Synthesis of New 2,5-Substituted 1,3-Oxathiolanes. Intermediates in Nucleoside Chemistry

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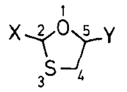
This publication is dedicated to Dr. Belleau's memory, Professor at McGill University.

A synthetic approach for new 2-hydroxymethyl-5-ethoxy-1,3-oxathiolane derivatives is described. These heterocyclic five membered rings are suitably substituted to be potential sugar candidates in nucleoside chemistry.

Even though the 1,3-oxathiolane ring system has been known for several decades,[1,2] its use as a possible sugar ring in nucleoside analogs has never been proposed. We wish to report new strategies for the synthesis of 1,3-oxathiolanes **1** carrying suitable functions as the 2 and 5 positions.



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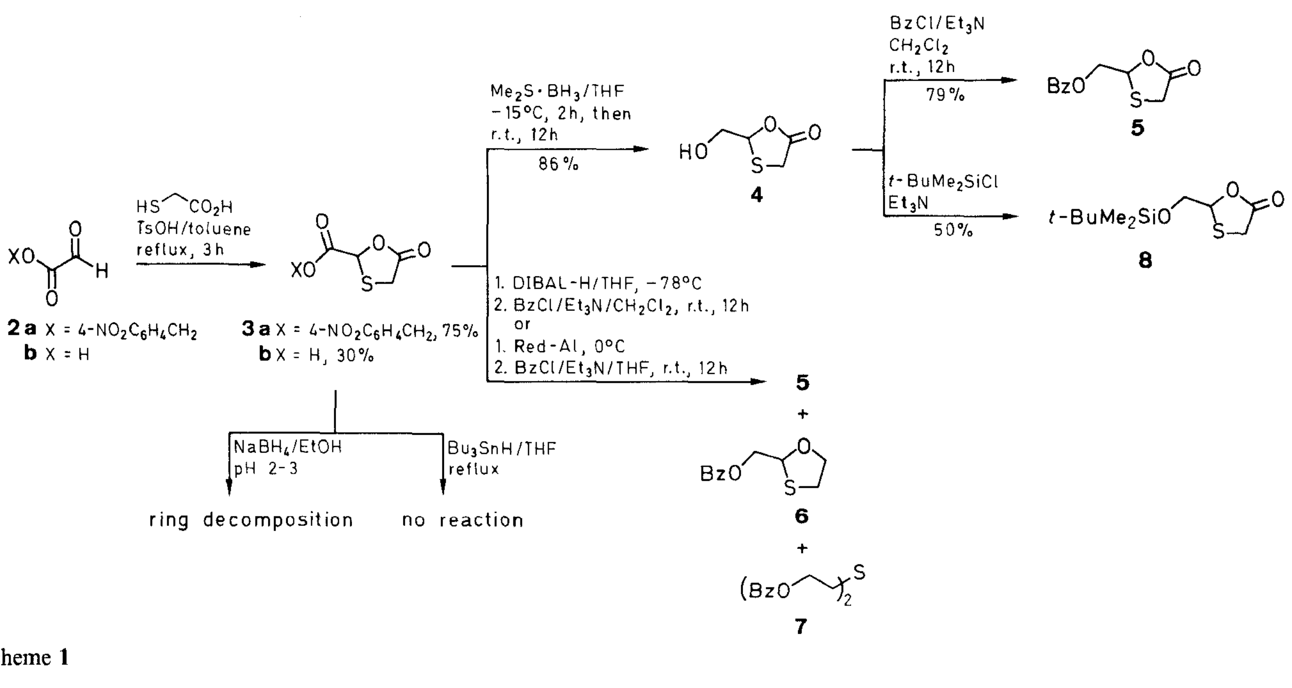
1	X	Y
a	CH_2OH	OH
b	CH_2OH	OEt
c	CH_2OB_z	OEt

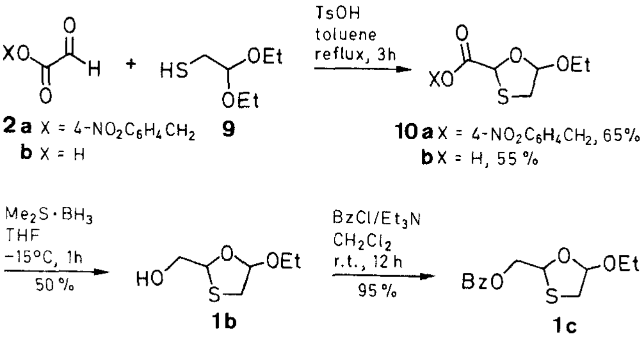
Two different strategies which involved as a key step, the cyclocondensation of various aldehydes with suitable functionalized thiols have been investigated. The first approach (Scheme 1) was based on the catalytic reduction of 2-substituted 1,3-oxathiolan-5-ones **3a,b**. These compounds were obtained by heating 4-nitrobenzyl glyoxylate (**2a**) or glyoxylic acid (**2b**) with mercaptoacetic acid in toluene and in the presence of *p*-toluenesulfonic acid as catalyst.[2,3] A requirement for the success of this reaction is that glyoxylic derivatives which exist in the hydrate form, have to be converted into the free aldehyde by azeotropic removal of water with toluene before the cyclocondensation. The next step was to complete the reduction of both lactone and carboxylic functions by using different catalytic reductive reagents. Reduction of **3a** with sodium borohydride in ethanol at pH 2–3 according to Taniguchi et al.[4] failed, leading to ring-opened products and 4-nitrobenzyl alcohol. When the reduction of **3a** and **3b** was carried out with a 10.0–10.2 M borane–methyl sulfide complex (BMS)[5] in dry tetrahydrofuran the corresponding 2-hydroxymethyl-1,3-oxathiolan-5-one (**4**) was isolated, indicating that only the carboxylic function was reduced. When the temperature was raised or a large excess of BMS was used, ring opening occurred leading to polar polymeric material. When the same reduction was done with diisobutylaluminum hydride (DIBAL-H)[6,7] at – 70 °C in dry tetrahydrofuran, two major compounds **5** and **6** and one minor compound **7** were isolated and fully characterized, after benzoylation.

Reduction of **3a** or **3b** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), in toluene at 0 °C as suggested by Kanazawa et al.[8] for partial reduction of lactones and esters also gave, after benzoylation, the compounds **5**, **6** and **7**. When tributyltin hydride was used as reducing agent[9], no reduction occurs. Finally, when the reduction was performed on the protected lactones **8** and **9**, it was not possible to isolate the desired compound **1a**, regardless of the catalytic reductive conditions.



Scheme 1

The second approach (Scheme 2), involved the cyclocondensation of anhydrous glyoxylates **2a** and **2b** with 2-mercaptoacetaldehyde diethyl acetal (**10**)[10] at reflux in toluene, leading to 5-ethoxy-1,3-oxathiolane derivatives **11a** and **11b**. Reduction of **11a** and **11b** with BMS at − 15 °C gave the corresponding 2-hydroxymethyl-1,3-oxathiolane (**1b**) in 50 % yield, which after benzoylation led to the desired compound **1c** as a 1:1 mixture of *cis* and *trans* isomers.



Scheme 2

In conclusion, new strategies have been developed for the synthesis of new 1,3-oxathiolanes carrying suitable functional groups at the 2 and 5 positions. These heterocyclic five membered rings are potential sugar substitutes in nucleoside chemistry.

All reagents were of commercial quality from freshly opened containers. Mercaptoacetic acid, TsOH, BzCl, glyoxylic acid, Bn_3SnH, *tert*-butyldimethylsilyl chloride, Borane–methyl sulfide complex, $NaBH_4$, Red-Al, DIBAL-H were purchased from Aldrich chemical Co. Reagent quality solvents were used without further purification. analytical TLC plates and silica gel 60 were purchased from Merck Co, Darmstadt. Microanalysis were obtained from Guelph Laboratories Guelph Ontario. ^{1}H-NMR spectra were obtained using a VARIAN XL 200 MHz or XL 300 MHz spectrometers. 2-Mercaptoacetaldehyde diethyl acetal (**9**) was prepared according Hesse and Jorder[10] procedure. 4-Nitrobenzyl glyoxylate hydrate (**2a**) was prepared by using known procedure.[11]

4-Nitrobenzyl 4-Oxo-1,3-oxathiolane-2-carboxylate (3a):

4-Nitrobenzyl glyoxylate (2.3 g, 10 mmol), mercaptoacetic acid (0.9 g, 10 mmol) and a catalytic amount of TsOH are dissolved in toluene (15 mL). The resulting suspension is refluxed for 3 h, the H_2O formed during the course of the reaction being removed continuously by azeotropic distillation. Then the solvent is removed under vacuum and the oily residue **3a** is chromatographed on a silica gel column using EtOAc/toluene (0.5 : 9.5) as eluent; yield: 75 %.

$C_{11}H_9NO_6S$	calc.	C 46.64	H 3.20	N 4.94
(283.2)	found	46.87	3.12	5.07

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.60 (s, 2H, S−CH_2), 5.38 (s, 2H, CH_2−O), 5.78 (s, 1H, O−CH−S), 7.50, 8.20 (2d, 4H_{arom}).

5-Oxo-1,3-oxathiolane-2-carboxylic Acid 3b:

Similarly, the reaction of glyoxylic acid (1.59, 20 mmol), mercaptoacetic acid (1.8 g, 20 mmol) and a catalytic amount of TsOH refluxed for 3 h in toluene (15 mL) gives product **3b**; yield: 30 %.

$C_4H_4O_4S$	calc.	C 32.42	H 2.72
(148.1)	found	32.64	2.61

2-Hydroxymethyl-1,3-oxathiolan-5-one (4):

In a dried, N_2-filled round-bottomed flask fitted with stirrer and addition funnel, 1 equiv (2 mmol) of **3a** or **3b** is dissolved in dry THF. The solution is cooled to − 15 °C, and 5 equiv (10 mmol) of BMS (1.5 mL) in THF are added at moderate rate. The solution is stirred at − 15 °C for 2 h, and one night (12 h) at r.t. The solvent is removed under vacuum, and the oily residue is dissolved in CH_2Cl_2. This solution is washed with H_2O (15 mL). The organic layer is extracted with CH_2Cl_2 and dried ($MgSO_4$). The solvent is evaporated and the crude product **4** is chromatographed on a silica gel column using CH_2Cl_2 as eluent, yield: 86 %.

$C_4H_6O_3S$	calc.	C 35.81	H 4.50
(134.2)	found	35.91	4.44

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.70 (s, 2H, S−CH_2), 4.20 (d, 2H, CH_2−OH), 5.54 (t, 1H, CH).

2-Benzoyloxymethyl-1,3-oxathiolan-5-one (5):

Under N_2, a mixture of **4** (192 mg, 1.43 mmol) dissolved in CH_2Cl_2, BzCl (221 mg, 1.57 mmol) and Et_3N (159.5 mg, 1.57 mmol) was stirred for one night at r.t. The solution is washed with H_2O (10 mL). The organic layer is extracted with CH_2Cl_2 and dried ($MgSO_4$). The solvent is evaporated and the crude product **5** is chromatographed on a silica gel column using CH_2Cl_2 as eluent; yield: 79 %.

$C_{11}H_{10}O_4S$	calc.	C 55.45	H 4.23
(238.25)	found	55.37	4.17

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.42 (s, 2H, CH_2−S), 4.32 (d, 2H, O−CH_2), 5.53 (t, 1H, CH), 7.20−7.85 (m, 5H_{arom}).

4-Nitrobenzyl 5-Ethoxy-1,3-oxathiolane-2-carboxylate (10a):

4-Nitrobenzyl glyoxylate (**2a**; 1.42 g, 6 mmol) and 2-mercaptoacetaldehyde diethyl acetal (**9**) are dissolved in toluene (25 mL). The resulting mixture is refluxed for 3 h. The solvent is removed under vacuum and the oily residue is chromatographed on a silica gel column using EtOAc/toluene (1 : 9) as eluent; yield 65 % mixture *cis* and *trans*.

$C_{13}H_{15}NO_6S$	calc.	C 49.82	H 4.82	N 4.47
(313.3)	found	49.91	4.76	4.52

cis isomer **10a**: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3H, CH_3), 3.21 (d, 2H, S−CH_2), 3.40−4.10 (m, 2H, O$\underline{CH_2}CH_3$), 5.35 (s, 2H, $\underline{CH_2}$−Ar), 5.58 (t, 1H, $\underline{CH}$−CH_2), 5.65 (s, 1H, CH−CO), 7.60, 8.20 (2d, 4H_{arom})

trans isomer **10a**: ^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3H, CH_3), 3.19 (2H, S−CH_2), 3.40−4.20 (m, 2H, O−$\underline{CH_2}$−CH_3), 5.35 (s, 2H, $\underline{CH_2}$−Ar), 5.65 (s, 1H, CH−CO), 5.68 (t, 1H, $\underline{CH}$−CH_2), 7.60, and 8.20 (2d, 4H_{arom})

4-Ethoxy-1,3-oxathiolane-2-carboxylic Acid (10b):

Glyoxylic acid (**2b**; 0.579, 6 mmol) and 2-mercaptoacetaldehyde diethyl acetal **9** are dissolved in toluene (15 mL). The resulting mixture is refluxed for 3 h. The solvent is removed under vacuum and the oily residue is dissolved in EtOAc. The solution is washed with H_2O (15 mL). The organic layer is extracted with EtOAc and dried ($MgSO_4$). The crude compound is used without further purification for the next step; yield: 55 %. (mixture of *cis* and *trans* isomer).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20 (t, 3H, CH_3), 3.20 (dd, 2H, S−CH_2), 4.40 (m, 2H, OCH_2), 5.62 (t, 1H, CH−O), 5.64 (s, 1H, CHCO).

2-Hydroxymethyl-5-ethoxy-1,3-oxathiolane (1b):

In a dried N_2-filled round-bottomed flask fitted with stirrer and addition funnel 1 equiv of **10a** or **10b** (3.6 mmol) is dissolved in dried THF (15 mL). The solution is cooled to − 15 °C, and 5 equiv of BMS (18 mmol) in THF are added at moderate rate. The solution is stirred at − 15 °C for 1 h, then quenched with cold H_2O (15 mL), CH_2Cl_2 (20 mL) is added and the organic phase is separated, washed with H_2O (15 mL), and dried ($MgSO_4$). The solvent is evaporated and the crude product **1b** is chromatographed on a silica gel column using EtOAc/toluene (2 : 3) as eluent; yield: 50 %.

$C_6H_{12}O_3S$	calc.	C 43.88	H 7.37
(164.2)	found	43.96	7.30

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.23 (t, 3H, CH_3), 3.20 (dd, 2H, S−CH_2−), 3.4−3.7 (m, 2H, O$\underline{CH_2}CH_3$), 3.85 (m, 2H, $\underline{CH_2}$OH), 5.3 (m, 1H, $\underline{CH}$−O−CH_2), 5.35 (m, 1H, CH−S).

2-Benzoyloxymethyl-5-ethoxy-1,3-oxathiolane (1c):

Under N_2, a mixture of **1b** (126 mg, 0.77 mmol) dissolved in CH_2Cl_2 (15 mL) BzCl (125 mg, 0.847 mmol) and Et_3N (156 mg, 1.54 mmol) is stirred for one night at r.t. The solution is washed with H_2O (10 mL). The solvent is evaporated and the crude compound **1c** is chromatographed on a silica gel column using CH_2Cl_2/hexane (1 : 1) as eluent; yield: 95%.

$C_{13}H_{17}O_4$	calc.	C 57.96	H 6.36
(269.3)	found	58.05	6.31

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