Lithium or Bromomagnesium 1,4- and 1,5-Dilithioalkan-2-yloxydes: Preparation and Synthetic Applications

José Barluenga*, José R. Fernandez, Miguel Yus

Departamento de Química, Orgánica, Facultad de Química, Universidad de Oviedo, Oviedo, Spain

Treatment of chloromethyl 2- or 3-chloroalkyl carbinols with butyllithium and then lithium naphthalenide or with ethylmagnesium bromide and then powdered lithium leads to the formation of lithium or bromomagnesium dilithioalkoxides, respectively, which represent trianionic species. The bromomagnesium 1,ω-dilithio-2-alkoxides undergo immediate elimination of lithium bromide and magnesium oxide to give ω-lithio-1-alkenes. These latter organometallic compounds as well as the lithium dilithioalkoxides react with various electrophiles to afford functionalized compounds.

We earlier reported the preparation of a lithiated compound with a trianion of the type

\[
\begin{align*}
\text{Li} & \quad \left[ \begin{array}{c}
\text{CH}_2 - \text{CH}\_2 - \text{Li} \\
\text{Li} & \quad \left[ \begin{array}{c}
\text{Li} - (\text{CH}_2)\_n - \text{CH} = \text{CH}_2 \\
\text{Li} & \quad \left[ \begin{array}{c}
\text{Li} - (\text{CH}_2)\_2 - \text{CH} = \text{CH}_2 \\
\end{array}\right]
\end{array}\right]
\end{align*}
\]

via Hg/Li transmetallation of the corresponding organomercury compound. In another investigation we obtained 2-lithioalkoxides by lithiation of appropriate chlorohydrins at low temperature. We now describe the direct preparation of 1,4- and 1,5-dilithioalkan-2-yloxydes (shorter: 1,4- and 1,5-dilithio-2-alkoxides) which represent a new type of oxygenated trianions.

When the dichlroalcohols 4a or 4b were allowed to react with butyllithium and then with lithium naphthalenide at low temperature (lithium powder did not effect lithiation, cf. Ref. 2) the trianionic lithiated intermediates 5 were obtained which were chemically characterized by reaction with dimethyl disulfide yielding products 6. However, when the dichlroalcohols 3a or 3b were first treated with ethylmagnesium bromide and the metallation was then performed with lithium powder at room temperature the initially formed trianions 7 underwent spontaneous β-elimination to give the unsaturated organolithium compounds 8. The intermediates 8 then reacted with various electrophiles to give products 9–12.

The dichlroalcohols 3 and 4 are easily prepared from commercially available 3-chloropropanoyl chloride (1a) or 3-chlorobutanoyl chloride (1b) by reaction with diazomethane followed by treatment with hydrogen chloride in ether (Clibbens-Nierenstein reaction) and either reduction of the resultant dichlroalkanones (2a, b) with sodium borohydride (to give 3) or reaction of the dichlroalkanones (2a, b) with allylmagnesium bromide (to give 4).

Table 1. Compounds 6, and 9–12 prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>n</th>
<th>E</th>
<th>( Y )</th>
<th>( X )</th>
<th>( \text{b.p.}^b/\text{torr} )</th>
<th>( \text{Molecular Formula}^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>2</td>
<td>H(_2)C=S=S-CH(_3)</td>
<td>H(_2)C=S-</td>
<td>37</td>
<td>63–65°/0.001</td>
<td>C(<em>8)H(</em>{18})OS(_2) (206.5)</td>
</tr>
<tr>
<td>6b</td>
<td>3</td>
<td>H(_2)C=S=S-CH(_3)</td>
<td>H(_2)C=S-</td>
<td>41</td>
<td>79–81°/0.001</td>
<td>C(<em>{10})H(</em>{22})OS(_2) (220.4)</td>
</tr>
<tr>
<td>9a</td>
<td>3</td>
<td>CO(_2)</td>
<td>CO(_2)</td>
<td>35°</td>
<td>...</td>
<td>b.p. 122°/760 torr</td>
</tr>
<tr>
<td>9b</td>
<td>3</td>
<td>CO(_2)</td>
<td>CO(_2)</td>
<td>40°</td>
<td>...</td>
<td>no data reported in Ref. 7</td>
</tr>
<tr>
<td>10b</td>
<td>3</td>
<td>(H(_2)C(_2))(_2)Cl</td>
<td>(H(_2)C(_2))(_2)Cl</td>
<td>44</td>
<td>...</td>
<td>C(<em>8)H(</em>{18})Si (142.3)</td>
</tr>
<tr>
<td>11b</td>
<td>3</td>
<td>H(_2)C=CH-CH=CH-</td>
<td>H(_2)C=CH-CH=CH-</td>
<td>43</td>
<td>38–41°/0.1</td>
<td>C(<em>8)H(</em>{13})O (142.2)</td>
</tr>
<tr>
<td>12b</td>
<td>3</td>
<td>C(_2)H(_5)-CHO</td>
<td>C(_2)H(_5)-CHO</td>
<td>49</td>
<td>80–83°/0.1</td>
<td>C(<em>{12})H(</em>{17})O (176.4)</td>
</tr>
</tbody>
</table>

* Yield of isolated pure product.

b Distillation interval.

c The microanalyses showed the following maximum deviations from the calculated values: C ± 0.25, H ± 0.35.

d Isolated as the methyl esters.

e Short-path distilled at 0.1 torr at room temperature.
Table 2. I.R.- and N.M.R.-Spectral Data of Compounds 2, 3, 4, 6, and 9-12

<table>
<thead>
<tr>
<th>Compound</th>
<th>I.R.* (neat) ν [cm⁻¹]</th>
<th>¹H.N.M.R. (CCl₄, D₂O capillary)b</th>
<th>δ [ppm]</th>
<th>¹³C-N.M.R. (CCl₄, D₂O capillary)b</th>
<th>δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1770</td>
<td>3.1 (t, 2H, J = 7 Hz, CH₂=CCl)</td>
<td>3.75 (t, 2H, J = 7 Hz, CH₂=CCl)</td>
<td>4.1 (t, 2H, CH₂=CCl)</td>
<td>3.85 (t, 2H, J = 7 Hz, CH₂=CCl)</td>
</tr>
<tr>
<td>2b</td>
<td>1740</td>
<td>1.98-2.25 (m, 2H, CH₂=CCl)</td>
<td>2.8 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
<td>3.6 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
<td>3.6 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
</tr>
<tr>
<td>3a</td>
<td>3460 (OH)</td>
<td>1.95 (q, 2H, J = 7 Hz, CH₂=CCl)</td>
<td>3.4 (s, 1H, OH)</td>
<td>3.45 (t, 2H, J = 6 Hz, CH₂=CH₂)</td>
<td>2.8 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
</tr>
<tr>
<td>3b</td>
<td>3450 (OH)</td>
<td>1.5-2.0 (m, 4H, CH₂=CH₂)</td>
<td>3.5 (s, 1H, OH)</td>
<td>3.5 (t, 2H, J = 6 Hz, CH₂=CH₂)</td>
<td>2.8 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
</tr>
<tr>
<td>4a</td>
<td>3480 (OH)</td>
<td>2.0 (t, 2H, J = 7 Hz, CH₂=CCl)</td>
<td>2.32 (d, 2H, J = 7 Hz, CH₂=CCl)</td>
<td>2.6 (s, 1H, OH)</td>
<td>3.45 (s, 2H, CH₂=CH₂)</td>
</tr>
<tr>
<td>4b</td>
<td>3500 (OH)</td>
<td>1.6-1.9 (m, 4H, CH₂=CH₂)</td>
<td>2.3 (d, 2H, J = 7 Hz, CH₂=CH₂)</td>
<td>2.8 (br.s, 1H, OH)</td>
<td>3.4 (s, 1H, CH₂=CH₂)</td>
</tr>
<tr>
<td>6a</td>
<td>3495 (OH)</td>
<td>1.5-1.85 (m, 2H, CH₂=CH₂)</td>
<td>2.6-2.1 (m, 2H, CH₂=CH₂)</td>
<td>2.6 (s, 1H, OH)</td>
<td>3.45 (s, 2H, CH₂=CH₂)</td>
</tr>
<tr>
<td>6b</td>
<td>3480 (OH)</td>
<td>1.6-2.0 (m, 2H, CH₂=CH₂)</td>
<td>2.25-2.58 (m, 9H, 2×CH₂=CH₂)</td>
<td>1.8-2.3 (m, 4H, CH₂=CH₂)</td>
<td>3.5 (t, 2H, J = 7 Hz, CH₂=CH₂)</td>
</tr>
<tr>
<td>9b</td>
<td>1750 (C=O)</td>
<td>1.9-2.3 (m, 4H, CH₂=CH₂)</td>
<td>3.45 (s, 3H, OCH₃)</td>
<td>4.6-5.1 (m, 2H, H₂C=C)</td>
<td>5.45-5.85 (m, 1H, CH)</td>
</tr>
<tr>
<td>10b</td>
<td>1650 (C=C)</td>
<td>0.05 (s, 9H, 3×OCH₃)</td>
<td>0.5-0.8 (m, 2H, CH₂=CH₂)</td>
<td>1.3-1.8 (m, 2H, CH₂=CH₂)</td>
<td>1.95-2.2 (m, 2H, CH₂=CH₂)</td>
</tr>
<tr>
<td>11b</td>
<td>3490 (OH)</td>
<td>0.8 (d, 3H, J = 6 Hz, 2×CH₃)</td>
<td>1.0-1.75 (m, 5H, CH=CH₂)</td>
<td>1.9-2.1 (m, 2H, CH₂=CH₂)</td>
<td>3.1-3.4 (m, 2H, CHO, OH)</td>
</tr>
<tr>
<td>12b</td>
<td>3440 (OH)</td>
<td>1.3-1.8 (m, 4H, CH₂=CH₂)</td>
<td>1.9-2.1 (m, 2H, CH₂=CH₂)</td>
<td>4.5 (t, 1H, J = 6 Hz, CH₂=CH₂)</td>
<td>4.85-5.1 (m, 2H, H₂C=C)</td>
</tr>
</tbody>
</table>

* Recorded with a Pye Unicam SP-1025 I.R. spectrometer.

b Recorded with a Varian FT-80 spectrometer.

c Isolated as its methyl ester (see footnote d in Table 1)

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Dichloroketones: 2; General Procedure:
A solution of the acyl chloride I (100 mmol) in ether (30 ml) is added to a solution of diazomethane (200 mmol) in ether (300 ml) at -30 °C (bath temperature) under argon. The mixture is allowed to warm to room temperature within 2 h and is then cooled to -30 °C. A solution of hydrogen chloride (200 mmol) in ether is added to the solution and the mixture is stirred for 30 min. The solvent is removed (15 torr) and the residue distilled in vacuo.

1.4-Dichlorobutane (2a); yield: 77%; b p. 38 -41 °C/0.001 torr.
C₉H₁₂Cl₂O calc. C 34.07 H 4.29
(141.0) found 34.1 4.15

1.5-Dichloro-2-pentanone (2b); yield: 82%; b p. 43 -45 °C/0.001 torr.
C₉H₁₄Cl₂O calc. C 38.74 H 5.20
(155.0) found 38.6 5.2
Dichloroalcohols 3; General Procedure:
To a stirred suspension of the dichloroketone 2 (50 mmol) and sodium hydrogen carbonate (4.0 g, 47 mmol) in ethanol (30 ml) and water (30 ml) is added a solution of sodium borohydride (0.94 g, 25 mmol) in water (40 ml) over 30 min. The mixture is then stirred for 2 h, hydrolyzed with sulfuric acid (12 ml) in water (25 ml), and extracted with dichloromethane (6 x 15 ml). The organic layer is washed with water (2 x 15 ml) and dried with sodium sulfate and the solvents are removed (15 torr). The residue is distilled in vacuo.

1.4-Dichloro-2-butanol (3a); yield: 70%; b.p. 79–81 °C/0.1 torr.
C₂H₅Cl₂O  c  c  33.59  H 5.64
(143.0)  found  33.4  5.6

1.5-Dichloro-2-pentanol (3b); yield: 82%; b.p. 84–85 °C/0.1 torr.
C₃H₇Cl₂O  c  c  38.24  H 6.42
(157.0)  found  38.15  6.35

Dichloroalcohols 4; General Procedure:
To a stirred suspension of the dichloroketone 2 (50 mmol) and magnesium bromide etherate (12.9 g, 50 mmol) in ether (50 ml) is added a solution of allylmagnesium bromide in ether (50 mmol) at -60 °C (bath temperature) over a 30 min period. The mixture is allowed to warm to room temperature during 6 h, then hydrolyzed with dilute hydrochloric acid (until neutral pH, and extracted with ether (3 x 15 ml). The organic layer is washed with water (2 x 15 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is distilled in vacuo.

6-Chloro-4-chloromethyl-4-hydroxy-1-hexene (4a); yield: 61%; b.p. 91–93 °C/0.001 torr.
C₆H₇Cl₂O  c  c  45.92  H 6.61
(183.1)  found  45.85  6.75

7-Chloro-4-chloromethyl-4-hydroxy-1-heptene (4b); yield: 64%; b.p. 95–97 °C/0.001 torr.
C₇H₈Cl₂O  c  c  48.75  H 7.16
(197.1)  found  48.7  7.2

4-Hydroxy-o-methylthio-4-methylthiomethyl-1-alkenes (6a, b); General Procedure:
A solution of butyllithium (22 mmol) in ether is added to a stirred solution of the dichloroalcohol 4 (20 mmol) in tetrahydrofuran (30 ml) at -20 °C (bath temperature) under argon. Stirring is continued for 30 min while the mixture is allowed to come to room temperature. The solution is then cooled to -78 °C, a solution of lithium naphthalenide (86 mmol) is added, and stirring is continued at -78 °C for 6 h. Dimethyl disulfide (4.3 ml, 48 mmol) is then added, the mixture stirred for 30 min, hydrolyzed with water, and neutralized with aqueous hydrochloric acid. The resultant mixture is extracted with ether (3 x 15 ml) and the organic layer is washed with water (2 x 15 ml) and dried with sodium sulfate. The solvents and naphthalene are removed at reduced pressure (15 and 0.001 torr) and the residue is distilled at 0.001 torr.

4- or 5-Substituted 1-Alkenes 10,11,12; General Procedure:
To a stirred solution of the dichloroalcohol 3 (20 mmol) in tetrahydrofuran (30 ml) is added a solution of ethylmagnesium bromide in ether (22 mmol) at -20 °C (bath temperature) under argon. The mixture is allowed to warm to 0 °C over ~1 h, then lithium powder (0.77 g, 110 mg-atom) is added and stirring is continued overnight at room temperature. The resultant suspension containing intermediate 8 is filtered, the electrophile E/ (20 mmol) is added to the filtrate, and the solution is stirred for 2 h. The mixture is then hydrolyzed with water (20 ml), neutralized with aqueous hydrochloric acid, and extracted with ether (3 x 15 ml). The organic layer is washed with water (2 x 15 ml), dried with sodium sulfate, and evaporated (15 torr). The residue is distilled or short-path distilled (at room temperature) in vacuo.

Methyl 4-Pentenoate and Methyl 5-Hexanoate (Methyl Esters of 9a and 9b):
The solution of the intermediate 8a or 8b is prepared as described above, cooled to -40 °C, and added with stirring to excess solid carbon dioxide. Stirring is continued for 4 h at -40 °C to -10 °C and the mixture is then hydrolyzed and worked up as above. The residue is treated with diazomethane in ether, excess diazomethane is destroyed by addition of a solution of hydrogen chloride in ether, the solvent evaporated, and the product purified by distillation.

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* Address for correspondence.
3 For β-elimination reactions of organometallic compounds of this type see, for example: Barluenga, J., Yus, M., Concénlon, J.M., Bernad, P., Alvarez, F. J. Chem. Res. [S] 1984, 122; and references cited therein.