Preparation of Acetals of Substituted Glyoxylic Esters (Methyl 2,2-Dimethoxyalkanoates)

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Acetals of z-oxoesters (2,2-dialkoxycarbonyl esters, A) are interesting intermediates in organic synthesis, for example, in the preparation of lactones and z-methylene lactones and in steroid chemistry. They may be prepared by esterification and acetalization of z-oxoacids, by alklylation of tetramethyloxethylene, or by z-functionalization of alkylene esters via a multistep reaction sequence.

Compounds A are useful starting materials for the synthesis of monoacetics of vic-diketones (by reaction with Grignard reagents in HMPT), z-methylene acetals and z-cyclopolyesteridene acetals (by carboxyl olefination with alkylene- or cyclopolyesteridene phosphonates), and corresponding carboxyl compounds (by acetal cleavage). The readily available S,S-acetals B<sup>10,11</sup> can be used for these purposes because their conversion to the S,S-acetals of monothio-vic-diketones (z-dialkylthioketones) can only be achieved with poor yield and acetal cleavage of the z-methylene-S,S-acetals or z-cyclopolyesteridene-S,S-acetals obtained by carboxyl olefination with phosphonates is difficult.\textsuperscript{7,8}

\[
\begin{align*}
\text{HCO}_2 \text{CH-COOCH}_3 & \xrightarrow{\text{LiN(C}_2\text{H}_5)_2/\text{THF}, -70^\circ \text{C}} \text{HCO}_2 \text{CH-COOCH}_3 \\
\text{HCO}_2 \text{CH-COOCH}_3 & \xrightarrow{\text{R-X (3) / THF; } -90^\circ \text{C}} \text{HCO}_2 \text{CH-COOCH}_3
\end{align*}
\]

In the present communication, we show that methyl 2,2-dimethoxyalkanoates (acetals of z-oxoesters, 4) are readily obtained by reaction of the lithio derivative of methyl dimethoxycetate (2) with alkyl halides (3) in tetrahydrofuran. By-products such as N,N-disopropylidimethoxacetamide (5) can be easily removed (except in the case of 4g) by column chromatography of the product over silica gel using ether/pentane as eluent.

\[
\begin{align*}
\text{HCO}_2 \text{CH-COOCH}_3 & \xrightarrow{\text{LiN(C}_2\text{H}_5)_2/\text{THF}, -70^\circ \text{C}} \text{HCO}_2 \text{CH-COOCH}_3 \\
\text{HCO}_2 \text{CH-COOCH}_3 & \xrightarrow{\text{R-X (3) / THF; } -90^\circ \text{C}} \text{HCO}_2 \text{CH-COOCH}_3
\end{align*}
\]

The lithio derivative 2 has previously been used to prepare alkyl 2,2-dimethoxyalkanoates of the type 4 by reaction with enolizable aldehydes or ketones followed by dehydration and hydrogenation.\textsuperscript{9}

Whereas disulfurated carbamions are frequently used in organic synthesis (see, for example, Ref. \textsuperscript{12,13}), their oxygen analogs (e.g. 2) which are less stable have rarely been used except in the conjugate addition to butenolides\textsuperscript{1} and in the reaction with carboxyl compounds.\textsuperscript{7}

**Methyl 2,2-Dimethoxyalkanoates (4): General Procedure:**

A solution of lithium diisopropylamide (5 mmol) is prepared by adding dropwise diisopropylamine (459 mg, 5 mmol) to a stirred solution of metyl lithium (5 mmol of a 2-18 molar solution in ether) in anhydrous tetrahydrofuran (6 mL) under an argon atmosphere at \(-5^\circ\text{C}\). After 15 min, the mixture is cooled to \(-70^\circ\text{C}\) and a solution of methyl dimethoxycetate\textsuperscript{10} (1.670 mg, 5 mmol) in tetrahydrofuran (6 mL) is added dropwise with stirring. The mixture is stirred for a further 15 min at \(-70^\circ\text{C}\). Upon addition of the solution of the alkyl halide (3; 5 mmol) in tetrahydrofuran (6 mL) is added dropwise over a 15 min period with stirring at \(-70^\circ\text{C}\). After a further 20 min, the mixture is gradually warmed to \(-70^\circ\text{C} \rightarrow -10^\circ\text{C} \rightarrow 0^\circ\text{C} \rightarrow 5^\circ\text{C}\), and poured into water (5 mL). The resultant mixture is stirred for 5 min, the organic phase is separated, and the aqueous phase extracted with 1.1 ethyl acetate/ether (4 x 15 mL). The organic phases are combined, washed with 10% hydrochloric acid (5 mL) and with water (5 mL). After filtration through a basic column, the filtrate is evaporated to dryness to give the methyl 2,2-dimethoxyalkanoates (4).

**Table. Methyl 2,2-Dimethoxyalkanoates (4)***

<table>
<thead>
<tr>
<th>3</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; [%]</th>
<th>b.p./torr&lt;sup&gt;b&lt;/sup&gt;</th>
<th>b.p./torr reported&lt;sup&gt;c&lt;/sup&gt;</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H-N.M.R. (CDCl&lt;sub&gt;3&lt;/sub&gt;) δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>4a</td>
<td>50</td>
<td>70/13</td>
<td>59.5/11&lt;sup&gt;14&lt;/sup&gt;</td>
<td>4 (s, 3H); 3.2 (s, 6H); 3.7 (s, 3H)</td>
</tr>
<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;—J</td>
<td>4b</td>
<td>50</td>
<td>87/13</td>
<td>77.10&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.78 (t, 3H); 1.82 (q, 2H); 3.2 (s, 6H); 3.7 (s, 3H)</td>
</tr>
<tr>
<td>n-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;—Br</td>
<td>4c</td>
<td>55&lt;sup&gt;e&lt;/sup&gt;</td>
<td>98/13</td>
<td>40 65&lt;sup&gt;13&lt;/sup&gt;</td>
<td>0.95 (t, 3H); 1.27 (m, 2H); 1.77 (t, 2H); 3.2 (s, 6H); 3.7 (s, 3H)</td>
</tr>
<tr>
<td>i-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;—J</td>
<td>4d</td>
<td>30</td>
<td>97/13</td>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.88 (d, 6H); 2.05 (m, 1H); 3.2 (s, 6H); 3.7 (s, 3H)</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>4e</td>
<td>50</td>
<td>102/13</td>
<td>25.50&lt;sup&gt;13&lt;/sup&gt;</td>
<td>2.55 (d, 2H); 3.2 (s, 6H); 3.68 (s, 3H); 4.82-6.02 (m, 3H)</td>
</tr>
<tr>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;—CH&lt;sub&gt;2&lt;/sub&gt;—Br</td>
<td>4f</td>
<td>70</td>
<td>172/13</td>
<td>95 105&lt;sup&gt;13&lt;/sup&gt;</td>
<td>3.09 (s, 2H); 3.28 (s, 6H); 3.48 (s, 3H); 7.15 (s, 3H)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields of the pure isolated products except for 4g which was not separated from the amide 5.
<sup>b</sup> Measured by bulb-to-bulb distillation.
<sup>c</sup> The reaction was carried out in the presence of HMPT (1 equiv) to improve the yield.
<sup>d</sup> C<sub>4</sub>H<sub>9</sub>O<sub>2</sub> calc. C 54.53 H 9.15 (176.2) found 54.08 9.28
<sup>e</sup> C<sub>6</sub>H<sub>13</sub>O<sub>2</sub> calc. C 55.16 H 8.10 (174.2) found 55.31 8.26

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0039-7881/79/0132-0033 © 03.00
water (15 ml), and dried with magnesium sulfate. The solvent is evaporated and the crude product chromatographed on a silica-gel column (20 g g; silica gel 60 Merck, for column chromatography, 70-230 mesh) using ether/pentane (20:80) as eluant. Product 4 is eluted first (except in the case of 4g which is eluted together with 5).

The general procedure is used for the synthesis of 4a, b, c, f. In the synthesis of 4c, d, g, HMPT (895 mg, 5 mmol) is added to the lithium diisopropylamide solution at −20° prior to the addition of methyl dimethoxycacetate at −70°. The general procedure is then followed except that at the end of the reaction the mixture is warmed to +10° and held at this temperature for 60 min.

Received: July 24, 1978

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