Short Synthesis of 2,4-Disubstituted 1,3-Oxathiolane and 1,3-Dithiolane Cytosine Nucleosides: Facile Introduction of a 4-Benzoate Group Using Benzoyl Peroxide

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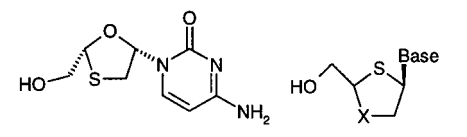
Abstract: Introduction of a benzoate group at position 4 in 2-substituted 1,3-oxathiolane and 1,3-dithiolane using benzoyl peroxide is described. The coupling reaction between 1,3-oxathiolane derivatives **3** and pyrimidine bases in the presence of TMSI produced *cis* nucleoside analogs selectively.

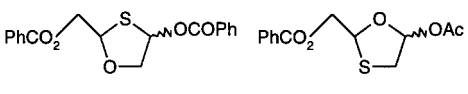
Key words: benzoyl peroxide, benzoate as leaving group, 1,3-oxathiolane, 1,3-dithiolane, pyrimidine bases, TMSI, *cis* nucleoside analogs selectively

Nucleoside analogs such as 3′-azido-3′-deoxythymidine (AZT),[1] 2′,3′-dideoxycytidine (ddC),[2] 2′,3′-dideoxyinosine (ddI),[3] and 3′-dideoxy-2′,3′-didehydrothymidine (d4T)[4] are amongst the most active agents against HIV-1 and HIV-2, the causative agents of AIDS.[5] Unfortunately, these compounds possess undesirable pharmacological properties[6] and they are susceptible to the development of resistant strains of HIV.[6,7] In an attempt to overcome some of these detrimental side effects, dideoxynucleoside analogs in which the furanosyl moiety has been replaced by other five-membered rings have been described.[6d,7] Amongst these analogs is (–)-2′-deoxy-3′-thiacytidine (3TC, Epivir) **1** which is presently in the market for AIDS and in advanced clinical trials for HBV chronic infections.[8]

We have considered an approach to further modify the oxathiolane ring by transposing the sulfur and oxygen atoms of **1** leading to the synthesis of 2,4-disubstituted-1,3-oxathiolane derivatives.[7] In fact, thioribonucleosides have been shown to be of biological interest.[9,10] Their resistance to bacterial cleavage[10] suggests that the replacement of the furanose ring oxygen with sulfur may also confer resistance to phosphorylases. In this communication, we wish to report a facile synthesis of the sugar portion of 2,4-disubstituted 1,3-oxathiolane and the related 1,3-dithiolane nucleoside analogs of the general structure **2**. We also describe the use of **3** in the preparation of the corresponding cytosine nucleosides in a *cis* diastereoselectivity.



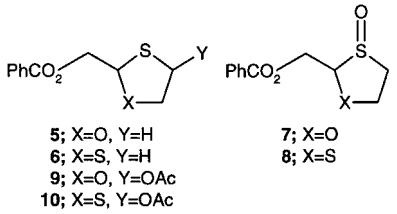
1; 3TC™ **2**; X=O, S



3 **4**

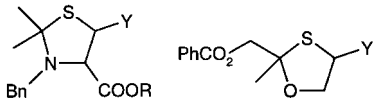
The initial synthetic route7[a–c] to **3** was based upon reacting benzyloxyacetaldehyde with 2-sulfanylethanol or ethane-1,2-dithiol in refluxing benzene in the presence of pTSA, followed by a Pummerer rearrangement. The latter consists of two steps: oxidation of benzoate **5** or **6** by mCPBA followed by acetylation and rearrangement of the sulfoxides **7** or **8** using harsh conditions i.e. refluxing acetic anhydride at 120 °C.

However, this approach particularly in the case of the dithiolane **10** resulted in very low yields <5%, and the presence of significant amounts of sulfoxides **7** or **8**, as well as formation of undesirable byproducts which limited the utility of this process. An alternative approach to the synthesis of acetate **9** or **10** was also not successful starting from thiocarboxylic acid and dithiocarboxylic acid upon cyclization with aldehyde followed by reduction of the thiolactone and acetylation. This method required several steps, gave low yields and it requires good purity of starting material i.e. thioacid.



5; X=O, Y=H
6; X=S, Y=H
9; X=O, Y=OAc
10; X=S, Y=OAc

7; X=O
8; X=S

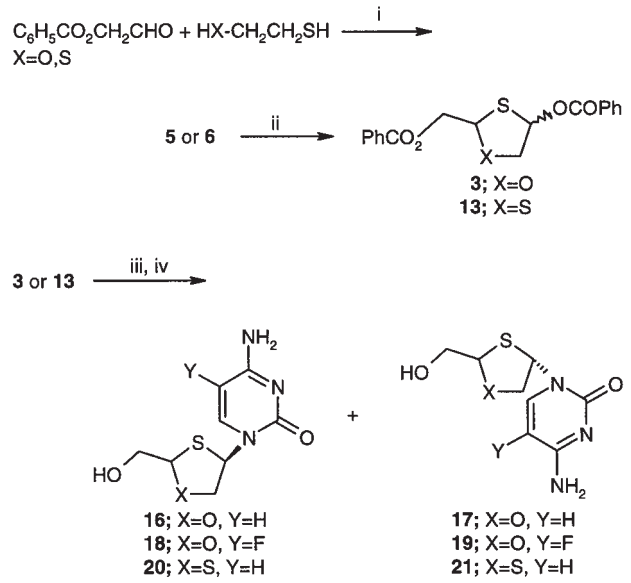


11; Y=H
12; Y=OCOPh

14; Y=H
15; Y=OCOPh

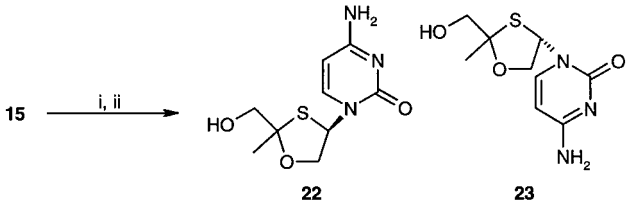
A novel approach was employed in order to circumvent these problems as well as to develop a short synthesis to prepare 1,3-oxathiolane and dithiolane rings bearing a leaving group at position 5. Szarek and co-workers[11] functionalized the protected L-cysteine derivative **11** α to the sulfur moiety by oxidation with benzoyl peroxide to give (4*R*)-3-benzoyl-5-benzoyloxy-4-methoxycarbonyl-2,2-dimethylthiazolidine (**12**). We, therefore, investigated the direct oxidation of **5** with this reagent (Scheme 1).

Indeed, treatment of **5** with benzoyl peroxide under refluxing conditions in dry benzene during four hours produced a mixture of benzoates **3**[12] (*cis*/*trans* 1:1) in 50% isolated yield. The corresponding dithiolane **6** also gave **13** in lower yield. In both cases some sulfoxides **7** and **8** were competing with the formation of **3** and **13**. No prod-



i: benzene, pTSA; ii: benzoyl peroxide, benzene, heat; iii: TMSI, CH_2Cl_2, 0 °C, silylated 5-fluorocytosine or silylated *N*-acetylcytosine; iv: NH_3/MeOH.

Scheme 1



i: TMSI, CH_2Cl_2, silylated cytosine; ii: NH_3/MeOH.

Scheme 2

uct arising from substitution at C2 was isolated (Scheme 1). In a related experiment, oxidation of **14** carrying a methyl group at C2 produced the benzoates **15** in a high yield (75%).

Compounds **3**, **13** and **15** are suitable for coupling with silylated cytosine or 5-fluorocytosine derivatives in the presence of the Lewis acid TMSI (Schemes 1 and 2). Thus, reaction of oxathiolane derivative **3** with silylated cytosine or 5-fluorocytosine produced, after deprotection with methanolic ammonia, the pure *cis* **16**[7a] or **18** as the major isomer (55% yield before deprotection) in a ratio of 5:2 relative to the *trans* isomers **17**[7a] or **19** respectively. Likewise, the nucleosides **22** and **23** were produced from **15** and silylated cytosine in the same ratio and the same yield. Similarly, 1,3-dithiolane **13** reacted with silylated *N*-acetylcytosine to give a mixture of nucleosides **20** and **21** (62%) with the *cis* isomer slightly predominating. No selectivity was noted when other Lewis acids such as $SnCl_4$[13] or TMSOTf were used. The *cis* diastereoselectivity in the cases of **16, 18**, and **22** was also observed in the preparation of racemic **1** when the 1,3-oxathiolane derivative **4** was reacted with silylated cytosine in the presence of TMSI.[14] The assignment of stereochemistry in this series was based on the ^{1}H NMR shifts of C4 at δ = 6.28 and 6.24 respectively.[15] It is interesting to note that in these systems the *cis* isomer was favored and it was observed in all the coupling with natural bases. In fact, the formation of the *cis* nucleosides in these cases as the major isomers facilitate their separation from the *trans* isomers by recrystallization. The exact reasons for this stereoselectivity are under investigation.

In conclusion, the above method represents a simple, practical and general route for the preparation of 2,4-disubstituted 1,3-oxathiolane and 1,3-dithiolane which react with silylated pyrimidines to provide novel nucleoside analogs. A relatively high *cis* stereoselectivity was observed in the coupling reaction between 1,3-oxathiolane derivatives **3** and pyrimidine bases in the presence of TMSI. This procedure has been employed to supply gram quantities of **3**, **13**, **18**, and **20** and offer the advantage of short route for the preparation of *cis* analogs.

Mp's were taken on a Fisher–Johns melting apparatus and are uncorrected. TLC was performed on Merck silica gel GOF_{254} plates. ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR–300 spectrometer. UV spectra were recorded on Perkin–Elmer 402 spectrophotometer and mass spectra on a Kratos MS-50 TA instrument.

***cis*- and *trans*-4-Benzoyloxy-2-benzoyloxymethyl-2-methyl-1,3-oxathiolane (15); Typical Procedure:**

2-Oxopropyl Benzoate:

A solution of benzoyl chloride (22.98 g, 163.51 mmol) in CH_2Cl_2 (100 mL) was added dropwise over a 1 h period to a solution of acetol (11.0 g, 148.64 mmol), Et_3N (22.52 g, 222.95 mmol) and DMAP (100 mg) in CH_2Cl_2 (100 mL) at 0 °C. After the addition was complete the solution was stirred for 1 h at 25 °C and poured into 10% Na_2CO_3 (100 mL) and stirred for 1 h. The organic layer was washed with 3 N HCl, water, brine, dried and concentrated to give a slightly yellow oil (25. 1 g, 99%).

^{1}H NMR ($CDCl_3$): δ = 2.21 (s, 3H, CH_3); 4.86 (s, 2H, CH_2); 7.44 (dt, $2H_{arom}$, J = 7 Hz); 7.56 (dd, $1H_{arom}$, J = 7, 1.5 Hz); 8.06 (dd, $2H_{arom}$, J = 7, 1.4 Hz).

2-Benzoyloxymethyl-2-methyl-1,3-oxathiolane (**14**):

To a solution of 2-oxopropyl benzoate (5.05 g, 28.37 mmol) in toluene (150 mL), was added 2-sulfanylethanol (2.43 g, 31.21 mmol) and pTSA (100 mg). The resulting mixture was refluxed using a Dean–Stark apparatus to remove water for 18 h. After this time the solution was washed with sat. $NaHCO_3$ (50 mL), water (75 mL), brine (75 mL), dried and concentrated to give a yellow oil. The oil was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to give pure **14** as a colorless oil (4.39 g, 65%).

^{1}H NMR ($CDCl_3$): δ = 1.74 (s, 3H, CH_3); 3.12 (m, 2H, CH_2-O); 4.22 (d, 1H, J = 12 Hz, CH-S); 4.23 (m, 2H, CH_2-OBz); 4.60 (d, 1H, J = 12 Hz, CH-S); 7.44 (t, $2H_{arom}$, J = 7.5 Hz); 7.57 (t, $1H_{arom}$, J = 7 Hz); 8.06 (d, $2H_{arom}$, J = 7 Hz).

cis- and trans-4-Benzoyloxy-2-benzoyloxymethyl-2-methyl-1,3-oxathiolane (**15**):

A solution of **14** (2.87 g, 12.06 mmol) and benzoyl peroxide (5.84 g, 24.12 mmol) in benzene (150 mL) was refluxed for 4 h. The mixture was poured into sat. $NaHCO_3$, and the organic phase was washed with water (75 mL), brine (75 mL) and concentrated to give an oil. This substance was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to give the title compound **15** (3.24 g, 75%) as a mixture (1:1) of *cis* and *trans* isomers as a colorless oil.

Table. Physical and Spectral Data of *cis*- and *trans*-2-Hydroxymethyl-4-(cytosin-1′-yl)-1,3-oxathiolane and -1,3-dithiolane Derivatives

Product	Yield (%)[a]	mp[b] (°C)	Molecular formula	UV λ_{max} (nm)[c]	^{1}H-NMR (DMSO-d_6) δ, J (Hz)	m/z[d] (M^+)
18[7a]	98	> 210 (dec)	$C_8H_{10}FN_3O_3S$	284	3.78 (m, 2H), 3.91 (dd, 1H, J = 4.6, 10.6), 4.44 (d, 1H, J = 10.5), 5.18 (t, 1H, J = 5.5), 5.44 (t, 1H, D_2O exchangeable), 6.28 (d, 1H, J = 2.6), 7.56 (b, 1H, D_2O exchangeable), 7.79 (lH, b, 1H, D_2O exchangeable)	247
19[7a]	94	> 200	$C_8H_{10}FN_3O_3S$	284	3.35 (m, 1H), 3.59 (m, 1H), 4.13 (dd, 1H, J = 4.7, 10.7), 4.25 (dd, 1H, J = 1.5, 10.7), 5.23 (t, 1H, D_2O exchangeable), 5.63 (dd, 1H, J = 4.5, 7.3), 6.24 (dd, 1H, J = 1.7, 3.0), 7.57 (b, 1H, D_2O exchangeable), 7.81 (1H, d, 1H, J = 6.9)	247
20	75	108	$C_8H_{11}N_3O_2S_2$	275	3.33 (m, 1H), 3.49 (m, 1H), 3.76 (t, 2H), 4.63 (t, 1H), 5.52 (t, 1H, D_2O exchangeable), 5.75 (d, 1H, J = 7.48), 6.49 (t, 1H, J = 4.33), 7.22 (d, 2H, D_2O exchangeable), 8.06 (d, 1H, J = 7.42)	246
21	77	202	$C_8H_{11}N_3O_2S_2$	275	3.48 (m, 1H), 3.52 (m, 2H), 4.76 (t, 1H), 5.39 (t, 1H, D_2O exchangeable), 5.72 (d, 1H, J = 7.57), 6.49 (t, 1H, J = 4.33), 7.30 (b, 2H, D_2O exchangeable), 7.93 (d, 1H, J = 7.57)	246
22	93	102–104	$C_9H_{13}N_3O_3S$	276	1.66 (s, 3H), 3.23 (dd, 1H, J = 12, 7), 3.26 (dd, 1H, J = 12, 5), 4.26 (dd, 1H, J = 11, 4), 4.30 (d, 1H, J = 11), 5.23 (t, 1H, J = 6), 5.80 (d, 1H, J = 8), 6.23 (d, 1H, J = 4), 7.21 (bs, 2H, D_2O exchangeable), 7.69 (d, 1H, J = 8)	244
23	86	110–112	$C_9H_{13}N_3O_3S$	276	1.50 (s, 3H), 3.61 (ds, 2H, J = 6), 4.30 (dd, 1H, J = 11, 4), 4.35 (d, 1H, J = 11), 5.41 (t, 1H, D_2O exchangeable), 6.27 (d, 1H, J = 4), 7.16 (bs, 2H, D_2O exchangeable), 7.93 (d, 1H, J = 8)	244

[a] Yield of isolated pure product of the last step (deprotection with ammonia).
[b] Uncorrected.
[c] log ε = 4.01
[d] HRMS (FAB): **18** ($C_8H_{11}FN_3O_3S$) calcd 247.0428, found 247.0452; **19** ($C_8H_{11}FN_3O_3S$) calcd 247.0428, found 247.0415; **20** ($C_8H_{12}N_3O_2S_2$) calcd 246.0371, found 246.0383; **21** ($C_8H_{12}N_3O_2S_2$) calcd 246.0371, found 246.0359; **22** ($C_9H_{14}N_3O_3S$) calcd 244.0756, found 244.0767; **23** ($C_9H_{14}N_3O_3S$) calcd 244.0756, found 244.0737.

^{1}H NMR ($CDCl_3$): δ = 1.87 + 1.74 (s's, 3H, CH_3, 4.30 (m, 2H, CH_2-O), 4.65 (m, 2H, CH_2-OBz), 6.54+6.48 (d's, 1H, CH-S, J = 3Hz), 7.48 (m, 6H_{arom}), 8.08 (m, 4H_{arom}).

cis- and trans-4-Benzoyloxy-2-benzoyloxymethyl-1,3-oxathiolane **(3)**: obtained by the Typical Procedure as a colorless oil.
^{1}H NMR ($CDCl_3$): δ = 4.25–4.32 (m, 2H, CH_2-O), 4.48-4.63 (m, 2H, CH_2-OBz), 5.79 (dd, 1H,CH-OBz, J = 3.5, 3.6 Hz), 6.51 (t, 1H, CH-S, J = 2.6 Hz), 7.41–7.46 (m, 4H_{arom}), 7.53–7.59 (m, 2H_{arom}), 8.01–8.07 (m, 4H_{arom}).
^{13}C NMR ($CDCl_3$): δ = 23.93, 25.43, 39.89, 65.33, 75.04, 82.53, 84.40,129.04, 130.35, 133.78, 134.12, 166.46, 166.56.
HRMS (FAB): M^+ calcd for $C_{18}H_{17}O_5S$ 345.0796, found 345.0779.

cis- and trans-4-Benzoyloxy-2-benzoyloxymethyl-1,3-dithiolane **(13)**: obtained by the Typical Procedure as a pale yellow oil.
^{1}H NMR ($CDCl_3$): δ = *trans*: 3.52–3.55 (m, 2H, CH_2-S), 4.51–4.54 (m, 2H, CH_2-OBz), 4.87–4.89 (m, 1H, CH-OBz), 6.92 (t, 1H, CH-S, J = 3.2 Hz), 7.41–7.51 (m, 4H_{arom}), 7.60–7.68 (m, 2H_{arom}), 8.04–8.16 (m, 4H). *cis*: 3.51–3.56 (m, 2H, CH_2-S), 4.36–4.48 (m, 2H, CH_2-OBz), 4.87–4.89 (m, 1H, CH-OBz), 6.82 (dd, 1H, CH-S, J = 1.5, 1.6 Hz), 7.41–7.51 (m, 4H_{arom}), 7.60–7.68 (1H, m, 2H_{arom}), 8.04–8.16 (m, 4H_{arom}).
^{13}C NMR ($CDCl_3$): δ = 42.70, 51.27, 67.89, 86.92, 129.45, 130.54, 133.80, 134.09, 172.96.
HRMS (FAB): M -1 calcd for $C_{18}H_{15}O_4S_2$ 359.0411, found 359.0409.

***cis*- and *trans*-4-(5′-Fluorocytosin-1′-yl)-2-hydroxymethyl-1,3-oxathiolane 18: Typical Procedure:**
5-Fluorocytosine (0.700 g, 5.4 mmol) was refluxed with HMDS (150 mL) and a catalytic amount of $(NH_4)_2SO_4$ (0.030 g). After the solid was dissolved (about 3 h), refluxing was continued for an additional 2 h. The HMDS was removed under reduced pressure and the silylated base was dried under high vacuum. To a solution of this base in CH_2Cl_2 (50 mL), 4-benzoyloxy-2-benzoyloxymethyl-1,3-oxathiolane (**13**) (1.25 g, 3.6 mmol) in CH_2Cl_2 (30 mL) followed by TMSI (0.75 mL, 4.5 mmol) were added. The resulting mixture was stirred for 24 h at 25 °C. The reaction was poured into sat. $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried and concentrated to give a residue. This was purified by flash chromatography (silica gel, 25% EtOAc/hexanes) to give pure benzoate *cis* isomer (0.682 g, 55%) and the *trans* isomer (0.27 g, 22 %) as white solids mp 235–236 °C (dec.).
^{1}H NMR ($CDCl_3$): δ = 3.98 (dd, 1H, CH-O, J = 4.7, 11 Hz); 4.61 (d, 1H, CH-O, J = 11 Hz); 4.73 (m, 2H, CH_2-OBz); 5.51 (t, 1H, CH-S, J = 3.8 Hz); 6.28 (d, 1H, CH-N, J = 3 Hz); 7.52 (m, 2H_{arom}); 7.58 (b, 1H, NH_2); 7.68 (m, 1H_{arom}); 7.80 (d, 2H, cytosine and 1H, NH_2); 7.94 (m, 2H_{arom}).
The *cis* nucleoside was dissolved in a saturated solution ofmethanolic ammonia (100 mL) and the mixture was stirred overnight. This afforded pure *cis* hydroxymethyl derivative **18** (0.43 g, 98%) as a white solid material (for data see Table).

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