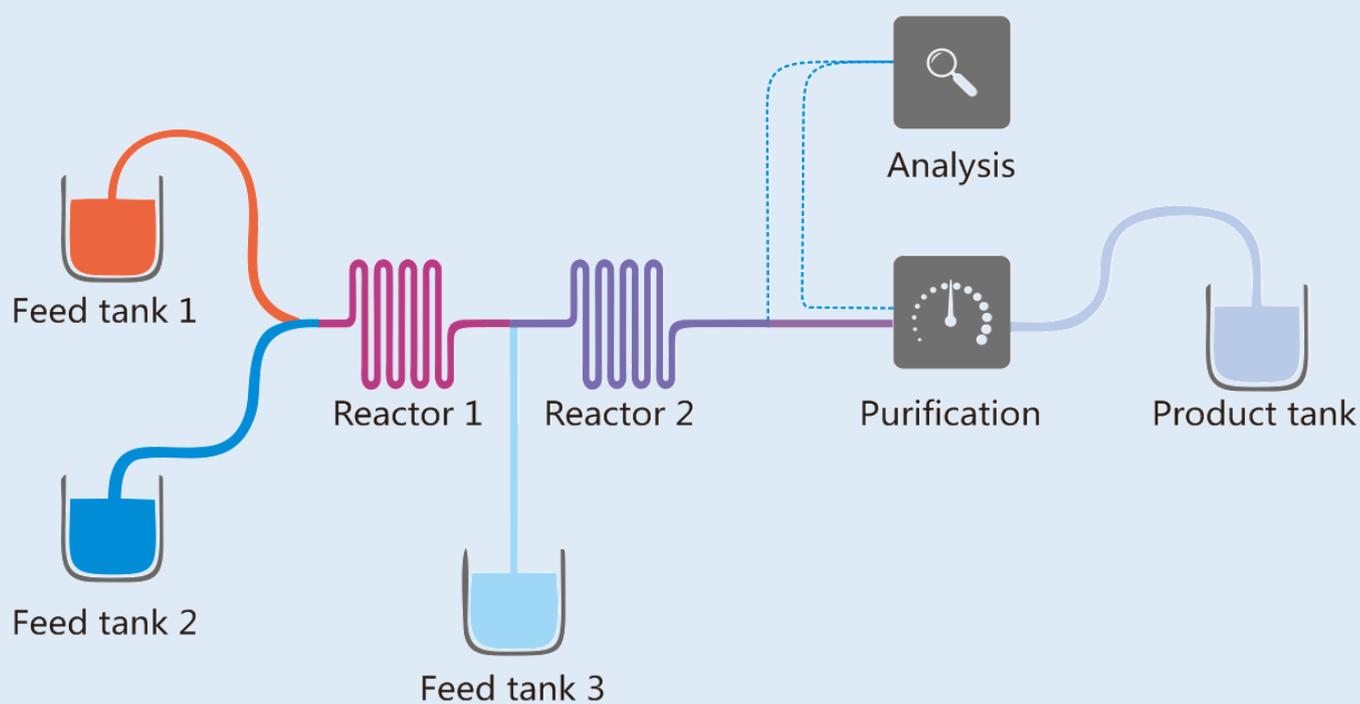


Flow chemistry

An optimized solution for diazotization reaction



The diazotization reaction is one of the most important and fundamental reactions on industrial scale¹⁻³. It is widely applied in the pharmaceutical and dye industry, and included in many classical reactions like the Sandmeyer Reaction, Gomberg-Bachmann Reaction, Meerwein Reaction, and Balz-Schiemann Reaction.

Challenges of the diazotization reaction

Maintaining constant low temperature for the formation of the diazonium salt is critical and can have a large impact on the product quality as side-reactions can occur very quickly at higher temperatures. This makes batch production more challenging.

Also, the diazonium salts produced by the diazotization reaction are high-energy compounds containing a diazonium group ($-N^+ \equiv N^-$) as shown in **Figure 1**. Such compounds have poor stability and could decompose easily and rapidly. Under some extreme conditions, the compounds generate 1 equivalent of nitrogen gas upon decomposition, which could cause an explosion. These compounds are also toxic, which will bring hazardous risks to the operators during batch production. Thus, the application of diazotization reactions in scaling-up or manufacturing is very challenging.

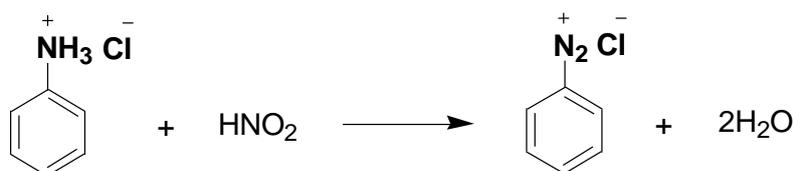


Figure 1. Simplified reaction for diazotization

Flow chemistry: An optimized solution for the diazotization reaction

Flow chemistry technology has been gaining in popularity over the past years. Flow reactors enhance the mass and heat transfer rate with high mixing efficiency, and enable a precise control over the reaction parameters, such as reagents charging times, residence times, reaction pressures, and reaction temperatures.

Compared to conventional batch reaction process, the continuous flow technology and reactor provide an opportunity for continuous direct conversion of small amounts of in situ generated diazonium salts to the desired products. Thus, a continuous flow reaction can effectively reduce hazardous risks to the operators, accordingly increasing the potential for expanding the use of diazo compounds in organic synthesis⁴⁻⁹. Especially with the development of micro flow reactors, which is a new approach to improve thermal conductivity and mass transfer performance, the risk of overheating will be significantly suppressed.

In addition, flow technology can increase the yield and purities of products, with less efforts spent on purification and lower cost of raw materials. Meanwhile, capital cost and delivery time will be greatly reduced as well, thereby accelerating the research and development for new drugs.

What makes PharmaBlock unique?

Extensive flow chemistry experience

- Pharmablock has successfully applied flow chemistry in multiple reaction types, including but not limited to high temperature and high pressure reactions, cryogenic reaction, oxidation reaction, Curtius rearrangement reaction, reaction with highly toxic substances, photocatalytic reactions, and Diazotization reactions.
- At PharmaBlock, our scientists' accumulated chemistry capabilities and comprehensive understanding of chemical properties is a plus for successful application of flow chemistry to tackle scale-up challenges.

Robust engineering capabilities to increase the flexibility of flow chemistry application

- Purchasing commercially available micro and flow reactors and equipment is a large expense and reactors usually need to be tailor-made for specific reactions.
- PharmaBlock has a professional team specialized in mechanical, electronic and automation engineering, and able to design and assemble the flow reactors with high flexibility.
- Currently, Pharmablock is already equipped with self-assembled flow reactors of diverse materials (PFA, SiC, SS316, etc.), and different volumes (ranged from 1 mL to 10 L). It also has some special equipment like micropacked bed and photocatalytic reactors. These flow reactors are applied in both the lab and manufacturing scale to serve different projects.



Figure 2. Flow-photo pilot scale (Self assembled)

Diazotization flow technology applications at PharmaBlock

1. Bromination via Diazotization

Case A: Pharmablock worked on a project for a customer with bromination via Sandmeyer reaction. The previous process involved an isoamyl nitrite/ CHBr_3 system with highly hazardous and explosive reagents. 100 kg+ scale diazotization was required. In Consideration of the hazardous risks and high cost, PharmaBlock developed a continuous flow diazotization process with lower-cost $\text{NaNO}_2/\text{CuBr}$ reagents shown in **Figure 3** below.

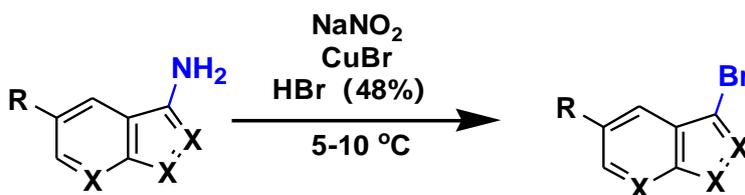


Figure 3. Case A: Bromination via Diazotization

By the optimized process, 162 kg of the final product was obtained. In the flow process, the residence time was 5 seconds, and the space-time yield could reach to 22 kg DP/h/L (micro reactor volume) to give 80-85% yield. Pharmablock's goal is for our clients' synthesis to run successfully and safely with shorter lead-times and lower cost.

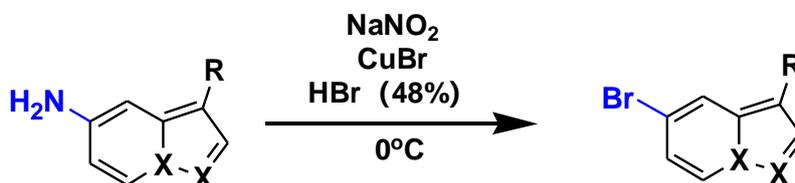
Case B:

Figure 4. Case B: Bromination via Diazotization

Another similar reaction for the Case B above, PharmaBlock determined it would be advantageous to apply flow technology to scale up the reaction and reduce risks.

- 100 kg final product
- 60-70% yield
- Space-time yield: 10-15 kg SM/h/L (micro reactor volume)
- Reaction time: 22 sec.

2. Hydrazine preparation via diazotization

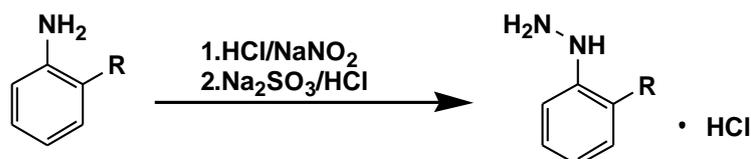


Figure 5. Hydrazine preparation via diazotization

This reaction is a case where the diazonium salt is reduced to hydrazine. The diazonium salt was formed at low temperature, and reduced with Na_2SO_3 and hydrochloric acid at high temperature to prepare hydrazine hydrochloride. In the batch process, the precise temperature control is difficult, therefore a significant amount of by-products was observed.

Transitioning the process to continuous flow chemistry as shown in **Figure 6** below, Pharmablock used a 3.6 kg DP/h/L micro reactor to improve the yield to 90-95% and are still working on applying the process to larger scale production.

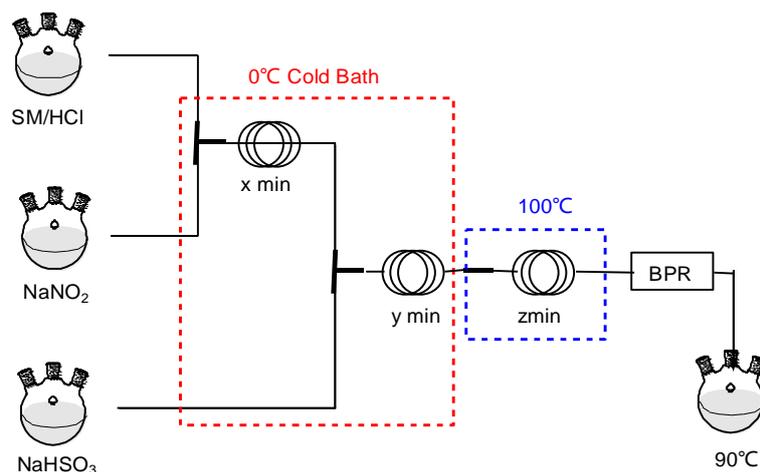


Figure 6. Scheme of Hydrazine preparation via diazotization

3. Aliphatic alcohol preparation via Diazotization.

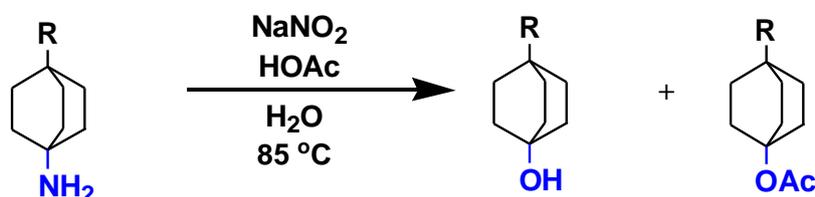


Figure 7. Aliphatic alcohol preparation via diazotization

This case is an example of aliphatic alcohol preparation via Diazotization. Because an alkyl diazonium salt is more unstable than the aromatic diazonium salt, Pharmablock developed a flow process to optimize and manufacture the product.

- Pilot-scale tubular reactor
- 10 kg final product
- 73% yield
- Space-time yield: 4.2kg SM/h/L (micro reactor volume)
- Reaction time: 55s.

4. Pyrazole formation via diazotization

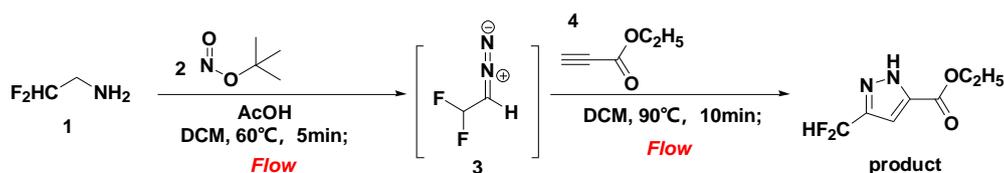


Figure 8. Pyrazole formation via diazotization

In this Pyrazole formation via diazotization case, the generated difluoroethyl diazonium salt (3) is gaseous at atmospheric pressure and extremely unstable. A slight friction can cause explosive decomposition.

In the flow process, diazo compound (3) is consumed continuously without any material accumulation. Then (3) is reacted with the alkyne reactant to obtain the final product directly. In this process, diazotization can be completed in 6 min in a DIY micro reactor (space-time yield: 1.35 kg DP/h/L) to give product in over 90% yield. The scheme is shown in Figure 9.

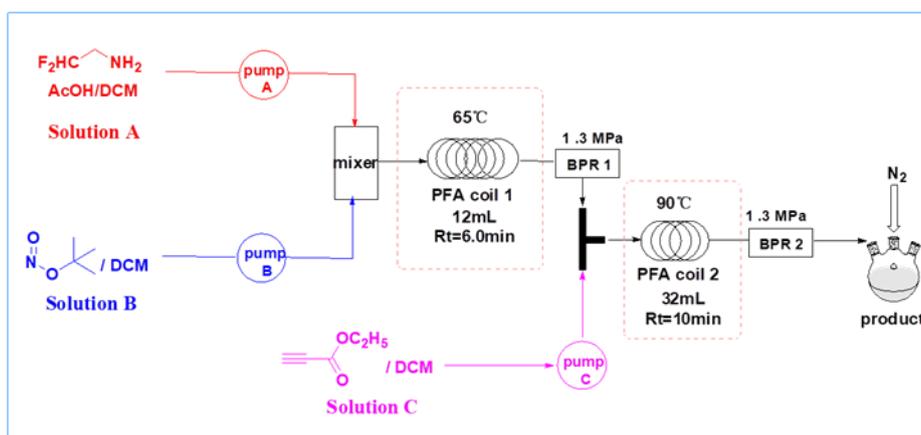


Figure 9. Pyrazole formation via diazotization

A glimpse into the future

As an emerging technology, continuous flow chemistry is being applied in more and more reactions. On the basis of ensuring safety, the flow chemistry process can facilitate scale-up production, improve quality, and enhance time and cost-efficiency of the diazotization reaction.

PharmaBlock is looking forward to expanding the application range of micro reactors in different reactions. With the increasing demand from customers, reactors of different sizes and types need to be designed and developed to accelerate pharmaceutical manufacturing. Another key point to its future will be the collaboration between AI or automated manufacturing and micro reactor technology to achieve multi-step continuous manufacturing.

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