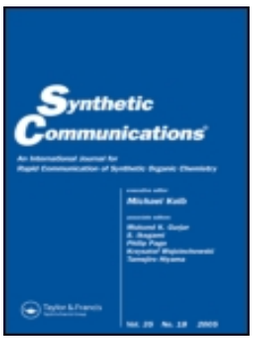

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STUDY ON THE THERMOLYSIS OF 5′-O-TRITYL-2′,3′-O-TRIPHENYL-PHOSPHORANEDIYLURIDINE

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ABSTRACT

A new method is introduced by thermolysis of 5′-O-trityl-2′,3′-O-triphenylphosphoranediyluridine (4) with or without the presence of methanol to afford the 3-N-methyl-5′-O-trityluridine (9) and 5′-O-trityl-2,2′-cyclouridine (5), respectively. Mechanism for this thermolysis is also proposed.

Substituted 1,2-diols reacted with diethoxytriphenylphosphorane (DTPP) to give the stable 1,3,2-dioxaphospholanes in neutral media, which were then cleaved to epoxides, ketones, or allylic alcohol and triphenylphosphine oxide when heated (1–3). For example, trans-1,2-cyclohexanediol afforded essentially quantitative yields (>95%) of cyclohexene oxide via an oxyphosphonium betaine intermediate. On the other hand, cis-1,2-cyclohexanediol reacted with pentaethoxyphosphorane to give a stable dioxyphosphorane (^{31}P-NMR δ −37.7 PPM), which was decomposed under vacuum thermolysis conditions (180°C, 10 torr) to give cyclohexanone

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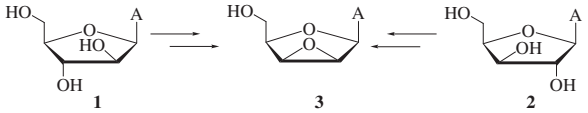

Scheme 1.

via 1,2-hydride migration (1,4). In an earlier report (5), triphenylphosphoranediyl-nucleosides were prepared by reaction of 9-(β-D-furanosyl)adenine derivatives with triphenylphosphine. Both 9-(β-D-Arabinofuranosyl)adenine (1) and 9-(β-D-Xylofuranosyl)adenine (2), containing the trans-2′,3′-diol system, gave the epoxides (3) at 70°C (Scheme 1). However, there was no report on the thermolysis of 2′,3′-O-triphenylphosphoranediylribonucleoside, which contained the cis-2′,3′-diol. In this paper, we describe the results of thermolysis of 5′-O-trityl-2′,3′-O-triphenylphosphoranediyluridine (4) and 4-N-benzoyl-5′-O-trityl-2′,3′-O-triphenylphosphoranediylcytidine (6).

2′,3′-O-Triphenylphosphoranediylnucleosides were traditionally prepared by the reaction of diethyl azodicarboxylate and triphenylphosphine (5,6). In this paper, N-chlorodiisopropylamine ($ClNPr^i_2$), an excellent reagent for the synthesis of spirophosphoranes (7,8), was employed for the reaction of 5′-O-trityluridine with triphenylphosphine. Although the procedure for the preparation of spirophosphorane involving $ClNPr^i_2$ generally is carried out under low temperature, such as −78°C, we found that 5′-O-trityluridine reacted quantitatively with equivalent amounts of $ClNPr^2_i$ and triphenylphosphine in THF at room temperature. The ^{31}P-NMR spectra supported the phosphorane structure (4) (−27.6 PPM), which was consistent with the chemical shift reported in the literature (5,9). This phosphorane intermediate (4) was applied to thermolysis without further isolation.

After overnight refluxing in THF, as indicated by ^{31}P-NMR spectrum, (4) remained unchanged. However, as the temperature of themolysis was raised by refluxing in xylene (140°C), 5′-O-trityl-2,2′-cyclouridine (5) was afforded in 84% yield. Since by TLC, there was no 5′-O-trityl-2′ (or 3′)-ketouridine detected in the reaction mixture, it would be a different mechanism from the 1,2-hydride migration. Therefore, this finding implied that O-2 of the uridine base attacked C-2′ with the elimination of triphenylphosphine oxide (Scheme 2). Similarly, 4-N-benzoyl-5′-O-trityl-2′,3′-O-triphenylphosphoranediylcytidine (6) was also applied to thermolysis under vacuum conditions (140°C, <0.1 mmHg) for half an hour. 5′-O-trityl-2,2′-cyclocytidine (7) was afforded in 42% yield (Scheme 2).

Interestingly, when phosphorane (4) was refluxed in THF/MeOH mixed solvent, a new product (9) was afforded in 56% yield. FAB-MS and ^{1}H-NMR indicated that it was a methylated derivative of 5′-O-trityluridine. In the ^{13}C-NMR spectrum, the methyl group displayed a signal at a higher field shift (27.2 PPM) than the representative chemical signal of CH_3-O. Thus, it could be concluded that the product (9) was 3-N-methyl-5′-O-trityluridine. LR-^{13}C-^{1}H COSY (in inverse

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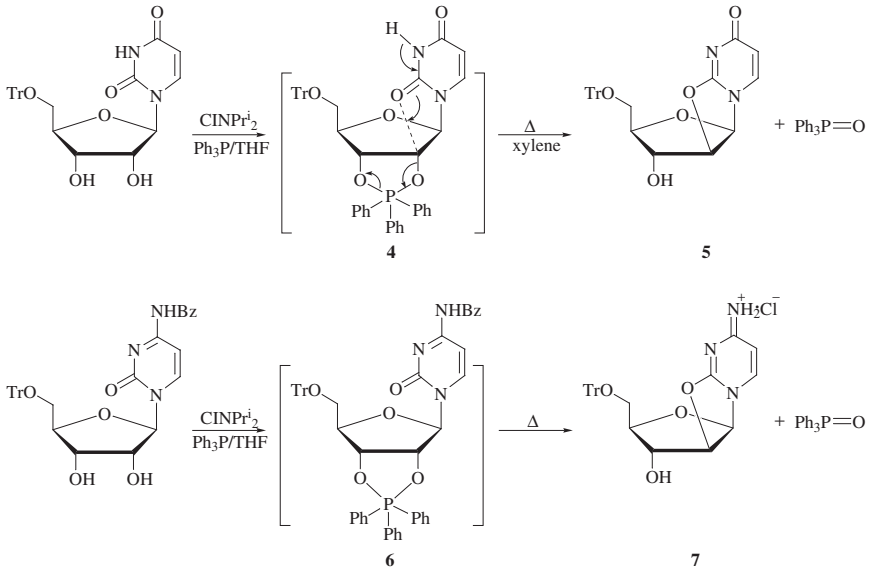


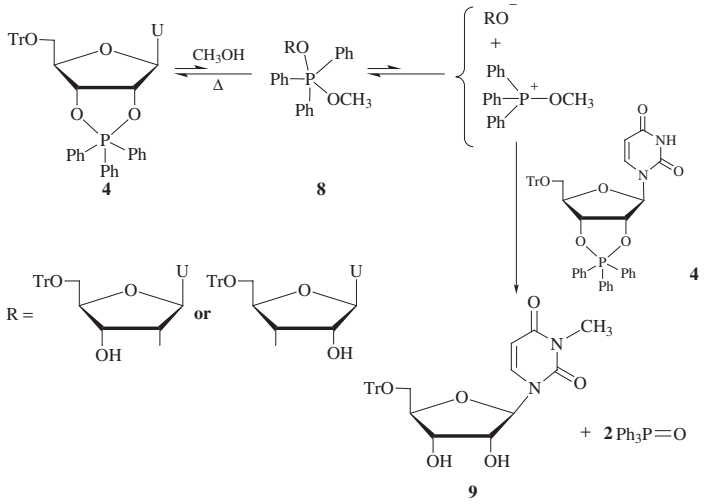
Scheme 2.

mode) also supported the structure of (9), in which the methyl group of ^{1}H-NMR had cross peaks with 2- and 4-carbonyl gruops of ^{13} C-NMR. In order to conirm its strucure, compound (9) was compared with authentic material. It was found that they had the same ^{1}H, ^{13}C-NMR spectra, and Rf value in TLC.

The formation of product (9) implied that the methyl group at 3-N should come from a good methyl donor. Since the methanol was the key reagent for this transformation, it was proposed that phosphorane (4) proceeded an ester exchange reaction with methanol (Scheme 3). This type of ester exchange reaction had been investigated intensively in our laboratory (10,11). It is worth noting that the resultant phosphorane (8) could act as the methylation reagent for uridine derivatives (Scheme 3), which is similar to the mechanism of Mitsunobu reaction (12–14). In the latter reaction, the phosphorane, $Ph_3P(OR)_2$, had been proved to be the intermediate (12,13). Similar alkylation on phthalimides and succinimides in Mitsunobu reaction had been reported in previous literature (14).

EXPERIMENTAL

All glassware was dried in an oven for at least 8 h at 120°C before use. Air-sensitive materials were transferred under nitrogen atmosphere. THF and xylene were dried by refluxing with sodium. ^{1}H, ^{13}C NMR, and ^{31}P-NMR spectra were



Scheme 3.

recorded on a Bruker AC200P spectrometer. ^{31}P chemical shifts are reported in PPM downfield (+) or upfield (−) from external 85% H_3PO_4.

Thermolysis of 5′-O-trityl-2′,3′-O-triphenylphosphoranediyluridine (4)

$ClNPr^i_2$ 0.272 g (2 mmol) in 2 mL THF was added dropwise to a solution of 5′-O-trityluridine 1.0 g (2 mmol) and triphenylphosphine 0.539 g (2 mmol) in THF 10 mL. The mixture was stirred at room temperature for 0.5 h. After the filtration of $HCl{\cdot}HNPr^i_2$ and removal of the solvent, compound (4) was afforded quantitatively as shown by ^{31}P-NMR spectrum (a single peak at −27.6 ppm). Without further isolation, this phosphorane intermediate was applied to the following thermolysis.

The resulting compound (4) was refluxed in xylene under N_2; precipitation took place shortly afterwards. After 4 h, the precipitation was collected and washed with $CHCl_3$. Elemental analytical pure 5′-O-trityl-2,2′-cyclouridine (5) was afforded in 84% yield. δ_H (200 M Hz, $(CD_3)_2SO$)): 7.94 (d, 1H, $J_{5,6}$ 7.5 Hz, H-6), 7.32–7.23 (m, 15H, Ar-H), 6.32 (d, 1H, $J_{1',2'}$ 5.6 Hz, H-1′), 5.98 (d, 1H, $J_{OH,3'}$ 4.3 Hz, 3′-OH), 5.86 (d, 1H, $J_{5,6}$ 7.5 Hz, H-5), 5.21 (d, 1H, $J_{1',2'}$ 5.6Hz, H-2′), 4.40–4.21 (m, 2H, H-3′, 4′), 2.96 (dd, 1H, $J_{5'a,4}$ 5.97, $J_{5'a,5'b}$ 10.1 Hz, H-5′a), 2.82 (dd, 1H, $J_{5'b,4}$ 7.34, $J_{5'a,5'b}$ 10.1 Hz, H-5′b); m.p. 203–205°C; ESI-MS: M/Z

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469.1 (M + 1); 491.2 (M + Na^+); 507.1 (M + K^+); Anal. calc. For $C_{25}H_{24}N_2O_5$: C, 71.78; H, 5.6; N, 5.98. Found: C, 71.40; H, 5.09; N, 6.22.

Thermolysis of 4-N-Benzoyl-5′-O-trityl-2′,3′-O-triphenylphosphoranediyl-cytidine (6)

Phosphorane (6) was prepared by the same procedure, however, without the filtration of $HCl{\cdot}HNPr^i_2$. After removal of THF, compound (6) was applied to thermolysis under vacuum conditions (140°C, <0.1 mmHg) for half an hour. When diluted with $CHCl_3$, a precipitaion was afforded as an elemental analytical pure product in 42% yield, which was characterized as 5′-O-trityl-2,2′-cyclocytidine (7). δ_H (200 M Hz, $(CD_3)_2SO$)): 9.68 and 9.40 (br, 2H, $=NH^+_2$), 8.38 (d, 1H, $J_{5.6}$ 7.3 Hz, H-6), 7.36–7.20 (m, 15H, Ar-H), 6.60 (d, 1H, $J_{5.6}$ 7.3 Hz, H-5), 6.56 (d, 1H, $J_{1',2'}$ 5.7 Hz, H-1′), 6.27 (d, 1H, $J_{OH,3'}$ 4.0 Hz, 3′-OH), 5.43 (d, 1H, $J_{1',2'}$ 5.7 Hz, H-2′), 4.42–4.20 (m, 2H, H-3′,4′), 2.97 (dd, 1H, $J_{5'a,4}$ 5.97, $J_{5'a,5'b}$ 10.1 Hz, H-5'a), 2.70 (dd, 1H, $J_{5'b,4}$ 7.34, $J_{5'a,5'b}$ 10.1 Hz, H-5'b); ESI-MS: M/Z 468.2 (M+1); Anal. calc. For $C_{28}H_{26}N_3O_4Cl$:C, 66.73; H, 5.20; N, 8.34; Found: C, 66.32; H, 5.33; N, 8.52.

Thermolysis of 5′-O-trityl-2′,3′-O-triphenylphosphoranediyluridine (4) in Methanol

Phosphorance (4) 1.2 g was prepared as described above and dissolved in a mixture of 15 mL THF and 5 mL CH_3OH. After refluxing for 5 h, a new product was found by TLC and chromatography on silica gel with $CHCl_3$ afforded 3-N-methyl-5′-O-trityluridine (9) in 56% yield. δ_H (200 M Hz, $CDCl_3$): 7.76 (d, 1H, $J_{5.6}$ 8.0 Hz, H-6), 7.38–7.25 (m, 15H, Ar-H), 5.80 (d, 1H, $J_{1',2'}$ 3.0 Hz, H-1′), 5.53 (d, 1H, $J_{5,6}$ 8.0 Hz, H-5), 4.34 (m, 2H, H-2′,3′), 4.26–4.23 (m, 1H, H-4′), 3.50 (dd, 1H, $J_{5'a,4}$ 2.7, $J_{5'a}$, 5′b 10.9 Hz, H-5′a), 3.41 (dd, 1H, $J_{5'b,4}$ 2.7, $J_{5'a,5'b}$ 10.9 Hz, H-5′b), 3.33 (s, 3H, CH_3-N); (200 M Hz, $(CD_3)_2SO$)): 5.60 (d, 1H, $J_{OH,3'}$, 4.0 Hz, 3′-OH), 5.21 (d, 1H, $J_{OH,2'}$ 4.0 Hz, 2′-OH): δ_C (200 M Hz, $(CD_3)_2SO$)): δ 143.4, 128.3,127.9 and 127.1 (Ph_3C-, Ar-C), 90.1 (Ph_3C-C), 161.9 (C-4), 150.6 (C-2), 138.8 (C-6), 100.4 (C-5), 86.4 (C-1′), 82.2 (C-2′), 73.5 (C-4′), 69.3 (C-3′), 63.0 (C-5′), 27.2 (CH_3-N); FAB-MS ($C_{29}H_{28}N_2O_6$): M/Z 501 (M + 1)

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