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# Generation of ynolates via reductive lithiation using flow microreactors

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## ABSTRACT

A new method has been developed for the generation and subsequent reaction of ynolates in a micro flow reactor system. This new procedure allowed for ynolates to be prepared at 0 °C or ambient temperature within 1 min via a reductive lithiation reaction, whereas the corresponding batch processes generally require low temperature control and extended reaction times of up to 1 h. The resulting ynolates were applied to the olefination of carbonyl compounds, with the reactions reaching completion in a much shorter reaction time in the continuous flow reactor than the batch reactor. These results highlight the practical utility of the ynolate reaction, and represent the first reported example of the use of lithium naphthalenide in a flow microreactor, which would contribute to progress of the flash chemistry.

We have reported a variety of new reactions with ynolates **1**,[1] including formal [*n* + 1] type cycloaddition reactions to give multisubstituted carbocycles[2] and heterocycles,[3] as well as a torquoselective olefination reaction for the construction of stereodefined multisubstituted olefins.[4] We have already developed a convenient and facile method for the preparation of ynolates via the thermal cleavage of ester dianions derived from the double lithiation of α,α-dibromo esters **2**.[5] This procedure can be readily performed, in that it involves the treatment of a THF solution of the α,α-dibromo ester with 4 equiv of *t*-, *s*- or *n*-BuLi at −78 °C for 10–15 min, with the resulting mixture being allowed to warm to 0 °C for 30 min (Scheme 1). Although this method is both practical and reproducible in a batch system on the bench-scale, where the butyllithium must be added slowly to maintain the low temperature, the exothermic nature of this step is difficult to control when scaling up the batch reaction because of differences in the ratio of the surface area to the reaction volume as the batch size increases. Our attempts to prepare ynolates at ambient temperature in a batch system were unsuccessful, even at a scale of less than 1 mmol, because the Li/Br exchange reactions of compounds such as **2** are extremely exothermic and result in numerous undesired side products following the reaction of the lithiated mixture with benzophenone. During the preparation of ynolates, since the second Li/Br exchange reaction (**3** → **4**) is slower than the first one (**2** → **3**), the lithium ynolate **3** generated by the initial Li/Br exchange may react with the unreacted starting ester **2** and other undesired reactions can also occur when the reaction is performed at higher temperatures. The lithium ester enolate intermediate **3**, in particular, is generally unstable over −20 °C and decomposes with the loss of lithium ethoxide to give a highly reactive ketene.[6] To suppress these self-condensation and ketene formation processes, the low temperature control must be applied.

Microflow systems have the potential to overcome the limitations encountered in batch systems, because they provide constant reaction parameters, such as temperature, reaction time, concentration, and mixing, which can be readily assured via time and space integration.[7] It was envisaged that microflow systems could be used to control the increase in temperature associated with the critical exothermic lithiation reaction that takes place during the preparation of ynolates.[8] Herein, we report the successful generation of ynolates via reductive lithiation using a microflow reactor. Importantly, these reactions did not need to be cooled to −78 °C.

We initially evaluated a variety of different microflow reactors for the preparation of ynolates via a Li/Br exchange reaction. The mixing of a hexane solution of *n*-butyllithium (1.5 M) and a THF solution of dibromoester in an integrated glass chip microchannel reactor (200 μm width and 100 μm depth) resulted only in the formation of a blockage at the junction, most likely because of the precipitation of lithium salts. This precipitation issue would not be observed in a batch system, and occurred at the contact area of the laminar flow (hexane–THF) in the microfluidic system. To

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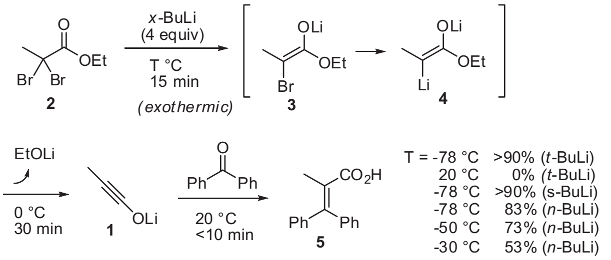


**Scheme 1.** Generation and reaction of ynolate.

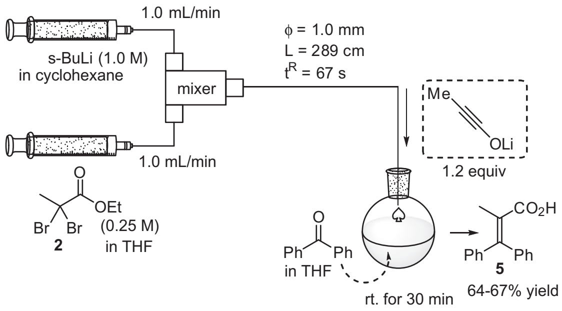


**Figure 2.** A flow microreactor system with a static mixer for the generation of an ynolate via a Li/Br exchange reaction.

avoid the formation of a blockage, we proceeded to evaluate an alternative microtube reactor consisting of a stainless steel static micromixer, which was originally designed for HPLC (Fig. 1, 150 μL, GL Science, Tokyo, Japan), and a stainless steel tube with an internal diameter of 1000 μm as a microreactor. The reaction was carried out at room temperature and the residence time ($t^R$) was controlled by the length of the tube reactor. The ynolate generated in the microreactor was subsequently trapped by its reaction with benzophenone in a flask at room temperature. The isolated yield of the resulting olefin was determined to allow for the efficiency of this method to be evaluated.

Solutions of *sec*-butyllithium (0.92 M in cyclohexane) and dibromoester (0.22 M in THF) were pumped into the reactor at a flow rate of 1.0 mL/min and mixed in the mixer at 20 °C, where the residence time was approximately 67 s. The resulting ynolate (1.2 equiv based on benzophenone) was reacted with a solution of benzophenone in THF at room temperature in a separate flask. Pleasingly, no blockages were observed in the reactor when the procedure was performed on a 1 mmol scale. After the flow was stopped, the reaction mixture was stirred for an additional 30 min before being worked up as usual to afford the desired olefin in 64–67% isolated yield (Fig. 2). These preliminary results indicated that the ynolate could be generated in the microreactor at ambient temperature. Given that this result could not be achieved with a batch system without low-temperature control, the use of a flow microreactor system in this regard proved to be particularly useful for the preparation of ynolates.

It is well known that butyllithium can readily react with THF at ambient temperature to give several byproducts such as ethylene,[9] which can itself react with butyllithium to form small amounts (a couple of percent of yields) of the byproducts **6** and **7**. These byproducts, as well as several other byproducts, such as **8**, which resulted from the reaction of *s*-BuLi with benzophenone, were detected by GC analysis (Fig. 3). To prevent the occurrence of these side reactions, we investigated the use of diethyl ether as the reaction solvent under various reaction conditions because it is not as reactive as THF. The use of diethyl ether, however, resulted in lower product yields in the range of 14–51%, probably due to the lower activation ability to alkyllithium.

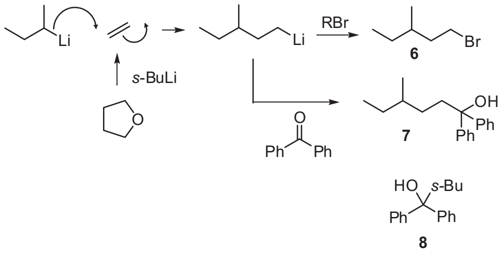


**Figure 3.** Byproducts derived from *sec*-butyllithium in a flow system.

We then proceeded to investigate the possibility of generating the ynolate and subjecting it to an olefination reaction in a flow micro system consisting of two micromixers (M1 and M2), as shown in Figure 4. A solution of the ynolate in THF, which was generated in M1 and R1, was mixed with a solution of benzophenone in THF in M2 with a flow rate of 2.0 mL/min and a residence time ($t^R$) of 3 s. When the reaction was conducted at temperatures of 0 and 30 °C ($t^{R1}$ = 30–60 s), it gave product yields in the range of 50–65%.

The stainless steel flow microreactor was equipped with a quartz glass tube ($\phi$ = 1 mm, $L$ = 10 mm) for the visualization of the flow (Fig. 5). Through this tube, we became aware of the generation of gas bubbles inside R1 when the reaction was conducted at ambient temperature. These gases were most likely butane and/or butene analogues, derived from butyllithium, and ethylene generated by the reaction of THF with butyllithium, as described

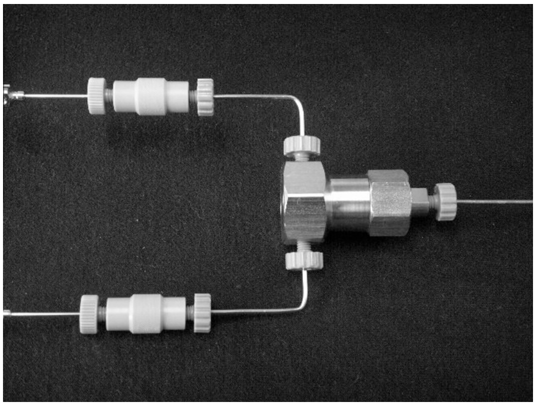


**Figure 1.** A static micromixer.

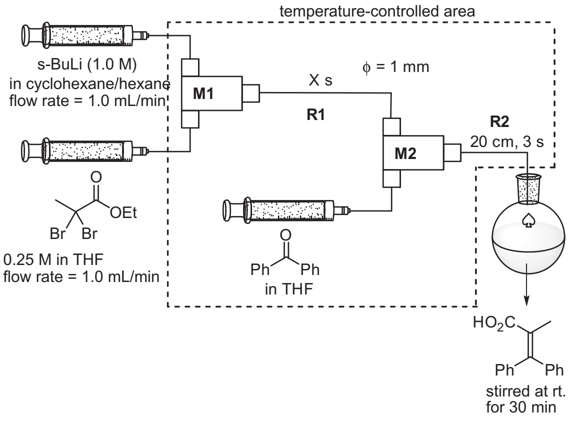


**Figure 4.** Generation and reaction of ynolate in flow microreactor.

**Figure 5.** Flow microreactor system equipped with a quartz glass tube.

above. The formation of these bubbles prevented the steady flow of the substrate solutions through the system and led to inconsistent and moderate yields.

The formation of byproducts derived from butyllithium would also be a problem as long as this reagent was being used to affect the Li/Br exchange reaction, and the use of an alternative lithiation method would be required to avoid this issue. With this in mind, we decided to use reductive lithiation instead of Li/Br exchange reaction to generate the ynolate species.[10] Lithium metal was added to a solution of naphthalene in THF in a batch system to give a lithium naphthalenide solution, which was mixed with a THF solution of dibromoester in M1 in a flow system. The resulting ynolate solution in R1 was mixed with a benzophenone solution in M2, and this olefination reaction mixture afforded a residence time of 50 s in R2 before being quenched into a flask of water (Fig. 6). The ynolate formation reaction was investigated over a variety of different residence times (i.e., $t^{R} = 3, 30, 60$ s) in R1 at temperatures in the range of −10–40 °C (Table 1). At −10 °C, the desired product was produced in 62% yield, and the yield increased up to 82% at 0 °C. Furthermore, the generation of the ynolate appeared to reach completion within 30 s at this temperature. Further increases in the temperature did not lead to further improvements in the yield, with a reaction temperature of 0 °C appearing to be optimal in terms of the yield. Since no bubbles were detected during the course of the ynolate formation using the reductive lithiation method, this method was therefore deemed to be more suitable for the preparation of ynolates than the Li/Br exchange method using butyllithium. Under the optimized reaction conditions for this flow system (i.e., $T = 0$ °C, $t^{R1} = 30$ s), we investigated the use of this continuous flow system on the gram scale. Unfortunately, however, the flow system failed on this scale because of the formation of a blockage in M2 following several min of the reaction. The use of an M2 mixer with a larger inner diameter may have allowed for this reaction to be successfully conducted on a gram scale, but it was not possible to adjust of the inner diameter of this device.

To achieve a gram-scale flow reaction, we investigated the use of Comet X-01 mixer (Techno Applications Co., Ltd, Tokyo, Japan).[11]

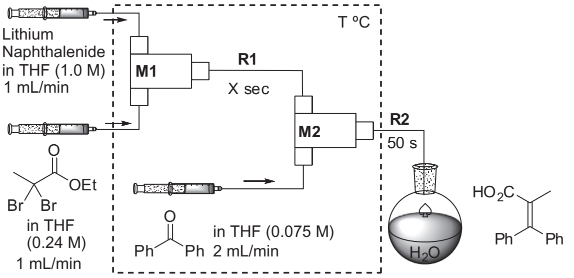


**Figure 6.** Generation and reaction of the ynolate via reductive lithiation.

**Table 1**
Microfluidic reductive lithiation method[a]

| $T$ (°C) | R1 (s) | | |
|---|---|---|---|
| | 3 | 30 | 60 |
| −10 | – | 62% | 62% |
| 0 | – | 82% | 79% |
| 25 | 46% | 73% | 76% |
| 40 | 55% | – | – |

[a] The reaction conditions are shown in Figure 6.

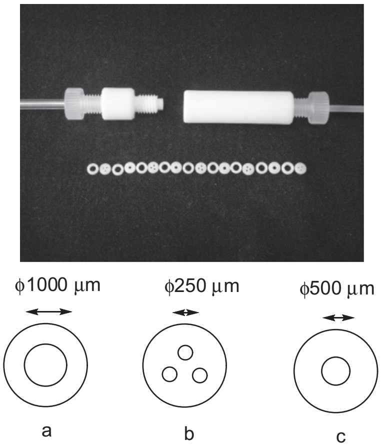


**Figure 7.** A mixer of micro flow reactor, Comet X contains three kinds (a, b and c) of round plates bearing micro holes.

The inner structure of this Teflon mixer consisted of 18 round plates bearing three different micro-hole plates inside each plate (Fig. 7 a, b and c) and, by changing the combination of these plates, the size of the flow channel could be readily adjusted. Although M1 could be used as a default combination (plates a, b and c) without having an adverse impact on the outcome on the reaction, the plate combination in M2 had to be tuned to avoid the formation of a blockage in the flow. Finally, using eight a plates and eight c plates in M2, we succeeded in achieving continuous flow without clogging the system to obtain 1.18 g of the product in 75% yield (Fig. 8).[12]

Using this flow system, we investigated the olefination of a variety of different ketones to afford the corresponding alkenes in good yield (Table 2).[13] Although the products were formed in similar yields to those obtained in a batch system,[14] the current flow system provided several advantages over the batch system, including the ability to readily control the temperature on scaling-up the reaction, as well as the reaction reaching completion in only one minute.

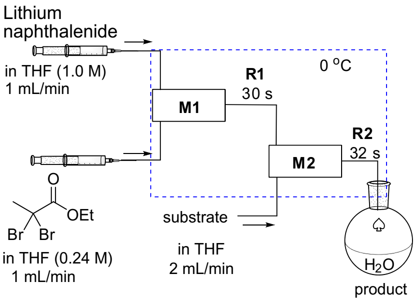
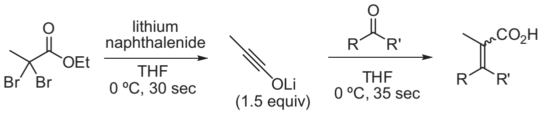


**Figure 8.** Schematic representation of the flow reactor system used for the preparation of the ynolate via the reductive lithiation reaction using the Comet X mixer. M1 contained the default combination of the three different kinds of micro plates (a, b and c) shown in Figure 7, whereas M2 had only two different types of micro plate (a and c).

**Table 2**
Flow synthesis of tetrasubstituted alkenes via the ynolate using the system shown in Figure 8



| Entry | R | R′ | Flow reaction[a] (%) | *E*:*Z* | Batch reaction (%) (*E*:*Z*) |
|---|---|---|---|---|---|
| 1 | Ph | Ph | 80 | – | 70 |
| 2 | Ph | Ph | 75[b] | – | 70 |
| 3 | Me | Ph | 60 | 84:16 | 76 (81:19) |
| 4 | PhCH = CH | Ph | 66 | 79:21 | 82 (79:21) |
| 5 | TMS | Me | 74[b] | <1:>99 | 59 (<1:>99) |
| 6 | CH(OTBS)Ph | H | 79 | <1:>99 | 43 (<1:>99) |

[a] 0.5 mmol scale.

[b] 20 °C in R2.

We have succeeded in developing a reaction for the generation of ynolates and their subsequent reaction with a range of ketones in the micro flow systems. The ynolate preparation process can be readily carried out at 0 °C or ambient temperature within 1 min. This represents a significant improvement over the corresponding batch systems, which require low temperature control and 1 h for the reaction to reach completion. The success of this process can be attributed to quick heat exchange properties of flow microreactors, which allowed for the decomposition of the ester enolate intermediate and self-condensation reactions that occurred before the second lithiation step to be avoided. The olefination of a series of carbonyl compounds with the ynolate proceeded to completion in much shorter overall reaction time using the continuous flow reactor. This result highlights the practical utility of the current method for the synthesis of ynolates, even though the overall yields were close to those obtained using batch systems. Furthermore, this work is the first example of use of lithium naphthalenide (reductive lithiation) in microreactors, and therefore represents a significant contribution towards general progress in flow chemistry.

## Acknowledgements

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11. A micromixing device, 'Comet X-01', is available from Techno Applications Co., Ltd, 34-16-204, Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan. Since it is made of teflon, the surface of the inlet port of mixer was partially blackened by lithium naphthalenide, but it was not a problem for the flow.
12. Naphthalene was recovered in more than 84%.
13. *Representative procedure (flow reaction):* A flow microreactor consisting of two teflon mixers (M1 and M2), two teflon microtube reactors (1000 μm, $L = 100$ cm (R1), 300 cm (R2)) was used. A twin syringe pump was charged with two 5 mL syringes, one containing lithium naphthalenide (1.0 mmol) in THF (4.1 mL), which was taken from a stock solution freshly prepared from lithium metal (100 mg, 14.4 mmol) and naphthalene (1.65 g, 12.9 mmol) in THF (13 mL) at 0 °C, and the other dibromoester **2** (1.03 mmol, 267 mg) in THF (4.1 mL). M1, M2, R1 and R2 were dipped in a cooling bath at 0 °C. Solutions of lithium naphthalenide in THF and dibromoester in THF were introduced to M1 (containing plates a, b, and c) by the syringe pumps in a flow rate of 1.0 mL/min each. The resulting solution was passed through R1 and was mixed with a THF solution (8.2 mL) of benzophenone (121 mg, 0.665 mmol) in M2 in a flow rate of 2.0 mL/min. The resulting solution was poured into water. After a steady state was reached, the product solution was collected for 60 s (corresponding to 0.162 mmol of benzophenone in 2 mL of 0.081 M THF solution). The collected mixture was extracted with 2% NaOH solution. The aqueous solution was acidified with 3 M HCl and extracted with AcOEt ($3 \times 25$ mL), The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with silica gel column chromatography (60% AcOEt/Hexane then 100% AcOEt) to yield the carboxylic acid **5** (31 mg, 80% based on benzophenone).
14. *Representative procedure (batch reaction):* To a solution of naphthalene (520 mg, 4.0 mmol) in THF (8 mL) was added lithium metal (30 mg, 4.3 mmol). The deep blue mixture was stirred for 3 h at room temperature under argon., A solution of ethyl 2,2-dibromopropionate (259 mg, 1.0 mmol) in THF (2 mL) was then added dropwise to the solution of lithium naphthalenide at −78 °C. The solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, 1,2-dibromoethane (1 drop) was added to quench the excess lithium naphthalenide, the resulting pale yellow solution was warm to room temperature and then a solution of benzophenone (120 mg, 0.66 mmol) in THF (2 mL) was added. After 1 h, the resulting mixture was quenched with $H_2O$, and extracted with aqueous 10% NaOH solution. The aqueous phase was acidified with 3 M HCl, and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give residue, which was purified by column chromatography to afford the 2-methyl-3,3-diphenylacrylic acid (109 mg, 70%).