Received, 2nd August, 2005, Accepted, 8th September, 2005, Published online, 13th September, 2005

NEW APPROACH TO THE SYNTHESIS OF NON-BENZENOID AROMATIC COMPOUNDS, FUNCTIONALIZED 1-AZAAZULENE DERIVATIVES: CYCLIZATION REACTIONS OF 2-SUBSTITUTED TROPONES WITH *N*-SILYLENAMINE AND ENAMINE

Norio Sakai, Naoto Hattori, Nanako Tomizawa, Noritaka Abe,[†] and Takeo Konakahara*

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, Noda, Chiba 278-8510, Japan
[†]Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi 753-8512, Japan

Abstract–The reaction of enamines with 2-subsituted tropones produced functionalized 1-azaazulene derivatives. When the reaction is conducted in an aprotic solvent, such as DMSO, the desired 1-azaazulene was obtained in 51% yield. The introduction of an electron-donating group on the enamine increased its nucleophilicity and improved the product yield. On the other hand, the reaction of enamines with 4-isopropyltropone-2-tosylate afforded a different 1-azaazulene derivative.

INTRODUCTION

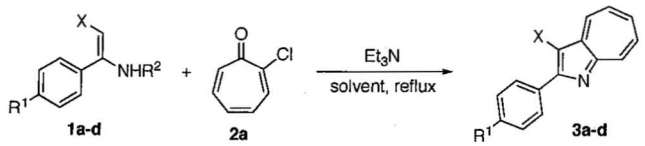
Tropones, 6π-conjugated compounds, have attracted the attention of organic chemists and pharmacists because of unique seven-membered ring structure and unusual electronic structure.[1] It is known that substituted tropones or troponoids undergo cyclization with a variety of nucleophiles to directly produce azulene derivatives.[2] On the other hand, although 1-azaazulene structures are found in many natural products and biologically active substances, for example the basic skeleton of some types of DNA intercalators[3] and pharmaceutically active compounds[4] that contain an azaazulene unit, a convenient preparation for such skeletons has not been extensively studied.[5] Therefore, the development for practical and facile methodologies for preparing 1-azaazulene skeletons would be highly desirable. We previously reported that an *N*-silylenamine, formed by the insertion of an aromatic nitrile into the silicon-carbon bond of an α-silylcarbanion and, after hydrolysis, reacts smoothly with Michael acceptors, such as

α,β-unsaturated ketones, α,β-diketones, and fluorinated olefins, producing polysubstitued pyrroles and pyridine derivatives in good yields, our studies confirmed that these intermediates act as an appropriate nucleophile to those acceptors.[6] Hence, it would be expected that the cyclization of 2-substituted tropones with enamines as a nitrogen source would produce the desired 1-azaazulene skeleton. We report herein on a practical and convenient synthesis of functionalized 1-azaazulene derivatives by the reaction of 2-substituted tropones with enamines. We also disclosure that the reaction of 4-isopropyltropone tosylate with an enamine produces a different type of 1-azaazulene skeleton.

RESULTS AND DISCUSSION

On the basis of our previous work,[6] we initially examined the reaction of four types of enamines (**1a-d**) having a heterocyclic/aromatic ring with 2-chlorotropone (**2a**) in the presence of triethylamine in THF as a model reaction, and the results are shown in Table 1. The reaction of enamine (**1a**) with tropone (**2a**) produced cycloadduct (**3a**) as red crystals in only 1 % yield (run 1). Although the product yield was rather low, spectral data clearly showed that product (**3a**) consisted of the desired 1-azaazulene skeleton. We then attempted the reaction using enamines (**1b**) and (**1c**), which contain an electron-donating group, in the hope of enhancing the nucleophilicity of the enamine. As expected, when enamine (**1b**), having a methoxy group, was employed as a nucleophile, the yield was increased to 10% (run 2). In the case of the further activated enamine (**1c**), a 20% yield of the product (**3c**) was clearly obtained (run 3). These results show that the activation of an enamine by an electron-donating group makes it possible to improve the product yield. On the other hand, when the reaction of *N*-silylenamine (**1d**) with 2-chlorotropone was conducted in C_6H_6 in the presence of KF, the 1-azaazulene derivative (**3d**) was obtained in 24% yield (run 4).

Table 1. Reaction of enamines (**1a**)-(**1c**) or *N*-silylenamine (**1d**) with 2-chlorotropone (**2a**)



run	enamine (**1**) X	R^1	R^2		solvent	time (h)	yield of **3** (%)[a]	
1	Ar[c]	H	H	**1a**	THF	50	**3a**	1
2	Ar[c]	MeO	H	**1b**	THF	48	**3b**	10
3	Ar[c]	Me_2N	H	**1c**	THF	48	**3c**	20
4[b]	2-pyridyl	H	Me_3Si	**1d**	PhH	44	**3d**	24

[a] Isolated yields.

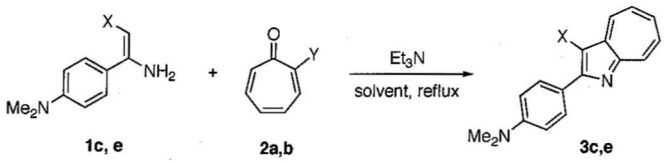
[b] KF was added as an additive.

[c] Ar = 3-methyl-5-isoxazolyl group.

Unfortunately, several attempts to improve the yield of product (**3d**), such as solvents and additives were not effective for the reaction system.[7]

To improve the product yield and to extend a reaction substrate, we then ran the reaction using several different solvents, enamines, and tropones. The results are summarized in Table 2. When C_6H_6 or DMSO was used as a solvent in the reaction of **1c** and **2a**, instead of THF, the yield was slightly increased to 33% (runs 1, 2 and 4). However, the use of MeCN had no effect on the yield (run 3). On the other hand, the employment of enamine (**1e**), containing a pyridine ring on the β-position did not affect the product yield (runs 5 and 6). We then carried out the reaction using tropolone tosylate (**2b**), which has a better leaving group than **2a**. The use of an aromatic solvent, such as benzene and toluene was not recommended in this reaction because of poor yields (runs 7 and 8). However, in the case of the aprotic solvent DMF, the product yield was increased to 40% (run 10). Furthermore, another aprotic solvent, DMSO, remarkably improved the yield of 1-azaazulene (**3c**) up to 51% (run 11), indicating that an aprotic dipolar solvent was effective for the present reaction.[8]

Table 2. Reaction of enamine (**1c**), (**1e**) with tropone (**2a**), (**2b**)



1c, e **2a,b** **3c,e**

run	enamine (**1**) X		tropone (**2**) Y		solvent	time (h)	yield of **3** (%)[a]	
1	Ar[b]	**1c**	Cl	**2a**	THF	48	**3c**	20
2	Ar[b]	**1c**	Cl	**2a**	PhH	48	**3c**	32
3	Ar[b]	**1c**	Cl	**2a**	MeCN	48	**3c**	25
4	Ar[b]	**1c**	Cl	**2a**	DMSO[c]	20	**3c**	33
5	2-pyridyl	**1e**	Cl	**2a**	PhH	48	**3e**	30
6	2-pyridyl	**1e**	Cl	**2a**	DMSO[c]	20	**3e**	32
7	Ar[b]	**1c**	OTs	**2b**	PhH	48	**3c**	11
8	Ar[b]	**1c**	OTs	**2b**	PhMe	48	**3c**	8
9	Ar[b]	**1c**	OTs	**2b**	MeCN	48	**3c**	25
10	Ar[b]	**1c**	OTs	**2b**	DMF	48	**3c**	40
11	Ar[b]	**1c**	OTs	**2b**	DMSO[c]	20	**3c**	51

[a] Isolated yields.

[b] Ar = 3-methyl-5-isoxazolyl group.

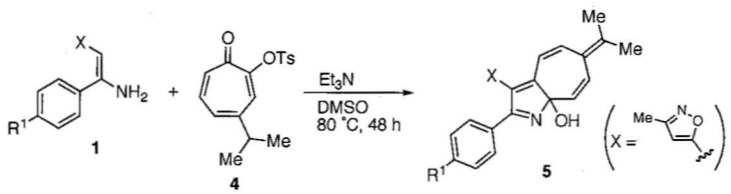
[c] Reaction was performed at 80 °C.

Lastly, we attempted the cycloaddition reaction of an enamine with 4-isopropyltropone-2-tosylate (**4**). Table 3 shows the results. For example, when the reaction of the enamine (**1b**) with the tropone (**4**) was

conducted in DMSO at 80 °C for 48 h, the 1-azaazulene derivative (**5b**), the structure of which is different from that produced in the previous reaction system, was obtained in 12% yield (run 2 in Table 3). The structure was confirmed by ^{1}H, ^{13}C, and DEPT NMR spectroscopy and HRMS. The peak at 1.64 ppm, which is assigned to two methyl groups of the isopropyl group, was a singlet, not a doublet. A branched sp^3 carbon peak was not observed by ^{13}C NMR and DEPT spectrum. The result does not show the existence of one proton on the isopropyl group. Two doublet peaks (each J = 8.7 Hz) at 6.89 and 7.75 ppm were assigned to four protons on the benzene ring. Two sets of two doublet resonances (each J = 10.8 Hz) at 7.96 and 8.08 ppm and at 8.61 and 8.66 ppm are assigned to four protons on a seven-membered ring. Moreover, HRMS indicated the molecular formula of the product (**5b**) to be $C_{23}H_{23}O_3N_2$, strongly supporting the proposed structure.

The reaction of other three types of enamines with the tosylate (**4**) also proceeded. Although the product yields were somewhat low in these reactions, we found that the increase of the electron density on the β-carbon of the enamine by a substituent improved the yield of the azaazulene derivative (**5**) (runs 1-3).[9]

Table 3. Reaction of enamine (**1**) with tropolone tosylate (**4**)

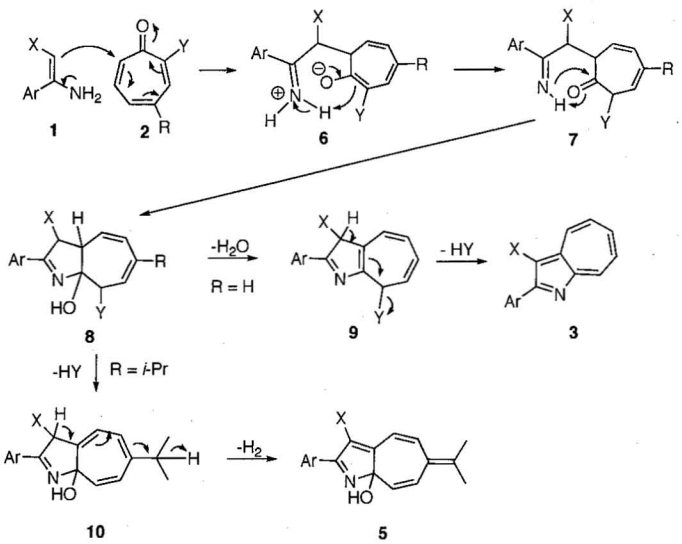


run	enamine (**1**) R[1]		yield of **5** (%)[a]	
1	Me	**1f**	**5f**	7
2	OMe	**1b**	**5b**	12
3	NMe_2	**1c**	**5c**	28

[a] Isolated yields.

A plausible mechanism for the cycloaddition of the enamine (**1**) with the tropone (**2**) leading to the 1-azaazulene derivative (**3**) is shown in Scheme 1. Theoretically, it is known that for a tropone having an electron-withdrawing group on the 2-position, the 7-position on the tropone is preferentially attacked by a nucleophile.[5c] Hence, the nucleophilic attack of the electron-rich β-carbon of the enamine (**1**) on the 7-position of the tropone (**2**) occurs to produce the betaine derivative (**6**), and a subsequent proton shift gives imine derivative (**7**). An intramolecular attack of the lone pair on the nitrogen atom to the carbonyl group on the tropone unit then forms the cycloadduct (**8**), followed by both the dehydration of **8** and the elimination of HY from **9**, leading to aromatization and the formation of the desired 1-azaazulene product (**3**). Although there are no clear explanations for the formation of azaazulene derivative (**5**), in the case of

a tropone containing an isopropyl group, the elimination of a leaving group and subsequent oxidation would occur, leading to the final product (**5**).



Scheme 1

CONCLUSION

In summary, we demonstrated the cycloaddition of several enamines with 2-substitued tropones, to directly produce functionalized 1-azaazulene derivatives. Of note is the finding that enamine derivatives having an electron-donating group effectively act as a good nucleophile in this type of cycloaddition, and in an aprotic solvent, such as DMSO the desired reaction proceeded smoothly. A reaction using a tropone containing an isopropyl group on the 4-position gave a different type of 1-azaazulene skeleton.

EXPERIMENTAL

Column chromatography was performed using Silica gel 60 (Merck). Benzene, toluene, and THF were distilled from sodium-benzophenone before use. Amines, DMF and DMSO were distilled from CaH_2 and dried over MS 4A. The other organic materials were distilled or recrystallized from the appropriate solvent prior to use. 2-Chlorotropone (**2a**), tropone-2-tosylate (**2b**), and 4-isopropyltropone-2-tosylate (**4**) were prepared according to previous reports.[10] All reactions were carried out under an argon atmosphere, unless otherwise noted. Melting points were obtained on a Yanagimoto micro-melting point apparatus MP-500D. IR spectra (KBr) were measured on a JASCO FT/IR-410. ^{1}H NMR spectra were measured at 500 (or 300) MHz using tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured at 125 (or 75) MHz using the chloroform peak (77.0 ppm) instead of an internal standard. HRMS were measured on a JEOL JMS-700 MStation using NBA (3-nitrobenzylalcohol) as a matrix.

General procedure for the reaction of enamine (1) with 2-substituted tropone (2).

To a DMSO (10 mL) solution of enamine (**1**, 1 mmol) and triethylamine (101 mg, 1 mmol) was added a DMSO solution (2 mL) of tropone (**2**, 1 mmol) *via* a syringe, and the mixture was heated at 80 °C. After 48 h, water (10 mL) was added to the reaction, the organic layer was extracted with $CHCl_3$ (10 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was adsorbed on silica gel and purified by column chromatography (hexane-AcOEt) to give the corresponding 1-azaazulenes (**3**).

3-(3-Methyl-5-isoxazolyl)-2-phenyl-1-azaazulene (**3a**): Red crystals (from hexane); mp 157.0-158.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 6.10 (s, 1H, isoxazolyl-H), 7.44-7.51 (m, 3H, PhH), 7.73-7.97 (m, 5H, Ph-H, azaazulene-H), 8.78 (d, 1H, *J* = 10.2 Hz, azaazulene-H), 8.92 (d, 1H, *J* = 10.2 Hz, azaazulene-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 11.2, 102.8, 110.1, 113.2, 127.0, 129.9, 130.4, 130.7, 134.2, 135.9, 136.9, 145.5, 158.2, 159.6, 160.2, 162.3, 162.5; MS (FAB) *m/z* 287 (M+H, 100%); HRMS (FAB): Calcd for $C_{19}H_{15}N_2O$: 287.1185, found 287.1177.

3-(3-Methyl-5-isoxazolyl)-2-(4-methoxyphenyl)-1-azaazulene (**3b**): Red crystals (from hexane); mp 134.3-135.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.09 (s, 1H, isoxazolyl-H), 6.96 (d, 2H, *J* = 8.4 Hz, PhH), 7.64-7.84 (m, 5H, PhH, azaazulenyl-H), 8.67 (d, 1H, *J* = 9.3 Hz, azaazulenyl-H), 8.72 (d, 1H, *J* = 9.3 Hz, azaazulenyl-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 11.1, 54.8, 103.8, 110.0, 113.6, 127.1, 130.1, 130.6, 130.8, 134.1, 135.9, 137.4, 145.6, 158.1, 159.6, 160.5, 165.3, 165.5; MS (FAB) *m/z* 317 (M+H, 100%); HRMS (FAB): Calcd for $C_{20}H_{17}N_2O_2$: 317.1290, found 317.1283.

3-(3-Methyl-5-isoxazolyl)-2-(4-dimethylaminophenyl)-1-azaazulene (**3c**): Red gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, CH_3), 2.95 (s, 6H, $N(CH_3)_2$), 6.15 (s, 1H, isoxazolyl-H), 6.65 (d, 2H, J = 8.7 Hz, PhH), 7.49-7.67 (m, 3H, azaazulenyl-H), 7.76 (d, 2H, *J* = 9.0 Hz, PhH), 8.46 (1H, d, *J* = 9.9 Hz, azaazulenyl-H), 8.53 (d, 1H, *J* = 9.9 Hz, azaazulenyl-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 12.0, 40.5, 104.8, 110.1, 112.1, 122.6, 130.7, 131.3, 131.4, 133.3, 135.3, 136.9, 146.8, 151.8, 159.2, 160.5, 166.6, 166.8; MS (FAB) *m/z* 330 (M+H, 100%); HRMS Calcd for $C_{21}H_{20}N_3O$: 330.1607, found 330.1603.

2-(4-Dimethylaminophenyl)-3-(2-pyridyl)-1-azaazulene (**3e**) Red gum; ^{1}H NMR (300 MHz, CD_3OD) δ 2.91 (s, 6H, $N(CH_3)_2$), 6.61 (d, 2H, *J* = 9.0 Hz, PhH), 7.34-7.40 (m, 2H, PyH, azaazulenyl-H), 7.46 (d, 2H, *J* = 9.0 Hz, PhH), 8.27 (d, 1H, *J* = 9.9 Hz, azaazulenyl-H), 8.48 (d, 1H, *J* = 10.5 Hz, azaazulenyl-H), 8.64 (d, 1H, *J* = 4.5 Hz, PyH); ^{13}C NMR (75.45 MHz, CD_3OD) δ 40.2, 112.8, 122.9, 123.6, 123.7, 128.1, 131.7, 132.1, 132.3, 134.3, 134.7, 138.3, 138.7, 146.9, 150.5, 152.8, 156.0, 158.7, 166.1; MS (FAB) *m/z* 326 (M+H, 100%); HRMS Calcd for $C_{22}H_{20}N_3$: 326.1657, found 326.1655.

General procedure for the reaction of enamine (1) with 2-chlorotropone (2a)

To a C_6H_6 solution (10 mL) of *N*-silylenamine (**1d**, 268 mg, 1.00 mmol) in the presence of 18-crown-6

(4.0 mg, 0.015 mmol) and KF (58 mg, 1.0 mmol) was added a C_6H_6 solution (2 mL) of 2-chlorotropone (**2a**, 140 mg, 1.00 mmol) and triethylamine (101 mg, 1 mmol). The mixture was heated at 80 °C. After 44 h, water (10 mL) was added to the reaction mixture, and the organic layer was extracted with CH_3Cl (10 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was adsorbed on silica gel and purified by column chromatography (hexane-AcOEt) to give 1-azaazulene (**3d**, 24%) as a red gum.

2-Phenyl-3-(2-pyridyl)-1-azaazulene (**3d**): Red gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.22 (m, 3H, PhH), 7.30-7.79 (m, 8H, PyH, PhH, azaazulenyl-H), 8.69-8.79 (m, 3H, PyH, azaazulenyl-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 121.4, 123.9, 126.3, 128.3, 129.0, 129.8, 130.0, 130.1, 135.4, 135.6, 136.1, 136.5, 137.9, 145.7, 149.8, 154.8, 158.0, 165.4; MS (FAB) *m/z* 283 (M+H. 100%); HRMS Calcd for $C_{20}H_{15}N_2$: 283.1235, found 283.1235.

General procedure for the reaction of enamine (1) with 4-isopropyltropone-2-tosylate (4)

To a DMSO solution (10 mL) of enamine (**1**, 1 mmol) was added a DMSO solution (2 mL) of tropone (**4**, 318 mg, 1 mmol) and triethylamine (101 mg, 1 mmol), and the mixture was heated at 80 °C. After the reaction, water (10 mL) was added to the reaction mixture, and the organic layer was extracted with CH_3Cl (10 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was adsorbed on silica gel and purified by column chromatography (hexane-AcOEt) to give the corresponding azaazulene (**5**).

6-Dimethylmethylene-9'-hydroxy-3-(3-methyl-5-isoxazolyl)-2-(4-methoxyphenyl)-1-azaazulene (**5b**): Red solid (from hexane); mp 49.3-50.0 °C; IR (KBr) 2923, 1607, 1432 (cm^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 6H, $CH(CH_3)_2$), 2.30 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.05 (s, 1H, isoxazolyl-H), 6.89 (d, 2H, *J* = 9.0 Hz, PhH), 7.74 (d, 2H, *J* = 9.0 Hz, PhH), 7.95 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 8.07 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 8.61 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 8.67 (d, 1H, *J* =10.8 Hz, azaazulenyl-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 11.6, 32.3, 55.3, 74.6, 104.0, 110.1, 114.1, 127.3, 128.0, 131.2, 134.3, 135.6, 144.7, 157.1, 160.0, 160.4, 161.0, 164.9, 166.0; MS (FAB) *m/z* 375 (M+H, 100%); HRMS Calcd for $C_{23}H_{22}N_2O_3$: 375.1630, found 375.1711.

2-(4-Diethylaminophenyl)-6-(dimethylmethylene)-9'-hydroxy-3-(3-methyl-5-isoxazolyl)-1-azaazulen e (**5c**): Red gum; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 6H, $CH(CH_3)_2$), 2.30 (s, 3H, CH_3), 2.92 (s, 6H, $N(CH_3)_2$), 3.72 (br s, 1H, OH), 6.07 (s, 1H, isoxazolyl-H), 6.59 (d, 2H, *J* = 8.7 Hz, PhH), 7.68 (d, 2H, *J* = 8.7 Hz, PhH), 7.81 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 7.95 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 8.33 (d, 1H, *J* =10.8 Hz, azaazulenyl-H), 8.41 (d, 1H, *J* =10.8 Hz, azaazulenyl-H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 11.6, 32.0, 40.0, 74.3, 104.0, 109.3, 111.6, 122.0, 127.9, 130.9, 132.5, 134.1, 145.0, 151.2, 157.5, 159.2, 160.0, 165.3, 166.4; MS (FAB) *m/z* 388 (M+H, 100%); HRMS Calcd for $C_{24}H_{26}N_3O_2$: 388.2025, found 388.2025.

6-Dimethylmethylene-9'-hydroxy-3-(3-methyl-5-isoxazolyl)-2-tolyl-1-azaazulene (5f): Red solid (from hexane); mp 154.6-156.1 °C; IR (KBr) 2964, 1598, 1434 (cm^{-1}); ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 6H, $CH(CH_3)_2$), 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.02 (s, 1H, isoxazolyl-H), 7.19 (d, 2H, J = 7.5 Hz, PhH), 7.67 (d, 2H, J = 7.5 Hz, PhH), 7.96 (d, 1H, J =10.8 Hz, azaazulenyl-H), 8.08 (d, 1H, J =10.8 Hz, azaazulenyl-H), 8.61 (d, 1H, J =10.8 Hz, azaazulenyl-H), 8.72 (d, 1H, J =10.8 Hz, azaazulenyl-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 21.4, 32.3, 74.6, 103.8, 110.6, 127.3, 127.8, 127.9, 129.3, 129.5, 132.3, 134.7, 136.1, 139.7, 144.6, 157.4, 159.9, 160.6, 166.1; MS (FAB) *m/z* 359 (M+H, 100%); HRMS Calcd for $C_{23}H_{23}N_2O_2$: 359.1759, found 359.1768.

ACKNOWLEDGEMENTS

This work was partially supported by Grants-in-Aid for Scientific Research from MEXT (16550148), 2004-2005, a grant from the Japan Private School Promotion Foundation and a fund for "High-Tech Research Center" Project for Private Universities: a matching fund subsidy from MEXT, 2000-2004.

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7. Either solvents, such as DMF or additives, such as 18-crown-6 did not improve the product yield.
8. When the reaction was carried out at 100 °C, the yield of the product (**3c**) decreased to 32%.
9. The use of an enamine containing a 4-chlorophenyl group decreased the product yield to 5%, as the result of a decrease in the reactivity of the enamine by the presence of a halogen atom.
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