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Nucleophilic Properties of Butyllithium versus Free Carboxylic Acids

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Abstract: In opposition to the generally accepted idea, butyl lithium is not only a deprotonating agent for free carboxylic acids, but can also act as a nucleophile on the carbon oxygen double bond.

It has been known for a long time that alkyl lithium reagents exhibit nucleophilic and basic properties at the same time.[1] When added in a 1:1 stoichiometry to a free carboxylic acid functionnality, they are considered generally to behave only as bases, with the result of producing the lithium carboxylate. In this note we wish to demonstrate that this commonly accepted idea needs a correction and that a free carboxylic acid can undergo a nucleophilic attack on its carbonyl group before deprotonation. This demonstration could be obtained by analysis of the reaction of excess benzoic acid (5 mmol in 5 mL of tetrahydrofurane (THF)) with n-butyllithium (1 mmol of a commercial salt free 1,06M solution in hexanes). The complex evolution of the system can be represented schematically in Fig. 1. With the relative amounts of the reagents engaged, a fast deprotonation would lead through the basic pathway, only to the lithium salt 3.

Experimentally we observed that 18% of n-butyl lithium has been used in the nucleophilic pathway, leading to the formation of 5% of ketone 6 and 6% of alcohol 7, the yields being calculated with respect to the initial organolithium reagent. Control experiments have shown that the latter adds to the carboxylate 3 with a relatively slow rate in comparison to the other reactions, and we can consider that the bis-lithium alkoxide 5 is virtually absent from the reaction mixture. Table 1 summarises the influence of several parameters in the evolution of this system.

Fig. 1

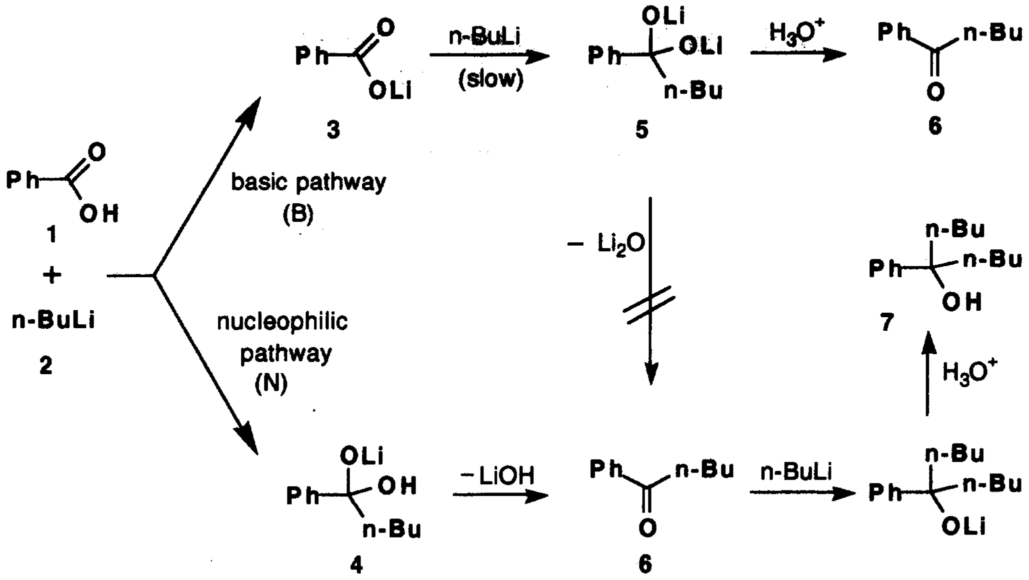

Table 1

Conditions		% acid	%BuLi	Ketone/alcohol
		consumed in (N) pathway		ratio
1M, THF,	67°C	16	24	1.1
	20°C	11	18	0.7
	-78°C	0	0	—
0.1M, THF,	20°C	16	24	1
1M, THF, 20°C, sonication		15	23	0.9
1M, THF-HMPA (4-1), 20°C		24	33	1.6
THF, Barbier conditions				
	sonication	12	22	0.3
	no sonication	7	13	0.3

The percentages with respect to the initial butyl lithium were determined by VPC analysis of the crude reaction mixture (neutral fraction) using n-pentadecane as internal standard. The sonications were effected in a Kerry Ultrasonics Pulsatron 250 cleaning bath (38 kHz) at 18°C. The reactions using the Barbier conditions were run with 5 mmol of benzoic acid, 10 mmol of n-butyl chloride and 2 mmol of lithium in 5 mL of dry THF.

Whereas concentration has a detectable but limited role, temperature is a factor of importance, and at low temperature, it can be considered that butyl lithium acts only as a base. On the other hand, the amount of reagent consumed by the nucleophilic addition becomes important by an increase of the temperature, the use of a polar cosolvent (HMPA) or under sonochemical conditions. Some important consequences result from the present experimental findings.

The conditions used in this work represent the early stages of the reaction between benzoic acid and butyllithium. In contrast to the accepted idea, deprotonation is not a very fast process with respect to the nucleophilic addition. Because of the slow rate of the reaction of the lithium salt 3, we can consider that, at this stage the ketone and alcohol products are formed via the nucleophilic pathway. Intermediate 4, known to be unstable,[2] is decomposed to the ketone which can undergo a second addition, probably rapidly especially under sonication and for Barbier conditions (low 6/7 ratio).

The above reactions were studied with some details in the case of benzoic acid, but we have shown (Table 2) that the same competition between the (B) and (N) pathways is present in many other cases.

Factors governing the overall process are not yet fully established. It seems from some examples that the pK of the acid and the steric hindrance at the C=O group could play an important role. At the present time, the more important conclusion that we reach is that the possibility of C=O attack before any deprotonation should be taken into account. This observation deserves consideration in synthetic operations.[2] In a second approach, if we consider that the nucleophilic addition of organometallic reagents to carbonyl compounds can proceed via electron transfers, the relative amounts of O-H and C=O attack would indicate which conditions enhance these transfers: the presence of an electron transporter (HMPA),[3] or the use of sonication.[4,5]

Table 2

Acid[a]	% acid	%BuLi	Ketone/alcohol
	consumed in (N) pathway		ratio
p-CH_3O-Ph-CO_2H	5	7	1.5
p-F-Ph-CO_2H	16	25	0.8
2,4,6-$(CH_3)_3$-Ph-CO_2H	0	0	—
n-C_7H_{15}-CO_2H	10	16	0.8
c-C_6H_{11}-CO_2H	2	3	0.8
n-C_7F_{15}-CO_2H	0	0	—

[a]Experiments effected with 1M BuLi in THF at 20°C.

These results, which may seem surprising at first sight, have in fact some more or less disguised precedents in the literature. For instance, hydrolysis of intermediate of type **5** in the presence of an excess organolithium reagent leads to substantial amounts of alcohol of type **7**. This result indicates that deprotonation of water by organolithium reagents occurs more slowly than the attack on the liberated carbonyl group[6-8].

Further experiments are conducted presently to obtain a reasonable and general understanding of these complex phenomena.

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