Review Article

Flow Synthesis: A Approach Towards Efficient Organic Synthesis

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Abstract

The notion of flow synthesis, i.e. high yielding and selective organic synthesis using flow techniques, is discussed. Flow synthesis of few drugs are explained with some instances. In terms of environmental compatibility, efficiency, and safety, flow methods outperform batch approaches. Flow method synthesis, on the other hand, is more challenging than batch method synthesis. Indeed, it has been suggested that while flow techniques may be used to produce basic gases, they are challenging to apply to the synthesis of complex compounds such as natural products and APIs. On the other hand, synthesis and reactions that attain high yields and high selectivities by flow methods are increasingly reported. Flow methods are leading candidates for the next generation of manufacturing methods that can mitigate environmental concerns toward sustainable society.

Keywords: Purification, Flow,Techniques,Active pharmaceutical ingredients

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Introduction

Chemical synthesis is mostly accomplished using either a batch or a flow approach. All starting ingredients, additives, solvents, and so on are put into a flask or a reaction vessel before the commencement of a reaction and released, together with the result, after the reaction, generally by performing a work-up procedure that includes purification. This method is now by far the most common in most organic chemistry and synthetic organic chemistry laboratories, and the production of fine chemicals such as active pharmaceutical ingredients (APIs), agrochemicals, electronic chemicals, fragrances, and so on has mostly been done by repeating batch methods.

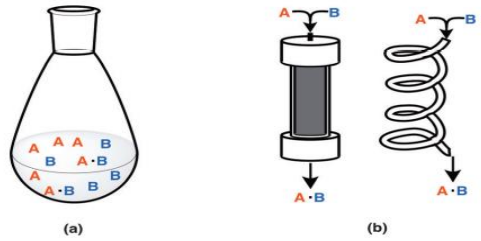


Figure 1. Batch method (a) and flow method (b).

Flow techniques, on the other hand, charge and discharge materials at the same time. Starting materials are constantly fed into one end of a column or a hollow loop, and the product is continuously eluted from the other end of the column or loop. Flow techniques have been employed in the large-scale production of basic chemicals via gas-molecule reactions; ammonia synthesis via the Haber–Bosch process is a classic example.[1,2]

more amenable to automation. Because starting material and reagent solutions are fed by pumps, the flow on/off and flow rate can be readily modified and programmed by a computer. The sequential reaction of diverse combinations of substrates and reagents is enabled by the switching of bulbs.Although millimetre and centimeter-sized reactors can be utilised in continuous flow synthesis, flow microreactors with micrometer-sized channels or tubes are frequently employed sequentially.[5,6,7]

Because of the following characteristics of micro spaces, flow microreactors with micrometer-size channels or tubes are frequently utilised.

(1) Rapid mixing: Many chemical reactions involve the combination of two components. As a result, mixing to achieve solution homogeneity is critical, especially for quick reactions. Mixing happens as a result of molecular diffusion.Therefore, according to molecular diffusion theory the time required for molecular diffusion is related to the square of the diffusion path length. As a result of the considerable shortening of the diffusion route based on micro structures, a mixing speed unattainable in a macro reactor is achieved.

(2) Phase-to-phase mass transfer: Much higher surface-to-volume ratios in flow microreactors improve the efficiency of phase boundary reactions such as gas/liquid, liquid/liquid, or solid/liquid reactions. This property of flow microreactors is also beneficial in photochemical and electrochemical processes.

The Benefits of Continuous Flow Synthesis

Continuous flow synthesis is often performed in channel or tube reactors. Pumping delivers starting materials and reagents to the reactor's inlets. While homogeneous catalysts are also supplied at the inlets, solid catalysts are typically supported inside the reactor.[3,4]As the solution flows from the inlet to the exit, the reaction continues.As a result, the progress of the reaction may be connected to the reactor's spatial position.Automation is required for the time-efficient synthesis of a large number of compounds for screening, and for batch processes, a range of automated synthesisers, such as 48-well and 96-well parallel reactors outfitted with several automated syringes controlled by a computer, have been created. Continuous flow operations, on the other hand, are

(3)Temperature management enables reactions that do not require cryogenic conditions: Temperature is frequently a critical element in controlling chemical reactions. Micro spaces have higher surface-to-volume ratios than macro spaces. Because of this property, heat transfer occurs quickly, allowing for fast cooling in a flow microreactor and, as a result, accurate temperature control. As a result, in batch macro reactors, processes that need cryogenic settings may be performed at considerably greater temperatures, such as ambient temperature.

(4) Extremely high temperatures and pressures: Fast heat transmission is also useful for high-temperature processes.Flowmicroreactors, when combined with high-pressure tolerance, enable unorthodox processes and extreme process conditions.[8]

Few examples of synthesis

Olanzapine is one of the world's best-selling medications. It inhibits the dopamine receptor type 4 (D4 receptor) and the serotonin receptor type 2 (5HT2 receptor), and it is used to treat bipolar disorder and schizophrenia. Olanzapine was synthesised in a multistep flow synthesis using the synthetic process depicted in Figure 2.The three-step continuous synthesis of thieno[1,5]benzodiazepine began with Pd-catalyzed amination of thiophene and aryl iodide. At 50 degrees Celsius (high-frequency inductive heating), a solution of thiophene, aryl iodide, Pd2 (dba)3, Xantphos, and nBu4NOAc in ethyl acetate was poured into a reactor packed with steel beads. The reaction stream was extracted in-line, then passed through a silica cartridge to eliminate any residues of Pd. The nitro group was then reduced by passing a solution and Et3SiH in ethyl acetate down a column filled with Pd/C and cotton wool.[9]

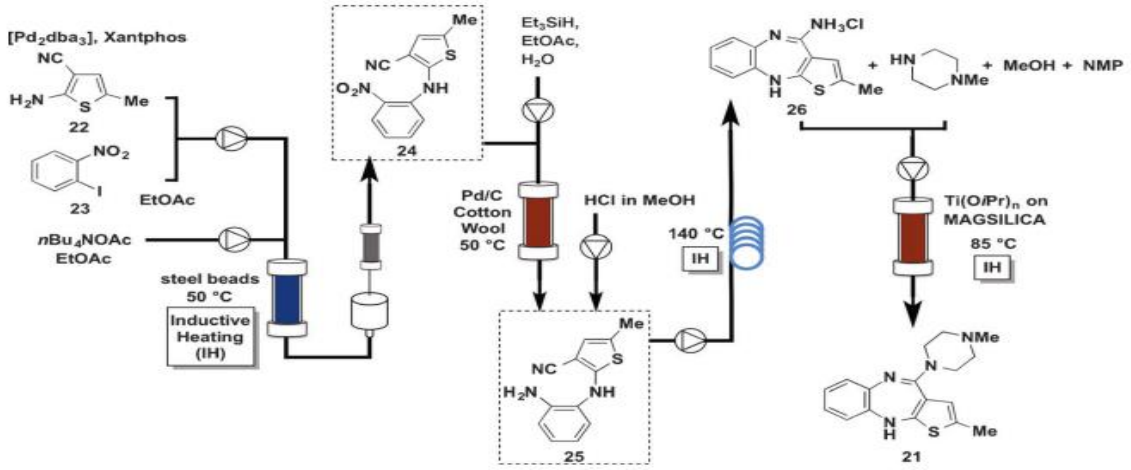


Figure 2. Flow synthesis of olanzapine

Ibuprofen is a nonsteroidal anti-inflammatory medication with a high volume of administration (NSAID). Two continuous-flow ibuprofen syntheses have been reported: the first, in 2009, is a basic, laboratory-scale synthesis, and the second, in 2015, is a scale-up synthesis including chemical engineering methods. The first three-step, continuous-flow synthesis of Ibuprofen was carried out in a simple microreactor that did not require any purification or isolation procedures. A detailed retrosynthetic study of Ibuprofen was done to obtain this continuous-flow synthesis. As a result, processes have to be planned in such a way that by-products and surplus reagents from one reaction may be used in subsequent reactions. Figure 3 and Figure 4 depicts the typical three-step synthesis of Ibuprofen.[10,11]

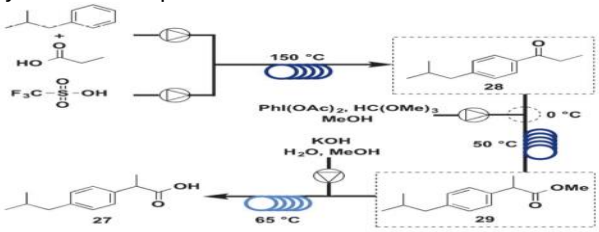


Figure 3. Flow synthesis of ibuprofen (27); Part 1.

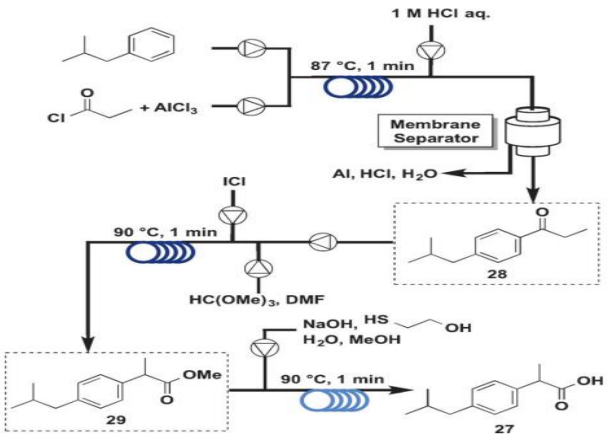


Figure 4. Flow synthesis of ibuprofen (27): Part 2.

Artemisinin is a sesquiterpeneendoperoxide that is particularly efficient against Plasmodium falciparum, the protozoan parasite that causes malaria. Artemisinin was semisynthesised using a continuous-flow approach that began with dihydroartemisinic acid (DHAA), which was obtained from artemisinic acid by hydrogenation or generated by fermentation in modified yeast. Artemisinic acid may be extracted in large volumes from the herb Artemisia annua (sweet wormwood) or generated in modified yeast.[12,13]

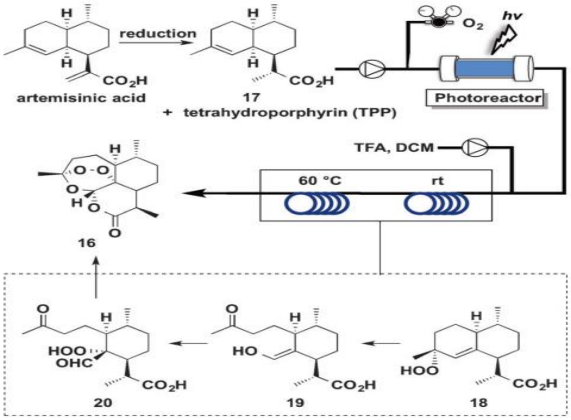


Figure 5. Flow synthesis of artemisinin

Continuous flow synthesis aided by microwaves

A continuous flow microwave reactor organic synthesis on an industrial scale has been presented. The reactor herein provides for the safe and efficient processing of organic reaction mixtures (with or without solvent) at high temperatures and pressures. This process results in extremely quick reactions that are practically difficult to achieve in batch mode on a large scale. Although the current research has concentrated on the benefits of this technology for organic transformations at high temperatures, the reactor may also be employed at lower temperatures, which are more important for the synthesis of pharmaceutical intermediates. The already specified laboratory-style microwave unit has a processing capacity of 20 l/h (500 l per day), which roughly matches to the limits of the pumps now in use. The system's throughput may easily be enhanced by extending the diameter of the tube, increasing the flow velocity, and using higher powerful magnetrons (e.g., 30 kW), which can assure quick and efficient volumetric heating of the reactor zone. The microwave frequency is a key additional aspect, since using, for example, 915 MHz technology allows for greater penetration depth while also increasing energy efficiency.[14]

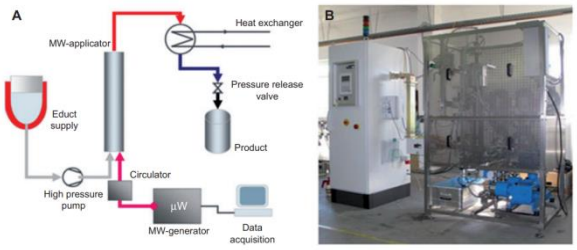
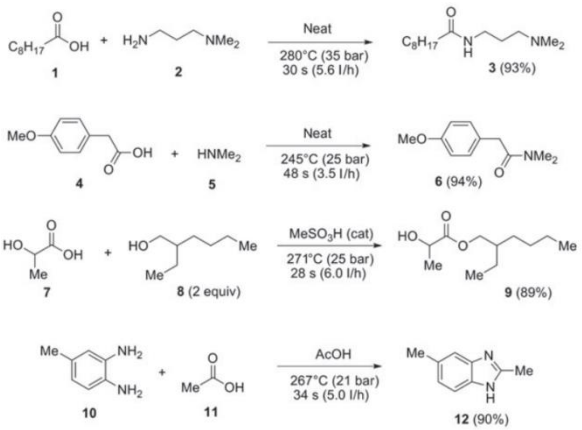


Figure 6(A) General design of the continuous microwave synthesis unit; (B) graphical image of the unit.

Examples of chemical transformations achieved utilising the flow microwave system introduced above are given in Scheme 6. To generate proof-of-concept and basic kinetic data, all reactions were first tested and adjusted on a small scale using a monomode microwave batch reactor (Biotage ® Initiator, Uppsala, Sweden).

Following that, the reactions were carried out in the flow equipment with a single input on scales ranging from 3 to 60 mol.The reaction zone was a 75 cm 1 cm i.d. Al $_2O_3$ ceramic tube positioned inside the applicator. The time values in Figure7 indicate the reaction mixture's average residence time inside the microwave heated zone.[14]



Scheme 1 Microwave flow conditions were used for high-T/p chemistry. With a power usage of 1.35 – 2.8 kW, 90 percent of microwave power was typically absorbed.

Conclusion

Flow synthesis is a very innovative procedure for the synthesis of organic compounds which is environment friendly and economic and saves times and has high yield and can be used for the synthesis of novel drugs as an alternative to batch synthesis.

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