$TiCl_4$ PROMOTED RING EXPANSION REACTIONS OF 5-HYDROXYMETHYL-2-ISOXAZOLINE-2-OXIDE METHANESULFONATES[1]

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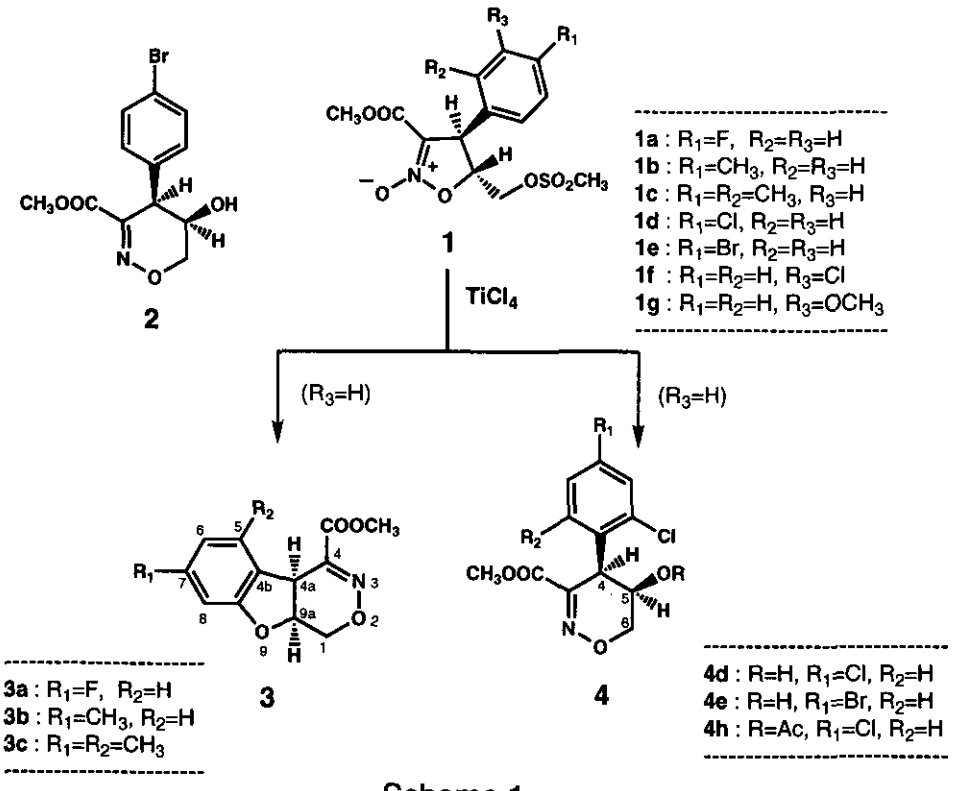
Abstract - 5-Hydroxymethyl-2-isoxazoline-2-oxide methanesulfonates(**1**) possessing a substituted phenyl ring were treated with $TiCl_4$ to afford either benzofuro[3,2-*d*]-1,2-oxazines(**3**) or 4-*o*-chlorophenyl-5,6-dihydro-4*H*-1,2-oxazines(**4**), depending on the nature of the substituents on the phenyl ring of **1**. The reaction mechanism of the formation of **3** and **4** is proposed, including 3*H*-indole-1-oxide zwitterion(**B**) as a key intermediate.

5,6-Dihydro-4*H*-1,2-oxazines are heterocycles of considerable synthetic potential.[2] They are usually prepared by Diels-Alder reaction of olefins and nitrosoalkenes generated from α-halo oximes.[3] However, only relatively few 4-substituted 5,6-dihydro-4*H*-1,2-oxazines are synthesized by this route because the appropriate α-halo oximes are not readily accessible. In the preceding paper, we showed that the reaction of 5-hydroxymethyl-2-isoxazoline-2-oxide methanesulfonates(**1**) with $TiBr_4$ undergoes a new type of ring expansion reaction and can afford convenient access to 4-substituted 5,6-dihydro-4*H*-1,2-oxazines(**2**).[4] In this paper we wish to report a novel formation of heterocyclic fused 1,2-oxazines, *i.e.*, 4a,9a-dihydro-1*H*-benzofuro[3,2-*d*]-1,2-oxazines(**3**) and monocyclic 4-*o*-chlorophenyl-5,6-dihydro-1,2-oxazines(**4**) through the reaction of **1** with $TiCl_4$. When compounds(**1a-g**)[4] were allowed to

react with four-fold excess of $TiCl_4$ in dichloromethane at 40℃, the expected 5,6-dihydro- 4*H*-1,2-oxazines(**2**) were not isolated in these cases, but benzofuro[3,2-*d*]-1,2-oxazines(**3a-c**) were obtained from **1a**,**1b**, and **1c** in 50-74% yields and 4-*o*-chlorophenyl-5,6-dihydro-4*H*-1,2-oxazines(**4d**,**e**) were isolated(60 % and 55 %) as an only product from **1d** and **1e**, respectively. *m*-Substituted phenyl-2-isoxazoline-2-oxides(**1f**,**g**) did not undergo these conversions but only starting materials were recovered probably because *meta* substituent inactivates the *ipso* carbon of the phenyl ring, so that the O atom on the isoxazoline ring becomes more acidic to prevent the Lewis acid from the initial electrophilic attacking to the O atom. (Scheme 1 and Table 1)

Structural determination of these new products (**3** and **4**) was carried out by spectroscopic methods and X-ray analyses. Thus, in the ^{1}H-nmr spectra of **3 a**, **3 b** and **4**, three aromatic



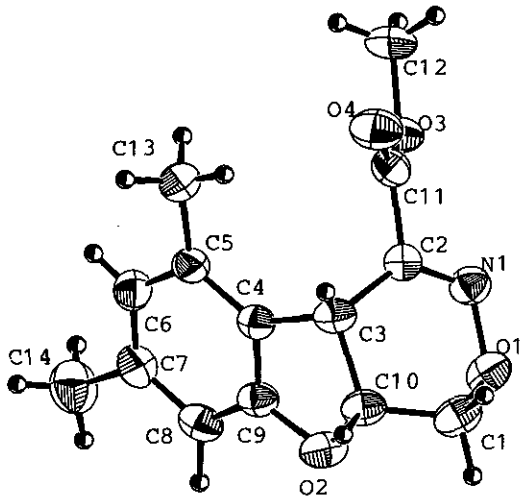
Scheme 1

Table I Physical Properties of Compounds(3 and 4)

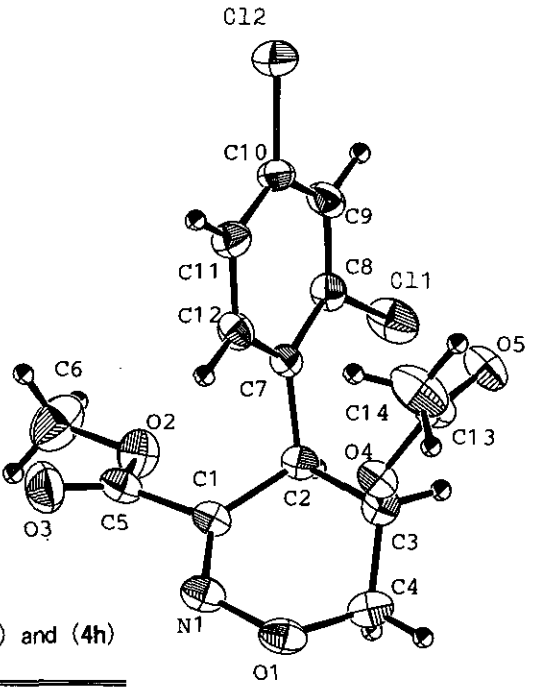
Product	R_1	R_2	Yield(%)	mp(℃)
3a	F	H	74	154–157
3b	CH_3	H	50	155–157
3c	CH_3	CH_3	50	124–125
4d	Cl	H	60	140–142
4e	Br	H	55	169–171

protons appeared at 6.54-7.62 ppm and one ring proton (4.51-4.74 ppm) was coupled with another vicinal ring proton (4.35-5.27 ppm) which was also coupled with methylene protons. OH absorption maxima were seen at 3400 cm^{-1} in the ir spectra of **4 d** and **4 e**, whereas no absorption maxima at the range of 3300-3450 cm^{-1} were seen in the ir spectra of **3a**, **3b**, and **3c**. These spectroscopic results indicate that both **3** and **4** may have 1,2-oxazine ring but apparently their structures are not identical with **2** of which spectrum was described in the preceding paper.[4] To confirm the structures of **3** and **4**, single crystal X-ray analyses of **3c** and **4h**, which were obtained by acetylation of **4d** (90% yield, mp 160-164℃), were carried out. Perspective drawings of the molecule of **3c** and **4h** are illustrated in Scheme 2. The compound(**3c**) has a tricyclic fused benzofuro[3,2-*d*]-1,2-oxazine ring. On the other hand, **4h** has a monocyclic 5,6-dihydro-4*H*-1,2-oxazine ring with a newly added chloro substituent at the site *meta* to the substituent R_1 on the phenyl ring as clearly seen in the ORTEP diagram of **4h**.

A reaction mechanism of the formation of **3** and **4** is proposed as follows : Initially, an electrophilic attack of Lewis acid to **1** causes the cleavage of N-O bond to give intermediate(A). Subsequent electrophilic attack of nitrogen atom of the nitrosonium species in A at the *ortho* position of the phenyl ring in **A** causes formation of intermediate(**B**).[5] Then, nucleophilic attack of oxygen lone pair[6] at the site *meta* to the substituent R_1 in **B** causes formation of furan ring and subsequent cleavage of the C-N bond to give intermediate(**C**) which finally cyclyzes to fused 1,2-oxazine(**3**) (route a). On the other hand, when nucleophilic attack of negative chlorine ion of $TiCl_4$ binding to the hydroxy oxygen[7] occurs at the site *meta* to the substituent R_1



3c



4h

Scheme 2

Perspective Drawings of **3c** and **4h**

Table II. Crystallographic Data for Compounds (**3c**) and (**4h**)

	3c	**4h**
Formula	$C_{14}H_{15}NO_4$	$C_{14}H_{13}NO_5Cl_2$
F_w	261.28	346.17
Crystal dimensions (mm)	0.4x0.1x0.8	0.2x0.3x0.2
Space group	$P2_1/c$	$P2_1/c$
Lattice parameters		
a/Å	8.691 (4)	12.6081 (8)
b/Å	17.628 (6)	9.1342 (5)
c/Å	9.359 (4)	14.1361 (4)
β/deg	114.78 (3)	108.061 (4)
V/Å^3	1302 (2)	1547.8 (2)
Z	4	4
Dc/gcm^{-3}	1.333	1.485
μ(Cu $K\alpha$)/cm^{-1}	7.76	40.51
$2\theta_{max}$/deg	140.4	139.9
Scan mode	ω-2θ	ω-2θ
No. of Observation ($Fo>3.00\sigma(Fo)$)	1491	2094
No. of Variables	184	199
R	0.066	0.062
R_w	0.064	0.063

in B, subsequent cleavage of C-N bond and removal of $TiCl_3$ afford intermediate(**D**) which cyclyzes to monocyclic 4-*o*-chlorophenyl-1,2-oxazine(**4**) (route b) (Scheme 3).

Of special interest in this scheme is the substituent effect on the direction of the intramolecular nucleophilic attack, *i.e.*, on the preference of route a or b. As the electron density at the site *meta* to the substituent R_1 of the phenyl ring in **B** should be lower than that of other sites of the phenyl ring by the effect of *o,p*-directing substituents R_1 and/or R_2, chlorine anion and oxygen lone pair compete in attacking at the site *meta* of the phenyl ring. The experimental results

Table III Positional Parameters and Their Estimated Standard Deviations for **3c**

Atom	*x*	*y*	*z*	B_{eq}
O1	1.0420(4)	0.3124(2)	0.04092(4)	5.5(2)
O2	1.2411(4)	0.1788(2)	0.5328(3)	5.4(1)
O3	0.6474(4)	0.2042(2)	0.0641(3)	5.3(2)
O4	0.5644(4)	0.1711(2)	0.2506(4)	6.3(2)
N1	0.8849(5)	0.2841(2)	0.2978(4)	4.7(2)
C1	1.0916(6)	0.2853(3)	0.5667(5)	5.4(2)
C2	0.8414(5)	0.2187(3)	0.3271(5)	3.8(2)
C3	0.9434(5)	0.1636(3)	0.4551(5)	4.0(2)
C4	1.0159(5)	0.1018(2)	0.3889(5)	3.7(2)
C5	0.9449(5)	0.0389(3)	0.2951(5)	4.1(2)
C6	1.0484(7)	−0.0026(3)	0.2454(6)	5.0(2)
C7	1.2161(6)	0.0159(3)	0.2837(6)	4.9(2)
C8	1.2873(6)	0.0774(3)	0.3822(6)	4.7(2)
C9	1.1848(5)	0.1176(3)	0.4318(5)	4.1(2)
C10	1.1046(6)	0.2014(3)	0.5734(5)	4.7(2)
C11	0.6683(5)	0.1954(3)	0.2097(5)	4.2(2)
C12	0.4829(6)	0.1851(3)	−0.0563(6)	6.5(3)
C13	0.7660(6)	0.0141(3)	0.2517(6)	5.8(2)
C14	1.3195(7)	−0.0303(3)	0.2214(7)	7.4(3)

Table IV Positional Parameters and Their Estimated Standard Deviations for **4h**

Atom	*x*	*y*	*z*	B_{eq}
Cl1	0.9458(1)	0.1556(2)	0.90131(9)	5.21(6)
Cl2	1.2553(1)	0.4175(2)	0.7750(1)	5.65(7)
O1	0.6617(3)	-0.0316(4)	0.5127(2)	4.2(1)
O2	0.9640(3)	-0.2144(4)	0.7413(2)	4.4(2)
O3	0.9695(3)	-0.2472(4)	0.5858(3)	5.6(2)
O4	0.7570(3)	0.2381(3)	0.5667(2)	3.2(1)
O5	0.8076(3)	0.4275(4)	0.6724(3)	5.0(2)
N1	0.7588(3)	-0.1164(4)	0.5399(3)	3.7(2)
C1	0.8361(4)	-0.0828(5)	0.6185(3)	2.9(2)
C2	0.8414(4)	0.0456(5)	0.6871(3)	2.8(2)
C3	0.7402(4)	0.1440(5)	0.6432(3)	3.2(2)
C4	0.6419(4)	0.0511(6)	0.5926(3)	3.9(2)
C5	0.9304(4)	-0.1902(5)	0.6440(4)	3.8(2)
C6	1.0508(5)	-0.3229(7)	0.7787(5)	6.8(3)
C7	0.9506(4)	0.1274(5)	0.7113(3)	2.7(2)
C8	1.0020(4)	0.1863(5)	0.8044(3)	3.1(2)
C9	1.0951(4)	0.2756(5)	0.8254(3)	3.6(2)
C10	1.1404(4)	0.3016(5)	0.7498(4)	3.5(2)
C11	1.0953(4)	0.2418(6)	0.6570(4)	3.7(2)
C12	1.0020(4)	0.1554(5)	0.6391(3)	3.3(2)
C13	0.7902(4)	0.3787(6)	0.5905(4)	3.8(2)
C14	0.8050(6)	0.4555(6)	0.5028(4)	6.0(3)

shows that the presence of electron-donating groups such as methyl groups at the *para* and/or *ortho* position of phenyl ring of **1** facilitates nucleophilic attack by the oxygen lone pair resulting the formation of **3** (route a), whereas electron-withdrawing groups such as chloro and bromo

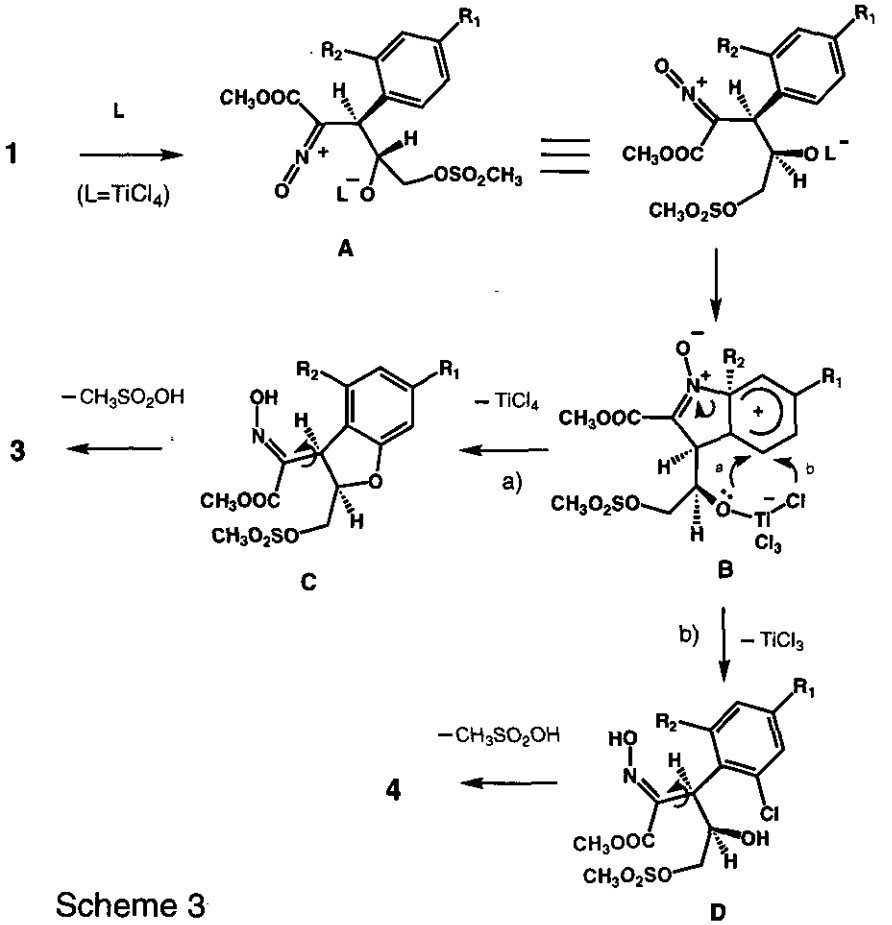
Table V Bond Lengths(Å) and Torsional Angles(°) for the Molecule(**3c**) with Their Estimated Standard Deviations in the Parentheses

A-X-Y-B	Bond length X-Y	Torsional angle along X-Y
O1-N1-C2-C3	1.280(5)	- 7.4(6)
O1-C1-C10-O2	1.482(6)	65.4(4)
O1-C1-C10-C3	1.482(6)	- 52.7(5)
O2-C10-C3-C4	1.528(6)	17.8(4)
N1-O1-C1-C10	1.433(5)	58.5(5)
C1-O1-N1-C2	1.417(4)	- 28.1(5)
C1-C10-C3-C2	1.528(6)	20.0(5)
C4-C3-C2-C11	1.507(6)	75.9(5)

Table VI Bond Lengths(Å) and Torsional Angles(°) for the Molecule(**4h**) with Their Estimated Standard Deviations in the Parentheses

A-X-Y-B	Bond length X-Y	Torsional angle along X-Y
O1-N1-C1-C2	1.267(5)	- 3.6(7)
O1-C4-C3-C2	1.489(6)	- 60.8(5)
O4-C3-C2-C7	1.526(6)	46.0(5)
N1-O1-C4-C3	1.442(6)	54.4(5)
N1-C1-C2-C3	1.511(6)	- 5.0(6)
C1-N1-O1-C4	1.398(5)	- 21.3(6)
C1-C2-C7-C8	1.510(6)	- 142.9(4)

groups except for fluoro group lead to form **4** as a result of nucleophilic attack by the chlorine anion of $TiCl_4$ binding to hydroxy oxygen in **B** (route b). These results may be elucidated in the light of HSAB principle that the oxygen lone pair, which is a soft base, should prefer direct bonding to a soft acceptor, and the hard chlorine anion should bind to a hard acceptor. As the site *meta* to the substituent R_1 is considerd to be a borderline acid, the softness (or hardness) of the attacking site may be directly influenced by the substituents, thus, it is concluded that the electron-donating substituents make the attacking site soft to give C-O bond, on the other hand,



Scheme 3

the electron-withdrawing groups make the attacking site hard to give C-Cl bond. This interpretation is consisted with the experimental results except for the case of R_1=F. Further detailed study on this mechanistic feature is now in progress.

EXPERIMENTAL

Melting points were measured with a Yamato MP-1 apparatus and are uncorrected. Spectral data were recorded on the following instruments : Jasco IRA-1(ir), JMS D-100(ms), and Varian EM-390(^{1}H-nmr). Tetramethylsilane was used as an internal standard for nmr measurement in chloroform-d. Column chromatography was done on a silica gel(Kanto Kagaku Co. ; up to 100 mesh) column.

Formation of 7-Substituted 4-Methoxycarbonyl-4a,9a-dihydro-1*H*-benzofuro-[3,2-*d*]-1,2-oxazine (3) and 4-*o*-Chlorophenyl-5,6-dihydro-4*H*-1,2-oxazines (4)

——— General Procedure

To a stirred solution of **1** (0.82 mmol) in 20 ml of CH_2Cl_2 was added $TiCl_4$ (0.35 ml, 3.24 mol) with ice-cooling, and stirring was continued at 40℃ overnight. The reaction mixture was quenched with 5% aqueous $NaHCO_3$ and the mixture was extracted with $CHCl_3$ followed by column chromatography of the extract on silica gel with hexane-ethyl acetate (1:1) as an eluent to afford **3**.

7-Fluoro-4-methoxycarbonyl-4a,9a-dihydrp-1*H*-benzofuro[3,2-*d*]-1,2-oxazine (3a): Yield 74 %. mp 102-104℃(ethyl acetate-hexane). Irv (KBr)cm^{-1}: 1730(ester), 1610(C=N). Ms(m/z): 251(M^+). ^{1}H Nmr($CDCl_3$, δ, ppm): 3.89(dd, $J_{1,1'}$=13.0 Hz, $J_{1,9a}$=4.0 Hz, 1H, H-1), 3.94(s, 3H, $COOCH_3$), 4.36(m, 1H, H-1'), 4.51(d, $J_{4a,9a}$=9.0 Hz, 1H, H-4a), 5.27(m, 1H, H-9a), 6.54(d, $J_{5,6}$=8.0 Hz, 1H, H-5), 6.65(s, 1H, H-8), 6.67(d, $J_{5,6}$=8,0 Hz, 1H, H-6). *Anal.* Calcd for $C_{12}H_{10}NO_4F$: C, 57.37; H, 4.01; N, 5.58. Found : C, 57.44; H, 4.22; N, 5.36.

4-Methoxycarbonyl-7-methyl-4a,9a-dihydro-1*H*-benzofuro[3,2-*d*]-1,2-

oxazine (3b): Yield 66 %. mp 153.0-157.0℃(ethyl acetate-hexane). Irv(KBr)cm^{-1}: 1720(ester), 1590(C=N). Ms(m/z): 247(M^+). ^{1}H Nmr($CDCl_3$, δ, ppm): 2.29(s, 3H, CH_3), 3.81(s, 3H, $COOCH_3$), 3.89(dd, $J_{1,1'}$=12.0 Hz, $J_{1,9a}$=4.0 Hz, 1H, H-1), 4.37(m, 1H, H-1'), 4.51(d, $J_{4a,9a}$=9.0 Hz, H-1, H-4a), 5.27(m, 1H, H-9a), 6.65(s, 1H, H-8), 6.67(d, $J_{5,6}$=7.5 Hz, 1H, H-6), 7.20(d, $J_{5,6}$=7.5 Hz, 1H, H-5). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found : C, 63.03; H, 5.35; N, 5.62.

5,7-Dimethyl-4-methoxycarbonyl-4a,9a-dihydro-1*H*-benzofuro[3,2-*d*]-1,2-oxazine (3c) : Yield 67 %. mp 124-125℃(ethyl acetate-hexane). Irv(KBr)cm^{-1}: 1730(ester), 1590(C=N). Ms(m/z) : 261(M^+). ^{1}H Nmr($CDCl_3$, δ, ppm): 2.14(s, 3H, CH_3), 2.25(s, 3H, CH_3), 3.69(dd, $J_{1,1'}$=13.0 Hz, $J_{1,9a}$=2.0 Hz, dd, 1H, H-1), 3.93(s, 3H, $COOCH_3$), 4.43(m, 1H, H-1'), 4.74(d, $J_{4a,9a}$=9.0 Hz, 1H, H-4a), 5.22(m, 1H, H-9a), 6.42(s, 1H, H-8), 6.49(s, 1H, H-6). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.35. Found: C, 64.27; H, 5.85; N, 5.04.

4-(2,4-Dichlorophenyl)-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine (4d) : Yield 60 %. mp 140-142℃(ethyl acetate-hexane). Irv(KBr)cm^{-1}: 3375(OH), 1740(ester), 1590(C=N). Ms(m/z): 303(M^+). ^{1}H Nmr($CDCl_3$, δ, ppm): 3.75(s, 3H, $COOCH_3$), 4.05(dd, $J_{6,6'}$=11.5 Hz, $J_{5,6}$=6.5 Hz, 1H, H-6), 4.16(dd, $J_{6,6'}$=11.5 Hz, $J_{5,6}$=1.5 Hz, 1H, H-6'), 4.35(m, 1H, H-5), 4.71(d, $J_{4,5}$=6.0 Hz, 1H, H-4), 6.93(d, $J_{5'',6''}$=8.0 Hz, 1H, phenyl H-6''), 7.23(dd, $J_{5'',6''}$=8.0 Hz, $J_{3'',5''}$=2.0 Hz, 1H, phenyl H-5''), 7.48(d, $J_{3'',5''}$=2.0 Hz, 1H, phenyl H-3'') . *Anal.* Calcd for $C_{12}H_{11}NO_4Cl_2 \cdot H_2O$: C, 44.86; H, 4.05; N, 4.36; Cl, 21.80. Found: C, 44.62; H, 4.32; N, 4.31; Cl, 21.71.

4-(4-Bromo-2-chlorophenyl)-5-hydroxy-3-methoxycarbonyl-5,6-dihydro-4*H*-1,2-oxazine (4e) : Yield: 76 %. mp 169-171℃(ethyl acetate-hexane). Irv(KBr)cm^{-1}:3400 (OH), 1730(ester), 1590(C=N). Ms(m/z): 346(M^+). ^{1}H Nmr($CDCl_3$, δ, ppm): 3.73(s, 3H, $COOCH_3$), 4.05(dd, $J_{6,6'}$=11.5 Hz, $J_{5,6}$=6.5 Hz, 1H, H-6), 4.17(dd, $J_{6,6'}$=6.5 Hz, $J_{5,6'}$=1.5 Hz, 1H, H-6'), 4.35(m, 1H, H-5), 4.71(d, $J_{4,5}$=6.0 Hz, 1H, H-4), 6.87(d, $J_{5'',6''}$=8.2 Hz, 1H, phenyl H-6''), 7.38(dd, $J_{5'',6''}$=8.2 Hz, $J_{3'',5''}$=2.0 Hz, 1H, phenyl H-5''), 7.62(d, $J_{3'',5''}$=2.0 Hz, 1H, phenyl H-3''). *Anal.* Calcd for $C_{12}H_{11}NO_4ClBr$: C, 41.35; H, 3.18; N, 4.02. Found: C, 41.69; H, 3.22; N, 4.05.

5-Acetoxy-4-(2,4-dichlorophenyl)-3-methoxycarbonyl-5,6-dihydro-4*H*-1, 2-oxazine (4h): To a mixture of 103 mg (0.34 mmol) of **4d** in 2.0 ml of pyridine was added 2.0 ml (21.3 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 3.5 h, and concentrated to dryness *in vacuo* to give 117.2 mg of crude product. The crude product was chromatographed on silica gel(hexane-ethyl acetate1:1) to afford 105.0 mg of **4h**. Yield 90 %. mp 160-164.0℃(ethyl acetate-hexane). Irv(KBr)cm^{-1}: 1750(acetyl), 1730(ester), 1590(C=N). Ms(m/z): 345(M^+). ^{1}H-Nmr($CDCl_3$, δ, ppm): 1.90(s, 3H, $COCH_3$), 3.75(s, 3H, $COOCH_3$), 4.00(dd, $J_{6,6'}$=11.5 Hz, $J_{5,6}$=6.0 Hz, 1H, H-6), 4.21(dd, $J_{6,6'}$=11.5 Hz, $J_{5,6'}$=1.5 Hz, 1H, H-6'), 4.79(d, $J_{4,5}$=6.0 Hz, 1H, H-4), 5.48(m, 1H, H-5), 6.9-7.5(m, 3H, phenyl H). *Anal.* Calcd for $C_{14}H_{13}NO_5Cl_2$: C, 48.57; H, 3.78; N, 4.05. Found: C, 48.50; H, 3.78; N, 4.19.

X-Ray Analyses of 3c and 4h

X-Ray structure analyses of **3c** and **4h** were carried out on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite monochromated Cu Kα(λ=1.54179Å) radiation at 23℃. The crystal data are summarized in Table II. The structures were solved by the direct method using the program MITHRIL (C. J. Gilmore : MITHRIL, an integrated direct method computer program, *J. Appl. Cryst.*, 1984, **17**, 42, Univ. of Glasgow, Scotland). The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located from a difference Fourier synthesis, and refined only the temperature factors isotropically. The positional parameters are listed in Tables III and IV. The torsional angles along the bonds connecting each group are listed in Tables V and VI.

ACKNOWLEDGMENT

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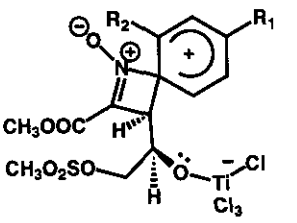
5. It can not be excluded that an unstable intermediate (**E**) exists as a key intermediate instead of **B** in this scheme. As the *o,p*-directing substituents (R_1 and R_2) activate the *ipso* position of the phenyl ring, it is reasonable that the electrophilic attack occures at the site *ipso* of the phenyl ring to lead intermediate (**E**).



E

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