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Extremely Fast Gas/Liquid Reactions in Flow Microreactors: Carboxylation of Short-Lived Organolithiums

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Carboxylic acids and their derivatives are important classes of compounds in organic chemistry. Although various methods for synthesis of carboxylic acids have been used so far, carboxylation using CO₂ gas as a carbon feedstock^[1] is useful and attractive from an environmental point of view.^[2] Despite recent remarkable advances in this field,^[3] classical carboxylation of organometallics with CO₂ still serves as a powerful method because of efficiency and convenience.^[4] However, the method suffers from the problem of incompatibility of electrophilic functional groups such as nitro, cyano, and carbonyl groups, which causes severe limitations in the synthesis of carboxylic acids and their derivatives having a variety of functions and biological activities.

Recently, we have reported that various short-lived highly unstable organolithiums such as aryllithiums bearing electrophilic functional groups could be generated and used for reactions with subsequently added electrophiles before they decompose^[5] by taking advantages extremely short residence times, which is one of the characteristic features of flow microreactors.^[6-8]

There are two hurdles that we expected in the implementation of CO₂ as an electrophile in the reactions of short-lived organolithium species; the mass transfer between the CO₂ gas phase and the solution phase and the rate of the chemical reaction of organolithium species with dissolved CO₂. The first one seems to be mainly the issue of fluidics although the mass transfer rate also depends on the nature of the gas and that of the solution. It is well known that the use of flow microreactors enables fast mass transfer in gas-liquid biphasic reactions.^[9,10] The second one is the issue of chemistry. The reaction with CO₂ should be faster than that with an electrophilic functional group in the organolithium species, although the rate depends on the concentration of CO₂ in the solution. The question is what kind of electrophilic functional groups are compatible with the carboxylation. Here, we show that these hurdles were overcome using the flow microreactor system and that aromatic carboxylic acids bearing electrophilic functional groups were synthesized from the corresponding aromatic halides.

The reactions were carried out using a flow microreactor system composed of three T-shaped micromixers (**M1**, **M2** and **M3**) and three microtube reactors (**R1**, **R2** and **R3**) as shown in Figure 1. An aryl halide and *n*BuLi or PhLi were mixed in **M1** and the halogen/lithium exchange was carried out in **R1** to generate the corresponding aryllithium. In the next step, CO₂ gas (1.5 eq) that was pressurized to 3.0 bar with a gas pressure regulator valve was introduced at **M2** using a flow controller, and the carboxylation was carried out in **R2**. In the last step the reaction was quenched by MeOH at **M3** and **R3**.

(Insert Figure 1)

The carboxylation of *p*-nitrophenyllithium^[11] was first examined. The iodine/lithium exchange reaction was carried out with the residence time of 0.014 s at -20 °C. In the previous work,^[11] we have already revealed that *p*-nitrophenyllithium can be effectively generated under these conditions. We have also revealed that *p*-nitrophenyllithium decomposes with the residence time longer than ca. 0.4 s at -20 °C. As shown in Table 1, the corresponding carboxylic acid was obtained in 78% yield. This means gas/liquid mass transfer and the chemical reaction of *p*-nitrophenyllithium with CO₂ are much faster than its decomposition. Under similar conditions *m*- and *o*-nitrophenyllithiums were carboxylated effectively. The carboxylation reactions of *p*-, *m*-, and *o*-cyanophenyllithiums^[12] were also successfully accomplished using the flow microreactor system. The carboxylation of alkoxy carbonylphenyllithiums^[13] was more challenging, because esters react with organolithiums very quickly. We have already revealed that *p*-ethoxycarbonylphenyllithium decomposes with the residence time longer than ca. 0.4 s at -60 °C.^[13] However, the carboxylation of *p*-ethoxycarbonylphenyllithium could be accomplished to obtain the corresponding carboxylic acid in a reasonable yield. Therefore, the gas/liquid mass transfer and the carboxylation reactions are unexpectedly fast, and are much faster than the decomposition even at low temperatures such as -60 °C. Thus, carboxylation of aryllithiums bearing electrophilic functional groups, which is very difficult or impossible by conventional batch reactions, was achieved by using flow microreactors.

The carboxylation of phenyllithiums bearing electron-donating substituents such as methoxy group and unsubstituted phenyllithium are easier as shown in Table 1. Notably, the carboxylation of phenyllithium using CO₂ (1.5 eq)^[14] could be carried out at 0 °C. It is known that at such temperatures the carboxylation of organolithiums using CO₂ often leads to the formation of significant amounts of byproducts. For example, the carboxylation of phenyllithium at 0 °C in a batch macro reactor gave a mixture of benzoic acid, benzophenone, and

triphenylmethanol, although the reaction at -78 °C gave benzoic acid in good selectivity (87% yield) (Scheme 1). In contrast, the reaction in the flow microreactor system gave benzoic acid in 87% yield even at 0 °C. This feature of flow microreactor systems, presumably because of fast heat transfer, is especially important from a view point of industrial production.

(Insert Scheme 1)

(Insert Table 1)

The initial products before quenching with methanol in the present reaction are lithium salts of carboxylic acids, which are highly reactive toward activating agents such as TSTU (*O*-(*N*-succinimidyl)-1,1,3,3-tetramethyl uronium tetrafluoroborate) or PyBop (1H-benzotriazole-1-yloxytris(pyrrolidine-1-yl)phosphonium hexafluorophosphate). Therefore, active esters (esters with a good leaving group), which are commonly used for making peptides from carboxylic acids can be directly synthesized. Thus, the product solutions were treated with the activating agents without methanol quenching. No intentionally added base was required. The corresponding active esters were obtained in good yields as shown in Figure 2.

(Insert Figure 2)

N-succinimidyl-4-[¹⁸F]fluorobenzoate ([¹⁸F]SFB) is most commonly used to acylate lysine residues and *N*-terminal amine groups of peptides for positron emission tomography (PET).^[15] The following application to this protocol demonstrates the power of the present method, although cold ¹⁹F was used instead of hot ¹⁸F. The carboxylation of *p*-fluorophenyllithium generated from 1-bromo-4-fluorobenzene with CO₂ followed by the reaction with TSTU was completed within 1 min to give the *N*-succinimidyl-4-fluorobenzoate (SFB) in 55% yield. Then, a solution of SFB and triethylamine in CH₃CN was added to a solution of *cyclo*(Arg-Gly-Asp-D-Phe-Lys) (c(RGDfK)) in H₂O and CH₃CN. The mixture was incubated at 37 °C for 10 min and was purified by preparative HPLC to give the desired coupling product in 91% (Figure 3). The present fast synthesis also demonstrates the possibility of synthesizing compounds containing short-lived positron emitting radionuclide ¹¹C (*t*_{1/2} = 20.4 min) using ¹¹CO₂.^[16]

(Insert Figure 3)

In conclusion, we have developed an extremely fast and efficient method for carboxylation of short-lived organolithiums with CO₂ gas by virtue of fast gas/liquid mass transfer and short and precise residence time control in flow microreactors. We anticipate that this new tactic will provide an access to a wide range of carboxylic acids and their derivatives bearing electrophilic functional groups. Further work is in progress to explore a wide range of applications of the present method.

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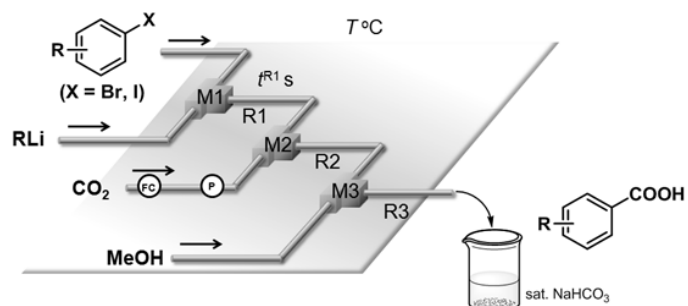


Figure 1. A flow microreactor system for the reactions of organolithiums with CO₂ gas. T-shaped micromixers: M1, M2, M3; microtube reactors: R1, R2, R3; flow controller: FC; pressure gage: P.

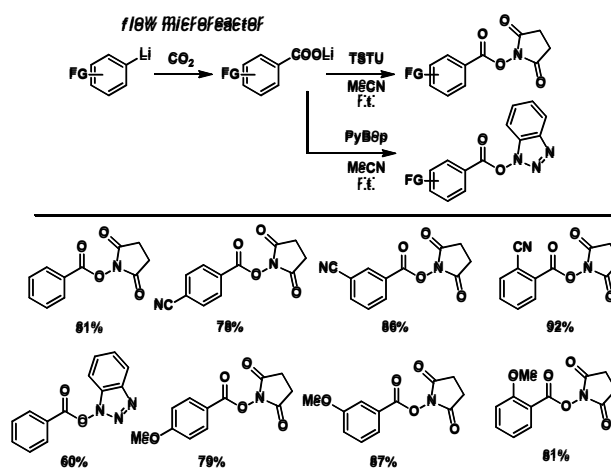


Figure 2. Flow microreactor synthesis of active esters.

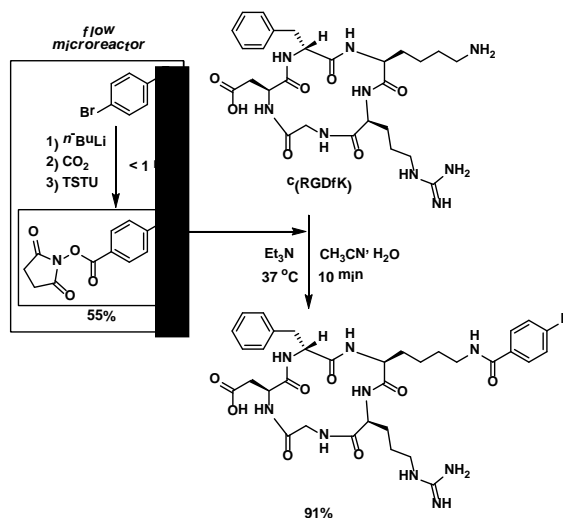
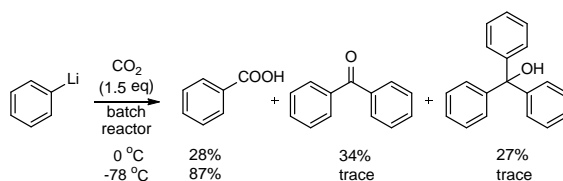
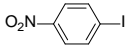
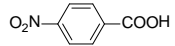

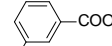

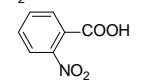
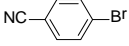
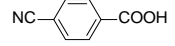

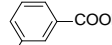

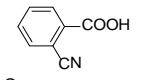
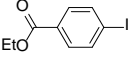
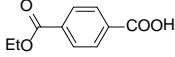

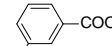
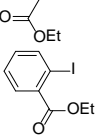
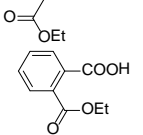
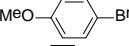
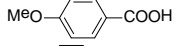

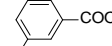

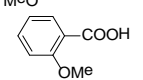

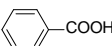


Figure 3. Coupling reaction of *cyclo*(Arg-Gly-Asp-D-Phe-Lys) (c(RGDfK)) with *N*-succinimidyl-4-fluorobenzoate (SFB).



Scheme 1. Reaction of phenyllithium with carbon dioxide using a conventional macro batch reactor.

Table 1. Carboxylation of aryllithiums with CO₂ gas using a flow microreactor system.^a

Halobenzene	RLi	T (°C)	t ^{R1} (s)	product	yield (%)
	PhLi	-20	0.014		78
	PhLi	-20	0.014		85
	PhLi	-20	0.014		59
	BuLi	-20	0.33		75
	BuLi	-20	0.33		88
	BuLi	-20	0.33		87
	PhLi	-60	0.055		87
	PhLi	-60	0.014		77
	PhLi	-60	0.014		89
	BuLi	-20	2.4		86
	BuLi	-20	2.4		88
	BuLi	-20	2.4		87
	BuLi	-20	4.7		85
		0	4.7		87

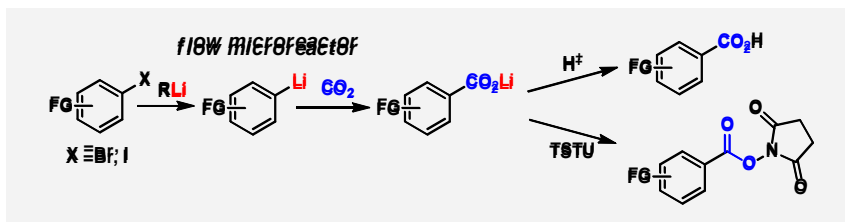
^a The reactions were carried out using 1.05 equiv of a lithiating agent and 1.50 equiv of CO₂.

Microreactors

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Extremely Fast Gas/Liquid Reactions in Flow Microreactors: Carboxylation of Short-Lived Organolithiums



Carboxylation of short-lived organolithiums bearing electrophilic functional groups such as nitro, cyano, and alkoxy carbonyl groups with CO₂ to give carboxylic acids and active esters was accomplished

in a flow microreactor system. The successful reactions indicates that gas/liquid mass transfer and the subsequent chemical reaction with CO₂ are extremely fast.

Keywords: microreactors · flow chemistry · carboxylation · lithiation