β -Substituted Organolithium Compounds; Direct Preparation and Reactivity

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Very reactive organolithium compounds bearing an alkoxide function at the β -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 β -functionalized organolithium compounds in which the metal is linked to an sp³ hybridized carbon atom is greatly hindered by the tendency of these systems to undergo β -elimination leading to the formation of olefins.¹ Recently, compounds (4) of this type have been prepared by mercury-lithium transmetallation at low temperature from β -substituted organomercury compounds, and their reactivity with electrophilic reagents has been investigated.² We report here the direct preparation of the organolithium compounds (4) bearing an alkoxide function in the β -position with respect to the metal by low-temperature metallation with lithium naphthalenide^{3†} of the corresponding compounds (3). Thus, treatment of the chlorohydrin (1) with n-butyllithium at -78 °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)

					Product (5) ^a		
Entry	Starting compound	Organolithium intermediate	Method	E+	x	% Yield ^b	B.p., $T/^{\circ}C$ ($p/mmHg$) or m.p., $T/^{\circ}C$ (solvent)
1	(1a)	(4 a)	Α	Me ₂ S ₂	MeS	35	56-59 (15)°
2	(1b)	(4b)	Α	$D_{v}O$	D	40	110-114 (760)
3	(1c)	(4c)	Α	$D_{2}O$	D	51	39-42 (15)
4	(1d)	(4d)	Aď	$D_{2}O$	D	88	51-53 (0.1) ^e
5	(1d)	(4d)	Α	\overline{O}_2	OH	77	67-69 (hexane) ^r
6	(1d)	(4d)	Α	CO_2	CO_2H^g	22	$141 - 143 (12)^{g,h}$
7	(1d)	(4 d)	Α	Me_2S_2	MeS	85	69—73 (0.001) ⁱ
8	(1d)	(4d)	Α	PhCHO	CH(OH)Ph	79	126-128 (hexane-ether) ^j
9	(1e)	(4 e)	Α	D_2O	D	55	118-121 (760)
10	(2f)	(4f)	в	$\overline{D_{2}O}$	D	46 ^k	54-59 (0.001)
11	(2f)	(4 f)	В	Me_2CO	$C(OH)Me_2$	23 ^k	80-85 (0.001)

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

Table 2. Repr	esentative	n.m.r. da	ta of the products (5).	
	Product	(5)	¹ Η N.m.r. (δ) ^a	¹³ C N.m.r. (δ) ^a
R1	R^2	X		
Н	Me	MeS	1.2 (3H, d, J 6 Hz, C-Me), 2.05 (3H, s, S-Me), 2.3-2.6 (2H, m, CH ₂), 3.7 (1H, s, OH), 3.8 (1H, m, CH)	15.71, 22.02, 43.14, 65.64
Н	Pr ⁱ	D	0.8–-1.1 (8H, m, 2 × Me and CH_2D), 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, Jсd 19.1 Hz, CH ₂ D), 34.79, 71.76

^a In CCl₄-D₂O capillary, in p.p.m. from SiMe₄. Recorded with a Varian CFT-80 spectrometer.



Scheme 1. Reagents and conditions: i, Bu^nLi , -78 °C; ii, $Li^+C_{10}H_8^-$, -78 °C; iii, $E^+ = D_2O$, O_2 , CO_2 , Me_2S_2 , Me_2CO , PhCHO; -78 to 20 °C; iv, HCl-H₂O.

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 -elimination¹ or proton abstraction from the solvent.⁴ The reaction of the intermediates (4) with various electrophilic agents (D₂O, O₂, CO₂, Me₂S₂, 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, $Bu^{n}Li$, $-78 \,^{\circ}C$; ii, $Li^{+}C_{10}H_{8}^{-}$, $-100 \,^{\circ}C$.

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).¹

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⁺ (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 (Na₂SO₄). 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 = D₂O) 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.