Formation and Reaction of Oxazoles through Acyl-substituted Nitrile Ylide

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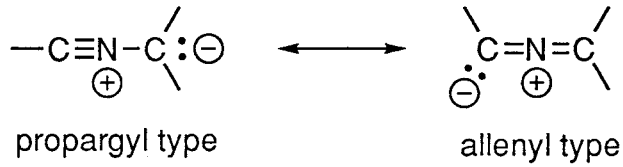
Contents

Chapter 1. General Introduction

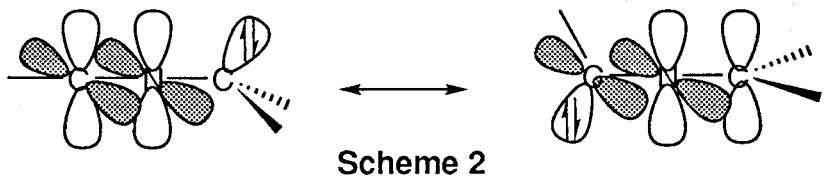
1-1 Nitrile Ylide[1)]

Nitrile ylide was first introduced by R. Huisgen in 1961 as one of the members of 1,3-dipole, during the development of general principle and concept of the 1,3-dipolar cycloaddition.[2)] It consists of C-N-C framework with six π electrons, and belongs to propargyl-allenyl type 1,3-dipole, which is represented by resonance of two main canonical structures shown in Scheme 1. The central nitrogen atom has a digonal *sp* hybridized orbital and a formal positive charge. A negative formal charge is distributed on both carbon termini.



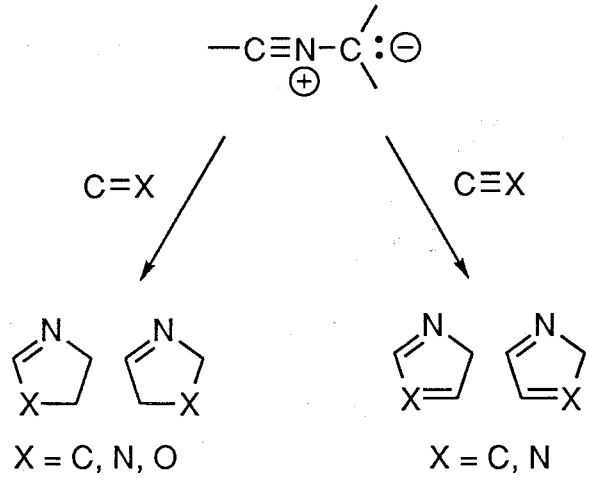
Scheme 1

The six π electrons of nitrile ylide is devided into the orthogonal two π systems, that is horizontal 2π system and vertical 4π system. The latter plays a main role in 1,3-dipolar cycloaddition, which is one of the most important reactions of nitrile ylide, in thermally allowed [4π + 2π] manner.



Scheme 2

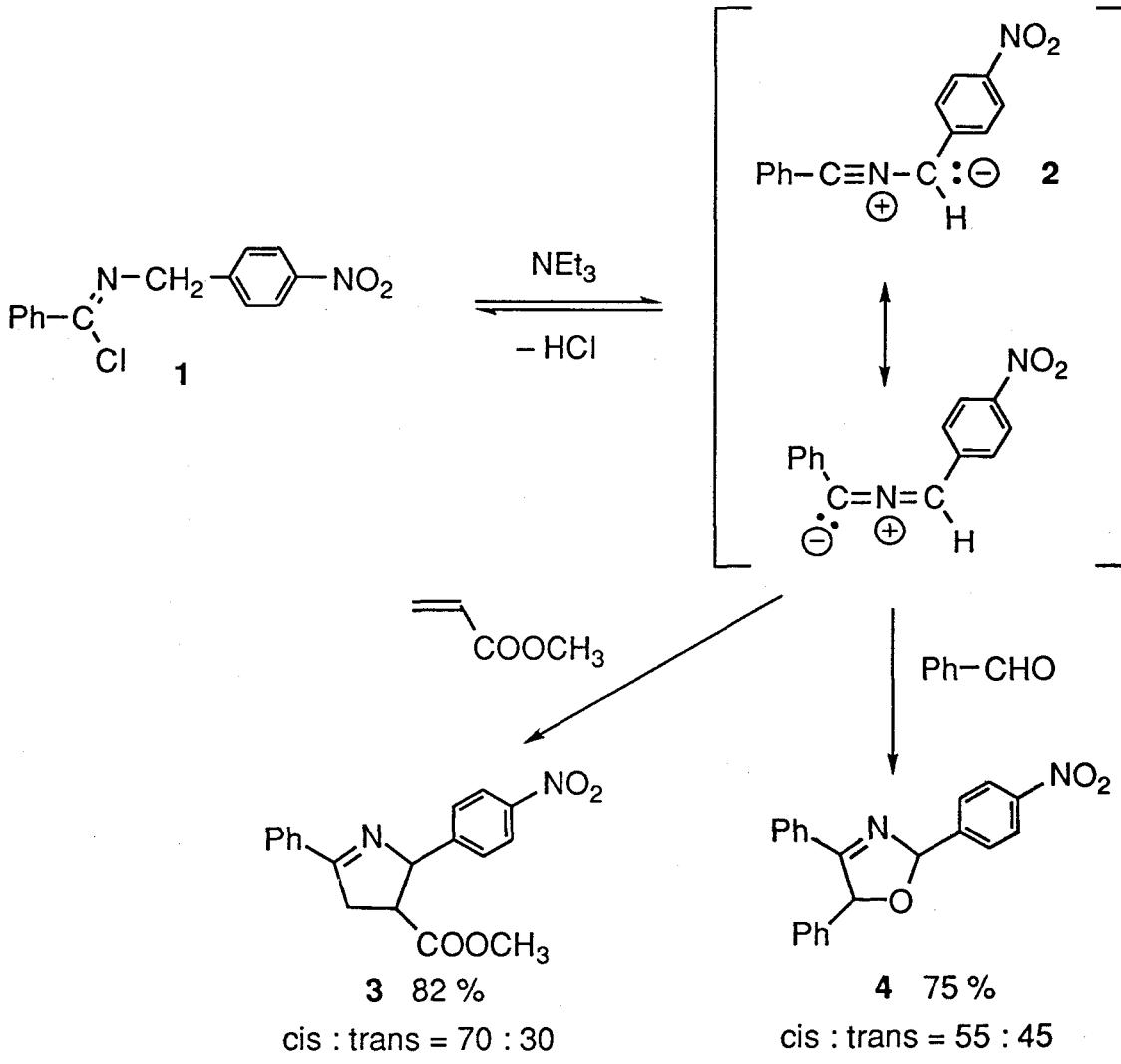
From the synthetic point of view, nitrile ylide is a versatile species for the construction of five-membered heterocycles containing C=N moiety.



Scheme 3

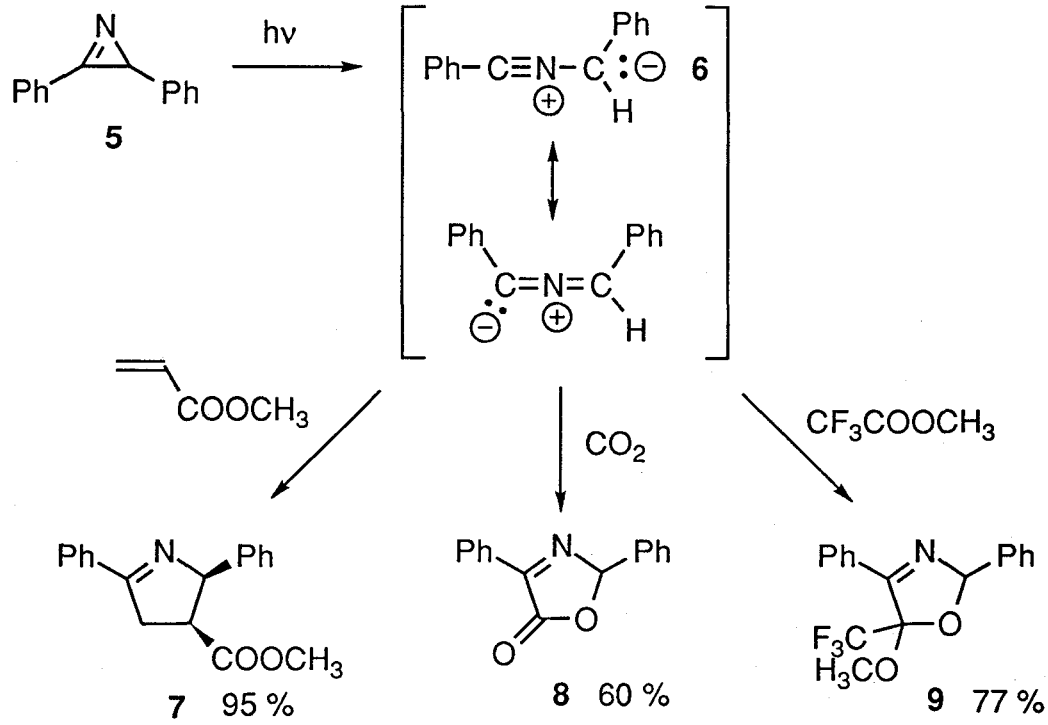
The 1,3-dipolar cycloaddition of nitrile ylide with C=X double bond gives pyrroline, imidazoline, or oxazoline, and also gives pyrrole or imidazole (so called *azoles*) in the reaction with C≡X triple bond as shown in Scheme 3.

The first access to nitrile ylide was demonstrated by HCl elimination from imidoyl chloride **1**. On the treatment of **1** with triethylamine in benzene at room temperature, the precipitation of triethylamine hydrochloride and the transient appearance of deep violet color were observed, which suggests the liberation of nitrile ylide intermediate. The generation of nitrile ylide was comfirmed by the 1,3-dipolar cycloaddition with methyl acrylate and benzaldehyde. The reactions gave the corresponding adducts, 1-pyrroline **3** and 3-oxazoline **4**, in high yields (Scheme 4).[3)]



Scheme 4

Further general and important method is photo-induced electrocyclic ring opening of 2*H*-azirines reported independently by A. Padwa's group[4] and H. Schmid's group[5] in early 1970's. This method offers a convenient access to wide range of substituted nitrile ylide, which has brought much prosperity in both synthetic and mechanistic researches in this area.

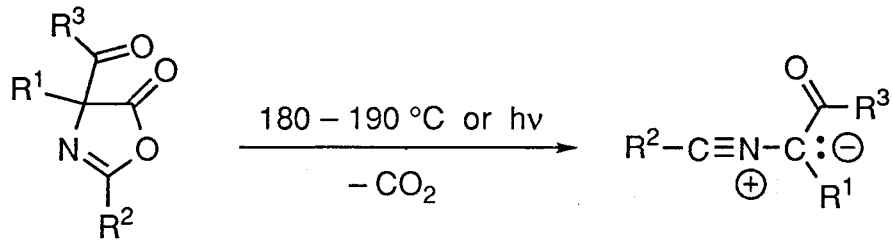


Scheme 5

Irradiation of **5** gives rise to nitrile ylide intermediate **6**, and in the presence of methyl acrylate, **6** affords cycloadduct **7** in high yield with high *cis*-selectivity. **6** can also be intercepted with carbon dioxide which is considered as less activated dipolarophile, and with carbonyl compounds such as methyl trifluoroacetate (Scheme 5).[6]

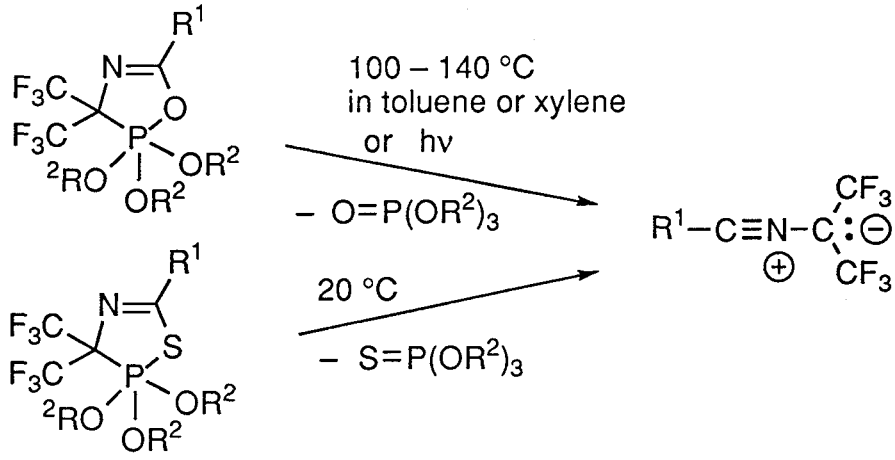
The other thermal and photochemical approaches to the nitrile ylide are listed below.[1]

(1) Carbon Dioxide Extrusion from Oxazolin-5-ones



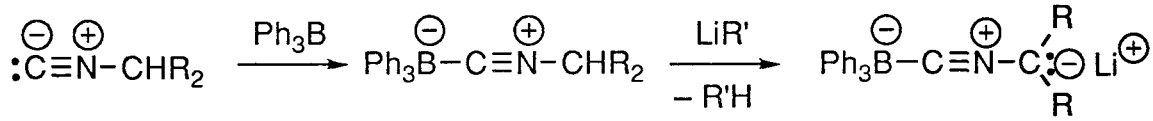
Scheme 6

(2) Alkyl Phosphate and Thiophosphate Extrusion from 2,3–Dihydro–1,4,2λ^5–oxazaphospholes and –thiazaphospholes



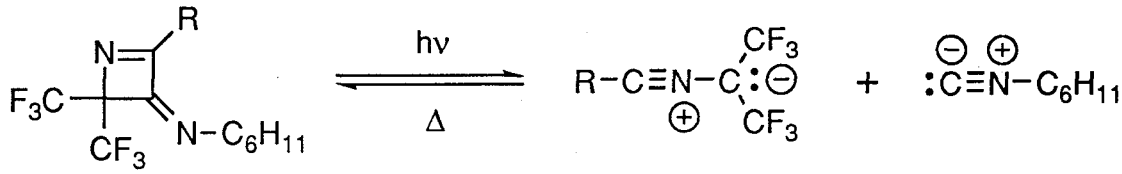
Scheme 7

(3) Addition of Triphenylborane to Isocyanides followed by Deprotonation



Scheme 8

(4) Isocyanide Extrusion from 3–Imino–1–azetines

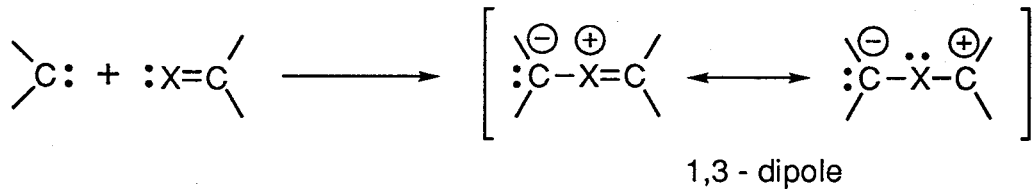


Scheme 9

Additionally, we have two other methods to generate nitrile ylide. One is the reaction of carbene with nitrile discovered in early 1980's. This is the most useful choice to get access to nitrile ylide as well as ring opening of 2*H*-azirines. The other one is the thermal ring opening of oxazole to give carbonyl substituted nitrile ylide. Although this reaction is known as the key step of the Cornforth rearrangement since 1949, it has little synthetic advantage, because recyclization affording rearranged oxazole is faster than the capture of the nitrile ylide intermediate with any dipolarophiles. These two methods will be explained in detail in the following sections in this chapter.

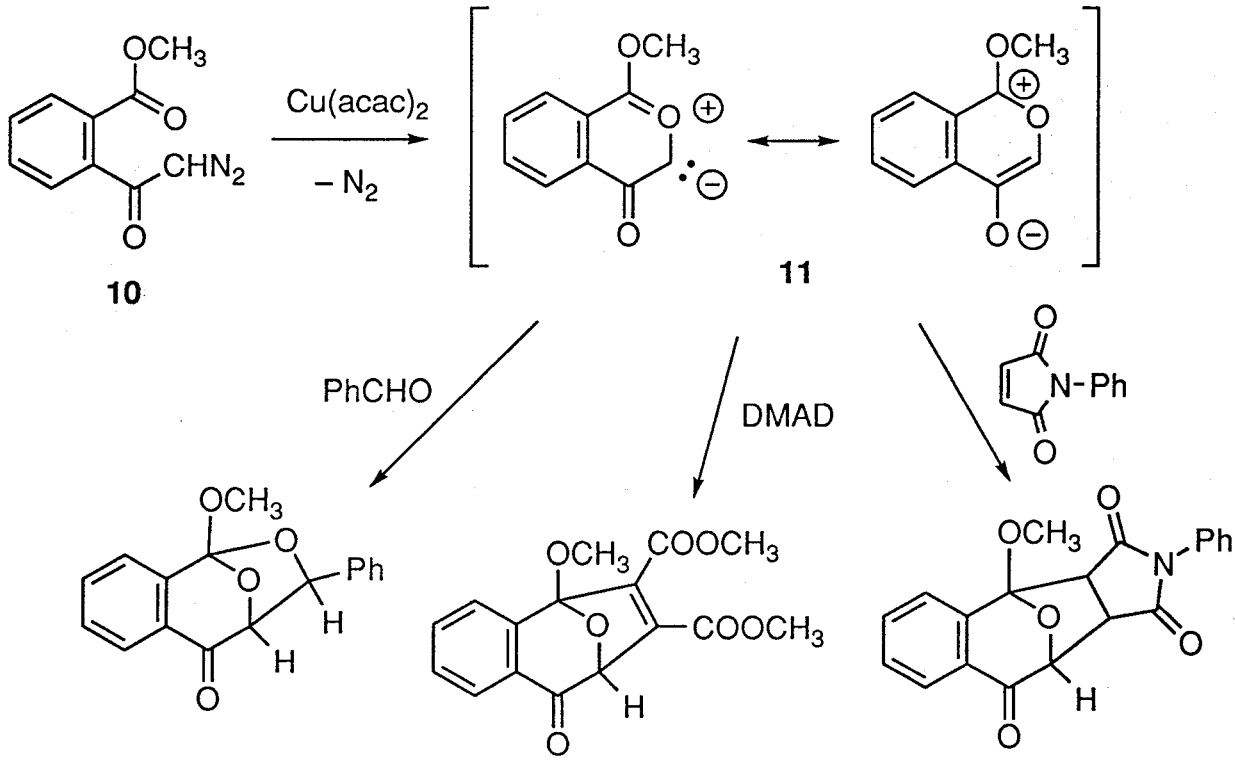
1-2 Carbene-Nitrile Reaction

The ylide formation of carbene or carbenoid by the electrophilic attack on unshared electrons of hetero-multiple bond has been considered as one of the most important methods of the generation of 1,3-diople in these decades.[7)]



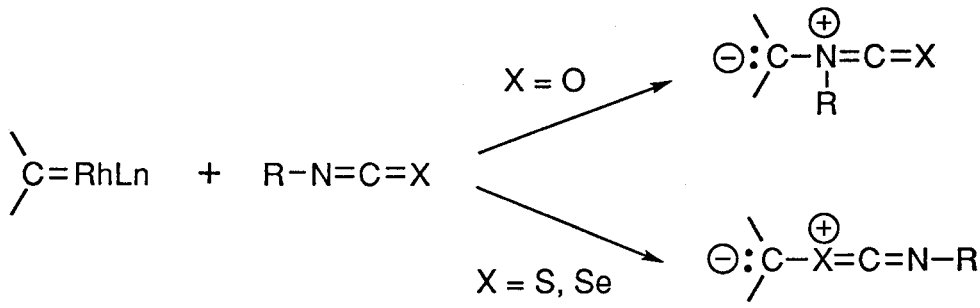
Scheme 10

Usually, copper or rhodium mediated generation of carbenoid from diazo compounds is considered the best choice, since a wide variety of substituent is available in this method. For example, Ibata et al. demonstrated the intramolecular carbonyl ylide formation by catalytic decomposition of *o*-methoxycarbonyl-α-diazoacetophenone (**10**) followed by the 1,3-dipolar cycloadditions with ethylenic, acetylenic and carbonyl compounds.[8)]



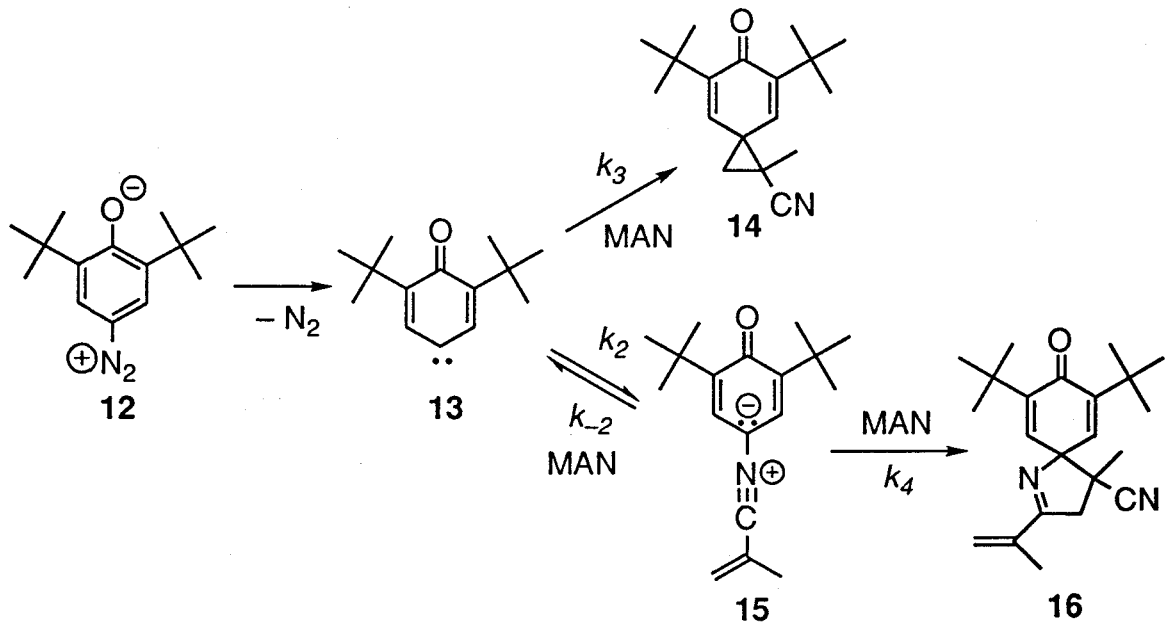
Scheme 11

Nakano et al.[9)] and Himori[10)] performed $Rh_2(OAc)_4$-catalyzed decomposition of α-diazocarbonyl compounds in the presence of hetero cummulenes such as isocyanates, isothiocyanates, and isoselenocyanates, in order to compare their reactivity and site selectivity of ylide formation.



Scheme 12

The formation of nitrile ylide by the carbene-nitrile reaction is first suggested by A. S. Kende et al. in 1982.[11] In the thermolysis of *p*-diazo oxide **12** in methacrylonitrile (MAN), they obtained spiro-dienone **14** together with 1:2-adduct (**16**) produced from carbene and MAN.

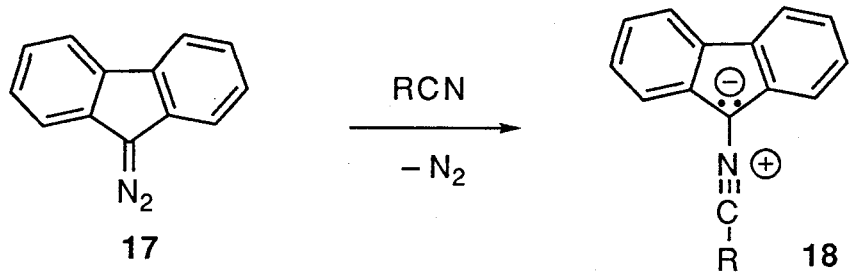


Scheme 13

They found that the molar product ratios ([**14**]/[**16**]) and the inverse of the concentration of MAN (1/[MAN]) gave a linear plot. It is explained by the following kinetic equation assuming reversible formtion of nitrile ylide intermediate **15**.

$$d[\mathbf{14}]/d[\mathbf{16}] = k_3/k_2 + k_{-2}k_3/k_2k_4 \cdot (1/[MAN])$$

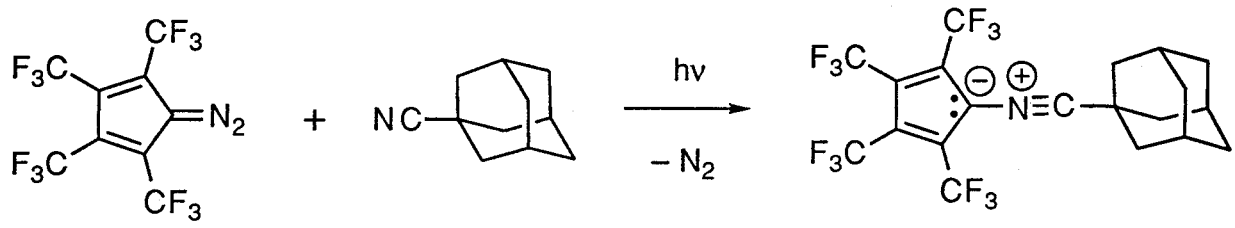
J. C. Scaiano's group[12] and Schuster's group[13] independently observed a transient absorption in 400 nm region in the laser flash photolysis of 9-diazofluorene (**17**) in nitrile, and they assigned the band to nitrile ylide **18**.



17 18

Scheme 14

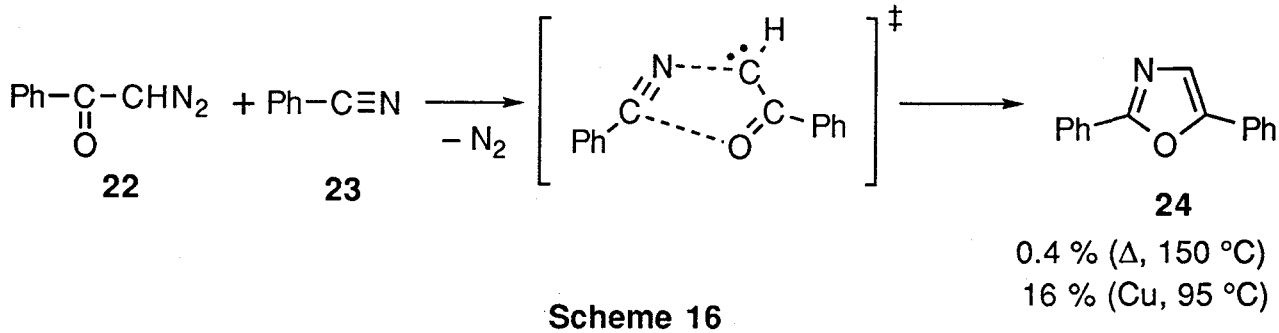
In 1984, A. J. Arduengo, III et al. isolated the nitrile ylide **21** by the irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene (**19**) in the presence of 1-adamantanecarbonitrile (**20**).[14]



19 **20** **21**

Scheme 15

The reaction of ketocarbenoid with nitrile was first demonstrated by R. Huisgen et al. in 1961.[15]



22 **23** **24**

0.4 % (Δ, 150 °C)
16 % (Cu, 95 °C)

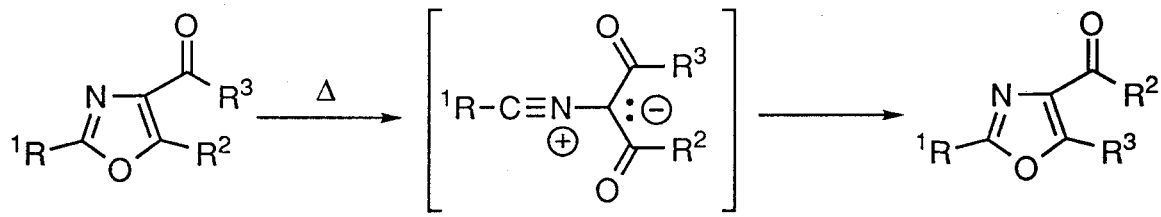
Scheme 16

Although the thermal decomposition of α-diazoacetophenone (**22**) in the presence of benzonitrile (**23**) gave only a trace amount of 2,5-diphenyloxazole (**24**), the yield of **24** increased up to 16 % in the copper catalyzed reaction. They explained this reaction by the 1,3-dipolar cycloaddition of ketocarbene with nitrile.

Nowadays, this reaction is believed to proceed in a stepwise mechanism through nitrile ylide intermediate considering the background described before. However, no experimental evidence concerning the presence of the intermediacy of acyl-substituted nitrile ylide was shown in this reaction.

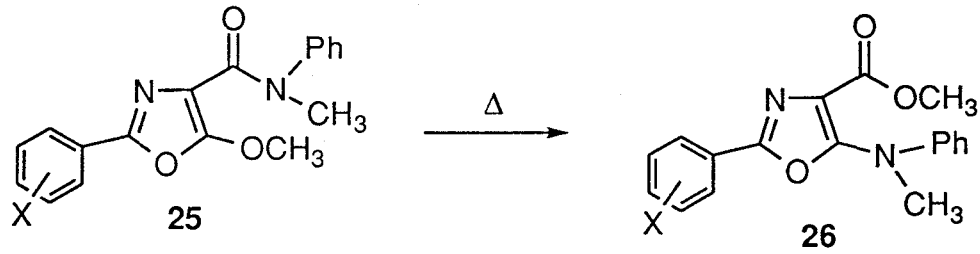
1-3 Ring Opening of Oxazole

The thermal rearrangement of 4-carbonyl substituted oxazole was first observed by Cornforth.[16] The mechanism of this reaction may involve the opening of oxazole ring to generate a nitrile ylide intermediate and subsequent ring closure to give the rearranged oxazole derivative.



Scheme 17

M. J. S. Dewar et al. investigated the mechanism of this reaction from kinetic and theoretical points of view in detail.[17]

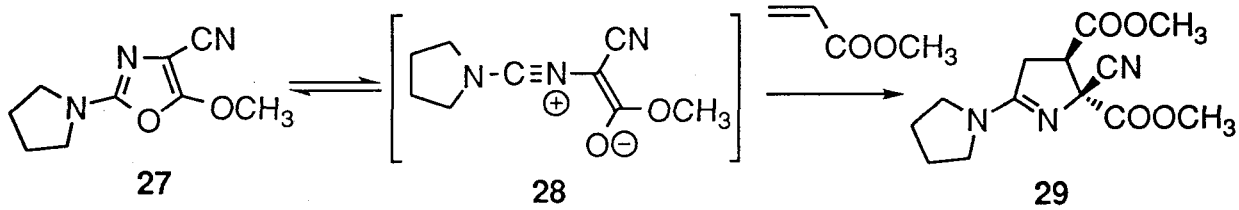


Scheme 18

A plot of log k *vs* σ^+ for the rearrangement of **25** to **26** showed linear relationship (r=0.976) for various substituents (X) with $\rho^+ = -1.16 \pm 0.11$. The negative value of ρ^+ implies that some electron-deficiency develops at 2-position of oxazole ring in the transition state of the reaction. However, the small negative magnitude of ρ^+ implies that no strong positive charge develops at this position in the transition state.

Although these observations do not conflict with nitrile ylide intermediate, they could not trap this intermediate, despite the addition of any dipolarophiles or alcohols in the reaction system.

The sole example of trapping of acyl-substituted nitrile ylide generated by the ring opening of oxazole has been reported by R. W. Saalfrank et al.[18]



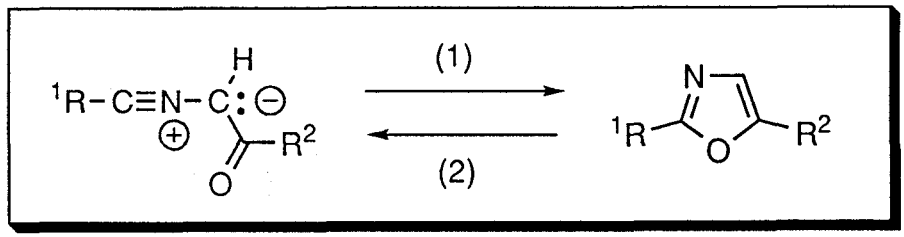
Scheme 19

In this reaction, each of methoxyl group at 5-position and cyano group at 4-position promotes the ring opening of oxazole **27**, and a pirrolidino group at 2-position accelerates both processes of ring opening of **27** and cycloaddition of nitrile ylide **28** with methyl acrylate to give pyrroline derivative **29**.

However, the utility of the ring opening of oxazole is still limited, and there is plenty of room for development in synthetic application.

1-4 Contents of the Thesis

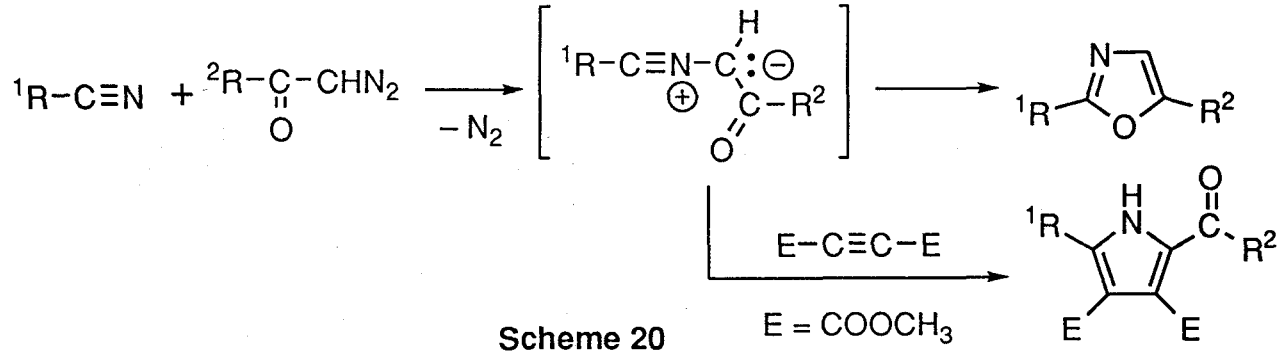
This thesis deals with two subjects: (1) the formation of oxazole by the 1,5-cyclization of acyl-substituted nitrile ylide, and (2) the reaction of oxazole through the intermediacy of acyl-substituted nitrile ylide.



It consists of the following six chapters.

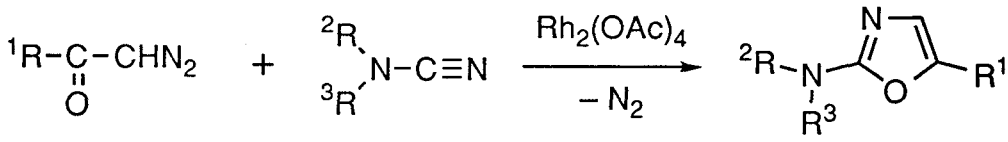
Chapter 1 is general introduction, in which the background of this research work is briefly mentioned.

Chapter 2 describes the successful trap of acyl-substituted nitrile ylide with typical dipolarophiles in the reaction of ketocarbenoid with benzonitrile. The formation of pyrrole derivatives clearly shows the existence of nitrile ylide intermediate in the pathway of oxazole formation from ketocarbene and nitrile.



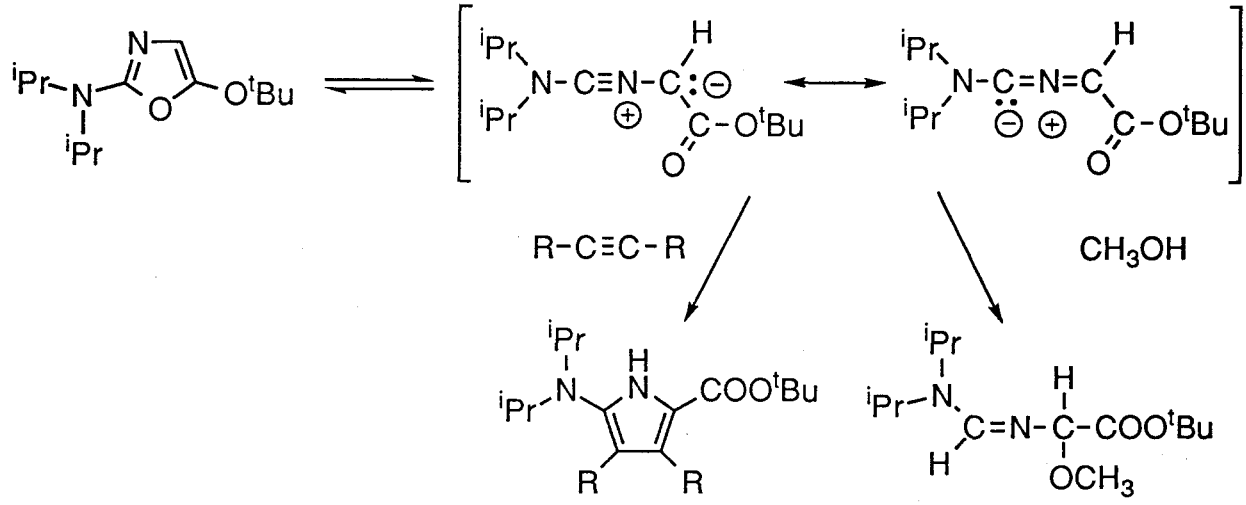
Scheme 20

Chapter 3 describes the application of the rhodium(II) acetate-catalyzed reaction of diazocarbonyl compounds with nitriles. The $Rh_2(OAc)_4$-catalyzed decomposition of α-diazoacetophenones in the presence of substituted cyanamides gave 2-aminooxazoles in high yields. α-Diazoacetates yielded unstable 2-amino-5-alkoxyoxazoles.



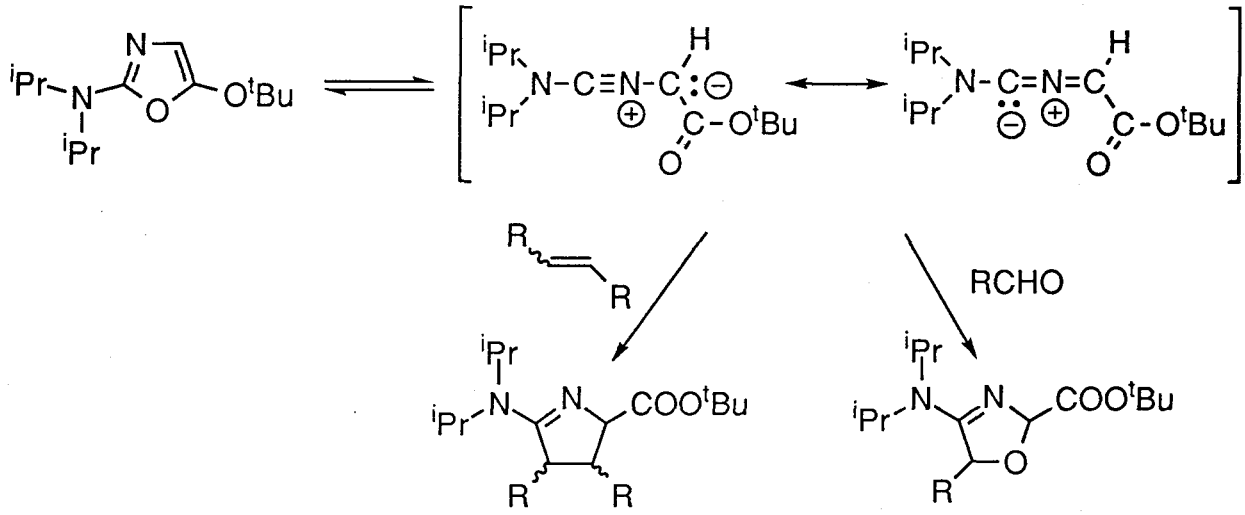
Scheme 21

In chapter 4, the mechanism of the reaction of 2-amino-5-alkoxyoxazole with DMAD to give pyrrole derivatives and the reaction with alcohols through nitrile ylide intermediate is described.



Scheme 22

Chapter 5 describes the 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide, generated by the ring opening of 2-amino-5-alkoxyoxazole, with ethylenic dipolarophiles and aldehydes.



Scheme 23

Chapter 6 is a conclusion of this thesis.

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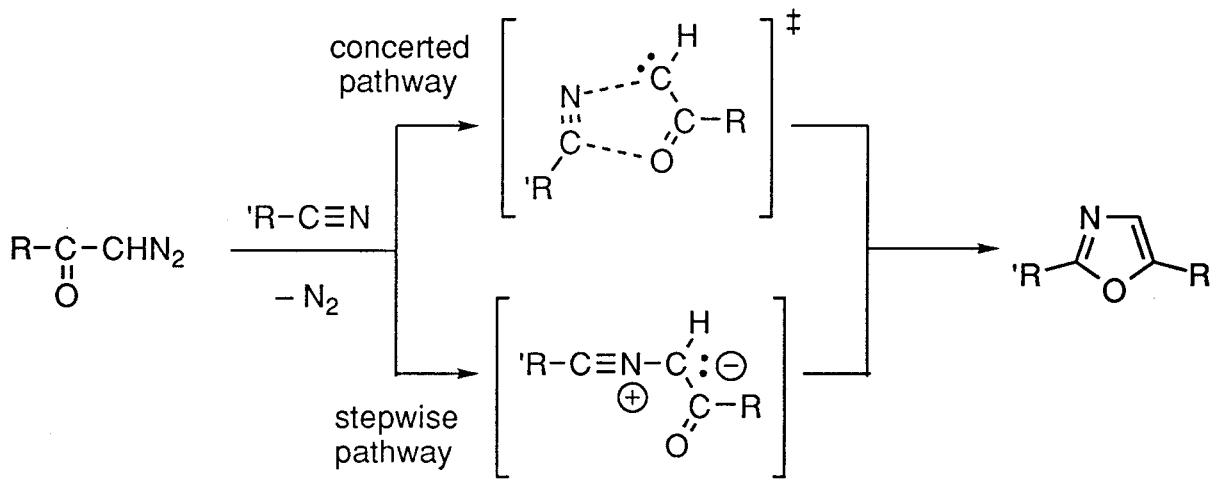
Chapter 2. Formation of Acyl-substituted Nitrile Ylide in the Reaction of Rhodium Carbenoid with Nitriles

2-1 Introduction

The catalytic decomposition of α-diazocarbonyl compounds in nitrile is known as one of the most useful method in oxazole syntheses. As mentioned in chapter 1, R. Huisgen introduced a use of copper catalyst to this oxazole synthesis, and explained the mechanism of the reaction by the 1,3-dipolar cycloaddition of ketocarbene with nitrile (Scheme 1).



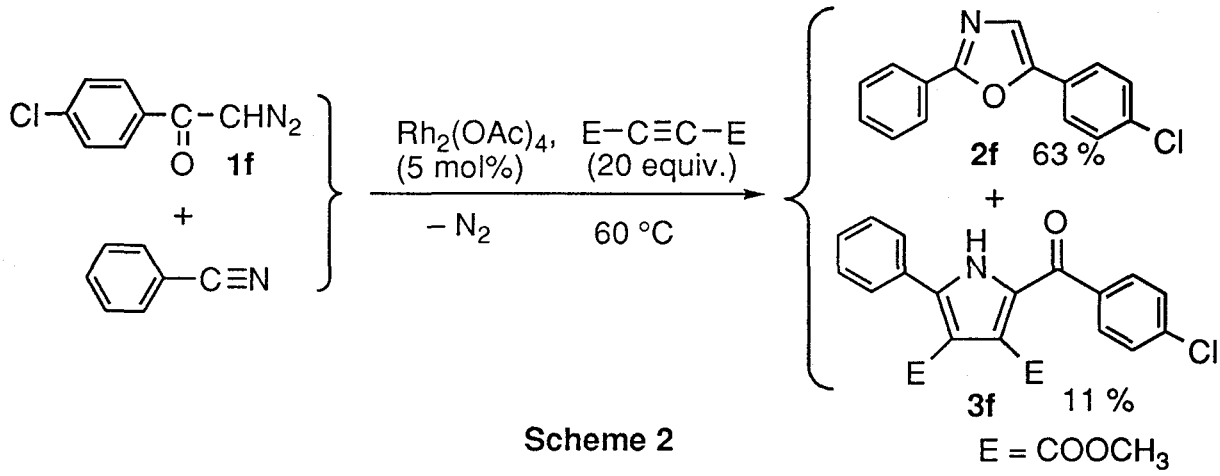
Scheme 1

Since the discovery of the carbene-nitrile reaction to generate nitrile ylide intermediate, the stepwise mechanism including the transient intermediacy of acyl-substituted nitrile ylide has been pointed out in this oxazole synthesis. However, there had been no evidence of the formation of acyl-substituted nitrile ylide by carbene-nitrile reaction, because of its facile 1,5-cyclization to give oxazole derivative.

In order to obtain the evidence of acyl-substituted nitrile ylide intermediate, reactions of ketocarbenoid with nitrile were carried out in the presence of dimethyl acetylenedicarboxylate (DMAD). The reactions gave pyrrole derivatives along with oxazole derivatives. The formation of the pyrrole derivatives supports the stepwise mechanism including nitrile ylide intermediate. In order to know the effect of substituents on the reactivity of the acyl-substituted nitrile ylide, reactions of α-diazoacetates with nitriles and *p*-nitro-α-diazoacetophenone with various cyano compounds were also carried out. In addition, the trapping with unsymmetrical dipolarophile such as methyl propiolate was carried out in order to know the regiochemistry of the reaction.

2-2 $Rh_2(OAc)_4$-catalyzed Decomposition of α-Diazoacetophenones in Benzonitrile in the Presence of DMAD

The catalytic decomposition of *p*-chloro-α-diazoacetophenone (**1f**) in the presence of 20 equivalents of dimethyl acetylenedicarboxylate (DMAD) was carried out in benzonitrile at 60 °C. A rhodium(II) acetate was employed as a catalyst for decomposition of α-diazocarbonyl compound, because the rhodium(II) acetate was reported to give oxazole derivatives in high yield.[1] The reaction gave 5-(*p*-chlorophenyl)-2-phenyloxazole (**2f**) and dimethyl 2-(*p*-chlorobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (**3f**) in 63 and 11 % yields, respectively (Scheme 2).



Scheme 2

The structure of the pyrrole derivative **3f** was determined by the result of elemental analysis and spectroscopic data (Figure 1): ^1H NMR shows two methoxyl groups at 3.44 and 3.73 ppm, and broad N-H signal at 10.09 ppm. IR spectrum shows the presence of N-H group at 3327 cm^{-1}, ester carbonyl group at 1725 cm^{-1}, and keto-carbonyl group at 1621 cm^{-1}. ^{13}C NMR shows three carbonyl carbons at 163.59, 164.90, and 185.19 ppm, and four sp^2 carbons in pyrrole ring at 113.82, 125.06, 128.12, and 140.46 ppm as doublet signals by the coupling with N-H proton.

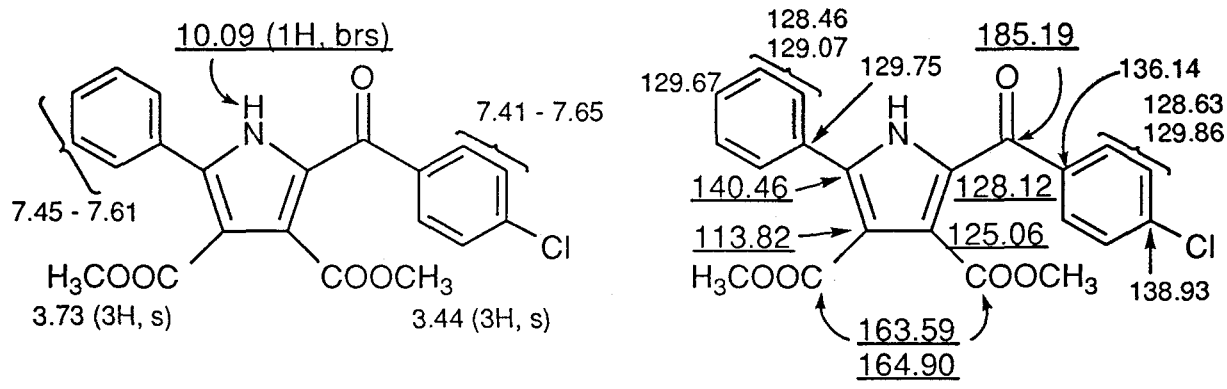


Figure 1. ^1H NMR and ^{13}C NMR of **3f** (δ)

The reaction of *p*-, *m*-, and *o*-substituted α-diazoacetophenones gave the corresponding oxazole derivatives **2** and pyrrole derivatives **3** in the yields listed in Table 1. While electron-withdrawing groups such as *p*-NO_2 and *p*-CN gave **2** and **3** in moderate yields (Runs e-i), electron-releasing substituents *p*-MeO and *p*-Me decrease total yield (**2**+**3**) (Runs a-c). This is attributed to the increased reactivity of α-diazoacetophenone **1** as 1,3-dipoles toward DMAD because of their high electron density due to electron-releasing substituents.

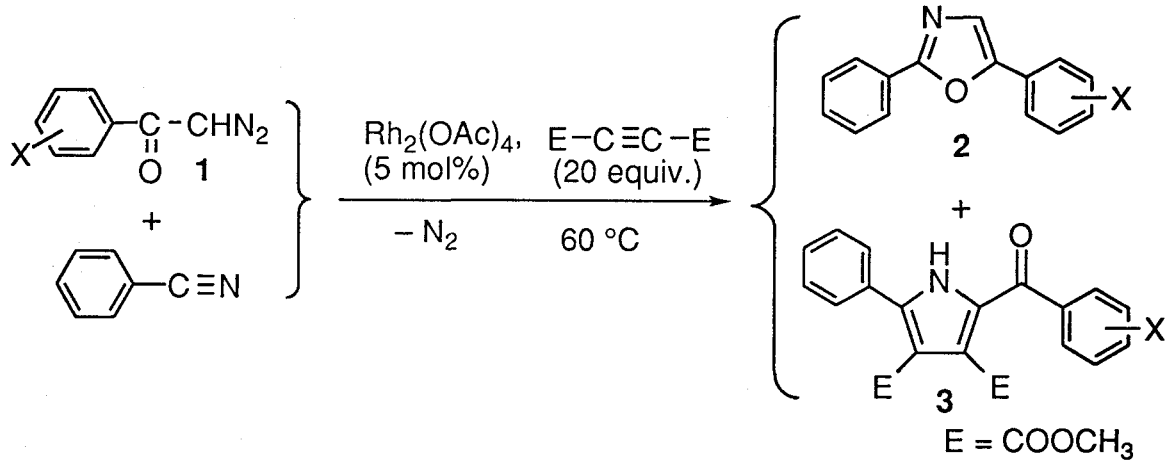
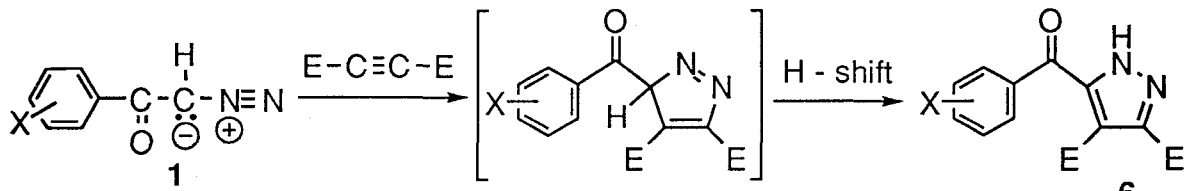


Table 1. Substituent Effect on Yield and Ratio of Oxazole **2** and Pyrrole **3** in $Rh_2(OAc)_4$-catalyzed Reaction of α-Diazoacetophenone with Benzonitrile

Run	X	Yield / %		Total Yield / %	Ratio
		2	**3**	**2 + 3**	**3 / 2+3**
a	*p*-OMe	38.2	5.8	44.0	0.13
b	*m*-Me	32.0	2.0	34.0	0.06
c	*p*-Me	44.6	9.8	54.4	0.18
d	H	50.6	11.0	61.6	0.18
e	*m*-Cl	62.6	15.1	77.7	0.19
f	*p*-Cl	63.0	11.0	74.0	0.15
g	*p*-CN	60.9	9.0	69.9	0.13
h	*m*-NO_2	60.5	12.5	73.0	0.17
i	*p*-NO_2	61.2	18.3	79.5	0.23
j	*o*-Me	3.0	0.0	3.0	0.00
k	*o*-Cl	9.0	1.5	10.5	0.14

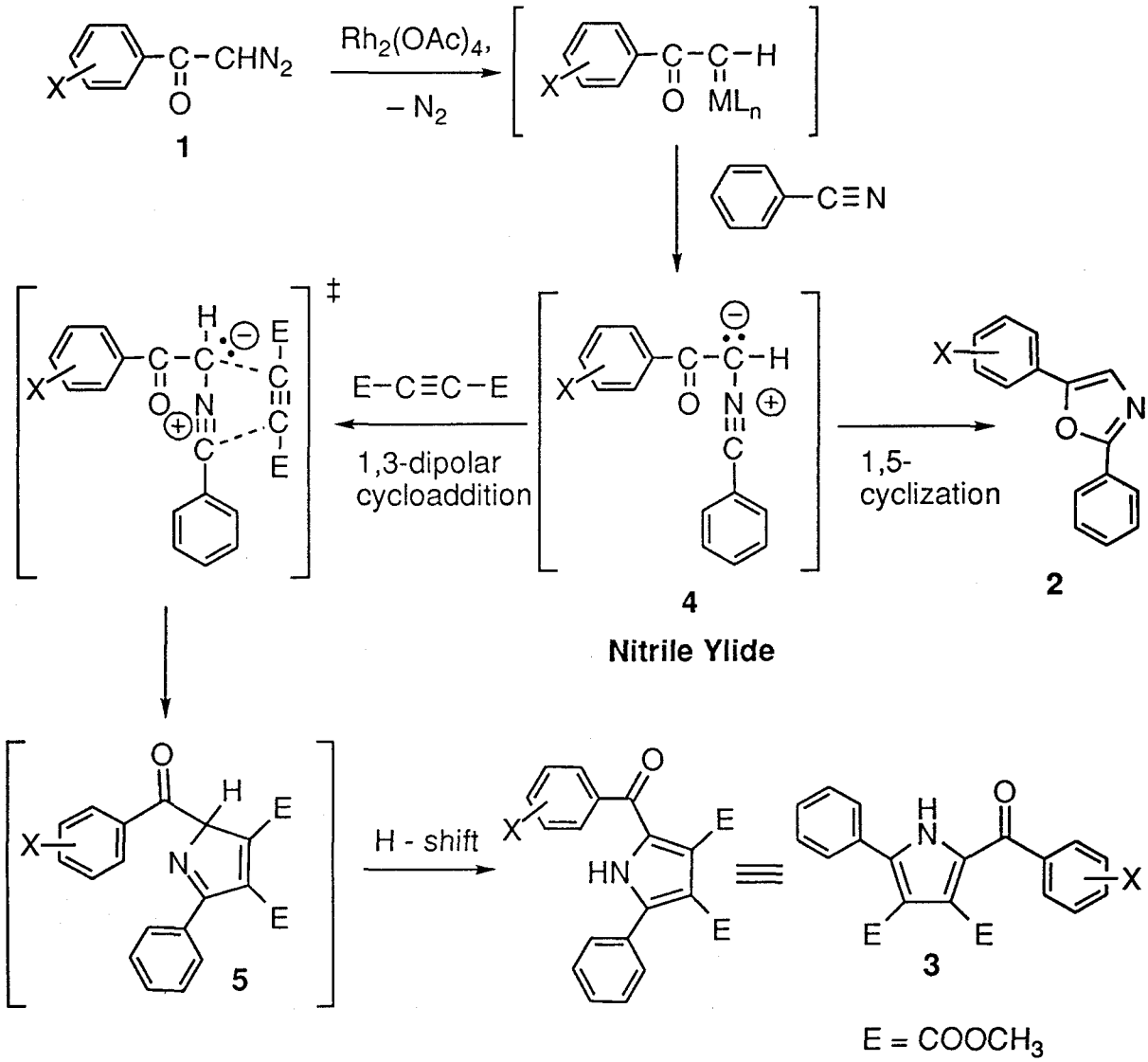
Especially in the cases of **1a** and **1b**, the corresponding pyrazole derivatives **6** were isolated in 25 and 8.9 % yields through 1,3-dipolar cycloaddition of **1** with DMAD followed by 1,5-hydrogen shift (Scheme 3).



Scheme 3

o-Substituted α-diazoacetophenones **1j** and **1k** gave **2** or **3** in low yields, since their substituents at *o*-position hindered the nitrile ylide formation (Runs j and k).

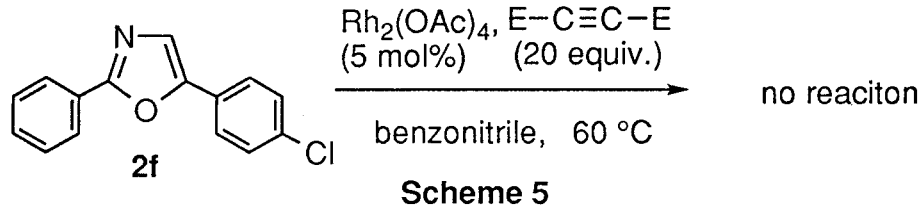
The formation of oxazole **2** and pyrrole **3** is rationalized by the following stepwise mechanism (Scheme 4).



Scheme 4

The rhodium carbenoid generated by catalytic decompositon of α-diazoacetophenone **1** reacts with benzonitrile to form acyl-substituted nitrile ylide intermediate **4**. Intramolecular 1,5-cyclization of **4** gives oxazole **2**. On the other hand, intermolecular 1,3-dipolar cycloaddition of **4** with DMAD gives the corresponding cycloadduct **5** which gives pyrrole derivative **3** by subsequent aromatization through 1,5-hydrogen migration. Therefore, the formation of pyrrole **3** indicates that the formation of oxazole proceeds stepwise and the nitrile ylide **4** exist as an intermediate in the pathway to oxazole **2**. In these two competing processes, however, both electron-releasing and electron-withdrawing substituents on para and meta positions of α-diazoacetophenones do not affect the ratio of the products.

Another possible route to pyrrole derivatives **3** is an abnormal Diels-Alder reaction of oxazole with DMAD. The abnormal Diels-Alder reaction occurs between C2-N3-C4 moiety of oxazole and dienephile to give five-membered heterocycles, which has been observed in the case of reactive oxazoles with reactive dienophiles such as tetracyanoethylene,[2] 4-phenyl 1,2,4-triazole-3,5(4*H*)-dione, diethyl azodicarboxylate,[3] or nitrosobenzene.[4] The reaction of oxazole with carbonyl compounds in the presence of Lewis acids[5] also gave formal [3+2] adduct through abnormal Diels-Alder reaction. In the present case, however, the pathway through the abnormal Diels-Alder reaction is completely excluded by the following control experiment (Scheme 5).



Scheme 5

The reaction of **2f** with DMAD under the same conditions gave no **3f** with quantitative recovery of **2f**. This clearly shows that DMAD does not react with oxazole **2**. Consequently, pyrrole **3** does not formed by the reaction of oxazole **2** with DMAD, but formed by the reaction with nitrile ylide intermediate **4** with DMAD as illustrated in Scheme 4.

Solvent effect on the reactivity of the nitrile ylide intermediate **4f** was studied in the reaction of *p*-chloro-α-diazoacetophenone (**1f**) with benzonitrile using non-polar solvents such as benzene and carbon tetrachloride and various polar solvents (Table 2). Product ratio in runs a-g shows the tendency that the ratio of the formation of pyrrole derivative **3f** increases with the increase of the solvent polarity. This trend is explained by the stabilization of the nitrile ylide intermediate by the polar media. This satabilization reduces the intramolecular 1,5-cyclization to lead oxazole **2f**. Upon attempted reaction in polar solvents such as DMF and DMSO, the color of the $Rh_2(OAc)_4$ changed from green to blue or wine red, respectively, and no oxazole or pyrrole derivative was obtained at all. This is attributed to the deactivation of the catalyst by the coordination of these solvent

molecules to the active site of the catalyst. Thus the generation of carbenoid was retarded in DMF and DMSO.

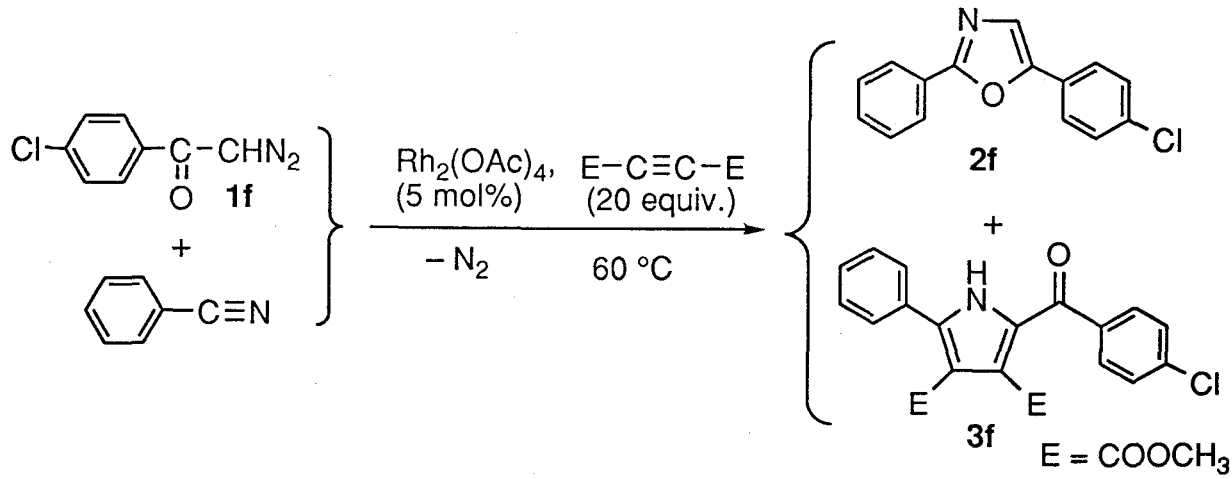


Table 2. Solvent Effect on Yield and Ratio of **2f** and **3f**

Run	Solvent (Dielectric Constant)	Yield / %		Total Yield / %	Ratio
		2f	**3f**	**2f + 3f**	**3f / 2f+3f**
a	CCl_4 (2.24)	48.6	2.4	51.0	0.05
b	C_6H_6 (2.27)	38.3	2.0	40.3	0.05
c	$CHCl_3$ (4.81)	33.6	4.4	38.0	0.12
d	C_6H_5Cl (5.02)	45.4	2.8	48.2	0.06
e	$CH_3COOC_2H_5$ (6.0)	10.8	0.8	11.6	0.07
f	*o*-$Cl_2C_6H_4$ (9.93)	41.3	3.8	45.1	0.08
g	C_6H_5CN (25.20)	63.0	11.0	74.0	0.17
h	THF (7.58)	0.0	3.5	3.5	1.00
i	DMF (36.71)	0.0	0.0	0.0	–
j	DMSO (46.68)	0.0	0.0	0.0	–

2-3 $Rh_2(OAc)_4$-catalyzed Decomposition of α-Diazoacetate in Nitrile in the Presence of DMAD

The results of the reactions of α-diazoacetophenones described in the previous section shows the presence of the acyl-substituted nitrile ylide intermediate. In order to know the effect of the acyl group on the reactivity of nitrile ylide, the reactions of α-diazoacetate were carried out.

Catalytic decomposition of α-diazoacetates (**7**) with $Rh_2(OAc)_4$ in acetonitrile in the presence of DMAD did not give the corresponding oxazole derivatives (**8**), but gave pyrroles **9a-c** in low yields (Table 3, Runs a-c). This may be ascribed to the side-reaction of carbenoid or nitrile ylide with DMAD, since oxazole **8c** was obtained in 80.6 % yield in the absence of DMAD, and **8c** was stable under the reaction conditions.

In order to stabilize the products and the intermediates, the reactions were carried out using benzonitrile as a substrate, and oxazole **8** and pyrrole **9** were obtained in moderate yields (Table 3, Runs d-f).

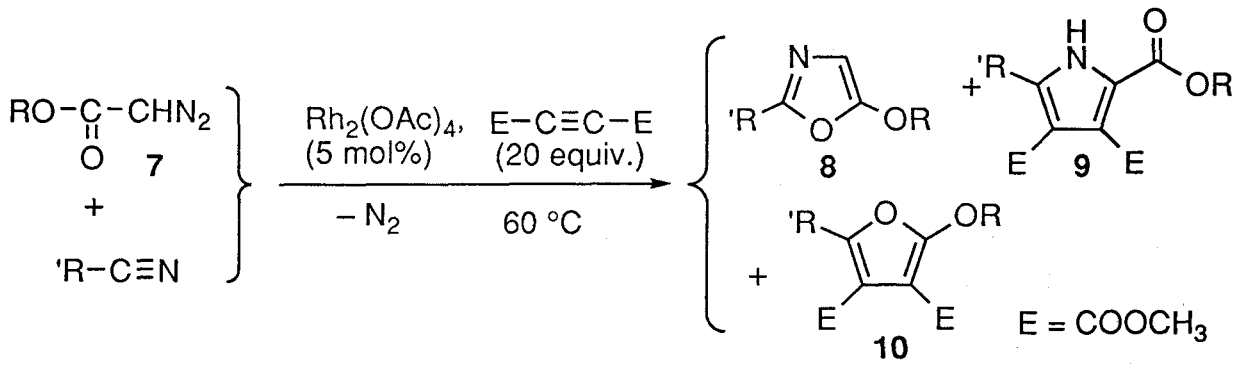


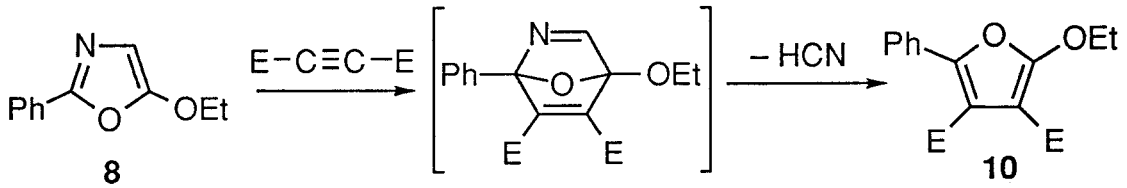
Table 3. $Rh_2(OAc)_4$-catalyzed Reaction of α-Diazoacetates with Nitrile in the Presence of DMAD

Run	R	R'	Yield / %		Total Yield / %	Ratio
			8	**9**	**8 + 9**	**9 / total**
a	Et	Me	–	12.6	12.6	–
b	^{t}Bu	Me	–	7.4	7.4	–
c	*p*-$NO_2C_6H_4$	Me	–	11.9	11.9	–
d*	Et	Ph	4.8	17.8	25.2#	0.71#
e	^{t}Bu	Ph	8.7	11.2	19.9	0.56
f	*p*-$NO_2C_6H_4$	Ph	28.0	13.9	41.9	0.33

* 2.6 % of furan **10** was obtained.
\# including furan **10**.

The reaction of ethyl diazoacetate with benzonitrile in the presence of DMAD gave the corresponding oxazole **8d** and pyrrole **9d** along with

dimethyl 2-ethoxy-5-phenylfuran-3,4-dicarboxylate (**10**). The formation of the products was explained by the mechanism similar to the case of α-diazoacetophenones (Scheme 4). However, oxazole **8d** reacts with electron deficient dienophile in [4+2] manner to give a Diels-Alder adduct because of the activation by ethoxyl group on 5-position. The extrusion of HCN from the adduct of **8d** with DMAD gives furan **10d** (Scheme 6). The bulky *tert*-butyl group hinders the intermolecular reactions decreasing the yield of pyrrole **9e**, but increasing the yield of oxazole **8e** without affording furan derivative (Table 3, Run e).



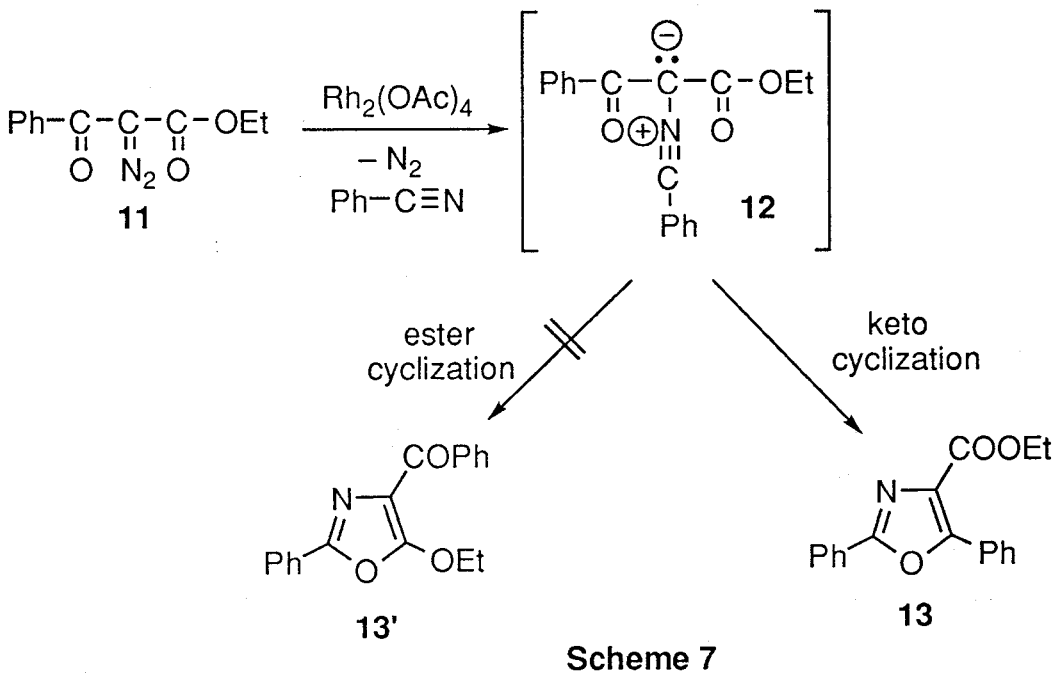
8 **10**

Scheme 6

$E = COOCH_3$

In Runs d-f, ratios of the yield of pyrrole **9** to the total yield of the products (**9**/total = 0.33-0.71) is higher than that of α-diazoacetophenones, in which the highest ratio (0.23) is observed in the reaction of *p*-NO_2-α-diazoacetophenone (Table 2, Run i).

In order to compare the cyclization facility of the keto- and ester carbonyl groups, ethyl diazobenzoylacetate (**11**) was catalytically decomposed under similar conditions in the presence of benzonitrile, and the corresponding oxazole **13** was obtained as a sole cyclization product of nitrile ylide **12** in 6 % yield (Scheme 7).



Scheme 7

An absorption of carbony group at 1724 cm^{-1} in IR spectrum and a signal of carbonyl carbon at 162.32 ppm in ^{13}C NMR spectrum showed the presence of ester group in the product **13**. This indicates that in the nitrile ylide intermediate **12**, keto-carbonyl cyclizes predominantly to give ethyl 2,5-diphenyloxazole-4-carboxylate (**13**) without affording 5-ethoxyoxazole **13'** through the cyclization of ester group. Therefore, this intramolecular competition implies that in ester-substituted nitrile ylide slow intramolecular 1,5-cyclization to afford oxazole derivative causes the decrease of the yield of oxazole, and then instead the increase of the yield of pyrrole derivatives.

2-4 $Rh_2(OAc)_4$-catalyzed Decomposition of *p*-Nitro-α-diazoacetophenone in Various Nitriles in the Presence of DMAD

In order to know the substituent effect at nitrile carbon on the reactivity of nitrile ylide, catalytic decompositions of *p*-nitro-α-diazoacetophenone (**1i**) with rhodium(II) acetate were carried out in various nitriles in the presence of 20 equivalents of DMAD at 60 °C (Table 4).

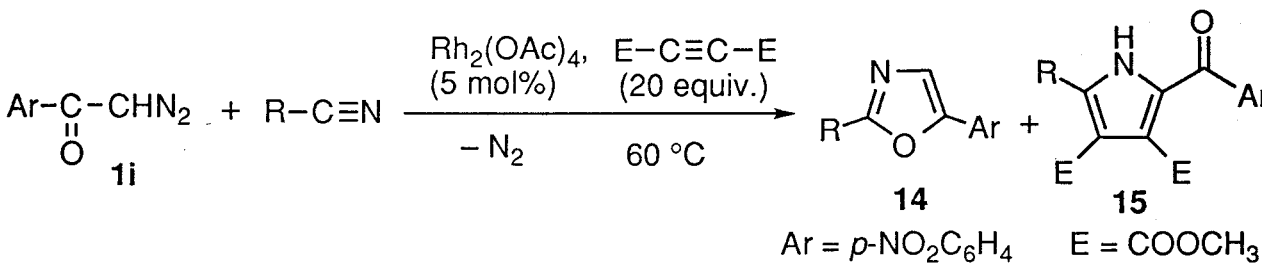


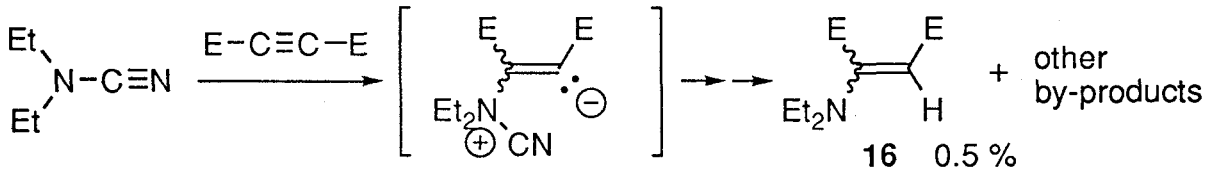
Table 4. $Rh_2(OAc)_4$-catalyzed Reaction of **1i** with Various Nitriles in the Presence of DMAD

Run	R	Yield / %		Total Yield / %
		14	**15**	
a	C_6F_5	58	0	58
b	C_6H_5O	63	0	63
c	Me_2N	0	0	0
d	Et_2N	12	0	12
e	$^iPr_2N$	71	8	79

The reaction in pentafluorobenzonitrile gave only oxazole **14a** in moderate yield, but did not give pyrrole derivative through the addition of

nitrile ylide intermediate with DMAD at all. This may be attributed to the electron-withdrawing effect of pentafluorophenyl group, which lowers the energy level of HOMO of nitrile ylide intermediate. This may be disadvantageous to 1,3-dipolar cycloaddition of the nitrile ylide with DMAD to give pyrrole **15**.

Although hetero-atom is expected to increase the reactivity of nitrile ylide toward dipolarophile because of its electron-donating property, phenyl cyanate also gave only oxazole **14b** in moderate yield. Dimethyl cyanamide gave a complex mixture of products, in which no oxazole **14**, pyrrole **15**, or other products containing carbenoid moiety could be identified. Diethyl cyanamide gave only oxazole **14d** in low yield without giving pyrrole **15**. It is ascribed to the side reaction of cyanamides with DMAD, because 0.5 % of **16** was formed by the conjugate addition of diethyl cyanamide to DMAD followed by successive protonation and elimination of cyano group (Scheme 8).



Scheme 8

In contrast, diisopropyl cyanamide gave oxazole **14e** and pyrrole **15e** in high yields. Bulky isopropyl groups hindered the reaction of cyanamide with DMAD. In this reaction, however, no significant advantage of hetero atom substitution to accelerate the 1,3-dipolar cycloaddition of nitrie ylide intermediate with DMAD to afford pyrrole **15** was recognized in comparison with the reaction of benzonitrile (Table 1, run i).

2-5 Reaction of Acyl-substitued Nitrile Ylide with Methyl Propiolate

The regiochemistry of the cycloaddition of nitrile ylide with unsymmetrical dipolarophiles has been discussed by many chemists. The cycloaddition of nitrie ylide is known to be controlled by HOMO of the ylide and LUMO of dipolarophiles, and accelerated by the electron-withdrawing group on dipolarophile.[6] In the following two possible transition states, almost all nitrile ylides react via transition state **TA** to give 4-substitued cycloadducts (**PA**) regioselectively (Figure 2).

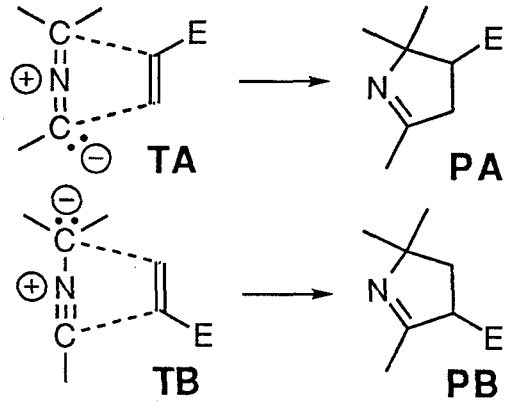


Figure 2 E : electron-withdrawing group

This selectivity was explained by Houk et al.[7] as follows; the nitrile ylide has been optimized to have a geometry of a bent allenyl form rather than a planar propargyl form with MINDO/3 and ab initio molecular orbital calculations, and thus the nucleophilic center of the ylide is nitrile carbon. However, Burger et al.[8] demonstrated that strong electron-withdrawing substituent such as trifluoromethyl groups on ylide carbon changes the electronic properties of the nitrile ylide, and promotes the cycloaddition through the transition state **TB**.

Although the successful trapping experiments of the acyl-substituted nitrile ylide have been reported by a few groups, the regiochemistry of the cycloaddition with unsymmetrical dipolarophiles has not been discussed sufficiently. In 1976, Hirai et al. reported the reaction of a nitrile ylide having penicilin moiety, generated by hydrogen chloride elimination from imidoyl chloride, with acrylonitrile to give pyrroline derivative through **TB**-type transition state.[9] In 1975, Fehlhammer showed that hydrogen chloride extrusion from the platinum-isonitrile complex generated the platinum substituted nitrile ylide[10] which also reacted with ethyl propiolate to give pyrrole derivative via **TB**-type transition state (Figure 3).

In both reactions, however, the regiochemistry of the cycloadducts was opposite to what can be expected from the ordinary case (transition state **TA**), and explained by the trasition state **TB**. These results may be explained by the strong perturbation on nitrile ylide due to the strained four membered ring or the effect of the substituted plaitnum metal, because it can stabilize negative charge on ylide carbon.

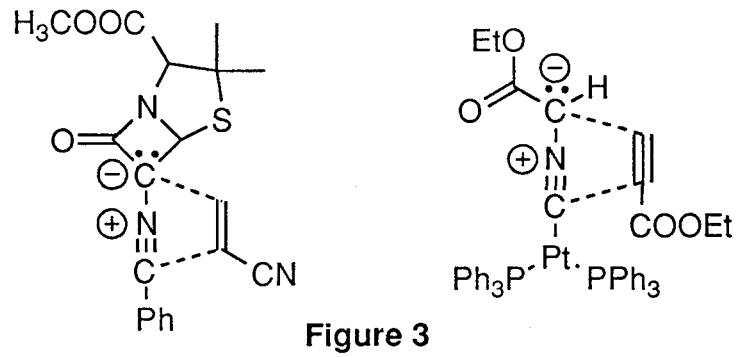


Figure 3

In order to clarify the regiochemistry of 1,3-dipolar cycloaddition of acyl substituted-nitrile ylide, $Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**1i**) was carried out in the presence of 20 equivalents of methyl propiolate in benzonitrile, and oxazole **17a** and pyrrole **18a** were obtained in 70 and 4 % yields, respectively (Table 5). The structure of **18a** was elucidated by the result of differential NOE experiment (Figure 4) which showed enhancement of the ortho-proton intensity on the phenyl group by the irradiation onto H-4 on the pyrrole ring at 7.05 ppm. The similar reaction in acetonitrile gave two pyrrole derivatives **18b** and **19b** in 4 and 1 % yields, along with oxazole **17b** (73 %). Reaction in diisopropyl cyanamide also gave **17c** and **18c** in 90 and 5 % yields, respectively. Their structures were also confirmed by differential NOE experiments. The major pyrrole derivatives **18b** and **18c** in these two reactions were determined to have the same regiochemistry as **18a**.

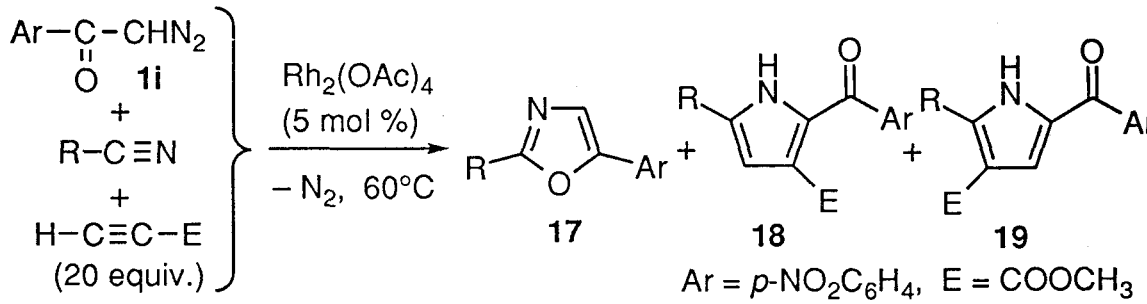


Table 5. $Rh_2(OAc)_4$-catalyzed Decomposition of **1i** in Various Nitriles in the Presence of Methyl Propiolate

Run	R	Yield / %		
		17	**18**	**19**
a	Ph	70	4	0
b	CH_3	73	4	1
c	$^iPr_2N$	90	5	0

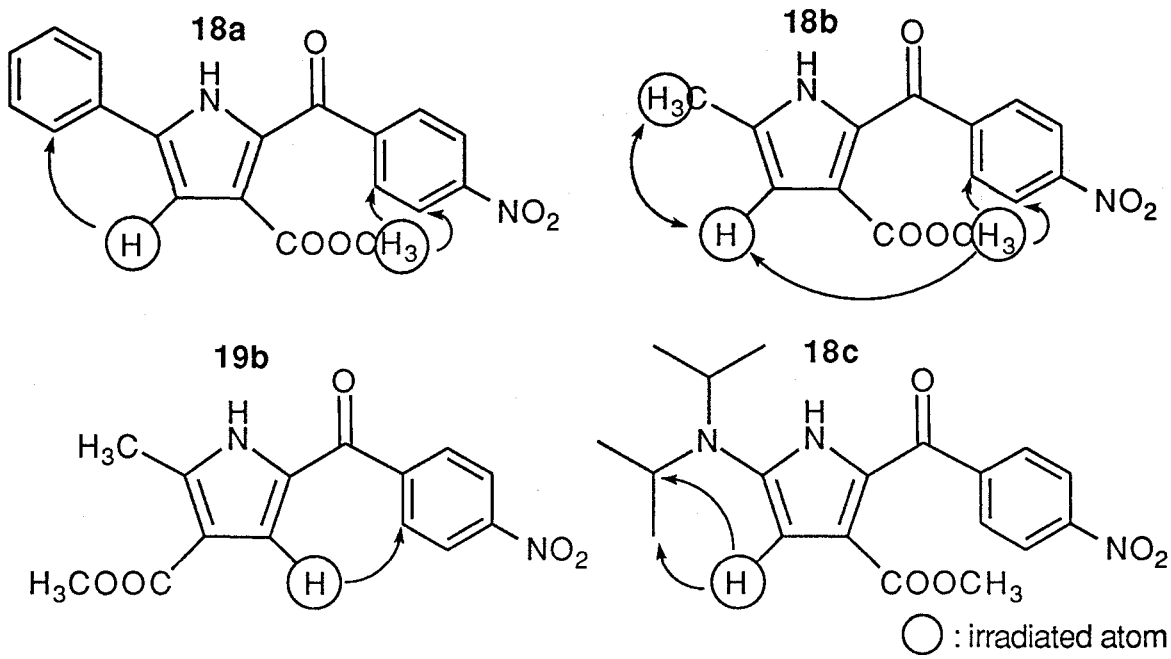
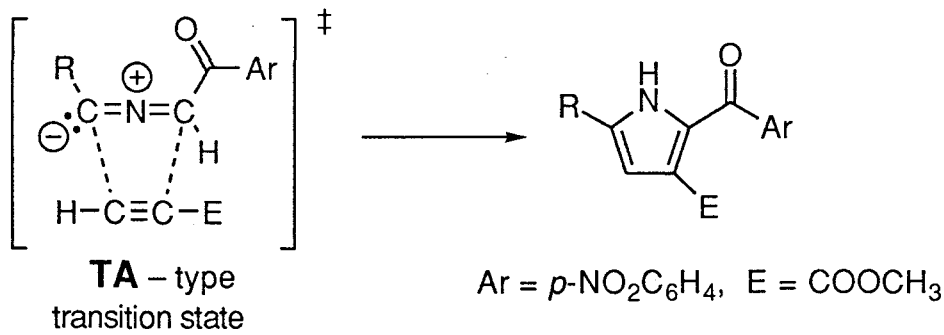


Figure 4. Differential NOE Corelations of **18a**, **18b**, **19b**, and **18c**.

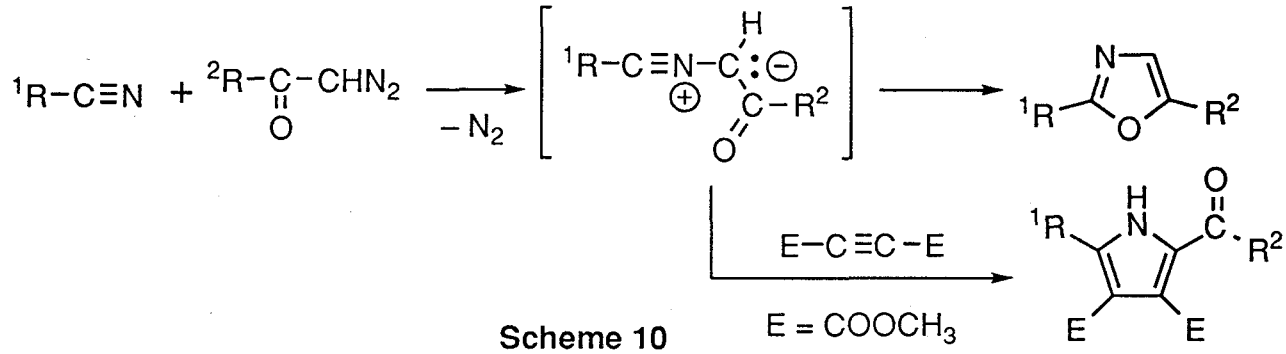
From the structure of the main adduct **18**, the cycloaddition is considered to proceed through **TA**-type transition state, in which the structure of the nitrile ylide is depicted as allenyl structure (Scheme 9). These results show that the regiochemistry of the 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide having no extra perturbation with unsymmetrical dipolarophile was essentially the same as the regiochemistry of alkyl or aryl substituted nitrile ylide, and opposite to the results of Hirai and Fehlhammer. Thus the electronic effect of the acyl group on the reactivity of nitrile ylide is not so large, and its reaction is controlled by the electronic property of allenyl type ylide moiety.



Scheme 9

2-6 Conclusion

In this chapter, the stepwise mechanism including nitrile ylide intermediate in the oxazole synthesis by the reaction of ketocarbenoid with nitrile is described. $Rh_2(OAc)_4$-catalyzed decomposition of diazocarbonyl compounds in nitrile in the presence of DMAD gave both oxazole and pyrrole derivatives. The formation of pyrrole derivatives is explained by the 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide with DMAD (Scheme 10).



Scheme 10

This result clearly shows the existence of nitrile ylide as an intermediate of the formation of oxazole, and excludes the old concept; that is, concerted 1,3-dipolar cycloaddition of ketocarbene with nitrile gives oxazole derivatives.

Although the introduction of ester group to nitrile ylide by using α-diazoacetates decreased the total yields of oxazoles and pyrroles, the ratios of the pyrrole derivatives in the products were increased. This may be attributed to the slow cyclization of ester carbonyl group.

The reaction with unsymmetrical dipolarophile such as methyl propiolate can give two regioisomers of pyrrole derivatives. On the basis of the structure of the major isomer, it is proved that allenyl-type resonance structure makes major contribution in the structure of the acyl-substituted nitrile ylide. This suggests that the electronic effect of the acyl group on the reactivity of nitrile ylide is not so large, and its reaction is controlled by the electronic property of allenyl type ylide moiety.

Experimental

Melting points were measured with a Yanagimoto Melting-point Apparatus and were not corrected. IR spectra were recorded on a Perkin-Elmer model 983. ^1H NMR (270.05 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL EX-270 in a $CDCl_3$ solution using TMS as an internal standard. Mass spectra were determined with a JEOL JMS-DX303 spectrometer and a SHIMADZU GCMS-QP2000A gas chromatograph mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-5.

Materials and Solvents. α-Diazoacetophenones were prepared by the reaction of the corresponding acid chlorides with excess of diazomethane in the presence of triethylamine according to Newman's method.[10] Ethyl diazoacetate was prepared by the diazotization of ethyl glycinate hydrochloride with sodium nitrite.[11] *t*-Butyl diazoacetate was prepared by the acyl cleavage of *t*-butyl diazoacetoacetate with sodium methoxide.[12] *p*-Nitrophenyl diazoacetate was prepared by the reaction of the *p*-nitrophenyl chlorocarbonate with excess of diazomethane in the presence of triethylamine.[13] Benzonitrile was purified by distillation after reflux on P_2O_5. Acetonitrile was purified by distillation after reflux on CaH_2. Other solvents were dried by appropriate methods and distilled just before use. DMAD was purified by distillation of the commercial reagent.

General Procedure for the Rhodium(II) Acetate-Catalyzed Decomposition of Diazocarbonyl Compound in the Presence of Nitrile and DMAD. A solution of diazocarbonyl compound (1.0 mmol) in 20 ml of nitrile was added dropwise to the solution of rhodium(II) acetate (22.1 mg, 5.0×10^{-2} mmol) and dimethyl acetylenedicarboxylate (20.0 mmol) in 10 ml of nitrile for 2 h under nitrogen atmosphere at 60 °C. After additional 1 h heating, the solution was concentrated under reduced pressure, and separated by medium pressure liquid chromatogaraphy (silica gel, eluted with ethyl acetate-hexane).

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-methoxy-α-diazoacetophenone (**1a**) with benzonitrile in the presence of DMAD gave **2a**, **3a**, and **6a**.

5-(*p*-Methoxyphenyl)-2-phenyloxazole (2a): 38.2 % yield; colorless crystals; mp 81.7-83.3 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.84 (3H, s, OCH_3), 6.96 (2H, d, J=8.9 Hz, arom-H), 7.31 (1H, s, 4-H), 7.41-7.51 (3H, m, arom-H of Ph), 7.64 (2H, d, J=8.9 Hz, arom-H), 8.06-8.10 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=55.29 (q, OCH_3), 114.36 (dd, $^3J_{CH}$=4.9 Hz, 3"-arom-CH), 120.85 (t, $^3J_{CH}$=7.9 Hz, 1"-arom-C), 121.92 (d, J_{CH}=192.6 Hz, 4-CH), 125.69 (dd, $^3J_{CH}$=7.3 Hz, 2"-arom-CH), 126.09 (dm, 2'-arom-CH of Ph), 127.56 (m, 1'-arom-C of Ph), 128.72 (dm, 3'-arom-CH of Ph), 130.03 (dt, $^3J_{CH}$=7.6 Hz, 4'-arom-C of Ph), 151.27 (dt, $^2J_{CH}$=16.8 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 159.78 (m, 4"-arom-C), 160.50 (m, 2-C); IR (KBr) 2919, 2840, 1730,

1697, 1611, 1565, 1540, 1498, 1460, 1447, 1299, 1290, 1279, 1256, 1176, 1128, 1111, 1059, 1026, 951, 934, 826, 774, 707, 689, and 669 cm^{-1}; MS (EI) 252, 251 (M^+), 236, 208, 196, 181, 165, 153, 135, 126, 112, 89, and 77. Found: C, 76.63; H, 5.31; N, 5.51 %. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57 %.

Dimethyl 2-(*p*-methoxybenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3a): 5.8 % yield; colorless crystals; mp 206.9-209.0 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.48 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 3.88 (3H, s, OCH_3), 6.95 (2H, d, J=8.9 Hz, arom-H), 7.45-7.47 (3H, m, arom-H of Ph), 7.59-7.63 (2H, m, arom-H of Ph), 7.75 (2H, d, J=8.9 Hz, arom-H), 9.76 (1H, brs, N-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.76 (q, $COO\underline{C}H_3$), 52.17 (q, $COO\underline{C}H_3$), 55.52 (q, OCH_3), 113.53 (d, $^3J_{CH}$=7.3 Hz, 4-C), 113.65 (dd, $^3J_{CH}$=4.9 Hz, 3"-CH of Ar), 124.13 (d, $^3J_{CH}$=6.1 Hz, 3-C), 128.43 (dt, $^3J_{CH}$=3.7 Hz, 2'-CH of Ph), 128.95 (d, $^2J_{CH}$=3.1 Hz, 2-C), 129.11(dm, 3'-CH of Ph), 129.52 (dt, $^3J_{CH}$=7.9 Hz, 4'-CH of Ph), 129.98 (m, arom-C), 130.49 (m, arom-C), 131.05 (dd, $^3J_{CH}$=6.7 Hz, 2"-CH of Ar), 139.69 (d, $^2J_{CH}$=4.3 Hz, 5-C), 163.38 (m, 4"-C of Ar), 163.91 (m, $\underline{C}OOCH_3$), 165.24 (m, $\underline{C}OOCH_3$), 185.28 (m, C=O); IR (KBr) 3298 (NH), 2954, 1719 (ester-C=O), 1616 (keto-C=O), 1598, 1566, 1508, 1482, 1460, 1443, 1432, 1418, 1299, 1242, 1198, 1170, 1143, 1089, 1016, 971, 922, 858, 839, 796, 760, 698, and 668 cm^{-1}; MS (EI) 394, 393 (M^+), 362, 361, 331, 330, 302, 287, 275, 254, 181, 165, 135, 107, 92, and 77. Found: C,67.91; H, 4.93; N, 3.59 %. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56 %.

Dimethyl 5-(*p*-methoxybenzoyl)pyrazole-3,4-dicarboxylate (6a): 24.8 % yield; colorless crystals; mp 146.7-148.7 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.85 (3H, brs, $COOCH_3$), 3.89 (3H, s, $COOCH_3$ or OCH_3), 3.97 (3H, s, $COOCH_3$ or OCH_3), 6.98 (2H, d, J=8.9 Hz, 3'-H of Ar), 8.15 (2H, br d, J=8.9 Hz, 2'-H of Ar), 11.25 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=52.86 (q, $COO\underline{C}H_3$), 52.99 (q, $COO\underline{C}H_3$), 55.54 (q, OCH_3), 113.82, (dd, $^3J_{CH}$=4.88 Hz, 3'-CH of Ar), 118.82 (s, 4-C), 128.91 (t, $^3J_{CH}$=7.93 Hz, 1'-C of Ar), 132,66 (dd, $^3J_{CH}$=7.33 Hz, 2'-CH of Ar), 135.33 (brs, 5-C), 147.96 (s, 3-C), 159.32 (q, $^3J_{CH}$=3.67 Hz, $\underline{C}OOCH_3$), 163.60 (q, $^3J_{CH}$=4.27 Hz, $\underline{C}OOCH_3$), 164.14 (m, 4'-C of Ar), 184.51 (t, $^3J_{CH}$=4.27 Hz, C=O); IR (KBr) 3255 (NH), 2960, 2849, 1744 (ester-C=O), 1640 (keto-C=O), 1604, 1577, 1511, 1483, 1447, 1382, 1311, 1286, 1250, 1217, 1182, 1168, 1100, 1046, 1009, 965, 913, 838, 821, 806, 790, 774, 762, and 669 cm^{-1}; MS (EI) 320, 319 (MH^+), 288, 287, 256, 229, 228, 227, 226, 201, 200, 199, 198, 171, 144, 136, 135, 107, 92, 77. Found: C, 56.41; H, 4.46; N, 8.73 %. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.80 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *m*-methyl-α-diazoacetophenone (**1b**) with benzonitrile in the presence of DMAD gave **2b**, and **3b**.

5-(*m*-Methylphenyl)-2-phenyloxazole (2b): 32.0 % yield; colorless crystals; mp 111.4-113.2 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.41 (3H, s, CH_3), 7.15 (1H, d, J=7.9 Hz, 6"-H of Ar), 7.32 (1H, t, J=7.9 Hz, 5"-

H of Ar), 7.42 (1H, s, 4-H), 7.44-7.53 (5H, m, arom-H), 8.09-8.13(2H, m, arom-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.46 (qt, $^3J_{CH}$=4.9 Hz, CH_3), 121.39 (dt, $^3J_{CH}$=7.3 Hz, 6"-CH of Ar), 123.34 (d, J_{CH}=192.3 Hz, 4-CH), 124.78 (dm, arom-CH), 126.27 (dm, 2'-CH of Ph), 127.51 (m, 1'-C of Ph), 127.92 (d, 1"-C of Ar), 128.80 (dd, 3'-CH of Ph), 128.84 (dd, 5"-CH of Ar), 129.27 (dm, arom-CH), 130.27 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 138.64 (m, 3"-C of Ar), 151.42 (dt, $^2J_{CH}$=17.0 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 161.05 (dt, $^3J_{CH}$=11.0 Hz, 4.9 Hz, 2-C); IR (KBr) 3097, 3061, 2950, 2917, 2861, 1714, 1610, 1598, 1564, 1539, 1484, 1445, 1343, 1251, 1174, 1155, 1133, 1076, 1066, 1042, 1024, 995, 963, 921, 913, 892, 859, 847, 835, 787, 776, 708, 689, and 669 cm^{-1}; MS (EI) 236, 235 (M^+), 207, 180, 179, 165, 118, 116, 103, 91, 89, 77, 65, 63, 51, and 39. Found: C, 81.68; H, 5.57; N, 5.95 %. Calcd for $C_{15}H_{13}NO$: C, 81.70; H, 5.56; N, 5.97 %.

Dimethyl 2-(*m*-methylbenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3b): 2.0 % yield; colorless solid (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.42 (3H, s, CH_3), 3.38 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 7.35-7.38 (2H, m, arom-H), 7.45-7.48 (3H, m, arom-H of Ph), 7.51-7.54 (2H, m, arom-H), 7.60-7.63 (2H, m, arom-H of Ph), 9.76 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.26 (CH_3), 51.79 ($COO\underline{C}H_3$), 52.08 ($COO\underline{C}H_3$), 113.48 (4-C), 124.99 (3-C), 125.51 (arom), 128.34 (arom), 128.50(CH of Ph), 129.04 (arom), 129.11 (CH of Ph), 129.72 (4'-CH of Ph), 129.85 (2-C), 133.30 (arom), 137.75 (arom), 138.25 (arom), 140.18 (5-C), 163.66 ($\underline{C}OOCH_3$), 165.21 ($\underline{C}OOCH_3$), 186.27 (C=O); IR (KBr) 3254 (NH), 2951, 1723 (ester-C=O), 1623 (keto-C=O), 1601, 1583, 1559, 1512, 1482, 1460, 1442, 1415, 1357, 1288, 1267, 1165, 1136, 1092, 1042, 976, 941, 852, 697, and 666 cm^{-1}.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-methyl-α-diazoacetophenone (**1c**) with benzonitrile in the presence of DMAD gave **2c**, and **3c**.

5-(*p*-Methylphenyl)-2-phenyloxazole (2c): 44.6 % yield; colorless crystals; mp 79.8-81.6 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.33 (3H, s CH_3), 7.19 (2H, d, J=8.3 Hz, 3"-H of Ar), 7.35 (1H, s 4-H), 7.39-7.47 (3H, m, arom-H of Ph), 7.56 (2H, d, J=8.3 Hz, 2"-H of Ar), 8.05-8.09 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.21 (qt, $^3J_{CH}$=4.3 Hz, CH_3), 122.67 (d, J_{CH}=192.26 Hz, 4-C), 124.01 (dd, $^3J_{CH}$=6.1 Hz, 3"-CH of Ar), 125.15 (m, 1"-C of Ar), 126.08 (dt, 2'-CH of Ph), 127.45 (m, 1'-C of Ph), 128.63 (dm, 2"-CH of Ar), 129.45 (dm, 3'-CH of Ph), 130.02 (dt, $^3J_{CH}$=7.6 Hz, 4'-CH of Ph), 138.29 (m, 4"-C of Ar), 151.33 (dt, $^2J_{CH}$=16.5 Hz, $^3J_{CH}$=4.6 Hz, 5-C), 160.65 (m, 2-C); IR (KBr) 3127, 3046, 3022, 2985, 2953, 2917, 2805, 2735, 2421, 2362, 2335, 1966, 1907, 1729, 1662, 1605, 1589, 1541, 1499, 1477, 1445, 1381, 1341, 1314, 1280, 1241, 1209, 1175, 1134, 1110, 1071, 1055, 1041, 1023, 978, 952, 935, 837, 818, 793, 775, 710, 695, and 668 cm^{-1}; MS (EI) 236, 235 (M^+), 207, 180, 179, 165, 118. 104, 103, 91, 89, 77, 65, 63, and 51. Found: C, 81.78; H, 5.67: N, 6.55 %. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95 %.

Dimethyl 2-(*p*-methylbenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (**3c**): 9.8 % yield; colorless crystals; mp 186.4-188.2 °C (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=2.41 (3H, s, CH_3), 3.39 (3H, s, $COOCH_3$), 3.71 (3H, s, $COOCH_3$), 7.23 (2H, d, J=7.9 Hz, 3"-H), 7.40-7.46 (3H, m, arom-H of Ph), 7.56-7.61 (4H, m, arom-H), 10.53 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.62 (qt, $^3J_{CH}$=4.4 Hz, CH_3), 51.68 (q, $COO\underline{C}H_3$), 51.97 (q, $COO\underline{C}H_3$), 113.54 (d, $^3J_{CH}$=7.3 Hz, 4-C), 124.68 (d, $^3J_{CH}$=6.1 Hz, 3-C), 128.31 (dm, arom-CH), 128.72 (dm, arom-CH), 128.81 (d, $^2J_{CH}$=3.1 Hz, 2-C), 128.95 (dm, arom-CH), 129.14 (dm, arom-CH), 129.44 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 129.89 (m, 4"-C of Ar), 135.19 (t, $^2J_{CH}$=7.3 Hz, 1"-C of Ar), 140.06 (d, 5-C), 143.36 (q, 1'-C of Ph), 163.82 (m, $\underline{C}OOCH_3$), 165.08 (m, $\underline{C}OOCH_3$), 186.40 (m, C=O); IR (KBr) 3317 (NH), 2941, 1724 (ester-C=O), 1624 (keto-C=O), 1605, 1559, 1516, 1481, 1457, 1440, 1414, 1282, 1262, 1240, 1194, 1178, 1138, 1088, 1039, 973, 923, 831, 794, 758, 698, and 669 cm^{-1}; MS (EI) 378, 377 (M^+), 346, 345, 330, 313, 314, 287, 286, 259, 173, 157, 119, 91, and 65. Found: C, 70.30; H, 5.16; N, 3.81 %. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71 %.

The $Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenone (**1d**) with benzonitrile in the presence of DMAD gave **2d**, and **3d**.

2,5-Diphenyloxazole (**2d**): 50.6 % yield; pale yellow crystals; mp 69.1-71.2 °C (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=7.31-7.38 (1H, m, arom-H), 7.42-7.53 (6H, m, arom-H and 4-H), 7.71-7.75 (2H, m, arom-H), 8.09-8.14 (2H, m, arom-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=123.38 (d, J_{CH}=192.3 Hz, 4-CH), 124.16 (dt, 2"-CH of 5-Ph), 126.24 (dm, 2'-CH of 2-Ph), 127.38 (m, 1'-C of 2-Ph), 127.95 (m, 1"-C of 5-Ph), 128.42 (dt, 4'-CH of 2-Ph), 128.80 (dm, arom-CH), 128.90 (dm, arom-CH), 130.31 (dtd, 4"-CH of 5-Ph), 151.22 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 161.10 (m, 2-C); IR (KBr) 3061, 1730, 1610, 1588, 1540, 1482, 1445, 1349, 1154, 1133, 1070, 1059, 1027, 953, 822, 775, 760, 707, and 686 cm^{-1}; MS (EI) 222, 221(M^+), 193, 166, 165, 116, 105, 90, 89, 77, 63, 51, and 39. Found: C, 81.41; H, 5.13; N, 6.34 %. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33 %.

Dimethyl 2-benzoyl-5-phenylpyrrole-3,4-dicarboxylate (**3d**): 11.0 % yield; colorless crystals; mp 159.5-162.0 °C (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=3.36 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 7.43-7.70 (10H, m, arom-H), 10.13 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.77 ($COO\underline{C}H_3$), 52.06 ($COO\underline{C}H_3$), 113.64 (4-C), 124.98 (3-C), 128.36 (arom-CH), 128.50 (arom-CH), 129.06 (arom-CH), 129.70 (arom-CH), 129.79 (2-C), 137.86 (arom-C), 138.04 (5-C), 140.13 (arom-C), 163.65 ($\underline{C}OOCH_3$), 165.01 ($\underline{C}OOCH_3$), 186.34 (C=O); IR (KBr) 3631, 3311(NH), 3055, 2991, 2951, 2860, 1728 (ester-C=O), 1624 (keto-C=O), 1596, 1573, 1558, 1513, 1482, 1464, 1444, 1408, 1360, 1319, 1290, 1268, 1231, 1195, 1153, 1135, 1093, 1041, 1020, 1001, 967, 942, 917, 817, 787, 764, 740, 698, and 662 cm^{-1}. Found: C, 69.88; H, 4.87; N, 3.66 %. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *m*-chloro-α-diazoacetophenone (**1e**) with benzonitrile in the presence of DMAD gave **2e**, and **3e**.

5-(*m*-Chlorophenyl)-2-phenyloxazole (**2e**): 62.6 % yield; colorless crystals; mp 115.1-116.1 °C (from hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=7.29-7.33 (1H, m, 6"-H of Ar), 7.35-7.41 (1H, t, J=7.8 Hz, 5"-H of Ar), 7.48 (1H, s, 4-H), 7.48-7.52 (3H, m, arom-H of Ph), 7.58-7.62 (1H, m, 4"-H of Ar) 7.72 (1H, t, J=1.9 Hz, 2"-H of Ar), 8.10-8.14 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=121.92 (dtd, $^2J_{CH}$=1.2 Hz, $^3J_{CH}$=6.7 Hz, 6"-CH of Ar), 123.84 (dm, 2"-CH of Ar), 124.23 (d, J_{CH}=192.9 Hz, 4-CH), 126.16 (dm, arom-CH of Ph), 126.96 (m, 1'-C of Ph), 128.05 (dm, 4"-CH of Ar), 128.61 (dm, arom-CH of Ph), 129.41 (m, 1"-C of Ar), 129.96 (d, 5"-CH of Ar), 130.31 (dt, $^3J_{CH}$=7.6 Hz, 4'-CH of Ph), 134.76 (m, 3"-C of Ar), 149.55 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.6 Hz, 5-C), 161.28 (m, 2-C); IR (KBr) 3103, 1730, 1610, 1586, 1534, 1473, 1446, 1429, 1346, 1141, 1098, 1082, 960, 898, 847, 783, 763, 709, 687, 668, and 659 cm^{-1}; MS (EI) 257, 256, 255 (M^+), 227, 200, 192, 165, 128, 116, 111, 89, 77, 63, and 51. Found: C, 70.48; H, 4.05; N, 5.44 %. Calcd for $C_{15}H_{10}NOCl$: C, 70.46; H, 3.94; N, 5.48 %.

Dimethyl 2-(*m*-chlorobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (**3e**): 15.1 % yield; colorless crystals; mp 159.2-160.8 °C (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=3.50 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 7.42 (1H, t, J=7.9 Hz, 5"-H of Ar), 7.47-7.51 (3H, m, arom-H of Ph), 7.54-7.58 (1H, m, arom-H), 7.60-7.64 (3H, m, arom-H of Ar and Ph), 7.72 (1H, m, 2"-H of Ar), 9.62 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.83 (q, $COOCH_3$), 52.32 (q, $COOCH_3$), 113.79 (d, $^3J_{CH}$=7.3 Hz, 4-C), 125.47 (d, $^3J_{CH}$=6.1 Hz, 3-C), 126.48 (dm, arom-CH), 127.77 (m, 1"-C of Ar), 128.42 (dm, arom-CH), 128.54 (dm, arom-CH of Ph), 129.08 (dm, arom-CH of Ph), 129.61 (m, 2-C), 129.77 (d, 5"-CH of Ar), 129.90 (dm, 4'-CH of Ph), 132.43 (dm, arom-CH), 134.48 (dm, 3"-CH of Ar), 139.27 (d, $^2J_{CH}$=8.6 Hz, 5-C), 140.71 (m, 1'-C of Ph), 163.47 (m, $\underline{C}OOCH_3$), 164.96 (m, $\underline{C}OOCH_3$), 184.71 (m, C=O); IR (KBr) 3333 (NH), 2951, 1722 (ester-C=O), 1621 (keto-C=O), 1561, 1509, 1481, 1465, 1437, 1422, 1289, 1261, 1195, 1141, 1088, 974, 933, 819, 792, 760, and 697 cm^{-1}; MS (EI) 399, 398, 397 (M^+), 367, 366, 365, 336, 335, 334, 308, 307, 306, 279, 254, 183, 139, 111, and 75. Found: C, 63.57; H, 4.14; N, 3.62 %. Calcd for $C_{21}H_{16}NO_5Cl$: C, 63.40; H, 4.05; N, 3.52 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-chloro-α-diazoacetophenone (**1f**) with benzonitrle in the presence of DMAD gave **2f**, and **3f**.

5-(*p*-Chlorophenyl)-2-phenyloxazole (**2f**): 63.0 % yield; colorless crystals; mp 105.4-107.1 °C (from hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=7.39 (2H, d, J=8.6 Hz, 2"-H of Ar), 7.42 (1H, s, 4-H). 7.44-7.51 (3H, m, arom-H of Ph), 7.62 (2H, d, J=8.6 Hz, 3"-H of Ar), 8.05-8.12 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=123.84 (d, J_{CH}=192.3 Hz, 4-CH), 125.42 (dd, $^3J_{CH}$=7.3 Hz, 2"-CH of Ar), 126.35 (dm, 2'-CH of Ph), 126.53 (m, arom-C), 127.27 (m, arom-C), 128.87 (dm, 3'-CH of Ph), 129.22 (dd, $^3J_{CH}$=5.5 Hz, 3"-CH

of Ar), 130.51 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 134.20 (tt, $^2J_{CH}$=11.0 Hz, $^3J_{CH}$=3.7 Hz, 4"-C of Ar), 150.28 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.9 Hz, 5-C), 161.40 (m, 2-C); IR (KBr) 2927, 1730, 1631, 1541, 1482, 1449, 1405, 1340, 1274, 1134, 1092, 1062, 1055, 1012, 952, 818, 772, 705, 689, and 669 cm^{-1}; MS (EI) 255 (M^+), 227, 200, 192, 165, 239, 128, 116, 89, and 77. Found: C, 70.20; H, 4.06; N, 5.34 %. Calcd for $C_{15}H_{10}NOCl$: C, 70.46; H, 3.94; N, 5.48 %.

Dimethyl 2-(*p*-chlorobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3f): 11.0 % yield; colorless crystals; mp 183.3-185.5 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.44 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 7.41-7.45 (2H, m, arom-H), 7.45-7.47 (3H, m, arom-H), 7.58-7.61 (2H, m, arom-H), 7.62-7.65 (2H, m, arom-H), 10.09 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.83 (q, $COO\underline{C}H_3$), 52.22 (q, $COO\underline{C}H_3$), 113.82 (d, $^3J_{CH}$=7.3 Hz, 4-C), 125.06 (d, $^3J_{CH}$=6.1 Hz, 3-C), 128.12 (d, $^2J_{CH}$=3.1 Hz, 2-C), 128.46 (dm, arom-CH of Ph), 128.63 (dd, $^3J_{CH}$=5.5 Hz, arom-CH), 129.07 (dm, arom-CH of Ph), 129.67 (dt, 4'-CH of Ph), 129.75 (m, 1"-C of Ar), 129.86 (dd, $^3J_{CH}$=6.7 Hz, arom-CH), 136.14 (t, $^2J_{CH}$=7.3 Hz, 1'-C of Ph), 138.93 (tm, $^2J_{CH}$=10.7 Hz, 4"-C of Ar), 140.46 (d, $^2J_{CH}$=3.7 Hz, 5-C), 163.59 (m, $\underline{C}OOCH_3$), 164.96 (m, $\underline{C}OOCH_3$), 184.71 (t, $^3J_{CH}$=3.7 Hz, C=O); IR (KBr) 3327 (NH), 2949, 1725 (ester-C=O), 1621 (keto-C=O), 1587, 1566, 1513, 1483, 1462, 1442, 1415, 1356, 1288, 1263, 1242, 1134, 1094, 1040, 1015, 973, 917, 837, 791, 769, 759, 734, and 697cm^{-1}; MS (EI) 397 (M^+), 365, 334, 306, 279, 139, and 111. Found: C, 63.28; H, 4.12; N, 3.53 %. Calcd for $C_{21}H_{16}NO_5Cl$: C, 63.40; H, 4.05; N, 3.52 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-cyano-α-diazoacetophenone (**1g**) with benzonitrile in the presence of DMAD gave **2g**, and **3g**.

5-(*p*-Cyanophenyl)-2-phenyloxazole (2g): 60.9 % yield; colorless crystals; mp 183.9-185.7 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.45-7.52 (3H, m, arom-H of Ph), 7.59 (1H, s, 4-H), 7.72 (2H, d, J=8.6 Hz, arom-H), 7.80 (2H, d, J=8.6 Hz, arom-H), 8.09-8.13 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=111.49 (t, $^3J_{CH}$=8.5 Hz, 4"-C of Ar), 118.52 (t, $^3J_{CH}$=5.2 Hz, CN), 124.32 (dd, $^3J_{CH}$=6.1 Hz, 2"-CH of Ar), 126.24 (d, J_{CH}=192.9 Hz, 4-CH), 126.52 (dm, arom-CH of Ph), 126.84 (m, 1'-C of Ph), 128.92 (dm, arom-CH of Ph), 130.94 (dt, $^3J_{CH}$=7.9 Hz, 4'-CH of Ph), 131.90 (t, $^3J_{CH}$=7.9 Hz, 1"-C of Ar), 132.78 (dd, $^3J_{CH}$=6.1 Hz, 3"-CH of Ar), 149.32 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 162.39 (m, 2-C); IR (KBr) 3121, 3070, 2360, 2227 (CN), 1610, 1539, 1495, 1476, 1413, 1344, 1182, 1137, 1055, 953, 839, 771, 708, 688, and 668 cm^{-1}; MS (EI) 247, 246 (M^+), 245, 218, 191, 190, 123, 116, 102, 89, 77, 63, 51, and 39. Found: C, 77.65; H, 4.25; N, 11.33 %. Calcd for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38 %.

Dimethyl 2-(*p*-cyanobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3g): 9.0 % yield; colorless crystals; mp 247.5-251.2 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.41 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 7.47-7.52 (3H, m, arom-H of Ph), 7.58-7.63 (2H, m, arom-H of Ph), 7.75-7.83 (4H, m, arom-H), 9.63 (1H, brs, NH); ^{13}C NMR (67.8 MHz,

$CDCl_3$) δ=51.92 ($COO\underline{C}H_3$), 52.27 ($COO\underline{C}H_3$), 115.71 (4-C), 117.83 (C≡N), 125.58, 127.54, 128.67 (arom-CH), 128.76 (arom-CH), 128.99 (arom-CH), 129.49, 130.09 (arom-CH), 132.12 (arom-CH), 132.39, 140.90, 141.50, 163.38 ($\underline{C}OOCH_3$), 164.66 ($\underline{C}OOCH_3$), 184.44 (C=O); IR (KBr) 3209 (NH), 2945, 2342, 2334, 2226 (CN), 1739 (ester-C=O), 1677 (keto-C=O), 1641, 1558, 1513, 1486, 1463, 1443, 1431, 1417, 1308, 1288, 1272, 1245, 1210, 1155, 1090, 1045,961, 907, 864, 821, 797, 759, 701, and 668 cm^{-1}; MS (EI) 389, 388 (M^+), 358, 357, 356, 355, 328, 327, 326, 325, 324, 298, 297, 270, 269, 254, 242, 241, 214, 178, 138, 130, 102, and 77. Found: C, 67.75; H, 4.37; N, 6.94 %. Calcd for $C_{22}H_{16}N_2O_5$: C, 68.04; H, 4.15; N, 7.21 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *m*-nitro-α-diazoacetophenone (**1h**) with benzonitrile in the presence of DMAD gave **2h**, and **3h**.

5-(*m*-Nitrophenyl)-2-phenyloxazole (2h): 60.5 % yield; colorless crystals; mp 150.3-151.8 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.49-7.54 (3H, m, arom-H of Ph), 7.61 (1H, s, 4-H), 7.64 (1H, t, J=7.9 Hz, 5"-H of Ar), 8.03 (1H, dt, J=7.9 Hz, 6"-H of Ar), 8.13-8.17 (2H, m, arom-H of Ph), 8.17-8.21 (1H, dm, 4"-H of Ar), 8.56 (1H, t, ^3J=7.9 Hz, 2"-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=118.89 (dt, $^3J_{CH}$=5.5 Hz, 2"-CH of Ar), 122.78 (dm, 4"-CH of Ar), 125.53 (d, J_{CH}=192.9 Hz, 4-CH), 126.56 (dm, 2'-CH of Ph), 126.88 (m, 1'-C of Ph), 128.95 (dm, 3'-CH of Ph), 129.56 (dt, $^3J_{CH}$=7.9 Hz, 6"-CH of Ar), 129.65 (m, 1"-C of Ar), 130.08 (d, 5"-CH of Ar), 130.93 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 148.84 (m, 3"-CH of Ar), 148.93 (m, 5-C), 162.23 (m, 2-C); IR (KBr) 3079, 2935, 2730, 1619, 1571, 1524 (NO_2), 1476, 1448, 1349 (NO_2), 1137, 1104, 965, 902, 867, 801, 776, 738, 711, 689, and 669 cm^{-1}; MS (EI) 267, 266 (M^+), 220, 192, 165, 133, 117, 116, 105, 96, 89, 77, and 63. Found: C, 67.37; H, 3.90; N, 10.48 %. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52 %.

Dimethyl 2-(*m*-nitrobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3h): 12.5 % yield; colorless crystals; mp 160.7-163.8 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.44 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 7.44-7.49 (3H, m, arom-H of Ph), 7.60-7.65 (2H, m, arom-H of Ph), 7.66 (1H, t, J=8.3 Hz, 5"-H of Ar), 7.99 (1H, d, J=7.6 Hz, 6"-H of Ar), 8.41-8.44 (dm, 4"-arom-H), 8.53 (1H, t, ^3J=1.8 Hz, 2"-H of Ar), 10.24 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.47 (q, $COO\underline{C}H_3$), 52.32 (q, $COO\underline{C}H_3$), 114.25 (d, $^3J_{CH}$=7.9 Hz, 4-C), 123.36 (dt, $^3J_{CH}$=5.2 Hz, arom-CH), 125.85 (d, $^3J_{CH}$=6.1 Hz, 3-C), 126.71 (dm, arom-CH), 127.38 (m, 1"-C of Ar), 128.51 (dm, arom-CH of Ph), 129.10 (dm, arom-CH of Ph), 129.42 (m, 2-C), 129.55 (dm, arom-CH), 129.99 (dt, $^3J_{CH}$=7.6 Hz, 4'-CH of Ph), 134.05 (dm, arom-CH), 139.07 (d, $^2J_{CH}$=7.9 Hz, 5-C), 141.29 (m, 1'-C of Ph), 147.86 (m, 3"-C of Ar), 163.36 (m, $\underline{C}OOCH_3$), 164.78 (m, $\underline{C}OOCH_3$), 183.78 (t, $^3J_{CH}$=4.3 Hz, C=O); IR (KBr) 3277, 3245 (NH), 2952, 1724 (ester-C=O), 1626 (keto-C=O), 1558, 1530 (NO_2), 1512, 1480, 1461, 1440, 1413, 1352 (NO_2), 1303, 1289, 1257, 1233, 1202, 1135, 1125, 1108, 836, 816, 796, 774, 761, 744, 725, and 698 cm^{-1}; MS (EI) 409, 408 (M+), 378, 377, 376, 375, 348, 347, 346, 345, 344, 318,

317, 300, 299, 298, 290, 271, 254, 244, 214, 188, 150, 140, 139, 104, and 76.; Found: C, 61.83; H, 3.95; N, 6.86 %. Calcd for $C_{21}H_{16}N_2O_7$: C, 61.83; H, 4.02; N, 6.79 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) with benzonitrile in the presence of DMAD gave **2i**, and **3i**.

5-(*p*-Nitrophenyl)-2-phenyloxazole (2i): 61.2 % yield; yellow crystals; mp 191.6-193.3 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.51-7.55 (3H, m, arom-H of Ph), 7.66 (1H, s, 4-H), 7.87 (2H, d, J=9.2 Hz, 2"-H of Ar), 8.32 (2H, d, J=9.2 Hz, 3"-H of Ar), 8.11-8.17 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=124.45 (dd, $^3J_{CH}$=6.7 Hz, arom-CH), 124.55 (dd, $^3J_{CH}$=4.3 Hz, arom-CH), 126.65 (dm, 2'-CH of Ph), 126.80 (m, 1'-C of Ph), 126.94 (d, J_{CH}=193.5 Hz, 4-CH), 128.98 (dm, 3'-CH of Ph), 131.11 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 133.74 (t, $^3J_{CH}$=8.6 Hz, 1"-C of Ar), 147.12 (m, 4"-C of Ar), 149.13 (d, $^2J_{CH}$=17.1 Hz, 5-C), 162.80 (m, 2-C); IR (KBr) 3197, 3157, 3076, 2935, 1602, 1539, 1517 (NO_2), 1473, 1448, 1378, 1334 (NO_2), 1180, 1143, 1110, 1076, 1055, 951, 934, 853, 840, 778, 752, 712, and 688 cm^{-1}; MS (EI) 267, 266 (M^+), 220, 192, 165, 133, 117, 116, 105, 96, 89, 77, and 63. Fuond: C, 67.87; H, 3.93; N, 10.48 %. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52 %.

Dimethyl 2-(*p*-nitrobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3i): 18.3 % yield; yellow crystals; mp 195.6-197.9 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.42 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 7.46-7.53 (3H, m, arom-H of Ph), 7.58-7.66 (2H, m, arom-H of Ph), 7.88 (2H, d, J=8.9 Hz, 2"-H of Ar), 8.33 (2H, d, J=8.9 Hz, 3"-H of Ar), 9.81 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.92 (q, $COO\underline{C}H_3$), 52.32 (q, $COO\underline{C}H_3$), 114.30 (d, $^3J_{CH}$=7.3 Hz, 4-C), 123.48 (dd, $^3J_{CH}$=4.6 Hz, arom-CH), 125.76 (d,$^3J_{CH}$=6.1 Hz, 3-C), 127.53 (m, 1"-C of Ar), 128.64 (dm, arom-CH of Ph), 129.01 (dm, arom-CH of Ph), 129.25 (dd, $^3J_{CH}$=6.7 Hz, arom-CH), 129.45 (m, 2-C), 130.08 (dt. $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 141.09 (m, 5-C), 143.06 (t, $^2J_{CH}$=7.6 Hz, 1'-CH of Ph), 149.83 (m, 4"-CH of Ar), 163.34 (m, $\underline{C}OOCH_3$), 164.64 (m, $\underline{C}OOCH_3$), 184.23 (m, C=O); IR (KBr) 3271 (NH), 2947, 1719 (ester-C=O), 1624 (keto-C=O), 1600, 1525 (NO_2), 1480, 1461, 1415, 1347 (NO_2), 1305, 1259, 1198, 1133, 1090, 1040, 1015, 969, 920, 853, 766, 736, and 702 cm^{-1}; MS (EI) 409, 408 (M^+), 377, 376, 330, 317, 299, 298, 290, 271, 254, 248, 214, 188, 150, 129, 104, and 76. Found: C, 62.13; H, 4.07; N, 6.98 %. Calcd for $C_{21}H_{16}N_2O_7$: C, 61.77; H, 3.95; N, 6.86 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *o*-methyl-α-diazoacetophenone (**1j**) with benzonitrile in the presence of DMAD gave **2j**.

5-(*o*-Methylphenyl)-2-phenyloxazole (2j): 3.0 % yield; colorless solid (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.54 (3H, s, $-CH_3$), 7.28-7.32 (3H, m, arom-H), 7.35 (1H, s, 4-H), 7.46-7.53 (3H, m, arom-H of Ph), 7.77-7.80 (1H, m, arom-H), 8.10-8.18 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.93 (qm, $-CH_3$), 126.13 (d, J_{CH}=192.9 Hz, 4-CH), 126.25 (dd,

arom-CH), 126.32 (dd, 2'-CH of Ph), 126.86 (dm, arom-CH), 127.29 (m, arom-CH), 127.43 (m, arom-CH), 128.45, (dd, $^3J_{CH}$=8.6 Hz, arom-CH), 128.85 (dm, 3'-CH of Ph), 130.38 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 131.27 (dm, 3"-CH of Ar), 134.95 (m, 2"-CH of Ar), 150.78 (dm, $^2J_{CH}$=14.0 Hz, 5-C), 160.85 (m, 2-C); IR (KBr) 3157, 3062, 2963, 2927, 2859, 2365, 2342, 2332, 1954, 1776, 1728, 1670, 1630, 1606, 1586, 1565, 1537, 1483, 1460, 1447, 1382, 1344, 1261, 1201, 1150, 1099, 1069, 1037, 953, 936, 922, 864, 836, 802, 778, 764, 717, 709, 688, 668, and 660 cm^{-1}.

The $Rh_2(OAc)_4$-catalyzed reaction of *o*-chloro-α-diazoacetophenone (**1k**) with benzonitrile in the presence of DMAD gave **2k** and **3k**.

5-(*o*-Chlorophenyl)-2-phenyloxazole (2k): 9.0 % yield; colorless crystals; mp 64.7-69.5 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.29 (1H, dd, J=7.6 Hz, 1.7 Hz 6"-H of Ar), 7.39 (1H, td, J=7.6 Hz, 1.7 Hz, arom-H), 7.47-7.52 (4H, m, 3', 4', 5'-H of Ph and arom-H), 7.89 (1H, s, 4-H), 7.93 (1H, dd, J=7.6 Hz, 1.7 Hz, 3"-arom-H), 8.10-8.17 (2H, m, 2', 6'-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=126.49 (dm, 2'-CH of Ph), 126.81 (m, arom-C), 127.09 (dd, $^3J_{CH}$=8.3 Hz, arom-CH), 127.17 (m, arom-C), 127.66 (dd, $^3J_{CH}$=7.9 Hz, arom-CH), 128.40(d, J_{CH}=197.8 Hz, 4-CH), 128.87 (dd, 3'-CH of Ph), 128.96 (dd, arom-CH), 130.61 (dt, $^3J_{CH}$=7.3 Hz, 2"-CH of Ar), 130.61 (tm, $^3J_{CH}$=11.0 Hz, 2"-C of Ar), 130.78 (dd, $^3J_{CH}$=7.9 Hz, arom-CH), 147.81 (dm, $^2J_{CH}$=14.0 Hz, 5-C), 160.99 (m, 2-C); IR (KBr) 3169, 1065, 2869, 2861, 2365, 2343, 2335, 1966, 1896, 1810, 1735, 1654, 1629, 1585, 1558, 1540, 1483, 1468, 1447, 1425, 1342, 1309, 1290, 1269, 1230, 1144, 1129, 1099, 1078, 1069, 1034, 954, 939, 920, 871, 830, 776, 763, 733, 720, 707, 688, and 668 cm^{-1}; MS (EI) 258, 257, 256 (MH^+), 228, 200, 167, 166, 165, 139, 117, 112, 89.

Dimethyl 2-(*o*-chlorobenzoyl)-5-phenylpyrrole-3,4-dicarboxylate (3k): 1.5 % yield; yellow oil; ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.34 (3H, s, $COOCH_3$), 3.69 (3H, s, $COOCH_3$), 7.32-7.65 (9H, m, arom-H), 9.57 (1H, brs, NH); IR (neat) 3414 (NH), 1729 (ester-C=O), 1639 (keto-C=O), 1482, 1380, 1247, and 1097 cm^{-1}.

The $Rh_2(OAc)_4$-catalyzed reaction of ethyl diazoacetate (**7a**) in the presence of DMAD in acetonitrile gave **9a**.

Dimethyl 2-ethoxycarbonyl-5-methylpyrrole-3,4-dicarboxylate (9a): 12.6 % yield; colorless crystals; mp 163.5-164.8 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.34 (3H, t, J=7.3 Hz, $COOCH_2\underline{CH_3}$), 2.55 (3H, s, CH_3), 3.81 (3H, s, $COOCH_3$), 3.92 (3H, s, $COOCH_3$), 4.31 (2H, q, J=7.3 Hz, $COO\underline{CH_2}CH_3$), 9.92 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=13.31 (q, CH_3), 14.09 (qt, $^2J_{CH}$=2.6 Hz, $COOCH_2\underline{C}H_3$), 51.51 (q, $COO\underline{C}H_3$), 52.62 (q, $COO\underline{C}H_3$), 61.36 (tq, $^2J_{CH}$=4.3 Hz, $COO\underline{C}H_2CH_3$), 112.02 (m, 4-C), 118.18 (d, $^2J_{CH}$=2.5 Hz, 2-C), 124.22 (d, $^3J_{CH}$=6.1 Hz, 3-C), 139.11 (m, 5-C), 160.16 (m, $\underline{C}OOEt$), 163.82 (m, $\underline{C}OOCH_3$), 166.32 (m, $\underline{C}OOCH_3$); IR (KBr) 3251 (NH), 2995, 2959, 1744 (C=O), 1714 (C=O), 1675 (C=O), 1571, 1516, 1483, 1438, 1375, 1349, 1280, 1226, 1119, 1102, 1068, 975, 954, 868, 818, 798, and 700 cm^{-1};

MS (EI) 269 (M^+), 238, 237, 192, 191, 178, 177, 165, 162, 149, 135, 107. Found: C, 53.63; H, 5.60; N, 5.11 %. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *tert*-butyl diazoacetate (**7b**) in the presence of DMAD in acetonitrile gave **9b**.

Dimethyl 2-*tert*-butoxycarbonyl-5-methylpyrrole-3,4-dicarboxylate (**9b**): 7.4 % yield; pale yellow crystals (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.53 (9H, s, CH_3 of ^tBu), 2.54 (3H, s, CH_3), 3.80 (3H, s, $COOCH_3$), 3.91 (3H, s, $COOCH_3$), 9.72 (1H, brs, NH); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=13.37 (q, CH_3), 28.15 (qspt, $^3J_{CH}$=4.3 Hz, CH_3 of ^tBu), 51.46 (q, $COO\underline{C}H_3$), 52.52 (q, $COO\underline{C}H_3$), 82.55 (m, $^2J_{CH}$=3.7 Hz, quaternary-C of ^tBu), 111.75 (m, 4-C), 119.49 (d, $^2J_{CH}$=3.1 Hz, 2-C), 123.55 (d, $^3J_{CH}$=6.7 Hz, 3-C), 138.48 (m, 5-C), 159.45 (s, $\underline{C}OO^tBu$), 163.92 (m, $\underline{C}OOCH_3$), 166.40 (m, $\underline{C}OOCH_3$); IR (KBr) 3259 (NH), 2979, 2950, 1735 (C=O), 1708 (C=O), 1690 (C=O), 1570, 1523, 1451, 1395, 1364, 1300, 1227, 1167, 1102, 1067, 1039, 958, 900, 850, 821, 792, 771, 752, and 703 cm^{-1}; MS (EI) 297 (M^+), 241, 224, 210, 209, 192, 178, 177.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitrophenyl diazoacetate (**7c**) in the presence of DMAD in acetonitrile gave **9c**.

Dimethyl 5-methyl-2-(*p*-nitrophenyloxycarbonyl)pyrrole-3,4-dicarboxylate (**9c**): 11.9 % yield; pale yellow powder; mp 210.0-212.4 °C (from benzene); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.61 (3H, s, CH_3), 3.85 (3H, s, $COOCH_3$), 3.93 (3H, s, $COOCH_3$), 7.38 (2H, d, J=9.23 Hz, 2'-H of Ar), 8.30 (2H, d, J=9.23 Hz, 3'-H of Ar), 9.29 (1H, brs, NH); IR (KBr) 3326 (NH), 3118, 3075, 3005, 2957, 2853, 1733 (C=O), 1706 (C=O), 1696 (C=O), 1612, 1588, 1568, 1522 (NO_2), 1489, 1464, 1437, 1427, 1379, 1342 (NO_2), 1301, 1268, 1234, 1209, 1166, 1154, 1107, 1053, 1009, 974, 950, 886, 866, 856, 825, 815, 792, 783, 760, 747, 709, and 685 cm^{-1}; MS (EI) 362 (M^+), 331, 224, 192, 162, 107. Found: C, 53.00; H, 3.95; N, 7.79 %. Calcd for $C_{16}H_{14}N_2O_8$: C, 53.04; H, 3.90; N, 7.73 %.

The $Rh_2(OAc)_4$-catalyzed reaction of ethyl diazoacetate (**7a**) in the presence of DMAD in benzonitrile gave **8d**, **9d**, and **10**.

5-Ethoxy-2-phenyloxazole (**8d**): 4.8 % yield; colorless crystals; mp 35.0-37.9 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.44 (3H, t, J=6.9 Hz, CH_3), 4.16 (2H, q, J=6.9 Hz, CH_2), 6.20 (1H, s, 4-H), 7.33-7.44 (3H, m, arom-H), 7.90-7.93 (2H, m, arom-H); ^{13}C NMR (270.05 MHz, $CDCl_3$) δ=14.55 (qt, $^2J_{CH}$=2.4 Hz, CH_3), 68.13 (tq, $^2J_{CH}$=4.3 Hz, CH_2), 100.80 (d, J_{CH}=196.53 Hz, 4-C), 125.31 (dm, 2'-C of Ph), 127.71 (t, $^3J_{CH}$=6.7 Hz, 1'-C of Ph), 128.69 (dm, 3'-C of Ph), 129.49 (dt, $^3J_{CH}$=7.9 Hz, 4'-C of Ph), 152.57 (dt, $^3J_{CH}$=11.0, 5.5 Hz, 2-C), 159.83 (dt, $^2J_{CH}$=15.3 Hz, $^3J_{CH}$=2.4 Hz, 5-C); IR (KBr) 3141, 2981, 2947, 2896, 1616, 1601, 1558, 1490, 1470, 1448, 1397, 1334, 1282, 1156, 1099, 1073, 1043, 1022, 1006, 923, 890, 772, 703, and 689 cm^{-1}.

Dimethyl 2-ethoxycarbonyl-5-phenylpyrrole-3,4-dicarboxylate (9d): 17.8 % yield; colorless crystals (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=1.29 (3H, t, J=6.9 Hz, CH_3), 3.71 (3H, s, $COOCH_3$), 3.94 (3H, s, $COOCH_3$), 4.22 (2H, q, J=6.9 Hz, CH_2), 7.39-7.47 (3H, m, arom-H), 7.49-7.63 (2H, m, arom-H), 9.76 (1H, brs, NH); IR (KBr) 3274, 2984, 2951,1735, 1711, 1682, 1630, 1568, 1522, 1486, 1465, 1443, 1371, 1352, 1285, 1266, 1232, 1203, 1148, 1073, 1024, 961, 863, 820, 797, 777, 760, and 699 cm^{-1}.

Dimethyl 2-ethoxy-5-phenylfuran-3,4-dicarboxylate (10); 2.6 % yield; colorless oil; ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=1.51 (3H, t, J=6.9 Hz, CH_3), 3.81 (3H, s, $COOCH_3$), 3.91 (3H, s, $COOCH_3$), 4.54 (2H, q, J=6.9 Hz, CH_2), 7.29-7.42 (3H, m, Ph), 7.56-7.60 (2H, m, Ph); ^{13}C NMR (270.05 MHz, $CDCl_3$) δ=14.98 (qt, $^2J_{CH}$=2.4 Hz, CH_3), 51.60 (q, $COO\underline{C}H_3$), 52.69 (q, $COO\underline{C}H_3$), 68.66 (tq, $^2J_{CH}$=4.3 Hz, CH_2), 114.75 (s, 3-C), 125.36 (dt, $^3J_{CH}$=6.7 Hz, 2'-C of Ph), 128.52 (dt, $^3J_{CH}$=7.3 Hz, 4'-C of Ph), 128.63 (t, $^3J_{CH}$=7.3 Hz, 1'-C of Ph), 128.71 (dd, $^3J_{CH}$=7.3 Hz, 3'-C of Ph), 141.98 (t, $^3J_{CH}$=4.9 Hz, 5-C), 160.56 (t, $^3J_{CH}$=3.7 Hz, 2-C), 162.36 (q, $^3J_{CH}$=4.3 Hz, $\underline{C}OOCH_3$), 165.13 (q, $^3J_{CH}$=4.3 Hz, $\underline{C}OOCH_3$);

The $Rh_2(OAc)_4$-catalyzed reaction of *tert*-butyl diazoacetate (**7b**) in the presence of DMAD in benzonitrile gave **8e** and **9e**.

5-*tert*-Butoxy-2-phenyloxazole (8e): 8.7 % yield; colorless oil; ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=1.44 (9H, s, CH_3 of ^{t}Bu), 6.41 (1H, s, 4-H), 7.41-7.45 (3H, m, arom-H of Ph), 7.91-7.96 (2H, m, arom-H of Ph); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=28.18 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of ^{t}Bu), 84.10 (m, quaternary-C of ^{t}Bu), 109.76 (d, J_{CH}=195.3 Hz, 4-CH), 125.49 (dm, 2'-CH of Ph), 127.88 (m, 1'-C of Ph), 128.69 (dm, 3'-CH of Ph), 129.67 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 154.44 (dt, $^3J_{CH}$=4.9 Hz, 10.4 Hz, 2-C), 156.21 (d, $^2J_{CH}$=15.3 Hz, 5-C); IR (neat) 3129, 3063, 2979, 2932, 1729, 1616, 1549, 1482, 1392, 1369, 1343, 1269, 1236, 1154, 1113, 1066, 1024, 986. 922, 850, 807, 775, 736, 708, and 690 cm^{-1}.

Dimethyl 2-*tert*-butoxycarbonyl-5-phenylpyrrole-3,4-dicarboxylate (9e): 11.2 % yield; colorless crystals; mp 147.1-149.1 °C (from benzene-hexane); ^{1}H NMR (270.05 MHz, $CDCl_3$) δ=1.45 (9H, s, CH_3 of ^{t}Bu), 3.70 (3H, s, $COOCH_3$), 3.93 (3H, $COOCH_3$), 7.40-7.44 (3H, m, arom-H of Ph), 7.50-7.57 (2H, m, arom-H of Ph), 9.69 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=28.06 (qm, CH_3 of ^{t}Bu), 51.54 (q, $COO\underline{C}H_3$), 52.58 (q, $COO\underline{C}H_3$), 82.83 (m, quaternary-C of ^{t}Bu), 111.83 (d, $^3J_{CH}$=7.3 Hz, 4-C), 121.17 (d, $^2J_{CH}$=3.1 Hz, 2-C), 124.06 (d, $^3J_{CH}$=6.1 Hz, 3-C), 128.32 (dm, arom-CH of Ph), 129.34 (dm, arom-CH of Ph), 129.43 (dm, 4'-CH of Ph), 130.29 (m, 1'-C of Ph), 139.63 (m, 5-C), 159.16 (s, $\underline{C}OO^tBu$), 163.30 (m, $\underline{C}OOCH_3$), 166.12 (m, $\underline{C}OOCH_3$); IR (KBr), 3275 (NH), 3086, 3055, 3025, 2997, 2981, 2949, 1735 (C=O), 1709 (C=O), 1687 (C=O), 1568, 1523, 1486, 1462, 1442, 1432, 1393, 1370, 1320, 1289, 1270, 1234, 1204, 1153, 1075, 1040, 1019, 999, 959, 926, 865, 847, 821, 806, 792, 763, 749, 701, 678, and 662 cm^{-1}; MS (EI) 359 (M^+), 304,

303, 285, 272, 271, 254, 240, 239, 228, 196, 195, 169. Found: C, 63.38; H, 5.91; N, 3.90 %. Calcd for $C_{19}H_{21}NO_6$: C, 63.50: H, 5.89; N, 3.90 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitrophenyl diazoacetate (**7c**) in the presence of DMAD in benzonitrile gave **8f** and **9f**.

5-*p*-Nitrophenyloxy-2-phenyloxazole (**8f**): 28.0 % yield; yellow crystals; mp 93.1-94.4 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=6.76 (1H, s, 4-CH), 7.22 (2H, d, J=9.2 Hz, 2"-CH of Ar), 7.43-7.48 (3H, m, CH of Ph), 7.93-7.99 (2H, m, CH of Ph), 8.27 (2H, d, J=9.2 Hz, 3"-CH of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=110.41 (d, J_{CH}=198.98 Hz, 4-CH), 116.68 (dd, $^3J_{CH}$=4.9 Hz, 2"-CH of Ar), 125.88 (dm, arom-CH of Ph), 126.07 (dd, $^3J_{CH}$=5.5 HZ, 3"-CH of Ar), 126.89 (m, 1'-C of Ph), 128.89 (dm, arom-CH of Ph), 130.62 (dt, $^3J_{CH}$=7.9 Hz, 4'-CH of Ph), 144.20 (m, 4"-C of Ar), 153.47 (d, $^2J_{CH}$=14.7 Hz, 5-C), 155.93 (dt, $^2J_{CH}$=11.0 Hz, $^3J_{CH}$=4.9 Hz, 2-C), 160.90 (tt, $^2J_{CH}$=10.4 Hz, $^3J_{CH}$=3.7 Hz, 1"-C of Ar); IR (KBr) 3197, 3110, 3085, 3014, 2839, 1610, 1600, 1576, 1512 (NO_2), 1486, 1449, 1411, 1338 (NO_2), 1308, 1289, 1274, 1255, 1216, 1175, 1160, 1106, 1073, 1062, 1020, 1009, 970, 936, 922, 868, 852, 820, 791, 772, 754, 724, 705, 691, 681, 668, and 662 cm^{-1}; MS (EI) 282 (M^+) 144, 116, 105, 89, 77, 63. Found: C, 63.85; H, 3.78; N, 9.76 %. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93 %.

Dimethyl 2-(*p*-nitrophenyloxycarbonyl)-5-phenylpyrrole-3,4-dicarboxylate (**9f**): 13.9 % yield; colorless crystals; mp 230.6-234.6 °C (from benzene-ethyl acetate); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.76 (3H, s, $COOCH_3$), 3.97 (3H, s, $COOCH_3$), 7.42 (2H, d, J=9.2 Hz, 2"-CH of Ar), 7.47-7.52 (3H, m, arom-CH of Ph), 7.57-7.62 (2H, m, arom-CH of Ph), 8.32 (2H, d, J=9.2 Hz, 3"-CH of Ar), 9.35 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.89 ($COO\underline{C}H_3$), 53.06 ($COO\underline{C}H_3$), 112.91 (4-C), 117.92 (2-C), 122.26 (2"-CH of Ar), 125.39 (3"-CH of Ar), 126.84 (3-C), 128.59 (2'-CH of Ph), 129.19 (3'-CH of Ph), 129.52 (1'-C), 130.11 (4'-CH), 141.38 (5-C), 145.58 (4"-C of Ar), 154.59 (1"-C of Ar), 156.77 ($\underline{C}OOAr$), 162.81 ($\underline{C}OOCH_3$), 165.48 ($\underline{C}OOCH_3$); IR (KBr) 3254 (NH), 3077, 2997, 2955, 2851, 1741 (C=O), 1714 (C=O), 1610, 1591, 1565, 1521 (NO_2), 1486, 1462, 1442, 1425, 1343 (NO_2), 1298, 1287, 1246, 1211, 1164, 1146, 1137, 1114, 1080, 1059, 1033, 1013, 956, 940, 925, 879, 864, 851, 810, 796, 767, 749, and 700 cm^{-1}; MS (EI) 425, 424 (M+), 394, 393, 380, 361, 349, 303, 287, 286, 255, 254, 226, 224, 211, 196, 170, 169, 140, 139, 129, 127, 115, 114, 113, 105, 104, 77, 59, and 39. Found: C, 58.85; H, 3.95; N, 6.57 %. Calcd for $C_{21}H_{16}N_2O_8$: C, 59.44; H, 3.80; N, 6.60 %.

The $Rh_2(OAc)_4$-catalyzed reaction of ethyl diazobenzoylacetate (**11**) in benzonitrile gave **13**.

Ethyl 2,5-diphenyloxazole-4-carboxylate (**13**): 6 % yield; colorless solid; ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.43 (3H, t, J=7.3 Hz, CH_3), 4.46 (2H, q, J=7.3 Hz, CH_2), 7.47-7.54 (6H, m, arom-H), 8.10-8.19 (4H, m, arom-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=14.30 (CH_3), 61.52 (CH_2), 121.62 (4-C), 126.36 (arom-CH), 126.88 (arom-CH), 127.11(arom-CH), 128.41 (arom-CH), 128.57

(arom-CH), 128.80 (arom-CH), 130.31 (arom-CH), 131.09 (arom-CH), 155.11 (5-C), 159.82 (2-C), 162.32 (COOEt); IR (KBr) 3030, 2957, 1724 (ester-C=O), 1579, 1561, 1492, 1445, 1374, 1354, 1326, 1304, 1215, 1105, 1070, 1040, 1022, 921, 841, 779, 762, 710, and 686 cm^{-1}; MS (EI) 295, 294 (MH^+), 266, 249, 222, 221, 105, 77.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of DMAD in pentafluorobenzonitrile gave **14a**.

5-*p*-Nitrophenyl-2-(pentafluorophenyl)oxazole (14a): 58 % yield; yellow needles; mp 170.4-171.5 °C (from benzene); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.79 (1H, s, 4-H), 7.89 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.35 (2H, d, J=8.9 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=103.45 (m, 1'-C of C_6F_5), 124.62 (dd, $^3J_{CH}$=4.3 Hz, 2"-CH of Ar), 125.05 (dd, $^3J_{CH}$=7.3 Hz, 3"-CH of Ar), 126.66 (d, J_{CH}=196.5 Hz, 4-CH), 132.66 (t, $^3J_{CH}$=7.9 Hz, 1"-C of Ar), 138.16 (dm, J_{CF}=257.6 Hz, CF of C_6F_5), 142.66 (dm, J_{CF}=260.0 Hz, CF of C_6F_5), 145.21 (dm, J_{CF}=260.6 Hz, CF of C_6F_5), 147.71 (m, 4"-C of Ar), 150.51 (dm, $^2J_{CH}$=18.3 Hz, 5-C), 151.86 (dm, 2-C); IR (KBr) 3135, 2919, 1658, 1608, 1546, 1522 (NO_2), 1488, 1335(NO_2), 1150, 1107, 1086, 1062, 1017, 992, 968, 946, 856, 846, 829, 754, 746, 709, and 693 cm^{-1}; MS (EI) 357, 356 (M^+), 327, 326, 310, 301, 298, 282, 270, 262, 255, 243, 206, 195, 179, 167, 150, 141, 117, 104, 89, 77, 76, 63, 51, 50, and 39. Found: C, 50.74; H, 1.59; N, 7.86 %. Calcd for $C_{15}H_5F_5N_2O_3$: C, 50.58; H, 1.41; N, 7.86 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of DMAD in phenyl cyanate gave **14b**.

5-*p*-Nitrophenyl-2-(phenyloxy)oxazole (14b): 63 % yield; yellow powder; mp 145.2-145.9 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=7.26-7.50 (5H, m, PhO), 7.40 (1H, s, 4-H), 7.70 (2H, d, J=8.9 Hz, 2"-H of Ar), 8.27 (2H, d, J=8.9 Hz, 3"-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=119.78 (2'-CH of PhO), 123.52 (2"-CH of Ar), 124.51 (3"-CH of Ar), 124.94 (4'-CH of PhO), 126.38 (4-CH), 129.97 (3'-CH of PhO), 133.48 (1"-C of Ar), 144.94 (5-C), 146.72 (4"-C of Ar), 152.81 (1'-C of PhO), 161.09 (2-C); IR (KBr) 3120, 3052, 1670, 1610, 1595, 1559 (NO_2), 1526, 1505, 1487, 1454, 1434, 1418, 1371, 1335 (NO_2), 1309, 1231, 1195, 1186, 1161, 1109, 1074, 1045, 1030, 1009, 994, 972, 938, 919, 847, 838, 788, 750, 735, 718, 688, and 668 cm^{-1}; MS (EI) 284, 283 (MH^+), 253, 243, 237, 193, 191, 177, 165, 150, 133, 132, 119, 105, 104, 77, 76. Found: C, 64.12; H, 3.78; N, 9.74 %. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of DMAD in diethylcyanamide gave **14d** and **16**.

2-Diethylamino-5-(*p*-nitrophenyl)oxazole (14d): 12 % yield; orange crystals; mp 92.7-95.0 °C (from hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.29 (6H, t, J=6.9 Hz, CH_3), 3.56 (4H, q, J=6.9 Hz, CH_2), 7.31 (1H, s, 4-H), 7.53 (2H, d, J=8.6 Hz, 2'-H of Ar), 8.18 (2H, d, J=8.6 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=13.41 (CH_3), 43.05 (CH_2), 121.76 (2'-CH of Ar), 124.53 (3'-CH of

Ar), 127.85 (4-CH), 134.75 (1'-C of Ar), 142.75 (5-C), 145.12 (4'-C of Ar), 162.08 (2-C); IR (KBr) 3099, 2967, 2933, 2871, 1618 (C=N), 1603, 1591 (NO_2), 1507, 1464, 1445, 1424, 1323 (NO_2), 1222, 1188, 1152, 1107, 1084, 1031, 931, 880, 850, 788, 751, 735, 692, and 668 cm^{-1}; MS (EI) 261 (M^+), 246, 232, 218, 200, 186, 172, 149. Found: C, 59.67; H, 5.80; N, 15.87 %. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08 %.

Dimethyl (diethylamino)ethylene-1,2-dicarboxylate (16); 0.5 % yield; yellow oil; ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.18 (6H, t, J=7.3 Hz, CH_3), 3.18 (4H, q, J=7.3 Hz, CH_2), 3.63 (3H, s, $COOCH_3$), 3.93 (3H, s, $COOCH_3$), 4.61 (1H, s, 2-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=12.69 (qm, CH_3), 44.89 (tm, CH_2), 50.71 (q, $COOCH_3$), 52.87 (q, $COOCH_3$), 82.94 (d, 2-CH), 153.82 (m, 1-C), 166.17 (m, $COOCH_3$), 168.38 (m, $COOCH_3$); IR (neat) 2980, 2947, 1742 (C=O), 1689 (C=O), 1569 (C=C), 1448, 1425, 1378, 1360, 1296, 1224, 1198, 1160, 1129, 1078, 1047, 1011, 973, 947, 927, 863, 825, 790, 749, and 680 cm^{-1}.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of DMAD in diisopropylcyanamide gave **14e** and **15e**.

2-Diisopropylamino-5-(*p*-nitrophenyl)oxazole (14e): 71 % yield; red crystals; mp 103.9-107.6 °C (benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.38 (12H, d, J=6.9 Hz, CH_3), 4.16 (2H, spt, J=6.9 Hz, CH of ^iPr), 7.32 (1H, s, 4-H), 7.54 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.21 (2H, d, J=8.9 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.77 (qqui, $^{2,3}J_{CH}$=4.3 Hz, CH_3), 47.73 (dsxt, $^2J_{CH}$=4.3 Hz, CH of ^iPr), 121.70 (dd, $^3J_{CH}$=6.7 Hz, 2'-CH of Ar), 124.64 (dd, $^3J_{CH}$=4.3 Hz, 3'-CH of Ar), 127.26 (d, J_{CH}=190.4 Hz, 4-CH), 134.86 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 142.53 (dt, $^2J_{CH}$=16.5 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 145.06 (m, 4'-C of Ar), 161.90 (dt, $^2J_{CH}$=12.2 Hz, $^3J_{CH}$=6.1 Hz, 2-C); IR (KBr) 3109, 2974, 1577 (NO_2), 1500, 1468, 1403, 1382, 1367, 1327 (NO_2), 1294, 1233, 1209, 1155, 1126, 1107, 1047, 1003, 938, 914, 851, 753, 735, and 689 cm^{-1}; MS (EI) 289 (M^+), 274, 247, 246, 232, 205, 186, 159, 149. Found: C, 62.42; H, 6.58; N, 14.35 %. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52 %.

Dimethyl 2-diisopropylamino-5-(*p*-nitrobenzoyl)pyrrole-3,4-dicarboxylate (15e); 8 % yield; yellow crystals; mp 170.0-172.7 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.28 (12H, d, J=6.6 Hz, CH_3), 3.36 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 3.87 (2H, spt, J=6.6 Hz, CH of ^iPr), 7.78 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.29 (2H, d, J=8.9 Hz, 3'-H of Ar), 8.88 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=22.26 (qd, $^2J_{CH}$=4.3 Hz, CH_3), 22.34 (qd, $^2J_{CH}$=4.3 Hz, CH_3), 50.40 (dm, CH of ^iPr), 51.57 (q, $COO\underline{C}H_3$), 52.17 (q, $COO\underline{C}H_3$), 106.45 (d, $^3J_{CH}$=6.7 Hz, 3-C), 121.63 (d, $^2J_{CH}$=3.1 Hz, 5-C), 123.28 (dd, $^3J_{CH}$=4.9 Hz, 2'-CH of Ar), 126.96 (d, $^3J_{CH}$=6.1 Hz, 4-C), 128.94 (dd, $^3J_{CH}$=7.3 Hz, 3'-CH of Ar), 143.79 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 146.17 (m, 2-C), 149.28 (m, 4'-C of Ar), 163.09 (q, $^3J_{CH}$=3.7 Hz, $\underline{C}OOCH_3$), 165.36 (q, $^3J_{CH}$=2.4 Hz, $\underline{C}OOCH_3$), 182.22 (t, $^3J_{CH}$=4.3 Hz, C=O); IR (KBr) 3453 (NH), 3198, 3106, 3071, 3032, 2962, 2875, 1731 (C=O), 1709 (C=O), 1609, 1593, 1569, 1539 (NO_2), 1517, 1457, 1439, 1405, 1369, 1344 (NO_2), 1320, 1295, 1261, 1247, 1197, 1167 1127, 1103, 1083, 1026, 1015, 985, 962, 936, 914, 869, 847, 816 788,

740, 717, and 670 cm^{-1}; MS (EI) 432, 431, (M^+), 430, 402, 357, 356, 342, 282, 222, 221, 208 207, 147, 73. Found: C, 58.38; H, 5.84; N, 9.72 %. Calcd for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of methyl propiolate in benzonitrile gave **17a** and **18a**.

Methyl 2-(*p*-nitrobenzoyl)-5-phenylpyrrole-3-carboxylate (18a): 4 % yield; yellow crystals; mp 225.4-227.0 °C (from benzene); ^1H NMR (270.05 MHz, $CDCl_3$) δ=3.40 (3H, s, $COOCH_3$), 7.05 (1H, d, J=3.0 Hz, 4-H), 7.38-7.54 (3H, m, arom-H of Ph), 7.61-7.67 (2H, m, arom-H of Ph), 7.91 (2H, d, J=8.9 Hz, 2"-H of Ar), 8.31 (2H, d, J=8.9 Hz, 3"-H of Ar), 9.78 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=51.56 (q, $COO\underline{C}H_3$), 111.15 (dd, $^3J_{CH}$=7.0 Hz, 4-CH), 123.06 (m, 3-C), 123.36 (dm, 2"-CH of Ar), 125.14 (dm, 2'-CH of Ph), 129.08 (dm, 4'-CH of Ph), 129.37 (dd, arom-CH), 129.50 (dd, arom-CH), 129.68 (m, 2-C), 130.15 (m, 5-c), 137.34 (1'-C of Ph), 144.44 (t, $^3J_{CH}$=7.6 Hz, 1"-C of Ar), 149.62 (m, 4"-C of Ar), 163.94 (m, $\underline{C}OOCH_3$), 184.99 (C=O); IR (KBr) 3293 (NH), 2949, 1728 (ester-C=O), 1618 (keto-C=O), 1597, 1513 (NO_2), 1458, 1431, 1348 (NO_2), 1298, 1275, 1259, 1204, 1098, 920, 866, 853, 774, 765, 742, 716, 689, and 668 cm^{-1}; MS (EI) 350 (M^+), 318, 272, 260, 244, 216, 196, 159, 140. Found: C, 65.34; H, 4.18; N, 7.84 %. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00 %.

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of methyl propiolate in acetonitrile gave **17b**, **18b**, and **19b**.

2-Methyl-5-(*p*-nitrophenyl)oxazole (17b): 73 % yield; yellow crystals; mp 163.3-165.9 °C (from benzene-hexane); ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.58 (3H, s, CH_3), 7.42 (1H, s, 4-H), 7.75 (2H, d, J=8.6 Hz, 2'-H of Ar), 8.27 (2H, d, J=8.6 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=14.19 (q, CH_3), 124.24 (dd, $^3J_{CH}$=7.3 Hz, 2'-CH of Ar), 124.47 (dd, $^3J_{CH}$=4.9 Hz, 3'-CH of Ar), 125.46 (d, J_{CH}=193.5 Hz, 4-CH), 133.89 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 146.99 (m, 4'-C of Ar), 149.13 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.9 Hz, 5-C), 162.92 (qd, $^2J_{CH}$=11.6 Hz, $^3J_{CH}$=7.9 Hz, 2-C); IR (KBr) 3121, 2931, 1710, 1608 (C=N), 1555, 1505 (NO_2), 1437, 1415, 1348, 1332(NO_2), 1281, 1218, 1134, 1107, 1061, 943, 854, 754, 690, and 669 cm^{-1}; MS (EI) 204 (M+), 174, 158, 146, 130, 117, 103, 89. Found: C, 58.54; H, 4.04; N, 13.59 %. Calcd for $C_{10}H_8N_2O_3$: 58.82; H, 3.95; N, 13.72 %.

Methyl 5-methyl-2-(*p*-nitrobenzoyl)pyrrole-3-carboxylate (18b): 4 % yield; yellow crystals; ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.39 (3H, s, CH_3), 3.35 (3H, s, $COOCH_3$), 6.49 (1H, d, J=3.0 Hz, 4-H), 7.85 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.28 (2H, d, J=8.9 Hz, 3'-H of Ar), 9.66 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=13.02 (qm, CH_3), 51.41 (q, $COO\underline{C}H_3$), 112.72 (dm, 4-CH), 122.62 (dd, $^2J_{CH}$=3.1 Hz, 3-C), 123.30 (dd, $^3J_{CH}$=4.3 Hz, 2'-C of Ar), 128.94 (dd, $^2J_{CH}$=3.1 Hz, 2-C), 129.47 (dd, $^3J_{CH}$=6.7 Hz, 3'-C of Ar), 134.98 (m, 5-C), 144.71 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 149.53 (m, 4'-C of Ar), 164.20 (m,

$\underline{C}OOCH_3$), 184.79 (m, C=O); IR (KBr) 3277 (NH), 2949, 1725 (ester-C=O), 1617 (keto-C=O), 1595, 1515 (NO_2), 1495, 1440, 1346 (NO_2), 1316, 1283, 1240, 1201, 1092, 920, 867, 853, 838, 794, 775, 740, 720, and 669 cm^{-1}.

Methyl 5-methyl-2-(*p*-nitrobenzoyl)pyrrole-4-carboxylate (19b): 1 % yield; yellow crystals; ^1H NMR (270.05 MHz, $CDCl_3$) δ=2.66 (3H, s, CH_3), 3.84 (3H, s, $COOCH_3$), 7.21 (1H, d, J=2.6 Hz, 3-H), 8.02 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.36 (2H, d, J=8.9 Hz, 3'-H of Ar), 9.72 (1H, brs, NH).

The $Rh_2(OAc)_4$-catalyzed reaction of *p*-nitro-α-diazoacetophenone (**1i**) in the presence of methyl propiolate in diisopropylcyanamide gave **17c**, and **18c**.

Methyl 2-diisopropylamino-5-(*p*-nitrobenzoyl)pyrrole-4-carboxylate (18c): 5 % yield; orange crystals; ^1H NMR (270.05 MHz, $CDCl_3$) δ=1.33 (12H, d, J=6.9 Hz, CH_3), 3.27 (3H, s, $COOCH_3$), 3.80 (2H, spt, J=6.9 Hz, CH of ^iPr), 5.92 (1H, s, 3-H), 7.76 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.26 (2H, d, J=8.9 Hz, 3'-H of Ar), 8.79 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.96 (qqui, $^{2,3}J_{CH}$=4.3 Hz, CH_3), 48.32 (dm, CH of ^iPr), 51.49 (q, $COO\underline{C}H_3$), 98.65 (dd, $^3J_{CH}$=4.3 Hz, 3-CH), 122.15 (d, $^3J_{CH}$=6.7 Hz, 4-C), 123.13 (dd, $^3J_{CH}$=4.3 Hz, 2'-CH of Ar), 125.83 (m, 5-C), 129.04 (dd, $^3J_{CH}$=7.3 Hz, 3'-CH of Ar), 145.23 (m, 2-C), 146.39 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 148.71 (m, 4'-C of Ar), 164.85 (m, $\underline{C}OOCH_3$), 179.86 (m, C=O); IR (KBr) 3240 (NH), 2962, 1718 (ester-C=O), 1608 (keto-C=O), 1541 (NO_2), 1520, 1467, 1341 (NO_2), 1264, 1204, 1176, 1146, 854, 834, and 668 cm^{-1}.

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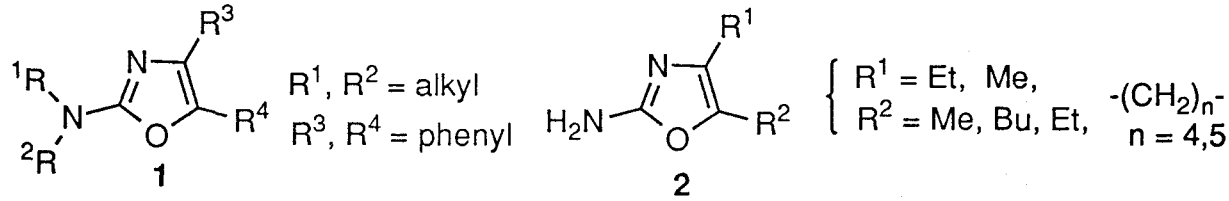
Chapter 3. Synthesis of 2-Aminooxazoles

3-1 Introduction

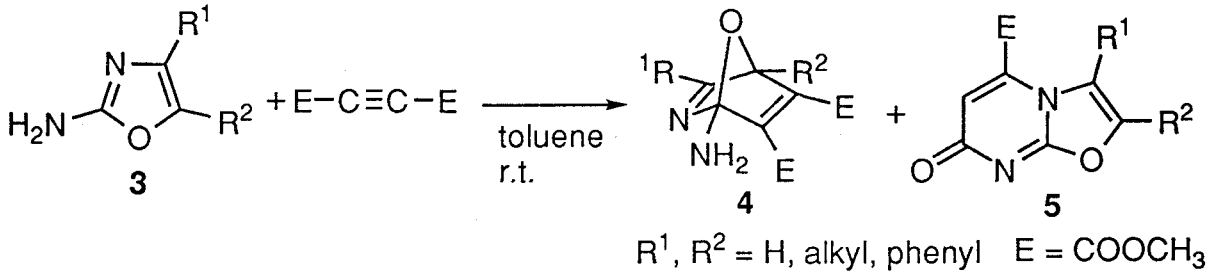
2-Aminooxazoles have been accepted as the most attracting chemicals of all oxazole derivatives because of their high biological activities.[1), 2)] For example, oxazole **1** is known to possess antiinflammatory and analgetic properties.[3),4),5)] Oxazole **2** is useful as hypertensive agents for increasing arterial pressure and diuresis.[6),7)]



1 **2**

Figure 1

A novel reactivity of 2-aminooxazole is reported by G. Crank et al.[8)] The reaction of 2-aminooxazole **3** with equimolar amount of DMAD was completed within a few minutes at room temperature, and gave Diels-Alder adduct **4** along with **5** (Scheme 1). Usually, a Diels-Alder adduct of oxazole with acetylene derivatives is too unstable to be isolated, and is easily converted into the furan derivative with loss of nitriles.



3 **4** **5**

Scheme 1

In 1978, Ibata et al. demonstrated that $BF_3 \cdot OEt_2$-catalyzed decomposition of α-diazocarbonyl compounds in nitriles gave oxazole derivatives in high yields.[9)] This method is applicable to the synthesis of a wide range of substituted oxazole, and is considered as one of the most powerful tools for oxazole syntheses. However, the application of this method to 2-aminooxazole synthesis did not give a fruitful result. The decomposition of α-diazoacetophenones **6** in the presence of dimethylcyanamide required excess amount of $BF_3 \cdot OEt_2$, and gave the corresponding 2-aminooxazoles **7** in low yields (Table 1). This is attributed to quenching of the activity of $BF_3 \cdot OEt_2$ catalyst by the coordination of dimethylcyanamide to BF_3.

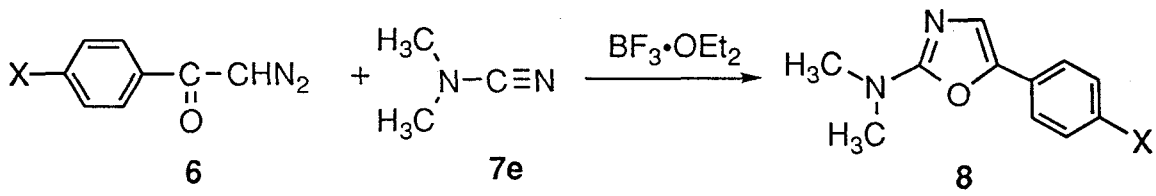


Table 1. BF_3•OEt_2-catalyzed Reaction of **6** with Dimethylcyanamide

X	Yield / %
CH_3O	33
H	29
Cl	5

As a continuation of the previous works, the use of $Rh_2(OAc)_4$ as a catalyst, which has much weaker Lewis acidity than BF_3•OEt_2, seems to be applicable to this reaction in order to develope the preparative method of the biologically active 2-aminooxazoles. In this chapter, $Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenones and α-diazoacetates with various substituted cyanamides is described.

3-2 $Rh_2(OAc)_4$-catalyzed Reaction of α-Diazoacetophenones with Various Cyanamides

The rhodium(II) acetate-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of large excess of *N*,*N*-diisopropylcyanamide (**7a**) at 60 °C gave 2-(*N*,*N*-diisopropylamino)-5-(*p*-nitrophenyl)oxazole (**8a**) in 95 % yield. Reactions of other para-substituted α-diazoacetophenones (**6b-f**) having an electron-releasing or electron-withdrawing substituent with **7a** also gave the corresponding 2-(*N*,*N*-diisopropylamino)-5-aryloxazoles in high yields (Table 2, Runs 2-6). Other *N*,*N*-dialkylcyanamides such as dimethyl-, diethyl-, ethylmethyl-, and methylphenylcyanamides also afforded the oxazoles in high yields in the reaction with *p*-nitro-α-diazoacetophenone (**6a**) as is shown in Table 1 (Runs 10-13).

However, unsubstituted cyanamide (**7b**) gave 2-amino-5-(*p*-nitrophenyl)oxazole (**8g**) only in 7 % yield with recovering of **6a** in 69 % (Run 7). Under these reaction conditions, the sharp color change of the reaction mixture from green to purple was observed, which indicates that the catalytic reactivity of $Rh_2(OAc)_4$ was much decreased by strong complexation of unsubstituted cyanamide (**7b**) to the active site of $Rh_2(OAc)_4$. Monoalkyl cyanamides such as *N*-methyl and *N*-*tert*-butylcyanamides also gave the corresponding oxazoles in low yields (Runs 8 and 9). Therefore, two alkyl groups on nitrogen atom are necessary to

obtain 2-aminooxazoles in good yield. The reaction of **6a** with *N*-cyanopiperidine (**7i**) gave 2-piperidino-5-(*p*-nitrophenyl)oxazole (**8n**) in 70 % yield (Run 14).

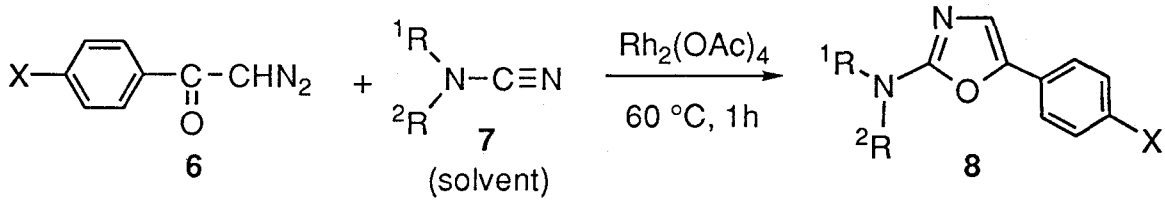


Table 2. $Rh_2(OAc)_4$-Catalyzed Reaction of α-Diazoacetophenones with Cyanamides.

Run	Diazoacetophenone		Cyanamide			Oxazole	
	6	X	7	R^1	R^2	8	Yield / %
1	**6a**	NO_2	**7a**	^{i}Pr	^{i}Pr	**8a**	95
2	**6b**	CN	**7a**	^{i}Pr	^{i}Pr	**8b**	79
3	**6c**	Cl	**7a**	^{i}Pr	^{i}Pr	**8c**	75
4	**6d**	H	**7a**	^{i}Pr	^{i}Pr	**8d**	76
5	**6e**	Me	**7a**	^{i}Pr	^{i}Pr	**8e**	83
6	**6f**	OMe	**7a**	^{i}Pr	^{i}Pr	**8f**	70
7[a)]	**6a**	NO_2	**7b**	H	H	**8g**	7
8[a)]	**6a**	NO_2	**7c**	H	Me	**8h**	13
9[a)]	**6a**	NO_2	**7d**	H	^{t}Bu	**8i**	33
10	**6a**	NO_2	**7e**	Me	Me	**8j**	82
11	**6a**	NO_2	**7f**	Et	Et	**8k**	98
12[a)]	**6a**	NO_2	**7g**	Me	Et	**8l**	74
13[a)]	**6a**	NO_2	**7h**	Me	Ph	**8m**	84
14[a)]	**6a**	NO_2	**7i**	$-(CH_2)_5-$		**8n**	70

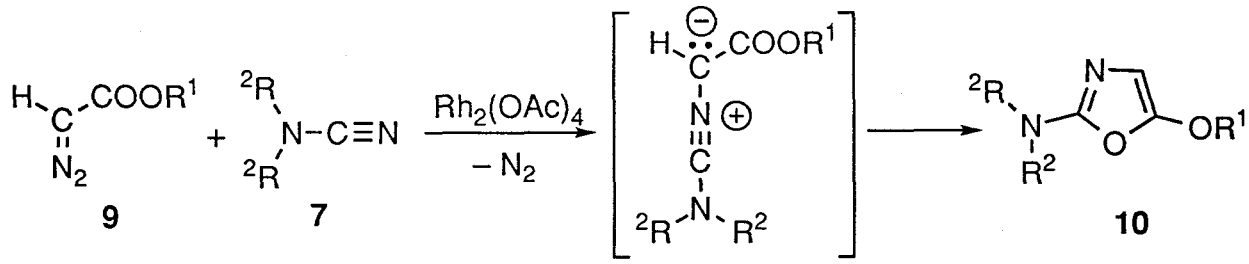
a) The reaction was carried out using 10 molar amounts of cyanamide in refluxing CH_2Cl_2.

Thermolysis and copper-catalyzed reactions of α-diazoacetophenones with benzonitrile have been reported by Huisgen to produce 2-phenyl-5-aryloxazoles in moderate yields.[10] However, the generality of this reaction has not been developed. Therefore, these results indicate that the

$Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenones with cyanamides can be the general method of the synthesis of 2-alkylamino-5-aryloxazoles (**8**) in comparison to the similar reaction catalyzed by $BF_3 \cdot OEt_2$.

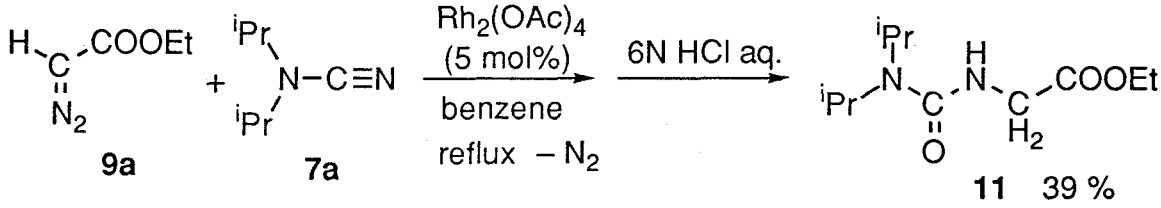
3-3 $Rh_2(OAc)_4$-catalyzed Reaction of α-Diazoacetates with Diisopropylcyanamide

It is well-known that 5-alkoxyoxazole has a high reactivity as 2-azadiene, because its alkoxyl group on 5-position increase the electron density of the oxazole ring. Thus, 2-amino-5-alkoxyoxazole is expected to possess higher reactivity toward the dienophiles having electron-defficient unsaturated bonds.



Scheme 2

The $Rh_2(OAc)_4$-catalyzed reactions of ethyl α-diazoacetate (**9a**) with 10 equivalents of diisopropylcyanamide (**7a**) at the reflux temperature of various solvents such as dichloromethane, benzene, and toluene gave no oxazole derivatives after treatment of column chromatography. However, the treatment of the reaction mixture with 6N HCl aq. gave urea derivative **11** in 39 % yield.



Scheme 3

Similar reactions of **9a** with **7a** in the presence of DMAD gave pyrrole derivative **12** in the yield listed in Table 3.

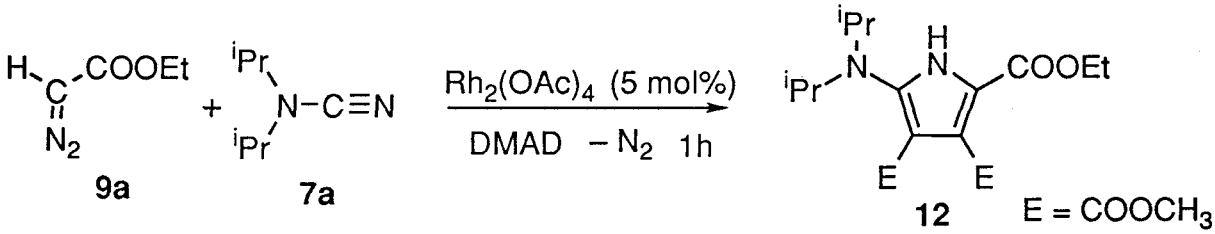
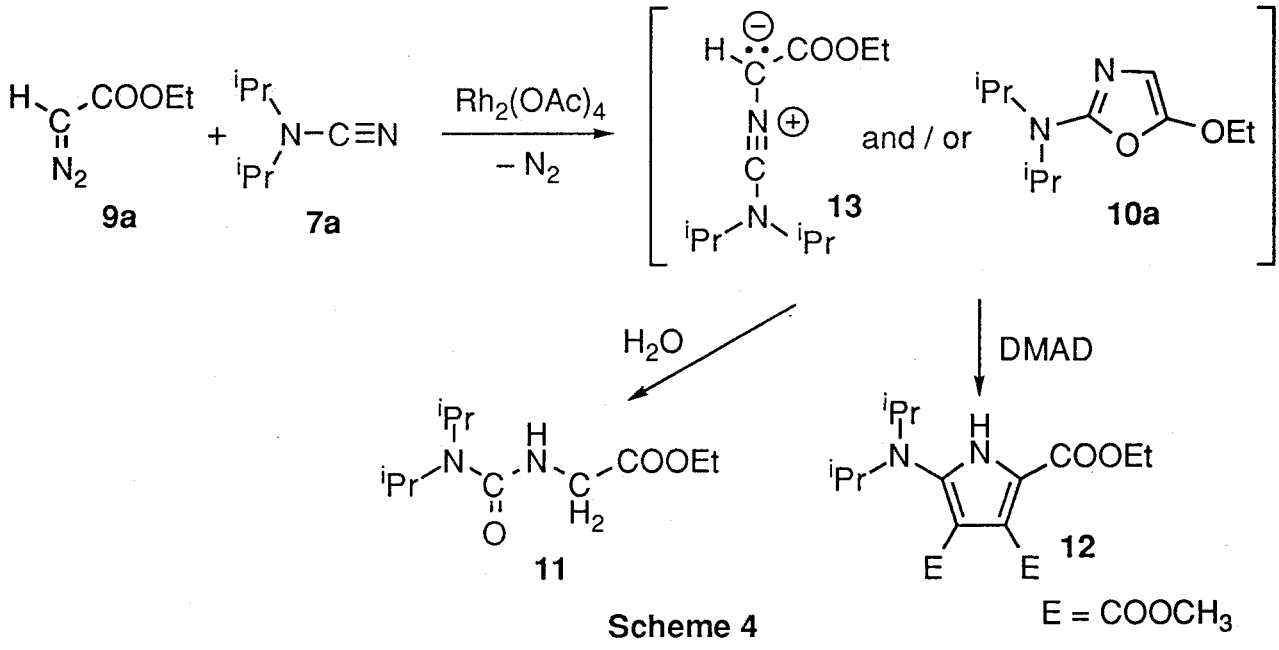


Table 3. $Rh_2(OAc)_4$-catalyzed Reaction of **9a** with **7a** in the Presence of DMAD

Run	DMAD / equiv.	Conditions	Yield / %
1	1	benzene, reflux	26
2	20	CH_2Cl_2, reflux	19
3	20	benzene, reflux	42

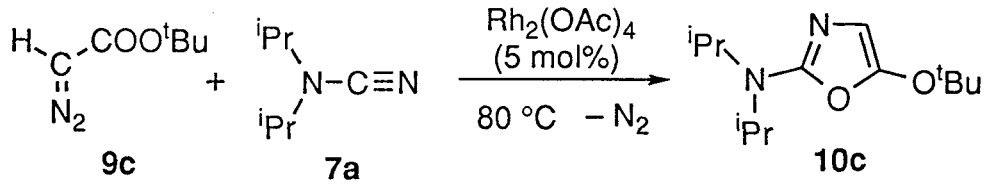
The formation of **11** and **12** is explained by the following mechanism including unstable intermediate, nitrile ylide **13**, and/or oxazole **10a** (Scheme 4). The $Rh_2(OAc)_4$-catalyzed reaction of **9a** with **7a** generated **13** and/or **10a** which gave urea **11** by hydrolysis and gave pyrrole **12** by cycloaddition with DMAD.



Scheme 4

The $Rh_2(OAc)_4$-catalyzed decomposition of isopropyl α-diazoacetate (**9b**) in diisopropylcyanamide also did not give the corresponding oxazole derivative **10b**. In these reactions of **9a** and **9b**, the ^1H NMR spectra of the reaction mixtures showed the existence of the similar oxazole derivatives, but their lability did not allowed their isolation.

On the other hand, *tert*-butyl α-diazoacetate **9c** afforded oxazole **10c** in 49 % yield.



Scheme 5

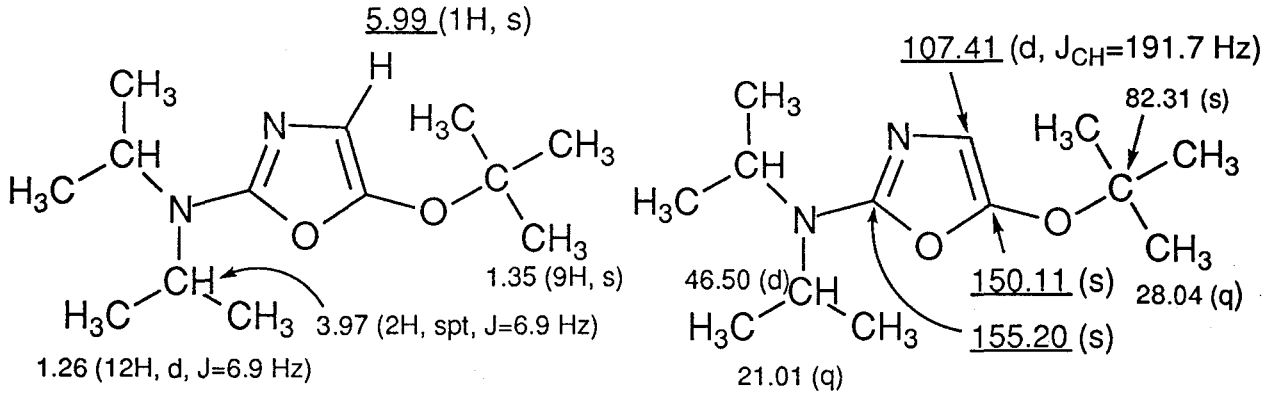


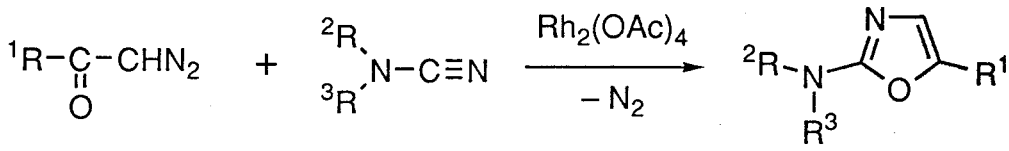
Figure 2. ^1H NMR and ^{13}C NMR of **10c** (δ)

^1H NMR spectrum of **10c** showed a singlet signal of H-4 of oxazole ring at 5.99 ppm. In ^{13}C NMR, three carbons of oxazole ring resonated at δ=155.20 (C-2), 107.41 (C-4), and 150.11 (C-5). Especially coupling constant of C-4 (J_{CH}=191.7 Hz) is typical value for that of oxazole dirivatives.[10] In IR spectrum, C=N absorption was observed at 1585 cm^{-1} without showing neither ester carbonyl group (ca. 1700 cm^{-1}) nor ylide moiety (ca. 2000 cm^{-1}). These spectroscopic properties support the elucidated structure of the isolated species **10c** which does not have an open structure like a nitrile ylide form, but have a oxazole ring.

The reaction and mechanism of 2-amino-5-alkoxyoxazole with various dipolarophiles will be disscussed in detail in the following chapters.

3-4 Conclusion

In this chapter, an application of the $Rh_2(OAc)_4$-catalyzed reaction of diazocarbonyl compounds with nitriles was described. The $Rh_2(OAc)_4$-catalyzed decomposition of α-diazoacetophenones in the presence of substituted cyanamides gave 2-aminooxazoles in high yields (Scheme 6). Although α-diazoacetates yielded unstable 2-amino-5-alkoxyoxazoles in low yields, this result provides the new efficient synthetic method of the biologically active 2-aminooxazole derivatives. The $Rh_2(OAc)_4$-catalyzed reaction proceeds under neutral and mild condition, which is advantageous over other methods ever known.



Scheme 6

Experimental

Melting points were measured with a Yanagimoto Melting-point Apparatus and were not corrected. IR spectra were recorded on a Perkin-Elmer model 983. ^{1}H NMR (270.05 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL EX-270 in a $CDCl_3$ solution using TMS as an internal standard. Mass spectra were determined with a JEOL JMS-DX303 spectrometer and a SHIMADZU GCMS-QP2000A gas chromatograph mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-5.

Materials and Solvents. α-Diazoacetophenones were prepared by the reaction of the corresponding acid chlorides with excess of diazomethane in the presence of triethylamine according to Newman's method.[11] Ethyl diazoacetate was prepared by the diazotization of ethyl glycinate hydrochloride with sodium nitrite.[12] Isopropyl diazoacetate and *tert*-butyl diazoacetate was prepared by the acyl cleavage of isopropyl diazoacetoacetate and *tert*-butyl diazoacetoacetate with sodium methoxide or potassium hydroxide.[13] Commercially available dimethyl-, diethyl-, and diisopropylcyanamides were distilled before use. Cyanamide (**7b**) was synthesized according to the literature.[14] Methylcyanamide (**7c**) and *tert*-butylcyanamide (**7d**) were synthesized by use of the modified method of the literature.[15] Ethylmethylcyanamide (**7g**), methylphenylcyanamide (**7h**), and *N*-cyanopiperidine (**7i**) were also synthesized by use of the modified method of the literature.[16] DMAD was purified by distillation of the commercial reagent.

Cyanamide (**7b**): A 40.36 g (0.5 mol) of calcium cyanamide was added to a mixture of 55 ml (0.75 mol) of acetic acid and 185 ml of water for 85 minutes. After stirring of the reaction mixture at room temperature for 2.5 h, the solvent was removed under reduced pressure, and then the residue was dried at 40-50 °C at 20mmHg for additional 13.5 h. The mixture was extracted with two portions of 400 ml of ether, which were saturated with water and added a few drops of acetic acid, with Soxhlet apparatus. The combined etheral solution was dried over anhydrous sodium sulfate, and the ether was removed under reduced pressure to give the crude product(193 mmol, 39 %), which was distilled under reduced pressure just before use. colorless oil: bp. 83 °C/5 mmHg: IR(KBr); 3340 (NH), 2245 (C≡N), 1625, 1576, and 1125 cm^{-1}.

Methylcyanamide (**7c**): A 693 mg (10 mmol) of methylamine hydrochloride was added to a suspension of 1.1 g (6.6 mmol) of cyanogen bromide and 2.15 g (20 mmol) of sodium carbonate in one portion at room temperature. After additional stirring at room temperature for 16 h, the reaction mixture was filtered, and the ether was removed under reduced pressure to give 401 mg of colorless oil (72 %), which was used in the next reaction without further purification. colorless oil; ^{1}H NMR (270 MHz,

$CDCl_3$); δ=2.88 (3H, d, J=5.0 Hz, CH_3), 3.43 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$); δ=32.67 (CH_3), 117.63 (C≡N).

***tert*-Butylcyanamide** (**7d**): A solution of 1.47 g (20 mmol) of *tert*-butylamine dissolved in 1 ml of ether was added dropwise to a suspension of 2.1 g (20 mmol) of cyanogen bromide and 4.25 g (40 mmol) of sodium carbonate in 10ml of ether cooled with dry ice-carbon tetrachloride bath at -20 °C for 10 minutes. The reaction mixture was stirred at -20 °C for 2 h, and then at 0 °C for 2 h, and filtered. The ether was removed under reduced pressure to give 1.368 g of crude product (70 %), which was distilled under reduced pressure just before use. colorless oil; ^1H NMR (270 MHz, $CDCl_3$); δ=1.30 (9H, s, CH_3), 4.24 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$); δ=29.11 (CH_3), 53.39 (quaternary-C), 115.07 (C≡N); IR (neat); 3197 (NH), 2969, 2877, 2211 (C≡N), 1465, 1442, 1396, 1370, 1234, 1207, 1153, 1035, 935, 894, and 773 cm^{-1}.

Ethylmethylcyanamide (**7g**): A 10 ml of etheral solution of 1.46 g (20 mmol) of dimethylethylamine was added dropwise to a suspension of 1.1 g (10 mmol) of cyanogen bromide in 10 ml of ether under reflux for 3 h. After additional heating for 1 h, the reaction mixture was concentrated to give 319 mg of colorless oil. The crude product was used in the next reaction without further purification (38 %). colorless oil: ^1H NMR(270MHz, $CDCl_3$); δ=1.27 (3H, t, J=7.3 Hz, CH_3 of Et), 2.83 (3H, s, CH_3), 3.03 (2H, q, J=7.3 Hz, CH_2 of Et); IR(neat); 3575, 3507, 2979, 2936, 2207 (C≡N), 1635, 1450, 1386, 1300, 1263, 1193, 1056, 958, 799, and 733 cm^{-1}.

Methylphenylcyanamide (**7h**): A 7.15 g (67.5 mmol) of cyanogen bromide was added to a 16.30 g (134.5 mmol) of *N,N*-dimethylaniline, and heated at 100 °C for 19 h. The reaction mixture was poured into a 200 ml of ether, and washed with 100 ml of 5 % of aqueous solution of hydrochloric acid. The etheral layer was washed with 100 ml of saturated aqueous solution of sodium bicarbonate and 50 ml of brine successively, and dried over anhydrous calcium sulfate. The ether was removed under reduced pressure, and 7.29 g of crude product was obtained (54.7 mmol, 81 %), which was distilled under reduced pressure just before use. pale yellow oil: bp. 81.5 °C/1.5mmHg; ^1H NMR (270MHz, $CDCl_3$); δ=3.35 (3H, s, CH_3), 7.08-7.14 (3H, m), 7.36-7.42 (2H, m); IR (neat); 3043, 2939, 2917, 2831, 2221 (C≡N), 1598, 1498, 1449, 1330, 1299, 1284, 1226, 1186, 1158, 1113, 1080, 1032, 961, 889, 818, 751, 722, and 689 cm^{-1}.

***N*-Cyanopiperidine** (**7i**): A 10 ml of etheral solution of 10.03 g (101 mmol) of *N*-methylpiperidine was added dropwise to a suspension of 5.1 g (48 mmol) of cyanogen bromide in 10 ml of ether with ice bath cooling for 40 min. The reaction mixture was stirred for additional 30 minutes at 0 °C, and then room temperature for 3 h. The reaction mixture was poured into a 40 ml of 5 % of aqueous solution of hydrochloric acid, and the separated aqueous layer was washed with 40 ml of ether. The combined etheral layer was washed with two portions of 20 ml of saturated aqueous solution of

sodium bicarbonate and 40 ml of brine successively, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure to give 1.52 g of crude product (13.8 mmol, 28 %), which was distilled under reduced pressure just before use. colorless oil: ^{1}H NMR(270 MHz, $CDCl_3$); δ=1.52-1.70 (6H, m, $CH_2 \times 3$), 3.16-3.20 (4H, m, *N*-CH_2): IR(neat); 3508, 2941, 2857, 2208 (C≡N), 1629, 1465, 1450, 1382, 1339, 1276, 1260, 1219, 1202, 1181, 1119, 1103, 1065, 1021, 989, 956, 910, 855, and 725 cm $^{-1}$.

General Procedure for $Rh_2(OAc)_4$-catalyzed Decomposition of α-Diazoacetophenones (6) in the Presence of Cyanamides (7): A solution of 1 mmol of α-diazoacetophenone (**6**) dissolved in 20 ml of cyanamide (**7**) or CH_2Cl_2 was added to the mixture of 5 mol% of $Rh_2(OAc)_4$ and an excess of cyanamide (10 ml) at 60 or 40 °C under Ar atmosphere for 2 h, then the reaction mixture was stirred for 1 h to complete the reaction. After removal of solvent and excess cyanamide under reduced pressure, the residue was separated by medium pressure column chromatography on silica gel using hexane-ethyl acetate as an eluent.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of diisopropylcyanamide (**7a**) gave 2-diisopropylamino-5-(*p*-nitrophenyl)oxazole (**8a**) in 95 % yield.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-cyano-α-diazoacetophenone (**6b**) in the presence of diisopropylcyanamide (**7a**) gave 5-*p*-cyanophenyl-2-(diisopropylamino)oxazole (**8b**).

5-*p*-Cyanophenyl-2-(diisopropylamino)oxazole (8b): 79 % yield colorless crystals; mp 155.3-156.8 °C (from benzene-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.36 (12H, d, J=6.9Hz, CH_3 of ^{i}Pr), 4.13 (2H, sep., J=6.9Hz, CH of ^{i}Pr), 7.24 (1H, s, 4-H), 7.50(2H, d, J=7.3 Hz, 2'-H of Ar), 7.59 (2H, d, J=7.3 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.77 (q quin., J_{CH}=126.3 Hz, $^2J_{CH}$ and $^3J_{CH}$=4.3 Hz, CH_3 of ^{i}Pr), 47.60 (d sext., J_{CH}=137.3 Hz, $^2J_{CH}$=4.3 Hz, CH of ^{i}Pr), 108.45 (t, $^3J_{CH}$=9.2 Hz, 4'-C of Ar), 119.23 (t, $^3J_{CH}$=9.2 Hz, CN), 121.97 (dd, J_{CH}=163.6 Hz, $^3J_{CH}$=6.1 Hz, 2'-CH of Ar), 126.11 (d, J_{CH}=189.8 Hz, 4-CH), 132.65 (dd, J_{CH}=166.0 Hz, $^3J_{CH}$=6.1 Hz, 3'-CH of Ar), 133.01 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 142.64 (dt, $^2J_{CH}$=16.5 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 161.61 (dt, $^3J_{CH}$=12.2 Hz, $^3J_{CH}$=6.1 Hz, 2-C): IR (KBr) 3126 (CH), 3049 (CH), 2971 (CH), 2215 (CN), 1578 (NO_2 and C=N), 1499, 1455, 1421, 1380, 1365, 1336 (NO_2), 1211, 1184, 1156, 1120, 1048, 1000, 941, 842, 770, 739, and 721 cm^{-1}; MS (EI) 269 (M^+), 254, 227, 226, 212, 185, 130, 129, 102. Found: C, 71.57; H, 7.13; N, 15.31 %. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60 %.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-chloro-α-diazoacetophenone (**6c**) in the presence of diisopropylcyanamide (**7a**) gave 5-*p*-chlorophenyl-2-(diisopropylamino)oxazole (**8c**).

5-*p*-Chlorophenyl-2-(diisopropylamino)oxazole (8c): 75 % yield; yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.34 (12H, d, J=6.9 Hz, CH_3), 4.10 (2H,

spt, J=6.9 Hz, CH), 7.05 (1H s, 4-H), 7.30 (2H, d, J=8.6 Hz, 2'-H of Ar), 7.38 (2H, d, J=8.6 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.84 (CH_3), 47.40 (CH), 122.51 (4-CH), 123.38 (2'-CH of Ar), 127.71 (1'-C of Ar), 128.89 (2'-CH of Ar), 131.48 (4'-C of Ar), 143.36 (5-C), 160.95 (2-C); IR (neat) 3202, 3110, 3079, 2971, 2873, 1595 (C=N), 1483, 1455, 1419, 1400, 1379, 1367, 1330, 1272, 1208, 1158, 1123, 1092, 1048, 1028, 1010, 940, 914, 847, 822, and 735cm^{-1}; MS (EI) 281, 280, 279 (MH^+), 264, 239, 238, 237, 236, 223, 222, 221, 196, 195, 194, 193, 141, 140, 139, 138, 111.

$Rh_2(OAc)_4$-catalyzed decomposition of α-diazoacetophenone (**6d**) in the presence of diisopropylcyanamide (**7a**) gave 2-diisopropylamino-5-phenyloxazole (**8d**).

2-Diisopropylamino-5-phenyloxazole (**8d**): 76 % yield; yellow oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.35 (12H, d, J=6.9 Hz, CH_3), 4.10 (2H, spt, J=6.9 Hz, CH), 7.06 (1H s, 4-H), 7.16 (1H, t, J=7.6.Hz, 4'-H of Ar), 7.33 (2H, t, J=7.6 Hz, 3'-H of Ar), 7.47 (2H, d, J=7.6 Hz, 2'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.86 (CH_3), 47.33 (CH), 121.90 (4-CH), 122.24 (3'-CH of Ar), 126.16 (4'-C of Ar), 128.70 (2'-CH of Ar), 129.22 (1'-C of Ar), 144.33 (5-C), 160.91 (2-C); IR (neat) 3397, 3202, 3111, 3076, 2970, 2933, 2873, 1599 (C=N), 1581, 1490, 1449, 1413, 1379, 1366, 1333, 1231, 1207, 1160, 1122, 1072, 1051, 1031, 1021, 996, 940, 914, 862, 824, 758, 733, and 690 cm^{-1}.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-methyl-α-diazoacetophenone (**6e**) in the presence of diisopropylcyanamide (**7a**) gave 2-diisopropylamino-5-(*p*-tolyl)oxazole (**8e**).

2-Diisopropylamino-5-(*p*-tolyl)oxazole (**8e**): 83 % yield; yellow oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.34 (12H, d, J=6.9 Hz, CH_3 of ^iPr), 2.34 (3H, s, CH_3), 4.09 (2H, spt, J=6.9 Hz, CH), 6.99 (1H s, 4-H), 7.15 (2H, d, J=7.9 Hz, 3'-H of Ar), 7.37 (2H, d, J=7.9 Hz, 2'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=20.88 (CH_3 of ^iPr), 21.20 (CH_3), 47.30 (CH), 121.02 (4-CH), 122.32 (3'-CH of Ar), 126.50 (1'-C of Ar), 129.36 (2'-CH of Ar), 135.95 (4'-C of Ar), 144.53 (5-C), 160.70 (2-C); IR (neat) 3075, 3022, 2970, 2871, 1586 (C=N), 1502, 1452, 1419, 1379, 1330, 1311, 1289, 1280, 1210, 1159, 1123, 1049, 1029, 1016, 1002, 941, 915, 861, 847, 814, 793, and 734 cm^{-1}.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-methoxy-α-diazoacetophenone (**6f**) in the presence of diisopropylcyanamide (**7a**) gave 2-diisopropylamino-5-(*p*-methoxyphenyl)oxazole (**8f**).

2-Diisopropylamino-5-(*p*-methoxyphenyl)oxazole (**8f**): 70 % yield; yellow viscous oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.34 (12H, d, J=6.9Hz, CH_3 of ^iPr), 3.82 (3H, s, OCH_3), 4.09 (2H, sep., J=6.9Hz, CH of ^iPr), 6.88-6.92 (2H, m, 3'-H of Ar), 6.92 (1H, s, 4-H), 7.39-7.43 (2H, m, 2'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.01 (CH_3 of ^iPr), 47.38 (CH of ^iPr), 55.41 (OCH_3), 114.34 (3'-CH of Ar), 120.15 (4-CH), 122.42 (1'-C of Ar), 123.92 (2'-CH of Ar), 144.42 (5-C), 158.33 (4'-C of Ar), 160.65 (2-C); IR(KBr) 3217 (CH), 3101 (CH), 3037 (CH), 2971 (CH), 2932 (CH), 2834 (CH), 1601 (C=N), 1586 (NO_2), 1501,

1457, 1425, 1410, 1379, 1367, 1331 (NO_2), 1310, 1299, 1250, 1210, 1176, 1160, 1123, 1052, 1034, 941, 914, 861, 829, 794, 734, and 717 cm^{-1}.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of cyanamide (**7b**) gave 2-amino-5-(*p*-nitrophenyl)oxazole (**8g**).

2-Amino-5-(*p*-nitrophenyl)oxazole (**8g**): 7 % yield; orange solid; ^1H NMR (270 MHz, $CDCl_3$) δ=4.91 (2H, brs, NH), 7.24 (1H s, 4-H), 7.59 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.23 (2H, d, J=8.9 Hz, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=122.66 (2'-CH of Ar), 124.53 (3'-CH of Ar), 126.20 (4-CH); IR (KBr) 3455 (NH), 3185, 3103, 2953, 2849, 1670, 1604 (C=N), 1569 (NO_2), 1505, 1422, 1381, 1326 (NO_2), 1301, 1176, 1108, 938, 846, 740, 688, and 668cm^{-1}.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of methylcyanamide (**7c**) gave 2-methylamino-5-(*p*-nitrophenyl)oxazole (**8h**).

2-Methylamino-5-(*p*-nitrophenyl)oxazole (**8h**): 13 % yield; orange powder; ^1H NMR (270 MHz, $CDCl_3$) δ=3.09 (3H, s, CH_3), 4.86 (1H, brs, NH), 7.29 (1H, s, 4-H), 7.57 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.22 (2H, d, J=8.9 Hz, 3'H of Ar); IR (KBr) 3207, 3161, 3093, 2965, 2935, 1670 (C=N), 1589 (NO_2), 1498, 1412, 1374, 1346, 1319 (NO_2), 1296, 1242, 1226, 1181, 1134, 1104, 1078, 1041, 938, 914, 850, 751, 737, 689, and 668 cm^{-1}; MS (EI) 219 (M^+), 189, 173, 149, 132, 117, 104, 103, 89.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of *tert*-butylcyanamide (**7d**) gave 2-*tert*-butylamino-5-(*p*-nitrophenyl)oxazole (**8i**).

2-*tert*-Butylamino-5-(*p*-nitrophenyl)oxazole (**8i**): 33 % yield; orange powder; ^1H NMR (270 MHz, $CDCl_3$) δ=1.49 (9H, s, CH_3), 5.38 (1H, brs, NH), 7.26 (1H, s, 4-H), 7.55 (2H, d, J=8.6 Hz, 2'-H of Ar), 8.22 (2H, d, J=8.6 Hz, 3'H of Ar); IR (KBr) 3271, 3178, 3064, 2965, 1652 (C=N), 1592 (NO_2), 1499, 1473, 1363, 1350, 1326 (NO_2), 1316, 1294, 1239, 1203, 1181, 1154, 1115, 1106, 1003, 930, 850, 828, 737, 688, 682, and 668 cm^{-1}; MS (EI) 261 (M^+), 246, 205, 189, 175, 159, 149.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of dimethylcyanamide (**7e**) gave 2-dimethylamino-5-(*p*-nitrophenyl)oxazole (**8j**).

2-Dimethylamino-5-(*p*-nitrophenyl)oxazole (**8j**): 82 % yield; red crystals; mp 180.8-182.8 °C (from benzene-hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=3.19 (6H, s, CH_3), 7.33 (1H, s, 4-H), 7.55 (2H, d, J=8.3 Hz, 2'-H of Ar), 8.20 (2H, d, 3'-H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=37.74 (qq, J_{CH}=138.6Hz, $^3J_{CH}$=3.7 Hz, CH_3), 121.97 (dd, J_{CH}=164.2 Hz, $^3J_{CH}$=7.3 Hz, 2'-CH of Ar), 124.55 (dd, J_{CH}=167.8 Hz, $^3J_{CH}$=4.3 Hz, 3'-CH of Ar), 127.66 (d, J_{CH}=190.4 Hz, 4-CH), 134.64 (t, $^3J_{CH}$=7.9 Hz, 1'-C of Ar), 143.26 (dt, $^2J_{CH}$=17.1 Hz, $^3J_{CH}$=4.3 Hz, 5-C), 145.35 (m, 4'-C of Ar), 162.96 (dm, $^3J_{CH}$=6.1 Hz, 2-C); IR(KBr) 3099 (CH),

2929 (CH), 1636 (C=N), 1590 (NO_2), 1502, 1419, 1387, 1348, 1319 (NO_2), 1298, 1266, 1162, 1108, 995, 934, 910, 875, 851, 844, 752, 732, and 693 cm^{-1}; MS (EI) 233 (M^+), 218, 204, 203, 187, 172, 163, 144, 117, 89. Found: C, 56.65; H, 4.83; N, 17.90 %. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02 %.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of diethylcyanamide (**7f**) gave 2-diethylamino-5-(*p*-nitrophenyl)oxazole (**8k**) in 98 % yield.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of ethylmethylcyanamide (**7g**) gave 2-ethylmethylamino-5-(*p*-nitrophenyl)oxazole (**8l**).

2-Ethylmethylamino-5-(*p*-nitrophenyl)oxazole (**8l**): 74 % yield; orange needles; mp 91.5-93.9 °C (from benzene-hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=1.27 (3H, t, J=7.3 Hz, CH_3 of Et), 3.15 (3H, s, CH_3), 3.57 (2H, q, J=7.3 Hz, CH_2 of Et), 7.31 (1H, s, 4-H), 7.54 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.20 (2H, d, J=8.9 Hz, 3'H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=12.36 (CH_3 of Et), 34.86 (CH_3), 45.26 (CH_2 of Et), 121.89 (2'-CH of Ar), 124.54 (3'-CH of Ar),127.71 (4-CH), 134.70 (1'-C of Ar), 142.98 (5-C), 145.26 (4'-C of Ar), 162.46 (2-C); IR (KBr) 3180, 3107, 3072, 2983, 2936, 1618, 1600, 1588(NO_2), 1500, 1460, 1442, 1425, 1412, 1380, 1347, 1322 (NO_2), 1254, 1223, 1173, 1149, 1105, 1073, 1042, 1014, 952, 939, 882, 849, 829, 704, 752, 734, 689, and 668 cm^{-1}; MS (EI) 248, 247 (M^+), 233, 219, 202, 189, 186, 173, 144, 132, 117, 115, 104, 103, 89, 76. Found: C, 58.11; H, 5.30; N, 16.91 %. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99 %.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of methylphenylcyanamide (**7h**) gave 2-methylphenylamino-5-(*p*-nitrophenyl)oxazole (**8m**).

2-Methylphenylamino-5-(*p*-nitrophenyl)oxazole (**8m**): 84 % yield; orange crystals (from benzene-hexane); mp 148.5-150.5 °C (from benzene-hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=3.60 (3H, s, CH_3), 7.25 (1H, m, 4"-H of Ph), 7.35 (1H, s, 4-H), 7.43-7.45 (4H, m, Ph), 7.51 (2H, d, J=8.3 Hz, 2'-H of Ar), 8.17 (2H, d, J=8.3 Hz, 3'H of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=38.42 (CH_3), 122.25 (2'-CH of Ar), 123.29 (2"-CH of Ph), 124.39 (3'-CH of Ar), 125.59 (4"-CH of Ph), 126.86 (4-CH), 129.20 (3"-CH of Ph), 134.14 (1'-C of Ar), 142.82 (5-C or 1"-C of Ph), 143.40 (5-C or 1"-C of Ph), 145.57 (4'-C of Ar), 160.79 (2-C); IR (KBr) 3128, 3068, 2915, 1604, 1586, 1588 (NO_2), 1499, 1451, 1430, 1413, 1384, 1324 (NO_2), 1291, 1270, 1230, 1189, 1106, 1095, 1035, 941, 846, 758, 725, and 693 cm^{-1}; MS (EI) 295 (M^+), 265, 249, 203, 91, 77. Found: C, 65.01; H, 4.60; N, 14.08 %. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23 %.

$Rh_2(OAc)_4$-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**6a**) in the presence of *N*-cyanopiperidine (**7i**) gave 5-*p*-nitrophenyl-2-(piperidino)oxazole (**8n**).

5-*p*-Nitrophenyl-2-(piperidino)oxazole (8n): 70 % yield; red needles; mp 125.8-129.1 °C (from benzene-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.69 (6H, m, CH_2 of piperidino group), 3.60 (4H, m, CH_2 of piperidino group), 7.31 (1H, s, 4-H), 7.55 (2H, d, J=8.9 Hz, 2'-CH of Ar), 8.20 (2H, d, J=8.9 Hz, 3'-CH of Ar); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=23.94 (CH of piperidino group), 25.14 (CH of piperidino group), 46.58 (CH of piperidino group), 121.99 (2'-CH of Ar), 124.53 (3'-CH of Ar), 127.46 (4-CH), 134.68 (1'-C of Ar), 142.82 (5-C), 145.32 (4'-C of Ar), 162.44 (2-C); IR(KBr) 3120 (C-H), 3057 (C-H), 3037 (C-H), 2985 (C-H), 2937 (C-H), 2857 (C-H), 1697, 1598 (C=N), 1578 (NO_2), 1500, 1465, 1448, 1417, 1392, 1340, 1325 (NO_2), 1304, 1284, 1267, 1238, 1229, 1187, 1160, 1139, 1120, 1107, 1059, 979, 960, 937, 912, 896, 846, 836, 754, 736, 720, 689, and 669 cm^{-1}; MS (EI) 273 (M^+), 258, 244, 227, 118, 117, 205, 175, 149, 132, 89. Found: C, 61.32; H, 5.57; N, 15.09 %. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38 %.

***N*-(Ethoxycarbonyl)methyl-*N'*, *N'*-diisopropylurea (11)**:
A solution of 0.5 mmol of ethyl α-diazoacetate (**9a**) dissolved in 10 ml of benzene was added to a solution of 5 mol% of $Rh_2(OAc)_4$ and an 10 molar excess of diisopropylcyanamide (**7a**) in 5ml of benzene at 80 °C under Ar atmosphere for 2 h, then the reaction mixture was stirred for 1 h to complete the reaction. The reaction mixture was washed with three portions of 10 ml of 6N HCl aq. The combined aqueous layer was neutralized with sodium bicarbonate, and extracted with three portions of 10 ml of ether. The combined etheral solution was dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure to give *N*-(ethoxycarbonyl)methyl-*N'*, *N'*-diisopropylurea (**11**) in 39 % yield. yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.27 (12H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 1.29 (3H, t, J=7.3 Hz, CH_3 of Et), 3.92 (2H, spt, J=6.9 Hz, CH of ^{i}Pr), 4.04 (2H, d, J=4.3 Hz, CH_2), 4.21 (2H, q, J=7.3 Hz, CH_2 of Et), 4.79 (1H, brs, NH); IR (neat) 3365 (NH), 2969, 1735 (C=O of ester), 1628 (C=O of urea), 1521, 1424, 1373, 1334, 1210, 1030, 861, and 767 cm^{-1}.

Dimethyl 2-diisopropylamino-5-(ethoxycarbonyl)pyrrole-3,4-dicarboxylate (12): A solution of 1 mmol of ethyl α-diazoacetate (**9a**) dissolved in 20 ml of benzene was added to a solution of 5 mol% of $Rh_2(OAc)_4$, DMAD, and 10 molar excess of diisopropylcyanamide (**7a**) in 10 ml of benzene at 80 °C under Ar atmosphere for 2 h, then the reaction mixture was stirred for 1 h to complete the reaction. After removal of solvent and excess diisopropylcyanamide (**7a**) under reduced pressure, the residue was separated by medium pressure column chromatography on silica gel using hexane-ethyl acetate as an eluent to give dimethyl 2-diisopropylamino-5-(ethoxycarbonyl)pyrrole-3,4-dicarboxylate (**12**):
colorless powder; mp 77.2-78.6 °C (from benzene-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.11 (12H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 1.33 (3H, t, J=7.3 Hz, CH_3 of Et), 3.69 (2H, sept., J=6.6 Hz, CH of ^{i}Pr), 3.76 (3H, s, $COOCH_3$), 3.91 (3H, s, $COOCH_3$), 4.29 (2H, q, J=7.3 Hz, CH_2 of Et), 8.69 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=14.18 (qt, J_{CH}=127.0 Hz, CH_3 of Et), 22.40 (qquin, J_{CH}=125.7 Hz,

$^3J_{CH}$=4.9 Hz, CH_3 of ^{i}Pr), 50.05 (dsxt, J_{CH}=137.9 Hz, $^2J_{CH}$=3.7 Hz, CH of ^{i}Pr), 51.27 (q, J_{CH}=146.5 Hz, $COO\underline{C}H_3$), 52.51 (q, J_{CH}=147.1 Hz, $COO\underline{C}H_3$), 61.13 (tq, J_{CH}=148.3 Hz, $^2J_{CH}$=4.3 Hz, CH_2 of Et), 108.92 (d, 3-C), 114.18 (d, 5-C), 123.77 (d, $^3J_{CH}$=6.1 Hz, 4-C), 143.03 (m, 2-C), 159.59 (t, $\underline{C}OOC_2H_5$), 163.04 (m, $\underline{C}OOCH_3$), 166.38 (q, $\underline{C}OOCH_3$); IR(neat) 3274 (N-H), 2970 (C-H), 1706 (C=O), 1563, 1508, 1449, 1368, 1341, 1299, 1235, 1196, 1096, 1063, 1020, 963, 868, 818, 795, and 685 cm^{-1}; MS (EI) 356, 355 (MH^+), 340, 324, 312, 308, 295, 281, 280, 262, 248, 234, 220, 219, 203, 187, 161. Found: C, 57.45; H, 7.33; N, 7.84 %. Calcd for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90 %.

2-Diisopropylamino-5-ethoxyoxazole (10a): A solution of 0.5 mmol of ethyl α-diazoacetate (**9a**) dissolved in 2 ml of benzene was added to a mixture of 1 mol% of $Rh_2(OAc)_4$ and 5 molar excess of diisopropylcyanamide (**7a**) at 80 °C under Ar atmosphere for 20 minutes, then the reaction mixture was stirred for 1 h to complete the reaction. The signals of 2-diisopropylamino-5-ethoxyoxazole (**10a**) was observed in almost quantitative yield in ^{1}H NMR spectrum of the reaction mixture: ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.38 (3H, t, J=7.3 Hz, CH_3 of Et), 3.94 (2H, spt, J=6.9 Hz, CH), 4.03 (2H, q, J=7.3 Hz, CH_2), 5.82 (1H, s, 4-H). The signal of CH_3 of ^{i}Pr was hidden in the signal of excess of diisopropylcyanamide. The isolation of **10a** using column chromatography was unsuccessful.

2-Diisopropylamino-5-isopropoxyoxazole (10b): A solution of 0.5 mmol of isopropyl α-diazoacetate (**9b**) dissolved in 2 ml of benzene was added to a mixture of 1 mol% of $Rh_2(OAc)_4$ and 5 molar excess of diisopropylcyanamide (**7a**) at 80 °C under Ar atmosphere for 20 minutes, then the reaction mixture was stirred for 1 h to complete the reaction. The signals of 2-diisopropylamino-5-isopropoxyoxazole (**10b**) was observed in almost quantitative yield in ^{1}H NMR spectrum of the reaction mixture: ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.95 (2H, m, CH of N^iPr_2), 4.26 (2H, m, CH of O^iPr), 5.90 (1H, s, 4-H). The signals of CH_3 of ^{i}Pr's were hidden in the signal of excess of diisopropylcyanamide. The isolation of **10b** using column chromatography was unsuccessful.

5-*tert*-Butoxy-2-(diisopropylamino)oxazole (10c): A solution of 0.5 mmol of *tert*-butyl α-diazoacetate (**9c**) dissolved in 2 ml of benzene was added to a mixture of 1 mol% of $Rh_2(OAc)_4$ and 5 molar excess of diisopropylcyanamide (**7a**) at 80 °C under Ar atmosphere for 20 minutes, then the reaction mixture was stirred for 1 h to complete the reaction. After removal of solvent and excess diisopropylcyanamide (**7a**) under reduced pressure, distillation of the residual oil with Kugel Rohre gave 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**10c**) in 49 % yield. colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.26 (12H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 1.35 (9H, s, CH_3 of ^{t}Bu), 3.97 (2H, spt, J=6.9 Hz, CH), 5.99 (1H, s, 4-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.01 (qqui, $^2J_{CH}$,$^3J_{CH}$=4.3 Hz, CH_3 of ^{i}Pr), 28.04 (qspt, $^3J_{CH}$=3.7 Hz, CH_3 of ^{t}Bu), 46.50 (dsxt, $^2J_{CH}$=4.3 Hz, CH), 82.31 (quaternary-C of ^{t}Bu), 107.41 (d, J_{CH}=191.7 Hz, 4-CH), 150.11 (sd, $^2J_{CH}$=13.4 Hz, 5-C), 155.20 (dt, $^3J_{CH}$=11.6

and 6.1 Hz, 2-C); IR (neat) 3124, 2973, 2932, 2832, 1730 (w), 1647, 1585 (C=N), 1455, 1420, 1389, 1367, 1327, 1266, 1227, 1207, 1150, 1130, 1035, 985, 963, 910, 853, 796, 775, 740, and 710 cm^{-1}.

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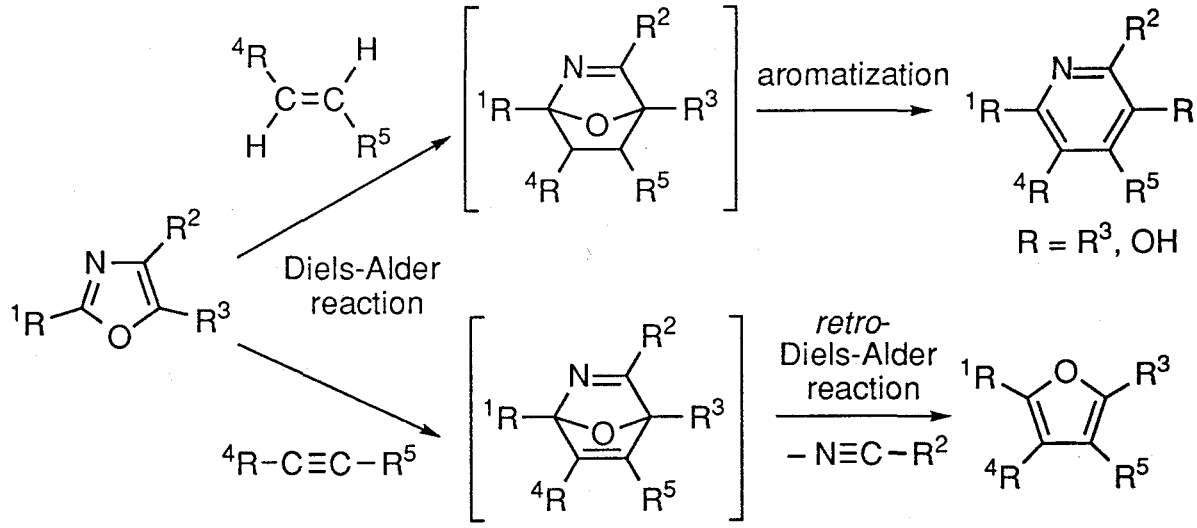
Chapter 4. Reaction of 2-Amino-5-alkoxyoxazole I: Mechanistic Study of the Reaction with DMAD and Methanol

4-1 Introduction

The hetero Diels-Alder reaction of oxazole, having 2-azadiene moiety, with ethylenic, acetylenic, or hetero dienophiles is known as a useful methodology to obtain heterocyclic compounds.

In general, the bicyclic adducts produced from oxazoles and dienophiles are unstable to be isolated and converted into the stable hetero aromatics through the successive reactions. For example, it is known that the reaction of oxazole with ethylenic dienophile gives pyridine derivatives by aromatization of the initial bicyclic adduct, and the reaction of acetylenic dienophile gives furan derivatives by elimination of R-CN from the initial adduct (Scheme 1).



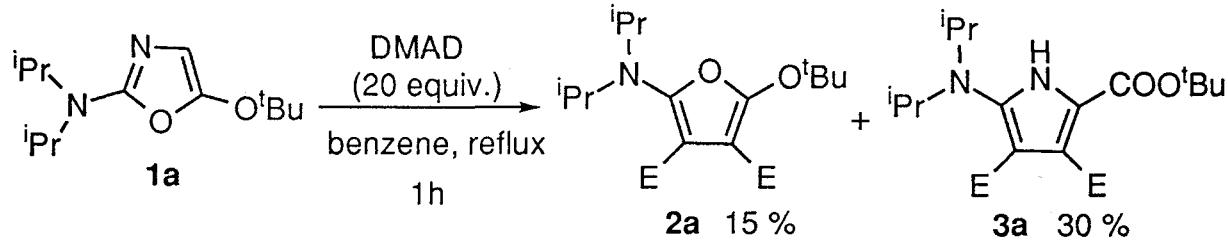
Scheme 1

According to the Fronteer Molecular Orbital theory, the hetero Diels-Alder reaction of oxazole derivatives and electron-defficient dienophiles are shown to be controlled by HOMO of oxazoles and LUMO of dienophiles, and to be accelerated by the electron-donating substituent on oxazole ring. In the previous chapter, preparation of new series of oxazole derivatives such as 2-amino-5-alkoxyoxazoles are introduced, and they are expected to have higher reactivity than other oxazole derivatives, because they have two electron-donating groups at 2- and 5-positions.

In this chapter, reactivity of the 2-amino-5-alkoxyoxazole is described. The reaction of 2-amino-5-alkoxyoxazole gave pyrrole derivative as a main product. This unusual reactivity is explained that the reaction proceeds through ring opening of 2-amino-5-alkoxyoxazole to give nitrile ylide intermediate by kinetic studies and molecular orbital calculations. An amino group stabilizes nitrile ylide intermediate, which promotes the ring opening of oxazole.

4-2 Reaction of 2-Amino-5-alkoxyoxazole with Acetylenic Dipolarophiles

In order to examine the reactivity of 2-amino-5-alkoxyoxazole, the reaction of isolated 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) with 20 equivalents of DMAD was carried out in refluxing benzene for 1 h to obtain furan **2a** and pyrrole derivative **3a** in 15 % and 30 % yields, respectively (Scheme 2).



Scheme 2

Similar reactions of oxazole **1b** (R=Et) and **1c** (R=^{i}Pr), produced *in situ*, with 20 equivalents of DMAD gave pyrroles **3b** and **3c** in moderate yields together with small amount of furans **2b** and **2c** (Table 1). In these reactions, pyrrole derivatives **3** were obtained as the major products through the formal [3+2] addition of $C_2=N_3-C_4$ moiety of oxazole **1** with DMAD.

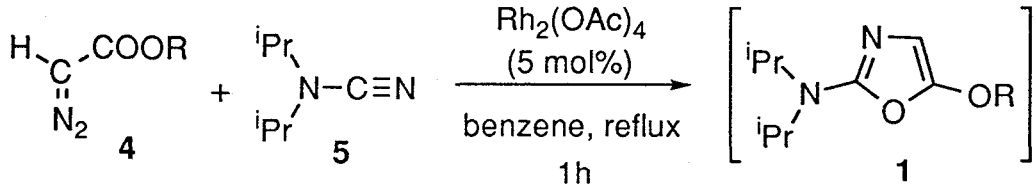
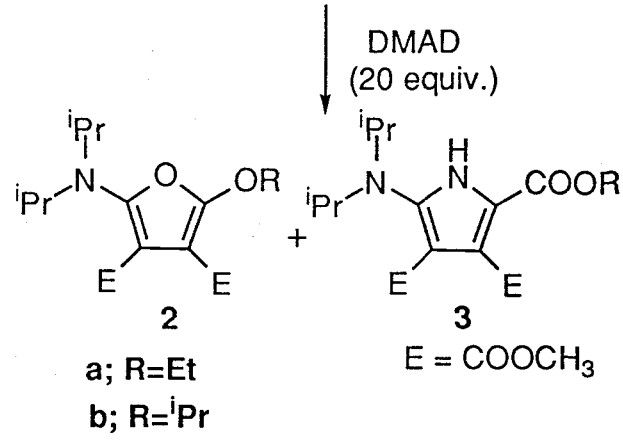


Table 1. Reaction of **1** generated *in situ* with DMAD.

Run	R	Yield / %	
		2	**3**
1	Et	trace	51
2	^{i}Pr	4	58

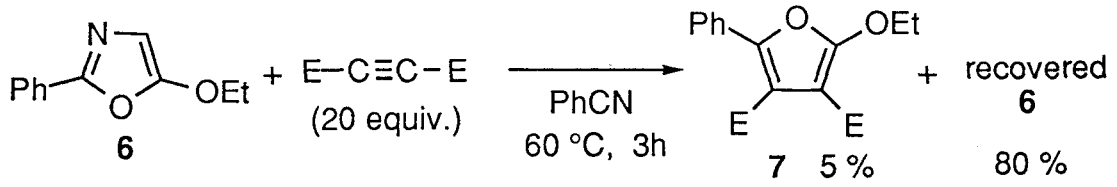


a; R=Et

b; R=^{i}Pr

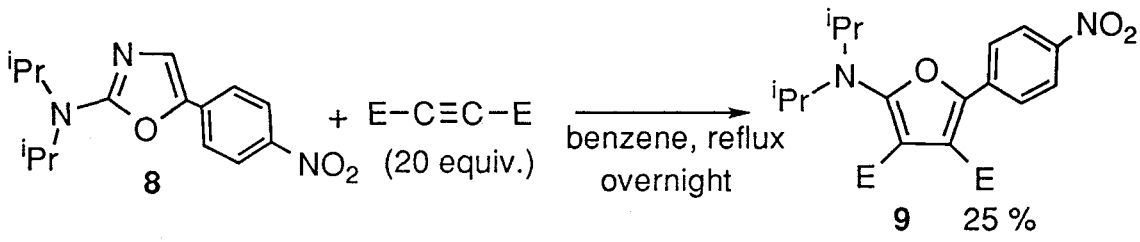
In order to confirm the effect of alkoxyl group at 5-position and amino group at 2-position on the reactivity of oxazole, the reactions of 2-phenyl-5-ethoxyoxazole (**6**) and 2-diisopropylamino-5-(*p*-nitrophenyl)oxazole (**8**) with 20 equivalents of DMAD were carried out. The reaction of **6** with DMAD at 60 °C for 3 h gave dimethyl 2-ethoxy-5-phenylfuran-3,4-dicarboxylate (**7**)

as a sole product in 5 % yield through the usual Diels-Alder reaction recovering 80 % of **6** (Scheme 3).



Scheme 3

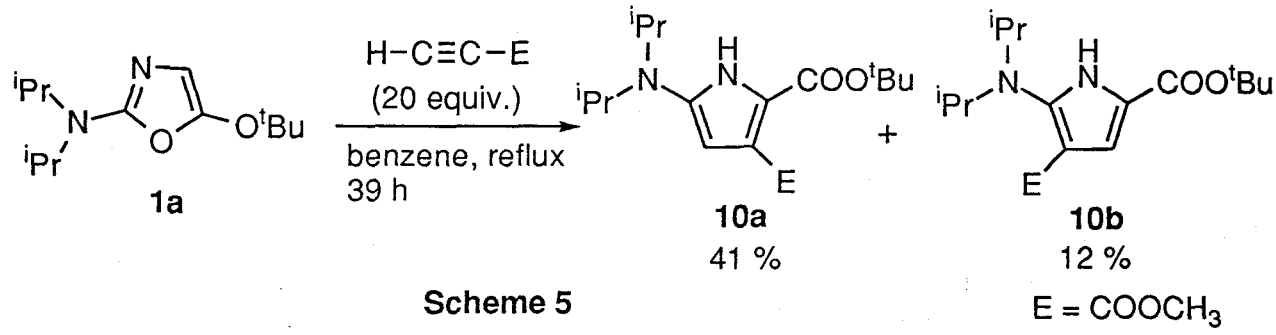
The reaction of **8** with 20 equivalents of DMAD under reflux in benzene overnight also gave dimethyl 2-diisopropylamino-5-(*p*-nitrophenyl)furan-3,4-dicarboxylate (**9**) in 25 % yield through Diels-Alder reaction (Scheme 4).



Scheme 4

The introduction of electron-releasing ethoxyl groups at 5-position (in **6**) or amino group at 2-position (in **8**) usually activate oxazole, and the cycloaddition with acetylenic dipolarophile proceeds in [4+2] manner to give furan derivatives. However, the reactions of 2-amino-5-alkoxyoxazole **1**, which have two electron-releasing groups such as alkoxyl group (at 5-position) and amino group (at 2-position), with DMAD proceeded in [3+2] manner to give pyrrole derivatives without affording furan derivatives. This unusual reactivity of **1** may be explained by stepwise mechanism including nucleophilic attack of oxazole toward DMAD followed by ring opening and cyclization, or ring opening to generate nitrile ylide intermediate followed by 1,3-dipolar cycloaddition with DMAD.

The reaction of **1a** with 20 equivalents of methyl propiolate gave two pyrrole derivatives (**10a** and **10b**) in 41 % and 12 % yield, respectively (Scheme 5).



Scheme 5

The regiochemistry of the products was determined by differential NOE technique. The formation of the products **10a** and **10b** can be explained by the 1,3-dipolar cycloaddition of nitrile ylide intermediate with methyl propiolate, and the regiochemistry of the major product **10a** is well accordance with the reaction of allenyl-type nitrile ylide described in chapter 2 (Figure 1).

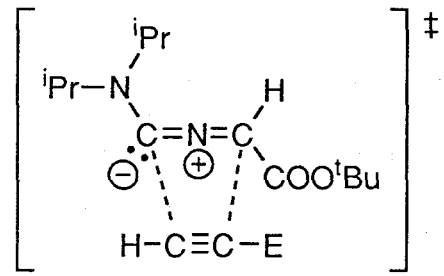
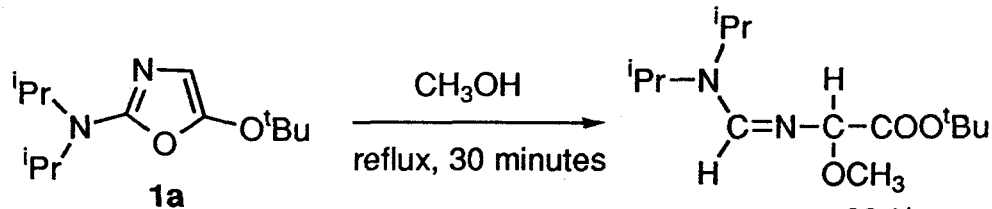


Figure 1

4-3 Reaction of 5-*tert*-Butoxy-2-(diisopropylamino)oxazole with Methanol

In order to clarify the mechanism of this reaction, the reaction of **1a** with methanol was carried out, and 1:1-adduct **11** was obtained in almost quantitative yield (Scheme 6).



Scheme 6

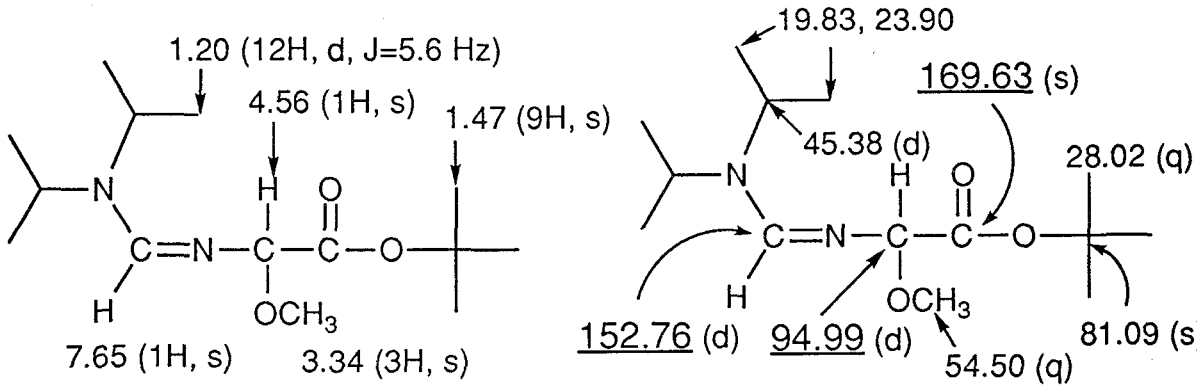
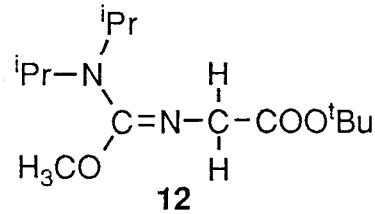
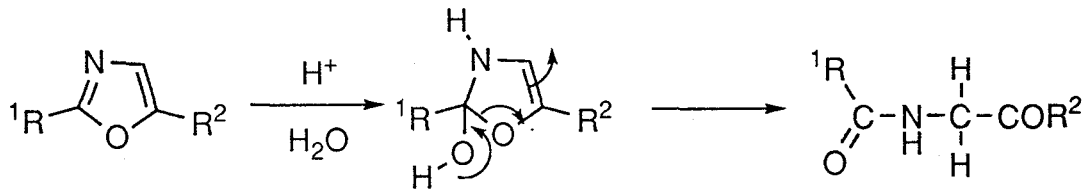


Figure 2. ^{1}H NMR and ^{13}C NMR of **11** (δ)

^{1}H NMR and ^{13}C NMR spectra of **11** clearly show that **11** is 1:1-adduct of **1a** with methanol (Figure 2). The ^{13}C NMR signal of **11** at 169.63 ppm is assigned to a carbonyl carbon of ester group which is generated by the opening of the oxazole ring. The open chain structure of **11** is also supported by the strong absorption of ester carbonyl group at 1745 cm^{-1} in its IR spectrum. The regiochemistry of the addition of methanol is confirmed by ^{13}C NMR spectrum as shown below. The observation of two doublet signals at 152.76 ppm and 94.99 ppm exclude the possibility of another structure of the adduct **12** having opposite regiochemistry which is expected in a similar manner as the acid catalyzed hydrolysis of oxazole (Scheme 7).

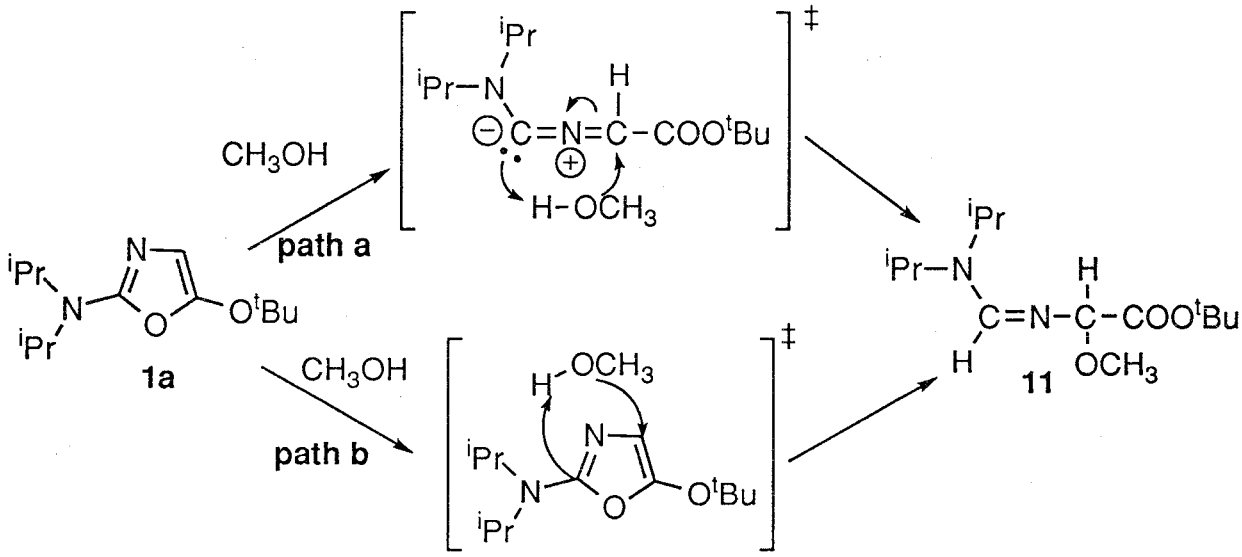


12



Scheme 7

There are two possible pathways in the reaction of **1a** with methanol to give **11** (Scheme 8). One is the ring opening of **1a** to generate nitrile ylide intermediate followed by addition of methanol (**path a**). The other is depicted as direct reaction of oxazole with methanol accompanying the ring opening of oxazole (**path b**).



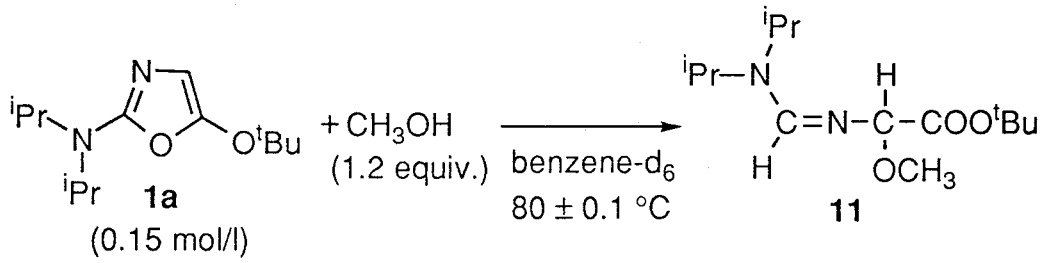
Scheme 8

However, **path b** includes some confliction. That is, it requires a nucleophilic attack of methoxyl group on 4-positon of oxazole having high electron density, because it corresponds to β-position of enol ether moiety. Therefore, **path a** seems to be preferable for this reaction.

4-4 Kinetic Study of the Reaction of 2-Amino-5-alkoxyoxazole with Methanol

In order to determine the mechanism of the reaction of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) with methanol, the kinetic studies were carried out as shown below.

A 0.15 M solution of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) and 1.2 equiv. of methanol in benzene-d_6 was heated in a sealed NMR tube monitoring the decrease of oxazole **1a** by NMR spectroscopy using H-4 at 5.99 ppm as a probe (Scheme 9). The first-order kinetics (r=0.997, $k=4.36\times10^{-5}$ sec^{-1}) was observed until 95 % of **1a** was consumed (Figure 3).



Scheme 9

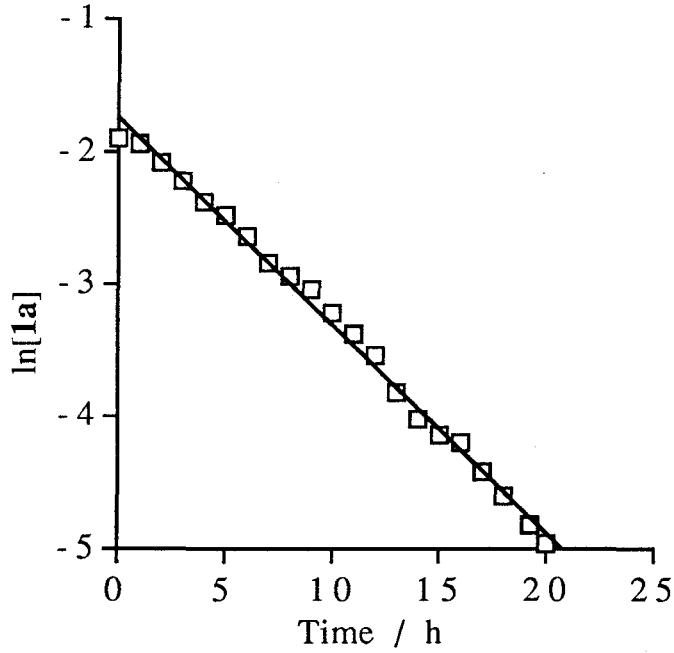
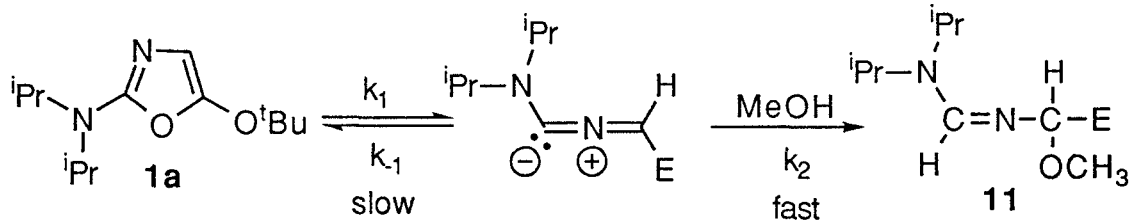


Figure 3. First order plots of the reaction of **1a** with methanol

This implied that the reaction of **1a** with methanol is a multistep reaction, and **1a** is the sole species involved in its rate-determining step.



Scheme 10

The following rate equation is obtained by considering the nitrile ylide as an intermediate and assuming the stationary state for the nitrile ylide intermediate, d[ny]/dt=0 (where [ny] is the concentration of nitrile ylide).

$$-d[\mathbf{1a}]/dt=k_1k_2[\mathbf{1a}][MeOH]/(k_{-1}+k_2[MeOH]) \qquad (1)$$

When k_{-1} is much smaller than $k_2[MeOH]$, k_{-1} can be neglected to give equation (2).

$$-d[\mathbf{1a}]/dt=k_1[\mathbf{1a}] \qquad (2)$$

Oxazole **1a** is in equilibrium with nitrile ylide intermediate under thermal condition. Since methanol reacts with nitrile ylide very fast ($k_2 \gg k_{-1}$), the

ring opening of **1a** is the rate-determining step in the whole reaction pathway. These results are illustrated by the energy diagram of the reaction in Figure 4.

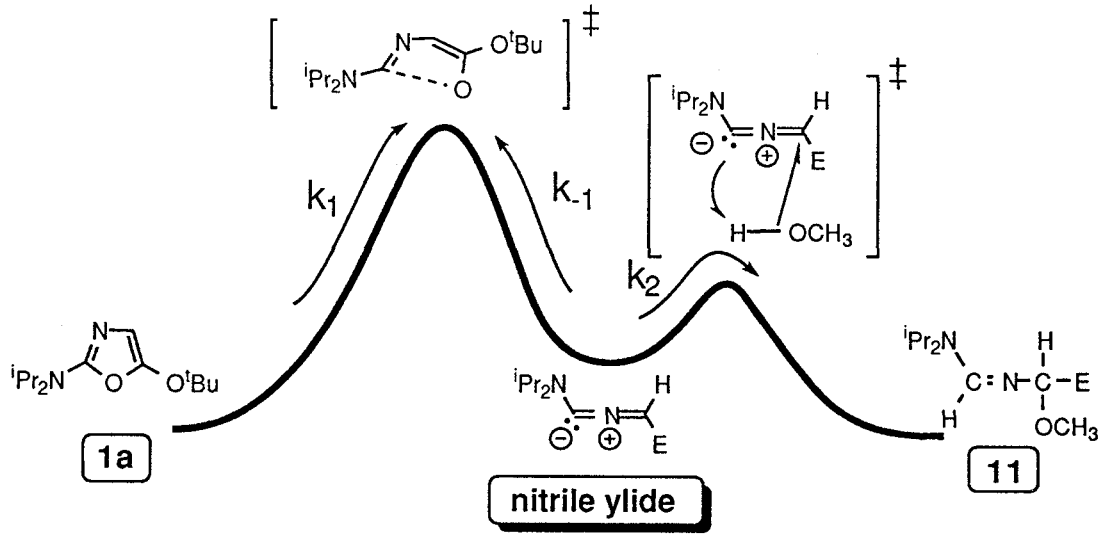


Figure 4

The effect of the temperature and solvent on the rate of the disappearance of **1a** was studied, and the activation parameters were obtained from Arrhenius plots (Table 2).

Table 2. Rate Constants and Activation Parameters for the Reaction of **1a** with Methanol.

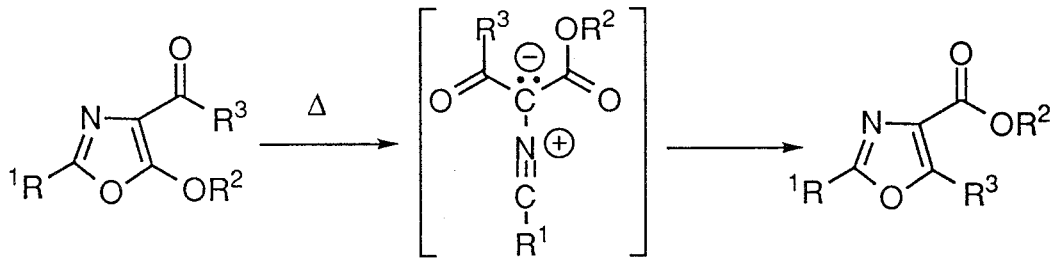
MeOH / equiv. (Solvent)	Temp °C	kx10^5 sec^{-1}	r	Ea kcalmol^{-1}	$\Delta H^{\neq}$ kcalmol^{-1}	$\Delta S^{\neq}$ e.u.	$\Delta G^{\neq}$ kcalmol^{-1}
1 (C_6D_6)	60.0	0.31					
1 (C_6D_6)	70.0	2.25	0.966	31.2	30.5±0.1	8.1±0.8	27.8±0.3
1 (C_6D_6)	80.0	4.36					
10 (C_6D_6)	49.0	8.33					
10 (C_6D_6)	59.1	15.0					
10 (C_6D_6)	69.2	23.3	0.998	10.6	10.1±0.1	-46.2±0.2	25.6±0.7
10 (C_6D_6)	79.2	35.0					
10 (CD_3CN)	69.2	8.33					
10 (CD_3CN)	79.1	11.7	0.982	6.2	6.1±0.1	-61.3±0.1	27.7±0.7
10 (CD_3CN)	89.3	13.8					

When 10 equivalents of methanol was used as a substrate, the increase of the rate constants was observed. The ratios of the rate constants are 15.0/0.31 at 60 °C, 23.3/2.25 at 70 °C, and 35.0/4.36 at 80 °C. These results indicate that the increase of the rate constant is ascribed to the solvent effect.

In the reaction of **1a** with one equivalent of methanol, the value for the entropy of activation ($\Delta S^{\neq}$) is positive, and it becomes large negative value as the polarity of the solvent increases. Although the value for the activation energy (Ea) and the enthalpy of activation ($\Delta H^{\neq}$) also decrease with increase of the polarity of the system, the values for the free energy ($\Delta G^{\neq}$) of activation are almost constant. This can be explained by the solvent effect in the transition state. The solvation stabilizes the polar transition state, and causes the decrease of the enthalpy. However, the solvation is, needless to say, accompanied by the arrangement of the solvent molecules around the polar species in the transition state, which causes the decrease of entropy. Therefore, the values of the free energy of activation are kept constant, because the decrease of the enthalpy and the decrease of the entropy compensate each other.

4-5 Similarity of the Reaction with Cornforth Rearrangement

Concerning the mechanism of the reaction, the Cornforth rearrangement[1] is well known to proceed through the ring opening of oxazole derivatives (Scheme 11). Therefore, comparison of the electronic and solvent effects of the reactivity of both reactions may help to understand the mechanisms of the reactions.



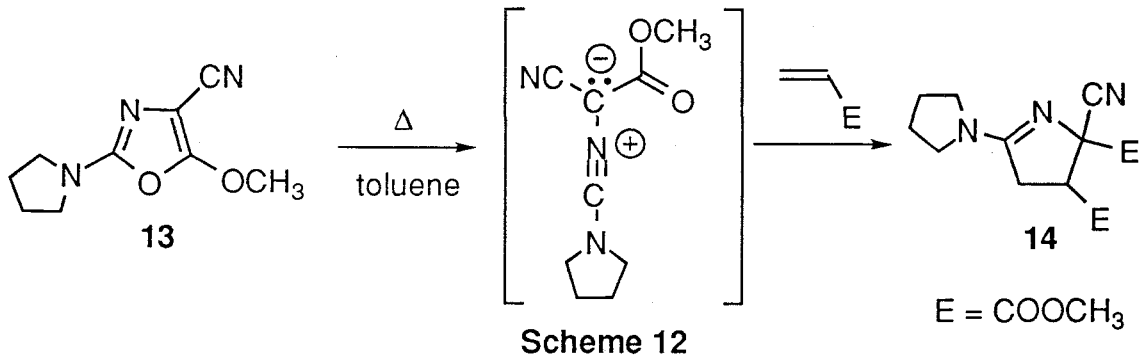
Scheme 11

In the Cornforth rearrangement, the presence of acyl group at 4-position of oxazole ring is essential to stabilize the increasing negative charge in the transition state and to promote recyclization. On the other hand, the electron-releasing substituents R^3 decrease the reactivity by hindering the transition state. An acceleration of the rearrangement by electron-releasing group at 2-position was also reported. The kinetic study of the Cornforth rearrangement reveals that influence of the polarity of the solvent is very small.[1c]

In our result, however, the electron-withdrawing substituent at 4-position of oxazole is not necessary, and the ring opening is promoted by the

effect of both the alkoxyl group at 5-position and amino group at 2-position. Although the influence of the polarity of the solvents is small on the rate of the reaction, activation parameters change to a considerable extent, which suggests that the transition state is stabilized by solvation.

Although the successful trapping of the nitrile ylide intermediate in Cornforth rearrangement was not reported, Saalfrank et al. reported a similar reaction of an oxazole through a nitrile ylide intermediate.[2] The reaction of 4-cyano-5-methoxy-2-(pyrrolidino)oxazole (**13**) with methyl acrylate in toluene at 60 °C gave pyrroline derivative **14** (Scheme 12).



Scheme 12

The result of Saalfrank et al. had been the sole example of trapping of the nitrile ylide generated by the ring opening of oxazole derivatives. The amino group at 2-position is anticipated to stabilize the nitrile ylide intermediate. However, the necessity of the amino group for the ring opening is not clear, because oxazole **13** has the electron-withdrawing cyano group at 4-position, which can also promote the opening of oxazole ring.

4-6 Molecular Orbital Calculation

In order to explain the effect of amino group on the ring opening of oxazole, the MINDO/3 molecular orbital calculations were carried out for the ring opening of oxazole having three sets of substituents (Figure 4).

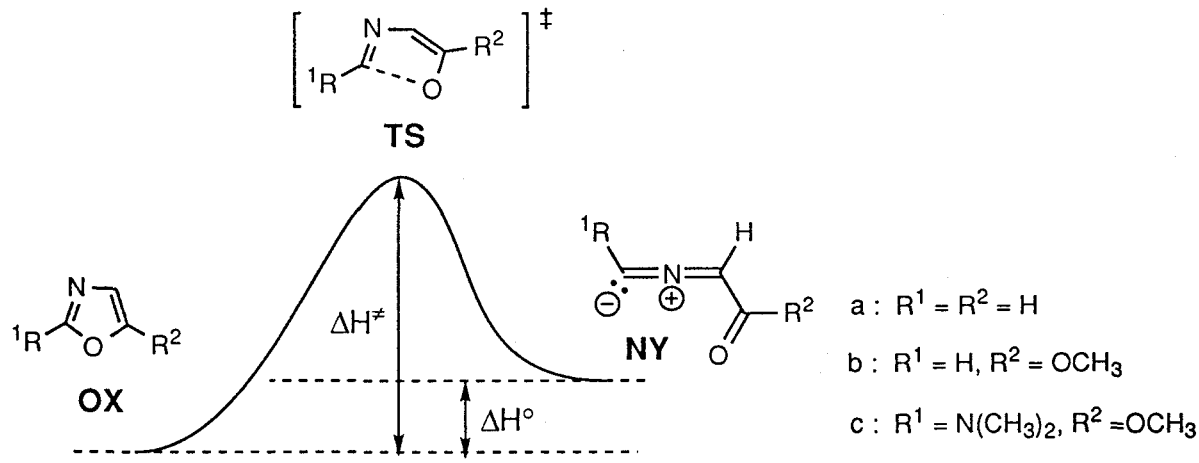


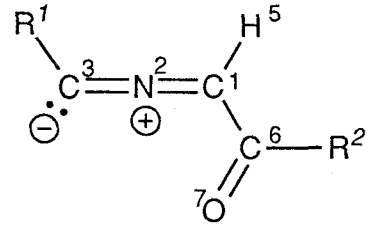
Figure 4

The calculated heat of formations (H_f) are listed in Table 3. The substitution of alkoxyl group at 5-position (Run b) lowers the difference of the heat of formation between oxazole and transition state ($\Delta H^{\neq}$). The substitution of amino group at 2-position also decreases the value of $\Delta H^{\neq}$ (Run c). These may be attributed to the higher stabilization of the transition state to generate nitrile ylide by the substituents than that of oxazole, which is correlated with a decrease of the value of $\Delta H°$.

Table 3. Heat of Formations of Oxazole (**OX**), Transition State (**TS**), and Nitrile Ylide (**NY**) Calculated by MINDO/3

Run	R^1	R^2	H_f / kcalmol^{-1}			$\Delta H^{\neq}$	$\Delta H°$
			OX	**TS**	**NY**	kcalmol^{-1}	kcalmol^{-1}
a	H	H	-7.42	35.54	2.80	42.96	10.22
b	H	OCH_3	-55.67	-19.77	-53.90	35.90	1.77
c	$N(CH_3)_2$	OCH_3	-55.10	-32.00	-63.24	23.10	-8.14

The optimized structures of nitrile ylides (**NYa-NYc**) are summarized in Table 4.



	R^1	R^2
NYa	H^4	H^8
NYb	H^4	O^8Me
NYc	N^4Me_2	O^8Me

Table 4. Optimized Structure of Nitrile Ylide by MINDO/3 Calculation

bond length (Å)

	C^1-N^2	N^2-C^3	C^3-H^4 (N^4)	C^1-H^5	C^1-C^6	C^6-O^7	C^6-H^8 (O^8)
NYa	1.289	1.198	1.107	1.113	1.449	1.199	1.136
NYb	1.285	1.203	1.111	1.113	1.478	1.215	1.335
NYc	1.262	1.260	1.340	1.122	1.491	1.210	1.333

bond order

	C^1-N^2	N^2-C^3	C^3-H^4 (N^4)	C^1-H^5	C^1-C^6	C^6-O^7	C^6-H^8 (O^8)
NYa	1.476	2.206	0.866	0.917	0.995	1.750	0.844
NYb	1.527	2.154	0.868	0.915	0.931	1.624	0.905
NYc	1.741	1.596	1.226	0.892	0.866	1.671	0.907

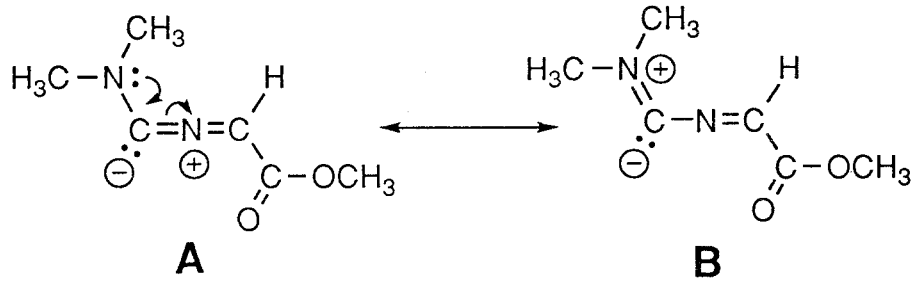
bond angle (°)

	C^1-N^2-C^3	N^2-C^3-H^4 (N^4)	H^5-C^1-N^2	C^6-C^1-N^2	O^7-C^6-C^1	H^8-C^6-C^1 (O^8)
NYa	168.8	126.0	116.4	125.1	128.7	109.6
NYb	169.3	123.3	115.6	122.0	124.1	105.0
NYc	168.4	124.2	119.7	124.6	125.0	102.9

dihedral angle (°)

	C^1-N^2-C^3-H^4 (N^4)	H^5-C^1-N^2-C^3	C^6-C^1-N^2-C^3	O^7-C^6-C^1-N^2	H^8-C^6-C^1-N^2 (O^8)
NYa	-176.8	81.4	-87.9	3.1	-174.9
NYb	-172.3	77.0	-91.4	5.1	-173.4
NYc	-172.1	77.5	-88.0	66.3	-113.0

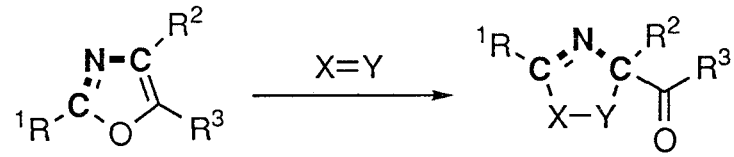
The optimized structures of all nitrile ylides (**NYa-NYc**) are depicted as a bent form, of which bond angles of N^2-C^3-H^4 (N^4) are 123.3-126.0 °. In the structure of **NYc**, the length of N^2-C^3 (1.260 Å) is longer than those of **NYa** and **NYb**. The bond order of N^2-C^3 (1.596) is much decreased, and that of C^3-N^4 (1.226) is increased in **NYc** in comparison to **NYa** and **NYb**. These structural feature indicate that the contribution of the resonance structure **B** is significant in amino-substituted nitrile ylide **NYc**, which has a long N^2-C^3 bond and a short C^3-N^4 bond. Therefore, introduction of amino goup on nitrile carbon stabilize nitrile ylide, because it contributes to the delocalization of positive charge on N^2 (Scheme 13).



Scheme 13

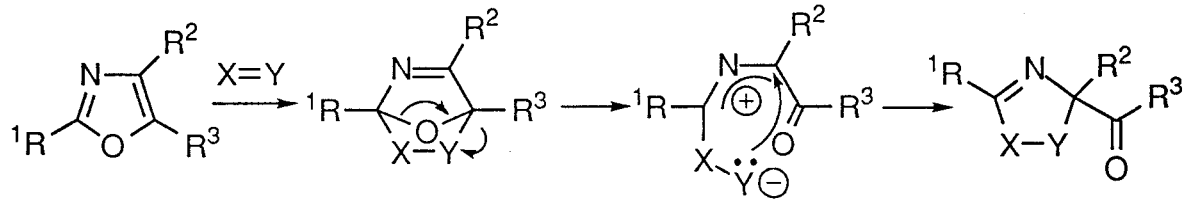
4-7 Comparison with Other Formal [3+2] Additions of Oxazole

Recently, the formal [3+2] addition of oxazole with reactive dienophiles has been paid much attention as a new synthetic method of five-membered heterocycles (Scheme 14).



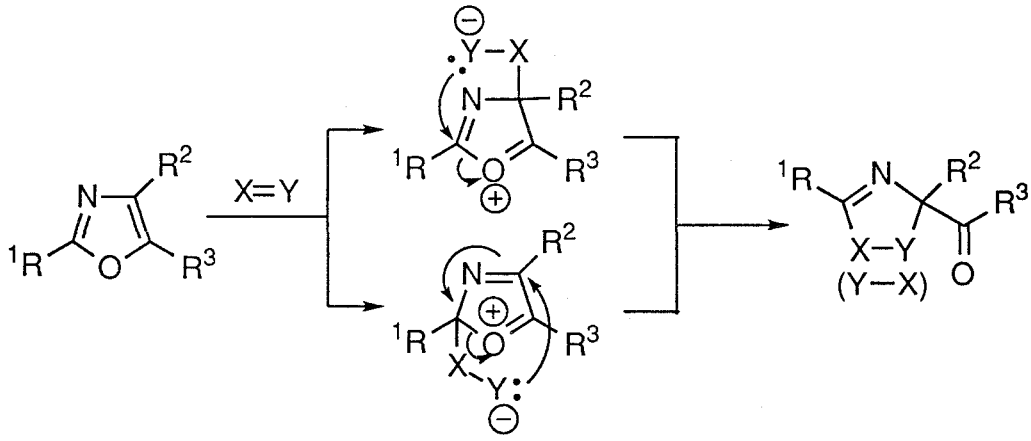
Scheme 14

Though the mechanism of these reactions are not decisively confirmed, three different pathways have been proposed. The first one is proposed by A. Hassner et al., which involves the sequence of the Diels-Alder reaction, ring opening, and recyclization (Scheme 15).[3)]



Scheme 15

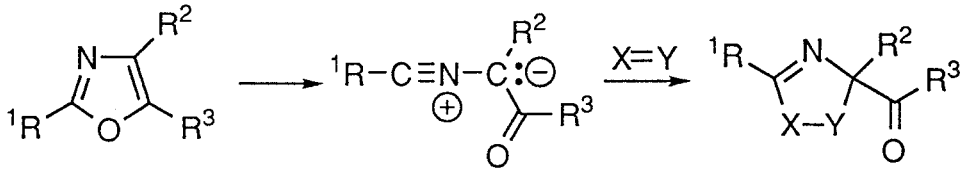
The second one is proposed by Ibata et al., which includes nucleophilic attack of oxazole from 2- or 4-position onto the electrophile (Scheme 16).[4)]



Scheme 16

This mechanism seems effective, when the electrophile (X=Y) is strongly electron deficient compounds such as TCNE and PTAD, or carbonyl compounds such as aldehyde and ketomalonate activated with Lewis acid.[4f-i)]

The third one involves nitrile ylide intermediate (Scheme 17), and had been considered as only a verbal possibility, except for the result reported by Saalfrank et al.[2)]



scheme 17

However, our results shows that this mechanism can realize, when R^1 is an amino goup and R^3 is an alkoxyl group. Moreover, this nitrile ylide route is the only mechanism established unequivocally.

In order to know the limitation of this nitrile ylide route, the reaction of 2-phenyl-5-ethoxyoxazole (**6**)[1] with alcohols were carried out (Scheme 18).

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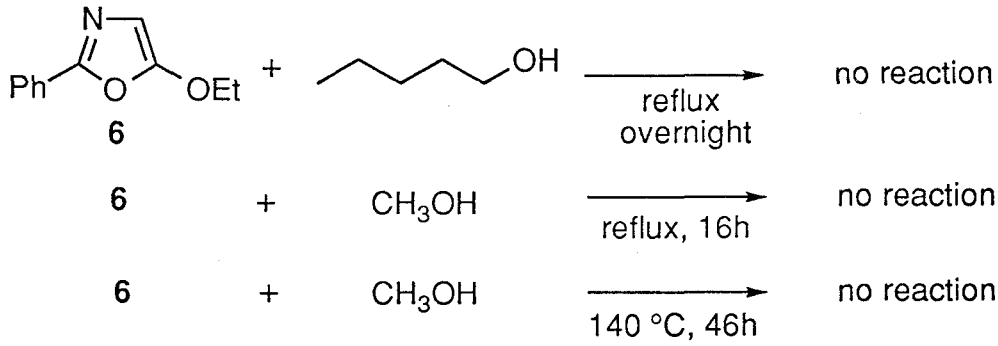
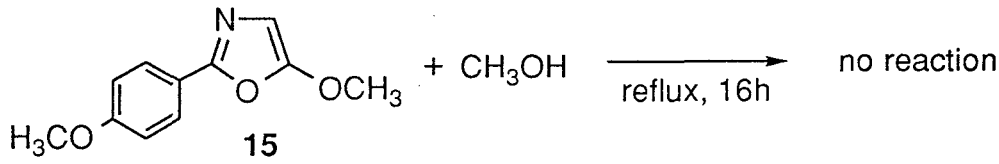
[1] 2-phenyl-5-ethoxyoxazole (**6**) was reported to react with diethyl ketomalonate at reflux in xylene for 46 h to give mixtures of 3- and 2- oxazoline in high yield.[3a)]



Scheme 18

In the reaction of **6** with pentanol (bp. 136-138 °C), no change was observed on TLC or by NMR spectroscopy with quantitative recovery of **6**. The reaction of **6** with methanol under reflux or 140 °C in a sealed tube did not give any product with quantitative recovery of **6**, either.

The reaction of 5-methoxy-2-(*p*-methoxyphenyl)oxazole (**15**)[2] with methanol also did not give any product with quantitative recovering of **15** (Scheme 19).



Scheme 19

These results indicate that the formal [3+2] addition of oxazole with dienophiles reported before does not proceed through nitrile ylide intermediate. Therefore, the reaction of 2-amino-5-alkoxyoxazoles **1** with DMAD or alcohols should be distinguished strictly from the formal [3+2] addition of oxazole reported before. In other word, the formal [3+2] additions of **6** and **15** proceeds through the stepwise mechanism, and the reactions of **1** described here, on the contrary, are determined to proceed through the nitrile ylide intermediate generated by the ring opening of oxazole prior to the attack of the reagents.

[2] 2-(*p*-Methoxyphenyl)-5-methoxyoxazole (**15**) was reported to react with carbonyl compounds in the presence of Lewis acid to give 2-oxazoline selectively in high yield below room temperature.[4f-i)]

4-8 Conclusion

This chapter describes the reaction of 2-amino-5-alkoxyoxazole with DMAD to give pyrrole derivatives. In order to explain this unusual reactivity, the reaction of 5-*tert*-butoxy-2-(diisopropylamino)oxazole with methanol was carried out to obtain 1:1-adduct in quantitative yield. In the kinetic study of this reaction, first order kinetics were observed. This indicates that 2-amino-5-alkoxyoxazole is converted to the nitirle ylide intermediate under the reaction conditions. The molecular orbital calculation indecates that the stability of nitrile ylide intermediate is increased by the introduction of amino group.

The ring opening of 2-amino-5-alkoxyoxazole provides a new method to generate nitrile ylide intermediate under mild conditions. Other significance of this reaction is summerized as follows.

(1) Comparison with the Cornforth rearrangement

The ring opening of 4-acyl-5-alkoxyoxazole is known as the key step of the Cornforth rearrangement. Although this reaction was investigated extensively in kinetic and theoretical points of view, all attempts to trap the nitrile ylide intermediate were unsuccessful except for a similar reaction reported by Saalfrank. In our result, however, nitrile ylide generated by the ring opening of 2-amino-5-alkoxyoxazole has a high rectivity toward DMAD and methanol. Therefore, this reaction has an advantage to the Cornforth rearrangement in synthetic point of view.

(2) Comparison with other formal [3+2] addition of oxazole

In the chemistry of oxazole, the formal [3+2] reaction is the latest topic. A 2-phenyl-5-ethoxyoxazole is reported to have a high rectivity toward ketomalonate. However, reactions of 2-phenyl-5-ethoxyoxazole with methanol did not proceed at all, which suggest 2-phenyl-5-ethoxyoxazole did not generate nitrile ylide intermediate. In contrast, 2-amino-5-alkoxyoxazole reacts with methanol easily. Therefore, there are two pathways in the reaction of oxazole with dipolarophiles; One is initiated by the reaction of oxazole with dipolarophile followed by the ring opening of oxazole, which is known as the formal [3+2] reaction of oxazole. The other is initiated by the ring opening of oxazole to generate nitrile ylide intermediate, which is described in this chapter. The reaction of 2-amino-5-alkoxyoxazole with DMAD must be differenciated strictly in the mechanistic point of view from other formal [3+2] reaction of oxazoles with strong dipolarophiles reproted before.

Experimental

Melting points were measured with a Yanagimoto Melting-point Apparatus and were not corrected. IR spectra were recorded on a Perkin-Elmer model 983. ^{1}H NMR (270.05 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL EX-270 in a $CDCl_3$ solution using TMS as an internal standard. Mass spectra were determined with a JEOL JMS-DX303 spectrometer and a SHIMADZU GCMS-QP2000A gas chromatograph mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-5.

Materials and Solvents. Ethyl diazoacetate was prepared by the diazotization of ethyl glycinate hydrochloride with sodium nitrite.[5] Isopropyl diazoacetate and *tert*-butyl diazoacetate were prepared by acyl cleavage of isopropyl diazoacetoacetate and *tert*-butyl diazoacetoacetate with sodium methoxide or potassium hydroxide.[6] Methanol was purified by distillation. DMAD was purified by distillation of the commercial reagent.

A solution of 0.5 mmol of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) in 15 ml of benzene was heated at reflux temperature and 10 mmol of DMAD was added dropwise for 5 minutes. After additional heating for 1 h, the benzene and excess DMAD were removed under reduced pressure. The residual oil was separated by column chromatography on silica gel using ethyl acetate-hexane as an eluent to give dimethyl 5-*tert*-butoxy-2-(diisopropylamino)furan-3,4-dicarboxylate (**2a**) and dimethyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-3,4-dicarboxylate (**3a**).

Dimethyl 5-*tert*-butoxy-2-(diisopropylamino)furan-3,4-dicarboxylate (**2a**): 15 % yield; yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.09 (12H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 1.47 (9H, s, CH_3 of ^{t}Bu), 3.41 (2H, spt. J=6.6 Hz, CH of ^{i}Pr), 3.77 (3H, s, $COOCH_3$), 3.80 (3H, s, $COOCH_3$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.83 (qqui, $^{2}J_{CH}$ and $^{3}J_{CH}$=3.7 and 4.9 Hz, CH_3 of ^{i}Pr), 28.71 (qqui, $^{3}J_{CH}$=3.7 Hz, CH_3 of ^{t}Bu), 50.47 (dm, CH of ^{i}Pr), 51.35 (q, $COO\underline{C}H_3$), 51.82 (q, $COO\underline{C}H_3$), 85.96 (m, quaternary-C of of ^{t}Bu), 97.55 (s, 3-C), 111.34 (s, 4-C), 146.67 (st, $^{3}J_{CH}$=5.5 Hz, 2-C), 155.20 (s, 5-C), 162.99 (sq, $^{3}J_{CH}$=4.3 Hz, $\underline{C}OOCH_3$), 164.43 (sq, $^{3}J_{CH}$=4.3 Hz, $\underline{C}OOCH_3$); IR (neat) 2973, 2874, 2626, 1723 (C=O), 1597, 1436, 1368, 1334, 1209, 1084, 1025, 962, 928, 890, 839, 812, 785, 769, and 664 cm^{-1}.

Dimethyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-3,4-dicarboxylate (**3a**): 30 % yield; colorless needles; mp 114.8-117.6 °C (from benzene-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.11 (12H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 1.53 (9H, s, CH_3 of ^{t}Bu), 3.67 (2H, spt, J=6.6 Hz, CH of ^{i}Pr), 3.75 (3H, s, $COOCH_3$), 3.89 (3H, s, $COOCH_3$), 8.57 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=22.39 (CH_3 of ^{i}Pr), 28.18 (CH_3 of ^{t}Bu), 50.01 (CH of ^{i}Pr), 51.19 ($COO\underline{C}H_3$), 52.40 ($COO\underline{C}H_3$), 82.17 (quaternary-C of of ^{t}Bu), 108.55 (3-C), 115.45 (5-C), 122.89 (4-C), 142.69 (2-C), 159.06 ($\underline{C}OO^{t}Bu$), 163.11 ($\underline{C}OOCH_3$),

166.45 ($\underline{C}OOCH_3$); IR (KBr) 3287 (NH), 2973, 2926, 2870, 1736 (C=O), 1723 (C=O), 1682 (C=O), 1616, 1558, 1497, 1481, 1444, 1429, 1382, 1364, 1354, 1298, 1242, 1206, 1163, 1122, 1095, 1066, 1042, 1016, 974, 941, 932, 891, 849, 819, 797, 781, 750, 726, 688, and 669 cm^{-1}; MS (EI) 384, 383 (MH^+), 352, 327, 313, 294, 293, 284, 283, 279, 277, 263, 261, 252, 251, 247, 237, 233, 220, 219, 207, 205, 203, 187, 175, 165, 161. Found: C, 59.68; H, 7.81; N, 7.22 %. Calcd for $C_{19}H_{30}N_2O_6$: C, 59.67; H, 7.91; N, 7.32 %.

A solution of 0.5 mmol of ethyl diazoacetate in 2 ml of benzene was added dropwise to a mixture of 2.5 mmol of diisopropylcyanamide and 5 mol% (2.5×10^{-2} mmol) of rhodium(II) acetate at 80 °C for 20 minutes. After additional heating for 1 h, 13 ml of benzene was added to the reaction mixture, and then 10 mmol of DMAD was added dropwise for 5 minutes. The reaction mixture was heated at reflux temperature for 1 h. The benzene, excess of DMAD, and excess of diisopropylcyanamide were removed under reduced pressure, and the residual oil was separated by column chromatography on silica gel using ethyl acetate-hexane as an eluent to give dimethyl 2-diisopropylamino-5-ethoxyfuran-3,4-dicarboxylate (**2b**) and dimethyl 2-diisopropylamino-5-(ethoxycarbonyl)pyrrole-3,4-dicarboxylate (**3b**).

Dimethyl 2-diisopropylamino-5-ethoxyfuran-3,4-dicarboxylate (2b): trace; ^1H NMR (270 MHz, $CDCl_3$) δ=1.07 (12H, d, J=6.6 Hz, CH_3 of ^iPr), 1.43 (3H, t, J=6.9 Hz, CH_3 of Et), 3.37 (2H, spt. J=6.6 Hz, CH of ^iPr), 3.76 (3H, s, $COOCH_3$), 3.81 (3H, s, $COOCH_3$), 4.38 (2H, q, J=6.9 Hz, CH_2 of Et).

A solution of 0.5 mmol of isopropyl diazoacetate in 2 ml of benzene was added dropwise to a mixture of 2.5 mmol of diisopropylcyanamide and 5 mol% (2.5×10^{-2} mmol) of rhodium(II) acetate at 80 °C for 20 minutes. After additional heating for 1 h, 13 ml of benzene was added to the reaction mixture, and then 10 mmol of DMAD was added dropwise for 5 minutes. The reaction mixture was heated at reflux temperature for 1 h. The benzene, excess of DMAD, and excess of diisopropylcyanamide were removed under reduced pressure, and the residual oil was separated by column chromatography on silica gel using ethyl acetate-hexane as an eluent to give dimethyl 2-diisopropylamino-5-isopropoxyfuran-3,4-dicarboxylate (**2c**) and dimethyl 2-diisopropylamino-5-(isopropoxycarbonyl)pyrrole-3,4-dicarboxylate (**3c**).

Dimethyl 2-diisopropylamino-5-isopropoxyfuran-3,4-dicarboxylate (2c): 4 % yield; yellow oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.07 (12H, d, J=6.6 Hz, CH_3 of N^iPr), 1.40 (6H, d, J=6.3 Hz, CH_3 of O^iPr), 3.38 (2H, spt. J=6.6 Hz, CH of N^iPr), 3.77 (3H, s, $COOCH_3$), 3.80 (3H, s, $COOCH_3$), 4.82 (1H, spt. J=6.3 Hz, CH of O^iPr).

Dimethyl 2-diisopropylamino-5-(isopropoxycarbonyl)pyrrole-3,4-dicarboxylate (3c): 58 % yield; yellow viscous oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.11 (12H, d, J=6.6 Hz, CH_3 of N^iPr), 1.31 (6H, d, J=6.3 Hz, CH_3 of O^iPr), 3.67 (2H, spt, J=6.6 Hz, CH of N^iPr), 3.75 (3H, s, $COOCH_3$), 3.91 (3H, s,

$COOCH_3$), 5.15 (1H, spt, J=6.3 Hz, CH of O^{i}Pr), 8.58 (1H, brs, NH); ^{13}CNMR (67.8 MHz, $CDCl_3$) δ=21.89 (CH_3 of N^{i}Pr), 22.37 (CH_3 of O^{i}Pr), 50.01 (CH of N^{i}Pr), 51.23 (COO$\underline{C}H_3$), 52.42 (COO$\underline{C}H_3$), 68.93 (CH of O^{i}Pr), 108.95 (3-C), 114.59 (5-C), 123.54 (4-C), 142.93 (2-C), 159.26 ($\underline{C}$OO^{i}Pr), 163.07 ($\underline{C}OOCH_3$), 166.39 ($\underline{C}OOCH_3$); IR (KBr) 3301 (NH), 2977, 2933, 1745 (C=O), 1722 (C=O), 1706 (C=O), 1680, 1510, 1449, 1372, 1331, 1299, 1255, 1234, 1199, 1179, 1108, 1064, 843, and 797 cm^{-1}; MS (EI) 370, 369 (MH^+), 354, 338, 326, 322, 295, 294, 280, 278, 262, 253, 252, 234, 219, 205, 203, 188, 187, 165, 161.

A solution of 0.1 mmol of 2-diisopropylamino-5-(*p*-nitrophenyl)oxazole (**8**) in 3 ml of benzene was heated at reflux temperature and 2 mmol of DMAD was added dropwise for 5 minutes. After additional heating overnight, the benzene and excess DMAD were removed under reduced pressure. The residual oil was separated by column chromatography on silica gel using ethyl acetate-hexane as an eluent to give dimethyl 2-diisopropylamino-5-(*p*-nitrophenyl)furan-3,4-dicarboxylate (**9**).

Dimethyl 2-diisopropylamino-5-(*p*-nitrophenyl)furan-3,4-dicarboxylate (**9**): 25 % yield; orange cyrstals; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.38 (12H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 3.76 (3H, s, $COOCH_3$), 3.94 (3H, s, $COOCH_3$), 4.04 (2H, spt. J=6.6 Hz, CH of ^{i}Pr), 7.66 (2H, d, J=8.9 Hz, 2'-CH of Ar), 8.22 (2H, d, J=8.9 Hz, 3'-CH of Ar); IR (KBr) 2977, 2947, 1731 (C=O), 1710 (C=O), 1679, 1610, 1591, 1562 (NO_2), 1510, 1444, 1395, 1369, 1335, (NO_2), 1301, 1236, 1169, 1130, 1110, 1087, 1035, 1022, 975, 942, 925, 850, 812, 785, 773, 753, 718, 694, and 668 cm^{-1}.

A solution of 0.5 mmol of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) in 15 ml of benzene was heated at reflux temperature and 10 mmol of methyl propiolate was added dropwise for 5 minutes. After additional heating for 39 h, the benzene and excess methyl propiolate were removed under reduced pressure. The residual oil was separated by column chromatography on silica gel using ethyl acetate-hexane as an eluent to give methyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-4-carboxylate (**10a**) and methyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-3-carboxylate (**10b**).

Methyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-4-carboxylate (**10a**): 41 % yield; yellow crystals; mp 90.9-94.0 °C (from benzene-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.12 (12H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 1.56 (9H, s, CH_3 of ^{t}Bu), 3.48 (2H, spt, J=6.6 Hz, CH of ^{i}Pr), 3.84 (3H, s, $COOCH_3$), 5.96 (1H, d, J=3.3 Hz, 3-H), 8.57 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=21.27 (qqui, $^3J_{CH}$=4.9 Hz, CH_3 of ^{i}Pr), 28.29 (qspt, $^3J_{CH}$=4.3 Hz, CH_3 of ^{t}Bu), 49.07 (dsxt, $^2J_{CH}$=3.7 Hz, CH of ^{i}Pr), 51.58 (q, COO$\underline{C}H_3$), 81.07 (ssxt, $^2J_{CH}$=4.3 Hz, quaternary-C of of ^{t}Bu), 102.27 (dd, $^3J_{CH}$=6.7 Hz, 3-CH), 116.73 (sdd, $^3J_{CH}$=6.1 Hz, $^2J_{CH}$=2.4 Hz, 5-C), 119.88 (sdd, $^3J_{CH}$=7.3 Hz, $^2J_{CH}$=6.7 Hz, 4-C), 139.91 (sm, 2-C), 159.56 (sm, $\underline{C}$OO^{t}Bu), 165.29 (sm, $\underline{C}OOCH_3$); IR (KBr) 3303 (NH), 2979, 2949, 2844, 1716 (C=O), 1676 (C=O), 1564, 1488, 1442, 1385, 1362, 1341, 1330, 1276, 1242, 1207, 1163, 1134, 1126, 1112, 1068,

1033, 1018, 967, 916, 862, 845, 836, 821, 798, 785, 776, and 750 cm^{-1}. Found: C, 62.55; H, 8.55; N, 8.50 %. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94; H, 8.70; N, 8.63 %.

Methyl 5-*tert*-butoxycarbonyl-2-(diisopropylamino)pyrrole-3-carboxylate (10b): 12 % yield; colorless crystals; mp. 103.5-104.7 °C (benzene-hexane); ^1H NMR (270 MHz, $CDCl_3$) δ=1.09 (12H, d, J=6.6 Hz, CH_3 of ^iPr), 1.56 (9H, s, CH_3 of ^tBu), 3.72 (2H, spt, J=6.6 Hz, CH of ^iPr), 3.77 (3H, s, $COOCH_3$), 7.14 (1H, d, J=3.0 Hz, 4-H), 8.56 (1H, brs, NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=22.35 (qm, CH_3 of ^iPr), 28.36 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of ^tBu), 49.79 (dsxt, $^2J_{CH}$=4.3 Hz, CH of ^iPr), 50.83 (q, $COO\underline{C}H_3$), 81.04 (sm, quaternary-C of of ^tBu), 110.29 (sdd, $^3J_{CH}$=7.3 Hz, $^2J_{CH}$=3.1 Hz, 3-C), 116.74 (dd, $^3J_{CH}$=6.1 Hz, 4-CH), 117.97 (sm, 5-C), 143.56 (sm, 2-C), 160.29 (s, $\underline{C}OO^tBu$), 164.24 (sm, $\underline{C}OOCH_3$); IR (KBr) 3308 (NH), 2976, 2931, 1721 (C=O), 1675 (C=O), 1558, 1482, 1449, 1421, 1381, 1367, 1351, 1334, 1253, 1205, 1182, 1164, 1122, 1107, 1084, 1039, 1014, 992, 963, 918, 863, 830, 790, 781, and 726 cm^{-1}. Found: C, 62.96; H, 8.59; N, 8.63 %. Calcd for $C_{17}H_{28}N_2O_4$: C, 62.94 %; H, 8.70 %; N, 8.63 %.

A solution of 0.1 mmol of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) in 3 ml of methanol was heated at reflux temperature for 30 minutes. After removal of excess of methanol, *N*^{1}-diisopropyl-*N*^{2}-(*tert*-butoxycarbonyl)methoxymethylamidine (**11**) was obtained.

***N*^{1}-diisopropyl-*N*^{2}-(*tert*-butoxycarbonyl)methoxymethylamidine (11)**: 99 % yield; yellow oil; ^1H NMR (270 MHz, $CDCl_3$) δ=1.20 (12H, brd, J= 5.6 Hz, CH_3 of ^iPr), 1.47 (9H, s, CH_3 of ^tBu), 3.34 (3H, s, OCH_3), 4.56 (1H, s, CH), 7.65 (1H, s, N=CH); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ=19.83 (brq, CH_3 of ^iPr), 23.90 (brq, CH_3 of ^iPr), 28.02 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of ^tBu), 45.38 (dm, CH of ^iPr), 54.50 (qd, $^3J_{CH}$=3.7 Hz, OCH_3), 81.09 (sxt, $^2J_{CH}$=4.3 Hz, quaternary-C of ^tBu), 94.99 (dm, CH), 152.76 (ddt, J=166.6 Hz, $^3J_{CH}$=8.6 and 4.3 Hz, N=CH), 169.63 (s, $\underline{C}OO^tBu$),; IR (neat) 2969, 2820, 1745 (C=O), 1628 (C=N), 1460, 1440, 1391, 1367, 1290, 1213, 1155, 1109, 1175, 1010, 950, 846, and 806 cm^{-1}.

Kinitic Studies

A solution of 36 mg (0.15 mmol) of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) and 1.2 equivalents of methanol dissolved in 1 ml of benzene-d_6 was heated in a sealed NMR tube with silicone bath. The decrease of **1a** was monitored by ^1H NMR spectroscopy using H-4 of **1a** as a probe. The logarithms of the concentration of **1a** were plotted as a function of time, and the rate constants were estimated by the least squares methods.

Reaction of **1a** with 1.2 equiv. of methanol in C_6D_6 at 80 °C

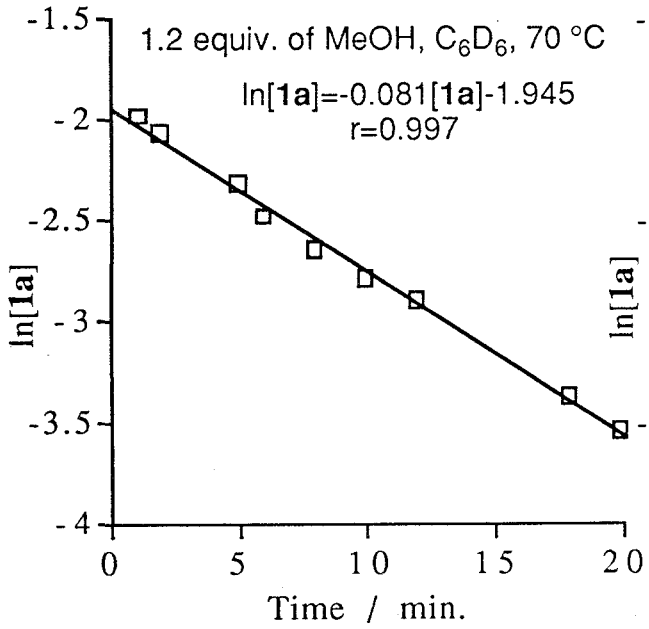
Time / h	[**1a**] / mol•l^{-1}
1	0.142
2	0.125
3	0.107
4	0.093
5	0.084
6	0.071
7	0.058
8	0.053
9	0.048
10	0.040
11	0.034
12	0.029
13	0.022
14	0.018
15	0.016
16	0.015
17	0.012
18	0.010
19.25	0.008
20	0.007

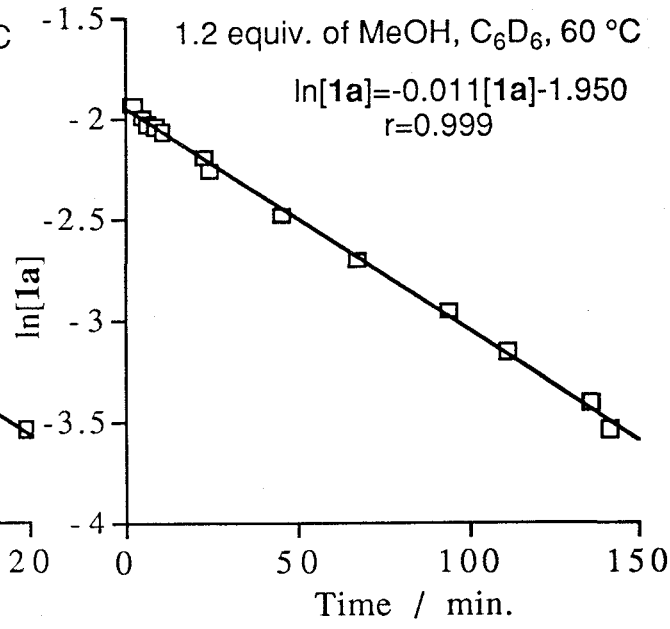
Reaction of **1a** with 1.2 equiv. of methanol in C_6D_6 at 70 °C

Time / h	[**1a**] / mol•l^{-1}
1.02	0.138
1.87	0.127
4.89	0.098
5.89	0.084
7.89	0..071
9.89	0.061
11.89	0.055
17.89	0.034
19.89	0.029

Reaction of **1a** with 1.2 equiv. of methanol in C_6D_6 at 60 °C

Time / h	[**1a**] / mol•l^{-1}
1	0.145
2	0.145
4	0.137
6	0.132
8	0.129
10	0.127
22	0.111
24	0.105
45.5	0.083
67.5	0.067
94	0.052
111.8	0.043
135.3	0.033
141.7	0.029





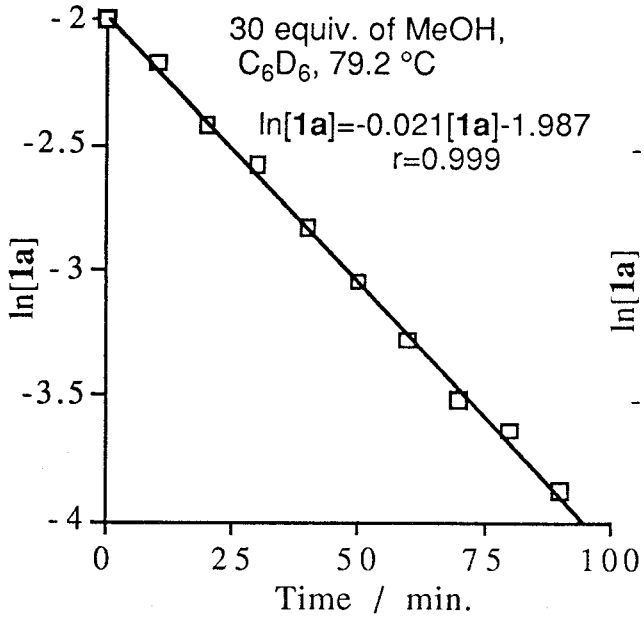
A solution of 36 mg (0.15mmol) of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) and 30 equivalents of methanol dissolved in 1 ml of benzene-d_6 was sealed in a NMR tube. The tube was placed in the NMR probe and heated. The decrease of **1a** was monitored by ^1H NMR spectroscopy using H-4 proton of oxazole ring as a probe. The temperature in the NMR probe was corrected with thermocouple.

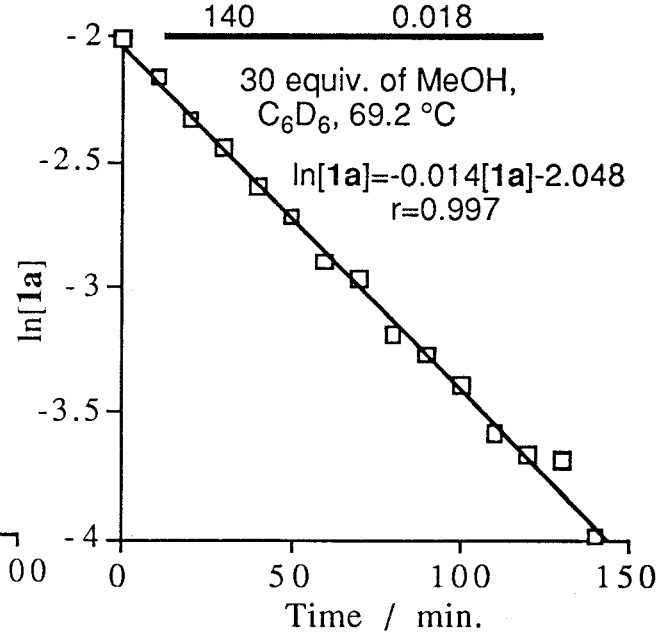
Reaction of **1a** with 30 equiv. of methanol in C_6D_6 at 79.2 °C

Time / min.	[**1a**] / mol•l^{-1}
0	0.135
10	0.114
20	0.089
30	0.075
40	0.059
50	0.047
60	0.038
70	0.030
80	0.026
90	0.021

Reaction of **1a** with 30 equiv. of methanol in C_6D_6 at 69.2 °C

Time / min.	[**1a**] / mol•l^{-1}
0	0.134
10	0.114
20	0.096
30	0.087
40	0.074
50	0.066
60	0.055
70	0.051
80	0.041
90	0.038
100	0.033
110	0.028
120	0.025
130	0.025
140	0.018



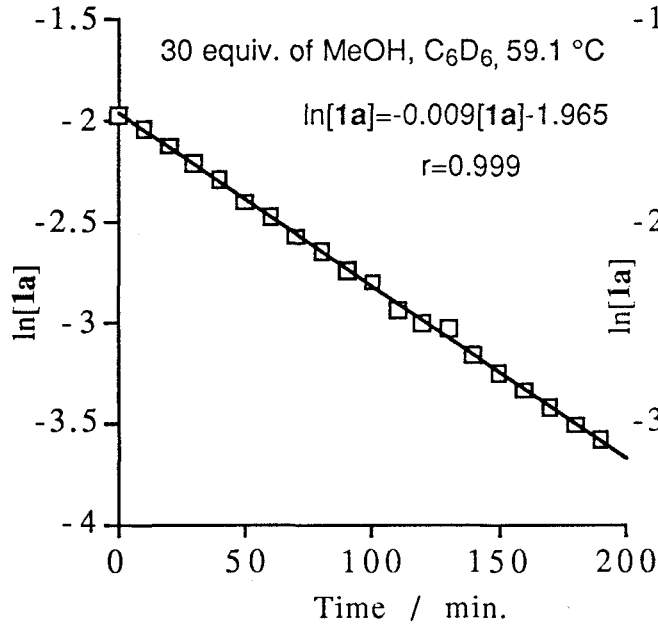


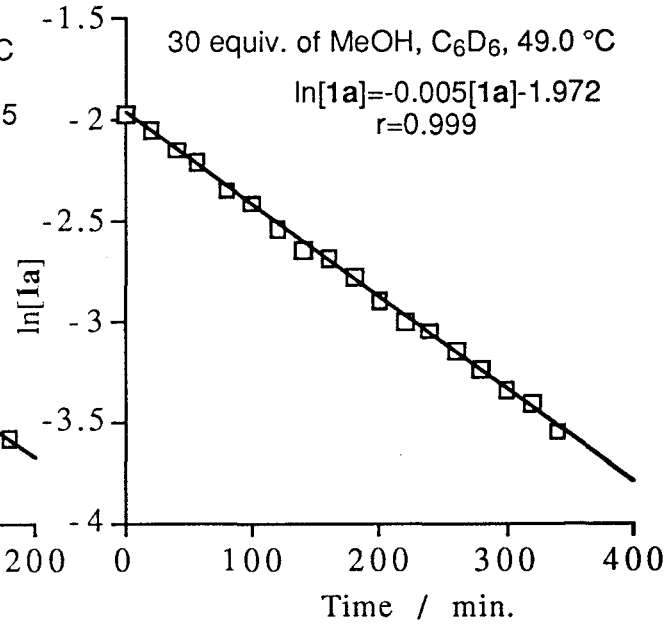
Reaction of **1a** with 30 equiv. of methanol in C_6D_6 at 59.1 °C

Time / min.	[**1a**] / mol•l^{-1}
0	0.138
10	0.130
20	0.119
30	0.109
40	0.100
50	0.090
60	0.084
70	0.076
80	0.070
90	0.064
100.1	0.061
110	0.053
120	0.049
130	0.048
140	0.042
150	0.039
160	0.035
170	0.032
180	0.030
190	0.027

Reaction of **1a** with 30 equiv. of methanol in C_6D_6 at 49.0 °C

Time / min.	[**1a**] / mol•l^{-1}
0	0.138
20	0.129
40	0.116
55	0.109
80	0.095
100.2	0.090
120	0.079
140	0.070
160	0.068
180	0.062
200	0.055
220	0.049
240	0.047
260	0.042
280	0.039
300	0.035
320	0.033
340	0.029





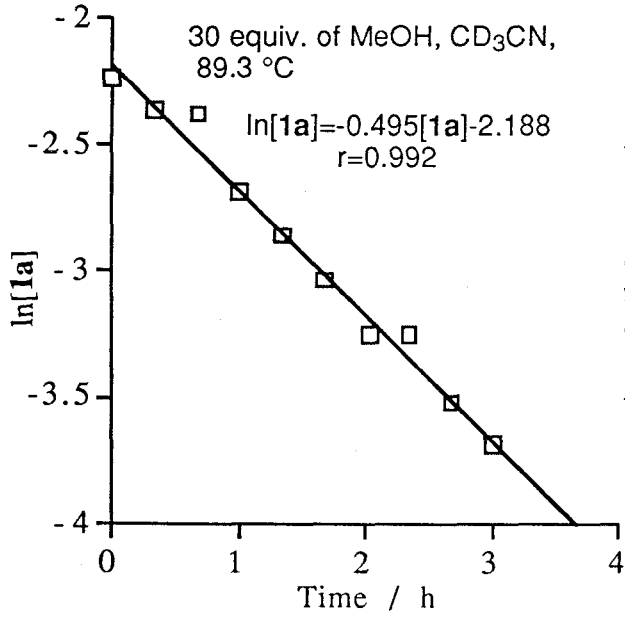
A solution of 36 mg (0.15mmol) of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) and 30 equivalents of methanol dissolved in 1 ml of acetonitrile-d_3 was sealed in a NMR tube. The tube was placed in the NMR probe and heated. The decrease of **1a** was monitored by ^{1}H NMR spectroscopy using H-4 proton of **1a** as a probe. The temperature in the NMR probe was corrected with thermocouple.

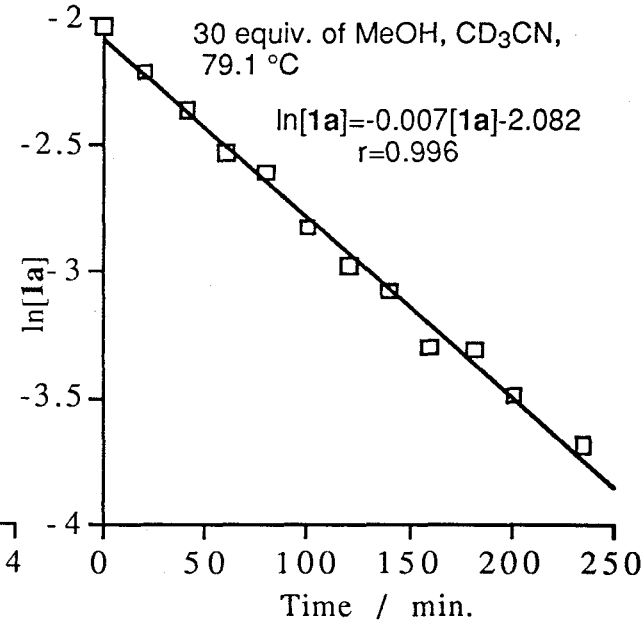
Reaction of **1a** with 30 equiv. of methanol in CD_3CN at 89.3 °C

Time / min.	[**1a**] / mol•l^{-1}
0	0.106
20	0.094
40	0.092
60	0.068
80	0.057
100	0.047
120	0.039
140	0.039
160	0.029
180	0.025

Reaction of **1a** with 30 equiv. of methanol in CD_3CN at 79.1 °C

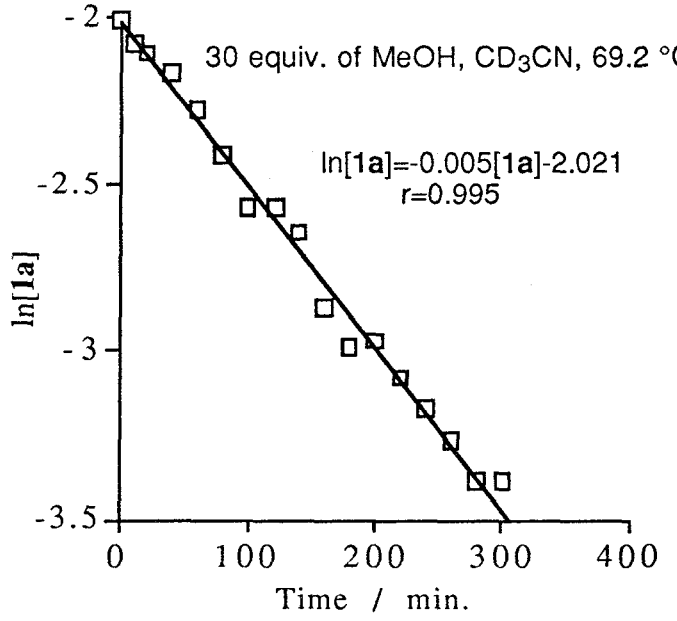
Time / min.	[**1a**] / mol•l^{-1}
0	0.131
20.2	0.109
41.3	0.094
60	0.080
80	0.073
100	0.059
120	0.051
140	0.046
160	0.037
182.3	0.036
201.5	0.030
234.3	0.025





Reaction of **1a** with 30 equiv. of methanol in CD_3CN at 69.2 °C

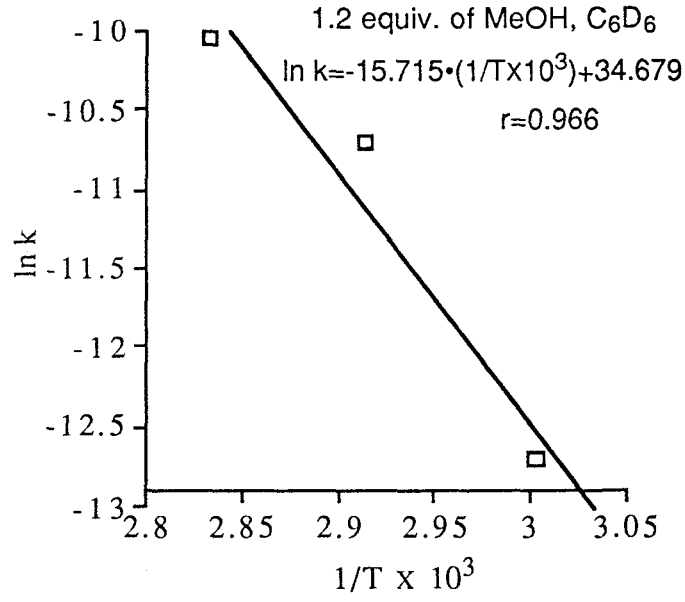
Time / min.	[**1a**] / mol•l^{-1}
0	0.134
10	0.125
20.1	0.122
40	0.115
60	0.102
80	0.089
100	0.076
121	0.076
140	0.071
160.1	0.056
180	0.050
200	0.051
220	0.046
240	0.042
260	0.038
280	0.034
300	0.034



The activation energies (Ea) of the reactions were obtained from Arrhenius plots. The activation parameters ($\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$) were calculated with Eyring's equation.

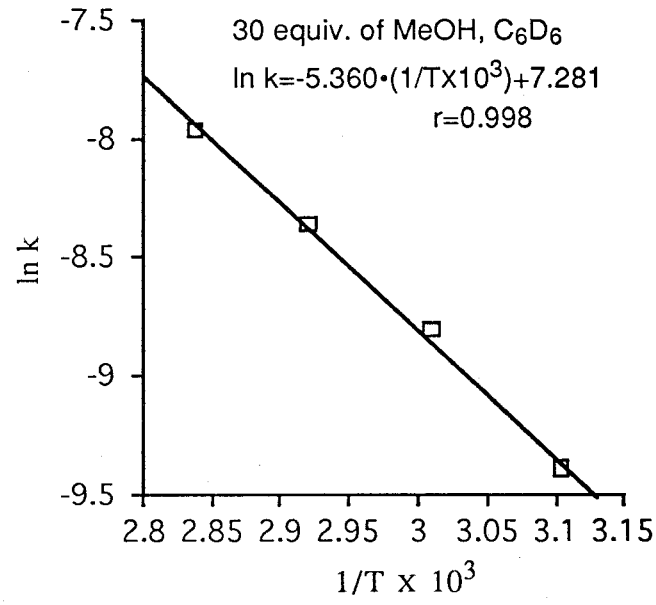
Logarithms of Rate Constants in the Reaction of **1a** with 1.2 equiv. of Methanol in C_6D_6.

Temp. / °C	ln *k*
60.0	-12.697
70.0	-10.702
80.0	-10.040



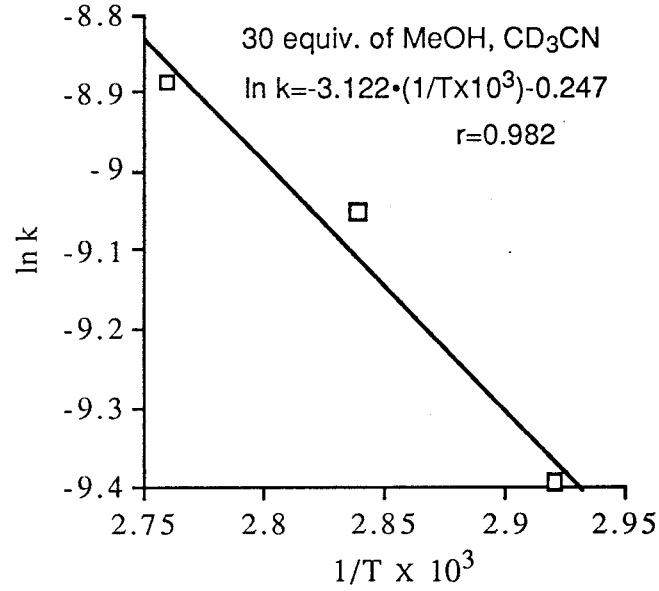
Logarithms of Rate Constants in the Reaction of **1a** with 30 equiv. of Methanol in C_6D_6.

Temp. / °C	ln *k*
49.0	-9.393
59.1	-8.805
69.2	-8.363
79.2	-7.958



Logarithms of Rate Constants in the Reaction of **1a** with 30 equiv. of Methanol in CD_3CN.

Temp. / °C	ln *k*
69.2	-9.393
79.1	-9.053
89.3	-8.888



Molecular Orbital Calculations:

The molecular orbital calculations were carried out using MINDO/3 hamiltonian in MOPAC ver. 6.20 on Macintoch Centris 660 AV. The structure of oxazoles and nitrile ylides was optimized by eigenvector following method (key word "EF"). The MINDO/3 hamiltonian gave a bent form as an optimized structure for each nitrile ylide. The structures of the transition state were obtained by "SADDLE", and optimized by eigenvector following method (key word "TS"). The force calculation of each optimized structure in transition state gave only one imaginary frequency, and its direction was along C-O bond.

Oxazole (OXa);

HEAT OF FORMATION	=	-7.423995 KCAL
ELECTRONIC ENERGY	=	-2805.642809 EV
CORE-CORE REPULSION	=	1878.324184 EV
DIPOLE	=	1.04748 DEBYE
NO. OF FILLED LEVELS	=	13
IONIZATION POTENTIAL	=	8.567859 EV
MOLECULAR WEIGHT	=	69.063
SCF CALCULATIONS	=	31
COMPUTATION TIME	=	1 MINUTES AND 7.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

MINDO/3 PRECISE XYZ VECTORS BONDS EF

C	.0000000	0	.000000	0	.000000	0	0	0	-.0530
N	1.4120312	1	.000000	0	.000000	0	1	0	-.1934
C	1.3032691	1	102.942953	1	.000000	0	2	1	0 .3541
H	1.1133895	1	130.365224	1	179.999781	1	3	2	1 .0010
H	1.1015332	1	121.394851	1	179.999791	1	1	2	3 .0294
C	1.3617810	1	108.757093	1	.000000	1	1	2	3 .1880
O	1.3447879	1	114.938828	1	.000000	1	3	2	1 -.3471
H	1.1021169	1	137.226166	1	179.999793	1	6	1	2 .0210

BOND ORDERS AND VALENCIES

		C 1	N 2	C 3	H 4	H 5	C 6	
C	1	3.867992						
N	2	1.089596	3.046450					
C	3	.029358	1.700511	3.742153				
H	4	.014165	.053237	.889548	.999999			
H	5	.921262	.018703	.012936	.003445	.999138		
C	6	1.707221	.043614	.086600	.016151	.021695	3.796267	
O	7	.075771	.126866	1.004206	.019889	.019196	1.009345	
H	8	.030617	.013922	.018993	.003563	.001901	.911642	

		O 7	H 8
O	7	2.274193	
H	8	.018919	.999558

Formyl nitrile ylide (NYa);

HEAT OF FORMATION	=	2.799299 KCAL
ELECTRONIC ENERGY	=	-2608.553133 EV
CORE-CORE REPULSION	=	1681.677824 EV
DIPOLE	=	3.69044 DEBYE
NO. OF FILLED LEVELS	=	13
IONIZATION POTENTIAL	=	8.641399 EV
MOLECULAR WEIGHT	=	69.063

SCF CALCULATIONS = 76
COMPUTATION TIME = 2 MINUTES AND 59.000 SECONDS

FINAL GEOMETRY OBTAINED

MINDO/3 PRECISE XYZ VECTORS BONDS EF

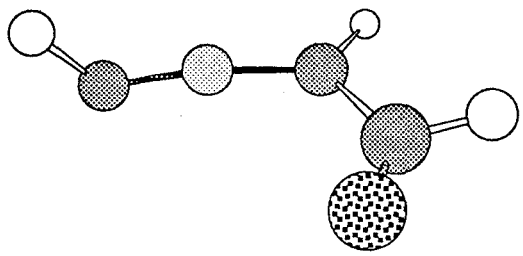
									CHARGE
C	.0000000	0	.000000	0	.000000	0	0	0	0	-.3178
N	1.2886512	1	.000000	0	.000000	0	1	0	0	.3645
C	1.1980970	1	168.774250	1	.000000	0	2	1	0	-.1886
H	1.1074640	1	125.952415	1	-176.774228	1	3	2	1	.0813
H	1.1127532	1	116.360895	1	81.443466	1	1	2	3	.0526
C	1.4494900	1	125.141481	1	-169.371422	1	1	2	5	.6515
O	1.1992243	1	128.714097	1	3.123721	1	6	1	2	-.5074
H	1.1363917	1	109.616995	1	-174.853133	1	6	1	2	-.1362

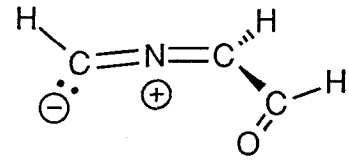
BOND ORDERS AND VALENCIES

		C 1	N 2	C 3	H 4	H 5	C 6	
C	1	3.757262						
N	2	1.476346	3.784427					
C	3	.184275	2.205566	3.361133				
H	4	.083588	.030982	.865801	.993383			
H	5	.916504	.009051	.039464	.000367	.997229		
C	6	.994712	.021181	.040012	.004642	.014711	3.669647	
O	7	.066180	.025805	.018711	.007022	.017089	1.750258	
H	8	.035657	.015497	.007304	.000980	.000043	.844132	

		O 7	H 8
O	7	1.962898	
H	8	.077834	.981446

The optimized structure of **NYa**





Transition state from OXa to NYa (TSa);

HEAT OF FORMATION = 35.540208 KCAL
ELECTRONIC ENERGY = -2742.553903 EV
CORE-CORE REPULSION = 1817.098346 EV
DIPOLE = 2.58829 DEBYE
NO. OF FILLED LEVELS = 13

IONIZATION POTENTIAL = 7.980672 EV
MOLECULAR WEIGHT = 69.063
SCF CALCULATIONS = 595
COMPUTATION TIME = 16 MINUTES AND 57.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

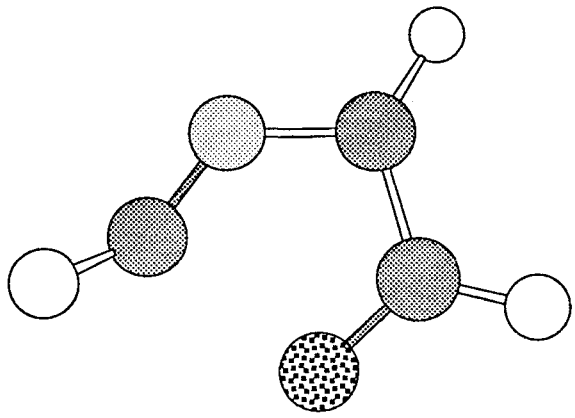
MINDO/3 PRECISE XYZ TS HESS=1 RECALC=5

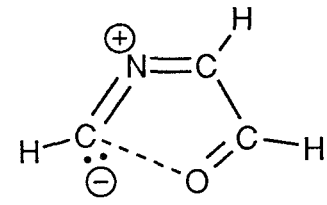
C	.0000000 0	.000000 0	.000000 0	0	0	0	-.3565
N	1.3497825 1	.000000 0	.000000 0	1	0	0	.2207
C	1.2024214 1	127.537538 1	.000000 0	2	1	0	.0429
H	1.0934283 1	145.576856 1	142.466391 1	3	2	1	.1049
H	1.0998169 1	120.717976 1	159.030939 1	1	2	3	.0660
C	1.4185139 1	105.534263 1	-5.048181 1	1	2	3	.5580
O	1.2392871 1	117.249536 1	-.842022 1	6	1	2	-.5616
H	1.1194489 1	119.761025 1	-179.987887 1	6	1	2	-.0744

DESCRIPTION OF VIBRATIONS

VIBRATION 1	ATOM PAIR	ENERGY CONTRIBUTION	RADIAL
FREQ. -567.87	C 3 -- O 7	-845.2% (-54.6%)	99.1%
T-DIPOLE 1.7447	C 3 -- H 4	-770.9%	9.5%
TRAVEL .1119	C 1 -- N 2	-325.6%	28.1%
RED. MASS 4.7436	N 2 -- C 6	-265.2%	57.0%
	C 6 -- O 7	-240.7%	11.6%
	C 6 -- H 8	-232.4%	5.2%
	C 1 -- C 6	-194.3%	70.6%
	C 1 -- C 3	-127.6%	19.6%
	C 1 -- H 5	-66.0%	.1%
	N 2 -- C 3	-64.5%	1.0%

The optimized structure of **TSa**





5-Methoxyoxazole (OXb);

HEAT OF FORMATION	=	-55.672840 KCAL
ELECTRONIC ENERGY	=	-5005.160197 EV
CORE-CORE REPULSION	=	3609.687702 EV
DIPOLE	=	1.98162 DEBYE
NO. OF FILLED LEVELS	=	19
IONIZATION POTENTIAL	=	7.941456 EV
MOLECULAR WEIGHT	=	99.089
SCF CALCULATIONS	=	187
COMPUTATION TIME	=	17 MINUTES AND 44.000 SECONDS

FINAL GEOMETRY OBTAINED — CHARGE

MINDO/3 PRECISE XYZ VECTORS BONDS EF

C	.0000000	0	.000000	0	.000000	0	0	0	0	-.2080
N	1.4121870	1	.000000	0	.000000	0	1	0	0	-.1594
C	1.2975951	1	103.996443	1	.000000	0	2	1	0	.3296
H	1.1125520	1	131.077611	1	-179.999739	1	3	2	1	.0089
H	1.0988337	1	121.651823	1	179.999596	1	1	2	3	.0627
C	1.3740730	1	107.924519	1	.000000	1	1	2	3	.5604
O	1.3512649	1	115.097749	1	.000000	1	3	2	1	-.4173
O	1.3198623	1	126.750819	1	-179.996117	1	6	1	2	-.4002
C	1.3438869	1	131.403299	1	-179.990129	1	8	6	1	.4302
H	1.1211284	1	106.087914	1	-179.971087	1	9	8	6	-.0503
H	1.1218544	1	115.385972	1	-62.065544	1	9	8	6	-.0782
H	1.1218586	1	115.379911	1	62.126679	1	9	8	6	-.0782

BOND ORDERS AND VALENCIES

	C 1	N 2	C 3	H 4	H 5	C 6
C 1	3.800064					
N 2	1.069238	3.062388				
C 3	.045847	1.739588	3.741119			
H 4	.015537	.050914	.890038	.999922		
H 5	.919842	.019057	.012399	.002884	.996074	
C 6	1.586782	.039870	.072736	.015621	.020103	3.696041
O 7	.065132	.121365	.955953	.019866	.019423	.966968
O 8	.070718	.013706	.022329	.004802	.001720	.956677
C 9	.019923	.006740	.000960	.000037	.000417	.014143
H 10	.003783	.001562	.000726	.000156	.000230	.021247
H 11	.001629	.000174	.000272	.000034	.000000	.000948
H 12	.001633	.000174	.000272	.000034	.000000	.000948

	O 7	O 8	C 9	H 10	H 11	H 12
O 7	2.203362					
O 8	.049372	2.137840				
C 9	.002914	.943377	3.763387			

H 10	.000544	.011021	.925889	.997471		
H 11	.000913	.032060	.924498	.016155	.993881	
H 12	.000912	.032060	.924490	.016159	.017197	.993880

3-Methoxycarbonyl nitrile ylide (NYb)

HEAT OF FORMATION	=	-53.896437 KCAL
ELECTRONIC ENERGY	=	-4786.073828 EV
CORE-CORE REPULSION	=	3390.678364 EV
DIPOLE	=	2.99436 DEBYE
NO. OF FILLED LEVELS	=	19
IONIZATION POTENTIAL	=	8.663107 EV
MOLECULAR WEIGHT	=	99.089
SCF CALCULATIONS	=	168
COMPUTATION TIME	=	14 MINUTES AND 39.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

MINDO/3 PRECISE XYZ VECTORS BONDS EF

C	.0000000	0	.000000	0	.000000	0	0	0	0	-.3021
N	1.2847000	1	.000000	0	.000000	0	1	0	0	.3449
C	1.2031628	1	169.284708	1	.000000	0	2	1	0	-.1801
H	1.1109636	1	123.300709	1	-172.313069	1	3	2	1	.0673
H	1.1134237	1	115.648802	1	-90.661015	1	1	2	4	.0663
C	1.4730905	1	122.004923	1	-168.400537	1	1	2	5	.8653
O	1.2148755	1	124.050655	1	5.051880	1	6	1	2	-.5912
O	1.3350234	1	104.998935	1	-173.362526	1	6	1	2	-.4925
C	1.3460785	1	132.969064	1	178.365742	1	8	6	1	.4400
H	1.1215099	1	114.848841	1	-61.889673	1	9	8	6	-.0788
H	1.1214823	1	107.383944	1	179.865403	1	9	8	6	-.0606
H	1.1214494	1	114.857866	1	61.598079	1	9	8	6	-.0784

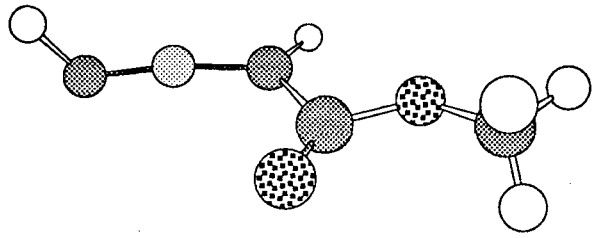
BOND ORDERS AND VALENCIES

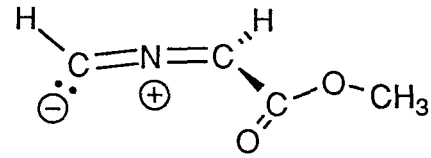
	C 1	N 2	C 3	H 4	H 5	C 6	
C 1	3.768463						
N 2	1.526865	3.775606					
C 3	.185171	2.153948	3.304503				
H 4	.089435	.028236	.867886	.995475			
H 5	.914893	.008540	.038977	.000227	.995605		
C 6	.931480	.019634	.035477	.003333	.016059	3.568138	
O 7	.059994	.017170	.011544	.004217	.016529	1.623813	
O 8	.031920	.014576	.007594	.001692	.000319	.905412	
C 9	.024055	.005037	.002884	.000268	.000014	.010979	
H 10	.000492	.000258	.000256	.000021	.000005	.002321	
H 11	.003730	.000956	.000667	.000053	.000029	.017287	
H 12	.000429	.000388	.000098	.000107	.000013	.002344	

0

		O 7	O 8	C 9	H 10	H 11	H 12
O	7	1.871313					
O	8	.122969	2.087952				
C	9	.008486	.932401	3.762032			
H	10	.001599	.029778	.926089	.993786		
H	11	.003358	.011583	.925639	.016513	.996324	
H	12	.001633	.029706	.926179	.016453	.016509	.993861

The optimized structure of **NYb**





Transition state from OXb to NYb (TSb);

HEAT OF FORMATION	=	-19.768579 KCAL
ELECTRONIC ENERGY	=	-4942.628034 EV
CORE-CORE REPULSION	=	3548.712465 EV
DIPOLE	=	1.08339 DEBYE
NO. OF FILLED LEVELS	=	19
IONIZATION POTENTIAL	=	7.983456 EV
MOLECULAR WEIGHT	=	99.089
SCF CALCULATIONS	=	94
COMPUTATION TIME	=	8 MINUTES AND 7.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

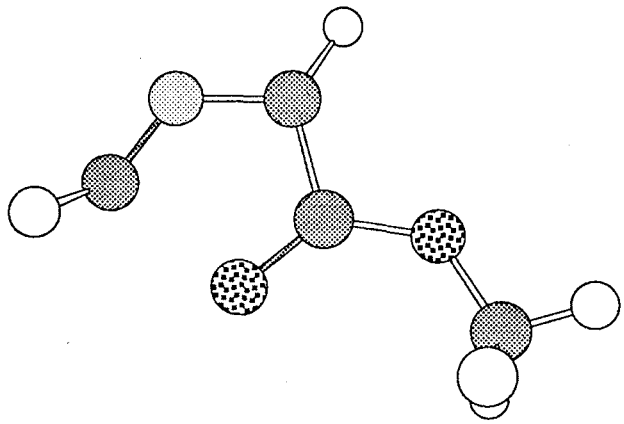
MINDO/3 PRECISE XYZ TS HESS=1 RECALC=30 T=36000

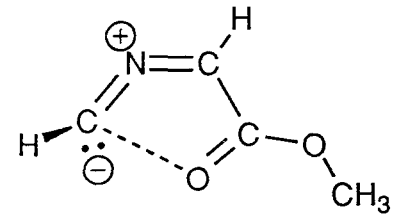
C	.0000000	0	.000000	0	.000000	0	0	0	0	-.3437
N	1.3307446	1	.000000	0	.000000	0	1	0	0	.1723
C	1.2199907	1	127.250264	1	.000000	0	2	1	0	.0548
H	1.1029228	1	136.631503	1	129.370490	1	3	2	1	.0714
H	1.1025246	1	121.493571	1	151.546738	1	1	2	3	.0703
C	1.4524822	1	104.506096	1	-6.996512	1	1	2	3	.8085
O	1.2524778	1	115.456037	1	-.196338	1	6	1	2	-.6090
O	1.3236431	1	113.164715	1	-179.508272	1	6	1	2	-.4484
C	1.3471404	1	131.225996	1	178.201432	1	8	6	1	.4323
H	1.1212322	1	106.768416	1	-179.510615	1	9	8	6	-.0562
H	1.1213032	1	115.074439	1	-61.419763	1	9	8	6	-.0761
H	1.1212893	1	115.016525	1	62.440555	1	9	8	6	-.0759

DESCRIPTION OF VIBRATIONS

VIBRATION 1	ATOM PAIR	ENERGY CONTRIBUTION	RADIAL
FREQ. -562.48	C 3 -- O 7	-115.4% (-60.9%)	99.8%
T-DIPOLE 2.4594	C 3 -- H 4	-110.9%	7.5%
TRAVEL .1079	N 2 -- C 6	-37.4%	88.4%
RED. MASS 5.1499	C 6 -- O 7	-34.9%	15.7%
	C 1 -- N 2	-31.7%	27.3%
	N 2 -- C 3	-22.4%	1.1%
	C 6 -- O 8	-21.8%	1.6%
	C 1 -- C 6	-21.2%	93.5%
	C 1 -- C 3	-12.2%	17.7%

The optimized structure of **TSb**





2-Dimethylamino-5-methoxyoxazole (OXc);

HEAT OF FORMATION	=	-55.104933 KCAL
ELECTRONIC ENERGY	=	-8838.225000 EV
CORE-CORE REPULSION	=	6922.784829 EV
DIPOLE	=	2.12008 DEBYE
NO. OF FILLED LEVELS	=	28
IONIZATION POTENTIAL	=	7.755335 EV
MOLECULAR WEIGHT	=	142.157
SCF CALCULATIONS	=	264
COMPUTATION TIME	=	1 HOURS 14 MINUTES AND 36.000 SECONDS

FINAL GEOMETRY OBTAINED

MINDO/3 PRECISE XYZ EF VECTORS BONDS T=36000

									CHARGE
C	.0000000	0	.000000	0	.000000	0	0	0	0	-.2085
N	1.4131526	1	.000000	0	.000000	0	1	0	0	-.1921
C	1.3042164	1	104.574918	1	.000000	0	2	1	0	.4310
N	1.3843732	1	129.093619	1	179.979084	1	3	2	1	-.1479
H	1.0993537	1	121.137242	1	-179.998434	1	1	2	3	.0604
C	1.3732381	1	108.123830	1	.000000	1	1	2	3	.5670
O	1.3579140	1	108.230769	1	.000000	1	6	1	2	-.4597

O	1.3206763	1	126.301035	1	-179.990379	1	6	1	2	-.4028
C	1.3434740	1	131.425032	1	-179.920589	1	8	6	1	.4321
H	1.1213030	1	106.153801	1	-179.993498	1	9	8	6	-.0521
H	1.1219786	1	115.422799	1	-62.102780	1	9	8	6	-.0793
H	1.1219869	1	115.416896	1	62.119097	1	9	8	6	-.0794
C	1.4234192	1	120.556728	1	-96.185886	1	4	3	2	.1972
C	1.4234066	1	120.561114	1	96.024361	1	4	3	2	.1972
H	1.1212556	1	112.430824	1	-140.330771	1	14	4	3	-.0450
H	1.1178844	1	113.800940	1	-21.233403	1	14	4	3	-.0333
H	1.1227356	1	115.429218	1	100.150429	1	14	4	3	-.0532
H	1.1212468	1	112.429638	1	140.424013	1	13	4	3	-.0450
H	1.1178895	1	113.797866	1	21.331980	1	13	4	3	-.0333
H	1.1227335	1	115.432190	1	-100.053612	1	13	4	3	-.0532

BOND ORDERS AND VALENCIES

	C 1	N 2	C 3	N 4	H 5	C 6	
C 1	3.796302						
N 2	1.064402	3.039313					
C 3	.043984	1.672321	3.720532				
N 4	.015103	.053059	.976986	3.199825			
H 5	.920222	.019112	.012223	.003801	.996353		
C 6	1.587528	.039835	.067132	.017833	.019571	3.698312	
O 7	.062068	.120882	.878071	.048077	.018222	.970869	
O 8	.070482	.013753	.020551	.007436	.001204	.952136	
C 9	.020004	.006734	.000885	.000169	.000401	.013980	
H 10	.003794	.001526	.000690	.000305	.000190	.021160	
H 11	.001626	.000185	.000255	.000032	.000001	.000944	
H 12	.001635	.000184	.000257	.000032	.000001	.000943	
C 13	.001944	.019405	.009154	.979208	.000491	.002140	
C 14	.001941	.019398	.009153	.979210	.000489	.002145	
H 15	.000360	.002590	.011019	.016543	.000038	.000905	
H 16	.000009	.000045	.000393	.010416	.000000	.000003	
H 17	.000415	.001623	.003023	.032331	.000174	.000140	
H 18	.000362	.002601	.011031	.016513	.000038	.000904	
H 19	.000009	.000046	.000391	.010427	.000000	.000003	
H 20	.000414	.001613	.003014	.032345	.000174	.000139	

	O 7	O 8	C 9	H 10	H 11	H 12	
O 7	2.163985						
O 8	.048493	2.136087					
C 9	.002989	.944643	3.763560				
H 10	.000528	.011056	.925588	.997284			
H 11	.000895	.032239	.924073	.016187	.993707		
H 12	.000892	.032237	.924062	.016189	.017245	.993702	
C 13	.003603	.000489	.000005	.000015	.000002	.000018	

C 14	.003622	.000492	.000005	.000015	.000018	.000002
H 15	.001892	.000388	.000005	.000017	.000005	.000000
H 16	.000020	.000005	.000000	.000000	.000000	.000000
H 17	.000476	.000046	.000006	.000002	.000001	.000000
H 18	.001887	.000386	.000005	.000017	.000000	.000005
H 19	.000021	.000005	.000000	.000000	.000000	.000000
H 20	.000478	.000046	.000006	.000002	.000000	.000001

	C 13	C 14	H 15	H 16	H 17	H 18
C 13	3.860374					
C 14	.008361	3.860375				
H 15	.000415	.939579	.997975			
H 16	.015159	.948864	.009359	.998890		
H 17	.000579	.930931	.014057	.011593	.997171	
H 18	.939610	.000414	.000430	.000000	.000369	.997977
H 19	.948850	.015156	.000000	.002731	.000290	.009354
H 20	.930926	.000582	.000371	.000290	.001115	.014051

	H 19	H 20
H 19	.998889	
H 20	.011605	.997173

1-Dimethylamino-3-methoxycarbonyl nitrile ylide (NYc);

HEAT OF FORMATION	=	-63.237795 KCAL
ELECTRONIC ENERGY	=	-8341.088191 EV
CORE-CORE REPULSION	=	6425.295354 EV
DIPOLE	=	3.24204 DEBYE
NO. OF FILLED LEVELS	=	28
IONIZATION POTENTIAL	=	8.438178 EV
MOLECULAR WEIGHT	=	142.157
SCF CALCULATIONS	=	508
COMPUTATION TIME	=	2 HOURS 15 MINUTES AND 45.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

MINDO/3 PRECISE XYZ EF VECTORS BONDS T=36000

C	.0000000	0	.000000	0	.000000	0	0	0	0	-.0892
N	1.2619519	1	.000000	0	.000000	0	1	0	0	.0721
C	1.2598461	1	168.438976	1	.000000	0	2	1	0	-.0394
N	1.3395546	1	124.242968	1	-172.148902	1	3	2	1	-.0252
H	1.1221687	1	119.741053	1	-89.834453	1	1	2	4	.0128
C	1.4908614	1	124.612315	1	-165.510969	1	1	2	5	.8373
O	1.2095921	1	124.971391	1	66.329393	1	6	1	2	-.5631
O	1.3327595	1	102.937745	1	-113.032679	1	6	1	2	-.4943
C	1.3481213	1	134.068699	1	-177.795620	1	8	6	1	.4320
H	1.1213150	1	114.763965	1	-61.838814	1	9	8	6	-.0778

H	1.1212554	1	107.616190	1	179.768168	1	9	8	6	-.0594
H	1.1213464	1	114.713352	1	61.396580	1	9	8	6	-.0781
C	1.4374158	1	129.016139	1	1.219848	1	4	3	2	.1258
C	1.4316185	1	115.229071	1	-178.145163	1	4	3	2	.1696
H	1.1184258	1	114.547626	1	174.760824	1	13	4	3	-.0326
H	1.1207424	1	113.980797	1	-65.259149	1	13	4	3	-.0406
H	1.1202396	1	113.796365	1	55.012681	1	13	4	3	-.0388
H	1.1206539	1	113.854018	1	119.842809	1	14	4	3	-.0422
H	1.1207565	1	113.763517	1	-120.210771	1	14	4	3	-.0432
H	1.1173795	1	113.969897	1	-.236651	1	14	4	3	-.0257

BOND ORDERS AND VALENCIES

	C 1	N 2	C 3	N 4	H 5	C 6	
C 1	3.843247						
N 2	1.741360	3.555814					
C 3	.132375	1.596263	3.130840				
N 4	.060942	.102015	1.225919	3.415723			
H 5	.892444	.020609	.030274	.007578	.999835		
C 6	.865867	.021951	.024939	.003664	.024582	3.555719	
O 7	.052570	.016704	.009107	.001384	.014584	1.670910	
O 8	.033335	.013520	.003500	.001582	.005405	.907489	
C 9	.025897	.006855	.001786	.001159	.001840	.012455	
H 10	.000451	.000326	.000096	.000042	.000005	.002592	
H 11	.003854	.001224	.000371	.000217	.000477	.016684	
H 12	.000429	.000245	.000063	.000043	.000249	.002772	
C 13	.018955	.007644	.040928	.947842	.000353	.000698	
C 14	.007690	.013355	.018483	.972830	.000346	.000479	
H 15	.002724	.000660	.014322	.008440	.000003	.000060	
H 16	.000957	.003412	.006526	.018102	.000428	.000060	
H 17	.000787	.002889	.005116	.016174	.000135	.000211	
H 18	.001155	.003420	.009955	.019264	.000076	.000290	
H 19	.001303	.003183	.010093	.019112	.000441	.000008	
H 20	.000153	.000178	.000723	.009410	.000006	.000009	

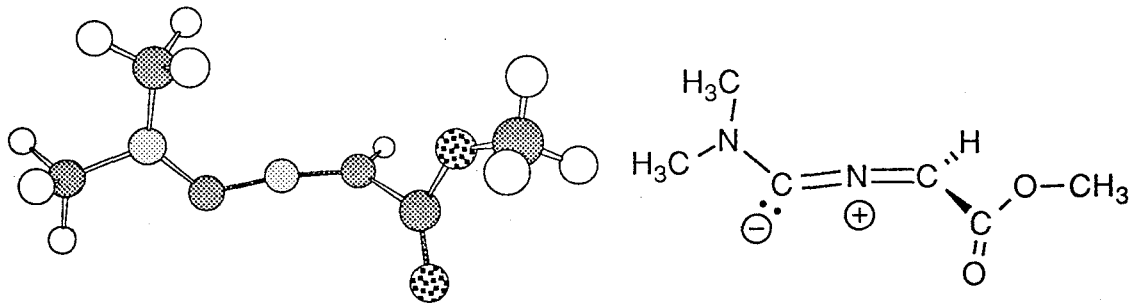
	O 7	O 8	C 9	H 10	H 11	H 12	
O 7	1.913445						
O 8	.130556	2.090937					
C 9	.009230	.925703	3.765568				
H 10	.001824	.029057	.927049	.993953			
H 11	.003484	.011422	.926038	.016361	.996467		
H 12	.001917	.028675	.927111	.016130	.016249	.993905	
C 13	.000848	.000128	.000050	.000000	.000006	.000012	
C 14	.000060	.000347	.000238	.000012	.000048	.000005	
H 15	.000101	.000025	.000017	.000000	.000003	.000002	
H 16	.000008	.000039	.000032	.000001	.000006	.000002	

H 17	.000104	.000017	.000006	.000001	.000002	.000000
H 18	.000028	.000124	.000094	.000005	.000020	.000002
H 19	.000019	.000014	.000007	.000000	.000001	.000000
H 20	.000009	.000001	.000000	.000000	.000000	.000000

	C 13	C 14	H 15	H 16	H 17	H 18
C 13	3.872410					
C 14	.006366	3.868524				
H 15	.952252	.002021	.998935			
H 16	.940081	.005436	.009245	.998350		
H 17	.942335	.007658	.008711	.012292	.998493	
H 18	.000222	.940141	.000051	.000176	.000278	.998218
H 19	.000290	.940153	.000155	.000318	.000099	.013153
H 20	.013401	.952856	.000142	.001230	.001678	.009763

	H 19	H 20
H 19	.998131	
H 20	.009782	.999340

The optimized structure of **NYc**



Transition state from OXc to NYc (TSc):

HEAT OF FORMATION	=	-31.998119 KCAL
ELECTRONIC ENERGY	=	-8739.864502 EV
CORE-CORE REPULSION	=	6825.426318 EV
DIPOLE	=	.95713 DEBYE
NO. OF FILLED LEVELS	=	28
IONIZATION POTENTIAL	=	7.681580 EV
MOLECULAR WEIGHT	=	142.157
SCF CALCULATIONS	=	416
COMPUTATION TIME	=	1 HOURS 40 MINUTES AND 56.000 SECONDS

FINAL GEOMETRY OBTAINED CHARGE

MINDO/3 PRECISE XYZ TS HESS=1 RECALC=30 T=36000

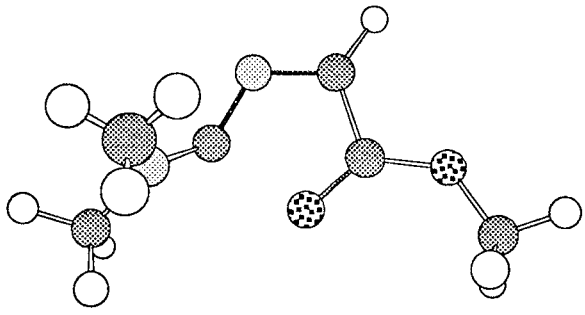
C	.0000000 0	.000000 0	.000000 0	0	0	0	-.1859
N	1.3074272 1	.000000 0	.000000 0	1	0	0	-.0119
C	1.3077417 1	120.191268 1	.000000 0	2	1	0	.1120

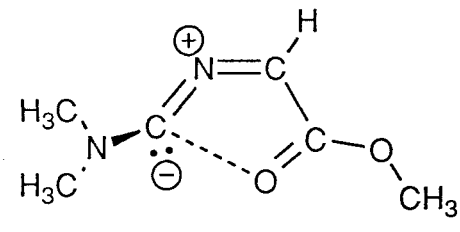
N	1.3313427 1	128.241214 1	131.038217 1	3	2	1	-.0077
H	1.1064091 1	122.872523 1	155.682882 1	1	2	3	.0452
C	1.4652047 1	108.271705 1	-10.564943 1	1	2	3	.7874
O	1.2485732 1	112.844983 1	2.556785 1	6	1	2	-.5831
O	1.3201835 1	114.831968 1	-179.923531 1	6	1	2	-.4573
C	1.3473766 1	132.696405 1	-177.560836 1	8	6	1	.4307
H	1.1212691 1	107.097939 1	-178.881502 1	9	8	6	-.0564
H	1.1212608 1	114.817832 1	62.923573 1	9	8	6	-.0760
C	1.4341741 1	117.205216 1	155.307020 1	4	3	2	.1656
C	1.4402062 1	128.652155 1	-28.459699 1	4	3	2	.1291
H	1.1213421 1	112.925376 1	-125.271663 1	13	4	3	-.0470
H	1.1170724 1	114.064078 1	-6.136352 1	13	4	3	-.0234
H	1.1198659 1	114.613324 1	115.086460 1	13	4	3	-.0340
H	1.1218290 1	113.175282 1	117.215224 1	14	4	3	-.0476
H	1.1204029 1	114.623705 1	-123.261750 1	14	4	3	-.0378
H	1.1167975 1	114.449584 1	-2.417047 1	14	4	3	-.0254

DESCRIPTION OF VIBRATIONS

VIBRATION 1	ATOM PAIR	ENERGY CONTRIBUTION		RADIAL
FREQ. -441.08	C 3 -- O 7	194.7%	(-80.0%)	99.7%
T-DIPOLE 2.7807	C 6 -- O 7	63.6%		9.6%
TRAVEL .1099	C 6 -- O 8	43.8%		2.4%
RED. MASS 6.3226	C 1 -- C 6	39.6%		53.2%
	N 2 -- C 6	39.2%		41.2%
	C 3 -- N 4	32.2%		2.3%
	C 1 -- N 2	26.8%		95.8%
	O 8 -- C 9	24.3%		.2%
	N 4 -- C13	19.6%		2.4%
	N 4 -- C14	17.6%		.0%

The optimized structure of **TSc**





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1) a) J. W. Cornforth, *The Chemistry of Penicillin*, Princeton University Press, Princeton, New Jersey, 700 (1949); b) M. J. S. Dewar, P. A. Spanninger, and I. J. Turchi, *J. Chem. Soc., Chem. Commun.*, 925 (1973); c) M. J. S. Dewer and I. J. Turchi, *J. Am. Chem. Soc.*, **96**, 6148 (1974); d) M. J. S. Dewer and I. J. Turchi, *J. Org. Chem.*, **40**, 1521 (1975); e) M. J. S. Dewer and I. J. Turchi, *J. Chem. Soc., Perkin Trans. 2*, 724 (1977).

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4) a) T. Ibata, Y. Isogami, S. Nakano, H. Nakawa, and H. Tamura, *J. Chem. Soc., Chem. Commun.*, 1692 (1986); b) T. Ibata, Y. Isogami, and H. Tamura, *Chem. Lett.*, 1551 (1988); c) H. Suga and T. Ibata, *Chem. Lett.*, 1221 (1991); d) T. Ibata, Y. Isogami, H. Nakawa, H. Tamura, H. Suga, X. Shi, and H. Fujieda, *Bull. Chem. Soc. Jpn.*, **65**, 1771 (1992); e) T. Ibata, H. Suga, Y. Isogami, H. Tamura, and X. Shi, *Bull. Chem. Soc. Jpn.*, **65**, 2998 (1992); f) H. Suga, X. Shi, H. Fujieda, and T. Ibata, *Tetrahedron Lett.*, **32**, 6911 (1991); g) H. Suga, X. Shi, and T. Ibata, *J. Org. Chem.*, **58**, 7397 (1993); h) H. Suga, X. Shi, and T. Ibata, *Chem. Lett.*, 1673 (1994); i) H. Suga, H. Fujieda, Y. Hirotsu, and T. Ibata, *J. Org. Chem.*, **59**, 3359 (1994).

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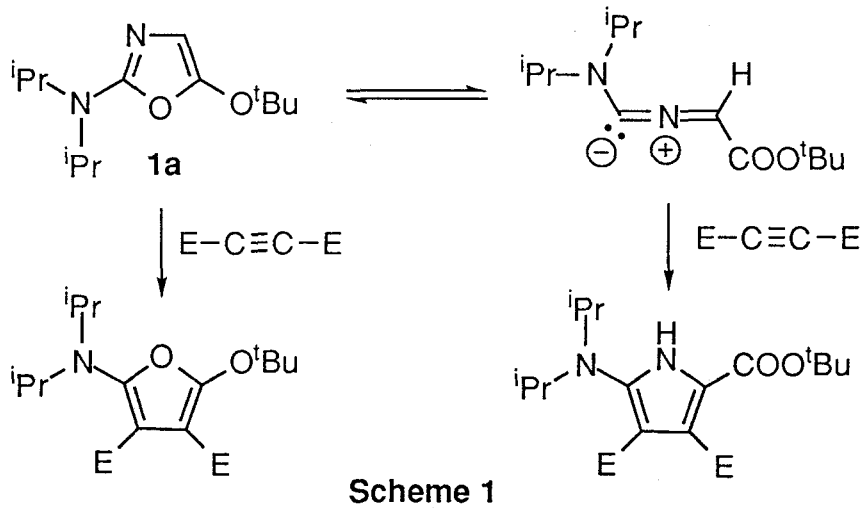
Chapter 5. Reaction of 2-Amino-5-alkoxyoxazoles II: Reaction with Ethylenic Dipolarophiles and Aldehydes

5-1 Introduction

As described in chapter 4, 2-amino-5-alkoxyoxazole **1** has a very high reactivity toward DMAD or alcohol. Especially, in the reaction with DMAD, **1** afforded both furan derivative through Diels-Alder reaction followed by the elimination of nitrile and pyrrole derivative through 1,3-dipolar cycloaddition of nitrile ylide intermediate generated by the ring opening of **1** with DMAD, respectively (Scheme 1).



Scheme 1

In thermally allowed [4π+2π] cycloaddition such as Diels-Alder reaction and 1,3-dipolar cycloaddition, electron-deficient ethylenic compunds such as fumarates, maleates, and maleimides are effective as 2π unit to give cyclic compounds as well as acetylenic compounds such as DMAD. Carbonyl compounds are also known to react as dienophile or dipolarophile to give heterocycles containing oxygen.

In this chapter, in order to know the scope and limitation of the reaction of 2-amino-5-alkoxyoxazole **1**, the reactions of **1** with several ethylenic dipolarophiles and *p*-substituted benzaldehydes were carried out. The determination of the structure of the adducts and mechanism of the reaction are also described. In addition, the application of the reaction of **1** with ethylenic dipolarophile to the diastereoselective 1,3-dipolar cycloaddition is described.

5-2 Reaction of 2-Amino-5-alkoxyoxazole with Dimethyl Fumarate, Dimethyl Maleate, and Methyl Acrylate

The reactions of 2-diisopropylamino-5-*tert*-butoxyoxazole (**1a**) with 5 equivalents of ethylenic dipolarophiles such as dimethyl fumarate (**2a**), dimethyl maleate (**2b**), and methyl acrylate (**2c**) were carried out in benzene at 80 °C for 20 h. The reaction of **1a** with **2a** gave 1-pyrroline derivatives **3** and **4**, in 47 and 21 % yields, respectively. On the other hand, the reaction of **1a** with **2b** gave **3** and **5** in 2:1 ratio in total yield of 32 %.

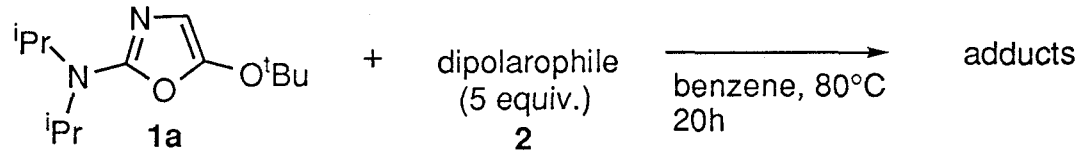
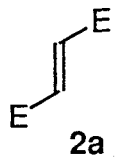
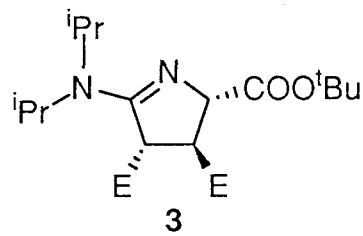
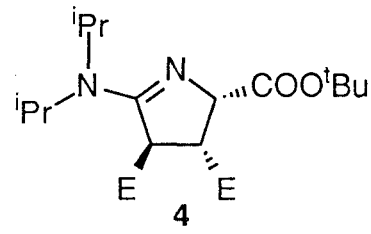
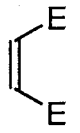
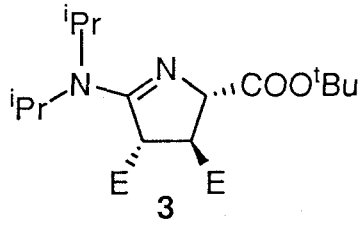
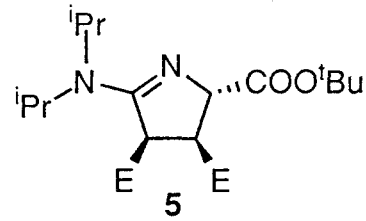
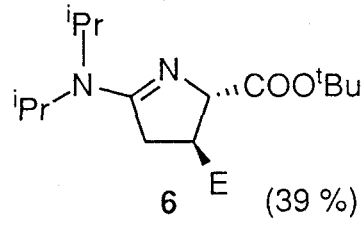


Table 1. Reaction of **1** with Ethylenic Dipolarophiles

Dipolarophile	Adducts (Yield / %)	Total Yield / %
 **2a**	 **3** (47 %)  **4** (21 %)	68
 **2b**	 **3**  **5** (**3** : **5** = 2 : 1)	32
 **2c**	 **6** (39 %)	39

E = $COOCH_3$

The structures of these products were determined on the basis of ^1H NMR, ^{13}C NMR, and IR spectroscopic data. These spectroscopic data shows that the products are the 1:1-adduct of **1a** and **2**. These products show the presence of an imino group at 1596-1601 cm^{-1} in their IR spectra. The stereochemistry of **3**, **4**, and **5** is elucidated on the basis of the coupling

constants in their ^{1}H NMR spectroscopic data. It is known that the coupling constant between H-4 and H-5 of 1-pyrroline derivatives is classified into two groups.[1] The coupling constant of about 9 Hz is assigned to that of *cis*-protons, while the smaller one than 6.5 Hz is assigned to that of *trans*-protons.

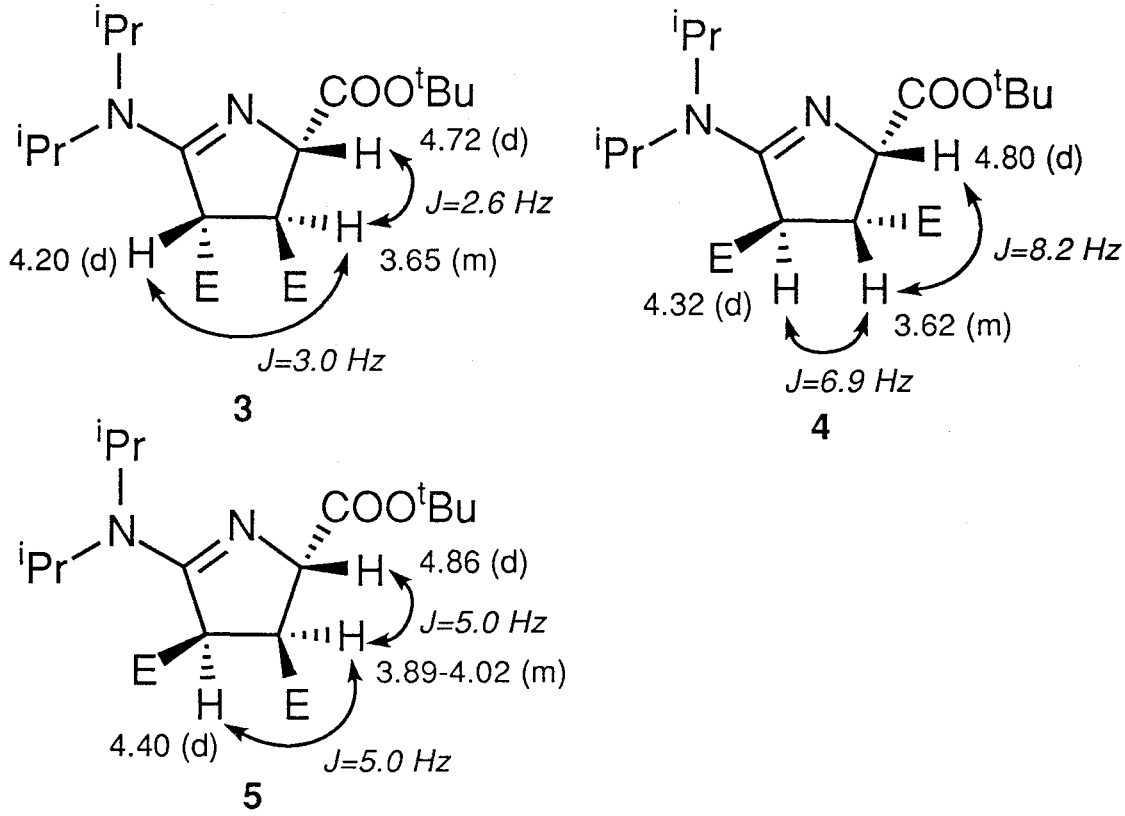
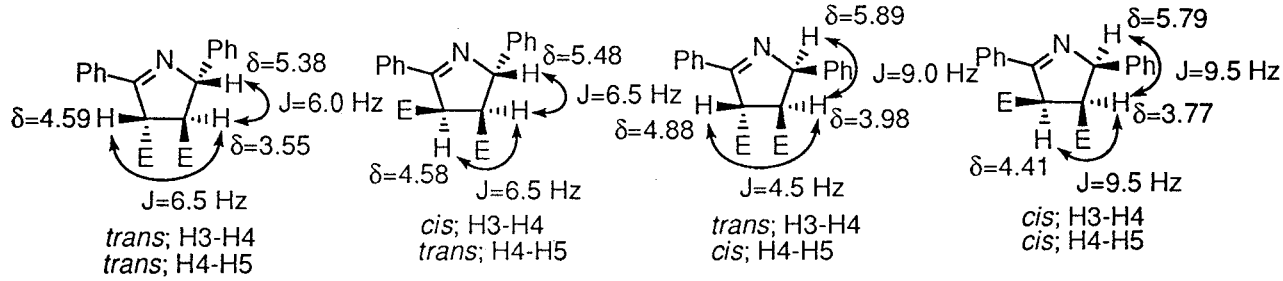


Figure 1. ^{1}H NMR spectroscopic data of **3**, **4**, and **5**

Based on the coupling constants, **3** (J=2.6 Hz) and **5** (J=5.0 Hz) were determined to have *trans*-configuration at 4- and 5-positions, and **4** (J=8.2 Hz) has *cis*-configuration. In addition, the fact that **3** is obtained in both reactions with **2a** and **2b** indicates that **3** is thermodynamically more stable than **5** (Figure 1).

---

[1]For example, A. Padwa et al. reported the formation and structure determination of the following compounds.



A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **95**, 1945 (1973)

The reaction of **1a** with dimethyl fumarate (**2a**) proceeded in a stereospecific manner to give **3** and **4** which have *trans* configuration at 3- and 4-positions. On the other hand, the reaction of **1a** with dimethyl maleate (**2b**) also gave **3** as a major product, which indicates that the reaction proceeded in a non-stereospecific manner. Such a loss of the stereochemistry is often observed in the reaction with dimethyl maleate (**2b**), and is explained by a rapid epimerization of the initial adduct which has *cis* configuration at 3- and 4-positions.[1)]

The reaction of **1a** with methyl acrylate (**2c**) also gave a 1:1-adduct **6**. The structure of **6** was elucidated by ^{1}H NMR spectroscopy (Figure 2).

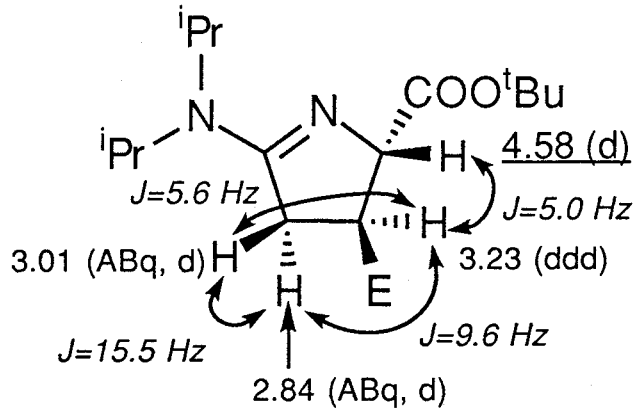


Figure 2. ^{1}H NMR spectroscopic data of **6**

A methoxycarbonyl group is determined to be attached at 4-position, because the doublet proton at 5-position (4.58 ppm) clearly indicates the presence of one proton at 4-position and excludes the isomer having opposite regiochemistry which has two protons at C-4. The small coupling constant between H-4 and H-5 indicates that two ester groups at 4- and 5-positions have *trans*-configuration.[2]

Total yield of the reaction was moderate in the case of dimethyl fumarate (**2a**). The decrease of the yield in the case of dimethyl maleate (**2b**) or methyl acrylate (**2c**) is well accordance with the HOMO (dipole) - LUMO (dipolarophile) controlled cycloaddition.

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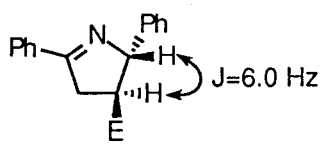
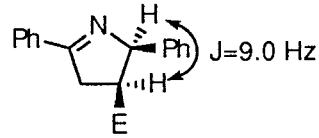
[2]R. Huisgen et al. reported the coupling constants of the following compounds.



trans; H4-H5



cis; H4-H5

R. Huisgen et al., *Chem. Ber.*, **105**, 1258 (1972)

5-3 Reaction of 2-Diisopropylamino-5-*tert*-butoxyoxazole with *N*-Substituted Maleimides

The reactions of **1a** with 5 equivalents of *N*-substituted maleimides (**7**) were carried out under similar conditions to give *trans*-1:1-adduct (**8**), *cis*-1:1-adduct (**9**), and 2:1-adducts (**10**), respectively.

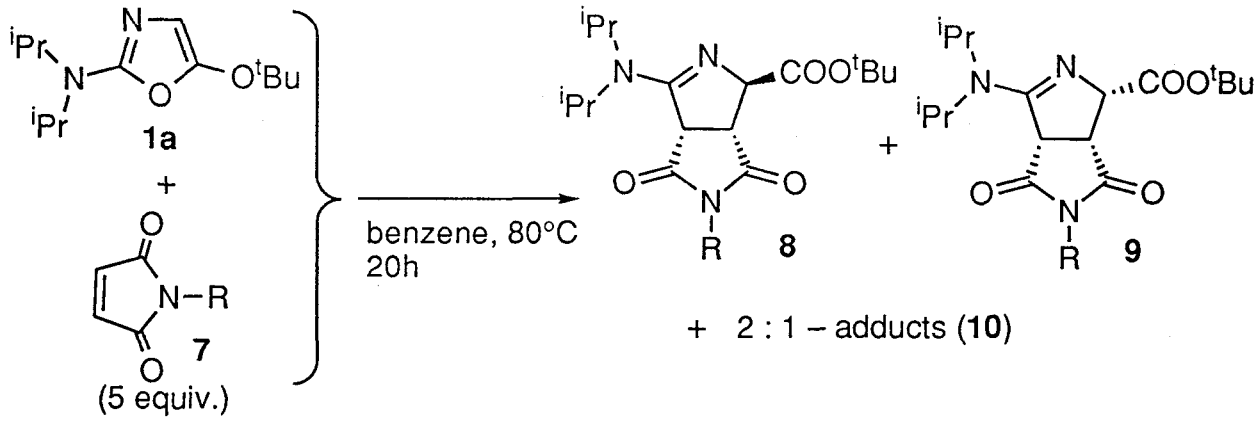


Table 2. Reaction of **1a** with *N*-Substituted Maleimides

Run	R	Yield / %			Total Yield / %
		8	**9**	**10**	
a	Me	80	8	2	90
b	Et	81	0	4	85
c	Ph	60	0	12	72

The initial reactions to give 1:1-adduct proceeded in high yields with high *exo* selectivity to give *trans*-adducts **8** together with minor *cis*-adduct in the case of *N*-methylmaleimide. The stereochemistry of the adducts **8** and **9** was determined by ^{1}H NMR spectroscopy.

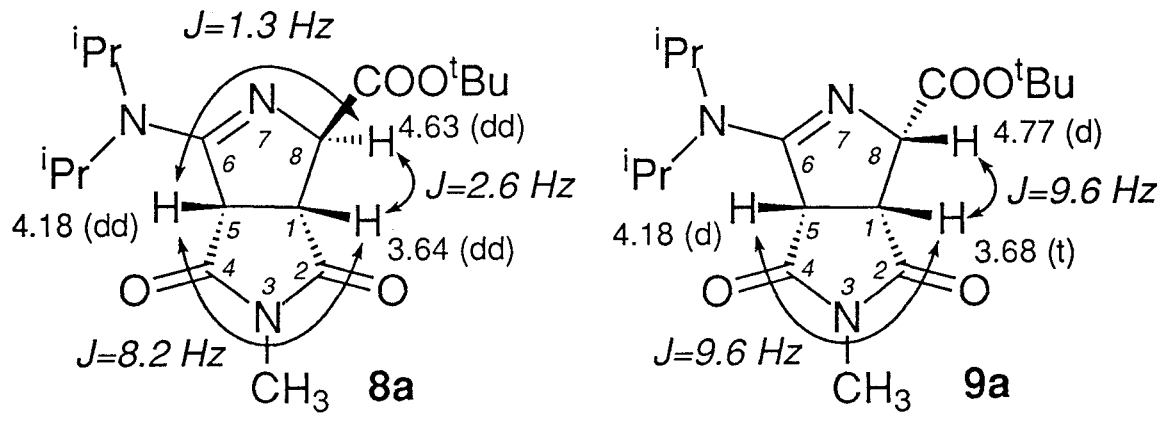


Figure 3. ^{1}H NMR of **8a** and **9a**

^{1}H NMR data of **8a** and **9a** are shown in Figure 3. **8a** is assigned to have *trans* configuration at C-1 and C-8 because of its small coupling constant (2.6 Hz). **9a** is assigned to the *cis* configuration at C1-C8 due to the large coupling constant (9.6 Hz).[3]

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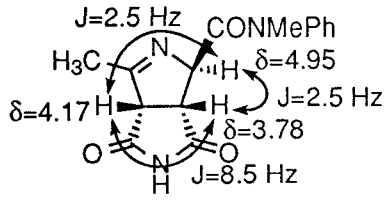
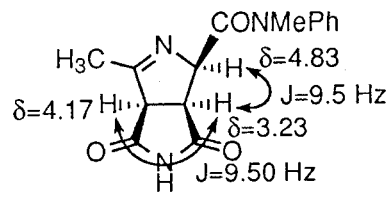
[3]G. Y. Kondrat'eva et al reported the structure of following compounds.



trans; H4-H5



trans; H4-H5

G. Y. Kondrat'eva, M. A. Aitzhanova, V. S. Bogdanov, and O. S. Chizov, *Izv. Akad. Nauk SSSR, Ser.Khim.*, 1313 (1979)

There also obtained four 2:1-adducts **10t-1**, **10t-2**, **10c-1**, and **10c-2** (Figure 4).

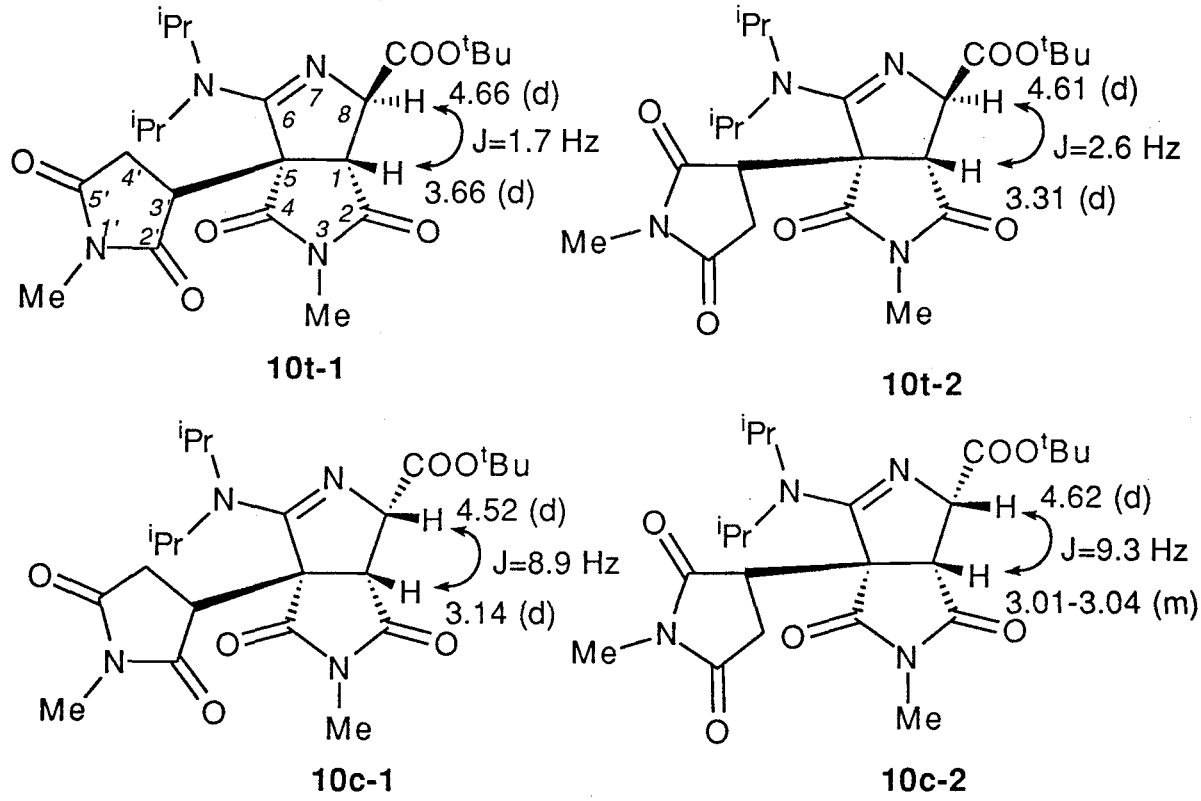
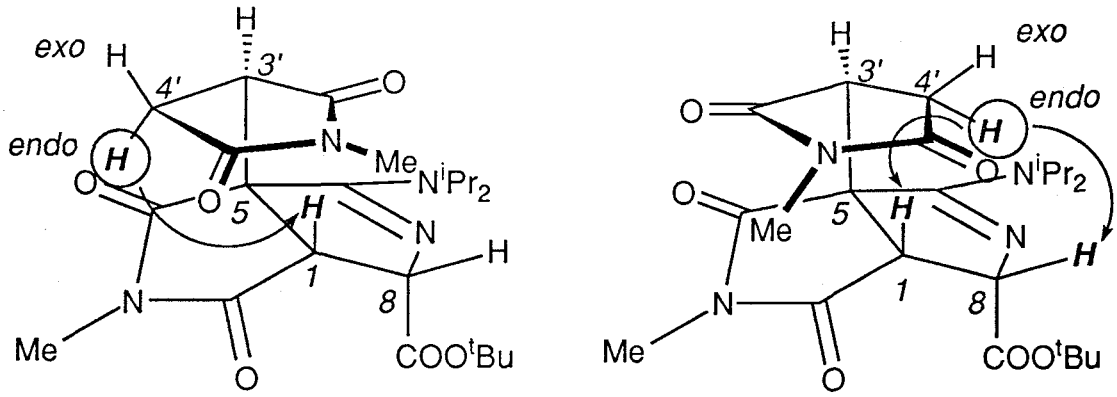


Figure 4. 2:1-Adducts of *N*-methylmaleimide with Nitrile Ylide and their ^{1}H NMR (δ)

10t-1 and **10t-2** are the adducts of **8a** with another molecule of *N*-methylmaleimide, and assigned to have *trans*-configuration at C1-C8, because they have small coupling constants (1.7 and 2.6 Hz) between H-1 and H-8. **10c-1** and **10c-2** are the adducts of **9a** with *N*-methylmaleimide, and assigned to have *cis*-configuration at C1-C8, because they also have large coupling constants (8.9 and 9.3 Hz) between H-1 and H-8.

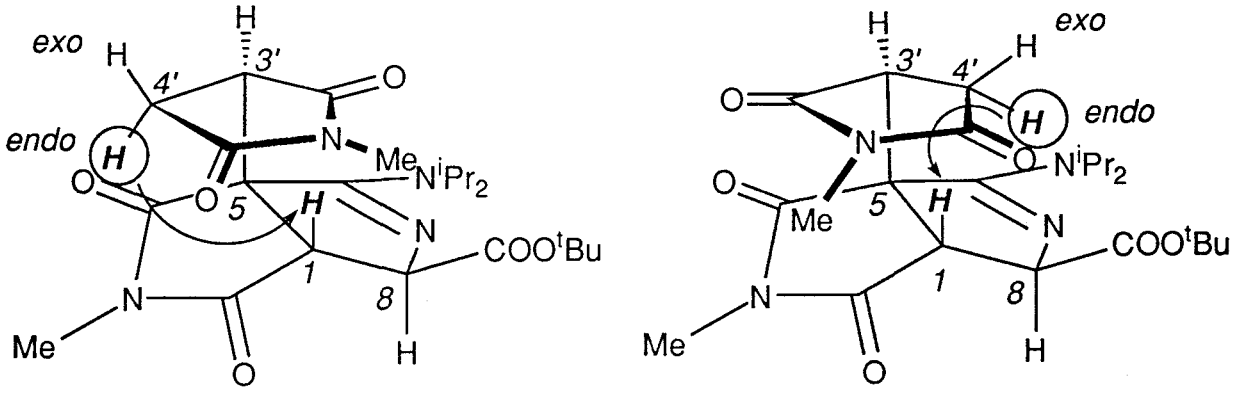
In these four 2:1-adducts, the structures of **10c-1** and **10c-2** are elucidated by differential NOE experiment (Figure 5). In **10c-1**, the irradiation on the *endo* proton at 4'-position caused an enhancement of only H-1, while in **10c-2**, the irradiation on the *endo* proton at 4'-position caused the enhancement of both H-1, and H-8. In **10c-1** and **10c-2**, the rotation around the single bond between C5-C3' is restricted because of the steric hindrance by large isopropyl groups, and the conformations of **10c-1** and **10c-2** are fixed as illustrated in Figure 5.



10c-1 **10c-2**

Figure 5. Differential NOE of **10c-1** and **10c-2**

On the other hand, the structures of **10t-1** and **10t-2** were not determined by differential NOE experiment only, because the irradiation on the *endo* proton at 4'-position caused the enhancement of only H-1 in both **10t-1** and **10t-2** (Figure 6).



10t-1 **10t-2**

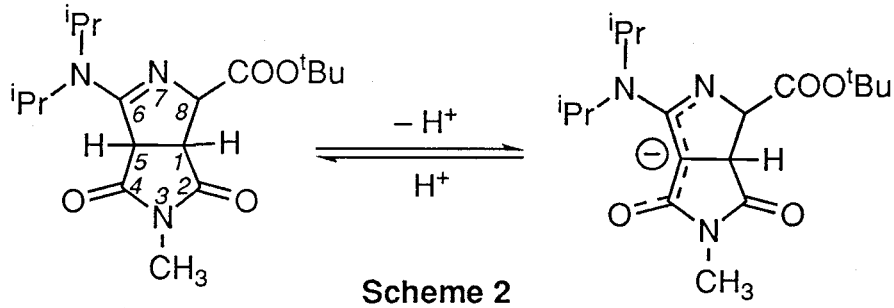
Figure 6. Differential NOE of **10t-1** and **10t-2**

However, the comparison of the chemical shift of *endo* proton at 4'-position gave another information (Table 3). In four protons listed in Table 3, the proton of **10t-2** was observed at lower field by 0.6-0.7 ppm than others. This low field shift can be explained by the steric compression effect between *endo* proton at 4'-position and *tert*-butoxycarbonyl group. Therefore, the structure of **10t-1** and **10t-2** are tentatively assigned as illustrated in Figure 6, in which the *endo* proton of **10t-2** lies very close to *tert*-butoxycarbonyl group at 8-position.

Table 3. Chemical Shift of *endo* 4'-proton

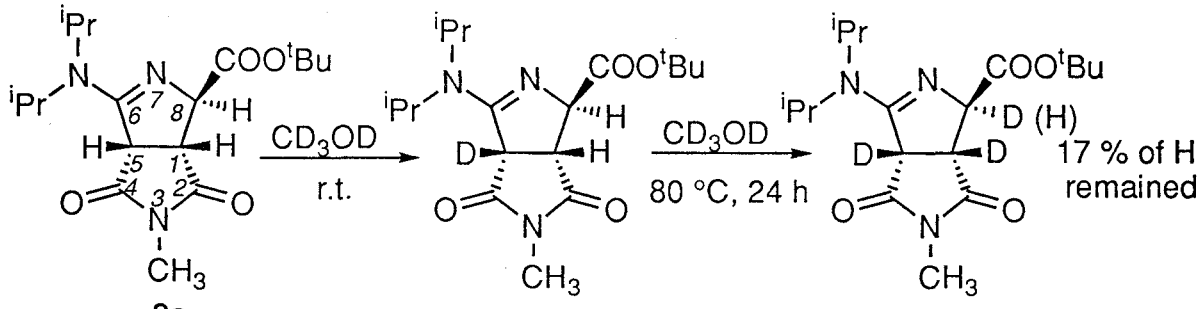
Compound	δ
10t-1	2.13
10t-2	2.85
10c-1	2.10
10c-2	2.28

The formation of these four 2:1-adducts is explained by the generation of enolate anion of **8a** or **9a** caused by the deprotonation at 5-position (Scheme 2), followed by the nucleophilic attack of the enolate to another molecule of maleimides.



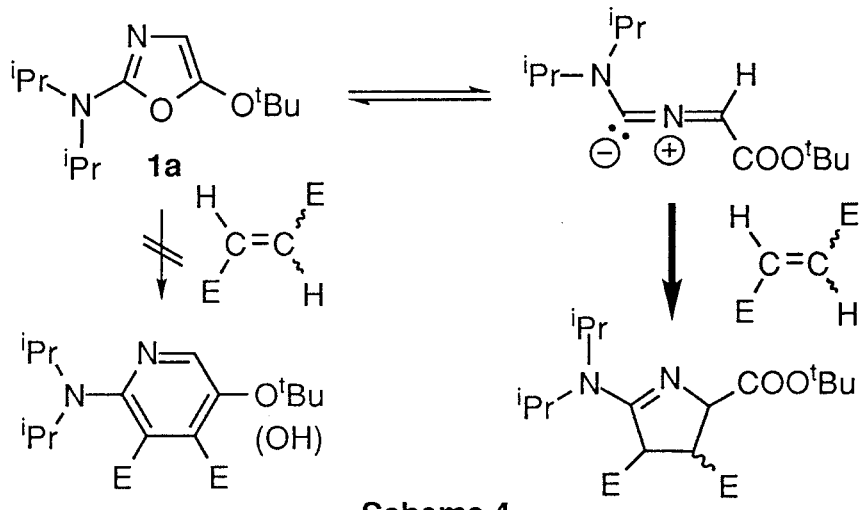
8a, 9a **Scheme 2**

The acidity of the 5-position is the strongest in the molecule, because it corresponds to a α-position of both imino-moiety and carbonyl group. This is exemplified by the treatment of **8a** with methanol-d_4 (Scheme 3). When the *trans*-adduct **8a** was dissolved in methanol-d_4, the signal of the H-5 in its ^{1}H NMR spectrum disappeared completely within 30 minutes. After heating at 80 °C for 24 h in a sealed tube, the proton at 1-position was also exchanged by D completely, while 17 % of H still remained at 8-position. Therefore, the acidity of 5-position is determined to be the strongest, and that of 8-position is the weakest of the three methine protons in **8a**.



8a **Scheme 3**

As mentioned in chapter 4, the reaction of **1a** with DMAD gave furan derivative through the Diels-Alder reaction followed by elimination of HCN, and pyrrole derivative through 1,3-dipolar cycloaddition of nitrile ylide intermediate with DMAD followed by the migration of hydrogen, in 15 and 30 % yields, respectively. However, the reactions of **1a** with ethylenic dipolarophiles gave only pyrroline derivatives, which is produced through 1,3-dipolar cycloaddition of nitrile ylide intermediate with dipolarophiles, and no pyridine derivative expected by the Diels-Alder reaction of oxazolefollowed by aromatization was obtained (Scheme 4).



Scheme 4

In order to know the reactivity of **1a** with ethylenic dipolarophiles, the reaction of **1a** with *N*-methylmaleimide were carried out in various conditions such as high pressure and various solvents (Table 4).

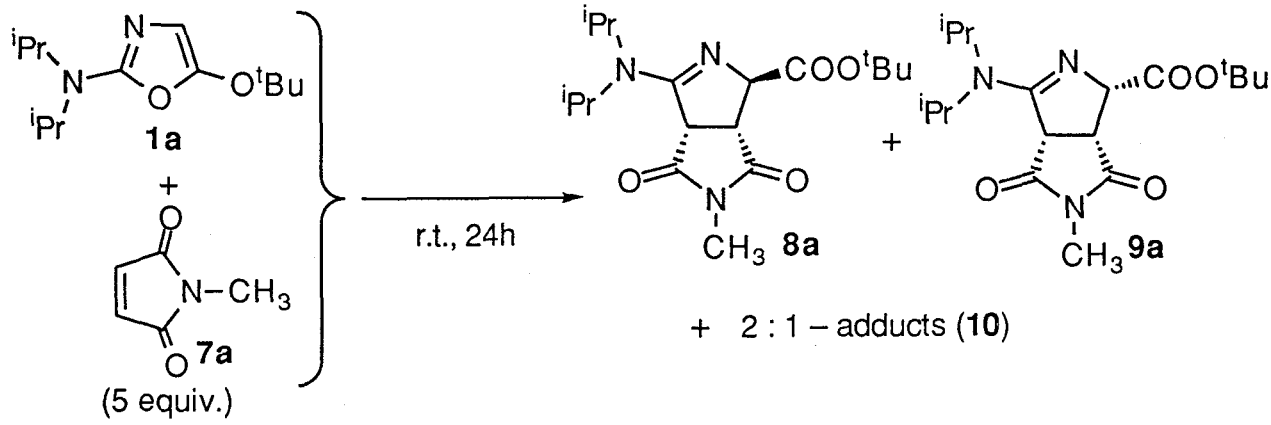


Table 4. Reaction of **1a** with *N*-Methylmaleimide (**7a**) under Various Conditions

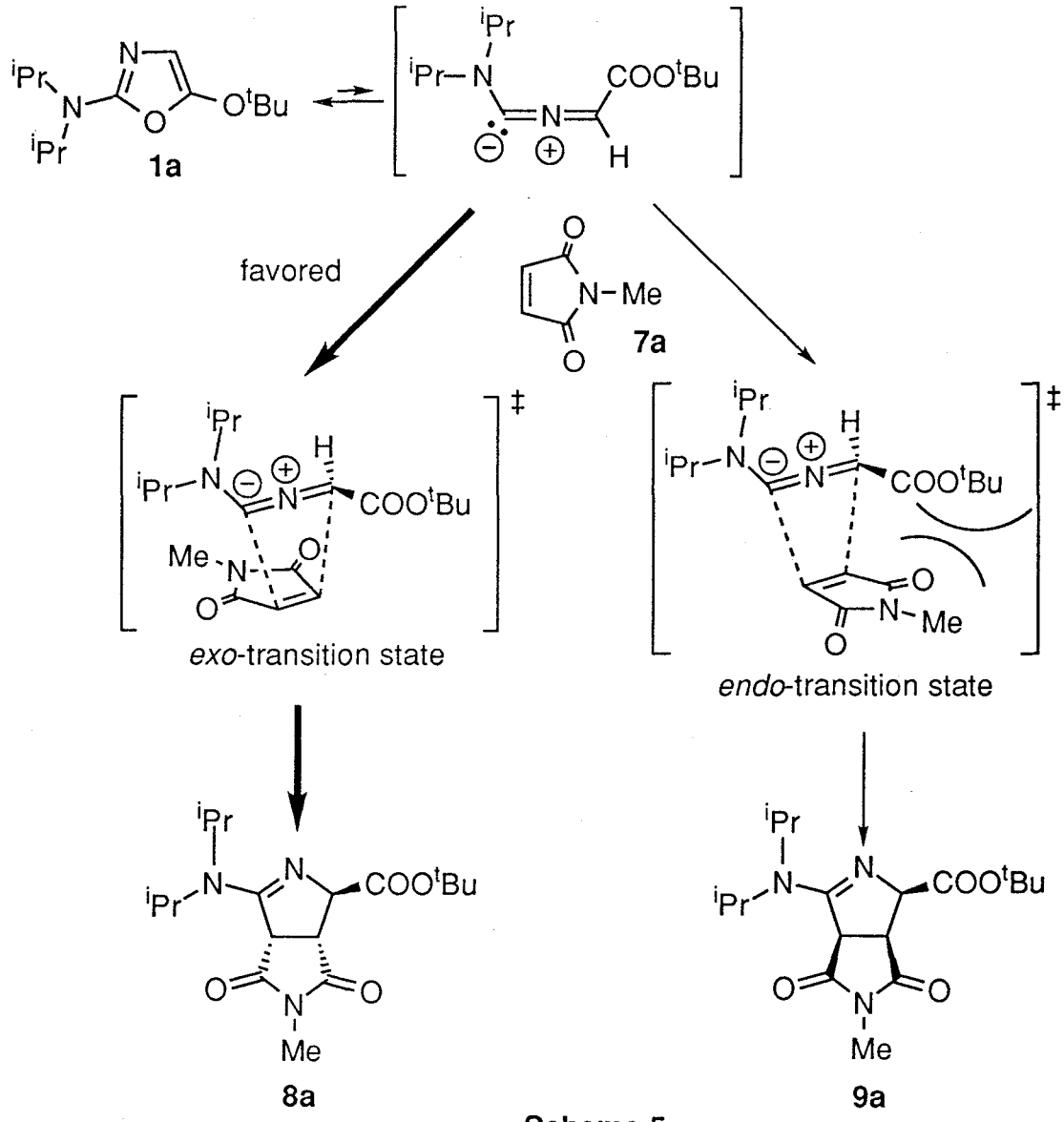
Run	Pressure / bar	Solvent	Yield / %						Total Yield / %
			8a	**9a**	**10t-1**	**10t-2**	**10c-1**	**10c-2**	
1	6000	THF	50	0	6	1	trace	1	58
2	3000	THF	50	0	5	1	1	1	58
3	1000	THF	60	0	2	1	0.3	1	64
4	1000	CH_3CN	68	8	1	0.4	1	1	79
5	1000	CH_2Cl_2	60	0	4	1	2	3	70
6	1000	toluene	79	7	1	0.4	trace	2	89
7	1	benzene	81	11	0.4	0	0.4	0.6	93

Recovered **7a**: Run 1, 0 %; Run 2, 0.7 %; Run 3, 14 %; Run 4, 0 %; Run 5, 30 %; Run 6, 48 %; Run 7, 46 %.

The reactions did not give any pyridine derivative even under high pressure despite the expectation of the acceleration of the Diels-Alder reaction under high pressure.[2] In the reactions under 3000 and 6000 bar in THF, the total yield was lowered, because the polymerization of excess of maleimide retarded the reaction (Runs 1 and 2). In the reaction in THF under 1000 bar, the total yield of *cis*-adducts (**9a** + **10c-1** + **10c-2**) is only 1.3 %, which may be attributed to the epimerization from *cis*-adducts to *trans*-adducts (Run 3). In the reaction in CH_2Cl_2 under 1000 bar, the total yield of *cis*-adducts (**9a** + **10c-1** + **10c-2**) is 5 %, which is rather higher than

the reactions in THF. This implies that the epimerization at C-8 decreased as the polarity of solvent decreased (Run 5). In these reactions, however, *cis*-1:1-adduct **9a** was not obtained at all. This is explained by the fast formation of enolate anion by the elimination of a proton at C-5 in these reaction conditions to produce 2:1 adducts (Runs 1-3, and 5). The reaction in acetonitrile under 1000 bar proceeded in high yield containing 8 % of **9a** (Run 4). This may be attributed to the solidification of the solvent and excess of maleimide under these conditions, which retarded any motion or approach of the molecules. Thus the formation of **8a** and **9a** occured quickly before solidification completed, and the side reactions such as the formation of 2:1-adducts and epimerization from *cis*-adduct to *trans*-adduct were suppressed. In the reactions in toluene under 1000 bar and in benzene at atmospheric pressure, the total yields were very high, and 1:1-adducts (**8a** and **9a**) were obtained as the major product with small amount of 2:1-adducts (Runs 6 and 7). This suggests that the reactions in non-polar solvent suppressed both the formation of 2:1-adducts through enolization at C-5 and epimerization from *cis*-adduct to *trans*-adduct through enolization at C-8.

The reaction of **1a** with ethylenic dipolarophiles can be explained by the 1,3-dipolar cycloaddition of the nitrile ylide intermediate generated by the ring opening of **1a** with dipolarophiles (Scheme 5).



Scheme 5

The steric hindrance between bulky *tert*-butoxycarbonyl group and dipolarophile is disadvantageous in the *endo*-transition state. Therefore, the reactions proceeded through the sterically less hindered *exo*-transition state, to give *trans*-adducts as the major products.

5-4 Reaction of 2-Diisopropylamino-5-*tert*-butoxyoxazole with Aromatic Aldehydes

The reactions of **1a** with 5 equivalents of *p*-substituted benzaldehydes (**11**) were carried out in benzene at 80 °C. The reaction gave *trans*-3-oxazoline (**12**), *cis*-3-oxazoline (**13**), and *trans*-2-oxazoline (**14**) in the yields as shown in Table 5.

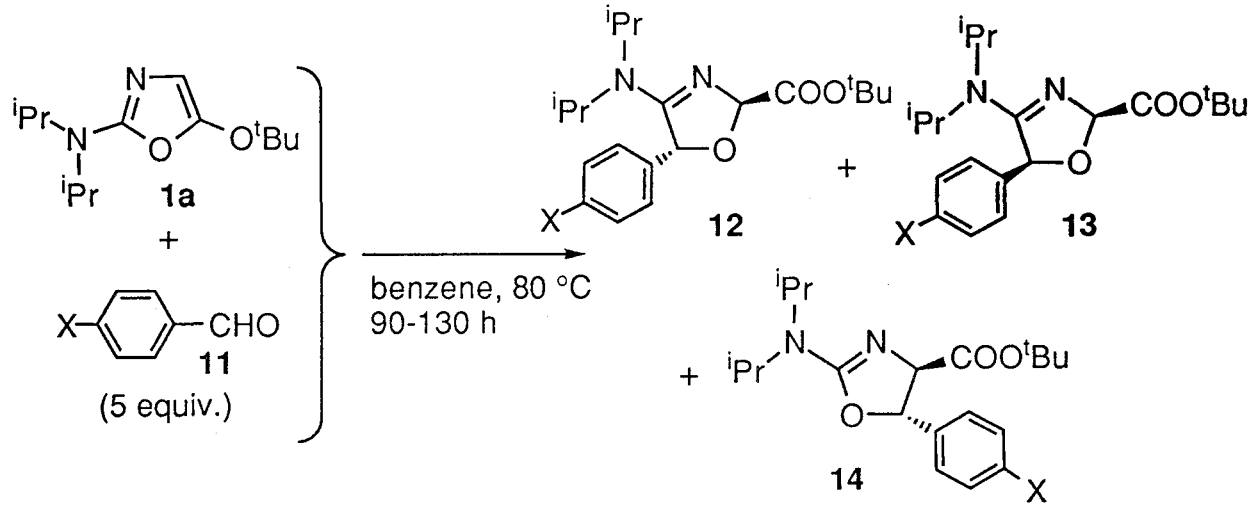


Table 5. Reaction of **1a** with *p*-Substituted Benzaldehyde

Run	X	Yield / %*			Total Yield / %
		12	**13**	**14**	
a	NO_2	63	6	11	80
b	Cl	33	2	5	40
c	H	15	1	0	16
d	CH_3	5	0	0	5

* The yields of **12** and **13** were determined by ^1H NMR.

The structures of the *trans*-3-oxazoline **12** and 2-oxazoline **14** were elucidated by the spectroscopic properties. The ^1H NMR and ^{13}C NMR spectroscopic data of **12a** and **14a** are shown in Figure 7. The 3-oxazoline structure of **12a** is supported by the signal of C-2 at 100.82 ppm in ^{13}C NMR. The *trans* configuration of **12a** is determined by the differential NOE technique (Figure 8). Irradiation on the 2'-proton of *p*-nitrophenyl group enhanced the intensity of H-2 and H-5, which is well accrodance with the *trans* structure. The large long range coupling constant (J=3.3 Hz) between H-2 and H-5 also supported the *trans* configuration of **12a**. In the case of **14a**, 2-oxazoline structure is supported by the signal of C-4 at 74.92 ppm in

^{13}C NMR, and *trans* configuration was supported by its small coupling constant (J=6.3 Hz) between H-4 and H-5.[4]

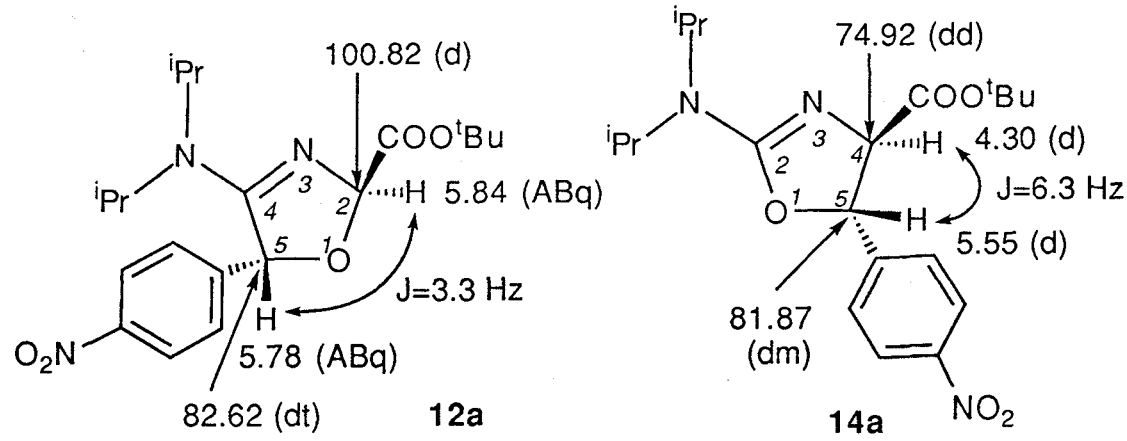


Figure 7. ^{1}H NMR and ^{13}C NMR of **12a** and **14a** (δ)

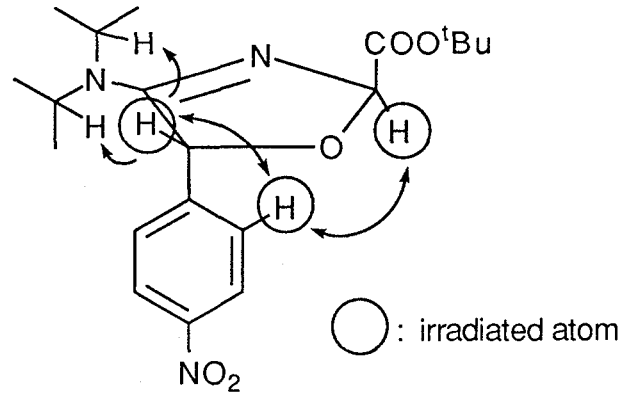


Figure 8. NOE Correlation in **12a**

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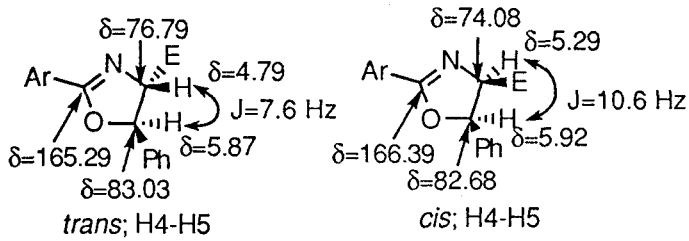
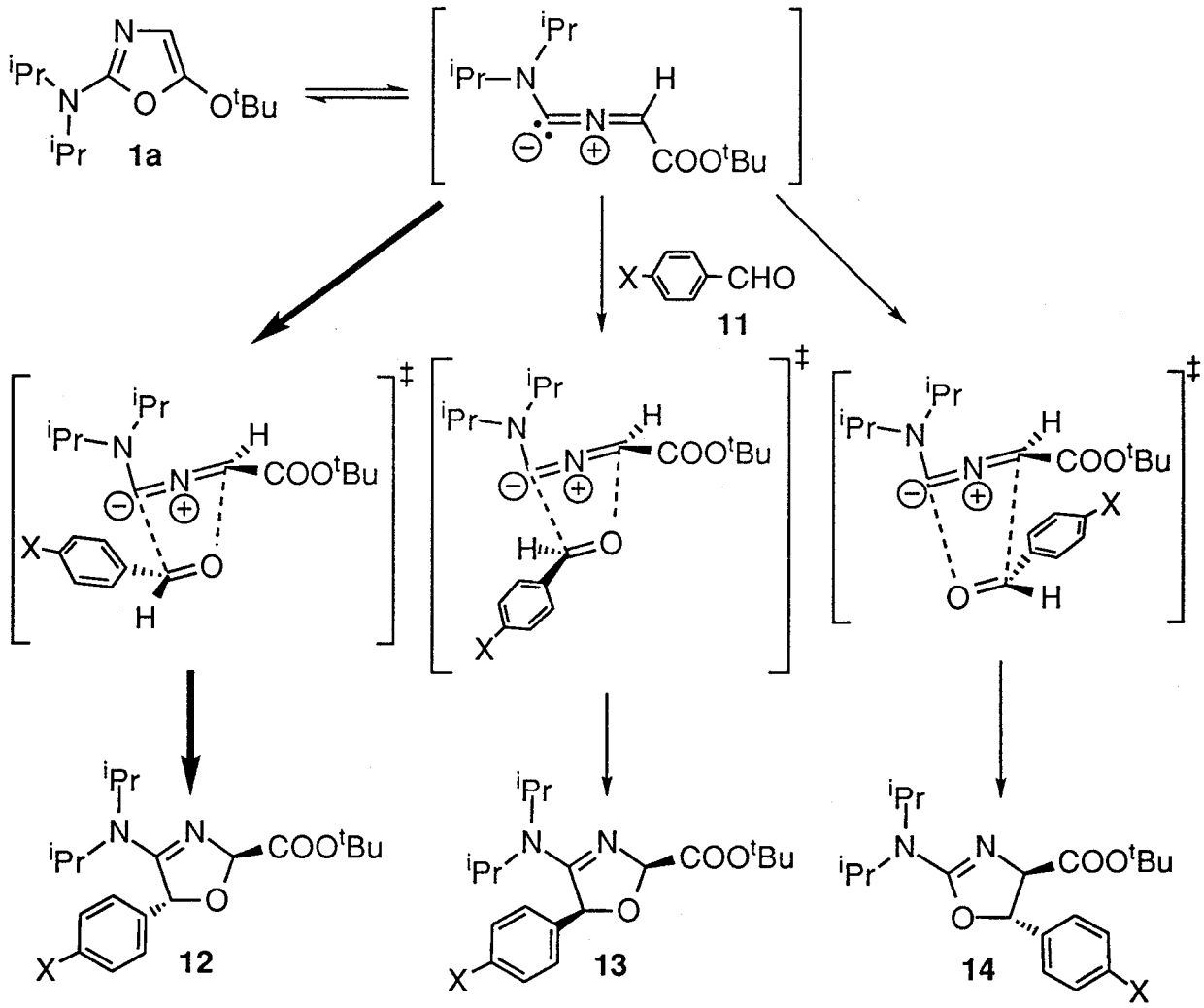
[4]H. Suga et al. reported the structure of 2-oxazoline-4-carboxylate.



H. Suga, X. Shi, and T. Ibata, *J. Org. Chem.*, **58**, 7397 (1993)

The reaction of **1a** with *p*-substituted benzaldehydes are also explained by the 1,3-dipolar cycloaddition of the nitrile ylide intermediate generated by the ring opening of **1a** with aldehydes (Scheme 6).



Scheme 6

The facts that *trans*-3-oxazoline (**12**) was the major product and *trans*-2-oxazoline (**14**) is the minor product are well accordance with the regiochemistry expected from the reaction of the allenyl type nitrile ylide described in chapter 2. The preferential formation of *trans*-isomer **12** to *cis*-isomer **13** may be explained by steric hindrance in the transition state or epimerization from **13** to **12** in the reaction conditions.

The total yield of the reaction decreased as the substituent varies from electron-withdrawing nitro group (80 %) to electron-donating methyl group (5 %). This can be explained by the dependence of the reactivity on the energy difference of HOMO of nitrile ylide and LUMO of aldehyde. In other word, electron-withdrawing group lowers the energy level of LUMO of aldehyde, and consequently decreases energy difference of HOMO (nitrile

ylide) and LUMO (aldehyde), which caused stabilization in the transition state.

5-5 Diastereoselective 1,3-Dipolar Cycloaddition of Chiral Nitrile Ylide with *N*-Ethylmaleimide

In the 1,3-dipolar cycloaddition chemistry, the stereoselective reactions such as diastereoselective reaction and enantioselective reaction have not been developed sufficiently in comparison with that of Diels-Alder reaction. Especially, the stereoselective 1,3-dipolar cycloaddition of nitrile ylide still remains as a great problem, which is far from understood. In the present work, the generation of alkoxycarbonyl nitrile ylide through the ring opening of 2-amino-5-alkoxyoxazole is provided. Using this nitrile ylide as a dipole moiety, it may be possible to develope the diastereoselective 1,3-dipolar cycloaddition of nitrile ylide. Thus, the introduction of a chiral auxiliary into the alkoxylcarbony group was tried to realize the face selection of nitrile ylide (Figure 9).

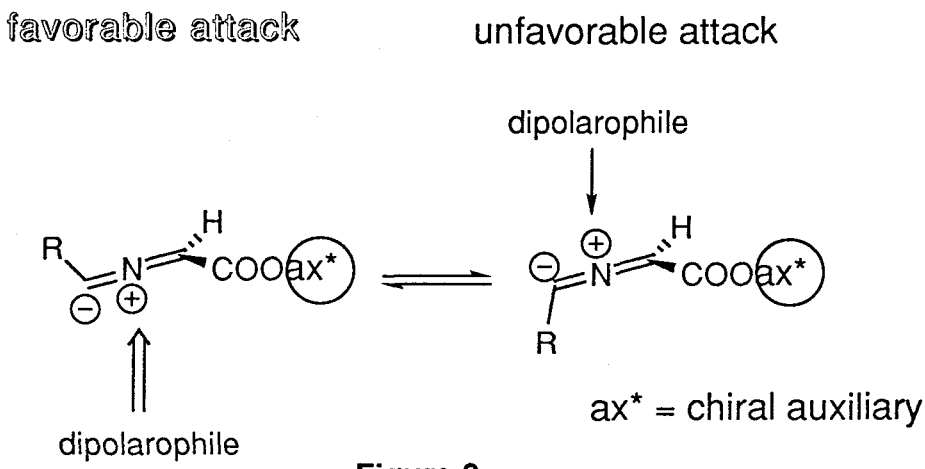
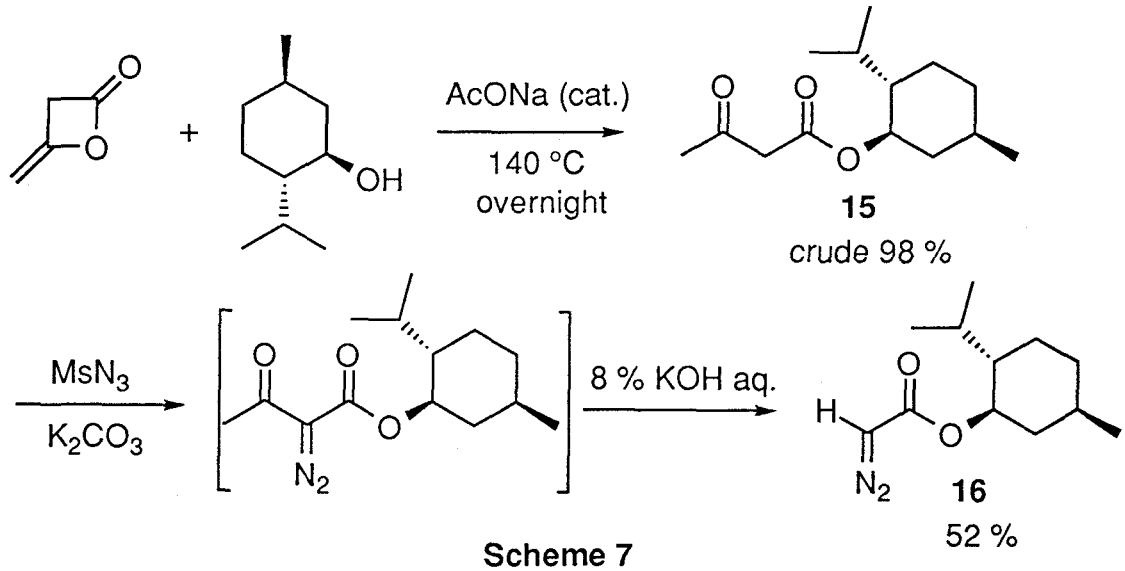
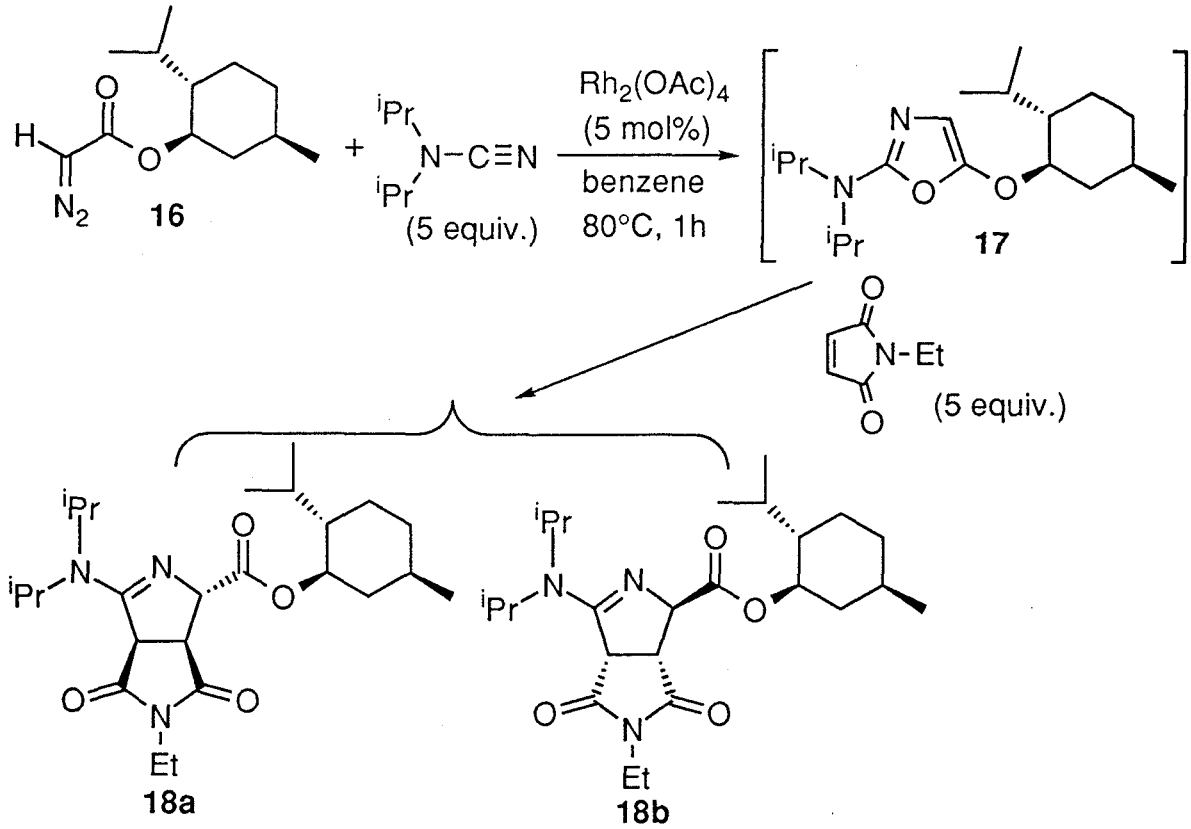


Figure 9

In order to attempt this diastereoselective 1,3-dipolar cycloaddition, *l*-menthyl group was chosen as a chiral auxiliary. The preparation of *l*-menthyl diazoacetate (**16**) is shown in Scheme 7. The addition of *l*-menthol to diketene catalyzed with sodium acetate at 140 °C gave *l*-menthyl acetoacetate (**15**). The diazo group transfer reaction of crude **15** with methanesulfonyl azide and potassium carbonate in acetonitrile at room temperature for 1h gave *l*-menthyl diazoacetoacetate, of which acyl group was cleaved by the successive treatment with 8 % of aqueous potassium hydroxide solution overnight to give *l*-menthyl diazoacetate (**16**) in 52 % yield from **15**.



Scheme 7



Scheme 8

The rhodium(II) acetate-catalyzed decomposition of *l*-menthyl diazoacetate (**16**) in the presence of 5 equivalents of diisopropylcyanamide was carried out at 80 °C for 1h (Scheme 8). However, the isolation of 2-diisopropylamino-5-*l*-menthyloxyoxazole (**17**) was unsuccessful with the complete decomposition of **17**, in spite of efforts to separate by column chromatography and crystallization. Therefore, **17** was employed without isolation for 1,3-dipolar cycloaddition with 5 equivalents of *N*-

ethylmaleimide to give the mixture of two diastereomers **18a** and **18b** in moderate yields (Table 6).

Table 6. Reaction of **17** Generated *in situ* with *N*-Ethylmaleimide

Conditions	Yield / %	Ratio
benzene, 80 °C, 20h	71	ca. 1.4:1
benzene, r.t., 20h	74	ca. 1.4:1

In both reaction conditions at 80 °C and at room temperature, the ratios of the two diastereomers were determined about 1.4:1 according to the ^1H NMR measurement of the mixture. This implies that the selection of the faces of nitrile ylide intermediate occured slightly. Therefore, the reaction of the chiral 2-amino-5-alkoxyoxazole with dipolarophile can be applicable to the diastereoselective 1,3-dipolar cycloaddition of nitrile ylide, and the optimization of the reaction conditions and the introduction of better chiral auxiliary will realize the highly differenciation of the both faces of nitrile ylide.

5-6 Conclusion

In this chapter, 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide, generated by the ring opening of 2-amino-5-alkoxyoxazole, with ethylenic dipolarophiles such as dimethyl fumarate, dimethyl maleate, methyl acrylate, and *N*-substituted maleimides was described. The reaction proceeded in high to moderate yields. Especially, *N*-substituted maleimedes showed high reactivity toward the nitrile ylide intermediate, and the reaction proceeded to give *trans*-1:1-adduct as a major product. The reaction with *p*-substituted benzaldehyde gave *trans*-3-oxazoline derivative selectively in moderate yield.

The reaction of chiral nitrile ylide with *N*-ethylmaleimide gave two diastereomers of *trans*-1:1-adducts in the ratio of 1.4:1. This result shows the possibility of stereoselective 1,3-dipolar cycloaddition of nitrile ylide.

Experimental

Melting points were measured with a Yanagimoto Melting-point Apparatus and were not corrected. IR spectra were recorded on a Perkin-Elmer model 983. ^1H NMR (270.05 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL EX-270 in a $CDCl_3$ solution using TMS as an internal standard. Mass spectra were determined with a JEOL JMS-DX303 spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-5.

Materials and Solvents. 2-Diisopropylamino-5-*tert*-butoxyoxazole (**1a**) was prepared by the $Rh_2(OAc)_4$-catalyzed reaction of *tert*-butyl diazoacetate with diisopropylcyanamide, and purified by distillation under reduced pressure. Benzene was purified by distillation from sodium-benzophenone just before use. The crystalline dipolarophiles were purified by recrystallization, and the oily dipolarophiles were purified by distillation.

General Procedure for the Reaction of 5-*tert*-Butoxy-2-(diisopropylamino)oxazole (1a) with Dipolarophiles;

To a solution of 120 mg (0.5 mmol) of 5-*tert*-butoxy-2-(diisopropylamino)oxazole (**1a**) in 10 ml of benzene, a solution of 2.5 mmol of dipolarophiles was added dropwise for 5 minutes. The reaction mixture was heated at reflux temperature for 1h. After the removal of the solvent, the reaction mixture was separated by medium pressure column chromatography.

The reaction of **1a** with dimethyl fumarate (**2a**) gave **3** and **4**.

Dimethyl 5-*tert*-butoxycarbonyl-2-diisopropylamino-*trans,trans*-pyrroline-3,4-dicarboxylate (3): yellow oil; ^1H NMR (270MHz, $CDCl_3$) δ=1.30 (d, J=6.6 Hz, CH_3 of ^iPr), 1.47 (s, CH_3 of ^tBu), 3.65 (m, CH of ^iPr and 4-H), 3.69 (3H, s, $COOCH_3$), 3.75 (3H, s, $COOCH_3$), 4.20 (1H, d, J=3.0 Hz, 3-H), 4.72 (1H, d, J=2.6 Hz, 5-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=19.78 (qm, CH_3 of ^iPr), 21.07 (qm, CH_3 of ^iPr), 28.00 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of ^tBu), 48.97 (brd, CH of ^iPr), 50.00 (ddd, $^2J_{CH}$ or $^3J_{CH}$=4.9 Hz and 3.1 Hz, 4-C), 52.42 (q, $COO\underline{C}H_3$), 52.66 (q, $COO\underline{C}H_3$), 53.46 (dt, $^2J_{CH}$ and $^3J_{CH}$=2.4 Hz, 3-C), 74.23 (dt, $^2J_{CH}$ and $^3J_{CH}$=3.7 Hz, 5-C), 81.03 (ssxt, $^2J_{CH}$=4.3 Hz, quaternary-C of ^tBu), 160.87 (dm, 2-C), 170.63 (sm, $\underline{C}OOCH_3$), 171.92 ($\underline{C}OO^tBu$), 173.08 (sm, $\underline{C}OOCH_3$); IR (neat) 2971, 1735 (C=O), 1601 (C=N), 1436, 1366, 1215, 1154, 1067, 1022, 969, 921, 898, 850, 808, and 773 cm^{-1}.

Dimethyl 5-*tert*-butoxycarbonyl-2-diisopropylamino-*trans,cis*-pyrroline-3,4-dicarboxylate (4): yellow oil; ^1H NMR (270MHz, $CDCl_3$) δ=1.24 (d, J=6.6 Hz, CH_3 of ^iPr), 1.41 (s, CH_3 of ^tBu), 3.62 (m, CH of ^iPr and 4-H), 3.68 (3H, s, $COOCH_3$), 3.75 (3H, s, $COOCH_3$), 4.32 (1H, d, J=6.9 Hz, 3-H), 4.80 (1H, d, J=8.2 Hz, 5-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=20.10 (qm, CH_3 of ^iPr), 20.56 (qm, CH_3 of ^iPr), 27.92 (qm, CH_3 of ^tBu), 48.99 (brd, CH of ^iPr), 51.36 (dm, 4-C), 52.11 (q, $COO\underline{C}H_3$), 52.69 (q, $COO\underline{C}H_3$), 54.34 (dm, 3-C), 73.13 (dm,

5-C), 81.00 (sm, quaternary-C of ^{t}Bu), 162.14 (sm, 2-C), 170.99 (sm, $\underline{C}OO^{t}Bu$), 171.11 (sm, $\underline{C}OOCH_3$), 172.32 (sm, $\underline{C}OOCH_3$); IR (neat) 2971, 1733 (C=O), 1596 (C=N), 1436, 1368, 1215, 1158, 1065, 1032, 989, 960, 938, 914, 853, 832, 788, and 766 cm^{-1}.

The reaction of **1a** with dimethyl maleate (**2b**) gave **3** and **5**.

Dimethyl 5-*tert*-butoxycarbonyl-2-diisopropylamino-*cis,trans*-pyrroline-3,4-dicarboxylate (5): yellow oil; ^{1}H NMR (270MHz, $CDCl_3$) δ=1.22-1.32 (m, CH_3 of ^{i}Pr), 1.49 (s, CH_3 of ^{t}Bu), 3.65 (m, CH of ^{i}Pr), 3.69 (3H, s, $COOCH_3$), 3.76 (3H, s, $COOCH_3$), 3.89-4.02 (m, 4-H), 4.40 (1H, d, J=5.0 Hz, 3-H), 4.86 (1H, d, J=5.0 Hz, 5-H).

The reaction of **1a** with methyl acrylate (**2c**) gave **6**.

Methyl 5-*tert*-butoxycarbonyl-2-diisopropylaminopyrroline-4-carboxylate (6): yellow oil; ^{1}H NMR (270MHz, $CDCl_3$) δ=1.28 (12H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 1.46 (9H, s, CH_3 of ^{t}Bu), 2.84 (1H, ABq, d, J=15.5 Hz and 9.6 Hz, 3-H), 3.01 (1H, ABq, d, J=15.5 Hz and 5.6 Hz, 3-H), 3.23 (1H, ddd, J=9.6 Hz, 5.6 Hz, and 5.0 Hz, 4-H), 3.73 (3H, s, $COOCH_3$), 3.78 (2H, qui, J=6.9 Hz, CH of ^{i}Pr), 4.58 (1H, d, J=5.0 Hz, 5-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=20.73 (qt, CH_3 of ^{i}Pr), 21.14 (qt, $^{3}J_{CH}$=4.3 Hz, CH_3 of ^{i}Pr), 28.05 (qqui, $^{3}J_{CH}$=4.3 Hz, CH_3 of ^{t}Bu), 36.61 (t, 3-C), 44.97 (d, 4-C), 48.12 (brd, CH of ^{i}Pr), 52.17 (q, $COO\underline{C}H_3$), 74.15 (brd, 5-C), 80.71 (sxt, $^{2}J_{CH}$=4.3 Hz, quaternary C of ^{t}Bu), 165.16 (sm, 2-C), 172.99 (sdd, $^{2}J_{CH}$ or $^{3}J_{CH}$=4.8 Hz and 5.5 Hz, $\underline{C}OO^{t}Bu$), 174.38 (m, $\underline{C}OOCH_3$); IR (neat) 2967, 2931, 1735 (C=O), 1599 (C=N), 1445, 1367, 1252, 1216, 1154, 1096, 1068, 1033, 971, 921, 880, 846, 803, and 764 cm^{-1}.

The reaction of **1a** with *N*-methylmaleimide (**7a**) gave **8a**, **9a**, and 2:1-adducts (**10**).

***trans*-8-*tert*-Butoxycarbonyl-6-diisopropylamino-3-methyl-2,4-dioxo-3,7-diazabicyco[3.3.0]oct-6-ene (8a)**: colorless crystals (from benzene-hexane); mp 126.1-130.7 °C (dec.); ^{1}H NMR (270MHz, $CDCl_3$) δ=1.27 (12H, brd, J=6.6 Hz, CH_3 of ^{i}Pr), 1.44 (9H, s, CH_3 of ^{t}Bu), 2.94 (3H, s, CH_3), 3.64 (1H, dd, J=8.2 Hz, and 2.6 Hz, 1-H), 4.18 (1H, d, J=8.2 Hz, 5-H), 4.63 (1H, dd, J=2.6 Hz, and 1.3 Hz, 8-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=20.07 (brq, CH_3 of ^{i}Pr), 20.65 (qt, $^{3}J_{CH}$=4.3 Hz, CH_3 of ^{i}Pr), 25.27 (q, CH_3), 28.01 (qqui, $^{3}J_{CH}$=4.3 Hz, CH_3 of ^{t}Bu), 46.94 (d, 1-C), 50.32 (brd, CH of ^{i}Pr), 53.49 (d, 5-C), 73.33 (dd, $^{2}J_{CH}$=2.4 Hz, 8-C), 81.49 (sm, quaternary C of ^{t}Bu), 159.02 (sm, 2-C), 171.76 (st, $^{2}J_{CH}$ and $^{3}J_{CH}$=5.5 Hz, $\underline{C}OO^{t}Bu$), 174.01 (sm, C=O), 177.00 (sm, C=O); IR (KBr) 2998, 2967, 2913, 1772, 1698 (C=O), 1595 (C=N), 1465, 1432, 1387, 1368, 1344, 1283, 1248, 1220, 1204, 1156, 1129, 1078, 1000, 968, 932, 920, 891, 846, 828, 813, 805, 792, 757, 722, and 676 cm^{-1}; MS (EI) 351 (M^{+}), 308, 280, 252, 250, 238, 208, 166, 149, 81. Found: C, 61.66; H, 8.20; N, 11.68 %. Calcd for $C_{18}H_{29}N_3O_4$: C, 61.52; H, 8.32; N, 11.96 %.

***cis*-8-*tert*-Butoxycarbonyl-6-diisopropylamino-3-methyl-2,4-dioxo-3,7-diazabicyco[3.3.0]oct-6-ene (9a)**: colorless crystals; ^{1}H NMR

(270MHz, $CDCl_3$) δ=1.35 (12H, brd, J=6.6 Hz, CH_3 of ^iPr), 1.40 (9H, s, CH_3 of ^tBu), 2.95 (3H, s, CH_3), 3.68 (1H, t, J=9.6 Hz, 1-H), 4.18 (1H, d, J=9.6 Hz, 5-H), 4.77 (1H, d, J=9.6 Hz, 8-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=20.23 (qm, CH_3 of ^iPr), 20.75 (qm, CH_3 of ^iPr), 25.14 (q, CH_3), 27.87 (qm, CH_3 of ^tBu), 46.96 (d, 1-C), 53.82 (d, 5-C), 72.30 (dm, 8-C), 81.57 (sm, quaternary C of ^tBu), 159.40 (sm, 2-C), 170.95 (st, $^2J_{CH}$ and $^3J_{CH}$=4.9 Hz, C̲OO^tBu), 173.52 (sm, C=O), 175.44 (sm, C=O); IR (KBr) 3001, 2966, 2930, 1764, 1698 (C=O), 1599 (C=N), 1435, 1386, 1367, 1347, 1288, 1250, 1221, 1155, 1131, 1078, 1019, 975, 941, 921, 904, 843, 828, 811, 774, 748, 704, 687, and 661 cm^{-1}.

***trans*-2:1-Adduct (10t-1) of *N*-methylmaleimide (7a) with 1a**; colorless crystals (from benzene-hexane); mp 209.1-211.3 °C (dec); ^1H NMR (270MHz, $CDCl_3$) δ=1.27 (6H, brd, CH_3 of ^iPr), 1.40 (6H, brs, CH_3 of ^iPr), 1.47 (9H, s, CH_3 of ^tBu), 2.13 (1H, dd, J=18.5 Hz and 4.9 Hz, *endo*-H-4'), 2.94 (1H, dd, J=18.5 Hz and 9.6 Hz, *exo*-H-4'), 2.98 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 3.66 (1H, d, J=1.7 Hz, H-1), 3.74 (1H, dd, J=9.6 Hz and 4.9 Hz, H-3'), 4.23 (brs, CH of ^iPr), 4.66 (1H, d, J=1.7 Hz, H-8); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=19.16 (brqm, CH_3 of ^iPr), 21.11 (qm, CH_3 of ^iPr), 25.34 (q, NCH_3), 25.87 (q, NCH_3), 28.16 (qm, CH_3 of ^tBu), 32.75 (tm, C-4'), 40.54 (dm, C-3'), 48.66 (brdm, CH of ^iPr), 49.95 (dm, C-1), 66.17 (sm, C-5), 70.97 (dd, c-8), 81.74 (sm, quaternary-C of ^tBu), 156.39 (sm, C-6), 170.32 (t, $^2J_{CH}$ and $^3J_{CH}$=6.1 Hz, C̲OOtBu), 174.20 (sm, C=O), 174.30 (sm, C=O), 175.48 (sm, C=O), 176.24 (sm, C=O); IR (KBr) 2971, 2930, 2887, 1774, 1706 (C=O), 1589 (C=N), 1435, 1381, 1330, 1286, 1255, 1207, 1160, 1077, 1042, 1020, 1002, 988, 952, 939, 918, 870, 845, 820, 785, 772, 760, 739, 728, 693, and 668 cm^{-1}; MS (EI) 462 (M^+), 419, 363, 361, 349, 319, 309, 277, 253, 250, 220, 178. Found: C, 59.72; H, 7.38; N, 11.94 %. Calcd for $C_{23}H_{34}N_4O_6$: C, 59.72; H, 7.41; N, 12.11 %.

***trans*-2:1-Adduct (10t-2) of *N*-methylmaleimide (7a) with 1a**; colorless oil; ^1H NMR (270MHz, $CDCl_3$) δ=1.09-1.40 (brm, CH_3 of ^iPr), 1.46 (9H, s, CH_3 of ^tBu), 2.75 (1H, dd, J=18.5 Hz and 9.2 Hz, *exo*-H-4'), 2.85 (1H, dd, J=18.5 Hz and 6.6 Hz, *endo*-H-4'), 2.99 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 3.31 (1H, d, J=2.6 Hz, H-1), 3.92 (1H, dd, J=9.2 Hz and 6.6 Hz, H-3'), 4.61 (1H, d, J=2.6 Hz, H-8).

***cis*-2:1-Adduct (10c-1) of *N*-methylmaleimide (7a) with 1a**; colorless solid; ^1H NMR (270MHz, $CDCl_3$) δ=1.30 (6H, brd, CH_3 of ^iPr), 1.38 (6H, brs, CH_3 of ^iPr), 1.47 (9H, s, CH_3 of ^tBu), 2.10 (1H, dd, J=18.5 Hz and 5.6 Hz, *endo*-H-4'), 2.97 (1H, dd, J=18.5 Hz and 9.2 Hz, *exo*-H-4'), 3.01 (3H, s, NCH_3), 3.02 (3H, s, NCH_3), 3.14 (1H, d, J=8.9 Hz, H-1), 3.75 (1H, dd, J=9.2 Hz and 5.6 Hz, H-3'), 4.23 (brs, CH of ^iPr), 4.52 (1H, d, J=8.9 Hz, H-8)

***cis*-2:1-Adduct (10c-2) of *N*-methylmaleimide (7a) with 1a**; colorless solid; ^1H NMR (270MHz, $CDCl_3$) δ=1.29 (12H, br, CH_3 of ^iPr), 1.44 (9H, s, CH_3 of ^tBu), 2.28 (1H, dd, J=18.8 Hz and 6.3 Hz, *endo*-H-4'), 2.87 (1H, dd, J=18.8 Hz and 9.6 Hz, *exo*-H-4'), 2.98 (3H, s, NCH_3), 3.01-3.04 (1H, d, J=1.7 Hz, H-1), 3.06 (3H, s, NCH_3), 3.89 (1H, dd, J=9.6 Hz and 6.3 Hz, H-3'), 4.62 (1H, d, J=9.3 Hz, H-8)

The reaction of **1a** with *N*-ethylmaleimide (**7b**) gave **8b** and 2:1-adducts (**10**).

***trans*-8-*tert*-Butoxycarbonyl-6-diisopropylamino-3-ethyl-2,4-dioxo-3,7-diazabicyco[3.3.0]oct-6-ene (8b)**: colorless crystals; mp 88.8-91.1 °C (from benzene-hexane); ^{1}H NMR (270MHz, $CDCl_3$) δ=1.14 (3H, t, J=6.9 Hz, CH_3 of Et), 1.30 (12H, brd, J=6.6 Hz, CH_3 of ^{i}Pr), 1.48 (9H, s, CH_3 of ^{t}Bu), 3.53 (2H, q, J=6.9 Hz, CH_2 of Et), 3.66 (1H, dd, J=8.3 Hz, and 2.6 Hz, 1-H), 4.1 (br, CH of ^{i}Pr), 4.20 (1H, d, J=8.3 Hz, 5-H), 4.66 (1H, d, J=2.6 Hz, 8-H); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=12.81 (CH_3 of Et), 20.06 (CH_3 of ^{i}Pr), 20.56 (CH_3 of ^{i}Pr), 27.96 (CH_3 of ^{t}Bu), 34.11 (CH_2 of Et), 46.94 (1-C), 49 (br, CH of ^{i}Pr), 53.37 (5-C), 73.28 (8-C), 81.40 (quaternary C of ^{t}Bu), 159.08 (2-C), 171.70 (COO^{t}Bu), 173.78 (C=O), 176.69 (C=O); IR (KBr) 2965, 2930, 1773, 1701 (C=O), 1595 (C=N), 1512, 1443, 1400, 1368, 1339, 1282, 1226, 1156, 1066, 1008, 930, 893, 845, 817, 800, 779, 735, and 672 cm^{-1}; MS (EI) 365 (M^+), 322, 266, 264, 252, 222, 180, 81. Found: C, 62.21; H, 8.44; N, 11.29 %. Calcd for $C_{19}H_{31}N_3O_4$: C, 62.44; H, 8.55; N, 11.50 %.

The reaction of **1a** with *N*-phenylmaleimide (**7c**) gave **8c** and 2:1-adducts (**10**).

***trans*-8-*tert*-Butoxycarbonyl-6-diisopropylamino-2,4-dioxo-3-phenyl-3,7-diazabicyco[3.3.0]oct-6-ene (8c)**: colorless amorphous; ^{1}H NMR (270MHz, $CDCl_3$) δ=1.32 (12H, brd, J=6.3 Hz, CH_3 of ^{i}Pr), 1.49 (9H, s, CH_3 of ^{t}Bu), 3.85 (1H, dd, J=8.3 Hz, and 3.0 Hz, 1-H), 4.38 (1H, dd, J=8.3 Hz and 1.0 Hz, 5-H), 4.81 (1H, dd, J=3.0 Hz and 1.0 Hz, 8-H), 7.24-7.27 (2H, m, Ph), 7.39-7.50 (3H, m, Ph); ^{13}C NMR (67.8MHz, $CDCl_3$) δ=20.05 (brq, CH_3 of ^{i}Pr), 20.53 (qt, $^3J_{CH}$=3.7 Hz, CH_3 of ^{i}Pr), 27.92 (qqui, $^3J_{CH}$=4.3 Hz, CH_3 of ^{t}Bu), 46.99 (d, 1-C), 53.39 (d, 5-C), 73.82 (dd, $^2J_{CH}$=2.4 Hz, 8-C), 81.46 (sxt, $^2J_{CH}$=4.3 Hz, quaternary C of ^{t}Bu), 126.39 (dt, $^3J_{CH}$=6.7 Hz, 2'-CH of Ph), 128.63 (dt, $^3J_{CH}$=7.3 Hz, 4'-CH of Ph), 129.07 (dd, $^3J_{CH}$=7.9 Hz, 3'-CH of Ph), 131.57 (st, $^3J_{CH}$=9.2 Hz, 1'-C of Ph), 158.87 (sm, 2-C), 171.50 (st, $^2J_{CH}$ and $^3J_{CH}$=6.1 Hz, COO^{t}Bu), 172.87 (sdd, $^2J_{CH}$ or $^3J_{CH}$=5.5 Hz and 3.7 Hz, 4-C=O), 175.82 (sq, $^2J_{CH}$ and $^3J_{CH}$=4.3 Hz, 2-C=O); IR (KBr) 2968, 2933, 1780, 1717 (C=O), 1596 (C=N), 1498, 1442, 1369, 1340, 1286, 1242, 1211, 1156, 1066, 1004, 981, 964, 927, 892, 843, 813, 783, 745, 693, and 668 cm^{-1}.

The reaction of **1a** with *p*-nitrobenzaldehyde (**11a**) gave **12a**, **13a**, and **14a**.

***tert*-Butyl 4-diisopropylamino-5-(*p*-nitrophenyl)-*trans*-3-oxazoline-2-carboxylate (12a)**; colorless powder (from benzene-hexane); mp 160.9-162.5 (dec.); ^{1}H NMR (270MHz, $CDCl_3$); δ=0.97 (6H, brs, CH_3 of ^{i}Pr), 1.32 (6H, brd, CH_3 of ^{i}Pr), 1.50 (9H, s, CH_3 of ^{t}Bu), 3.36 (2H, spt, J=6.6 Hz, CH of ^{i}Pr), 5.78 (1H, ABq, ^{4}J=3.3 Hz, 5-H), 5.84 (1H, ABq, ^{4}J=3.3 Hz, 2-H), 7.47 (2H, d, J=8.6 Hz, 2'-H of Ar), 8.25 (2H, d, J=8.6 Hz, 3'-H of Ar); ^{13}C NMR (67.8MHz, $CDCl_3$); δ=19.42 (qqui, CH_3 of ^{i}Pr), 20.12 (brq, CH_3 of ^{i}Pr), 27.98 (qqui, CH_3 of ^{t}Bu), 48.88 (brd, CH of ^{i}Pr), 81.66 (sm, quaternary-C of ^{t}Bu),

82.62 (dt, 5-C), 100.82 (d, 2-C), 124.18 (dd, 3'-C of Ar), 128.82 (ddd, 2'-C of Ar), 145.91 (t, $^3J_{CH}$=7.9 Hz, 4'-C of Ar), 147.94 (1'-C of Ar), 161.22 (sm, 4-C), 169.65 (C=O); IR (KBr), 3103, 3070, 2964, 2918, 2967, 1731 (C=O), 1610 (C=N), 1517 (NO_2), 1490, 1465, 1448, 1384, 1366, 1348 (NO_2), 1315, 1297, 1255, 1226, 1214, 1194, 1155, 1108, 1082, 1056, 1014, 991, 958, 938, 906, 866, 846, 827, 809, 767, 757, 740, 723, 708, 698, and 669 cm^{-1}. Found: C, 61.32; H, 7.42; N, 10.72 %. Calcd for $C_{20}H_{29}N_3O_5$: C, 61.36; H, 7.47; N, 10.73 %.

The signal of ***tert*-Butyl 4-diisopropylamino-5-(*p*-nitrophenyl)-*cis*-3-oxazoline-2-carboxylate (13a)** was observed in ^1H NMR spectrum of the mixture **12a**; δ=5.63 (d, J=1.65 Hz, 5-H).

***tert*-Butyl 2-diisopropylamino-5-(*p*-nitrophenyl)-*trans*-2-oxazoline-4-carboxylate (14a)**; pale yellow powder (from benzene-hexane); mp 160.9-162.5 °C (dec.); ^1H NMR (270MHz, $CDCl_3$); δ=1.29 (6H, d, J=6.9 Hz, CH_3 of ^iPr), 1.30 (6H, d, J=6.9 Hz, CH_3 of ^iPr), 1.52 (9H, s, CH_3 of ^tBu), 4.01 (2H, spt, CH of ^iPr), 4.30 (1H, d, J=6.3 Hz, 4-H), 5.55 (1H, d, J=6.3 Hz, 5-H), 7.52 (2H, d, J=8.9 Hz, 2'-H of Ar), 8.25 (2H, d, J=8.9 Hz, 3'-H of Ar); ^{13}C NMR (67.8MHz, $CDCl_3$); δ=21.10 (qm, CH_3 of ^iPr), 21.27 (qm, CH_3 of ^iPr), 28.10 (qspt, CH_3 of ^tBu), 47.47 (dm, CH of ^iPr), 74.92 (d, 4-C), 81.83 (ssxt, quaternary-C of ^tBu), 81.87 (dm, 5-C), 126.04 (dd, 3'-C of Ar), 126.22 (ddd, 2'-C of Ar), 147.73 (m, 4'-C of Ar), 147.89 (1'-C of Ar), 161.54 (sm, 2-C), 171.57 (t, $^2J_{CH}$ and $^3J_{CH}$=5.5 Hz, C=O); IR (neat); 3077, 2973, 2933, 1732 (C=O), 1635 (C=N), 1606, 1525 (NO_2), 1492, 1473, 1445, 1368, 1348 (NO_2), 1322, 1287, 1238, 1213, 1154, 1038, 1013, 972, 850, 793, 752, 733, 716, and 698 cm^{-1}.

The reaction of **1a** with *p*-chlorobenzaldehyde (**11b**) gave **12b**, **13b**, and **14b**.

***tert*-Butyl 5-(*p*-chlorophenyl)-4-diisopropylamino-*trans*-3-oxazoline-2-carboxylate (12b)**; ^1H NMR (270MHz, $CDCl_3$); δ=1.30 (6H, brs, CH_3 of ^iPr), 1.48 (6H, brs, CH_3 of ^iPr), 1.49 (9H, s, CH_3 of ^tBu), 3.38 (2H, spt, J=6.6 Hz, CH of ^iPr), 5.67 (1H, d, ^4J=3.3 Hz, 5-H), 5.79 (1H, d, ^4J=3.3 Hz, 2-H), 7.21 (2H, d, J=8.3 Hz, 2'-H of Ar), 7.35 (2H, d, J=8.3 Hz, 3'-H of Ar).

The signal of ***tert*-Butyl 5-(*p*-chlorophenyl)-4-diisopropylamino-*cis*-3-oxazoline-2-carboxylate (13b)** was observed in ^1H NMR spectrum of the mixture with **12b**; δ=5.52 (d, 5-H), 5.77 (d, 2-H).

***tert*-Butyl 5-(*p*-chlorophenyl)-2-diisopropylamino-*trans*-2-oxazoline-4-carboxylate (14b)**; pale yellow viscous oil; ^1H NMR (270MHz, $CDCl_3$); δ=1.27 (12H, d, J=6.9 Hz, CH_3 of ^iPr), 1.50 (9H, s, CH_3 of ^tBu), 4.00 (2H, spt, J=6.9 Hz, CH of ^iPr), 4.30 (1H, d, J=6.3 Hz, 4-H), 5.42 (1H, d, J=6.3 Hz, 5-H), 7. (2H, d, J=8.6 Hz, 2'-H of Ar), 7. (2H, d, J=8.6 Hz, 3'-H of Ar); ^{13}C NMR (67.8MHz, $CDCl_3$); δ=21.14 (qm, CH_3 of ^iPr), 21.23 (qm, CH_3 of ^iPr), 28.09 (qm, CH_3 of ^tBu), 47.38 (dm, CH of ^iPr), 74.55 (dd, 4-C), 81.48 (ssxt, quaternary-C of ^tBu), 82.51 (dd, 5-C), 127.00 (ddd, 2'-C of Ar), 128.87 (dd, 3'-C of Ar),

134.02 (sm, 4'-C of Ar), 139.13 (sm, 1'-C of Ar), 161.82 (sm, 2-C), 171.91 (st, C=O)

The reaction of **1a** with benzaldehyde (**11c**) gave **12c** and **13c**.

***tert*-Butyl 4-diisopropylamino-5-phenyl-*trans*-3-oxazoline-2-carboxylate (12c)**; ^{1}H NMR (270MHz, $CDCl_3$); δ=1.00 (6H, brs, CH_3 of ^{i}Pr), 1.30 (6H, brm, CH_3 of ^{i}Pr), 1.49 (9H, s, CH_3 of ^{t}Bu), 3.40 (2H, spt, J=6.6 Hz, CH of ^{i}Pr), 5.68 (1H, d, ^{4}J=3.3 Hz, 5-H), 5.83 (1H, d, ^{4}J=3.3 Hz, 2-H), 7.25-7.41 (5H, m, Ar).

The signal of ***tert*-Butyl 4-diisopropylamino-5-phenyl-*cis*-3-oxazoline-2-carboxylate (13c)** was observed in ^{1}H NMR spectrum of the mixture with **12c**; δ=5.53 (d, 5-H).

The reaction of **1a** with *p*-tolualdehyde (**11d**) gave **12d**.

***tert*-Butyl 4-diisopropylamino-5-(*p*-tolyl)-*trans*-3-oxazoline-2-carboxylate (12d)**; ^{1}H NMR (270MHz, $CDCl_3$); δ=1.00 (6H, brs, CH_3 of ^{i}Pr), 1.30 (6H, brm, CH_3 of ^{i}Pr), 1.49 (9H, s, CH_3 of ^{t}Bu), 2.34 (3H, s, CH_3), 3.41 (2H, spt, J=6.6 Hz, CH of ^{i}Pr), 5.66 (1H, d, ^{4}J=3.3 Hz, 5-H), 5.79 (1H, d, ^{4}J=3.3 Hz, 2-H), 7.15 (4H, s, Ar).

Preparation of ***l*-menthyl α-diazoacetate (16)**

To a mixture of 1.563 g (10 mmol) of *l*-menthol and 5.2 mg (0.6 mol%) of sodium acetate, 852 mg (10 mmol) of diketene was added for 1 minutes at 140 °C. The reaction mixture was heated for 13.7 h, and treated with short column on silica gel eluted with 50 % of ethyl acetate-hexane to give 2.36 g of *l*-menthyl acetoacetate (**15**) as a dark brown oil (98 %)

***l*-Menthyl acetoacetate (15)**; yellow oil (containing ca. 20 % of enol); ^{1}H NMR (270MHz, $CDCl_3$); signals of keto-form; δ=0.77 (3H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 0.89 (3H, d, J=6.9 Hz, CH_3 of ^{i}Pr), 0.91 (3H, d, J=6.6 Hz, CH_3), 0.85-1.12 (3H, m, axial protons of CH_2 of menthyl group × 3), 1.38 (1H, tt, J=11.2 Hz, and 3.0 Hz, ^{i}PrC<u>H</u> of menthyl group), 1.49 (1H, m, CH_3C<u>H</u> of menthyl group), 1.65-1.71 (2H, m, equatorial protons of CH_2 of menthyl group × 2), 1.88 (1H, sptd, J=6.9 Hz, and 3.0 Hz, CH of ^{i}Pr), 2.03 (1H, m, equatorial proton of CH_2 of menthyl group), 2.26 (2.4H, s, C<u>H</u>$_3$CO), 3.43 (1.6H, s, COC<u>H</u>$_2$CO), 4.74 (1H, td, J=11.2 Hz and 4.3 Hz C<u>H</u>-O of menthyl group); signals of enol-form; δ=1.95 (s, C<u>H</u>$_3$CO), 4.96 (s, olefin proton), 12.19 (s, OH); ^{13}C NMR (67.8MHz, $CDCl_3$); signals of keto-form; δ=16.16 (qm, CH_3 of ^{i}Pr), 20.74 (qm, CH_3 of ^{i}Pr), 21.98 (brq, CH_3), 23.31 (brtm, CH_2 of menthyl group), 26.15 (brd, CH of ^{i}Pr), 30.04 (q, <u>C</u>H$_3$CO), 31.40 (brd, CH_3C<u>H</u> of menthyl group), 34.17 (brt, CH_2 of menthyl group), 40.71 (brt, CH_2 of menthyl group), 46.89 (brd, ^{i}Pr<u>C</u>H of menthyl group), 50.55 (t, CO<u>C</u>H$_2$CO), 75.50 (brd, <u>C</u>H-O of menthyl group), 166.73 (std, $^2J_{CH}$=7.3 Hz, $^3J_{CH}$=3.7 Hz, ester-C=O), 200.63 (ssxt, $^2J_{CH}$=6.1 Hz, keto-C=O); signals of enol-form; δ=16.44 (CH_3 of ^{i}Pr), 21.19 (CH_3 of ^{i}Pr), 22.02 (CH_3), 23.58 (CH_2 of menthyl group), 26.32 (CH of ^{i}Pr), 31.40 (CH_3C<u>H</u> of menthyl

group), 34.26 (CH_2 of menthyl group), 41.05 (CH_2 of menthyl group), 47.08 ($^iPr\underline{C}H$ of menthyl group), 73.71 ($\underline{C}H$-O of menthyl group), 90.07 (dqui, $CH_3C(OH)=\underline{C}HCO$), 172.35 (sd, $^2J_{CH}$=3.1 Hz, ester-C=O), 175.25 (m, $CH_3\underline{C}(OH)=CHCO$); IR (neat) 3439 (OH), 2953, 2867, 1725 (C=O), 1715 (C=O), 1643 (C=O), 1450, 1411, 1360, 1313, 1243, 1180, 1149, 1097, 1080, 1039, 1010, 983, 964, 911, 845, 800, and 737 cm^{-1}.

To a solution of 1.20 g (5 mmol) of *l*-menthyl acetoacetate (**15**) and 691.4 mg (5 mmol) of potassium carbonate in 50 ml of acetonitrile, a solution of 631.0 mg (5.2 mmol) of methanesulfonyl azide in 40 ml of acetonitrile was added dropwise for 5 minutes at room temperature. The reaction mixture was stirred for 4.5 h at room temperature, and the 100 ml of 8 % aqueous solution of potassium hydroxide was added in one portion. After additional stirring for 9.5 h at room temperature, 100 ml of water was added into the reaction mixture. The reaction mixture was extracted with 100 ml of ether, and the aqueous layer was extracted with additional two portions of 100 ml of ether. The combined etheral solution was dried over anhydrous sodium sulfate for 1 d. From the mixture, sodium sulfate was removed by filtration, and the ether was removed under reduced pressure. The residual oil was separated by column chromatography on silica gel eluted with 1 % of ethyl acetate-hexane to give 583 mg of yellow oil, which crystallized in the freezer (52.0 %).

***l*-Menthyl diazoacetate (16)**; yellow leaflet; mp. 45.6-47.2 °C; ^1H NMR (270MHz, $CDCl_3$); δ=0.79 (3H, d, J=6.9 Hz, CH_3 of ^iPr), 0.90 (3H, d, J=6.9 Hz, CH_3 of ^iPr), 0.91 (3H, d, J=6.6 Hz, CH_3), 0.83-1.15 (3H, m, axial protons of CH_2 of menthyl group × 3), 1.36 (1H, tt, J=11.2 Hz, and 3.3 Hz, $^iPrC\underline{H}$ of menthyl group), 1.50 (1H, m, $CH_3C\underline{H}$ of menthyl group), 1.68 (2H, dm, equatorial protons of CH_2 of menthyl group × 2), 1.89 (1H, sptd, J=6.9 Hz, and 2.6 Hz, CH of ^iPr), 2.04 (1H, dm, equatorial proton of CH_2 of menthyl group), 4.71 (1H, s, HCN_2), 4.76 (1H, td, J=11.2 Hz and 4.3 Hz $C\underline{H}$-O of menthyl group); ^{13}C NMR (67.8MHz, $CDCl_3$); δ=16.32 (CH_3 of ^iPr), 20.47 (CH_3 of ^iPr), 21.78 (CH_3), 23.51 (CH_2 of menthyl group), 26.24 (CH of ^iPr), 31.23 ($CH_3C\underline{H}$ of menthyl group), 34.07 (CH_2 of menthyl group), 41.08 (CH_2 of menthyl group), 45.89 ($^iPr\underline{C}H$ of menthyl group), 47.01 ($C=N_2$), 74.52 ($\underline{C}H$-O of menthyl group), 166.22 (C=O); IR (KBr); 3097, 2959, 2931, 2919, 2867, 2851, 2105 ($C=N_2$), 1670 (C=O), 1450, 1394, 1373, 1342, 1322, 1310, 1268, 1241, 1203, 1181, 1152, 1107, 1096, 1080, 1057, 1038, 1010, 993, 981, 961, 920, 878, 843, 808, 780, 744, 689, and 668 cm^{-1}.

The reaction of **16** with diisopropylcyanamide.

To a mixture of 11.8 mg (5 mol%) of $Rh_2(OAc)_4$ and 0.75 ml (2.5 mmol) of diisopropylcyanamide, a solution of 115.6 mg (0.52 mmol) of l-menthyl diazoacetate (**16**) in 2 ml of benzene was added dropwise for 6 minutes at 80 °C. After 1h heating, 9 ml of benzene was added to the reaction mixture, and then, a solution of 316.4 mg (2.5 mmol) of *N*-ethylmaleimide in 3 ml of benzene was added dropwise for 5 min. The mixture was heated at 80 °C

for 19 h, and the benzene and excess of diisopropylcyanamide were removed under reduced pressure. The residual oil was separated by column chromatography to give 161 mg of the mixture of **18a** and **18b**.

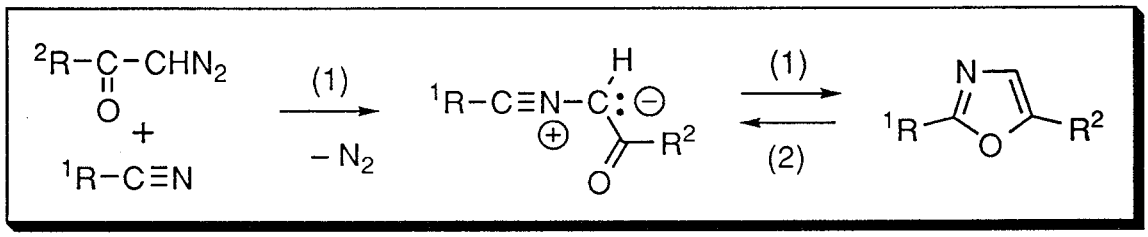
^{1}H NMR of the mixture of **18a** and **18b** (270 MHz, $CDCl_3$) δ=0.72 (d, J=6.9 Hz), 0.86-0.92 (m), 0.98-1.07 (m), 1.14 (t, J=7.3 Hz, CH_3 of Et), 1.30 (d, J=6.6 Hz), 1.45 (tm J=10.9 Hz), 1.68 (dm, J=13.2 Hz), 2.00 (m), 3.54 (q, J=7.3 Hz, CH_2 of Et), 3.74 (dd, J=8.3 Hz and 3.0 Hz, 1-C), 4.22 (dd, J=8.3 Hz and 1.0 Hz, 5-C), 4.70 (td, J=10.9 Hz and 4.6 Hz), 4.73 (dd, J=3.0 Hz and 1.0 Hz, 8-C); the signals of minor isomer were observed as follows in the mixture; ^{1}H NMR (270 MHz, $CDCl_3$) δ=0.76 (d, J=6.9 Hz), 3.68 (dd, J=8.3 Hz and 3.0 Hz, 1-C).

References

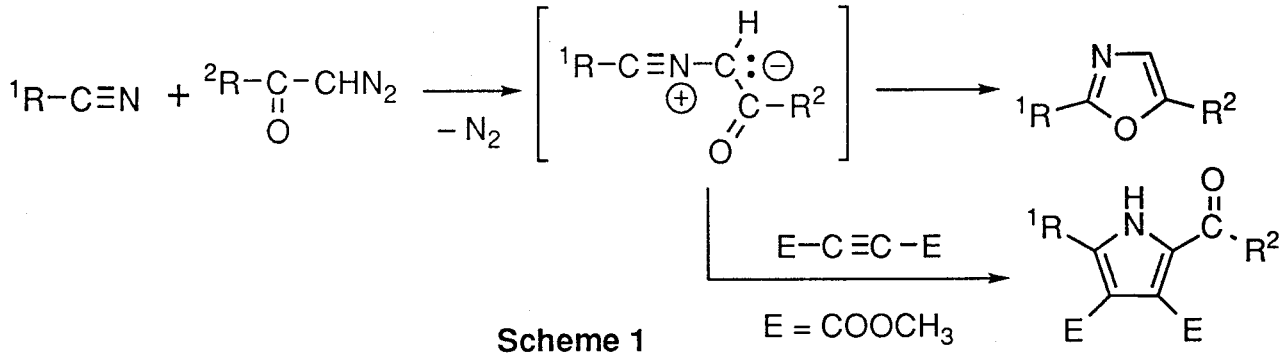
1) H.-J. Hansen and H. Heimgartner, "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, New York (1984), pp 234-237, and references sited therein.
2) a) T. Ibata, S. Nakano, H. Nakawa, J. Toyoda, and Y. Isogami, *Bull. Chem. Soc. Jpn.*, **59**, 433 (1986); b) T. Ibata, H. Nakawa, Y. Isogami, and K. Matsumoto, *Bull. Chem. Soc. Jpn.*, **59**, 3197 (1986); c) T. Ibata, J. Toyoda, H. Tamura, and K. Ogawa, *Bull. Chem. Soc. Jpn.*, **60**, 432 (1987).

Chapter 6. General Conclusion

In the present thesis, the formation and the reaction of oxazole derivatives through acyl-substituted nitrile ylide is described. Especially, the present studies were carried out in the following two points of view. One is the generation of acyl-substituted nitrile ylide intermediate by the reaction of ketocarbenoid with nitrile, which gives oxazole derivatives by 1,5-cyclization (1). The other is the ring opening of 2-amino-5-alkoxyoxazole to generate acyl-substituted nitrile ylide (2).

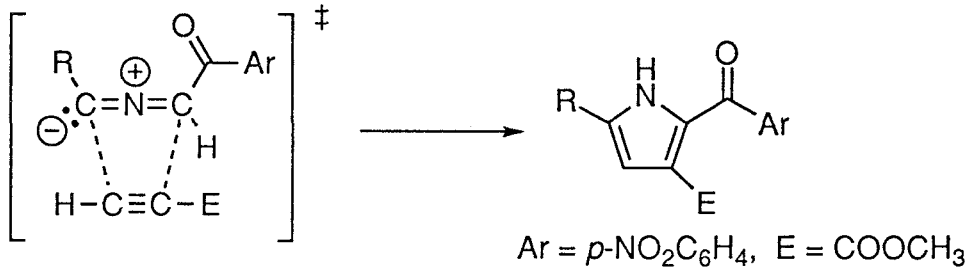


In chapter 2, the successful trap of acyl-substituted nitrile ylide, generated by the reaction of ketocarbenoid with nitrile, with DMAD is described. $Rh_2(OAc)_4$-catalyzed decomposition of diazocarbonyl compounds in nitrile in the presence of DMAD gave both oxazole and pyrrole derivatives. The formation of pyrrole derivatives can be explained by the 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide with DMAD (Scheme 1). This result clarifies the existence of nitrile ylide intermediate in the pathway of oxazole formation from ketocarbenoid and nitrile, and excludes the old concept; that is, concerted 1,3-dipolar cycloaddition of ketocarbene with nitrile gives oxazole derivative.



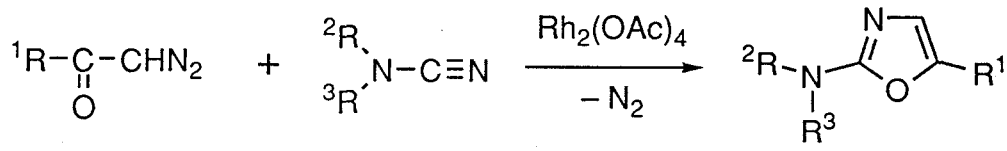
Scheme 1

The reactions with unsymmetrical dipolarophile such as methyl propiolate gave two regioisomers of pyrrole derivatives. On the basis of the structure of the major isomer, it is proved that allenyl-type resonance structure makes major contribution in the structure of the acyl-substituted nitrile ylide. This suggests that the electronic effect of the acyl group on the reactivity of nitrile ylide is not so large, and its reaction is controlled by the electronic property of allenyl type ylide moiety (Scheme 2).



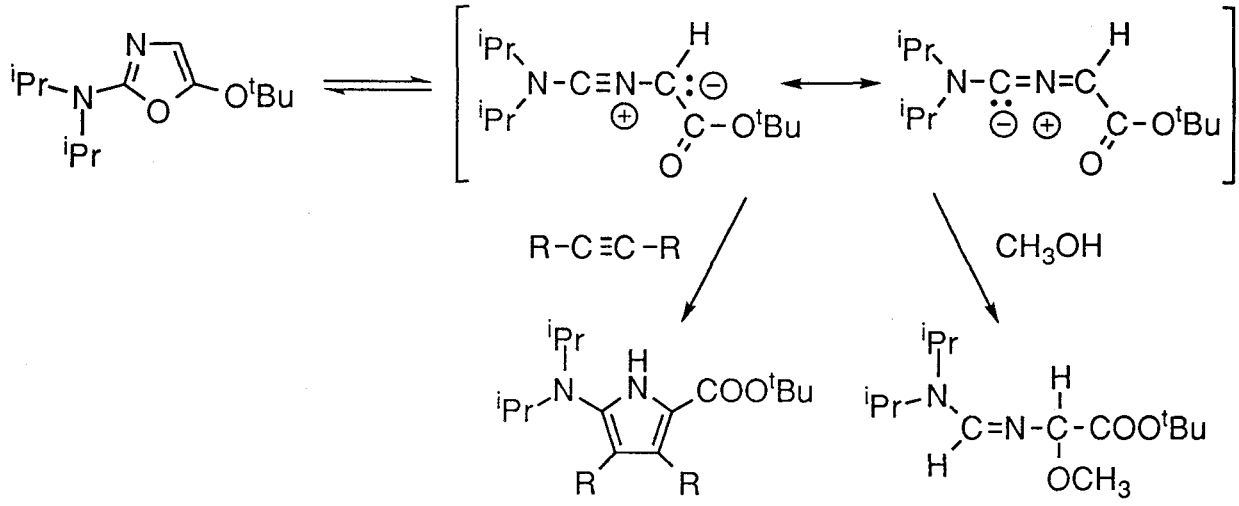
Scheme 2

Chapter 3 describes the application of the $Rh_2(OAc)_4$-catalyzed reaction of diazocarbonyl compounds with nitriles. The $Rh_2(OAc)_4$-catalyzed decomposition of α-diazoacetophenones in the presence of substituted cyanamides gave 2-aminooxazoles in high yields (Scheme 3). Although α-diazoacetates yielded unstable 2-amino-5-alkoxyoxazoles in low yields, this result provides the new efficient synthetic method of the biologically active 2-aminooxazole derivatives. The reaction procceds under neutral and mild condition, which is advantageous over other methods ever known.



Scheme 3

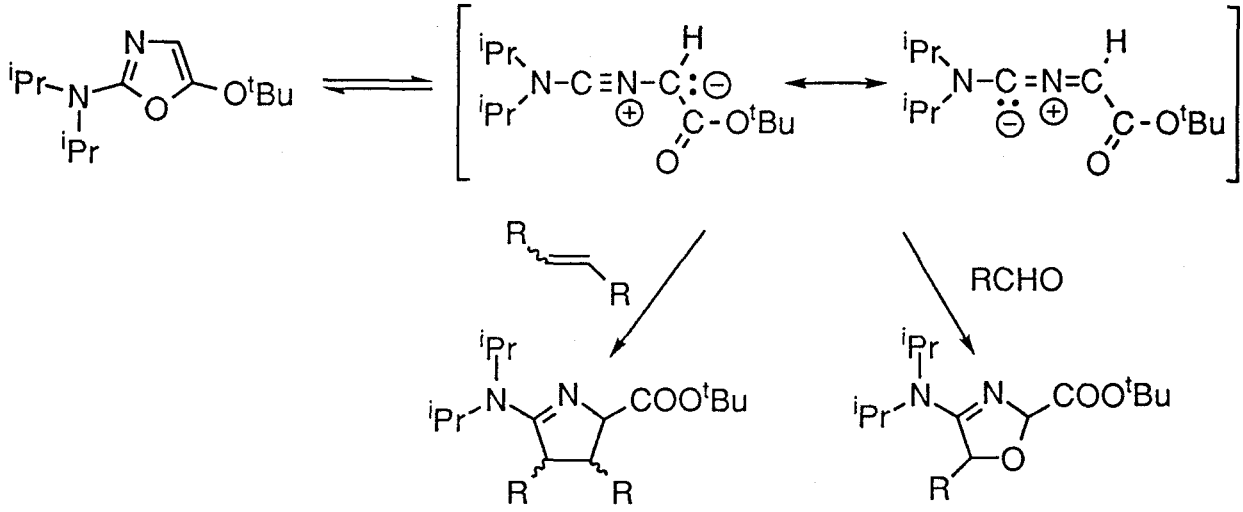
In chapter 4, the reaction of 2-amino-5-alkoxyoxazole with DMAD to give pyrrole derivatives is described. The reaction of 5-*tert*-butoxy-2-(diisopropylamino)oxazole with methanol gave 1:1-adduct, and the first order kinetics was observed. This indicates that 2-amino-5-alkoxyoxazole is converted to the nitrile ylide intermediate under the reaction conditions (Scheme 4).



Scheme 4

The molecular orbital calculation suggest that an introduction of amino group stabilize nitrile ylide.

Chapter 5 describes the 1,3-dipolar cycloaddition of acyl-substituted nitrile ylide, generated by the ring opening of 2-amino-5-alkoxyoxazole, with ethylenic dipolarophiles such as dimethyl fumarate, dimethyl maleate, methyl acrylate, and *N*-substituted maleimides proceeded in high to moderate yields. *N*-Substituted maleimedes showed high reactivity toward the nitrile ylide intermediate, and the reaction proceeded to give *trans*-1:1-adduct as a major product. The reaction with *p*-substituted benzaldehyde gave *trans*-3-oxazoline derivative selectively in moderate yield (Scheme 5).



Scheme 5

The reaction of chiral nitrile ylide, generated *in situ* by the $Rh_2(OAc)_4$-catalyzed reaction of *l*-menthyl diazoacetate with diisopropylcyanamide, with *N*-ethyl maleimide showed the possibility of the stereo-controlled 1,3-dipolar cycloaddition.

The ring opening of 2-amino-5-alkoxyoxazole provides a new method to generate nitrile ylide intermedeate reversibly under mild conditions. Other significance of this reaction are summerized as follows.

(1) Although the ring opening of 4-acyl-5-alkoxyoxazole was known as the key step of the Cornforth rearrangement, the driving force of the reaction (stabilization of the nitrile ylide intermediate) is rather different from the ring opening of 2-amino-5-alkoxyoxazole. In addition, our result is superior to the Cornforth rearrangement in synthetic point of view, because the nitrile ylide generated from 2-amino-5-alkoxyoxazole can react with various dipolarophiles as shown in chapter 5, whereas the nitrile ylide generated in the Cornforth rearrangement did not react with any dipolarophile or alcohol except for the similar case reported by Saalfrank et al.

(2) The reaction of 2-amino-5-alkoxyoxazole with dipolarophile gave the corresponding formal [3+2] adduct through 1,3-dipolar cycloaddition of the nitrile ylide intermediate with dipolarophile. This reaction must be distinguished strictly from the reported formal [3+2] addition of 5-

alkoxyoxazole having no amino group at 2-position. The result described in this thesis suggests that there are two pathways in the formal [3+2] reaction of oxazole. In the formal [3+2] addition reported before, the attack of oxazole on dipolarophile is prior to the ring opening, whereas the ring opening to generate nitrile ylide is the initial step in the reaction of 2-amino-5-alkoxyoxazole.

(3) The ring opening of 2-amino-5-alkoxyoxazole provides nitrile ylide intermediate having ester group. An introduction of chiral groups into the ester moiety is known as one of the effective methods in stereoselective reaction. Therefore, this reaction will be able to realize the stereo-controlled 1,3-dipolar cycloaddition, especially diastereoselective 1,3-dipolar cycloaddition, of nitrile ylide using chiral auxiliary as an ester group. The advantage of the ring opening of 2-amino-5-alkoxyoxazole is the reversibility of the reaction. The ester-substituted nitrile ylide without amino group cyclizes to give oxazole derivative irreversibly, and the competition with cyclization lowers the yield of cycloadduct.

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福島 和明

Kazuaki Fukushima
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