BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (6), 1903—1904 (1978)

Studies on Nucleosides and Nucleotides. VI.[1] A Facile Cleavage of the Anhydro Bond of 2′,3′-*O*-Isopropylidene-*O*^{2},5′-cyclouridine with the Use of Proton Acid or Lewis Acid

Junji Kimura and Oyo Mitsunobu

Department of Chemistry, College of Science and Engineering, Aoyama Gakuin University, Chitosedai, Setagaya-ku, Tokyo 157

(Received November 9, 1977)

Synopsis. When 2′,3′-*O*-isopropylidene-*O*^{2},5′-cyclouridine (**1**) was allowed to react with methanol in the presence of *p*-toluenesulfonic acid at room temperature, 5′-*O*-methyl-2′,3′-*O*-isopropylideneuridine was obtained in good yield. Similarly, with the use of boron trifluoride etherate, **1** reacted smoothly with diphenyl phosphate to give the corresponding 5′-phosphorylated product.

Cyclonucleosides are versatile reagents for the synthesis of nucleoside derivatives.[2] Except for a few cases, however, the reactions of cyclonucleosides with nucleophiles were carried out under rather drastic conditions.[3] It is, therefore, of interest to find out the conditions under which the anhydro bond of cyclonucleosides easily cleaves.[4]

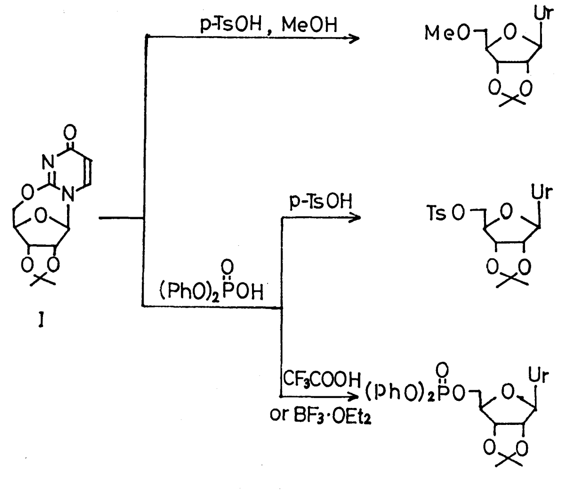
We wish to report herewith a facile cleavage of 2′,3′-*O*-isopropylidene-*O*^{2},5′-cyclouridine by nucleophiles in the presence of a proton acid or Lewis acid.

It is known that the cleavage of *O*^{2},5′-cyclouridine occurs in two directions. As an example, 2′,3′-*O*-isopropylidene-*O*^{2},5′-cyclouridine (**1**) reacts with methanol to form *O*^{2}-methyl-2′,3′-*O*-isopropylideneuridine.[5] On the other hand, it reacts with phosphate ester to give 5′-phosphorylated uridine.[3a,b]

These results suggest that, when N^3-position of uracil moiety is first protonated, 5′-substituted uridines are predominantly formed. For the sake of clarification, we examined the reaction of **1** with methanol in the presence of a proton acid.

When a solution of **1** in dry methanol was stirred with an equimolar amount of *p*-toluenesulfonic acid at room temperature for 1 day, 5′-*O*-methyl-2′,3′-*O*-isopropylideneuridine[6] was obtained as expected in 80% yield. The 5′-*O*-tosyl-2′,3′-*O*-isopropylideneuridine was treated with methanol at room temperature for 1 day. The starting material was recovered quantitatively. The possibility of intermediary formation of the tosylate in the above reaction was thus ruled out. The reaction seems to proceed through initial protonation of uracil moiety followed by the attack of methanol on the 5′-carbon atom.

The reaction was further applied to phosphorylation of uridine. When **1** was reacted with diphenyl phosphate in the presence of *p*-toluenesulfonic acid in tetrahydrofuran (THF) at room temperature, 5′-*O*-tosyl-2′,3′-*O*-isopropylideneuridine[7] was unexpectedly obtained in 81% yield. On the other hand, when the reaction was carried out in the presence of trifluoroacetic acid, 2′,3′-*O*-isopropylideneuridine 5′-(diphenyl)phosphate (**2**) was isolated in 58% yield. The yield of **2** increased to 77%, when a solution of **1** and diphenyl phsophate in THF was stirred with boron trifluoride etherate at room temperature for 2 h. This shows that boron trifluoride activates the *O*^{2},5′-anhydro bond by interaction with N^3(or *O*^{4})-position of uracil moiety.



In order to obtain a carbon-carbon bond at the 5′-position of uridine, we studied the reaction of **1** with silyl enol ether in the presence of Lewis acid. A solution of 2′,3′-*O*-isopropylidene-*O*^{2},5′-cyclouridine and cyclohexanone trimethylsilyl enol ether in THF was stirred with boron trifluoride at room temperature for 2 h. Examination by TLC revealed the formation of several products. No attempt was made to identify the products. Next, **1** was allowed to react with two molar equivalents of the silyl enol ether and titanium(IV) chloride[8] at 0 °C for 30 min. 5′-Chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine[9] was unexpectedly obtained in 84% yield.

2′,3′-*O*-Isopropylidene-*O*^{2},5′-cyclouridine was allowed to react with benzylmagnesium bromide in THF at room temperature for 3 h to form 5′-bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine (79%).[9] So far no report seems to have appeared on halogenation with the use of Grignard reagents. The reason why no benzylation takes place is not obvious.

Experimental

*5′-*O*-Methyl-2′,3′-*O*-isopropylideneuridine.* A solution of **1** (266 mg, 1 mmol) in dry methanol (25 ml) was stirred with *p*-toluenesulfonic acid (190 mg, 1 mmol) in the presence of molecular sieve at room temperature for 1 day and the resulting mixture was evaporated *in vacuo*. The product was separated by preparative TLC (Merck silica gel PF$_{254}$, 20 × 30 cm plate, developing solvent; ethyl acetate) to give 238 mg (80%) of 5′-*O*-methyl-2′,3′-*O*-isopropylideneuridine (foamy glass, $\lambda_{\max}^{\mathrm{MeOH}}$ 262 nm $\lambda_{\min}$ 231 nm, NMR (CDCl$_3$–TMS) δ 10.22

(1H, br s, N^3H) 3.41 (3H, s, OCH_3).[6]

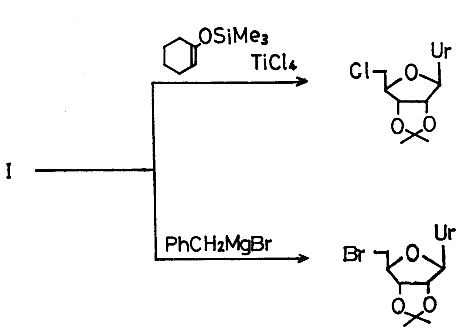
*Reactions of **1** with Diphenyl Phosphate.* *In the Presence of* p-*Toluenesulfonic Acid*: 2′,3′-*O*-Isopropylidene-O^2,5′-cyclouridine (1 mmol) was stirred with diphenyl phosphate (500 mg, 2 mmol) in the presence of *p*-toluenesulfonic acid (1 mmol) in THF (5 ml) at room temperature for 1 day. The reaction mixture was separated by preparative TLC (developing solvent; ethyl acetate). 5′-*O*-Tosyl-2′,3′-*O*-isopropylideneuridine was obtained in 81% yield (mp 152—154 °C, recrystallization from methanol, λ_{max}^{MeOH} 226 nm (ε 12500), 260 nm (ε 8500), λ_{min} 241 nm).[7] No phosphorylated product was obtained.

In the Presence of Trifluoroacetic Acid: When trifluoroacetic acid (*ca.* 2 mmol), instead of *p*-toluenesulfonic acid, was used in the above reaction, 2′,3′-*O*-isopropylidene 5′-(diphenyl)-phosphate (**2**) was isolated in 58% yield by preparative TLC (developing solvent; chloroform: methanol=10: 1). Rechromatography was carried out with ethyl acetate (colourless glass, λ_{max}^{MeOH} 261 nm, λ_{min} 230 nm, NMR($CDCl_3$–TMS) δ 10.10 (1H, s, N^3H) 7.19 (11H, PhO–, C^6H)).

In the Presence of Boron Trifluoride Etherate: The yield of **2** increased to 77% when a solution of **1** and diphenyl phosphate in THF was stirred with boron trifluoride etherate at room temperature for 2 h.

Attempts to form Carbon-Carbon Bond. *Use of Titanium-(IV) Chloride*: Titanium(IV) chloride (1 mmol) was added to a solution of 1 (1 mmol) and cyclohexanone silyl enol ether (170 mg, 2 mmol) in THF (5 ml) at 0 °C. After 30 min, satd. aqueous sodium hydrogen carbonate solution (2 ml) was added. The product was extracted with chloroform (5 ml×2) and separated by preparative TLC (developing solvent; ethyl acetate). 5′-Chloro-5′-deoxy-2′,3′-*O*-isopropylideneuridine was obtained in 84% yield (mp 178—179 °C, lit,[9] 175.5—176.5 °C) and 10% of 2′,3′-*O*-isopropylideneuridine was recovered.

Use of Grignard Reagent: A suspension of **1** (1 mmol) in THF (1 ml) was added to a freshly prepared solution of benzylmagnesium bromide (3 mmol) in THF (3 ml) at 0 °C. The reaction mixture was kept stirring at room temperature for 2 h and to it was added satd. aqueous ammonium chloride solution (20 ml). The solution was extracted with chloroform (20 ml×3) and the organic layer was evaporated *in vacuo*. 5′-Bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine was obtained in 79% yield (mp 187—189 °C, lit,[9] 184—186 °C) by preparative TLC (developing solvent; chloroform: ethyl acetate=1:1).



This work was carried out with financial support from the Ministry of Education.

References

1) Part V: S. Shimokawa, J. Kimura, and O. Mitsunobu, *Bull. Chem. Soc. Jpn.*, **49**, 3357 (1976).

2) J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969); M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969); M. Ikehara and T. Ueda, *Yuki Gosei Kagaku Kyokaishi*, **32**, 402 (1974).

3) a) J. Zemlicka and J. Smrt, *Tetrahedron Lett.*, **1964**, 2081; b) J. Nagyvary, *Biochemistry*, **5**, 1316 (1966); c) J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, *J. Org. Chem.*, **36**, 250 (1971) and refs. therein.

4) 2′,3′-*O*-Isopropylidene-O^2,5′-cyclouridine reacts with tributylammonium salt of (*O*-benzyl phosphoric)benzoic anhydride at 37 °C in dioxane. Y. Mizuno, T. Sasaki, T. Kanai, and H. Igarashi, *J. Org. Chem.*, **30**, 1533 (1965).

5) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, **1957**, 868.

6) J. T. Kusmierek, J. Giziewicz, and D. Shugar, *Biochemistry*, **12**, 194 (1973).

7) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **106**, 113 (1934).

8) Mukaiyama *et al.* have extensively studied the reaction of silyl enol ether with various substrates in the presence of $TiCl_4$. *Cf. e. g.* K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).

9) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **37**, 2289 (1972); Y. Fujisawa and O. Mitsunobu, *J. Chem. Soc., Chem. Commun.*, **1973**, 201.