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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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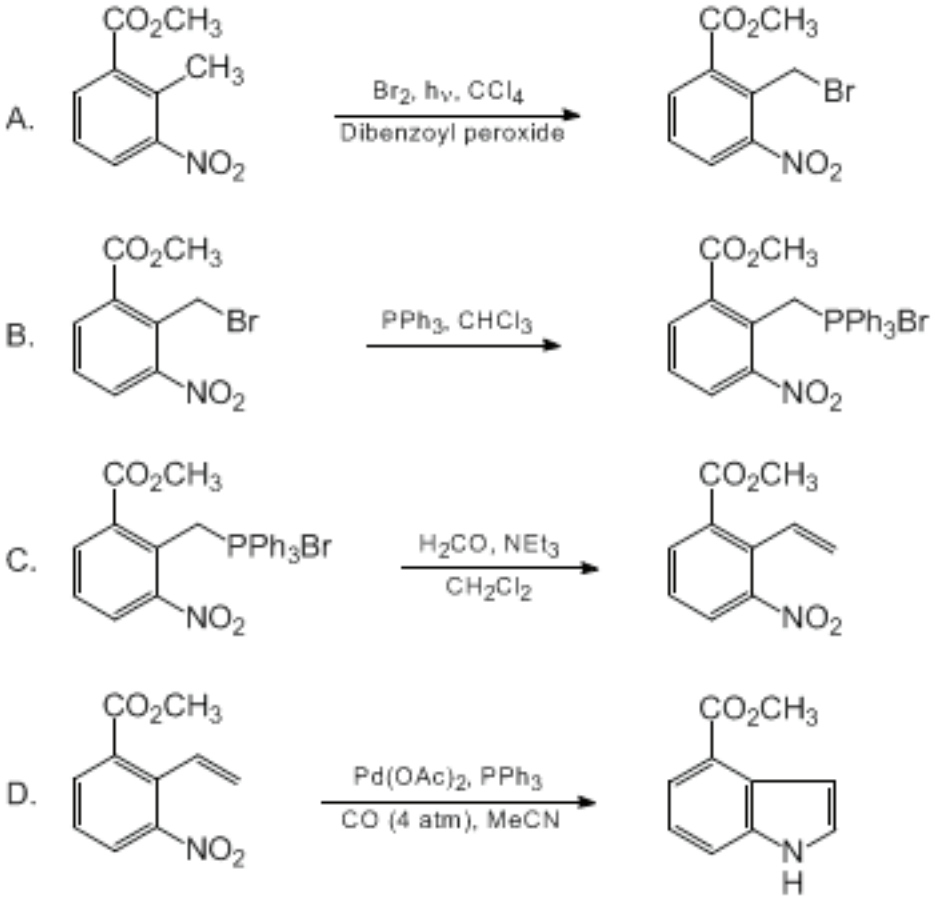
SYNTHESIS OF INDOLES BY PALLADIUM-CATALYZED REDUCTIVE N-HETEROANNULATION OF 2-NITROSTYRENES: METHYL INDOLE-4-CARBOXYLATE

[(1H-Indole-4-carboxylic acid, methyl ester)]



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Checked by J. David Warren and Louis S. Hegedus.
Discussion Addendum: *Org. Synth.* **2011**, *88*, 291.

1. Procedure

A. Methyl 2-bromomethyl-3-nitrobenzoate. To a 250-mL, two-necked, round-bottomed flask, equipped with a condenser and addition funnel, is added methyl 2-methyl-3-nitrobenzoate (19.1 g, 97.9 mmol, (Note 1)),

dibenzoyl peroxide (1.21 g, 5.00 mmol, (Note 2)), and 100 mL of carbon tetrachloride (Note 3). The mixture is heated to reflux, and a clear, pale yellow solution is formed. A solution of bromine (16.1 g, 100.6 mmol) (Note 2) in 20 mL of carbon tetrachloride is added over 10 min to the boiling solution under irradiation using a 100-W flood lamp. The reaction mixture is heated and irradiated for 24 h. The resulting orange solution is allowed to cool to ambient temperature; 50 mL of dichloromethane is added, and the solution is washed with three 50-mL portions of saturated aqueous sodium bicarbonate. The organic phase is dried ($MgSO_4$), filtered, and the solvents are removed at water aspirator pressure on a rotary evaporator affording 25.90 g (96.5%) of methyl 2-bromomethyl-3-nitrobenzoate as pale yellow crystals. The material is used in the next step without further purification (Note 4).

B. (2-Carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide. To a 500-mL, round-bottomed flask is added methyl 2-bromomethyl-3-nitrobenzoate (25.90 g, 94.5 mmol) and 150 mL of chloroform (Note 5). Triphenylphosphine (28.44 g, 108.4 mmol) (Note 2) is added in one portion and the resulting yellow solution is heated to reflux for 1.5 h. After cooling to ambient temperature, the orange solution is poured into 400 mL of anhydrous diethyl ether (Note 6) with vigorous stirring to precipitate the Wittig salt. The slurry is cooled in a freezer (−20 °C, 1 h). The white solids are collected by filtration, washed with 4 × 100 mL of anhydrous diethyl ether, and dried under high-vacuum to give crude (2-carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide. A ^{1}H NMR spectrum indicated that the product contained some triphenylphosphine, thus the salt was washed again with diethyl ether (2 × 100 mL). After drying, a considerably purer product (50.91 g) was obtained. The salt is used in the next step without further purification (Note 7).

C. Methyl 2-ethenyl-3-nitrobenzoate. Paraformaldehyde (30 g) (Note 8) is placed in a 250-mL, two-necked, round-bottomed flask. An argon inlet is connected to one of the necks. The other neck is connected to a 1-L, two-necked, round-bottomed flask via Tygon tubing (2 cm id) and two male 24/40 joints (Note 9). In the 1-L flask, 2-carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide (50.91 g) is dissolved in 500 mL of dichloromethane. A glass tube is attached to the Tygon tubing such that the end extends several cm into the solution. Triethylamine (39.13 g, 53.8

mL, 386.7 mmol) is added to the 1-L flask, resulting in the immediate formation of a deep blue/purple solution; a condenser is attached to the second neck of the flask. Argon is then passed over the paraformaldehyde so that a steady stream of gas is constantly bubbling through the purple ylide solution. The paraformaldehyde is heated to 160 °C (oil bath) in order to generate formaldehyde, which flows through the solution (Note 10). Upon completion of the addition of formaldehyde, the purple color of the ylide slowly changes from deep purple to brown over a period of 1-2 h, indicating completion of the reaction. The resulting solution is poured into 500 mL of hexanes, forming a precipitate, which is removed by filtration. The precipitate is washed with 100 mL of hexanes and the combined filtrate and wash are concentrated at water aspirator pressure on a rotary evaporator. The crude yellow-brown solid is dissolved in 100 mL of dichloromethane; 30 g of silica gel is added and the mixture is concentrated again. The resulting powder applied to a pre-packed silica gel column (40 × 4 cm) (Note 11), and eluted with 7:3 hexanes:ethyl acetate to give methyl 2-ethenyl-3-nitrobenzoate (15.87 g, 76.6 mmol, 81%, Notes 12-14) as pale yellow crystals.

D. Caution! Due to the toxicity of carbon monoxide and the risk of an explosion in handling pressurized glassware, this transformation should be carried out in a well vented fume hood with a blast shield and the hood sash down. Users should exercise appropriate caution at all times.

Methyl indole-4-carboxylate. To a threaded glass, 200-mL reaction vessel, equipped with a Teflon stirring bar, is added methyl 2-ethenyl-3-nitrobenzoate (10.35 g, 50.0 mmol), triphenylphosphine (3.23 g, 12.3 mmol) and 100 mL of acetonitrile (Note 15). The mixture is stirred for 10 min to dissolve the reagents. Palladium acetate (0.673 g, 3.00 mmol) (Note 16) is added; a yellow precipitate is immediately formed. The tube is attached to a pressure head (Note 17) and the solution is saturated with carbon monoxide (four cycles to 59 psi of CO) (Note 18). The reaction mixture is heated to 90 °C (oil bath temperature) under CO (59 psi) for 50 h. A red-brown solution forms after heating for a few minutes. In order to remove carbon dioxide that is formed and to monitor the progress of the reaction, the vessel is removed from the oil bath for 15 min, carefully vented, and repressurized with CO every 10-12 h (Note 19). After 50 h, the reaction mixture is cooled and concentrated using a rotary evaporator at water aspirator pressure, giving a

dark brown/black oil. The crude product is purified by chromatography on a pre-packed 40 × 4 cm silica column (Note 11) using 7:3 hexanes:CH_2Cl_2 (0.80 L), then 1:1 hexanes:CH_2Cl_2 (2.80 L) as eluents affording methyl indole-4-carboxylate (7.95 g, 44.75 mmol, 91%) as a pale yellow solid (Note 20).

2. Notes

1. Methyl 2-methyl-3-nitrobenzoate was used as received from Aldrich Chemical Company, Inc., or prepared from 2-methyl-3-nitrobenzoic acid in >97% yield according to the literature procedure.[2]

2. Dibenzoyl peroxide, bromine, and triphenylphosphine were used as received from Aldrich Chemical Company, Inc.

3. Carbon tetrachloride (anhydrous) was used as received from Aldrich Chemical Company, Inc.

4. The checkers did not observe complete conversion to the bromide. Analytical data: mp 63-66 °C (uncorrected). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.97 (s, 3 H), 5.13 (s, 2 H), 7.52 (t, J = 8.1, 1 H), 7.93 (dd, J = 8.1, 1.2, 1 H), 8.08 (dd, J = 7.7, 1.2, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.2, 53.4, 128.0, 129.4, 132.5, 132.8, 134.9, 150.7, 166.0; IR (neat) cm^{-1}: 1726, 1532, 1270. Anal. Calcd for $C_9H_8BrNO_4$: C, 39.44; H, 2.94. Found: C, 39.33; H, 2.94.

5. Chloroform (anhydrous) was used as received from Aldrich Chemical Company, Inc.

6. Diethyl ether (anhydrous) was used as received from Fisher Scientific.

7. Analytical data: mp 217-229 °C (sealed capillary, uncorrected); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.67 (s, 3 H), 5.69 (d, J_{PH} = 14.6, 2 H), 7.55-7.82 (overlapping multiplets, 16 H), 7.95 (d, J = 8.1, 1 H), 8.09 (d, J = 7.9, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.3 (d, J_{CP} = 51.7), 53.5, 117.7 (d, J_{CP} = 86.4), 124.8 (d, J_{CP} = 8.4), 129.1 (d, J_{CP} = 2.8), 130.0 (d, J_{CP} = 12.5), 130.8, 133.8 (d, J_{CP} = 9.8), 135.2 (d, J_{CP} = 2.9), 135.7, 150.9, 165.5; IR (neat) cm^{-1}: 1717, 1532, 1437, 1275, 1108.

8. Paraformaldehyde was used as received from Fisher Scientific.

9. Formaldehyde is generated according to the procedure of Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M. *Org. Synth., Coll. Vol. VII* **1990**, *271*; see Figure 1, p. 272.

10. The glass inlet tube has a tendency to clog. This problem can be remedied by lifting the tube out of the solution, discontinuing heating, and removing the obstruction. It is important to closely follow the pyrolysis. If insufficient heat is supplied, the ylide solution may be sucked into the flask containing paraformaldehyde. If too much heat is supplied, the joints may separate, usually resulting in a small flame at the joint.

11. Silica gel (200-400 mesh) from Natland International Corp. was used.

12. The yield is based on methyl-2-bromomethyl-3-nitrobenzoate.

13. A small amount (1.5%) of hydrolysis product, methyl 2-methyl-3-nitrobenzoate, was observed at times.

14. Analytical data: mp 39-40 °C (uncorrected); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3 H), 5.23 (dd, *J* = 17.6, 0.8, 1 H), 5.43 (dd, *J* = 11.3, 0.8, 1 H), 7.18 (dd, *J* = 17.6, 11.5, 1 H), 7.47 (t, *J* = 7.9, 1 H), 7.88 (dd, *J* = 8.3, 1, 1 H), 7.98 (dd, *J* = 7.7, 1.2, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.9, 119.7, 126.5, 128.1, 132.1, 132.2, 133.2, 134.2, 150.4, 166.8; IR (neat) cm^{-1}: 1730, 1531, 1292, 1264, 1124, 707. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38. Found: C, 57.72; H, 4.47.

15. Acetonitrile was distilled from calcium hydride prior to use.

16. Palladium acetate was used as received from Pressure Chemical Co.

17. The pressure head is assembled as follows using, if possible, stainless steel parts: A tee, equipped with a pressure relief valve (preset to open at 120 psi) and a pressure gauge (0-400 psi), is connected to a cross via a nipple. A ball valve (for pressure release and sample removal) is attached to the top of the cross, a valve (for introduction of CO) on one side of the cross, and a nipple connected to a Swagelok Teflon adapter attached to the bottom of the cross. An autoclave or a metal reaction vessel can be substituted for this reaction assembly.

18. UHP-grade carbon monoxide is used as purchased from Matheson Gas Products, Inc.

19. The reaction is monitored by thin layer chromatography on 60 Å silica gel (R_f = 0.15; 4:6 hexanes:CH_2Cl_2).

20. After ca. 500 mL of solvent, 20-mL fractions are collected and analyzed by thin layer chromatography. The plates are visualized at 254 nm, and the product appears as a bright fluorescent blue spot. Test tubes

containing the product are combined into two major fractions the first (1.173 g) contaminated by a small amount of an unknown impurity (higher R_f) and the second (6.663 g) as pure methyl indole-4-carboxylate. The ^{1}H NMR spectra of the two fractions are identical; however; a slight melting point depression is observed for the first fraction. Uncorrected melting points: first fraction 64-66 °C; second fraction 68-69 °C. Note: A range of melting points has been reported for this compound: Lit. mp 63 °C;[3] 64-65 °C;[4] 67-69 °C;[2] 69-71 °C.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.99 (s, 3 H), overlapping 7.19 (br d, J = 3.0, 1 H), 7.23 (t, J = 7.7, 1 H), 7.34 (t, J = 3.0, 1 H), 7.59 (d, J = 8.1, 1 H), 7.93 (d, J = 7.5, 1 H), 8.48 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.2, 103.9, 116.5, 121.3, 121.6, 123.6, 126.8, 127.6, 136.9, 168.4; IR (neat) cm^{-1}: 3355, 1699, 1276.

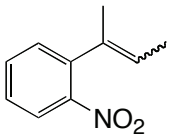
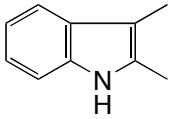
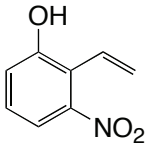
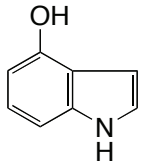
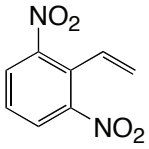
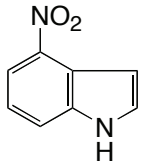
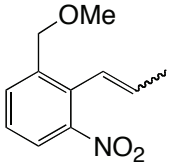
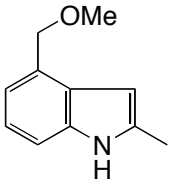
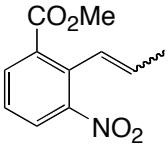
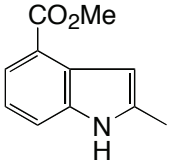
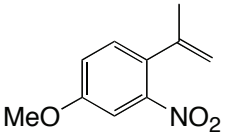
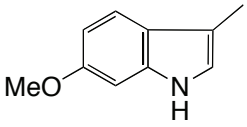
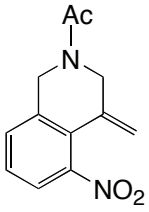
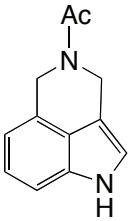
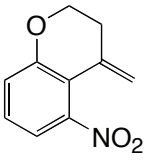
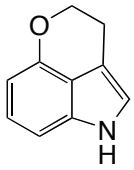
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here illustrates an efficient and relatively mild synthesis of methyl indole-4-carboxylate in 72% overall yield starting from commercially available materials. The synthetic sequence compares favorably to the previously described Batcho-Leimgruber indole syntheses of this substance.[2,3] In general, the palladium/phosphine-catalyzed *N*-heteroannulation of 2-nitrostyrenes offers a very flexible entry to functionalized indoles.[6] A few examples of this reaction, performed on a 1-2 mmol scale, are shown in the Table below. A number of palladium reagents, both palladium(0) and palladium(II), can be used as precatalyst for the reaction. For example, palladium diacetate, bis(acetonitrile)palladium dichloride, bis(dibenzylidenacetone)palladium and palladium on carbon (10% Pd) have all been shown to produce indoles in the presence of carbon monoxide and a catalytic amount of phosphine.[6a] Perhaps the most important feature of the reaction is its compatibility with other functional groups. For example, functionalities such as bromides, triflates, alcohols, ethers, esters, ketones, nitriles, and additional nitro groups all remain unaffected in this reaction. In contrast to the Batcho-Leimgruber route, indoles substituted in the 2- and/or 3-position can readily be prepared from 2-nitrostyrenes. More complex, fused indoles, can be obtained by annulation of bicyclic nitrostyrene derivatives (entries 7-8).

Table
Indoles By Reductive *N*-Heteroannulation of 2-Nitrostyrenes

Entry	Styrene	Indole	Yield (%)
1			97
2			96
3			89
4			76
5			90
6			81
7			41
8			63

1. Department of Chemistry, West Virginia University, Morgantown, WV 26506.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl indole-4-carboxylate: 1*H*-Indole-4-carboxylic acid, methyl ester (9); (39830-66-5)

Methyl 2-methyl-3-nitrobenzoate: Benzoic acid, 2-methyl-3-nitro-, methyl ester (9); (59382-59-1)

Methyl 2-bromomethyl-3-nitrobenzoate: Benzoic acid, 2-bromomethyl-3-nitro-, methyl ester (9); (98475-07-1)

Dibenzoyl peroxide: Peroxide, dibenzoyl (8,9); (94-36-0)

(2-Carbomethoxy-6-nitrobenzyl)triphenylphosphonium bromide: Phosphonium, [[2-(methoxycarbonyl)-6-nitrophenyl]methyl]triphenyl-, bromide; (195992-09-7)

Methyl 2-ethenyl-3-nitrobenzoate: Benzoic acid, 2-ethenyl-3-nitro-, methyl ester; (195992-04-2)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

Paraformaldehyde (8,9); (30525-89-4)

Triethylamine: Ethanamine, *N,N*-diethyl- (9); (121-44-8)

Carbon monoxide (8,9); (630-08-0)

Palladium acetate: Acetic acid, palladium(2+) salt (8,9); (3375-31-3)