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Palladium-catalyzed synthesis of 3-alkoxysubstituted indoles

Ronald W. Clawson Jr., Robert E. Deavers III, Novruz G. Akhmedov and Björn C. G. Söderberg*

C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045, United States

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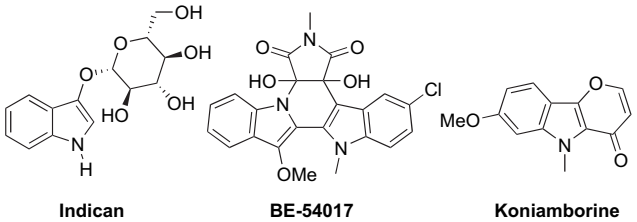
Abstract—Indoles having an electron-donating alkoxy-group in the 3-position were prepared from 1-(2-nitrophenyl)-1-alkoxyalkene derivatives via a palladium-catalyzed reductive N-heteroannulation using carbon monoxide as the ultimate reducing agent. The required starting materials were prepared by a Stille coupling of 2-halonitroarenes with tributyl(1-ethoxyethenyl)stannane or tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane.

1. Introduction

Indoles oxygenated in the 3-position are relatively rare in nature but a few have been isolated, for example, indican the precursor to indigo,[1] the anti-tumor compound BE-54017,[2] and koniamborine (Fig. 1).[3] In addition, a variety of synthetic 3-alkoxyindoles have been prepared as potential 5-HT1A receptor antagonism with SSRI activities,[4] reversible inhibitors of aminopeptidase N/CD13,[5] tubulin polymerization inhibitors,[6] and selective serotonin 5-HT2 receptor ligands.[7]

3-Alkoxyindole-2-carboxylic acid derivatives are readily prepared by direct O-alkylation of the corresponding anion using alkyl halides, diazomethane[8] or dialkylsulfates.[9] In contrast, 2-unsubstituted or 2-alkylated 3-alkoxyindoles cannot be selectively prepared in this manner due to competing C-2-alkylation. Thus, 3-alkoxyindole derivatives of this type are usually prepared by decarboxylation of 3-alkoxyindole carboxylic acids at elevated temperatures.[10,11] More recently developed methodologies include palladium-catalyzed cyclization of *N*-alkyl-2-siloxyallylanilines,[12] rhodium-catalyzed oxygen–hydrogen bond insertion using 3-diazoindole,[13] and benzoylperoxide oxidation of *N*-alkylindoles.[14]



Indican BE-54017 Koniamborine

Figure 1.

Palladium-catalyzed reductive N-heteroannulation of 1-(2-nitroaryl)-1-alkenes is emerging as a versatile methodology for the preparation of a variety of functionalized indoles.[15–19] Synthetic application of this reaction include tjipanazoles,[20] 1*H*-indole-2-yl-1*H*-quinolin-2-ones,[21] murrayaquinone,[22] bauerine A,[23] and mushroom metabolites.[24] The 1-(2-nitrophenyl)-1-alkenes used to date has been limited to substrates with alkyl-, aryl-, or electron-withdrawing groups on the alkene moiety. In an attempt to extend the palladium-catalyzed heteroannulation reaction to substrates having an electron-rich alkene and to develop a short methodology for the synthesis of 3-alkoxysubstituted indoles, 1-(2-nitrophenyl)-1-alkoxyethene (**3**) was prepared via a Stille coupling of 2-iodo-1-nitrobenzene (**1**) and tributyl(1-ethoxyethenyl)stannane (**2**). Submitting **3** to the annulation conditions previously used to prepare tetrahydrocarbazolones, bis(dibenzylideneacetone)palladium (6 mol %), 1,3-bis(diphenylphosphino)propane (6 mol %), and 1,10-phenanthroline (6 mol %) in the presence of carbon monoxide, gave the expected 3-ethoxyindole (**4**) in good yield. With this initial result in hand, a number of additional examples were examined and herein is presented the formation of 3-alkoxysubstituted indoles via palladium-catalyzed reductive N-heteroannulation of 1-(2-nitrophenyl)-1-alkoxyalkenes (Scheme 1).

2. Results and discussion

Seven additional nitroaryl-substituted alkenes (**12–18**) were prepared using a Stille coupling of 2-nitroarylbromides or iodides (**5–11**) employing either stannane **2** or tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane. The results of the cross-coupling reactions are summarized in Table 1. A 52–82%

* Corresponding author. Tel.: +1 304 293 3435; fax: +1 304 293 4904; e-mail: bjorn.soderberg@mail.wvu.edu

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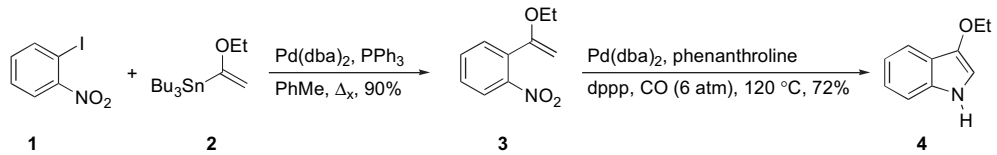


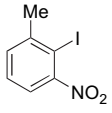
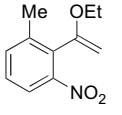
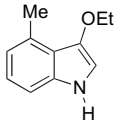
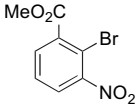
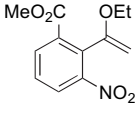
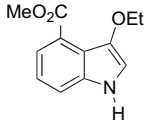
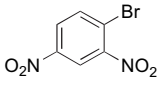
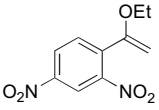
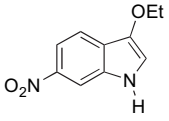
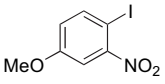
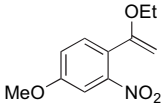
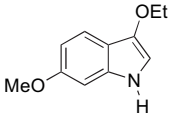
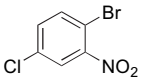
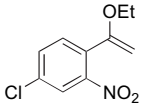
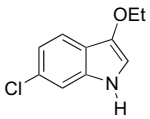
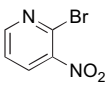
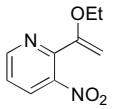
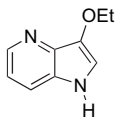
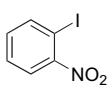
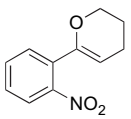
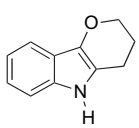
1 2 3 4

Scheme 1.

yield was obtained after chromatography in the cases examined. The compounds were selected to have either electron-donating or electron-withdrawing substituents on the benzene ring, to be sterically congested around the alkene (entries 1 and 2), one heterocyclic substrate (entry 6), and one substrate having a substituent adjacent to the alkoxy-group on the alkene (entry 7).

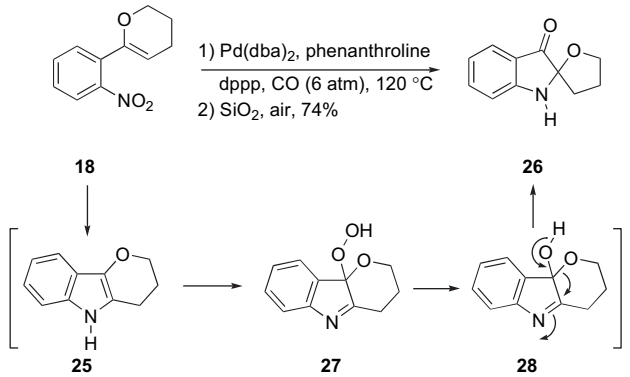
Subjecting the nitro alkenyl ethers to the reaction conditions described above for compound **3**, produced the anticipated 3-alkoxysubstituted indole in 63–87% isolated yield after column chromatography on silica gel. As was earlier observed, the substituents on the aromatic ring had little or no effect on the annulation reaction.[17] It should be noted that all compounds prepared (**12**–**25**) were relatively unstable and slowly decomposed upon standing. The alkoxyalkenes decomposed to the corresponding ketones and the indoles to deep blue or purple colored products of unknown identity. The pyranoindole **25** was particularly problematic and the compound could not be isolated without significant or complete oxidation. The oxidation product was identified as the spiroindolone **26** (Scheme 2) and its structure was determined by ^{1}H, ^{13}C, HETCOR, long-range HETCOR, and DPFGSENoE NMR experiments. Compound **26** is probably formed via the peroxide **27** and the alcohol **28**. Related oxidative-rearrangements in air have been reported in a number of cases.[25–30]

Table 1. Stille coupling and reductive N-heteroannulation

Entry	Nitroarene	Stille product[a,b]	3-Alkoxyindole[a,b]
1	 **5**	 **12** (81%)	 **19** (84%)
2	 **6**	 **13** (66%)	 **20** (87%)
3	 **7**	 **14** (52%)	 **21** (85%)
4	 **8**	 **15** (68%)	 **22** (79%)
5	 **9**	 **16** (56%)	 **23** (63%)
6	 **10**	 **17** (67%)	 **24** (85%)
7	 **11**	 **18** (81%)	 **25** (decomposed)

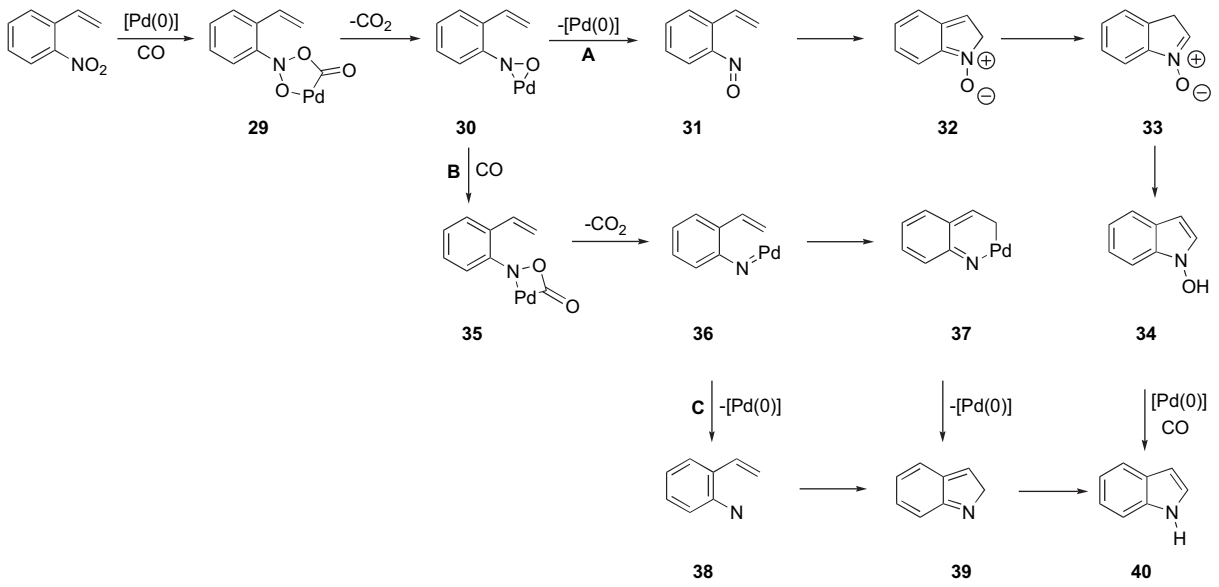
[a] For experimental details and analytical data, see Section 2.
[b] Isolated yields in parentheses.

The mechanism of the palladium-catalyzed reductive N-heteroannulation of 1-(2-nitroaryl)-1-alkenes to give indoles has previously been examined in some detail and a few different reaction paths have been proposed (**A**–**C**, Scheme 3). It is generally accepted that the initial transformation involves a reduction (deoxygenation) of the nitro to a nitroso group via the metallacycle **29**. The nitroso group may either be metal bound (**30**) or free (**31**). In path **A**, the nitrosoarene **31** undergoes an intramolecular electrocyclic reaction to give nitronate **32** followed by a 1,5-hydrogen shift and tautomerization (**32**→**33**→**34**) to give an *N*-hydroxyindole (**34**). Reduction of **34** using palladium and a second molecule of carbon monoxide would give the product (**40**).[31] Path **A** has been demonstrated to be viable using computational methods.[32] *N*-Hydroxyindoles have been isolated in a few cases from 1-(2-nitroaryl)-1-alkenes via palladium-catalyzed annulations using carbon monoxide[33,31] or tin dichloride[34] as the reducing agent. In addition, in situ formation of nitrosoarenes by oxidation of 1-(2-hydroxylaminoaryl)-1-alkenes also furnished *N*-hydroxyindoles.[35–37] However, *N*-hydroxyindoles are not isolated



18 26 25 27 28

Scheme 2.



Scheme 3.

in an overwhelming majority of palladium-catalyzed reductive N-heteroannulations. This may be due to a very rapid reduction of the intermediately formed *N*-hydroxyindole or a different mechanism. Path **B** involves a second deoxygenation prior to cyclization, most likely via the metallacyclobutane **35**. Loss of carbon dioxide from **35** would furnish a palladium-bound nitrene **36** that via a 6π-electron electrocyclic reaction affords a six-membered heterocycle **37**. A related rhodium-bound nitrene has been isolated and characterized by X-ray diffraction.[38] Reductive elimination regenerating the palladium(0) catalyst followed by a 1,5-hydrogen-shift (**37**→**39**→**40**) affords the observed product. An alternative path **C** can also be envisioned involving a free nitrene (**38**) followed by an electrocyclization to give **39** and 1,5-hydrogen shift to give **40**.

In summary, we have developed a rapid and expedient synthesis of 3-alkoxysubstituted indoles based on two palladium-catalyzed reactions. The indoles were prepared in good yield from readily available starting materials in a few synthetic steps.

3. Experimental

3.1. General procedures

NMR spectra were determined in $CDCl_3$ at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR) and for compound **26** at 600 and 150 MHz. The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) used as internal standards. ^{1}H–^{1}H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test)—^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.

Tetrahydrofuran (THF), 1,4-dioxane, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Benzene and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Hexanes, dichloromethane, and ethyl acetate were distilled from calcium hydride. Toluene was dried by filtration through activated alumina prior to use. Chemicals prepared according to literature procedures have been footnoted; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in an oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Chromatography was performed on silica gel 60 (35–75 μm, VWR). Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

3.1.1. 1-Ethoxy-1-(2-nitrophenyl)ethene (3). A solution of 2-iodonitrobenzene (**1**) (236 mg, 0.948 mmol), bis(dibenzylideneacetone)palladium Pd(dba$_2$) (27.4 mg, 0.0476 mmol), and triphenylphosphine (PPh_3) (50 mg, 0.19 mmol) in toluene (55 mL) was stirred (5 min) under a positive flow of nitrogen. To the yellow solution was added tributyl(1-ethoxy-1-ethenyl)stannane (**2**)[39] (391 mg, 1.08 mmol) dissolved in toluene (10 mL). The yellow solution was heated at reflux (36 h) whereupon a dark brown solution was formed. The progress of the reaction was monitored to completion using TLC (hexanes). The reaction mixture was cooled to ambient temperature, washed with NH_4OH (10% aqueous, 50 mL), and dried over anhydrous $MgSO_4$. Filtration and removal of solvent gave a black viscous oil that was purified by chromatography (hexanes/EtOAc, 7:3) to give **3** (166 mg, 0.859 mmol, 90%) as a pale yellow oil. ^{1}H NMR δ 7.75 (d, J=7.9 Hz, 1H), 7.65–7.38 (m, 3H), 4.48 (d, J=2.8 Hz, 1H), 4.37 (d, J=2.8 Hz, 1H), 3.86 (q, J=6.9 Hz, 3H), 1.29 (t, J=7.1 Hz, 2H); ^{13}C NMR δ 158.4 (+), 149.4 (+), 132.3 (+), 132.1 (−), 130.4 (−), 129.2 (−), 123.8 (−), 86.5 (+), 64.4 (+), 13.9 (−); IR (neat) 2983, 1533 cm^{-1}; MS (EI) *m*/*z* 193 (M$^+$), 135, 79 (100%); Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.84; H, 6.04; N, 7.08.

3.1.2. 1-Ethoxy-1-(6-methyl-2-nitrophenyl)ethene (12). Reaction of 2-iodo-3-nitrotoluene (**5**)[40] (270 mg, 1.03 mmol) with **2** (447 mg, 1.24 mmol) in the presence of $Pd(dba)_2$ (30 mg, 0.051 mmol) and PPh_3 (54 mg, 0.21 mmol) in toluene (65 mL), as described for **3** (76 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **12** (172 mg, 0.830 mmol, 81%) as a pale yellow oil. ^{1}H NMR δ 7.63 (d, J=7.9 Hz, 1H), 7.43 (d, J=7.5 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 4.41 (d, J=2.8 Hz, 1H), 4.13 (d, J=2.8 Hz, 1H), 3.93 (q, J=6.9 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 155.6 (+), 150.0 (+), 139.4 (−), 134.1 (−), 131.5 (+), 128.5 (−), 121.0 (−), 87.0 (+), 63.8 (+), 19.6 (−), 14.3 (−); IR (neat) 2983, 1531 cm^{-1}; MS (EI) m/z 207 (M^+), 149, 120 (100%); Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 64.09; H, 6.42; N, 6.87.

3.1.3. 1-Ethoxy-1-(6-methoxycarbonyl-2-nitrophenyl)-ethene (13). Reaction of methyl 2-bromo-3-nitrobenzoate (**6**)[22] (120 mg, 0.46 mmol) and **2** (220 mg, 0.55 mmol) in the presence of $Pd(dba)_2$ (13 mg, 0.023 mmol) and PPh_3 (24 mg, 0.092 mmol) in toluene (70 mL), as described for **3** (52 h), gave, after extraction and chromatography (hexanes/EtOAc, 9:1), **13** (76 mg, 0.30 mmol, 66%) as a dark yellow oil. ^{1}H NMR δ 7.90–7.83 (m, 2H), 7.52 (t, J=7.9 Hz, 1H), 4.36 (d, J=3.0 Hz, 1H), 4.27 (d, J=3.0 Hz, 1H), 3.97 (s, 3H), 3.88 (q, J=7.1 Hz, 2H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 168.4 (+), 154.9 (+), 151.8 (+), 151.2 (+), 150.0 (+), 133.0 (+), 132.6 (−), 125.9 (−), 87.4 (+), 64.5 (+), 52.7 (−), 14.2 (−); IR (neat) 2942, 1774, 1542 cm^{-1}; MS (EI) m/z 251 (M^+), 193, 161 (100%); Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.33; H, 5.63; N, 5.49.

3.1.4. 1-Ethoxy-1-(2,4-dinitrophenyl)ethene (14). Reaction of 1-bromo-2,4-dinitrobenzene (**7**) (140 mg, 0.57 mmol) with **2** (246 mg, 0.681 mmol) in the presence of $Pd(dba)_2$ (16 mg, 0.028 mmol) and PPh_3 (30 mg, 0.11 mmol) in toluene (75 mL), as described for **3** (64 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **14** (70 mg, 0.29 mmol, 52%) as a yellow oil. ^{1}H NMR δ 8.59 (d, J=2.2 Hz, 1H), 8.40 (dd, J=8.5, 2.2 Hz, 1H), 7.77 (d, J=8.5 Hz, 1H), 4.62 (d, J=3.2 Hz, 1H), 4.53 (d, J=3.1 Hz, 1H), 3.88 (q, J=7.1 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 156.5 (+), 148.8 (+), 147.5 (−), 137.8 (−), 131.5 (−), 126.5 (−), 119.5 (+), 89.1 (+), 64.9 (+), 13.8 (−); IR (neat) 2984, 1545 cm^{-1}; MS (EI) m/z 238 (M^+), 180 (100%), 134; Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.42; H, 4.63; N, 11.19.

3.1.5. 1-Ethoxy-1-(4-methoxy-2-nitrophenyl)ethene (15). Reaction of 4-iodo-3-nitro-1-methoxybenzene (**8**) (279 mg, 1.00 mmol) with **2** (412 mg, 1.14 mmol) in the presence of $Pd(dba)_2$ (28.9 mg, 0.0503 mmol) and PPh_3 (53 mg, 0.20 mmol) in toluene (75 mL), as described for **3** (56 h), gave, after extraction and chromatography (hexanes/EtOAc, 8:2), **15** (151 mg, 0.676 mmol, 68%) as a dark yellow oil. ^{1}H NMR δ 7.44 (d, J=8.5 Hz, 1H), 7.26 (d, J=2.6 Hz, 1H), 7.04 (dd, J=8.5, 2.6 Hz, 1H), 4.40 (d, J=2.8 Hz, 1H), 4.30 (d, J=2.8 Hz, 1H), 3.91–3.80 (m, 5H), 1.28 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 159.9 (+), 158.3 (+), 149.5 (+), 131.5 (−), 124.7 (+), 118.0 (−), 109.1 (−), 85.7 (+), 64.3 (+), 55.9 (−), 14.0 (−); IR (neat) 2359, 1537 cm^{-1}; MS (EI) m/z 223 (M^+), 165, 109 (100%); Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.17; H, 6.22; N, 6.43.

3.1.6. 1-Ethoxy-1-(4-chloro-2-nitrophenyl)ethene (16). Reaction of 1-bromo-4-chloro-2-nitrobenzene (**9**) (118 mg, 0.499 mmol) with **2** (206 mg, 0.570 mmol) in the presence of $Pd(dba)_2$ (15 mg, 0.025 mmol) and PPh_3 (26 mg, 0.10 mmol) in toluene (70 mL), as described for **3** (72 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **16** (65 mg, 0.27 mmol, 56%) as a pale yellow oil. ^{1}H NMR δ 7.73 (d, J=1.6 Hz, 1H), 7.51–7.43 (m, 2H), 4.45 (d, J=3.0 Hz, 1H), 4.36 (d, J=3.0 Hz, 1H), 3.82 (q, J=6.9 Hz, 2H), 1.26 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 159.9 (+), 158.3 (+), 149.5 (−), 131.5 (+), 124.7 (+), 118.0 (−), 109.1 (−), 85.7 (+), 64.3 (+), 14.0 (−); IR (neat) 2349, 1531 cm^{-1}; MS (EI) m/z 229 (M^++2), 227 (M^+), 171, 169 (100%), 113; Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.87; H, 4.51; N, 6.23.

3.1.7. 1-Ethoxy-1-(3-nitro-2-pyridyl)ethene (17). Reaction of 2-bromo-3-nitropyridine (**10**) (176 mg, 0.867 mmol) with **2** (376 mg, 1.04 mmol) in the presence of $Pd(dba)_2$ (25 mg, 0.044 mmol) and PPh_3 (45 mg, 0.17 mmol) in toluene (55 mL), as described for **3** (42 h), gave, after extraction and chromatography (hexanes/EtOAc, 95:5), **17** (113 mg, 0.582 mmol, 67%) as a pale yellow oil. ^{1}H NMR δ 8.73 (dd, J=4.7, 1.8 Hz, 1H), 7.98 (dd, J=8.1, 1.4 Hz, 1H), 7.42 (dd, J=8.1, 4.8 Hz, 1H), 5.10 (d, J=2.6 Hz, 1H), 4.56 (d, J=2.6 Hz, 1H), 3.91 (q, J=6.9 Hz, 2H), 1.31 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 157.2 (+), 151.2 (−), 148.1 (+), 146.2 (+), 131.6 (−), 123.4 (−), 89.2 (+), 64.6 (+), 13.9 (−); IR (neat) 2984, 1537 cm^{-1}; MS (EI) m/z 194 (M^+), 136, 78 (100%); Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.88; H, 5.50; N, 14.06.

3.1.8. 3,4-Dihydro-6-(2-nitrophenyl)-2*H*-pyran (18).[41,42] Reaction of **1** (180 mg, 0.72 mmol), $Pd(dba)_2$ (21 mg, 0.036 mmol), and PPh_3 (38 mg, 0.14 mmol) with tributyl(3,4-dihydro-2*H*-pyran-6-yl)stannane[43] (324 mg, 0.868 mmol) in toluene (75 mL total), as described above for **3** (48 h), gave, after extraction and chromatography (hexanes), **18** as a yellow oil (120 mg, 0.58 mmol, 81%). Spectral data (^{1}H NMR) in complete accordance with literature values.[41]

3.1.9. 3-Ethoxyindole (4). 1-Ethoxy-1-(2-nitrophenyl)-ethene (**3**) (47 mg, 0.24 mmol), $Pd(dba)_2$ (9 mg, 0.02 mmol), 1,3-bis-(diphenylphosphino)propane (dppp) (6 mg, 0.01 mmol), and 1,10-phenanthroline (phen) (6 mg, 0.03 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 120 °C (oil bath temperature) under CO (6 atm) until all starting material was consumed (96 h), as judged by TLC. Water (10 mL) was added and the brown solution was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (hexanes/EtOAc, 7:3) to afford **4** (28 mg, 0.17 mmol, 72%) as a purple oil. ^{1}H NMR δ 7.68 (d, J=7.9 Hz, 1H), 7.45 (br s, 1H), 7.25

(dd, J=8.0, 1.0 Hz, 1H), 7.18 (dt, J=8.1, 1.2 Hz, 1H), 7.07 (dt, J=7.4, 1.2 Hz, 1H), 6.67 (d, J=2.6 Hz, 1H), 4.07 (q, J=6.9 Hz, 2H), 1.46 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 140.8 (+), 134.3 (+), 122.7 (−), 120.0 (+), 118.9 (−), 118.0 (−), 111.1 (−), 105.2 (−), 66.7 (+), 15.1 (−); IR (neat) 3478, 909, 731 cm^{-1}; MS (EI) m/z 161 (M$^+$), 132 (100%); Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.79; H, 6.95; N, 8.75.

3.1.10. 3-Ethoxy-4-methylindole (19). Reaction of **12** (37 mg, 0.18 mmol) in the presence of Pd(dba)$_2$ (6 mg, 0.01 mmol), dppp (6 mg, 0.01 mmol), phen (4 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (48 h), gave, after chromatography (hexanes/EtOAc, 9:1), **19** (27 mg, 0.15 mmol, 84%) as a dark green oil. ^{1}H NMR δ 7.76–7.01 (m, 3H), 6.83–6.78 (m, 1H), 6.64 (d, J=2.6 Hz, 1H), 3.99 (q, J=6.9 Hz, 2H), 2.70 (s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 142.6 (+), 134.5 (+), 130.4 (+), 122.7 (−), 120.0 (−), 118.9 (+), 108.5 (−), 104.4 (−), 66.8 (+), 18.9 (−), 15.1 (−); IR (neat) 3470, 908, 734 cm^{-1}; MS (EI) m/z 175 (M$^+$), 147 (100%); Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.41; H, 7.58; N, 8.00.

3.1.11. Methyl 3-ethoxyindole-4-carboxylate (20). Reaction of **13** (21 mg, 0.084 mmol) in the presence of Pd(dba)$_2$ (3 mg, 0.005 mmol), dppp (2 mg, 0.005 mmol), phen (2 mg, 0.01 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 95:5) **20** (16 mg, 0.078 mmol, 87%) as a yellow oil. ^{1}H NMR δ 7.78 (br s, 1H), 7.53 (dd, J=7.2, 0.7 Hz, 1H), 7.43 (dd, J=8.2, 0.8 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 6.85 (d, J=2.5 Hz, 1H), 4.00 (q, J=6.9 Hz, 2H), 3.97 (s, 3H), 1.46 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 169.1 (+), 140.6 (+), 134.9 (+), 124.0 (+), 121.7 (−), 121.5 (−), 115.8 (+), 114.8 (−), 108.0 (−), 67.2 (+), 51.9 (−), 15.1 (−); IR (neat) 3251, 1742, 908, 734 cm^{-1}; MS (EI) m/z 219 (M$^+$), 190, 159 (100%); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.59; H, 6.12; N, 6.38.

3.1.12. 3-Ethoxy-6-nitroindole (21). Reaction of **14** (48 mg, 0.20 mmol) in the presence of Pd(dba)$_2$ (7 mg, 0.01 mmol), dppp (5 mg, 0.01 mmol), phen (5 mg, 0.03 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 95:5), **21** (36 mg, 0.17 mmol, 85%) as a dark yellow oil.[44] ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 7.92 (d, J=1.0 Hz, 1H), 7.69 (dd, J=8.7, 1.6 Hz, 1H), 7.66 (d, J=8.5 Hz, 1H), 7.10 (d, J=2.4 Hz, 1H), 6.88 (d, J=2.8 Hz, 1H), 4.11 (q, J=7.1 Hz, 2H), 1.49 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.9 (+), 141.6 (+), 135.4 (+), 132.7 (+), 118.6 (−), 112.9 (−), 109.7 (−), 109.5 (−), 66.9 (+), 15.4 (−); IR (neat) 3422, 1545, 1348, 908, 734 cm^{-1}.

3.1.13. 3-Ethoxy-6-methoxyindole (22). Reaction of **15** (28 mg, 0.13 mmol) in the presence of Pd(dba)$_2$ (5 mg, 0.008 mmol), dppp (3 mg, 0.008 mmol), phen (3 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (96 h), gave, after chromatography (hexanes/EtOAc, 95:5) **22** (19 mg, 0.10 mmol, 79%) as a yellow solid.[44] Mp 62–63 °C; ^{1}H NMR δ 7.52 (d, J=9.3 Hz, 1H), 7.29 (br s, 1H), 6.76 (d, J=2.2 Hz, 1H), 6.74 (dd, J=6.1, 2.1 Hz, 1H), 6.56 (d, J=2.4 Hz, 1H), 4.05 (q, J=6.9 Hz, 2H), 3.83 (s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 140.8 (+), 134.5 (+), 122.3 (+), 118.8 (−), 109.1 (−), 94.5 (−), 66.6 (+), 60.6 (+), 55.7 (−), 15.2 (−), 14.3 (−); IR (neat) 3422, 908, 741 cm^{-1}; MS (EI) m/z 191 (M$^+$), 162 (100%).

3.1.14. 6-Chloro-3-ethoxyindole (23). Reaction of **16** (126 mg, 0.553 mmol) in the presence of Pd(dba)$_2$ (19 mg, 0.033 mmol), dppp (14 mg, 0.033 mmol), phen (13 mg, 0.066 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 7:3) **23** (62 mg, 0.32 mmol, 63%) as a yellow solid.[44] Mp 85.5–86.5 °C; ^{1}H NMR δ 7.57 (d, J=8.5 Hz, 1H), 7.45 (br s, 1H), 7.22 (d, J=1.2 Hz, 1H), 7.05 (dd, J=8.3, 1.8 Hz, 1H), 6.63 (d, J=2.4 Hz, 1H), 4.03 (q, J=6.9 Hz, 2H), 1.42 (t, J=7.1 Hz, 3H); ^{13}C NMR δ 140.9 (+), 134.6 (+), 128.8 (−), 119.7 (−), 119.1 (+), 118.6 (−), 111.1 (+), 105.5 (−), 66.8 (+), 15.1 (−); IR (neat) 3478, 908, 731 cm^{-1}; MS (EI) m/z 197 (M$^+$+2), 195 (M$^+$), 168, 166 (100%).

3.1.15. 3-Ethoxy-1*H*-pyrrolo[3,2-*b*]pyridine (24). Reaction of **17** (31 mg, 0.16 mmol) in the presence of Pd(dba)$_2$ (6 mg, 0.01 mmol), dppp (4 mg, 0.01 mmol), phen (4 mg, 0.02 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (72 h), gave, after chromatography (hexanes/EtOAc, 8:2), **24** (22 mg, 0.14 mmol, 85%) as a yellow solid.[44] Mp 84–85 °C; ^{1}H NMR δ 8.44 (dd, J=4.7, 1.5 Hz, 1H), 7.83 (br s, 1H), 7.58 (dd, J=8.2, 1.2 Hz, 1H), 7.11 (dd, J=8.4, 4.7 Hz, 1H), 6.96 (d, J=2.7 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 1.49 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 142.7 (−), 127.5 (+), 118.5 (+), 118.4 (−), 117.6 (+), 114.9 (−), 109.4 (−), 66.9 (+), 15.1 (−); IR (neat) 3418, 909, 734 cm^{-1}; MS (EI) m/z 162 (M$^+$), 147, 79 (100%).

3.1.16. 2,3,4,5-Tetrahydropyrano[3,2-*b*]indole (25)[45] and 4,5-dihydrospiro[furan-2(3*H*),2′-[2*H*]indol]-3′-(1′*H*)-one (26). Reaction of **18** (193 mg, 0.941 mmol), Pd(dba)$_2$ (32 mg, 0.056 mmol), dppp (22 mg, 0.11 mmol), phen (23 mg, 0.056 mmol), and CO (6 atm) in DMF (2 mL), as described for **4** (80 h), gave, after chromatography (hexanes/EtOAc/acetone, 95:4:1), a 3.5:1 mixture of **25** and **26** as a yellow oil (152 mg). Spectral data of **25** from the mixture: ^{1}H NMR δ 7.50 (d, J=7.5 Hz, 1H), 7.39 (br s, 1H), 7.20 (d, J=7.1 Hz, 1H), 7.11 (dt, J=7.1, 1.4 Hz), 7.04 (dt, J=6.9, 1.2 Hz, 1H), 4.23 (t, J=4.9 Hz, 2H), 2.77 (t, J=6.3 Hz, 2H), 2.10 (pent, J=5.1 Hz, 2H); ^{13}C NMR δ 133.1 (+), 132.2 (+), 122.4 (+), 121.5 (−), 119.2 (+), 118.9 (−), 116.4 (−), 110.7 (−), 67.2 (+), 22.6 (+), 20.1 (+). (Lit.[31] ^{1}H NMR δ 7.60–6.85 (m, 5H), 4.18 (t, J=5.0 Hz, 2H), 2.78 (t, J=6.2 Hz, 2H), 2.30–1.86 (m, 2H).

Complete oxidative-rearrangement of **25** to **26** was accomplished using the following procedure. Silica gel (approx. 500 mg) was added to a solution of the mixture of **25** and **26** in acetone (10 mL). The solvent was removed and the residual solid was allowed to stand open to the air overnight (14 h). Purification by chromatography (hexanes/EtOAc/acetone, 95:4:1) afforded **26** as a bright yellow oil (131 mg, 0.692 mmol, 74% from **18**). ^{1}H NMR (600 MHz) δ 7.55 (d, J=7.8 Hz, 1H), 7.42 (dt, J=7.8, 1.2 Hz, 1H), 6.81 (t, J=7.8 Hz, 1H), 6.77 (d, J=8.4 Hz, 1H), 4.77 (br s, 1H), 4.13 (m, 2H), 2.28 (m, 2H), 2.07 (m, 1H), 1.99 (m, 1H); ^{13}C NMR δ (150 MHz) 200.9 (+), 159.6 (+), 137.8 (−), 125.1 (−), 119.7 (−), 119.2 (+), 112.2 (−), 95.0 (+),

69.3 (+), 34.0 (+), 25.8 (+); IR (neat) 3250, 1702, 1007 cm^{-1}; HRMS calcd for $C_{11}H_{12}NO_2$ (M^++H) 190.0868, found 190.0862.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.101.

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