Abnormal Diels-Alder Reaction of Oxazoles with 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione and Diethyl Azodicarboxylate, and X-Ray Crystal Structure of an Adduct

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(Received June 19, 1992)

The reaction of substituted oxazoles with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) or diethyl azodicarboxylate gave the corresponding 1,2,4-triazoline derivatives through formal [3+2] cycloaddition accompanying ring opening of oxazoles. The molecular structure of an adduct of 5-methoxy-4-methyl-2-(*p*-tolyl)oxazole with PTAD was determined by means of X-ray crystallography.

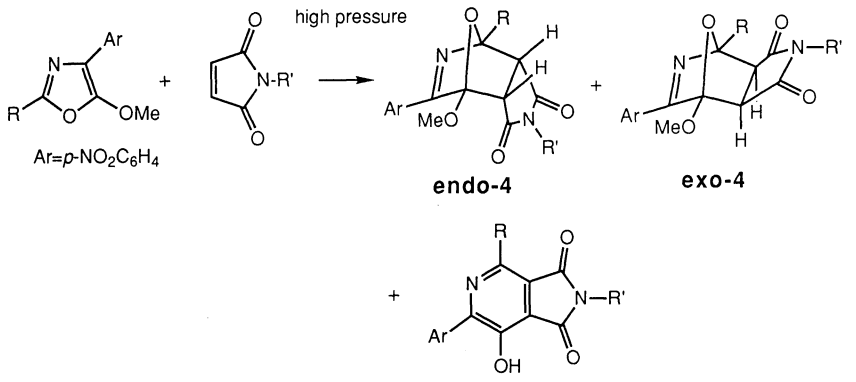
Diels-Alder reactions of oxazoles with electron-deficient olefins or acetylenes are useful methods for the syntheses of pyridine or furan derivatives, respectively.[1] For example, these reactions have been used to synthesize vitamin B_6[2] and natural products containing a furan ring.[1e] In the previous paper of our research on oxazoles, endo selectivity of the initial adducts was reported in the high pressure Diels–Alder reaction of 5-methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole with *N*-methyl- and *N*-phenylmaleimides or dimethyl maleate (Scheme 1).[3]

On the other hand, we found that the reaction of 5-alkoxyoxazoles with tetracyanoethylene (TCNE) did not give Diels–Alder adducts but gave formal [3+2] cycloadducts through ring opening of oxazoles.[4] The mechanism of these cycloadditions was explained to proceed through a stepwise pathway involving zwitterionic intermediates. On the basis of this reaction mechanism, it is assumed that dienophiles having strong electron-accepting character will accelerate the reaction. Therefore, we studied the reaction of oxazoles with electron-deficient azo dienophiles having comparable structure with *N*-alkylmaleimide or dimethyl maleate. In this paper, we provide a full account of our investigation of the reaction of 5-alkoxy and 5-alkyloxazoles with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) or diethyl azodicarboxylate (DEAD) to give 5-alkoxycarbonyl- and 5-acyl-1,2,4-triazol-3-ine derivatives through formal [3+2] cycloaddition, respectively.[5]

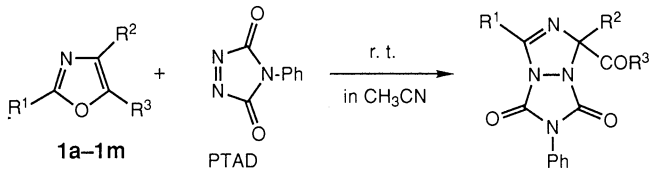
When we published preliminary paper of the reactions with PTAD,[5] there had been reported only a few papers concerning the abnormal Diels–Alder reaction of 5-dialkylamino or 5-alkoxyoxazoles.[4,6] Thereafter, similar type of cycloadditions of alkoxyoxazoles with thioaldehyde,[7] DEAD,[8] diethyl oxomalonate,[8] 1*H*-imidazole-2,5-dione,[8] aldehydes,[9] and also cycloadditions of 5-alkyl and 5-alkoxyoxazoles with nitrosobenzene[10] were reported.

Results and Discussion

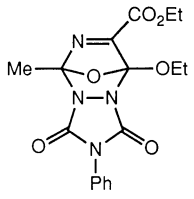
Reaction of Oxazoles 1 with PTAD. The reaction of ethyl 5-ethoxy-2-methyloxazole-4-carboxylate (**1a**) with PTAD was carried out in similar reaction conditions with the reaction of TCNE.[4] Treatment of oxazole **1a** with equimolar amount of PTAD in dry acetonitrile (MeCN) at room temperature resulted in rapid disap-



Scheme 1.



a: R^1=Me, R^2=CO_2Et, R^3=OEt
b: R^1=Me, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
c: R^1=Et, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
d: R^1=i-Pr, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
e: R^1=t-Bu, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
f: R^1=*p*-Tolyl, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
g: R^1=*p*-$MeOC_6H_4$, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
h: R^1=Ph, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
i: R^1=Me, R^2=Me, R^3=OMe,
j: R^1=*p*-Tolyl, R^2=Me, R^3=OMe
k: R^1=Me, R^2=H, R^3=*p*-$MeOC_6H_4$
l: R^1=Me, R^2=Me, R^3=Me
m: R^1=Me, R^2=Ph, R^3=Ph



3a

Scheme 2.

Table 1. Reactions of Oxazoles **1** with PTAD[a)]

Run	Oxazole **1**	R^1	R^2	R^3	Product	Yield/%[b)]
a	**1a**	Me	CO_2Et	OEt	**2a**	99
b	**1b**	Me	*p*-$NO_2C_6H_4$	OMe	**2b**	94
c	**1c**	Et	*p*-$NO_2C_6H_4$	OMe	**2c**	100
d	**1d**	*i*-Pr	*p*-$NO_2C_6H_4$	OMe	**2d**	99
e	**1e**	*t*-Bu	*p*-$NO_2C_6H_4$	OMe	**2e**	98
f	**1f**	*p*-Tolyl	*p*-$NO_2C_6H_4$	OMe	**2f**	99
g	**1g**	*p*-$MeOC_6H_4$	*p*-$NO_2C_6H_4$	OMe	**2g**	99
h	**1h**	Ph	*p*-$NO_2C_6H_4$	OMe	**2h**	99
i	**1i**	Me	Me	OMe	**2i**	88
j	**1j**	*p*-Tolyl	Me	OMe	**2j**	76
k	**1k**	Me	H	*p*-$MeOC_6H_4$	**2k**	89
l	**1l**	Me	Me	Me	**2l**	62
m	**1m**	Me	Ph	Ph	**2m**	78[c)]

a) All reactions were carried out in an acetonitrile solution at room temperature using equimolar amount of oxazole and PTAD. b) Isolated yields by column chromatography on silica gel. c) The reaction was carried out at 70 °C for 24 h.

pearance of deep carmine red of PTAD in a few seconds and gave a colorless crystalline product **2a** in 99% yield. The elemental analysis of **2a** revealed that the product is a 1 : 1 adduct of oxazole **1a** with PTAD. The ^1H (Table 2) and ^{13}C NMR spectra (see experimental section) show that **2a** has two identical ethoxycarbonyl groups in a molecule. Signals of characteristic quaternary carbon at 91.65 and sp^2-carbon at 147.98 ppm indicate that the adduct does not have a normal Diels–Alder structure **3a** but has a 1,2,4-triazoline structure with two equivalent ethoxycarbonyl groups in the molecule. Signals of two carbons mentioned above could be assigned to C-3 (147.98 ppm) and C-5 (91.65 ppm) of 1,2,4-triazoline ring formed through expected formal [3+2] cycloaddition.

Other oxazoles having various substituents on C-2, C-4, and C-5 were also confirmed to give similar type of adducts in the reaction with PTAD in high yields (Table 1). ^1H NMR data of the adducts **2a**—**2m** were listed in Table 2 together with data of Diels–Alder adducts **4a** of *N*-methylmaleimide. Low-field shifts of methoxyl groups of **2b**—**2j** (3.77—3.80 ppm) and methyl groups (2.40—2.55 ppm) of **2a, 2b, 2i, 2k, 2l,** and **2m** in comparison with the chemical shifts of methoxyl and methyl groups of the Diels–Alder adducts **4a** suggest that these adducts do not have a Diels–Alder structure but have the same structure as **2a** (Table 2). High yields of **2b**—**2e** indicate that bulkiness of the substituents R^1 on C-2 of oxazoles gives no effect on the reactivity of **1** toward PTAD (Table 1, Runs b—e). This is attributed to much higher reactivity of PTAD than that of TCNE.[4)] For example, a bulky *t*-butyl group on C-2 of oxazole **1e** depressed the reactivity toward TCNE, but

Table 2. ^{1}H NMR Data of 1,2,4-Triazolines **2**[a)]

Adduct	R^1	R^2	R^3	Ph
2a	2.50 (Me, s)	1.33 (t) 4.35 (q)	1.33 (t) 4.35 (q)	7.44
2b	2.54 (Me, s)	(7.89 (ABq, J=9.3 Hz) 8.19	3.78 (OMe, s)	7.49
2c	1.38 (t) 2.88 (q)	(7.92 (ABq, J=9.0 Hz) 8.24	3.77 (OMe, s)	7.49
2d	1.39 (dd) 3.27 (sep)	(7.93 (ABq, J=9.0 Hz) 8.23	3.77 (OMe, s)	7.49
2e	1.50 (s)	(7.98 (ABq, J=9.0 Hz) 8.25	3.77 (OMe, s)	7.48
2f	2.39 (s) (7.23 (ABq, J=8.4 Hz) 8.02	(8.03 (ABq, J=8.4 Hz) 8.23	3.79 (OMe, s)	7.48
2g	3.87 (s) (6.96 (ABq, J=9.0 Hz) 8.08	(8.03 (ABq, J=8.4 Hz) 8.25	3.77 (OMe, s)	7.45
2h	7.17—8.30 (m)	(8.02 (ABq, J=9.3 Hz) 8.23	3.79 (OMe, s)	7.47
2i	2.43 (Me, s)	1.95 (s)	3.80 (OMe, s)	7.45
2j	2.40 (s) (7.22 (ABq, J=7.8 Hz) 7.86	2.05 (s)	3.80 (OMe, s)	7.42
2k	2.43 (Me, s)	6.92 (s)	3.89 (s) (6.99 (ABq, J=8.7 Hz) 8.14	7.51
2l	2.40 (Me, s)	1.93 (s)	2.33 (s)	7.45
2m	2.55 (Me, s)	7.21—7.91 (m)		
endo-**4a**	2.09 (Me, s)	(8.18 (ABq, J=9.4 Hz) 8.29	3.61 (OMe, s)	2.55 (N-Me, s)
exo-**4a**	2.01 (Me, s)	(8.24 (ABq, J=9.3 Hz) 8.36	3.54 (OMe, s)	3.04 (N-Me, s)

a) Chemical shifts (δ/ppm) and coupling constants were shown (90 MHz).

gave no effect on the reaction with PTAD. It is interesting to note that not only 5-alkoxyoxazoles but also 5-alkyl **1l** or 5-aryloxazoles **1k** and **1m** reacted with PTAD to give the corresponding 5-acyl derivatives **2k**—**2m** in good yields. Substitution of aryl group on C-2 and/or C-4 does not decrease the reactivity of oxazoles (Table 2, Runs b—h and j). However, introduction of plural phenyl groups on C-5 and C-2 and/or C-4 seems to lower the reactivity of oxazole. For example, 2-methyl-4,5-diphenyloxazole (**1m**) requires heating at 70 °C for 24 h to complete the reaction, and 2,5-diphenyloxazole shows no reaction even under refluxing for 20 h in MeCN. This seems to be attributed to the decrease of the reactivity of oxazole by the conjugate stabilization due to phenyl substitution.

Following ^{13}C NMR data of **2l** also supported the 5-acetyl-1,2,4-triazol-3-ine structure: C-5 (at 84.22 ppm), C-3 (at 164.78 ppm) and carbonyl carbon of acetyl group (at 186.87 ppm).

X-Ray Crystal Analysis of 2j. In order to confirm the structure of the 1,2,4-triazol-3-ine moiety deduced from the NMR data, the crystal structure of **2j** has been determined by X-ray structure analysis. Single crystals of **2j** were obtained from a benzene–hexane solution. The crystal data and experimental details are listed in Table 3. The X-ray intensity data were collected on a Rigaku four-circle diffractometer AFC-5R with the Ni-

Table 3. Crystal Data and Experimental Details of **2j**

Molecular Formula	$C_{20}H_{18}N_4O_4$
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	16.267 (2)
b/Å	10.739 (2)
c/Å	11.133 (1)
β/°	103.036 (9)
V/Å^3	1894.6 (4)
Z	4
D_m/Mg m^{-3}	1.328
D_x/Mg m^{-3}	1.326
μ(Cu $K\alpha$)/cm^{-1}	8.0
Scan method	ω ($0° < 2\theta < 60°$) ω–2θ ($60° \leq 2\theta \leq 125°$)
Scan speed in ω/deg min^{-1}	4
Scan width/degree	$1.8+0.15\tan\theta$
Back ground/s	2×4
No. of reflections	3020
No. of reflections ($\lvert F_o\rvert \geq 2\sigma(F_o)$)	2379
R (wR)	0.085 (0.060)
R (wR) ($\lvert F_o\rvert \geq 2\sigma(F_o)$)	0.062 (0.067)
Crystal size/mm^3	0.2×0.2×0.3
$2\theta_{max}$ (Cu $K\alpha$)/degree	125

filtered Cu $K\alpha$ radiation. Corrections were made for Lorentz and polarization effects, but not for absorption.

The structure was solved by direct methods, and refined by block-diagonal least-squares techniques. The function minimized was $w(|F_o|-|F_c|)^2$, with $w=(\sigma^2(F_o)+0.0315|F_o|+0.0001|F_o^2|)^{-1}$. The non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically to give the final R value 0.062. All the atomic scattering factors were taken from "International Tables for X-Ray Crystallography".[11] The computations were carried out with The Universal Crystallographic Computing System-Osaka,[12] MULTAN 80[13] and ORTEP II[14] on an ACOS-S850 computer at the Research Center for Protein Engineering, Institute for Protein Research, Osaka University. Lists of observed and calculated structure factors, anisotropic thermal parameters, and H-atom parameters have been deposited as Document No. 9041 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Table 4 listed the final atomic and thermal parameters with their estimated standard deviations. The ORTEP drawing scheme is shown in Fig. 1. It was confirmed from this structure that the assignment of the configuration to **2** on the basis of the NMR data was correct. The bond distances and angles are given in Fig. 2 and Fig. 3, respectively. Each of the 1,2,4-triazol-3-ine ring and 1,2,4-triazolidine-3,5-dione ring has an envelope form: The dihedral angle of the plane through the N2, C9, and N4 atoms and the best plane (Plane 1) through the N2, N3, C13, and N4 atoms is 8.1°; that of the plane (Plane 2) through the C7, N1, and C8 atoms and the best plane (Plane 3) through the C7, N2, N3, and C8 is 10.1°. Plane 1 and Plane 3 make a dihedral angle of 39.6°. A dihedral angle of the best plane of the tolyl ring and Plane 1 is 22.2°, and that of the best plane of phenyl ring and Plane 2 is 72.4°. The hydrogen atoms (H41 and H42) at para-position of *N*-phenyl group are disordered with occupancy factors of 0.35 and 0.65, respectively.

Reaction of Oxazoles 1 with DEAD. Reactions of oxazoles **1** with DEAD were also carried out in MeCN to give cycloadducts **5** in high yields (Scheme 3, Table 5). In the ^{1}H NMR spectra of the adducts **5**, low-field shifts of methyl signals of **5a, 5b, 5i, 5l,** and **5m** (2.38—2.51 ppm) suggests that the adducts have 1,2,4-triazol-3-ine structure similar to PTAD adducts (Table 6). ^{13}C NMR spectra also support the 1,2,4-triazol-3-ine structure of compounds **5** (Table 7). For example, the spectrum of **5b** shows signals of C-3, C-5 of triazoline ring and carbonyl carbon of ester group at 157.12 (q, $^2J_{C-H}$=7.6 Hz), 93.51 (s) and 167.49 (s), respectively.

The oxazoles having bulky substituent on C-2 such as **1e** or having alkoxycarbonyl group on C-4 such as **1a** required a reflux temperature to promote the reaction. It is interesting to note that not only 5-alkoxyoxazoles but also trialkyloxazole **1l** or tri(alkyl, aryl)oxazoles **1m** and **1n** reacted with DEAD to give the corresponding 1,2,4-triazol-3-ines. The reaction of 2-methyl-4,5-diphenyloxazole (**1m**) with DEAD gave a different result from that of Hassner's which showed the absence of 1,2,4-triazoline **5m** under the reaction conditions at 80°C in benzene.[8] It is also interesting that the reaction of **1m**

Table 4. Atomic Coordinates of Non-H Atoms and Equivalent Isotropic Thermal Parameters with Their esd's in Parentheses

Atom	x	y	z	B_{eq}/Å^2
C(1)	0.3591(2)	0.4171(3)	0.5563(3)	3.77(9)
C(2)	0.3930(3)	0.5348(4)	0.5772(3)	5.07(12)
C(3)	0.4085(3)	0.5824(4)	0.6947(4)	5.90(14)
C(4)	0.3924(3)	0.5126(5)	0.7896(4)	5.92(13)
C(5)	0.3600(3)	0.3953(4)	0.7693(3)	5.90(14)
C(6)	0.3418(3)	0.3457(4)	0.6505(3)	4.73(11)
C(7)	0.2788(2)	0.4160(4)	0.3377(3)	4.14(9)
C(8)	0.3916(2)	0.2825(3)	0.3915(3)	3.74(9)
C(9)	0.2827(2)	0.3979(4)	0.1118(3)	4.86(11)
C(10)	0.1972(3)	0.3823(5)	0.0245(4)	6.83(16)
C(11)	0.3120(2)	0.5349(4)	0.1225(3)	5.02(12)
C(12)	0.4146(3)	0.6726(4)	0.2374(5)	6.43(16)
C(13)	0.3859(2)	0.2547(3)	0.1624(3)	4.07(9)
C(14)	0.4566(2)	0.1715(3)	0.1597(3)	3.97(9)
C(15)	0.5066(2)	0.1964(4)	0.0760(3)	4.47(11)
C(16)	0.5747(2)	0.1208(4)	0.0730(3)	4.73(11)
C(17)	0.5948(2)	0.0192(3)	0.1508(3)	4.26(10)
C(18)	0.5430(2)	−0.0067(4)	0.2332(3)	4.50(11)
C(19)	0.4747(2)	0.0688(3)	0.2371(3)	4.31(11)
C(20)	0.6682(3)	−0.0621(4)	0.1449(4)	6.00(14)
N(1)	0.3407(2)	0.3684(3)	0.4335(2)	3.74(7)
N(2)	0.2804(2)	0.3446(3)	0.2353(2)	4.14(8)
N(3)	0.3505(2)	0.2619(3)	0.2680(2)	3.88(8)
N(4)	0.3484(2)	0.3252(3)	0.0736(2)	4.66(9)
O(1)	0.2307(2)	0.5000(3)	0.3419(2)	5.80(9)
O(2)	0.4544(2)	0.2340(3)	0.4502(2)	5.09(8)
O(3)	0.2818(2)	0.6156(3)	0.0535(3)	7.55(12)
O(4)	0.3785(2)	0.5488(3)	0.2159(2)	5.26(8)

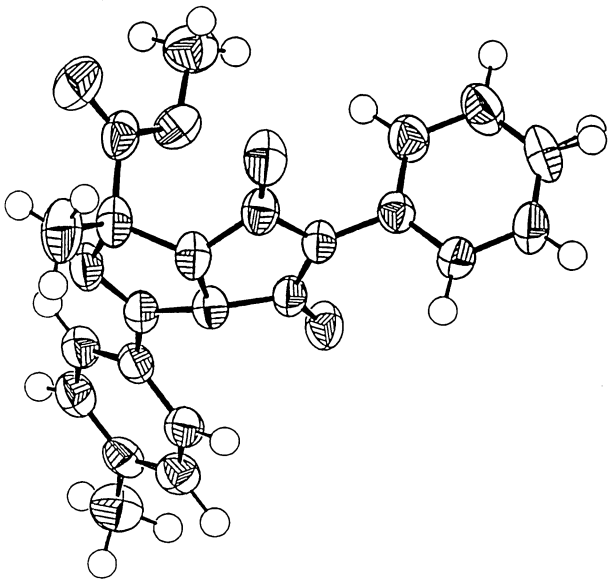


Fig. 1. ORTEP drawing of **2j**.

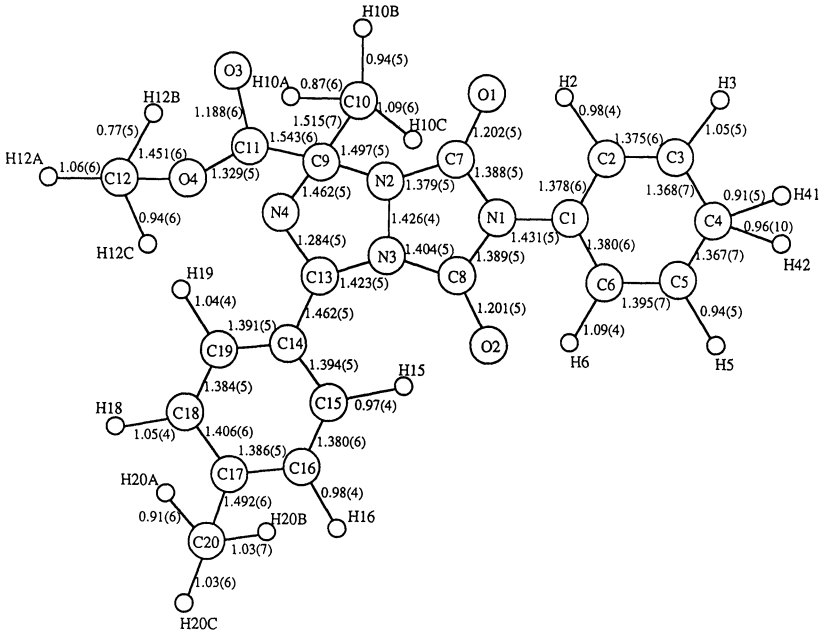


Fig. 2. Bond lengths of **2j**.

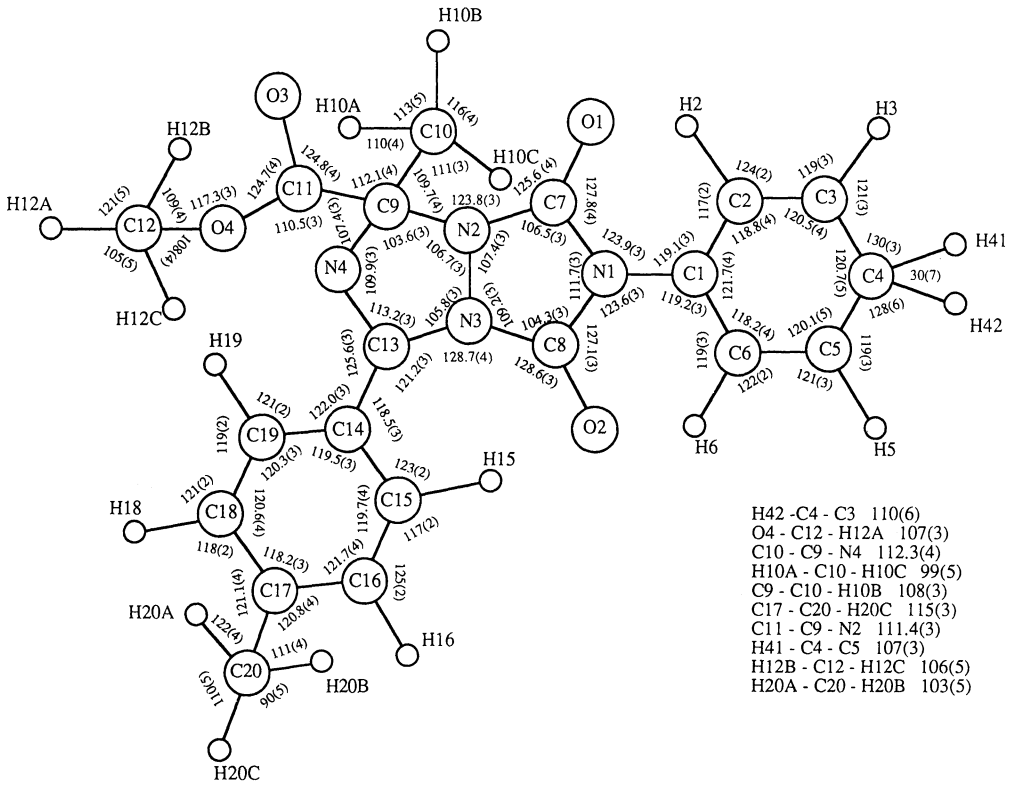


Fig. 3. Bond angles of **2j**.

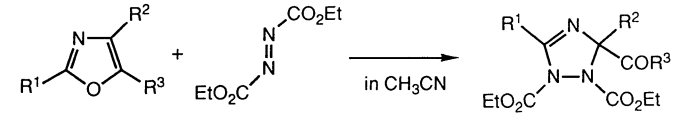
was accelerated under high pressure (0.85 GPa, 50 °C) (Table 5, Run j).

Mechanism of Abnormal Diels-Alder Reaction. The similarity of the structure of the adducts **2** and **5** with that of TCNE suggests that the reaction proceeds in a similar stepwise mechanism. The electrophilic attack of an azo nitrogen of PTAD or DEAD on C-4 or C-2 of the oxazole initiates the reaction to give a zwitterionic intermediate **A** or **B**, respectively. And the intermediates give other type of zwitterions **C** or **D** through ring

Table 5. Reactions of Oxazoles **1** with DEAD[a)]

Run	Oxazole	Conditions		Product	Yield/%[b)]
		Temp	Time/h		
a	**1a**	Reflux[f)]	120	**5a**	84
b	**1b**	r.t.	63	**5b**	92[c)]
c	**1c**	r.t.	67.5	**5c**	80
d	**1d**	r.t.	74	**5d**	91[d)]
e	**1e**	Reflux	23.5	**5e**	75[d)]
f	**1f**	r.t.	96	**5f**	90[e)]
g	**1i**	r.t.	4	**5i**	83
h	**1l**	r.t.	52	**5l**	80
i	**1m**	Reflux	264	**5m**	25[g)]
j	**1m**	50 °C (0.85 GPa)[f)]	192	**5m**	58
k	**1n**	50 °C	74	**5n**	52

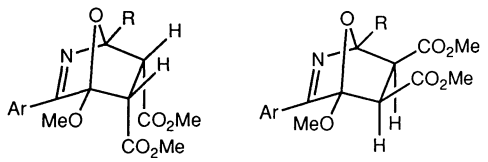
a) All reactions were carried out in MeCN using equimolar amount of oxazole and DEAD. b) Isolated yields by column chromatography on silica gel. c) Recovered **1b**: 5%. d) A trace amount of recovered **1** was detected by TLC. e) Recovered **1f**: 4%. f) Two molar amounts of DEAD were used. g) Recovered **1m**: 64%.



1a–1f, 1i, 1l–1m DEAD **5a–5f, 5i, 5l–5m**

a: R^1=Me, R^2=EtO_2C, R^3=OEt
b: R^1=Me, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
c: R^1=Et, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
d: R^1=i-Pr, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
e: R^1=t-Bu, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
f: R^1=*p*-Tolyl, R^2=*p*-$NO_2C_6H_4$, R^3=OMe
i: R^1=Me, R^2=Me, R^1=OMe
l: R^1=Me, R^2=Me, R^3=Me
m: R^1=Me, R^2=Ph, R^3=Ph
n: R^1=*p*-ClC_6H_4, R^2=Me, R^3=Me,

Scheme 3.

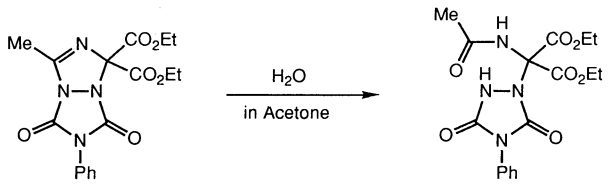


6a (endo-endo) **6b** (exo-exo)

opening of oxazole, which cyclize to afford the adduct **2** or **5**.

Alternative mechanisms through normal Diels–Alder adduct and through nitrile ylide intermediate are not completely excluded, but this stepwise pathway is more likely by the reason similar to the reaction with TCNE.[4,19)]

Hydrolysis of 1,2,4-Triazol-3-ine 2a. Triazoline **2a** was easily hydrolyzed by standing with equimolar amount of water in acetone at room temperature for 24 h to give crystalline product **7** in a quantitative yield. Elemental analysis revealed that **7** is a 1 : 1 adduct of triazoline **2a** with water. IR spectrum of **7** shows an NH absorption band at 2985 cm^{-1}. Two broad signals at 8.87 and 9.96 ppm in its ^1H NMR in $CDCl_3$ containing a small amount of DMSO-d_6 can be assigned to two amide NHs. ^1H NMR spectrum also shows signals of two equivalent ethyl esters at 1.33 (t) and 4.35 (q) ppm and a methyl signal of *N*-acetyl group at 2.09 (s) ppm. Moreover, ^{13}C NMR spectrum of **7** shows two carbonyl carbons of 1,2,4-triazolidine-3,5-dione at 151.86 and 152.53 ppm, ester carbonyl carbon at 163.10 ppm, and amide carbonyl carbon at 170.30 ppm. On the basis of these spectroscopic data, the product was determined to have *N*-acetylamino ester structure **7**.



2a **7**

Methanolysis of triazoline **2a** was unsuccessful under a similar condition using methanol instead of water. Treatment of **2a** in methanol solution in the presence of *p*-TsOH at 50 °C for 6 h recovered **2a.**

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer model 983 spectrometer. ^1H NMR spectra were recoreded on a Varian EM-390 (90 MHz), a JEOL GX-500 (500 MHz) or a JEOL GSX-400 instrument (400 MHz), and ^{13}C NMR on a Bruker AM 360 or a JEOL GX-500 or a JEOL GSX-400 spectrometer. Chemical

Table 6. ^{1}H NMR Data of Adducts **5**[a)]

5 or **6**	R^1	R^2	R^3	N-CO_2Et
5a[c)]	2.48 (Me, s)	1.28 (t, J=7.1 Hz), 1.32 (t, J=7.1 Hz), 1.34 (t, J=7.1 Hz), 4.18—4.38 (m) (R^2, R^3, and N-CO_2Et)		
5b[d)]	2.46 (Me, s)	7.82 (ABq, J=8.9 Hz), 8.21	3.77 (OMe, s)	1.30 (t, J=7.0 Hz), 1.33 (t, J=7.0 Hz), 4.22—4.35 (m)
5c[d)]	1.29 (t, J=7.3 Hz), 4.22—4.35 (m)	7.83 (ABq, J=9.2 Hz), 8.21	3.76 (OMe, s)	1.30 (t, J=7.1 Hz), 1.32 (t, J=7.1 Hz), 4.22—4.35 (m)
5d[b)]	1.36 (d, J=6.6 Hz), 3.33 (sep)	7.77 (ABq, J=9.0 Hz), 8.15	3.42 (OMe, s)	1.33 (t, J=7.2 Hz), 4.24 (q, J=7.2 Hz)
5e[b)]	1.43 (s)	7.74 (ABq, J=8.7 Hz), 8.18	3.42 (OMe, s)	1.27 (t, J=7.2 Hz), 1.30 (t, J=7.2 Hz), 4.19 (q, J=7.2 Hz), 4.27 (q, J=7.2 Hz)
5f[c)]	2.41 (s), 7.24 (ABq, J=7.9 Hz), 7.77	7.90 (ABq, J=9.0 Hz), 8.25	3.75 (OMe, s)	1.08 (t, J=7.1 Hz), 1.35 (t, J=7.2 Hz), 4.03—4.48 (m)
5i[b)]	2.38 (Me, s)	1.72 (s)	3.39 (OMe, s)	1.25 (t, J=7.2 Hz), 1.33 (t, J=7.2 Hz), 4.15 (q, J=7.2 Hz), 4.28 (q, J=7.2 Hz)
5l[d)]	2.41 (Me, s)	1.67 (s)	2.13 (s)	1.26 (t, J=7.1 Hz), 1.35 (t, J=7.1 Hz), 4.16—4.35 (m)
5m[d)]	2.51 (Me, s)	7.26—7.78 (m) (R^2 and R^3)		0.98 (t, J=7.1 Hz), 1.32 (t, J=7.1 Hz), 3.90 (q, J=7.1 Hz), 4.30 (q, J=7.1 Hz)
5n[c)]	7.41 (ABq, J=8.8 Hz), 7.81	1.73 (s)	2.12 (s)	1.15 (t, J=7.2 Hz), 1.30 (t, J=7.2 Hz), 4.16—4.29 (m)
6a[b)]	2.00 (Me, s)	8.26 (ABq, J=2.3 Hz), 8.32	3.50, 3.59, 3.65 (each s, each OMe), 3.56 (d, CH, J=10.3 Hz), 3.67 (d, CH, J=10.3 Hz)	
6b[b)]	2.15 (Me, s)	8.17 (ABq, J=2.3 Hz), 8.34	3.50, 3.69, 3.77 (each s, each OMe), 3.01 (d, CH, J=9.1 Hz), 3.18 (d, CH, J=9.1 Hz)	

a) Chemical shifts (δ/ppm) and coupling constants were listed. b) 90 MHz. c) 400 MHz. d) 500 MHz.

Table 7. ^{13}C NMR Data of Adducts **5**[a)]

Adduct	C-3	C-5	C$\underline{O}$$R^3$
5a	158.33	91.57	165.28
5b	157.12	93.51	167.49
5c	161.53	93.50	167.59
5f	159.56	93.23	167.32
5l	156.23	93.15	200.46
5m	156.32	97.41	192.07
5n	158.04	92.81	199.78

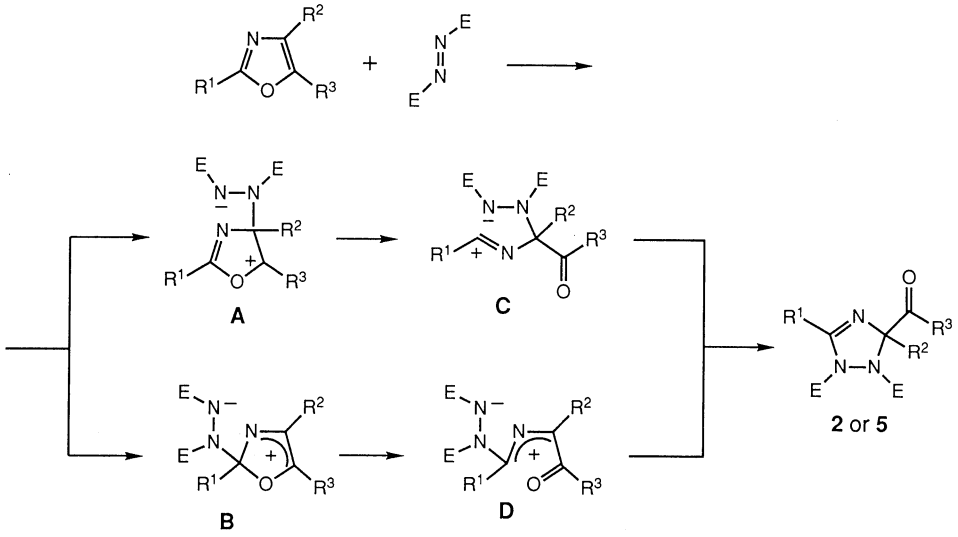
a) Shown in ppm.

shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL JMS-DX303 mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-3. For preparative column chromatography, Wakogel C-300 and Silica gel 60 (Merck) were employed. Medium pressure liquid chromatography was carried out on a Yamazen No. 540 pump using a column packed with Silica gel 60 (Merck, size: 0.040—0.063 mm). Solvents were evaporated with a Tokyo Rikakikai rotary evaporator at about 40°C.

Materials and Solvents. All 2-alkyl-5-methoxy-4-(*p*-nitrophenyl)oxazoles (**1b**—**1h**) and 5-(*p*-methoxyphenyl)-2-methyloxazole (**1k**) were prepared by the BF_3-catalyzed reaction of methyl *p*-nitrophenyldiazoacetate and 4′-methoxy-α-diazoacetophenone with the corresponding nitriles.[15] Ethyl 5-ethoxy-2-methyloxazole-4-carboxylate (**1a**) and 2-alkyl-5-methoxy-4-methyloxazoles (**1i** and **1j**) were synthesized by the dehydrocyclization of diethyl 2-acetylaminomalonate and *N*-acylalanine methyl ester using P_2O_5 in chloroform solution.[16] Commercially available 2,4,5-trimethyloxazole (**1l**) and DEAD were used without further purification. 2-Methyl-4,5-diphenyloxazole (**1m**)[17] and PTAD[18] were prepared according to the reported method.

Acetonitrile was purified by distillation first from P_2O_5 and then from CaH_2, and kept over molecular sieves type 4A.

General Procedure of the Reaction of Oxazole 1 with PTAD. To a solution of oxazole **1** (1.0 mmol) in dry acetonitrile (10 ml) was added PTAD (1.0 mmol) and the mixture was stirred at room temperature for a few seconds until deep carmine red of PTAD faded. After evaporation of acetonitrile in vacuo, the residue was separated by medium



Scheme 4.

pressure column chromatography on silica gel by using benzene-hexane as an eluent to give 1,2,4-triazol-3-ine **2**. Products were characterized by elemental analysis and IR, ^{1}H NMR (Table 2), and ^{13}C NMR spectra.

2a: Colorless oil; IR (neat) 1743 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=13.91 (Me of OEt×2), 14.36 (3-Me), 63.86 (CH_2 of OEt×2), 91.65 (C-5), 126.29, 129.12, 129.39, 130.51 (each Ph), 147.98 (C-3), 152.27, 155.19 (each imide C=O), and 163.68 (ester C=O×2).

2b: Colorless needles (benzene-hexane); mp 166—167 °C; IR (KBr) 1735 (C=O) cm^{-1}. Found: C, 55.74; H, 3.69; N, 16.78%. Calcd for $C_{19}H_{15}N_5O_6$: C, 55.75; H, 3.69; N, 17.11%.

2c: Colorless needles (benzene-hexane); mp 174—175 °C; IR (KBr) 1726 (C=O) cm^{-1}. Found: C, 56.93; H, 4.09; N, 16.38%. Calcd for $C_{20}H_{17}N_5O_6$: C, 56.74; H, 4.05; N, 16.54%.

2d: Colorless needles (benzene-hexane); mp 159—160.5 °C; IR (KBr) 1737 cm^{-1}. Found: C, 57.88; H, 4.45; N, 15.79%. Calcd for $C_{21}H_{19}N_5O_6$: C, 57.66; H, 4.38; N, 16.01%.

2e: Colorless needles (benzene-hexane); mp 198—201 °C; IR (KBr) 1735 cm^{-1}. Found: C, 59.07; H, 4.68; N, 15.33%. Calcd for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69; N, 15.53%.

2f: Colorless needles (benzene-hexane); mp 207—208 °C; IR (KBr) 1735 cm^{-1}. Found: C, 61.99; H, 4.01; N, 14.27%. Calcd for $C_{25}H_{19}N_5O_6$: C, 61.85; H, 3.94; N, 14.43%.

2g: Colorless needles (benzene-hexane); mp 97—99 °C; IR (KBr) 1736 cm^{-1}. Found: C, 60.08; H, 3.98; N, 13.34%. Calcd for $C_{25}H_{19}N_5O_7$: C, 59.88; H, 3.82; N, 13.97%.

2h: Colorless needles (benzene-hexane); mp 97—98 °C; IR (KBr) 1735 cm^{-1}. Found: C, 61.20; H, 3.75; N, 14.74%. Calcd for $C_{24}H_{17}N_5O_6$: C, 61.15; H, 3.63; N, 14.86%.

2i: Colorless oil; ^{13}C NMR ($CDCl_3$) δ=21.75, 23.48 (each Me), 53.69 (OMe), 90.47 (C-5), 122.15, 126.04, 128.89, 129.13, 129.27, 130.45, 130.88, 144.35 (C-1 and *o*-, *m*-, *p*-C of Ar), 148.25 (C-3), 153.64, 153.92 (each imide C=O), and 167.45 ($\underline{C}O_2Me$). No satisfactory analytical result was obtained due to the instability of **2i**.

2j: Colorless needles (benzene-hexane); mp 149—150 °C; IR (KBr) 1735 cm^{-1}. Found: C, 63.39; H, 4.78; N, 14.73%. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.49; H, 4.79; N, 14.81%.

2k: Colorless needles (benzene-hexane); mp 141—145 °C; IR (KBr) 1733 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=14.37 (q, Me), 55.64 (q, OMe), 84.22 (d, C-5), 114.32, 125.99, 128.92, 129.36, 131.99 (each d, *o*-, *m*-, *p*-C of Ph and *o*-, *m*-C of Ar), 126.28, 130.73, 149.35 (each s, 1- or 4-C of Ar), 153.32, 154.18 (each s, each imide C=O), 164.78 (C-3), and 186.87 (C=O). Found: C, 62.62; H, 4.44; N, 15.36%. Calcd for $C_{19}H_{16}N_4O_4$: C, 62.36; H, 4.43; N, 15.38%.

2l: Colorless oil. No satisfactory analytical result was obtained due to the instability of **2l**.

2m: Colorless needles (benzene-hexane); mp 156—158 °C; IR (KBr) 1735 cm^{-1}. Found: C, 70.37; H, 4.56; N, 13.59%. Calcd for $C_{24}H_{18}N_4O_3$: C, 70.23; H, 4.42; N, 13.65%.

General procedure of the Reaction of Oxazole 1 with DEAD. As a typical procedure, the reaction of **1b** with DEAD is described below. To a solution of oxazole **1b** (0.234 g, 1.0 mmol) in dry acetonitrile (5 ml) was added a solution of DEAD (0.174 g, 1.0 mmol) in dry acetonitrile (5 ml). The mixture was stirred for 63 h at room temperature under nitrogen. After the evaporation of acetonitrile in vacuo, the residue was chromatographed over silica gel using hexane-ethyl acetate (4 : 1 vol/vol) to give **5b** (0.377 g, 92%) and **1b** (0.012 g, 5%).

The same procedure employing **1a—1f, 1i,** and **1l—1n** at the conditions listed in the Table 5 gave **5a—5f,5i,** and **5l—5n**.

5a: Colorless prisms (diethyl ether-hexane); mp 53.5—55.5 °C; IR (KBr) 1758, 1743 (C=O), and 1646 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=13.94, 14.17, 14.45 (each q, Me of OEt), 17.02 (q, 3-Me), 62.96, 63.14, 64.04 (each t, CH_2 of OEt), 91.57 (s, C-5), 150.82, 154.52 (each s, $\underline{C}O_2Et$), 158.33 (s, C-3), and 165.28 (s, 5-$\underline{C}O_2Et$×2); MS (FAB) 374 (M+H). Found: C, 47.92; H, 6.16; N, 11.39%. Calcd for $C_{15}H_{23}N_3O_8$: C, 48.25; H, 6.21; N, 11.25%.

5b: Colorless needles (benzene-hexane); mp 112—113.5 °C; IR (KBr) 1741, 1719 (C=O), and 1647 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=14.18, 14.30 (each q, Me of OEt), 17.01 (q, 3-Me), 53.73 (q, OMe), 63.61, 64.12 (each t, CH_2 of OEt), 93.51 (s, C-5), 123.17, 128.52 (each d, *o*, *m*-C of Ar), 144.70 (s, C-4 of Ar), 148.07 (s, C-1 of Ar), 150.90 (t, $^3J_{C-H}$=3.1 Hz, $\underline{C}O_2Et$), 155.15 (t, $^3J_{C-H}$=3.1 Hz, $\underline{C}O_2Et$), 157.12 (q, $^2J_{C-H}$=7.5 Hz,C-3), and 167.49 (s, $\underline{C}O_2Me$); MS (FAB) 485

(M+H). Found: C, 49.84; H, 4.93; N, 13.64%. Calcd for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72%.

5c: Colorless prisms (benzene–hexane); mp 113—116°C; IR (KBr) 1753, 1736 (C=O), and 1646 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=10.49 (q, Me of Et), 14.18, 14.32 (each q, Me of OEt), 23.81 (t, CH_2 of Et), 53.68 (q, OMe), 63.53, 64.00 (each t, CH_2 of OEt), 93.50 (s, C-5), 123.16, 128.56 (each d, *o*-, *m*-C of Ar), 144.96 (s, C-4 of Ar), 148.11 (s, C-1 of Ar), 151.09 (t, $^3J_{C-H}$=3.2 Hz, $\underline{C}O_2Et$), 155.22 (t, $^3J_{C-H}$=3.2 Hz, $\underline{C}O_2Et$), 161.53 (s, C-3), 167.59 (q, $^3J_{C-H}$=3.7 Hz, $\underline{C}O_2Me$). Found: C, 51.03; H, 5.26; N, 13.15%. Calcd for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.26%.

5d: Colorless prisms (benzene–hexane); mp 135—137°C; IR (KBr) 1750 (C=O) and 1645 cm^{-1}. Found: C, 52.06; H, 5.52; N, 12.69%. Calcd for $C_{19}H_{24}N_4O_8$: C, 52.29; H, 5.54; N, 12.84%.

5e: Colorless prisms (benzene–hexane); mp 105—106°C; IR (KBr) 1762, 1749, 1718 (C=O), and 1637 (C=N) cm^{-1}. Found: C, 53.31; H, 5.76; N, 12.37%. Calcd for $C_{20}H_{26}N_4O_8$: C, 53.33; H, 5.82; N, 12.44%.

5f: Colorless cotton like needles (benzene–hexane); mp 162—163°C; IR (KBr) 1761, 1744 (C=O), and 1627 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=13.85, 14.42 (each q, Me of OEt), 21.70 (q, Me of *p*-tolyl). 53.74 (q, OMe), 63.52, 64.13 (each t, CH_2 of OEt), 93.23 (s, C-5), 123.29, 128.57, 128.67, 130.19 (each d, *o*-, *m*-C of Ar), 125.13 (s, C-1 of *p*-tolyl), 143.11 (s, C-4 of *p*-tolyl), 144.55 (s, C-4 of Ar), 148.17 (s, C-1 of Ar), 152.35, 154.81 (each s, $\underline{C}O_2Et$), 159.56 (s, C-3), and 167.32 (s, $\underline{C}O_2Me$); MS (FAB) 485 (M+H). Found: C, 57.05; H, 5.05; N, 11.55%. Calcd for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.99; N, 11.56%.

5i: Colorless viscous oil; IR (neat) 1750 (C=O) and 1648 (C=N) cm^{-1}. Found: C, 47.36; H, 6.32; N, 13.74%. Calcd for $C_{12}H_{19}N_3O_8$: C, 47.84; H, 6.36; N, 13.95%.

5l: Pale yellow viscous oil; IR (neat) 1735 (C=O) and 1647 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=14.20, 14.22 (each Me of OEt), 17.04 (3-Me), 22.29 (5-Me), 23.97 (CO$\underline{Me}$), 62.82, 63.93 (each CH_2 of OEt), 93.15 (C-5), 151.51, 154.48 (each $\underline{C}O_2Et$), 156.23 (C-3), and 200.46 ($\underline{C}$OMe). No satisfactory analytical result was obtained due to the instability of **5l**.

5m: Colorless viscous oil: IR (neat) 1735 (C=O) and 1641 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=13.80, 14.19 (each Me of OEt), 17.10 (3-Me), 62.79, 63.79 (each CH_2 of OEt), 97.41 (C-5), 127.94, 128.04, 128.07, 128.78, 130.15, 132.67, 134.53, 138.16 (each C-Ph), 151.07, 155.52 (each $\underline{C}O_2Et$), 156.32 (C-3), and 192.07 ($\underline{C}$OPh). No satisfactory analytical result was obtained due to the instability of **5m**.

5n: Colorless viscous oil; IR (neat) 1737, 1709 (C=O), and 1628 (C=N) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ=13.09, 14.33 (each q, Me of OEt), 21.37 (q, 5-Me), 23.83 (q, CO$\underline{Me}$), 62.88, 64.23 (each t, CH_2 of OEt), 92.81 (s, C-5), 127.05 ($\underline{C}$-4 of Ar), 138.33 ($\underline{C}$-1 of Ar), 128.29, 131.27 (each d, *o*-, *m*-C of Ar), 152.91, 153.57 (each s, $\underline{C}O_2Et$), 158.04 (s, C-3), and 199.78 (s, $\underline{C}$OMe); MS (FAB) 382 (M+H). Found: C, 53.14; H, 5.36; 10.86%. Calcd for $C_{17}H_{20}N_3O_5Cl$: C, 53.48; H, 5.28; N, 11.01%.

Hydrolysis of 2a. To a solution of **2a** in acetone was added equimolar amount of water. The mixture was allowed to stand for 24 h to give **7** in a quantitative yield after evaporation of solvent in vacuo.

7: Colorless prisms; mp 159—161°C; IR (KBr) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32 (6H, t, J=7.5 Hz, Me of OEt), 2.09 (3H, s, COMe), 4.36 (4H, q, J=7.5 Hz, CH_2 of OEt), 5.27 (1H, s, NH), and 7.27—7.57 (5H, m, Ar-H). Found: C, 51.94; H, 5.06; N, 14.29%. Calcd for $C_{17}H_{20}N_4O_7$: C, 52.04; H, 5.14; N, 14.28%.

The authors are grateful to Mr. Hiroshi Moriguchi, Faculty of Engineering, Osaka University for obtaining mass spectra.

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