

## 1-Alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry

Sergey Zavgorodny,<sup>\*\*</sup> Michael Polianski,<sup>\*</sup> Evgeni Besidsky,<sup>\*</sup> Vladimir Kriukov,<sup>\*</sup> Andrei Sanin,<sup>\*</sup>  
Marla Pokrovskaya,<sup>\*\*</sup> Galina Gurskaya,<sup>\*</sup> Harri Lönnberg<sup>†</sup> and Alex Azhayev<sup>\*,†</sup>

<sup>\*</sup>Chimtech Ltd., Mikhukho-Maklaya str. 16/10, 117871 Moscow, USSR, <sup>\*</sup>Institute of Molecular Biology, USSR Academy of Sciences, Vavilov str. 32, 117984 Moscow, USSR, and <sup>†</sup>Department of Chemistry, University of Turku, SF-20500 Turku, Finland

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**Abstract:** Treatment of appropriately protected nucleosides with a mixture of acetic acid, acetic anhydride and dialkylsulfide was shown to give *O*-(1-alkylthioalkylated) nucleosides that were oxidized to the corresponding sulfoxides and sulfones, or converted *via* *O*-halogenomethyl derivatives to various *O*-substituted nucleosides.

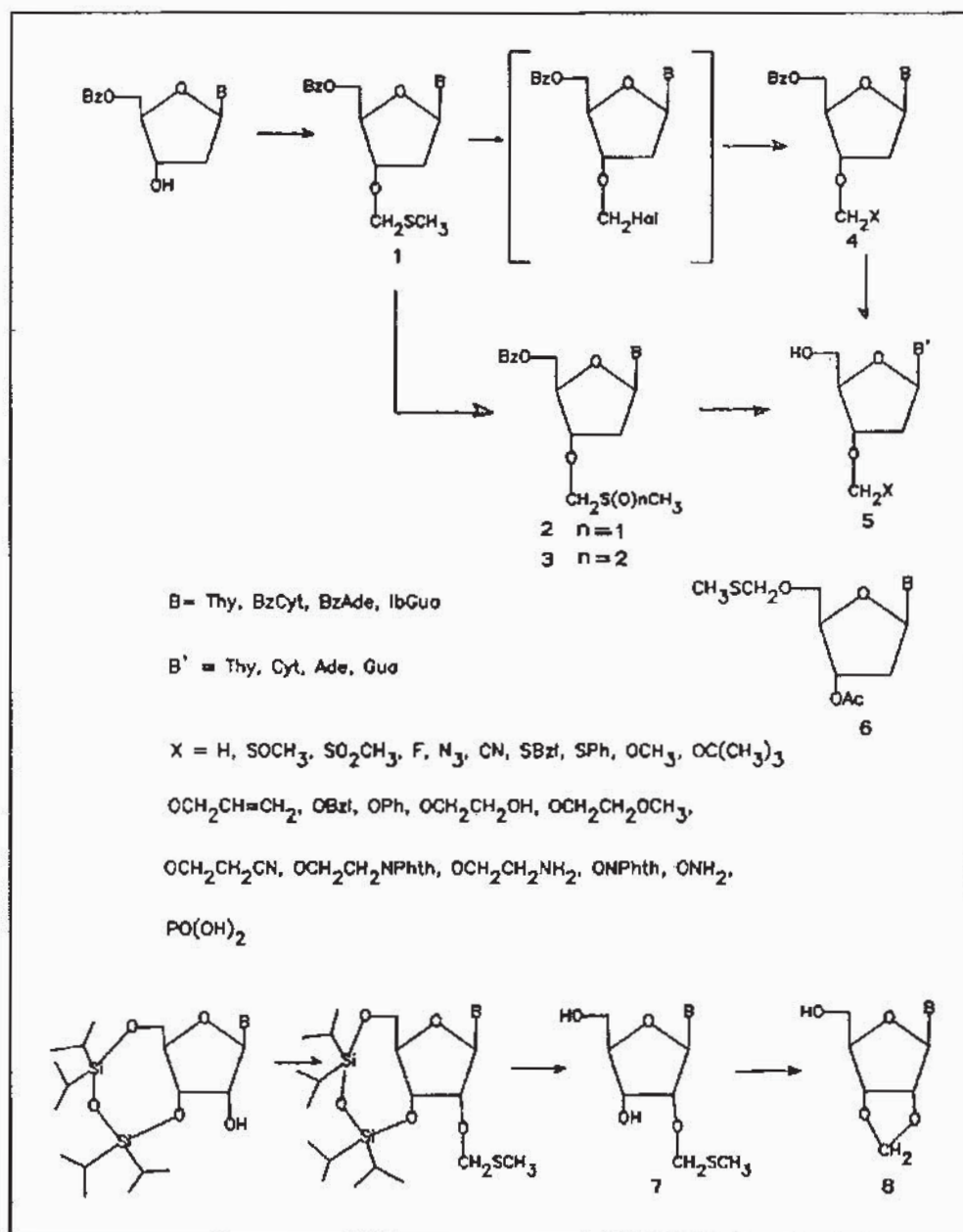
It is known that Pummerer's rearrangement<sup>1</sup> gives, in the presence of alcohols, 1-alkoxyalkyl sulfides in satisfactory yields.<sup>2</sup> Although this approach has not earlier been applied to obtain *O*-(1-alkylthioalkyl) nucleosides, oxidation of sugar hydroxyls with a mixture of acetic anhydride and DMSO is known to give *O*-methylthiomethyl derivatives as side products.<sup>3,4</sup> For example, 3'-*O*-methylthiomethylthymidine (5, B' = Thy, X = SCH<sub>3</sub>) was recently obtained in this manner.<sup>5</sup>

1-Alkylthioalkyl groups have also been proposed as potential protecting groups of the sugar hydroxyl functions of nucleosides, and they were introduced by acid-catalyzed addition of the hydroxyl group on 1,2-unsaturated sulfides.<sup>6</sup> The shortcoming of this method is that it cannot be applied to insert alkylthiomethyl groups or groups containing a chiral centre in position 2. Owing to acid-catalyzed depurination, derivatives of purine 2'-deoxyribonucleosides can be prepared only in low yields.

We now report on preparation of *O*-(1-alkylthioalkyl) substituted nucleosides by a modified Pummerer's rearrangement. Treatment of base protected (except with Thy) 5'-*O*-benzoyl-2'-deoxyribonucleosides with a mixture of acetic acid, acetic anhydride and DMSO (11:35:54, v/v) for 60 h at 20 °C gave the corresponding 3'-*O*-methylthiomethyl nucleosides (1) in good yield. A similar approach has earlier been applied to prepare *O*-methylthiomethyl substituted carbohydrates.<sup>7</sup> The sulfides (1) obtained were oxidized to the corresponding sulfoxides (2) with sodium periodate,<sup>8</sup> or to sulfones (3) under more drastic conditions. Sulfones were also obtained by using potassium permanganate as an oxidizing agent.<sup>12</sup>

<sup>\*</sup>Present address: Institute of Chemical Physics, USSR Academy of Sciences, Kosygin str. 4, 117977 Moscow, USSR

The sulfides (1) were converted to 3'-*O*-bromomethyl nucleosides (4, X = Br) by displacing the methylthio group with bromine, as described for thioacetals and mixed *O,S*-acetals.<sup>13,14</sup> Displacement of the bromide ion from 4 (X = Br) with various nucleophiles (see below) then gave a large selection of *O*-substituted nucleosides (4). However, with guanine nucleosides an alternative procedure was preferred.



The sulfide (1, B = *N*<sup>2</sup>-isobutyl-Gua) was converted to 3'-*O*-chloromethyl nucleoside (4, B = *N*<sup>2</sup>-isobutyl-Gua, X = Cl) with sulfonyl chloride. The halogenomethyl derivatives (4, X = Br, Cl) were also reduced to 3'-*O*-methyl nucleosides (4, X = H) with sodium borohydride. Desulfurization of 1 with Raney nickel gave the same product.

The following nucleophiles were used to displace the halogen ion from 3'-*O*-halogenomethyl nucleosides (4, X = Br, Cl): alcohols, phenols, thioalcohols, thiophenols, F<sup>-</sup>, N<sub>3</sub><sup>-</sup>, CN<sup>-</sup>, acetate ion, hydroxylamine and phthaloylhydroxylamine. Thus treatment of 4 (X = Br, Cl) with alcohols or phenols gave 3'-*O*-alkoxymethyl or 3'-*O*-aryloxymethyl nucleosides, respectively. 3'-*O*-Alkoxymethyl derivatives were also obtained by treating 1 with alcohol in the presence of mercury(II) chloride and oxide,<sup>15</sup> but the reaction times were much longer, leading in some cases to detectable side reactions. It is worth noting that alkoxyalkyl groups are widely used as protecting groups of nucleoside hydroxyl functions. For example, 1-alkoxyethyl, 1-alkoxyisopropyl, tetrahydropyranyl and 4-methoxy-5,6-dihydropyranyl derivatives are usually obtained by acid-catalyzed reactions of nucleosides with vinyl ethers, acetals, or aldehydes and alcohols. These reactions suffer from limitations analogous to those described above for reactions of 1,2-unsaturated sulfides. 3'-*O*-Methoxymethyl derivatives of thymidine (5, B' = Thy, X = OCH<sub>3</sub>), 2'-deoxycytidine (5, B = Cyt, X = OCH<sub>3</sub>) and uridine were recently prepared by treating the appropriately protected nucleoside with dimethoxymethane in the presence of Lewis acids.<sup>16</sup> Nevertheless this reaction cannot be regarded as a generally applicable synthetic route. For instance, it cannot be used to obtain compounds, such as 3'-*O*-*tert*-butoxymethyl (4, X = OC(CH<sub>3</sub>)<sub>3</sub>) and 3'-*O*-allyloxymethyl (4, X = OCH<sub>2</sub>CH=CH<sub>2</sub>) nucleosides. The approach described in the present report is not limited by the use of Lewis acids. It is also noteworthy that alkoxyethylphosphonates (4, X = PO(OH)<sub>2</sub>) may be obtained by Michaelis-Arbuzov reaction of 4 (X = Br) with tris(trimethylsilyl)phosphite.

Besides DMSO, several other sulfoxides, such as diethyl, diisopropyl and dibenzyl sulfoxides, were successfully employed to result in alkylthioalkylation of nucleoside hydroxyl functions. The alkylation product was a 1:1 mixture of diastereomers, as shown by <sup>1</sup>H NMR spectroscopy. By contrast, methyl phenyl sulfoxide gave rather low yields, oxidation of the hydroxyl group being the predominant reaction. 2-Heterosubstituted dialkyl sulfoxides, such as bis-(2-acetoxyethyl) sulfoxide, could also be used as alkylating agent, and this possibility significantly increases the synthetic applicability of the method.

In addition to 3'-*O*-methylthiomethyl substituted 2'-deoxyribonucleosides (1), their 5'-*O*-analogs (6) and 2'-*O*-substituted ribonucleosides (7) were prepared by the method described above. Compounds 7 were further converted to 2',3'-*O*-methyleneribonucleosides (8). All the compounds prepared (1-4, 6-8) were finally deprotected with methanolic ammonia, and characterized by UV, IR and NMR spectroscopy.<sup>17</sup>

The compounds discussed above are useful specifically blocked synthons. For example, alkylthioalkyl groups can be removed with methyl iodide,<sup>7</sup> mercury(II)<sup>6</sup> and silver(I)<sup>18</sup> salts, tritylium tetrafluoroborate,<sup>19</sup> or bromine/water treatment. *O*-Methoxymethyl substituted nucleosides may be deprotected according to Nishino,<sup>16</sup> and acetoxymethyl and 2-cyanoethoxymethyl groups undergo elimination under alkaline conditions. Azidomethyl group is of special interest, since it can be removed under very specific and mild conditions, viz. with triphenylphosphine in aqueous pyridine at 20 °C.

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9. According to  $^1\text{H}$  NMR spectroscopy, in each case a 1:1 mixture of diastereomeric sulfoxides was obtained. Repeated crystallizations from ethanol gave in pure form that of the diastereomers of **5** ( $\text{B}' = \text{Thy}$ ,  $\text{X} = \text{SOCH}_3$ ) that had a longer retention time on RP column. X-ray analysis of the crystals obtained revealed the structure of *R*-form of the sulfoxide group ( $\chi = -148.8^\circ$ ;  $P = 148.4^\circ$ ,  $\text{C2}'\text{-endo/C1}'\text{-exo}$ ,  $\tau_m = 35.4^\circ$ ,  $g^+$ ). The X-ray structure of the corresponding sulfide (**1**,  $\text{B9} = \text{Thy}$ ,  $\text{X} = \text{SCH}_3$ ) showed:  $\chi = 116.4^\circ$ ;  $P = 167.7^\circ$ ,  $\tau_m = 34.9^\circ$ ,  $g^+$ . For details, see Ref. 10. The X-ray data perfectly fit with the  $^1\text{H}$  NMR data in  $^2\text{H}_2\text{O}$ .<sup>11</sup>
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17. The compounds obtained were UV spectroscopically identical with the nucleosides employed as starting material. The IR spectra of 3'-*O*-azidomethyl derivatives (**5**,  $\text{X} = \text{N}_3$ ) showed the characteristic band at 2130-2140  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectra were compatible with those of the unsubstituted nucleosides, the shifts of both sugar and base protons remaining virtually unchanged. The conversions of sulfides (**1**) to sulfoxides (**2**), and sulfoxides to sulfones (**3**) were accompanied by downfield shifts of proton resonances of the methyl group (2.14, 2.59 and 2.95 ppm with **1**, **2** and **3**, respectively). The 3'-fluoro derivative (**5**,  $\text{X} = \text{F}$ ) exhibited a  $^{19}\text{F}$  resonance at approximately 149 ppm with  $J_{\text{HF}} = 55.5$  Hz.
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