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

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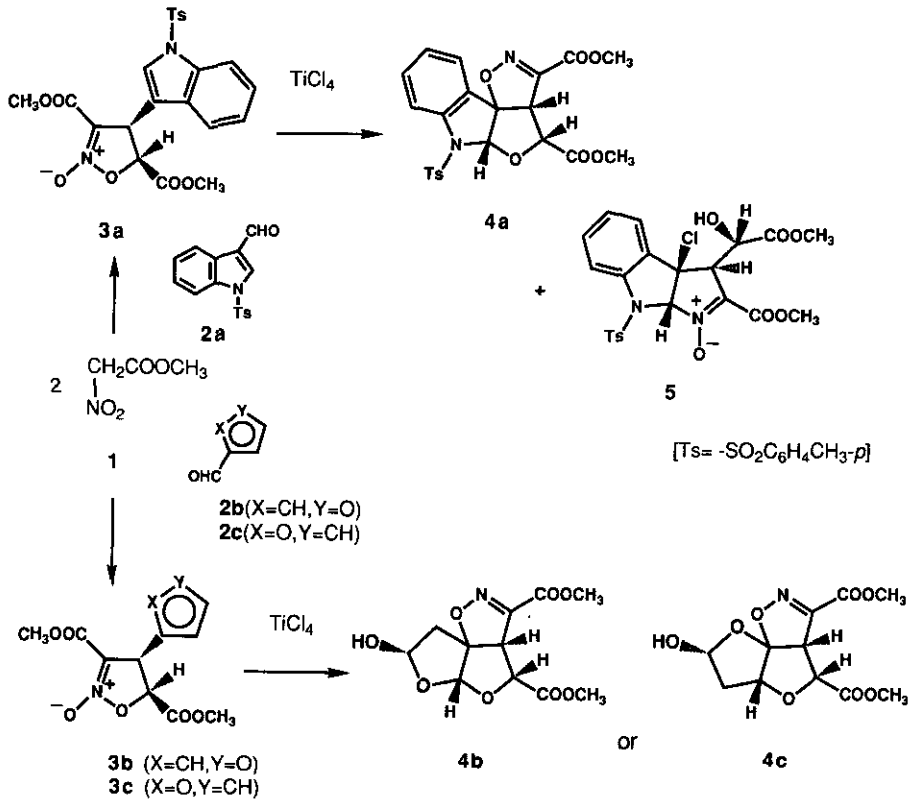
**Abstract** - Novel heterocyclic-annulated furo[3,3a-*d*]isoxazoles were synthesized through the ring transformation reaction of heterocyclic ring-substituted isoxazoline-2-oxides promoted by Lewis acid such as titanium tetrachloride. Structural determinations by single crystal X-ray and nmr analyses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

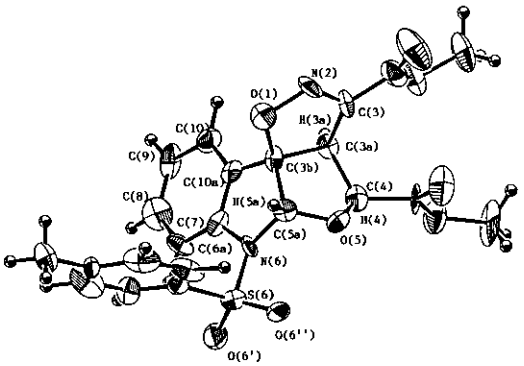
Isoxazoline-2-oxides (**3 a**, **3 b**, and **3 c**)[3] were prepared[4] by the reaction of the corresponding aldehydes (**2 a**, **2 b**, and **2 c**) with two molar amount of methyl nitroacetate (**1**) in the presence of diethylamine, then employed in a following manner. Compound (**3 a**) was allowed 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 $\delta$ 5.95 in the spectrum of **4b**. On the other hand, H-5a at $\delta$ 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

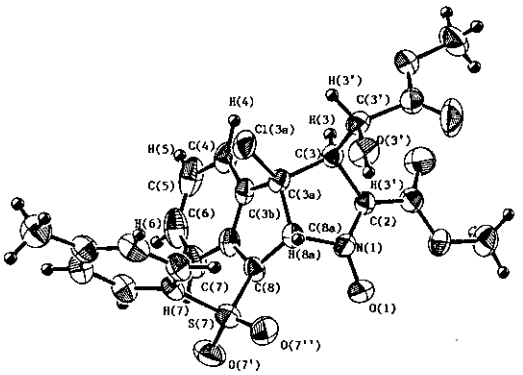



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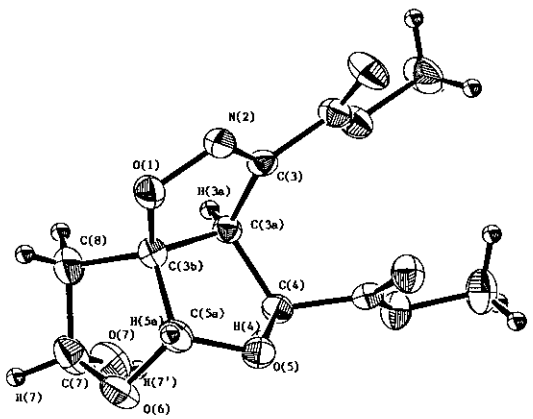
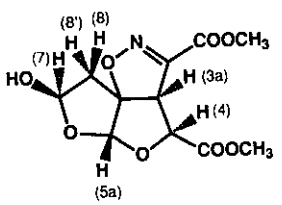
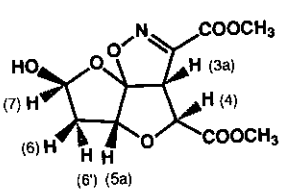
**Figure 1.** Perspective Drawings of Compounds (**4a**,**5**, and **4b**)




**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 | | —— | |

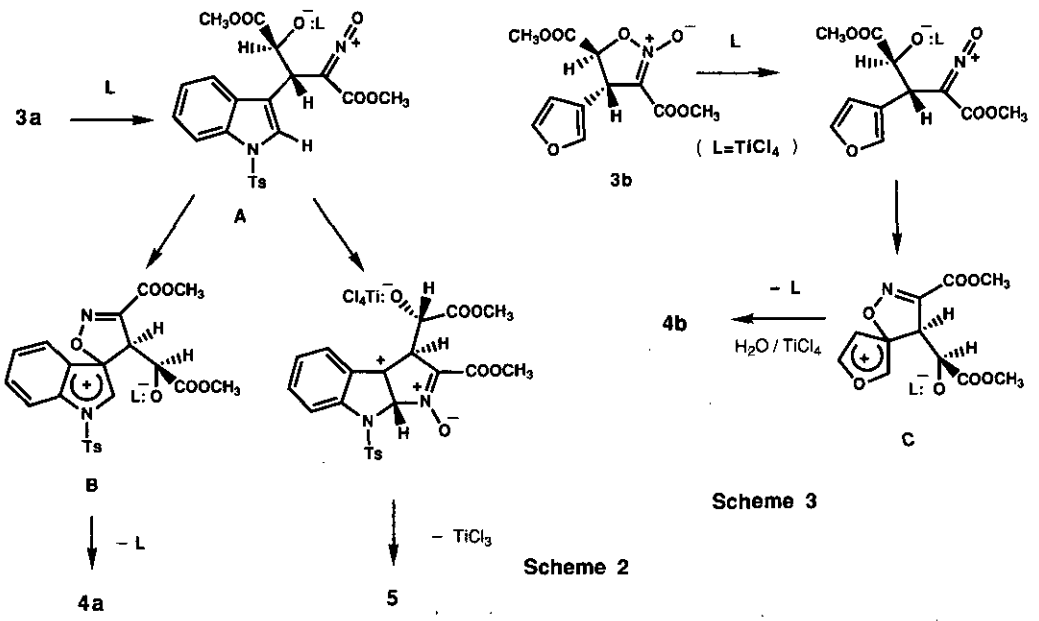



Table 2. Crystallographic Data for Compounds **4a**, **5**, and **4b**

| | **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) |
| $\alpha$/deg | ——— | ——— | 102.08(1) |
| $\beta$/deg | 99.93(2) | 102.037(7) | 90.59(1) |
| $\gamma$/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 |
| $\mu$(Cu *K*$\alpha$)/cm$^{-1}$ | 17.18 | 27.70 | 11.40 |
| 2$\theta$max/deg | 110.1 | 140.2 | 140.4 |
| Scan mode | $\omega$-2$\theta$ | $\omega$-2$\theta$ | $\omega$-2$\theta$ |
| No. of Observation (*Fo*>3.00$\sigma$(*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.

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3. **3a** : Yield 76%; mp 181.5-184° C; Ir$\nu$(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; Ir$\nu$(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; Ir$\nu$(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.
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5. Ir$\nu$(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. Ir$\nu$(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. Ir$\nu$(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. Ir$\nu$(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 K$\alpha$ ($\lambda$=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.
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