Supplementary Material for Organic & Biomolecular Chemistry

A Straightforward Approach towards Thiazoles and Endothiopeptides *via* Ugi Reaction

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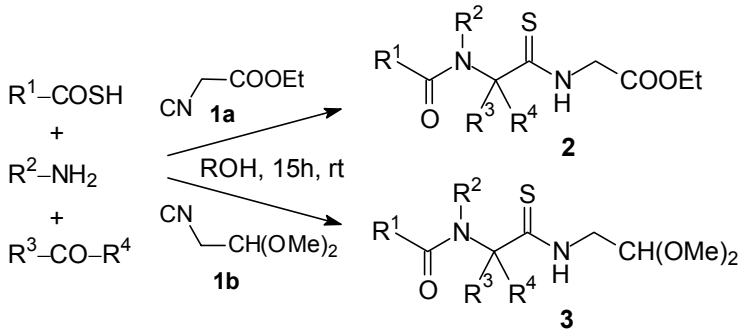
Analytical / Spectroscopic Data of Endothiopeptides and Thiazoles

Due to the formation of rotamers and a resulting poor resolution of some NMR spectra, a few signals in the ^{1}H and ^{13}C NMR spectra (mainly quarternary centers) are missing.

The Ugi products were obtained according to:



Ethyl [2-(benzoyl-benzylamino)-3-methyl-thiobutyryl]-glycinate (2b)

According to the general procedure for thio Ugi reactions, **2b** was obtained after purification by column chromatography (hexanes/EtOAc 8:2) and recrystallisation (PE/EtOAc 1:1) in a 2.00 mmol range as white rhombic crystals in 82 % yield , m_p = 93–95°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 1.25 (t, *J* = 7.0, 3H), 3.04 (bs, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 4.27 (d, *J* = 4.9 Hz, 1 H), 4.43 (d, *J* = 5.5 Hz, 1 H), 4.59 (d, *J* = 5.8 Hz, 1 H), 7.09–7.70 (m, 8 H), 7.72 (m, 2 H), 10.4 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ = 14.2, 20.4, 28.2, 44.1, 47.3, 60.4, 61.5, 126.7, 127.9, 128.4, 128.6, 130.0, 136.5, 168.1, 174.7, 202.8. HRMS (CI): calcd. for $C_{23}H_{28}N_2O_3S$ ($[M]^+$), 412.1821; found, 412.1850. Elemental analysis: $C_{23}H_{28}N_2O_3S$ (412.55) . calcd.: C 66.96 H 6.79 N 6.79; found: C 67.33 H 6.76 N 6.19.

Ethyl [2-(acetyl-benzylamino)-3,3-dimethyl-thiobutyryl]-glycinate (2c)

According to the general procedure for thio Ugi reactions, **2c** was obtained after purification by column chromatography (hexanes/EtOAc 7:3) and recrystallisation (PE/EtOAc 3:7) in a 2.00 mmol range as orange crystals in 72 % yield, m_p = 106–107°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 1.24 (t, *J* = 7.3 Hz, 3 H), 2.10 (s, 3H), 4.15–4.21 (m, 4 H), 4.22–4.35 (m, 3 H), 7.12–7.25 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) : δ = 14.1, 29.7, 36.8, 45.0, 61.5, 62.1, 128.8, 168.2, 174.5, 201.1. HRMS (CI): calcd. for $C_{19}H_{28}N_2O_3S$ ($[M]^+$), 364.1821; found, 364.1819. Elemental analysis: $C_{19}H_{28}N_2O_3S$ (364.51) calcd.: C 62.61 H 7.74 N 7.69; found: C 62.10 H 7.74 N 7.57.

Ethyl [2-(benzoyl-benzylamino)-3,3-dimethyl-thiobutyryl]-glycinate (2d)

According to the general procedure for thio Ugi reactions, **2d** was obtained after purification by column chromatography (hexanes/EtOAc 8:2) and recrystallisation (PE/EtOAc 3:7) in a 2.00 mmol range as white needles in 89 % yield, m_p = 144–145°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 4.18–4.22 (m, 3 H), 4.26 (d, *J* = 15.2 Hz, 1 H), 4.43 (dd, *J* = 18.3 Hz, *J* = 5.8 Hz, 2 H), 4.77 (bs, 1 H), 7.06–7.41 (m, 8 H), 7.72 (m, 2 H), 10.30 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 29.8, 36.9, 47.7, 61.5, 126.8, 127.9, 128.5, 128.8, 130.1, 136.7, 168.3, 175.4, 201.4. HRMS (CI): calcd. for $C_{24}H_{30}N_2O_3S$ ($[M]^+$), 426.1977; found, 426.1971. Elemental analysis: $C_{24}H_{30}N_2O_3S$ (426.58) calcd.: C 67.58 H 7.09 N 6.57; found: C 67.45 H 6.89 N 6.87.

Ethyl [2-(benzoyl-benzylamino)-2-phenylthioacetyl]-glycinate (2e)

According to the general procedure for thio Ugi reactions, **2e** was obtained after purification by column chromatography (hexanes/EtOAc 6:4) and recrystallisation (*tert*-butyl-methyl-ether) in a 2.00 mmol range as white cubes in 65 % yield, m_p = 132–134°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.3 Hz, 3 H), 4.24 (q, *J* = 7.3 Hz, 2 H), 4.38 (dd, *J* = 18.2 Hz, *J* = 4.3 Hz, 1 H), 4.45 (dd, *J* = 18.2 Hz, *J* = 4.8 Hz, 1 H), 4.62 (s, 1 H), 4.64 (s, 1 H), 6.00 (s, 1 H), 7.15–7.78 (m, 15 H), 8.45 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 44.9, 60.4, 61.9, 72.3, 126.7, 127.1, 128.4, 129.1, 135.1, 137.0, 138.2, 168.5, 173.6, 201.4. Elemental analysis: $C_{26}H_{26}N_2O_3S$ (446.57) calcd.: C 69.93 H 5.87 N 6.27; found: C 69.93 H 5.90 N 6.31.

Ethyl [1-(benzoyl-benzylamino)-cyclohexanecarbothioyl]-glycinate (2f)

According to the general procedure for thio Ugi reactions, **2f** was obtained after purification by column chromatography (hexanes/EtOAc 8:2) and recrystallisation (*tert*-butyl-methylether) in a 2.00 mmol range as white cubes in 55 % yield, m_p = 120–122°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.3 Hz, 3 H), 1.49–1.79 (m, 8 H), 2.21 (m, 2 H), 4.10 (d, *J* = 4.6 Hz, 2 H), 4.27 (q, *J* = 7.0 Hz, 2 H), 4.64 (s, 2 H), 7.01 (m, 2 H), 7.02–7.14 (m, 3 H), 7.42–7.44 (m, 3 H), 7.65 (m, 2 H), 10.54 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 22.4, 25.4, 35.3, 47.9, 52.2, 61.5, 69.8, 127.4, 128.0, 128.4, 128.7, 130.9, 137.2, 168.5, 176.9, 208.4. HRMS (CI): calcd. for $C_{25}H_{30}N_2O_3S$ ($[M]^+$), 438.1977; found, 438.1972. Elemental analysis: $C_{25}H_{30}N_2O_3S$ (438.59) calcd.: C 68.46 H 6.89 N 6.39; found: C 68.53 H 6.76 N 6.34.

Ethyl (2-acetylamino-3,3-dimethyl-thiobutyryl)-glycinate (2g)

2g was obtained according to the general procedure for thio Ugi reactions. As amine served a 2 M solution of ammonia in methanol. So 2g could be isolated after purification by column chromatography (hexanes/EtOAc 1:1) and recrystallisation (*tert*-butyl-methylether) in a 2.00 mmol range as a white solid in 31 % yield, m_p = 148–149°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (s, 9 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 4.12 (dd, *J* = 18.3 Hz, *J* = 4.7 Hz , 1 H), 4.16 (q, *J* = 6.7 Hz, 2 H), 4.44 (dd, *J* = 18.3Hz, *J* = 5.3 Hz, 1 H), 4.76 (d, *J* = 9.5 Hz, 1 H), 6.69 (d, *J* = 9.5 Hz, 1 H), 8.96 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.1, 22.7, 25.8, 35.4, 46.0, 59.4, 63.8, 167.1, 168.6, 202.1. HRMS (CI): calcd. for $C_{12}H_{23}N_2O_3S$ ($[M]^+$), 275.1429; found, 275.1400. Elemental analysis: $C_{12}H_{22}N_2O_3S$ (274.39) calcd.: C 52.53 H 8.08 N 10.21; found: C 52.39 H 7.86 N 10.05.

Ethyl (2-benzoylamino-3,3-dimethyl-thiobutyryl)-glycinate (2h)

2h was obtained according to the general procedure for thio Ugi reactions. As amine served a 2 M solution of ammonia in methanol. So 2h could be isolated after purification by column chromatography (hexanes/EtOAc 1:1) and recrystallisation (*tert*-butyl-methylether) in a 2.00 mmol range as a white solid in 35 % yield, m_p = 160–162°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 1.20 (t, *J* = 7.3 Hz, 3 H), 4.04 (dd, *J* = 18.0 Hz, *J* = 4.7 Hz, 1 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 4.56 (dd, *J* = 18.0 Hz, *J* = 5.7 Hz, 1 H), 5.08 (d, *J* = 9.5 Hz, 1 H), 7.37 (m, 2 H), 7.44 (m, 1 H), 7.47 (d, *J* = 9.2 Hz, 1 H), 7.76 (m, 2 H), 9.27 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 26.9, 36.5, 46.9, 61.7, 65.1, 127.1, 128.7, 131.8, 134.2, 166.7, 167.9, 203.1. Elemental analysis: $C_{17}H_{24}N_2O_3S$ (336.45) calcd.: C 60.69 H 7.19 N 8.33; found: C 60.66 H 7.10 N 8.31.

N-(2,2-Dimethoxy-ethyl)-2-(acetyl-benzylamino)-3-methyl-thiobutyric acid amide (3b)

According to the general procedure for thio Ugi reactions, **3b** was obtained after purification by column chromatography (hexanes/EtOAc 1:1) in a 2.00 mmol range as a yellow oil in 51 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.67 (d, *J* = 6.0 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3 H), 2,05 (s, 3 H), 2.75 (bs, 1 H), 3.34 (s, 6 H), 3.81 (t, *J* = 5.7 Hz, 2 H), 4.49 (t, *J* = 5.1 Hz, 1 H), 4.54 (m, 2 H), 4.66 (m, 1 H), 7.31–7.25 (m, 5 H), 9.39 (d, *J* = 6.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 22.4, 30.4, 46.7, 49.2, 53.2, 57.0, 103.4, 129.5, 129.8, 130.8, 138.2, 175.7, 204.1. GC-MS(EI) calcd. for $C_{18}H_{28}N_2O_3S$, 352; found, 352.

N-(2,2-Dimethoxy-ethyl)-2-(benzoyl-benzylamino)-3,3-dimethyl-thiobutyric acid amide (3c)

According to the general procedure for thio Ugi reactions, **3c** was obtained after purification by column chromatography (hexanes/EtOAc 7:3) in a 2.00 mmol range as a yellow oil in 71 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (s. 9 H), 3.35 (s, 6 H), 3.70 (m, 2 H), 4.24 (m, 1 H), 4.46 (m, 1 H), 4.56 (t, *J* = 5.7 Hz, 1 H), 4.76 (s, 1 H), 7.02–7.33 (m, 10 H), 10.20 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 29.8, 36.8, 47.3, 54.3, 60.3, 100.8, 126.6, 127.5, 127.9, 128.2, 128.5, 131.5, 136.8, 175.3, 200.6. HRMS (CI) calcd. for $C_{24}H_{32}N_2O_3S$ ($[M]^+$), 428.2134; found, 428.2126.

N-(2,2-Dimethoxy-ethyl)-2-(acetyl-benzylamino)-1-cyclohexyl-thiobutyric acid amide (3d)

The reaction was started according to the general procedure for thio Ugi reactions. When the reaction was complete, the solvent was removed *in vacuo* and the crude product was purified by recrysallisation from methanol. So **3d** could be obtained in a 2.00 mmol range as white rhombic crystals in 55 % yield, m_p = 115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18–1.55 (m, 8 H), 2.01 (s, 3 H), 2.84 (m, 2 H), 3.35 (s, 6 H), 3.78 (t, *J* = 5.4 Hz, 2 H), 4.55 (t, *J* = 5.4 Hz, 1 H), 4.68 (s, 2 H), 7.17–7.30 (m, 5 H), 8.84 (s, 1 H). ^{13}C NMR (22.9, 24.8, 25.2, 35.1, 47.4, 49.8, 54.1, 69.3, 101.1, 125.9, 127.1, 128.7, 138.8, 174.4, 205.6. HRMS (CI) calcd. for $C_{20}H_{30}N_2O_3S$ ($[M]^+$), 378.1977; found, 378.1948. Elemental analysis: $C_{20}H_{30}N_2O_3S$ (378.58) calcd.: C 63.45 H 7.99 N 7.40; found: C 63.95 H 7.81 N 7.23.

N-(2,2-Dimethoxy-ethyl)-2-(acetyl-methylamino)-3,3-dimethyl-thiobutyric acid amide (3e)

According to the general procedure for thio Ugi reactions, **3e** was obtained after purification by column chromatography (hexanes/EtOAc 3:7) in a 2.00 mmol range as yellow cubes in 55 % yield, m_p = 80–81°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 2.06 (s, 3 H), 3.21 (s, 6 H), 3.65 (m, 2 H), 4.50 (t, *J* = 5.4 Hz, 1 H), 5.21 (bs, 1 H), 8.00 (bs, 1 H). 20.9, 22.7, 28.8, 36.2, 46.5, 54.1, 60.3, 100.9, 172.9, 200.1. HRMS (CI) calcd. for $C_{13}H_{26}N_2O_3S$ ($[M]^+$), 290.1664; found, 290.1669. Elemental analysis: $C_{13}H_{26}N_2O_3S$ (290.43) calcd.: C 53.76 H 9.02 N 9.65, found: C 53.67 H 8.99 N 9.61.

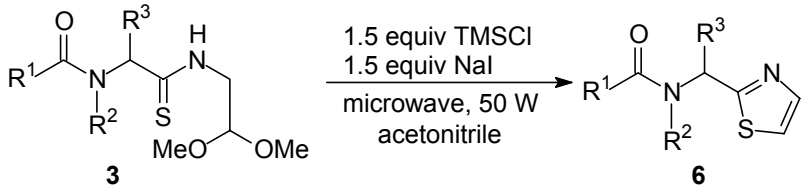
N-(2,2-Dimethoxy-ethyl)-2-(benzoyl-methylamino)-3,3-dimethyl-thiobutyric acid amide (3f)

According to the general procedure for thio Ugi reactions, **3e** was obtained after purification by column chromatography (hexanes/EtOAc 1:1) and recrystallisation (PE/EtOAc 1:1) in a 2.00 mmol range as yellow cubes in 55 % yield, m_p = 80–81°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 2.15 (s, 3 H), 3.39 (s, 6 H), 3.81 (m, 2 H), 4.61 (t, *J* = 5.5 Hz, 1 H), 4.84 (bs, 1H), 7.30–7.51 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9, 36.4, 46.8, 54.1, 100.9, 127.1, 128.5, 130.2, 136.2, 174.2, 200.2. HRMS (CI) calcd. for $C_{18}H_{28}N_2O_3S$ ($[M]^+$), 352.1821; found, 352.1820. Elemental analysis: $C_{18}H_{28}N_2O_3S$ (352.50) calcd.: C 61.33 H 8.01 N 7.95; found: C 60.94 H 8.03 N 7.47.

N-(2,2-Dimethoxy-ethyl)-2-(benzoyl-amino)-3,3-dimethyl-thiobutyric acid amide (3g)

3g was obtained according to the general procedure for thio Ugi reactions. As amine served a 2 M solution of ammonia in methanol. So 3g could be isolated after purification by column chromatography (hexanes/EtOAc 7:3) and recrystallisation (*tert*-butyl-methylether) in a 2.00 mmol range as a white solid in 71 % yield, m_p = 142–143°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 3.28 (s, 6 H), 3.56 (dt, *J* = 14.2 Hz, *J* = 5.1 Hz, 1 H), 3.95 (dt, *J* = 14.2 Hz, *J* = 5.1 Hz, 1 H), 4.51 (t, *J* = 5.4 Hz, 1 H), 5.04 (d, *J* = 9.5 Hz, 1 H), 7.37 (m, 2 H), 7.42 (m, 1 H), 7.60 (m, 1 H), 7.60 (d, *J* = 9.5 Hz, 1 H), 7.81 (m, 2 H), 8.88 (bs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.9, 36.4, 46.9, 54.2, 64.9, 100.9, 127.2, 128.6, 131.7, 134.2, 166.6, 202.4. HRMS (CI) calcd. for $C_{17}H_{26}N_2O_3S$ ($[M]^+$), 338.1664; found, 338.1656. Elemental analysis: $C_{17}H_{26}N_2O_3S$ (338.47) calcd.: C 60.33 H 7.74 N 8.28; found: C 60.03 H 7.79 N 8.15.

The thiazoles were obtained according to:



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2-[1-(Acetyl-benzylamino)-2-metyl-propyl]-thiazole (6b)

After the general procedure for thiazole synthesis using microwaves, **6b** was obtained after purification by column chromatography (hexanes/EtOAc 7:3) in a 0.10 mmol range as a yellow oil in 87 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.3 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 1.91 (s, 3 H), 2.67 (m, 1 H), 4.50 (d, *J* = 17.3 Hz, 1 H), 4.84 (d, *J* = 17.3 Hz, 1 H), 5.69 (d, *J* = 11.1 Hz, 1 H), 6.67 (m, 1 H), 6.91–7.11 (m, 5 H), 7.45 (d, *J* = 3.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 19.7, 22.4, 30.1, 48.6, 60.3, 119.2, 125.6, 126.7, 128.3, 137.6, 142.3, 167.4, 171.9. HRMS (CI) calcd. for $C_{16}H_{20}N_2OS$ ($[M]^+$), 288.1297; found, 288.1281.

2-[1-(Benzoyl-benzylamino)-2,2-dimethyl-propyl]-thiazole (6c)

After the general procedure for thiazole synthesis using microwaves, **6c** was obtained after purification by column chromatography (hexanes/EtOAc 7:3) in a 0.10 mmol range as a white solid in 91 % yield, m_p = 122–125°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 5.15 (d, *J* = 17.3 Hz, 1 H), 5.39 (d, *J* = 16.7 Hz, 1 H), 6.17 (s, 1 H), 6.78–7.72 (m, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 31.6, 51.5, 60.4, 118.9, 125.9, 127.5, 127.9, 128.9, 137.5, 139.1, 143.1, 165.6, 173.7. HRMS (CI) calcd. for $C_{22}H_{24}N_2OS$ ($[M]^+$), 364.1609; found, 364.1627.

2-[1-(Acetyl-methylamino)-2,2-dimethyl-propyl]-thiazole (6e)

After the general procedure for thiazole synthesis using microwaves, **6e** was obtained after purification by column chromatography (hexanes/EtOAc 3:7) in a 0.10 mmol range as a yellow oil in 66 % yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 2.05 (s, 3 H), 5.98 (s, 1 H), 7.19 (d, *J* = 3.5 Hz, 1 H), 7.71 (d, *J* = 3.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 28.3, 34.2, 37.3, 59.7, 118.8, 142.4, 167.1, 171.5. HRMS (CI) calcd. for $C_{11}H_{18}N_2OS$ ($[M]^+$), 226.1139; found, 226.1153.

2-[1-(Benzoyl-amino)-2,2-dimethyl-propyl]-thiazole (6g)

After the general procedure for thiazole synthesis using microwaves, **6g** was obtained after purification by column chromatography (hexanes/EtOAc 7:3) in a 0.10 mmol range as a white solid in 91 % yield, m_p = 133–135°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 5.37 (d, *J* = 9.5 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 1 H), 7.18 (d, *J* = 3.2 Hz, 1 H), 7.44 (m, 1 H), 7.68 (d, *J* = 3.2 Hz, 1 H), 7.75 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.7, 36.2, 58.6, 118.5, 127.0, 128.6, 131.6, 134.4, 142.2, 166.8, 168.1. HRMS (CI) calcd. for $C_{15}H_{18}N_2OS$ ($[M]^+$), 274.1140; found 274.116.