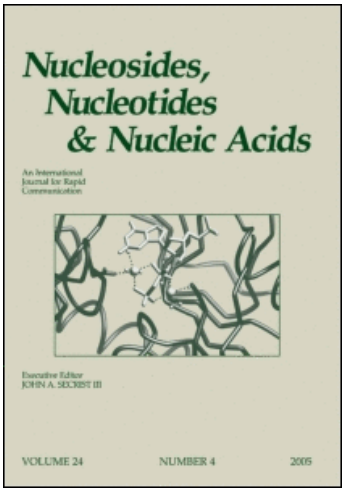

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A Simple, Preparative Procedure for N^3-Anisoyluridine and O^6-Diphenylcarbamoylguanosine 2'-O-(Tetrahydropyran-2-YL) Derivatives via The Corresponding 3',5'-Dibenzoates

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A SIMPLE, PREPARATIVE PROCEDURE FOR N^3-ANISOYLURIDINE AND O^6-DIPHENYLCARBAMOYLGUANOSINE 2'-O-(TETRAHYDROPYRAN-2-YL) DERIVATIVES VIA THE CORRESPONDING 3',5'-DIBENZOATES[1]

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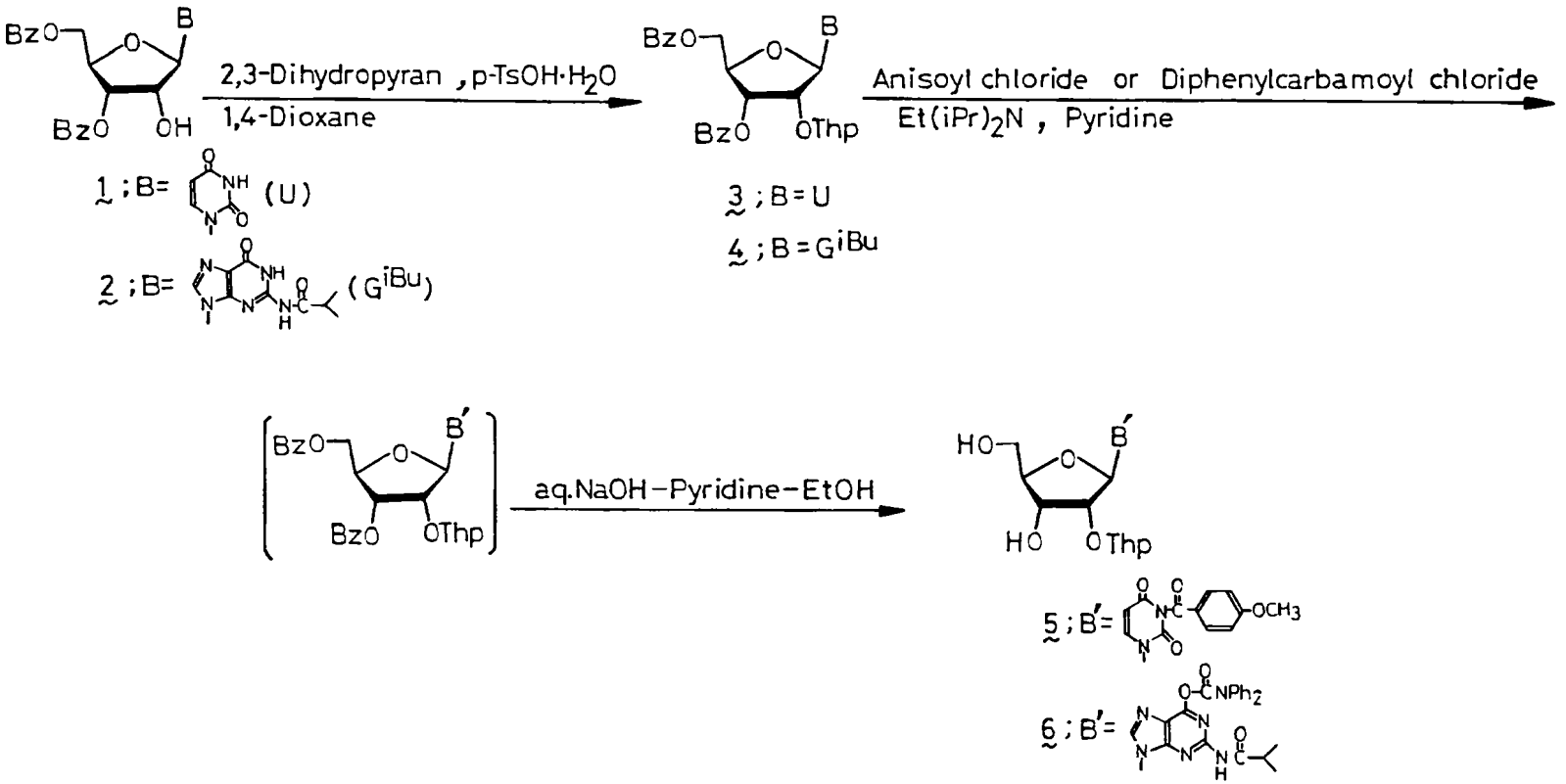
Abstract: 3',5'-Di-O-benzoyl-2'-O-(tetrahydropyran-2-yl)uridine and 3',5'-di-O-benzoyl-N^2-isobutyryl-2'-O-(tetrahydropyran-2-yl)guanosine are converted into N^3-anisoyl-2'-O-(tetrahydropyran-2-yl)uridine (less and more polar diastereoisomers in 37% and 42% yields, respectively) and O^6-diphenylcarbamoyl-N^2-isobutyryl-2'-O-(tetrahydropyran-2-yl)-guanosine (less and more polar diastereoisomers in 15% and 59% yields, respectively), respectively, by N^3-anisoylation and O^6-diphenylcarbamoylation, followed by 3',5'-di-O-debenzoylation.

INTRODUCTION

The necessity to protect the portion of nucleic acid base moieties of guanosine and uridine involving active hydrogen during oligonucleotide synthesis has been noted by Reese *et al.*[2], and is caused by side reactions on those moieties inevitably induced in nucleotide coupling reactions. These problems have given an impetus for the development of a facile and useful technique for the protection of the nitrogen heterocycles. Studies on protecting groups for the N^3-position of uridine and the O^6-position of guanosine have resulted in the development of anisoyl[3,4] and diphenylcarbamoyl groups,[5] *etc.* for this purpose. Typical intermediates employed in oligonucleotide syntheses are N^3-anisoyl-2'-O-(tetrahydropyran-2-yl)uridine[3,4] (5) and O^6-diphenylcarbamoyl-N^2-isobutyryl-2'-O-(tetrahydropyran-2-yl)guanosine[5] (6). Both 5 and 6 can be prepared by variety of methods, but the most effective way has been to use 1,3-dichloro-1,1,3,3-tetraisopropyldisoloxane for the temporary, simultaneous protection of the hydroxyl groups at the 3' and 5' positions.[3,4,5]



1 ; B= (U)

2 ; B= (G^{iBu})

3 ; B = U

4 ; B = G^{iBu}

5 ; B′=

6 ; B′=

COMPOUNDS

RESULTS AND DISCUSSION

Such aspects as described above led us to explore putting 5 and 6 to more practical use by the use of 3',5'-di-O-benzoyl-2'-O-(tetrahydropyran-2-yl)uridine (3) and 3',5'-di-O-benzoyl-N^2-isobutyryl-2'-O-(tetrahydropyran-2-yl)guanosine (4), which were respectively isolated as a glassy mixture of their diastereoisomers from each of the reaction mixtures of 2'-O-(tetrahydropyran-2-yl)ation of 3',5'-di-O-benzoyluridine[6] (1) and 3',5'-di-O-benzoyl-N^2-isobutyrylguanosine[6] (2).

Compound 3 was subjected to anisoylation with anisoyl chloride – $Et(iPr)_2N$,[4] followed by 3',5'-di-O-debenzoylation with 2 M NaOH solution in 1:2 pyridine – EtOH; both diastereoisomers of 5 were thus isolated in 37% (less polar) and 42% yields (more polar isomer). Compound 4 was subjected to O^6-diphenylcarbamoylation with diphenylcarbamoyl chloride – $Et(iPr)_2N$,[5] followed by the 3',5'-di-O-debenzoylation; both diastereoisomers of 6 were isolated in 15% (less polar) and 59% yields (more polar isomer).

The use of 1 and 2 for the preparation of 5 and 6 via 3 and 4, respectively, was concluded to be practically useful in the field of oligonucleotide synthesis.

EXPERIMENTAL

General methods. A melting point was determied by a Yanagimoto Micro-melting-point apparatus, and is uncorrected. T.l.c. was conducted on Merck silica gel F_{254} by developing with 9:1 chloroform – methanol system (Solvent A). Column chromatography was performed on silica gel (Wakogel C-300; purchased from Wako Pure Chemicals, Co. Ltd.) by the use of chloroform – methanol system. ^{1}H-n.m.r. spectra were recorded on a JEOL JNM FX 200 apparatus with tetramethylsilane (TMS) as the internal standard. Elemental analyses were achieved with a Perkin-Elmer 240-002 apparatus.

Isolation of 3 from the Mixture of (Tetrahydropyran-2-yl)ation of 1: A solution of 1 (2.7145 g, 6 mmol) in dried 1,4-dioxane (15 mL) was treated with 2,3-dihydropyran (4.1 mL, 45 mmol) and $TsOH \cdot H_2O$ (0.2853 g, 1.5 mmol) at room temperature. After stirring for 30 min, the resulting mixture was neutralized with 5% aqueous sodium bicarbonate solution, extracted with chloroform (40 mL) and washed with water (20 mL x 2).

The organic layer was evaporated and the residue was subjected to the chromatography on the column (4.5 cm, diameter x 10 cm, length; chloroform – methanol system) to give a glassy mixture of the diastereoisomers of 3 (2.9295 g, 91% yield), R_F 0.48 (Solvent A). ^{1}H-N.m.r. ($CDCl_3$ – TMS): δ 1.24 – 1.90 (6H, m, C-C$\underline{H}_2$-C x 3), 3.34 – 3.71 (2H, m, O-C$\underline{H}_2$-C), 4.55 – 4.92 (5H, m, H-2', 4', 5', 5", and O-C$\underline{H}$-O), 5.48 – 5.63 (2H, m, H-3' and 5), 6.11 and 6.14 (1H, d x 2, $J_{1',2'}$ 3.90 Hz and 5.86 Hz, H-1'), 7.27 – 7.65 and 8.03 – 8.12 (10H, m x 2, Ph proton x 10), and 9.30 – 9.50 (1H, m, N$\underline{H}$).

Conversion of 3 into 5: Compound 3 (2.9295 g, 5.46 mmol) was treated with anisoyl chloride (2.7945 g, 16.38 mmol) in the presence of $Et(iPr)_2N$ (2.85 mL, 16.38 mmol) in pyridine (27 mL) for 30 min at room temperature with stirring. After quenching the resulting mixture with water (5 mL) at room temperature with stirring for 30 min, the mixture was extracted with $CHCl_3$ (100 mL) and the extract was washed successively with 5% aqueous $NaHCO_3$ solution (50 mL x 2) and water (50 mL). The organic solution was evaporated and the residue was dissolved in 1:2 pyridine – ethanol (60 mL); the solution was treated with 2 M aqueous NaOH solution (6 mL) for 10 min at the temperature in an ice-NaCl bath. The resulting solution was neutralized with Dowex 50W (pyridinium form) resin and the resin was filtered off. The resind was washed with 1:2 pyridine – ethanol (100 mL), and the filtrate and the washing were combined and evaporated. The residue was subjected to the chromatography on the column with chloroform – methanol system to give the less polar [0.9444 g, 37% yield; R_F 0.40 (Solvent A)] and more polar diastereoisomers [1.0611 g, 42% yield; R_F 0.30 (Solvent A)] of 5. The former was crystallized from ethanol (0.7323 g, 29% yield).

The less polar isomer had m.p. 169 – 171°C, ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.44 – 1.90 (6H, m, C-C$\underline{H}_2$-C x 3), 3.14 – 3.38 (2H, m, O-C$\underline{H}_2$-C), 3.68 – 4.00 (2H, m, H-5' and 5"), 3.84 (3H, s, OC$\underline{H}_3$), 4.04 – 4.10 (1H, m, H-4'), 4.24 (1H, t, $J_{2',3'}$ 5.25 Hz, H-3'), 4.34 – 4.40 (1H, m, H-2'), 4.61 – 4.67 (1H, m, O-C$\underline{H}$-O), 5.76 – 5.79 (1H, m, H-1'), 5.77 (1H, d, $J_{5,6}$ 8.3 Hz, H-5), 6.92 (2H, d, J 8.79 Hz, Ph proton x 2), 7.85 (2H, d, J 8.79 Hz, Ph proton x 2), and 7.93 – 8.04 (1H, m, H-6).

Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.02; H, 5.67; N, 6.09.

The more polar isomer was a glass, ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.27 – 2.08 (6H, m, C-CH_2-C x 3), 2.88 – 3.01 and 3.12 – 3.28 (2H, m, HO-3' and 5'), 4.42 – 4.56 (2H, m, O-CH_2-C), 4.68 – 4.92 (2H, m, H-5" and 5"), 3.88 (3H, s, OCH_3), 4.08 – 4.13 (1H, m, H-4'), 4.30 – 4.36 (1H, m, H-4'), 4.30 – 4.36 (1H, m, H-3'), 4.55 (1H, t, H-2'), 4.72 (1H, br. s, O-CH-O), 5.82 (1H, d, $J_{5,6}$ 8.06 Hz, H-5), 5.85 (1H, d, $J_{1',2'}$ 5.1 Hz, H-1'), 6.96 (2H, d, J 9 Hz, Ph proton x 2), 7.70 (1H, d, H-6), and 7.90 (2H, d, J 9 Hz, Ph proton x 2).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.39; H, 5.80; N, 6.16.

Isolation of 4 from the Mixture of (Tetrahydropyran-2-yl)ation of 2: The mixture obtained by treating 2 (2.5270 gm 4.5 mmol) with 2,3-dihydropyran (3.33 mL, 33.75 mmol) in the presence of $TsOH \cdot H_2O$ (0.8560 g, 4.5 mmol) in 1,4-dioxane (11.25 mL) was worked up as described above and was subjected to the chromatography with chloroform – methanol system to give a glassy mixture of the diastereoisomers of 4 (2.5723 g, 90% yield), R_F 0.58 (Solvent A), ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.19 – 2.49 (6H, m, C-CH_2-C x 3), 1.277, 1.284, 1.31, and 1.32 [6H, s x 4, $C(CH_3)_2$], 2.68 – 2.84 (1H, m, $CHMe_2$), 3.10 – 3.22 (2H, m, O-CH_2-C), 4.62 – 4.92 (4H, m, H-4', 5', 5", and O-CH-O), 5.20 (1H, t, H-2'), 5.87 – 5.97 (1H, m, H-3'), 6.00 – 6.03 (1H, d x 2, $J_{1',2'}$ 5.86 Hz, H-1'), 7.23 – 8.13 (10H, m, Ph proton x 10), 9.54 and 9.60 (1H, br. s x 2, N^2H), 12.06 and 12.09 (1H, br. s x 2, H-1).

Conversion of 4 into 6: Compound 4 (2.5723 g, 4.05 mmol) was treated with diphenylcarbamoyl chloride (1.8766 g, 8.10 mmol) in the presence of $Et(iPr)_2N$ (1.06 mL, 6.08 mmol) in pyridine (20.25 mL) with stirring for 2 h at room temperature. The resulting mixture was quenched with water (5 mL) and stirred for 30 min. The mixture was extracted with chloroform (100 mL), and the organic layer was successively washed with 5% aqueous $NaHCO_3$ solution (50 mL x 2) and water (50 mL). The organic solution was evaporated and the residue was further used for the subsequent 3',5'-di-O-debenzoylation without purification. The residue obtained above was dissolved in 1:2 pyridine – EtOH (8 mL), and treated with 2 M aqueous NaOH solution (5.4 mL) at 0°C for 15 min with stirring. The mixture was neutralized with Dowex 50W (pyridinium form), and the resin was filtered off. The resin was

washed with 1:2 pyridine – water (50 mL). The filtrate and the washing were combined and evaporated; the residue was subjected to the chromatography with chloroform – methanol system to give the less polar [0.3952 g, 15% yield; R_F 0.39 (Solvent A)] and the more polar diastereoisomers [1.5153 g, 59% yield; R_F 0.34 (Solvent A)] of 6.

The less polar isomer was a glass, ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.24 – 1.27 [6H, s x 2, $C(C\underline{H}_3)_2$], 1.37 – 2.21 (6H, m, C-$C\underline{H}_2$-C x 3), 2.67 – 2.81 (1H, m, $C\underline{H}Me_2$), 3.45 – 3.52 and 3.58 – 3.81 (3H, m x 2, O-$C\underline{H}_2$-C and HO-3'), 3.96 – 4.03 (2H, m, H-5' and 5"), 4.31 (1H, br. s, O-$C\underline{H}$-O), 4.40 – 4.43 (1H, m, H-3'), 4.54 – 4.57 (1H, m, H-3'), 4.84 (1H, dd, $J_{2',3'}$ 4.88 Hz, H-2'), 4.86 – 4.94 (1H, m, HO-5'), 5.91 (1H, d, $J_{1',2'}$ 7.32 Hz, H-1'), 7.22 – 7.46 (10H, m, Ph proton x 10), 8.02 (1H, s, H-8), and 8.18 (1H, br. s, $N^2\underline{H}$).

Anal. Calcd for $C_{32}H_{36}N_6O_8 \cdot 2H_2O$: C, 57.53; H, 6.03; N, 12.57. Found: C, 57.77; H, 5.74; N, 12.31.

The more polar isomer was a glass, ^{1}H-n.m.r. ($CDCl_3$ – TMS): δ 1.23 and 1.27 [6H, s x 2, $C(C\underline{H}_3)_2$], 1.38 – 2.13 (6H, m, C-$C\underline{H}_2$-C x 3), 2.66 – 2.80 (1H, m, $C\underline{H}Me_2$), 2.97 – 3.08 and 3.33 – 3.41 (3H, m x 2, O-$C\underline{H}_2$-C and HO-3'), 3.76 – 4.02 (2H, m, H-5' and 5"), 4.18 – 4.23 (1H, m, H-4'), 4.47 – 4.58 (2H, m, O-$C\underline{H}$-O and HO-5'), 4.72 – 4.77 (1H, m, H-3'), 4.96 (1H, t, H-2'), 5.99 (1H, d, $J_{1',2'}$ 6.65 Hz, H-1'), 7.21 – 7.45 (10H, m, Ph proton x 10), 8.01 (1H, s, H-8), and 8.25 (1H, br. s, $N^2\underline{H}$).

Anal. Calcd for $C_{32}H_{36}N_6O_8 \cdot H_2O$: C, 59.07; H, 5.89; N, 12.92. Found: C, 58.77; H, 5.65; N, 12.93.

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