Supporting Information

Potassium Isopropyl Xanthate (PIX): An Ultra-Efficient Palladium Scavenger

Hong Ren*, Christopher A. Strulson, Guy Humphrey, Rong Xiang, Guangtao Li,

Donald R. Gauthier, Kevin M. Maloney*

Typical Procedure for Palladium removal with PIX: Ceftolozane-TFA (14.3 g at 56 wt%) and 48 mL of a 2.5:1:2 water:DMAc:acetonitrile v:v:v (50:19:31 w/w) were combined and stirred at 22 °C to give a slurry. Isopropylxanthic acid potassium salt (PIX) (0.104 g, 5 mol%) was added in one portion and the resulting reaction slurry was stirred at 22 °C for 30 min. A second portion of isopropylxanthic acid potassium salt (0.104 g, 5 mol%) was added and the reaction mixture was stirred at 22 °C for 30 min. Iodine (0.076 g, 2.5 mol%) was then added and the reaction slurry was stirred at 22 °C for 1 h. The slurry was then filtered and the resulting waste cake was washed with 8 mL of a 2.5:1:2 water: DMAc: acetonitrile. The filtrate and wash were combined and cooled to 15 °C. Ammonium bisulfate (ammonium hydrogen sulfate) (1.449 g, 1.05 equiv) was added and stirred at 15 °C for 15 min. Acetonitrile (12 mL) was added, followed by Ceftolozane Sulfate DMAc solvate (0.08 g). The resulting slurry was aged at 15 °C for 3 h. Acetonitrile (100 mL) was then charged over 10 h and the resulting slurry was aged at 15 °C for 1 h. Solids were filtered, washed with water:DMAc:acetonitrile (2.5:1:13) followed by acetonitrile, and then dried under vacuum with a nitrogen sweep at 25 °C for 17 h to afford Ceftolozane Sulfate DMAc solvate (9.51 g, 89% yield).

Typical Procedure for the preparation of PIX and derivatives: Charge isopropyl alcohol (105g, 1750 mmol, 35 equiv) to reactor and begin cooling to 0 °C. Charge potassium tert-butoxide (6.17 g, 55 mmol, 1.1 equiv) to reactor and stir the mixture for 10 minute at 0°C. Adjust batch temperature to 22-25 °C and age batch for 2 hours. Charge PIX (0.5 g) seed to still. Age batch for 15 minutes at 20-25°C and verify presence of seed bed. Charge CS_2 (3.81 g, 50 mmol, 1 equiv) in 2 hours. Age batch for 2 hours at 22-25 °C after addition of CS_2 is complete. Filter batch. Charge 10X (by volume) isopropyl alcohol to crystallizer, transfer to filter, and displacement wash through cake. Dry cake under vacuum at 22°C. Collected light yellow PIX solid, (7.56 g, 87% yield).

Typical Procedure for Palladium Removal with Activated Carbons and Specialty Resins: Ceftolozane-TFA (2.8 g at 56 wt%) and 9.6 mL of a 2.5:1:2 water:DMAc:acetonitrile v:v:v (50:19:31 w/w) were combined and stirred at 22 °C to give a slurry. Activated carbon or specialty resin (0.14 g, 5 wt%) was added in one portion and the resulting reaction slurry was stirred at 22 °C for 30 min. The slurry was then filtered and the resulting waste cake was washed with 8 mL of a 2.5:1:2 water: DMAc: acetonitrile. The filtrate and wash were combined and cooled to 15 °C. Ammonium bisulfate (ammonium hydrogen sulfate) (0.29 g, 1.05 equiv) was added and stirred at 15 °C for 15 min. Acetonitrile (0.25 mL) was added, followed by Ceftolozane Sulfate DMAc solvate (0.016 g). The resulting slurry was aged at 15 °C for 3 h.

Acetonitrile (20 mL) was then charged over 10 h and the resulting slurry was aged at 15 °C for 1 h. Solids were filtered, washed with water:DMAc:acetonitrile (2.5:1:13) followed by acetonitrile, and then dried under vacuum with a nitrogen sweep at 25 °C for 17 h to afford Ceftolozane Sulfate DMAc solvate.

Typical Procedure for Direct UV-Measurement Study of PIX Stability:
All UV measurements were performed in a solution of 2.5:1:2 water:DMAc:acetonitrile v:v:v (50:19:31 w/w) that was pH adjusted to the appropriate pH using TFA. pH measurements were made using a calibrated pH probe (Mettler Toledo). PIX was added to the pH-adjusted solution to initiate each experiment, and the concentration of PIX varied from 0.03-0.008 mg/mL. The total volume of each reaction was 1.5 mL. Stability experiments were initiated by the addition of PIX. A Hewlett Packard 8452 spectrophotometer equipped with a temperature-controlled cell holder was used for UV measurements. Before each UV measurement, a solution of 2.5:1:2 water:DMAc:acetonitrile v:v:v (50:19:31 w/w) without PIX was used to zero the instrument. Experiments were conducted with the UV temperature cell at 22 °C and stirring at 300 rpm during analysis. 1 cm pathlength quartz cuvettes were used for analysis. The UV profile from 250-350 nm was obtained for each time point measured and the time points of measurement varied for each condition depending on the rate of degradation. For quantitation, the UV absorbance maximum at each condition was used. Each absorbance measurement plotted within a given experiment was the average of at least two trials ± standard deviation of the experiments. Parameters for the kinetics analysis were obtained using least-squares fitting either to a linear or single exponential equation by KaleidaGraph (Synergy Software).

Typical Procedure for HPLC Monitoring of PIX Stability:
Stability experiments were initiated by addition of 4 mg of PIX to a 2 mL solution of 2.5:1:2 water:DMAc:acetonitrile v:v:v (50:19:31 w/w) pH adjusted to the appropriate pH using TFA, which were measured using a calibrated pH probe (Mettler Toledo). An Agilent 1100 series HPLC system (Palo Alto, CA, U.S.A.) was used for chromatographic analysis. The separation was performed on an Atlantis T3 column (150 mm × 3 mm, 3 μm) temperature; 22 °C; detection: UV 319 nm; flow rate: 1 mL/min; mobile phase: eluent A, 10 mM ammonium bicarbonate in water; eluent B, acetonitrile; gradient: initial 5% B; 0−10 min, 30% B; 10−15 min, 95%; 5 min equilibration. PIX concentration from stability experiments was determined by comparing to a response factor from a PIX standard.