Pergamon

Tetrahedron, Vol. 52, No. 13, pp. 4877-4882, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00159-7

One-pot Deoxygenative Conversion of A Ribonucleoside to Enaminonucleosides Involving 1,2-Hydride Shift Rearrangement[#].

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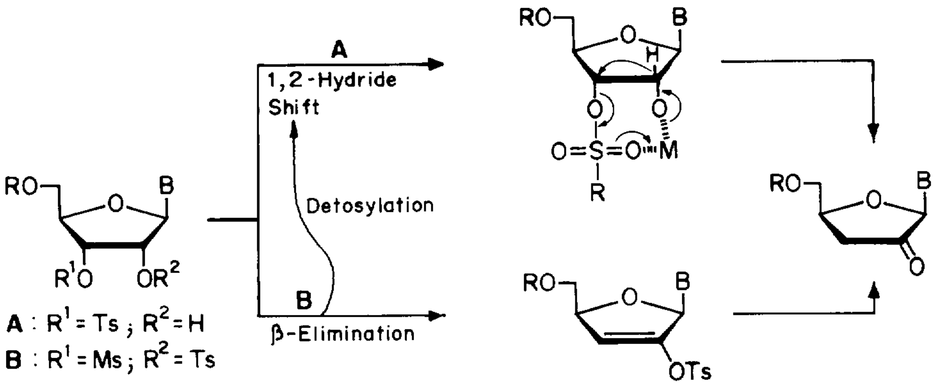
Abstract: 5'-O-Trityl-3'-O-mesyluridine on reaction with secondary amines produced 1-(2,3-dideoxy- 2-N-dialkylamino-5-O-trityl- D-*glycero*-pent-2-enofuranosyl) uracil involving 1,2-hydride shift. The reaction proceeded through the formation of 2'-ketouridine *in situ* which was evident from the formation of both the α- and β- anomers of the enaminonucleosides.

INTRODUCTION

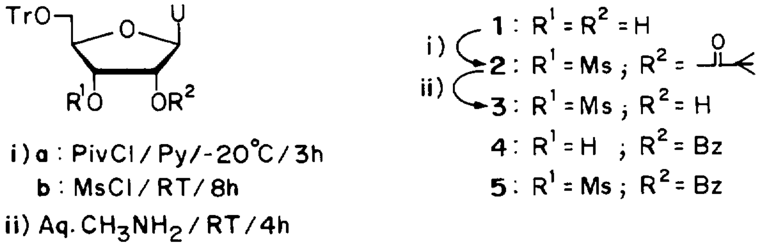
The stereoselective reduction of ribonucleotides to the corresponding 2'-deoxynucleotide compounds is catalysed by ribonucleoside diphosphate reductase[1]. A non-enzymatic, stereoselective, deoxygenation of ribofuranose derivatives involving 1,2-hydride shift was reported[2] by Kawana and his co-workers in 1975. The synthetic utility of this method was demonstrated later by various groups by synthesising novel carbohydrate[3] or nucleoside[4] derivatives. In this reaction, in case of the deoxygenation at the 3'-centre, the 2'-hydroxyl group (either free or as its sulphonyloxy derivative) adjacent to the 3'-sulphonyloxy group was converted to a carbonyl group with concomitant displacement of the sulphonyloxy group, either by an intramolecular hydride ion or through a β-elimination mechanism (Scheme 1)[4b,d,e,h]. It has, however, been shown unambiguously by using deuterium labeled carbohydrate[2] compound (compound **A**) and nucleoside[4b] (compound **B**) with free 2(2')-hydroxyl group, that the keto formation went exclusively through 1,2-hydride shift. Interestingly, all the reactions involving 1,2-hydride shift rearrangement of carbohydrates or nucleosides reported so far were carried out using reagents containing metal ions and it was proposed that the metal ion (Et_3B in case of $LiEt_3BH$)[4b] formed a complex with the free hydroxyl group and the sulphonate function of the 1,2-cis diol system.

RESULTS AND DISCUSSION

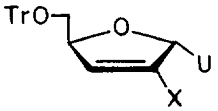
During the course of our studies[5-7] on the reactions of amines with various sulphonylated pyrimidine nucleosides we reported[7] that 1-(2,3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl) uracil **9** on reaction with secondary amines generated a new class of enaminonucleosides, namely, 1-(2,3-dideoxy-2-N-dialkylamino-5-O-trityl-D-*glycero*-pent-2-enofuranosyl) uracil. As we have established earlier that the generation of 2'-ketouridines *in situ* was a prerequisite for the formation of these enaminonucleosides, we envisaged that any nucleoside derivative capable of forming 2'-ketouridines in the reaction medium under basic or nucleophilic conditions would also generate enaminonucleosides. For reasons



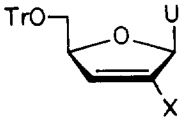
Scheme-1



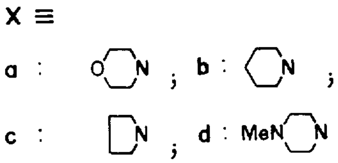
Scheme-2

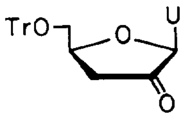


6a-d



7a-d





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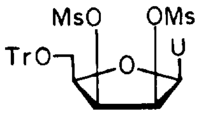

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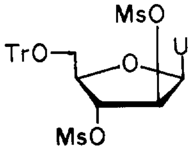

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discussed earlier (Introduction) we decided to study the reactions of 3'-O-mesyl-5'-O-trityluridine **3** with secondary amines. As a result of this study we report for the first time a one-pot conversion of a ribonucleoside derivative to enaminonucleosides involving 1,2-hydride shift without using any metal ion containing reagents.

The compound under study was synthesised in improved yield using the following sequence: uridine → **1** → **2** → **3** (Scheme **2**). Compound **3** was then reacted with morpholine, piperidine, pyrrolidine and N-methylpiperazine to furnish mixture of enamines **6a/7a**, **6b/7b**, **6c/7c** and **6d/7d** respectively in good yields. These reactions and the product distribution are more or less similar to the reactions between compound 1-(2,3-di-O-mesyl-5-O-trityl- β-D-*lyxo*furanosyl) uracil **9** and secondary amines as reported earlier[7]. To illustrate the point that products obtained from these reactions were indeed the same enamines reported earlier[7], compounds **6a** and **7a** were separated, as representative examples, from the mixture following the same procedure; both the compounds were found to be identical (^{1}H-NMR) with the earlier repoted[7] isomers.

An attempt to react 2'-O-pivaloyl-3'-O-mesyl-5'-O-trityluridine **2** with secondary amines failed and the unreacted starting material was recovered. This observation indicated that the generation of 2' free hydroxyl group was necessary for the enamine formation to take place. This assumption was further strengthened by the fact that when 2'-O-benzoyl-3'-O-mesyl-5'-O-trityluridine **5** was reacted with piperidine at elevated temperature enaminonucleoside (**6b/7b**) formation took place *via* generation of the 2'-free hydroxy derivative **3** as was evident by tlc.

A discussion on the mechanism of formation of compounds **6** and **7** from **3** would be pertinent here. It is obvious that the formation of the 2'-ketouridines is a prerequisite for the formation of the anomeric mixture of enamines **6** and **7**. The 2'-ketonucleosides **8** was shown[4b,d,e,h] to form directly from compound **3** through 1,2-hydride shift. Although all reports of 1,2-hydride shift in case of nucleosides involved metal ions, the present report on the conversion of compound **3** to the 2'-ketouridines **8** strongly argues in favour of the 1,2-hydride shift mechanism as under no circumstances a *2'-free hydroxy* nucleoside with a leaving group at the 3'-position was ever shown to form an enolic intermediate through β-elimination. It should also be noted here that although the conversion of any sulphonylated uridine to the 2'-ketouridine can take place either by 1,2-hydride shift or by the elimination of the mesylate, the pathway is controlled by the configurations at the 2'- and 3'-centers of the starting materials. For the formation of the ketouridines from the *lyxo*- derivative **9**, both the 1,2-hydride shift and mesylate elimination processes have the equal chance to operate. For *ara*- derivative **10** (ref 8), however, only β-elimination of mesylate is possible[9] as 1,2-hydride shift can take place only from the same side of the ring and the formation of compound **8** from compound **3** is possible by 1,2-hydride shift only.

In this paper, we have demonstrated for the first time that a ribonucleoside, such as uridine, as its 5'-O-trityl-3'-O-mesyluridine derivative, on reaction with secondary amines produced enaminonucleosides *via* 1,2-hydride shift. It should also be noted that our earlier studies on the reactions of the *lyxo*-uridine derivative, compound **9** with secondary amines were carried out[7] to establish the reaction pattern of a dimesyl derivative in the absence of intramolecular participation; in the present case, however, the same results were obtained from a ribonucleoside **3** with a free 2'-hydroxy group.

EXPERIMENTAL

Melting points were uncorrected. Uridine was purchased from Pharma Waldhof GmbH, Germany and used as received. Thin Layer Chromatography was performed on Merk precoated 60 F_{254} plates. Compounds were visualised on TLC plate under UV light. Column chromatographic separations were done using silica gel (Silica gel 60, 60-100 mesh, E. Merck) or basic alumina (Brockmann Grade I for Chromatography, S.D. Fine Chem. Ltd., India). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on Bruker ACF200 NMR spectrometer (δ scale) using TMS or solvent chloroform-d as internal standards. Mass spectra were recorded on Finnigan MAT 1020B GC/MS.

2'-O-Pivaloyl-3'-O-mesyl-5'-O-trityluridine 2: 5'-O-Trityluridine **1** (10mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (60ml) and the reaction mixture was cooled to -20°C in a ice-salt bath. Pivaloyl chloride (13mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was stirred at same temperature. After 3 hours, methanesulphonyl chloride (30 mmol) in pyridine (20ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 8 hours. The reaction mixture was then poured in to the aqueous saturated sodium bicarbonate solution (500ml) and was extracted with ethyl acetate (3x200ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column to furnish compound **2**. Yield: 80 %; m.p. 110°C. ^{1}H-NMR ($CDCl_3$): δ 9.25 (bs, 1H) NH; 7.64 (d, 8 Hz, 1H) H-6; 7.46-7.25 (m, 15H) trityl; 6.16 (d, 5.6 Hz, 1H) H-1'; 5.55 (t, 5.6 Hz, 1H)/5.43-5.36 (m, 2H) H-5/H-2'/H-3'; 4.39 (m, 1H) H-4'; 3.6 (d, 2.4 Hz, 2H) H-5', H-5''; 3.0 (s, 3H) mesyl CH_3; 1.26 (s, 9H) pivaloyl $(CH_3)_3$. ^{13}C-NMR ($CDCl_3$): δ 177.3, pivaloyl CO; 163.4, C-4; 150.5, C-2; 142.9, trityl; 139.9, C-6; 128.7, 128.1, 127.6, trityl; 103.1, C-5; 88.1, trityl; 86.9/82.1/75.9/72.6, C-1'/C-2'/C-3'/C-4'; 62.2, C-5'; 38.9, pivaloyl; 38.2, mesyl CH_3; 27.0, pivaloyl $(CH_3)_3$.

3'-O-Mesyl-5'-O-trityluridine 3: Compound **2** (3mmol) was treated with aqueous methylamine (3ml) at room temperature for 4 hours. After completion of the reaction (tlc), the reaction mixture was poured into water (100ml) and was extracted with ethylacetate. Ethylacetate solution was dried over anhydrous sodium sulphate and evaporated to oily material. The residue thus obtained was purified on silica gel column to produce compound **3**. Yield: 68%; m.p. 152°C. ^{1}H-NMR ($CDCl_3$): δ 10.99 (bs, 1H) NH; 7.81 (d, 8 Hz, 1H) H-6; 7.46-7.2 (m, 15H) trityl; 5.99 (d, 4.4 Hz, 1H) H-1'; 5.41-5.21 (m, 3H) H-5/ 2'-OH/H-3'; 4.76 (m, 1H) H-4'; 4.45 (m, 1H) H-2'; 3.57 (m, 2H) H-5', H-5''; 3.23 (s, 3H) mesyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 163.4, C-4; 152.1, C-2; 143.2, trityl; 140.0, C-6; 128.8, 128.3, 127.7, trityl; 102.9, C-5; 89.4, trityl; 88.1/82.0/77.5/73.6, C-1'/C-2'/C-3'/C-4'; 62.2, C-5'; 38.2, mesyl CH_3.

Reactions of 3'-O-mesyl-5'-O-trityluridine 3 with morpholine: A solution of compound **3** (0. 5mmol) in neat morpholine (2ml) was heated under reflux for 30h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl) uracil **6a** and 1-(2,3-dideoxy-2-N-morpholino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl) uracil **7a**. Yield: 72%.

Reactions of 3'-O-mesyl-5'-O-trityluridine 3 with piperidine: A solution of compound **11** (0. 5mmol) in neat piperidine (2ml) was heated at 90°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford

1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl) uracil **6b** and 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl) uracil **7b**. Yield: 65%.

Reactions of 3'-O-mesyl-5'-O-trityluridine 3 with pyrrolidine: A solution of compound 3 (0. 5mmol) in neat pyrrolidine (2ml) was heated at 80°C for 30h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl) uracil **6c** and 1-(2,3-dideoxy-2-N-pyrrolidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl) uracil **7c**. Yield: 60%.

Reactions of 3'-O-mesyl-5'-O-trityluridine 3 with N-methylpiperazine: A solution of compound 3 (0. 5mmol) in neat N-methylpiperazine (2ml) was heated at 100°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-(N-methylpiprazino)-5-O-trityl-α-D-*glycero*-pent-2- enofuranosyl) uracil **6d** and 1-(2,3-dideoxy-2-N- (N-methylpiprazino)-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl) uracil **7d**. Yield: 65%.

2'-O-Benzoyl-3'-O-mesyl-5'-O-trityluridine 5: 5'-O-Trityluridine (5mmol) was dried by coevaporation with dry pyridine and redissolved in same solvent (25ml). The reaction mixture was cooled to 0°C and benzoyl chloride (6.5mmol) in pyridine (10ml) was added dropwise to it. After completion of the addition, the reaction mixture was stirred at the same temperature for 6 hours. The reaction mixture was then poured into aqueous saturated sodium bicarbonate solution (300ml) and was extracted with ethyl acetate (3x100ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel (230-400 mesh) column to furnish 2'-O-benzoyl-5'-O-trityluridine **4** in 20% yield. 2'-O-Benzoyl-5'-O-trityluridine **4** (1mmol) was dissolved in dry pyridine (10ml). The solution was cooled at 0°C and methanesulphonyl chloride (2.5mmol) in pyridine (5ml) was added dropwise to it. After completion of the addition, the reaction mixture was allowed to warm up to room temperature and left at that temperature for 4 hours. The reaction mixture was then poured into aqueous saturated sodium bicarbonate solution (150ml) and was extracted with ethyl acetate (3x50ml). Ethyl acetate solution was evaporated to dryness and the residual pyridine was coevaporated with toluene. The residue thus obtained was purified on silica gel column to furnish compound **5**. Yield: 86%; m.p. 104°C. ^{1}H-NMR ($CDCl_3$): δ 9.1 (bs, 1H) NH; 8.12 (m, 2H) and 7.75-7.2 (m, 19H) trityl, benzoyl and H-6; 6.42 (d, 6.6 Hz, 1H) H-1'; 5.7 (t, 5.7 Hz and 6.3 Hz, 1H)/5.6 (m, 1H) H-2'/H-3'; 5.4 (d, 8 Hz, 1H) H-5; 4.5 (m, 1H) H-4'; 3.65 (m, 2H) H-5', H-5''; 2.95 (s, 3H) mesyl CH_3. ^{13}C-NMR ($CDCl_3$): δ 165.6, benzoyl CO; 163.3, C-4; 150.6, C-2; 142.9, trityl; 139.8, C-6; 134.2, 130.21, benzoyl; 128.9, 128.3, 127.7, trityl; 103.4, C-5; 88.4, trityl; 86.3/82.8/77.8/73.5; C-1'/C-2'/C-3'/C-4'; 62.7, C-5'; 38.4, mesyl CH_3. MS (EI): m/z 668 (M^+); 590 (M^+-CH_3SO_2); 504 (M^+-$C_6H_5CO_2$-NHCO); 460 (M^+-uracil-CH_3SO_3H); 425 (M^+-$C_{19}H_{15}$); 409 (M^+-$C_{19}H_{15}O$); 315 (M^+-$C_{19}H_{15}O$-CH_3SO_3H); 304 (M^+-$C_{19}H_{15}$-$C_6H_5CO_2$).

Reactions of 2'-O-benzoyl-3'-O-mesyl-5'-O-trityluridine 5 with piperidine: A solution of compound 5 (0. 5mmol) in neat piperidine (2ml) was heated at 90°C for 28h. After completion of the reaction, the amine was removed under reduced pressure. The oily residue was purified by column chromatography on basic alumina to afford 1-(2,3-dideoxy-2-N-piperidino-5-O-trityl-α-D-*glycero*-pent-2-enofuranosyl) uracil **6b** and 1-(2,3-

dideoxy-2-N-piperidino-5-O-trityl-β-D-*glycero*-pent-2-enofuranosyl) uracil **7b**. Yield: 55%.

Acknowledgement: *K.S. thanks CSIR, New Delhi for a fellowship. T.P. is grateful to the Department of Science and Technology, Government of India for financial support (Grant no. SR/OY/C03/92).*

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(*Received in UK* 24 *November* 1995; *revised* 2 *February* 1996; *accepted* 8 *February* 1996)