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O-tert-Butyl-*N*-(chloromethyl)-*N*-methyl Carbamate as a Source of the $MeNHCH_2^-$ Synthon

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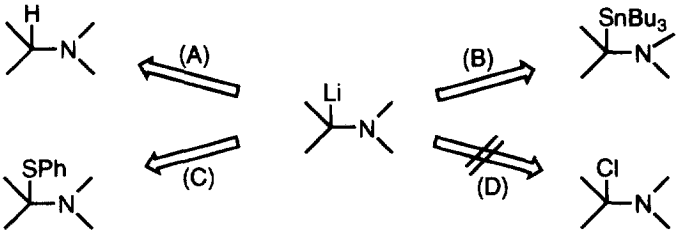
Abstract: The reaction of *O-tert*-butyl-*N*-(chloromethyl)-*N*-methyl carbamate (**1**) with lithium powder and a catalytic amount of DTBB (2.5 mol %) in the presence of different electrophiles [Me_3SiCl, Bu^iCHO, Bu^tCHO, PhCHO, $(CH_2)_4CO$, Et_2CO, PhCOMe, Ph_2CO] in THF at -78°C leads, after hydrolysis with water, to the expected functionalised carbamates **2**. As an example, the hydrolysis of compound **2e** with hydrogen chloride affords easy deprotection of the amine functionality yielding the corresponding 1,2-aminoalcohol **3e**. Copyright © 1996 Elsevier Science Ltd

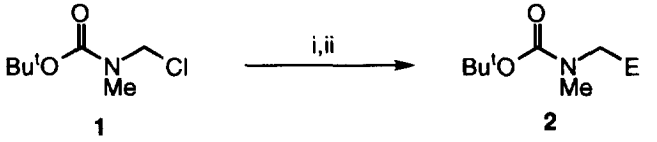
The introduction of the aminomethyl moiety in an organic structure can be performed by the 'normal' strategy, consisting in the reaction of an imine (activated or not) with a nucleophile -usually a Grignard reagent- or the 'umpolung'[1] version, condensing a α-nitrogenated carbanion with an electrophile. This second choice is particularly interesting when carbon dioxide, or its derivatives, are used as electrophilic components, as α-aminoacids are directly obtained.[2]

α-Aminated organolithium compounds[3] have been generated following three different strategies: (a) α-deprotonation of activated amine derivatives (Method A), which is the most used method;[4] (b) tin-lithium transmetallation from α-aminated organostannanes (Method B);[5] and (c) sulfur-lithium exchange from α-aminated phenyl thioethers (Method C).[6] To the best of our knowledge the other possible route, chlorine-lithium exchange (Method D: the most useful method for the obtention of organolithium compounds[7]) has not been used until now for the generation of this type of d^1-reagents[1] (Scheme 1). In this paper we apply the arene-catalysed lithiation of chlorinated precursors[8] to the preparation of a α-functionalised organolithium compound[9] by chlorine-lithium exchange and report its *in situ* reaction with electrophilic reagents under Barbier-type reaction conditions.[10,11]



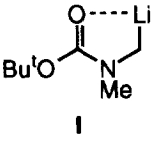
Scheme 1.

Treatment of *O-tert*-butyl-*N*-(chloromethyl)-*N*-methyl carbamate (**1**)[12] 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 an electrophile [Me_3SiCl, Bu^iCHO, Bu^tCHO, PhCHO, $(CH_2)_4CO$, Et_2CO, PhCOMe, Ph_2CO] in THF at -78°C led, after 2 h and subsequent hydrolysis with water, to the expected functionalised carbamates **2** (Scheme 2 and Table 1).



Scheme 2. *Reagents and conditions*: i, Li, DTBB cat. (2.5 mol %), E+ = Me_3SiCl, Bu^iCHO, Bu^tCHO, PhCHO, $(CH_2)_4CO$, Et_2CO, PhCOMe, Ph_2CO, THF, -78°C, 2 h; ii, H_2O.

The reaction has to be carried out at low temperature and under Barbier-type reaction conditions[10] in order to avoid decomposition of the *in situ* generated *N*-lithiomethyl carbamate intermediate **I**: under the reaction conditions assayed it prefers to react with the electrophile present in the reaction medium better than to react intra or intermolecularly with the carbamate moiety present in its structure.



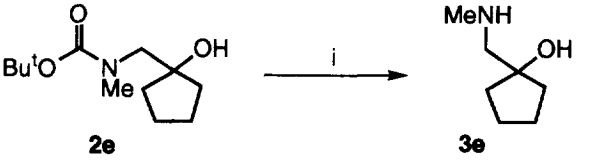
I

Finally, and in order to prove the validity of our methodology to introduce the unity $MeNHCH_2^-$ in an electrophilic reagent, we studied the deprotection of compounds **2**. Thus, as an example, when compound **2e** was hydrolysed with a saturated solution of hydrogen chloride in ethyl acetate at room temperature for 30 min, the expected 1,2-aminoalcohol **3e**[13] was isolated in 98% yield[14] (Scheme 3).

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	69	0.81
2	Bu^iCHO	**2b**	Bu^iCHOH	65	0.36
3	Bu^tCHO	**2c**	Bu^tCHOH	65	0.45
4	PhCHO	**2d**	PhCHOH	64	0.30
5	$(CH_2)_4CO$	**2e**	$(CH_2)_4COH$	40	0.27
6	Et_2CO	**2f**	Et_2COH	53	0.43
7	PhCOMe	**2g**	PhC(OH)Me	82	0.41
8	Ph_2CO	**2h**	Ph_2COH	74	0.68

[a] All products were ≥95% 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 **2b**), hexane/ethyl acetate] based on the starting material **1**. [c] Silica gel, pentane/ethyl acetate: 4/1.



2e **3e**

Scheme 3. *Reagents and conditions*: i, AcOEt-HCl sat., 20°C, 30 min.

As a conclusion, we have shown in this paper a new methodology which allows the easy *in situ* generation of a α-aminated organolithium intermediate and its reaction with electrophiles, mainly carbonyl compounds, giving 1,2-aminoalcohols after deprotection.

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13. $R_f = 0.75$ (silica gel, pentane/ethyl acetate: 1/4).
14 In other examples for the transformation **2**→**3** carried out in our laboratory we obtained yields better than 90%.

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