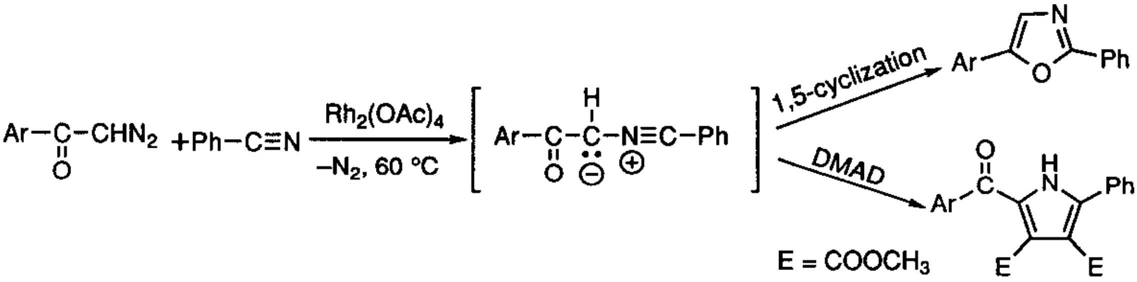
FORMATION OF 2-ALKYLAMINOOXAZOLES BY THE $Rh_2(OAc)_4$-CATALYZED REACTION OF α-DIAZOCARBONYL COMPOUNDS IN THE PRESENCE OF CYANAMIDES

Kazuaki Fukushima and Toshikazu Ibata*

Department of Chemistry, Faculty of Science, Osaka University
Toyonaka, Osaka 560, Japan

Abstract — The $Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenones with *N,N*-dialkylcyanamides gave the corresponding 2-(*N,N*-dialkylamino)-5-aryloxazoles in high yields. Although para-substituents of the diazoacetophenone and the *N*-alkyl groups of cyanamide did not affect the yields of the oxazole, unsubstituted and monosubstituted cyanamides gave the corresponding 2-aminooxazoles in low yields. 2-(*N,N*-Dialkylamino)-5-alkoxyoxazoles formed by the similar reaction of diazoacetates with *N,N*-dialkylcyanamides were found to be unstable upon isolation.

Chemistry of nitrile ylide has been studied extensively in these two decades from the synthetic and theoretical interests and many methods to generate the nitrile ylide have been reported.[1] Although the formation of nitrile ylide through the reaction of carbene with nitriles is one of the important methods,[2] no paper has been reported on the formation of acyl substituted nitrile ylide through the carbenoid reaction. The hydrogen chloride elimination from the appropriate precursor and photolysis of 2-acyl-1-azirine have also been known as the method to generate the acyl substituted nitrile ylide.[3] In the previous paper of this series, we have reported the formation of the acyl substituted nitrile ylide by the $Rh_2(OAc)_4$-catalyzed decomposition of α-diazoacetophenones in the presence of benzonitrile affording the corresponding oxazoles through the intramolecular cyclization of the nitrile ylide and the pyrroles by the intermolecular 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) followed by the hydrogen migration, respectively.[4]



Due to the interesting biological properties[5] applicable as antibacterial, antimicrobial, antiviral, and antiinflammatory drugs, the synthesis of 2-amino substituted oxazoles has been studied extensively.[6] As a continuation of our previous works we studied the $Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenones with *N,N*-disubstituted cyanamides to develope the preparative method of the biologically active 2-(*N,N*-dialkylamino)-5-aryloxazoles.

The rhodium(II) acetate-catalyzed decomposition of *p*-nitro-α-diazoacetophenone (**1a**) in the presence of large excess of *N,N*-diisopropylcyanamide (**2a**) at 60 °C gave 2-(*N,N*-diisopropylamino)-5-(*p*-nitrophenyl)oxazole (**3a**) in 95% yield. The reaction of other para-substituted α-diazoacetophenones (**1b-f**) having an electron-releasing or electron-withdrawing substituent with **2a** also gave the corresponding 2-(*N,N*-diisopropylamino)-5-aryloxazoles in high yields (Table 1, Runs 2-6).[7,8]

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 as is shown in Table 1 (Runs 10-13).[7,8] However, unsubstituted cyanamide (**2b**) gave 2-amino-5-(*p*-nitrophenyl)oxazole (**3g**) only in 7% yield with recovering of **1a** in 69% (Run 7).[9] Monoalkyl cyanamides also gave the corresponding oxazoles in low yields (Runs 8 and 9). The reaction of **1a** with *N*-cyanopiperidine (**2i**) gave 2-piperidino-5-(*p*-nitrophenyl)oxazole (**3n**) in 70% yield (Run 14).

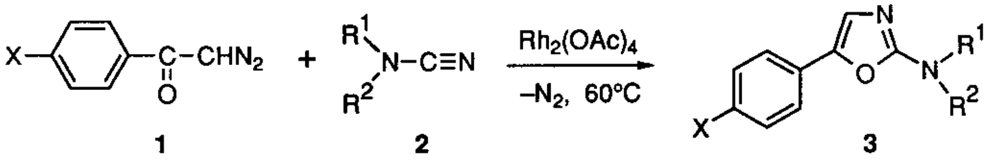


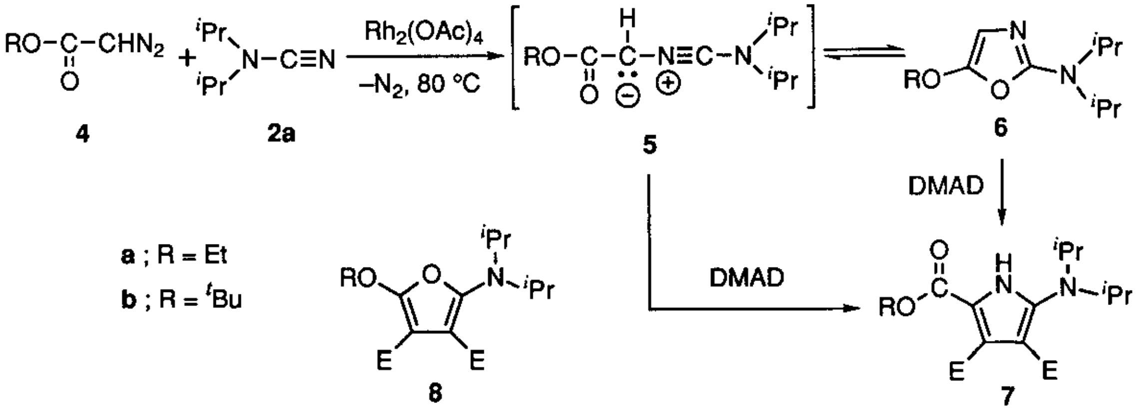
Table 1. Yields of 2-Aminooxazoles in the Reaction of α-Diazoacetophenones with Cyanamides.

Run	Diazoacetophenone		Cyanamide			Oxazole	
	1	X	**2**	R^1	R^2	**3**	Yield / %
1	**1a**	NO$_2$	**2a**	^{i}Pr	^{i}Pr	**3a**	95
2	**1b**	CN	**2a**	^{i}Pr	^{i}Pr	**3b**	79
3	**1c**	Cl	**2a**	^{i}Pr	^{i}Pr	**3c**	75
4	**1d**	H	**2a**	^{i}Pr	^{i}Pr	**3d**	76
5	**1e**	Me	**2a**	^{i}Pr	^{i}Pr	**3e**	83
6	**1f**	OMe	**2a**	^{i}Pr	^{i}Pr	**3f**	70
7a)	**1a**	NO$_2$	**2b**	H	H	**3g**	7
8a)	**1a**	NO$_2$	**2c**	H	Me	**3h**	13
9a)	**1a**	NO$_2$	**2d**	H	^{t}Bu	**3i**	33
10	**1a**	NO$_2$	**2e**	Me	Me	**3j**	82
11	**1a**	NO$_2$	**2f**	Et	Et	**3k**	98
12a)	**1a**	NO$_2$	**2g**	Me	Et	**3l**	74
13a)	**1a**	NO$_2$	**2h**	Me	Ph	**3m**	84
14a)	**1a**	NO$_2$	**2i**	−(CH$_2$)$_5$−		**3n**	70

a) The reactions were carried out using 10 molar amounts of cyanamides in refluxing CH_2Cl_2.

Thermolysis and copper-catalyzed reactions of 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, our results indicate that the $Rh_2(OAc)_4$-catalyzed reaction of diazoacetophenones with cyanamides can be the general method of the synthesis of 2-alkylamino-5-aryloxazoles (**3**) in comparison to the similar reaction catalyzed by BF_3-etherate reported before.[11]

Similar reaction of ethyl diazoacetate (**4a**) with diisopropylcyanamide (**2a**) did not give the corresponding oxazole (**6a**) after the usual work up, but by the nmr measurement the almost quantitative formation of the oxazole was observed in the reaction mixture before column chromatography separation.[12] The addition of DMAD to the reaction mixture after the complete decomposition of **4a** gave dimethyl 2-(*N*,*N*-diisopropylamino)-5-ethoxycarbonylpyrrole-3,4-dicarboxylate (**7a**) in 58% yield, together with a trace amount of dimethyl 2-(*N*,*N*-diisopropylamino)-5-ethoxyfuran-3,4-dicarboxylate (**8a**) formed by the Diels-Alder reaction of **6a** with DMAD followed by the HCN elimination.[13] The formation of **7a** is explained by the abnormal Diels-Alder reaction of oxazole (**6a**) with DMAD[14] or by the reaction of DMAD with nitrile ylide (**5a**) which is thought to be in equilibrium with **6a**.[15] This suggests the possibility of the equilibrium between the oxazole (**6**) and the nitrile ylide (**5**) in the reaction mixture.[15] In contrast, in the reaction of *t*-butyl diazoacetate (**4b**) with **2a**, the corresponding oxazole (**6b**) was isolated in 41% yield.[16]



Further mechanistic investigation for the formation of pyrrole derivatives by the reaction of oxazole (**6**) with DMAD are now in progress.

REFERENCES

1. H.-J. Hansen and H. Heimgartner, "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, New York, 1984, pp. 177-290.
2. A. S. Kende, P. Hebeisen, P. J. Sanfilippo, and B. H. Toder, *J. Am. Chem, Soc.*, 1982, **104**, 4244; E. P. Janulis, Jr., S. R. Wilson, and A. J. Arduengo, *Tetrahedron Lett.*, 1984, **25**, 405; A. Padwa, J. R. Gasdaska, M. Tomas, N. J. Turro, Y. Cha, and I. R. Gould, *J. Am. Chem. Soc.*, 1986, **108**, 6739.
3. K. Hirai, Y. Iwano, T. Saito, T. Hiraoka, and Y. Kishida, *Tetrahedron Lett.*, 1976, **17**, 1303; W. P. Fehlhammer, K. Bartel and W. Petri, *J. Organomet. Chem.*, 1975, **87**, C34; A. Hassner and B. Fischer, *Tetrahedron*, 1989, **45**, 3535.
4. T. Ibata and K. Fukushima, *Chem. Lett.*, **1992**, 2197.
5. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, 1975, **75**, 389; L. Peshakova, V. Kalcheva, and D. Simov, *Khim. Geterotsikl. Soedin.*, 1981, 1011.
6. R. Gompper and O. Christmann, *Chem. Ber.*, 1959, **92**, 1944; A. F. Cockerill, A. Deacon, R. G. Harrison, D. J. Osborne, D. M. Prime, W. J. Ross, A. Todd, and J. P. Verge, *Synthesis*, 1976, 591; A. M. van Leusen, H. J. Jeuring, J. Wildemann, and S. P. J. M. van Nispen, *J. Org. Chem.*, 1981, **46**, 2069.
7. New compounds obtained in this work showed the satisfactory results of elemental analysis and spectroscopic measurements.
8. General Procedure of the Reaction: A solution of 1 mmol of α-diazoacetophenone dissolved in 20 ml of cyanamide 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 N_2 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.
9. The catalytic reactivity of $Rh_2(OAc)_4$ was decreased very much in these reaction conditions by strong complexation of cyanamide to the active site of $Rh_2(OAc)_4$.
10. R. Huisgen, H. Koeing, G. Binsch, and H. J. Sturm, *Angew. Chem.*, 1961, **73**, 368 ; R. Huisgen, G. Binsch, and L. Ghosez, *Chem. Ber.*, 1964, **97**, 2628; R. Huisgen, H. J.

Sturm, and G. Binsch, *Chem. Ber.*, 1964, **97**, 2864.

11. T. Ibata, T. Yamashita, M. Kashiuchi, S. Nakano, and H. Nakawa, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2450.

12. Although a methyl signal of diisopropyl groups in the product was hidden in the signal of the starting diisopropylcyanamide, following signals of **6a** were observed in its ^{1}H nmr spectrum: δ=1.38 (3H, t, J=7.3 Hz, CH_3), 3.94 (2H, sep., J=6.9 Hz, CH), 4.04 (2H, q, J=7.3 Hz, CH_2), and 5.82 (1H, s, 4-H).

13. D. L. Boger and S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Syntheis," Academic Press, Inc., 1987, pp. 306-310 and references cited therein.

14. T. Ibata, Y. Isogami, S. Nakano, and H. Tamura, *J. Chem. Soc., Chem. Commun.*, **1986**, 1692; T. Ibata, Y. Isogami, H. Nakawa, H. Tamura, H. Suga, X. Shi, and H. Fujieda, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1771; T. Ibata, Y. Isogami, and H. Tamura, *Chem. Lett.*, **1988**, 1551; T. Ibata, H. Suga, Y. Isogami, H. Tamura, and X. Shi, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2998; and references cited therein.

15. R. W. Saalfrank, C.-J. Lurz, J. Hassa, D. Danion, and L. Toupet, *Chem. Ber.*, 1991, **124**, 595.

16. Almost quantitative amount of **6b** was observed by the nmr measurement of the reaction mixture before column chromatography. Structure of **6b** was characterized by the spectroscopic measurements as shown below: 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, sept., J=6.9 Hz, CH of ^{i}Pr), 5.99 (1H, s, 4-H); ^{13}C nmr (67.8 MHz, $CDCl_3$) δ = 21.01 (q, CH_3 of ^{i}Pr), 28.04 (q, CH_3 of ^{t}Bu), 46.50 (d, CH of ^{i}Pr), 82.31 (s, quaternary C of ^{t}Bu), 107.41 (d, J_{C-H}=191.7 Hz, 4-C), 150.11 (s, 5-C), 155.20 (s, 2-C); ir (neat) 3124, 2973, 2932, 2873, 1647, 1585, 1455, 1420, 1389, 1367, 1327, 1266, 1227, 1207, 1150, 1130, 1035, 985, 963, 910, 853, 796, 775, 740, 710 cm^{-1}.

Received, 9th May, 1994