Tetrahedron Vol 49, No 4, pp 823-832, 1993
Printed in Great Britain

0040-4020/93 $6 00+ 00

Synthesis and 1,3-Dipolar Cycloaddition Reaction of Homoadamantane-Incorporated Nitrones and Rearrangement of the Cycloadducts to Homoadamantane-Fused Pyrroles

Yang Yu, Masatomi Ohno, Shoji Eguchi*

Institute of Applied Organic Chemistry, Faculty of Engineering,
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan

(*Received in Japan* 28 *September* 1992)

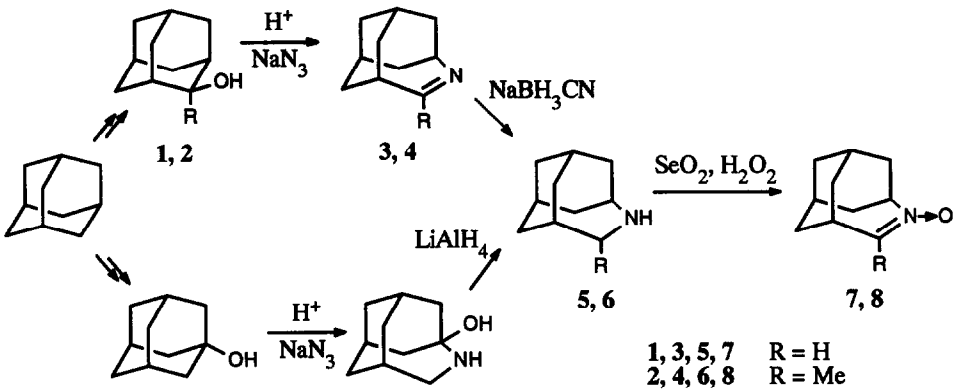
Abstract *The bridging nitrones 7, 8 incorporated in a homoadamantane ring system were obtained by oxidation of 4-azahomoadamantane 5, 6 with SeO_2/H_2O_2. The 1,3-dipolar cycloaddition reaction of these nitrones with the electron-deficient alkynes proceeded regiospecifically at 0 ℃-r t. to give 4-substituted isoxazolines The reaction with phenylacetylene required forced conditions, where 5-substituted isoxazoline 9d was obtained from 7 using the dipolarophile as a solvent, and rearranged pyrrole 12d was formed directly from 8 at a higher reaction temperature. The resulted cycloadducts from ketonitrone 8 were further converted to homoadamantane-fused pyrroles In this case, 2-substituted and 3-substituted pyrroles 12a and 12e were obtained respectively from the same starting material via the different mechanism The former arose via an acylaziridine route by thermolysis and the latter via an enamine route in protic solvents*

The 1,3-dipolar cycloaddition reactions are useful tools for constructing a variety of five-membered heterocycles It is attractive to apply this type of reaction for synthesis of adamantane-heterocycles since such compounds have drawn much attention for their potential pharmacological activities.[1] For the thorough survey in this field, we have developed 4-azahomoadamantene (*e.g.* **3**, **4**) as a key compound to access homoadamantane-fused heterocycles, and covered various related derivatives utilizing the cyclization methods involving cycloaddition reactions [2, 5] Along this line, the bridging nitrone in this ring system seems to be a promising intermediate, because nitrone-cycloadducts are documented to be widely applicable in synthesis [3] In the previous communication, we reported the first synthesis of 4-azahomoadamant-4-ene *N*-oxides (4-azatricyclo[4 3 1 $1^{3,8}$]undec-4-ene *N*-oxides) **7**, **8**, for which 1, 3-dipolar cycloaddition reactivity was examined and remarkable high regioselectivity due to a steric effect was observed [4] Herein are described full details of these results involving novel rearrangement of the cycloadduct to a homoadamantane-fused pyrrole under mild conditions in protic solvents

RESULTS AND DISCUSSION

Synthesis of 4-Azahomoadamant-4-ene *N*-Oxides.

The synthesis of nitrones **7**, **8** starts from inserting a nitrogen atom into the adamantane ring system This could be done by the ring expansion of 2-adamantanols **1**, **2** with sodium azide[5] The $NaBH_3CN$ reduction[6] of the obtained imines **3**, **4** afforded the corresponding amines **5**, **6** in excellent yields For unsubstituted amine **5**, the ring expansion of 1-adamantanol with sodium azide followed by $LiAlH_4$ reduction[7] gave much better overall yield based on adamantane (Scheme 1)



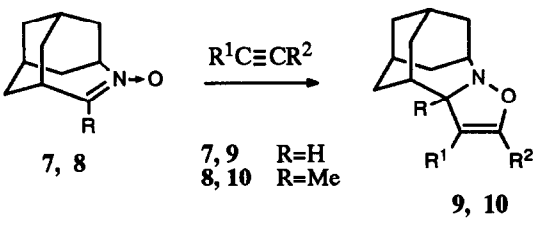
Scheme 1

The oxidation of amines **5**, **6** to aldo- and ketonitrones **7** and **8** was performed according to the method developed recently by Murahashi using combinations of SeO_2 and H_2O_2 [8] In this case, the oxidation must be undertaken with care, the reaction of **5**, when followed faithfully by the reported conditions, caused serious decomposition of the product Rather, the oxidation of **5** proceeded satisfactorily at -5 – 0℃, and the reaction period longer than 30 minutes extremely reduced the yield For the synthesis of ketonitrone **8**, the amine **6** was treated with the oxidants at 0 ℃ for 1 h while white precipitates appeared, and it was allowed to react at ambient temperature for further 3 h during which the precipitates disappeared The reaction should have been quenched before the solution colored pale brown, otherwise the yield was lowered by side reactions The reaction mixture was simply worked-up by extraction with dichloromethane and separation by thin layer or column chromatography (alumina) to give the nitrones in good yields Generally, aliphatic nitrones are known to be more or less unstable and tend to dimerize, therefore they must be used *in situ* after preparation In contrast, both nitrones **7** and **8** are stable and storable at room temperature, because they intrinsically have a rigid and bulky structure However they are highly hygroscopic compounds which turn to oils after exposure to air, dehydration of oily samples over phosphorus pentoxide in a vacuum overnight regained the amorphous solid state The infrared spectra of these aldonitrone **7** and ketonitrone **8** showed the N → O stretching frequency at 1155 and 1148 cm^{-1}, and C=N stretching frequency at 1605 and 1615 cm^{-1}, respectively, the C=N frequency of parent imines appears at 1660 and 1670 cm^{-1} The ^1H NMR spectrum of aldonitrone **7** showed C_3–H at 4 16 ppm as a multiplet peak, C_5–H at 7 35 ppm as a quartet peak with vicinal (J = 8 0) and long range coupling constants (J = 2 0 Hz), and C_6–H at 2 53 ppm as a multiplet peak That of ketonitrone **8** showed the chemical shift of C_3–H at 4 29 ppm and C_6–H at 2.64 ppm each as a multiplet peak together with a methyl proton at 2 16 ppm as a singlet peak The mass spectral data of both aldo- and ketonitrones showed a fragment peak (M–16) resulted from loss of oxygen in addition to the expected molecular ion peak, this is a peak of diagnostic value for *N*-oxides [9] The peak (M–30) also appeared in their fragmentation, which implies the NO elimination from nitrones This fragmentation pattern was not found in the literatures on hand

The 1,3-Dipolar Cycloaddition Reaction with Alkynes.

It is well documented that nitrones react efficiently with alkynes to form 4-isoxazolines[3] In the case of homoadamantane-incorporated nitrones **7** and **8**, the 1,3-dipolar cycloaddition reactions proceeded smoothly at or below room temperature with electron-deficient acetylenes such as methyl propiolate, cyanoacetylene and dimethyl acetylenedicarboxylate to give polycyclic 4-isoxazolines **9a–c** and **10a–c** in satisfactory yields (Scheme 2) With unsymmetrical acetylenes the cycloaddition was found to be regiospecific, thus, the nitrone **7** reacted with methyl propiolate and cyanoacetylene to form solely 4-substituted isoxazolines **9a** and **9b**,

respectively, which were isolated by thin layer chromatography (here the reaction with methyl propiolate occurred cleanly when the temperature was lowered to 0 °C, and furthermore, the cycloadducts **9** should be separated quickly in order to prevent partial decomposition on silica gel). The ketonitrone **8** reacted similarly to give relatively stable cycloadducts **10a,b** also in the same regiospecific manner. They underwent thermal rearrangement to homoadamantane-fused pyrroles as was discussed in the next section The observed regiospecificity in homoadamantane-incorporated nitrones is in contrast with the reported non-regioselectivity in a sterically unhindered *N*-(*t*-butyl)nitrone where the cycloaddition with these alkynes can not be regio-controlled only by orbital interactions.[10]

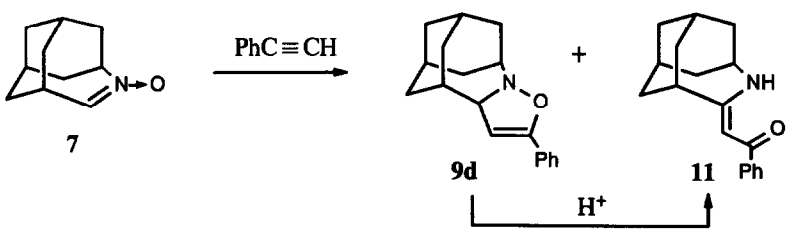


	R^1	R^2
a	CO_2CH_3	H
b	CN	H
c	CO_2CH_3	CO_2CH_3
d	H	Ph

Scheme 2

The structures of the cycloadducts obtained above were confirmed by the spectral inspections Particularly, there are two possible directions in cycloaddition leading to 4- and 5-substituted isoxazoline, which were undoubtedly distinguished by the ^{1}H NMR spectra. The cycloadduct **9a** is representative, the mass spectrum indicated a 1 1 cycloadduct from the expected molecular ion peak (m/e 249) and the infrared spectrum showed the presence of an ester group (1695 cm^{-1}) and a double bond (1610 cm^{-1}) The ^{1}H NMR spectrum revealed an olefinic proton at 7 39 ppm as a doublet peak (J = 1.6 Hz), consistent with the 4-methoxycarbonyl substituted isoxazoline, Houk reported that the 5-substituted isomer in cycloaddition reaction of a *N*-(*t*-butyl)nitrone with ethyl propiolate had the chemical shift at 7 11 ppm with a coupling constant J = 2 0 Hz [10] Such comparisons allowed the other products to be assigned as 4-substituted isoxazolines

The cycloaddition reaction with phenylacetylene was so sluggish under the above conditions that it was performed only by using the dipolarophile as a solvent Thus the aldonitrone **7** reacted at room temperature for 2 days to give the desired cycloadduct **9d** in 45% yield In this case, however, the regiochemistry determined was opposite to that found in electron-deficient alkynes; the ^{1}H NMR signal at 5 00 ppm was attributed to C_4-H of an isoxazoline ring This product was thermo- and acid-labile[11], and underwent facile ring opening even during NMR measurement in $CDCl_3$ (used as received) to the vinylogous amide **11**, which was identified by the appearance of absorptions due to NH and CO groups in the infrared spectrum The structure was also supported by the signals due to the corresponding vinylogous amide moiety together with a C_s symmetrical azahomoadamantane ring in the ^{13}C NMR spectrum.



Scheme 3

There was observed no reaction between ketonitrone **8** and phenylacetylene under the above conditions When the temperature was raised to 80℃, two products were initially formed after 24 h (TLC), one of which is regarded as the rearranged pyrrole **12d** (*vide infra*), and the other might be a primary cycloadduct such as **10d**, but the amount was too small to isolate. Prolonged reaction time caused increase of the pyrrole, and finally the reaction at 170℃ gave only the pyrrole as a separable product (see Scheme 4).

Nitrone cycloadditions are believed to be a process with the similarity of LUMO and HOMO energies in dipole and dipolarophile As such, both HOMO(dipole)–LUMO(dipolarophile) and LUMO(dipole)–HOMO(dipolarophile) interactions may be important in determining reactivity and regiochemistry [10,12] For nitrones **7**, **8** and cyanoacetylene as well as phenylacetylene, the FMOs of these molecules by our own AM1 calculation are shown in Table 1.[13] As a result, both interactions seems to be involved, or otherwise the former interaction might be relatively a little important in which carbon and oxygen sites of the nitrone dipole have almost the same coefficients (*i.e*, equal "size"). In any event, these informations predicted a competitive formation of 4– and 5–substituted isoxazolines However, as a matter of fact, 4–substituted product, *i e* **10b** was formed regiospecifically We believe this is attributed to a steric factor, even if any interaction participates in the cycloaddition reaction to certain degrees, concerted but nonsynchronous pathway disfavors the approach of a dipolarophile to the carbon center of nitrone because of intrinsic blocking due to axial ring protons It could cause the preferential development of bond formation between β–carbon of cyanoacetylene (larger

Table 1 FMO Calculation results for nitrones **7**, **8** and alkynes by AM1

	7	**8**		HC≡C–CN	HC≡C–Ph
E_{HOMO} *eV*	–8 765	–8 497	E_{HOMO} *eV*	–11 651	–9.296
C^{O}_{HOMO}	–0 656	–0 641	C^{α}_{HOMO}	0 553	0 248
C^{C}_{HOMO}	0 654	0 628	C^{β}_{HOMO}	0 606	0 405
E_{LUMO} *eV*	0 723	0 701	E_{LUMO} *eV*	0 244	0.007
C^{O}_{LUMO}	0 395	0 393	C^{α}_{LUMO}	–0.464	0 208
C^{C}_{LUMO}	0 618	0 607	C^{β}_{LUMO}	0 602	–0 357

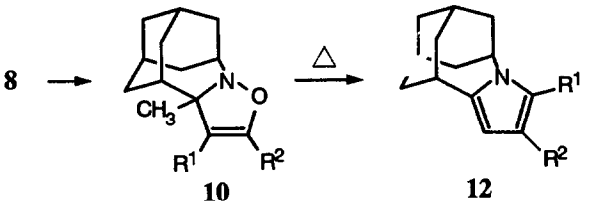
coefficient) and oxygen of the nitrone (free from steric restrictions) In the case of phenylacetylene, relatively bulky phenyl group no longer allows to react in this way as suggested by model study, and supposedly, α–carbon (attached to a phenyl group) interacts with more free oxygen center of the nitrone leading to the 5–substituted product However, more detailed calculation for the transition state must be awaited

Rearrangement to Homoadamantane–Fused Pyrroles.

Thermolysis of 3–methyl–Δ^4–isoxazolines

3–Methyl–Δ^4–isoxazolines are known to rearrange to pyrroles through ring–opening and subsequent cyclodehydration [11, 14] In the case of the isoxazolines **10** derived from *C*–methyl ketonitrone **8**, the same rearrangement occurred by heating in toluene to give homoadamantane–fused pyrroles **12** (Scheme 4) Compared with the reported non–fused isoxazolines which rearrange at 130℃ within a few hours,[14] **10a–c** required higher temperature and prolonged reaction time, cyano–substituted **10b** accomplished the ring transformation at 150 ℃ for 8 h, and in turn methoxycarbonyl–substituted **10a** at 170 ℃ for 20 h Bismethoxycarbonyl substitution made the rearrangement more difficult, and hence, only 33% of **10c** was converted to the corresponding pyrrole under the same conditions even after 48 h, and further heating resulted

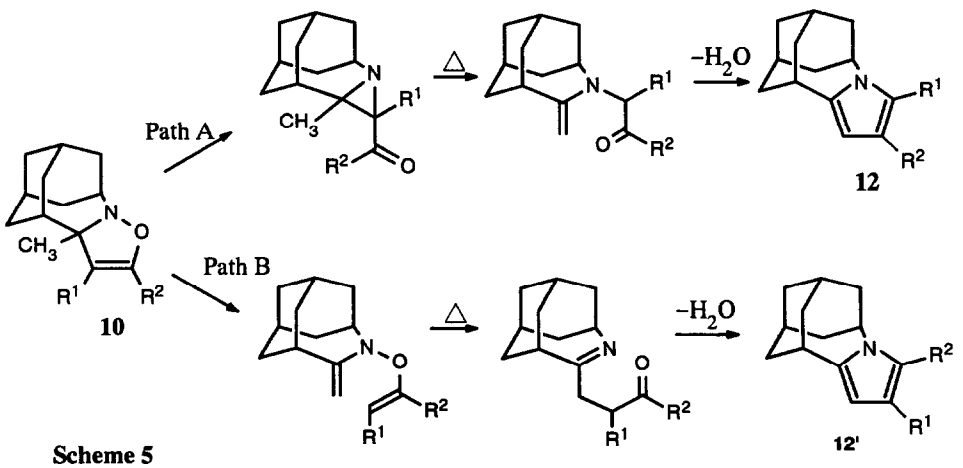
in decomposition of both isoxazoline and pyrrole. Thus, a substituent has different stabilizing effect to the isoxazoline ring The rearranged structures were determined as a 2-substituted pyrrole by spectral inspections or comparison with an authentic sample [2a] For **12b**, the mass measurement indicated M^+ ion peak as a cyclodehydrated product, and the ^1H NMR spectrum showed a cyano group substituted at 2-position, two doublet peaks at 6 59 ppm and 5 83 ppm with a coupling constant J = 3 8 Hz were assignable to C_3-H and C_4-H of the pyrrole ring. Consequently, tandem cycloaddition reaction of ketonitrone **8** with electron-deficient alkynes and thermolysis of the cycloadduct gave rise to 2-substituted pyrroles fused with a homoadamantane ring



	R^1	R^2
a	COOMe	H
b	CN	H
c	COOMe	COOMe
d	H	Ph

Scheme 4

As mentioned earlier, phenylacetylene did not react with ketonitrone **8** at room temperature, yet the reaction took place at 170℃ to give pyrrole **12d** directly In this case a phenyl group was located at 3-position of the pyrrole ring. The contrasting result can be rationalized by the regiochemistry in the first step of cycloaddition, on the analogy of nitrone **7** (*vide supra*), the cycloadduct **10d** (5-phenyl substituted isoxazoline) formed initially and it rearranged to **12d** (3-phenyl substituted pyrrole) exactly via the same pathway as above Winterfeldt studied the mechanism of the thermal rearrangement of 3-methyl-Δ^4-isoxazolines and suggested two pathways involving an acylaziridine (path A) and an enamine (path B) [14b] For the present homoadamantane system, the path A is the most plausible because the shift of position of the substituent from Δ^4-isoxazoline to pyrrole is in good agreement with the acylaziridine pathway (Scheme 5) According to this mechanism, 4-substituted 3-methylisoxazoline **10a,b** was transformed to 2-substituted pyrroles **12a,b**, whereas the 3-substituted pyrrole **12d** was formed from the reaction of ketonitrone **8** with phenylacetylene through the 5-substituted isoxazoline **10d** under such conditions



Scheme 5

The reaction of ketonitrone 8 with methyl propiolate in protic solvents

During the course of examination for the solvent effect, unexpected interesting reaction was discovered The reaction of **8** with methyl propiolate was attempted first by changing the solvent from toluene to acetonitrile, although it was decelerated slightly, the product obtained was a normal cycloadduct **10a.** When this was carried out in methanol, there was obtained an unusual product in addition to **10a** in a ratio of 25/75 The structure of the product was characterized as 3-substituted pyrrole **12e** (a positional isomer of **12a**) by comparison of an authentic sample [2b] The product ratio of **12e/10a** was maximized to 54/46 in a 1 2 mixed solvent of methanol and water, but acid (AcOH, HCl) and base (NaOH) did not improve the ratio. The products in acetonitrile–water were similar to that in methanol–water These results are summarized in Table 2

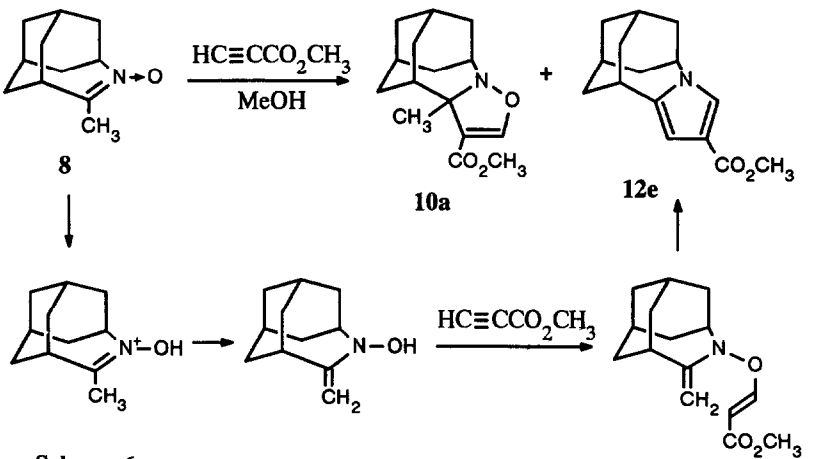
Table 2 Protic solvent effect to cycloaddition reaction

No	Solvent	Temp (℃)	Time (h)	Products[a] 10a	12e	Yield[b] (%)
1	Toluene	r t	2	100	0	73
2	MeCN	r t	4	100	0	86
3	MeOH	r t	12	75	25	94
4	MeOH + H_2O (3 1)	r t	12	58	42	79
5	MeOH + H_2O (1.2)	r t	12	46	54	*
6	MeOH + AcOH (10 1)	r t	12	69	31	*
7	MeOH + HCl (cat.)	r t	8	-	-	0
8	MeOH + NaOH	r t	12	-	-	0
9	MeCN + H_2O (1 2)	r t	12	55	45	*

a The product ratio **10a/12e** was calculated from the isolated yield (No 1–4) or estimated from ^1H NMR data (No 5, 6 and 9)

b Isolated yield, * corresponds to not isolated case

The present novel one-step conversion of a nitrone to a pyrrole seems to be catalyzed by moderately acidic proton from a solvent Considering the substitution pattern obtained (*i e* , 3-substituted pyrrole), an



Scheme 6

enamine pathway may be involved as shown in Scheme 5. Therefore, it is assumed that an enamine, which may originate from protonation to **8** and subsequent addition of a resulted hydroxyenamine[15] to methyl propiolate, is responsible for the formation of the final product **12e** through hetero-Cope rearrangement and cyclodehydration (Scheme 6). Such a mechanism is closely related to the addition reaction of oximes with alkynes to form a pyrrole ring [16] Apart from the detailed mechanism, it is concluded in these sections that positional isomers, homoadamantane-fused 2- and 3-substituted pyrroles, can be prepared from the same nitrone depending on reaction conditions

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR 5300 spectrometer ^1H and ^{13}C NMR spectra were obtained with a GEMINI 200 spectrometer at 200 MHz for ^1H NMR and at 50 MHz for ^{13}C NMR in $CDCl_3$ as a solvent Chemical shifts are reported in part per million (ppm) relative to $(CH_3)_4Si$ as an internal standard and coupling constants in Hz, and only characteristic ^1H NMR peaks are reported Elemental analyses were performed on a PERKIN-ELMER 2400 CHN Elemental Analyzer Mass spectra were obtained using an ESCO EMD-05B mass spectrometer at 70 eV

Reduction of 4-azahomoadamant-4-ene (3).

The reduction was carried out according to the literature method [6] To a solution of **3** (1.03 g, 6 81 mmol) and a trace of bromocresol green in methanol (5 ml) was added $NaBH_3CN$ (428 mg, 6.81 mmol), while the solution immediately turned deep blue Then 2*N* HCl-methanol was added to this solution until the color became yellow The stirring was continued and 2*N* HCl was added occasionally to keep the yellow color After the yellow color no more changed, the solution was stirred for additional 1 h The solvent was evaporated off and the residue was basified with 10% NaOH (50 ml) The product was extracted with chloroform (10 ml × 5), and dried over K_2CO_3 After evaporation of the solvent, the residue was sublimed (150℃/5 mmgH) to give the pure amine **5** (0.95 g, 91 %), m p 171-173 ℃ (lit m p 374-378 ℃ as HCl salt) [17]

Reduction of 5-methyl-4-azahomoadamant-4-ene (4).

The reduction of **4** in the same manner as above gave the pure amine **6** as a gummy oil (98 %) IR(KBr)ν(cm^{-1}) 3302, 2957, 2903, 2847, 1441, 1373, 1335, 1267, 1175, 1123, 1078; ^1H NMR ($CDCl_3$) δ 3 30 (m, 1H), 3 18 (q, J = 6 6 Hz, 1H), 1 08 (d, J = 6 6 Hz, 1H) (lit m. p 295-298 ℃(dec) as HCl salt) [5a, b]

Synthesis of 4-azahomoadamant-4-ene *N*-oxide (7).

To a mixture of **5** (153 mg, 1 00 mmol) and SeO_2 (5 mg, 0 05 mmol) in acetone (2 ml) was added aqueous 30% H_2O_2 (0 22 ml, 2 2 mmol) dropwise at -5 - 0℃ under an atmosphere of nitrogen, and stirring was continued at this temperature for 30 min Then the acetone was removed under reduced pressure The product was extracted with dichloromethane (2 ml × 4) and dried over K_2CO_3 After evaporation of the solvent, the residue was subjected to thick layer chromatography (alumina, dichloromethane/methanol 30 1) The eluted product in dichloromethane was dried over anhydrous K_2CO_3 and removal of the solvent under reduced pressure gave the nitrone **7** as an amorphous solid (113 mg, 65 %) m p 250-253 ℃ (sub), IR(KBr)ν(cm^{-1}) 2920, 2853, 1610, 1445, 1362, 1244, 1155, 1049, 914, 806, 768, ^1H NMR ($CDCl_3$) δ 7 35 (dd, J = 8 0, J = 2 0, 1H), 4 16 (m, 1H), 2 53 (m, 1H), MS m/e (%) 165 (M^+, 16), 149 (4), 135 (22), 79 (96), 67 (100), Anal Calcd for $C_{10}H_{15}NO$ (165 24) C, 72 69, H, 9 15, N, 8 48 Found C, 72 76, H, 9 10, N, 8 45

Synthesis of 5-methyl-4-azahomoadamant-4-ene *N*-oxide (8).

To a mixture of **6** (165 mg, 1 00 mmol) and SeO_2 (5 mg, 0 05 mmol) in acetone (2 ml) was added aqueous 30% H_2O_2 (0 22 ml, 2.2 mmol) dropwise at 0℃ under an atmosphere of nitrogen After stirring at

0℃ for 1 h, the mixture was allowed to warm to ambient temperature and stirring was continued for 3 h The same work-up and separation as above gave the nitrone **8** as an amorphous solid (151 mg, 84 %): m. p 98 5-102 5℃; IR(KBr)ν(cm^{-1}) 2919, 2853, 1610, 1445, 1372, 1240, 1150, 1094, 880, 745; ^{1}H NMR ($CDCl_3$) δ 4.29 (m, 1H), 2 64 (m, 1H), 2.16 (s, 3H), MS m/e (%) 179 (M^+, 27), 163 (14), 149 (10), 79 (100), 67 (70), Anal. Calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9 56, N, 7 81 Found C, 73 63; H, 9.68; N, 7 75

Methyl 3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene-5-carboxylate (9a).

A solution of **7** (33 mg, 0.20 mmol) and methyl propiolate (34 mg, 0 40 mmol) in toluene (0.5 ml) was stirred at 0℃ for 2 h, while the reaction was monitored by TLC (alumina, dichloromethane/methanol 40 1) After removal of the solvent under a reduced pressure, separation of the residue with preparative TLC (silica gel, hexane/ethyl acetate 3·1) gave the oily product **9a**, which solidified after standing at room temperature overnight (39 mg, 78 %). m p 42.5-45.5℃, IR(KBr)ν(cm^{-1}) 2915, 2850, 1695, 1610, 1440, 1335, 1310, 1240, 1120, 1080, ^{1}H NMR ($CDCl_3$) δ 7 39 (d, J = 1.6, 1H), 4 93 (m, 1H), 3.81 (m, 1H), 3 70 (s, 3H), 2 56 (m, 1H), MS m/e (%) 249 (M^+, 8), 84 (100); Anal Calcd for $C_{14}H_{19}NO_3$ (249 31) C, 67 44; H, 7 68, N, 5 62 Found C, 67.37, H, 7 71; N, 5 66.

Methyl 6-methyl-3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene-5-carboxylate (10a).

A solution of **8** (50 mg, 0 28 mmol) and methyl propiolate (50 mg, 0 59 mmol) in toluene (0 5 ml) was stirred at room temperature for 2 h. The same work-up and separation as above gave the oily product **10a** (54 mg, 73 %) IR(neat)ν(cm^{-1}) 2920, 2850, 1710, 1625, 1440, 1340, 1150, ^{1}H NMR ($CDCl_3$) δ 7 42 (s, 1H), 3 70 (s+m, 3+1H), 2.64 (m, 1H), 1 55 (s, 3H); MS m/e (%) 263 (M^+, 74), 79 (100); ^{13}C NMR ($CDCl_3$) δ 164 7, 153 8, 113 9, 74.7, 60.4, 51 1, 36 1 (2), 34.4 (2), 31 4, 30 8, 30 2, 26.6, 26 3; Anal. Calcd for $C_{15}H_{21}NO_3$ (263 34) C, 68 41, H, 8 04; N, 5.32 Found· C, 68 53, H, 7.91, N, 5.33

5-Cyano-3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene (9b).

A solution of **7** (33 mg, 0.20 mmol) and cyanoacetylene (10 mg, 0 40 mmol) in toluene (0.5 ml) was stirred at room temperature for 5 min The same work-up and separation as above gave the oily product **9b** (34 mg, 79 %) IR(neat)ν(cm^{-1}) 2920, 2850, 2215, 1630, 1445, 1150, ^{1}H NMR ($CDCl_3$) δ 7 21 (d, J = 1 8, 1H), 4 92 (m, 1H), 3.80 (m, 1H), MS m/e (%) 216 (M^+, 74), 78 (100), Anal Calcd for $C_{13}H_{16}N_2O$ (216 28)· C, 72 19, H, 7 46; 12 95. Found C, 72 34, H, 7 43; N, 12.81

6-Methyl-5-cyano-3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene (10b).

A solution of **8** (20 mg, 0 11 mmol) and cyanoacetylene (22 mg, 0 44 mmol) in toluene (0 5 ml) was stirred at room temperature for 30 min The same work-up and separation as above gave the solid product **10b** (24 mg, 93 %) m p. 98 5-100 5℃; IR(KBr)ν(cm^{-1}) 2920, 2853, 2209, 1626, 1443, 1381, 1265, 1238, 1154, 1105, 905, 727, 693, ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 1H), 3 70 (m, 1H), 1 55 (s, 3H), MS m/e (%) 230 (M^+, 10), 215 (58), 79 (100), Anal Calcd for $C_{14}H_{18}N_2O$ (230 31) C, 73 01, H, 7 88, N, 12 17 Found C, 73 16, H, 7 75, N, 12 15

Dimethyl 3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene-4,5-dicarboxylate (9c).

A solution of **7** (33 mg, 0 20 mmol) and dimethyl acetylenedicarboxylate (50 mg, 0 35 mmol) in toluene (0 5 ml) was stirred at room temperature for 1 h The same work-up and separation as above gave the solid product **9c** (43 mg, 70 %). m p 83.5-86.5℃, IR(KBr)ν(cm^{-1}) 2915, 2850, 1760, 1705, 1655, 1440, 1310, 1130, 1065, 785, ^{1}H NMR ($CDCl_3$) δ 5 07 (d, J = 2 6 Hz, 1H), 3 89 (s, 3H), 3 82(m, 1H), 3.72 (s, 3H), 2 50 (m, 1H), MS m/e (%) 307 (M^+, 18), 248 (100), Anal Calcd for $C_{16}H_{21}NO_5$ (307 35) C, 62 52, H, 6 88, N, 4 56 Found· C, 62 75, H, 6 91, N, 4 29

Dimethyl 6-methyl-3-oxa-2-azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec-4-ene-4,5-dicarboxylate (10c).

The same treatment of **8** with dimethyl acetylenedicarboxylate as above gave a solid product **10c** (63 %) m p. 89 0–91 0 ℃, IR(KBr)ν(cm^{-1}) 2982, 2928, 2853, 1755, 1713, 1649, 1437, 1342, 1310, 1240, 1199, 1090, 1067, 1003, 837, 780, ^{1}H NMR ($CDCl_3$) δ 3 89 (s, 3H), 3.72 (s+m, 3+1H), 2.56 (m, 1H), 1.60 (s, 3H), MS m/e (%) 321 (M^+, 6), 306 (100), 262 (90), Anal Calcd for $C_{17}H_{23}NO_5$ (321 37) C, 63 53, H, 7 21, N, 4 36 Found C, 63 63, H, 7 23; N, 4 36

4–Phenyl–3–oxa–2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradec–4–ene (9d) and 5–Phenacylidene–4–azahomo–adamantane (11).

A solution of **7** (50 mg, 0 30 mmol) in phenylacetylene (0 5 ml) was stirred at room temperature for 24 h After removal of the excess phenylacetylene *in vacuo*, the residue was subjected to TLC separation (silica gel, hexane/ethyl acetate 3 1) to give products **9d** (36 mg 45 %) as the first fraction and **11** (16 mg, 20 %) as the second fraction **9d** m p 98–106℃; IR(KBr)ν(cm^{-1}) 2909, 2843, 1657, 1493, 1447, 1277, 1151, 1057, 1024, 949, 918, 754, 704, 691, ^{1}H NMR ($CDCl_3$) δ 7 54 (m, 2H), 7 34 (m, 3H), 5 00 (s+m, 2H), 3 82 (m, 1H), MS m/e (%) 267 (M^+, 2), 251 (47), 225 (100), ^{13}C NMR ($CDCl_3$) δ 152.3, 128 9, 128 7 (2), 125.7 (3), 97 8, 75 9, 59 5, 37 3, 36 6, 35 7, 33 9, 32 0, 31 7, 26 8, 26 1, Anal Calcd for $C_{18}H_{21}NO$ (267 37) C, 80 86, H, 7 92, N, 5 24, Found C, 80.79, H, 7 95, N, 5 27 **11** m p 97–102℃; IR(KBr)ν(cm^{-1}) 3055, 2907, 2851, 1597, 1553, 1526, 1375, 1354, 1327, 1302, 1263, 1204, 1117, 1053, 1028, 955, 743, 696, 654; ^{1}H NMR ($CDCl_3$) δ 11 9 (brs, 1H), 7 87 (m, 2H), 7 34 (m, 3H), 5 64 (s, 1H), 3 69 (m, 1H), 2 58 (m, 1H), MS m/e (%) 267 (M^+, 85), 266 (100), 250 (10), 189 (23), ^{13}C NMR ($CDCl_3$) δ 188 8, 175 6, 141 2, 130 7, 128 5 (2), 127 2 (2), 90 2, 49 2, 40 6, 36 0 (2), 35 0, 33 0 (2), 27 1 (2), Anal Calcd for $C_{18}H_{21}NO$ (267 37) C, 80 86; H, 7 92, N, 5 24, Found C, 80 69, H, 8 01, N, 5 30

Methyl 2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca–3,5–diene–3–carboxylate (12a).

A solution of **10a** (10 mg, 0 038 mmol) in dry toluene (0 5 ml) was heated in a sealed tube at 170℃ for 20 h under an atmosphere of nitrogen After evaporation of the solvent, the product was separated on preparative TLC (silica gel, hexane/ethyl acetate 3 1) to give the product **12a** as a crystal (7 mg, 75 %), which was identical with an authentic sample in all spectral data [2a]

3–Cyano–2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca–3,5–diene (12b).

In the same way as above except for heating the solution of **10b** (8 mg, 0.038 mmol) in dry toluene (1 ml) at 150℃ for 8 h, **12b** was obtained as a crystal (5 mg, 78 %) m. p 112–114 5℃; IR(KBr)ν(cm^{-1}) 2903, 2847, 2203, 1480, 1449, 1404, 1354, 1292, 1190, 1152, 1030, 785, 777, 710, ^{1}H NMR ($CDCl_3$) δ 6 59 (d, J = 3 8, 1H), 5 83 (d, J = 3 8, 1H), 4 57 (m, 1H), 3 14 (m, 1H), MS m/e (%) 212 (M^+, 100), Anal Calcd for $C_{14}H_{16}N_2$ (212 29) C, 79 21, H, 7 60, N, 13 20 Found C, 79 28, H, 7.64, N, 12 94

Dimethyl 2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca–3,5–diene–3,4–dicarboxylate (12c)

A solution of **10c** (5 mg, 0 016 mmol) was heated in toluene at 170 ℃ for 48 h, only 33% of the isoxazoline was converted to the pyrrole **12c**, which was identical with an authentic sample in all spectral data [2a] Further heating decomposed both the product and starting material

4–Phenyl–2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca–3,5–diene (12d).

A solution of **8** (35 mg, 0 20 mmol) and phenylacetylene (41 mg, 0 40 mmol) in toluene (0 5 ml) was heated in a sealed tube at 170 ℃ for 8 h under an atmosphere of nitrogen After removing the solvent, the residue was separated on preparative TLC [silica gel, hexane/ethyl acetate (4/1)] to give the solid product **12d** (32 mg, 72%), which was identical with an authentic sample in all spectral data [2b]

Methyl 2–azatetracyclo[7.3.1.1^{7,11}.0^{2,6}]tetradeca–3,5–diene–4–carboxylate (12e).

A solution of **8** (50 mg, 0 28 mmol) and methyl propiolate (50 mg, 0 59 mmol) in methanol (2 ml) was

stirred at room temperature for 1 day. After removal of the solvent under reduced pressure, separation of the residue with preparative TLC (silica gel, hexane/ethyl acetate 3·1) gave two products **10a** (38 mg, 72%) as the second fraction and **12e** (12 mg, 24%) as the first fraction, which was identical with an authentic sample in all spectral data [2b]

ACKNOWLEDGEMENT

Y Yu is specially thankful to the Fujisawa Foundation for a scholarship.

REFERENCES

1 a) Fort, R. C , Jr. in *Adamantane- The Chemistry of Diamond Molecules*, Marcel Dekker, New York, 1976; Chapter 7 b) Cody, V ; Suttan, P. A ; Welsh, W. J. *J Am. Chem Soc* **1987**, *109*, 4053

2. a) Eguchi, S., Asai, K., Sasaki, T. *Heterocycles* **1989**, *28*, 125 b) Eguchi, S , Wakata, Y , Sasaki, T *J Chem. Research (M)* **1985**, 1728; *J Chem. Research (S)* **1985**, 146 c) Eguchi, S , Asai, K , Takeuchi, H.; Sasaki, T. *J. Chem. Soc Perkin Trans. 1* **1987**, 1171 d) Eguchi, S ; Asai, K , Sasaki, T *J. Chem. Soc., Chem. Commun.* **1984**, 1147

3 a) Tufariello, J. J. in *1,3-Dipolar Cycloaddition Chemistry*, ed. by Padwa, A., John Wiley and Sons, New York, 1988, Vol 2, Chapter 9. b) Breuer, R , Aurich, H. G., Nielsen, A. T in *Nitrones, Nitronates and Nitroxides*; ed. by Patai, S , John Wiley and Sons; New York, 1989, pp 139–312 c) Confalone, P. T., Huie, E. M. in *Organic Reactions;* John Wiley and Sons, New York, 1988; Vol 36, pp 1–174. d) Deshonng, P , Langer, Jr , S W , Leginus, J M , Dicken, C M in *Advances in Cycloaddition*, JAI Press, London, 1988, pp 87–128. e) Black, D. C.; Crozier, R F , Davis, V C *Synthesis* **1975**, *4*, 205.

4 Yu, Y., Ohno, M , Eguchi, S *Tetrahedron Lett.* **1991**, *32*, 4965.

5 a) Sasaki, T.; Eguchi, S ; Toi, N *Heterocycles* **1977**, *7*, 315 b) Sasaki, T , Eguchi, S , Toi, N *J Org Chem.* **1978**, *43*, 3810. c) Sasaki, T , Eguchi, S., Toi, N *J. Org. Chem.* **1979**, *44*, 3711

6 a) Borch, R F , Durst, D *J Am. Chem Soc* **1969**, *91*, 3996 b) Borch, R F , Bernstein, M D , Durst, D. *J Am. Chem Soc.* **1971**, *93*, 2897.

7 Kovacic, P , Liu, J -H , Levi, E M , Roscos, P D *J Am. Chem. Soc* **1971**, *93*, 5801

8 Murahashi, S-I., Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383

9. Grigg, R , Odell, B G *J. Chem. Soc. (B)* **1966**, 218

10 Sims, J.; Houk, K N. *J Am. Chem Soc* **1973**, *95*, 5798

11 Freeman, J P *Chem Rev.* **1983**, *83*, 241

12 a) Houk, K N *Acc Chem Res.* **1975**, *8*, 361 b) Houk, K N , Sims, J , Duke, Jr , R E , Strozier, R W , George, J. K. *J. Am Chem. Soc* **1973**, *95*, 7287 c) Houk, K. N , Sims, J , Watts, C R , Luskus, L W., George, L J *J Am Chem. Soc.* **1973**, *95*, 7301

13 MOPAC Ver 5 00 (QCPE No 445) Stewart, J J P QCPE Bull 1989, 9, 10, Hirano, T JCPE Newsletter, 1989, 1(2), 36, Revised as Ver 5 01 by Toyoda, J for Apple Macintosh ®

14 a) Grigg, R ; *Chem Commun.* **1966**, 607. b) Schmidt, G , Stracke, H-U.; Winterfeldt, E *Chem Ber* **1970**, *103*, 3196 c) Adachi, I., Harada, K., Miyazaki, R., Kano, H *Chem. Pharm. Bull* **1974**, *22*, 61

15 Nitrone–hydroxyenamine tautomerism was discussed in ref 3c, p 152

16 Pinna, G A., Pirisi, M A , Paglietti, G *J Chem Research(M)* **1990**, 2777, *J Chem Research(S)* **1990**, 360

17 a) Keizer, G V , Korsloot, J G *J Med Chem.* **1971**, *14*, 411 b) Quast, H , Eckert, P *Liebigs Ann Chem* **1974**, 1728