Flow Synthesis of Triptycene via Triple Cycloaddition of Ynolate to Benzyne

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Abstract

Flow synthesis of triptycene was achieved using triple cycloaddition of ynolate to benzyne. Employing the borate-type benzyne precursor, side reactions triggered by the addition of alkyllithium to benzyne were efficiently suppressed under microflow conditions, thus producing triptycene with a higher yield than that obtained under the corresponding batch conditions. Furthermore, ynolate prepared from \( n\)-\( n\)-dibromoester under microflow conditions was continuously added to the flow reaction with benzyne, which successfully synthesized triptycene in only one minute.

Keywords triptycene, ynolate, benzyne, flow synthesis, cycloadditionborate

Triptycenes are symmetric compounds with three benzene rings fixed by a bicyclo[2.2.2]octatriene bridgehead system. Based on their unique and rigid skeleton, the compounds have been utilized in fields such as host–guest chemistry, supramolecular chemistry, and material chemistry. Studies have reported several synthetic methods for triptycene synthesis, e.g., the Diels–Alder reaction of anthracenes and benzenes or quinones, the intramolecular Friedel–Crafts reaction, and the \([2+2+2]\) cycloaddition of alkynes. Furthermore, we have recently developed a new synthetic method for triptycene based on a triple cycloaddition of one ynolate \( 1 \) to three benzenes \( 2 \) (Scheme 1). This method can be easily performed, where alkyllithium is added to a mixture of ynolate and a benzyne precursor. The yield of triptycene \( 3 \) varies from 27–69% when employing fluorobenzene or 3-fluoroanisole as the benzyne precursor. In the cases that resulted in low yields, abundant benzyne byproducts were produced. Generally, short-lived benzenes should be trapped by an excess of arynophiles. However, the triple cycloaddition reaction does not use the excess ynolate because the reaction needs at least three equivalents of benzyne to ynolate. Therefore, it is important to generate benzenes incrementally. Moreover, the generation of benzyne using a strong base, such as alkyl- or aryllithium, competes with the side reactions triggered by the addition of the base to benzyne. Thus, suppression of these side reactions is key to improving the yield but is not easily achieved in a batch system because inefficient mixing causes an uneven distribution of concentration and temperature in the reaction vessel.

Scheme 1 Synthesis of triptycene via triple cycloaddition of ynolate to benzyne

These issues in the batch system could be solved using microflow systems, which have the potential to provide constant reaction parameters, such as reaction temperature, time, and concentration, due to high mixing efficiency and rapid heat transfer. Furthermore, the rapid diffusion of the reaction mixture helps suppress undesired contact of intermediates or the product with the starting materials and reagents. Therefore, it has been illustrated that the microflow conditions are beneficial in many exothermic reactions via unstable intermediates such as alkyllithium-initi-
ated reactions. For example, Yoshida and co-workers reported that the efficient formation and reaction of benzyne were achieved using microflow systems. We have reported the flow synthesis of ynolate from 0,0-dibromoester using alkylolithium or lithium naphthalenide and achieving other reactions of ynolates under microflow conditions. Based on these results, we envisioned that microflow systems could improve the efficiency of the synthesis of triptycene through the precise control of reaction conditions. Thus, this report details the flow synthesis of triptycene via triple cycloaddition of ynolate and benzyne using flow microreactors.

The investigation began with the reaction using o-bromoiodobenzene and PhLi for the preparation of benzyne (Table 1). The reaction was carried out using a Comet X-01 mixer (Techno Applications Co., Ltd, Tokyo, Japan) as a microreactor. A solution of lithium ynolate 1 was prepared in advance by our method in a batch system. In entry 1, a solution of PhLi (0.97 M) and a mixture of ynolate 1 (0.12 M) and benzyne precursor 2 (0.70 M) were pumped into the reactor at a 1.0 mL/min in a ratio of 1/2/PhLi = 1:6:8. The solutions were mixed at –20 °C, and the resulting mixture flowed through a tube with 0.8 mL volume, where the residence time was approximately 24 s, into the aqueous HCl solution to quench the reaction. The yield of triptycene 3 was estimated by NMR to be approximately 21%. In entries 2 and 3, the reaction temperature was increased to 0 °C and 22 °C, which resulted in higher yields of 3. When the ratio of 1/2/PhLi was changed to 1:8:11 and 1:3:4, the yields were diminished (entries 4 and 5). The faster flow rates (1.5 mL/min and 2.0 mL/min), with residence times of 16 s and 12 s, were effective, thus synthesizing the product with yields of 33% and 31%, respectively (entries 6 and 7).

For comparison, the reaction was also performed in the batch system under the conditions corresponding to entry 6 in Table 1, and triptycene 3 was obtained with a 31% NMR yield (25% isolated yield), which was slightly less than that obtained in the microflow conditions (Scheme 2). This may indicate that the microflow system improved the efficiency of the triple cycloaddition of ynolate to benzyne. However, we realized that it is not easy to suppress the side reactions under these microflow conditions, because the formation of many byproducts was still observed on the GC–MS analysis of the crude products (see Figure S1 in the Supporting Information). The major byproducts were biphenyls and o-terphenyls, which would be formed by the addition of aryllithium intermediates to benzyne. Although this result indicates that benzyne was generated efficiently, most of the benzyne was wasted in the side reactions.

Table 1: Flow Synthesis of Triptycene Using o-Bromoiodobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concn of 1 (M)</th>
<th>1/2/PhLi</th>
<th>T (°C)</th>
<th>s (mL/min)</th>
<th>t (s)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.12</td>
<td>1:6:8</td>
<td>–20</td>
<td>1.0</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>1.0</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>0.12</td>
<td>1:6:8</td>
<td>22</td>
<td>1.0</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>0.075</td>
<td>1:8:11</td>
<td>5</td>
<td>1.0</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>0.20</td>
<td>1:3:4</td>
<td>0</td>
<td>1.0</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>1.5</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>2.0</td>
<td>12</td>
<td>31</td>
</tr>
</tbody>
</table>

* Molar ratio of concentrations.

** NMR yields.

Thus, we changed the precursor of benzyne to o-(trifluoro-omethanesulfonyloxy)phenylboronic acid pinacol ester 4 developed by Hosoya and co-workers (Table 2). It has been reported that the treatment of alkylolithium with 4 generates borate complex 5, which is stable at 0 °C and then converts into benzyne when warmed to room temperature. Based on this, we envisioned that the undesired addition reactions to benzyne could be suppressed using precursor 4 because, by the formation of the borate complex in advance, the coexistence of nucleophilic butyllithium and benzyne can be avoided. Slow generation of benzyne could also be achieved by temperature control of the borate complex solutions in the second step. The microreactor system consisted of two mixers, A and B. The solutions of precursor 4 and s-BuLi were introduced into the microreactor and combined in mixer A at –78 °C. The resulting solution of borate complex 5 was mixed with a solution of ynolate 1 in mixer B and then passed through the tube maintained at the indicated temperature. In entry 1, the ratio of 1/4/s-BuLi was 1:6:6, and the reaction was performed at 23 °C to provide triptycene 3 with a 19% yield. When the reaction temperature was elevated to 40 °C and 60 °C, the yield of 3 increased to 33% and 29%, respectively (entries 2 and 3). However, the use of 5 or 8 equivalents of 4 and s-BuLi diminished the

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yield (entries 4 and 5). In entry 6, the reaction employed a higher concentration of the solutions in comparison with entry 2, which resulted in no influence on the NMR yield and a 31% isolated yield of 3. It should be emphasized that GC-MS analysis of the crude products indicated considerable suppression of side reactions (see Figure S2 in the Supporting Information). The main byproducts were o-bromophenylboronic acid pinacol ester and biphenylene formed via dimerization of benzyne. These results suggest that almost complete consumption of s-BuLi was achieved in the first step, and thus, the competitive addition reactions to benzyynes were largely suppressed. Therefore, although the yield was as much as one of the first approach as shown in Table 1, purification of triptycene 3 was much easier to perform in this approach. Furthermore, the batch reaction, which was performed under the conditions corresponding to entry 6 in Table 2, synthesized triptycene 3 with a 21% yield (24% NMR yield, Scheme 3). Thus, the reaction efficiency of the triple cycloaddition reaction was also improved under the microflow conditions probably due to the high mixing efficiency.

Finally, ynolate 1, prepared under the microflow conditions, was directly employed for the flow synthesis of triptycene (Scheme 4). The solutions of a,a-dibromomethylene (1.20 M) and lithium naphthalenide (0.25 M) were mixed in mixer A at 22 °C to produce ynolate 1. At the same time, the solutions of benzyne precursor 4 (0.38 M) and s-BuLi (0.38 M) were pumped into mixer B. These two resulting solutions were then introduced into mixer C, and the reaction mixture passed through a tube maintained at 40 °C for 16 s. Triptycene 3 was successfully obtained with a 16% yield judged by the NMR spectra. Although the yield was less than that of the prior flow systems, the current flow system provided advantages, including that the whole reaction was completed in only one minute.

In conclusion, we have developed flow synthesis of triptycene using triple cycloadditions of ynolate-benzyne under microflow conditions. Using Hosoya’s benzyne precursor, dramatic suppression of side reactions, and improvement in yield compared with the corresponding batch system was achieved. This can be attributed to the microflow conditions, such as efficient mixing and rapid heat.

### Table 2 Flow Synthesis of Triptycene Using O-(Trifluoromethanesulfonyloxy)phenylboronic Acid Pinacol Ester

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc of 1 (M)</th>
<th>1</th>
<th>/s-BuLi</th>
<th>T (°C)</th>
<th>t (s)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>0.05</td>
<td>1:6:6</td>
<td>23</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>0.05</td>
<td>1:6:6</td>
<td>40</td>
<td>16</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>0.05</td>
<td>1:6:6</td>
<td>60</td>
<td>32</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>4c</td>
<td>0.05</td>
<td>1:5:5</td>
<td>40</td>
<td>32</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>0.05</td>
<td>1:3:8</td>
<td>40</td>
<td>32</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>6d</td>
<td>0.075</td>
<td>1:6:6</td>
<td>40</td>
<td>16</td>
<td>33 (31)b</td>
<td></td>
</tr>
</tbody>
</table>

a Molar ratio of concentrations.
b NMR yields.
c Residence time between mixer A and B: 24 s.
d Residence time between mixer A and B: 48 s.
e Isolated yield.

### Scheme 3 Batch synthesis of triptycene 3 using borate-type benzyne precursor 4

### Scheme 4 Flow synthesis of triptycene, including the preparation of ynolate
transfer. The flow reaction was also performed using ynolate, which was prepared under microflow conditions, synthesizing the triptycene in only one minute. This is the first report for flow synthesis of triptycene, as far as we know. Further improvement of the reaction efficiency is now under investigation in our group.

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Supporting Information
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References and Notes