developing solvent; chloroform : methanol = 10 : 1) to give 73% yield of 14 (mp. 189-190°C, $UV_{max}$ ($H_2O$) 228, 250 (sh) nm, Calcd. for $C_{13}H_{16}N_2O_6$; C, 52.70; H, 5.44%. Found; C, 52.28; H, 5.71%).

This work was supported financially by the Ministry of Education of Japan.

Table $^1$H-NMR Chemical Shifts (ppm) at 60 MHz and Coupling Constants(Hz) in $CDCl_3$ (* in DMSO-$d^6$).

| Compound | 5-H | 6-H | 5'-H | 6'-H | $J_{5,6}$ | $J_{5',6'}$ | $J_{4',5'}$ | Others |
|---|---|---|---|---|---|---|---|---|
| 6 | 5.95 d | 7.50 d | | | 8.0 | | | 7.55, 7.33 (quinone ring proton, d) 1.28 (t-Bu, s) |
| 7 | 5.80 d | 7.45 d | | | 8.0 | | | 7.55, 7.33 (quinone ring proton, d) 1.31 (t-Bu, s) |
| 8 | 5.80 d | 7.45 d | | | 8.5 | | | 7.63 (NH, br s) 1.23 ($CH_3$-C, t) |
| 12 | 5.83 d | 7.38 d | 6.91 dd | 6.35 d | 8.0 | 16.0 | 4.5 | |
| 13 | 5.97 | 7.94 8.01 d | | | 7.8 | | | 6.88 (NH, br d) 4.04, 3.47, 3.42 ($CH_3O$-, s) |
| 14* | 6.00 d | 7.73 d | 7.00 dd | 6.20 d | 7.8 | 16.0 | 5.6 | |

References


1) Part IX. Part VIII: J. Kimura, K. Yagi, H. Suzuki, and O. Mitsunobu, Bull. Chem. Soc. Jpn., 53, 3670 (1980).

2) N.P. Damodaran, G.H. Jones, and J.G. Moffatt, J. Am. Chem. Soc., 93, 3812 (1971). K.S. Kim and W.A. Szarek, Can. J. Chem., 59, 878 (1981).

3) O. Mitsunobu, J. Kimura, T. Shimizu, and A. Kawashima, Chem. Lett., 1980, 927.

4) M. Wada and O. Mitsunobu, Tetrahedron Lett., 1972, 1279.

5) When reaction of $O^2$-methyl- or $N^3$-methyl-uridine was allowed to react with 1 in the presence of an equimolar amount of 2 and 3, 6 or 7 was scarcely obtained. It was considered 2',3'-O-(or 3',5'-O-)triphenylphosphoranediyluridine was formed. See ref. 1.

6) Szarek et al. have recently reported the synthesis of 1-[5-(E)-enofuranosyl]uracils using DMSO-DCC oxidation of $N^3$-methyl-2',3'-O-isopropylideneuridine. See ref. 2.

7) mp. 128-130°C, $UV_{max}$ ($H_2O$) 219, 260 nm, Calcd. for $C_{13}H_{16}N_2O_6$; C,52.70; H, 5.44; N, 9.46%. Found; C, 52.20; H, 5.44; N, 9.50%.

8) J.S. Meek and J.S. Fowler, J. Org. Chem., 32, 2531 (1967).

9) mp. 124-125°C, $UV_{max}$ (MeOH) 230, 250 nm, Calcd. for $C_{14}H_{20}N_2O_7$; C, 51.24; H, 6.22; N, 8.40%. Found; C, 51.21; H, 6.14; N, 8.53%. $^1$H-NMR Spectra (6-H and methyl protons) suggests the product is about a 1 : 1 mixture of diastereomers.


(Received August 25, 1981)