

Supporting Information

Palladium-Catalyzed Three-Component Reaction: A Novel Method for the Synthesis of *N*-acyl Propiolamides

Yan He,^{a,†} Yingchun Wang,^{b,†} Xinping Liang,^a Bin Huang,^a Hengshan Wang,^{a,*} and
Yingming Pan^{a,*}

^a State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People's Republic of China

^b College of Chemistry and Chemical Engineering, Jishou University, Jishou 416000, People's Republic of China

Phone: (+86)-773-5846279; fax: (+86)-773-5803930; e-mail: panym@mailbox.gxnu.edu.cn;
whengshan@163.com

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General

Melting points were measured with a SGW X-4 melting point instrument (uncorrected). Proton nuclear magnetic resonance spectra (^1H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 400 MHz and 100 MHz, respectively, using CDCl_3 as reference standard (δ 7.26 ppm) for ^1H NMR and (δ 77 ppm) for ^{13}C NMR. HRMS (ion trap) were recorded using ESI. Precoated silica gel plates GF-254 were used for thin-layer analytical chromatography. Column chromatography was performed on silica gel (300-400 mesh). Unless otherwise noted, all reagents were obtained commercially and used without further purification.

General procedure for the synthesis of *N*-acyl propiolamide

A mixture of phenylacetylene (**1a**) (1.0 equiv., 1 mmol), benzyl isocyanide (**2a**) (2.5 equiv., 2.5 mmol), sodium acetate (**3a**) (2 equiv., 2 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mol %) and 6.0 mL CH_3CN was stirred at 60 °C for 2 h in the air. The progress of the reaction was monitored by thin-layer chromatography. Upon completion, the mixture was evaporated under reduced pressure, and the residue was separated by column chromatography (ethyl acetate/petroleum ether = 1:50 to 1:20) to give the pure product **4a** (232.9 mg, 84% isolated yield).

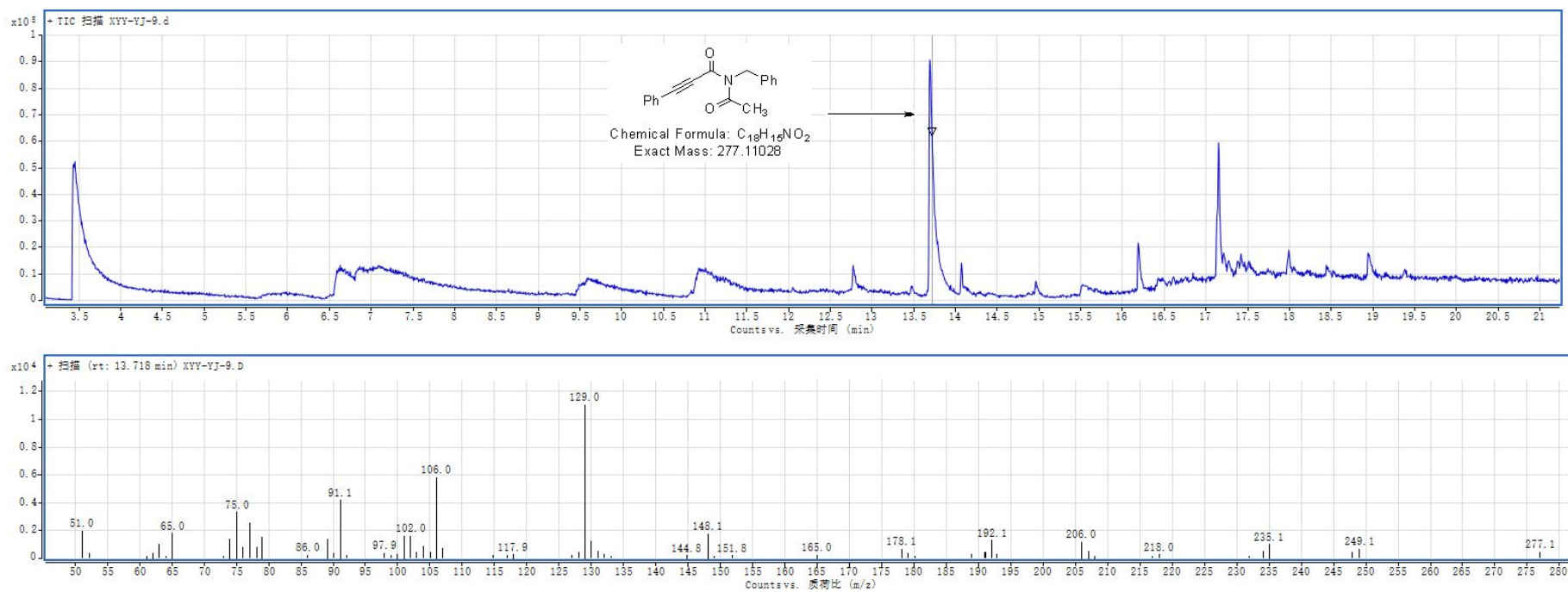


Figure S1. no ^{18}O -labeled product [^{18}O]-**4a** was detected in the presence of $H_2^{18}O$ under the standard conditions.

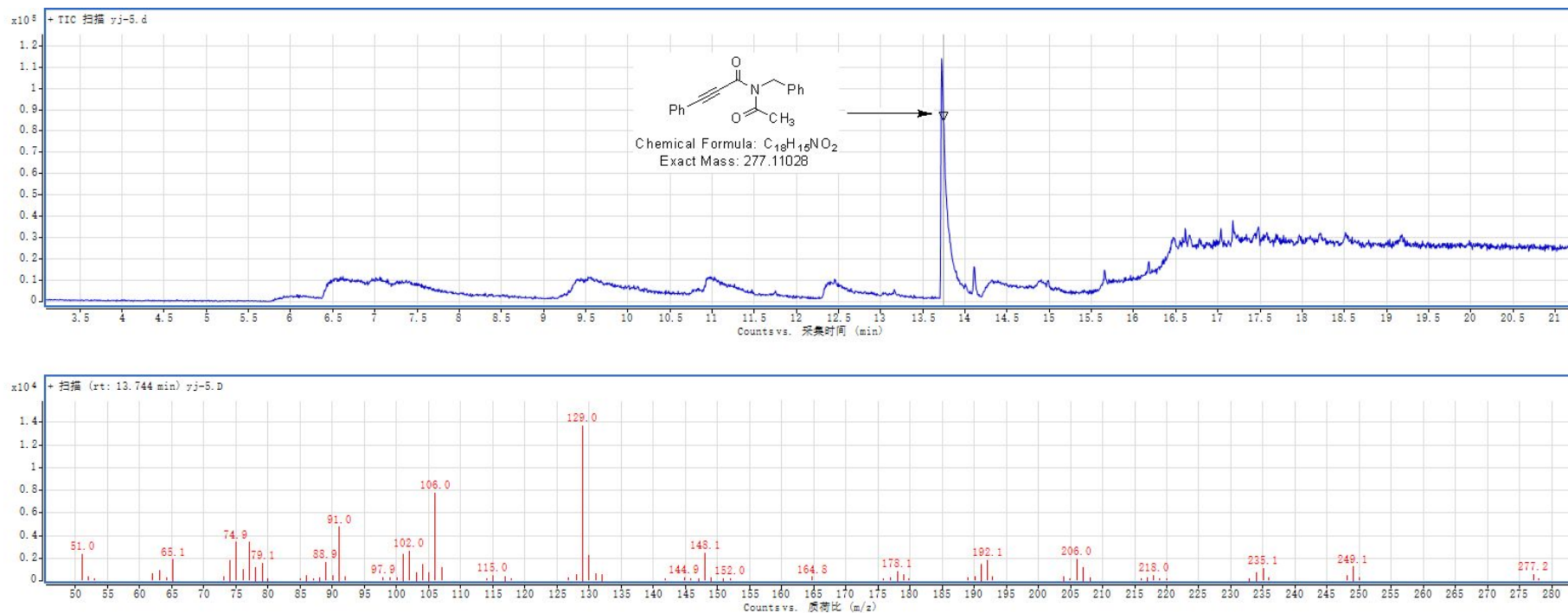
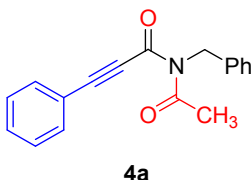
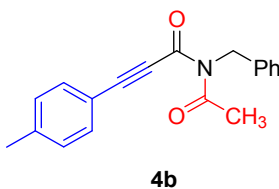


Figure S2. no ^{18}O -labeled product [^{18}O]-**4a** was detected in the presence of ^{18}O under the standard conditions.

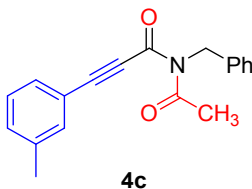
Spectral data of all compounds



N-acetyl-*N*-benzyl-3-phenylpropiolamide(**4a**). Light yellow oil (70.7 mg, 85%); ^1H NMR (400 MHz, CDCl_3) δ 7.5-7.4 (m, 3H), 7.4 (d, J = 7.2 Hz, 2H), 7.3 (dd, J = 5.8, 2.1 Hz, 4H), 7.3-7.2 (m, 1H), 5.3 (s, 2H), 2.6 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 155.7, 137.0, 132.7, 131.0, 128.7, 128.6, 127.5, 127.3, 119.3, 94.1, 82.7, 48.6, 27.6 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_2$ 278.1176 [$\text{M}+\text{H}^+$]; found 278.1169.

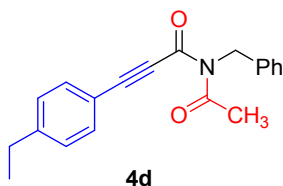


N-acetyl-*N*-benzyl-3-(*p*-tolyl)propiolamide(**4b**). Yellow solid (75.1 mg, 86%); m.p. 46-48 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.4 (dd, J = 9.3, 2.8 Hz, 3H), 7.3-7.3 (m, 4H), 7.3-7.3 (m, 2H), 7.2 (d, J = 7.9 Hz, 2H), 5.2 (s, 2H), 2.6 (s, 3H), 2.4 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 155.9, 141.9, 137.2, 132.8, 129.5, 128.7, 128.6, 128.5, 127.9, 127.5, 127.4, 116.3, 94.8, 82.6, 48.7, 27.6, 21.8 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ 292.1332 [$\text{M}+\text{H}^+$]; found 292.1334.

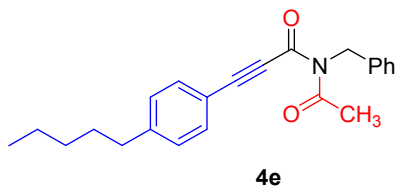


N-acetyl-*N*-benzyl-3-(*m*-tolyl)propiolamide(**4c**). Yellow solid (74.2 mg, 85%); m.p. 30-32 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.3 (d, J = 6.8 Hz, 4H), 7.2 (t, J = 5.0 Hz, 5H), 5.2 (s, 2H), 2.6 (s, 3H), 2.3 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 155.6,

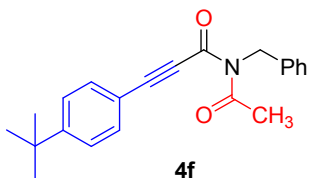
138.4, 137.0, 133.1, 131.8, 129.7, 128.5, 128.4, 127.4, 127.2, 119.1, 94.3, 82.4, 48.5, 27.5, 21.0 ppm; **HRMS** (m/z) (APCI): calcd for $C_{19}H_{18}NO_2$ 292.1332 $[M+H^+]$; found 292.1329.



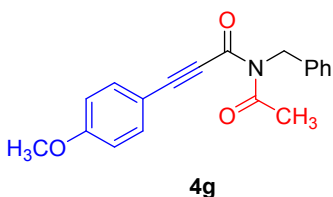
***N*-acetyl-*N*-benzyl-3-(4-ethylphenyl)propiolamide(4d).** Yellow oil (78.6 mg, 86%); **1H NMR** (400 MHz, $CDCl_3$) δ 7.4-7.4 (m, 2H), 7.4-7.3 (m, 4H), 7.3 (dd, J = 9.2, 2.7 Hz, 1H), 7.2 (d, J = 8.2 Hz, 2H), 5.2 (s, 2H), 2.7-2.6 (m, 2H), 2.6 (s, 3H), 1.2 (t, J = 7.6 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.6, 155.9, 148.1, 137.2, 132.9, 129.0, 128.6, 128.3, 127.5, 127.4, 116.6, 94.8, 82.6, 48.7, 29.0, 27.6, 15.1 ppm; **HRMS** (m/z) (APCI): calcd for $C_{20}H_{20}NO_2$ 306.1489 $[M+H^+]$; found 306.1489.



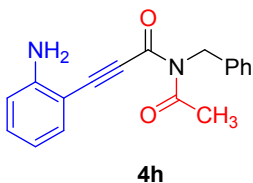
***N*-acetyl-*N*-benzyl-3-(4-pentylphenyl)propiolamide(4e).** Light yellow solid (91.6 mg, 88%); m.p. 31-33 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.4 (d, J = 8.0 Hz, 2H), 7.4-7.3 (m, 4H), 7.3-7.2 (m, 1H), 7.2 (d, J = 8.0 Hz, 2H), 5.2 (s, 2H), 2.6 (s, 3H), 2.6 (d, J = 8.0 Hz, 2H), 1.6 (dt, J = 14.4, 7.3 Hz, 2H), 1.4-1.3 (m, 5H), 0.9 (t, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 155.7, 146.7, 137.1, 132.7, 128.7, 128.5, 127.4, 127.2, 116.4, 94.6, 82.5, 48.5, 35.9, 31.3, 30.6, 27.5, 22.4, 13.9 ppm; **HRMS** (m/z) (APCI): calcd for $C_{23}H_{26}NO_2$ 348.1958 $[M+H^+]$; found 348.1967.



***N*-acetyl-*N*-benzyl-3-(4-(*tert*-butyl)phenyl)propiolamide(4f).** Yellow oil (88.9 mg, 89%); ^1H NMR (400 MHz, CDCl_3) δ 7.4 (dd, $J = 9.8, 3.3$ Hz, 4H), 7.3 (d, $J = 6.6$ Hz, 4H), 7.3 (dd, $J = 7.9, 4.8$ Hz, 1H), 5.2 (s, 2H), 2.6 (s, 3H), 1.3 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 155.8, 154.8, 137.1, 132.6, 128.5, 127.4, 127.3, 125.7, 116.3, 94.6, 82.4, 48.6, 35.0, 30.9, 27.5 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_2$ 334.1802 $[\text{M}+\text{H}^+]$; found 334.1811.

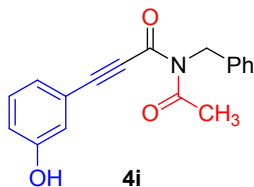


***N*-acetyl-*N*-benzyl-3-(4-methoxyphenyl)propiolamide(4g).** Yellow solid (79.2 mg, 86%); m.p. 60-62 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.4 (d, $J = 8.7$ Hz, 2H), 7.3-7.3 (m, 4H), 7.3 (d, $J = 3.0$ Hz, 1H), 5.2 (s, 2H), 3.8 (s, 3H), 2.6 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 161.8, 155.9, 137.1, 134.7, 128.5, 127.4, 127.2, 114.4, 111.1, 95.1, 82.4, 55.4, 48.6, 27.5 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3$ 308.1281 $[\text{M}+\text{H}^+]$; found 308.1287.

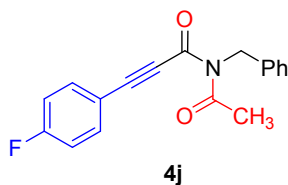


***N*-acetyl-3-(2-aminophenyl)-*N*-benzylpropiolamide(4h).** Yellow solid (74.4 mg, 85%); m.p. 108-110 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.3 (d, $J = 7.3$ Hz, 2H), 7.3-7.2 (m, 4H), 7.2 (dd, $J = 11.3, 4.2$ Hz, 1H), 6.7-6.6 (m, 2H), 5.2 (s, 2H), 4.4 (s, 2H), 2.6 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 155.2, 150.7, 136.7, 133.6, 132.7, 128.7, 127.5,

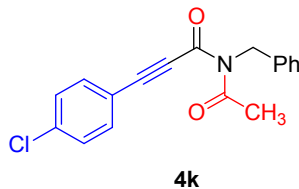
126.6, 117.5, 114.5, 102.9, 92.6, 89.0, 48.3, 26.9 ppm; **HRMS** (m/z) (APCI): calcd for $C_{18}H_{17}N_2O_2$ 293.1285 $[M+H^+]$; found 293.1292.



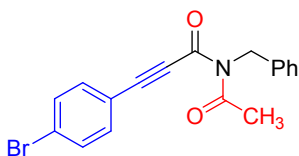
***N*-acetyl-*N*-benzyl-3-(3-hydroxyphenyl)propiolamide(4i).** Light yellow solid (72.0 mg, 82%); m.p. 93-96 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.3 (d, J = 4.4 Hz, 4H), 7.3-7.2 (m, 1H), 7.2-7.2 (m, 1H), 7.0 (d, J = 7.6 Hz, 1H), 7.0-6.9 (m, 2H), 6.5 (s, 1H), 5.22 (s, 2H), 2.63 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 156.0, 136.7, 130.0, 128.6, 127.6, 127.3, 125.0, 120.1, 119.2, 118.9, 94.6, 82.2, 48.7, 27.6 ppm; **HRMS** (m/z) (APCI): calcd for $C_{18}H_{16}NO_3$ 294.1125 $[M+H^+]$; found 294.1113.



***N*-acetyl-*N*-benzyl-3-(4-fluorophenyl)propiolamide(4j).** Light yellow solid (69.0 mg, 78%); m.p. 52-54 °C. **1H NMR** (400 MHz, $CDCl_3$) δ 7.5-7.4 (m, 2H), 7.3-7.3 (m, 4H), 7.3-7.3 (m, 1H), 7.1-7.0 (m, 2H), 5.2 (s, 2H), 2.6 (s, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5, 164.1 (d, $^1J_{CF}$ = 253 Hz), 155.6, 137.1, 135.1, 135.1 (d, $^3J_{CF}$ = 9.0 Hz), 128.7, 127.6, 127.2, 116.3 (d, $^2J_{CF}$ = 23.0 Hz), 93.1, 82.7, 48.6, 27.6 ppm; **HRMS** (m/z) (APCI): calcd for $C_{18}H_{15}FNO_2$ 296.1081 $[M+H^+]$; found 296.1080.

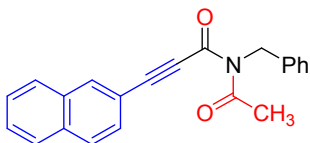


***N*-acetyl-*N*-benzyl-3-(4-chlorophenyl)propiolamide(4k).** Yellow solid (71.8 mg, 77%); m.p. 50-55 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.4 (t, *J* = 4.4 Hz, 4H), 7.3-7.3 (m, 4H), 7.3 (dd, *J* = 4.8, 3.1 Hz, 1H), 5.2 (s, 2H), 2.6 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 155.5, 137.5, 137.0, 133.9, 129.2, 128.7, 127.6, 127.2, 117.9, 92.8, 83.5, 48.6, 27.6 ppm; HRMS (*m/z*) (APCI): calcd for C₁₈H₁₅ClNO₂ 312.0786 [M+H⁺]; found 312.0791.



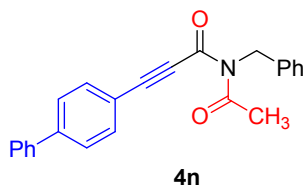
4l

***N*-acetyl-*N*-benzyl-3-(4-bromophenyl)propiolamide(4l).** Yellow oil (80.9 mg, 77%); ¹H NMR (400 MHz, CDCl₃) δ 7.5-7.5 (m, 2H), 7.3-7.3 (m, 1H), 7.3 (dd, *J* = 3.6, 1.5 Hz, 4H), 7.3-7.2 (m, 2H), 5.2 (s, 2H), 2.6 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 172.5, 155.5, 137.0, 134.0, 132.2, 128.7, 127.6, 127.2, 125.9, 118.3, 92.8, 83.6, 48.6, 27.6 ppm; HRMS (*m/z*) (APCI): calcd for C₁₈H₁₅BrNO₂ 356.0281, 358.0260 [M+H⁺]; found 356.0272, 358.0250.

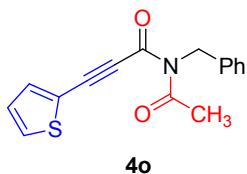


4m

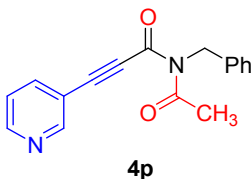
***N*-acetyl-*N*-benzyl-3-(naphthalen-2-yl)propiolamide(4m).** Light yellow solid (79.4 mg, 81%); m.p. 64-66 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.0 (s, 1H), 7.8 (dd, *J* = 12.8, 5.0 Hz, 3H), 7.5 (ddd, *J* = 10.9, 6.3, 3.6 Hz, 2H), 7.4 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.4-7.3 (m, 4H), 7.3-7.3 (m, 1H), 5.3 (s, 2H), 2.7 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 155.7, 137.1, 134.2, 134.0, 132.5, 128.6, 128.5, 128.2, 127.9, 127.8, 127.5, 127.3, 127.1, 116.5, 94.6, 83.0, 48.7, 27.6 ppm; HRMS (*m/z*) (ESI): calcd for C₂₂H₁₈NO₂ 328.1332 [M+H⁺]; found 328.1322.



3-([1,1'-biphenyl]-4-yl)-N-acetyl-N-benzylpropiolamide(4n). Light yellow solid (90.0 mg, 85%); m.p. 84-86 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.6 (t, *J* = 7.4 Hz, 4H), 7.6 (d, *J* = 8.3 Hz, 2H), 7.5 (t, *J* = 7.5 Hz, 2H), 7.4 (t, *J* = 6.4 Hz, 5H), 7.3 (d, *J* = 6.4 Hz, 1H), 5.3 (s, 2H), 2.7 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 172.5, 155.7, 143.8, 139.5, 137.0, 133.2, 128.9, 128.9, 128.6, 128.2, 127.5, 127.3, 127.2, 127.0, 118.0, 94.1, 83.3, 48.6, 27.5 ppm; HRMS (*m/z*) (APCI): calcd for C₂₄H₂₀NO₂ 354.1489 [M+H⁺]; found 354.1498.

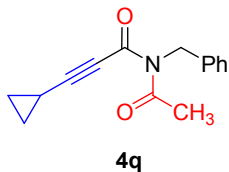


N-acetyl-N-benzyl-3-(thiophen-2-yl)propiolamide(4o). Brown oil (64.5 mg, 76%); ¹H NMR (400 MHz, CDCl₃) δ 7.5 (d, *J* = 4.9 Hz, 1H), 7.4 (d, *J* = 3.5 Hz, 1H), 7.3 (d, *J* = 4.3 Hz, 4H), 7.3-7.3 (m, 1H), 7.1 (dd, *J* = 4.8, 3.9 Hz, 1H), 5.2 (s, 2H), 2.6 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 155.5, 137.0, 136.7, 131.8, 128.6, 128.4, 127.7, 127.5, 127.3, 119.1, 88.2, 87.1, 48.5, 27.5 ppm; HRMS (*m/z*) (APCI): calcd for C₁₆H₁₄NO₂S 284.0740 [M+H⁺]; found 284.0759.

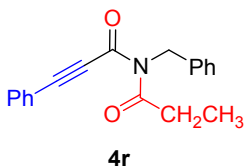


N-acetyl-N-benzyl-3-(pyridin-3-yl)propiolamide(4p). Light yellow solid (65.0 mg, 78%); m.p. 141–143 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.7-8.6 (m, 2H), 7.8-7.7 (m, 1H), 7.3-7.3 (m, 6H), 5.2 (s, 2H), 2.6 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.4,

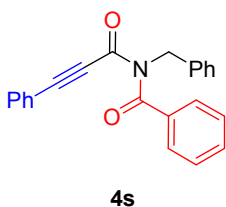
155.2, 153.0, 151.0, 139.6, 136.8, 128.7, 127.7, 127.0, 123.3, 116.9, 90.3, 85.4, 48.6, 27.6 ppm; **HRMS** (m/z) (APCI): calcd for $C_{17}H_{15}N_2O_2$ 279.1128 $[M+H^+]$; found 279.1126.



***N*-acetyl-*N*-benzyl-3-cyclopropylpropiolamide(4q).** Light yellow oil (53.5 mg, 74%); 1H NMR (400 MHz, $CDCl_3$) δ 7.3-7.3 (m, 2H), 7.3 (t, J = 6.2 Hz, 3H), 5.1 (s, 2H), 2.6 (s, 3H), 1.4-1.4 (m, 1H), 1.0-0.9 (m, 2H), 0.8-0.8 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 155.6, 137.2, 128.5, 127.3, 127.1, 101.7, 70.9, 48.5, 27.6, 9.5, -0.2 ppm; **HRMS** (m/z) (APCI): calcd for $C_{15}H_{16}NO_2$ 242.1176 $[M+H^+]$; found 242.1169.

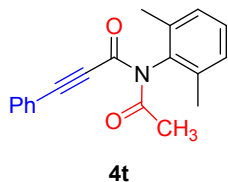


***N*-benzyl-3-phenyl-*N*-propionylpropiolamide(4r).** Yellow solid (70.7 mg, 81%); m.p. 53–55 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.4 (dd, J = 13.7, 7.3 Hz, 3H), 7.4-7.3 (m, 6H), 7.3-7.2 (m, 1H), 5.2 (s, 2H), 3.0 (q, J = 7.2 Hz, 2H), 1.2 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 155.5, 137.1, 132.6, 130.9, 128.6, 128.5, 127.4, 127.2, 119.4, 93.7, 82.8, 48.8, 32.9, 8.9 ppm; **HRMS** (m/z) (APCI): calcd for $C_{19}H_{18}NO_2$ 292.1332 $[M+H^+]$; found 292.1359.

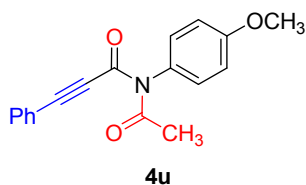


***N*-benzyl-*N*-(3-phenylpropioloyl)benzamide(4s).** Light yellow solid (81.3 mg, 80%); m.p. 73-75 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.6 (d, J = 7.3 Hz, 2H), 7.4 (t, J = 7.4 Hz, 3H),

7.3 (t, $J = 7.5$ Hz, 2H), 7.2 (t, $J = 7.4$ Hz, 3H), 7.2 (d, $J = 7.2$ Hz, 1H), 7.1 (t, $J = 7.7$ Hz, 2H), 7.0 (d, $J = 7.4$ Hz, 2H), 5.1 (s, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.0, 154.8, 136.8, 135.9, 132.6, 132.5, 130.5, 129.2, 128.5, 128.4, 128.4, 128.2, 127.6, 119.2, 95.9, 82.7, 48.5 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_2$ 340.1332 [$\text{M}+\text{H}^+$]; found 340.1346.



***N*-acetyl-*N*-(2,6-dimethylphenyl)-3-phenylpropiolamide(4t).** Light yellow solid (61.9 mg, 71%); m.p. 62–65 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.4–7.3 (m, 1H), 7.3–7.2 (m, 3H), 7.2 (d, $J = 7.6$ Hz, 2H), 7.1–7.1 (m, 2H), 2.7 (s, 3H), 2.2 (s, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 154.7, 136.7, 136.7, 133.2, 130.8, 129.1, 128.4, 128.3, 119.2, 93.1, 82.1, 26.8, 17.8 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ 292.1332 [$\text{M}+\text{H}^+$]; found 292.1312.



***N*-acetyl-*N*-(4-methoxyphenyl)-3-phenylpropiolamide(4u).** Yellow oil (63.2 mg, 72%); ^1H NMR (400 MHz, CDCl_3) δ 7.4 (dd, $J = 4.9, 3.7$ Hz, 1H), 7.3 (d, $J = 7.9$ Hz, 2H), 7.2–7.1 (m, 4H), 7.0–6.9 (m, 2H), 3.9 (s, 3H), 2.6 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 172.6, 159.9, 154.9, 132.9, 130.9, 130.7, 130.5, 128.4, 119.5, 114.6, 96.1, 82.8, 55.5, 27.2 ppm; HRMS (m/z) (APCI): calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_3$ 294.1128 [$\text{M}+\text{H}^+$]; found 294.1128.

Copies of ^1H and ^{13}C NMR spectra of compounds 4a-4u

