

## $\beta$ -Substituted Organolithium Compounds; Direct Preparation and Reactivity

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Very reactive organolithium compounds bearing an alkoxide function at the  $\beta$ -position with respect to the metal are obtained by direct metallation with lithium naphthalenide at low temperature of the corresponding lithium chlorhydrin salt; the reaction of these dianions with different electrophilic agents leads to the corresponding mono- and bi-functionalized compounds.

The preparation of  $\beta$ -functionalized organolithium compounds in which the metal is linked to an  $sp^3$  hybridized carbon atom is greatly hindered by the tendency of these systems to undergo  $\beta$ -elimination leading to the formation of olefins.<sup>1</sup> Recently, compounds (**4**) of this type have been prepared by mercury-lithium transmetallation at low temperature from  $\beta$ -substituted organomercury compounds, and their reactivity with electrophilic reagents has been investigated.<sup>2</sup>

We report here the direct preparation of the organolithium compounds (**4**) bearing an alkoxide function in the  $\beta$ -position with respect to the metal by low-temperature metallation with lithium naphthalenide<sup>3†</sup> of the corresponding compounds (**3**). Thus, treatment of the chlorhydrin (**1**) with *n*-butyllithium at  $-78^\circ\text{C}$  (Method A) and then lithium naphtha-

† The metallation with lithium metal at low temperature failed.

**Table 1.** Formation of the intermediates (**4**) and reaction with electrophiles; preparation of compounds (**5**)

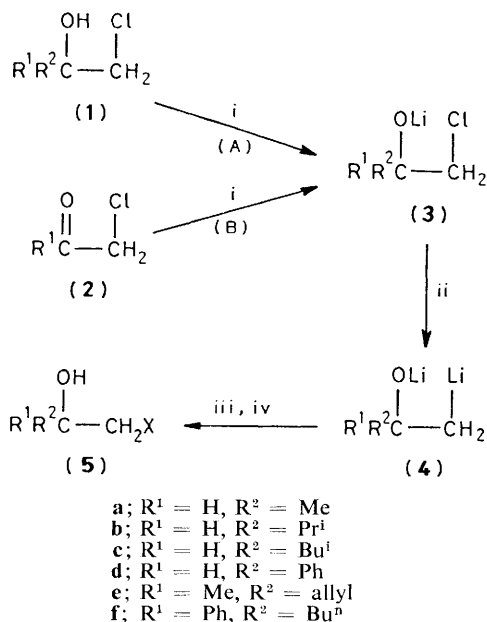
| Entry | Starting compound | Organolithium intermediate | Method         | E <sup>+</sup>                 | Product ( <b>5</b> ) <sup>a</sup> |                      |   |
|-------|-------------------|----------------------------|----------------|--------------------------------|-----------------------------------|----------------------|---|
|       |                   |                            |                |                                | X                                 | % Yield <sup>b</sup> | B.p., T/ $^\circ\text{C}$ (p/mmHg) or m.p., T/ $^\circ\text{C}$ (solvent) |
| 1     | ( <b>1a</b> )     | ( <b>4a</b> )              | A              | Me <sub>2</sub> S <sub>2</sub> | MeS                               | 35                   | 56–59 (15) <sup>c</sup>   |
| 2     | ( <b>1b</b> )     | ( <b>4b</b> )              | A              | D <sub>2</sub> O               | D                                 | 40                   | 110–114 (760)   |
| 3     | ( <b>1c</b> )     | ( <b>4c</b> )              | A              | D <sub>2</sub> O               | D                                 | 51                   | 39–42 (15)  |
| 4     | ( <b>1d</b> )     | ( <b>4d</b> )              | A <sup>d</sup> | D <sub>2</sub> O               | D                                 | 88                   | 51–53 (0.1) <sup>e</sup>  |
| 5     | ( <b>1d</b> )     | ( <b>4d</b> )              | A              | O <sub>2</sub>                 | OH                                | 77                   | 67–69 (hexane) <sup>f</sup>   |
| 6     | ( <b>1d</b> )     | ( <b>4d</b> )              | A              | CO <sub>2</sub>                | CO <sub>2</sub> H <sup>g</sup>    | 22                   | 141–143 (12) <sup>g,h</sup>   |
| 7     | ( <b>1d</b> )     | ( <b>4d</b> )              | A              | Me <sub>2</sub> S <sub>2</sub> | MeS                               | 85                   | 69–73 (0.001) <sup>i</sup>  |
| 8     | ( <b>1d</b> )     | ( <b>4d</b> )              | A              | PhCHO                          | CH(OH)Ph                          | 79                   | 126–128 (hexane-ether) <sup>j</sup>                                       |
| 9     | ( <b>1e</b> )     | ( <b>4e</b> )              | A              | D <sub>2</sub> O               | D                                 | 55                   | 118–121 (760)   |
| 10    | ( <b>2f</b> )     | ( <b>4f</b> )              | B              | D <sub>2</sub> O               | D                                 | 46 <sup>k</sup>      | 54–59 (0.001)   |
| 11    | ( <b>2f</b> )     | ( <b>4f</b> )              | B              | Me <sub>2</sub> CO             | C(OH)Me <sub>2</sub>              | 23 <sup>k</sup>      | 80–85 (0.001)   |

<sup>a</sup> All new compounds exhibited satisfactory spectral and analytical data. <sup>b</sup> Based on compound (**1**). Yields of isolated product have not been optimized. <sup>c</sup> Lit. (M. Hunt and C. S. Marvel, *J. Am. Chem. Soc.*, 1935, **57**, 1691): b.p.  $67^\circ\text{C}$  (20 mmHg). <sup>d</sup> Lithium 1-(di-methylamino)naphthalenide (T. Cohen and J. R. Matz, *Synth. Commun.*, 1980, **10**, 311) was used instead of lithium naphthalenide. <sup>e</sup> Lit. (F. J. Fañanás, Ph.D. Thesis, Oviedo University, 1979): b.p.  $86\text{--}88^\circ\text{C}$  (10 mmHg). <sup>f</sup> Lit. (ref. 5): m.p.  $68\text{--}69^\circ\text{C}$ . <sup>g</sup> Isolated as its methyl ester by treatment of the hydroxy-acid with diazomethane. <sup>h</sup> Lit. (ref. 5): b.p.  $140\text{--}143^\circ\text{C}$  (12 mmHg). <sup>i</sup> Lit. (ref. 2): b.p.  $76\text{--}77^\circ\text{C}$  (0.001 mmHg). <sup>j</sup> Lit. (H. E. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, 1954, **76**, 2285): m.p.  $128\text{--}130^\circ\text{C}$ . <sup>k</sup> Based on compound (**2**).

**Table 2.** Representative n.m.r. data of the products (5).

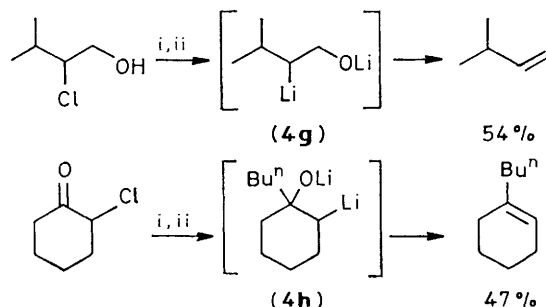
| R <sup>1</sup> | Product (5)<br>R <sup>2</sup> | X   | <sup>1</sup> H N.m.r. (δ) <sup>a</sup>  | <sup>13</sup> C N.m.r. (δ) <sup>a</sup>  |
|----------------|-------------------------------|-----|---|--|
| H              | Me                            | MeS | 1.2 (3H, d, <i>J</i> 6 Hz, C-Me), 2.05 (3H, s, S-Me), 2.3–2.6 (2H, m, CH <sub>2</sub> ), 3.7 (1H, s, OH), 3.8 (1H, m, CH) | 15.71, 22.02, 43.14, 65.64   |
| H              | Pr <sup>i</sup>               | D   | 0.8–1.1 (8H, m, 2 × Me and CH <sub>2</sub> D), 1.25–1.65 (1H, m, Me-CH), 3.0 (1H, s, OH), 3.5 (1H, m, O-CH)               | 17.82, 18.12, 19.57 (t, <i>J</i> <sub>CD</sub> 19.1 Hz, CH <sub>2</sub> D), 34.79, 71.76 |

<sup>a</sup> In CCl<sub>4</sub>-D<sub>2</sub>O capillary, in p.p.m. from SiMe<sub>4</sub>. Recorded with a Varian CFT-80 spectrometer.



**Scheme 1.** Reagents and conditions: i, Bu<sup>n</sup>Li, -78 °C; ii, Li<sup>+</sup>C<sub>10</sub>H<sub>8</sub><sup>-</sup>, -78 °C; iii, E<sup>+</sup> = D<sub>2</sub>O, O<sub>2</sub>, CO<sub>2</sub>, Me<sub>2</sub>S<sub>2</sub>, Me<sub>2</sub>CO, PhCHO; -78 to 20 °C; iv, HCl-H<sub>2</sub>O.

lenide at the same temperature led to the β-functionalized organolithium compounds (4). The reaction can also be carried out starting with the α-chloro-carbonyl compounds (2) by addition of an organolithium compound in the first step of the reaction (Method B). The organolithium intermediates (4) are stable at -78 °C but above -78 °C they decompose via either β-elimination<sup>1</sup> or proton abstraction from the solvent.<sup>4</sup> The reaction of the intermediates (4) with various electrophilic agents (D<sub>2</sub>O, O<sub>2</sub>, CO<sub>2</sub>, Me<sub>2</sub>S<sub>2</sub>, and carbonyl compounds) at -78 °C led to the corresponding mono- and bi-functionalized compounds (5) (see Scheme 1 and Tables 1 and 2).



**Scheme 2.** Reagents and conditions: i, Bu<sup>n</sup>Li, -78 °C; ii, Li<sup>+</sup>C<sub>10</sub>H<sub>8</sub><sup>-</sup>, -100 °C.

When the lithium atom is linked to a secondary carbon atom the corresponding organolithium intermediates (4g) and (4h) are very unstable and decompose at -100 °C by β-elimination yielding the corresponding olefins (see Scheme 2).<sup>1</sup>

The dianion derivatives (4) are highly reactive intermediates acting as synthons for introduction of the HO-C-C group in reactions with electrophiles.

In a typical reaction, an ether solution of n-butyl-lithium (22 mmol) was added to a stirred solution of the chlorohydrin (1) (20 mmol) (Method A) or the α-chloro-ketone (2) (Method B) in tetrahydrofuran (25 ml) at -78 °C under argon. After 15 min a tetrahydrofuran solution of lithium naphthalenide (42 mmol) was added and the mixture stirred for 5 h at -78 °C. The electrophile E<sup>+</sup> (25 mmol)‡ was then added, the mixture stirred for 2 h at -78 °C, and the temperature allowed to rise to 20 °C overnight. The mixture was hydrolysed with water, neutralized with hydrochloric acid, and was extracted with methylene dichloride, and the organic layer was washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed (15 mmHg) and naphthalene was removed by sublimation (0.001 mmHg).§ The residue was distilled or recrystallized (see Table 1). The more volatile products (5) (entries 1–3, and 9) were distilled off before the sublimation of naphthalene (Table 1).

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‡ In the oxidation of (4d), dry oxygen (purity > 99%) precooled at -78 °C was bubbled for 3 h at -78 °C. In the deuterolyses (E = D<sub>2</sub>O) an excess of deuterium oxide (3 ml, 150 mmol) was used.

§ When lithium 1-(dimethylamino) naphthalenide was used (see footnote d in Table 1) the corresponding 1-(dimethylamino)-naphthalene was readily removed by extraction with aqueous hydrochloric acid.