Tetrahedron Letters, Vol. 34, No. 48, pp. 7785-7788, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Dimethyldioxirane Oxidations: A New And Efficient desulfurization of Thiopyrimidine and Thiopurine Nucleosides.

Claudia Crestini, Raffaele Saladino*, Roberta Bernini and Enrico Mincione*.

Dipartimento Agrochimico Agrobiologico Università degli studi di Viterbo "La Tuscia", Via San Camillo de Lellis, 01100 Viterbo, Italy.

Abstact: Dimethyldioxirane reacts with 2',3',5'-tri-O-acetyl-4(3H)thiouridine **1** and 2-acetamido-6-thio-9-(2',3',5'-tri-O-acetyl-β-D-ribosyl)purine **2** to afford several interesting desulfurized products.

Thiopyrimidine and thiopurine nucleosides occur as components of transfer-ribonucleic acids (t-RNA)[1]. Little is known about the function of these thio-derivatives, but they probably play an important role in controlling the t-RNA conformation. Therefore, there has been considerable interest in their structural properties[2] and chemical modifications involving the sulphur atom especially with regard to the selective oxidation of the thioamide group[3].
Several synthetic methods are available for the conversion of thioamides into their corresponding amides; for example, m-chloroperbenzoic acid[4], phase transfer catalysed methods[5], dimethyl sulfoxide with acids[6] or iodine[7], ozone in glacial acetic acid-water solution[8], have all been used. However, the different reagents used for this conversion show varying degree of success as well as limitations due to side reactions.

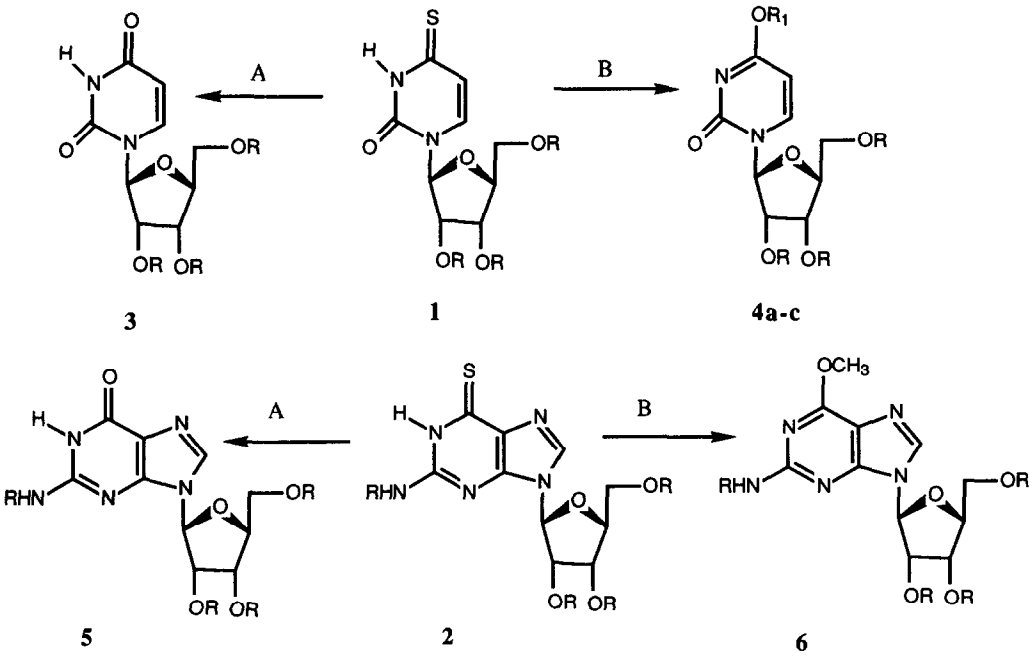
Recently, Nambiar and coworkers[9] have reported a procedure for the preparation of 2'-deoxy-4-pyrimidinone (dH^2U) and 2'-deoxy-5-methyl-4-pyrimidinone (DH^2T) nucleosides through desulfurization of the corresponding 2-thio-analogues by treatment with a m-chloroperbenzoic acid-pyridine solution; on the other hand, few data are available for the selective desulfurization of 4-thiopyrimidine and 6-thiopurine nucleosides. In this communication, we describe a new, mild and efficient procedure to effect the desulfurization of 2',3',5'-tri-O-acetyl-4(3H)thiouridine[10] **1** and 2-acetamido-6-thio-9-(2',3',5'-tri-O-acetyl-β-D-ribosyl)purine **2** using isolated dimethyldioxirane[11,12].

Brief treatment of compound **1** (1 mmol) with a freshly prepared solution of dimethyldioxirane (1 eq/mol., 0.05N acetone solution) in CH_2Cl_2 at 25°C (Method A) afforded the corresponding 2',3',5'-tri-O-acetyl-4(3H)uridine **3** in very good yield (Scheme, Table, entry 1)[13]. Moreover, the same reaction carried out in CH_2Cl_2 at 25°C in presence of alcohols (methanol, ethanol and n-butanol) as nucleophiles (1:1 v/v) afforded a separable mixture of 2',3',5'-tri-O-acetyl-4(3H)uridine **3** as main

product and 2',3',5'-tri-O-acetyl-4-alkoxyuridine **4a-c** as by-products[14].

In the formation of compound **3** the moisture present in the distilled dioxirane-acetone solution is an essential ingredient; in fact, the yield of **3** became lower when the dioxirane acetone solution was dried[15] before use over $MgSO_4$. Under these experimental conditions, using dry CH_2Cl_2 and dried alcohols (Method B), the 4-alkoxyuridine derivatives **4a-c** became the main products, and they were obtained in good yield (Table, entry 2). It is interesting to note that the oxidation of the thioamide group is faster than other possible reactions: For instance, no product of oxidation of the 5,6-double bond was recovered, in spite of the general reactivity of α,β-unsaturated ketones[16] and β-enamino ketones[17] with dimethyldioxirane.

SCHEME



R= $COCH_3$

4a: R_1=CH_3. **4b**: R_2=CH_2CH_3. **4c**: R_3=$CH_2(CH_2)_2CH_3$.

Method A: Dimethyldioxirane (1 eq/mol, 0.05 N acetone solution), CH_2Cl_2, 25 °C. Method B: dimethyldioxirane (1 eq/mol, 0.05 N acetone solution) dried before use over $MgSO_4$, dry alcohol-CH_2Cl_2 (1:1 v/v), 25 °C.

In a similar manner, oxidation of 2-acetamido-6-thio-9-(2',3',5'-tri-0-acetyl-β-D-ribosyl)purine **2** gave, 2-acetamido-6-hydroxy-9-(2',3',5'-tri-O-acetyl-β-D-ribosyl)purine **5** when performed in CH_2Cl_2[13] and 2-acetamido-6-methoxy-9-(2',3',5'-tri-O-acetyl-β-D-ribosyl)purine **6** in dry CH_2Cl_2-CH_3OH solution[18] (1:1 v/v)

[Scheme, Table, entry 3].

According to results obtained in the course of our studies[8] on the ozonation of substituted 2-thiouracils and pyrimidine-2-thione, it is resonable to suggest that the reaction migth proceed through a reactive sulfinic or persulfinic acid intermediate[19] (not isolated in our case) formed by exhaustive oxidation of the thioamide group. This intermediate, depending on the reactions conditions, can lose sulphur dioxide to give compounds **3** and **5** in presence of water, or 4-alkoxy-derivatives **4a-c** and **6** in presence of alcohols.

Table. Oxidations of compounds 1 and 2 by dimethyldioxirane[a].

Entry	Substrate	Method	Product(s)	Yield (%)
1	1	A	3	95
2	1	B[b]	4a (3)	70 (22)
			4b (3)	65 (18)
			4c (3)	75 (20)
3	2	A	5	97
	2	B[b]	6 (5)	78 (9)

a All oxidations were carried out using dimethyldioxirane in isolated form. b The yields of compounds **3** and **5** in in these experimental conditions are reported in parenthesis.
Method A: Dimethyldioxirane (1eq/mol, 0.05 N acetone solution), CH_2Cl_2, 25 °C. Method B: Dimethyldioxirane (1eq/mol, 0.05 N acetone solution) dried before use over $MgSO_4$, dry alcohol-CH_2Cl_2 (1:1 v/v), 25 °C.

The results reported above show that the oxidations of thiopyrimidine and thiopurine nucleosides with dimethyldioxirane provide a new and mild method for the conversion of thioamide-containing nucleosides into their oxygen analogues and for the selective synthesis of their alkoxy-derivatives.

Acknowledgements: We are grateful to Dott. P. Lupattelli for the spectroscopic analyses and to R. Ciafrino and L. Barcherini for the preparation of some samples; financial support from Italian MURST is acknowledged.

References and Notes.

1. Lipsett, M.N. *J. Biol. Chem.* **1965**, 240, 3975.
2. (a) Saenger, W. Angew. Chem. **1973**, 85, 680-690. (b) Saenger, W. *Angew. Chem. Internat. Edit.* **1973**, 12, 591.
3. (a) Hall, R.H. "*The Modified Nucleosides in Nucleic Acids*" Columbian University Press, New York and London **1971**, p. 347. (b) "*Organic Chemistry of Nucleic Acids*" Koechetkov, N.K. and Budovskii, E.I. Eds. Plenum Press, London and New York **1971**, part. B, p. 374. (c) "*Procedures in Nucleic Acids Research*" Cantoni, G.L. and Davies, D.R. Eds. Harper and Row Publishers New York, Evaston San Francisco London **1971**, Vol. 2, p. 643.
4. Kocchar, K.S.; Cottrel, D.A.; Pinnick, H.W. *Tetrahedron Lett.* **1983**, 24, 1323-1326.
5. Alper, H.; Kwiatkowskac, C.; Petrignani, J.F.; Sibtain, F. *Tetrahedron Lett.* **1986**, 27, 5449-5450.
6. Mikolajzyk, M.; Luczak, J. *J. Chem. Ind. (London)* **1974**, 701-702.
7. Mikolajzyk, M.; Luczak, J. *Synthesis* **1975**, 114-115.
8. Crestini, C.; Saladino, R.; Nicoletti, R. *Tetrahedron Lett.* **1993**, 34, 1631-1634.

9. Kuimelis, R.G.; Nambiar, K.P. *Tetrahedron Lett.* **1993**, 34, 3813-3816.
10. Fox, J.J.; Van Praag, S.; Wempen, I.; Doerr, I.L.; Cheong, L.; Knoll, J.E.; Eidinoff, M.L.; Bendich, A. *J. Am. Chem. Soc.* **1959**, 81, 178-187.
11. Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, 52, 699-700.
12. For recent reviews, see: (a) Curci, R. in "*Advances in Oxygenated Processes*" Baumstark, A.L. Ed.; JAI: Greenwich, C.T., **1990**; Vol. 2, chapter I, p. 1-59. (b) Adam, W.; Hadjiarapoglou, L.P.; Curci, R.; Mello, R. in "*Organic Peroxides*" Ando, W. Ed.; Wiley: New York, **1992**; chapter 4, p. 195-219.
13. All well known products were compared with authentic samples and all spectroscopic data were in agreement with those reported in literature.
14. 4-Methoxy-1-(2',3',5'-tri-O-acetyl-β-D-ribosyl)uracil **4a**- oil, Mass spectrum m/e= 384(M+, 12%). Anal. Calcd. for $C_{16}H_{20}N_2O_9$: C, 50% ; H, 5.24% ; N, 7.29% . Found. C, 50.18% ; H, 7.32% ; N, 7.18%. I.R. ($CHCl_3$) vmax: 1760, 1680, and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.64 (1H, d, J= 7.5 Hz, C5-H), 6.14 (1H, d, J= 4.2 Hz, C1'-H), 5.90 (1H, d, J= 7.5 Hz, C6-H), 5.31 (2H, m, C2'-H and C3'-H), 4.34 (3H, m, C4'-H and C5'-H), 3.93 (3H, s, OCH_3), 2.09 (9H, s, $COCH_3$).
4-Ethoxy-1-(2',3',5'-tri-O-acetyl-β-D-ribosyl)uracil **4b**- oil, Mass spectrum m/e= 398(M+, 18%). Anal. Calcd. for $C_{17}H_{22}N_2O_9$: C, 51.25% ; H, 5.57% ; N, 7.03% . Found. C, 51.16% ; H, 5.52% ; N, 7.12%. I.R. ($CHCl_3$) ν_{max}: 1760, 1680, and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.65 (1H, d, J= 7.2 Hz, C5-H), 6.18 (1H, d, J= 3.2 Hz, C1'-H), 5.90 (1H, d, J= 7.2 Hz, C6-H), 5.32 (2H, m, C2'-H and C3'-H), 4.37 (5H, m, OCH_2, C4'-H and C5'-H), 2.09 (9H, s, $COCH_3$), 1.32 (3H, m, CH_3).
4-Butoxy-1-(2',3',5'-tri-O-acetyl-β-D-ribosyl)uracil **4c**- oil, Mass spectrum m/e= 426(M+, 8%). Anal. Calcd. for $C_{19}H_{26}N_2O_9$: C, 53.52% ; H, 6.14% ; N, 6.57% . Found. C, 53.61% ; H, 6.10% ; N, 6.65%. I.R. ($CHCl_3$) ν_{max}: 1760, 1680, and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 7.65 (1H, d, J= 7.7 Hz, C5-H), 6.17 (1H, d, J= 3.2 Hz, C1'-H), 5.91 (1H, d, J= 7.7 Hz, C6-H), 5.32 (2H, m, C2'-H and C3'-H), 4.39 (5H, m, OCH_2, C4'-H and C5'-H), 2.10 (9H, s, $COCH_3$), 1.3-1.7 (4H, m, CH_2), 0.97 (3H, m, CH_3).
15. Murray, R.W.; Jeyaraman, R. *J. Org. Chem.* **1985**, 50, 2847-2853.
16. Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1990**, 31, 331-334.
17. Lupattelli, P.; Saladino, R.; Mincione, E. to be published in *Tetrahedron Lett.* .
18. 2-acetamido-6-methoxy-9-(2',3',5,-tri-O-acetyl-β-D-ribosyl)purine **6**- oil, Mass spectrum m/e= 465(M+, 3%). Anal. Calcd. for $C_{19}H_{23}N_5O_9$: C, 49.0% ; H, 4.98% ; N, 15.05% . Found. C, 49.12% ; H, 5.02% ; N, 15.12%. I.R. ($CHCl_3$) ν_{max}: 1760, 1680, and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 8.03 (1H, broad singlet, NH), 7.90 (1H,s, C8-H), 6.05 (1H, d, J= 4.5 Hz, C1'-H), 5.90 (1H, m, C2'-H), 5.68 (1H, m, C3'-H), 4.42 (3H, m, C4'-H and C5'-H), 4.11 (3H, s, OCH_3), 2.52 (3H, s, $NCOCH_3$), 2.06 (9H, s, $COCH_3$).
19. Evans, R.M.; Jones, P.G.; Palmer, P.J.; Stephens, F.F. *J. Chem. Soc.* **1956**, 4, 4106-4113.

(Received in UK 10 August 1993; accepted 24 September 1993)