CHEMISTRY LETTERS, pp. 965-968, 1982.

PROTECTION OF IMIDE GROUP OF URACIL MOIETY BY MEANS OF 2,2,2-TRICHLORO-TERT-BUTYLOXYCARBONYL CHLORIDE: A SELECTIVE SYNTHESIS OF 2'-O-METHYLURIDINE

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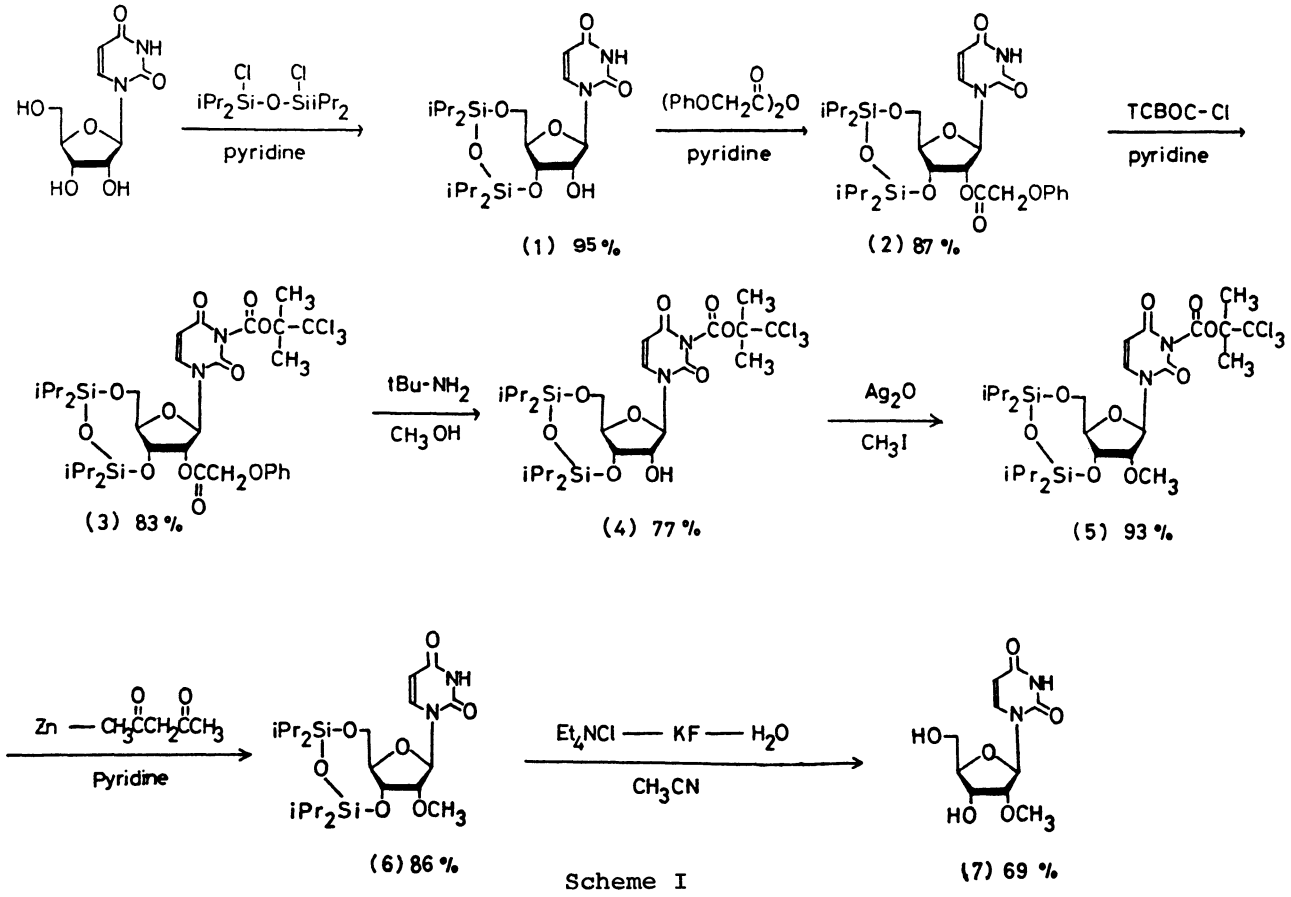
Summary: *2,2,2-Trichloro-tert-butyloxycarbonyl group (TCBOC) was useful protecting group for the protection of imide function of uracil moiety. Starting from N^3-TCBOC uridine derivative, 2'-O-methyluridine was selectively synthesized without formation of N^3-methyluridine derivatives.*

There have been several protecting groups for amino and hydroxyl functions in nucleoside chemistry. However, little attention[1] has been paid to imide group of nucleoside bases. Recently, Reese[2] and our laboratory[3] have demonstrated some of side reactions which may proceed during the coupling reactions for the synthesis of oligonucleotides. Synthesis of 2'-O-methyluridine exists in the same situation. When the methylation reaction of appropriately protected uridine was performed, methyl groups were introduced not only at the 2'-O-hydroxyl group but also the N^3-imide function.[4] In order to avoid such side reactions, we have to tackle to find out an appropriate protecting group for these groups of nucleoside bases.

After several screenings 2,2,2-trichloro-t-butyloxycarbonyl group (TCBOC) was found to be the most suitable protecting group for the imide function of uracil residue. This group can be introduced in high yield on N^3-position of uridine by means of 2,2,2-trichloro-t-butyloxycarbonyl chloride (TCBOC-Cl) which was used as a reagent for protection of amino group of amino acids in peptide synthesis[5] and is removed by treatment with zinc powder under very mild conditions.

The outline for the synthesis of 2'-O-methyluridine is shown in Scheme 1.

Procedure of each step is described as follows: When uridine (0.63 g, 2.57 mmol) was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSiCl_2) (0.85 g, 2.70 mmole) in dry pyridine (20 ml) at room temperature overnight, the corresponding 3',5'-cyclic silylether derivative of uridine (1)[6] was obtained in 95% yield (1.19 g).



Scheme I

Compound 1 (0.88 g, 1.81 mmole) was further treated with phenoxyacetic anhydride (1.55 g, 5.42 mmole)[7] in dry pyridine (10 ml) at 0°C. 2'-O-Phenoxyacetyl-3',5'-cyclic silylether derivative (2) was obtained in 87% yield (0.98 g) as a white powder.

^{1}H-NMR($CDCl_3$) δ=1.04, 1.08, 1.10(28, Si-CH(CH_3)$_2$), 3.86-4.42(4, H-3',4',5'), 4.72 (s, 2, C(O)-CH_2-OPh), 5.48(d, 1, $J_{2'-3'}$=4Hz, H-2'), 5.66(d, 1, J_{5-6}=8Hz, H-5), 5.76(s, 1, H-1'), 6.82-7.30(m, 5, O-Ph), 7.68(d, 1, H-6), 10.10(br.s, 1, H-3). Found: C, 53.09; H, 7.22; N, 4.74%. Calcd for $C_{29}H_{44}O_9N_2Si_2 \cdot 2H_2O$: C, 53.03; H, 7.37; N, 4.26%.

Compound 2 (0.98 g, 1.58 mmole) was allowed to react with TCBOC-Cl (0.95 g, 3.94 mmole) in dry pyridine at room temperature overnight to afford the corresponding N^3-TCBOC uridine derivative (3) in 83% yield (1.07 g) as a white powder.

^{1}H-NMR($CDCl_3$) δ=1.06, 1.10, 1.12(28, Si-CH(CH_3)$_2$), 2.10(s, 6, C(CH_3)$_2$$CCl_3$), 3.88-4.44(4, H-3',4',5'), 4.70(s, 2, C(O)-CH_2-OPh), 5.50(d, 1, $J_{2'-3'}$=4Hz, H-2'), 5.68 (d, 2, J_{5-6}=8Hz, H-5), 5.72(s, 1, H-1'), 6.82-7.30(m, 5, O-Ph), 7.66(d, 1, H-6). Found: C, 48.55; H, 6.13; N, 3.33; Cl, 12.48%. Calcd for $C_{34}H_{49}O_{11}N_2Si_2Cl_3 \cdot H_2O$: C, 48.48; H, 6.10; N, 3.33; Cl, 12.63%.

The phenoxyacetyl group was selectively removed from the fully protected uridine derivative (3) (0.96 g, 1.16 mmole) by treatment with t-butylamine (0.255 g, or 0.366 ml, 3.49 mmole) in methanol (25 ml) at room temperature for 20 min. The

corresponding 2'-hydroxyl derivative (4) was obtained in 77% yield (0.614 g) as a white powder.
^{1}H-NMR($CDCl_3$) δ=1.04, 1.08, 1.10(28, Si-CH(CH_3)$_2$), 2.08(s, 6, C(CH_3)$_2$$CCl_3$), 3.12 (s, 1, OH-2'), 4.04-4.40(5, H-2',3',4',5'), 5.70(s, 1, H-1'), 5.72(d, 1, J_{5-6}=8Hz, H-5), 7.68(d, 1, H-6). Found: C, 45.08; H, 6.36; N, 4.07; Cl, 16.06. Calcd for $C_{26}H_{43}O_9N_2Si_2Cl_3$: C, 45.25; H, 6.28; N, 4.06; Cl, 15.41%.

Compound 4 (0.5 g, 0.724 mmol) was methylated by use of excess methyl iodide (15.06 g, 0.106 mole) in the presence of silver oxide[4a] (0.912 g, 3.93 mmole) under reflux for 7 h. 2'-O-Methylated product (5) was obtained in 93% yield (0.472 g) as a white powder.
^{1}H-NMR($CDCl_3$) δ=1.08, 1.12(28, Si-CH(CH_3)$_2$), 2.10(s, 6, C(CH_3)$_2$$CCl_3$), 3.64(s, 3, 2'-$OCH_3$), 3.74(d, 1, $J_{2'-3'}$=4Hz, H-2'), 4.04-4.32(4, H-3',4'5'), 5.68(d, 1, J_{5-6}= 8Hz, H-5), 5.72(s, 1, H-1'), 7.90(d, 1, H-6). Found: C, 46.21; H, 6.42; N, 3.94; Cl, 14.51%. Calcd for $C_{27}H_{45}O_9N_2Si_2Cl_3$: C, 46.05; H, 6.44; N, 3.98; Cl, 15.10%.

The TCBOC group was removed by treatment of 5 (0.408 g, 0.579 mmole) with zinc powder (0.568 g, 8.69 mmole) in the presence of acetylacetone[8] (0.87 g, 8.69 mmole) in dry pyridine (15 ml) at room temperature for 15 min. The deblocked material (6) was obtained in 86% yield (0.25 g) as a white powder.
^{1}H-NMR($CDCl_3$) δ=1.08, 1.12(28, Si-CH(CH_3)$_2$, 3.66(s, 3, 2'-OCH_3), 3.72(d, 1, $J_{2'-3'}$ =4Hz, H-2'), 4.02-4.30(4, H-3',4',5'), 5.64(d, 1, J_{5-6}=8Hz, H-5), 5.72(s, 1, H-1'), 7.88(d, 1, H-6), 10.10(br.s, 1, H-3). Found: C, 52.85; H, 8.34; N, 5.44%. Calcd for $C_{22}H_{40}O_7N_2Si_2$: C, 52.77; H, 8.05; N, 5.59%.

Desilylation from 6 (93 mg, 0.186 mmole) was performed by use of potassium fluoride (62.5 mg, 1.12 mmole) and tetraethylammonium chloride (234 mg, 1.12 mmole) in aqueous acetonitrile(67:1 v/v, 4.06 ml) at 53°C for 0.5 h[9]. 2'-O-Methyluridine (7) was obtained in 69% yield which was estimated by UV absorption. (ε_{263}=10,100[4b] in 95% EtOH).
^{1}H-NMR(D_2O/t-BuOH internal) δ=3.60(s, 3, 2'-OCH_3), 3.72-4.44(5, H-2',3',4',5'), 5.94(d, 1, J_{5-6}=8Hz, H-5), 6.00(d, 1, $J_{1'-2'}$=4Hz, H-1'), 7.96(d, 1, H-6).

Quite recently, Reese[10] has reported the protection of imide and amide group with aryl group. The application of TCBOC-protected uridine unit to the oligoribonucleotide synthesis is now in progress.

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(Received April 10, 1982)