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ARTICLE

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

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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 9g h^{-1} (11.5 mol h^{-1} L^{-1}). The process minimizes the isolation and handling of strong alkylating or energetic intermediates, while minimizing water and organic solvent consumption.

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 conveyer-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[2]. 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[3].

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[13–15,6]. 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.

PLEASE INSERT SCHEME 1.TIFF HERE

Scheme 1. Retrosynthetic sequence of rufinamide.

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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 1[20]. 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 formed[21,22]. Mudds et al. proposed a solventless batch sequence using (E)-methyl 3-methoxyacrylate (5) as an alternative[23]. 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 conditions[24]. 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 reagents[25]. 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,

PLEASE INSERT SCHEME 2.PNG HERE

Scheme 2. Proposed alternative reagents to prepare rufinamide precursor.

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 assessment[26] 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.

Step 1- Chlorodehydroxylation

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[27] (HCl (aq)) or hydrogen chloride[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 (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 (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. Figure 1.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.

PLEASE INSERT FIGURE 1.PNG HERE

Figure 1. a. Schematic representation of 2,6-difluorobenzyl chloride synthesis and optimization results. b. Schematic representation of 2,6-difluorobenzyl azide synthesis and optimization results. c. Schematic representation of 5-stage multi-step process to deliver rufinamide precursor.

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[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

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reagent was relatively stable and not shock sensitive[24]. Borukhova et al. demonstrated safe cycloaddition of organoazides with a variety of dipolarophiles under high temperature and pressure in micro flow reactors[30]. The most straightforward synthesis of azide is the use of organohalide and azide source, such as sodium azide. Upon solvation of sodium azide (NaN_3) in water the highly toxic and explosive hydrazoic acid (HN_3) is formed as shown in (1).

$$NaN_3 + H_2O \rightleftharpoons HN_3 + NaOH \quad (1)$$

Table 1. Intermediate results for optimization of 2-step 2,6-difluorobenzyl azide synthesis from 2,6-difluorobenzyl alcohol.

Entry	T (C)	Res. time (min)	NaN_3 (eq)	NaOH (M)	Conv. (%)	Yield (%)
1	140	30	-	0.4	28	**0**
2	140	30	1.1	0.4	73	**60**
3	140	30	1.5	0.4	77	**66**
4	150	30	1.5	0.4	83	**72**
5	150	30	1.5	0.2	91	**86**
6	150	40	1.5	0.2	98	**92**
7	160	30	1.5	0.2	98	**91**
8	160	40	1.6	0.2	>99	**95**

In order to force an 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 ran without the base. Figure 1.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 Figure 1.b. Decreasing equivalents of base increased the selectivity towards 2,6-difluorobenzyl azide. However, more equivalents of NaN_3 were needed to obtain full conversion in 30 min residence time.

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 Figure 1.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 azide. Higher temperatures and NaN_3 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.

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[27]. 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.

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[24]. The most important benefit is the increased safety due to the circumvention of any

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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}).

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[31]. 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 (NaN_3) 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:

- Operating time is drastically decreased from days to hours;
- Solvent use is circumvented without compromising the safety usually afforded by dilution;
- Overall isolated yield is higher;
- 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.

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Experimental Section

General Information. HPLC pumps were purchased from Knauer, while ETFE micro capillary reactors along with connections were purchased from IDEX Health & Science Technologies. Reagents were pumped via pumps into the ETFE T- or Y-mixers. Hastelloy tubing and stainless steel connections were ordered from Valco instruments.

Hydrogen chloride gas was purchased in 10 L bottle from Linde Gas Benelux. 2,6-difluorobenzyl alcohol was provided by Ajinomoto OmniChem N.V. The rest of the chemicals were purchased from Sigma-Aldrich and used as received without any additional purifications.

Continuous synthesis of 2,6-difluorobenzyl chloride. The HPLC pump was first purged with isopropanol and then with the 2,6-difluorobenzyl alcohol. The reactor tubing was connected directly to the pump and the reactor was filled with alcohol. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 0.128 ml/min (1.1 mmol/min). The pressure was set to 12 bar at the Equilibar back pressure regulator (BPR), the heating

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plate was turned on and reaction temperature was set. After three times a residence time of 40 min, the product was collected into a vial containing water and ethyl acetate. The product was extracted and organic phase was analysed further with GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, *J*= 4 Hz, 1H), 6.92 (t, *J*= 8 Hz, 2H), 4.67 (s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 162.45 (d, *J*= 7 Hz), 159.94 (d, *J*= 7 Hz), 132.63 (t, *J*= 10 Hz), 114.08 (t, *J*= 9 Hz), 111.61 (q, *J*= 5 Hz), 32.40 (t, *J*=5 Hz).

Continuous synthesis of 2,6-difluorobenzyl azide. 25 gr of 2,6-difluorobenzyl chloride was melted and mixed with 10 ml of toluene. The solution was allowed to cool down to room temperature. HPLC pumps were first purged with isopropanol and the first pump was purged with the solution, while a second with aqueous sodium azide solution (4.0 M). 2,6-difluorobenzyl chloride solution was pumped at 21 µl/min, while sodium azide solution was pumped at 46 µl/min. Two streams were mixed within an ETFE T-mixer and proceeded into a 2 ml ETFE reactor (0.03" ID). The inline 7 bar (100 psi) BPR was attached to the other end of the reactor and the reactor was heated to 140°C. After three times residence time of 30 min, the product was collected into a vial containing water and ethyl acetate. The product was extracted and organic phase was analysed further with GC. Toluene served as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, *J*= 4 Hz, 1H), 6.95 (t, *J*= 8 Hz, 2H), 4.43 (s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 162.80 (d, *J*= 7 Hz), 160.31 (d, *J*= 7 Hz), 132.65 (t, *J*= 10 Hz), 111.74 (d, *J*= 6 Hz), 111.41 (d, *J*= 6 Hz), 41.79 (t, *J*=3 Hz).

Two-step continuous synthesis of 2,6-difluorobenzyl azide. Two HPLC pumps were first purged with isopropanol. 2.6 gr (65 mmol) of NaOH and 26 gr (400 mmol) of NaN_3 were dissolved in water to yield 100 ml of solution. The first pump was purged with 2,6-difluorobenzyl alcohol, while the second with demi water. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). All the reactors were connected and immersed into heating baths. A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 128 µl/min (1.1 mmol/min). Another pump was set to 128 µl/min to pump pure water, and mixed streams flowed into a second reactor of 24 ml (1.6 mm ID). For this experiment two inline cartridge BPRs of 7 bar pressure were used. One BPR was attached first, after a significant pressure was attained within the reactor, the second BPR was attached. The first heating bath was set to 110°C, while second to 70°C. After one residence time (40 min), the pure water solution was replaced by the NaOH and NaN_3 solution and the flowrate was gradually increased to 460 µl/min. The second heating bath was set to 160°C. After the period equivalent to two residence times, the BPR outlet was connected to the inline liquid-liquid separator. An ultra-low volume adjustable BPR was attached to the aqueous outlet 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. The first millilitre of the product was discarded, which was followed by a collection.

Third step- continuous synthesis of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate. All HPLC pumps were purged with isopropanol and later with either 2,6-difluorobenzyl azide, EMMA or methanol. The collected 2,6-difluorobenzyl azide was pumped at 100 µl/min (0.7 mmol/min) into a T-mixer to mix with EMMA, pumped at 112 µl/min (1.05 mmol/min), in order to proceed into 3.2 ml Hastelloy micro capillary reactor. MeOH was pumped at 3.2 ml/min (15 v/v) to dilute the product stream. A closed heating bath (Lauda Proline 8) was heated to 210°C and 15 min residence time was allowed for the reaction to take place. After passing through a mixing zone of 1 ml volume Hastelloy micro capillary (0.04" ID) and BPR of 1000 psi, the product was collected. The collected solution was cooled to room temperature and later to 5°C in the fridge overnight. The precipitated yellow product was then filtered and dried under vacuum overnight. Yield 88%; mp 136-137°C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 7.49 (m, *J*= 4 Hz, 1H), 7.15 (t, *J*= 8 Hz, 2H), 5.71 (s, 2H), 3.80 (s, 3H); ^{13}C (100 MHz, DMSO-d6) δ 162.43 (d, *J*= 8 Hz), 160.98, 159.95 (d, *J*= 7 Hz), 138.90, 132.30 (t, *J*= 10 Hz), 129.91, 112.38 (q, *J*= 5 Hz), 111.25 (t, *J*= 19 Hz), 51.25, 41.77 (t, *J*=4 Hz).

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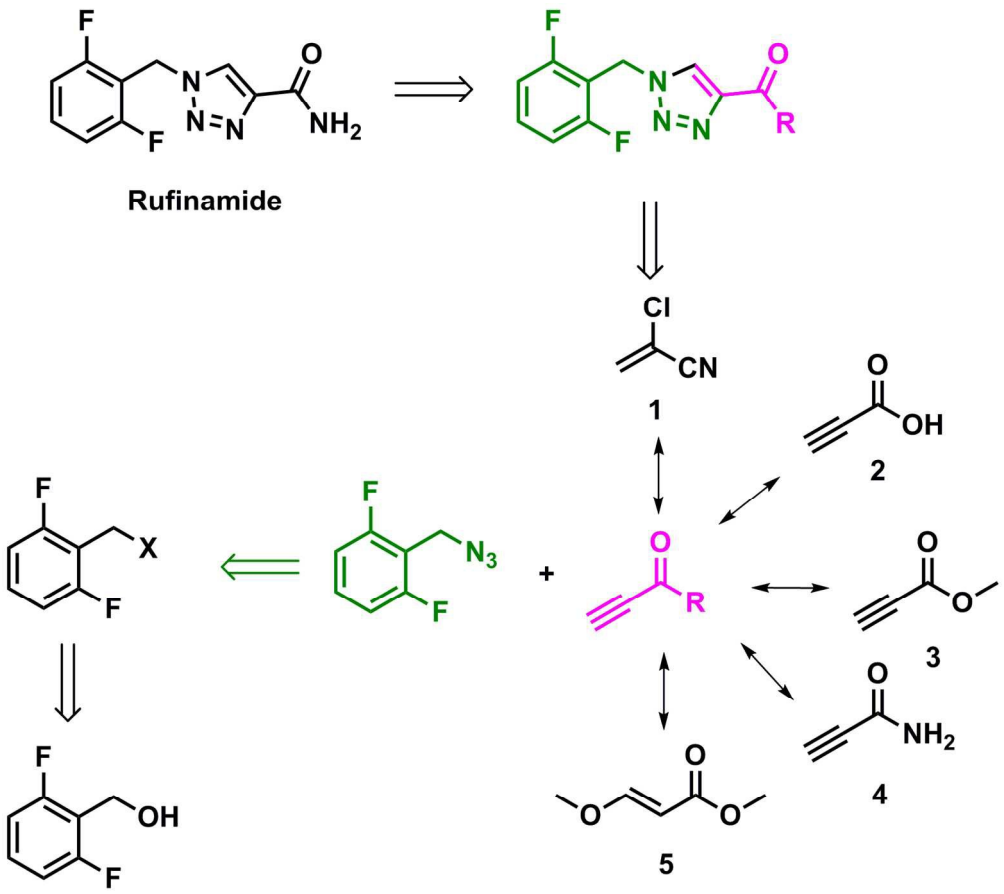

Scheme 1. Retrosynthetic sequence of rufinamide.
148x132mm (300 x 300 DPI)

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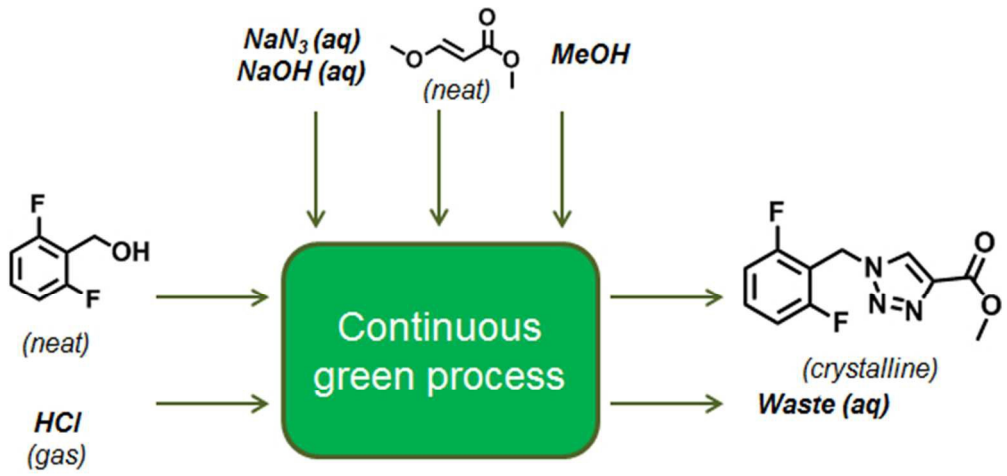

Scheme 2. Proposed alternative reagents to prepare rufinamide precursor.

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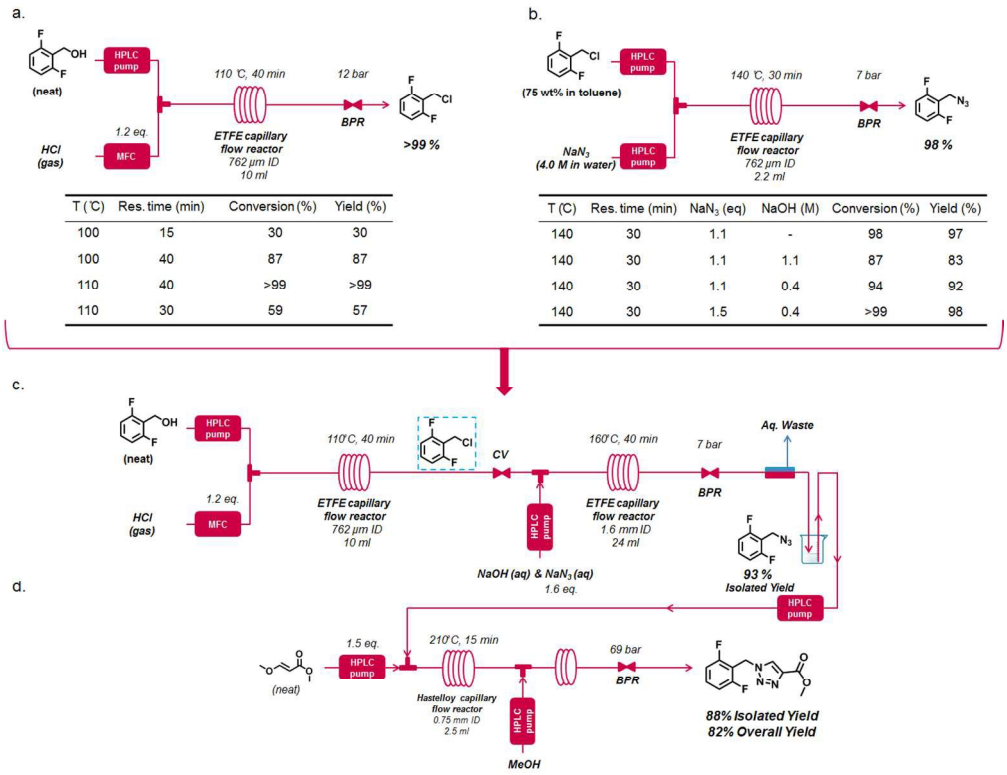

T (°C)	Res. time (min)	Conversion (%)	Yield (%)
100	15	30	30
100	40	87	87
110	40	>99	>99
110	30	59	57

T (°C)	Res. time (min)	NaN_3 (eq)	NaOH (M)	Conversion (%)	Yield (%)
140	30	1.1	-	98	97
140	30	1.1	1.1	87	83
140	30	1.1	0.4	94	92
140	30	1.5	0.4	>99	98

Figure 1. a. Schematic representation of 2,6-difluorobenzyl chloride synthesis and optimization results. b. Schematic representation of 2,6-difluorobenzyl azide synthesis and optimization results. c. Schematic representation of 5-stage multi-step process to deliver rufinamide precursor.

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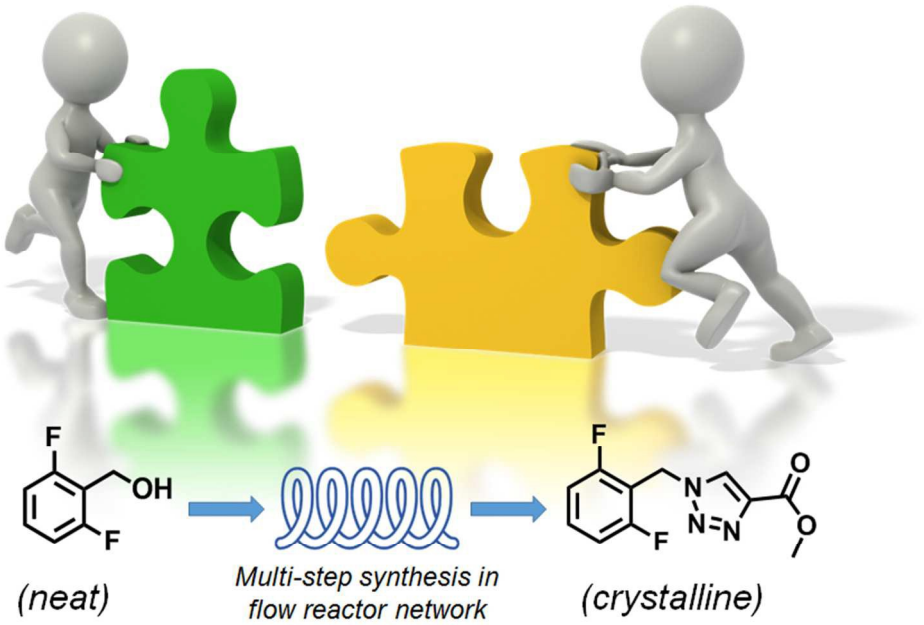

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Supporting information

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

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1. General Reagent Information

Hydrogen chloride gas was purchased in 10 L bottle from Linde Gas Benelux. 2,6-difluorobenzyl alcohol was provided by S.A. Ajinomoto OmniChem N.V. The rest of the chemicals were purchased from Sigma-Aldrich and used as received without any additional purifications.

HPLC pumps were purchased from Knauer, while ETFE micro capillary reactors along with connections were purchased from IDEX Health & Science Technologies. Reagents were pumped via pumps into the ETFE T- or Y-mixers. Hastelloy tubing and stainless steel connections were ordered from Valco instruments.

2. General Analytical Information

NMR (Bruker- Avance 400 (400 MHz)) and GC-MS (Shimadzu GC-2010 Plus coupled to a Mass Spectrometer, Shimadzu GCMS-QP 2010 Ultra) were used for characterization of isolated products. ^{1}H- NMR and ^{13}C- NMR spectra were used to characterize and determine the purity of isolated products. ^{1}H chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) (0.00 ppm), while ^{13}C chemical shifts are reported relative to $CDCl_3$ (77.2 ppm). Multiplicity of the peaks is abbreviated as s - singlet, d - doublet, t - triplet, q- quartet, m- multiplet and br-broad. GC-FID was used to quantify product distribution. GC-MS was used to identify the decomposition products.

3. GC method

GC method for follow-up of 2,6-difluorobenzyl alcohol and chloride conversion

Parameter	Specification
Column	CP-Sil 5 CB
Length	30 m
Inner Diameter	250 µm
Film thickness	1.0 µm
Internal Pressure	1.8 psi (He)
Injection volume	0.2 µl
Split ratio	1/5
Injection temperature	220 ˚C
Detector temperature	280 ˚C
Air	300 ml/min
Steam	30 ml/min
Make up	25 ml/min
Initial temperature	80 ˚C (2 min)
Ramp 1	15 ˚C/min (till 200˚C, hold 10 min)
Ramp 2	20 ˚C/min (till 240˚C, hold 0 min)

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HPLC method for follow up of 1,2,3-triazole formation

Parameter	Specification
Column	C18
Length	150 mm
Inner Diameter	4.6 mm
Pore size	5 µm
Column temperature	35 ˚C
Injection volume	1 µl
Eluent	775 ml of DW, 1 ml of Formic acid (98%), 150 ml MeOH, 75 ml THF
Detection	UV, 230 nm
Flow rate	1 ml/min
Running time	35 min

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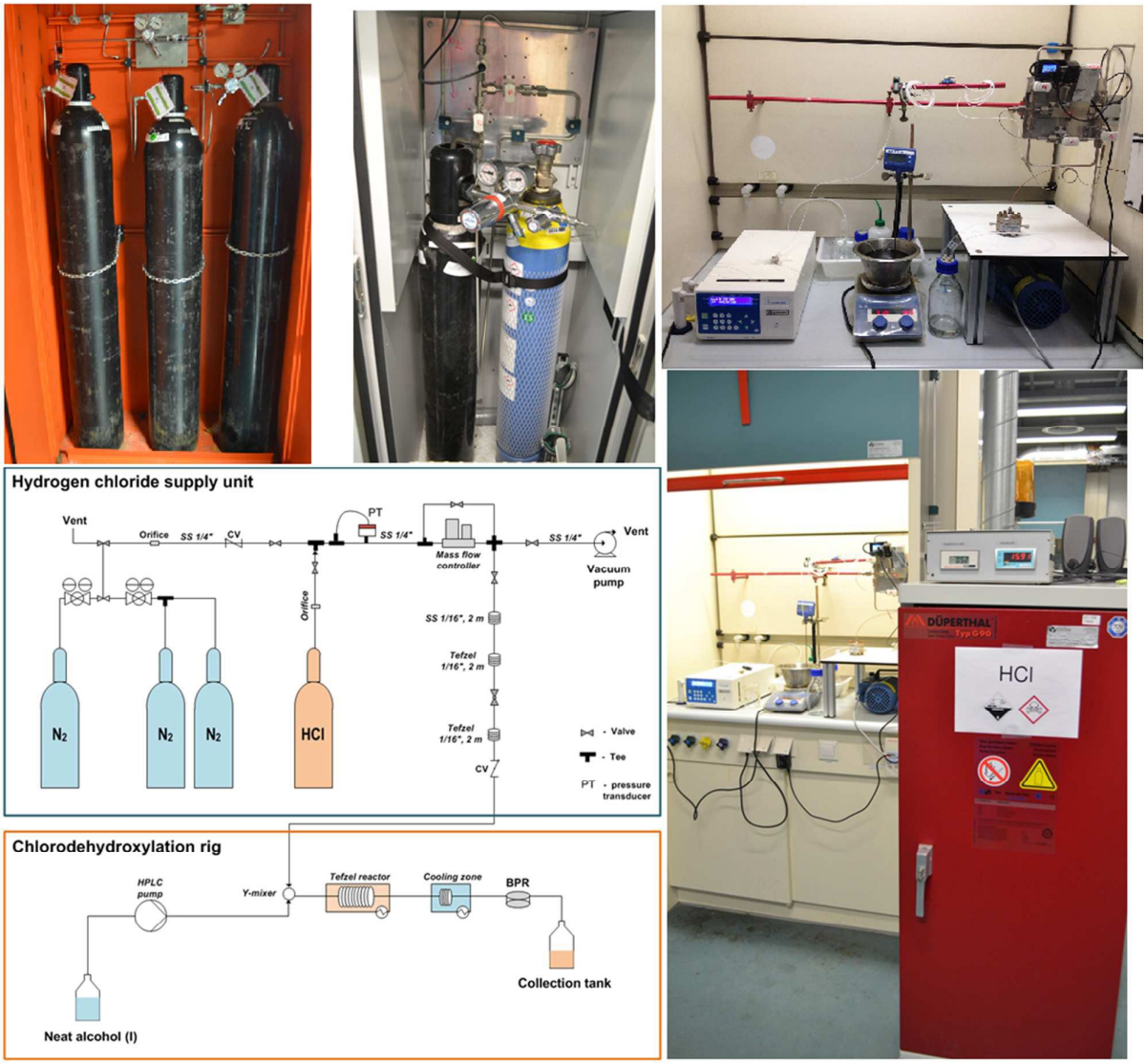
4. General Information Regarding experimental setups and experimental procedure

4.1 Continuous chlorodehydroxylation

4.1.1 Reaction setup for continuous chlorodehydroxylation

Scheme S1. Schematic representation of setup assembled for chlorodehydroxylation including hydrogen chloride gas delivery unit (with a permission from [1] Copyright © 2016, American Chemical Society). More detailed information on assembly and operation is available in ref. 1.



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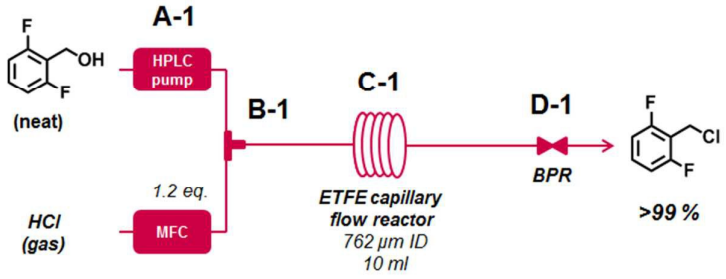
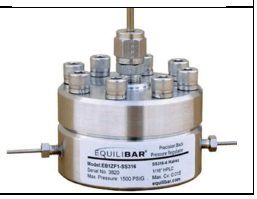
Scheme S2. Schematic representation of setup assembled for continuous chlorodehydroxylation



Component	Description	Scheme
A-1	Knauer HPLC pumps of Smartline 1050 series	
B-1	Y-mixer (P-512 from IDEX-HS)	
C-1	ETFE tubing of 1/16" external diameter and 0.03" internal diameter (1530L from IDEX-HS)	
D-1	Equilibar back pressure regulator	

4.1.2 Experimental procedure for continuous chlorodehydroxylation of 2,6-difluorobenzyl alcohol

The HPLC pump was first purged with isopropanol and then with the 2,6-difluorobenzyl alcohol. The reactor tubing was connected directly to the pump and the reactor was filled with alcohol. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 0.128 ml/min (1.1 mmol/min). The pressure was set to 12 bar at the Equilibar back pressure regulator (BPR), the heating plate was turned on and reaction temperature was set. After three times a residence time of 40 min, the product was collected into a vial containing water and ethyl acetate. The product was extracted and organic phase was analysed further with GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, *J*= 4 Hz, 1H), 6.92 (t, *J*= 8 Hz, 2H), 4.67 (s, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 162.45 (d, *J*= 7 Hz), 159.94 (d, *J*= 7 Hz), 132.63 (t, *J*= 10 Hz), 114.08 (t, *J*= 9 Hz), 111.61 (q, *J*= 5 Hz), 32.40 (t, *J*=5 Hz).

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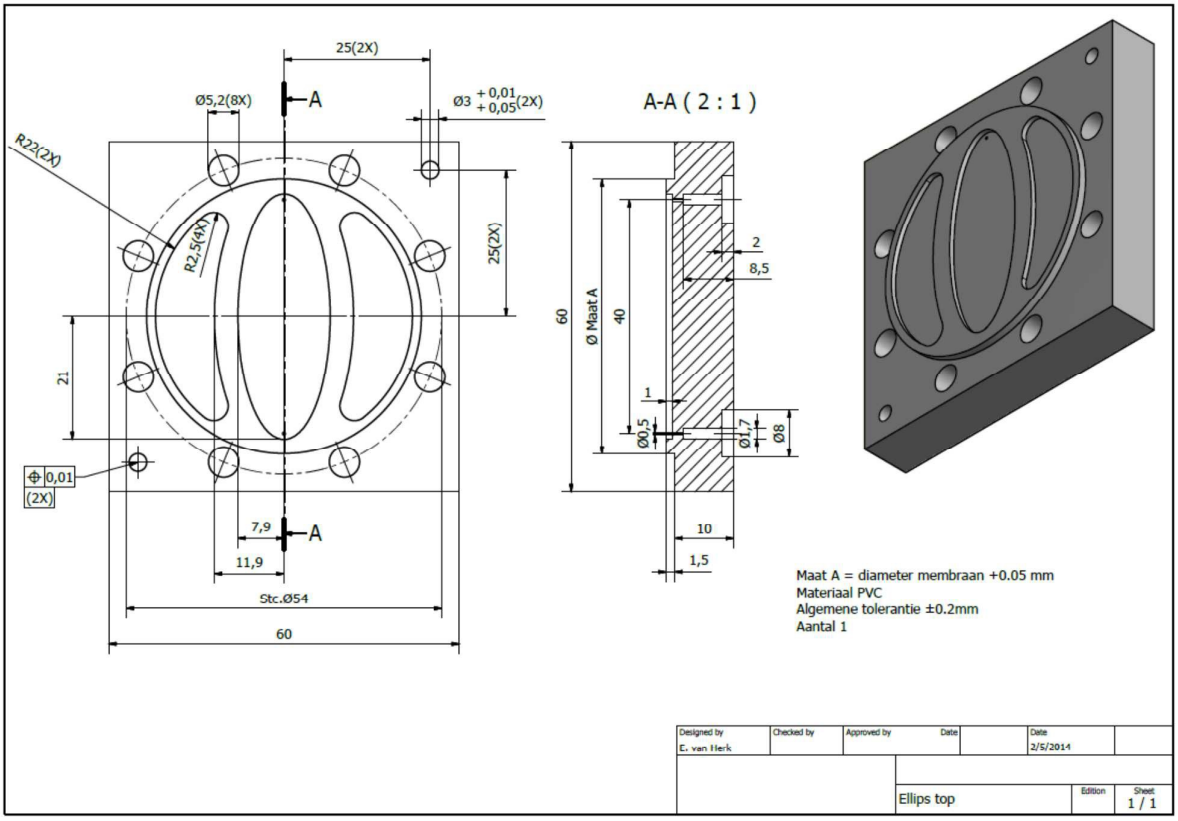
4.2 Continuous 2-step synthesis

4.2.1 Reaction setup for 2-step continuous synthesis of 2,6-dilfuorobenzyl azide

Reaction setup for 2-step synthesis consisted of the chlorination setup, shown in scheme S1, connected to a liquid- liquid separator, shown in scheme S3. Two inserts were modelled and fabricated from ETFE. Inserts were used to compress hydrophobic Zefluor membrane (P5PQ047), available from Pall Corporation. Two stainless steel holders were used to create a shell for the separator.

Scheme S3. Liquid-liquid membrane based separator (with a permission from [1]. Copyright © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

a. Design of the top insert with two drillings for inlet of slug-flow and outlet of aqueous phase.



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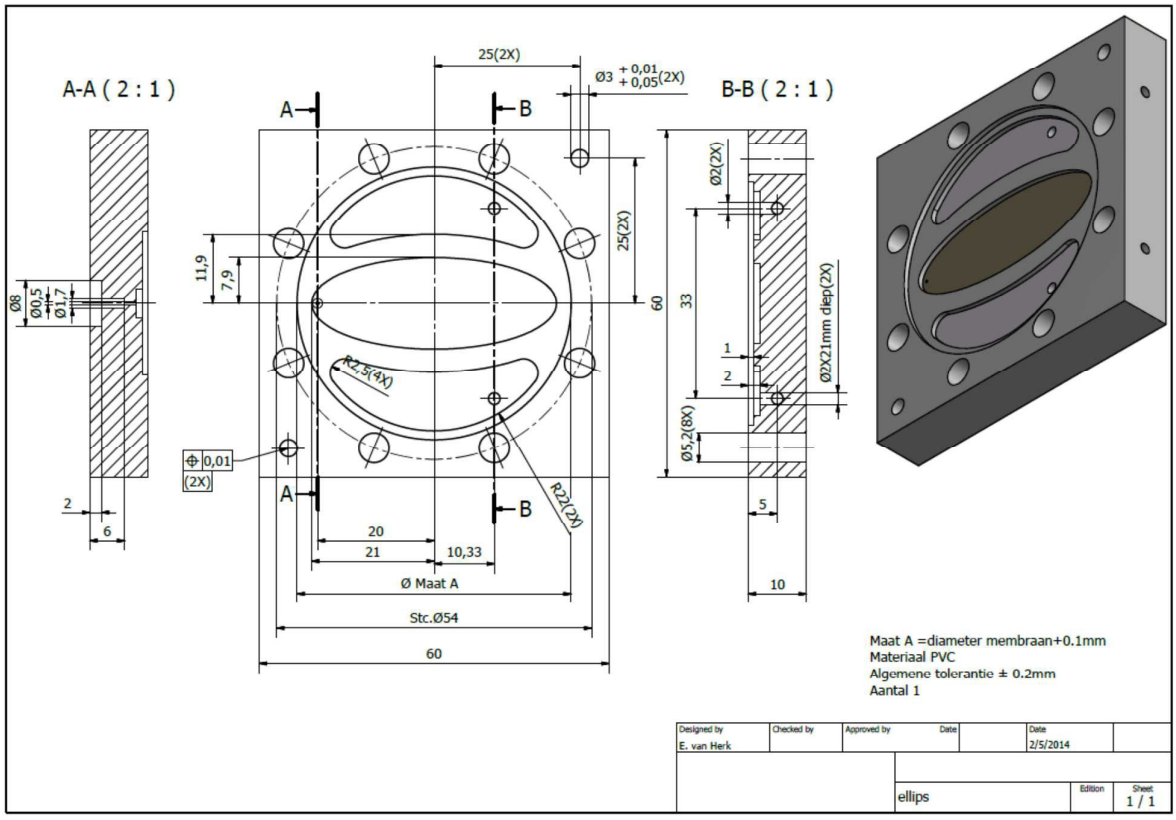
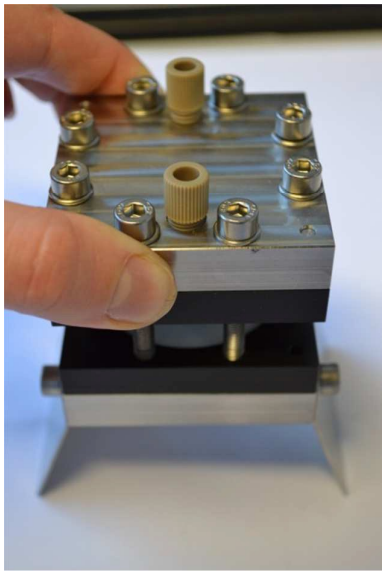
b. Design of the bottom insert with single drilling for outlet of organic phase.



c. Photograph of a liquid-liquid separator with white membrane in between two inserts.



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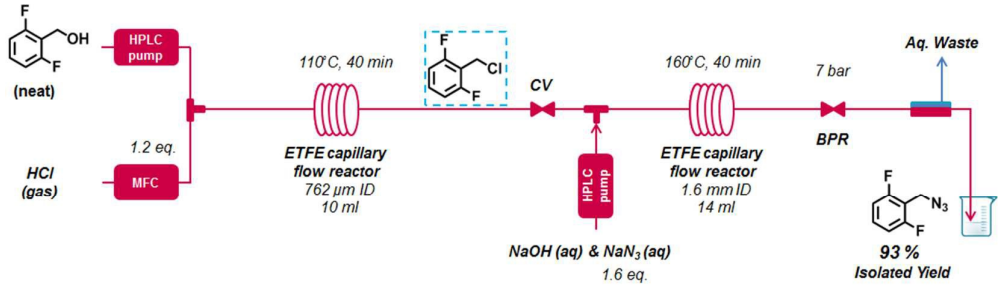
4.1.1 Experimental procedure for 2-step continuous synthesis

Two HPLC pumps were first purged with isopropanol. 2.6 gr (65 mmol) of NaOH and 26 gr (400 mmol) of NaN_3 were dissolved in water to yield 100 ml of solution. The first pump was purged with 2,6-difluorobenzyl alcohol, while the second with demi water. Meanwhile, the hydrogen chloride bottle was opened, followed by the mass flow controller being set to 0.05 g/min (1.4 mmol/min). All the reactors were connected and immersed into heating baths. A Y-mixer was attached to the gas, alcohol and reactor outlets. 2,6-difluorobenzyl alcohol was pumped at 128 µl/min (1.1 mmol/min). Another pump was set to 128 µl/min to pump pure water, and mixed streams flowed into a second reactor of 24 ml (1.6" ID). For this experiment two inline cartridge BPRs of 7 bar pressure were used. One BPR was attached first, after a significant pressure was attained within the reactor, the second BPR was attached. The first heating bath was set to 110℃, while second to 70℃. After one residence time (40 min), the pure water solution was replaced by the NaOH and NaN_3 solution and the flowrate was gradually increased to 460 µl/min. The second heating bath was set to 160℃. After the period equivalent to two residence times, the BPR outlet was connected to the inline liquid-liquid separator. An ultra-low volume adjustable BPR was attached to the aqueous outlet 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. The first millilitre of the product was discarded, which was followed by a collection.

Scheme S4. Schematic representation of setup assembled for 2-step continuous synthesis



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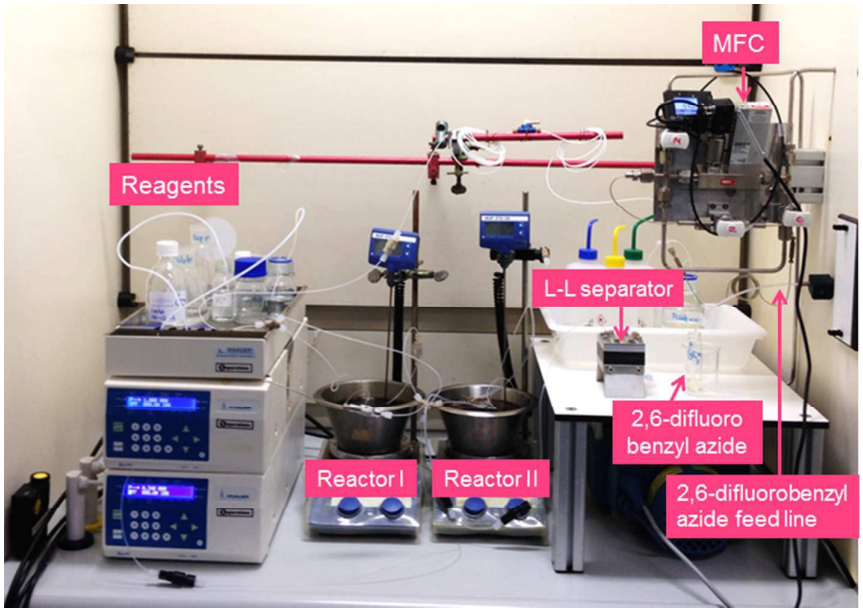
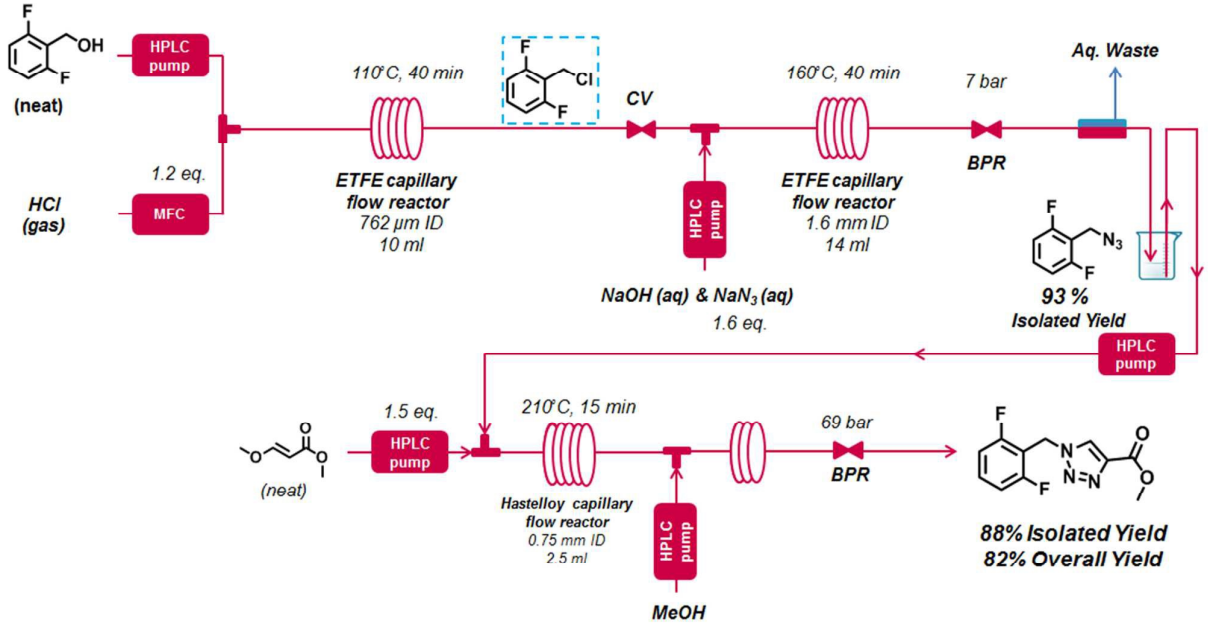
Scheme S5. Photograph of a setup for 2-step continuous synthesis



4.3 Synthesis of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate



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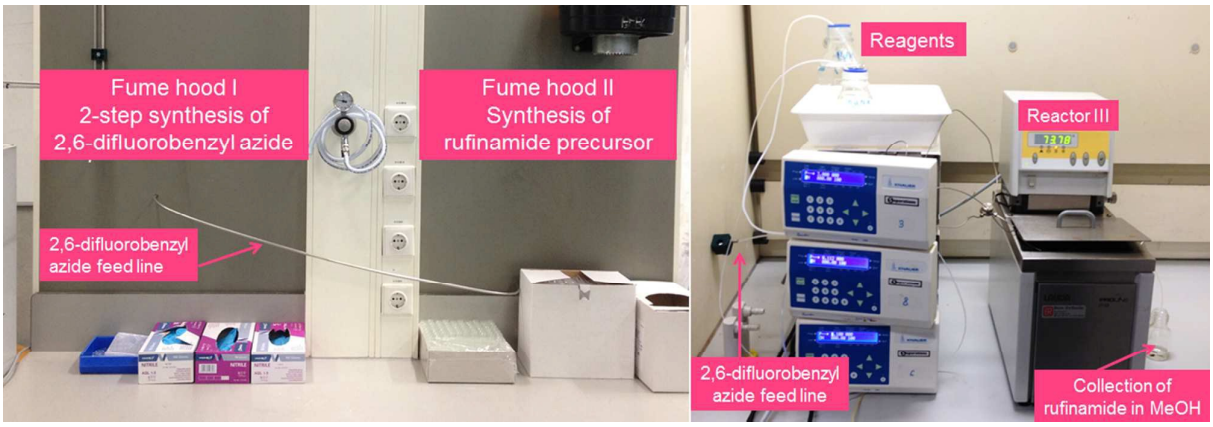
Scheme S6. Schematic representation of setup assembled for 3-step continuous synthesis of rufinamide precursor.



Experimental procedure for 3-step continuous synthesis of methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate:

All HPLC pumps were purged with isopropanol and later with either 2,6-difluorobenzyl azide, EMMA or methanol. The collected 2,6-difluorobenzyl azide was pumped at 100 µl/min (0.7 mmol/min) into a T-mixer to mix with EMMA, pumped at 112 µl/min (1.05 mmol/min), in order to proceed into 3.2 ml Hastelloy micro capillary reactor. MeOH was pumped at 3.2 ml/min (15 v/v) to dilute the product stream. A closed heating bath (Lauda Proline 8) was heated to 210℃ and 15 min residence time was allowed for the reaction to take place. After passing through a mixing zone of 1 ml volume Hastelloy micro capillary (0.04" ID) and BPR of 1000 psi, the product was collected. The collected solution was cooled to room temperature and later to 5℃ in the fridge overnight. The precipitated product was then filtered and dried under vacuum overnight. Yield 88%; mp 136-137℃; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 7.49 (m, *J*= 4 Hz, 1H), 7.15 (t, *J*= 8 Hz, 2H), 5.71 (s, 2H), 3.80 (s, 3H); ^{13}C (100 MHz, DMSO-d6) δ 162.43 (d, *J*= 8 Hz), 160.98, 159.95 (d, *J*= 7 Hz), 138.90, 132.30 (t, *J*= 10 Hz), 129.91, 112.38 (q, *J*= 5 Hz), 111.25 (t, *J*= 19 Hz), 51.25, 41.77 (t, *J*=4 Hz).