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Editor's Choice

Switching Reaction Pathways of Benzo[*b*]thiophen-3-yllithium and Benzo[*b*]furan-3-yllithium Based on High-resolution Residence-time and Temperature Control in a Flow Microreactor

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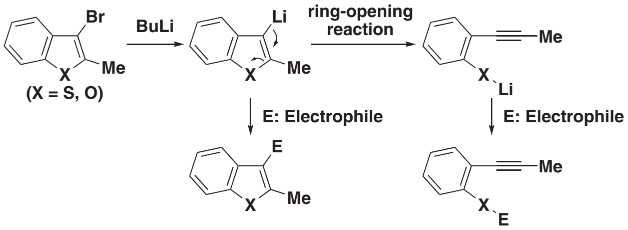
Reaction-pathway control of benzo[*b*]thiophen-3-yllithium and benzo[*b*]furan-3-yllithium was accomplished in flow microreactor systems. We could switch between the reaction with an electrophile before ring-opening and that after ring-opening at will by choosing an appropriate residence-time and temperature.

Chemical synthesis in flow microreactor systems has received significant research interest from both academia and industry.[1,2] Recent investigations revealed significant features of flow microreactor systems including fast mixing stemming from short diffusion path and fast heat transfer by virtue of high surface-to-volume ratio. Such features often enhance the selectivity of chemical reactions. Short residence time in a micro channel is beneficial for controlling highly reactive intermediates. By taking advantage of such features of flow microreactor systems, various chemical reactions for organic synthesis have been developed so far.[3] Flow microreactors are also effective for integration of reactions to enhance the power of organic synthesis.[4]

Recently, we have reported that the generation of highly reactive aryllithium compounds based on halogen–lithium exchange followed by reactions with electrophiles could be conducted in flow microreactor systems.[5] We have also studied generation and reactions of heteroaryllithiums because they serve as important reagents for synthesis of pharmaceuticals and functional materials.[6] During the course of our studies on synthesis of photochromic diarylethenes[7] using flow microreactor systems, we observed that heteroaryllithiums generated by the halogen–lithium exchange reaction of 3-bromo-2-methylbenzothiophene and 3-bromo-2-methylbenzofuran underwent the ring-opening reaction shown in Scheme 1.[8] In connection with our interest in extending the synthetic potential of the flow microreactor method, we studied this in detail, and herein we report that the reaction pathways can be switched at will based on residence-time and temperature control in a flow microreactor.

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) shown in Figure 1 was used for halogen–lithium exchange reaction of 3-bromo-2-methylbenzothiophene followed by the reaction of an electrophile. To get deeper insight into the conditions that control the reaction pathways, the reactions were carried out with varying residence time (t^R) in **R1**, and temperature (T).

The results obtained with 3-bromo-2-methylbenzothiophene and iodomethane are summarized in Figure 2 (See the Supporting Information for details[9]). In Figure 2a, the conversion of the starting material is plotted against the temperature (T) and the residence time in **R1** (t^R) as a contour map with scattered overlay. In the low temperature ($T < 0\,°C$)–short residence time ($t^R < 0.1$ s) region, the starting material remained unchanged to some extent because halogen–lithium exchange is rather slow at low temperatures. In Figure 2b, the yields of the methylated product, 2,3-dimethylbenzothiophene are plotted against T and t^R. High yields were obtained with longer residence times at low temperatures (such as $t^R > 1.0$ s, $T < -28\,°C$). The increase in T caused the decrease in the yield presumably because the ring-opening reaction of benzo[*b*]thiophen-3-yllithium intermediate took place. In fact, at higher temperatures ($T > 0\,°C$), the product derived from the ring opening, 1-methylsulfanyl-2-(prop-1-ynyl)benzene was obtained in good yields (Figure 2c). Therefore, we can control the reaction pathways by choosing an appropriate temperature–residence time. For example, 2,3-dimethylbenzothiophene, the product derived from the benzo[*b*]thiophen-3-yllithium without ring opening was obtained in 86% yield at $t^R = 1.6$ s and $T = -48\,°C$, while 1-methylsulfanyl-2-(prop-1-ynyl)benzene, the product derived from ring opening was obtained in 78% yield at $t^R = 3.1$ s and $T = 24\,°C$.



Scheme 1. Control of ring-opening reaction of benzo[*b*]thiophen-3-yllithium and benzo[*b*]furan-3-yllithium.

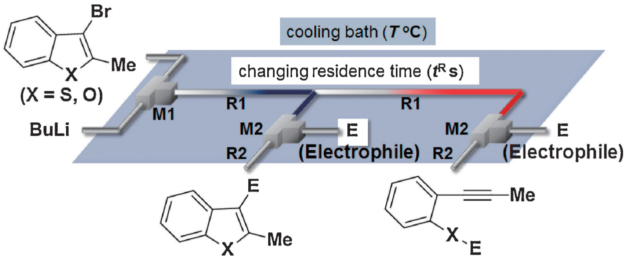


Figure 1. A flow microreactor system for the halogen–lithium exchange reaction of 3-bromo-2-methylbenzothiophene or 3-bromo-2-methylbenzofuran with *n*-BuLi followed by reaction with iodomethane (X = S) or methanol (X = O). T-shaped micromixers: **M1** and **M2**, microtube reactors: **R1** and **R2**.

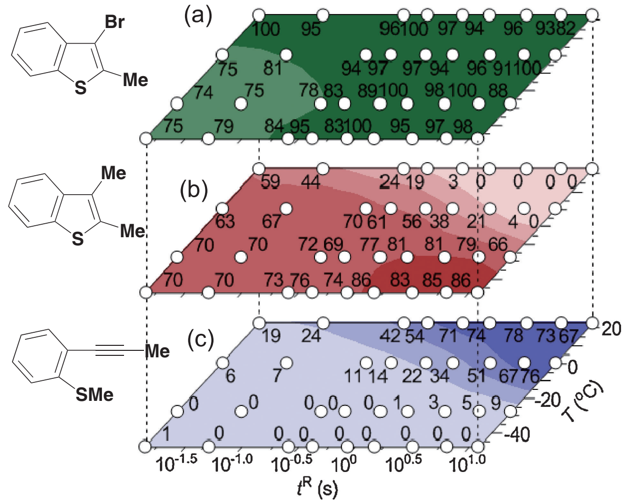


Figure 2. Temperature–residence time (in **R1**) map for the halogen–lithium exchange reaction of 3-bromo-2-methylbenzothiophene with *n*-BuLi followed by the reaction with iodomethane: (a) Contour plot with scatter overlay of the conversion of 3-bromo-2-methylbenzothiophene, (b) contour plot with scatter overlay of the yield of 2,3-dimethylbenzothiophene, and (c) contour plot with scatter overlay of the yield of 1-methylsulfanyl-2-(prop-1-ynyl)benzene.

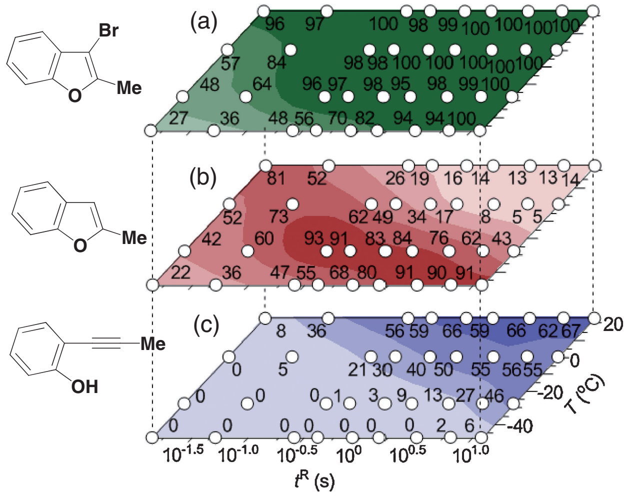


Figure 3. Temperature–residence time (in **R1**) map for the halogen–lithium exchange reaction of 3-bromo-2-methylbenzofuran with *n*-BuLi followed by reaction with methanol: (a) Contour plot with scatter overlay of the conversion of 3-bromo-2-methylbenzofuran, (b) contour plot with scatter overlay of the yield of 2-methylbenzofuran, and (c) contour plot with scatter overlay of the yield of 2-(prop-1-ynyl)phenol.

Next, the halogen–lithium exchange reaction of 3-bromo-2-methylbenzofuran followed by reaction with methanol was examined using the flow microreactor system. As shown in Figure 3a, the conversion of the starting material indicates that halogen–lithium exchange of 3-bromo-2-methylbenzofuran is slower than that for 3-bromo-2-methylbenzothiophene (Figure 2a), although quantitative conversions were obtained at high temperature–long residence times. The high yield region for 2-methylbenzofuran, the product derived from benzo[*b*]furan-3-yllithium without ring opening (Figure 3b) is slightly smaller than that for 2,3-dimethylbenzothiophene (Figure 2b), implying that benzo[*b*]furan-3-yllithium intermediate is slightly less stable than benzo[*b*]thiophen-3-yllithium. At high temperature–long residence times, 2-(prop-1-ynyl)phenol, the product derived from the ring-opening of benzo[*b*]furan-3-yllithium was obtained in good yields (Figure 3c).

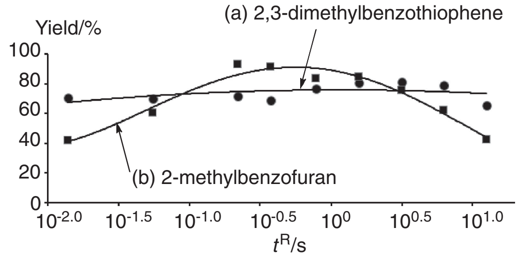


Figure 4. Plots of the yields of the products obtained without ring opening of the heteroaryllithium intermediates against the residence time (t^R) at −28 °C in the flow microreactor system: (a) 2,3-dimethylbenzothiophene and (b) 2-methylbenzofuran.

Figure 4 clearly demonstrates the difference in the reactivity between benzo[*b*]thiophen-3-yllithium and benzo[*b*]furan-3-yllithium; the former is produced within 0.01 s while the latter is produced more slowly because the halogen–lithium exchange is slower, but the latter isomerizes more rapidly through the ring opening. The reason for the difference in reactivity is not clear at present.

In conclusion, we have demonstrated that the precise control of the residence time and the temperature in a flow microreactor system enables the switch of the pathway of the reactions involving heteroaryllithiums. It is also important to note that the residence time–temperature maps serve as powerful tools for analyzing behavior of reactive intermediates. Further work is in progress to explore the full range of reactivity of heteroaryllithium species and to develop synthetic applications of such useful intermediates.

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