

## Communications to the Editor

### Smooth and Efficient Deoxygenation of Secondary Alcohols. A General Procedure for the Conversion of Ribonucleosides to 2'-Deoxynucleosides<sup>1</sup>

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We wish to report the first general procedure for the specific conversion of ribonucleosides to 2'-deoxynucleosides. Selective protection of the 3'- and 5'-hydroxyl functions of ribonucleosides with a cyclic disiloxane group followed by thioacylation, radical-induced reductive cleavage, and deprotection provides an efficient four-step chemical analogy for this ubiquitous de novo biosynthetic pathway. Further generality of this mild deoxygenation method is demonstrated with carbohydrate and steroid examples.

Chemical 2'-deoxygenation of nucleosides has been long studied but has been somewhat elusive.<sup>3</sup> Pyrimidine 2'-deoxynucleosides can be obtained via intramolecular cyclization of the ribonucleoside<sup>4</sup> followed by opening of the O-2'→2' anhydro bridge at C-2' by halide and reductive dehalogenation.<sup>5</sup> However, analogous O-8→2' cyclonucleoside interconversions in the purine nucleoside series retain an unnatural substituent at C-8. Deoxygenation at C-8 and desulfurization of S-8→2' cyclonucleosides have provided limited overall yields.<sup>6</sup>

S<sub>N</sub>2 displacement at C-2' of nucleosides is inhibited by steric and electronic factors.<sup>7</sup> Cation formation (S<sub>N</sub>1) at C-2' is precluded by bonding to the adjacent electron-deficient anomeric carbon. Generation of anionic character at C-2' has resulted in elimination of the base at C-1'.<sup>8,9</sup> Thus, homolytic cleavage of the C-2'-O-2' bond is the only feasible approach, an observation consistent with the free-radical-mediated deoxygenations of nucleotides to the corresponding DNA components effected by ribonucleotide reductase enzymes in nature.<sup>11</sup>

(1) This contribution constitutes Nucleic Acid Related Compounds. 32. For the previous paper in this series, see: Robins, M. J.; Barr, P. J. *Tetrahedron Lett.*, in press.

(2) NRCC Graduate Research Fellow, 1978-1979; University of Alberta Graduate Research Fellow, 1979-1980.

(3) For comprehensive reviews see: (a) Goodman, L. In "Basic Principles in Nucleic Acid Chemistry"; Ts'o, P. O. P., Ed.; Academic Press: New York, 1974; Vol. I, pp 93-208. (b) Moffatt, J. G. In "Nucleoside Analogues: Chemistry, Biology, and Medical Applications"; Walker, R. T.; De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York, 1979; pp 71-164 and references therein.

(4) See ref 3b, pp 92-101, and references quoted.

(5) See ref 3b, pp 101-108, 117-118, and references therein.

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(9) See examples involving uridine: (a) Jain, T. C.; Jenkins, I. D.; Russell, A. F.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30. (b) Adachi, T.; Iwasaki, T.; Inoue, I.; Miyoshi, M. *Ibid.* **1979**, *44*, 1404.

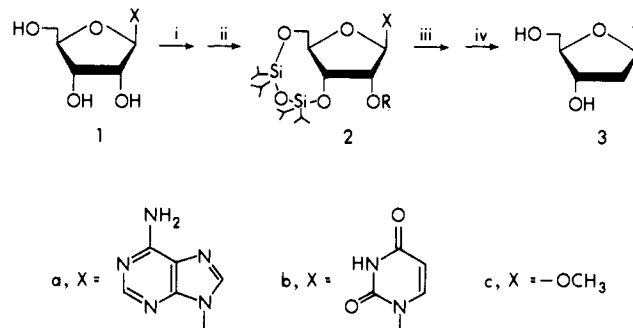
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Table I

Entry	Starting Material	Product	Overall Yield (%)
1			78
2			68
3			58
4			85
5			a, 85 b, 78

Scheme I<sup>a</sup>



<sup>a</sup> (i) [(*i*-Pr)<sub>2</sub>SiCl<sub>2</sub>O]/pyridine/room temperature/2 h. (ii) C<sub>6</sub>H<sub>5</sub>OCSCl/4-(dimethylamino)pyridine/CH<sub>3</sub>CN/room temperature/6 h. (iii) *n*-Bu<sub>3</sub>SnH/AIBN/PhCH<sub>3</sub>/N<sub>2</sub>/75 °C/3 h. (iv) *n*-Bu<sub>4</sub>N<sup>+</sup>F<sup>-</sup>.

Homolytic deoxygenation of alcohols by photochemical processes<sup>12</sup> and tin radical cleavage of thiono esters have been noted recently.<sup>13</sup> Strong absorbance by the heterocyclic base of nucleosides complicates photochemical approaches and the methods tried were not promising. Problems arose when the thiobenzoyl and methyl dithiocarbonate procedures of Barton and co-workers were used.<sup>13a</sup> Basic conditions for introduction of these groups are incompatible with certain protecting groups, and dual reaction pathways have been observed in the cleavage step with tri-*n*-butyltin hydride.<sup>13a,14</sup>

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(13) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. (b) Barton, D. H. R.; Subramanian, R. *Ibid.* **1977**, 1718.

We sought a thiocarbonyl reagent that could be introduced by simple acylation. A second consideration was that the intermediate radical species resulting from attack of tin at thione sulfur would not be stabilized at the  $\alpha$ -carbon. Such  $\alpha$  stabilization could allow abstraction of hydrogen from the trialkylstannane to compete effectively with alkyl carbon-oxygen bond homolysis. Dethiation (thiobenzoylester  $\rightarrow$  benzyl ether) and collapse (dithiocarbonate ester  $\rightarrow$  alcohol starting material) byproducts have been observed by using the  $\alpha$ -benzylic- and  $\alpha$ -thiol-stabilized species.<sup>13a,14</sup>

Treatment of thiophosgene with phenol gave phenyl chlorothionocarbonate.<sup>15</sup> Pyridine effectively catalyzed reactions of this thioacyl chloride with relatively unhindered alcohols, but 4-(dimethylamino)pyridine was required<sup>16</sup> for smooth conversion of nucleosides to their 2'-*O*-phenoxythiocarbonyl derivatives. Reductive cleavage of these compounds occurred readily when tri-*n*-butylstannane in toluene at 75 °C with  $\alpha,\alpha'$ -azobisisobutyronitrile as initiator was used.<sup>17</sup> No dethiation or alcohol byproducts were detected in cases we have examined. As seen in Table I, thioacylation (generally quantitative) and reductive cleavage (proceeds to completion in 3 h) give good overall yields of deoxygenation of isolated secondary alcohols (entries 4, 5). An epoxide function is tolerated (entry 5b).

Selective 3' and 5' protection was required for specific 2'-deoxygenation of ribonucleosides. Multistep procedures have been required previously,<sup>7</sup> but a hindered bifunctional disiloxane reagent became available recently.<sup>18</sup> Treatment of ribofuranosyl compounds (1) with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane in pyridine gave the cyclic 3',5'-trioxadisila derivatives (2, R = H) in over 90% yields (Scheme I). Thioacylation of 2 (R = H) gave the 2'-*O*-phenoxythiocarbonyl esters (2, R = CSOC<sub>6</sub>H<sub>5</sub>). Reductive cleavage of this function gave the 2'-deoxynucleosides protected as the cyclic 3',5'-trioxadisila intermediates. Deprotection was effected by using tetra-*n*-butylammonium fluoride<sup>19</sup> to give the 2'-deoxynucleosides (3).

Adenosine (1a) was converted to 2'-deoxyadenosine (3a) in 78% overall yield by this sequence. This is superior to yields obtained in prior chemical syntheses of 2'-deoxyadenosine by any route.<sup>3,6a,7,13b</sup> Uridine (1b) was converted to 2'-deoxyuridine in 68% yield in this manner. This yield is higher, even, than routes involving O-2 $\rightarrow$ 2' cyclonucleoside interconversions.<sup>4,5</sup> It clearly demonstrates the generality of the method since cyclonucleoside formation did not intervene. This was a concern since treatment of 5'-*O*-trityluridine with thiocarbonyldiimidazole in hot toluene was known to produce the 2,2'-anhydroarabino compound in over 85% yield.<sup>20</sup>

Finally, methyl  $\beta$ -D-ribofuranoside (1c) was subjected to this sequence. The product (3c) was converted into its crystalline 3,5-di-*O*-*p*-toluyl ester derivative<sup>21</sup> in 58% overall yield for the five steps. No cleavage of our thionocarbonate ester (2c, R = CSOC<sub>6</sub>H<sub>5</sub>) to starting alcohol was observed, in contrast to side reactions reported in an analogous application of the thiobenzoate and dithiocarbonate methods.<sup>14</sup>

The present sequence of reactions thus provides smooth and efficient access to 2'-deoxynucleosides from ribonucleosides, a process for which general methods were lacking. Demonstration of its applicability with nucleoside antibiotics and evaluation of

the stereoselectivity of reduction will be reported with details of the present work.

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### Conformational Analysis of the C(6)-O(1)-C(5)-C(4) Fragment in Acetylcholine by <sup>13</sup>C NMR Spectroscopy

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The conformation of acetylcholine (ACh) is still a subject of interest.<sup>1-3</sup> Lately, changes in the Raman spectra of ACh halides (AChBr, AChCl, and AChI) on going from solid state to aqueous solution have been attributed to conformational differences in the choline fragment.<sup>2</sup> It has been suggested<sup>4</sup> that the conformational change could arise from rotation around the O(1)-C(5) bond (see Figure 1). It is known that the conformations adopted by ACh cation in the crystals of its halides differ essentially because of the fragment C(6)-O(1)-C(5)-C(4), which is trans in the crystal of its chloride ( $\tau_1 = 193^\circ$ )<sup>5</sup> and gauche in the crystal of its bromide ( $\tau_1 = 79^\circ$ )<sup>6</sup> and iodide ( $\tau_1 = 83^\circ$ ),<sup>3</sup> whereas in aqueous solution the conformational equilibrium appears to be independent of the counterion.<sup>2,7,8</sup> On the basis of the NMR acylation shift of the CH<sub>2</sub>O protons, Culvenor and Ham<sup>8</sup> proposed an essentially trans arrangement for this fragment. It follows that Raman and <sup>1</sup>H NMR spectroscopic techniques suggest a different conformational behavior as concerns  $\tau_1$  for AChCl when moving from solid state to aqueous solution. In view of the biological importance of this angle,<sup>9</sup> the conformational features around the O(1)-C(5) bond would be better established in aqueous solution. In this communication, measurements of the vicinal C(6)-O(1)-C(5)-H coupling constant in the temperature range 10-70 °C suggest the trans-C(6)/C(4) conformation ( $\tau_1 \sim 180^\circ$ ) is preferred; however, a distorted gauche conformation ( $\tau_1 \sim 90^\circ$ ) also displays significant population. The population ratio ranges from 0.688/0.312 at 10 °C to 0.625/0.375 at 70 °C.

The proton-coupled <sup>13</sup>C NMR spectra were recorded at 25.2 MHz on a Varian XL-100-12 spectrometer, with a digital resolution of 0.12 Hz. The concentration of AChCl was about 1 M in D<sub>2</sub>O and a small amount of sodium 4,4-dimethyl-4-silapentane-1-sulfonate was added to generate the internal reference signal.

The <sup>13</sup>C(6) resonance displays a symmetrical pattern which can easily be identified as a quartet of triplets. The signal multiplicity allows the assignment of the larger coupling constant (6.9 Hz) to the two-bond <sup>13</sup>C(6)-C(7)-H coupling and the smaller one (2.85 Hz at 70 °C) to the vicinal <sup>13</sup>C(6)-O(1)-C(5)-H coupling. Cooling of ACh aqueous solution from 70 to 10 °C is accompanied by a change in <sup>3</sup>J<sub>C(6)-O(1)-C(5)-H (from 2.85 to 2.55 Hz) (Table I) but not in <sup>2</sup>J<sub>C(6)-C(7)-H. We interpret this fact as indicative of the</sub></sub>

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