

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

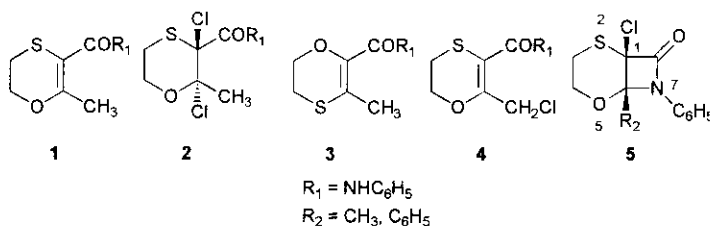
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Abstract - Transformation of dichloro-1,4-oxathiane anilides (**2**) to bicyclic β -lactam (**5**) is described. In the presence of sodium hydride, an intramolecular nucleophilic substitution of nitrogen to anomeric carbon of **2** gave (*1R**, *6R**)-1-chloro-6-methyl-7-phenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]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-carboxamide (**4**) under the neutral conditions, or 2,3-dihydroxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxamide (**9**) in aqueous solution, or bicyclic β -lactam (**5**) in the presence of sodium hydride were proposed.

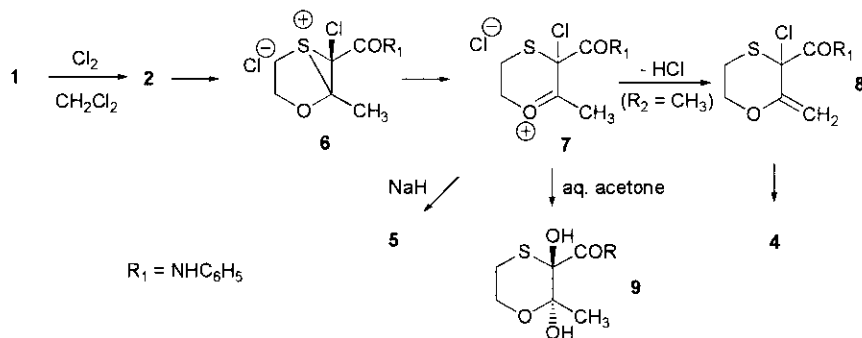
INTRODUCTION

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 compared with the previous report.^{2,3}



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 intermolecular 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** ($R_2 = \text{CH}_3$) 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

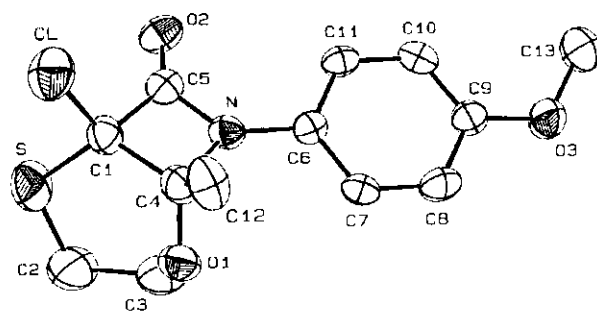
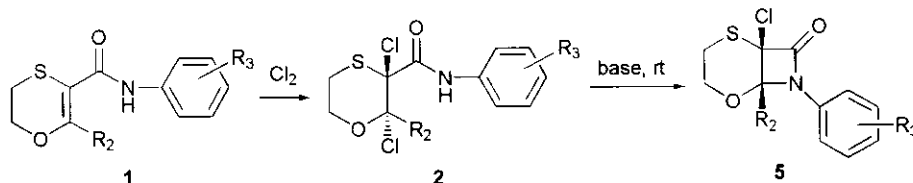


Figure 1. ORTEP plots of *p*-methoxy analogue of **5** with heteroatoms labeled.

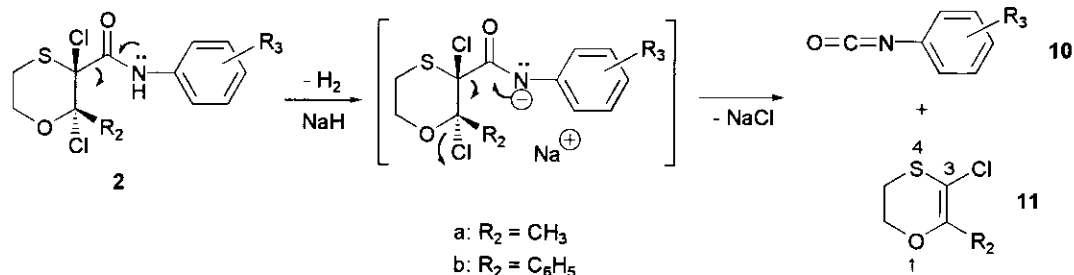
Since **2** gradually converts to chloromethyl compound (**4**) at room temperature it is conceivable that prompt treatment of **2** with sodium hydride immediately after chlorination is critical for high yields of **5**. Similar results were obtained from the substituted anilides and phenyl derivative.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



| 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 | <i>p</i> -OCH ₃ | NaH/THF | 31 | 118-119 | 11a |
| 4 | CH ₃ | <i>o</i> -OCH ₃ | NaH/THF | 33 | 97-98 | 11a |
| 5 | CH ₃ | <i>o</i> -NO ₂ | NaH/THF | 48 | 109-110 | 11a |
| 6 | CH ₃ | <i>p</i> -Cl | NaH/THF | 25 | 113-114 | 11a |
| 7 | CH ₃ | <i>p</i> -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 ₆ H ₅ | H | NaH/THF | 11 | 137-138 | 11b C ₆ H ₅ COCH ₂ CONHC ₆ H ₅ |
| 10 | C ₆ H ₅ | H | (C ₂ H ₅) ₃ N/CHCl ₃ | 20 | - | 1 |
| 11 | C ₆ H 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 ^1H 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 intermolecular 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 dichloro-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 ^1H 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 (MgSO₄). Evaporation of the solvent gave a yellow solid (0.42 g, 78%), which was chromatographed on silica gel (Kieselgel GF254, 230-400 mesh) using ethyl acetate:n-hexane = 1:4 as eluent to give **5** as a white solid.

(1*R, 6*R**)-1-Chloro-6-methyl-7-phenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** Evaporation of the solvent gave a yellow solid (0.42 g, 78%), which was chromatographed on silica gel (Kieselgel GF254, 230-400 mesh) using ethyl acetate:n-hexane = 1:4 as eluent gave **5** as a white solid. ¹H NMR 1.91 (s, CH₃), 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 C₁₂H₁₂NO₂ClS: C, 53.43, H, 4.48, N, 5.19. Found, C, 53.72, H, 4.50, N, 5.04.

(1*R, 6*R**)-1-Chloro-7-(4-methoxyphenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ¹H NMR 1.87 (s, CH₃), 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, OCH₃), 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 C₁₃H₁₄NO₃ClS: C, 52.09, H, 4.71, N, 4.67. Found, C, 52.21, H, 4.81, N, 4.67.

(1*R, 6*R**)-1-Chloro-7-(2-methoxyphenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ¹H NMR 1.77 (s, CH₃), 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, OCH₃), 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 C₁₃H₁₄NO₃ClS: C, 52.09, H, 4.71, N, 4.67. Found, C, 52.26, H, 4.79, N, 4.60.

(1*R, 6*R**)-1-Chloro-6-methyl-7-(2-nitrophenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ¹H NMR 1.88 (s, CH₃), 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 C₁₂H₁₁N₂O₄ClS: C, 45.79, H, 3.52, N, 8.90. Found, C, 46.00, H, 3.71, N, 8.77.

(1*R, 6*R**)-1-Chloro-7-(4-chlorophenyl)-6-methyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one** ¹H NMR 1.85 (s, CH₃), 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 (axial)), 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.

(1*R, 6*R**)-1-chloro-6-methyl-7-(4-methylphenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one**

1H NMR 1.87(s, CH_3), 2.36 (s, Ar CH_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.

(1*R, 6*R**)-1-chloro-6-methyl-7-(2,4,6-trimethylphenyl)-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one**

1H NMR 1.68 (s, CH_3), 2.25, 2.26 and 2.37 (3s, Ar CH_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.

(1*R, 6*R**)-1-Chloro-6,7-diphenyl-5-oxa-2-thia-7-azabicyclo[4,2,0]octan-8-one**

1H 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): 1H 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): 1H 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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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, $V = 1372.5(6)$ Å³, $Z = 4$, $d_{\text{calc}} = 1.451$ gcm⁻³, $\mu = 0.433$ mm⁻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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