Supporting Information

Efficient, Stereoselective Synthesis of Oxazolo[3,2-*a*]pyrazin-5-ones: Novel Bicyclic Lactam Scaffolds from the Bicyclocondensation of 3-Aza-1,5-Ketoacids and Amino Alcohols

Josef R. Bencsik, Timothy Kercher,* Michael O'Sullivan and John A. Josey

Array BioPharma, 3200 Walnut Street, Boulder CO 80301

tim.kercher@arraybiopharma.com

General Experimental Information

Unless otherwise stated, all reactions were carried out under an atmosphere of dry nitrogen. Reaction solvents were EM Science DriSolv[®] solvents and were used without additional purification or drying. Silica gel plug filtrations and silica gel column chromatography were performed using Merck silica gel 60. Potassium Hydride (30 % dispersion in mineral oil) was purchased from Aldrich Chemical and was washed with dry hexanes prior to use. Wet palladium on carbon was Degussa Type E101 NE/W (10 dry wt %, 50% water) purchased from Aldrich Chemicals. Osmium tetroxide (98.8 %) was purchased from Aldrich Chemicals. ¹H NMR spectra were acquired using a Varian 400 MHz instrument and gradient NOESY experiments were carried out using a Varian 500 MHz instrument. Proton resonances are shown relative to tetramethylsilane (0.00 ppm)

Synthesis of Aryl Substituted 3-Aza-1,5-Ketoacids (1a-e)

1) A suspension glycine methyl ester hydrochloride (16.7g, 120 mmol) in anhydrous DMF (90.0 mL) was treated at rt with DIEA (41.8 mL, 240 mmol) and the

mixture was stirred for 10 min. A solution of the bromoacetophenone (60.0 mmol) in DMF (25.0 mL) was added dropwise over 40 min and the mixture was stirred at rt for 2 h. The reaction mixture was poured into 1:1 brine-H₂O (200 mL) and the mixture was extracted with EtOAc (4X). The combined organic extracts were washed with brine, concentrated and the crude product was used directly in the next step.

2) To a solution of the above, crude product in THF (150 mL) was added 1M Na₂CO₃ (72.0 mL, 72.0 mmol) and the mixture was cooled to 0 °C. Benzyl chloroformate (10.8 mL, 72.0 mmol) was added over 5 min via a syringe. The mixture was allowed to reach rt over 2h and was stirred at rt for 18h. The reaction was carefully poured into 1N HCl and the mixture extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The crude aza-ketoester was purified via silica gel chromatography (20% EtOAc-hexanes for elution).

3) To a solution of the aza-ketoester in THF (350 mL) was added 1M LiOH (150 mL, 150 mmol) and the reaction was stirred at rt for 2h. The THF was removed in vacuo and the aqueous mixture was diluted with water (200 mL). The aqueous mixture was treated with EtOAc (100 mL) and acidified to pH 2-3 by the addition of 2M HCl while maintaining vigorous stirring. The organic layer was removed and the aqueous layer extracted with EtOAc (3X). The combined organic fractions were washed with brine, dried over MgSO₄ and filtered through a MgSO₄-capped silica gel plug (EtOAc elution) to give the pure 3-aza-1,5-ketoacid. Yield range for (1a-e) was 67-79 % over the three steps.

Synthesis of Methyl Substituted 3-Aza-1,5,-Ketoacid (1f)

[Benzyloxycarbonyl-(2-methyl-allyl)-amino]-acetic acid ethyl ester (2). A suspension of dry, hexane-washed potassium hydride (8.18 g, 204 mmol) in anhydrous THF (200 mL) was cooled to 0 °C and a solution of *N*-Cbz glycine ethyl ester (40.3 g,

170 mmol) in THF (200 mL) was added over 10 minutes via a canula while maintaining vigorous stirring. The mixture was stirred at 0 °C for 30 min and at rt for 30 min during which time gas evolution was observed to cease. The reaction mixture was cooled to 0 °C and a solution of methallyl bromide (26.0 g, 187 mmol) in THF (75.0 mL) was added via canula. The mixture was stirred at 0 °C for 30 min and at rt for 16 h. The reaction was carefully quenched by the addition of H₂O (200 mL) and was poured into 1 M HCl (400 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2X). The combined organic fractions were washed with sat NaHCO₃ (2X), brine and dried over MgSO₄. The dried solution was eluted through a MgSO₄-capped SiO₂ plug (EtOAc elution) and concentrated to give olefin **2** (41.3 g, 87 %) as a gold tinted oil.

[Benzyloxycarbonyl-(2-oxo-propyl)-amino]-acetic acid ethyl ester (3). A biphasic mixture of olefin **2** in 2:1 H₂O-THF (600 mL) was treated with OsO₄ (1.13 g, 4.44 mmol) in one portion at room temperature. The darkened reaction mixture was stirred at rt for 10 min and NaIO₄ (95.0 g, 444 mmol) was added. The reaction was stirred vigorously at room temperature for 2 h after which time the mixture was diluted with water. The precipitous mixture was filtered through a Buchner funnel and the collected solid was washed thoroughly with Et₂O. The supernatant liquid and Et₂O washes were combined in a separatory funnel and the organic layer was removed. The aqueous layer was extracted with Et₂O (3X). The combined organic fractions were treated with 0.5 M TMEDA and stirred vigorously for 1h during which the organic layer turned from brown to colorless. The organic layer was removed, washed with brine and dried over MgSO₄. The solution was filtered through a MgSO₄-capped SiO₂ plug (Et₂O elution) and concentrated to give methyl ketone **3** (40.5 g, 93%) as a colorless viscous oil.

[Benzyloxycarbonyl-(2-oxo-propyl)-amino]-acetic acid (1f). A solution of **3** in THF (700 mL) was cooled to 0 °C and 1 M LiOH (400 mL, 400 mmol) was added. The mixture was stirred at 0 °C for 2h after which the reaction was concentrated by the removal of THF under vacuum. The remaining mixture was diluted with cold water (600 mL) and extracted with Et₂O (3X). The aqueous portion was covered with EtOAc and acidified to pH 2-3 by the addition of 2M HCl with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc (2X). The combined organic fractions were washed with brine, dried over MgSO₄, filtered through a MgSO₄-capped silica gel plug (EtOAc) and concentrated. The residue was purified by SiO₂ chromatography (40:60:3 EtOAc/hexanes/HOAc for elution) to give aza ketoacid **1f** (29.1 g, 80%) as a viscous, colorless oil.

Bicyclocondensation: Synthesis of Oxazolo[3,2-*a*]pyrazin-5-ones (**4a-p**)

1) A round-bottom flask equipped with a Dean-Stark trap was charged with the 3-aza-1,5-ketoacid (14.0 mmol), the 1,2-aminoalcohol (15.4 mmol) and dry toluene (70 mL). The mixture was treated with camphorsulfonic acid (97.6 mg, 0.42 mmol) and stirred for 10 minutes at rt followed by heating at reflux for 20 h during which time accumulation of water was observed in the trap. The reaction mixture was cooled to rt and diluted with EtOAc (70 mL). The mixture was washed sequentially with 1 M Na₂CO₃ (2X) and brine. The solution was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was eluted through a silica gel plug (2:1 hexanes/EtOAc) to give the desired, Cbz-protected oxazolo[3,2-*a*]pyrazin-5-one.

2) A solution of the Cbz-protected oxazolo[3,2-*a*]pyrazin-5-one in 2:1 EtOH-EtOAc (150 mL) was treated in one portion with Pd on carbon (1.49 g, 0.70 mmol). The reaction flask was purged with hydrogen gas and the reaction was stirred at rt for 2 h under a balloon atmosphere of hydrogen. The reaction flask was purged with nitrogen and the mixture was diluted with hexanes. The mixture was filtered through a thin SiO₂ plug capped with MgSO₄ (EtOAc elution) and concentrated to furnish the desired oxazolo[3,2-*a*]pyrazin-5-one. If necessary, purification was carried out by SiO₂ chromatography (EtOAc then 10 % [9:1 MeOH/NH₄OH]/EtOAc for elution). Yield range for **4a-p** was 45-87 % over the two steps.

^1H NMR of compound 1a, Cbz rotational isomers (CDCl_3)

¹H NMR of compound 1b, Cbz rotational isomers (CDCl₃)

¹H NMR of compound **1d**, Cbz rotational isomers (CDCl₃)

^1H NMR of compound **1e**, Cbz rotational isomers (CDCl_3)

¹H NMR of compound **1f**, Cbz rotational isomers (CDCl₃)

¹H NMR of compound 4b (CDCl₃)

¹H NMR of compound 4a HCl salt (DMSO)

^1H NMR of compound **4c** (CDCl_3)

^1H NMR of compound 4d, Cbz rotational isomers (CDCl_3)

¹H NMR of compound 4e HCl salt (D₂O)

¹H NMR of compound 4g (CDCl₃)

Gradient NOESY data for **4g** (CDCl₃)

¹H NMR of compound 4h (CDCl₃)

¹H NMR of compound 4j (CDCl₃)

¹H NMR of compound 4k (CDCl₃)

¹H NMR of compound 4l (CDCl₃)

¹H NMR of compound **4m** (CDCl₃)

¹H NMR of compound **4n** (CDCl₃)

¹H NMR of compound **4o** (CDCl₃)

¹H NMR of compound **4p**, Cbz rotational isomers (CDCl₃)

^1H NMR of compound 5, Cbz rotational isomers (CDCl_3)

¹H NMR of compound 6, Cbz rotational isomers (CDCl₃)

^1H NMR of compound **7a** (CDCl_3)

¹H NMR of compound **7b** (CDCl₃)

¹H NMR of compound 7c (CDCl₃)

^1H NMR of compound **7e** (CDCl_3)

¹H NMR of compound **7f** (CDCl₃)

¹H NMR of compound **7g** (CDCl₃)