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Harnessing [1,4]-, [1,5]-, and [1,6]-Anionic Fries-type Rearrangements by Reaction Time Control in Flow

*Heejin Kim, Keita Inoue, and Jun-ichi Yoshida**

Abstract: A series of anionic Fries-type rearrangements of carbamoyl-substituted aryllithiums can be controlled by using flow microreactor systems. For [1,4]- and [1,5]-rearrangements, either the carbamoyl-maintained or migrated aryllithium intermediates can be subjected to the subsequent reactions with electrophiles at will based on precise residence time and the temperature (-25 °C to -50 °C) control. In contrast, the [1,6]-rearrangement is rather slow even at -25 °C. The absence of cross-over products indicates the intramolecular nature of the carbamoyl group migration.

Controllability of extremely fast reactions is one of the most powerful advantages of flow chemistry using microreactors.[1-3] By using flow microreactors, we can accomplish a desired reaction before an undesired fast reaction proceeds. Based on the concept of flash chemistry,[4] various synthetic transformations involving short-lived intermediates have been developed using flow microreactors.[5] In flash chemistry the reaction time can be precisely adjusted even to milliseconds or less, allowing switching of reactions from go to stop, or vice versa, at will according to the synthetic plan.

Rearrangement reactions serve as important methods for constructing organic molecules because they change molecular skeletons dramatically, and many of them take place intramolecularly. Because such intramolecular reactions proceed at a rate irrespective of the mixing speed or the concentration of reaction components, the control of intramolecular reactions still remains challenging.

Anionic Fries rearrangement[6] is well-known as an intramolecular [1,3]-rearrangement and comprise the migration of a carbamoyl group from an oxygen atom to a carbanion (typically an organolithium) carbon atom to generate an oxyanion (a lithium alkoxide) (Figure 1a). The reaction proceeds by a 4-exo-trig type intramolecular cyclization. Based on the concept of flash chemistry, we recently reported that the fast 1,3-migration of acyl group as well as carbamoyl group in Fries rearrangement can be effectively controlled by using microfluidic devices.[7] The intramolecular [1,4]- and [1,5]-rearrangements, however, are typically much faster than [1,3]-rearrangement, because 5- and 6-exo-trig type cyclization is usually faster than 4-exo-trig cyclization. (Figure 1).[8] It is also interesting to know how fast the corresponding 7-exo-trig type cyclization takes place ([1,6]-rearrangement). We report herein that [1,4]-, [1,5], and [1,6]-anionic Fries-type rearrangements can be harnessed based on precise reaction time control using flow microreactors.

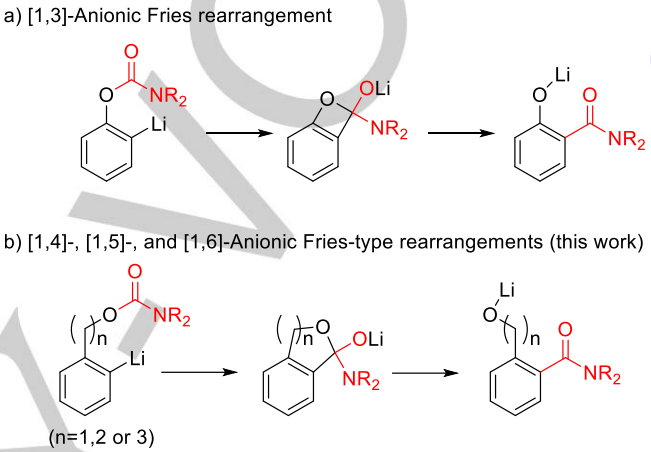

Figure 1. Anionic Fries-type rearrangements.

First, we examined the reactions in a batch reactor at -78 °C, and the results are summarized in Table 1. The iodobenzenes bearing a carbamate group **1a**-**1d** (n=0-3) were prepared as starting materials. The reaction of **1a** (n=0), which is a substrate for normal Fries rearrangement, with *n*-BuLi at -78 °C followed by the reaction with ethyl chloroformate after 10 min exclusively gave product **3a** (81% yield) via carbamoyl-remained intermediate **2a** (entry 1, Table 1). Compound **5a**, which is derived from carbamoyl-migrated intermediate **4a** was not detected. The result indicates that normal anionic Fries rearrangement is not too fast at -78 °C to trap carbanion intermediate **2a** (n=0) by the subsequent bimolecular reaction. In contrast, the reaction of substrate **1b** gave no **3b,** which is derived from carbamoyl-maintained intermediate **2b** under the same conditions. Instead, **5b** derived from carbamoyl-migrated intermediate **4b** was obtained selectively (entry 2, Table 1). With a shorter reaction time (1 min), a small amount of **3b** (7%) was obtained but the major product was **5b** (87%, entry 3, Table 1). Similarly, the reaction of **1c** also gave **5c** derived from carbamoyl-migrated intermediate **4c** as a major product with a small amount of **3c** (entries 4 and 5, Table 1). These results indicate that the [1,4]- and [1,5]-rearrangements of **2b** and **2c**, respectively, are much faster than [1,3]-rearrangement of **2a**. This is consistent with a general tendency that five- and six-membered ring cyclization reactions are faster than four-membered ring cyclization reactions. The corresponding seven-membered ring cyclization is slower. The reaction of compound **1d** gave **3d** (82%)**,** which is derived from carbamoyl-maintained intermediate **2d** with a small amount of **5d** (8%), which is derived from carbamoyl-migrated

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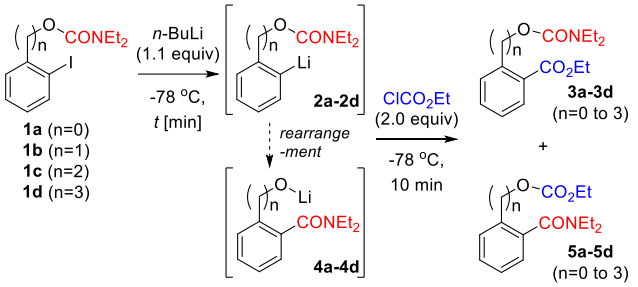
intermediate **4d** (entry 6, Table 1). The rearrangement of **2d** seems to be slightly faster than that of **2a**, but much slower than those of **2b** and **2c**.

Table 1: Anionic Fries-type rearrangements using a batch reactor at -78 °C.



Entry	Substrate	Rearrangement type	*t* [min]	Yield of **3** [%][a]	Yield of **5** [%][a]
1	**1a**	[1,3]	10	**81**	0
2	**1b**	[1,4]	10	0	**97**
3			1	7	**87**
4	**1c**	[1,5]	10	3	**92**
5			1	5	**89**
6	**1d**	[1,6]	10	**82**	8

[a] ^{1}H NMR yield.

Next, we examined the reactions of **1b**, **1c**, and **1d** as well as **1a** using a flow microreactor system consisting of two micromixers (inner diameter: 250 μm for M1 and 500 μm for M2) and two microtube reactors (R1 and R2, Figure 2a). The reactions with *n*-BuLi were carried out at higher temperatures (*T* °C) than that for the batch reaction with varying the residence time. Ethyl chloroformate was added at the same temperature. Then, the temperature was raised to 25 °C to ensure the full conversion (for details, see the Supporting Information). The results were summarized in Figure 2b-2e.

The rearrangement of **2b** (n=1) to give **4b** was complete within 110 ms at -25 °C (Figure 2b). The product **5b** derived from **4b** was obtained exclusively with the residence time longer than 110 ms at this temperature. At lower temperatures such as -30, -40 and -50 °C, the rearrangement is slower. The product **3b** derived from **2b** was obtained exclusively with the residence time of 14 ms at -50 °C. The rearrangement of **2c** (n=2) to give **4c** is slightly faster (Figure 2c), indicating that [1,5]-rearrangement is slightly faster than [1,4]-rearrangement. The rearrangement of **2d** (n=3) is much slower than those of **2b** and **2c** (Figure 2d), indicating that the [1,6]-rearrangement is much slower than [1,4] and [1,5]-rearrangements. However, at 25 °C [1,6]-rearrangement is complete within 220 ms (For details, see the Supporting Information). Also, the rearrangement of **2a** (n=0) is somewhat slower than that of **2d** (Figure 2e).

Therefore, the rate of the rearrangement increases in the order [1,3] < [1,6] ≪ [1,4] ≤ [1,5].

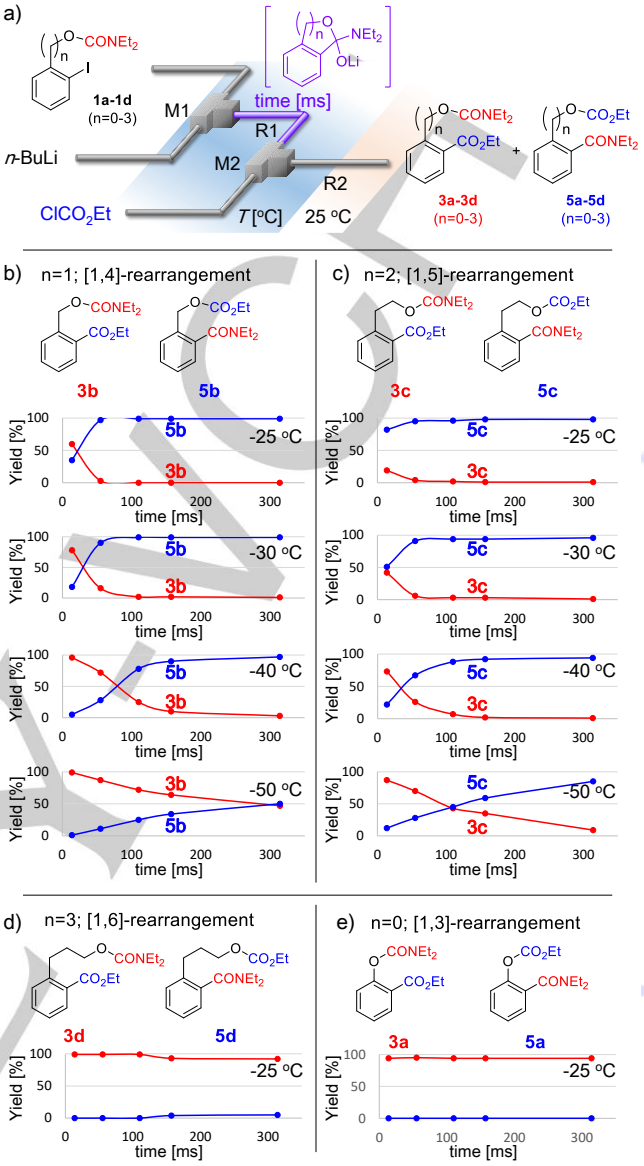


Figure 2. Anionic Fries-type rearrangements using a flow microreactor system. a) A flow microreactor system consisting of two micromixers (M1 and M2) and two microreactors (R1 and R2). b-d) Plots of the yield of **3** derived from the carbamoyl-maintained intermediate and that of **5** derived from the carbamoyl-migrated intermediate against the residence time in R1.

Both the unrearranged intermediates (**2b**, **2c**, and **2d**) and the rearranged intermediates (**4b**, **4c**, and **4d**) could be successfully trapped with various electrophiles at will by optimizing the residence time and temperature, and the desired products were obtained in high selectivity. The results are summarized in Table 2 (For details, see the Supporting Information).

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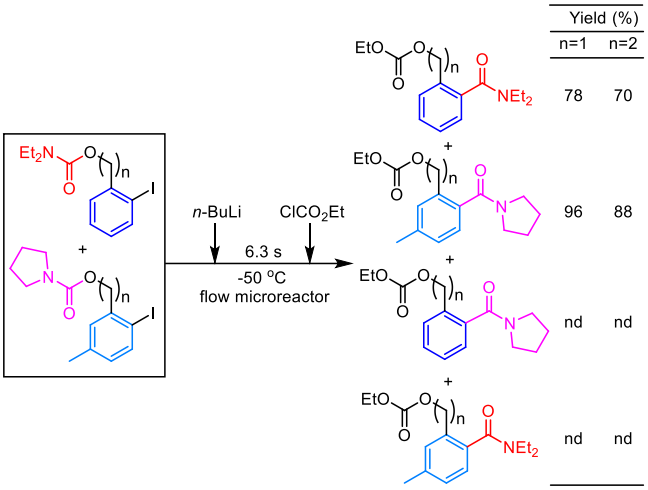
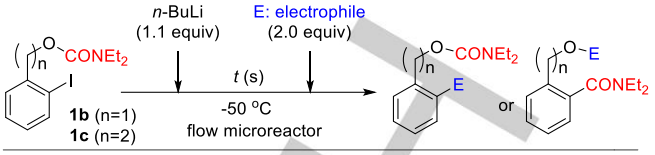


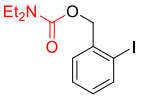
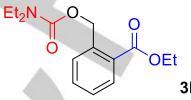
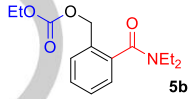
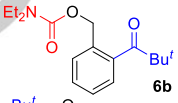
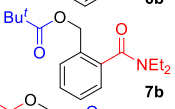
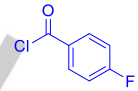
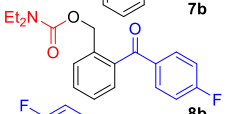
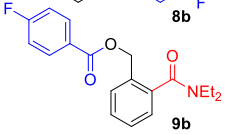
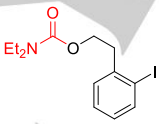
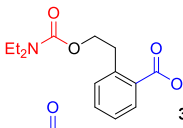
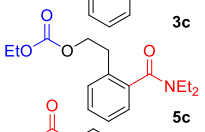
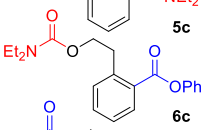
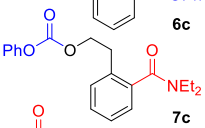
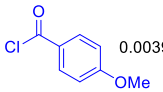
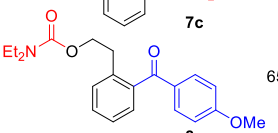
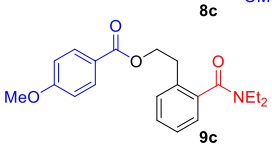
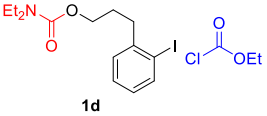
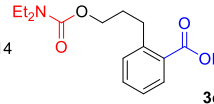
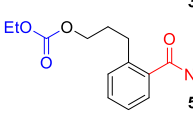
Figure 3. Crossover experiments of [1,4]- and [1,5]-anionic Fries-type rearrangements.

It is important to know whether the rearrangement takes place intramolecularly or intermolecularly. To answer to this question, the crossover experiments were carried out using the flow microreactor system, wherein an equimolar mixture of two substrates was reacted with BuLi followed by the reaction with ethyl chloroformate. As shown in Figure 3, any possible crossover products were not observed, indicating that carbamate-migration occurs truly intramolecularly.

The present systematic studies on [1,3]-, [1,4]-, [1,5]-, and [1,6]-anionic Fries-type rearrangements using the flow microreactor system revealed that the rerrangement rate increases in the order [1,3] < [1,6] ≪ [1,4] ≤ [1,5]. Also, the product derived from unrearranged intermediates could be obtained selectively at will even for extremely fast [1,4]- and [1,5]-cases, indicating the power of the flash method using flow microreactor systems. Further work aimed at exploration and control of various type of fast rearrangements using flow microreactors is currently in progress in our laboratory.

Table 2: The control of [1,4]-, [1,5]-, and [1,6]-anionic Fries-type rearrangements using various electrophiles



Substrate	Electrophile	*t* (s)	Product	Yield (%)[a]
 **1b**		0.014	 **3b**	89
		1.0	 **5b**	90
		0.014	 **6b**	79
		1.0	 **7b**	74
		0.014	 **8b**	84
		1.0	 **9b**	82
 **1c**		0.0039	 **3c**	89
		6.3	 **5c**	90
		0.0039	 **6c**	78
		6.3	 **7c**	74
		0.0039	 **8c**	65
		6.3	 **9c**	76
 **1d**		0.014	 **3d**	95[b]
		0.22	 **5d**	99[b,c]

[a] Yield of isolated product. [b] ^{1}H NMR yield. [c] The reaction was carried out at 25 °C.

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Experimental Section

General method. A flow microreactor system consisting of two micromixers (M1 and M2) and two microtube reactors (R1 and R2) was used. The reaction system was immersed in a cooling bath (*T* °C). A solution of substrate **1** (0.1 M in THF, 6 mL/min) and a solution of *n*-BuLi (0.42 M in hexane, 1.5 mL/min) were introduced to M1 (inner diameter Φ=250 μm) by syringe pumps. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.22 M in THF, 3.0 mL/min) in M2 (Φ=500 μm). The resulting solution was passed through R2 (Φ=1000 μm, length=450 cm; 50 cm at *T* °C and 400 cm at 25 °C). After a steady state was reached, the product solution was collected for 30 s, while being quenched with saturated NH_4Cl aqueous solution. The crude product was extracted with diethyl ether (15 mL x 3) washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography.

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Keywords: Intramolecular rearrangement • flow chemistry • microreactor • Fries rearrangement • reactive intermediates

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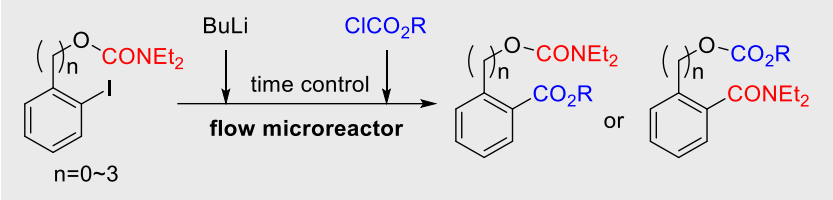

A series of anionic Fries-type rearrangements of carbamoyl-substituted aryllithiums can be controlled by using flow microreactor systems. For [1,4]- and [1,5]-rearrangements, either the carbamoyl-maintained or migrated aryllithium intermediates can be subjected to the subsequent reactions with electrophiles at will based on precise residence time and the temperature control.

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Harnessing [1,4]-, [1,5]-, and [1,6]-Anionic Fries-type Rearrangements by Reaction Time Control in Flow