Catalytic Multicomponent Reactions for the Synthesis of *N*-Aryl Trisubstituted Pyrroles

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Supporting Information

Table of Contents

General Information.....	S2
General Procedure for the multicomponent assembly reaction.....	S3
Characterization data.....	S3
¹ H and ¹³ C NMR Spectra	S7

General Information

All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. THF, Et₂O, CH₂Cl₂ and toluene were purified by passage through a bed of activated alumina.¹ DME was distilled from sodium. 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, or phosphomolybdic acid followed by heating. Melting points are uncorrected. 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; integration. Commercial Dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate (DMAD and DEAD, **3a** and **3b**) were used without purification. Copper(I) trifluoromethanesulfonate was prepared by a modified method of Kochi and coworkers.³ Imines were prepared by combining the corresponding aldehyde (freshly distilled), appropriately substituted aniline, and either activated 4Å molecular sieves or anhydrous magnesium sulfate in dichloromethane.⁴ The reactions were stirred for 16 h, then filtered and concentrated in vacuo. If necessary, the resulting imines were re-crystallized from a suitable organic solvent mixture to afford imines that were >95% pure by ¹H NMR analysis.

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

(2) Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

(3) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897.

(4) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099-5100. (b) Derdau, V.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 1992-1998. (c) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358-8359.

General Procedure for the Multicomponent reaction:

To a flame-dried two-necked round bottom flask fitted with a reflux condenser containing a magnetic stirring bar was added catalyst, imine and acetylene diester in CH_2Cl_2 (3 mL). The mixture was heated to a gentle reflux and the diazoacetone nitrile solution was added via syringe pump (1.5 mL per hour). After complete addition, the mixture was heated for a further 1-2 hours (12 hours in the case of compounds **5** & **8**) and then allowed to cool. The unpurified reaction mixture was filtered through a silica plug with CH_2Cl_2 (50 mL). The solvent was evaporated, and purification by flash chromatography on silica gel provided the title compounds as described below.

Dimethyl 1,2-diphenyl-1H-pyrrole-3,4-dicarboxylate (4): Prepared according to general procedure using imine **1a** (213 mg, 1.2 mmol), DMAD **3a** (49 μL , 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (6-12%) afforded 94 mg (71%) of **4** as a viscous white foam. Analytical data for **4**: R_f 0.24 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 2947.9, 2860.2, 1722.7, 1560.1; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (s, 1H), 7.36-7.08 (m, 10H), 3.84 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.5, 163.6, 138.7, 135.1, 130.4, 129.9, 129.0, 128.1, 127.9, 127.7, 125.9, 117.0, 115.7; LRMS (electrospray): Exact mass calcd for $\text{C}_{20}\text{H}_{17}\text{NO}_4$ $[\text{M}]^+$, 335.12. Found $[\text{M}+\text{H}]$, 336.5. See: Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 346-350.

Dimethyl 1-(4-iodophenyl)-2-phenyl-1H-pyrrole-3,4-dicarboxylate (5): Prepared according to the general procedure using imine **1b** (364 mg, 1.2 mmol), DMAD **3a** (49 μL , 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). medium pressure liquid chromatography EtOAc/toluene (1:9) afforded 111 mg (61%) of **5** as a waxy solid. Analytical data for **5**: R_f 0.27 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 3130.7, 3001.3, 2947.5, 1722.8; ^1H NMR (400 MHz, acetone- d_6) δ 7.62-7.60 (d, 2H), 7.44 (s, 1H), 7.28-7.07 (m, 5H), 6.79-6.81 (m, 2H) 3.85 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) 165.1, 163.0, 138.8, 135.1, 130.0, 129.9, 129.1, 128.1, 127.9, 127.7, 126.0, 117.1, 115.7, 51.4, 51.3; LRMS (electrospray): Exact mass calcd for $\text{C}_{20}\text{H}_{16}\text{INO}_4$ $[\text{M}]^+$, 461.01. Found $[\text{M}+\text{H}]$, 462.3.

Dimethyl 1-(3-methylphenyl)-2-phenyl-1H-pyrrole-3,4-dicarboxylate (6): Prepared according to the general procedure using imine **1c** (256 mg, 1.2 mmol), DMAD **3a** (49 μL , 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). medium pressure liquid chromatography using gradient elution

mixtures of EtOAc/toluene (4-8%) afforded 88 mg (63%) of **6** as a viscous white foam. Analytical data for **6**: R_f 0.25 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 2935.4, 2858.9, 1721.3; ^1H NMR (500 MHz, CDCl_3) δ 7.47 (s, 1H), 7.26-7.08 (m, 7H), 6.92 (s, 1H), 6.79-6.81 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.3, 164.3, 139.6, 138.7, 135.6, 130.6, 130.2, 129.9, 129.1, 128.9, 128.4, 128.2, 126.6, 123.2, 115.5, 52.3, 51.8, 21.5; LRMS (electrospray): Exact mass calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4$ $[\text{M}]^+$, 349.13. Found $[\text{M}+\text{H}]$, 350.5.

Dimethyl 1-phenyl-2-p-tolyl-1H-pyrrole-3,4-dicarboxylate (7): Prepared according to the general procedure using imine **1d** (230 mg, 1.2 mmol), DMAD **3a** (49 μL , 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (5-15%) afforded 92 mg (66%) of **7** as an oil. Analytical data for **7**: R_f 0.25 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 2935.4, 2858.9, 1721.3; ^1H NMR (500 MHz, CDCl_3) δ 7.48 (s, 1H), 7.32-7.04 (m, 9H), 3.86 (s, 3H), 3.78 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.4, 164.3, 138.9, 138.4, 135.9, 130.4, 129.8, 129.4, 128.9, 128.1, 127.0, 126.1, 115.5, 52.4, 51.8, 21.6; LRMS (electrospray): Exact mass calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4$ $[\text{M}]^+$, 349.13. Found $[\text{M}+\text{H}]$, 350.4.

Dimethyl 2-(4-bromophenyl)-1-phenyl-1H-pyrrole-3,4-dicarboxylate (8): Prepared according to the general procedure using imine **1e** (312 mg, 1.2 mmol), DMAD **3a** (49 μL , 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (5-15%) afforded 98 mg (59%) of **11** as a viscous white foam. Analytical data for **11**: R_f 0.27 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 2922.6, 2852.9, 1722.5, 1597.0, 1499.5; ^1H NMR (500 MHz, CDCl_3) δ 7.43 (s, 1H), 7.30-7.04 (m, 9H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, acetone- d_6) δ 166.2, 164.1, 138.5, 135.1, 132.2, 131.9, 129.7, 128.7, 128.1, 127.9, 127.7, 122.9, 117.1, 115.7, 52.4, 51.9; LRMS (electrospray): Exact mass calcd for $\text{C}_{20}\text{H}_{16}\text{BrNO}_4$ $[\text{M}]^+$, 413.29. Found $[\text{M}+\text{H}]$, 414.5.

Dimethyl 2-(4-chlorophenyl)-1-phenyl-1H-pyrrole-3,4-dicarboxylate (9):

Prepared according to the general procedure using imine **1f** (254 mg, 1.2 mmol), DMAD **3a** (49 μ L, 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using EtOAc/pentanes (10%) afforded 78 mg (53%) of **9** as a viscous white viscous foam. Analytical data for **9**: R_f 0.27 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 3004.1, 2955.0, 1722.0, 1507.8; ^1H NMR (500 MHz, CDCl_3) δ 7.47 (s, 1H), 7.30–7.04 (m, 9H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.4, 163.4, 138.0, 134.2, 133.9, 131.5, 131.4, 129.2, 128.1, 128.0, 127.9, 125.7, 116.8, 115.4, 51.4, 51.3; LRMS (electrospray): Exact mass calcd for $\text{C}_{20}\text{H}_{16}\text{NClO}_4$ $[\text{M}]^+$, 369.08. Found $[\text{M}+\text{H}]$, 370.5. See: Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 346–350.

Diethyl 2-(4-chlorophenyl)-1-phenyl-1H-pyrrole-3,4-dicarboxylate (10):

Prepared according to the general procedure using imine **1g** (255 mg, 1.2 mmol), DEAD **3b** (57 μ L, 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (4–12%) afforded 87 mg (55%) of **10** as a white foam. Analytical data for **10**: R_f 0.30 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 3056.7, 2946.0, 1720.9, 1480.2; ^1H NMR (400 MHz, CDCl_3) δ 7.51 (s, 1H), 7.32–7.05 (m, 9H), 4.36–4.33 (q, J = 6.9 Hz, 2H), 4.26–4.22 (q, J = 6.9 Hz, 2H), 1.38–1.35 (t, J = 7.2 Hz, 3H), 1.22–1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 163.0, 138.0, 134.2, 133.9, 131.5, 131.4, 129.2, 128.1, 128.0, 127.9, 125.7, 116.8, 115.4, 60.3, 60.0, 14.3, 13.9; LRMS (electrospray): Exact mass calcd for $\text{C}_{22}\text{H}_{20}\text{NClO}_4$ $[\text{M}]^+$, 397.11. Found $[\text{M}+\text{H}]$, 398.4. See: Katritzky, A. R.; Yao, J.; Bao, W.; Qi, M.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 346–350.

Dimethyl 2-(3,4-dichlorophenyl)-1-phenyl-1H-pyrrole-3,4-dicarboxylate (11):

Prepared according to the general procedure using imine **1h** (300 mg, 1.2 mmol), DEAD **3b** (57 μ L, 0.4 mmol), and a solution of DAN **2** in methylene chloride, (4.0 mL, 0.45 M). Flash column chromatography using gradient elution mixtures of EtOAc/toluene (4–12%) afforded 87 mg (55%) of **11** as a white foam. Analytical data for **11**: R_f 0.32 (3:1 EtOAc/hexanes); IR (film) cm^{-1} 3010.2, 2954.0, 1720.9, 1480.2; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (s, 1H), 7.38–6.99 (m, 8H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.8, 163.0, 138.0, 134.2, 133.9, 131.5, 131.4, 129.2, 128.1, 128.0, 127.9, 125.7, 116.8, 115.4, 60.3, 60.0, 14.3, 13.9; LRMS (electrospray): Exact mass calcd for $\text{C}_{20}\text{H}_{15}\text{NCl}_2\text{O}_4$ $[\text{M}]^+$, 403.04. Found $[\text{M}+\text{H}]$, 404.4.

^1H and ^{13}C NMR Spectra:

Compound 11 **Compound 4**

Compound 4

Compound 6 **Compound 6**

Compound 10 **Compound 10**