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Synthesis and metallation of 2-(pyridyl)benzoic acids and ethyl 2-(pyridyl)benzoates: a new route to azafluorenones

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Abstract—The ring deprotonation of 2-(2- and 4-pyridyl)benzoic acids using lithium dialkylamides in THF at rt, and the in situ cyclization afforded 4- and 2-azafluorenones, respectively. 1-Azafluorenone was obtained from ethyl 2-(3-pyridyl)benzoate using a similar protocol.

1. Introduction

The directed *ortho*-metallation plays an important role in the modern organic synthesis.[1] Despite the maturity gained by the method since long, the way a substituent acts in its vicinity is not completely understood.

A heteroatom-containing unit (known as the directed metallation group, DMG) coordinates the base and, by amplifying this interaction at the transition state, lowers the energy of activation for the deprotonation process; it also stabilizes the 'metallated' derivative. However, while an electron-donating substituent only facilitates the deprotonation at nearby sites (not necessarily at the *ortho* position) through coordination to the Lewis acidic metal, an electron-withdrawing substituent too acidifies the ring hydrogens in its environment (mostly at the *ortho* position).[2]

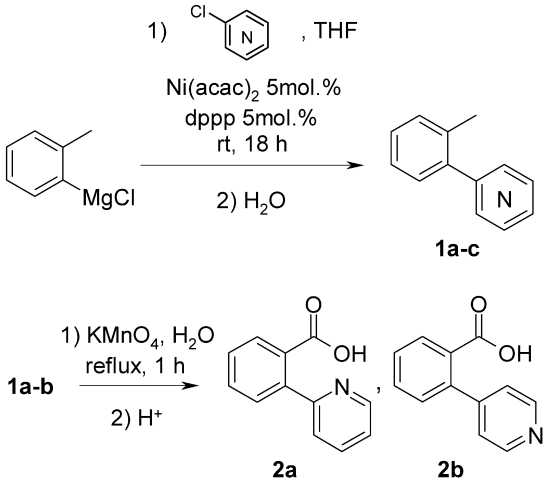
From all the directing groups, the carboxylic acid and derived functions stand out as particularly useful for subsequent elaborations. In the π-deficient aza-aromatic series, lithium pyridinecarboxylates, pyridineoxazolines and pyridinecarboxamides have been deprotonated at ring positions adjacent to the DMG.[3] Moreover, studies concern the deprotonation of a pyridine ring followed by in situ condensation with remote *N*,*N*-dialkylcarboxamide groups[2d,4] or ester function.[5]

Because of our interest in the lithiation of unprotected azinecarboxylic acids,[6] we decided to synthesize 2-(pyridyl)benzoic acids and to study their metallation. The behavior of the corresponding ethyl esters was also investigated.

2. Results and discussion

For this purpose, all the 2-(pyridyl)benzoic acids (**2a** and **c**) were synthesized.

First, the (2-methylphenyl)pyridines **1a**–**c** were easily prepared by cross-coupling reactions between 2-methylphenylmagnesium chloride and the required chloropyridines under nickel catalysis.[7] Next, oxidation of the compounds **1a** and **b** was performed using a published procedure,[8] to furnish the corresponding benzoic acids **2a** and **b** (Scheme 1, Table 1).



Scheme 1.

Keywords: metallation; pyridines; carboxylic acids; esters.

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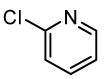
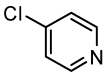
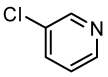
Table 1. Synthesis of the 2-(pyridyl)benzoic acids **2a** and **b**

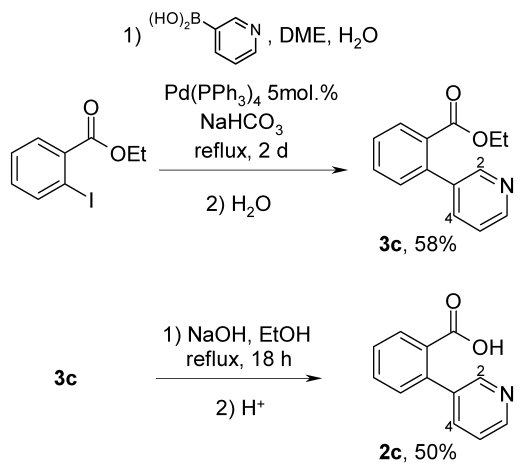
Entry	Chloropyridine	Product, yield (%)[a]
1		**1a**, 88 **2a**, 65
2		**1b**, 92 **2b**, 56
3		**1c**, 50

[a] Isolated yields based on the starting chloropyridine.

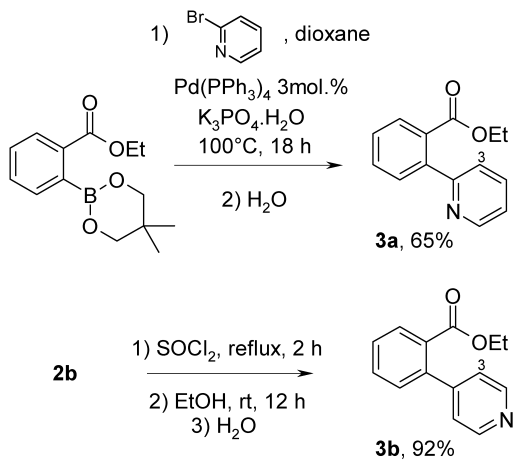
To obtain acid **2c**, another two steps synthesis was preferred: cross-coupling reaction between 3-pyridylboronic acid[9] and ethyl 2-iodobenzoate under Suzuki's conditions[10] allowed the ester **3a** to be obtained, the latter was then hydrolyzed to give compound **2c** (Scheme 2).

The two other ethyl 2-(pyridyl)benzoates **3a** and **b** were prepared. Cross-coupling reaction was led from 2-bromopyridine and ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate, as described[11] by Vedsø and co-workers for the syntheses of substituted biphenyls, to give the ester **3a**. Esterification of the carboxylic acid **2b** furnished the ester **3b** (Scheme 3).

First examples of metallation and subsequent intramolecular condensation with a remote metal carboxylate unit were reported by Snieckus and co-workers in the triphenylphosphine oxide,[12] 1,1′-oxybis[benzene][4] and 1,1′-sulfonylbis[benzene][4] series using lithium diisopropylamide (LDA). Studies of Mortier and co-workers showed more recently that the Schlosser–Lochmann base LICKOR,[13] when used in benzene at 60°C, allowed [1,1′-biphenyl]-2-carboxylic acid to be deprotonated, the intermediate at C2′ instantaneously cyclizing to fluorenone.[14] Since the alkyllithiums are renowned for undergoing a facile nucleophilic addition to the C=N bond of the azines (low LUMO energy values),[3] we turned to the lithium dialkylamides, which usually leads to preferential protophilic attack,[3] to conduct experiments on the 2-(pyridyl)benzoic acids **2a**–**c**.



Scheme 2.

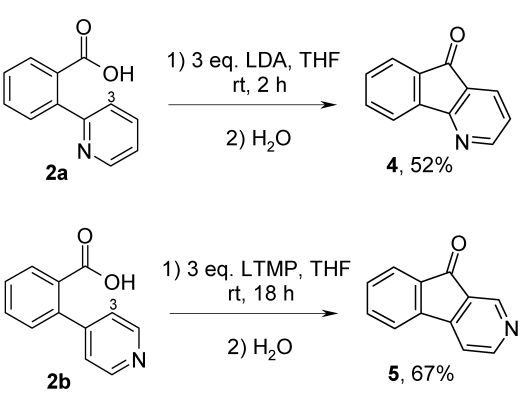


Scheme 3.

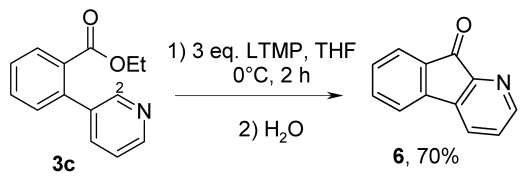
Interestingly, when exposed to LDA in tetrahydrofuran (THF) at rt, the acid **2a** was deprotonated and the lithio derivative at the remote pyridine position was converted in situ to 4-azafluorenone (**4**). For the acid **2b**, the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP, pK_a 37.3 against 35.7 for LDA) and a longer reaction time led to 2-azafluorenone (**5**) in 67% yield (Scheme 4).

On the other hand, the acid **2c** either remained unchanged or underwent degradation reactions on exposure to the lithium dialkylamides, depending on the conditions used. This observation could be interpreted by comparing the stabilities of the pyridyllithiums formed. The 3-pyridyllithiums obtained from **2a** and **b** react with the carboxylate group at rt. A more stable 4-pyridyllithium,[3] which could result either from a direct lithiation of **2c** at C4, or an isomerization of a 2-pyridyllithium initially formed, could be inert towards the function under the conditions used.[15]

Metallation of pyridine rings with a remote methyl ester function, followed by condensation to azaanthraquinones, was reported by Epsztajn and co-workers using LDA.[5] Nevertheless, a survey of the literature revealed that LTMP was capable of deprotonate ethyl benzoate at the *ortho* position while LDA was found to react with the function.[11] We thus decided to examine the behavior of the ethyl 2-(pyridyl)benzoates **3a**–**c**, carrying out the reaction with LTMP.



Scheme 4.



Scheme 5.

The ester **3c** could be easily deprotonated at C2′ using LTMP in THF at 0°C, and converted in situ to 1-azafluorenone (**6**) (Scheme 5).

The kinetic lithio derivative formed at C2′ (chelation of the lithium atom of the base by both the ester function and the ring nitrogen) is intercepted through cyclization before isomerization to a more stable lithio derivative at C4′ (no more electronic repulsion between the carbanion and the lone pair of the azine nitrogen).[3]

Unlike the ester **3c**, when the isomers **3a** and **b** were involved in a reaction using the same base, they either remained unchanged or underwent degradation reactions at higher temperatures. The difficulty of the ester function to compete with the pyridine nitrogen in chelating the lithium atom of the base could be responsible for the result observed.

3. Conclusion

We have described syntheses of 1-, 2- and 4-azafluorenones, using as the key step the tandem metallation—in situ cyclization of ethyl 2-(3-pyridyl)benzoate, 2-(4-pyridyl)-benzoic acid and 2-(2-pyridyl)benzoic acid, respectively.

Whereas the ethyl ester function seems to behave mostly as an in situ trap, the lithium carboxylate could both chelate the Lewis acidic metal of the base and stabilize the lithio derivative formed.

The azafluorenones are common skeletons in natural products and molecules of pharmacological interest. We provide a regiospecific method for building these structures under mild anionic conditions thus superceding classical methods requiring harsh conditions that are of limited scope.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Bruker AM 300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were recorded with a Jeol JMS-AX500 spectrometer, and the molecular peak is given. IR spectra were taken on a Perkin–Elmer FT IR 205 spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

Starting materials. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[16] Reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. 2-Methylphenylmagnesium chloride (1.0 M) in THF, *i*PrMgCl (2.0 M) in THF, and BuLi (2.5 M) in hexane were purchased from Aldrich. Ethyl 2-iodobenzoate was supplied by Lancaster, $Ni(acac)_2$ by Acros, and dppp by Lancaster. $Pd(PPh_3)_4$,[17] ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate,[11] and 3-pyridylboronic acid[9] were prepared according to published procedures. Petrol refers to petroleum ether (bp 40–60°C).

Unless otherwise noted, the aqueous solution was extracted several times with CH_2Cl_2 after the reaction. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and the crude compound was chromatographed on a silica gel column (eluent is given in the product description).

4.2. General procedure 1: preparation of 2-, 3- and 4-(2-methylphenyl)pyridines (1a–c)

$Ni(acac)_2$ (13 mg, 50 μmol), dppp (21 mg, 50 μmol) and, 10 min later, the halo derivative (1.0 mmol) were added to THF (3 mL). 2-Methylphenylmagnesium chloride (1.2 mmol) was added dropwise at rt. After stirring for 18 h at rt, the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL).

4.2.1. 2-(2-Methylphenyl)pyridine (1a). The general procedure 1, starting from 2-chloropyridine (95 μL), gave **1a** (eluent: CH_2Cl_2) as a pale yellow oil. Yield: 88%. The spectral data are in accordance with those described.[18]

4.2.2. 4-(2-Methylphenyl)pyridine (1b). The general procedure 1, starting from 4-chloropyridinium chloride (0.15 g), and using 2-methylphenylmagnesium chloride (2.4 mmol), gave **1b** (eluent: CH_2Cl_2) as a colorless oil. Yield: 92%. The ^1H NMR data are in accordance with those of the literature;[19] ^{13}C NMR ($CDCl_3$) δ 20.6 (Me), 124.6 ($C_{3,5}$), 126.5 ($C_{4'}$), 128.8 ($C_{6'}$), 129.6 ($C_{5'}$), 131.0 ($C_{3'}$), 135.4 ($C_{1'}$), 139.5 ($C_{2'}$), 150.0 ($C_{2,6}$), 150.2 (C_4); IR (KBr) ν 3401, 3063, 3023, 1595, 1542, 1480, 1409, 830, 762, 747, 726, 618 cm^{-1}; mass (CI): *m*/*z* 170 (100%, $M+H^+$).

4.2.3. 3-(2-Methylphenyl)pyridine (1c).[20] The general procedure 1, starting from 3-chloropyridine (95 μL), gave **1c** (eluent: petrol/AcOEt 95:5) as a colorless oil. Yield: 50%. The spectral data are in accordance with those described;[19,20] IR (KBr) ν 3369, 3021, 2953, 2924, 1588, 1562 cm^{-1}.

4.3. Preparation of 2-(2-, 3- and 4-pyridyl)benzoic acids (2a–c)

4.3.1. 2-(2-Pyridyl)benzoic acid (2a). The title compound was prepared according to a described procedure.[8] Yield: 65%; mp 200–202°C (lit.[8] 202°C). The ^1H NMR data are in accordance with those of the literature;[8] ^{13}C NMR (DMSO-d_6) δ 122.6 ($C_{3'}$), 123.1 ($C_{5'}$), 128.6 (C_4), 129.3 (C_5), 130.1 (C_3), 130.9 (C_6), 133.5 (C_1), 136.9 ($C_{4'}$), 140.3 (C_2), 149.1 ($C_{6'}$), 158.3 ($C_{2'}$), 170.1 (CO); IR (KBr) ν 3085, 2772, 2452, 1689, 1599, 1564 cm^{-1}.

4.3.2. 2-(4-Pyridyl)benzoic acid (2b).[21] A mixture of **1b** (1.7 g, 10 mmol) and water (20 mL) was heated under reflux with $KMnO_4$ (1.8 g, 11 mmol). After removal of the coloration, and addition of $KMnO_4$ (1.5 g, 9.5 mmol) and water (10 mL), reflux was pursued similarly. After filtration over celite®, the aqueous phase was washed with Et_2O and then acidified to pH 5 using a 3 M aqueous solution of hydrochloric acid. Compound **2b** was recovered by filtration and drying under vacuum. Yield: 56%; mp 180°C; ^{1}H NMR (DMSO-d_6) δ 7.40 (d, 2H, J=6.0 Hz, $H_{3',5'}$), 7.47 (d, 1H, J=7.5 Hz, H_3), 7.61 (t, 1H, J=7.5 Hz, H_5), 7.70 (t, 1H, J=7.5 Hz, H_4), 7.90 (d, 1H, J=7.5 Hz, H_6), 8.64 (d, 2H, J=6.0 Hz, $H_{2',6'}$); ^{13}C NMR (DMSO-d_6) δ 123.8 ($C_{3',5'}$), 128.8 (C_5), 130.0 (C_2), 130.7 (C_3), 131.8 (C_4), 131.9 (C_1), 139.3 (C_6), 149.1 ($C_{4'}$), 149.5 ($C_{2',6'}$), 169.1 (CO); IR (KBr) ν 3075, 3050, 2373, 1945, 1686, 1612, 1478, 1413, 1273, 1009, 842, 765, 625 cm^{-1}. Anal. calcd for $C_{12}H_9NO_2$ (199.21): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.11; H, 4.44; N, 6.93%.

4.3.3. 2-(3-Pyridyl)benzoic acid (2c). A mixture of **3c** (0.91 g, 4.0 mmol) and NaOH (0.32 g, 8.0 mmol) in EtOH was heated under reflux for 18 h. After removal of the solvent, the residue was dissolved in water (10 mL) and the pH was adjusted to 6. The precipitate thus obtained was recovered by filtration and dried under vacuum to give **2c**. Yield: 50%; mp 180°C; ^{1}H NMR (DMSO-d_6) δ 7.3 (m, 2H, $H_{3,5'}$), 7.39 (td, 1H, J=7.5, 0.75 Hz, H_5), 7.49 (td, 1H, J=7.1, 1.1 Hz, H_4), 7.63 (dt, 1H, J=7.9, 1.9 Hz, $H_{4'}$), 7.71 (dd, 1H, J=7.5, 1.1 Hz, H_6), 8.39 (d, 1H, J=1.9 Hz, $H_{2'}$), 8.43 (dd, 1H, J=4.9, 1.1 Hz, $H_{6'}$); ^{13}C NMR (DMSO-d_6) δ 123.4 ($C_{5'}$), 128.3 ($C_{4'}$), 130.0 (C_3), 131.1 (C_5), 131.4 (C_4), 136.1 (C_6), 137.2 ($C_{3'}$), 138.2 (C_1), 148.4 ($C_{6'}$), 148.9 ($C_{2'}$), 153.3 (C_2), 169.4 (CO); IR (KBr) ν 3425, 3067, 2961, 1601, 1290, 1048, 818, 754, 702 cm^{-1}. Anal. calcd for $C_{12}H_9NO_2$ (199.21): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.09; H, 4.28; N, 6.79%.

4.4. Preparation of ethyl 2-(2-, 3- and 4-pyridyl)benzoates (3a–c)

4.4.1. Ethyl 2-(2-pyridyl)benzoate (3a).[22] A degassed mixture of 2-bromopyridine (0.11 mL, 1.2 mmol), $Pd(PPh_3)_4$ (35 mg, 30 μmol), dioxane (10 mL), ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (0.26 g, 1.0 mmol), and $K_3PO_4{\cdot}3H_2O$ (0.53 g, 2.0 mmol) was heated at 100°C for 18 h. The solvents were removed under reduced pressure and water (10 mL) was added. Yield (eluent: CH_2Cl_2/Et_2O 95:5): 65%; pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.1 Hz, Me), 4.05 (q, 2H, J=7.1 Hz, CH_2), 7.17 (dd, 1H, J=7.1, 5.6 Hz, $H_{5'}$), 7.4 (m, 2H, $H_{4,3'}$), 7.5 (m, 2H, $H_{6,4'}$), 7.65 (td, 1H, J=7.5, 1.5 Hz, H_5), 7.75 (d, 1H, J=7.1 Hz, H_3), 8.55 (d, 1H, J=4.9 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 14.2 (Me), 61.3 (CH_2), 122.4 ($C_{3'}$), 123.2 ($C_{5'}$), 128.7 (C_5), 130.1 (C_3), 130.1 (C_4), 131.5 (C_6), 132.2 (C_1), 136.6 ($C_{4'}$), 141.4 (C_2), 149.4 ($C_{6'}$), 159.2 ($C_{2'}$), 169.2 (CO); IR (KBr) ν 3423, 3068, 2983, 2898, 1725, 1588 cm^{-1}. Anal. calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 74.01; H, 5.73; N, 6.17%.

4.4.2. Ethyl 2-(4-pyridyl)benzoate (3b). A mixture of **2b** (2.4 g, 12 mmol) and $SOCl_2$ (30 mL) was heated under reflux for 2 h. After removal of the excess of $SOCl_2$, EtOH (40 mL) was introduced dropwise at 0°C. After 12 h at rt, EtOH was evaporated and water (10 mL) was added. Yield (eluent: CH_2Cl_2/Et_2O 80:20): 92%; mp 67°C; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.1 Hz, Me), 4.05 (q, 2H, J=7.1 Hz, CH_2), 7.18 (d, 2H, J=5.7 Hz, $H_{3',5'}$), 7.25 (dd, 1H, J=7.6, 1.5 Hz, H_3), 7.42 (td, 1H, J=7.5, 1.1 Hz, H_4), 7.48 (td, 1H, J=7.5, 1.5 Hz, H_5), 7.86 (dd, 1H, J=7.5, 1.1 Hz, H_6), 8.56 (d, 2H, J=5.7 Hz, $H_{2',6'}$); ^{13}C NMR ($CDCl_3$) δ 12.6 (Me), 60.1 (CH_2), 122.5 (C_5), 127.3 (C_3), 129.2 (C_4), 129.3 ($C_{3',5'}$), 129.6 (C_2), 130.6 (C_6), 138.9 (C_1), 148.3 ($C_{2',6'}$), 148.6 ($C_{4'}$), 166.7 (CO); IR (KBr) ν 3035, 2977, 2903, 1702, 1598, 1300, 1138, 834, 766, 710 cm^{-1}. Anal. calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.72; H, 5.62; N, 6.02%.

4.4.3. Ethyl 2-(3-pyridyl)benzoate (3c). A degassed mixture of ethyl 2-iodobenzoate (0.28 g, 1.0 mmol), $Pd(PPh_3)_4$ (58 mg, 50 μmol), dimethoxyethane (8 mL), 3-pyridylboronic acid (0.13 g, 1.1 mmol), $NaHCO_3$ (0.25 g, 3.0 mmol), and water (4 mL) was heated under reflux for 2 days. The solvents were removed under reduced pressure and water (10 mL) was added. Yield (eluent: CH_2Cl_2/Et_2O 95:5): 58%; pale yellow oil. The spectral data are in accordance with those described;[23] ^{13}C NMR ($CDCl_3$) δ 14.1 (Me), 61.4 (CH_2), 123.1 ($C_{3'}$), 128.4 ($C_{5'}$), 130.8 (C_3), 131.1 ($C_{4'}$), 131.2 (C_5), 132.0 (C_4), 136.1 (C_6), 137.7 (C_1), 139.4 (C_2), 148.6 ($C_{6'}$), 149.4 ($C_{2'}$), 168.1 (CO); IR (KBr) ν 3420, 2982, 1715, 1600, 1410, 1288, 1253, 1131, 1092, 760, 713 cm^{-1}. Anal. calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.75; H, 6.02; N, 6.24%.

4.5. Preparation of 1-, 2- and 4-azafluorenones (4–6)

4.5.1. 5*H*-Indeno(1,2-*b*(pyridin-5-one (4,4-azafluorenone). To a solution of **2a** (0.10 g, 0.50 mmol) in THF (3 mL) at 0°C was added a solution of LDA (obtained by adding BuLi (1.5 mmol) to a solution of diisopropylamine (0.22 mL, 1.6 mmol) in THF (2 mL) at 0°C(. The mixture was stirred at rt for 2 h before hydrolysis with water (2 mL). Yield (eluent: CH_2Cl_2/Et_2O 90:10): 52%; mp 139–140°C (lit.[24] 138–140°C). The ^{1}H NMR data are in accordance with those of the literature;[24] ^{13}C NMR ($CDCl_3$) δ 121.4 (C_3), 123.7 (C_9), 124.6 (C_4), 131.4 (C_7), 131.8 (C_6), 135.2 (C_c), 135.8 (C_8), 143.9 (C_a), 154.5 (C_2), 155.7 (C_b), 165.5 (C_d), 192.2 (CO); IR (KBr) ν 3065, 2984, 1836, 1715, 1592, 1405, 1259, 1092, 1021, 743 cm^{-1}.

4.5.2. 9*H*-Indeno(2,1-*c*(pyridin-9-one (5,2-azafluorenone). To a solution of **2b** (0.10 g, 0.50 mmol) in THF (3 mL) at 0°C was added a solution of LTMP (obtained by adding BuLi (1.5 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.6 mmol) in THF (2 mL) at 0°C(. The mixture was stirred at rt for 18 h before hydrolysis with water (2 mL). Yield (eluent: CH_2Cl_2/Et_2O 90:10): 67%; mp 157°C (lit.[25] 156–157°C). The spectral data are in accordance with those described;[25] ^{13}C NMR ($CDCl_3$) δ 115.8 (C_4), 122.3 (C_5), 125.1 (C_8), 128.7 (C_a), 131.9 (C_7), 134.3 (C_b), 135.4 (C_6), 142.2 (C_d), 145.5 (C_1), 152.2 (C_c), 156.2 (C_3), 193.0 (CO). Anal. calcd for $C_{12}H_7NO$ (181.20): C, 79.55; H, 3.89; N, 7.73. Found: C, 79.27; H, 4.12; N, 7.64%.

4.5.3. 9*H*-Indeno(2,1-*b*(pyridin-9-one (6,1-azafluorenone). To a solution of **3c** (0.10 g, 0.44 mmol) in THF (3 mL) at 0°C was added a solution of LTMP (obtained by adding BuLi (1.3 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.24 mL, 1.4 mmol) in THF (2 mL) at 0°C). The mixture was stirred at 0°C for 2 h before hydrolysis with water (2 mL). Yield (eluent: CH_2Cl_2/Et_2O 95:5): 70%; mp 125–127°C (lit.[25] 126–127°C). The IR data are in accordance with those described;[25] ^{1}H NMR ($CDCl_3$) δ 7.25 (dd, 1H, J=7.5, 4.9 Hz, H_3), 7.3 (m, 1H, H_7), 7.47 (m, 2H, $H_{5,6}$), 7.67 (d, 1H, J=7.2 Hz, H_8), 7.77 (dd, 1H, J=7.5, 1.1 Hz, H_4), 8.51 (dd, 1H, J=4.9, 1.1 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 120.1 (C_5), 123.9 (C_3), 126.1 (C_7), 126.8 (C_8), 129.1 (C_4), 131.4 (C_b), 134.5 (C_6), 140.0 (C_c), 140.6 (C_d), 149.4 (C_2), 152.2 (C_a), 191.5 (CO); mass (EI): *m*/*z* 181.

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