Supplementary material (19 pages)

An expeditious approach to 5-aryl-pyrrolidinones by a novel PIFA-mediated alkyne amidation reaction.

Sonia Serna, Imanol Tellitu,* Esther Domínguez,* Isabel Moreno, and Raul SanMartín.

General information:

All reagents were purchased from Aldrich, Fluka and Across Organics and used as received. (*E*)-(2-bromo-vinyl)benzene was prepared according a literature procedure.¹ THF was freshly distilled prior to use from Na/benzophenone.

¹H NMR spectra were recorded on a Bruker ACE-250 MHz spectrometer in chloroform-*d* or DMSO-*d*₆. All signals are reported in ppm relative in TMS with the internal solvent signal (CDCl₃: 7.26 ppm, (CD₃)₂SO: 2.50 ppm) as standard. The data is reported as (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet or unresolved, br=broad singlet, coupling constant(s) in Hz, integration).

¹³C NMR spectra were recorded on a Bruker ACE-62.8 MHz spectrometer in chloroform-*d* or DMSO-*d*₆. All signals are reported in ppm relative in TMS with the internal solvent signal (CDCl₃: 77.0 ppm, (CD₃)₂SO: 39.6 ppm) as standard, the attached protons were assigned by recording DEPT spectra.

Infrared spectra were recorded on a Perkin-Elmer R-1420 spectrometer as thin films and the data are reported in cm⁻¹.

Melting points were measured in a Büchi apparatus using open glass capillaries and are uncorrected.

High resolution mass spectrometric measures were recorded at the University of Vigo on a VG Autospec M instrument.

N-(4-Methoxyphenyl)pent-4-ynamide (4).

To a solution of EDC·HCl (10.1 g, 52.6 mmol) and HOBT (6.63 g, 49.1 mmol) in CH₂Cl₂ (100 mL) was added a solution of 4-pentynoic acid (3.44 g, 35.1 mmol) in CH₂Cl₂ (25 mL) followed by a solution of *p*-anisidine (6.48 g, 52.6 mmol) in CH₂Cl₂ (25 mL). The mixture was cooled to 0 °C and Et₃N (7.3 mL, 52.6 mmol) was added dropwise; the reaction was slowly warmed to room temperature and stirred overnight. The reaction was diluted with CH₂Cl₂, washed successively with water, aqueous HCl 5

¹ Das, J. P.; Roy, S. *J. Org. Chem.* **2002**, 67, 7861.

%, saturated NaHCO₃, brine, dried over Na₂SO₄, and solvent was evaporated under reduced pressure. The crude product was triturated in Et₂O to give **4** as a white solid (6.59 g, 92%). mp: 145-147 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.05 (s, 1H), 2.52-2.64 (m, 4H), 3.79 (s, 3H), 6.85 (d, *J*=8.7, 2H), 7.33-7.43 (m, 3H). ¹³C NMR (62.8 MHz, CDCl₃) δ 14.8, 36.1 (CH₂), 55.4 (CH₃), 69.6 (C), 82.8, 114.1, 121.8 (CH), 130.7, 156.5, 168.9 (C). IR (thin film, cm⁻¹) ν 3252, 2964, 2918, 2833, 1657, 1608, 1549, 1514, 1413, 1314, 1239. MS (EI) *m/z* (relative intensity): 204 (10), 203 (69), 124 (8), 123 (100), 108 (76). HRMS calculated for C₁₂H₁₃NO₂ 203.0946 found 203.0952.

General procedure 1 (GP 1). Sonogashira cross-coupling reaction.

***N*-(4-Methoxyphenyl)-5-phenyl-pent-4-ynamide (5a).**

A solution of Pd(PPh₃)₄ (1.31 g, 1.14 mmol), CuI (433 mg, 2.27 mmol), iodobenzene (1.27 mL, 11.3 mmol) and Et₂NH (60 mL) was stirred for 5 minutes at room temperature under argon. Then, a solution of **4** (2.77 g, 13.6 mmol) in THF (15 mL) was added dropwise and the reaction was stirred until completion by TLC. The mixture was diluted with EtOAc, filtered and washed with saturated NH₄Cl. The aqueous layer was extracted with EtOAc (3x40 mL), dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, CH₂Cl₂:EtOAc/95:5) to yield 2.40 g of the title compound as a white solid (76%). mp: 160-161 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 1.67-1.72 (m, 2H), 1.80-1.86 (m, 2H), 2.81 (s, 3H), 5.98 (d, *J*= 7.9, 2H), 6.43 (s, 5H), 6.63 (d, *J*=7.9, 2H), 8.99 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 15.3, 35.4 (CH₂), 55.2 (CH₃), 80.8, 89.9 (C), 113.9, 120.7, 128.1, 128.7, 131.3 (CH), 123.2, 132.4, 155.2, 169.0 (C). IR (thin film, cm⁻¹) ν 3289, 3254, 2884, 1654, 1606, 1544, 1510, 1245, 1176, 1034. MS (EI) *m/z* (relative intensity): 280 (19), 279 (100), 278 (15), 251 (11), 128 (14), 123 (81), 122 (12), 115 (33), 108 (46). HRMS calculated for C₁₈H₁₇NO₂ 279.1259 found 279.1258.

***N*-(4-Methoxyphenyl)-5-(4-methoxyphenyl)pent-4-ynamide (5b).**

Prepared according to GP 1 using 1.0 g (4.92 mmol) of **4** and 4-iodoanisole (961 mg, 4.10 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 1.16 g (77%) of **5b** as a white solid. mp: 160-161 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.59-2.65 (m, 2H), 2.78-2.84 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 6.79-6.86 (m, 4H), 7.32 (d, *J*=8.3, 2H), 7.40 (d, *J*=9.1, 2H), 7.52 (br s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.9, 36.6 (CH₂), 55.2, 55.4 (CH₃), 81.8, 86.6 (C), 113.9, 114.1, 121.8, 132.9 (CH), 115.3, 130.8, 156.4, 159.3, 169.4 (C). IR (thin film, cm⁻¹) ν 3275, 2957, 2839, 1653, 1605, 1510, 1247, 1031. MS (EI) *m/z* (relative intensity): 310 (20), 309 (100), 308 (26), 281 (17), 280 (15), 187 (14), 147 (36), 145 (35), 123 (45), 108 (32). HRMS calculated for C₁₉H₁₉NO₃ 309.1365 found 309.1372.

***N*-(4-Methoxyphenyl)-5-(2-methylphenyl)pent-4-ynamide (5c).**

Prepared according to GP 1 using 300 mg (1.48 mmol) of **4** and 2-iodotoluene (0.16 mL, 1.23 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 115 mg (32%) of **5c** as a white solid. mp: 122-123 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.37 (s, 3H), 2.61-2.66 (m, 2H), 2.82-2.88 (m, 2H), 3.74 (s, 3H), 6.81 (d, *J*=8.7, 2H), 7.09-7.18 (m, 3H), 7.33-7.43 (m, 3H), 7.96 (br s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 16.0, 36.4 (CH₂), 20.6, 55.3 (CH₃), 80.5, 92.1 (C), 113.9, 121.9, 125.4, 127.8, 129.3, 131.7 (CH), 123.0, 130.8, 139.9, 156.3, 169.6 (C). IR (thin film, cm⁻¹) ν 3297, 2915, 2837, 1651, 1540, 1510, 1244, 1029. MS (EI) *m/z* (relative intensity): 294 (21), 293 (100), 292 (14), 147 (11), 129 (19), 128 (23), 123 (76), 122 (11), 108 (34). HRMS calculated for C₁₉H₁₉NO₂ 293.1446 found 293.1411.

***N*-(4-Methoxyphenyl)-5-(3-methylphenyl)pent-4-ynamide (5d).**

Prepared according to GP 1 using 200 mg (0.98 mmol) of **4** and 3-iodotoluene (0.10 mL, 0.82 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 155 mg (64%) of **5d** as a white solid. mp: 128-130 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.29 (s, 3H), 2.59-2.65 (m, 2H), 2.78-2.84 (m, 2H), 3.76 (s, 3H), 6.83 (d, *J*=8.7, 2H), 7.09-7.20 (m, 4H), 7.41 (d, *J*=9.1, 2H), 7.74 (br s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.9, 36.3 (CH₂), 21.1, 55.3 (CH₃), 81.9, 87.8 (C), 114.0, 121.9, 128.1, 128.5, 128.8, 132.1 (CH), 122.9, 130.8, 137.9, 156.3, 169.5 (C). IR (thin film, cm⁻¹) ν 3290, 3258, 2928, 2832, 1656, 1604, 1548, 1511, 1410, 1244, 1034. MS (EI) *m/z* (relative intensity): 294 (17), 293 (82), 292 (14), 265 (10), 129 (43), 128 (23), 123 (100), 122 (18), 115 (11), 108 (56). HRMS calculated for C₁₉H₁₉NO₂ 293.1416 found 293.1421.

***N*-(4-Methoxyphenyl)-5-(4-methylphenyl)pent-4-ynamide (5e).**

Prepared according to GP 1 using 500 mg (2.46 mmol) of **4** and 4-iodotoluene (447 mg, 2.05 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 405 mg (56%) of **5e** as a white solid. mp: 183-184 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 1.42 (s, 3H), 1.68-1.74 (m, 2H), 1.81-1.86 (m, 2H), 2.85 (s, 3H), 6.01 (d, *J*=9.1, 2H), 6.27 (d, *J*=7.9, 2H), 6.38 (d, *J*=7.9, 2H), 6.65 (d, *J*=9.1, 2H), 9.02 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 15.3 (CH₂), 21.0 (CH₃), 35.5 (CH₂), 55.2 (CH₃), 80.8, 89.0 (C), 113.9, 120.7, 129.3, 131.2 (CH), 120.1, 132.4, 137.7, 155.2, 169.0 (C). IR (thin

film, cm^{-1}) ν 3289, 3257, 2832, 1656, 1545, 1509, 1407, 1246, 1181, 1038. MS (EI) m/z (relative intensity): 294 (19), 293 (100), 292 (22), 265 (17), 147 (14), 129 (34), 128 (20), 123 (69), 122 (12), 108 (38). HRMS calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_2$ 293.1416 found 293.1414.

***N*-(4-Methoxyphenyl)-5-(1-naphthyl)pent-4-ynamide (5f).**

Prepared according to GP 1 using 450 mg (2.21 mmol) of **4** and 1-iodonaphthalene (0.27 mL, 1.85 mmol). Purification by FC (SiO_2 , CH_2Cl_2 : EtOAc/95:5) gave 426 mg (70%) of **5f** as a white solid. mp: 123-125 $^\circ\text{C}$ (Et_2O). ^1H NMR (250 MHz, CDCl_3) δ 2.67-2.72 (m, 2H), 2.93-2.98 (m, 2H), 3.73 (s, 3H), 6.80 (d, $J=8.7$, 2H), 7.34-7.49 (m, 5H), 7.60 (d, $J=7.1$, 1H), 7.76-7.85 (m, 3H), 8.28 (d, $J=7.9$, 1H). ^{13}C NMR (62.8 MHz, CDCl_3) δ 16.3, 36.5 (CH_2), 55.4 (CH_3), 79.8, 93.2 (C), 114.0, 121.9, 125.1, 126.04, 126.3, 126.6, 128.1, 128.3, 130.1 (CH), 120.9, 130.8, 133.0, 133.3, 156.4, 169.5 (C). IR (thin film, cm^{-1}) ν 3288, 3055, 2911, 2831, 1650, 1604, 1537, 1510, 1245, 1033, 826, 800, 773. MS (EI) m/z (relative intensity): 330 (24), 329 (100), 328 (27), 301 (14), 179 (13), 178 (17), 165 (35), 123 (23), 108 (13). HRMS calculated for $\text{C}_{22}\text{H}_{19}\text{NO}_2$ 329.1416 found 329.1422.

5-(4-*N*-Ethoxycarbonylamino-phenyl)-*N*-(4-methoxyphenyl)pent-4-ynamide (5g).

Prepared according to GP 1 using 365 mg (1.80 mmol) of **4** and 1-(*N*-ethoxycarbonylamino)-4-iodobenzene (436 mg, 1.50 mmol). Purification by FC (SiO_2 ,

CH₂Cl₂: EtOAc/95:5) gave 261 mg (47%) of **5g** as a white solid. mp: 176-177 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 0.12 (t, *J*=7.3, 3H), 1.42-1.48 (m, 2H), 1.56-1.61 (m, 2H), 2.60 (s, 3H), 3.01 (q, *J*=7.3, 2H), 5.77 (d, *J*=9.1, 2H), 6.15 (d, *J*=9.1, 2H), 6.31 (d, *J*=9.1, 2H), 6.39 (d, *J*=9.1, 2H), 8.66 (br s, 1H), 8.81 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 14.6 (CH₃), 15.3, 35.5 (CH₂), 55.2 (CH₃), 60.4 (CH₂), 80.8, 88.5 (C), 113.9, 117.9, 120.7, 131.9 (CH), 116.7, 132.4, 139.1, 153.4, 155.2, 169.0 (C). IR (thin film, cm⁻¹) ν 3307, 2979, 2835, 1708, 1667, 1596, 1530, 1512, 1319, 1237, 1171, 1073, 823. MS (EI) *m/z* (relative intensity): 367 (25), 366 (100), 365 (21), 338 (15), 337 (13), 320 (24), 202 (13), 147 (45), 123 (71), 122 (14), 108 (40). HRMS calculated for C₂₁H₂₂N₂O₄ 366.1580 found 366.1581.

***N*-(4-Methoxyphenyl)-5-(2-thienyl)pent-4-ynamide (5h).**

Prepared according to GP 1 using 599 mg (2.95 mmol) of **4** and 2-iodothiophene (0.27 mL, 2.46 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 415 mg (59%) of **5h** as a white solid. mp: 166-167 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 1.67-1.75 (m, 2H), 1.86-1.92 (m, 2H), 2.86 (s, 3H), 6.02 (d, *J*=9.2, 2H), 6.16-6.19 (m, 1H), 6.34 (d, *J*=3.0, 1H), 6.64-6.67 (m, 3H), 9.03 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 15.5, 35.1 (CH₂), 55.2 (CH₃), 74.0, 94.0 (C), 113.9, 120.8, 127.5, 131.7, (CH), 122.9, 132.4, 155.3, 168.9 (C). IR (thin film, cm⁻¹) ν 3288, 3256, 2921, 2827, 1655, 1607, 1544, 1509, 1245, 1177, 1033. MS (EI) *m/z* (relative intensity): 286 (20), 285 (100), 284 (21), 257 (16), 147 (25), 123 (38), 121 (18), 108 (24). HRMS calculated for C₁₆H₁₅NO₂S 285.0824 found 285.0822.

5-(4-Chlorophenyl)-N-(4-methoxyphenyl)pent-4-ynamide (5i).

Prepared according to GP 1 using 450 mg (2.21 mmol) of **4** and 1-chloro-4-iodobenzene (441 mg, 1.85 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 427 mg (74%) of **5i** as a white solid. mp: 173-174 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 1.68-1.73 (m, 2H), 1.82-1.87 (m, 2H), 2.83 (s, 3H), 5.99 (d, *J*=8.5, 2H), 6.49 (s, 4H), 6.64 (d, *J*=8.5, 2H), 9.01 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 15.28, 35.2 (CH₂), 55.2 (CH₃), 79.7, 91.2 (C), 113.9, 120.7, 128.8, 133.0 (CH), 122.0, 132.4, 132.8, 155.2, 168.9 (C). IR (thin film, cm⁻¹) ν 3276, 2928, 2832, 1654, 1647, 1559, 1490, 1406, 1247, 1036, 827. MS (EI) *m/z* (relative intensity): 315 (31), 314 (22), 313 (89), 312 (14), 149 (26), 128 (11), 123 (100), 122 (15), 108 (56). HRMS calculated for C₁₈H₁₆ClNO₂ 313.0870 found 313.0879.

N-(4-Methoxyphenyl)-5-(3-pyridyl)pent-4-ynamide (5j).

Prepared according to GP 1 using 160 mg (0.79 mmol) of **4** and 3-iodopyridine 135 mg (0.66 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/1:1) gave 146 mg (79%) of **5j** as a white solid. mp: 138-140 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.59-2.65 (m, 2H), 2.79-2.85 (m, 2H), 3.74 (s, 3H), 6.80 (d, *J*=8.9, 2H), 7.19 (dd, *J*=7.9, 4.9, 1H), 7.41 (d, *J*=8.9, 2H), 7.63 (d, *J*=7.9, 1H), 8.41-8.47 (m, 2H), 8.59 (s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.8, 35.9 (CH₂), 55.3 (CH₃), 78.0, 92.2 (C), 113.9, 121.8, 123.0, 138.6, 147.9, 152.0 (CH), 120.7, 131.0, 156.3, 169.3 (C). IR (thin film, cm⁻¹) ν 3288, 1653, 1646, 1542, 1508, 1409, 1242, 1179, 1032, 826. MS (EI) *m/z* (relative intensity): 281 (19), 280 (100), 279 (13), 123 (88), 122 (11), 116 (17), 108 (50). HRMS calculated for C₁₇H₁₆N₂O₂ 280.1212 found 280.1216.

***N*-(4-Methoxyphenyl)-5-(4-nitrophenyl)pent-4-ynamide (5k).**

Prepared according to GP 1 using 489 mg (2.41 mmol) of **4** and 1-iodo-4-nitrobenzene (500 mg, 2.00 mmol). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 359 mg (55%) of **5k** as a yellow solid. mp: 181-183 °C (Et₂O). ¹H NMR (250 MHz, (CD₃)₂SO) δ 1.71-1.76 (m, 2H), 1.83-1.98 (m, 2H), 2.81 (s, 3H), 5.98 (d, *J*=8.5, 2H), 6.61-6.72 (m, 4H), 7.28 (d, *J*=8.5, 2H), 9.02 (br s, 1H). ¹³C NMR (62.8 MHz, (CD₃)₂SO) δ 15.4, 35.0 (CH₂), 55.2 (CH₃), 79.5, 95.9 (C), 113.9, 120.7, 123.9, 132.4 (CH), 130.1, 146.6, 155.3, 168.8 (C). IR (thin film, cm⁻¹) ν 3252, 2961, 2830, 1646, 1591, 1543, 1508, 1347, 1250, 1107, 1033. MS (EI) *m/z* (relative intensity): 325 (21), 324 (100), 123 (88), 122 (11), 108 (46). HRMS calculated for C₁₈H₁₆N₂O₄ 324.1110 found 324.1105.

***N*-(4-Methoxyphenyl)hept-6-en-4-ynamide (5l).**

Prepared according to GP 1 using 599 mg (2.95 mmol) of **4** and 2.46 mL (2.46 mmol) of vinyl bromide (1M in THF). Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 455 mg (81%) of **5l** as a white solid. mp: 129-130 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.53-2.59 (m, 2H), 2.70-2.76 (m, 2H), 3.78 (s, 3H), 5.43 (dd, *J*=10.7, 2.4, 1H), 5.57 (dd, *J*=17.4, 2.4, 1H), 5.71-5.84 (m, 1H), 6.85 (d, *J*=8.9, 2H), 7.40 (d, *J*=8.9, 2H), 7.67 (br s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.7, 36.1 (CH₂), 55.4 (CH₃), 80.5, 88.9 (C), 114.0, 117.1, 121.9 (CH), 126.5 (CH₂), 130.8, 156.4, 169.4 (C). IR (thin film, cm⁻¹) ν 3290, 3257, 2924, 2833, 1656, 1607, 1543, 1510, 1410, 1246, 1037, 965, 829. MS (EI) *m/z* (relative intensity): 230 (16), 229 (100), 123 (11), 123 (98), 122 (11), 108 (59). HRMS calculated for C₁₄H₁₅NO₂ 229.1103 found 229.1099.

(Z)-N-(4-Methoxyphenyl)-6-methyloct-6-en-4-ynamide (5m).

Prepared according to GP 1 using 835 mg (4.12 mmol) of **4** and 0.35 mL (3.43 mmol) of (Z)-2-bromo-2-butene. Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 362 mg (41%) of **5m** as a white solid. mp: 84-85 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 1.72-1.78 (m, 6H), 2.53-2.59 (m, 2H), 2.71-2.77 (m, 2H), 3.75 (s, 3H), 5.65 (q, *J*=6.3, 1H), 6.79 (d, *J*=8.9, 2H), 7.38 (d, *J*=8.9, 2H), 8.05 (br s, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.9 (CH₂), 23.1 (2xCH₃), 36.5 (CH₂), 55.3 (CH₃), 80.9, 91.8 (C), 113.9, 121.9, 131.6 (CH), 118.4, 130.8, 156.3, 169.8 (C). IR (thin film, cm⁻¹) ν 3289, 2968, 2917, 2835, 1654, 1542, 1523, 1409, 1366, 1248, 1183, 1030, 826. MS (EI) *m/z* (relative intensity): 258 (14), 257 (69), 214 (18), 123 (100), 122 (25), 108 (61), 93 (18), 91 (19), 77 (17). HRMS calculated for C₁₆H₁₉NO₂ 257.1416 found 257.1423.

(E)-N-(4-Methoxyphenyl)-7-phenylhept-6-en-4-ynamide (5n).

Prepared according to GP 1 using 762 mg (3.76 mmol) of **4** and 573 mg (3.13 mmol) of (E)-(2-bromovinyl)benzene. Purification by FC (SiO₂, CH₂Cl₂: EtOAc/95:5) gave 372 mg (37%) of **5n** as a white solid. mp: 161-162 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 2.58-2.63 (m, 2H), 2.78-2.83 (m, 2H), 3.79 (s, 3H), 6.14 (d, *J*=16.2, 1H), 6.85-6.91 (m, 3H), 7.29-7.44 (m, 8H). ¹³C NMR (62.8 MHz, CDCl₃) δ 16.1, 36.4 (CH₂), 55.4 (CH₃), 81.1, 90.6 (C), 108.1, 114.1, 121.8, 126.1, 128.5, 128.7, 140.9 (CH), 130.8, 136.2, 156.4, 169.3 (C). IR (thin film, cm⁻¹) ν 3278, 3255, 2907, 2831, 1653, 1606, 1549, 1509, 1410, 1245, 1181, 1034, 952, 830. MS (EI) *m/z* (relative intensity): 306 (20), 305 (93), 304 (24), 156 (10), 155 (17), 147 (13), 141 (25), 124 (10), 123 (100),

122 (16), 115 (24), 108 (51). HRMS calculated for $C_{20}H_{19}NO_2$ 305.1416 found 305.1413.

General procedure 2 (GP 2). PIFA mediated alkyne amidation.

5-Benzoyl-N-(4-methoxyphenyl)pyrrolidin-2-one (6a).

A suspension of amide **5a** (1.70 g, 6.08 mmol) in CF_3CH_2OH (80 mL) was cooled to $0\text{ }^{\circ}C$ and a solution of PIFA (3.93 g, 9.13 mmol) in CF_3CH_2OH (40 mL) was added dropwise. The reaction mixture was stirred at $0\text{ }^{\circ}C$ until completion by TLC (2 h). Aqueous Na_2CO_3 10 % was added and extracted with CH_2Cl_2 (3x50mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and the solvent evaporated. Purification of the crude by flash chromatography (SiO_2 , EtOAc) followed by crystallization in MeOH, gave the desired product **6a** as a brown solid (1.11 g, 62%). mp: $136\text{--}138\text{ }^{\circ}C$ (MeOH). 1H NMR (250 MHz, $CDCl_3$) δ 2.04–2.19 (m, 1H), 2.54–2.70 (m, 3H), 3.73 (s, 3H), 5.62–5.67 (m, 1H), 6.65 (d, $J=8.9$, 2H), 7.35 (d, $J=8.9$, 2H), 7.50 (t, $J=7.5$, 2H), 7.63 (t, $J=7.5$, 1H), 7.96 (d, $J=7.5$, 2H). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 23.3, 30.3 (CH_2), 55.3 (CH_3), 64.2, 114.1, 124.5, 128.3, 129.0, 134.0 (CH), 131.1, 133.8, 157.3, 174.5, 196.3 (C). IR (thin film, cm^{-1}) ν 1694, 1513, 1248, 1222, 1032. MS (EI) m/z (relative intensity): 295 (13), 191 (12), 190 (100). HRMS calculated for $C_{18}H_{17}NO_3$ 295.1208 found 295.1205.

5-(4-Methoxybenzoyl)-*N*-(4-methoxyphenyl)pyrrolidin-2-one (6b).

Prepared according to GP 2 using 350 mg (1.13 mmol) of **5b**, the desired product **6b** (309 mg, 84%) was isolated by FC (SiO₂, EtOAc) as a brown solid. mp: 142-143 °C (MeOH). ¹H NMR (250 MHz, CDCl₃) δ 2.02-2.17 (m, 1H), 2.50-2.76 (m, 3H), 3.73 (s, 3H), 3.87 (s, 3H), 5.58-5.61 (m, 1H), 6.82 (d, *J*=8.7, 2H), 6.96 (d, *J*=8.7, 2H), 7.34 (d, *J*=8.7, 2H), 7.94 (d, *J*=8.7, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 23.6, 30.4 (CH₂), 55.3, 55.5 (CH₃), 63.9, 114.1, 114.2, 124.4, 130.6 (CH), 126.8, 131.26, 157.2, 164.1, 174.6, 194.8 (C). IR (thin film, cm⁻¹) ν 1696, 1599, 1512, 1247, 1171. MS (EI) *m/z* (relative intensity): 325 (14), 191 (12), 190 (100). HRMS calculated for C₁₉H₁₉NO₄ 325.1314 found 325.1314.

***N*-(4-Methoxyphenyl)-5-(2-methylbenzoyl)pyrrolidin-2-one (6c).**

Prepared according to GP 2 using 75 mg (0.26 mmol) of **5c**, the desired product **6c** (61 mg, 77%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/8:2) as a white solid. mp: 78-79 °C (MeOH). ¹H NMR (250 MHz, CDCl₃) δ 2.01-2.13 (m, 1H), 2.42-2.76 (m, 6H), 3.75 (s, 3H), 5.48-5.53 (m, 1H), 6.85 (d, *J*=8.7, 2H), 7.27-7.45 (m, 5H), 7.61 (d, *J*=7.1, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 21.2 (CH₃), 23.0, 30.2 (CH₂), 55.3 (CH₃), 65.9, 114.2, 124.7, 125.9, 128.1, 132.3, 132.4 (CH), 131.1, 134.5, 139.6, 157.3, 174.6, 200.0 (C). IR (thin film, cm⁻¹) ν 1694, 1513, 1248, 1218, 1033. MS (EI) *m/z* (relative

intensity): 309 (7), 191 (12), 190 (100). HRMS calculated for C₁₉H₁₉NO₃ 309.1365 found 309.1361.

***N*-(4-Methoxyphenyl)-5-(3-methylbenzoyl)pyrrolidin-2-one (6d).**

Prepared according to GP 2 using 99 mg (0.34 mmol) of **5d**, the desired product **6d** (73 mg, 70%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/1:1) as a white solid. mp: 102-103 °C (*hexanes*). ¹H NMR (250 MHz, CDCl₃) δ 2.04-2.18 (m, 1H), 2.42 (s, 3H), 2.55-2.71 (m, 3H), 3.74 (s, 3H), 5.62-5.65 (m, 1H), 6.84 (d, *J*=9.1, 2H), 7.33-7.46 (m, 4H), 7.74-7.77 (m, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 21.3 (CH₃), 23.5, 30.3 (CH₂), 55.4 (CH₃), 64.2, 114.2, 124.6, 125.5, 128.9, 134.9 (CH), 131.2, 133.9, 139.0, 157.3, 174.6, 196.5 (C). IR (thin film, cm⁻¹) ν 1694, 1513, 1249, 1033. MS (EI) *m/z* (relative intensity): 309 (20), 191 (12), 190 (100). HRMS calculated for C₁₉H₁₉NO₃ 309.1365 found 309.1362.

***N*-(4-Methoxyphenyl)-5-(4-methylbenzoyl)pyrrolidin-2-one (6e).**

Prepared according to GP 2 using 75 mg (0.26 mmol) of **5e**, the desired product **6e** (46 mg, 58%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/8:2) as a white solid. mp: 105-106 °C (*hexanes*). ¹H NMR (250 MHz, CDCl₃) δ 2.01-2.16 (m, 1H), 2.42 (s, 3H), 2.52-2.70 (m, 3H), 3.72 (s, 3H), 5.60-5.63 (m, 1H), 6.82 (d, *J*=9.1, 2H), 7.27-7.36 (m, 4H), 7.86 (d, *J*=7.9, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 21.6 (CH₃), 23.4, 30.3 (CH₂),

55.3 (CH₃), 64.0, 114.1, 124.4, 128.4, 129.7 (CH), 131.2, 131.3, 145.1, 152.2, 174.5, 195.9 (C). IR (thin film, cm⁻¹) ν 1696, 1605, 1512, 1247, 1226, 1188. MS (EI) m/z (relative intensity): 309 (13), 191 (12), 190 (100). HRMS calculated for C₁₉H₁₉NO₃ 309.1365 found 309.1366.

***N*-(4-Methoxyphenyl)-5-(naphthoyl)pyrrolidin-2-one (6f).**

Prepared according to GP 2 using 100 mg (0.26 mmol) of **5f**, the desired product **6f** (73 mg, 69%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/8:2) as a brown solid. mp: 50-52 °C (Hexanes). ¹H NMR (250 MHz, CDCl₃) δ 2.04-2.20 (m, 1H), 2.43-2.86 (m, 3H), 3.74 (s, 3H), 5.63-5.67 (m, 1H), 6.86 (d, J =8.7, 2H), 7.41 (d, J =8.7, 2H), 7.48-7.61 (m, 3H), 7.83-7.90 (m, 2H), 8.04 (d, J =8.3, 1H), 8.50 (d, J =7.1, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 23.2, 30.2 (CH₂), 55.3 (CH₃), 66.5, 114.3, 124.2, 124.9, 125.3, 126.9, 127.7, 128.5, 133.8 (CH), 130.5, 131.1, 132.5, 133.9, 157.5, 174.7, 200.2 (C). IR (thin film, cm⁻¹) ν 1694, 1512, 1295, 1248, 1179. MS (EI) m/z (relative intensity): 345 (11), 191 (12), 190 (100). HRMS calculated for C₂₂H₁₉NO₃ 345.1365 found 345.1357.

5-(4-*N*-Ethoxycarbonylamino)benzoyl)-*N*-(4-methoxyphenyl)pyrrolidin-2-one (6g).

Prepared according to GP 2 using 75 mg (0.20 mmol) of **5g**, the desired product **6g** 56 mg (71%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/6:4) as a white solid. mp: 161-163 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 1.29 (t, J =7.1, 3H), 2.02-2.16 (m,

1H), 2.54-2.70 (m, 3H), 3.70 (s, 3H), 4.21 (q, $J=7.1$, 2H), 5.59-5.62 (m, 1H), 6.79 (d, $J=9.1$, 2H), 7.32 (d, $J=9.1$, 2H), 7.53 (d, $J=9.1$, 2H), 7.73 (br s, 1H), 7.88 (d, $J=9.1$, 2H). ^{13}C NMR (62.8 MHz, CDCl_3) δ 14.4 (CH_3), 23.5, 30.3 (CH_2), 55.3 (CH_3), 61.5 (CH_2), 63.9, 114.1, 117.8, 124.5, 129.8 (CH), 128.2, 131.0, 143.9, 153.2, 157.3, 174.9, 195.0 (C). IR (thin film, cm^{-1}) ν 3306, 1730, 1683, 1589, 1531, 1507, 1219, 1172, 1061. MS (EI) m/z (relative intensity): 382 (9), 191 (13), 190 (100). HRMS calculated for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5$ 382.1529 found 382.1538.

***N*-(4-Methoxyphenyl)-5-(thiophene-2-carbonyl)pyrrolidin-2-one (6h).**

Prepared according to GP 2 using 75 mg (0.26 mmol) of **5h**, the desired product **6h** (59 mg, 74%) was isolated by FC (SiO_2 , CH_2Cl_2 :EtOAc/8:2) as a brown solid. mp: 118-119 °C (MeOH). ^1H NMR (250 MHz, CDCl_3) δ 2.11-2.23 (m, 1H), 2.50-2.74 (m, 3H), 3.72 (s, 3H), 5.40-5.44 (m, 1H), 6.82 (d, $J=8.7$, 2H), 7.15 (dd, $J=5.1$, 3.6, 1H), 7.33 (d, $J=8.7$, 2H), 7.71 (d, $J=5.1$, 1H), 7.77 (d, $J=3.6$, 1H). ^{13}C NMR (62.8 MHz, CDCl_3) δ 23.8, 30.3 (CH_2), 55.3 (CH_3), 65.2, 114.2, 124.5, 128.5, 132.6, 135.1 (CH), 130.9, 140.5, 157.3, 174.5, 190.0 (C). IR (thin film, cm^{-1}) ν 1694, 1681, 1513, 1415, 1247, 1032. MS (EI) m/z (relative intensity): 301 (13), 191 (12), 190 (100). HRMS calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{S}$ 301.0773 found 301.0767.

5-(4-Chlorobenzoyl)-*N*-(4-methoxyphenyl)pyrrolidin-2-one (6i).

Prepared according to GP 2 at 65 °C using 60 mg (0.19 mmol) of **5i**, the desired product **6i** (20 mg, 33%) was isolated by FC (SiO₂, EtOAc) as a brown solid. mp: 134-136 °C (*hexanes*). ¹H NMR (250 MHz, CDCl₃) δ 2.04-2.15 (m, 1H), 2.54-2.69 (m, 3H), 3.73 (s, 3H), 5.57-5.60 (m, 1H), 6.83 (d, *J*=8.7, 2H), 7.32 (d, *J*=8.7, 2H), 7.46 (d, *J*=8.7, 2H), 7.89 (d, *J*=8.7, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 23.3, 30.2 (CH₂), 55.3 (CH₃), 64.2, 114.2, 124.6, 129.3, 129.7 (CH), 130.9, 132.1, 140.6, 157.4, 174.4, 195.3 (C). IR (thin film, cm⁻¹) ν 1696, 1587, 1512, 1401, 1248, 1220, 1091, 1032, 829. MS (EI) *m/z* (relative intensity): 329 (6), 191 (13), 190 (100). HRMS calculated for C₁₈H₁₆ClNO₃ 329.0819 found 329.0815.

***N*-(4-Methoxyphenyl)-5-(2-methyl-but-2-enoyl)pyrrolidin-2-one (6m).**

Prepared according to GP 2 using 100 mg (0.39 mmol) of **5m**, the desired product **6m** (68 mg, 64%) was isolated by FC (SiO₂, CH₂Cl₂:EtOAc/8:2) as a brown oil. ¹H NMR (250 MHz, CDCl₃) δ 1.79 (d, *J*=7.1, 3H), 1.87-2.04 (m, 4H), 2.33-2.71 (m, 3H), 3.74 (s, 3H), 4.99-5.04 (m, 1H), 5.96 (q, *J*=7.1, 1H), 6.84 (d, *J*=9.1, 2H), 7.28 (d, *J*=9.1, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 15.7, 20.2 (CH₃), 22.1, 30.1 (CH₂), 55.3 (CH₃), 65.9, 114.1, 124.6, 137.8 (CH), 131.1, 132.9, 157.3, 174.5, 201.1 (C). IR (thin film, cm⁻¹) ν 1698, 1512, 1458, 1396, 1247, 1032, 829. MS (EI) *m/z* (relative intensity): 273 (7), 191 (12), 190 (100). HRMS calculated for C₁₆H₁₉NO₃ 273.1365 found 273.1364.

5-Cinnamoyl-N-(4-methoxyphenyl)pyrrolidin-2-one (6n).

Prepared according to GP 2 using 125 mg (0.41 mmol) of **5n**, the desired product **6n** (91 mg, 68%) was isolated by FC (SiO₂, EtOAc) as a brown solid. mp: 82-84 ° C (*hexanes*). ¹H NMR (250 MHz, CDCl₃) δ 2.04-2.13 (m, 1H), 2.45-2.76 (m, 3H), 3.73 (s, 3H), 4.95-5.00 (m, 1H), 6.78-6.87 (m, 3H), 7.34-7.53 (m, 7H), 7.70 (d, *J*=15.8, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 22.6, 30.5 (CH₂), 55.3 (CH₃), 67.0, 114.2, 120.5, 123.9, 128.5, 128.9, 131.1, 145.5 (CH), 131.0, 133.8, 157.2, 174.5, 197.2 (C). IR (thin film, cm⁻¹) ν 1694, 1609, 1513, 1296, 1249, 1181, 1085, 1033, 831. MS (EI) *m/z* (relative intensity): 321 (8), 191 (12), 190 (100). HRMS calculated for C₂₀H₁₉NO₃ 321.1365 found 321.1372.

General procedure 3 (GP 3). CAN mediated deprotection.

5-Benzoylpyrrolidin-2-one (7a).

To a cold solution (0 °C) of the pyrrolidinone **6a** (1.44 g, 4.87 mmol) in CH₃CN:H₂O (5:1, 60 mL) was added CAN (13.4 g, 24.4 mmol) in one portion. The reaction was stirred at 0 °C until completion (TLC, 30 min). The reaction was diluted with EtOAc, washed with saturated aqueous NaHCO₃ (2x50 mL), H₂O (1x50 mL), brine (1x50 mL), dried over Na₂SO₄, filtered, and solvent evaporated under reduced pressure. Purification of the crude by FC (SiO₂, EtOAc:MeOH, 96:4) afforded 656 mg

(71%) of the desired product **7a** as a white solid. mp: 155-156 °C (*n*-pentane). All spectroscopic data were in agreement with the literature.²

5-(4-Methoxybenzoyl)pyrrolidin-2-one (7b).

Prepared according to GP 3 using 167 mg (0.51 mmol) of **6b**, the desired product **7b** (85 mg, 76%) was isolated by FC (SiO₂, EtOAc:MeOH/96:4) as a white solid. mp: 139-141 °C (*n*-pentane). ¹H NMR (250 MHz, CDCl₃) δ 2.01-2.15 (m, 1H), 2.27-2.46 (m, 2H), 2.51-2.66 (m, 1H), 3.85 (s, 3H), 5.09 (dd, *J*=8.3, 5.7, 1H), 6.80 (br s, 1H), 6.94 (d, *J*=8.7, 2H), 7.89 (d, *J*=8.7, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 25.8, 29.4 (CH₂), 55.4 (CH₃), 58.2, 114.0, 130.6 (CH), 126.6, 163.9, 178.1, 195.5 (C). IR (thin film, cm⁻¹) ν 3243, 1696, 1599, 1510, 1241, 1171. MS (EI) *m/z* (relative intensity): 219 (4), 136 (10), 135 (100), 84 (30). HRMS calculated for C₁₂H₁₃NO₃ 219.0895 found 219.0892.

5-(4-Methylbenzoyl)pyrrolidin-2-one (7c).

Prepared according to GP 3 using 68 mg (0.22 mmol) of **6e**, the desired product **7c** (28 mg, 62%) was isolated by FC (SiO₂, EtOAc:MeOH/96:4) as a white solid. mp: 168-170 °C (*n*-pentane). ¹H NMR (250 MHz, CDCl₃) δ 2.04-2.19 (m, 1H), 2.29-2.56 (m, 5H), 2.59-2.70 (m, 1H), 5.13 (dd, *J*=8.7, 5.9, 1H), 6.51 (br s, 1H), 7.30 (d, *J*=8.1, 2H), 7.83 (d, *J*=8.1, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 21.7 (CH₃), 25.7, 29.4 (CH₂), 58.4, 128.4, 129.6 (CH), 131.3, 144.9, 177.9, 196.6 (C). IR (thin film, cm⁻¹) ν 3199, 3101, 1703, 1677, 1652, 1602, 1231. MS (EI) *m/z* (relative intensity): 203 (5), 120 (8), 119 (88), 91 (32), 84 (100). HRMS calculated for C₁₂H₁₃NO₂ 203.0946 found 203.0939.

² Ookawa, A.; Soai, K. *J. Chem. Soc.; Perkin Trans. I* **1987**, 1465.

5-(Thiophene-2-carbonyl)pyrrolidin-2-one (7d).

Prepared according to GP 3 using 39 mg (0.13 mmol) of **6h**, the desired product **7d** (20 mg, 79%) was isolated by FC (SiO₂, EtOAc:MeOH/96:4) as a white solid. mp: 164-166 °C (*n*-pentane). ¹H NMR (250 MHz, CDCl₃) δ 2.16-2.29 (m, 1H), 2.38-2.45 (m, 2H), 2.57-2.72 (m, 1 H), 4.97 (dd, *J*=8.7, 5.5, 1H), 6.44 (br s, 1H), 7.19 (dd, *J*=4.8, 3.9, 1H), 7.72-7.77 (m, 2H). ¹³C NMR (62.8 MHz, CDCl₃) δ 26.2, 29.3 (CH₂), 59.2, 128.5, 132.5, 134.8 (CH), 140.4, 178.0, 190.4 (C). IR (thin film, cm⁻¹) ν 3195, 3095, 1697, 1663, 1243. MS (EI) *m/z* (relative intensity): 195 (4), 110 (18), 84 (100). HRMS calculated for C₉H₉NO₂S 195.0354 found 195. 0361.

5-Cinnamoylpyrrolidin-2-one (7e).

Prepared according to GP 3 using 82 mg (0.26 mmol) of **6n**, the desired product **7e** (24 mg, 72%) was isolated by FC (SiO₂, EtOAc:MeOH/96:4) as a white solid. mp: 153-155 °C (*n*-pentane). ¹H NMR (250 MHz, CDCl₃) δ 2.03-2.20 (m, 1H), 2.38-2.65 (m, 3H), 4.53 (dd, *J*=8.7, 6.3, 1H), 6.70 (br s, 1H), 6.85 (d, *J*=16.0, 1H), 7.40-7.43 (m, 3H); 7.56-7.60 (m, 2H); 7.73 (d, *J*=16.0, 1H). ¹³C NMR (62.8 MHz, CDCl₃) δ 24.7, 29.5 (CH₂), 61.1, 120.6, 128.6, 129.1, 131.2, 145.3 (CH), 133.9, 178.1, 196.8 (C). IR (thin film, cm⁻¹) ν 3229, 3089, 1700, 1690, 1612, 1450, 1140, 1076. MS (EI) *m/z* (relative intensity): 215 (4), 131 (45), 103 (19), 84 (100), 77 (17). HRMS calculated for C₁₃H₁₃NO₂ 215.0946 found 215.0945.