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Synthesis of pyrido[1,2-*a*]benzimidazoles by photo-stimulated C–N bond formation via $S_{RN}1$ reactions

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ABSTRACT

The photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia afforded pyrido[1,2-*a*]benzimidazoles via $S_{RN}1$ mediated C–N bond forming reactions in moderate to excellent yields (58–94%). This general synthetic strategy was also extended to a 2-(2-bromophenylamino)pyrazine to give pyrazino[1,2-*a*]benzimidazole. Attempts to employ this reaction using *N*-(2-chlorophenyl)-3-isoquinolinamine, however, resulted in C–C bond formation generating 7*H*-indolo[2,3-*c*]isoquinoline.

1. Introduction

Benzimidazole is a heterocycle present in an array of therapeutic agents and biologically active compounds.[1] This heterocycle can also be found embedded in numerous tricyclic rings systems, such as pyrido[1,2-*a*]benzimidazoles. Many of these compounds demonstrate interesting and potentially useful biological activities. For example, **1**–**3** (Fig. 1) have been reported to possess antifungal activity via inhibition of β-1,6-glucan synthesis, anticancer properties, and antimalarial activity through inhibition of *Plasmodium* species, respectively.[2–4] In addition to biological properties, pyrido[1,2-*a*]benzimidazoles demonstrate characteristics making them useful to other fields, including material science.

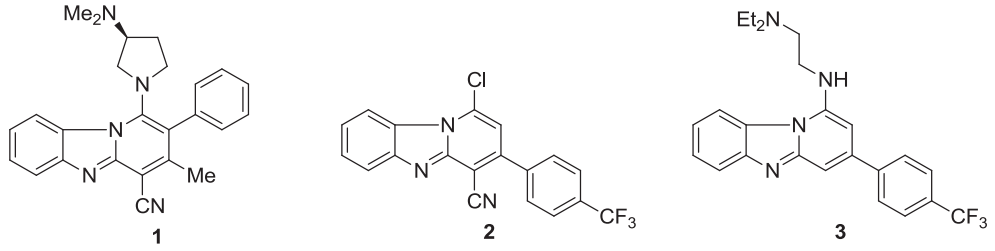

Fig. 1. Examples of biologically active pyrido[1,2-*a*]benzimidazoles **1**–**3**.

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Several strategies have been utilized for the synthesis of pyrido[1,2-*a*]benzimidazoles. A number of classical methods for synthesizing this heterocycle have been recently demonstrated include anionic[5] and reductive cyclizations,[6] condensations,[7] and hypervalent iodine mediated dehydrogenative coupling.[8] Photomediated processes have been described.[9–12] A number of metal-mediated methods, including Pd,[13] Cu,[14] and Cu and/or Cu/Fe C–H bond activation,[15,16] have also been reported.

The photo-stimulated unimolecular radical nucleophilic substitution ($S_{RN}1$) reaction has emerged as another synthetically useful methodology for bond constructions.[17,18] $S_{RN}1$ reactions have been utilized to mediate an array of C–C and C–N bond couplings in the synthesis of various heterocyclic systems.[19–29] Herein, we report the use of the photo-stimulated intramolecular $S_{RN}1$ reaction of 2-(2-halophenylamino)pyridines as a method of synthesizing pyrido[1,2-*a*]benzimidazoles.

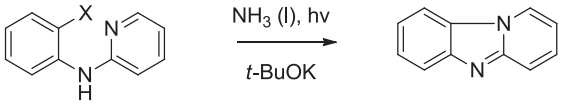
2. Results and discussion

2.1. Photo-stimulated cyclization of 2-(2-halophenylamino) pyridines via $S_{RN}1$ reactions

Nucleophiles derived from nitrogen have been shown to react with aryl radicals to form C–C and/or C–N bonds. For example, the reaction of 2-naphthylamine anion with iodoarenes via a photo-stimulated $S_{RN}1$ process gave the C–C bond product 1-aryl-2-naphthylamines in 45–63% yield, with the N-arylation product formed in only 2–6% yield (Fig. 2, Eq. 1).[30] The electrochemical-induced reaction of pyrrole anion with aryl chlorides gave two C–C bond forming products (Eq. 2).[31] Similar reactivity has been reported for 4-methylimidazole.[32] The photo-stimulation of *N*-(2-halobenzyl)arylamine derived anions has been found to give substituted phenanthridines through C–C bond formation in good to excellent yields.[21] However, the photo-stimulated reaction of *N*-(2-iodobenzyl)pyridin-2-amine, where the aromatic radical intermediate can react to form a C–C or C–N bond, afforded only 6% yield of benzo[*c*][1,8]naphthyridine through C–C bond formation and 61% yield of 6*H*-pyrido[1,2-*a*]quinazoline through C–N bond formation (Eq. 3).[21] These results suggest that the intermolecular coupling of radicals with nucleophiles derived from nitrogen favor C–C bond formation. However, for intramolecular reactions C–N bond construction may be preferred.

Based on these observations, the photo-stimulated $S_{RN}1$ reaction of 2-(2-halophenylamino)pyridines was anticipated to form pyrido[1,2-*a*]benzimidazoles via C–N bond construction and not α-carbolines by C–C formation. In order to test this hypothesis, 2-(2-bromophenylamino)pyridine (**4a**) was subjected to photostimulation in liquid ammonia for 120 min in the presence of 2 equiv of potassium *tert*-butoxide. The reaction gave complete substrate consumption and a 93% isolated yield of pyrido[1,2-*a*]benzimidazole (**5**, Table 1, entry 1). The yield of bromide ions generated was determined potentiometrically to be 96%. A similar reaction conducted in DMSO for 60 min only generated **5** in 33% yield, as determined by gas chromatography, despite a bromide ion yield of 93% (entry 2). Photo-stimulation of the chloride derivative **4b**[14] in liquid ammonia for 60 min also generated **5** in excellent yield (entry 3). Again utilizing DMSO as solvent with either 60 or 120 min photo-stimulation resulted in lower yields of **5** (entries 4 and 5). Next, a time course for the photo-stimulation of **4b** in liquid ammonia was conducted (entries 6–8). Excellent yields of **5** were obtained after 30 and 15 min. However, a lower yield was observed after only 5 min of irradiation. These results demonstrate that photo-stimulated cyclization of 2-(2-halophenylamino)pyridines occurs very rapidly compared to several metal-mediated processes,

Table 1
Optimization of photo-stimulated cyclization of **4a** and **4b** via $S_{RN}1$ reactions to afford **5**



4a X = Br
4b X = Cl

5

Entry	Substrate	Conditions	Reaction time (min)	Recovered **4a** or **4b**	X^- (%)	GC yield of **5** (%)
1	**4a**	hν, NH_3(l)	120	0	96	93[a]
2	**4a**	hν, DMSO	60	0	93	33
3	**4b**	hν, NH_3(l)	60	0	94	93
4	**4b**	hν, DMSO	60	ND[b]	86	44
5	**4b**	hν, DMSO	120	0	98	27
6	**4b**	hν, NH_3(l)	30	0	100	98
7	**4b**	hν, NH_3(l)	15	0	100	97
8	**4b**	hν, NH_3(l)	5	0	92	81
9	**4b**	Dark, NH_3(l)	60	100	< 5	0
10	**4b**	hν, NH_3(l), 30 mol % *p*-DNB	5	ND[b]	32	44

[a] Isolated yield.
[b] Not determined.

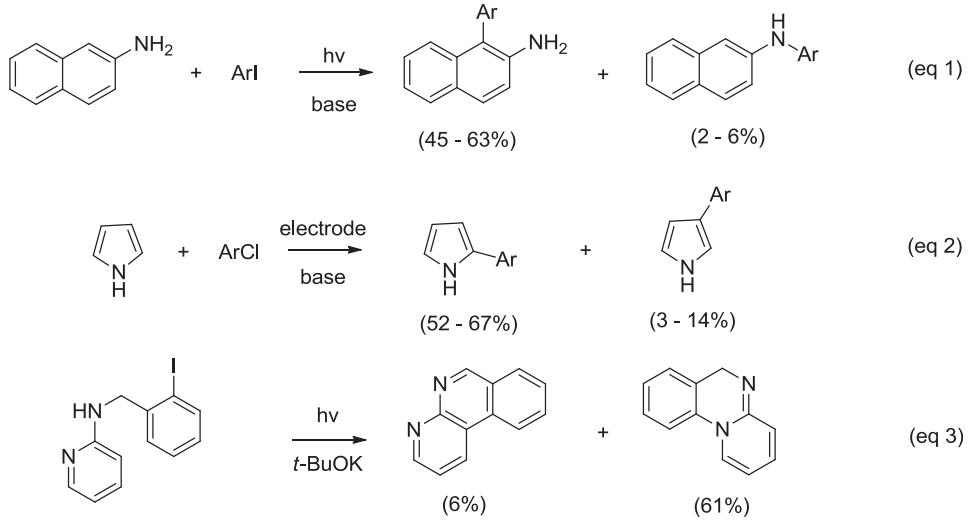
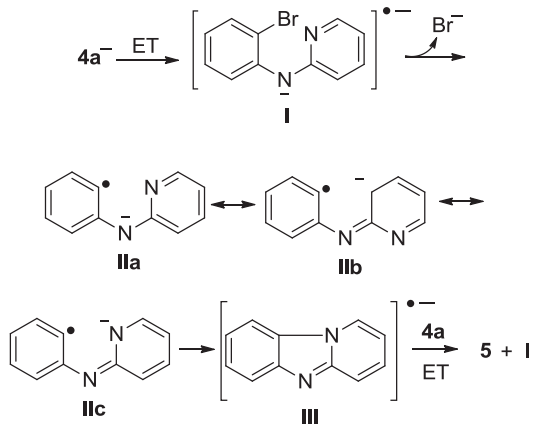


Fig. 2. Examples of nitrogen nucleophiles reacting with aryl radicals to form C–C and/or C–N bonds.

which require prolong heating.[15,16] The reaction did not proceed without photo-stimulation (entry 9). Likewise, the photo-stimulated reaction was partially inhibited by 1,4-dinitrobenzene (entry 10).[17]

A proposed reaction mechanism for the photo-stimulated $S_{RN}1$ reaction of 2-(2-bromophenylamino)pyridine (**4a**) is presented in Scheme 1.[17,18] In the initiation step, the radical dianion of the substrate (**I**) can be formed by an electron transfer (ET) reaction. For some substrates this step is spontaneous, but in many cases such as with 2-(2-halophenylamino)pyridines, induction by light is required. The radical dianion can then fragment yielding the distonic radical anion **II** and bromide anion (Br^-). The resonance distonic radical anion **II** can cyclize to give the conjugated radical anion **III**, which by an ET to the anion of **4a** can give pyrido[1,2-*a*]benzimidazole (**5**) and the intermediate **I** required to continue the propagation cycle. Presumably, it is the pyridine nitrogen anionic canonical form **IIc**, as opposed to the carbon anionic canonical form **IIb** that dictates the regioselectivity resulting in generation of pyrido[1,2-*a*]benzimidazole **5** and not α-carboline.



Scheme 1. Proposed mechanism of the $S_{RN}1$ reaction of 2-(2-bromophenylamino) pyridine (**4a**).

2.2. Scope of the photo-stimulated cyclization of 2-(2-halophenylamino)pyridines

Next, the scope of the photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia via $S_{RN}1$ mediated C–N bond forming reactions was investigated. Substrates containing electron donating or electron withdrawing substituents at the 4- or 5-positions of the phenyl underwent cyclization to give pyrido[1,2-*a*]benzimidazoles **7a**–**7d** in moderate to excellent yields (Table 2, entries 1–4). Likewise, addition of a methyl at the 3-, 4- or 5-positions of the pyridine substrate was also well tolerated providing pyrido[1,2-*a*]benzimidazoles **7e**–**7g** in excellent yields (entries 5–7). However, a substrate containing a methyl at the 6-position of the pyridine substrate (e.g., **6h**) provided the desired product **7h** in 58% yield after 60 min of photo-stimulation with 22% of the starting material recovered (entry 8). Finally, the photo-stimulated cyclization of 2-(2-bromophenylamino)pyrazine (**6i**) generated pyrazino[1,2-*a*]benzimidazole (**7i**), albeit in only 29% yield with 71% recovery of substrate (entry 9).

With the successful syntheses of pyrido[1,2-*a*]benzimidazoles via photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia, the substrate scope was expanded to include *N*-(2-chlorophenyl)-3-isoquinolinamine (**8**). However, unlike the pyridine substrates this material cyclized through C–C bond formation generating only 7*H*-indolo[2,3-*c*]isoquinoline **9**[33] in modest yield (29%). The regioselectivity of this reaction may be influenced by the stability of carbon-base anion resonance structure **V** in the benzylic position of the isoquinolyl moiety, as opposed to the nitrogen-based anion resonance structure **IV**, resulting in the observed C–C bond formation (Scheme 2).

3. Conclusion

In conclusion, pyrido[1,2-*a*]benzimidazoles were conveniently synthesized in moderate to excellent yields utilizing photo-stimulated cyclization of 2-(2-halophenylamino)pyridines in liquid ammonia and in the presence of potassium *tert*-butoxide. The reaction proceeded by $S_{RN}1$ mediated C–N bond formation and was quite tolerant to various substituents on both the phenyl and pyridine rings. Pyrazino[1,2-*a*]benzimidazole was also prepared using this methodology. However, the substrate *N*-(2-chlorophenyl)-3-isoquinolinamine cyclized via C–C bond formation to give 7*H*-indolo[2,3-*c*]isoquinoline **9**. The photo-stimulated $S_{RN}1$ mediated synthesis of pyrido[1,2-*a*]benzimidazoles and related heterocycles has several advantages over other methods, such as requiring short reaction times (≤3 h), proceeding at low temperature, and tolerating aryl chloride substrates. This methodology provides a complementary method to other approaches, including recently reported metal-mediated approaches, and will likely be useful for the preparation of other fused heterocycles.

4. Experimental section

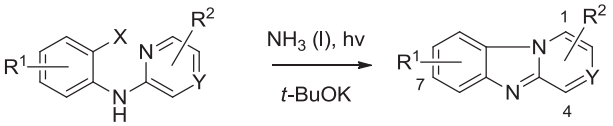
4.1. General information and materials

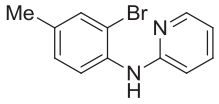
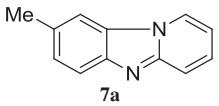
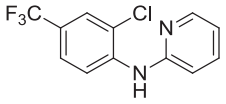
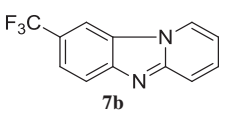
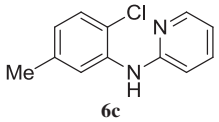
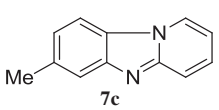
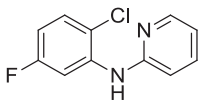
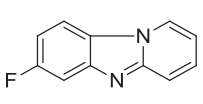
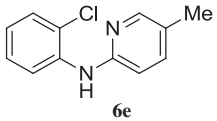
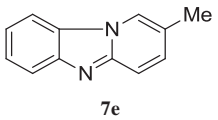
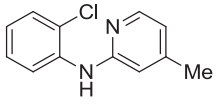
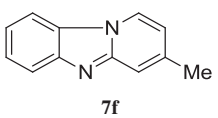
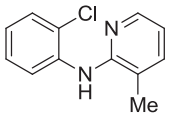
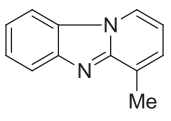
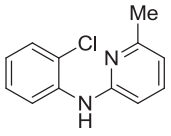
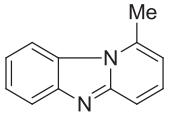
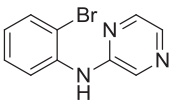
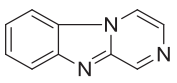
Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without purification. DMSO was stored over molecular sieves (4 Å). Silica gel (0.063–0.200 mm) was used in column chromatography. ^{1}H NMR (500, 400 or 300 MHz), ^{13}C NMR (126 or 100 MHz), and ^{19}F NMR (376 MHz) were conducted on a high-resolution spectrometer in $CDCl_3$ or CD_3COCD_3 as a solvent. Coupling constants are given in hertz (Hz), and chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, dd=double doublet, dt=double triplet, td=triple doublet, ddd=double double doublet, m=multiplet), and coupling constants (*J*). Gas chromatographic (GC) analyses were performed on an instrument with a flame ionization detector equipped with a VF-5ms column (30 m×0.25 mm×0.25 μm). GC–MS analyses were carried out on a GC–MS equipped with a quadrupole detector and a VF-5ms column (30 m×0.25 mm×0.25 μm). High-resolution mass spectra were performed in an MS/MS instrument in pure products. These data were obtained by ESI or APPI mode ionization and TOF detection. Melting points were performed with an electrical instrument and are uncorrected. 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.

4.2. General synthesis of 2-(2-halophenylamino)pyridines[34]

A mixture of aniline (3 mmol), 2-halopyridine (3 mmol), Cs_2CO_3 (9 mmol), $Pd(OAc)_2$ (0.12 mmol), and BINAP (0.12 mmol) in toluene (5 mL) under an argon atmosphere was stirred at 100 °C for 14 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated and the residue purified by column chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate to give the desired products.

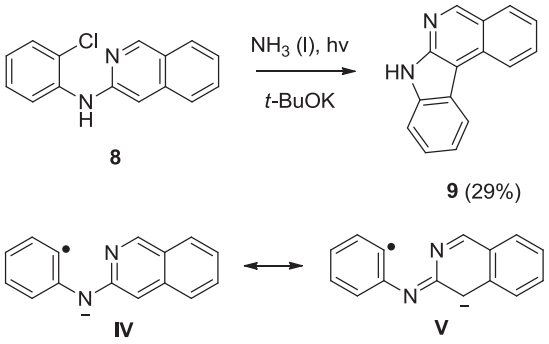
Table 2
Substrate scope of the photo-stimulated $S_{RN}1$ reaction



Entry	Substrate	Product	Time (min)	X^- (%)	Isolated yield (%)
1	 **6a**	 **7a**	60	95	62
2	 **6b**	 **7b**	60	99	79
3	 **6c**	 **7c**	60	100	94
4	 **6d**	 **7d**	90	99	83
5	 **6e**	 **7e**	120	98	83
6	 **6f**	 **7f**	120	96	94
7	 **6g**	 **7g**	60	100	81
8	 **6h**	 **7h**	60	75	58[a]
9	 **6i**	 **7i**	180	33	29[b]

[a] Starting material recovered: 22%.
[b] Starting material recovered: 71%.

*4.2.1. 2-(2-Bromo-4-methylphenylamino)pyridine (**6a**).* Light tan solid; mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 6.68 (br s, 1H), 6.75–6.77 (m, 1H), 6.79 (d, J=8.4, 1H), 7.09 (dd, J=8.4, 1.2, 1H), 7.40 (d, J=1.2, 1H), 7.48–7.52 (m, 1H), 7.80 (d, J=8.0, 1H), 8.22–8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 109.3, 114.8, 115.5, 120.8, 128.7, 133.1, 133.4, 135.8, 137.6, 148.3, 155.4; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.30/20.4, 6.75–6.77/115.5, 6.79/109.3, 7.09/128.7, 7.40/133.1, 7.48–7.52/137.6, 7.80/120.8, 8.22–8.23/



Scheme 2. Photo-stimulated $S_{RN}1$ reaction of *N*-(2-chlorophenyl)-3-isoquinolinamine (**8**) and proposed intermediate **V**.

148.3; $^1H/^1H$ COSY NMR ($CDCl_3$) δ_H/δ_H 2.30/7.09, 2.30/7.40, 6.75–6.77/4.78–7.52, 6.75–6.77/8.22–8.23, 7.09/7.40, 7.09/7.80; $^1H/^{13}C$ HMBC NMR ($CDCl_3$) δ_H/δ_C 2.30/128.7, 2.30/133.1, 6.75–6.77/109.3, 6.75–6.77/148.3, 6.79/115.5, 7.09/133.1, 7.09/135.8, 7.40/114.8, 7.40/128.7, 7.40/135.8, 7.48–7.52/148.3, 7.48–7.52/155.4, 7.80/114.8, 7.80/133.4, 7.80/135.8, 8.22–8.23/115.5, 8.22–8.23/137.6, 8.22–8.23/155.4; GC/MS EI *m/z* 183 ($M-Br^+$), 262 (M^+), 264 (M+2); HRMS (ESI) *m/z* obsd 263.0199, calcd 263.0178 for $C_{12}H_{12}BrN_2$ ($M+H^+$).

*4.2.2. 2-(2-Chloro-4-trifluoromethylphenylamino)pyridine (**6b**).* Yield 89%; white solid; mp 115–117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89–6.92 (m, 2H), 7.07 (s, 1H), 7.47 (dd, *J*=8.5, 1.5, 1H), 7.60–7.64 (m, 2H), 8.31–8.32 (m, 1H), 8.46 (d, *J*=8.5, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 111.7, 117.2, 117.9, 121.5, 122.8, 123.3 (q, *J*=33.4 Hz), 124.9 (q, *J*=3.6 Hz), 126.5 (q, *J*=3.9 Hz), 138.1, 140.5, 148.2, 154.0; HRMS (ESI) *m/z* obsd 273.0420, calcd 273.0401 for $C_{12}H_9ClF_3N_2$ ($M+H^+$).

*4.2.3. 2-(2-Chloro-5-methylphenylamino)pyridine (**6c**).* Yield 92%; white solid; mp 134–136 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.74–6.76 (m, 1H), 6.78–6.81 (m, 1H), 6.85–6.86 (m, 2H), 7.25 (d, *J*=8.0, 1H), 7.51–7.55 (m, 1H), 7.86 (d, *J*=1.5, 1H), 8.26–8.27 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 110.0, 115.9, 120.3, 120.4, 123.5, 129.2, 136.9, 137.6, 137.8, 148.3, 155.1; HRMS (ESI) *m/z* obsd 219.0715, calcd 219.0684 for $C_{12}H_{12}ClN_2$ ($M+H^+$).

*4.2.4. 2-(2-Chloro-5-fluorophenylamino)pyridine (**6d**).* Yield 86%; white solid; mp 110–112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (dt, *J*=3.0, 8.0, 1H), 6.83–6.87 (m, 2H), 6.95 (s, 1H), 7.27 (dd, *J*=6.0, 2.5, 1H), 7.56–7.59 (m, 1H), 8.20 (dd, *J*=2.5, 11.0, 1H), 8.29 (d, *J*=5.0, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 105.9 (d, *J*=115.5), 108.3 (d, *J*=95.0), 111.3, 116.7, 129.8 (d, *J*=39.0), 137.9, 138.6, 148.1, 154.3, 161.0, 162.8; HRMS (ESI) *m/z* obsd 223.0464, calcd 223.0433 for $C_{11}H_9ClFN_2$ ($M+H^+$).

*4.2.5. 2-(2-Chlorophenylamino)-5-methylpyridine (**6e**).* Yield 96%; white solid; mp 170–172 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 6.80–6.83 (m, 2H), 6.88 (dt, *J*=1.5, 8.0, 1H), 7.21–7.24 (m, 1H), 7.36 (dd, *J*=1.5, 8.0, 2H), 8.01 (dd, *J*=1.0, 8.0, 1H), 8.09–8.10 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.7, 110.1, 118.8, 121.8, 122.6, 125.2, 127.5, 129.6, 137.8, 138.7, 148.0, 152.8; HRMS (ESI) *m/z* obsd 219.0707, calcd 219.0684 for $C_{12}H_{12}ClN_2$ ($M+H^+$).

*4.2.6. 2-(2-Chlorophenylamino)-4-methylpyridine (**6f**).* Yield 94%; white solid; mp 144–146 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.68 (d, *J*=5.0, 1H), 6.72 (s, 1H), 6.88 (s, 1H), 6.94 (dd, *J*=1.0, 8.0, 1H), 7.26–7.30 (m, 1H), 7.41 (dd, *J*=1.5, 8.0, 1H), 8.11 (dd, *J*=1.0, 8.0, 1H), 8.16 (d, *J*=5.0, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2, 110.5, 117.6, 119.7, 122.3, 123.1, 127.5, 129.6, 137.5, 147.9, 149.0, 155.1; HRMS (ESI) *m/z* obsd 219.0702, calcd 219.0684 for $C_{12}H_{11}ClN_2$ ($M+H^+$).

*4.2.7. 2-(2-Chlorophenylamino)-3-methylpyridine (**6g**).* Yield 90%; white solid; mp 110–112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 6.76 (dd, *J*=5.0, 7.5, 1H), 6.90–6.95 (m, 2H), 7.30 (t, *J*=8.0, 1H), 7.37–7.42 (m, 2H), 8.19 (d, *J*=5.0, 1H), 8.71–8.73 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.2, 116.0, 119.1, 119.6, 121.6, 121.9, 127.6, 129.0, 137.5, 138.0, 145.3, 153.3; HRMS (ESI) *m/z* obsd 219.0725, calcd 219.0684 for $C_{12}H_{12}ClN_2$ ($M+H^+$).

*4.2.8. 2-(2-Chlorophenylamino)-6-methylpyridine (**6h**).*[35] Yield 92%; brown oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 6.66–6.72 (m, 2H), 6.80 (s, 1H), 6.88–6.94 (m, 1H), 7.20–7.25 (m, 1H), 7.36–7.46 (m, 2H), 8.00 (dd, *J*=1.5, 8.4, 1H).

4.3. Synthesis of 2-(2-bromophenylamino)pyrazine (6i)[37]

A mixture of pyrazin-2-amine (3 mmol), 2-bromoiodobenzene (3 mmol), *t*-BuONa (4.5 mmol), $Pd_2(dba)_3$ (0.15 mmol), and DPPF (0.15 mmol) in toluene (5 mL) under an argon atmosphere was stirred at 100 °C for 14 h.[36] After cooling, the mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated, and purified by silica gel column chromatography using *c*-hexane/AcOEt (10:1) as eluent to give a pale yellow solid (91%). Mp 107–109 °C (133–135 °C);[38] ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (dt, *J*=1.5, 7.5, 2H), 7.31–7.35 (m, 1H), 7.58 (dd, *J*=1.5, 8.0, 1H), 8.05 (d, *J*=3.0, 1H), 8.16–8.18 (m, 2H), 8.27 (d, *J*=1.5, 1H).

4.4. Synthesis of *N*-(2-chlorophenyl)-3-isoquinolinamine (8)

A mixture of 1-aminoisoquinoline (3 mmol), 2-chloroiodo benzene (3 mmol), *t*-BuONa (4.5 mmol), $Pd_2(dba)_3$ (0.15 mmol), and DPPF (0.15 mmol) in toluene (5 mL) under an argon atmosphere was stirred at 100 °C for 14 h. After cooling, the mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated, and purified by silica gel column chromatography using *c*-hexane/AcOEt (10: 1) as eluent to give a pale yellow solid (85%). Mp 152–154 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98–7.02 (m, 2H), 7.25 (s, 1H), 7.30–7.33 (m, 1H), 7.37–7.40 (m, 1H), 7.46 (dd, *J*=1.5, 8.0, 1H), 7.57–7.60 (m, 1H), 7.63–7.65 (m, 1H), 7.87–7.90 (m, 2H), 9.05 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.3, 118.8, 122.3, 123.5, 124.3, 125.0, 125.4, 127.6, 127.8, 129.9, 130.8, 138.0, 138.4, 150.7, 152.1; HRMS (ESI) *m/z* obsd 255.0722, calcd 255.0684 for $C_{15}H_{12}ClN_2$ ($M+H^+$).

4.5. General procedure for the synthesis of pyrido[1,2-*a*] benzimidazoles in liquid ammonia

*4.5.1. Pyrido[1,2-a]benzimidazole (**5**).*[36] Liquid ammonia (200 mL), previously dried over Na metal, was distilled into a 250 mL three-necked, round-bottomed flask equipped with a cold-finger condenser, a nitrogen inlet, and a magnetic stirrer. The base (*t*-BuOK, 45 mg, 0.40 mmol) and the 2-(2-bromophenylamino)pyridine (**4a**,[36] 50 mg, 0.20 mmol) were added to the liquid ammonia and the solution was irradiated for 120 min. The reaction was quenched with an excess of 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 $MgSO_4$, filtered, and the solvent was removed under reduced pressure to leave the crude product. The yield of bromide ions in the aqueous solution was determined potentiometrically. The crude product was purified by radial TLC eluting with petroleum ether (bp 60–80 °C)/ethyl acetate (50:50) to give **5**[36] (93%) as light yellow crystals. It was recrystallized from dichloromethane to give colorless crystals. Mp 184–185 °C (lit. 179–182 °C);[36] ^1H

NMR (400 MHz, $CDCl_3$) δ 6.84 (t, J=6.8, 1H), 7.35–7.44 (m, 2H), 7.53 (t, J=7.4, 1H), 7.69 (d, J=9.6, 1H), 7.89 (d, J=8.4, 1H), 7.95 (d, J=8.0, 1H), 8.44 (d, J=6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 110.4, 118.0, 119.9, 121.0, 125.2, 125.6, 128.6, 129.3, 144.5, 148.4; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 6.84/110.3, 7.35–7.44/121.0, 7.35–7.44/129.3, 7.53/125.6, 7.69/118.0, 7.89/110.4, 7.95/119.9, 8.44/125.2; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.84/7.35–7.44, 6.84/8.44, 7.35–7.44/7.53, 7.35–7.44/7.69, 7.35–7.44/7.89, 7.53/7.95; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 6.84/118.0, 6.84/125.2, 7.35–7.44/119.9, 7.35–7.44/125.2, 7.35–7.44/128.6, 7.35–7.44/148.4, 7.53/110.4, 7.53/144.5, 7.69/110.3, 7.69/148.4, 7.89/125.6, 7.89/144.5, 7.95/121.0, 7.95/128.6, 8.44/110.3, 8.44/129.3, 8.44/148.4; GC/MS EI m/z 168 (M^+, 100).

*4.5.2. 8-Methylpyrido[1,2-a]benzimidazole (**7a**).*[39] This compound was purified by chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate gradient (100:0→0:100) and then recrystallized from dichloromethane to give colorless crystals. Mp 127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 6.81 (td, J=6.8, 1.2, 1H), 7.35–7.39 (m, 2H), 7.64–7.68 (m, 2H), 7.82 (d, J=8.4, 1H), 8.39 (dt, J=6.8, 1.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 110.1, 118.1, 119.5, 125.0, 127.4, 128.7, 131.1, 142.6, 148.3; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.59/21.8, 6.81/110.0, 7.35–7.39/127.4, 7.35–7.39/128.7, 7.64–7.68/110.1, 7.64–7.68/118.1, 7.82/119.5, 8.39/125.0; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.81/7.35–7.39, 6.81/8.39, 7.35–7.39/7.64–7.68, 7.35–7.39/7.82; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 2.59/110.1, 2.59/127.4, 2.59/131.1, 6.81/118.1, 6.81/125.0, 7.35–7.39/110.1, 7.35–7.39/125.0, 7.35–7.39/142.6, 7.35–7.39/148.3, 7.64–7.68/110.1, 7.64–7.68/127.4, 7.64–7.68/142.6, 7.64–7.68/148.3, 7.82/128.7, 7.82/131.1, 8.39/110.1, 8.39/128.7, 8.39/148.3; GC/MS EI m/z 182 (M^+, 100).

*4.5.3. 8-(Trifluoromethyl)pyrido[1,2-a]benzimidazole (**7b**).*[16] This compound was purified by chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate gradient (100:0→25:75) and then recrystallized from dichloromethane to give light yellow crystals. Mp 166–167 °C (lit. 158–160 °C);[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (td, J=6.8, 1.2, 1H), 7.53–7.55 (m, 1H), 7.73–7.78 (m, 2H), 8.00 (d, J=8.4, 1H), 8.19–8.20 (m, 1H), 8.51 (dt, J=7.2, 1.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5 (q, J_{C-F}=4), 111.2, 118.3, 120.3, 122.4 (q, J_{C-F}=3), 122.9 (q, J_{C-F}=32), 124.7 (q, J_{C-F}=270), 125.4, 128.0, 130.7, 146.5, 150.3; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 6.95/111.24, 7.53–7.55/130.72, 7.73–7.78/118.29, 7.73–7.78/122.44, 8.00/120.30, 8.19–8.20/108.47, 8.51/125.35; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.95/7.53–7.55, 6.95/8.51, 7.53–7.55/7.73–7.78, 7.73–7.78/8.00, 7.73–7.78/8.19–8.20; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 6.95/118.3, 6.95/125.4, 7.53–7.55/118.3, 7.53–7.55/125.4, 7.53–7.55/150.3, 7.73–7.78/108.5, 7.73–7.78/111.2, 7.73–7.78/120.3, 7.73–7.78/130.7, 7.73–7.78/146.5, 7.73–7.78/150.3, 8.00/122.4, 8.00/122.9, 8.00/128.0, 8.19–8.20/122.4, 8.19–8.20/124.7, 8.19–8.20/146.5, 8.51/111.2, 8.51/130.7, 8.51/150.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.3; GC/MS EI m/z 236 (M^+, 100).

*4.5.4. 7-Methylpyrido[1,2-a]benzimidazole (**7c**).*[40] This compound was purified by chromatography on silica gel eluting with dichloromethane/ethanol gradient (100:0→98:2) and then recrystallized from dichloromethane to give light yellow crystals. Mp 152–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 6.78 (t, J=6.8, 1H), 7.17 (d, J=8.4, 1H), 7.34–7.39 (m, 1H), 7.65 (dd, J=9.2, 0.8, 1H), 7.70 (br s, 1H), 7.72 (d, J=8.4, 1H), 8.37 (dd, J=7.0, 1.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 109.8, 109.9, 117.8, 119.4, 122.7, 125.0, 126.8, 128.9, 135.6, 144.9, 148.5; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.56/21.9, 6.78/109.9, 7.17/122.7, 7.34–7.39/128.9, 7.65/117.8, 7.70/119.4, 7.72/109.8, 8.37/125.0; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 2.56/7.70, 6.78/7.34–7.39, 6.78/8.37, 7.17/7.72, 7.34–7.39/7.65; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 2.56/119.4, 2.56/122.7, 2.56/135.6, 6.78/117.8, 6.78/125.0, 7.17/119.4, 7.17/126.8, 7.34–7.39/125.0, 7.34–7.39/148.5, 7.65/109.9, 7.65/148.5, 7.70/122.7, 7.70/126.8, 7.72/135.6, 7.72/144.9, 8.37/109.9, 8.37/128.9, 8.37/148.5; GC/MS EI m/z 182 (M^+, 100).

*4.5.5. 7-Fluoropyrido[1,2-a]benzimidazole (**7d**).*[16] This compound was obtained according to the general procedure as solid and recrystallized from dichloromethane/petroleum ether (bp 60–80 °C) as yellow crystals. Mp 194–196 °C (lit. 172–173 °C);[16] ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.03 (t, J=6.2, 1H), 7.23 (td, J=9.4, 2.4, 1H), 7.55–7.56 (m, 2H), 7.66 (d, J=9.2, 1H), 8.34 (dd, J=8.8, 5.0, 1H), 9.09 (d, J=6.8, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 104.0 (d, J_{C-F}=25), 108.9 (d, J_{C-F}=25), 110.7, 113.2 (d, J_{C-F}=12), 116.7, 125.5, 127.2, 130.5, 144.7 (d, J_{C-F}=12), 149.2, 160.6 (d, J_{C-F}=236); ^{1}H/^{13}C HSQC NMR (CD_3COCD_3) δ_H/δ_C 7.03/110.7, 7.23/108.9, 7.55–7.56/104.0, 7.55–7.56/130.5, 7.66/116.7, 8.34/113.2, 9.09/127.2; ^{1}H/^{1}H COSY NMR (CD_3COCD_3) δ_H/δ_H 7.03/7.55–7.56, 7.03/9.09, 7.23/7.55–7.56, 7.23/8.34, 7.55–7.56/7.66; ^{1}H/^{13}C HMBC NMR (CD_3COCD_3) δ_H/δ_C 7.03/116.7, 7.03/127.2, 7.23/104.0, 7.23/125.5, 7.23/160.6, 7.55–7.56/108.9, 7.55–7.56/125.5, 7.55–7.56/127.2, 7.55–7.56/149.2, 7.55–7.56/160.6, 7.66/110.7, 7.66/149.2, 8.34/144.7, 8.34/160.6, 9.09/110.7, 9.09/130.5, 9.09/149.2; GC/MS EI m/z 186 (M^+, 100).

*4.5.6. 2-Methylpyrido[1,2-a]benzimidazole (**7e**).*[14] The compound was purified by chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate gradient (100:0→25:75) and then recrystallized from dichloromethane to give white crystals. Mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (d, J=1.2, 3H), 7.26 (dd, J=9.2, 1.6, 1H), 7.33 (ddd, J=8.4, 7.2, 1.2, 1H), 7.49 (ddd, J=8.4, 7.2, 1.2, 1H), 7.60 (d, J=9.6, 1H), 7.83 (d, J=8.4, 1H), 7.91 (d, J=8.4, 1H), 8.19 (d, J=0.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 110.3, 117.3, 119.8, 120.7, 122.6, 125.3, 128.6, 132.6, 144.6, 147.7; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.39/18.1, 7.26/132.6, 7.33/120.7, 7.49/125.3, 7.60/117.3, 7.83/110.3, 7.91/119.8, 8.19/122.6; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 2.39/8.19, 7.26/7.60, 7.26/8.19, 7.33/7.49, 7.33/7.83, 7.49/7.91; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 2.39/119.8, 2.39/122.6, 2.39/132.6, 7.26/122.6, 7.26/147.7, 7.33/119.8, 7.33/128.6, 7.49/110.3, 7.49/144.6, 7.60/119.8, 7.60/147.7, 7.83/125.3, 7.83/144.6, 7.91/120.7, 7.91/128.6, 8.19/132.6, 8.19/147.7; GC/MS EI m/z 182 (M^+, 100).

*4.5.7. 3-Methylpyrido[1,2-a]benzimidazole (**7f**).*[14] The compound was purified by chromatography on silica gel eluting with ethyl acetate/ethanol (98:2) to give light yellow crystals. Mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.65 (d, J=6.0, 1H), 7.31 (t, J=7.6, 1H), 7.42 (s, 1H), 7.49 (t, J=7.6, 1H), 7.82 (d, J=8.4, 1H), 7.89 (d, J=8.0, 1H), 8.29 (d, J=6.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 110.1, 113.0, 116.0, 120.0, 120.5, 124.2, 125.3, 128.6, 140.7, 144.7, 149.0; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.45/21.8, 6.65/113.0, 7.31/120.5, 7.42/116.0, 7.49/125.3, 7.82/110.1, 7.89/119.6, 8.29/124.2; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.65/7.42, 6.65/8.29, 7.31/7.49, 7.31/7.82, 7.49/7.89; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 2.45/113.0, 2.45/116.0, 2.45/140.7, 6.65/116.0, 6.65/124.2, 7.31/119.6, 7.31/140.7, 7.42/113.0, 7.49/110.1, 7.49/144.7, 7.82/125.3, 7.82/144.7, 7.89/120.5, 7.89/128.6, 8.29/140.7, 8.29/149.0; GC/MS EI m/z 182 (M^+, 100); HRMS (ESI) m/z obsd 183.0913, calcd 183.0917 for $C_{12}H_{10}N_2$ ($M+H^+$).

*4.5.8. 4-Methylpyrido[1,2-a]benzimidazole (**7g**).*[9] This compound was obtained according to the general procedure as slightly colored solid and recrystallized from dichloromethane/petroleum ether (bp 60–80 °C) as light yellow crystals. Mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 6.74 (t, J=6.8, 1H), 7.20 (d, J=6.8, 1H), 7.32–7.36 (m, 1H), 7.49–7.53 (m, 1H), 7.84 (d, J=8.0, 1H),

7.98 (d, J=8.4, 1H), 8.29 (d, J=6.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 110.3, 110.4, 119.9, 120.9, 122.8, 125.4, 127.5, 127.7, 129.1, 144.2, 149.1; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 2.69/17.5, 6.74/110.4, 7.20/127.5, 7.32–7.36/120.9, 7.49–7.53/125.4, 7.84/110.3, 7.98/119.9, 8.29/122.8; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.74/7.20, 6.74/8.29, 7.32–7.36/7.49–7.53, 7.32–7.36/7.84, 7.49–7.53/7.98; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 2.69/127.5, 2.69/149.1, 6.74/122.8, 6.74/127.7, 7.20/122.8, 7.20/149.1, 7.32–7.36/119.9, 7.32–7.36/129.1, 7.49–7.53/110.3, 7.49–7.53/144.2, 7.84/125.4, 7.84/144.2, 7.98/120.9, 7.98/129.1, 8.29/127.5, 8.29/149.0; GC/MS EI m/z 182 (M^+, 100).

*4.5.9. 1-Methylpyrido[1,2-a]benzimidazole (**7h**).*[14] The compound was purified by chromatography on silica gel eluting with ethyl acetate/ethanol gradient (100:0→80:20) as colorless crystals. Mp 106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 3H), 6.56 (d, J=6.4, 1H), 7.28–7.34 (m, 2H), 7.51 (t, J=7.6, 1H), 7.58 (d, J=9.2, 1H), 7.95 (d, J=8.0, 1H), 8.11 (d, J=8.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 110.7, 114.6, 115.3, 119.6, 120.5, 125.1, 129.2, 129.9, 139.0, 145.0, 149.6; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 3.00/21.3, 6.56/110.7, 7.28–7.34/120.5, 7.28–7.34/129.2, 7.51/125.1, 7.58/115.3, 7.95/119.6, 8.11/114.6; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 6.56/7.28–7.34, 7.28–7.34/7.51, 7.28–7.34/7.58, 7.28–7.34/8.11, 7.51/7.95; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 3.00/110.7, 3.00/139.0, 6.56/115.3, 6.56/139.0, 7.28–7.34/119.6, 7.28–7.34/129.9, 7.28–7.34/139.0, 7.28–7.34/149.6, 7.51/114.6, 7.51/145.0, 7.58/110.7, 7.58/149.6, 7.95/120.5, 7.95/129.9, 8.11/125.1, 8.11/145.0; GC/MS EI m/z 182 (M^+, 100).

*4.5.10. Pyrazino[1,2-a]benzimidazole (**7i**).*[41] This compound was purified by chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate gradient (50:50→0:100) as a light brown crystal. Mp 199–200 °C (197–198 °C);[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.54 (m, 1H), 7.63–7.67 (m, 1H), 7.97–7.99 (m, 2H), 8.07 (d, J=8.4, 1H), 8.36–8.37 (m, 1H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.2, 117.8, 121.6, 123.3, 127.1, 127.2, 127.7, 142.2, 144.3, 145.8; ^{1}H/^{13}C HSQC NMR ($CDCl_3$) δ_H/δ_C 7.50–7.54/123.3, 7.63–7.67/127.2, 7.97–7.99/111.8, 7.97–7.99/127.1, 8.07/121.6, 8.36–8.37/117.8, 9.30/145.8; ^{1}H/^{1}H COSY NMR ($CDCl_3$) δ_H/δ_H 7.50–7.54/7.63–7.67, 7.50–7.54/7.97–7.99, 7.63–7.67/8.07, 7.97–7.99/8.36–8.37, 8.36–8.37/9.31; ^{1}H/^{13}C HMBC NMR ($CDCl_3$) δ_H/δ_C 7.50–7.54/121.6, 7.50–7.54/127.7, 7.63–7.67/111.2, 7.63–7.67/144.3, 7.97–7.99/117.8, 7.97–7.99/127.2, 7.97–7.99/144.3, 7.97–7.99/145.8, 8.07/123.3, 8.07/127.7, 8.36–8.37/127.1, 8.36–8.37/142.2, 9.30/127.1, 9.30/142.2; GC/MS EI m/z 169 (M^+, 100).

*4.5.11. 7H-Indolo[2,3-c]isoquinoline (**9**).*[33] This compound was purified by chromatography on silica gel eluting with petroleum ether (bp 60–80 °C)/ethyl acetate gradient (90:10→50:50) and then recrystallized from ethyl acetate to give light yellow crystals. Mp 265–266 °C (lit. 259–260 °C);[33] ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.35 (t, J=7.6, 1H), 7.48 (t, J=7.6, 1H), 7.58 (t, J=7.6, 1H), 7.66 (d, J=8.0, 1H), 7.90–7.94 (m, 1H), 8.26 (d, J=8.4, 1H), 8.56 (d, J=8.0, 1H), 8.72 (d, J=8.4, 1H), 9.20 (s, 1H), 12.24 (br s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 105.1, 111.8, 120.0, 121.1, 122.1, 122.4, 123.5, 124.1, 124.8, 129.4, 131.2, 131.9, 137.2, 147.8, 150.6; ^{1}H/^{13}C HSQC NMR (CD_3COCD_3) δ_H/δ_C 7.35/120.0, 7.48/124.8, 7.58/123.5, 7.66/111.8, 7.90–7.94/131.2, 8.26/129.4, 8.56/122.1, 8.72/122.4, 9.20/150.6; ^{1}H/^{1}H COSY NMR (CD_3COCD_3) δ_H/δ_H 7.35/7.48, 7.35/8.56, 7.48/7.66, 7.58/7.90–7.94, 7.58/8.26, 7.90–7.94/8.72, 9.20/9.20, 12.24/12.24; ^{1}H/^{13}C HMBC NMR (CD_3COCD_3) δ_H/δ_C 7.35/111.8, 7.35/121.1, 7.48/122.1, 7.48/137.2, 7.58/122.4, 7.58/124.1, 7.66/120.0, 7.66/121.1, 7.90–7.94/129.4, 7.90–7.94/131.8, 8.26/131.2, 8.26/131.9, 8.26/150.6, 8.56/105.1, 8.56/124.8, 8.56/137.2, 8.72/105.1, 8.72/123.5, 8.72/124.1, 8.72/131.9, 9.20/124.1, 9.20/129.4, 9.20/131.9, 9.20/147.8, 12.24/105.1, 12.24/121.1, 12.24/137.2, 12.24/147.8; GC/MS EI m/z 218 (M^+, 100).

4.6. General procedure for the synthesis of pyrido[1,2-*a*] benzimidazoles in DMSO

*4.6.1. Pyrido[1,2-a]benzimidazole (**5**).* 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, *t*-BuOK (22 mg, 0.20 mmol) was added, 2-(2-bromophenylamino)pyridine (**4a**, 25 mg, 0.10 mmol) was added, and the reaction mixture was irradiated for 60 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 (2×20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give the crude products. The bromide ions in the aqueous solution were determined potentiometrically.

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Supplementary data

NMR spectra (^{1}H and ^{13}C NMR) of the compounds are provided. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.087.

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