SYNTHESIS OF HOMOADAMANTANO[4,5-*e*]-2*H*-AZEPINES VIA CYCLOADDITION OF HOMOADAMANTANO[4,5-*c*]CYCLOPENTADIENONES WITH 1-AZIRINES (1)

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Abstract : Thermal cycloaddition reaction of homoadamantano[4,5-*c*]cyclopentadieneones 1 with 1-azirines 2 underwent on heating at 150 °C to afford homoadamantano[4,5-e]-2*H*-azepines 4 selectively.

Introduction

The cyclopentadienone system is known as one of reactive dienes in the Diels-Alder reactions with acetylenic dienophiles to afford arene annulation products via facile decarbonylation of the initial cycloadducts (2,3). We have reported previously that 2',5'-disubstituted homoadamantano[4,5-*c*]cyclopentadienones 1 are useful dienes having diene reactivity comparable to 3,4-dimethyl-2,5-diphenyl- and 2,3,4,5-tetraphenylcyclopentadienones and are used for synthesis of homoadamantano[4,5]fused benzene derivatives (4). On the other hand, Hassner and coworkers demonstrated that the reaction of 1-azirines with cyclopentadienones affords 2*H*- and 3*H*-azepines via [4+2]cycloaddition followed by decarbonylation of the initial adduct (5). We now report the cycloaddition of the cyclopentadienones 1 with 1-azirines 2, which provided a facile route to homoadamantano[4,5-*e*]-2*H*-azepines 4 (6).

Results and Discussion

2',5'-Dimethylhomoadamantano[4,5-*c*]cyclopentadienone **1a** (0.50 mmol) and 2-phenyl-1-azirine **2a** (0.81 mmol) (7, 8) in toluene (2 mL) were heated under an atmosphere of argon at 150 °C for 9.5 h in a sealed heavy-walled Pyrex tube. The solvent was removed *in vacuo* and the residue was purified on a preparative TLC (aluminum oxide) to afford a crystalline product (**5a**) of *Rf* = 0.70 (CH_2Cl_2) and an oily product (**4a**) of *Rf* = 0.20 (CH_2Cl_2) in 6.3 and 44 % yields respectively based on 1a. In the mass spectra (EI), both products had M^+

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ion peak at *m/z* 317 ($C_{23}H_{27}N$) as the base peak indicating that these are derived from decarbonylation of the 1:1 cycloadducts. In ^{1}H NMR spectrum, 4a exhibited characteristic doublet signals (J = 10.5 Hz) at δ 4.08 (1H) and 3.04 (1H) ppm assignable to methylene protons (He and Ha respectively, see Figure 1a) of 2*H*-azepines (5,8,9), and a broad singlet at δ 3.0-2.6 (2H) ppm due to bridgehead protons, and hence, 4a was assigned as 4',7'-dimethyl-3'-phenylhomoadamantano[4,5-e]-2*H*-azepine (Scheme 1). The minor product 5a had IR absorptions at 3345 and 3360 cm^{-1}, suggesting the presence of NH group. Appearance of D_2O exchangeable broad singlet (2H) at δ 3.05 ppm in the ^{1}H NMR spectrum supported the presence of a NH_2 group. Other ^{1}H NMR signals at δ 7.60-7.10 (m, 5H, C_6H_5), 3.40 (br s, 2H, two bridgehead protons), 2.08 (s, ca. 6H, two CH_3), and 2.30-1.78 (m, 12H, remaining homoadamantane ring protons) ppm were compatible with the given 1'-amino-3',6'-dimethyl-2'-phenylhomoadamantano[4,5-*d*]benzene structure 5a. The rearrangement of 7-unsubstituted azepines to such aniline derivatives on heating in acetic acid is reported by Hassner and co-workers (10). The formation of 5a could be explained via presumably unstable 1*H*-azepine (8π-electron system, not shown in Scheme 2 but see 7a in Figure 2) and azanorcaradiene 6a based on the proposed mechanism (Scheme 2).

The reactions of 1a with 2-(4-methylphenyl)- 2b and 2-(3-methylphenyl)-1-azirines 2c, and 2',5'-diphenylcyclopentadienones 1b with 2a, 2b, and 2c underwent similarly on heating to afford the corresponding 2*H*-azepine derivatives 4b-4f as the major products. These results are summarized in Table 1.

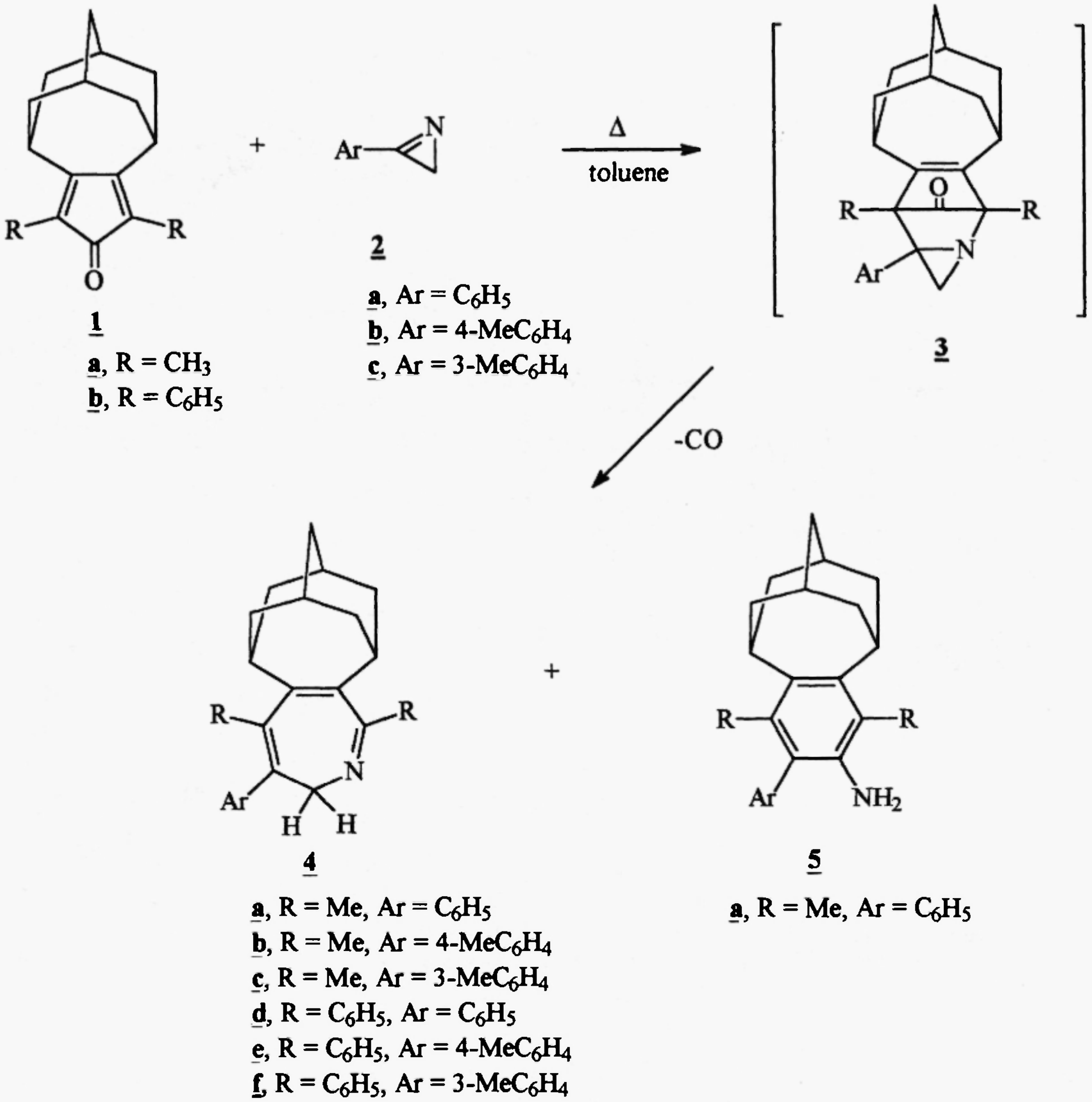
Table 1: Cycloadditions of Cyclopentadieneones 1a, b with 1-Azirines 2a-c.

Dienone	Azirine[a]	Solvent	Temp,°C/Time, h	Product	Yield,%[b]	Mp,°C	(solvent)[c]
1a	2a	toluene	150/10	4a	44.1	oil	
				5a	6.3	168-170	(CH_2Cl_2)
1a	2b	toluene	150/9.0	4b	27.1	oil	
1a	2c	toluene	150/23	4c	14.8	oil	
1b	2a	xylene[d]	150/23	4d	28.2	187-189	(D-H)[e]
1b	2b	xylene[d]	150/31	4e	35.4	240-242	(CH_2Cl_2)
1b	2c	xylene[d]	150/37	4f	23.2	209-210	(MeOH)

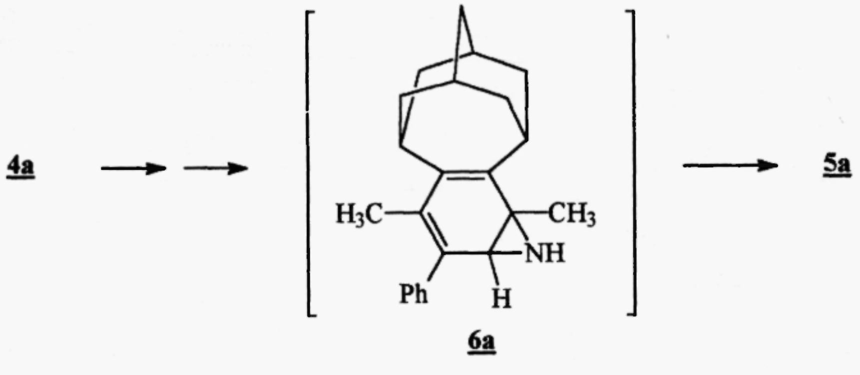
[a] A 1.6 fold equivalent amount was used. [b] Isolated yields. [c] Crystallization solvent. [d] Xylene (isomers and ethylbenzene mixture), bp 137-144 °C was used. [e] CH_2Cl_2-hexane.

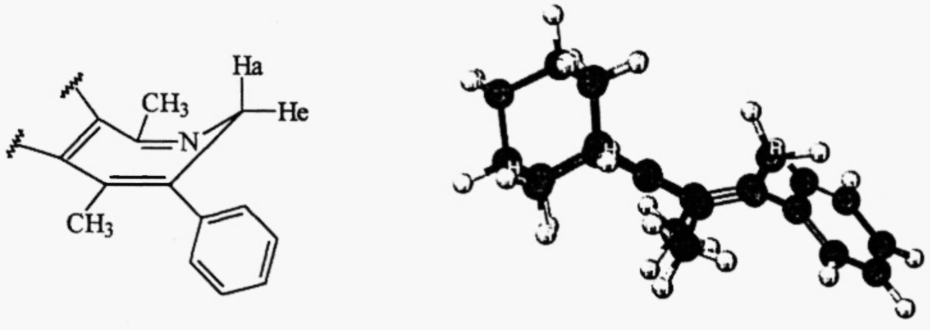
Other tautomeric forms of 4a such as 7a-10a are conceivable (Figure 2), however, only 4a, 2*H*-azirine was obtained selectively in the reaction of 1a with 2a. The observed selective formation of 4a may be due to

Scheme 1



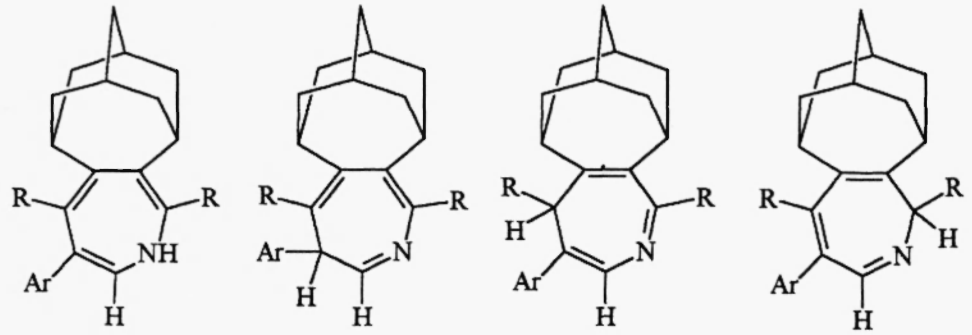
Scheme 2





(a) (b)

Figure 1: The most stable conformer of 4a calculated by PM3 method.



4a (36.96)

7a (61.24)

8a (58.45)

9a (39.56)

10a (41.96)

Figure 2: Other tautomeric forms 7a-10a (R = CH_3, Ar = C_6H_5) of 4a and respective heat of formation (kcal/mol) calculated by PM3 method is given in parenthesis.

the stability differences of these tautomers. Therefore, their heat of formation has been calculated by semiempirical MNDO PM3 method as given in Figure 2 (11). These values indicate the relative stability order as 4a>9a>10a>8a>7a and hence, the selective formation of the most stable 4a could be rationalized. The selective formation of 4b-f could be explained similarly.

In summary, thermal cycloaddition reaction of homoadamantano[4,5-*c*]cyclopentadieneones 1 with 1-azirines 2 afforded novel homoadamantano[4,5-e]-2*H*-azepines 4 selectively.

Experimental

Melting points were taken on a Yanagimoto micro-melting points hot-stage apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 2400S elemental analyzer. ^{1}H NMR spectra were obtained at 25 °C with a JEOL JMN-C-60 HL instrument at 60 MHz for samples in $CDCl_3$ or CCl_4 solution with $(CH_3)_4Si$ as internal standard. IR spectra were recorded on a JASCO A-100 spectrometer. EI Mass spectra were obtained on a ESCO EMD-05B spectrometer at 70 eV. TLC (Thin layer chromatography) was performed on Merck Kieselgel 60 F_{254} unless otherwise specified, and/or on Merck Aluminium oxide F_{254}.

General procedure for cycloaddition reaction of homoadamantano[4,5-c]cyclopentadieneones 1 with 1-azirines 2

A solution of homoadamantano[4,5-*c*]cyclopentadienone 1 (0.50 mmol) and 1-azirine 2 (0.80 mmol) in toluene (2 mL) or xylene (2 mL) was heated under an atmosphere of argon at 150 °C for 9.0-37 h in a sealed heavy-walled Pyrex tube. The solvent was removed *in vacuo* and the residue was purified on a preparative TLC (Merck aluminum oxide 60 PF_{254} abbreviated as Alumina or Wako silica gel Wakogel B-5F abbreviated as Silicagel) to afford azepines 4 as the main products. The results are summarized in Table 1. *Rf* values and spectral properties of the products are given below.

4',7'-Dimethyl-3'-phenylhomoadamantano[4.5-e]-2H-azepine 4a:

Rf 0.20 (Aluma, CH_2Cl_2); IR(film) 3050, 3010, 2905, 2845, 1690, 1600, 1440, 760, 730, 700 cm^{-1}; ^1H NMR (CCl_4) δ 7.45-7.10 (5H, m), 4.08 (1H, d, *J* = 10.5 Hz, He), 3.04 (1H, d, *J* = 10.5 Hz, Ha), 2.80 (2H, br s), 2.04 (ca. 3H, s), 1.78 (ca. 3H, s), 2.3-1.5 (12 H, m); MS m/z (EI) (%) 318 (29), 317 (M^+, 100), 278 (15), 234 (15), 232 (46), 102 (7), 91 (26), 79 (29), 77 (31), 67 (26); Anal. Calcd for $C_{23}H_{27}N$: C, 87.02; H, 8.57; N, 4.41. Found: C, 86.98; H, 8.97; N, 4.05.

3',6'-Dimethyl-2'-phenylhomoadamantano[4.5-*d*]-aniline 5a:

Rf 0.70 (Aluma, CH_2Cl_2); IR(KBr) 3445, 3360, 2970, 2900, 2835, 1610, 1435, 720, 700 cm^{-1}; ^1H NMR (CCl_4) δ 7.6-7.1 (5H, m), 3.40 (2H, br s, bridgehead protons at C_3 and C_6), 3.05 (2H, br s, NH_2, D_2O exchangeable), 2.08 (ca. 6H, s, 2 x CH_3), 2.30-1.78 (12 H, m); MS m/z (EI) (%) 318 (31), 317 (M^+, 100), 302 (4.9), 260 (6.5), 248 (7.2), 232 (21), 102 (38), 77 (8.6), 76 (10), 69 (6.1); Anal. Calcd for $C_{23}H_{27}N$: C, 87.02; H, 8.57; N, 4.41. Found: C, 87.02; H, 8.71; N, 4.28.

4',7'-Dimethyl-3'-(4-methylphenyl)homoadamantano[4.5-e]-2H-azepine 4b:

Rf 0.50 (Silicagel, AcOEt); IR(film) 3030, 2920, 2845, 1615, 1555, 1510, 1440, 1360, 1265, 995, 820, 790, 735 cm^{-1}; ^1H NMR (CCl_4) δ 7.30-6.90 (4H, AB q type m), 4.04 (1H, d, *J* = 10.5 Hz, He), 3.04 (1H, d, *J* = 10.5 Hz, Ha), 2.82 (2H, br s), 2.35 (3H, s), 2.02 (ca. 3H), 1.76 (ca. 3H, s), and 2.3-1.6 (12 H, m); MS m/z (EI) (%) 331(M^+, 39), 330 (100), 262 (5.7), 149 (5.7), 115 (5.7), 105 (6.0), 91 (14), 79 (6.6), 77 (11), 59 (17), 55 (18); Anal. Calcd for $C_{24}H_{29}N$: C, 86.96; H, 8.82; N, 4.23. Found: C, 86.95; H, 8.93; N, 4.13.

4',7'-Dimethyl-3'-(3-methylphenyl)homoadamantano[4.5-e]-2H-azepine 4c:

Rf 0.50 (Silicagel, AcOEt); IR(film) 3030, 2915, 2840, 1615, 1600, 1580, 1445, 1270, 995, 790, 740, 715 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 7.20-6.85 (4H, m), 4.05 (1H, d, *J* = 10.5 Hz, He), 3.02 (1H, d, *J* = 10.5 Hz, Ha), 2.82 (2H, br s), 2.38 (3H, s), 2.05 (ca. 3H, s), 1.76 (ca. 3H, s), and 2.3-1.7 (12 H, m); MS m/z (EI) (%) 332 (4.3), 331(M$^+$, 24), 330 (53), 317 (3.1), 262 (3.0), 149 (2.7), 115 (3.3), 91 (9.1), 88 (12), 86 (60), 84 (94), 52 (100); Anal. Calcd for $C_{24}H_{29}N$: C, 86.96; H, 8.82; N, 4.23. Found: C, 86.76; H, 8.92; N, 3.98.

3', 4',7'-Triphenylhomoadamantano[4.5-e]-2H-azepine 4d:

Rf 0.30 (Alumina, 1:1 hexane:CH$_2$Cl$_2$); IR(film) 3070, 3040, 3010, 2910, 2840, 1590, 1485, 1440, 1280, 1025, 755, 690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.7-6.9 (15H, m), 4.13 (1H, d, *J* = 10.5 Hz, He), 3.25 (1h, Br s), 2.85 (1H, br s), 2.10 (ca. 1H, d, *J* = 10.5 Hz, Ha), 2.15-1.45 (12 H, m); MS m/z (EI) (%) 442 (44), 441(M$^+$, 100), 91 (4.9), 69 (4.8), 57 (10), 55 (12); Anal. Calcd for $C_{33}H_{31}N$: C, 89.75; H, 7.08; N, 3.17. Found: C, 89.83; H, 7.19; N, 2.99.

4',7'-Diphenyl-3'-(4-methylphenyl)homoadamantano[4.5-e]-2H-azepine 4e:

Rf 0.40 (Silicagel, CH$_2$Cl$_2$); IR(film) 3070, 3050, 3020, 2930, 2840, 1620, 1600, 1510, 1490, 1445, 1290, 815, 755, 690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.6-6.9 (10H, m), 6.79 (4H, s), 4.76 (1H, d, *J* = 9.1 Hz, He), 3.62 (1H, d, *J* = 9.1 Hz), 2.45 (2H, unsymmetrical br s), 2.19 (ca. 3H, s), 2.4-1.4 (12 H, m); MS m/z (EI) (%) 457 (11), 456 (43), 455 (M$^+$, 100), 115 (2.5), 91 (5.1), 77 (3.7), 56 (3.5), 51 (3.7); Anal. Calcd for $C_{34}H_{33}N$: C, 89.63; H, 7.30; N, 3.07. Found: C, 89.37; H, 7.48; N, 3.14.

4',7'-Diphenyl-3'-(3-methylphenyl)homoadamantano[4.5-e]-2H-azepine 4f:

Rf 0.20 (Silicagel, CH$_2$Cl$_2$); IR(film) 3050, 3010, 2910, 2840, 1590, 1575, 1490, 1440, 1295, 1280, 1030, 755, 695 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 7.76-6.7 (14H, m), 4.54 (1H, d, *J* = 8.5 Hz, He), 3.52 (1H, d, *J* = 8.5 Hz), 2.48 (ca. 2H, br s), 2.22 (ca. 3H, s), 2.3-1.5 (12 H, m); MS m/z (EI) (%) 457 (11), 456 (47), 455 (M$^+$, 100), 454 (6.5), 227 (15), 115 (7.4), 91 (9.4), 77 (12), 58 (9.9), 56 (13), 52 (12); Anal. Calcd for $C_{34}H_{33}N$: C, 89.63; H, 7.30; N, 3.07. Found: C, 89.45; H, 7.48; N, 3.06.

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References and Notes

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