Tetrahedron Letters, Vol. 33. No. 50, pp. 7719-7720, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

RUTHENIUM TETRAOXIDE CATALYZED OXIDATION OF NUCLEOSIDES: A FACILE SYNTHESIS OF 5'-CARBOXYLIC ACID DERIVATIVES

Rajender S. Varma* and Michael E. Hogan

The Center for Biotechnology, Baylor College of Medicine,
4000 Research Forest Drive, The Woodlands, TX 77381, U. S. A.

Key *Words:* Ruthenium tetraoxide; Potassium persulfate; Oxidation; Nucleosides; AZT; Carboxylic acids

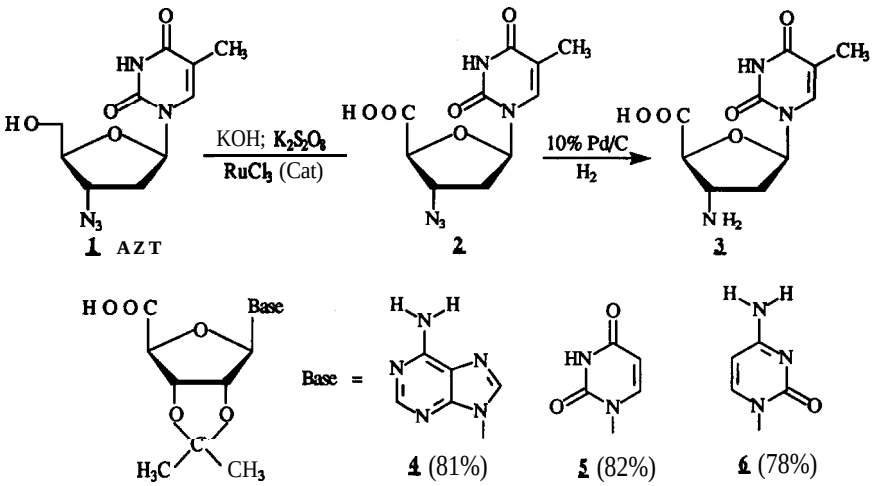
Abstract: ***Purine and pyrimidine nucleosides have been oxidized to the corresponding 5'-carboxylic acids using potassium persulfate and ruthenium trichloride under basic conditions. The method provides easy access to nucleosides bearing 3'-amino and 5'-carboxylic acid functionalities from 3'-azido compounds as exemplified by oxidation of AZT followed by reduction of the acid.***

The modification of hydroxymethylene moiety at the 5' position of nucleosides is central to the preparation of various pharmacologically important nucleoside derivatives including vasoactive agents.[1-3] There are few methods available for the oxidation of the 5'-hydroxymethylene functionality to 5'-carboxylates; they involve either the use of molecular oxygen in the presence of platinum catalyst[4,5] which gives poor yields, or involve potassium permanganate[6,7] which is applicable only to purines. In view of the growing application of ruthenium tetraoxide assisted oxidation reactions.8 we have used ruthenium trichloride ($RuCl_3$) to prepare purine 5'-carboxylic acids[9] with $NaIO_4$ as a co-oxidant under Sharpless conditions.10 Unfortunately, this method has only limited application among purines as the complete loss of chromophore occurred in case of pyrimidines, cytidine, thymidine, and uridine.[9]

In continuation of our studies, we explored a variety of co-oxidants for the ruthenium tetraoxide catalyzed reactions that may find application in the oxidation of both, purine and pyrimidine nucleosides. We wish to report that using potassium persulphate/$RuCl_3$, 5'-carboxylic acid derivatives are obtained in good yields (**2**, **4-6**).[11] The oxidation of AZT, **1**, is representative of the general procedure employed, To a well-stirred solution of AZT (lmmol) in 1M potassium hydroxide (10ml) is added potassium persulphate (3-4mmol) followed by ruthenium trichloride trihydrate (2-4mg) at room temperature. Upon completion of the reaction (3 hrs), monitored on TLC ($BuOH:AcOH:H_2O$; 5:3:2, v/v), the pH of the reaction mixture is adjusted to -7.0 with dilute HCl and the solvent removed under reduced pressure. The crude product is purified by flash chromatography on silica gel (230-400 mesh) column to afford *1-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl-5-uronic acid)thymine*, **2**, in 80% yield;

Dedicated to Dr. G. R. (Ray) Revankar on the occasion of his 55th birthday

mp **176-77°C** (dec.); FT-IR(neat): 3440, **2109(N_3)**, 1744, 1712, 1697 and 1606 cm-l; ^{1}H NMR **(DMSO-d_6): δ1.77(s, 3H, CH_3), 2.05-2.25(m, 2H,** 2-H' & 2-H"), **[4.13,** 4.45, 6.131 **(1H** each, ***4'-H, 3'-H,*** and ***1'-H)*** and 9.07 (s, **1H, C_6-*H*); ^{13}C** NMR **(DMSO-d_6):** 6172.16 (COOH), 1163.76, and 150.431 (base **-*C*=O's),** 138.43 **(*C_6*),** 106.50 **(*C_5*), [64.93,** 64.45, 65.08, and 36.5, (sugar C's)]; and 12.12 (CH3); Anal. Calcd. for **$C_{10}H_{11}N_5O_5$: C,42.71; H,3.94; N,24.91.** Found: **C,42.63;** H, 3.76; N, 25.24. The reduction of **2** under catalytic hydrogenation conditions **(10%Pd/C, 40psi,** 3 hrs, methanol) affords amino acid, ***1-(3-amino-2,3-dideoxy-β-D-erythro-pentofuranosyl-5-uronic acid)thymine, 3,*** mp **245°C** (dec) ; ^{1}H NMR **(DMSO-d_6): δ1.75(s, 3H, CH_3), 2.00-2.45(m, 2H,** 2-H' & 2-H"). **3.90(m, 1H, *4'-H*), 4.25(m, 1H, *3'-H*), 5.34(br, NH_2), 6.35(d, J=6.6Hz, 1H, *1'-H*)** and **8.8(s, 1H, C_6-*H*);** Anal. Calcd. for **$C_{10}H_{13}N_3O_5$.1/4 H_2O): C,46.24; H,5.23; N,16.18.** Found: **C,46.08; H,5.29; N,16.00.**



Our simple method for the synthesis of nucleoside **5'-carboxylic** acids may find newer applications in the synthesis of novel nucleosides and oligonucleotide analogues.

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11. Products (unoptimized and isolated yields) exhibited spectral and physical properties in accord with the assigned structures. We thank Dr. B.K. Bhattacharya for a helpful comment.

(Received in USA 24 July 1992; accepted 23 September 1992)