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Direct Preparation of Nucleoside Vinyl Disulfides from 2-(Trimethylsilyl)ethyl Sulfides, an Access to Vinylthiols

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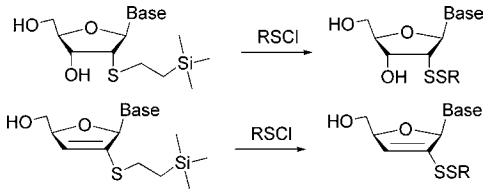
ABSTRACT



We report here a straightforward preparation of various nucleoside vinyl disulfides in high yields under mild conditions using the new reaction of vinyl 2-(trimethylsilyl)ethyl (TMSE) sulfides with sulfenyl chlorides. This reaction allows the preparation of various mixed disulfides from stable silyl sulfides without formation of oxidizable and/or unstable thiols. The easy preparation of vinyl disulfides through this reaction should offer new perspectives in vinylthiol chemistry.

The reduction of the natural ribonucleoside 5′-diphosphates to the corresponding 2′-deoxyribonucleotides catalyzed by the enzyme ribonucleoside diphosphate reductase (RDPR) is considered to be a rate-limiting step in the biosynthesis of DNA and in the mammalian cell proliferation.[1a,b] This enzyme uses a radical chemistry to perform the reduction of the four natural substrates.

Modifications of the sugar moiety of ribonucleoside 5′-diphosphates at the 2′-position have led to a number of mechanism-based inhibitors of RDPR or/and anticancer agents.[1] These nucleotides appeared ineffective in vivo, being unable to penetrate in cells. To become pharmacologically active, the corresponding modified ribonucleosides must be phosphorylated to the 5′-diphosphates by cellular kinases. For example, the anticancer drug 2′-deoxy-2′,2′-difluorocytidine (gemcitabine) inhibits RDPR after phosphorylation in vivo.[2]

The catalysis of the ribonucleotide reduction involves three cysteine residues at the active site, and one of them is converted to a cysteinyl free radical that initiates the reaction.[1] In the search for mechanism-based inhibitors of RDPR, an interesting modification in ribonucleot(s)ides can be the replacement of the 2′-hydroxy function by a thiol group able to react with the reducing cysteine residues. 2′-Deoxy-2′-thiouridine 5′-diphosphate was found to be in vitro a potent inhibitor of the enzyme RDPR through reaction of the 2′-thiol function at the active site leading to a perthiyl free radical in the protein.[3a−c] In the search for prodrugs of such thionucleotides, the methyl disulfide of 2′-deoxy-2′-

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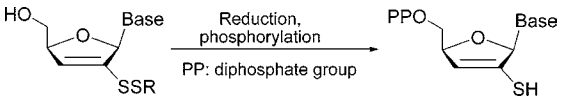
thiocytidine was found to be able to inhibit the proliferation of human lymphoblastoid cells probably after reduction, phosphorylation, and inactivation of RDPR.[3d] However, the cytotoxicity of this compound in various cancer cell lines appeared too low for further evaluation in animals.

2′,3′-Unsaturated 2′-thionucleosides (Scheme 1) also could, after in vivo phosphorylation, inactivate RDPR through free radical reactions. In this approach, the corresponding disulfides could be reduced and lead to the vinylthiol diphosphate able to react at the active site from the double bond and/or the thiol function.

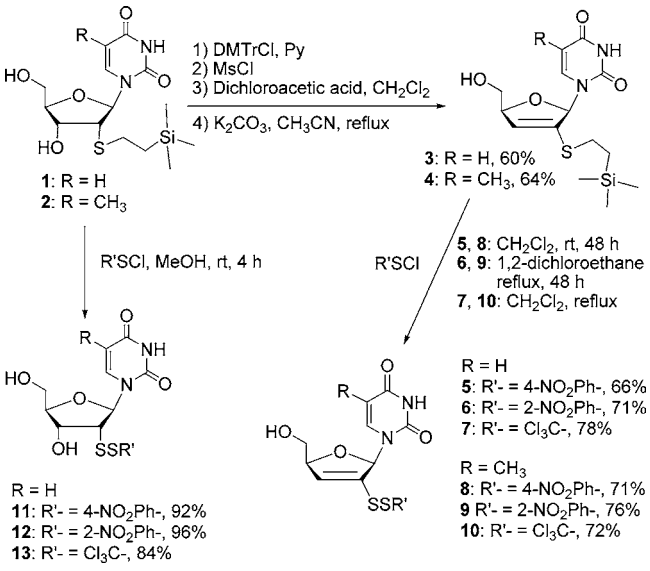
Scheme 1. Structure of the Target Nucleoside Vinyl Disulfides and Their Possible Bioactive Derivatives



2′,3′-Unsaturated nucleosides have shown interesting antiviral effects, for example, the anti-HIV drug 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T).[4] A limited number of vinyl disulfides have been described in the literature, and their preparation required the formation of the corresponding unstable intermediate "vinylthiol" (enethiol) or drastic conditions.[5]

We now report a straightforward preparation of various nucleoside vinyl disulfides in high yields under mild conditions using a new reaction of vinyl 2-(trimethylsilyl)ethyl (TMSE) sulfides with commercially available sulfenyl chlorides (Scheme 2). Previously, 2-TMSE alkyl sulfides

Scheme 2. Preparation of the Uridine and 5-Methyluridine Derivatives

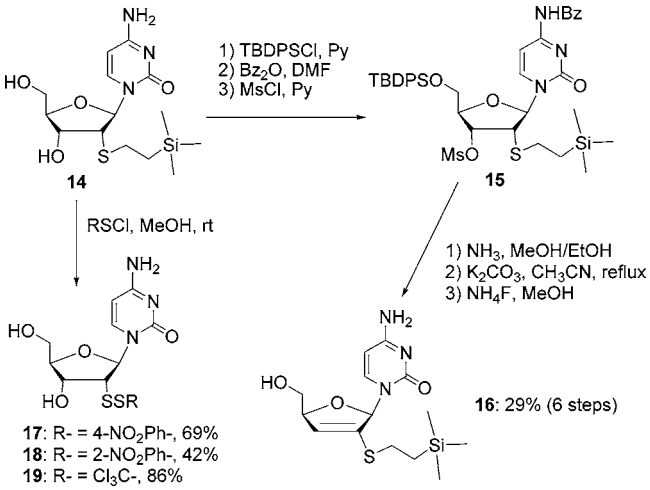


have been converted to the corresponding methyl disulfides by treatment with dimethyl(methylthio)sulfonium tetrafluoroborate,[6] but this method failed in the preparation of vinyl disulfides. The reported reaction constitutes the first example of direct conversion of a vinyl sulfide to the corresponding disulfide.

The unsaturated silyl uridine derivative **3** and its 5-methyl analogue **4** were prepared in four steps from the TMSE sulfides **1**[6b] and **2**, respectively (Scheme 2, 60 and 64% yields): (i) 4,4′-dimethoxytritylation of the 5′-hydroxyl function, (ii) mesylation at the 3′-position in the same pot, (iii) removal of the trityl group under acidic conditions, and (iv) elimination with K_2CO_3.

The unsaturated silyl cytidine derivative **16** was prepared in six steps from the silyl sulfide **14**[6b] (Scheme 3, 29%): (i)

Scheme 3. Preparation of the Cytidine Derivatives



5′-silylation with *tert*-butyldiphenylsilyl chloride, (ii) protection of the amino group with benzoic anhydride, (iii) 3′-mesylation, (iv) deprotection of the amino group with ammonia, (v) elimination in the presence of K_2CO_3, and (vi) removal of the 5′-silyl protecting group with ammonium fluoride.

Attempts to convert the unsaturated silyl nucleosides **3** and **4** to the corresponding methyl disulfides by treatment with dimethyl(methylthio)sulfonium tetrafluoroborate[6a,b] failed under different conditions as well as attempts to convert these sulfides to the corresponding thiols by treatment with fluoride ions. Previously, we have shown that TMSE sulfides can be converted selectively and in high yield to the corresponding thiocyanates through the von Braun reaction with cyanogen bromide in methanol.[7] Different thiocyanato nucleosides have been prepared using this reaction. For example, treatment of the sulfide **1** with cyanogen bromide in methanol led to the corresponding thiocyanate, but surprisingly, the reaction

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in dichloromethane afforded the corresponding symmetrical uridine disulfide.[7]

Such a reaction could proceed through formation of intermediate 2′-deoxyuridine 2′-sulfenyl bromide which then reacts with the starting silyl sulfide **1**. Therefore, it appeared interesting to study the reaction of TMSE sulfides with various sulfenyl halides such as trichloromethanesulfenyl, 2-, and 4-nitrobenzenesulfenyl chlorides (TCMSCl, 2NBSCl, and 4NBSCl).

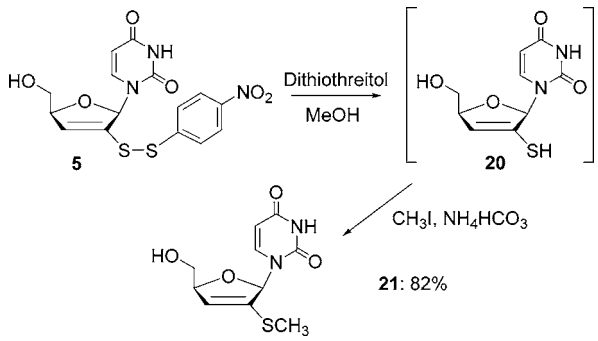
When one of these sulfenyl chlorides (3 equiv) was added at room temperature (rt) to a solution of the silyl nucleoside **1** or **14** in methanol, a clean reaction rapidly occurred (4 h, Schemes 2 and 3). The mixed disulfides **11**−**13** and **17**−**19** (Scheme 3) were obtained in high yields (84−96%) except for **17** (69%) due to reaction of 4NBSCl with the amino group of cytosine (addition by parts) and for **18** (42%), due to the difficulty of purification by chromatography on silica gel. Such a reaction could be interesting in the preparation of oligonucleotides incorporating 2′- or 3′-thionucleotide(s) as tools for the study of structures and functions of nucleic acids.[8]

The 2′,3′-unsaturated silyl sulfides **3** and **4** were also converted in good yields (66−78%) to the corresponding mixed disulfides **5**−**10** (Scheme 2) in the presence of 3 equiv of sulfenyl chloride. Unfortunately, it was not possible to obtain the corresponding mixed disulfides from the unsaturated cytidine derivative **16** (decomposition).

In order to observe the formation of vinylthiols (Scheme 4), the disulfides **5** and **10** were treated with dithiothreitol (3 equiv) at rt in MeOH-d_4, and the reaction was monitored by ^{1}H NMR. After 30 min, the formation of a new nucleoside was observed. Progressively, this compound led completely to a second nucleoside identified as the symmetrical vinyl disulfide characterized after isolation. The intermediate compound observed from the disulfide **5** is probably the vinylthiol **20** (δ 3′H: 6.55 ppm) that appeared easily oxidizable.

To confirm the formation of the vinylthiol, the disulfide **5** was reduced and the resulting nucleoside was alkylated in situ with methyl iodide in methanol at rt. The main product

Scheme 4. Formation of the Vinylthiol **20** from the Disulfide **5** and Trapping to the Sulfide **21**



was isolated in a 82% yield and characterized as being the methyl sulfide **21** (Scheme 4). This result shows that vinylthiols can be generated in situ from the corresponding disulfides and trapped efficiently for preparing various sulfides.

In conclusion, the reaction between a 2-(trimethylsilyl)-ethyl sulfide nucleoside and a sulfenyl chloride afforded under mild conditions disulfides in good to high yields without protection of the hydroxyl and amino groups. This reaction allows the preparation of vinyl disulfides from the corresponding stable silyl sulfides without intermediary formation of oxidizable and/or unstable thiols. It offers new perspectives in vinylthiol chemistry, for example, new unsaturated nucleosides of medicinal interest should be obtained from such intermediates.

A first attempt of reaction of butyl TMSE sulfide with benzenesulfinyl chloride showed that thiosulfinates also can be directly prepared from TMSE sulfides.

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Supporting Information Available: Experimental details for the synthesis and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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