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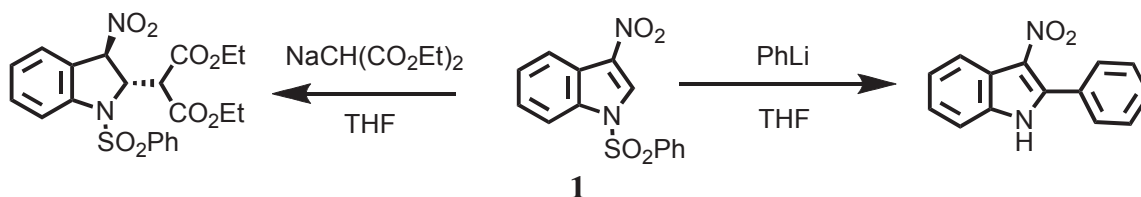
NUCLEOPHILIC ADDITION OF HETARYLLITHIUM COMPOUNDS TO 3-NITRO-1-(PHENYLSULFONYL)INDOLE: SYNTHESIS OF TETRACYCLIC THIENO[3,2-*c*]- δ -CARBOLINES

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Abstract – 3-Nitro-1-(phenylsulfonyl)indole undergoes addition of aryl- and hetaryllithium nucleophiles to produce 2-substituted-3-nitroindoles. Mild reductive–acylation provides excellent access to 3-amido-2-hetarylindoles from which new thieno[3,2-*c*]- δ -carboline are synthesized by cyclodehydration.

The biochemical ubiquity and medicinal success of the indole motif has earned this substructure ‘privileged’ status in drug discovery and a deep history of investigation stretching well over a century.¹ Typical of π -excessive heteroaromatics, the literature of indole is characterized by electrophilic substitution.² Reversal of this traditional reactivity offers an opposite and complementary utility; the conception of electrophilic indole has captured the imagination of several groups.³ Early pioneers employed a complicit leaving group at N-1 to facilitate a formal S_N2' by attack at C-3.⁴ The chemistry of 1-hydroxyindole has proven to be a versatile methodology^{4b} that continues to yield new applications,^{4c} though the substitution itself remains particularly specialized. Arylsulfonyl groups provide a flexible⁵ and accessible alternative in exchange for greatly attenuated reactivity. Although 1-(phenylsulfonyl)indole does not engage in S_NAr , if augmented with powerful withdrawing groups, the polarizable indole double bond becomes receptive to a variety of nucleophiles.⁶



Scheme 1. 3-Nitro-1-(phenylsulfonyl)indole as a Michael acceptor

[†] Dedicated to Professor Akira Suzuki in celebration of his 80th birthday

During our first survey of highly deactivated 3-nitro-1-(phenylsulfonyl)indole (**1**) we observed the direct addition of diethyl malonate anion to furnish the *trans*-dihydroindole product.^{6a} Due to the conventional nucleophilicity of indole, formation of carbon-carbon bonds at C-2 often relies on α -lithiation⁷ and is limited to electrophilic reagents; 2-hetarylindoles with π -excessive hetaromatics are especially inaccessible without the use of precious metals.⁸ We now report our investigation of nucleophilic addition to 3-nitro-1-(phenylsulfonyl)indole (**1**) using hetaryllithium compounds as a means of effecting arylation at C-2. In contrast with our initial enolate example,^{6a} conjugate addition of aryllithium produces the unprotected 2-aryl-3-nitroindole (Scheme 1). Access to 2-hetaryl substituted indoles has allowed us to synthesize the previously unknown tetracyclic hetero[3,2-*c*]- δ -carboline ring system.

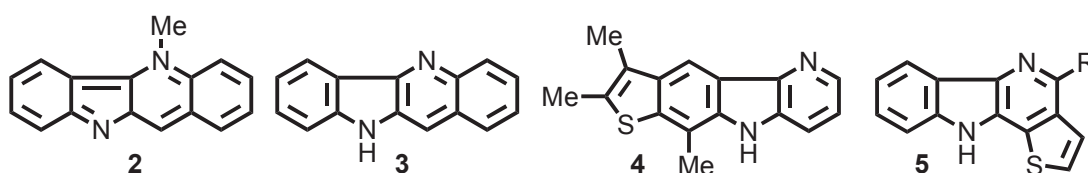
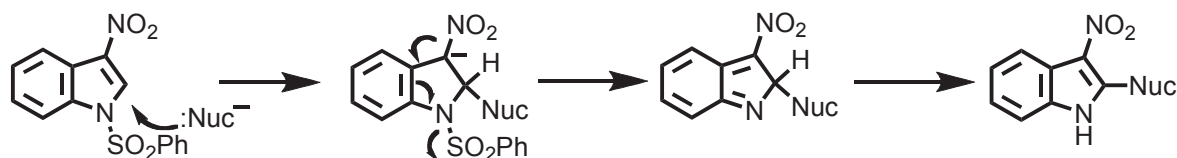


Figure 1. Cryptolepine (**2**), Quindoline (**3**), a potent phototherapeutic **4**, and novel system **5**

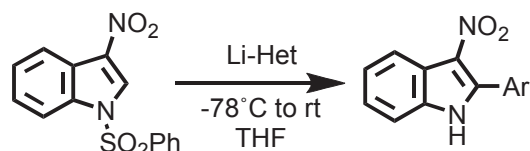
The relatively obscure δ -carboline system is represented in only a handful of natural products, predominantly the indoloquinoline alkaloids of *Cryptolepis sanguinolenta*.⁹ While the extensive biological activity of the cryptolepine family encompasses antibacterial,^{10a} antiplasmodial,^{10b} antihyperglycemic,^{10c} antimuscarinic,^{10d} and anti-inflammatory activity,^{10e} synthetic benzo- δ -carbolines have primarily been investigated as antimalarial and anticancer agents.¹¹ Isomeric and analogous systems attract much of the same focus.¹² Despite a renewed interest in novel heterocyclic ring structures, reported new systems average fewer than 10 per year.¹³ The first thieno- δ -carboline (**4**), synthesized in 2006 as an ellipticine analogue, has found success as a photosensitizer against human tumor cells.¹⁴ The indolo[3,2-*b*]thieno[2,3-*d*]pyridine system (**5**), isoelectronic with a score of biologically active compounds, represents a novel ring system.

Synthesis of 2-aryl and 2-hetaryl-3-nitroindoles

Conjugate addition of hetaryllithium and aryllithium compounds to 3-nitro-1-(phenylsulfonyl)indole^{6a} (**1**) furnished 2-substituted-3-nitroindoles **6-13**. Addition is presumed to proceed in a Michael fashion producing a stabilized carbanion at C-3 (Scheme 2). Tandem loss of phenylsulfinate was prompt in most cases and resulted in exclusive formation of the indole product (Table 1).



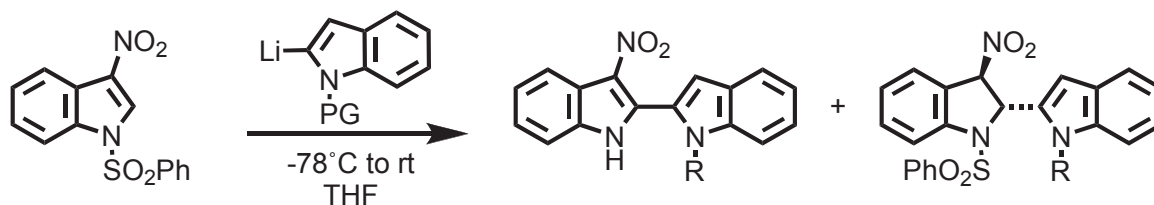
Scheme 2. Proposed mechanism of addition/elimination

**Table 1.** Addition of Hetaryllithiums to 3-Nitro-1-(Phenylsulfonyl)indole **1**

Entry	Product	Yield	Entry	Product	Yield
6^a		60%	10^b		86%
7^a		64%	11^b		67%
8^a		58%	12^b		61%
9^a		79%	13^c		75%

Hetaryllithium prepared by various methods: a. direct lithiation by LDA b. lithium-bromine exchange with *t*-Buli c. lithium-iodine exchange with *t*-Buli

N-Protected pyrrolyllithium and indolyllithium nucleophiles (Table 2) produced mixtures of indole and indoline products. Pyrrolylindole **8** was accompanied by a small amount of indoline product (9%) which was minimized by long reaction times. Formation of indolines **14b-15b** could be due in part to stabilization of the intermediate lithium nitronate by the newly incorporated protecting group. Addition of carboxylate protected indole gave indoline **15b** as the major product.

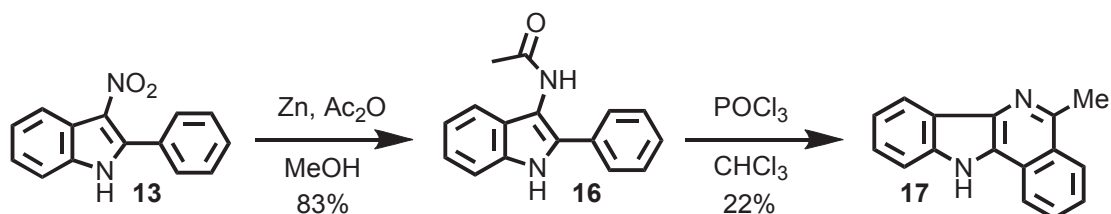
**Table 2.** 2-Lithio-*N*-protected indole and pyrroles produced both indoline and indole products

Entry	Nucleophile	Indole	Indoline
14^a		14a 31%	14b 27% R = SO ₂ Ph
15^b		15a trace	15b 53% R = H

a. *t*-BuLi. b. 1,2-Dilithio indolecarboxylate via Katritzky method¹⁵ i. *t*-BuLi. ii. CO₂ iii. *t*-BuLi

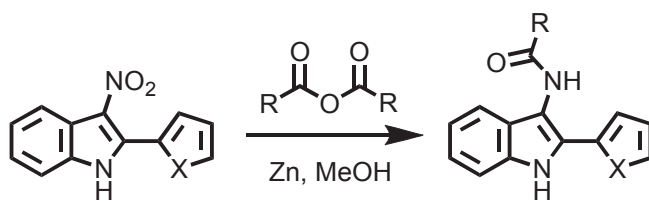
Synthesis of tetracyclic δ -carbolines

Huang-Hsinmin and Mann demonstrated that 5-methylindolo[3,2-*c*]quinoline (**17**) could be generated from 3-acetamido-2-phenylindole by a Bischler-Napieralski reaction, although in low yield.¹⁶ To confirm our structure, we synthesized known acetamide **16** by extension of our earlier work.¹⁷ Classical Bischler-Napieralski conditions¹⁸ furnished **17** in yields comparable to earlier methods.¹⁶



Scheme 3. Synthesis of 5-methylindolo[3,2-*c*]isoquinoline (**17**)

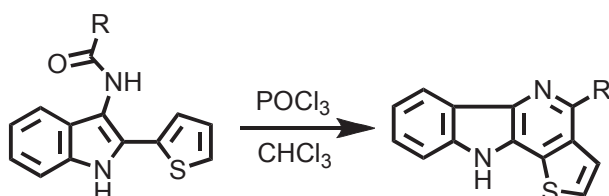
Since many hetero[*c*]- δ -carbolines represent novel ring systems, we investigated the above sequence as a route to these structures. Reductive-acylation of 2-hetaryl-3-nitroindoles proceeded readily at room temperature to afford 3-acylaminoindoles **18-21**; zinc metal was used to excellent effect in preference over indium, tin, or iron. The advantage of such mild conditions is readily apparent in the case of the labile furan and *N*-BOC pyrrole groups.



Scheme 4. Mild reductive-acylation

Product	R	X	Yield
18	Me	N-Boc	92%
19	Me	O	95%
20	Me	S	96%
21	Ph	S	94%

Bischler-Napieralski reaction of **20-21** successfully produced the corresponding δ -carbolines in higher yields than the phenyl precedent. While previous work suggested difficulties with cyclodehydrations of this type due to the unprotected indole nitrogen,¹⁶ heteromatics **18-21** are more activated substrates. Though our pyrrole **18** and furan **19** substrates gave complex mixtures under these conditions, thiophenes **20-21** were more tolerant and afforded good yield of tetracyclic thieno[3,2-*c*]- δ -carbolines **22-23**.



Scheme 5. Bischler-Napieralski reaction

Product	R	X	Yield
22	Me	S	81%
23	Ph	S	88%

In conclusion, we report a method for the hetarylation of 3-nitroindoles at C-2 by nucleophilic addition of hetaryl lithium compounds to 3-nitro-1-(phenylsulfonyl)indole. Reductive acylation of the resulting 3-nitro-2-hetarylindoles proceeds in high yields. A subsequent Bischler-Napieralski cyclodehydration

provides examples of the previously unknown thieno[3,2-*c*]- δ -carboline ring system.

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19. **Representative procedure:** A solution of thiophene (0.05 mL, 52.6 mg, 0.63 mmol) in dry THF (5 mL) at -78 °C was treated with a lithium diisopropylamide (2.0 M in THF, 0.35 mL, 0.70 mmol) and stirred for 1 h. A solution of 3-nitro-1-(phenylsulfonyl)indole (0.160 g, 0.530 mmol) in dry THF (3 mL) was added dropwise and the mixture was stirred at -78 °C for 2 h and then allowed to warm to RT overnight. The reaction was quenched with water, neutralized with 10% aqueous NH₄Cl, and the separated aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with water, brine, dried over MgSO₄, and then concentrated by rotary evaporation. Purification by column chromatography on silica gel (2:1 Hexanes:DCM) produced a bright yellow solid which recrystallized from MeOH:Et₂O to form yellow crystals of **6** (78 mg, 60%).
- 3-Nitro-2-(thien-2-yl)indole (6):** bright yellow crystals; mp 246-247° C; ¹H NMR (CDCl₃) δ 9.50 (s, br, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 3.3 Hz, 1H), 7.67 (d, *J* = 1.3 Hz, 1H), 7.39-7.46 (m, 3H), 6.72 (m, 1H); ¹³C NMR (CDCl₃) δ 145.0, 143.9, 133.4, 130.6, 125.7, 124.5, 122.4, 121.8, 118.7,

117.1, 113.8, 111.6; HRMS (ESI) m/z calcd for $C_{12}H_{19}N_2O_2S$ (MH^+) 245.0385, found 245.0383.

2-(Furan-2-yl)-3-nitroindole (7): bright yellow crystals; mp 230-231 °C (decomp); 1H NMR ($CDCl_3$) δ 9.25 (s, br, 1H) 8.41-8.43 (d, $J = 6.9$ Hz, 1H), 8.04 (d, $J = 3.8$ Hz, 1H), 7.68 (d, $J = 1.6$ Hz, 1H), 7.28-7.47 (m, 3H), 6.72-6.73 (m, 1H); ^{13}C NMR (DMSO) δ 147.0, 144.0, 134.7, 131.1, 125.8, 124.7, 123.7, 122.1, 120.9, 118.4, 114.0, 113.6; HRMS (ESI) m/z calcd for $C_{12}H_9N_2O_3$ (MH^+) 229.0608, found 229.0613.

3-Nitro-2-(thiazol-2-yl)indole (8): yellow crystals; 223-224 °C (decomp); 1H NMR (CD_3COCD_3) δ 12.2 (s, br, 1H), 8.31 (dd, $J = 1.5, 7.0$ Hz, 1H), 8.16 (d, $J = 3.0$ Hz, 1H), 8.04 (d, $J = 3.0$ Hz, 1H), 7.77 (dd, $J = 1.5, 7.0$ Hz, 1H), 7.45-7.48 (m, 2H); ^{13}C NMR (CD_3COCD_3) δ 154.5, 143.9, 134.3, 126.2, 125.1, 124.5, 121.9, 121.1, 113.3, 113.2; HRMS (ESI) m/z calcd for $C_{11}H_8N_3O_2S$ (MH^+) 246.0341, found 246.0337.

2-(1-Methylimidazol-2-yl)-3-nitroindole (9): yellow crystals; mp 258-261 °C (decomp); 1H NMR ($CDCl_3$) δ 13.62 (s, br, 1H) 8.33 (d, $J = 7.8$ Hz, 1H), 7.25-7.42 (m, 4H), 7.19 (s, 1H) 3.78 (s, 3H); ^{13}C NMR (DMSO) δ 137.9, 134.6, 131.1, 129.6, 127.2, 125.9, 125.0, 125.0, 121.3, 120.8, 113.9, 34.3; HRMS (ESI) m/z calcd for $C_{12}H_{11}N_4O_2$ (MH^+) 243.0882, found 243.0882.

tert-Butyl 2-(3-nitro-indol-2-yl)pyrrole-1-carboxylate (10): bright yellow crystals, 124-128°C (decomp); 1H NMR ($CDCl_3$) δ 8.88 (s, br, 1H), 8.32 (d, $J = 8.3$ Hz, 1H), 7.52 (m, 1H), 7.30-7.48 (m, 3H), 6.53 (dd, $J = 1.7, 3.4$, 1H), 6.31 (t, $J = 3.4$, 1H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 148.8, 133.5, 132.9, 129.8, 129.3, 125.2, 125.1, 124.5, 121.8, 121.7, 121.3, 111.8, 111.0, 85.0, 27.7; HRMS (ESI) m/z calcd for $C_{17}H_{18}N_3O_4$ (MH^+) 328.1297, found 328.1296.

tert-Butyl 2-(3-nitro-indolin-2-yl)pyrrole-1-carboxylate (10b): light yellow solid; 145-146°C (decomp); 1H NMR (CD_3COCD_3) 7.98 (d, $J = 6.4$ Hz, 2H), 7.83 (d, $J = 8.3$ Hz, 1H), 7.68 (m, 1H), 7.54-7.61 (m, 3H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.28 (m, 1H), 7.15 (td, $J = 7.6, 1.0$ Hz, 1H), 6.35 (s, 1H), 6.33 (1H, m), 6.14 (1H, t, 3.4 Hz), 1.62 (9H, s); ^{13}C NMR (CD_3COCD_3) 149.4, 143.2, 138.0, 134.1, 132.6, 131.3, 129.5, 128.0, 126.8, 125.1, 124.8, 122.8, 115.4, 113.1, 110.7, 89.2, 85.1, 64.7, 27.4.

3-Nitro-2-(pyridin-2-yl)indole (11): yellow solid; mp 202-204 °C (decomp); 1H NMR ($CDCl_3$) δ 10.48 (br s, 1H), 8.68-8.71 (m, 2H), 8.39 (d, 1H, 7 Hz), 7.91 (m, 1H), 7.46 (m, 1 H), 7.39-7.43 (m, 3H); ^{13}C ($CDCl_3$) δ 149.6, 147.2, 141.0, 137.8, 137.1, 133.2, 126.4, 126.1, 125.3, 124.9, 123.6, 122.3, 112.4; IR (film) 3455, 1477, 1361, 1216 cm^{-1} ; UV (EtOH) λ max 276, 364 nm; HRMS (ESI) m/z calcd for $C_{13}H_{10}N_3O_2$ (MH^+) 240.0773, found 240.0784.

3-Nitro-2-(pyridin-3-yl)indole (12): mp 206-209 °C; 1H NMR ($CDCl_3$) δ 13.05 (s, 1H), 8.94 (d, 1H, $J = 1.7$ Hz), 6.74 (dd, 1H, $J = 1.7, 4.9$ Hz), 8.17-8.22 (m, 2H), 7.57-7.61 (m, 2H), 7.39-7.43 (m, 2H); ^{13}C NMR (CD_3OD) δ 150.0, 150.0, 145.1, 142.3, 140.6, 137.7, 130.2, 128.6, 128.1, 125.8, 125.8, 125.8, 118.0, 107.8; HRMS (ESI) m/z calcd for $C_{13}H_{10}N_3O_2$ (MH^+) 240.0773, found 240.0781.

3-Nitro-2-phenylindole (13): yellow crystals; mp 237-238 °C; ^1H NMR (CD_3COCD_3) δ 11.62 (s, br, 1H), 8.27 (d, $J = 7.6$ Hz, 1H), 7.81 (m, 2H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.57 (m, 3H), 7.40 (m, 2H); ^{13}C (CD_3COCD_3) δ 141.5, 1234.2, 130.5, 130.2, 120.1, 128.5, 128.0, 124.7, 124.0, 122.3, 120.8, 112.7; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2$ (MH $^+$) 239.0821, found 239.0831.

2-(1'-(Phenylsulfonyl)indol-2'-yl)-3-nitroindole (14a): bright yellow crystals; mp 226-227 °C; ^1H (CD_3COCD_3) δ 12.1 (s, br, 1H), 8.30-8.33 (m, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 7.67-7.71 (m, 4H), 7.62 (t, $J = 7$ Hz, 1H), 7.45-7.50 (m, 5H), 7.35 (t, $J = 8$ Hz, 1H) 7.28 (s, 1H); ^{13}C (CD_3COCD_3) δ 138.4, 138.3, 135.3, 130.6, 130.3, 129.8, 127.7, 127.1, 125.94, 125.92, 125.91, 125.3, 125.1, 125.0, 122.9, 122.2, 121.4, 117.5, 116.1, 113.6; IR (film) 3277, 2911, 1444, 1367, 1172, 744 cm^{-1} ; UV (EtOH) λ max 256, 364 nm; HRMS m/z calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$ (M^+) 417.0783, found 417.0785.

trans-2-(1'-(Phenylsulfonyl)indol-2'-yl)-3-nitro-1-(phenylsulfonyl)indoline (14b): clear colorless crystals; mp 185-186 °C; ^1H (CDCl_3) δ 8.13 (d, $J = 8$ Hz, 1H) 7.94-7.99 (m, 4 H), 7.88 (d, $J = 8$ Hz, 1H), 7.50-7.79 (m, 9H), 7.23-7.38 (m, 2H), 7.14 (t, $J = 7$ Hz, 1H), 7.00 (m, 1H), 6.81 (m, 1H), 5.93 (s, 1H); ^{13}C NMR (CDCl_3) δ 142.5, 137.9, 137.8, 137.2, 136.6, 134.6, 134.3, 132.7, 129.7, 129.4, 129.1, 127.9, 127.1, 126.8, 125.8, 124.6, 124.4, 121.7, 115.5, 114.8, 113.0, 89.3, 64.5; HRMS (EI) calcd for $\text{C}_{28}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2$ ($\text{M}^+ - \text{HNO}_2$) 512.0864, found 512.0874.

trans-2-(Indol-2'-yl)-3-nitro-1-(phenylsulfonyl)indoline (15b): colorless crystals; mp 156-158 °C; ^1H NMR (CDCl_3) δ 10.41 (s, br, 1H), 7.88 (m, 3H), 7.61 (m, 3H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.43-7.5 (m, 3H), 7.24 (t, $J = 7.6$, 1H), 7.15 (t, $J = 7.1$, 1H), 7.06 (t, $J = 7.1$, 1H), 6.58 (s, 1H), 6.45 (s, 1H), 6.23 (s, 1H); ^{13}C NMR (DMSO) δ 142.9, 137.6, 137.3, 135.1, 134.2, 132.7, 129.5, 128.2, 128.2, 127.7, 125.2, 124.9, 122.5, 120.7, 120.0, 116.3, 111.8, 101.0, 89.3, 63.7; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}_4\text{S}$ (MH $^+$) 420.1018, found 420.1033.

General Procedure for Reductive Acylation: A solution of 3-nitro-2-(thien-2-yl)indole (0.256 g, 1 mmol) in MeOH (5 mL) was treated with acetic anhydride (513 mg, 5 mmol), and zinc dust (0.327 g, 5 mmol). The bright yellow mixture was stirred at room temperature and monitored by TLC. The solution become clear and nearly colorless by completion. The mixture was filtered and the solvent was removed by rotary evaporation. The resulting oil was neutralized with sat. aqueous NaHCO_3 , extracted with EtOAc (3 x 100 mL), washed with brine, dried over MgSO_4 , and concentrated in vacuo. The resulting gray crude solid was purified by column chromatography (1:2 EtOAc/Hexanes) to yield white crystals (236 mg, 92%). Recrystallization from methanol produced a mixture of rotomers characteristic of these compounds.¹⁶

N-(2-Phenyl-1H-indol-3-yl)acetamide (16): colorless crystals, 190-192°C; major isomer: ^1H NMR (CD_3COCD_3) δ 10.60 (s, br, 1H), 9.29 (s, 1H), 8.16 (d, $J = 7.1$ Hz, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 7.51-7.93 (m, 2H), 7.42 (t, $J = 8.1$ Hz, 2H), 7.32 (t, $J = 7.3$ Hz, 1H), 7.17 (t, $J = 7.1$ Hz, 1H), 7.07 (t,

$J = 7.3$, 1H), 1.31 (s, 1.31); ^{13}C NMR (CD_3OD) δ 170.3, 137.7, 134.0, 133.4, 129.2, 126.7, 125.3, 125.1, 123.4, 121.7, 118.3, 113.8, 110.0, 21.7; HRMS (ESI) m/z calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$ (M+) 250.11062, found 250.10993.

***tert*-Butyl 2-(3-acetamido-1*H*-indol-2-yl)-pyrrole-1-carboxylate (18)**: clear colorless crystals, 128-131°C (decomp); major isomer: ^1H NMR (CD_3COCD_3) 10.23 (s, 1H), 8.47 (s, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 7.43 (m, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.13 (t, $J = 7.1$ Hz, 1H), 7.01 (t, $J = 7.1$ Hz, 1H), 6.45 (m, 1H), 6.29 (t, $J = 3.4$ Hz, 1H), 2.06 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (CD_3OD) 172.4, 149.3, 134.8, 125.7, 124.4, 123.9, 122.9, 121.9, 118.9, 118.2, 116.9, 111.7, 110.9, 110.6, 83.7, 26.7, 21.2; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_3$ (MH+) 340.1661, found 340.1659.

***N*-(2-(Furan-2-yl)-1*H*-indol-3-yl)acetamide (19)**: colorless crystals, 183-185 °C; major isomer: ^1H NMR (CD_3OD) δ 10.55 (s), 8.68 (s), 7.65 (d, $J = 1.2$ Hz, 1H), 7.47 (d, $J = 7.8$ Hz, 1H) 7.40 (d, $J = 8.3$ Hz, 1H), 7.13 (t, $J = 7.1$ Hz, 1H), 7.03 (t, $J = 7.1$ Hz, 1H), 6.77 (d, $J = 3.4$ Hz, 1H), 6.60 (dd, $J = 1.7$ Hz, 3.4 Hz, 1H), 2.23 (3H, s) ^{13}C NMR ($\text{C}_{\text{D}_3}\text{OD}$) δ 172.3, 146.7, 142.1, 135.2, 125.5, 124.0, 122.4, 119.6, 117.9, 111.5, 111.2, 108.8, 107.0, 21.5; HRMS (EI) m/z calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ (M+) 240.008988, found 240.09005.

***N*-(2-(Thiophen-2-yl)-1*H*-indol-3-yl)acetamide (20)**: colorless crystals; 198-199°C; major isomer: ^1H NMR (DMSO- d_6) δ 11.46 (s, 1H), 9.38 (s, 1H), 7.58, (d, $J = 4.2$ Hz, 1H), 7.54 (d, $J = 3.7$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.17 (m, 1H), 7.11 (t, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 7.3$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR ($\text{C}_{\text{D}_3}\text{OD}$) δ 173.2, 135.3, 133.3, 128.1, 127.0, 126.0, 125.5, 124.0, 122.5, 119.7, 117.6, 111.1, 109.2, 21.7 HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{OS}$ (MH+) 257.0749, found 257.0760.

***N*-(2-(Thiophen-2-yl)-1*H*-indol-3-yl)benzamide (21)**: colorless crystals, 195-197°C; major isomer: ^1H NMR (CD_3COCD_3) δ 10.68 (s, 1H), 9.18 (s, 1H), 8.20 (d, $J = 7.0$, 2H), 7.64 (m, 1H), 7.57-7.63 (m, 3H), 7.49 (m, 2H), 7.34 (m, 1H), 7.13-7.16 (m, 2H), 7.06 (m, 1H), ^{13}C NMR (CD_3OD) δ 169.8, 135.4, 134.6, 133.4, 133.4, 131.9, 128.6, 127.8, 127.0, 126.3, 125.5, 124.0, 122.5, 119.7, 117.8, 111.1, 109.5; HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{OS}$ (MH+) 319.0905, found 319.0913.

Representative Procedure for the Bischler-Napieralski reaction: A solution of 3-acetamido-2-(thien-2-yl)indole (50 mg, 0.20 mmol) in chloroform (3 mL) was treated with POCl_3 (0.02 mL) 30 mg, 0.21 mmol) and refluxed for 1 d while being intermittently monitored by TLC. The solvent was removed *in vacuo* and the resulting red residue was quenched with water then neutralized with Na_2CO_3 . The mixture was extracted with EtOAc (3 x 50 mL), washed with brine, dried over MgSO_4 , then concentrated *in vacuo*. The resulting red oil was purified by column chromatography (1:3 EtOAc/Toluene) to yield an orange-yellow solid. Recrystallization from MeOH produced white crystals of **22** (38.5 mg, 81% yield).

5-Methyl-11H-indolo[3,2-c]isoquinoline (17): white crystals, mp 244-245°C, ¹H NMR (CD₃COCD₃) 11.23 (s, br, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 8.37 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.87 (t, *J* = 7.1, 1H), 7.71 (t, *J* = 8.1, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 3.07 (s, 3H); ¹³C NMR (CD₃COCD₃) spots 150.5, 142.4, 137.6, 132.8, 129.7, 127.2, 126.0, 125.5, 125.4, 121.5, 119.9, 119.6, 116.7, 111.8, 110.0, 30.0; HRMS (EI) *m/z* calcd for C₁₆H₁₂N₂ (M⁺) 232.09938, found 232.10005.

4-Methyl-10H-indolo[3,2-b]thieno[2,3-d]pyridine (22): white crystals, mp 238-240 °C; ¹H NMR (CD₃COCD₃) δ 11.99 (s, br, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 5.1 Hz, 1H), 7.80 (d, *J* = 5.4 Hz, 1H), 7.58 (d, *J* = 4.08, 1H), 7.45 (t, *J* = 7.32, 1H), 7.26 (t, *J* = 7.32, 1H), 2.96 (s, 3H); ¹³C NMR (CD₃COCD₃) δ 153.8, 134.8, 128.6, 128.2, 126.2, 126.0, 125.1, 124.3, 124.1, 120.1, 120.1, 111.8, 110.0, 22.3; HRMS (ESI) *m/z* calcd for C₁₄H₁₁N₂S (MH⁺) 239.0643, found 239.0649.

4-Phenyl-10H-indolo[3,2-b]thieno[2,3-d]pyridine (23): light orange crystals, 229-231°C; ¹H NMR (CD₃COCD₃) δ 11.95 (s, br, 1H), 8.34 (d, *J* = 7.6, 1H), 7.98 (m, 2H), 7.83 (d, *J* = 5.5 Hz, 1H), 7.78 (d, *J* = 5.5 Hz, 1H), 7.67 (d, *J* = 8.4, 1H), 7.60 (t, *J* = 8.2, 2H), 7.51 (t, *J* = 8.2, 2H), 7.33 (t, *J* = 7.0 Hz, 1H); ¹³C NMR (CD₃COCD₃) δ 148.3, 141.5, 140.3, 132.8, 131.6, 129.6, 128.5, 128.1, 127.7, 126.7, 125.8, 125.1, 123.6, 120.4, 120.4, 114.3, 112.0; HRMS (ESI) *m/z* calcd for C₁₉H₁₃N₂S (MH⁺) 301.0799, found 301.0790.