Supporting Information

for

Microwave-assisted efficient and facile synthesis of tetramic acid derivatives via a one-pot post-Ugi cascade reaction

Yong Li, Zheng Huang, Jia Xu, Yong Ding, Dian-Yong Tang, Jie Lei, Hong-yu Li, Zhong-Zhu Chen and Zhi-Gang Xu

Beilstein J. Org. Chem. 2020, 16, 663–669. doi:10.3762/bjoc.16.63

General information, general experimental procedure, characterization data, and copies of $^1$H and $^{13}$C NMR spectra
Table of contents

1. General information ........................................................................................................S3
2. Experimental procedures and characterization data ..................................................S4
3. References ....................................................................................................................S9
4. Copies of $^1$H and $^{13}$C NMR spectra ...................................................................S10
General information

$^1$H and $^{13}$C NMR were recorded on a Bruker 400 spectrometer. $^1$H NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), relative intensity. $^{13}$C NMR data are reported as follows: chemical shift in ppm (δ). LC/MS analyses were performed on a Shimadzu-2020 LC-MS instrument using the following conditions: Shim-pack VP-ODS C18 column (reversed phase, 150 × 4.6 mm); a linear gradient from 10% water and 90% acetonitrile to 75% acetonitrile and 25% water over 6.0 min; flow rate of 0.5 mL/min; UV photodiode array detection from 200 to 400 nm. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q Exactive Plus System. The products were purified by Biotage Isolera™ Spektra Systems and hexane/EtOAc solvent systems. All reagents and solvents were obtained from commercial sources and were used without further purification. All microwave irradiation experiments were carried out in a Biotage® Initiator Classic microwave apparatus with continuous irradiation power from 0 to 400 W with utilization of the standard absorbance level of 250 W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with microwave cavity. The reaction was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then, it was cooled to 50 °C with gas jet cooling.

All reagents, unless otherwise stated, were used as received from commercial suppliers.
Experimental procedures and characterization data

General procedure for tetramic acid derivatives 7a–l: In a similar manner as described in reference [1] the reactions were conducted as follows: To a magnetically stirred solution of the ethyl glyoxylate (1.0 mmol) in MeOH (1.0 mL) was added the amine (0.5 mmol) in a 5 mL microwave vial, and the resulting solution was stirred at room temperature for 10 min. The acid (0.50 mmol) and the isocyanide (0.50 mmol) were then added separately. The mixture was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC. The solvent was removed under a stream of nitrogen, and the residue was dissolved in DMF (3.0 mL), and then DBU (1.0 mmol) was added. The mixture was then placed in a microwave synthesizer and heated to 120 °C for 10 min. The mixture was then cooled to room temperature, and the residue was dissolved in EtOAc (15.0 mL). The solution was washed with brine, and the organic layer was dried with MgSO₄ and filtered. The filtrate was concentrated, which gave a residue that was purified by silica gel column chromatography (ethyl acetate/hexane, 10–60%) to afford the product 7a–l.

N-Benzyl-4-(4-chlorophenyl)-3-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7a): Yellow solid (65% yield).¹H NMR (400 MHz, DMSO-d₆) δ 12.23 (s, 1H, OH), 8.86 (t, J = 5.8 Hz, 1H, NH), 7.93 (d, J = 8.5 Hz, 2H, ArH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.45 (d, J = 8.5 Hz, 2H, ArH), 7.35 (t, J = 7.8 Hz, 2H, ArH), 7.23 – 7.16 (m, 3H, ArH), 7.12 (t, J = 7.3 Hz, 1H, ArH), 7.05 – 6.96 (m, 2H, ArH), 5.37 (s, 1H, CH), 4.31 – 4.23 (m, 2H, CH₂). ¹³C NMR (100 MHz, DMSO-d₆) δ 170.33, 166.73, 165.99, 139.03, 138.59, 131.07, 130.73, 129.69, 129.12, 128.59, 128.35, 127.25, 124.02, 120.93, 104.39, 64.55, 55.37, 42.94. HRMS: m/z calculated for C₂₄H₂₀ClN₂O₃ [M+H]⁺: 419.11570, found 419.11606. The analytical data matched those reported in the literature [2].
**N,1-Dibenzyl-4-(4-chlorophenyl)-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7b):** Yellow solid (64% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.98 (s, 1H, OH), 8.77 (s, 1H, NH), 7.99 (d, J = 8.7 Hz, 2H, ArH), 7.45 – 7.40 (m, 2H, ArH), 7.33 (t, J = 7.3 Hz, 4H, ArH), 7.29 – 7.22 (m, 4H, ArH), 7.19 (d, J = 7.1 Hz, 2H, ArH), 4.41 (s, 1H), 4.30 – 4.22 (m, 2H, CH$_2$), 4.00 (d, J = 15.7 Hz, 1H, CH$_2$). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 171.61, 165.42, 166.42, 163.67, 163.15, 139.16, 138.07, 131.10, 130.86, 129.28, 128.96, 128.76, 128.31, 127.91, 127.85, 127.58, 127.42, 103.69, 63.74, 44.18, HRMS: m/z calculated for C$_{25}$H$_{21}$ClN$_2$O$_3$ [M+H]$^+$: 433.1315, found 433.1319. The analytical data matched those reported in the literature [2].

**N-Benzyl-4-(3,4-dimethoxyphenyl)-3-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7c):** Yellow solid (57% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.83 (s, 1H, OH), 8.86 (t, J = 5.8 Hz, 1H, NH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 7.49 (s, 1H, ArH), 7.40 (d, J = 8.3 Hz, 1H, ArH), 7.33 (t, J = 7.9 Hz, 2H, ArH), 7.21 (d, J = 6.5 Hz, 3H, ArH), 7.10 (t, J = 7.3 Hz, 1H, ArH), 7.04 (d, J = 5.9 Hz, 2H, ArH), 6.98 (d, J = 8.5 Hz, 1H, ArH), 5.33 (s, 1H, CH$_2$), 4.32 – 4.24 (m, 2H, CH$_2$), 3.77 (s, 6H, OCH$_3$). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 169.63, 165.15, 163.67, 147.45, 146.92, 138.01, 137.84, 128.02, 127.51, 126.18, 122.76, 120.06, 119.58, 111.19, 104.67, 63.16, 54.84, 41.84. HRMS: m/z calculated for C$_{26}$H$_{25}$N$_2$O$_5$ [M+H]$^+$: 445.17580, found 445.17474. The analytical data matched those reported in the literature [2].

S5
**N-Benzyl-1-(4-bromophenyl)-4-(2-fluorophenyl)-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7d):** Yellow solid (69% yield).\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.13 (s, 1H, OH), 9.02 (s, 1H, NH), 7.58 (d, \(J = 9.0\) Hz, 2H, ArH), 7.50 (d, \(J = 8.9\) Hz, 2H, ArH), 7.46 – 7.32 (m, 1H, ArH), 7.40 – 7.33 (m, 1H, ArH), 7.28 – 7.18 (m, 5H, ArH), 7.14 – 7.06 (m, 2H, ArH), 5.37 (s, 1H, CH), 4.31 (d, \(J = 5.9\) Hz, 2H, CH\(_2\)). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 170.38, 165.89, 161.77, 159.31, 139.16, 138.45, 132.43, 132.39, 131.91, 129.55, 128.60, 127.39, 127.25, 124.20, 124.17 121.68, 118.79, 115.93, 115.72, 115.26, 100.79, 64.50, 42.90. HRMS: \(m/z\) calculated for C\(_{24}\)H\(_{19}\)BrF\(_N\)\(_2\)O\(_3\) [M+H]^+: 481.05576, found 481.05576. The analytical data matched those reported in the literature[2].

**N-Benzyl-3-hydroxy-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7e):** Yellow solid (73% yield).\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.80 (t, \(J = 5.9\) Hz, 1H, NH), 8.36 (d, \(J = 9.1\) Hz, 2H, ArH), 8.21 (d, \(J = 9.1\) Hz, 2H, ArH), 7.48 (d, \(J = 9.0\) Hz, 2H, ArH), 7.23 – 7.16 (m, 3H, ArH), 6.98 (d, \(J = 3.5\) Hz, 2H, ArH), 6.92 (d, \(J = 9.0\) Hz, 2H, ArH), 5.25 (s, 1H, CH), 4.36 – 4.18 (m, 2H, CH\(_2\)), 3.77 (s, 3H, OCH\(_3\)). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 169.35, 165.07, 155.27, 143.15, 139.74, 138.01, 130.50, 127.43, 126.22, 126.05, 125.77, 122.68, 122.61, 113.22, 64.78, 54.66, 41.76. HRMS: \(m/z\) calculated for C\(_{25}\)H\(_{22}\)N\(_3\)O\(_6\) [M+H]^+: 460.15037, found 460.15076. The analytical data matched those reported in the literature[2].

**N-Benzyl-1-(2-bromobenzyl)-3-hydroxy-4-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7f):** Yellow solid (67% yield).\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 11.54 (s, 1H, OH), 8.78 (s, 1H, NH), 7.87 (dd, \(J = 9.2, 2.4\) Hz, 2H, OH), 7.51 (d, \(J = 8.9\) Hz, 2H, ArH), 3.83 (s, 3H, OCH\(_3\)). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 170.38, 165.07, 155.27, 143.15, 139.74, 138.01, 130.50, 127.77, 126.22, 126.05, 125.77, 122.68, 122.61, 113.22, 64.78, 54.66, 41.76. HRMS: \(m/z\) calculated for C\(_{25}\)H\(_{22}\)N\(_3\)O\(_6\) [M+H]^+: 460.15037, found 460.15076. The analytical data matched those reported in the literature[2].
ArH), 7.63 (d, J = 7.9 Hz, 1H, ArH), 7.37 – 7.19 (m, 7H, ArH), 7.10 (d, J = 7.5 Hz, 1H, ArH), 6.94 (d, J = 7.7 Hz, 2H, ArH), 4.85 (d, J = 16.6 Hz, 1H, CH₂), 4.57 (d, J = 2.6 Hz, 1H,CH₂), 4.36 (dd, J = 14.7, 5.9 Hz, 1H), 4.20 (dd, J = 21.9, 11.3 Hz, 2H), 3.76 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-d₆) δ 172.21, 166.08, 164.52, 158.06, 139.08, 136.93, 132.98, 129.56, 129.07, 128.75, 128.39, 127.82, 127.40, 124.43, 122.54, 113.78, 104.66, 63.83, 55.48, 44.78, 43.22. HRMS: m/z calculated for C₂₆H₂₄BrN₂O₄ [M+H]⁺: 507.09140, found 507.09128.

N-Cyclohexyl-3-hydroxy-4-(4-methoxyphenyl)-5-oxo-1-phenethyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7g): Yellow solid (51% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 11.23 (s, 1H, OH), 8.22 (d, J = 7.8 Hz, 1H, NH), 7.82 (d, J = 8.8 Hz, 2H, ArH), 7.35 – 7.27 (m, 2H, ArH), 7.22 (d, J = 7.4 Hz, 3H, ArH), 6.91 (d, J = 8.9 Hz, 2H, ArH), 4.54 (s, 1H, CH), 3.87 – 3.78 (m, 1H, CH), 3.75 (s, 3H, OCH₃), 3.62 (d, J = 4.2 Hz, 1H, CH₂), 3.09 – 2.98 (m, 1H, CH₂), 2.91 – 2.82 (m, 1H, CH₂), 2.78 – 2.64 (m, 1H, CH₂), 1.79 (d, J = 8.6 Hz, 2H, CH₂), 1.70 (d, J = 12.6 Hz, 2H, CH₂), 1.57 (d, J = 12.1 Hz, 1H, CH₂), 1.32 – 1.22 (m, 5H, CH₂). ¹³C NMR (100 MHz, DMSO-d₆) δ 171.80, 165.11, 164.05, 157.88, 139.66, 128.94, 128.91, 126.67, 124.71, 113.69, 104.84, 63.65, 55.45, 48.71, 41.93, 34.41, 32.82, 32.43, 25.65, 24.86. HRMS: m/z calculated for C₂₆H₃₁N₂O₄ [M+H]⁺: 435.22783, found 435.22805. The analytical data matched those reported in the literature[2].

N-Cyclohexyl-1-(2,6-dimethylphenyl)-3-hydroxy-4-(4-nitrophenyl)-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7h): Yellow solid (75% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (d, J = 9.1 Hz, 2H, ArH), 8.27 – 8.17 (m, 2H, ArH), 7.97 (d, J = 7.7 Hz, 1H, NH), 7.25 – 7.03 (m, 3H, ArH), 4.80 (s, 1H,
CH), 3.48-3.46 (m, 1H, CH), 2.14 (s, 3H, CH₃), 2.12 (s, 3H, CH₃), 1.80 – 1.64 (m, 2H, CH₂), 1.54 – 1.38 (m, 2H, CH₂), 1.26 – 1.11 (m, 4H, CH₂), 1.09 – 0.98 (m, 1H, CH₂), 0.85 – 0.71 (m, 1H, CH₂). ¹³C NMR (100 MHz, DMSO-d₆) δ 170.46, 164.54, 144.76, 140.23, 139.53, 137.45, 135.28, 128.59, 128.22, 127.29, 123.69, 102.27, 64.82, 48.57, 32.33, 25.55, 24.78, 18.48, 18.25. HRMS: m/z calculated for C_{25}H_{28}N₃O₅ [M+H]^+: 450.20235, found 450.20279. The analytical data matched those reported in the literature [2].

4-(2-Bromophenyl)-3-hydroxy-5-oxo-N₁-diphenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7i): Yellow solid (67% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 11.93 (s, 1H, OH), 10.64 (s, 1H, NH), 7.72 – 7.56 (m, 5H, ArH), 7.44 (t, J = 7.3 Hz, 1H, ArH), 7.43 – 7.28 (m, 6H, ArH), 7.17 – 6.98 (m, 2H, ArH), 5.54 (s, 1H, CH). ¹³C NMR (100 MHz, DMSO-d₆) δ 170.21, 165.66, 139.07, 138.81, 133.58, 132.75, 132.14, 130.12, 129.38, 129.36, 127.72, 125.44, 124.54, 123.56, 119.79, 119.24, 107.77, 64.53. HRMS: m/z calculated for C_{23}H_{18}BrN₂O₃ [M+H]^+: 449.04953, found 449.04910. The analytical data matched those reported in the literature [2].

4-(4-Chlorophenyl)-3-hydroxy-1-isobutyl-5-oxo-N-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7j): Yellow solid (53% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 11.99 (s, 1H, OH), 10.40 (s, 1H, NH), 8.00 (d, J = 8.6 Hz, 2H, ArH), 7.65 (d, J = 7.9 Hz, 2H, ArH), 7.45 – 7.33 (m, 4H, ArH), 7.13 (d, J = 7.4 Hz, 1H, ArH), 4.79 (s, 1H, CH), 3.39 – 3.33 (m, 1H, CH₂), 2.81 (dd, J = 13.8, 6.4 Hz, 1H, CH₂), 2.03 – 1.86 (m, 1H, CH), 0.86 (d, J = 6.6 Hz, 3H, CH₃), 0.80 (d, J = 6.6 Hz, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-d₆) δ 171.86, 165.95, 164.98, 138.85, 131.23, 130.76, 129.34, 129.22, 128.27, 124.60, 120.10, 103.87, 64.97, 48.23, 27.48, 20.63, 20.39. HRMS: m/z calculated for C_{21}H_{22}ClN₂O₃ [M+H]^+: 385.13135, found 385.13074. The analytical data matched those reported in the literature [2].
1-Benzyl-4-(4-bromophenyl)-N-(2,6-dimethylphenyl)-3-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxamide (7k): Yellow solid (63% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 10.27 (s, 1H, OH), 9.50 (s, 1H, NH), 8.44 (d, J = 8.6 Hz, 2H, ArH), 7.32 (t, J = 7.2 Hz, 2H, ArH), 7.21 (dd, J = 18.8, 8.0 Hz, 5H, ArH), 7.03 (s, 3H, ArH), 5.23 (d, J = 15.2 Hz, 1H, CH$_2$), 3.94 (s, 1H, CH), 3.89 (d, J = 15.2 Hz, 1H, CH$_2$), 2.13 (s, 6H, ArCH$_3$). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 182.44, 176.42, 167.45, 139.76, 138.30, 135.75, 135.55, 130.00, 128.83, 128.18, 127.92, 127.13, 126.51, 125.07, 112.18, 90.05, 65.26, 44.23, 18.66. HRMS: m/z calculated for C$_{26}$H$_{24}$BrN$_2$O$_3$ [M+H]$^+$: 491.09648, found 491.09662.

4-(Benzo[d][1,3]dioxol-5-yl)-N-(2,6-dimethylphenyl)-3-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-2-carboxamide (7l): Yellow solid (71% yield). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 10.32 (s, 1H, OH), 9.67 (s, 1H, NH), 8.15 (s, 1H, ArH), 8.01 (d, J = 8.9 Hz, 1H, ArH), 7.73 (d, J = 8.1 Hz, 2H, ArH), 7.19 (t, J = 7.8 Hz, 2H, ArH), 7.00 (s, 3H, ArH), 6.82 (t, J = 7.2 Hz, 1H, ArH), 6.71 (d, J = 8.3 Hz, 1H, ArH), 5.86 (s, 2H, OCH$_2$O), 4.81 (s, 1H, CH), 2.13 (s, 6H, ArCH$_3$). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 181.13, 175.23, 167.35, 146.41, 141.84, 141.40, 135.90, 135.68, 133.08, 128.51, 127.89, 126.52, 120.13, 117.96, 116.52, 107.62, 104.67, 66.66, 18.71. HRMS: m/z calculated for C$_{26}$H$_{23}$N$_2$O$_5$ [M+H]$^+$: 443.16015, found 443.16035.

References

[1] Li, Y.; Lei, J.; Chen, Z.; Tang, D.; Yuan, H.; Wang, M.; Zhu, J.; Xu, Z. Eur. J. Org. Chem. 2016, 2016, 5770-5776.

[2] Chen, Z.; Xu, Z. CN 000107434778 A, 2017.12.05.
Copies of $^1$H and $^{13}$C NMR spectra

Compound 7a
Compound 7c
Compound 7d
Compound 7e
Compound 7f
Compound 7g
Compound 7h
Compound 71
Compound 7j
Compound 71

[Chemical structure and NMR spectrum]