AN ONE-POT SYNTHESIS OF 5,11-ETHENOISOXAZOLO[5''',4''':3',4']-FURO[2'',3'':7',8']NAPHTHO[2',3':4,5]FURO[3,4-*d*]ISOXAZOLES FROM 2-ISOXAZOLINE-2-OXIDES[1]

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Abstract - 4-Aryl-3,5-bis(methoxycarbonyl)-2-isoxazoline-2-oxides were allowed to react with titanium tetrachloride by one-pot synthesis to afford novel fused heterocycles, 5,11-ethenoisoxazolo[5''',4''':3',4']furo[2'',3'':7',8']-naphtho[2',3':4,5]furo[3,4-*d*]isoxazoles, which were also formed by stepwise synthesis *via* Diels-Alder dimerization of 3a,4-dihydro-5a,*H*-benzofuro[3,3a-*d*]-isoxazoles attainable from the above isoxazoline-2-oxides. The structure determination of the dimer by single crystal X-ray analysis is reported.

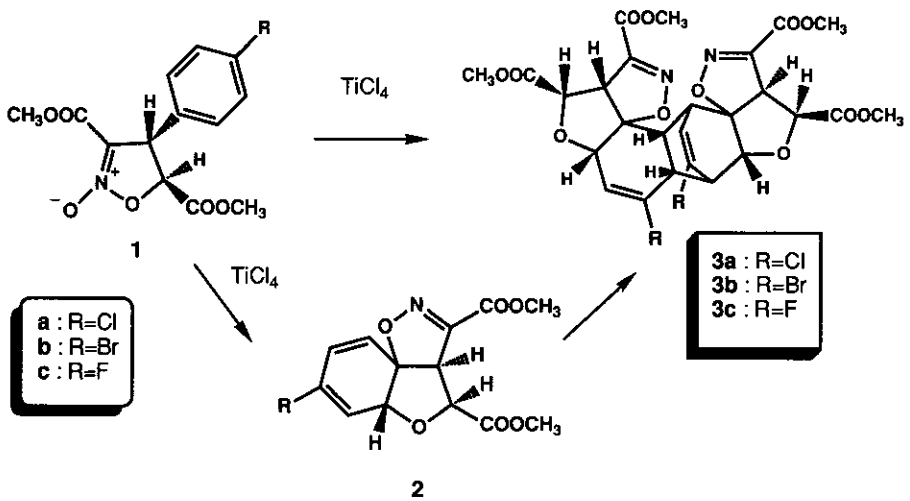
In previous papers,[2] unique ring transformation of 4-aryl-3,5-bis(methoxycarbonyl)-2-isoxazoline-2-oxides(**1**) was demonstrated for the synthesis of dimethyl 7-substituted 3a,4-dihydrobenzofuro[3,3a-*d*]isoxazole-3,4-dicarboxylates(**2**) by the action of Lewis acid such as titanium tetrachloride. We describe herein a facile one-pot synthetic method for novel fused polycyclic heterocycles; 5,11-ethenoisoxazolo[5''',4''':3',4']furo[2'',3'':7',8']naphtho[2',3':4,5]furo[3,4-*d*]isoxazoles(**3**) by the reaction of **1** with titanium tetrachloride. (Scheme 1)

In a typical procedure, titanium tetrachloride (0.45 ml, 4 mmol)) was added to a solution of isoxazoline-2-oxide(**1 a**: R=Cl)[3] (313 mg, 1 mmol) in dichloromethane (10 ml) at 0° C and the resulting mixture was stirred at room temperature for 15 h. After the reaction mixture was quenched with 10% aqueous sodium carbonate and extracted with chloroform, purification by column chromatography on silica gel (hexane-ethyl acetate, 3:1) afforded 72 mg of compound (**3 a**)[4] in a yield of 23%,[5] mp 245-246° C (from chloroform-methanol). This procedure was applied to **1 b**(R=Br)[3] and **1 c**(R=F)[3] to afford **3 b**[6] (22%, mp 225-226° C) and **3 c**[7] (26%, mp 273-276° C), respectively. The structure of **3 a** was determined by single crystal X-ray analysis.[8] A perspective drawing of the molecule of **3 a** is illustrated in Figure 1. The structure of **3 a** reveals that the molecule results from Diels-Alder dimerization of **2 a**, in which C_6=C_7-C_8=C_9 and C_5=C_7 moieties correspond to diene and dienophile components respectively, in the Diels-Alder reaction for **3 a**. The stereochemistry of **3 a** was confirmed to be *endo* configuration, *i.e.,* as depicted in Figure 1, the bulky cyclohexene ring (C_{10}-C_{11}-C_{12}-C_{13}-C_{14}-C_{15}) (dienophile component) is under the bridge (C_5-C_7-C_8-C_9) (diene). The molecule is also assigned to be *anti* π -facial diastereomer[9] with respect to

the furan ring (C_2-C_3-C_4-C_5-O_2).

The reaction pathway for **3 a** as a Diels-Alder dimer of **2 a** was supported by the following experiments : A solution of **2 a** (500 mg, 1.6 mmol) in 5 ml of toluene was refluxed overnight. After removal of the solvent, the residue was chromatographed on silica gel (hexane-ethyl acetate, 1:1) to afford **3a** (390 mg) in a yield of 78%. The similar Diels-Alder dimerization of **2b** and **2c** occurred to give **3b** (75%) and **3c** (72%), respectively (Scheme 1) . These results clearly show that this one-pot formation of **3** from **1** proceeds *via* the initial ring transformation[2] into the intermediate (**2**) followed by the dimerization *in situ* to give **3** (Scheme 2).

Further detailed studies are now in progress.



1 2

Scheme 1

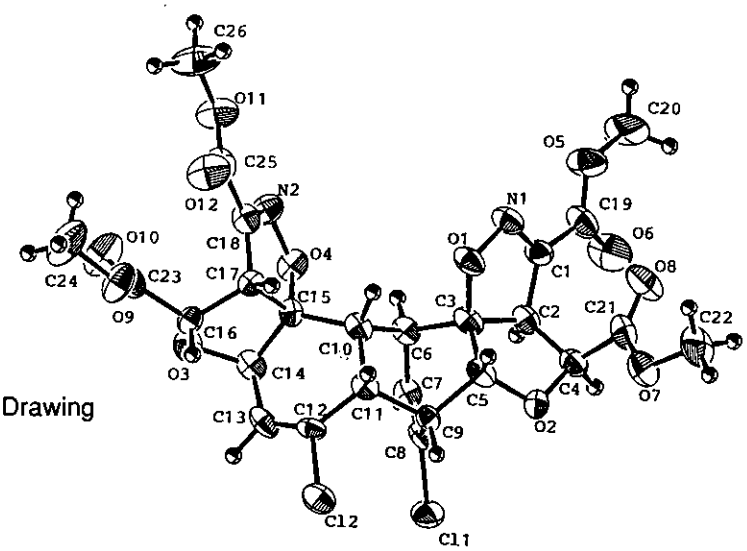
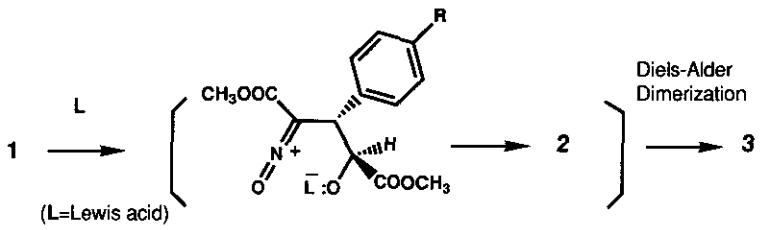


Figure 1. A Perspective Drawing of **3 a**



Scheme 2

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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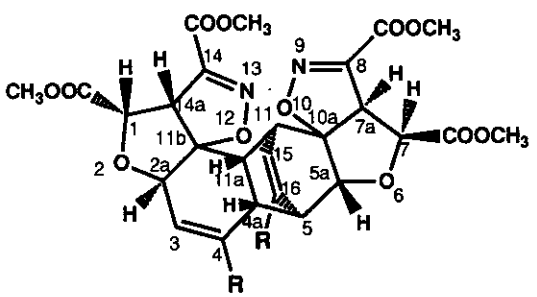
3. K. Takahashi, E. Kaji, and S. Zen. *Nippon Kagaku Kaishi,* **1983**, 1678.
4. Ir ν_{max}(KBr)cm^{-1} : 1750($COOCH_3$), 1620(C=N). Ms(m/z) : 626(M^+), 628(M^++2). Nmr : summarized in Tables 1 and 2. Anal. Calcd for $C_{26}H_{24}N_2O_{12}Cl_2$: C, 49.52; H, 3.86; N, 4.47; Cl, 11.30. Found : C, 49.52; H, 4.07; N, 4.26; Cl, 11.86.
5. Compound (**2 a**) was also isolated in a yield of 30%. When the reaction was carried out for 30 min, compound (**2 a**) was obtained as a major product (86% yield) and **3 a** was not isolated : See Ref. 2.
6. Ir ν_{max}(KBr)cm^{-1} : 1755($COOCH_3$), 1620(C=N). Ms(m/z) : 655(M^+), 657(M^++2). Nmr : Tables 1 and 2. Anal. Calcd for $C_{26}H_{24}N_2O_{12}Br_2$: C, 43.60; H, 3.38; N, 3.91; Br, 22.31. Found : C, 43.89; H, 3.50; N, 3.85; Br, 22.43.
7. Ir ν_{max}(KBr)cm^{-1} : 1750($COOCH_3$), 1620(C=N). Ms(m/z) : 594(M^+). Nmr : Tables 1 and 2. Anal. Calcd for $C_{26}H_{24}N_2O_{12}F_2$: C, 52.25; H, 3.23; N, 4.71. Found : C, 52.16; H, 3.33; N, 4.59.

Table 1 ^{1}H-Nmr Chemical Shifts(ppm) and Coupling Constants(Hz) for **3a**, **3b**, and **3c** (300 MHz, in $CDCl_3$)

	3a		3b		3c	
H-1	4.54	d	4.49	d	4.54	d
H-2a	4.55	s	4.56	s	4.56	s
H-3	5.87	d	6.09	d	5.88	d
H-4a	2.98	dd	3.08	dd	2.98	dd
H-5	3.67	dd	3.97	dd	3.68	dd
H-5a	4.74	d	4.72	d	4.73	d
H-7	4.83	d	4.83	d	4.83	d
H-7a	4.04	d	4.02	d	4.05	d
H-11	3.54	dd	3.54	dd	3.55	dd
H-11a	3.20	dd	3.15	dd	3.20	dd
H-14a	3.97	d	3.97	d	3.97	d
H-15	6.10	dd	6.37	dd	6.13	dd
CH_3	3.65	3.69	3.66	3.70	3.65	3.69
CH_3	3.84	3.88	3.84	3.89	3.84	3.88
$J_{1,14a}$	7.0		7.0		7.0	
$J_{4a,11a}$	9.0		9.0		9.0	
$J_{7,7a}$	9.2		9.0		9.0	
$J_{5,5a}$	3.0		3.0		3.0	
$J_{5,15}$	2.5		2.3		2.3	
$J_{11,11a}$	2.0		2.0		2.0	

Table 2 Selected ^{13}C-Nmr Chemical Shifts(ppm, 75 MHz, in $CDCl_3$)

	3a	3b	3c
C-1	77.35	77.43	77.34
C-2a	78.92	79.45	78.90
C-3	126.70	131.63	126.70
C-4a	42.37	44.67	42.36
C-5	49.35	50.95	49.35
C-5a	87.73	88.16	87.73
C-7	81.13	81.17	81.14
C-7a	58.92	58.93	58.93
C-10a	102.59	102.23	102.56
C-11	40.02	41.12	40.18
C-11a	35.85	36.07	35.85
C-11b	98.32	98.19	98.30
C-14a	59.56	59.49	59.56
C-15	122.05	127.00	122.00



8. 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 Kα radiation. The crystal data : $C_{26}H_{24}N_2O_{12}Cl_2$, FW=627.39, triclinic, space group $P\bar{1}$, a=13.174(4)Å, b=19.400(7)Å, c=10.751(3)Å, α=94.66(3)°, β=90.70(2)°, γ=80.30(3)°, V=2699(2)Å^3, Z=4, Dcal=1.544 gcm^{-3}, D_m=1.54 gcm^{-3}, μ for Cu Kα =28.02 cm^{-1}. The structure was solved by the program MITHRIL(C.J. Gilmore : MITHRIL, an integrated direct method computer program, *J. Appl. Cryst.*,1984, **17**, 42, Univ. of Glasgow, Scotland) and refined anisotropically by using a total of 3744 reflections (I>3 σ (I)) to give R=0.055, R_w=0.042. A pair of enantiomers was solved as a unit. Only one of them is depicted in Figure 1.

Selective bond distances(Å), bond angles(°), and torsion angles(°) : O(1)-N(1) 1.409(7), C(3)-C(6) 1.530(9), C(3)-C(5) 1.543(9), C(6)-C(7) 1.51(1), C(7)-C(8) 1.303(9), C(8)-C(9) 1.540(9), C(5)-C(9) 1.521(9), C(6)-C(10) 1.562(9), C(9)-C(11) 1.580(9), C(10)-C(11) 1.567(9), C(11)-C(12) 1.492(9), C(12)-C(13) 1.299(9) ; C(3)-C(6)-C(10) 103.8(6), C(5)-C(9)-C(11) 110.8(6), C(6)-C(7)-C(8) 112.8(7), C(7)-C(8)-C(9) 117.3(7) ; O(1)-C(3)-C(6)-C(7) -178.8(6), C(6)-C(7)-C(8)-C(9) 2(1), C(5)-C(9)-C(11)-C(12) 171.9(6), C(11)-C(12)-C(13)-C(14) -6(1), O(4)-C(15)-C(10)-C(6) -40.6(8).

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