FLASH CHEMISTRY: FAST CHEMICAL SYNTHESIS IN FLOW MICROREACTORS

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ABSTRACT

The length of time that the solution remains inside the reactor channels—the residence time—can be greatly reduced by adjusting the length of the channels in flow microreactors. This feature is extremely useful in controlling reactive species. Unstable short-lived reactive species can be generated and transferred to another location to be used in the next reaction before they decompose. Therefore, chemical transformations that are impossible in macro-size reactors such as flasks should be made possible by using flow microreactors. The method serves as a powerful tool for organic synthesis.

KEYWORDS: Flow Microreactor, Organic Synthesis, Reactive Intermediate, Residence Time Control

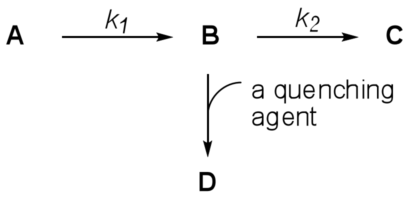
INTRODUCTION

These days downsizing has been occurring in many areas of science and technology including chemistry. The advantage of downsizing is that it provides better efficiencies while also answering society's demands for conservation of resources and energy. Downsizing in the chemistry has been occurring predominantly in the area of analysis, known as micro TAS, or micro total analysis systems, which have enjoyed various applications. Meanwhile, downsizing in the fields of chemical synthesis such as polymer synthesis and organic synthesis has lagged behind. Recently, however, much research is being conducted in this area as well. The micro device used for conducting chemical reactions is called a microreactor. A microreactor is a reactor having channels on the micrometer scale, where a chemical reaction occur. Although the reactor's capacity at any one time is small, total production capacity over time is much greater than may be imagined because microreactors are normally set up as flow-type reactors (flow microreactors) with a continuous flow of solution through the reaction channel. Therefore, microreactors are not necessarily used solely to produce small amounts of chemical substances. In fact, microreactors that can produce several tons – thousands tons of a product per year have been developed in industry.

Characteristic features of flow microreactors can influence the very essence of chemical reactions. Based on such features we have proposed a concept of flash chemistry [1]. Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce desired compounds with high selectivity. Fast heat and mass transfer derived from large surface-to-volume ratios of microreactors enable to conduct extremely fast and exothermic reactions in a controlled way. High surface-to-volume ratios of microreactors also make phase boundary reactions such as gas/liquid, liquid/liquid or solid/liquid reactions more efficient. In this paper we focus on another important features of flow microreactors, residence time control. The length of time that the solution remains inside the reactor channels—the residence time—can be greatly reduced by adjusting the length of the channels and flow rate. This feature of flow microreactors is extremely useful in controlling reactive species. In short, unstable short-lived reactive species can be generated and transferred to another location to be used in the next reaction before they decompose. Therefore, chemical transformations that are impossible in macro-size reactors such as flasks should be made possible by using flow microreactors.

THEORY

How can we control reactions involving unstable short-lived reactive intermediate using the residence time control in a flow microreactor? Let us consider a simple reaction shown Scheme 1. **A** is a reactant, **B** is an unstable intermediate, and **C** is a decomposed product derived from **B**. Intermediate **B** is transformed to a desired product **D** by adding a quenching agent. For simplicity, we assume a sequence of first-order processes (rate constants: k_1 and k_2). We assume that k_2 is much smaller than k_1, because otherwise **B** cannot be accumulated in solution. We also assume that the quenching reaction of **B** is much faster than decomposition of **B** to give **C**.



Scheme 1.

In some cases, the reaction of **A** to give **B** takes place first and goes nearly to completion before the decomposition of **B** to **C** occurs. In such cases we can get **D** in good yield by adding a quenching agent. However, **B** is an unstable short-lived intermediate, and therefore **B** may survive only in a short time, i.e. millisecond or second order. A quenching agent should be added precisely within such a small time domain (after completion of the formation of **B** and before decomposition of **B**) This kind of high-resolution time-domain control cannot be achieved in flask chemistry. Therefore, a flow microreactor system is essential for this purpose.

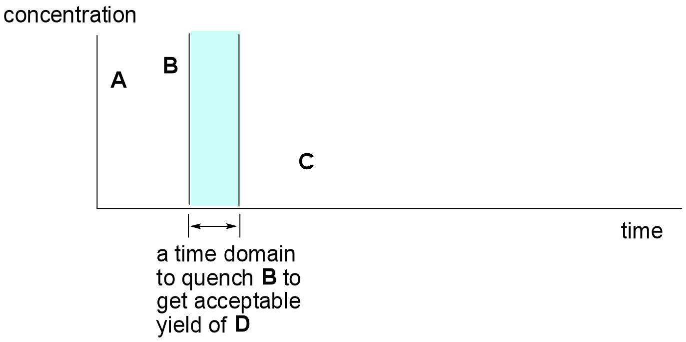


Figure 1: Concentrations of A, B, C as a function of time for the reaction shown in Scheme 1.

EXPERIMENTAL

We usually conduct reactions in a flow microreactor systems consisting of T-shaped micromixers and microtube reactors. The stainless-steel micromixers were specially designed to minimize dead volumes by our group, were manufactured by mechanical fabrication. The diameters of the channels range from 250 – 500 μm. The microtube reactors were also made of stainless steel, and the inner diameter ranges from 250 to 1000 μm. A schematic diagram of a typical system consisting two micromixers and two microtube reactors is shown in Figure 1. Solutions are introduced by syringe pumps. Sometimes plunger pumps are also used. The whole system is dipped in a cooling bath to control the temperature.

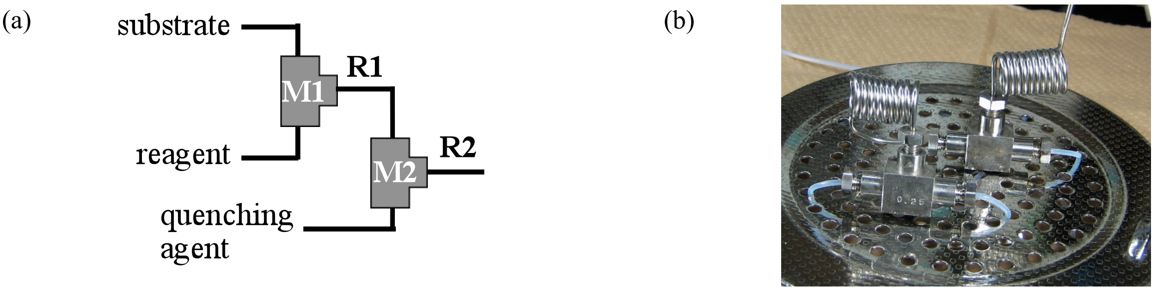
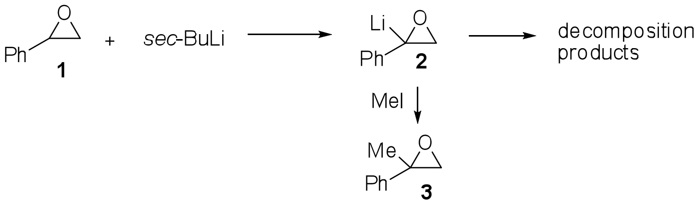


*Figure 2: A schematic diagram (a) and a picture (b) of a typical flow microreactor system consisting of two micromixers (**M1**and **M2**) and two microtube reactors (**R1**and **R2**)*

RESULTS AND DISCUSSION

First, we chose to study reactions of oxiranyllithiums as short-lived reactive intermediates [2]. Generation of oxiranyllithiums by deprotonation of epoxides followed by trapping with an electrophile serves as a powerful method for synthesis of functionalized epoxides, which are versatile intermediates and building blocks in organic synthesis. It is well-known that oxiranyllithiums exhibit carbene-like reactivity and undergo various decomposition reactions. For example, in a macrobatch system, 1,2-epoxyethylphenyllithium is usually generated by deprotonation of styrene oxide with *tert*-BuLi or *sec*-BuLi in the presence of TMEDA at very low temperatures such as -95 °C, which are unusual even in laboratory synthesis. At higher temperatures decomposition takes place to give various byproducts. In fact, deprotonation of syterne oxide with 2.4equiv of *sec*-BuLi in the absence of TMEDA (1 min) followed by reaction with methyl iodide (MeI) at -78 ^{o}C in a macrobatch reactor gave the desired product only in 34% yield (Scheme 2).



Scheme 2.

Thus, a flow microreactor system was used. Mixing of styrene oxide with *sec*-BuLi at **M1** leads to generation of 1,2-epoxyethylphenyllithium in **R1**. In **M2**, 1,2-Epoxyethylphenyllithium was trapped with MeI as a quenching agent to give the product. The reactions were carried with varying the residence time (t^{R}) in **R1** at various temperatures, and the results are summarized in Figure 3.

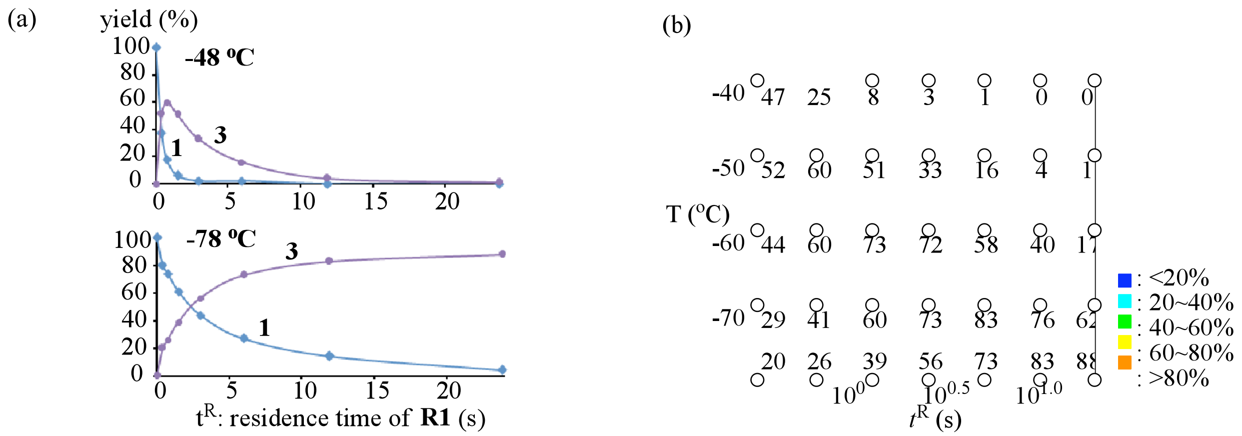
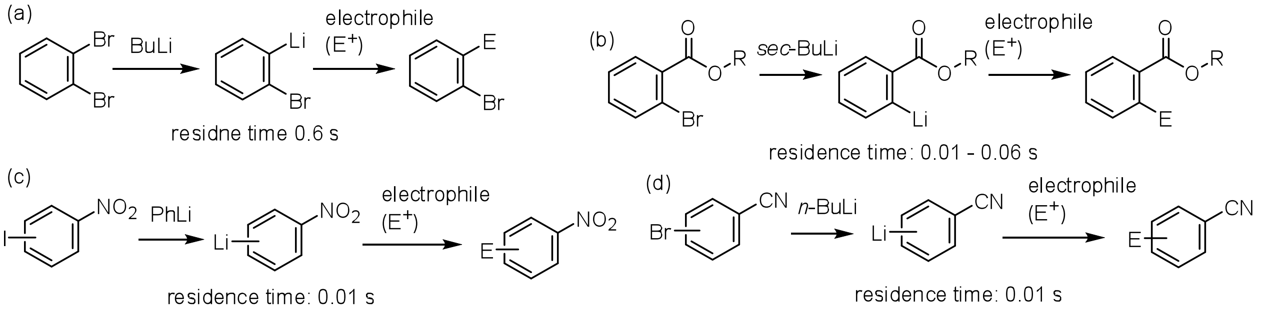


*Figure 3: Effects of the reaction temperature (T) and residence time (t^R) on the yield of **3**. (a) The amount of reaction components as a function of time. (b) Counter plots with scatter overlay of the yields of **3** (%).*

At -48 °C, the amount of **3** increases with t^R very rapidly at the expense of **1**, indicating that deprotonation is very fast. However, in the region of $t^R > 1$ s, **3** was consumed very rapidly. Presumably, the decomposition of **2** takes place very rapidly at this temperature. By lowering the temperature, the decomposition could be slowed down, although the deprotonation was also slowed down. It is interesting to note that at -78 °C the amount of **3** did not decrease appreciably with an increase in the residence time until most of **1** was consumed. This means that **2** can be used for the subsequent reaction before it decomposes within such a range of time (<25 s) at this temperature. On the basis of the information, deprotonation of epoxides followed by trapping with various electrophiles were successfully carried out in a preparative manner without decomposition of the oxyranyllithium intermediates.

Based on the present concept, several reactions that are very difficult in macro-size reactors could be achieved as shown in Scheme 3 [3,4,5,6]. Products were usually obtained in mmol/min scale in laboratory synthesis.



Scheme 3.

CONCLUSION

In conclusion, we could obtain a deeper insight into the chemical stabilities of reactive intermediates using the residence time – temperature analysis using flow microreactor systems. The present method opens a new aspect in mechanistic studies of fast organic reactions involving an unstable intermediate. In addition, the method also serves as a time-efficient way to optimize reaction conditions. Under the optimized conditions, desired compounds are synthesized with high selectivity and good productivity avoiding decomposition of reactive intermediates. Therefore, flash chemistry using flow microreactors adds a new dimension both in mechanistic studies and chemical synthesis.

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