A New and Efficient Synthesis of Cytidine and Adenosine Derivatives by Dimethyldioxirane Oxidation of Thiopyrimidine and Thiopurine Nucleosides

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Dimethyldioxirane oxidation of thiopyrimidine and thiopurine nucleosides, in the presence of amines in stoichiometric amount, afforded selectively and under mild experimental conditions cytidine and adenosine nucleosides.

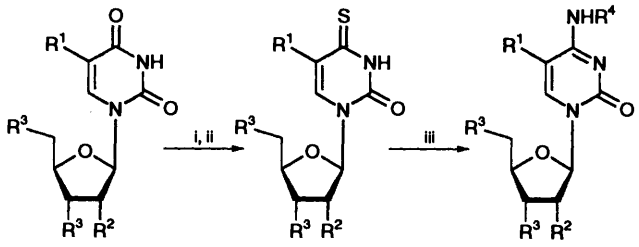
Thiopyrimidine and thiopurine nucleosides occur as minor bases in bacterial tRNA.[1] Although little is known about the function of these thio derivatives, they probably play an important role in controlling the tRNA conformation. Therefore, several studies have been performed to understand the biological significance of these derivatives and there has been considerable interest in their chemical modification especially with regard to the oxidation of the thioamide group. A modification of these derivatives which is both fundamental and interesting is their transformation to cytidine and adenosine nucleosides. For example, potassium permanganate,[2] sodium metaperiodate,[3] osmium tetraoxide,[4] iodine,[5] cyanogen bromide[6] and iodosylbenzene[7] have all been used for the transformation of 4-thiouridine to uridine or, in presence of added nucleophiles such as ammonia or methylamine, to uridine plus cytidine derivatives. However, the reagents used for this conversion sometimes require drastic experimental conditions which, because of the limitations imposed by side reactions, show varying degrees of success.

Recently, we have employed the oxidation of substituted thiouracils,[8] thiopyrimidine and thiopurine nucleosides[9] with dimethyldioxirane in alcohols for site-specific introduction of alkoxyl moieties at C-2 (C-4) and C-6 of uracil and guanine residues, respectively. Although Danishefsky[10] described the ready oxidation of amines to hydroxylamines by dioxirane, to the best of our knowledge, there are no reports dealing with the dioxirane oxidation of the thioamide moiety in the presence of easily oxidisable amines. Here we describe new and efficient reactions in which suitably protected thionucleosides are selectively converted, under mild experimental conditions, by dimethyldioxirane in the presence of amines in stoichiometric amount, to the corresponding cytidine and adenosine derivatives.

Uridine **1** was first converted (Scheme 1) *via* its 2',3',5'-tri-*O*-acetyl derivative (not shown) into the corresponding 2',3',5'-tri-*O*-acetyl-4-thiouridine **2** in 87% overall yield for the two steps, as described by Fox and co-workers.[11]

Compound **2** was then allowed to react with a freshly prepared solution of dimethyldioxirane (0.08 mol dm^{-3} acetone solution[12]; 1.5 equiv. mol^{-1}) in CH_2Cl_2 (5 cm^3) at 25 °C in the presence of a stoichiometric amount of various amines (ammonia, methylamine, propylamine and *p*-toluidine) as the nucleophile to give the corresponding acetylated cytidine derivatives **3a–d**. These were then deacylated with an excess of ammonia in methanol to give cytidine **4a** and cytidine nucleosides **4b–d** in high yields (**4a**, 83%; **4b**, 77%, **4c**, 71%; **4d**, 78% overall yields for the two steps).

By the use of the same general approach, two biologically important nucleosides, 1-(2'-deoxy-β-D-ribosyl)-5-methylcytosine **11** (5 mC) and 1-(2'-deoxy-β-D-ribosyl)cytosine **12**,[13] have been synthesized (Scheme 1). 3',5'-Di-*O*-acetyl-4-thiothymidine



a R^4 = H; **b** R^4 = Me; **c** R^4 = Pr; **d** R^4 = C_6H_4Me-*p*

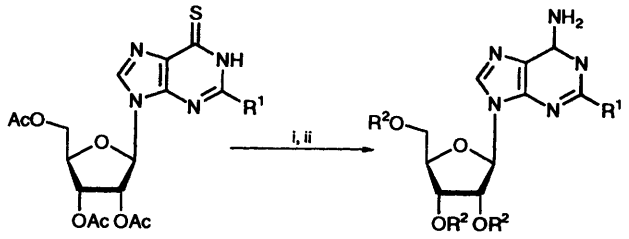
1, 4a-d R^1 = H, R^2 = R^3 = OH
2, 3a-d R^1 = H, R^2 = R^3 = OAc
5, 11 R^1 = Me, R^2 = H, R^3 = OH, R^4 = H
6, 9 R^1 = Me, R^2 = H, R^3 = OH, R^4 = H
7, 12 R^1 = R^2 = H, R^3 = OH, R^4 = H
8, 10 R^1 = R^2 = H, R^3 = OAc, R^4 = H

Scheme 1 *Reagents and conditions:* i, AcOH, AcCl, Ac_2O, 25 °C, 24 h; ii, Py, P_2S_5, H_2O, reflux; iii, dimethyldioxirane (1.5 equiv. mol^{-1}), amine (1.1 equiv. mol^{-1}), CH_2Cl_2, 25 °C; iv, ammonia (2.0 mol dm^{-3} solution in MeOH; 15 equiv. mol^{-1}), 24 h

6, prepared starting from thymidine **5** as described by Fox,[11] and 2',3'-di-*O*-acetyl-2'-deoxy-4-thiouridine[11] **8**, easily prepared from 2'-deoxyuridine **7**, reacted under the previously described conditions with dioxirane and ammonia (1.1 equiv. mol^{-1}) to give 3',5'-di-*O*-acetyl-5-methylcytidine **9** and 3',5'-di-*O*-acetyl-2'-deoxycytidine **10**. Deacetylation of compounds **9** and **10** afforded products **11** and **12** in 81 and 87% overall yields, respectively.

Attention was next turned to the use of 6-thiopurine nucleosides, 6-thio-9-(2',3',5'-tri-*O*-acetyl-β-D-ribosyl)purine **13** and 2-acetamido-6-thio-9-(2',3',5'-tri-*O*-acetyl-β-D-ribosyl)purine **14**, as starting materials for the synthesis of adenosine nucleosides (Scheme 2). Compounds **13** and **14** reacted with dioxirane and ammonia (1.1 equiv. mol^{-1}) to give the acetylated adenosine derivatives **15** and **16**. Finally, deprotection of the last mentioned compounds **15** and **16** afforded adenosine **17** and 2-aminoadenosine (^{NH_2}A) **18** in satisfactory overall yields (79 and 73%, respectively) for the two steps.

It is interesting to note that the reported amination of the thioamide moiety present in thiopyrimidine and thiopurine nucleosides by dimethyldioxirane was very selective. In fact, no desulfurized products and *N*-hydroxylamine derivatives were detected, showing that the possible desulfurization[8] and/or the amine oxidation pathways were uncompetitive reactions under these experimental conditions. Moreover, we detected no trace



13 R^1 = H
14 R^1 = NHAc

15 R^1 = H, R^2 = Ac
16 R^1 = NHAc, R^2 = Ac
17 R^1 = R^2 = H
18 R^1 = NH_2, R^2 = H

Scheme 2 *Reagents and conditions:* i, Dimethyldioxirane (1.5 equiv. mol^{-1}), ammonia (2.0 mol dm^{-3} solution in MeOH; 1.1 equiv. mol^{-1}), 25 °C, 4 h; ii, ammonia (2.0 mol dm^{-3} solution in MeOH; 15 equiv. mol^{-1}), 25 °C, 24 h

of a product formed by C–H(1′) oxygen insertion on the ribosyl or 2′-deoxyribosyl moieties, in spite of reported reactivity of acetal derivatives with dioxirane.[14] Work is in progress in our laboratories to study the use of this procedure for the site-specific modifications of oligonucleotides containing thio-nucleosides.

Experimental

Typical Procedure for the Synthesis of Cytidine and Adenosine Derivatives.—To a solution of 2′,3′,5′-tri-*O*-acetyl-4-thiouridine **2** (240 mg, 0.74 mmol) and propylamine (0.065 cm^3, 0.8 mmol) in CH_2Cl_2 (5 cm^3) at 25 °C, was added a freshly prepared solution of dimethyldioxirane (0.08 mol dm^{-3} solution; 1.5 equiv. mol^{-1}). After 3 h the reaction mixture was evaporated and the residue was purified by flash chromatography ($CHCl_3$ as eluent) to give 2′,3′,5′-tri-*O*-acetyl-N^4-propylcytidine **3c** (243 mg, 80%). Compound **3c** (243 mg, 0.59 mmol) was then treated with an excess of ammonia in methanol (2 mol dm^{-3} solution; 2 cm^3) at 25 °C for 12 h to give N^4-propylcytidine **4c** (120 mg, 71%) as an oil; δ_H(CD_3OD, 200 MHz) 0.86 (3 H, t, *J* 4, CH_3), 1.50 (2 H, m, CH_2), 3.26 (3 H, m, 4′-, 5′-, 5″-H), 3.72 (2 H, m, CH_2), 3.96 (2 H, m, 2′-, 3′-H), 5.70 (2 H, m, 1′-, 5-H), 7.78 (1 H, d, *J* 2.5 Hz, 6-H); δ_C[CD_3OD, 200 MHz] 10.27 (CH_3), 21.41 (CH_2), 41.69 (CH_2), 60.12 (CH_2), 62.54 (CH), 68.70 (CH), 74.27 (CH), 83.87 (CH), 95.37 (CH), 139.23 (CH), 156.99 (C) and 163.51 (C); *m/z* 285 (M^+, 25%).

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