Flow Reactor Networks for integrated synthesis of active pharmaceutical ingredients

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The current thesis presents the realization of the Novel Process Windows (NPW) concept, which relies on two intensification principles. The first is the chemical intensification of a single reaction step with the purpose of intensifying the intrinsic kinetics. This is usually achieved by confining the reactants within a system under high temperature, high pressure and high concentration. The second principle is process-design intensification, which aims at integrating reaction steps and simplifying the overall process. In this context, the thesis describes the development of flow reactor networks with the goal of intensifying single reaction steps and subsequently constructing a multi-step process to deliver active pharmaceutical ingredients. In order to deliver sustainable processes, special attention is given to the chemical reagents used and their characteristics such as toxicity, chemical stability and cost. Green chemistry and green engineering principles serve as a guideline in the decision making process.

Organochlorides represent a class of valuable intermediates in the pharmaceutical industry. The biggest concern associated with the way organochlorides are prepared is the use of chlorinating agents. They are used in stoichiometric or excessive amounts leading to a low atom economy and a substantial generation of waste. To address this concern, chapter 2 presents a process where hydrochloric acid is used to convert alcohols to the corresponding chlorides. Hydrochloric acid presents a valid alternative to the toxic and wasteful chlorinating agents since only water is generated as a by-product. The synthesized chlorides are further used in a micro flow network consisting of multi-step synthesis of antiemetic drugs and antihistamines. Cinnarizine and a buclizine derivative were constructed from bulk alcohols in a 6-stage 4-reaction step processes. The whole sequence was realized in 90 minutes with good overall yields (>80%) at a production rate of 2 mmol of final product per hour. The drawbacks of the process were the excessive amount of hydrochloric acid required and the use of a reagent loop, leading to only a partial continuity of the process. Chapter 3 presents a solution to aforementioned drawbacks, in the form of a fully continuous process with the use of 1.2 equivalents of hydrogen chloride. The process was superior due to the switch from hydrochloric acid to pure hydrogen chloride gas. Furthermore, water use minimization was achieved due to the switch from hydrochloric acid, where hydrogen chloride gas is dissolved in water, to pure gas. Safe pressurization in micro flow allowed the maximization of hydrogen chloride solubility in alcohol and its local concentration even further. To the best of our knowledge, this was the first documented use of pure hydrogen chloride gas in a continuous process.

High temperature, pressure and concentration are the main tools in chemical intensification as mentioned above. Chapter 4 aims to investigate the effects of pressure...
on chemical reaction kinetics and regioselectivity of 1,3-dipolar cycloaddition. Increasing pressure within the reactor from 500 bar to 1800 bar favored the selectivity demonstrated by a 30% increase of the 1,4-regioisomer of cycloadduct. Meanwhile, only a marginal increase of 8% in conversion leading to a final conversion of 78% was observed. Bringing the reaction system into a continuous-flow micro reactor did not improve the conversion when high pressure was used. Instead, it was shown that high pressure was a good tool to achieve superheated conditions allowing a greater extent of chemical intensification by temperature. Chapter 5 concentrates on a further intensification of 1,3-dipolar cycloaddition to produce a rufinamide precursor in a continuous mode using inexpensive and relatively green dipolarophile. Due to the low reactivity the reaction in batch takes more than 24 hrs. When the cycloaddition was performed in a micro flow capillary reactor under neat conditions at 210 °C and 70 bar, reaction time decreased to 10 min. The rufinamide precipitated a problem of blockage within the reactor of micro dimensions, as it is in its solid state under atmospheric conditions. In order to avoid crystallization of the cycloadduct, an anti-solvent was introduced into the hot product flow in its molten state. Upon cooling in the collection vessel, the product precipitated in its crystalline form. Such an approach allowed to merge the reaction and separation stages, simplifying the process.

Chapter 6 describes the combination of the single-step intensifications described earlier to develop a continuous process of a rufinamide precursor and realize process-design intensification. 2,6-difluorobenzyl alcohol was converted to the corresponding chloride through the use of hydrogen chloride gas. Subsequently, without intermediate separation, the chloride was converted to 2,6-difluorobenzyl azide. The latter was then separated in an in-house developed inline L-L separator and further fed into a final reactor to undergo the aforementioned cycloaddition to an inactive, but green dipolarophile. Upon collection cycloadduct crashed out of the anti-solvent in 82% overall yield. The entire process relied on no solvent, nor catalyst, and a minimum amount of water. Thus, an own momentum of process-design intensification was identified, which is more than the added momenta of chemical intensification.

Chapter 7 presents an evaluation of the developed 5-stage 3-reaction step process to produce a rufinamide precursor. Batch and flow process models were developed to be compared in terms of material and energy requirements. In the batch process, large amounts of organic solvents are used. Moreover, intermediate separations require a significant amount of water. Thus, when compared against the batch process, the continuous flow process is more efficient in terms of material use and waste generation. The cost of the equipment was calculated to be similar, while operating expenditures are expected to be lower for continuous flow process than for batch. A life cycle assessment showed the environmental profile of process in terms of environmental, toxicity and health aspects. The human toxicity factor was found to be marginal in the case of the continuous flow process as opposed to the batch process. The global warming potential of the batch process was found to be remarkably higher than that of the flow process. This is mainly attributed to the air emissions which account for 53% of the total GWP profile of the batch process. The next contributory factor is the energy needed for solvent production. In overall, the continuous-flow process was found to be more favorable in terms of economic and environmental impacts. Finally, chapter 8 gives an overview of the research impacts achieved in each area related to continuous manufacturing of pharmaceuticals in micro flow.

The current thesis represents one branch of a concerted research cluster, supported by the ERC Advanced Grant “Novel Process Windows – Boosted Micro Process Technology” (no. 267443). As mentioned above, it covers comprehensive investigations of NPWs using the classical chemical-engineering activation means, such as high temperature, pressure and concentration. The activation means are exploited within the exploration of new chemical transformations taking place in constructed flow reactor networks for which the achievement of process simplification was crucial. This connects to the other principle of NPW, process design intensification, explored in the thesis of I. Vural-Gursel (ISBN: 978-90-386-3957-4). The overall concerted NPW approach is fully realized when investigation of green solvents’ use for NPWs (thesis S. Stouten, ISBN: 978-94-6233-355-0), exploration of new activation means via electromagnetic waves (thesis of E. Shahbazali, to be published in March 2017), and assurance of intrinsic safety provided in micro-flow (thesis of M. Shang, ISBN: 978-90-386-4061-7) are demonstrated.
To my men, Mirotje and Marktje.
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While still living in Uzbekistan, I remember learning that our tall and handsome neighbor was a PhD student, a term I never heard before at the age of 11. After inquiring about the prerequisites, as in having completed bachelors and masters, benefits, as in how high was the salary, and future prospects, as in whether a job was guaranteed, I concluded that our neighbor was a naive lunatic with no future prospects. Yet, here I am at the end of my PhD years needing to say a bittersweet good bye. Over the past four years, I had the pleasure to work among talented and inspiring people who enabled me in multiple aspects.

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CHAPTER 1

Introduction

This chapter is based on:


1.1. CONTINUOUS MANUFACTURING IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry continuously investigates, discovers, develops and delivers new treatments to existing and emerging diseases\(^1\). Meanwhile, it faces the challenges such as slower success rate, expirations of patents, intense price competition with generics and tighter constraints due to environmental concerns\(^2\). According to a recent Pharma Profile report less than 12% (Figure 1) of the candidate medicines that are successful in phase I clinical trials are approved by the FDA\(^3\). Developing a new medicine on average takes at least 10 years and costs $2.6 billion. The economic pressure has been on since early 2000s, when the number of approved medicines has essentially decreased, while research and development expenditures soared as shown in Figure 2\(^4\).

Malet-Sanz et al. described a usual sequence of events in drug development carried out in Pfizer\(^5\). From the beginning of the development, a large number of hits is identified, followed by the lead discovery stage, where the structures are varied to deliver the desired target activity, selectivity, metabolism and pharmacokinetics. At this stage only 5-10 mg of the compound is needed for primary testing. Selected compounds are categorized into 1-3 series based on their structural similarity. At this point less than 100 compounds are prepared in the amounts of 500 mg to 1 g for pharmacokinetic studies. Within the investigated compounds a particularly interesting compound will then be synthesized to yield 1-2 g of solid material for pharmacokinetic and toxicity studies. If the study results in a promising fate for a candidate, a first exploratory toxicology study will require 5-30 g of the compound, followed by yet another scale-up to deliver 30-500 g for second species toxicity studies. In case of a positive outcome the commercial route to drug will be designed and kilograms of the drug will be needed for the clinical trials. As the product moves along the development process, production batches get larger as more material is required. Figure 3 shows how the process development of a drug consists of a series of scale-ups. Consequently, process that can operate at various scales with a constant quality becomes one of the necessities in the pharmaceutical industry. Continuous processing offers a variable production volume that serves as a solution at every stage of the development process. Moreover, early investigation of the continuous processing leads to a better understanding of process and of the critical product attributes, which in turn contributes to an easy transition from medicinal chemistry to commercial route.

In pharmaceutical industry chemical reactions are run continuously in either continuous flow stirred-tank (CSTR) or plug flow reactors (PFR)\(^6\). Despite their wide applicability and mechanical simplicity, CSTRs operate in highly nonlinear mode in terms of the degree of mixing and fluid motion. The complexity grows with the increasing number of phases, presenting a great challenge during the switch from lab to a larger scale. As opposed to CSTRs, PFRs provide a more uniform environment for the reactants and a more efficient use of a reactor volume. Uniform environment due to the enhanced mixing on a molecular level can be achieved when static mixers\(^7,8\) or mechanical elements, such as spinning disc or rotating tube-in-tube, are incorporated\(^9,10\). In addition, packed bed reactors...
with immobilized catalyst or enzymes benefit from decreased diffusion path and increased contact area leading to higher reaction rates per given volume. Further control over operating parameters and outcomes can be achieved when micro flow reactors are used, as discussed in the following section.

1.2. MICRO FLOW CHEMISTRY

Micro reactors came into play within organic synthesis since the advancement of microfabrication techniques in 1990s. Microfabrication allowed the production of reactors with channel size ranging from submicrometers to submillimeters. The main advantage of the decreased channel dimensions, under otherwise same operating parameters, is the increase in the Reynolds number, which leads to a decrease in the diffusion path and increase in the specific heat and mass transfer areas, resulting in a high control over the temperature and reactant distribution. The biggest drawback, however, is the large pressure drop along the narrower channels, which leads to the requirement of lower flow rates resulting in laminar flows. Laminar flow is a constant unidirectional flow of fluid elements that move with a constant velocity with respect to the stream axis. Viscous forces dominate over inertial forces, resulting in an undesired well-defined parabolic flow that results in wider residence time distribution. Thus, the convective mass transfer takes place along the direction of the fluid only, limiting the mixing of species to diffusional transport.

Similarly to the large scale industrial PFRs, diffusional transport of mass and heat can be enhanced in micro reactors when secondary flows are created by active or passive methods. Active methods rely on an external source of energy, such as ultrasound, microwave or piezoelectricity. Certain mechanical tools can be incorporated as well, such as actuators or pulsating walls. However, due to the simplicity and lower risk of mechanical malfunction passive methods are preferred over active. Passive methods rely on the flow energy gained from the pressure provided by an upstream pump and on the geometry of the micro channels. Based on the geometry and size of the channel multiple lamellae can be formed leading to a drastic decrease in the diffusion path. Flow focusing, split-and-recombine, colliding jets and recirculation techniques can further be used to decrease the diffusion path and increase heat and mass transfer. As a result, plug flow behaviour and narrow residence time distribution are attained.

Given the advantages of operation within the micro channel, micro flow environment on its own provides two classes of intensification: mass transfer intensification and heat transfer intensification. Mass transfer intensification provides a more uniform distribution of reactants and products due to a better mixing, which leads in some cases to higher selectivity and faster reaction times. Decreasing channel size increases the heat transfer coefficient, which in combination with increased surface area maximizes the heat transfer. In this way, the formation of hot spots is minimized and thermal overshooting is avoided, leading to a safer operation and in some cases higher selectivity. Finally, due to the fact that micro flow reactors can be used in continuous processes, the process can not only be intensified due to the mass and heat transfer intensification, but also by establishing a continuous process when batch chemistry is transferred into continuous.

1.2.1 Classification of reactions in micro flow

Despite the intensification brought by micro flow reactors, not every reaction can be carried out in micro reactors. Roberge and coworkers analyzed 22 large scale processes employed in fine chemicals and pharmaceuticals synthesis in Lonza Exclusive Synthesis. Based on the analysis, 50% of the reactions can benefit when carried out in micro flow. The reactions are categorized based on their kinetics into four classes, A, B, C and D. Class A represents extremely fast and exothermic reactions that occur within the mixing zone and completed within a seconds range. Tight control over heat transfer minimizes the formation of hot spots leading to higher selectivity in parallel-competitive reactions. Class B reactions represent reaction usually carried out at cryogenic conditions. Class C reaction are exothermic reactions that are completed in less than 10 min time and benefit from better mixing and better heat transfer, while still requiring some time to react due to slower reaction kinetics. Class D encompasses slower reactions that are
kinetically limited and pose some safety concerns, such as autocatalysis and thermal accumulation. Finally, class D reactions proceed very slowly in the hours and day range, and need an intensification of intrinsic kinetics by harsh process conditions.

### 1.2.2 Classification of micro flow reactors

Reactions can be carried out in various flow reactors that are fabricated from various materials depending on the particular application. Chemical compatibility and physical robustness are two main factors determining the choice of the material. Reactors can be constructed from glass, quartz, diamond, polymethylmethacrylate (PMMA), polydimethylsiloxane (PDMS), polytetrafluoroethylene (PTFE), perfluoroalkoxy alkane (PFA), fluorinated ethylene propylene (FEP), ethylene tetrafluoroethylene (ETFE), ceramic, silicone, copper, stainless steel, nickel, and Hastelloy. Based on the phase of process development and/or production rate requirements, reactors can range in scale:

- **Micro scale flow reactors** are based on a channel of dimensions lower than a millimeter. They can be fabricated as chips, plate reactors, straight tube, coiled tube or packed bed reactors. Micro scale flow reactors are mainly used for process optimization and/or to prepare small amounts of material. Macchi and Roberge et al. presented a toolbox approach in transferring batch processes to continuous, where reactors are selected based on the reaction types and reacting phases. Knowledge of the kinetics of a particular reaction determines the choice of a particular reactor. Very fast, exothermic (Class A and B) reactions benefit from smaller dimensions, high mass and heat transfer, and therefore are usually performed in chips or plate-type reactors. Meanwhile, slower reactions are carried out in coil or tubular reactor (Class C and D) of larger dimensions and volumes. Reactions requiring heterogeneous catalysts are performed in packed bed reactors.

- **Mesoscale flow reactors** have higher production rate when compared to micro scale flow reactors. An increase in productivity can be achieved via stacking of multiple micro scale flow reactors or parallelization, due to increase in flow rates and/or an increase in a channel diameter. Furthermore, combination of the techniques is possible. It is essential that fluid dynamics and mixing characteristic remain the same throughout the scale-up of the process.

- **Large scale flow reactors** (Figure 5) can deliver more than 100 megatons per year and can be fabricated based on the same techniques as mesoscale flow reactors. Companies such as Chemineer, Alfa Laval, Chemtrix and Sulzer Chemtech produce ready-to-use large scale flow reactors.

### 1.3. GREEN CHEMISTRY AND GREEN ENGINEERING

In 2005, continuous processing and process intensification were defined as key green engineering research areas for sustainable manufacturing by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable. Figure 6 shows the main drivers to implement continuous manufacturing. Logistics and quality aspects can be improved through the advantages brought by flow chemistry in production capacity, speed of implementation and minimization of inventory and validation stocks. Production capacity is limited in batch by limited throughput when slow dosing, low temperature
and high dilution are required. Continuous processing can accelerate the slowest steps and contribute to faster deliveries of the material based on the medicinal chemistry route. Speed of implementation can be significantly increased since there is no need for a sequential scale-up and construction of different scale facilities. Use of the same equipment to produce both clinical and commercial products decreases the total development time. Moreover, the construction of flow plants can be seen as operational expenditures rather than capital costs. Inventory and validation stocks can be minimized due to the precise overlap between supply and demand due to the variable operational volume.

Flow technology offers a larger playground in terms of process conditions. Reaction temperatures below -40°C or above 200°C are outside the limits of standard batch reactors, however safely reachable in micro flow. Moreover, cooling or heating the whole installation to those limits takes a longer time and requires more energy input than in the case of flow reactors. Flow reactors allow safe operation in that thermal range along with the creation of novel environments for the molecules to react in the most efficient way with minimization of energy input and reaction time\(^{18,45}\). Tight control over process conditions improves selectivity and thus the yield of a reaction\(^{46}\). Finally, in downstream processing continuous countercurrent extractions have been shown to simplify the separation in case of unfavorable extraction coefficients\(^{47}\).

Safety concerns associated with highly exothermic reactions can be minimized due to the efficient heat removal and temperature control available in flow reactors\(^{48}\). Moreover, due to a smaller operating volume only limited amounts of chemicals engage in a failure scenario as opposed to a whole batch contents in batch procedures. High pressure facilities require special precautions during the construction. Meanwhile, operating with hazardous, flammable, explosive or toxic gases presents higher risk in case of over-pressure and/or leakages. Again due to a smaller hold-up of the flow reactors pressurization can be achieved with a smaller amount of gas leading to a limited amount available at a time. The absence of headspace in liquid-filled reactors prevents condensation of low-boiling hazardous substances that normally can lead to an explosion (e.g., hydrazoic acid)\(^{50,51}\). Manual handling can be minimized through automatization. Moreover, used disposable flow reactors can be implemented if highly potent or cytotoxic chemicals are used to avoid contamination.

1.4. CHEMICAL AND PROCESS-DESIGN INTENSIFICATION VIA NOVEL PROCESS WINDOWS

In 2008, Hessel introduced the concept of Novel Process Windows (NPW) into the field of micro reaction technology\(^{26,49,52,53}\). Novel Process Windows reside on two mutually connected pillars of process design and development as shown in Figure 7. First pillar is the chemical intensification, where harsh operating conditions intensify the intrinsic reaction kinetics with the target of maximizing the productivity. Chemical intensification has been observed in multiple cases when temperature, pressure and/or concentration are increased\(^{54–59}\). All of the parameters affect reaction rate and thus present a potential to speed-up a reaction. Temperature affects reaction rate according to the well-known...
Arrhenius equation. An increase in temperature increases energy of the system and facilitates the shift from reactants to products. Micro reactors provide an opportunity for rapid heat transfer and thus safe operation under non-classical conditions, such as elevated temperature and pressure. Heating the reaction medium beyond its boiling point demands an increase in pressure (high-p) and results in superheated conditions. Apart from facilitating superheated conditions, high pressure affects the reaction by influencing the reaction equilibrium and rate constants. In case volume occupied by product of the reaction is lower than that of the sum of two separate reactants, the overall volume change is negative. Thus, increase in pressure will have an acceleration effect on the reaction rate constant at constant temperature.

Second pillar of NPW is the process-design intensification, which forces integration of intensified step changes into an existing process or to rethink the whole sequence of process steps with the aim to simplify and intensify the process as a whole.

New chemical transformations occur at the interface of chemical and process-design intensification. Examples are multi-step synthesis comprising a flow reactor network and one-pot processes translated into telescoped one-flow processes. Based on the large-scale process analysis performed by Roberge and coworkers the average production campaign involves 2.7 work-up unit operations for 2.1 reaction unit operations. Thus, in order to be industrially relevant multi-step flow processes have to be developed with connected reaction steps omitting intermediate separations when possible.

1.5. MULTI-STEP SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS IN MICRO FLOW

Multiple exemplary uninterrupted multi-step processes to deliver active pharmaceutical ingredients have been published. Uninterrupted in this case means that a particular intermediate does not undergo any batch unit-operations or manual handling, apart from being collected in a reservoir with an inserted feed line for the next reactor on its way to the subsequent reaction. Moreover, the reactants are introduced into a reaction platform continuously and not based via loops, which contain only limited amount of reactants and thus result in a limited amount of operating time in between the refills.

1.5.1 Aliskiren

The most extensive and complete end-to-end synthesis performed in micro flow reactors was developed by Trout et al. in collaboration with Novartis International AG. The target API in this process was aliskiren hemifumarate, shown in Figure 8, existing under the brand name of Tekturna (US) or Rasilez (UK). The API is used in the management of hypertension.

An end-to-end integrated continuous manufacturing plant was built to manufacture tablets containing 112 mg of the free base form of aliskiren with a total nominal throughput of 45 g/h, which corresponds to 2.7 million tablets per year. The capacity ranges from 20 to 100 g/h. The plant fits into a conventional university building and occupies a 2.4 by 7.3 m² area. The process, shown in Figure 8 (right), starts off with the introduction of a melted intermediate at 100°C into a tubular reactor to undergo an amide formation under neat conditions. Performing the step in flow intensified the reaction, which led to a decrease in reaction time from 72 h needed in batch down to 4 h in flow. The amide is extracted in the in-line membrane based liquid-liquid extractor with the addition of water and ethyl acetate. The typical recrystallization and filtration is translated by the addition of heptane with a subsequent cooling of the suspension to 5°C. The slurry was
filtered on a rotating porous plate while vacuum was applied to the back of the plate. The slurry is then washed with ethanol and ethyl acetate, prior to being scraped off and sent to another vessel. A density flow cell was integrated to adjust the flow rate of the ethyl acetate and control the concentration of 4 at the outlet. The stream is then sent to a second reactor for an acid-catalyzed deprotection of the amine. The reaction is quenched with sodium hydroxide which proceeds in an isothermal manner in a flow reactor. The product stream is worked up by the addition of ethyl acetate to dilute the product to the concentration of 6 wt%. The sodium chloride formed upon the neutralization of hydrochloric acid precipitates within the flow, which is than filtered via a microfiltration membrane and the concentration is measured with an inline UV flow cell. Finally the flow passes through a column packed with molecular sieves in order to remove traces of water. The final product is obtained by performing reactive crystallization with fumaric acid. The addition of fumaric acid is controlled by an inline UV detector to maintain 0.55 equivalents of the acid with respect to the amine.

The crystallization of 6 takes place in two stages, the first crop is obtained at 20°C, followed by crystallization at -10°C. The crystals are then washed and mixed with the first excipient (SiO₂). The mixed slurry is then dried in two convection-heated drums, scraped off and sent into a vacuum chamber. Further, the dried flakes are transported through the heated tubes with the aim of final solvent removal. Later, the dried matter is mixed with PEG and melted at 60°C to provide a good mixing, and create tablets with a predefined geometry. The final tablets underwent a quality testing. One major impurity was detected, but was kept within specification limits.

The described process employs custom-built equipment with incorporated PAT tools. The characteristic dimensions of the reactors are in the range of millimeters, while the reaction times are in the range of hours. The process represents a bridge in terms of reactor and time dimensions between lab scale flow chemistry and not yet widely accessible production scale.

1.5.2 Artemisinin
Malaria poses a serious threat on undeveloped regions, where underpaid infected are in desperate need for a cure⁶⁷. Currently, the most effective treatment is offered by artemisinin. It is extracted from the plant Artemisia annua (sweet wormwood), however the high demand and limited supply results in an elevated cost of the drug⁶⁸. The precursor to artemisinin, artemisinic acid is a simpler structure and can be extracted from the same wood in higher yields. The challenge is to convert available artemisinic acid to highly desired artemisinin. Seeberger et al. developed a simple, fast, efficient and inexpensive continuous process of converting the reduction product of artemisinic acid, dihydroartemisinic acid, into the target compound, artemisinin⁶⁶,⁶⁹, as shown in Figure 9.

By wrapping transparent FEP tubing around a Schenk photochemical reactor containing a 450W mercury lamp that was cooled to 25°C, the authors afforded the generation of singlet oxygen in the presence of tetraphenylporphyrin. The ene reaction of artemisinic acid and singlet oxygen resulted in generation of tertiary allylic hydroperoxide (91% conversion, 75% yield). Hock cleavage was afforded by treating the product with trifluoroacetic acid in the first 16 mL of reactor at room temperature and then raising the temperature of the last 10 mL to 60°C. Hock cleavage was followed by the addition of triplet oxygen and condensation reactions to completion, and afforded 39% yield after chromatographic purification. The authors calculated that at the current capacity 1500 of photochemical flow setups will be needed to meet the estimated annular demand of 225 million of artemisinin doses.

The process represents a brilliant approach to access a highly important pharmaceutical. The employed equipment has a small foot-print, which can lead to worldwide distribution of artemisinin producing stations around the areas affected by the disease. Moreover, such
stations could prevent a wide-spread problem of fake medicines circulating in the aforementioned areas. However, before the implementation the final yield of the compound needs to be increased and chromatography-based separation to be circumvented, if possible.

1.5.3 Gleevec

Gleevec (imatinib mesylate) was developed by Novartis AG and is used for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumours. The synthesis of the target molecule in flow by Ley et al. started with the formation of the amide core via a reaction of acid chloride and aniline (Figure 10). Polystyrene-supported DMAP within a glass column was followed by a column with supported dimethylamine, in order to facilitate the reaction and neutralize the hydrochloric acid formed as a by-product. Connecting the outlet stream to the next step of nucleophilic substitution of chloride by N-methyl piperazine turned out to be problematic due to the dispersion of the product within the stream, and changing concentration, as was indicated by in-line monitoring through a UV spectrometer. An automated fraction collector was then attached to the UV spectrometer and programmed to collect the output of the reaction with a pre-defined UV absorption threshold. The most concentrated fraction of 4 mL (75% isolated yield) was then premixed with N-methyl piperazine. The second reaction was optimized when the concentration of the collected product was increased, by evaporating the DCM from the collected 4 mL of the product solution. The output of the first reaction was combined with the N-methyl piperazine in DMF, after that nitrogen was aspirated over the solution heated up till 50°C and the evaporated DCM was removed from the headspace to an exhaust. The evaporation of the volume took 30 min, and was followed by the injection of the reactant mixture into a column containing calcium carbonate heated to 80°C. To scavenge unreacted N-methyl piperazine on polystyrene-supported isocyanate followed the calcium carbonate column. In order to catch the product silica-supported sulfonic acid was used. Later, the product was released into the mixture of ammonia in methanol resulting in 80% yield and >90% purity. The final step on the way to the target molecule is Buchwald-Hartwig amination, which was achieved by using 10 mol% of a BrettPhos Pd precatalyst and 4.0 equivalents of amine and sodium tert-butoxide. Thus, three-step synthesis of Gleevec was afforded with 32% overall yield and >95% purity.

The current process represents a proof-of-concept approach and requires extensive improvement to be translated to a larger scale. The main requirements are minimization of cartridge use for the sake of entrapment of the unreacted reagents. In addition, minimization of equivalents of reagents and catalyst used is needed, especially in Buchwald-Hartwig amination. Finally, the yield of 32% needs to be increased to be considered a potential alternative to the batch process.

1.5.4 Ibuprofen

Jamison et al. reduced the total synthesis of Ibuprofen down to 3 minutes with 72% overall yield and initial productivity of 8.1 g/h. The first step of the Friedel-Crafts acylation takes place under neat conditions in 1 min yielding 95% yield of the product. Quenching of the reaction occurs when HCl is introduced into the reacting stream (Figure 11). The organic and aqueous phases are then separated within a membrane based liquid-liquid separator. The organic outlet is immersed into a reservoir, where the product is collected and pumped into the subsequent reactor with a separate pump (144 µl/min) to mix with trimethylorthoformate in DMF (630 µl/min). Iodine chloride used in the following step was pumped in its neat melted form (109 µl/min). The absence of a solvent prevented
the formation of iodine precipitate. Finally, the product stream of the second reactor is diluted by a factor of 4 upon meeting with the stream of sodium hydroxide and a 2-mercaptoethanol in water-methanol mixture (3 ml/min).

This process demonstrates an improvement to a previously developed process to deliver ibuprofen\(^7\). The current process minimizes the use of solvent and increases the yield from 51\% to 72\%, while decreasing the total residence time and increasing productivity. This improvement demonstrates how significant process-design intensification can be attained when the process is rethought in a holistic manner.

1.5.5 Rufinamide
Rufinamide (Figure 12, (1)), used in the treatment of Lennox-Gastaut syndrome, exists under the brand names of Inovelon and Banzel and is produced by Eisai. Recently the total synthesis of rufinamide in flow was published by Jamison et al. 2,6-difluorobenzyl bromide (2) dissolved in DMSO was mixed with sodium azide (3) solution to yield a final 0.29 M concentration of 2,6-difluorobenzyl bromide within the reactor, with 1.3 equivalents of sodium azide\(^7\). Nucleophilic substitution took place in 1 min at room temperature. The dipolarophile, needed to construct 1,2,3-trizole moiety in rufinamide, was synthesized from neat methyl propiolate (4) and aqueous ammonium hydroxide (5) in 5 min and 0°C. Finally, 2,6-difluorobenzyl azide and propiolamide were combined in copper tubing to facilitate a catalyzed [3+2]-Huisgen cycloaddition at 110°C and given 6.2 min residence time. Thus, the total synthesis took 11 min and resulted in 92\% overall yield. The product was purified by addition of 2 equivalents of water with respect to reaction mixture, filtering off the precipitate and drying. The productivity of the sequence was 217 mg/h.

The current approach is an example of lowering the chemical barriers for the sake of making a final molecule and presents large room for improvement. Nucleophilic substitutions are known to proceed tremendously fast in non-protic polar solvents, such as DMSO. However, the separation of DMSO and its use are not favorable in industrial applications. Moreover, after iodine, substitution of bromide is one of the easiest, however it leads to large waste generation due to its large molecular weight. The methyl propiolate, a dipolarophile, used in 1,3-dipolar Huisgen cycloaddition is highly electron-deficient, thus very reactive. It is also an expensive reagent. During cycloaddition, regioselectivity is directed by leached-out copper species from copper tubing, which brings about a concern of toxic metal separation from the product mixture.

1.6. MULTI-STEP SYNTHESES OF ACTIVE PHARMACEUTICAL INGREDIENTS IN MESO AND LARGE-SCALE FLOW REACTORS

While micro reactors largely and to a somewhat fewer extent also flow chemistry is a European development, the recently seen strong push towards continuous manufacturing in pharmaceutical manufacturing has been strongly enforced by large US companies, US academics, the industrially guided ACS Green Chemistry Institute Roundtable, and the FDA. This kind of joined initiative is active in publishing the success of their emerging technologies and this will be described in particular in the following. It is expected that similar investigations are done in Europe and possibly in the Far East, yet publications hereabout are rare.

1.6.1 Hydroxypyrrolotriazine (Bristol-Myers-Squibb)
LaPorte et al. described the design of the process for manufacturing of an intermediate in the synthesis of brivamib alaninate\(^7\). Hydrogen peroxide is used as the oxidant in a benzylic hydroperoxide rearrangement. However, its combination with an acid catalyst brings about a thermal runaway potential at ambient conditions. A chemical hazard analysis concluded that the reaction was unsafe for operating at more than 0.5 kg of starting material in batch. Alternative chemistries were not sufficient for the quality expected, therefore the engineering solution of transferring batch process into continuous was devised. In order to prevent the decomposition of hydrogen peroxide and minimize side reactions, the mixing section of the compounds was kept at -5°C as shown in Figure 13. A process simulation showed that operating the reactor in two temperature regimes
1.6.2 2,2-Dimethylchromenes (Bristol-Myers-Squibb)

2,2-Dimethylchromenes represent a highly interesting class of compounds due to their biological activity in plants and animals\(^76\). Multi-step synthesis of the compound involves thermal Claisen rearrangement. Its execution at large scale in batch poses a safety risk, in addition to decomposition of the product. Therefore, Polomski and Soundararajan et al. performed a DSC study, and subsequently developed a mathematical model that could identify the key parameters in the optimization of the reaction outcome as well as maximizing the safety\(^76\). A stainless steel capillary reactor (80 ml) of 1/8” ID dimensions was heated within an oil bath to 195-200 °C. A flow of 20 mL/min allowed 4 min residence time and resulted in 98% yield with a productivity of 7 kg/h.

1.6.3 Fused-Bicyclic Isoxazolidines (Eli Lilly and Company)

Process intensification in synthesizing bicyclic isoxazolidines via 1,3-dipolar cycloaddition of nitrene was achieved because a flow reactor could be heated up to much higher temperatures than a conventional batch reactor\(^77\). The process was realized in a stainless steel tubular coil (1/8” OD, 343 mL) at 210 °C in 10 min residence time. The concentration of the reactant in toluene was 0.24 M, which was pumped with 34.3 ml/min and resulted in a productivity of 120 g/h (50% yield).

1.6.4 7-Ethyltryptophol on the way to etodolac

Indole moiety is often found in natural products and biologically active compounds\(^78\). 7-ethyltryptophol is a key intermediate for the anti-inflammatory drug etodolac. Etodolac proved to be safe with respect to gastrointestinal and renal tract and to slow down the progression of skeletal changes in rheumatoid arthritis. The benchmark method consists of hydrozone formation, followed by the [3+3]-sigmatropic rearrangement. The instability of hydrozones poses a safety concern on a large scale calling for one-pot procedures. Su et al. developed a continuous process to synthesize 7-ethyltryptophol\(^79\). Two reacting streams of 2-ethylphenylhydrazine and 4-hydroxybutraldehyde were mixed at a total flow rate of 230 mL/min within a mixing T (ID 7 mm). A tubular reactor was heated within an oil bath. It was observed that decomposition of hydrozone could be minimized by shortening the reaction time to 20 s, after which sulphuric acid was added to promote [3+3]-sigmatropic rearrangement to the final product. In total, the one-pot process took 280 s, including cooling of 20 s. On a 10 kg-scale the developed procedure afforded 74 % yield of the final product.
product with 83% purity. The authors state that during the manufacturing the isolation of 7-ethyltryptopol would not be necessary and the process could go on to the synthesis of etodolac.

1.6.5 6-Hydroxybuspirone (Bristol-Myers-Squibb)
LaPorte et al. designed a process in line with PAT to deliver a safer and more efficient continuous process on production scale. The process consisted of converting buspirone to 6-hydroxybuspirone via hydroxylation in three steps, first enolization with sodium bis(trimethylsilylamide) in THF at or below -70 °C in the presence of excess of triethylphosphite (Figure 14). Once enolization is complete, air is introduced to afford oxidation, which is followed by the reduction of formed hydroperoxy anion to hydroxide. Equivalents of base govern the formation of the by-product, diol. Moreover, premature introduction of oxygen leads to the formation of residuals of unreacted sodium bis(trimethylsilylamide) and unreacted buspirone enolate, which may result in the deprotonation of the intermediate that can be oxidized to diol impurities. A high excess (3.5–5 eq.) of triethylphosphite is needed to maintain sufficient progress in the reduction and prevent formation of amino acids and other impurities. Apart from possible waste generation, there is a danger coming from the exothermic oxidation within flammable solvent in the presence of oxygen.

Therefore, the headspace of the reactor is continuously diluted with nitrogen. The complications listed above lead to the design of a continuous process. The reactant and base were mixed within a T-mixer with internal dimensions of 3/8”, followed by one static mixer (0.5” ID with 27 elements) at room temperature to avoid a sudden precipitation of base and a second mixer that was cooled with a jacket containing glycol to -15 °C. The enolation was allowed to reach completion within the heat exchanger. A React-IR DiComp probe was installed at the outlet of the enolatation reactor to perform on-line FTIR measurements. The product stream was then split in four streams that entered a trickle bed reactor containing four columns. Oxygen was fed in a counter-current fashion, since it lead to a higher selectivity. The oxidation reactor (600 mL) was cooled down to -37 with the same fluid used to cool the heat exchanger used in enolation. Unreacted oxygen flowed out the top of the reactor, where it was diluted with nitrogen and sent to the plant’s thermal oxidizer, while the product flowed by gravity along the reactor into a tank with a level control system. When a certain level was reached the level output signal would make the valve on the outlet of a piston pump open and allow the product stream to flow into the quench tank. The product flow rate into the quench tank was 168 ml/min and the pH was kept constant by continuous addition of HCl. In total, the continuous process took 4 min as total residence time, while the batch process took 8 h in lab, and 16-24 h on a pilot plant scale. In three pilot-plant campaigns with the continuous process more than 100 kg of API was produced.

Thus, the current process benefited from speeded-up kinetics, higher safety due to no accumulation and limited reactive species in handling, higher selectivity and thus less generation of waste.

1.6. SCOPE AND OUTLINE OF THE THESIS

The current thesis presents the development of flow reactor networks with the goal of intensifying single reaction steps and subsequently constructing a multi-step process to deliver active pharmaceutical ingredients. When a single reaction step is investigated, attention is first given to the chemical reagents used and their characteristics, such as toxicity, stability and cost. Green chemistry and green engineering principles serve as guidelines in the decision making process. The principles of Novel Process Windows, presented above, are followed in the two subsequent stages, first during single-step chemical intensification and later process-design intensification is realized while connecting several steps. As a result, sometimes synergistic effects arise benefitting the process in overall.

Organohalides represent a class of valuable intermediates in the pharmaceutical industry. Among several synthetic route alternatives is the conversion of alcohols to chlorides by the use of chlorinating agents. The biggest concern associated with the latter is a low atom economy and stoichiometric generation of waste. Chapter 2 presents a process where hydrochloric acid was used instead of toxic and wasteful chlorinating agents. The synthesized chlorides were further used in a flow network consisting of 4-step multi-step synthesis of antiemetic drugs and antihistamines. The drawbacks of the process were the requirement of 3 equivalents of hydrochloric acid and use of a reagent loop, which resulted in only a partial continuity. Chapter 3 presents a further improvement of the process. The continuity and the decrease in equivalents was achieved by switching from hydrochloric acid to pure hydrogen chloride gas. Safe pressurization in micro flow allowed the maximization of hydrogen chloride solubility in alcohol. To our best knowledge, it was the first documented use of pure hydrogen chloride gas in a continuous process. Finally, less water was involved in the synthesis due to the switch from acid to pure gas.

High temperature, pressure and concentration are the main tools in chemical intensification as mentioned above. Chapter 4 investigated the influence of pressure on the regioselectivity of 1,3-dipolar cycloaddition in an autoclave reactor with an operating pressure reaching 1800 bar. The selectivity towards the 1,4-regiosomer increased by 30% when operating pressure was increased from 500 bar to 1800 bar. In flow experiments pressure effects were not observed due to a lower pressure limit imposed by the available...
equipment. However, a clear activation by temperature was observed. The reaction proceeded at a higher speed and with a greater productivity in flow micro capillary reactors. Chapter 5 concentrates on a further intensification of 1,3-dipolar cycloaddition. The aim was to use organoazide and the highly inactive, but inexpensive and relatively green dipolarophile to synthesize a key precursor to rufinamide. The reaction time decreased from >24 hrs required in batch to 10 min when the reaction was performed in a micro flow capillary reactor under near neat conditions at 210 °C and 70 bar.

Chapter 6 describes the combination of single-step intensifications to develop a continuous process of a rufinamide precursor and realize process-design intensification. 2,6-difluorobenzyl alcohol was converted to the corresponding chloride through the use of hydrogen chloride gas. Immediately after the reaction a sodium azide stream was injected into the product stream to synthesize 2,6-difluorobenzyl azide. The product was then separated in an in-house developed inline L-L separator and further pumped to undergo the aforementioned cycloaddition. In order to avoid crystallization of the cycloadduct, a methanol stream was injected into the product stream. Upon collection the cycloadduct crashed out of the mother liquor in 82% overall yield. The entire process relied on no solvent, nor catalyst, and water use was minimized via a combination of a quenching agent, sodium hydroxide, and sodium azide in one stream. In 95 min 3 reaction steps and 2 separations were carried out resulting in 9 g/hr productivity. Thus, an overall momentum of process-design intensification was identified, which is more than the added momenta of chemical intensification. Finally, Chapter 7 presents an evaluation of the developed 5-stage 3-reaction step process to produce a rufinamide precursor. Batch and flow process models were developed to be compared in terms of material and energy requirements. Due to the use of organic solvents in and required intermediate separations in the batch process, which employed water, a significant difference in material requirements was observed. Meanwhile, in the continuous-process process 50% of employed materials were reagents. Further, an economic and environmental evaluation was performed. Once again, the continuous-flow process was found to be favourable in terms of economic and environmental impacts.

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CHAPTER 1

Introduction

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CHAPTER 2

Continuous-flow multi-step synthesis of Cinnarizine, Cyclizine and a Buclizine derivative from bulk alcohols

This chapter is based on:

ABSTRACT

Cinnarizine, cyclizine, buclizine and meclizine belong to a family of antihistamines that resemble each other in terms of 1-diphenylmethylpiperazine moiety. Current chapter presents the development of 4-step multistep continuous process to generate the final antihistamines using bulk alcohols as starting compounds. Hydrochloric acid is used to synthesize the intermediate chlorides in short reaction time and excellent yields. The methodology presented offers a great way to synthesize intermediates to be used in drug synthesis. Inline separation allows collection of pure products and their immediate consumption in the following steps. Overall isolated yields for cinnarizine, cyclizine and a buclizine derivatives are 82, 94 and 87%, respectively. The total residence time for four steps is 90 min with productivity of 2 mmol/hr.

2.1. INTRODUCTION

Functional group interconversion is one of the most used techniques in drug synthesis1. The conversion of hydroxyl groups to their corresponding halides is arguably one of the most versatile transformations, which is often followed by a nucleophilic substitution. Therefore, it is one of the key research areas in the synthesis of active pharmaceutical ingredients (API)1. Chlorides are very interesting due to their abundance in nature and their low molecular weight. Synthesis of chloride derivatives from alcohols usually requires use of chlorinating agents such as thionyl chloride1, phosphorus chlorides4, pivaloyl chloride5, Vilsmeier reagent6, tosyl chloride7, 2,4,6-trichloro-[1,3,5]triazine with DMF8, oxalyl chloride9 and phosgene10. Unfortunately, these chlorinating agents constitute major concerns due to their high toxicity11. Moreover, since only a part of the chlorinating agent molecule is used in the reaction, waste is generated in stoichiometric amounts leading to a process that is not atom efficient nor green12.

The ideal process to convert primary alcohols to corresponding chlorides would be based on neat alcohol reacting with hydrogen chloride. This will maximize atom efficiency and result in water as sole by-product. Although possible, handling hydrogen chloride gas is challenging, especially on a large scale. Hydrochloric acid can be used as an alternative. However, low to average temperatures need to be maintained to keep the solubility of hydrogen chloride in water sufficiently high13. Thus, reaction rates can only be increased to a limited extent in batch reactors. In contrast to batch reactors, micro flow technology offers a great platform to enable this sort of processes14–17. The absence of headspace and safe pressurization within micro channels assists in keeping hydrogen chloride dissolved at high reaction temperatures. Multiple examples of reaction rate acceleration in micro reactors under high temperature and pressure exist18–21. In addition, modularity of continuous-flow reactors allows constructing reaction networks to deliver natural products22,23 and APIs24–29 in a safe, quick and efficient way.

Several milestones have been reached on conversion of alcohols to chlorides, i.e. chlorodehydroxylation. Tundo et al. have described a solvent-free synthetic method, i.e. gas-liquid phase-transfer catalysis (GL-PTC), in which gaseous reagents flow through a molten phase-transfer catalyst supported on solid30,31. Microwave heating technology showed high efficiency in the field of chlorodehydroxylations32. Reid et al. combined microwave heating of ionic liquids and aqueous hydrochloric acid for a range of alcohols with and without added catalysts32. Short chain alcohols have been converted in high yields and selectivity within 10 minutes under pressurized microwave conditions. The reaction rates were measured to be in the order of 100 times faster than non-microwave high temperature chlorodehydroxylations. Kappe et al. have extended the microwave heating
technology with hydrochloric acid to a continuously operating microchip-based flow setup\textsuperscript{15}. Full conversion of n-butanol was obtained with 3 equivalents of hydrochloric acid, within 15 minutes residence time at 160 °C and 20 bar. When applying the optimal conditions to n-hexanol and n-decanol, the reactivity decreased with the increased chain length.

In the present chapter bulk alcohols are converted into corresponding chlorides that are subsequently consumed in continuous multi-step synthesis of antiemetic agents and antihistamines such as, cyclizine, meclizine and buclizine derivative, and cinnarizine. The progress in the field of chlorodehydroxylation is extended by applying milder conditions on a wider scope of substrates in the capillary reactor. This offers a robust and more accessible alternative to microchips, as well as higher versatility regarding the production volume and rate. Due to the high abundance of the benzyl moiety in active pharmaceutical ingredients, we started with optimizing the conversion of benzyl alcohol to benzyl chloride. Integrating an in-line liquid-liquid separator with the reactor afforded pure benzyl chloride, which was readily coupled to subsequent reactions. Finally, a step by step procedure to carry out four-step continuous synthesis to prepare relevant APIs, such as cinnarizine, cyclizine and a buclizine derivative is demonstrated.

### 2.2. SYNTHESIS OF ALKYL CHLORIDES

Synthesis of chlorides started from similar conditions applied by Kappe et al., where 3 eq of hydrochloric acid was used with 15 min as a residence time\textsuperscript{15}. The results of the initial screening at 120 °C are shown in Table 1. Already 88% of 1-chlorobutane was obtained in 15 min residence time. Extending the residence time to 30 min increased the formation of di-butyl ether and resulted in a decrease in yield to 77%. For hexanol, the reaction was slower and longer residence times improved the yield. nor any other by-products present in GC chromatogram in 15 min residence time.

Due to the fact that benzyl moiety is widely used in API synthesis, our target compound was benzyl chloride. At the same conditions, 100% yield of benzyl chloride was obtained with no di-benzyl ether, me. We speculated that the partial solubility of benzyl alcohol in water minimizes the mass transfer limitations. Moreover, due to the lower solubility of benzyl chloride in water than that of benzyl alcohol, the equilibrium of the reaction shifts to the product side. Decreasing the equivalents of hydrochloric acid, while allowing more residence time leads to incomplete conversion along with formation of di-benzyl ether.

Subsequently, the optimal conditions found for the reaction with benzyl alcohol were applied to other alcohols. Scheme 1 shows the chlorides synthesized at 120 °C within 15 min residence time, along with their yields. Chloride derivatives of alcohols are usually more volatile due to weaker intermolecular forces, therefore those products were collected into a sealed vial with deuterated chloroform containing an external standard (1,3-dimethoxybenzene) and later analysed as such. In case of terminal alkyne, 4-pentyn-1-ol, the formation of dark viscous agglomerates with low yield of the chloride was observed. The reaction with tetrahydrofurfuryl alcohol resulted in partial cleavage of ether and gave a mixture of mono- and di-substituted chloropentanes. When the same conditions were applied to 1,5-pentanediol, full conversion was observed and 19% of di-chloropentane was formed. Aromatic compounds included in the scope differed in the solubility in aqueous phase, which can explain differences in yields in the substitution on benzylic position. For solid compounds such as dodecanol, cyclohexanol, naphthalenemethanol, diphenyl methanol and cinnamyl alcohol, a toluene:acetone (2:1) solvent combination was used to afford solutions of 2.2 M.

### 2.3. UTILIZATION OF BENZYL CHLORIDE

Micro flow technology allows the connection of subsequent reactions to afford truly continuous operation with a minimum of manual handling\textsuperscript{14,15}. To see the potential in application of continuous chloride synthesis, we connected the product stream of the benzyl chloride forming reaction to a second reactor, where another nucleophilic substitution would take place. The connection relied on continuous inline liquid-liquid separation that occurred in a Teflon membrane-based separator. Similar separators have been previously used in multi-step continuous syntheses\textsuperscript{14,15}. The design and operation of

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Table 1. Results of initial screening of synthesis of primary chlorides and optimization of benzyl chloride synthesis.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Residence time</th>
<th>HCl (eq)</th>
<th>GC Yield (%)\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-butanol</td>
<td>15</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>1-butanol</td>
<td>30</td>
<td>3</td>
<td>77</td>
</tr>
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<td>1-hexanol</td>
<td>15</td>
<td>3</td>
<td>46</td>
</tr>
<tr>
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<td>1-hexanol</td>
<td>30</td>
<td>3</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>Benzyl alcohol</td>
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<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>Benzyl alcohol</td>
<td>15</td>
<td>2</td>
<td>97\textsuperscript{[c]}</td>
</tr>
<tr>
<td>7</td>
<td>Benzyl alcohol</td>
<td>30</td>
<td>2</td>
<td>98\textsuperscript{[c]}</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} The experiments were performed at 120 °C in the micro capillary based setup (Scheme 1) with aqueous HCl (36 wt%). \textsuperscript{[b]} The yields were calculated based on GC-FID response with respect to 1,3-dimethoxybenzene as an internal standard. Calibrations were performed with corresponding chlorides purchased from Sigma-Aldrich. \textsuperscript{[c]} Presence of unconverted alcohol and di-benzyl ether.
this separator is described in greater detail within the supporting information of the publication current chapter is based on. For a complete separation, the right pressure difference should be applied over the membrane to allow permeate to pass through the membrane without causing a breakthrough of the retained phase, or alternatively, without carrying the permeate within the retentate. Using a 5 psi back pressure regulator at the aqueous outlet afforded perfect separation with no loss of benzyl chloride. A loop of a larger volume (35 ml), filled with hydrochloric acid, was used in this two-step synthesis to allow longer uninterrupted operation. After letting 3 volumes of reacting mixture pass through the reactor, separated benzyl chloride was collected in an Erlenmeyer flask (10 ml). The flowrate of benzyl chloride at the organic outlet of liquid-liquid separator was 40 µl/min (21 mmol/hr). Two hour of collection time was allowed prior to pumping the product into a second reactor via another HPLC pump as shown on Scheme 2.

Our choice of nucleophiles for the subsequent reaction fell upon nitrogen-containing substrates, due to their presence in API structures. Thus piperazine, n-methyl piperazine, morpholine and ethyl isonpecotate were used as nucleophiles. When combined with benzyl chloride, piperazine was the only insoluble substrate. The other substrates, even though miscible at first, resulted in precipitate at the end of the reaction. Relatively high volumes of ethanol dissolved the products indicating the need for larger amounts of solvent and lower concentrations. Diethylene glycol monomethyl ether (methyl carbitol) afforded homogeneous reaction mixtures under relatively high concentrations (1.1 M). For piperazine the addition of water (methyl carbitol: water-2:1) was needed to maintain the product soluble. The homogeneity of the reactant and product mixtures allowed the translation of batch to continuous conditions. The reaction of benzyl chloride and n- methyl piperazine (1.2 eq) at 120 °C, given 15 min residence time, resulted in 81% conversion of benzyl chloride, and 100% selectivity. The conversion increased up to >99%, when the temperature was increased to 160 °C, residence time to 30 min and 1.5 equivalents of n-methyl piperazine was used. More information on optimization is given within the supporting information of the publication current chapter is based on. The isolated yields obtained at those conditions are given in Scheme 2.

2.4. APPLICATIONS IN API SYNTHESIS

The diphenylmethyl moiety is widely found in antiemetic, antimigraine and antihistamine drugs. The diphenyl piperazine substrate is a key constituent of cyclizine, cinnarizine, meclizine, cetirizine, hydroxyzine, buclizine, dotarizine and other drugs of the same family. The ease of connecting the synthesis of chloride with a subsequent reaction motivated expanding the scope to commercially available APIs, such as cyclizine, cinnarizine and 1-diphenylmethyl-4-benzylpiperazine, which resembles meclizine and buclizine as shown in Scheme 3. Therefore, synthesis along with inline separation of diphenyl methyl chloride was optimized to pave a way to these final compounds.

2.4.1. Synthesis of Cyclizine

Cyclizine is an antihistamine used in treatment of nausea, vomiting and dizziness associated with motion sickness, vertigo and consequences of anaesthesia and use of opioids. Its chemical name is 1-diphenylmethyl-4-methyl piperazine and it is constructed via nucleophilic substitution of diphenylmethyl chloride with n-methyl piperazine. The two-
Continuous-flow multi-step synthesis

2.4.2. Synthesis of meclizine and buclizine derivatives

Meclizine and buclizine are alike in terms of their chemical structures and are built from 1-chloro-4-phenylmethyl benzene, piperazine and benzyl moieties. 1-chloro-4-phenylmethyl benzene resembles diphenyl methyl moiety, therefore we decided to build 1-diphenylmethyl-4-benzylpiperazine as a common derivative. Scheme 5 shows the schematic representation of the overall synthesis. More information on assembly of the setup and its operation is provided in the supporting information. The synthesis and separation of diphenyl methyl and benzyl chlorides took place as described above. The synthesis of 1-(diphenylmethyl)piperazine started with repeating the conditions for benzyl chloride (in methyl carbitol: water (2:1)). However, at full conversion of chlorodiphenylmethane, only a minor formation of 1-(diphenylmethyl) piperazine (<15 % yield) was formed, while major products were ((2-(2-methoxyethoxy)ethoxy) methylene) dibenzene and diphenylmethanol. Similar results were obtained when ethanol and methanol were used as solvents. We concluded that due to the higher steric hindrance of diphenylmethyl chloride, compared to benzyl chloride, nucleophilic substitution by smaller molecules, such as water or alkoxides were faster. Alternative organic solvents such as toluene, heptane, dimethyl formamide, acetonitrile, dimethoxyethane, methyl tetrahydrofuran, 4-methyl pentanone, acetone, dichloromethane and various combinations could not dissolve piperazine. Combination of dichloromethane and...
acetone (4:1) dissolved piperazine with a maximum concentration of 1.26 M. However, the mixture was metastable and lead to precipitation of piperazine when pumped through a reactor tubing. Therefore, we switched to tetrahydrofuran, which dissolved piperazine with concentrations only up to 0.5 M. Nevertheless, precipitation within the reactor was observed. Switching to a tubular reactor of a larger internal diameter of 1.58 mm allowed visual observation of the precipitate formation. Stopping the reaction, followed by pushing out the precipitate indicated that it was unreacted piperazine. One of the causes for the precipitation could be bubble formation within the reactor, followed by decrease of available solvent due to evaporation, causing the precipitation of piperazine. Thus, we increased the pressure from the theoretically required 100 psi to 250 psi. As a result less precipitation was observed. The fact that the crystals formed towards the end of the reactor lead us to believe that those might be piperazine hydrochloride or 1-(diphenylmethyl) piperazine hydrochloride. Mixing water into the product stream dissolved the unreacted reactant, and allowed optimization of the reaction. When conversion was incomplete, diphenyl methanol was formed upon mixing with water at the outlet. Due to a lower concentration and non-polar solvent the reaction was slower.

Full conversion with 92% selectivity towards 1-(diphenylmethyl)piperazine was observed at 150 °C given 45 min of residence time and with 1.5 equivalents of piperazine. Finally, no precipitation was observed when water addition stopped after 2 volumes of the reactants have passed.

Subsequently, in order to synthesize buclizine and the meclizine derivative, 1-(diphenylmethyl) piperazine needed to react with synthesized and separated benzyl chloride. Prior to the flow experiments, batch investigations showed the precipitation of the product from the reacting mixture. Methanol, used in an equivolumetric amount with respect to the product mixture, was sufficient to afford homogeneity. Thus, methanol along with 2.0 eq of benzyl chloride were injected into a product stream of 1-(diphenylmethyl)piperazine via a cross as shown in Scheme 5. At 100 °C and 15 min residence time, 67% yield was observed. This result could be further increased to 71% when the temperature was raised till 120 °C. Increasing temperature to 150 °C resulted in full conversion of 1-(diphenylmethyl)piperazine and a yield of 89% based on diphenyl methanol was obtained. Benzyl piperazine, dibenzylpiperazine, benzyl alcohol and benzyl methyl ether were formed as byproducts in the final product mixture. Isolated yield experiments were performed without the addition of internal standard. In order to separate the product, all volatile solvents were removed from the collected sample. Water was added to the product and pH was adjusted to <3. Ethyl acetate was then used to extract excess of benzyl chloride and formed benzyl methyl ether. Subsequently, the pH of the aqueous phase was adjusted to 4 with acetic acid/sodium acetate trihydrate buffer. At this point secondary amines were extracted into an aqueous phase. Evaporation of ethyl acetate followed by recrystallization of 1-diphenylmethyl-4-benzylpiperazine from EtOH afforded 87% of isolated yield.

2.4.3. Synthesis of cinnarizine

In order to synthesize cinnarizine, 1-diphenylmethyl piperazine needed to react with synthesized and separated cinnamyl chloride. The optimal conditions for benzyl chloride synthesis were not optimal for the synthesis of cinnamyl chloride. Lower temperatures, 60 °C gave higher selectivity and maximum yield of 95% yield at 5.0 M concentration in toluene. Batch investigations showed that homogeneous conditions were afforded, when the final reaction was carried out in the solution of equal volumes of acetone and 25 wt% NaOH in water. Therefore, the solution and 2.0 eq of cinnamyl chloride were injected into a product stream of 1-(diphenylmethyl)piperazine via a cross without its intermediate separation. At 100 °C and 15 min residence time 77% yield was observed, increasing time to 30 min lead to full conversion of 1-(diphenylmethyl)piperazine and 85% yield of cinnarizine based on diphenyl methanol. Isolated yield experiments were performed without addition of internal standard in the similar manner to the synthesis
of 1-diphenylmethyl-4-benzylpiperazine. However, MeOH was used for recrystallization of cinnarizine and afforded 82% of isolated yield.

2.5. CONCLUSION

We have demonstrated a simplification and acceleration of chemical reactions with the help of micro flow technology. Bulk alcohols were used in a sequence of nucleophilic substitution reactions to build meclizine and a buclizine derivative, and commercially available cyclizine and cinnarizine. Our continuous-flow protocol delivered excellent yield of benzyl chloride in 15 min residence time, under superheated conditions of 120 °C and 100 psi using hydrochloric acid as chlorinating agent. The same conditions were applied to available cyclizine and cinnarizine. Our continuous-flow protocol delivered excellent yield of 1-diphenylmethyl-4-benzylpiperazine. However, MeOH was used for recrystallization of cinnarizine and afforded 82% of isolated yield.

In order to connect chlorodehydroxylation reactions to a subsequent reaction step, a membrane-based liquid-liquid separator was designed and integrated in the reactor network. This allowed separation of intermediate chlorides and their consumption in building target molecules. Overall 4-steps were realized in 90 minutes with good yield at a production rate of 2 mmol/hr of final products.

The pumps used within the study were corroded upon their contact with hydrochloric acid, despite the fact that pump heads were made of titaania. As a solution corrosive hydrochloric acid was delivered via a loop, which has to be refilled, while continuous operation of chlorination steps is paused. Therefore, the greatest limitation of the current method is the supply of hydrochloric acid. HCl gas supply could revolutionize the synthesis, however its supply into micro flow environment is not yet developed. The methodology demonstrated herein allows easy and a more accessible way to chlorides.

REFERENCES

CHAPTER 3

Hydrogen chloride gas in solvent-free continuous conversion of alcohols to chlorides in micro flow

This chapter is based on:

ABSTRACT

Chlorides represent a class of valuable intermediates that are utilized in the preparation of bulk and fine chemicals. An earlier milestone to convert bulk alcohols to corresponding chlorides was reached when hydrochloric acid was used instead of toxic and wasteful chlorinating agents. This chapter presents the development of an intensified solvent-free continuous process by using hydrogen chloride gas only. The handling of corrosive hydrogen chloride became effortless when the experimental setup was split into dry and wet zones. The dry zone is used to deliver gas and prevent corrosion, while the wet zone is used to carry out the chemical transformation. The use of gas instead of hydrochloric acid allowed a decrease in hydrogen chloride equivalents from 3 to 1.2. In 20 min residence time, full conversion of benzyl alcohol yielded 96 wt% of benzyl chloride in the product stream. According to green chemistry and engineering principles, the developed process is of an exemplary type due to its truly continuous nature, no use of solvent and formation of water as a sole by-product.

3.1. INTRODUCTION

Sustainable manufacturing of active pharmaceutical ingredients (APIs) encompasses several aspects such as continuous processing, process intensification, minimization of solvent use and advances in bioprocesses. Currently, continuous processing is one aspect within process intensification, which targets the reduction of equipment size, costs, energy consumption, solvent utilization and waste generation. Micro reactor technology is an actively studied platform aiming at implementing continuous processing, achieving process intensification and finally assisting in delivering sustainable processes for the production of APIs.

In case of biologically active compound synthesis, the final target is constructed from intermediates. The quality of the final product and its cost are inevitably dependent on the manner intermediates are produced. Chlorides serve as good intermediates in the synthesis of APIs, usually in nucleophilic substitutions exemplified on Scheme 1, where a chloride atom is substituted by a nucleophile in the subsequent step. Due to the lower molecular weight of chloride, when compared to other halogens, substitution of chloride generates less waste. Unfortunately, synthesis of chlorides from alcohols requires highly toxic and waste-intensive chlorinating agents such as thionyl chloride, phosphorus chlorides, pivaloyl chloride, Vilsmeier reagent, tosyl chloride, 2,4,6-trichloro-[1,3,5]triazine with DMF, oxalyl chloride and phosgene. Mostly, chlorinating agents are used in stoichiometric or excessive amounts that lead to high generation of waste.

Therefore, the ideal process would involve conversion of neat alcohols to chlorides by hydrogen chloride (HCl). This will minimize waste generation since the sole by-product is water. As stated in Chapter 2, Kappe et al. showed utilization of 30 wt% aqueous hydrochloric acid in chlorination of 1-butanol, 1-hexanol and 1-decanol within a micro reactor. In 15 min residence time, with 3 equivalents of 30 wt% aqueous HCl and at elevated temperatures quantitative yields were obtained. Chapter 2 presents the development of a process utilizing 37 wt% aqueous HCl to afford a wider scope of aliphatic and benzylic substrates in the same time range. Furthermore, prepared chlorides were coupled with piperazine derivatives to synthesize cinnarizine, cyclizine and buclizine derivatives in multi-step continuous synthesis. The main drawback of both processes was the need for 3 equivalents of hydrochloric acid to prevent synthesis of by-products, such as ethers. In addition, continuity of the process was limited by the need to stop to refill the hydrochloric acid loop, which was used to circumvent corrosion of the pumps.

The limited solubility of hydrogen chloride in water leads to a limitation in its concentration. The maximum available concentration in hydrochloric acid is 37wt%, meaning that in the nucleophilic substitution case chloride competes with water as nucleophile. In order
to maximize the concentration of hydrogen chloride within a medium, pure hydrogen chloride gas can be used. Using hydrogen chloride gas can also solve the problem of the aforementioned limited continuity and allows truly continuous processing. Large pressurized reaction vessels need to be under constant observation when such toxic and corrosive gases are used, requiring special precautions such as dedicated high-pressure facilities to avoid any leakages and allow moderate solubility of gaseous reagents in the reaction media. Gas-liquid reactions in large batch reactors are usually performed at lower temperatures to increase gas solubility and minimize associated risks. Finally, due to the low interfacial areas in batch reactors and low temperatures, reactions take place in extended times, which most of the times does not justify the effort.

Meanwhile, microreactors offer a great platform for gas-liquid reactions due to the formation of distinct, regular flow patterns with high periodicity or symmetry. These offer a high surface-to-volume ratio leading to high heat and mass transfer rates. Moreover, due to the low operating volumes of micro reactors only small volumes are pressurized at a time, while continuously performing the reaction. The higher safety associated with micro reactors allows investigation of a wide range of process conditions, usually leading to process intensification. A number of examples utilizing gases as reagents within micro flow reactors, such as CF$_3$I, C$_2$H$_5$, C$_2$H$_4$, CH$_2$O, CH$_2$N$_2$, Cl$_2$, CO, CO$_2$, F$_2$, H$_2$, NH$_3$, O$_2$, and O$_3$ have been published.

Herein, we report for the first time the use of hydrogen chloride gas as a reagent for a continuous synthesis of chloroalkanes in micro flow. Highly corrosive in the presence of moisture, hydrogen chloride requires special precautions during the design of the process. We present related challenging aspects and corresponding solutions. Finally, the merit of the use of hydrogen chloride along with its limitations are presented.

3.2 EXPERIMENTAL PLATFORM

In order to control the flow rate of hydrogen chloride, a gas mass flow controller is needed. In general, mass flow controllers are made of stainless steel and hastelloy, which are susceptible to corrosion. Hydrogen chloride in its pure state is harmless to stainless steel and hastelloy. However, the moment the moisture content rises above 10 ppm, severe corrosion starts to take place. Therefore, absolute dry conditions are needed to prevent the corrosion of the device. By splitting the experimental setup into two zones, dry and wet, first as a hydrogen chloride gas delivery unit and second as a reaction rig, the corrosion was circumvented.

**Hydrogen chloride delivery unit**

Figure 1 (top) shows the assembly of the hydrogen chloride supply unit. In order to keep moisture out of the unit all connections were of VCR type from Swagelok. Moreover, due to the fact that polymer based tubing is permeable to moisture, stainless steel tubing of ⅛” size was used. One out of three nitrogen bottles was set to 40 bar for startups and shutdowns of the system. The other two were set to 15 bar pressure to be used in constant purging of the system in between experiments to prevent diffusion of moisture into the mass flow controller. Despite purging, a diffusion front is still present, which takes place in the direction opposite to the flowing nitrogen. Therefore, a stainless steel 2 m long ‘pig tail’ with 250 µm internal diameter was added following the last valve of the delivery unit. In our experience, inline non-metallic check valves sometimes fail at high pressures and allow liquid to enter the gas stream. In case of such an unexpected failure, the liquid shall destroy the mass flow controller upon reaching it due to corrosion.

In order to visually verify if any liquid ever was moving towards the mass flow controller, transparent ethylene tetrafluoroethylene (ETFE) tubing of 250 µm was added after stainless steel tubing. A polyether ether ketone (PEEK) valve was attached, which can be shut in case liquid flow was detected. Another 2 m of ETFE tubing of 750 µm was added after, followed by an inline check valve.

In order to enhance desorption of water molecules from the surface of the tubing used in construction of the setup, a vacuum line was installed. A cyclic vacuum-purge procedure was applied before the start of the operation and before disassembling the setup. It is
important to mention that in case of no vacuum, and sole purging, components of the setup corrode upon disassembly and exposure to air. A by-pass around the mass flow controller was installed to assist vacuuming of the mass flow controller from both ends. Before introducing hydrogen chloride into the unit for the first time, a dew point transmitter was used to measure moisture content. A moisture content of 0.8 ppm was typical for our system due to the dry nitrogen that was used for purging after purge-vacuum procedure. Pictures with more detailed information regarding the setup are enclosed within the supporting information of the publication the current chapter is based on.

**Chlorodehydroxylation rig**

Alcohols that are liquid under atmospheric conditions were pumped with a Knauer HPLC pump. A gas-liquid slug flow initiated in a Y-mixer and continued into the ETFE reactor as shown in Figure 1 (bottom). **NOTE:** A T-mixer was not suitable due to the liquid slugs appearing on the gas feed line prior to the mixer. As a result, these penetrations brought about fluctuations in the gas flow rate observed on the mass flow controller. The reactor was made of ETFE tubing of 762 µm internal diameter. When 1 mm inner diameter tubing was used instead, escape of gas into the heating media upon operation was observed, due to the thinner wall thickness. A hot product stream was allowed to flow through 30 cm long tubing prior to entering the Equilibar back pressure regulator (BPR) to allow cooling. For present application, an Equilibar BPR demonstrated a unique ability to apply pressure and keep gas-liquid flows stable up to 16 bar pressure. Its use circumvented the need for gas-liquid separation prior to the pressurization unit. **NOTE:** Inline cartridge based BPRs could not provide constant flow, and resulted rather in stop-flow behavior, which affected the operation of the mass flow controller, thus causing inaccuracy in the gas flow rate. Table 1 demonstrates the window of operating conditions of the operating platform.

### 3.3 RESULTS AND DISCUSSION

Benzyl chloride is used as an intermediate in the preparation of pharmaceuticals, flavorants, plasticizers and perfumes. According to Gerrard et al., hydrogen chloride dissolves in benzyl alcohol under atmospheric pressure to a significant extent as shown in Figure 2. Significant absorption of gas, as shown in Figure 3, was observed when benzyl alcohol and hydrogen chloride were mixed in the tubing prior to entering the reactor coil (at room temperature under 5 bar pressure). In theory, the solubility of gas in liquid increases with pressure and decreases with temperature. In addition, throughout the reactor the gas is consumed as the reaction progresses. With an increase in temperature, the extent of gas expansion, and thus residence time as well, are hard to quantify due to its substantial expansion and faster consumption. Therefore, the sole measure of success of a reaction was based on the yield of synthesized chloride, while residence time was estimated based on flow behavior. In-line absorption measurements to determine the residence time were avoided due to the corrosive nature of the product stream.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor volume</td>
<td>4 ml</td>
</tr>
<tr>
<td>Reactor internal diameter</td>
<td>762 µm</td>
</tr>
<tr>
<td>Gas mass flow rate</td>
<td>0.001-0.600 g/min (0.1-80 ml/min)</td>
</tr>
<tr>
<td>Reactant flow rate</td>
<td>0.09-0.15 ml/min</td>
</tr>
<tr>
<td>Temperature</td>
<td>25-120 °C</td>
</tr>
<tr>
<td>Pressure</td>
<td>16 bar</td>
</tr>
</tbody>
</table>
One of the goals in using gas was to minimize excess of HCl used, thus generated waste. In our previous investigations with 3 equivalents hydrochloric acid, in 15 min residence time at 120°C >99% yield of benzyl chloride was obtained. Decreasing equivalents of HCl gas to one and allowing the same residence time resulted in 80wt% at 60°C and 89wt% at 100°C. Higher temperatures were not investigated due to a significant expansion of gas slugs, leading to significantly reduced residence time. Dibenzyl ether was formed as a sole side-product in 3wt% at 60°C and 5wt% at 100°C. Important to stress is that no gas slugs were observed at the inlet of BPR, and minor amount of gas slugs was observed at the outlet.

Figure 2. Solubility of hydrogen chloride gas in 1-butanol and benzyl alcohol (redrawn with permission of John Wiley and Sons from).

To see whether benzyl ether formation could be minimized, while maximizing the yield of benzyl chloride, the effect of hydrogen chloride excess was studied. Gradually, increasing equivalents from 1.0 to 2.0 led to no change in side-product formation at 100°C. We therefore decided to screen different reaction temperatures at 1.1 and 1.5 equivalents. The results tabulated in Table 2 show that the selectivity does not improve with excess of hydrogen chloride. With the increase of equivalents, gas-hold up in the reactor increased, which led to a marginal decrease in residence time. Assuming that dibenzyl ether is formed due to insufficient hydrogen chloride, prompted us to increase the system pressure to allow a higher concentration of hydrogen chloride within the liquid phase. Figure 4 shows the pressure effect on the reactant, product and side-product weight distribution at 80°C. Benzyl chloride production increases with pressure from 79wt% at 5 bar to 93wt% at 16 bar, while the formation of byproduct stays the same and equal to 3-4wt%. Thus, higher concentration of hydrogen chloride increased the conversion, while showing no effect on selectivity. No change in conversion was observed with increasing pressure at 90°C and 100°C. Dibenzyl ether formed in 4wt% at 90°C with 92wt% of benzyl chloride, and in 5wt% at 100°C with 95wt% of benzyl chloride. We proceeded further with increasing equivalents at higher pressure (10, 12, 16 bar) at 100°C. The minimum concentration of dibenzyl ether was 4% at 10 bar at 1.2 and more equivalents. Therefore, those conditions, i.e. 100°C, 1.2 equivalents, 20 min residence time and 10 bar were set as optimal, yielding full conversion and 96wt% of benzyl chloride.

3.3.1 Expansion of scope

Optimized conditions for benzyl alcohol were applied to a range of aliphatic and benzylic alcohols. Scheme 2 shows corresponding yields at 100°C, 1.2 equivalents and 10 bar.
CHAPTER 3

Table 2. Effect on benzyl chloride and dibenzyl ether formation at various temperatures and equivalents of hydrogen chloride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq HCl</th>
<th>T (°C)</th>
<th>BenzCl (wt%)</th>
<th>DBE (wt%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>80</td>
<td>89</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>90</td>
<td>92</td>
<td>5</td>
</tr>
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<td>3</td>
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<td>100</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>80</td>
<td>87</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>90</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>100</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>100</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

When, aliphatic alcohols were used a significant decrease in gas solubility was observed that lead to large gas slugs both at the Y-mixer and at the BPR outlet. Increase in gas slugs drastically decreased the residence time to <5 min in the reactor (4 ml) used for benzyl alcohol. In order to have a similar residence time as for benzyl alcohol experiments, a 10 ml reactor was used instead, which led to residence time ranging from 15-20 min depending on the substrate used. The difference in residence time is due to the different extent of gas absorption within the liquid phase.

The rate of nucleophilic substitution reactions depends on the type of nucleophile, electrophile, solvent and leaving group. In order to assist nucleophilic substitution, either polar protic (S$_{N1}$) or aprotic (S$_{N2}$), solvents are used as solvents. One of the frequently used reaction systems in solvent-free nucleophilic substitutions is solvolysis, when the solvent is used as a nucleophile. The current investigation comprises a reverse system, where electrophile is a solvent. While the nucleophile is a chloride anion resulting from dissociation of hydrogen chloride.

Primary alkanes undergo S$_{N2}$ type of nucleophilic substitution, which occurs via a back-attack of an electrophile$^{33}$. Due to insufficient polarity and relatively low hydrogen bonding in primary aliphatic alcohols, dissociation to release a free chloride anion as a nucleophile is not favorable. In contrast, due to the higher polarity and/or stronger hydrogen bonding present within pentanediol, both solubility of HCl gas and conversion of the alcohol were significantly increased. Conversion of pentanediol increased to 98%, resulting in the formation of 1,5-dichloro pentane as a sole side product. Secondary alkanes can react via S$_{N2}$ or S$_{N1}$ depending on the steric hindrance of an electrophilic carbon or stabilization of the cationic intermediate. Higher yields in isopropyl alcohol and cyclohexyl alcohol cases can be explained by this additional path being available. Among benzylic species 3-methoxy benzyl alcohol resulted in the largest gas consumption and the highest yield with no traces of a dibenzyl ether derivative forming. Conversion decreased when 2,6-difluorobenzyl alcohol was used, while no side product was formed. In case of 2-phenylethanol absolutely no conversion was observed. These observations indicate that resonance stabilization of the benzyl cation is responsible for better yields when compared to aliphatic substrates and that S$_{N1}$ is a main path for the reactions to take place.

In case with secondary and benzylic alcohols dissociation of protonated alcohols results in water and carbocation. As the reaction proceeds, more of the water is formed promoting dissociation of hydrogen chloride, increasing not only the absorption of HCl, but also the rate of S$_{N1}$ reactions. Looking back at the optimization of benzyl alcohol, it can be concluded that at the start of the reaction when limited water is formed as a by-product, resulting in a limited amount of chloride anion, benzyl cation associates with both benzyl alcohol and chloride. Once a certain threshold concentration of water is reached, the chloride prevails in the reaction to combine with the benzyl cation. The S$_{N1}$ reaction pathway is also supported by the fact that no effect on the selectivity was observed when an excess of hydrogen chloride was used.

3.4 CONCLUSION

A continuous synthesis of chlorides from bulk alcohols via use of hydrogen chloride gas instead of toxic and wasteful chlorinating agents is demonstrated. The most challenging aspect of safe handling of this corrosive gas was its continuous controlled delivery into the reacting system. The elimination of moisture by continuous purging of the setup with dry nitrogen solved any corrosion issues.
The use of a micro flow reactor allowed the application of process conditions that are beyond the limits of conventional batch technology. High temperature and pressure, easily applicable within the reacting system allowed reaching the initial objective of minimizing the excess of HCl used from 3 equivalents to 1.2. However, the developed process is more beneficial for S<sub>1</sub> type reactions than S<sub>2</sub>. As a result, further investigations are needed for the synthesis of specific target chloroalkanes. One of the possible steps is minimal addition of polar aprotic solvents to promote S<sub>2</sub>. Based on green chemistry and engineering principles, a significant improvement is demonstrated due to the truly continuous nature of the process, no use of solvent and formation of only water as a by-product.

ACKNOWLEDGMENT

We would like to thank Erik van Herk from Eindhoven University of Technology, Bert Metten from Omnichem and Bart van Heugten from TSCC Technology for their help during different stages of our investigation. Funding by the Advanced European Research Council Grant “Novel Process Windows - Boosted Micro Process Technology” (Grant number: 267443) is kindly acknowledged.

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CHAPTER 4

Pressure accelerated azide-alkyne cycloaddition

This chapter is based on:

ABSTRACT

Pressure effects on regioselectivity and yield of cycloaddition reactions have been shown to exist. Nevertheless, high pressure synthetic applications with subsequent benefits in the production of natural products are limited by the general availability of the equipment. Meanwhile, the virtues and limitations of micro flow equipment in the standard environment are well established. Herein, we apply Novel Process Windows (NPW) principles, such as intensification of intrinsic kinetics of a reaction via high temperature, pressure and concentration, on azide-alkyne cycloaddition towards Rufinamide precursor. We applied the three main activation modes on uncatalyzed and catalyzed azide-alkyne cycloaddition. We compare performances of two reactors, a specialized autoclave batch reactor for high-pressure operation up to 1800 bar and a capillary flow reactor (up to 400 bar). A differentiated and comprehensive picture is given for the two reactors and three modes of activation, i.e. uncatalyzed batch, uncatalyzed flow and catalyzed flow. Reaction speed-up and consequent increases in space-time yields were reached, while widening process windows maps of favorable operation to selectively produce Rufinamide precursor in good yields. The best conditions were applied to several azide-alkyne cycloadditions to widen the scope of the presented methodology.

4.1. INTRODUCTION

High temperature, pressure, concentration and/or addition of catalyst can maximize reaction kinetics of most chemical reactions\(^1\). Provided that activation energy of a particular reaction is positive (\(E_a>0\)), its reaction rate constant will increase at higher temperature. Similarly, as long as activation volume (\(\Delta V<0\)) of a reaction is negative, increasing pressure will facilitate the reaction\(^2,3\). Thus, application of relatively high temperature and pressure on a reactive system may lead to a chemical intensification\(^4\). Novel Process Windows (NPWs) is a concept that embraces the opportunities presented by chemical and process-design intensification\(^4\). Reducing the size of equipment to a micro scale leads to a process intensification due to the enhanced heat- and mass-transfer\(^8\). Continuous micro flow operation is a very desirable mode in pharmaceutical industry due to a possible high degree of control over reaction parameters, a higher safety, a reduced manual handling, a flexibility of production volume, an easier reproducibility, a possibility of reaction telescoping, and a potential for an integrated purification\(^9,10\). Even though high-temperature processing in micro flow reactors resulted in numerous successful cases\(^6,11-15\), high pressure operations, having a potential of accelerating reactions and directing selectivity, still constitute to a mystery nowadays. Up to now, pressure effects in micro flow have been observed (i) under sub- or supercritical conditions and (ii) in enhancement of interfacial mass transfer for a gas-liquid reactions\(^16-21\). In the case of pressure impact on reaction with negative activation volume as envisaged in this study, notable impact with capillaries or microchips was mostly achieved under non-continuous, stop-flow, conditions\(^17\). Most powerful high-pressure experimental installations can sustain the pressure of up to 3 GPa (30,000 bar) and are based on a diamond anvil cell or piston-cylinder type reactors\(^22-24\). Such reactors supply new kind of information on physical properties of matter as well as on the reaction dynamics and mechanism. High fabrication cost, limited volume, high energy cost and constrained safety are however the main reasons for not being widely applicable on a larger scale. To our best knowledge industrially used high pressure reactors range in 5-2000 bar, and require special precautions, advanced safety control installation, regular check of tightened areas for leaks and constant monitoring during the operation. In micro flow, high pressure applications fall into a much narrower space of only 5-600 bar\(^20,25-27\). Pressure of a few hundred bars can be applied and sustained within a micro flow reactor of any desired volume by HPLC pumps with an appropriate back pressure regulators. It is expected that the handling of flow reactors at high pressures is generally easier\(^17\). Flow reactors allow high pressures to be easily reached due to their lower inventory, the low share of tightening areas and they provide a variable volume for production.
As mentioned earlier, reactions with negative activation volume constitute to a class of reactions facilitated by high pressure. Thus, reactions such as cycloadditions, condensations, reactions proceeding via cyclic transition state, such as Cope and Claisen rearrangements, reactions involving formation of dipolar transition states, such as electrophilic aromatic substitutions, and reactions with steric hindrance can be influenced by high pressure. Moreover, based on the difference in volume occupied by a product, distribution of the reaction products can be altered. One of the most extensively studied class of reactions under high pressure is [4+2] Diels-Alder cycloadditions due to their wide applications in general, and second most negative change in activation volume, -25— -50 mL/mol. High pressure was shown to direct regioselectivity of cycloaddition due to the difference in volume of regioisomers, changes in electronic demand and steric hindrance. Moreover, the combination of catalysis and high pressure was demonstrated to have a synergistic effect, when Lewis acid was used to catalyze cycloaddition of pyrrole derivative with an electron-rich diene. Finally, high pressure affects the reaction medium by affecting its physical properties, such as boiling and melting points, density, viscosity, dielectric constant, compressibility, conductivity and surface tension; however, this is out of the scope of the present study.

Several reactions have been performed in micro reactors under high-pressure and stop-flow regime. Nucleophilic aromatic substitution reaction among p-halonitrobenzenes with cyclic amines has been investigated in micro capillary under batch conditions under the pressures up to 600 bar. Rate enhancements by a factor of 2.7, 1.7, and 1.5 were observed for pyrrolidine, piperidine and morpholine, respectively. Diels-Alder reaction of 2- and 3-furylmethanol with maleimides, performed under elevated pressure, demonstrated that pressure increases the rate of the 2-furylmethanol, which is less reactive than 3-furylmethanol under atmospheric conditions. Larger negative change in the reaction volume of exo-product when compared to endo-product formation resulted in a slight increase in the formation of exo-product. An increase of the reaction rate of the Diels-Alder reaction, between cyclopentadiene and phenylmaleimide, by a factor of 14 was observed upon increasing the pressure to 150 bars in high-pressure glass micro reactor. Kappe et al. reported multiple high-pressure, high-temperature accelerations in the reaction rates of Newman-Kwart and Claisen rearrangements, a Fischer indole synthesis and nucleophilic substitution.

Due to their lower activation volumes, [3+2] Huisgen cycloadditions are less popular class of reactions in being studied under high pressure. [3+2] Huisgen cycloaddition takes place when 1,3-dipole reacts with a dipolarophile to form 5-membered cyclic compounds. Azides represent one class of 1,3-dipoles and their reaction with terminal alkynes results in a mixture of 1,4- and 1,5-cycloadducts, unless selectivity is directed by a catalyst in favor of a single cycloadduct. Azide-alkyne cycloaddition, when catalyzed by copper, serves as one of the best examples of a ‘perfect’ reaction termed as ‘click’ reaction by Kolb and Sharpless in 2001. In the last decade, click reaction became a synthetic target tool with a special accent in the use of combinatorial chemistry to yield natural products on the way of drug development. Copper-catalyzed cycloaddition of alkyl azides and terminal alkynes results in 1,4-substituted 1,2,3-triazole, which is the building block of many natural products. One of the best-selling 200 drugs of recent years is an antiepileptic drug, 1,2,3-triazole-Rufinamide (Scheme 1). The production process was initially developed by Novartis and now realized by Eisai Ltd., under the commercial names of Inovelon and Banzel. The anticonvulsant is used in the treatment of seizures associated with Lennox-Gastaut syndrome of patients older than 4 years old. Total continuous flow synthesis of Rufinamide starting from 2,6-difluorobenzyl bromide and methyl propiolate was recently reported by Jamison et al.

Herein, we focus on optimization of 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide and methyl propiolate, which leads to 4-substituted 1,2,3-triazole, Rufinamide precursor (Scheme 2). Separation of 1,5-cycloadduct is a requirement in the industrially applied process, when performed without Cu-catalyst. We investigate the effect of pressure on the regioselectivity to maximize the yield of the desired 1,4-cycloadduct. Moreover, we look into a synergy between high pressure and catalyst in affecting the reaction outcome. Additionally, the performances of the high-pressure autoclave reactor and the flow reactor, two specialised apparatus built for the current study, are compared in the light of the herein mentioned advantages and disadvantages. Finally, best flow conditions are applied on a wider scope of azide-alkyne cycloadditions.
4.2. OPERATING PLATFORMS

4.2.1 Process windows of reactors under study

The reaction of interest was studied using three systems different in operating pressure and temperature limits, as well as in operating mode. The first system is the standard round bottom flask under atmospheric conditions, that is limited in terms of temperature by the boiling point of the solvent.

The second system is the high pressure autoclave reactor setup having operating limits of 2500 bar and 300 °C. The reactor of 14 mL reactor volume was constructed according to a schematic representation shown in Figure 1 (left). No copper or ruthenium-containing material was used in the construction of the reactor. Two heating jackets surrounded upper and lower halves of the reactor. Thermocouple was inserted in one of the four inlets, with the tip located in the middle of the reactor. Two pumps were needed to deliver the reacting mixture and generation of a higher pressure. One of the pumps was auxiliary and was used to fill the syringe pump and the reactor with a reacting mixture, while the syringe pump was used to apply pressure. Pressure was measured by a transducer, located between the syringe pump and the reactor with a reacting mixture, while the syringe pump was used to apply pressure. Pressure was measured by a transducer, located between the syringe pump and the reactor. Rupture disc with the upper limit of 2500 bar was inserted at another outlet of the reactor as a barrier with an emergency outlet. In case of pressure build-up higher than 2500 bar, reactor contents would be sucked in from the reactor interior, minimizing the risk of the experiments. The components of the setup were connected in a manner demonstrated by Figure 1 (right).

Figure 1. Left: Autoclave reactor with 14 ml of internal volume and operating limits of 2500 bar and 300 °C. Four outlets: inlet, sample collection outlet, thermocouple and connection to the safety line with rupture disk, withstandting 2500 bar. Right: Autoclave batch high-pressure setup consists (from left to right) of feed tank, auxiliary manual pump (250 bar), three valves, manual syringe pump (3000 bar), pressure transducer and autoclave reactor, surrounded with electrical heating jackets.

High temperature, high pressure (HPHT) flow setup was assembled from the commercially available equipment and is shown in Figure 2. HPLC pumps can operate at pressures up to 400 bar, while BPR keeps the system under the set pressure. SS micro capillary reactor was heated in the oil bath with upper temperature limit of 300 °C. Second bath was used to cool down the reacting mixture with the goal of quenching the reaction and preparing the stream for the safe sample collection. The valve was used as a sample collection loop so that dead volume of BPR would not contribute to residence time of reactants. The BPR was selected to be combined with a control valve applicable at relatively low flow rates, 2 - 20 ml/min. Residence time was manipulated by change in flow rate and length of the capillary tubing. Due to the lower internal volume (2 mL) and faster existing p, T process window of the standard batch reactor could be considerably widened by the use of more advanced, such as autoclave and micro flow, reactors.

4.3. RESULTS AND DISCUSSION

We performed our investigations in three stages:

1. Batch experiment in a stirred glass round bottom flask under uncatalyzed conditions;
2. High-pressure and -temperature experiments in a non-stirred autoclave reactor under uncatalyzed conditions;
3. High-pressure and -temperature experiments in HPHT flow reactor under un- and catalyzed conditions.
4.3.1 Exploring the pressure and temperature windows in the standard and autoclave batch reactors

We performed cycloaddition in a stirred round bottom glass flask at 90°C and 0.25 M concentration of 2,6-difluorobenzyl azide. After 24 hrs the yield of 55% of 1,4-cycloadduct was obtained, leading to 60% yield in 6 days. The product distribution remained the same throughout the reaction with the ratio of 1,4-:1,5-cycloadducts of 2.8:1. In order to determine the activation volume and pressure effect on 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide to methyl propiolate, we performed high-pressure experiments in the non-stirred autoclave batch reactor. Performing the reaction at 500 bar and otherwise same conditions resulted in a yield of 72% of the 1,4-cycloadduct with increased preference to a desired product, giving ratio of 3.6:1 of 1,4-:1,5-cycloadducts, as shown in Figure 3. as reference and calculating relative multiplication factor of subsequent reaction rates lead to a calculation of activation volume of -21.13 mL/mol, which is consistent with published literature results for 1,3-dipolar cycloadditions. Calculations of activation volume are described within the supporting information of the publication the current chapter is based on. Switching our focus to temperature effect we performed the reaction at 1200 bar in batch reactor allowing again 24 hrs as a reaction time, under diluted conditions (0.25 M). Lower yields due to the decomposition of 2,6-difluorobenzyl azide were obtained at higher temperatures, i.e. 66% and 2% at 175°C and 250°C, respectively. Thus, the high-temperature processing has its intrinsic limitations and motivated the study reported hereon.

4.3.2 Exploring the pressure, temperature and concentration windows in the micro capillary reactor

Based on the availability of equipment, namely pumps and BPRs, maximum pressure reachable in our home-built micro flow setup was 400 bar. Experience with batch experiments showed that reaction kinetics at relatively low temperature is relatively slow. Although possible, long reaction times in flow are not desirable. Thus, the uncatalyzed azide-alkyne cycloaddition under interest was studied in the HPHT micro capillary flow setup with a shorter reaction time than in batch. Residence time of 30 min was allowed for the reaction at 90°C and pressures up to 400 bar. Under atmospheric pressure and same diluted, 0.25 M, conditions as in batch 48% yield of 1,4-cycloadduct was obtained in 30 min. Increase of pressure to 400 bar resulted in 58% yield of desired regioisomer. No significant change in product distribution was observed with increasing pressure, the product distribution raised from 3.5 at 1 bar to 3.6 at 400 bar. Increasing temperature under same diluted conditions as in batch showed that the highest yield of 80% of 1,4-cycloadduct under the given the conditions could be obtained.

Next, we investigated effect of residence time at various reaction temperatures under diluted conditions of 0.25 M. Figure 4 shows that time effect is diminished at temperatures higher than 140°C, resulting in a full conversion of 2,6-difluorobenzyl azide at all
investigated residence times. Decrease in the yield is observed at higher temperatures than 140°C and longer residence time than 10 min. This observation can be explained by decomposition of 2,6-difluorobenzyl azide at high temperatures and longer contact times, similar to the case in our previous study\textsuperscript{a,b}.

Reactions when performed at higher concentrations, provided with better mixing and higher temperatures proved to proceed in a safer manner in flow than in batch with an additional benefit of having faster kinetics. In this case, however, temperature was kept constant at 90°C for the sake of comparison with previously performed batch experiments and reducing the competing pressure and temperature effects. Increasing the concentration of 2,6-difluorobenzyl azide to 0.5 and 1.0 M was possible and speeded up the kinetics as shown in Figure 5. Throughout the whole pressure range investigated a yield increase of approximately 10% was found for each value of concentration. The highest yield of 81% of desired 1,4-cycloadduct was obtained at 1.0 M, 90°C and 400 bar given 30 min residence time.

4.3.3 Exploring the concentration, pressure and temperature windows in the micro capillary reactor with catalyst

As mentioned in the introduction section, combination of catalysis and high pressure may have a synergistic effect.\textsuperscript{[12]} When catalyzed by copper the reaction of azide-alkyne cycloaddition constitutes to a class of Click reactions. According to mechanistic studies, copper directs regioselectivity of cycloaddition. The directing power of copper varies for different combination of catalyst and reactants based on their individual reactivity.\textsuperscript{[15]} Thus, 100% regioselective cycloaddition is not always guaranteed. In order to check the merit of reaction activation and regioselectivity control by a catalyst we moved on to investigate copper catalyst in HPHT micro capillary based flow system. We investigated copper catalyzed cycloaddition by using 1.0 mol% of homogeneous copper catalyst-(1,10-phenanthroline) bis(triphenylphosphine) copper (I) nitrate dichloromethane adduct. The choice of the catalyst was based on its recently exhibited superior performance\textsuperscript{[59]}, that resulted in 96% yield of 1,4-cycloadduct in 3 min reaction time when phenyl acetylene and phenyl azide reacted under solvent-free conditions at room temperature in batch. We performed cycloaddition of methyl propiolate with 2,6-difluorobenzyl azide under diluted batch conditions (0.25 M) and 90°C. Only 5% of 1,4-cycloadduct was obtained after 90 min reaction time, while no 1,5-cycloadduct was observed. In order to perform the reaction in flow, an extra pump was used to introduce the Cu-catalyst into the stream of 2,6-difluorobenzyl azide before mixing with methyl propiolate. Pre-mixing was reported to result in the formation of copper-alkyne aggregated complexes\textsuperscript{[53]}. Methyl propiolate was introduced into the mixed stream via an HPIMM mixer (Re= 55), constructed for high pressure and based on flow lamination/hydrodynamic focusing (Figure 6). Increasing the concentration to 0.5 M under otherwise same conditions with no pressure applied, given 1 min as residence time, 7% yield of 1,4-cycloadduct was obtained. We studied the reaction with increased to 0.5 M azide concentration in the same range of process

Figure 5. Pressure and concentration effect on yield of 1,4-substituted 1,2,3-triazole at different concentrations 0.25 M, 0.5 M and 1.0 M when experiments performed within the pressure range of 1-400 bar in high pressure flow setup at 90°C and 30 min reaction time.

Figure 6. High pressure, high temperature (HPHT) micro capillary based flow system with added stream of homogeneous [Cu(phen)(PPh3)2]NO3 catalyst. The setup consists of stainless steel (SS) capillary (500 µm ID, 10 m), three HPLC pumps of Knauer 1000 series, T- and high pressure IAM mixers, heating and cooling Lauda oil baths, sample loop connected to a 6-port Vici Valco valve, and one Bronkhorst back-pressure regulator (BPR).
conditions as in uncatalyzed case. Figure 7 shows rapid decrease in regioselectivity with increasing temperature, which speeds up the reaction as demonstrated by the increase of the 1,4-cycloadduct yield. The highest yield obtained was 77% of the desired cycloadduct, with 1,4:1,5 cycloadduct ratio of 4.2, at 160°C in 5 min and in the presence of the Cu-catalyst. A slight increase in yield due to pressure is observed at moderate temperatures which is less pronounced as found for the uncatalyzed reaction in flow.

Figure 7. Temperature effect on the yield of 1,4-cycloadduct and regioselectivity expressed as a ratio of 1,4- to 1,5-cycloadduct is monitored in the presence of [Cu(phen)(PPh$_3$)$_2$]NO$_3$ catalyst at various temperature (60–200°C) and pressure (1–400 bar) values.

Figure 8 gives an overview about all the findings reported above with the boundaries of the process windows resulting in higher than 70% yield of the desired 1,4-cycloadduct. The pressure-temperature window for the uncatalyzed autoclave reactor is large showing the good capability of this reactor and in general the wide flexibility which are commonly acknowledged for batch operation. It allows operation in pressure regions, which the flow reactor cannot exploit at this point of time due to technological limitations. Moreover, a change in regioselectivity in favor of desired regioisomer can be achieved. Yet, long processing times are needed which results in a drop in productivity, meaning also more energy per given unit manufactured product. Here the much shorter processing times of the uncatalyzed flow reactor provide good alternative, and even more if safety under high pressure and energy minimization is an issue. Here activation by pressure is somewhat helpful, yet the big activation boost comes from the temperature and concentration flexibility. Yet, the small pressure effect is not intrinsic to flow, but the pressure range utilizable simply is lower at this time of technological development for flow reactors. Figure 8 also shows the process window coordinates for the best yields obtained for the three processing types.

The non-catalytic presents a case where both modes are used and this presents the core information of this chapter. Additional difference is the time needed for the obtained yield, a 48-fold reduction in residence time is given for the non-catalyzed flow reactor as compared to the uncatalyzed autoclave reactor.

Catalyst use is justified at lower temperatures and longer residence times, since it affords only 1,4-cycloadduct. Regioselectivity reduces rapidly when temperature increases, being highest at 25°C when no formation of 1,5-cycloadduct is detected, decreasing the ratio of 1,4:1,5 to 64 at 60°C, and rapidly falling to 4.6 at 120°C. Overview of the best conditions for flow in terms of the yield of 1,4-cycloadduct, at 160°C and 400 bar given 5 min reaction time, shows that merit of using catalyst is only 1% more of a desired product. Use of catalyst adds an additional downstream operation within the production process. Separation of toxic metal is required prior to the final stage of API production. It is evident that the flow operation demands the use of higher temperatures to achieve its best yields.

Although our primary synthetic target was Rufinamide precursor, we applied the best conditions of 140°C and 400 bar to other substrates. The results shown in Table 1 imply that the more electron-deficient the dipolarophile is, the higher is its activity towards 1,3-dipolar cycloaddition. The opposite is true for the dipole, azidobenzene is the most active among investigated azides, due to the higher conjugation and higher electron density over the azide dipole.
CHAPTER 4 Pressure accelerated azide-alkyne cycloaddition

4.4. CONCLUSION

Novel Process Windows principles were applied to the 1,3-dipolar cycloaddition to yield the Rufinamide precursor. The activation means of the reaction and regioselectivity towards the 1,4-cycloadduct, the desired precursor, served as two foci of the study. Concerning both aspects, merits of high pressure, high temperature, high concentration and catalyst were compared (4 of 6 NPW means as given in ref. 3). Moreover, the comparison was made in between home-built high pressure autoclave and high pressure and high temperature micro capillary flow reactors. The reaction was on the order of several days when carried out in a round bottom flask under atmospheric conditions, resulting in 60% yield after 6 days.

When the high-pressure autoclave reactor was used, speed-up of the reaction kinetics and improvement in regioselectivity were observed. Yield of the desired precursor rose to 84% in 24 hrs, and resulted in a 1,4:1,5-cycloadduct ratio of 6.3 at 1800 bar with no catalyst present. Increasing concentration could speed up the reaction further, however due to the possible decomposition of the azide and subsequent pressure build-up we did not pursue this option which also would never be viable as industry’s production way. Use of such a reactor on a production scale even within given limits is still questionable, due to the fabrication costs and safety issues.

In turn, the flow reactor can be scaled-up by external numbering-up and smart scale-out (small widening of characteristic dimensions) without a major loss of performance. Operation in a capillary flow reactor allowed to increase temperatures up to the superheated range, make use of pressure up to 400 bar, and increase the reactants’ concentration values. The combined action of these three activation modes resulted in a yield of 81% of the desired 1,4-cycloadduct in 30 min residence time. Copper-based catalysis was investigated as an additional activation mode for the cycloaddition in the flow reactor. 76-77% yield at various individual temperature-pressure combinations, given 5 min residence time, was obtained. Thus, although not optimized, the investigated process window showed that 5 times acceleration is possible when compared with noncatalyzed flow operation. However, formation of the undesired 1,5-cycloadduct was present even in the presence of the catalyst.

To give a differentiated, comprehensive picture, process windows maps of favorable operation (pure 1,4 isomeric-yield >70%) were given. The best conditions were applied to a wider selection of azides and alkynes. The results obtained in the current study also have given some insight on the often claimed easiness of pressure operation with micro flow reactors. Indeed, data collection process was much faster with the micro flow setup due to the faster heating and shorter reaction times, and easier sampling due to the installed sample loop. In addition, the much larger volume used for the autoclave reactor restricted exploration of temperatures above a certain limit. Thus, the range of information, as related to the expansion of the process windows, was better for the micro flow reactor. Moreover, combination of catalysis and harsh conditions was slightly advantageous when compared to the uncatalyzed process. Presence of catalyst requires

Table 1. 1,2,3-triazoles synthesized under catalyst-free conditions in micro capillary flow reactor in 30 min residence time at 140 °C and either 10 or 400 bar.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Alkyne</th>
<th>Product (1,4-regiosomer)</th>
<th>Total yield (%)</th>
<th>10 bar/400 bar</th>
<th>1,4/1,5 bar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₃</td>
<td>O</td>
<td></td>
<td>99</td>
<td>99</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>N₃</td>
<td>O</td>
<td></td>
<td>50</td>
<td>62</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>N₃</td>
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<td>46</td>
<td>59</td>
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<td>99</td>
<td>99</td>
<td>3.6</td>
</tr>
<tr>
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<td>O</td>
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<td>58</td>
<td>65</td>
<td>1.1</td>
</tr>
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<td>N₃</td>
<td>O</td>
<td></td>
<td>72</td>
<td>78</td>
<td>1.5</td>
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<td>N₃</td>
<td>O</td>
<td></td>
<td>23</td>
<td>24</td>
<td>1.5</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: azide (1 eq, 0.25 M), alkyne (ene) (2 eq, 0.5 M) in n-methyl pyrrolidone, at 140 °C given 30 min residence time. [b] Yields were calculated by using 1H NMR spectroscopy with the use of 1,3,5-trimethoxy benzene as an internal standard.
extra downstream operation, thus overall benefit is higher when no catalyst is used with harsh conditions applied.

4.5. OUTLOOK

The design of continuous micro flow-based processes enables either new types of process integration or leads to process simplification. Maximum impact is here typically gained for entirely new chemical transformations, which are only realizable in flow. Those when combined in a sequence, as in multi-step synthesis, aim at compactness and therefore bring a special attention to slow reactions that need the highest activation. In our case, the cycloaddition to synthesize 1,2,3-triazole precursor of Rufinamide constitutes to such a reaction within its multi-step synthesis.

A key to process-design intensification is high space-time yield, allowing to make reactors very compact which facilitates or even enables system integration likewise in electronics industry. Based on this motivation we calculated space-time yields for the three types of operation (and two types of reactors) investigated (see Table 2). In reactor engineering, comparison of STYs is only possible at same conversion. Yet, we were after order-of-magnitude changes and had to accept the fact that conversions were somewhat different. In addition, there is a never-completed discussion among the micro reactor engineering community, if the inner or outer volume of the reactor is to be taken as reference. We used the inner volume (i.e. the fluid reaction volume) as reference to calculate the space-time yield. It is evident in both projections that the flow reactor is more productive than the autoclave reactor, which needs a substantial outer mass to enable its high-pressure operation. Yet, it can compensate by larger volume partly what is lost by lower activation. Naturally, our data are lab-based and production reactors will behave somewhat different; yet this will not change the overall message. The compactness of the flow reactor resembles Ramshaw’s first definition of process intensification, ‘to shrink down the plant’.

<table>
<thead>
<tr>
<th>Operation type</th>
<th>Space-time yield (mol L⁻¹ h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-catalyzed autoclave reactor</td>
<td>0.0084</td>
</tr>
<tr>
<td>Non-catalyzed flow reactor</td>
<td>4.56</td>
</tr>
<tr>
<td>Catalyzed flow reactor</td>
<td>4.62</td>
</tr>
</tbody>
</table>

ACKNOWLEDGEMENTS

We would like to thank Flowid B.V. for lending us HPIMM mixer to be used in our investigations, Jan Volkers and Guus Honcoop from Knauer for their help with setting up the pumps, and Erik van Herk from Eindhoven University of Technology for helping with building the HPHT flow setup. Funding by the Advanced European Research Council Grant “Novel Process Windows - Boosted Micro Process Technology” (Grant number: 267443) is kindly acknowledged.
### CHAPTER 4

Pressure accelerated azide-alkyne cycloaddition

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CHAPTER 5

Solvent- and catalyst-free Huisgen cycloaddition towards Rufinamide

This chapter is based on:

ABSTRACT

Novel Process Windows promotes chemical intensification via operating at high temperature, pressure and concentration. Herein, we describe the development of a continuous-flow process for the formation of the 1,2,3-triazole precursor Rufinamide. The precursor is synthesized via a 1,3-dipolar Huisgen cycloaddition of 2,6-difluorobenzylazide and greener, less expensive dipolarophile under catalyst-free and solvent-free reaction conditions. It was found that the use of elevated temperatures boosted the reaction rate significantly, allowing the synthesis of the 1,2,3-triazole precursor in only 10 minutes residence time as opposed to >24 hr required in batch. Clogging was efficiently avoided by working at reaction temperatures above the melting point of the target compound. In addition, by introduction of recrystallization solvent purification was realized upon product collection.

5.1. INTRODUCTION

The 1,2,3-triazole moiety constitutes an interesting class of heterocycles that displays many useful biological activities, such as anti-convulsant\(^1\), anti-HIV\(^2\), anti-allergic\(^3\), and anti-microbial activity against Gram positive bacteria\(^4\). One of the best-selling five-membered heterocyclic pharmaceuticals of recent years is an antiepileptic drug which contains a 1,2,3-triazole moiety, called Rufinamide\(^5\). It prevents seizures by deactivating sodium ion channels, and is currently used in the treatment of Lennox-Gastaut syndrome\(^6,7\). Rufinamide is manufactured by Eisai under commercial names of Inovelon and Banzel.

Various industrial synthetic routes have been disclosed in the patent literature over the past three decades\(^8–10\). The formation of 1,2,3-triazole precursor via a 1,3-dipolar Huisgen cycloaddition of 2,6-difluorobenzylazide (2) with an appropriate dipolarophile is a key step in the synthesis of Rufinamide (Scheme 1). Table 1 lists the various commercially available dipolarophiles, which have been utilized so far. 2-chloroacrylonitrile results in a regioselective addition yielding the desired 1,4-cycloadduct in good yield (Table 1, Entry 1)\(^8\). However, it is a highly toxic and flammable substance which, in combination with the explosive nature of organic azides, causes significant safety issues for scale up. Propiolic acid is less toxic and is, due to the higher electronic deficiency, more reactive (Table 1, Entry 2)\(^9\).

Nevertheless, a transition metal catalyst is required to induce high regioselectivity. In addition, the benefits of catalyst use becomes controversial when high purity standards for active pharmaceutical ingredients (APIs) are taken into consideration\(^11\). Similar arguments

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Scheme 1. General synthetic sequence towards Rufinamide 1.

Scheme 2. Proposed mechanism for 1,3-dipolar cycloaddition accompanied by elimination of methanol.
Table 1. Overview and comparison of patented (Entry 1-3) and alternative (Entry 4) syntheses with respect to the choice of dipolarophile used in 1,3-dipolar Huisgen cycloaddition to afford 1,2,3-triazole, precursor of Rufinamide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipolarophile</th>
<th>R</th>
<th>Toxicity (NFPA)</th>
<th>Cost* ($/mol)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>T (°C)</th>
<th>Equivalents</th>
<th>Solvent/ Additives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁴⁻</td>
<td>( \text{ON} )</td>
<td>-CN</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>72</td>
<td>80</td>
<td>1.5</td>
<td>Neat</td>
</tr>
<tr>
<td>2⁴⁻</td>
<td>( \text{OH} )</td>
<td>-COOH</td>
<td>3</td>
<td>13</td>
<td>2</td>
<td>80</td>
<td>25</td>
<td>1</td>
<td>Water+ tBuOH/ Ascorbic acid/ CuSO₄</td>
</tr>
<tr>
<td>3⁴⁻</td>
<td>( \text{OH} )</td>
<td>-COOMe</td>
<td>2</td>
<td>45</td>
<td>5</td>
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</tr>
<tr>
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</tbody>
</table>

*2-chloroacrylonitrile- 5 kg for $680 (AOKBIO), propionic acid- 10 kg for $1840 (Beta Pharma Scientific), methyl propiolate- 1000 kg for $330/kg (D-L Chiral Chemicals), (E)-methyl 3-methoxyacrylate- 10kg for $160 (Apichemical (Shanghai))

...hold for methyl propiolate (Table 1, Entry 3)⁴⁻. Apart from toxicity and regioselectivity issues, the high cost of the starting material is a hurdle for selection of this synthetic route for production scale. Recently, Mudd et al. reported a greener route utilizing a non-toxic and inexpensive (E)-methyl 3-methoxyacrylate (E-MMA) as a dipolarophile (Table 1, Entry 4)⁴⁻. 100% regioselectivity towards desired 1,4-cycloadduct is afforded due to the presence of leaving methoxy group. Scheme 2 shows the cyloaddition accompanied by elimination to regain aromaticity of 1,2,3-triazole ring. Thus, no catalyst, nor its subsequent separation are needed to favor cycloadition to yield desired regioisomer. However, this route requires 28 hours of reaction time for a completion when performed at 135 °C under solvent-free conditions. Apart from the long operating time issue, the reaction temperature is very high for a conventional batch operation in the pharmaceutical industry. This is especially true when the exothermic nature of the reaction is taken into account. Moreover, solvent-free large scale batch processing of organic azides at high temperature is not recommendable in view of the limited stability of these compounds. This might lead to a runaway decomposition with gas formation and concomitant pressure build-up.

Extended reaction times can be shortened significantly by intensifying the intrinsic kinetics of the reaction in a microreactor environment⁴⁻. Such intensification can be achieved by so-called Novel Process Windows (NPW), which addresses this issue via a chemical intensification through elevated temperatures, pressures and increased reaction concentration⁴⁻⁵⁻. In addition, the NPW concept introduces a process-design intensification stage, where the goal is to simplify the process at its initial design by integration of several stages within the process⁴⁻⁵⁻. Continuous micro flow processing is a very desirable feature in pharmaceutical industry since it allows a high degree of control over reaction parameters, a higher safety, a reduced manual handling, a flexibility of production volume, an easier reproducibility, a possibility of reaction telescoping, and a potential for in-line purification⁴⁻⁵⁻. Reducing the size of equipment to a micro scale allows to increase heat- and mass-transfer and to safely operate superheated, runaway and other harsh process conditions⁴⁻⁵⁻.

Current chapter presents a collaboration between academia and industry to realize a new process that embraces green chemistry and green engineering principles. It starts off with a combined cost-sustainability guided choice of the dipolarophile and proceeds with micro flow-process intensification to accelerate the reaction to make the process productive and safe for industrial implementation. While cost arguments are considered by the raw material price and the potential for a patent-free process, environmental arguments relate to toxicity, raw material and solvent use, in addition to generated waste.

Herein, we present an alternative, intensified method to produce 1,2,3-triazole ester, a key intermediate for the production of Rufinamide 1. The novelty of the proposed synthesis lies in its continuous nature, the decrease in the reaction time from hours to minutes, and the utilization of a greener and cheaper starting compound under solvent- and catalyst-free conditions. In addition, purification is integrated within the reaction step, demonstrating an application of process-design intensification.

5.2. RESULTS AND DISCUSSION

We commenced our investigations by verifying the batch procedure described by Mudd et al.⁴⁻. The original procedure required two intermediate additions of E-MMA, at 2 and 18 hours after start, to reach full conversion. The desired product is reported to be purified by recrystallization from methanol (MeOH)⁴⁻. In our hands, a single addition of E-MMA (3) resulted in 43% yield after one hour and 78% isolated yield after 12 hours of reaction time, as shown in Figure 1. We observed that upon cooling the reaction mixture to room temperature the target compound crystallized rapidly.

To avoid clogging issues within the micro capillary reactor and, consequently, facilitate the transition from batch to continuous-flow, we followed the reaction progress in batch under more diluted conditions using N-methyl-2-pyrollidone (NMP) as a highly polar solvent, which could solubilize all the reactants and products. However, poor conversions were observed under these diluted reaction conditions; only 13 and 16% yield was reached within the first hour of reaction with 0.5 and 1 M concentration of 2,6-difluorobenzyl azide (2), respectively.
Based on our observations in batch, we have built a micro capillary assembly as shown in Figure 2. One of the very first requirements for continuous-flow operations is to ensure a complete homogeneity of the reaction mixtures. Due to the rapid decrease in reaction rate under diluted homogeneous reaction conditions as observed in batch, the use of solvent-free reaction conditions was preferred to attain a higher reaction rate. However, it was observed that target compound 4 was sparingly soluble under these neat reaction conditions, therefore, requiring special handling when 100% conversion is desired. Nevertheless, we envisioned that continuous-flow processing was feasible when the entire reactor coil (Stainless Steel capillary tubing, 750 µm ID, 4.7 m length) was maintained at a temperature above the melting point of the product (mp 4 = 136-137°C). Moreover, purification could be integrated by introducing a stream of acetonitrile (ACN) (1/10 v/v) or MeOH (1/15 v/v), which yielded crystallized product in a collection tank upon cooling. Analytical pure compound can be collected by simple filtration. Notably, it was found that the mixing tee, used to merge the reaction and ACN or MeOH, needed to be heated to the reaction temperature to avoid uncontrollable crystallizations. The combined diluent and reaction stream was subsequently cooled down to 60°C prior to passing it through a back pressure regulator (BPR, 1000 psi). This BPR ensured that a steady continuous flow was maintained within the capillary microreactor and prevented boiling of E-MMA (bp = 155°C).

One of the key parameters to accelerate the reaction rate is the use of elevated temperatures. Microreactor technology enables a safe and reliable use of such harsh reaction conditions, which are otherwise difficult to attain on a batch scale. Figure 3 depicts the temperature dependence on the catalyst- and solvent-free Huisgen cycloaddition to yield 4 in continuous-flow with a residence time of one hour. At 140°C, 56% yield could be obtained within one hour. The optimal reaction temperature was 200°C which resulted in the formation of 4 in 82% yield. Further increase of the reaction temperature resulted in a decrease in yield. Although one hour residence time is still acceptable for basic investigations in continuous-flow chemistry, it is far from ideal from a production standpoint. Thus, we decided to study the reaction behaviour in more detail via Differential Scanning Calorimetry (DSC). As an additional advantage, solvent-free conditions afford more accurate modelling due to the absence of solvent-reactant interactions. Based on the energy evolution, DSC predicted that while one hour is required to obtain full conversion at 200°C, only 5 min might be necessary to afford the same result at 240°C (Figure 4). It should be noted that the observed energy evolution is not only observed for the exothermic [3+2] cycloaddition, but can also be due to the decomposition of starting materials.

It is generally known that azides are heat sensitive and decompose rapidly at elevated temperatures with concomitant evolution of nitrogen gas.

In order to study the decomposition rate of 2,6-difluorobenzyl azide (2), pure 2 was introduced into the micro reactor assembly and subjected to elevated reaction conditions.

Figure 1. Progress of the [3+2]-cycloaddition of 2,6-difluorobenzyl azide 2 with (E)-methyl 3-methoxyacrylate 3 at 135°C under solvent-free or diluted conditions in batch.

Figure 2. Schematic representation of the micro capillary assembly for the solvent- and catalyst-free Huisgen cycloaddition of 2,6-difluorobenzyl azide 2 with (E)-methyl 3-methoxyacrylate 3. More details are given within the supporting information of the publication the current chapter is based on. Picture shows the precipitation of product 4. (BPR = back pressure regulator.)
Figure 4. Differential Scanning Calorimetry predictions for the [3+2]-cycloaddition of 2,6-difluorobenzyl azide 2 with (E)-methyl 3-methoxyacrylate 3 under solvent-free reaction conditions.

Figure 5. Above: Decomposition rate of 2,6-difluorobenzyl azide 2 at different reaction temperatures in continuous-flow. Below: Color change observed upon decomposition of 2. The numbering on the vials is matched with the one in the above graph.

temperatures (Figure 5). At a reaction temperature of 200 °C, only 4% of the azide was decomposed after a residence time of 10 minutes. However, at 230 °C, already 34% of 2 was decomposed within 10 minutes residence time as was evident from the increased nitrogen gas evolution. Analysis of the reaction sample with GC-MS, revealed the formation of 2,6-difluorotoluene and 2,6-difluorobenzyl amine together with some other minor decomposition products. These results demonstrate the existence of a sensitive balance between decomposition rate of the reagents and acceleration of reaction rate to form the desired compound at elevated reaction temperatures. In order to fine-tune the operating conditions, we investigated the influence of the residence time on the yield of 4 at the temperatures ranging from 200 to 240 °C, and residence time ranging from 2.5 min to 15 min. HPLC results suggested that 210 °C was the optimal reaction temperature. Isolated yield experiments on a large scale (20 mmol) revealed that the highest yield was obtained after a residence time of 10 minutes, resulting in 83% yield (4.2 g product, 30 min collection time) in the first crop (Table 2, Entry 2). A second crop obtained from the mother liquor increased the total yield to 86%.

5.3. CONCLUSION

We have investigated the potential of the Novel Process Windows concept on an industrially relevant example, i.e. the synthesis of a key intermediate for the production of Rufinamide. A continuous-flow process was developed for the formation of the 1,2,3-triazole precursor via a 1,3-dipolar Huisgen cycloaddition of 2,6-difluoro-benzylazide and (E)-methyl 3-methoxyacrylate under catalyst-free and solvent-free reaction conditions. Moreover, we have made a switch to a greener and less expensive dipolarophile possible, while adhering to green chemistry and green engineering principles. It was found that the use of elevated temperatures boosted the reaction rate significantly, allowing the synthesis of the 1,2,3-triazole precursor in only 10 minutes residence time. Clogging was efficiently avoided by working at reaction temperatures above the melting point of the target.
compound. In addition, by introduction of recrystallization solvent purification was realized upon product collection. Finally, it was shown that continuous-flow processing, as shown herein, constitutes an environmentally benign alternative for the currently employed procedures in the industry.

ACKNOWLEDGEMENTS

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REFERENCES

CHAPTER 6

From alcohol to 1,2,3-triazole via multi-step continuous-flow synthesis of rufinamide precursor

This chapter is based on:

CHAPTER 6
From alcohol to 1,2,3-triazole via multi-step continuous-flow

ABSTRACT

Rufinamide is an antiepileptic drug used to treat the Lennox-Gastaut syndrome. It comprises a relatively simple molecular structure. Rufinamide can be synthesized from an organohalide in three steps. Recently we have shown that microreactor flow networks have better sustainability profiles in terms of life-cycle assessment than the respective consecutive processing in batch. The analysis was based on results of a single step conversion from batch to continuous mode. An uninterrupted continuous process towards rufinamide was developed, starting from an alcohol precursor, which is converted to the corresponding chloride with hydrogen chloride gas. The chloride is then converted to the corresponding organoazide that yields the rufinamide precursor via cycloaddition to the greenest and cheapest dipolarophile available on the market. The current process demonstrates chemical and process-design intensification aspects encompassed by Novel Process Windows. Single reaction steps are chemically intensified via a wide range of conditions available in a microreactor environment. Meanwhile, the connection of reaction steps and separations results in process-design intensification. With two in-line separations the process consists of five stages resulting in a total yield of 82% and productivity of \(9\,\text{g h}^{-1}\) (11.5 \(\text{mol h}^{-1}\text{L}^{-1}\)). The process minimizes the isolation and handling of strong alkylating or energetic intermediates, while minimizing water and organic solvent consumption.

6.1. INTRODUCTION

In nature, complex molecules are constructed into one entity via series of reactions such as bio-assembly lines\(^1\). According to Fujita, a bio-assembly line represents an energy-driven conveyor-belt, where a product undergoes a series of modifications on its way to the end\(^1\). Within a cell, single reactions are carried out continuously within the bio-assembly line under simple operating conditions, such as a single set of solvent type, temperature and pressure values. The activation of reactions is realised via use of enzymes, while compartmentalization takes place in supramolecular structures or organelles\(^1\). On the contrary, in fine chemical and active pharmaceutical ingredient (API) synthesis it is common to build molecules from intermediates that are gathered from various sites in the world or produced on a site in quantities governed by the capacity of the equipment available. We believe that by mimicking nature we can increase the sustainability and maximize the efficiency in chemical processes. A first technological equivalent to a bio-assembly line is a micro flow reactor network based on reactor cascades operated under non-classical conditions with integrated separation units\(^1\).

Our aim was to design and realize such a flow microreactor network consisting of a multi-step synthesis in compartmentalized continuous manner in micro flow reactors. The biggest advantage behind the use of micro flow reactors is the access to a larger playground in terms of process conditions without compromising safety\(^4\). Chemical reactions can be kinetically accelerated via high temperature, concentration and pressure\(^5–8\). In addition, a combination of those operating parameters may lead to new chemical transformations and operating regimes that are not accessible in standard batch technology\(^9–12\). The aforementioned operating conditions accompanied with a fresh attitude on process design with the aim of intensification, comprise Novel Process Windows\(^6,13–15\). Substantial numbers of reactions and processes have been shown to benefit from the concept\(^16–19\).

In collaboration with Ajinomoto OmniChem N.V., we aimed at developing a continuous process to synthesize a rufinamide precursor, while leaving amidation, the last step, to be handled according to a conventional batch procedure. Rufinamide is a sodium-channel blocker that is used in treatment of a type of epilepsy called Lennox-Gastaut syndrome. Herein, we describe a five-stage multi-step process with minimized use of organic solvent and catalyst. The process consists of gas-liquid, biphasic liquid-liquid and solid forming reactions and two in-line separation steps.
6.2. BACKGROUND

Rufinamide was developed by Novartis Pharma, AG in 2004 and currently is marketed by Eisai. The initial synthetic path developed by Novartis relied on constructing the 1,2,3-triazole precursor via 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide to 2-chloroacrylonitrile (1) as shown in Scheme 120. Alkynes (2)-(4) have been shown to be readily reactive, however, regioselectivity needs to be directed by a copper catalyst, otherwise a mixture of 1,4- and 1,5-cycloadduct products is formed21,22. Mudds et al. proposed a solventless batch sequence using (E)-methyl 3-methoxyacrylate (5) as an alternative23. The alkene is a significantly safer and cheaper alternative to all previously mentioned dipolarophiles. In addition, due to the presence of the methoxy leaving group no catalyst is needed to direct regioselectivity. However, the biggest drawback is its relatively low reactivity requiring high concentrations. Furthermore solventless reactions with such potentially energetic compounds are not scalable in batch.

Following batch procedure developments, continuous-flow processes have been developed. First, Borukhova et al. showed how the reactivity of (5) can be enhanced in a micro flow capillary reactor under neat and superheated conditions24. The reaction time was reduced from ~24 hrs to 10 min when the temperature was increased from 135 °C in batch to 210 °C in flow. Moreover, continuous synthesis was combined with crystallization of the rufinamide ester precursor upon collection and cooling of the product. 86% of isolated yield with a productivity of 9 g/h (16.6 mol h⁻¹ L⁻¹) was obtained. Subsequently, Jamison et al. demonstrated a total synthesis of rufinamide using 2,6-difluorobenzyl bromide and methyl propiolate (3) as starting reagents25. 2,6-difluorobenzyl bromide was converted to 2,6-difluorobenzyl azide, while (3) was converted to the corresponding amide (4) after reacting with aqueous ammonia. Without any intermediate separation, the intermediates reacted to form rufinamide in the copper tubing, where the reaction was catalysed by the leached ionic copper species within the reaction stream. The overall process concentration was 0.25 M in DMSO and resulted in 92% yield in 11 min with a productivity of 217 mg/h (2.1 mol h⁻¹ L⁻¹).

Novel Process Windows, apart from concentrating on chemical and process-design intensification, advocate a holistic approach to the process design to yield green processes and sustainable manufacturing. Recently, we performed a life-cycle assessment26 and saw a potential within the synthetic route based on 2,6-difluorobenzyl alcohol and (5) as key reagents, as shown in Scheme 2. It is proposed that in order to minimize waste, instead of high-weight halides, like bromides, chlorides should be used in the synthesis of 2,6-difluorobenzyl azide. Another green alternative is the route to the chloride itself, by using pure hydrogen chloride gas and generates water as the sole by-product. The chloride is converted into the azide. Finally, due to the immediate consumption of synthesized 2,6-difluorobenzyl azide in cycloaddition to yield triazole (Scheme 2), minimal amounts are available at any point in time, minimizing the risk associated with detonation of organic azides in general.
CHAPTER 6

6.3. STEP 1- CHLORODEHYDOXYLATION

The first step of the 5-stage multi-step synthesis is chlorodehydroxylation of 2,6-difluorobenzyl alcohol to afford 2,6-difluorobenzyl chloride. Recently, we realized the continuous synthesis of chloroalkanes from alcohols using either concentrated hydrochloric acid\(^\text{27}\) (HCl \(\text{(aq)}\)) or hydrogen chloride\(^\text{28}\) (HCl) gas as greener alternatives to more wasteful chlorinating agents. Valuable intermediates were formed with water as a sole by-product. The intermediates were further continuously utilized in the construction of antiemetic drugs and antihistamines. In order to prepare the chlorides, HCl \(\text{(aq)}\) was introduced into a continuous flow reactor via a reagent loop, which was refilled when needed. Rapid conversion of neat alcohols was afforded with 3 equivalents of HCl \(\text{(aq)}\) in 15 min residence time at 120 °C. Despite the great practicality of the process, the use of HCl gas proved to be an even greener alternative to the use of aqueous HCl due to the possibility of truly continuous operation (without any need for reagent loop) and of less equivalents needed for a full conversion of investigated alcohols. Benzyl alcohol served as a model compound, which was fully converted to a corresponding chloride in 20 min residence time at 100 °C with 1.2 equivalents of HCl gas. When the same conditions were applied to 2,6-difluorobenzyl alcohol 87% yield was obtained. The lower yield was attributed to the presence of fluorine atoms, that slow down the dissociation of the protonated hydroxyl group to yield the benzylic cation. Scheme 3.a shows a schematic representation of the experimental platform, where further optimization was performed. When the temperature was increased from 100 °C to 110 °C, a temporary decrease in flowrate at the outlet was observed. The decrease in flow rate can be explained by the higher consumption of HCl gas, which results in a larger volume available for the liquid phase to occupy. The constant flow of liquid phase was once again observed after 40 min reaction time. The resulting product contained >99wt% of 2,6-difluorobenzyl chloride and no dibenzyl ether by-product was observed.

6.4. STEP 2- SYNTHESIS OF AZIDE

Organoazides are often high energetic substances that are prone to detonate upon the release of nitrogen under minimal energy input, such as friction, pressure, heat or light\(^\text{29}\). Thus, the production and storage of large quantities of organoazides present high safety risks. Previously performed safety assessment of the 2,6-difluorobenzyl azide indicated that the reagent was relatively stable and not shock sensitive\(^\text{24}\). Borukhova et al. demonstrated safe cycloaddition of organoazides with a variety of dipolarophiles under high temperature and pressure in micro flow reactors\(^\text{30}\). The most straightforward synthesis of azide is the use of organohalide and azide source, such as sodium azide. Upon solvation of sodium azide \(\text{NaN}_3\) in water the highly toxic and explosive hydrazoic acid \(\text{HN}_3\) is formed as shown in (1).

\[
\text{NaN}_3 + \text{H}_2\text{O} \rightleftharpoons \text{HN}_3 + \text{NaOH}
\]  

(1)

In order to force equilibrium to the reactant side and prevent the formation of the acid, sodium hydroxide (NaOH) can be added. However, to see if there was any effect of the base on conversion and reaction, the reaction was first run without the base. Scheme 3.b shows the experimental platform used along with the conditions applied and corresponding results. It should be noted that 2,6-difluorobenzyl chloride is a solid under atmospheric conditions. Since the aim was to work with as concentrated conditions as possible, 2,6-difluorobenzyl chloride was melted and 10 wt% of toluene was added. However, this lead to crystallization upon cooling. Finally, 25 wt% of toluene was needed to afford homogeneous reactant solution.
2,6-difluorobenzyl chloride and sodium azide solutions were mixed within an ETFE T-mixer to yield a two-phase slug flow and heated 140°C. The starting operating conditions were the ones previously investigated in the optimization of benzyl azide synthesis. As expected, the addition of base increased the hydrolysis of 2,6-difluorobenzyl chloride and decreased the conversion, as tabulated in scheme 3.b. Decreasing equivalents of base increased the selectivity towards 2,6-difluorobenzyl azide. However, more equivalents of NaN₃ were needed to obtain full conversion in 30 min residence time.

### 6.5. Step 1+2+ Separation

In order to connect the synthesis of 2,6-difluorobenzyl chloride to the synthesis of azide, the chloride had to be separated from the acidified water phase, formed in the course of the reaction. However, crystallization of the product occurred at the outlet of the inline liquid-liquid separator. Moreover, 2,6-difluorobenzyl chloride is a lachrymator, which is less stable and more toxic than the corresponding azide. Therefore, in order to minimize the handling of the chloride it was decided to connect two steps by the neutralization of the excess of HCl (aq), without any intermediate separation, as shown in Scheme 3.c. A significant difference in results was observed between the optimization results for azide synthesis only and the azide synthesis in 2-in-1 flow. The results of the optimization are tabulated in Table 1. The same concentration of 0.4 M NaOH, after the neutralization of excess HCl from reaction 1, was maintained in reactor 2, which led to partial hydrolysis of the chloride. Decreasing the concentration of base improved the results, again increasing the selectivity towards 2,6-difluorobenzyl azide. Higher temperatures and NaN₃ equivalents were required to reach full conversion of 2,6-difluorobenzyl chloride, indicating higher mass transfer barrier due to the stronger phase separation at higher concentration of sodium chloride formed during the neutralization.

<table>
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2,6-difluorobenzyl azide is liquid under atmospheric conditions and immiscible with water. Previously, Borukhova et al. described the design and fabrication of an inline Teflon membrane-based liquid-liquid separator[12]. In order to afford a perfect separation, the ‘right’ pressure difference should be applied over the membrane to allow permeate, organic phase, to pass through the membrane without causing a breakthrough of the retained, aqueous, phase or alternatively, without carrying the permeate within the retentate. An ultra-low volume adjustable BPR was attached to the aqueous outlet of the separator and a pressure of 2 psi was set. Meanwhile, 2,6-difluorobenzyl azide was collected at the organic side via a tubing of 20 cm with 250 µm ID. After reaching steady-state, 2,6-difluorobenzyl azide was collected for 4 hr resulting in 93% isolated yield. Meanwhile, 1.2% of total organic phase was lost based on the collected volume measurements. Karl Fischer titration indicated the presence 0.8% of water within the separated organic phase.

By connecting two steps, the separation of the hazardous chloride intermediate and the complication due to its precipitation that would require the addition of a solvent or a phase transfer catalyst were circumvented. Thus, a decrease in the number of unit operations and solvent use was achieved. Total residence time of 80 min was needed for the two-step synthesis of 2,6-difluorobenzyl azide via two nucleophilic substitutions. If desired, the rate of the reactions could be increased by the addition of a polar solvent, which would accelerate the reactions. However, due to the fact that our goal was to deliver a solvent-free process, we avoided the addition of any solvent.

### 6.6. Step 1+2+ Separation+3+ Crystallization

The intensified cycloaddition of 2,6-difluorobenzyl azide to (5) greatly benefited from being carried out in a continuous manner under superheated conditions[14]. The most important benefit is the increased safety due to the circumvention of any significant decomposition of organic azide. Similarly to a previously published process, 2,6-difluorobenzyl azide was mixed with (5), heated to 210°C and allowed 10 min reaction time. In order to carry out continuous synthesis and purification, a stream of methanol was introduced at the outlet of the reactor. The streams were allowed to mix within a 1 ml mixing zone. Upon collection needle-like crystals crashed out of the solution. However, the analysis of the mother liquor indicated the presence of unconverted azide. We attribute the difference in the results to the difference in the starting composition of the azide feed. Therefore, we increased the residence time to 15 min, which gave full conversion of the azide. GC-MS showed that the main side-products were benzyl alcohol, and decomposition products of 2,6-difluorobenzyl azide. Further cooling, filtration and drying under vacuum resulted...
in 88% isolated yield based on 2,6-difluorobenzyl azide, leading to an overall 82% yield based on 2,6-difluorobenzyl alcohol used. As a result, a productivity of the rufinamide precursor of 9 g/h was afforded (11.5 mol h⁻¹ L⁻¹).

6.7. CONCLUSION

Continuous flow and solvent-free processing comprise two eminent issues of Green Chemistry and Green Engineering. Yet, these two processing issues are difficult to combine due to the high susceptibility of micro flow reactors to clog. Nevertheless, we believe that the combination should be the next step in the synthesis of fine chemicals to minimize solvent waste and energy used within a given process. Moreover, incorporation of Novel Process Windows as a concept to assist in chemical and process-design intensification proves to be an important stepping stone on the way to sustainable and efficient processes.

Herein, we demonstrated a 5-stage 3-step continuous synthesis with integrated separation steps. A total yield of 82% of rufinamide precursor with productivity of 9 g/h (11.5 mol h⁻¹ L⁻¹) was delivered. The total residence time needed for the whole process is 95 min, which is relatively long when compared to other continuous-flow 5-stage processes. This stems from the absence of solvent. In this case nucleophilic substitutions could proceed at much higher rates if diluted with polar solvents. However, when considering the separation of the solvent and its recycling or disposal, and the purity of the final product, prevention of the waste generation surpasses the benefits of higher reaction speed. The aim of minimizing solvent use and, thus, energy needed for its later separation was realized. Similarly, water use was minimized by combining introduction of a quenching reagent (NaOH) and a reactant for the subsequent step (NaN₃) at once. Moreover, isolation of toxic and unstable lachrymator, alkylating chloride intermediate, was circumvented by connecting its synthesis to the synthesis of the corresponding azide. Finally, in the isolation of 2,6-difluorobenzyl azide no organic extractant was added, instead the azide was separated in its neat form and used as it is in the subsequent step. All of the mentioned factors contribute to a better sustainability profile of the individual steps and the flow microreactor network as a whole.

Finally, if compared to conventional batch process:

- Production capacity is variable based on demand;
- Inline separation minimizes manual handling;
- Meanwhile, if the process is compared to the existing continuous total synthesis:
- Synthetic route starts off with a cheaper, greener and more accessible starting compound;
- No solvent is used, as opposed to DMSO use;
- 9 times longer residence times are needed to make a precursor;
- No catalyst is used, thus no leached metal in the final product;
- Inline separation affords more concentrated intermediate;
- 6 times higher space time yield is obtained.

ACKNOWLEDGEMENTS

We would like to thank Erik van Herk from Eindhoven University of Technology for his work on mechanical aspect of the process. Funding by the Advanced European Research Council Grant “Novel Process Windows - Boosted Micro Process Technology” (Grant number: 267443) is kindly acknowledged.
REFERENCES

CHAPTER 7

Economic and environmental evaluation of integrated continuous and batch manufacturing of rufinamide precursor

This chapter is based on:

CHAPTER 7 Economic and environmental evaluation of continuous manufacturing

7.1. INTRODUCTION

Pharmaceutical industry is facing tighter economic constraints which lead to consideration of alternative to conventional ways of manufacturing. Continuous manufacturing is becoming increasingly appealing due to the potential of decreasing the production costs and improving the product quality. Throughout lifetime of a drug development the production scale increases from micro grams needed for initial pharmokinetic studies to kilograms needed for clinical trials. Within the scale-up stages quality of the product may vary leading to the waste of chemicals among other resources. Meanwhile, a plethora of lab scale continuous syntheses of active pharmaceutical ingredients performed in micro flow reactors has been described. Common benefits observed from converting batch processes to continuous-flow are tighter control over operating conditions, higher safety, better mass and heat transfer leading to higher selectivity and thus productivity, and a possibility to use alternative reagents leading to greener processes.

The greenness of continuous processes have been evaluated for several examples. Conceptual process modelling, economic evaluation and environmental analysis have been performed for continuous processes of ibuprofen and artemisinin. Trout et al. performed an economic analysis of integrated continuous and batch processes of Aliskiren tablet production and concluded that overall cost savings of 9 to 40% are possible at equal to batch process yields, and higher in case of better yields. In terms of environmental assessment production of pharmaceutical chemicals poses a more challenging task due to the structural complexity of the reagents and solvents involved. It has been shown that production of pharmaceuticals results in significantly greater environmental impacts per kilogram when compared to bulk chemicals. For instance, Cumulative Energy Demand (CED) and Global Warming Potential (GWP) have been shown to be 20 and 25 times greater, respectively.

Several mass-based green metrics, such as environmental factor (E-factor), mass efficiency, reaction mass efficiency, atom economy, and process mass intensity (PMI) exist and are used in comparison of the process alternatives. The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable evaluated the aforementioned metrics and presented PMI as a key mass-based green measure in sustainability of pharmaceutical processes. Meanwhile, the Roundtable stressed that PMI did not address concerns associated with health and safety of the raw materials or waste generated. Alternatively, it was proposed to carry out Life-cycle Assessment (LCA) to evaluate the processes further. LCA comprises a methodology evaluating expanded environmental impact, which is known as ‘cradle-to-grave’ assessment. It evaluates the processes based on extraction of raw materials, production, transportation, distribution, sale and final fate of the product. Moreover, resource consumption, pollutants emitted and waste generated are also taken into account. ‘Cradle-to-grave’ approach can be split into ‘cradle-to-gate’ and ‘gate-to-cradle’ assessments. The former option is used when two chemical routes or processes are compared, such as in the current analysis.

Recently, Ott, Borukhova and Hessel performed a simplified LCA on several alternative batch and continuous-flow processes to produce rufinamide. The scenarios evaluated were a mixture of published and envisioned processes. Herein, we perform a conceptual scale-up of a recently developed lab-scale continuous-flow process to deliver a precursor to rufinamide. In addition, we perform economic and LCA analyses based on the developed process and compare it to the batch process described within the patents.

7.2. PROCESS MODEL DEVELOPMENT

7.2.1. Starting point- lab-scale continuous-flow process

The flowsheet development for a continuous-flow process is based on the lab-scale process developed by Borukhova et al. The flowsheet development for a continuous-flow process is based on the lab-scale process developed by Borukhova et al. Figure 1 shows process flow diagram (PFD) for the continuous flow process. In the first reactor, neat 2,6-difluorobenzyl alcohol (DFB-OH) reacts with pure hydrogen chloride gas (HCl) (1.2 equivalents) at 140 °C and 7 bar to yield >99% of 2,6-difluorobenzyl chloride (DFB-Cl). At the end of the first reactor an aqueous stream of sodium hydroxide (NaOH) and sodium azide (NaN₃) is introduced. NaOH is used to quench the excess of 0.2 equivalents of HCl used in the previous step, while NaN₃ is a reactant for a following reaction where 2,6-difluorobenzyl azide (DFB-N₃) is formed. Thus, intermediate separation of unstable lachrymator, DFB-Cl, is avoided and the product flows directly into the second continuous reactor. In the end of the second reaction, isolation of DFB-N₃ takes place within the ETFE-membrane-based liquid-liquid separator. The process benefits from a sufficient difference among surface tension of the product and aqueous phase and does not require any addition of the organic extracting solvent. Isolated product is collected and later pumped into a third reactor from an open vessel. DFB-N₃ is then pumped into a third reactor along with methyl trans-3-methoxy acrylate (EMMA) to produce ester precursor of rufinamide in 100% regioselectivity and 88% isolated yield, resulting in 82% overall yield. The final separation of the precursor takes place when it is mixed in its molten phase with methanol (MeOH) and precipitates upon cooling within a product collection vessel. Lab-scale process produced 9 g h⁻¹ (11.5 mol h⁻¹ L⁻¹) of a precursor corresponding to 72 kg yr⁻¹.

7.2.2. Scale-up of continuous-flow process

Based on the annual sale and the price of rufinamide tablets containing 400 mg dose, we estimated a yearly production of the compound to be 5 tons. Mass balance calculations...
CHAPTER 7

Economic and environmental evaluation of continuous manufacturing

Table 1. Annual energy requirement for continuous and batch processes to produce 5 tons of rufinamide precursor.

<table>
<thead>
<tr>
<th>Energy Requirements (MJ/yr)</th>
<th>Continuous*</th>
<th>Batch</th>
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</thead>
<tbody>
<tr>
<td>Heating requirement</td>
<td>33.4</td>
<td>7433</td>
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<tr>
<td>Cooling requirement</td>
<td>27.7</td>
<td>1616.2</td>
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<tr>
<td>Total</td>
<td>61.1</td>
<td>9049.2</td>
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</table>

*excluding distillation column needed for the recycle of methanol.

Figure 1. Top: Process flow diagram (PFD) for the lab-scale continuous flow synthesis of rufinamide precursor. Bottom: Mass flow balance of the lab-scale process depicted in PFD.

Shows the PFD and amounts used per one stage. API. Another assumption was that every campaign is completed in four stages. Figure 3 calculations performed. In order, to reach the same capacity of annual production of 5 tons, the lab-scale needs to be multiplied by the factor of 46 to meet the required productivity in 8000 hrs/year of operation. Higher flowrates result in faster intermediate collection of DFB-N3, allowing faster flow rates into the consequence reactor. Therefore, flowrate of stream 12 was multiplied by a factor of 1.4. Due to the large consumption of methanol within the process, its separation with a recycle stream entering the crystallizer feed stream was incorporated within the process. The calculations were based on the steady-state operation. Operating conditions within the reactors and stoichiometry of the feed streams were assumed to be the same as in the lab-scale process. Figure 2 shows the PFD of the continuous-flow large scale process.

7.2.3. Batch process

Batch process described herein is based on the information compiled from available patents. The process starts off with chlorination of DFB-OH with thionyl chloride (2 eq.) (SOCl₂) in dichloromethane (DCM) at 0°C. The reaction is completed within 30 min, which is followed by addition of water to quench SOCl₂. Gaseous products of the reaction, i.e. hydrogen chloride gas (HCl) and sulfur dioxide (SO₂) are separated in their gaseous form, while biphasic mixture is transferred into a settling tank to extract DFB-Cl from water and DCM. The amount of water added is based on required amount for quenching and full solubility of DCM.

Separated in 97% yield DFB-Cl is then mixed with sodium azide in DMSO to produce DFB-N3. The product is then extracted into toluene, which also serves as a solvent for the next step. Consequently, methyl propiolate is added to DFB-N3 in toluene and heated up to 60-65°C for 4-5 hrs. The resulting mixture contains both 1,4- and 1,5-regiosomers. After the final separation, 1,4-regiosomer is isolated in 55% yield. No information has been provided on separation of 1,5-regiosomer and therefore is not included within the calculations performed. In order, to reach the same capacity of annual production of 5 tons, it was assumed that 10 batches are carried out each time delivering 500 kg of the API. Another assumption was that every campaign was completed in four stages. Figure 3 shows the PFD and amounts used per one stage.
### Flows g/h

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<th>2 HCl gas feed</th>
<th>3 NaOH gas feed</th>
<th>4 DMSO feed</th>
<th>5 Alcohol liquid</th>
<th>6 HCl liquid</th>
<th>7 NaOH liquid</th>
<th>8 DMSO liquid</th>
<th>9 Reactor I inlet</th>
<th>10 Reactor I outlet</th>
<th>11 Reactor II inlet</th>
<th>12 Reactor II outlet</th>
<th>13 Reactor III inlet</th>
<th>14 Reactor III outlet</th>
<th>15 Catalyst feed</th>
<th>16 Water feed</th>
<th>17 Alcohol waste</th>
<th>18 HCl waste</th>
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* Cryolite (1,2,3-triazolyl) precursor of rufinamide

**Figure 2:** Top: Process flow diagram (PFD) for large scale continuous flow synthesis of rufinamide precursor. Bottom: Mass flow balance of the large scale process illustrated on top.

**Figure 3:** Top: Process flow diagram (PFD) for large scale batch process to produce rufinamide precursor. Bottom: Mass flow balance of the batch process shown above.
7.3. ENERGY REQUIREMENTS

Heating and cooling requirements were calculated based on the heat needed to be added or removed to the reagents within the reactors based on the optimized procedures. The results should be considered as a theoretical minimum since actual energy consumed by the heating or cooling equipment was not considered here. Specific heat capacities under constant pressure of reagents not listed within the Ullmann encyclopedia were calculated based on the estimation methodology proposed by Rihani et al.\(^2\). The approximation is based on equation 1, where \(n_i\) is the number of occurrences of functional group \(i\) within a specific molecule. \(a_i\), \(b_i\), \(c_i\), and \(d_i\) are given based on the functional group type, while \(T\) is the reference temperature.

\[
C_p = \sum n_i a_i + \sum n_i b_i T + \sum n_i c_i T^2 + \sum n_i d_i T^3
\] (1)

Table 1 shows the energy requirements for large scale continuous-flow and batch processes. Due to the intensive use of the solvents in case of batch process significant energy consumption is required, even though the temperature differences are lower.

7.4. MATERIALS CONSUMPTION

Raw material requirements were calculated based on the large scale flow and batch processes. The price for each chemical was acquired from vendors providing the chemicals in the bulk quantities (>50 kg). Table 2 shows the results of the calculations. Water contributes to more than 90% of the consumed materials in batch process. As mentioned earlier, it is used to remove DCM and DMSO from intermediate reagents. In terms of the costs, batch process requires >8 times larger investment for raw materials to produce the same amount of the final product.

Table 2. Annual raw materials requirements and associated costs for continuous and batch processes to produce 5 tons of rufinamide precursor.

<table>
<thead>
<tr>
<th>Materials</th>
<th>raw materials requirements (kg/yr)</th>
<th>raw materials costs (€/yr)</th>
</tr>
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<tbody>
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<td>Continuous</td>
<td>Batch</td>
</tr>
<tr>
<td>Organic reagents</td>
<td>6,345</td>
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<tr>
<td>Inorganic reagents</td>
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<td>Organic solvents</td>
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<td>Total</td>
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</table>

7.5. EQUIPMENT COSTS

Based on the required productivity, we selected similar equipment employed in continuous-flow process, but with a higher capacity. The quotations were obtained from the providers of the corresponding equipment. Meanwhile, the price of the distillation column required for the recycle of methanol was estimated in ASPEN. Table 3 shows the equipment cost for the continuous-flow process.

Costs for batch equipment were obtained from an online equipment cost calculator\(^2\). For the reactors it was assumed that 80% of the reactor is filled in order to account for vortex formation during mixing. Moreover, due to the corrosive nature of HCl formed in the first reactor, and use of sodium azide in the following reactors, glass-lined stainless reactors were chosen. It was assumed that reactors could also be used for extraction of a product. Mixer costs were not included in batch equipment cost calculation due to the lack of information regarding the power input needed.

Total equipment costs for continuous process are three times more expensive than those of batch. Capital Expenditures (CapEx) are proportional to the equipment cost, thus the CapEx calculations were not further carried out. Operating Expenditures (OpEx) are expected to be substantially lower for continuous process due to the following factors:

- twice as many operators would be required for batch process than continuous\(^1\);
- materials handling and storage can be estimated to be 40% of batch;
- off-spec product is minimal for continuous process;
- quality assurance and control is cheaper in case of continuous process due to the inline analytical measurements;
- utility expenditures are less in case of continuous process;
- waste disposal is lower for continuous process due to the lower use of water and solvents and higher material efficiency.

7.6. ENVIRONMENTAL ANALYSIS

7.6.1. Process Mass Intensity

A PMI evaluation was carried out to provide an overview for improvements brought by the switch from batch to continuous process in terms of material consumption. PMI is defined as the total mass of materials consumed to deliver a specified mass of product. Ideally PMI equals 1 when no waste is generated and all of the materials are incorporated within the final product. The Roundtable developed a PMI calculator tool, which allows...
7.6.2. Life cycle assessment

As stated in the introduction, PMI only shows the mass intensity of the process leaving out concerns regarding the environment, health and safety of the materials employed or produced. Therefore, LCA needs to be performed to shine the light on the aforementioned concerns.

System Boundaries

The LCA study was carried out using Umberto NXT LCA software. The system boundaries were defined as “cradle to gate”, meaning the inclusion of all activities commencing from the extraction of raw materials to the production of the final product. In Figure 6 the system boundaries of both examined flow and batch systems are presented with respect to their elementary material and energy exchanges. For both processes, the energy costs linked to the recycle of the methanol and toluene solvents have not been considered and, thus, the final product is perceived to be the produced ester dissolved in the respective amount of solvent. In the given LCA study, the waste and emissions generated from both processes have been treated in the same way as presented in Figure 6. Moreover, the storage and transportation of the final product has also not been taken into account.

Inventory Analysis

The functional unit of the present LCA study is defined to be 1 kg ester dissolved/suspended in the respective solvent- methanol and toluene for flow and batch processes,
respectively. Regarding the raw material extraction and the energy provision to the flow and batch production systems, unit-operations embedded in the Umberto software have been employed for all material and energy inputs as shown in Figure 6. The relevant mass and energy flows for the flow and batch processes have been acquired from the Figures 2 and 3 and are expressed per functional unit in Tables 4 and 5, respectively. Furthermore, as far as the life cycle inventory (LCI) data is concerned, the Ecoinvent 3.0 (v3.1) database incorporated in Umberto NXT LCA software has been deployed. Inventory data of the energy exchanges and the majority of the chemical components has been directly available from the database. However, for those components with no available entries in the database and no complete background information, LCI data of similar chemical components from the database has been utilized instead. The list of all the inventory data employed in the given LCA study is presented in Table 6. Considering the

![Diagram of flow and batch processes](image)

**Figure 6.** System boundaries of flow and batch processes for the production of 1 kg ester (in solution).

### Table 4. Material and energy input for the flow process expressed per kg of ester.

<table>
<thead>
<tr>
<th>Material/Energy</th>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFB-OH</td>
<td>0.73 kg</td>
<td>-</td>
</tr>
<tr>
<td>HCl</td>
<td>0.22 kg</td>
<td>-</td>
</tr>
<tr>
<td>NaOH</td>
<td>0.05 kg</td>
<td>0.01 kg</td>
</tr>
<tr>
<td>NaN₃</td>
<td>0.53 kg</td>
<td>0.21 kg</td>
</tr>
<tr>
<td>EMMA</td>
<td>0.53 kg</td>
<td>0.04 kg</td>
</tr>
<tr>
<td>MeOH</td>
<td>11.31 kg</td>
<td>10.74 kg</td>
</tr>
<tr>
<td>MeOH (waste)</td>
<td>-</td>
<td>0.57 kg</td>
</tr>
<tr>
<td>DFB-Cl</td>
<td>-</td>
<td>0.04 kg</td>
</tr>
<tr>
<td>Water</td>
<td>1.42 kg</td>
<td>1.53 kg</td>
</tr>
<tr>
<td>DFB-N₃</td>
<td>-</td>
<td>0.05 kg</td>
</tr>
<tr>
<td>Ester</td>
<td>-</td>
<td>1.00 kg</td>
</tr>
<tr>
<td>Ester (waste)</td>
<td>-</td>
<td>0.08 kg</td>
</tr>
<tr>
<td>NaCl</td>
<td>-</td>
<td>0.34 kg</td>
</tr>
<tr>
<td>Cooling Energy</td>
<td>5.54E-03 MJ</td>
<td>-</td>
</tr>
<tr>
<td>Heat</td>
<td>6.68E-03 MJ</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 5. Material and energy input for the batch process expressed per kg of ester.

<table>
<thead>
<tr>
<th>Material/Energy</th>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFB-OH</td>
<td>0.61 kg</td>
<td>-</td>
</tr>
<tr>
<td>SOCl₂</td>
<td>1.00 kg</td>
<td>-</td>
</tr>
<tr>
<td>DCM</td>
<td>6.06 kg</td>
<td>6.06 kg</td>
</tr>
<tr>
<td>Water</td>
<td>253.26 kg</td>
<td>253.26 kg</td>
</tr>
<tr>
<td>DFB-Cl</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NaN₃</td>
<td>0.26 kg</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>8.29 kg</td>
<td>8.29 kg</td>
</tr>
<tr>
<td>Toluene</td>
<td>6.63 kg</td>
<td>6.63 kg</td>
</tr>
<tr>
<td>DFB-N₃</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methyl Propiolate</td>
<td>0.33 kg</td>
<td>-</td>
</tr>
<tr>
<td>Ester</td>
<td>-</td>
<td>1.00 kg</td>
</tr>
<tr>
<td>HCl</td>
<td>-</td>
<td>0.15 kg</td>
</tr>
<tr>
<td>SO₂</td>
<td>-</td>
<td>0.27 kg</td>
</tr>
<tr>
<td>NaCl</td>
<td>-</td>
<td>0.23 kg</td>
</tr>
<tr>
<td>Cooling Energy</td>
<td>0.32 MJ</td>
<td>-</td>
</tr>
<tr>
<td>Heat</td>
<td>1.49 MJ</td>
<td>-</td>
</tr>
</tbody>
</table>
CHAPTER 7  Economic and environmental evaluation of continuous manufacturing

Table 6. Inventory data incorporated in the LCA study.

<table>
<thead>
<tr>
<th>Material/Energy Exchanges</th>
<th>Inventory Data (Ecoinvent 3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH (input)</td>
<td>methyl acrylate production [GLO]*</td>
</tr>
<tr>
<td>NaOH (input)</td>
<td>market for sodium hydroxide, without water, in 50% solution state [GLO]*</td>
</tr>
<tr>
<td>EMMA (input)</td>
<td>methyl acrylate production [GLO]*</td>
</tr>
<tr>
<td>NaN₃ (input)</td>
<td>atrazine production [RER]*</td>
</tr>
<tr>
<td>DFB-OH (input)</td>
<td>benzyl alcohol production [RER]*</td>
</tr>
<tr>
<td>HCl (input)</td>
<td>hydrochloric acid production, from the reaction of hydrogen with chlorine [RER]*</td>
</tr>
<tr>
<td>SO₂ (input)</td>
<td>thionyl chloride production [RER]*</td>
</tr>
<tr>
<td>Toluene (input)</td>
<td>toluene production, liquid [RER]*</td>
</tr>
<tr>
<td>DMSO (input)</td>
<td>dimethyl sulfoxide production [RER]*</td>
</tr>
<tr>
<td>DCM (input)</td>
<td>dichloromethane production [RoW]*</td>
</tr>
<tr>
<td>Methyl propiolate (input)</td>
<td>methyl acrylate production [GLO]*</td>
</tr>
<tr>
<td>Water (input)</td>
<td>water production, deionised, from tap water, at cogen unit with absorption chiller 100kW [CH]*</td>
</tr>
<tr>
<td>Cooling Energy (input)</td>
<td>cooling energy, from natural gas, at cogen unit with absorption chiller 100kW [CH]*</td>
</tr>
<tr>
<td>Heat (input)</td>
<td>heat production, natural gas, at industrial furnace &gt;100kW [Europe without Switzerland]*</td>
</tr>
<tr>
<td>Ester (product)</td>
<td>Esters of versatic acid [intermediate exchange]</td>
</tr>
<tr>
<td>Methanol (product stream)</td>
<td>Methanol [Intermediate exchange]</td>
</tr>
<tr>
<td>NaCl (waste)</td>
<td>Sodium chloride, in ground [natural resource/in ground]</td>
</tr>
<tr>
<td>NaN₃ (waste)</td>
<td>Hydroxide [water/ground-]</td>
</tr>
<tr>
<td>Water (waste)</td>
<td>Wastewater, average</td>
</tr>
<tr>
<td>EMMA (waste)</td>
<td>Methyl acrylate [water/ground-]</td>
</tr>
<tr>
<td>Methanol (waste)</td>
<td>Methanol [water/ground-]</td>
</tr>
<tr>
<td>DFB-CI (waste)</td>
<td>Methane, dichlorofluoro-, HFC-21 [water/ground-]</td>
</tr>
<tr>
<td>DFB-N₃ (waste)</td>
<td>Methane, dichlorofluoro-, HFC-21 [water/ground-]</td>
</tr>
<tr>
<td>HCl (emissions)</td>
<td>Hydrogen chloride [air/unspecified]</td>
</tr>
<tr>
<td>SO₂ (emissions)</td>
<td>Sulphur trioxide [air/unspecified]</td>
</tr>
<tr>
<td>Toluene (product stream)</td>
<td>Toluene, liquid [intermediate exchange]</td>
</tr>
<tr>
<td>DCM (waste)</td>
<td>Methane, dichloro-, HCC-30 [water/ground-]</td>
</tr>
<tr>
<td>DMSO (waste)</td>
<td>Dimethyl ether [water/ground-]</td>
</tr>
</tbody>
</table>

*Refers to activity datasets embedded in the Ecoinvent 3.0 database

The interpretation of the generated LCA results has been established upon the individual environmental impact of the elementary material and energy exchanges. More precisely, the distribution of the selected impact categories values among the unit-operations linked to the material and energy exchanges, as well as, the emissions/waste directly produced from the process is reflected in a normalized manner for both flow and batch processes in a pivot graph shown in the results section. In that graph the components, which have been replaced by similar ones with respect to the inventory data, are presented with both components names. However, in the discussion of the LCA results their environmental contribution will be expressed only in terms of the initial component names so as to avoid any potential ambiguity.

Regarding the replacement of the missing components in the Ecoinvent 3.0 database with similar ones, there has been a given group of available choices for some of these components, and more precisely for the EMMA as an input material and the NaN₃ as an input and output exchange flows. In order to evaluate the possible influence of those alternatives on the overall environmental profile of the batch and flow processes, a sensitivity analysis has been conducted. The results from this analysis have demonstrated no remarkable fluctuation in the values of the majority of the impact categories as to the ones presented below.
Results
In Figure 7 the normalized impact categories of the flow and batch processes are presented against the process with the higher nominal value. As it can be deduced, the GWP of the batch process is remarkably higher than that of the flow process. This is mainly attributed to the air emissions directly given off by the batch process which account for 53% of the total GWP profile. The next contributory factors are the DCM production with a share of 21% and the use of toluene and DMSO with a corresponding share of 10%.

In the case of the flow process, the GWP is mainly dominated by the impact of the methanol and sodium azide production which accounts for 40% and 29%, respectively. The use of DFB-OH is the third factor influencing the overall GWP value of the flow process by 20%. The use of HCl and NaOH along with the cooling and heat requirements contribute the least to the overall emissions of the process by a total percentage of 2%.

In terms of the FDP, FEP and MDP impact categories, the batch process remains inferior to the flow process but to a lesser extent and with different material/energy distribution as compared to the GWP profile. To elaborate, the certain impact categories for the batch process are majorly prevailed by the impact of the toluene and DMSO. On the other hand, for the flow process the same trend is followed as in the GWP profile with respect to the individual impact of materials and energy exchanges.

As far as the HTPinf is concerned, the contribution of the emissions in the batch process reaches the percentage of 85%. On the contrary, the profile of the flow process, with a nominal HTPinf value lower by 91%, is mainly controlled by the MeOH and NaH, input flows whose shares are 36% and 28%, correspondingly. Additionally, the flow process exhibits also markedly lower value as to the batch one for the ODPinf impact category, with the profile of the latter process being dominated by the DCM material flow.

The environmental performance of the flow process seems to be inferior to that of the batch process for the NTLP and TETPinf impact categories. More specifically, the methanol production and the generated waste are the main factors influencing those impact categories with a respective share of 75% and 100%. Regarding the remaining category of POFP, the profile of both production systems follows a similar trend as to that of the TAP100 with certain fluctuations in the individual share of the major contributory materials.

7.7. CONCLUSION
Continuous processes are developed as alternative to batch processes due to economic and environmental benefits. In the last decade, multiple continuous flow processes have been developed on a lab-scale in academia. Their accurate comparison to existing batch process is usually difficult due to the lack of information disclosed by industry. The approach, followed herein, was based on the assembly of overall process acquired from available patents. From the comparison, it was found that continuous flow process based on existing lab-scale process requires less energy and less materials to deliver the final product. The cost of the equipment was calculated to higher for continuous flow process than for batch.

Environmental analysis was based on the process mass intensity (PMI) and life cycle assessment (LCA). Continuous process is based on solvent-free reaction steps, which leads to substantially lower PMI than that of batch process. Finally, LCA analysis showed environmental profile of process in terms of environmental, toxicity and health
aspects. Human toxicity factor was found to be marginal in the case of continuous flow process as opposed to the batch. In the remaining categories, continuous flow process outweighs batch in terms of negative impact in terrestrial ecotoxicity and natural land transformation. Methanol production and the generated waste were found to be the main factors influencing those impact categories.

REFERENCES

CHAPTER 8
Research Impact and Further Recommendations
8.1. CONTINUOUS MANUFACTURING OF ACTIVE PHARMACEUTICAL INGREDIENTS VIA MULTI-STEP CONTINUOUS-FLOW PROCESSES

Highlights
Micro flow chemistry as mentioned throughout the current thesis is an exceptional operating platform to deliver APIs at different scales with consistent quality. The current thesis presented the development of a process to deliver antiemetic and antihistaminic piperazine-based drugs. Cinnarizine and a buclizine derivative were constructed from bulk alcohols in 6-stage 4-reaction step processes. The whole sequence was realized in 90 minutes with good overall yields (>80%) at a production rate of 2 mmol/hr of final products. If so desired, the scale could be increased by using wider and/or longer reactors and/or the employment of several parallel reactors. Furthermore, a precursor for an antiepileptic drug, rufinamide, was synthesized from alcohol in a 5-stage 3-reaction step process. A total yield of 82% with productivity of 9 g h⁻¹ (11.5 mol h⁻¹ L⁻¹) within a total residence time of 95 min was achieved.

Recommendations
In order to improve the continuous manufacturing of these particular APIs the secondary production process would be the next aspect to look into. Continuous separation of solid APIs in order to prepare the final solid tablets would complete the production sequence. Luckily, the secondary API production stage is already continuous or semi-continuous. The missing link is bringing down the scale to meet the one micro- or meso-scale is capable of delivering. As a step closer, the research described herein served as a base for a submission of a Proof-of-Concept project proposal, which passed the evaluation threshold and is currently in a waiting list. Finally, the study also stimulated a bigger scale EU proposal such as Fast-Track-to-Innovation. The proposal is concentrated on a flow multi-step pilot study and pilot-scale flow equipment development.

8.2. MICRO FLOW PROCESS TECHNOLOGY

Highlights
Based on our knowledge, we were the first to construct and successfully operate a continuous process utilizing the highly corrosive pure hydrogen chloride gas. Usually, when the highly oxidative gas is used less expensive and less accurate valves are used to minimize the equipment cost in case of failure. Within the current design, the operation was possible with no harm to the equipment fabricated from stainless steel. The highly accurate mass flow controller employed saw no harm due to the division of the setup into dry and wet zones. The dry zone was employed as a gas delivery unit, while the wet zone was used to carry out the reaction. After operating for more than 6 months no corrosion was observed within the dry zone. The use of a micro flow reactor allowed the application of process conditions that are beyond the limits of conventional batch technology. Operation at high pressures increased the solubility of hydrogen chloride gas within the reagent increasing the rate of the reaction, while not requiring as much excess as when hydrochloric acid was used as an alternative.

A membrane based liquid-liquid separator was designed and constructed to deliver integrated processes, comprising micro flow networks.

In order to investigate high pressure effects on the intrinsic kinetics of 1,3-dipolar cycloaddition, a high-pressure micro flow operating platform was built. The upper threshold of operating pressure was limited by the availability of HPLC pumps that could operate only up to 400 bar. Even though the pressure was not sufficient to affect kinetics by itself, it allowed operation under superheated conditions that are not attainable in conventional batch reactors.

The continuous synthesis of 1,2,3-triazole involved organoazide requires special precaution when carried out in batch due to its temperature sensitive nature and predisposition to decompose to yield nitrogen, which leads to explosions. Carrying out the reaction at 210 °C and 70 bar in micro flow presented no explosion concerns.

Operation under superheated conditions above the melting point of the solid API precursor prevented the common problem of precipitation, leading to clogging of micro reactors. In addition, by introduction of recrystallization solvent purification was realized upon product collection.

Recommendations
During operation under superheated conditions polymer-reactors were observed to have a limited life-time due to the harsh conditions as a consequence of using high temperature and pressure. More robust, stainless steel capillaries coated with polymer on the inside would present a better alternative and increase the safety. In addition, when the gas-liquid reaction was connected to the liquid phase reaction and separated by a check valve, the latter would fail in case the reagents were pumped into the second part of the combination. We attributed that due to the creation of a low pressure region due to the consumption of the gas, thus a decrease of the volume within the first reactor. Meanwhile, superheated operation within the second reactor required high pressure. Therefore, the flow of reagents fed into the second reactor would flow in the opposite to expected
direction through the check valve. The problem was solved by allowing pressure within
the first reactor to build up, while gradually increasing the flow rate of the reagents for
the second reactor. While the solution was good enough at the lab-scale, a more robust
solution has to be created for the larger scale to avoid failure of the operation.

The residence time was estimated based on the internal volume and the flow rate of the
reagents. However, a more accurate way to measure the actual residence time would lead
to a deeper understanding of the flow and reaction dynamics.

Finally, the consumption of the chemicals during the optimization stage could be decreased
if inline analytics were integrated. The best option for the current project would be
an installation of the inline FLOWIR made available by METTLER TOLEDO. Monitoring of
alcohol, organohalide and organoazide production and consumption could benefit the
overall process optimization.

8.3. GREEN CHEMISTRY AND GREEN ENGINEERING

Highlights
Circumvention of employing wasteful chlorinating agents in a continuous synthesis of
chlorides from bulk alcohols was afforded via use of hydrogen chloride gas instead. The
initial need for an occasional stop of the continuous operation in the case hydrochloric
acid was used, was gone when hydrogen chloride was utilized. High temperature and
pressure, easily applicable within the reacting system, allowed minimizing the excess
of HCl used from 3 equivalents to 1.2. Moreover, no use of solvent was needed and the
formation of only water as a by-product was observed.

The isolation of the toxic and unstable lachrymator, an alkylating chloride intermediate,
was circumvented by connecting its synthesis to the synthesis of the corresponding azide.
When the separation was initially needed, a liquid-liquid separator required no addition
of extracting solvent to isolate organohalides and organoazides. The aim of minimizing
solvent use and, thus, energy needed for its later separation was realized. Similarly,
water use was minimized by combining the introduction of a quenching reagent (NaOH)
and a reactant for the subsequent step (NaN₃) at once.

When the high-pressure autoclave reactor was used, speed-up of the reaction kinetics
and improvement in regioselectivity were observed. Yield of the desired precursor rose
to 84% in 24 hrs, and resulted in a 1,4:1,5-cycloadduct ratio of 6.3 (30% increase) at 1800
bar with no catalyst present.

A continuous-flow process developed for the formation of the 1,2,3-triazole precursor via
a 1,3-dipolar Huisgen cycloaddition was carried out under catalyst-free and solvent-free
reaction conditions.

Recommendations
As mentioned above intensive use and waste of materials took place during the optimization
and the development of the process. Incorporation of the inline process analytical tools
would minimize the waste. Moreover, automatization of the equipment control would
minimize the manual labor even further.

8.4. NOVEL PROCESS WINDOWS

Highlights
NPW is relying on several tools introduced in Chapter 1 with the aim of reaching chemical
and process design intensification. When applied at the same time the outcomes are
synergistic, benefitting the process on several levels. Within the carried out research we
observed;

– simplification and acceleration of chemical reactions when carried out under high
temperature, pressure and concentration;
– when the high-pressure autoclave reactor was used, speed-up of the reaction
kinetics and improvement in regioselectivity were achieved;

Table 1 shows examples of findings due to the application of NPW tools.

Recommendations
In order to minimize the use of resources, it is advised to first check the potential of
chemical intensification by carrying a particular reaction under superheated conditions
in microwave. This approach will also provide initial understanding of solvent use and
separation requirements.
<table>
<thead>
<tr>
<th>Novel Process Windows</th>
<th>Findings</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High T</td>
<td>Reaction rate acceleration</td>
<td>Cycloaddition in 10 min vs &gt;24 hrs</td>
</tr>
<tr>
<td>High p</td>
<td>Reaction rate acceleration Increase in regioselectivity</td>
<td>Increased solubility of HCl gas in organic phase at high temperatures 30% increase in regioselectivity towards 1,4-cycloadduct</td>
</tr>
<tr>
<td>High c</td>
<td>Reaction rate acceleration Process simplification</td>
<td>Cycloaddition in 10 min vs &gt;24 hrs Circumvention of intermediate separation and use of organic solvents in extraction</td>
</tr>
<tr>
<td>New chemical transformation Process simplification and integration</td>
<td>Process simplification</td>
<td>HCl gas used as a reagent Circumvention of intermediate separation and use of organic solvents in extraction Conversion of bulk alcohols to complex APIs Minimization of water use by combining the quench of one reaction and introduction of the reagent for the subsequent reaction.</td>
</tr>
</tbody>
</table>
LIST OF PUBLICATIONS
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