A Mukaiyama–Claisen Approach to 3,5-Diketo Esters

Qinggang Wang
Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany
list@mpi-muelheim.mpg.de

Dedicated to ’uncle Peter’, in deep admiration for his marvelous contributions to chemical synthesis, including Synlett.

Abstract

A thermally promoted synthesis of 3,5-diketo esters via a Mukaiyama–Claisen reaction of 4H-1,3-dioxin-4-one derivatives with silyl enolates has been developed. The desired oligocarbonyl compounds were obtained with moderate to good yields.

Key words 3,5-diketo esters, Mukaiyama–Claisen reaction, thermal reaction, silylated nucleophiles

Oligocarbonyl compounds, especially 3,5-diketo ester derivatives, are important building blocks for the synthesis of polyketides and polyols, such as erythromycin A, rosuvastatin, tetracycline and wailupemycin F (Figure 1).1–3

Therefore, approaches towards their synthesis are of interest. Several methodologies have previously been developed to synthesize oligocarbonyl compounds.4 Among them, Claisen condensation approaches have proven efficient in building up the carbon backbone. The Langer group recently reported the reaction of silylated nucleophiles with acyl chloride to give 3,5-diketo esters.4a–d Tanabe and co-workers utilized a similar strategy to access analogous 1,3-dicarbonyl compounds.4e,f However, to our knowledge, esters themselves have not been used as electrophiles in Mukaiyama-type Claisen condensations. Notably, 4H-1,3-dioxin-4-one derivatives are useful synthetic equivalents for 1,3-dicarbonyls. In the context of a different study, we have recently described a single example in which a 3,5-diketo ester was accessed by reacting an enol silane with a 4H-1,3-dioxin-4-one derivative.5,6 Herein, we explore the generality of this unique transformation and report an improved thermal approach for the synthesis of 3,5-diketo esters via a Mukaiyama–Claisen reaction of 4H-1,3-dioxin-4-one derivatives with silyl ketene acetals.

Under optimized conditions both aliphatic and α,β-unsaturated 4H-1,3-dioxin-4-one derivatives could be employed in the thermally promoted Mukaiyama–Claisen reaction. Simply treating compounds 1 with an excess of silyl ketene acetal 2a or 2b, gave the corresponding 3,5-diketo esters in good yields after desilylation (Table 1). Using an N-Boc carbamate containing substrate, the corresponding tricarbonyl products 3a and 3b were obtained in 85% and 78% yield, respectively. With an O-TBS protected substrate, the reactions proceeded smoothly, giving 3c and 3d in 85% and 84% yield, respectively. Reactions involving a conjugated alkenyl substrate required higher temperature (110 °C), and the corresponding products 3e and 3f were obtained in 61% and 73% yield, respectively. Using the simple, methyl-substituted substrate, the desired tricarbonyl compounds 3g and 3h were obtained in 73% and 75% yield, respectively.

Figure 1 Representative examples of polyketides and polyols

1.02.12.2014
Accepted after revision: 14.01.2015
Published online: 10.02.2015

SYNLETT 0936-52141437-2096 © Georg Thieme Verlag Stuttgart · New York — Synlett 2015, 26, 1525–1527
Interestingly, when a silyl enol ether \(2c\) was explored as the nucleophile, an intramolecular cyclization was observed and 2-methyl-6-phenyl-4H-pyran-4-one \(4\) was isolated in 59% yield (Scheme 1). Presumably, under these conditions, a triketone is initially formed and subsequently undergoes cyclization to heterocycle \(4\).\(^7\)

In summary, a thermally promoted synthesis of 3,5-diketo esters via a Mukaiyama–Claisen reaction of 4H-1,3-dioxin-4-one derivatives with silylated enolate nucleophiles has been developed.\(^8\) The desired oligocarbonyl compounds were obtained in good yields. This methodology may find applications in the synthesis of bioactive polyketides or polyols.

### Table 1 Substrate Scope of the Mukaiyama–Claisen Reaction

<table>
<thead>
<tr>
<th>Entry (^a)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>84</td>
</tr>
<tr>
<td>5(^b)</td>
<td>3e</td>
<td>61</td>
</tr>
<tr>
<td>6(^b)</td>
<td>3f</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were carried out with \(1\) (0.1 mmol) and \(2\) (0.4 mmol) in toluene (1 mL) for 4–5 h at 90 °C.

\(^b\) Reactions were carried out at 110 °C.

**Acknowledgment**

Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant ‘High Performance Lewis Acid Organocatalysis, HIPOCAT’) is gratefully acknowledged.

**Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380145.

**References and Notes**


(6) An acyl ketene intermediate has recently been proposed in thermal reactions of 4H-1,3-dioxin-4-ones (Scheme 2):

\[
\begin{align*}
\text{Scheme 2} & \\
\text{R} & \text{O} \\
\text{O} & \Delta \text{R} \text{O} \\
\end{align*}
\]


(8) A cooling-finger-capped Schleck tube with a stirring bar was charged with the corresponding 4H-1,3-dioxin-4-one derivative \( \mathbf{1} \) (0.1 mmol), silylated nucleophile \( \mathbf{2} \) (0.4 mmol), and anhydrous toluene (1 mL). The resulting mixture was heated to 90 °C or 110 °C for 4–5 h until full consumption of the starting material was observed (monitored by TLC). The solvent was removed under reduced pressure, MeOH (1 mL) and KHF\(_2\) (10 equiv) were added, and the reaction mixture was stirred at r.t. for 10 min. After filtering through a thin layer of Celite, the residue was purified by column chromatography (isohexanes–EtOAc, 5:1 to 1:1).