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A SHORT-STEP SYNTHESIS OF ONYCHINE AND THE RELATED 4-AZAFLUORENONES *VIA* HETERO DIELS-ALDER REACTION OF 5-SUBSTITUTED ISOTELLURAZOLES

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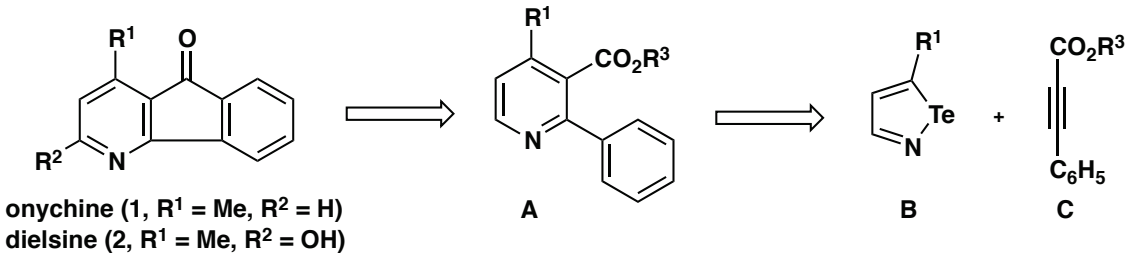
Abstract – Synthesis of onychine and the related 4-azafluorenones was achieved from 5-substituted isotellurazoles through a two-step procedure involving hetero Diels-Alder reaction with methyl phenylpropiolate and the subsequent Friedel-Crafts ring closure of the resulting pyridine derivatives.

INTRODUCTION

Onychine (**1**) was isolated as a constituent from *Onychopetalum amazonicum*, *Guatteria dielsiana*, *Cleistopholis patens*, and so on,[1] and recently onychine (**1**) and the related 4-azafluorenone alkaloids are widely recognized to possess a variety of important biologically-activities[2] as well as the synthetic importance as the intermediate of other related polycyclic alkaloids such as dielsine (**2**)[3] and eupolauridine.[4] 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.[5] 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[6] 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 isotelluraozles bearing various substituents at the C-3 and C-5 positions,[7] 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.[8]

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.

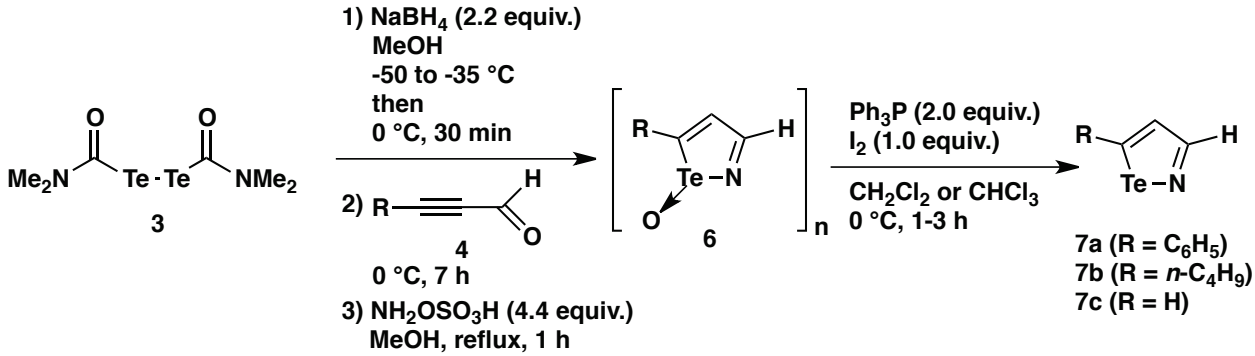


Scheme 1. Retrosynthetic pathway for 4-azafluorenones from 5-substituted isotellurazoles **B**

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 phenylpropiolate 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) $NaBH_4$ (2.2 equiv.), (2) alk-2-ynal **4** bearing an alkyl or aryl group at the substituent R, (3) NH_2OSO_3H (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 Ph_3P (2.0 equiv.) and I_2 (1.0 equiv.) at room temperature for a few hours to obtain the

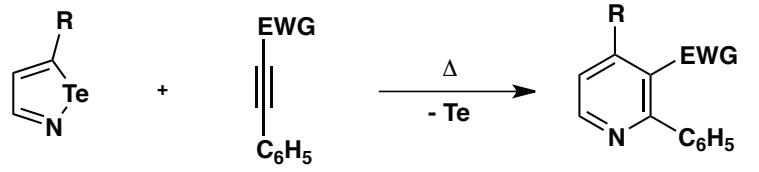


Scheme 2. Synthetic procedure for 5-substituted isotellurazoles **7** starting from bis(*N,N*-dimethylcarbamoyl) ditelluride (**3**)

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.[6] 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 = C_6H_5) or **7b** (R = *n*-C_4H_9) 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 phenylpropiolonitrile (**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.* phenylpropiolonitrile (**9**) or phenylpropynal (**10**), afforded the corresponding pyridine derivatives **12c** and

Table 1. Synthesis of Pyridine Derivatives **11-13** *via* Hetero Diels-Alder Reaction of 5-Substituted Isotellurazoles **7** with a Reactive Acetylenic Dienophile **8-10**



7a (R = C_6H_5) **8 (EWG = CO_2Me)** **11 (EWG = CO_2Me)**
7b (R = *n*-C_4H_9) **9 (EWG = CN)** **12 (EWG = CN)**
7c (R = Me) **10 (EWG = CHO)** **13 (EWG = CHO)**

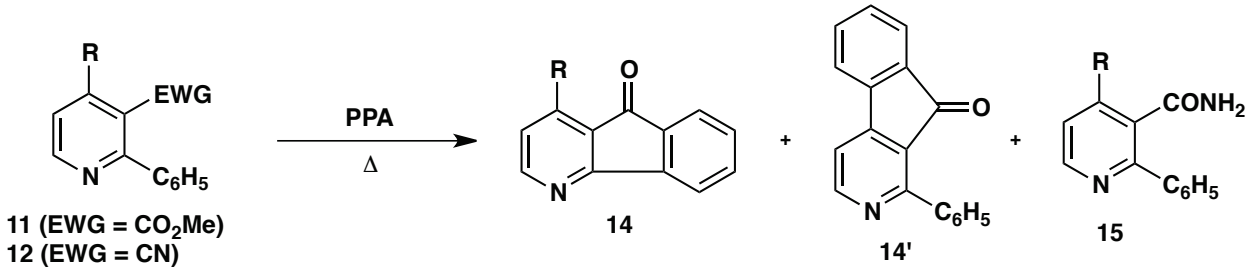
Substrate		Dienophile (**8-10**)		Solvent	Temp	Time	Yield (**11-13**)
R	**7**	EWG	(equiv.)		(°C)	(h)	(%)
C_6H_5	**7a**	CO_2Me	**8** (1.5)	toluene	reflux	24	99 (**11a**)
C_6H_5	**7a**	CN	**9** (1.5)	toluene	reflux	5	80 (**12a**)
C_6H_5	**7a**	CHO	**10** (1.5)	toluene	reflux	9	68 (**13a**)
n-C_4H_9	**7b**	CO_2Me	**8** (1.5)	toluene	reflux	24	80 (**11b**)
Me	**7c**	CO_2Me	**8** (1.5)	toluene	reflux	24	10 (**11c**)
Me	**7c**	CO_2Me	**8** (5.0)	THF	reflux	72	51 (**11c**)
Me	**7c**	CO_2Me	**8** (5.0)	neat	80	2	56 (**11c**)
Me	**7c**	CN	**9** (1.5)	toluene	reflux	5	80 (**12c**)
Me	**7c**	CHO	**10** (1.5)	toluene	reflux	9	68 (**13c**)

13c 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 phenylpropiolate (**8**) as a dienophile in contrast to **9** and **10** besides the possibility of sublimation of substrate **7c** under the heating condition.

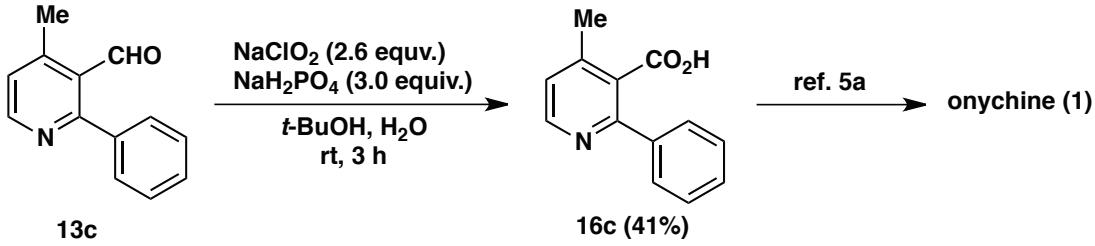
Compounds **11a-c** were then subjected to Friedel-Crafts cyclization by treating with Lewis acids,[10] and in our cases treatment of **11** with an excess amount of PPA at high reaction temperature (up to 210 °C) for 2 h afforded the best result for the conversion into the corresponding 1-substituted 4-azafluorenone derivatives **14**.[8] 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 = C_6H_5) 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 ^{1}H NMR and ^{13}C 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,[5u] 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 intemetiate 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 = $CONH_2$, 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 = CO_2H) in 41% yield by treating with $NaClO_2$.[11] Further conversion of **16c** into onychine (**1**) was already reported by Taylor,[5a] 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**



Substrate			Temp	Time	Yield (%)		
R	EWG	**11**, **12**	(°C)	(h)	**14**	**14'**	**15**
C_6H_5	CO_2Me	**11a**	210	2	10 (**14a**)	66 (**14a'**)	-
C_4H_9	CO_2Me	**11b**	210	2	70 (**14b**)	-	-
Me	CO_2Me	**11c**	210	2	77 (**14c** = **1**)	-	-
Me	CN	**12c**	180	4	27 (**14c** = **1**)	-	61 (**15c**)



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 ynones 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.[12] 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 $NaBH_4$ (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 Na_2SO_4 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 Na_2SO_4 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**.[5c]

General Procedure for Deoxygenation of Isotellurazole *Te*-Oxide Oligomers 6 by Treating with Ph_3P and I_2. A CH_2Cl_2 solution of isotellurazole *Te*-oxide oligomer **6** (0.349 mmol) was treated with Ph_3P (183 mg, 0.698 mmol, 2.0 equiv.) and I_2 (89 mg, 0.349 mmol, 1.0 equiv.) at 0 °C for 3 h. The reaction was then quenched by addition of saturated aqueous Na_2SO_3 solution, and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with water and was dried over anhydrous Na_2SO_4 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**.[7b]

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 = CO_2Me), **12** (EWG = CN), or **13** (EWG = CHO), respectively, in moderate to high yields.

11a ($R^1 = C_6H_5$, R^2 = H, $R^3 = C_6H_5$, EWG = CO_2Me)[5w,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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.3 (q), 122.8 (d), 128.0 (d), 128.3 (s), 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 ($R^1 = n$-C_4H_9, R^2 = H, $R^3 = C_6H_5$, EWG = CO_2Me): 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9 (q), 22.6 (t), 32.7 (t), 32.9 (t), 52.3 (q), 122.7 (d), 128.3 (d), 128.5 (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 $C_{17}H_{19}NO_2$: *m/z* 269.1416. Found: *m/z* 269.1420.

11c (R^1 = Me, R^2 = H, $R^3 = C_6H_5$, EWG = CO_2Me): Colorless oil; IR (neat) 1729, 1584, 1572, 1461, 1440, 1401, 1309, 1275, 1241, 1189, 1132, 1107, 1078, 1065, 832, 765, 700, 593 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6 (q), 52.4 (q), 123.7 (d), 128.3 (d), 128.5 (d), 128.8 (d), 129.0 (s), 140.1 (s), 145.7 (s), 149.9 (d), 156.7 (s), 169.4 (s). HRMS Calcd for $C_{14}H_{13}NO_2$: *m/z* 227.0946. Found: *m/z* 227.0946.

12c (R^1 = Me, R^2 = H, $R^3 = C_6H_5$, EWG = CN): Pale yellow oil; IR (neat) 3059, 2223, 1571, 1460, 1440, 1396, 837, 794, 750, 698, 591, 430 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.65 (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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{13}H_{10}N_2$: *m/z* 194.0844. Found: *m/z* 194.0843.

13c (R^1 = Me, R^2 = H, $R^3 = C_6H_5$, 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{13}H_{11}NO$: *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 = CO_2Me, 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 $NaHCO_3$ aqueous solution, and the reaction mixture was extracted with $CHCl_3$ for three times. The organic layer was washed with water, and was dried over anhydrous Na_2SO_4 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 ($R^1 = C_6H_5$, R^2 = H, minor)[5u]: 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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' ($R^1 = C_6H_5$, R^2 = 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{18}H_{11}NO$: C, 84.03; H, 4.31; N, 5.44%. Found: C, 84.08; H, 4.58; N, 5.40%.

14b (R^1= *n*-C_4H_9, R^2 = 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%. Found: C, 80.98; H, 6.49; N, 5.83%.

14c (R^1 = Me, R^2 = H)[1a,4b,5n]: 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, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $NaHCO_3$ aqueous solution, and the reaction mixture was extracted with $CHCl_3$ for three times. The organic layer was washed with water, and was dried over anhydrous Na_2SO_4 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 (R^1 = Me, R^2 = H, R^3 = C_6H_5, EWG = $CONH_2$): 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, 700, 685, 634, 597, 448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{13}H_{12}N_2O$: *m/z* 212.0950. Found: *m/z* 212.0956.

Procedure for $NaClO_2$ Oxidation of Pyridine 13c. Pyridine **13c** (EWG = CHO, 72 mg, 0.365 mmol) was solved in a mixed solvent of *t*-BuOH (3.7 mL) and water (2.6 mL), and the solution was treated with $NaClO_2$ (86 mg, 0.949 mmol, 2.6 equiv.) and NaH_2PO_4•$2H_2O$ (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 Na_2SO_4 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 (R^1 = Me, R^2 = H, R^3 = C_6H_5, EWG = COOH)[5a]: Colorless solid, mp 204.0-205.0 °C [Lit.[14] 214.0-216.0 °C]; ^1H NMR (500 MHz, DMSO-d_6) 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).

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