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Reactions of difunctional electrophiles with functionalized aryllithium compounds: remarkable chemoselectivity by flash chemistry.

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Benzyllithiums Bearing Aldehyde Carbonyl Groups. A Flash Chemistry Approach**

Atsuhiko Nagaki, Yuta Tsuchihashi, Suguru Haraki, and Jun-ichi Yoshida*

Cemosel ectivity is one of the central issues in chemistry and chemical synthesis.[1] One of the goals in synthetic chemistry is the development of chemoselective transformations without affecting highly reactive functional groups that are not involved in the desired transformation. We have been interested in organolithium reactions without affective aldehyde carbonyl groups as an extreme case of chemoselective transformations.[2] According to textbooks of organic chemistry, organolithiums react with aldehyde very quickly and they are not compatible with each other. On the other hand, aldehyde carbonyl groups are very common functional groups and organolithium reactions are frequently used in organic synthesis.[3] Therefore, if we could perform organolithium reactions without affecting aldehyde carbonyl groups, such reactions would serve as powerful synthetic methods. We took an approach to this challenge based on flash chemistry,[4] in which a highly unstable reactive species are generated and transferred to another location to be used in the next reaction before they decompose by high-resolution residence time control using flow microreactor systems.[6-8] Here, we show that flash chemistry enables the generation of benzyllithiums bearing aldehyde carbonyl groups and their use in the reactions with subsequently added electrophiles without affecting the aldehyde carbonyl groups.

Recently, we have reported the generation and reactions of aryllithiums bearing ketone carbonyl groups.[5] Because aldehyde carbonyl groups are more reactive than ketone carbonyl groups in general, we envisaged that faster generation is necessary to solve the more challenging problem of aldehyde cases. Therefore, we chose to use reductive lithiation of benzyl halides instead of halogen/lithium exchange of aryl halides.[9,10]

Thus, we focused on the generation of benzyllithiums[10] bearing aldehyde carbonyl groups by reductive lithiation of benzyl halides (Figure 1).[11] In addition to functional group compatibility, there is another problem, i.e. Wurtz-type coupling, the coupling of benzyllithiums with starting benzyl halides.[12] We envisioned that extremely fast micromixing is effective to avoid undesired Wurtz-type coupling because it is known that the product selectivity of fast consecutive reactions[13] can be improved by extremely fast micromixing.[14]

At first, we examined the generation of simple benzylithium. It was reported that benzyllithium can be generated from benzyl chloride by using lithium naphthalenide (LiNp) in a mixed solvent (Et2O/THF/light petroleum = 4:3:1) at –95 °C in a conventional batch reactor.[14] However, the reaction in THF and/or at higher temperatures such as –78 °C leads to a dramatic decrease in the yield because of Wurtz-type coupling. The use of benzyl bromide also leads to Wurtz-type coupling. Keeping such backgrounds in mind, we examined the reactions of benzyl halides with LiNp in a flow microreactor system, which consists of two T-shaped micromixers (M1 (φ = 250 µm) and M2 (φ = 250 µm)) and two microtube reactors (R1 (φ = 1000 µm, length = 3.5 cm) and R2 (φ = 1000 µm, length = 50 cm)) shown in Figure 2. For the reactions with very short residence times such as 1.3 ms (R1 (φ = 250 µm, length = 1.0 cm)), a built-in type system (Figure 2a) was used, whereas a conventional modular type system was used for the reactions with longer residence times, (Figure 2b).

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of benzyllithium at 20 °C, although the reactions should be carried out at −95 °C in a conventional batch macro reactors. It is also advantageous that THF can be used instead of the mixed solvent. Furthermore, benzyl bromide can be used as a starting material, although such transformation is impossible in a conventional batch macro reactor. These remarkable features seem to be ascribed to extremely fast 1:1 (molar ratio) mixing in the micromixer.

Table 1. Effect of the flow rate and the inner diameter of M1 on the lithiation of benzylic halides using the flow microreactor system.[a]

<table>
<thead>
<tr>
<th>X</th>
<th>Benzyl halide</th>
<th>LInP total</th>
<th>yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>flow rate [mL/min]</td>
<td>inner diameter of M1 [µm]</td>
<td>toluene bibenzyl</td>
</tr>
<tr>
<td>Cl</td>
<td>6.0</td>
<td>3.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Br</td>
<td>6.0</td>
<td>3.0</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>1.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>6.0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>1.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.75</td>
<td>2.25</td>
</tr>
</tbody>
</table>

[a] R1: Φ = 250 µm, L = 3.5 cm, 20 °C. [b] Determined by GC using an internal standard.

Under the optimized conditions, the reactions of benzyllithium with other electrophiles, such as methyl iodide, aldehydes, ketones, trimethylsilyl chloride, and isocyanates were examined. As shown in Table 2, the corresponding products were obtained in good yields. Notably, the lithiation of 2-(chloromethyl)thiophene followed by the reaction with an electrophile was successfully achieved, although conventional batch reactions often suffer from the ring-opening side reaction.[16]

Table 2. The generation of benzyllithiums followed by reaction with an electrophile.[a]

<table>
<thead>
<tr>
<th>X</th>
<th>Benzyl halide</th>
<th>Electrophile</th>
<th>product</th>
<th>yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>MROH</td>
<td>CHO</td>
<td>89[1]</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>MROH</td>
<td>CHO</td>
<td>82[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PhCHO</td>
<td>CHO</td>
<td>80[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CH3)2CO</td>
<td>CHO</td>
<td>42[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph2CO</td>
<td>CHO</td>
<td>93[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mr3SiCl</td>
<td>CHO</td>
<td>80[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MROH</td>
<td>CHO</td>
<td>80[1]</td>
<td></td>
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<tr>
<td></td>
<td>MROH</td>
<td>CHO</td>
<td>82[1]</td>
<td></td>
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<tr>
<td></td>
<td>PhCHO</td>
<td>CHO</td>
<td>75[1]</td>
<td></td>
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<tr>
<td></td>
<td>Ph2CO</td>
<td>CHO</td>
<td>71[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MROH</td>
<td>CHO</td>
<td>97[1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mr3SiCl</td>
<td>CHO</td>
<td>72[1]</td>
<td></td>
</tr>
</tbody>
</table>

[a] R1: Φ = 250 µm, L = 3.5 cm, 20 °C. Benzyl chloride: total flow rate = 9 mL/min. Benzyl bromide, 2-(chloromethyl)thiophene: flow rate of benzyl halide = 18 mL/min. [b] Determined by GC using an internal standard. [c] Isolated yield.

Figure 3. Effects of the temperature and the residence time in R1 on the yield of the protonated product for the lithiation of (a) p-propanoylbenzyl chloride and (b) p-formylbenzyl chloride with LInp followed by trapping with methanol using the flow microreactor system. Contour plots with scattered overlay of the yields of the protonated product for the lithiation of p-propanoylbenzyl chloride, which has a ketone carbonyl group, followed by trapping with methanol. The yield decreases with an increase in the temperature although the effect of the temperature is not large. The optimal yield (80%) was obtained with the residence time of 1.3 ms at −78 °C.

The effects of the residence time and the temperature are more significant in the lithiation of p-formylbenzyl chloride, which has an aldehyde carbonyl group (Figure 3b). As it can be seen by comparing Figs 3a and 3b, p-formylbenzyl lithium is significantly more unstable than p-propanoylbenzyl lithium. With the residence time of 1.3 ms at −78 °C, however, p-formylbenzyl lithium can be generated and used in the subsequent reaction with methanol to give the protonated product in a reasonable yield (68%). This means that
the aldehyde carbonyl group can survive in the organolithium reaction.

Table 3. The generation of benzylolithiums bearing ketone and aldehyde carbonyl groups followed by reaction with an electrophile.[a]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Electrophile</th>
<th>Yields [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>Ph</td>
<td>Me</td>
<td>Et</td>
<td>PhNCO</td>
<td>78%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>PhNCO</td>
<td>86%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>PhCHO</td>
<td>60%</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>PhCHO</td>
<td>62%</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>Me3SiOTf</td>
<td>68%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCHO</td>
<td>69%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCHO</td>
<td>69%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCHO</td>
<td>69%</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCHO</td>
<td>69%</td>
</tr>
</tbody>
</table>

[a] R1: \( \phi = 250 \, \mu m, \ L = 1.0 \, cm, \ -78 \, ^\circ{ C} \). [b] Isolated yield. [c] Determined by GC. [d] Diastereomeric ratio = 88:12 (determined by \(^1\)H NMR). [e] Diastereomeric ratio = 60:40 (determined by \(^1\)H NMR).

Under the optimized conditions several benzylolithiums bearing ketone and aldehyde carbonyl groups were generated and reacted with several electrophiles including phenylisocyanate, benzaldehyde, TMSOTf, and MeOTf. The results are summarized in Table 3. Such transformations are very difficult or practically impossible by using conventional batch macro reactors.

As an application of the present method, we accomplished the synthesis of a \(\pi\)-conjugated system shown in Figure 4. The reaction of benzaldehyde with (5-formylthiophen-2-yl)methylithium followed by the elimination of bis[a,a,a-bis(trifluoromethyl)benzenemethanolate]diphenylsulfur (Martin sulfuran) gave aldehyde 1 in 61% isolated yield. The aldehyde carbonyl group in 1 was used for the subsequent reaction with benzylithium. The subsequent dehydispation gave compound 2 (78% isolated yield), in which one thiopehe ring and two benzene rings are connected by carbon-carbon double bonds.[17]

In conclusion, flash chemistry using flow microreactor systems enables the generation and reactions of benzylolithiums bearing aldehyde carbonyl groups. Extremely fast micromixing is responsible for the generation of benzylolithiums avoiding Wurtz-type coupling, and high-resolution residence time control is responsible for survival of aldehyde carbonyl groups. The present findings open a new aspect of protecting-group-free\(^{18}\) organolithium chemistry.

**Experimental Section**

Typical procedure for flow microreactor system for the lithiation of electrophilic-functionalized benzyl halides with lithium naphthalenide (LiNp) followed by the reaction with electrophiles: A flow microreactor system consisting of the build-in type system in which two T-shaped micromixers (M1 and M2) and a microtube reactor (R1) were combined, a microreactor R2, and three pre-tube (R3). The mixing solution was passed through R1 (\( \phi = 250 \, \mu m, \ L = 1.0 \, cm \) cm). The reaction mixture was mixed with a solution of electrophile (0.05 M in THF) was introduced to M1 by a plunger pump (15 mL/min). A solution of lithium naphthalenide (LiNp) (0.22 M in THF) was introduced to M1 by a micro feeder pump (7.5 mL/min). The mixing solution was passed through R1 (\( \phi = 250 \, \mu m, \ L = 1.0 \, cm \) cm). The reaction mixture was passed with a solution of electrophile (0.20 M in THF) in M2 (\( \phi = 250 \, \mu m \) by a plunger pump (7.5 mL/min), and the resulting solution was passed through R2 (\( \phi = 1000 \, \mu m, \ L = 50 \, cm \) cm). After a steady state was reached, an aliquot of the product solution was collected and was treated with sat. aqueous NH4Cl solution. The reactions were carried out at -78 °C. Organic layer was analyzed by gas chromatography or isolated by flash chromatography or GPC.

**Keywords:** microreactors, lithiation, carbonyl group

[4] Flash chemistry is defined as a field of chemical synthesis where extremely fast reactions are conducted in a highly controlled manner to produce the desired compounds with high selectivity: a) J.


Microreactors

Aiichiro Nagaki, Yuta Tsuchihashi, Suguru Haraki, and Jun-ichi Yoshida*

Benzyllithiums Bearing Aldehyde Carbonyl Groups. A Flash Chemistry Approach

Reductive lithiation of benzyl halides bearing aldehyde carbonyl groups followed by the reaction with subsequently added electrophiles was successfully accomplished without affecting the carbonyl groups by taking advantage of short residence times in flow microreactors.