FORMATION OF TRISUBSTITUTED γ-BUTYROLACTONES BY NOVEL RING TRANSFORMATION OF 2-ISOXAZOLINE-2-OXIDES[1]

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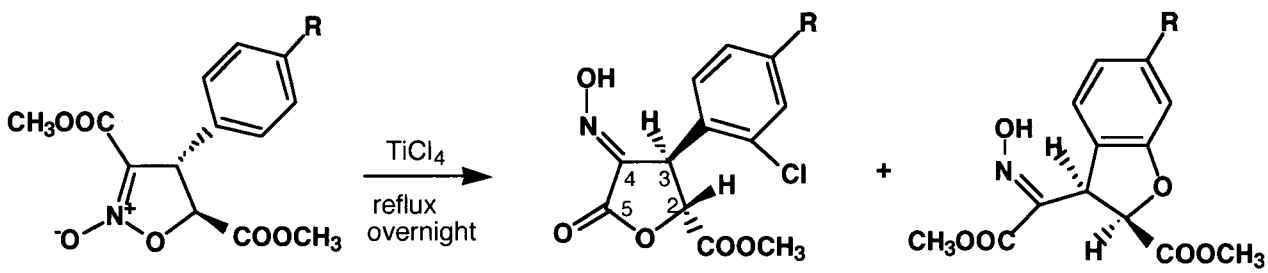
Abstract - 2-Isoxazoline-2-oxides (**1**) reacted with excess $TiCl_4$ to yield trisubstituted γ-butyrolactones (**2**). The results of the structural determination by single crystal X-Ray analysis and a possible mechanism for this reaction are reported.

2-Isoxazoline 2-oxides would be expected to give rise to unique transformations, since they share the structural characteristics of both an isoxazoline ring and a cyclic nitronic ester.[2,3] However, very few examples of synthetically useful reactions of 2-isoxazoline 2-oxides have been reported. We have previously reported unique ring transformations from 2-isoxazoline-2-oxides (**1**) to fused ring systems such as furo[3,4-*d*]isoxazoles,[4] indolo[2,3-*b*]-1-pyrroline-1-oxides,[5] 4*H*-1,2-benzoxazines,[6] benzofuro[3,2-*d*]-1,2-oxazines,[7] benzofuro[2,3-*c*]tetrahydropyrans,[8] and monocyclic 1,2-oxazines[9] by the action of Lewis acid. These ring transformations are characteristic to 2-isoxazoline 2-oxides as a cyclic nitronic ester and have been proved to be a useful synthetic method for the heterocycles described above which are not readily accessible by other procedures. In the continuing study, we found a simple ring transformation from **1** to γ-butyrolactones. The γ-butyrolactone skeleton is important, since it comprises many natural products including sesquiterpenes and metabolites from the shikimic acid pathway, some of which show interesting biological activities.[10]

In this study, 4-(4-chlorophenyl)-3,5-bis(methoxycaronyl)-2-isoxazoline-2-oxide (**1a**) was treated with 4 ~ 5 molar equivalents titanium tetrachloride at 40 ℃[11] for 4 h to give methyl 3-(2,4-dichlorophenyl)-4-hydroxyimino-5-oxotetrahydrofuran-2-carboxylate (**2a**) in 33% yield along with the 2,3-dihydrobenzofuran



1
a : R = Cl
b : R = Br

2
a : R = Cl
b : R = Br

3
a : R = Cl
b : R = Br

Scheme 1

oxime previously reported[4e] as another ring transformed product (**3a**, 14% yield, Scheme 1). This procedure was also applicable to 4-bromophenyl analog (**1b**) to afford **2b** in 38% yield. Effects of molar ratio of $TiCl_4$ are listed in Table 1. The structure of **2b** was unambiguously determined by single crystal X-Ray analysis. A perspective drawing of the molecule (**2b**) is illustrated in Figure 1. The molecule (**2b**) consists of a 2-tetrahydrofuranone ring with a methoxycarbonyl group at C(2), 4-bromo-2-chlorophe-nyl group at C(3) resulted from the chlorination[7] of 4-bromophenyl group of **1** by titanium tetrachloride, and an oxime group at C(4) which is *anti* to the ring carbonyl carbon (C(5)). From the configuration of the oxime group, the molecule has the *E*-configuration. The two substituents at C(2) and C(3) exist in a stable *trans* relationship.

Formation of **2** can be postulated to occur *via* opening of the isoxazoline ring by an electrophilic attack of $TiCl_4$ to give the nitrosonium ion intermediate (**A**).[12] The subsequent formation of the 3*H*-indole 1-oxide intermediate (**B**)[7] results from electrophilic attack of the nitrogen atom of the nitrosonium species in **A** at the *ortho* position on the phenyl ring in **1**. Then, nucleophilic attack of the negative chlorine ion of $TiCl_4$ binding to the hydroxy oxygen occurs at the site *meta* to the substituent R in **B**. Similar chlorination of aromatic ring was previously observed for the synthesis of benzofuro[3,2-*d*]-1,2-oxazines.[7] Subsequent cleavage of C-N bond and removal of $TiCl_3OH$ afford intermediate (**C**) which condenses to give the lactone (**2**). On the other hand, competitive nucleophilic substitution of anionic oxygen of the intermediate (**A**) forms byproduct (**3**) by way of an another intermediate (**D**) (Scheme 2). Further studies on the ring transformation including an application to the synthesis of some terpene compounds are now in progress.

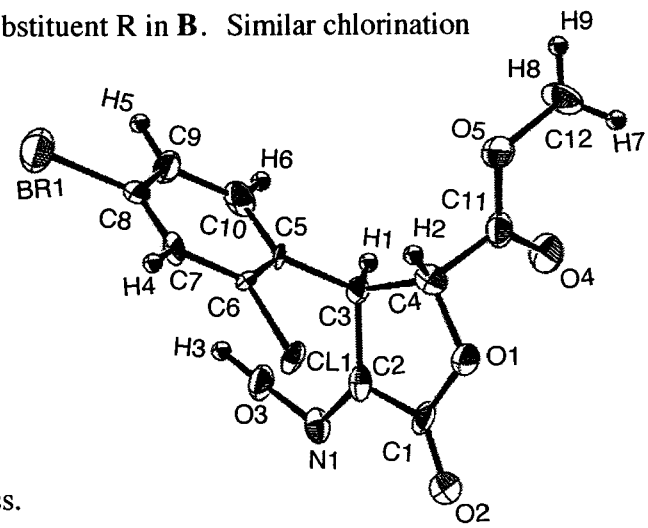
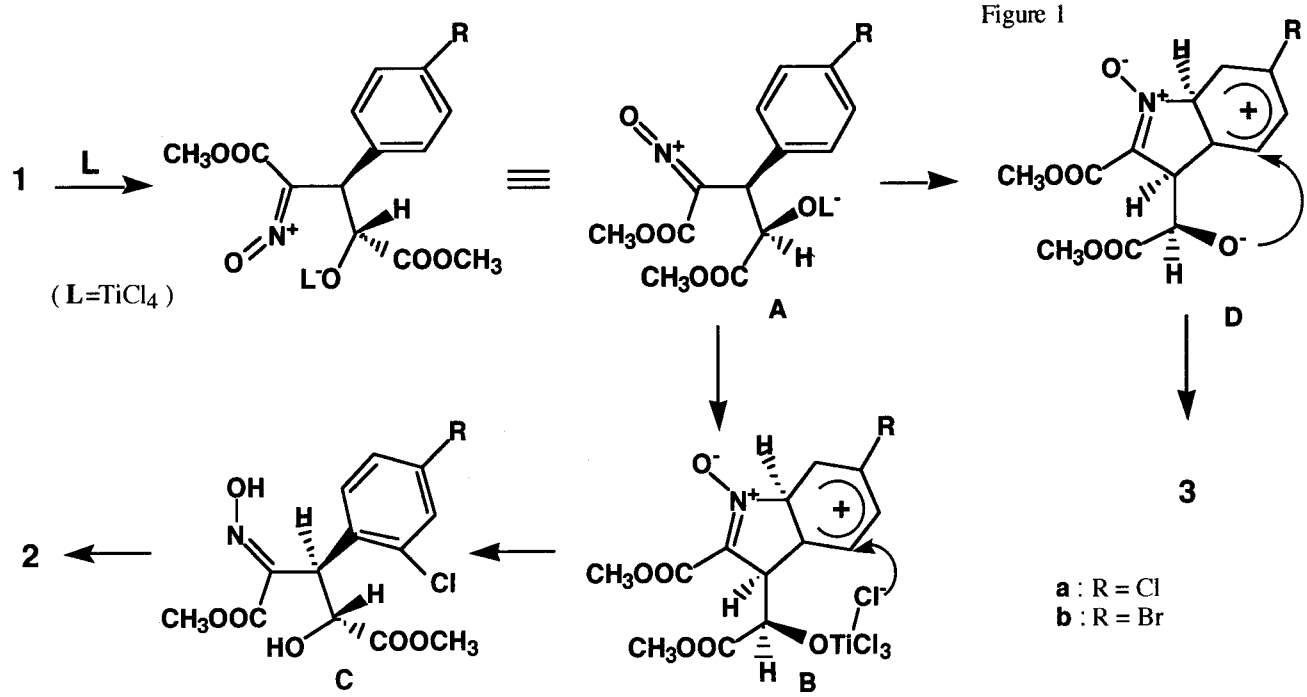


Figure 1



Scheme 2

Table 1 Effects of molar ratio of $TiCl_4$

molar ratio **1b** : $TiCl_4$	Yield(%) of **2b**
1 : 2	8
1 : 4	28
1 : 5	38
1 : 6	38

EXPERIMENTAL

Melting points were measured with a Yanaco MP apparatus and are uncorrected. Spectral data were recorded on the following instruments ; Jasco IR-810 (ir), JMS DX-300 (ms) and Varin XL-400 and VXR-300 (^{1}H-nmr). Column chromatography was carried out on silica gel (Kanto Kagaku Co.; up to 100 mesh) column.

Methyl 3-(2,4-Dichlorophenyl)-4-hydroxyimino-5-oxotetrahydrofuran-2-carboxylate (2a): Titanium tetrachloride (0.54 mL, 4.80 mmol) was added to a solution of 2-isoxazoline-2-oxide (**1a** : R=Cl) (300 mg, 0.96 mmol) in dichloromethane (10 mL) at 0 °C and the mixture was stirred at 40 °C for 4 h. After the reaction mixture was neutralized with 10% aqueous sodium carbonate, the resulting suspension was extracted with chloroform (3 x 30 mL). The organic layer was collected, dried (Na_2SO_4) and evaporated to give a residue, which was then purified by column chromatography on silica gel with hexane-ethyl acetate (3:1) . The major fraction was concentrated to give 99 mg (33% yield) of **2a** as colorless crystals: mp 132-134°C (ethyl acetate - hexane). IR ν (KBr) cm^{-1} : 3420(OH), 1780(C=O), 1740(C=O), 1585(C=N). MS(m/z) : 317 (M^+). ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.88(s, 3H, $COOCH_3$), 4.84(d, $J_{4,5}$=3.6 Hz, 1H, H-4), 4.94(d, $J_{4,5}$=3.6 Hz, 1H, H-5), 7.11(d, $J_{10,11}$=8.4 Hz, 1H, H-11), 7.21(dd, $J_{8,10}$=2.0 Hz, $J_{10,11}$=8.4 Hz, 1H, H-10), 7.49(d, $J_{8,10}$=2.0 Hz, 1H, H-8). *Anal.* Calcd for $C_{12}H_9NO_5Cl_2 \cdot 1/2H_2O$: C, 44.17 ; H, 3.09; N, 4.30. Found : C, 44.10; H, 3.13; N, 4.18.

Methyl 3-(4-Bromo-2-chlorophenyl)-4-hydroxyimino-5-oxotetrahydrofuran-2-carboxylate (2b): Compound (**2b**) was obtained analogously as described for **2a** : Yield 38%. mp 97-103°C (ethyl acetate - hexane). IR ν (KBr) cm^{-1} : 3430(OH), 1785(C=O), 1750(C=O), 1590(C=N). MS (m/z) : 361 (M^+). ^{1}H NMR ($CDCl_3$, δ, ppm) : 3.87(s, 3H, $COOCH_3$), 4.80(d, $J_{4,5}$=4.0 Hz, 1H, H-4), 4.94(d, $J_{4,5}$= 4.0 Hz, 1H, H-5), 7.04(d, $J_{10,11}$= 8.0 Hz, 1H, H-11), 7.41(dd, $J_{8,10}$=2.0 Hz, $J_{10,11}$=8.0 Hz, 1H, H-10), 7.61(d, $J_{8,10}$= 2.0 Hz, 1H, H-8). *Anal.* Calcd for $C_{12}H_9NO_5BrCl \cdot 1/2H_2O$: C, 38.78; H, 2.71; N, 3.76. Found : C, 38.65; H, 3.00; N, 3.71.

X-Ray Analysis of 2b

X-Ray crystallography was carried out on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data were measured with graphite monochromated Cu$K\alpha$ radiation. The structure was solved by the program MITHRIL (an integrated direct method computer program, *J. Appl. Cryst.*, 1984, **17**, 42, Univ. of Glasgow, Scotland). The crystallographic data and the positional parameters of **2b** are listed in Table 2 and Table 3, respectively. The intramolecular distances and bond angles for **2b** are listed in Table 4.

Table 2

A. Crystal Data		**B.Intensity Measurements**	
Empirical Formula	$C_{12}H_{11}O_6BrCl$	Scan Type	ω-2θ
Fomula weight	380.582	$2\theta_{max}$	140.5°
Crystal Dimensions (mm)	0.100x0.200x0.200	No.of Reflections Measured	Total: 3014
Crystal System	monoclinic		Unique: 2818(R_{int}=0.127)
Lattice Parameters:	a=9.022(2)Å		
	b=6.898(2)Å		
	c=23.151(2)Å		
	β=94.91(2)°		
	$V=1435.6(6)Å^3$	**C. Structure Solution and Refinement**	
Space Group	$P2_{1/c}$(#14)	No.Observations(I>350σ(I))	1461
Z_{value}	4	No.Variables	190
D_{cal}	$1.761g/cm^3$	Reflection/Parameter Ratio	7.69
μ(Cu$K\alpha$)	$59.48cm^{-1}$	Rasiduals:R; Rw	0.077; 0.063

Table 3 Positional Parameters and B(eq)

atom	x	y	z	B(eq)
Br(1)	0.5734(1)	0.2264(2)	0.82004(6)	4.83(7)
Cl(1)	0.8949(3)	-0.3472(3)	0.7241(1)	2.2(1)
O(1)	1.0745(7)	-0.329(1)	0.6054(3)	3.3(3)
O(2)	0.9449(7)	-0.581(1)	0.5686(4)	4.2(4)
O(3)	0.5942(7)	-0.176(1)	0.5658(3)	3.2(3)
O(4)	1.1574(8)	-0.038(1)	0.5339(3)	4.0(4)
O(5)	1.2097(8)	0.137(1)	0.6154(3)	3.1(3)
O(6)	0.6314(8)	0.184(1)	0.9988(4)	5.1(4)
N(1)	0.6954(8)	-0.322(1)	0.5640(3)	2.6(4)
C(1)	0.944(1)	-0.413(2)	0.5847(4)	2.6(4)
C(2)	0.824(1)	-0.279(2)	0.5849(3)	2.4(4)
C(3)	0.883(1)	-0.086(1)	0.6109(4)	1.9(4)
C(4)	1.053(1)	-0.132(2)	0.6227(4)	2.6(4)
C(5)	0.8075(8)	-0.012(1)	0.6636(4)	1.7(4)
C(6)	0.8063(9)	-0.112(1)	0.7147(4)	1.6(4)
C(7)	0.740(1)	-0.044(2)	0.7632(4)	2.2(4)
C(8)	0.669(1)	0.132(1)	0.7562(4)	2.4(4)
C(9)	0.666(1)	0.235(2)	0.7073(4)	2.8(4)
C(10)	0.737(1)	0.162(2)	0.6607(4)	3.1(5)
C(11)	1.147(1)	-0.012(2)	0.5845(5)	2.9(5)
C(12)	1.303(1)	0.261(2)	0.5837(5)	4.3(5)

Table 4. Intramolecular Distances and Bond Angles

atom	atom	distance	atom	atom	atom	angle
Br1	C8	1.89(1)	Cl	O1	C4	111.4(8)
Cl1	C6	1.814(9)	N1	O3	H3	179.06
O1	C1	1.36(1)	O3	N1	C2	114.3(8)
O1	C4	1.44(1)	O2	C1	C2	130(1)
O2	C1	1.21(1)	N1	C2	C1	121(1)
O3	N1	1.364(9)	N1	C2	C3	129.2(9)
N1	C2	1.26(1)	C1	C2	C3	109.3(8)
C1	C2	1.42(1)	C2	C3	H1	107.76
C2	C3	1.53(1)	C4	C3	H1	109.23
C3	C4	1.57(1)	C5	C3	H1	107.50
			O1	C4	H2	111.80
			C3	C4	H2	109.16
			C11	C4	H2	111.56

Distances are in angstromes. Estimated Standaed deviations in the least significant figure are given in parentheses.

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

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12. See ref. 1, 7, 8.

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