# Development of a Continuous Plug Flow Process for Preparation of a Key Intermediate for Brivanib Alaninate

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**ABSTRACT:** A thermal runaway potential was identified for the conversion of a tertiary alcohol to a hydroxypyrrolotriazine intermediate in the synthesis of brivanib alaninate. A continuous process was developed to mitigate the potential thermal runaway and allow for safer scale-up. This paper describes the hazard analysis, process development, reactor development, reaction engineering model development, and scale-up of the continuous process. The process includes three separate and stable feed streams that are mixed in distinct order using in-line static mixers. Heat exchangers are arranged and connected to facilitate a "plug flow" reactor scheme allowing sufficient residence time for reaction completion. The process has been scaled-up to the pilot plant and to manufacturing.

# 1. INTRODUCTION

Processing in the pharmaceutical industry is conducted predominantly batchwise; however, continuous processing has become more prevalent in the past decade.<sup>1</sup> Enhanced safety is a primary reason for employing continuous processing.<sup>2</sup> Most safety-related continuous processing includes hazardous chemistry or chemistry with a thermal runaway potential.<sup>5-</sup> Hazardous chemistry refers to chemistry involving hazardous reagents or products. A thermal runaway reaction may not use or generate hazardous chemicals but may, under certain conditions, generate large amounts of gas and heat. The rate of heat produced exceeds the rate of heat removal at or near some critical onset temperature. These are highly energetic reactions, and the energy released may be due to the desired reaction, degradation of reactants or products, side reactions, or autocatalytic reactions. Continuous processing can provide a safer scale-up of chemistry that would be deemed unsafe in a batch reactor due to potential thermal runaway considerations.

Continuous reactors are typically much smaller than batch reactors of equivalent throughput. As a result, the surface area to volume ratio of a continuous reactor is much higher, leading to enhanced heat transfer rates that help to remove the heat generated by the reaction. The improved temperature control helps to ensure that the onset temperature of a thermal runaway reaction is not realized (reduced probability). Another advantage of the smaller reactor size is a reduced instantaneous inventory of reactive species in the process, corresponding to a reduced energy release if a thermal runaway condition were to unexpectedly occur (reduced severity). Consequently, in a risk assessment where the risk is the product of the severity and probability of a thermal runaway,<sup>8</sup> a continuous process is of inherently lower risk relative to a batch process.

This manuscript describes the development of a continuous process to prepare a key intermediate, hydroxypyrrolotriazine 2, in the synthesis of brivanib alaninate. This intermediate was not isolated but telescoped into the next step to form the first regulatory starting material for brivanib alaninate.<sup>9</sup> The reaction uses hydrogen peroxide as the oxidant in a benzylic

hydroperoxide rearrangement reaction (Scheme 1). The advantage of using hydrogen peroxide as an oxidizing reagent is low mass transfer limitations in such a liquid–liquid system.<sup>10–12</sup> However, it is not uncommon to observe thermal runaway potential for reactions involving organic peroxides or hydrogen peroxide with acids.<sup>13,14</sup> The hazard analysis of this chemistry determined that thermal runaway potential exists at ambient conditions. Alternate chemical routes were scouted for the target hydroxypyrrolotriazine **2**, but none proved acceptable. Hence, an engineering solution (continuous processing) was devised to enable the safe scale-up of the intermediate.<sup>15</sup>

# 2. RESULTS AND DISCUSSION

**2.1. Chemical Hazard Analysis.** Chemical hazard analysis of a small-scale batch benzylic hydroperoxide rearrangement reaction utilizing hydrogen peroxide and hydrochloric acid as a catalyst (Scheme 1) showed that the reaction is exothermic, and without proper cooling, the heat of reaction will trigger a thermal runaway reaction. A summary of the thermal stability testing for the original aqueous batch process (entries 1–4) is shown in Table 1. The influence of peroxide molar equivalents and concentration was investigated. Under all conditions studied, a low onset temperature of less than 30 °C was observed. Dilution of the reaction mixture with water reduced the rate of runaway as noted by the resulting self-heat and pressure rise rates. However, the fully aqueous reaction mixture resulted in a thick slurry that was difficult to agitate (an hence unsafe) and impractical for scale-up.

Many solvents are incompatible with hydrogen peroxide and hydrogen peroxide is unstable in the presence of HCl at 80 °C. Further, hydrogen peroxide and the reaction byproduct acetone are not thermally compatible. The unstable and explosive species triacetone triperoxide may also form.<sup>16</sup> The pyrrolotriazine hydroperoxide intermediate **4** (Scheme 2) may also facilitate a

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Scheme 1. Conversion of tertiary alcohol, 1, to the desired hydroxypyrrolotriazine, 2



Table 1. Thermal stability of batch reaction mixtures

entry	process	onset temp. (°C)	self-heat rate (°C/min)	max. temp. (°C)	pressure rise rate (psi/min)
1	20 wt % tertiary alcohol 1, H <sub>2</sub> O <sub>2</sub> (12 equiv) + 1 N HCl (0.0355 equiv)	25	3000	150	>5000
2	20 wt % tertiary alcohol 1, $H_2O_2$ (24 equiv) + 1 N HCl (0.084 equiv)	~23	2500	270	>5000
3	10 wt % tertiary alcohol 1, $H_2O_2$ (12 equiv) + 1 N HCl (0.0355 equiv)	30	2000	180	2000-5000
4	5 wt % tertiary alcohol 1, $H_2O_2$ (12 equiv) + 1 N HCl (0.0355 equiv)	30	40	200	30
5	solution of water, 50% H <sub>2</sub> O <sub>2</sub> and 1 N HCl	80	1000	1000	490
6	solution of water, 50% H <sub>2</sub> O <sub>2</sub> , 1 N HCl, and acetone	80	1000	1000	490
7	solution of THF and 50% H <sub>2</sub> O <sub>2</sub>	100	1000	1000	500
8	solution consisting of tertiary alcohol 1, THF + $H_2O_2$	30	90	220	400
9	one shot addition of methanesulfonic acid + water to a solution of tertiary alcohol 1, THF + H <sub>2</sub> O <sub>2</sub>	25	3000	200	10000

thermal runaway side reaction by decomposing to an unknown species. The results indicate that a low-temperature thermal runaway reaction cannot be explained solely by either hydrogen peroxide decomposition or a reaction between acetone and hydrogen peroxide (Table 1, entries 5–7). The low temperature thermal runaway reaction may require all components to be present.

A wide variety of acids catalyze the benzylic hydroperoxide rearrangement. Thermochemical testing demonstrated that a thermal runaway potential exists for this reaction, even in the absence of an acid catalyst (Table 1, entry 8). Initial testing in a batch reaction showed that methanesulfonic acid produced a lower self-heating rate than HCl in the reaction mixture. In addition, methanesulfonic acid caused much less product degradation relative to HCl and was thus chosen for further process development. The higher levels of methanesulfonic acid in the final process to support faster kinetics led to significant process constraints due to the thermal runaway potential. The thermal stability of the tertiary alcohol with and without methanesufonic acid (MSA) in the presence of THF and hydrogen peroxide (representing the final process) is shown in Table 1, entries 9 and 8. The data show onset temperatures of 25 and 30 °C for the thermal runaway reactions, respectively.

On the basis of the hazard testing, this reaction was deemed unsafe for operating at  $\geq$ 500 g of starting material 1 in a batch mode. This required the conversion of the batch process into a continuous process in order to mitigate the hazardous potential of the existing chemistry.

**2.2. Reaction Chemistry.** *2.2.1. Mechanistic Considerations.* A proposed reaction mechanism is shown in Scheme 2. In an acidic environment, the hydrogen peroxide concentration drives the formation of intermediate hydroperoxide 4 and minimizes the formation of olefin 5. At high hydrogen peroxide equivalents, the overall reaction rate-determining step is the rearrangement of the intermediate peroxide 4 to the product 2. The kinetics of this reaction are controlled by the equivalents of acid present. In the case of low equivalents of hydrogen peroxide, cation 3 will react with the product 2 to form the dimer impurity, 6. 2.2.2. In-Process Controls. During process optimization, the levels of tertiary alcohol 1, intermediate peroxide 4, impurity 6, and product 2 were monitored using HPLC. The acceptance criterion for the unquenched reaction mixture is shown in Table 2. A level of 2% or less for the intermediate peroxide 4 was targeted for reaction completion, and this served as the primary in-process control to ensure that the level of tertiary alcohol 1 is very low. The level of the olefin impurity 5 is well-controlled by reagent order of addition, hydrogen peroxide followed by acid, and by molar equivalents of hydrogen peroxide. The typical values of the various species in the quenched reaction mixture are also shown in Table 2.

**2.3. Reaction Development.** The transformation of this batch process to a continuous process focused on several key objectives. First, the reaction mixture should be a homogeneous solution for practical and safety concerns. Second, in order to have a practical process, the reaction times needed to be fast (on the order of minutes). Third, the amount of hydrogen peroxide should be reduced for practical and safety concerns. Each excess equivalent of hydrogen peroxide must be quenched at the end of the reaction. Finally, the reaction should operate at least 10 °C below the thermal runaway onset temperature.

To ensure homogeneous solutions throughout the process, cosolvents were used. A solubility screen demonstrated a system of 20% water in tetrahydrofuran afforded the greatest solubility for the product and starting material. Homogeneous solutions mitigate the potential for clogging or fouling of the equipment which can hamper long-term operations. From a safety perspective, homogeneous solutions help to ensure all transfers are representative of the bulk solution with no accumulation of reactive species (reagents, active intermediates, etc.).

The next step was to shorten the reaction time by optimizing the number of equivalents of acid. Excess MSA is also not desirable as this requires additional base to neutralize the quenched reaction mixture as the product is most stable at neutral pH. Kinetic studies led to optimization of the concentration of MSA at 12.6 equiv relative to the starting material **1**. This level allowed for reaction completion in less than 20 min while operating with at least a 10 °C temperature buffer below the thermal runaway onset.

### Scheme 2. Proposed reaction mechanism



Table 2. Acceptance criteria for reaction mixture

	unquenched specification $(RAP)^a$	quenched typical value $(RAP)^a$				
tertiary alcohol input 1	≤2.0	≤2.0				
intermediate peroxide 4	$\leq 2.0$					
dimer impurity 6		5				
product 2		≥85				
olefin impurity 5		<1				
${}^{a}$ RAP = relative area percent by HPLC.						

Based on the experimental results, the amount of hydrogen peroxide was set at 8.8 mol equiv relative to the starting material 1. This level of hydrogen peroxide ensured the formation of the intermediate peroxide 4 to be sufficiently fast so as to minimize the formation of impurity, 6.

The reaction mixture was charged as three separate feed streams since the inputs were not compatible. The first stream contained the bulk of the reaction solvent and all of the starting material. The starting material was not stable with either hydrogen peroxide or with the acid (MSA). The order of addition of the feed streams was also important to the final product quality. Hence, the starting material solution was first mixed with the hydrogen peroxide solution and then combined with the methanesulfonic acid feed solution.

After reaction completion, the product **2** was not stable to the reaction conditions and undergoes further oxidative degradation with additional reaction time. For both process safety and product quality, when the reaction is completed, the excess hydrogen peroxide must be quenched, and the stream brought to neutral pH conditions without delay. This was achieved with an aqueous solution containing sodium bisulfite to quench the hydrogen peroxide and ammonium hydroxide to neutralize the MSA. This quench is exothermic with a theoretical adiabatic temperature rise of 65 °C. The quench was completed in a "reverse" mode of operation. In this mode, the reaction mixture flowed into a large reservoir containing the precooled quench solution needed for the entire processing cycle. The pH was maintained between 7.0 and 7.5 during the quenching process with the addition of base as needed using a pH feedback loop.

**2.4. Reaction Engineering.** *2.4.1. Kinetic Studies.* Experiments were undertaken to develop a kinetic model to describe



the reactions in the continuous process. The resulting kinetic model added to process understanding and facilitated the development of a model to simulate reaction performance in a continuous reactor.

The kinetics of the reaction were studied by varying concentration, temperature, and equivalents of the two key reagents (hydrogen peroxide and methanesufonic acid). An initial mechanistic model was formulated based on the previously proposed scheme (Scheme 2). This was further reduced down to three reactions as shown in Scheme 3. The cation 3 cannot be detected and was not included in the model. For simplicity, the equilibrium between the starting material 1 and the cation 3 was combined with the equilibrium between the cation 3 and the intermediate peroxide 4 and designated as reaction 1 (Scheme 3). The equilibrium expression between the cation 3 and the olefin 5 (Scheme 2) was not included in the model due to the low levels of the olefin 5 that are observed. The rearrangement to form the product 2 and the formation of the impurity 6 were the other two modeled reactions.

The rate expressions for the modeled equations are shown in Table 3. For the conversion of the intermediate peroxide to the

Tał	ole	3.	Rate	Exp	pressions	for	Mo	de	led	l Ec	juati	ons
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reaction	equilibrium/rate expression				
1	$K_1 = [4][water]/[1][H_2O_2]$				
2	$rate_4^{\alpha}: d[4]/dt = -k_2 [4]^{\alpha} [MSA]^{\beta}$				
3	$rate_2: d[2]/dt = -k_3 [2][1][MSA]$				
${}^a \alpha$ and ß are determined via kinetic model fitting.					

product (reaction 2), an empirical model was utilized. The proposed empirical model has the hydrogen peroxide concentration raised to a power  $\alpha$  and the MSA concentration raised to a power  $\beta$ . The third equation modeled the formation of the impurity **6** as a reaction between the starting material **1** and the product **2** and catalyzed by MSA.

DynoChem was used to determine the kinetic parameters by fitting the experiments to the model. The varied experimental parameters were temperature, MSA concentration, hydrogen peroxide concentration, and starting material concentration. The kinetic parameters fitted were the activation energy and the frequency factor (based on Arrhenius' law) for each reaction and the exponents  $\alpha$  and  $\beta$ . The measured concentrations of starting material 1, intermediate peroxide 4, product 2, and dimer impurity 6 were inputted along with the recorded reaction temperature during the course of each experiment. Each experiment was nonisothermal but performed within a narrow temperature band based on active cooling to control the exothermic reaction while maintaining a safe buffer from thermal runaway. The resultant parameters are shown in Table 4. A good

Table 4. Regressed kinetic parameters

reaction	rate constant, $k_i$	activation energy (kJ/mol)	equilibrium constant, K <sub>eq</sub>
1	0.803 L/(mol·s)	1153	642
2	$3.41 \times 10^{-5} \text{ L}^3/(\text{mol}^3 \cdot \text{s})$	170	
3	$1.79 \times 10^{-11} \text{ L}^2/(\text{mol}^2 \cdot \text{s})$	893	

fit was obtained for an " $\alpha$ " value of 1 and a " $\beta$ " value of 3. Hence, a small variation in the MSA concentration led to a significant change in the reaction rate particularly when this final conversion of the intermediate peroxide was the rate-limiting step. Comparisons of experimental measurements with simulated results for the batch reaction for two experiments are shown in Figure 1. The first figure (a) shows the reaction progression under expected slow reaction kinetics with the temperature at -1 °C and with 6.2 equiv of MSA. The reaction did not go to completion over the sampled 4 h. In the second figure (b), the reaction progressed under fast reaction kinetics with a batch temperature of 11 °C and with 12.4 equiv of MSA. Here the reaction reached its end point in less than 20 min. a) 2.2 equiv H<sub>2</sub>O<sub>2</sub>, 6.2 Equiv MSA, 3.1 wt% Starting material, -1°C



b) 8.8 equiv H<sub>2</sub>O<sub>2</sub>, 12.4 equiv MSA, 3.8 wt% Starting material,  $10^{\circ}$ C





The heats of reaction were needed to properly simulate the reaction in plug flow since the reaction was nonisothermal. Early experiments established the total heat of reaction and the heat of mixing when the MSA feed was added to the reaction stream. The heat of mixing is measured with no starting material present. This represents any heat produced not associated with the starting material or associated intermediates and product. In order to determine the heats of reaction for the individual modeled reactions of Scheme 3, a HEL AutoMATE multireactor system (with calorimetry option) was used to measure the heat generated during reaction. Samples were taken and analyzed by HPLC, while the reaction mixture was dosed with the MSA feed stream over 30 min and then for an additional 30 min (Figure 2). The HPLC data was fitted to the kinetic model using DynoChem. The individual heats of reaction were fitted to the heat profile generated in the experiment in combination with the kinetic data. The heat generated from mixing was constant during the 30 min of MSA dosing. The combined heats of reaction for the modeled reactions accounted for the remaining measured heat over the course of the experiment. The fitted heats of reaction for the three modeled reactions are shown in Table 5.

2.4.2. Process Simulation. In practice, ideal plug flow is not realized in many "plug flow" reactors. Either laminar or turbulent



Figure 2. Reaction calorimetry with MSA dose control.

flow could be present in these reactors depending on operating parameters.<sup>17</sup> However, for convenience in this paper, the reactor described will be referred to as a plug flow reactor. The value of a plug flow reactor model was to assess the operating parameters and their impact upon product quality, productivity, and safe operation, facilitating the design of the scale-up reactor. The generated kinetic parameters, the heats of reaction, and the heat of mixing were utilized to develop a plug flow reactor model.

Table 5. Experimentally determined and fitted heats of reaction/mixing

	heat of reaction or mixing (kJ/mol starting material)
addition of MSA to the reaction $mixture^{a}$	-191
intermediate peroxide formation (Rxn 1)	-44
oxidative rearrangement (Rxn 2)	-150
dimer impurity formation (Rxn 3)	-2
<sup>a</sup> Determined with no starting material pres	sent.

The plug flow reactor model presented here is similar to that used by LaPorte et al. for the formation of a cyclopropanating reagent in a plug flow reactor.<sup>18</sup> The model allows for nonisothermal behavior since the required cooling duty varies throughout the length of the reactor. The mass/energy balance (Figure 3) has several key assumptions. The reaction stream is

$$u\rho C_p \frac{dT}{dz} = \Delta H_m r_m + \Delta H_1 r_1 + \Delta H_2 r_2 + \Delta H_3 r_3 - UA_V (T - T_c)$$

u = reaction stream velocity

 $\rho$  = reaction stream density

 $C_{P}$  = reaction stream heat capacity

T = reaction stream temperature

 $T_C$  = temperature of jacket coolant

z = axial position in plug flow reactor

 $\Delta H_i$  = heat of reaction i

 $\Delta H_m$  = heat of mixing

 $r_i$  = rate of reaction i

 $r_m = \text{mixing rate}$ 

U = overall heat transfer coefficient

 $A_V$  = specific heat transfer area (area/unit volume)

Figure 3. Simplified mass/energy balance for a non-isothermal plug flow reaction model at a steady state.

assumed to be completely mixed in the radial direction with no diffusion in the axial flow direction. In addition, the temperature of the shell side of the heat exchanger is assumed constant with a high volume flow of coolant relative to the process stream flow rate. Finally, the process stream is assumed to have a constant density and heat capacity.

The model begins with the mixing of the final feed stream (MSA feed). The mixing of the reaction stream with MSA was modeled as first order over the length of the in-line static mixer. The reaction mixture was assumed to be completely mixed as it exits the static mixer with heat released instantaneously and proportional to the extent of mixing over the length of the static mixer. The kinetic reaction expressions along with the energy balance were utilized in DynoChem to simulate the course of the reaction throughout the length of the plug flow reactor.

The heat transfer coefficient utilized in the simulation was 400 W/m<sup>2</sup>·K (based on correlations).<sup>19</sup> The simulated reaction conversions are shown in Figure 4 for 900 s of plug flow reaction. At jacket temperatures of 0 and 5 °C, the reaction failed to go to completion within the allotted time. At a jacket temperature of 10 °C, the reaction went to completion within the allotted time. However, with a jacket temperature of 10 °C, the temperature exceeded the thermal runaway onset temperature



Figure 4. Conversion with respect to jacketed temperature for the simulated plug flow reactor.

at the start of the reaction. In contrast, the initial operation with a jacket temperature of 0  $^{\circ}$ C followed by a shift to 12  $^{\circ}$ C on the jacket after 2 to 3 min provided the most efficient operation under safe conditions. The initial low temperature zone maintained a safe buffer with the onset thermal runaway condition, while the latter higher temperature zone drove the reaction to completion while operating at nearly isothermal conditions. The temperature and conversion are plotted in Figure 5 for the process under the established operating conditions.



Figure 5. Simulated temperature and conversion along the length of plug flow reactor for a two-zone temperature scenario.

An example comparing the conversion of the reaction simulated by the plug flow reactor model and an experiment run in the laboratory development reactor (see Experimental Section for additional details) is shown in Figure 6. The reaction conversion was measured along of the length of the plug flow reactor at fixed sampling ports. There was a high level (32%) of reaction conversion in the very early portion of the plug flow reactor, mainly due to the resultant high reaction temperature from rapid mixing and the concomitant release of heat which drives the faster initial reaction kinetics.

**2.5. Reactor Development.** In order to manage heat production during the reaction while optimizing throughput, a reactor with two temperature operating regimes was developed. The selection of these regimes was based on the heat production rate and the desire to minimize total reaction time. At the beginning of the reaction, the reaction produced the most heat as a result of the heat of mixing with MSA and, to a lesser extent, the heat of reaction. A first temperature zone of 0 °C



Figure 6. Simulated and experimental results for the laboratory development plug flow reactor. Experiment used 8.0 equiv of MSA and operated at -5 to 3 °C.



Figure 7. Lab scale plug flow reactor setup.

was used at the beginning of the reaction. The second temperature zone was controlled at 12-15 °C in order to increase the reaction rate and drive the reaction to completion. The heat generated in this second regime was relatively low since the bulk of the reaction was already complete.

A lab scale plug flow reactor was utilized to demonstrate proof of concept for the continuous process (Figure 7). This reactor was designed to process 0.5 mL/min of reaction solution. All feed solutions were held at ambient temperature in separate feed bottles. The starting material feed solution and the hydrogen peroxide feed solution were pumped and mixed continuously using a jacketed, cooled (-5 °C) microreactor. This solution was then mixed with the methanesulfonic acid feed solution in a second jacketed (-5 °C) microreactor. This combined reaction mixture flowed into a heat exchanger

controlled at -5 °C which provided additional reaction time in a plug flow mode. After 2 min of residence time in the heat exchanger, the reaction mixture then entered the higher temperature zone (12–15 °C) of the reactor. The residence time of this portion of the reactor was approximately 12 min. The total reactor volume (two microreactors and four heat exchangers) was approximately seven milliliters.

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The starting material feed, the hydrogen peroxide feed, and the MSA feed solutions were charged at the predetermined flow rates to maintain the proper ratio of all reactants. This in turn ensured the quality of the product and the safe operation of the process. The total flow rate can be adjusted while maintaining the ratios of the individual feed streamflow rates to increase or decrease the total residence time as needed to meet the in-process control specification for material exiting the reactor.

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Figure 8. Twenty hour test run of the continuous process.



Figure 9. Scheme of pilot plant reactor system and associated equipment.

An extended run experiment was conducted at lab scale to test for steady state operation that would be representative of a scale-up run. Steady state operation was demonstrated in a 20 hour experiment with samples taken periodically throughout (Figure 8).

**2.6. Scale-up.** *2.6.1. Kilo-Lab.* The main scale-up criterion for a continuous plug flow reaction is residence time. Hence, the first scale-up reactor was designed to provide enough reactor volume with a given flow rate to meet that criterion residence time. The composition and ratio of the flow rates of each of the feeds were maintained throughout scale-up.

The first scale-up of the process took place in our kilo-lab. Details of the reactor can be found in Section 4.3. The kilo-lab reactor system was able to process 5.6 kg of starting material per day to produce the key intermediate, **2**, for use in the synthesis of the active pharmaceutical ingredient for clinical supplies.

2.6.2. Pilot Plant. 2.6.2.1. Pilot Plant Reactor. Based on increased material demand, the continuous reactor was further scaled-up to the pilot plant. The designed reactor was similar to the kilo lab system maintaining the scale parameter of 14 min total residence time. A scheme of the pilot plant reactor system and accessories is shown in Figure 9. There are three feed tanks,

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a feed tank of THF/water (for flushing the system), a tank with ammonium hydroxide (pH control in quench tank), a waste tank, and a quench tank. After completion of production, the collected product in the quench tank is worked up in batch mode.

2.6.2.2. Pilot Plant Operations. Pilot plant process flow rates were: 230 g/min for the starting material feed solution, 126 g/min for the MSA feed (70% in water), and 44.2 g/min for the hydrogen peroxide feed (50 wt % in water). The total volumetric flow rate was 400 mL/min and represented an 800-fold scale-up from the laboratory reactor system (Table 6).

Table	6.	Reactor	Capad	cities
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	total flow rate	productivity (kg starting material processed per day)	scale-up
lab screening reactor	0.5	material processed per day)	1.0
kilo lab reactor	100	5.6	200
pilot plant reactor	400	22.4	800
commercial reactor	800	44.8	1600

A defined startup protocol was established to minimize waste of inputs and to achieve steady state operation in minimum time. A fourth feed solution containing only THF and water was pumped through the system instead of the starting material solution to thermally equilibrate the reactor system at startup. After an initial period of thermal equilibration, the feed solution was switched from THF/water to the starting material solution.

During startup, the product stream was directed to a waste tank containing sodium bisulfite to quench hydrogen peroxide. This ensured no potential thermal runaway reactions in the waste streams. Additionally, all process samples were quenched prior to discard. The initial product stream was not expected to meet product specifications until a steady state was obtained. Samples were taken from the product stream periodically during operation and analyzed by HPLC until the in-process control was met ( $4 \le 2.0$  RAP). Once reaction conversion specifications were met, the stream was diverted to the quench tank. During processing, if the product stream did not meet specifications, actions that may be taken would be reducing or increasing the total flow rate while maintaining the feed stream ratios. Hence, if the reaction did not meet the conversion specification, the flows would be reduced to increase the residence time.

The pilot plant results are shown in Figure 10. The reaction stream from the reactor exit was sampled every hour and



Figure 10. Pilot plant steady-state operation.

analyzed for the key species of product 2, starting material 1, intermediate peroxide 4, and dimer impurity 6. A steady state was maintained throughout the entire run. The mean level of product was 91 relative area percent (RAP), while the intermediate peroxide level was below the in-process control specification of 2.0 RAP throughout the run.

The process stream temperature was monitored at different points in the reactor. The temperature at the outlet of the second static mixer was about 10  $^{\circ}$ C. This point represents complete mixing of all feed streams and after the heat of mixing is released. After this point the stream was cooled down in the lower temperature zone of the reactor. After 2 min the stream was heated in the high temperature zone to promote reaction completion.

**2.7. Manufacturing.** This continuous process has also been demonstrated at a manufacturing scale using a total flow rate of twice that demonstrated in the pilot plant (Table 6). At the manufacturing scale, a second quench tank was available and allowed for longer run times of the continuous reactor. Once the first quench tank filled with the predetermined amount of reaction mixture, the exit process stream was diverted to a second quench tank. The batch in the first quench tank was worked up, and the tank was prepped for the next cycle of product collection. The reaction time cycle at manufacturing scale ranged from 10 to 24 h depending on quench tank size and overall flow rates.



Figure 11. Continuous reactor constructed in a kilo lab.

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# 3. CONCLUSIONS

A safe and scalable continuous process was developed for the conversion of a tertiary alcohol to a hydroxypyrrolotriazine intermediate. A two-stage temperature control strategy was employed to maximize safety and efficiency while producing high quality and high yielding product. Steady-state operation was achieved quickly and maintained throughout processing. More than two metric tons of the hydroxypyrrolotriazine product **2** have been produced at commercial scale utilizing this continuous process. The process was demonstrated for up to 33 days of continuous operation with no safety- or quality-related incidents.

# 4. EXPERIMENTAL SECTIONS

**4.1. Hazard Analysis.** Thermal stability analysis was performed using a model 2910 differential scanning calorimeter (TA Instruments). The CRC90 isothermal flow calorimeter was used to evaluate the heat effects of the process steps. The thermal stability of the various reaction streams was evaluated using the Advanced Reactive System Screening Tool (ARSST), Fauske and Associates, Inc. and the Accelerating Rate Calorimeter (ARC), Columbia Scientific Inc.

**4.2. Lab Development Reactor.** The lab development reactor was a standardized continuous reactor setup built for screening and development work. It possessed a three independent feed capability. Each feed was thermally conditioned prior to mixing. The reactor system had two microreactors (mikroglas, single T-mixer,  $\sim$ 1 mL internal volume): one to mix feed 1 and feed 2 and then a second to mix the combined with feed 3. There were heat exchangers after each microreactor: one after the first and then multiple after the second. There were multiple sampling ports throughout the serially connected heat exchangers after the second microreactor. The heat exchangers were 1/8 in. Hastelloy C-276 tubing coiled within a larger tube (1 in.).

**4.3. Kilo-Lab Reactor.** The kilo-lab scale-up reactor was designed with static mixers and tube-in-tube heat exchangers to provide the bulk volume of the reactor. The static mixers were jacketed to provide additional cooling during the mixing. Since the mixing was rapid with the static mixer, the cooling requirement was initially very high. Figure 11 shows the reactor setup in our kilo-lab. The components were mounted on a vertical steel plate placed within a SmartBox adjacent to several reactors. The heat exchangers were oriented for upward flow such



Figure 12. Pilot plant reactor on portable rack. Low temperature parts were insulated.

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that any gas bubbles would be forced up and out of the reactor. All of the low temperature components were wrapped in insulation. All wetted components were either PTFE or Hastelloy C-276. Although 316 stainless steel is chemically compatible with the process streams, Hastelloy was chosen to minimize any potential that rust could contaminate a process stream and lower the onset thermal runaway temperature.

**4.4. Pilot Plant Reactor.** The reactor was built on a portable skid (Figure 12) which facilitated the layout of the heat exchangers and mixers in an efficient manner. Consideration was given to the cooling fluid access points throughout the system and how the various components were integrated together.

The two Kenics static mixers used were a 3/8 in. outside diameter tube mixer (Chemineer, Inc.). Each mixer contained 21 helical elements. A jacket was constructed around the mixer using a 3/4 in. pipe and various fittings.

The low temperature zone heat exchangers that made up the reactor were tube-in-tube style similar to that used in the kilolab setup. The heat exchangers used for this reactor system had an inner tube that was 3/8 in. outside diameter and made of Hastelloy C276. The outer tube (jacket) was 3/4 in. outside diameter. The high temperature reaction zone consisted of two shell and tube heat exchangers. Each heat exchanger was made of  $81 \times 1/4$  in. Hastelloy C276 tubes housed within a 4 in. pipe with services for a heat transfer fluid. The combined volume of the overall reactor system was approximately 5.6 L.

A pulse-less magnetically coupled gear pump was used for each feed stream. The flow rate was monitored by a Coriolis mass flow meter and adjusted automatically with a feedback control system. The accuracy of the pumps used was  $\pm 1\%$ .

The reactor system was also equipped with check valves to protect against back flow of streams. Several three-way valves were installed at low points to ensure complete drainage of the system if required. The process stream exiting from the reactor was charged above the liquid surface in the quench tank. The quench tank also possessed pressure control and proper pressure relief devices.

**4.5. Manufacturing Reactor.** The manufacturing reactor was a reproduction of the pilot plant reactor with twice the reactor volume. The volume was doubled by doubling the number of tube-in-tube heat exchangers in the low temperature zone and by doubling the volume of the shell and tube heat exchangers in the higher temperature zone. The same static mixers were used in the pilot and manufacturing scale.

**4.6. Analytical.** Sample analysis for kinetic studies utilized a Shimadzu high-performance liquid chromatograph (LC-10AT VP) with a Waters Symmetry Shield RP8 column ( $3.5 \mu$ m, 4.6 150 mm). HPLC samples were not quenched but diluted sufficiently to stall additional reaction and were quenched after analysis. Markers were utilized for each tracked species in the kinetic model.

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# Notes

The authors declare no competing financial interest.

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