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SYNTHESIS OF 2-AMINO-1-CYANOAZULENES: SUBSTITUENT EFFECT ON 2*H*-CYCLOHEPTA[*b*]FURAN-2-ONES TOWARD THE REACTION WITH MALONONITRILE

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Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – 3-Substituted 2-amino-1-cyanoazulene derivatives were prepared by the reaction of 2*H*-cyclohepta[*b*]furan-2-ones with malononitrile in the presence of triethylamine as a base. The great influence of the substituent at their 3-position on the reactivity to form the 2-aminoazulene derivatives was revealed. The intramolecular charge transfer (ICT) characters of 2-amino-1-cyano-3-vinylazulenes were investigated by UV/Vis spectroscopy and theoretical calculations. The structure of compounds **13b** and **14b** was clarified by single crystal X-ray analysis.

INTRODUCTION

Azulene has attracted the interest of many research groups owing to its unusual properties as well as its beautiful blue color. Therefore, various synthetic methods for azulene and its derivatives have been developed so far.[1] 2*H*-Cyclohepta[*b*]furan-2-one (CHF) is well known as a heteroazulene.[2] Since the CHFs are convertible to azulenes by the reaction with highly reactive alkenes,[3] enamines,[4] and active methylene compounds,[5] the preparation of novel azulene derivatives have been achieved by using these methods. Thus, the CHFs are one of the versatile precursors for azulene derivatives.

The 2-aminoazulene derivatives are important synthetic precursors for the extended π-conjugated molecules,[6] because the 2-amino function could be readily transformed into 2-halo functions to afford

versatile substrates for the cross-coupling reactions, by the Sandmeyer reaction.[7] Furthermore, the amino group on the 2-position of azulene promotes the bromination at the 6-position, which is normally inactive site to the electrophilic reaction, to produce 6-bromoazulenes.[6] The 2-aminoazulene derivatives have been prepared by the reaction of CHFs with malononitrile in the presence of sodium alkoxides,[5,8,9] but the method is restricted to the CHF derivatives with the substituents having resistance to the strong basic conditions. Therefore, the development of a synthetic procedure for the 2-aminoazulene derivatives under the milder basic conditions brings great benefits to the general and practical synthesis of these azulene derivatives.

Herein, we report the modified procedure for the synthesis of 2-aminoazulene derivatives by the reaction of CHFs having several substituents including at their 3-position with malononitrile under the milder basic conditions. We have clarified the substituent effect on the CHFs toward the reaction with malononitrile under the conditions, which revealed the great influence on the reactivity by the substituent at their 3-position to form the 2-aminoazulene derivatives. The characteristic features on the optical properties of the vinyl derivatives **16**−**19** were clarified by UV/Vis spectroscopy and theoretical calculations.

RESULTS AND DISCUSSION

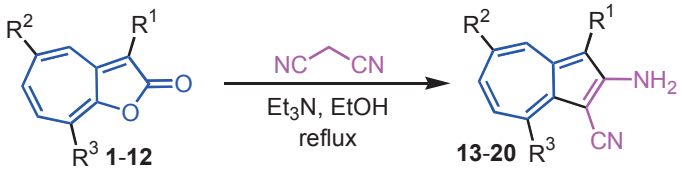
Synthesis: The CHF derivatives **1**−**12**, a precursor of 2-aminoazulenes, were prepared by the reported procedure. The secondary amines such as pyrrolidine and piperidine, react with CHFs having an electron-withdrawing substituent at their 3-position to produce aminoheptafulvene derivatives.[10] Thus, we have examined the use of Et_3N, the most widely used tertiary amine, as a base for the preparation of the 2-aminoazulene derivatives by the reaction of CHFs with malononitrile under the milder basic conditions. Indeed, synthesis of the 2-aminoazulene derivatives was established by the reaction with 2 equiv. of malononitrile in the presence of Et_3N in the refluxing EtOH. Having examined the structure of the starting materials, we have clarified the substituent effect on the CHFs toward the reaction with malononitrile under the conditions. The structure and the yield of the 2-aminoazulene derivatives are summarized in Table 1.

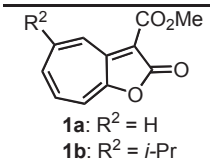
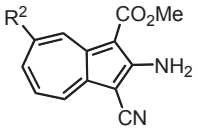
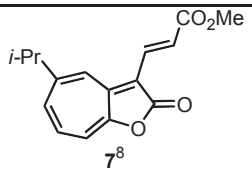
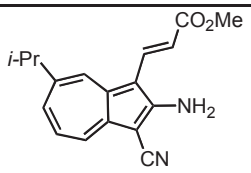
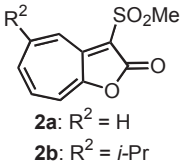
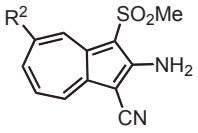
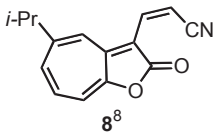
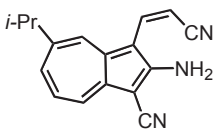
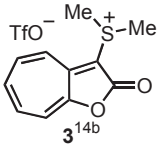
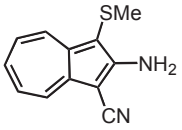
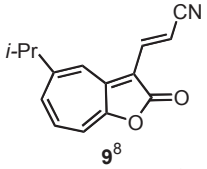
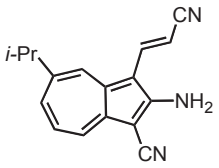
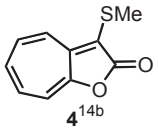
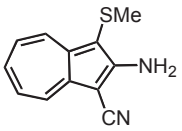
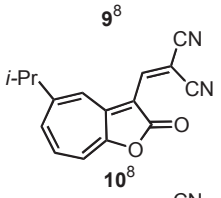
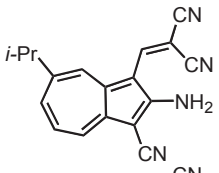
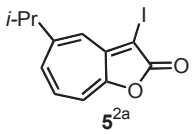
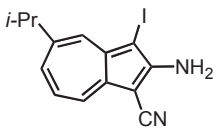
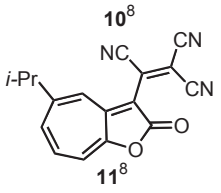
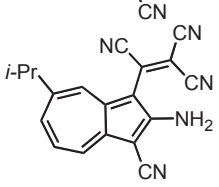
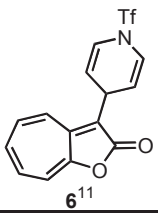
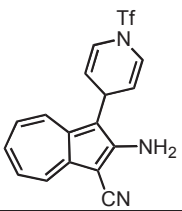
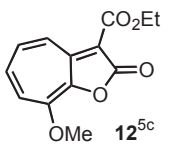
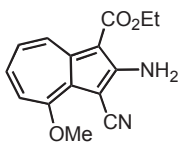
We found the reactivity of CHFs with malononitrile was significantly influenced by the electronic properties of the R^1 substituent at their 3-position on the starting materials **1**−**12** (Table 1). The reaction of CHFs **1**−**3** having an electron-withdrawing substituent at their R^1 position gave the corresponding products **13a**,**b**, **14a**,**b**, and **15** in excellent yields (89−93%). Since the reaction of **1a**,**b** and **2a**,**b** gave the desired **13a**,**b** and **14a**,**b** in almost the same yields, the isopropyl substituent at their 5-position (R^2) on the CHFs should not affect the yield of the product. Whereas, the reaction of CHFs **4**−**6**[11] without an electron-withdrawing substituent at their R^1 position was resulted into the recovery of the starting

materials.

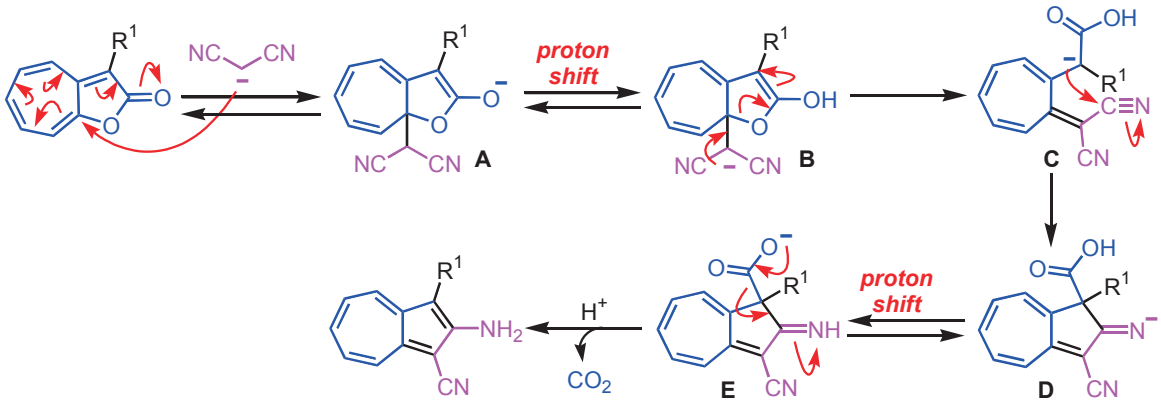
Plausible reaction mechanism for the formation of 2-aminoazulene derivatives is illustrated in Scheme 1. Namely, the reaction should be initiated by the conjugate addition of malononitrile anion to the CHFs at their 8a-position to give the intermediate **A**, followed by the proton transfer to result into the formation of the intermediate **B**. Then, the ring-opening of the dihydrofuran moiety on the intermediate **B** occurs to generate **C**, which converts to the dihydroazulene intermediate **D** by the intramolecular nucleophilic addition of the enolate anion to the cyano group. Finally, the proton transfer in the intermediate **D** results

Table 1. Synthesis of 2-amino-1-cycaoazulene derivatives



Substrate	Product	Yield [%][a]	Substrate	Product	Yield [%][a]
 **1a**: R^2 = H **1b**: R^2 = *i*-Pr		**13a**,[12] 91 **13b**, 93	 **7**[8]		**16**, 88
 **2a**: R^2 = H **2b**: R^2 = *i*-Pr		**14a**: 87 **14b**: 89	 **8**[8]		**17**, 90
 **3**[14b]		**15**, 90	 **9**[8]		**18**, 88
 **4**[14b]		no reaction	 **10**[8]		**19**,[13] 92
 **5**[2a]		no reaction	 **11**[8]		decomp. of **11**
 **6**[11]		no reaction	 **12**[5c]		**20**,[5c] 85

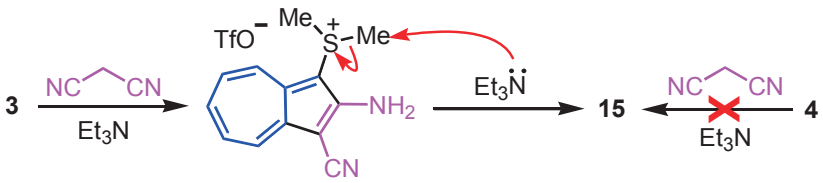
[a] isolated yield.



Scheme 1. Plausible reaction mechanism of CHFs with malononitrile

into the formation of **E**, which produces 2-amino-1-cyanoazulene derivatives by following decarboxylation and protonation. The difference with the reactivity of CHFs **1**–**3** and **4**–**6** might be ascribed to the stability of the anionic intermediate **C** owing to the difference in the electronic character of the R^1 substituent on the CHFs. For example, the CHFs **1**–**3** having an electron-withdrawing R^1 group should stabilize the anionic intermediate **C** by the resonance with the R^1 substituent. On the other hand, the reaction of CHFs **4**–**6** did not take place with malononitrile anion resulted into the recovery of the starting materials, because the R^1 group on the CHFs **4**–**6** does not stabilize the anionic intermediate **C** to prevent the progress of the reaction.

Previously, we have reported the treatment of CHF **3** with Et_3N to afford compound **4** in excellent yield (97%).[14] The mechanism of this reaction is believed to be S_N2-type reaction of Et_3N to the methyl group on the sulfonium moiety to give the sulfide **4** as a leaving group. However, we found CHF **3** reacted with malononitrile in the presence of Et_3N to give the product **15**. In contrast, the reaction of CHF **4** with malononitrile did not take place to give the product **15** under the same conditions. Therefore, it should be concluded the formation of the azulene ring of **15** occurs prior to the nucleophilic attack of the base toward the sulfonium moiety on CHF **3** (Scheme 2).



Scheme 2. Plausible reaction path of **3** and **4** with malononitrile

The CHF derivatives **7**–**10** with an electron-withdrawing vinyl substituent on their R^1 position also reacted with malononitrile under the similar conditions to afford the corresponding 3-vinylazulene derivatives **16**–**19** in excellent yields (88–92%). In particular, the *cis-trans* geometry of the alkene moiety of compounds **7**–**9** was retained in products **16**–**18**. However, the reaction of CHF **11** showed complete

decomposition of the starting material instead of the formation of the corresponding 2-aminoazulene derivative, owing to the instability of **11** even under the milder basic conditions. The CHF **12** having an electron-donating methoxy group at the 8-position also reacted to give the corresponding azulene derivative **12** in 85% yield. In all cases, pure product could be obtained by simple filtration, because the product was obtained as a precipitate by simply pouring the reaction mixture into water as a normal workup procedure. These results demonstrate the high versatility of the modified method for the 2-aminoazulene derivatives within the limitations on the reaction of CHFs with an electron-withdrawing substituent at their R^1 position.

Spectroscopic properties: These new compounds were fully characterized based on their spectroscopic data, as summarized in the Experimental Section. The assignments of the ^{1}H NMR signals of the reported compounds were confirmed by COSY experiments. The HRMS spectra of the new compounds ionized by EI showed the expected molecular ion peaks. The characteristic stretching vibration bands of the C≡N moieties of **13**–**20** were observed at ν = 2195–2214 cm^{-1} in their IR spectra. Since the single crystals were obtained from the slow evaporation of the solvent, the molecular structures of **13b** and **14b** were clarified

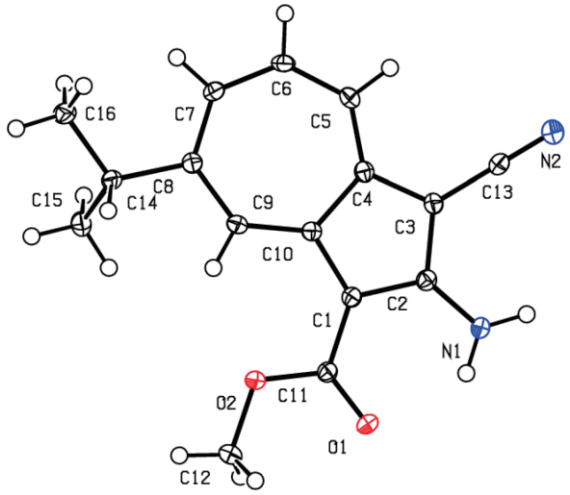


Figure 1. ORTEP drawing of **13b**; ellipsoids are drawn at the 50% probability level; Pccn; a=13.6263(3) Å, b=19.7171(4) Å, c=20.1122(5) Å, α=90°, β=90°, γ=90°; V=5403.6(2) Å^3; Z=16; D_{calcd}=1.319 gcm^{-3}; μ(Mo-Kα)=0.882 cm^{-1}; R_1 [I>2σ(I)]=0.0483, wR_2 [all data]=0.1198

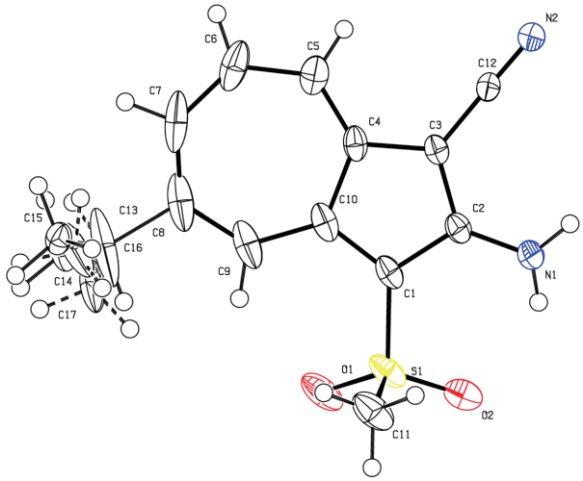


Figure 2. ORTEP drawing of **14b**; ellipsoids are drawn at the 50% probability level; Pbca; a=9.9716(3) Å, b=16.6939(7) Å, c=16.7630(6) Å, α=90°, β=90°, γ=90°; V=2790.45(18) Å^3; Z=8; D_{calcd}=1.373 gcm^{-3}; μ(Mo-Kα)=2.346 cm^{-1}; R_1 [I>2σ(I)]=0.0668, wR_2 [all data]=0.1499

Table 2. Absorption maxima and coefficients of **16–19** and **21** in CH_2Cl_2

Sample	λ_{max} [nm], (log ε)
16	345 sh (4.61), 356 (4.64), 397 sh (3.99), 428 sh (3.62), 500 sh (2.99)
17	340 (4.82), 355 (4.90), 395 (3.85), 418 (3.83), 440 (3.55)
18	345 sh (4.62), 356 (4.66), 395 sh (4.01), 432 sh (3.62), 505 sh (3.00)
19	349 sh (4.75), 364 (4.92), 399 (3.90), 426 (3.80), 447 (3.49)
21	366 (4.19), 417 sh (4.71), 431 (4.73), 511 sh (3.50)

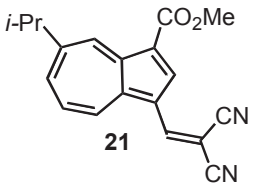


Figure 3. Structure of **21**

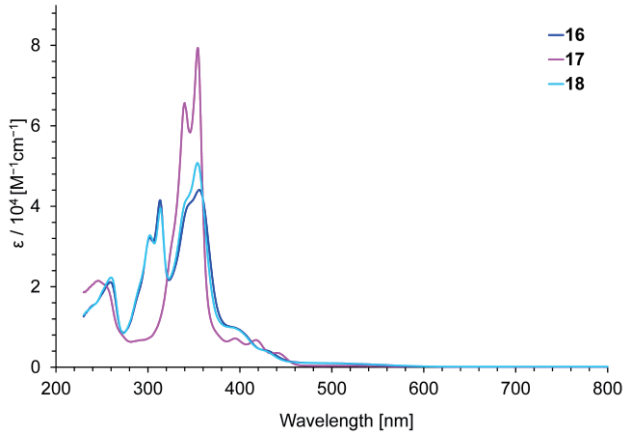


Figure 4. UV/Vis spectra of **16** (blue line), **17** (pink line), and **18** (light-blue line) in CH_2Cl_2

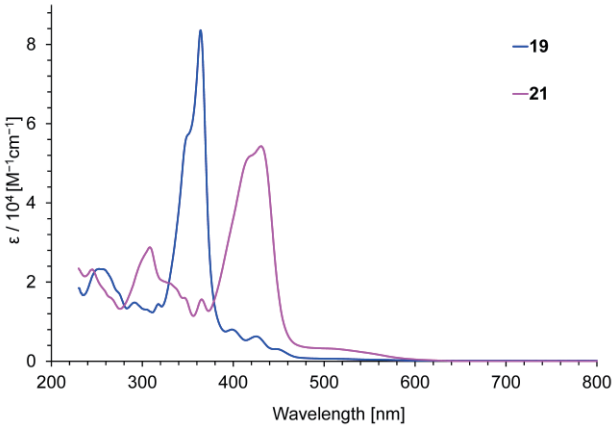


Figure 5. UV/Vis spectra of **19** (blue line) and **21** (pink line) in CH_2Cl_2

by single-crystal X-ray structure analysis.[15] These results are consistent with the given structures of the products.

The UV/Vis spectra of **16–19**, as well as **21** (Figure 3), in CH_2Cl_2 are shown in Figures 4 and 5. The absorption maxima (λ_{max}) and their coefficients (log ε) of **16–19** and **21** are summarized in Table 2. Compounds **16** and **18** with *trans*-structure in their R^1 position showed almost the similar absorption spectra (**16**: λ_{max} = 356 nm, **18**: λ_{max} = 356 nm), which spread into almost 600 nm. In contrast, compound **17** having *cis*-type structure in the R^1 position exhibited the absorption band with a larger molar extinction coefficient at the most intense absorption maxima (λ_{max} = 355 nm), compared with that of **16** and **18** (Figure 4). Furthermore, the broad absorption observed by that of **16** and **18** was not displayed at around 450−600 nm on the spectrum of **17**. These results indicate that the *cis-trans* geometry at the vinyl moiety affects the electronic transition probably due to the steric congestion in the *cis*-isomer, but the terminal electron-withdrawing substituent on the vinyl group have only a slight influence on an electronic contribution.

The compound **19** showed weak absorption band in the visible region despite the expected charge transfer (CT) character between 2-amino group and dicyanovinyl group (i.e., donor and acceptor, respectively). In contrast, the similar compound **21** without the 2-amino function showed the presumed strong CT absorption band in the visible region (λ_{max} = 431 nm) (Figure 5). These results are ascribed to the low planarity of the compound **19** caused by the steric hindrance of the 2-amino group about the dicyanovinyl moiety resulted into less effective π-conjugation of the donor and acceptor substituents in **19**. Indeed, the DFT calculations revealed that the optimized structure of **19** showed a twisted structure, in which the dihedral angle of the azulene ring and the dicyanovinyl group was 18.96° (Figure 6), although the structure of **21** was optimized as almost a planar structure (0.11°, Figure 7).[16] Furthermore, the contribution of the resonance structure of the *ortho*-quinoidal form **19'** should be small, since the *ortho*-quinoidal form is relatively unstable chemical species (Scheme 3). Therefore, the intramolecular CT based on the donor-acceptor structure is prevented by these synergistic effects, and in consequence the absorption maximum of **19** in the UV/Vis spectrum did not exhibit the presumed bathochromic shift, compared with that of **21**.

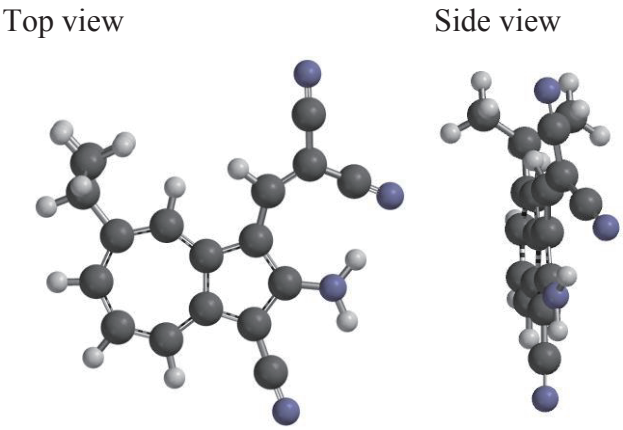


Figure 6. Optimized structure of **19** calculated by B3LYP/6-31G** level

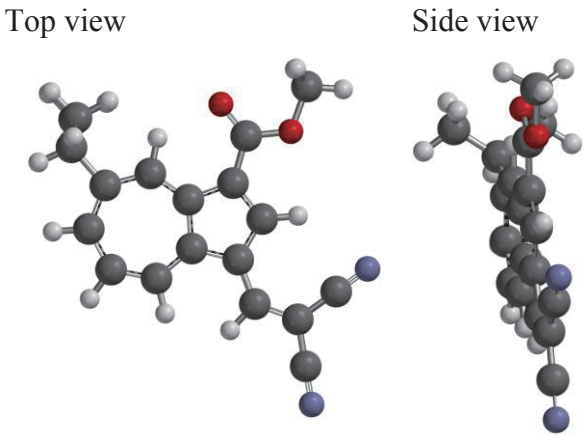
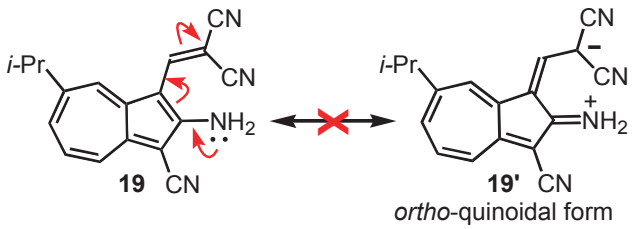


Figure 7. Optimized structure of **21** calculated by B3LYP/6-31G** level



Scheme 3. Presumed resonance structure of **19**

CONCLUSION

In conclusion, the 2-aminoazulene derivatives **13**−**20** with various substituents at their 3-position were successfully synthesized by the reaction of CHFs with malononitrile under the milder basic conditions in excellent yields (85−93%), compared with those of the previous method. Furthermore, this procedure has an advantage in the workup process compared with that of the previous method, since the products are obtained as a pure precipitate that is easily isolated by the simple filtration techniques. The difference among the optical properties of 2-amino-3-vinylazulenes **16**–**19** was also clarified by UV/Vis spectroscopy and theoretical calculations, in which *cis*-*trans* geometry in the vinyl moiety significantly affected the maximum absorption wavelength in their UV/Vis spectra.

As described above, 2-aminoazulene derivatives are one of the versatile precursors for 2-halo- and 6-haloazulenes. Thus, to evaluate the reactivity of the compounds **13**−**20**, conversion of **13**−**20** into 2-halo- and 6-haloazulenes is currently progress in our laboratory.

EXPERIMENTAL

Melting points were determined with a Yanagimoto MPS3 micro melting apparatus. Mass spectra were obtained with a Bruker APEX II instrument. IR and UV/Vis spectra were measured with JASCO FT/IR-4100 and Shimadzu UV-2550 spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL ECA500 spectrometer at 500 MHz and 125 MHz, respectively. Experimental details and copies of ^{1}H and ^{13}C NMR spectra of the reported compounds are summarized in the Supporting Information.

Compound 13a: Malononitrile (661 mg, 10.0 mmol) in Et_3N (10 mL) was added to a solution of **1a** (1.02 g, 5.00 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **13a** (1.03 g, 91%) as yellow crystals. mp 199−201 °C (lit. 135−137 °C);[12] IR (AT−IR): ν_{max} = 3433 (w), 3328 (m), 3265 (w), 3213 (w), 3112 (w), 3026 (w), 2956 (w), 2195 (s), 1657 (s), 1615 (s), 1575 (m), 1533 (w), 1517 (m), 1506 (m), 1454 (m), 1420 (m), 1389 (w), 1337 (w), 1315 (w), 1263 (m), 1231 (s), 1189 (m), 1157 (m), 1118 (m), 1053 (w), 989 (w), 939 (w), 902 (w), 875 (m), 784 (m), 739 (m), 703 (w), 690 (w), 669 (w), 655 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.03 (d, 1H, *J* = 10.0 Hz, H_4), 8.14 (d, 1H, *J* = 10.0 Hz, H_8), 7.62−7.52 (m, 3H, $H_{5,6,7}$), 6.50 (br. s, 2H, NH_2), 3.99 (s, 3H, CO_2Me) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 166.33, 160.86, 147.34, 144.23, 134.10, 133.00, 132.57, 132.14, 130.48, 115.93, 99.66, 83.38, 51.34 ppm; HRMS (EI, positive): calcd for $C_{13}H_{10}N_2O_2^+$ $[M]^+$, 226.0742; found: 226.0742.

Compound 13b: Malononitrile (661 mg, 10.0 mmol) in Et_3N (10 mL) was added to a solution of **1b** (1.23 g, 5.00 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 6 h. The reaction

mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **13b** (1.25 g, 93%) as orange crystals. mp 141−143 °C; IR (AT−IR): ν_{max} = 3418 (w), 3393 (w), 3315 (w), 3222 (w), 2957 (w), 2940 (w), 2212 (m), 1672 (m), 1634 (s), 1622 (s), 1576 (m), 1526 (m), 1509 (m), 1446 (s), 1421 (w), 1391 (w), 1379 (w), 1319 (w), 1262 (m), 1215 (m), 1190 (m), 1163 (m), 1102 (s), 1043 (w), 1012 (w), 993 (w), 969 (w), 913 (w), 903 (w), 888 (w), 874 (w), 848 (w), 807 (w), 784 (m), 732 (w), 711 (w), 697 (w), 671 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 9.15 (s, 1H, H_4), 8.03 (dd, 1H, *J* = 10.9, 1.9 Hz, H_8), 7.52−7.46 (m, 2H, $H_{6,7}$), 6.53 (br. s, 2H, NH_2), 4.00 (s, 3H, CO_2Me), 3.15 (sept, 1H, *J* = 6.9 Hz, *i*-Pr), 1.38 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 166.29, 160.88, 154.93, 147.30, 144.32, 133.40, 132.47, 131.90, 128.93, 116.24, 98.70, 82.21, 51.23, 39.67, 24.57 ppm; HRMS (EI, positive): calcd for $C_{16}H_{16}N_2O_2^+$ $[M]^+$, 268.1212; found: 268.1204.

Compound 14a: Malononitrile (297 mg, 4.50 mmol) in Et_3N (5 mL) was added to a solution of **2a** (505 mg, 2.25 mmol) in EtOH (5 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **14a** (482 mg, 87%) as yellow solid. mp 246−248 °C; IR (AT−IR): ν_{max} = 3452 (w), 3332 (w), 3230 (w), 2203 (w), 1671 (w), 1633 (m), 1579 (w), 1528 (m), 1502 (m), 1454 (w), 1426 (w), 1360 (m), 1324 (w), 1278 (s), 1219 (w), 1197 (w), 1113 (s), 964 (w), 951 (s), 879 (m), 859 (w), 843 (w), 792 (w), 766 (s), 744 (m), 728 (w), 711 (w), 678 (w), 665 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.75 (dd, 1H, *J* = 10.0, 2.0 Hz, H_4), 8.24 (dd, 1H, *J* = 10.0, 2.0 Hz, H_8), 7.68−7.63 (m, 3H, $H_{5,6,7}$), 6.34 (br. s, 2H, NH_2), 3.14 (s, 3H, $MeSO_2$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 157.41, 146.56, 142.48, 135.15, 133.39, 132.83, 131.55, 130.52, 115.06, 104.04, 83.76, 45.39 ppm; HRMS (EI, positive): calcd for $C_{12}H_{10}N_2O_2S^+$ $[M]^+$, 246.0463; found: 246.0456.

Compound 14b: Malononitrile (462 mg, 7.00 mmol) in Et_3N (7 mL) was added to a solution of **2b** (932 mg, 3.50 mmol) in EtOH (7 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **14b** (898 mg, 89%) as orange crystals. mp 198−199 °C; IR (AT−IR): ν_{max} = 3434 (w), 3323 (m), 3218 (w), 2968 (w), 2208 (m), 1672 (w), 1625 (s), 1580 (w), 1526 (s), 1504 (m), 1465 (w), 1450 (w), 1424 (m), 1406 (w), 1358 (m), 1315 (w), 1284 (m), 1218 (w), 1201 (w), 1151 (w), 1127 (w), 1110 (s), 1045 (w), 1016 (w), 948 (m), 908 (w), 880 (w), 856 (w), 807 (m), 774 (s), 737 (w), 709 (w), 694 (w), 686 (w), 676 (w), 664 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.75 (s, 1H, H_4), 8.10 (d, 1H, *J* = 10.9, 2.4 Hz, H_8), 7.58−7.56 (m, 2H, $H_{6,7}$), 6.30 (br. s, 2H, NH_2), 3.17 (sept, 1H, *J* = 6.9 Hz, *i*-Pr), 3.12 (s, 3H, $MeSO_2$), 1.38 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 157.57, 155.45, 146.41, 142.31,

134.13, 132.52, 130.41, 129.89, 115.35, 102.86, 82.47, 45.35, 39.61, 24.49 ppm; HRMS (EI, positive): calcd for $C_{15}H_{16}N_2O_2S^+$ $[M]^+$, 288.0932; found: 288.0941.

Compound 15: Malononitrile (422 mg, 6.38 mmol) in Et_3N (10 mL) was added to a solution of **3** (1.14 g, 3.19 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **15** (615 mg, 90%) as orange solid. mp 155−157 °C; IR (AT−IR): ν_{max} = 3431 (m), 3325 (m), 3220 (w), 2916 (w), 2200 (m), 1676 (w), 1624 (s), 1591 (w), 1517 (s), 1504 (s), 1454 (m), 1412 (m), 1363 (m), 1314 (m), 1286 (m), 1227 (w), 1179 (w), 1112 (m), 1037 (w), 967 (m), 949 (m), 927 (w), 908 (w), 874 (m), 850 (m), 807 (w), 774 (m), 742 (s), 702 (m), 676 (w), 664 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.32 (dd, 1H, *J* = 11.2, 2.0 Hz, H_8), 8.06 (dd, 1H, *J* = 11.2, 2.0 Hz, H_4), 7.47−7.42 (m, 3H, $H_{5,6,7}$), 5.57 (br. s, 2H, NH_2), 2.20 (s, 3H, SMe) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 159.32, 145.33, 145.09, 133.04, 130.19, 129.69, 129.55, 128.71, 116.63, 104.80, 80.56, 19.25 ppm; HRMS (EI, positive): calcd for $C_{12}H_{10}N_2S^+$ $[M]^+$, 214.0565; found: 214.0568.

Compound 16: Malononitrile (119 mg, 1.80 mmol) in Et_3N (5 mL) was added to a solution of **7** (218 mg, 0.80 mmol) in EtOH (5 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **16** (207 mg, 88%) as red solid. mp 211−213 °C; IR (AT−IR): ν_{max} = 3381 (w), 3347 (w), 3217 (m), 2966 (w), 2205 (m), 1668 (m), 1587 (m), 1523 (s), 1504 (s), 1427 (s), 1397 (w), 1346 (w), 1311 (w), 1292 (w), 1201 (w), 1173 (w), 1119 (w), 1076 (w), 1017 (w), 960 (m), 950 (w), 920 (w), 875 (m), 800 (s), 780 (w), 771 (w), 754 (w), 720 (w), 695 (w), 686 (w), 673 (w), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.19 (d, 1H, *J* = 16.0 Hz, CH=CH), 8.16 (s, 1H, H_4), 8.01 (dd, 1H, *J* = 10.3, 1.9 Hz, H_8), 7.48−7.42 (m, 2H, $H_{6,7}$), 6.19 (d, 1H, *J* = 16.0 Hz, CH=CH), 5.45 (br. s, 2H, NH_2), 3.85 (s, 3H, CO_2Me), 3.16 (sept, 1H, *J* = 6.9 Hz, *i*-Pr), 1.37 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 168.46, 157.38, 152.20, 145.69, 142.32, 135.36, 133.41, 130.65, 129.57, 128.66, 116.27, 113.49, 107.27, 82.93, 51.80, 39.52, 24.53 ppm; HRMS (EI, positive): calcd for $C_{18}H_{18}N_2O_2^+$ $[M]^+$, 294.1368; found: 294.1370.

Compound 17: Malononitrile (264 mg, 4.00 mmol) in Et_3N (5 mL) was added to a solution of **8** (479 mg, 2.00 mmol) in EtOH (5 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **17** (470 mg, 90%) as brown solid. mp > 300 °C; IR (AT−IR): ν_{max} = 3470 (w), 3375 (w), 3232 (w), 2964 (w), 2208 (m), 2188 (m), 1686 (m), 1636 (s), 1581 (s), 1558 (m), 1538 (m), 1521 (m), 1507 (m), 1474 (m), 1439 (s), 1417 (s), 1389 (m), 1363 (m), 1341 (m), 1322 (m), 1278 (m), 1203 (m), 1140 (m), 1118 (m), 1018 (m),

939 (m), 896 (m), 877 (m), 859 (m), 808 (s), 797 (s), 779 (s), 748 (m), 739 (m), 723 (m), 699 (m), 672 (m), 663 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.46 (d, 1H, *J* = 1.4 Hz, H_4), 8.43 (d, 1H, *J* = 10.3 Hz, H_8), 8.38 (d, 1H, *J* = 8.8 Hz, CH=CH), 7.59 (d, 1H, *J* = 10.3 Hz, H_6), 7.51 (t, 1H, *J* = 10.0 Hz, H_7), 6.67 (d, 1H, *J* = 8.8 Hz, CH=CH), 5.70 (br. s, 2H, NH_2), 3.21 (sept, 1H, *J* = 6.9 Hz, *i*-Pr), 1.43 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm, Low solubility hampered the measurement of ^{13}C NMR; HRMS (EI, positive): calcd for $C_{17}H_{15}N_3^+$ $[M]^+$, 261.1266; found: 261.1270.

Compound 18: Malononitrile (330 mg, 5.00 mmol) in Et_3N (5 mL) was added to a solution of **9** (598 mg, 2.50 mmol) in EtOH (5 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **18** (575 mg, 88%) as red solid. mp 246−247 °C; IR (AT−IR): ν_{max} = 3381 (w), 3347 (w), 3217 (m), 2966 (w), 2205 (m), 1668 (m), 1587 (m), 1523 (s), 1504 (s), 1427 (s), 1397 (w), 1346 (w), 1311 (w), 1292 (w), 1201 (w), 1173 (w), 1119 (w), 1076 (w), 1017 (w), 960 (m), 950 (w), 920 (w), 875 (m), 800 (s), 780 (w), 771 (w), 754 (w), 720 (w), 695 (w), 686 (w), 673 (w), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 8.06−8.04 (m, 2H, $H_{4,8}$), 7.82 (d, 1H, *J* = 16.6 Hz, CH=CH), 7.51−7.47 (m, 2H, $H_{6,7}$), 5.57 (d, 1H, *J* = 16.6 Hz, CH=CH), 5.35 (br. s, 2H, NH_2), 3.15 (sept, 1H, *J* = 6.9 Hz, *i*-Pr), 1.39 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 157.00, 152.92, 145.72, 140.82, 134.22, 131.24, 129.33, 129.29, 119.81, 119.76, 115.87, 106.85, 91.59, 83.57, 39.60, 24.53 ppm; HRMS (EI, positive): calcd for $C_{17}H_{15}N_3^+$ $[M]^+$, 261.1266; found: 261.1270.

Compound 19: Malononitrile (695 mg, 10.5 mmol) in Et_3N (10 mL) was added to a solution of **10** (1.39 g, 5.26 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **19** (1.39 g, 92%) as brown solid. mp 262−264 °C decomp. (lit. 260.0−263.0 °C decomp.);[11] IR (AT−IR): ν_{max} = 3454 (w), 3318 (w), 3064 (w), 2981 (w), 2214 (m), 2197 (m), 1673 (w), 1654 (s), 1585 (s), 1538 (s), 1508 (w), 1435 (s), 1386 (m), 1328 (m), 1284 (m), 1255 (m), 1223 (m), 1155 (w), 1124 (w), 1093 (w), 1021 (w), 1002 (w), 956 (w), 929 (w), 899 (m), 878 (w), 810 (w), 795 (m), 777 (m), 746 (w), 735 (w), 722 (w), 661 (w) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ_H = 9.27 [s, 1H, CH=C(CN)$_2$], 8.83 (s, 1H, H_4), 8.27 (d, 1H, *J* = 10.0 Hz, H_8), 7.78−7.70 (m, 2H, $H_{6,7}$), 7.35 (br. s, 2H, NH_2), 3.23 (sept, 1H, *i*-Pr), 1.37 (d, 6H, *J* = 6.9 Hz, *i*-Pr) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ_C = 161.05, 160.19, 154.51, 150.11, 138.51, 135.64, 133.82, 133.50, 132.24, 118.03, 116.38, 114.89, 89.99, 88.48, 38.79, 24.16 ppm; HRMS (EI, positive): calcd for $C_{18}H_{14}N_4^+$ $[M]^+$, 286.1218; found: 286.1224.

Compound 20: Malononitrile (660 mg, 10.0 mmol) in Et_3N (10 mL) was added to a solution of **12** (1.24 g, 5.00 mmol) in EtOH (10 mL) and the resulting mixture was refluxed for 6 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was corrected by filtration to give **20** (1.15 g, 85%) as yellow crystals. mp 166−168 °C (lit. 182 °C);[5c] IR (AT−IR): ν_{max} = 3437 (w), 3329 (m), 2984 (w), 2942 (w), 2195 (m), 1660 (s), 1608 (s), 1590 (m), 1532 (w), 1515 (m), 1496 (w), 1479 (m), 1454 (m), 1433 (m), 1416 (s), 1383 (w), 1365 (w), 1351 (w), 1333 (w), 1263 (s), 1227 (s), 1209 (m), 1165 (s), 1126 (m), 1095 (w), 1023 (m), 972 (m), 930 (w), 911 (m), 787 (s), 766 (w), 732 (m), 723 (m), 693 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H = 9.14 (d, 1H, *J* = 10.3 Hz, H_4), 7.48 (t, 1H, *J* = 10.3 Hz, H_6), 7.34 (t, 1H, *J* = 10.3 Hz, H_5), 7.19 (d, 1H, *J* = 10.3 Hz, H_7), 6.42 (br. s, 2H, NH_2), 4.44 (q, 2H, *J* = 7.2 Hz, CO_2Et), 4.15 (s, 3H, OMe), 1.46 (t, 3H, *J* = 7.2 Hz, CO_2Et) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 165.95, 159.76, 159.52, 141.52, 135.16, 133.95, 132.69, 127.47, 117.71, 114.92, 98.69, 82.20, 60.02, 56.61, 14.74 ppm; HRMS (EI, positive): calcd for $C_{15}H_{14}N_2O_3^+$ $[M]^+$, 270.1004; found: 270.1007.

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15. CCDC 1827834 (compound **13b**) and CCDC 1827837 (compound **14b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
16. Theoretical calculations were performed with Spartan'10, Wavefunction, Irvine, CA.