

Supplementary Information

Development of a fully automated continuous, integrated production system for all reaction processes of ibuprofen

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General information

In our flow system, PFA tubing (1/16" OD, 1 mm ID) was used for the flow channel, and a syringe pump (KD Scientific Inc.) and diaphragm pump Q5 (Tacmina Co.) were employed for the liquid feed. Furthermore, SEP-10 (Zaiput Flow Technologies) was used for liquid-liquid separation, and V-10 Touch (Biotage Japan Ltd.) was used for solvent evaporation and exchange. Nitromethane was used after dehydration with molecular sieves 4A. All other chemical compounds, including solvents, were commercially available and used without further purification. DFC Ltd (Kyoto in Japan) supplied the photoreactor, 365 nm (6W) LED light source, and Y-shaped mixer (ϕ 1.0 mm). The seven-axis robot arm (Panda) was purchased from Franka Emika GmbH in Germany. XYZ printing Ltd supplied the 3D printer and filaments.

General procedure

A syringe pump was used to introduce solution **1** (1.2 mmol) and AlCl₃ (2 eq.) in MeNO₂ (1.9 mL) as well as solution **2** (1.2 equiv.) in MeNO₂ (2.1 mL) into different channels. Both streams were mixed at room temperature in a Y-shaped mixer and reacted in the PFA tubing (1/16" OD, 1 mm ID, 1.33 m). The reaction mixture was continuously quenched in a tube with 1-N HCl aq. (100 μL/min), which was injected into the main tube using a syringe pump through a Y-shaped mixer. The reaction mixture was liquid–liquid separated by the first SEP-10 (made by Zaiput Flow Technologies) equipped with OB-900, a hydrophobic membrane with a medium pore size. The separated nitromethane solution was washed continuously with distilled water (150 μL/min), injected into the main tube through pump Q5 using a Y-shaped mixer, and separated by a second SEP-10 with OB-900 to collect the nitromethane solution, including intermediate **3** in a 30-mL vial. The collected solution in the vial was evaporated using the high-speed evaporator, V-10 touch, and the solvent (acetone/H₂O (9: 1)/propylene oxide) was exchanged by pump Q5 automatically with robot arm Panda for the next photoreaction. A continuous syringe pump (Fig. 4) injected the solution into the PFA tubing, which was spirally wound around the LED light (365 nm, 6 W) source tube. After 40 min of ice cooling, the reaction mixture was collected in a vial to evaporate and exchange the solvent (acetone/H₂O/propylene oxide→toluene) with the V-10Touch for purification. The solution, which was then injected into the PFA tubing, was continuously quenched in the tube with 0.1 N NaOH aq. (300 μL/min) injected into the tube via a syringe pump through a Y-shaped mixer, and the reaction mixture was liquid–liquid separated by a third SEP-10 equipped with an OB-900. The separated aqueous solution was continuously acidified with 0.5-N HCl aq. (300 μL/min), which was injected by a continuous syringe pump (see SI) through a Y-shaped mixer; pump Q5 was used to add toluene (500 μL/min) to extract and separate the product by using the fourth SEP-10 with OB-900 to collect the toluene solution, including the pure ibuprofen (total yield 38%). Purity of the ibuprofen was determined through NMR measurements, in which no impurities were detected.

Picture S1. Continuous injection system with check valves on the push/pull type syringe pump

