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REACTIONS OF METHYL 3-BROMOACETYLAZULENE-1-CARBOXYLATE WITH 2-AMINOPYRIDINES AND RELATED COMPOUNDS. SYNTHESIS OF AZULENES BEARING IMIDAZOLE-FUSED NITROGEN-HETEROCYCLES

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Abstract - Methyl 3-bromoacetylazulene-1-carboxylate (**1**) reacted with 2-aminopyridines (**2a-f**) to give methyl 3-(imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylates (**3a-f**). Similarly, the reactions with 2-aminopyrimidines (**5a-c**) and 2-amiono-1,2,4-triazines (**8a**,**b**) gave the corresponding imidazo[1,2-*a*]pyrimidine-(**6a-c**) and imidazo[1,2-*b*][1,2,4]triazine-substitutrd azulenes (**9a**, **b**), respectively. Additionally, the substitution products (**4e**,**f** and **7c**) were isolated.

Nitrogen heterocycles are found in a large number of commonly used drugs which have diverse pharmacological activities. Interest in the synthesis of heterocycle-fused pyridine and related compounds has increased in recent years because of their biological activities. The synthesis of phenyl-substituted pyridines has been also widely investigated.[1,2a-d] On the other hand, azulene is theoretically interesting compound with many unusual properties. Physiological activities have been also found in azulene derivatives.[3a-c]

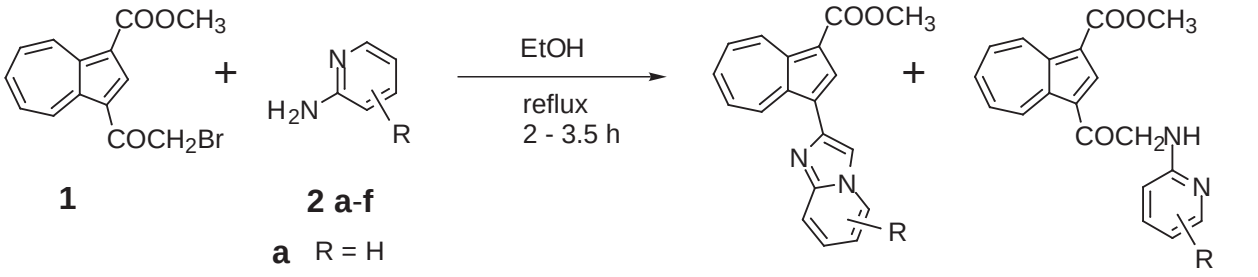
Previously, synthesis of pyridine-substituted azulenes, such as 4-(2-pyridyl)azulene,[4] 6-(4-pyridyl)azulene,[5] and 1-(2-pyridyl)azulene,[6] were reported. Recently, we reported that 1-cinnamoylazulenes and related compounds reacted with malononitrile to afford 1-(2-pyridyl)- and 1-(4-pyridyl)azulene derivatives.[7] In addition to the preparation of 5-(2-quinolyl)azulene,[8] 1- and 2-(2-quinoyl)azulenes were obtained by the Friedländer reaction of 1- and 2-acetylazulenes with 2-aminobenzaldehydes.[9] To expand our investigation, we examined the synthesis of azulenes having imidazole-fused pyridine, pyrimidine, and 1,2,4-triazine by the reactions of 1-bromoacetylazulene with 2-aminopyridines and related compounds.

Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

RESULTS AND DISCUSSION

The starting material, methyl 3-bromoacetylazulene-1-carboxylate (**1**), was obtained by the bromination of methyl 3-acetylazulene-1-carboxylate with trimethylphenylammonium tribromide.[10]

An ethanolic solution of methyl 3-bromoacetylazulene-1-carboxylate (**1**) and three molar equivalents of 2-aminopyridine (**2a**) was heated for 2 h under reflux to afford methyl 3-(imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3a**) in 79% yield. The reactions with 2-amino-3-, 4-, and 5-methylpyridines (**2b-d**) gave the corresponding products (**3b-d**) in 90, 79, and 72% yields. These structures were confirmed by their elemental analyses and spectral data. As an example, the compound (**3a**) was determined to be $C_{19}H_{14}N_2O_2$ from the elemental analysis and MS spectral data. The IR spectrum showed the ester carbonyl absorption at 1698 cm^{-1}. In the ^1H NMR spectrum, characteristic signals for the imidazo[1,2-*a*]pyridine ring were observed at δ 6.64-6.69 (1H, m, 6'-H), 7.11-7.16 (1H, m, 7'-H), 7.63 (1H, d, *J* = 9.0 Hz, 8'-H), 7.82 (1H, s, 3'-H), and 8.06 (1H, d, *J* = 6.6 Hz, 5'-H) as well as the signals for azulene ring.

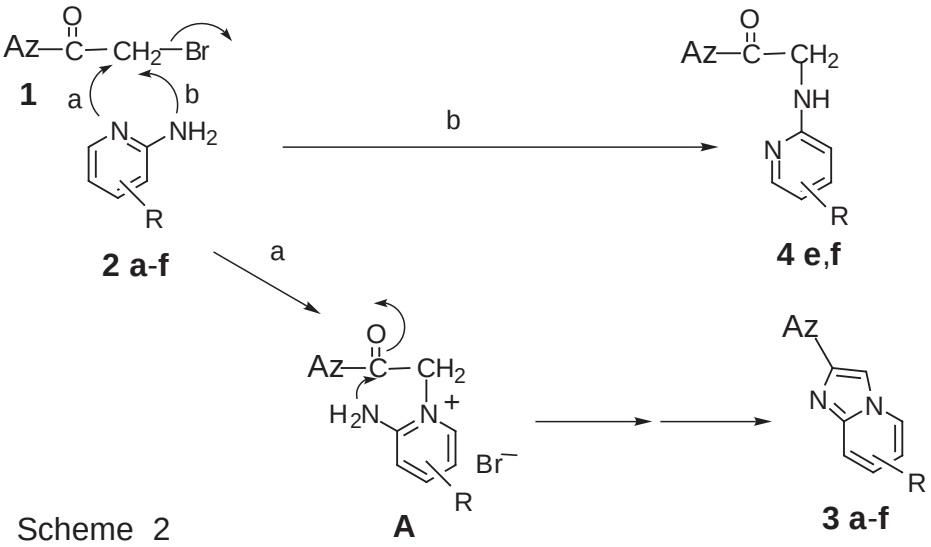


Scheme 1

On the other hand, the reaction using 2-amino-6-methylpyridine (**2e**) gave two products by chromatographic separation. One of them was the cyclized product on the bromoacetyl group, methyl 3-(5-methyl-imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3e**). Another one was found to be substitution product, methyl 3-[(6-methylpyrid-2-yl)aminoacetyl]azulene-1-carboxylate (**4e**) from its elemental analysis ($C_{20}H_{16}N_2O_2$) and spectral data. The IR spectrum showed two carbonyl absorptions at 1692 ($COOCH_3$) and 1649 cm^{-1} ($COCH_2$). In the ^1H NMR spectrum, the methylene protons were observed at δ 4.88 as a doublet signal upon spin-spin coupling with the neighboring NH proton which was observed at δ 5.65 as a broad signal. The ^{13}C NMR spectrum exhibited two signals for carbonyl carbon atoms at δ 164.9 (*C*$OOCH_3$) and 191.3 (*C*OCH_2). The reaction with 2-amino-4,6-dimethylpyridine (**2f**) also gave the cyclization product (**3f**) and the substitution product (**4f**) in 9 and 50% yields, respectively. It is well

known that electrophilicity of the carbonyl function at the 1- and 3-positions in azulene is decreased because of electron-donating effect caused by 6π-stabilization of the seven-membered ring. However, it was revealed that the carbonyl character was found in these reactions.

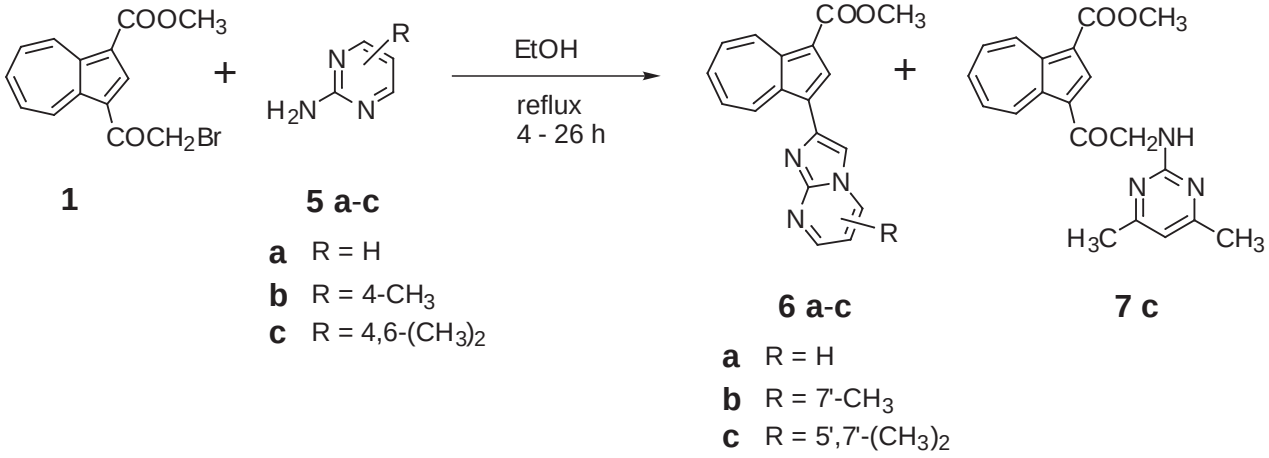
From these results, the following plausible mechanism is considered, as shown in Scheme 2. Nucleophilic attack of the ring nitrogen atom in the pyridines (**2a-f**) on the bromo-substituted methylene carbon atom gives imtermediate [**A**], and successive reaction of the amino nitrogen atom on the carbonyl carbon atom leads to the products, methyl 3-(imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylates (**3a-f**). On the other hand, additional products, methyl 3-[(2-pyridinyl)aminoacetyl]azulene-1-carboxylates (**4e**,**f**) might be obtained by the nucleophilic attack of the amino nitrogen atom, because of steric hindrance of the methyl group at the 6-position.



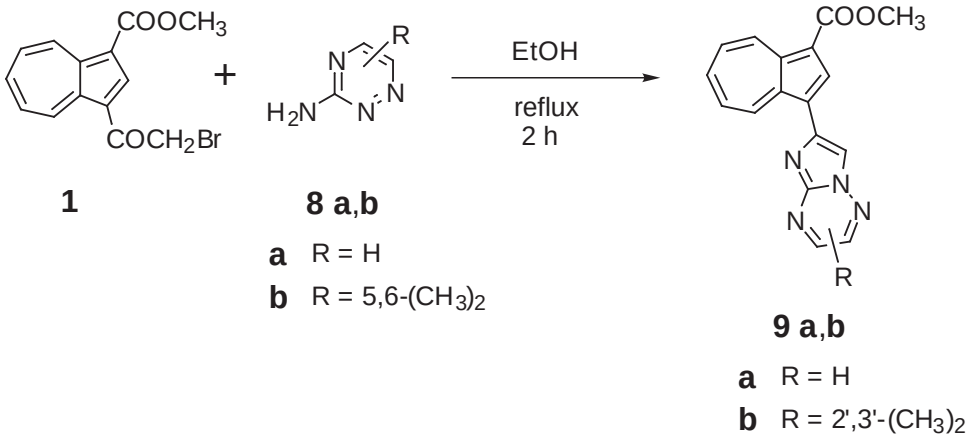
Scheme 2

When a mixture of azulene (**1**) and 2-aminopyrimidine (**5a**) in ethanol was heated for 4 h under reflux temperature, methyl 3-(imidazo[1,2-*a*]pyrimid-2-yl)azulene-1-carboxylate (**6a**) was obtained in 50% yield. In a similar manner, the reaction with 2-amino-4-methylpyrimidine (**5b**) gave 7'-methyl product (**6b**) in 33% yield. In the reaction with 2-amino-4,6-dimethylpyrimidine (**5c**), methyl 3-(5,7-dimethylimidazo[1,2-*a*]pyrimid-2-yl)azulene-1-carboxylate (**6c**) and methyl 3-[(4,6-dimethylpyrimid-2-yl)aminoacetyl]azulene-1-carboxylate (**7c**) were obtained in very low yields (3 and 6%), after heating for 26 h in boiling ethanol. These results mean that both methyl groups at the 4- and 6-positions of the pyrimidine (**5c**) inhibited nucleophilic attack of the ring nitrogen atoms in the pyrimidine ring and the amino nitrogen atom.

Furthermore, an ethanolic solution of azulene (**1**) and 3-amino-1,2,4-triazine (**8a**) was refluxed for 2 h to afford 3-(imidazo[1,2-*b*][1,2,4]triazin-6-yl)azulene-1-carboxylate (**9a**) in 11% yield, whereas the reaction with 3-amino-5,6-dimethyl-1,2,4-triazine (**8b**) gave 2,3-dimethyl compound (**9b**) in 79% yield. The high yield in the latter might be based on the electronic effect of the two methyl groups of compound (**8b**).



Scheme 3



Scheme 4

EXPERIMENTAL

All the melting points were determined with a Yanagimoto MP JP-3 apparatus and are uncorrected. The IR spectra were taken on a JASCO A-102 spectrophotometer. The NMR spectra were recorded with a JEOL JNM-EX 300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C). The MS spectra were obtained with JEOL JMS-DX303HF apparatus. All the elemental analyses were performed at the Instrumental Analysis Center, Kumamoto University.

Reactions of Methyl 3-Bromoacetylazulene-1-carboxylate (1) with 2-Amonopyridines (2a-e). General Procedure: A solution of methyl 3-bromoacetylazulene-1-carboxylate (**1**) (154 mg, 0.5 mmol) and 2-aminopyridine (**2a-e**) (1.5 mmol) in ethanol (10 mL) was refluxed for 2-3.5 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform to give

methyl 3-(imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylates (**3a-f**) and methyl 3-[(2-pyridyl)aminoacetyl]-azulene-1-carboxylates (**4e**,**f**).

Methyl 3-(Imidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3a**): This compound (**3a**) was obtained by refluxing for 2 h as bluish violet needles (from dichloromethane-hexane); yield 118 mg (79%); mp 165 ^{o}C; IR (KBr): ν = 1698 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 3.96 (3H, s, $COOCH_3$), 6.64-6.69 (1H, m, 6'-H), 7.11-7.16 (1H, m, 7'-H), 7.48 (1H, dd, *J* = 9.9, 9.6 Hz, 5-H), 7.49 (1H, dd, *J* = 9.9, 9.6 Hz, 7-H), 7.63 (1H, d, *J* = 9.0 Hz, 8'-H), 7.75 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 7.82 (1H, s, 3'-H), 8.06 (1H, d, *J* = 6.6 Hz, 5'-H), 8.66 (1H, s, 2-H), 9.61 (1H, d, *J* = 9.9 Hz, 4-H), 9.71 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 51.1 ($COO\mathit{C}H_3$), 109.4 (=CH-), 112.3 (=CH-), 115.9 (=C<), 117.2 (=CH-), 121.7 (=C<), 124.3 (=CH-), 125.3 (=CH-), 127.8 (=CH-), 128.0 (=CH-), 137.9 (=CH-), 138.9 (=CH-), 139.5 (=CH-), 139.9 (=CH-), 140.2 (=C<), 142.2 (=C<), 142.8 (=C<), 145.5 (=C<), 165.7 ($\mathit{C}OOCH_3$); MS (EI): m/z (%) 302 (M^+, 100), 287 (23), 271 (29), 243 (100). HRMS calcd for $C_{19}H_{14}N_2O_2$: M^+, 302.1055. Found: M^+, 302.1008. *Anal.* Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.21; H, 4.39; N, 9.35.

Methyl 3-(8-Methylimidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3b**): This compound (**3b**) was obtained by refluxing for 2 h as bluish violet needles (from dichloromethane-hexane); yield 142 mg (90%); mp 136 ^{o}C; IR (KBr): ν = 1688 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.68 (3H, s, CH_3), 3.96 (3H, s, $COOCH_3$), 6.63 (1H, dd, *J* = 6.9, 6.6 Hz, 6'-H), 6.92 (1H, d, *J* = 6.9 Hz, 7'-H), 7.46 (1H, dd, *J* = 9.9, 9.6 Hz, 5-H), 7.48 (1H, dd, *J* = 9.9, 9.6 Hz, 7-H), 7.75 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 7.80 (1H, s, 3'-H), 7.94 (1H, d, *J* = 6.6 Hz, 5'-H), 8.67 (1H, s, 2-H), 9.61 (1H, d, *J* = 9.9 Hz, 4-H), 9.76 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 16.2 (CH_3), 50.2 ($COO\mathit{C}H_3$), 108.9 (=CH-), 111.3 (=CH-), 114.9 (=C<), 121.1 (=C<), 122. (=CH-), 122.4 (=CH-), 126.3 (=C<), 126.8 (=CH-), 126.9 (=CH-), 136.9 (=C<), 138.1 (=CH-), 138.6 (=CH-), 138.9 (=C<), 139.5 (=CH-), 141.1 (=CH-), 144.3 (=C<), 145.0 (=C<), 164.9 ($\mathit{C}OOCH_3$); MS (EI): m/z (%) 316 (M^+, 100), 285 (18), 257 (91), 128 (12). HRMS calcd for $C_{20}H_{16}N_2O_2$: M^+, 316.1212. Found: M^+, 316.1270. *Anal*. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.03; H, 4.93; N, 8.90.

Methyl 3-(7-Methylimidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3c**): This compound (**3c**) was obtained by refluxing for 2 h as bluish violet needles (from dichloromethane-hexane); yield 122 mg (79%); mp 161-162 ^{o}C; IR (KBr): ν = 1694 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.38 (3H, s, CH_3), 3.96 (3H, s, $COOCH_3$), 6.56 (1H, d, *J* = 6.6 Hz, 6'-H), 7.39 (1H, s, 8'-H), 7.49 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.76 (1H, s, 3'-H), 7.76 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 7.96 (1H, d, *J* = 6.6 Hz, 5'-H), 8.67 (1H, s, 2-H), 9.61 (1H, d, *J* = 9.9 Hz, 4-H), 9.71 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 21.3 (CH_3), 51.1 ($COO\mathit{C}H_3$), 108.7 (=CH-), 114.8 (=CH-), 115.6 (=CH-), 115.9 (=C<), 122.0 (=C<), 124.5 (=CH-), 127.7 (=CH-), 127.9 (=CH-), 135.3 (=C<), 137.8 (=CH-), 138.9 (=CH-), 139.5 (=CH-), 139.8 (=CH-), 140.2 (=C<), 142.2 (=C<), 142.6 (=C<), 145.9 (=C<), 165.8 ($\mathit{C}OOCH_3$); MS (EI): m/z (%) 316 (M^+, 100), 285 (14), 257 (85), 128 (15). HRMS calcd for $C_{20}H_{16}N_2O_2$: M^+, 316.1212. Found: M^+, 316.1196.

Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.81; H, 5.08; N, 8.76.

Methyl 3-(6-Methylimidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3d**): This compound (**3d**) was obtained by refluxing for 2 h as green micro-crystals (from dichloromethane-hexane); yield 114 mg (72%); mp 185-186 °C; IR (KBr): ν = 1686 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.32 (3H, s, CH_3), 3.97 (3H, s, $COOCH_3$), 7.01 (1H, d, *J* = 9.3 Hz, 7'-H), 7.47-7.58 (3H, m, 5-,7-,8'-H), 7.82 (1H, s, 3'-H), 7.83 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 7.96 (1H, d, *J* = 6.6 Hz, 5'-H), 8.68 (1H, s, 2-H), 9.63 (1H, d, *J* = 9.9 Hz, 4-H), 9.76 (1H, d, *J* = 10.2 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 18.8 (CH_3), 51.9 ($COOCH_3$), 109.9 (=CH-), 116.6 (=CH-), 117.1 (=C<), 122.5 (=C<), 122.7 (=C<), 123.8 (=CH-), 128.2 (=CH-), 128.4 (=CH-), 128.6 (=CH-), 138.5 (=CH-), 139.6 (=CH-), 140.1 (=CH-), 140.6 (=CH-), 140.8 (=C<), 142.9 (=C<), 143.2 (=C<), 145.2 (=C<), 166.4 ($COOCH_3$); MS (EI): m/z (%) 316 (M^+, 95), 301 (20), 285 (16), 257 (100), 139 (10). HRMS calcd for $C_{20}H_{16}N_2O_2$: M^+, 316.1212. Found: M^+, 316.1270. *Anal*. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.96; H, 5.13; N, 8.73.

Methyl 3-(5-Methylimidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3e**): This compound (**3e**) was obtained by refluxing for 3 h as green micro-crystals (from dichloromethane-hexane); yield 10 mg (7%); mp 149 °C; IR (KBr): ν = 1689 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.65 (3H, s, CH_3), 3.98 (3H, s, $COOCH_3$), 6.65 (1H, d, *J* = 6.9 Hz, 6'-H), 7.17 (1H, dd, *J* = 9.1, 6.9 Hz, 7'-H), 7.54 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.60 (1H, d, *J* = 9.1 Hz, 8'-H), 7.79 (1H, s, 3'-H), 7.81 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.74 (1H, s, 2-H), 9.64 (1H, d, *J* = 9.9 Hz, 4-H), 9.83 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 18.7 (CH_3), 50.9 ($COOCH_3$), 106.7 (=CH-), 111.5 (=CH-), 114.7 (=CH-), 115.9 (=C<), 121.9 (=C<), 124.5 (=CH-), 127.9 (=CH-), 128.0 (=CH-), 134.1 (=C<), 138.0 (=CH-), 139.2 (=CH-), 139.5 (=CH-), 139.9 (=CH-), 140.4 (=C<), 142.3 (=C<), 143.1 (=C<), 146.1 (=C<), 165.8 ($COOCH_3$); MS (EI): m/z (%) 316 (M^+, 95), 301 (20), 285 (16), 257 (100), 139 (10). HRMS calcd for $C_{20}H_{16}N_2O_2$: M^+, 316.1212. Found: M^+, 316.1230. *Anal*. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.01; H, 5.23; N, 8.58.

Methyl 3-[(6-Methylpyrid-2-yl)aminoacetyl]azulene-1-carboxylate (**4e**): This compound (**4e**) was obtained as red micro-crystals (from dichloromethane-hexane); yield 94 mg (56%); mp 128-129 °C; IR (KBr): ν = 1692 ($COOCH_3$), 1649 cm^{-1} ($COCH_2$); ^{1}H NMR ($CDCl_3$): δ = 2.41 (3H, s, CH_3), 3.98 (3H, s, $COOCH_3$), 4.88 (2H, d, *J* = 4.2 Hz, $COCH_2$), 5.65 (1H, br, NH), 6.36 (1H, d, *J* = 8.1 Hz, 5'-H), 6.46 (1H, d, *J* = 7.2 Hz, 3'-H), 7.32 (1H, dd, *J* = 8.1, 7.2 Hz, 4'-H), 7.75 (2H, dd, *J* = 9.9, 9.9 Hz, 5-,7-H), 7.96 (1H, dd, *J* = 9.9, 9.9 Hz, 6-H), 8.85 (1H, s, 2-H), 9.74 (1H, d, *J* = 9.9 Hz, 4-H), 9.93 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 23.6 (CH_3), 48.9 ($COOCH_3$), 50.6 ($COCH_2$), 104.1 (=CH-), 111.5 (=CH-), 115.5 (=C<), 120.4 (=C<), 130.7 (=CH-), 131.6 (=CH-), 136.8 (=CH-), 138.7 (=CH-), 139.8 (=CH-), 140.6 (=CH-), 141.4 (=CH-), 142.9 (=C<), 143.6 (=C<), 155.9 (=C<), 156.8 (=C<), 164.9 ($COOCH_3$), 191.3 ($COCH_2$); MS (EI): m/z (%) 334 (M^+, 26), 213 (84), 121 (100), 92 (16). HRMS calcd for $C_{20}H_{18}N_2O_3$: M^+, 334.1317. Found: M^+, 334.1328. *Anal*. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 72.11; H, 5.39; N, 8.41.

Methyl 3-(5,7-Dimethylimidazo[1,2-*a*]pyrid-2-yl)azulene-1-carboxylate (**3f**): This compound (**3f**) was obtained by refluxing for 3 h as green micro-crystals (from dichloromethane-hexane); yield 14 mg (9%); mp 168 ^{o}C; IR (KBr): ν = 1691 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.40 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.98 (3H, s, $COOCH_3$), 6.47 (1H, s, 6'-H), 7.35 (1H, s, 8'-H), 7.52 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.70 (1H, s, 3'-H), 7.79 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.72 (1H, s, 2-H), 9.63 (1H, d, *J* = 9.9 Hz, 4-H), 9.80 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 18.7 (CH_3), 21.3 (CH_3), 51.2 ($COO\mathit{C}H_3$), 106.1 (=CH-), 113.2 (=CH-), 114.1 (=CH-), 115.9 (=C<), 122.2 (=C<), 127.7 (=CH-), 127.9 (=CH-), 133.2 (=C<), 135.5 (=C<), 137.9 (=CH-), 139.1 (=CH-), 139.5 (=CH-), 139.9 (=CH-), 140.3 (=C<), 142.2 (=C<), 142.7 (=C<), 146.5 (=C<), 165.8 ($\mathit{C}OOCH_3$); MS (EI): m/z (%) 330 (M^+, 100), 315 (20), 299 (15), 271 (90), 165 (12), 135 (9). HRMS calcd for $C_{21}H_{18}N_2O_2$: M^+, 330.1368. Found: M^+, 330.1392. *Anal*. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.11; H, 5.51; N, 8.39.

Methyl 3-[(4,6-Dimethylpyrid-2-yl)aminoacetyl]azulene-1-carboxylate (**4f**): This compound (**4f**) was obtained as red micro-crystals (from dichloromethane-hexane); yield 88 mg (50%); mp 160-161 ^{o}C; IR (KBr): ν = 3409 (NH), 1708 ($COOCH_3$), 1649 cm^{-1} ($COCH_2$); ^{1}H NMR ($CDCl_3$): δ = 2.17 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.94 (3H, s, $COOCH_3$), 4.80 (2H, d, *J* = 3.6 Hz, $COCH_2$), 5.60 (1H, br, NH), 6.14 (1H, s, 5'-H), 6.29 (1H, s, 3'-H), 7.67 (2H, dd, *J* = 9.9, 9.9 Hz, 5-,7-H), 7.89 (1H, dd, *J* = 9.9, 9.9 Hz, 6-H), 8.76 (1H, s, 2-H), 9.65 (1H, d, *J* = 9.9 Hz, 4-H), 9.84 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 20.9 (CH_3), 24.2 (CH_3), 49.8 ($CO\mathit{C}H_2$), 51.3 ($COO\mathit{C}H_3$), 105.2 (=CH-), 114.0 (=CH-), 116.2 (=C<), 121.1 (=C<), 131.4 (=CH-), 132.2 (=CH-), 139.4 (=CH-), 140.5 (=CH-), 141.3 (=CH-), 142.1 (=CH-), 143.5 (=C<), 144.2 (=C<), 148.4 (=C<), 156.3 (=C<), 157.8 (=C<), 164.9 ($\mathit{C}OOCH_3$), 192.1 ($\mathit{C}OCH_2$); MS (EI): m/z (%) 348 (M^+, 8), 213 (36), 135 (100), 106 (12). *Anal*. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.40; H, 5.67; N, 8.14.

Reactions of Methyl 3-Bromoacetylazulene-1-carboxylate (**1**) **with 2-Amonopyrimidines** (**5a-c**). **General Procedure**: A solution of methyl 3-bromoacetylazulene-1-carboxylate (**1**) (154 mg, 0.5 mmol) and 2-aminopyrimidine (**5a-c**) (1.5 mmol) in ethanol (10 mL) was refluxed for 4-26 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform to give methyl 3-(imidazo[1,2-*a*]pyrimidin-2-yl)azulene-1-carboxylates (**6a-c**) and methyl 3-[(4,6-dimethylpyrimidin-2-yl)aminoacetyl]azulene-1-carboxylate (**7c**).

Methyl 3-(Imidazo[1,2-*a*]pyrimidin-2-yl)azulene-1-carboxylate (**6a**): This compound (**6a**) was obtained by refluxing for 4 h as deep green micro-crystals (from dichloromethane-hexane); yield 69 mg (50%); mp 196-197 ^{o}C; IR (KBr): ν = 1698 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 3.98 (3H, s, $COOCH_3$), 6.84 (1H, d, *J* = 5.4 Hz, 6'-H), 7.56 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.83 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 7.87 (1H, s, 3'-H), 8.42-8.50 (2H, m, 4'-,6'-H), 8.68 (1H, s, 2-H), 9.63 (1H, d, *J* = 9.9 Hz, 4-H), 10.13 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 51.2 ($COO\mathit{C}H_3$), 107.2 (=CH-), 108.7 (=CH-), 116.1 (=C<), 120.4 (=C<), 128.4 (=CH-), 128.5 (=CH-), 132.5 (=CH-), 138.2 (=CH-), 139.0 (=CH-),

140.0 (=CH-), 140.4 (=CH-), 140.6 (=C<), 142.6 (=C<), 145.1 (=C<), 149.1 (=CH-), 158.3 (=C<), 165.7 (C=O); MS (EI): m/z (%) 303 (M^+, 99), 288 (22), 272 (22), 244 (100), 139 (14). HRMS calcd for $C_{18}H_{13}N_3O_2$: M^+, 303.1008. Found: M^+, 303.0996. *Anal.* Calcd for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.13; H, 4.47; N, 13.60.

Methyl 3-(4-Methylimidazo[1,2-*a*]pyrimidin-2-yl)azulene-1-carboxylate (**6b**): This compound (**6b**) was obtained by refluxing for 4 h as deep green micro-crystals (from dichloromethane-hexane); yield 51 mg (33%); mp 242-243 °C; IR (KBr): ν = 1686 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.68 (3H, s, CH_3), 3.96 (3H, s, $COOCH_3$), 6.62 (1H, d, *J* = 6.6 Hz, 6'-H), 7.51 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.70 (1H, s, 3'-H), 7.79 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.19 (1H, d, *J* = 6.6 Hz, 5'-H), 8.60 (1H, s, 2-H), 9.59 (1H, d, *J* = 9.9 Hz, 4-H), 10.18 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 24.8 (CH_3), 51.1 ($COO\mathit{C}H_3$), 106.7 (=CH-), 109.4 (=CH-), 111.2 (=CH-), 115.9 (=C<), 120.7 (=C<), 128.1 (=CH-), 128.2 (=C<), 131.9 (=CH-), 138.0 (=CH-), 138.7 (=CH-), 140.2 (=CH-), 140.4 (=C<), 142.4 (=C<), 144.2 (=C<), 157.8 (=CH-), 159.3 (=C<), 165.7 (C=O); MS (EI): m/z (%) 317 (M^+, 100), 286 (21), 258 (84). HRMS calcd for $C_{19}H_{15}N_3O_2$: M^+, 317.1164. Found: M^+, 317.1101. *Anal.* Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.94; H, 4.69; N, 13.02.

Methyl 3-(5,7-Dimethylimidazo[1,2-*a*]pyrimidin-2-yl)azulene-1-carboxylate (**6c**): This compound (**6c**) was obtained by refluxing for 26 h as green micro-crystals (from dichloromethane-hexane); yield 4 mg (3%); mp 250-251 °C; IR (KBr): ν = 1691 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.62 (6H, s, 5'-,7'-CH_3), 3.98 (3H, s, $COOCH_3$), 6.59 (1H, s, 6'-H), 7.55 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.72 (1H, s, 3'-H), 7.83 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.70 (1H, s, 2-H), 9.63 (1H, d, *J* = 9.9 Hz, 4-H), 10.30 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 18.3 (CH_3), 24.8 (CH_3), 51.2 ($COO\mathit{C}H_3$), 103.8 (=CH-), 108.9 (=CH-), 110.6 (=C<), 115.9 (=C<), 120.9 (=C<), 128.1 (=CH-), 128.3 (=CH-), 138.0 (=CH-), 138.7 (=CH-), 140.3 (=CH-), 140.5 (=CH-), 142.0 (=C<), 142.5 (=C<), 144.3 (=C<), 159.2 (=CH-), 162.8 (=C<), 167.8 (C=O); MS (EI): m/z (%) 317 (M^+, 100), 286 (21), 258 (84). *Anal.* Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.51; H, 4.98; N, 13.03.

Methyl 3-[(4,6-Dimethylpyrimidin-2-yl)aminoacetyl]azulene-1-carboxylate (**7c**): This compound (**9c**) was obtained as red micro-crystals (from dichloromethane-hexane); yield 11 mg (6%); mp 218-219 °C; IR (KBr): ν = 1707 ($COOCH_3$), 1661 cm^{-1} ($COCH_2$); ^{1}H NMR ($CDCl_3$): δ = 2.33 (6H, s, CH_3 x 2), 4.00 (3H, s, $COOCH_3$), 5.03 (2H, d, *J* = 4.5 Hz, $COCH_2$), 6.12 (1H, br, NH), 6.37 (1H, s, 5'-H), 7.83 (1H, dd, *J* = 9.9, 9.9 Hz, 7-H), 7.85 (1H, dd, *J* = 9.9, 9.9 Hz, 5-H), 8.04 (1H, dd, *J* = 9.9, 9.9 Hz, 6-H), 8.97 (1H, s, 2-H), 9.84 (1H, d, *J* = 9.9 Hz, 4-H), 10.05 (1H, d, *J* = 9.9 Hz, 8-H); ^{13}C NMR ($CDCl_3$): δ = 23.9 (CH_3 x 2), 49.6 ($CO\mathit{C}H_2$), 51.5 ($COO\mathit{C}H_3$), 110.2 (=CH-), 116.4 (=C<), 121.3 (=C<), 131.6 (=CH-), 132.5 (=CH-), 139.7 (=CH-), 140.9 (=CH-), 141.5 (=CH-), 142.4 (=CH-), 143.9 (=C<), 144.6 (=C<), 161.9 (=C<), 165.2 (=C<), 167.5 ($\mathit{C}OOCH_3$), 192.0 ($\mathit{C}OCH_2$); MS (EI): m/z (%) 349 (M^+, 28), 213 (100), 136 (56). *Anal*. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.75; H, 5.33; N, 11.98.

Reactions of Methyl 3-Bromoacetylazulene-1-carboxylate (1) with 2-Amono-1,2,4-triazines (8a,b). General Procedure: A solution of methyl 3-bromoacetylazulene-1-carboxylate (**1**) (154 mg, 0.5 mmol) and 2-aminopyrimidine (**8a**,**b**) (1.5 mmol) in ethanol (10 mL) was refluxed for 4-26 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform to give methyl 3-(imidazo[1,2-*b*][1,2,4]triazin-6-yl)azulene-1-carboxylate (**9a**,**b**).

Methyl 3-(Imidazo[1,2-*b*][1,2,4]triazin-6-yl)azulene-1-carboxylate (**9a**): This compound (**9a**) was obtained by refluxing for 2 h as green micro-crystals (from dichloromethane-hexane); yield 17 mg (11%) mp 267-268 ^{o}C; IR (KBr): ν = 1698 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 3.99 (3H, s, $COOCH_3$), 7.62 (1H, dd, *J* = 9.9, 9.6 Hz, 5-H), 7.65 (1H, dd, *J* = 9.9, 9.6 Hz, 7-H), 7.90 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.37 (1H, s, 3'-H), 8.39 (1H, d, *J* = 1.8 Hz, 2'-H), 8.40 (1H, d, *J* = 1.8 Hz, 3'-H), 8.60 (1H, s, 2-H), 9.59 (1H, d, *J* = 9.9 Hz, 4-H), 10.18 (1H, d, *J* = 9.9 Hz, 8-H); MS (EI): m/z (%) 304 (M^+, 100), 273 (13), 245 (20), 218 (18), 191 (18), 164 (16), 110 (16). HRMS calcd for $C_{17}H_{12}N_4O_2$: M^+, 304.0960. Found: M^+, 304.0913. *Anal.* Calcd for $C_{17}H_{12}N_4O_2$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.89; H, 4.13; N, 18.26.

Methyl 3-(2,3-Dimethylimidazo[1,2-*b*][1,2,4]triazin-6-yl)azulene-1-carboxylate (**9b**): This compound (**9b**) was obtained by refluxing for 2 h as bluish green micro-crystals (from dichloromethane-hexane); yield 132 mg (79%); mp 287-288 ^{o}C; IR (KBr): ν = 1674 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.60 (3H, s, CH_3), 2.66 (3H, s, CH_3), 3.99 (3H, s, $COOCH_3$), 7.58 (2H, dd, *J* = 9.9, 9.6 Hz, 5-,7-H), 7.86 (1H, dd, *J* = 9.6, 9.6 Hz, 6-H), 8.15 (1H, s, 7'-H), 8.71 (1H, s, 2-H), 9.66 (1H, d, *J* = 9.9 Hz, 4-H), 10.19 (1H, d, *J* = 9.9 Hz, 8-H). MS (EI): m/z (%) 332 (M^+, 100), 291 (18), 273 (23), 232 (16), 191 (19), 164 (21). HRMS calcd for $C_{19}H_{16}N_4O_2$: M^+, 332.1273. Found: M^+, 332.1292. *Anal.* Calcd for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.51; H, 4.90; N, 17.05.

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