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Radical-based transformation of vicinal diols to olefins via thioxocarbamate derivatives: a simple approach to 2′,3′-didehydro-2′,3′-dideoxynucleosides

Makoto Oba, Mitsuteru Suyama, Atsushi Shimamura and Kozaburo Nishiyama*

Department of Material Science and Technology, Tokai University, 317 Nishino, Numazu, Shizuoka 410-0395, Japan

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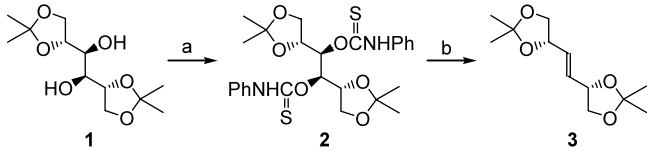
Abstract—The bis-*O*-thioxocarbamate derivatives obtained from the reaction of vicinal diols with phenyl isothiocyanate are shown to be reduced with tris(trimethylsilyl)silane in the presence of azobisisobutyronitrile to afford the corresponding olefins in good yields. In this way, 2′,3′-didehydro-2′,3′-dideoxy analogs of adenosine, guanosine, inosine, cytidine and uridine were prepared by the radical-based deoxygenation of the corresponding ribonucleosides via the bis-*O*-thioxocarbamate derivatives. © 2003 Published by Elsevier Science Ltd.

Radical-based deoxygenation of aliphatic alcohols has been shown to be a useful reaction in the synthesis and modification of complex polyfunctionalized molecules, because radical reactions are compatible with sensitive functional groups and less susceptible to steric retardation.[1] Most of the methods available for the deoxygenation reactions involve reduction of *O*-thiocarbonyl derivatives of the corresponding alcohols. Since the advent of the original Barton–McCombie reaction, in which *S*-methyl dithiocarbonate and thioxobenzoate were involved,[2] numerous modifications were reported up to now.[3–9] Although substituted phenyl chlorothioxocarbonates and diimidazolyl thioketone are found to be effective and versatile reagents, the problems associated with the price and low stability toward moisture prompted a search for other derivatizing reagents.

Recently, we have shown that *N*-acetyl- and *N*-phenylthioxocarbamate, obtained from the reaction of aliphatic alcohols with acetyl and phenyl isothiocyanates, were reduced with various silanes as well as tributyltin hydride under radical conditions to give the corresponding deoxygenated products in excellent yields.[10,11] We have assumed that the application of this radical-based deoxygenation protocol to vicinal diols would provide a simple method for the olefin preparation. We here describe a facile approach to 2′,3′-didehydro-2′,3′-dideoxynucleosides from ribonucleosides via the corresponding 2′,3′-bis-*O*-thioxocarbamate derivatives. Some of them and their 2′,3′-saturated analogs are known as potent antivirus agents against human immunodeficiency virus (HIV).[12–14]

As a suitable model compound, we took 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**). Treatment of the vicinal diol **1** with phenyl isothiocyanate in the presence of sodium hydride gave 3,4-bis-*O*-(*N*-phenylthioxocarbamoyl)-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**2**) in 89% yield (Scheme 1).

The radical-based deoxygenation of the bis-*O*-thioxocarbamate **2** was carried out using various silanes. The reaction conditions and the results are compiled in Table 1. Typically, the reduction of **2** with 2 equiv. of tris(trimethylsilyl)silane[15] in benzene (0.05 M) was carried out at 80°C in the presence of a catalytic amount (0.2 equiv.) of azobisisobutyronitrile (AIBN) for 3 h. Direct GC analysis of the reaction mixture showed the formation of olefin **3** in 84% yield (run 6). With simple aryl silanes, higher temperature was required to obtain fair yields (runs 1 and 4). It was previously shown that



Scheme 1. *Reagents and conditions*: (a) PhNCS, NaH, THF, 89%; (b) $(Me_3Si)_3SiH$, AIBN, benzene, 80°C, 84%.

* Corresponding author. Tel.: +81-55-968-1111; fax: +81-55-968-1155; e-mail: nishiyam@wing.ncc.u-tokai.ac.jp

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Table 1. Transformation of bis-*O*-thioxocarbamate **2** into olefin **3**

Run	Reducing agent (2 equiv.)	Initiator (0.2 equiv.)	Solvent (0.05 M)	Temp (°C)	Time (h)	Yield[a] (%)
1	Ph_3SiH	DTBP[b]	PhCl	130	4	46
2	Ph_2SiH_2	AIBN	Benzene	80	4	12
3	Ph_2SiH_2	Et_3B[c]	Benzene	rt	1	19
4	Ph_2SiH_2	DTBP[b]	PhCl	130	4	62
5	DSA[d]	AIBN	Benzene	80	4	17
6	$(Me_3Si)_3SiH$	AIBN	Benzene	80	3	84
7	Bu_3SnH	AIBN	Benzene	80	4	43

[a] Determined by GC analysis.
[b] Di-*tert*-butyl peroxide.
[c] 1.2 equiv. of Et_3B was used.
[d] 9,10-Dimethyl-9,10-dihydro-9,10-disilaanthracene.

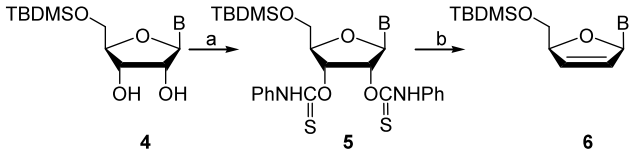
triethylborane facilitated the silane reduction at room temperature;[8,10,11,16] however, the initiator did not work well in this case (run 3). The conventional tributylstannane[17] and 9,10-dimethyl-9,10-dihydro-9,10-disilaanthracene (DSA), recently developed by us,[18,19] were also tested, but these reagents were not so effective in the present reaction system (runs 5 and 7). Consequently, the tris(trimethylsilyl)silane–AIBN system was used for the following examinations.

Several methods for the preparation of 2′,3′-didehydro-2′,3′-dideoxynucleosides can be seen in the literature,[20–24] whereas the direct synthesis of the 2′,3′-unsaturated nucleosides from the corresponding ribonucleosides based on mild radical chemistry are limited to the reduction of bisxanthate derivatives.[25,26] The *O*-phenoxythiocarbonyl and *O*-imidazolylthiocarbonyl derivatives were used only in a free radical β-elimination of 2′- or 3′-halogenated deoxynucleosides leading to the 2′,3′-unsaturated systems.[27,28]

We next demonstrated the direct conversion of five representative ribonucleosides **4**, such as adenosine, guanosine, inosine, cytidine and uridine, into the corresponding 2′,3′-unsaturated nucleosides **6** via radical-based deoxygenation of the bis-*O*-thioxocarbamate derivatives **5** (Scheme 2).

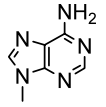
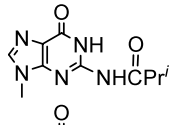
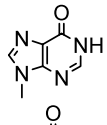
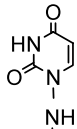
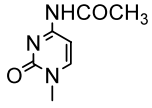
When a solution of 5′-*O*-(*tert*-butyldimethylsilyl)-adenosine (**4a**) and phenyl isothiocyanate in dimethylsulfoxide was treated with 5 M aqueous NaOH solution, the corresponding 2′,3′-bis-*O*-(*N*-phenylthioxocarbamoyl)adenosine **5a** was obtained in 85% yield. In this case, the use of sodium hydride as a base afforded **5a** in somewhat lower yield. The obtained adduct **5a** was then subjected to the deoxygenation reaction using the $(Me_3Si)_3SiH$–AIBN system to give 5′-*O*-TBDMS-2′,3′-didehydro-2′,3′-dideoxyadenosine (**6a**) in 78% yield (Table 2, entry 1).

Other 5′-*O*-silylated ribonucleosides **4b–e** were similarly treated with phenyl isothiocyanate in the presence of sodium hydride to give 2′,3′-bis-*O*-thioxocarbamate derivatives **5b–e** in good yields. In the case of guanosine and cytosine, N^2-isobutyryl and N^4-acetyl protective groups, respectively, were necessary to inhibit the predicted side reactions based on the highly nucleophilic amidine amino moiety. The radical-based deoxygenation of the adducts **5b–e** with $(Me_3Si)_3SiH$ in the presence of AIBN furnished the corresponding 5′-*O*-TBDMS-2′,3′-didehydro-2′,3′-dideoxynucleosides **6b–e** in fair yields. The results are also summarized in Table 2.



Scheme 2. *Reagents and conditions*: (a) PhNCS, base; (b) $(Me_3Si)_3SiH$, AIBN, benzene, 80°C, 4 h.

Table 2. Conversion of ribonucleosides **4** to 2′,3′-didehydro-2′,3′-dideoxynucleosides **6**

Entry	B		**5**, %	**6**, %	Overall, %[a] (lit.[b])
1		(**a**)	85	78	66 (65)
2		(**b**)	81	70	57 (44)
3		(**c**)	87	82	71 (52)
4		(**d**)	78	69	54 (78)
5		(**e**)	74	49	36 (30)

[a] Isolated yields of 2',3'-unsaturated nucleosides **6** based on ribonucleosides **4**.

[b] Overall yields obtained by the bisxanthate method.[26]

The overall transformation of the ribonucleosides into the 2′,3′-unsaturated nucleosides could generally be accomplished in better yields than the bisxanthate procedure. Furthermore, the bisxanthate method requires β-bromopropionitrile as an alkylating agent in order to prevent undesirable *N*-alkylation in some cases.

In conclusion, we have developed a simple and general method for the preparation of 2′,3′-didehydro-2′,3′-dideoxynucleosides by radical-based deoxygenation of the corresponding ribonucleosides via the 2′,3′-bis-*O*-thioxocarbamate derivatives.

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