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Carbamoyl and Thiocarbamoyl Lithium: A New Route by Naphthalene-Catalysed Chlorine-Lithium Exchange

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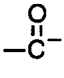
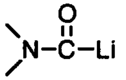
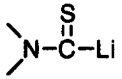
Abstract: **The reaction of *N,N*-diisopropylcarbamoyl or *N,N*-dimethylthiocarbamoyl chloride (1a or 1b) with an excess of lithium powder and a catalytic amount of naphthalene (3 mol %) in the presence of a carbonyl compound 2 at temperatures ranging between -78 and 20°C, under Barbier-type conditions leads, after hydrolysis with water, to the corresponding α-hydroxy amides or thioamides 3, respectively.**

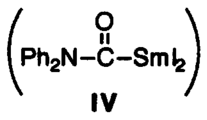
Acyl anions **I**[1] having umpolung reactivity[2] are interesting intermediates in order to introduce the acyl group in an electrophilic reagent. Consequently many different synthons of this unity have been developed[1]. The corresponding carbamoyl lithiated species of the type **II** have been prepared at low temperatures by three different methods: (a) carbonylation of lithium amides[3]; (b) direct deprotonation of the corresponding formamides[4]; (c) mercury-lithium transmetallation from the corresponding biscarbamoylmercury compounds[5]. In the case of the sulphur analogous, the thiocarbamoyl species of the type **III**, they have been prepared using the method (b) starting from the adequate thioformamides[6]. To the best of our knowledge, the samarium intermediate **IV** is the only carbamoyl derivative postulated as intermediate in a process *which starts from a carbamoyl chloride*[7]. In this paper we report a general method for the preparation of intermediates of the type **II** and **III** starting from the corresponding chlorides by a naphthalene-catalysed[8] lithiation at low temperature[9].


$-\overset{O}{\overset{\|}{C}}^{-}$

I

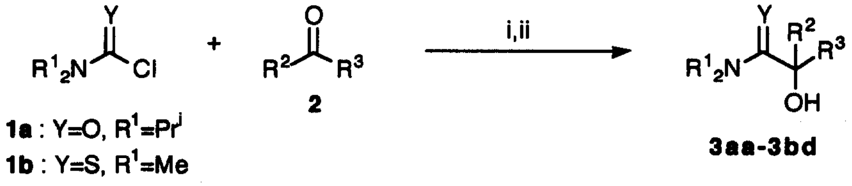

II


III


$\left(Ph_2N-\overset{O}{\overset{\|}{C}}-SmI_2\right)$

IV

The reaction of a green suspension of a carbonyl compound **2** (1:1.2 molar ratio[10]), lithium powder (1:5.8 molar ratio[10]) and naphthalene (1:0.06 molar ratio; 3 mol %) with commercially available *N,N*-diisopropylcarbamoyl chloride **1a** in tetrahydrofuran at temperatures ranging between -78 and 20°C led, after hydrolysis with water, to the corresponding products **3aa-3ad** (Scheme 1 and Table 1, entries 1-4). The same reaction starting from *N,N*-dimethylthiocarbamoyl chloride, also commercially available, yielded the expected products **3ba-3bd** (Table 1, entries 5-8).



Scheme 1. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (*ca.* 3 mol %), THF, -78 to 20°C (see text); ii, H_2O.

The Barbier-type reaction shown in Scheme 1 can be alternatively carried out in a two-steps process, preparing first the corresponding solution of the intermediate of the type **II** at low temperature. In this case we observed poorer yields, probably due to a partial decomposition of the carbamoyllithium intermediate. As an example, the catalytic lithiation of starting material **1a** in absence of a carbonyl compound for 30 min at -78°C[11] followed by treatment with benzaldehyde and worked up as above, yielded the expected product **3ab** in only 42% isolated yield (compare to Table 1, entry 2). On the other hand, the described Barbier-type reaction for **3ab** performed at 0°C and using di-*tert*-butylbiphenyl as catalyst[8e,f,12] afforded only 30% isolated yield: under these reaction conditions the intermediate of the type **II** suffers partial decomposition before reacting with the carbonyl compound present in the reaction media.

From the results described in this paper we conclude that this methodology represents a new, easy and useful alternative route for carbamoyl and thiocarbamoyl lithium reagents of the type **II** and **III**, starting from commercially available materials.

In a *typical reaction*: To a suspension of lithium (100 mg, 14 mmol; 1:5.8 molar ratio[10]), the corresponding carbonyl compound (3.0 mmol) and naphthalene (20 mg, 0.16 mmol; 1:0.06 molar ratio[10], *ca.* 3 mol %) in tetrahydrofuran (5 ml) was added a mixture of the chlorinated precursor **1** (2.5 mmol) in tetrahydrofuran (10 ml) at -78°C under an argon atmosphere. The reaction mixture was stirred for *ca.* 45 min at the same temperature until the typical green colour of lithium naphthalenide appeared. Then the temperature was allowed to rise to 0°C (*ca.* 1 h) and the resulting mixture was hydrolysed with water (20 ml), neutralysed with 2 N hydrochloric acid and extracted with ethyl acetate (3x20 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to afford the corresponding compounds **3**.

Acknowledgements

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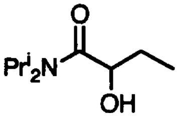
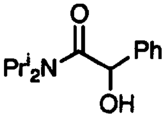
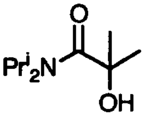
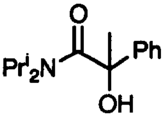
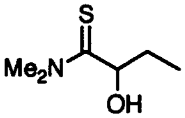
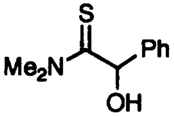
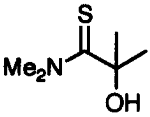
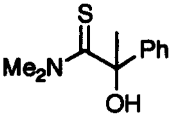
Table 1. Preparation of Hydroxy Amides and Thioamides **3**

Entry	Starting amide **1**	Carbonyl Compound **2** R2	R3	Product **3**[a] no.	structure	yield (%)[b]	mp (°C)[c] or R_f[d]
1	**1a**	Et	H	**3aa**		71	0. 51[4e]
2	**1a**	Ph	H	**3ab**		79	94-96[4e]
3	**1a**	Me	Me	**3ac**		62	81-83[4e]
4	**1a**	Ph	Me	**3ad**		79	118-120[13]
5	**1b**	Et	H	**3ba**		83	0.51[6a]
6	**1b**	Ph	H	**3bb**		70	94-96[6a]
7	**1b**	Me	Me	**3bc**		84	0.47[6a]
8	**1b**	Ph	Me	**3bd**		40	0.47[e,6a]

[a] All compounds **3** were >95% pure and were characterised by analytical (for **3ad**) and spectroscopic methods (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on starting material **1**. [c] Hexane/ethyl acetate. [d] Hexane/ethyl acetate: 3/2. [e] Hexane/ethyl acetate: 4/1.

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10. Molar ratio based on the chlorinated precursor **1**.
11. After this time the starting material **1a** desapeared (GLC).
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13. ν_{max} (melted) 3360 (OH), 3040 (Ph) and 1610 (C=O); δ_H ($CDCl_3$) 0.46, 1.01 (2x3 H, 2 d, *J*=6.6 Hz, 2xCH_3CH), 1.44 (6 H, d, *J*=6.9 Hz, 2xCH_3CH), 1.78 (3 H, s, CH_3CO), 3.31, 3.75 (2x1 H, 2 septets, *J*=6.9 and 6.6 Hz, respectively, 2xCHN), 5.77 (1 H, s, OH) and 7.20-7.40 (5 H, m, Ph); δ_C 18.3, 19.75, 19.9, 20.1, 24.15, 46.65, 48.9, 74.2, 125.45 (2xC), 127.45, 128.5 (2xC), 143.4 and 173.65; *m/z* 221 (M^+-28, <1%), 121 (20), 86 (40), 77 (11), 43 (100) and 41 (15) (Anal. calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.0; H, 9.2; N, 5.3).

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