FORMATION OF BICYCLIC β-LACTAMS FROM DICHLORO-1,4-OXATHIANE-3-CARBOXANILIDES: NUCLEOPHILIC SUBSTITUTION OF NITROGEN ON ANOMERIC CARBON

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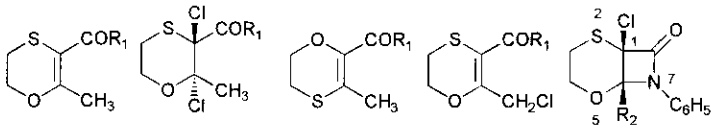
Abstract - Transformation of dichloro-1,4-oxathiane anilides (**2**) to bicyclic β-lactam (**5**) is described. In the presence of sodium hydride, an intramolecular nucleophilic substitution of nitrogen to anomeric carbon of **2** gave *(1R*, 6R*)*-1-chloro-6-methyl-7-phenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-ones (**5**). The reason for facile displacement at C-2 is attributable to neighboring group participation of sulfur and C-2 is anomeric. Plausible mechanisms for the formation of 2-chloromethyl-5,6-dihydro-*N*-phenyl-1,4-oxathiin-3-carboxyamide (**4**) under the neutral conditions, or 2,3-dihydroxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxyamide (**9**) in aqueous solution, or bicyclic β-lactam (**5**) in the presence of sodium hydride were proposed.

INTRODUCTION

Neighboring group participation (NGP) by a heteroatom or hetero-substituent at a remote reaction center is a well-known phenomenon that generally enhances the reactivity of certain classes of reactions.[1] A synthesis of an isomeric dihydro-1,4-oxathiin (**3**) from dihydro-1,4-oxathiin (**1**) through dichloro-1,4-oxathiane (**2**)[2] and a mechanistic study on the conversion of **2** to chloromethyl compound (**4**) were reported previously.[3] In these reactions, the high reactivity at C-2 carbon of **2** arises from the NGP of the sulfur as well as the fact that it is anomeric. As an extension of our studies on the reactivity of **2**, we now report the formation of a bicyclic β-lactam (**5**) by intramolecular nucleophilic displacement of nitrogen on the anomeric carbon assisted by NGP of the sulfur. This investigation provides results on the reactivity of the dichloro-1,4-oxathiane (**2**) when to compared with the previous report.[2, 3]



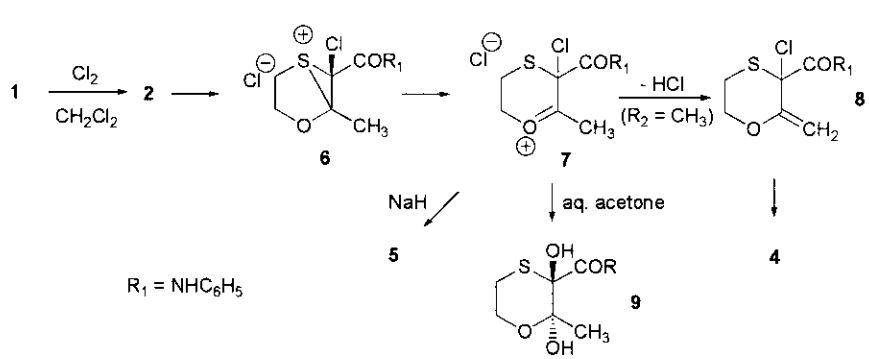
1 2 3 4 5

$R_1 = NHC_6H_5$

$R_2 = CH_3, C_6H_5$

RESULTS AND DISCUSSION

Synthesis of starting dihydro-1,4-oxathiin (**1**) was achieved by the previously known method.[4] As shown in Scheme 1, chlorination of **1** with chlorine at room temperature gave dichloro-1,4-oxathiane (**2**) quantitatively. The dichloro-1,4-oxathiane (**2**) was unstable and gradually rearranges to chloromethyl compound (**4**) through **8** at room temperature ($t_{1/2}$ = 3 h) and the solvolysis of **2** in aqueous acetone gave a dihydroxy-1,4-oxathiane (**9**).[2] As shown in Scheme 1, the sulfur in **2** is postulated to attack the anomeric carbon to give a thiiranium ion (**6**) which would open to more stable oxonium ion (**7**). In this reaction, the reason for facile displacement of chlorine atom at C-2 is attributable to NGP of sulfur and that C-2 is anomeric. We attempted an interamolecular nucleophilic displacement of nitrogen on C-2 to form bicyclic β-lactam because β-lactam ring, particularly in bicyclic system, is of importance in pharmaceutics. Since a tertiary chloride is too sensitive to water, leading to dihydroxy-1,4-oxathiane (**9**), **2** was treated with triethylamine under the anhydrous conditions. However, **2** underwent conversion to chloromethyl compound (**3**), which was the same result obtained without triethylamine. Upon treatment with sodium hydride, stronger **2** produced **5** (R_2 = CH_3) in good yield (70%), resulting from the direct nucleophilic substitution by anilide nitrogen. Treatment of **2** with sodium hydroxide solution dissolved in aqueous acetone at room temperature also furnished the bicyclic β-lactam (**5**) albeit in low yield (25%) and the dihydroxy-1,4-oxathiane (**9**) (10%) by solvolysis. The structure of **5** was determined by means of an X-Ray crystallographic analysis (see Figure 1 for *p*-methoxy analogue of **5**).[5] In the ^1H NMR spectrum, the chemical shifts (δ 2.81, δ 3.09, δ 3.96, δ 4.15) and coupling constants (J = 13.2 Hz, 12.0 Hz, 8.1 Hz, 6.1 Hz, 5.3 Hz, 4.4Hz) of the four protons at C-3 and C-4 in **5** supported structure.



Scheme 1

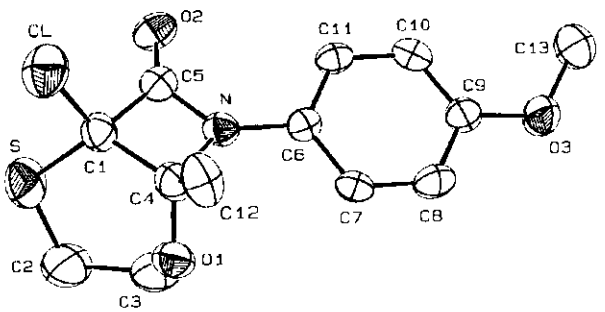
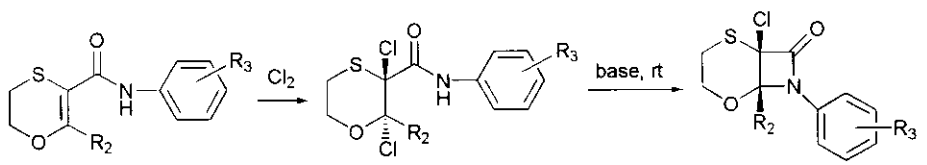


Figure 1. ORTEP plots of *p*-methoxy analogue of **5** with heteroatoms labeled.

Since **2** gradually converts to chloromethyl compound (**4**) at room temperature it is conceivable that prompt treatment of **2** with sodium hydride immediately after chlorination is critical for high yields of **5**. Similar results were obtained from the substituted anilides and phenyl derivative. Table 1 shows yields and melting points of the products.

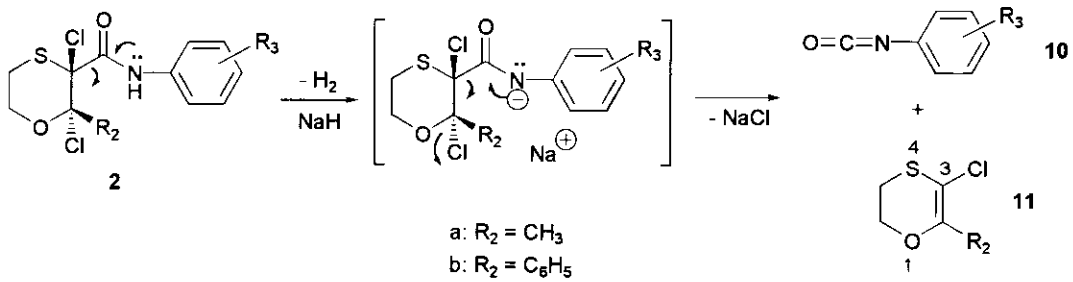
Table 1. The cyclization of dichloro-1,4-oxathianes (**2**) to bicyclic β-lactams (**5**) at room temperature.



1 **2** **5**

entry	R_2	R_3	base/solvent	yield (%) [6]	mp (°C)	by-products
1	CH_3	H	NaH/THF	70	127-129	**11a**
2	CH_3	H	NaOH/aq. acetone	25	-	**9**
3	CH_3	*p*-OCH_3	NaH/THF	31	118-119	**11a**
4	CH_3	*o*-OCH_3	NaH/THF	33	97-98	**11a**
5	CH_3	*o*-NO_2	NaH/THF	48	109-110	**11a**
6	CH_3	*p*-Cl	NaH/THF	25	113-114	**11a**
7	CH_3	*p*-CH_3	NaH/THF	26	91-92	**11a**
8	CH_3	2,4,6-$(CH_3)_3$	NaH/THF	29	99-100	**11a**
9	C_6H_5	H	NaH/THF	11	137-138	**11b** $C_6H_5COCH_2CONHC_6H_5$
10	C_6H_5	H	$(C_2H_5)_3N/CHCl_3$	20	-	**1**
11	C_6H_5	H	pyridine/$CHCl_3$	0	-	no reaction

The low yields probably arise from an elimination of the carboxanilide group at C-3. Thus, a significant amount of 3-chlorooxathiin (**11**) was isolated, identified by ^{1}H NMR and MS spectrometry (Scheme 2). We did not attempt isolation of phenyl isocyanate (**10**).[7]



Scheme 2

The elimination reaction to afford **11** is competitive with the interamolecular nucleophilic substitution to form **5**. Where a sterically hindered phenyl group is substituted at C-2 (entry 9), the 3-chlorooxathiin (**11b**) (73%) is major product whereas **5** (11%) is minor product. Improved yield (20%) of **5** was obtained by the treatment of **2** with triethylamine (entry 10). In this case, dihydro-1,4-oxathiin (**1**) was formed in 25% yield, presumably by dehalogenation of dichoro-1,4-oxathiane (**2**). No reaction was occurred when pyridine was used as the base. We could obtain **11b** as a white solid whereas **11a** was highly volatile, therefore afforded low yields (3 ~ 17%) after work up.

It is of interest that the dichloro-1,4-oxathiane (**2**) can be transformed to either chloromethyl compound (**4**) or dihydroxy-1,4-oxathiane (**9**), or bicyclic β-lactam (**5**) by appropriate choice of the reaction conditions.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. All ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shift (δ) are in ppm and the coupling constants (*J*) are in Hz. IR spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm^{-1}. MS spectra were recorded on a Hewlet Packard 5890 series GC/MSD. Elemental analysis was performed using a Fisons EA1108 analyzer.

Preparation of bicyclic β-Lactams (General Procedure)

To a stirred solution of dihydro-1,4-oxathiin (2 mmol) in tetrahydrofuran (10 mL) under the nitrogen atmosphere was added a 3% solution of chlorine dissolved in methylene chloride (3.0 mL) at rt. The reaction mixture was stirred for 5 min and then treated either with excess 60% sodium hydride (0.24 g, 6

mmol) in oil or with triethylamine (0.61 g, 6 mmol) for 2 h at rt. Evaporation of the solvent gave an oily residue which was dissolved in ethyl acetate (50 mL). The solution was washed with brine (3 times) and then dried ($MgSO_4$). Evaporation of the solvent gave an yellow solid (0.42 g, 78%), which was chromatographied on silica gel (Kieselgel GF254, 230-400 mesh) using ethyl acetate:n-hexane = 1:4 as eluent to give **5** as a white solid.

(1R, 6R*)*-**1-Chloro-6-methyl-7-phenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** Evaporation of the solvent gave an yellow solid (0.42 g, 78%), which was chromatographied on silica gel (Kieselgel GF254, 230-400 mesh) using ethyl acetate:n-hexane = 1:4 as eluent gave **5** as a white solid. ^{1}H NMR 1.91 (s, CH_3), 2.81 (ddd, J = 4.4, 5.3, 13.2, 3-CH (equatorial)), 3.09 (ddd, J = 6.1, 8.1, 13.2, 3-CH (axial)), 3.96 (ddd, J = 4.4, 8.1, 12.0, 4-CH (axial)), 4.15 (ddd, J = 5.3, 6.1, 12.0, 4-CH (equatorial)), 7.18-7.62 (m, ArH); IR 1770 (C=O); MS, m/z (relative intensity) 271 (M^++2, 0.07), 269 (M^+, 0.21), 150 (100); *Anal.* Calcd for $C_{12}H_{12}NO_2ClS$: C, 53.43, H, 4.48, N, 5.19. Found, C, 53.72, H, 4.50, N, 5.04.

(1R, 6R*)*-**1-Chloro-7-(4-methoxyphenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.87 (s, CH_3), 2.80 (ddd, J = 4.4, 5.3, 13.2, 3-CH (equatorial)), 3.08 (ddd, J = 6.1, 8.1, 13.2, 3-CH (axial)), 3.81 (s, OCH_3), 3.96 (ddd, J = 4.4, 8.1, 11.9, 4-CH (axial)), 4.13 (ddd, J = 5.3, 6.1, 11.9, 4-CH (equatorial)), 6.90-7.54 (m, ArH); IR 1774 (C=O); MS, m/z (relative intensity) 301 (M^++2, 3.2), 299 (M^+, 7.8), 143 (100); *Anal.* Calcd for $C_{13}H_{14}NO_3ClS$: C, 52.09, H, 4.71, N, 4.67. Found, C, 52.21, H, 4.81, N, 4.67.

(1R, 6R*)*-**1-Chloro-7-(2-methoxyphenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.77 (s, CH_3), 2.89 (ddd, J = 4.0, 5.0, 13.1, 3-CH (equatorial)), 3.10 (ddd, J = 5.5, 8.7, 13.1, 3-CH (axial)), 3.88 (s, OCH_3), 4.09 (ddd, J = 5.0, 5.5, 12.0, 4-CH (axial)), 4.33 (ddd, J = 4.0, 8.7, 12.0, 4-CH (equatorial)), 6.94-7.35 (m, ArH). IR 1784 (C=O); MS, m/z (relative intensity) 299 (M^+, not found), 265, (32.9), 150 (100); *Anal.* Calcd for $C_{13}H_{14}NO_3ClS$: C, 52.09, H, 4.71, N, 4.67. Found, C, 52.26, H, 4.79, N, 4.60.

(1R, 6R*)*-**1-Chloro-6-methyl-7-(2-nitrophenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.88 (s, CH_3), 2.82 (ddd, J = 4.0, 4.0, 13.0, 3-CH (equatorial)), 3.16 (ddd, J = 5.5, 9.3, 13.0, 3-CH (axial)), 4.16 (ddd, J = 4.0, 9.3, 12.0, 4-CH (axial)), 4.24 (ddd, J = 4.0, 5.5, 12.0, 4-CH (equatorial)), 7.37-7.96 (m, ArH). IR 1784 (C=O); MS, m/z 314 (M^+, not found), 150 (100); *Anal.* Calcd for $C_{12}H_{11}N_2O_4ClS$: C, 45.79, H, 3.52, N, 8.90. Found, C, 46.00, H, 3.71, N, 8.77.

(1R, 6R*)*-**1-Chloro-7-(4-chlorophenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.85 (s, CH_3), 2.78 (ddd, J =4.0, 5.0, 13.2, 3-CH (equatorial)), 3.11 (ddd, J = 5.9, 8.4, 13.2, 3-CH (axial), 3.93 (ddd, J = 4.0, 8.4, 12.0, 4-CH (axil)), 4.15 (ddd, J = 5.0, 5.0, 12.0, 4-CH (equatorial)),

7.33-7.58 (m, ArH); IR 1770 (C=O); MS, m/z (relative intensity) 307 (M^++4, 14), 305 (M^++2, 64), 303 (M^+, 100); *Anal.* Calcd for $C_{12}H_{11}NO_2Cl_2S$: C, 47.38, H, 3.64, N, 4.60. Found, C, 47.71, H, 3.64, N, 4.55.

(1R, 6R*)*-**1-chloro-6-methyl-7-(4-methylphenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.87(s, CH_3), 2.36 (s, $ArCH_3$), 2.81(ddd, J = 4.4, 5.3, 13.2, 3-CH (equatorial)), 3.08(ddd, J = 6.1, 8.1, 13.2, 3-CH (axial)), 3.95 (ddd, J = 4.4, 8.1, 11.9, 4-CH (axial)), 4.11(ddd, J = 5.3, 6.1, 11.9, 4-CH (equatorial)), 7.15-7.49 (m, ArH); IR 1768 (C=O); MS, m/z (relative intensity) 285 (M^++2, 0.44), 283 (M^+, 1.06), 150 (100); *Anal.* Calcd for $C_{13}H_{14}NO_2ClS$: C, 55.02, H, 4.97, N, 4.94. Found, C, 55.23, H, 5.11, N, 4.91.

(1R, 6R*)*-**1-chloro-6-methyl-7-(2,4,6-trimethylphenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 1.68 (s, CH_3), 2.25, 2.26 and 2.37 (3s, $ArCH_3$), 2.84 (ddd, J = 3.3, 6.1, 13.4, 3-CH (equatorial)) 3.01 (ddd, J = 5.8, 10.0, 13.4, 3-CH (axial)), 4.01(ddd, J = 3.3, 5.8, 11.5, 4-CH (axial)), 4.26 (ddd, J = 6.1, 10.0, 11.5, 4-CH (equatorial)), 6.89 (s, ArH); IR 1772 (C=O); MS, m/z (relative intensity) 311 (M^+ not found), 150 (100); *Anal.* Calcd for $C_{15}H_{18}NO_2ClS$: C, 57.78, H, 5.82, N, 4.49. Found, C, 57.79, H, 6.03, N, 4.41.

(1R, 6R*)*-**1-Chloro-6,7-diphenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ^{1}H NMR 2.99 (ddd, J = 4.8, 5.8, 13.2, 3-CH (equatorial)), 3.19(ddd, J = 6.7, 7.4, 13.2, 3-CH (axial)), 4.05 (ddd, J = 4.8, 7.4, 12.2, 4-CH (axial)), 4.32 (ddd, J = 5.8, 6.7, 12.2, 4-CH (equatorial)), 7.14-7.56(m, ArH). IR 1784 (C=O); MS, m/z (relative intensity) 333 (M^++2, 0.86), 331 (M^+, 2.25), 105 (100); *Anal.* Calcd for $C_{17}H_{14}NO_2ClS$: C, 61.53, H, 4.25, N, 4.22. Found, C, 61.20, H, 4.20, N, 4.13.

3-Chloro-5,6-dihydro-2-methyl-1,4-oxathiin (11a): ^{1}H NMR 1.99 (s, CH_3), 3.07-3.10 (m, SCH_2), 4.28-4.31 (m, OCH_2); MS, m/z (relative intensity) 152 (M^++2, 36.4), 150 (M^+, 100).

3-Chloro-5,6-dihydro-2-phenyl-1,4-oxathiin (11b): ^{1}H NMR 3.22-3.25 (m, SCH_2), 4.46-4.49 (m, OCH_2), 7.33-7.58 (m, ArH); MS, m/z (relative intensity) 214 (M^++2, 12.9), 212 (M^+, 34.7) 105 (100).

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REFERENCES AND NOTE

1. a. T. H. Fife, R. Bembi, and R. Natarajan, *J. Am. Chem. Soc.*, 1996, **118**, 12956. b. S. Winstein, L. Goodman, and R. Boschan, *J. Am. Chem. Soc.*, 1950, **72**, 2311.

2. H.-G. Hahn, K. -H. Chang, and W. S. Lee, *Heterocycles,* 1995, **41**, 921.

3. W. S. Lee, O. S. Park, J. K. Choi, and K. D. Nam, *J. Org. Chem.*, 1987, **52**, 5374.

4. B. V. Schmeling, M. Kulka, D. S. Thiara, and W. A. Harrison, U.S. Patent 3,249,499, **1966** (*Chem. Abstr.*, 1966, **65**, 7190g).

5. The X-Ray analysis was performed with the *p*-methoxy bicyclic β-lactam (see entry 3 in Table 1). The data was collected on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-Ray tube and a graphite crystal monochromator. Orthorhombic space group $Pna2_1$ (No. 62) with a = 14.433(4) Å, b = 13.175(3) Å, c = 7.218(2) Å, V = 1372.5(6) Å^3, Z = 4, d_{calc} = 1.451 gcm^{-3}, μ = 0.433mm^{-1}. A total of 979 independent absorption-corrected reflections were collected. The structure was solved using SHELXS86 and SHELXL93 programs. The resulting structural parameters were refined to convergence of R_1 = 0.0428 for 979 independent reflections with $I > 2\sigma$ (I) using full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms.

6. Isolated yields after flash chromatography.

7. In the GC/MS spectrum of the whole mixture, M^+ of the corresponding phenyl isocyanate (**10**) was found clearly.

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