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EXPLORING NEW TECHNOLOGIES IN SYNTHESIS USING FLOW CHEMISTRY

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Abstract— **Increases in efficiency, reduction of turnaround time, and many other factors have long influenced the pursuit of new technologies in chemistry. With the goal of effective synthesis of previously unattainable compounds and the more efficient synthesis of libraries of compounds, these methods continue to evolve and have grown to include tandem orientation of various tools. Through the use of flow systems, many significant advances have been made in the field of organic synthesis: for example, unattended automation, resin tethered reagents, and extensive library production. New methodology and instrumentation of flow systems are constantly evolving and adapting to new developing research. The goal of this research project was to apply flow chemistry to various projects, produce novel syntheses of various compounds that, in the end, demonstrate the versatility of flow methodology.**

The synthesis of amide libraries was explored in a project executed at Merck & Co., Inc. The goal of this project was to use the Syrris AFRICA system to decrease the turnaround time between synthesis and screening of libraries of compounds. With the improvement on the turnover time of libraries, the efficiency and throughput of the drug discovery process would largely improve by allowing the screening many additional extended libraries with ease. Also, the method included unattended synthesis of these libraries, with a carboxylic acid tethered to a macroporous (MP) resin via an activated tetrafluorophenol (TFP) ester linkage. In this project, a library of 20 pure amides was synthesized consecutively, and in dimethyl sulfoxide (DMSO), which provided the molecules a straight route to assay. The TFP-MP resin column was re-used over 36 times, with reproducible efficiency, in a coupling time of an hour.

A project was then initiated that extended this resin-bound reaction technology further to include methodology for efficient, high-throughput radiolabeling of many different substrates, ranging from small molecules to proteins and other biomolecules. Rapid and direct fluorination of biologically sensitive molecules is not possible. The use of a linker between the molecule and the radiolabel is needed and had to be chosen carefully. After exploring the use of 4-fluorobenzaldehyde as a fluorine source and boc-aminooxyacetic acid as a linker, a N-succinimidyl-4-fluorobenzoate moiety was chosen to fulfill both requirements. A synthetic route was developed to rapidly radiolabel proteins and peptides with ease. These labeled molecules may be used to develop new imaging agents for positron emission tomography (PET) imaging.

Index Terms— **Flow Chemistry, Scavenging Reagents, HPLC column, Micro Reacter, TFP.**

I. INTRODUCTION

Flow Chemistry

The chemical industry is constantly developing new technologies to increase the ease of syntheses. In the past five years, technologies such as microwaves and flow chemistry for small scale reactions have emerged and have been widely implemented in synthesis and other applications. Flow chemistry has long been employed in manufacturing, but a need for implementation on the small scale was needed. There are many types of flow chemistry, however, the three primary performed on a small scale include micro flow (Figure 1), meso flow (Figure 2), and flow using tethered reagents (Figure 3).1,4 Micro flow technology is when there are a series of interconnecting channels in a planar surface, usually a chip. The reagents are brought together, mixed, and allowed to react for a specific period of time. Meso flow is similar to micro flow, but instead of the two reagents mixing in channels in micrometer sized channels in a chip, they mix in a tube reactor, therefore these reactions can be done on a larger scale. Flow chemistry using tethered reagents can be performed in two fashions. First the reagent could flow through the column, displace the tethered reagent C to combine and make product B or reagent A could flow through the column, couple to reagent C to make B and then have to be cleaved off of the resin, as can be seen in Figure 3.1 These types are not only seen as an alternative route to perform syntheses, but are now slowly becoming the preferred route for certain types of reactions, particularly in those reactions where unstable intermediates are formed.

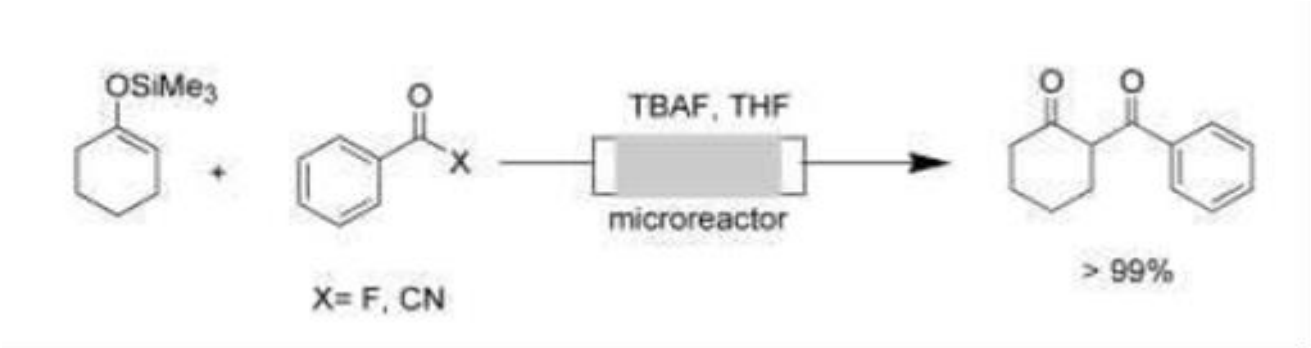

Figure 1 : Micro Flow reaction

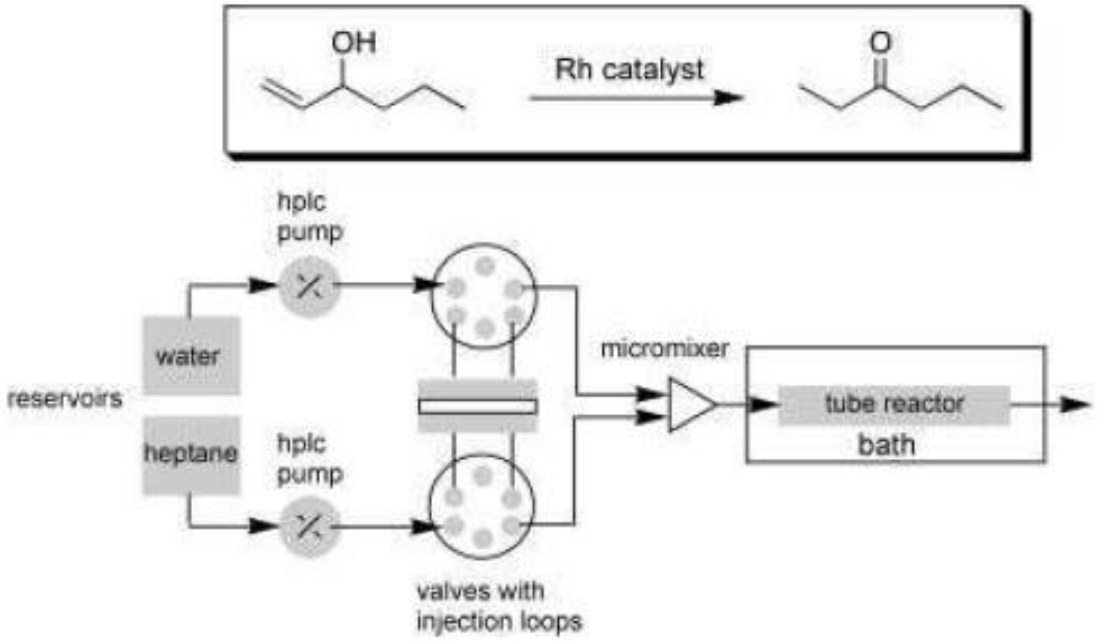

Figure 2 : Meso Flow reaction

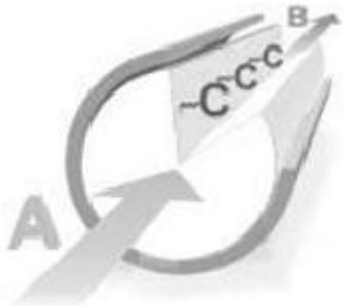

Figure 3 : Flow reaction using tethered Reagent

Flow chemistry has many advantages over conventional batch chemistry. One advantage is that reactions can be run in a temperature that is higher than the boiling point of the solvent that the reaction is in, by pressurizing the vessel that the reaction is flowing through. This can especially be done in micro flow reactions, where the reaction flows through a chip that can easily and safely be pressurized because of its small size and design.5 Another advantage to flow chemistry is that multi-step reactions can be set up in-line and be performed in a continuous sequence, as seen in Figure 4.1 This can be done with all three types of flow chemistry mentioned above, by using a resin tethered catalyst or reagent, by flowing a new reagent further down the line, or even by heating at certain points of the sequence to perform a reaction. This process can be very helpful when the products from one step are very unstable and need to be reacted in the next step immediately.3 Another reaction that can be easily performed with flow chemistry, and can be used in-line in a multi-step reaction, is one that incorporates a gaseous reagent, such as hydrogen which can be bubbled through the flow line to hydrogenate reactants.

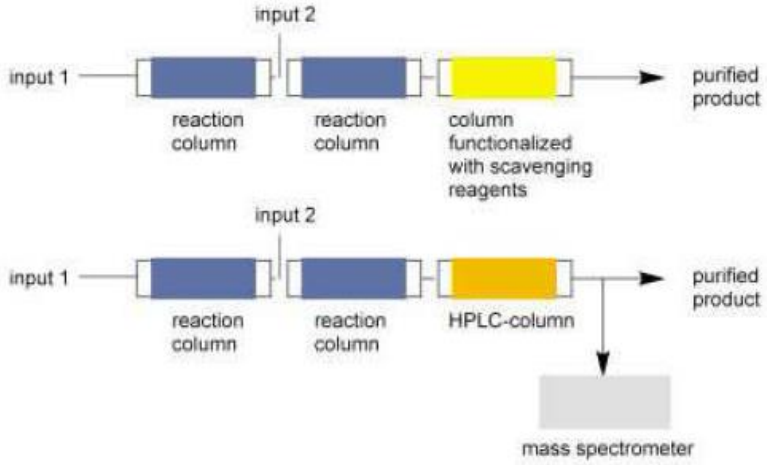

Figure 4. Multi-step reactions using flow methodology

In general, flow chemistry can increase efficiency, reproducibility, and safety. First, the efficiency of a scientist may be increased significantly when using flow chemistry for a number of reasons, the primary being automation. After the preparation of the system, automation can do a majority of the manipulations, while the scientist is freed to do other tasks. Also, if the flow reactions being performed are using a resin tethered reagent or catalyst, the column can often be easily recharged or decoupled. This allows for a quick turnaround time in between each reaction which, in turn, reduces the 16 cycle time of each reaction. In addition, efficiency can be increased because flow chemistry reactions are generally very easily scaled up to make larger batches. Among other ways, this can be achieved by flowing through more reagents or making a larger column with tethered reagents. Second, reproducibility is often increased through the use of flow chemistry because consistent conditions of mixing and heat transfer are applied to the reaction. With automation, reactions can also have improved reproducibility, since all the parameters are set exactly each time the reaction is run, often removing the aspect of human error Lastly, safety of the scientist is greatly increased when using flow chemistry. The pressure in the reactor can be controlled, further reducing the risk of injury due to exploding reaction vessels. In addition, since the reaction is occurring in a relatively small volume, the impact of a dangerous runaway reaction is significantly reduced. In non-automated mode, the use of a calibrated manual injector can improve reproducibility.

Although flow chemistry has many advantages over conventional chemistry, one disadvantage with it is that the method development is quite tedious because of the multitude of variables that must be taken into account. Also, when the chemistry methodology is understood, the instrumentation and method often need to be optimized with each new synthesis. However, once the method and instrumentation are optimized, the efficiencies generated can greatly compensate for the time used for optimization and the method can also be used for various other reactions with little additional modification.

Another disadvantage of flow chemistry is that only homogeneous reactions can be performed. Suspensions cannot be used with this methodology because this solution could easily clog the tubing of the system. Lastly, a significant disadvantage to flow chemistry is the cost of the equipment. Whether a complete instrument is bought or a custom system is built, the cost of all the components is large when compared to standard laboratory glassware (round bottom flasks, etc). This can limit the applications of flow chemistry methodology.

II. OBJECTIVES

The objective of this project is to provide a proof of concept that libraries of pure products can be made in a quick efficient manner. For this proof of concept experiment, libraries of amides were synthesized from amines. The overall goal is to develop an in-line synthesis and screening of compounds to reduce cycle time and to improve the feedback loop. To accomplish this the parameters needed are synthesizing our libraries using a fast reaction with a short retention time so the synthesis should be efficient, producing pure products so that no purification is needed.

All of the libraries will be were synthesized. During method development, these methods will be performed using manual injection, but further optimized using the automation line described above. After each synthesis, the products will be collected in tared vials and evaporated in a Genevac. All the yields reported are based on weight. All solvent evaporation will be was done in a Genevac centrifugal solvent evaporator. 1H NMR spectra will be recorded on a 500 MHz Varian instrument and were presented in ppm downfield relative to trimethylsilane as an internal standard.

REFERENCES

[1] Jas, G.; Kirschning, A. Continuous Flow Techniques in Organic Synthesis Chem. Eur. J. 2003, 9, 5708-5723

[2] Salvino, J.W.; et.al Polymer-Supported Tetrafluorophenol: A New Activated Resin for Chemical Library Synthesis J.Comb.Chem. 2000, 2,691-697

[3] Baxendale, I.R.; Ley, S.V. Solid Supported Reagents in Multi-Step Flow Synthesis New Avenues to Efficient Chemical Synthesis: Emerging Technologies. Ernst Schering Foundation Symposium Proceedings 2006-3, Eds P.H. Seeberger, T. Blume, Springer-Verlag: Berlin, Heidelburg, 2007, Chp 3, pages 151-185

[4] Shi, B.; Scobie, M.; Boyle, R.W. Parallel Synthesis of Un symmetrically Substituted Tetraphenyl Porphyrins on Wang Resin Tetrahedron Lett. 2003, 44, 5083-5086.

[5] Lee, Y.S.; et.al. An Improved Method of 18F Peptide Labeling: Hydrazone Formation with HYNIC-conjugated c(RGDyK) Nucl. Med. Bio. 2006, 33, 677-683.

[6] Poethko, T.; et al. Two-Step Methodology for High-Yield Routine Radiohalogenation of Peptides: 18F-Labeled RGD and Octreotide Analogs. J. Nuc. Med. 2004, 45, 892-902.

[7] Sutcliffe-Goulden, J.L.; O'Doherty, M.J.; Bansal, S.S. Solid Phase Synthesis of [18F] Labeled Peptides for Positron Emission Tomography Biorg. Med. Chem. Lett. 2000, 10, 1501-1503.

[8] Vaidyanathan, G.; Zalutsky, M.R.; Synthesis of N-succinimidyl 4-[18F] fluorobenzoate, an Agent for Labeling Proteins and Peptides with 18F. Nat. Protoc. 2006, 4, 1655-1661.

[9] Miller, P.W.; Long, N.J.; Vilar, R.; Gee, A.D. Synthesis of 11C, 18F, 15O, and 13N Radiolabels for Positron Emission Tomography Angew. Chem. Int. Ed. 2008, 47, 8998-9033.

[10] Stanger, K.H.; Krchnak, V. Incorporation of the Wang Linker upon Cleavage from Polystyrene-based Resin to form O-(4-Hydroxy)benzyl Derivatives J. Comb. Chem. 2006, 8, 652-654.

[11] Arimitsu, K.; Ichimura, K. Nonlinear Organic Reaction of 9-fluorenylmethyl Carbamates as Base Amplifiers to Proliferate Aliphatic Amines and the Application to a Novel

Photopolymer System J. Mater. Chem. 2004, 14, 336-343.

[12] Baumann, M.; Baxendale, I.R.; Martin, L.J.; Ley, S.V. Development of Fluorination Methods using Continuous-Flow Microreactors Tetrahedron 2009, 65, 6611-6625..