

Single Flask Synthesis of *N*-Acylated Indoles by Catalytic Dehydrogenative Coupling with Primary Alcohols

Brooks E. Maki and Karl A. Scheidt*

Department of Chemistry, Northwestern University,
2145 Sheridan Road, Evanston, Illinois, 60208

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General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Toluene, MeOH, and CH₂Cl₂ were purified by passage through a bed of activated alumina.¹ Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.² Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium permanganate, or phosphomolybdic acid followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz;

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1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometal.* **1996**, *15*, 1518-1520.
 2. Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd Ed., Pergamon Press, Oxford. 1988.

integration. Proton-decoupled ^{13}C -NMR spectra were recorded on a Varian Inova 500 (125 MHz) or Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer and Micromass Quadro II Spectrometer.

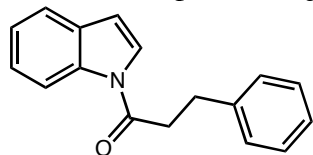
Representative Procedure for Oxidation:

Activated powdered 4\AA molecular sieves (500 mg), *N*-methylmorpholine *N*-oxide (3 equiv, 2 mmol, 335 mg), and 3-phenyl-1-propanol (0.67 mmol, 90 μL) were stirred in 1 mL acetonitrile. Tetrapropylammonium perruthenate (0.02 mmol, 6 mg) was added and the mixture was stirred for 15-45 minutes until consumption of the alcohol was complete (as evidenced by TLC). Indole (0.67 mmol, 78 mg), DBU (0.67 mmol, 100 μL), and an additional portion of TPAP (0.02 mmol, 6 mg) were added, and the mixture was stirred at room temperature until consumption of the aldehyde (TLC, 4-24 hours). The reaction mixture was filtered through a plug of silica gel (washed with ethyl acetate) and purified by column chromatography (10% ethyl acetate/hexanes) to give **10a** as a white solid (135 mg, 81% yield).

All reactions run at the same 0.66 mmol scale with 1 mL of solvent.

Characterization of New Compounds:

Data for compounds **10j**, **10k**,³ **10l**, **10p**,⁴ and **10q**⁵ were found to match all published data.



N-(3-phenylpropanoyl)indole (10a): After 8 h, **10a** isolated as a white solid (133 mg, 81% yield)

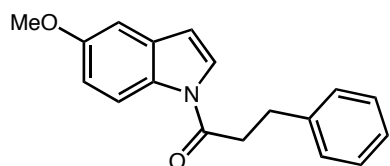
$R_f = 0.6$ (4:1 hexanes:ethyl acetate)

¹H NMR (500 MHz, CDCl₃) δ 8.51 (d, $J=8.3$ Hz, 1H); 7.59 (d, $J=7.8$ Hz, 1H); 7.45 (d, $J=3.4$ Hz, 1H); 7.27-7.39 (m, 7H); 6.65 (d, $J=3.4$ Hz, 1H); 3.26 (dd, $J=7.8$ Hz, 7.8 Hz, 2H); 3.20 (dd, $J=7.8$ Hz, 7.8 Hz, 2H);

¹³C NMR (125 MHz, CDCl₃) δ 170.8, 140.6, 128.9, 128.7, 128.6, 128.5, 126.7, 125.4, 124.6, 123.9, 121.1, 116.8, 109.5, 37.9, 30.7;

IR (film): 3050, 2940, 1735, 1450 cm⁻¹

LRMS (ES): Mass calculated for C₁₇H₁₅NO: 249.1. Found: 249.0



N-(3-phenylpropanoyl)5-methoxyindole (10b): After 8 h, **10b** isolated as a white solid (158 mg, 86% yield)

$R_f = 0.68$ (4:1 hexanes:ethyl acetate)

¹H NMR (500 MHz, CDCl₃) δ 8.41 (d, $J=8.7$ Hz, 1H); 7.27-7.40 (m, 6H); 7.05 (d, $J=2.5$ Hz, 1H); 6.99 (dd, $J=3.9$ Hz, 2.5 Hz, 1H); 6.57 (d, $J=3.9$ Hz, 1H); 3.88 (s, 3H); 3.20 (m, 4H);

¹³C NMR (125 MHz, CDCl₃) δ 170.3, 156.6, 140.6, 131.4, 130.5, 128.8, 128.6, 126.6, 125.2, 117.5, 113.6, 109.2, 103.7, 55.7, 37.5, 30.7;

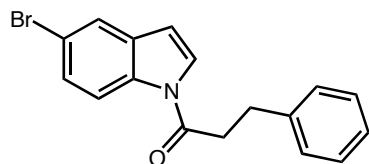
IR (film): 3040, 2920, 1730, 1430 cm⁻¹

LRMS (ES): Mass calculated for C₁₈H₁₇NO₂: 279.1. Found: 279.3

³ Oldroyd, D. L.; Weedon, A. C. *J. Org. Chem.* **1994**, *59*, 1333-1343.

⁴ Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757-761.

⁵ Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137-3139.



N-(3-phenylpropanoyl)5-bromoindole (10c): After 14 h, **10c** isolated as a yellow oil (164 mg, 76% yield)

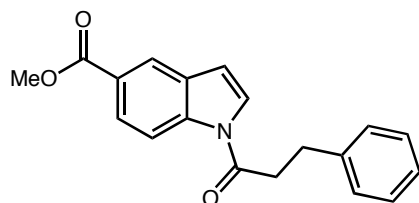
$R_f = 0.57$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.36 (d, $J=8.8$ Hz, 1H); 7.69 (d, $J=2.0$ Hz, 1H); 7.45 (dd, $J=8.8$ Hz, 2.0 Hz, 1H); 7.42 (d, $J=3.7$ Hz, 1H); 7.2-7.38 (m, 5H); 6.56 (d, $J=3.6$ Hz, 1H); 3.23 (dd, $J=7.5$ Hz, 7.5 Hz, 2H); 3.21 (dd, $J=7.5$ Hz, 7.5 Hz, 2H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.7, 140.4, 134.5, 132.2, 128.9, 128.6, 128.2, 126.8, 125.7, 123.7, 118.2, 117.2, 108.6, 37.8, 30.6;

IR (film): 3040, 2950, 1740, 1420 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{17}\text{H}_{14}\text{BrNO}$: 327.0. Found: 326.5



Methyl N-(3-phenylpropanoyl)indole-5-carboxylate (10d): After 8 h, **10d** isolated as a white solid (148 mg, 73% yield)

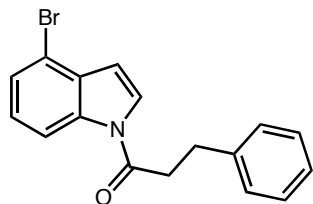
$R_f = 0.4$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.51 (d, $J=8.8$ Hz, 1H); 8.29 (d, $J=1.4$ Hz, 1H); 8.05 (dd, $J=8.8$ Hz, 1.4 Hz, 1H); 7.49 (d, $J=3.9$ Hz, 1H); 7.2-7.35 (m, 5H); 6.69 (d, $J=3.9$ Hz, 1H); 3.94 (s, 3H); 3.25 (dd, $J=7.3$ Hz, 7.3 Hz, 2H); 3.18 (dd, $J=7.3$ Hz, 7.3 Hz, 2H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.9, 167.6, 140.3, 138.4, 130.3, 128.9, 128.7, 126.8, 126.7, 125.8, 125.7, 123.3, 116.5, 109.8, 52.3, 38.0, 30.6; (some residual hexanes visible at 14.1, 22.7, and 31.6 ppm in spectrum published below)

IR (film): 3050, 2940, 1750, 1670, 1450 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{19}\text{H}_{17}\text{NO}_3$: 307.1. Found: 307.2



***N*-(3-phenylpropanoyl)4-bromoindole (10e)**: After 14 h, **10e** isolated as a pale yellow solid (160 mg, 74% yield)

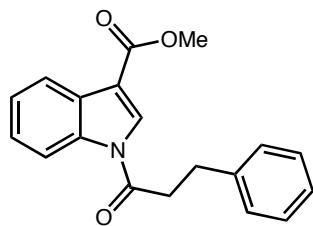
$R_f = 0.66$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.44 (d, $J=8.3$ Hz, 1H); 7.20-7.47 (m, 8H); 6.70 (d, $J=3.9$ Hz, 1H); 3.23 (dd, $J=7.8$ Hz, 6.7 Hz, 2H); 3.18 (dd, $J=7.8$ Hz, 6.8 Hz, 2H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.9, 140.4, 129.0, 128.7, 128.5, 126.9, 126.8, 126.4, 125.8, 125.2, 124.7, 115.9, 109.2, 38.0, 30.6;

IR (film): 3020, 2930, 1735, 1440 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{17}\text{H}_{14}\text{BrNO}$: 327.0. Found: 327.0



methyl *N*-(3-phenylpropanoyl)indole-3-carboxylate (10f): After 24 h, **10f** isolated as a white solid (142 mg, 70% yield)

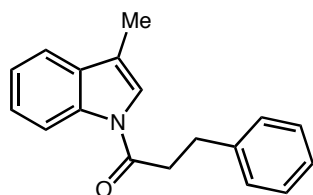
$R_f = 0.37$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.47 (d, $J=7.8$ Hz, 1H); 8.15 (d, $J=7.4$ Hz, 1H); 8.12 (s, 1H); 7.25-7.42 (m, 7H); 3.94 (s, 3H); 3.29 (dd, $J=7.8$ Hz, 7.2 Hz, 2H); 3.18 (dd, $J=7.8$ Hz, 7.1 Hz, 2H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.9, 164.5, 140.1, 130.6, 128.9, 128.7, 128.6, 127.4, 126.8, 126.2, 125.0, 121.7, 116.7, 113.9, 51.8, 37.7, 30.4;

IR (film): 3030, 2940, 1750, 1665, 1450 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{19}\text{H}_{17}\text{NO}_3$: 307.1. Found: 307.0.



***N*-(3-phenylpropanoyl)3-methylindole (10g)**: After 24 h, **10g** isolated as a white solid (109 mg, 63% yield)

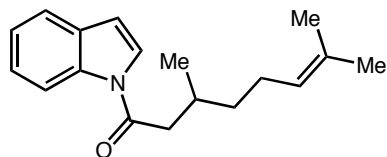
$R_f = 0.66$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.48 (bs, 1H); 7.51 (d, $J=7.3$ Hz, 1H); 7.16-7.39 (m, 8H); 3.18 (m, 4H); 2.28 (s, 3H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 170.5, 140.8, 128.9, 128.8, 128.7, 128.6, 126.7, 126.6, 125.5, 123.7, 121.7, 119.1, 118.7, 38.0, 30.7, 10.0;

IR (film): 3040, 2960, 1740, 1435 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{18}\text{H}_{17}\text{NO}$: 263.1. Found: 263.4



***N*-(3,7-dimethyl-6-octenoyl)indole (10m)**: After 16 h, **10m** isolated as a clear oil (130 mg, 73% yield)

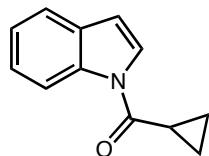
$R_f = 0.74$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.50 (d, $J=8.1$ Hz, 1H); 7.55 (d, $J=7.8$ Hz, 1H); 7.43 (d, $J=3.4$ Hz, 1H); 7.34 (dd, $J=7.8$ Hz, 7.6 Hz, 1H); 7.26 (dd, $J=8.1$ Hz, 7.6 Hz, 1H); 6.61 (d, $J=3.4$ Hz, 1H); 5.11 (bs, 1H); 2.90 (dd, $J=15.4$ Hz, 5.4 Hz, 1H); 2.66 (dd, $J=15.4$ Hz, 8.3 Hz, 1H); 1.9-2.1 (m, 3H); 1.69 (s, 3H); 1.61 (s, 3H); 1.20-1.55 (m, 2H); 1.05 (d, $J=6.6$ Hz, 3H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.3, 135.9, 132.0, 130.6, 125.3, 125.1, 124.4, 123.8, 121.0, 117.0, 109.1, 43.4, 37.3, 30.2, 26.0, 25.8, 20.1, 18.0;

IR (film): 3050, 2930, 1740, 1420 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{18}\text{H}_{23}\text{NO}$: 269.2. Found: 269.5.



N-cyclopropanoylindole (10n): After 16 h, **10n** isolated as a white solid (79 mg, 65% yield)

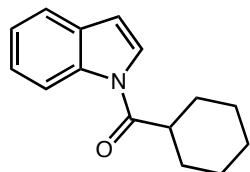
$R_f = 0.7$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.44 (d, $J=8.3$ Hz, 1H); 7.71 (d, $J=3.7$ Hz, 1H); 7.58 (d, $J=7.6$ Hz, 1H); 7.34 (dd, $J=7.7$ Hz, 7.3 Hz, 1H); 7.27 (dd, $J=8.3$ Hz, 7.3 Hz, 1H); 6.68 (d, $J=3.5$ Hz, 1H); 2.30 (m, 1H); 1.33 (dd, $J=3.2$ Hz, 7.6 Hz, 2H); 1.09 (dd, $J=3.2$ Hz, 7.6 Hz, 2H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 171.0, 136.8, 130.3, 125.2, 125.1, 123.7, 121.0, 116.8, 109.1, 14.3, 10.0;

IR (film): 3060, 2940, 1735, 1480, 1470 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{12}\text{H}_{11}\text{NO}$: 185.1. Found 185.1



N-cyclohexanoylindole (10o): After 16 h, **10a** isolated as a pale yellow solid (103 mg, 69% yield)

$R_f = 0.71$ (4:1 hexanes:ethyl acetate)

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.51 (d, $J=8.3$ Hz, 1H); 7.57 (d, $J=7.8$ Hz, 1H); 7.51 (d, $J=3.7$ Hz, 1H); 7.36 (dd, $J=8.2$ Hz, 7.3 Hz, 1H); 7.28 (dd, $J=7.7$ Hz, 7.3 Hz, 1H); 6.65 (d, $J=3.7$ Hz, 1H); 3.02 (m, 1H); 2.02 (d, 2H); 1.91 (m, 2H); 1.69-1.76 (m, 3H); 1.31-1.43 (m, 3H);

$^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 175.2, 136.0, 130.6, 125.3, 124.8, 123.8, 120.9, 117.1, 109.1, 44.0, 29.8, 26.0, 25.9;

IR (film): 3050, 2940, 1730 cm^{-1}

LRMS (ES): Mass calculated for $\text{C}_{15}\text{H}_{17}\text{NO}$: 227.1. Found: 227.5

Alternative Oxidation Procedure with Molecular Oxygen:

Oxygen was bubbled through a solution of 3-methoxybenzyl alcohol (0.67 mmol, 83 μ L) and TPAP (0.02 mmol, 6 mg) in toluene (1 mL). After complete oxidation of the alcohol, indole (0.67 mmol, 78 mg) and TPAP (0.04 mmol, 12 mg) were added and the mixture stirred at room temp until consumption of the aldehyde. Reaction filtered through silica gel and purified by column chromatography (10% ethyl acetate/hexanes) to give the acylated product **10q** (136 mg, 81% yield).

Oxidative Cyclization of *N*-Acylated Indole Derivative:

Cyclization was carried out according to the procedure of DeBoef et al.⁶ using **10q** as the substrate (0.5 mmol, 125 mg). 8-methoxy-6*H*-isoindolo[2,1-*a*]indol-6-one (**12**) was yielded as a yellow powder (107 mg, 86% yield). All characterization data matched those found in the literature.

⁶ Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137-3139.

NMR Spectra of New Compounds:

