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Masked β-, γ- and δ-lithium ester enolates: useful reagents in organic synthesis[†]

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Abstract—The reaction of ω-chloro orthoesters **1** with lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5% molar) in the presence of different electrophiles [$\mathrm{Bu^tCHO}$, PhCHO, $(CH_2)_5CO$, Et_2CO, PhCOMe, PhCH=NPh, Me_3SiCl] in THF at −78°C leads, after hydrolysis and acid-catalysed methanolysis, to functionalised methyl esters **2**. In the case of chlorotrimethylsilane, hydroxyethyl esters **2′** are isolated. The reaction is also applied to bicyclic orthoesters **3**: whereas β-chloro derivatives and carbonyl compounds gives directly γ-lactones **4** after hydrolysis, the corresponding γ-chloro derivative affords the expected methyl esters after methanolysis. © 2001 Elsevier Science Ltd. All rights reserved.

Normal metal enolates **I** (α-enolates) are important intermediates in synthetic organic chemistry mainly in reactions with carbonyl compounds, which afford aldol-type products having 1,3-functionality.[1] However, higher-order metal enolates **II** (β-, γ-, δ-,… enolates) are far more difficult to use because they have a tendency to decompose spontaneously to give metal cycloalcoholates **III**. Intermediates of the type **II** would be interesting from a synthetic point of view because reacting with carbonyl compounds as electrophiles they could generate 1,4-, 1,5-, 1,6-,… functionality (1,4- and 1,6-difunctionalised compounds being 'umpolung' products[2]), which is not easily available using conventional methodologies. Among different possibilities concerning either the metal or *n* in synthons of the type **II**, lithium derivatives (Met = Li) and homoenolates (β-enolates: $n=1$) are the most studied intermediates described in the literature.[3] In general, the methodologies involving lithium homoenolates use either protected carbonyl compounds[4] or functionalised allyllithium systems[3b] and they are prepared by deprotonation,[3b] chlorine–lithium exchange[4,5] or tin–lithium transmetallation.[6] Very few reports can be found in the literature for γ- or δ-enolates derived from carbonyl compounds, being generated in all cases by chlorine–lithium exchange.[7]

In the last few years we have been using an arene-catalysed lithiation[8–11] for the preparation of very reactive organolithium compounds under very mild reaction conditions: this methodology allowed us to develop new procedures for preparing organolithium compounds from non-halogenated materials,[12] functionalised organolithium compounds[13] from chlorinated materials[14] or heterocyclic precursors,[15] and polylithium synthons.[16] In this paper, we apply the mentioned methodology, arene-catalysed lithiation, for the generation of masked high order (β-, γ- and δ-) ester enolates by chlorine–lithium exchange.

The reaction of compounds **1** with an excess of lithium powder (1:5 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 1:0.1 molar ratio, 5% molar) in the presence of different electrophiles [E = $\mathrm{Bu^tCHO}$, PhCHO, $(CH_2)_5CO$, Et_2CO, PhCOMe, PhCH=NPh, Me_3SiCl] (Barbier-type conditions[17]) in THF at −78°C for 30 min led, after hydrolysis with phosphate buffer (pH ≈ 7) and final *p*-toluenesulfonic

I

II : n = 1, 2, 3, ...

III

Keywords: chlorine–lithium exchange; functionalised esters; γ-lactones; DTBB-catalysed lithiation.

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[†] This paper is warmly dedicated to Professor Rafael Usón on the occasion of his 75th birthday.

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Table 1. Preparation of compounds **2** from chloro orthoesters **1**

Entry	Starting material	Electrophile E	Product **2**[a]				
			No.	*n*	X	Yield (%)[b]	R_f[c]
1	**1a**	$\mathrm{Bu^tCHO}$	**2aa**	3	$\mathrm{Bu^tCHOH}$	58	0.31
2	**1a**	PhCHO	**2ab**	3	PhCHOH	63 (54)[d] (47)[e]	0.20
3	**1a**	$\mathrm{(CH_2)_5CO}$	**2ac**	3	$\mathrm{(CH_2)_5COH}$	59	0.29
4	**1a**	$\mathrm{Et_2CO}$	**2ad**	3	$\mathrm{Et_2COH}$	51	0.24
5	**1a**	PhCOMe	**2ae**	3	PhC(OH)Me	52	0.23
6	**1a**	PhCH=NPh	**2af**	3	PhCHNHPh	57	0.46
7	**1a**	$\mathrm{Me_3SiCl}$	**2′ag**[f]	3	$\mathrm{Me_3Si}$	40	0.25
8	**1b**	$\mathrm{Bu^tCHO}$	**2ba**	4	$\mathrm{Bu^tCHOH}$	62	0.28
9	**1b**	PhCHO	**2bb**	4	PhCHOH	66	0.24
10	**1b**	$\mathrm{(CH_2)_5CO}$	**2bc**	4	$\mathrm{(CH_2)_5COH}$	56	0.25
11	**1b**	$\mathrm{Et_2CO}$	**2bd**	4	$\mathrm{Et_2COH}$	52	0.24
12	**1b**	PhCOMe	**2be**	4	PhC(OH)Me	49	0.18
13	**1b**	PhCH=NPh	**2bf**	4	PhCHNHPh	54	0.49
14	**1b**	$\mathrm{Me_3SiCl}$	**2′bg**[f]	4	$\mathrm{Me_3Si}$	47	0.28

[a] All compounds **2** were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).

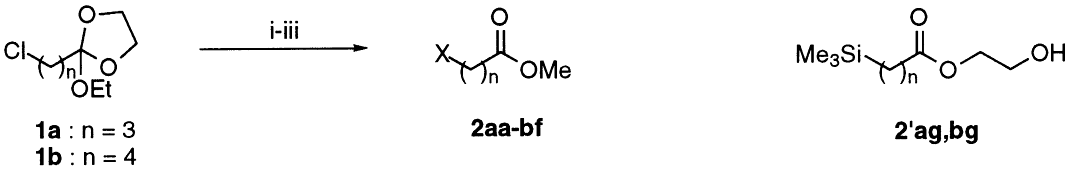
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro orthoester **1**.

[c] Silica gel, hexane/ethyl acetate: 5/1.

[d] Yield corresponding to the reaction at 0°C.

[e] Yield corresponding to the two-step reaction.

[f] The corresponding hydroxyethyl ester **2′** was isolated (see text).

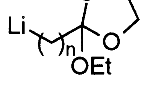


Scheme 1. (i) Li, DTBB (5% molar), E = $\mathrm{Bu^tCHO}$, PhCHO, $\mathrm{(CH_2)_5CO}$, $\mathrm{Et_2CO}$, PhCOMe, PhCH=NPh, $\mathrm{Me_3SiCl}$, THF, −78°C, 30 min; (ii) phosphate buffer (pH≈7), −78 to 20°C, ca. 15 min; (iii) MeOH, PTSA (cat.), 20°C, overnight.

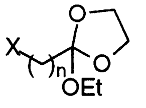
acid (PTSA)-catalysed methanolysis, to the corresponding functionalised methyl esters **2**[18] (Scheme 1 and Table 1). When the same process was carried out at 0°C or in a two-step reaction (Grignard-type conditions), lower yields were obtained (Table 1, entry 2 and footnotes d and e, respectively). On the other hand, a different result was observed when using chlorotrimethylsilane: in this case silylated hydroxyethylesters **2′** were the only reaction products isolated (Table 1, entries 7 and 14, and footnote f).

From a mechanistic point of view, intermediates **IV** and **V** are probably involved in the process before the last tandem hydrolysis–methanolysis treatment. The generation of compounds **2′** can be explained by the anchimeric assistance of the silicon atom in the hydrolysis step through the intermediate **VI**.

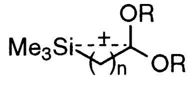
Starting materials **1** were prepared in 70–80% yield from the corresponding ω-chloronitriles by an acid-catalysed methanolysis followed by ketalysation with ethyleneglycol.[19]



IV



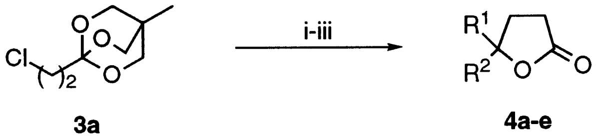
V



VI

The application of the reaction shown in Scheme 1 to the corresponding β-derivatives (**1**, *n* = 2) was not possible because we could not prepare the starting material in a pure form following the same methodology: a ca. 1:1 inseparable mixture of the expected product and the corresponding α,β-unsaturated orthoester (resulting from a dehydrochlorination process) was obtained.

In order to overcome the former problem, the bicyclic orthoester **3a** was prepared and submitted to the same reaction conditions as for compounds **1** [E = $\mathrm{R^1R^2CO}$: $\mathrm{Bu^tCHO}$, PhCHO, $\mathrm{Et_2CO}$, $\mathrm{(CH_2)_5CO}$, PhCOMe]. After controlled hydrolysis and final treatment with a cata-



Scheme 2. (i) Li, DTBB (5% molar), $\mathrm{R^1R^2CO}$ = $\mathrm{Bu^tCHO}$, PhCHO, $\mathrm{(CH_2)_5CO}$, $\mathrm{Et_2CO}$, PhCOMe, THF, −78°C, 30 min; (ii) phosphate buffer (pH≈7), −78 to 20°C, ca. 15 min; (iii) PTSA (cat.), 20°C, overnight.

Table 2. Preparation of compounds **4** from chloro orthoester **3a**

Entry	Carbonyl compound (E)	Product **4**[a]				
		No.	R^1	R^2	Yield (%)[b]	R_f[c]
1	Bu^{t}CHO	**4a**	Bu^t	H	45	0.37
2	PhCHO	**4b**	Ph	H	43 (<5)[d]	0.36
3	$(CH_2)_5CO$	**4c**	$(CH_2)_5$		39	0.48
4	Et_2CO	**4d**	Et	Et	38	0.39
5	PhCOMe	**4e**	Ph	Me	37	0.35

[a] All compounds **2** were ≥96% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).

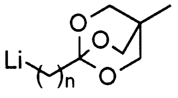
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro orthoester **3a**.

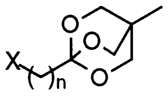
[c] Silica gel, hexane/ethyl acetate: 9/1.

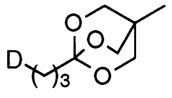
[d] Yield corresponding to the reaction at 0°C.

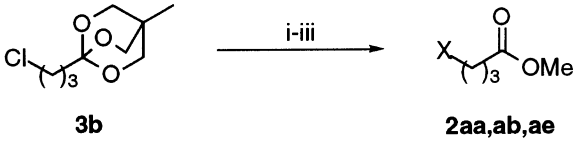
lytic amount of PTSA, the corresponding γ-lactones **4** were obtained (Scheme 2 and Table 3). For compound **3a** it is better not to perform the methanolysis in the last step of the process in order to avoid the generation of a mixture of the lactone **4** and the corresponding methyl ester. In the case of performing the reaction at higher temperature (0°C), lower yields are obtained (Table 2, entry 2 and footnote d).

Of course, the process described in Scheme 2 can be applied to the corresponding γ-derivatives. Thus, when compound **3b** was allowed to react under the conditions shown in Scheme 1, but at 0°C, the expected compounds **2** were isolated (Scheme 3 and Table 3). In this case, the reaction at lower temperature (−78°C) afforded poorer yield (Table 3, entry 2 and footnote d). The participation of intermediates **VII** and **VIII** was demonstrated by performing the corresponding deuterolysis with deuterium oxide instead of the hydrolysis: deuterated compound **5** was isolated in 87% yield and 85% deuterium incorporation.


VII


VIII


5



Scheme 3. (i) Li, DTBB (5% molar), E = Bu^{t}CHO, PhCHO, PhCOMe, THF, 0°C, 30 min; (ii) phosphate buffer (pH ≈ 7), 0 to 20°C, ca. 15 min; (iii) MeOH, PTSA (cat.), 20°C, overnight.

Starting materials **3** were prepared by successive treatment of the corresponding ω-chloro acyl chlorides with 3-hydroxymethyl-3-methyloxetane and boron trifluoride etherate.[20]

Finally, we can conclude that the methodology described in this paper is a reasonable entry to β-, γ-, and δ-lithio carboxylic acid synthons by DTBB-catalysed chlorine–lithium exchange. The reaction of these intermediates with different electrophiles, mainly carbonyl compounds, allows the remote functionalisation of carboxylic acids.

Table 3. Preparation of compounds **2** from chloro orthoester **3b**

Entry	Carbonyl compound (E)	Product **2**[a]			
		No.	X	Yield (%)[b]	R_f[c]
1	Bu^{t}CHO	**2aa**	Bu^{t}CHOH	38	0.31
2	PhCHO	**2ab**	PhCHOH	41 (30)[d] (37)[e]	0.20
3	PhCOMe	**2ae**	PhC(OH)Me	37	0.23

[a] All compounds **2** were ≥95% pure (GLC and/or 300 MHz ^{1}H NMR) and were fully characterised by spectroscopic means (IR, ^{1}H and ^{13}C NMR, and MS).

[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloro orthoester **3b**.

[c] Silica gel, hexane/ethyl acetate: 5/1.

[d] Yield corresponding to the reaction at −78°C.

[e] Yield corresponding to the two-step process.

Acknowledgements

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18. *General procedure for compounds* **2**: To a dark green suspension of lithium powder (ca. 70 mg, 10 mmol) and DTBB (53 mg, 0.2 mmol, 5% molar) in THF (10 ml) was slowly added (ca. 1 h) a solution of the orthoester **1** (2 mmol) and the corresponding electrophile (2.2 mmol) in THF (3 ml) at −78°C. After stirring for an additional 30 min, the reaction mixture was hydrolysed with a phosphate buffer solution ($\mathrm{pH} \approx 7$, 10 ml) and extracted with ethyl acetate (3×10 ml). The organic phase was successively washed with brine (10 ml) and water (10 ml) and dried with Na_2SO_4. After evaporation of the solvents (15 Torr), the resulting residue was dissolved in dry methanol (20 ml). The resulting solution was treated with PTSA (10 mg) and stirred at room temperature overnight. After adding water (20 ml), the resulting mixture was extracted with ether (5×10 ml), the organic layer successively washed with 0.1 M NaOH (2×10 ml) and water (10 ml) and dried ($MgSO_4$). Evaporation of the solvents (15 Torr) gave a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate) to yield the pure title compounds **2**.
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