CuBr Catalyzed Synthesis of 1,4,5-trisubstituted 1,2,3-Triazoles Through Cycloaddition of Azides to Alkenes

Bo Yang,^{*,a} Mian-Chen Zou,^b Feng Chen,^b Kai-Jie Fan^a

^a Department of Thoracic Surgery, PLA General Hospital, Fuxing Rd 28, Haidian District, Beijing 100853, China.

^b State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Xue Yuan Rd. 38, Beijing 100191, China,

E-mail: 301yangbo@gmail.com; Phone & Fax: +86-10-66938313

General Remarks

All manipulations were conducted under air atmosphere. ¹H-NMR spectra were recorded on a Bruker AVANCE III-400 spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in CDCl₃ as an internal standard. ¹³C-NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl₃ ($\delta = 77.00$ ppm). High Resolution Mass spectra were recorded using a Fourier Transform Ion Cyclotron Resonance Mass spectrometer (APEX IV, Bruker). Fourier-transform infrared (FTIR) spectra were obtained with a Nicolet Nexus 470 Fourier transform infrared spectrometer.

Experimental Section

Typical procedure:

(5-(4-chlorophenyl)-1-(cyclohexylmethyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone(**3ba**):

The mixture of (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**1b**) (0.6 mmol, 145.6 mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3 mg), copper bromide (0.003 mmol, 4.0 mg), DMF (2.0 mL) was stirred at 110 °C under air. After 36 hours, water (5 mL) was added to the mixture and extracted with ethyl acetate (10.0 mL×3). Dried with anhydrous magnesium sulfate and concentrated and purified by flash chromatography on silicon gel (eluent: petroleum ether / ethyl acetate = 10:1) to afford 187 mg (82%) of **3ba**.

Analytical data for compounds

3aa

1)

(1-(cyclohexylmethyl)-4-phenyl-1*H*-1,2,3-triazol-5-yl)(phenyl)methanone (**3aa**)

The reaction of (*E*)-chalcone (**1a**) (0.6 mmol, 124.8 mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 168 mg (81 %) of **3aa**. mp: 108 °C. ¹H NMR (400 MHz, CDCl₃) δ = 8.2–8.17 (m, 2H), 7.51–7.45 (m, 1H), 7.44–7.36 (m, 5H), 7.3–7.28 (m, 2H), 4.02 (d, *J*=7.4 Hz, 2H), 1.89–1.76 (m, 1H), 1.56 (dd, *J*=19.0 Hz, 8.1, 3H), 1.44 (d, *J*=11.3 Hz, 2H), 1.14–0.98 (m, 3H), 0.76 (dt, *J*=12.3 Hz, 7.6, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ = 186.4, 143.4, 141.9, 137.1, 132.8, 130.6, 129.8, 129.7, 128.7, 128.1, 126.7, 54.0, 38.2, 30.3, 25.9, 25.3. cm⁻¹; IR (KBr): 3433, 2919, 2849, 1656, 1547, 1487, 1452 cm⁻¹. HRMS: (ESI) calcd for C₂₂H₂₄N₃O [M+H]⁺ 346. 1914, found: 346. 1912.

3ba

2)

(5-(4-chlorophenyl)-1-(cyclohexylmethyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone(3ba):

The reaction of (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**1b**) (0.6mmol, 145.6mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 187 mg (82 %) of **3ba**. mp: 132 °C. ¹H NMR (CDCl₃, 400 MHz): δ = 8.29 (d, *J* = 7.2 Hz, 2H), 7.59-7.53 (m, 1H), 7.51-7.43 (m, 4H), 7.34(d, *J* = 8.4 Hz, 2H), 4.08(d, *J* = 7.2 Hz, 2H), 1.95-1.83 (m, 1H), 1.68-1.60 (m, 3H), 1.51(d, *J* = 11.6 Hz, 2H), 1.23-0.88 (m, 3H), 0.86-0.79 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 186.1, 143.4, 140.7, 136.9, 136.0, 132.9, 131.1, 130.5, 128.9, 128.1, 125.1, 54.0, 38.2, 30.2, 25.8, 25.2. IR (KBr): 3433, 2928, 2853, 1656, 1483, 1451 cm⁻¹. HRMS: (ESI) calcd for C₂₂H₂₂ClN₃O [M+H]⁺ 380.1529, found: 380.1525.

3)

(4-chlorophenyl)(5-(4-chlorophenyl)-1-(cyclohexylmethyl)-1H-1,2,3-triazol-4-yl)methanone (3ca):

The reaction of (*E*)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (**1c**) (0.6mmol, 166.3mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 184 mg (74 %) of **3ca**. mp: 141 °C. ¹H NMR (CDCl₃, 400 MHz): δ = 8.30 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.08 (d, *J* = 7.2 Hz, 2H), 1.96-1.84 (m, 1H), 1.69-1.61 (m, 3H), 1.52 (d, *J* = 12 Hz, 2H), 1.22-1.03 (m, 3H), 0.90-0.80 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ = 184.6, 143.1, 141.0, 139.4, 136.2, 135.2, 132.0, 131.0, 129.0, 128.4, 124.8, 54.0, 38.2, 30.2, 25.8, 25.2. IR (KBr): 3435, 2924, 2849, 1654, 1479, 1449 cm⁻¹. HRMS: (ESI) calcd for C₂₂H₂₁Cl₂N₃O [M+H]⁺ 414.1140, found: 414.1126.

4)

(1-(cyclohexylmethyl)-5-(p-tolyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone(3da):

The reaction of (*E*)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (**1d**) (0.6mmol, 133.3mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 133 mg (62 %) of **3da**. mp: 152 °C. ¹H NMR (CDCl₃, 400 MHz): δ = 8.29 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.29 (q, *J* = 8.0 Hz,

4H), 4.10 (d, $J = 7.6$ Hz, 2H), 2.42(s, 3H), 1.97-1.87 (m, 1H), 1.68-1.59 (m, 3H), 1.53 (d, $J = 12$ Hz, 2H), 1.23-1.03 (m, 3H), 0.90-0.80 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 186.3, 143.2, 142.0, 139.8, 137.1, 132.7, 130.6, 129.5, 129.4, 128.0, 123.5, 53.9, 38.1, 30.2, 25.8, 25.3, 21.4$. IR (KBr): 3393, 2929, 2852, 1656, 1504, 1449 cm^{-1} . HRMS: (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 360.2075, found: 360.2070.

5)

(1-(cyclohexylmethyl)-5-phenyl-1H-1,2,3-triazol-4-yl)(4-fluorophenyl)methanone (3ea):

The reaction of (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (**1e**) (0.6mmol, 136.0mg), (azidomethyl)cyclohexane (**2a**) (0.9 mmol, 125.3mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 170 mg (78 %) of **3ea**. mp: 110 °C. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.43\text{-}8.34$ (m, 2H), 7.52 (t, $J = 3.4$ Hz, 3H), 7.41-7.36 (m, 2H), 7.16-7.10 (m, 2H), 4.10 (d, $J = 7.6$ Hz, 2H), 1.94-1.86 (m, 1H), 1.68-1.59 (m, 3H), 1.52 (d, $J = 11.6$ Hz, 2H), 1.27-1.03 (m, 3H), 0.90-0.80 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 184.5, 165.2$ (d, $J = 252$), 143.1, 142.0, 133.4, 133.3 (d, $J = 9.0$), 129.8, 129.6, 128.6, 126.6, 115.2 (d, $J = 22.0$), 54.0, 38.1, 30.2, 25.8, 25.3. IR (KBr): 2922, 2849, 1653, 1599, 1484, 1459 cm^{-1} . HRMS: (ESI) calcd for $\text{C}_{22}\text{H}_{22}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 364.1825, found: 364.1825.

6)

(5-(4-chlorophenyl)-1-nonyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (3bb):

The reaction of (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**1b**) (0.6mmol, 145.6mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 118 mg (48 %) of **3bb**. ^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.22\text{-}8.17$ (m, 2H), 7.51-7.46 (m, 1H), 7.43-7.35 (m, 4H), 7.29-7.25 (m, 2H), 4.16 (t, $J = 7.4$ Hz, 2H), 1.75-1.68 (m, 2H), 1.18-1.11 (m, 12H), 0.78 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 186.2, 143.5, 140.3, 136.9, 136.2, 133.0, 131.0, 130.6, 129.1, 128.1, 125.0, 48.2, 31.7, 29.8, 29.1, 29.0, 28.7, 26.2, 22.5, 14.0$. IR (KBr): 3359, 2925, 2854, 1655, 1600, 1480, 1454 cm^{-1} . HRMS: (ESI) calcd for $\text{C}_{24}\text{H}_{28}\text{ClN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 410.1999, found: 410.1993.

7)

(4-chlorophenyl)(5-(4-chlorophenyl)-1-propyl-1H-1,2,3-triazol-4-yl)methanone (3cb):

The reaction of (*E*)-1,3-bis(4-chlorophenyl)prop-2-en-1-one (**1c**) (0.6mmol, 166.3mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 114.1 mg (43 %) of **3cb**. mp: 70 °C. ¹H NMR (CDCl₃, 400 MHz): δ = 8.32-8.28 (m, 2H), 7.53-7.49 (m, 2H), 7.47-7.43 (m, 2H), 7.38-7.34 (m, 2H), 4.25 (t, *J* = 7.4 Hz, 2H), 1.84-1.80 (m, 2H), 1.30-1.21 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 184.7, 143.3, 140.6, 139.5, 136.3, 135.2, 132.1, 131.0, 129.1, 128.5, 124.9, 48.3, 31.7, 29.8, 29.1, 29.0, 28.7, 26.2, 22.5, 14.0. IR (KBr): 2925, 2855, 1655, 1587, 1480, 1457 cm⁻¹. HRMS: (ESI) calcd for C₂₄H₂₇Cl₂N₃O [M+H]⁺ 444.1609, found: 444.1607.

8)

(4-methoxyphenyl)(5-(4-methoxyphenyl)-1-propyl-1H-1,2,3-triazol-4-yl)methanone(3fb):

The reaction of (*E*)-1,3-bis(4-methoxyphenyl)prop-2-en-1-one (**1f**) (0.6mmol, 161.0mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 186.5 mg (84 %) of **3fb**. ¹H NMR (CDCl₃, 400 MHz): δ = 8.36-8.32 (m, 2H), 7.37-7.32 (m, 2H), 7.03-7.00 (m, 2H), 6.97-6.92 (m, 2H), 4.26 (t, *J* = 7.4 Hz, 2H), 3.850(s, 3H), 3.846(s, 3H), 1.84-1.78 (m, 2H), 1.27-1.20 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 184.8, 163.3, 160.5, 143.5, 141.0, 132.9, 130.9, 130.0, 118.4, 114.1, 113.3, 55.2, 55.1, 48.0, 31.6, 29.7, 29.1, 29.0, 28.7, 26.2, 22.4, 13.9. IR (KBr): 2927, 2855, 1648, 1600, 1497, 1460 cm⁻¹. HRMS: (ESI) calcd for C₂₆H₃₃N₃O [M+H]⁺ 436.2600, found: 436.2599.

9)

(1-propyl-5-(p-tolyl)-1H-1,2,3-triazol-4-yl)(p-tolyl)methanone(3gb):

The reaction of (*E*)-1,3-di-p-tolylprop-2-en-1-one (**1g**) (0.6 mmol, 142.0 mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 132.0 mg (55 %) of **3gb**. ¹H NMR (CDCl₃, 400 MHz): δ = 8.22 (d, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 4H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.25 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H), 1.84-1.75 (m, 2H), 1.30-1.15 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 185.9, 143.5, 141.3, 139.8, 134.5, 130.7, 129.31, 129.29, 128.7, 123.5, 47.9, 31.63, 31.58, 29.7, 29.0, 28.9, 28.6, 26.1, 22.4, 21.5, 21.3, 13.9. IR (KBr): 2925, 2855, 1651, 1607, 1496, 1455 cm⁻¹. HRMS: (ESI) calcd for C₂₆H₃₃N₃O [M+H]⁺ 404.2702, found: 404.2707.

10)

(1-nonyl-5-(p-tolyl)-1H-1,2,3-triazol-4-yl)(phenyl)methanone(3db):

The reaction of (*E*)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (**1d**) (0.6mmol, 133.3 mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 116.3 mg (50 %) of **3db**. ¹H NMR (CDCl₃, 400 MHz): δ = 8.19 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.23-7.17 (m, 4H), 4.16 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.72 (t, *J* = 6.8 Hz, 2H), 1.18-1.10 (m, 12H), 0.77 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 186.3, 143.3, 141.5, 140.0, 137.1, 132.7, 130.5, 129.4, 129.3, 128.0, 123.4, 48.0, 31.6, 29.7, 29.1, 29.0, 28.6, 26.2, 22.5, 21.3, 13.9. IR (KBr): 3028, 2926, 2855, 1656, 1499, 1453 cm⁻¹. HRMS: (ESI) calcd for C₂₅H₃₁N₃O [M+H]⁺ 390.2545, found: 390.2547.

11)

(4-fluorophenyl)(5-phenyl-1-propyl-1H-1,2,3-triazol-4-yl)methanone(3eb):

The reaction of (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one(**1e**) (0.6 mmol, 126.0 mg), 1-azidononane (**2b**) (0.9 mmol, 152.1mg), CuBr (0.003 mmol, 4.0 mg), DMF (2 mL) at 110 °C for 36 hours, afford 159 mg (78 %) of **3eb**. ¹H NMR (CDCl₃, 400 MHz): δ = 8.40-8.36 (m, 2H), 7.54-7.51 (m, 3H), 7.42-7.38 (m, 2H), 7.12 (t, *J* = 5.6 Hz, 2H), 4.27 (t, *J* = 7.4 Hz, 2H), 1.85-1.78 (m, 2H), 1.28-1.20 (m, 12H), 0.87 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ = 184.6, 165.27(d, *J* = 253), 143.3, 141.7, 133.4, 133.3 (d, *J* = 9.7), 130.0, 129.6, 128.8, 126.6, 115.3 (d, *J*

= 21.4), 48.3, 31.7, 29.9, 29.2, 29.1, 28.7, 26.3, 22.6, 14.0. IR (KBr): 3361, 2925, 2854, 1657, 1598, 1485 cm^{-1} . HRMS: (ESI) calcd for $\text{C}_{24}\text{H}_{28}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 394.2294, found: 394.2291.