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LETTERS

Lithium- α-lithioacetate and β-lithiopropionate: useful intermediates in organic synthesis

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Abstract

The reaction of chloroacetic acid and 3-chloropropionic acid with a base (LDA or Bu^nLi, respectively) and then with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5%) in the presence of different electrophiles [Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe] in THF at −78°C leads, after hydrolysis with water, to the expected hydroxy acids, which in the second case are directly cyclised under acidic conditions to give the expected γ-lactones. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: chlorine/lithium exchange; β-hydroxy acids; γ-lactones; DTBB-catalysed lithiation.

Dianions[1] derived from carboxylic acids (**I**, **II**) are interesting intermediates in synthetic organic chemistry because they are able to transfer the carboxylic acid functionality in only one reaction step by reaction with electrophiles. In the case of the α-derivatives, the so-called carboxylate enolates (**I**),[2] they have been prepared by double deprotonation using strong and hindered bases (in order to minimise their nucleophilic character). However, to the best of our knowledge, from the examples described in the literature the simplest acetic acid dianion is rare, its reaction with *n*-butyl bromide,[3] ethyl chloroformiate[4] and some aromatic aldehydes[5] being the only reactions described so far: this fact is probably due to the low solubility of this dianion in common organic solvents.[6] Concerning β-enolates (**II**), also called carboxylate homoenolates,[7,8] the corresponding deprotonation works only if a stabilising group is present at the β-position or when it is at an allylic[9] or benzylic position.[10] Other alternatives to the deprotonation reaction, which are useful for normal carboxylates such as the simple propionate, are tin/lithium transmetallation[11] and bromine/lithium exchange.[12] On the other hand, in the last few years we have been using an arene-catalysed lithiation[13–16] for the generation of: (a) organolithium reagents from non-halogenated precursors;[17] (b) functionalised organolithium compounds[18] from chlorinated materials,[19a] phenyl ethers[19b] or thioethers,[19c] or heterocyclic compounds;[19d,e] and (c) polylithium synthons[20]

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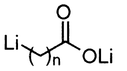
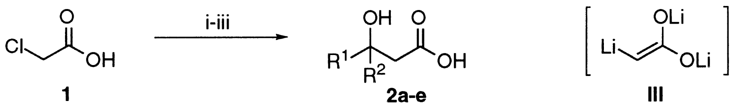
from polychlorinated precursors. In this paper we report the application of the arene-catalysed lithiation to the generation of lithium α- and β-lithio carboxylates by chlorine/lithium exchange and their reaction with electrophiles.

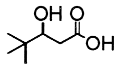
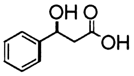
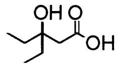
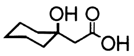
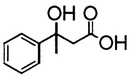

I: n = 1
II: n = 2

The reaction of chloroacetic acid (**1**) with lithium diisopropylamide (LDA, 1:2 molar ratio) in THF at −78°C for 30 min, followed by treatment of the resulting mixture with a green suspension of an excess of lithium powder (1:10 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5 mol%) and the corresponding electrophile [Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe][21] at the same temperature for 1 h led, after final hydrolysis with water, to the formation of the expected β-hydroxy acids **2a**–**e** (Scheme 1 and Table 1). From a mechanistic point of view, intermediate **III** (resulting from a double deprotonation of the acid **1** followed by chlorine/lithium exchange) is probably involved in the process. The reaction has to be performed



Scheme 1. (i) 2 LDA, THF, −78°C; (ii) Li, DTBB cat. (5 mol%), R^1R^2CO=Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, −78°C; (iii) H_2O, −78 to 20°C

Table 1
Preparation of hydroxy acids **2**

Entry	Carbonyl compound	Product **2**[a]			
		Structure	No.	Yield (%)[b]	R_f[c]
1	Bu^{t}CHO		**2a**	52	0.32
2	PhCHO		**2b**	65 (36)[d]	0.25
3	Et_2CO		**2c**	50	0.34
4	$(CH_2)_5CO$		**2d**	46	0.31
5	PhCOMe		**2e**	63	0.26

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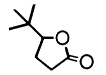
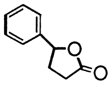
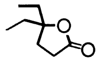
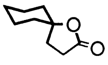
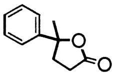
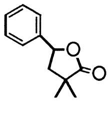
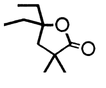
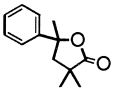
[a] All compounds **2** were ≥95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Isolated yield after column chromatography (neutral silica gel, hexane/ethyl acetate) based on the starting chloroacid **1**. [c] Silica gel, hexane/ethyl acetate: 3/1. [d] Yield corresponding to the step by step reaction.

in the presence of the electrophile (Barbier-type conditions)[21] in order to get the higher yields (Table 1, entry 2 and footnote d). As a comparison with the stoichiometric version of the lithiation, when it was carried out using lithium-naphthalene[22] under Barbier-type conditions and with benzaldehyde as electrophile, only decomposition products were detected.

β-Hydroxy acids **2** are interesting starting materials for the formation of β-lactones by intramolecular dehydration.[23,24] As an example of this transformation, compound **2c** was treated with benzenesulfonyl chloride (1:2 molar ratio) in dry pyridine at 0°C overnight yielding, after hydrolysis with water at the same temperature, the expected 3,3-diethyl-β-propiolactone in 67% isolated yield.

In the second part of this study we lithiated in situ generated lithium 3-chloropropionate (derived from compound **3a**) under catalytic conditions (DTBB, 5% molar) and in the presence of different carbonyl compounds [Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe] in THF at –78°C to give, after hydrolysis with water and treatment of the crude reaction product with a catalytic amount of *p*-toluenesulfonic acid (10% molar) under benzene reflux (Dean–Stark), the expected γ-butyrolactones **4aa–ae** (Scheme 2 and Table 2, entries 1–5). The last treatment is

Table 2
Preparation of γ-lactones **4**

Entry	Starting chloroacid	Carbonyl compound	Product **4**[a] Structure	No.	Yield (%)[b]	R_f[c]
1	**3a**	Bu^{t}CHO		**4aa**	52	0.37
2	**3a**	PhCHO		**4ab**	61 (20)[d](43)[e]	0.36
3	**3a**	Et_2CO		**4ac**	42	0.39
4	**3a**	$(CH_2)_5CO$		**4ad**	38	0.48
5	**3a**	PhCOMe		**4ae**	46	0.35
6	**3b**	PhCHO		**4bb**	69	0.34
7	**3b**	Et_2CO		**4bc**	46	0.41
8	**3b**	PhCOMe		**4bd**	51	0.32

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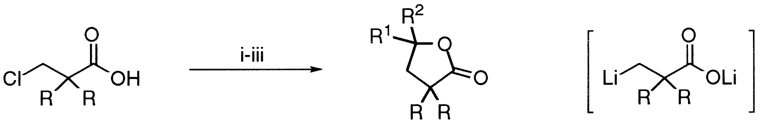
[a] All compounds **4** were ≥95% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and MS). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroacid **3**. [c] Silica gel, hexane/ethyl acetate: 9/1. [d] Yield corresponding to the step by step reaction. [e] Naphthalene was used as the electron transfer catalyst.



3a: R = H
3b: R = Me

4aa-bd

IV

Scheme 2. (i) Bu^{n}Li, Li, DTBB (5 mol%), R^1R^2CO=Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, THF, −78°C; (ii) H_2O, −78 to 20°C; (iii) *p*-TSA (10 mol%), PhH reflux

convenient in order to purify the mixture of the lactone **4** and the corresponding γ-hydroxy acid obtained at the end of the reaction. Intermediate **IV** probably takes part in the reaction shown in Scheme 2. On the other hand, DTBB is shown to be a better electron transfer reagent than naphthalene (Table 2, entry 2 and footnote e).

In order to see if the reaction could work better in the absence of hydrogen atoms at the α-position in the starting 3-chloropropionic acid we applied the protocol shown in Scheme 2 to the corresponding α,α-dimethyl derivative **3b**. As can be seen in Table 2 (entries 6–8), the yields of isolated lactones are comparable in both cases, so we can conclude that there is no influence of the mentioned α-protons.

From the results described here we conclude that this methodology allows to accede to β-hydroxy acids (easily transformed into the corresponding β-lactones) or directly to γ-lactones. In both cases this is a simple and new way for these types of compounds, which are important units in many naturally occurring compounds.

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