A Novel Anionic Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenone Ring Systems

Jon D. Rainier* and Qing Xu

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721
rainier@u.arizona.edu

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ABSTRACT

We have identified an unprecedented anionic condensation, fragmentation, and elimination sequence from the coupling of bicyclo[2.2.1]heptenones with aldehydes. This reaction leads to the stereoselective formation of disubstituted five-membered rings which are present in a wide array of bioactive molecules.

Substituted furans are a key architectural feature in a wide array of biologically active molecules. Our interest in the 2,5-disubstituted furan-containing marine natural products gymnodimine1,2 and eleutherobin3,4 has directed our attention to the synthesis of these structural units. As envisioned, our approach to the synthesis of substituted furans included (a) an aldol condensation between an oxabicyclo[2.2.1]heptenone5 and an aldehyde, (b) a subsequent fragmentation reaction,6 and (c) an elimination reaction to the corresponding olefin (Scheme 1). As described in this Letter, in the course of these investigations we have uncovered an unprecedented anion-mediated condensation, fragmentation, and elimination reaction during which all of the goals outlined above were accomplished in a single flask.7

To investigate the sequence depicted in Scheme 1, we initially examined the condensation of oxabicyclo[2.2.1]-

(2) For synthetic efforts to gymnodimine, see: Ishihara, J.; Miyakawa, J.; Tujimoto, T.; Murai, A. Synlett. 1997, 1417–1419.
(6) For other uses of oxabicyclo[2.2.1] fragmentation reactions in the synthesis of substituted furans, see ref 5.
(8) The trisubstituted olefin geometry was determined through the identification of the appropriate NOESY cross-peaks (see the Supporting Information for more details).]
heptenone 4 with benzaldehyde (Table 1, entry 1). Surprising-ingly, rather than the simple condensation product, we isolated disubstituted furan 5 exclusively as its Z-alkene isomer in 83% yield after esterification. To our delight, we had achieved the condensation, fragmentation, and elimination in a single flask.

With the notion that this reaction might lead to the efficient synthesis of a number of substituted furans, we set out to determine the scope. As is depicted in Tables 1 and 2, other aldehydes and bicyclo[2.2.1] ring systems successfully underwent the reaction. For example, the condensation of isobutyraldehyde with 4 gave furan 6 exclusively as the Z-alkene isomer in 78% yield (Table 1, entry 2). The reaction is not specific to 4 as unsubstituted oxabicyclo[2.2.1]-β-keto ester 7 also underwent the condensation, fragmentation, and elimination reaction sequence. The unoptimized coupling of 7 with benzaldehyde and isobutyraldehyde gave furans 8 and 9, respectively (Table 1, entries 3 and 4). Interestingly, while 4 gave exclusively the Z-alkene isomer with both benzaldehyde and isobutyraldehyde, 7 gave a 3:1 E:Z alkene mixture when condensed with benzaldehyde and a 1:2 E:Z mixture when condensed with isobutyraldehyde.8

We have also examined the reaction between bicyclo-[2.2.1]heptenone 10 and aldehydes (Table 2). As with the synthesis of the furans mentioned previously, the condensa-

<table>
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<tr>
<th>Entry</th>
<th>Ketone</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Furan</th>
<th>Yield</th>
<th>E:Z</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>Ph</td>
<td>5</td>
<td>83%</td>
<td>0:1</td>
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<tr>
<td>2</td>
<td>4</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>iPr</td>
<td>6</td>
<td>78%</td>
<td>0:1</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>8</td>
<td>56%</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>H</td>
<td>iPr</td>
<td>9</td>
<td>45%</td>
<td>1:2</td>
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</tbody>
</table>

Table 2. Single Flask Condensation, Fragmentation, and Elimination to 1,4-Disubstituted Cyclopentenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Cyclopentene</th>
<th>Yield</th>
<th>E:Z</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>KOH-Bu</td>
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<tr>
<td>2</td>
<td>iPr</td>
<td>KOH-Bu</td>
<td>12</td>
<td>91%</td>
<td>2:1</td>
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<tr>
<td>3</td>
<td>iPr</td>
<td>NaH</td>
<td>12</td>
<td>94%</td>
<td>3:1</td>
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</tbody>
</table>

Table 1. Single Flask Condensation, Fragmentation, and Elimination to 2,5-Disubstituted Dihydrofurans

Scheme 2. Determination of the Olefin Geometry in Furans 5 and 6

Scheme 3. Possible Mechanism for the Condensation, Fragmentation, and Elimination Reaction of Bicyclo[2.2.1]heptenes

In contrast to 5 and 6, the NOESY spectra of substituted furans 5 and 6 were devoid of information. However, we were able to determine the olefin geometry in 5 and 6 after derivatization of the furan (Scheme 2). That is, treatment of 5 and 6 with methanolic KOH resulted in hydrolysis, decarboxylation, and aromatization to give 13 and 14, respectively. DIBAL reduction gave allyl alcohols 15 and 16.9 As depicted, NOESY cross-peaks were observed between the isopropyl/phenyl hydrogens and the methylene hydrogens of the hydroxy methyl group, thereby establishing the trisubstituted olefin geometry.

While any detailed mechanistic discussion requires further experimentation, a reasonable working hypothesis is depicted in Scheme 3. It is highly likely that aldol condensation to
give 18 precedes fragmentation as attempted aldol coupling between furan 21\(^\text{10}\) and isobutyraldehyde resulted in the recovery of 21. Lactol formation provides oxetane 19.\(^\text{7}\) Oxetane fragmentation then leads to furan 20. The nature of the substrate dependence on the \(E,Z\)-olefin selectivity is not readily apparent and is thus the focus of our current efforts.\(^\text{11}\)

The bicyclo[2.2.1] ring systems used in this study are readily accessible using a Diels–Alder cycloaddition reaction between bromopropynoate 22 and the appropriate diene (Scheme 4).\(^\text{12–14}\) A subsequent two-step hydrolysis of the resulting bromoacrylate derivative gave \(\beta\)-keto esters 4, 7, and 10.

To conclude, we have identified a novel anion-mediated condensation, fragmentation, and elimination reaction of bicyclo[2.2.1]heptene ring systems. Our current efforts are focusing on the nature of the selectivity in this reaction as well as its use in the synthesis of furan-containing natural products.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds 4–12, 15, and 16. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) Thus far, we have been unable to selectively reduce the ethyl ester in 5 or 6.
(10) 21 is available from the reaction of 4 and NaOCH\(_3\).
(11) Thus far, our attempts to equilibrate the olefin in 5 with base have been unsuccessful.