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Life Cycle Assessment of Multi-Step Rufinamide Synthesis – from Isolated Reactions in Batch to a Continuous Microreactor Networks

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Rufinamide is an antiepileptic drug to treat Lennox–Gastaut syndrome, in combination with other medications. Rufinamide is one of the best-selling 5-membered ring heterocyclic pharmaceuticals. Its 1,2,3-triazole moiety is made by click chemistry-based cycloaddition of a dipolarophile and azide. We have recently shown the feasibility of a continuous solvent- and catalyst-free flow process utilizing relatively inexpensive and green new dipolarophile. The problem of its low reactivity was solved when harsh operating conditions (i.e. novel process windows, NPW) were applied within a continuous micro-flow reactor to gain the activation needed. In addition to this chemical intensification, we present here the idea of using chlorides for azide formation instead of the (more reactive) bromides commonly used. Meanwhile, the chloride is produced by utilization of benzyl alcohol and hydrogen chloride. Herein, we analyse the reaction sequence starting from benzyl alcohol to rufinamide, focusing on these three process optimisations. The choice of intermediates is assessed with help of simplified green chemistry metrics and holistic life-cycle assessment (LCA) about their impact on the full process chain. From those material-related green chemistry advancements, the next step in flow-based NPW is undertaken which is process-related (end-to-end process design). The reaction system is accordingly analysed with the goal to determine the best fully continuous multi-reaction network, having the flow uninterrupted from first step until the end product. Three such multi-step microreactor networks are evaluated by green metrics and LCA, including telescoping in flow. Solvent recycling is considered throughout all investigations to reduce the solvent load.

Keywords: Rufinamide, Life Cycle Assessment, Green Pharmacy, Process Intensification, Multi-step Continuous Flow Processing, Reaction Telescoping

1 Introduction

Pharmaceutical industry is challenged by the rising demand for new drugs, while aiming at shortening development time to reduce time-to-market, complying with strict regulations, and simultaneously reducing ecological impacts. In 2005, the ACS Green Chemistry Institute® and global pharmaceutical corporations launched the Pharmaceutical Roundtable, aiming at encouraging innovation by simultaneously implementing green chemistry [1] and green engineering [2] targets in pharmaceutical industry [3]. In this context, flow chemistry and continuous processing have gained increasing interest and represent nowadays promising alternatives to conventional batch manufacturing in fine chemical and pharmaceutical production.[4]

Microreaction technology and flow chemistry are described as important enabling tools, see, *e.g.* reference [5]. Process intensification in micro flow is based on, *e.g.*, enhanced mass and heat transfer and higher safety [5b, 6]. This on its own can lead to reduced capital or operational costs as well as ecological improvements [6a, 7]. The emerge of flow chemistry has given insight in chemical intensification, which means, *e.g.*, boosting of reactivity by unusual novel process windows [5b, 14]. That can be high temperature, pressure, concentration or use of modern non-thermal activation (*e.g.* by photocatalysis) and master solvents such as ionic liquids, see, *e.g.* reference [8].

We have recently applied high-temperature and high-pressure activation in micro flow for the central step of the multi-step synthesis of rufinamide, all in all comprising up to 9 steps according to retrosynthetic analyses as shown later. This is one of the best-selling 5-membered ring heterocyclic pharmaceuticals [9]. It is used as an antiepileptic drug in combination with other medications to treat Lennox–Gastaut syndrome.[10] Rufinamide was discovered by Novartis [11] and is currently is distributed by Eisai under the commercial names of Inovelon® and Banzel®.

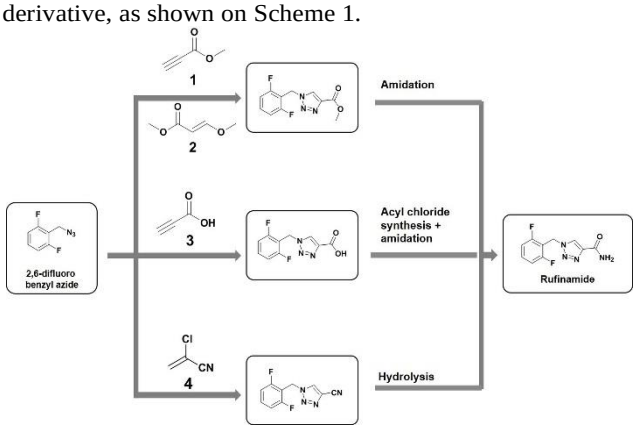
Meanwhile, large number of cost- and life-cycle based process optimisation and intensification studies were published for micro-flow based process intensification [5b, 12]. This usually just refers to one reaction, or at best including its separation. In process terminology, this refers to microreactor 'drop-in' to a conventional process scheme, i.e. leaving all other steps with traditional technology. Thus, to our best knowledge, hardly any cost and life cycle assessment of microreactor implementing throughout the full process scale has been described. A first

attempt in that direction was made by the authors for the micro-flow based epoxidation of soybean oil with the benefits of the reaction drop-in being extrapolated to the purification part [13].

Recently, the authors made a further step by delivering both a cost and LCA study, where optimisation of the purification part was performed [7c, 14]. The study focused on holistic life-cycle based process optimisation and intensification of a low volume production process of active pharmaceutical ingredient (API) for anti-cancer therapy, produced by Sanofi. Striving for process intensification by transfer from batch to continuous processing as well as utilizing an alternative catalytic system, Ott and Dencic *et al.* could observe significant improvements in costs and environmental impacts. For example, cost reductions of 33 % and reduction of greenhouse emissions by 765 kg CO_2 equivalents per kg API could be achieved after resolving the bottlenecks and implementing improvement potentials within further process development activities [7c, 14].

2 Rufinamide - Production and State-of-the-Art in Flow

Several patents have been published in the last two decades proposing various synthetic paths to rufinamide. The common route to the triazole ring moiety involves the reaction of 2,6-difluorobenzyl azide and dipolarophiles *via* 1,3-dipolar Huisgen cycloaddition, see Scheme 1. Typically, methyl propiolate (**1**), propiolic acid (**3**) or 2-chloroacrylonitrile (**4**) are used as dipolarophiles. More recently, (E)-methyl 3-methoxy acrylate (EMMA) (**2**) was used on a lab scale to yield the rufinamide precursor [15]. Depending on the substituents, the formation of the 1,2,3-triazole moiety is followed by subsequent treatments to yield the final carboxamide moiety within the substituted triazole derivative, as shown on Scheme 1.



Scheme 1. Common routes to rufinamide, a substituted triazole derivative (1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide) via Huisgen 1,3 dipolar cycloaddition of 2,6-difluorbenzylazide followed by the implementation of the carboxamide functionality.

Regioselective synthesis to yield the 1,2,3-triazole as a 1,4-cycloadduct in Huisgen cycloaddition either requires a directing group or a catalyst. A copper catalyst is used in most cases when azide-alkyne cycloaddition is to result in 1,4-cycloadducts. However, stringent ICH guidelines for copper content have to be followed to match the high purity standards for API production. In the absence of catalysts, thermal activation is required, however. Due to the explosive nature of azides and high flammability nature of the dipolarophiles, operating temperatures are kept low, while dilution extent is kept high at the production scale, resulting in a high demand of solvent. To our best knowledge, the industrial multi-step synthesis to rufinamide starting from benzyl alcohol is done in multiple subsequent batches. Several attempts to convert the batch-scale rufinamide lab process continuous have been published.

Zhang *et al.* recently described a continuous flow total synthesis of rufinamide [16], starting with the continuous production of 2,6-difluorobenzyl azide from 2,6-difluorobenzyl bromide, and *in situ* generation of propiolamide from methyl propiolate and ammonia gas. Both intermediates are combined in a copper capillary reactor to undertake cycloaddition at 0.25 M concentration in DMSO (dimethyl sulfoxide), and give the final product in an overall yield of 92 %, in total residence time of 11 minutes. Quadrapure Thiourea copper-scavenging resin is added at the end of the synthetic chain to purify the final compound from the leaching copper [17].

Alternatively, the catalyst and solvent-free Huisgen cyclo-addition to obtain the precursor of rufinamide was recently demonstrated by Borukhova *et al.* [18] The cycloaddition of 2,6-difluorobenzyl azide and the less reactive, but less toxic and less expensive dipolarophile (E)-methyl 3-methoxy acrylate needs long reaction times for completion. However, the authors could accelerate the reaction in micro flow to 10 min by increasing the reaction temperature up to 210 °C. 86 % yield of 1,2,3-triazole ester precursor of rufinamide in its crystalline form was obtained [18]. Purification was integrated by introducing methanol into a hot stream of the reactor outlet, which afforded pure crystallized product upon cooling.

Following these lines, we investigate in the following manifold variations in the current rufinamide process by means of green chemistry metrics as well as life-cycle assessment. As a result, we explore the connection of continuous steps in order to give directions for future rufinamide processes.

3 Objective of this Environmental Assessment

The scope of this study encompasses the four last synthetic steps leading to rufinamide as shown in Scheme 2: chloridehydroxy-lation, azidation, [3+2] Huisgen cycloaddition (click chemistry) and amidation. It also encompasses suggestions on the improvement in the upstream chain down to bulk-scale starting molecules.

As stated above, we have recently demonstrated the feasibility of the use of a relatively inexpensive and green dipolarophile in the [3+2] Huisgen cycloaddition. Subsequent cost analysis showed that 30% reduction in costs related to the dipolarophile could be achieved, if the implementation of the cycloaddition was the sole change.[18] Seeing the process improvements we set two targets.

The first target was to investigate the feasibility of step-by-step batch to flow conversion, where every step on the way from benzyl alcohol towards rufinamide is done continuously. The second target was an attempt to mimic nature in bringing several subsequent steps together to create a multi-step microreactor network.

3.1 Target 1: single-step optimisation within a flow process network

The multi-step synthesis of rufinamide starts off with the conversion of benzyl alcohol to benzyl halide, for its subsequent substitution by sodium azide. Due to the fact that halide is essentially a waste on the way from alcohol to azide, choosing chloride is the greenest option when compared to bromide or iodide.

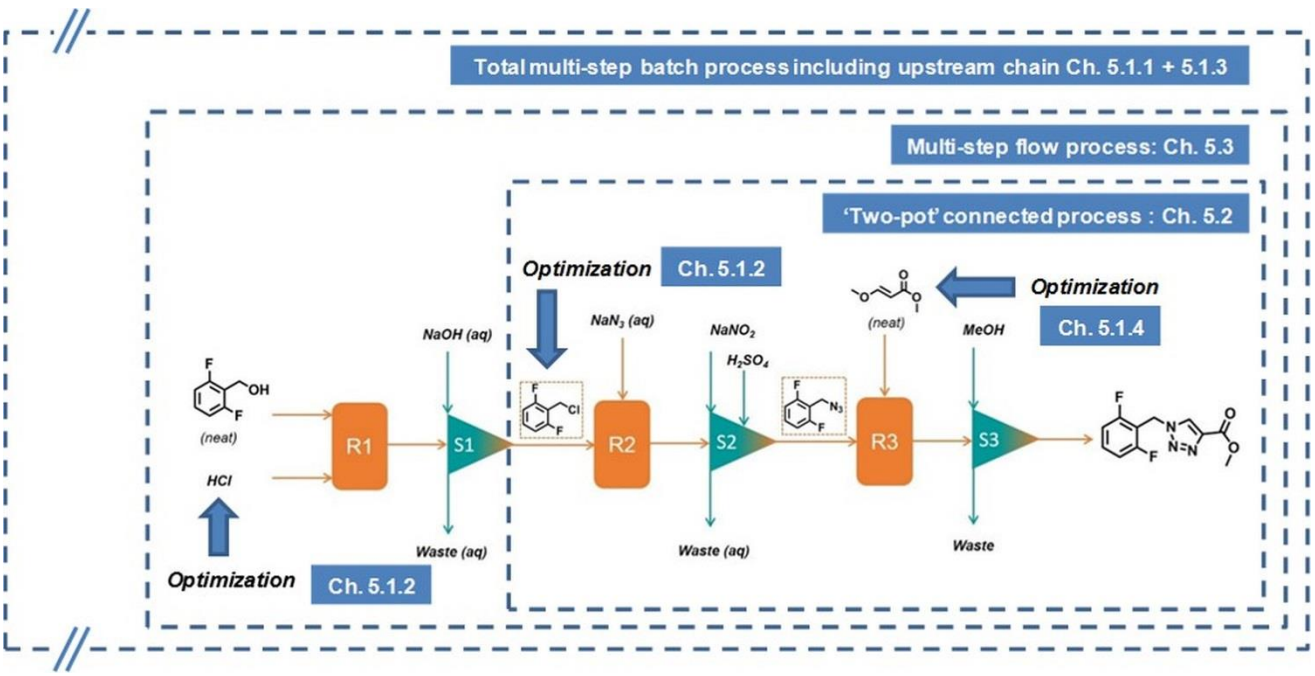
Chlorodehydroxylation of alcohols usually requires highly toxic chlorinating agents such as thionyl chloride [19], phosphorus chloride [20], pivaloyl chloride [21], the Vilsmeier reagent [22], tosyl chloride [23], 2,4,6-trichloro-[1,3,5] triazine with DMF [24], oxalyl chloride [25], and phosgene [26]. Unfortunately, these chlorinating agents constitute major concerns due to their high toxicity [27]. 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 green [28]. In ideal case, aqueous HCl can convert an alcohol to chloride generating water as sole by-product. Although favourable due to their greenness, chlorides are less reactive than the bromides. Thus, once more, an activation boost has to be supplied by harsh conditions, i.e. using high temperature, which can be safely performed in micro-flow [18]. Further process improvement can be achieved by solvent load reduction down to neat processing and solvent recycling as powerful measures to reach environmental friendliness, being in the focus of pharmaceutical industry [29].

All three process optimisations are analysed in this paper by life-cycle assessment (LCA) to reveal the impact on the full process chain with the depth in green information that is common for LCA.

3.2 Target 2: Proposition of new multi-step microreactor networks

Having demonstrated the greenness of those changes, we like to approach the next step in flow-based NPW which is to propose an end-to-end process design with uninterrupted flow from first step until the end product rufinamide. This follows a recent trend in flow chemistry literature towards an original process design in flow (end-to-end) [7d]. Microreactor networks, having multiple steps in a flow process chain, form the spearhead in the process design paradigm shift [30], which includes small-scale modular plants (containers) as production platforms, see several examples for pharmaceutical processing [12, 31, 32]. This is opposed to the practice to consider only the intensification of one reaction step which then results in the drop-in concept common in today's pharmaceutical industry.

Three continuous multi-step microreactor networks are evaluated here by green metrics and LCA, including telescoping in flow (see Scheme 2). The comparison is also made between flow and batch multi-step processing. The extreme case of microreactor networking is when reactions are telescoped with one microreactor unit, alike the corresponding multi-component one-pot batch syntheses (the Ugi reaction being a famous example). This is also considered in the following analysis.



Scheme 2. Process flow sheet for the multi-step flow synthesis from 2,6-difluorobenzyl alcohol to the rufinamide precursor. Process optimisations are indicated and the chapter (Ch.) where this is discussed.

The comparison of the networks also comprises the proposition of improved upstream chains so that a total chain optimisation is predicted, as given in Scheme 2.

4 Methodology

We like to use both simplified metrics and holistic LCA investigations for determining the greenness of the new reaction.

4.1 Analysis *via* Simplified Metrics

For initial selection and screening, simplified environmental and economic criteria were used: yield to rufinamide (direct after process or after purification), process mass intensity, cumulative energy demand, solvent rate, NFPA rating regarding health, flammability and reactivity, and costs of raw materials. Whereas yield, NFPA and cost data are self- explanatory, process mass intensity, cumulative energy demand and solvent rate are defined as follows.

The metric "process mass intensity" (PMI, equation 1) is defined as the key mass-based green metric for benchmarking the greenness of pharmaceutical processes by the Pharmaceutical Roundtable [33]. Due to the fact that solvents have been found as major mass contributors, particularly within the pharmaceutical sector [34], the metric "solvent rate" (equation 2) was chosen as further representative key criterion.

Last but not least, the screening was round off by the "cumulative energy demand" (CED, equation 3) providing a more holistic view on the environmental burdens of different dipolarophiles used [35]. CED represents the energy demand (considering renewable and nonrenewable energy) during the entire life cycle of a product or process, and is accepted as a suitable screening indicator, predicting environmental burdens of production and reflecting many of the energy-related life cycle impact categories of an LCA, *e.g.*, Global Warming Potential or Abiotic Resource Depletion Potential. Thus, CED is often used as an impact category in the context of simplified life cycle assessment (SLCA) studies [36]. Initially, due to missing LCI data CED was predicted using the Finechem software tool by Wernet *et al.*, being a molecular-structure-based approach based on neural network models [37]. As claimed by the FineChem tool software developer, results gained by FineChem cannot replace a thorough process analysis, being due to the limited amount of input information to the neural network model training set.

$$PMI = \frac{mass\ of\ raw\ materials}{mass\ of\ product} \quad \left[\frac{kg}{kg}\right] \quad (1)$$

$$Solvent\ rate = \frac{mass\ of\ solvent}{mass\ of\ product} \quad \left[\frac{kg}{kg}\right] \quad (2)$$

$$CED = \frac{energy\ resource\ consumption}{mass\ of\ product} \quad \left[\frac{MJ}{kg}\right] \quad (3)$$

This screening was realized by our own experimental data for the three key steps in Rufinamide synthesis (chloride-azide-triazole) and otherwise by literature experimental data, as indicated below. Due to the fact that in some cases the experimental procedures described in the literature do not contain mass specific information on solvent consumption, assumptions were made. However, to estimate the sensitivity, the amount of these solvents was firstly varied by ± 50 %, indicated by process metrics error values. These assumptions, being sufficient for a first hot-spot evaluation, are based on experiences, solubility information and comparison of literature data.

4.2 Holistic LCA Investigations

Methodology In order to support the process redesign and optimisation efforts, a comparative environmental assessment and holistic decision making procedure was pursued according to previous studies, see *e.g.*, references [7f, 7g, 13-14]. The LCA methodology was chosen to quantify and assess the potential environmental impacts associated with the processes under investigation.[38] For evaluating the entire synthesis holistically, life cycle inventory (LCI) data need to be gathered. The herein chosen LCI data gathering approach in case of low data availability is consistent with the one applied in several data gathering projects in Ecoinvent [39].

Functional unit The functional unit to which all LCI analyses are referred to is 1 kg product, being either rufinamide or the direct precursor to rufinamide (before ammonolysis).

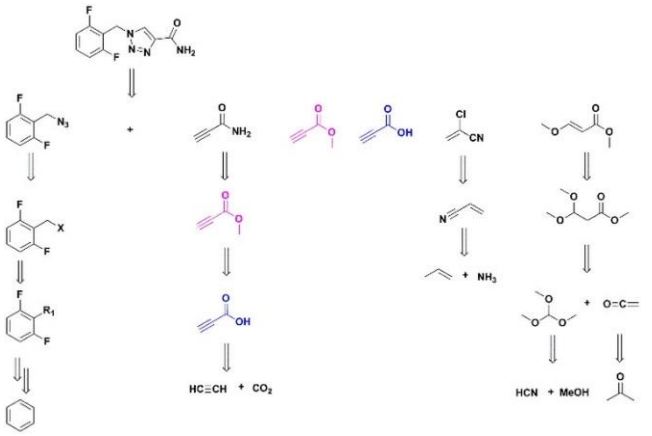
Data sources – global, for rufinamide synthesis The LCI data for the three key steps in rufinamide synthesis (chloride-azide-triazole-rufinamide) in flow come from our own experimental data as given in Tables 2 and 3 and in literature – for chloride: [40], azide: [41], triazole, rufinamide: [18]. These data were then compared to literature data, as indicated below.

Data sources – global, upstream syntheses Yet, from an holistic view, also the LCI data upstream to the chloride synthesis needs to be considered, i.e. leading to benzyl alcohol finally. This is done in retrosynthetic fashion out of base starting bulk materials, as given in Scheme 3 and discussed below. Scheme 3 shows the retrosynthetic breakdown of the rufinamide molecule. LCI analysis of the dipolarophiles, i.e. of propiolic acid, methyl propiolate, (E)-methyl 3-methoxy acrylate and 2-chloroacrylonitrile were modelled according to Scheme 3 and based on reference [42]. LCI analysis of the rufinamide backbone is described in the text below. LCI information for solvents, catalyst or auxiliary materials were mostly available.

If there were no direct production data or information from manufacturers available for this LCI upstream chain modelling, information platforms like SciFinder® [43], Web of Science [44] or Espacenet [45] were used. Further, information within, *e.g.*, Ullmann's Encyclopedia of Industrial Chemistry [46], Handbook of petrochemicals and processes [47] as well as the references therein were used.

Data sources – selected individual cases to monitor sensitivity on data choice In case of missing information or data for chemical substances, LCI data of either chemically similar

substances were used (for *tert*-butanol and bromine, LCI data of *iso*-butanol and chlorine were used), or were substituted by generic data (for ascorbic acid, the LCI data module "chemicals, organic, at plant" was used, being established based on manufacturing data of 20 organic substances belonging to the top 100 chemicals [39]).



Scheme 3. Retrosynthesis of rufinamide based on benzyl azide building block and possible dipolarophiles.

Further, an average organic solvent recovery rate of 71 % and 84 % was assumed, depending on the type of solvent [48]. For rufinamide gate-to-gate production, the effect of solvent recovery was also investigated consulting this approach. In general, process waste (liquid, solid organics) was considered to be disposed of by hazardous waste incineration and waste water treatment (aqueous waste), respectively.

Data sources – global, for utilities, infrastructure and energy In case of low process data availability, the LCI analysis approach by Hischier *et al.* [49] was followed, allowing for integration of average values regarding transports [50], energy and water consumption [51] and plant infrastructure. For instance, especially regarding energy aspects, this approach often becomes necessary, as even manufacturers generally only record energy data on a plant scale (if at all) [52]. Also Kim and Overcash estimated the gate-to-gate process energy in organic chemical manufacturing, being up to 4 MJ per kg [53]. The values used herein are in the upper range of those, thus verifying the use of this generic data set for process energy consumption within the framework of upstream chain modelling.

These data sources allowed the generation of a mass balance of all mass based input and output flows for each synthetic step. Overall, the data choice concerning the rufinamide synthesis itself is the central issue for the quality of the predictions made. This is largely experimentally based, as mentioned, and here particular care was given.

Software tools used LCI analysis and impact assessment was supported by the software tools Umberto® 5.6 and the LCI database Ecoinvent v.2.2 [39, 54]. In general, environmental impacts were estimated in a cradle-to-gate boundary for European production. Life cycle impact assessment was conducted applying the LCIA methodology "ReCiPe 2008" by Goedkoop *et al.*, one of the most up-to-date LCIA methods today [55].

Impact potentials as 'meters' in this study Therefrom, ten ReCiPe impact potentials, namely Global Warming Potential (GWP), Ozone Depletion Potential (ODP), Terrestrial Acidification Potential (TAP), Freshwater Eutrophication Potential (FEP), Human Toxicity Potential (HTP), Photochemical Oxidant Formation Potential (POFP), Terrestrial Ecotoxicity Potential (TETP), Natural Land Transformation Potential (NLTP), Metal Depletion Potential (MDP) and Fossil Fuel Depletion Potential (FDP) were addressed at the midpoint level and hierarchist perspective. This perspective is in accordance to the most common policy principles with regard to time-frame and other issues [55]. Each method (midpoint, endpoint) contains factors according to three cultural perspectives (individualist, hierarchist, egalitarian). These perspectives represent a set of choices on issues like time or expectations that proper management or future technology development can avoid future damages.

All LCIA potentials were equally considered. In some cases, LCIA and interpretation were simplified by applying only selected impact potentials, namely GWP and HTP. Global warming due to anthropogenic emissions is one of the most urgent environmental problems and is directly related to cost-intensive energy consumptions, thus particularly awakening stakeholder's interests. In addition, HTP addresses toxicological issues related with potential emissions occurring within the considered system boundary.

System boundary overview and inventory analysis

This is given in Scheme 4. In the centre the nine synthesis steps to rufinamide are show, the last four of which are done by us and the first five serve for retrosynthesis of our starting material, the alcohol.

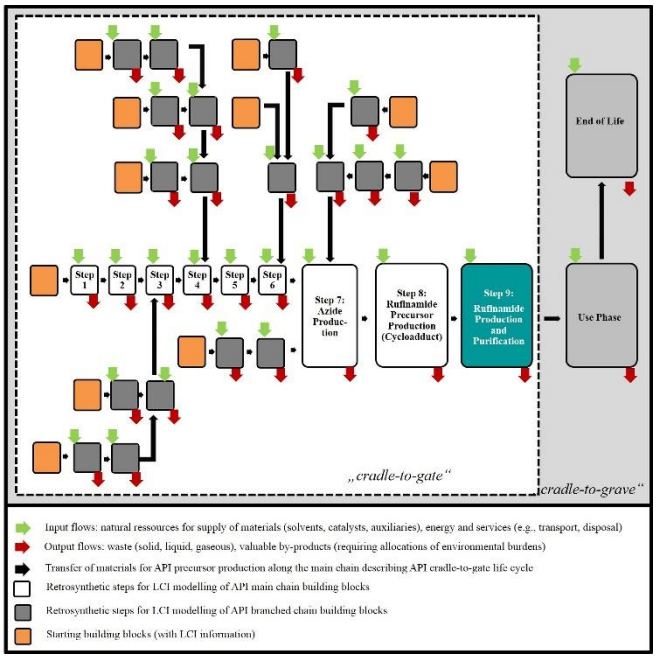
Each step has in- and output flows. Several retrosyntheses lead to this main synthesis line providing the key reactants to flow in. The retrosynthesis always ends with a molecule for which LCI information is at hand. The retrosyntheses starting from benzyl alcohol are given in Scheme 2 as reaction equations.

The system boundaries are "cradle to gate" and ends with the rufinamide production. This considers process waste disposal as well. The case "cradle to grave" further considers the downstream processing, use phase and final waste disposal ('end of life') as well.

5 Results and Discussion

The whole discussion is structured in its subchapters based on process innovations. This is explained in chapter 2 and illustrated and summarized in Scheme 2. Optimisations are taken on the reaction level (given in 5.1.2 and 5.1.4) and compared to the upstream chain without them (5.1.1 and 5.1.3). Thereafter, a two-step ('two-pot') process scheme is analysed (given in 5.2). Then 3

steps are considered referred to as total multi-step flow process (given in 5.3).



Scheme 4. Schematic system boundary overview and inventory analysis.

5.1 One-Reaction Analysis – Single-Step Optimisation

5.1.1 Sustainability analysis up to azide stage (step 7) for the initial upstream chain

First the GWP impact of the upstream chain was investigated with the goal to learn about the individual sustainability contributions from the single reaction steps and the inflowing streams related to compounds, solvents, disposal, and others. Second goal was to improve it with own approaches developed previously *via* experiments in flow.

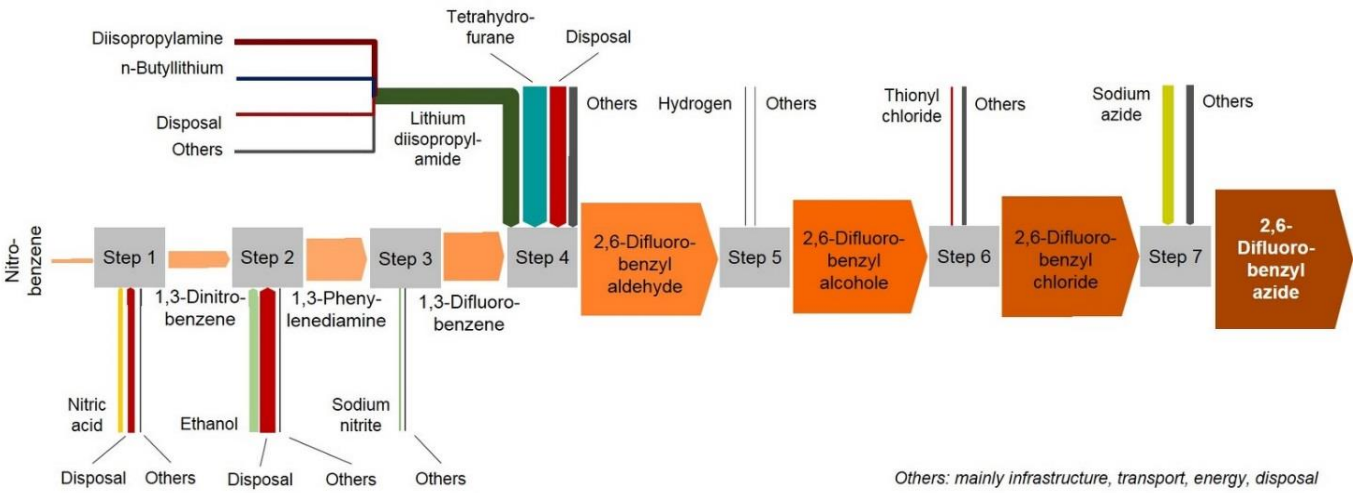
A first retrosynthetic modelling was performed using literature references [19, 42b, 46, 56] and advice from industrial partners. This starts from 2,6-difluorobenzyl azide in 7 steps back to 'cradle', which is nitrobenzene as bulk material, for which LCI data were available.

Scheme 5 represents a Sankey diagram which provides a visual reproduction of the major flows contributing to the overall GWP. The thickness of the lines and size of the squares corresponds to their relative GWP share, i.e. sustainability impact. This also visualizes the ever increasing ecological burden.

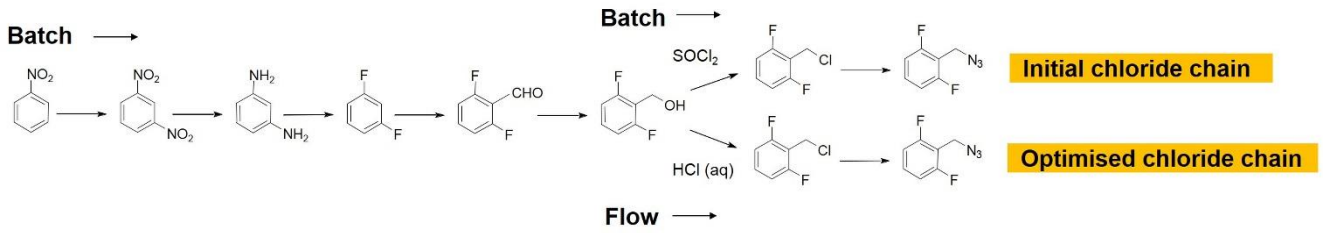
It is evident that the steps before the starting material considered in our flow synthesis, which is the 2,6-difluorobenzyl alcohol, provide already a considerable ecological backpack. Especially the formation of the 1,3-diphenylenediamine (step 2), and to an even larger extent of the 2,6-difluorobenzyl aldehyde (step 4) contribute more than average. The flows are of manifold origin – reactants, solvent and also disposal have each large effect, while others is less. Ecologically less friendly materials are, *e.g.*, lithium diisopropylamide or tetrahydrofurane. After step 4, the processes come which were previously considered for transfer to flow, since flow and process intensification typically is successful with advanced molecules. The ecological burden rises still, but with a somewhat smaller increase.

In the following, we proceed with a step-to-step-optimisation starting from the synthesis of 2,6-difluorobenzyl azide (step 7) and going further downwards.

Despite the fact that there is no simple replacement for sodium azide within the azide formation, our aim was to increase the yield already obtained by literature and thus decrease the ecological backpack. In addition, step 6, the hydrochlorination of 2,6-difluorobenzylalcohol, offers another real opportunity and



Scheme 5 Sankey diagram illustrating the ecological backpack of upstream chain processes and intermediates by means of their share in the overall GWP of 2,6-difluorobenzyl azide production starting from nitrobenzene (as a possible and common retrosynthetic pathway).



Scheme 6. Schematical comparison of literature batch route (via "initial chloride chain") and by the authors developed flow route (via "optimised chloride chain) to 2,6-difluorobenzyl azide.

challenge for optimisation as given in 3.1. This is the replacement of the very reactive thionyl chloride by less reactive aqueous HCl. Thus, activation is needed and this can be done by the harsh conditions accessible by flow. 2,6-difluorobenzyl chloride can be then considered as intermediate directly flowing into step 7, so that it comprises one of the innovations introduced by flow.

In the following, a new upstream chain is formed for the steps 6 and 7 based on our own respective flow processes; in particular on the use of aqueous HCl and having the chloride as intermediate to the azide. This is shown in Scheme 6; experimental details can be found later in Table 3.

5.1.2 Sustainability analysis up to azide stage (step 7) for the optimised upstream chain

Here, a comparative analysis is done, i.e. the difference of the 10 LCIA impact categories between the initial and new optimised chains is given (see scheme 6). The room of consideration comprises the last two steps (6 and 7), likewise chosen in 5.1.1. The retrosynthesis of 2,6-difluorobenzyl azide was done accordingly from 2,6-difluorobenzyl alcohol and chloride and modelled according to references [19, 57]. Thus, this compares the literature batch-batch synthesis with the newly developed, experimentally proven continuous flow-flow synthesis.

The ecological impact of the new continuous two-step process is projected in Figure 1. The two optimised steps reduce the environmental impact massively and throughout, by approximately 30-90 %, depending on the LCIA category (see Figure 1).

This is mainly due to higher yields experimentally obtained (literature overall yield for both steps: 65 %; experimental yield for flow steps: 88 %), but also due to the avoidance of materials like dichloromethane and thionyl chloride as well as the corresponding waste management due to sulphur dioxide emissions in the alcohol synthesis, which dominate the environmental burdens within ODP and TAP.

Nevertheless, it is obvious that there is still a high optimisation potential left for upstream chain supply. Beside the route described above (… →2,6-difluorobenzene → 2,6-difluorobenzyl aldehyde → 2,6-difluorobenzyl alcohol → 2,6-difluorobenzyl chloride) another route for 2,6-difluorobenzyl chloride supply is possible (… →2,6-difluorobenzene → 2,6-difluorotoluene → 2,6-difluorobenzyl chloride) [58], which will be focused later in the text.

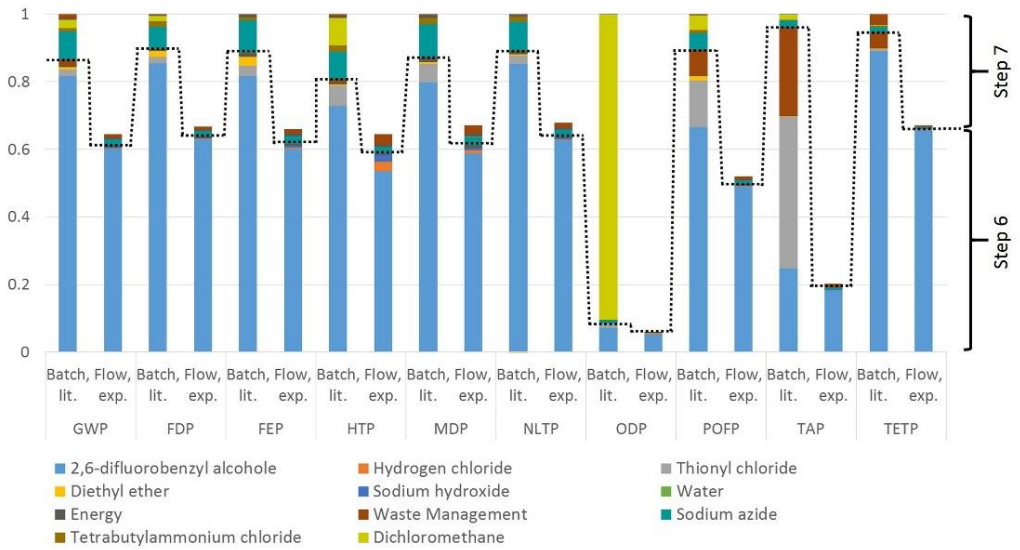


Figure 1. Reduction of LCIA categories for 2,6-difluorobenzyl azide supply by changing its upstream process pathways.

The next question then is how large the ecological backpack of the 2,6-difluorobenzyl azide is concerning the last two steps (8 and 9) to rufinamide. Due to the comparison of different status-quo literature approaches and to have a common basis, the following assessments are firstly made by considering the unoptimised upstream chains, i.e. without the achievements made above. *The optimised upstream chain route will be then relevant again in chapters 5.3.1 ff.*

5.1.3 Sustainability analysis up to rufinamide stage (step 9) for the initial upstream chain

Having analyzed the innovation brought to the first 7 steps, we like now to extend the sustainability view to the last two steps up to rufinamide (step 9). We consider here accordingly only the steps 8 and 9 to investigate the overall impact of the azide and dipolarophile on the rufinamide supply. The dipolarophile was fixed to (E)-methyl 3-methoxyacrylate, used in our prior flow experiments. In 5.1.5, the dipolarophile will be varied among four choices.

Figure 2 represents a fingerprint analysis of the total life cycle impact of rufinamide production according to the initial literature process route for steps 8 and 9 by Mudd and Stevens [15] (entry 3, table 1), i.e. the batch-batch route. In such plot, all 10 impact categories are normalized to unit "1". That makes their shares comparable (in %).

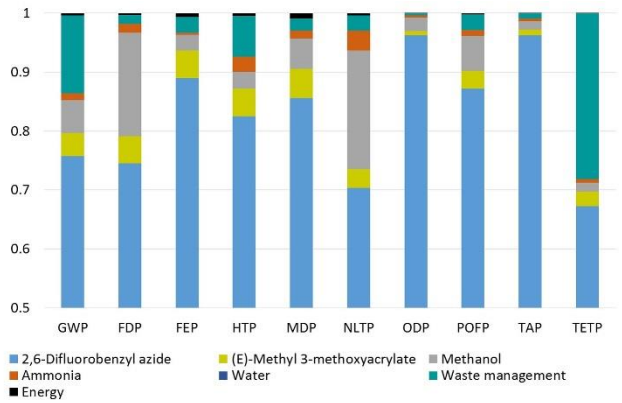


Figure 2. Fingerprint analysis of the initial two-pot batch rufinamide production process starting from 2,6-difluorobenzyl azide according to Mudd and Stevens [15]. For a clearer arrangement, ordinate values begins with 0.5.

By the dominance of the blue-colored azide share (between about 65-95%), it is immediately evident, that it was the right direction to optimise the original upstream route. Furthermore, the use of methanol as well as disposal efforts in step 9 (amidation) significantly contribute to the overall environmental impact, while the key reagent (ammonia) has minor impact.

Figure 2 also indicate that at a first glance and in terms of life cycle aspects our initial guess on optimising the choice of dipolarophile seems to has much less impact than optimising the azide synthesis. Yet, a more extended investigation will be given in the following chapter.

5.1.4 Sustainability analysis up to rufinamide stage (steps 8 and 9) for the initial upstream chain

Choice of dipolarophiles

Four different dipolarophiles, namely methyl propiolate, propiolic acid, propiolamide and (E)-methyl-3 methoxyacrylate are considered and their life cycle data is derived from patents and related literature (sources given in chapter 3).

These dipolarophiles react with 2,6-difluorobenzyl azide in a 1,3-dipolar Huisgen cycloadditon yielding a rufinamide precursor, followed by a second transformation to the final product. In the following, the evaluation starts with safety and process metrics and then switches to analysis of the cumulative energy demand and the global warming potential through life cycle assessment.

Green chemistry and process metrics

Table 1 presents the results of the screening assessment of commonly performed multi-step batch processes to rufinamide by means of CED, NFPA rating, costs, yield, PMI, and solvent rate.

Table 1. Overview on common rufinamide batch process routes: multi-step, two pot routes starting from azide, entries 1-4 based on references [15, 57b] and ex-ante evaluation results. * NFPA hazard rating system regarding health, flammability and reactivity [59], ** according to Borukhova *et al.* [18], *** after ester ammonolysis (entries 1, 3), after acyl chloride synthesis and ester ammonolysis (entry 2).

Process options	Entry 1	Entry 2	Entry 3	Entry 4
1,3-dipolar Huisgen cycloaddition **Dipolarophile assessment**	*Methyl propiolate*	*Propiolic acid*	*(E)-Methyl-3-methoxy-acrylate*	*2-Chloro-acrylo-nitrile*
NFPA rating HFR*	2;3;0	3;2;0	2;2;0	4;3;2
Costs [$/mol] **	45	13	2	12
CED Median value [MJ/kg]	60	55	271	94
Solvent for synthesis	*Ethanol*	*tBuOH/ H_2O*	*Neat*	*Water*
NFPA rating HFR*	0;3;0	1;3;0	-	-
Solvent for work-up	*Ethyl acetate*	*Ethyl ether*	*Methanol*	*Cyclo-hexane*
NFPA rating HFR*	1;3;0	1;4;1	1;3;0	1;3;0
Catalyst	*$CuSO_4$* 5 H_2O*	*$CuSO_4$/ ascorbic acid*	-	-
Reaction temperature [°C]	25	40	135	80
Reaction time [h]	12	2	28	24

Yield to rufinamide precursor [%]	94	94	85	86
Overall yield to rufinamide * [%]**	**82**	**86**	**79**	**85**
Process metrics				
PMI w/o H_2O [kg/kg]	**23 ± 6**	**59 ± 10**	**18 ± 2**	**4**
PMI incl. H_2O [kg/kg]	**39 ± 13**	**76 ± 10**	**19 ± 3**	**30**
Solvent rate [kg/kg]	**16 ± 4**	**36 ± 10**	**14 ± 2**	**2**

Hazard potential The NFPA ratings confirm that – in the holistic view of dipolarophile/solvent/catalyst – EMMA ranks best. This is similar to the outcome of our previous paper [18]. On the one hand, this is due to the solvent-less click reaction, but also due to the environmentally friendlier methanol compared to ethyl acetate and ethyl ether for work-up. EMMA itself also feature a lower hazard than the dipolarophiles methyl propiolate and propiolic acid, which possess a higher flammability and health hazard risk.

Process and economic aspects

However, EMMA is the cheapest option among the four. In contrast, entries 1, 2 and 4 result in higher overall yield of rufinamide compared to entry 3, as shown by Table 1. The longest time is required for the EMMA route, due to the low reactivity of this compound when compared to other dipolarophiles. But, due to the presence of the methoxy group only one, cycloadduct is formed, namely the 1,4-regioisomer. On the contrary, for the other dipolarophiles either a catalyst or subsequent separation of the undesired regioisomer is required. This leads to a higher PMI and solvent rate values, when compared to the route *via* EMMA. Even if taking into account an uncertainty of solvent consumption by ± 50 %, the trend remains clear.

Life cycle assessment

CED of dipolarophile supply, standing for ecological backpack

As reflected by the CED data, the ecological backpack for the supply of methyl propiolate, propiolic acid and 2-chloroacrylonitrile is much lower than for EMMA (see Table 1). Propiolic acid can be prepared *via* direct carboxylation of acetylene [42a] It represents a key compound to other dipolarophiles for rufinamide preparation like methyl propiolate or propiolamide. As a consequence, its ecological backpack is lower than for its related downstream chemicals. However, as an additional information, in case of the propiolic acid route, (entry 2) the additional acyl chloride synthesis step consumes thionyl chloride, (i) being toxic, (ii) emitting sulphur dioxide and HCl during reaction and thus (iii) imposing a great burden or risk on the environment and human health. Similarly, 2-chloroacrylonitrile is a highly toxic and flammable substance.

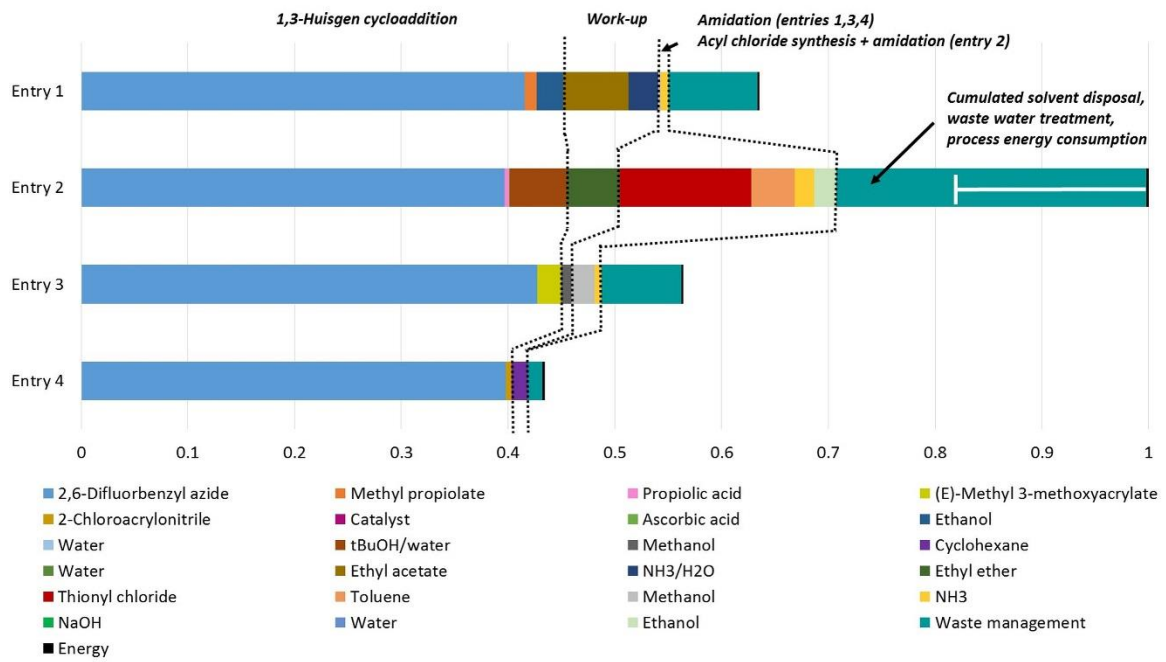


Figure 3 Comparative evaluation of rufinamide process route according to table 1. Share of single components in the LCIA categories GWP. Scaled effects.

Consequently, the assignment of EMMA as green dipolarophile given earlier [18] based on a single solely toxicity-related parameter could be confirmed here and deepened by a standard hazard analysis. Yet in view of CED as sustainability parameter EMMA does not appear as green dipolarophile. This shows the complexity in the assignment of the ecological backpack.

In the following, a GWP analysis by LCA makes evident the single contributions for each of the four dipolarophile routes to the rufinamide (see Figure 3).

GWP, total routes compared (steps 1-9) In an overall view, the methyl propiolate and propiolic acid dipolarophile routes are worse in GWP impact than EMMA, while 2-chloro-acrylonitrile scores best. This route also has been implemented as a one-pot process[46]; however, due to a comparable yield output than for the two-pot route, the further optimisation potential can be estimated to be negligibly low.

Azide share in impact (steps 1-7) Even at a glance it is evident that the 2,6-difluorbenzyl azide-related impact dominates by far the environmental impact of all four dipolarophiles. With the exception of entry 2, this accounts for more than 70% of the GWP. In other words, this is the key to the greenness of the rufinamide synthesis. This is in line with the analysis given for all LCIA categories for the dipolarophile EMMA.

GWP, share of dipolarophile (step 8) Concerning details of the impact shares, it is striking how less the dipolarophile itself contributes and how much, in turn, the last processing step to the amide changes. The environmental burden increases roughly in the order of propiolic acid < 2-chloroacrylonitrile ≲ methyl propiolate < (E)-methyl 3-methoxyacrylate. Methyl propiolate (entry 1) derives from propiolic acid, thus carrying a heavier backpack. However, the difference between the individual dipolarophiles has a negligible low impact on the overall GWP response.

GWP share of solvent and auxiliaries The second major share is caused by the need for solvent disposal and waste water for the propiolic acid route (entry 2) as well as the activation by the thionyl chloride almost doubling the GWP impact and thus turning a possibly good situation into a worse one. Thionyl chloride is industrially mainly produced *via* the reaction of sulfur trioxide and sulfur dichloride, whereas the supply of the latter (*via* sulphur and chlorine [19, 60]) accounts for the largest share in both LCIA categories. Vice versa, recycling of thionyl chloride (used in 40-fold excess typically) can change that for the better, but not completely outweigh the negative impact (white line in Figure 3).

GWP share of ammonolysis (step 9) The third major share is the last step, *i.e.* ammonolysis, which however is less than 10 %, due to lower environmental burdens of starting material supply as well as the comparable high reaction efficiency (yields ≳ 90 %).

GWP share of post-treatment Furthermore, it is obvious that in case of entries 3 and 4 post-treatment steps following the Huisgen cycloaddition have negligible low impact, since the high regioselectivity of these routes demands for lower efforts for purification.

Decision making Entry 3 has attracted special attention to the authors and was chosen for further consideration, i.e. the (E)-methyl 3-methoxyacrylate route. This is due to its lower cost and hazards, comparably low PMI and solvent rate, whilst at the same time featuring open improvement potential. Even with its lower yields the overall environmental profile of EMMA is quite competitive. Thus, entry 3 using the dipolarophile (E)-methyl 3-methoxyacrylate for Huisgen cycloaddition was focused as promising candidate for further optimisation.

5.1.5 Conclusion from previous single-step analyses

As a consequence from the analysis given in 5.1.1-5.1.4 the following is concluded:

- choice of the chloride route to make 2,6-difluorobenzyl azide
- choice of the HCl-chlorination method to convert the alcohol to the chloride
- choice of the dipolarophile EMMA
- exploring in the second part of the paper the impact of new end-to-end process-design towards microreactor networks for these choices

Concerning the latter, benefits might come from reduced work up procedures to reduce product losses, especially between sequenced process stages. In addition, they might facilely allow the incorporation of efficient work-up procedures including efficient product and starting material recovery strategies such as integrated solvent recycling.

Thus, the focus in the following section will be on process design and microreactor networks, following the recommendations derived here. This is done in two steps, the first considering two-step batch and mixed flow-batch (chapter 5.2) and then moving to full-step flow synthesis of Rufinamide (chapter 5.3).

5.2 "Two-Reactor Network" Process Designs

5.2.1 Two-pot conti-batch process and one-pot batch process alternatives

The two last steps of the rufinamide synthesis – the Huisgen dipolar cycloaddition of EMMA and ammonolysis - serve well to show the effects of

(i) connecting reactors (scenario batch-batch),

(ii) exchanging batch-to-flow (scenario batch-flow), telescoping (scenario one-pot batch), and

(iii) changing the interim purification through crystallization with respect to solvent load.

(i) to (iii) are given similarly for the other two upstreams steps of the Rufinamide synthesis. This will be presented in the next chapter in a global fashion.

Table 2. From two-pot batch processing to one-pot batch and flow processing: rufinamide production alternatives based on entry 3, table 1, investigated in more detail. Batch and flow process sequences based on references [15, 18].

Process options	***Two-Pot: "Batch-Batch"***	***Two-Pot: "Conti-Batch"***	***One-Pot: "Batch"***	***One-Pot: "Batch recycled"***
1,3-dipolar Huisgen cycloaddition				
Dipolarophile	(E)-Methyl 3-methoxyacrylate	(E)-Methyl 3-methoxyacrylate	(E)-Methyl 3-methoxyacrylate	(E)-Methyl 3-methoxyacrylate
Solvent	-	-	-	-
Reaction temperature [°C]	135	210	135	135
Reaction/residence time [h]	28	0.17	24	24
Reactor	Stirred tank reactor	Stainless steel microcapillary reactor	Stirred tank reactor	Stirred tank reactor
Operation mode	Batch	Conti	Batch	Batch
Yield to 1,2,3-triazole precursor [%]	**85**	**86**		
Conditions for ammonolysis	Batch NH_3/MeOH, 25 °C, 18 h, washing with water	Batch NH_3/MeOH, 25 °C, 18 h, washing with water	Batch, NH_3/MeOH, 25 °C, 72 h, washing with MeOH	Batch, NH_3/MeOH, 25 °C, 72 h, washing with MeOH
Solvent recycling rate [%]	-	-	-	84
Product and reactant recovery [%]	-	-	-	3
Overall yield to rufinamide [%]	**79**	**80**	**89**	**92**
Product scale	**5 g**	**5 g**	**35 g**	**35 g**

The data for the experimental (batch-batch, flow-batch and one-pot batch) and hypothetical scenarios (batch recycled) given in Table 2 were taken from experiments as reported in Borukhova *et al.* [18] (flow route) and Mudd *et al.* [15] (batch routes).

Two-pot batch-batch and conti-batch behave almost the same, with a difference of just 1% yield in favour of the latter (before and after ammonolyis). A slight effect can be seen when comparing the LCA categories, given in Figure 4. Especially for TETP, GWP, FDP and NLTP small yet noticeable differences are seen. The lower the decagon area, the more environmentally friendly the process.

This is due to the slight increase in reaction yield, causing a lower demand of azide, and the orders-by-magnitude reduction of reaction time from 28 hours in batch to 10 minutes in flow by access to faster intrinsic kinetics. Moreover, in-line addition of a recrystallization solvent in the flow step provided crystalline product upon cooling the collected product to room temperature. Furthermore, by a transfer to a micro flow environment the process safety is expected to be enhanced – despite harsher reaction conditions and solvent-less conditions [7g]. Yet, while all these effects are notable on a reaction level, their impact is still small on the overall environmental friendliness. The reason is that chemistry (starting materials, selectivity) is almost untouched and that continuous engineering on its own hardly pays off for environmental issues (yet well on costs), as prior experience has shown.

Two-pot and one-pot batch are different. There is a clear effect of telescoping, especially strong on the product side (yield) as given in Table 2 and also noticeable in Figure 4 for the overall LCIA profiles. By switching from a two-pot to a one-pot procedure, intermediate work-up steps can be passed thoroughly, i.e. reducing product losses (overall yield: 89 %) and the consumption of further materials. The One-Pot scenario is based on experimental results given in [15].

One-pot batch and one-pot batch recycled are very different. The latter is also very different to the two other scenarios. We learn that the most dramatic decrease of environmental effects (approximately 20–40 %,), can be reached by the recovery of the starting material and product from the filtrate as well as by reusing the solvent.

Conclusion of this chapter: In total, this motivates to head for construction of total continuous microreactor networks – in the direction of connecting, telescoping, and solvent recycling. The next chapter will show if that indeed has an environmental effect.

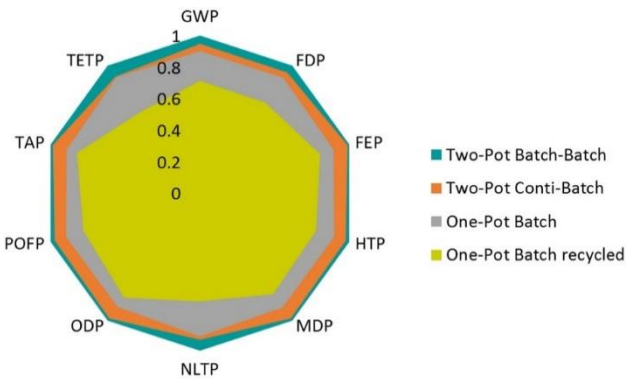


Figure 4. Life cycle impact assessment of experimental and hypothetical scenarios according to Mudd and Stevens [15] and Borukhova et al. [18], scaled effects of LCIA categories.

5.3 "Three-Reaction Network" Process Designs

The promising insights were taken as basis for developing a continuous flow process, in the ultimate projection aiming at total flow telescoping routes.

Traditionally, synthetic protocols are characterized by single transformation units followed by separation and purification steps at each time. If multi-step approaches are shrunk to a single continuous reactor periphery, advantages such as less material and energy requirements, less product losses by reducing the number of work-up steps, and thus reduced environmental impacts and costs are expected [4d, 61]. Streamlining or telescoping [62,63] of multi-step reactions is undoubtedly a "paradigm" shift, and streamlining multi-step synthesis combined with flow techniques is investigated for several applications in fine chemical and pharmaceutical industry [64].

In the following, we have developed a continuous total flow process route to rufinamide and performed an environmental comparison to the approach by Zhang *et al.* [16] Afterwards, see chapter 5.3.2, we took a next step forward and evaluated artificial end-to-end approaches by means of life cycle approaches, to identify the potentials and bottlenecks of telescoped continuous flow reactions compared to common multi-step batch rufinamide manufacturing procedures.

5.3.1 Multi-step total flow processing – multiple drop-in

Definition of two kinds of multi-step total flow processes

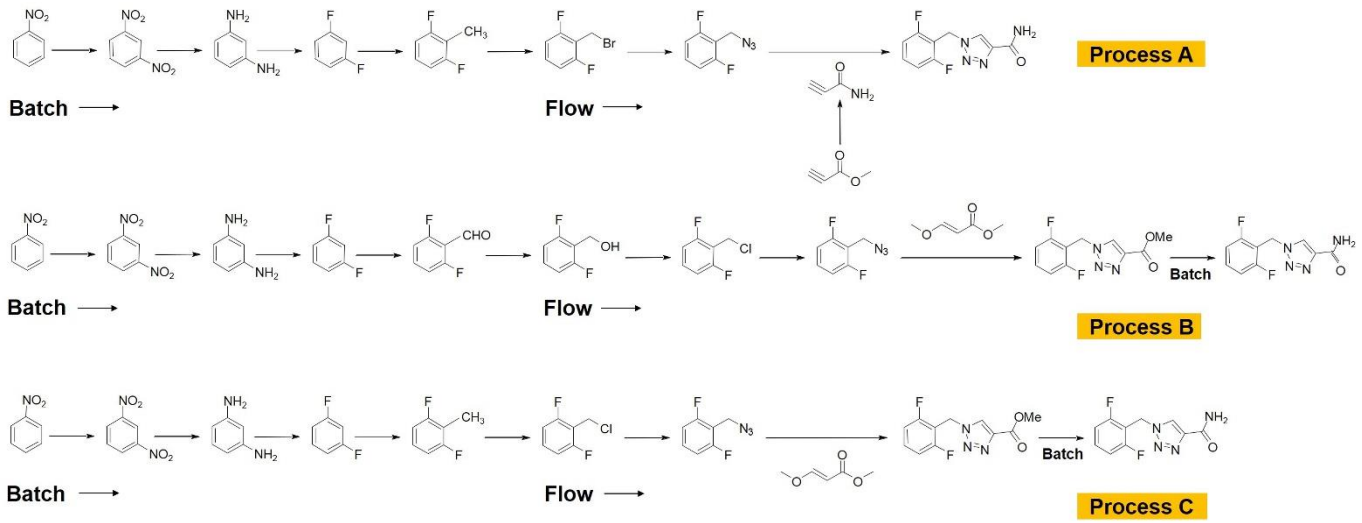
Table 3 roughly outlines our whole continuous flow process to produce the rufinamide precursor, methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate based on real experimental data. The latter is converted to the target compound, rufinamide, in batch due to its low solubility in any solvents, except DMSO. The idea of the proposed alternative flow sequence is based on the target of minimizing the solvent use. Therefore, making the final step more feasible by treatment of the precursor in methanol with ammonia, upon which the ester is converted to the amide which precipitates in high purity.

Process in detail, with foci on separations This procedure, as also shown schematically in Scheme 2, starts off with neat 2,6-difluorobenzyl alcohol and aqueous hydrogen chloride to produce 2,6-difluorobenzyl chloride. Excess of hydrogen chloride is needed to diminish to speed up the reaction.

Sodium hydroxide solution is used to neutralize the acid, afterwards the aqueous and organic phases containing stream is separated in a hydrophobic membrane-based extractor. 2,6-Difluorobenzyl chloride is sparingly soluble in water and leaves the extractor at the 'organic side' without addition of any other organic solvent usually used for extraction. Afterwards, neat 2,6-difluorobenzyl chloride proceeds to second reactor where it comes into a contact with sodium azide, dissolved in water, to result in the synthesis of 2,6-difluorobenzyl azide. Separation of the remaining azide containing aqueous stream from 2,6-difluorobenzyl azide take place next, in order to supply neat 2,6-difluorobenzyl azide. Cycloaddition of 2,6-difluorobenzyl azide and (E)-methyl 3-methoxyacrylate takes place in the third reactor. The product of the third reaction, methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate, is a sparingly soluble solid. To prevent its precipitation, a stream of methanol is introduced in the hot outlet stream of the third reactor. The collected mass results in solid crystallized product with all the impurities dissolved in methanol. Simple filtration results in the final precursor product. The synthesis does not extend to the final product rufinamide due to its low solubility in most solvents. Although solvents such as N-methyl pyrrolidone and dimethyl sulfoxide dissolve the precursor, they add an extra step in the purification of the final product. Meanwhile, the final product can be obtained by continuous stirring of the obtained precursor in MeOH and dosing of ammonia gas. The final product can then be filtered and recrystallized from methanol as a final purification stage.

Table 3. Development of a continuous multi-step synthesis of rufinamide: rough summary of current process steps and conditions. Current productivity: approximately 8 g/h.†

	Flow Step 1	***Flow Step 2***	***Flow Step 3***	***Batch Step 4***
Product	**2,6-Difluorobenzyl chloride**	**2,6-Difluorobenzyl azide**	**Methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate**	**1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide (Rufinamide)**
Reactants	2,6-Difluorobenzyl alcohol HCl	2,6-Difluorobenzyl chloride NaN_3	2,6-Difluorobenzyl azide (E)-Methyl 3-methoxyacrylate	Methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate NH_3
Solvent	Water	Water	Neat	MeOH
Temperature [°C]	60	160	210	60
Pressure [bar]	30	15	64	20
Reaction time [h]	1	0.5	0.17	1
Work-up	**aq. NaOH**	**L-L separation**	**MeOH**	**MeOH**
Reaction yield	**99 %**	**98 %**	**86 %**	**95 %**
Separation efficiency	**95 %**	**95 %**	**95 %**	



Scheme 7. Comparison of rufinamide process routes discussed in chapter 5.3.1.

Literature example of total flow process – proof of concept Up to now, the development of a continuous total flow rufinamide synthesis implementing upstream process steps could be successfully demonstrated by *Zhang et al.*, who have recently published a continuous flow total synthesis of rufinamide from 2,6-difluorobenzyl azide and propiolamide in a copper tubing reactor, obtaining an overall yield of 92 %. Both starting compounds were prepared *in situ*, starting from the corresponding benzyl bromide and methyl propiolate [16].

Comparability to total flow process proposed here The comparison of both flow approaches is difficult up to now, not at least due to the fact of scale issues. As the rufinamide output *via* the herein proposed route amounts approximately 8 g/h, Zhang *et al.* developed a process currently featuring a capacity of 0.2 g/h rufinamide [16]. The route by Zhang *et al.* might suffer some disadvantages, *e.g.* leaching of copper from the reactor equipment and usage of dimethyl sulfoxide as reaction medium, which is not readily biodegradable and features a high boiling point, which results in an extra effort for downstream purification. Further the therein used raw materials methyl propiolate and 2,6-difluorobenzyl bromide are more expensive than (E)-methyl 3-methoxyacrylate and 2,6-difluorobenzyl chloride. Both processes are schematically shown in Scheme 7; the process developed by Zhang *et al.* [16] is named as "process A", whereas our process currently under development is named as "process B".

Comparative metrics study

Table 4 summarizes a comparison of both experimental routes by using simple metrics.

Although an overall yield difference of 13 % exists, the overall PMI of process B is lower, which is mainly due to the high consumption of water as solvent for the ammonolysis and purification afterwards within process A. In contrast, the amount of organic solvents used is comparably low. Current developments within process B integrate the reuse of methanol, which is used for purification purposes after flow step 3, see Table 3, for utilizing it in the amidation step, which results in a decrease of PMI from 46 to 18 kg solvent per kg rufinamide. Other raw material consumptions are comparably low.

However, process B considers the consumption of sodium nitrite and sulphuric acid for waste treatment after azide synthesis. This increases the PMI from 2 to 4 kg raw material per kg rufinamide, whereas for process A no information on sodium azide separation was available.

Since both processes were not streamlined to tackle exactly the same issues, the information provides a state of the art snapshot and, more relevant, creates a learning curve where to improve processes most efficiently.

Table 4. Metrics comparison of multi-step flow synthesis of rufinamide. Detailed information can be found in table 3 (process B) and in Zhang *et al.* (process A). To ensure comparability, the assessment includes the process steps of 2,6-difluoro azide production, Huisgen cycloaddition and ammonolysis.

	Process A	Process B
Overall yield to rufinamide [%]	92	79
Productivity [g/h]	0.22	8
Process metrics		
PMI [kg/kg]	58	23
PMI solvent [kg/kg]	18 (DMSO)	18 (MeOH)
PMI water [kg/kg]	38	1
PMI raw materials [kg/kg]	2	4

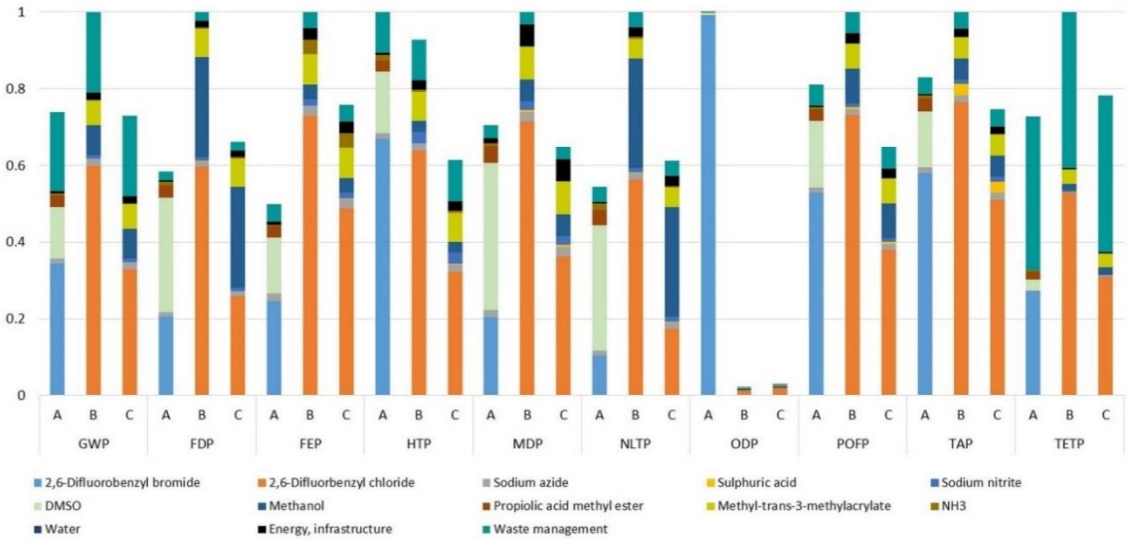


Figure 5. Life cycle impact comparative assessment of a continuous flow total rufinamide production process according to Zhang et al. (process A) and multi-step continuous processes currently under development (processes B and C). Scaled effects.

Comparative LCA study

<u>*Total flow processes A vs. B*</u> From a holistic point of view, different results and optimisation strategies can be derived, see Figure 5.

Although a more efficient route to produce 2,6-difluorobenzyl alcohol and thus the corresponding chloride was developed, at a first glance the supply of 2,6-difluorbenzyl bromide for process route A turns out to be environmentally more benign. The latter was modelled *via* 2,6-difluorobenzene → 2,6-difluorotoluene → 2,6-difluorobenzyl bromide as more common route [58, 65], see Scheme 7. Here less upstream process steps are required. Only within the LCI category ODP a significant increase of environmental burdens occurs, being due to the use of chlorocarbon solvents used for the production of 2,6-difluorobenzyl toluene and 2,6-difluorobenzyl bromide. But, to ensure comparability, the supply of 2,6-difluorobenzyl chloride was modelled additionally according the same route *via* 2,6-difluorobenzene → 2,6-difluorotoluene → 2,6-difluorobenzyl halide [46], as already indicated in chapter 5.1.2. This is indicated by "Process C" in Scheme 7 and Figure 5. As in the case of process A, this route features less upstream chain steps and material flows, reflected in a better ecological profile. *As obvious, if the optimisation stops here, the ecological backpack will be the key driver of an environmental benign rufinamide synthesis.* As a consequence and motivation, now we are currently striving for a deep experimental investigation of the chloride route *via* 2,6-difluorotoluene in flow, which will be presented at a later time.

However, differences in the environmental impact of solvents used can be identified. As the amount of solvents is comparable, the environmental burdens of the solvent supplies are different. Dimethyl sulfoxide carries a higher ecological backpack (process A). A distillation and refeeding of DMSO is possible, however this would be connected with higher efforts than in the case of methanol refeeding (process B).

The environmental drawback of the 2,6-difluorobenzyl chloride supply (process B) will be overcome, once higher overall yields of rufinamide would be reached. Higher separation efficiencies within intermediate work-up steps as well as solvent recycling will also work in favour of that route. This will be demonstrated within the next chapter.

<u>*Multi-step flow vs. batch*</u> Figure 6 shows the GWP-HTP impact for the multi-step flow processes, when being normalized to the multi-step batch performance. Compared to the initial scenario "multi-step batch" (entry 3, Table 1), improvements by approximately 20 %†† can be found when reactions are networked through flow. This is due to the lower environmental burdens for the upstream chain processing. Although a higher demand of methanol becomes necessary for flow processing, the environmental consequences are marginal in contrast to the benefits gained.

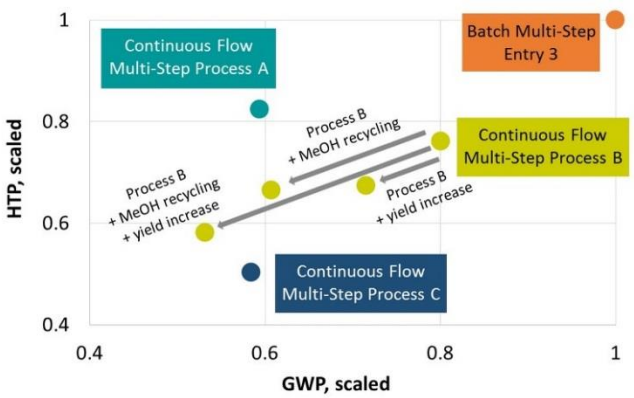


Figure 6. Overall life cycle impact assessment comparison of batch and continuous multi-step processing of rufinamide by means of GWP and HTP. Scaled effects.

Theoretic potential for flow improvement It shall be reiterated that the flow process development (both for processes A and B) is still at an early, not- the fully optimised stage, while batch is fully optimised. Thus, there remains theoretical potential to get an even better than it already is ecological profile, as discussed as follows.

Naturally, the key is in the materials and that refers to the product yield. Assuming an overall yield increase by 4 %, *e.g.*, which may become realistic when assuming an overall separation efficiency of 100 %, the environmental impact will decrease by 11 % in comparison to the current status of development of process B. In addition, the integration of an efficient methanol recycling procedure will lead to an overall decrease of 24 % and 13 % in GWP and HTP, respectively. Finally, if all improvement possibilities would be considered and practically implemented for the flow process B, a GWP/HTP reduction by 47%/42% and 11%/29% would occur compared to the multi-step batch procedure by Mudd *et al.* [15] and flow procedure by Zhang *et al.* [16], respectively.

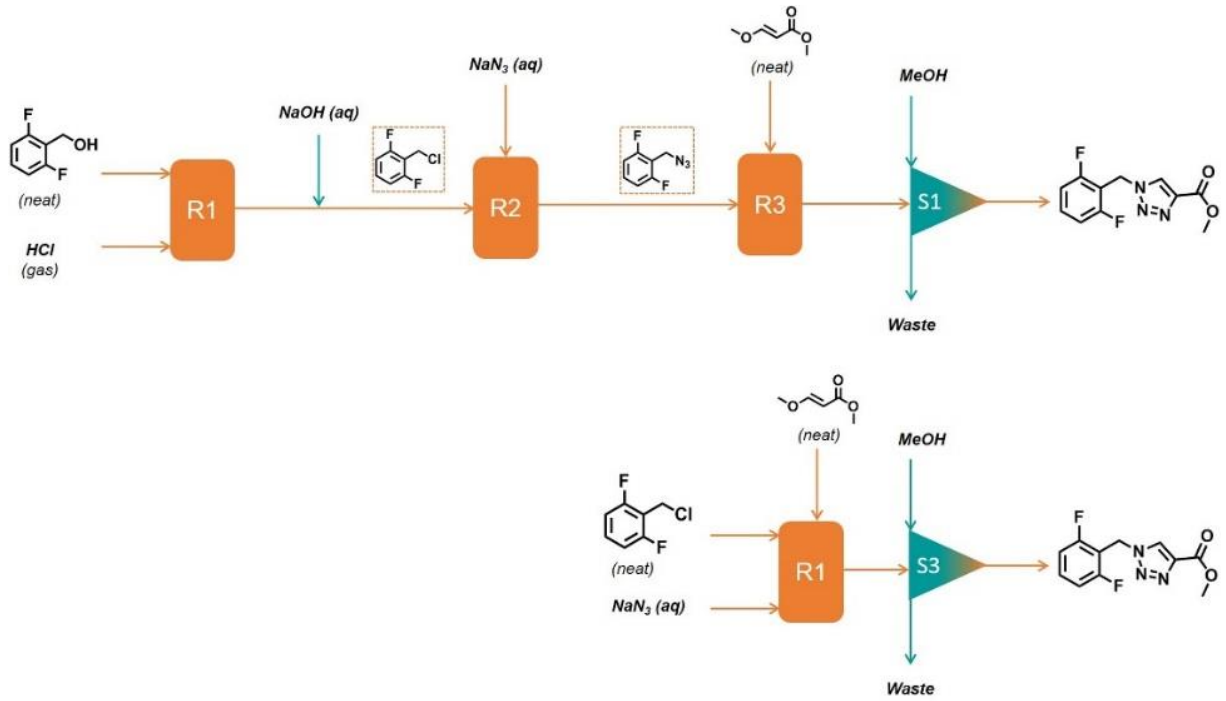
In addition, the preliminary results for process C are shown, justifying to intensively deal with immediately. Although the upstream processes to 2,6-difluorobenzyl chloride are not yet optimized nor transferred to flow, this route come off well. 2,6-difluorobenzyl azide could be as well synthesized *via* direct transformation of the hydroxyl or carbonyl moiety of 2,6-difluorobenzyl alcohol [66] or aldehyde [67], requiring less reaction steps and thus possibly further reducing the environmental burdens. These last aspects will be investigated in depth in the near future.

It goes without saying that theoretical potential improvements are also given for flow process A; yet were not identified here.

5.3.2 Telescoping of multi-step reactions to one process in flow: an end-to-end approach

Seeing the results of the analysis of the last chapters, it is obvious that the highest optimisation potential could be gained by efficient flow processing coupled with a minimum amount of intermediate work-up steps. This will avoid product losses. The extreme case of such vision is provided by the one-pot one-flow processing, which is analogous to telescoping reactions in organic chemistry. We have realized that experimentally for a quite similar dipolarophile-azide cycloaddition as discussed here, starting from the bromide stage [68]. We go further here in telescoping complexity by assuming the following.

Hence, different possible end-to-end approaches starting from 2,6-difluoro benzyl alcohol were assumed and compared to our currently developed continuous flow multi-step process (process B, see above). The focus within this chapter is again on the rufinamide precursor production, i.e. methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate. The material and energy flows related to the ammonolysis steps can be considered as equal, *i.e.* were not considered. The selection of the approaches was guided by our long-term experience as well as the expert opinion of industrial rufinamide producers.



Scheme 8. Proposed hypothetical scenarios of process sequence streamlining to yield rufinamide precursor methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate; above: multi-injection single-flow process, below: single-injection single-flow process.

Comparative study of HTP and GWP as LCIA categories Table 5 and Scheme 8 summarize the proposed theoretical scenarios and outputs that will be discussed in the following.

Table 5. Comparison of multi-step and streamlined flow syntheses of rufinamide precursor methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate.

Yields [%]	Multi-step flow	Multi-injection single flow	Single-injection single flow
2,6-Difluorobenzyl chloride	94	99	94
2,6-Difluorobenzyl azide	93	84	95
Methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate (crude)	86	86	
Separation (batch)	95	95	95
Overall yield to methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate	**72**	**68**	**85**

<u>*Multi-injection single-flow*</u> As one alternative to multi-step flow processing, a "multi-injection single-flow" process starting with 2,6-difluorobenzyl alcohol was considered. Thereby, a continuous one-flow process is realized by a non-tandem reaction, adding all necessary reagents and solvents at different stages of the reaction. No intermediate product isolation and purification are needed, thus no losses will take place. However, orthogonality is the main challenge. It is difficult to identify suitable solvents for the whole continuous process chain. As a consequence, compared to a multi-step multi-flow process, lower yields for intermediate azide production can be expected. Due to the water dependent equilibrium between 2,6-difluorobenzyl chloride and corresponding -alcohol, the addition of water necessary for solubilizing sodium azide moves the state of equilibrium from 2,6-difluorobenzyl chloride back to benzyl alcohol. In comparison, both routes might result in similar environmental outputs, see Figure 7.

<u>*Multi-injection single-flow*</u> On the other hand, a "single-injection single-flow" process was investigated, being classified as orthogonal tandem reaction, *i.e.* all reagents and catalysts are present from the outset of the reaction. In this case a reagent incompatibility will occur which is that hydrochloric acid will quench the nucleophilic property of sodium azide. Therefore, this process needs to start off with pure 2,6-difluorobenzyl chloride. For this option a yield enhancement might result, due to (i) no separation losses, and (ii) possibly less decomposition of 2,6-difluorobenzyl azide. As a consequence, this processing could lead to an increase of environmental benefits by approximately 20 %, see Figure 7.

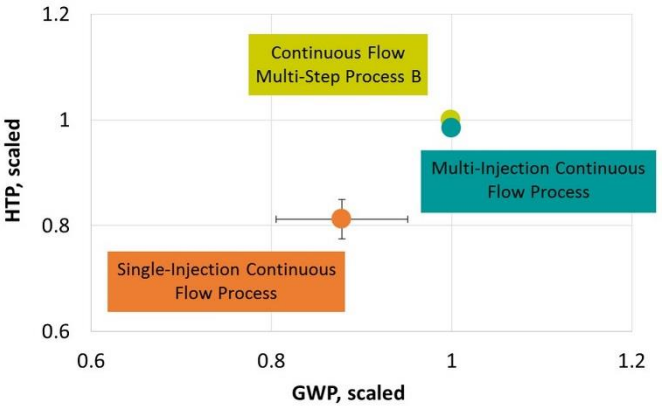


Figure 7. Overall life cycle impact assessment comparison of continuous multi-step and streamlined processing of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate by means of GWP and HTP. Scaled effects.

Due to the large differences in composition of the reaction stream compared to the other scenarios, the consumption of methanol for isolating methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate can only be estimated in accordance to the other scenarios, integrating a ± 25 % uncertainty factor. If methanol is recycled adequately, then the environmental impact will finally decrease by approximately 35 % compared to the multi-step flow process.
However, due to the presence of water, the formation of 2,6-difluorobenzyl alcohol instead of azide could be possible. If so, the yield to methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate should amount to at least 80 % in order to be environmentally competitive to "multi-step flow" and "multi-injection single flow" processing.

6 Conclusions

Herein, for the first time an environmental assessment and optimisation study of different rufinamide production pathways was performed. Thereby, current routes used in industrial production and in the literature were evaluated and improvement potentials were accessed. The latter were recruited from common process intensification activities and green chemistry optimisation (*e.g.*, change of reactants and solvents). For several green chemistry optimisation scenarios – reagent replacements in the upstream chain reactions as well as solvent recycling – a better environmental profile was found. We identified processes moving the azide formation – which determines largely the whole rufinamide environmental backpack – in a greener direction. In a previous paper [18] we made reagent choices based only on metrics and expert opinion. With the detailedness of LCA analysis here, we could confirm and deepen that.

Yet, the detailed investigations concerning LCA have, once more, given complex answers which are not at all unidirectional and thus do not lead unanimously to one decision. For example, the EMMA dipolarophile (E)-Methyl 3-methoxyacrylate) was already assigned in a previous snapshot analysis as green.[18] The

hazard and cost analysis confirmed that, while the CED and GWP contributions for its making were higher than for other dipolarophiles. Finally, the EMMA-based process route to rufinamide has much better solvent rate and PMI as well as GWP impact. Thus, seen holistically, it is the best dipolarophile. In this sense, it is more a "green process enabler" than itself being a green molecule.

To highlight the impact of intermediate separation (which was considered throughout), two connected reaction steps were analyzed, and thereafter the same was done for the total flow reaction system. These were the formation of azide and the subsequent Huisgen dipolar cycloaddition to yield the rufinamide precursor molecule methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate. A metrics and simplified life-cycle assessment (LCIA) for batch-batch and batch-conti processes showed only minor differences, which basically is due to the fact that the flow process reaches the batch performance, but does not exceed it (which is the major key to better ecology). The potential analyses for batch optimisation feature a limiting factor and are more or less exhausted. A stronger effect is given by when changing from two-pot batch to one-pot batch. This is seen as a step towards the telescoping scenario investigated later for the total flow reaction network. The large effect is due saving intermediate separation and consequently less solvent. The relevance of the latter is even more highlighted when a recycling mode is considered for the solvents, which presents another way to deal with the issue. This 'batch recycled' mode was considerably better as well. Not only the amount, but also the choice of solvents is essential. Thus, a search for environmental and process compatible solvents could play a central role in the overall environmental balance, see, *e.g.*, the impact of DMSO in Figure 5.

From there onwards the analysis moved towards diverse scenarios of the total connected flow process to rufinamide (in our case, including 3 out of 4 steps, because ammonolysis is made batch-wise for given reasons). A clear environmental benefit could be shown when switching from multi-step batch to flow. Taking into account, all improvements considered in the investigations given above, we could identify a significant reduction of all LCIA potentials by an average of 45 % if switching from multi-step batch to multi-step flow processing by simultaneously integrating solvent recycling strategies.

To our best knowledge, this is the first kind of such study for flow chemistry. In a last scenario, the superficial telescoping of flow process steps was investigated (while before the analysis was to a major part based on experimental results from literature and patents). A multiple- and single-injection point mode of telescoping was investigated. The best case was given by a combination of single-injection single flow processing and methanol recycling which is predicted to result in a reduction of all impact categories by 33 % on average ††† compared to the multi-step flow procedure developed so far.

7 Outlook

In the future, the experimental feasibility of other superficial scenarios will be investigated. The experimental investigations will also concentrate on the optimisation of the solvent demand. Possibly lower amounts could be used without leading to clogging within the micro channels. Cost calculations will round up the study to quantify the overall eco-efficiency and competitiveness in comparison to current rufinamide manufacturing approaches.

There is an increasing interest in microreactor networks chemistry and material synthesis – thus, in end-to-end process design in flow. Once this merges with enzyme/bio-catalysis, the door is open to biochemo catalyst cascades in flow which are meanwhile (advanced) state of the art in batch chemical synthesis. Thus, such design would be biomimetic - processes in nature follow a continuous series of highly regulated catalytic cascades leading to a highly efficient 'biochemical assembly line" [69]. These cascades serve mainly as metabolic pathways [70] and signalling pathways [71] (examples: preakuammicine metabolic cascade [69]; tissue factor pathway for blood coagulation through fibrin formation [72]).

Even nature has no silver bullet to synthesis [69], which is the reason for the complexity of cascade approaches. In particular, reaction telescoping require, most notably, orthogonality along the whole cascade. In case of incompatibility or limited stability issues, the utilization or development of solvent switches, catch and release techniques or compartmentalization strategies for the separation of process units is advised. Ley *et al.* have developed multiple tools to solve incompatibility issues and allow single-flow multi-step processes, see *e.g.* [73].

Detailed insights into the optimisation studies as well as experimental procedures for rufinamide production in flow are underway for publishing.

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9 Abbreviations

API	active pharmaceutical ingredient
CED	cumulative energy demand [MJ/FU]
DMSO	dimethyl sulfoxide
eq	equivalents
EMMA	(E)-methyl 3-methoxyacrylate
FDP	fossil depletion potential [kg oil-eq/FU]
FEP	freshwater eutrophication potential [kg P-eq/FU]
FU	functional unit
GWP	global warming potential [kg CO_2-eq/FU]
HTP	human toxicity potential [kg 1,4-DCB/FU]
LCA	life cycle assessment
LCI	life cycle inventory

LCIA	life cycle impact assessment
MDP	metal depletion potential [kg Fe-eq/FU]
MeOH	methanol
NLTP	natural land transformation potential [m^2/FU]
NMVOC	non-methane volatile organic compounds
NPW	novel process windows
ODP	ozone depletion potential [kg CFC-11-/FU]
PMI	process mass intensity [kg/kg]
POFP	photochemical oxidant formation potential [kg NMVOC/FU]
RM	raw material
TAP	terrestrial acidification potential [kg SO_2-eq/FU]
TETP	terrestrial ecotoxicity potential [kg 1,4-DCB/FU]

10 Notes and references

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† Process output was calculated based on isolated yield obtained from one reactor. Details can be found in [18].
†† Overall reduction: GWP 20 %, FDP 17 %, FEP 25 %, HTP 24 %, MDP 23 %, NLTP 17 %, ODP 89 %, POFP 39 %, TAP 76 %, TETP 13 %.
††† Overall reduction: GWP 37 %, FDP 37 %, FEP 24 %, HTP 31 %, MDP 26 %, NLTP 40 %, ODP 39 %, POFP 28 %, TAP 27 %, TETP 45 %.

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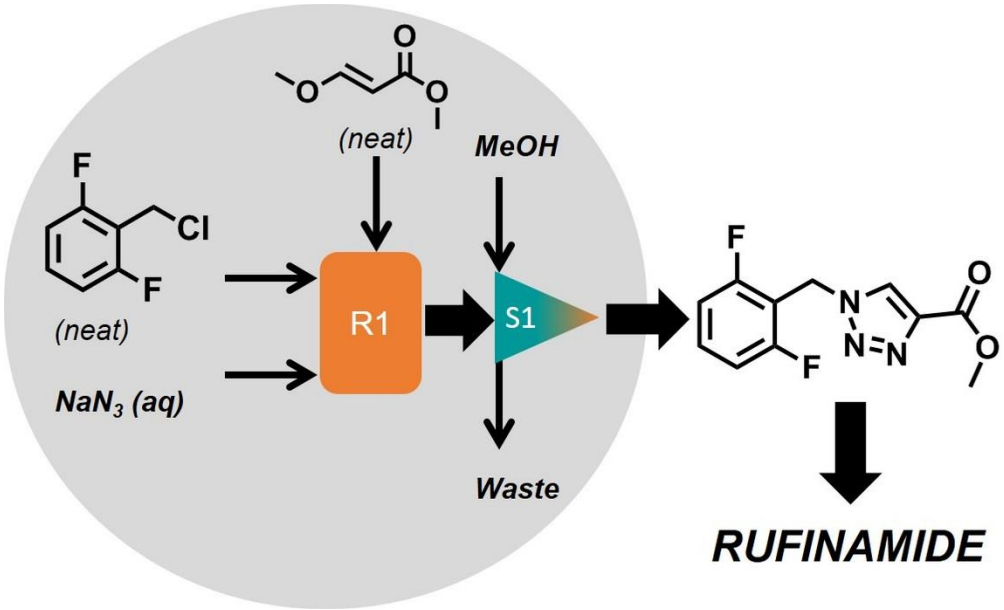
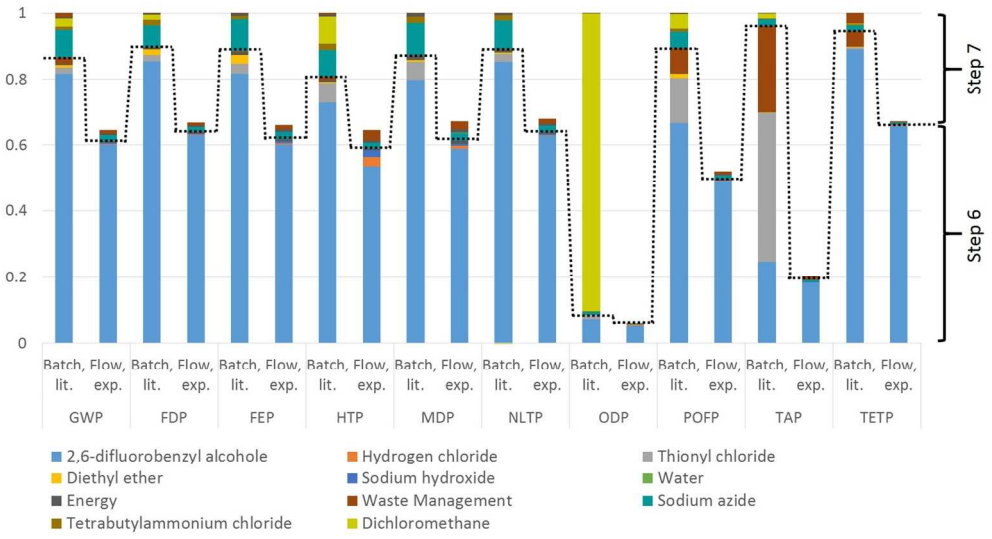
Cover Picture





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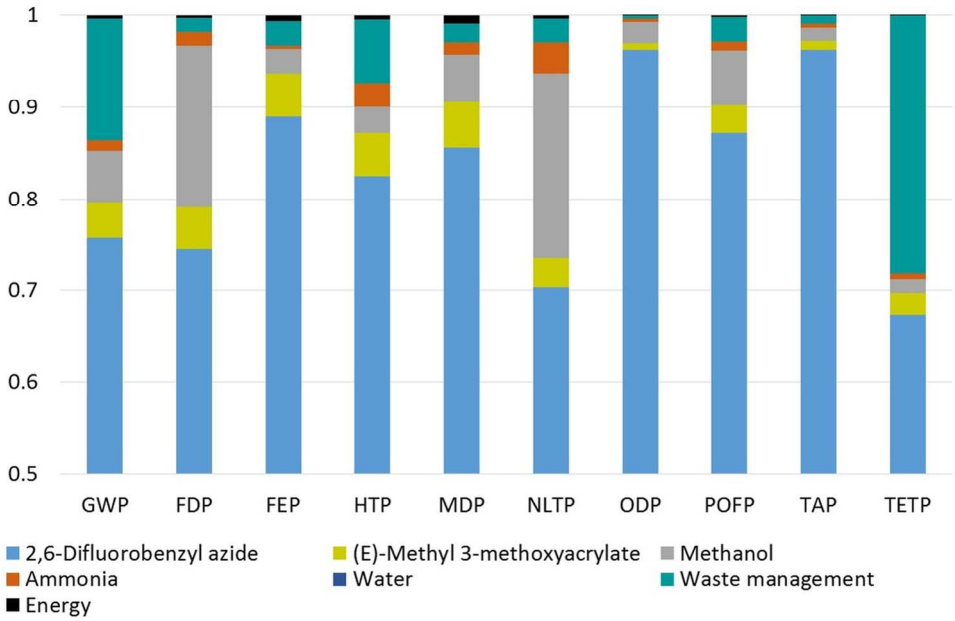

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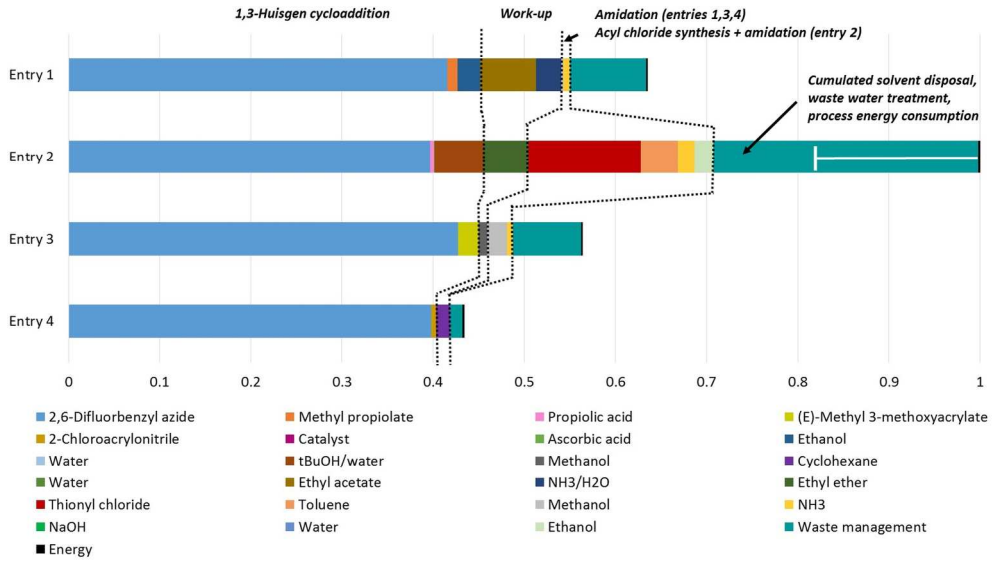

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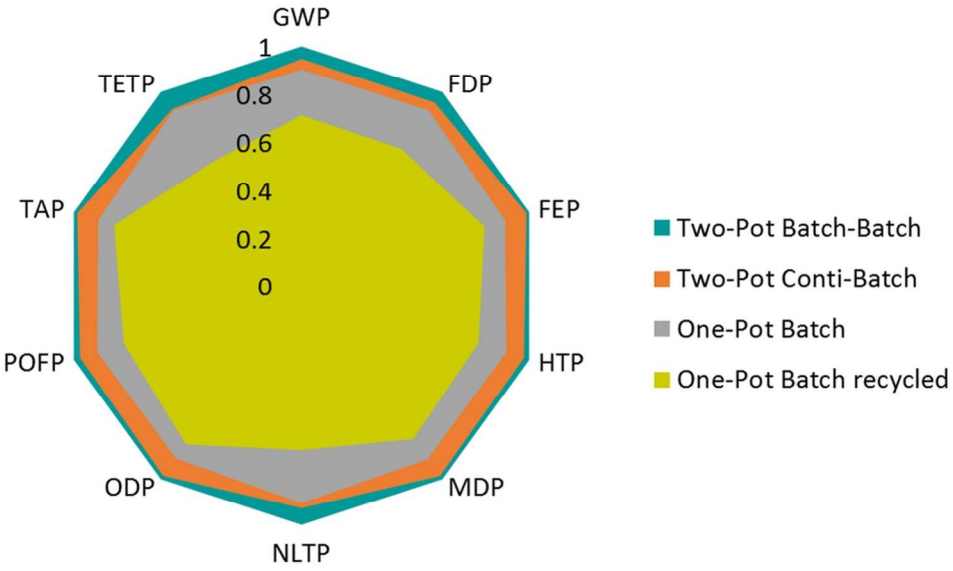

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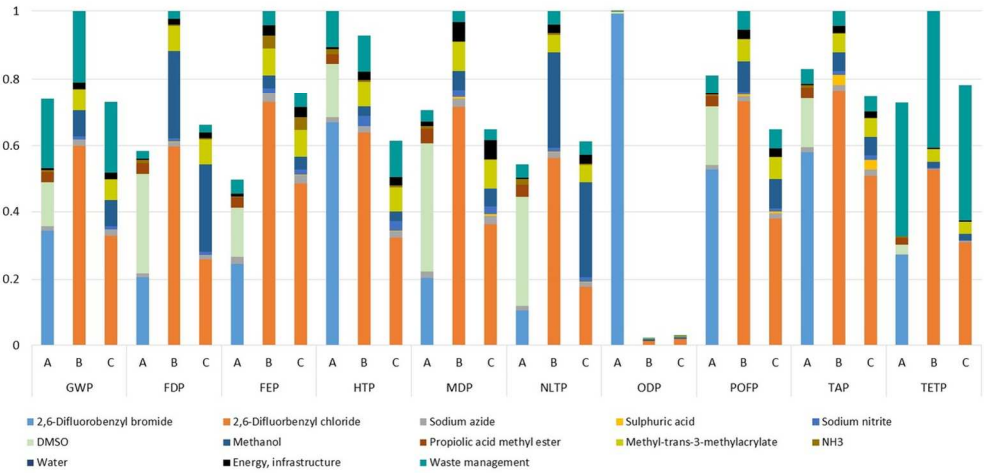

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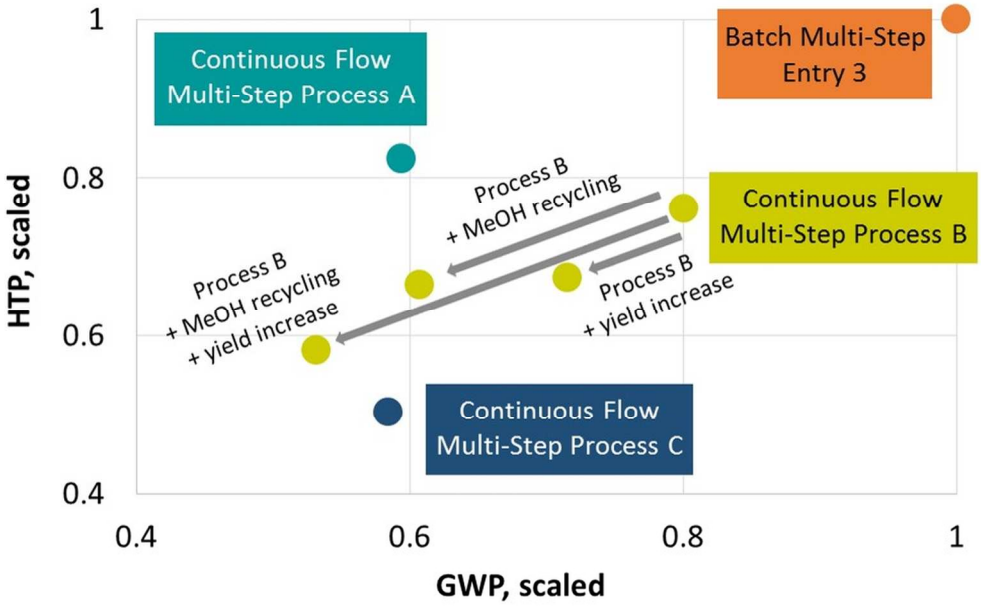

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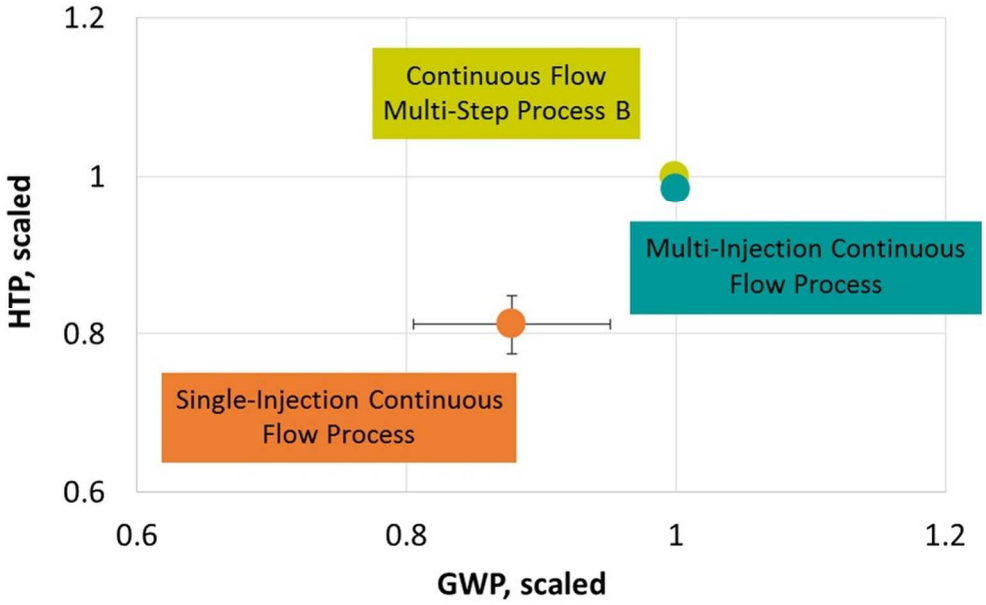

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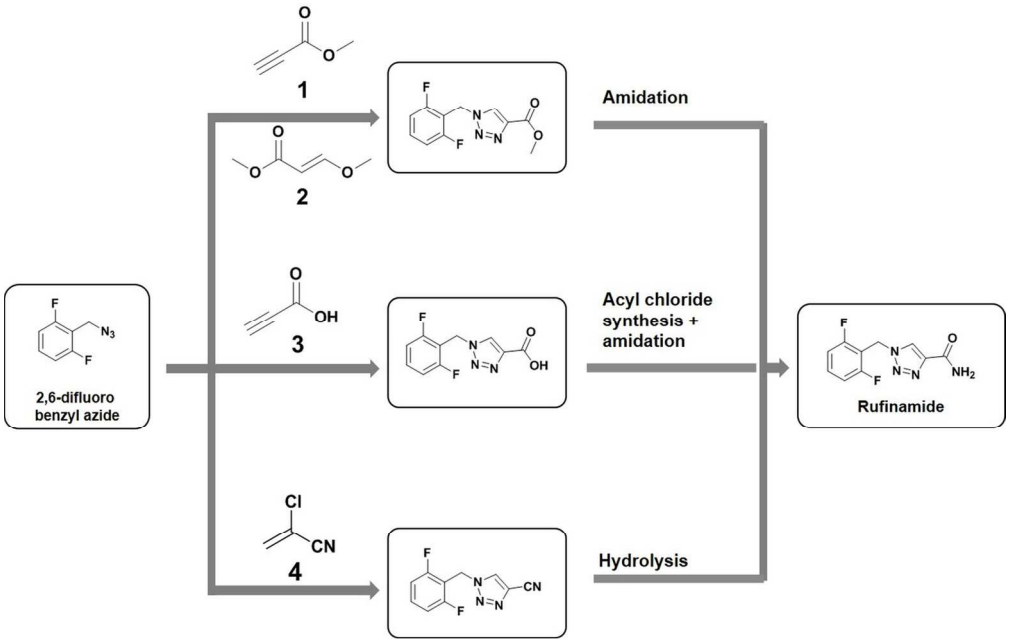

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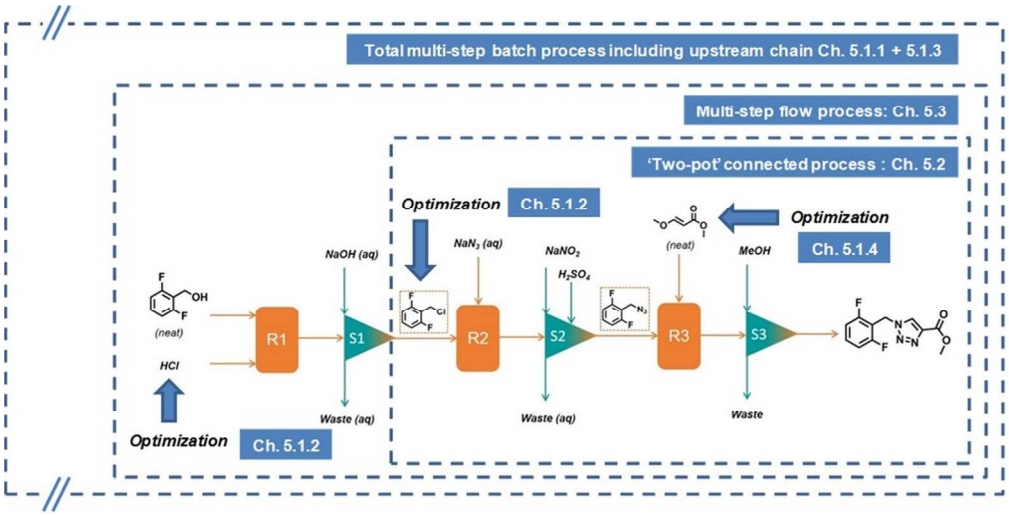

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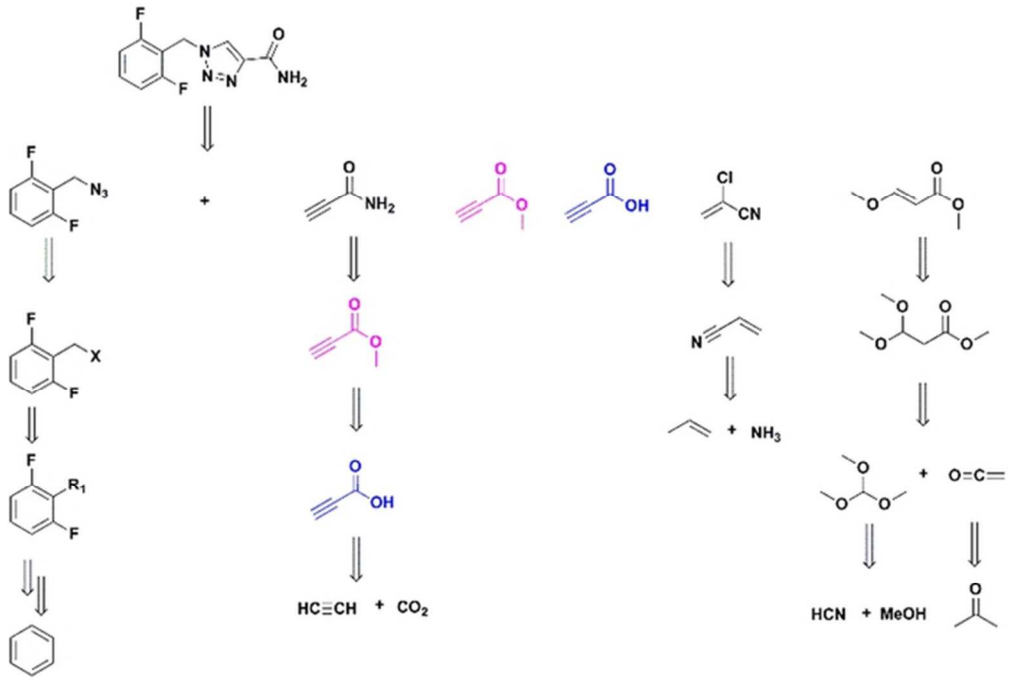

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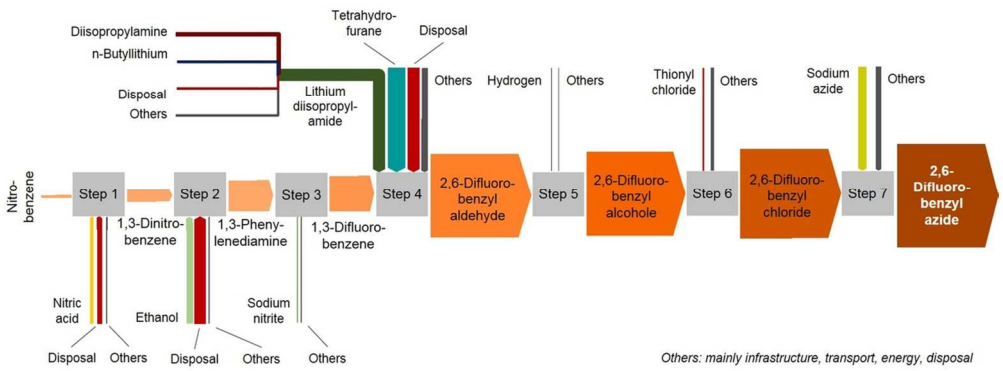

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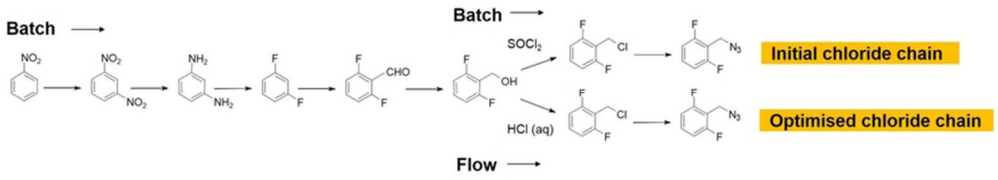

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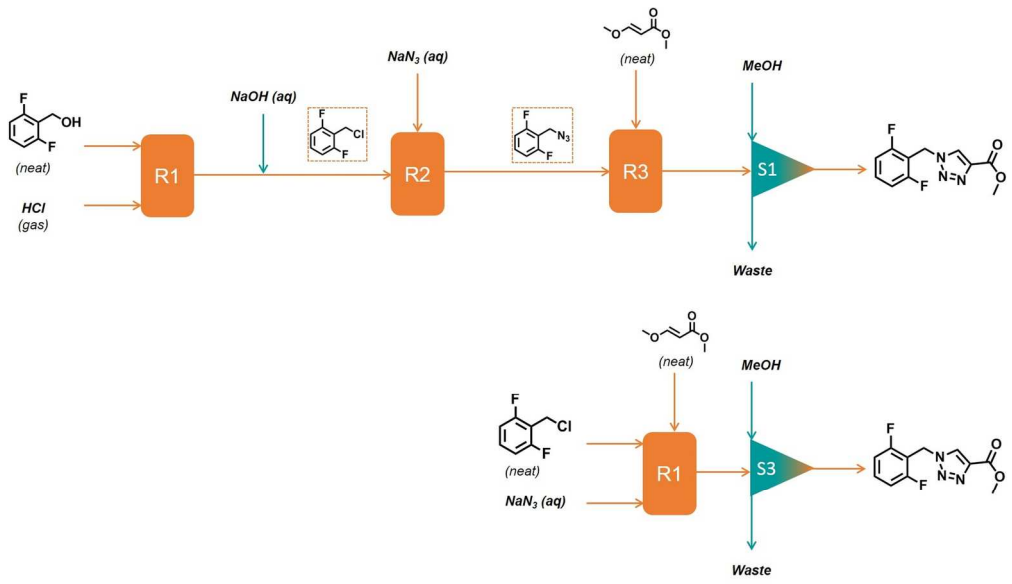

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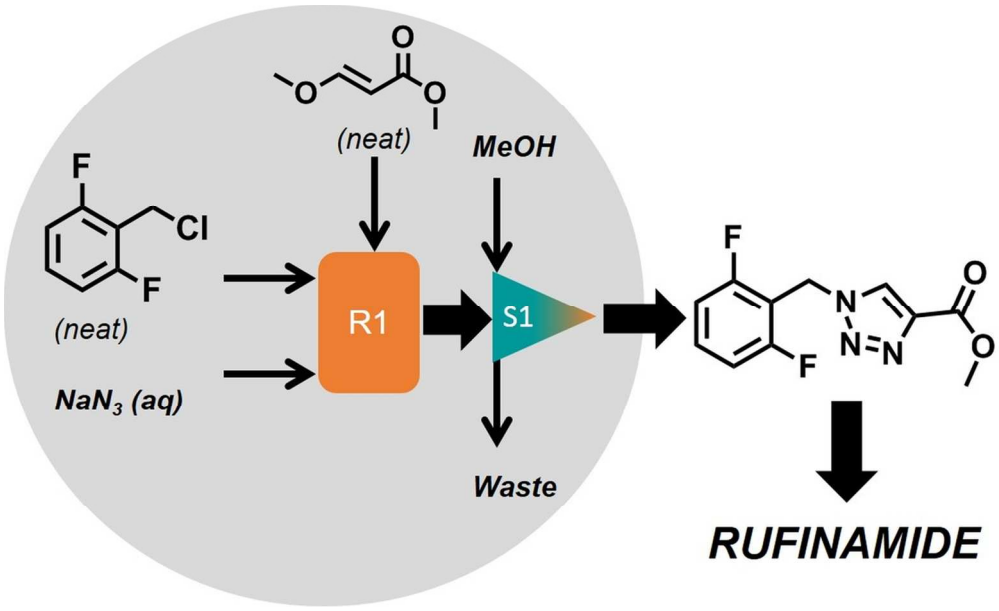

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