Supplementary Materials: Tandem Catalysis of an Aldol-‘Click’ Reaction System within a Molecular Gel

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1. Materials

4-Bromobutyric acid, N,N’-Dicyclohexylcarbodiimide, N-hydroxysuccinimide, sodium azide, 4-pentynoic acid and Phenylacetylene were purchased on Acros Organics and used as received.

2. Synthesis of the Phenyltriazole Derivative Compounds

2.1. Synthesis of Compound I

A solution of N,N-dicyclohexylcarbodiimide (6.240 g, 30.24 mmol) in anhydrous CH₂Cl₂ (15 mL) was added dropwise to a suspension of bromobutyric acid (5 g, 29.94 mmol) and N-hydroxysuccinimide (3.446 g, 29.94 mmol) in CH₂Cl₂ (30 mL) under N₂ at 0 °C. After stirring overnight between at rt, the white precipitate was filtered and the resultant solution concentrated to half and put into the freezer (−20 °C) overnight. The remaining dicyclohexylurea was filtered again and the resultant solution evaporated, giving a pale brown solid (4.060 g, 70%). Characterization: 1H-NMR (300 MHz, DMSO): δ (ppm) 3.59 (t, J = 6.8 Hz, BrCH₂CH₂-, 2H), 2.85–2.81 (m, CH₂CONCOCH₂CH₂-, 6H), 2.15 (q, J = 6.8 Hz, BrCH₂CH₂-, 2H). 13C-NMR (75 MHz, CDCl₃): δ (ppm) 169.00, 167.75, 31.48, 29.48, 27.45, 25.57.

2.2. Synthesis of Compound II

Compound II was synthesized as previously reported [1].

2.3. Synthesis of Compound III

A solution of I (1 g, 3.67 mmol) in THF (15 mL) was added dropwise to a solution of II (2.133 g, 8.08 mmol) in THF (10 mL) under N₂ at rt. After stirring for 2 h, the resultant precipitate was filtered, washed with 0.1 M NaOH (10 mL) and water (20 mL), and dried under vacuum, affording III as a white solid. The compound was directly used in the next step without further purification.

2.4. Synthesis of Compound IV

A solution of compound III (0.860 g, 1.508 mmol) in DMF (10 mL) was added to a suspension of NaN₃ (0.980 g, 15.08 mmol) in DMF (10 mL) and heated under N₂ to 80 °C overnight. After cooling to rt, the crude was poured into cold water and the resultant precipitate filtered, washed with water (10 mL) and dried under vacuum, obtaining N₃ValN₃ as a bright brown solid (0.425 g; 57%). Characterization: 1H-NMR (300 MHz, DMSO): δ (ppm) 7.87 (m, -CONHCH₂CONHCH₂, 2H), 4.05
(t, J = 7.9 Hz, -CONHCH, 1H), 3.27 (m, N3CH2CH2CH2-, 2H), 3.10 (m, -CONHCH 2, 2H), 2.23 (m, N3CH2CH2CH2-, 2H), 1.92 (m, -CH(CH3)2, 1H), 1.73 (m, N3CH2CH2CH2-, 2H), 1.50 (m, -CH3CH2, 2H), 0.82 (d, J = 6.7 Hz, -CH(CH3)2, 6H). 13C-NMR (75 MHz, DMSO): δ (ppm) 171.81, 171.42, 58.40, 50.77, 36.65, 32.46, 30.71, 29.55, 25.04, 19.64, 18.09. ESI-MS (m/z) = 495.3152 [M + H]+; C21H38N10O4. Calculated for C21H38N10O4: 491.3156.

2.5. Synthesis of Compound PhTzVal3

Phenylacetylene (233 µL, 2.12 mmol) was added to a suspension of IV (0.350 g, 0.71 mmol) in mixture of 2:1 t-BuOH:H2O (15 mL), followed by the addition of sodium hydrogenocarbonate (0.019 g, 0.226 mmol), CuSO4·5H2O (0.027 g, 0.106 mmol, 5 mol%) and sodium ascorbate (0.084 g, 0.425 mmol). After stirring at room temperature for 48 h, t-BuOH was evaporated and treated with 1 M HCl (10 mL). The resultant precipitate was filtered under vacuum and washed with water (3 × 10 mL) and diethyl ether (1 × 10 mL). The product was filtered through silica (90:10 CHCl3:MeOH) to remove possible coordinated copper, giving PhTzVal3 as a pale yellow solid (0.346 g; 70%). Characterization: 1H-NMR (300 MHz, DMSO): δ (ppm) 8.55 (s, triazole-H, 1H), 7.86 (m, Ph-H + -CONHCH + CONHCH2, 4H), 7.43 (t, J = 7.4 Hz, Ph-H, 2H), 7.31 (t, J = 7.4 Hz, Ph-H, 1H), 4.38 (t, J = 6.6 Hz, Triazole-CH2CH2CH2-, 2H), 4.06 (t, J = 7.8 Hz, -CONHCH, 1H), 3.4 (m, -CONHCH2, 2H), 2.21 (m, Triazole-CH2CH2CH2-, 2H), 2.07 (m, Triazole-CH2CH2CH2-, 2H), 1.91 (m, CH(CH3)2, 1H), 1.51 (m, -CH3CH2, 1H), 0.81 (d, J = 6.4 Hz, -CH(CH3)2, 6H). 13C (75 MHz, DMSO): δ (ppm) 171.64, 171.43, 146.77, 131.31, 129.30, 128.22, 125.57, 121.79, 58.40, 49.57, 36.69, 32.31, 29.58, 26.35, 19.66, 18.68. ESI-MS (m/z) = 721.3912 [M + Na]+; C37H50N10O4. Calculated for C37H50N10O4: 721.3914.

2.6. Synthesis of Compound 1

Compound 1 was synthesized as previously reported [2].

2.7. Synthesis of Compound 6

Acetoazide (0.2 g; 2.03 mmol; 0.181 mL) and phenylacetylene (0.228 g; 2.23 mmol; 0.245 mL) were dissolved in 1:1 t-BuOH:H2O (4 mL). To this solution, CuSO4·5H2O (0.050 g; 0.203 mmol) and sodium ascorbate (0.161 g; 0.812 mmol) were added, and the mixture stirred for 16 h at room temperature. EtOAc (20 mL) was added to the crude product and the organic phase washed with a saturated solution of NaHCO3 (3 × 5 mL) and brine (3 × 5 mL). The organic extracts were dried over anhydrous MgSO4 and the solvents removed on the rotavapor to give a pale yellow solid (0.31 g; 76%). Characterization: 1H-NMR (300 MHz, CDCl3): δ (ppm) 7.82 (m, triazole-H + Ph-H, 3H), 7.35 (m, Ph-H +, 3H), 5.23 (s, -COCH3, 2H). 13C-NMR (75 MHz, CDCl3): δ (ppm) 199.03, 148.29, 130.29, 128.83, 125.80, 120.95, 58.53, 27.21. ESI-MS (m/z) = 202.0981 [M + Na]+; C7H9N3O. Calculated for C7H9N3O: 202.0980.
3. $^1$H- and $^{13}$C-NMR Spectra

**Figure S2.** $^1$H-NMR spectrum of compound I (DMSO-$d_6$, 300 MHz).

**Figure S3.** $^{13}$C-NMR spectrum of compound I (CDCl$_3$, 300 MHz).
Figure S4. $^1$H-NMR spectrum of compound IV (DMSO-$d_6$, 300 MHz).

Figure S5. $^{13}$C-NMR spectrum of compound IV (DMSO-$d_6$, 300 MHz).
Figure S6. $^1$H-NMR spectrum of compound PhTzVal$_3$ (DMSO-$d_6$, 300 MHz).

Figure S7. $^{13}$C-NMR spectrum of compound PhTzVal$_3$ (DMSO-$d_6$, 300 MHz).
Figure S8. $^1$H-NMR spectrum of compound 6 (CDCl$_3$, 300 MHz).

Figure S9. $^{13}$C-NMR spectrum of compound 6 (CDCl$_3$, 300 MHz).
4. Typical $^1$H-NMR Spectrum of a Catalysis

Figure S10. Typical $^1$H-NMR spectrum of a catalytic reaction in the presence of 10 mol% Cu(I)-PhTzVal$_3$ (CDCl$_3$, 300 MHz).

5. Mass Spectra of Final Product from the Tandem Catalytic System

Figure S11. High-resolution mass spectrometry of the final product, isolated by type II alumina column chromatography of the crude belonging to the three component reaction carried for 2 days in the presence of 10 mol % Cu(I)-PhTzVal$_3$. 

6. HPLC Chromatogram for the Determination of Enantiomeric Excess of the Final Product from the Tandem Catalytic System

Figure S12. HPLC Chromatogram of the three-component reaction carried for 2 days in the presence of 10 mol\% Cu(I)-PhTzVal.

References

1. Becerril, J.; Bolte, M.; Burguete, M.; Galindo, F.; Garcia-España, E.; Luis, S.; Miravet, J. Efficient macrocyclization of u-turn preorganized peptidomimetics: The role of intramolecular H-bond and solvophobic effects. J. Am. Chem. Soc. 2003, 125, 6677–6686.

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