Pergamon

Tetrahedron Letters, Vol. 36, No. 34, pp. 6099-6100, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01213-3

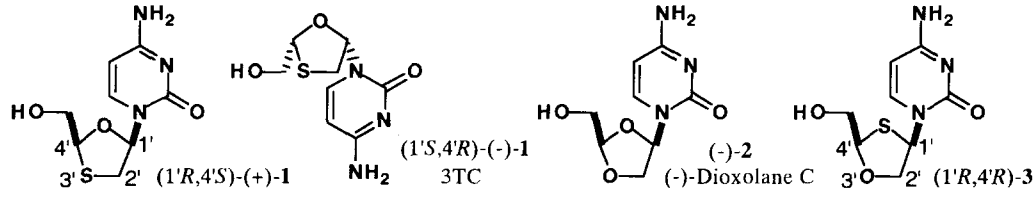
Synthesis of 1,3-Oxathiolane Derivatives as Novel Precursors of 2',3'-Dideoxy-3'-oxa-4'-thioribonucleosides

Junzo Nokami,* Kazuyo Ryokume, and Junya Inada

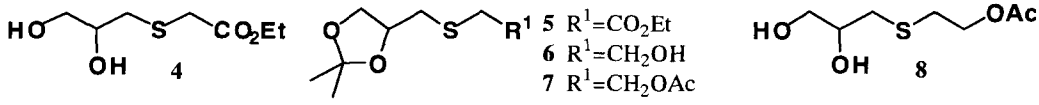
Department of Applied Chemistry, Faculty of Engineering
Okayama University of Science, Ridai, Okayama 700, Japan

Abstract: 1,3-Oxathiolanes were prepared *via* electrochemical chemoselective α-acetoxylation of β'-hydroxy sulfides and were converted into 4-acetoxy-1,3-oxathiolanes, precursors of 2',3'-dideoxy-3'-oxa-4'-thioribonucleosides, by the electrolytic acetoxylation of the 1,3-oxathiolane or by Pummerer rearrangement *via* sulfoxide.

Antiviral nucloside analogues containing more than one heteroatom in the sugar ring have received much attention because of their potent anti-HIV and anti-HBV activities. For example, syntheses of 1,3-oxathiolane derivatives (+)-**1**[1] and dioxolane derivatives (-)-**2**[2] and their antiviral activities have been reported. Interestingly, it has been found that the antipode (-)-**1** (3TC) and the racemate (±)-**1** (BHC-189) show much higher anti-HIV and anti-HBV activities than (+)-**1**.[1] More recently, Jin et al. have reported synthesis of optically active 2',3'-dideoxy-3'-oxa-4'-thioribonucleoside (1'*R*,4'*R*)-**3**, which shows anti-HIV activity similar to that of its enantiomer (1'S,4'S)-**3**.[3b]



These facts prompted us to synthesize a variety of 1,3-oxathiolanes **11** through electrolytic acetoxylation of β-hydroxy sulfides **9**[4] which were prepared from 2-mercaptoethanol or 3-mercapto-1,2-propanediol (thioglycerol) and α-halo esters. A typical procedure is as follows.



Treatment of thioglycerol with ethyl bromoacetate in refluxing acetone in the presence of finely powdered sodium carbonate (3 equiv) gave ethyl (2,3-dihydroxypropylthio)acetate **4** (98%). The diol **4** was converted to acetonide **5** by treatment with 2,2-dimethoxypropane and *p*-TolSO3H (cat.) in acetone. Subsequent reduction of **5** with LAH at 0 °C~r.t. in ether afforded alcohol **6** (96%). The alcohol **6** was allowed to react with acetic anhydride and triethylamine (excess) in dichloromethane to give the acetate **7**. The protecting group (acetonide) was removed by hydrolysis in acetic acid-H2O-THF (3:1:1) at 50°C for 5 h affording 3-(2-acetoxyethylthio)propane-1,2-diol **8** (97%). Acetylation of the terminal hydroxy group of **8** was performed with 1.1 equiv. of acetic anhydride and triethylamine at 0°C to give **9c** (78%). Electrolysis of the sulfide **9c** was carried out in acetic acid (0.5 M) with sodium acetate (1.0 M) using two platinum plates (electrode) without

cooling.[5] After passing 2.5 F/mol of electricity at a constant current (50 mA/cm^2), usual work-up gave α-acetoxy sulfide **10c** (41%). The α-acetoxy β'-hydroxy sulfide **10c** was treated with BF_3 etherate (1.1 equiv) in dichloromethane at 40°C to give 1,3-oxathiolane **11c** (93%).

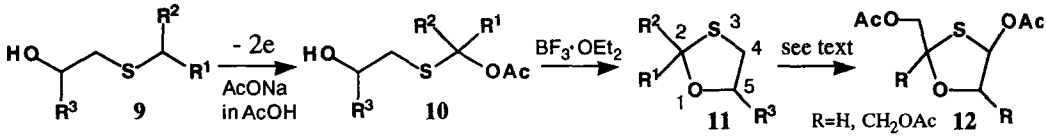


Table 1 Synthesis of 1,3-oxathiolanes **11** *via* α-acetoxylation of β'-hydroxy sulfides **10**

	R^1=	R^2=	R^3=	F/mol[a]	**10** (yield/%)	**11** (yield/%)
a	CO_2Me	H	H	3.0	55	63
b	CO_2Et	H	CH_2OAc	3.0	60	67[b, c]
c	CH_2OAc	H	CH_2OAc	2.5	41	93[b]
d	CO_2Et	CO_2Et	H	3.0	49	53[c]

a. Electricity passed. b. E/Z mixture (ca. 1/1). c. Carried out in refluxing 1,2-dichloroethane.

1,3-Oxathiolanes **11a**, **11b**, and **11d**, prepared in a similar manner (Table 1), were converted to 2-hydroxymethyl, 2,5-dihydroxymethyl, and 2,2-dihydroxymethyl-1,3-oxathiolanes by treatment with LAH, DIBAH, and $NaBH_4$, respectively, and then to the corresponding acetates **11e** (R^1=CH_2OAc, R^2=R^3=H), **11c**, and **11f** (R^1=R^2=CH_2OAc, R^3=H), respectively, by treatment with acetic anhydride and triethylamine (64~77%). α-Acetoxylation of **11c** to **12c** was performed by the revised Pummerer rearrangement *via* sulfoxides[3] while that of the sterically hindered sulfide **11f** to the corresponding 4-acetoxy derivatives **12f** was successfully performed by the electrolysis.[4] Some of 2',3'-dideoxy-3'-oxa-4'-thioribonucleosides were synthesized from **12c** and **12f** by the usual method.[3] The details as well as the bioactivities will be described elsewhere.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area of Electroorganic Chemistry from the Ministry of Education, Science and Culture, Japan.

References

1) J. W. Beach, L. S. Jeong, A. J. Alves, D. Pohl, H. O. Kim, C.-N. Chang, S.-L. Doong, R. F. Schinazi, Y.-C. Cheng, and C. K. Chu, *J. Org. Chem.*, **57**, 2217 (1992), and references cited therein.

2) D. W. Norteck, S. Spanton, S. Broder, and H. Mitsuya, *Tetrahedron Lett.*, **30**, 6263 (1989); H. O. Kim, S. K. Ahn, A. J. Alves, J. W. Beach, L. S. Jeong, B. G. Choi, P. V. Roey, R. F. Schinazi, and C. K. Chu, *J. Med. Chem.*, **35**, 1987 (1992), and references cited therein.

3) a) B. Belleau, L. Brasili, L. Chan, M. P. DiMarco, B. Zacharie, and N. Nguyen-Ba, *Bioorg. Med. Chem. Lett.*, **3**, 1723 (1993). b) W. Wang, H. Jin, and T. S. Mansour, *Tetrahedron Lett.*, **35**, 4739 (1994).

4) a) J. Nokami, M. Hatate, S. Wakabayashi, and R. Okawara, *Tetrahedron Lett.*, **21**, 2557 (1980). b) Other reports on α-oxydation of sulfides; T. Fuchigami, Y. Nakagawa, T. Nonaka, *ibid.*, **27**, 3869 (1986); J. Yoshida and S. Isoe, *Chem. Lett.*, **1987**, 631; M. Kimura, K. Koie, S. Matsubara, Y. Sawaki, and H. Iwamura, *J. Chem. Soc., Chem. Commun.*, **1987**, 122.

5) The temperature rose to 45~50 °C under the reaction conditions.

(*Received in Japan* 13 *May* 1995; *revised* 26 *June* 1995; *accepted* 27 *June* 1995)