Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting Information

Stereoselective NaN_3-Catalyzed Halonitroaldol-Type Reaction of Azetidine-2,3-diones in Aqueous Media

Benito Alcaide,*[a] Pedro Almendros,*[b] Amparo Luna,[a] and M. Rosario Torres,[c]

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain*

[b]*Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain*

[c]*Laboratorio de Difracción de Rayos X, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain*

E-mail: alcaideb@quim.ucm.es; iqoa392@iqog.csic.es

Procedure for the Halonitroaldol-Type Reaction of Azetidine-2,3-diones 1 Catalyzed by NaI in Anhydrous Medium. Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol) and sodium iodide (23 mg, 0.15 mmol) in THF (8 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before being extracted with ethyl acetate (3 x 5 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 compounds **2**.

Procedure for the Halonitroaldol-Type Reaction of Azetidine-2,3-diones 1 Catalyzed by LiI in Anhydrous Medium. Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol) and

lithium iodide (20 mg, 0.15 mmol) in THF (8 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before being extracted with ethyl acetate (3 x 5 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 compounds **2**.

Procedure for the Halonitroaldol-Type Reaction of Azetidine-2,3-diones 1 Catalyzed by KI in Anhydrous Medium. Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol) and potassium iodide (25 mg, 0.15 mmol) in THF (8 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before being extracted with ethyl acetate (3 x 5 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 compounds **2**.

Procedure for the Halonitroaldol-Type Reaction of Azetidine-2,3-diones 1 Catalyzed by NaN_3 in Anhydrous Medium. Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol) and sodium azide (9.7 mg, 0.15 mmol) in THF (8 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before being extracted with ethyl acetate (3 x 5 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 compounds **2**.

Procedure for the Halonitroaldol-Type Reaction of Azetidine-2,3-diones 1 Catalyzed by NaN_3 in an Aqueous Medium. Bromonitromethane (1.0 mmol) was added to a well stirred solution of the corresponding azetidine-2,3-dione **1** (1.0 mmol)

and sodium azide (9.7 mg, 0.15 mmol) in THF/brine (1:5, 12 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the α-keto-β-lactam (TLC). Saturated aqueous ammonium chloride (2.5 mL) was added, before being extracted with ethyl acetate (3 x 5 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 compounds **2**.

3-[Bromo(nitro)methyl] 3-hydroxy-2-azetidinone 2b. From 42 mg (0.15 mmol) of azetidine-2,3-dione **1b**, 41 mg (70%) of compound *anti*-**2b**, containing *ca.* 20% of its *syn*-**2b** epimer, was obtained as colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1); $[\alpha]_D$ = –13.3 (*c* 3.0 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.36 (m, 5H), 6.15 (s, 0.2H), 6.13 (s, 0.8H), 4.94 and 4.23 (d, *J* = 14.7 Hz, each 0.8H), 4.89 and 4.22 (d, *J* = 14.7 Hz, each 0.2H), 4.38 (m, 1H), 4.24 (d, *J* = 5.1 Hz, 1H), 4.13 (m, 1H), 3.84 (dd, *J* = 9.3, 5.4 Hz, 0.8H), 3.75 (dd, *J* = 9.3, 5.4 Hz, 0.2H), 1.49 (s, 2.4H), 1.43 (s, 0.6H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 165.0 (M + m), 134.3 (M), 134.1 (m), 129.2 (m), 129.0 (M), 128.8 (m), 128.7 (M), 128.5 (m), 128.3 (M), 110.4 (M + m), 85.5 (m), 85.2 (M), 75.9 (M + m), 74.5 (M + m), 66.3 (M), 64.0 (m), 61.2 (m), 60.4 (M), 46.3 (m), 45.6 (M), 26.3 (M + m), 24.9 (M + m); IR ($CHCl_3$): ν = 3325, 1745, 1566 cm^{-1}; MS (EI): *m/z* (%): 416 (100) $[M + 2]^+$, 414 (98) $[M]^+$.

3-[Bromo(nitro)methyl] 3-hydroxy-2-azetidinone 2c. From 40 mg (0.18 mmol) of azetidine-2,3-dione **1c**, 48 mg (72%) of compound *anti*-**2c**, containing *ca.* 20% of its *syn*-**2c** epimer, was obtained as colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 1/1); $[\alpha]_D$ = –34.9 (*c* 2.3 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 6.24 (s, 0.2H), 6.14 (s, 0.8H), 5.79 (m, 1H), 5.60 (m, 1H), 5.30 (m, 2H), 4.37 (m, 1.8H), 4.26 (ddt, *J* = 15.0, 4.9, 1.5 Hz, each 0.2H), 4.17 (m, 2H), 3.98 (m, 1.2H), 3.84 (dd, *J* = 9.2, 5.2 Hz, 0.2H), 3.76 (dd, *J* = 15.1, 8.4 Hz, 0.8H), 1.48 (s, 2.4H), 1.45 (s, 0.6H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 164.9 (M + m), 130.6 (M + m),

120.5 (M + m), 110.4 (M + m), 85.6 (M), 85.2 (m), 75.8 (M), 75.2 (m), 74.3 (M + m), 66.2 (M + m), 63.5 (m), 61.1 (M), 44.3 (M + m), 26.4 (M), 26.3 (m), 24.9 (M + m); IR ($CHCl_3$): ν = 3326, 1744, 1561 cm^{-1}; MS (EI): *m/z* (%): 366 (100) $[M + 2]^+$, 364 (98) $[M]^+$.

3-[Bromo(nitro)methyl] 3-hydroxy-2-azetidinone 2d. From 107 mg (0.36 mmol) of azetidine-2,3-dione **1d**, 122 mg (80%) of compound *anti*-**2d**, containing *ca.* 15% of its *syn*-**2d** epimer, was obtained as yellow solid after purification by flash chromatography (hexanes/ethyl acetate, 2/1); mp: 122–124 ^oC (hexanes/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ = 7.28 (m, 6H), 6.82 (m, 2H), 6.48 (s, 0.15H), 6.32 (s, 0.85H), 5.87 (s, 1H), 3.79 (m, 2.55H), 3.76 (s, 0.45H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 160.8 (M + m), 157.1 (M + m), 139.9 (M + m), 130.1 (M + m), 129.1 (M + m), 128.1 (M + m), 127.9 (M + m), 119.4 (M + m), 114.5 (M + m), 85.4 (M + m), 76.1 (M + m), 63.4 (M + m), 55.4 (M + m), 21.3 (M + m); IR ($CHCl_3$): ν = 3328, 1750, 1562 cm^{-1}; MS (EI): *m/z* (%): 422 (100) $[M + 2]^+$, 420 (98) $[M]^+$.