Eur. J. Org. Chem. **2008** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2008 · ISSN 1434–193X

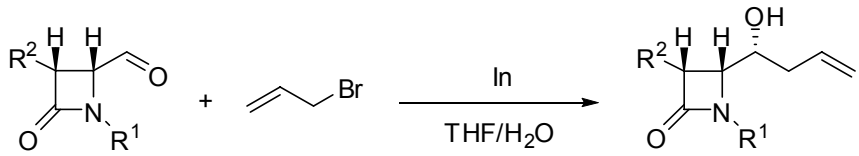
SUPPORTING INFORMATION

Title: Synthesis of Novel Bis(β-lactam)-1,3-diynes by Copper-Promoted Homo- or Cross-Coupling of Alkynyl-2-azetidinones

Author(s): Benito Alcaide,* Pedro Almendros,* Rocío Carrascosa, Raquel Rodríguez-Acebes

Ref. No.: O200701083

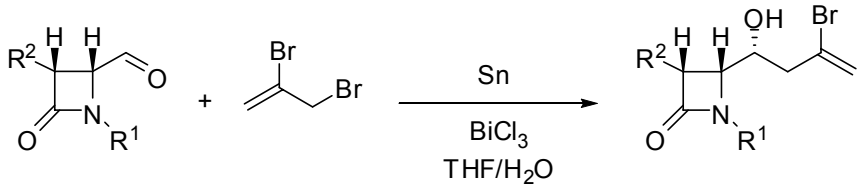
Indium Promoted Reaction between Allyl Bromide and 4-Oxoazetidine-2-carbaldehydes in an Aqueous Medium. General Procedure for the Synthesis of β-Lactam Homoallylic Alcohols. Allyl bromide (1.0 mmol) was added to a well stirred suspension of the corresponding 4-oxoazetidine-2-carbaldehyde (0.5 mmol), and indium powder (115 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) at 0 ^oC. The mixture was stirred at room temperature until complete disappearance of the starting aldehyde (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 x 3 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure homoallylic alcohols. Spectroscopic and analytical data for previously undescribed homoallylic alcohols follow.



Homoallylic Alcohol (+)-1c. From 92 mg (0.55 mmol) of 3-methoxy-1-prop-2-ynyl-4-oxoazetidine-2-carbaldehyde, 91 mg (79%) of compound (+)-**1c** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). Colorless oil. $[\alpha]_D$ = +43.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 2.29 (t, 1H, *J* = 2.4 Hz), 2.33 (br s, 1H), 2.35 (m, 2H), 3.60 (s, 3H), 3.83 (t, 1H, *J* = 4.9 Hz), 3.93 (dt, 1H, *J* = 8.0, 4.8 Hz), 3.92 (dd, 1H, *J* = 17.7, 2.6 Hz), 4.39 (dd, 1H, *J* = 17.7, 2.6 Hz), 4.48 (d, 1H, *J* = 4.9 Hz), 5.19 (m, 2H), 5.87 (ddd, 1H, *J* = 17.1, 10.0, 7.1 Hz). ^{13}C-NMR: δ 166.7, 133.9, 118.4, 83.4, 76.2, 72.8, 69.8, 59.8, 59.4, 38.6, 31.0. IR ($CHCl_3$, cm^{-1}): ν 3426, 1739. MS (EI), *m/z*: 210 (M^+ + 1, 16), 209 (M^+, 100). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.35; H, 7.31; N, 6.76.

Tin Promoted Reaction between 2,3-Dibromopropene and 4-Oxoazetidine-2-carbaldehydes in an Aqueous Medium Containing $BiCl_3$. General Procedure for the Synthesis of Bromohomoallylic Alcohols. 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well stirred suspension of the appropriate 4-oxoazetidine-2-carbaldehyde (1.0 mmol), tin powder (178 mg, 1.5 mmol) and bismuth(III) chloride (63 mg, 0.2 mmol) in THF/H_2O (1:1, 10 mL) at room temperature. After dissapearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 ºC, and the mixture was allowed to warm to room temperature, before being extracted with

ethyl acetate (3 x 10 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure bromohomoallylic alcohols. Spectroscopic and analytical data for previously undescribed bromohomoallylic alcohols follow.



Bromohomoallylic Alcohol (+)-1d. From 297 mg (1.78 mmol) of 3-methoxy-1-prop-2-ynyl-4-oxoazetidine-2-carbaldehyde, 421 mg (82%) of compound (+)-**1d** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/1). $[\alpha]_D$ = +33.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.31 (td, 1H, *J* = 2.6, 0.5 Hz), 2.70 (m, 3H), 3.61 (s, 3H), 3.86 (d, 1H, *J* = 4.4 Hz), 3.92 (dd, 1H, *J* = 15.2, 2.6 Hz), 4.24 (m, 1H), 4.38 (dd, 1H, *J* = 17.7, 2.6 Hz), 4.52 (d, 1H, *J* = 4.9 Hz), 5.57 (d, 1H, *J* = 1.7 Hz), 5.78 (d, 1H, *J* = 1.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 167.0, 129.5, 120.4, 83.6, 76.9, 73.2, 68.3, 59.7, 46.0, 31.1. IR ($CHCl_3$, cm^{-1}): ν 3430, 1741. MS (EI), *m/z*: 289 (M^+ + 2, 100), 287 (M^+, 98). Anal. Calcd for $C_{11}H_{14}NO_3Br$: C, 45.85; H, 4.90; N, 4.86. Found: C, 45.64; H, 4.97; N, 4.80.

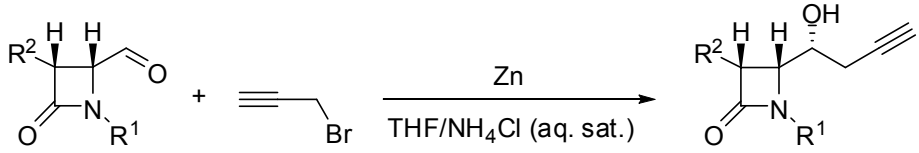
Bromohomoallylic Alcohol (+)-1e. From 206 mg (1.14 mmol) of 3-methoxy-1-but-3-ynyl-4-oxoazetidine-2-carbaldehyde, 206 mg (60%) of compound (+)-**1e** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/2). $[\alpha]_D$ = +43.2 (*c* 0.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.02 (t, 1H, *J* = 2.7 Hz), 2.53 (td, 2H, *J* = 0 6.8, 2.6 Hz), 2.68 (m, 3H), 3.38 (m, 1H), 3.60 (s, 3H), 3.63 (m, 1H), 3.84 (t, 1H, *J* = 5.4 Hz), 4.22 (m, 1H), 4.51 (d, 1H, *J* = 4.9 Hz), 5.58 (d, 1H, *J* = 1.7 Hz), 5.74 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 167.9, 129.5, 120.3, 83.2, 81.2, 70.5, 69.1, 60.6, 59.6, 45.9, 40.5, 18.0. IR ($CHCl_3$, cm^{-1}): ν 3422, 1742. MS (EI), *m/z*: 303 (M^+ + 2, 100), 301 (M^+, 98). Anal. Calcd for $C_{12}H_{16}NO_3Br$: C, 47.70; H, 5.34; N, 4.64. Found: C, 47.92; H, 5.41; N, 4.72.

Bromohomoallylic Alcohol (+)-1i. From 286 mg (1.10 mmol) of 1-(4-methoxyphenyl)-3-prop-2-ynyloxy-4-oxoazetidine-2-carbaldehyde, 278 mg (66%) of compound (+)-**1i** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ = +131.2 (*c* 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.58 (t, 1H, *J* = 2.3 Hz), 2.62 (m, 2H), 3.79 (s, 3H), 4.36 (dd, 1H, *J* = 5.3, 4.5 Hz), 4.44 (m, 1H), 4.53 (dd, 2H, *J* = 4.4, 2.4 Hz), 4.99 (d, 1H, *J* = 5.1 Hz), 5.53 (d, 1H, *J* = 1.7 Hz), 5.65 (dt, 1H, *J* = 1.8, 0.9 Hz), 6.87 and 7.39 (d, each 2H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 164.3, 156.8, 130.2,

129.4, 120.4, 119.9, 114.1, 79.7, 78.1, 76.2, 68.6, 60.0, 58.9, 55.3, 45.3. IR ($CHCl_3$, cm^{-1}): ν 3431, 1742. MS (EI), *m/z*: 381 (M^+ + 2, 18), 379 (M^+, 18), 149 (100). Anal. Calcd for $C_{17}H_{18}NO_4Br$: C, 53.70; H, 4.77; N, 3.68. Found: C, 53.48; H, 4.84; N, 3.61.

Bromohomoallylic Alcohol (±)-1j. From 150 mg (0.617 mmol) of 1-(4-methoxyphenyl)-3-prop-2-ynyl-4-oxoazetidine-2-carbaldehyde, 140 mg (62%) of the compound (±)-**1j** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3/1). ^{1}H-NMR: δ 2.11 (t, 1H, *J* = 2.7 Hz), 2.71 (m, 4H), 3.58 (dt, 1H, *J* = 9.2, 5.7 Hz), 3.79 (s, 3H), 4.28 (dd, 1H, *J* = 5.7, 4.8 Hz), 4.51 (m, 1H), 5.57 (d, 1H, *J* = 1.7 Hz), 5.68 (m, 1H), 6.86 and 7.36 (d, each 2H, *J* = 9.0 Hz). ^{13}C-NMR: δ 166.3, 157.1, 130.9, 129.3, 121.4, 120.7, 114.4, 91.4, 70.8, 68.5, 58.3, 55.7, 50.3, 47.8, 14.8. IR ($CHCl_3$, cm^{-1}): ν 3429, 1742. MS (EI), *m/z*: 365 (M^+ + 2, 30), 363 (M^+, 30), 149 (100). Anal. Calcd for $C_{17}H_{18}NO_3Br$: C, 56.06; H, 4.98; N, 3.85. Found: C, 56.15; H, 5.00; N, 3.83.

Zinc Promoted Reaction between Propargyl Bromide and 4-Oxoazetidine-2-carbaldehydes in an Aqueous Medium Containing NH_4Cl. General Procedure for the Synthesis of Homopropargylic Alcohols. Propargyl bromide (178 mg, 1.5 mmol) was added to a well stirred suspension of the corresponding 4-oxoazetidine-2-carbaldehyde (0.5 mmol) and zinc powder (195 mg, 3.0 mmol) in THF/NH_4Cl (aq sat) (1:5, 5 mL) at 0 ºC. The mixture was stirred at room temperature until complete disappearance of the aldehyde (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 x 3 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure homopropargylic alcohols. Spectroscopic and analytical data for previously undescribed homopropargylic alcohols follow.



Homopropargylic Alcohol (+)-1g. From 126 mg (1.14 mmol) of 1-(2-bromoallyl)-3-methoxy-4-oxoazetidine-2-carbaldehyde, 80 mg (55%) of compound (+)-**1g** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ = +9.1 (*c* 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.10 (t, 1H, *J* = 2.7 Hz), 2.51 (dd, 2H, *J* = 6.0, 2.6 Hz), 2.61 (d, 1H, *J* = 4.4 Hz), 3.62 (s, 3H), 3.95 (d, 1H, *J* = 4.9 Hz), 3.99 (m, 1H), 4.05 (d, 1H, *J* = 16.1 Hz), 4.42 (dt, 1H, *J* = 15.9, 1.1 Hz), 4.57 (d,

1H, *J* = 5.1 Hz), 5.65 (dd, 1H, *J* = 2.2, 0.7 Hz), 5.88 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 167.8, 127.1, 120.4, 83.2, 79.6, 71.8, 69.4, 59.5, 49.7, 24.3. IR ($CHCl_3$, cm^{-1}): ν 3431, 1738. MS (EI), *m/z*: 289 (M^+ + 2, 100), 287 (M^+, 98). Anal. Calcd for $C_{11}H_{14}NO_3Br$: C, 45.85; H, 4.90; N, 4.86. Found: C, 45.67; H, 4.96; N, 4.81.

Homopropargylic Alcohol (+)-1h. From 392 mg (1.32 mmol) of 1-(2-bromobenzyl)-3-methoxy-4-oxoazetidine-2-carbaldehyde, 223 mg (50%) of compound (+)-**1h** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ = +21.3 (*c* 1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.99 (t, 1H, *J* = 2.7 Hz), 2.42 (dd, 2H, *J* = 6.3, 2.7 Hz), 2.66 (d, 1H, *J* = 4.6 Hz), 3.62 (s, 3H), 3.78 (t, 1H, *J* = 5.4 Hz), 4.01 (m, 1H), 4.47 (d, 1H, *J* = 15.6 Hz), 4.53 (d, 1H, *J* = 5.1 Hz), 4.81 (d, 1H, *J* = 15.6 Hz), 7.16 (td, 1H, *J* = 7.6, 1.9 Hz), 7.30 (td, 1H, *J* = 7.3, 1.5 Hz), 7.39 (td, 1H, *J* = 7.6, 2.0 Hz), 7.55 (td, 1H, *J* = 7.8, 1.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 168.0, 134.7, 133.2, 130.8, 129.5, 127.8, 123.5, 83.2, 79.8, 71.6, 69.4, 59.7, 59.6, 46.2, 24.2. IR ($CHCl_3$, cm^{-1}): ν 3429, 1740. MS (EI), *m/z*: 339 (M^+ + 2, 100), 337 (M^+, 98). Anal. Calcd for $C_{15}H_{16}NO_3Br$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.09; H, 4.82; N, 4.18.

Homopropargylic Alcohol (±)-1m. From 167 mg (0.66 mmol) of (*S*)-1-(4-methoxyphenyl)-4-*p*-tolylazetidine-2,3-dione, 131 mg (60%) of compound (±)-**1m** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 3/1). ^{1}H-NMR ($CDCl_3$): δ 2.13 (t, 1H, *J* = 2.7 Hz), 2.37 (s, 3H), 2.90 (d, 2H, *J* = 2.5 Hz), 2.99 (d, 1H, *J* = 2.7 Hz), 3.76 (s, 3H), 5.23 (s, 1H), 6.81 and 7.30 (d, each 2H, *J* = 9.0 Hz), 7.24 (s, 4H). ^{13}C-NMR ($CDCl_3$): δ 165.5, 156.5, 138.9, 130.3, 130.1, 129.9, 127.3, 119.0, 114.4, 84.0, 77.9, 72.0, 66.5, 55.4, 25.5, 21.2. IR ($CHCl_3$, cm^{-1}): ν 3429, 1740. MS (EI), *m/z*: 339 (M^+ + 2, 100), 337 (M^+, 98). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.90; H, 5.91; N, 4.40.

Copper(II) Acetate/Palladium(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing K_2CO_3 and Ar. Copper (II) acetate (0.47 mmol), palladium (II) acetate (0.02 mmol), and potassium carbonate (0.26 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.21 mmol) in acetonitrile (5 mL). The resulting suspension was stirred under an argon atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(II) Acetate/Palladium(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing K_2CO_3 and O_2. Copper (II) acetate (0.47 mmol), palladium (II) acetate (0.02 mmol), and potassium carbonate (0.26 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.21 mmol) in acetonitrile (5 mL). The resulting suspension was stirred under an oxygen atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(I) Iodide/Palladium(II) Chloride Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing Et_3N, PPh_3, and O_2. Copper (I) iodide (0.002 mmol), palladium (II) acetate (0.004 mmol), and triphenylphosphine (0.08 mmol), and triethylamine (0.23 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.21 mmol) in acetonitrile (5 mL). The resulting suspension was stirred under an oxygen atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing Et_3N and Ar. Copper (II) acetate (1.05 mmol) and triethylamine (0.6 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred under an argon atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing Et_3N and O_2. Copper (II) acetate (1.05 mmol) and triethylamine (0.6 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred under an oxygen atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in the Absence of Base. Copper (II) acetate (1.05 mmol) was added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give analytically pure bis-β-lactam-1,3-diynes.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing K_2CO_3 and Ar. Copper (II) acetate (1.05 mmol) and potassium carbonate (0.6 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred under an argon atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give analytically pure bis-β-lactam-1,3-diynes **2**.

Copper(II) Acetate Promoted Homocoupling Reaction of 2-Azetidinone-Tethered Alkynes 1 in a Medium containing K_2CO_3 and O_2. Copper (II) acetate (1.05 mmol) and potassium carbonate (0.6 mmol) were sequentially added to a well stirred solution of the appropriate alkynyl 2-azetidinone **1** (0.5 mmol) in acetonitrile (12 mL). The resulting suspension was stirred under an oxygen atmosphere at room temperature until disappearance (TLC) of the starting material. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give analytically pure bis-β-lactam-1,3-diynes **2**.