Efficient Preparation of 2-Indolyl-1-nitroalkane Derivatives Employing Nitroalkenes as Versatile Michael Acceptors: New Practical Linear Approach to Alkyl 9H- β -Carboline-4-carboxylate.

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General Methods. Most solvents and reagents were used without purification unless mentioned otherwise. Solvents (EtOAc and hexane) for flash chromatography were distilled. Dry xylene was prepared by distillation from sodium under a nitrogen atmosphere and used immediately. The indoles used as starting materials were obtained from commercial sources and the nitro alkenes used were commercially available or prepared according to literature procedures.¹ All air- or moisture-sensitive reactions were carried out in the flame-dried glassware under nitrogen atmosphere. Melting points are uncorrected. Reactions with compounds sensitive to air or moisture were performed under nitrogen. TLC was run on silica gel 60 F₂₅₄ plates (0.25 mm thick), and visualized by UV light or Iodine or a Ce-Mo staining solution (phosphomolybdate, 25 g; Ce(SO₄)₂·4H₂O, 10 g; H₂SO₄ 60 mL, concentrated; water, 940 mL) with heating. Flash chromatography was performed using a silica gel 60 (mesh size 0.040-0.063 mm) using a silica gel:crude compound weight ratio of ca. 30:1. Analytical GC was performed using a capillary fused silica column (0.32 mm x 25 m), stationary phase OV1 (film thickness 0.40-0.45 µm). Infrared spectra were taken in Nujol or neat with a Fourier Transform spectrophotometer using thin films on NaCl plates. Only the characteristic peaks are reported. ¹H NMR (300 MHz) spectra were taken in CDCl₃ or DMSO-d₆ with residual signals of solvent as an internal standard. ¹³C NMR (75.5 MHz) spectra were recorded in CDCl₃ or DMSO-d₆ and chemical shifts are reported relative to the center line of the triplet at 77.00 ppm for deuteriochloroform or relative to the line at 39.51 ppm for methyl sulfoxide hexadeuterated, respectively. Mass spectra were determined with a capillary GC operating in split mode with helium as the carrier gas and fitted with mass-selective detector (MSD) by means of the EI technique (70 eV) and with a system LC/MS HP1100 by means a source API-Electrospray, respectively.

Synthesis of 2-indolyl-1-nitroalkanes 3. Representative experimental procedure. Silica gel (0.5 g) was added to a mixture of CeCl₃·7H₂O (0.112 g, 0.30 mmol) and NaI (0.045 g, 0.30 mmol) in acetonitrile (10 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation and the resulting mixture was stored in a bottle at room temperature.

To the CeCl₃·7H₂O-NaI combination supported on silica gel (0.439 g) prepared as above was added indole (**1c**) (0.10 g, 0.76 mmol) and *trans*-β-nitrostyrene (**2a**) (0.113 g, 0.76 mmol), and 4 mL of CH₃CN (the solvent is necessary only when all two reagents are solids). The mixture was stirred for 30 min at room temperature, the solvent was removed and the resulting mixture reaction was then stirred at room temperature until the disappearance of the starting indole (24 hours, checked by TLC and GC analyses). After addition of Et₂O the mixture was passed through a short pad of Celite and the filtrate was concentrate under reduced pressure. The crude was purified by flash chromatography on a silica gel column (eluent, hexanes-ethyl acetate, 70:30) to give 0.16 g of the corresponding Michael adduct **3ca**.

¹ (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850-3856. (b) Ballini, R.; Castignani, R.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 2160-2162

5-Hydroxy-3-(2-nitro-1-phenylethyl)-1H-indole (3ca): (yield 74%); IR (nujol) 3419, 3326, 1551, 1379 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.83-5.12 (m, 4H), 6.73-6.83 (m, 2H), 6.97 (d, 1H, $J = 2.56$ Hz), 7.18 (d, 1H, $J = 8.43$ Hz), 7.22-7.31 (m, 5H), 8.05 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 37.6, 84.2, 102.3, 104.6, 107.9, 116.7, 124.0, 124.7, 127.3, 131.2, 131.6, 134.3, 148.6, 155.4; EI-MS m/z 282 $[\text{M}^+]$, 265, 205 (100), 132, 116, 115, 91, 77, 74. Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.00; H, 4.95; N, 9.86.

3-(2-Nitro-1-phenylethyl)-1H-5-indolecarbonitrile (3da): (yield 85%); IR (nujol) 3390, 2218, 1557, 1538, 1377 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.89-5.12 (m, 3H), 7.26-7.45 (m, 8H), 7.73 (s, 1H), 8.81 (bs, 3H, NH); ^{13}C NMR (CDCl_3) δ 43.2, 88.2, 100.3, 109.2, 109.9, 118.2, 122.6, 124.7, 125.8, 126.6, 130.9, 143.6, 150.0; EI-MS m/z 291 $[\text{M}^+]$, 281, 257, 244 (100), 231, 229, 207, 115, 103, 77. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.03; H, 4.46; N, 14.36.

3-(2-Nitrocyclohexyl)-1H-indole (anti-3ac): IR (neat) 3401, 1669, 1560, 1379 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.47-2.23 (m, 7H), 2.38-2.47 (m, 1H), 3.44-3.58 (m, 1H), 4.87 (dt, 1H, $J = 11.35$ and 4.02 Hz), 7.01 (d, 1H, $J = 2.20$ Hz), 7.08-7.23 (m, 2H), 7.27-7.36 (m, 1H), 7.64-7.68 (m, 1H), 8.05 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 25.0, 27.6, 29.6, 34.2, 42.5, 89.3, 112.0, 120.3, 122.6, 122.9, 125.0, 127.8, 138.9; EI-MS m/z 244 $[\text{M}^+]$, 197, 186, 131, 128, 115 (100), 103, 57, 46, 30. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.72; H, 6.59; N, 11.38.

3-(2-Nitrocyclohexyl)-1H-indole (syn-3ac): IR (neat) 3396, 1675, 1555, 1375; ^1H NMR (CDCl_3) δ 1.47-1.69 (m, 2H), 1.87-2.14 (m, 4H), 2.34-2.54 (m, 2H), 3.51-3.63 (m, 1H), 5.09 (q, 1H, $J = 4.40$ Hz), 7.01 (d, 1H, $J = 2.56$), 7.11-7.25 (m, 2H), 7.31-7.41 (m, 1H), 7.55-7.61 (m, 1H), 8.07-8.27 (m, 1H); ^{13}C NMR (CDCl_3) δ 25.0, 26.8, 28.3, 32.6, 40.9, 89.3, 11.9, 119.0, 122.8, 124.6, 129.4, 140.0; EI-MS m/z 244 $[\text{M}^+]$, 197, 186, 131, 128, 115 (100), 103, 57, 46, 30. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.79; H, 6.55; N, 11.45.

3-[1-(2-Furyl)-2-nitropropyl]-1H-indole (3ad): (yield 80%); IR (nujol) 3417, 3098, 1548, 1359 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.46 (d, 2H, $J = 6.59$ Hz), 1.57 (d, 1H, $J = 6.59$ Hz), 4.96 (t, 1H, $J = 10.44$ Hz), 5.27-5.44 (m, 1H), 6.18-6.33 (m, 2H), 7.11-7.49 (m, 5H), 7.66-7.68 (m, 1H), 8.17 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 18.0, 18.45, 41.4, 41.5, 86.2, 86.3, 107.2, 108.3, 110.0, 111.9, 118.8, 126.8, 136.1, 136.6, 141.3, 142.2, 152.0, 152.8; EI-MS m/z 270 $[\text{M}^+]$, 223, 203, 195 (100), 115, 107, 88, 67. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.61; H, 5.17; N, 10.28.

3-[2-nitro-1-(3-pyridyl)ethyl]1H-indole (3ae): (yield 93%); IR (nujol) 3396, 1552, 1460, 1376 cm^{-1} ; ^1H NMR (CDCl_3) δ 4.88-5.25 (m, 3H), 7.01-7.28 (m, 4H), 7.24-7.42 (m, 2H), 7.61-7.67 (m, 1H), 8.39-8.53 (m, 2H), 8.64 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 40.1, 86.2, 113.2, 116.2, 118.9, 124.6, 124.9, 127.3, 133.2, 139.4, 147.2, 149.3; EI-MS m/z 281 $[\text{M}^+]$, 234, 208 (100), 131, 115, 78, 53, 46, 30. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.37; H, 4.86; N, 15.65.

Methyl 2-(5-hydroxy-1H-3-indolyl)-3-nitropropanoate (3cg): (yield 86%); IR (neat) 3406, 3368, 3052, 1745, 1558, 1372 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.74 (s, 3H), 4.57-4.72 (m, 2H), 5.15-5.27

(m, 1H), 6.83 (dd, 1H, $J = 8.79$ and 2.56 Hz), 7.04 (d, 1H, $J = 2.20$ Hz), 7.13 (d, 1H, $J = 2.56$ Hz), 7.25 (d, 1H, $J = 8.79$ Hz), 8.16 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 40.8, 50.9, 75.3, 106.6, 112.5, 113.2, 120.8, 124.0, 126.5, 151.2, 172.0; LC-MS (ESI) m/z 265 $[\text{M}+\text{H}]^+$, 287 $[\text{M}+\text{Na}]^+$, 303 $[\text{M}+\text{K}]^+$. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.99; H, 4.85; N, 11.28.

Methyl 2-(1H-3-indolyl)-3-nitropropanoate (3ag): (yield 91%); IR (neat,) 3406, 3030, 1745, 1376 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.74 (s, 3H), 4.61-4.82 (m, 2H), 5.17-5.29 (m, 1H), 7.12-7.31 (m, 3H), 7.38-7.42 (m, 1H), 7.66 (d, 1H, $J = 8.42$ Hz), 8.32 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 40.7, 53.0, 75.4, 111.8, 120.6, 123.1, 123.2, 125.8, 136.4, 171.9; EI-MS m/z 248 $[\text{M}^+]$, 201, 160, 143 (100), 142, 115, 73, 62. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.99; H, 4.85; N, 11.28.

Methyl 3-amino-2-(1H-3-indolyl)propanoate hydrochloride (4). A vigorously stirred mixture of indole **3ag** (0.524 g, 2.11 mmol), ethanol (107 mL), and Raney nickel (3.05 g) was hydrogenated at atmospheric pressure for 20 h. The nickel was then removed by filtration over Celite and washed with hot ethanol (500 mL). Evaporation of the filtrate in vacuum afforded a syrup that was treated with 1 equiv of 4N HCl-dioxane. The product was filtered and the HCl salt resulting residue of **4** (0.42 g, 78% yield) was sufficiently pure for further use: ^1H NMR (D_2O) δ 3.33-3.61 (m, 5H), 4.27 (t, 1H, $J = 7.50$ Hz), 4.65 (s, 3H), 6.99-7.17 (m, 2H), 7.26 (s, 1H), 7.37-7.48 (m, 1H).

Methyl 1,2,3,4-tetrahydro-1H- β -carboline-4-carboxylate hydrochloride (5). A solution of **4** (0.221 g, 0.87 mmol) and 37% formaline (90 mg, 1.044 mmol; 80 μL) in MeOH (20 mL) was stirred at room temperature for a night. The mixture was diluted with ether, and the resulting crystals were collected by filtration and dried to give **5**·HCl as colorless needles. The HCl salt was converted to the free base on treatment with EtOAc (25 mL) and with 6% K_2CO_3 (7.5 mL). The resulting mixture was stirred at room temperature for 1 h, then the organic layer was dried (MgSO_4), and the solvent was evaporated in vacuum. The residue was chromatographed on silica gel and eluted with hexanes/ethyl acetate/ethanol (6:3:1) to yield methyl 1,2,3,4-tetrahydro-1H- β -carboline-4-carboxylate (**5**; 0.183 g, 90%): mp 160-163 $^\circ\text{C}$ (EtOH); IR (nujol) 3401, 1731, 1463, 1456 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.26 (bs, 1H, NH), 3.05 (dd, 1H, $J = 13.73$ and 4.56 Hz), 3.60 (dd, 1H, $J = 13.73$ and 2.14 Hz), 3.72 (s, 3H), 3.78-3.80 (m, 1H), 3.99-3.99 (m, 2H), 7.09-7.19 (m, 2H), 7.26-7.31 (m, 1H), 7.60-7.63 (m, 1H), 8.10 (bs, 1H, NH); ^{13}C NMR (CDCl_3) δ 36.2, 46.0, 52.7, 53.0, 104.0, 111.9, 121.3, 122.7, 122.9, 124.6, 139.7, 142.3, 175.2. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$: Found: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.69; H, 6.10; N, 12.09.

Methyl 9H- β -carboline-4-carboxylate (6). The compound **5** (0.15 g, 0.65 mmol) was dissolved in anhydrous xylene (20 mL), and 10% palladium on charcoal catalyst (0.10 g) was added. The mixture was heated under reflux with vigorous stirring for 4 h until no tetrahydro- β -carboline **5** remained, as indicated by TLC using toluene-ethanol (9:2) as developer. The catalyst was removed by filtration over Celite and washed with ethyl acetate. Evaporation of the filtrate gave an residue which was purified by chromatography on silica gel column (eluent, hexanes/ethyl acetate/ethanol, 6:3:1), yielding 0.124 g (83% yield) of crystalline β -carboline **6**: mp 195-197 $^\circ\text{C}$ (EtOH); IR

(nujol,) 3386, 1735 cm^{-1} ; ^1H NMR (DMSO-d_6) δ 4.02 (s, 3H), 7.23-7.32 (m, 1H), 7.57-7.68 (m, 2H), 8.79-8.87 (m, 2H), 9.12 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 52.3, 112.0, 119.1, 119.2, 125.4, 126.2, 129.1, 136.2, 137.9, 140.4, 141.6, 166.8; EI-MS m/z 226 [M^+] (100), 195, 167, 140, 113. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$: Found: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.92; H, 4.42; N, 12.26.