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[57] 3',5'-O-(TETRAISOPROPYLDISILOXANE-1,3-DIYL)RIBONUCLEOSIDES

Simultaneous Protection of 3'- and 5'-Hydroxyl Groups of Nucleosides

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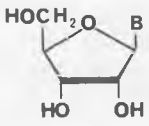
INTRODUCTION

The development of the first reagent for the simultaneous protection of the 3'- and 5'-hydroxyl groups of nucleosides, namely, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1), permits ready access to 3',5'-O-protected ribonucleosides.[1] 3',-



3a, B = uracil-1-yl
b, B = cytosin-1-yl
c, B = N^4-benzoyl-cytosin-1-yl
d, B = adenin-9-yl
e, B = guanin-9-yl

5'-O-(Tetraisopropyldisiloxane-1,3-diyl)ribonucleosides (3) are important intermediates, e.g., for the synthesis of oligoribonucleotides[1,2] and 2-O-p-tolylsulfonylribonucleosides.[1] Compounds 3 can be prepared by two alternative methods[1]; one involves use of imidazole as the base in N,N-dimethylformamide, and the other uses pyridine as the base and solvent.

PROCEDURE

General Method of Silylation

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane[1] (1) (1.1 equiv; d = 1 g/mL) is added to a magnetically stirred solution or sus-

pension of ribonucleoside[a] 2 (1 equiv.) in anhydrous pyridine[b] (2-3 mL/mmol of 2) at room temperature. Compound 2 dissolves in ~0.5 h, and pyridine hydrochloride separates. The reaction is complete[c,d] in ~2-8 h. The suspension is evaporated, and the residue is partitioned between chloroform (10 mL/mmol of 2) and the same volume of saturated, aqueous $NaHCO_3$. The aqueous layer is extracted twice with chloroform (2 x 5 mL/mmol of 2), and the extracts are combined, dried (magnesium or sodium sulfate), and evaporated to dryness under diminished pressure. Traces of pyridine are removed by several additions and evaporations of toluene,[e] the residue is dissolved in chloroform, and pure 3 is isolated in 70-80% yield by chromatography on a short column of silica gel. The column is eluted first with chloroform and then with chloroform-methanol.[f]

3',5',-O-(Tetraisopropyldisiloxane-1,3-diyl)uridine (3a)

Evaporation of the appropriate fractions gives a solid foam of 3a; R_f 0.54[c] ^1H NMR ($CDCl_3$[g]): δ 7.87 (d, 1 H, J 7 Hz,

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[a]Anhydrous nucleoside 2 must be used. Compound 2 is soluble in pyridine, and can be dried by the addition and evaporation of this solvent. For 2e, the silylation is conducted in a mixture of pyridine and N,N-dimethylformamide.

[b]Dried by refluxing with calcium hydride, distilling, and storing over molecular sieves.

[c]The progress of the reaction can be monitored by TLC on glass plates coated with Merck silica gel HF (0.25 mm layer) with 9:1 (v:v) chloroform-methanol.

[d]The reaction mixture can be kept overnight with impunity.

[e]Alternatively, pyridine is removed by coevaporation with isopropyl alcohol in the case of 3, which forms gels in toluene.

[f]The chromatography is performed on a short column of Merck TLC silica gel type H, and the concentration of methanol in chloroform is 0-5%.

[g]Further evidence of 3',5'di-O-substitution is obtained by the acetylation[1] of 3 and the appearance of a signal for H-1' as a singlet.

H-6), 5.76 (d, J 7 Hz, 1 H, H-5), and 5.81 (s, 1 H, H-1').

3',5'-O-(Tetraisopropylidisiloxan-1,3-diyl)cytidine (3b)

Pure 3b is obtained by crystallization from methanol (m.p. 165-167°) and further amounts of 3b are obtained by chromatography on a column of silica gel; R_f 0.24[c]; ^{1}H NMR[g] (Me_2SO-d_6): δ 7.72 (d, J 7 Hz, 1 H, H-6), 5.68 (d, J 7 Hz, 1 H, H-5), and 5.57 (s,

N^4-Benzoyl-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)cytidine (3c)

Evaporation of the appropriate fractions, and crystallization from hexane, gives 3c, m.p. 100-101°, R_f 0.63[c]; ^{1}H NMR[g] ($CDCl_3$): δ 8.32 (d, J, 7 Hz, 1 H, H-6)

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)guanosine (3d)

Evaporation of the appropriate fractions gives foam-like 3d; R_f 0.42[c]; ^{1}H NMR[g] ($CDCl_3$): δ 8.36 (s, 1 H, H-2 or 8), 8.07 (s, 1 H, H-8 or 2), and 6.05 (s, 1 H, H-1').

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)guanosine (3e)

To a solution of guanosine[a] (2e) (2.83 g, 10 mmol) in anhydrous N,N-dimethylformamide[h] (5 mL) are added pyridine (15 mL) followed by 1 (3.47 mL, 11 mmol), and the mixture is magnetically stirred at room temperatare. The reaction is complete overnight, as shown by TLC (R_f 0.22). Water (50 mL) is then added, and the mixture is shaken. The precipitate is filtered off, carefully washed with water, and crystallized from ethanol, to give 3e; yield 3.78 g (72%), m.p. 284-286°; R_f 0.22[c]; ^{1}H NMR[g] (Me_2SO-d_6): δ 7.80 (s, 1 H, H-8).

REFERENCES

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2. W. T. Markiewicz, E. Biala, R. W. Adamiak, K. Grzeskowiak, R. Keirzek, A. Kraszewski, J. Stawinski, and M. Wiewiorowski, Nucleic Acids Res. Symp. Ser., 115 (1980).

[h] N,N-Dimethylformamide is dried by boiling under reflux with phosphorus pentaoxide, distilling under water-pump pressure, and storing over molecular sieves.