Direct Synthesis of Pyrroles from Imines, Alkynes, and Acid Chlorides: An Isocyanide Mediated Reaction

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I General Procedures

Imines are stored and used in a Vacuum Atmospheres 553-2 dry box. All reagents were purchased from Aldrich® and used as received. Acetonitrile was distilled from CaH₂ under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 4Å molecular sieves. Chloroform and deuterated chloroform were dried over 4Å molecular sieves. Imines¹ and dibenzoylacetylene² were prepared as per standard literature procedures.

¹H and ¹³C NMR spectra were recorded on Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra were obtained from the McGill University mass spectral facilities.

II Synthesis

Synthesis of 3-benzyl-2-(4-methoxy-phenyl)-4-p-tolyl-1,3-oxazolium 5-(N-*t*-Butylimine) (9a)

A solution of (4-CH₃C₆H₄)HC=N(CH₂C₆H₅) (189 mg, 0.903 mmol) and *p*-methoxybenzoyl chloride (154 mg, 0.903 mmol) in ca. 0.5 mL acetonitrile was prepared in a glovebox. After 30 min at room temperature, *t*-butylisocyanide (75 mg, 0.903 mmol) was added and the final volume of acetonitrile brought up to ca. 2 mL. The solution was stirred for 1 h, K₃PO₄ (383 mg, 2.7 mmol) was added followed by an additional 4h stirring at room temperature. The K₃PO₄ was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in Hexanes/ Et₂O and cooling at – 40 °C led to precipitation of **9a** (88 mg, 23 %). A significant amount of material was sacrificed to obtain higher purity.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.61-7.55 (m, 2H), 7.38-7.16 (m, 7H), 7.06-7.01 (m, 2H), 6.78-6.73 (m, 2H), 6.0 – 3.8 (very broad, 2H), 3.74 (s, 3H), 2.37 (s, 3H), 0.92 (s, 9H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 181.8, 172.3, 161.2, 138.2, 135.1, 131.3, 130.0, 129.5, 129.3, 129.2, 128.6, 128.2, 127.6, 122.6, 113.4, 87.1, 61.3, 55.5, 51.2, 30.1, 21.5. HRMS for C₂₈H₃₁N₂O₂⁺; calculated: 427.23800, found: 427.23755 (error m/z = 1.1 ppm)

Conditions for Isocyanide Scanning (Table 1)

A solution of (4-CH₃C₆H₄)HC=N(CH₂C₆H₅) (105 mg, 0.50 mmol) and trimethyl(phenyl)silane internal standard (11 μ L, 0.064 mmol) in 0.5 mL deuterated-acetonitrile was prepared in the glovebox and placed in a septum sealed NMR tube. The following reagents were injected by syringe in 2 min intervals in the order listed: p-methoxybenzoyl chloride (103 μ L, 0.75 mmol), dimethylacetylenedicarboxylate (92 μ L, 0.75 mmol), isocyanide (0.75 mmol), and base (0.55 mmol). The reaction was allowed to stand for 24 h at room temperature and the yield of pyrrole was determined by ¹H NMR relative to the trimethyl(phenyl)silane internal standard.

Typical Procedure for Synthesis of Pyrroles (Table 2)

A solution of (4-CH₃C₆H₄)HC=N(CH₂C₆H₅) (105 mg, 0.50 mmol) and dimethyl acetylenedicarboxylate (92 μ L, 0.75 mmol) in 0.5 mL acetonitrile was prepared in the glovebox and placed in a septum sealed tube with (or without) a stir bar. Outside the glovebox, p-methoxybenzoyl chloride (103 μ L, 0.75 mmol) was injected by syringe. After 20 min at room temperature cyclohexylisocyanide (68 μ L, 0.55 mmol) was injected. After 10 min at room temperature diisopropylethylamine (98 μ L, 0.55 mmol) was injected and the reaction was stirred at room temperature overnight (19 h). The solution was concentrated *in vacuo* to give the crude product as an oily mixture which was purified by column chromatography using ethyl acetate / hexanes as eluent.

When the acid chloride or alkyne were solids, these were injected as chloroform solutions. When the organic insoluble base K₃PO₄ was used, it was added by briefly opening the reaction vessel.

Synthesis of of Pyrrole 1g

A solution of (*i*-Pr)HC=N(CH₂C₆H₅) (81 mg, 0.50 mmol) and dimethyl acetylenedicarboxylate (92 μ L, 0.75 mmol) in 0.5 mL CH₂Cl₂ was prepared in the glovebox and placed in a septum sealed tube. Outside the glovebox and at – 15 °C, *p*-methoxybenzoyl chloride (103 μ L, 0.75 mmol) was injected by syringe. After 20 min cyclohexylisocyanide (68 μ L, 0.55 mmol) was injected. The solution was warmed to 0 °C and maintained at this temperature for 1 h. Diisopropylethylamine (98 μ L, 0.55 mmol) was injected and the reaction allowed to stand at room temperature overnight (19 h). The solution was concentrated *in vacuo* to give the crude

product as an oily mixture which was purified by column chromatography using ethyl acetate / hexanes as eluent.

III Spectroscopic Data on Pyrroles

1-Benzyl-2-(4-methoxy-phenyl)-5-p-tolyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester

(1a). Isolated Yield: 86%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.24-7.02 (m, 9H), 6.88-6.76 (m, 2H), 6.63-6.51 (m, 2H), 4.89 (s, 2H), 3.79 (s, 3H), 3.67 (s, 6H), 2.33 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.6₉, 165.6₅, 159.9, 138.7, 137.6, 137.3, 137.2, 132.1, 130.6, 129.1, 128.5, 127.8, 127.4, 126.3, 122.9, 122.9, 114.8₁, 114.8₀, 113.8, 55.5, 52.0, 48.7, 21.8. HRMS for $\text{C}_{29}\text{H}_{28}\text{NO}_5^+$; calculated: 470.19620, found: 470.19541 (error m/z = 1.7 ppm).

1-Benzyl-2-phenyl-5-p-tolyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1b).

Isolated Yield: 85%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.36-7.05 (m, 12H), 6.61-6.53 (m, 2H), 4.93 (s, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.7, 165.6, 138.9, 137.6, 137.5, 137.3, 131.0, 130.8, 130.7, 129.2, 128.9, 128.5, 128.3, 127.8, 127.5, 126.3, 115.1, 115.0, 51.8₅, 51.8₂, 48.7, 21.6. HRMS for $\text{C}_{28}\text{H}_{26}\text{NO}_4^+$; calculated: 440.18564, found 440.18588 (error m/z = 0.5 ppm).

1-Allyl-2-(4-iodo-phenyl)-5-(4-methoxy-phenyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1c).

Isolated Yield: 80%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.75-7.69 (m, 2H), 7.32-7.26 (m, 2H), 7.15-7.09 (m, 2H), 6.94-6.88 (m, 2H), 5.54-5.38 (m, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 17.2 Hz, 1H), 4.27-4.17 (m, 2H), 3.80 (s, 3H), 3.64 (s, 6H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.6, 165.4, 160.2, 137.5, 137.2, 135.6, 133.6, 132.6, 132.1, 130.5, 122.6, 117.3, 115.0, 114.8, 113.9, 95.4, 55.5, 51.9, 51.9, 47.3. HRMS for $\text{C}_{24}\text{H}_{23}\text{INO}_5^+$; calculated: 532.06154, found: 532.06182 (error m/z = 0.5 ppm). Elemental Analysis: calculated: C, 54.25; H, 4.17; N, 2.64; found: C, 54.42; H, 4.29; N, 2.69.

1-Hexyl-2,5-di-p-tolyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1d). Isolated Yield: 71%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.32-7.21 (m, 8H), 3.72-3.62 (m, 8H), 2.39 (s, 6H), 1.23-1.08 (m, 2H), 1.06-0.90 (m, 2H), 0.90-0.75 (m, 4H), 0.69 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 165.8, 138.7, 136.9, 130.6, 129.2, 128.3, 114.4, 51.7, 45.0, 30.9, 30.3, 25.9, 22.3, 21.6, 14.0. HRMS for C₂₈H₃₄NO₄⁺; calculated: 448.24824, found: 448.24820 (error *m/z* = 0.1 ppm).

1-Prop-2-ynyl-2,5-di-p-tolyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1e). Isolated Yield: 57%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.46-7.41 (m, 2H), 7.29-7.24 (m, 2H), 4.25 (d, *J* = 2.4 Hz, 2H), 3.68 (s, 6H), 2.41 (s, 6H), 2.29 (t, *J* = 2.3 Hz, 1H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 165.6, 139.2, 137.0, 130.8, 129.3, 127.3, 114.8, 79.5, 73.5, 51.9, 35.4, 21.7. HRMS for C₂₅H₂₄NO₄⁺; calculated: 402.16999, found: 402.17027 (error *m/z* = 0.7 ppm).

1-Ethyl-2-phenyl-5-thiophen-2-yl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1f). Isolated Yield: 67%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.48-7.36 (m, 6H), 7.19-7.16 (m, 1H), 7.13-7.08 (m, 1H), 3.79 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.61 (s, 3H), 0.93 (t, *J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 165.7, 165.0, 137.7, 131.1, 130.7, 130.6, 130.5, 129.1, 128.5, 128.2, 127.6, 127.3, 117.4, 114.4, 52.0, 51.7, 40.3, 16.6. HRMS for C₂₀H₂₀NO₄S⁺; calculated: 370.11076, found: 370.11115 (error *m/z* = 1.1 ppm). Elemental Analysis: calculated: C, 65.02; H, 5.18; N, 3.79; S, 8.68; found: C, 64.90; H, 5.24; N, 3.84; S, 8.70.

1-Benzyl-2-isopropyl-5-phenyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1g). Isolated Yield: 72%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.34-7.18 (m, 8H), 6.89-6.81 (m, 2H), 4.98 (s, 2H), 3.87 (s, 3H), 3.60 (s, 3H), 2.97 (septuplet, *J* = 7.1 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 6H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 167.5, 165.3, 140.7, 137.6, 136.6, 131.2, 130.8, 129.0, 128.9, 128.3, 127.7, 125.7, 114.0, 113.5, 52.1, 51.5, 48.1, 26.7, 21.6. HRMS for C₂₄H₂₆NO₄⁺; calculated: 392.18564, found: 392.18592 (error *m/z* = 0.7 ppm).

1-Allyl-2-(4-fluoro-phenyl)-5-thiophen-2-yl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1h). Isolated Yield: 65%. ¹H NMR (300 MHz, CDCl₃): δ 7.46-7.31 (m, 3H), 7.18-7.06 (m, 4H), 5.67-5.52 (m, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.69 (d, *J* = 17.0 Hz, 1H), 4.33-4.27 (m, 2H), 3.72

(s, 3H), 2.64 (s, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.6, 165.0, 164.9, 161.7, 137.1, 133.7, 132.8, 132.7, 130.6, 130.0, 128.3, 128.2, 127.2, 126.7, 126.6, 117.6, 117.4, 115.7, 115.4, 114.6, 52.1, 51.8, 47.5. HRMS for $\text{C}_{21}\text{H}_{19}\text{FNO}_4\text{S}^+$; calculated: 400.10133, found: 400.10161 (error m/z = 0.7 ppm).

1-Benzyl-2-isobutyl-5-p-tolyl-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester (1i). Isolated Yield: 81%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.31-7.04 (m, 7H), 6.83-6.73 (m, 2H), 5.01 (s, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 2.66 (d, J = 7.3 Hz, 2H), 2.3 (s, 3H), 1.98-1.80 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 166.5, 165.7, 138.7₁, 138.6₉, 137.4, 136.1, 130.6, 129.1, 129.0, 127.7₁, 127.6₅, 125.7, 115.5, 113.1, 51.8, 51.5, 48.0, 34.1, 29.7, 22.6, 21.5. HRMS for $\text{C}_{26}\text{H}_{30}\text{NO}_4^+$; calculated 420.21694, found: 420.21661 (error m/z = 0.8 ppm).

1-Benzyl-2,5-di-p-tolyl-1H-pyrrole-3-carboxylic acid methyl ester (1j). Isolated Yield: 65%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.29-7.12 (m, 11H), 6.81 (s, 1H), 6.71-6.64 (m, 2H), 5.07 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.36 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 165.0, 140.3, 138.6, 138.2, 137.7, 135.3, 130.8, 130.0, 129.5, 129.4, 129.3, 128.8, 128.5, 127.2, 126.2, 114.2, 110.7, 59.6, 48.6, 21.6, 21.4, 14.5. HRMS for $\text{C}_{28}\text{H}_{28}\text{NO}_2^+$; calculated: 410.21146, found 410.21174 (error m/z = 0.7 ppm).

(4-Benzoyl-1-benzyl-2,5-di-p-tolyl-1H-pyrrol-3-yl)-phenyl-methanone (1k) Isolated Yield: 61%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.53-7.42 (m, 4H), 7.31-6.97 (m, 13H), 6.76-6.65 (m, 2H), 5.11 (s, 2H), 2.27 (s, 6H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 192.6, 139.8, 138.7, 137.9, 137.8, 131.9, 131.1, 129.2, 129.0, 128.7, 128.0, 127.7, 127.5, 126.3, 124.1, 48.6, 21.5. HRMS for $\text{C}_{39}\text{H}_{32}\text{NO}_2^+$; calculated 546.24276, found: 546.24285 (error m/z = 0.2 ppm). Elemental Analysis: calculated: C, 85.84; H, 5.73; N, 2.57; found: C, 85.44; H, 5.76; N, 2.56.

[4-Benzoyl-1-benzyl-2-(4-chloro-phenyl)-5-phenyl-1H-pyrrol-3-yl]-phenyl-methanone (1l) Isolated Yield: 70%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.54-7.44 (m, 4H), 7.36-7.06 (m, 18H), 6.72-6.63 (m, 2H), 5.09 (s, 2H). ^{13}C NMR (75.5 MHz, CDCl_3): δ (ppm) 192.4₄, 192.3₇, 139.6, 138.2, 137.3, 136.4, 135.0, 132.6, 132.2, 132.0, 131.2, 130.5, 129.2, 129.1, 129.0, 128.8₉,

128.8₇, 128.8₂, 128.6, 128.4, 128.1, 128.0, 127.7, 126.2, 124.6, 124.2, 48.9. HRMS for C₃₇H₂₇ClNO₂⁺; calculated 552.17248, found: 552.17201 (error m/z = 0.9 ppm).

3-(4-Methoxy-phenyl)-pyrrolo[2,1-a]isoquinoline-1,2-dicarboxylic acid dimethyl ester (10)

Isolated Yield: 50%. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.55 (d, *J* = 7.9 Hz, 1H), 7.59-7.49 (m, 3H), 7.48-7.42 (m, 1H), 7.42-7.35 (m, 2H), 7.07-7.00 (m, 2H), 6.79 (d, *J* = 7.4 Hz, 1H), 4.02 (s, 3H), 3.88 (s, 3H), 3.72 (s, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ (ppm) 168.0, 165.3, 160.5, 132.5, 129.8, 128.5, 128.4, 128.2, 127.8, 127.4, 125.5, 124.5, 121.9, 121.5, 117.1, 114.4, 114.2, 109.2, 52.6, 52.8, 52.0. HRMS for C₂₃H₂₀NO₅⁺; calculated: 390.13360, found 390.13434 (error m/z = 1.9 ppm).

IV References

1. Layer, R. *Chem. Rev.* **1963**, 63, 489-510.
2. Zhang, J.-J.; Schuster, G. B. *J. Am. Chem. Soc.* **1989**, 111, 7149.
3. Arndtsen, B. A.; Dhawan, R.; Dghaim, R., Can. Pat. Appl. (2003), CA 2387644.

V ¹H and ¹³C NMR Spectra

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SpinWorks 2.5: 13C OBSERVE

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STANDARD 1H OBSERVE

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d1 1.000 werr
tof 0 wexp
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gain not used
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lms 2.000
nm cdc ph