

Solvent and Ligand Effects on the Tandem Addition-Lithiation-Electrophilic Substitution of Phenyllithium on α,β -Unsaturated Carbonyl Compounds[†]

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Abstract: The reaction of phenyllithium with *E*-cinnamaldehyde is extremely sensitive to the reaction conditions and surprising changes in the product distribution were observed upon changes in the solvent, concentrations, duration or temperature of the reaction. For these reasons the above mentioned reaction was considered an appropriate model to examine solvent and aggregation effects of PhLi. On the other hand, when two or three equiv of phenyllithium are used, instead of one, the reaction transforms into a surprising tandem addition-lithiation- β -alkylation sequence, that can be successfully applied to the synthesis of substituted dihydrochalcones. The observed effects upon changes in the reaction conditions, as well as the effects of additives that modify the PhLi dimer-monomer equilibrium are consistent with a reaction pathway in which dimeric phenyl lithium attacks to the *E*-cinnamaldehyde without previous deaggregation. Usually, monomers are found to be more reactive than dimers, but, in this reaction the opposite effect is observed, and the tandem reaction spectacularly decreases with the (PhLi)₂ concentration.

Keywords: Phenyllithium; tandem reactions; aggregates; cinnamaldehyde; chalcones

Introduction

The knowledge of the effects of donor solvents in altering the reactivity and in many cases also the regio- and stereochemistry of organolithium compounds is a very helpful tool to the synthetic chemist, since it helps to choose the right organolithium-solvent combination for leading the reaction to the desired synthetic goal [1]. The seminal work by Seebach in 1984 and a second paper in 1998, alerted synthetic organic chemists to the possible consequences of aggregation in organolithium chemistry [2]. We have recently reported a marked effect of the reaction conditions on the reactivity of phenyllithium with α,β -unsaturated aldehydes, that results in a complete change of the reaction products leading to a new tandem addition-lithiation-electrophilic substitution [3].

Tandem reactions with organolithium compounds are being actively studied at present, since they constitute a powerful tool for sustainable organic synthesis as an alternative to the conventional stepwise methodologies [4]. In spite of their enormous influence on the reactivity, the origin of the aggregation effects in solution has not been well understood and there is intense research activity in that field. Apart from self-association, mixed aggregation effects have been also reported for organolithium compounds [5]. Particularly phenyllithium is one of the most studied of all organolithium reagents [6]; its unique characteristics as a base for betaine-ylide generation [6b], and the aggregation in phenyllithiums *ortho*-substituted with ether and amine chains, amenable to chelate effects, have been recently described [6c]. In the present paper we selected the reaction of PhLi with *E*-cinnamaldehyde to gain insight into the effect of several solvents and additives on the reactivity of PhLi.

Results and Discussion

The reactions of PhLi with *E*-cinnamaldehyde (**1**) were carried out in several solvents, at temperatures varying between -78 and 25°C . Concentration of the reagents and time of reaction were also relevant variables in the reaction conditions. The reaction gives the expected addition product, *E*-1,3-diphenyl-2-propen-1-ol (**2**), as the main reaction product. By-side products were *E*-cinnamyl alcohol (**3**), *E*-chalcone (**4**), and *E*-1,2-dihydrochalcone (**5**), as shown in Scheme 1.

Scheme 1. Reaction of PhLi with *E*-cinnamaldehyde, **1**, with $[\text{PhLi}]:[\mathbf{1}] = 1$.

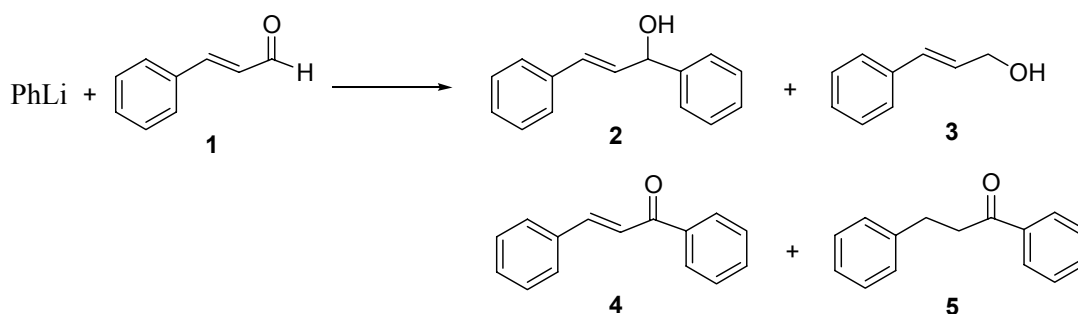


Table 1 gathers some results from previous studies [3,7] and it shows the yields of the several reaction products determined when carrying out the reaction in three solvents, namely: ethyl ether, toluene and THF. In all cases, the time of reaction was 3h, and it can be observed that the results are

quite dependable of the reaction conditions. At low temperatures, the higher yield of **2** is observed in toluene, then in ether and the lower yield in THF; furthermore, the reaction is faster and almost complete in the first two solvents, while in THF a 19% of substrate remained still unchanged after 3 h.

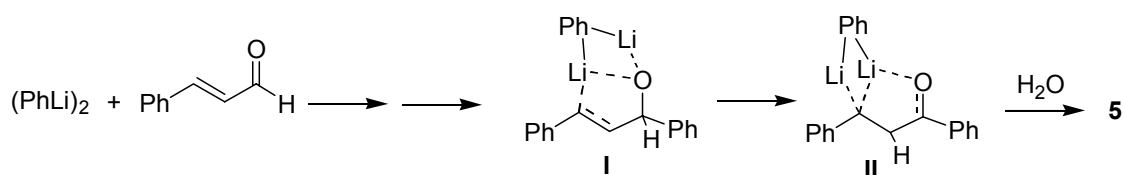
Table 1. Effects of Solvents on the Addition of PhLi to *E*-cinnamaldehyde at Several Temperatures.^a

Temperature °C	Solvent	%Yields				% 1 recovered	% Total reaction products
		2	3	4	5		
-78	Ether	72	7	14	3	0	96
	Toluene	86	5	9	0	0	100
	THF	58	7	8	0	19	73
-20	Ether	68	0	6	7	0	81
	Toluene	85	5	9	1	0	100
	THF	76	8	3	0	14	87
0	Ether	52	19	15	2	1	88
	Toluene	75	0	13	8	0	96
	THF	94	0	6	0	0	100
20	Ether	76	0	6	4	1	86
	Toluene	81	0	13	0	0	94
	THF	95	0	5	0	0	100

^a PhLi = **1** = 0.07 M. %Yields were determined by quantitative GC analysis

The reaction in toluene is practically insensitive to changes in the temperature, with yields of the expected addition product **2** in the 75-85% range; the main side product being the *E*-chalcone **4**. For the reactions in ether, increasing the temperature from -78 to 0°C, results in a decrease in the yield of the normal addition product and a substantial increase in the formation of by-products, specially of the reduction product, the *E*-cinnamyl alcohol **3**. But the reaction in THF is the most sensitive to the temperature effects. It can be observed in Table 1 that the reaction rate increases with increasing temperature and at temperatures $\geq 0^\circ\text{C}$ the consumption of **1** is complete in 3 h and it is almost quantitatively converted into the expected addition product. Therefore, the enthalpy of the reaction in THF seems to be much higher than in the less polar solvents.

Since the unexpected reaction products, specially **4** and **5**, are synthetically more appealing, efforts were then concentrated toward optimizing the production of those products. It was observed that by increasing the [PhLi]:[**1**] ratio up to three, an almost quantitatively conversion of **1** into the 1,2-dihydrochalcone **5** is observed after 6 h reaction [3]. This result, together with the high sensitivity of the reaction to the medium effects, could be interpreted as a consequence of the dimeric phenyllithium attacking **1** without previous de-aggregation as shown in the Scheme 2.

Scheme 2. Reaction of PhLi with *E*-cinnamaldehyde, **1**, in [PhLi]:[**1**] ≥ 2.

If the reaction is quenched after short reaction times hydrolysis of the first reaction intermediate, **I**, would produce the expected addition product, **2**. On the other hand, if the reaction is allowed to continue for longer, **I** transforms into **II**, which by hydrolysis produces compound **5** in high yields. Studies by ^{13}C -, ^6Li - and ^7Li -NMR [8,9], and by the powerful isotopic fingerprint technique [10] have been carried out to determine the aggregation state in several solvents. Recent variable temperature ^{13}C -NMR studies [9] confirmed that phenyllithium exists as a mixture of monomer and dimer, as it was suggested by earlier determinations [11].

If the mechanism proposed in the Scheme 2 is correct, intermediate **II** is also an organo-lithium reagent that could react with an electrophile. Indeed, by carrying out the reaction in the presence of propylbromide the 3-propyl-1,3-diphenylpropanone is produced in high yield (up to 91%) [3]. To confirm that the real reagent is dimeric phenyllithium, reactions were then run in the presence of certain additives that are known to form mixed aggregates.

For the case of lithium amides, a variety of NMR studies carried out mainly by Collum and coworkers [12,13], revealed they usually form stable dimers that can be readily transformed into mixed aggregates under special conditions. We have previously shown how the formation of mixed aggregates of cyclic lithium amides can be useful to change the yields and even the nature of the reaction products in the carbonylation reactions [14]. Consistently, it has been demonstrated recently that mixed aggregates do intervene along the reaction coordinate and their influence on the reaction rates is highly sensitive to the choice of solvent [15].

Table 2. Effects of phosphoroamides on the formation of 3-propyl-1,3-diphenylpropanone ^a

[HMPT]:[PhLi]	[HMPA]:[PhLi]	Reaction time (h)	Yield %
1:9	—	7	62
1:9	—	7	60
1:3	—	7	30
1:3	—	7	18
1:1	—	7	23
—	1:6	7	69
—	1:6	3	74
—	1:6	5	49
—	4:3	3	14
—	4:3	5	4

^a **1** = 0.07 M. %Yields were determined by quantitative GC analysis

Table 2 shows the results of the addition of additives in the reaction carried out in THF at room temperature using $[\text{PhLi}]:[\mathbf{1}] = 3$ and propylbromide as the electrophile, conditions under which a good conversion of $\mathbf{1}$ into 3-propyl-1,3-diphenylpropanone is observed through the tandem addition-lithiation- β -alkylation sequence. The effects of two additives, namely hexamethylphosphoric amide (HMPA) and hexamethylphosphorous triamide (HMPT), were examined.

It has been recently reported that HMPA interacts with PhLi producing a variety of species, some of which could be securely identified from ^6Li - and ^{31}P -NMR [6]. With one equiv. of HMPA a single new species is formed that was ascribed to $\text{PhLi}\cdot(\text{HMPA})$. Above one equiv. other species with higher HMPA contents were also identified. Hexamethyltriethylenetetraamine (HMTTA) also results in monomer formation but several equiv. are required [6]. These studies reveal that mixed aggregates competes with dimeric PhLi, and the presence of additives as co-solvents in THF converts PhLi to monomer.

Table 2 shows that the addition of this type of ligands that modify the monomer-dimer equilibrium favoring the monomer species, in all cases decreases the yield of the tandem addition-lithiation- β -alkylation product. These results clearly confirm that dimeric PhLi is the real reagent in the reactions shown in Scheme 2 and also in the further tandem alkylation when an electrophile is added to the reaction mixture. Indeed, as the $[\text{HMPT}]:[\text{PhLi}]$ increases, the yield of the reaction product gradually diminishes up to less than 30% when the ratio equals 1. Similar behaviour is observed for HMPA, the yield is extremely low when most of dimeric PhLi was converted into monomer PhLi which is in the form of a mixed aggregate $\text{PhLi}\cdot(\text{HMPA})$ for $[\text{HMPA}]:[\text{PhLi}] \geq 1$.

Conclusions

The reaction of PhLi with *E*-cinnamaldehyde is extremely sensitive to the solvent effects. The knowledge of the interactions of the reagent with the reaction media could be a useful tool to change the course of the reaction and lead it to other desired synthetic goals. The present study clearly demonstrates that dimeric PhLi is the real reagent in the tandem addition-lithiation- β -alkylation sequence. In fact, the addition of co-solvents, such as HMPA and HMPT, that are known to form mixed aggregates with PhLi when they are in one equiv. concentration or higher, has a marked effect on the yield of the reaction. Usually, these co-solvents increase the reactivity of PhLi favouring formation of the monomer, while in the present case the tandem sequence is greatly decreased. These results clearly demonstrate that dimeric PhLi do intervene along the reaction coordinate and the influence of aggregates on the reaction rates is highly sensitive to the choice of solvent and co-solvents.

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Experimental

Reagents and Solvents

THF, hexane, ethyl ether and toluene were purified and dried as previously described, assuring the absence of peroxides for the ethers [7]. In all cases, they were distilled from sodium benzophenone ketyl immediately before use. Butyl- and phenyllithium were prepared by a methodology developed in our laboratory [16], and titrated by the double titration method [17].

General Reaction Procedure.

1 M solution of PhLi (1 mL) in the required dry solvent, contained in a septum-capped round-bottomed reaction flask under nitrogen atmosphere, was cooled at the desired temperature. Then the same solvent (14 mL) and of *E*-cinnamaldehyde (132 mg, 1 mmol) were added to the stirred solution all at once; by this procedure, both reagents have a final concentration of 0.07 M. Reactions were carried out protected from light. The reaction mixtures were worked up by treating with saturated NH₄Cl solution (0.5 mL), extracted with ethyl ether and the % yields determined by GC following procedures already described [3].

Reaction in excess of PhLi

1M PhLi in anhydrous THF (3 mL) was placed in a septum-capped round-bottomed reaction flask, at 20 °C under nitrogen atmosphere. THF (12 mL) and *E*-cinnamaldehyde (132 mg, 1 mmol) were added at once to the stirred solution. Quenching was carried out after 7 h by addition of 1 mmol of the electrophile (RX). The solution was allowed to stir until decoloration and worked up as above. When the reaction was carried out in the presence of ligands, the phosphoramidate was added before the (*E*)-cinnamaldehyde.

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