Revisiting the Cleavage of Evans Oxazolidinones with LiOH/H₂O₂

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Batch Mode Preparation of (R)-2-((1s,4S)-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanoic acid (9): To a 1800-L glass-lined reactor under a nitrogen sweep was charged 254.1 kg of THF and 57.0 kg (127.7 mol, LR) of 8 followed by 127.0 kg of THF. To the mixture was charged 66.9 kg (590 mol, 4.6 eq) of a 30% (w/w) solution of hydrogen peroxide in water followed by 2.0 kg of water. The mixture was heated to 25 °C and a solution of 8.7 kg LiOH monohydrate (207 mol, 1.6 eq) in 57.3 kg of water was charged over 4 hours while maintaining the temperature at 25°C and the oxygen content at < 2.5 %. To the reactor was charged 9.9 kg of water and 152.4 kg of THF. The reaction was held for 3 h. The mixture was cooled to 5 °C and 73.2 kg (703 mol, 5.5 eq) of sodium bisulfite in 171.8 kg of water was charged slowly while maintaining the temperature at < 30 °C. The mixture was held for 30 minutes with agitation, then held for 30 minutes without agitation. The phases were split and the bottom aqueous layer was discarded. To the mixture was charged 161.0 kg of N,N-dimethylacetamide (DMAC) and 48.9 kg of THF, followed by vacuum distillation at 130 mbar until a temperature of 70 °C was obtained. To the mixture 26.8 kg of DMAC was added at 70 °C followed by 154.6 kg of water added over 30 minutes. The batch was held at 70 °C for 1.5 hours and 103.0 kg of water was added over 30 minutes. The batch was held at 70 °C for 1.5 hours. The mixture was cooled to 20 °C over 6 hours and held for 60 hours. The slurry was filtered and washed with twice with 167 kg of 1:1 DMAC:Water. The cake was washed two times with 162 kg of 1:3 acetonitrile:water and dried at 50 °C under vacuum to afford 35.0 kg of **9** as a white solid (91.1% yield). ¹H NMR (600 MHz, DMSO-d₆) δ 12.09 (s, 1H), 8.80 (d, J = 4.5 Hz, 1H), 8.06 (dd, J = 9.2, 5.8 Hz, 1H), 7.91 (dd, J = 10.9, 2.8 Hz, 1H), 7.61 (ddd, J = 9.1, 8.2, 2.8 Hz, 1H), 7.45 (d, J = 4.5 Hz, 1H), 3.41–3.27 (m, 1H), 2.72–2.63 (m, 1H), 1.86–1.61 (m, 9H), 1.08 (d, J = 6.8 Hz, 3H); ¹³C NMR (150 MHz, DMSO-d₆) δ 177.7, 159.9, 152.2, 149.8, 145.1, 132.6, 127.2, 118.9, 118.7, 107.1, 39.1, 37.2, 35.7, 28.7, 27.8, 27.2, 26.2, 15.6; HRMS (ESI) calculated for C₁₈H₂₁FNO₂ [M + H]⁺: 302.1551, found 302.1563.





CSTR Mode Preparation of (R)-2-((1s,4S)-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanoic acid (9): To a 250-mL reactor under N₂ sweep was added 50 mL THF. This reactor was connected to a second 1-L reactor containing 30 g sodium bisulfite (288.9 mmol) dissolved in 60 mL water via a teflon line with a diaphragm pump. The base of the Teflon line was maintained at 100 mL volume mark of the 250 mL reactor to maintain a 20 mL residence time. Three HPLC pumps were then used to charge reagent solutions to the 250 mL reactor. Pump 1 delivered hydrogen peroxide (30 wt% H₂O, 145.6 mmol, 6.5 equiv, 0.26 mL/min). Pump 2 delivered a solution of 10.0 g of 8 in 100 mL THF (22.40 mmol, 2.0 mL/min). Pump 3 delivered tetrabutylammonium hydroxide solution (55 wt% H₂O, 35.83 mmol, 1.6 equiv, 0.30 mL/min). Pumps were started sequentially and allowed to run for 60 min before starting diaphragm pump to remove reaction mixture to 1-L quench tank. Assay of the final quenched reaction mixture at the end of addition showed >99% conversion and 80% in-process yield. The lower aqueous layer was then removed and 35 mL DMAC was added. The solution was then distilled at 50 mmHg with a 40 °C jacket to remove the bulk of the THF. The solution was then heated to 70 °C for slow addition of 28 mL water. Upon completion of the addition a suspension had formed and the mixture was cooled to 20 °C. An additional 18 mL of water was added and the resulting slurry aged for 1h at 20 °C. The suspension was filtered, washed with 30 mL 1:1 DMAC:water and dried under N₂/vacuum sweep to obtain 4.8 g of 9 as a white solid (68% yield). Final solids contained 1.0 AP of hydroxyamide 10.



(R)-2-((1s,4S)-4-(6-fluoroquinolin-4-yl)cyclohexyl)-N-((R)-2-hydroxy-1-phenylethyl)propanamide (10): To a 4-neck flask were charged 10.0 g 8 (22.40 mmol, LR), 20 mL water and 80 mL THF. The mixture was cooled to 0 °C for addition of a solution of 2.8 g LiOH-H₂O (67.2 mmol, 3.0 eq.) in 25 mL H₂O over 60 min before warming to 20–25 °C. The reaction mixture was stirred until 8 was consumed. Added 50 mL brine, extracted twice with 50 mL EtOAc then dried combined organic phases over MgSO₄. Concentrated to a low volume, filtered and washed solids with 20 mL DCM to afford 5.0 g of **10** as a white solid (53% yield). ¹H NMR (401 MHz, CD₃OD) δ 8.87 (d, *J* = 4.5 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.10 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.97 (dd, *J* = 11.0, 2.7 Hz, 1H), 7.67 (td, *J* = 8.8, 2.7 Hz, 1H), 7.56 (d, *J* = 4.6 Hz, 1H), 7.34 (d, *J* = 4.4 Hz, 4H), 7.24 (dq, *J* = 8.6, 4.1 Hz, 1H), 4.91 (dd, *J* = 14.5, 6.6 Hz, 1H), 4.81 (t, *J* = 5.0 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.42 – 3.31 (m, 1H), 2.80 (dq, *J* = 13.5, 6.7 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.90 – 1.58 (m, 8H), 1.00 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (101 MHz, DMSO) δ 180.2, 164.9 (d, *J* = 244.6 Hz), 157.6 (d, *J* = 5.6 Hz), 154.7, 150.2, 146.4, 137.6 (d, *J* = 9.4 Hz), 133.0, 132.2 (d, *J* = 9.4 Hz), 131.9, 131.6, 124.0 (d, *J* = 25.7 Hz), 123.7, 112.2 (d, *J* = 22.5 Hz), 69.6, 59.4, 42.6, 40.4, 33.4, 32.6, 32.4, 31.4, 21.1. HRMS (ESI) Calcd. for [C₂₆H₃₀FN₂O₂⁺] ([M+H]⁺): 421.2286, found: 421.2285. IR: 3282, 3059, 2929, 2859, 1631, 1514, 1453, 1217, 1169, 1070, 854, 830, 722, 700, 523, 431 cm⁻¹



