Supporting Information for

Regioselective Synthesis of Substituted Pyrroles: Efficient Palladium-Catalyzed Cyclization of Internal Alkynes and 2-Amino-3-Iodoacrylate Derivatives

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Sections Include:

- General Information and Methods
- General, Representative and Important Experimental Procedures
- Detailed Characterization Data for All New Compounds
- ^{1}H and ^{13}C NMR Spectra for All New Compounds
- NOESY, HMBC, and HSQC for Select Compounds

General Information and Methods

All glassware used in anhydrous reactions was dried under nitrogen. Moisture or oxygen sensitive reactions were performed under an atmosphere of nitrogen gas. All solvents were used without further purification from commercial sources. All reagents were obtained from commercial sources in 98% or greater purity and, except for lithium chloride, used as received. Lithium chloride was dried overnight under high vacuum prior to each use. Purification by flash chromatography was performed on RediSep columns using an Isco CombiFlash Companion 4. Melting points were obtained with an Electrothermal melting point apparatus and are uncorrected.

NMR Spectra: ^{1}H NMR, ^{13}C NMR, NOESY, HMBC, and HSQC spectra were run either on a Varian Inova 400 MHz spectrometer or a Varian Inova 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the standard.

LCMS: All mass spectra were acquired using a Waters (Micromass) ZMD single quadrupole mass spectrometer equipped with a Z-spray electrospray interface and probe. The LC instrumentation used was a Waters Alliance 2690 equipped with a 5-carousel, 120 vial position autosampler, and a model 996 PDA (photodiode) array detector, scanning from 210 to 400 nM. The column used was a Atlantis MS C18, 2.1 x 50 mm, 5 μM particle size, with a 90/10-5/95 0.1% formic acid in water / acetonitrile gradient at a flow rate of 0.8 mL / minute over 2 minutes (1.2 minute hold time).

HRMS: All high resolution mass spectra were obtained on Agilent 6210 TOF mass spectrometer.

Analytical HPLC: Purity analysis was performed using a Waters Xterra RP18 (150 x 4.6 mm, 3.5 μM particle size) column with a 85/15-5/95 pH 3.5 ammonium formate buffer acetonitrile / methanol mobile phase, for 10 minutes, hold 4 minutes, at 1.2 mL/minutes. Detection was from 210-370 nM.

General, Representative and Important Experimental Procedures

General Experimental for the Cyclization of Acrylate **2** with Alkynes **3**: **Method A**

(*Z*)-Methyl 2-acetamido-3-iodoacrylate **2** (135 mg, 0.500 mmol), lithium chloride (21.2 mg, 0.500 mmol), potassium carbonate (346 mg, 2.50 mmol) and palladium(II) acetate (11.2 mg, 0.050 mmol) were dissolved in DMF (5 mL) and treated with the appropriate alkyne **3a-3k** (1.50 mmol). The solution was degassed, placed under N_2 atmosphere, and heated to 65 °C with stirring until alkyne **3** was consumed (1 to 24 h). The solution was filtered to remove solids, diluted with ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), and the organic layer dried over sodium sulfate. After concentration *in vacuo*, silica gel chromatography (ethyl acetate / hexanes gradient) afforded products **4/5a-4/5k**.

General Experimental for the Cyclization of Acrylate **2** with Alkynes **3**: **Method B**

(*Z*)-Methyl 2-acetamido-3-iodoacrylate **2** (135 mg, 0.500 mmol), lithium chloride (21.2 mg, 0.500 mmol), potassium carbonate (346 mg, 2.500 mmol) and palladium(II) acetate (11.2 mg, 0.050 mmol) were dissolved in DMF (5 mL) and treated with the appropriate alkyne **3a-3k** (1.50

mmol). The solution was degassed, placed under N_2 atmosphere, and heated to 65 °C with stirring until alkyne **3** was consumed (1 to 24 h). 0.2 mL of water was added and the solution stirred an additional 3 to 6 h at 65 °C, until LCMS indicated complete deacylation of product. The solution was filtered to remove solids, diluted with ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), and the organic layer dried over sodium sulfate. After concentration *in vacuo*, silica gel chromatography (ethyl acetate / hexanes gradient) afforded products **4/5a-4/5k**.

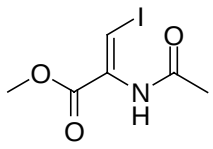
Synthesis of *methyl 1-acetyl-4,5-dipropyl-1H-pyrrole-2-carboxylate* **4a**

(*Z*)-Methyl 2-acetamido-3-iodoacrylate **2** (135 mg, 0.500 mmol), lithium chloride (21.2 mg, 0.500 mmol), potassium carbonate (346 mg, 2.500 mmol) and palladium(II) acetate (11.2 mg, 0.050 mmol) were dissolved in DMF (5 mL) and treated with 4-octyne **3a** (165 mg, 1.50 mmol). The solution was degassed, placed under N_2 atmosphere, and heated to 65 °C with stirring for 1 h. The solution was filtered to remove solids, diluted with ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), and the organic layer dried over sodium sulfate. After concentration *in vacuo*, silica gel chromatography (0-10% ethyl acetate / hexanes gradient) afforded product **4a** as a slightly yellow oil (102 mg, 81%).

Synthesis of *methyl 4,5-dipropyl-1H-pyrrole-2-carboxylate* **5a**

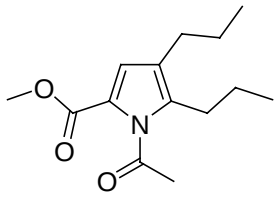
(*Z*)-Methyl 2-acetamido-3-iodoacrylate **2** (135 mg, 0.500 mmol), lithium chloride (21.2 mg, 0.500 mmol), potassium carbonate (346 mg, 2.500 mmol) and palladium(II) acetate (11.2 mg, 0.050 mmol) were dissolved in DMF (5 mL) and treated with 4-octyne **3a** (165 mg, 1.50 mmol). The solution was degassed, placed under N_2 atmosphere, and heated to 65 °C with stirring for 1 h. Water (0.2 mL) was added and the solution stirred 16 h additional at 65 °C. The solution was filtered to remove solids, diluted with ethyl acetate (25 mL), washed with water (25 mL), brine (25 mL), and the organic layer dried over sodium sulfate. After concentration *in vacuo*, silica gel chromatography (0-20% ethyl acetate / hexanes gradient) afforded product **5a** as a white solid (98 mg, 94%).

Detailed Characterization Data for All New Compounds



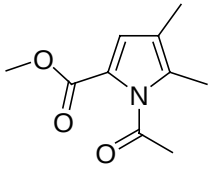
2

(*Z*)-Methyl 2-acetamido-3-iodoacrylate (**2**). White solid, 51% yield; mp 97-97.5 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.50 (s, 1H), 7.43 (s, 1H), 3.66 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 169.3, 162.8, 138.8, 90.7, 53.0, 22.9; HRMS *m*/*e* calcd for $C_6H_9INO_3$ $[M+H]^+$ 269.9627, found 269.9644; Analytical HPLC: purity 96.3%, t_r = 3.8 min.



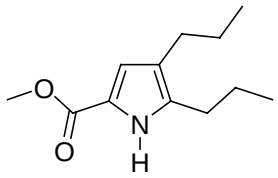
4a

Methyl 1-acetyl-4,5-dipropyl-1H-pyrrole-2-carboxylate (**4a**). Yellow oil, 81% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.84 (s, 1H), 3.75 (s, 3H), 2.55 (t, J = 6.2 Hz, 2H), 2.46 (s, 3H), 2.32 (t, J = 6.3 Hz, 2H), 1.55-1.45 (m, 4H), 0.91-0.85 (m, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 175.0, 161.1, 138.0, 123.5, 121.7, 121.0, 52.3, 29.1, 27.3, 26.9, 23.8, 23.7, 14.4, 14.3; HRMS *m*/*e* calcd for $C_{14}H_{22}NO_3$ $[M+H]^+$ 252.1600, found 252.1592; Analytical HPLC: purity 97.3%, t_r = 10.7 min.



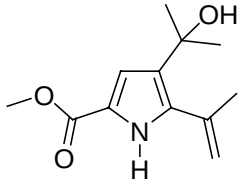
4b

Methyl 1-acetyl-4,5-dimethyl-1H-pyrrole-2-carboxylate (**4b**). Colorless oil, 58% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.75 (s, 1H), 3.69 (s, 3H), 2.41 (s, 3H), 2.11 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 174.7, 161.1, 133.9, 122.2, 121.6, 118.2, 52.3, 28.8, 11.4, 11.0; HRMS *m*/*e* calcd for $C_{10}H_{13}NO_3$ $[M]^+$ 195.0895, found 195.0898; Analytical HPLC: purity 97.3%, t_r = 10.7 min.



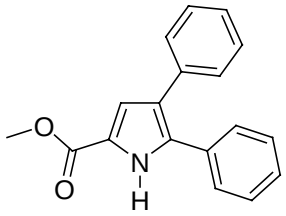
5a

Methyl 4,5-dipropyl-1H-pyrrole-2-carboxylate (5a). White solid, 94% yield; mp 46-47 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.30 (s, 1H), 6.51 (s, 1H), 3.65 (s, 3H), 2.44 (t, J = 6.8 Hz, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.50-1.40 (m, 4H), 0.84-0.77 (m, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 136.3, 121.8, 119.4, 116.0, 51.3, 27.8, 27.7, 24.4, 23.5, 14.4 14.3; HRMS *m*/*e* calcd for $C_{12}H_{19}NO_2$ $[M+H]^+$ 210.1494, found 210.1487; Analytical HPLC: purity 99.4%, t_r = 10.4 min.



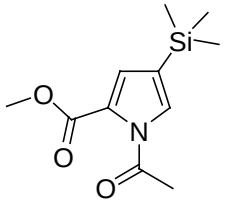
5d

Methyl 4-(2-hydroxypropan-2-yl)-5-(prop-1-en-2-yl)-1H-pyrrole-2-carboxylate (5d). Colorless oil, 62% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.36 (s, 1H), 6.68 (s, 1H), 5.2 (d, J = 5.0 Hz, 2H), 4.58 (s, 1H), 3.67 (s, 3H), 2.02 (s, 3H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 138.2, 135.8, 131.4, 119.0, 119.1 114.9, 68.4, 51.5, 32.1, 24.9; HRMS *m*/*e* calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287, found 224.1289; Analytical HPLC: purity 97.0%, t_r = 7.0 min.



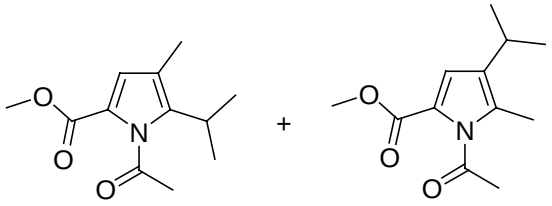
5e

Methyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (**5e**). White solid, 77% yield; mp 153-154 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.33-7.15 (m, 10H), 6.93 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 136.1, 134.3, 132.2, 129.3, 129.0, 128.9, 128.7, 128.4, 126.7, 123.6, 122.7, 117.0, 51.8; HRMS *m*/*e* calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1181, found 278.1183; Analytical HPLC: purity 99.6%, t_r = 10.6 min.



4f

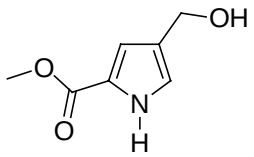
Methyl 1-acetyl-4-(trimethylsilyl)-1H-pyrrole-2-carboxylate (4f). Colorless oil, 60% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.73 (s, 1H), 6.06 (s, 1H), 3.62 (s, 3H), 1.92 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.7, 164.5, 138.3, 108.5, 107.9, 99.9, 52.7, 22.5, 0.0; HRMS *m*/*e* calcd for $C_{11}H_{18}NO_3Si$ $[M+H]^+$ 240.1056, found 240.1071; Analytical HPLC: purity 99.4%, t_r = 8.2 min.



1.5 **4g** 1.0

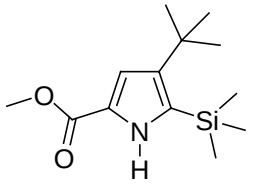
Methyl 1-acetyl-5-isopropyl-4-methyl-1H-pyrrole-2-carboxylate and methyl 1-acetyl-4-isopropyl-5-methyl-1H-pyrrole-2-carboxylate (4g). Colorless oil, 1.5: 1.0 mixture, 82% yield; ^{1}H NMR (500 MHz, d_6-DMSO) δ **Major product** [6.88 (s, 1H), 3.75 (s, 3H), 2.83-2.77 (m, 1H), 2.47 (s, 3H), 2.19 (s, 3H), 1.11 (d, J = 6.9 Hz, 6H)] **Minor product** [6.75 (s, 1H), 3.73 (s, 3H), 3.05-2.98 (m, 1H), 2.51 (s, 3H), 2.06 (s, 3H), 1.24 (d, J = 6.9 Hz, 6H)]; ^{13}C NMR (100 MHz, d_6-

DMSO) δ See attached spectra; HRMS *m*/*e* calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287, found 224.1285; Analytical HPLC: purity 99.7%, t_r = 9.6 min.



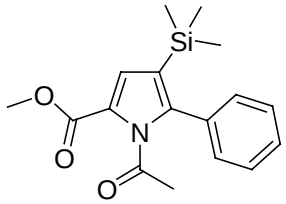
5h

Methyl 4-(hydroxymethyl)-1H-pyrrole-2-carboxylate (5h). Yellow oil, 40% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.62 (s, 1H), 6.85 (s, 1H), 6.66 (s, 1H), 4.68 (t, J = 5.6 Hz, 1H), 4.26 (d, J = 5.6 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.4, 127.0, 122.6, 122.0, 114.9, 57.0, 51.6; HRMS *m*/*e* calcd for $C_7H_{10}NO_3$ $[M+H]^+$ 156.0661, found 156.0679; Analytical HPLC: purity 95.1%, t_r = 3.4 min.



5i

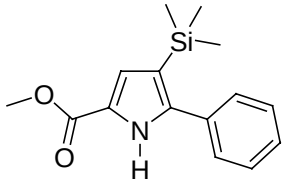
Methyl 4-tert-butyl-5-(trimethylsilyl)-1H-pyrrole-2-carboxylate (5i). Colorless oil, 53% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.17 (s, 1H), 6.72 (s, 1H), 3.69 (s, 3H), 1.21 (s, 9H), 0.31 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.5, 143.6, 130.5, 122.3, 113.1, 49.9, 31.4, 30.2, 0.0; HRMS *m*/*e* calcd for $C_{13}H_{24}NO_2Si$ $[M+H]^+$ 254.1576, found 254.; Analytical HPLC: purity 99.2%, t_r = 11.2 min (9), t_r = 11.3 min (1).



4j

Methyl 1-acetyl-4-phenyl-5-(trimethylsilyl)-1H-pyrrole-2-carboxylate (4j). Amorphous yellow solid, 15% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.41-7.37 (m, 3H), 7.32-7.29 (m, 2H), 6.98 (s, 1H), 3.84 (s, 3H), 2.61 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 174.8, 160.1, 136.8, 135.6, 128.9, 127.5, 126.9, 125.2, 120.8, 51.6, 27.7, 0.0; HRMS *m*/*e* calcd

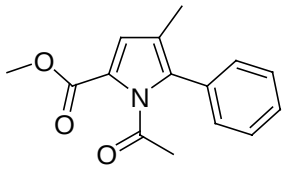
for $C_{17}H_{22}NO_3Si$ $[M+H]^+$ 316.1639, found 316.1638; Analytical HPLC: purity 97.4%, t_r = 11.3 min.



5j

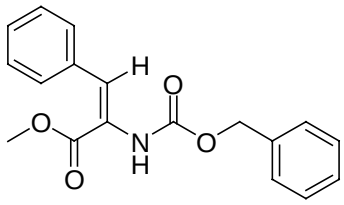
Methyl 4-phenyl-5-(trimethylsilyl)-1H-pyrrole-2-carboxylate (5j). White solid, 81% yield; mp 134-135 °C; ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.17 (s, 1H), 7.48-7.37 (m, 5H), 6.92 (s, 1H), 3.76 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2, 143.0, 133.0. 128.4, 127.6, 127.5, 122.6, 116.1, 50.6, 0.0; HRMS *m*/*e* calcd for $C_{15}H_{20}NO_2Si$ $[M+H]^+$ 274.1263, found 274.1259; Analytical HPLC: purity 99.2%, t_r = 11.0 min.

Methyl 1-acetyl-4-methyl-5-phenyl-1H-pyrrole-2-carboxylate and methyl 1-acetyl-5-



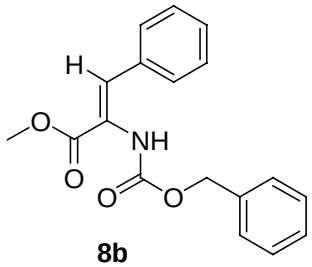
4k

methyl-4-phenyl-1H-pyrrole-2-carboxylate (4k). Colorless oil, 5.0: 1.0 mixture in 62% yield; ^{1}H NMR (400 MHz, d_6-DMSO) δ **Major product** [7.43-7.36 (m, 3H), 7.27-7.24 (m, 2H), 6.86 (s, 1H), 3.73 (s, 3H), 2.30 (s, 3H), 1.89 (s, 3H)] **Minor product** [7.43-7.36 (m, 3H), 7.27-7.24 (m, 2H), 7.05 (s, 1H), 3.75 (s, 3H), 2.28 (s, 3H), 1.88 (s, 3H)] ^{13}C NMR (100 MHz, d_6-DMSO) δ **Major product** 174.2, 161.1, 136.1. 131.2, 130.2, 129.2, 129.1, 129.0, 122.5, 120.8, 52.5, 29.3, 11.6; HRMS *m*/*e* calcd for $C_{15}H_{15}NO_3$ $[M+H]^+$ 257.1052, found 257.1045; Analytical HPLC: purity 99.3%, t_r = 9.7 min.



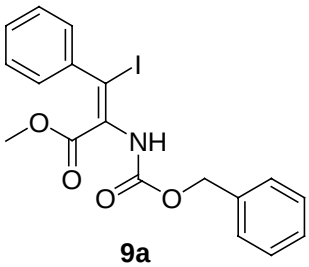
8a

(*E*)-methyl 2-(benzyloxycarbonylamino)-3-phenylacrylate (8a). Colorless oil, 4% yield; All characterization data was consistent with reported data.[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (brs, 1H), 7.36-7.20 (m, 10H), 6.98 (s, 1H), 5.15 (s, 2H), 3.58 (s, 3H); HRMS *m*/*e* calcd for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1236, found 312.1203; Analytical HPLC: purity 95.5%, t_r = 9.5 min.



8b

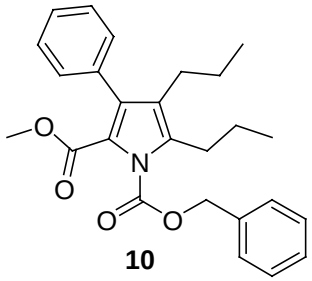
(*Z*)-methyl 2-(benzyloxycarbonylamino)-3-phenylacrylate (8b). White solid, 90% yield; All characterization data was consistent with reported data.[12] mp 64-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.7.44 (m, 2H), 7.34-7.30 (m, 9H), 6.32 (brs, 1H), 5.10 (s, 2H), 3.78 (s, 3H). HRMS *m*/*e* calcd for $C_{18}H_{18}NO_4$ $[M+H]^+$ 312.1236, found 312.1203; Analytical HPLC: purity 98.8%, t_r = 9.3 min.



9a

(*Z*)-methyl 2-(benzyloxycarbonylamino)-3-iodo-3-phenylacrylate (9a). White solid, 63% yield; mp 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (m, 10H), 6.58 (brs, 1H), 5.15 (s, 2H), 3.44 (brs, 3H); ^{3}C NMR (100 MHz, d_6-DMSO) δ 162.3, 153.2, 140.7, 135.4, 133.7, 129.1,

129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 69.4, 68.3, 52.7; HRMS *m*/*e* calcd for $C_{18}H_{17}NNO_4$ $[M+H]^+$ 438.0202, found 438.0211; Analytical HPLC: purity 96.3%, t_r = 9.9 min.



10

1-benzyl 2-methyl 3-phenyl-4,5-dipropyl-1H-pyrrole-1,2-dicarboxylate (10). Yellow oil, 44% yield; ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.41-7.25 (m, 10H), 5.30 (s, 2H), 3.34 (s, 3H), 2.61 (t, J = 8.4 Hz, 2H), 2.19 (t, J = 7.7 Hz, 2H), 1.44-1.38 (m, 2H), 1.12-1.04 (m, 2H), 0.79 (t, J = 7.7 Hz, 3H), 0.61 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 161.7, 151.3, 135.8, 135.0, 133.9, 133.3, 130.0, 129.4, 129.2, 128.5, 128.0, 123.3, 121.0, 70.6, 52.1, 27.4, 26.0, 24.0, 23.9, 14.5, 14.4; HRMS *m*/*e* calcd for $C_{26}H_{30}NO_4$ $[M+H]^+$ 420.2175, found 420.2180; Analytical HPLC: purity 96.9%, t_r = 11.9 min.

References (numbered as per main paper)

12) Spectra for **8a** and **8b** consistent with those reported by Sai, H., Ogiku, T.; Ohmizu, H. *Synthesis* **2003**, *2*, 201.