PharmaBlock 2024 ACS Green Chemistry Awarded Project:

Sustainable Manufacturing Process for Commercial & Developmental Stage Intermediates through Two Consecutive Flow Reactions by Micro-packed Bed Technology

PharmaBlock's Technological Advancements

Over the past few years, PharmaBlock has been successful in implementing micro-packed bed technology in various hydrogenation processes for the production of pharmaceutical intermediates. This implementation has led to significant improvements in safety, cost-effectiveness, and speed. Recently, PharmaBlock has broadened the application of this valuable technology by upgrading the production process for tert-Butyl 3-oxoazetidine-1-carboxylate (hereafter as **2**) and its derivatives tert-Butyl 3-aminoazetidine-1-carboxylate (hereafter as **3**). These building blocks are used as raw materials or key intermediates for many drugs and drug candidates.

The upgraded process (as illustrated in Figure 1), equipped with advanced automated engineering designs, has been implemented in the ton-scale of step1 oxidation and hundred-kilo-scales for the step2 reductive amination. The application has delivered substantial improvements in equipment volume efficiency, process mass intensity (PMI), safety, environmental impacts, and ultimately overall cost efficiency.

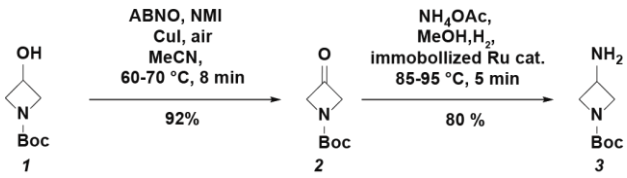

Figure 1. Continuous Oxidation and Reductive Amination

Issues in the Conventional Route

The conventional production process of **2** involves a batch oxidation process, as shown in Figure 2. This process raises safety and environmental concerns due to the use of trichloroisocyanuric acid (TCCA) and dichloromethane (DCM) leading to substantial waste generation and a high PMI. On top of that, the conventional manufacturing process of making **3** relies on a series of steps, which requires the use of malignant reaction solvents like DCM dimethyl formamide (DMF), and hazardous sodium azide (NaN3). Overall, the conventional way not only leads to safety concerns but also massive waste. Therefore, it is imperative to develop a greener approach to manufacturing the two building blocks.

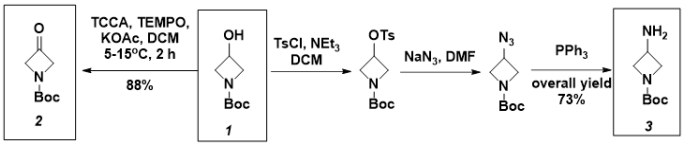

Figure 2. Conventional Batch Mode Production

Innovations by PharmaBlock

PharmaBlock has addressed the above issues by successfully applying enhanced continuous air oxidation and continuous hydrogenative reductive amination.

During the oxidation reaction, the starting material and reagents are pre-mixed and co-injected with air to micro packed bed reactors. After liquid-gas separation, the residual gas undergoes volatile organic chemicals (VOC) treatment. A significant portion of the acetonitrile can be recycled and reused after removing residual water with a membrane technology.

Following batch workup, **2** can be isolated as the final product or proceed to the downstream process. In the reductive amination step, **2** is mixed with ammonium acetate in methanol and the resulting solution is injected together with hydrogen gas into micropacked bed reactors. After completion of the reaction and liquid-gas separation, the residual hydrogen is recycled and reused. Methanol is recycled via distillation, and **3** is obtained after batch workups. It should be highlighted that the whole process is equipped with an automated engineering design that monitors the concentration of acetonitrile vapor and hydrogen. Together with an automatic shut-off function, the design ensures further safety.

In this hydrogenative reductive amination, an immobilized ruthenium catalyst was applied, thanks to its better longevity and performance. 1 kg such catalyst can deliver over 200 kg desired **3**. Additionally, the Ru form used catalysts are also recycled to manufacture new batches of catalysts (as illustrated in **Figure 3**). The refinery of precious metals greatly mitigates environmental impact and can further reduce the overall cost of goods.

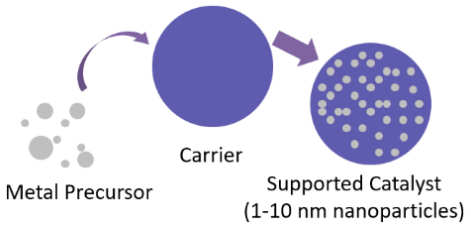

Figure 3. Illustration of the Immobilized Catalysts' Preparation.

Comparison

PharmaBlock has used both conventional and new processes, for tert-Butyl 3-oxoazetidine-1-carboxylate and its derivatives tert-Butyl 3-aminoazetidine-1-carboxylate, in mTs and 200 kg scale. As summarized in Table 1, there is a dramatic improvement with the continuous micropacked bed reaction process. Besides the synthetic route design, the greener alternatives for reagents and solvents are also carefully selected. The new processes use much fewer halogenated substances and avoid hazardous chemicals such as TsCl and NaN3. Both the oxidation and hydrogenation are safely carried out in continuous mode, with much less material being held in vibrant conditions at any time point.

2 MT Campaign to Ketone	**Conventional - Batch**	**New - Continuous Flow**
Instrument VT (volume*time)	5000+ m3*h/ton	800+ m3*h/ton (85%↓)
PMI	20+	≈6 (75%↓)
Halogenated solvent	26 ton/ton	0
200 Kg Campaign to Amine	**Conventional - Batch**	**New - Continuous Flow**
Instrument VT (volume*time)	7,000+ m3*h/ton	≈3000 m3*h/ton (60%↓)
PMI	40+	30+ (≈30%↓)
Halogenated solvent	51 ton/ton	0

Table 1. Comparison of Conventional Process and New Process.

Micropacked bed technology at PharmaBlock

Committed to technological innovation, PharmaBlock continues to explore new manufacturing methods and process optimization solutions. Since its first successful implementation of commercial mT scale hydrogenation five years ago, hundreds of hydrogenation processes and other tri-phase reactions have been applied in PharmaBlock for many clients with micropacked bed technology, which allow PharmaBlock to offer its business partners significant advancements in safety, cost-effectiveness, and speed. In the future, PharmaBlock will keep its focus on innovating chemistry and low-carbon technology for industry sustainability.

P1. Micropacked Bed Technology

About PharmaBlock

PharmaBlock (Stock code: 300725.SZSE) is a global, fully integrated CRDMO that offers innovative chemistry products and services throughout the pharmaceutical R&D process and commercial manufacturing. Officially operated in 2008, PharmaBlock has partnered with almost all the top 20 pharmaceutical companies and hundreds of biotech companies around the world. Its dedication to advancing innovation in chemistry and low-carbon manufacturing supports partners to accelerate drug discovery and development, ensure consistent quality, reduce R&D and manufacturing costs, and foster a greener and more sustainable future.

P2. PharmaBlock Nanjing Site