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N-(Chloromethyloxycarbonyl)pyrrolidine as a Source of the HOCH$_2^-$ Synthon

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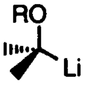
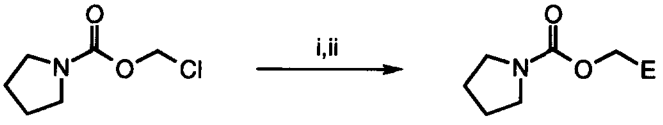
Abstract: The reaction of *N*-(chloromethyloxycarbonyl)pyrrolidine (**1**) with lithium powder and a catalytic amount of DTBB (2.5 mol %) in the presence of different electrophiles [Me_3SiCl, Bu^{i}CHO, Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Ph_2CO] in THF at -78°C leads, after hydrolysis with water, to the expected functionalised carbamates **2**. Deprotection of the acetophenone derivative **2g** with DIBALH at THF reflux yields, after hydrolysis, the corresponding 1,2-diol **3g**.

α-Oxygenated organolithium compounds (**I**),[1] which can be considered as d^1-reagents following Seebach's nomenclature,[2] are interesting functionalised carbanion intermediates[3] in synthetic organic chemistry due to their ability to transfer an oxygenated functionality to an electrophilic reagent, so making possible the direct preparation of polyfunctionalised molecules. The generation of the corresponding alkyl derivatives (**I** with R=alkyl: α-alkoxy carbanionic synthons of the type RO-C$^-$) can be carried out by (1) tin-lithium transmetallation with *n*-butyllithium,[4] (2) sulfur-lithium exchange using activated lithium (*eg*. lithium naphthalene),[5] (3) direct deprotonation in special cases (alkyl benzyl ethers,[6a] *tert*-butyl methyl ether[6b]) using a coreagent (TMEDA or potassium *tert*-butoxide) together with *sec*-butyllithium, or (4) a chlorine-lithium exchange[7] using lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB).[8] However, in the case of the corresponding alcohol derivatives [**I** with R=H (Met) or COX: α-hydroxy carbanionic synthons of the type HO-C$^-$], they can be prepared, to our best knowledge, following the routes (1)[9] and (3),[10] using in the last case either very hindered aryl esters[10a] or *O*-benzylic carbamates.[10b,c,11] In this paper we describe for the first time the transformation of *O*-chloromethyl carbamate into the corresponding lithiated species and its *in situ* trapping by different electrophiles.



I

The reaction of *O*-chloroethyl carbamate **1** [easily prepared by reaction of pyrrolidine and chloromethyl chloroformate in the presence of pyridine (>95%)] with an excess of lithium powder (1:7 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 1:0.05 molar ratio; 2.5 mol %) in the presence of different electrophiles [Me_3SiCl, Bu^iCHO, Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Ph_2CO][12] in THF at temperatures ranging between -78 and -60°C[13] for 2 h led, after hydrolysis with water, to the corresponding reaction products **2** (Scheme 1 and Table 1).



1 **2**

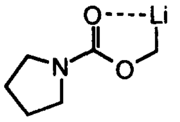
Scheme 1. *Reagents and conditions*: i, Li powder, DTBB cat. (2.5 mol %), E^+=Me_3SiCl, Bu^iCHO, Bu^tCHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, Ph_2CO, THF, -78 to -60°C, 2 h; ii, H_2O, -78 to 20°C.

Table 1. Preparation of Compounds **2**

Entry	Electrophile E^+	Compound **2**[a]			
		No.	E	Yield (%)[b]	R_f[c]
1	Me_3SiCl	**2a**	Me_3Si	81	0.68
2	Bu^iCHO	**2b**	Bu^iCHOH	68	0.32
3	Bu^tCHO	**2c**	Bu^tCHOH	63	0.44
4	PhCHO	**2d**	PhCHOH	72	0.48
5	Et_2CO	**2e**	Et_2COH	80	0.36
6	$(CH_2)_5CO$	**2f**	$(CH_2)_5COH$	73	0.24
7	PhCOMe	**2g**	PhC(OH)Me	64	0.36
8	Ph_2CO	**2h**	Ph_2COH	72	0.48

[a] All products were ≥96% pure (GLC and/or 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and mass spectra). [b] Isolated yield after column chromatography [neutral alumina (Florisil®) for compounds **2a** and **2d**), hexane/ethyl acetate] based on the starting material **1**. [c] Silica gel, hexane/ethyl acetate: 1/1.

It is important to perform the reaction shown in Scheme 1 under Barbier-type reaction conditions[12] in order to avoid decomposition of the corresponding intermediate **II** even at low temperature. This intermediate, which could decompose either by nucleophilic addition of the carbanionic carbon atom to the carbonyl group of the amide moiety, or by reaction with the excess of lithium, is stabilised by intramolecular coordination of the carbonylic oxygen with the lithium atom (CIPE effect[14]); intermediate **II** reacts mainly with the electrophile present in the reaction medium, avoiding so its destruction.



II

Finally, we studied the deprotection of functionalised carbamates **2**. As an example, the treatment of compound **2g** with DIBALH under THF reflux[10b] during 6 h led, after hydrolysis with water, to the expected 1,2-diol **3g**[15] in 96% yield[16] (Scheme 2). This is a clear demonstration of the real synthetic role of intermediate **II** for the introduction of the $HOCH_2^-$ unit to an electrophile, in this case acetophenone.

2g **3g**

Scheme 2. *Reagents and conditions*: i, DIBALH, THF reflux, 6 h; ii, H_2O.

As a conclusion, we have shown in this paper a new, simple and versatile methodology which allows the preparation of a synthetic equivalent of *C*-lithiated methanol and its *in situ* trapping with electrophiles. Work is under way in order to study the synthetic scope of this methodology.

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15. $R_f = 0.35$ (silica gel, hexane/ethyl acetate: 1/1).
16. In other examples for the transformation **2**→**3** carried out in our laboratory we obtained yields better than 90%. These results are in good agreement with the literature data (ref 10b).

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