A SHORT-STEP SYNTHESIS OF ONYCHINE AND THE RELATED 4-AZAFLUORENONEs VIA HETERO DIELS-ALDER REACTION OF 5-SUBSTITUTED ISOCELLURAZOLES

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Abstract – Synthesis of onychine and the related 4-azafluorenone alkaloids was achieved from 5-substituted isotellurazoles through a two-step procedure involving hetero Diels-Alder reaction with methyl phenylpropiolate and the subsequent Friedel-Crafts ring closure of the resulting pyridine derivatives.

INTRODUCTION

Onychine (1) was isolated as a constituent from Onychopetalum amazonicum, Guatteria dielsiana, Cleistopholis patens, and so on, and recently onychine (1) and the related 4-azafluorene alkaloids are widely recognized to possess a variety of important biologically-activities as well as the synthetic importance as the intermediate of other related polycyclic alkaloids such as dielsine (2) and eupolaudridine. Actually, Koyama reported the first synthesis of onychine in 1979, and since then several groups attempted the synthesis of onychine (1) and its related compounds by using a variety of procedures. However, these previous procedure commonly required the long-step procedure and the synthetic efficiency were not satisfactory enough, and especially selective construction of polysubstituted fused-pyridine core still remains the problem in the synthetic research of these compounds. In the course of our research work on the synthesis of higher row chalcogen-containing heteroaromatic compounds, we have recognized the synthetic potentiality of isotellurazoles having a tellurium-bridged cisoid heterodiene substructure along with a weak carbon-tellurium and nitrogen-tellurium bonds and the enhanced ring strain of the ring systems involving a tellurium atom with a large atomic radius, and we have already reported a convenient and selective preparation of isotellurazoles bearing various substituents at the C-3 and C-5 positions, selective and efficient construction of substituted pyridines by using hetero Diels-Alder reactions of isotellurazoles with acetylenic dienophiles as the key step, and the subsequent construction of polycyclic pyridine alkaloid skeletons through Friedel-Crafts ring closure.
These successful results envisaged us to a new and straightforward synthesis of onychine (1) and the related derivatives through a novel hetero Diels-Alder approach of 5-substituted isotellurazoles.

Scheme 1. Retrosynthetic pathway for 4-azafluorenones from 5-substituted isotellurazoles B

The retrosynthetic pathway for the targeted monoalkylated 4-azafluorenones in this research work is outlined in Scheme 1 in which the synthesis of key intermediate A via hetero Diels-Alder reaction of isotellurazole B with a phenylpropionate estes C is involved based on our previously reported methodology. In this report, we would like to describe a convenient synthesis of onychine (1) and the related 1-substituted 4-azafluorenones through a concise pathway involving the strategic combination of a one-pot conversion of alk-2-enals into monosubstituted isotellurazoles B, hetero Diels-Alder reaction of monosubstituted isotellurazoles B for the regioselective synthesis of substituted pyridine derivatives A, and the subsequent Friedel-Crafts ring closure of pyridine derivatives A as shown in Scheme 1.

RESULTS AND DISCUSSION

Isotellurazole Te-oxide oligomers 6 were at first prepared through a one-pot three-step procedure starting from bis(N,N-dimethylcarbamoyl) ditelluride (3) [(1) NaBH₄ (2.2 equiv.), (2) alk-2-ynal 4 bearing an alkyl or aryl group at the substituent R, (3) NH₂OSO₃H (6.0 equiv.)] without the isolation of β-(N,N-dimethylcarbamoyltelluro)alk-2-enals 5, and the subsequent deoxygenation of 6 was carried out by treating with Ph₃P (2.0 equiv.) and I₂ (1.0 equiv.) at room temperature for a few hours to obtain the
corresponding isotellurazoles 7 in high yields without the contamination of any byproducts. Especially, the first preparation of 5-methylisotellurazole 7c (R = Me) was accomplished through this method, and 7c was isolated as a stable crystalline compound. The synthetic procedure for 5-substituted isotellurazoles 7a-c from compound 3 are shown below.

When a toluene solution of 5-substituted isotellurazoles 7a (R = C₆H₅) or 7b (R = n-C₄H₉) was treated with methyl phenylpropiolate (8, 1.5 equiv.) at refluxing temperature for 24 h, the corresponding pyridine derivatives 11a and 11b were obtained in 99% and 80% yields, respectively, and treatment of 7a with phenylpropionitrile (9) or phenylpropynal (10) also afforded the corresponding pyridine derivatives 12 or 13 in high yields. In contrast, a similar treatment of 5-methylisotellurazole (7c, R = Me) with 8 in toluene afforded desired pyridine derivative 11c in rather low yield. However, lowering of the temperature of thermal reaction was effective for improving the yield of 11c by using THF as a solvent in place of toluene, and after several attempts for optimization of the reaction procedures and conditions, the yield of 11c was dramatically raised up to 56% yield by heating 7c with 8 (5.0 equiv.) in a sealed tube at 80 °C without the use of any solvents. A similar treatment of 7c with a highly reactive dienophile, i.e. phenylpropionitrile (9) or phenylpropynal (10), afforded the corresponding pyridine derivatives 12c and

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Dienophile (8-10)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Yield (11-13)</th>
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<tr>
<td>R</td>
<td>7</td>
<td>EWG</td>
<td>(equiv.)</td>
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<td>(h)</td>
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<tr>
<td>C₆H₅</td>
<td>7a</td>
<td>CO₂Me</td>
<td>8 (1.5)</td>
<td>toluene reflux</td>
<td>24</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>7a</td>
<td>CN</td>
<td>9 (1.5)</td>
<td>toluene reflux</td>
<td>5</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>7a</td>
<td>CHO</td>
<td>10 (1.5)</td>
<td>toluene reflux</td>
<td>9</td>
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<tr>
<td>n-C₄H₉</td>
<td>7b</td>
<td>CO₂Me</td>
<td>8 (1.5)</td>
<td>toluene reflux</td>
<td>24</td>
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<tr>
<td>Me</td>
<td>7c</td>
<td>CO₂Me</td>
<td>8 (1.5)</td>
<td>toluene reflux</td>
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<tr>
<td>Me</td>
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<td>8 (5.0)</td>
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<td>7c</td>
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<td>10 (1.5)</td>
<td>toluene reflux</td>
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in 80% and 68% yields, respectively, and these results suggested that the low yield of 11c from 7c was attributed to the relatively low reactivity of methyl phenylpropionate (8) as a dienophile in contrast to 9 and 10 besides the possibility of sublimation of substrate 7c under the heating condition.

Compounds 11a-c were then subjected to Friedel-Crafts cyclization by treating with Lewis acids, and in our cases treatment of 11 with an excess amount of PPA at high reaction temperature (up to 210 °C) for 2 h afforded the best result for the conversion into the corresponding 1-substituted 4-azafluorenone derivatives 14. Especially, the physical and spectral data of product 14c were fully identical in all respects with those of onychine (1), and this result indicated that the total synthesis of onychine (1) was achieved successfully through our synthetic procedure involving two step conversion with 42% overall yield from 5-methylisotellurazole (7c). On the other hand, a similar treatment of pyridine 11a (R = C6H5) bearing two phenyl groups at the C-2 and C-4 position with PPA afforded a separable mixture of two isomeric products 14a and 14a’ in 10% and 66% yields, respectively. The spectral patterns of 1H NMR and 13C NMR spectra of 14a and 14a’ revealed a high similarity with each other. The physical and spectral data of minor 14a were identical with those of 1-phenyl-4-azafluorenone 14a reported by Mongin, and the structure of major product 14a was confirmed to be 1-phenyl-4-azafluorenone. The structure of 14a’ was also supported by the data of mass spectrum and elemental analysis. Formation of the isomeric mixture of 14a and 14a’ was rationalized by the Friedel-Crafts ring closure of acyl cationic intemitiate with each phenyl group of 11a, and, especially, formation of major product 14a’ was explained as the regiochemical counterpart of minor product 14a through the preferable ring closure with the phenyl group attached to the less electron deficient C-4 position of pyridine ring of 11a.

Synthesis of onychine (1) was also attempted by using 3-cyanopyridine derivative 12c (EWG = CN) or aldehyde 13c (EWG = CHO) as alternative synthetic precursors. However, direct treatment of 12c with PPA in a similar manner just afforded amide 15c (EWG = CONH2, 61% yield) as a major product besides the formation of onychine (1) in rather low yield, and the further conversion of 15c into onychine (1) was unsuccessful at all even by treating with PPA under heating at 200 °C for a long time. On the other hand, aldehyde 13c was easily converted into carboxylic acid 16c (EWG = CO2H) in 41% yield by treating with NaClO2. Further conversion of 16c into onychine (1) was already reported by Taylor, and this result was also recognized to be a route for the formal synthesis of onychine (1). However, the yield of 16c remained unsatisfactory to the synthetic level in spite of our efforts for optimization of the reaction procedure and conditions.
Table 2. Synthesis of 1-Substituted 4-Azafluorenones 14 from Substituted Pyridine Derivatives 11 or 12

\[
\begin{array}{ccccccc}
\text{Substrate} & \text{Temp (°C)} & \text{Time (h)} & \text{Yield (%)} & \text{14} & \text{14'} & \text{15} \\
\hline
\text{R} & \text{EWG} & \text{11, 12} & \text{11a} & 210 & 2 & 10 (14a) & 66 (14a') & - \\
C_6H_5 & CO_2Me & 11b & 210 & 2 & 70 (14b) & - & - \\
C_4H_9 & CO_2Me & 11c & 210 & 2 & 77 (14c = 1) & - & - \\
Me & CO_2Me & 12c & 180 & 4 & 27 (14c = 1) & 61 (15c) & - \\
\end{array}
\]

Scheme 3. Alternative formal synthesis of onychine (1) from pyridine derivative 13c

CONCLUSION

In conclusion, we could establish a new two-step synthetic methodology for onychine (1) and related 4-azafluorenones starting from substituted isotellurazoles 7 by using hetero Diels-Alder reaction as the key step of construction of the alkaloid skeleton. Further applications of our synthetic protocol to the short-step and regioselective construction of other various pyridine-fused polycyclic alkaloid skeletons are under way in our laboratory.

EXPERIMENTAL

Instruments:

The melting points were determined with a Barnstead International MEL-TEMP. \(^1\)H NMR spectra were recorded on a Bruker DRX-400P (400 MHz) spectrometer or a Bruker AVANCE III 500 (500 MHz) spectrometer, and the chemical shifts of the \(^1\)H NMR spectra are given in δ relative to internal tetramethylsilane (TMS). \(^13\)C NMR spectra were recorded on a Bruker DRX-400P (100 MHz) or a Bruker AVANCE III 500 (126 MHz). Mass spectra were recorded on a JEOL JMS-700T mass spectrometer with
electron-impact ionization at 20 or 70 eV using a direct inlet system. High resolution mass spectra (HRMS) were also recorded on a JEOL JMS-700T spectrometer. IR spectra were recorded for thin film (neat) or KBr disks on a JASCO FT/IR-7300 spectrometer. Elemental analyses were performed using a Yanagimoto CHN corder MT-5.

**Starting Materials:**

Bis(N,N-dimethylcarbamoyl) ditelluride (1) was prepared from elemental tellurium, sodium metal or sodium hydride, and N,N-dimethylformamide (DMF), and yrones and ynals (2) were prepared through Friedel-Crafts type acylation of terminal acetylenic compounds or oxidation of substituted propargyl alcohols according to the previous papers. All other chemicals used in this study were commercially available.

**A Typical Procedure for Preparation of Isotellurazole Oxide Oligomers from Bis(N,N-dimethylcarbamoyl) Ditelluride (3) and Alk-2-ynals 4.** To a DMF solution of bis(N,N-dimethylcarbamoyl) ditelluride (3, 398 mg, 1.00 mmol) was added a MeOH solution (5 mL) of NaBH₄ (84 mg, 2.2 equiv.) at -50 °C, and the reaction mixture was then treated with alk-2-ynals 4 (2.2 equiv.) at 0 °C for 7 h. The reaction was quenched by addition of water, and the reaction mixture was extracted with benzene. The organic layer was washed twice with water and was dried over anhydrous Na₂SO₄ powder. The organic solvent was removed in vacuo, and the residual crude products were subjected to column chromatography on silica gel to obtain Te-alkenyl N,N-dimethyltellurocarbamates 5 in high to moderate yields as yellow crystals. Then, a MeOH solution (10 mL) of compounds 5 was treated with hydroxylamine-O-sulfonic acid (4.4 equiv.) at reflux temperature for 1 h. The reaction mixture was cooled to room temperature and was quenched by addition of water, and the crude reaction mixture was extracted with benzene. The organic layer was washed with water and was dried over anhydrous Na₂SO₄ powder. The organic solvent was removed in vacuo, and the residual crude products were subjected to column chromatography on silica gel to obtain isotellurazole Te-oxide oligomers 6 as main products besides a small amount of isotellurazoles 7.

**General Procedure for Deoxygenation of Isotellurazole Te-Oxide Oligomers 6 by Treating with Ph₃P and I₂.** A CH₂Cl₂ solution of isotellurazole Te-oxide oligomer 6 (0.349 mmol) was treated with Ph₃P (183 mg, 0.698 mmol, 2.0 equiv.) and I₂ (89 mg, 0.349 mmol, 1.0 equiv.) at 0 °C for 3 h. The reaction was then quenched by addition of saturated aqueous Na₂SO₃ solution, and the reaction mixture was extracted with CHCl₃. The organic layer was washed with water and was dried over anhydrous Na₂SO₄ powder. After removing the organic solvent in vacuo, the crude product was subjected to purification by using column chromatograph on silica gel to isolate isotellurazole 7.

**General Procedure for Conversion of Isotellurazoles 5 into Substituted Pyridine Derivatives 11-13.** A toluene or a THF solution of isotellurazole 7 (1.0 mmol) was treated with an acetylenic dienophile
(methyl phenylpropiolate (8), phenylpropiolonitriles (9), or phenypropynal (10), 1.5-5.0 equiv.) at rt or under heating for several hours, and the reaction mixture was filtered to remove the precipitated elemental tellurium. After removal of the solvent from the filtrate in vacuo, the residual matter was subjected to column chromatography on silica gel to obtain the corresponding pyridines 11 (EWG = CO₂Me), 12 (EWG = CN), or 13 (EWG = CHO), respectively, in moderate to high yields.

11a (R¹ = C₆H₅, R² = H, R³ = C₆H₅, EWG = CO₂Me)⁵⁻¹³: Colorless needles, mp 95.6-96.0 °C; IR (KBr) 3055, 2999, 2945, 1721, 1583, 1569, 1541, 1493, 1450, 1435, 1400, 1316, 1285, 1258, 1131, 1064, 1026, 866, 856, 839, 808, 766, 744, 699, 647, 618, 584, 526 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.47 (3H, s), 7.29 (1H, d, J = 5.0 Hz), 7.39-7.46 (8H, m), 7.62-7.64 (2H, m), 8.75 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 52.3 (q), 122.8 (d), 128.0 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.7 (d), 128.8 (d), 128.9 (d), 138.1 (s), 139.7 (s), 148.7 (s), 150.0 (d), 156.9 (s), 169.1 (s).

11b (R¹ = n-C₄H₉, R² = H, R³ = C₆H₅, EWG = CO₂Me): Colorless oil; IR (neat) 2955, 2932, 2871, 1729, 1583, 1571, 1560, 1461, 1440, 1404, 1308, 1287, 1270, 1237, 1132, 1112, 1059, 835, 766, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.5 Hz), 1.39 (2H, sext, J = 7.5 Hz), 1.60-1.66 (2H, m), 2.69 (2H, t, J = 7.5 Hz), 3.64 (3H, s), 7.16 (1H, d, J = 5.0 Hz), 7.38-7.44 (3H, m), 7.58-7.60 (2H, m), 8.61 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 13.9 (q), 22.6 (t), 32.7 (t), 32.9 (t), 52.3 (q), 122.7 (d), 128.3 (d), 128.7 (d), 128.8 (s), 140.1 (s), 149.9 (d), 150.3 (s), 156.7 (s), 169.4 (s). HRMS Calcd for C₁₇H₁₉NO₂: m/z 269.1416. Found: m/z 269.1420.

11c (R¹ = Me, R² = H, R³ = C₆H₅, EWG = CO₂Me): Colorless oil; IR (neat) 1729, 1583, 1571, 1560, 1461, 1440, 1404, 1308, 1287, 1270, 1237, 1132, 1112, 1059, 835, 766, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.42 (3H, s), 3.66 (3H, s), 7.15 (1H, d, J = 5.0 Hz), 7.38-7.45 (3H, m), 7.57-7.60 (2H, m), 8.59 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 19.6 (q), 52.4 (q), 123.7 (d), 128.3 (d), 128.5 (d), 129.0 (s), 140.1 (s), 145.7 (s), 149.9 (d), 156.7 (s), 169.4 (s). HRMS Calcd for C₁₄H₁₃NO₂: m/z 227.0946. Found: m/z 227.0946.

12c (R¹ = Me, R² = H, R³ = C₆H₅, EWG = CN): Pale yellow oil; IR (neat) 3059, 2223, 1729, 1584, 1572, 1461, 1440, 1401, 1309, 1275, 1241, 1189, 1132, 1107, 1078, 1065, 832, 765, 700, 593 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.68 (3H, s), 7.25 (1H, dd, J = 5.0, 0.5 Hz), 7.50-7.54 (3H, m), 7.86-7.89 (2H, m), 8.70 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 20.8 (q), 108.5 (s), 116.6 (s), 123.0 (d), 128.6 (d), 129.0 (d), 130.0 (d), 137.6 (s), 151.7 (d), 152.7 (s), 161.6 (s). HRMS Calcd for C₁₃H₁₀N₂: m/z 194.0844. Found: m/z 194.0843.

13c (R¹ = Me, R² = H, R³ = C₆H₅, EWG = CHO): Pale yellow needles, mp 47.0-47.5 °C; IR (KBr) 1691, 1567, 1461, 1441, 1375, 1261, 891, 793, 755, 705 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.68 (3H, s), 7.22 (1H, d, J = 5.0 Hz), 7.45-7.56 (5H, m), 8.67 (1H, d, J = 5.0 Hz), 10.0 (1H, s); ¹³C NMR (126 MHz, CDCl₃) δ 21.0 (q), 125.7 (d), 128.6 (d), 128.9 (s), 129.5 (d), 130.5 (d), 138.1 (s), 149.5 (s), 151.8 (d), 163.3 (s), 193.7 (d). HRMS Calcd for C₁₃H₁₁NO: m/z 197.0841. Found: m/z 197.0837.
A General Procedure for Conversion of Pyridines 11 into the Corresponding 4-Azafluorenones 14.

Pyridine 11e-g (EWG = CO₂Me, 1.0 mmol) was treated with an excess amount of polyphosphoric acid (PPA) at 210 °C for 4 h. The reaction was then quenched by addition of saturated NaHCO₃ aqueous solution, and the reaction mixture was extracted with CHCl₃ for three times. The organic layer was washed with water, and was dried over anhydrous Na₂SO₄ powder. After removal of the solvent in vacuo, the residual matter was subjected to column chromatography on silica gel to obtain the corresponding 4-azafluorenones 14 in high yields.

14a (R¹ = C₆H₅, R² = H, minor): Pale yellow powder, mp 168.8-169.2 °C; IR (KBr) 1713, 1604, 1585, 1552, 1450, 1383, 1347, 1177, 919, 855, 760, 743, 695, 684, 620, 540, 424 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.15 (1H, d, J = 5.5 Hz), 7.43 (1H, td, J = 7.5, 1.0 Hz), 7.49-7.50 (3H, m), 7.59-7.62 (3H, m), 7.68 (1H, d, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz), 8.59 (1H, d, J = 5.5 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 120.9 (d), 124.0 (d), 124.2 (s), 124.9 (d), 128.4 (d), 129.2 (d), 129.8 (d), 131.2 (d), 134.9 (s), 135.0 (s), 135.3 (d), 143.0 (s), 149.2 (s), 153.4 (d), 166.2 (s), 191.3 (s).

14a' (R¹ = C₆H₅, R² = H, major): Pale yellow plates, mp 156.1-156.5 °C; MS (m/z) 257 (M⁺; bp); IR (KBr) 1716, 1604, 1583, 1572, 1469, 1435, 1344, 1182, 912, 859, 819, 769, 756, 698, 620, 440, 413 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.44-7.46 (2H, m), 7.48-7.51 (3H, m), 7.58 (1H, td, J = 7.5, 1.0 Hz), 7.65 (1H, d, J = 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz), 7.86-7.88 (2H, m), 8.79 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 114.0 (d), 121.4 (d), 124.6 (s), 124.6 (d), 128.0 (d), 129.8 (d), 129.9 (d), 131.6 (d), 133.9 (s), 134.9 (d), 136.9 (s), 141.3 (s), 153.8 (s), 155.2 (d), 157.8 (s), 192.1 (s). Calcd for C₁₈H₁₁NO: C, 84.03; H, 4.31; N, 5.44%. Found: C, 84.08; H, 4.58; N, 5.40%.

14b (R¹ = n-C₄H₉, R² = H): Pale yellow needles, mp 44.8-45.0 °C; IR (KBr) 2951, 2927, 2861, 1712, 1596, 1562, 1461, 1450, 1389, 1353, 1290, 1258, 1174, 1093, 916, 905, 879, 832, 755, 682, 638, 512 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.96 (3H, t, J = 7.5 Hz), 1.42 (2H, sext, J = 7.5 Hz), 1.61-1.67 (2H, m), 3.04 (2H, t, J = 7.5 Hz), 6.99 (1H, d, J = 5.0 Hz), 7.42 (1H, td, J = 7.5, 0.5 Hz), 7.58 (1H, td, J = 7.5, 1.0 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.83 (1H, d, J = 7.5 Hz), 8.44 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 14.0 (q), 22.6 (t), 30.7 (t), 32.1 (t), 120.8 (d), 123.8 (d), 124.8 (d), 125.6 (s), 130.9 (d), 135.0 (s), 135.1 (d), 143.2 (s), 152.7 (s), 153.1 (d), 165.5 (s), 193.2 (s). Calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90%. Found: C, 80.98; H, 6.49; N, 5.83%.

14c (R¹ = Me, R² = H): Pale yellow needles, mp 128.7-129.0 °C; IR (KBr) 1705, 1598, 1565, 1384, 920, 878, 829, 759, 681, 583, 505, 433 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.61 (3H, s), 6.94 (1H, d, J = 5.5 Hz), 7.40 (1H, td, J = 7.5, 1.0 Hz), 7.56 (1H, td, J = 7.5, 1.0 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.79 (1H, d, J = 7.5 Hz), 8.39 (1H, d, J = 5.5 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 17.4 (q), 120.8 (d), 123.7 (d), 125.9 (d), 126.0 (s), 130.9 (d), 135.0 (s), 135.1 (d), 143.1 (s), 147.6 (s), 152.9 (d), 165.3 (s), 193.2 (s).
Procedure for Conversion of Pyridines 12c into the Corresponding 4-Azafluorenones 14c. Pyridine 12c (EWG = CN, 1.0 mmol) was treated with an excess amount of polyphosphoric acid (PPA) at 210 °C for 4 h. The reaction was then quenched by addition of saturated NaHCO₃ aqueous solution, and the reaction mixture was extracted with CHCl₃ for three times. The organic layer was washed with water, and was dried over anhydrous Na₂SO₄ powder. After removal of the solvent 

in vacuo, the residual matter was subjected to column chromatography on silica gel to obtain the corresponding 4-azafluorenones 14c in moderate yields along with the formation of amides 15c as the main products.

15c (R¹ = Me, R² = H, R³ = C₆H₅, EWG = CONH₂): Colorless needles, mp 171.2-171.5 °C; IR (KBr) 3330, 3085, 3059, 1673, 1620, 1588, 1430, 1370, 1147, 1132, 1068, 881, 829, 801, 749, 685, 634, 597, 448 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.45 (3H, s), 5.56 (1H, s), 5.83 (1H, s), 7.14 (1H, d, J = 5.0 Hz), 7.40-7.43 (3H, m), 7.68-7.71 (2H, m), 8.51 (1H, d, J = 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 19.4 (q), 124.0 (d), 128.6 (d), 128.8 (d), 129.0 (d), 131.5 (s), 139.3 (s), 145.9 (s), 149.7 (d), 155.2 (s), 170.7 (s). HRMS Calcd for C₁₃H₁₂N₂O: m/z 212.0950. Found: m/z 212.0956.

Procedure for NaClO₂ Oxidation of Pyridine 13c. Pyridine 13c (EWG = CHO, 72 mg, 0.365 mmol) was solved in a mixed solvent of ²-BuOH (3.7 mL) and water (2.6 mL), and the solution was treated with NaClO₂ (86 mg, 0.949 mmol, 2.6 equiv.) and NaH₂PO₄•2H₂O (131 mg, 1.095 mmol, 3.0 equiv.) at rt for 3 h. The reaction was quenched by addition of water and ethyl acetate, and the reaction mixture was extracted with EtOAc. The organic layer was then washed with water and brine, and was dried over anhydrous Na₂SO₄ powder. The organic solvent was evaporated in vacuo to obtain crude pale yellow oil. The crude products were purified by column chromatography on silica gel to obtain pyridine 16c (EWG = COOH, 32 mg, 41% yield) as colorless solid.

16c (R¹ = Me, R² = H, R³ = C₆H₅, EWG = COOH): Colorless solid, mp 204.0-205.0 °C [Lit. 214.0-216.0 °C]; ¹H NMR (500 MHz, DMSO-d₆) δ 2.37 (3H, s), 7.34 (1H, d, J = 5.0 Hz), 7.42-7.47 (3H, m), 7.61-7.64 (2H, m), 8.56 (1H, d, J = 5.0 Hz).

ACKNOWLEDGEMENTS
This work was partially supported by a Grant-in-Aid for Scientific Research (No. 23550039) from the Ministry of Education, Science, Sports, and Culture of Japan.

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