Microreactors

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Generation and Reaction of Carbamoyl Anions in Flow: Applications in the Three-Component Synthesis of Functionalized α-Ketoamides

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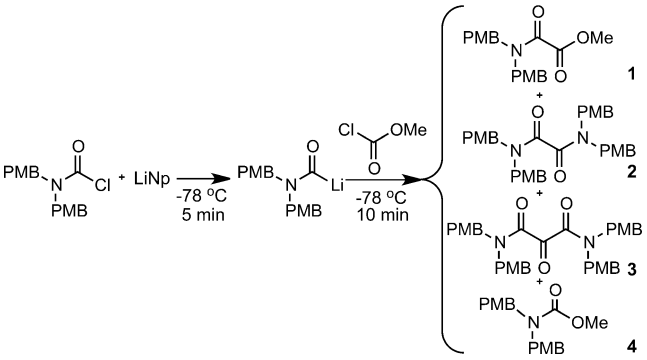
Abstract: *Using a flow microreactor system, carbamoyllithium compounds were successfully generated and used for reactions with electrophiles to give various amides, including α-ketoamides. The present method could be applied to the three-component synthesis of functionalized α-ketoamides using a carbamoyllithium compound, methyl chloroformate, and a functionalized organolithium reagent.*

Carbonyl groups are key functionalities in organic chemistry and the use of carbonyl anions, in principle, can serve as one of the most straightforward methods for constructing carbonyl compounds.[1] However, carbonyl anions are too unstable to be used in organic synthesis, and therefore carbanions with masked or protected carbonyl groups are often used as carbonyl anion equivalents in organic synthesis. However, such an approach suffers from problems of atom economy[2] and step economy[3] because of the need to use deprotection steps. To avoid such problems, the direct use of carbonyl anions is highly desirable in organic synthesis. We previously proposed a protecting-group-free synthetic method[4] using flow microreactors,[5–7] in which highly unstable reactive intermediates are generated and used before they decompose by taking advantage of extremely short residence times.[8] We envisaged that flow microreactors enable the use of carbonyl anions.

In this study we focused on the use of carbamoyl anions as carbonyl anions because they are useful for making amide structures which are often present in naturally occurring and/or biologically active compounds. A carbamoyl anion or a carbamoyllithium species was first generated from bis(diethylcarbamoyl)mercury by Schöllkopf and Gerhart in 1967.[9] Lithium–tellurium exchange,[10] lithium–hydrogen exchange, or deprotonation of formamides with lithium diisopropylamide (LDA),[11] and reductive lithiation[12] can also be used for generating carbamoyllithium. Although carbamoyllithium compounds are among the most stable of the carbonyllithium derivatives, even those bearing bulky isopropyl groups on the nitrogen center should generated and used quickly for reactions with electrophiles at very low temperatures. Moreover, in most cases carbamoyllithium species need to be generated in the presence of electrophiles because of their instability. Such requirements, however, limit the scope of potential electrophiles and therefore significantly decreases the usefulness of carbamoyllithium compounds. In this work, we show that flash chemistry[13] using flow microreactors solves the problem.

First, we chose to study the reductive lithiation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride with lithium naphthalenide (LiNp) to generate the carbamoyllithium followed by trapping with methyl chloroformate. The conventional batch method suffers from low yields of desired product **1**, as shown in Table 1. Wurtz-type coupling gave **2** and the consecutive reaction of **1** with the carbamoyllithium gave 1,2,3-tricarbonyl compound **3**. Release of carbon monoxide from the carbamoyllithium gave methyl carbamate **4**. The reverse addition improved the yield of **1**, but the yield was still unsatisfactory.

Table 1: Generation of carbamoyllithium species followed by reaction with methyl chloroformate under batch conditions.



Addition method	Conv. [%][a]	Yield [%]			
		1[b]	**2**[a]	**3**[a]	**4**[b]
LiNp added to carbamoyl chloride	100	9	44	n.d.	9
carbamoyl chloride added to LiNp	100	44	2	18	14

[a] Determined by HPLC analysis. [b] Determined by GC analysis. n.d. = not detected. PMB = *p*-methoxybenzyl.

Thus, a flow microreactor system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 (inner diameter $\varphi = 1000$ μm, length = 100 cm) and R2 ($\varphi = 1000$ μm, length = 100 cm) was used for the generation and trapping of the carbamoyllithium species (Figure 1).

As shown in Table 2, the product selectivity strongly depends on the total flow rate. The yield of **1** was low at a low flow rate (run 1), but at higher flow rates, satisfactory yields were obtained (runs 2–5). Because the mixing speed generally

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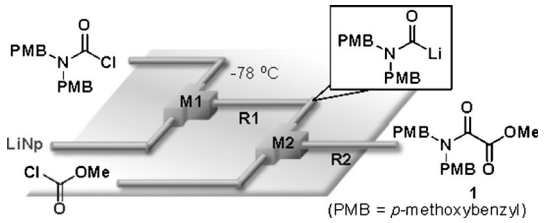


Figure 1. A flow microreactor system for the generation of carbamoyllithium species followed by reaction with methyl chloroformate.

Table 2: Generation of the carbamoyllithium species followed by reaction with methyl chloroformate using flow microreactors.

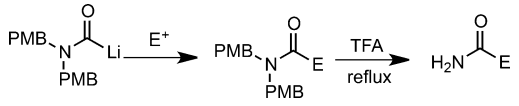
Run	Internal Diameter [μm]		Total Flow Rate [mL min^{-1}]		Conv. [%][a]	Yield [%]			
	M1	M2	M1	M2		**1**[b]	**2**[a]	**3**[a]	**4**[b]
1	250	250	6	9	73	24	18	4	9
2	250	250	12	18	100	72	2	14	3
3	250	250	15	22.5	100	76	1	14	4
4	250	250	18	27	100	83	1	13	2
5	250	250	21	31.5	100	81	1	14	2
6	500	250	12	18	94	58	4	9	7
7	1000	250	12	18	94	57	5	8	7
8	250	500	12	18	100	62	1	23	5
9	250	1000	12	18	100	64	1	24	6
10	1000	1000	12	18	98	48	3	18	10

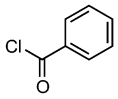
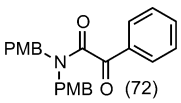
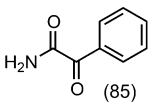
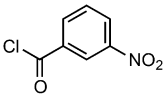
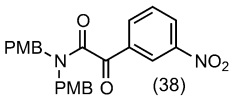
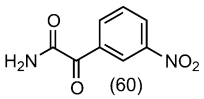
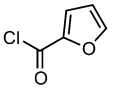
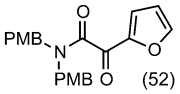
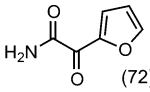
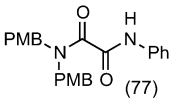
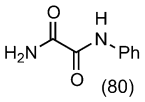
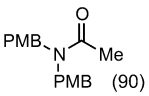
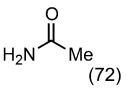
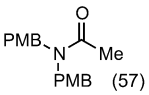
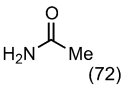
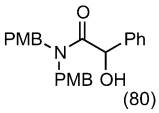
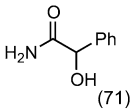
[a] Determined by HPLC analysis. [b] Determined by GC analysis.

depends on the flow rate, the results indicate that the good selectivity detected at high flow rates is ascribed to high mixing speeds. Although the reaction time also changes with the flow rate, it was confirmed that the carbamoyllithium did not decompose appreciably within this timeframe at −78 °C (see Table S1 in the Supporting Information). The mixing speed also depends on the internal diameter of the micromixers. The increase in the internal diameter of micromixer M1 causes a decrease in the yield of **1** (runs 2, 6, and 7). The increase in the internal diameter of M2 also caused a decrease in the yield of **1** (runs 2, 8, and 9). Therefore, it is reasonable to conclude that extremely fast micromixing is responsible for the selective formation of **1**.

Under the optimized conditions (Table 2, run 4; inner diameter of M1 = 250 μm, inner diameter of M2 = 250 μm, total flow rate at M1 = 18.0 mL min^{-1}, total flow rate at M2 = 27.0 mL min^{-1}), we next examined reactions with various electrophiles. The reaction with benzoyl chloride was successfully carried out to obtain the corresponding α-ketoamides in good yields (Table 3). The use of benzoyl chloride functionalized with a nitro group led to very low yields of the desired product, presumably because of the reaction of the carbamoyllithium with the nitro group. The reactions with other electrophiles, such as 2-furoyl chloride, phenylisocyanate, methyl trifluoromethanesulfonate, and benzaldehyde also took place to give the corresponding products in good yields. Notably, the *p*-methoyxbenzyl (PMB) protecting groups could be successfully removed by treatment with trifluoroacetic acid to obtain the products with two hydrogen atoms on the nitrogen center in good yields.[10]

Table 3: Generation of bis(*p*-methoxybenzyl)carbamoyllithium followed by reactions with various electrophiles and subsequent deprotection with trifluoroacetic acid (TFA) in a flow microreactor system.



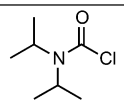
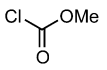
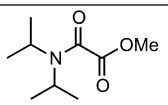
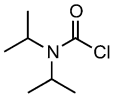
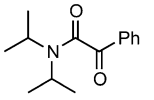
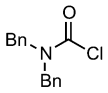
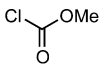
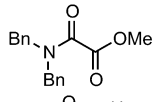
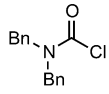
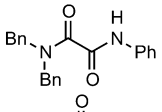
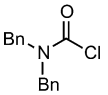
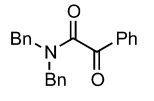
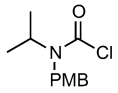
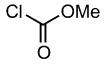
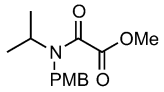
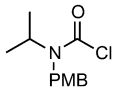
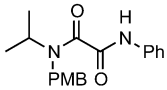
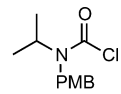
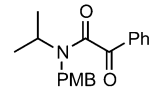
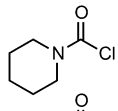
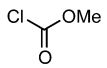
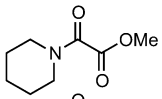
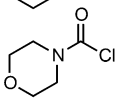
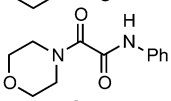
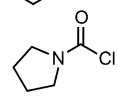
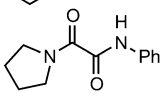
Electrophile (E)	Product (Yield [%])[a]	Deprotected Product (Yield [%])[a]
	 (72)	 (85)
	 (38)	 (60)
	 (52)	 (72)
PhNCO	 (77)	 (80)
MeOTf	 (90)	 (72)
MeI[b]	 (57)	 (72)
PhCHO	 (80)	 (71)

[a] Yield of isolated product. [b] MeI (20 equiv) were used. PMB = *p*-methoxybenzyl.

Next, the generation and subsequent reactions of various carbamoyllithium derivatives were examined, with the corresponding products being obtained in good yields (Table 4). Ketoamides occur in various natural products as well as in drug candidates.[14] They are also very useful precursors for various functional-group transformations.[15] Consequently, to date a number of methods for the synthesis of α-ketoamides have been developed: the amidation of α-ketoacids and α-keto acyl halides, [16] the oxidation of α-hydroxyamides and α-aminoamides,[17] transition-metal-catalyzed double carbonylative amination of aryl halides,[18] and others.[19] However, the reaction of carbamoyllithium compounds with acid halides is one of the most straightforward and useful methods for synthesizing α-ketoamides. However, the method suffers from problems of compatibility of the functional groups in acid halides.

For example, reaction of the carbamoyllithium with *m*-nitrobenzoyl chloride gave the desired product only in a low yield as shown in Table 3, presumably because of nucleophilic attack on the nitro group.[20] Thus, we envisioned that a three-component synthesis involving the reaction of the carbamoyllithium species with methyl chloroformate followed by

Table 4: Generation of various carbamoyllithium species followed by reaction with electrophiles in a flow microreactor.

Carbamoyl species	Electrophile	Product	Yield [%][a]
			78
			74
			66
	PhNCO		71
			54
			72
	PhNCO		85
			73
			65
	PhNCO		47
	PhNCO		54

[a] Yield of isolated product.

reaction with functionalized organolithium reagents would solve the problem (Figure 2).

For the three-component synthesis, the set-up for the integrated flow microreactor system shown in Figure 3 was employed. A carbamoyllithium derivative was generated by reductive lithiation in M1/R1. Trapping of the carbamoyllithium with methyl chloroformate in M2/R2 gave the

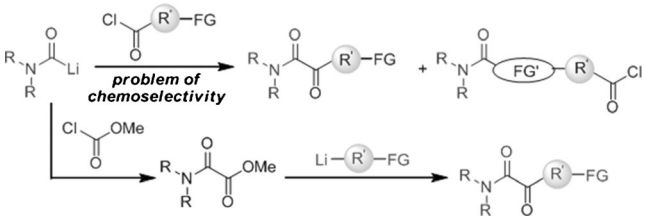


Figure 2. Synthesis of functionalized α-ketoamides through carbamoyllithium species. FG = functional group.

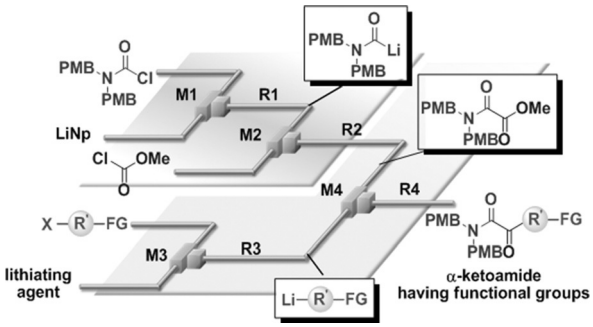
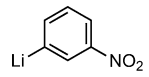
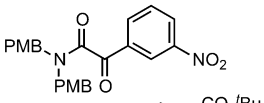
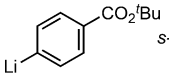
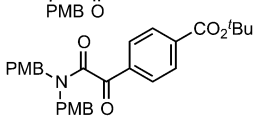
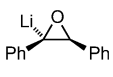
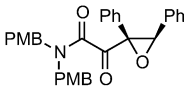
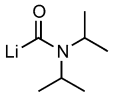
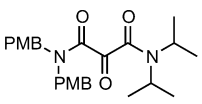


Figure 3. The integrated flow microreactor system used for the three-component coupling of carbamoyllithium species, methyl chloroformate, and functionalized organolithium reagents. M1, M2, M3, and M4 are T-shaped micromixers, R1, R2, R3, and R4 are microtube reactors.

corresponding α-amide ester. A functionalized organolithium was generated in M3/R3 and was allowed to react with the α-amide ester in M4/R4. We have already reported that functionalized organolithium derivatives can be generated and used in flow microreactors by ensuring short residence times.[21] As shown in Table 5, the reactions were successfully

Table 5: Three-component coupling using functionalized organolithium compounds.

Functionalized Organolithium	Lithiating Agent	Residence Time in R3 [s]	Product	Yield [%][a]
	PhLi	6.4		63
	*s*-BuLi	5.4		70
	*s*-BuLi	5.4		61
	LiNp	2.7		51

[a] Yield of isolated product.

achieved to obtain the corresponding three-component coupling products, α-ketoamides, in good yields. It should be noted that the batch method cannot be applied to this transformation because functionalized organolithium derivatives decompose very quickly. Extremely short residence times and effective heat transfer are key for the successful synthesis of functionalized α-ketoamide molecules.

The following formal total synthesis of a 5-amino-1,2,4-triazine derivative, GW356194, a potential sodium channel blocker for the treatment of disorders of the central nervous system, demonstrates the power and usefulness of the present method. Generation of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyllithium followed by reaction with methyl chloroformate and subsequent reaction with (2,3,5-trichlorophenyl)lithium afforded **5** in 55% yield (Figure 4). Deprotection with

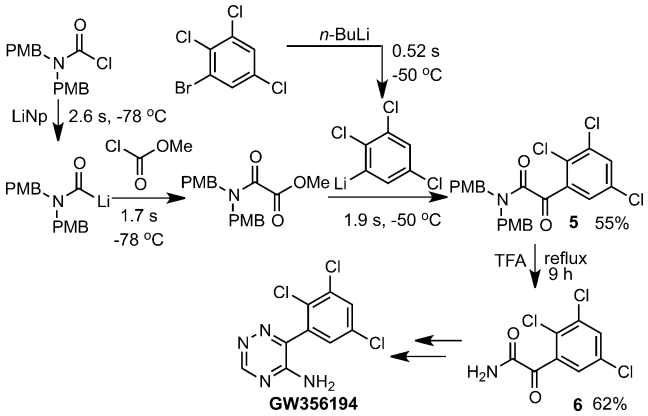


Figure 4. Formal synthesis of GW356194.

trifluoroacetic acid gave **6** in 62% yield, which can be converted into 5-amino-1,2,4-triazine derivative GW356194 according to a literature procedure.[22]

In conclusion, we have developed a flash method for harnessing unstable carbamoyl anions, that is, carbamoyllithium, using a flow microreactor system. The extremely fast mixing in the system renders the method successful. The method can be applied to the synthesis of various amides, including α-ketoamides. Functionalized α-ketoamides can be efficiently synthesized by the three-component reaction of a carbamoyllithium, methyl chloroformate, and a functionalized organolithium reagent. Such transformations are practically impossible when the conventional batch method is used. The power of the method was demonstrated by the straightforward synthesis of GW356194, a potential sodium channel blocker. Further work is in progress to explore the full scope of this useful transformation and its applications in organic synthesis.

Experimental Section

Typical procedure for the generation of carbamoyllithium compounds followed by reaction with electrophiles using a flow microreactor system: A flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2), and three tube pre-cooling units (P1, P2, and P3; inner diameter $\varphi =$ 1000 μm, length $l = 300$ cm) was used. A solution of a carbamoyl chloride (0.10 M in THF; flow rate = 9.0 mL min^{-1}) and a solution of lithium naphthalenide (0.22 M in THF; flow rate = 9.0 mL min^{-1}) were introduced into M1 by using a plunger pump and a microfeeder pump, respectively, and the mixture was passed through R1 ($\varphi = 1000$ μm, $l = 100$ cm). The resulting solution was mixed with an electrophile (0.30 M; flow rate = 9.0 mL min^{-1}) in M2. The mixture was passed through R2 ($\varphi = 1000$ μm, $l = 100$ cm). After a steady state was reached, the product solution was collected for 2 min while being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography followed by preparative HPLC.

Typical procedure for three-component coupling using a flow microreactor system: A flow microreactor system consisting of four T-shaped micromixers (M1, M2, M3, and M4), four microtube reactors (R1, R2, R3, and R4), and five tube pre-cooling units (P1, P2, P3, P4, and P5; inner diameter $\varphi = 1000$ μm, length $l = 300$ cm) was used. A solution of *N*,*N*-bis(*p*-methoxybenzyl)carbamoyl chloride (0.10 M in THF; flow rate = 9.0 mL min^{-1}) and a solution of lithium naphthalenide (0.22 M in THF; flow rate = 9.0 mL min^{-1}) were introduced into M1 ($\varphi = 250$ μm) by using a plunger pump and a microfeeder pump, respectively. The mixture was passed through R1 ($\varphi = 1000$ μm, $l =$ 100 cm). The resulting solution was mixed with methyl chloroformate (0.30 M in THF; flow rate = 9.0 mL min^{-1}) in M2 ($\varphi = 250$ μm). The mixture was passed through R2 ($\varphi = 1000$ μm, $l = 100$ cm) and was introduced into M4 ($\varphi = 500$ μm). A solution of a functionalized organic compound and a solution of a lithiating agent were introduced into M3 ($\varphi = 250$ μm) by using plunger pumps, and the mixture was passed through R3. The resulting solution was introduced into M4. After a steady state was reached, the product solution was collected for 1 min while being quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography followed by preparative HPLC.

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