Microwave Accelerated Cycloaddition Reactions of Nitrile Oxides and Allylic Alcohols

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The application of microwaves in promoting the cycloaddition reactions of allyl alcohols with nitrile oxides using a domestic microwave oven and a focused monomode microwave reactor have demonstrated that not only was the reaction time substantially reduced, but also the reaction yields were significantly improved over the conventional stirred reactions. Microwave irradiation alters the regioselectivity of the cycloaddition reaction which favors the non-hydrogen-bond directed cycloadduct, isoxazoline **4**.

Substituted Δ^2-isoxazolines, resulting from 1,3-dipolar cycloaddition of nitrile oxides to olefins, are versatile intermediates for the synthesis of a wide variety of useful compounds[1] including 1,3-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles, unsaturated oximes, and β-hydroxy esters, which are often used in the total synthesis of natural products.[2] We have reported recently the 1,3-dipolar cycloaddition reactions of nitrile oxides with 1,3-dioxolanes of α,β-unsaturated aldehydes[3] and have successfully enhanced the reactivity of the reaction by employing ultrasound irradiation.[4] The application of microwaves in promoting organic reactions has received intense attention recently.[5] Inspired by the immense potential of rate acceleration of organic reactions by microwave, we hope to be able to improve the reactivity of the cycloaddition reaction by applying microwave technology. Herein, we wish to report a highly efficient microwave-promoted 1,3-dipolar cycloaddition reaction of nitrile oxides to allylic alcohols.

The cycloaddition reaction of 2-cyclopenten-1-ol with benzonitrile oxide was reported by Curran.[6] A regioselectivity of 67:33 was achieved in favor of the hydrogen-bond directed regioisomer when the reaction was performed in benzene. In reacting allyl alcohol with benzonitrile oxide using Curran's conditions, the dimerization of nitrile oxide must be kept to a minimum to achieve high yield for the cycloaddition reaction. Consequently, a search was made initially for the optimum rate of formation of the nitrile oxide. As shown in Scheme I,

Scheme I

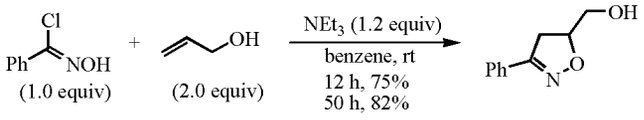
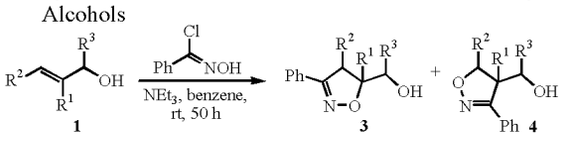


Table 1. Cycloaddition Reactions of Benzonitrile Oxide with Allyl Alcohols



Entry	Alcohol **1** R^1	R^2	R^3	Yield (%)	Ratio[a] **3** : **4**
1	H	H	H	82	100:0
2	H	CH_3	H	53	68:32
3	H	(*Z*)-C_2H_5	H	46	60:40
4	H	(*E*)-C_2H_5	H	56	60:40
5	H	(*Z*)-C_3H_7	H	40	63:37
6	H	(*E*)-C_3H_7	H	54	57:43
7	H	Ph	H	43	34:66
8	CH_3	H	H	84	100:0
9	H	H	CH_3	71	100:0
10	H	H	C_2H_5	80	100:0
11	H	$-CH_2CH_2-$		78	67:33

[a] Determined by GC-MS analysis of the crude reaction mixture.

when benzonitrile oxide was generated over 50 h the reaction afforded a higher yield than that of 12 h.

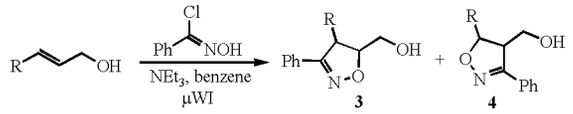
As summarized in Table 1, the cycloaddition reactions of benzonitrile oxide with a series of allyl alcohols provided cycloadducts in moderate to good yields. (*E*)-1,2-Disubstuted allylic alcohols afforded higher yields than the corresponding (*Z*)-1,2-disubstuted allylic alcohols did. Monosubstituted dipolaropohiles gave a single cycloadduct **3** as the only product while 1,2-disubstuted dipolarophiles yielded two regioisomeric adducts **3** and **4** with regioselectivities ranging from 68:32 to 57:43 in favor of the hydrogen-bond directed regioisomer except in the case of isoxazolines derived from cinnamyl alcohol (34:66).

The acceleration by microwave irradiation in the

Dedicated to the memory of the late Pro Ta-shue Chou (

cycloaddition reaction of allyl alcohols with benzonitrile oxide was then studied using a domestic microwave oven. The power[8] and the duration[9] of irradiation were systematically varied to optimize the reaction yields. The results compiled in Table 2 indicate that the best reaction conditions for allyl alcohol and cinnamyl alcohol involve irradiation at 70 W for 2 minutes (Method B) or at 400 W for 30 seconds (Method C), respectively. Such protocols were applied to the cycloaddition reaction of differently substituted allylic alcohols with benzonitrile oxide.

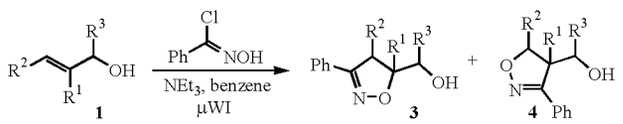
Table 2. Influence of Microwave Power And Reaction Time on Reaction Yields



μWI: microwave irradiation

Power (W)	R	Time	Yield (%)
70	H	1.0 m	82
70	H	2.0 m	83
70	Ph	2.0 m	55
70	Ph	4.0 m	74
70	Ph	8.0 m	73
400	Ph	30 s	90
400	Ph	1.0 m	50
400	Ph	2.0 m	61
520	Ph	15 s	56
520	Ph	30 s	78
520	Ph	1.0 m	82

Table 3. Microwave Promoted Cycloaddition Reactions of Benzonitrile Oxide and Allyl Alcohols



Entry	Alcohol **1** R^1	R^2	R^3	Method[a]	Yield (%)	Ratio[b] **3**:**4**
1	H	H	H	B	82	100:0
2	H	H	H	C	60	100:0
3	H	CH_3	H	B	15	55:45
4	H	CH_3	H	C	23	56:44
5	H	(*Z*)-C_2H_5	H	B	32	45:55
6	H	(*Z*)-C_2H_5	H	C	25	46:54
7	H	(*E*)-C_2H_5	H	B	48	48:52
8	H	(*E*)-C_2H_5	H	C	29	43:57
9	H	(*Z*)-C_3H_7	H	B	28	46:54
10	H	(*Z*)-C_3H_7	H	C	32	42:58
11	H	(*E*)-C_3H_7	H	B	53	46:54
12	H	(*E*)-C_3H_7	H	C	43	46:54
13	H	Ph	H	B	55	19:81
14	H	Ph	H	C	64	24:76
15	CH_3	H	H	B	90	100:0
16	CH_3	H	H	C	71	100:0
17	H	H	CH_3	B	59	100:0
18	H	H	CH_3	C	70	100:0
19	H	H	C_2H_5	B	84	100:0
20	H	H	C_2H_5	C	85	100:0
21	H	$-CH_2CH_2-$		B	77	50:50
22	H	$-CH_2CH_2-$		C	59	50:50

[a] Method B: 70 W, 2 min. Method C: 400 W, 30 s.
[b] Determined by GC-MS analysis of the crude reaction mixture.

As shown in Table 3, except for the 1,2-dialkyl substituted ones, the cycloaddition reaction of the allylic alcohols with benzonitrile oxide furnished the desired isoxazolines in higher yields than the conventional method, and the reaction time was considerably shortened.

The yields and regioselectivities of the cycloaddition reactions of benzonitrile oxide and allyl alcohols under conventional stirring and microwave assisted conditions are compared in Table 4.

The following observations can be made:

1. Monosubstituted and 1,1-disubstituted allylic alcohols gave the hydrogen-bond directed, 5-substituted, isoxazoline **3** as the sole cycloadduct (Table 4, entries 1, 8-10). In addition, the yields are across the board higher than the combined yields of two regioisomers of the 1,2-disubstituted allylic alcohols.

2. The percentage of the non-hydrogen-bond directed cycloadduct, isoxazoline **4**, increases as the size of the R^2 substituent increases (Table 4, entries 3-6). Microwave irradiation seems to further enhance the trend.

3. In contrast to alkyl substituted allylic alcohols, the non-hydrogen-bond directed regioisomer, isoxazoline **4g**, is the major cycloadduct. The preference is more profound in microwave accelerated reactions.

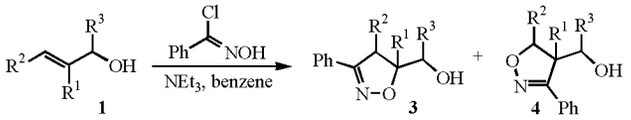
4. (*E*)-1,2-Dialkyl substituted allylic alcohols (Table 4, entries 4 and 6) gave the cycloadducts in higher yields than the (*Z*)-1,2-dialkyl substituted allylic alcohols did (Table 4, entries 3 and 5).

In order to improve the yields of 1,2-alkyl-disubstituted allylic alcohols, the irradiation time of these dipolarophiles with benzonitrile oxide was extended from 30 seconds to 90 seconds using 400 W of microwave power. The results in Table 5 clearly show that the yields have been all improved to the same level as those of the conventional method but with less than 1/2000 of the reaction time of the conventional method.

Structural identification of the known cycloadducts was established by comparison of the ^{1}H NMR, ^{13}C NMR and MS spectral data with those reported by Curran[10] and Kanemasa.[11] The ^{1}H NMR of isoxazolines **3** and **4** are compiled in Table 6 and Table 7, respectively, which exhibited the following characteristics:

1. The C_4-H of isoxazoline **3g** (δ 4.64) showed up at

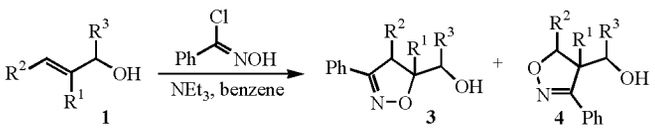
Table 4. Comparison of Yields and Regioselectivities of the Cycloaddition Reactions of Benzonitrile Oxide and Allyl Alcohols under Conventional and Microwave Conditions



1 3 4

Entry	Allylic Alcohol R^1	R^2	R^3	Thermal Yield	3:4	MW, 70 W Yield	3:4	MW, 400 W Yield	3:4
1	H	H	H	82	100:0	83	100:0	60	100:0
2	H	CH_3	H	53	68:32	15	55:45	23	56:44
3	H	(*Z*)-C_2H_5	H	46	60:40	32	45:55	25	46:54
4	H	(*E*)-C_2H_5	H	56	60:40	48	48:52	29	43:57
5	H	(*Z*)-C_3H_7	H	40	63:37	28	46:54	32	42:58
6	H	(*E*)-C_3H_7	H	54	57:43	53	46:54	43	46:54
7	H	Ph	H	43	34:66	55	19:81	90	24:76
8	CH_3	H	H	84	100:0	90	100:0	71	100:0
9	H	H	CH_3	71	100:0	59	100:0	70	100:0
10	H	H	C_2H_5	80	100:0	84	100:0	85	100:0
11	H	$-CH_2CH_2-$		78	67:33	77	50:50	59	50:50

Table 5. Comparison of Yields and Regioselectivities of the Cycloaddition Reactions of Benzonitrile Oxide and Allyl Alcohols under Conventional and Microwave Conditions



1 3 4

Allylic Alcohol R^1	R^2	Thermal Yield	3:4	MW, 400 W, 30 s Yield	3:4	MW, 400 W, 90 s Yield	3:4
H	CH_3	53	68:32	23	56:44	42	57:43
H	(*E*)-C_2H_5	56	60:40	29	43:57	44	47:53
H	(*E*)-C_3H_7	54	57:43	43	46:54	56	44:56

more than 1 ppm lower field than the C_4-H of the other isoxazolines **3** (except that from cyclopent-2-en-1-ol) presumably due to deshielding by the C_4-phenyl group. By the same token, the C_5-H of isoxazoline **4g** appeared at a considerably lower field (δ 5.75) than those of the other isoxazolines **4**.

2. The C_4-H of the cycloadducts derived from (*Z*)-1,2-disubstituted allylic alcohols (**3c**, **3e**, **4c**, **4e**) always appeared at 0.10-0.14 ppm lower field than that of the isoxazolines derived from the corresponding (*E*)-1,2-disubstituted allylic alcohols (**3d**, **3f**, **4d**, **4f**).

3. The chemical shifts of C_{3a}-H, C_{6a}-H, and C_6-H of **3k** as well as C_{3a}-H, C_{6a}-H, and C_4-H of **4k** are 0.13-0.77 ppm further down field than the corresponding protons of other cycloadducts; this is possibly caused by the ring strain of the bicyclo[3.3.0]octane system.

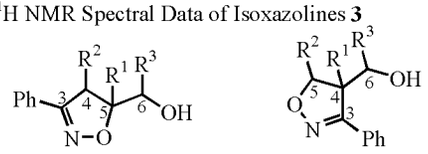
4. The C_5-H of H-bond directed 4,5-*cis*-disubstituted cycloadducts **3c** and **3e** appeared at lower field than the C_5-H of the regioisomeric 4,5-*cis*-disubstituted isoxazolines **4c** and **4e**. However, the opposite is true for the 4,5-*trans*-disubstituted isoxazolines (**3b**, **3d**, **3f** and **3g** vs. **4b**, **4d**, **4f** and **4g**).

5. The chemical shift differences between the two diastereotopic C_6-H of the 4,5-*cis*-disubstituted cycloadducts (**3c**, **3e**, **4c** and **4e**) are smaller than those of the 4,5-*trans*-disubstituted isoxazolines (**3b**, **3d**, **3f**, **3g**, **4b**, **4d**, **4f**, **4g**).

6. The C_6-H of isoxazolines **3i*a*** and **3j*a*** are 0.35 and 0.32 ppm down field than the C_6-H of **3i*s*** and **3j*s***.

In conclusion, an extremely efficient and economical method has been established for the 1,3-dipolar cycloaddition reaction of allylic alcohols and benzonitrile oxide using microwave irradiation. Microwave irradiation alters the regioselectivity of the cycloaddition reaction which favors the non-hydrogen-bond directed cycloadduct, isoxazoline **4** more. We are currently studying the scope and application of these conditions to other dipolarophiles as well as other nitrile oxides.

Table 6. ^{1}H NMR Spectral Data of Isoxazolines **3**



3 **4**

Cpd.	Alcohol **1**			Cpd. **3**				
	R^1	R^2	R^3	4–H	4'–H	5–H	6–H	6'–H
a	H	H	H	3.40 (dd)	3.29 (dd)	4.88 (dddd)	3.88 (dd)	3.69 (dd)
b	H	CH_3	H	3.63 (dq)	–	4.44 (dt)	3.77 (dd)	3.68 (dd)
c	H	(*Z*)-C_2H_5	H	3.62 (ddd)	–	4.74 (ddd)	4.06 (dd)	4.01 (dd)
d	H	(*E*)-C_2H_5	H	3.51 (dt)	–	4.56 (ddd)	3.75 (dd)	3.65 (dd)
e	H	(*Z*)-C_3H_7	H	3.67 (dt)	–	4.73 (ddd)	4.01 (dd)	3.97 (dd)
f	H	(*E*)-C_3H_7	H	3.53 (dt)	–	4.56 (ddd)	3.73 (dd)	3.64 (dd)
g	H	Ph	H	4.64 (d)	–	4.52 (m)	3.78 (dd)	3.67 (dd)
h	CH_3	H	H	3.50 (d)	3.01 (d)	–	3.73 (d)	3.58 (d)
is[a]	H	H	CH_3	3.40 (dd)	3.18 (dd)	4.59 (ddd)	3.80 (m)	–
ia[b]	H	H	CH_3	3.42 (dd)	3.25 (dd)	4.66 (ddd)	4.15 (m)	–
js[a]	H	H	C_2H_5	3.40 (dd)	3.29 (dd)	4.69 (ddd)	3.55 (m)	–
ja[b]	H	H	C_2H_5	3.41 (dd)	3.21 (dd)	4.68 (ddd)	3.87 (m)	–
k[c]	H	$-CH_2CH_2-$		4.12 (ddd)	–	5.01 (dd)	4.22 (ddd)	–

[a]*syn*-cycloadduct, [b]*anti*-cycloadduct, [c]4-H and 5-H correspond to 3a-H and 6a-H of **3k**, respectively.

Table 7. ^{1}H NMR Spectral Data of Isoxazolines **4**

Cpd.	Alcohol **1**			Cpd. **4**			
	R^1	R^2	R^3	4–H	5–H	6–H	6'–H
b	H	CH_3	H	3.48 (ddd)	4.86 (dq)	3.87 (dd)	3.75 (dd)
c	H	(*Z*)-C_2H_5	H	3.63 (ddd)	4.54 (dt)	3.92 (dd)	3.85 (dd)
d	H	(*E*)-C_2H_5	H	3.53 (dt)	4.66 (dt)	3.87 (dd)	3.76 (dd)
e	H	(*Z*)-C_3H_7	H	3.62 (ddd)	4.62 (dt)	3.90 (dd)	3.82 (dd)
f	H	(*E*)-C_3H_7	H	3.53 (dt)	4.72 (dt)	3.87 (dd)	3.77 (ddd)
g	H	Ph	H	3.84 (ddd)	5.75 (d)	4.01 (ddd)	3.92 (ddd)
k[a]	H	$-CH_2CH_2-$		4.03 (d)	5.37 (dd)	4.49 (m)	–

[a]4-H, 5-H and 6-H correspond to 3a-H, 6a-H and 4-H of **4k**, respectively.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra ($CDCl_3$ solutions) were measured on a 300 MHz spectrometer. Solvents and reagents were dried prior to use as required. Flash chromatography was carried out utilizing silica gel 60, 70-230 mesh ASTM. Medium-pressure liquid chromatography was carried out using Merck Lobar prepacked silica gel columns and a Fluid Metering, Inc. pump. The ratio of the regioisomer pairs was determined by the GC-MS chromatogram of the crude reaction mixture using a 50 m × 0.22 mm i.d. BP5 capillary column (SGE; 1.0 mm film thickness) and He as carrier gas or by HPLC analysis using a 25 cm × 4 mm i.d. Merck Hibar RT LiChrosorb Si 60 column and 2-propanol/*n*-hexane or chloroform/*n*-hexane mixture as the eluent.

General Procedure for Method A

To a 10 mL round-bottomed flask containing benzoximoyl chloride (0.6 mmol) was added a solution of the allylic alcohol (1.2 mmol, 2.0 equiv) in benzene (3.0 mL). A solution of Et_3N (0.66 mmol, 1.1 equiv) in benzene (3.5 mL) was added over 50 h at rt using a syringe pump. After the addition was complete, the solvent was removed under reduced pressure and EtOAc (40 mL) was added. The organic layer was washed successively with saturated $NaHCO_3$ (10 mL x 1) and brine (10 mL × 1), dried ($MgSO_4$), and concentrated. The ratio of the regiomers was determined by ^{1}H NMR or GC-MS of the crude reaction mixture. The crude reaction was purified by flash column chromatography (hexane/EtOAc) to furnish the desired products. Some of the regioisomeric pairs required the use of MPLC to effect the separation to give analytically pure samples as indicated for each compound.

General Procedure for Method B and Method C

To a 10 mL round-bottomed flask containing benzoximoyl chloride (0.6 mmol) was added allylic alcohol (1.2 mmol, 2.0 equiv), Et_3N (0.66 mmol, 1.1 equiv), and benzene (3.5 mL). A liquid nitrogen condenser was fitted to the flask and the reaction was quickly put into the center of the cavity of a domestic microwave oven. The reaction was irradiated using Med power (400 W) for 30 seconds (Method B) or Low power (70 W) for 2 minutes (Method C). The reaction was worked-up as in Method A.

5-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (3a)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69~7.65 (m, 2H, Ph), 7.44~7.38 (m, 3H, Ph), 4.88 (dddd, J = 3.0, 4.5, 7.7, 10.5 Hz, 1H, C_5–H), 3.88 (dd, J = 3.0, 12.2 Hz, 1H, C_6–H), 3.69 (dd, J = 4.5, 12.2 Hz, 1H, C_6–H), 3.40 (dd, J = 10.5, 16.6 Hz, 1H, C_4–H), 3.29 (dd, J = 7.7, 16.6 Hz, 1H, C_4–H), 2.00~1.55 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (C_3), 130.0 (CH), 129.1 (C), 128.6 (CH), 126.6 (CH), 81.2 (CH, C_5), 63.5 (CH_2, C_6), 36.3 (CH_2, C_4); MS: *m/z* 177 (M^+, 72.7%), 146 (M^+-CH_2OH, 69.2%), 118 (M^+-CH_2OH-CO, 97.2%), 103 ($PhCN^+$, 16.8%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 28.2%); HRMS: cacld for $C_{10}H_{11}NO_2$: 177.0789; found: 177.0783.

***Trans*-5-Hydroxymethyl-4-methyl-3-phenyl-4,5-dihydroisoxazole (3b)[11]**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.64 (m, 2H, Ph), 7.45~7.38 (m, 3H, Ph), 4.44 (dt, J = 3.6, 5.2 Hz, 1H, C_5–H), 3.77 (dd, J = 3.6, 12.0 Hz, 1H, C_6–H), 3.68 (dd, J = 5.6, 12.0 Hz, 1H, C_6–H), 3.63 (dq, J = 5.6, 7.2 Hz, 1H, C_4–H), 1.34 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C_3), 131.0 (CH), 129.9 (C), 129.3 (CH), 127.8 (CH), 82.3 (CH, C_5), 62.8 (CH_2, C_6), 57.7 (CH, C_4), 23.3 (CH_3); MS: *m/z* 191 (M^+, 61.6%), 160 (M^+-CH_2OH, 8.0%), 146 (M^+-CH_3-CH_2O, 100.0%), 130 (M^+-H_2O-CH_3CHCHO, 13.0%), 77 (Ph^+, 29.4%), 51 ($C_4H_3^+$, 8.9%).

***Trans*-4-Hydroxymethyl-5-methyl-3-phenyl-4,5-dihydroisoxazole (4b)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78~7.65 (m, 2H, Ph), 7.45~7.38 (m, 3H, Ph), 4.86 (dq, J = 4.4, 6.4 Hz, 1H, C_5–H), 3.87 (dd, J = 4.2, 11.1 Hz, 1H, C_6–H), 3.75 (dd, J = 6.8, 11.1 Hz, 1H, C_6–H), 3.48 (ddd, J = 4.2, 4.4, 6.8 Hz, 1H, C_4–H), 1.39 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C_3), 129.9 (CH), 128.6 (CH), 128.3 (C), 126.9 (CH), 88.6 (CH, C_5), 63.2 (CH_2, C_6), 43.6 (CH, C_4), 17.7 (CH_3); MS: *m/z* 191 (M^+, 41.7%), 160 (M^+-CH_2OH, 92.5%), 132 (M^+-CH_2OH-CO, 92.7%), 117 (M^+-CH_2OH-CO-CH_3, 16.8%), 104 ($PhCNH^+$, 29.0%), 103 ($PhCN^+$, 26.1%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 52.3%).

***Cis*-4-Ethyl-5-hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (3c)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75~7.60 (m, 2H, Ph), 7.52~7.40 (m, 3H, Ph), 4.74 (ddd, J = 3.6, 6.6, 9.3 Hz, 1H, C_5–H), 4.06 (dd, J = 6.6, 11.9 Hz, 1H, C_6–H), 4.01 (dd, J = 3.6, 11.9 Hz, 1H, C_6–H), 3.62 (ddd, J = 4.8, 7.2, 9.3 Hz, 1H, C_4–H), 1.73~1.63 (m, 2H, CH_2 of Et), 0.95 (t, J = 8.8 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6 (C_3), 130.1 (CH), 129.1 (C), 128.8 (CH), 127.1 (CH), 84.4 (CH, C_5), 60.5 (CH_2, C_6), 49.6 (CH, C_4), 19.4 (CH_2 of Et), 12.7 (CH_3); MS: *m/z* 205 (M^+, 65.0%),174 (M^+-CH_2OH, 99.3%), 146 (M^+-CH_2OH-CO, 73.0%), 130 (M^+-C_2H_4-CH_2OH-NH_2, 52.1%), 118 (M^+-CH_2OH-CO-C_2H_2, 26.9%), 104 ($PhCNH^+$, 49.0%), 103 ($PhCN^+$, 20.4%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 47.5%); HRMS: cacld for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1110. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.20; H, 7.43; N, 6.91.

***Cis*-5-Ethyl-4-hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (4c)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75~7.65 (m, 2H, Ph), 7.50~7.40 (m, 3H, Ph), 4.54 (dt, J = 6.0, 8.4 Hz, 1H, C_5–H), 3.92 (dd, J = 5.6, 11.6 Hz, 1H, C_6–H), 3.85 (dd, J = 3.3, 11.6 Hz, 1H, C_6–H), 3.63 (ddd, J = 3.3, 5.6, 8.4 Hz, 1H, C_4–H), 2.09-1.93 (m, 2H, CH_2 of Et), 1.17 (t, J = 7.2 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (C_3), 130.1 (CH), 129.1 (C), 128.9 (CH), 126.9 (CH), 86.1 (CH, C_5), 58.7 (CH_2, C_6), 50.9 (CH, C_4), 21.4 (CH_2 of Et), 11.5 (CH_3); MS: *m/z* 205 (M^+, 78.2%),176 (M^+-Et, 4.5%), 146 (M^+-Et-CH_2O, 100.0%), 130 (M^+-H_2O-CH_3CHCHO, 9.7%); HRMS: cacld for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1102. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.44; H, 7.41; N, 6.76.

***Trans*-4-Ethyl-5-hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (3d)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.63 (m, 2H, Ph), 7.43~7.38 (m, 3H, Ph), 4.56 (ddd, J = 3.6, 4.8, 6.2 Hz, 1H, C_5–H), 3.75 (dd, J = 3.6, 12.1 Hz, 1H, C_6–H), 3.65 (dd, J = 6.2, 12.1 Hz, 1H, C_6–H), 3.51 (dt, J = 4.8, 8.0 Hz, 1H, C_4–H), 1.84~1.59 (m, 2H, CH_2 of Et), 0.95 (t, J = 7.4 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (C_3), 130.0 (CH), 129.8 (C), 128.6 (CH), 126.7 (CH), 86.0 (CH, C_5), 64.3 (CH_2, C_6), 50.3 (CH, C_4), 24.0 (CH_2 of Et), 10.7 (CH_3); MS: *m/z* 205 (M^+, 28.7%), 174 (M^+-CH_2OH, 88.0%), 146 (M^+-CH_2OH-CO, 68.8%), 130 (M^+-C_2H_4-CH_2OH-NH_2, 40.5%), 118 (M^+-CH_2OH-CO-C_2H_2, 25.3%), 104 ($PhCNH^+$, 48.7%), 103 ($PhCN^+$, 27.6%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 29.0%); HRMS: calcd for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1105. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found:

C, 70.12; H, 7.40; N, 6.76.

Trans-5-Ethyl-4-hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75~7.65 (m, 2H, Ph), 7.45~7.35 (m, 3H, Ph), 4.66 (ddd J = 4.0, 6.6, 6.9 Hz, 1H, C_5–H), 3.87 (dd, J = 4.0, 10.8 Hz, 1H, C_6–H), 3.76 (dd, J = 6.9, 10.8 Hz, 1H, the C_6–H), 3.53 (dt, J = 4.0, 6.9 Hz, 1H, C_4–H), 1.81~1.59 (m, 2H, CH_2 of Et), 1.03 (t, J = 7.6 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (C_3), 129.8 (CH), 128.9 (C), 128.7 (CH), 126.7 (CH), 86.1 (CH, C_5), 62.1 (CH_2, C_6), 54.8 (CH, C_4), 28.1 (CH_2 of Et), 9.4 (CH_3); MS: *m/z* 205 (M^+, 43.4%), 176 (M^+-Et, 4.35%), 146 (M^+-Et-CH_2O, 100.0%), 130 (M^+-H_2O-CH_3CHCHO, 22.2), 105 ($PhCO^+$, 25.9%), 77 (Ph^+, 44.0%), 51 ($C_4H_3^+$, 11.3%); HRMS: calcd for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1107. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.22; H, 7.49; N, 6.78.

Cis-5-Hydroxymethyl-3-phenyl-4-propyl-4,5-dihydroisoxazole (3e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65~7.60 (m, 2H, Ph), 7.45~7.40 (m, 3H, Ph), 4.73 (ddd, J = 4.5, 6.8, 9.1 Hz, 1H, C_5–H), 4.01 (dd, J = 6.8, 12.0 Hz, 1H, C_6–H), 3.97 (dd, J = 4.4, 12.0 Hz, 1H, C_6–H), 3.67 (dt, J = 3.6, 9.1 Hz, 1H, C_4–H), 1.66 (ddd, J = 7.2, 8.4, 14.2 Hz, 1H, CH_2 of *n*-Pr), 1.56 (ddd, J = 3.6, 7.2, 14.2 Hz, 1H, CH_2 of *n*-Pr), 1.36 (s', J = 7.2 Hz, 2H, CH_2 of *n*-Pr), 0.89 (t, J = 7.5 Hz, 3H, CH_3 of *n*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (C_3), 130.0 (CH), 129.1 (C), 128.8 (CH), 127.1 (CH), 84.3 (CH, C_5), 60.6 (CH_2, C_6), 48.1 (CH, C_4), 28.4 (CH_2 of *n*-Pr), 21.6 (CH_2 of *n*-Pr), 14.1 (CH_3); MS: *m/z* 219 (M^+, 31.1%), 188 (M^+-CH_2OH, 66.6%), 160 (M^+-CH_2OH-CO, 29.9%), 132 (M^+-CH_2OH-CO-C_2H_4, 34.4%), 130 (M^+-C_2H_4-CH_2OH-NH_2, 48.6%), 104 ($PhCNH^+$, 48.2%), 103 ($PhCN^+$, 20.1%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 39.5%).

Cis-4-Hydroxymethyl-3-phenyl-5-propyl-4,5-dihydroisoxazole (4e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78~7.72 (m, 2H, Ph), 7.46~7.39 (m, 3H, Ph), 4.62 (td, J = 5.2, 8.8 Hz, 1H, C_5–H), 3.90 (dd, J = 5.8, 11.6 Hz, 1H, C_6–H), 3.82 (dd, J = 3.5, 11.6 Hz, 1H, C_6–H), 3.62 (ddd, J = 3.5, 5.8, 8.8 Hz, 1H, C_4–H), 2.04~1.87 (m, 2H, CH_2 of *n*-Pr), 1.75~1.46 (m, 2H, CH_2 of *n*-Pr), 1.03 (t, J = 7.6 Hz, 3H, CH_3 of *n*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9 (C_3), 130.0 (CH), 129.0 (C), 128.7 (CH), 126.8 (CH), 84.3 (CH, C_5), 58.7 (CH_2, C_6), 51.2 (CH, C_4), 30.3 (CH_2 of *n*-Pr), 20.4 (CH_2 of *n*-Pr), 14.2 (CH_3); MS: *m/z* 219 (M^+, 25.9%), 176 (M^+-Pr, 2.7%), 147 (M^+-C_3H_6-CH_2O, 10.7%), 146 (M^+-Pr-CH_2O, 100.0%), 130 (M^+-H_2O-CH_3CH_2CHCHO, 29.5), 104 ($PhCNH^+$, 16.9%), 77 (Ph^+, 66.8%).

Trans-5-Hydroxymethyl-3-phenyl-4-propyl-4,5-dihydroisoxazole (3f)[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.65 (m, 2H, Ph), 7.45~7.38 (m, 3H, Ph), 4.56 (ddd, J = 3.6, 4.2, 5.6 Hz, 1H, C_5–H), 3.73 (dd, J = 3.6, 12.0 Hz, 1H, C_6–H), 3.64 (dd, J = 5.6, 12.0 Hz, 1H, C_6–H), 3.53 (dt, J = 4.2, 7.5 Hz, 1H, C_4–H), 1.73~1.53 (m, 2H, CH_2 of *n*-Pr), 1.40 (s', J = 7.5 Hz, 2H, CH_2 of *n*-Pr), 0.93 (t, J = 7.5 Hz, 3H, CH_3 of *n*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0 (C_3), 129.9 (CH), 128.7 (CH), 128.5 (C), 126.9 (CH), 86.4 (CH, C_5), 64.0 (CH_2, C_6), 48.9 (CH, C_4), 33.2 (CH_2 of *n*-Pr), 19.9 (CH_2 of *n*-Pr), 13.8 (CH_3); MS: *m/z* 219 (M^+, 88.9%), 188 (M^+-CH_2OH, 69.0%), 160 (M^+-CH_2OH-CO, 69.0%), 145 (M^+-CH_2OH-Pr, 18.4%), 132 (M^+-CH_2OH-CO-C_2H_4, 38.7%), 130 (M^+-C_3H_6-CH_2OH-NH_2, 70.1%), 104 ($PhCNH^+$, 38.7%), 103 ($PhCN^+$, 21.7%), 77 (Ph^+, 79.0%), 51 ($C_4H_3^+$, 16.2%).

Trans-4-Hydroxymethyl-3-phenyl-5-propyl-4,5-dihydroisoxazole (4f)[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75~7.65 (m, 2H, Ph), 7.50~7.38 (m, 3H, Ph), 4.72 (dt, J = 6.0, 7.2 Hz, 1H, C_5–H), 3.87 (dd, J = 4.4, 11.2 Hz, 1H, C_6–H), 3.77 (ddd, J = 0.8, 7.2, 11.2 Hz, 1H, C_6–H), 3.53 (dt, J = 4.4, 7.2 Hz, 1H, C_4–H), 1.78~1.62 (m, 2H, CH_2 of *n*-Pr), 1.60~1.40 (m, 2H, CH_2 of *n*-Pr), 0.97 (t, J = 7.2 Hz, 3H, CH_3 of *n*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5 (C_3), 129.9 (CH), 128.9 (C), 128.7 (CH), 126.7 (CH), 84.8 (CH, C_5), 61.8 (CH_2, C_6), 55.3 (CH, C_4), 37.2 (CH_2 of *n*-Pr), 18.3 (CH_2 of *n*-Pr), 13.9 (CH_3); MS: *m/z* 219 (M^+, 37.2%), 176 (M^+-Pr, 13.9%), 147 (M^+-C_3H_6-CH_2O, 15.9%), 146 (M^+-Pr-CH_2O, 100.0%), 130 (M^+-H_2O-CH_3CH_2CHCHO, 29.2), 105 ($PhCO^+$, 19.9%), 77 (Ph^+, 45.8%), 51 ($C_4H_3^+$, 13.8%).

***trans*-5-Hydroxymethyl-3,4-diphenyl-4,5-dihydroisoxazole (3g)[11]**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55~7.45 (m, 2H, Ph), 7.25~7.10 (m, 8H, Ph), 4.64 (d, J = 5.6 Hz, 1H, C_4–H), 4.54~4.50 (m, 1H, C_5–H), 3.78 (dd, J = 4.0, 12.4 Hz, 1H, C_6–H), 3.67 (dd, J = 4.4, 12.4 Hz, 1H, C_6–H), 2.90~2.75 (br, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6 (C_3), 138.9 (C), 129.8 (CH), 129.2 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 125.0 (C), 90.5 (CH, C_5), 63.0 (CH_2, C_6), 55.6 (CH, C_4); MS: *m/z* 253 (M^+, 44.4%), 222 (M^+-CH_2OH, 49.7%), 194 (M^+-CH_2OH-CO, 48.5%), 193 (M^+-CH_2OH-HCO, 30.4%), 116 (M^+-CH_2OH-HCO-Ph, 11.5%), 103 ($PhCN^+$, 12.1%), 91 ($PhCH_2^+$, 18.4%), 77 (Ph^+, 31.9%), 51 ($C_4H_3^+$, 18.9%).

***Trans*-4-hydroxymethyl-3,5-diphenyl-4,5-dihydroisoxazole (4g)[11]**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74~7.68 (m, 2H, Ph), 7.42~7.26 (m, 8H, Ph), 5.75 (d, J = 4.4 Hz, 1H, C_5–H), 4.01 (ddd, J = 4.2, 5.2, 10.7 Hz, 1H, C_6–H), 3.92 (ddd, J = 5.2, 6.6, 10.7 Hz, 1H, C_6–H), 3.84 (ddd, J = 4.2, 4.4, 6.6 Hz, 1H, C_4–H), 1.75~1.60 (t, J = 5.2, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1 (C_3), 141.0 (C), 130.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (C), 127.9 (CH), 126.9 (CH), 125.2 (CH), 85.7 (CH, C_5), 61.8 (CH_2, C_6), 59.2 (CH, C_4); MS: *m/z* 253 (M^+, 100.0%), 222 (M^+-CH_2OH, 48.0%), 146 (M^+-$PhCH_2O$, 44.3%), 130 (M^+-H_2O-PhCO, 65.9%), 105 ($PhCO^+$, 84.8%), 104 ($PhCNH^+$, 37.5%), 103 ($PhCN^+$, 21.4%), 77 (Ph^+, 83.9%), 51 ($C_4H_3^+$, 29.0%).

5-Hydroxymethyl-5-methyl-3-phenyl-2-isoxazoline (3h)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68~7.62 (m, 2H, Ph), 7.42~7.36 (m, 3H, Ph), 3.73 (d, J = 11.8 Hz, 1H, C_6–H), 3.58 (d, J = 11.8 Hz, 1H, C_6–H), 3.50 (d, J = 16.6 Hz, 1H, C_4–H), 3.01 (d, J = 16.6 Hz, 1H, C_4–H), 2.52-2.28 (br, 1H, OH), 1.43 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (C_3), 130.0 (CH), 129.6 (C), 128.6 (CH), 126.5 (CH), 87.4 (CH, C_5), 67.2 (CH_2, C_6), 41.9 (CH_2, C_4), 22.6 (CH_3); MS: *m/z* 191 (M^+, 19.2%),160 (M^+-CH_2OH, 46.6%), 118 (M^+-CH_2OH-CH_2CO, 100%), 103 ($PhCN^+$, 10.6%), 77 (Ph^+, 41.8%), 51 ($C_4H_3^+$, 22.3%). HRMS: cacld for $C_{11}H_{13}NO_2$: 191.0946; found: 191.0943.

(5*RS*)-5-[(1*RS*)-Hydroxyethyl]-3-phenyl-4,5-dihydroisoxazole (3i*s*)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78~7.72 (m, 2H, Ph), 7.46~7.39 (m, 3H, Ph), 4.59 (ddd, J = 5.8, 7.4, 10.6 Hz, 1H, C_5–H), 3.84-3.76 (m, 1H, C_6–H), 3.40 (dd, J = 10.6, 16.6 Hz, 1H, C_4–H), 3.18 (dd, J = 7.4, 16.6 Hz, 1H, C_4–H), 1.30 (d, J = 6.8 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9 (C_3), 130.1 (CH), 129.2 (C), 128.6 (CH), 126.6 (CH), 84.7 (CH, C_5), 69.2 (CH, C_6), 37.1 (CH_2, C_4), 19.0 (CH_3); MS: *m/z* 191 (M^+, 8.4%), 146 (M^+-$CH(CH_3)OH$, 8.0%), 119 ($PhC(CH_3)NH^+$, 34.6%), 118 (M^+-$CH(CH_3)OH$-CO, 42.9%), 104 ($PhCNH^+$, 77.8%), 103 ($PhCN^+$, 25.0%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 65.9%).

(5*SR*)-5-[(1*RS*)-Hydroxyethyl]-3-phenyl-4,5-dihydroisoxazole (3i*a*)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.65 (m, 2H, Ph), 7.33~7.28 (m, 3H, Ph), 4.66 (ddd, J = 3.2, 8.8, 11.2 Hz, 1H, C_5–H), 4.18~4.12 (m, 1H, C_6–H), 3.42 (dd, J = 8.8, 16.4 Hz, 1H, C_4–H), 3.25 (dd, J = 11.2, 16.4 Hz, 1H, C_4–H), 1.23 (d, J = 6.0 Hz, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (C_3), 130.0 (CH), 129.3 (C), 128.6 (CH), 126.6 (CH), 85.1 (CH, C_5), 67.1 (CH, C_6), 34.2 (CH_2, C_4), 18.1 (CH_3); MS: *m/z* 191 (M^+, 27.3%), 146 (M^+-$CH(CH_3)OH$, 21.1%), 119 ($PhC(CH_3)NH^+$, 51.3%), 118 (M^+-$CH(CH_3)OH$-CO, 56.9%), 104 ($PhCNH^+$, 94.3%), 103 ($PhCN^+$, 25.5%), 77 (Ph^+, 100.0%), 51 ($C_4H_3^+$, 73.6%).

(5*RS*)-5-[(1*RS*)-Hydroxypropyl]-3-phenyl-4,5-dihydroisoxazole (3j*s*)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.65 (m, 2H, Ph), 7.45~7.38 (m, 3H, Ph), 4.69 (ddd, J = 4.6, 8.0, 10.6 Hz, 1H, C_5–H), 3.58-3.52 (m, 1H, C_6–H), 3.40 (dd, J = 8.0, 16.6 Hz, 1H, C_4–H), 3.29 (dd, J = 8.0, 16.6 Hz, 1H, C_4–H), 1.71-1.58 (m, 2H, CH_2 of Et), 1.07 (t, J = 7.6 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0 (C_3), 130.0 (CH), 129.2 (C), 128.5 (CH), 126.5 (CH), 83.2 (CH, C_5), 74.2 (CH, C_6), 37.0 (CH_2, C_4), 26.5 (CH_2, CH_2 of Et), 10.1 (CH_3); MS: *m/z* 205 (M^+, 34.3%), 146 (M^+-CH(Et)OH, 23.3%), 119 ($PhC(CH_3)NH^+$, 75.5%), 118 (M^+-CH(Et)OH-CO, 42.4%), 104 ($PhCNH^+$, 100.0%), 103 ($PhCN^+$, 17.8%), 77 (Ph^+, 50.7%), 51 ($C_4H_3^+$, 17.1%).

(5*SR*)-5-[(1*RS*)-Hydroxypropyl]-3-phenyl-4,5-dihydroisoxazole (3j*a*)[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70~7.62 (m, 2H, Ph), 7.42~7.38 (m, 3H, Ph), 4.68 (ddd, J = 3.6, 8.8, 10.6 Hz, 1H, C_5–H), 3.90~3.84 (m, 1H, C_6–H), 3.41 (dd, J = 8.8, 16.6 Hz, 1H, C_4–H), 3.21 (dd, J = 10.6, 16.6 Hz, 1H, C_4–H), 1.61-1.31 (m, 2H, CH_2 of Et), 1.03 (t, J = 7.3 Hz, 3H, CH_3 of Et); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (C_3), 130.0 (CH), 129.3 (C), 128.6 (CH), 126.6 (CH), 84.1 (CH, C_5), 72.4 (CH, C_6), 34.2 (CH_2, C_4), 25.6 (CH_2 of Et), 10.1 (CH_3); MS: *m/z* 205 (M^+, 33.9%), 146 (M^+-CH(Et)OH, 27.2%), 119 ($PhC(CH_3)NH^+$, 68.0%), 118 (M^+-CH(Et)OH-CO, 41.0%), 104 ($PhCNH^+$, 100.0%), 103 ($PhCN^+$, 19.7%), 77 (Ph^+, 60.9%), 51 ($C_4H_3^+$, 20.2%).

6-Hydroxy-3-phenyl-3aα,5,6α,6aα-tetrahydro-4*H*-cyclopenta[d]isoxazole (3k)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68~7.62 (m, 2H, Ph), 7.45~7.38 (m, 3H, Ph), 5.01 (dd, J = 4.8, 8.8, Hz, 1H, C_{6a}–H), 4.22 (ddd, J = 5.2, 8.8, 9.3 Hz, 1H, C_6–H), 4.12 (ddd, J = 4.8, 7.0, 9.3 Hz, 1H, C_{3a}–H), 2.00~1.88 (m, 2H, C_5–H), 1.58~1.47 (m, 2H, C_4–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (C_3), 130.0 (CH), 128.7 (C), 128.0 (CH), 127.0 (CH), 85.4 (CH, C_{6a}), 76.7 (CH, C_6), 51.0 (CH, C_{3a}), 31.2 (CH_2, C_5), 26.9 (CH_2, C_4); MS: *m/z* 203 (M^+, 84.8%), 146 (M^+-C_3H_5O, 46.9%), 104 ($PhCNH^+$, 100%), 77 (Ph^+, 67.1%).

4-Hydroxy-3-phenyl-3aα,5,6,6aα-tetrahydro-4α*H*-cyclopenta[d]isoxazole (4k)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84~7.78 (m, 2H, Ph),

7.54~7.48 (m, 3H, Ph), 5.37 (dd, J = 5.0, 8.7, Hz, 1H, C_{6a}–H), 4.49 (m, 1H, C_4–H), 4.03 (d, J = 8.7, Hz, 1H, C_{3a}–H), 2.38~2.20 (m, 2H, C_5–H), 1.90~1.78 (m, 2H, C_6–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (C_3), 129.8 (CH), 129.0 (C), 128.7 (CH), 126.7 (CH), 87.2 (CH, C_{6a}), 76.6 (CH, C_4), 61.8 (CH, C_{3a}), 33.1 (CH_2, C_5), 32.6 (CH_2, C_6); MS: *m/z* 203 (M^+, 58.1%), 159 (M^+-CH_2CHOH, 7.5%), 146 (M^+-C_3H_5O, 100%), 104 ($PhCNH^+$, 15.0%), 91 ($PhCH_2^+$, 10.9%), 77 (Ph^+, 28.9%).

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Key Words

Microwave; Nitrile oxide; Cycloaddition; Allylic alcohol; Isoxazoline; Regioselectivity.

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