ANNULATION OF HETEROCYCLES *VIA* RING TRANSFORMATION OF ISOXAZOLINE-2-OXIDES BY LEWIS ACID[1]

Kazuho Harada,* Kuniaki Sasaki, Eisuke Kaji, and Shonosuke Zen

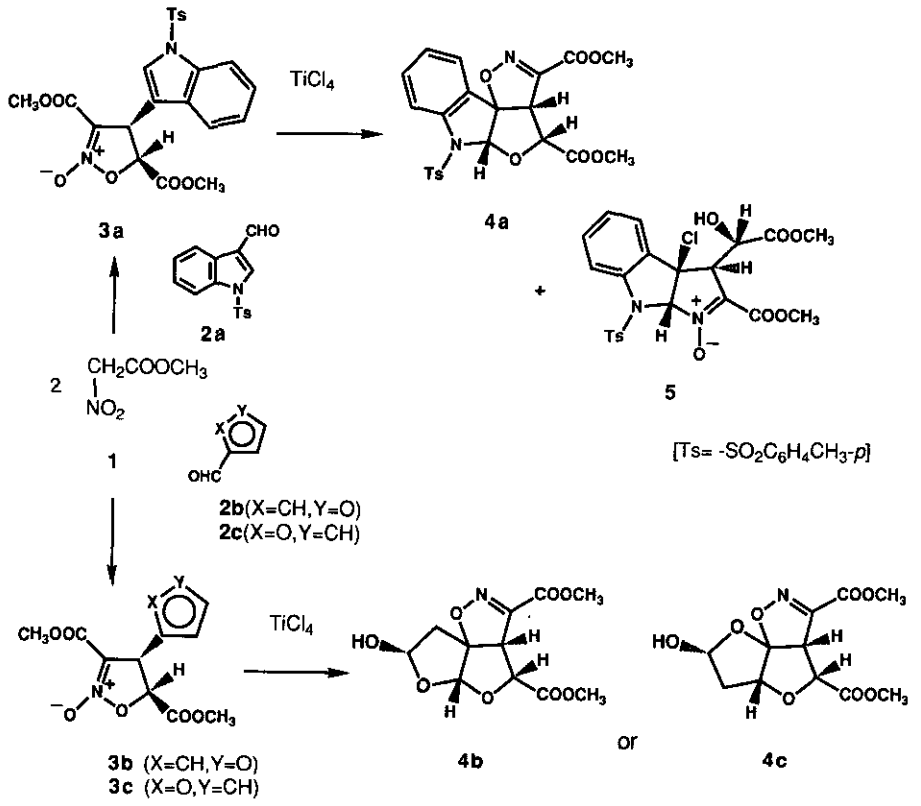
School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

Abstract - Novel heterocyclic-annulated furo[3,3a-*d*]isoxazoles were synthesized through the ring transformation reaction of heterocyclic ring-substituted isoxazoline-2-oxides promoted by Lewis acid such as titanium tetrachloride. Structural determinations by single crystal X-ray and nmr analyses are reported.

Previously we described novel ring transformation of 3,5-bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxides into benzofuro[3,3a-*d*]isoxazoles in the presence of Lewis acid such as $TiCl_4$.[2] To exploite this ring transformation, we used heteroaromatic ring-substituted isoxazoline-2-oxides in this ring transformation and wish to report here the synthesis of novel heterocyclic annulated furo[3,3a-*d*]isoxazoles (**4 a**, **4 b**, and **4 c**) through the ring transformation of indole- or furan- substituted isoxazoline-2-oxides (**3 a**, **3 b**, and **3 c**) by Lewis acid such as titanium tetrachloride(Scheme 1).

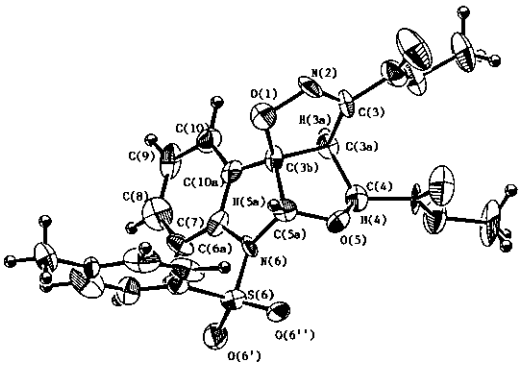
Isoxazoline-2-oxides (**3 a**, **3 b**, and **3 c**)[3] were prepared[4] by the reaction of the corresponding aldehydes (**2 a**, **2 b**, and **2 c**) with two molar amount of methyl nitroacetate (**1**) in the presence of diethylamine, then employed in a following manner. Compound (**3 a**) was allowed to react with four-fold molar excess of titanium tetrachloride in dichloromethane for 1.5 h at room temperature, and then the reaction mixture was quenched with 10% aqueous sodium carbonate and extracted with chloroform. Purification by column chromatography on silica gel(hexane-ethyl acetate, 1:1) afforded two fractions, *i.e.*, dimethyl 3a,4-dihydro-6-tosyl-5a*H*-indo[2,3-*b*]furo-[3,3a-*d*] isoxazole-3,4-dicarboxylate (**4 a**)[5] (58%, mp 86.0-88.0° C from benzene-petroleum ether) and methyl 3a-chloro-α-hydroxy-2-methoxycarbonyl-1-oxido-8-tosylindo[2,3-*b*]-1-pyrroline-3-acetate (**5**)[6] (22%, mp 190-193° C from ethyl acetate-hexane). On the other hand, when compound (**3b** and **3 c**) were allowed to react with two-fold molar excess of titanium tetrachloride in dichloromethane for 1 h at 0° C, 6-hydroxyfuro[2,3-*b*]furo[3,3a-*d*]isoxazole (**4 b**)[7] (33%, mp 134-136° C) and 7-hydroxyfuro[3,2-*b*]furo[3,3a-*d*] isoxazole(**4 c**)[8] (28%, mp 96-98° C) were isolated from the complex reaction mixture, respectively.

Structures of these products were confirmed as follows : Compounds (**4 a**, **5**, and **4 b**) were

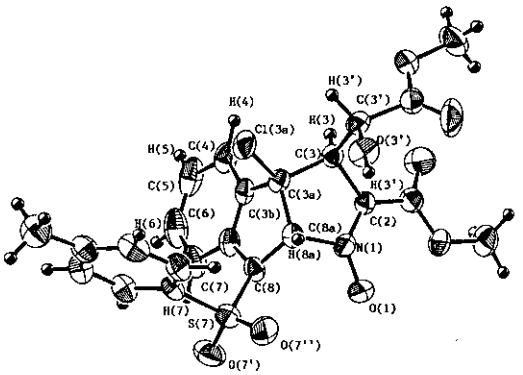


Scheme 1

analysed by single crystal X-ray analyses[9]. The ORTEP drawing of **4a**,**5**, and **4b** are shown in Figure 1. The structure of **4c** was assigned by comparing the ^{1}H-^{1}H chemical shif correlation spectra (COSY) of **4c** with those of **4b** : H-5a appears as a singlet at δ 5.95 in the spectrum of **4b**. On the other hand, H-5a at δ 4.98 is coupled with methylene protons (H-6 and H-6') on the furan ring and the methylene protons are coupled with one ring proton(H-7) (J=11.0 and 6.0 Hz) in the spectrum of **4c**. Other correlation of ^{1}H signals between the spectra of **4b** and **4c** are almost identical (Table 1). By these spectroscopic results, the structure of **4c** was determined as a constitutional isomer of **4b**, *i.e.*, 7-hydroxyfuro[3,2-*b*]furo[3,3a-*d*]isoxazole. The postulated mechanisms of the formation of **4a**,**5**, and **4b** are illustrated in Schemes 2 and 3 . The formation of spiro-intermediate(**B**) from the nitrosonium intermediate(**A**)[10] through an intramolecular *ipso*-attack[11] by oxygen atom of nitrosonium species in **A** leads to afford **4a**. On the other hand, intramolecular addition of nitrosonium species at C-2 of the indole ring in the intermediate(**A**), followed by chlorination with $TiCl_4$ gives product (**5**) (Scheme 2). The former mechanism is also adopted in the formation of **4b**, except introduction of a hydroxy group into the furan ring in the intermediate(**C**) through the acid-catalysed hydration to afford **4b** (Scheme 3).

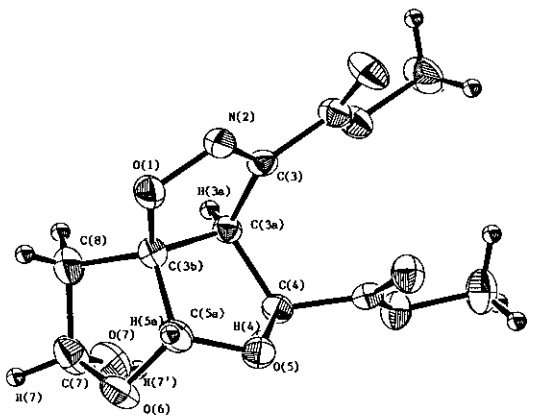


4a

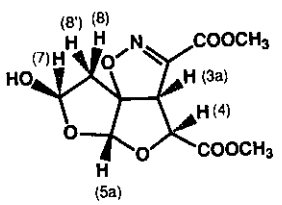


5

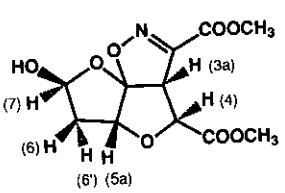
Figure 1. Perspective Drawings of Compounds (**4a**,**5**, and **4b**)



4b



4b



4c

Table 1. Selected ^{1}H-Nmr Shifts(ppm) and Coupling Constants(Hz) for **4b** and **4c** (300 MHz, in $CDCl_3$)

	4b		**4c**	
H-3a	4.32	d	4.20	d
H-4	5.23	d	4.66	d
H-5a	5.95	s	4.98	m
H-6	——		2.36	m
H-6'	——		2.45	m
H-7	5.68	dd	5.85	dd
H-8	2.35	dd	——	
H-8'	2.72	dd	——	
$J_{3a,4}$	6.5		6.3	
$J_{5a,6}$	——		8.0	
$J_{5a,6'}$	——		5.0	
$J_{6,6'}$	——		15.0	
$J_{6,7}$	——		6.0	
$J_{6',7}$	——		11.0	
$J_{7,8}$	3.0		——	
$J_{7,8'}$	5.0		——	
$J_{8,8'}$	14.0		——	

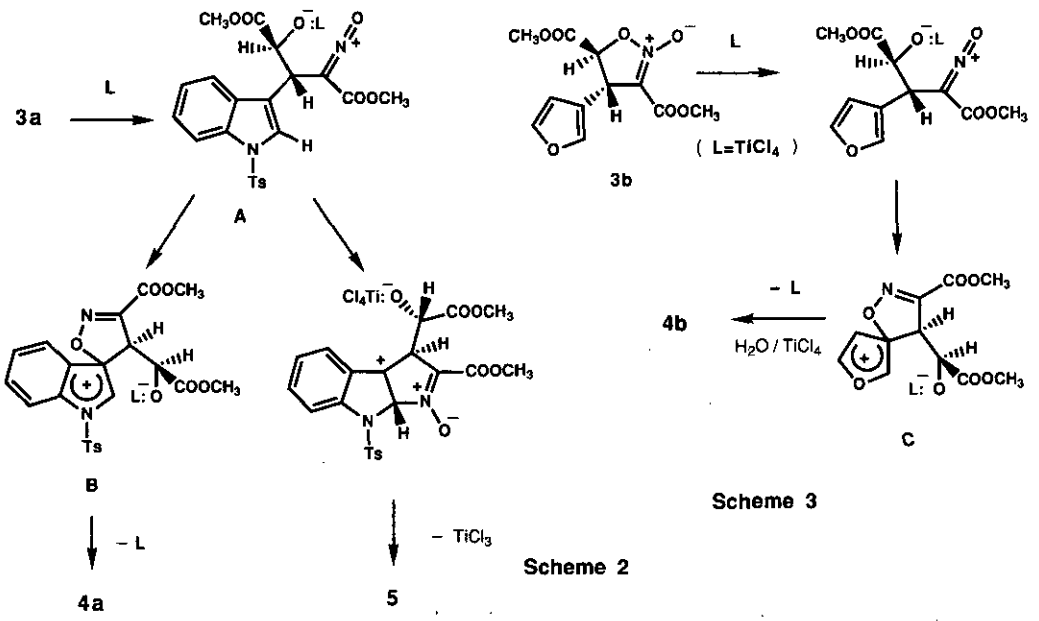


Table 2. Crystallographic Data for Compounds **4a**, **5**, and **4b**

	4a	**5**	**4b**
Formula	$C_{22}H_{20}N_2O_6S$	$C_{22}H_{21}N_2O_6ClS$	$C_{11}H_{13}NO_3$
F_w	472.47	508.93	287.23
Crystal dimensions (mm)	0.2x0.2x0.3	0.2x0.3x0.2	0.2x0.3x0.2
Crystal System	monoclinic	monoclinic	triclinic
Space group	*P*21/*a*	*P*21/*a*	$P\bar{1}$
Lattice parameters			
a/Å	10.796(4)	12.210(1)	8.870(1)
b/Å	30.556(8)	14.616(2)	12.159(1)
c/Å	13.565(4)	13.151(1)	6.0696(6)
α/deg	———	———	102.08(1)
β/deg	99.93(2)	102.037(7)	90.59(1)
γ/deg	———	———	71.110(8)
V/Å^3	4408(4)	2295.4(4)	604.5(1)
Z	8	4	2
Dc/gcm^{-3}	1.424	1.473	1.578
μ(Cu *K*α)/cm^{-1}	17.18	27.70	11.40
2θmax/deg	110.1	140.2	140.4
Scan mode	ω-2θ	ω-2θ	ω-2θ
No. of Observation (*Fo*>3.00σ(*Fo*))	1591	2734	1513
No. of Variables	595	351	181
R	0.060	0.047	0.049
R_w	0.038	0.043	0.049

ACKNOWLEDGMENT

The authors thank the Suzuken Memorial Foundation and the Japanese Ministry of Education, Science and Culture(Grant-in-Aid for General Scientific Research, No 04671305) for support of this study.

REFERENCES AND NOTES

1. Part X of a series on "Synthetic Reactions of Isoxazoline-2-oxides".
2. S. Zen, K. Takahashi, E. Kaji, H. Nakamura, and Y. Iitaka, *Chem. Pharm. Bull.*, 1983, **31**, 1814 : K. Takahashi, E. Kaji, and S. Zen, *Synth. Commun.*, 1984, **14**, 139 ; K. Takahashi, E. Kaji, and S. Zen, *Nippon Kagaku Kaishi*, **1984**, 1933 ; S. Zen, E. Kaji, and K. Takahashi, *Nippon Kagaku Kaishi*, **1986**, 55.
3. **3a** : Yield 76%; mp 181.5-184° C; Irν(KBr)cm^{-1} : 1758(*ester*), 1735(ester), 1620(C=N) ; ms(m/z): 472(M^+) ; ^{1}H nmr(300MHz, in $CDCl_3$) : 2.35(s,3H,CH_3), 3.73(s,3H,$COOCH_3$), 3.91(s,3H,$COOCH_3$), 4.98(d, $J_{4,5}$=3.5 Hz,1H,H-4), 5.13(d,$J_{4,5}$=3.5 Hz,1H,H-5), 7.2-8.1(m,9H, aromatic protons) ; *Anal.* Calcd for $C_{22}H_{20}N_2O_8S$: C, 55.92; H, 4.27; N, 5.93. Found : C, 55.81; H, 4.30; N, 5.88.
3b : Yield 87%; mp 104-106° C; Irν(KBr)cm^{-1} : 1760(ester), 1740(ester), 1635(C=N), ms(m/z): 269(M^+) ; ^{1}H nmr($CDCl_3$) : 3.79(s,3H,$COOCH_3$), 3.86(s,3H,$COOCH_3$), 4.84(d,$J_{4,5}$=2.5 Hz,1H, H-4), 4.92(d,$J_{4,5}$= 2.5 Hz,1H,H-5), 6.42(d,J=3.0 Hz,1H,furan proton), 7.43(d,J=3.0 Hz,1H,furan proton), 7.47(s,1H,furan proton) ; *Anal.* Calcd for $C_{11}H_{13}NO_8$: C, 46.00; H, 4.56; N, 4.88. Found : C, 46.17; H, 4.58; N, 4.72.
3c : Yield 73%; mp 102-105° C; Irν(KBr)cm^{-1} : 1750(ester), 1710(ester), 1640(C=N), ms(m/z): 269(M^+); ^{1}H nmr($CDCl_3$) : 3.80(s,3H,$COOCH_3$), 3.87(s,3H,$COOCH_3$), 5.03(d,$J_{4,5}$=3.0 Hz,1H, H-4), 5.07(d,$J_{4,5}$= 3.0 Hz,1H,H-5), 6.33(d,J=4.0 Hz,1H,furan proton), 6.37(dd,J=2.0 and 4.0 Hz, 1H,furan proton), 7.41(d,J=2.0 Hz,1H,furan proton) ; *Anal.* Calcd for $C_{11}H_{13}NO_8$: C, 46.00; H, 4.56; N, 4.88. Found : C,46.10; H, 4.60; N, 4.79.
4. K. Takahashi, E. Kaji, and S. Zen, *Nippon Kagaku Kaishi*, **1983**,1678 ; L. Kh. Vinograd and N.N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1970, **11**, 1505 (*Chem. Abstr.*, 1971, **74**, 53610h).
5. Irν(KBr)cm^{-1} : 1750(ester), 1610(C=N) ; ms(m/z) : 472(M^+) ; ^{1}H nmr($CDCl_3$) : 2.40(s,3H,CH_3), 3.76(s,3H,$COOCH_3$), 3.89(s,3H,$COOCH_3$), 4.30(d,$J_{3a,4}$=6.5 Hz,1H,H-3a), 4.82(d,$J_{3a,4}$=6.5Hz, 1H,H-4), 6.25(s,1H,H-5a), 7.2-7.8(m,8H, aromatic protons) ; *Anal.* Calcd for $C_{22}H_{20}N_2O_8S$: C, 55.92; H, 4.27; N, 5.93. Found : C, 55.98; H, 4.58; N, 5.54.
6. Irν(KBr)cm^{-1} : 3475(OH), 1740(ester), 1700(ester) ; ms(m/z) : 508(M^+) ; ^{1}H nmr($CDCl_3$): 2.39(s,3H,CH_3), 3.31(d,J=6.0 Hz,1H,OH), 3.74(s,3H,$COOCH_3$), 3.90(s,3H,$COOCH_3$), 4.13 (d,$J_{3,3'}$=2.0 Hz,1H,H-3), 5.08(dd,$J_{3,3'}$=2.0 Hz,J=6.0 Hz,1H,H-3'), 6.46(s,1H,H-8a), 7.12-7.40(m, 4H, H-4,H-5,H-6 and H-7), 7.28(d,J=8.5 Hz,2H, tosyl-H), 7.92(d,J=8.5 Hz,2H, tosyl-H) ; *Anal.* Calcd for $C_{22}H_{21}N_2O_8ClS$: C, 51.96; H, 4.13; N, 5.51; S, 6.30; Cl, 6.98. Found : C, 51.77;

H, 4.16; N, 5.68; S, 6.33; Cl, 6.89.

7. Irν(KBr)cm^{-1} : 3500(OH), 1740(ester), 1590(C=N) ; ms(m/z) : 287(M^+) ; ^{1}H nmr : summarized in Table 1 ; *Anal.* Calcd for $C_{11}H_{13}NO_8$: C, 46.00; H, 4.56; N, 4.88. Found : C, 46.17; H, 4.58; N, 4.72.
8. Irν(KBr)cm^{-1} : 3425(OH), 1730(ester), 1570(C=N) ; ^{1}H nmr : summarized in Table 1 ; *Anal.* Calcd for : $C_{11}H_{13}NO_8$: C, 46.00; H, 4.56; N, 4.88. Found : C, 46.01; H, 4.58; N, 4.62.
9. X-Ray structure analyses of **4 a**,**5**, and **4 b** 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° C. The crystal data are summarized in Table 2. 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, **1 7**, 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.
10. K. Takahashi, E. Kaji, and S. Zen, *Chem. Pharm. Bull.*, 1985, **3 3**, 8.
11. A. R. Butler, "Organic Reaction Mechanism 1979", ed. by A.C. Knipe and W.E. Watts, John Wiley and Sons, Ltd., New York, 1981, p. 275 ; H. Suzuki, *Yuki Gosei Kagaku Kyokai Shi*, 1979, **3 7**, 290.

Received, 23th October, 1992