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Safe, Convenient *ortho*-Claisen Thermal Rearrangement Using a Flow Reactor

Juan A. Rincón,*,[†] Mario Barberis,[†] María González-Esguevillas,[†,§] Martin D. Johnson,[‡] Jeffry K. Niemeier,[‡] and Wei-Ming Sun[‡]

[†]Centro de Investigación Lilly S.A., Avda. de la Industria, 30, Alcobendas-Madrid 28108, Spain

[‡]Eli Lilly & Company LTC-South, Indianapolis, Indiana 46285-4813, United States

S *Supporting Information*

ABSTRACT: The [3,3] Claisen rearrangement is a well-known reaction that has been very useful for the synthesis of *o*-allyl phenols. The thermally induced rearrangement could present safety and operational issues at large batch scale. Herein, we report a process that utilized a tube reactor to make 80 g of an early phase intermediate in a short time while mitigating the potential chemistry hazards. Thus, both project material demands and flow chemistry proof of concept were achieved.

INTRODUCTION

During the development of one of our research projects, phenol **1** was identified as a key piece for one of the most advanced platforms. The 3-step sequence involved a [3,3] sigmatropic shift of the allyl aryl ether (**2**) leading to the *o*-allyl phenol (**3**), which was easily hydrogenated to the desired product (Scheme 1).

Although the original procedure[1] described this rearrangement using neat 4-(allyloxy)acetophenone (**2**) at 230 °C, our medicinal chemists found that the use of diphenyl ether as solvent facilitated the handling and the isolation of the product at 15−20 g scale. However, the operational issues associated with the high temperature of the process and the range of concentration used (>25% w/w) made us look for an alternative reactor technology (ART) that would provide a large amount of this material in a safe and timely fashion.

RESULTS AND DISCUSSION

Batch Chemistry. The commercially available 1-(4-hydroxyphenyl)ethanone was transformed in high yield to the allyl ether (**2**) in a similar manner as previously described in the literature.[2] Then, a mixture of the resulting oil crude and biphenyl ether was heated to 250 °C for the thermal rearrangement, and the *o*-allyl phenol (**3**) had to be isolated at a higher temperature than the melting point of the solvent (25−27 °C). After some experimentation, we also observed that the optimal temperature for the reaction was 220 °C (with a ratio of 2 g Ph_2O/g substrate). At lower temperatures, the reaction times were too long (>48 h), and many tar byproducts began to form. At higher temperatures decomposition of the product was observed. Under desired conditions, the product precipitated in high yield during the cooling process and the biphenyl ether could be removed by washing with hexane. Subsequent catalytic hydrogenation led to the desired product in 60% of overall yield.

An accelerating rate calorimeter (ARC) test on neat **2** showed an exotherm onset of 172 °C, a maximum self-heat rate of 2.3 °C/min, and a heat of reaction of 366 J/g ($\Phi = 2.0$) The main reaction went directly into an exothermic gassy secondary reaction at 265 °C as shown in Figure 1. The secondary reaction was not identified but is believed to be due to decomposition of product.

With a reaction temperature of 220 °C a moderate exotherm could cause the temperature to rise to the boiling point of diphenyl ether (259 °C) and cause vaporization. If venting were not sufficient the reactor could increase in temperature and pressure and the secondary reaction could initiate. The heat of reaction of 366 J/g for the desired reaction would be sufficient to cause an adiabatic temperature rise of about 180 °C if the reaction were run neat. These factors indicate a potentially hazardous or at least difficult to control process in the case of a large-scale batch campaign, so we considered these data significant enough to change the process conditions.

Since the discovery of the Claisen rearrangement almost one century ago,[3] it has been focus of attention by many research groups.[4] Many synthetic methods involving Al(III) or bismuth(III) derivatives,[5] lanthanides triflates,[6] clays or zeolites,[7] or more recently, gold[8] as catalysts for the sigmatropic rearrangements of allyl aryl ethers have been reported.

We tried some of these additives to see if we could run the reaction at lower temperatures. Unfortunately, none of the conditions tested led to the selective formation of desired product, and in many cases, degradation to byproduct were observed (Table 1). These results made us reconsider the process in thermal (noncatalytic) conditions but in a safer way.

Continuous Chemistry. Although the batch conditions for the rearrangement reaction seemed to work well, we were concerned about how well it would work on a larger scale. The concerns were the following:

- Standard large-scale reactors are not equipped to run at temperatures above 200 °C due to limitations in heat transfer systems.

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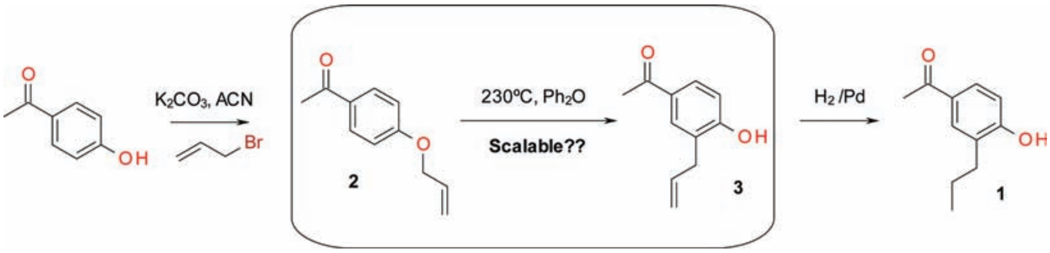
Scheme 1. Synthetic Route



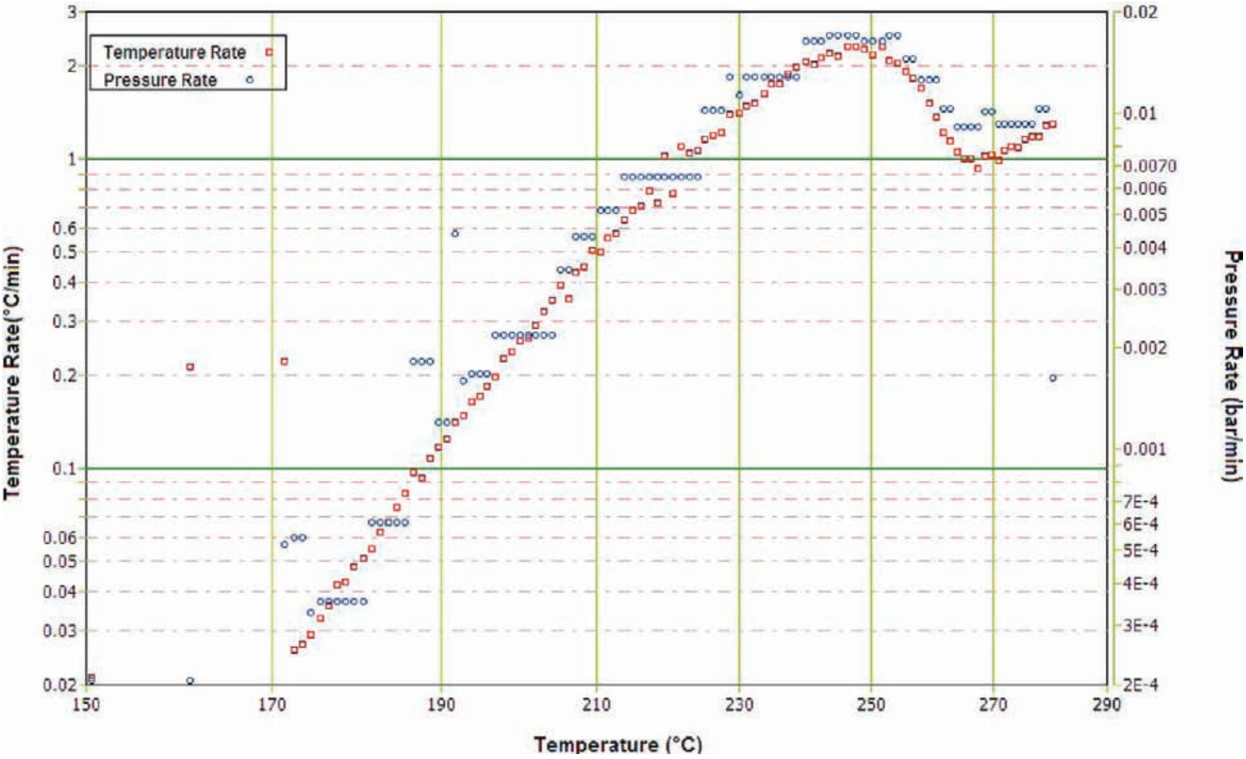


Figure 1. ARC results for neat **2**.

Table 1. Catalyzed Sigmatropic Rearrangement

solvent	additive	temp	Results
toluene/hexane	Et_2AlCl	rt to 70 °C	dimerization
toluene/heptane	Et_2AlCl (1 M in hexanes)	rt	degradation
toluene	Florisil (30−60 mesh)	110 °C	no reaction
toluene	*p*-TsOH/SiO2	110 °C	messy reaction
toluene	*p*-TsOH	110 °C	no reaction
acetonitrile	$Yb(OTf)_3$	reflux	degradation
toluene	$Yb(OTf)_3$	reflux	no reaction
DMF	$Yb(OTf)_3$	130 °C	no reaction
toluene	$Bi(OTf)_3$	reflux	degradation

- Although safety and temperature control could be improved by running the reaction more dilute and utilizing a semibatch process (by dosing a starting material solution) rather than a batch process, calorimetry data indicated there could still be a substantial temperature and pressure rise if the starting material (**2**) was accidentally added all at once.
- A batch process may be prone to decompose the product since the heat-up and cool-down times would be longer and the product would be exposed to high temperature for a longer time.

All of this data brought to our attention the possibility of performing the reaction using alternative reactor technology (ART) in a flow-chemistry fashion. Typically, the reaction would take place on a minimum scale but in a continuous way, using a long tube reactor and leading to the same result as in large batch reactor while minimizing the risks of the process.

The key point for this technique is that all the reagents must be in solution to avoid plugging the reaction tube. The use of Ph_2O as solvent could be a problem as both the starting material and the final product only came into solution when heating the reaction.

We decided to use *N*-methylpyrrolidinone (NMP) as solvent for the experiment because of its high boiling point and low vapor pressure; it is a nonoxidizing agent at that temperature and turned out to be a powerful solvent for our substrate (2 mL/g).

An accelerating rate calorimeter (ARC) test of a 50 wt % sample of (**2**) in NMP gave an exotherm detection temperature

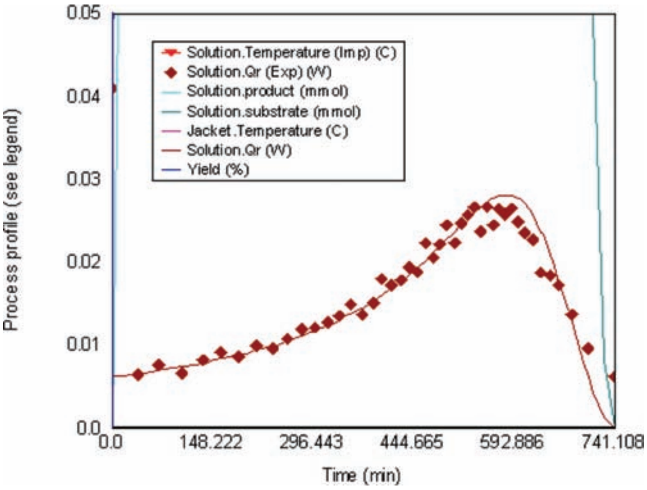


Figure 2. ARC self-heat rate data and model fit.

Table 2. Predicted Conversion in a Batch Reactor at Different Temperatures

temp (°C)	time (h)	conversion (%)
200	13	96
210	8	100
220	4.5	100
230	2.5	100

of 181 °C with a maximum self-heat rate of 0.23 °C/min and a heat of reaction of 170 J/g total mixture (Φ factor = 1.8). Although the exotherm observed was mild, the onset temperature was much lower than the desired process temperature and the 30 min to maximum temperature rate was only 204 °C (corrected for Φ factor). A secondary exotherm was detected at 245 °C (80 J/g).

In this case there were several safety advantages to running the reaction in a tube reactor. Heat transfer surface area per unit volume of the flow tube reactor is much higher than for a batch reactor. The 220 mL flow tube reactor had A/V = 2050 m^2/m^3. In comparison, if a 1-L batch reactor were used for producing 80 g compound instead, it would have A/V about 45 m^2/m^3. Therefore, heat transfer surface area per unit volume is about 40–50 times higher for the flow tube reactor than a batch reactor with comparable throughput. In runaway reactions, the concept of critical temperature is important. This is the temperature where the heat generation rate equals heat removal rate. At higher temperatures a runaway reaction will occur unless extra cooling is added. Increasing heat removal rate increases critical temperature.

Furthermore, standard stainless steel tubing reactors have pressure rating about 100–300 bar, which is much higher than standard batch reactors. This is important because critical temperature is based solely on heat transfer and does not address pressure build-up. Hazardous pressure buildup could occur in a closed system at temperatures below the critical temperature. For this reason, the high pressure rating of the tube reactor is a backup line of defense against mechanical failure and rupture in the event of thermal decomposition (assuming the maximum pressure during a runaway is considered).

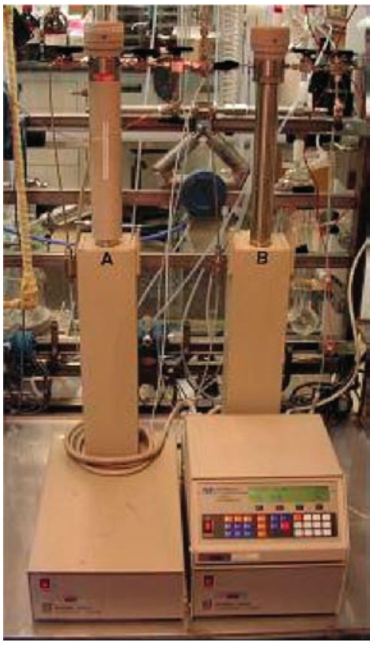


Figure 3. ISCO syringe pumps (0–510 bar, 0.001–107 mL/min).

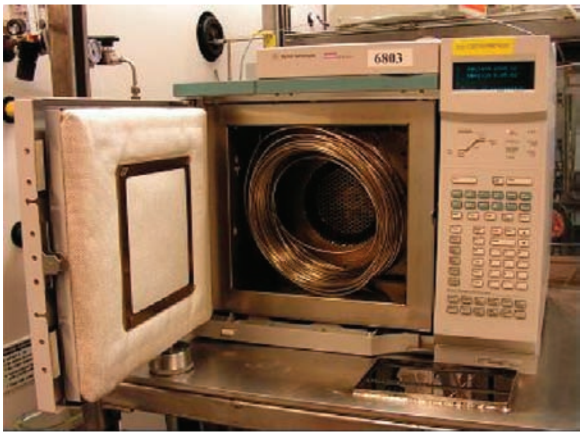


Figure 4. Oven, rt to 350 °C, 27 cm × 30 cm × 16 cm.

The ARC heat flow data was used to develop a kinetic model with DynoChem software.[9] As we have observed in the batch experiments, the optimal temperature for the reaction was 220 °C, and it matched very well that predicted in the ARC experiment when using the Dynochem model. Figure 2 shows that the model fits the data very well, so the confidence in the model should be high.

With a working kinetic model in hand we could predict the required reaction times at various temperatures. This is helpful when setting flow rates (and hence residence times) in flow reactors. In Table 2 we can see the model-predicted conversion and time of reaction for different temperatures below and above 220 °C.

A plug flow tube reactor will exhibit the same conversion versus time as a batch reactor (residence time in the case of the flow reactor). Past experience had indicated the small tube reactors behave much like a plug flow reactor with negligible axial dispersion (sometimes called backmixing). Therefore, the

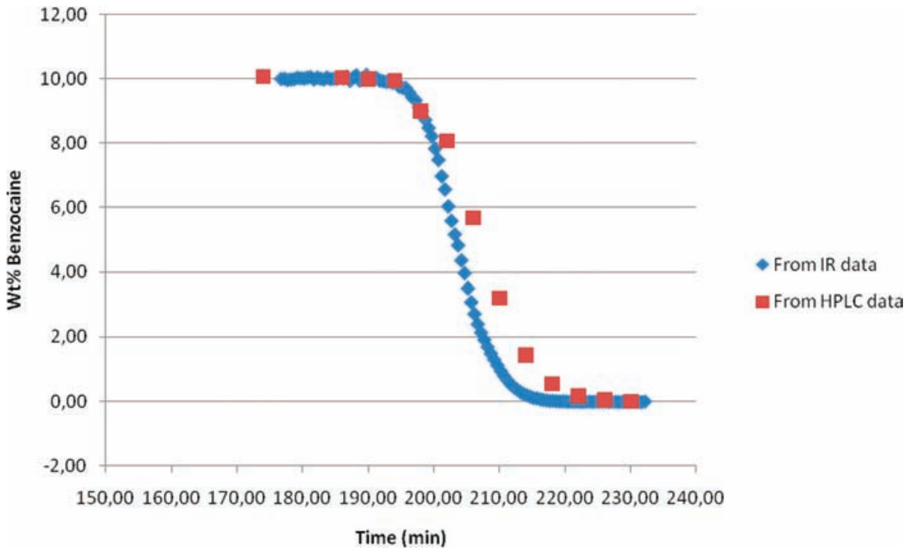


Figure 5. Dispersion data for 1/8″ tube reactor.

Table 3. Comparison of Batch and Continuous Processes

	batch process	continuous process
solvent	diphenyl ether	*N*-methyl pyrrolidinone (NMP)
concentration	33 wt %	50 wt %
chosen reaction temperature	220 °C	230 °C
solvent boiling point	259 °C	202−204 °C
solvent vapor pressure at reaction temperature	0.41 bar	1.8 bar
operating pressure	1 bar	15 bar
workup	crystallization on cooling (potential to freeze solvent if temperature is less than 27 °C)	aqueous drown out and extraction
reaction time	5 h	4 h
safety	potential for runaway reaction causing solvent boiling and/or gas generation especially in large-scale manufacturing	improved heat transfer provides better temperature control; contained system; potential to run reaction more concentrated without safety hazards
manufacturability	220 °C not easily reached by typical batch reactor heat transfer systems	230 °C easily reached in ovens
robustness	reaction temperature profile will vary with scale due to changes in heating and cooling capabilities, which can lead to variation in yield and purity	reaction temperature profile can be reproduced with little variation

predicted conversion versus time for a batch reactor (as shown in Table 2) should be close to that observed in the tube reactor. Armed with this information, plans were made to produce material in a 1/8″ tube reactor.

The dissolved reagent was pumped continuously (using ISCO Syringe pumps, Figure 3) through the 1/8″ stainless steel tube, which was heated inside a GC oven. The product solution continuously flowed out the end of the tube into a product collection vessel.

Some experimentation was needed to optimize the temperature and the residence time of the process. The best conditions found were 230 °C, pressure about 15 bar,[10] in a 73.5-m long tube, and residence time of 4 h (Figure 4). The linear velocity of liquid pumping through the tube was about 30 cm/min; the tube volume was about 222 mL, and the volumetric flow rate was 0.92 mL/min. At the end of the process the entire product was pushed out at the end with fresh NMP at the same flow rate.

The actual axial dispersion of the tube reactor was measured after the campaign was completed when time permitted. A surrogate molecule (Benzocaine) was used for the study. The reactor was filled with a 10 wt % solution of Benzocaine in NMP, and the feed was quickly changed to pure NMP to initiate a concentration step change. The dispersion was monitored by tracking the outlet concentration of Benzocaine. An IR flow cell was installed near the outlet of the reactor to compliment data collected by HPLC grab samples (Figure 5). For a plug flow reactor the concentration change at the outlet of the reactor would also be a step change from 10 to 0 wt %. Some dispersion will occur in any real reactor, especially those using laminar flow conditions. However, the dispersion was relatively low in this case (dispersion number ($D/\mu L$) = 0.00024). For kinetic modeling purposes this amount of dispersion can be ignored, and the reactor can be assumed to be plug flow. Additional background on the effect of dispersion on kinetics can be found in the Supporting Information.

Another observation is that the HPLC data indicated more dispersion data than the IR data. This makes sense because the HPLC grab samples were collected after the stream passed through a series of small pressure vessels. These vessels would create some additional dispersion.

The IR flow cell is a valuable option for collecting concentration data in flow reactors. It has the advantages of providing real-time data, greater sample frequency, no requirement for sample preparation, and no data interference due to additional back-mixing. However, it does have some requirements: the flow cell must be capable of withstanding the system pressures; the flow cell material of construction must be suitable for the mixture; the molecule of interest must have a spectrum sufficiently different from the rest of the mixture to allow concentration tracking; and an IR calibration curve must be created.

CONCLUSIONS

In summary, scaling this thermal rearrangement in a flow tube reactor provided several advantages:

- High temperature was easily obtained compared to a batch reactor.
- Safety was enhanced.
- The time−temperature profile can be easily reproduced regardless of material requirements. The reaction mixture quickly reaches temperature upon entering the high temperature zone and quickly cools after leaving the high temperature zone. This allows better control over side reactions (such as product decomposition in this case).

This process allowed us to make 80 g of the material in a short time while mitigating the potential chemistry hazards. A comparison of the batch and continuous processes are shown in Table 3.

EXPERIMENTAL SECTION

Batch Reaction. A mixture of 1-(4-(allyloxy)phenyl)ethanone (96.47 mmol; 17.0 g) and diphenyl ether (34.0 g) was placed into a open vial and heated to 220 °C under N_2 for 5 h. The mixture was then cooled to 40 °C, 100 mL of hexanes was added, and the mixture was cooled further to 0 °C. The solid was filtered off and washed with 100 mL of hexanes. The brown solid was stirred in 160 mL of MTBE/hexane (2:1) overnight. The solid was rinsed with 20 mL of hexanes to give a first crop of 3-allyl-4-hydroxyacetophenone (4.3 g, >98% pure).

Liquors were concentrated in vacuo, and the solid was stirred in 120 mL of hexane/MTBE (5:1). The solid was filtered to give a second crop (7.68 g, 91%). Both solids were mixed to give a single lot of 3-allyl-4-hydroxyacetophenone (11.98 g, 70.47% yield, 94% pure.

Flow Reaction. A solution of 82 g of 1-(4-(allyloxy)-phenyl)ethanone in 174 mL of NMP was pumped through a 73.5-m long continuous thermal tube reactor (GC oven, V = 221 mL, o.d. = 3.175 mm, i.d. = 2.0 mm) heated at 230 °C and pressurized to 15 bar. At the beginning of the run, before reagents were pumped through the reactor tube, the tube was prepressurized with 15 bar nitrogen and preheated. High pressure ISCO syringe pumps were used to continuously push reagent solution through the tube and maintain constant liquid flow rate of 0.92 mL/min for the entire run. The product solution continuously flowed out the end of the reactor tube, through a cooling tube heat exchanger, and through a back pressure regulating device. Product continuously dripped out the back pressure regulator into the collection vessel at room temperature and atmospheric pressure. Average hydraulic residence time in the hot zone (230 °C) of the reactor tube was 4 h. When the reaction solution ran out, the high-pressure syringe pump was switched from pumping reaction solution to pumping NMP only without stopping flow for the last 4 h. Therefore, all reagent solution had precisely 4 h average hydraulic residence time in the thermal tube reactor to complete the reaction. Flow rate, reactor pressure, and reactor temperature remained the same during the continuous NMP pushout of the reactor. The reactor tube contained NMP solvent only at the end of the experiment. The product solution from the collection tank was worked up and isolated in batch mode. Thus, the mixture was transferred to a 2 L RBF, and 1 L of water was added and extracted with MTBE (700 mL). The mixture was filtered through a short pad of Celite to give a clear phase cut. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was stirred in 1000 mL of hexane/MTBE (10:1), filtered, and dried to give 3-allyl-4-hydroxyacetophenone (80.8 g, 73.45% yield, 93% pure).

ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H NMR spectra for **1**, **2**, and **3**. ARC plots for neat **2** and in NMP solution. Rationale about the effect of flow reactor dispersion on reaction kinetics. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: rinconja@lilly.com.

Present Address

[§]Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.

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(9) DynoChem software is a product of Scale-up Systems Ltd., Dublin, Ireland. The kinetics were modeled using the first order reaction (**2**) → (**3**)

(10) Backpressure of 15 bar was utilized to prevent the solvent from boiling at the reaction temperature.