Synthesis of 6-Substituted Pyrido[2,3-*b*]indoles by Electrophilic Substitution

Cédric Schneider,[a] David Gueyrard,[a] Florence Popowycz,[b] Benoît Joseph,[b] Peter G. Goekjian*[a]

[a] ICBMS, CNRS, UMR5246, Laboratoire Chimie Organique 2 – Glycochimie, Université de Lyon, Université Lyon 1, Bât. 308, CPE Lyon, 43, Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France
Fax +33(4)72448349; E-mail: peter.goekjian@univ-lyon1.fr

[b] ICBMS, CNRS, UMR5246, Laboratoire Chimie Organique 1, Université de Lyon, Université Lyon 1, Bât. 308, CPE Lyon, 43, Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

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Dedicated to Prof. Yoshito Kishi on the occasion of his 70th birthday

Abstract: Regioselective electrophilic aromatic substitutions, acylation, bromination, and formylation, of unprotected pyrido[2,3-*b*]indole (α-carbolines) at the C-6 position are described. Alternative conditions for the nitration were investigated, which led to the unexpected appearance of the minor C-8 isomer.

Key words: electrophilic aromatic substitutions, regioselectivity, heterocycles, acylations, halogenation, azacarbazole

Pyrido[2,3-*b*]indoles (α-carbolines) display a number of interesting biological properties.[1] For example, natural products such as grossularine-1 and grossularine-2 (Figure 1), marine alkaloids isolated from *Dendrodoa grossularia* in 1989, have attracted considerable interest since the report of their antiproliferative activity.[2] Similarly, mescengricin, isolated from *Streptomyces griseoflavus*, was found to protect neuronal cells by suppressing the excitotoxicity induced by L-glutamate (Figure 1).[3]

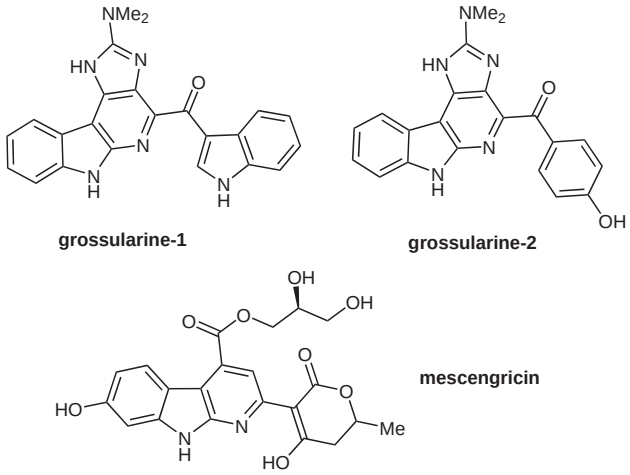

Figure 1 α-Carboline natural products.

Recently, the syntheses of substituted α-carbolines **I** and **II** with potent cyclin-dependent kinase (CDK) inhibitory activities have been disclosed (Figure 2).[4] Much effort has been devoted to the synthesis of α-carbolines. In most cases, the substitution is incorporated prior to the formation of the α-carboline ring system, resulting in lengthy synthetic routes or in limitations in the availability of substituted starting materials. These approaches are thus based on substituted indole,[5–7] arylalkyne[8] or arylalkene,[9] oxoindole,[10,11] azaindole,[12] or pyridine[13,14] starting materials.

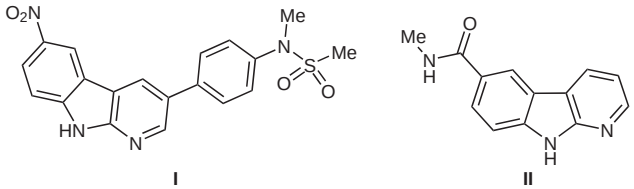

Figure 2 α-Carboline CDK inhibitors.

Surprisingly, the direct functionalization of the α-carboline skeleton has been studied only briefly.[4b,15] Nitration at the C-6 position was described in 1966 by Saxena using concentrated nitric acid.[15a] Stephenson later prepared the C-6 halogenated compound via the derived diazonium salt.[15b] More recently, reports on the bromination, nitration and carboxylation of α-carbolines by Dininno et al.[15d] and Sennhenn et al.[4b] have appeared in the patent literature. A more detailed investigation of the electrophilic aromatic substitution of the pyrido[2,3-*b*]indole system thus seemed warranted as a simple and flexible access to substituted analogues. This paper describes new routes to 6-acyl-, 6-bromo-, 6-nitro- and 6-carboxaldehyde pyrido[2,3-*b*]indoles.

The modified Graebe–Ullmann synthesis was chosen as a convenient route to the starting pyrido[2,3-*b*]indole nucleus (Scheme 1).[16] This reaction can be realized in polyphosphoric acid (PPA) under photolysis,[16b] thermal,[16c] or microwave irradiation[16d] conditions. As previously described, yields depend on the nature of the substituents on the pyridylbenzotriazole intermediate.[16b,c] The desired pyrido[2,3-*b*]indole **4a** was prepared according to Alvarez–Builla's procedure,[16d] followed by protection of the nitrogen. The Graebe–Ullmann reaction allows readily for substitution on the pyridine ring, via substituted pyridines, but substitution on the benzene ring is more troublesome, as substituted benzotriazole starting materials are not widely available and lead to regioisomeric mixtures of α-carbolines.[16b,d]

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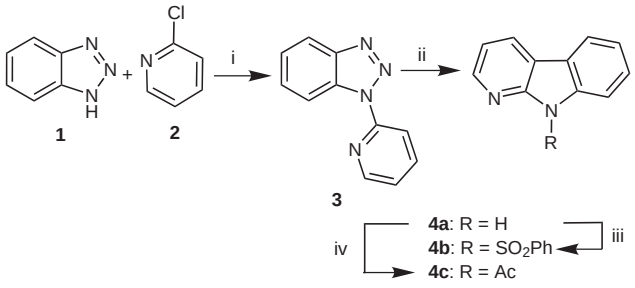
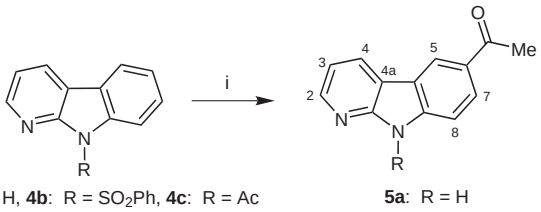


Scheme 1 *Reagents and conditions*: (i) 150–160 °C, 2 h, 77% (solvent-free); (ii) PPA, 150–160 °C, 2 h, 36%; (iii) NaH, $PhSO_2Cl$, THF, r.t., 12 h, 63%; (iv) NaH, Ac_2O, DMF, r.t., 12 h, 75%.

We first studied the acetylation reaction of the α-carboline scaffold (**4a**–**c**) by screening various parameters (Scheme 2). We decided to work with an excess of Lewis acid (4.5 equiv), according to a recent procedure for the acylation of 7-azaindole developed by Wang et al.[17] We investigated the nature of the Lewis acid ($SnCl_4$ or $AlCl_3$), the solvent (CS_2, $CHCl_3$ or CH_2Cl_2), the temperature, and the presence and the nature of the protective group on the central nitrogen of the carboline (Table 1).



Scheme 2 *Reagents and conditions*: (i) Lewis acid (4.5 equiv), MeCOCl (2 equiv), solvent, reflux, 4 h, see Table 1.

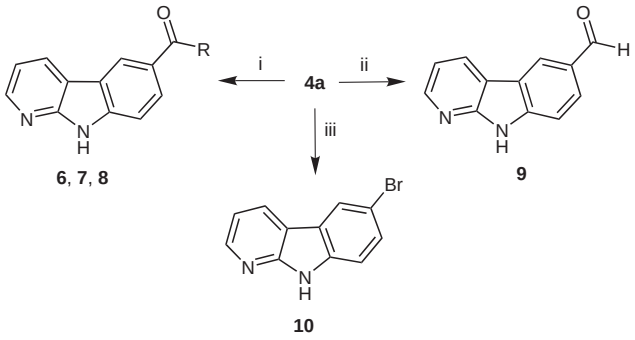
Table 1 Optimization of the Acetylation Reaction on α-Carbolines

Entry	Compound	Lewis acid	Solvent	Yield
1	**4a**	$SnCl_4$	CS_2	SM[a]
2	**4b**	$SnCl_4$	CS_2	SM
3	**4a**	$SnCl_4$	CH_2Cl_2	SM
4	**4a**	$AlCl_3$	CH_2Cl_2	**5a** (78%)
5	**4b**	$AlCl_3$	$CHCl_3$	degradation
6	**4c**	$AlCl_3$	CH_2Cl_2	SM

[a] SM: Starting material.

Acetylation at the C-6 position was observed only with the unprotected α-carboline **4a**, using 4.5 equivalents of $AlCl_3$ and two equivalents of acetyl chloride in refluxing CH_2Cl_2 (Table 1, entry 4). These conditions afforded **5a** in a good yield (78%).[18] The remaining conditions were either too mild, or led to decomposition of the protected α-carboline. The fact that the unprotected α-carboline gave better results than the protected forms, in addition to being of practical significance, suggests that the reactive species may be an aluminum complex,[17] rather than the N-acetylated intermediate **4c**. The regiochemistry of **5a** could be assigned unambiguously based on the three-bond correlations from the carbonyl carbon to the H-5 proton, from the H-5 proton to the C-4a carbon, and from the C-4a carbon to the H-3 proton in the heteronuclear multiple bond correlation spectra (HMBC).

The synthesis of a series of 6-acylated α-carbolines **6**–**8** (Scheme 3) was achieved under these conditions in good yields (71–90%).[19–21] Reactions were realized at room temperature or at reflux depending on the electrophilic character of the acyl chloride. Structure assignments were based on NMR data, and on the chemical correlation of the acid **7** to the known ethyl ester derivative prepared by an independent route.[4a]



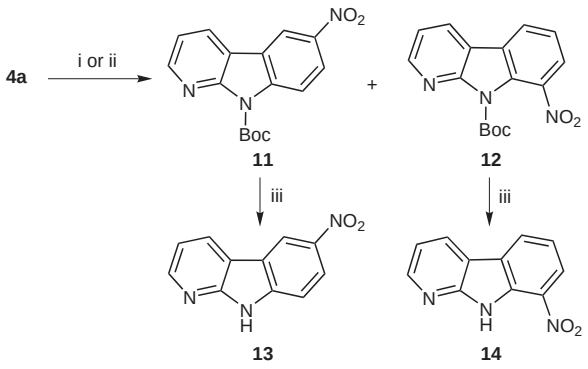
Scheme 3 *Reagents and conditions*: (i) $AlCl_3$ (4.5 equiv), RCOCl (2 equiv; MeO_2COCl, $(COCl)_2$, or PhCOCl), CH_2Cl_2, r.t. or reflux, 2–4 h, see Table 2; (ii) (a) $AlCl_3$ (7 equiv), $MeOCHCl_2$ (3 equiv), CH_2Cl_2, –78 °C to r.t., 12 h; (b) H_2O, 46%; (iii) Br_2 (1.1 equiv), CH_2Cl_2, r.t., 1 h, 91%.

Table 2 Acylation Reaction on α-Carbolines

Compound	COR	T (°C)	Yield (%)
6	$COCO_2Me$	r.t.	90
7	CO_2H	r.t.	71
8	COPh	Reflux	78

The formylation of pyrido[2,3-*b*]indole **4a** was investigated. While the experimental conditions described by Vilsmeier–Haack[22] and Duff[23] did not afford the desired formylated α-carboline, the use of α,α-dichloromethyl methyl ether ($MeOCHCl_2$) associated with a Lewis acid according to the Rieche procedure[22a] allowed us to obtain the desired compound. Thus, treatment of **4a** with an excess of $AlCl_3$ in CH_2Cl_2 at –78 °C followed by the addition of three equivalents of $MeOCHCl_2$ afforded the pyrido[2,3-*b*]indole-6-carboxaldehyde (**9**) in a moderate 46% yield (Scheme 3).[24] The halogenation of **4a** was investigated in order to extend our methodology to the preparation of a larger range of 6-substituted α-carbolines. The treatment of **4a** with a slight excess of bromine in CH_2Cl_2 at room temperature gave the compound **10** in 91% yield in one hour (Scheme 3).[25] Finally, we investigated alternative conditions for the nitration of **4a** (Scheme 4). While the use of HNO_3 has been described for the nitration of the

α-carboline scaffold at the C-6 position,[15] we found that nitronium tetrafluoroborate[26] (BF_4NO_2) or cerium(IV) ammonium nitrate[27] (CAN) also allowed the nitration of pyrido[2,3-*b*]indole. The use of CAN as nitrating agent afforded, after Boc protection, compounds **11** and **12** in a higher overall yield of 83% from **4a**. Nevertheless, two regioisomers at the C-6 and C-8 positions were obtained in ca. 3.5:1 ratio with both reagents. It is interesting to note that Saxena reported a highly regioselective nitration of **4a** using nitric acid at 0 °C.[15a] Repeating this reaction at room temperature led to the appearance of a small amount of the minor 8-nitro isomer. The lower selectivity observed with BF_4NO_2 and CAN may thus reflect a temperature effect, although other factors may also play a role.[28] Protection of the nitrogen atom was necessary for the separation of the two regioisomers due to solubility problems. NMR data (^1H, ^{13}C NMR, HSQC, COSY, HMBC) showed that *N*-Boc-6-nitro-α-carboline **11** was the major product. Finally, treatment of **11** and **12** with TFA in refluxing CH_2Cl_2 led to the deprotected compounds **13**[29] and **14**,[30] respectively, in 79% and 80% yields.



Scheme 4 *Reagents and conditions*: (i) BF_4NO_2 (2 equiv), tetramethylene sulfone (0.5 M), 150 °C, 12 h, then Boc_2O (1.1 equiv), DMAP, MeCN, r.t., 12 h, **11** (55%), **12** (15%); (ii) CAN (2 equiv), MeCN (0.5 M), reflux, 12 h, then Boc_2O (1.1 equiv), DMAP, MeCN, r.t., 12 h, **11** (63%), **12** (20%); (iii) TFA, CH_2Cl_2, reflux, 2 h, **13** (79%), **14** (80%).

In summary, we have developed efficient regioselective acylation, formylation, bromination and nitration at the C-6 position of pyrido[2,3-*b*]indoles. These methods permit the preparation of various 6-substituted α-carbolines in only three steps from 2-chloropyridines.

Acknowledgment

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(18) **Typical Procedure for Acylation**: At r.t. and under an inert atmosphere, $AlCl_3$ (714 mg, 5.36 mmol, 4.5 equiv) and acetyl chloride (178 μL, 2.38 mmol, 2 equiv) were added to a suspension of **4a** (0.2 M, 200 mg, 1.19 mmol) in anhyd CH_2Cl_2. The mixture was stirred at reflux until completion

of the reaction (monitored by TLC). In the case of methyl oxalyl chloride and oxalyl chloride, the chloride was added as a 50% solution in CH_2Cl_2 and the reaction was stirred at r.t. The resulting mixture was then cautiously quenched at 0 °C with H_2O. The mixture was extracted with a mixture of EtOAc–DMF (99:1). The resulting organic layer was washed with a sat. aq $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure. Trituration of the crude residue from MeOH followed by filtration afforded 6-acetylpyrido[2,3-*b*]indole **5a** (168 mg) as a white solid. The filtrate was evaporated and purified by flash chromatography [gradient: EtOAc–PE (1:1) → EtOAc] to give additional **5a** (26 mg); yield: 78%; mp 242 °C (MeOH). IR (KBr): 3045, 1668, 1602, 1571, 1496, 1468, 1246, 763, 710 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.21 (br s, 1 H, NH), 8.90 (d, *J* = 1.5 Hz, 1 H, H-5), 8.67 (dd, *J* = 1.7, 7.7 Hz, 1 H, H-4), 8.47 (dd, *J* = 1.7, 4.9 Hz, 1 H, H-2), 8.08 (dd, *J* = 1.5, 8.5 Hz, 1 H, H-7), 7.56 (d, *J* = 8.5 Hz, 1 H, H-8), 7.29 (dd, *J* = 4.9, 7.7 Hz, 1 H, H-3), 2.67 (s, 3 H, Me). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 197.0 (CO), 151.6 (C), 145.7 (CH), 141.8 (C), 129.9 (CH), 129.2 (C), 127.0 (CH), 123.0 (CH), 120.1 (C), 116.2 (C), 115.9 (CH), 111.3 (CH), 26.7 (Me). MS (EI): *m*/*z* = 210 [M^+·]. Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.35; H, 4.81; N, 13.26.

(19) **Analytical Data of Compound 6**: The compound **6** was obtained by flash chromatography [gradient: EtOAc–PE (1:1) → EtOAc]; yield: 90%; white solid; mp 207 °C (MeOH). IR (KBr): 3049, 2850, 1734, 1622, 1599, 1496, 1473, 1408, 1234, 1201, 752 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.5 (br s, 1 H, NH), 8.86 (d, *J* = 1.5 Hz, 1 H, H-5), 8.74 (dd, *J* = 1.6, 7.8 Hz, 1 H, H-4), 8.52 (dd, *J* = 1.6, 4.9 Hz, 1 H, H-2), 8.05 (dd, *J* = 1.5, 8.6 Hz, 1 H, H-7), 7.66 (d, *J* = 8.6 Hz, 1 H, H-8), 7.33 (dd, *J* = 4.9, 7.8 Hz, 1 H, H-3), 4.00 (s, 3 H, Me). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 186.2 (CO), 165.3 (CO), 152.7 (C), 147.9 (CH), 143.2 (C), 129.7 (CH), 127.9 (CH), 125.1 (CH), 123.4 (C), 120.7 (C), 116.4 (CH), 115.3 (C), 112.0 (C), 52.9 (Me). MS (ESI): *m*/*z* = 255 [M + H^+]. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.22; H, 4.03; N, 10.92.

(20) **Analytical Data of Compound 7**: The compound **7** was obtained by trituration from MeOH; yield: 71%; white solid; mp >295 °C (MeOH). IR (KBr): 3219, 1682, 1597, 1493, 1476, 1405, 909, 746 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.73 (br s, 1 H, OH), 12.18 (br s, 1 H, NH), 8.83 (br s, 1 H, H-5), 8.66 (dd, *J* = 1.6, 7.6 Hz, 1 H, H-4), 8.47 (dd, *J* = 1.6, 4.9 Hz, 1 H, H-2), 8.06 (dd, *J* = 1.7, 8.6 Hz, 1 H, H-7), 7.55 (d, *J* = 8.6 Hz, 1 H, H-8), 7.27 (dd, *J* = 4.9, 7.6 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.9 (CO), 152.5 (C), 146.8 (CH), 141.7 (C), 129.2 (CH), 127.9 (CH), 123.5 (CH), 121.9 (C), 120.2 (C), 115.8 (CH), 115.4 (C), 111.0 (CH). MS (EI): *m*/*z* = 212 [M^+·]. HRMS (EI): *m*/*z* calcd for $C_{12}H_8N_2O_2$: 212.0586; found: 212.0584.

(21) **Analytical Data for Compound 8**: The compound **8** was obtained by flash chromatography [gradient: EtOAc–PE (1:1) → EtOAc]; yield: 78%; white solid; mp 212 °C (MeOH). IR (KBr): 3040, 1647, 1603, 1565, 1494, 1466, 1254, 769, 702 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.29 (br s, 1 H, NH), 8.65–8.67 (m, 2 H, H-4, H-5), 8.48 (dd, *J* = 1.5, 4.9 Hz, 1 H, H-2), 7.90 (dd, *J* = 1.5, 8.0 Hz, 1 H, H-7), 7.76–7.79 (m, 2 H, H_{ar}), 7.56–7.68 (m, 4 H, H-8, H_{ar}), 7.26 (dd, *J* = 4.9, 8.0 Hz, 1 H, H-3), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.5 (CO), 152.6 (C), 147.0 (CH), 141.7 (C), 138.3 (C), 132.0 (CH), 129.5 (2 × CH), 129.4 (CH), 128.7 (CH), 128.6 (C), 128.5 (2 × CH), 124.3 (CH), 120.4 (C), 115.9 (CH), 115.5 (C), 111.1 (CH). MS (ESI): *m*/*z* = 273 [M + H^+]. Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.40; H, 4.44; N, 10.29. Found: C, 79.48; H, 4.44; N, 10.29.

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(24) **Typical Procedure and Analytical Data for Compound 9**: At –78 °C and under an inert atmosphere, $AlCl_3$ (714 mg, 5.36 mmol, 4.5 equiv) was added portionwise to a suspension of **4a** (0.02 M, 200 mg, 1.19 mmol) in anhyd CH_2Cl_2. After stirring for 5 min, α,α-dichloromethyl methyl ether (318 μL, 3.57 mmol, 3 equiv) was added dropwise to the mixture. The reaction mixture was stirred at –78 °C and then allowed to warm to r.t. for 12 h. The resulting mixture was then cautiously quenched at 0 °C with H_2O and extracted with a mixture of EtOAc–DMF (99:1). The combined organic layers were washed with a sat. aq $NaHCO_3$ solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc–PE, 1:1) to afford **9** (100 mg, 46%) as a white solid; mp 262 °C (MeOH). IR (KBr): 3043, 3014, 2824, 1690, 1604, 1569, 1470, 1410, 761 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.35 (br s, 1 H, NH), 10.06 (s, 1 H, CHO), 8.79 (d, *J* = 1.1 Hz, 1 H, H-5), 8.66 (dd, *J* = 1.1, 7.7 Hz, 1 H, H-4), 8.50 (dd, *J* = 1.5, 4.9 Hz, 1 H, H-2), 7.99 (dd, *J* = 1.5, 8.5 Hz, 1 H, H-7), 7.64 (d, *J* = 8.5 Hz, 1 H, H-8), 7.30 (dd, *J* = 4.7, 7.7 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 191.9 (CO), 152.6 (C), 147.1 (CH), 142.8 (C), 129.3 (CH), 128.9 (C), 127.5 (CH), 124.9 (CH), 120.6 (C), 116.1 (CH), 115.4 (C), 111.7 (CH). MS (EI): *m*/*z* = 196 [M^+·], 195 [M^+· – H], 167 [M^+· – H – CO]. Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.15; H, 4.39; N, 14.28.

(25) **Typical Procedure and Analytical Data for Compound 10**: At r.t. and under an inert atmosphere, a solution of bromine (1.2 equiv, 0.7 M) in anhyd CH_2Cl_2 was added to a suspension of **4a** (0.45 M, 200 mg, 1.19 mmol) in anhyd CH_2Cl_2. The mixture was stirred for 1 h at r.t. Excess bromine was destroyed by addition of a sat. aq $Na_2S_2O_3$ solution. The resulting mixture was extracted with EtOAc–DMF (99:1). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Trituration of the crude residue from MeOH followed by filtration afforded **10** (241 mg). The filtrate was evaporated and purified by flash chromatography [gradient: EtOAc–PE (1:1) → EtOAc] to give additional **10** (27 mg); yield: 91%; mp 250 °C (MeOH, lit.[15a] mp 266–270 °C). IR (KBr): 3052, 1604, 1586, 1493, 1448, 768, 610 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.95 (br s, 1 H, NH), 8.56 (dd, *J* = 1.5, 7.7 Hz, 1 H, H-4), 8.45 (dd, *J* = 1.5, 4.7 Hz, 1 H, H-2), 8.43 (d, *J* = 1.9 Hz, 1 H, H-5), 7.58 (dd, *J* = 1.9, 8.5 Hz, 1 H, H-7), 7.46 (d, *J* = 8.5 Hz, 1 H, H-8), 7.23 (dd, *J* = 4.7, 7.7 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.0 (C), 146.9 (CH), 137.5 (C), 129.2 (CH), 128.9 (C), 123.8 (CH), 122.3 (C), 115.4 (CH), 114.3 (C), 113.2 (CH), 111.4 (C). MS (EI): *m*/*z* = 246 [M^+·]. HRMS (EI): *m*/*z* calcd for $C_{11}H_7BrN_2$: 245.9793; found: 245.9797

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(28) The higher temperature required using the more reactive BF_4NO_2 salt suggests a possible involvement of an *N*-nitro intermediate. Further studies are underway to clarify the origin of the selectivity.

(29) **Analytical Data for Compound 13**: mp >295 °C (MeOH) (lit.[15a] mp >320 °C). IR (KBr): 3066, 1612, 1587, 1573, 1498, 1456, 1327, 749 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.58 (br s, 1 H, NH), 9.25 (d, *J* = 2.2 Hz, 1 H, H-5), 8.80 (dd, *J* = 1.7, 7.8 Hz, 1 H, H-4), 8.54 (dd, *J* = 1.7, 4.8 Hz, 1 H, H-2), 8.35 (dd, *J* = 2.2, 9.0 Hz, 1 H, H-7), 7.65 (d, *J* = 9.0 Hz, 1 H, H-8), 7.35 (dd, *J* = 4.8, 7.8 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.0 (C), 147.9 (CH), 142.6 (C), 140.5 (C), 130.2 (CH), 122.2 (CH), 120.3 (C), 118.4 (CH), 116.6 (CH), 115.5 (C), 111.6 (CH). MS (ESI): *m*/*z* = 214 [M + H^+]. HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{11}H_7N_3O_2$: 214.0617; found: 214.1017.

(30) **Analytical Data for Compound 14**: mp 253 °C (MeOH). IR (KBr): 3046, 1600, 1573, 1525, 1474, 1362, 732 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 12.15 (br s, 1 H, NH), 8.63 (dd, *J* = 1.5, 7.7 Hz, 1 H, H-4), 8.62 (d, *J* = 7.7 Hz, 1 H, H-7), 8.58 (dd, *J* = 1.5, 4.8 Hz, 1 H, H-2), 8.35 (d, *J* = 8.2 Hz, 1 H, H-5), 7.43 (dd, *J* = 7.7, 8.2 Hz, 1 H, H-6), 7.36 (dd, *J* = 4.8, 7.7 Hz, 1 H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.4 (C), 147.6 (CH), 132.1 (C), 131.9 (C), 128.9 (CH), 128.1 (CH), 124.5 (C), 122.1 (CH), 118.9 (CH), 116.5 (CH), 114.0 (CH). MS (EI): *m*/*z* = 213 [$M^{+}\cdot$]. HRMS (EI): *m*/*z* calcd for $C_{11}H_7N_3O_2$: 213.0538; found: 213.0535.