

A GENERAL LARGE SCALE SYNTHESIS OF 2-ALKYL-7-METHOXYINDOLES

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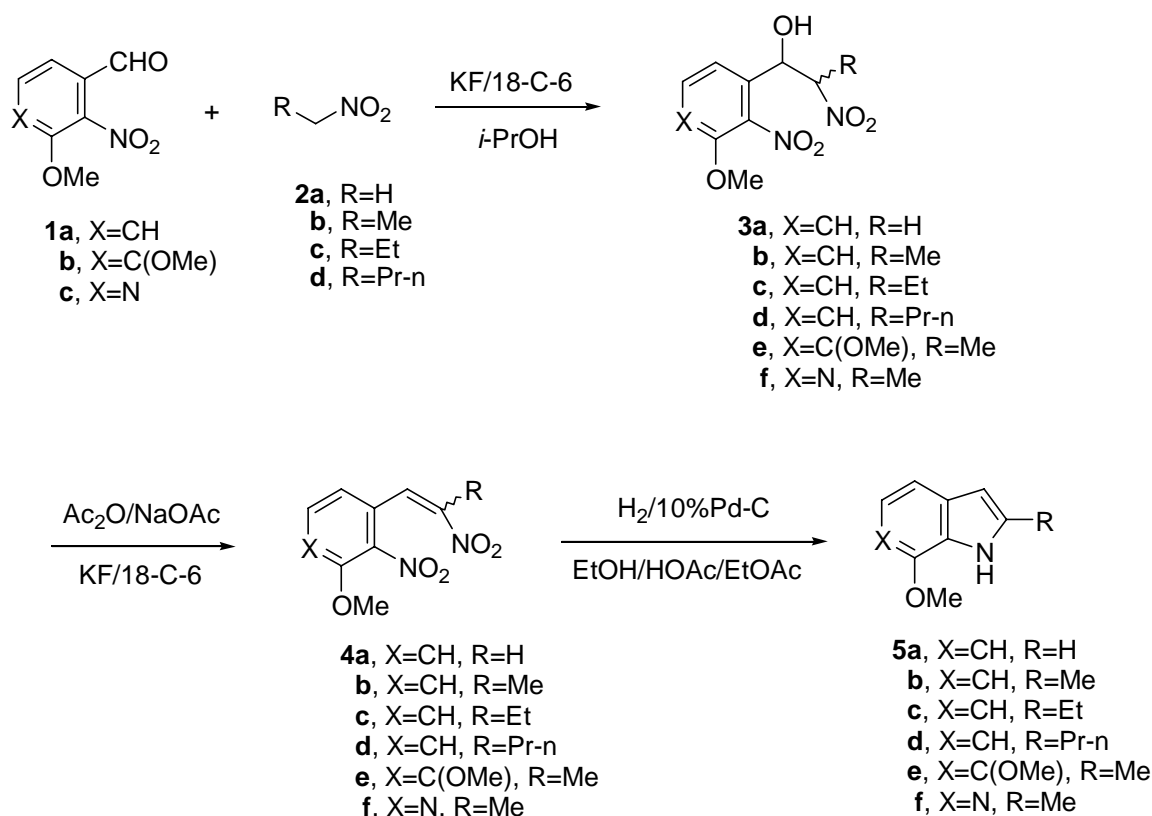
Abstract - A general method has been developed for the large scale synthesis of 2-alkyl-7-methoxyindoles and analogs. This method involves an efficient preparation of the key intermediates, 1-(2-nitroaryl)-2-nitroalkanols and 1-(2-nitroaryl)-2-nitroalkenes, and affords 2-alkyl-7-methoxyindoles and analogs in 3 steps with good overall yields.

2-Alkyl-7-methoxyindoles are common structural units found in a number of biologically important molecules.¹ They are also intermediates in the synthesis of medicinally useful agents,² and in the synthesis of natural products.³ Several methods have been previously reported for the preparation of 2-alkyl-7-methoxyindoles.³⁻⁸ Many of these methods, however, were not effective primary due to the unique substitution pattern in 2-alkyl-7-methoxyindole molecules.³⁻⁵ Perhaps the most direct approach to 2-alkyl-7-methoxyindoles is the reaction of 2-nitroanisoles with vinyl Grignard reagents. Unfortunately, this approach has little synthetic value as shown in the reaction of 2-propenylmagnesium bromide with 4-methyl-2-nitroanisole.³ Only 5% of the desired 7-methoxyindole was obtained even with 3 equivalents of the vinyl Grignard reagent.³ The classical Fisher,⁴ and Bischler⁵ type approaches are also ineffective. In both cases, 2-alkyl-7-methoxyindoles were obtained in <10% yields. While the yields of the indole formation were improved to some degree (~40% vs. <10%) by using the Madelung,³ or Gassman's⁶ method, the high reaction temperature,³ the use of chlorine gas⁶ and Raney nickel⁶ rendered them impractical for large scale synthesis. The best methods reported so far for the synthesis of 2-alkyl-7-methoxyindoles involved reductive cyclization of 3-methoxy-2-nitrobenzylketones,⁷ or deprotective cyclization of 3-methoxy-2-*N*-(*tert*-butoxycarbonyl)aminobenzylketones.⁸ However, the number of steps required for the preparation of the ketone precursors in addition to diazomethane and Raney nickel

used in the former method,⁷ and the strong base as *s*-BuLi used for aromatic lithiation in the latter,⁸ made them unattractive for large scale synthesis. In one of our drug discovery programs, we required a facile preparation of 2-alkyl-7-methoxyindoles in large quantity. Herein, we describe a general large scale synthesis of the titled compounds.

Our synthesis of 2-alkyl-7-methoxyindoles (**5**) entails the reductive cyclization of β -alkyl-3-methoxy-2, β -dinitrostyrenes (**4**) (Scheme 1). The reduction of the parent 2, β -dinitrostyrene to indole was reported in 1925 and this chemistry has been successfully extended to the preparation of other 2-unsubstituted indoles including 2-unsubstituted 7-methoxyindoles.¹⁰ However, report on the application of this approach to the synthesis of 2-alkylindoles is rare.¹¹ To the best of our knowledge, no report has appeared on the synthesis of the titled compounds using this approach.

Scheme 1



Initially, we tried to prepare the key intermediates, β -alkyl-3-methoxy-2, β -dinitrostyrenes (**4**), by direct condensation of 3-methoxy-2-nitrobenzaldehydes with nitroalkanes. Thus, treatment of **1a** with excess nitroethane (**2b**) using ammonium acetate in refluxing acetic acid, a common condition for this type of condensation,¹² did afford the desired product (**4b**) directly. However, the conversion was disappointing. Only about 33% of **4b** was observed by HPLC, along with ~13% of the starting aldehyde (**1a**) and numerous other unidentified products. Use of methylamine hydrochloride¹³ instead of ammonium

acetate improved the conversion only slightly to ~45% by HPLC. These results, coupled with polymeric materials obtained from the reaction, indicate that the resulting 3-methoxy-2,β-dinitrostyrenes, compared to their des-3-methoxy counterparts, are more prone to oligomerization and or polymerization under these reaction conditions through Michael additions.¹⁴ Considering the success of fluoride anion mediated coupling of nitroalkanes with aldehydes to give β-hydroxy nitroalkanes and nitroalkenes,¹⁵ we turned our attention to the step-wise protocol for the preparation of our β-alkyl-3-methoxy-2,β-dinitrostyrenes (**4**). By isolating the hydroxy dinitro intermediates (**3**) formed in the first step to remove any excess nitroalkane, the potential oligomerization and or polymerization of the resulting **4** in the next step is expected to be minimized, if not eliminated. Thus, treatment of the commercially available 3-methoxy-2-nitrobenzaldehyde (**1a**) with nitroethane (**2b**) in isopropanol in the presence of potassium fluoride and 18-crown-6 (18-C-6) at room temperature overnight cleanly afforded the hydroxy dinitro product (**3b**) in 96% isolated yield as a mixture of diastereomers. Treatment of **3b** with acetic anhydride and sodium acetate in the presence of potassium fluoride and 18-crown-6 (18-C-6) gave 3-methoxy-β-methyl-2,β-dinitrostyrene (**4b**) in 96% isolated yield. Reductive cyclization of **4b** was carried out using H₂ and 10% Pd/C in a mixture of solvents, giving 7-methoxy-2-methylindole (**5b**) in 62% isolated yield. Other 2-alkyl-7-methoxyindoles were prepared in a similar manner as summarized in Table 1.

Table 1: Preparation of 2-Alkyl-7-methoxyindoles

Entry	X	R	3		4		5	
			Time (h) ^a	Yield (%) ^b	Time (h) ^a	Yield (%) ^b	Time (h) ^a	Yield (%) ^b
1	CH	H	20	98	64	91	2.5	58 ^c
2	CH	Me	16	96	64	96	3	62
3	CH	Et	20	93	64	88	2.5	45 ^c
4	CH	Pr-n	20	97	64	87	2.5	32 ^c
5	C(OM	Me	16	96 ^d	72	61	12	81 ^c
6	e)	Me	16	97 ^d	72	89 ^d	12	66 ^c

N

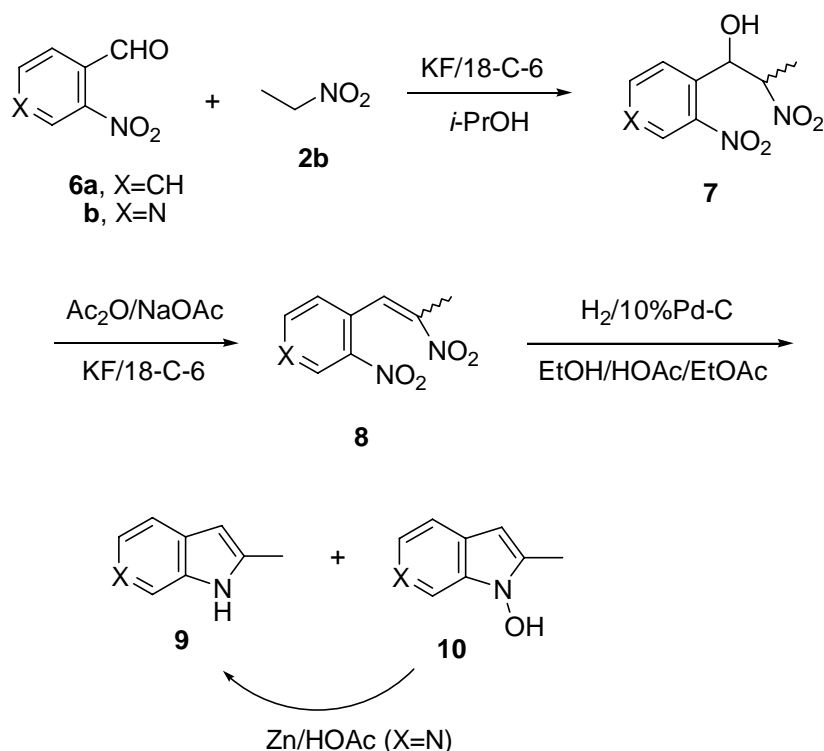
^aReaction time. ^bIsolated yield by crystallization unless otherwise indicated. ^cIsolated yield after flash chromatography. ^dIsolated yield after extractive work-up.

As can be seen from Table 1, the step-wise procedure worked very well for the preparation of β-alkyl-3-methoxy-2,β-dinitrostyrenes (**4**). The length of the alkyl chain of nitroalkanes (**2**) had little effect on the overall yields (Table 1, Entries 1-4), although the substituent group on the phenyl ring showed some

effect (compare Table 1, Entries 2 and 5). For the reductive ring closure of **4** to give indoles (**5**), as the length of the 2-alkyl chain increased, the overall yield tended to decrease (Table 1, Entries 2-4). Importantly, the new method not only worked for the preparation of 2-alkyl-7-methoxyindoles (Table 1, Entries 2-5), but also worked for 7-methoxy-6-azaindole (Table 1, Entry 6) and 2-unsubstituted 7-methoxyindole (Table 1, Entry 1).

To extend the scope of this new process, two aldehydes (**6a**) and (**6b**), without a methoxy group on the aromatic ring, were examined (Scheme 2). In both cases, the corresponding β -methyl-2,3-styrenes (**8a**) and (**8b**) were obtained in 89 and 83% yields, respectively. Hydrogenation of **8a** on 10% Pd-C as described above gave 2-methylindole (**9a**) in 81% yield. Interestingly, hydrogenation of **8b** under the same reaction conditions afforded after isolation a mixture of 2-methylazaindole (**9b**) and the corresponding *N*-hydroxyindole (**10b**) in a ratio of 3:1 as determined by ^1H NMR.¹⁶ Subjecting this mixture to zinc powder in acetic acid at reflux cleanly afforded **9b** in 94% yield.

Scheme 2



In summary, a general method has been developed for the large scale synthesis of 2-alkyl-7-methoxyindoles. This new method was also found to work well for the preparation of other indole molecules such as 2-unsubstituted 7-methoxyindoles, 2-alkylindoles, 2-alkyl-6-azaindoles and 2-alkyl-6-aza-7-methoxyindoles. In addition, the new efficient procedures developed for the synthesis of

intermediates (**3**, **4**, **7** and **8**) are of synthetic value since these compounds are useful intermediates in the synthesis of important molecules other than indoles.^{17,18}

EXPERIMENTAL

Proton and carbon-13 NMR spectra were recorded in CDCl₃ using TMS as internal standard. Melting points are uncorrected. 3-Methoxy-2-nitrobenzaldehyde (**1a**) and 3,4-dimethoxy-2-nitrobenzaldehyde (**1b**) were obtained from Aldrich Company and used as received. 2-Methoxy-3-nitropyridine-4-carboxaldehyde (**1c**)^{19a} and 3-nitropyridine-4-carboxaldehyde (**6b**)^{19b} were prepared according to literature procedures.

Preparation of 1-(3-Methoxy-2-nitrophenyl)-2-nitropropanol (3b): To a 2L round bottomed flask equipped with a magnetic stirrer and a nitrogen bubbler were added 2-nitro-3-methoxybenzaldehyde (**1a**, 125.7 g, 0.69 mol), nitroethane (**2b**, 72.94 g, 0.97 mol), 18-C-6 (18.34 g, 0.069 mol), isopropanol (420 mL) and KF (20.17 g, 0.35 mol). The mixture was stirred at rt for 16 h. The solvent was removed on a rotary evaporator to give an oil. Isopropanol (100 mL) and de-ionized water (250 mL) were added. The mixture was put on a rotary evaporator to remove isopropanol to give a slurry. The slurry was stirred for 1 h and filtered. The cake was washed with de-ionized water (4x100 mL) and dried to give 1-(3-methoxy-2-nitrophenyl)-2-nitropropanol (**3b**) as a diastereomeric mixture in a ratio of 3:2 (170.3g, 96%) which was used in the next reaction without further purification. ¹H NMR for the major isomer: (CDCl₃) δ 7.05-7.52 (m, 3H), 5.08 (d, J=8.6 Hz, 1H), 4.90 (m, 1H), 3.92 (s, 3H), 2.94 (s, 1H), 1.38 (d, J=6.9 Hz, 3H).

1-(3-Methoxy-2-nitrophenyl)-2-nitroethanol (3a): prepared similarly in 98% yield from **1a** and **2a** and used in the next reaction without further purification. ¹H NMR (CDCl₃) δ 7.08-7.52 (m, 3H), 5.47 (m, 1H), 4.63 (m, 2H), 3.92 (s, 3H), 3.63 (br, 1H).

1-(3-Methoxy-2-nitrophenyl)-2-nitrobutanol (3c): prepared similarly in 93% yield as a mixture of diastereomers in a ratio of 4:1 from **1a** and **2c** and used in the next reaction without further purification: ¹H NMR for the major isomer: (CDCl₃) δ 7.04-7.50 (m, 3H), 5.06 (d, J=8.4 Hz, 1H) 4.70-4.75 (m, 1H), 3.93 (s, 3H), 2.97 (br, 1H), 1.86-1.94 (m, 1H), 1.45-1.51 (m, 1H), 0.90 (t, J=7.4 Hz, 3H).

1-(3-Methoxy-2-nitrophenyl)-2-nitropentanol (3d): prepared similarly in 97% yield as a mixture of diastereomers in a ratio of 3:1 from **1a** and **2d** and used in the next reaction without further purification. ¹H NMR for the major isomer: (CDCl₃) δ 7.04-7.51 (m, 3H), 5.05 (d, J=8.3 Hz, 1H) 4.80-4.85 (m, 1H), 3.92 (s, 3H), 1.86-1.94 (m, 2H), 1.27-1.36 (m, 2H), 0.88 (m, J=7.3 Hz, 3H).

1-(3,4-Dimethoxy-2-nitrophenyl)-2-nitropropanol (3e): prepared similarly in 96% yield as a mixture of diastereomers in a ratio of 3:2 from **1b** and **2b** and used in the next reaction without further purification. ¹H NMR for the major isomer (CDCl₃) δ 7.70-7.06 (m, 2H), 5.01 (m, 1H), 4.90 (m, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 1.36 (d, J=6.9 Hz, 3H).

1-(3-Methoxy-2-nitro-4-pyridinyl)-2-nitropropanol (3f): prepared similarly in 97% yield as a mixture of diastereomers in a ratio of 3:2 from **1c** and **2b** and used in the next reaction without further purification. ¹H NMR for the major isomer (CDCl₃) δ 8.33 (d, J=5.2 Hz, 1H), 7.07 (d, J=5.3 Hz, 1H), 5.16 (d, J=8.1 Hz, 1H), 4.89 (m, 1H), 4.07 (s, 3H), 1.46 (d, J=6.9 Hz, 3H).

1-(2-Nitrophenyl)-2-nitropropanol (7a): prepared similarly in 93% yield as a mixture of diastereomers in a ratio of 5:4 from **6a** and **2b** and used in the next reaction without further purification. ¹H NMR for the major isomer (CDCl₃) δ 7.54-8.15 (m, 4H), 6.12 (br s, 1H), 5.20 (m, 1H), 3.21 (br s, 1H), 1.58 (d, J=6.9 Hz, 3H).

1-(2-Nitro-4-pyridinyl)-2-nitropropanol (7b): prepared similarly in 86% yield as a mixture of diastereomers in a ratio of 2:1 from **6b** and **2b** and used in the next reaction without further purification. ¹H NMR for the major isomer (CDCl₃) δ 9.22 (s, 1H), 8.87 (d, J=5.1 Hz, 1H), 7.62 (d, J=5.1 Hz, 1H), 6.18 (br s, 1H), 4.88 (m, 1H), 3.25 (br s, 1H), 1.45 (d, J=7.0 Hz, 3H).

Preparation of 1-(3-Methoxy-2-nitrophenyl)-2-nitropropene (4b): To a 5L three-necked round bottomed flask equipped with a mechanical stirrer and a nitrogen bubbler were added **3b** (169.0 g, 0.659 mol), acetic anhydride (450 mL), 18-C-6 (17.41 g, 0.067 mol) and KF (38.25 g, 0.658 mol). The reaction mixture was stirred at rt for 64 h. The reaction mixture was cooled in an ice-water bath. De-ionized water (2250 mL) was added slowly. The resulted slurry was stirred at 0°C for 2 h and then filtered. The cake was washed with de-ionized water (3x250 mL) and suction dried for 20 h to give 1-(3-methoxy-2-nitrophenyl)-2-nitropropene (**4b**) (150.7 g, 96%) and used in the next reaction without further purification. ¹H NMR (CDCl₃) δ 7.89 (s, 1H), 7.53 (pseudo t, J=8.1 Hz, 1H), 7.13 (d, J=8.5 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 3.95 (s, 3H), 2.30 (s, 3H).

1-(2-Nitro-3-methoxyphenyl)-2-nitroethene (4a): prepared similarly in 91% yield from **3a** and used in the next reaction without further purification. The spectroscopic data were consistent with those reported for this compound.²⁰

1-(3-Methoxy-2-nitrophenyl)-2-nitrobutene (4c): prepared similarly in 88% yield from **3c** as a mixture of E/Z isomers and used in the next reaction without further purification.

1-(3-Methoxy-2-nitrophenyl)-2-nitropentene (4d): prepared similarly in 87% yield from **3d** as a mixture of E/Z isomers and used in the next reaction without further purification.

1-(3,4-Dimethoxy-2-nitrophenyl)-2-nitropropene (4e): prepared similarly in 61 % yield from **3e** and used in the next reaction without further purification. ^1H NMR (CDCl_3) δ 7.75 (s, 1H), 7.01 (dd, $J=11.9$, 3.2 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.27 (s, 3H).

1-(3-Methoxy-2-nitro-4-pyridinyl)-2-nitropropene (4f): prepared similarly in 89% yield from **3f** and used in the next reaction without further purification. ^1H NMR (CDCl_3) δ 8.39 (d, $J=5.2$ Hz, 1H), 7.88 (s, 1H), 6.89 (d, $J=5.1$ Hz, 1H), 4.11 (s, 1H), 2.3 (s, 3H).

1-(2-Nitrophenyl)-2-nitropropene (8a): prepared similarly in 89% yield from **7a** and used in the next reaction without further purification. The spectroscopic data were consistent with those reported for this compound.¹²

1-(2-Nitro-4-pyridinyl)-2-nitropropene (8b): prepared similarly in 83% yield from **7b** and used in the next reaction without further purification. ^1H NMR (CDCl_3) δ 9.46 (s, 1H), 8.97 (d, $J=4.9$ Hz, 1H), 8.28 (s, 1H), 7.36 (d, $J=4.9$ Hz, 1H), 2.27 (s, 3H).

Preparation of 2-Methyl-7-methoxyindole (5b): To a 2L hydrogenation flask were added **4b** (43.72 g, 0.1854 mol), 10% Pd/C (4.37 g, ~50% water wet), ethyl acetate (595 mL), acetic acid (90.5 mL) and absolute ethanol (75 mL). The reaction mixture was hydrogenated at <60 psi for 3 h and then filtered. The cake was washed with EtOAc (3x100 mL). The filtrate was concentrated to remove ethyl acetate and ethanol. De-ionized water (200 mL) was then added slowly. The resulted slurry was stirred for 0.5 h at rt and filtered. The cake was washed with 1:2 HOAc/H₂O (2x30 mL) 1:4 HOAc/H₂O (50 mL), water (2x80 mL) and suction dried for 18 h to give 7-methoxy-2-methylindole (**5b**) (18.3 g, 62%). mp 78-80°C, lit.,⁶ mp 79-81°C. ^1H NMR (CDCl_3) δ 8.10 (s, 1H), 7.12 (d, $J=7.7$ Hz, 1H), 6.97 (pseudo t, $J=7.7$ Hz, 1H), 6.57 (d, $J=7.7$ Hz, 1H), 6.18 (pseudo t, $J=1.1$ Hz, 1H), 3.94 (s, 3H), 2.42 (s, 3H).

7-Methoxyindole (5a): prepared similarly from **4a**, 58% yield as an oil. The spectroscopic data were consistent with those reported for this compound.²¹

2-Ethyl-7-methoxyindole (5c): prepared similarly from **4c**, 45% yield as an oil: ^1H NMR (CDCl_3) δ 8.10 (br s, 1H), 7.15 (d, $J=7.8$ Hz, 1H), 6.98 (pseudo t, $J=7.7$ Hz, 1H), 6.58 (d, $J=7.8$ Hz, 1H), 6.21 (s, 1H) 3.94 (s, 3H), 2.74-2.79 (m, 2H), 1.32 (t, $J=7.5$ Hz, 3H); ^{13}C NMR δ 145.9, 141.4, 130.5, 126.5, 120.3, 113.1, 101.6, 99.5, 55.7, 21.8, 13.8; HRMS 175.0999 [ESI, (M+H)⁺] calcd for C₁₁H₁₄NO₂ 175.0997.

2-(*n*-Propyl)-7-methoxyindole (5d): prepared similarly from **4d**, 32% yield as an oil: ^1H NMR (CDCl_3) δ 8.09 (br s, 1H), 7.16 (d, $J=7.7$ Hz, 1H), 7.00 (pseudo t, 1H), 6.62 (d, $J=7.7$ Hz, 1H), 6.23 (s, 1H) 3.97 (s, 3H), 1.81-1.74 (m, 2H), 1.02 (t, $J=7.4$ Hz, 3H); ^{13}C NMR δ 145.9, 139.8, 130.5, 126.4,

120.2, 113.1, 101.4, 100.3, 55.7, 30.7, 23.0, 14.3; HRMS 189.1153 [ESI, (M+H)⁺] calcd for C₁₁H₁₄NO₂ 189.1154.

2-Methyl-6,7-dimethoxyindole (5e): prepared similarly from **4e**, 81% yield: mp 76-77 °C (hexane); ¹H NMR (CDCl₃) δ 7.89 (br s, 1H), 6.98 (d, J=8.5 Hz, 1H), 6.62 (d, J=8.5 Hz, 1H), 5.96 (s, 1H) 3.84 (s, 3H), 3.75 (s, 3H), 2.23 (s, 3H); ¹³C NMR δ 146.8, 135.2, 134.3, 130.8, 126.0, 114.8, 108.4, 100.7, 61.2, 55.7, 14.3; HRMS 192.1028 [ESI, (M+H)⁺] calcd for C₁₁H₁₄NO₂ 192.1025. Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.51; H, 6.54; N, 6.89.

2-Methyl-6-aza-7-methoxyindole (5f): prepared similarly from **4f**, 66% yield: mp 146 °C (hexane); ¹H NMR (CDCl₃) δ 8.43 (br s, 1H), 7.74 (d, J=5.6 Hz, 1H), 7.07 (d, J=5.6 Hz, 1H), 6.21 (d, J=0.8 Hz, 1H), 4.10 (s, 3H), 2.47 (s, 3H); ¹³C NMR (CDCl₃) δ 150.9, 137.8, 135.8, 135.6, 121.0, 109.9, 101.1, 53.3, 14.1; HRMS 163.0878 [ESI, (M+H)⁺] calcd for C₉H₁₀N₂O 162.0793. Anal. Calcd for C₉H₁₀N₂O: C, 66.64; H, 6.21; N, 17.27; Found: C, 66.41; H, 6.07; N, 17.08.

2-Methylindole (9a): prepared similarly from **8a**, 81% yield: mp 59-60 °C, lit.,²² mp 59-61 °C. ¹H NMR (CDCl₃) δ 7.90 (br s, 1H), 7.55-7.10 (m, 4H), 6.23 (s, 1H), 2.45 (s, 3H).

2-Methyl-6-azaindole (9b): prepared similarly from **8b**. After hydrogenation, the reaction mixture was filtered and concentrated on a rotary evaporator. Acetic acid (20 mg/mL) and powdered zinc (3 equiv) were added and the reaction heated at reflux for 3 h. The reaction mixture was concentrated to an oil and purified *via* flash chromatography (10% MeOH/CH₂Cl₂). The product (**9b**) was isolated in 94% yield: mp 182 °C, lit.,²³ mp 185 °C; ¹H NMR (CDCl₃) δ 10.72 (br s, 1H), 8.67 (s, 1H), 8.12 (d, J=5.5 Hz, 1H), 7.37 (d, J=5.8 Hz, 1H), 6.18 (s, 1H), 2.45 (s, 3H).

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