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UNPRECEDENTED CHLORINATION OF 2,2'-ANHYDRO-5,6-DIHYDROPYRIMIDINE NUCLEOSIDES DURING DDQ OXIDATION

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Abstract: Chloride ion, derived from 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ), was found to participate in opening of the 2,2'-anhydro bond of 5,6-dihydropyrimidine nucleosides, but not their 5,6-unsaturated counterparts. The increased basicity of the nucleosidic nitrogen is believed to be a factor in this unprecedented reaction. © 1997 Elsevier Science Ltd.

We recently reported a method for the preparation of diastereomeric 5,6-dihydrothymidines **2** starting from aminooxazoline **1**, and their subsequent conversion to thymidines **3**.[1] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) oxidation of the diastereomeric 3',5'-*bis*-silyl derivative **2a** proceeded to give thymidine **3a** in acceptable yields.[2] On the other hand, the use of MnO_2 resulted in the selective oxidation of one diastereomer in quantitative yield.[1] Unfortunately, the successful oxidation with DDQ was limited to the *bis*-silyl ether **2a** which detracted from its synthetic utility on large scales due to the high cost associated with DDQ and T-BDMSCl. Hence, we looked into using easily prepared and inexpensive 3',5'-*bis* carboxy esters to study their oxidation with DDQ whose by-product, 2,3-dicyano-5,6-dichloro-*p*-dihydroquinone (DDHQ) can be recycled to DDQ.

Ester **2b** was prepared in the usual manner and was subjected to DDQ oxidation (Scheme 1). As can be seen in Table 1, diacetate **2b** did not survive the reaction conditions (Toluene, 120 °C, 3h). The 3',5'-dipivaloyl ester **2c** was then chosen based on the assumption that it is closer in size to the silyl group, and has no α-protons, making it more stable to the reaction conditions. Indeed, oxidation of **2c** furnished the desired thymidine **3c** but in low yields. An additional less polar side-product **4c** was also formed in higher yields prompting us to elucidate its structure.

^{1}H NMR analysis of **4c** showed the presence of two pivaloyl esters and one methyl group at δ 1.1 ppm. The chemical shift of the latter coupled with the absence of an H-6 signal strongly suggested that oxidation, which results in deshielding the C-5 methyl signal to δ 1.9 ppm, did not take place, and that the by-product was still a 5,6-dihydrothymidine derivative. There was, in addition, a D_2O exchangeable proton at δ 8.6 ppm which could only be assigned to an N-H group indicating that cleavage of the 2,2'-anhydro bond had taken place. The fact that the 2'-proton did not experience a shift (δ = 5.2 ppm) strongly suggested that it is still attached to an electronegatively substituted C-2'. A simple Beilstein's test[3] as well as elemental analysis[4] clearly established the presence of chlorine in the product.

The position of the chlorine as well as its stereochemistry were determined by independent synthesis of the by-product and by its conversion to a known derivative. Treatment of **2c** with acetyl chloride furnished the 2'-chloro derivative **4c**[1] which proved to be identical with the by-product obtained from the DDQ oxidation. Furthermore, base treatment of the by-product furnished the starting material **2c**, thus confirming the position and the α-stereochemistry of the chlorine at C-2'.

Scheme 1

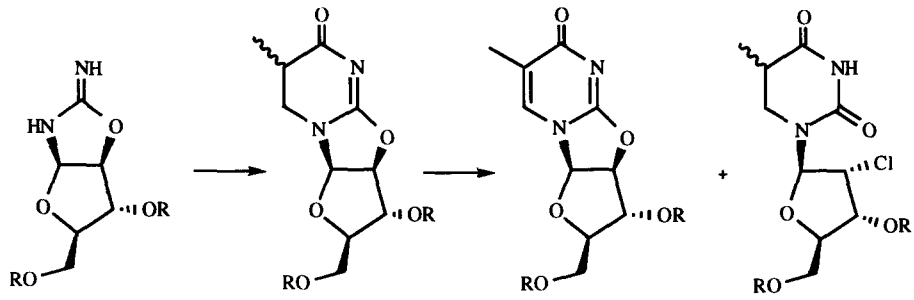


Table 1

2	3 (% yield)	4 (% yield)
a: R = TBDMS	70%	------
b: R = Ac	-----	6%
c: R = Pivaloyl	21%	48%
d: R = *p*-Tolyl	30%	45%
e: R = Tosyl	-----	------

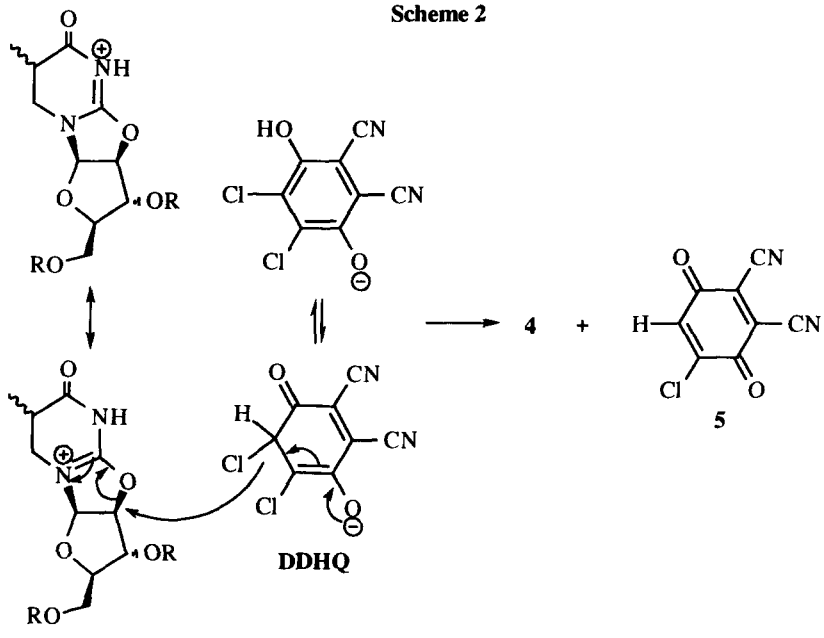
Having established the structure of the by-product attention was focused on the mechanism and scope of this unusual transformation. It seemed reasonable to assume that chlorination did not proceed by a radical mechanism since the intermediacy of a radical could lead to a mixture of stereoisomers at C-2'. The formation of a single isomer strongly suggested that an ionic mechanism is operative. It was subsequently felt that DDQ, having no acidic protons, was an unlikely source of a chloride ion leaving DDHQ as the only viable alternative. Indeed, when **2c** was treated with DDHQ the only isolated product was **4c** along with a complex mixture of polar material.

In an attempt to determine the generality and scope of this reaction, other esters were prepared. As can be seen in the table, carboxy, but not sulfonyl, esters provided the 2'-chloro derivatives **4**. Surprisingly, when the oxidized (5,6-unsaturated) 2,2'-anhydro compound **3c** was treated with DDHQ

under the same conditions, no reaction took place with recovery of the starting material. This was attributed to increased stability and/or decreased basicity of the heterocycle where initial protonation is believed to provide the driving force for opening the anhydro bond. Literature analogy for this observation is found in the furanose-pyranose isomerization of tetrahydropyrimidine nucleosides. Ring opening and closure of the sugar took place in an aqueous or acidic medium and was proposed to be facilitated by the lone pair of electrons at N-1 of the heterocycle.[5]

Based on the above findings, it is believed that the reaction is initiated by protonation of the heterocycle. Tautomerism of the resultant phenolate is followed by extrusion of the chloride ion from an *sp*3 hybridized carbon which then participates in the facilitated opening of the 2,2'-anhydro bond as depicted in Scheme 2. Attempts to isolate the dechlorinated product **5** were not successful possibly due to instability under the reaction conditions as evidenced by the formation of black polar material.

Scheme 2



A thorough search of the literature failed to reveal any precedence for this reaction.

References

1. Pragnacharyulu, P. V. P.; Vargeese, C.; McGregor, M.; Abushanab, E. *J. Org. Chem.* **1995**, *60*, 3096.
2. Subsequent to our original report (Ref 1), we have found an additional 5'-desilylated 2,2'-anhydrothymidine, raising the overall oxidation yield with DDQ to 95%.
3. Shriner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. *The Systemic Identification of Organic Compounds*, John Wiley and Sons: New York, 1980, pp. 81-82.
4. All new compounds had correct elemental analyses. Representative ^{1}H NMR data follow:
   3c δ (ppm): 1.0-1.3 (m, 21H), 2.3-2.6 (m, 1H), 3.0-3.3 (m, 1H), 3.4-3.7 (m, 1H), 3.7-4.1 (m, 2H), 4.2 (d, J = 7.0 Hz, 1H), 5.0-5.3 (m, 2H), 5.75 (d, J = 6Hz, 1H).
   3d δ (ppm): 1.9 (3H, s), 2.4 (s, 6H), 4.4 (d, J = 6Hz, 3H), 4.5-5.8 (m, 1H), 5.5-5.8 (m, 2H), 6.3 (d, J = 6Hz, 1H), 7.1-7.4 (m, 4H), 7.7-8.0 (m, 4H).
   4c δ (ppm): 1.0-1.5 (m, 21H), 2.4-2.9 (m, 1H), 1.9-3.7 (m, 2H), 4.0-4.4 (m, 4H), 5.0-5.3 (m, 1H), 6.0 (d, J = 7H, 1H), 8.33 (br s, 1H, D_2O exchangeable).
   4d δ (ppm): 1.0 (d, J = 7.0Hz, 3H), 2.4-2.8 (m, 7H), 2.8-3.8 (m, 2H), 4.2-5.0 (m, 4H), 5.3-5.6 (m, 1H), 7.3 (d, J = 8Hz, 4H), 7.8-8.1 (m, 4H), 8.3-8.6 (br s, 1H, D_2O exchangeable).
5. Kelly, J. A.; Driscoll, J. S.; McCormack, J. J.; Roth, J. S.; Marquez, V. E., *J. Med. Chem.* **1986**, *29*, 2351. Other isomerization reactions listed in this reference include nucleosides whose glycosidic nitrogen is derived from urea, 5,6-dihydrouracil, aminopyrimidine, and anthranilonitrile.

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