SYNTHESIS AND REACTIVITY OF N-DIPHENYLPHOSPHINOYLTROPONIMINE: SYNTHETIC ENTRY INTO 1-AZAAZULENE DERIVATIVES

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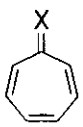
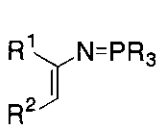
Abstract--A novel N-diphenylphosphinoyltroponimine (5), which is highly polarized and has a low lying LUMO, was prepared. The attempted reaction of 5 with enolate ions and enamines derived from cyclic ketones gave 1-azaazulene derivatives, albeit in low yields.

2,4,6-Cycloheptatrien-1-imines (troponimines) (**1**) possess dipolar properties due to the contribution of 6π electronic aromatic structures as in the case of 2,4,6-cycloheptatrien-1-one (tropone) (**2**).[1] Although troponimines are known to react with electron-deficient acetylene[2] and heterocumulenes as 8π component,[3] no reaction of them with electron-rich olefins like enamines has been reported. Previously, we have demonstrated the simple preparation of (vinylimino)phosphoranes (**3**),[4] which were found to react with activated tropones[5] and their vinylogues[6] in an enamine-type alkylation followed by intramolecular aza-Wittig reaction to provide novel route to 1-azaazulenes and their vinylogues. The azaallyl anions (**4**), which are conveniently derived from the corresponding imines[7] by base treatment,[8] are also shown to give



1 : X = NR; 2 : X = O



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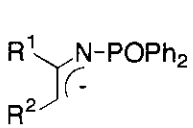

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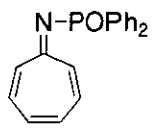

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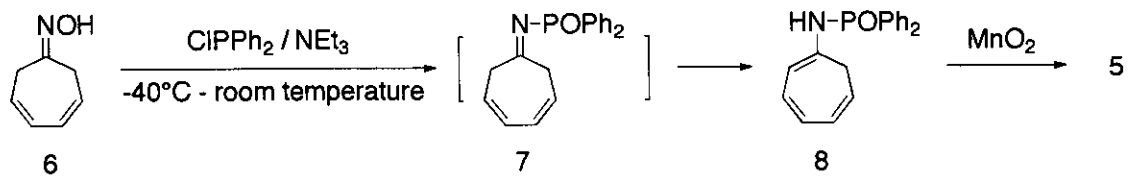
Scheme 1.

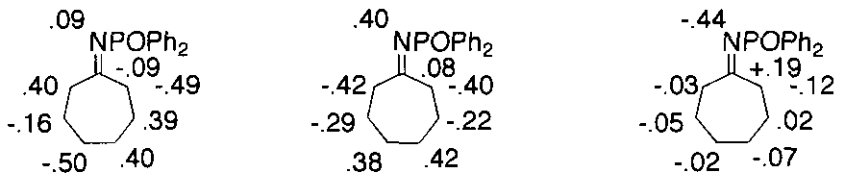
1-azaazulenes in a similar fashion.[9] Since 1-azidocycloalkenes[10] and diphenylphosphinoylazaallyl anions[8,9] derived from imines of the corresponding cyclic ketones are not readily available, those methodologies are not conveniently applicable to the preparation of 2,3-ring-annulated 1-azaazulenes. In connection with the studies, we have embarked on the exploration of methodology synthesizing versatile 1-azaazulene derivatives. In this paper, we have studied a novel preparation of N-diphenylphosphinoyltroponimine (**5**) and its reaction with enolate ions (**14a-d**) as well as enamines (**15a-d**) to give 1-azaazulene derivatives, albeit in low yields. The results are described here.

According to the reported procedure,[7] the novel imine (**5**) was prepared as follows: the reaction of readily available 3,5-cycloheptadienone oxime (**6**) with chlorodiphenylphosphine in the presence of triethylamine at -40 °C - 0 °C afforded N-(1,3,5-cycloheptatrienyl)diphenylphosphinamide (**8**), which probably arose from hydrogen migration of **7**. The compound (**8**) was then dehydrogenated by MnO_2 at room temperature to give **5** (Scheme 2). Attempted reaction of tropone oxime with chlorodiphenylphosphine under similar conditions, however, afforded no **5** except for tarry materials. The compounds (**8**) and (**5**) are new and the structures were unequivocally assigned on the basis of the physical data. The Scheme 3 presents LUMO, HOMO energies and coefficients as well as charge densities of **5** as obtained by the MNDO method.[11] The calculations suggest that LUMO and HOMO energies of **5** are slightly lower than those of tropone(**2**) (LUMO: -0.82; HOMO: -9.3), and the coefficients of **5** are similar to those of **2**. The high charge density on the nitrogen atom of **5** suggests a highly polarized nature of **5**. Thus the reactivity of **5** seemed to be similar to those of **2**. The reaction of **5** with excess amount of benzenesulfonyl isocyanate (**9**) proceeded slowly to give **13**,[3e,13] in addition to the starting material **5** (Scheme 3). The compound (**13**) has been

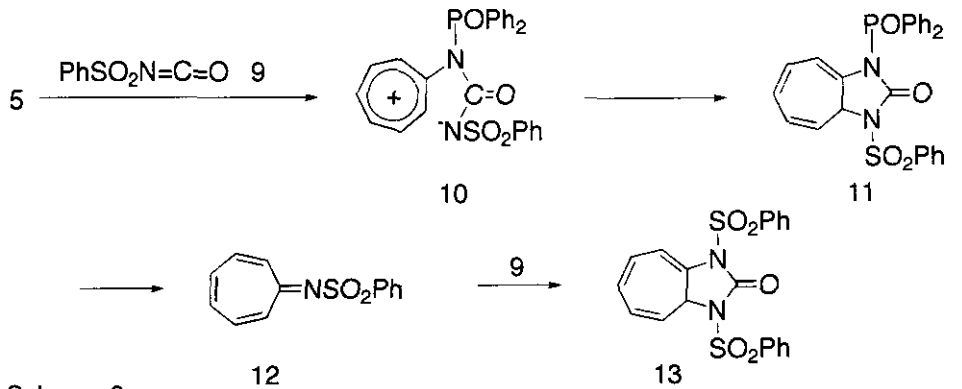


Scheme 2.

obtained by the reaction of tropone (2) or N-methoxytroponimine with 9.[3e,11] The reaction is considered to proceed through a nucleophilic attack of the nitrogen atom of 5 to the central carbon atom of 9 to give an intermediate (10),[3e] which then cyclize to give 11. The hydrogen migration in 11 or direct formation of 1,8-adduct from 10, and subsequent elimination of diphenylphosphinoyl isocyanate gives 12. The compound 12 reacts further with 9 to give 13.



Energy levels and coefficients of MO and charge densities of 5

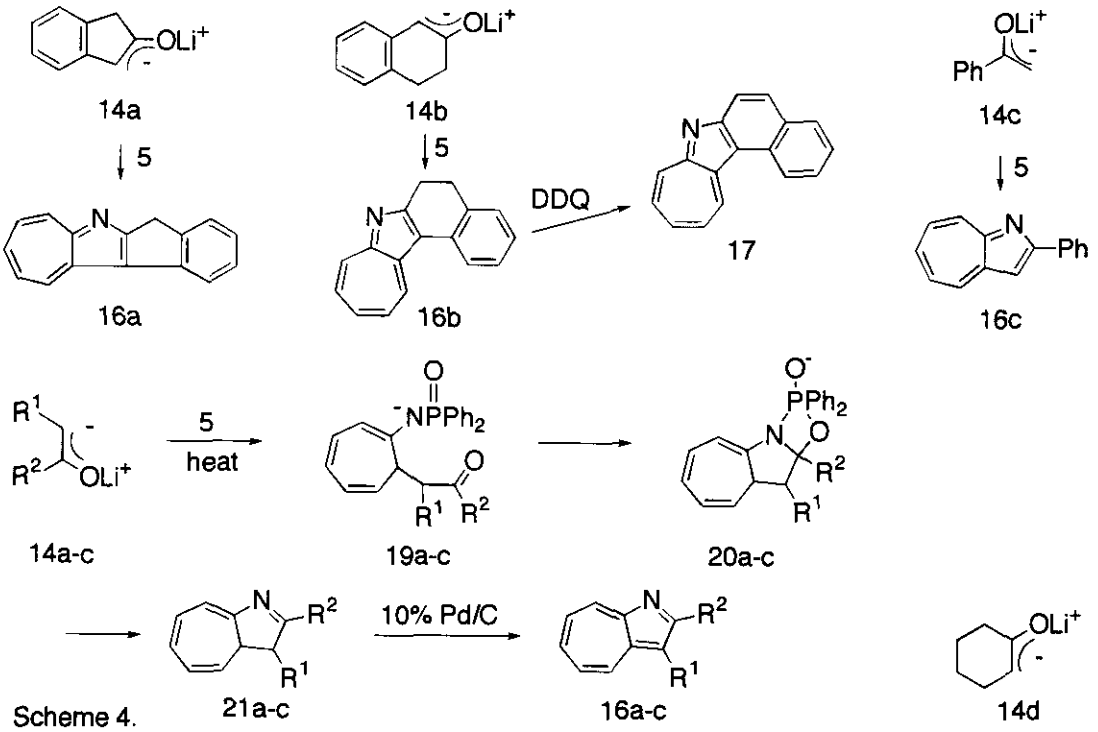


Scheme 3.

Tropone (2) undergoes reaction with enolate ions[13] and enamines[14] to give 2-substituted 3,5-cycloheptadienones and formal [8 + 2]-cycloadducts, respectively. Thus we studied the reaction of 5 with enolate ions. The general procedure for the reaction of 5 with enolate ions, which are generated from the corresponding cyclic ketones and acetophenone, is as follows (Scheme 4): after enolate ions (**14a-d**) were generated by treatment of the corresponding ketones with $LiN(SiMe_3)_2$ in THF at -78 °C for 30 min, 5 was added to the solution and, after stirring under refluxing, catalytic amount of 10% Pd/C was added to the reaction mixture, and the mixture was further heated under refluxing for the periods indicated in Table 1. The reaction conditions

and the yields of the products are summarized in Table 1 (Entries 1-4). The compounds (**14a,b,c**) reacted with **5** to give 1-azaazulene derivatives (**16a,b,c**) in low yields, respectively (Entries 1-3). However, the enolate ion (**14d**) generated from cyclohexanone gave no product except for tarry materials (Entry 4). Thus no generality of the reaction of **5** with enolate ions has been observed. The compounds (**16a**),[5b] and (**16c**)[5a] are known and the structures were assigned on the basis of the comparison of the physical data with those reported in the literatures. The spectral data for **16b** were satisfactory for its structure. Furthermore, compound (**16b**) was dehydrogenated by DDQ in benzene under refluxing to give benzo[e]-cyclohept[b]indole (17)[15] in 29% yield. Thus the structure of **16b** was unequivocally assessed.

The postulated pathways for the formation of **16a-c** are depicted also in Scheme 4. The enolate-addition onto C-2 of **5** gives the intermediate (**19**). The following intramolecular aza-Wittig reaction[4,8a,b] gives **21a-c**, dehydrogenation of which in the presence of 10% Pd/C gives **16a-c**.

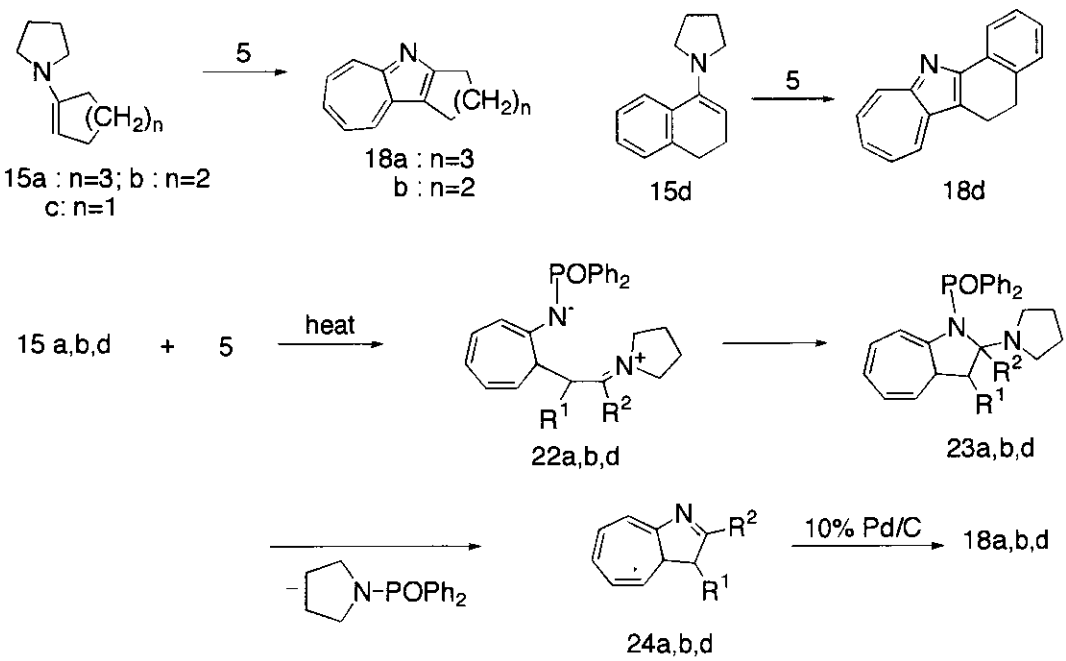


Scheme 4.

Table 1. The reaction of **5** with enolate ions (**14a–d**) and enamines (**15a–d**).

Entry	Compd	Molar ratio of 5/14 or 5/15	Solvent	Reaction conditions Time[a]/h	Time[b]/h	Product	Yield/%
1	**14a**	1/1	THF	15	11	**16a**	11
2	**14b**	1/1	THF	18	--	**16n**	19
3	**14c**	1/1	THF	15	11	**16c**	4
4	**14d**	1/1	THF	15	11	none	--
5	**15a**	1/3	CH_3CN		2	**18a**	25
6	**15b**	1/3	CH_3CN		2	**18b**	10
7	**15c**	1/3	PhH		2	none	--
8	**15d**	1/3	PhH		15	**18d**	21

a. Heated under reflux. b. Heated under reflux after the addition of 10% Pd/C.



Scheme 5.

Thermal reactions of **5** with enamines (**15a–d**) in the presence of 10% Pd/C were carried out to give 2,3-ring-annulated 1-azaazulenes (**18a,b**) and (**18d**) (Scheme 5). The reaction does not seem to be general, and 1-(N-pyrrolidinyl)cyclopentene (**15c**) gave only tarry materials. The reaction conditions and the yields of the products are also summarized in Table 1 (Entries 5-8). The structure of **18d** was unequivocally assigned on the basis of the comparison of the physical data with those reported previously.[9] On the basis of the proton assignment of ^{1}H-nmr spectra and picrate formation, as well as on consideration of the structural relation with starting materials (**15a,b**), new compounds (**18a**) and (**18b**) were assigned for 2,3-ring-annulated 1-azaazulenes.

The reaction seems to follow the pathways depicted in Scheme 5. The enamine alkylation process onto C-2 of 5 gives the intermediates (**22a,b,d**), cyclization of which gives (**23a,b,d**). Then the elimination of diphenylphosphinamide in **23a,b,d** would occur to give **24a,b,d**, which are dehydrogenated with 10% Pd/C to give 1-azaazulene derivatives (**18a,b,d**). One may consider that the remarkable difference between **15a,b,d** and five-membered ring of **15c** in the reactions is due to a ring size effect depending on the ring strain of the cyclization process from **22** to **23**, unlike in the case of the aza-Wittig reaction of **19a** leading to **21a** in Scheme 4. However, this is unclear here.

In summary, tropone (2) undergoes reaction with enolate ions[13] and enamines.[14] As in the cases of tropone (2), the low lying LUMO or highly polarized nature of **5** (Scheme 3) seemed to cause a preferable reactivity toward enolate ions[13] and/or enamines[14] to give 1-azaazulene ring system. Unexpectedly, 1-azaazulenes are obtained in low yields, and thus no generality of the reaction has been clarified here. Further search for methodology synthesizing versatile 1-azaazulene derivatives by using troponimines are now underway.

EXPERIMENTAL

^{1}H- and ^{13}C-nmr were recorded on a Hitachi R-90H, a JEOL EX270, a JEOL JNM-GSX400, and a GE-Omega 500 spectrophotometers in $CDCl_3$, and chemical shifts were given in ppm (δ) relative to the internal $SiMe_4$ standard. Ir spectra were recorded on a Shimadzu IR-400 spectrometer. Mass spectral studies and high resolution mass spectral studies

were conducted by using a Shimadzu GCMS QP-1000 and a JEOL JMS-DX300 spectrometers. Mps were recorded on a Yamato mp-21 apparatus and are uncorrected. All the reactions were carried out under dry nitrogen atmosphere.

Preparation of 3,5-cycloheptadienone oxime (6). A solution of 3,5-*cycloheptadienone*[17] (791 *mg*, 7.32 *mmol*), hydroxylamine hydrochloride (993 mg, 14.2 mmol), and sodium acetate (1.19 g, 14.5 mmol) in EtOH (30 ml) was heated under reflux for 10 min. After evaporation of the solvent, the residual oily materials were extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4. Evaporation of the CH_2Cl_2 afforded 6 (783 mg, 87%): unstable oil, ^{1}H-nmr (90 MHz) δ 3.15 (2H, d, J=4.8 Hz, H-2 or 7), 3.26 (2H, d, J=4.4 Hz, H-2 or 7), 5.55-6.35 (4H, m, H-3, 4, 5, and 6), 8.50 (1H, broad s, OH); ^{13}C-nmr (67 MHz) δ 28.8, 35.2, 127.1, 127.4, 127.5, 128.0, 162.7; ir ($CHCl_3$) 1670, 1610, and 1408 cm^{-1}; ms (m/z) 123 (M^+, 65%), 109 (100%). High resolution ms Calcd for C_7H_9NO: 123.0685. Found: 123.0681.

Preparation of N-(1,3,5-cycloheptatrienyl)diphenylphosphinamide (8). To a stirred solution of 6 (278 *mg*, 2.3 *mmol*) and NEt_3 (346 *mg*, 3.4 *mmol*) in a mixture of hexane (5 ml) and CH_2Cl_2 (5 ml) was added a solution of chlorodiphenylphosphine (650 mg, 3.0 mmol) in CH_2Cl_2 (5 ml) at -40 °C - -50 °C. The mixture was stirred for 3 h at -40 °C - -50 °C, and further stirred at 0 °C for 1 h. After the reaction was completed, ether was added to the reaction mixture and filtered to remove Et_3NHCl, and the filtrate was concentrated. The residue was dissolved in benzene, and ether was added dropwise and the precipitates were collected by filtration to give 8 (405 mg, 55%): colorless powder; mp 174-175 °C (from PhH); ^{1}H-nmr (90 MHz) δ 2.49 (2H, d, J=6.8 Hz), 4.80-5.47 (2H, m), 5.81 (1H, d, J=5.7 Hz), 6.05-6.60 (2H, m), 7.30-8.05 (10H, m): ^{13}C-nmr (100.5 MHz) δ 33.8 (1C, d, J_{PC}=5.9 Hz), 107.1 (1C, d, J_{PC}=5.9 Hz), 116.5 (1C), 125.2 (1C), 127.7 (1C), 128.7 (4C, d, J_{PC}=13.2), 128.7 (1C, d, J_{PC}=2.2 Hz), 129.5 (1C), 131.5 (2C, d, J_{PC}=129.1 Hz), 131.9 (4C, d, J_{PC}=9.5 Hz), 132.2 (2C, d, J_{PC}=2.9 Hz); ^{31}P-nmr (270 MHz) δ 16.4; ir ($CHCl_3$) 1620, 1450, 1425, 1130, and 1118 cm^{-1}; ms (m/z) 307 (M^+, 25%), 106 (100%). High resolution ms Calcd for $C_{19}H_{18}NOP$: 307.1127. Found: 307.1118. Anal. Calcd for $C_{19}H_{18}NOP$: C, 74.26; H,

5.90; N, 4.56. Found: C, 74.36; H, 5.67; N, 4.31.

Dehydrogenation of 8. To a stirred solution of **8** (200 mg, 0.66 mmol) in PhH (10 ml), MnO_2 (591 mg, 6.8 mmol) was added and the mixture was stirred at room temperature for 14 h. The reaction mixture was then filtered through Celite and the filtrate was concentrated to give N-(diphenylphosphinyl)troponimine(**5**): mp 97-98 °C; ^{1}H-nmr (400 MHz) δ 6.80-6.95 (4H, m, H-2, 4, 5, and 6), 7.37-7.47 (6H, m, Ph-H), 7.72 (2H, d, J=11.6 Hz, H-2 and 7), 7.78-7.96 (4H, m, Ph-H); ^{13}C-nmr (100.5 MHz) δ 128.2 (4C, d, J_{PC}=12.5 Hz), 131.5 (4C, d, J_{PC}=9.5 Hz), 135.2 (2C), 135.6 (2C, J_{PC}=130.6 Hz), 136.0 (2C), 141.3 (1C), 141.5 (1C), 174.1 (1C, J_{PC}=6.6 Hz); ^{31}P-nmr (270 MHz) δ 16.0; ir ($CHCl_3$) 1652, 1533, 1438, 1178, and 1138 cm^{-1}; ms (m/z) 305 (M^+, 100%). High resolution ms Calcd for $C_{19}H_{16}NOP$: 305.0970. Found: 305.1007. Anal. Calcd for $C_{19}H_{16}NOP$: C, 74.75; H,5.28; N, 4.59. Found: C, 74.34; H, 5.59; N, 4.45.

Reaction of 5 with N-benzenesulfonyl isocyanate (9). A solution of **5** (87 mg, 0.3 mmol) and **9** (160 mg, 0.9 mmol) in PhH (2 ml) was heated under reflux for 18 h. The reaction mixture was concentrated and the residue was separated by tlc on silica gel (hexane/AcOEt: 1/1) to give **13**[3e,12] (5 mg, 4%) and **5** (30 mg, 30%).

Reaction of N-diphenylphosphinoyltroponimine (5) with enolate ions (14a-d). To a stirred solution of the corresponding ketones (1 mmol) in THF (5 ml) was added $LiN(SiMe_3)_2$ (0.5 M solution in toluene, 2 ml) at -78 °C and the mixture was stirred for 30 min to generate enolate ions (**14a-d**). To this mixture was added troponimine(**5**)(305 mg, 1 mmol) and stirred for 1 h at room temperature. The reaction mixture was heated under refluxing for 15 h, and then added 10% Pd/C (9 mg) and the mixture was further heated under reflux for the periods indicated in Table 1. The reaction mixture was then filtered through Celite and the filtrate was concentrated, extracted with benzene, and the extract was dried over Na_2SO_4. After evaporation of the solvent, the residue was separated by tlc on silica gel (hexane-AcOEt: 1/1) to give 1-azaazulene derivatives (**16a**),[5b] (**16b**),[9] and (**16c**).[5a,17] The reaction conditions and the yields of

the products are summarized in Table 1. For 10,11-dihydrocyclohepta[b]naphtho[1,2-d]pyrrole (**16b**): purple oil; ^{1}H-nmr (270 MHz) δ 3.11 (2H, dd, J-7.6, 6.9 Hz, H-10), 3.37 (2H, dd, J=7.6, 6.9 Hz), H-11), 7.28-7.50 (3H, m, H-7, 8, an 9), 7.60 (1H, dd, J=9.2, 9.6 Hz, H-3), 7.66 (1H, dd, J-8.6, 9.6 Hz, H-4), 7.76 (1H, dd, J=9.2, 10.2 Hz, H-2), 8.54 (1H, d, J=8.6 Hz, H-5), 8.89 (1H, d, J=10.2 Hz, H-1); ^{13}C-nmr (67 MHz) δ 27.1, 29.8, 120.9, 124.1, 126.3, 127.0, 128.8, 128.9, 129.5, 132.3, 132.9, 134.7, 136.0, 137.0, 139.5, 159.2, 172.4; ir ($CHCl_3$) 1601, 1581, 1428, 1399, and 1328 cm^{-1}; ms (m/z) 231 (M^+, 100%). High resolution ms Calcd for $C_{17}H_{13}N$: 231.1049. Found: 231.1031.

Dehydrogenation of 16b. A solution of **16b** (11 mg, 0.05 mmol) and DDQ (23 mg, 0.10 mmol) in PhH (3 ml) was heated under reflux for 5 h. To the reaction mixture was added basic alumina (300 mg) and the mixture was stirred or 16 h at room temperature. The mixture was then filtered and the filtrate was concentrated and purified by tlc on silica gel (AcOEt) to give benzo[e]cyclohepta[b]indole (**17**) [3 mg, 29%, mp 201-202 °C; lit.,[15] 201 °C)].

Reaction of 5 with enamines (15a-d). A solution of **5** (1 mmol) and enamines (**15a-d**) (3 mmol), and 10% Pd/C (9 mg) in MeCN (5 ml) or in PhH (5 ml) was heated under refluxing for the periods indicated in Table 1. The reaction mixture was filtered through Celite and the filtrate was concentrated, and the residue was purified by tlc on alumina to give 1-azaazulene derivatives (**18a**), (**18b**), and (**18d**).[9] The reaction conditions and the yields of the products are summarized in Table 1. For **18a**: dark red oil; ^{1}H-nmr (400 MHz) δ 1.77-1.81 (2H, m), 1.83-1.88 (2H, m), 1.97-2.03 (2H, m), 3.02 (2H, t, J=5.7 Hz), 3.30 (2H, t, J=5.7 Hz), 7.48 (1H, dd, J=9.7, 10.3 Hz), 7.58 (1H, dd, J=9.3, 9.9 Hz), 7.67 (1H, dd, J=9.7, 9.9 Hz), 8.22 (1H, d, J=10.3 Hz), 8.44 (1H, d, J=9.3 Hz);^{13}C-nmr (100.4 MHz), δ 25.3, 27.1, 28.7, 32.6, 34.4, 126.7, 127.3, 128.1, 131.3, 133.5, 135.8, 142.5, 156.9, 174.8; ms (m/z) 197 (M^+, 100%). High resolution ms Calcd for $C_{14}H_{15}N$: 197.1205. Found: 197.1207. For picrate of **18a**: mp 202-204 °C (from MeOH). Anal. Calcd for $C_{20}H_{18}N_4O_7$: C, 56.34; H, 4.26; N, 13.14. Found: C, 56.56; H, 4.06; N, 13.42. For **18b**: dark red oil; ^{1}H-nmr (400 MHz) δ 1.94-2.06 (4H, m), 3.00 (2H, dd, J=5.7, 5.8 Hz), 3.22 (1H, dd, J=5.7, 6.2 Hz),

7.54 (1H, dd, J=9.5, 9.7 Hz), 7.63 (1H, d, J=9.5, 9.9 Hz), 7.73 (1H, dd, J=9.7, 9.9 Hz), 8.22 (1H, d, J=9.7 Hz), 8.48 (1H, d, J=9.5 Hz); ^{13}C-nmr (100.4 MHz) δ 21.9, 23.2, 23.4, 28.5, 122.5, 127.1, 128.5, 131.1, 133.6, 135.8, 142.7, 157.7, 170.0; ms (m/z) 183 (M^+, 81%), 155 (100%). High resolution ms Calcd for $C_{13}H_{13}N$: 183.1048. Found: 183.1056. For picrate of **18b**: mp 199-202 °C (from MeOH). Anal. Calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.45; H, 4.36; N, 13.86.

REFERENCES

1. H, Kuroda and T. Kunii, Theor. Chim. Acta, 1967, 7, 220; T. Machiguchi, T. Hoshi, and J. Yoshino, Tetrahedron Lett., 1973, 3873.
2. K. Kanechika, S. Kajigaishi, and S. Kanemasa, Chem. Lett., 1977, 861.
3. (a) K. Ito, K. Saito, and K. Takahashi, Heterocycles, 1991, 32, 1117; (b) K. Ito, K. Saito, and K. Takahashi, Bull. Chem. Soc. Jpn., 1992, 65, 812; (c) K. Ito, K. Saito, S. Takeuchi, and K. Takahashi, Heterocycles, 1992, 34, 1415; (d) K. Ito, K. Saito, and K. Takahashi, Heterocycles, 1992, 34, 2339; (e) K. Ito, Y. Hara, R. Sakakibara, and K. Saito, Heterocycles, 1995, 41, 1675; and references cited therein.
4. M. Nitta, Rev. Heteroatom Chem., 1993, 57, 87.
5. (a) M. Nitta, Y. Iino, E. Hara, and T. Kobayashi, J, Chem. Soc., Perkin Trans. 1, 1969, 61; (b) M. Nitta, Y. Iino, and K. Kamata, Heterocycles, 1989, 29, 1655; (c) M. Nitta, Y. Iino, T. Sugiyama, and A. Akaogi, Tetrahedron Lett., 1993, 34, 835.
6. N. Kanomata, K. Kamae, Y. Iino, and M. Nitta, J. Org. Chem., 1992, 57, 5313.
7. B. Krzyzanowska and W. J. Stec, Synthesis, 1978, 270; idem, ibid., 1978, 521.
8. (a) T. Kobayashi, H. Kawate, and H. Kakiuchi, Bull. Chem. Soc. Jpn., 1990, 63, 1937; (b) T. Kobayashi, H. Kakiuchi, and H. Kato, Bull. Chem. Soc. Jpn., 1991, 64, 392.
9. K. Ito and M. Nitta, Heterocycles, 1993, 36, 2247.
10. J. N. Denis, J. Vicens, and A. Krief, Tetrahedron Lett., 1979, 2697.
11. MNDO calculations were carried out by using MOPAC program; H. Tomioka and M. Nitta, Heterocycles, 1994, 38, 829.
12. R. Gompper, A. Studeneer, and W. Elser, Tetrahedron Lett., 1968, 1019.
13. J. H. Rigby, C. H. Senanayake, and S. Rege, J. Org. Chem., 1988, 53, 4596.

14. M. Oda, M. Funamizu, and Y. Kitahara, Chem. Commun., 1969, 737.

15. C. W. Muth and E. S. Hanrahan, J. Org. Chem., 1958, 23, 251.

16. D. I. Schuster, J. M. Palmer, and B. C. Dickman, J. Org. Chem., 1966, 31, 4281.

17. Y. Sugimura, N. Soma, and Y. Kishida, Bull. Chem. Soc. Jpn., 1972, 45, 3174.

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