A Valuable Synthesis of Pyrrolo[1,2-*a*]quinoxalines, Indolo[1,2-*a*]quinoxalines and their Aza-Analogues by Palladium-Catalyzed Intramolecular Carbon–Nitrogen Bond Formation

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Abstract: A novel and efficient method for the construction of pyrrolo[1,2-*a*]quinoxalines, indolo[1,2-*a*]quinoxalines and their aza-analogues is described. The reaction involves a Pd-catalyzed intramolecular cyclization as the key step and provides the desired products in only two steps and good overall yields.

Key words: palladium catalyst, aminations, cyclizations, fused-ring systems, indoles, lactams

In recent years, pharmacological evaluation and structure–activity relationships of a series of simple or fused quinoxalinones have been described. Pyrroloquinoxalines and heteroaromatic-related derivatives like pyridopyrroloopirazine have become interesting in the fields of anti-HIV agents (**A**, Figure 1),[1] as hypoglycemic[2] compounds and especially as 5-HT_3 receptor agonists (**B**, Figure 1).[3]

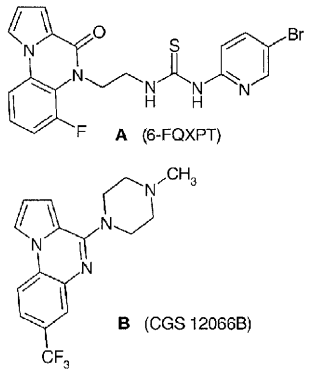

Figure 1

The potential therapeutic role of 5-HT_3 receptor agonists was based on their modulation of acetylcholine release in vivo, which makes these compounds of interest for the treatment of neurodegenerative and neuropsychiatric disorders. These compounds were also evaluated to have analgesic-like properties.[3c] A series of these derivatives have been patented and described as antiallergics,[4] antiasthmatics,[4] and anxiolytics.[3b,4] Tetrahydropyrrolo[1,2-*a*]quinoxalines and tetrahydropyrido[3,2-*e*]pyrrolo[1,2-*a*] pyrazines were reported to show antihypertensive and vascular smooth muscle relaxant activities.[5]

Few methods are available for the synthesis of pyrroloquinoxalines and their aza-analogues. Most of them are based on the N-arylation of pyrrole with 2-nitroaryl derivatives, followed by reduction of the nitro group and cyclization to form the oxo-piperazine ring.[3,4,6] However, these pathways require the use of activated substrates, hazardous reagents such as phosgene or harsh reaction conditions. Also, the procedures for azole arylation are limited. Phenylation with electrophilic aromatic compounds was reported,[7] while the reaction mediated by KF adsorbed onto alumina was efficient only with electron-poor aryl halides.[8] The copper-mediated azole arylation requires high temperatures and often toxic solvents,[9] the aza-Wittig reaction of iminophophorane pyrrole derivatives was also reported.[10] The indoloquinoxalines were prepared starting from 1-(2-nitrophenyl)indol-2-carboxylate[11] in a similar manner as reported for pyrrole derivatives or via photocyclization of 2-aroylquinoxalines.[12]

A technique which involves the transition metal-catalyzed displacement of a suitable leaving group would be particularly useful, since many transition metal coupling reactions occur under mild conditions and are highly tolerant of a variety of functional groups.[13] In particular the catalysis by palladium has become an efficient and useful process for the synthesis of heterocyclic systems.[14] In this context, the Pd-catalyzed amination of aryl halides is an important methodology for C–N bond formation and has many applications for the synthesis of functionalized anilines.[15] In contrast, the Pd-catalyzed coupling to form aryl nitrogen bonds in *N*-aryl azoles has been reported only recently,[16] but intermolecular reactions were exclusively observed.

As a part of our ongoing program to develop synthetic applications of Pd-catalyzed amination reactions on heterocyclic substrates,[17] we report here the synthesis of pyrroloquinoxalines and indoloquinoxalines by way of pyrrole-2-carboxamides or indole-2-carboxamides bearing a suitable *o*-halosubstituted aryl- or heteroaryl group at the amide nitrogen. The synthetic strategy, involving few steps, was based on the palladium-catalyzed intramolecular N-arylation forming a C–N bond on the oxo-piperazine ring. Starting from pyrrole- or indole-2-carboxylic acids **1** and 2-haloanilines or halopyridines **2**, the amides

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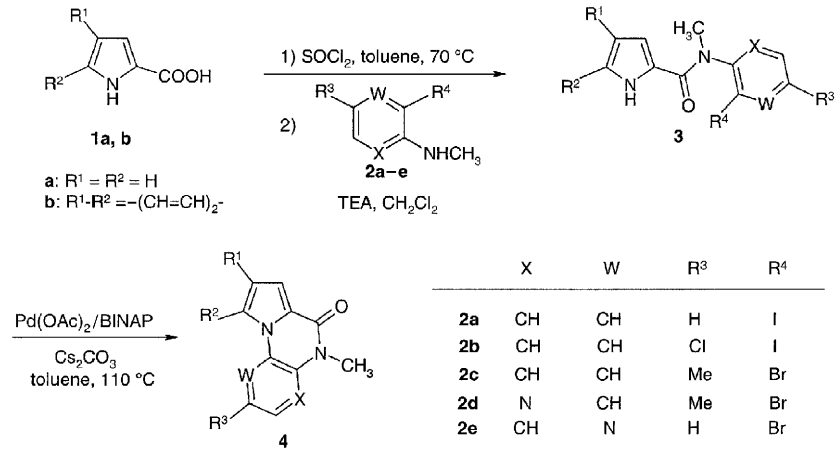

	X	W	R³	R⁴
2a	CH	CH	H	I
2b	CH	CH	Cl	I
2c	CH	CH	Me	Br
2d	N	CH	Me	Br
2e	CH	N	H	Br

Scheme 1

3 were prepared via unisolable acyl chlorides in the presence of triethylamine. The preliminary methylation of the commercially available 2-haloanilines or halopyridines was effected to avoid later a concomitant palladium complexation. The amides **3** were then treated following the Buchwald–Hartwig reaction conditions to give the cyclized products **4** as depicted in Scheme 1.

Table 1 Compounds **3**,**4** Prepared

Substrates		Products (Yield in %)	
1a	**2a**	**3aa** (78)	**4aa** (91)
1a	**2b**	**3ab** (82)	**4ab** (79)
1a	**2c**	**3ac** (58)	**4ac** (90)
1a	**2d**	**3ad** (59)	**4ad** (95)
1a	**2e**	**3ae** (64)	**4ae** (74)
1b	**2a**	**3ba** (66)	**4ba** (98)
1b	**2b**	**3bb** (63)	**4bb** (77)
1b	**2c**	**3bc** (68)	**4bc** (66)
1b	**2d**	**3bd** (55)	**4bd** (69)
1b	**2e**	**3be** (60)	**4be** (74)

The best conditions were $Pd(OAc)_2$ (5 mol%) in presence of BINAP (10 mol%) and Cs_2CO_3 as base in toluene as solvent, heating the mixture at 110 °C for 24 h. The possible concomitant Heck pathway involving cyclization on the 3-position of the pyrrole nucleus was never observed. As shown in Table 1, our approach is general for the preparation giving good yields of pyrrolo[1,2-*a*]quinoxalin-4-ones and indolo[1,2-*a*]quinoxalin-6-ones from haloanilines as well as of pyridopyrrolopirazines and pyridoindolopirazines from haloaminopyridines. The latter goal – the obtainment of pyrido-fused compounds **4ad**, **4ae**, **4bd** and **4be** – is particularly noteworthy in view of the paucity of representatives as well as synthetic entries reported in the literature.[3b,c,4a,b]

In summary, a concise and efficient synthetic sequence to various heteropolycyclic products is reported. Different isomeric and homologous derivatives are under study.

Melting points were measured with a Büchi B-540 heating unit and are not corrected. NMR spectra were recorded with an AVANCE 400 Bruker at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$. Chemical shifts, relative to TMS as internal standard, are given as δ values in ppm. IR spectra were taken with a Perkin-Elmer 1725X FT-IR spectrophotometer. Compounds **2a**[18] and **2c**[19] were prepared according to literature procedures.

Synthesis of (4-Chloro-2-iodophenyl)methylamine (2b)

A solution of 4-chloro-2-iodo-aniline (2.53 g, 10 mmol) in anhyd THF (50 mL) was cooled to –78 °C under N_2 atmosphere, then *n*-BuLi 1.6 M (7.5 mL, 12 mmol) was added dropwise and the resulting solution was stirred at –78 °C for 30 min. After this time $(CH_3)_2SO_4$ (1.42 mL, 15 mmol) was added and the mixture was allowed to warm to r.t. After 16 h the solvent was evaporated and the residue diluted with 1 M HCl (10 mL) and extracted with Et_2O (30 mL). The organic layer was stirred 30 min with concd NH_4OH (30 mL) and the aqueous layer was removed. The organic phase was washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (light petroleum → CH_2Cl_2–light petroleum, 5:1).

Yield: 76%, mp 53–54 °C (white crystals from hexane).

IR (Nujol): 3405 cm^{-1}.

^{1}H NMR: δ = 2.81 (s, 3 H), 4.20 (br s, 1 H, absent after deuteration), 6.46 (dd, *J* = 1.8, 7.4 Hz, 1 H), 7.26 (d, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR: δ = 36.0 (q), 89.2 (s), 121.0 (d), 124.0 (s), 124.7 (d), 140.5 (d), 149.3 (s).

Anal. Calcd for C_7H_7ClIN (267.49): C, 36.23; H, 3.04; N, 6.04. Found: C, 36.43; H, 2.97; N, 6.15.

Synthesis of *N*-(3-Bromo-5-methylpyridin-2-yl)-*N*-methylamine (2d)

To a solution of 2-amino-3-bromo-5-methylpyridine (2 g, 10.7 mmol) in anhyd THF (50 mL) cooled to 0 °C, 60% NaH (556 mg, 13.9 mmol) was added in small portions under N_2 atmosphere. The

resulting mixture was stirred and allowed to warm to r.t., then MeI (1.34 mL, 21.4 mmol) was added dropwise in anhyd THF (5 mL). After 4 h the solvent was evaporated and the residue diluted with 1 M HCl (10 mL) and extracted with Et_2O (2 × 20 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (CH_2Cl_2).

Yield: 87%, yellow oil.

IR (film): 3440 cm^{-1}.

^1H NMR: δ = 2.32 (s, 3 H), 2.47 (s, 3 H), 4.41 (br s, 1 H, absent after deuteration), 7.81 (d, *J* = 1.7 Hz, 1 H), 8.27 (d, *J* = 1.7 Hz, 1 H).

^{13}C NMR: δ = 26.4 (q), 34.1 (q), 105.6 (s), 124.7 (s), 139.6 (d), 148.0 (d), 158.2 (s).

Anal. Calcd for $C_7H_9BrN_2$ (201.07): C, 41.82; H, 4.51; N, 13.93. Found: C, 41.65; H, 4.59; N, 13.81.

Synthesis of *N*-(2-Bromopyridin-3-yl)-*N*-methylamine (2e)

2 M LDA (6.95 mL, 13.9 mmol) was added dropwise to an anhyd THF solution (50 mL) of 3-amino-2-bromopyridine (2 g, 11.6 mmol) at –78 °C, under N_2 atmosphere. The mixture was warmed to 0 °C and allowed to react for 1 h, then cooled to –78 °C before MeI (1.44 mL, 23.2 mmol) was added dropwise. The reaction was kept at –78 °C for 1 h, then allowed to warm to r.t. overnight. Aq NH_4Cl (30 mL) and EtOAc (30 mL) were added. The organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). The mixture was filtered and concentrated under vacuum. The crude product was purified by chromatography on silica gel (light petroleum → light petroleum–Et_2O, 5:1).

Yield: 85%, yellow oil.

IR (film): 3420 cm^{-1}.

^1H NMR: δ = 2.88 (s, 3 H), 4.42 (br s, 1 H, absent after deuteration), 6.81 (d, *J* = 8.1 Hz, 1 H), 7.09 (dd, *J* = 7.9, 8.1 Hz, 1 H), 7.68 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR: δ = 36.2 (q), 124.6 (d), 125.2 (d), 134.6 (s), 142.3 (d), 149.1 (s).

Anal. Calcd for $C_6H_7BrN_2$ (187.04): C, 38.53; H, 3.77; N, 14.98. Found: C, 38.70; H, 3.65; N, 14.87.

Preparation of the Heteroamides 3; General Procedure

A solution of **1** (10 mmol) and $SOCl_2$ (3.2 mL, 44.5 mmol) in toluene (10 mL) was stirred at 70 °C for 2.5 h. After evaporation of the solvent, the residue was taken up with CH_2Cl_2 (20 mL). A solution of **2** (13.3 mmol) and TEA (1.9 mL, 13.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. After stirring for 5 h at r.t. the solution was washed with 5% HCl (2 × 20 mL) and then with 5% aq NaOH (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on a silica gel column (CH_2Cl_2) to give compounds **3**. Compounds **3aa**, **3ab**, **3ae**, **3bc** were directly crystallized.

***N*-(2-Iodophenyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (3aa)[20]**

Yield: 78%, mp 182–183 °C (white crystals from CH_2Cl_2–hexane).

IR (Nujol): 1619, 3259 cm^{-1}.

^1H NMR: δ = 3.37 (s, 3 H), 4.83 (br s, 1 H), 5.95 (br s, 1 H), 6.85 (s, 1 H), 7.17 (ddd, *J* = 1.6, 7.4, 8.6 Hz, 1 H), 7.38 (dd, *J* = 1.8, 8.6 Hz, 1 H), 7.45 (ddd, *J* = 1.8, 7.4, 8.2 Hz, 1 H), 7.97 (dd, *J* = 1.6, 8.2 Hz, 1 H), 9.49 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 37.8 (q), 100.2 (s), 109.9 (d), 113.8 (d), 121.6 (d), 126.6 (d), 130.1 (d), 130.3 (d), 134.1 (s), 138.4 (d), 146.7 (s), 162.0 (s).

Anal. Calcd for $C_{12}H_{11}IN_2O$ (325.99): C, 44.19; H, 3.40; N, 8.59. Found: C, 44.02; H, 3.58; N, 8.46.

***N*-(4-Chloro-2-iodophenyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (3ab)**

Yield: 82%, mp 195 °C (cream crystals from CH_2Cl_2–hexane).

IR (Nujol): 1623, 3296 cm^{-1}.

^1H NMR: δ = 3.31 (s, 3 H), 4.72 (d, *J* = 1.4 Hz, 1 H), 5.97 (d, *J* = 2.2 Hz, 1 H), 6.84 (d, *J* = 1.4 Hz, 1 H), 7.26 (d, *J* = 6.6 Hz, 1 H), 7.41 (d, *J* = 6.6 Hz, 1 H), 7.95 (dd, *J* = 1.4, 2.2 Hz, 1 H), 9.49 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 37.4 (q), 102.0 (s), 109.7 (d), 113.4 (d), 122.2 (d), 125.3 (s), 130.7 (d), 131.4 (d), 134.4 (s), 139.5 (d), 146.3 (s), 161.1 (s).

Anal. Calcd for $C_{12}H_{10}ClIN_2O$ (360.58): C, 39.97; H, 2.80; N, 7.77. Found: C, 39.80; H, 2.99; N, 7.90.

***N*-(2-Bromo-4-methylphenyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (3ac)**

Yield: 58%, mp 207–210 °C (cream powder from CH_2Cl_2–hexane).

IR (Nujol): 1633, 3296 cm^{-1}.

^1H NMR: δ = 2.44 (s, 3 H), 3.36 (s, 3 H), 4.94 (s, 1 H), 5.95 (s, 1 H), 6.85 (s, 1 H), 7.20–7.28 (2 H, overlapping), 7.55 (s, 1 H), 9.74 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 21.3 (q), 37.3 (q), 110.3 (d), 113.2 (d), 121.3 (d), 123.9 (s), 125.4 (s), 130.1 (d), 130.4 (d), 134.7 (d), 140.7 (s), 140.9 (s), 161.7 (s).

Anal. Calcd for $C_{13}H_{13}BrN_2O$ (293.17): C, 53.26; H, 4.47; N, 9.56. Found: C, 53.39; H, 4.56; N, 9.64.

***N*-(3-Bromo-5-methylpyridin-2-yl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (3ad)**

Yield: 59%, mp 161–162 °C (cream crystals from Et_2O).

IR (Nujol): 1603, 3295 cm^{-1}.

^1H NMR: δ = 2.43 (s, 3 H), 3.40 (s, 3 H), 5.05 (d, *J* = 1.6 Hz, 1 H), 5.95 (d, *J* = 2.7 Hz, 1 H), 6.84 (d, *J* = 1.6, 2.7 Hz, 1 H), 7.83 (d, *J* = 2.1 Hz, 1 H), 8.38 (d, *J* = 2.1 Hz, 1 H), 9.71 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 18.1 (q), 35.6 (q), 110.2 (d), 112.5 (d), 120.3 (s), 121.6 (d), 125.5 (s), 135.8 (s), 143.4 (d), 149.2 (d), 152.6 (s), 161.9 (s).

Anal. Calcd for $C_{12}H_{12}BrN_3O$ (294.15): C, 49.00; H, 4.11; N, 14.29. Found: C, 49.19; H, 3.95; N, 14.38.

***N*-(2-Bromopyridin-3-yl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (3ae)**

Yield: 64%, mp 185–187 °C (ivory crystals from Et_2O).

IR (Nujol): 1601, 3296 cm^{-1}.

^1H NMR: δ = 3.40 (s, 3 H), 4.95 (br s, 1 H), 5.98 (s, 1 H), 6.88 (s, 1 H), 7.42 (dd, *J* = 7.6, 7.7 Hz, 1 H), 7.70 (dd, *J* = 1.7, 7.7 Hz, 1 H), 8.49 (dd, *J* = 1.7, 7.6 Hz, 1 H), 9.82 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 37.3 (q), 110.5 (d), 113.6 (d), 122.0 (d), 123.8 (d), 124.9 (s), 139.1 (d), 141.1 (s), 144.2 (s), 149.9 (d), 161.1 (s).

Anal. Calcd for $C_{11}H_{10}BrN_3O$ (280.13): C, 47.17; H, 3.60; N, 15.00. Found: C, 47.23; H, 3.71; N, 14.87.

***N*-(2-Iodophenyl)-*N*-methyl-1*H*-indole-2-carboxamide (3ba)**

Yield: 66%, mp 201–202 °C (white crystals from Et_2O).

IR (Nujol): 1608, 3279 cm^{-1}.

^1H NMR: δ = 3.42 (s, 3 H), 5.14 (s, 1 H), 7.04 (dd, *J* = 7.2, 7.4 Hz, 1 H), 7.18–7.24 (overlapping, 2 H), 7.33–7.50 (overlapping, 4 H),

7.99 (dd, *J* = 1.0, 7.6 Hz, 1 H), 9.38 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 37.8 (q), 100.0 (s), 106.6 (d), 111.9 (d), 120.4 (d), 122.4 (d), 124.6 (s), 124.8 (d), 130.1 (d), 130.3 (d), 130.6 (d), 135.7 (s), 140.4 (s), 140.6 (d), 146.4 (s), 162.0 (s).

Anal. Calcd for $C_{16}H_{13}IN_2O$ (376.20): C, 51.08; H, 3.48; N, 7.45. Found: C, 51.17; H, 3.57; N, 7.60.

_N_-(4-Chloro-2-iodophenyl)-_N_-methyl-1_H_-indole-2-carboxamide (3bb)

Yield: 63%, mp 188–190 °C (cream crystals from EtOAc–hexane).

IR (Nujol): 1605, 3281 cm^{-1}.

^{1}H NMR: δ = 3.42 (s, 3 H), 5.31 (s, 1 H), 7.06 (dd, *J* = 7.5, 7.7 Hz, 1 H), 7.25 (d, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.40–7.48 (overlapping, 2 H), 7.50 (dd, *J* = 2.3, 8.3 Hz, 1 H), 8.01 (d, *J* = 2.3 Hz, 1 H), 9.67 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 38.0 (q), 100.5 (s), 106.9 (d), 112.1 (d), 120.8 (d), 122.7 (d), 125.2 (d), 128.2 (s), 129,6 (s), 130.5 (d), 130.7 (d), 135.5 (s), 135.9 (s), 140.2 (d), 145.4 (s), 162.1 (s).

Anal. Calcd for $C_{16}H_{12}ClIN_2O$ (410.64): C, 46.80; H, 2.95; N, 6.82. Found: C, 46.97; H, 2.99; N, 6.96.

_N_-(2-Bromo-4-methylphenyl)-_N_-methyl-1_H_-indole-2-carboxamide (3bc)

Yield: 68%, mp 235–236 °C (cream crystals from CH_2Cl_2).

IR (Nujol): 1601, 3280 cm^{-1}.

^{1}H NMR: δ = 2.33 (s, 3 H), 3.28 (s, 3 H), 5.17 (s, 1 H), 6.86 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.06 (dd, *J* = 7.4, 7.7 Hz, 1 H), 7.12 (d, *J* = 7.7 Hz, 1 H), 7.16 (d, *J* = 8.3 Hz, 1 H), 7.24 (d, *J* = 7.4 Hz, 1 H), 7.30 (d, *J* = 8.3 Hz, 1 H), 7.43 (s, 1 H), 10.10 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 21.1 (q), 37.5 (q), 105.9 (d), 112.2 (d), 120.0 (d), 122.1 (d), 123.3 (s), 124.2 (d), 127.7 (s), 130.1 (d), 130.2 (d), 134.5 (d), 135.9 (s), 140.4 (s), 140.9 (s), 141.0 (s), 162.2 (s).

Anal. Calcd for $C_{17}H_{15}BrN_2O$ (343.23): C, 59.49; H, 4.41; N, 8.16. Found: C, 59.60; H, 4.47; N, 7.99.

_N_-(3-Bromo-5-methylpyridin-2-yl)-_N_-methyl-1_H_-indole-2-carboxamide (3bd)

Yield: 55%, mp 205–206 °C (light yellow crystals from CH_2Cl_2–hexane).

IR (Nujol): 1621, 3299 cm^{-1}.

^{1}H NMR: δ = 2.46 (s, 3 H), 3.47 (s, 3 H), 5.34 (br s, 1 H), 7.05 (dd, *J* = 7.3, 7.7 Hz, 1 H), 7.25 (dd, *J* = 7.7, 8.0 Hz, 1 H), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 1.8 Hz, 1 H), 8.42 (d, *J* = 1.8 Hz, 1 H), 9.30 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 18.2 (q), 36.0 (q), 105.9 (d), 112.0 (d), 120.7 (d), 121.3 (s), 122.5 (d), 123.1 (s), 125.0 (s), 126.1 (d), 135.9 (s), 136.0 (s), 143.5 (d), 149.3 (d), 152.5 (s), 162.8 (s).

Anal. Calcd for $C_{16}H_{14}BrN_3O$ (344.21): C, 55.83; H, 4.10; N, 12.21. Found: C, 55.72; H, 3.97; N, 12.33.

_N_-(2-Bromopyridin-2-yl)-_N_-methyl-1_H_-indole-2-carboxamide (3be)

Yield: 60%, mp 195–196 °C (ochre crystals from CH_2Cl_2–hexane).

IR (Nujol): 1632, 3183 cm^{-1}.

^{1}H NMR: δ = 3.49 (s, 3 H), 5.31 (br s, 1 H), 7.06 (dd, *J* = 7.4, 7.6 Hz, 1 H), 7.26 (dd, *J* = 7.4, 7.9 Hz, 1 H), 7.40–7.47 (overlapping, 3 H), 7.77 (dd, *J* = 1.8, 7.7 Hz, 1 H), 8.56 (dd, *J* = 1.8, 4.7 Hz, 1 H), 9.77 (br s, 1 H, absent after deuteration).

^{13}C NMR: δ = 37.6 (q), 106.9 (d), 112.1 (d), 120.9 (d), 122.6 (d), 124.1 (d), 125.4 (d), 128.0 (s), 129.2 (s), 135.9 (s), 138.8 (s), 139.0 (d), 139.4 (s), 149.8 (d), 150.2 (s).

Anal. Calcd for $C_{15}H_{12}BrN_3O$ (330.19): C, 54.57; H, 3.66; N, 12.73. Found: C, 54.66; H, 3.78; N, 12.90.

Cyclization of Heteroamides 3 to Give Compounds 4; General Procedure

A mixture of compound **3** (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), BINAP (62 mg, 0.1 mmol) and Cs_2CO_3 (325 mg, 1 mmol) in toluene (10 mL) was stirred at 110 °C for 24 h. The residue was diluted with brine (15 mL) and extracted with Et_2O (2 × 20 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on a silica gel column, eluent CH_2Cl_2–Et_2O (10:1) to give compounds **4**. Compound **4aa** was directly crystallized.

5-Methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (4aa)[6c]

Yield: 91%, mp 134–135 °C (cream crystals from CH_2Cl_2–hexane).

IR (Nujol): 1624 cm^{-1}.

^{1}H NMR: δ = 3.70 (s, 3 H), 6.68 (dd, *J* = 3.1, 3.1 Hz, 1 H), 7.25–7.28 (overlapping, 2 H), 7.33–7.39 (overlapping, 2 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR: δ = 28.8 (q), 113.0 (d), 113.6 (d), 114.9 (d), 116.0 (d), 116.3 (d), 123.2 (d), 123.7 (s), 124.4 (s), 125.9 (d), 130.7 (s), 155.9 (s).

Anal. Calcd for $C_{12}H_{10}N_2O$ (198.23): C, 72.71; H, 5.08; N, 14.13. Found: C, 72.65; H, 5.17; N, 13.99.

8-Chloro-5-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (4ab)

Yield: 79%, mp 189–190 °C (ochre crystals from CH_2Cl_2).

IR (Nujol): 1637 cm^{-1}.

^{1}H NMR: δ = 3.64 (s, 3 H), 6.68 (dd, *J* = 1.2, 3.4 Hz, 1 H), 7.21–7.24 (overlapping, 2 H), 7.28 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.58 (d, *J* = 1.2 Hz, 1 H), 7.64 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR: δ = 28.9 (q), 113.6 (d), 114.1 (d), 115.0 (d), 116.6 (d), 117.1 (d), 123.6 (s), 125.0 (s), 125.7 (d), 128.7 (s), 129.3 (s), 155.5 (s).

Anal. Calcd for $C_{12}H_9ClN_2O$ (232.66): C, 61.95; H, 3.90; N, 12.04. Found: C, 61.81; H, 3.97; N, 11.86.

5,8-Dimethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (4ac)

Yield: 90%, mp 125–126 °C (light yellow crystals from CH_2Cl_2–hexane).

IR (Nujol): 1639 cm^{-1}.

^{1}H NMR: δ = 2.45 (s, 3 H), 3.65 (s, 3 H), 6.79 (dd, *J* = 1.2, 3.4 Hz, 1 H), 7.20–7.27 (overlapping, 2 H), 7.31 (dd, *J* = 1.0, 8.8 Hz, 1 H), 7.61 (d, *J* = 1.2 Hz, 1 H), 7.73 (d, *J* = 1.0 Hz, 1 H).

^{13}C NMR: δ = 19.4 (q), 28.2 (q), 112.6 (d), 114.2 (d), 115.4 (d), 116.6 (d), 117.5 (d), 123.8 (d), 125.4 (s), 125.5 (d), 128.7 (s), 129.3 (s), 165.5 (s).

Anal. Calcd for $C_{13}H_{12}N_2O$ (212.09): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.70; H, 5.55; N, 13.39.

2,5-Dimethylpyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (4ad)

Yield: 95% mp 241–244 °C (ivory crystals from Et_2O).

IR (Nujol): 1650 cm^{-1}.

^{1}H NMR: δ = 2.45 (s, 3 H), 3.77 (s, 3 H), 6.69 (dd, *J* = 1.2, 3.6 Hz, 1 H), 7.23 (d, *J* = 1.2 Hz, 1 H), 7.61 (d, *J* = 3.6 Hz, 1 H), 7.73 (s, 1 H), 8.19 (s, 1 H).

^{13}C NMR: δ = 18.2 (q), 28.4 (q), 113.2 (d), 113.6 (d), 116.4 (d), 120.2 (s), 122.3 (d), 123.9 (s), 128.2 (s), 140.8 (s), 144.8 (d), 156.5 (s).

Anal. Calcd for $C_{12}H_{11}N_3O$ (213.14): C, 67.59; H, 5.20; N, 19.71. Found: C, 67.70; H, 5.07; N, 19.90.

5-Methylpyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one (4ae)
Yield: 74%, mp 196–197 °C (ivory crystals from Et_2O).

IR (Nujol): 1644 cm^{-1}.

^{1}H NMR: δ = 3.62 (s, 3 H), 6.67 (s, 1 H), 7.25–7.29 (overlapping, 2 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 8.08 (s, 1 H), 8.20 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR: δ = 28.4 (q), 113.8 (d), 114.5 (d), 117.9 (d), 121.3 (d), 122.8 (d), 123.6 (s), 126.5 (s), 136.4 (s), 141.7 (d), 155.4 (s).

Anal. Calcd for $C_{11}H_9N_3O$ (199.21): C, 66.32; H, 4.55; N, 21.09. Found: C, 66.44; H, 4.63; N, 20.90.

5-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4ba)
Yield: 98%, mp 158–160 °C (cream crystals from CH_2Cl_2–hexane).

IR (Nujol): 1631 cm^{-1}.

^{1}H NMR: δ = 3.71 (s, 3 H), 7.31–7.39 (overlapping, 4 H), 7.51 (ddd, *J* = 0.8, 8.1, 8.6 Hz, 1 H), 7.58 (s, 1 H), 7.89 (d, *J* = 7.9 Hz, 1 H), 8.25 (d, *J* = 8.6 Hz, 1 H), 8.34 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR: δ = 29.3 (q), 107.2 (d), 114.6 (d), 115.7 (d), 115.9 (d), 122.8 (d), 123.6 (d), 123.8 (d), 124.5 (d), 125.7 (d), 127.0 (s), 128.5 (s), 129.6 (s), 130.2 (s), 134.6 (s), 156.9 (s).

Anal. Calcd for $C_{16}H_{12}N_2O$ (248.29): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.52; H, 4.97; N, 11.37.

2-Chloro-5-methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4bb)
Yield: 77%, mp 204–206 °C (ivory crystals from CH_2Cl_2–hexane).

IR (Nujol): 1627 cm^{-1}.

^{1}H NMR: δ = 3.63 (s, 3 H), 7.10 (d, *J* = 7.3 Hz, 1 H), 7.17 (d, *J* = 7.0 Hz, 1 H), 7.23 (s, 1 H), 7.33 (dd, *J* = 7.3, 7.6 Hz, 1 H), 7.50 (dd, *J* = 7.0, 7.6 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.24 (s, 1 H).

^{13}C NMR: δ = 29.9 (q), 107.8 (d), 114.3 (d), 115.7 (d), 116.9 (d), 123.2 (d), 123.6 (d), 124.2 (d), 126.1 (d), 127.9 (s), 128.2 (s), 128.8 (s), 128.9 (s), 129.4 (s), 134.7 (s), 156.5 (s).

Anal. Calcd for $C_{16}H_{11}ClN_2O$ (282.73): C, 67.97; H, 3.92; N, 9.91. Found: C, 67.80; H, 3.97; N, 9.84.

2,5-Dimethylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (4bc)
Yield: 66%, mp 216–217 °C (ivory crystals from Et_2O).

IR (Nujol): 1627 cm^{-1}.

^{1}H NMR: δ = 2.54 (s, 3 H), 3.71 (s, 3 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 1 H), 7.38 (dd, *J* = 7.0, 7.4 Hz, 1 H), 7.53 (ddd, *J* = 1.0, 7.0, 8.6 Hz, 1 H), 7.59 (s, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H), 8.18 (s, 1 H), 8.30 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR: δ = 21.6 (q), 29.3 (q), 107.1 (d), 114.7 (d), 115.8 (d), 116.3 (d), 122.7 (d), 123.6 (d), 125.2 (d), 125.5 (d), 127.0 (s), 128.0 (s), 128.7 (s), 129.6 (s), 133.5 (s), 134.6 (s), 156.9 (s).

Anal. Calcd for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.71; H, 5.43; N, 10.79.

2,5-Dimethylpyrido[2′,3′:5,6]pyrazino[1,2-*a*]indol-6(5*H*)-one (4bd)
Yield: 69%, mp 145 °C (cream crystals from Et_2O–hexane).

IR (Nujol): 1630 cm^{-1}.

^{1}H NMR: δ = 2.53 (s, 3 H), 3.82 (s, 3 H), 7.41 (dd, *J* = 7.4, 7.6 Hz, 1 H), 7.55 (dd, *J* = 7.6, 8.2 Hz, 1 H), 7.62 (s, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 8.17 (s, 1 H), 8.20 (d, *J* = 7.4 Hz, 1 H), 8.37 (s, 1 H).

^{13}C NMR: δ = 20.6 (q), 29.7 (q), 107.5 (d), 111.6 (s), 114.1 (d), 122.9 (d), 123.2 (d), 123.9 (d), 126.0 (d), 128.3 (s), 128.4 (s), 129.7 (s), 134.7 (s), 142.7 (d), 157.6 (s).

Anal. Calcd for $C_{16}H_{13}N_3O$ (263.30): C, 72.99; H, 4.98; N, 15.96. Found: C, 72.80; H, 4.91; N, 15.88.

5-Methylpyrido[3′,2′:5,6]pyrazino[1,2-*a*]indol-6(5*H*)-one (4be)
Yield: 74%, mp 197–199 °C (white crystals from CH_2Cl_2–hexane).

IR (Nujol): 1633 cm^{-1}.

^{1}H NMR: δ = 3.69 (s, 3 H), 7.26 (dd, *J* = 7.3, 8.0 Hz, 1 H), 7.41 (dd, *J* = 7.4, 7.5 Hz, 1 H), 7.54–7.60 (overlapping, 3 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 8.35 (d, *J* = 7.3 Hz, 1 H), 9.21 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR: δ = 28.8 (q), 108.5 (d), 117.9 (d), 119.5 (d), 122.1 (d), 122.6 (d), 123.7 (d), 125.9 (s), 126.2 (d), 127.7 (s), 129.0 (s), 134.9 (s), 139.6 (s), 141.8 (d), 156.4 (s).

Anal. Calcd for $C_{15}H_{11}N_3O$ (249.27): C, 72.28; H, 4.45; N, 15.86. Found: C, 72.41; H, 4.57; N, 15.93.

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