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Pressure-Accelerated Azide–Alkyne Cycloaddition: Micro Capillary versus Autoclave Reactor Performance

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Pressure effects on regioselectivity and yield of cycloaddition reactions have been shown to exist. Nevertheless, high pressure synthetic applications with subsequent benefits in the production of natural products are limited by the general availability of the equipment. In addition, the virtues and limitations of microflow equipment under standard conditions are well established. Herein, we apply novel-process-window (NPWs) principles, such as intensification of intrinsic kinetics of a reaction using high temperature, pressure, and concentration, on azide–alkyne cycloaddition towards synthesis of Rufinamide precursor. We applied three main activation methods (i.e., uncatalyzed batch, uncatalyzed flow, and catalyzed flow) on uncatalyzed and catalyzed azide–alkyne cycloaddition. We compare the performance of two reactors, a specialized autoclave batch reactor for high-pressure operation up to 1800 bar and a capillary flow reactor (up to 400 bar). A differentiated and comprehensive picture is given for the two reactors and the three methods of activation. Reaction speedup and consequent increases in space–time yields is achieved, while the process window for favorable operation to selectively produce Rufinamide precursor in good yields is widened. The best conditions thus determined are applied to several azide–alkyne cycloadditions to widen the scope of the presented methodology.

Introduction

High temperature, pressure, concentration, and/or addition of a catalyst can maximize the reaction kinetics of most chemical reactions.[1] Provided that the activation energy of a particular reaction is positive ($E_a > 0$), its reaction rate constant will increase at higher temperatures. Similarly, as long as the activation volume ($\Delta V^{\neq} < 0$) of a reaction is negative, increasing pressure will facilitate the reaction.[2] Thus, application of relatively high temperature and pressure on a reactive system may lead to a chemical intensification.[3] Novel process windows (NPWs) is a concept that embraces the opportunities presented by chemical and process-design intensification.[3] Reducing the size of equipment to a microscale leads to process intensification because of enhanced heat and mass transfer.[4] Continuous microflow operation is a very desirable method in pharmaceutical industry because of a possible high degree of control over reaction parameters, a higher safety, a reduced manual handling, a flexibility of production volume, an easier reproducibility, a possibility of reaction telescoping, and a potential for an integrated purification.[5] Even though high-temperature processing in microflow reactors resulted in numerous successful cases,[6] high-pressure operations, having a potential of accelerating reactions and directing selectivity, still constitute to a mystery nowadays. Up to now, pressure effects in microflow have been observed (i) under sub- or supercritical conditions and (ii) in enhancement of interfacial mass transfer for gas–liquid reactions.[7] In the case of pressure impact on a reaction with a negative activation volume as envisaged in this study, notable impact of the capillaries or microchips use was mostly achieved under non-continuous, stop-flow conditions.[7b]

Most of the powerful high-pressure installations can sustain a pressure of up to 3 GPa (30 000 bar) and are based on a diamond anvil cell or piston–cylinder-type reactors.[8] Such reactors supply new information on physical properties of matter as well as on reaction dynamics and mechanism. High fabrication cost, limited volume, high energy cost, and constrained safety are, however, the main reasons for not being widely applicable on a larger scale. To the best of our knowledge industrially used high pressure reactors have a range of 5–2000 bar and require special precautions, advanced safety control installation, regular check of tightened areas for leaks, and constant monitoring during the operation. In microflow, high pressure applications fall into a much narrower space of only 5–600 bar.[7e,9] A few hundred bars can be applied and sustained within a microflow reactor of any desired volume by using HPLC pumps equipped with an appropriate back-pressure regulator. It is expected that the handling of flow reactors at high pressures is generally easier.[7b] Flow reactors allow high pressures to be easily reached because of the smaller internal di-

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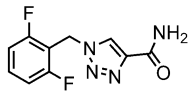
mensions and smaller overall size, low numbers of tightening areas, and variable volume for production.

As mentioned above, reactions with negative activation volume constitute a class of reactions facilitated by high pressure.[2] Thus, cycloaddition and condensation reactions, reactions proceeding via cyclic transition state (such as Cope and Claisen rearrangements), reactions involving the formation of dipolar transition states (such as electrophilic aromatic substitutions), and reactions with a steric hindrance can be influenced by high pressure. Moreover, based on the difference in volume occupied by a product, the distribution of reaction products can be altered. One of the most extensively studied class of reactions under high pressure are [4+2] Diels–Alder cycloadditions because of their wide application in general and their change in activation volume being the second most negative (-25 to -50 mL mol^{-1}).[10] High pressure was shown to direct regioselectivity of cycloaddition due to the difference in volume of regioisomers, changes in electronic demand, and steric hindrance.[11] Moreover, the combination of catalysis and high pressure was demonstrated to have a synergistic effect when a Lewis acids was used to catalyze the cycloaddition of a pyrrole derivative with an electron-rich diene.[12] Finally, high pressure affects the reaction medium by affecting its physical properties, such as boiling and melting points, density, viscosity, dielectric constant, compressibility, conductivity, and surface tension;[2,8a] however, this is out of the scope of the present study.

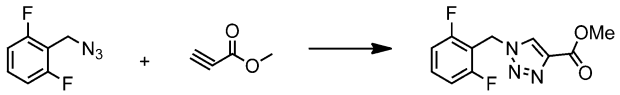
Several reactions have been performed in microreactors under high pressure and stop–flow regime. The nucleophilic aromatic substitution reaction of *p*-halonitrobenzenes with cyclic amines has been investigated in a microcapillary under batch conditions at pressures up to 600 bar.[7b] Rate enhancements by a factor of 2.7, 1.7, and 1.5 were observed for pyrrolidine, piperidine, and morpholine, respectively. The Diels–Alder reaction of 2- and 3-furylmethanol with maleimides, performed under elevated pressure, demonstrated that high pressure increases the rate of the 2-furylmethanol reaction with maleimides, which is less reactive than 3-furylmethanol under atmospheric conditions. A larger negative change in the reaction volume of the formation of the *exo* product in comparison to the *endo* product resulted in a slight increase in the amount of *exo* product formed. An increase of the reaction rate of the Diels–Alder reaction of cyclopentadiene with phenylmaleimide by a factor of 14 was observed upon increasing the pressure to 150 bar in a high-pressure glass microreactor. Razzaq et al[6e] and Tilstam et al.[13] reported multiple high-pressure, high-temperature acceleration of reaction rates of Newman–Kwart and Claisen rearrangements, a Fischer indole synthesis, and nucleophilic substitution.

Because of their lower activation volumes, [3+2] Huisgen cycloadditions are less studied under high pressure.[14] [3+2] Huisgen cycloaddition takes place when 1,3-dipole reacts with a dipolarophile to form five-membered cyclic compounds. Azides are a class of 1,3-dipoles, and their reaction with terminal alkynes results in a mixture of 1,4- and 1,5-cycloadducts, unless selectivity is directed by a catalyst in favor of a single cycloadduct.[14a] Azide–alkyne cycloaddition, when catalyzed by copper, serves as one of the best examples of a 'perfect' reaction termed as 'click' reaction.[15] In the last decade, click reaction became a synthetic tool with a special emphasis on the use of combinatorial chemistry to yield natural products on the way of drug development.[16] Copper-catalyzed cycloaddition of alkyl azides and terminal alkynes results in 1,4-substituted 1,2,3-triazole, which is the building block of many natural products.[17] One of the bestselling 200 drugs of recent years is an antiepileptic drug, 1,2,3-triazole-Rufinamide (Scheme 1).[18] The production process was initially developed by Novartis and is now realized by Eisai Ltd. under the commercial names Inovelon and Banzel. The anticonvulsant is used in the treatment of seizures associated with the Lennox–Gastaut syndrome of patients older than 4 years.[19] We have previously published a study on the combination of high concentration and high temperature, where relatively unreactive enol ether was used to synthesize the crystalline Rufinamide precursor under solvent-free conditions in a microcapillary reactor.[6a] Synthesis of Rufinamide completely based on continuous flow starting from 2,6-difluorobenzyl bromide and methyl propiolate was recently reported by Jamison et al.[20]



Scheme 1. Rufinamide structure.

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



Scheme 2. 1,3-dipolar cycloaddition to Rufinamide precursor.

Results and Discussion

The reaction of interest was studied using three systems different in operating pressure and temperature limits as well as in operation method. Details on the reaction methods can be found in the Experimental Section. We performed our investigations in three stages:

1. Batch experiment in a stirred glass round bottom flask under uncatalyzed conditions.
2. High-pressure and -temperature (HPHT) experiments in a non-stirred autoclave reactor under uncatalyzed conditions.
3. HPHT experiments in a HPHT flow reactor under uncatalyzed and catalyzed conditions.

Pressure and temperature windows in standard and autoclave batch reactors

We performed the cycloaddition in a stirred round bottom glass flask at 90 °C and 0.25 M of 2,6-difluorobenzyl azide in *N*-methyl-2-pyrrolidone (NMP). After 24 h 55 %yield of 1,4-cycloadduct was obtained, giving rise to 60 % yield in 6 days. The product distribution remained the same throughout the reaction with the ratio of the 1,4-/1,5-cycloadducts of 2.8:1. To determine the activation volume and pressure effect on 1,3-dipolar cycloaddition of 2,6-difluorobenzyl azide to methyl propiolate, we performed high-pressure experiments in the non-stirred autoclave batch reactor. Performing the reaction at 500 bar and otherwise same conditions resulted in a yield of 72 % of the 1,4-cycloadduct with increased preference to the desired product, giving a ratio of 3.6:1 for the 1,4- and 1,5-cycloadducts, as shown in Figure 1. Increasing pressure further resulted in a close to linear increase in yield. At 1800 bar, the upper limit of our investigations, a final yield of 84 % of the 1,4-cycloadduct, was achieved. Thus, an overall increase of 30 % in yield of the 1,4-cycloadduct was observed when compared to stirred batch conditions under atmospheric pressure. Regioselectivity increased in favor of the 1,4-cycloadduct with a 1,4-/1,5-cycloadduct regioisomeric ratio from 2.8 at atmospheric conditions to 6.3 at 1800 bar. Taking the reaction rate constant at 500 bar as reference and calculating relative multiplication factors of subsequent reaction rates lead to a calculation of an activation volume of −21.13 mL mol^{-1}, which is consistent with published results for 1,3- dipolar cycloadditions.[2b] Calculations of activation volume are described in the Supporting Information. Switching our focus to the temperature effect we performed the reaction at 1200 bar in batch reactor again for 24 h, under the same conditions). Lower yields due to the decomposition of 2,6-difluorobenzyl azide were obtained at higher temperatures, that is, 66 % and 2 % at 175 and 250 °C, respectively.

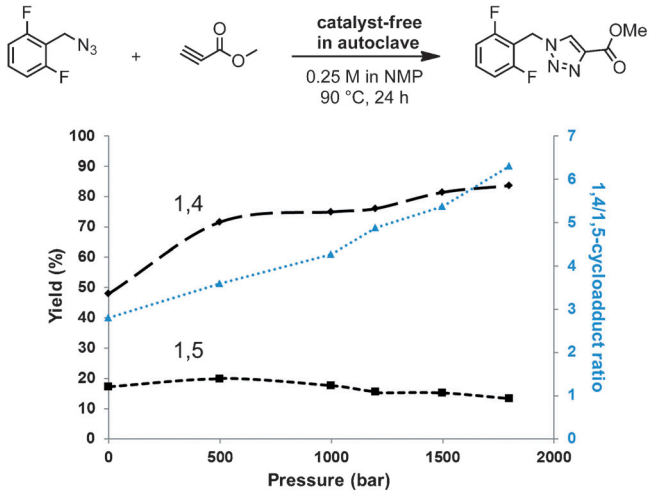


Figure 1. Pressure effect on the yield of uncatalysed azide–alkyne cycloaddition of 2,6-difluorobenzyl azide and methyl propiolate (2 equiv) when experiments were performed in high pressure autoclave reactor at 90 °C, 0.25 M for 24 h. Blue line represents yield ratio of 1,4- to 1,5 cycloadduct.

Pressure, temperature, and concentration windows in microcapillary reactor

Based on the availability of equipment, namely pumps and back-pressure regulators (BPRs), the maximum pressure reachable in our home-built microflow setup is 400 bar. Experience with batch experiments showed that reaction kinetics at relatively low temperature is relatively slow. Although possible, long reaction times in flow are not desirable. Thus, the uncatalyzed azide–alkyne cycloaddition under interest was studied in the HPHT microcapillary flow setup at a shorter reaction time than in batch. A residence time of 30 min and pressures up to 400 bar were allowed for the reaction at 90 °C. Under atmospheric pressure and same concentration of 0.25 M as in the batch experiment, 48 % yield of 1,4-cycloadduct was obtained in 30 min. An increase of pressure to 400 bar resulted in 58 % yield of the desired regioisomer. No significant change in product distribution was observed with increasing pressure: the product distribution increased from 3.5 at 1 bar to 3.6 at 400 bar. Increasing the temperature showed that the highest yield of 80 % of the 1,4-cycloadduct under the given the conditions could be obtained at 140 °C and 400 bar.

Next, we investigated the effect of residence time at various reaction temperatures. Figure 2 shows that the time effect is diminished at temperatures higher than 140 °C, resulting in a full conversion of 2,6-difluorobenzyl azide at all investigated residence times. Decrease in the yield is observed at temperatures higher than 140 °C and residence times of more than 10 min. This observation can be explained by the decomposition of 2,6-difluorobenzyl azide at high temperatures and longer contact times, similar to our previous study.[3b]

Reactions performed at higher concentrations have been proven to proceed in a safer manner in flow than in batch, with an additional benefit of faster kinetics. In this case, however, the temperature was kept constant at 90 °C for the sake of comparison with previously performed batch experiments and reducing the competing pressure and temperature effects. Increasing the concentration of 2,6-difluorobenzyl azide to 0.5 and 1.0 M was possible and speeded up the kinetics as shown in Figure 3. Throughout the whole investigated pressure range, an increase in yield of approximately 10 % was found for each concentration. The highest yield of 81 % of the desired 1,4-cycloadduct was obtained at 1.0 mol L^{-1}, 90 °C, and 400 bar at 30 min residence time.

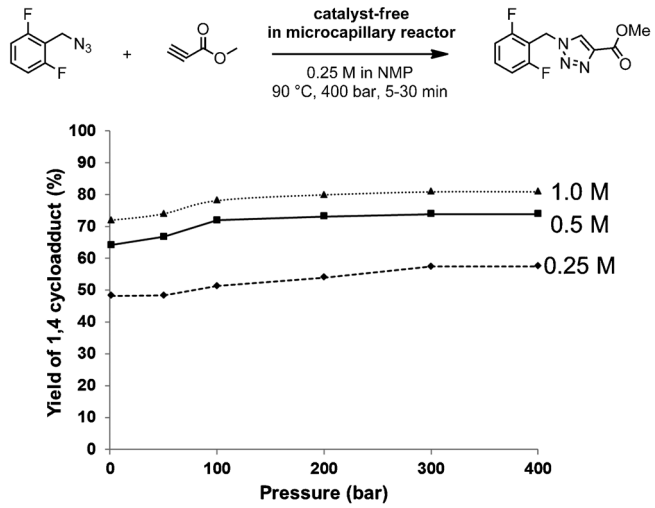


Figure 2. Temperature effect on the yield of 1,4-cycloadduct in [3+2] cycloaddition, when performed at 400 bar, 0.25 M and 5, 10, 20, and 30 min residence time.

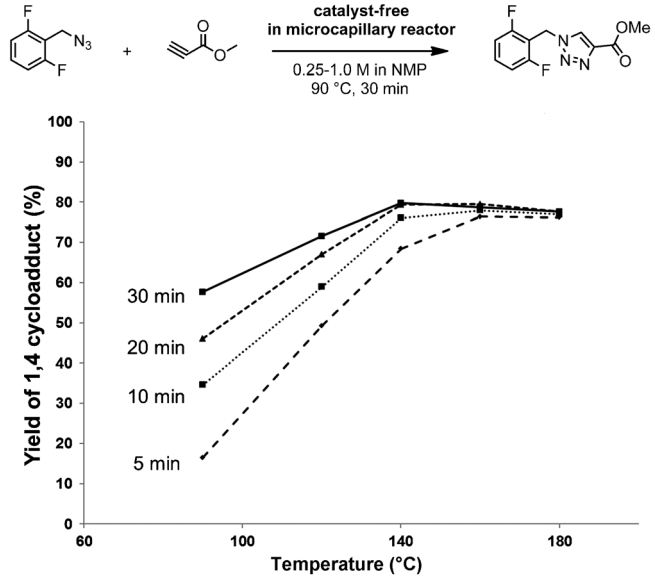


Figure 3. Pressure and concentration effect on yield of 1,4-substituted 1,2,3-triazole at different concentrations (0.25, 0.5, and 1.0 mol L^{-1}) for experiments performed at 1–400 bar in a high pressure flow setup at 90 °C and 30 min reaction time.

Concentration, pressure, and temperature windows in microcapillary reactor with catalyst

As mentioned in the Introduction, combination of catalysis and high pressure may have a synergistic effect.[12] When catalyzed by copper the azide–alkyne cycloaddition constitutes a class of Click reactions. According to mechanistic studies, copper directs the regioselectivity of cycloaddition. The directing power of copper varies for each different combination of catalyst and reactants based on their individual reactivity.[15] Thus, 100% regioselective cycloaddition is not always guaranteed. To test the merits of reaction activation and regioselectivity control by a catalyst, we tested a copper catalyst in a HPHT microcapillary-based flow system. We performed the copper-catalyzed cycloaddition by using 1.0 mol% of the homogeneous copper catalyst (1,10-phenanthroline)bis(triphenylphosphine)–copper(I) nitrate dichloromethane adduct ($[Cu(phen)(PPh_3)_2]NO_3$). The choice of the catalyst was based on its recently exhibited superior performance[21] resulting in 96% yield of the 1,4-cycloadduct in 3 min when phenyl acetylene and phenyl azide reacted under solvent-free conditions at room temperature in batch. We performed cycloaddition of methyl propiolate with 2,6-difluorobenzyl azide in NMP (0.25 M) at 90 °C. Only 5% of 1,4-cycloadduct was obtained after 90 min, whereas the formation of 1,5-cycloadduct was not observed. To perform the reaction in flow, an extra pump was used to introduce the copper catalyst into the stream of 2,6-difluorobenzyl azide before mixing with methyl propiolate. Premixing was reported to result in the formation of copper–alkyne aggregated complexes.[22] Methyl propiolate was introduced into the mixed stream through a High Pressure IMM mixer (with Reynolds number of 55) constructed for high pressure and based on flow lamination/hydrodynamic focusing (Figure 4). Increasing the concentration to 0.5 M under otherwise same conditions with no pressure applied and 1 min residence time, 7% yield of 1,4-cycloadduct was obtained. We studied the reaction with increased azide concentration of 0.5 M in the same range of process conditions as in the uncatalyzed case. Figure 5 shows rapid decrease in regioselectivity with increasing temperature, which speeds up the reaction as demonstrated by the increase of the 1,4-cycloadduct yield. The highest yield obtained was 77% of the desired cycloadduct, with a 1,4-/1,5-cycloadduct ratio of 4.2 at 160 °C in 5 min and in the presence of the copper catalyst. A slight increase in yield due to pressure is observed at moderate temperatures, which is less pronounced than for the uncatalyzed reaction in flow.

Figure 6 gives an overview of all the findings reported above with the boundaries of the process windows resulting in higher than 70% yield of the desired 1,4-cycloadduct. The pressure–temperature window for the uncatalyzed autoclave reactor is large, showing the good potential of this reactor and in general the wide flexibility commonly acknowledged for batch operation. It allows operation in pressure regions in which a flow reactor cannot be used at this point of time due to technological limitations. Moreover, a change in regioselectivity in favor of the desired regioisomer can be achieved. Yet, long processing times are needed, which results in a drop in productivity, thus requiring also more energy per given unit of manufactured product. Here, the much shorter processing times of the uncatalyzed flow reactor provide a good alternative, even more if safety under high pressure and energy minimization is an issue: activation by pressure is somewhat helpful, yet the big activation boost comes from the temperature and concentration flexibility. However, the small pressure effect is not intrinsic to flow, but the pressure range utilizable simply is lower for flow reactors at this time of technological development.

Figure 6 also shows the process window coordinates for the best yields obtained for the three processing types. The activation in the flow reactor is mostly temperature based and pres-

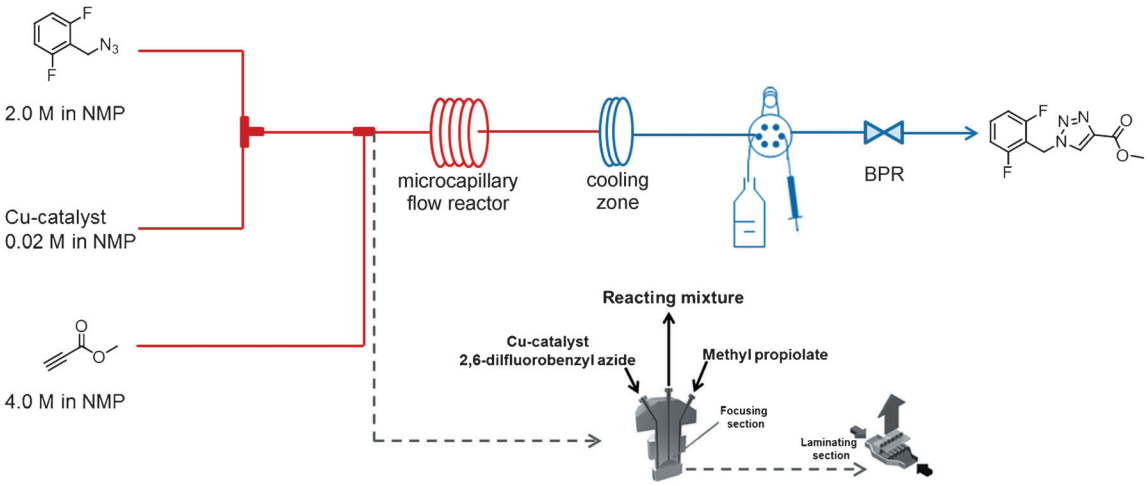


Figure 4. HPHT microcapillary-based flow system with added stream of homogeneous $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst. The setup consists of a stainless steel (SS) capillary, three HPLC pumps, T- and high-pressure IMM mixers, heating and cooling oil baths, sample loop connected to a six-port valve, and one BPR.

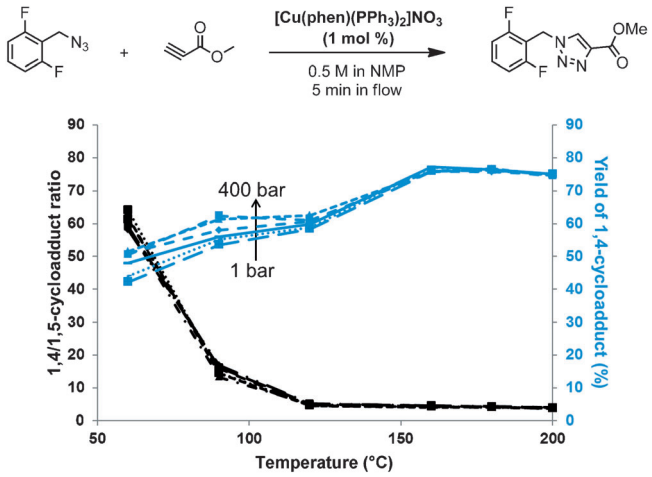


Figure 5. Temperature effect on the yield of 1,4-cycloadduct and regioselectivity expressed as a ratio of 1,4- to 1,5-cycloadduct in the presence of $[Cu(phen)(PPh_3)_2]NO_3$ as catalyst at various temperatures (60–200 °C) and pressures (1–400 bar).

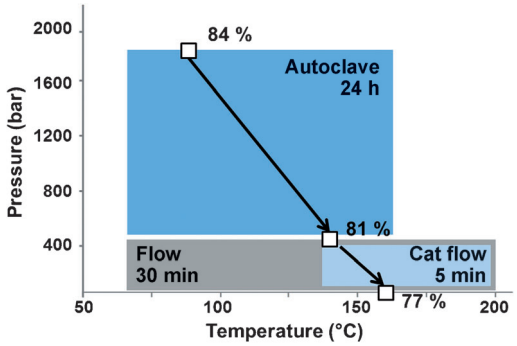


Figure 6. Process windows for the yields of desired regioisomer above 70% in high pressure autoclave reactor, uncatalyzed, and catalyzed processes in flow reactor.

sure-based for the autoclave reactor. The uncatalyzed reaction presents a case where both modes are used and this presents the core information of this paper. An additional difference is the time needed to achieve the yield, a 48-fold reduction in residence time is given for the uncatalyzed flow reactor compared to the uncatalyzed autoclave reactor.

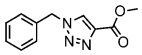
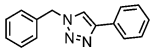
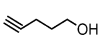
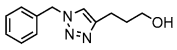
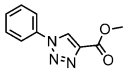
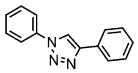
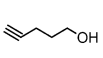
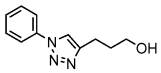
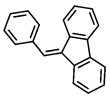
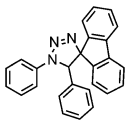
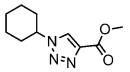
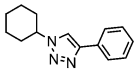
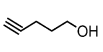
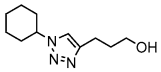
Use of a catalyst is justified at lower temperatures and longer residence times as only 1,4-cycloadduct is formed. Regioselectivity is rapidly reduced as the temperature increases, being highest at 25 °C when no formation of 1,5-cycloadduct is detected; the ratio of the 1,4-/1,5-cycloadduct is reduced to 64 at 60 °C and rapidly falls to 4.6 at 120 °C. An overview of the best conditions for flow in terms of yield of the 1,4-cycloadduct at 160 °C and 400 bar for 5 min shows that the merit of using a catalyst is an increase of only 1% in the yield of the desired product. The use of catalyst adds an additional downstream operation within the production process. Separation of toxic metal is required prior to the final stages of pharmaceuticals' production. It is evident that the flow operation demands the use of higher temperatures to achieve best yields.

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

Conclusions and Outlook

Novel process windows (NPW) principles were applied to the 1,3-dipolar cycloaddition to yield the Rufinamide precursor. The conditions for the activation of the reaction and the regioselectivity towards the 1,4-cycloadduct, the desired precursor, served as two foci of the study. Concerning both aspects, merits of high pressure, high temperature, high concentration,

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

Entry	Azide	Alkyne	Product (1,4-regioisomer)	Total yield[b] [%] 10 bar	400 bar	1,4-/1,5-cycloadduct 10 bar	400 bar
1				99	99	2.5	2.5
2				50	62	1.2	1.4
3				46	59	1.1	0.9
4				99	99	3.6	3.5
5				58	65	1.1	1.3
6				72	78	1.5	1.4
7				41	49	2.1	2.1
8				99	99	3.2	2.1
9				33	42	1.4	1.8
10				23	24	1.5	1.5

[a] Reaction conditions: azide (1 equiv, 0.25 M), alkyne (ene) (2 equiv, 0.5 M) in NMP at 140 °C for 30 min residence time. [b] Yields were calculated by using ^{1}H NMR spectroscopy with the use of 1,3,5-trimethoxy benzene as internal standard.

and catalyst were compared (four out of six NPW conditions as given in Ref. [3]). In addition, a comparison was made between a home-built high pressure autoclave and a high pressure and high temperature microcapillary flow reactors. The reaction was on the order of several days when carried out in a round bottom flask under atmospheric conditions, resulting in 60% yield after 6 days. In contrast, when the high-pressure autoclave reactor was used, speedup of the reaction kinetics and improvement in regioselectivity were observed. Increasing the concentration could speed up the reaction further; however, due to the possible decomposition of the azide and subsequent pressure buildup we did not pursue this option, which also would never be industrially viable. Use of such a reactor on production scale even within given limits is still questionable due to the fabrication costs and safety issues.

The flow reactor, on the other hand, can be scaled up by increasing the number of reactors and smart scale-out (small widening of characteristic dimensions) without a major loss of performance. Operation in a capillary flow reactor allowed to increase temperatures up to the superheated range, making use of pressures up to 400 bar and increase the reactants' concentrations. The combined action of these three activation methods resulted in a yield of 81% of the desired 1,4-cycloadduct in 30 min.

Copper-based catalysis was investigated as an additional activation method for the cycloaddition in the flow reactor. 76–77% yield at various individual temperature–pressure combinations for 5 min was obtained. Thus, although not optimized, the investigated process window showed that a fivefold acceleration is possible when compared with uncatalyzed flow operation. However, formation of the undesired 1,5-cycloadduct occurred even in the presence of the catalyst.

To provide a differentiated, comprehensive picture, process windows maps of favorable operation conditions (pure 1,4 isomeric yield $>70\%$) are given. The best conditions were applied to a wider selection of azides and alkynes.

The results obtained in this paper have also provided some insight into the often claimed easiness of pressure operation using microflow reactors. Indeed, data collection was much faster with the microflow setup because of faster heating, shorter reaction times, and easier sampling due to the installed sample loop. In addition, the much larger volume used for the autoclave reactor restricted exploration of temperatures above a certain limit. Thus, the range of information, with regard to the expansion of the process windows, was better for the microflow reactor. The combination of catalysis and harsh conditions was slightly advantageous when compared to the uncatalyzed process, where the presence of a catalyst required extra downstream operation, thus the overall benefit is higher when no catalyst is used with harsh conditions.

The consequences of the process design of our reaction intensification will be reported in a separate paper, including cost analysis and life-cycle assessment: Process-design intensification in flow improves cost, sustainability, and energy.[3,23] The design of continuous microflow-based processes enables either the use of new types of process integration or process simplification. Maximum impact is typically gained for entirely new chemical transformations only realizable in flow. Those, when combined in sequence as in multi-step syntheses, aim at compactness and, therefore, bring special attention to slow reactions that need to be intensified. In our case, the cycloaddi-

tion to synthesize the 1,2,3-triazole precursor of Rufinamide constitutes such a reaction.

A key to process-design intensification is a high space–time yield, allowing the preparation of very compact reactors, which facilitates or even enables system integration in electronics industry. Based on this motivation we calculated space–time yields for the three types of operation (and two types of reactors) investigated (Table 2). There is a never-completed discussion among the microreactor engineering community whether the inner or outer volume of the reactor is to be taken as reference. We used the inner volume (i.e., the fluid reaction volume) as reference to calculate the space–time yield. It is evident in both projections that the flow reactor is more productive than the autoclave reactor. The autoclave reactor, although offering a higher activation by pressure, has a limited and low volume. Naturally, our data are lab based and production reactors will behave somewhat different; however, this will not change the overall message. The compactness of the flow reactor resembles Ramshaw's first definition of process intensification: 'to shrink down the plant'.[24]

Table 2. Space–time yield for the three types of operation (and two types of reactors).

Operation type	Space–time yield [mol $L^{-1} h^{-1}$]
uncatalyzed autoclave reactor	0.0084
uncatalyzed flow reactor	4.56
catalyzed flow reactor	4.62

Experimental Section

Operating platforms—Process windows of reactors under study

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

The second system was a high pressure autoclave reactor setup with operating limits of 2500 bar and 300 °C. The 14 mL reactor was constructed according to the schematic representation shown in Figure 7 left. No copper or ruthenium-containing material was used in the construction of the reactor. Two heating jackets surrounded the upper and lower halves of the reactor. A thermocouple was inserted into one of the four inlets, with the tip located in the middle of the reactor. Two pumps were needed to deliver the reacting mixture and for the generation of a higher pressure. One of the pumps was auxiliary and was used to fill the syringe pump and the reactor with a reacting mixture whereas the syringe pump was used to apply pressure. The pressure was measured by a transducer located between the syringe pump and the reactor. A rupture disc with the upper limit of 2500 bar was inserted at another outlet of the reactor as a barrier with an emergency outlet. In case of a pressure build up higher than 2500 bar, the reactor contents would be sucked in from the reactor interior, thus minimizing the risk of the experiments. The components of the setup were connected as shown in Figure 7 right. Compounds bearing an azide group should be handled with caution. In a previous study we studied the decomposition of 2,6-difluorobenzyl azide using differential scanning calorimetry.[6a] To avoid any incidents caused by a possible nitrogen evolution upon decomposition of organic azide in the autoclave reactor ,we decided to keep the upper limit of concentration at 0.25 M.

The third platform was a HPHT microcapillary-based flow system (Figure 8), with operating limits of 400 bar and 300 °C. The setup consisted of a SS capillary (500 μm inner diameter, 10 m long), two HPLC pumps (Knauer 1000 series), heating and cooling oil baths (Lauda), sample loop connected to a six-port valve (Vici Valco), and one Bronkhorst BPR. HPLC pumps could be operated at pressures up to 400 bar whereas the BPRs kept the system at the set pressure. The SS microcapillary reactor was heated in the oil bath with upper temperature limit of 300 °C. A second bath was used to cool the reacting mixture with the goal of quenching the reaction and preparing the stream for safe sample collection. The valve was used as a sample collection loop so that the dead volume of the BPRs would not contribute to the residence time of reactants. The BPR was selected to be combined with a control valve applicable at relatively low flow rates, 2–20 mL min^{-1}. The residence time was manipulated by changing the flow rate and length of the capillary tubing. Due to the lower internal volume (2 mL) and faster processing, 1.00 M concentration of 2,6-difluorobenzyl azide was kept as an upper limit. Thus, the existing *p*–*T* process window of the standard batch reactor could be considerably widened by the use of more advanced reactors, such as autoclave and microflow reactors.

Synthesis

Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate in high pressure autoclave reactor: 2,6-difluorobenzyl azide (2.1 g,

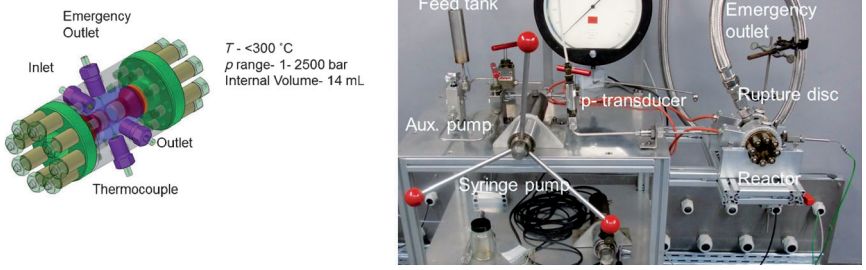


Figure 7. Left: Autoclave reactor with 14 mL internal volume and operating limits of 2500 bar and 300 °C. Four outlets: inlet, sample collection outlet, thermocouple, and connection to the safety line with rupture disk withstanding 2500 bar. Right: Autoclave batch high-pressure setup consisting of (from left to right) feed tank, auxiliary manual pump (250 bar), three valves, manual syringe pump (3000 bar), pressure transducer, and autoclave reactor surrounded with electrical heating jackets.

Figure 8. HPHT microcapillary-based flow system with operating limits of 400 bar and 300 °C. The setup consists of a SS capillary, two HPLC pumps, heating and cooling oil baths, sample loop connected to a six-port valve, and one BPR.

12.5 mmol) and methyl propiolate (2.1 g, 25 mmol) were dissolved in *N*-methyl-2-pyrrolidone (NMP; 50 mL). The solution was filled into the feed tank and pumped through the pipelines into the reactor. After the first drop leaving the reactor, the system was sealed, the last valve before the reactor was closed. The valve between auxiliary pump and the feed syringe was opened and the auxiliary pump was used to pump the solution from the feed tank into the syringe. After the syringe pump was filled, the valve was closed and the one next to the reactor was opened. By turning the 'steering wheel' of the syringe, the piston located within applied pressure. The turning was stopped at 200 bar below the desired set-point. The resulting mixture was then heated to 90 °C, and the resulting increase in pressure (if any) was measured. Upon heating the reactor, extra pressure buildup was observed. Finally, the pressure was adjusted to the final set-point and the reactor was left for 24 h. Demineralized water (10 mL) was added to a collected sample (14 mL), and the mixture was extracted using ethyl acetate (4×10 mL). The collected organic phase was washed using demi water (2×10 mL) and brine (1×10 mL) and dried over $MgSO_4$. All volatiles were evaporated under vacuum at 50 °C. For a further purification the precipitate was recrystallized from MeOH (1:10). mp 136–137 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.85$ (s, 1H), 7.50 (t, $J = 16$ Hz, 1H), 7.16 (m, $J = 12$ Hz, 2H), 5.73 (s, 2H), 3.81 ppm (s, 3H); ^{13}C (100 MHz, [D$_6$]DMSO): $\delta = 162.49$ (d, $J = 8$ Hz), 160.99, 160.00 (d, $J = 7$ Hz), 138.94, 132.30 (t, $J = 10$ Hz), 129.89, 112.38 (m, $J = 12$ Hz), 111.26 (t, $J = 19$ Hz), 51.24, 41.79 ppm (t, $J = 3$ Hz); ^{19}FNMR (400 MHz, [D$_6$]DMSO): $\delta = 114.05$ ppm (s, 2F); HRMS calculated for $C_{11}H_9F_2N_3O_2Na$ 276.0561, found 276.0566 (M^+Na^+). ^{1}H chemical shifts are reported in ppm downfield from tetramethylsilane (TMS), whereas ^{13}C chemical shifts are reported downfield from TMS with the resonance of the [D$_6$]DMSO as the internal standard.

Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate in flow reactor: 2,6-difluorobenzyl azide (5.1 g, 30 mmol) and propiophenone as internal standard (0.8 g 6 mmol) were weighed and diluted to 60 mL using NMP; methyl propiolate (5.0 g, 60 mmol) was diluted to yield 60 mL. The solutions were pumped using two pumps to be mixed in a T-mixer, resulting in 0.25 M solution of 2,6-difluorobenzyl azide and 0.5 M solution of methyl propiolate. The reactants reacted in a reaction zone of 2 mL internal volume. The flow rates were adjusted based on the desired residence time. The reaction zone was heated inside the oil bath while pressure was applied using a BPR. A sample loop was installed between the cooling zone and the BPR to allow sample collection with accurate residence time. The temperature for cooling was kept at 20 °C regardless of the temperature of the reaction mixture. After flushing three reactor volumes to ensure steady-state data collection, three samples were collected. 250 μL was collected each time within the loop and pushed into a GC-vial using a syringe filled with an acetonitrile/water (50:50) mixture. The contents of the GC-vial were then analyzed using a GC (for 2,6-difluorobenzyl azide conversion) and a HPLC (for the determination of the yield); calculations are based on internal standard. Notes: The thermal stability of the internal standard was investigated prior to the experiments.

Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate in flow reactor (catalyzed): 2,6-difluorobenzyl azide (71.0 g, 420 mmol) and 1,3,5-trimethoxybenzene (internal standard; 14.1 g, 84 mmol) were weighed and diluted to 240 mL using NMP; $[Cu(phen)(PPh_3)_2]NO_3$ (3.7 g, 4.2 mmol) was diluted to 240 mL using NMP whereas methyl propiolate (35.3 g, 420 mmol) was diluted to 420 mL. Solutions were pumped using three pumps to be mixed in a T-mixer: 2,6-difluorobenzyl azide and catalyst mix first, later a stream of methyl propiolate was introduced to result in a 0.5 M solution of 2,6-difluorobenzyl azide and a 0.5 M solution of methyl propiolate. Reactants reacted in the reaction zone of 2 mL internal volume. Flowrates were adjusted based on the desired residence time. The reaction zone was heated inside the oil bath while pressure was applied through a BPR. A sample loop was installed between the cooling zone and the BPR to allow sample collection with accurate residence times. The temperature for cooling was kept at 20 °C regardless of the temperature of the reaction mixture. After flushing three reactor volumes to ensure steady-state data collection, three samples were collected. 250 μL were collected each time within the loop, pushed out into a GC-vial using syringe filled with an acetonitrile/water (50:50) mixture. Contents of the GC-vial were then analyzed using a GC (for 2,6-difluorobenzyl azide conversion) and a HPLC (for the determination of the yield); calculations are based on internal standard.

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Keywords: 1,3-dipolar cycloaddition · high pressure · microflow chemistry · novel process windows · rufinamide

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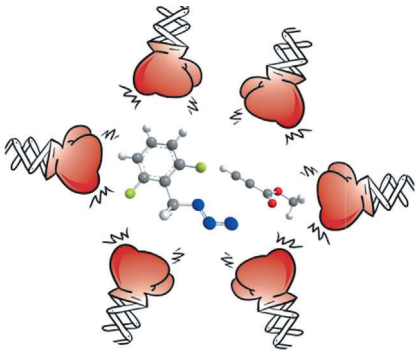
Pressure-Accelerated Azide–Alkyne Cycloaddition: Micro Capillary versus Autoclave Reactor Performance



Press to access! The potential of pressure in chemical intensification of intrinsic kinetics of 1,3-dipolar cycloaddition is investigated along with high temperature and concentration effects. Two reactors are compared, a specialized autoclave batch reactor for high-pressure operation up to 1800 bar and a capillary flow reactor for up to 400 bar. Reaction speedup and increases in space-time yields are reached while widening process windows of favorable operation to selectively produce Rufinamide precursor in good yields.