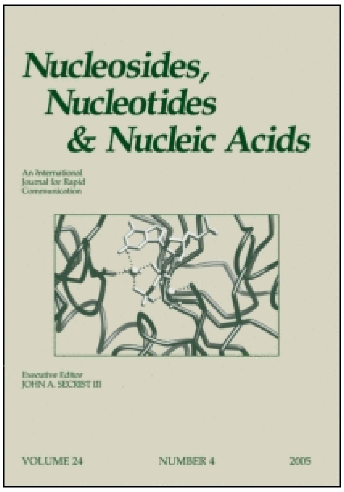


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Isomerization of Cytidine 2',3'-Thionocarbonates

L. W. Dudycz[a]
[a] Department of Pharmacology, University of Massachusetts Medical School, Worcester, MA, U.S.A.

To cite this Article Dudycz, L. W.(1989) 'Isomerization of Cytidine 2',3'-Thionocarbonates', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 939 — 941

To link to this Article: DOI: 10.1080/07328318908054249

URL: http://dx.doi.org/10.1080/07328318908054249

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 939-941 (1989)

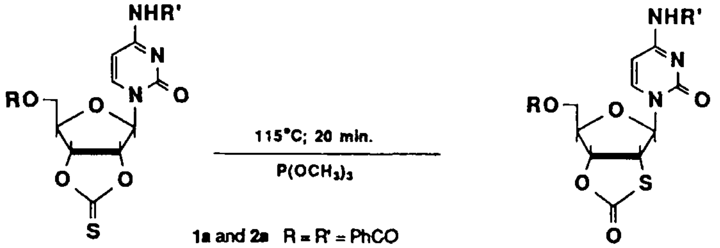
ISOMERIZATION OF CYTIDINE 2′,3′-THIONOCARBONATES

L. W. Dudycz
Department of Pharmacology, University of Massachusetts Medical School
55 Lake Avenue North, Worcester, MA 01655, U.S.A.

Abstract—*N^4,5′-Protected cytidine 2′,3′-thionocarbonates isomerize at elevated temperatures to 2′-deoxy-2′-thiocytidine 2′,3′-carbonates.*

Ribonucleoside 2′,3′-thionocarbonates appeared to be promising as key intermediates for the synthesis of 2′,3′-didehydro-2′,3′-dideoxyribonucleosides via the Corey-Winter reaction. However, many attempts to employ this method for nucleosides were unsuccessful due to multiple side-reactions[1]. Recently, we reported a very efficient application of this method to uridine[2]. A N^6,5′-protected adenosine 2′,3′-thionocarbonate was also efficiently converted by the Corey-Winter method into its 2′,3′-didehydro-2′,3′-dideoxy derivative[3]. These findings encouraged us to explore further the chemistry of ribonucleoside 2′,3′-thionocarbonates in order to understand the previously reported failures and to resolve these problems.

Our recent investigations have shown that some cytidine 2′,3′-thionocarbonates, **1a** and **1b**, are not stable at elevated temperatures and undergo a fast isomerization at the conditions of the Corey-Winter reaction to isomeric thiolocarbonates similarly to that of the cyclic thionocarbonate of ethylene glycol[4] and diarylthionocarbonates in the Schönberg rearrangement[5].



1 **2**

1a and 2a R = R' = PhCO

1b and 2b R = t-BuMe$_2$Si, R' = CH$_3$CO

2c R = H, R' = CH$_3$CO

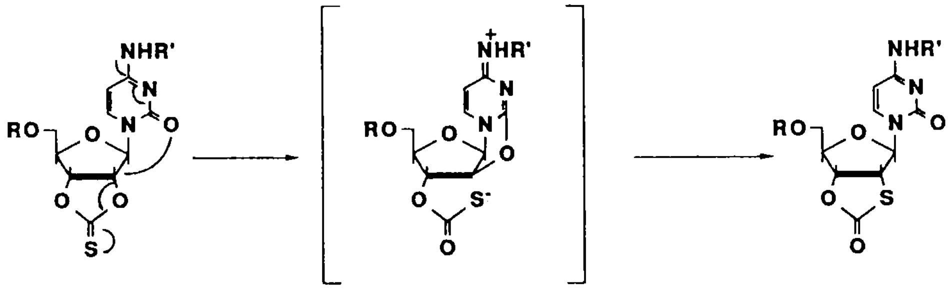
The 4-amino and 5′-hydroxyl groups of cytidine have been protected prior to the reaction with 1,1′-thiocarbonyldiimidazole. N^4,5′-Dibenzoyl cytidine was obtained by the method of Nishino et al.[6]. N^4-Acetyl-5′-(*tert*-butyldimethylsilyl)cytidine was prepared in two steps employing procedures of Otter and Fox[7], and Ogilvie et al.[8]. The 2′,3′-O-thiocarbonates, **1a** and **1b**, were heated in trimethyl phosphite at 115°C for 20 minutes. After 15 minutes the reaction mixture contained only traces of the starting material. The products **2a** and **2b** precipitated from the reaction mixture after cooling to ambient temperature. The pure products were obtained in yields of approximately 70% by crystallization from ethanol. Elemental analyses have shown that these products contain sulfur, and that they have the same elemental composition as the starting materials.

The determination of C-2′ as the site of isomerization was based on the analysis of ^{1}H NMR spectra of **2a** and **2b**. These spectra have shown a large ($\Delta\delta \approx 1.2$ ppm) up-field change in the chemical shift of H-2′ protons in comparison to these of the substrates, **1a** and **1b**, and a much smaller change, $\Delta\delta \approx 0.3$ ppm, for H-3′ protons. Virtually identical changes of $\Delta\delta$ of ethylene protons have been reported by Jones and Andreades for 1,3-oxathiolane-2-one and its isomer, 1,3-dioxolane-2-thione[4].

Compound **2c**, obtained from **2b** by a treatment with tetra-n-butylammonium fluoride in THF, decomposes in aqueous NaOH solution to cytosine and a sugar residue. This N-glycosidic bond cleavage at alkaline conditions can be explained by the intramolecular attack of the 2′-thiolate group on 1′-carbon in **2c** with elimination of cytosine. A similar reaction for 2′-deoxy-2′-thiouridine has been previously reported by Imazawa et al.[9].

The isomerization of **1a** and **1b** does not proceed exclusively in trimethyl phosphite. These compounds isomerize also in other aprotic solvents, as chloroform and toluene. In a stricking contrast to the compounds remain their close analogs, 5′-substituted uridine 2′-3′-thionocarbonates, which are stable in boiling toluene, and in trimethyl phosphite are converted into 2′,3′-didehydro-2′,3′-dideoxy derivatives[2].

The mechanism of the isomerization is not yet clear, and at this moment the participation of O^2,2′-anhydrocytidine intermediate (shown below) in this reaction can not be excluded.



Acknowledgements. This project was supported by BRSG Grant S07 RR05712 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health.

References

1. W. V. Ruyle, T. Y. Shen, and A. A. Patchett, J.Org.Chem. 30, 4353 (1965); G. L. Tong, W. W. Lee and L. Goodman, J.Org.Chem 30, 2854 (1965).
2. L. W. Dudycz, Nucleosides & Nucleotides 7, 000 (1988).
3. The Corey-Winter reaction was conducted at 90°C to prevent the decomposition of the product to N^6-acetyladenine and a sugar residue. L. W. Dudycz, unpublished data.
4. F.N. Jones and S. Andreades, J.Org.Chem. 34, 3011 (1969).

5. A. Schönberg and L. Vargha, Chem. Ber. **63**, 178 (1930).

6. S. Nishino, M. A. Rahman, H. Takamura, and Y. Ishido, Tetrahedron **41**, 5503 (1985).

7. B. A. Otter and J. J. Fox, in *"Synthetic Procedures in Nucleic Acid Chemistry"*, V.1, p.285, Eds. W. W. Zorbach and R. S. Tipson, Interscience Publishers, 1968.

8. K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault, and K. L. Sadana, Can.J.Chem. **56**, 2768 (1978).

9. M. Imazawa, T. Ueda, and T. Ukita, Chem.Pharm.Bull. **23**, 604 (1975).