Improved Synthesis of α-Formylcarboxylic Esters

Title

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Improved Synthesis of α-Formylcarboxylic Esters

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Two improved routes to α-formylcarboxylic esters (4) from the corresponding trimethylsilyl ketene acetics (1) are described. The TiCl₄-catalyzed reaction of 1 with 2-ethoxy-1,3-oxathiolane affords 2-(1,3-oxathiolan-2-yl)carboxylic esters (2) in good yields which on hydrolysis with chloramine-T trihydrate furnished 4 in almost quantitative yields. The reaction of 1 with ethyl orthoformate in the presence of TiCl₄ also furnished 4 in almost quantitative yields in a single step.

KEY WORDS: α-Formylcarboxylic esters/ Trimethylsilyl Ketene acetics/ 2-Ethoxy-1,3-oxathiolane/ 2-(1,3-Oxathiolan-2-yl)carboxylic esters/ Chloramine-T/ Ethyl orthoformate

Recently there has been a considerable interest in the selective α-formylation of carboxylic esters for their use as intermediates. Attempts have occasionally been made for the development of a simple, general and highly selective strategy for the preparation of α-formylcarboxylic esters (4), but not much progress could be made. The condensation of carboxylic esters with alkyl formates in the presence of NaH did not find much applicability due to some side reactions. Another approach involving alkylation of 2-carboethoxymethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine followed by the reduction of the oxazine ring and hydrolysis was limited as the starting dihydro-1,3-oxazine derivatives are not easily accessible. There has been reports on the preparation of formylcarboxylic esters from the corresponding α,β-unsaturated carboxylic esters by the cobalt- and rhodium-catalyzed reactions at high pressure. There has been a report recently on the diphosphine-rhodium complex-catalyzed hydroformylation of α,β-unsaturated carboxylic esters at 150°C under 100 atm of synthesis gas. Though high α-selectivity has been achieved in some cases, the β- and γ-formyl derivatives and hydrogenated products are also formed.

We have been interested in the development of a simple, general and high yield methodology for the preparation of 4. Though our initial efforts were not successful, we have been able to develop a simple method by the reaction of trimethylsilyl ketene acetals (1) with Vilsmeier reagent which gave α-formylated products in moderate yields. We now wish to report in this manuscript two improved methods for the preparation of title compounds. Our approach was based on the synthesis of 2-(1,3-oxathiolan-2-yl)carboxylic esters (2) by the reaction of 1 with 2-ethoxy-1,3-oxathiolane in the presence of TiCl₄. The reaction proceeded smoothly at room temperature affording 2 in 59-96% yields (Table I). Though the regeneration of the
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carbonyl compounds by the acid-catalyzed hydrolysis and Raney nickel desulfurization has been reported, the use of chloramine-T trihydrate has proved a better reagent. The hydrolysis of 2 was therefore performed with chloramine-T trihydrate. The treatment of 2d-h with chloramine-T trihydrate furnished the objective α-formylcarboxylic esters (4d-h) in almost quantitative yields. However, treatment of

\[
\begin{align*}
\text{R}_1(\text{R}_2)\text{C} &= \text{C} + \text{HOC}_2\text{H}_5 \xrightarrow{\text{TiCl}_4} \text{R}_1(\text{R}_2)\text{C} = \text{CO}_2\text{CH}_3 \\
\text{R}_1(\text{R}_2)\text{C} &= \text{CO}_2\text{CH}_3 \\
\end{align*}
\]

Table I. Preparation of 2

<table>
<thead>
<tr>
<th>Starting compound and yield (%)</th>
<th>Physical properties of product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a</strong> 79 <strong>2a</strong> 73-74 (6)</td>
<td>0.90 (t, 3H), 1.3-1.8 (m, 2H), 2.2-2.7 (m, 1H), 2.8-3.3 (m, 2H), 3.70 (s, 3H), 3.8-4.4 (m, 2H) and 4.99 and 5.08 (d and d, 1H)</td>
</tr>
<tr>
<td><strong>1b</strong> 91 <strong>2b</strong> 75-76 (5)</td>
<td>0.8-1.2 (m, 5H), 1.6-2.3 (m, 2H), 2.3-2.7 (m, 2H), 2.8-3.2 (m, 2H), 3.75 (s, 3H), 4.0-4.4 (m, 2H) and 5.29 and 5.37 (d and d, 1H)</td>
</tr>
<tr>
<td><strong>1c</strong> 81 <strong>2c</strong> Not</td>
<td>1.06 (s, 9H), 2.51 (d, 1H), 2.8-3.1 (m, 2H), 3.62 (s, 3H), 4.0-4.4 (m, 2H) and 5.10 and 5.37 (d and d, 1H)</td>
</tr>
<tr>
<td><strong>1d</strong> 96 <strong>2d</strong> 74-76 (5)</td>
<td>1.14 (s, 3H), 1.22 (s, 3H), 2.7-3.0 (m, 2H), 3.76 (s, 3H), 4.2-4.6 (m, 2H) and 5.30 (s, 1H)</td>
</tr>
<tr>
<td><strong>1e</strong> 68 <strong>2e</strong> Not</td>
<td>0.80 (t, 3H), 1.11 (s, 3H), 1.4-1.8 (m, 2H), 2.5-2.8 (m, 2H), 3.47 (s, 3H), 4.0-4.4 (m, 3H) and 5.12 (s, 1H)</td>
</tr>
<tr>
<td><strong>1f</strong> 59 <strong>2f</strong> 77-78 (3)</td>
<td>0.92 (t, 6H), 1.5-2.0 (m, 4H), 2.7-3.0 (m, 2H), 3.74 (s, 3H), 4.2-4.6 (m, 2H) and 5.40 (s, 1H)</td>
</tr>
<tr>
<td><strong>1g</strong> 76 <strong>2g</strong> 84-85 (0.4)</td>
<td>1.5-2.3 (m, 8H), 2.7-3.2 (m, 2H), 3.72 (s, 3H), 4.2-4.6 (m, 2H) and 5.64 (s, 1H)</td>
</tr>
<tr>
<td><strong>1h</strong> 67 <strong>2h</strong> 96-97 (0.5)</td>
<td>1.0-2.4 (m, 10H), 2.8-3.2 (m, 2H), 3.78 (s, 3H), 4.2-4.6 (m, 2H) and 5.21 (s, 1H)</td>
</tr>
</tbody>
</table>

a) Isolated yield by column chromatography.
2a-c did not yield the expected products. It is not clear how the presence of a hydrogen at α-position affects the hydrolytic step so drastically. The compounds 2 have not been previously reported and were characterized by spectral methods. The formation of 2 can be explained by the electrophilic attack of the 1,3-oxathiolan-2-ium ion on the 1 releasing trimethylsilyl group. The conversion of 2 to 4 can be explained via the formation of an unstable sulfilimine and zwitter ion.6)

In search of a more general method, we investigated the reaction of 1 with ethyl orthoformate in the presence of TiCl$_4$. The TiCl$_4$-catalyzed direct formylation of 1 with a slight excess of ethyl orthoformate in dichloromethane at room temperature proceeded smoothly and the objective 4 were obtained in almost quantitative yields (Tabel III). The formation of 4 from 1 by the TiCl$_4$-catalyzed reaction with ethyl orthoformate can also be explained by an analogous route as in the previous case.

Table II. Conversion of 2 into 4

<table>
<thead>
<tr>
<th>Starting compound</th>
<th>Product and yield (%)</th>
<th>Physical properties of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2d</td>
<td>4d, 75</td>
<td>1.34 (s, 6H), 3.74 (s, 3H) and 9.61 (s, 1H)</td>
</tr>
<tr>
<td>2e</td>
<td>4e, 90</td>
<td>0.88 (t, 3H), 1.31 (s, 3H), 1.6–2.1 (m, 2H), 3.80 (s, 3H) and 9.69 (s, 1H)</td>
</tr>
<tr>
<td>2f</td>
<td>4f, 94</td>
<td>0.88 (t, 6H), 1.68 (q, 4H), 3.82 (s, 3H) and 9.51 (s, 1H)</td>
</tr>
<tr>
<td>2g</td>
<td>4g, 96</td>
<td>1.4–2.3 (m, 8H), 3.76 (s, 3H) and 9.59 (s, 1H)</td>
</tr>
<tr>
<td>2h</td>
<td>4h, 94</td>
<td>1.1–2.2 (m, 10H), 3.77 (s, 3H) and 9.48 (s, 1H)</td>
</tr>
</tbody>
</table>

Table III. One-step Synthesis of 4 with Ethyl Orthoformate

<table>
<thead>
<tr>
<th>Starting compound</th>
<th>Product and yield (%)</th>
<th>Physical properties of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>4a, 85</td>
<td>Ketonic form: 0.98 (t, 3H), 1.5–2.4 (m, 2H), 3.0–3.4 (m, 1H), 3.29 (s, 3H) and 9.68 (d, 1H)</td>
</tr>
<tr>
<td>1d</td>
<td>4d, 87</td>
<td>Enolic form: 1.02 (t, 3H), 1.5–2.4 (m, 2H), 3.29 (s, 3H), 6.87 (d, 1H) and 11.30 (d, 1H)</td>
</tr>
</tbody>
</table>

The following was confirmed from the $^1$H-NMR spectral data: The compound 4a consisted initially of the ketonic form, but it gradually changed to an equilibrium mixture containing approximately half of the enolic form.
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The attack by the diethoxycarbonium ion on 1 releasing trimethylsilyl cation seems to give intermediate 3 which are hydrolyzed during aqueous work-up.

The present results indicate that two new methods are now available for the preparation of 4 selectively. The existence of these methods in addition to previously known methods make the compounds 4 more easily accessible.

EXPERIMENTAL

Preparation of 2-(1,3-Oxathiolan-2-yl)carboxylic Esters (2) and Their Hydrolysis into α-Formylcarboxylic Esters (4). To a cooled (−78°C) solution containing 1.0 mmol of one of 1 and 1.1 mmol (0.15 g) of 2-ethoxy-1,3-oxathiolane in 10 ml of dichloromethane was added during 5 min 1.1 mmol (0.21 g) of TiCl₄. The reaction mixture was allowed to warm to room temperature and stirred for 2 h at that temperature, and then treated with 20 ml of aqueous NaHCO₃. The organic layer was separated and combined with ethereal extracts (20 ml x 2) of the aqueous phase. It was dried over MgSO₄ and concentrated under reduced pressure to afford a residue which was purified by column chromatography (silica gel, 10% ethyl acetate-hexane as an eluent) to give either one of 2. To a suspension of 2.0 mmol (0.57 g) of chloramine-T trihydrate in 10 ml of water was added at room temperature during 5 min 1.0 mmol of one of 2 above-mentioned. The reaction mixture was stirred at that temperature during 15–30 min, and then treated with 20–30 ml of carbon tetrachloride. The resulting precipitate was collected on a filter and washed with carbon tetrachloride (10 ml x 2). The organic layer of the filtrate was combined with the washings, dried over MgSO₄, and concentrated under reduced pressure to afford a residue which was subjected to column chromatography (silica gel, 40% ethyl acetate-hexane as an eluent) to give the corresponding 4.

One-step Conversion of Trimethylsilyl Ketene Acetals (1) into α-Formylcarboxylic Esters (4). To a cooled (−78°C) solution containing 1.0 mmol of one of 1 and 1.1 mmol (0.17 g) of ethyl orthoformate in 10 ml of dichloromethane was added during 5 min 1.1 mmol (0.21 g) of TiCl₄. The reaction mixture was allowed to warm to room temperature and stirred for 1–3 h at that temperature, and then treated with 20 ml of aqueous NaHCO₃. The organic layer was combined with ethereal extracts (20 ml x 3) of the aqueous phase, dried over MgSO₄, and concentrated under reduced pressure to afford a crude product which was purified similarly as above.

REFERENCES