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THE REACTION OF [(1-AZAAZULEN-2-YL)IMINO]PHOSPHORANE WITH ARYLALDEHYDES: FORMATION OF BIS[(1-AZAAZULEN-2-YL)AMINO]ARYLMETHANES

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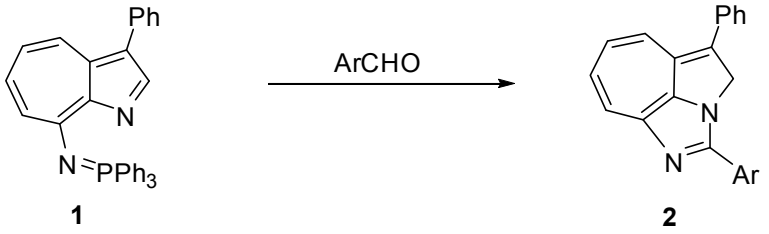
Abstract – Reaction of [(3-ethoxycarbonyl-1-azaazulen-2-yl)imino]triphenylphosphorane with arylaldehydes gave bis[(3-ethoxycarbonyl-1-azaazulen-2-yl)amino]arylmethanes *via* corresponding azaazulenylimine intermediacy.

Aza-Wittig reaction is a useful method for the synthesis of imines and nitrogen-containing heterocycles, where the intermolecular reaction of iminophosphoranes with aldehydes and ketones gives imine derivatives and the tandem aza-Wittig reaction/intramolecular cyclization produces nitrogen-containing heterocycles.[1-10] Generally, a simple aza-Wittig reaction with aldehydes proceeds to give the corresponding imines.

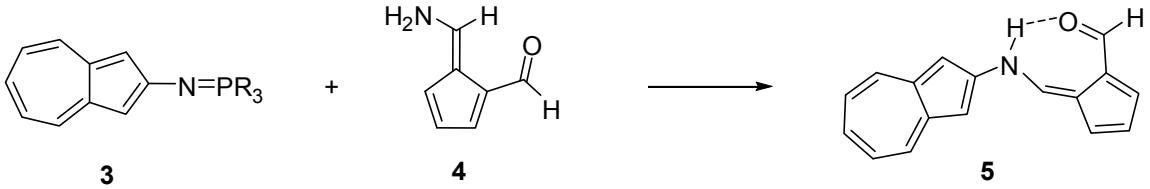
In the azaazulene chemistry, aza-Wittig reactions have been also used for synthesis of azaazulene fused heterocycles.[8,11] It is thought that azulenylimines and azaazulenylimines would be good precursors for constructing azaazulene fused heterocycles, but the synthesis of azulenylimines and azaazulenylimines from azulenylamines and azaazulenylamines have not been reported. Only few reports, where the reaction of [(1-azaazulen-8-yl)imino]phosphorane (**1**) with arylaldehydes gave **2**[12] (Scheme 1) and [(azulen-2-yl)imino]phosphorane (**3**) with aldehydes (**4**) gave **5**[13] (Scheme 2), showed the possibility of the formations of azulenylimine and azaazulenylimines as intermediacy. Therefore, we investigated the synthesis of (1-azaazulen-2-yl)imines by the reaction of [(1-azaazulen-2-yl)imino]phosphorane with

arylaldehydes. In the reaction, expected (1-azaazulen-2-yl)imines were not isolated, but an interesting reaction was observed and bis[(3-ethoxycarbonyl-1-azaazulen-2-yl)amino]arylmethanes were obtained.



1 **2**

Scheme 1

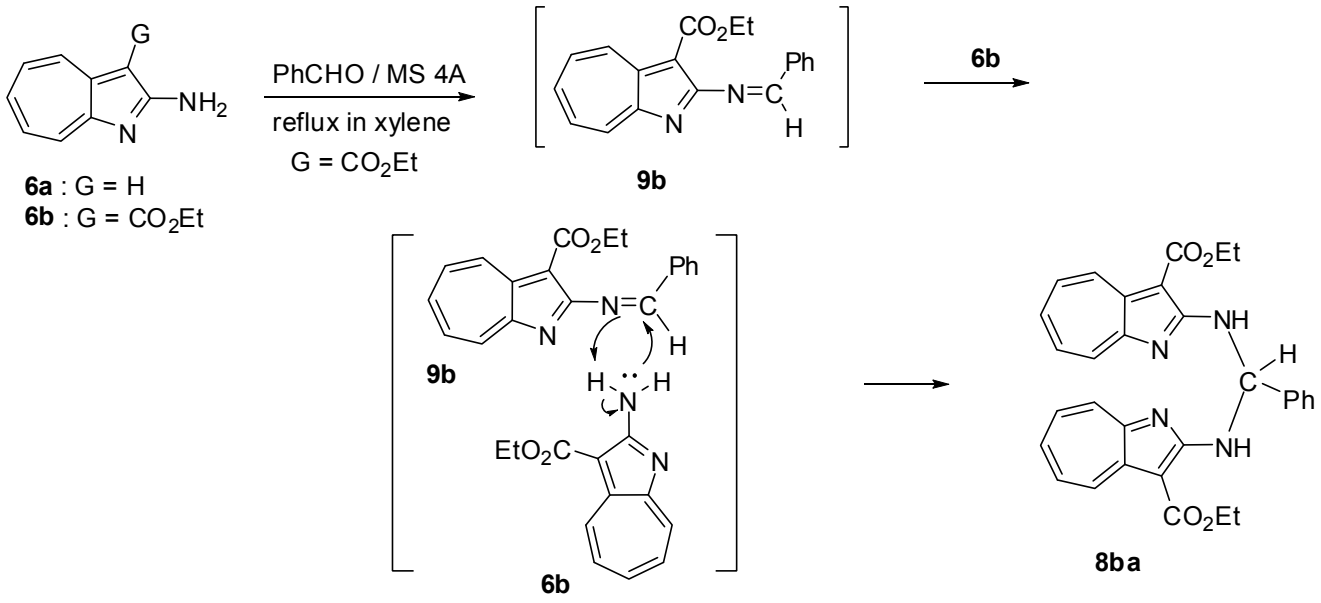


3 **4** **5**

Scheme 2

For the synthesis of (1-azaazulen-2-yl)imine, we examined the condensation reaction of 2-amino-1-azaazulene with arylaldehyde at first. Treatment of 2-amino-1-azaazulene (**6a**) with benzaldehyde (**7a**) in the presence of MS 4A under reflux in dry benzene for 24 h did not proceed. Treatment of ethyl 2-amino-1-azaazulene-3-carboxylate (**6b**) with **7a** in the presence of MS 4A under reflux in dry xylene for 75 h gave bis[(3-ethoxyxcarbonyl-1-azaazulen-2-yl)amino]phenylmethane (**8ba**) in 48% yield together with recovered **6b** (33%) (Scheme 3). It is considered that the produced imine (**9b**) *in situ* might react with **6b** in the reaction to give **8ba**. The structure of **8ba** was deduced by spectroscopic data as well as elemental analysis and mass spectrum. In the ^{1}H NMR spectrum of **8ba**, ^{1}H triplet assignable to a methine proton appeared at δ 7.79 (J 8.5), which was coupled with 2H broad doublet assignable to NH appeared at δ 8.60 (J 8.5), together with seven-membered protons (10H) and two ethyl ester protons (10H). In the ^{13}C NMR spectrum, a methine carbon appeared at δ 64.22. From these results, we assigned the structure. Although (1-azaazulen-2-y)imine was not isolated, the formation of reactive (1-azaazulen-2-y)imine in the reaction was shown.

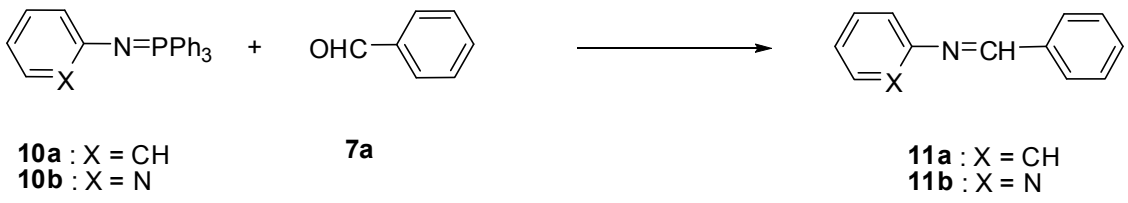
The results show that the amino group on the 1-azaazulene, being blocked of the reactive C-3, reacted with the aldehyde. Ito reported about the reaction of 2-aminoazulene with aldehydes, where initial reaction of the aldehyde occurred but not at the amino group at C-1 of azulene nuclei.[14] The result suggests that the amino group of the 1,3-position blocked 2-aminoazulenes would be possible to react with aldehydes.



Scheme 3

As mentioned above, aza-Wittig reaction is an excellent method for the conversion of a P=N bond into a C=N bond, being conducted under neutral conditions in the absence of catalysts and generally at mild temperature,[1-10] and a further reaction of the iminophosphoranes with the produced imines did not occur.[15,16] It is reported that the aza-Wittig reaction of [(1-azaazulen-2-yl)imino]phosphorane with 2-bromotropone gave 6,7-diazaazuleno[1,2-*a*]azulene[17] and the reactions of [(1-azaazulen-2-yl)imino]phosphoranes or [(1,3-diazaazulen-2-yl)imino]phosphoranes with aryl isocyanate proceeded *via* both aza-Wittig reaction and abnormal aza-Wittig reaction to give corresponding triazine ring fused heterocycles.[18-20] These results suggested that the possibility of the synthesis of (1-azaazulen-2-yl)imines by aza-Wittig reaction. Therefore, we next investigated the reaction of [(1-azaazulen-2-yl)imino]phosphoranes with arylaldehydes.

For affirmation of the formation of (arylbenzylidene)arylimines, we examined the reaction of simple aryliminophosphoranes (**10a**,**b**) with **7a** under slightly severe conditions. Thus, the reactions of **7a** and **10b** with **7a** were performed in dry xylene at 125 ºC for 250 h and the corresponding imines (**11a** : 65% and **11b** : 55%) were isolated (Entry 1 and 2) (Scheme 4). In the reactions, the secondary reaction products, such as the products from the reaction of **11** with **10**, were not obtained.



Scheme 4

Then, we examined the reaction of [(1-azaazulen-2-yl)imino]phosphoranes with arylaldehydes. Reaction of [(1-azaazulen-2-yl)imino]triphenylphosphorane (**12a**) with benzaldehyde (**7a**) in dry xylene at 60 ºC for 94 h did not proceed and **12a** was recovered (Entry 3). When the reaction was carried out in xylene at 125 ºC for 140 h, the reaction occurred but presented a complex feature; no distinct product was obtained (Entry 4). We previously reported about the reaction of **1** with arylaldehydes, the existence of $Pd(OAc)_2$ improved the reacton.[12] So, the reaction of **12a** with **7a** was carried out in the presence of $Pd(OAc)_2$, but the reaction presented a complex feature again (Entry 5).

Table 1. Reactions of the iminophosphoranes ($ArNPPh_3$) with arylaldehydes

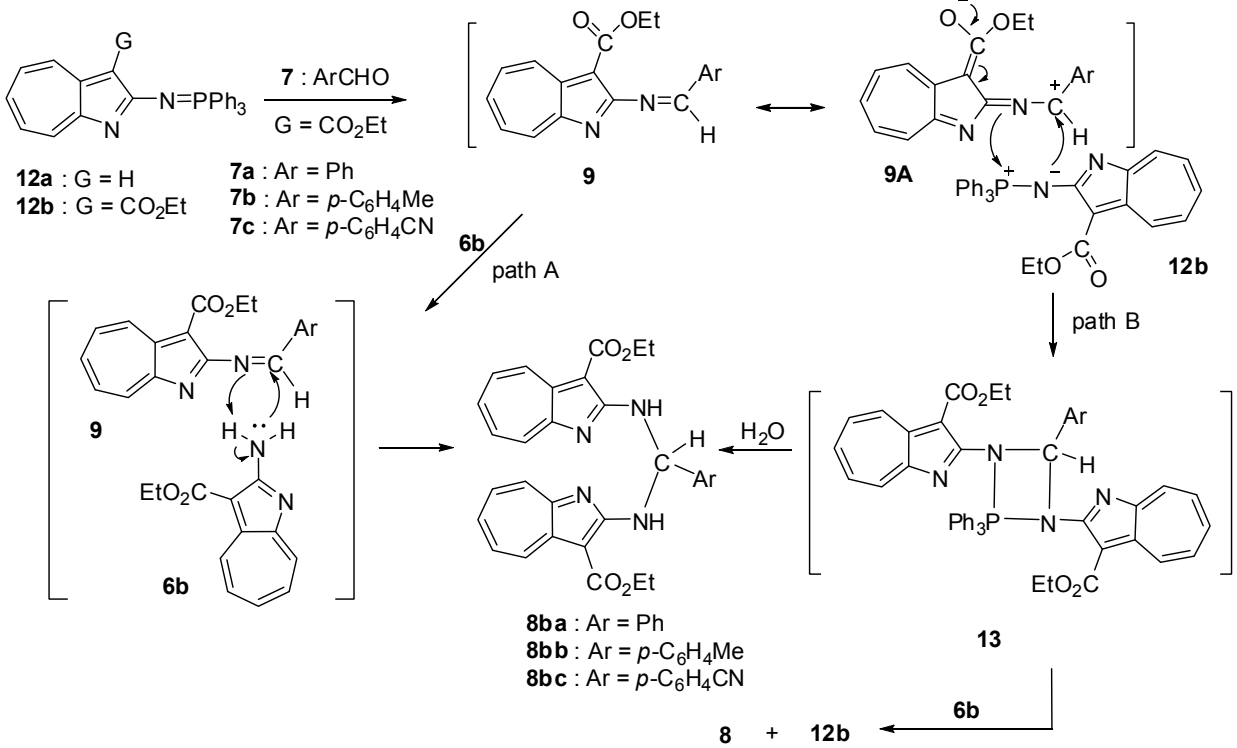
Entry	$ArNPPh_3$	Aldehyde	Conditions		Products (Yield / %)		
			Additive	Temp/ ºC	Time/h			
1	**10b**	**7a**		125	250	**11a** (65)		
2	**10b**	**7a**		125	250	**11b** (55)		
3	**12a**	**7a**	-	60	94	**12a** (89)		
4	**12a**	**7a**	-	125	140	complex mixture		
5	**12a**	**7a**	$Pd(OAc)_2$	125	200	complex mixture		
6	**12b**	**7a**	-	125	200	**8ba** (20)	**12b** (25)	**6b** (0.1)
7	**12b**	**7a**	$Pd(OAc)_2$	125	200	complex mixture		
8	**12b**	**7b**	-	125	200	**8bb** (24)	**12b** (11)	**6b** (19)
9	**12b**	**7c**	-	125	200	**8bc** (56)	**12b** (2)	**6b** (16)
10	**12b**	**7c**	**6b**, MS 4A	125	50+50	**8bc** (92)	**12b** (3)	**6b** (1)

When **12b** was treated with **7a** in dry xylene at 125 ºC for 200 h, **8ba** was obtained in 20% yield together with recovered **12b** (25%) and **6b** (0.1%) (Entry 6). In the reaction, the (1-azaazulen-2-yl)imine was not isolated; even under the conditions where the recovery of [(1-azaazulen-2-yl)imino]phosphorane existed. The result showed that the electron-withdrawing group accelerated the reaction. Addition of $Pd(OAc)_2$ as a catalyst gave a complex feature again (Entry 7). The reaction of **12b** with *p*-tolualdehyde (**7b**) gave a similar result as the case of the reaction with benzaldehyde (Entry 8). The reaction of **12b** with *p*-cyanobenzaldehyde (**7c**) gave **8bc** in good yield (56%) together with **12b** (2%) and **6b** (16%) (Entry 9). Interestingly, when **6b** (about 10% to **12b**) and MS 4A were added in the midway of the reaction, the reaction was accelerated and **8bc** was obtained in 92% yield (Entry 10).

Plausible mechanistic pathways are shown in Scheme 5. Two pathways could be considerable for the reaction. Aza-Wittig reaction of the iminophosphorane (**12b**) with aldehydes gave the

(1-azaazulen-2-yl)imine (**9**). Successive reaction of **9** with 2-amino-1-azaazulene (**6b**), which would be produced by hydration of **12b**, gives **8** (path A). The imine (**9**) have a resonance form **9A**. When the reaction underwent between **9A** and **12b**, it considers that the reaction proceed as follows: the nitrogen of the iminophosphorane (**12b**) attacks to the benzylic cationic carbon of **9A** by squeezing the electrons on the oxide moiety to the nitrogen as shown with arrows, and the nitrogen of imine of **9A** attacks to phosphonium of **12b** concurrently, and the diazaphosphetane (**13**) could be formed as an intermediate. Hydrolysis of **13** by work-up with H_2O furnishes **8** (path B).

It seems that the result, being addition of **6b** enhanced the reaction, supports path A at a glance. Never the less, the possibility of being under way on path B remains. The reaction of **6b** with **13** could give **8** and **12b**. This would come to cause the catalytic acceleration of the reaction of **6b**. In fact, the amount of added **6b** is little in the reaction, but the enhancement of the yield is large, and the reaction time is shortened. In addition, the reaction was performed under water-free conditions, and a considerable amount of **12b** was recovered after work-up, even after the chromatography on silica gel. These implied that the hydrolysis of **12b** under the conditions is implausible. Furthermore, the results that the reaction underwent in the case of using **12b**, having an ester group at C-3 of 1-azaazulene skeleton, and the *p*-cyano group on phenyl group accelerated the reaction are suggestive. Regarding the reaction of iminophosphorans, Nitta reported that an iminophosphorane can undergo a nucleophilic attack to the methylene, and the reaction depends on the nature of the Michael acceptor.[13] From these considerations, we prefer path B to path A.



Scheme 5

CONCLUSION

Reaction of [(3-ethoxycarbonyl-1-azaazulen-2-yl)imino]triphenylphosphorane (**12b**) with arylaldehydes was investigated. From the reaction bis[(3-ethoxycarbonyl-1-azaazulen-2-yl)amino]arylmethanes (**8**) were obtained. The reaction is thought to undergo *via* forming (1-azaazulen-2-yl)imine (**9**), and a successive reaction of **9** with **12b** gave diazaphosphetane (**13**) as an intermediate, and hydrolysis of **13** furnished **8**.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point MP JP-3 apparatus and are uncorrected. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400S (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) using $CDCl_3$ as a solvent with tetramethylsilane as an internal standard; *J* values are recorded in Hz. IR spectra were recorded for KBr pellets on a Nicolet FT-IR AVTAR 370DTGS unless otherwise stated. MS spectra were taken with a LC-MS Waters Integrity System. Merck Kieselgel 60 was used for column chromatography. Benzene and xylene were distilled on CaH_2.

Reaction of ethyl 2-amino-1-azaazulene-3-carboxylate (6b) with benzaldehyde

A mixture of ethyl 2-amino-1-azaazulene-3-carboxylate (**6b**) (0.300 g, 1.39 mmol) and benzaldehyde (**7a**) (1 mL) in dry xylene (30 mL) in the presence of MS 4A (1.50 g) was refluxed for 75 h. The solvent was evaporated and chromatography of the residue with hexane-$CHCl_3$ (1:1) gave bis[(3-ethoxycarbonyl-1-azaazulen-2-yl)amino]phenylmethane (**8ba**) (0.0172 g, 48%) and **6a** (0.100 g, 33%), successively.

8ba: Yellow needles (MeCN), mp 177.0-179.0 ºC; ^{1}H NMR δ 1.45 (6H, t, *J* 7.1, CH_3), 4.44 (8H, q, *J* 7.1, OCH_2), 7.29 (1H, t, *J* 7.1, H-*p*-phenyl), 7.36 (2H, dd, *J* 7.6 and 7.1, H-*m*-phenyl), 7.48 (2H, t, *J* 9.6, H-6,6'), 7.63 (4H, like-t, *J* 9.6, H-5,7,5',7'), 7.66 (2H, d, *J* 7.6, H-*o*-phenyl), 7.79 (1H, t, *J* 8.5, N-CH-N), 8.17 (2H, d, *J* 9.8, H-8,8'), 8.60 (2H, br d, *J* 8.5, NH), and 8.86 (2H, d, *J* 10.3, H-4,4'); ^{13}C NMR δ 15.07, 60.40, 64.22, 98.19, 126.74, 128.37, 129.07, 129.91, 130.82, 132.56, 133.52, 134.04, 140.96, 148.50, 161.79, 166.57, and 168.18; IR ν_{max} / cm^{-1} 3379 (NH), 1668 (C=O); MS *m/z* (rel intensity) 521 (M^+ + 1, 4), 369 (21), 306 (74), 275 (63), 259 (100), 216 (36), 170 (36), 144 (23), 105 (37), 91 (34), and 77 (40). *Anal*. Calcd for $C_{31}H_{28}N_4O_4 \cdot 1/2CH_3CN$: C, 71.03; H, 5.50; N. 11.65. Found: C, 71.22; H, 5.64; N, 11.53.

Reaction of (arylimino)triphenylphosphoranes with benzaldehyde

A mixture of (phenylimino)triphenylphosphorane (**10a**) (0.176 g, 0.50 mmol), benzaldehyde (**7a**) (0.052

mL, 0.50 mmol) in dry xylene (3 mL) was stirred for 250 h under heating at 125 ºC. The solvent was evaporated. Chromatography of the residue with hexane-ethyl acetate (3:1) gave benzylideneaniline[21] (**11a**) (0.0586 g, 65%).

11a: Pale yellow solid, mp 49-51 ºC (lit.,[21] 49-51 ºC); ^{1}H NMR δ 7.20 (2H, dd, *J* 7.3 and 0.9, H-*o*-*N*-phenyl), 7.21 (1H, td, *J* 7.3 and 0.9, H-*p*-*N*-phenyl), 7.38 (2H, t, *J* 7.3, H-*m*-*N*-phenyl), 7.44-7.66 (3H, m, H-*m*,*p*-phenyl), 7.79 (2H, m, H-*o*-phenyl), and 8.49 (1H, s, C<u>H</u>=N); ^{13}C NMR δ 120.85, 125.91, 128.74, 128.79, 129.12, 131.35, 136.19, 152.06, and 160.36; IR ν_{max} / cm^{-1} 1627 (C=N); MS *m/z* (rel intensity) 181 (M$^+$, 35), 180 (41), 105 (11), 104 (11), 85 (64), 83 (100), and 77 (32). *Anal*. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.04; H, 6.22; N, 7.65.

In a similar manner, the reaction of **10b** with **7a** gave **11b**[21] (55%).

11b: Pale yellow oil; ^{1}H NMR δ 7.15 (1H, dd, *J* 7.4, 7.3, and 1.0, Py-H-5), 7.32 (1H, d, *J* 7.9, Py-H-3), 7.44-7.50 (3H, m, H-*m*,*p*-phenyl), 7.72 (1H, ddd, *J* 7.9, 7.4, and 1.9, Py-H-4), 7.99 (2H, dd, *J* 7.3 and 2.3, H-*o*-phenyl), 8.49 (1H, ddd, *J* 4.9, 1.9, and 1.0, Py-H-6), and 9.14 (1H, s, C<u>H</u>=N); ^{13}C NMR δ 119.77, 121.84, 128.74, 129.46, 131.90, 135.85, 138.09, 148.83, 161.09, and 162.87; IR ν_{max} / cm^{-1} (neat) 1625 (C=N); MS *m/z* (rel intensity) 183 (M$^+$+1, 9), 182 (M$^+$, 11), 181 (26), 107 (11), 105 (17), 94 (11), 79 (100), 78 (25), and 77 (20). *Anal*. Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.36; H, 5.68; N, 15.18.

Reaction of (1-azaazulen-2-ylimino)triphenylphosphoranes with arylaldehyde

Typical procedure – a) Under argon atmosphere, a mixture of [(3-ethoxycarbonyl-1-azaazulen-2-yl)imino]triphenylphosphorane (**12b**) (0.120 g, 0.25 mmol), benzaldehyde (**7a**) (0.063 mL, 0.60 mmol) in dry xylene (3 mL) was stirred for 200 h under heating at 125 ºC. The solvent was evaporated and chromatography of the residue with hexane-EtOAc (3:1) gave bis[(3-ethoxycarbonyl-1-azaazulen-2-yl)amino]phenylmethane (**8ba**) (0.0129 g, 20%), **12b** (0.030 g, 25%), and ethyl 2-amino-1-azaazulene-3-carboxylate (**6b**) (0.0001 g, 0.1%).

b) Under argon atmosphere, a mixture of **12b** (0.2404 g, 0.50 mmol), *p*-cyanobenzaldehyde (**7c**) (0.1301 g, 1.00 mmol) in dry xylene (3 mL) was stirred for 50 h under heating at 125 ºC. Then, to the mixture were added **6b** (0.010 g, 0.046 mmol) and MS 4A (0.050 g), and the heating was continued for 50 h at 125 ºC. The solvent was evaporated and chromatography of the residue with hexane-EtOAc (3:1) gave **8bc** (0.1254 g, 92%), **12b** (0.0078 g, 3%), and **6b** (0.002 g, 1%).

The results of the reactions of **12b** with **7a-c** were shown in Table 1.

8bb: Yellow needles (benzene-hexane), mp 152.5-154.5 ºC; ^{1}H NMR δ 1.44 (6H, t, *J* 7.1, CH_3), 2.32 (3H, s, CH_3), 4.44 (8H, q, *J* 7.1, OCH_2), 7.15 (2H, d, *J* 8.1, H-2'',6''-phenyl), 7.46 (2H, dd, *J* 10.5 and 9.2,

H-6,6'), 7.55 (2H, d, *J* 8.1, H-3'',5''-phenyl), 7.62 (2H, dd, *J* 10.2 and 9.2, H-5,5'), 7.64 (2H, dd, *J* 10.5, and 9.9, H-7,7'), 7.74 (1H, t, *J* 8.5, N-CH-N), 8.16 (2H, d, *J* 9.9, H-8,8'), 8.54 (2H, br d, *J* 8.5, NH), and 8.85 (2H, d, *J* 10.2, H-4,4'); IR ν_{max} 3350 (NH), 1665 (C=O). *Anal*. Calcd for $C_{32}H_{30}N_4O_4 \cdot 1/2C_6H_6$: C, 73.28; H, 5.80; N. 9.77. Found: C, 73.60; H, 5.55; N, 10.08.

8bc: Yellow needles (benzene-hexane), mp 121.0-122.5 ºC; ^{1}H NMR δ 1.44 (6H, t, *J* 7.1, CH_3), 4.44 (8H, q, *J* 7.1, OCH_2), 7.52 (2H, t, *J* 9.7, H-6,6'), 7.64 (2H, dd, *J* 10.4 and 9.7, H-5,5'), 7.66 (2H, d, *J* 8.4, H-3'',5''-phenyl), 7.68 (2H, dd, *J* 10.0, and 9.7, H-7,7'), 7.71 (1H, t, *J* 8.3, N-CH-N), 7.75 (2H, d, J 8.4, H-2'',6''-phenyl), 8.15 (2H, d, *J* 10.0, H-8,8'), 8.79 (2H, br d, *J* 8.3, NH), and 8.89 (2H, d, *J* 10.4, H-4,4'); ^{13}C NMR δ 14.07, 60.11, 64.10, 98.00, 111.52, 118.90, 127.43, 130.03, 130.68, 132.38, 132.70, 133.29, 133.71, 141.92, 148.25, 153.80, 161.03, and 166.03; IR ν_{max} 3342 (NH), 2227 (CN), 1663 (C=O); MS *m/z* (rel intensity) 544 (M^++1, 1), 331 (9), 301 (28), 285 (29), 217 (100), 170 (37), 144 (28), 86 (83), and 77 (18). *Anal*. Calcd for $C_{32}H_{27}N_5O_4 \cdot 1/2C_6H_6$: C, 71.90; H, 5.17; N. 11.98. Found: C, 71.59; H, 4.93; N, 11.90.

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