Synthesis of 2,5-Dihydro-1,2,4-oxadiazoles through Formal [3+2] Cycloaddition of Oxazoles with Nitrosobenzene Derivatives

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(Received January 5, 1998)

The reactions of substituted oxazoles with nitrosobenzene gave 2-phenyl-2,5-dihydro-1,2,4-oxadiazoles regioselectively through formal [3+2] cycloadditions proceeding via a ringopening of oxazoles by an attack of nitrosobenzene. The reactions with 1-chloro- and 1-methyl-4-nitrosobenzenes also produced the corresponding 2,5-dihydro-1,2,4-oxadiazoles regioselectivity.

Diels–Alder reactions of oxazoles with olefins and acetylenes are well-known to give pyridine and furan derivatives under the elimination of alcohols or nitriles.[1] Recently, we and others have found that oxazoles do not give Diels–Alder adducts, but 1,3-cycloadducts in a reaction with tetracyanoethylene (TCNE),[2] 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD),[3,4] diethyl azodicarboxylate (DEAD),[4,5] dihydrohidantine,[5] diethyl oxomalonate,[5,6] aldehydes,[7] and thioaldehydes.[8] We also reported regio-,[6] stereo-,[7] or enantio-control[9] of this [3+2] cycloaddition to diethyl oxomalonate and aldehydes using a Lewis acid as a catalyst. The mechanism of these cycloadditions was explained to proceed through a stepwise pathway involving zwitterionic intermediates, showing that the dienophiles are activated by electron-withdrawing substituents. In this paper we give full accounts of our investigations of the formal [3+2] cycloadditions of oxazoles to nitrosobenzene derivatives to afford a new synthetic route to 2,5-dihydro-1,2,4-oxadiazoles.[10] We explain mechanistically the high regioselectivity for the cycloadditions compared to that for the cycloaddition to diethyl oxomalonate particularly under thermal conditions.[5,6] We also indicate that a high regioselective reaction similarly occurs using *p*-substituted nitrosobenzenes.

Results and Discussion

Reaction of Oxazoles with Nitrobenzene. A solution containing 5-methoxy-2-methyl-4-(*p*-nitrophenyl)oxazole **1a** and nitrosobenzene in dry acetonitrile was stirred at room temperature for 16.5 h under a nitrogen atmosphere. At the end point of the reaction, the color of the reaction-mixture changed from green to yellow, and an adduct **2a** was obtained in 98% yield after chromatographic separation (Scheme 1).

The spectroscopic data and an elemental analysis show that **2a** is a 1 : 1 adduct of **1a** and nitrosobenzene. The ^{13}C NMR spectrum of **2a** shows signals of imino carbon at 161.83 ppm (q, $^{2}J_{C-H} = 6.9$ Hz), quaternary carbon at 104.79 ppm (t, $^{3}J_{C-H} = 3.7$ Hz) and ester carbonyl carbon at 168.73 ppm (Table 2). 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 product **2a** is not the corresponding Diels–Alder adduct **3**, but a 2,5-dihydro-1,2,4-oxadiazole derivative containing a methoxycarbonyl group at the 5-position. The regiochemistry for cycloaddition giving **2a** was determined by an differential NOE experiment (*ortho*-H of the N–Ph / 3-Me) and by the upfield shift of the methyl group (1.99 ppm) at the 3-position, compared to the methyl group of **4a**, **5a**, or **6a**; 2.46 ppm[4] for **4a**, 2.30 ppm[6] for **5a**, or 2.37 ppm[6] for **6a**. The upfield shift of 3-methyl of **2a** is presumably due to a shielding effect by the 2-phenyl substituent.

The reactions of some other 2-substituted and/or 4-substituted 5-alkoxyoxazoles, **1b**—**1e** and **1h**, with nitrosobenzene proceeded smoothly to give the corresponding 2,5-dihydro-1,2,4-oxadiazoles, **2b**—**2e** and **2h**, in high yield (Table 1). It is interesting that not only 5-alkoxyoxazoles **1a**—**1e** and **1h**, but also 5-methyloxazole **1i** underwent the same type of reaction to give **2i** in moderate yield.

The ^{13}C NMR spectra of the imino carbon C-3, (160.20—166.13 ppm), C-5 (97.82—107.28 ppm), and carbonyl carbon (166.73–204.65 ppm) of the products, **2b**—**2e**, **2h**, and **2i**, obviously indicate that the adducts are not Diels–Alder adducts, but the same type of formal [3+2] products as **2a** (Table 2). Especially, the signals of C-5 of products **2e** (d, 98.71 ppm) and **2h** (d, 97.82 ppm) having $R^2 = H$ strongly suggest that the structure does not have the CH=N moiety of normal Diels–Alder adducts **3e** and **3h**, because the off-resonance spectra of those carbons was observed as a doublet. The upfield shift of R^1 (Table 3) also well supports that the reactions are exclusively regioselective as well as the reaction of **1a**. The 3-Me groups of dihydrooxadiazoles **2c**, **2h**, and **2i** were observed more up-field (1.93—1.94 ppm) than that of dihydrotriazoles **4a** and **4c** (2.38—2.46 ppm) and

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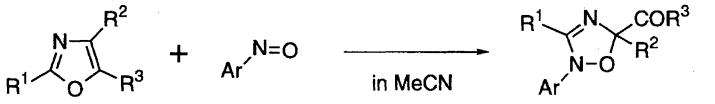
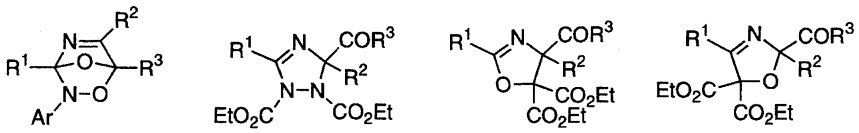


1

2: Ar = Ph
7: Ar = *p*-ClC$_6$H$_4$
8: Ar = *p*-MeC$_6$H$_4$

a: R^1 = Me, R^2 = *p*-NO$_2$C$_6$H$_4$, R^3 = OMe
b: R^1 = *p*-MeC$_6$H$_4$, R^2 = *p*-NO$_2$C$_6$H$_4$, R^3 = OMe
c: R^1 = Me, R^2 = Me, R^3 = OMe
d: R^1 = nonyl, R^2 =CO$_2$Et, R^3 = OEt
e: R^1 = *p*-MeOC$_6$H$_4$, R^2 = H, R^3 = OMe
f: R1 = *p*-MeOC$_6$H$_4$, R^2 = Ph, R^3 = OMe
g: R^1 = *p*-MeOC$_6$H$_4$, R^2 = Me, R^3 = OMe
h: R^1 = Me, R^2 = H, R^3 = OEt
i: R^1 = Me, R^2 = Me, R^3 = Me



3 **4** **5** **6**

Scheme 1.

Table 1. Reactions of Oxazoles **1** with Nitrosobenzene, 1-Chloro-4-nitrosobenzene, and 1-Methyl-4-nitrosobenzene[a)]

Oxazole **1**	Nitroso compound	Temp/°C	Time/h	Product	Yield/%
1a	Nitrosobenzene	R.T.[b)]	16.5	**2a**	98
1b	Nitrosobenzene	R.T.[b)]	118	**2b**	70 (96)[c)]
1c	Nitrosobenzene	R.T.[b)]	1.5	**2c**	65
1d	Nitrosobenzene	Reflux[b)]	48	**2d**	61 (87)[c)]
1e	Nitrosobenzene	R.T.	72	**2e**	93
1h	Nitrosobenzene	R.T.[b)]	9	**2h**	80
1i	Nitrosobenzene	R.T.[b)]	52	**2i**	50
1c	1-Chloro-4-nitrosobenzene	R.T.	1	**7c**	38
1e	1-Chloro-4-nitrosobenzene	R.T.	44	**7e**	93
1f	1-Chloro-4-nitrosobenzene	R.T.	2	**7f**	100
1g	1-Chloro-4-nitrosobenzene	R.T.	0.5	**7g**	99
1f	1-Methyl-4-nitrosobenzene	R.T.	21	**8f**	98
1h	1-Methyl-4-nitrosobenzene	R.T.	21	**8h**	87
1i	1-Methyl-4-nitrosobenzene	R.T.	48	**8i**	29

a) The reaction was carried out using 1.5 molar amount of nitroso compound in dry acetonitrile under nitrogen atmosphere unless otherwise noted. b) Equimolar amount of nitrosobenzene was used. c) Yield based on the consumed oxazole.

dihydrooxazoles **5a** and **6a** (2.30—2.37 ppm). The aromatic protons (R^1 =*p*-MeC$_6$H$_4$) of **2b** (Ar, 7.11 and 7.63 ppm) were observed more up-field compared with that of **4b** (Ar, 7.24 and 7.77 ppm). The upfield shift of the aromatic protons (R^1 =*p*-MeOC$_6$H$_4$) of **2e** (Ar, 6.79 and 7.67 ppm) was also observed in comparison with that of **5e** (Ar, 6.92 and 7.99 ppm).

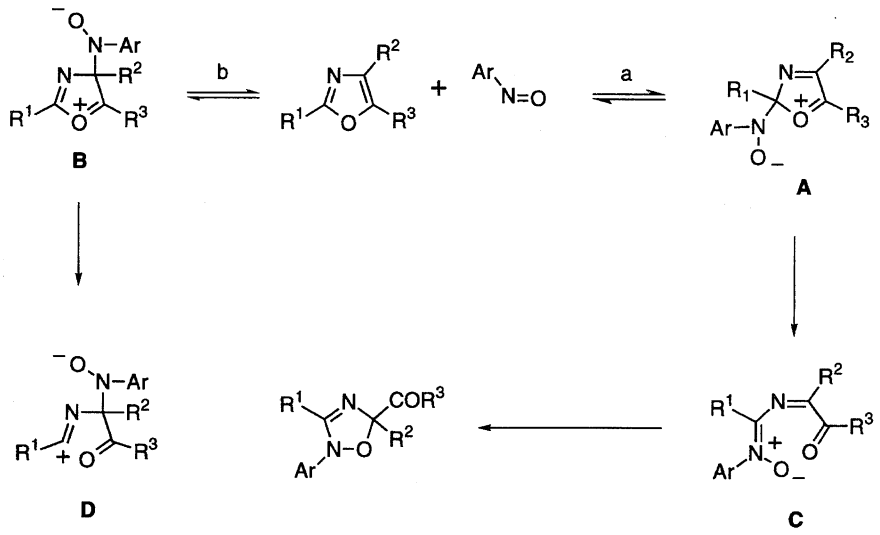
It is interesting to point out that the regioselectivity is extremely independent of the substituent at the 2- and 4-positions of oxazole in comparison with that for the reactions with diethyl oxomalonate.[6)] For example, under thermal conditions, the reaction of oxazole **1h** with diethyl oxomalonate gives a 1 : 1.2 ratio of regio-isomers.[5)] The high regioselectivity of the reaction with nitrosobenzene derivatives may be explained by considering that the initial step of the reaction is in equilibrium (Scheme 2); a nucleophilic attack of oxazole to nitroso compounds is possible in two ways (path a and path b) by attacking the 2- and 4-positions of oxazole to produce zwitterion intermediates **A** and **B**, respectively. Because imino nitron intermediate **C** is much more stable than intermediate **D**, the resulting zwitterion intermediate **A** easily undergoes a ring opening of oxazole to give intermediate **C**, affording the adducts by cyclization. Thus, the regioselectivity is probably only controlled by the stability of the intermediates, not by the bulkiness of the substituents.

Reaction of Oxazoles with *p*-Substituted Nitrosoben-

Table 2. ^{13}C NMR Spectra of 2,5-Dihydro-1,2,4-oxadiazoles **2**, **7**, and **8**[a)]

Adduct	C=N	C-5	C=O
2a	161.83	104.79	168.73
	(q, $^2J_{C-H}$ = 6.9 Hz)	(t, $^3J_{C-H}$ = 3.7 Hz)	(q, $^3J_{C-H}$ = 4.1 Hz)
2b	162.98	106.10	168.86
2c	160.69	103.95	170.22
	(q, $^2J_{C-H}$ = 6.9 Hz)	(q, $^3J_{C-H}$ = 5.5 Hz)	
2d	166.13	103.51	166.73
2e	162.72	98.71 (d)	168.52
2h	161.79	97.82 (d)	167.99
2i	160.20	107.28	204.65
7c	160.37	104.05	170.06
	(q, $^2J_{C-H}$ = 6.7 Hz)	(q, $^2J_{C-H}$ = 4.9 Hz)	
7e	162.46	98.65	168.41
7f	162.82, 162.35[b)]	107.02	169.80
8f	162.06, 162.23[b)]	106.66	170.02
8h	162.16	97.65	168.03
8i	160.74	107.13	204.98

a) Chemical shifts were listed in δ/ppm unit. b) The chemical shift of C-4 of *p*-$MeOC_6H_4$ was also shown.



Scheme 2.

zene. (2-Substituted and/or 4-substituted 5-alkoxy- and 5-methyl)oxazoles **1a**—**1h** also reacted with 1-chloro- and 1-methyl-4-nitrosobenzenes to give 2,5-dihydro-1,2,4-oxadiazoles in high-to-moderate yield (Table 1). The ^{13}C NMR spectra of imino carbon, C-5, and the carbonyl carbon suggest that the products have 2,5-dihydro-1,2,4-oxadiazole structures (Table 2). All of the reactions with 1-chloro- and 1-methyl-4-nitrosobenzenes were also exclusively regioselective. Those products were found to possess the same regiochemistry as that of the 2,5-dihydro-1,2,4-oxadiazole **2a** due to the fact that R^1 of **2** shows a similar upfield shift (Table 3). The regioselectivity is also extremely independent of the electronic character of *p*-substituents of nitrosobenzene derivatives.

In conclusion, this novel reaction of oxazoles with nitrosobenzene and its derivatives provides a new route to the synthesis of 2,5-dihydro-1,2,4-oxadiazole heterocycles. The high regioselectivity of the reaction could be explained by a stepwise mechanism containing an imino nitron intermediate.

Experimental

General. The melting points were determined on a Yanagimoto melting-point apparatus and are uncorrected. The IR spectra were taken with a Perkin–Elmer (model 983) spectrometer. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz), a JEOL GX-500 (500 MHz), a JEOL GSX-400 (400 MHz) or JEOL EX-270 instrument (270 MHz), and ^{13}C NMR on a JEOL GX-500, a JEOL GSX-400 or JEOL EX-270 spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra were measured with a JEOL JMS-DX303 mass spectrometer. Elemental analyses were performed on a Yanaco CHN corder MT-3. For preparative column chromatography, Wakogel C-300 and Silica gel 60 (Merck) were employed. Medium-pressure liquid chromatography was carried out on Yamazen No. 540 pump using a column packed with Silica gel 60 (Merck, size 0.040—0.063 mm). The solvents were evap-

Table 3. ^{1}H NMR Spectra of 2,5-Dihydro-1,2,4-oxadiazoles **2**, **7**, and **8**[a)]

Adduct	R^1	R^2	R^3
2a	1.99 (Me, s)	7.87 (Ar, ABq, J = 8.9 Hz) 8.26	3.82 (OMe, s)
2b	7.11 (Ar, ABq, J = 8.3 Hz) 7.63	7.87 (Ar, ABq, J = 8.9 Hz) 8.22	3.79 (OMe, s)
2c	1.93 (Me, s)	1.80 (Me, s)	3.83 (OMe, s)
2d	2.18 (CH_2, t, J = 7.8 Hz)	1.34 (Me of OEt, t, J = 7.1 Hz) 4.30—4.40 (CH_2 of OEt, m)	
2e	6.79 (Ar, ABq, J = 8.9 Hz) 7.67	6.23 (5-H, s)	3.76, 3.81 (OMe, s)[b)]
2h	1.94 (Me, s)	6.10 (5-H, q, J = 1.2 Hz)	1.35 (Me of OEt, t, J = 7.1 Hz) 4.28—4.35 (CH_2 of OEt, m)
2i	1.94 (Me, s)	1.67 (Me, s)	2.37 (Me, s)
7c	1.94 (Me, s)	1.80 (Me, s)	3.84 (OMe, s)
7e	6.82 (Ar, ABq, J = 8.9 Hz) 7.65	6.27 (5-H, s)	3.78, 3.82 (OMe, s)[b)]
7f	6.80 (Ar, ABq, J = 8.9 Hz), 7.70	7.15—7.39 (Ph, m) 7.65—7.70	3.74, 3.75 (OMe, s)[b)]
7g	6.82 (Ar, ABq, J = 8.9 Hz) 7.65	1.83 (Me, s)	3.76 (OMe, s)[b)]
8f	6.73 (Ar, ABq, J = 8.6 Hz) 7.67—7.73	7.24—7.36 (Ph, m) 7.67—7.73	3.61, 3.69 (OMe, s)[b)]
8h	1.90 (Me, d, J = 1.0 Hz)	6.09 (5-H, q, J = 1.0 Hz)	1.34 (Me of OEt, t, J = 7.3 Hz) 4.30 (CH_2 of OEt, m)
8i	1.91 (Me, s)	1.67 (Me, s)	2.35, 2.37 (Me, s)
4a	2.46 (Me, s)	7.82 (Ar, ABq, J = 8.9 Hz) 8.21	3.77 (OMe, s)
4b	7.24 (Ar, ABq, J = 7.9 Hz), 7.77	7.90 (Ar, ABq, J = 9.0 Hz) 8.25	3.75 (OMe, s)
4c	2.38 (Me, s)	1.72 (Me, s)	3.39 (OMe, s)
5a	2.30 (Me, s)	7.90 (Ar, ABq, J = 9.0 Hz) 8.19	3.71 (OMe, s)
6a	2.37 (Me, s)	7.93 (Ar, ABq, J = 8.9 Hz) 8.23	3.75 (OMe, s)
5e	6.92 (Ar, ABq, J = 8.9 Hz) 7.99	5.56 (4-H, s)	3.77, 3.85 (OMe, s)[b)]
5g	6.93 (Ar, ABq, J = 8.9 Hz) 7.98	1.68 (Me, s)	3.69, 3.85 (OMe, s)[b)]

a) Chemical shifts (δ/ppm) and coupling constants were listed. b) The chemical shift of *p*-MeOC$_6$H$_4$ was also shown.

orated with a Tokyo Rikakikai rotary evaporator at about 40 °C. All of the reactions were carried our under an argon atmosphere in dried glassware.

Materials and Solvents. 4-(*p*-Nitrophenyl)oxazoles **1a** and **1b** were prepared by the BF_3-catalyzed reaction of methyl (*p*-nitrophenyl)diazoacetate with the corresponding nitriles.[11)] 5-Methoxy- or 5-ethoxyoxazoles **1c**—**1h** were synthesized by dehydrocyclization of the corresponding *N*-acylglycine or *N*-acylalanine esters.[12)] 1-Chloro-4-nitrosobenzene and 1-methyl-4-nitrosobenzene were prepared by methods described in the literature.[13)] Commercially available 2,4,5-trimethyloxazole (**1i**) and nitrosobenzene were used without further purification.

Acetonitrile was purified by distillation, first from P_2O_5 and then from CaH_2.

General Procedure of the Reaction of Oxazole 1 with Nitrosobenzenes. To a solution of oxazole **1** (1.0 mmol) in dry acetonitrile (5 mL) was added nitrosobenzene (1.0—1.5 mmol), 1-chloro-4-nitrosobenzene (1.5 mmol), or 1-methyl-4-nitrosobenzene (1.5 mmol) in dry acetonitrile (5 mL); the mixture was stirred at room temperature for the times listed in Table 1. After evaporation of acetonitrile in vacuo, the residue was separated by medium-pressure column chromatography on silica gel by using ethyl acetate—hexane as an eluent to give 2,5-dihydro-1,2,4-oxadiazoles. The eluents used are as follows: **2a**, **2b**, **2c**, **2e**, and **2i**: hexane–ethyl acetate (4 : 1 v/v); **2d**: hexane–ethyl acetate (19 : 1 v/v); **2h**: hexane–ethyl acetate (17 : 3 v/v); **7c**: hexane–ethyl acetate (37 : 3 v/v); **7e** and **7f**: hexane–ethyl acetate (9 : 1 v/v); **7g**: hexane–ethyl acetate (47 : 3 v/v); **8f**: hexane–ethyl acetate (187 : 17 v/v); **8h**: hexane–ethyl acetate (93 : 7 v/v); **8i**: hexane–ethyl acetate (22 : 1 v/v).

5-Methoxycarbonyl-3-methyl-5-(*p*-nitrophenyl)-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2a): Yellow viscous oil; IR (Neat) 1750 (C=O), 1639 (C=N), 1593, 1522, 1488, 1382, 1351, 1316, 1300, 1283, 1251, 1107, 1025, 855, 754, and 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.99 (3H, s, 3-Me), 3.82 (3H, s, OMe), 7.33—7.44 (5H, m, Ph), 7.87 (2H, dt, J = 8.9 Hz, J = 2.3 Hz, Ar-H), 8.26 (2H, dt, J = 8.9 Hz, J = 2.3 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.34 (q, 3-Me), 53.41 (q, OMe), 104.79 (t, $^3J_{C-H}$ = 3.7 Hz, 5-C), 123.62, 124.53, 127.28, 129.55 (each d, *o*-, *m*-C of Ar and Ph), 128.78 (d, *p*-C of Ph), 140.97 (s, 1-C of Ph), 145.63 (t, $^3J_{C-H}$ = 7.8 Hz, 4-C of Ar), 148.36 (s, 1-C of Ar), 161.83 (q,

$^2J_{C-H}$ = 6.9 Hz, 3-C), 168.73 (q, $^3J_{C-H}$ = 4.1 Hz, CO_2Me). Found; C, 59.86; H, 4.50; N, 12.31%. Calcd for $C_{17}H_{15}O_5N_3$: C, 59.82; H, 4.43; N, 12.31%.

5-Methoxycarbonyl-5-(*p*-nitrophenyl)-2-phenyl-3-(*p*-tolyl)-2,5-dihydro-1,2,4-oxadiazole (2b): Pale yellow needles; mp 129.5—132.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.31 (3H, s, Me), 3.79 (3H, s, OMe), 7.11 (2H, d, J = 8.3 Hz, Ar-H), 7.23—7.31 (5H, m, Ph-H), 7.63, (2H, d, J = 8.3 Hz, Ar-H), 7.87 (2H, dt, J = 8.9 Hz, J = 2.3 Hz, Ar-H), 8.22 (2H, dt, J = 8.9 Hz, J = 2.3 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 21.53 (Me), 53.40 (OMe), 106.10 (5-C), 123.53, 123.75, 127.26, 127.41, 129.20, 129.26, 129.30, 129.43, 142.61, 143.12, 146.22, 148.25, (Ar and Ph), 162.98 (3-C), 168.86 (CO_2Me). Found: C, 65.89; H, 4.75; N, 9.95%. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07%.

5-Methoxycarbonyl-3,5-dimethyl-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2c): Pale yellow oil; IR (Neat) 1745 (C=O), 1643 (C=N), 1593, 1488, 1445, 1382, 1267, 1194, 1133, and 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.80 (3H, s, 5-Me), 1.93 (3H, s, 3-Me), 3.83 (3H, s, OMe), 7.28—7.42 (5H, m, Ph); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.38 (q, 5-Me), 24.11 (q, 3-Me), 52.77 (q, OMe), 103.95 (q, $^2J_{C-H}$ = 5.5 Hz, 5-C), 123.95, 128.02, 129.34 (each d, *o*-, *m*-, *p*-C of Ph), 141.38 (s, 1-C of Ph), 160.69 (q, $^2J_{C-H}$ = 6.9 Hz, 3-C), 170.22 (s, CO_2Me). Found; C, 60.90; H, 5.99; N, 12.07%. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.53; H, 6.02; N, 11.96%.

5,5-Bis(ethoxycarbonyl)-3-nonyl-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2d): Pale yellow oil; IR (Neat) 2924, 2855, 1750 (C=O), 1636 (C=N), 1593, 1489, 1465, 1367, and 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.87 (3H, t, J = 7.3 Hz, Me of nonyl), 1.21—1.37 (12H, m, CH_2 of nonyl), 1.34 (6H, t, J = 7.1 Hz, Me of OEt), 1.61—1.69 (2H, m, CH_2 of nonyl), 2.18 (2H, t, J=7.8 Hz, CH_2 of nonyl), 4.30—4.40 (4H, m, CH_2 of OEt), 7.33—7.45 (5H, m, Ph-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 14.03, 14.06 (each Me of OEt), 22.65, 26.41, 26.81, 28.92, 29.09, 29.21, 29.35, 31.86 (each, CH_2 of nonyl), 62.56 (CH_2 of OEt), 103.51 (5-C), 125.43, 128.96, 129.42 (*o*-, *m*-, *p*-C of Ph), 141.27 (1-C of Ph), 166.13, 166.73 (3-C and CO_2Et). No satisfactory analytical result was obtained due to the instability of **2d**.

5-Methoxycarbonyl-3-(*p*-methoxyphenyl)-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2e): Yellow viscous oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 3.76 (3H, s, OMe), 3.81 (3H, s, OMe), 6.28 (1H, s, 5-H), 6.79 (2H, dt, J = 8.9 Hz, J = 2.8 Hz, Ar-H), 7.24—7.38 (5H, m, Ph-H), 7.67 (2H, dt, J = 8.9 Hz, J = 2.8 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 52.70, 55.32 (each q, each OMe), 98.71 (d, 5-C), 113.96, 127.07, 128.83, 129.34, 131.01 (each d, *o*-, *m*-, *p*-C of Ar and Ph), 119.21 (t, $^3J_{C-H}$ = 7.8 Hz, 1-C of Ar), 143.97 (s, 1-C of Ph), 162.34 (s, 4-C of Ar), 162.72 (dt, $^3J_{C-H}$ = 4.1 Hz, $^3J_{C-H}$ = 4.1 Hz, 3-C), 168.52 (dq, $^2J_{C-H}$ = 0.92 Hz, $^3J_{C-H}$ = 3.7 Hz, CO_2Me). Found: C, 65.44; H, 5.29; N, 9.18%. Calcd for $C_{17}H_{16}O_4N_2$: C, 65.38; H, 5.16; N, 8.97%.

5-Ethoxycarbonyl-3-methyl-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2h): Yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.35 (3H, t, J = 7.1 Hz, Me of OEt), 1.94 (3H, d, J = 1.2 Hz, 3-Me), 4.28—4.35 (2H, m, CH_2 of OEt), 6.10 (1H, q, J = 1.2 Hz, 5-H), 7.28—7.46 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.26, 14.12 (each Me), 61.94 (CH_2 of OEt), 97.82 (5-C), 124.35, 128.30, 129.37, (*o*-, *m*-, *p*-C of Ph), 141.96 (1-C of Ph), 161.79 (3-C), 167.99 (CO_2Et). Found; C, 61.75; H, 6.17; N, 11.93%. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96%.

5-Acetyl-3,5-dimethyl-2-phenyl-2,5-dihydro-1,2,4-oxadiazole (2i): Pale yellow liquid; IR (Neat) 1725 (C=O), 1642 (C=N), 1593, 1488, 1354, 1280, 766, and 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.67 (3H, s, 5-Me), 1.94 (3H, s, 3-Me), 2.37 (3H, s, COMe), 7.28—7.43 (5H, m, Ph-H); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ = 13.47 (3-Me), 22.58 (5-Me), 24.74 (COMe), 107.28 (5-C), 123.76, 128.02, 129.44 (*o*-, *m*-, *p*-C of Ph), 141.77 (1-C of Ph), 160.20 (3-C), 204.65 (COMe). Found: C, 66.27; H, 6.68; N, 12.79%. Calcd for $C_{12}H_{14}O_2N_2$: C, 66.04; H, 6.47; N, 12.84%.

2-(*p*-Chlorophenyl)-5-methoxycarbonyl-3,5-dimethyl-2,5-dihydro-1,2,4-oxadiazole (7c): Yellow viscous oil; IR (neat) 3479, 2996, 2951, 1744 (C=O), 1645 (C=N), 1486, 1442, 1380, 1263, 1134, 1013, 839, and 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 1.80 (3H, s, Me), 1.94 (3H, s, Me), 3.84 (3H, s, OMe), 7.30—7.40 (4H, m, *p*-ClC_6H_4); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 13.35 (q, Me), 24.03 (q, Me), 52.92 (q, OMe), 104.05 (q, $^2J_{C-H}$ = 4.9 Hz, 5-C), 125.01, 129.51 (each d, *o*, *m*-C of *p*-ClC_6H_4), 133.53, 140.20 (each s, 1,4-C of *p*-ClC_6H_4), 160.37 (q, $^2J_{C-H}$ = 6.7 Hz, 3-C), 170.06 (s, CO_2Me). Found: *m/z* 268.0601. Calcd for $C_{12}H_{13}O_3N_2Cl$: M, 268.0615.

2-(*p*-Chlorophenyl)-5-methoxycarbonyl-3-(*p*-methoxyphenyl)-2,5-dihydro-1,2,4-oxadiazole (7e): Yellow viscous oil; IR (KBr) 3323, 2951, 2839, 1750 (C=O), 1687 (C=N), 1609, 1571, 1511, 1485, 1438, 1422, 1307, 1261, 1214, 1175, 1090, 1027, 1015, and 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 3.78 (3H, s, OMe), 3.82 (3H, s, OMe), 6.27 (1H, s, 5-H), 6.82 (2H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$), 7.26—7.33 (4H, m, *p*-ClC_6H_4), 7.65 (2H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 52.81 (q, OMe), 55.34 (q, OMe), 98.65 (d, 5-C), 114.06, 128.31, 129.55, 130.98 (each d, *o*, *m*-C of Ar), 118.70 (t, $^2J_{C-H}$ = 7.9 Hz, 1-C of *p*-$MeOC_6H_4$), 134.62 (s, *p*-ClC_6H_4), 142.47 (s, *p*-ClC_6H_4), 162.46 (s, 4-C, of *p*-$MeOC_6H_4$ and 3-C), 168.41 (q, $^3J_{C-H}$ = 3.7 Hz, CO_2Me). Found; *m/z* 346.0711. Calcd for $C_{17}H_{15}O_4N_2Cl$: M, 346.0720.

2-(*p*-Chlorophenyl)-5-methoxycarbonyl-3-(*p*-methoxyphenyl)-5-phenyl-2,5-dihydro-1,2,4-oxadiazole (7f): Yellow viscous oil; IR (KBr) 3424, 1746 (C=O), 1622 (C=N), 1607, 1510, 1485, 1448, 1333, 1306, 1258, 1174, 1086, 1029, 1015, and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 3.74 (3H, s, OMe), 3.75 (3H, s, OMe), 6.80 (2H, dt, J = 8.9, 2.0 Hz, *p*-$MeOC_6H_4$), 7.15—7.39 (7H, m, *p*-ClC_6H_4, Ph-H), 7.65—7.70 (2H, m, Ph-H), 7.70 (2H, dt, J = 8.9, 3.0 Hz, *p*-$MeOC_6H_4$); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 53.11 (q, OMe), 55.28 (q, OMe), 107.02 (t, $^3J_{C-H}$ = 3.7 Hz, 5-C), 113.96, 125.93, 128.34, 128.39, 128.95, 129.43, 131.04 (each d, *o*, *m*-C of Ar, *o*, *m*, *p*-C of Ph), 134.42 (s, *p*-ClC_6H_4), 118.87 (t, $^2J_{C-H}$ = 7.9 Hz, 1-C of *p*-$MeOC_6H_4$), 139.15 (t, $^2J_{C-H}$ = 6.7 Hz, 1-C of Ph), 142.24 (t, $^2J_{C-H}$ = 7.3 Hz, *p*-ClC_6H_4), 161.82 (t, $^3J_{C-H}$ = 3.7 Hz, 3-C), 162.35 (s, 4-C of *p*-$MeOC_6H_4$), 169.80 (q, $^3J_{C-H}$ = 3.7 Hz, CO_2Me). Found; *m/z* 422.1060. Calcd for $C_{23}H_{19}O_4N_2Cl$: M, 422.1033.

2-(*p*-Chlorophenyl)-5-methoxycarbonyl-3-(*p*-methoxyphenyl)-5-methyl-2,5-dihydro-1,2,4-oxadiazole (7g): Yellow viscous oil; IR (neat) 3466, 3000, 2950, 2839, 1750 (C=O), 1627 (C=N), 1509, 1255, 1026, 980, 884, 838, 767, and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 1.83 (3H, s, Me), 3.76 (6H, s, OMe), 6.82 (2H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$), 7.21—7.29 (4H, m, *p*-ClC_6H_4), 7.65 (2H, d, J = 8.9 Hz, *p*-$MeOC_6H_4$). Found: *m/z* 360.0865. Calcd for $C_{18}H_{17}O_4N_2Cl$: M, 360.0877.

5-Methoxycarbonyl-3-(*p*-methoxyphenyl)-5-phenyl-2-(*p*-tolyl)-2,5-dihydro-1,2,4-oxadiazole (8f): Yellow viscous oil; IR (KBr) 3453, 2951, 1745 (C=O), 1622 (C=N), 1607, 1570, 1510, 1448, 1421, 1334, 1306, 1257, 1173, 1120, 1104, 1091, 1069, 1030, 841, 760, and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 2.18 (3H, s, Me), 3.61 (3H, s, OMe), 3.69 (3H, s, OMe), 6.73 (2H, d, J = 8.6 Hz, *p*-$MeOC_6H_4$), 6.99 (2H, d, J = 8.6 Hz, *p*-MeC_6H_4), 7.14 (2H, d, J = 8.6 Hz, *p*-MeC_6H_4), 7.24—7.36 (3H, m, Ph), 7.67—7.73 (4H, m, Ph and *p*-$MeOC_6H_4$); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ = 21.01

(Me), 52.89, 55.11 (each OMe), 106.66 (5-C), 113.74, 119.14, 125.92, 127.38, 128.27, 128.75, 129.86, 130.97, 139.04, 139.51, 141.04, 162.06, 162.23, (Ph, Ar and 3-C), 170.02 (CO_2Me). Found: *m/z* 402.1588. Calcd for $C_{24}H_{22}O_4N_2$: M, 402.1580.

5-Ethoxycarbonyl-3-methyl-2-(*p*-tolyl)-2,5-dihydro-1,2,4-oxadiazole (8h): Yellow viscous oil; IR (KBr) 3443, 3395, 2921, 1752 (C=O), 1643 (C=N), 1505, 1382, 1294, 1205, 1029, and 823 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) $\delta = 1.34$ (3H, t, $J = 7.3$ Hz, Me of OEt), 1.90 (3H, d, $J = 1.0$ Hz, Me), 2.35 (3H, s, Me), 4.30 (2H, qd, $J = 6.9$ Hz, 1.7 Hz, CH_2 of OEt), 6.09 (1H, q, $J = 1.0$ Hz, 5-H), 7.20 (2H, d, $J = 8.3$ Hz, *p*-MeC_6H_4), 7.34 (2H, d, $J = 8.3$ Hz, *p*-$MeOC_6H_4$); ^{13}C NMR ($CDCl_3$, 67.80 MHz) $\delta = 13.16$, 14.10, 21.10 (each Me), 61.86 (CH_2 of OEt), 97.65 (5-C), 124.83, 129.95, 138.62, 139.38 (each Ar), 162.16 (3-C), 168.03 (CO_2Et). Found: *m/z* 248.1153. Calcd for $C_{13}H_{16}O_3N_2$: M, 248.1161.

5-Acetyl-3,5-dimethyl-2-(*p*-tolyl)-2,5-dihydro-1,2,4-oxadiazole (8i): Yellow viscous oil; IR (neat) 2991, 2929, 1725 (C=O), 1670, 1640 (C=N), 1608, 1582, 1540, 1505, 1422, 1380, 1354, 1316, 1295, 1276, 1244, 1187, 1112, 1041, and 821 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) $\delta = 1.67$ (3H, s, Me), 1.91 (3H, s, Me), 2.35 (3H, s, Me), 2.37 (3H, s, Me), 7.22 (4H, brs, Ar-H); ^{13}C NMR ($CDCl_3$, 67.80 MHz) $\delta = 13.42$, 21.12, 22.61, 24.78 (each Me), 107.13 (5-C), 124.47, 130.04, 138.52, 139.20 (each Ar), 160.74 (3-C), 204.98 (COMe). Found: *m/z* 232.1229. Calcd for $C_{13}H_{16}O_2N_2$: M, 232.1212.

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

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