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How to Convert a Walk-in Hood into a Manufacturing Facility: Demonstration of a Continuous, High-Temperature Cyclization to Process Solids in Flow

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S *Supporting Information*

ABSTRACT: An intramolecular thermal cyclization protocol was developed in a flow reactor to take advantage of the high pressures and temperatures that are easily obtained in small scale autoclave reactors that have been modified to handle slurries. This reactor was equipped with a fill/empty pumping system to enable easy and nearly complete transfer of slurries. The reaction conditions were designed to take advantage of the insolubility of the product in order to separate it from residual starting material by filtration after short reaction times. Recycling of the filtrate maximized the yield and throughput while minimizing decomposition. Recycles were accomplished using a strip to dryness protocol that was easily performed in a rotary evaporator. This new equipment set was designed with lab-hood manufacturing in mind, a minimized footprint, and the system was completely automated for charging, emptying, rinsing, and reacting. Additional efforts for quick screening and alternate modes of addition were also investigated.

■ INTRODUCTION

Quinoline compounds play a key role as intermediates in the synthesis of a variety of potential drug therapies including Alzheimer's,[1] antimalarials,[2] and antibiotics[3] among others. While batch Gould−Jacobs thermal cyclizations and other high-temperature reactions are well-precedented, it was desirable to develop an alternate method that would avoid some of the issues observed in batch, such as long reaction times, difficulty in achieving desired reaction temperatures, and undesirable solvents such as diphenyl ether or Dowtherm.[4,5] The temperatures necessary for these cyclizations require specialized batch equipment that can heat to temperatures as high as 310 °C. Recent large-scale requirements for this type of cyclization published in this journal have avoided this transformation entirely by developing a new synthetic route[6] or effecting the same transformation under acidic conditions with Eaton's reagent.[7] There are examples of these cyclizations under alternative conditions such as microwaves[8] including examination of microwaves on larger scale in flow,[9] but mostly on smaller scale in plug flow reactors (PFR) with solvent[10] and neat.[11]

Another aspect complicating the synthesis of these types of molecules is the fact that the product readily precipitates from most solvent systems. Solids in continuous fine chemical processes have historically been viewed as problematic in small-scale PFR equipment,[12] but improvements have been made with an understanding of better equipment design and improved reaction conditions to avoid fouling.[13] Despite these new methodologies, we hoped to isolate via a direct filtration without performing a rework on the isolated solids which was a requirement of some of the previous flow efforts mentioned above. Finally, the key to streamlining the overall process was to take advantage of our previously disclosed expansion zone technology to easily transfer slurries.[14] This equipment has a small footprint and was aimed at becoming a tool for quick reaction screening as well, obviating the tedious generation of product or intermediate solubility data in order to expedite condition screening given that the reagent feed solutions were homogeneous.

■ EQUIPMENT

An automated fill-empty stirred tank reactor was envisioned as an effective alternative for continuous reactions with solids in flow. While the flow is intermittent rather than truly continuous, this reactor type has many of the characteristics of continuous reactors. The reactor size is small compared to the volumetric throughput, as there are many reactor volume turnovers per day, and the reactor remains at one temperature as material flows in and out (similar to a PFR). Reagents flowing in are heated quickly, the residence time in the reactor is precisely controlled, and the products flowing out are cooled quickly. The small reactor size also makes implementation of extreme temperatures and pressures possible. All of these attributes are typical characteristics of a continuous reactor, but this reactor type can also handle solids in flow for an extended run without plugging or clogging.

The reactor that was chosen for this chemistry was a 25 mL modified Parr autoclave reactor with overhead stirring as shown in Figure 1. The Parr ceramic heaters used to heat these reactors are designed to readily achieve the temperatures necessary to effect these cyclizations.[15] The reactor itself is rated well above the 600 psi necessary to keep the solvents of interest in the

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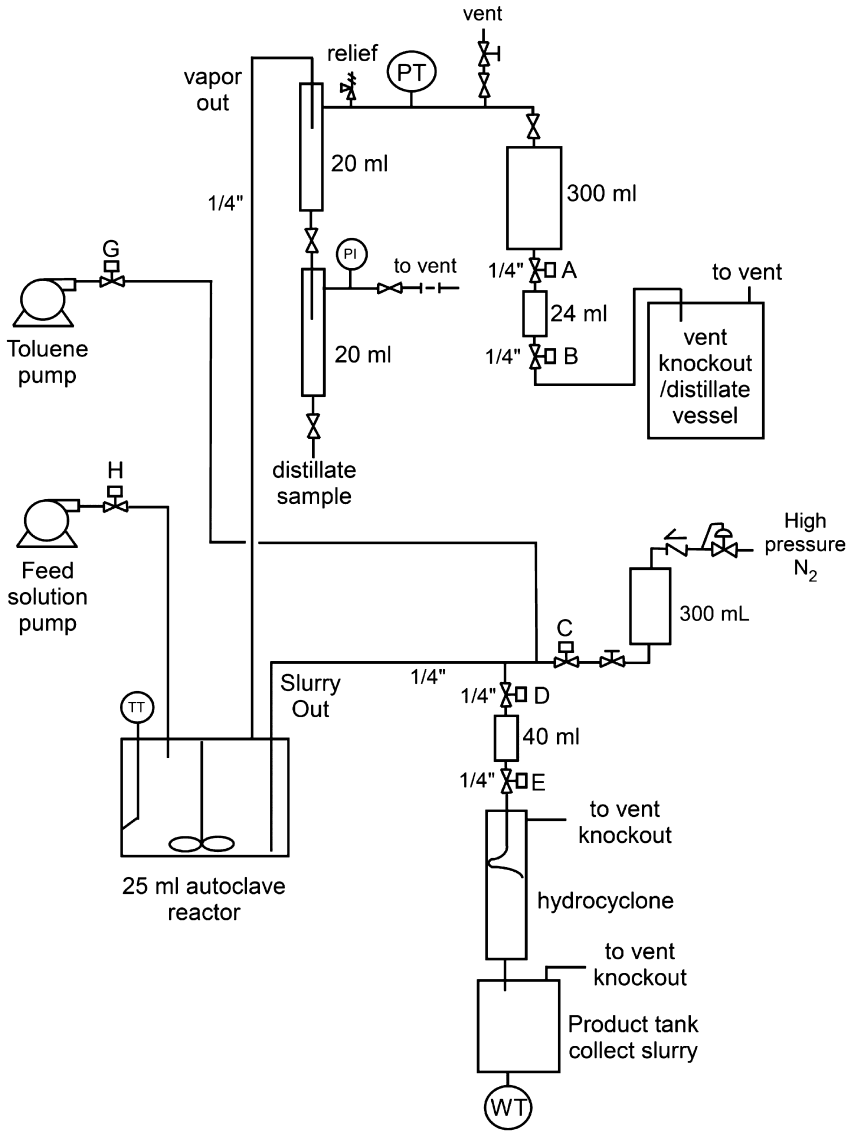


Figure 1. High temperature, fill/empty reactor cart.

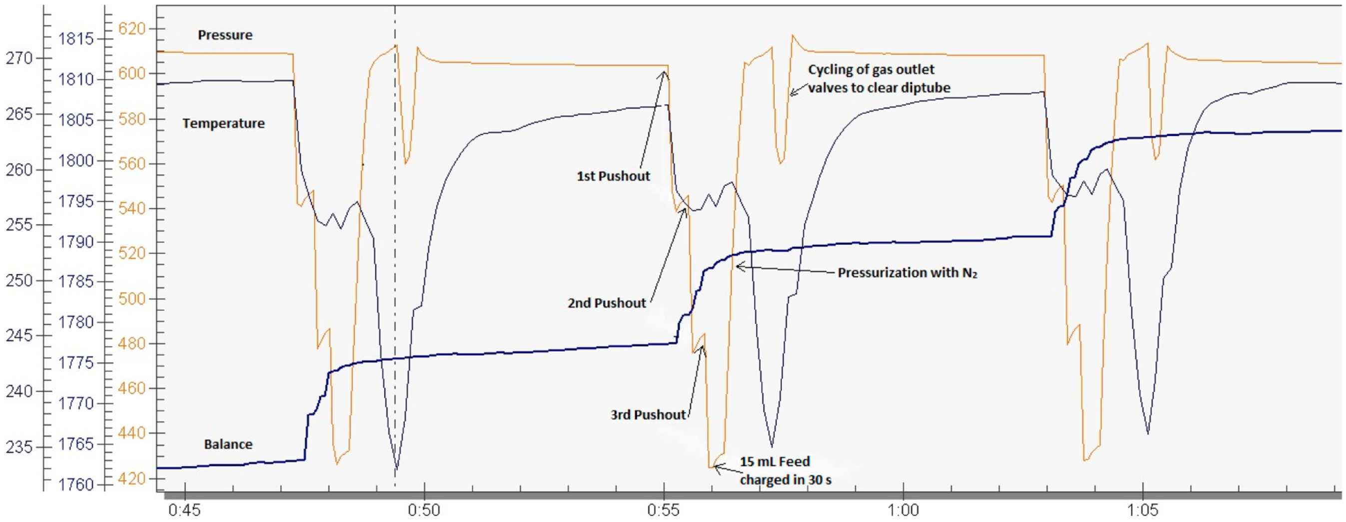


Figure 2. Pressure (orange line), balance trend (blue) and temperature (gray) profile of 5 min reaction cycle.

liquid phase at 265 °C (for example, the boiling point temperature for toluene at 600 psig is 325 °C).[16] Also, because more than 100 volume turnovers could be possible in a day, the reactor is more than 100 times smaller than a batch reactor for the same throughput. Reagents are heated from 20 to 265 °C in approximately 2 min when introduced into the reactor, and they are cooled from 265 °C to near 40 °C in less than 1 min when removed from the reactor while the residence time is precisely controlled. None of this is feasible in conventional batch equipment at any scale. The product slurry flowed out of the reactor system through expansion chambers in series and a hydrocyclone. Product slurry was pushed out of the reactor intermittently through a 1/4″ OD and 0.18″ ID stainless steel diptube into expansion chambers in series separated by automated block valves. This design allows a process to run for extended periods without solids plugging at the outlet because of turbulent intermittent flow through the 1/4″ automated block valves. The flow was zero when the valves are closed followed by very high velocity flow out when the valves are open due to the 550−600 psig pressure difference from one chamber to the next. There are no restricting orifices like in most conventional back pressure regulators, because the restricting orifices clog with solids. Instead, the flow path is greater than 3 mm in diameter when each of the block valves are opened in sequence with pressure driving the force to achieve turbulent flow, which prohibits clogging with solids.

■ AUTOMATION

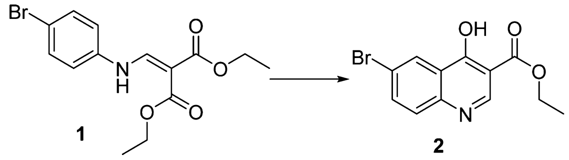
The computerized automated valve sequence which repeated more than 700 times and was vital to successful operation was as follows: when valve D opened (Figure 1), the high pressure of the reactor system immediately pushed the product slurry (pushout) into a 40 mL stainless steel tube which was initially at 0 psig pressure. The reactor pressure only dropped by 10% when pressure equalized with the 40 mL zone because the total interconnected reactor headspace was about 400 mL. As seen in Figure 2, the reactor pressure dropped from approximately 600 psig to about 545 psig. This sudden drop in pressure represents the speed that the slurry was pushed out of the reactor through the 4.5 mm ID tubing, which minimized the potential for solids clogging. The product slurry settled to the bottom of this 40 mL zone due to gravity, and the headspace high pressure nitrogen was trapped when valve D closed. Subsequently, automated valve E opened, and the product slurry was immediately pushed to a hydrocyclone, which separated vapor from the slurry as it depressurized. The slurry gradually accumulated in a product vessel over time as each cycle flowed out of the reactor. This pushout sequence was repeated two additional times to ensure the contents of the reactor had been removed prior to charging the next starting material cycle. The reactor pressure dropped about 10% each time valves D and E were cycled. The lowest pressure during this operation was about 430 psig, which is significantly higher than the vapor pressure of toluene at 265 °C (285 psig). The next section of feed was immediately charged to the hot reactor by the automated intermittent flow feed pump.

The temperature of the liquid phase was constantly measured, but the temperature control was based on the reactor wall temperature.[17] Typical temperature, pressure and balance profiles for a complete fill-empty sequence are shown in Figure 2. This highlights the sequence of events showing the three pushout sequences resulting in a lower temperature and pressure, followed by the addition of the next segment of feed requiring approximately 2 min to reach 260 °C and 3 min to achieve the desired 265 °C reaction temperature. The high thermal mass of the reactor on 25 mL scale was adequate for this fast heat up from room temperature solution. After feed addition, it was anticipated that some amount of the solution was pushed into the dip tube. In order to push this material back into the reactor and avoid solids buildup in the dip tube, the reactor was repressurized to 600 psig through valve C. Toluene wash cycles were also introduced through the diptube to rinse the tube and reactor every third cycle from a second feed pump in order to prevent solids build up. The automated cycle repeated for the duration of the planned run time depending on the amount of feed material to be reacted.

■ DISCUSSION

The cyclization of interest was the formation of hydroxyquinoline **2** (Scheme 1). Batch methodology to generate this molecule has been well-documented but only reported on a small scale in diphenyl ether.[18] In this case, a preferred solvent replacement for high boiling solvents was 2-methyltetrahydrofuran (2-MeTHF) because of its utility as a green solvent.[19] An early proof of concept for using this solvent for the formation of **2** was previously published using the equipment set described above but was not fully optimized.[20] As efforts to optimize this process were pursued, the shortcomings of this solvent under these reaction conditions came to light. 2-MeTHF suffers from high thermal expansion: when 2-MeTHF is heated from 20 to 260 °C, its volume increases 2.13 times. While acceptable reaction profiles were observed, thermal expansion began to impede throughput since less starting solution could be charged in each cycle. Alternatively, when toluene is heated from 20 to 260 °C, its volume only increases 1.48 times, so toluene was chosen for additional studies.[21] To exemplify the throughput issue, the maximum reaction charge to a 25 mL reactor was 15 mL of toluene feed but only 10 mL of 2-MeTHF feed.

Scheme 1. Thermal cyclization to form 2



Safety and yield were significant concerns with the existing batch process. When **1** was processed at 250 °C, a 55.0% yield was isolated as a brown solid with 96.2−99.0% purity. As mentioned previously, the quinoline product has very low solubility in most room temperature solvents, but **1** has very high solubility (32 wt %) as well as excellent stability in toluene, reinforcing the solvent choice mentioned previously. Due to the high solubility of the starting material in toluene, a starting feed consisting of **1** in only 4.2 L/kg of toluene was investigated.[22] Batch screening studies were initiated in port connector reactors to determine the optimal reaction time and temperature.[23] The reactors enabled rapid screening of time, temperature, and concentration to build a data package to inform initial continuous processing. These runs suggested that high conversion and good yield could be obtained at 250 °C with a 2 h residence time; so these conditions were selected for the first continuous run.

Using the reactor described in Figure 1 at 250 °C and residence time of 2 h, the reactor plugged after less than 36 h, which was detected from the pressure transmitter shown in

Figure 1. After cooling and depressurizing the reactor the contents appeared as dark waxy solids (Figure 3). With high wt % solutions in toluene, even the use of wash cycles was not enough to efficiently empty the thick slurry from the reactor, which gradually became packed with solids. The particles were very fine and at this dilution were not well behaved in terms of mobility. During this phase of development, longer reaction times and lower temperatures were also investigated, but these conditions did not alleviate reactor fouling.

Figure 3. Twenty-five mL reactor after fouling, running with 4.2 L/kg of toluene.

OPTIMIZATION

At this point a better understanding behind the behavior of the reaction was required for improvements to be possible. An investigation of solvent volumes showed better conversion over time with more volumes of toluene (Figure 4). Upon considering the mechanism of the reaction, the equivalent of ethanol generated during the reaction could be problematic (Scheme 2). Once intermediate **3** is generated, the desired product can form, starting material can be regenerated, or decomposition can occur. To prove that the presence of ethanol was detrimental to conversion, an equivalent of ethanol was added to the starting feed and half the conversion was observed compared to the case without ethanol present for a 1 h reaction at 250 °C. This also helps explain the observation that a more dilute reaction (10 L/kg) results in higher conversion as a larger ethanol "sink" was available. Traditional batch conditions have the option of removing the ethanol via distillation, but since the continuous reactor was a closed system at high pressure, distillation was not an option.

Temperature was investigated as a handle to drive the conversion further. As seen in Figure 5, improved conversion is indeed observed until no starting material remains after 10 min at 300 °C. Unfortunately, disappearance of starting material in this case did not translate to higher yield, as the decomposition pathways became predominant. It was already well-documented that cyclizations such as these are temperature-dependent with regard to decomposition.[24] A longer term temperature study for this substrate was initiated at 240 °C, and both product and starting material were monitored. As seen in Figure 6, product formation levels off quickly, and the decomposition pathway takes over.

While increasing the toluene to 15 L/kg seems counter-intuitive to the goal of a greener process, the additional yield and shorter reaction times that could be achieved may outweigh the additional solvent requirements. Upon reconsidering the data in Figure 5, after only 10 min at 260 °C, 40% conversion was observed. While this yield is not close to the desired target, it does mitigate the decomposition issues. The product cleanly precipitates and due to its insolubility, no significant levels of **2** are observed in the mother liquor. Also, due to the exceptional solubility of the starting material, only low levels were trapped in the resulting solids. However, while the mother liquor contains clean starting material, the presence of ethanol would continue to hamper conversion to the desired product. A rotovap strip to dryness operation has previously been disclosed as a viable unit operation for continuous processing[25] and allowed removal of

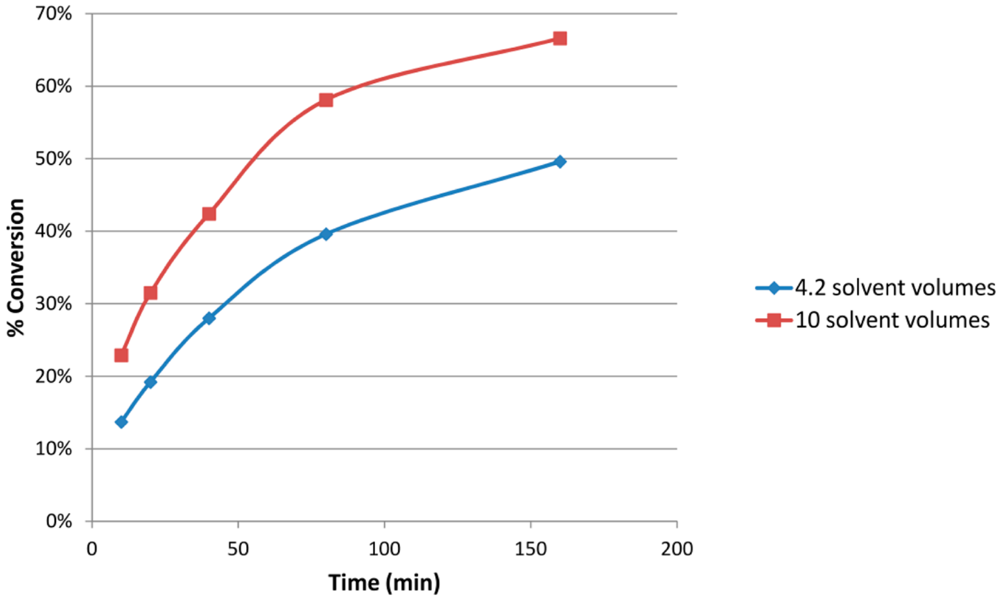
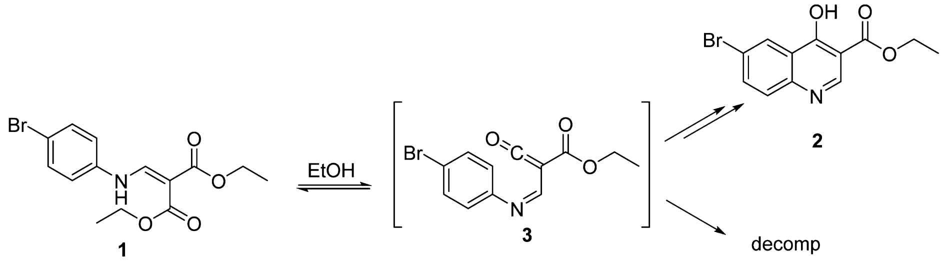


Figure 4. Solvent volume comparison for conversion of **1**.

Scheme 2. Mode of decomposition



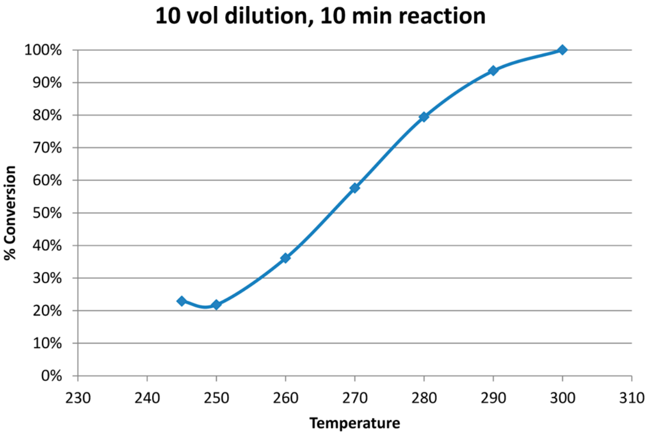


Figure 5. Temperature dependence on conversion.

the ethanol. Subsequent reconstitution of the resulting solids in 15 L/kg of toluene afforded feed ready for resubmission to the reaction conditions. The recycled feed resulted in similar conversion to product because the ethanol had been removed from the system.[26] Here, the operating premise of accepting a low single pass conversion with a subsequent recycle was selected because continuous reactions with recycle of unreacted reagents can improve the overall yield, throughput, and efficiency. Listed below are general drivers for consideration of a recycle process (i.e., continuous reaction with continuous recycle):

1. Late forming impurities in the process;
2. Removal of a reaction byproduct enables higher conversion or purity;
3. For competing reactions, an intermediate conversion point exists where there is a maximum ratio of desired product to impurity;
4. The process benefits from a very high stoichiometric ratio between two reagents;
5. The process has a solubility issue or fluid mechanics and mixing difficulty at low conversion;
6. Catalyst recycle achieves a lower overall catalyst loading but higher instantaneous catalyst loading to the reactor;
7. Solvent recycle results in a lower PMI;
8. Product is lost to the filtrate which could be recovered during recycle.

A separation step is typically employed to remove byproduct and solvents from the recycled material so that it enters the reactor at the same concentration as the fresh feed. For this cyclization a separations step to reconstitute feed was easily accomplished. This process was viewed as a good candidate for recycle in a continuous reactor with an integrated downstream

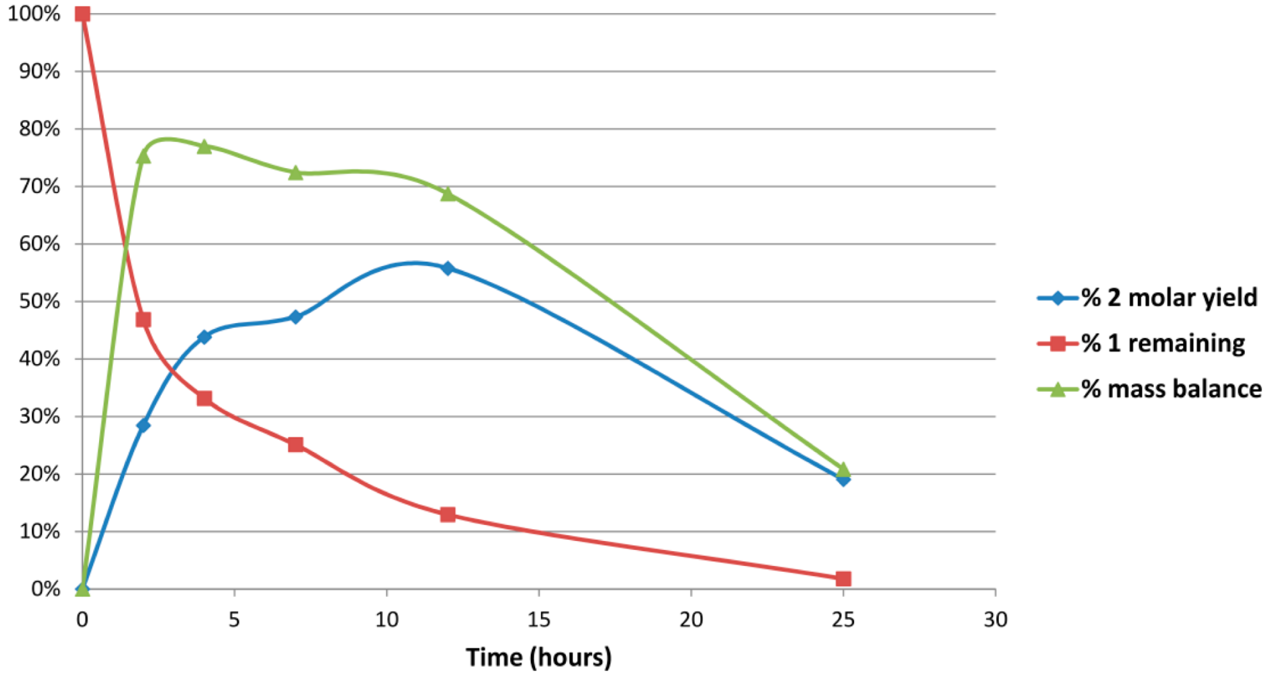


Figure 6. Decomposition of **2** over time at 240 °C.

Table 1. Data from the 300 g run

	yield	mass balance	product balance	HPLC area %	isolated **2** (g)	potency
fraction 1	25.6%	64.0%	52.2%	95.5	12.47	76.7%
fraction 2	49.2%	110.7%	105.1%	96.3	25.14	94.5%
fraction 3	48.6%	87.6%	104.3%	97.0	23.87	94.0%
fraction 4	46.4%	92.0%	100.6%	97.2	23.92	97.3%
fraction 5	47.0%	93.4%	93.9%	97.6	19.57	94.2%
first pass cumulative	43.4%	89.6%	91.4%			
recycle 1	49.5%	93.4%	86.2%	96.4	52.48	94.5%
second pass cumulative	65.1%	90.8%	89.8%			
recycle 2	52.1%	64.2%	92.5%	93.7	27.04	85.5%
process cumulative	76.2%[29]	86.9%	95.4%		169.46	

continuous separation step (rotovap strip to dryness) because drivers 1−3 applied.

EXTENDED RUN

After minimal optimization of temperature and residence time, a 300 g long duration run was planned at 265 °C with a 5 min reaction time utilizing a feed of **1** in 15 L/kg of toluene. Due to concerns about fouling of the diptube and solid buildup in the reactor, a 15 mL toluene wash after every three reaction cycles (15 mL of reaction feed per cycle) was planned. For this run material was collected as five bulk fractions and filtered offline. As seen in Table 1, very comparable solid isolated yields of **2** were collected for each of these fractions in good purity.[27] The mass balance[28] and product balance were monitored throughout the run and were good with the exception of the first section. The first section was less potent and exhibited inferior product and mass balances, possibly suggesting decomposition. The yield of the first section was correspondingly lower, but the remaining sections were well understood and as expected. At this time, a root cause for the low mass balance observed in the first section has not been identified. The mother liquor from the first five sections was combined and concentrated to a solid. After dissolving in 15 L/kg of toluene, it was resubjected to the reaction conditions. After filtration, the resulting mother liquor was again concentrated, redissolved, and submitted to the reaction for a third pass. As seen in Table 2, the potency of the solids after removal of toluene decreased with each pass through the reactor, so only minimal benefit from a fourth pass was expected, and this material was discarded. No evidence of solids buildup or fouling was observed during this run. Figure 7 shows the reactor was very clean and would have been expected to continue running without solids fouling for a considerable length of time.

Table 2. Potency of 1 in mother liquor

mother liquor	g/sol of reconstituted feed	wt of stripped solids (g)	potency
end of first pass lot 5	24.10	25.48	94.58%
section of first recycle lot 6	21.10	23.87	88.39%
second recycle	28.77	39.26	73.27%

When the recycles were factored in, the total volume charged to the reactor was over 10 L, including washes, equating to a total number of reactor turnovers for the run including the recycle fractions of over 700. The equipment ran successfully for a total operating time during this 300 g campaign of 3.9 days without fouling. While for this campaign, the recycles were discrete separate runs, in the future this recycle will be a percentage of the flow combined with clean feed and a percentage of mother liquor going to waste. Determining the percentage of mother liquor going to waste (recycle ratio) is defined as the filtrate mass recycling back to the reactor divided by the filtrate mass flowing to waste and would be 66% for this process going forward.

Next, a shorter run to process 60.2 g of **1** for over 100 reactor turnovers without toluene washes[30] was completed. No fouling or impact on product purity was observed over the operating time of 14 h. It is also important to note that the issues observed during startup as discussed above for the first section of the extended run were not observed here. Therefore, there is no reason to believe the startup will be problematic for every new run. The yield was 71.2%, and the purity of the product was 95.0 HPLC area %. After opening the reactor, no evidence of solid buildup was observed, and the inside of the reactor was visually similar to the run that had incorporated washes (Figure 7), implying that the toluene wash was not necessary. Elimination of the toluene wash would have a significant impact on throughput and decrease toluene usage by 25%. As seen in Table 3, a readily available one gallon autoclave with no wash cycle would be capable of producing over 80 kg of product per week in a lab hood.

TESTING OF ADDITIONAL SUBSTRATES

To test the scope of this equipment set, a quick screen of other thermal cyclizations that are known in the literature were chosen to determine if improvement was possible for these substrates as well (Table 4). Both trifluoromethyl isomers **4** and **6** were examined, and while the cyclization to **4** was not as high yielding in this equipment set, the cyclization to form **7** appeared to be a significant improvement when a recycle was employed. Even more impressive was the yield increase for the methoxy substrate **8**, which saw a significant improvement to 52%. While all the substrates suffer from some degree of decarboxylation, xylene **10** afforded the desired Gould−Jacobs product along with significant levels of **12** resulting from ester hydrolysis and decarboxylation. When the reaction was run under the continuous conditions used to generate **2** (265 °C for 5 min), 20% of this impurity was observed in the isolated solids. Lowering the temperature to 250 °C with the same 5 min residence time resulted in a significant improvement (only 6.9% of the decarboxylated impurity). Changes in reaction temperature could increase the levels of either of the two products, but without further optimization neither pure **11** or **12** was generated. Based on the improvements resulting from minor changes for compound **2**, optimization could lead to a protocol for generating any of these molecules in synthetically useful yields and purity.

Figure 7. Reactor after processing over 300 g of **1**.

Table 3. Comparison of first pass throughput in different reactors with reaction parameters

	25 mL reactor	1000 mL reactor[a]	1 gal/no wash[a]
residence time (sec)	300	300	300
additional operation time (sec)	167	167	167
time for 4 cycles (3 rxn, 1 wash)	1868	1868	NA
wt % feed	7.2	7.2	7.2
density feed	0.88	0.88	0.88
mL per cycle	15	600	2300
2 (g) per 4 cycles (first pass 50% yield)	1.23	49	249
2 (g) per day	57	2280	11500
2 (g) per week	399	16000	81000

[a] Projected throughput.

An important point to remember is that previously reported small scale literature yields may not be repeatable in large scale batch equipment and route redesign may be required.[6,7] While these reactions utilized a single reagent stream, slow addition of one reagent to another or true continuous stirred tank reactor conditions could be explored if there was a benefit to operating at end of reaction conditions in this equipment. It is worth noting that the proposed scale up to generate 80 kg per week in a one gallon reactor represents a 151× scale up over the 25 mL reactor demonstrated here. For a similar batch scale up to a 500 L reactor from a 25 mL batch demonstration, this is a 20 000× scale up that would require good understanding of heating and cooling times and require demonstration on intermediary scales. Furthermore, if this chemistry was scaled to a 500 L batch reactor, toluene would not be used due to the high pressures required. The reaction would instead be run in a higher boiling solvent which could complicate product isolation.

■ CONCLUSIONS

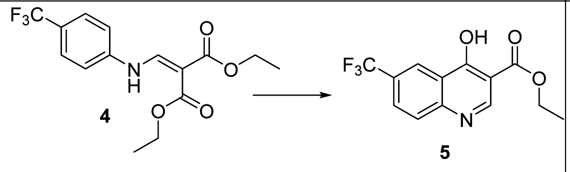
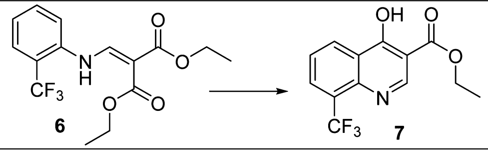
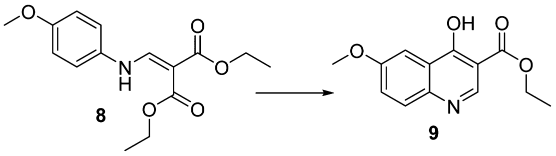
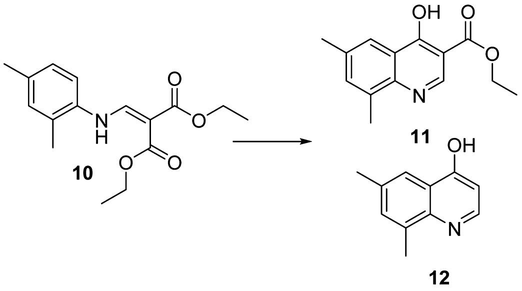
An improved protocol for the thermal cyclization to form **2** was developed in a high temperature/high pressure, fill/empty reactor that readily handled solids in flow. The reactor utilized expansion chambers in series with sequenced automated block valves and a hydrocyclone to control the slurry flowing out of the reactor, maintain reactor back-pressure on reactor at all times, depressurize the product slurry to atmospheric pressure, separate slurry from vapor, and transport slurry to a product collection tank. The process was demonstrated in flow for 3.9 d equating to over 700 turnovers without fouling or significant buildup of solids in the reactor when a toluene rinse was introduced after every three reaction cycles. The total run time of the automated reactor system was 94 h with no solids plugging or clogging. The yield was increased and similar purity delivered compared to the batch conditions. A shorter duration run was demonstrated without a toluene rinse between reaction cycles, which would result in a greener process and increase throughput.[35]

This reactor type is a legitimate alternative for high-temperature, high-pressure continuous reaction with solids in flow. The value of running this setup with the potential for manufacturing in a lab hood setting would result in a significant reduction in capital investment for new equipment, utilize modified equipment that was readily available, and increase temperature and pressure capabilities compared to standard batch reactors. Furthermore, scale up in a batch autoclave is not capable of achieving 3 min heat up to the 265 °C reaction temperature, precisely controlled 5 min reaction time, and less than 1 min cool down to room temperature after the desired reaction time. Therefore, scale up in a batch reactor would not achieve the same in situ yield and impurity profile as the automated intermittent flow reactor. Additional examples were quickly screened ,and while optimization would be required if higher purity material was necessary, these reactions showed great potential for an improved process in this equipment set for these substrates as well. Investigations are ongoing to determine the root cause of poor results during the first section of the long run to generate **2**. Larger scale efforts are being explored in order to examine energy consumption and toluene recycling as additional potential green benefits to the process.

■ EXPERIMENTAL SECTION

General. Starting materials and reagents were purchased commercially and used without further purification. The reaction feed and toluene rinse were delivered by 1000D ISCO pumps[36] to accurately supply feeds under high pressure with automation control. Reagent feeds flowed into the reactor through 1/8″ OD, 0.069″ ID stainless steel tubing from the automated intermittent flow high pressure feed pumps. The diptube was designed with minimal clearance to almost completely remove the reaction slurry from the reactor, and the reactor itself was machined to allow clearance of the diptube with the pitched blade impeller resulting in approximately one mL of slurry heel remaining in the reactor after emptying. DeltaV[37] was used to control all automation for all pumps and

Table 4. Screening of additional substrates[a]

	First pass Run Time (h)	Overall Yield	Purity	Potency	Literature yield
	5	27.0	93.6	96.7	95%[31]
	6	62.3	95.1 96.6[b]	94.8 98.5[b]	45%[32]
	6	52.0	89.9 92.3[b] 92.5[c]	91.3 92.1[b] 91.8[c]	14%[33]
	6	35.6	90.0	90.0	83%[34]

[a]All reactions run at 600 psig, 265 °C with a 5 min tau with the exception of 10 which was run at 250 °C. [b]First recycle. [c]Second recycle.

valve sequences and to trend temperatures and the product balance. Initially Teflon gaskets that are rated to 350 °C were used, but the changes in pressure caused the slightly melted PTFE to flow into the reactor.[38] The better option was inexpensive Grafoil gaskets which are replaced every time the reactor is taken apart. Additional details about the equipment utilized has been well-described in the body of this paper with further details in the Supporting Information. The reported yields are corrected for potency and reactions were monitored by HPLC and purities and potencies quoted herein refer to HPLC area % at 220 nm. HPLC method: Zorbax SB-C8, 3.5 μm 4.6 mm × 75 mm column; flow rate 2 mL/min; mobile phase A: 0.1% trifluoroacetic acid in water; mobile phase B: 0.1% trifluoroacetic acid in acetonitrile; gradient: 96:4 A/B to 10:90 A/B over 12 min, 3 min at 96:4 A/B. Temperature: 30 °C. Injection volume: 2 μL. Retention times are expressed in minutes. Cyclization substrates **1**, **4**, **6**, **8**, and **10** were all generated via known literature procedures.[39,31−34] Melting points were collected on a Buchi Melt Point B-540 and are uncorrected. NMR data was collected in TFA-*d* or solids were dissolved in minimal TFA-*d* and diluted with acetonitrile-d_3.

Ethyl 6-bromo-4-hydroxyquinoline-3-carboxylate (2). Diethyl 2-(((4-bromophenyl)amino)methylene)malonate **1** (300.0 g, 876.7 mmol) was dissolved in toluene (4.5 L), and a portion was transferred to a 1000D ISCO pump, while a second 1000D ISCO pump was filled with toluene. The pump then feeds 15 mL of this solution to a 25 mL reactor at 265 °C and 600 psi nitrogen to remain above the vapor pressure of the reaction solution. After 5 min in the reactor, the resulting slurry exits the reactor through a valve via a diptube to near the bottom of the reactor to a 40 mL depressurization and cooling zone. Finally, a second valve in series opens and the trapped nitrogen pressure sends the slurry to a 300 mL depressurization hydrocyclone zone. This sequence to empty the reactor was repeated 2 additional times as described above to ensure the residual slurry was removed to a minimal volume. Then, the reactor was refilled with reagent solutions and repressurized from approximately 430 psi to 600 psi through the diptube. After an additional 2 cycles were performed in this fashion, toluene (15 mL) was sent to the reactor, held for 5 min, and sent to the collection bottle in the same fashion as reaction slurry. A total of 5 reaction sections were collected, each was filtered, washed with toluene (75 mL), and dried under vacuum at 50 °C. Each section was approximately 100 reactor turnovers. The mother liquors were combined and concentrated on a rotary evaporator at 60 °C bath temperature. The resulting solid (147.0 g) was dissolved in toluene (2.2 L). This recycle was submitted to the same procedure as the first pass material. Finally, the mother liquor from the recycle was concentrated as above, and the resulting solid (63.13 g) was dissolved in toluene (950 mL). This material was subjected to the same conditions as above. After drying the 6-bromo-4-hydroxyquinoline-3-carboxylic acid ethyl ester was collected as 7 lots as beige solids (12.47 g (76.7% potency), 25.14 g (94.5% potency), 23.87 g (94.0% potency), 23.92 g (97.3% potency), 19.57 g (94.2% potency), 52.48 g (recycle lot, 94.5% potency), 27.04 g (2nd recycle lot, 85.5% potency), 170.18 g (potency corrected), 575.0 mmol) for a 65.6% yield. Mp = 327.8 to 328.9 °C; HPLC: t_R = 4.63 min. ^{1}H NMR: (400 MHz, TFA-d), 1.52 (3H, t, J = 7.04 Hz), 4.67 (2H, q, J = 7.03 Hz), 8.03 (1H, d, J = 8.79 Hz), 8.28 (1H, d, J = 8.79 Hz), 8.80 (1H, s), 9.32 (1H, s); ^{13}C NMR (100 MHz, TFA-d), 11.9, 64.7, 105.3, 121.0, 121.2, 124.9, 126.9, 137.9, 141.1, 145.0, 167.2, 172.4.

Ethyl 4-hydroxy-6-(trifluoromethyl)quinoline-3-carboxylate (5). Diethyl 2-(((4-(trifluoromethyl)phenyl)amino)methylene)malonate **4** (30.09 g, 90.8 mmol) was dissolved in toluene (450 mL) and reacted in the same manner as **1**. After drying, 7.22 g (96.7% potency) of **5** were collected as a tan solid for a 27.0% yield. Mp = 324.2 to 333.4 °C; HPLC: t_R = 5.10 min. ^{1}H NMR (499 MHz, acetonitrile-d_3) δ 1.43 (t, J = 7.09 Hz, 3H), 4.57 (q, J = 7.09 Hz, 2H), 8.31 (d, J = 9.10 Hz, 1H), 8.35 (dd, J = 9.10, 1.90 Hz, 1H), 8.81−8.84 (m, 1H), 9.37 (s, 1H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 14.4, 66.1, 108.1, 121.5, 123.9, 124.3 (q, J = 4.8 Hz), 124.7 (q, J = 271.8 Hz), 133.0 (q, J = 34.3 Hz), 134.7 (q, J = 2.9 Hz), 142.7, 149.4, 169.0, 175.1.

Ethyl 4-hydroxy-8-(trifluoromethyl)quinoline-3-carboxylate (7). Diethyl 2-(((2-(trifluoromethyl)phenyl)amino)methylene)malonate **6** (30.00 g, 90.6 mmol) was dissolved in toluene (450 mL) and reacted in the same manner as **1**. After the resulting amber solution stood at room temperature solids precipitated and the solution was filtered. After drying, 13.85 g (94.8% potency) of **7** was collected as a tan solid for 50.8% yield. The filtrate was concentrated on a rotary evaporator and reconstituted in toluene and resubjected to the reaction conditions. An additional 3.01 g (98.5% potency) was collected for an additional 11.5% yield. The overall yield for the process was 62.3%. Mp = 219.2 to 220.2 °C; HPLC: t_R = 3.95 min. ^{1}H NMR (499 MHz, acetonitrile-d_3) δ 1.43 (t, J = 7.09 Hz, 3H), 4.58 (q, J = 7.10 Hz, 2H), 8.04 (dd, J = 8.30, 7.80 Hz, 1H), 8.52 (d, J = 7.83 Hz, 1H), 8.82 (d, J = 8.31 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 14.5, 66.4, 108.2, 122.1 (q, J = 33.5 Hz), 123.2, 124.4 (q, J = 272.8 Hz), 131.1, 131.4, 137.1, 137.5 (q, J = 5.2 Hz), 148.9, 168.9, 175.4.

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (9). Diethyl 2-(((4-methoxyphenyl)amino)methylene)malonate **8** (30.00 g, 102.3 mmol) was dissolved in toluene (450 mL) and reacted in the same manner as **1**. After drying 8.85 g (91.3% potency) of **9** was collected as a tan solid for a 32.0% yield. The filtrate was concentrated and resubjected to the reaction conditions. An additional 3.88 g (92.1% potency) was collected for an additional 14.1% yield. This filtrate was concentrated and resubjected to the reaction conditions a second time. An additional 1.63 g (91.8% potency) was collected for an additional 5.9% yield. The overall yield for this process was 52.0%. Mp = 292.2 to 293.4 °C; HPLC: t_R = 5.18 min. ^{1}H NMR (499 MHz, acetonitrile-d_3) δ 1.39 (t, J = 7.09 Hz, 3H), 3.95 (s, 3H), 4.52 (q, J = 7.09 Hz, 2H), 7.71 (dd, J = 9.30, 2.90 Hz, 1H), 7.74 (d, J = 2.90 Hz, 1H), 7.98 (d, J = 9.29 Hz, 1H), 9.03 (s, 1H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 14.6, 57.6, 66.0, 104.3, 106.9, 123.7, 123.7, 131.4, 136.8, 144.4, 162.7, 169.7, 173.3

Ethyl 4-hydroxy-6,8-dimethylquinoline-3-carboxylate (11). Diethyl 2-(((2,4-dimethylphenyl)amino)methylene)malonate **10** (30.19 g, 103.6 mmol) was dissolved in toluene (465 mL) and reacted in the same manner as **1** but with a reactor setpoint temperature of 250 °C. After drying, 10.06 g (90.0% potency) of **11** were collected as a tan powder for a 35.6% yield. mp =282.8 to 285.2 °C; HPLC: t_R = 4.71 min. ^{1}H NMR (499 MHz, acetonitrile-d_3) δ 1.42 (t, J = 7.09 Hz, 3H), 2.53 (s, 3H), 2.67 (s, 3H), 4.55 (q, J = 6.85 Hz, 2H), 7.83 (s, 1H), 8.16 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 14.5, 17.7, 22.0, 65.8, 106.8, 122.2, 123.0, 131.1, 138.7, 142.0, 143.1, 145.4, 169.5, 174.3.

■ ASSOCIATED CONTENT

Supporting Information

Details of the equipment used. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Temperature control was performed by the controller for the reactor, and the thermocouple was in contact with the wall of the reactor to avoid overheating while the reactor was empty between cycles.

(16) Parr reactors have a rating of 3000 psi, and this system was set up with a pressure relief valve set at 1400 psi and pumps set to stop at 1000 psi.

(17) A great deal of effort was put into this as the high temperatures for successful cyclization are also close to decomposition temperatures for some molecules. When temperature control was performed off the liquid temperature, the empty reactor would overheat prior to the next charge of material, and tars would form. Once tars formed, even the most granular of solids could get trapped and have difficulty exiting the reactor. No heat exchanger was necessary on this scale, but the larger scale equipment set discussed later in this paper would require a heat exchanger on the inlet and outlet.

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(22) Even more desirable was direct telescoping of the reaction of 4-bromoaniline and diethyl ethoxymethylenemalonate followed by cyclization to **2**. Reduced reactivity and lower purity of the reaction resulted in the decision to run the process stepwise.

(23) See Supporting Information for some details around these reactors and a paper regarding this equipment set and their safe use will be published in due course.

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(27) Typical HPLC area % impurity levels were 2% of the decarboxylated product of **2**, 1% toluene, and 0.6% **1**.

(28) Mass balance was expected to be low due to solvent loss during expansion upon exiting the system via the hydrocyclone. The mass deficiency is a close approximation of the solvent loss during this expansion.

(29) This yield number is higher than reported in the experimental because it is based on the potency corrected **1** placed back into recycle rather than a dry in/dry out calculation, and the product dry weight is not corrected for potency.

(30) This run utilized a first and second recycle, and a rinse was added to the reactor to hold at temperature as the slurry was filtered and the mother liquor concentrated and redissolved for reprocessing.

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