CHEMISTRY LETTERS, pp. 1221−1224, 1991.

Reaction of Oxazoles with Nitrosobenzene. A Route to 1,2,4-Oxadiazolines

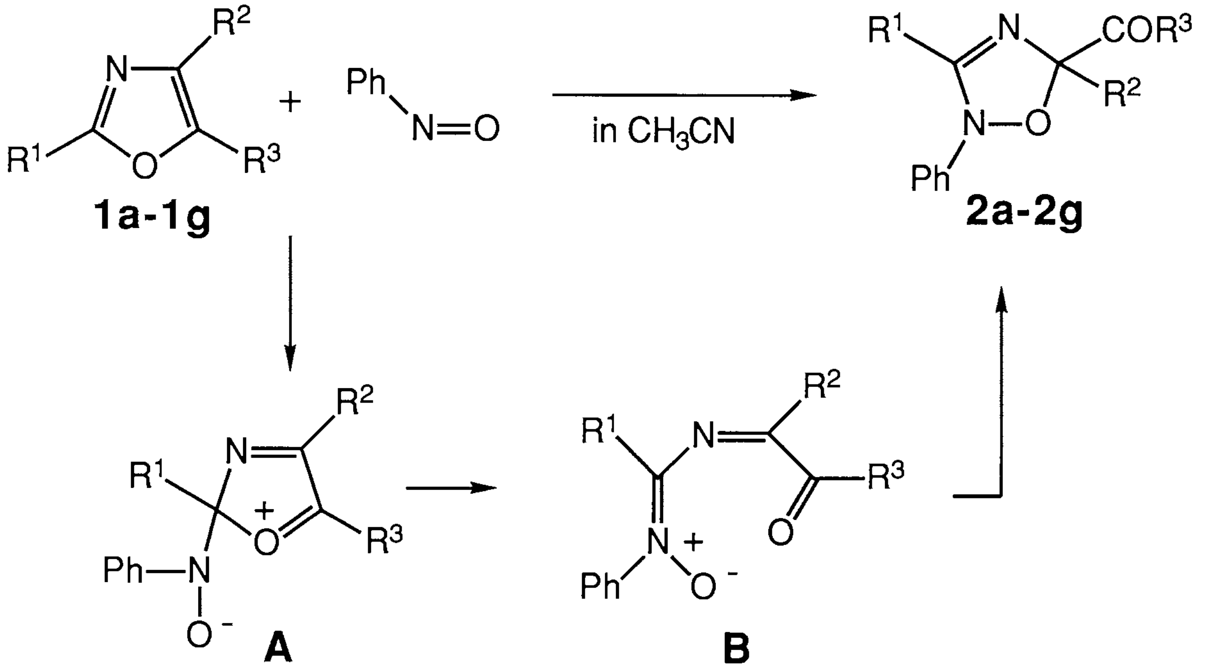
Hiroyuki SUGA and Toshikazu IBATA*

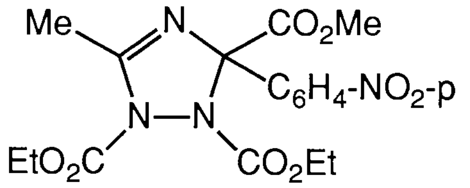
Institute of Chemistry, College of General Education, Osaka University, Toyonaka, 560

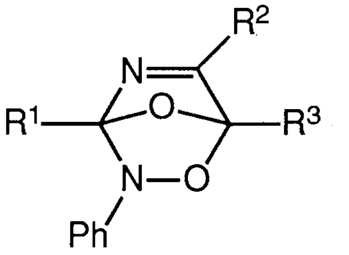
The reaction of substituted oxazoles with nitrosobenzene gave 2-phenyl-1,2,4-oxadiazolines in good yields through a ring opening of oxazole.

Oxazoles are well-known to undergo Diels-Alder reaction with electron-deficient olefins as a 2-azadiene moiety, and the adducts were generally unstable in the reaction conditions to give pyridine derivatives.1) While, in the previous papers of this series, we found that the reaction of oxazoles with one of the most reactive dienophiles such as tetracyanoethylene (TCNE)2) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)3) did not yield Diels-Alder adducts but gave 1,3-cycloadducts (4,5-dihydro-3H-pyrroles and Δ^3-1,2,4-triazolines, respectively) through ring opening of oxazoles.4) The mechanism of these cycloadditions was explained to proceed through the stepwise pathway involving zwitterionic intermediates, and the dienophiles should be activated by electron-withdrawing substituents according to the proposed mechanism. In this paper, we report the reaction of oxazoles with nitrosobenzene to afford a new synthetic route to 1,2,4-oxadiazolines. Regiochemistry of the cycloaddition was also discussed.

A solution of 5-methoxy-2-methyl-4-(p-nitrophenyl)oxazole (**1a**) and nitrosobenzene in dry acetonitrile was stirred at room temperature for 16.5 h under nitrogen atmosphere. At the end point of the reaction, the green reaction mixture turned to yellow and an adduct **2a** was obtained in 98% yield after chromatographic separation (silica gel / hexane-ethyl acetate). The elemental analysis and ^{1}H NMR spectrum show that **2a** is the 1:1 adduct of **1a** and nitrosobenzene. The ^{13}C NMR spectrum of **2a** shows signals of imino carbon at 161.83 ppm (q, $^2J_{C\text{-}H}$ = 6.9 Hz), quaternary carbon at 104.79 ppm (t, $^3J_{C\text{-}H}$ = 3.7 Hz) and ester carbonyl carbon at 168.73 ppm.5) IR spectrum of **2a** shows ester carbonyl absorption at 1750 cm^{-1} and C=N absorption at 1639 cm^{-1} These spectroscopic data indicate that the product **2a** is not the corresponding Diels-Alder adduct but a 1,2,4-oxadiazoline derivative containing methyl ester at 5-position. Similar adducts were reported to form in the reaction with TCNE and PTAD.2,3) The regiochemistry of **2a** was determined by an NOE experiment (ortho-H of the N-Ph / 3-Me) and by the chemical shift of methyl group at 3-position (1.99 ppm).[6] The upfield shift of 3-Me of **2a** (0.47 ppm in comparison to **3**) is presumably due to the shielding effect by the 2-Ph substituent.




3


4

Some other 2-substituted- and/or 4-substituted 5-alkoxyoxazoles **1b-1f** also reacted with nitrosobenzene to give the corresponding 1,2,4-oxadiazolines **2b-2f** in good yields (Table 1). It is interesting that not only 5-alkoxyoxazoles **1a-1f** but also 5-methyloxazole **1g** underwent the same type of reaction to give **2g** in moderate yield. All these reactions of **1b-1g** were exclusively regioselective; The regioisomers **2b-2g** were found to possess the same regiochemistry as the oxadiazoline **2a**. Thus, the methyl or the aryl group for R^1 of **2** were observed upfield in comparison with those of the corresponding 1,2,4-triazolines.[7]

The observed regiochemistry of adducts **2** suggests that the reaction presumably proceeds through the stepwise mechanism initiated by the nucleophilic attack of the C-2 carbon of oxazole **1** to the nitrogen of nitrosobenzene. The resulting zwitterion intermediate **A** undergoes the ring opening of oxazole to the imino nitrone intermediate **B**, which affords the adduct **2** by cyclization. Although there is a possibility that Diels-Alder adduct **4** would be the precursor of intermediate **A** or **B**, the stepwise pathway is more likely because the reaction occurred only with the dienophiles having strong electron acceptor character.

Table 1. Reactions of Oxazoles **1a-1g** with Nitrosobenzene[a)]

Oxazole **1**	R^1, R^2, R^3	Conditions	Product	Yield/%
1a	R^1 = Me, R^2 = p-$NO_2C_6H_4$, R^3 = OMe	r.t., 16.5 h	**2a**	98
1b	R^1 = p-MeC_6H_4, R^2 = p-$NO_2C_6H_4$, R^3 = OMe	r.t., 118 h	**2b**	70 (96)[b)]
1c	R^1 = Me, R^2 = Me, R^3 = OMe	r.t., 1.5 h	**2c**	65
1d	R^1 = n-nonyl, R^2 = CO_2Et, R^3 = OEt	reflux, 48 h	**2d**	61 (87)[b)]
1e	R^1 = p-$MeOC_6H_4$, R^2 = H R^3 = OMe	r.t., 72 h[c)]	**2e**	93
1f	R^1 = Me, R^2 = H, R^3 = OEt	r.t., 9 h	**2f**	80
1g	R^1 = Me, R^2 = Me, R^3 = Me	r.t., 52 h	**2g**	50

a) The reaction was carried out in dry acetonitrile under nitrogen atmosphere.

b) Yields based on the consumed oxazole.

c) 1.5 Equivalents of nitrosobenzene was used.

This reaction of oxazoles with nitrosobenzene provides a new route to the synthesis of 1,2,4-oxadiazoline heterocycles. Study on the scope and limitation of this new reaction and the screening study on effective catalysts for the reaction are now in progress.

References

1) D. L. Boger and S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Synthesis," as Vol. 47 in "Organic Chemistry: A Series of Monographs," ed by H. H. Wasserman, Academic Press, San Diego, New York, Berkeley, Boston, London, Sydney, Tokyo, Toronto (1987), Chap. 10, pp. 300-310.

2) T. Ibata, Y. Isogami, S. Nakano, and H. Tamura, *J. Chem. Soc., Chem. Commun.*, **1986**, 1692.

3) T. Ibata, Y. Isogami, and H. Tamura, *Chem. Lett.*, **1988**, 1551.

4) Similar reactions were reported by E. Vedejs (with thioaldehyde) and A. Hassner (with diethyl azodicarboxylate and diethyl ketomalonate): E. Vedejs and S. Fields, *J. Org. Chem.*, **53**, 4663 (1988); A. Hassner and B. Fisher, *Tetrahedron*, **45**, 3535 (1989).

5) Spectroscopic data: Compound **2a**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.99 (3H, s, 3-Me), 3.82 (3H, s, CO_2Me), 7.33-7.44 (5H, m, Ph), 7.87 (2H, dt, J = 8.9 Hz and J = 2.3 Hz, Ar-H), and 8.26 (2H, dt, J = 8.9 Hz and J = 2.3 Hz, Ar-H).

^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.34 (q, 3-Me), 53.41 (q, CO_2Me), 104.79 (t, $^3J_{C\text{-}H}$ = 3.7 Hz, 5-C), 123.62, 124.53, 127.28, 128.78, 129.55 (each d, o-, m-C of Ar and Ph, and p-C of Ph), 140.97 (s, 1-C of Ph), 145.63 (s, 4-C of Ar), 148.36 (s, 1-C of Ar), 161.83 (q, $^2J_{C\text{-}H}$ = 6.9 Hz, 3-C), 168.73 (q, $^3J_{C\text{-}H}$ = 4.1 Hz, CO_2Me).

6) The 3-methyl group of 1,2-diethoxycarbonyl-5-methoxycarbonyl-3-methyl-5-(p-nitrophenyl)-1,2,4-triazoline (**3**)$^{7)}$ was observed at 2.46 ppm.

7) Unpublished result. The corresponding 1,2,4-triazolines were prepared with the reaction of oxazoles **1** with diethyl azodicarboxylate. Chemical shifts of the substituents at 3-position of the oxadiazolines and those of the corresponding triazolines (designated in parentheses) are shown below.

2a: δ 1.99 (2.46); **2b**: δ 7.11, 7.63 (7.24, 7.77); **2c**: δ 1.93 (2.38); **2e**: δ 6.79, 7.67 (6.92, 7.84); **2f**: δ 1.94 (2.49); **2g**: δ 1.94 (2.41).

(Received April 15, 1991)