**TITLE:**

**Continuous Flow Chemistry: Reaction of Diphenyldiazomethane with *P*-Nitrobenzoic Acid**

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**SHORT ABSTRACT**

Flow chemistry carries environmental and economic advantages by leveraging superior mixing, heat transfer and cost benefits. Herein, we provide a blueprint to transfer chemical processes from batch to flow mode. The reaction of diphenyldiazomethane (DDM) with *p*-nitrobenzoic acid, conducted in batch and flow, was chosen for proof of concept.

**LONG ABSTRACT**

Continuous flow technology has been identified as instrumental for its environmental and economic advantages leveraging superior mixing, heat transfer and cost savings through the “scaling out” strategy as opposed to the traditional “scaling up”. Herein, we report the reaction of diphenyldiazomethane with *p*-nitrobenzoic acid in both batch and flow modes. To effectively transfer the reaction from batch to flow mode, it is essential to *first* conduct the reaction in batch. As a consequence, the reaction of diphenyldiazomethane was first studied in batch as a function of temperature, reaction time and concentration to obtain kinetic information and process parameters. The glass flow reactor set-up is described and combines two types of reaction modules with “mixing” and “linear” microstructures. Finally, the reaction of diphenyldiazomethane with *p*-nitrobenzoic acid was successfully conducted in the flow reactor, with up to 95% conversion of the diphenyldiazomethane in 11 minutes. This proof of concept reaction aims to provide insight for scientists to consider flow technology’s competitiveness, sustainability, and versatility in their research.

**INTRODUCTION**

Green chemistry and engineering are creating a culture change for the future direction of industry 1-4. Continuous flow technology has been identified as instrumental for its environmental and economic advantages leveraging superior mixing, heat transfer and cost savings through the “scaling out” strategy as opposed to the traditional “scaling up”5-10.

Although the industries producing high-value products like the pharmaceutical industry have long favored batch processing, the advantages of flow technology have become attractive due to mounting economic competition and commercial production benefits 11. For example, when *scaling up* batch processes, pilot scale units must be built and operated to ascertain accurate heat and mass transfer mechanisms. This is hardly sustainable and subtracts substantially from the marketable patent life of the product. In contrast, continuous flow processing allows for the advantages of *scale out*, eliminating the pilot-plant phase and engineering associated with production scale—a significant financial incentive. Beyond the economic impact, continuous technology also enables atomic and energy efficient processes. For instance, enhanced mixing improves mass transfer for biphasic systems, leading to improved yields, catalyst recovery strategies and subsequent recycling schemes. Additionally, the ability to accurately manage the reaction temperature leads to precise control of reaction kinetics and product distribution.12 The enhanced process control, quality of product (product selectivity) and reproducibility are impactful both from environmental and financial standpoints.

Flow reactors are available commercially with a wide variety of sizes and designs. In addition, customization of reactors to meet process needs can easily be achieved. Herein, we report experiments conducted in a glass continuous flow reactor (Figure 1). The assembly of microstructures (161 mm x 131 mm x 8 mm) made of glass is compatible with a wide range of chemicals and solvents and is corrosion-resistant over a wide range of temperatures (-25 °C to 200 °C) and pressures (up to 18 bar). The microstructures and their arrangement were designed for multi-injection, high-performance mixing, flexible residence time, and precise heat transfer. All of the microstructures are equipped with two fluidic layers (-25 °C to 200 °C, up to 3 bar) for heat exchange on either side of the reaction layer. Heat transfer rates are proportional to the heat transfer surface area and inversely proportional to its volume. Thus, these microstructures facilitate an optimum surface-to-volume ratio for improved heat transfer. There are two types of microstructures (i.e. modules): “mixing” modules and “linear” modules (Figure 2). The heart-shaped “mixing” modules are designed to induce turbulence and maximize mixing. In contrast, the linear modules provide additional residence time.

As proof of concept, we selected the well-described reaction of diphenyldiazomethane with carboxylic acids.13-17 The reaction scheme is shown in Figure 3. The initial transfer of the proton from the carboxylic acid to the diphenyldiazomethane is slow and is the rate-determining step. The second step is rapid and yields the reaction product and nitrogen. The reaction was initially investigated to compare relative acidity of organic carboxylic acids in organic solvent (aprotic and protic). The reaction is first-order in the diphenyldiazomethane and first-order in carboxylic acids.

Experimentally, the reaction was conducted in presence of large excess of carboxylic acid (10 molar equivalents). As a consequence, the rate was pseudo first order with respect to the diphenyldiazomethane. The second order rate constant can then be obtained by dividing the experimentally obtained pseudo first order rate constant by the initial concentration of the carboxylic acid. Initially, the reaction of diphenyldiazomethane with benzoic acid (pKa = 4.2) was investigated. In batch, the reaction appeared to be relatively slow, reaching about 90% conversion in 96 minutes. As the reaction rate is directly proportional to the acidity of the carboxylic acid, we chose as a reaction partner the more acidic carboxylic acid, *p*-nitrobenzoic acid (pKa =3.4) to shorten the reaction time. The reaction of *p*-nitrobenzoic acid with diphenyldiazomethane in anhydrous ethanol was thus investigated in batch and flow (Figure 4). The results are provided in detail in the following section.

When the reaction is carried out in ethanol, three products can be formed: (i) benzhydryl-4-nitrobenzoate, which results from the reaction of *p*-nitrobenzoic acid with the diphenylmethane diazonium intermediate; (ii) benzhydryl ethyl ether that is obtained from reaction of the solvent, ethanol, with the diphenylmethane diazonium; and (iii) nitrogen. The product distribution was not studied as it is well documented in literature; rather we focused our attention to the technology transfer of the batch reaction to continuous flow 13-15. Experimentally the disappearance of the diphenyldiazomethane was monitored. The reaction proceeds with a vivid color change, which can be visually observed by UV-Vis spectroscopy. This results from the fact that the diphenyldiazomethane is a strongly purple compound whereas all other products from the reaction are colorless. Therefore, the reaction can be visually monitored on a qualitative basis and quantitatively followed by UV spectroscopy (i.e. disappearance of the diphenyl diazomethane absorption at 525 nm). Herein, we first report the reaction of diphenyldiazomethane and *p*-nitrobenzoic acid in ethanol in batch as a function of time. Secondly, the reaction was successfully transferred and carried out into the glass flow reactor. The progress of the reaction was ascertained by monitoring the disappearance of diphenyldiazomethane using UV-spectroscopy (in batch and flow modes).

**PROTOCOL:**

**Health Warnings and Specification of Reagents:**

Benzophenone Hydrazone: May cause irritation of the digestive tract. The toxicological properties of this substance have not been fully investigated. May cause respiratory tract irritation. The toxicological properties of this substance have not been fully investigated. May cause skin irritation and eye irritation 18.

Activated manganese oxide (MnO2): (Health MSDS rating of 2) Hazardous in case of skin contact, eye contact, ingestion, and inhalation 19.

Dibasic potassium phosphate (KH2PO4): (Health MSDS rating of 2) Hazardous in case of skin contact, eye contact, ingestion, and inhalation 20.

Dichloromethane: (Health MSDS rating of 2, Fire rating of 1) Very hazardous in case of eye contact (irritant), of ingestion, of inhalation. Hazardous in case of skin contact (irritant, permeator). Inflammation of the eye is characterized by redness, watering, and itching 21.

1. **Synthesis of diphenyldiazomethane (DDM):**
2. Before beginning synthesis of DDM, ensure all necessary materials listed are present as well as necessary reagents to ensure that proper synthesis can be conducted.
3. Add 10 g (.72 equivalent) of anhydrous KH2PO4 and 31 g of activated manganese dioxide, MnO2 (3.5 equivalents) to a 250 mL 3-neck round bottom flask (1), and a magnetic stirrer.
4. Add 20 g of benzophenone hydrazone into a separate 100-mL 2–neck round bottom flask (2), a magnetic stirrer, and store at room temperature.
5. Add 67 mL of dichloromethane (DCM) and equip both flasks (1 and 2) with stoppers, thermometer, and thermocouple.
6. After purging both flasks with inert gas for 15 min, apply an ice bath to the KH2PO4 and MnO2 solution (flask 1). Ensure that the temperature of the solution stays constant at 0 °C for at least 30 min.
7. After 30 min of constant temperature reading, transfer the benzophenone hydrazone (flask 2) into the flask containing KH2PO4 and MnO2 (flask 1). Carry out the reaction for 24 h to reach completion.
8. **Purification of DDM:**
9. After 24 h, add 120 mL of pentane to the reaction mixture (a deep, red purple solution).
10. Filter the solution rapidly through neutral silica gel (50-200 µm). It is important that the contact time of the product with the silica does ***not*** exceed 5 min. DDM is acid sensitive; significant decomposition will occur with longer contact time22.
11. Carry out the filtration with a medium porosity sintered glass funnel, attached to a vacuum filtration system or a fume hood vacuum system.
12. Transfer the filtrate and remove solvent with a rotary evaporator *in vacuo*. The resulting crude product is a deep-purple oil.

2.3.1) Wrap aluminum foil around the flask to keep light away from DDM. DDM is light sensitive.

1. After covering the flask with aluminum foil, store pure DDM in the freezer, sealed and under an atmosphere of inert gas.
2. Monitor for crystallization to occur, which usually takes 2-3 days. Remove the flask from the freezer and allow it to reach room temperature. **A further purification step is necessary.** Add 200-proof ethyl alcohol to the flask, filter and then use a rotary evaporator to remove the remaining solvent. At this point, most impurities remaining should be removed.
   * 1. Analyze the resulting deep, reddish purple crystals of DDM by UV spectroscopy. The experimental molar absorptivity was measured to be (ε) 94.8, which matched literature values.

**Caution:** Below are the relevant health warnings and specifications of reagents for the proper and safe handling of carrying out the reaction protocol for DDM. When dealing with these substances, ensure proper PPE **at all times** and working conditions under a fume hood.

DDM: Prolonged or repeated exposure may cause allergic reactions in certain sensitive individuals 23.

*p*-nitrobenzoic acid: (MSDS health rating of 2) ensure that reagent is kept away from heat. Keep away from sources of ignition. Empty containers pose a fire risk; evaporate the residue under a fume hood. Ground all equipment containing material. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes 24.

Ethyl Alcohol, 200 Proof: (MSDS health rating of 2, Health Rating of 3) Hazardous in case of skin contact, eye contact, and inhalation. Ethanol rapidly absorbs moisture from the air, and can react vigorously with oxidizers 25.

Toluene: (MSDS health rating of 2, Health Rating of 3) Hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, and of inhalation. Slightly hazardous in case of skin contact (permeator). Highly flammable 26.

*o*-xylene: (MSDS health rating of 2, Health Rating of 3) possibility of developing teratogenic effects, developmental toxicity to reproductive system in males, and toxic if ingested to kidneys, liver, upper respiratory tract, skin, eyes, and central nervous system. Keep away from skin contact (irritant, permeator), eye contact (irritant), of ingestion, and inhalation. 27

1. **Preparing solution of DDM for Continuous Flow:**
2. Rinse a 100-mL volumetric flask with ethanol.
3. Tare a 6-dram vial on an analytical balance, and add .1942 g of DDM into the dram vial. Add anhydrous ethanol (5 mL) to the vial in 2 to 3 increments until all the DDM goes into solution. With a pipette, transfer the solution from the 6-dram vial into the clean 100 mL volumetric flask.
4. Carefully add ethanol until the minimum point of the meniscus aligns with the line denoted on the volumetric flask.
5. Add 1 mL of toluene, the internal standard, into the flask. The volumetric flask can now be capped and stored until both the DDM solution and *p*-nitrobenzoic acid solution are ready for the continuous flow reaction.
6. **Preparation of 0.1 M stock solution of *p*-nitrobenzoic acid:**
7. Rinse the 250-mL volumetric flask multiple times with anhydrous ethanol.
8. Tare a 6-dram vial on an analytical balance. Add 4.1780 g of *p*-nitrobenzoic acid into the dram vial. After adding the acid, add anhydrous ethanol (5 mL) into 2 to 3 increments to the vial until all the *p*-nitrobenzoic acid goes into solution.
   1. With a pipette, transfer the solution from the 6-dram vial into the clean 250 mL volumetric flask.
   2. Carefully add ethanol until the minimum point of the meniscus aligns with the line of the volumetric flask.
   3. Add 1 mL of *o*-xylene, the internal standard, into the flask. The volumetric flask can now be capped and stored as needed.
9. **Preparation of the continuous flow reactor:**
10. Check that the transducer is connected to the pump controller in portal A for both ISCOs, and empty collecting beakers at the end of each exit tube to collect reaction solutions, waste, and solvent.
11. Set-up and check both ISCO 1 (*p*-nitrobenzoic acid) and ISCO 2 (DDM), as shown in Figure 9.

1. Set-up each ISCO pump with its own controller to independently control reagent streams. This allows for the flow rates to be independently adjusted as necessary.
2. In a separate beaker, add 400 mL of ethanol. This will be utilized to flush the reactor.
3. Turn the inlet HIP valve counter-clockwise until the valve is fully open (denoted as valve A and B, respectively). Press “Constant Flow” on the pump controller, and then “A”, which denotes the inlet which the transducer is linked to the ISCO. This action prompts the user to enter the desired flow rate.
4. Enter a flowrate of “70”, and press “Enter”. When ready, hit “Refill” to communicate to the system to draw up the solution at a rate of 70 mL/min.
5. Begin drawing the ethanol solvent through the inlet tube. Note that if the flow rate is drawing the solvent in, the flow rate on the ISCOs should read -70.000 mL/min. The solvent level in the flask will begin to decrease.

Note: It is perfectly normal if the volume of solvent does not match the volume that is shown on the controller. Air will be partially drawn into the system as well.

1. When both ISCO 1 and ISCO 2 have been completely filled and the controller indicates this by reading “Cylinder Full” and “Stopped”, turn the inlet valve A and B completely closed by turning the valve fully clockwise.
2. Open the outlet valve which operates similarly to the inlet valve, which is the valve leading to the reactor, by turning it counterclockwise. The outlet valve feeds through the filter, past the one-way valve, and from there past the pressure relieve valve and into the flow reactor.
3. At this point, change the flow rate. The maximum total flow rate recommended on a single run should not exceed 30 mL/min.

5.5.1) Clean each ISCO separately, running each at a flow rate of 30 mL/min.

1. Press “A” on the ISCO that is currently set up to run the ethanol through the system. Change the flow rate by entering the desired flow rate of “30”, “Enter”, and finally “Run”. This communicates to the system to run at a rate of 30 mL/min.

Note: As the flow equilibrates, the solvent begins flowing through the system.

1. Monitor the reactor for leakage or blockage, and that there is solvent flowing throughout the whole reactor. Once both ISCOs have been cleaned 2-3 times, the system is now ready to run the experiment.
2. **Setting up the .01 M DDM ISCO 2 pump:**
3. Place the inlet feed in the 100-mL volumetric flask of DDM. Open the inlet valve B (Feed 2 in Figure 9).
4. Set the ISCO to a flow rate of 70 mL/min. Begin drawing the solution up until all of it is taken up into the syringe by hitting “Refill”.
5. Note that the volume of solution in the ISCO and the original volume of solution in the flask can be slightly different. Air is also pulled in the ISCO pump.
6. If there is leftover DDM after the ISCO has reached max volume after the uptake of solution, press “Run” to push out the air that was drawn along with the flask from the inlet. Once DDM begins pushing out, hit “Stop”, and then “Refill” to begin refilling the ISCO.
7. Keep repeating these steps until all DDM has been taken up (this will be applied to *p*-nitrobenzoic acid as well).
8. Flow about 1 mL of DDM from pump. ISCO 2 pump is now ready to be run. The solvent level is in line and ready to begin flowing through the continuous flow reactor.
9. Close inlet valve B by turning the HIP valve clockwise until it cannot be turned further, and open the outlet valve which feeds into the continuous flow reactor by turning the valve counter clockwise until it is fully open. Transfer the 1 mL of DDM and toluene solution into a cuvette for UV-Vis analysis.
10. Set the flow rate to 1.42 mL/min. Do not hit “Run” until the *p*-nitrobenzoic acid ISCO 1 has been set-up by the same protocol at a flow rate of 3.58 mL/min and is ready to be run in tandem.
11. **Setting up the .1 M *p*-nitrobenzoic acid ISCO 1 pump:**
12. Open the inlet valve A of ISCO 1 pump, with the 250-mL volumetric flask of *p*-nitrobenzoic acid at the end of the feeding tube.
13. Once the feed tube is completely submerged in the volumetric flask, set the ISCO to a flow rate of 70 mL/min. Again, check to see if the flow rate on the controller reads 70.00 mL/min upon hitting “Refill”.
14. Begin drawing the solution up until all of it is taken up into the syringe, using the same technique listed above to get all of the solution into the system.
15. Close the inlet valve by turning the HIP valve clockwise until it is fully closed. Open the outlet valve which feeds into the continuous flow reactor by turning the valve counter clockwise until it is fully open.
16. Set the flow rate to 3.58 mL/min. The total flow rate including the 1.42 mL/min of DDM will be 5.00 mL/min, for a total residence time within the reactor of approximately 11 minutes with a ratio of 10:1 *p*-nitrobenzoic acid to DDM.
17. **Conducting the reaction in flow with 10:1 molar equivalence of *p*-nitrobenzoic acid and DDM:**
18. Once each pump is ready with the reagent’s solutions, the valves properly adjusted, and the correct flow rates have been entered, hit “Run” on both pumps. After the one-way valve pressure has equilibrated, the reagent’s solutions will begin flowing into the reactor modules.
19. Monitor flow. DDM’s feed enters at module 1, *p*-nitrobenzoic acid’s feed into module 2, and mixing take place at module 3. The residence time is approximately 11 minutes.
20. Monitor color change (indicative of reaction progress). The color in module 2, prior to mixing, is strong pink. The color intensity decreases, it becomes fainter pink in module 3, and pale pink in module 4. The modules thereafter are colorless.
21. **Cleaning the continuous flow reactor:**
22. Once both runs of DDM and *p*-nitrobenzoic acid are completed, fill a beaker with 400 mL ethanol. This will be used to clean the reactor and the ISCO pumps.
23. Turn the inlet HIP valve counter-clockwise until the valve is fully open.
24. Set the flow rate to 70, press “Enter” and “Refill” to begin drawing the ethanol solvent through the inlet tube (note that if the flow rate is drawing the solvent in, the flow rate on the ISCOs should read 70 mL/min).
25. Once the ISCOs have been filled, the ISCOs will automatically stop, and the controller will read “Cylinder Full” and “Stopped”. At this point, turn the inlet valve completely closed, by turning the valve clockwise until the HIP valve cannot be turned further.
26. Open the outlet valve which operates similarly to the inlet valve, by turning it counterclockwise. The outlet valve feeds through the filter, passes the one-way valve, and from there flows through the pressure relieve valve and into the flow reactor.
27. Adjust the flow rate to not exceed 30 mL/min.
28. Press “A” on the ISCO that is currently set up to run the ethanol through the system. Change the flow rate by entering the desired flow rate of “10”, hit “Enter”, and then hit “Run”. Check the system to see there is no leakage or blockage, and that there is solvent flowing throughout the whole system.

Note: Once both ISCOs have been cleaned 2 times with ethanol and once with just air following procedures noted above, the system is now ready to run for future experiments.

**REPRESENTATIVE RESULTS**

*Batch Reaction.*

Diphenyldiazomethane was prepared according to literature 28,29. The compound was crystallized from petroleum ether:ethyl acetate (100:2) and the purple crystalline solid was analyzed by H1 NMR, melting point and MS. The analyses were consistent with the structure and reported literature values.

The reaction of diphenyldiazomethane (1.0 mM) with benzoic acid (10 mM) in anhydrous ethanol was carried out at 21 °C in dry ethanol. The progress of the reaction was monitored using UV-Vis spectrometry (max= 525 nm). After 96 minutes, about 90% of the diphenyldiazomethane was consumed. The pseudo-first order rate constant was calculated to be 0.0288 min-1 and the resulting second rate constant to be 0.58 mol-1.min-1.L. The second-order rate constant is in agreement with literature values (~ 0.7 mol-1.min-1.L at 26 °C).17 The reaction was then investigated with the more acidic *p*-nitrobenzoic acid. The reaction of diphenyldiazomethane (1 mM) with *p*-nitrobenzoic acid (10mM) in anhydrous ethanol was conducted at 21 °C and monitored in-situ by UV-Vis at = 525 nm (Figure 5). UV-vis spectra were taken at 1.5 minutes intervals. Figure 6 shows a representative spectrum of the UV-absorbance of diphenyldiazomethane as a function of the progression of the reaction with *p*-nitrobenzoic acid in anhydrous ethanol.

Figures 7 and 8 show the concentration of DDM as a function of time and the pseudo-first order ln(Abs/Abs0) as a function of time. From the latter plot, an apparent first-rate of reaction of 0.135 min-1 was obtained, which corresponds to a second order rate constant of 1.80 mol-1.min-1.L. The data are consistent with reported literature values.17 Importantly, the reaction reaches about 94% completion within 20 minutes (Figure 8), which is amenable to the flow reactor. The next step was to transfer the reaction to the glass flow reactor.

*Flow reaction.*

The schematic and photograph of the flow process used herein is shown in Figure 9. The two reactant streams are introduced into a pre-heating/cooling module (1 and 2 in Figure 9). Modules 1 and 2 allows to control the temperature of each incoming feeds. The mixing of the two reactant feeds occurs at the module 3 (Figure 9) before proceeding into three mixing modules (4, 5, & 6 in Figure 9) and two linear modules (7 & 8 in Figure 9). Each reactant stream was independently controlled and introduced via syringe pumps. The reactant solutions were each prepared with internal standards (1vol% toluene/ortho-xylene) to measure accurately the concentrations of reactant. The residence times of the reactions are controlled by changing the total flow rate. For example, residence times of 1 min 52 s, 3 min 44 s, and 11 min 12 s corresponded to total flow rates of 30 mL/min, 15 mL/min, and 5 mL/min.

Operationally, two stock solutions were prepared: (1) A solution of diphenyldiazomethane in anhydrous ethanol (0.02M) and (2) A solution of *p*-nitrobenzoic acid (0.1 M). Both solutions were fed into the reactor (Feeds 1 & 2 in Figure 9) at rate of 1.42 mL/min of and 3.58 mL/min respectively. Accounting for the initial concentrations of diphenyldiazomethane and *p*-nitrobenzoic and their respective flow-rate, the molar ratio of diphenyldiazomethane to *p*-nitrobenzoic acid was 1 to 10. Experimentally, the total flow rate was approximately 5 mL/min leading to a residence time of 11 minutes. Aliquots were taken as a function of time and analyzed by GC-FID (gas chromatography with flame ionization detector) and by UV-Vis spectroscopy. GC-FID analyses were used to measure the accurate concentration ratio of reagents using internal standards. Toluene was used as the internal standard (0.107 M) in the diphenyldiazomethane solution and *ortho*-xylene was present in the *p*-nitrobenzoic acid (0.072 M). The UV-Vis analyses quantitatively measured the progress of the reaction by monitoring the disappearance of diphenyldiazomethane as a function of time (the method was established and described for the batch reaction).

The results shown in Figure 10 shows that 95% completion is reached within the 11 minutes residence time. To reach complete conversion, the residence time can be extended to 33 minutes or less. Operationally, full conversion can be obtained with slower flow rate (as shown) or by increasing residence time (additional microstructures/modules) and/or increase of temperature. However, the proof of concept shows that the reaction can successfully be conducted in flow with 95% conversion in 11 minutes.

Figure 1. Schematic of continuous flow microstructures.

Figure 2. Mixing (left) and linear (right) microstructures.

Figure 3. Reaction of diphenyldiazomethane with an acid (X-H).

Figure 4. Reaction of diphenyldiazomethane with p-nitrobenzoic acid in anhydrous ethanol.

Figure 5. Reaction of diphenyldiazomethane (1eq) with ethanol and p-nitrobenzoic acid (10 eq).

Figure 6: Absorbance as a function of wavelength for the reaction of diphenyldiazomethane with p-nitrobenzoic acid. The maximum absorbance for diphenyldiazomethane is 525 nm. Each line represents one spectra taken at different time intervals (each 1.5 min) from time = 0.

Figure 7: pseudo-first order reaction (ln(Abs/Abs0) vs. Time (min) as a function of time for the reaction of diphenyldiazomethane and p-nitrobenzoic acid at 21 °C in ethanol in batch.

Figure 8: Concentration of diphenyldiazomethane as a function of time for the reaction of diphenyldiazomethane and p-nitrobenzoic acid at 21 °C in ethanol in batch.

Figure 9. Schematic of the continuous flow reactor.

Figure 10. Concentration of diphenyldiazomethane as a function of time for the reaction of diphenyldiazomethane and p-nitrobenzoic acid at 21 °C in ethanol in flow.

Figure 11. Reaction of diazoketone, tert-butyl (S)-(4-diazo-3-oxo-1-phenylbutan-2-yl)

Carbamate.

**DISCUSSION**

Flow chemistry has gained much attention recently with an average of about 1500 publications on the topic annually in research areas of Chemistry (29%) and Engineering (25%). Many successful processes have been conducted in flow. In numerous cases, flow chemistry was demonstrated to exhibit superior performances to batch for many applications such as the preparations of pharmaceutically active ingredients 30,31, natural products 32, and specialty, high-value chemicals like high-performance polymers 33-36. We leveraged and reported continuous flow processes for the preparation and reaction of diazoketone 37, Meerwein-Ponndorf-Verley reduction of ketone and aldehydes to alcohols 38 and metal-catalyzed Homo-Nazarov cyclization 39. Especially interesting is the example of the preparation and reaction of thermally unstable and highly reactive anhydride in the reaction of diazoketone, tert-butyl (S)-(4-diazo-3-oxo-1-phenylbutan-2-yl) carbamate (Figure 11) 37,40.

Because of the enhanced temperature control and mixing, the flow technology was demonstrated to be superior to batch process for the following criteria: (i) the implementation of a less expensive mixed anhydride (ii) the use of the relatively safer trimethyl silyldiazomethane than diazomethane (iii) the temperature, 4 °C in flow instead of -20 °C in batch with consistent 100% yield (iv) shortened reaction time (10 min) and (v) significant reduction in waste-stream (atomic economy).

Herein, we have provided a blueprint for the successful transfer of diphenyldiazomethane with *p*-nitrobenzoic acid reaction from batch mode to continuous flow. Our blueprint emphasizes that it is critical to conduct studies in batch mode to establish accurate reaction rate, the reaction profile as a function of time, and the optimum concentration and temperature. These parameters are essential to take into consideration prior to transferring the reaction to continuous flow technology. The design of the reactor was described in detail and was tailored to be amenable with regards to the reaction characteristics. Finally, the reaction was successfully conducted in flow and monitored qualitatively by visual observation (i.e. loss of color). Quantitative assessment of the progress of the reaction (e.g. disappearance of diphenyldiazomethane) was obtained by UV-Vis. About 94% consumption was achieved with 11 minutes residence time in flow at 21 °C.

Limitation and considerations:

The formation of solids (i.e. precipitates) during the reaction is an important parameter when considering flow processes. In those instances, one must consider: (i) modifying the protocol in batch-mode to maintain homogeneity throughout the reaction (i.e. changing reagents, solvent, temperature, etc.) or (ii) design the reactor to allow for the processing of slurries. The second option may be viable with optimization and tailored reactor design. In practice, the two most limiting factors for flow processes are (i) viscous solutions: the ability to pump viscous liquids and the resulting pressure drop are often prohibitive and (ii) using heterogeneous (solid/liquid) feeding streams. It is difficult to consistently and effectively pump fine suspensions (for example in the cases of heterogeneous catalyst). In addition, accumulation of particles in the reactor can lead to blockage, and ultimately failure.

Overall, flow chemistry has been demonstrated to be superior (to batch processes) for synthetic transformations that (i) require precise temperature control (i.e. avoid hot spot, competitive reaction, etc.) (ii) involve the formation of highly reactive or unstable intermediates, or (iii) require enhanced mixing with multi-liquid phases for example. The resulting increase of product quality and reproducibility (via enhanced and precise control of the process parameters) is impactful both from an environmental and a financial standpoint. Flow technology may not be the universal solution but can open new avenues for chemical pathways that were deemed not viable in batch (i.e. too reactive or too unstable intermediates) as well as provide process optimization in terms of energy consumption, atom economy and downstream-purification. To conclude, it is a powerful tool to effectively conduct multi-step processes for high-value added chemicals.

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**DISCLOSURES**

None of the authors within this protocol have any competing financial interests or conflict of interest.

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