1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides with 1,3-Dioxolanes of α,β-Unsaturated Aldehydes

Ta-Jung Lu,* Jyh-Ferng Yang, and Lij-Jyi Sheu

Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 40227, Republic of China

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Introduction

Dipolar cycloaddition reactions have recently been recognized as powerful tools for the synthesis of complex natural products.[1,2] 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[3] 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.[4]

Although monosubstituted dipolarophiles usually exhibit high regioselectivity,[5] 1,2-disubstituted ones often give mixtures of regioisomers.[6] For example, the reaction of nitrile oxides with methyl *trans*-cinnamate and methyl crotonate afforded the corresponding isoxazolines only with poor to moderate regioselectivity.[7] Moreover, the reaction between nitrile oxides and α,β-unsaturated esters or ketones has been studied extensively,[6a,8] but the same reaction with α,β-unsaturated aldehydes has rarely been reported. To the best of our knowledge, the only example is that reported by De Sarlo.[9] The reactivity of nitrile oxides toward *trans*-cinnamaldehyde was low and gave, in addition to the expected formyldihydroisoxazoline, a bis-cycloadduct resulting from the addition of nitrile oxide to the carbonyl group of the initial cycloadduct.

In view of the limited study of the 1,3-dipolar cycloaddition reactions of α,β-unsaturated aldehydes with nitrile oxides, the possibility of further reaction of the carbonyl group with nitrile oxide to form the bis-adduct, and the facile oxidation of the resulting isoxazoline to the isoxazole, we decided to investigate the reaction using α,β-unsaturated acetals.[10,11] By changing the electronic characteristics of the double bond, the dioxolane ring of the α,β-unsaturated acetal may alter the reactivity of the double bond toward a nitrile oxide. The dioxolane ring may also affect the regiochemistry of the cycloaddition reaction by altering the steric demands of the neighboring double bond. A further advantage of using an unsaturated acetal as a dipolarophile is that it provides us with a possible means to control the absolute stereochemistry of the adduct by the use of a chiral unsaturated acetal.[12] Herein, we would like to report our results on the cycloaddition reactions of α,β-unsaturated acetals with nitrile oxides.

Results and Discussion

The α,β-unsaturated acetals were prepared in good yields by reacting the corresponding α,β-unsaturated aldehydes with ethylene glycol in refluxing benzene in the presence of anhydrous magnesium sulfate and tartaric acid.[13] The cycloaddition reaction was carried out in a variety of solvents at different temperatures to examine the influence of solvent polarity and reaction temperature on the efficiency and the orientation of the reaction. The effects of substrate and nitrile oxide structure on reaction regioselectivity as well as reaction yield were evaluated with the acetals **1a–c** possessing aryl and alkyl substituents of varying steric demands and three structurally diverse nitrile oxides **2a–2c** having an electron-withdrawing or donating substituent (Scheme 1).[14]

Since the nitrile oxide itself dimerizes to form the furoxan readily, it had to be prepared *in situ* at an appropriate speed in order to achieve high yield for the cycloaddition reaction.[15] Consequently, a search was

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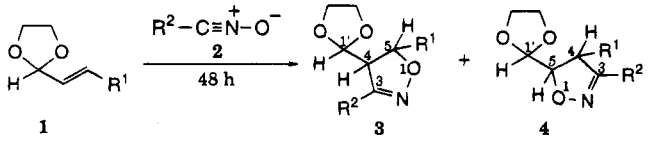
0022-3263/95/1960-7701$09.00/0

Scheme 1



made initially for the optimum rate of formation of the nitrile oxide. The best results were obtained when 4 equiv of the dipole was generated over a 48 h period.[12a] The cycloaddition reactions of the unsaturated acetals **1a–c** with nitrile oxides **2a–c** were carried out with the acetals as the limiting reagent because the olefins might be considered as the valuable reaction component in the asymmetric version of this reaction, where chiral acetals will be used as the dipolarophiles. As shown in Table 1, adducts **3** were formed predominantly in the cycloaddition of nitrile oxides to α,β-unsaturated acetals.[16] In comparison, when the reaction was performed under exactly the same conditions utilizing the corresponding aldehyde as the dipolarophile, only starting material was recovered. Under more forceful conditions, *i.e.* higher temperature and longer reaction time, the cycloaddition reaction did take place but only aromatized product was isolated.

Good to excellent regioselectivities were realized and the ratio of the two adducts **3** and **4** was estimated by HPLC or GC/MS analysis of the crude reaction mixture. Of the three nitrile oxides studied, carbethoxyformonitrile oxide (CEFNO, **2b**) displayed the highest regioselectivity (**3**:**4** ranging from 5.2:1 to 99.0:1) toward all the unsaturated acetals. With propiononitrile oxide **2c**, product **3** again was preferred, although not as strongly: **3**:**4** ratio ranged from 6.7:1 to 13.8:1. The lowest product ratios, ranging from 2.8:1 to 7.1:1, were observed for benzonitrile oxide **2a** except when the reaction was run in EtOAc solvent (19.0:1). It is noteworthy that the regioselectivity of the unsaturated acetals is, in general, better than those of the corresponding α,β-unsaturated ketones and esters. There is no convincing explanation for the regioselectivity but it might be associated with dipole-dipole interactions of the nitrile oxides and the α,β-unsaturated acetals.[17]

Some trends can be drawn from the data in Table 1. (1) Acetal **1a** reacted more readily with nitrile oxides than acetals **1b** and **1c** and afforded the cycloadducts in higher isolated yields while the yields are comparable for acetals **1b** and **1c** with all three of the nitrile oxides. (2) The regioselectivities achieved by acetal **1a** with nitrile oxides **2a** and **2b** were superior to those realized by acetals **1b** and **1c** with the same dipoles. On the other hand, when the reactions were carried out with nitrile oxide **2c**, the order was reversed as the regioselectivities with acetal **1a** were inferior to those achieved by acetals **1b** and **1c**. (3) The regioselectivities were similar when the reactions were carried out using nitrile oxide **2a** with acetals **1b** and **1c**. (4) Higher regioselectivities were realized in the reaction of nitrile oxide **2b** with acetal **1c** than those with acetal **1b**. However, apart from the reaction in EtOAc, lower regioselectivities were observed for nitrile oxide **2c** and acetal **1c** than those with acetal **1b**. (5) For nitrile oxide **2c**, the reaction yields were better in general than those obtained with nitrile oxides **2a** and **2b**. (6) Ethyl acetate appeared to be the solvent of choice based both on the reaction yields and regioselectivities of the cycloadducts.

The structural assignment of isoxazolines **3ba** and **4ba**, the cycloadducts derived from acetal **1b** and benzonitrile oxide **2a**, was based on the chemical shifts and the coupling pattern of C_5–H of **3ba** (4.90 ppm, qd) and C_4–H of **4ba** (3.75 ppm, qd). The C_5–H of **3ba** is a methine proton on an oxygen-containing carbon whereas the C_4–H of **4ba** is alpha to an imine and therefore it is reasonable that the C_5–H is further downfield than that of C_4–H. Since these two protons are coupled with a methine proton and a methyl group they appeared as doublet of quartets. Furthermore, the other two corresponding protons, namely the C_4-H of **3ba** and C_5–H of **4ba**, emerge at 3.63 and 4.34 ppm, respectively, which are compatible with their individual chemical environment. The $C_{1'}$–H absorptions of adducts **3ba** and **4ba** appear at 5.12 and 4.95 ppm, respectively. As in isoxazolines **3ba** and **4ba**, the $C_{1'}$–H and C_5–H of **3bb** and **3bc** all appear at lower field than the $C_{1'}$–H and C_4–H of **4bb** and **4bc**; however, the C_4-H of isoxazolines **3bb** and **3bc** emerged at higher field than the C_5–H of adducts **4bb** and **4bc**.[18] Similar trends can be observed for the $C_{1'}$–H, C_4–H, and C_5–H absorptions of the rest of the cycloadduct pairs **3aa/4aa**, **3ab/4ab**, **3ac/4ac**, **3ca/4ca**, **3cb/4cb**, and **3cc/4cc**, suggesting that their regiochemistry is the same as **3ba/4ba**. Inspection of the ^{13}C NMR spectra of the cycloadducts provided more evidence for the assignment of regiochemistry. Except adducts **3bc** and **4bc**, the absorptions of $C_{1'}$ of all the isoxazolines **3** appear at higher field than those of isoxazolines **4**. The chemical shifts of C_4 of each of the adducts **3** are at lower field than those of C_5 of adducts **4**. On the other hand, the C_5 of isoxazolines **3** emerge at higher field than those of C_4 of isoxazolines **4**. Furthermore, except for adducts **3bb** and **4bb**, the R_f values of all the isoxazolines **3** on TLC analysis are higher than those of the adducts **4**.

The regiochemistry of the isoxazolines was further confirmed by the comparison of the chemical shifts of the corresponding protons in each of the regioisomers **3** and **4** with those of related isoxazolines **6a** and **6b** whose structures were determined by X-ray analysis.[19] The chemical shifts of the $C_{1'}$–H, C_4–H, and C_5–H absorptions of isoxazolines **3** are close to those absorptions of the C_4–H, $C_{4'}$–H, and $C_{5'}$–H of isoxazolines **6** and **7**. Conversely, the corresponding protons of cycloadducts **4** are different from those of isoxazolines **6** and **7**. Similarly, the $C_{1'}$, C_4, and C_5 absorptions of adducts **3** are closer than those of cycloadducts **4** to the absorptions of

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(16) The cycloaddition reactions gave better yields when carried out at higher concentration.

(17) Kamimura and Hori rationalized the regiochemistry of the cycloaddition of nitrile oxides to β-substituted acetals based on the results of MNDO calculations, see ref. 11.

(18) ^1H and ^{13}C NMR spectral data for diagnostic absorptions of regioisomers **3**, **4**, **6**, and **7** are compiled in the Supplementary Material.

(19) The cycloaddition reactions of the α,β-unsaturated acetals **5**, derived from (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol, with nitrile oxides gave the 4-isoxazolines **6** and **7** as the major products. The structures of isoxazolines **6a** and **6b** were unequivocally determined by X-ray diffraction analysis. Lu, T.-J.; Lee, J.-I., unpublished results (see ref 12a).

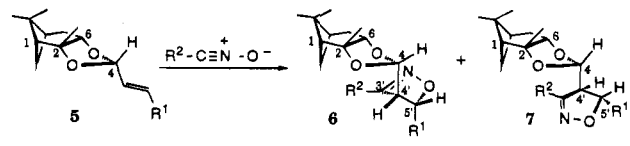

Table 1. Cycloaddition Reactions of α,β-Unsaturated Acetals with Nitrile Oxides

entry	acetal	R^1	nitrile oxide	R^2	solvent	temp (°C)	recovered sm (%)	yield[a] (%)	ratio[b] 3:4
1	**1a**	Ph	**2a**	Ph	THF	23	26	40 (54)	7.1:1
2	**1a**	Ph	**2a**	Ph	EtOAc	23	24	56 (74)	19.0:1
3	**1a**	Ph	**2a**	Ph	toluene	23	27	58 (79)	6.1:1
4	**1a**	Ph	**2b**	CO_2Et	ether	23	26	46 (62)	99.0:1
5	**1a**	Ph	**2b**	CO_2Et	ether	4	29	49 (69)	99.0:1
6	**1a**	Ph	**2b**	CO_2Et	EtOAc	23	28	51 (71)	99.0:1
7	**1a**	Ph	**2b**	CO_2Et	toluene	23	31	48 (70)	53.0:1
8	**1a**	Ph	**2c**	Et	EtOAc	23	28	52 (72)	13.3:1[c]
9	**1a**	Ph	**2c**	Et	toluene	23	28	52 (72)	6.7:1[c]
10	**1a**	Ph	**2c**	Et	benzene	75	26	56 (76)	6.7:1[c]
11	**1b**	CH_3	**2a**	Ph	THF	23	12	27 (31)	3.4:1
12	**1b**	CH_3	**2a**	Ph	EtOAc	23	9	27 (30)	4.0:1
13	**1b**	CH_3	**2a**	Ph	toluene	23	16	30 (36)	3.0:1
14	**1b**	CH_3	**2b**	CO_2Et	ether	23	12	26 (30)	6.7:1
15	**1b**	CH_3	**2b**	CO_2Et	ether	4	14	24 (28)	7.8:1
16	**1b**	CH_3	**2b**	CO_2Et	EtOAc	23	12	30 (34)	5.7:1
17	**1b**	CH_3	**2b**	CO_2Et	toluene	23	22	35 (45)	5.2:1
18	**1b**	CH_3	**2c**	Et	EtOAc	23	45	32 (58)	12.1:1[c]
19	**1b**	CH_3	**2c**	Et	toluene	23	35	40 (62)	12.1:1[c]
20	**1b**	CH_3	**2c**	Et	benzene	75	33	42 (63)	10.0:1[c]
21	**1c**	C_3H_7	**2a**	Ph	THF	23	36	32 (55)	3.8:1
22	**1c**	C_3H_7	**2a**	Ph	EtOAc	23	38	33 (53)	3.3:1
23	**1c**	C_3H_7	**2a**	Ph	toluene	23	42	38 (65)	2.8:1
24	**1c**	C_3H_7	**2b**	CO_2Et	ether	23	33	27 (40)	7.6:1
25	**1c**	C_3H_7	**2b**	CO_2Et	ether	4	36	29 (45)	7.4:1
26	**1c**	C_3H_7	**2b**	CO_2Et	EtOAc	23	32	31 (45)	13.3:1
27	**1c**	C_3H_7	**2b**	CO_2Et	toluene	23	27	37 (51)	8.3:1
28	**1c**	C_3H_7	**2c**	Et	EtOAc	23	34	27 (41)	13.8:1[c]
29	**1c**	C_3H_7	**2c**	Et	toluene	23	49	29 (57)	9.0:1[c]
30	**1c**	C_3H_7	**2c**	Et	benzene	75	28	46 (64)	8.1:1[c]

[a] Isolated yields. The yields based on recovered starting material are in parentheses. [b] Determined by HPLC. [c] Determined by GC-MS.

the C_4, $C_{4'}$, and $C_{5'}$ of isoxazolines **6** and **7**. These facts suggest that the regiochemistry of the major cycloadducts **3** is the same as that of isoxazolines **6** and **7** which also are the predominant products of the cycloaddition reactions.

Various solvents (THF, ether, ethyl acetate, toluene, and benzene) were used to study the solvent effect. Acetals **1a-c** were treated with nitrile oxides **2a-c** under the conditions noted in Table 1. Lower temperatures were used when the reactions were carried out in ether due to its volatility. The cycloaddition reactions went sluggishly in benzene at room temperature, and thus the reactions were carried out at higher temperature. The results outlined in Table 1 reveal that both the reaction yield and regioselectivity are not very sensitive to solvent changes. EtOAc appeared to be the solvent of choice based on both the regioselectivities and the yields of cycloaddition reactions. Higher regioselectivity was observed when the reaction of acetal **1b** and CEFNO was carried out at 4 °C (entry 15) as compared to 23 °C (entry 14). However, no marked effect of reaction temperature on regiochemistry was observed in other cases.

The reactions between acetals **1a–c** and 1-nitropropane were carried out using Mukaiyama's method for the generation of the nitrile oxides.[14a] The desired isoxazoline in each case could be detected by the ^1H NMR analysis of the crude reaction mixture. Unfortunately, the cycloadduct could not be isolated due to the close polarity of the desired product and the diphenylurea byproduct. Different solvent systems were tried but to no avail. As a result, tosyl isocyanate was used in the generation of nitrile oxides to avoid the formation of diphenylurea. To our dismay, however, no isoxazoline product could be found in the reaction mixture using a variety of reaction temperatures and different amounts of tosyl isocyanate. Therefore, the nitrile oxide was prepared utilizing ethyl chloroformate to give the 2-isoxazolines in synthetically useful yields (Table 1).[20]

The use of ethyl chloroformate improved the yields of the desired isoxazolines considerably. The isolation of products was facilitated not only by eliminating the formation of diphenylurea but also by the formation of water soluble side products (EtOH + HCl + CO_2) which were easily removed. Consequently, the crude product mixture was much cleaner than that using phenyl isocyanate as revealed by the ^1H NMR.

We conclude that the 1,3-dipolar cycloaddition reaction between α,β-unsaturated acetals and nitrile oxides exhibits higher reactivity than the corresponding α,β-unsaturated aldehydes. The regioselectivities accomplished with unsaturated acetals as the dipolarophiles are generally higher than those with α,β-unsaturated ketones and esters and thus are preparatively more advantageous. The successful utilization of α,β-unsaturated acetals in this reaction provides an important extension of the scope of the cycloaddition process. Ongoing studies are being directed toward improving the efficiency, extending the scope, and developing enantioselective variants of this reaction.

Experimental Section

Melting points are uncorrected. ^1H 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

(20) Shimizu, T.; Hayashi, Y.; Shibafuchi, H.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2827.

column (SGE; 1.0 μm 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 A: To a 10 mL round-bottomed flask containing a solution of the unsaturated acetal (1.0 equiv) and Et_3N (4.0 equiv) in a solvent specified in Table 1 (0.5 mL) was added a solution of chlorooxime (4.0 equiv) in the same solvent (6.5 mL) over 48 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 × 1) and brine (10 mL × 1), dried ($MgSO_4$), and concentrated. The crude reaction mixture was purified by flash column chromatography (hexane/EtOAc) to furnish the desired products. Some of the regioisomeric pairs required the use of either MPLC or HPLC to effect the separation to give analytically pure samples as indicated for each compound.

General Procedure B. To a mixture of the unsaturated 1,3-dioxolane (1.0 equiv), Et_3N (11.0 equiv) and 1-nitropropane (4.0 equiv) in a 25 mL two-necked round-bottomed flask, equipped with a condenser, was added a solvent specified in table 1 (0.5 mL). A solution of ethyl chloroformate (5.0 equiv) in the same solvent (6.5 mL) was added with a syringe pump over 48 h at rt. After the addition was complete, the reaction was worked-up the same way as in Method A.

4-(2′,5′-Dioxacyclopentyl)-3-phenyl-5-phenyl-Δ²-isoxazoline (3aa). The title compound **3aa** was isolated as a colorless solid by flash chromatography (hexane/EtOAc: 20/1 → 8/1). The small amount of unseparated mixture of **3aa** and **4aa** can be separated either by MPLC (hexane/EtOAc: 16/1 → 10/1 → 7/1) or HPLC (hexane/EtOAc/$CHCl_3$: 7/3/1; RI detector); mp 161.9–162.3 °C. IR ($CHCl_3$) 1494 cm^{-1}; ^1H NMR δ 7.74–7.70 (m, 4H), 7.41–7.25 (m, 6H), 5.80 (d, J = 4.8 Hz, 1H), 5.24 (d, J = 3.3 Hz, 1H), 4.15–3.84 (m, 5H); ^{13}C NMR δ 154.7, 141.5, 130.0, 129.7, 128.7, 127.9, 127.3, 125.2, 101.5, 83.1, 65.7, 65.4, 60.1; MS m/z 295 (M^+, 36.13); HRMS calcd for $C_{18}H_{17}NO_3$ 295.121, found 295.1206; Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.13; H, 5.81; N, 5.06.

5-(2′,5′-Dioxacyclopentyl)-3-phenyl-4-phenyl-Δ²-isoxazoline (4aa). The title compound **4aa** was obtained as a colorless liquid; IR ($CHCl_3$) 1470 cm^{-1}; ^1H NMR δ 7.75–7.07 (m, 10H), 5.09 (d, J = 4.3 Hz, 1H), 4.76 (d, J = 4.9 Hz, 1H), 4.54 (t, J = 4.5 Hz, 1H), 4.16–3.84 (m, 4H); ^{13}C NMR δ 157.4, 140.1, 129.3, 129.2, 128.7, 128.6, 127.5, 126.2, 102.8, 89.1, 65.6, 65.3, 55.2; MS m/z 295 (M^+, 3.25); HRMS calcd for $C_{18}H_{17}NO_3$ 295.121, found 295.1207; Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.12; H, 5.76; N, 4.86.

4-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-5-phenyl-Δ²-isoxazoline (3ab). Compound **3ab** is a pale yellow liquid after flash chromatography (hexane/EtOAc: 20/1 → 8/1). The small amount of unseparated mixture of **3ab** and **4ab** can be separated by MPLC (hexane/EtOAc: 15/1); IR ($CHCl_3$) 1726, 1588 cm^{-1}; ^1H NMR δ 7.39–7.26 (m, 5H), 5.79 (d, J = 6.6 Hz, 1H), 5.40 (d, J = 3.0 Hz, 1 H), 4.35 (q, J = 7.2 Hz, 2H), 4.15–3.94 (m, 4H), 3.84 (dd, J = 6.6, 3.0 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.5, 149.2, 140.1, 128.8, 128.3, 125.3, 100.3, 84.9, 65.6, 65.5, 62.1, 58.7, 14.0; MS m/z 291 (M^+, 50.33); HRMS calcd for $C_{15}H_{17}NO_5$ 291.111, found 291.1104; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.72; N, 4.77.

5-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-4-phenyl-Δ²-isoxazoline (4ab). Compound **4ab** is a colorless liquid; IR ($CHCl_3$) 1726, 1589 cm^{-1}; ^1H NMR δ 7.39–7.18 (m, 5H), 5.09 (d, J = 3.3 Hz, 1H), 4.72 (dd, J = 5.4, 3.3 Hz, 1H), 4.58 (d, J = 5.4 Hz, 1H), 4.22 (q, J = 6.6 Hz, 2H), 4.12–3.94 (m, 4H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 159.8, 155.9, 138.0, 129.2, 128.0, 127.5, 102.5, 91.1, 65.8, 65.7, 62.9, 53.4, 13.7; MS m/z 291 (M^+, 1.8); HRMS calcd for $C_{15}H_{17}NO_5$ 291.111, found 291.1104; Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.77; H, 5.79; N, 4.79.

4-(2′,5′-Dioxacyclopentyl)-3-ethyl-5-phenyl-Δ²-isoxazoline (3ac). The title compound **3ac** was isolated as a colorless liquid by flash chromatography (hexane/EtOAc: 20/1 → 8/1); IR ($CHCl_3$) 1494 cm^{-1}; ^1H NMR δ 7.35–7.26 (m, 5H), 5.53 (d, J = 6.3 Hz, 1H), 5.08 (d, J = 4.8 Hz, 1H), 4.12–3.91 (m, 4H), 3.38 (t, J = 5.7 Hz, 1H), 2.62–2.24 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 158.0, 141.5, 128.6, 127.8, 125.5, 102.2, 82.3, 65.6, 65.1, 62.1, 20.8, 10.7; MS m/z 247 (M^+, 35.5); HRMS calcd for $C_{14}H_{17}NO_3$ 247.121, found 247.1202; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.72; N, 5.60.

5-(2′,5′-Dioxacyclopentyl)-3-ethyl-4-phenyl-Δ²-isoxazoline (4ac). Compound **4ac** was obtained as a colorless liquid; IR ($CHCl_3$) 1456 cm^{-1}; ^1H NMR δ 7.37–7.15 (m, 5H), 5.01 (d, J = 3.3 Hz, 1H), 4.44 (dd, J = 5.4, 3.3 Hz, 1H), 4.22 (d, J = 5.4 Hz, 1H), 4.05–3.90 (m, 4H), 2.33–2.01 (m, 2H), 1.07 (t, J = 7.7 Hz, 3H); ^{13}C NMR δ 161.9, 138.4, 129.2, 127.8, 103.1, 87.8, 65.6, 65.5, 57.3, 19.6, 10.7; MS m/z 192 ($M^+-C_3H_5N$, 1.8); HRMS calcd for $C_{11}H_{12}O_3$ ($M^+-C_3H_5N$) 192.079, found 192.0780; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.96; H, 6.78; N, 5.57.

4-(2′,5′-Dioxacyclopentyl)-5-methyl-3-phenyl-Δ²-isoxazoline (3ba). The title compound **3ba** was isolated as a colorless liquid by flash chromatography (hexane/EtOAc: 25/1). The small amount of unseparated mixture of **3ba** and **4ba** can be separated by MPLC (hexane/EtOAc: 20/1); IR ($CHCl_3$) 1462 cm^{-1}; ^1H NMR δ 7.75–7.72 (m, 2H), 7.41–7.38 (m, 3H), 5.12 (d, J = 3.3 Hz, 1H), 4.90 (qd, J = 6.3, 4.8 Hz, 1H), 4.03–3.78 (m, 4H), 3.63 (dd, J = 4.8, 3.3 Hz, 1H), 1.39 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 155.0, 129.8, 129.5, 128.6, 127.2, 101.6, 78.6, 65.5, 65.3, 57.9, 21.3; MS m/z 233 (M^+, 15.8); HRMS calcd for $C_{13}H_{15}NO_3$ 233.105, found 233.1048; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.36; N, 5.87.

5-(2′,5′-Dioxacyclopentyl)-4-methyl-3-phenyl-Δ²-isoxazoline (4ba). Compound **4ba** was obtained as a colorless liquid; IR ($CHCl_3$) 1463 cm^{-1}; ^1H NMR δ 7.72–7.67 (m, 2H), 7.43–7.27 (m, 3H), 4.95 (d, J = 4.2 Hz, 1H), 4.34 (t, J = 4.2 Hz, 1H), 4.11–3.90 (m, 4H), 3.75 (qd, J = 7.2, 4.2 Hz, 1H), 1.36 (d, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.7, 130.0, 128.8, 128.5, 127.2, 102.9, 88.1, 65.6, 65.5, 43.2, 18.0; MS m/z 233 (M^+, 10.7); HRMS calcd for $C_{13}H_{15}NO_3$ 233.105, found 233.1046; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.42; N, 6.02.

4-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-5-methyl-Δ²-isoxazoline (3bb). Flash chromatography (hexane/EtOAc: 20/1 → 8/1) afforded compound **3bb** as a colorless liquid; IR ($CHCl_3$) 1722, 1598 cm^{-1}; ^1H NMR δ 5.31 (d, J = 3.0 Hz, 1H), 4.89 (dq, J = 7.2, 6.6 Hz, 1H), 4.35 (q, J = 6.6 Hz, 2H), 4.06–3.87 (m, 4H), 3.47 (dd, J = 7.2, 3.0 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.9, 149.5, 100.4, 80.8, 65.5, 62.0, 56.7, 21.1, 14.1; MS m/z 228 (M^+-H, 15.8); HRMS calcd for $C_{10}H_{14}NO_5$ (M^+-H) 228.087, found 228.0869; Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.27; H, 6.55; N, 6.27.

5-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-4-methyl-Δ²-isoxazoline (4bb). The title compound **4bb** is a colorless liquid; IR ($CHCl_3$) 1724, 1466 cm^{-1}; ^1H NMR δ 4.99 (d, J = 3.3 Hz, 1H), 4.38 (dd, J = 6.9, 3.3 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 4.10–3.91 (m, 4H), 3.54 (q′, J = 6.9 Hz, 1H), 1.37 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 160.3, 155.3, 102.5, 90.0, 65.7, 65.6, 62.0, 42.3, 17.5, 14.0; MS m/z 228 (M^+-H, 0.9); HRMS calcd for $C_{10}H_{14}NO_5$ (M^+-H) 228.087, found 228.0871.

4-(2′,5′-Dioxacyclopentyl)-3-ethyl-5-methyl-Δ²-isoxazoline (3bc). Purification by flash chromatography (hexane/EtOAc: 20/1 → 8/1) gave compound **3bc** as a colorless liquid; IR ($CHCl_3$) 1476 cm^{-1}; ^1H NMR δ 4.94 (d, J = 5.1 Hz, 1H), 4.59 (qd, J = 6.3, 4.8 Hz, 1H), 4.06–3.85 (m, 4H), 3.01 (dd, J = 5.1, 4.8 Hz, 1H), 2.58–2.33 (m, 2H), 1.35 (d, J = 5.1 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 158.7, 102.3, 77.6, 65.4, 64.9, 59.9, 20.8, 20.7, 10.6; MS m/z 185 (M^+, 49.9); HRMS calcd for $C_9H_{15}NO_3$ 185.105, found 185.1048; Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.02; H, 7.96; N, 7.67.

5-(2′,5′-Dioxacyclopentyl)-3-ethyl-4-methyl-Δ²-isoxazoline (4bc). Compound **4bc** was isolated as a colorless liquid; IR ($CHCl_3$) 1477 cm^{-1}; ^1H NMR δ 4.92 (d, J = 5.4 Hz, 1H), 3.99–3.77 (m, 5H), 3.22 (qd, J = 6.1, 5.7 Hz, 1H), 2.51–2.09 (m, 3H), 1.37 (d, J = 6.0 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.7, 102.2, 87.8, 64.7, 64.4, 45.3, 30.5, 16.6, 10.2; MS m/z 184 (M^+-H, 5.4); HRMS calcd for $C_9H_{14}NO_3$ (M^+-H) 184.097, found 184.0950.

4-(2′,5′-Dioxacyclopentyl)-3-phenyl-5-*n*-propyl-Δ²isoxazoline (3ca). Separation by flash chromatography (hexane/EtOAc: 20/1 → 8/1) furnished compound **3ca** as a colorless liquid; IR ($CHCl_3$) 1466 cm^{-1}; ^1H NMR δ 7.76–7.72 (m, 2H), 7.41–7.38 (m, 3H), 5.11 (d, J = 3.3 Hz, 1H), 4.78 (td, J = 6.9,

4.5 Hz, 1H), 4.03–3.78 (m, 4H), 3.67 (dd, J = 4.5, 3.3 Hz, 1H), 1.78–1.42 (m, 4H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 155.0, 129.8, 128.6, 127.2, 101.7, 82.2, 65.5, 65.3, 56.2, 37.5, 18.2, 13.8; MS m/z 261 (M^+, 16.7); HRMS calcd for $C_{15}H_{19}NO_3$ 261.136, found 261.1367. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.76; H, 7.26; N, 5.28.

5-(2′,5′-Dioxacyclopentyl)-3-phenyl-4-*n*-propyl-Δ²-isoxazoline (4ca). The title compound **4ca** is a colorless liquid; IR ($CHCl_3$) 1467 cm^{-1}; ^{1}H NMR δ 7.70–7.67 (m, 2H), 7.42–7.39 (m, 3H), 4.94 (d, J = 3.6 Hz, 1H), 4.45 (t, J = 3.7 Hz, 1H), 4.08–3.90 (m, 4H), 3.68 (td, J = 6.2, 3.7 Hz, 1H), 1.75–1.51 (m, 2H), 1.39 (sextet, J = 7.6 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 159.7, 130.0, 128.8, 127.2, 103.1, 85.9, 65.6, 65.5, 48.4, 33.3, 19.8, 13.7; MS m/z 261 (M^+, 10.0); HRMS calcd for $C_{15}H_{19}NO_3$ 261.136, found 261.1367; Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.52; N, 5.64.

4-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-5-*n*-propyl-Δ²-isoxazoline (3cb). Flash chromatography (hexane/EtOAc: 20/1 → 8/1) provided compound **3cb** as a colorless liquid; IR ($CHCl_3$) 1716, 1590 cm^{-1}; ^{1}H NMR δ 5.27 (d, J = 2.8 Hz, 1H), 4.78 (dq, J = 6.9, 3.6 Hz, 1H), 4.35 (q, J = 6.3 Hz, 2H), 4.03–3.88 (m, 4H), 3.51 (dd, J = 3.6, 2.8 Hz, 1H), 1.73–1.35 (m, 7H), 0.95 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 160.9, 149.5, 100.5, 84.4, 65.5, 65.4, 61.9, 55.0, 37.2, 17.9, 14.0, 13.7; MS m/z 257 (M^+, 5.2); HRMS calcd for $C_{12}H_{19}NO_5$ 257.126, found 257.1260; Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.97; H, 7.56; N, 5.47.

5-(2′,5′-Dioxacyclopentyl)-3-ethoxycarbonyl-4-*n*-propyl-Δ²-isoxazoline (4cb). Isomer **4cb** was obtained as a colorless liquid; IR ($CHCl_3$) 1722, 1464 cm^{-1}; ^{1}H NMR δ 4.93 (d, J = 3.3 Hz, 1H), 4.48 (dd, J = 5.0, 3.3 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.06–3.88 (m, 4H), 3.46 (dt, J = 5.0, 3.9 Hz, 1H), 1.90–1.62 (m, 4H), 1.35 (t, J=7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.5, 151.9, 102.7, 87.9, 65.8, 65.7, 62.0, 47.3, 33.0, 20.0, 14.1, 13.7; MS m/z 212 ($M^+-C_2H_5O$, 2.7); HRMS calcd for $C_{10}H_{14}NO_4$ ($M^+-C_2H_5O$) 212.092, found 212.0919; Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.27; H, 7.65; N, 5.40.

4-(2′,5′-Dioxacyclopentyl)-3-ethyl-5-*n*-propyl-Δ²-isoxazoline (3cc). Purification by flash chromatography (hexane/EtOAc: 20/1 → 8/1) gave compound **3cc** as a colorless liquid. The small amount of unseparated mixture of **3cc** and **4cc** can be separated by MPLC (hexane/EtOAc: 15/1 → 10/1); IR ($CHCl_3$) 1462 cm^{-1}; ^{1}H NMR δ 4.92 (d, J = 5.1 Hz, 1H), 4.49 (dt, J = 6.9, 4.8 Hz, 1H), 4.06–3.85 (m, 4H), 3.04 (t, J = 5.4 Hz, 1H), 2.59–2.23 (m, 2H), 1.69–1.36 (m, 4H), 1.18 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 158.4, 102.5, 81.2, 65.4, 64.9, 58.4, 37.3, 20.9, 18.3, 13.8, 10.7; MS m/z 213 (M^+, 4.7); HRMS calcd for $C_{11}H_{19}NO_3$ 213.136, found 213.1358; Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.73; H, 9.13; N, 6.43.

5-(2′,5′-Dioxacyclopentyl)-3-ethyl-4-*n*-propyl-Δ²-isoxazoline (4cc). Compound **4cc** was isolated as a colorless liquid; IR ($CHCl_3$) 1464 cm^{-1}; ^{1}H NMR δ 4.87 (d, J = 3.9 Hz, 1H), 4.22 (dd, J = 5.1, 3.9 Hz, 1H), 4.03–3.80 (m, 4H), 3.12 (dt, J = 5.1, 3.6 Hz, 1H), 2.51–2.10 (m, 2H), 1.48–1.22 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 162.5, 103.3, 84.3, 65.5, 65.4, 50.3, 32.6, 19.8, 19.6, 13.8, 10.7; MS m/z 212 (M^+–H, 5.0); HRMS calcd for $C_{11}H_{18}NO_3$ (M^+ – H) 212.129, found 212.1288; Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.88; H, 9.07; N, 6.66.

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Supporting Information Available: Tables of the ^{1}H and ^{13}C NMR spectral data for compounds **3**, **4**, **6**, and **7** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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