HETEROCYCLES, Vol. 92, No. 1, 2016, pp. 133 - 140. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 12th November, 2015, Accepted, 26th November, 2015, Published online, 11th December, 2015
DOI: 10.3987/COM-15-13364

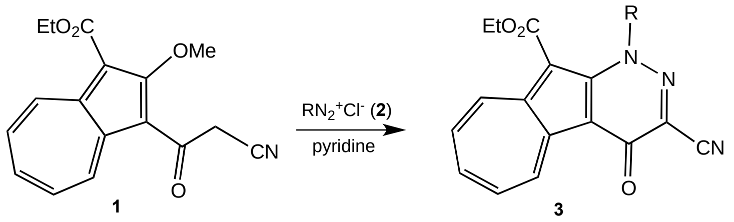
AN EFFICIENT ONE-POT SYNTHESIS OF AZULENO[2,1-*b*]PYRIDAZINES

Dao-Lin Wang,* Jian Ma, Xiao-Ce Shi, and Jian-Ying Wu

Liaoning Key Laboratory of Synthesis & Application of Functional Compound, College of Chemistry & Chemical Engineering, Bohai University, Jinzhou 121001, P. R. China; wangdaolin@sina.com

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 heterocyle-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 heterocyle-fused azulenes have attracted the interest owing to its unusual chemical properties.[10] Thus, preparation and reactivities of a number of heterocyle-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 azulene[13] to 1-aryl-3-cyano-4-oxo-10-ethoxycarbonylazuleno[2,1-*b*]pyridazines (**3**) by condensation of ethyl 1-cyanoacetyl-2-methoxy-azulene-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 ($C_{22}H_{15}N_3O_3$). 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, $OCH_2\underline{CH_3}$), 3.57 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), and phenyl at *δ* 7.48-7.53 (m, 5H). In the ^{13}C 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_2O	12	47
7	pyridine	6	82

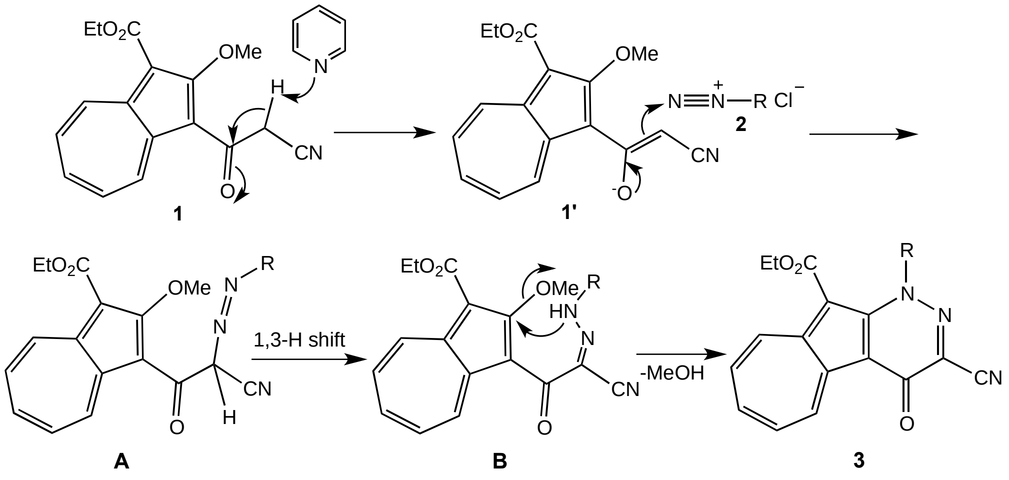
[a] Reaction conditions: **1** (1.0 mmol), phenyldiazonium salt (**2a**, 1.0 mmol), solvent (20 mL).
[b] Isolated yield.

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_6H_5	6	**3a**	82
2	**2b**	$2\text{-}MeC_6H_4$	6	**3b**	80
3	**2c**	$3\text{-}MeC_6H_4$	5	**3c**	85
4	**2d**	$4\text{-}MeC_6H_4$	4	**3d**	84
5	**2e**	$3,5\text{-}Me_2C_6H_3$	5	**3e**	87
6	**2f**	$2,4,6\text{-}Me_3C_6H_2$	6	**3f**	78
7	**2g**	$2\text{-}MeOC_6H_4$	8	**3g**	84
8	**2h**	$4\text{-}MeOC_6H_4$	7	**3h**	86
9	**2i**	$4\text{-}ClC_6H_4$	10	**3i**	79
10	**2j**	$4\text{-}NO_2C_6H_4$	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-arylhydrazolononitrile 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 ^{1}H 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 HC1 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 ºC; IR (KBr) 2231, 1708, 1625 cm^{-1}; ^{1}H NMR δ 0.96 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 3.57 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{22}H_{15}N_3O_3$: 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 ºC; IR (KBr) 2235, 1702, 1634 cm^{-1}; ^{1}H NMR δ 1.06 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.37 (s, 3H, CH_3), 3.63 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{23}H_{17}N_3O_3$: 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}; ^{1}H NMR δ 1.06 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.34 (s, 3H, CH_3), 3.82 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{23}H_{17}N_3O_3$: 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}; ^{1}H NMR δ 0.97 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.45 (s, 3H, CH_3), 3.56 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{23}H_{17}N_3O_3$: 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}; ^{1}H NMR δ 0.96 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.03 (s, 6H, CH_3), 2.44 (s, 3H, CH_3), 3.58 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{24}H_{19}N_3O_3$: 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}; ^{1}H NMR δ 1.12 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.99 (s, 6H, 2xCH_3), 2.37 (s, 3H, CH_3), 3.68 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{25}H_{21}N_3O_3$: 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}; ^{1}H NMR (CDCl$_3$): *δ* 1.46 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 4.30 (s, 3H, OCH_3), 4.48 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{23}H_{17}N_3O_4$: 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}; ^{1}H NMR δ 0.94 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 3.54 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{23}H_{17}N_3O_4$: 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}; ^{1}H NMR δ 1.01 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 3.67 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{22}H_{14}ClN_3O_3$: 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}; ^{1}H NMR δ 0.96 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 3.65 (q, *J* = 7.2 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 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 $C_{22}H_{14}N_4O_5$: C, 63.77; H, 3.41; N, 13.52. Found: C, 63.89; H, 3.52; N, 13.67.

REFERENCES

1. J. M. Conteras, Y. M. Rival, S. Chayer, J. J. Borguignon, and C. G. Wermuth, *J. Med. Chem.*, 1999, **42**, 730.
2. A. A. Siddiqui, R. Mishra, and M. Shaharyar, *Eur. J. Med. Chem.*, 2010, **45**, 2283.
3. Z. K. Sweeney, J. P. Dunn, Y. Li, G. Heilek, P. Dunten, T. R. Elworthy, X. C. Han, S. F. Harris, D. R. Hirschfeld, J. H. Hogg, W. Huber, A. C. Kaiser, D. J. Kertesz, W. Kim, T. Mirzadegan, M. G. Roepel, Y. D. Saito, T. M. P. C. Silva, S. Swallow, J. L. Tracy, A. Villasenor, H. Vora, A. S. Zhou, and K. Klumpp, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4352.
4. M. Sonmez, I. Borber, and E. Akbas, *Eur. J. Med. Chem.*, 2006, **41**, 101.
5. L. Costantino, G. Rastelli, G. Cignarella, and D. Barlocco, *Il Farmaco*, 2000, **55**, 544.
6. S. K. Kwon and A. Moon, *Arch. Pharm. Res.*, 2005, **28**, 391.
7. T. Yanagisawa, S. Wakabayashi, T. Tomiyama, M. Yasunami, and K. Takase, *Chem. Pharm. Bull.*, 1988, **36**, 641.
8. A. E. Asato, A. Peng, M. Z. Hossain, T. Mirzadegan, and J. S. Bertram, *J. Med. Chem.*, 1993, **36**, 3137.
9. D. A. Becker, J. J. Ley, L. Echegoyen, and R. Alvarado, *J. Am. Chem. Soc.*, 2002, **124**, 4678.
10. G. Fischer, *Adv. Heterocycl. Chem.*, 2009, **97**, 131.
11. (a) D.-L. Wang and K. Imafuku, *Heterocycles*, 2001, **54**, 647; (b) K. Imafuku and D.-L. Wang, *Heterocycles*, 2002, **58**, 405; (c) H. Matsuo, K. Fujimori, A. Ohta, A. Kakehi, M. Yasunami, and T. Nozoe, *Heterocycles*, 2003, **61**, 271; (d) M. Nishiura, I. Ueda, and K. Yamamura, *Heterocycles*, 2007, **74**, 951; (e) S. Ito, T. Okujima, S. Kikuchi, T. Shoji, N. Morita, T. Asao, T. Ikoma, S. Tero-Kubota, J. Kawakami, and A. Tajiri, *J. Org. Chem.*, 2008, **73**, 2256; (f) T. Okujima, T. Terazono, S. Ito, N. Morita, and T. Asao, *Heterocycles*, 2000, **54**, 667; (g) S. Ito, T. Kubo, M. Kondo, C. Kabuto, N. Morita, T. Asao, K. Fujimori, M. Watanabe, N. Harada, and M. Yasunami, *Org. Biomol. Chem.*, 2003, **1**, 2572; (h) T. Shoji, E. Shimomura, Y. Inoue, M. Maruyama, A. Yamamoto, K. Fujimori, S. Ito, M. Yasunami, and N. Morita, *Heterocycles*, 2013, **87**, 303; (i) S. Ito, S. Yamazaki, S. Kudo, R.

Sekiguchi, J. Kawakami, M. Takahashi, T. Matsuhashi, K. Toyota, and N. Morita, *Tetrahedron*, 2014, **70**, 2796.

12. (a) J. Xu, D.-L. Wang, and K. Imafuku, *Synth. Commun*., 2009, **39**, 2196; (b) D.-L. Wang, L.-N. Lin, S.-F. Li, W. Li, and Y.-F. Li, *Chin. J. Org. Chem*., 2010, **30**, 1774; (c) D.-L. Wang, S.-F. Li, W. Li, Y.-F. Li, and L.-N. Lin, *Chin. Chem. Lett.*, 2011, **22**, 789; (d) D.-L. Wang, Y.-F. Li, J. Xu, W. Li, S.-F. Li, and L.-N. Lin, *Heterocycles*, 2011, **83**, 365; (e) D.-L. Wang, S.-S. Feng, Q.-T. Cui, and J.-Y. Yu, *Heterocycles*, 2012, **85**, 441.
13. (a) D.-L. Wang, Q.-T. Cui, S.-S. Feng, and J.-Y. Yu, *Heterocycles*, 2012, **85**, 697; (b) D.-L. Wang, Z. Dong, Q.-T. Cui, F.-F. Yang, and W. Zhao, *Heterocycles*, 2013, **87**, 2343.