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Manufacture of a β-Hydroxyester via a Continuous Reformatsky Process

Gabriel Loh,*[†] Ryo Tanigawara,[‡] Salim M. Shaik,[†] Kanicha Sa-ei,[†] Loretta Wong,[†] and Paul Nicholas Sharratt[†]

[†]Institute of Chemical and Engineering Sciences (ICES), A*STAR 1, Pesek Road, Jurong Island, Singapore 627833

[‡]Shionogi & Co., Ltd., 7, Moriyama, Nishine, Kanegasaki-cho, Isawa-gun, Iwate 029-4503, Japan

ABSTRACT: The use of continuous processing in a Reformatsky reaction has been investigated as a means to control the large heat of reaction and reduce the inventory of hazardous materials. A laboratory-scale continuous miniplant for manufacture of an aromatic β-hydroxyester has been designed and built for a production rate of about 100 mL/h. The plant operated at steady state for several hours and provided strong evidence that a larger-scale continuous plant could readily be designed. For this chemistry, the use of continuous processing is not only a safer and more efficient technology (as compared to the typical batch process) but also cleaner, giving fewer byproduct and at much lower concentration.

■ INTRODUCTION

The production of fine chemicals and pharmaceuticals has been traditionally achieved via batch processes. Recently, there has been interest in using continuous and intensified reactors for manufacturing. These efforts in process intensification via continuous processing are generally thought to have positive impacts in terms of smaller equipment footprint, significantly reduced in-process inventory, improved mixing control, excellent heat transfer, expanded operating conditions and reduced residence time. Moreover, they can bring about environmental benefits such as reduced byproduct and enables recycling of streams so as to reduce solvent and material usage.

The unpredictability of the Reformatsky reagent formation means that there is always a high risk of runaway reactions and large solvent volumes are required to provide a heat sink. The **IN**tegrated **CO**ntinous **M**ultipurpose **E**ngineering (INCOME) team in the Institute of Chemical and Engineering Sciences (ICES) studies various aspects of innovative processing including continuous process development. We undertook the process development of a continuous Reformatsky process to access a potentially safer way carrying out the reaction at scale. We investigated the benefits of continuous processing in terms of process efficiency, yield/conversion, processing flexibility and robustness.

The model Reformatsky reaction comprises the zinc-mediated formation of a β-hydroxyester from an α-haloester and an aldehyde. It is typically carried out by first chemically activating the zinc to remove the zinc oxide layer on the surface and to obtain a high surface area of clean zinc which will enhance mass transfer at the interface. Zinc enolate, or the "Reformatsky reagent", is then formed via the reaction between the activated zinc and the α-haloester. The Reformatsky reagent then reacts with an aldehyde to afford the β-hydroxyester product. The reaction is quenched by the addition of citric acid. The reaction scheme used is illustrated in Scheme 1.

The use of the Reformatsky reaction in large-scale batch to synthesise β-hydroxyesters and related compounds is well established.[1−3] Several known engineering and chemistry issues which have inhibited a safe scale-up of the process have been previously reported.[4−6] The unpredictability with the high exothermicity of the Reformatsky reagent formation and the several competing side reactions pose challenging scale-up problems.

The unpredictability of the initiation and the highly exothermic nature of the Reformatsky reagent formation are of severe safety concerns during scale-up. They might lead to a sudden temperature excursion which without timely or sufficient cooling would lead to secondary decomposition reactions and pressure buildup. The high possibility of a runaway reaction means that the process is usually carried out with high volumes of solvent content which is used as a heat sink. Moreover, the synthesis of β-hydroxyester is subjected to a number of competing side reactions including self-condensation of the bromoester and carbonyl components and elimination or retrograde aldol condensation of the Reformatsky reagent, β-alkoxyzinc ester, which cause low yield.[4] These problems could potentially be minimised via the use of continuous processing, which has been acknowledged for the benefits of excellent heat transfer, high mixing efficiency, low in-process inventories, processing flexibility, and robustness and higher selectivity (though obviously the benefits are process-dependent). Recent work by Hiroshi Osato and co-workers has demonstrated a safer means of scaling up a similar batch Reformatsky-type process.[6] However, the process developed still has a high inventory, and a batch reactor will still have relatively poor heat transfer performance, and thus, the process cannot be seen as inherently safe.

■ RESULTS AND DISCUSSION

Process Development. The Reformatsky process can be broadly classified into three sequential stages: stage 1 -

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Scheme 1. Reformatsky reaction scheme

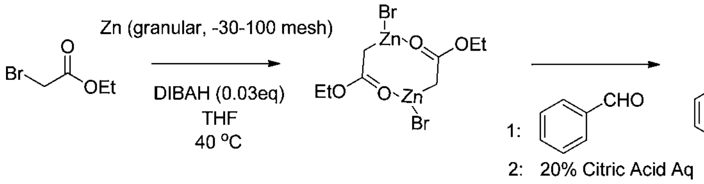

Table 1. Summary of process safety assessment methodology

process safety assessment activities	required information	source of information
initial hazards screening	chemical reactivity, thermal stability, toxicity, flammability, material compatibility, etc.	literature (e.g., MSDS, journals, etc.), experimental (DSC, TGA, etc.)
desired reaction assessment	reaction enthalpy, estimated adiabatic temperature rise, maximum temperature of the synthesis reaction (MTSR), thermal accumulation, etc.	reaction calorimetry
undesired reaction assessment	adiabatic temperature rise, rate of temperature and pressure increase, runaway onset temperature, etc.	adiabatic calorimetry
hazards identification	process safety and operability issues, plausible worst case scenarios, etc.	risk assessment, hazards and operability (HAZOP) study, "what-if" analysis, etc.

Reformatsky reagent formation, stage 2 - Reformatsky reaction, and stage 3 - quench, as illustrated in Scheme 1. The initial development work was carried out in small batches of 50-mL volume in the Mettler Toledo Multimax reactor system and in an 80-mL Mettler Toledo RC1e calorimeter. The procedure of choice was largely based on the work reported by Girgis et al.[5] Data obtained from the batch experiments outlined below were then used for the design of both the continuous process and the equipment required for its operation.

Reformatsky Reagent Formation. This reaction is typically carried out by first removing the zinc oxide layer and exposing a larger, specific surface area of free zinc metal. Various methods such as treatment with iodine,[2,5] chlorotrimethylsilane,[2,5,7] 1,2-dibromoethane,[5,7] copper chloride,[2,5] and methyl magnesium bromide[2] have been tried to activate zinc, but they have proved to be unsuccessful in providing a means of immediate initiation. Due to the unpredictability of the initiation and the high exothermicity, scaling up the process safely remains a challenge. In order to scale up, an efficient yet safe zinc activation and Reformatsky reagent formation will be necessary. The procedure of choice was based on the work carried out by Girgis et al.[5] at Novartis who successfully identified and developed a procedure for undelayed zinc activation using DIBAL-H as the activator. Fast zinc activation is crucial for the safe scale-up of such processes.

Five and five tenths grams (3.5 equiv) of zinc granule[a] was charged into the reactor containing 25 mL of THF. The suspension was then heated to 40 °C prior to the addition of a small quantity of ethyl bromoacetate (0.3 mL, approximately 5%) which was required for good activation. This was then followed by the addition 0.4 mL of 1 M DIBAL-H in THF as the reducing activator for the removal of the oxide layer on the zinc granule over a period of 10−15 min as described by Girgis' work.[5] The addition of the remaining 5 mL (2 equiv) of ethyl bromoacetate was carried out over a period of about 1 h due to the exothermicity of the reaction. The good activation of zinc was evidenced by immediate initiation of both zinc activation and zinc enolate formation, thus preventing chemical energy accumulation in the reactor.

Since Reformatsky reactions using organic bromide are intrinsically fast and therefore essentially diffusion-controlled, the rate of zinc enolate formation reaction is limited by the available zinc surface. It was decided to use an excess of zinc in the process to allow the rate to be controlled by the addition of organic bromide. This approach allowed control of the thermal/chemical energy accumulation in the system and at the same time reduced the need for highly efficient mixing required to produce a well-mixed biphasic (solid−liquid) system.

Investigation to determine the sensitivity of the zinc activation and the subsequent Reformatsky reagent formation to mixing intensity was carried out. It was evident that with −30 to 100 mesh zinc granule size, complete suspension was not possible. However, in the investigated agitation range of 800−1450 rpm in a 50-mL Mettler Toledo Multimax reactor, the experiments showed good reactivity, as demonstrated by similar heat generation rate with no delayed initiation which was consistent with the results shown by Girgis et al.[5] This result was also replicated in a larger 700-mL reaction volume using an agitation speed of 450 rpm. The mixing study was carried out to demonstrate that there was no need for highly intensive mixing; it was sufficient to have good liquid motion without anything approaching homogeneous solids dispersion.

Reformatsky Reaction and Quench. 2.4 mL (1 equiv) of neat benzaldehyde was slowly added to the zinc enolate reaction mixture over a period of about 30 min. An instantaneous exotherm of 3−5 °C was observed throughout the period of addition which indicated that the reaction was fast; the heat generation could be controlled by the dosing rate. Subsequently, the reaction mixture was aged for another 10 min prior to the quench step.

The destruction of the excess zinc enolate was carried out using 50 mL of 20 wt % citric acid solution. The product-containing reaction mixture was slowly added over a period of about 30 min to the citric acid solution at 5 °C, and similarly, an instantaneous exotherm of 3−5 °C was observed. The biphasic mixture was allowed to stand for approximately 10−15 min prior to decanting off the organic layer and sampled for further analysis.

Process Safety Assessment. As a part of the process development effort, process safety and hazards assessment activities were carried out. Initial screening of the materials in the process was carried out to identify the inherent hazards of the materials. Information such as chemical reactivity, thermal stability, toxicity, etc. were important factors considered during the design of the continuous process. This was followed by hazards characterisation activities. The thermochemistry of the synthesis reaction stages (stage 1- Reformatsky reagent formation, stage 2 - Reformatsky reaction, and stage 3 - quench) were evaluated using a reaction calorimeter. Subsequently, a number of plausible worst-case scenarios identified in an extensive risk assessment were simulated in an adiabatic calorimeter. These calorimetric data were required for both process design and process safety evaluation purposes. Table 1 summarizes the process assessment methodology adopted in ICES as a part of the process development effort.

Initial Hazards Screening. Initial screening of all the materials in the process (starting material, intermediate and final products, or byproduct) was carried out to determine the associated inherent hazards. Information such as chemical reactivity, thermal stability, toxicity, flammability, material compatibility, etc. can be obtained from literature (e.g., material safety data sheets) or experimentally. Such data were important for both process design and safety evaluation purposes.

For example, thermal stability analysis was carried out to identify any decomposition hazards and to develop a safe envelope of process operating parameters. Information such as enthalpy of decomposition and the onset temperature can be readily obtained using a DSC and TGA or from reliable literature. The information obtained can be used to determine the envelope of safe operating conditions at which a runaway scenario will not trigger secondary reactions such as the decomposition of the materials present in the system.

Using information from the reaction calorimeter or the adiabatic calorimeter, it was possible to estimate or obtain the adiabatic temperature rise of the reaction. With the designated operating temperature, the maximum temperature of the synthesis reaction (MTSR) of the Reformatsky reagent reaction of about 170 °C should be below the onset temperature of decomposition of any material present in this stage of the process, e.g. ethyl bromoacetate gave an onset temperature of 331 °C. Table 2 gives the enthalpy of decomposition, $\Delta H_{\mathrm{decomp}}$, and onset temperature, T_0, for key components in the system.

Table 2. Thermal stability information of various compounds[8]

materials	$\Delta H_{\mathrm{decomp}}$ (J/g)	T_0 (°C)
benzaldehyde	N/A	250
ethyl bromoacetate	535.13	331

Desired Reaction Assessment. The thermochemistry of the different stages of the Reformatsky process was studied using a 80-mL Mettler Toledo RC1e calorimeter. Calorimetric analysis was used to determine the information necessary for the design and scale-up of a continuous process and for process safety evaluation purposes. The experiments were carried out under operating conditions of temperature, pressure, and concentrations the same as those for the designed continuous process. Various information such as reaction enthalpy, estimated adiabatic temperature rise, and MTSR could be obtained. These data are important not only for process safety assessment but also for process and equipment design, e.g. enthalpy of reaction was used for the heat exchanger or the continuous stirred tank reactor (CSTR) surface area sizing and reagent flow rates.

For example, the stage 2 coupling reaction was carried out with first having a batch of Reformatsky reagent (2 mol equiv) mixture prepared earlier from the calorimetry analysis of stage 1 of the Reformatsky process. Benzaldehyde was added over a period of 30 min with an immediate exotherm constantly observed over the period of addition, with a small trailing temperature profile after the completion of addition (refer to Figure 1). Such observations, as with the other stages of the process were indications of a fast reaction which are favorable for continuous processing. A reaction enthalpy of about 71 kJ/mol, with estimated adiabatic temperature rise and MTSR of about 72 and 112 °C, respectively, was obtained, following some heat balance calculation, or from the iControl RC1e software directly. The obtained data for stage 2 of the process are summarised in Table 3.

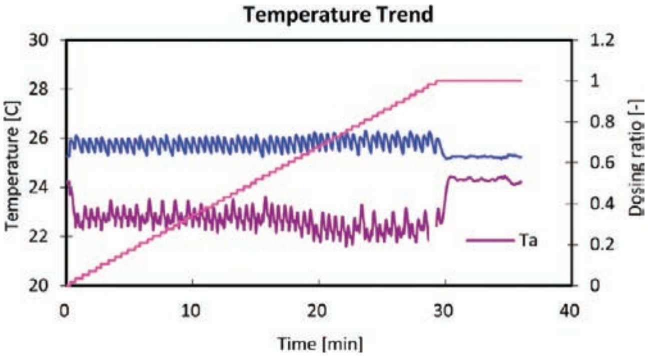

Figure 1. Reaction calorimetry temperature trends of the Reformatsky coupling reaction.

Table 3. Information obtained from the reaction calorimetry experiment

no.	information	
1	presence of delayed initiation?	no
2	rate dosing controlled reaction?	yes
3	reaction enthalpy	70.98 kJ/mol
4	max. heat output	100 W/L
5	heat capacity (C_p)	1.20 kJ/kg·K
6	heat transfer coefficient (UA)	1.54−1.58 W/K
7	thermal accumulation	<5%
8	$T_{\mathrm{adiabatic}}$	72.4 K
9	maximum temperature attainable by the synthesis reaction (MTSR)	365.4 K

Undesired Reaction Assessment. A hazard and operability study (HAZOP) was carried out to systematically examine the process and identify and evaluate any potential problems which may represent risk to individuals or equipment. The study group, consisting of an experienced study leader, process engineers, and chemists, highlighted various potential hazards and operation issues and also identified a number of credible worst-case scenarios which could potentially lead to a runaway reaction. These scenarios were then simulated in the automatic pressure tracking adiabatic calorimeter (APTAC) so as to track the system temperature and pressure during a runaway situation. Figures 2 and 3 show the temperature and pressure profile of a runaway scenario where loss of ethyl bromoacetate-dosing control resulted in a large, single charge of the substrate into the reactor.

A highly energetic runaway reaction with large instantaneous temperature and pressure excursion of a rate about 700 °C/min and 230 kPa/min, respectively, with no indication of secondary

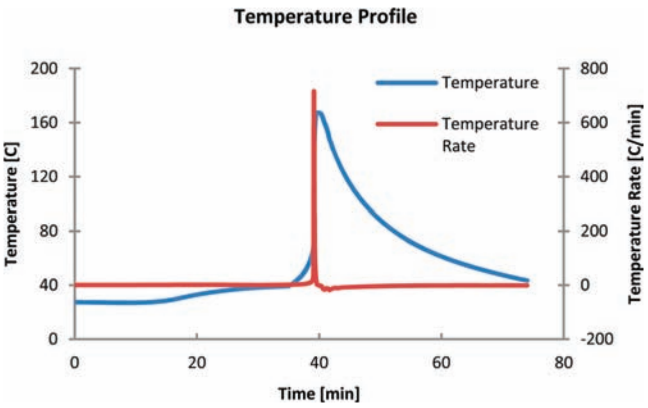

Figure 2. APTAC temperature trend.

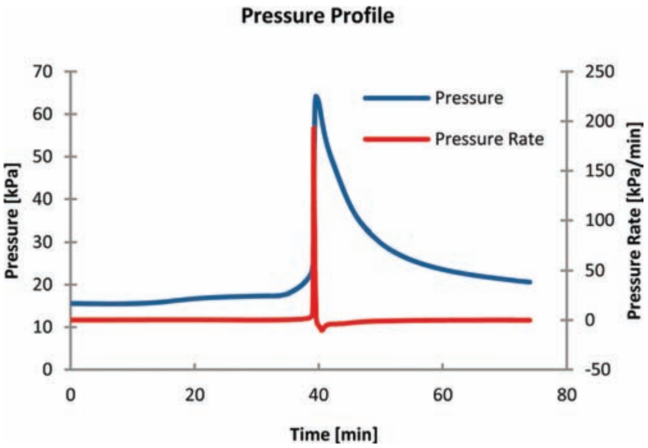

Figure 3. APTAC pressure trend.

decomposition reaction, was observed in the simulated runaway reaction. An adiabatic temperature rise of about 130 °C could be observed. With such rapid temperature and pressure increases, implementation of remedial actions such as "crash" cooling or quench may not be possible. Thus, using the experimental data, appropriate sizing of the relief system employing various techniques such as the Design Institute for Emergency Relief Systems (DIERS) methodology can be carried out.[9] In this case, the condenser vent was open to the atmosphere and of sufficient capacity—in the worst-case runaway event, the reaction mixture would start to boil, and the pressure would be relieved via the vent.

Process Design. The batch experiments and the calorimetric information provided the basis for designing a continuous Reformatsky process with the key objectives of process intensification, scalability, and safety. A glass reactor system with a nominal flow of about 100 mL/h was designed.

Stage 1. β-Hydroxyester Reagent Formation. . The zinc activation and Reformatsky reagent formation reactions were carried out in a 700-mL CSTR with a heat transfer contact area of approximately 0.027 m^2. Because the reaction involved both liquid and solid phases, a CSTR is an appropriate choice. This allowed the reactor to operate with an inventory of zinc and to be controlled by the rate of addition of bromacetate. A modified solid glass screw feeder from Sigma Aldrich was used to provide automatic zinc feed into the reactor at the desired rate of 1.1 g/min to match the rate of zinc consumption during reagent formation. This also avoided the need for precise control of solids addition.

One of the challenges of continuous process is the ability to effectively process solids-containing process fluids. A tube with a large internal diameter, sized to ensure that the linear velocity in the tube was below the settling velocity of a zinc particle of 100-fold reduction in the original size was used. By doing so, large zinc particles will not be carried downstream to cause blockage problems. Calorimetry data allowed us to size the reactor on the basis of the reaction enthalpy of 270 kJ/mol with the capability of operating the process at higher concentration. The reaction mixture was then cooled in a glass, coiled heat exchanger to ambient temperature in preparation for the coupling reaction.

Stage 2. Reformatsky Coupling Reaction. . Given that the exothermic reaction was a single-phase mixture, the choice of a jacketed static mixer as the reactor was obvious. It provided high mixing efficiency and high surface area-to-volume ratio which meant that such reactors have high heat transfer coefficients. One of the concerns raised during the HAZOP study was the temperature excursion at the entrance of such continuous flow reactors which may be of both safety and product quality concerns. As such, the decision was made to have two static mixers in series with split benzaldehyde flow as illustrated in Figure 4. This not only provided better distribution of heat across the reactors, and thus better heat control, but also minimised or prevented side reactions which might have occurred during temperature excursion. With a reaction enthalpy of 71 kJ/mol, the minimum heat exchange surface area was determined for appropriate sizing of the static mixers.

Stage 3. Quench and Phase Separation. . The quenching of the reaction mixture using 20 wt % citric acid to destroy excess Reformatsky reagent and the phase separation of the product-rich THF and the aqueous citric acid containing water-

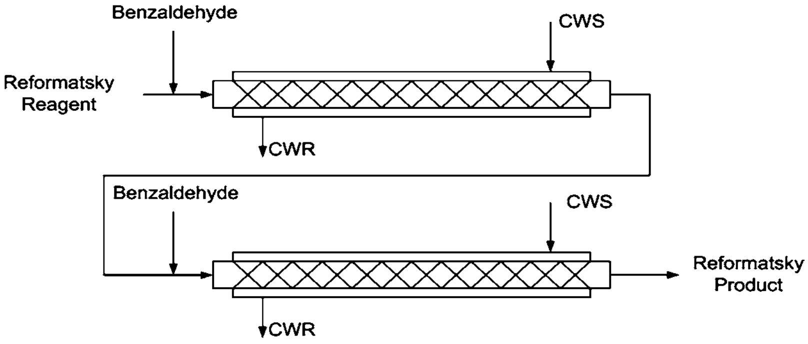

Figure 4. Two plug flow reactor in series.

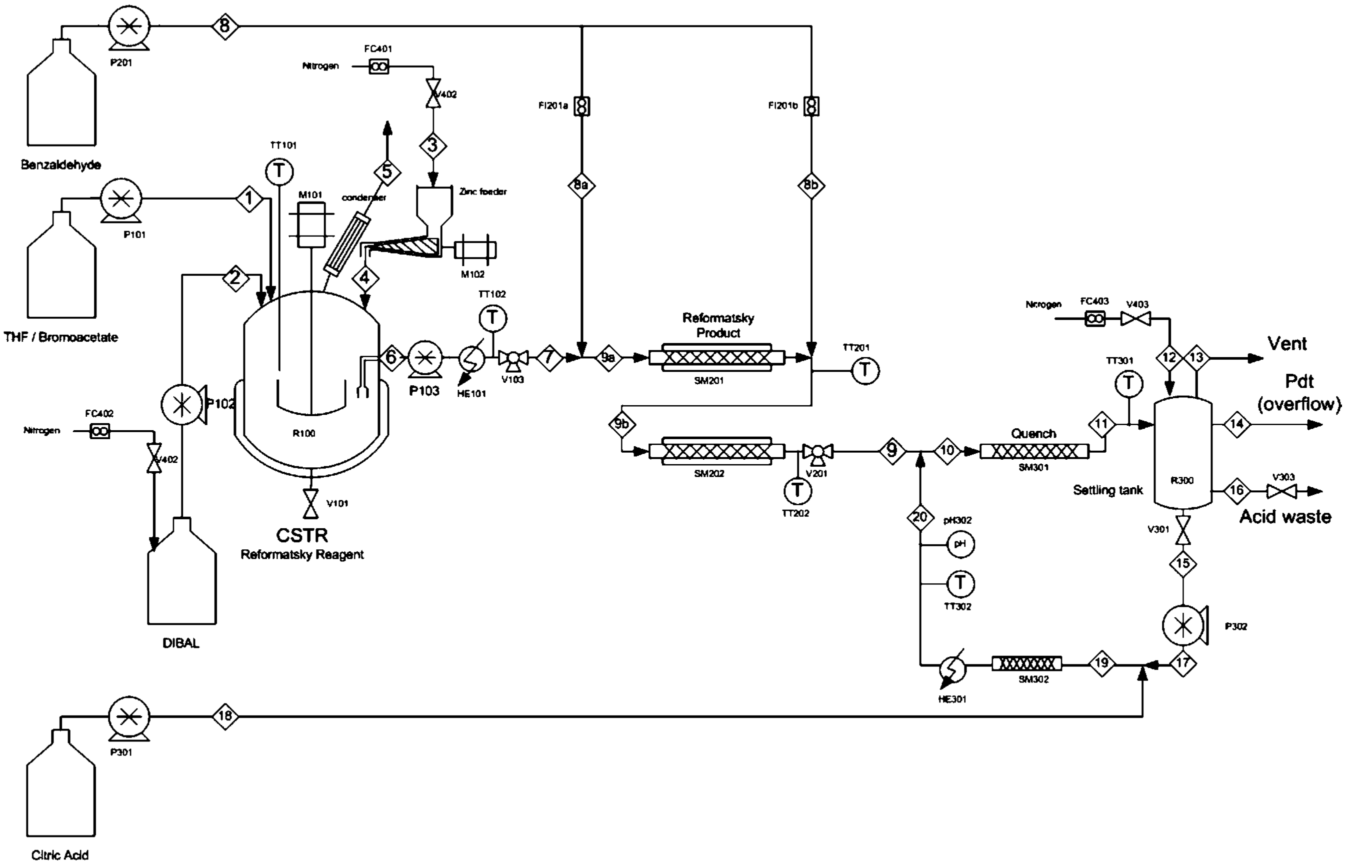

Figure 5. Process diagram of the glass reactor rig.

soluble zinc bromide were to take place in a static mixer and a hold vessel, respectively. The static mixer created an emulsion of organic phase in the continuous aqueous phase. With the increased available interfacial surface area and therefore good mass transfer between the two phases, excess zinc enolate was rapidly destroyed. The flow of the citric acid which was used as a heat sink was designed to allow an adiabatic temperature rise of not more than 20 °C. The warm citric acid was then cooled back to ambient temperature using a plate heat exchanger. During the operation, a fresh citric acid feed flow with a constant discharge was used to prevent an accumulation of zinc bromide which may then precipitate, causing operability issues.

A 500-mL holding vessel which acted as a phase separator provided the residence time for efficient phase separation of the organic–aqueous emulation created in the static mixer. The top THF layer overflowed and was collected in a separate bottle, while the bottom citric acid aqueous phase was continuously recycled back to the quench stage.

The system was controlled and monitored via temperature measurements and sampling. Temperature was controlled using external cooling circulators and monitored via thermocouples positioned at various points of the system. Thin layer chromatography (TLC) and GC–MS were used for offline product quality analysis. The system was considered to be in a steady state when these properties did not change with time. Three-way valves were installed after the CSTR and the jacketed static mixers to provide a means for sampling and waste discharge of "unsteady state" process flows. The whole system, as shown in Figure 5, was designed to have a product flow of about 100 mL/h and with high emphasis on scalability. As such, all equipment, instruments, and vessels used in the process are readily available at manufacturing scale.

Continuous Reformatsky Process Operation. The continuous Reformatsky process was operated on four separate runs with varying concentrations to demonstrate the robustness of continuous processing in terms of heat management and also process optimisation. The description of the procedure in this section was based on the last (fourth) run.

The reactor system was first preflushed with THF and a solvent boil-up in the CSTR as a cleaning regime of the process. The reactors and the lines in the system were then subjected to constant nitrogen flow of about 500 mL/min to ensure that water is not present in the CSTR due to the presence of water-sensitive DIBAL-H and Reformatsky reagent in stage 1 of the process.

An initial batch of Reformatsky reagent was first prepared in the CSTR. About 550 mL of THF with 122 g of zinc granules (3.5 equiv) were charged into the reactor and heated to 40 °C while being agitated using a pitch blade impeller. Due to the lack of baffles, the agitation rate was limited to 450 rpm at which the formation of a vortex was minimal, and yet there was still significant movement of the zinc particles. A small charge of 6.7 mL of ethyl bromoacetate was then added. After which, 8.9 mL of DIBAL-H was slowly added to the suspension of zinc in THF, and a small exotherm was observed. An olive-green continuous phase could be observed as shown in Figure 6. Subsequently, the remaining 111 mL of ethyl bromoacetate (overall 2 equiv) was charged using a syringe pump over a period of about 1 h. A constant exotherm was observed during the whole period of addition. A reddish-brown continuous

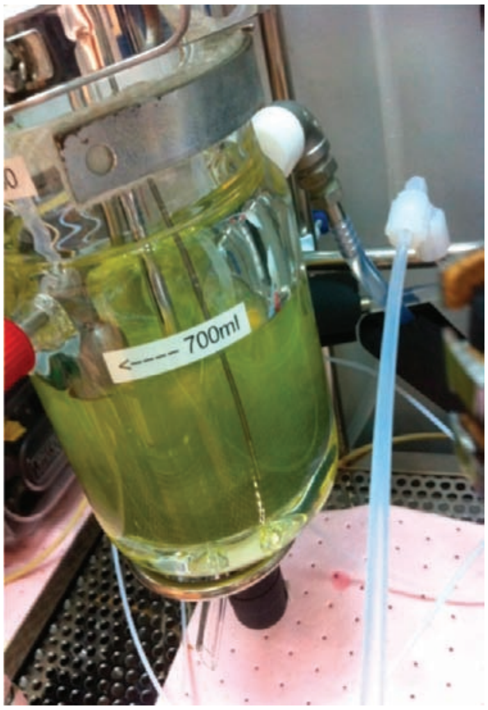

Figure 6. Reaction mixture after zinc activation.

phase was afforded after complete addition of ethyl bromoacetate as shown in the photograph of Figure 7.

Figure 7. Stage 1 reaction mixture.

Once the process temperature had been stabilised at 40 °C, the addition of 25 wt % ethyl bromoacetate in THF (premixed), DIBAL-H using Watson Marlow Peristaltic pumps 520S/R2 at a precalibrated flow rate of 10.9 mL/min (2 equiv), 0.04 mL/min (0.02 equiv), respectively, was started. Zinc granule feed rate of about 1 g/min (2 equiv) was delivered using a precalibrated screw feeder to replenish the depleting zinc due to the continuous formation of zinc enolate in the CSTR. With the reagents continuously added to the reactor, the reaction mixture was then pumped out of the CSTR to a glass coiled heat exchanger and discharged into a waste bottle until the temperature of both reactor content and the process flow reached and steadily maintained the desired set points of 40 and 25 °C, respectively.

Next, the process flow was diverted back online to the jacketed static mixer for stage 2 of the process where benzaldehyde at a combined flow rate of 0.86 mL/min was introduced at the entrance of each reactor. Flow meters were used to control the split flows accurately so as to ensure equal distribution of benzaldehyde. Similarly, the process flow will be diverted to a waste bottle until the exit temperatures of the reactors were stabilised at 25 °C, and off-line analysis using thin layer chromatography and GC−MS showed no indication of the substrate, benzaldehyde.

Finally, the "on-spec" process fluid was quenched with a continuous citric acid solution at a flow rate of 29.2 mL/min at the downstream static mixer and then was phase separated in the holding vessel. The interface of the two phases was maintained at approximately 2/3 of the liquid height by throttling a constant citric acid waste discharge. The top organic phase then overflowed and was collected in a separate, labelled bottle. Fresh citric acid at a flow rate of 5.8 mL/min was added to the recycled citric acid stream prior to cooling in a plate heat exchanger.

The steady state continuous operation of the process was maintained for about 4 h (Figure 8) before stopping the flows of reagents to the CSTR while the processing of the residual zinc enolate mixture continued. When the level of the reaction mixture in the CSTR was sufficiently low, the process was systematically shut down and made safe.

The continuous Reformatsky process was carried out at various concentrations at different occasions, demonstrating the excellent heat transfer of continuous reactors. A number of processing issues were encountered, mainly precipitation of zinc bromide which could be resolved by having higher fresh citric acid flow rate and discharge. This issue has pointed out one of the challenges of continuous processing of solid-containing flows. However, this could also be addressed by engineering or possibly by chemistry solutions.

It is widely known that the Reformatsky reaction is subjected to a number of competing side reactions which include self-condensation of the α-bromo ester and carbonyl components, as well as elimination or aldol condensation of the intermediate β-alkoxyzinc ester.[4] These side reactions often cause the yield of the process to be highly variable and low which would require more separation or purification steps.

The crude organic product was analysed using a GC−MS, and the results indicated that the crude product obtained from the continuous process was much cleaner than those obtained from previous batch experiments which had more side products (refer to GC−MS spectrum in Figure 9). This is consistent with the findings by Ruppert et al.[4] which indicated that the side reactions can be greatly reduced by minimising the contact of the starting material and product. Given that each stage of the continuous process occurs in a different reactor or vessel, there was limited exposure of the reaction product to the starting material and itself. Such an environment minimised the occurrence of side reactions. Control was important in this as

Figure 8. Steady-state operation of continuous Reformatsky process.

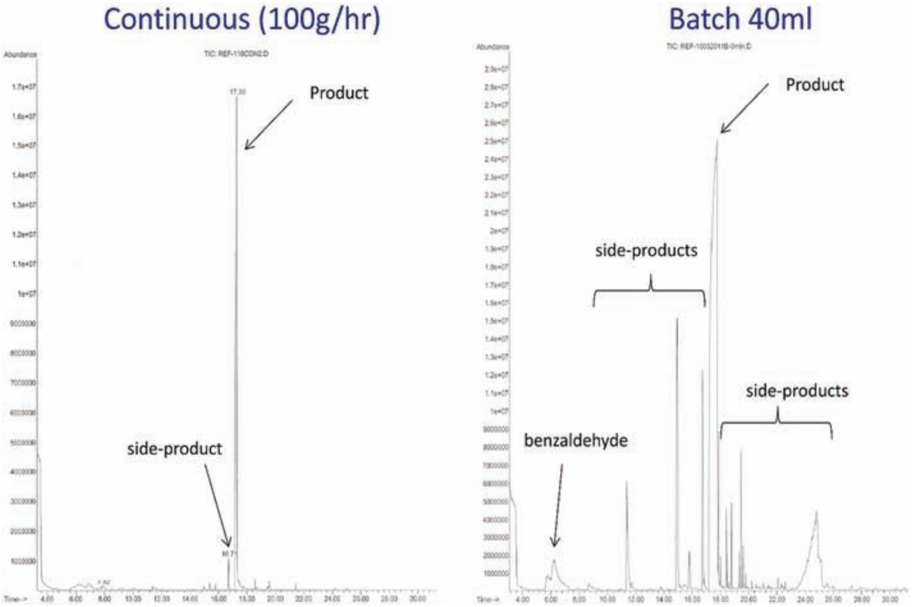

Figure 9. GC−MS spectra of crude product from both continuous (left) and batch (right) processes.

there were greater impurities when "unsteady state" flow was allowed to pass downstream through the process.

On the basis of the relative area percentage, a higher yield was obtained from the continuous Reformatsky process with almost all of the benzaldehyde depleted as compared to the batch process, where a significant amount of residual unreacted substrate was detected. Although the individual impurities were not identified and quantified, in all cases the continuous impurities are present at a much lower level than in the batch. The continuous product has no impurities that even approach the level of the same impurity in the batch version.

In a batch process, it is suspected that self-reaction may have significantly reduced the enolate reagent, preventing completion of the reaction; this was not observed in the continuous process as the short residence time in the whole process and in between each individual stages or operations may have suppressed the formation of side products. In other words, more starting material will be required in batch to produce sufficient reagent to drive the coupling reaction to completion and also more separation and purification steps, which will incur higher capital and operating costs.

In the context of the Reformatsky process, continuous processing has successfully demonstrated high selectivity with lower material usage. The relative cleanliness of the product increases the possibility of cleaning solvent for recycle. Further work is planned to couple the system with a wiped film evaporator and to explore the extent to which solvent can be recycled within the process.

■ CONCLUSION

The continuous Reformatsky process development was based on small-scale batch experiments, and with the necessary information obtained from calorimetry, we were able to design a continuous process within a time frame similar to that of a typical batch process development project. There is a perception that continuous process development is slow due to the complexity of operation and the high level of information required for process control, and therefore cannot meet short laboratory-to-market cycle times. We have demonstrated otherwise. Within a short time span of about 3 months, of which the majority was of equipment and chemical procurement lead time, we managed to develop a viable continuous Reformatsky process of high yield and purity from a literature batch method. Given adequate process understanding, the process can be controlled solely on the basis of the heat of reaction at the various stages of the process and, therefore, may not require in-depth understanding in terms of chemical kinetics, mass transfer behaviour, etc.

The miniplant with a product flow of about 100 mL/h has an annual throughput of about 500 kg which is comparable to that of a small-batch plant. It has shown that, unlike those of a batch plant, the size of the production facilities and associated overheads can be reduced by using the continuous process which potentially reduces the capital cost of the plant. With excellent heat transfer and mixing efficiency of continuous processing equipment, it is possible to operate at more intensive operating conditions, for example, concentration, temperature, and pressure, to increase the throughput of the plant. This is usually not possible for batch processes as they are typically limited by the ability to remove heat and the need for higher solvent content which acts as a heat sink in highly exothermic or hazardous processes such as the Reformatsky or Grignard reaction. The concept of process intensification involves low inventory, and with higher thermal inertia, the continuous Reformatsky process will be inherently safer as compared to the batch process.

The heat management robustness of a continuous process was demonstrated in the experiments operating at various concentrations as high as 2.0 equiv with respect to ethyl bromoacetate. The excellent heat transfer of continuous reactors enabled us to operate at higher concentrations as compared to batch processes where heat generation is often the limiting factor in their process development. The increased precipitation of zinc bromide at the quench stage prohibited further increase in the concentration which highlighted one of the disadvantages of continuous process which involves moving solids.

The implementation of a continuous solvent recovery and recycle via a distillation operation such as a wiped film evaporator reduces the amount of solvent usage and therefore waste generation. A continuous process allows inline process monitoring, control, and quality control via the use of various process analytical technologies (PATs); it also allows real-time product quality checks without interruption to the manufacturing operation and conceivably allows recycling or discharge of "off-specification" product flows. With high chemical conversion and cleaner reaction, the continuous Reformatsky process would not require multiple separation and purification steps which will incur higher capital and operating costs. In this particular context, continuous processing not only creates less waste and is therefore more environmentally friendly but also increases productivity for a lean and sustainable manufacturing model.

In conclusion, the demonstration not only opened the way to explore the same approach to deliver a range of other hazardous organometallic chemistries which are synthetically useful yet industrially problematic but has also paved the way to the future of a more green and sustainable manufacturing technology via the following:

(1) higher selectivity and cleaner reaction due to lower residence time which reduces processing steps;
(2) low equipment footprint and possibly lower capital cost;
(3) inherently safer process via process intensification and lower inventory;
(4) ability to operate the process at a higher concentration, temperature, and pressure to increase conversion so as to obtain higher productivity and yield/conversion and a cleaner reaction;
(5) ability to incorporate PAT as a means of precise control of reagent dosing to minimise unreacted materials and thus reduce processing steps and at the same time allow recycling or discharge of "off-specification" products so as to ensure constant product quality and minimal waste generation;
(6) ability to implement continuous solvent recovery and internal recycling which reduces solvent usage and waste.

This work opens the possibility of developing this and other similarly hazardous chemistry in larger-scale, multipurpose, continuous facilities at ICES. With existing modular skids available for feeding, a continuous oscillatory baffled reactor, and a wiped film evaporator, it would be practicable to run the process at a nominal scale of about 20 L/h by the addition of a larger-scale version of the reagent preparation reactor.

■ EXPERIMENTAL SECTION

Materials. Zinc granule of −30 to 100 mesh size, 1 M DIBAL-H in THF, benzaldehyde, and citric acid were obtained from Sigma Aldrich. Ethyl bromoacetate was obtained from Wacko, Japan, and analytical grade tetrahydrofuran (THF) was obtained from Fisher Scientific. The materials were used for both batch and continuous process experiments without any additional purification.

Analytical Method. The crude reaction mixture samples obtained after phase separation were analysed using Agilent 5975C inert MSD with a triple-axis detector. A DB-5ht 30 m × 250 μm × 0.1 μm column with an oven-temperature profile of 45 °C isothermal for 5 min, then 15 °C/min ramp to 260 °C, and held isothermally for 7 min were used.

Batch Reformatsky Reaction. All three stages of the process were carried out in a nitrogen-blanketed 50-mL Mettler Toledo Multimax reactor equipped with a three-blade propeller-type impeller; 5.5 g (3.5 equiv) of zinc granule was charged into the reactor containing 25 mL of THF. The suspension was then heated to 40 °C prior to the addition of a small quantity of ethyl bromoacetate (0.3 mL, approximately 5%) which was required for good activation. This was then followed by the addition 0.4 mL of 1 M DIBAL-H in THF as the reducing activator for the removal of the oxide layer on the zinc granule over a period of 10−15 min as described by Girgis' work.[5] The addition of the remaining 5 mL (2 equiv) of ethyl bromoacetate was carried out over a period of about 1 h.

The reaction mixture containing the Reformatsky reagent, zinc enolate from the earlier stage of the process, was then cooled to ambient temperature of 25 °C under nitrogen atmosphere. Slow addition of 2.4 mL of benzaldehyde (1 equiv) over 30−40 min to the zinc enolate reaction mixture was carried out while maintaining the temperature at 25 °C.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gabriel_loh@ices.a-star.edu.sg.

Notes

The authors declare no competing financial interest.

ADDITIONAL NOTE

[a] We have tried zinc powder prior to granules. We have observed that zinc activation was somewhat more unpredictable and more DIBAL was required. We suspected that it was due to the variability of the high surface area of zinc powder. We did not continue with investigation after obtaining reliable activation with granules.

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