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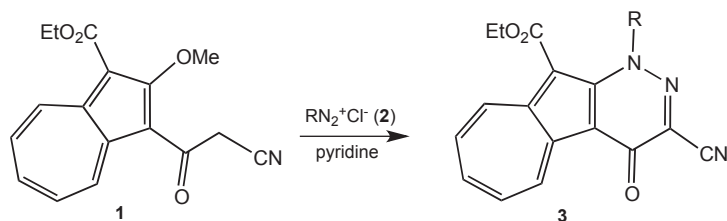
AN EFFICIENT ONE-POT SYNTHESIS OF AZULENO[2,1-*b*]PYRIDAZINES

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Abstract – A simple and efficient procedure was developed for the synthesis of 1-aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazines (**3**) in good yields by condensation of ethyl 1-cyanoacetyl-2-methoxyazulene-3-carboxylate (**1**) with aryldiazonium salt (**2**) in pyridine via a domino reaction. This reaction provides a new procedure for synthesis of heterocycle-fused azulenes.

The pyridazine nucleus is an interesting heterocyclic ring that plays the role of a pharmacophore in several classes of derivatives that show a variety of pharmacological properties.¹ During the last decade, considerable attention has been devoted to various pyridazinones because of their synthetic versatility, their well-balanced physicochemical properties, and the wide range of pharmacological activities such as antihypertensive,² anti-HIV,³ antibacterial,⁴ aldose reductase inhibitor,⁵ and hepatoprotective agents.⁶ On the other hand, azulenes have attracted interest in medicine as antiulcer drugs,⁷ anticancer agents,⁸ and as antioxidant therapeutics for neurodegenerative conditions.⁹ A variety of heterocycle-fused azulenes have attracted the interest owing to its unusual chemical properties.¹⁰ Thus, preparation and reactivities of a number of heterocycle-fused azulenes have already been revealed by many research groups.¹¹ Recently, our research group has reported the synthesis of new heteroarylazulene derivatives.¹² As part of a continuing effort in our laboratory toward the development of azulene chemistry, we became interested in exploring the reactivity and synthetic applications of cyanoacetylated azulene¹³ to 1-aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazines (**3**) by condensation of ethyl 1-cyanoacetyl-2-methoxyazulene-3-carboxylate (**1**) with aryldiazonium salt (**2**) *via* a domino reaction under mild reaction conditions (Scheme 1).



Scheme 1. Synthesis of azuleno[2,1-*b*]pyridazines

In this study, we first optimized the reaction of ethyl 1-cyanoacetyl-2-methoxyazulene-3-carboxylate (**1**) with phenyldiazonium salt (**2a**) as model substrates. In our preliminary experiments 1.0 mmol of **1** was treated with 1.0 mmol of **2a** in pyridine at room temperature. The reaction was complete in 6 h. After work-up of the reaction mixture, 3-cyano-1-phenyl-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (**3a**) was obtained in 82% as orange needles. Its structure was determined from the spectral data as well as elemental analysis (C₂₂H₁₅N₃O₃). In the IR spectrum, two carbonyl signals at 1708 and 1625 cm⁻¹ and CN signals at 2231 cm⁻¹ are observed. The ¹H NMR spectrum shows signals at δ 7.59 (dd, *J* = 9.2, 9.2 Hz, 1H), 7.87 (dd, *J* = 9.6, 9.6 Hz, 1H), 7.95 (dd, *J* = 9.6, 9.6 Hz, 1H), 8.94 (d, *J* = 10.4 Hz, 1H), and 10.08 (d, *J* = 9.2 Hz, 1H) for seven-membered protons, together with ethoxycarbonyl protons at δ 0.96 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 3.57 (q, *J* = 7.2 Hz, 2H, CO₂CH₂CH₃), and phenyl at δ 7.48-7.53 (m, 5H). In the ¹³C NMR spectrum, two carbonyl signals at 167.1 and 171.5 are observed.

In an initial endeavor, we carried out the reaction of **1** and phenyldiazonium salt (**2a**) using the different solvents (Table 1). We screened different solvents such as ethanol, methanol, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide, water and pyridine at room temperature. As shown in the Table 1, the best yield was obtained when pyridine was used as a solvent.

Table 1. Effect of various solvent on the model reaction^a

Entry	Solvent	Time (h)	Yield (%) ^b
1	EtOH	9	63
2	MeOH	8	68
3	MeCN	10	54
4	THF	8	65
5	DMF	6	70
6	H ₂ O	12	47
7	pyridine	6	82

^a Reaction conditions: **1** (1.0 mmol), phenyldiazonium salt (**2a**, 1.0 mmol), solvent (20 mL).

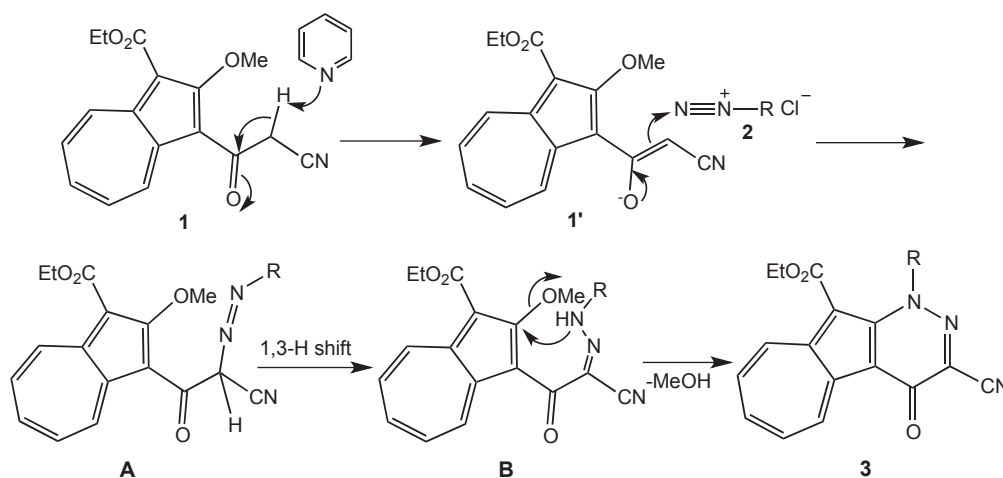
^b Isolated yield.

Using the optimized conditions, we next explored the scope and generality of the process. Our preparative results are summarized in Table 2. A variety of azuleno[2,1-*b*]pyridazines **3** containing neutral, electron-rich, and electron-poor aryl substituents could be isolated in good yields.

Table 2. Synthesis of 1-aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazines (**3**)

Entry	2 / R	Time / h	Product	Yield / %
1	2a C ₆ H ₅	6	3a	82
2	2b 2-MeC ₆ H ₄	6	3b	80
3	2c 3-MeC ₆ H ₄	5	3c	85
4	2d 4-MeC ₆ H ₄	4	3d	84
5	2e 3,5-Me ₂ C ₆ H ₃	5	3e	87
6	2f 2,4,6-Me ₃ C ₆ H ₂	6	3f	78
7	2g 2-MeOC ₆ H ₄	8	3g	84
8	2h 4-MeOC ₆ H ₄	7	3h	86
9	2i 4-ClC ₆ H ₄	10	3i	79
10	2j 4-NO ₂ C ₆ H ₄	12	3j	75

The proposed mechanism of the process is summarized in Scheme 2. The sequence involves an initial conjugate addition of **1** with aryldiazonium salt (**2**) in pyridine to producing the 2-arylhydrazolonitrile B. This then undergoes S_NAr cyclizations of the 2-methoxy of azulenyl group by attack of NH group via loss of methanol leads to yield the tricyclic product (**3**).



Scheme 2. Proposed reaction mechanism for the formation of compound **3**

In conclusion, we have successfully developed facile and efficient method to prepare a series of 1-aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine derivatives *via* a domino reaction of ethyl 1-cyanoacetyl-2-methoxyazulene-3-carboxylate with aryldiazonium salt in good yields. Further investigations to elaborate the scope of this methodology and to show the synthetic utility of the heterocycle-fused azulene derivatives obtained are currently in progress in our laboratory.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) in CDCl_3 using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H and N analyses were performed by a HP-MOD 1106 microanalyzer. The preparation of ethyl 1-cyanoacetyl-2-methoxyazulene-3-carboxylate was according to the literature procedure.^{13a} All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 1-Aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazines.

3-Cyano-1-phenyl-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3a): To a stirred solution of **1** (295 mg, 1.0 mmol) in pyridine (20 mL) was added phenyldiazonium salt (**2a**) [prepared by addition of NaNO_2 solution (69 mg, 1.0 mmol) to a cold solution of aniline (93 mg, 1.0 mmol) containing the appropriate quantity of HCl at 0 °C with stirring] and the mixture was left at room temperature for 6 h. The solid product formed was collected and recrystallized from EtOH to give **3a** (302 mg, 82%); orange needles; mp 240-242 °C; IR (KBr) 2231, 1708, 1625 cm^{-1} ; ^1H NMR δ 0.96 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.57 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.48-7.50 (m, 1H, benzene ring aromatic H), 7.51-7.53 (m, 4H, benzene ring aromatic H), 7.59 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.87 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 7.95 (t, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.94 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.08 (d, $J = 9.2$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.9, 61.3, 97.9, 105.6, 109.9, 111.1, 123.5, 129.2, 130.7, 134.9, 137.7, 137.9, 138.1, 140.7, 141.0, 141.1, 146.9, 150.2, 167.1, 171.5. Anal. Calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.62; H, 4.23; N, 11.56.

3-Cyano-1-(2-methylphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3b): orange needles; mp 218-220 °C; IR (KBr) 2235, 1702, 1634 cm^{-1} ; ^1H NMR δ 1.06 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 2.37 (s, 3H, CH_3), 3.63 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.24-7.25 (m, 1H, benzene ring aromatic H), 7.28-7.32 (m, 1H, benzene ring aromatic H), 7.43-7.45 (m, 2H benzene ring aromatic H), 7.80 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.85 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.93 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.94 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.08 (d, $J =$

9.2 Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 16.3, 24.7, 61.5, 98.2, 105.6, 109.9, 111.1, 112.6, 113.3, 125.1, 127.0, 129.8, 131.9, 132.8, 133.3, 134.5, 137.3, 137.8, 140.7, 144.3, 146.9, 167.1, 171.5. Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.13; H, 4.55; N, 11.15.

3-Cyano-1-(3-methylphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3c): orange needles; mp 216-218 °C; IR (KBr) 2233, 1701, 1628 cm^{-1} ; ^1H NMR δ 1.06 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 2.34 (s, 3H, CH_3), 3.82 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.26-7.28 (m, 1H, benzene ring aromatic H), 7.34-7.36 (m, 1H, benzene ring aromatic H), 7.42-7.45 (m, 2H, benzene ring aromatic H), 7.79 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.91 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 8.01 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.95 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.07 (d, $J = 9.2$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.3, 25.6, 60.6, 100.2, 112.1, 113.4, 118.6, 125.2, 127.7, 129.8, 131.9, 132.6, 133.4, 135.7, 135.9, 137.3, 137.9, 142.0, 144.4, 145.7, 150.5, 165.5, 172.8. Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.19; H, 4.53; N, 11.14.

3-Cyano-1-(4-methylphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3d): orange needles; mp 264-266 °C; IR (KBr) 2239, 1705, 1634 cm^{-1} ; ^1H NMR δ 0.97 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 2.45 (s, 3H, CH_3), 3.56 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.35 (d, $J = 8.4$ Hz, 2H, benzene ring aromatic H), 7.46 (d, $J = 8.4$ Hz, 2H, benzene ring aromatic H), 7.84 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.93 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.03 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 9.07 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.07 (d, $J = 9.2$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.9, 19.2, 63.7, 105.6, 109.9, 111.1, 123.1, 123.5, 129.9, 130.4, 134.9, 135.8, 137.3, 137.7, 138.0, 141.2, 141.7, 143.3, 145.8, 146.9, 167.1. Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.17; H, 4.61; N, 11.13.

3-Cyano-1-(3,5-dimethylphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3e): orange needles; mp 215-217 °C; IR (KBr) 2234, 1704, 1629 cm^{-1} ; ^1H NMR δ 0.96 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 2.03 (s, 6H, CH_3), 2.44 (s, 3H, CH_3), 3.58 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.31-7.37 (m, 1H, benzene ring aromatic H), 7.39-7.44 (m, 2H, benzene ring aromatic H), 7.82 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 7.91 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.01 (dd, $J = 9.2, 9.2$ Hz, 1H, azulene ring aromatic H), 9.02 (d, $J = 9.6$ Hz, 1H, azulene ring aromatic H), 10.07 (d, $J = 9.0$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.2, 25.4, 25.6, 60.1, 100.5, 112.6, 113.5, 118.7, 125.2, 127.4, 129.8, 131.9, 132.4, 133.0, 135.3, 137.1, 138.9, 142.2, 144.3, 147.7, 150.8, 168.4. Anal. Calcd for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.64; H, 4.96; N, 10.69.

3-Cyano-1-(2,4,6-trimethylphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3f): orange needles; mp 246-248 °C; IR (KBr) 2232, 1704, 1631 cm^{-1} ; ^1H NMR δ 1.12 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 1.99 (s, 6H, 2x CH_3), 2.37 (s, 3H, CH_3), 3.68 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.02 (s, 2H, benzene ring aromatic H), 7.77 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 7.90 (dd, $J = 9.6, 9.6$ Hz, 1H,

azulene ring aromatic H), 7.99 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.68 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.04 (d, $J = 9.6$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 14.9, 21.3, 25.2, 25.6, 60.7, 100.2, 112.1, 118.6, 125.4, 127.7, 132.6, 133.4, 135.7, 135.9, 137.3, 137.9, 138.9, 142.0, 144.4, 145.7, 150.5, 166.3, 170.4. Anal. Calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 73.12; H, 5.29; N, 10.34.

3-Cyano-1-(2-methoxyphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3g): orange needles; mp 174-176 °C; IR (KBr) 2232, 1704, 1626 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.46 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 4.30 (s, 3H, OCH_3), 4.48 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.88-6.91 (m, 1H, benzene ring aromatic H), 7.05 (t, $J = 9.2$ Hz, 1H, benzene ring aromatic H), 7.18 (t, $J = 9.2$ Hz, 1H, benzene ring aromatic H), 7.61-7.69 (m, 2H, benzene ring aromatic H + azulene ring aromatic H), 7.67 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 7.75 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.72 (d, $J = 10.0$ Hz, 1H, azulene ring aromatic H), 9.25 (d, $J = 10.0$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.2, 55.2, 61.5, 99.6, 104.6, 109.9, 111.4, 112.6, 113.5, 125.1, 127.9, 129.8, 131.6, 132.8, 133.5, 134.1, 137.3, 137.6, 140.7, 144.6, 146.2, 166.1, 172.1. Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_4$: C, 69.17; H, 4.29; N, 10.52. Found: C, 69.29; H, 4.46; N, 10.69.

3-Cyano-1-(4-methoxyphenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3h): orange needles; mp 258-260 °C; IR (KBr) 2233, 1705, 1626 cm^{-1} ; ^1H NMR δ 0.94 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.54 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.88 (s, 3H, OCH_3), 7.04 (d, $J = 9.2$ Hz, 2H, benzene ring aromatic H), 7.49 (d, $J = 9.2$ Hz, 2H, benzene ring aromatic H), 7.83 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 7.92 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.02 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 9.04 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 10.06 (d, $J = 9.2$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 14.9, 55.8, 61.2, 106.4, 113.6, 114.7, 117.8, 125.0, 130.2, 133.1, 133.5, 137.5, 138.0, 140.7, 140.8, 144.0, 145.2, 159.9, 163.9, 165.9, 171.7. Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_4$: C, 69.17; H, 4.29; N, 10.52. Found: C, 69.31; H, 4.43; N, 10.67.

1-(4-Chlorophenyl)-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3i): orange needles; mp 270-272 °C; IR (KBr) 2233, 1704, 1627 cm^{-1} ; ^1H NMR δ 1.01 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.67 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 8.06-8.09 (m, 4H, benzene ring aromatic H), 8.15 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.20 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.26 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 9.02 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 9.93 (d, $J = 9.2$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.3, 60.4, 105.7, 113.4, 114.7, 118.6, 125.2, 130.2, 133.2, 133.5, 137.4, 138.3, 140.5, 140.7, 144.0, 145.2, 160.2, 163.7, 166.4, 173.2. Anal. Calcd for $\text{C}_{22}\text{H}_{14}\text{ClN}_3\text{O}_3$: C, 65.43; H, 3.49; N, 10.41. Found: C, 65.57; H, 3.64; N, 10.56.

3-Cyano-1-(3-nitrophenyl)-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazine (3j): orange needles; mp 291-293 °C; IR (KBr) 2237, 1691, 1722 cm^{-1} ; ^1H NMR δ 0.96 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.65 (q,

$J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 7.94-7.96 (m, 1H, benzene ring aromatic H), 7.98-8.02 (m, 2H, benzene ring aromatic H), 8.13 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.22 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.32 (dd, $J = 9.6, 9.6$ Hz, 1H, azulene ring aromatic H), 8.57 (s, 1H, benzene ring aromatic H), 9.08 (d, $J = 10.4$ Hz, 1H, azulene ring aromatic H), 9.97 (d, $J = 10.0$ Hz, 1H, azulene ring aromatic H); ^{13}C NMR δ 15.9, 60.8, 105.2, 112.5, 113.4, 118.8, 125.7, 127.9, 129.7, 131.9, 133.6, 133.8, 135.7, 135.9, 137.3, 140.8, 142.3, 144.5, 145.7, 150.8, 165.7, 172.1. Anal. Calcd for $\text{C}_{22}\text{H}_{14}\text{N}_4\text{O}_5$: C, 63.77; H, 3.41; N, 13.52. Found: C, 63.89; H, 3.52; N, 13.67.

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