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Can Accelerated Reactions in Droplets Guide Chemistry at Scale?

Michael Wleklinski, Caitlin E. Falcone, Bradley P. Loren, Zinia Jaman, Kiran Iyer, H. Samuel Ewan, Seok-Hee Hyun, David H. Thompson*, and R. Graham Cooks*

Abstract: Mass spectrometry (MS) is used to follow chemical reactions in droplets. In almost all cases, such reactions are accelerated relative to the corresponding reactions in bulk, even after correction for concentration effects, and they serve to predict the likely success of scaled up reactions performed in microfluidic flow systems. The particular chemical targets used in these test studies are diazepam, atropine and diphenhydramine. In addition to a yes/no prediction of whether scaled up reaction is possible, in some cases valuable information was obtained which helped in optimization of reaction conditions, minimization of by-products and choice of catalyst. In a variant on the spray-based charged droplet experiment, the Leidenfrost effect was used to generate larger, uncharged droplets and the same reactions were studied in this medium. These reactions were also accelerated but to smaller extents than in microdroplets and they gave results that corresponded even more closely to microfluidics data. The fact that MS was also used for on-line reaction monitoring in the microfluidic systems further enhances the potential role of MS in exploratory organic synthesis.

Introduction

This study is part of a larger project, the overall goal of which is to develop an automated scalable and continuous synthesis system. A key objective is to test possible synthetic pathways quickly on a small scale seeking a go/no-go result. We "spot test" particular routes using a chemical pruning step which employs reaction acceleration in droplets with independent mass spectrometric analysis. A simple yes/no answer to product or (in multistep reactions) intermediate formation is sought using the charged droplet reactor. We use electrospray (ESI) for both synthesis and analysis with careful control of parameters to avoid unwanted reaction during analysis.[1]

Charged microdroplets are produced by ESI. It is known that reaction rates increase as the solvent evaporates because of changes in concentration, pH, surface/volume ratios, and interfacial effects.[1b, 1c, 2] The acceleration factors can be remarkably large.[3] A recent review covers the topic of accelerated reactions in droplets, including evidence that partial solvation of reagents at interfaces contributes to the orders of magnitude reaction rate acceleration that can be seen.[1a] The hypothesis investigated here is that the accelerated reactions that occur in droplets might assist in rapidly evaluating reactivity in microfluidic systems.

A second method of producing droplets is based on the Leidenfrost effect.[4] It has recently been shown that accelerated organic reactions occur in Leidenfrost droplets.[5] These droplets differ from ESI based droplets in that they are i) larger ii) net neutral and iii) involve elevated temperatures. The difference in droplet size means that larger amounts of reagent can be studied, but the surface/volume ratio is greatly decreased. The measured reaction acceleration factors for three previously studied Leidenfrost reactions, hydrazone formation, Katritsky pyrylium to pyridinium conversion and Claisen-Schmidt condensation, are about an order of magnitude.[5]

Note that we do not expect to be able to transfer optimized conditions exactly from the droplet scale to the microfluidics scale, in part because of uncertainty about the origins of acceleration effects in the two systems. We do expect that these optimized conditions will represent a starting point for efficient optimization of the conditions in the microfluidics reactor. We also expect that information on reaction intermediates and mechanisms might be acquired from the study of droplet reactions. This information is already being obtained in experiments in which the degree of desolvation of the initial droplets is varied by changing the distance that the droplets travel before analysis.[1b] Information obtained from the droplet reactor on experimental parameters including solvent, catalyst, pH, etc. is also readily acquired and we examine how transferable this information is in optimizing the microfluidics flow reactor.

The identification of suitable pathways to target molecules is just one step towards an online, automated flow-through synthesizer, for which the groundwork has been laid by several groups. Notable are the mole-scale, end-to-end, continuous manufacturing pilot plant developed by MIT/Novartis,[6] the refrigerator sized, reconfigurable, on demand synthesizer of pharmaceuticals of MIT,[7] the nanomole-scale robotic high-throughput synthesizer of Merck[8] and the automated synthesis laboratory of Eli Lilly.[9] The mole-scale MIT synthesizer was used to produce aliskiren hemifumarate in tablet form, from a complex intermediate in a continuous fashion.[6] The Merck nanomole system was used to screen 1,500 reactions per day to identify potential candidate reactions for large scale synthesis. The Lilly system combined automated synthesis with analysis performed remotely controlled in real-time, to produce gram-scale products.

The main question underlying this study is whether droplet reactions may be used to predict chemical reactivity in flow chemistry systems, in particular in microfluidics. The mechanism for acceleration observed in microdroplets is certainly different from that in microfluidics in that evaporation is not significant in microfluidics; however, interfacial effects may still play an important role especially in droplet microfluidics.[10] The speed of data acquisition in droplets makes this approach attractive. Note that false negatives (predict no reaction, but reaction can be observed) is not expected to be a serious problem because there are usually many available routes to test. On the other hand, a false positive result will lead to wasted effort in seeking an analogous flow reaction. Note, too, that use of droplets for a simple yes/no regarding occurrence of reaction represents only one level of enquiry, even though it is the most important one. As will be seen in the results now to be discussed, information on reaction conditions is also obtained, although the quality of this information remains to be evaluated further by studying more cases.

Results and Discussion

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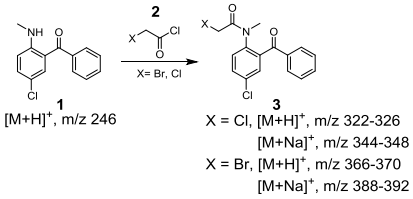
The charged droplet and microfluidic based synthesis of amide **3**, generated by N-acylation of **1** with the 2-haloacetyl chloride **2**, was examined due to its importance as a synthetic step in the pathway to diazepam (Scheme 1). An electrospray droplet reactor was used to evaluate potential solvents for the



Scheme 1. Reaction of **1** and **2** (X = Cl, Br) to form amide **3**.

N-acylation reaction using chloroacetyl chloride. Offline charged droplet reactions were performed using a mixture of **1** and **2** (X = Cl) in various solvents, and conversion to product as analyzed by ESI MS was compared to a 30-minute batch reaction (Figure S1). Before analysis, samples are quenched in order to ensure no further reaction by diluting the collected product into the solvent used in the prior step. The results indicate that there is significant acceleration of the reaction when the solvent is DMF, ACN, or toluene. Acceleration in microdroplets is associated with evaporation and is proposed to be due, in part, to intrinsic rate acceleration at the interface.[2c] These initial results encouraged a more extensive reaction screening, where the effect of the chosen 2-haloacetyl chloride (Cl or Br) and the solvent (ACN, toluene) was investigated using a droplet reactor. Interestingly, the droplet reactor data indicated nearly complete conversion of starting materials to product for both the chloro and bromo starting materials in acetonitrile (Figure 1) and in toluene (Figure S2). Starting material **1**, is observed at m/z 246 and product, **3** appears in either its protonated (X = Cl, m/z 322-326 or X = Br, m/z 366-370) or sodiated (X = Cl, m/z 344-348 or X = Br, m/z 388-392). A small amount of S_N2 product (*m/z* 322) was observed for bromoacetyl chloride in ACN but not in toluene. In the case of the chloro starting material (**2**), the S_N2 and acylation products have identical molecular formulae and are not differentiable; however, the presence of only small amounts of the S_N2 product using bromo starting material, provides evidence that the chloro reacts mainly to form the desired acylation product.

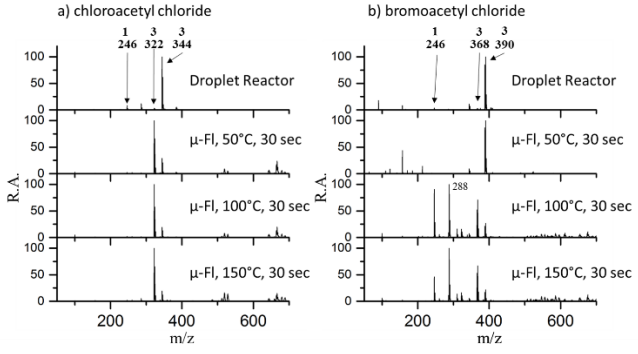
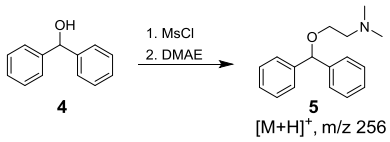


Figure 1. Synthesis of **3** in ACN using a) chloroacetyl chloride and b) bromoacetyl chloride in droplet reactor and microfluidics (μ-Fl)

Flow experiments were performed using the same concentrations as in the droplet reactor, while screening the effect of temperature for a fixed residence time of 30 seconds. High conversion to **3** was observed with chloroacetyl chloride in both solvents at 50°C. More interestingly, a major difference was observed with bromoacetyl chloride in ACN, wherein a major amount of S_N2 reaction product was observed, especially at higher temperatures (100 and 150°C). The presence of a by-product (ion *m/z* 288) arising from the initial S_N2 reaction product was confirmed by NMR and MS/MS (data not shown). The droplet reactor predicted formation of the desired intermediate, which was observed in flow. However, under higher temperature conditions in flow, the proportion of S_N2 product increased. This difference can be explained by the fact that evaporative cooling occurs during flight in the droplet reaction at room temperature, thus reducing the reaction temperature.[11] Nonetheless, the droplet reaction demonstrated reaction feasibility and showed that specific solvents (ACN, toluene) are better than others a fact reiterated under microfluidic conditions for this transformation.

The ability of droplet reactivity to guide chemistry at scale was investigated for another important drug, diphenhydramine. The flow based synthesis of diphenhydramine was demonstrated by the reaction of dimethylaminoethanol (DMAE) with chlorodiphenylmethane.[12] This synthesis featured 100% atom economy; however, chlorodiphenylmethane is an expensive starting material, which motivated an effort to develop a more cost effective process by replacing chlorodiphenylmethane using a commodity starting material, benzhydrol, **4**. To synthesize diphenhydramine **5,** benzhydrol (**4**) was converted to the corresponding mesyl ester, which was subsequently treated with DMAE to produce **5** (Scheme 2). The droplet reactor synthesis of **5** was demonstrated by performing two sequential charged droplet reactions in either a toluene or acetonitrile solvent system. First benzhydrol and mesyl chloride were sprayed to produce the mesyl ester. This material was recovered and re-dissolved before



Scheme 2. Mesylation of **4** followed by reaction with dimethylaminoethanol (DMAE) to form diphenhydramine,**5.**

introduction of the second reagent, dimethylaminoethanol (20 equivalents) and repetition of the spray process (Figure 2). The MS analysis of the two-step spray product indicated that ACN is overall a better solvent for the synthesis of diphenhydramine, **5** (m/z 256), than toluene. Unreacted DMAE (m/z 90), mesylated DMAE (*m/z* 168), and a dimer of DMAE with methanesulfonic acid (m/z 275) were observed with the charged microdroplets. A similar trend was observed in flow (Figure S3, S4), where optimized conditions gave diphenhydramine in 35% and <1% yield in ACN and toluene, respectively, using one equivalent of dimethylaminoethanol. Good agreement is observed between the charged droplet reactor and flow in this synthesis.

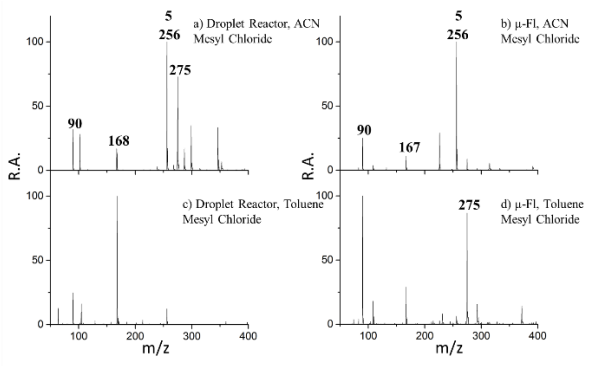
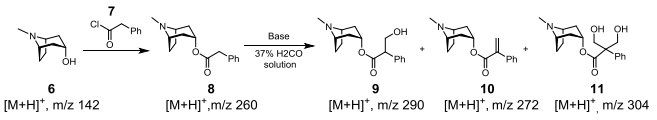


Figure 2. Charged microdroplet (a,c) and microfluidic (b,d) reaction telescoping for diphenhydramine synthesis in two solvents (ACN, toluene)

The charged droplet and microfluidic synthesis of atropine also was achieved by telescoping two reaction steps. The intermediate ester **8** (Scheme 3) was prepared from the commercially available starting material tropine **6** and phenylacetyl chloride **7**.



Scheme 3. Esterification reaction of **6** with **7** to synthesize **8** followed by base catalyzed aldol condensation with formaldehyde to synthesize atropine, **9**.

The intermediate **7** was used without further purification for the aldol condensation reaction to produce the final product, atropine. The first step was optimized for solvent and reactant stoichiometry. The droplet reactor indicated dimethylacetamide as the best solvent and this was confirmed in microfluidics (data not shown). Using the unpurified intermediate ester **8** (m/z 260), a base screen with the droplet reactor determined the effectiveness of three bases in synthesizing atropine, **9** (m/z 290). Each base was successful in the droplet reactor, producing significant amounts of atropine (and byproducts), with 1,5-diazabicyclo[4.3.0]dec-5-ene being the most effective (Figure 3, Figure S5). In flow, each base produced atropine (and byproducts) with 1,5-diazabicyclo[4.3.0]dec-5-ene again being the most efficient. There is also some agreement between flow and charged droplets on the type and extent of byproduct formation. For example, using 1,5-diazabicyclo[4.3.0]dec-5-ene, atropine and its dehydration product (*m/z* 272, **10**) are observed. However, with MeOK the same type of byproducts could be observed, but their proportions were quite different. (Scheme 3). The major byproduct in flow, characterized by *m/z* 304, **11**, is barely formed in charged droplets. One possible reason for this difference is that formaldehyde with its high vapor pressure escapes the droplets rapidly obviating formation of this byproduct. Finally, good agreement between the two methods was observed with NaOH, where the α,β-unsaturated product (*m/z* 272, **10**) is the major byproduct for both droplet reactor and microfluidics. Thus, for the synthesis of atropine, the charged droplet reactor was useful in guiding the choice of solvent and base.

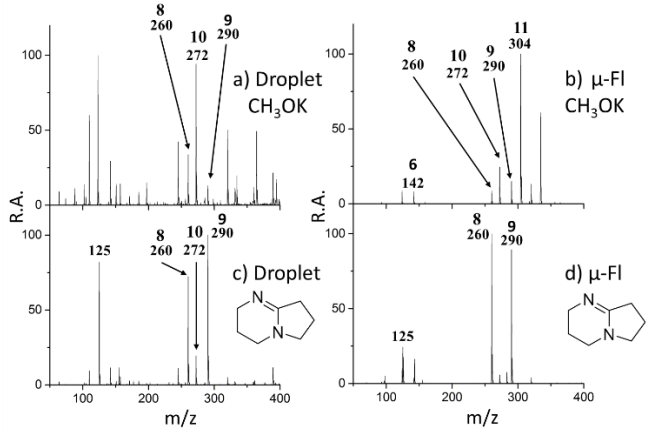


Figure 3. Charged microdroplet (a,c) and microfluidic (b,d) reaction telescoping for atropine synthesis using potassium methoxide or 1,5-diazabicyclo[4.3.0]dec-5-ene

The occurrence of accelerated organic reactions in Leidenfrost droplets[5] is at least in part a surface property (partial solvation of reagent molecules at the surface reduces activation energies). Consistent with this, and the smaller surface/volume ratios of Leidenfrost droplets, acceleration factors are smaller than in electrosprayed microdroplets. However, the larger droplets (0.5 mL volume) mean that conditions in the Leidenfrost droplets are closer to those in microfluidic solutions and in the bulk, so the predictive power of Leidenfrost droplet reactions might be even greater than that of electrospray generated droplets. The lack of a formal charge also strengthens the expected analogy with scaled-up chemistry.

This expectation is met when one considers data for the first step of the diazepam synthesis using bromoacetyl chloride and chloroacetyl chloride. First, consider the mass spectra recorded for charged droplets in ACN and in toluene versus those for Leidenfrost droplets in the same two solvents (Figure 4, Figure S6). The assignment of m/z is the same as figure 1 and scheme 1. The conversion in the Leidenfrost experiment is not as great (more starting material seen) as in the charged droplet reactions, but both methods give almost exclusively the desired acylation intermediate as opposed to the S_N2 product. There is not a large difference in the results for ACN versus toluene as solvent, except that the conversion is slightly higher in ACN. If we now consider the difference between microfluidic flow and Leidenfrost droplet data, we find remarkable similarities. Microfluidic synthesis at 50°C results primarily in desired acylation product as is the case in the Leidenfrost droplets. One difference is in the formation of a minor species seen at *m/z* 260 in the Leidenfrost case.

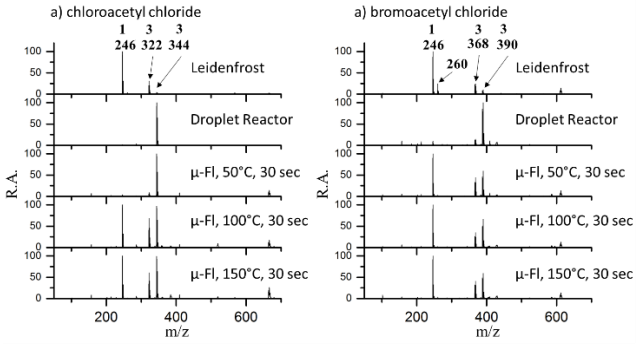


Figure 4. Synthesis of **3** in toluene using chloroacetyl chloride a) and bromo acetylchloride b) in Leidenfrost, charged microdroplets and microfluidics

The ion *m/z* 260 is believed to be due to a ring closure product resulting from acylation. The uncharged Leidenfrost droplets closely mirror the chemistry in microfluidics, except when the temperature in the microfluidics reaction is greatly elevated. Under these circumstances different byproducts are generated as S_N2 becomes more competitive.

The complete synthesis of diazepam in Leidenfrost droplets was demonstrated by adding 7 or 70 equivalents of NH_3 to intermediate **3** (not isolated) in a telescoped reaction. The chloro intermediate was unable to produce diazepam in quantity. However, the bromo intermediate produced diazepam (confirmed by MS/MS) in agreement with a reported flow synthesis.[7]

Conclusions

This study provides evidence for the importance of MS, not only in the traditional sense as an analytical method, but as a fast, predictive means to perform small scale continuous synthesis. The data encourage the use of spray ionization as a

method of screening for successful reaction pathways in flow reactions. At a secondary level, we find some parallels in the favored catalysts, solvents, mole ratios of reagents, and other operating conditions. However, little is known of droplet reaction mechanisms (an important topic in its own right), so extrapolation from conditions that favor reactions in nanodroplets to microfluidic chemistry may not be simple or universal. Nevertheless, as we show in this study, a useful guide to the global aspects of flow chemistry is obtained in these cases.

Limitations in further extending this approach to reaction screening (and to on-line reaction monitoring) are to be found in the size, cost and complexity of commercial mass spectrometers, many of the features of which are unnecessary for this type of study. What is needed for the purposes described here is a small, portable, unit resolution, low mass/charge range (to *m/z* 1000) instrument which has ambient ionization and tandem mass spectrometry capabilities. A recent review of miniature MS instruments[13] describes a few systems of this type.

Experimental Section

Droplet Reactor Experiments: These experiments used electrospray ionization (ESI) by spraying the reaction mixture either i) directly into the MS or ii) onto a collection surface before taking up the residue in solvent and performing ESI-MS product analysis. Figure 5 illustrates these two options, which are distinguished by the fact that i) is virtually instantaneous (10 – 15 s) while ii) can take a few minutes, but ii) is more versatile in that the reaction and analysis occur in separate steps, more product is formed, and the procedure allows temperature and other conditions to be varied and optimized. In both cases, the primary question being asked is whether the desired reaction occurs or not. Products, byproducts and residual reagents were identified from mass spectra recorded at unit resolution while tandem mass spectrometry (MS/MS) was used to confirm identifications.

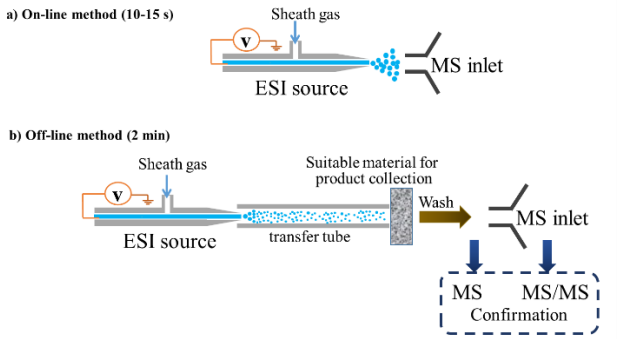


Figure 5. Methods used to perform microdroplet reactions, based on ESI either a) with on-line product analysis by MS or b) with sprayed droplet deposition and subsequent off-line MS product analysis

Offline Droplet Reactor: Offline droplet experiments were performed using a homebuilt electrospray ionization source. In the cases of atropine and diazepam, the reagents were premixed and subjected to offline electrospray at 10 µl/min with +5kV voltage and 100 PSI N_2. For diphenhydramine, reagents were mixed inline using a mixing tee and offline electrospray was performed under the same conditions. After the electrospray deposition was complete, reaction product was rinsed from the collection surface and then analyzed by nanoESI. Samples were diluted at least 100-fold before analysis in order to quench the reaction and ensure no further reaction could occur during the analysis step. For two- step reactions, the washed material was drawn back into a syringe and mixed with the second step reagent and then electrosprayed, collected, and washed as before.

Leidenfrost Droplet Experiments: Reactions in Leidenfrost droplets[5] differ in that these are i) larger ii) net neutral and iii) involve elevated temperatures. Reaction mixtures were added in aliquots over a 2 min period to maintain a constant droplet volume (Figure S7). The droplet (ca. 2 mm diameter) was levitated in a petri dish atop a heater with a surface temperature of 400 – 500 °C [CARE!]. Reactions occurred at temperatures close to, but below, the boiling point of the solvent.[14]

Mass spectrometry: Mass spectral analysis of reaction products was performed using an LTQ ion trap mass spectrometer (Thermo Fisher Scientific, San Jose, CA) with nanoESI ionization. All product samples (spray, Leidenfrost, or flow reactions) were diluted 1:100 into acetonitrile before analysis unless otherwise noted. The distance between the tip of the spray emitter and ion transfer capillary to the MS was held constant at ca. 1 mm. Experiments were performed using borosilicate glass pulled to a ca. 1-3 um aperture. A spray voltage of either positive or negative 2.0 kV was used for all analysis. Positive ion mode was used for all chemical analysis unless otherwise noted. Product ion (MS/MS) spectra were recorded using collision induced dissociation (CID) with a normalized collision energy of 25 (manufacturer's unit).

Synthesis of Diazepam Precursor: Reactions were performed with 100 mM 5-Chloro-2-(methylamino)benzophenone and 100 mM 2-haloacetyl chloride (halo = Cl, Br) dissolved in either toluene or acetonitrile. Solutions were either mixed prior to use (droplet reactor, Leidenfrost) or mixed online (microfluidics) to give a final reaction concentration of 50 mM. Other conditions were explored as indicated in the results section.

Diphenhydramine

Reactions were performed in a two-step manner. First, 500 mM benzhydrol was mixed with 500 mM mesyl chloride, then in the second step 20 equivalents of dimethylaminoethanol was used in the droplet reactor, while 1 equiv was used for microfluidics. Other conditions were explored as indicated in the results section.

Atropine: The atropine intermediate was first synthesized by reacting 1 M phenylacetyl chloride and 1 M tropine dissolved in DMA. For the second step, 7 equiv of base in DMA and 7 equiv of formaldehyde in H_2O was used. Other conditions were explored as indicated in the Results section.

Microfluidics: Microfludic reactions were performed using a Labtrix S1 system from Chemtrix, Ltd. The Chemtrix system is comprised of syringe pumps to deliver regents, microfluidic chips, a Peltier element, back pressure regulator, and a collection carousel. For the synthesis of diphenhydramine a homebuilt Peltier controlled system coupled with the Chemtrix microfluidic platform was used to allow for multi-step reactions to be performed with control over the temperature of each step.

Chemicals and reagents: All chemicals were purchased from Sigma Aldrich and used without further purification.

Acknowledgements

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Keywords: reaction kinetics • mass spectrometry • reaction acceleration • flow chemistry • Leidenfrost effect

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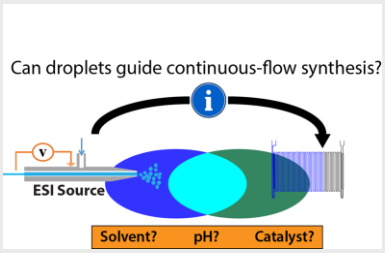
Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

This paper asks whether the course of reaction in charged microdroplets and uncharged Leidenfrost droplets can be used as a guide to reactions in microfluidic flow systems. Synthesis of three important pharmaceutical drugs is explored with the droplet reactor providing information on solvent, catalysts, and byproducts in flow.



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