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Continuous Flow Synthesis of a Key 1,4-Benzoxazinone Intermediate via a Nitration/Hydrogenation/Cyclization Sequence

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Supporting Information

ABSTRACT: The preparation of a functionalized 4H-benzo-[1,4]-oxazin-3-one was completed via a three-step nitration/hydrogenation/cyclization sequence. The unstable nature of the nitro and amino intermediates, in addition to the hazards associated with the nitration of organic compounds in general, makes this procedure exceedingly difficult to perform on industrial scale. To overcome these limitations, we have developed a fully integrated continuous protocol in which the aromatic starting material (2,2-difluoro-2-(3-fluorophenoxy)-*N*,*N*-dimethylacetamide) is subjected to an initial continuous flow dinitration using 20% oleum in combination with 100% HNO_3 (2.5 equiv) using a microstructured device heated to 60 °C. This was followed directly by continuous flow hydrogenation of the dinitrointermediate over a Pd/C fixed bed catalyst at 45 °C. The resulting air-sensitive diamino derivative was then directly cyclized to the desired 6-amino-2,2,7-trifluoro-4H-benzo-[1,4]-oxazin-3-one target compound via an acid-catalyzed cyclization step at 80 °C using a tubular reactor. Uninterrupted continuous flow processing was achieved by integrating liquid−liquid membrane separation technology and the inline removal of excess of hydrogen gas using gas permeable tubing into the process. The overall product yield for the continuous flow process was 83%, a significant increase compared to yield reported for the batch process (67%).

INTRODUCTION

Benzoxazinones are an important class of naturally occurring compounds involved in the defense mechanisms of plants against pests.[1] Owing to their well-known antifungal, antimicrobial, phytotoxic, and antifeedant properties, benzoxazinone derivatives are being the subject of intense research efforts as natural templates for the preparation of novel herbicides.[1,2] Certain benzoxazinones also possess interesting pharmacological properties, with applications as analgesics and muscle relaxants, anti-inflammatories, antidepressants, or anticontraceptives.[3] Therefore, extensive research on structure−activity relationship, phytotoxicity enhancement, as well as development of efficient synthetic routes toward these types of compounds have been carried out over the past few decades.[2]

While the biosynthetic route for the generation of benzoxazinones in plants follows the indole pathway,[4] chemists have developed many alternative synthetic procedures starting from readily available precursors,[2] thus enabling access to tailored benzoxazinones with enhanced biological properties. In this context, 6-amino-2,2,7-trifluoro-4*H*-benzo-[1,4]-oxazin-3-one (**1**) (ABO) (Figure 1) is an important intermediate in the preparation of herbicidal benzoxazinones for phytosanitary compositions.[5]

Using 2,2-difluoro-2-(3-fluorophenoxy)-*N*,*N*-dimethylacetamide (FPAA, **2**) as starting material the desired ABO compound can be prepared in a three-step sequence (Scheme 1).[6] In the first step FPAA (**2**) is dinitrated using a suitable nitrating mixture. Then, the nitro groups are selectively reduced and the resulting diamino-FPAA (**4**) is then cyclized under acidic conditions (Scheme 1). This apparently straightforward

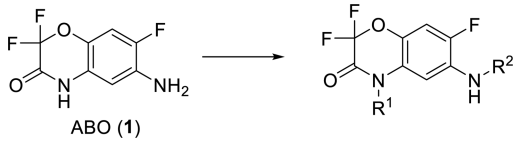

Figure 1. Preparation of herbicidal benzoxazinones from ABO.

procedure presents, however, significant complications especially when carried out on large scale. The first intermediate in the sequence, dinitro-FPAA (**3**), is a potentially explosive material as indicated by the Könen tube test.[7] Thus, isolation, handling and/or storage of the dinitro intermediate **3** is undesired, especially in large quantities. Moreover, diamino-FPAA (**4**) is an unstable, air and light sensitive compound, particularly problematic when stored in solution. Due to these limitations, a one-pot sequential process which directly transforms FPAA (**2**) into ABO (**1**) would be highly desirable.

Apart from the above-mentioned issues related to the stability of the dinitro- and diamino-FPAA intermediates **3** and **4**, nitration and hydrogenation reactions on their own constitute inherently hazardous transformations when performed on a large scale. Nitration reactions are generally highly exothermic and constitute one the most hazardous industrial processes.[8] Safety risks are even more significant when the produced nitro compound has explosive properties as in the case of dinitro-FPAA (**3**). Against that background, continuous flow processing has been shown as a safe alternative for the

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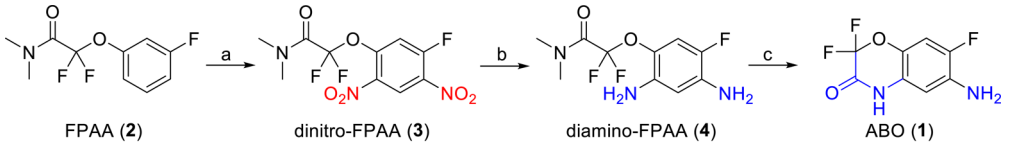
Scheme 1. Synthetic Sequence for the Preparation of the ABO Benzoxazinone.[6]



generation and use of hazardous reaction intermediates.[9] The enhanced heat transfer experienced in microfluidic devices can control the exotherm generated during nitration reactions. Therefore, these hazardous processes can be carried out in a safe, controlled, and scalable manner using flow devices.[9] Application of these principles to nitration reactions have received particular attention, with examples being reported as early 1956.[10,11] A typical experimental setup for continuous nitration of aromatic compounds consist of two feeds, containing the substrate and the nitrating agent, respectively. The two feeds are mixed in a micromixing device under thermostated conditions, followed by a residence time unit.[11] Catalytic hydrogenations using batch conditions are also inherently hazardous as pressurized hydrogen gas can cause explosions. Thus, pressure resistant autoclave reactors and special safety precautions are typically required.[12] Continuous flow hydrogenation is a common technique in modern organic synthesis,[13] and specifically designed reactors for catalytic hydrogenations on laboratory scale are commercially available. In addition to the safe, on demand generation of hydrogen gas characteristic of this type of devices, prepacked catalyst cartridges are employed, thus avoiding the handling of often pyrophoric metal catalysts.[13]

To overcome the above-mentioned issues for the large scale preparation of this type of benzoxazinones, we envisaged a fully continuous flow protocol for the synthesis of ABO **1** in which FPAA (**2**), used as starting material, is subjected to a sequential continuous flow nitration/hydrogenation/cyclization. The explosive dinitro-FPAA (**3**) generated is extracted from the nitrating mixture using a suitable organic solvent and separated with a continuous liquid–liquid membrane separator. The organic phase is then subjected to continuous hydrogenation, immediately consuming the dinitro-FPAA (**3**) without the need for isolation or purification, thus avoiding the handling of this dangerous material. The resulting solution of the labile diamino-FPAA (**4**) is directly acidified and heated under flow conditions, providing the desired ABO product (**1**) via a cyclization process. Herein, we describe in detail a fully continuous uninterrupted three-step process for the generation of ABO (**1**) on a laboratory scale.

RESULTS AND DISCUSSION

Initial Considerations. Our study initiated with a batch investigation and continuous flow optimization of the dinitration reaction. In principle, nitration of FPAA (**2**) to dinitro-FPAA (**3**) is the most challenging reaction step in the sequential process and we expected to face several issues regarding temperature control and mixing efficiency. The hydrogenation of dinitro-FPAA (**3**) to diamino-FPAA (**4**) is the only step in the sequential process in which the scale cannot be easily modified using the lab scale H-Cube Pro hydrogenator.[13] This is due to the fact that the packed bed reactors (CatCarts) have fixed dimensions (70 × 4 mm, 0.8 mL internal volume). Thus, the flow rate and throughput (mmol h^{-1}) of the overall process will depend on the maximum flow rate that can be used in the H-Cube Pro hydrogenation since the reactor dimensions cannot be increased. All other reactor parts (nitration, separation, cyclization) will therefore have to be adapted to the optimal flow rate of this reaction step. Thus, when the hydrogenation in the H-Cube Pro was optimized, the obtained maximum throughput was used to develop the other reactor parts building two separate continuous setups: (1) dinitration/liquid–liquid extraction/phase separation; (2) hydrogenation/gas removal/cyclization. Once both processed were individually optimized the complete setup was constructed using the optimized reaction parameters.

Crude reaction mixtures have been analyzed by quantitative HPLC (215 nm), GC-MS, and in the case of the final ABO product ICPMS analysis has been carried out to determine any potential leaching of the Pd catalyst during the hydrogenation (for details on the analytics and experimental procedures see the Experimental Section and Supporting Information).

Nitration of FPAA (2): Batch Experiments and Continuous Flow Optimization. The patent procedure for the synthesis of dinitro-FPAA (**3**) utilizes 100% HNO_3 (4.7 equiv) combined with concentrated H_2SO_4 (98%) and occurs at 40 °C during a period of 3 h.[6] Our initial goal was to optimize the dinitration reaction conditions to reduce as much as possible the reaction time and enhance the selectivity of the process. As small amounts of water in the reaction mixture can easily cleave the ArO–CF_2 bond 98% H_2SO_4 was substituted by oleum (20% free SO_3) to scavenge the water which is formed during the nitration.

A set of preliminary batch experiments was carried out in order to obtain information on the required reaction time, temperature, and amount of nitrating agent required. For this purpose silicon carbide (SiC) parallel heating platforms[14] were used to ensure rapid heat transfer to the reaction mixture (see Experimental Section for details). As the initial exotherm produced during the reagents mixing is expected to affect the observed reaction time, addition of the substrate to the nitrating mixture was carried out slowly (over 1 min) at 0 °C. Subsequently, the vial containing the reaction mixture was transferred to a SiC platform preheated at the desired temperature. The data obtained (Figure 2) reveal that at 50 °C the reaction is not complete after 30 min, both when 2.2 equiv or 2.5 equiv of 100% HNO_3 were used. The temperature was then increased to 60 °C and the amount of nitrating agent kept at 2.5 equiv. Under these conditions good results were obtained, with a 95% conversion to the desired dinitro-FPAA (**3**) (HPLC analysis) in the crude reaction mixture. These conditions (2.5 equiv HNO_3, 60 °C, 30 min) were selected for the initial flow experiments. It is worth noting that an alternative protocol using NH_4NO_3 as a nitrating agent was also evaluated. In this case the reaction was much faster, and after ca. 15 min nearly full conversion is obtained (see Figure S4 in the Supporting Information). However, due to safety

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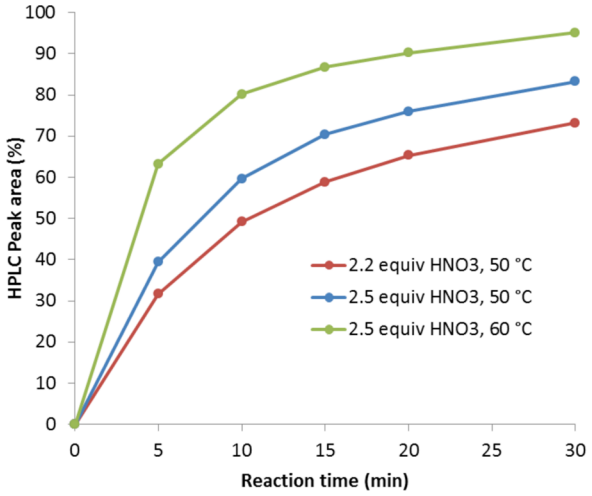

Figure 2. Preliminary batch experiments for the dinitration of FPAA (**2**).

reasons relating to the potential use of NH_4NO_3 on large scale reactions using this reagent were not further evaluated.

The initial flow setup consisted of two feeds containing a sulfonitric mixture (5 M HNO_3 in oleum) prepared in a volumetric flask (Feed A) and the neat substrate FPAA (**2**) (Feed B) (for details see Figure S5 in the Supporting Information). Oleum is highly corrosive for many materials, and therefore the components of the setup had to be carefully selected. The two feeds were injected using glass syringe pumps (Syrris), and were mixed in a standard Teflon T-mixer (i.d. 0.5 mm). Perfluoroalkoxy alkanes (PFA) tubing and Teflon connections were used in all the reactor parts. Other connection materials, such as PEEK, showed rapid degradation in contact with the nitrating mixture.

For the preliminary flow experiments a total flow rate of 100 μL min^{-1} was selected. The correct stoichiometry is hence achieved using 73.6 μL min^{-1} for Feed A and 26.3 μL min^{-1} for Feed B. HPLC analysis of aliquots of the crude reaction mixture collected from the reaction output revealed a nonconstant conversion/purity profile over time most probably due to inefficient mixing of the reaction components in the standard T-mixer (Figure 3). The nitrating mixture in oleum as well as the neat FPAA (**2**) substrate are very viscous liquids.[15] When

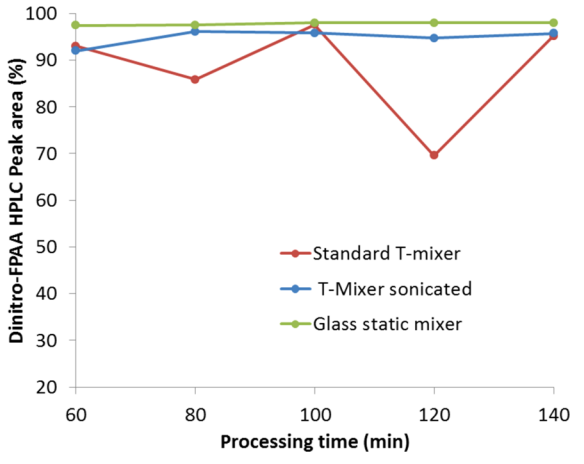

Figure 3. Conversion profiles obtained for the continuous flow dinitration of FPAA (**2**) using different mixing methods.

the continuous mixing in the flow reactor is not at adequate concentration gradients, inhomogeneous mixtures will be produced along the tubing, resulting in a nonconstant composition of the crude reaction mixture obtained over time. Notably, an improved conversion profile was obtained when the T-mixer was sonicated during processing (Figure 3). Gratifyingly, excellent and constant conversion and purity for the dinitro-FPAA **3** were achieved when a glass static mixer (Uniqsis, 1 mm i.d. channels with active mixing geometries, 1.5 mL internal volume) was installed. In this case the mixer (1.5 mL internal volume) was used both for mixing and as residence time unit. Thus, it was directly immersed in the water bath at 60 °C. For this experiment the flow rate was reduced to 67 μL min^{-1} in total. At this flow rate the residence time is ca. 18 min. Under these conditions a constant stream with high purity for the desired dinitro-PFAA (**3**) was obtained during the complete processing time (see Figure 4).

To demonstrate that the dinitration process can be readily scaled using our optimized conditions we decided to intensify the process by increasing the throughput to 1 mmol min^{-1}. Thus, the injection of neat FPAA **2** was increased to 179 μL min^{-1} and the nitration mixture to 500 μL min^{-1}. To compensate this flow rate increase and keep the residence time constant an additional residence time unit (PFA tubing, 0.8 mm internal diameter, 13.5 mL internal volume) was installed at the output of the glass static mixer (Figure 5). Moreover, two additional feeds with water (quench) and toluene were incorporated to obtain a solution of dinitro-FPAA (**3**) in the organic solvent suitable to be used for the next step of the synthesis. The flow rate for the toluene and water in the intensified process were set to 3.3 mL min^{-1} and 5 mL min^{-1}, respectively, and mixed in an ice bath (0 °C) to avoid a possible partial nitration of toluene with the excess of nitric acid. At these flow rates a 0.3 M solution of dinitro-FPAA (**3**) in toluene can be obtained. The setup was run and after 1 h of stabilization several fractions of the biphasic mixture were collected at intervals of 5 min. Quantitative HPLC analysis of the organic phase revealed an average yield for the desired dinitro-FPAA (**3**) of 93%.

Continuous Flow Hydrogenation of Dinitro-FPAA (3). Hydrogenation reactions employing heterogeneous catalysts in fixed bed reactors exhibit several benefits using continuous-flow processing apart from the obvious safety advantages.[12] In continuous flow hydrogenations, the hydrogen/substrate mixture is pumped through packed catalyst columns by high-pressure pumps (Figure 6). Due to the large interfacial areas and the short diffusion paths in the packed columns, very efficient gas−liquid−solid interactions, and thus hydrogenation, takes place.[12]

Hydrogenation of dinitro-FPAA (**3**) under continuous flow conditions was performed in a commercial high pressure hydrogenator (H-Cube Pro, Thales Nanotechnology Inc.) enabling heterogeneous hydrogenations at temperatures up to 150 °C and 100 bar of hydrogen pressure.[12] The reaction mixture is introduced into the reactor by a HPLC pump (max 3 mL min^{-1}). The system was equipped with a prepacked, commercially available cartridge (70 mm length ×4 mm i.d., 0.8 mL volume) of the heterogeneous 10% Pd/C catalyst. In all cases, the instrument was set to "full H_2" mode which corresponds to a gas flow rate of 60 mL min^{-1}.

The nitration/extraction process preceding the hydrogenation step produces a solution of dinitro-FPAA (**3**) in toluene, which then enters the H-Cube Pro hydrogenator.

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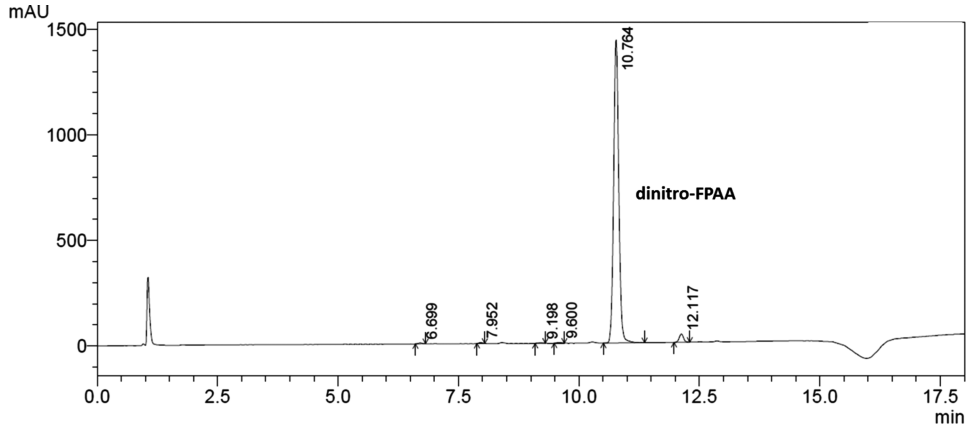

Figure 4. Representative HPLC chromatogram (215 nm) of the crude nitration reaction mixture obtained from the reactor output using the glass static mixer.

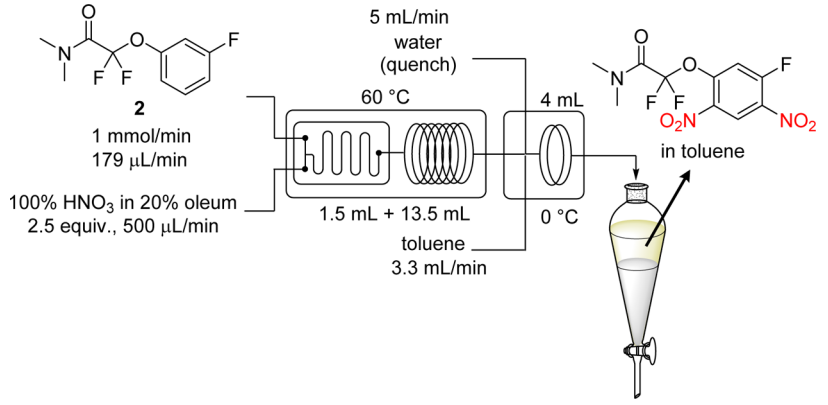

Figure 5. Continuous flow setup for the continuous dinitration process using an increased throughput of 1 mmol min^{-1}.

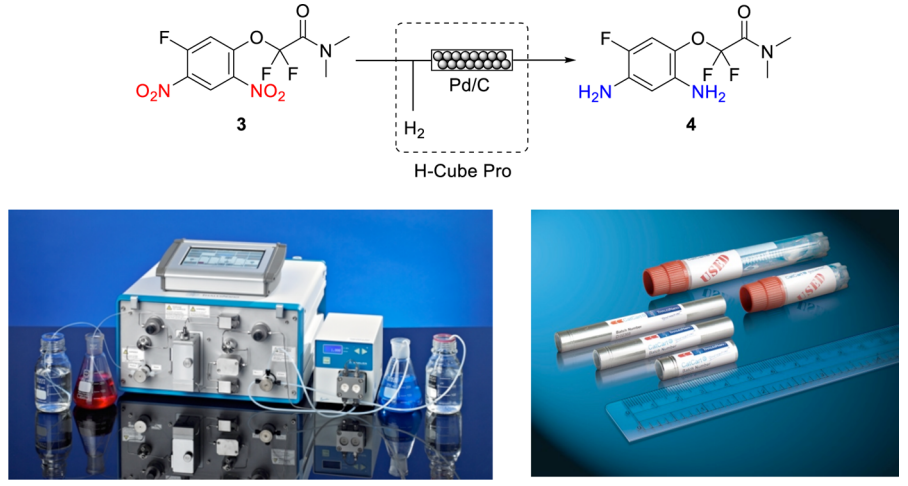

Figure 6. Schematic diagram of the continuous flow hydrogenation of dinitro-FPAA (**3**) (top), and H-Cube Pro continuous flow hydrogenator and prepacked CatCart column reactors used in this work.

However, the resulting diamino-FPAA (**4**) product is not soluble in toluene and clogging of the reactor may occur during the hydrogenation if no cosolvent is added. Solubility tests indicated that diamino-FPAA (**4**) is well soluble in a toluene/methanol 2:1 mixture even at a concentration of 0.2 M. Thus, addition of methanol after the liquid/liquid extraction step is necessary.

A set of continuous flow reductions was carried out to establish the optimal reaction conditions, in particular H_2 pressure and flow rate. A 0.2 M solution of dinitro-PFAA (**3**) in toluene/methanol 2:1 was used as starting reaction mixture in all cases, and the temperature was set to 45 °C in accordance with the literature batch protocol.[6] The results (Table 1) indicated that a successful reduction can be carried out up to a flow rate of 1 mL min^{-1}. Although dinitro-FPAA (**3**) was consumed in all cases, it was not fully converted to diamino-FPAA (**4**) when a flow rate of 2 mL min^{-1} was employed, even at a pressure of 20 bar. In these cases variable amounts of the

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Table 1. Results Obtained for the Continuous Hydrogenation of Dinitro-FPAA 3 in the H-Cube Pro Using Pd/C as Catalyst

entry	flow rate (mL min^{-1})	pressure (bar)	substrate conversion (%)[a]	diamino/monoamino selectivity (%)[b]
1	0.5	1	> 99	> 99
2	1	1	> 99	> 99
3	1	10	> 99	> 99
4	1	20	> 99	> 99
5	2	1	> 99	21
6	2	10	> 99	38
7	2	20	> 99	77

[a]HPLC peak integration area (215 nm). [b]GC-MS peak integration area.

nitro/amino-FPAA intermediate were observed. HPLC and GC-MS analyses of the crude reaction mixtures obtained at 1 mL min^{-1} revealed that the desired diamino-FPAA (**4**) was obtained in very high purity (see Figure S6 in the Supporting Information), with small amount of the final ABO (**1**) material being the main side product.

As mentioned above, the scale of the hydrogenation reaction using the H-Cube Pro instrument is limited by the size of the commercially available CatCart catalyst cartridges (70 mm length ×4 mm i.d., 0.8 mL volume). Under these conditions an optimal productivity of 0.2 mmol min^{-1} can be obtained. This value was used as reference for adjusting the flow rates of the other parts of the sequential process adapted for a throughput of 0.2 mmol min^{-1}.

Sequential Continuous Dinitration/Liquid–Liquid Extraction Process. With the aim of obtaining a continuous stream of dinitro-FPAA (**3**) in toluene ready to be introduced in the hydrogenation reactor (after inline addition of methanol) a nitration setup incorporating a membrane based liquid–liquid separator was built.[16] Details on the optimization of the nitration process are described above. The flow rates for the neat FPAA (**2**) substrate, nitration mixture, and toluene were set according to the values calculated for a productivity of 0.2 mmol min^{-1} (Figure 7). To obtain a residence time of ca. 20 min in the thermostated bath a residence time unit (1.5 mL volume, 0.8 mm inner diameter PFA tubing) was added to the glass static mixer output. The residence time unit then entered a second water bath at 0–10 °C, where water and toluene are added simultaneously to the reaction mixture using an X-mixer. By adding both solvents simultaneously at low temperature precipitation of the dinitro-FPAA (**3**) in the water phase and a possible nitration of toluene are avoided. For the extraction process a 4 mL volume tubing was installed. The inner diameter for the extraction tubing was increased to 1.6 mm to augment the contact surface between the toluene and water phases and enhance the extraction. A picture of the setup with details on the liquid–liquid segments is contained in the Supporting Information (Figure S7). A commercial membrane based liquid/liquid separator (Zaiput) was utilized to separate the organic and aqueous phases in continuous flow.[16]

The continuous flow reactor was started setting all parameters as stated in Figure 7. The system was run for 60 min to ensure stability and steady-state concentration conditions. Then, 10 mL of the toluene phase were collected from the corresponding membrane separator output. In a separate cylinder 10 mL of the aqueous phase were additionally collected from the water output of the membrane separator. HPLC analyses of the organic and aqueous phase revealed excellent efficiency in the extraction process, with a toluene/water dinitro-FPAA (**3**) distribution coefficient of 38:1 (determined by 215 nm peak area integration) (HPLC chromatograms of the organic and aqueous phases are shown in Figure S8 in the Supporting Information). The organic phase was then evaporated under reduced pressure until all volatiles were removed. Cyclohexane was added and the pale yellow precipitate filtered off,[17] yielding 92% of pure, dinitro-FPAA (**3**) (^{1}H NMR spectrum of the solid product obtained without further purification is shown in Figure S9 in the Supporting Information). This remarkable yield and purity is in stark contrast with the reported batch protocol, in which 82% yield of dinitro-FPAA (**3**) with 78% purity could be obtained.[6]

Sequential Continuous Hydrogenation/Cyclization Process. The hydrogenation reaction mixture exiting the H-Cube Pro reactor consists of a solution of diamino-FPAA (**4**) in toluene/methanol 2:1 together with a large amount of H_2 gas. Although the presence of H_2 gas should not affect the cyclization reaction, it does have an influence in the process because the residence time cannot be easily controlled. We therefore performed an inline removal of the excess of H_2 after the reduction using gas permeable Teflon AF2400 tubing.[18,19] As diamino-FPAA (**4**) is relatively unstable in the presence or air and light, we decided to optimize both degassing and cyclization simultaneously, directly using the crude reaction mixture obtained from the hydrogenator. Thus, a Teflon AF2400 tubing (1.5 mL volume) in the form of a "tube-in-tube" reactor (Uniqsis)[18] was installed at the output of the H-Cube Pro (Figure 8). The advantage of using a tube-in-tube reactor is that the H_2 released from the inner to the outer tube can be readily removed by the ventilation system of the fume hood. HCl (37%) was introduced into the system after the tube-in-tube reactor with a standard T-mixer (20 μL min^{-1}, 1.2 equiv). The acidified solution entered a new residence time unit (0.8

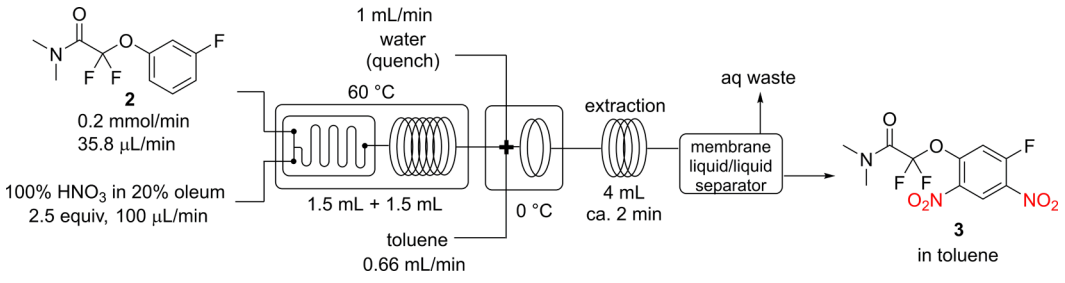

Figure 7. Schematic diagram of the setup used for the combined flow dinitration/liquid–liquid extraction process. For a photograph of the continuous flow setup see Figure S7 in the Supporting Information.

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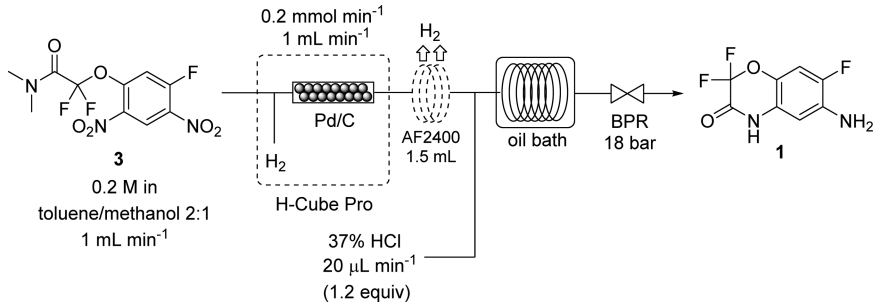

Figure 8. Schematic diagram of the setup used for the continuous hydrogenation/cyclization process. BPR: back pressure regulator. For a photograph of the experimental flow setup see Figure S10 in the Supporting Information.

mm inner diameter tubing) immersed in an oil bath (Figures 8 and S9). A back pressure regulator (BPR) was installed at the end of the reactor. The purpose of the BPR is to avoid boiling of the solvent during the cyclization if high temperatures are required, and to enhance removal of H_2 through the AF2400 material. Several BPR were tested, and complete removal of the H_2 excess within the 1.5 mL AF2400 tube was achieved when the pressure was increased to 18 bar.

It is worth pointing out that since an 18 bar BPR was installed at the end of the system, the hydrogenation reaction will also take place at this level of pressure. Under these conditions full conversion of the dinitro-FPAA (**3**) to the diamino-FPAA (**4**) can be assured (cf. Table 1). A residence time of 10 min at 120 °C was initially tested for the cyclization step. At this temperature full conversion of the diamino-FPAA (**4**) intermediate was expected and possible side products for the reaction could be evaluated. As anticipated, HPLC and GCMS analyses of the crude reaction mixture collected from the output revealed complete conversion of the starting dinitro-FPAA (**3**) as well as the diamino-FPAA (**4**) intermediate. The desired ABO product was formed with very good selectivity, although a small amount (1% according to GCMS) of hydrolysis product was also observed possibly due to the high temperature used in this process. Reaction temperature and residence time were gradually decreased (Table 2) to ultimately reveal 80 °C and 5 min residence time as optimal conditions for the cyclization. Under these conditions excellent product selectivity with high purity profiles in both HPLC and GCMS analyses were achieved. Further temperature decrease (entry 5, Table 2) reduced the conversion of the diamino-FPAA (**4**) intermediate.

Table 2. Results Obtained for the Sequential Hydrogenation/Cyclization Continuous Flow Process

entry	temperature (°C)	cyclization residence time (min)	conversion to ABO (%)[a]	selectivity (%)[a]
1	120	10	> 99	99
2	100	10	> 99	> 99
3	100	5	> 99	> 99
4	**80**	**5**	**> 99**	**> 99**
5	60	5	77	> 99

[a]Evaluated by GCMS and HPLC peak integration area (215 nm).

Fully Integrated Sequential Dinitration/Liquid−Liquid Extraction/Hydrogenation/Cyclization Process. For the experiments described herein we assembled the two main reactor parts described above (i.e., dinitration/liquid−liquid extraction + hydrogenation/degassing/cyclization). For this purpose, the output of the liquid−liquid membrane separator was connected to a T-mixer where the stream was mixed with methanol, and then fed to the input pump of the H-Cube Pro (Figure 9) (for a picture of the complete flow setup for the sequential process see Figure S11 in the Supporting Information).

All 6 feeds in the continuous flow setup were started, setting all reaction parameters as stated in Figure 9. The system was let run for 60 min to ensure stability and steady-state concentration conditions of the dinitration part of the setup. After ensuring that the initial dinitration/liquid−liquid extraction part of the setup was performing as expected, the inlet of the H-Cube Pro was switched from solvent to the reaction mixture (after the hydrogenation/degassing/cyclization part of the setup had been previously stabilized). After approximately 15 min the crude dark brown reaction mixture was collected in fractions of 15 min each, diluted with methanol to a known volume, and analyzed by quantitative HPLC.

After minor modifications in the setup (the residence time for the cyclization was increased from 5 to 10 min) the fully integrated continuous flow process to obtain ABO was carried out for more than 75 min providing excellent results. After ca. 100 min we could observe that dinitro-FPAA (**3**) was no longer fully hydrogenated to diamino-FPAA (**4**), with 1−2% of the mononitro/monoamino-FPAA intermediate being detected. ICP-MS analysis of the crude reaction mixture revealed a Pd content of 14.6 ppm. This value corresponds to a total amount of Pd being leached from the cartridge of 1.3 μg over a 100 min operation period. This amount can be considered insignificant compared to the total Pd contained in the CatCart catalyst cartridge utilized (27.5 mg). We ascribe the small decrease in conversion observed to poisoning of the heterogeneous catalyst with some of the reaction components. To achieve longer process operation recovery of the catalyst by cleaning with additional solvents has been described.[20] Quantitative HPLC analysis of the crude reaction mixture obtained during the initial 60 min revealed a product yield for the overall process of 83%. After the analysis a 3 M aqueous solution of NaOH was added dropwise to the crude reaction mixture until a pH of 4−5 was reached. The solvent was then evaporated under reduced pressure to ca. 20% of the initial volume and 150 mL of water were added. The precipitate formed was filtered off, washed with cold water, and dried at 50 °C under reduced pressure (2.28 g, 87% yield, 91% pure by quantitative HPLC). Notably, the product yield obtained for the overall continuous flow process was significantly superior compared to the reported batch protocol (ca. 67%).[6]

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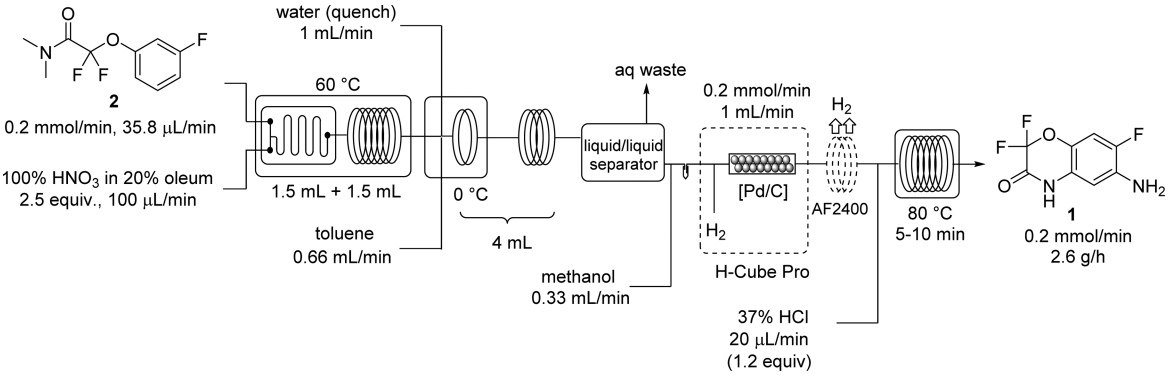

Figure 9. Continuous flow setup utilized for the integrated synthesis of ABO (**1**).

CONCLUSIONS

We have developed a continuous flow protocol for the preparation of 6-amino-2,2,7-trifluoro-4H-benzo-[1,4]-oxazin-3-one (ABO, **1**) using a fully continuous, three-step sequential nitration/hydrogenation/cyclization process. The sequence starts from the FPAA (**2**) precursor, which is dinitrated using 100% HNO_3 in oleum. Control of the reaction exotherm and very efficient mixing has been achieved using a glass static mixer, thus ensuring constant conversion profiles and purity for the dinitro intermediate. The nitration mixture was then quenched with water and extracted with toluene at 0 °C. A membrane based liquid−liquid separator was used after the extraction process to separate the aqueous and organic phases. The first nitration step took place with excellent yield (92% isolated) and purity for the desired dinitro-FPAA (**3**). The toluene solution of dinitro-FPAA (**3**), after mixing with methanol, entered a continuous flow hydrogenator, where dinitro-FPAA (**3**) was reduced to diamino-FPAA (**4**) using heterogeneous Pd/C as catalyst at 45 °C. The reduced intermediate was then acidified inline with HCl 37% and cyclized to ABO (**1**) at 80 °C for 10 min using an additional residence time unit. The overall yield for the continuous flow process was 83% (quantitative HPLC) (87% isolated with 91% purity), improving significantly the yield obtained in the reported batch protocol for the three-step sequence.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC-UV (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. Details on the gradients applied are collected in the Supporting Information. GC/MS monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL min^{-1} in constant-flow mode. All chemicals were purchased from commercial sources and were used without further purification. FPAA (**2**) was prepared according to ref 6. Catcart prepacked Pd/C catalyst cartridges (THS X1175) for the H-Cube Pro were obtained from ThalesNano. ICPMS analyses were performed on an Agilent 7500ce instrument. Samples were digested at 250 °C for 30 min with HNO_3 and properly diluted prior analysis.

CAUTION: Reactions/products described herein have the potential to release large amounts of energy in an uncontrolled way. Nitrations should not be undertaken without stringent hazard assessment and proper safety precautions put in place.

Batch Nitration of FPAA (2). To a vial containing fuming sulfuric acid (oleum, 20% SO_3) (1 mL) was added 100% nitric acid (2.2 or 2.5 equiv) (Figure 2) under stirring at 0 °C. Subsequently, FPAA (**2**) (2 mmol, 358 μL) was added dropwise, under vigorous stirring, over a period of 40−60 s. The vial was capped and heated at 50−60 °C. Reaction monitoring was carried out by collecting aliquots (~2 μL) from the crude reaction mixture, diluting with 2 mL MeCN/H_2O, and analyzing by HPLC after 5, 10, 15, 20, and 30 min reaction time.

Sequential Continuous Flow Nitration/Liquid−Liquid Extraction. Using the setup depicted in Figure 7, FPAA (**2**) (Feed A, 35.8 μL/min) and a solution of 100% HNO_3 (2.5 equiv) in oleum (20% SO_3) (Feed B, 100 μL/min) were pumped through the reactor using two syringe pumps (Syrris). The two streams were mixed using a static glass mixer (1.5 mL internal volume, Uniqsis) and entered a 1.5 mL residence time unit (PFA tubing, 0.8 mm i.d. and 1.59 mm o.d.). The reaction mixture was mixed with water and toluene using a X-mixer at 0 °C, and entered a second residence time unit (4 mL volume, PFA tubing with 1.6 mm i.d. and 3.2 mm o.d) connected to a membrane liquid−liquid separator (Zaiput, 0.5 μm pore size, 42 × 15 mm). The organic phase obtained was used directly for the next step of synthesis without further purification. A 10 mL aliquot of the organic phase was collected and evaporated under reduced pressure. The residue was precipitated with cyclohexane (20 mL) and filtered off, providing 0.97 g (92%) of dinitro-FPAA (**3**) as a pale yellow solid; mp. 67−68 °C.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 10.9 Hz, 1H), 3.25 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.1, 155.7, 147.9, 124.6, 119.4, 115.7, 112.2, 111.9, 37.2.

Continuous Flow Hydrogenation of Dinitro-FPAA (3). A 0.3 M solution of dinitro-FPAA (**3**) in toluene (1.33 mL) (see above) was diluted with methanol (0.66 mL). The hydrogen level of the H-Cube Pro was set to "full H_2" mode, the reactor containing a Pd/C cartridge was preheated to 45 °C and the flow rate and pressure were set according to Table 1. When the system was stable the reaction mixture was pumped through the reactor. The crude solution obtained from the

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reactor output was diluted with acetonitrile and analyzed by HPLC.

Sequential Continuous Flow Nitration/Hydrogenation/Cyclization of FPAA (2). The continuous flow reactor depicted in Figure 9 was started, setting all parameters as stated. The thermostated baths and the column reactor from the H Cube Pro were preheated to the appropriate temperatures. The H Cube Pro pump was set to 1 mL min^{-1} and the instrument to "full H_2 mode". Susequently, neat FPAA (**2**) (35.8 μL min^{-1}) was pumped through the reactor. When the system had stabilized, the crude reaction was collected from the reactor output for 60 min. The obtained biphasic mixture was homogenized with methanol (40 mL) and the pH adjusted with 3 M NaOH to 4−5. The solvent was evaporated under reduced pressure to approximately 20% of the initial volume. After addition of water and stirring for 10 min the precipitate was filtered off, washed with water, and dried at 50 °C (2.28 g, 87%, 91% pure by quantitative HPLC); mp. 210−220 °C (dec.); ^{1}H NMR (300 MHz, DMSO) δ 11.71 (s, 1H), 7.13 (d, J = 11.1 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ 154.6, 154.1, 153.6, 148.0, 144.9, 134.7, 134.6, 127.6, 127.5, 121.6, 121.6, 117.2, 113.7, 110.2, 105.5, 105.2, 102.8.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00409.

Additional experimental information and supplementary figures (PDF)

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Notes

The authors declare no competing financial interest.

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(15) FPAA (**2**) viscosity at 25 °C: 11.7 mPas. 100% HNO_3/oleum viscosity at 20 °C: 45.1 mPas.

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(17) CAUTION: handling and storage of pure dinitro-FPAA (**3**) is potentially hazardous due to its explosive properties. Hazard assessment and proper safety precautions should be taken.

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