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1,3-Dipolar Cycloaddition Reactions of Substituted 3,4-Dihydroisoquinoline *N*-Oxides with Allenes

Bao-Xiang Zhao and Shoji Eguchi*

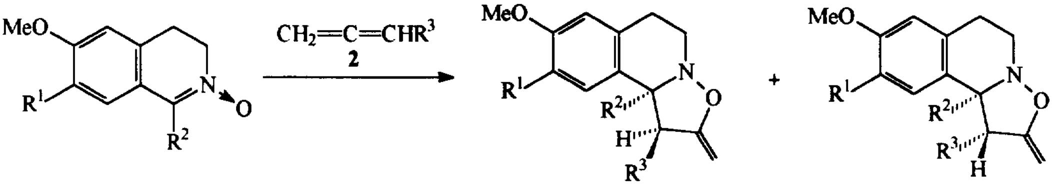
Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University
Furo-cho, Chikusa-ku, Nagoya 464-01, Japan

Abstract: *A study of the 1,3-dipolar cycloaddition behavior of a series of substituted 3,4-dihydroisoquinoline N-oxides with electron-deficient allenes has been carried out. The 1,3-dipolar cycloaddition reaction proceeds in high yield with complete regioselectivity to give 5-methylene isoxazolidines. The stability of these 5-methylene isoxazolidines was depending on the structure of nitrones and allenes.* © 1997 Elsevier Science Ltd.

The 1,3-dipolar cycloaddition reaction has long been recognized as a powerful strategy for the synthesis of heterocyclic rings, often with a high degree of stereochemical control, and nitrones as a class of 1,3-dipoles have attracted considerable attention for the cycloaddition reaction.[1] Allenes are an interesting group of substrates since they contain two positions for attack. The Diels-Alder reaction of allenes with dienes has been studied in some details,[2] and the use of allenes in 1,3-dipolar cycloaddition reaction has also attracted considerable interest recently. The reaction of nitrones with simple allenes was previously reported to provide 3-pyrrolidinones derived from an initial 1,3-dipolar cycloaddition reaction followed by a spontaneous rearrangement of a transient isoxazolidine intermediate.[3] The reaction of some of nitrones with substituted allenes and the rearrangement to isoxazolidine *via* a 1,3-hydrogen shift has also been reported[4] and the cycloaddition reaction of *N*-phenylnitrones with activated allenes has been applied to synthesize the benzazepin-4-one or indoles.[5] However, the nitrones examined seems to be limited in contrast to the plethora of examples dealing with the cycloaddition reaction of nitrones with alkenes,[6] and the reaction of 3,4-dihydroisoquinoline *N*-oxides with allenes has not been reported heretofore. We thought that further extensive study of the cycloaddition reactions of nitrones with allenes is necessary for the efficient synthetic application of nitrones. We were interested in the use of 3,4-dihydroisoquinoline *N*-oxides and their cycloaddition reactions to synthesize new heterocyclic compounds such as isoquinoline fused-pyrroles.[7] We report here the cycloaddition reactions of the substituted 3,4-dihydroisoquinoline *N*-oxides with electron-deficient allenes.

RESULTS AND DISCUSSION

The 3,4-dihydroisoquinoline *N*-oxides **1** were prepared according to our previous report.[8] The 1,3-dipolar cycloaddition reactions of a variety of nitrones **1a-c** with electron-deficient allenes **2a, 2b** in dichloromethane were carried out at room temperature for 1-6 h to give regioselectively isoxazolidine **3a-d, f** and **4a-f** that are the 5-exo methylene isomers and they could be separated by silica gel chromatography, in the case of cycloaddition reaction of **1c** and **2a** only **4e** was obtained (Scheme 1).



1 **3** **4**

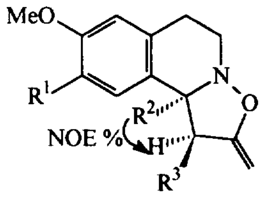
1a: R^1 = MeO, R^2 = H
1b: R^1 = MeO, R^2 = Me
1c: R^1 = H, R^2 = Me

2a: R^3 = CN
2b: R^3 = CO_2Et

3a, 4a: R^1 = MeO, R^2 = H, R^3 = CN
3b, 4b: R^1 = MeO, R^2 = H, R^3 = CO_2Et
3c, 4c: R^1 = MeO, R^2 = Me, R^3 = CN
3d, 4d: R^1 = MeO, R^2 = Me, R^3 = CO_2Et
3e, 4e: R^1 = H, R^2 = Me, R^3 = CN
3f, 4f: R^1 = H, R^2 = Me, R^3 = CO_2Et

Scheme 1

The stereochemical assignment of **3a** and **4a** was readily made on the basis of the magnitude of the vicinal coupling constant (J_{cis} = 9-10 Hz vs. J_{trans} = 7-8.5 Hz);[9] the coupling constant in **3a** is 10 Hz and in **4a** is 8.0 Hz. However, in the case of **3b** and **4b**, it is difficult to assign the stereoisomers based on the magnitude of the vicinal coupling constant because they have a same magnitude, *i.e.*, 9.6 Hz, therefore, the stereoisomers were determined by NOE spectrum. When R^2 were methyl and phenyl, stereoisomers were similarly determined by NOE spectral data (see Fig. 1).



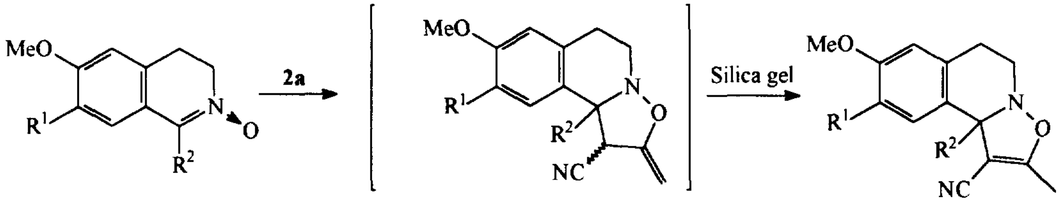
3

	NOE %
3b: R^1 = MeO, R^2 = H, R^3 = CO_2Et	5
3c: R^1 = MeO, R^2 = Me, R^3 = CN	7
3d: R^1 = MeO, R^2 = Me, R^3 = CO_2Et	11
3f: R^1 = H, R^2 = Me, R^3 = CO_2Et	10
3g: R^1 = MeO, R^2 = Ph, R^3 = CN	12

Fig. 1

It has been reported that the cycloaddition reaction of *N*-methyl-*C*-phenylnitrone with cyanoallene gave 5-exo methylene isomer which rearranged easily to Δ^4-isoxazoline *via* a 1,3-hydrogen shift rather than by N-O bond scission. In our studies, we found that the 5-exo methylene isomers **3a-d**, **f** and **4a-f** were considerably stable on silica gel and no thermal rearrangement was observed at 80 °C.

To the contrary, the cycloaddition reactions of 1-aryl substituted 3,4-dihydroisoquinoline *N*-oxide **1d-g** with cyanoallene **2a** gave initially 5-exo methylene isomers detected by ^{1}H NMR, however, the 1,3-hydrogen shift easily occurred when they were separated by silica gel chromatography. In the case of R^2 = Ph, one pure 5-exo methylene isomer was isolable and assigned as **3g** on the basis of its spectroscopic properties and NOE enhancements, while a mixture of **4g** and **5g** could not be separated each other because their R_f value on silica gel chromatography were almost same when ethyl acetate / hexane solvent systems were used as an eluent. When R^2 = *p*-$MeOC_6H_4$, the reaction gave a 5-exo methylene isoxazolidine **3i** (or **4i**) and a mixture of **4i** (or **3i**) and Δ^4-isoxazoline **5i** (Scheme 2). Furthermore, when R^2 = *p*-$NO_2C_6H_4$, Δ^4-isoxazoline **5j** was readily formed from **3j** and **4j** on silica gel chromatography and separated as the major product.

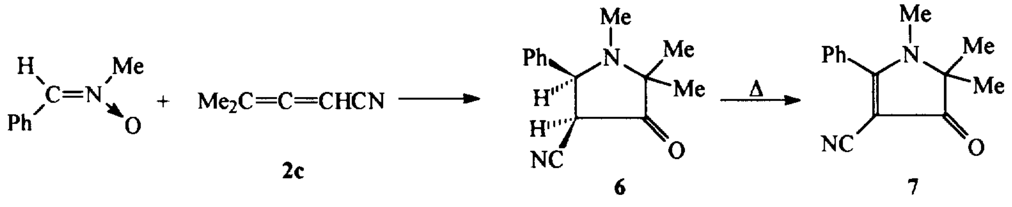


1 **3/4** **5**

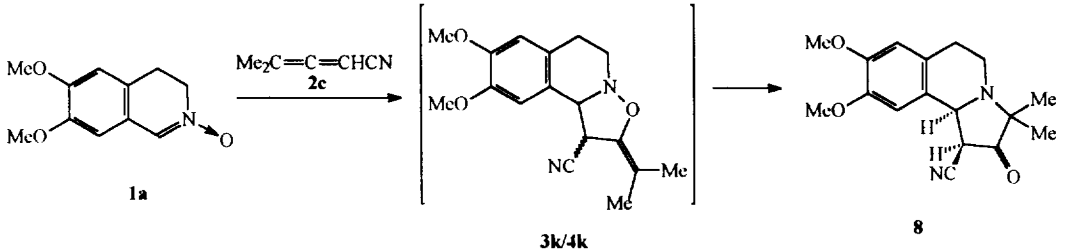
1d: R^1 = MeO, R^2 = Ph	**3g, 4g, 5g**: R^1 = MeO, R^2 = Ph
1e: R^1 = H, R^2 = Ph	**3h, 4h, 5h**: R^1 = H, R^2 = Ph
1f: R^1 = MeO, R^2 = *p*-$MeOC_6H_4$	**3i, 4i, 5i**: R^1 = MeO, R^2 = *p*-$MeOC_6H_4$
1g: R^1 = MeO, R^2 = *p*-$NO_2C_6H_4$	**3j, 4j, 5j**: R^1 = MeO, R^2 = *p*-$NO_2C_6H_4$

Scheme 2

Having established the experimental feasibility of the cycloaddition reactions of nitrones **1a-g** with allenes **2a** and **2b**, we directed our attention to using another allene, *i.e.*, 4-methyl-2,3-pentadienenitrile **2c**. Firstly, we examined the reaction of *C*-phenyl-*N*-methylnitrone with **2c** (Scheme 3). After stirring a mixture of these two compounds in toluene at room temperature for 6 h, a single pyrrolidinone **6** was obtained in 56% yield. The pyrrolidinone **6** was easily dehydrogenated in toluene at 90 °C for 2 h to give 4-cyano-1,2,2-trimethyl-5-phenylpyrrolin-3(2*H*)-one **7** in 65% yield. Similarly, we examined the cycloaddition reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide **1a** with **2c**. By stirring a mixture of these two compounds in dichloromethane at 0 °C for 1 h, two spots in TLC were appeared, which were assumed to be the 5-exo methylene isomers. However, these spots were converted to a new spot at room temperature for 6 h which was isolated and assigned as pyrrolidinone **8** (Scheme 4).



Scheme 3



Scheme 4

We can conclude from the fact described above that the rearrangement of 5-exo methylene isoxazolidine is not only particularly sensitive to the kind of the substituent groups on the double bond, but also obviously affected by the structure of the nitrone.

The regio- and stereoselectivities of 1,3-dipolar cycloaddition reactions are very important in its synthetic use. The fact that all cycloaddition reactions described above gave the 5-exo methylene isoxazolidines initially indicates that the cycloaddition process proceeded with high regioselectivity. Based on FMO theory, allenes possessing electron-withdrawing substituents are expected to react more readily and to undergo 1,3-dipolar cycloaddition reaction across the activated C_1-C_2 π-bond. It has been reported that MNDO calculations of several substituted allenes indicate that the introduction of an electron-withdrawing group on the double bond causes a significant lowering of the LUMO energy level compared with parent allene and the largest LUMO coefficient resides on the central carbon and the next on the position bearing the activating group, therefore, the reaction of *C*-phenyl-*N*-methylnitrone with electron-deficient allenes proceeds in a highly regioselective fashion and gives rise to the 5-exo methylene isoxazolidine.[4] This was also the case when substituted 3,4-dihydroisoquinoline *N*-oxides were used. We calculated the HOMO and the LUMO of the nitrones and allenes based on PM3.[10] The HOMO and LUMO levels of the nitrones and allenes are summarized in Table 1. The nitrone HOMO-dipolarophile LUMO interaction is of smallest energy. On the other hand, the stereochemistry of nitrone additions to alkenes has received considerable attention. Nitrone cycloaddition reaction may proceed through exo or endo transition states as for Diels-Alder reactions. A generally accepted view of these reactions involves an approach of the addends in two parallel planes. A possibility of nitrone *E*-*Z* isomerization give rise to four kinds of transition state, *i.e.*, *E*-endo, *E*-exo and *Z*-endo, *Z*-exo. In present, because the configurationally-fixed nitrones were employed, only two kinds of transition state can be expected to occur, *i.e.*, *E*-endo and *E*-exo. This indeed proved to be the case. In order to avoid the influence of TLC, we determined the ratio of *cis* and *trans* isomers of 5-exo methylene isoxazolidine obtained by the reactions of **1a-g** with **2a** based on ^{1}H NMR before isolation work up (Table 2). The results indicate that the cycloaddition reactions are nearly nonstereoselective.

Table 1. HOMO and LUMO Levels (eV) of the Nitrones and Allenes

nitrone	HOMO	LUMO	allenes	HOMO	LUMO
1a	-8.701	-0.605	CH_2=C=CH_2	-10.174	1.111
1b	-8.654	-0.606	CH_2=C=CHCN	-10.436	-0.182
1c	-8.459	-0.407	CH_2=C=$CHCO_2Et$	-10.545	-0.054
1d	-8.548	-0.630	Me_2C=C=CHCN	-10.251	-0.062
1e	-8.468	-0.431			
1f	-8.482	-0.463			
1g	-9.097	-1.102			

Table 2. The Ratios of *cis*- and *trans*-Isomers of 5-exo Methylene Isoxazolidine Determined by ^{1}H NMR

3 and 4	ratio (3/4)	3 and 4	ratio (3/4)
a	50/50	**h**	58/42
c	25/75	**i**	54/46
g	58/42	**j**	47/53

The 1,3-dipolar cycloaddition reaction of substituted 3,4-dihydroisoquinoline *N*-oxides with electron-deficient allenes proceeds in high yield with complete regiospecificity to give 5-exo methylene isoxazolidines which are stable isolated products or rearranged to Δ^4-isoxazoline by 1,3-hydrogen shift or to pyrrolidinone by N-O bond scission depending on both the structures of nitrones and allenes.

Studies of the thermal rearrangement of some 5-exo methylene isoxazolidines in higher temperature and their application toward the synthesis of fused-pyrrole are in progress and will be reported in due the course.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra of liquids were measured as films on sodium chloride plates and those of solids were measured in pressed potassium bromide discs on a JASCO FT/IR 5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian GEMINI 200 spectrometer at 200 and at 50 MHz, respectively. Chemical shifts are recorded in part per million (ppm) for samples in $CDCl_3$ solution with Me_4Si as an internal standard. Coupling constants *J* are reported in Hz. Elemental analysis were carried out on a Perkin-Elmer 2400S elemental analyzer. Mass spectra (EI) were obtained using a JEOL JMS-AX505 HA mass spectrometer at 70 eV. The thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254}.

General Procedures

A solution of 3,4-dihydroisoquinoline *N*-oxide (**1**) (0.2 mmol) and allene (**2**) (0.4 mmol) in dichloromethane (2 mL) was stirred at room temperature for 1-6 h, while the reaction was monitored by TLC. After removal of the solvent under a reduced pressure, separation of the residue with preparative TLC or column chromatography gave the products.

***cis*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (3a)**. A white solid, yield 48 %, mp 136-139 °C, R_f = 0.44 (ethyl acetate / hexane, 1:1); IR (KBr) 2245, 1668, 1610, 1524, 1470, 1415, 1367, 1348, 1259, 1231, 1121, 1020, 974, 949, 887 cm^{-1}; ^{1}H NMR δ 2.73-3.19 (m, 3H), 3.44-3.52 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 4.04 (dt, 1H, *J* = 10 and 2.2), 4.45 (dd, 1H, *J* = 3.2 and 2.2), 4.68 (dd, 1H, *J* = 3.2 and 2.2), 4.86 (d, 1H, *J* = 10), 6.63 (s, 1H), 6.89 (s, 1H); ^{13}C NMR δ 28.1, 41.2, 49.7, 56.1, 56.2, 65.7, 84.6, 109.5, 111.2, 117.8, 121.7, 125.1, 148.8, 149.6, 156.3; MS *m/z* (%) 272 (M$^+$, 55), 271 (21), 205 (100), 191 (55), 190 (63). *Anal* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.29; H, 6.11; N, 9.97.

***trans*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4a)**. A white solid, yield 30 %, mp 141-144 °C, R_f = 0.32 (ethyl acetate / hexane, 1:1); IR (KBr) 2245, 1657, 1613, 1522, 1470, 1449, 1368, 1259, 1225, 1128, 1014, 864 cm^{-1}; ^{1}H NMR δ 2.84-3.03 (m, 2H), 3.39-3.45 (m, 2H), 3.88 (s, 6H), 4.36 (dt, 1H, *J* = 8.0 and 1.8), 4.49 (dd, 1H, *J* = 1.8 and 3.2), 4.74 (dd, 1H, *J* = 1.8 and 3.2), 4.92 (d, 1H, *J* = 8.0), 6.61 (s, 1H), 6.67 (s, 1H); ^{13}C NMR δ 27.3, 40.9, 49.5, 56.0, 56.3, 63.9, 86.3, 110.2, 111.3, 117.8, 121.3, 126.6, 148.7, 149.5, 156.3; MS *m/z* (%) 272 (M$^+$, 100), 271 (91), 205 (43), 191 (66), 190 (46). *Anal* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.21; H, 5.88; N, 10.15.

***cis*-Ethyl 1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3b)**. A white solid, yield 40 %, mp 99-101 °C, R_f = 0.12 (ethyl acetate / hexane, 1:2); IR (KBr) 2971, 1744, 1719, 1672, 1611, 1518, 1460, 1369, 1258, 1225, 1157, 1128, 1016, 943, 881, 817, 772 cm^{-1}; ^{1}H NMR δ 0.98 (t, 3H, *J* = 7.2), 2.27-2.81 (m, 1H), 2.96-3.13 (m, 1H), 3.34-3.42 (m, 1H), 3.62-3.70 (m, 1H), 3.85 (s, 6H), 3.83 (q, 2H, *J* = 7.2), 4.22 (t, 1H, *J* = 2.2), 4.32 (dt, 1H, *J* = 9.6 and 2.0), 4.68 (t, 1H, *J* = 2.2), 5.06 (d, 1H, *J* = 9.6), 6.58 (s, 1H), 6.60 (s, 1H); ^{13}C NMR δ 13.9, 28.2, 49.2, 55.6, 55.9, 56.1, 61.3, 64.4, 84.8, 110.7, 110.9, 122.7, 126.7, 147.7, 148.7, 160.4, 170.6; MS *m/z* (%) 319 (M$^+$, 48), 318 (100), 246 (11), 205 (10), 191 (17), 176 (11). *Anal* Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.81; H, 6.72; N, 4.31.

***trans*-Ethyl 1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (4b)**. A white solid, yield 40 %, mp 113-115 °C, R_f = 0.18 (ethyl acetate / hexane, 1:2); IR (KBr) 2980, 1725, 1672, 1612, 1524, 1472, 1366, 1345, 1300, 1263, 1211, 1182, 1119, 1049, 1017, 952, 866, 804, 772 cm^{-1}; ^{1}H NMR δ 1.35 (t, 3H, *J* = 7.2), 2.75-2.86 (m, 1H), 2.96-3.16 (m, 2H), 3.37-3.45 (m, 1H), 3.81 (s, 3H), 3.86 (s, 3H), 3.93 (dt, 1H, *J* = 9.6 and 2.2), 4.25 (t, 1H, *J* = 2.2), 4.33 (q, 2H, *J* = 7.2), 4.53 (t, 1H, *J* = 2.2), 5.10 (d, 1H, *J* = 9.6), 6.61 (s, 1H), 6.63 (s, 1H); ^{13}C NMR δ 14.3, 28.0, 49.9, 55.8, 56.1, 62.0, 64.6, 82.6, 109.7, 111.1, 125.2, 148.4, 148.9, 159.5, 170.4; MS *m/z* (%) 319 (M$^+$, 37), 246 (60), 205 (100), 191 (57), 190 (39), 176 (22). *Anal* Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.98; H, 6.57; N, 4.41.

***cis*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (3c)**. A white solid, yield 18.0 %, mp 125-127 °C, R_f = 0.19 (ethyl acetate / hexane, 1:1); IR

(KBr) 2245, 1657, 1613, 1516, 1466, 1356, 1265, 1208, 1157, 1073, 968, 916, 864, 770 cm^{-1}; ^{1}H NMR δ 1.69 (s, 3H), 2.76-3.05 (m, 2H), 3.31-3.59 (m, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 4.12 (t, 1H, *J* = 2.0), 3.33 (dd, 1H, *J* = 2.0 and 3.2), 4.56 (dd, 1H, *J* = 2.0 and 3.2), 6.62 (s, 1H), 6.83 (s, 1H); ^{13}C NMR δ 25.8, 28.3, 47.0, 48.7, 56.0, 56.3, 68.4, 84.2, 110.1, 111.3, 117.2, 126.0, 126.4, 146.5, 149.1, 155.3; MS *m/z* (%) 286 (M$^+$, 13), 271 (100), 229 (18), 205 (15). *Anal* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.19; H, 6.38; N, 9.71.

trans-1,5,6,10b-Tetrahydro-8,9-dimethoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4c). A white solid, yield 50 %, mp 123-124 °C, R_f = 0.27 (ethyl acetate / hexane, 1:1); IR (KBr) 2245, 1676, 1612, 1516, 1464, 1362, 1259, 1213, 1144, 1086, 1067, 970, 819, 768 cm^{-1}; ^{1}H NMR δ 1.76 (s, 3H), 2.71-2.80 (m, 1H), 2.93-3.18 (m, 2H), 3.46-3.53 (m, 1H), 3.87 (s, 3H), 3.91 (s, 3H), 4.17 (t, 1H, *J* = 2.4), 4.40 (dd, 1H, *J* = 2.4 and 3.2), 4.62 (dd, 1H, *J* = 2.4 and 3.2), 6.59 (s, 1H), 6.93 (s, 1H); ^{13}C NMR δ 24.8, 28.0, 45.7, 50.2, 56.1, 56.2, 67.5, 84.1, 108.7, 111.1, 117.2, 124.8, 128.4, 148.8, 149.1, 156.0; MS *m/z* (%) 286 (M$^+$, 46), 271 (42), 243 (10), 229 (18), 221 (20), 206 (19), 205 (100), 204 (34), 190 (28). *Anal* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.21; H, 6.25; N, 9.82.

cis-Ethyl 1,5,6,10b-Tetrahydro-8,9-dimethoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (3d). A white solid, yield 30 %, mp 83-85 °C, R_f = 0.20 (ethyl acetate / hexane, 1:2); IR (KBr) 2975, 1742, 1636, 1613, 1518, 1466, 1337, 1263, 1211, 1159, 1032, 934, 878, 822 cm^{-1}; ^{1}H NMR δ 1.01 (t, 3H, *J* = 7.0), 1.71 (s, 3H), 2.67- 2.79 (m, 1H), 2.95-3.11 (m, 1H), 3.34-3.43 (m, 1H), 3.74-3.96 (m, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.05 (t, 1H, *J* = 2.0), 4.14 (t, 1H, *J* = 2.0), 4.62 (t, 1H, *J* = 2.0), 6.57 (s, 1H), 6.64 (s, 1H); ^{13}C NMR δ 13.9, 28.1, 32.1, 49.5, 55.9, 56.2, 61.3, 62.5, 69.4, 84.0, 110.3, 110.8, 126.6, 128.1, 147.8, 148.4, 160.7, 170.8; MS *m/z* (%) 333 (M$^+$, 66), 318 (100), 246 (63), 221 (50), 205 (99), 190 (26). *Anal* Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.96; H, 7.01; N, 4.17.

trans-Ethyl 1,5,6,10b-Tetrahydro-8,9-dimethoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (4d). A pale yellowish oil, yield 60 %, R_f = 0.16 (ethyl acetate / hexane, 1:2); IR (neat) 2936, 1740, 1672, 1612, 1516, 1464, 1360, 1260, 1217, 1142, 1034, 970, 862, 814, 769 cm^{-1}; ^{1}H NMR δ 1.35 (t, 3H, *J* = 7.2), 1.59 (s, 3H), 2.71-3.02 (m, 2H), 3.26-3.50 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.97 (t, 1H, *J* = 1.8), 4.07 (t, 1H, *J* = 1.8), 4.24-4.40 (m, 2H), 4.43 (t, 1H, *J* = 1.8), 6.56 (s, 1H), 6.72 (s, 1H); ^{13}C NMR δ 14.3, 24.7, 25.4, 47.9, 56.0, 56.3, 60.2, 61.7, 67.9, 82.3, 109.9, 111.1, 125.5, 130.3, 148.3, 148.6, 158.3, 170.3; MS *m/z* (%) 333 (M$^+$, 44), 318 (49), 221 (52), 205 (100), 190 (19). *Anal* Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.81; H, 6.88; N, 4.26.

trans-1,5,6,10b-Tetrahydro-8-methoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4e). A pale yellowish oil, yield 52 %, R_f = 0.34 (ethyl acetate / hexane, 1:2); IR (neat) 2939, 2247, 1676, 1612, 1505, 1466, 1381, 1333, 1254, 1221, 1138, 1030, 960, 925, 822 cm^{-1}; ^{1}H NMR δ 1.74 (s, 3H), 2.77-2.87 (m, 1H), 2.95-3.21 (m, 2H), 3.46-3.54 (m, 1H), 3.80 (s, 3H), 4.14 (t, 1H, *J* = 2.2), 4.40 (dd, 1H, *J* = 2.2 and 3.2), 4.61 (dd, 1H, *J* = 2.2 and 3.2), 6.65 (d, 1H, *J* = 2.8), 6.86 (dd, 1H, *J* = 2.8 and 8.8), 7.40 (d, 1H, *J* = 8.8); ^{13}C NMR δ 25.0, 28.6, 45.9, 50.0, 55.5, 67.6, 84.2, 113.5, 113.9, 117.1, 127.8, 128.8, 134.1, 156.1, 159.5; MS *m/z* (%) 256 (M$^+$, 33), 241 (21), 213 (11), 199 (11), 175 (100). *Anal* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.28; H, 6.30; N, 10.93. Found: C, 70.22; H, 6.26; N, 10.98.

cis-Ethyl 1,5,6,10b-Tetrahydro-8-methoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-

carboxylate (3f). A yellowish oil, yield 32 %, R_f = 0.36 (ethyl acetate / hexane, 1:2); IR (neat) 2978, 1738, 1668, 1511, 1505, 1462, 1337, 1258, 1173, 1032, 916, 814 cm^{-1}; ^{1}H NMR δ 1.01 (t, 3H, *J* = 7.2), 1.69 (s, 3H), 2.73-2.84 (m, 1H), 2.99-3.16 (m, 1H), 3.34-3.43 (m, 1H), 3.68-3.97 (m, 3H), 3.78 (s, 3H), 4.04 (t, 1H, *J* = 1.8), 4.14 (dd, 1H, *J* = 1.8 and 2.4), 4.61 (dd, 1H, *J* = 1.8 and 2.4), 6.10 (d, 1H, *J* = 2.6), 6.74 (dd, 1H, *J* = 8.6 and 2.6), 7.10 (d, 1H, *J* = 8.6); ^{13}C NMR δ 13.8, 28.7, 32.1, 49.4, 55.4, 61.3, 62.7, 69.4, 83.9, 112.5, 113.1, 128.6, 128.7, 135.5, 158.8, 160.7, 170.8; MS *m/z* (%) 303 (M$^+$, 28), 288 (100), 216 (34), 191 (20), 175 (45). *Anal* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.52. Found: C, 67.36; H, 6.90; N, 4.71.

***trans*-Ethyl 1,5,6,10b-Tetrahydro-8-methoxy-10b-methyl-2-methylene-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carboxylate (4f)**. A pale yellowish oil, yield 51 %, R_f = 0.30 (ethyl acetate / hexane, 1:2); IR (neat), 2393, 1742, 1672, 1611, 1503, 1464, 1372, 1321, 1263, 1173, 1032, 966, 814 cm^{-1}; ^{1}H NMR δ 1.34 (t, 3H, *J* = 7.2), 1.57 (s, 3H), 2.76-3.09 (m, 2H), 3.27-3.49 (m, 2H), 3.79 (s, 3H), 3.96 (dd, 1H, *J* = 1.6 and 2.6), 4.05 (t, 1H, *J* = 1.8), 4.31 (qd, 2H, *J* = 1.2 and 7.2), 4.30 (dd, 1H, *J* = 1.8 and 2.4), 6.61 (d, 1H, *J* = 2.6), 6.80 (dd, 1H, *J* = 2.6 and 8.8), 7.17 (d, 1H, *J* = 8.8); ^{13}C NMR δ 14.3, 24.7, 26.1, 47.8, 55.4, 60.3, 61.6, 67.9, 82.3, 113.0, 113.6, 128.5, 130.7, 134.5, 158.3, 158.8, 170.2; MS *m/z* (%) 303 (M$^+$, 49), 288 (56), 216 (27), 191 (52), 175 (100). *Anal* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.52. Found: C, 67.42; H, 6.89; N, 4.59.

***cis*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-10b-phenyl-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (3g)**. A pale yellowish solid, yield 31 %, mp 50-53 °C, R_f = 0.38 (ethyl acetate / hexane, 1:2); IR (KBr) 2210, 1655, 1518, 1464, 1364, 1263, 1209, 1138, 1020, 852, 752 cm^{-1}; ^{1}H NMR δ 2.76-2.90 (m, 1H), 3.05-3.20 (m, 1H), 3.24-3.3 (m, 1H), 3.53-3.65 (m, 1H), 3.78 (s, 3H), 3.90 (s, 3H), 4.36 (dd, 1H, *J* = 2.0 and 3.2), 4.51 (dd, 1H, *J* = 2.0 and 3.2), 4.99 (t, 1H, *J* = 2.0), 6.68 (s, 1H), 6.80 (s, 1H), 7.35-7.37 (m, 5H); ^{13}C NMR δ 24.8, 46.4, 47.3, 56.0, 56.2, 73.6, 83.2, 110.9, 111.1, 112.3, 117.2, 124.0, 127.4, 128.3, 128.6, 129.0, 129.1, 140.5, 148.1; MS *m/z* (%) 348 (M$^+$, 12), 271 (100). *Anal* Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.46; H, 5.72; N, 8.15.

***trans*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-10b-phenyl-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4g)** and **5,6-Dihydro-8,9-dimethoxy-2-methyl-10b-phenyl-10b*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (5g)**. This fraction was an inseparable (1:4) mixture of **4g** and **5g**, yield 33 %, a pale yellowish solid, mp 43-45 °C, R_f = 0.30 (ethyl acetate / hexane, 1:2); IR (KBr) 2209, 1651, 1607, 1516, 1449, 1362, 1261, 1136, 1024, 851, 750 cm^{-1}; The **4g** showed the following ^{1}H NMR spectral data, δ 2.72-3.64 (m, 4H), 3.76 (s, 3H), 3.89 (s, 3H), 4.54 (dd, 1H, *J* = 2.4 and 3.2), 4.58 (dd, 1H, *J* = 2.4 and 3.2), 4.67 (t, 1H, *J* = 2.4), 6.65 (s, 1H), 6.67 (s, 1H), 7.20-7.46 (m, 5H); The **5g** showed the following ^{1}H NMR spectral data, δ 2.17 (s, 3H), 2.65-3.65 (m, 4H), 3.73 (s, 3H), 3.89 (s, 3H), 6.57 (s, 1H), 6.65 (s, 1H), 7.20-7.46 (m, 5H); MS *m/z* (%) 348 (M$^+$, 13), 271 (100). *Anal* Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.51; H, 5.85; N, 8.01.

***cis*-1,5,6,10b-Tetrahydro-8-methoxy-2-methylene-10b-phenyl-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (3h)**. A pale yellowish solid, yield 18 %, mp 38-40 °C, R_f = 0.33 (ethyl acetate / hexane, 1:2). IR (KBr) 2210, 1655, 1610, 1503, 1447, 1254, 1132, 1039, 970, 816, 754, 698 cm^{-1}; ^{1}H NMR δ 3.04-3.15 (m, 2H), 3.35-3.46 (m, 1H), 3.5-3.68 (m, 1H), 3.81 (s, 3H), 4.43 (dd, 1H, *J* = 1.8 and 3.2), 4.58 (dd, 1H, *J* = 1.8 and 3.2), 4.98 (t, 1H, *J* = 1.8), 6.73 (d, 1H, *J* = 2.6), 6.81 (dd, 1H, *J* = 2.6 and 8.6), 7.14 (d, 1H, *J* = 8.6), 7.30-7.38 (m, 5H); ^{13}C NMR δ 26.7, 45.9, 48.4, 55.4, 73.9, 84.3, 113.4, 113.8, 117.3, 125.7, 127.9, 128.8, 129.0, 131.0, 135.9, 141.7, 156.0, 159.4. *Anal* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.76; N, 8.88.

***trans*-1,5,6,10b-Tetrahydro-8-methoxy-2-methylene-10b-phenyl-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4h) and 5,6-Dihydro-8-methoxy-2-methyl-10b-phenyl-10b*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (5h)**. This fraction was an inseparable (1:1) mixture of **4h** and **5h**, yield 37 %, a pale yellowish solid, mp 45-47 °C, R_f = 0.28 (ethyl acetate / hexane, 1:2); IR (KBr) 2213, 1657, 1611, 1503, 1449, 1265, 1039, 817, 754, 698 cm^{-1}; The **4h** showed the following ^1H NMR spectral data, δ 2.88-3.58 (m, 4H), 3.82 (s, 3H), 4.50 (dd, 1H, *J* = 2.2 and 3.2), 4.55 (t, 1H, *J* = 2.2), 4.30 (dd, 1H, *J* = 2.2 and 3.2), 6.71 (d, 1H, *J* = 2.8), 6.83 (dd, 1H, *J* = 2.8 and 8.8), 7.18 (d, 1H, *J* = 8.8), 7.33-7.38 (m, 5H); The **5h** showed the following ^1H NMR spectral data, δ 2.17 (s, 3H), 2.88-3.58 (m, 4H), 3.80 (s, 3H), 6.72 (d, 1H, *J* = 2.8), 6.76 (dd, 1H, *J* = 2.8 and 8.8), 7.02 (d, 1H, *J* = 8.8), 7.33-7.38 (m, 5H). *Anal* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.66; N, 8.76.

1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-10b-(*p*-methoxyphenyl)-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (3i or 4i). A pale yellowish solid, yield 11 %, mp 52-54 °C, R_f = 0.21 (ethyl acetate / hexane, 1:2); IR (KBr) 2936, 2211, 1610, 1514, 1464, 1366, 1258, 1136, 1030, 955, 829 cm^{-1}; ^1H NMR δ 2.69-2.84 (m, 1H), 3.05-3.28 (m, 2H), 3.49-3.62 (m, 1H), 3.80 (s, 6H), 3.90 (s, 3H), 4.32 (dd, 1H, *J* = 1.8 and 3.2), 4.46 (dd, 1H, *J* = 2.2 and 3.2), 4.93 (t, 1H, *J* = 2.0), 6.67 (s, 1H), 6.85 (s, 1H), 6.86 (dd, 2H, *J* = 2.2 and 7.0), 7.26 (dd, 2H, *J* = 2.2 and 7.0); ^{13}C NMR δ 24.3, 46.6, 46.8, 55.5, 55.9, 56.2, 73.2, 82.7, 111.1, 112.4, 114.3, 117.2, 123.9, 127.5, 129.7, 131.9, 148.0, 149.2, 155.0, 160.1; MS *m/z* (%) 378 (M^+, 23), 263 (17), 335 (42), 271 (100). *Anal* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.89; H, 5.78; N 7.46.

1,5,6,10b-Tetrahydro-8,9-dimethoxy-2-methylene-10b-(*p*-methoxyphenyl)-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (4i or 3i) and 5,6-Dihydro-8,9-dimethoxy-2-methyl-10b-(*p*-methoxyphenyl)-10b*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (5i). This fraction was an inseparable (4:7) mixture of **4i** and **5i**, yield 44 %, a pale yellowish solid, mp 58-60 °C, R_f = 0.16 (ethyl acetate / hexane, 1:2); The **4i** or **3i** showed the following ^1H NMR spectral data, δ 2.67-3.65 (m, 4H), 3.77 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 4.51 (dd, 1H, *J* = 2.0 and 3.2), 4.55 (dd, 1H, *J* = 2.2 and 2.6), 4.65 (dd, 1H, *J* = 2.6 and 3.2), 6.65 (s, 1H), 6.68 (s, 1H), 6.85 (d, 2H, *J* = 9.2), 7.36 (d, 2H, *J* = 9.2); The **5i** showed the following ^1H NMR spectral data, δ 2.15 (s, 3H), 2.67-3.65 (m, 4H), 3.74 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 6.59 (s, 1H), 6.64 (s, 1H), 6.88 (d, 2H, *J* = 9.0), 7.72 (d, 2H, *J* = 9.0).

5,6-Dihydro-8,9-dimethoxy-2-methyl-10b-(*p*-nitrophenyl)-10b*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (5j). A pale yellowish solid, yield 60 %, mp 57-59 °C, R_f = 0.10 (ethyl acetate / hexane, 1:2); IR (KBr) 2211, 1653, 1609, 1520, 1464, 1350, 1261, 1140, 1015, 849, 779 cm^{-1}; ^1H NMR δ 2.21 (s, 3H), 2.81-3.10 (m, 2H), 3.38-3.53 (m, 2H), 3.73 (s, 3H), 3.90 (s, 3H), 6.51 (s, 1H), 6.67 (s, 1H), 7.58 (d, 2H, *J* = 9.0), 8.22 (d, 2H, *J* = 9.0); ^{13}C NMR δ 12.5, 24.7, 49.0, 56.1, 56.2, 75.5, 89.8, 110.5, 111.2, 115.9, 124.1, 125.9, 126.3, 129.4, 148.1, 148.8, 149.2, 151.1, 169.4; MS *m/z* (%) 393 (M^+, 22), 378 (13), 350 (20), 310 (25), 304 (15), 271 (100). *Anal* Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.21; H, 4.85; N, 10.71.

***cis*-4-Cyano-1,2,2-trimethyl-5-phenylpyrrolidin-3(*2H*)-one (6)**. A white solid, yield 56 %, mp132-134 °C; IR (KBr) 2172, 1593, 1460, 1379, 1258, 1157, 756, 702 cm^{-1}; ^1H NMR δ 1,17 (s, 3H), 1.35 (s, 3H), 2.16 (s, 3H), 3.27 (d, 1H, *J* = 10.2), 3.94 (d, 1H, *J* = 10.2), 7.38-7.48 (m, 5H); ^{13}C NMR δ 15.2, 23.8, 31.6, 66.0, 67.5, 115.0, 127.6, 129.5, 129.6, 137.9, 206.4; MS *m/z* (%) 228 (M^+, 11), 213 (100), 200 (47), 71 (91). *Anal* Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.66; H, 6.85; N, 12.20.

4-Cyano-1,2,2-trimethyl-5-phenylpyrrolin-3(*2H*)-one (7). A white solid, yield 65%, mp 194-197 °C; IR (KBr) 2201, 1672, 1606, 1581, 1545, 1512, 1475, 1360, 1184, 758, 704 cm^{-1}; ^1H NMR δ 1.42 (s, 6H), 3.10 (s, 3H), 7.5-7.6 (m, 5H); ^{13}C NMR δ 21.8, 30.0, 70.1, 83.6, 115.2, 127.7, 128.5, 128.9, 129.7, 132.4, 176.4, 198.8; MS *m/z* (%) 226 (M^+,100), 211 (8), 197 (15), 183 (8), 118 (10), 71(16). *Anal* Calcd for $C_{14}H_{14}N_2O$: C, 74.34; H, 6.24; N, 12.38. Found: C, 74.38; H, 6.16; N, 12.35.

***cis*-1,5,6,10b-Tetrahydro-8,9-dimethoxy-3,3-dimethyl-2-oxo-2*H*-isoxazolo[3,2-*a*]isoquinoline-1-carbonitrile (8)**. A white solid, yield 40 %, mp 170-174 °C, R_f = 0.32 (ethyl acetate / hexane, 1:1); IR (KBr) 2245, 1772, 1610, 1520, 1467, 1383, 1258, 1219, 1161, 1130, 1076, 1036, 866, 790 cm^{-1}; ^1H NMR δ 1.16 (s, 3H), 1.31 (s, 3H), 2.64-2.85 (m, 2H), 2.97-3.18 (m, 2H), 3.38 (d, 1H, J = 10.6), 3.88 (s, 3H), 3.89 (s, 3H), 4.29 (d, 1H, J = 10.6), 6.65 (s, 1H), 7.00 (s, 1H); ^{13}C NMR δ 15.3, 23.3, 29.0, 41.3, 43.8, 56.0, 56.1, 59.6, 65.1, 107.8, 112.0, 116.6, 126.5, 126.8, 148.1, 148.9, 206.5; MS *m/z* (%) 300 (M^+, 66), 272 (10), 233 (100), 218 (19). *Anal* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.81; H, 6.87; N, 9.22.

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