**The Copper Catalyzed Coupling Of Imines, Acid Chlorides, and Alkynes: A
Multicomponent Route to Propargylamides**

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General Procedures

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. Acetonitrile was distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but were transferred under vacuum from the drying agent, and stored over $4\text{\AA}$ molecular sieves. Deuterated DMSO and chloroform were dried over $3\text{\AA}$ molecular sieves. Imines were prepared as per standard literature procedures.¹ Propargyl acetate was prepared in analogy to a standard literature procedure.² All other reagents were purchased from Aldrich[®] and used as received.

^1H , and ^{13}C were recorded on JEOL 270, Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra were obtained from the McGill University mass spectral facilities.

Typical Procedure for Catalytic Synthesis of Propargylamides

(4- $\text{CH}_3\text{C}_6\text{H}_4$) $\text{HC}=\text{N}(\text{CH}_2\text{Ph})$ (100.0 mg, 0.48 mmol), benzoyl chloride (87.4 mg, 0.62 mmol) and phenylacetylene (48.9 mg, 0.48 mmol) were mixed in 3 mL of acetonitrile and added to a solution of CuI in 2 mL of acetonitrile and EtN^iPr_2 (92.8 mg, 0.72 mmol) in 2 mL of acetonitrile. The reaction was allowed to stir at ambient temperature for 15 minutes. The mixture was concentrated in vacuo, and the product isolated by column chromatography using ethyl acetate / hexanes as eluent. (In the case of acetylchloride, it is important the amine base is the last reagent added (to inhibit competitive ketene formation).)

N-benzyl-N-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-benzamide (1, Table 1) Isolated Yield: 82 %. ¹H NMR (270 MHz, 130°C, d⁶-DMSO): δ 7.55-7.28 (m, 13H), 7.26-7.10 (m, 6H), 6.49 (s, 1H), 4.73 (d, 1H), 4.39 (d, 1H), 2.32 (s, 3H). ¹³C NMR (68.0 MHz, 130°C, d⁶-DMSO): δ 171.8, 138.8, 138.3, 137.0, 134.8, 132.0, 130.2, 129.8, 129.3, 129.1, 129.0, 128.4, 127.9, 127.9, 127.1, 127.1, 122.6, 87.9, 86.8, 53.6, 48.6, 21.0. HRMS calculated for C₃₀H₂₅NO: 415.1936; found: 415.1932.

N-ethyl-N-[1-(4-methylsulfanyl-phenyl)-3-phenyl-prop-2-ynyl]-benzamide (3, Table 1) Isolated Yield: 87 %. ¹H NMR (270 MHz, 100 °C, d⁶-DMSO): δ 7.53-7.25 (m, 14H), 6.45 (s, 1H), 3.43 (m, 1H), 3.20 (m, 1H), 2.42 (s, 3H), 0.97 (t, 3H). ¹³C NMR (68.0 MHz, 100°C, d⁶-DMSO): δ 169.9, 137.9, 136.0, 133.6, 130.8, 128.8, 128.3, 128.0, 127.9, 127.2, 126.2, 125.7, 121.3, 86.0, 85.5, 50.6, 40.4, 14.5, 13.9. HRMS calculated for C₂₅H₂₃NOS: 385.1500; found: 385.1497.

4-[1-(benzoyl-benzyl-amino)-3-trimethylsilanyl-prop-2-ynyl]-benzoic acid methyl ester (4, Table 1) Isolated Yield: 77 %. ¹H NMR (270 MHz, 125°C, d⁶-DMSO): δ 7.87-7.84 (d, 2H), 7.50-7.47 (d, 2H), 7.36-7.30 (s, 5H), 7.12-7.02 (m, 5H), 6.34 (s, 1H), 4.58 (d, 1H), 4.28 (d, 1H), 3.79 (s, 3H), 0.03 (s, 9H). ¹³C NMR (68.0 MHz, 125°C, d⁶-DMSO): δ 170.5, 165.1, 141.2, 137.0, 135.4, 129.2, 128.9, 128.6, 127.7, 127.0, 126.8, 126.6, 125.9, 125.7, 100.8, 92.9, 52.1, 51.1, 47.9, -1.2. HRMS calculated for C₂₈H₂₉NO₃Si: 455.1917; found: 455.1922.

N-benzyl-N-(1-furan-2-yl-3-trimethylsilanyl-prop-2-ynyl)-benzamide (5, Table 1) Isolated Yield: 86 %. ¹H NMR (270 MHz, 100°C, d⁶-DMSO): δ 7.50 (s, 1H), 7.40-7.34 (m, 5H), 7.18-7.03 (m, 5H), 6.33 (d, 2H), 6.15 (s, 1H), 4.57 (d, 1H), 4.37 (d, 1H), 0.06 (s, 9H). ¹³C NMR (68.0 MHz, 100°C, d⁶-DMSO): δ 170.3, 148.9, 143.1, 137.3, 135.2, 129.1, 127.9, 127.2, 126.4, 125.9, 125.8, 109.9, 109.1, 99.4, 90.9, 47.4, 46.9, -1.1. HRMS calculated for C₂₄H₂₅NO₂Si: 387.1655; found: 387.1650.

N-benzyl-N-(1-tert-butyl-3-phenyl-prop-2-ynyl)-benzamide (6, Table 1) Isolated

Yield: 92 %. ¹H NMR (270 MHz, 130 °C, d⁶-DMSO): δ 7.40-7.06 (m, 15H), 5.47 (s, 1H), 4.81 (s, 2H), 1.14 (s, 9H). ¹³C NMR (68.0 MHz, 130 °C, d⁶-DMSO): δ 171.2, 138.5, 136.4, 130.4, 128.4, 127.6, 127.6, 127.3, 127.0, 125.9, 125.8, 125.5, 121.5, 86.1, 85.8, 57.4, 49.4, 37.4, 26.4. HRMS calculated for C₂₇H₂₇NO: 381.2093; found: 381.2095.

[Benzoyl-(3-phenyl-1-p-tolyl-prop-2-ynyl)-amino]-acetic acid methyl ester (7, Table 1)

Isolated Yield: 87 %. ¹H NMR (270 MHz, 125 °C, d⁶-DMSO): δ 7.58-7.31 (m, 12H), 7.27-7.18 (d, 2H), 6.46 (s, 1H), 4.17 (d, 1H), 3.96 (d, 1H), 3.50 (s, 3H), 2.33 (s, 3H). ¹³C NMR (68.0 MHz, 125 °C, d⁶-DMSO): δ 171.4, 169.3, 138.3, 136.1, 134.2, 132.0, 130.3, 129.7, 129.4, 129.0, 127.8, 127.7, 127.1, 122.4, 87.8, 85.8, 52.9, 52.0, 46.6, 20.9. HRMS calculated for C₂₆H₂₃NO₃: 397.1678; found: 397.1681.

N-Benzyl-N-(3-phenyl-1-p-tolyl-prop-2-ynyl)-acetamide (8, Table 1) Isolated Yield:

76 %. ¹H NMR (270 MHz, 75 °C, CD₃CN): δ 7.65-7.08 (m, 15H), 4.70-4.50 (q, 2H), 2.39 (s, 3H), 2.07 (s, 3H). ¹³C NMR (68.0 MHz, 75 °C, CD₃CN): δ 170.2, 139.0, 138.3, 135.4, 131.7, 129.5, 128.9, 128.6, 128.5, 127.8, 127.0, 126.9, 122.7, 86.8, 86.7, 50.6, 48.8, 21.8, 20.3. HRMS for C₂₅H₂₃NO, calculated: 353.1780, found: 353.1775.

3-Methyl-but-2-enoic acid [1-(4-bromo-phenyl)-3-phenyl-prop-2-ynyl]-ethyl-amide (9, Table 1)

Isolated Yield: 81 %. ¹H NMR (270 MHz, 60 °C, CDCl₃): δ 7.56-7.26 (m, 9H), 7.09 (s, 1H), 5.93 (s, 1H), 3.57-3.21 (m, 2H), 2.08 (s, 3H), 1.93 (s, 3H), 1.22-1.07 (t, 3H). ¹³C NMR (68.0 MHz, 75 °C, CD₃CN): δ 167.8, 138.4, 131.9, 131.8, 131.6, 129.8, 129.1, 128.9, 122.7, 121.7, 118.0, 86.6, 86.3, 55.8, 39.7, 25.6, 19.7, 14.9. HRMS for C₂₂H₂₂⁷⁹BrNO, calculated: 395.0885, found: 395.0878. HRMS for C₂₂H₂₂⁸¹BrNO, calculated: 397.0864, found: 397.0862.

N-benzyl-N-(3-phenyl-1-p-tolyl-prop-2-ynyl)-isobutyramide (10, Table 1) Isolated

Yield: 84 %. ¹H NMR (270 MHz, 130 °C, d⁶-DMSO): δ 7.44-7.10 (m, 14H), 6.79 (s, 1H), 4.67 (d, 1H), 4.51 (d, 1H), 2.82 (m, 1H), 2.31 (s, 3H), 1.11-0.95 (m, 6H). ¹³C NMR (68.0 MHz, 130 °C, d⁶-DMSO): δ 176.6, 138.0, 136.6, 134.3, 130.5, 128.4, 127.8, 127.6, 127.2,

126.4, 125.9, 125.8, 121.3, 86.1, 85.7, 49.8, 47.2, 30.0, 19.7, 18.8, 18.4. HRMS calculated for $C_{27}H_{27}NO$: 381.2093; found: 381.2096.

N-Ethyl-3-methyl-N-(3-phenyl-1-phenylethynyl-allyl)-butyramide (11, Table 1)

Isolated Yield: 93 %. 1H NMR (270 MHz, 75 °C, CD_3CN): δ 7.53-7.14 (m, 10H), 6.90 (d, 1H), 6.22 (q, 1H), 5.29-5.16 (m, 1H), 4.69 (d, 1H), 3.63-3.34 (m, 2H), 2.36-2.02 (m, 3H), 1.14 (dt, 3H), 0.89 (dd, 6H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ (two rotamers) 171.8, 170.8, 141.8, 136.8, 132.7, 131.8, 131.6, 129.3, 128.9, 128.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.2, 126.9, 126.2, 122.9, 111.0, 90.1, 86.4, 86.1, 85.2, 42.7, 42.6, 42.2, 39.4, 38.9, 36.4, 26.0, 25.7, 22.2, 22.1, 15.6, 12.1. HRMS for $C_{24}H_{27}NO$, calculated: 345.2093, found: 345.2096.

N-phenyl-N-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-benzamide (12, Table 1)

Isolated Yield: 99 %. 1H NMR (270 MHz, 130 °C, d^6 -DMSO): δ 7.43-7.34 (m, 6H), 7.34-7.28 (m, 3H), 7.27-7.07 (m, 9H), 6.97-6.89 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (68.0 MHz, 130 °C, d^6 -DMSO): δ 168.8, 139.0, 136.7, 135.5, 133.9, 130.5, 129.4, 128.5, 128.2, 127.9, 127.8, 127.4, 127.2, 127.2, 126.8, 126.6, 121.4, 86.6, 85.9, 51.1, 19.7. HRMS calculated for $C_{29}H_{23}NO$: 401.1780; found: 401.1774.

N-(4-chloro-1-*p*-tolyl-but-2-ynyl)-N-ethyl-benzamide (13, Table 1)

Isolated Yield: 84 %. 1H NMR (270 MHz, 80 °C, d^6 -DMSO): δ 7.50-7.41 (s, 5H), 7.34 (d, 2H), 7.21 (d, 2H), 6.31 (s, 1H), 4.56 (s, 2H), 3.37 (m, 1H), 3.12 (m, 1H), 2.30 (s, 3H), 0.92 (t, 3H). ^{13}C NMR (68.0 MHz, 80 °C, d^6 -DMSO): δ 170.0, 137.2, 136.0, 133.3, 129.0, 128.8, 128.1, 126.5, 125.7, 82.7, 81.8, 50.3, 39.1, 30.3, 20.1, 14.0. HRMS calculated for $C_{20}H_{20}NO^{35}Cl$: 325.1233; found: 325.1235. HRMS calculated for $C_{20}H_{20}NO^{37}Cl$: 327.1204; found: 327.1210.

N-benzyl-N-(4-hydroxy-1-*p*-tolyl-but-2-ynyl)-benzamide (14, Table 1)

Isolated Yield: 90 %. 1H NMR (270 MHz, 130 °C, d^6 -DMSO): δ 7.48-7.37 (m, 5H), 7.35-7.30 (d, 2H), 7.21-7.05 (m, 7H), 6.26 (s, 1H), 4.67 (s, 1H), 4.59 (d, 1H), 4.38 (d, 1H), 4.13 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (68.0 MHz, 130 °C, d^6 -DMSO): δ 170.4, 137.4, 136.7, 135.7,

133.4, 128.7, 128.3, 127.6, 126.9, 126.6, 126.6, 125.7, 125.6, 87.2, 79.6, 51.9, 48.5, 47.2, 19.7. HRMS calculated for C₂₅H₂₃NO₂: 369.1729; found: 369.1724.

5-(benzoyl-benzyl-amino)-5-*p*-tolyl-pent-3-ynoic acid methyl ester (15, Table 1)

Isolated Yield: 89 %. ¹H NMR (270 MHz, 130°C, d⁶-DMSO): δ 7.46-7.37 (s, 5H), 7.34-7.25 (d, 2H), 7.22-7.05 (m, 7H), 6.29 (s, 1H), 4.68 (s, 1H), 4.62 (d, 1H), 4.32 (d, 1H), 2.31 (s, 3H), 2.03 (s, 3H). ¹³C NMR (68.0 MHz, 130°C, d⁶-DMSO): δ 171.5, 169.8, 138.3, 138.1, 136.5, 133.9, 130.1, 129.6, 128.9, 128.2, 128.1, 127.6, 126.9, 126.8, 83.1, 82.8, 60.0, 52.0, 48.3, 20.9, 20.7. HRMS calculated for C₂₇H₂₅NO₃: 411.1834; found: 411.1826.

***N*-benzyl-*N*-(1-*p*-tolyl-hept-2-ynyl)-benzamide (16, Table 1)** Isolated Yield: 93 %. ¹H NMR (270 MHz, 85°C, d⁶-DMSO): δ 7.52-7.36 (s, 5H), 7.33-7.27 (d, 2H), 7.26-7.06 (m, 7H), 6.17 (s, 1H), 4.60 (d, 1H), 4.23 (d, 1H), 2.29 (s, 3H), 2.17 (t, 2H), 1.45-1.25 (m, 4H), 0.86 (t, 3H). ¹³C NMR (68.0 MHz, 85°C, d⁶-DMSO): δ 170.5, 137.8, 136.9, 135.8, 134.0, 129.1, 128.6, 128.0, 127.2, 127.1, 126.7, 126.6, 125.9, 87.9, 76.0, 52.3, 46.9, 29.5, 20.8, 20.0, 17.2, 12.7. HRMS calculated for C₂₈H₂₉NO: 395.2249; found: 395.2246.

***N*-benzyl-*N*-(1-*p*-tolyl-3-trimethylsilylprop-2-ynyl)-benzamide (17, Table 1)**

Isolated Yield: 99 %. ¹H NMR (270 MHz, 125°C, d⁶-DMSO): δ 7.38-7.31 (m, 5H), 7.23 (d, 2H), 7.16-7.04 (m, 7H), 6.19 (s, 1H), 4.55 (d, 1H), 4.22 (d, 1H), 2.24 (s, 3H), 0.06 (s, 9H). ¹³C NMR (68.0 MHz, 125°C, d⁶-DMSO): δ 170.4, 137.4, 136.9, 135.6, 133.1, 128.8, 128.4, 127.7, 127.0, 126.5, 126.5, 125.7, 125.6, 101.6, 91.8, 52.3, 47.2, 19.7, -1.2. HRMS calculated for C₂₇H₂₉NOSi: 411.2018; found: 411.2025.

Ethyl-(3-phenyl-1-phenylethynyl-allyl)-carbamic acid benzyl ester (1, Table 2)

Isolated Yield: 70 %. ¹H NMR (270 MHz, 75°C, CD₃CN): δ 7.55-7.14 (m, 15H), 6.91 (d, 1H), 6.30 (m, 1H), 5.92 (d, 1H), 5.19 (s, 2H), 3.64-3.36 (m, 2H), 1.15 (m, 3H). ¹³C NMR (68.0 MHz, 75°C, CD₃CN): δ 155.7, 137.6, 136.8, 132.9, 131.8, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.0, 127.0, 126.5, 122.8, 86.3, 86.0, 67.3, 50.7, 39.6, 14.8. HRMS calculated for C₂₇H₂₅NO₂: 395.1885; found: 395.1889.

Ethyl-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-carbamic acid benzyl ester (2, Table 2)

Isolated Yield: 74 %. ¹H NMR (270 MHz, 125 °C, d⁶-DMSO): δ 7.53-7.26 (m, 12H), 7.20 (d, 2H), 6.39 (s, 1H), 5.21 (s, 2H), 3.45-3.19 (m, 2H), 2.31 (s, 3H), 1.06 (t, 3H). ¹³C NMR (68.0 MHz, 125 °C, d⁶-DMSO): δ 154.4, 136.5, 136.0, 134.1, 130.5, 128.2, 127.8, 127.7, 127.4, 126.9, 126.6, 126.2, 121.3, 85.7, 85.2, 66.0, 50.8, 38.4, 19.6, 13.4. HRMS calculated for C₂₆H₂₅NO₂: 383.1885; found: 383.1880.

[1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-prop-2-ynyl]-ethyl-carbamic acid benzyl ester (3, Table 2)

Isolated Yield: 82 %. ¹H NMR (270 MHz, 125 °C, d⁶-DMSO): δ 7.61-6.96 (m, 20H), 6.68 (s, 1H), 5.42 (s, 2H), 5.26 (s, 2H), 3.42-3.22 (m, 2H), 0.97 (t, 3H). ¹³C NMR (68.0 MHz, 125 °C, d⁶-DMSO): δ 154.4, 137.2, 136.3, 130.7, 128.1, 127.8, 127.8, 127.7, 127.6, 127.0, 126.9, 126.6, 126.3, 125.6, 124.5, 121.6, 121.2, 118.8, 118.2, 111.2, 109.7, 86.8, 83.3, 66.1, 48.8, 44.6, 37.6, 13.6. HRMS calculated for C₃₄H₃₀N₂O₂: 498.2307; found: 498.2312.

4-(Benzyloxycarbonyl-ethyl-amino)-4-*p*-tolyl-but-2-ynoic acid methyl ester (4, Table 2)

Isolated Yield: 68%. %. ¹H NMR (270 MHz, 45 °C, CDCl₃): δ 7.45-7.27 (m, 7H), 7.24-7.17 (d, 2H), 6.35 (s, 1H), 5.19 (s, 2H), 3.79 (s, 3H), 3.40-3.13 (m, 2H), 2.34 (s, 3H), 1.06-1.00 (t, 3H). ¹³C NMR (68.0 MHz, 45 °C, CDCl₃): δ 153.6, 150.5, 138.4, 136.5, 132.9, 129.4, 128.5, 128.1, 127.9, 127.4, 84.5, 77.6, 67.7, 52.7, 51.1, 39.7, 21.0, 14.5. HRMS calculated for C₂₂H₂₃NO₄: 365.1627; found: 365.1630.

Ethyl-(1-*p*-tolyl-3-phenyl-prop-2-ynyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (5, Table 2)

Isolated Yield: 88 %. ¹H NMR (270 MHz, 100 °C, d⁶-DMSO): δ 7.88-7.79 (d, 2H), 7.67-7.60 (d, 2H), 7.53-7.11 (m, 13H), 6.18 (s, 1H), 4.62 (m, 2H), 4.32 (t, 1H), 3.16-2.88 (m, 2H), 2.30 (s, 3H), 0.79 (t, 3H). ¹³C NMR (68.0 MHz, 100 °C, d⁶-DMSO): δ 155.5, 144.5, 144.4, 141.5, 137.9, 135.1, 131.9, 129.6, 129.1, 127.5, 127.4, 125.2, 125.2, 122.4, 120.4, 86.7, 86.3, 67.1, 51.6, 47.6, 39.3, 21.0, 14.5. HRMS calculated for C₃₃H₂₉NO₂: 471.2198; found: 471.2195.

Phenyl-(2-phenylethynyl-2*H*-pyridin-1-yl)-methanone (4) Isolated Yield: 73 %. ¹H NMR (300 MHz, 60 °C, CDCl₃): δ 7.68-7.54 (d, 3H), 7.52-7.37 (m, 7H), 6.42 (br, 1H), 6.13 (m, 2H), 5.82 (br, 1H), 5.40 (br, 1H). ¹³C NMR (68.0 MHz, 60 °C, CDCl₃): δ 169.4, 133.9, 131.9, 130.9, 128.7, 128.4, 128.3, 128.1, 126.7, 122.6, 122.3, 120.0, 106.7, 86.1, 83.0, 43.0. HRMS for C₂₀H₁₅NO, calculated: 285.1154, found: 285.1149.

References

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2. Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, 54, 3229-3230.

Entry 1, Table 1 (above spectrum); Entry 3, Table 1 (below spectrum)

Entry 4, Table 1 (above spectrum); Entry 5, Table 1 (below spectrum)

N-Benzyl-*N*-(1-*tert*-butyl-3-phenyl-prop-2-ynyl)-benzamide

Entry 6, Table 1 (above spectrum); Entry 7, Table 1 (below spectrum)

[Benzoyl-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-amino]-acetic acid methyl ester

Entry 8, Table 1 (above spectrum); Entry 9, Table 1 (below spectrum)

2.7

Entry 10, Table 1 (above spectrum); Entry 11, Table 1 (below spectrum)

Entry 12, Table 1 (above spectrum); Entry 13, Table 1 (below spectrum)

Entry 14, Table 1 (above spectrum); Entry 15, Table 1 (below spectrum)

Entry 16, Table 1 (above spectrum); Entry 17, Table 1 (below spectrum)

Ethyl-(3-phenyl-1-phenylethynyl-allyl)-carbamate benzyl ester

Entry 1, Table 2 (above spectrum); Entry 2, Table 2 (below spectrum)

Ethyl-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-carbamate benzyl ester

Entry 3, Table 2 (above spectrum); Entry 4, Table 2 (below spectrum)

Entry 5, Table 2 (above spectrum); 4 (below spectrum)