JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

Synthesis of Carbolines by Photostimulated Cyclization of Anilinohalopyridines

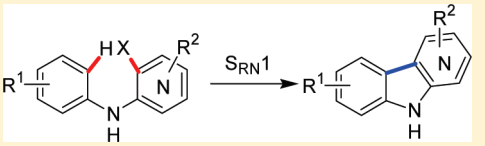
Joydev K. Laha,[†] Silvia M. Barolo,[‡] Roberto A. Rossi,*[,‡] and Gregory D. Cuny*[,†]

[†]Laboratory for Drug Discovery in Neurodegeneration, Harvard NeuroDiscovery Center, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne Street, Cambridge, Massachusetts 02139, United States

[‡]INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, Argentina

Supporting Information

ABSTRACT: A general synthetic route to prepare all four carboline regioisomers by photostimulated cyclization of anilinohalopyridines is described. The methodology affords various substituted carbolines in good to excellent yields. In the case of α-carbolines, the $S_{RN}1$ methodology complements previously reported palladium-catalyzed cyclization approaches.



Carbolines (pyrido[*x*,*y*-*b*]indoles), **1** (Figure 1), are a prominent class of nitrogen-containing heterocycles that comprise many natural products and bioactive compounds.[1−5] Depending upon the position of the nitrogen present in the fused pyridine ring, four regioisomers of carbolines are known. From among them, β-carbolines (pyrido[3,4-*b*]indoles) are most widely distributed in nature. Compounds containing β-carbolines have been found to exhibit a wide range of biological activities, such as central nervous system (CNS) and antitumor properties (e.g., I_KB kinase and PDE5 inhibition).[1] γ-Carbolines (pyrido[4,3-*b*]-indoles) can also be found in various natural products and in a number of antitumor agents.[2] The natural abundance of α- and δ-carbolines (pyrido[2,3-*b*]indoles and pyrido[3,2-*b*]indoles, respectively) has so far been more limited, however, to only a few sources. For example, the α-carboline natural product mescengricin has been isolated from *Streptomyces griseoflavus* and reported to inhibit L-glutamate excitotoxicity in neurons.[3]

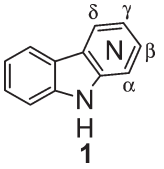
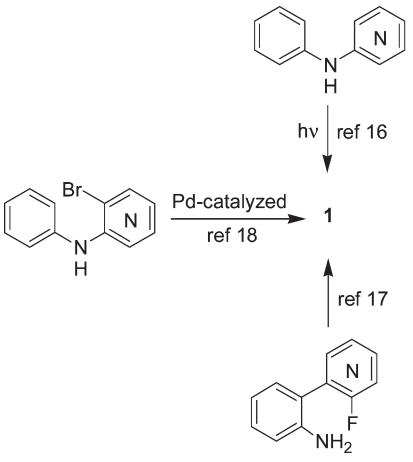


Figure 1. General structure of carbolines.

Several synthetic α-carbolines have also been shown to have an array of biological properties, such as anxiolytic, anti-inflammatory, and CNS-stimulating activities.[4] δ-Carbolines have been studied extensively for antitumor and antibiotic properties.[5]

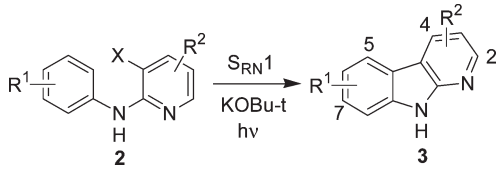
Although various synthetic strategies to one[1,2,6−9] or more carboline regioisomers[10−15] have been previously reported, general approaches that allowed access to the synthesis of all four carboline regioisomers have been limited. Clark et al. reported the photocyclization of anilinopyridines to give carbolines, often as a mixture of regioisomers (eq 1).[16] Quéguiner et al. employed a combination of palladium-catalyzed cross-couplings of iodofluoropyridines with aminophenylboronic acids followed by intramolecular nucleophilic substitutions.[17] Sakamoto et al. reported a two-step approach that consists of palladium-catalyzed amination followed by intramolecular arylation of anilinobromopyridines, which allowed access to the four parent carboline regioisomers in 31−61% yield.[18]



Recently, we described a one-pot synthesis of α-carbolines via palladium-catalyzed sequential aryl amination of anilines and 2,3-dihalopyridines followed by intramolecular arylation of the 2-anilino-3-halopyridine intermediates.[6b] Although a variety of α-carbolines were obtained in moderate to excellent yields using this methodology, some limitations were encountered.

Received: May 13, 2011
Published: July 08, 2011

Table 1. Synthesis of Substituted α-Carbolines by Photostimulated $S_{RN}1$ Reaction[a]

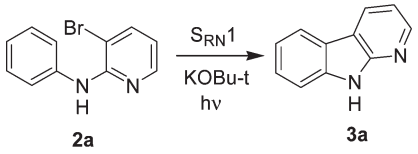


entry	substrate	X	R^1	R^2	product	yield[b] (%)
1	**2b**	Cl	H	H	**3a**	75
2[c]	**2c**	Br	H	2-OEt	**3b**	63
3	**2d**	Br	H	3-Me	**3c**	90
4	**2e**	Cl	H	4-Me	**3d**	84
5	**2f**	Br	6-CO_2Bu-*t*	H	**3e**	79
6	**2g**	Cl	6-CN	H	**3f**	51
7	**2h**	Cl	7-OBn	H	**3g**	37
			5-OBn	H	**3h**	19
8	**2i**	Cl	5-OMe	4-Me	**3i**	54
			7-OMe	4-Me	**3j**	21
9	**2j**	Cl	5,7-di-OMe	H	**3k**	90
10	**2k**	Cl	5,8-di-Me	H	**3l**	67

[a] Condition A: liquid NH_3, *hν*, 60 min. [b] Isolated yield. [c] 120 min.

For example, poor yields of α-carbolines were observed with 4-, 5-, or 6-substituted 2,3-dihalopyridines. Similar results were obtained with anilines containing electron-donating substituents in the 2,5- or 3,5-positions. In many instances, these one-pot reactions did produce the 2-anilino-3-halopyridine intermediates in good yields but failed to cyclize to α-carbolines. On the basis of these limitations, an alternate method was sought for the synthesis of α-carbolines that would also be applicable to *β*-, *γ*-, and *δ*-carbolines.

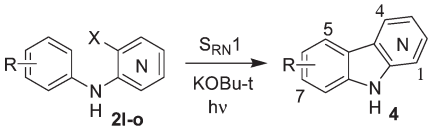
The unimolecular radical nucleophilic substitution ($S_{RN}1$) reaction is a synthetically useful process to mediate aromatic nucleophilic substitutions for the preparation of carbocycles and heterocycles.[19,20] For example, Rossi et al. has recently demonstrated the application of $S_{RN}1$ reactions in the synthesis of substituted carbazoles in excellent yields (81−99%).[21] Herein is described a general method for the synthesis of all four carboline regioisomers from anilinohalopyridines using photostimulated $S_{RN}1$ reactions.

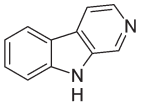
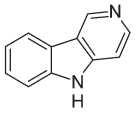
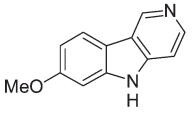
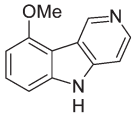
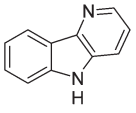


(2)

The application of $S_{RN}1$ reactions to the synthesis of α-carbolines was initially studied with 3-bromo-*N*-phenylpyridin-

Table 2. Synthesis of *β*-, *γ*-, and *δ*-Carbolines by Photostimulated $S_{RN}1$ Reaction[a]



Entry	Substrate	X	N[b]	R	Condition[a]	Product[c]	Yield (%)
1	**2n**	Br	2	H	A	 **4a**	70
2	**2n**	Br	2	H	B[d]	**4a**	70[e]
3	**2l**	Cl	3	H	A	 **4b**	72
4	**2m**	Cl	3	7-OMe or 5-OMe	A	 **4c** +  **4d**	ca. 70[f]
5	**2o**	Br	4	H	A	 **4e**	80
6	**2o**	Br	4	H	B	**4e**	76

[a] Condition A: liquid NH_3, *hν*, 60 min. Condition B: DMSO, *hν*, 60 min. [b] Position of nitrogen. [c] Isolated yields. [d] 180 min. [e] Determined by gas chromatography. [f] **4c**:**4d** ≈ 1:1.

dx.doi.org/10.1021/jo200923n |*J. Org. Chem.* 2011, 76, 6421–6425

2-amine, **2a** (λ_{max} 269 nm in DMSO).[18] Photostimulation for 60 min in the presence of KOBu-*t* (2 equiv) in liquid ammonia under a nitrogen atmosphere (condition A) afforded 88% yield of α-carboline, **3a**[17] (eq 2). A modestly lower yield of **3a** (67%) was obtained when DMSO was used as solvent (condition B). In THF, however, no reaction was observed. As anticipated, no reaction was detected in the absence of light or in the presence of the radical initiator $FeCl_2$, and the photostimulated reaction was partially inhibited by 1,4-dinitrobenzene.[19]

In order to prepare various substituted carbolines, the 2-anilino-3-halopyridines **2c**−**k** were generated from anilines and 2,3-dihalopyridines using a palladium-catalyzed coupling reaction previously described.[6b] Similarly, the substrates **2l** and **2m** were synthesized in 42−45% yield from the corresponding anilines and 3,4-dichloropyridine using a higher catalyst loading. All anilines and dihalopyridines were commercially available, except 4-methyl-2,3-dichloropyridine[22] that was synthesized from 2,3-dichloropyridine using regioselective lithiation chemistry.

Next, the scope of the $S_{RN}1$ reaction for the synthesis of various substituted α-carbolines using condition A was explored. For example, with 3-chloro-*N*-phenylpyridin-2-amine, **2b**,[6b] α-carboline, **3a**, was obtained in 75% yield (Table 1, entry 1), demonstrating that the reaction was useful for both chlorine- and bromine-containing substrates. Next, the method was applied to the synthesis of α-carbolines containing a substituent on either the pyridine or benzene rings. When the photostimulated reactions were carried out with substrates **2c**,[6b] **2d**,[23] or **2e** having a substitution at the 2-, 3-, or 4-positions on the pyridine ring, the corresponding α-carbolines **3b**,[6b] **3c**,[24] and **3d**[25] were obtained in 63−90% yields (entries 2−4). Similarly, substrates **2f**,[6b] **2g**, or **2h** having monosubstitution on the benzene ring also afforded the α-carbolines **3e**,[6b] **3f**,[25] and a separable mixture of **3g**[6b] and **3h**[6b] in moderate yields (entries 5−7). In the case of **2h**, the two regioisomers **3g** and **3h** were generated in a ∼2:1 ratio as determined by ^{1}H NMR. Good yields of α-carbolines were also obtained for a variety of disubstituted anilinohalopyridines (entries 8−10). Substrate **2i** afforded two regioisomeric α-carbolines **3i** and **3j** in 54% and 21% isolated yields (entry 8). The photostimulation of 5,7-dimethoxy- **2j**[6b] or 5,8-dimethylanilinochloropyridines **2k**[6b] produced α-carbolines **3k** and **3l**[6b] in 90% and 67% yields, respectively (entries 9 and 10). In several instances, the $S_{RN}1$ methodology proved more efficient than the previously reported palladium-catalyzed one-pot process. For example, the α-carbolines **3b**, **3e**, and **3l** were obtained in only poor yields (19%, 37%, and 25%, respectively) using the palladium-mediated process, while **3d** and **3k** could not be generated.[6b]

The photostimulated $S_{RN}1$ methodology was further extended to the synthesis of *β*-, *γ*-, and *δ*-carbolines. The photostimulation of 4-bromo-*N*-phenylpyridin-3-amine, **2n**,[18] gave *ss*-carboline **4a**[17] in 70% and 54% yields under conditions A and B, respectively (Table 2, entry 1). A significant amount (12%) of unreacted **2n** was recovered when condition B was used. However, longer photostimulation time (180 min) in DMSO improved the yield of **4a** to 70% (entry 2). *γ*-Carboline **4b**[17] was obtained from 3-chloro-*N*-phenylpyridin-4-amine, **2l**, in 72% yield using condition A (entry 3). Substrate **2m** similarly underwent photostimulated cyclization resulting in an inseparable mixture of regioisomers **4c** and **4d** produced in nearly equal amounts (entry 4). Finally, 2-bromo-*N*-phenylpyridin-3-amine, **2o**,[18] under condition A gave *δ*-carboline **4e**[17] in 80% isolated yield (entry 5). A similar result (76% yield) was obtained using condition B (entry 6).

In summary, a general high yielding method for the synthesis of all four carboline regioisomers by photostimulated $S_{RN}1$ cyclization of anilinohalopyridines has been developed. This process also provides a complementary approach to metal-catalyzed methods for the synthesis of α-carbolines. In some cases, the $S_{RN}1$ reaction was successful when palladium-mediated methods were not. Further exploration of photostimulated $S_{RN}1$ reactions should prove useful for extending this methodology to the synthesis of other heterocyclic systems.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without purification. All palladium-coupling reactions were degassed with argon. The proton and carbon NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 using a 400 or 500 MHz spectrometer and are reported in *δ* units ppm. Coupling constants (*J* values) are reported in Hz. Column chromatography was performed on silica gel (grade 60, 230−400 mesh) or utilizing a CombiFlash Sg 100c separation system with disposable silica gel columns. Mass spectra (MS) were recorded with an ESI source. High-resolution mass spectra were obtained by using a Tesla FTMS. All melting points were taken in glass capillary tubes and are uncorrected. Gas chromatographic (GC) analyses were performed on an instrument with a flame ionization detector equipped with a VF-5 ms column (15 m × 0.25 mm × 0.25 *μ*m). Quantification by GC was performed by the internal standard method. GC-MS analyses were carried out on a spectrometer equipped with a quadrupole detector and a VF-5 ms column (30 m × 0.25 mm × 0.25 *μ*m). The photochemical reactor consists of an oval mirror-type wall of ca. 30 cm maximum radius equipped with two Philips HPI-T 400 W lamps of metallic iodide inserted into a water-refrigerated Pyrex flask placed ca. 20 cm from the reaction vessel. The spectrum of the light source showed five broad emission maxima at about 380, 410, 440, 530, and 570 nm. Potentiometric titrations of halide ions were performed in a pH meter with an Ag/Ag^+ electrode.

All anilines and dihalopyridines except 4-methyl-2,3-dichloropyridine were purchased from commercial vendors.

Synthesis of 4-Methyl 2,3-dichloropyridine (for the preparation of 2e).[22] A solution of 2,3-dichloropyridine (740 mg, 5.00 mmol) in anhydrous THF (10 mL) was treated dropwise with LDA (3 mL, 6.00 mmol, 2 M in THF) at −78 °C for 10 min. After the mixture was stirred for 1 h at −78 °C, CH_3I (850 mg, 6.00 mmol) was added dropwise, and the reaction mixture was allowed to warm to −20 °C over 1 h. At this temperature, the reaction was quenched by adding aqueous NH_4Cl. Excess ethyl acetate was added to the reaction mixture, the organic layer was then washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated. Chromatography [silica, hexane/ethyl acetate (9:1)] of the crude mixture afforded a viscous liquid (665 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 2.40 (s, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 20.8, 124.9, 130.7, 146.3, 148.6, 149.6.

General Procedure for Aryl Amination. A mixture of 2,3-dihalopyridine (1 mmol), aniline (1.1 mmol), $Pd(OAc)_2$ (5−10 mol %), PPh_3 (10−20 mol %), and NaOBu-*t* (1.2 mmol) in 2.5 mL toluene (or *o*-xylene) was degassed with argon for about 5 min and then heated at 120 °C (140 °C in the case of *o*-xylene) for 3−18 h in a screw-capped sample vial. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), and the solution was washed several times with water and then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified

dx.doi.org/10.1021/jo200923n |*J. Org. Chem.* 2011, 76, 6421–6425

by column chromatography on silica gel using hexane/ethyl acetate as eluent (9:1 to 7:3) to give the anilinohalopyridines.

3-Chloro-4-methyl-*N*-phenylpyridin-2-amine (2e): 66% yield; colorless viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.64 (d, J = 4.5 Hz, 1H), 7.02−7.06 (m, 2H), 7.32−7.36 (m, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.99 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 115.3, 116.2, 117.4, 120.1, 122.7, 129.0, 140.1, 144.8, 145.5, 145.9, 151.4; HRMS obsd 219.0683, calcd 219.0681 for $C_{12}H_{12}N_2Cl$ (M + H).

3-Chloro-*N*-(4-cyano)-phenylpyridin-2-amine (2g): 67% yield; white solid; mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, J = 7.5, 5.0 Hz, 1H), 7.23 (br, 1H), 7.60−7.63 (m, 2H), 7.65 (dd, J = 7.5, 2.0 Hz, 1H), 7.80−7.84 (m, 2H), 8.20 (dd, J = 5.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.8, 117.0, 117.1, 118.8, 119.6, 133.3, 137.3, 144.0, 145.8, 150.2; HRMS obsd 230.0479, calcd 230.0477 for $C_{12}H_9N_3Cl$ (M + H).

3-Chloro-*N*-(3-benzyloxy)phenylpyridin-2-amine (2h): 69% yield; white solid; mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 2H), 6.69−6.75 (m, 2H), 7.01 (br, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.33−7.37 (m, 1H), 7.39−7.43 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.54−7.60 (m, 3H), 8.15 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 106.8, 109.2, 112.6, 115.4, 116.3, 127.7, 128.1, 128.7, 129.7, 136.8, 137.3, 141.1, 146.0, 151.3, 159.6; HRMS obsd 311.0962, calcd 311.0946 for $C_{18}H_{16}ClN_2O$ (M + H).

3-Chloro-4-methyl-*N*-(3-methoxy)phenylpyridin-2-amine (2i): 65% yield; colorless viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.82 (s, 3H), 6.60 (dd, J = 7.5, 2.0 Hz, 1H), 6.65 (d, J = 4.5 Hz, 1H), 7.04 (br, 1H), 7.11 (dd, J = 7.5, 2.0 Hz, 1H), 7.23 (t, J = 8.5 Hz, 1H), 7.40 (dd, J = 2.5, 2.0 Hz, 1H), 8.00 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 55.4, 105.9, 108.1, 112.4, 116.3, 117.4, 129.7, 141.4, 144.8, 145.5, 151.4, 160.4; HRMS obsd 249.0789, calcd 249.0786 for $C_{13}H_{14}ClN_2O$ (M + H).

3-Chloro-*N*-phenylpyridin-4-amine (2l): 42% yield; white solid; mp 90−92 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.91 (d, J = 6.0 Hz, 1H), 7.15−7.18 (m, 1H), 7.29 (d, J = 7.5 Hz, 2H), 7.38−7.42 m, 2H), 8.08 (d, J = 5.5 Hz, 1H), 8.33 (s. 1H), 8.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.5, 117.7, 123.4, 125.6, 129.9, 138.6, 147.1, 148.6, 149.2; HRMS obsd 205.0527, calcd 205.0527 for $C_{11}H_{10}ClN_2$ (M + H).

3-Chloro-*N*-(3-methoxy)phenylpyridin-4-amine (2m): 45% yield; white solid; mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.46 (br, 1H), 6.74−6.78 (m, 2H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 7.00 (d, J = 5.5 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 8.15 (dd, J = 5.5, 1.5 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 107.9, 109.1, 110.8, 115.4, 117.8, 130.6, 139.8, 147.0, 148.5, 149.2, 160.9; HRMS obsd 235.0632, calcd 235.0628 for $C_{12}H_{12}ClN_2O$ (M + H).

General Procedure for the Synthesis of Carbolines in Liquid Ammonia Exemplified in the Synthesis of 9*H*-Pyrido-[2,3-*b*]indole (3a). Liquid ammonia (150 mL), previously dried over Na metal, was distilled into a 250 mL three-necked, round-bottomed flask equipped with a coldfinger condenser and a magnetic stirrer under a nitrogen atmosphere. KOBu-*t* (45 mg, 0.40 mmol) and **2a** (50 mg, 0.20 mmol) were added to the liquid ammonia and the solution was irradiated for 60 min. The reaction was quenched by addition of excess solid NH_4NO_3, and the ammonia was allowed to evaporate. Water (50 mL) was added to the residue, and the mixture was extracted with dichloromethane (3 × 30 mL). The organic extract was washed with water (2 × 20 mL), dried over anhydrous $MgSO_4$, and then filtered. The solvent was removed under reduced pressure to obtain the crude product. The bromide ions in the aqueous solution were determined potentiometrically.

General Procedure for the Synthesis of Carbolines in DMSO Exemplified in the Synthesis of 9*H*-Pyrido[3,4-*b*]indole (4a). The reaction was carried out in a Schlenk tube equipped with a nitrogen inlet and magnetic stirrer at room temperature. DMSO (5 mL) was dried and deoxygenated, KOBu-*t* (45 mg, 0.40 mmol) was added, **2n** (50 mg, 0.20 mmol) was added, and the reaction mixture was irradiated for 180 min. The reaction was quenched with water and excess solid ammonium nitrate. The residue was extracted with dichloromethane (3 × 30 mL), and the organic extracted was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the crude products. The bromide ions in the aqueous solution were determined potentiometrically.

3-Methyl-9*H*-pyrido[2,3-*b*]indole (3c).[24] Compound **3c** was purified by column chromatography on silica gel eluting with dichloromethane: ethanol (98:2) and then recrystallized from dichloromethane to give white needles: mp 276−277 °C; ^{1}H NMR (400.16 MHz, DMSO-d_6) δ 2.44 (s, 3H), 7.18 (ddd, J = 8.0, 7.0 Hz, 1.2, 1H), 7.40−7.48 (m, 2H), 8.10 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 8.29 (s, 1H), 11.61 (s, 1H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 18.00, 111.12, 114.90, 119.08, 120.13, 121.00, 123.46, 126.36, 128.40, 139.23, 146.47, 150.48; ^{1}H−^{13}C HSQC NMR (DMSO-d_6) δ_H/δ_C 2.44/18.00, 7.18/119.08, 7.40−7.48/111.12, 7.40−7.48/126.36, 8.10/121.00, 8.26/146.47, 8.29/128.40; GC/MS EI m/z 182 (M^+, 100).

4-Methyl-9*H*-pyrido[2,3-*b*]indole (3d).[25] Compound **3d** was purified by recrystallization from dichloromethane to give white crystals: mp 211−212 °C; ^{1}H NMR (400.16 MHz, DMSO-d_6) δ 2.80 (s, 3H), 7.00 (d, J = 4.8 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H); 7.45 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 4.8 Hz, 1H), 11.78 (s, 1H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 19.53, 111.06, 113.96, 116.74, 119.40, 120.82, 122.72, 125.93, 138.58, 141.62, 145.80, 151.82; ^{1}H−^{13}C HSQC NMR (DMSO-d_6) δ_C/δ_H 2.80/19.53, 7.00/116.74, 7.23/119.40, 7.45/125.93, 7.52/111.06, 8.11/122.72, 8.28/145.80; GC/MS EI m/z 182 (M^+, 100).

5-Methoxy-4-methyl-9*H*-pyrido[2,3-*b*]indole (3i). Compound **3i** was purified by column chromatography on silica gel eluting with petroleum ether/ ethyl acetate gradient (75:25 → 30:70) to give white crystals: mp 252−253 °C; ^{1}H NMR (400.16 MHz, DMSO-d_6) δ 2.90 (s, 3H), 3.95 (s, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 8.20 (d, J = 4.8 Hz, 1H), 11.80 (br, 1H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 22.57, 55.14, 100.89, 104.15, 109.97, 113.83, 117.79, 127.35, 140.15, 141.61, 145.05, 151.43, 154.68; ^{1}H−^{13}C HSQC NMR (DMSO-d_6) δ_H/δ_C 2.90/22.57, 3.95/55.14, 6.73/100.89, 6.96/117.79, 7.08/104.15, 7.36/127.35, 8.20/145.05. ^{1}H−^{1}H COSY NMR (DMSO-d_6) δ_H/δ_H 2.90/2.90, 3.95/3.95, 7.36/6.73, 7.36/7.08, 8.20/6.96, 11.80/11.80; GC/MS EI m/z 212 (M^+, 100); HRMS (ESI) m/z obsd 213.1025, calcd 213.1022 for $C_{13}H_{13}N_2O$ (M+ H^+).

7-Methoxy-4-methyl-9*H*-pyrido[2,3-*b*]indole (3j). Compound **3j** was purified by column chromatography on silica gel eluting with petroleum ether: ethyl acetate gradient (75:25 → 30:70) to give light yellow crystals: mp 212−213 °C; ^{1}H NMR (400.16 MHz, DMSO-d_6) δ 2.75 (s, 3H), 3.85 (s, 3H), 6.84 (dd, J = 8.4, 2.0 Hz, 1H), 6.96−6.98 (m, 2H), 7.97 (d, J = 8.6 Hz, 1H), 8.18 (d, J = 4.8 Hz, 1H), 11.64 (s, 1H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 19.36, 55.24, 94.63, 108.42, 114,28, 114.46, 116.75, 123.52, 140.04, 140.10, 144.25, 151.96, 158.52; ^{1}H−^{13}C HSQC NMR (DMSO-d_6) δ_H/δ_C 2.75/19.36, 3.85/55.24, 7.97/123.52, 6.84/108.42, 6.96−6.98/94.63, 6.96−6.98/116.75, 7.97/123.52, 8.18/144.25; ^{1}H−^{1}H COSY NMR (DMSO-d_6) δ_H/δ_H 2.75/2.75, 3.85/3.85, 6.84/6.96−6.98, 6.84/7.97, 6.96−6.98/8.17, 11.64/11.64; GC/MS EI m/z 212 (M^+, 100). HRMS (ESI) m/z obsd 213.1040, calcd 213.1022 for $C_{13}H_{13}N_2O$ (M + H^+).

5,7-Dimethoxy-9*H*-pyrido[2,3-*b*]indole (3k). Compound **3k** was purified by chromatography on silica gel eluting with dichloromethane: ethanol (98:2) and then recrystallized from dichloromethane to give colorless crystals: mp 247−249 °C; ^{1}H NMR (400.16 MHz, DMSO-d_6) δ 3.85 (s, 3H), 3.98 (s, 3H), 6.38 (s, 1H), 6.60 (s, 1H), 7.12 (dd, J = 7.6, 4.8 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 4.8 Hz, 1H), 11.69 (s, 1H); ^{13}C NMR (100.62 MHz, DMSO-d_6) δ 55.44, 55.50, 87.32, 91.29, 103.40, 114.80, 115.12, 128.05, 140.86, 143.34, 151.31, 156.52, 160.46; ^{1}H−^{13}C HSQC NMR (DMSO-d_6) δ_H/δ_C 3.85/55.44,

3.98/55.50, 6.38/91.29, 6.60/87.32, 7.12/115.12, 8.22/128.05, 8.25/143.34; ^{1}H−^{1}H COSY NMR (DMSO-d_6) δ_H/δ_H 3.85/3.85, 3.98/3.98, 6.38/6.60, 6.73/7.36, 7.08/7.36, 6.96/8.20, 11.69/11.69; GC/MS EI m/z 228 (M^+, 100). HRMS (ESI) m/z obsd 229.0977, calcd 229.0972 for $C_{13}H_{13}N_2O_2$ ($M + H^+$).

7-Methoxy-5*H*-pyrido[4,3-*b*]indole (4c). Compound **4c** could not be separated from the mixture of **4c** and **4d**: ^{1}H NMR (400.16 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.81 (dd, J = 8.4, 2.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 9.16 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 55.61, 95.40, 106.44, 109.48, 115.04, 120.64, 121.32, 141.06, 141.66, 142.92, 144.78, 156.16; ^{1}H−^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 6.87/95.40, 6.81/109.48, 7.25/106.44, 7.88/121.32, 8.36/142.92, 9.16/141.06; ^{1}H−^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 3.73/3.73, 6.81/7.88, 6.87/6.87, 7.25/8.36, 9.16/9.16; HRMS obsd 199.0892, calcd for 199.0866 $C_{12}H_{11}N_2O$ ($M + H$).

5-Methoxy-5*H*-pyrido[4,3-*b*]indole (4d). Compound **4d** could not be separated from the mixture of **4c** and **4d**: ^{1}H NMR (400.16 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.63 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.28−7.32 (m, 2H), 8.41 (d, J = 5.6 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 55.52, 101.30, 104.37, 106.24, 111.01, 120.02, 127.98, 141.59, 142.97, 143.94, 144.08, 159.80; ^{1}H−^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 6.63/101.30, 7.05/104.37, 7.28−7.32/106.24, 7.28−7.32/127.98, 8.41/142.97, 9.46/144.08; ^{1}H−^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 3.96/3.96, 6.63/7.28−7.32, 7.05/7.28−7.32, 7.28−7.32/8.41, 9.46/9.46; HRMS obsd 199.0892, calcd for 199.0866 $C_{12}H_{11}N_2O$ ($M + H$).

■ ASSOCIATED CONTENT

Supporting Information. Spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rossi@fcq.unc.edu.ar; gcuny@rics.bwh.harvard.edu.

■ ACKNOWLEDGMENT

We greatly appreciate financial support from the Harvard NeuroDiscovery Center and Consejo Nacional de Investigaciones Científicas y Técnicas, FONCYT and SECYT, Universidad Nacional de Córdoba.

■ REFERENCES

(1) (a) Rosillo, M.; Gonzalez-Gomez, A.; Dominguez, G.; Perez-Castells, J. *Targets Heterocycl. Syst.* **2008**, *12*, 212–257. (b) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479–500.

(2) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 889–925.

(3) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431–3434.

(4) Semenov, A. A.; Tolstikhina, V. V. *Chem. Heterocycl. Compd.* **1984**, 345–356.

(5) Kumar, E. V. K. Suresh; Etukala, J. R.; Ablordeppey, S. Y. *Mini Rev. Med. Chem.* **2008**, *8*, 538–554.

(6) For examples of synthetic approaches to α-carbolines, see ref 4; also see: (a) Chavan, N. L.; Nayak, S. K.; Kusurkar, R. S. *Tetrahedron* **2010**, *66*, 1827–1831. (b) Laha, J. K.; Petrou, P.; Cuny, G. D. *J. Org. Chem.* **2009**, *74*, 3152–3155 and references cited therein.

(7) For examples of synthetic approaches to β-carbolines, see ref 1; also see: Wu, M.; Wang, S. *Synthesis* **2010**, 587–592.

(8) For examples of synthetic approaches to γ-carbolines, see ref 2; also see: (a) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540–1543. (b) Chiba, S.; Xu, Y-J; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886–12887.

(9) For examples of synthetic approaches to δ-carbolines, see: (a) Papamicael, C.; Queguiner, G.; Bourguignon, J.; Dupas, G. *Tetrahedron* **2001**, *57*, 5385–5391. (b) Rao, M. V. B.; Kumar, U. K. S.; Ila, H.; Junjappa, H. *Tetrahedron* **1999**, *55*, 11563–11578. (c) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Heterocycles* **1999**, *50*, 215–226. (d) Trudell, M. L.; Fukada, N.; Cook, J. M. *J. Org. Chem.* **1987**, *52*, 4293–4296. (e) Velezheva, V. S.; Nevskii, K. V.; Suvorov, N. N. *Khim. Geterotsikl. Soedinenii* **1985**, 230–235. (f) Velezheva, V. S.; Yarosh, A. V.; Kozik, T. A.; Suvorov, N. N. *Zh. Org. Khim.* **1978**, *14*, 1712–1723.

(10) Molina, P.; Fresneda, P. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1819–1822.

(11) Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1261–1267.

(12) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740–1743.

(13) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibiho, S. *J. Org. Chem.* **2001**, *66*, 8793–8798.

(14) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318–9330.

(15) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540–1543.

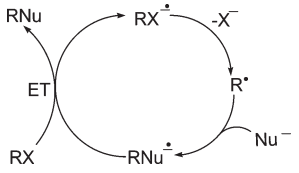
(16) Clark, V. M.; Cox, A.; Herbert, E. J. *J. Chem. Soc. C* **1968**, 831–833.

(17) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 49–64.

(18) Iwaki, T; Yashuara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505–1510.

(19) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71–167.

(20) In the initiation step of the $S_{RN}1$ mechanism (schematic presentation shown below), the radical anion of substrate $RX^{\bullet-}$ can be formed by an electron transfer (ET) from the nucleophile or from a suitable electron source. In some systems the ET step is spontaneous; however, in others, light is required to catalyze the reaction. The $RX^{\bullet-}$ fragments to afford the radical $R^{\bullet}$ and the anion of the leaving group. The radical then reacts with the nucleophile to give a radical anion of the substitution product $RNu^{\bullet-}$, which by ET to the substrate forms the intermediates required to continue the propagation cycle.



(21) Budén, M. E.; Vaillard, V. A.; Martín, S. E.; Rossi, R. A. *J. Org. Chem.* **2009**, *74*, 4490–4498.

(22) Smith, N.; Bonnefous, C.; Govek, S. P.; Wu, D.; Pinkerton, A. B.; Kahraman, M.; Cook, T.; Noble, S. A.; Borchardt, A. J.; Prins, T. *PCT Int. Appl.* WO 2009117421, September 2009.

(23) Adam, M. S. S.; Kindermann, M. K.; Koeckerling, M.; Heinicke, J. W. *Eur. J. Org. Chem.* **2009**, 4655–4665.

(24) Sharbatyan, P. A.; Kost, A. N.; Men'shikov, V. V.; Yudin, L. G.; Chernyshova, N. B. *Khim. Geterotsikl. Soedinenii* **1980**, 1227–1234.

(25) Stephenson, L.; Warburton, W. K. *J. Chem. Soc. C* **1970**, 1355–1364.