

β -Oxidofunctionalized Organolithium Intermediates from Ketones: A Simple New Access

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Chloromethyl-lithium generated *in situ*, reacts at -78°C with ketones (5) to afford, after lithiation with lithium naphthalenide, β -oxidoalkyl-lithium compounds (1), which on reaction with electrophiles (deuterium oxide, dimethyl disulphide, carbon dioxide, cyclohexanone, and allyl bromide) yield bifunctionalized compounds (6).

β -Oxidofunctionalized organolithium compounds (1) are interesting intermediates in organic synthesis because (a) they are very unstable and decompose by β -elimination yielding alkenes¹ even at low temperatures, and (b) they are appropriate intermediates for the direct synthesis of bifunctionalized organic compounds. Dianions of type (1) have recently been prepared starting from organomercurials (2),² chlorohydrins (3),³ and epoxides (4)⁴ by lithiation at low temperature.

We report here the preparation of intermediates (1) starting from the more readily available ketones (5). Thus, the reaction of ketones (5) with chloromethyl-lithium⁵ (generated

in situ by the reaction of chloriodomethane with methyl-lithium) at -78°C , followed by lithiation with lithium

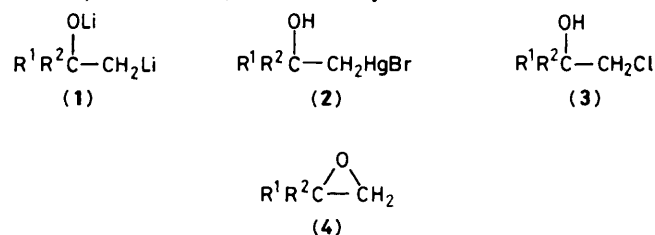
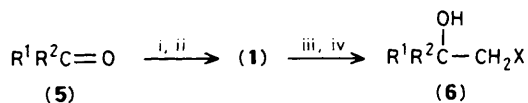


Table 1. Reaction of intermediates (1) or (7) with electrophiles E^+ to give (6) or (8).

Starting ketone	Intermediate	Electrophile	Product (6) or (8)	
			Yield ^a (%)	B.p./ $^\circ\text{C}$ (mmHg) or m.p./ $^\circ\text{C}$ (solvent)
(5a)	(1a)	D_2O	(6a; X = D)	50 55—59(15)
(5b)	(1b)	D_2O	(6b; X = D)	60 37—40(0.1)
(5b)	(1b)	Me_2S_2	(6b; X = MeS)	50 46—50(0.1)
(5c)	(1c)	D_2O	(6c; X = D)	45 ^b 43—46(0.001)
(5d)	(1d)	D_2O	(6d; X = D)	90 78—80(CCl_4) ^c
(5d)	(1d)	Me_2S_2	(6d; X = MeS)	95 85—88(0.001)
(5d)	(1d)	CO_2	(6d; X = CO_2H) ^d	91 96—98 ^{d,e} (CCl_4)
(5d)	(1d)	$[\text{CH}_2]_5\text{C}=\text{O}$	(6d; X = $[\text{CH}_2]_5\text{C}-\text{OH}$)	90 106—108(CCl_4)
(5d)	(1d)	$\text{BrCH}_2\text{CH}=\text{CH}_2$	(6d; X = $\text{CH}_2\text{CH}=\text{CH}_2$)	74 70—73(0.001)
(5e)	(1e)	Me_2S_2	(6e; X = MeS)	60 45—47(0.001)
(5d)	(7d)	Me_2S_2	(8d; X = MeS)	94 77—79(CCl_4)
(5d)	(7d)	CO_2	(8d; X = CO_2H) ^d	72 74—76(0.001) ^d
(5d)	(7d)	$[\text{CH}_2]_5\text{C}=\text{O}$	(8d; X = $[\text{CH}_2]_5\text{C}-\text{OH}$)	73 177—179(CCl_4)

^a Isolated yield based on the starting ketone (5). ^b Lithium 1-dimethylaminonaphthalenide was used instead of lithium naphthalenide. ^c Lit.,⁷ b.p. $89-91^\circ\text{C}$ (0.001 mm Hg). ^d Isolated as the methyl ester by treatment of the hydroxy acid with diazomethane. ^e Lit.,⁷ m.p. $96-100^\circ\text{C}$.



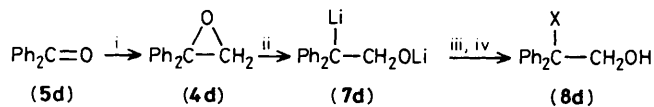
- a; $\text{R}^1, \text{R}^2 = [\text{CH}_2]_4$
 b; $\text{R}^1, \text{R}^2 = [\text{CH}_2]_5$
 c; $\text{R}^1, \text{R}^2 = [\text{CH}_2]_7$
 d; $\text{R}^1 = \text{R}^2 = \text{Ph}$
 e; $\text{R}^1 = \text{Me}, \text{R}^2 = \text{CHMeCH}_2\text{NMe}_2$

Scheme 1. Reagents and conditions: i, ClCH_2Li , -78°C ; ii, $\text{Li}^+\text{C}_{10}\text{H}_8^-$, -78°C ; iii, electrophile = D_2O , Me_2S_2 , CO_2 , $[\text{CH}_2]_5\text{C}=\text{O}$, or $\text{BrCH}_2\text{CH}=\text{CH}_2$, -78 to 20°C ; iv, $\text{HCl}-\text{H}_2\text{O}$.

naphthalenide at the same temperature leads to the corresponding intermediates (1), which on treatment with different electrophiles (deuterium oxide, dimethyl disulphide, carbon dioxide, cyclohexanone, or allyl bromide) afford the expected products (6) (Scheme 1 and Table 1).[†]

When the reaction mixture was allowed to warm to room temperature after the addition of chloromethyl-lithium, the

[†] *Typical procedure:* to a solution of chloriodomethane (11 mmol) and the starting ketone (5) (10 mmol) in tetrahydrofuran (THF) (25 ml) was added a 1 M diethyl ether solution of methyl-lithium (11 mmol) over 15 min at -78°C under argon and the mixture was stirred for 45 min. The reaction mixture was treated with a solution of lithium naphthalenide (44 mmol) in THF (50 ml) at -78°C and stirring was continued for 2 h at the same temperature; the corresponding electrophile (40 mmol) or an excess of anhydrous solid carbon dioxide was then added and the mixture was stirred for 1 h at -78°C , and then allowed to warm to room temperature overnight. The resulting solution was hydrolysed with aqueous HCl, extracted with diethyl ether, and the ethereal layer dried (Na_2SO_4). The solvents were removed (15 mmHg) and the corresponding products (6) isolated after or before sublimation of naphthalene. When lithium 1-dimethylaminonaphthalenide was used [(5c) \rightarrow (6c)] or in the case of (6e) the products were isolated by acidic work-up. In the case of (8d) the reaction mixture was allowed to warm to room temperature *in vacuo* (0.1 mmHg) before treatment with lithium naphthalenide (22 mmol) as above.



Scheme 2. Reagents and conditions: i, ClCH_2Li , -78 to 20°C ; ii, $\text{Li}^+\text{C}_{10}\text{H}_8^-$, -78°C ; iii, electrophile = Me_2S_2 , CO_2 , $[\text{CH}_2]_5\text{C}=\text{O}$, -78 to 20°C ; iv, $\text{HCl}-\text{H}_2\text{O}$.

corresponding epoxide was formed.^{6,7‡} Thus, in the case of the ketone (5d) the *in situ* metallation of the epoxide (4d) with lithium naphthalenide⁴ yields the corresponding intermediate regioisomer (7d), which on treatment with dimethyl disulphide, carbon dioxide, or cyclohexanone affords (8) (Scheme 2 and Table 1).

The method described in this communication provides simple access to intermediates (1) from commercially available ketones (5).

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[‡] Hydrolysis of the reaction mixture after this treatment, in the case of (5d), yielded styrene oxide in 95% yield.